The NEURONS and NEURAL SYSTEM: a 21st CENTURY PARADIGM

This material is excerpted from the full β-version of the text. The final printed version will be more concise due to further editing and economical constraints.

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A few citations have yet to be defined and are indicated by “xxx.”

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August 1, 2016
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Stage 1, Signal Generating

Can you measure the difference between one kind of smell and another? It is very obvious that we have very many different kinds of smells, all the way from the odor of violets and roses up to asafetida. But until you can measure their likeness and differences you can have no science of odor.  

"Science is made up with facts as a house is made from stones. But a collection of facts is no more a science than a pile of stones is a house."  

—Poincaré, Hypotheses in Physics (1952)

"In order to understand any part of nature, one must have both experimental data and a theory for interpreting the data and predicting new data."  

—Shepherd, Outline of a Theory of Olfaction, 2005

This Part provides detailed discussion of the sensory receptors related to Olfaction

8.6 The olfactory modality

The literature contains no contiguous theory of olfactory modality operation at this time. No definitive hypothesis of how stimulants are transduced into neural signals, or how those signals are processed by the brain, has appeared in the literature. Wise, Olsson & Cain confirmed this position and opened their 2000 paper with the above quotation from Alexander Graham Bell. In March, 2011, a team at a leading research center focused on the transduction problem, "how olfactory receptors ‘read’ molecular structure remains unknown." While significant progress has been made...
in understanding the interconnection of the sensory neurons and the glomeruli of the olfactory bulb, subsequent descriptions of the interconnection of the glomeruli and the CNS revert to conceptual sketches based on histology and electrophysiological traffic analysis.

This work offers a comprehensive description of the olfactory modality based on the Electrolytic Theory of the Neuron. For the first time, it offers an independent parameter that describes a given odorant as perceived by human subjects. It is believed to apply to all animal species, with appropriate adjustment based on their environmental niche.

It is important to distinguish between the olfactory modality and both the vomeronasal modality and the nocent modality when discussing the signaling and perception aspects of olfaction. While the complete saliency map of perception involves signals from the stage 4 engines of all of these modalities, failure to separate their individual outputs presented in the saliency map leads to endless confusion in understanding the operation of the olfactory modality.

As an example, hydrochloric acid is not a stimulant of the olfactory modality but an irritant affecting the nociceptors of the nocent modality. This fact is in spite of its long time use as a reference in psychophysical testing related to olfaction.

The role of naphthalene may lead to a more complex question. Can an organic molecule affect both the olfactory and nocent modalities? Naphthalene consists of a bicyclic aromatic molecule without any other chemical groups? While it exhibits a d-value (defined below) of 2.419 Angstrom, it is not generally associated with odorants with similar d-values. Its nocent properties appear to be more important than its olfactory properties.

Many more complex multicyclic aliphatic ring structures, including those incorporating both simple (1 carbon) and decorated (multiple carbon) top hats have also been associated with olfaction. In the absence of associated aliphatic side chains containing orbitals and/or C≡C bonds, or C–C bonds within their structure, many of these appear to be better classified as nocents than odorants. See Section 8.6.2.7.

This section will present a comprehensive theoretical description of the sensory transduction, and stage 1 signal generation, aspects of the olfactory modality of mammals. When combined with other sections related to subsequent stages, a complete description of the operation of the olfactory modality is presented in this work.

It is important to differentiate between the olfactory modality of animals and a potentially equivalent modality in insects involving receptors on their external antennae. While potentially serving a similar overall function, it has not been shown that the functions are similar at the detailed level. The apparent interaction between insect and animal species, along with the interaction of both phylum with the plants appears to add an additional complexity to this part of any discussion. Section 8.6.2.4.2 & 8.6.11.9 will address the insect modality in greater detail. Those sections will note the greater physiological similarity between the olfactory pit of insects and the taste bud of mammals than the similarity between the olfactory pit of insects and the olfactory epithelium of mammals.

This analysis began by building on the author’s earlier work on vision, then hearing and finally gustation as they appeared to provide an invaluable foundation for explaining olfaction. The work began with an effort to understand the previous work of others in the context of the above work. It focused on what chemical avenues were open to unlocking the secrets of olfaction. As quickly became obvious, olfaction necessarily relied upon coordinate chemistry over valence, or reaction, chemistry.

The basics of coordinate chemistry are introduced in Section 8.4.4.4 and various citations within that section. The so-called coordinate (dative) bond of conventional valence chemistry does not play a significant role in coordinate chemistry. It is the London type coordinate bond that is of primary interest.

The new hypothesis presented here involved a considerable degree of reiteration involving the chemistry of the odorants and the potential OR’s of olfaction before arriving at its final form. Only
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the results of those iterations can be provided here. Section 8.6.2.9 will summarize the major features of the odorants according to this hypothesis. Section 8.6.4 will summarize the proposed chemistry of the OR's used in the first step in transduction

It had long been known that no chemical residues of a reaction had ever been observed or isolated. In recent times, up through the current time, it had also become known there was no obvious relationship between the structural relationship between the chemical groups defined by both industry and the academic community and the perceived scents resulting from operation of the olfactory modality. It quickly became likely that an extension of the AH,B,X concepts of Shellenberger & Acree, of Kier and of a few others offered excellent possibilities for explaining olfaction, particularly when it became likely that the sour channel of gustation and the pungent channel of olfaction were probably separate manifestations of the same mechanism. This led to initial attempts to exam the more prominent molecules of olfaction using elementary computational chemistry techniques, including observing the vast variation in bond lengths between atoms in the formation of molecules. Fortunately, the field of computer assisted representation of three dimensional molecular structures appeared on the scene at this time. Unfortunately, this field was still new and it took several monthsthis discovery that many of the individual efforts to implement such representations were still immature. As will be noted later, the most developed representations were found to employ the representation software known as DS3.5 from Accelyrs, now BioVia with the Jmol descriptive tabulations of molecular geometry being assembled into a data base by the Royal Society of Chemistry (London).

After examining a large group of molecules involved in olfaction, it became obvious that while they partitioned into (sometimes very) large groups, there was no way to establish a pivotal member among each group. This led to a search of the potential olfactory receptors (OR) that could provide a partner in a dual antiparallel coordinate bond (DACB) relationship as suggested by Kier et al. in the 1970's. The chemistry of the odorants affecting the modality were virtually devoid of protein materials for valid reasons. Hence, the likelihood that the OR's were of protein derivation appeared small. Riddiford noted during a roundtable discussion with his peers in 1971 that, "I think if one is ever going to find receptor proteins (assuming that they exist), then the insect system is probably the best one to examine." Riddiford then elaborated on the difficulty in isolating the proteins extracted from various cells and then determining their functional role. Instead of being proteinic, it was found, like in gustation, that a small set of amino acids could be esterified to the molecules normally found in the exterior lemma of (sensory) neurons in order to provide the necessary stimulant sensitive complexes (SSC) required in olfaction. It was also found that the signals from this small set could be combined combinatorially, as in gustation, to provide a complete description of the perceived olfactory experience. This combinatorial process relied upon the fact the neural system treated each neural sensory channel of a given sensory type as statistically independent and therefore orthogonal to the other channels (just as found earlier in the other sensory modalities). The above activity led to the very explicit hypothesis and several corollaries described below. The hypothesis and corollaries provided can explain operation of the olfactory modality at a far broader level than anticipated and is offered as a Null Hypothesis open to verification or falsification by the community. The Null Hypothesis shows that fewer than two dozen OR's and at the next higher level SSC's are required to discriminate between the estimated 10,000 known odorants, and confirms that many odorants (molecules) incorporate multiple odorophores (the primary structural arrangements forming DACB couples with the OR's, but not recognized as unique molecules or molecular residues within the field of chemistry).

The empirical efforts to describe semantically the relatively unique "properties" (more fundamental than scents) perceived through olfaction have been largely unproductive. This has been partly due to the richness of the major languages of the world. Since these terms are not orthogonal in any sense, they do not contribute easily to equating them to a small group of fundamental OR's. As a result, an arbitrary set of property labels (less than a dozen) will be selected here to represent the principle property associated with each OR type. It becomes very difficult to associate a larger group of words with each property label because of the n-dimensional arrangement of the property labels and the lack of any orthogonality with the more common words. This is particularly obvious when the fact that the neural system measured an analog intensity parameter of each odorophore

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after its selection by the OR and reports this intensity to the higher cognitive engines. This method of reporting obscures the orthogonality of the reporting channels and allows vectorial manipulations that allow the cognitive engines to identify the full panoply of ~10,000 odorants.

A question is occasionally encountered as to how an inexperienced subject could recognize the character of a newly introduced odorant? The question is easily addressed based on the combinatorial approach to olfaction proposed here. The subject need only be familiar with nine fundamental sensations, those associated with the nine olfactory receptor (OR) channels of this work. Most of these may be present at or shortly after birth. There is significant information available that small animals will seek a source of food (typically sweet milk) within a few minutes of birth (the kangaroo baby is critically dependent on this capability).

Figure 8.6.1-1 will define the basic terms used in this major section related to olfaction.

### Figure 8.6.1-1

**Semiachemicals—signing chemicals**

- Common Odor-secreted signing chemicals affecting multiple species
- Odorophores—molecules containing *only* one active structure
- Odorants—molecules containing more than one active structure

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A special issue of the Annals of the New York Academy of Sciences in 1964 summarized all that was known about olfaction up to that time. The review by Moulton & Tucker was comprehensive as was the review by Amoore who indicated that as many as “24 more or less distinct theories of odor.” Only those discussed in Section 8.6.1 have gained any following in recent times. Dravnieks performed diffusion calculations relative to the mucosa. He also reported the incompatibility of the low energy of odor transduction and the norms of chemosorption and chemical reaction. The laboratory techniques available were primitive and limited to vacuum tube amplifiers of limited input impedance, relative to the neural system. Gesteland reported gross negative electrical voltage changes (a few millivolts within 0.8 seconds) of the mucosa in response to most odorants.

The stimulants generally associated with olfaction include:
1. Inorganics, primarily Lowry-Bronsted acids (involving an ionized hydrogen atom). [xxx and not Lewis acids??]
2. Aliphatic (acyclical) organics
3. Aromatic (resonant and homocyclical) organics
4. Other organics involving double bonds between pairs of carbon atoms
5. Fused-aromatic-ring (also resonant) and heterocyclical organics
6. Other chemical molecules (including the nitrobenzenes and nitrophenols)

This work will focus on categories 2, 3 & 4. Most of the category 1 chemicals are rare in the natural environment, and stimulate nociceptors rather than the olfactory receptors. The category 5 materials, while very common, are not well enough understood to be addressed from a theoretical perspective. Professor Liu appears to be a leader in employing molecular mechanics (MM) in this area as of 2010. However, his focus appears to be on the hydrogen atoms. Some materials

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associated with category 6 will be addressed on a case-by-case basis.

The materials in categories 2, 3 & 4 all involve a special relationship with the sensory neuron receptors of olfaction, known as a coordinate bond pair. The spacing between the pair of bonds will be seen to be critically important. These bonds are generally associated with oxygen or nitrogen atoms. However, it will be seen that one of the bonds can be associated with the π-electron cloud associated with aromatic ring chemicals or even the π-electrons associated with the double bond between adjacent carbon atoms. Citral is a complicated aliphatic aldehyde of category 4, employing the AH,B,X concept. It uses this concept in both of its isomers, geranial and neral to elicit a unique “citrus” sensation in humans (frequently described as a lemon aroma and bitttaste). The X of the odorophile is a π-bond between two carbons remote from the aldehyde group (Section 8.6.7.3.1).

Citral should not be confused with citric acid, a simple tri-carboxylic acid also known as limonene. xxx

This work will also differentiate between “the olfactory code” employed to control what odorants stimulate which sensory channel receptors, and “the electrophysiological code” used to communicate the status of the sensory channel sensory neurons to the central nervous system.

In developing the olfactory code, it will become clear that “proteins” play virtually no role in the operation of the odorophile-receptor complexes of the olfactory modality. The receptors are all based on phospholipids modified from the phospholipids normally found in the outer bilayer of the lemma of neurons.

As Amoore (1969) noted, “most naturally occurring odors encountered in practice have been proved by gas chromatography to be composed of a hundred or more individual odorous compounds (odorants of this work).” Specific odorants of high molecular weight will be seen to frequently contain multiple odorophores. Thus, it is important to focus on simple, low molecular weight chemicals of specific chemical conformations when attempting to define the operation of the olfactory sensory neurons.

As defined below, high molecular weight odorants may not exhibit sufficient volatility to be observed in situ via the normal nasal path (orthonasally). These odorants are frequently observed only retronasally as a result of the chewing (mastication) process (Section 8.6.1.2).

Unfortunately, the data gathered from gas chromatography does not gather chemical bond length of use in olfaction where the material is necessarily solvated and in many cases hydrated before stimulating the sensory neurons.

This work will generally contribute to the overall plan of attack on olfaction outlined by Amoore with the exception that the term protein will be replaced by phospholipid. The key to understanding olfaction is the anti-polar double bond originally introduced into gustation by Shallenberger & Acree. When introduced into olfaction generally by allowing the distance between the anti-polar bonds to become a variable, a solution to the mystery of both gustation and olfaction is obtained. By combining the known stereo-chemical formula of the various odorants with this AH,B or AH,B,X coordinate chemistry of the 1960's, the excellent material of Amoore and others, even extending to the (frequently truncated) multi-cyclic carbohydrates of Macleod8 can be profitably exploited. Without introducing coordinate chemistry, the stereo-chemistry of Macleod remains intractable; this is obvious from the first sentence of the conclusion of his 1980 paper..

While the morphology of the olfactory modality is highly tailored to its challenge of sensing volatile chemicals in the immediately surrounding environment, its physiology appears quite similar to the other modalities of the neural system.

As a rule of thumb, odorants have a molecular weight of less than 300. As a consequence, lower molecular weight carboxylic acids are effective in stimulating both the gustatory and olfactory modalities.

The cluster diagram of Wright & Michels suggests three or four individual sensory channels in stage 1 olfaction. While the extensive stage 2 signal processing associated with the glomeruli of the olfactory bulbs suggests olfactory discrimination on the order of that found in the chrominance channels of vision. Stage 3 and beyond of the olfactory modality appears virtually identical to the other sensory modalities.

The challenge is to identify the particular chemistry involved in olfaction and thereby complete the definition of the complete olfactory modality architecture. It is likely olfactory transduction involves coordinate chemistry occurring within the mucosa without any odorant penetrating the lemma of the sensory neurons.

Figure 8.6.1-2 offers a block diagram from Graziadei\(^9\) showing the extensive system of engines employed in the olfactory modality (including the often controversial vomeronasal organ when discussing the human). The dispersal of the signals from the olfactory bulb and accessory olfactory bulb are not always easy to track histologically in the CNS as many of the engines are located on internal and obscure features of the cerebral cortex. He notes, “The complexity of the olfactory central pathways is not completely understood at present (1990) and markedly contrast with the apparent simplicity of the sensor organ.” Stage numbers compatible with this work have been added on the left. Wilson & Stevenson (2006, page 46) have provided a somewhat simpler, “highly schematized,” figure that is compatible with Graziadei. Their figure does not differentiate between the olfactory and oskonyatory (vomeronasal) pathways. The full gamut of connections between the stage 2 and stage 4 engines of the oskonyatory modalities have not been explored.

8.6.1.1 The historical record of olfaction research

Olfactory research has long been dominated by empirical efforts related to the perfume and packaged food industries. Only in the last few decades has the technology been available to
Doty edited a handbook of olfaction and gustation in 2003 that provides both academic and clinical material\textsuperscript{10}. It offers considerably more detailed information than Finger et al\textsuperscript{11}. It focuses on anatomy and the chemicals of olfaction but does not address the neurophysiology of olfaction or gustation at a significant level. The authors writing in Doty review many of the earlier theories of olfaction and gustation and generally finds them wanting. On the other hand, they do not converge on one specific theory or model that is able to describe chemical sensing. The handbook is very useful for data mining but offers no significant theory of chemical sensing. See Section 8.4.

Before undertaking any analysis of olfaction, it would be wise to review the introductory comments of Turin & Yoshii in the 2003 handbook (chapter 13) edited by Doty. The comments provide a valuable perspective on how much of the literature has evolved and why the behavioral labels appear so whimsical\textsuperscript{12}. After discounting virtually all Structure-Odor-Relationships (SOR) research to date, “Most reviews of SORs are collections of disparate facts with no unifying theme save a basic postulate: odor must be related to molecular structure.”, they review the meager theoretical state of the art in olfaction.

Schutz had introduced a set of subjective names in 1964 to a set of classifications based on specific simple chemicals\textsuperscript{13}. However, his classifications placed simple alcohols under all of the titles of etherish, sweet, rancid, oily & metallic. His system is very difficult to comprehend or support. Schafer & Brower have provided an early report addressing odors under their conventional chemical group names\textsuperscript{14}. They found that experienced organic chemists could associate all of the odorants they used with their appropriate chemical designation, except for the ethers and halides. While the labels were simple, many of their chemicals were not, adding to the lower scores in some categories. They did note the ease of separating aromatic and aliphatic compounds.

The Internet provides endless reviews of the terminology of perfumes from this author’s perspective. One of these providing some perspective follows;

“There are six categories of modern perfume. There is the `bright and floral` which contains scents such as a single or bouquet smell. Another one called `Green` features smells such as cut grass and cucumber. Aquatic is a type that holds a synthetic cologne smell, `Citrus` has many different citrus scents, `Fruity` has the smells of many fruits excluding citrus. And Gourmand is a type that has `edible` qualities to it, scents such as chocolate or coconut would fall under this. Experts also use a fragrance wheel that they use to classify perfume. There is the floral, wood, oriental, fougere and the fresh. They contain both the modern and traditional categories of perfume.

Perfume is divided into three notes; top, middle and base. The top note is the initial smell a
person has, when the molecules rush to release into the air. The middle is the 'heart' of the smell and that happens just as the top begins to fade. The base smell arrives about thirty minutes after being applied. Many people think that perfume fades because the nose gets used to the smell, so it is interesting to see just how perfume transforms itself as it sits on the skin.” (Roberto Sedycias)

Initially quoting the long-standing situation described by Alexander Graham Bell in 1914, Wise et al. reviewed the complexities of quantifying the sensations associated with olfaction and the difficulty of developing a useful theory to guide future laboratory work in 2000. They noted, “Theory has accordingly had few data to explain and has stimulated little research.” They interpret Bell’s position, “As Bell saw, it is axiomatic that any account of odor quality should develop around a corpus of measurements. Science makes incremental progress through cycles of data-collection followed by theorizing or model-building followed by more data collection. In the case of odor, few trustworthy measurements of likenesses and differences have preceded theory and few have followed. Theory has accordingly had few data to explain and has stimulated little research.”

The abstract of Wise et al. opens with “The relationship between odor quality and molecular properties is arguably the most important issue in olfaction. Despite sophistication in the chemical characterization of molecules, accompanying perceptual characterization has had little quantitative usefulness, relying mostly on enumerative description. As a result of weak interest in the topic outside industry and little agreement regarding how to measure quality, the field of olfactory psychophysics has failed to develop a substantial database for odor quality and has offered little help to other researchers, e.g. neurobiologists, in choice of stimuli, interpretation of outcome or testable hypotheses.” Wise et al. then provide a background on the problem as of 2000.

They go on under the title, “Criteria for a measure,” to note three demanding standards to be met in laboratory data collection; “Techniques to measure quality could usefully meet three criteria: (i) they should resolve quite small differences since the clearest insights into molecular determinants of quality will undoubtedly come in the quest to account for small differences; (ii) they should produce indices with properties of interval-scale measurement (Stevens, 1950, 1960) to allow metric comparisons with molecular properties; and (iii) they should avoid subjectivity. The third criterion places the most serious constraint on the techniques, for almost all used through the years have a subjective aspect, a matter not always acknowledged explicitly.”

Using a report from Thiboud, 1991, they note that no rationally defined objective test criteria have been developed for evaluating olfactophores or the chemical complexes in which they are normally found. Thiboud was actually talking about fragrances (odorants) in the commercial environment and not odorophores in the scientific sense. Wise et al. discuss the merits of objective versus subjective data based on a lower threshold than adopted in this work: “Before moving on, definitions of objective and subjective (as the terms will be used in this piece) might prove useful. An objective assessment is based on performance, whereas a subjective assessment is based on a report of mental content. Suppose, for example, one wishes to assess the qualitative similarity of two odors. One might determine how well a subject can tell the two odors apart (a performance-based, or objective, assessment) or ask the subject how different the odors seem (a report of mental content, or subjective, assessment).”

While the above definition is useful, it lacks an independent parameter related to molecules that supports a numerical description of an odorophore independent of any human involvement.

Wise et al. note that a complex subjective framework has evolved that does allow workers in the food and perfume industries to communicate effectively, even if their materials remain largely

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uncharacterized. Nevertheless, they describe in some detail, three liabilities of using subjective evaluations “(all we have)” in current olfactory research. Briefly;

1. “Subjective answers are frequently circumstantial in that they depend on context, on attitude, on culture and on personal factors of unspecified origin.”

2. “Subjective measures can lead to rapid generation of data, but the speed comes with a price, namely an inability to give careful consideration to individual differences.”

3. “Subjective techniques generally preclude isometric comparisons between the data of humans and that of other animals.”

A consequence of these liabilities plus the limited size of the typical stimulant set and reporting subject set is the dendrograms and MDS graphs prepared by a laboratory can seldom be reproduced by that or another laboratory, due to statistical limitations, and cannot be compared directly with similar work by other laboratories.

Wise et al provided two extensive “composite” dendrograms (over 100 chemical names in each) employing different categories. Their figure 4 contains a variety of trivial names involving mixtures. No discussion of the figure was provided now was any citation provided. In their figure 5, they defined seven “primary” odorants, one in each major category. However, the categories are distinctly different from those in figure 4 and the primaries were actually reference odorants in the differential experiments of Amoore (1969). This material will be compared to the theory of this work in Section 8.6.7.

Contributing to the philosophical problems related to olfaction has been the use, not only of trivial chemical names, of frequently misleading short-hand names. Like the use in political discussion of today, where the term carbon-dioxide is abbreviated to carbon (a respectable name for a totally different chemical of immense importance), the abbreviation of glutamic acid to glutamate in the food industry and the abbreviation of the names of a wide variety of complex phenol derivatives to just phenol with a suffix in the perfume community has led to confusion in and stagnation of serious research.

The use of the short-hand term glutamate is particularly troubling since it can and frequently does relate to either mono-sodium glutamate or to glutamic acid (relying only upon context to distinguish between these two usages.

Beyond the use of the above collection of trivial names, the failure to develop a simple and consistent set of names for humanly perceived odors has led to endless confusion within the research community.

Amoore provided a far-ranging discussion of odor theory and odor classification in 1982 that included a review of a variety of short lived hypotheses. He concluded that review by noting that, “The majority of existing theories of odor have been neglected, not necessarily because they lack convincing elements, but often because nobody, not even their authors, pursued them actively.” His effort concluded with a discussion of the lack of an adequate scientific hypothesis in the presence of a great deal of artistic creativity among the perfumers and their marketing support.

Hoffman & Pauluth provided a paper in 1985 which provided a Table 2 describing a variety of perceived odors associated with the terpenes and terpenoids associated with the ambergris family. However, the semantics were not tied to any conceptual framework. They did provide a few one word perceptions for a few out of a set of terpineols. Section 8.6.2.10.4 will suggest these experiments be repeated under a new more rigorous protocol.

Dodd & Persaud presented their suggestions on how to develop a plausible theory of olfaction at

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about the same time\(^19\). While thoughtful and therefore useful, it was based on the assumption of conventional valence chemistry, the high likelihood that the modality employed stereochemistry based on conventional chemical groups and other conventional assumptions of that time. It included a variety of pores and channels through membrane walls. Thus their approach was essentially Bayesian, relying on past ideas that they were comfortable with. They did supply some odorant thresholds but also noted that “Much experimental work is un-repeated, and the amount of reliable data is so minute that it is not possible to offer support for any particular olfactory mechanism.”

Avenet & Lindeman offered a number of papers in the late 1980's relevant to olfaction. Their perspective was based on the chemical theory of the neuron which is not supported here. Their “topical review” of 1989 contained a great many conceptual possibilities\(^20\). However, they offered little in the way of an actual model or framework for olfaction. Their one table included a variety of question marks and limited continuity. Unfortunately, they used the nutritionist's term, glutamate, when discussing the chemical known as monosodium glutamate; thereby failing to recognize the potential for one substance exciting both the sodium and sweet channels of taste (discussed in Section 8.5). They did include an appendix on the importance of not isolating a sensory neuron from its (chemical and electrical) support structure in order to carry out patch-clamp techniques.

MacDonald, et al\(^21\). edited a major book in 1990 with a strong focus on the behavioral aspects of both olfaction and osknation. Other than a brief chapter by Gower, it avoided the chemistry of chemical sensing almost entirely. It did use the term semiochemistry to represent the chemistry of signaling within the vertebrate community. In the first chapter of part 1, Novotny et al, citing Ablone (1984), made the point that there were two “extreme views on the composition, chemical complexity and mode of action of mammalian chemosignals which affect the choice of approach to identifying the responsible components. In the so-called response-guided strategy, the pheromone-containing material is subjected successively refined fractionations...while activity is followed by the use of a bioassay.” In “the second approach, termed the chemical image strategy, assumes that the perception of the entire matrix is important in mammalian chemical communications” Neither of these approaches resulted in any major advances because they lacked an adequate foundation and sufficient understanding of the basic processes involved in chemical sensing. Their work provided considerable nuclear magnetic resonance (NMR) information, which was a new technology at the time, and relied up it for much of the theoretical interpretations without achieving a satisfactory null hypothesis of chemical sensing. The only sketch of a chemical sensing neuron in the book is superficial and incomplete, and thereby misleading.

Rossiter explored the framework required for developing a successful theory of olfaction in 1996\(^22\). The introduction to her paper opened with;

“Olfactory research has long been challenged by such questions as the following:

(1) How do we recognize and discriminate between thousands of odors?
(2) Which molecular properties determine the smell of a compound?
(3) Why, in some cases, do compounds which are completely different in structure have similar odors?
(4) And conversely, why do compounds which are very similar in structure have dramatically different odors?
(5) How can our sense of smell respond to chemicals which we have never encountered before and do so in a way that enables us to describe and categorize the odor?

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For a compound to be smelt by air-breathing animals it needs to be volatile at ambient temperature. As a consequence odorants are nonionic compounds with molecular weights of less than 300. They are usually hydrophobic organic compounds containing a limited number of functional groups. However, the presence of a functional group is not necessarily a prerequisite for odor. Even alkanes can have pronounced odors, two notable examples being 2,4,4-trimethylpentane and cyclooctane, which are both strongly camphoraceous. In aquatic animals the molecular criteria for odorants are quite different with water-soluble materials, such as amino acids, being among the best.”

This work will generally address the above ideas and concepts in developing a new theory of olfaction based on the Electrolytic Theory of the Neuron which has been so successful in elucidating the features and performance of the other sensory modalities. It will take an exception to Rossiter’s assertion that the stimulants to the olfactory modality are typically hydrophobic. Upon closer analysis, they typically incorporate features designed to enhance their coordination chemistry with water as part of the transduction process.

Rossiter introduced the concept of osmophores. “This has led to an increase in the number of postulated “osmophores”, which are usually expressed as distance criteria between key structural fragments.” While using a different conceptual framework than for the sugars in the previous sections, the concept of the distance between two active atoms or electronic centers will play a key role in the following development.

Rossiter included a brief survey of earlier theories of olfaction.

“The “stereocohemical theory”, which was postulated by Amoore in 1952, links odor quality to molecular shape and incorporates the concept of primary odors. The primary odor theory is analogous to the visual perception of color. Amoore considered that all odor sensations are based on various combinations of a limited number of primary odors, with each primary odor being detected by a different receptor in the nose. Seven primary odors were originally suggested on the basis of their frequency of occurrence in the literature: ethereal, camphoraceous, musty, floral, minty, pungent, and putrid. Amoore subsequently carried out “specific anosmia” experiments in an attempt to prove the existence of primary odors and identify them all. This work was inspired by Guillot’s suggestions that specific anosmia, the inability to detect one particular odor, was due to the affected person lacking one of the primary odor receptors. One of the main objections to the stereochemicl theory is that there are many examples of substances that have a similar shape but very different odors because of a difference in functional group.”

“The vibrational theory was first postulated by Dyson in 1937 and later extended by Wright in the 1950s and 1960s. They believed that olfactory receptors selectively enter into resonance with odorous molecules. Objections to this theory concern, firstly, optical isomers and, secondly, isotopic substitution. Enantiomers have identical far-infrared spectra whereas in some cases, but not always, their odor qualities can be quite different. Deuteration of an odorant molecule alters the vibrational frequencies of the molecules but does not change its...
odor. These and other old “theories of olfaction” have been reviewed recently by Laffort\textsuperscript{28}. Recently Wright’s theory has been given a new lease on life by Turin\textsuperscript{29} who has proposed an electron tunneling mechanism as the olfactory detection method. He postulates that electron tunneling through a molecule excites it vibrationally and that therefore there is a degree of correlation between odor and vibrational spectra.\textsuperscript{2}

“Recent reviews on this topic are provided by Breer et al\textsuperscript{30} and Ronnett\textsuperscript{31}.”

Turin took up the vibration theory banner during the 1990’s but without a comprehensive approach to the sensing problem that includes any description of a sensory neuron and its mode of operation. This situation remained true in March 2011.

Rossiter makes several other clear statements that are supported here.

“Aroma chemicals have two sensory odor properties: intensity (strong, moderate, weak) and quality (floral, woody, etc). The first very important step in the determination of a relationship between these properties and molecular structure is the collation of good, precise, reproducible odor data. Without this all subsequent SAR work is a waste of time!”

Unfortunately, her criteria remain subjective at this time.

This work will adopt a slightly different description of odorophores related to their intensity and their coordinate chemistry valence (CCV), a measure of their ability to associate with a specific olfactory receptor. The CCV will be described by a d-value, a parameter related to the distance between active elements of an odorophore. The d-value also relates to a similar distance associated with the active elements of the receptor of a specific neural sensory channel. The CCV defines which sensory channel is excited and the quality describes the sensation elicited by that channel. The conventional use of valence in its common chemical role of describing a state of oxidation does not play a role in olfaction.

The Rossiter paper is an excellent source of information on the more complex stimulants, used in perfumery particularly. It concentrates on many complex substitutions and the resulting elicited sensations. This work will begin with the simplest stimulants in the development of a theory of olfaction and hope to reach a merging point with Rossiter’s lexicon of chemicals, intermediate rules (SAR and SOR) and results.

\[xxx\ add Sells 1997 \]

Jackson & Linskens provided an “Analysis of Taste & Aroma\textsuperscript{32}” as Volume 21 of an on-going series in 2002. The series changed its name from “Modern Methods of Plant Analysis” to Molecular Methods of Plant Analysis with that volume to recognize the growing importance of Molecular chemistry in this field. The book offers no insights into the operation of the olfactory modality but does provide some data relative to the odorants and potential odorophores of strawberries, beer and citrus.

\begin{enumerate}
\end{enumerate}
They did offer a Table 3.6 describing the complex set of semantic terms (unrelated to the chemistry) used to describe the flavor components of beers. They note the difficulty of making direct judgements and the common practice of employing relative tastes and employing simple procedures in attempts to control the mechanism of adaptation.

A group of very complex multi-cyclic structures labeled flavinoids play a major role in both gustation and olfaction. However, their structural complexities will not be discussed in this work. It appears their perceived odors and tastes are describable based on the hypotheses of this work. Talapatra et al. have discussed the multiple families of the flavinoids in considerable detail.

Leffingwell provided a very comprehensive account of the chemistry of olfaction from a perfume industry perspective.

Laffort has provided several chapters of a book in 1994 cited above. Chapter 6 provides a concise description of the theories of olfaction over time. He lists them as;

1. Radiative theories - poorly defined and dating from the time of Aristotle. They rely on some form of electromagnetic radiation from the source of the odors.
2. Molecular/receptor resonance theory - Attributed to Wright during the third quarter of the 20th Century and involving the subsequent change in the Raman or other molecular vibrations in the IR energy spectra creating a neural signal.
3. Thermodynamic activity theory - Totally abandoned after some interest during the 1940's.
4. Chromatographic theory - Undeveloped beyond the concept arising from general chemistry.
5. Membrane penetration theory - Originally developed in analogy to Hodgkin & Katz ideas of a neuron and based on molecules diffusing through a membrane and thereby opening a canal through which small ions could pass through. With the recognition that odor molecules did not pass through the membrane, the concept was abandoned.
6. Primary odor concepts - Conceptually developed by Amoore and others in the fourth quarter of the 20th Century and based on the “stereochemical theory of olfaction.” To date, it has failed to explain the transduction of stimulants into a neural signal.
7. The current pragmatic situation - In absence of a comprehensive theory, the community has reverted to a pragmatic approach defining between chemical structure and activity relationships (SAR) and structure and odor relationships (SOR).

The pragmatic approach has sought to relate the mechanism of transduction to a series of receptor proteins embedded in the sensory neuron cilia. Laffort notes, “Unfortunately, all attempts carried out to date have failed, at least as far as the identification of highly specific proteins are concerned (page 163).” Moon & Ronnett have proposed an alternative. They have suggested the proteins present in the mucosa act as odorant binding proteins (OBP’s) but not odorant receptor proteins (ORP’s). They even go farther, “Alternately, OBP may function to remove odorants from sensory epithelium and cilia.”

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33 Talapatra, xxx. Talapatra, xxx (2015) xxx Chapter 14
Nef described the potential theories of olfaction in 1998.  

1. A "molecular approach" model for rodents.
3. A genetic approach to investigate odor responses in the nematode C. elegans, which possesses 14 types of chemoosensory neurons and responds to dozens of odors.  

These approaches were not detailed in this short paper. However, it was suggested that a combination of these approaches might offer a useful outcome.

Nef notes a confusion factor related to the genetic approach, “Some members of the OR gene family, indistinguishable from those expressed in olfactory neurons, have been found to be expressed in tissues unrelated, in appearance, to olfaction. Without a clear function, OR-positive cells are observed 1) in the tongue (gustatory receptor, tongue morphogenesis), 2) in sperm cells (spermatogenesis, sperm maturation), 3) in the developing rat heart (cardiac morphogenesis), and 4) in the avian notochord. While this work supports a commonality between the OR’s of olfaction and the GR’s of gustation, the non-uniqueness of genetic models is obvious based on the Nef citations. Nef concludes, “Therefore, data addressing the specificity or the affinity of the odor/receptor complex are still missing. Thus a final model on how odor molecules are detected, discriminated, and encoded remains mostly hypothetical, because the binding affinities of odor molecules to their receptors are lacking. The missing data could dramatically affect the proposed models.”

Turin & Yoshii readdressed what they considered the two remaining hypotheses in the above discussion from their perspective, the fragments of molecular shape or odotope approach and the molecular vibration approach. Turin and Yoshii focus on the premise that the olfactory modality relies upon an “enzyme-substrate and receptor-ligand binding relies on molecular recognition between protein and ligand.” The description of an odotope in Turin & Yoshii as a functional group as defined in conventional chemistry is not sustainable. They do however describe the vast number of odorants that could be delineated while employing a combinatorial scheme based on only a small number of sensory receptors.

"Consider, for instance, a molecule having 20 exposed atoms and assume that each odotope involves three of these. A binary (on-off) one-odotope recognition system would then be able to detect 1140 molecules. If odotopes involved four atoms, the number would rise to 4850, etc. Combining odotopes, and adding to this basic scheme a measure of intensity of excitation for each receptor, clearly enables it to detect a vast number of odorants."

This odotope approach if realizable would clearly explain why there is no need for at least a thousand sensory receptors as currently proposed by the genetics community. They also note the role of many of the proteins identified by the genetic community play roles in other non-olfactory tissue (Dreyer, 1998). Some of these proteins may actually play a role in the developmental process rather than in sensing directly.

Turin & Yoshii resurrect the molecular vibration approach after detailing its demise in the 1980’s. They interject a new concept, involving electron tunneling, and suggest this “might be a plausible mechanism enabling proteins to act as vibrational spectroscopes.” After a significant discourse, they offer no explicit model of their molecular vibration hypothesis. They then change subject to “The Puzzle of Odorant Intensity.”

"The question of odorant intensity (strong vs weak) as distinct from odor character (the sum of descriptors) raises issues of unexpected subtlety. Odotope theory implicitly assume that odorant intensity is part of the odor character, i.e., that a molecule can be described legitimately as, say, green-weak or green-powerful.”

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Turin & Yoshii offer no solution to their puzzle after a page of discourse.

Shepherd discussed an “Unsolved Mystery” in 2004. The paper was totally behavior oriented and did not develop any theory of olfaction. A color wheel, without any coordinates or dimensions, categorized olfaction in mouse and human as exhibiting identical olfactory sectors. At the same time, Yanagida et al. repeated the common refrain, “However, there are various reasons that olfaction has been left in the back country of the Virtual Reality research field. For example:

(1) Olfaction is activated by chemical stimuli. This is very different from visual, auditory, and haptic sensations, which are activated by physical stimuli.
(2) A set of “primary odors,” i.e., a small number of bases to represent arbitrary smells, has not been found.

Their paper did not explore what they meant by chemical stimuli.

In 2006, Gottfried et al., repeated the common refrain, “The relationship between odorant structure and odor quality has been a focus of olfactory research for 100 years, although no systematic correlations are yet apparent.” After discussing the recent history suggesting a correlation between perceived odor and the conventionally noted chemical properties of the odorants, they note, “However, the above observations conflict with human psychophysical studies showing that structurally related odorants may smell different and that structurally unrelated odorants may smell alike, highlighting an undetected relationship between olfactory sensation and odor perception.” These comments rely upon the conventional chemistry of well defined groups within a molecule. They are totally overturned by the concept of “overlay groups” developed below.

This work will follow a totally different approach than any of the above hypotheses, based on greater focus on the lipid chemistry of the neural cell membrane and the Electrolytic Theory of the Neuron to expand the stereochemical theory of olfaction into a cohesive overall theory. To avoid confusion, the term odorophore will be used to describe the overlay group, or moiety, of a molecule forming the critical portion that coordinate bonds to the four actual, identified and non-protein, sensory receptor ligands. This overlay moiety does not conform to the typical ligands of chemistry. See Section 8.6.1.6 to 8.6.1.8 will provide a summary of the hypothesis before proceeding to the development of the theory.

The number of carbon atoms in a molecule plays a minor or negligible role in olfaction as long as the number is greater than that required to support the physical distance, the d-value, between the appropriate orbitals of olfaction.

Amoore has quantified the wide range in sensitivity of the olfaction modality in the human population. This variation makes experimental procedures particularly subject to error if not accounted for. He noted, “the standard deviation among 443 subjects was ±1.7 binary dilution steps in a geometric concentration scale. Hence, taking the normal mean detection threshold as unity, approximately 95% of the population should have personal thresholds between 1/10th and 10 times the mean threshold concentration for a given odorant.” This is the typical two-sigma range of a log-normal distribution. Assuming the log-normal distribution fits the data, 67% of the population should be within the one-sigma range (1/3 to 3 times the mean).

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18 Neurons & the Nervous System

After a wide ranging discussion, this section will converge on a basic theory of olfaction; the one receptor-one sensory neuron approach combined with the one odotope-one receptor approach. It will show the perception resulting from a specific stimulant is represented by an analog bit-parallel word stored in the saliency map of the parietal lobe and available to the cognitive powers of stage 5. The concept of one stimulant-one sensory neuron type is not supported. The receptors are very simple proteins consisting of only a few amino acid groups most likely present as transition metal complexes on the surface of the lemma of the neurons.

Elsaesser and Paysan have provided an extensive history of olfaction research focused on the chemical theory of the neuron 42. Much of that theory rests on a model first introduced by two graduate students in 1976, Bert Menco and Adnan Menevse.

Wolstenholme & Knight edited a very useful proceeding in 1970 on taste and smell in vertebrates 43. While much of the work is now seriously out of date, it provides considerable background on the subject. The discussion, such as pages 281-290, are particularly useful. The Davies reference to the “penetration and puncturing theory of olfaction” is a case in point. In the absence of a rational gain mechanism, such as provided by the transistor-action of the Activa, that theory hypothesizes a hole in a chemoreceptor neuron membrane caused by the stimulant and a rush of ions through that hole. The rush of ions represents a current gain relative to the initial stimulant molecule. This hypothesis is now archaic. Martin (pages 285-286) tears apart the puncture theory. The comment on page 284 relative to a bilayer membrane being at the center of a five layer structure, including a “fuzz” of mucopolysaccharides and mucoproteins, has more relevance currently. Adey (page 284) notes the sensitivity of this multilayer structure to detergents such as EDTA and EGTA. This observation is very important.

Doving (page 283) speculates on the presence of 25 possible physicochemical parameters (now determinants) associated with the transduction mechanism of olfaction. Davies suggests (page 286) the cell wall of insect antennae are two strong to support holes forming due to single stimulant molecule penetration. He speculates that the molecular determinants may relate to pseudocrystalline or liquid crystalline structures on the surface of the membranes.

Adey (page 288) references a proposal by Wei 44 that the plasma membrane acts as a transistor. However, the conceptual proposal was for a totally different orientation than proposed here.

Wright touched on one crux of the problem, whether the stimulant molecule was consumed during transduction or employed in a “touch and go mechanism.” He notes that penetration of the plasma membrane introduces the difficult problem of metabolizing the intruding molecule.

Lancet provided an excellent and extensive discussion of vertebrate olfactory reception in 1986 45. Some of the conceptual material is now dated. However, the measured values are important.

Getchell provided an excellent review of the olfaction modality in 1986 46. It provides a wealth of information available up to that time including stressing the parametric character of the only action potentials recorded from olfactory sensory neurons (page 789).

Bruch et al. provided a review in 1988 that is all textual; there are no figures and no significant

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values\textsuperscript{47}. The discussion centers on the probable nutritional aspects of olfaction. It is of little use at the theoretical level.

Serby & Chobor edited a 1992 volume that provides a much broader formal structure of olfaction (including separating the main and auxiliary olfactory bulbs) and excellent new data (including an artist's cross section of the olfactory tissue, page 52), a chapter on planning future studies and chapters on olfactory diseases and hallucinations. However, the included hypotheses are seriously dated\textsuperscript{48}.

Macleod has presented a table of Sensory neuron density in olfactory epithelium of a variety of common laboratory animals and humans (page 40).

Farbman has provided a volume that discusses many of the histological and “functional” aspects of olfaction in many species. While noting the “primary focus of the book is cell biology, . . .”, he does not discuss the cytological and detailed operational (circuit) aspects of the individual cells\textsuperscript{49}. He differentiates animals with a keen sense of smell (macrosmatics) from many primates (among the microsmatics) by the level of folding in the turbinals of the nasal cavities. The size of the olfactory bulb, relative to the size of the brain, also reflects the sensitivity of smell.

He attributes the location of the soma of the olfactory sensory neurons to the primitiveness of the modality in vertebrates (page 19). The location of the non-neurologically functional soma appears to be chosen by packaging convenience more than by phylogenetic age. He also notes the axons of the olfactory sensory neurons are unmyelinated. This fact is characteristic of sensory neurons with tonic generator waveforms as their output. The axons are typically 0.2 microns in diameter. He notes on page 20, the signals from the olfactory sensory neurons do not project directly to the thalamus (although he does not demonstrate that no such neurons project directly to the thalamus). He asserts some of the signals are passed to the thalamus from the morphologically defined piriform cortex (which occupies a space directly adjacent to the thalamus). He defines the types of cells in the olfactory epithelium as the sensory cell, the supporting (sustentacular) cell and the basal cell. He reports the epithelium thickness varies from 30 to 400 microns among various species and the cells of the epithelium form a tight surface just below the surface of the epithelium. This tight surface is a barrier to the flow of large molecules and ions of the epithelium. It is not clear whether this surface is a barrier to electrolytic currents between the mucosa and the epithelium from his description. He does note the presence of Schwann cells enclosing multiple sensory axons within the groups of axons known as fascicles. These fascicles pass through the supporting structure called the lamina propria before penetrating the cribriform plate. There are about 44 fascicles in humans, 22 on each side. In some mammals, the total number reaches 200-300 (page 38).

He provides schematic and both histological and freeze-fracture electron microscope sections of the epithelium and lamina propria. The number of olfactory neurons per unit area does not vary a great deal among species (page 27). The density ranges from 4 \times 10^4 to about 12 \times 10^4 per square millimeter (with one report of 43 \times 10^4). Farbman does introduce the subject of olfactory sensory neuron maturation and replacement (page 27). He notes the olfactory epithelium is an exception to the general principle that neurons do not regenerate in adult warm-blooded vertebrates. He notes neurogenesis of cells of the olfactory epithelium continues throughout life. He estimates a sensory neuron life time constant of about 30 days in mammals on page 57.

Farbman is unable to differentiate between the use of the term cilia and microvilli among different investigators when referring to the structures emanating from the dendritic knob (page 31). These microtubules are typically 0.3 microns in diameter and 30 to 200 microns long in vertebrates. They are splayed away from the knob in order to occupy a mucosa that is up to 35 microns thick in some amphibians but typically 5-10 microns thick in mammals (page 75).


This work will tend toward the use of cilia to describe the outer extensions from the knob associated with olfactory receptor neurons and microvilli for the sensory portion of the microvillar neurons found in parallel with the olfactory neurons of the epithelium. These microvillar neurons will be associated with the nociceptors of the somatosensory modality.

Citing Macrides & Davis, 1983, and Halasz & Shepherd, 1983, Farbman makes an unusual, and potentially important statement on page 39. “Although olfactory sensory neurons have been extensively studied, none of the well-known neurotransmitters of other neurons has been shown to be present in the axon terminals.” This finding is consistent with the Electrolytic Theory of the Neuron. He discusses the potential for other neurotransmitters in the context of the chemical theory of the neuron in his section 5.7.1. He returns to the potential of carnosine (a dipeptide) as a neurotransmitter in his section 7.5 where he notes “there are conflicting data about the true function of this molecule. There has been little or no recent work directed to this problem; no other putative neurotransmitter has been proposed.” Burd et al. have shown the creation of carnosine in the immediate area of the olfactory sensory neurons. However, their autoradiographic resolution did not expose whether the material was formed or functioned in either the glia or the sensory neurons. Boldyrev et al. have suggested carnosine may be involved in homeostasis rather than neural operations.

Farbman develops the pros and cons for leaning toward what he calls stimulant sensing complexes (SSC’s) being proteins in his section 3.2. In this work, it is only the olfactory receptor portion of the SSC that is concerned with transduction. The rest of the SSC is common across all sensory modalities. He notes (page 86), “Although no one of these observations, in itself, proves the existence of protein receptors in membranes of sensory cells in the olfactory apparatus of vertebrates, taken together they make a compelling argument for their existence. However, the evidence is all indirect, and direct proof for the isolation of a receptor molecule remains elusive” (in 1992). He addresses the alternative that the SSC’s are lipids in his section 3.2.3.6. All of his discussions employ caricatures rather than detailed models. See Section 8.6.3.1.4 for further discussion of this point.

Farbman references several investigators to support the fact the resting potential of olfactory neurons is -30 to -60 mV relative to the surrounding matrix. Stimulation normally leads to depolarization.

xxx has provided a useful description of the performance of the olfactory modality in the dog (with citations).

“Dogs can accurately distinguish and identify a large number of people by general body scent alone. In standard competition trials, bloodhounds can follow the trail of a person who waded over rough moorland 24 hours before and identify the person they have tracked. If a dog approaches a recently (3-20 minutes old) laid human track at right angles, it spends 3-5 seconds sniffing intensively at 2-5 footprints and then begins to track rapidly in the direction in which the tail layer moved.”

Laska has analyzed the difference in human olfaction related to the differences in configuration of the aliphatic C6 alcohols.

Franco et al. (2011) have evaluated the differences in perception of normal and deuterated 1-
octanol by *Drosophila melanogaster*. All hydrogens were replaced except that associated with the hydroxyl group. The empirical results are interesting. There was no attempt to describe the sensing process. Their deuteration results in a change in molecular weight from 130 to 148 and suggests a significant change in the IR spectra of the two molecules. The longer bond length associated with the IR spectral change suggests a change in the dipole potential between the molecules. However, the symmetry of the aliphatic alcohols suggests this change may be small.

Lledo et al. have provided a very recent review of the olfactory system. The presentation is primarily narrative with artistic caricatures.

The fragrance and flavor chemist, Kaiser has published a comprehensive work on olfaction. The work is an invaluable cross-reference in olfactory chemistry. While it remains focused on stylized Fischer Diagrams to describe the chemistry of olfaction, it provides a long list of IUPAC chemical names that are easily correlated to the diagrams. The diagrams also provide the largest known sequential list of (unduplicated) diagram numbers (about 232). With a little effort, it also provides considerable material on homologous relationships among a large number of odorants. The appendices include lists of all of the volatiles they recovered from a wide range of locations (including from the top of the rain forest canopy). The complexity of these lists is remarkable. Pages 32-35 describe the dirigible used to access the canopy of the rainforest in a variety of locations around the world.

Kaiser does not attempt to isolate specific odorants or odorophores in order to establish their specific perceived smell. His percentages describing the presence of various chemicals in his samples relate strictly to the concentration of a chemical and has nothing to say concerning the olfactory relevance of the chemical. His focus is on the smell elicited by natural (and very complex) mixtures of odorants as found in the field.

Major efforts to determine the number of odorants that can be identified by differential scent sampling have recently been reported. Both activities used the “olfactory three alternative forced choice discrimination tests that are also known as triangle tests. For these tests, subjects were presented with three odor vials, two of which contained the same mixture, whereas the third contained a different mixture.” Initially Weiss et al. attempted to determine the concentrations required among a large group of mixtures (odorants) to achieve equal perceived intensities by humans. Their group included professional perfumers. Based on the title of the paper, their goal was to define “an olfactory white” based on their understanding of a “visual white” that is not traceable to this work.

Bushdid et al provided a calculated number of discriminatable odorants using the normalized values from Weiss et al. They identified all of their individual odorants by a C.A.S. number and provided the percent of the odorant in their identified solvent. They then prepared mixtures of 10, 20 and 30 of the identified and diluted odorants for their presentation to test subjects.

They provided a formal description of the mathematical probability of identification of a difference between the prepared mixtures based on the three alternative forced choice discrimination test method. Based on their mathematical procedure, they estimated that humans can discriminate between over one trillion (a thousand million) stimuli (odorants). In their words;

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57Bushdid, C. Magnasco, M. Vosshall, L. & Keller, A. (2014) Humans can discriminate more than 1 trillion olfactory stimuli *Science* vol 343, pp 1370-1372 and supplement
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“One can calculate the number of mixtures that can be discriminated by either using the discrimination capacity of subjects or by the discriminability of stimulus pairs. Depending on what criteria are used, our results show that humans can discriminate $1.72 \times 10^{12}$ or $5.58 \times 10^{13}$ mixtures of 30 components out of the collection of 128 odorous molecules. $1.72 \times 10^{12}$ may seem like an astonishingly large number. However, there are $1.54 \times 10^{29}$ possible mixtures of 30 from the 128 components used here. Therefore, if there are $1.72 \times 10^{12}$ discriminable stimuli, this means that for each mixture tested there will be $8.95 \times 10^{16}$ other mixtures that cannot be discriminated from it.”

A trillion odors is a far larger number than the number of individual sensory receptor neurons cited in Section 8.6.1.3 (six to 50 million receptors in the human olfactory epithelium). Several aspects of their work are worthy of further discussion. A significant critique is provided in Section 8.6.8.5 following development of the full theory of this work.

8.6.1.1 Odor classification and profiling

Olfactory stimulants have traditionally been classified by their similarity to that from a specific plant, animal, or environmental condition (a potato bin). Major classifications prior to the advent of organic chemistry as a science occurred long ago during the last half of the 18th Century. Even a recent classification system, that of Zwaardemaker, dates from the first quarter of the 20th Century. More recent classification activities have attempted to add second and third order nuances to the designations, some of which vary with time following exposure to the stimulant. These are generally described as "notes."

Sklar has provided a potentially useful categorization of odorants. However, it selects citral vs as a point of reference; this molecule is quite complex and contains at least three distinct odorophores as opposed to limonene with only one (with $d=4.303$ Angstrom). The paper is discussed in greater detail in Section 8.6.8.4 using additional annotation based on this work.

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Many attempts have been made to portray the range of human perception in graphical form. Henning’s odor prism of 1916 is shown in two forms in Getchell et al. (page 193). These characterizations have lacked any scientific framework. As Getchell et al. also note, these classification schemes, “have fallen out of favor in the past decade or two” in favor of two alternate “approaches, termed odor profiling and multidimensional scaling.

Odor profiling continues to be completely subjective and relies upon the judgement of an experienced perfumer, or other person in the application of stimulants to the olfactory modality. It has followed the above classifications in relying upon descriptive labels associated with the natural environment to develop profiles of initial and subsequent perceptions of stimulants (sometimes specific odorants) in terms of their qualities, components and “notes.”

Table 7. Stimulation by Odorants of the GTP-Dependent Adenylyl Cyclase in Frog Olfactory Cilia*

<table>
<thead>
<tr>
<th>Odorant (100 μM)</th>
<th>Stimulation (%)</th>
<th>Odorant (100 μM)</th>
<th>Stimulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>14 ± 8(3)</td>
<td>Furfuryl mercuran</td>
<td>29 ± 9(3)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10 ± 7(3)</td>
<td>Triethylamine</td>
<td>4 ± 7(5)</td>
</tr>
<tr>
<td>Chloroform</td>
<td>5 ± 2(3)</td>
<td>Phenylethylamine</td>
<td>0 ± 7(3)</td>
</tr>
<tr>
<td>Butanol</td>
<td>4 ± 10(3)</td>
<td>Isobutyric acid</td>
<td>-2 ± 7(3)</td>
</tr>
<tr>
<td>Pyridine</td>
<td>4 ± 22(4)</td>
<td>Pyrrolidine</td>
<td>-4 ± 6(2)</td>
</tr>
<tr>
<td>Xylene</td>
<td>-2 ± 3(2)</td>
<td>Isovaleric acid</td>
<td>-6 ± 8(5)</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>-14 ± 33(3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fruity

<table>
<thead>
<tr>
<th>Odorant (100 μM)</th>
<th>Stimulation (%)</th>
<th>Odorant (100 μM)</th>
<th>Stimulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citralva</td>
<td>100</td>
<td>Isomethone</td>
<td>105 ± 10(3)</td>
</tr>
<tr>
<td>Citral dimethyl acetate</td>
<td>69 ± 10(5)</td>
<td>t-Carvone</td>
<td>74 ± 31(6)</td>
</tr>
<tr>
<td>Citronellol</td>
<td>56 ± 5(3)</td>
<td>Menthone</td>
<td>71 ± 3(4)</td>
</tr>
<tr>
<td>Citronellol</td>
<td>55 ± 5(3)</td>
<td>Eucalyptol</td>
<td>45 ± 8(4)</td>
</tr>
<tr>
<td>Citronellol</td>
<td>50 ± 9(4)</td>
<td>3-Hexyl pyridine</td>
<td>118 ± 10(3)</td>
</tr>
<tr>
<td>Isoamyl acetate</td>
<td>19 ± 11(8)</td>
<td>2-Hexyl pyridine</td>
<td>107 ± 8(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>5 ± 4(5)</td>
<td>3-Hexyl pyridine</td>
<td>107 ± 8(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Hedione/MDHI</td>
<td>63 ± 4(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Coniferan</td>
<td>60 ± 20(2)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Geraniol</td>
<td>58 ± 3(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Helional</td>
<td>53 ± 6(5)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Decanal</td>
<td>53 ± 8(2)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Amyleisiclyte</td>
<td>40 ± 10(2)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Dimethyloctanol</td>
<td>33 ± 9(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Acetophenone</td>
<td>30 ± 4(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>α-Pinene</td>
<td>21 ± 12(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Phenylethylalcohol</td>
<td>19 ± 4(3)</td>
</tr>
<tr>
<td>Lyral</td>
<td>-4 ± 6(2)</td>
<td>Lilial</td>
<td>-1 ± 4(2)</td>
</tr>
</tbody>
</table>

*From Sklar et al. (1986).

*Adenylate cyclase activity was measured as described in Sklar et al. (1986). Odorants were tested at 100 μM in the presence of 10 μM GTP. Data are expressed as a percentage of the activity observed in the presence of 100 μM citralva.

*Nomenclature for odorants not listed in Merck Index, 10th ed. (M. Windholz, S. Budavari, R. F. Blumberg, and E. S. Osterbein, eds.), 1983, Merck & Co., Rahway, New Jersey, is as follows: citralva, 3,7-dimethyl-2,6-octadienal; citral dimethyl acetate, 3,7-dimethyl-2,6-octadienal; citral dimethyl 1,1-dimethoxy-3,7-dimethyl-2,6-octadienal; citronellal acetate, 3,7-dimethyl-6-oxa-1-ol acetate; lyral, 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde; hedione, 3-oxo-2-pentylicyclopentanecarboxylic acid methyl ester; coniferan, 2,4-pentylicyclohexanone acetal; helional, α-methyl-1,3-benzodioxole-5-propanol; lilial, 4-(1,1-dimethylthyl)-α-methyl-benzeneepropanol.
The methods of stimulant application remain difficult to reproduce with precision. Figure 8.6.1-5 shows the simple techniques usually employed. The major problem is controlling the concentration of the volatiles in the air actually entering the nasal cavity. In many cases, the samples are prepared and then the air in the sample bottle, tube etc. is allowed to equilibrate with the adjacent solution in order to achieve some level of repeatability. Doty discusses the complications related to these techniques in Chapter 5 of Laing et al. (1991).

Multidimensional scaling (MDS) is a mathematical procedure of statistics designed to uncover hidden statistical features of a data set. It involves collecting considerable amounts of subjective data from cooperating subjects, but without providing the subjects any feedback concerning their performance. The technique became useful with the advent of modern odorant and odorophore isolation and synthesis techniques. Having pure odorophores available has allowed the use of MDS at significant levels of precision.

Unfortunately, the use of MDS (and particularly the canned computer programs require to support it) requires a very experienced investigator if useful results, rather than pretty figures, are to be obtained. This subject is discussed in more detail in Section 8.5.2.3 through 8.5.2.6.

Ham & Jurs classified a set of 71 monocyclic benzoïds (38 musks and 33 non-musks) using pattern recognition techniques60. It was asserted the odorophores were completely described by 13 molecular structure descriptors. Based on their analyses, a set of 29 other compounds were predicted. Their analyses only addressed a minuscule fraction of the odorants available. The major problem with the Ham & Jurs approach is presented in Section 8.6.2.6.

Even in 2005, the science of odorophores continued to rely upon the study of the chemical structure (predominantly using two-dimensional Haworth diagrams) and recognized chemical classes to attempt to uncover the underlying mechanism(s) of olfaction61. The studies were based primarily on genetic hypotheses. Sanz et al. did not pursue any discussion of the mechanism of sensory neuron stimulation or of coupling between the...
simple carbohydrates studied and the appropriate neural tissue.

A good but short smell oriented cross index between chemical names and common names can be found at, http://chemconnections.org/Smells/. Although the program activity associated with it appears to have died. The hyperlinks all lead to a 404 error. A much larger chemical database is, http://www.chemsynthesis.com/, last updated in 2011 but the material is not in .mol format. It does show the amino acids in neutral form (using Fischer Diagrams) and provide various numeric labels for different databases. The lists focus on the more complex molecules.

Zarzo & Stanton have provided a large statistical analysis of the scent names associated with olfaction62. They interpreted the odor profiles of 309 compounds based on 30 descriptors. Their findings did not achieve new understanding; “Our findings suggest that it is possible to develop standard sensory maps of perfumery odor descriptors, if a consensus is first reached regarding which odorants best represent particular odor qualities.” Failure to recognize that an odorant can incorporate more than one odorophore doomed their study. They prepared long tables of semantic descriptions of 30 reference materials (many essential oils) and their “attributes.” There is great duplication in the semantics used for each material. It was their goal to reduce these differences through statistical analysis and largely arbitrary combining of various descriptors. Their results repeatedly demonstrate the classic problem of displaying an n-dimensional data set in a two dimensional graphic. There is no clarity related to the original data. They rearranged their two dimensional graphic presentations repeatedly without achieving any useful results. None have been reproduced here.

8.6.1.1.2 A major semantic difficulty with citrus

The label citrus has played a major role in human culture and agriculture since at least the beginning of written records. The term has been modified, extended and proliferated in nearly every language since then, and generally applied to any fruit associated with a tree bearing spherical yellow to orange colored fruit with a thick outer coat. This has led to great difficulty in coordinating these terms in a modern scientific context. As will become clear below, the major species of citrus exhibit significantly different primary odorophores that stimulate different olfactory receptors (Figure 8.6.1-5) thereby justifying their distinct identities.

The details related to these species will be addressed in Sections 8.6.2.6.3 & 8.6.2.6.4. [xxx straighten out citronella before publishing ]

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8.6.1.1.3 Odor concentrations and thresholds

Doty has discussed the definitions and procedures related to quantitative olfaction. Amoore (1982) has provided an extensive analysis of the chemical relationships involved in the transport of odorants from a source to the sensory neurons immersed in the mucosa. He has presented several selected lists of the properties of odorants and the threshold concentrations of a separate list of odorants. Figure 8.6.1-6 shows the great range of vapor pressures and concentrations of several materials at 25 °C. Note the small range of molecular weights. Note also the wide range and almost direct proportionality between the vapor pressure and the concentration in the air of these materials.

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Getchell & Getchell provided textual material in line with the above values in 1991 (page 66) with some information on the viscosity of the mucosa. They arrived at the conclusion that the diffusion time through the mucosa to the OR cilia was between 0.3 and 1.5 seconds. They also give one of the few discussions of the source and character of the “odorant-binding proteins” (OBP). It is noted here that the OBP’s are similar to the Rhodonines of vision in that they are produced by cells other than the sensory cells and are transported to the area of the sensory cells. They assert the OBP belong to a family of proteins whose primary function is to transport lipophilic molecules through the water based mucosa.

Amoore also provided a table of air-water partition coefficients for a series of five carbon straight chain aliphatic chemicals at 25°C, Figure 8.6.1-7. The variation in molecular weights is negligible. However, the partition coefficient, indicating how much of the material will go into solution at an air-water interface, is on the order of one million to one, proportional to the vapor pressure times the molecular weight divided by the solubility for solubilities less than 10 g/liter. This ratio ignores any special properties of the mucosa favoring or discouraging solubility, and the presence of any other chemicals in the mucosa at the time. Amoore proceeds to discuss a range of other conditions applicable to optimizing a perfume for longevity, rather than for exceeding the OR threshold sensitivity.
Figure 8.6.1-7 Air-water partition coefficients of five-carbon compounds at 25 °C. Sklar et al., 1986, provides a more extensive list of partition coefficients. From Amoore & Buttery, 1978.

Figure 8.6.1-8, also from Amoore, provides a set of olfactory thresholds for humans following a description of the methodology of obtaining the data. He noted the enormous range in sensitivity (eleven orders of magnitude under conditions designed to avoid adaptation). Based on the hypothesis of this work, this range and the names of the chemicals suggest several significant points. First, there are chemicals like ethane, and particularly methanol and benzene that are probably attacking the mucosa and being reported by the nocent modality. Chloroform and probably camphor are also probably affecting the cooling sensitivity of the nocent modality. Finally, the androstenone variant listed is believed to be a vodorophore (pheromone) that is probably stimulating the sensory neurons within the vomeronasal organ (VNO) rather than those in the olfactory epithelium. The last in the list is a well-known component in wines. It is an unsaturated heterocyclic ring containing two nitrogen atoms and an oxygen attached directly to the ring. The last compound needs to be explored to see if it participates in an AH,B,X type DACB coupling with an OR, and should be described as a super-odorant.
Unfortunately, there is not a common chemical among these three figures. Amoore discusses the variation in human olfaction from the perspective of general and specific anosmias, including the common observation of a bimodal distribution in sensitivities among a large group of subjects. He reports general anosmia among about 0.2% of the population. He also discusses the ratio of sensitivity between the olfactory receptors and the nocent receptors for pyridine (about ten binary steps, 1000:1) and for isobutyraldehyde (18 steps, 250,000:1). He cited the literature relating to specific anosmia as of 1982. It contained many chemicals without tying them to any specific OR channel. The community at that time noted the value in studying the specific anosmics in greater detail. The result was the description of a series of specific anosmias (Table IV, updated in 1978 from a previous Table 40 in Amoore, 1977). This list was consolidated into a short list that was believed to be closing in on a small set of proposed “established primary odorants” as shown in Figure 8.6.1-9. He noted the values may vary with different subject populations and chemical purities. Several features stand out. His primary odors formed a popular list of the time. His significant occurrence of a specific anosmia associated with 5α-Androst-16-en-3-one (believed currently to be a vodorophore (pheromone) affecting the vomeronasal organ (VNO), and the large defect factor, suggest why the arguments over the presence of human conspecific pheromones continues to rage. Amoore asked the question, “How many primary odors are there?” and then asserted the existence of at least 8 established primary odorants, but recognized there may be more. This work will establish there are more likely nine distinct olfactory receptor channels (OR’s), at least three distinct channels associated with the vomeronasal organ (VR’s) and a variety of nocent receptors affecting the perception of scents not yet identified (but including perceptions of cool and hot as a minimum). The proposed channels do not depend on the presence of defined chemical groups but on the distance between certain electrophilic and electrophobic orbitals forming a dual antiparallel coordinate bond (DACB) with a specific receptor of the neural system.

The table has been modified by adding a sensory channel designation based on this work on the right. Isovaleric acid is one of the ideal primary odors affecting the first olfactory receptor channel (OR 1) of this work.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Odor threshold concn. in air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mg/m³)</td>
</tr>
<tr>
<td>Ethane</td>
<td>1.5 x 10⁵</td>
</tr>
<tr>
<td>Methanol</td>
<td>6.6 x 10²</td>
</tr>
<tr>
<td>Chloroform</td>
<td>3.2 x 10²</td>
</tr>
<tr>
<td>Benzene</td>
<td>1.7 x 10¹</td>
</tr>
<tr>
<td>Camphor</td>
<td>1.1 x 10⁰</td>
</tr>
<tr>
<td>Furfural</td>
<td>2.3 x 10⁻¹</td>
</tr>
<tr>
<td>Isoamyl acetate</td>
<td>3.8 x 10⁻²</td>
</tr>
<tr>
<td>5α-Androst-16-en-3-one</td>
<td>2.1 x 10⁻³</td>
</tr>
<tr>
<td>2-Methoxy-3-isobutylpyrazine</td>
<td>3.6 x 10⁻⁶</td>
</tr>
</tbody>
</table>

Figure 8.6.1-8 Odor detection thresholds of selected compounds. ADD. From Amoore & Hautala, 1981.
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The use of labels such as OR 1, OR 2, etc. in this work, to designate receptor molecules, are not related in any way to similar designations (either of the OR 1 or OR1 configuration) employed by the (Hugo Gene Nomenclature Committee (HGNC)) to identify individual genes and related proteins. That organization lists many thousands of genes, by codes involving extensive suffixes, foreign to the sensory neuron receptor function. Many of the codes may refer to other functions within cells associated with sensory neurons. However, no data is provided showing they relate to the actual receptor molecules involved in transduction. The Human Genome Organisation (HUGO) is non-governmental body operating from Geneva, Switzerland and funded by HHMI and the Welcome Trust.

Hugo does not currently catalog genes under the designations, VR 1 or VR1, GR 1 or GR1, or other similar designations for the sensory receptor neurons used in this work.

The variant of androsterenone previously cited is an excellent stimulant for the second oskotary receptor channel (VR 2) of the vomeronasal organ. Amoore wrote subsequently about the likelihood of contamination when employing ω-pentadecalactone in experiments. He suggested that this chemical is probably odor-free and is frequently contaminated by members of the pyrroline family. l-carvone is not a good choice for a primary odor as it contains two odorophores in the context of this work, stimulating both OR 2 and OR 5 of the olfactory modality and potentially the “cool” receptor of the nocent modality. 1,8-Cineole is also known as eucalyptol, a chemical with a very complex structure (with oxygen embedded in the top hat of a six-sided ring) not yet explored within this work (Sec 8.6.1.6.1). It may be stimulating primarily the nocent modality of chemical sensing rather than the olfactory modality.

Isobutyraldehyde is probably odorless in its molecular form. However, it is likely to form complexes by hydrogen bonding when introduced into solution and the resulting chemical structure may exhibit a significant pungent odor, generally associated with OR 2 of the olfactory modality. In fact, “pure” isobutyraldehyde is usually only available as an azeotrope containing 6% water. It cannot be further purified by distillation. The high level of specific anosmia and large defect factor for this chemical are noted. The roles of l-pyrroline and trimethylamine will be discussed later in this work.

The Amoore papers contain considerably more material of interest to the psychophysicist.

Much can be gleaned about the overall olfactory process from the trends presented by Amoore, even if continuity among the chemicals is a problem.

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64 http://www.genenames.org/genefamilies/OR
First, the partition coefficient suggests that odorants are released by plants and animals by secretion mechanisms that are largely free of water based solutions.

Second, the dominant factors in the propagation of odors involves their volatility and their partial pressures. Their molecular weight plays only a minor role in the propagation of the materials.

Third, the partition coefficient generally favors the entrance of the major odorants into mucosal solution, and is probably a major factor in their removal from the mucosa in due time.

Fourth, these guidelines are first order in character. The presence of agents designed to enhance the olfactory process beyond that sketched by Amoore have not been considered.

8.6.1.1.4 Variation in odor thresholds in humans

Beets has presented a well developed description of specific anosmias in humans in an attempt to determine the underlying structural chemistry involved. He reviewed a broad range of chemical principles that might be of use in developing a framework for understanding olfaction. He did not consider the potential of hydrogen bonding in olfaction or the dipole potential (as distinct from dipole moment) of his many candidate odorants. He did not concern himself with the structure of the odorant receptors (OR's), only the odorants. He provides a variety of statistics on specific anosmias in his search for a framework for olfaction. After noting the preliminary data of Amoore suggesting up to 30 individual channels, he suggests that his studies could only identify eight. He struggled to associate specific chemicals with this list of eight largely conceptually named perceived scents (Table II). It would be valuable if this table could be used to simplify the list of “the voluminous and wooly vocabulary of the traditional perfumer by a short list of descriptors, . . .” (page 120).

Writing in 1996, Rossiter illustrates the “wooly” aspect of the perfumers descriptions. In discussing the detailed odor profile of a series of esters, “The odor profile of these esters was defined using a set of 57 odor descriptors.” and “For example, all three methyl derivatives have lemon, citrus, honey-like, sweet, aromatic, and parsley root notes which are absent in the n-propyl, isobutyl, and tert-butyl derivatives.”

Beets tries on pages 100-119 using his framework but without concise results. The interpretation of this table must wait until the analyses of Section 8.6.11 concerning the oskonyatory channel (vomeronasal) receptors are introduced. While attempting to describe some of the chemicals as “primary odorants,” the names are actually generic for a group of enantiomers where each enantiomer may incorporate multiple odorophores. These differences may account for the high level of anosmia associated with these generic chemicals.

Beets made an assertion seldom seen in scientific literature (page 83); “It is obvious that we can never hope to detect the relationship between the complex total information contained in the structure of the odorant molecule and the equally complex information present in the odor.” He does provide some comments softening this position that are in line with the procedure adopted in this work.

His review does include many nuggets of information applicable to the more successful framework presented below in this work, including the likelihood of a two-step transduction mechanism (page 82), and the suggestion of “a reversible physical contact” that “generates an energy effect.” He notes the unreliability of much of the earlier work due to inadequate purification methods when parts per billion of a contaminant are significant. He does outline a combinatorial framework for olfaction in his two postulates, and his conclusions appear to point toward the expanded framework developed in the following section.

Beets provides a good discussion (with citations) of the structural properties of many enantomeric molecules and their perceived scent. However, the material does not converge into a null hypothesis. It only specifies three desirable results of a continuing research program.

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8.6.1.1.5 An alternate sensorial framework

Gilbertson & Margolskee have reviewed a commonly employed framework for discussing the physiology of gustation\(^6\). The framework has matured over time but is too simple to be used effectively in the level of detail employed in this work. The primary problems revolve around how the word code or coding are used among the behavioral community and the explicit separation of the various forms of the words perception and sensation in the broader neuroscience community.

Lacking a physiological model of the gustatory process and mechanisms, the introduction of Gilbertson & Margolskee can be largely ignored. Their descriptive list requires significant expansion.

<table>
<thead>
<tr>
<th>Simple terminology (Their figure 1)</th>
<th>Symbol</th>
<th>Expanded terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Concentration</td>
<td>$\phi_i$</td>
<td>Physical Concentration of tastants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical concentration of gustaphores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical concentration of receptors (by type and loc.)</td>
</tr>
<tr>
<td>Psychophysical function</td>
<td></td>
<td>Stimulus efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adaptation state of receptors</td>
</tr>
<tr>
<td>Perceived sensation</td>
<td>$\psi_i$</td>
<td>Electrical sensation intensity at stage 1 output</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrical sensation at output of stage 2 channels</td>
</tr>
<tr>
<td>Coding function</td>
<td></td>
<td>Signal coding within stage 3 signal propagation</td>
</tr>
<tr>
<td>Coded sensation</td>
<td>$S_i$</td>
<td>Place representation in stage 4 information extract</td>
</tr>
<tr>
<td>Judgement function</td>
<td></td>
<td>Cognition within stage 5</td>
</tr>
<tr>
<td>Overt Response</td>
<td>$R_i$</td>
<td>Overt instruction by stage 5, cognition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overt command prepared by stage 6 command gen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overt command implementation by stage 7 muscles.</td>
</tr>
</tbody>
</table>

In the new terminology, coding refers to the translation of signal information into a different form more suitable for propagation within the neural system; the term code is reserved for its normal use, to name the specific translation algorithm employed in the coding operation. Their figure 9 from De Graaf & Frijters, 1989, requires similar expansion to better conform to the actual situation within the neural system.

### 8.6.1.1.6 Artificial noses (analogs)

The desire to develop an artificial nose of broad capability is a long-sought goal of industry. Persaud & Pelosi attacked the problem in 1985 with a good early discussion of the task. Reineccius addressed the subject briefly in 2000 and provided several references. Persaud provided a brief overview of potential technologies in 2003. While the field is continuing to advance, none of the identified mechanisms approaches the sensitivity of the human (much less the canine) nose. Typical approaches involve quartz or other nanotechnology micro-balances. Metal oxide transistors with chemically sensitized gate structures and various conducting polymers.

More recently, Park & Jang have proposed, and assembled a prototype based on marrying protein chemistry and nanotubes of conducting polymer material in a field effect transistor configuration.

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that with modification may result in a useful artificial nose\(^70\), \(^71\).

Odotech, Inc. currently offers commercial artificial noses employing SnO\(_2\) type sensors. Typically 15 sensory channels are used to identify alcohols, aldehydes and ketones (e.g. acetaldehyde), carboxylic acids and fatty acids (e.g. butyric acid), amines (including NH\(_3\), R-NH\(_2\), indole, methylamine, etc.), sulfurous compounds (including H\(_2\)S, DMS, DMDS, Mercaptans, etc.), aromatics (BTEX, terpenes, etc.).

See Section 8.6.5.1 for details related to the odor units of olfactometry.

Gelperin & Hopfield\(^72\) provide an interesting discussion on artificial noses. They define multiple types of noses;

BNOSE - The biological nose
CNOSE - The computational nose
ENOSE - The electronic nose

in an overview of the state-of-the-art in 2002. Their introduction is useful but general in character. They note at the onset, that the mechanism of decoding the multidimensional signals associated with a given odorant remain to be elucidated (with citations).

They touch lightly on a variety of ENOSE approaches including organic transistors (similar to the organic LED display technology).

They focused on sensing agricultural produce for practical reasons and give their results of using a twelve channel ENOSE with respect to differentiating two types of oranges (Valencia and Florida oranges) and several types of apples. Unfortunately, their designations of oranges were based on the commercial trade and not their scientific designation. Virtually all oranges are hybrids dating from ancient times (Section 8.6.2.5.7). They presented both 2D and 3D MDS analyses for three types of apples. The 3D MDS is reproduced as Figure 8.6.1-10. The results are impressive. The 2D analyses is more difficult to interpret without the 3D presentation as discussed elsewhere in this work.


\(^71\) - - - Polypyrrole Nanotubes Conjugated with Human Olfactory Receptors http://www3.interscience.wiley.com/journal/122246937/abstract

They also present data for a set of organic transistors designed for odor detection. The results are impressive and demonstrate that all saturated alcohols exhibit similar odorophores (figure 5 right) with some variation in signal intensity (figure 5 left) not defined in greater detail. Their subsequent discussion of computational olfaction is useful but largely preliminary. They indicate consternation at the literature indicating 2000 different sensory receptor types in the rat when only ten types are needed to perceive millions of different odors using a computational approach. They suggest that if 2000 receptor types are needed in the BNOSE, there must be other requirements than olfaction involved.

With respect to “odorant modeling,” they suggest a constancy of perceived odor over a stimulus intensity range on the order of 1000:1. If defendable, this observation is relevant to the dulcal channel where significant differences in perceived odors at extremes in intensity are well documented. Similar variations in other channels are less well documented but probable. See Section 8.6.7.1.1. Their discussion suggests the need to use logarithmic mathematics in the ENOSE because of its general usage within the BNOSE.

8.6.1.2 The terminology of olfaction used in this section

As expected in an ancient area of business endeavor, and wide current commercial involvement, the origin of the names and terminology used in perfumery and other aspects of olfaction are obscure. This work will not attempt to change that situation. However, it is advisable to set some guidelines. When referring to sources of odors, the following hierarchy will be used;

**Anosmia**– The inability of a subject to perceive odorants/odorophores. The condition may be limited to specific OR channels suggesting an error in OR formation at the sensory receptor.

**Cilia**– A small cylindrical (hollow) structure generally fluid filled and associated with the structures beyond the dendritic knob in olfaction.

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**Figure 8.6.1-10** 3D MDS plot using the three eigenvectors for apples with the highest variance. Star=Fuji, circle=Red Delicious, plus=Rome. From xxx, 2002.
Essential oils— are a mixture of chemicals extractable from a describable collection of organic materials.

Fragrance— are a mixture of chemicals which in total are perceived as stimulating a distinctive scent that is reportable by speech and writing to another third person.

Normosmia— A term used to describe a subject with normal olfactory performance.

Odorant— A specific chemical known to stimulate the olfactory modality.

Primary Odorant— A single odorant (which may include multiple odorophores) asserted to be uniquely associated with a single OR channel. See single odorophore odorant and preferred odorophore.

Pure odorants— Odorants that stimulate pure olfactory sensations, i.e., odorants uncontaminated by trigeminal activity. (Doty & Cometto-Muniz, 2003)

Single channel odorant (SCO)— (preferred Single odorophore odorant SOO) An odorant containing only a single odorophore and therefore able to target an individual OR. Preferably such an odorophore with a d-value near the central d-value of the targeted OR.

Odorophore— A specific structural arrangement of atomic orbitals and more complex structures within an odorant that stimulates a specific olfactory receptor (OR) within the olfactory neural modality. An odorant may contain multiple odorophores. Each odorophore is characterized by a distinct d-value, the distance between a pair of orbitals or more complex electronic structures participating in a dual antiparallel coordinate bond (DACB).

Preferred odorophore— A single odorophore that is most clearly identified with, and optimally stimulates a specific OR channel of the olfactory modality.

Villi— A small rod shaped (solid) structure typically related to hair and whiskers. The material filling the villi is typically proteinaceous. See cilia, a typically hollow, fluid filled structure with which villi is frequently confused.

Volatile oils— a mixture of chemicals, considered odorants, that can be described as stimulating the olfactory modality.

Highly volatile oils— Those volatile oils that are typically sensible at a considerable distance from their source via the nose and nasal passages.

Minimally volatile oils— Those volatile oils that are typically sensible at only short distance from their source and frequently requiring mastication or other processing to optimize their scent. The scent is frequently perceived via retro-nasal application from the oral cavity.

Generally, multiple odorophores are required to characterize a specific odorant, oil or fragrance.

The olfactory modality is optimally designed to report the presence of organic odorophores, odorants and fragrances. However, it does respond to and report a variety of low molecular weight inorganic materials of high or minimal volatility. These materials are typically reported using the OR channels designed for olfaction. More frequently, the inorganic materials stimulate the nociceptor receptors associated with warning the system of danger to its physical or chemical integrity. It is not always easy for the engines of later neural stages of an organism to differentiate between signals originating in the olfactory modality from those originating in the nocent modality. See Section 8.8.3.

It is particularly important to note hydrochloric acid, while frequently taken as a reference in olfaction studies, is not an organic odorant, or in fact any odorant. It is an inorganic acid that attacks the mucosa and tissue of animals. It is reported by the nociceptors, not the olfactory receptors, OR’s. Hydrochloric acid has no role to play in any scientific study of olfaction.

8.6.1.2.1 Communications used in its broadest form
While this work is focused on communications within the neural system of an organism, the term takes on a much broader term in biological communications between organisms. Wyatt\(^{73}\) has noted the difficulty of defining this broader definition of communications, devoted an entire page to its definition (page 3) and cited several variants used to define the term beginning in the 1970’s. The discussion even veers into the ritualistic dances of certain species (beyond the dances of bees to provide directional information). Both olfaction and the specialized action of pheromones clearly involve signaling of a non-neuronal and non-electrical-based communications.

**8.6.1.2.2 The primary and major categories of odorophores**

This section will define nine types of olfactory receptors, OR’s, in Section 8.2.6.2 [xxx 8.6.xxx ]along with nine preferred odorophores where each of these odorophores stimulate only one of the OR’s. It then groups many odorophores derived from or present in various odorants and fragrances. The scope of this work will not allow even a partial description of all or any of these groups.

It is noteworthy that the frequently encountered descriptive designation rose-like is subsidiary to the designation floral when discussing perceived scents in this work. The many odorophores found in roses are the same as found in many other florals. Only the relative concentrations of the odorophores present varies among the florals.

Kaiser lists about a dozen roses and about 40 chemicals found among the volatile chemicals associated with each one. The lists are not similar except for about ten chemicals. Only a few of these chemicals are the major odorants for each species of rose and these odorants are shared with many other non-rose florals.

**8.6.1.2.3 Selected glossary**

The Perfume Shrine offers a well thought out description of the terms used in perfumery on their blog\(^{74}\):

“Perfume vocabulary is diverse and often confusing. Therefore we have compiled an extensive reference on Perfume Shrine, analyzing the various perfume terms applied by perfumers with examples of actual perfumes. Today’s terms comprise some of the more “acquired taste” definitions on fragrant materials & finished compositions. More perfume jargon than marketing copy, the sheer force and almost visceral effect they have leaves no one indifferent.”

It is supported by blogger.com, a Google property, and it will accept your Google credentials.

One of the extended definitions from the Perfume Shrine is offered for camphoraceous below in order to support the argument that most terms in olfactory are of semantic rather than scientific origin and based on hedonic rather than technical considerations (unless using a taxonomy designation is considered technical).

An anonymous note on the blog is supportive of this position.

“Isn’t it profoundly interesting to see that indeed how we talk influences how we think, as you succinctly say? It’s the old “Λόγος” from the Greek standing for both speech and logic. It’s a concept that fascinates me!”

The definition of camphoraceous given below suggests that the stimulating element of camphor actually affects the nociceptors of the nocent modality via the trigeminal nerve rather than the olfactory receptors.

Another page of the Perfume Shrine attempts to define the “notes” found in perfumery to a more

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\(^{74}\) [http://perfumeshrine.blogspot.com/2012/02/definition-terpenic-phenolic.html](http://perfumeshrine.blogspot.com/2012/02/definition-terpenic-phenolic.html)
detailed level than found previously. As an example,

**Cabbage note:** Due to Methanethiol (also known as methyl mercaptan). Naturally occurring in nuts and cheese.

The source of this information is not clear and the association between cabbage note and nuts or cheese is not obvious. But just incorporating a chemical name in such a description is a positive step.

Many of the following definitions from the literature can be made more specific based on the individual odorophores defined in this work.

**Balsam, Tolu**- is comprised of 3/4 fragrant resinous compound, containing approximately 15% free cinnamic acid and benzoic acid and about 40% of the benzyl and related esters of these free acids.

**Camphor**- An aromatic crystalline compound, $C_{10}H_{16}O$, obtained naturally from the wood or leaves of the camphor tree. See nocent modality.

**Camphoraceous**- (alt. camphorous) “Familiar to us from common ‘moth balls’ which utilize the white crystals. The cooling, sharp and pungent scent of camphor which triggers the trigeminal nerve in the nose (hence the intense repulsion it can produce to sensitive individuals) is also a constituent, small but very significant of certain fragrant plants: Eucalyptus and the camphor laurel (from which camphor is often derived, though not exclusively as it can be made synthetically as well) are the obvious suspects, but camphoraceous smells also include one end of the lavender essence spectrum (that medicinal top note, the other end is caramelic), patchouli and the top note of tuberose and gardenia.” See nocent modality.

**Floral**- Typically referring to the scent of hedonic flowers.

**Fougere**- Fem in French. Possibly related to the term herbaceous at a fundamental level.

**Fruity**- Typically, but not exclusively referring to citrus fruit in the commercial olfactory literature.

**Fruity floral**- Used variously.

1. A fragrance based on a floral basic skeleton with a light woody/white musk underpinning for longevity and copious amounts of fruits OTHER than hespirides for succulent accents throughout. Patently a relatively recent trend, the trope was established in the last 20 years or so. In fact the first fruity floral came out in 1993 (Perfume Shrine.blogspot.com)

**Herbaceous**- A plant that has leaves and stems that die down at the end of the growing season to the soil level, not woody. Typically with green leaves, stems and main stalk. Herbs is a broad label for a wide variety of garden plants offering disparate perceived tastes and smells.

**Metallic**- Used as an inadequately defined secondary descriptor in psychophysics experiments.

**Nocent modality**- A neural sensory modality complementary to the gustation and olfaction modalities but separate from them. Supporting the sensing of pain, temperature, touch, and proprioception.

**Oily**- Used as an inadequately defined secondary descriptor in psychophysics experiments. Probably relates more to somatosensory perception than olfaction.

**Olfactory modality**- Those sensory neurons originating in the olfactory epithelium and passing through the cribiform plate and the olfactory bulb as they progress to the cerebral cortex. Distinct from sensory neurons originating in the vomeronasal organ and the sensory neurons of the nocent modality passing from the nasal cavity via the trigeminal nerve (n. V) to the cerebral cortex.

http://perfumeshrine.blogspot.com/search/label/notes
**Stone**—referring to the hard central seed (the pit) of many fruits.

**Trigeminal nerve**—Primary facial nerve (n. V) supporting the nocent modality rather than olfaction or gustation.

**Vomeronasal organ**—A distinctly different section of the olfactory modality believed to be centered on identity of species and even individuals within a species for purposes of mating and possibly family maintenance among some species.

**Woody**—A perception associated with an odorophore derived from a plant with a structurally rigid cellulosic stalk. Frequently due to the action of a fungus digesting an element of the stalk, or due to an exudent of the stalk, and not due to the stalk itself.

### 8.6.1.3 Morphology of the peripheral/central parts of the olfactory modality

It is interesting to consider the olfactory modality as an evolutionary extension of the gustatory modality, employing a different means of acquiring the stimulants from remote sources rather than through contact means. This is particularly with regard to the first six organic acids. While these acids have boiling points in the 100-239 Celsius range, they are sufficiently volatile, and the OR’s sufficiently sensitive to be considered odoriferous to humans and probably most mammals. Thus it is rational to consider the initial organic acid sensory receptors of the olfactory modality to be primarily morphological offshoots of the equivalent GR’s and merely located within a different portion of the oral/nasal cavity. A similar evolutionary extension would lead to the distinction between the vomeronasal sensory organ and the primary nasal sensory organ in many mammals.
Based on these opening comments and the similarity between all of the sensory modalities of the neural systems of all animals studied to date, a top level block diagram is shown in Figure 8.6.1-11.

The discussion of the details related to this figure will be delayed until later in this major section.
Figure 8.6.1-12 shows the nasal cavities of the human. Both orthonasal and retronasal access is available to volatile stimulants. Lanza & Clerico (1995) assert the glands within the human nose produce 1–2 liters of mucus per day, which is about 96% water and 4% glycoproteins. These glands are typically labeled Bowman's glands.

Laurent has addressed the anatomy of the olfactory modality in a variety of animals in a review that is actually used to propose his new hypothesis76. While very interesting, he illustrates his hypothesis with gross sketches that do not address the actual circuit architecture of the olfactory modality.

A feature seldom discussed in detail is the nasal septum, a combination of bone and membrane separating the nasal cavity into distinctly separate and isolated left and right chambers extending from the nose to the pharynx. The large shaded area in the above figure represents the nasal septum. This separation becomes important when distinguishing the operation of the olfactory and nocent modalities within the nasal cavity. Clerico, To and Lanza77 describe the detailed morphology of the nasal cavity in Doty. Their figure 5 emphasizes the complex structural packaging involved in this area (with label 4 applying to the nasal septum and the lower portion of that nasal septum being defined as the unpaired vomer bone (page 9).

Johnson has provided a comprehensive anatomy of the olfactory modality in Figure 8.6.1-1378. His rendition of the oral/nasal cavities includes the location of the vomeronasal organ (which may only be rudimentary in humans but is highly developed in many other mammals.


Several sources estimate the olfactory mucosa of humans as 2.5 square centimeters, containing about 50 million sensory receptor neurons in each nostril. On the other hand, Doty, writing recently in Ramachandran\(^79\), has described the adult human olfactory modality as collectively the ~6,000,000 odorant-sensitive receptor cells located within the olfactory neuroepithelium that send axons to the olfactory bulbs.

Dodd & Squirrel (1980) provided an alternate view of the olfactory epithelia that stresses the complex intertwining of the olfactory cilia at the mucosal surface. They also stress the tight physical junctions between the cells forming the structure under the mucosal surface. The basal cells constitute a basal membrane.

Elsaesser et al. have made an interesting proposal that there is a subset of olfactory sensory neurons that do not project to the olfactory bulb\(^80\).

Ronnett & Moon have noted, “The basal cells underlie the ORNs and serve as precursors for the generation of new ORNs throughout adulthood.

Figure 8.6.1-13 shows a schematic of the cells within an olfactory epithelium\(^81\). It shows Bowman’s gland irrigating the mucociliary complex in support of the OR’s within the olfactory epithelium on the left. Bowman’s gland is described as a sustentacular cell with secretory processes that resemble


those in goblet cells. The level of irrigation is believed to be controlled by the trigeminal neurons whose soma are located in the lamina propria. The signals from the OR neurons and the trigeminal neurons take separate, non-intersecting paths to the central nervous system.

Getchell et al. provides several citations asserting that Bowman’s gland continuously irrigates the mucous membrane at a low level under autonomic control with enhanced irrigation controlled by signals from the trigeminal neurons. This arrangement allows the system to react quickly and on a large scale to noxious stimuli.

Akeson presented a paper in 1988 describing the morphology of individual olfactory neurons. The material is largely archaic. He did note, “Most olfactory neurons are morphologically identical.” He then carried on a soliloquy describing two distinct classes of neurons within the olfactory mucosa, those neurons with cilia extending into the mucosal space and those neurons with elongated bodies and axon-like cytoplasmic processes extending through the epithelium toward the basal lamina but have microvilli rather than cilia. The former are clearly olfactory neurons and the latter are clearly nocent modality neurons (as shown in the above figure from Getchell et al. in the same volume). The rest of the paper is unrelated to the function of olfaction.

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Figure 8.6.1-15 shows the gross morphology of the olfactory neural pathways to the CNS according to Pansky. Note the bifurcation of each olfactory tract before reaching the CNS with one branch going to the temporal lobe and the other to the midbrain. The precise path to the midbrain will be discussed further below.

Figure 8.6.1-16 shows the peripheral olfactory paths in more detail. Note the significant interconnection of the two bulbs via the anterior commissure. Note the lateral olfactory striae to the temporal lobe and the intermediate olfactory striae to the midbrain, specifically the olfactory tubercle to the anterior perforated substance. Brennan & Zufall provide details of the neurons extending to the amygdala. While some investigators have asserted there is no direct connection between the peripheral system and the thalamus, Noback has provided a more complete discussion of these connections. Noback asserts there is no primary connection between the peripheral system and the thalamus (pg 223). These comments relate more to physical size than to functional importance. Shepherd has recently indicated, “Olfactory cortex contains areas that project directly or indirectly through the thalamus to the neocortex.” This interesting statement suggests the olfactory cortex is not part of the neocortex but is akin to the lateral and medial geniculate nuclei of the diencephalon. Eyzaguirre & Fidone describe second-order gustatory neurons terminating in the thalamic nucleus ventralis posteromedialis (VPM).


Figure 8.6.1-16 Interconnection of the peripheral olfactory system with the CNS. From Pansky, 1988.
**Figure 8.6.1-17** shows the “Secondary” olfactory pathway in a lateral view according to Johnson. This path can be expanded to include the saliency map formed in the parietal lobe by from the thalamus and accessed by the orbitofrontal cortex.
Figure 8.6.1-18 Kandel et al. provide an alternate schematic showing more individual signaling paths but based primarily on putative traffic flow based on various investigators. The Kandel text gives more credence to the vomeronasal organ in humans than many earlier works.

Figure 8.6.1-18 Schematic of the traffic flow from olfactory bulb to CNS. Note the singular path from the accessory olfactory bulb to the amygdala in this presentation. From Kandel et al., 2000.

8.6.1.3.1 Anatomy of the vomeronasal organ (VNO)

Only during the last two decades have adequate tools been available to study the vomeronasal organ (a.k.a. Jacobson’s organ or Ruysch tube) in detail. Brennan & Keverne87 have reviewed the subject while incorporating the most recent understanding as of 2003. Earlier investigations were frequently superficial and frequently failed to locate any vomeronasal organ in human due to their unexpectedly shielded arrangement within the nasal cavity. Before 1991, the VNO in humans was generally believed to have degenerated to a vestigial state shortly after birth. In 1991, Garcia-Velasco and Moudragon reported they were able to identify the vomeronasal organ in 808 of 1000

human patients\(^{88}\), clearly statistical proof of their presence in humans (Doty, pg 3). They performed additional examination and/or corrective surgery on the remaining 192 and confirmed the presence of the vomeronasal organ in all but 23 cases. Thus, the final count was 977 out of 1000 cases exhibited a VNO, i.e., overwhelming proof of the existence of a VNO in humans. Johnson, writing in his medical physiology text, 2\(^{nd}\) ed. in 1998 supports the presence of the VNO in humans (page 749). This organ is now identified as a blind pouch in the septal mucosa. “The opening to the vomeronasal organ is located near the base of the nasal septum approximately 10-17 mm posterior to the anterior nasal spine.” Unfortunately, as late as 2005, papers, some formally unpublished, were still appearing that doubted the existence of a functional VNO in humans beyond the neonate stage\(^{89}\).

While the human VNO may be relatively small compared to some other conspicuous species, and may involve a sparse array of VR’s compared to otherspecies, it is not necessarily inactive. Johnston has discussed the issue of the VNO in humans recently\(^{90}\). He left the question unresolved and sought additional research related to the question.

The operational aspects of the VNO and the osknation modality are developed in Section 8.6.11.

8.6.1.4 The histology of the peripheral portion of the olfactory modality

Morrison & Costanzo have provided excellent electron micrographs of the olfactory sensory neuron matrix (an epithelium below the olfactory mucosa)\(^{91}\). They identify four types of cells in this structure, the olfactory receptor neurons, the supporting cells and the basal cells along with a microvillar-like cell of unknown function (but probably somatosensory).

The olfactory receptor neurons are described as morphologically bipolar with a long fine unmyelinated axon. Beyond the soma, a long inner segment ends in a knob. The knob generally has a single cilia emanating from it. This cilia exhibits a 9(2)+2 set of microtubules that separate from the cilia in order to form a chalice of individual microtubules. The microtubules of all of the neurons form an unstructured matrix near the mucosal surface.

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8.6.1.4.1 The olfactory mucosa and sensory neurons

Getchell et al. have provided imagery of the mucosa of the salamander\(^92\). Figure 8.6.1-19 shows the plan view of the microtubules of the olfactory neurons of xxx from Morrison & Costanzo. The absorption cross-section of each sensory neuron is optimized by the splaying of the microtubules.

Rhein & Cagan have explored the role of the cilia in olfactory recognition\(^93\). Here, the term cilia is used to describe the fine structures emanating from the knob at the extreme peripheral end of the olfactory sensory neuron.

These cilia are not protein filled, like true hairs, and are not driven by a muscle but are the ultimate ramifications of the dendritic portion of the neuron. These cilia exhibit the diagnostic cross section showing “9(2)+2 internal microtubules” near their root. This complex structure degenerates to a variable number of singlet fibers farther from the root. They note the key difficulty in odorant receptor macromolecule identification “will be the ability to identify the isolated molecules as receptors.”

Mozell & Jagodowicz provided one of the few tabulations of the relative retention time of various stimulants in the mucosa (of the frog)\(^94\).

8.6.1.4.2 The glomeruli of the olfactory bulb

Figure 8.6.1-20 shows the morphology of the olfactory bulb used by Johnson & Leon. They unfurl the surface of the olfactory bulb to obtain their two-dimensional mapping shown in [Figure 8.6.xxx-11].

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The number of individual glomeruli appears to be very large, but vary considerably with species. Shepherd\(^5\) has indicated that for rabbit, there are about 50 million receptor neurons, and individual 2000 glomeruli resulting in a convergence ratio of 25,000:1. He also suggests the human has as many

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as 6,000 glomeruli. Citations in Section 8.6.1.3 suggest six to 50 million sensory receptors in the human olfactory epithelium, resulting in a convergence ratio for humans in the range of 1000:1 and 8000:1. An estimate of the additional convergence associated with the glomeruli to the stage 3 mitral cells has not been located in the literature. Neither has a convergence ratio between the mitral axons and the initial number of stage 4 neurons found in the olfactory cortex. Based on this work, with about 6 million receptors in human epithelium and only nine signaling channels near the output of stage 4 information extraction, the overall convergence ratio would approximate 600,000:1.

A convergence ratio of even a few hundred within the glomeruli strongly suggests the synapse are biased as "active" diodes based on a three-terminal active device (Section 2.4.3.3) in order to minimize noise in the summed signals delivered to the mitral neurons. The biasing of a synapse by varying the potential applied to the poditic terminal does not affect the biasing of the orthodromic neuron it is associated with.

LaMantia, Pomeroy & Purves have provided extensive data on the size of the glomeruli in mice. They used cell fluorescent techniques and observed, "Glomeruli can be observed by vital fluorescent staining and laser-scanning confocal microscopy without causing acute or long-term damage to brain tissue." Figure 8.6.1-21 reproduces their figure 1B.

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**Figure 8.6.1-21** The mouse olfactory bulb as prepared for imaging. ADD: "The dendrites" of the mitral cells are not in conformity with that proposed in this work. See text. From LaMantia et al., 1992

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**Figure 8.6.1-22** reproduce their figure 2. A mean glomeruli diameter of 35.4 ± 0.8 microns was given later in the paper. The paper provides a great deal of additional information of interest to the laboratory investigator and those following the maturation of the glomeruli over time.

![Image of glomeruli](image-url)

**Figure 8.6.1-22** Size and distribution of glomeruli in mice. Comparison of images of glomeruli on the dorsal surface of the olfactory bulb in a living 4-d-old mouse obtained with epifluorescence microscopy (A) and laser-scanning confocal microscopy (B). Both images are unprocessed and have been printed with identical contrast. Although the glomerular pattern can be discerned with epifluorescence microscopy, the boundaries of individual glomeruli are seen more clearly with confocal microscopy. The asterisks in A indicate several glomeruli (4, 5, 6), the borders of which are obscured by out-of-focus information and light scattering arising from fluorescent staining of overlying tissue. From LaMantia et al., 1992.

Dawson, Dawson & Wamsley (pages 101-103) provide individual density maps of various substances, including GABA and serotonin, within the olfactory bulb.

### 8.6.1.4.3 Potential analog sensing mechanisms in olfaction

In the absence of a detailed description of how the olfactory receptor cells operate, it has been impossible to describe how the transduction process operates. The Electrolytic Theory of the Neuron has overcome this problem and the descriptions available for how the visual and auditory receptors operate suggest how the chemical receptors operate.

The literature contains many orderings of odorous material by chemical structure, but no clear description of the important feature(s) accounting for their olfactory performance.

Doving has provided considerable early information on the number of independent dimensions in olfaction. He explored three different experimental ordering criteria leading to three different odor spaces based exclusively on perceived biological data. Just investigating twelve aliphatic alcohols, he determined there were nine dimensions with a significance level of <0.001, three more with a

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significance <0.01 and three more with a significance of <0.1. The parameters of highest significance were:

- Hydrogen binding
- Molecular cross-section
- Adsorption energy, $\Delta G_{O/W}$
- Molecular weight
- Polar factor
- Adsorption energy, $\Delta G_{O/A}$
- Adsorption coefficient
- Calculated olfactory threshold
- Adsorption energy, $\Delta G_{A/W}$

Doving proceeds to show the close graphic parallel between the hydrogen binding of the alcohols and the perceived biological data and a series of statistical tree arrangements. Doving’s analyses did not surface any steric relevance to olfaction.

Jacob has summarized the variety of theories of olfaction transduction found in the literature for purposes of an Internet tutorial on the subject:

1. Molecular shape stereochemistry approach
2. Diffusion pore relative diffusion rate approach
3. Piezo-effect a poorly defined potential mechanism
4. Molecular resonance sensing the molecular vibration typically at infra-red frequencies
5. Nose as a spectroscope odorant causes a band transition within the receptor cell.

Not in this list is a strictly electrochemical approach.

Imamura and colleagues have reported experiments that may be important in understanding the segregation of roles (or lack of same) between the olfactory and gustatory modalities. They introduced both sugars and carboxylic acids into the olfactory chambers of rabbits. Imamura (figure 11) provides a mapping of one of the MOB and its accessory olfactory bulb (AOB) relative to the frontal pole of the neocortex. The figure also shows the location of the mitral cells sensitive to the carboxylic acids they explored.

The response of the system to stimuli by a homologous set of sugars shows the intrinsic sensing and perception of olfactory signals in the system is clearly analog. It also shows the transduction process involves smaller differences than the length of the carbon chain as proposed by Imamura et al. Most of the sugars explored in taste and smell research have involved six-carbon (hexose) sugars of alternate stereochemistry. Mori, Mataga & Imamura recognized this fact in a concurrent paper. Understanding how these stereochemically different sugars are sensed is critical to the understanding of taste and smell related to organic chemicals.

It appears clear that some of the sensory receptors hypothesized for gustation are also found in the olfactory modality (at least in the case of rabbit). This situation will be important in developing the mechanisms of olfactory sensory receptors in Section 8.6.3

### 8.6.1.4.4 The neurogenesis of the olfactory neurons

It is becoming recognized that the sensory neurons of the olfactory modality in particular are routinely replaced during the life of most organisms. Mackay-Sim has discussed the subject in a recent handbook.

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8.6.1.5 Architecture of the individual olfactory sensory neurons

The sensory neurons of the olfactory and gustatory system are known to be bipolar in morphological form and to be highly adaptive functionally. Their interconnection with the stage 2 signal processing within the peripheral olfactory bulbs suggest they are interconnected much like the photoreceptors of the visual system.

Pfaffmann et al. have described the adaptation properties and the relative sensitivity to different sugars of the olfactory neurons (page 19).

Maue & Dionne have provided considerable patch clamp data for the olfactory neuron. Unfortunately, all of their data are based on both a single compartment sensory neuron and a passive sensory neuron. They do describe the difficulty of using the technique on the small sensory neurons. They describe a series of waveforms in terms of various conceptual channel openings and closings while in-vitro.

Getchell & Getchell described their conceptual interpretation of the functional characteristics of the olfactory sensory neuron in 1991. Their view was conventional and did not account for the processes proposed in any detail. They did clarify their concept of a second messenger.

Shepherd has discussed the compartmented structure of the olfactory sensory neurons in a conceptual table. He could not define the role of the soma and arbitrarily combined it with the role of the dendrite. While he asserts, "The olfactory sensory neuron is one of the most complex cells in the body.", it can be seen from this work that the olfactory sensory neuron is virtually identical in topology and cytology to the layout of all sensory neurons. Only the elements of the cilia (and some time constants related to the local environment) change between modalities.

The Electrolytic Theory of the Neuron provides a definitive description of the sensory neurons not available in the largely conceptual character of the conventional chemical theory.

8.6.1.5.1 Electrophysiology of the olfactory receptor & first Acitav

Getchell & Getchell provided some textual material on the potentials associated with the stage 1 olfactory neurons. They attempted to interpret this material in terms of the chemical theory of the neuron of that time. They did note the axons of the olfactory neurons were non-myelinated and unbranched in their projection to the olfactory bulb. Their text includes a rare reference to a phosphatidylinositol pathway associated with olfaction (page 67). Unfortunately no citation was offered. They describe "ten to thirty cilia, which range in length from about 100 to 150 microns, project from each receptor knob terminating the dendrite. They do confirm that neither the dendrites themselves or the soma of the sensory neurons are sensitive to odorants. Only the surface of the cilia is sensitive. Unfortunately, they do describe the analog generator waveform at the sensory neuron axon as an action potential. This was a common occurrence of the time period.

Getchell & Getchell provide some very coarse electrical measurements associated with a few OR's that are strictly of the steady-state Ohm's Law variety (page 69). No mapping of the potentials within the various chambers of the sensory neurons was provided.

8.6.1.5.2 Circuitry of the olfactory receptor & first Acitav


The electrolytic circuitry of the sensory neurons is intimately involved with the cytology of the cell.

Moulton speculated on the location of the sensory receptors on the surface of the sensory olfactory neurons in depth in 1970 but there has been little discussion of the subject since. The discussion was exploratory and drew no conclusions. He did note the vast surface area of the cilia of the sensory neurons compared to the estimated 3 sq. cm. of the olfactory epithelium in humans.

**Figure 8.6.1-23** shows the proposed electrophysiology of the olfactory microvilli. The microvilli lemma leaf closest to the dendroplasm is proposed to be primarily insulating except for the region of type 4 lemma where it is acts as an electrolytic diode. The leaf contacting the mucosa of the lingual pore is insulating in the type 1 area and acts as an electrolytic diode in the type 2 and 4 area. The bilayer acts as an active electrolytic device, an Activa, in the type 2 region when biased by the electrostenolytic process shown at the top of the type 2 column. The current through this Activa is controlled by the electrical potential of the hydronium of the type 2 area via the horizontal shaded area from the type 4 lemma column. In this instance, hydronium refers to the liquid crystalline form of hydrogen-bonded water (H₂O)²⁺, and not the simpler ionic form of hydrated hydrogen (H₃O)⁺ discussed in many introductory textbooks. The current that passes through the diode of the outer leaf is determined by the chemical change in the polar head of the receptor forming the leaf in this region. The operation of the type 4 lemma area is the same as developed in [Sections 2.xxx & 8.5.1.6](#) for the gustatory modality. [xxx check bias of -24 mV versus several hundred in the gustatory description ]

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The paths through the outer and inner bilayers of the dendrolemma and reticulum constitute directionally semiconducting (diode) pathways. These diodes are interconnected and biased so they form a base-controlled Activa as shown on the left. This circuit provides a deterministic current gain that is typically 200:1 in similar man-made devices.

Vogel et al. have demonstrated the conductivity of the typical phospholipid is sufficient to allow the measurement of a finite potential between its two ends when present as a monolayer film.\textsuperscript{106}

The C/D response shown at the lower left represents the quantum-mechanical transduction process resulting from the coordinate bonding of multiple stimulant molecules to the sensory receptors over time. The response is a single continuous function of time (including a deterministic time delay, $\Delta$), that exhibits different attack and decay time constants (Section xxx). The waveform is shown in ideal form. It does not show any limitations due to using a limited bandwidth, or improperly compensated, oscilloscope probe. Neither does it show any affects due to the adaptation characteristics of the more complete electrolytic circuit.

### 8.6.1.6 Summary of the Electrolytic Coordinate Chemistry Theory of Olfaction

Because of the success of the gustatory modality hypothesis presented in Section 8.5.1, an

\textsuperscript{106}Vogel, V. & Mobius, D. (1988) Local surface potentials and electric dipole moments of lipid monolayers: contributions of the water/lipid and the lipid/air interfaces J Colloid Interface Sci vol 126(2), pp 408-420
abbreviated hypothesis of the olfactory modality will be stated here that follows and only expands as necessary on that of the gustatory modality.

The primary difference between the two modalities are focused on;

1. the means of stimulant application,
2. the added significance of the very large aromatic class of chemicals,
3. the necessity of addressing non-atom based orbitals such as the benzene ring and its derivatives, and the C=C bond.
4. the recognition of the much larger number of “dimensions” in the olfactory neural space.

As will be developed in this major section, a set of potential OR’s have been defined that appear to satisfy the requirements of the olfactory modality.

To satisfy these requirements and define the proposed set of OR’s more precisely, a set of corollaries are defined here that are subsidiary to the main hypothesis. The main hypothesis remains demonstrated but not independently validated; because of its success to date, it will be labeled the Electrolytic Coordinate Chemistry Theory of Olfaction.

Following application of exterior stimulants to sensory neurons within the oral or nasal cavities, exterior chemical sensing involves a 2-step process (selection of a gustaphore or odorophore by a specific GR or OR and measurement of the dipole potential of that stimulant) involving an AH,B or AH,B,X relationship where A and B are a pair of electrophilic and electrophobic orbitals from the general set of oxygen, nitrogen, sulfur, and occasionally phosphorous.

Corollary I: The list of “orbitals” in olfaction is increased to include the electrophobic cloud of delocalized electrons associated with a benzyl ring and the electrophobic cloud associated with the π-bond of stand-alone carbon-carbon double bonds. As their designation implies, these structures are sources of electrons.

Corollary II: Odorants generally exhibit a primary odorophore satisfying the AH,B requirement for the molecule to form a DACB with the matching OR. The odorant may also exhibit a secondary (a tertiary, etc.) odorophore satisfying the AH,B requirement for the molecule to form a DACB with one or more additional OR’s.

Corollary III: The one odorophore present in all odorants arising in a single family is defined as the primary odorophore. It may be labeled by the common name for the simplest odorant in that family.

Corollary IV: The number of independent OR’s is larger than the set of GR’s in gustation, resulting in a multidimensional perception space of at least the seventh order. Most of the known odorophores can be accounted for by a seven-node orthogonal perception space.

Corollary V: A successful set of OR’s can be described as the esters of the amino acids, along with one or two derivatives of these acids, and phosphatidic acid (of the same character as those used in gustation). As in gustation, no proteins are directly involved in the transduction process in olfaction.

not yet resolved in this work is illustrated by cis-β-terpineol_8418 and similar molecules where one or more of the orbitals are located at a position that can vary depending on the rotation around a single carbon bond (generally between two carbon atoms). A d-value of 5.031 Angstrom is measured for the molecule in the Jmol library. However, by rotating the groups attached to C11 about the C9-C11 bond, the larger d-value of ~5.875 Angstrom is measured. The question is how is this variation accounted for during organoleptic evaluations and in the Jmol documentation? See Section 8.6.2.10.4.

Pending resolution of this question, this work will assume that the conformation shown in the Jmol file provided by the Royal Society of Chemistry for a particular molecule is the predominant conformal isomer.
The following material will develop the theory of the olfactory modality as an explanation of the empirical data in the literature based on the Electrolytic Theory of the Neuron and transduction via a coordinate chemistry mechanism for each of the sensory channels of smell. The theory is comprehensive. It encompasses the sensing of all recognized sensations of smell.

The theory of olfactory sensing recognizes an n-dimensional perceptual smell space with the individual neural channels occupying the vertices of this space. In this context, the n-dimensional space of olfaction is much more complex than that of the other external sensory modalities.

Moving from a conceptual understanding of olfaction to a more formalized theory has provided new insights. These insights can be grouped as follows.

[xxx subdivide the following into groups with rational names.]

**Group 1 Olfactory Transduction, global aspects**

- Olfactory transduction involves a coordination chemical process of very low energy that is totally reversible. No chemical "reaction" is involved in the transduction process.
- Transduction occurs totally external to the sensory neuron lemma. No stimulant components pass through the cell wall.
- The transduction mechanism uses a set of phospholipids, widely recognized as being present in neural tissue but of previously unknown utility, as the olfactory sensory receptors (OR’s).
- The transduction mechanism employs a short-term coordinate chemical union between the sensory receptors and the stimulant that is stereo-chemically specific.

**Group 2 Olfactory Transduction, Details**

- The phospholipids forming a specific active region of a OR are present as a liquid crystal portion of the dendritic tree, known cytologically as the cilia.
- There are multiple specific types of OR in olfaction that selectively isolate the individual gustaphores found among a wide range of stimulants.
- The individual odorophore is associated with the appropriate OR through a dual anti-parallel coordinate bond (DACB) arrangement.
- The perception of a smell is the result of a 2-step transduction process.
  - Step one involves the initial isolation of odorophores affecting a given OR type through the formation of a DACB (Section 8.6.4).
  - Step two involves the subsequent measurement of the dipole potential of the individual stimulant when bonded to the OR (Section 8.6.5).
- The net dipole potential change due to a specific stimulant may be influenced by the specific electrostatic field presented to the OR, resulting in the perception of super-effective stimulant qualities (like those of gustation but not currently documented here).

**Group 3 Additional details of transduction**

- The transduction mechanism results in a change in dipole potential of the phospholipids that are known to be polar. This change in dipole potential is sensed by the first Activa of the sensory neuron.
- The net change in dipole potential of the individual phospholipid OR is highly sensitive to nearby electrostatic fields, particularly those of the associated odorophore.
- The histology and physiology of the sensory neurons following the transduction mechanism is the same as that of other sensory neurons. They exhibit an external axon and share a microcilia structure similar to the visual sensory neurons.
The sensory channels of the olfactory system exhibit the same excitation/de-excitation function and the same adaptation functions as other sensory modalities. Only the time constants vary to accommodate anatomical and vascular conditions.

The olfactory modality exhibits the same neural architecture as all other sensory modalities but the stage 2 signal processing occurring outside the cranium appears to be minimal.

Group 4 The Perception of stimulants within the neural system

The olfactory modality uses a small group of sensory receptors (greater than eight but nominally less than 32) to sense a wide variety of chemical structures (in the thousands).

The small number of sensory channels operate independently and can therefore be represented as statistically independent and therefore orthogonal, resulting in a n-dimensional smell space within the neural system (Section 8.6.6). This space can be unfolded into a single dimensional space, the d-value space (Section 8.6.2), equivalent to the spectra of the gustatory, visual and auditory modalities.

The unfolded representation of the taste space highlights the common feature wherein many stimuli are able to stimulate multiple sensory channels.

As in the case of gustation, the response of the olfactory modality to inorganic acids, many inorganic gases and various astringents is minimal. These materials primarily affect the nocent modality of the neural system in order to prevent damage to the biological system.

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- The “salty” sensory receptor is in fact only sensitive to the fully hydrated sodium ion; the chlorine ion plays no role in the transduction mechanism.

- The “sour” sensory channel is primarily sensitive to the carboxyl group of organic (Lewis) acids.

- The “sweet” sensory channel is primarily sensitive to a group, consisting mostly of either oxygen or hydroxyl oxygen at positions 1,2 of a cis-glycol, generally in a cyclic structure. [See a more precise definition of the 1,2 equatorial-trans-glycol given below]

- The “sweet” sensory channel exhibits an overlay mode of operation, involving a three-point stereochemistry, that is supersensitive to man-made sweeteners (super-sweet glycophores).

- The “bitter” sensory channel is primarily sensitive to organics with two orbitals capable of sharing an electron-pair and separated by a distance of 4.746 Angstrom.

- The “bitter” sensory channel also exhibits an overlay mode of operation, involving a three-point stereochemistry, that is supersensitive to primarily man-made stimulants (super-bitter picrophores).

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As noted in Section 8.4.7.1, particularly with respect to olfaction, the identity of the specific OR’s is not as well identified as in the case of the GR’s. As a result, the stimulant data base is more heavily relied upon to establish the mean d-value of a specific OR. To this end, it is important to differentiate between odorophores involving the single bond versus double bond connection to the terminal orbital. It is also important in some cases to differentiate between aliphatic molecules involving only single bonds and those containing double bonds at what may appear to be arbitrary locations remote from the terminal orbitals.

In the development of this work, a large number of odorants were examined from the perspective of their (frequently multiple) d-values. The result was a large table of odorants arising from a variety of source coupled with their major internal odorophores (including their Chemspider designation to avoid semantic confusion) with the d-values of each odorant shown in columns across the page. The d-values were obtained using the Jmol library from the Royal Chemical Society and the Discover 3.5 rendering software from Accylers. The columns were quantized to suggest how individual odorophores might be identified by a finite set of olfactory receptors. The table of these
values can be found in Sheet 1 of the following file; http://neuronresearch.net/smell/pdf/TablePreferredDescriptors.xls#Sheet1!A1

8.6.1.6.1 Additional extension of the hypothesis is needed

The hypothesis and corollaries presented here do not address some odorants of very complex structure, particularly hat structures bridging hexane rings (camphor and eucalyptol as examples).

Eucalyptol is currently represented by eucalyptol 2656 and eucalyptol 21111689 in Chemspider although they have identical structures based on the DS3.5 visualizer and the Jmol files. The latter has the designation (1s,4s) preceding the systemic name for both.

Additional analysis is warranted to find out, how these structures can satisfy the DACB arrangement for stimulating the major OR’s of olfaction, or how they circumvent the DACB requirement.

Kaiser (page 59) has described the complications brought on by these bridge structures in producing “woody” scents. Some of the most important woody scents are actually due to a fungus attacking the wood and creating distinctly separate odorants. Lawrence has provided a recent review of the enormous number of sesquiterpenes important to this area of perfumery\(^{107}\). This report followed a 1985 report describing the fungus residues, \(\alpha\)-agarofuran 9032313 (\(d = 2.947\)), \(\beta\)-agarofuran and other chemicals\(^ {108}\). As seen below, \(\alpha\)-agarofuran would be expected to stimulate OR 2 resulting in a fundamentally dulcal perceived scent.

A dulcal scent is typified by a sweetness at low concentrations (jasmine) and a fetidness at high concentrations (fecal matter).

As noted, many inorganic substances have been used in the study of the operation of the olfactory modality in the past. However, these materials are usually irritants that actually stimulate the nocent modality (Section 8.7.3) and the nociceptors rather than the OR’s.

The current hypothesis does not readily address acetone, menthol or the saturated alcohols when described in their isolated form. Acetone is easily addressed when hydrated (Section 8.6.1.8). It is likely menthol is also sensed when in a hydrated or other coordinate bonded form (Section 8.6.3.3) and the alcohols are generally believed to be odorless in their isolated form (Section 8.6.7.3).

8.6.1.6.2 Spatial representation of the odorophores of olfaction

The large number of OR’s, and related independent neural paths reporting the sensed information, believed to be used in the olfactory modality, suggests a higher dimensionality in the resultant olfactory sensory space.

Simultaneously, the potential for common OR/GR associated with the volatile/nonvolatile organic acids suggests at least one common node in the overall spatial representation of the exterior chemical sensing space associated with the pharyngeal space in mammals.

Because of these two features, it is tempting to consider an overall spatial representation of the exterior chemical sensory space similar to the Hertzsprung-Russell diagram used in astronomy. That diagram has a main sequence representing stars in midlife and a separate subsidiary sequence related to stars approaching extinction.

Figure 8.6.1-24 shows such a representation keyed to what appears to be a common node related to the organic acids (2.268 Angstrom). The most useful scales for such a diagram have yet to be determined. A logarithmic representation might describe the closeness of the members of one


8.6.1.6.3 Major current problems with the RSC J mol Library

Upon close examination of the J mol files of the Royal Society of Chemistry (acting as a storage facility and not performing curation on the J mol data sets), most of their files only present 2D representations of a given molecule and the visualizer used attempts to recreate a 3D representation based on plausible (to the computer) constraints. As a result, this section can only present plausible representations of the chemicals found to be important in olfaction.

The RSC indicated to this investigator that if undefined stereo-centers are indicated on their main page for a chemical, their 2D & 3D representation of the molecule are at best approximations. They also indicated that various visualizers will prepare a reasonable representation of the molecule using stored bond lengths (of uncertified or identified...
Luo has presented a full handbook\(^{109}\) of bond dissociation energy (BDE), (a quantity usually believed to correlate with bond lengths) for individual bonds between two atoms as found in large numbers of molecules. Just the BDE’s for the C-H bond of the saturated hydrocarbons covers four pages of significantly different molecules with a range from 95 to 105 kcal/mole.

Relying upon any visualizer to estimate the distance between two orbitals in a molecule is totally unacceptable within the research community!!!

The Jmol program will have long term positive impact on organic and biological chemistry. However, at this time, it lacks significant curation and fact checking by the RSC. The staff listed on the RSC website is surprisingly limited in its chemistry credentials. As a result, virtually anyone is allowed to submit a molecular description to the Jmol library. Not even the source’s name is required to be included in the record submitted. There appears to be no peer-review of the submissions.

**News flash:** The Jmol files are no longer available in 3D based on the cancellation of their internet security certification based on the “Cessation of Activity” as of 15 October 2015. It appears these files are being supplanted by the JSmol files curated by the same RSC. However, the JSmol database was taken off the internet for an unspecified period as of 19 Nov 2015 (as was the ability to contact the curator via the website). While the JSmol files examined frequently have more header information than the Jmol files, the information is frequently disguised with a dummy author’s name (Marvin) appearing on large numbers of JSmol files. No citation has been provided to date regarding the bond lengths used in the Jmol and JSmol files the RSC has provided.

The XYZ file format most frequently used with Jmol files is designed to accommodate a number of variants as defined by the Jmol.org\(^{110}\). A major problem arises when incomplete data sets from undefined sources are incorporated into the database.

The following material is reproduced from the Jmol.org wiki (with italics added)\(^{111}\),

There are often MOL and 3D files with two-dimensional data (i.e., all atoms have Z=0); Jmol will read them too, but the resulting flat model will not be realistic. The defining tag (2D or 3D) must be located in line 2, columns 21-22, but is ignored by Jmol, which just uses the Z coordinates provided, be they zero or not.

Jmol v.12 has two ways to deal with such flat models:

- you can run the minimize command after loading; this will apply a simple UFF force field to reach a reasonable 3D structure;
- or you can load the file using the filter “2D” switch of the load command, in this way:

```
load myfile.mol filter "2D"
```

This will load the flat model and, before it is displayed, will add hydrogens if needed and then run a minimization; the result is a 3D model of the input 2D structure with a feasible conformation.

**MOL header lines:**

The first line is reserved for the molecule name and will be so used by Jmol in the popup menu. The second line is in principle reserved for information on the originating program, date, user, etc. (Jmol will ignore this line).

The third line is for comments, and may contain an inline script starting with jmolscript:


While the feasible conformation mentioned in the wiki may be adequate for pedagogical purposes, it is not adequate for describing the odorants and odorophores of olfaction. Another source explains,

"Note that the XYZ format doesn't contain connectivity information. This intentional omission allows for greater flexibility: to create an XYZ file, you don't need to know where a molecule's bonds are; you just need to know where its atoms are. Connectivity information is generated automatically for XYZ files as they are read into XMol-related applications. Briefly, if the distance between two atoms is less than the sum of their covalent radii, they are considered bonded."

The Jmol format was initially documented in the journal literature in 1992112. The paper was not subject to a serious peer-review or review by any committee within the chemical community. As an example, two values to be entered in the Count Line are labeled, "number of atoms" followed by "number of bonds." The two labels should read "exclusive of hydrogen atoms" and similarly for the bond count. The company MDL became Accelyrs and has recently become BioVia. The Accelrys organization reviewed the Jmol and other file formats in the family in 2011113. The paper introduces a new level of understanding related to complex molecules, "Here we introduce the self-contained sequence representation (SCSR). SCSR combines the best features of bioinformatics and cheminformatics notations. SCSR is the first general, extensible, and comprehensive representation of biopolymers in a compressed format that retains chemistry detail."

Chen et al. summarize what they seek to solve, "Biomolecules stored in bioinformatics databases are text strings. Chemical modifications and cross-links are usually handled as annotations (Figure 1) and retrieved using text search approaches. The bioinformatics sequence representation based on one-letter residue names has two inherent limitations. First, there are only 26 alphabetic letters and 20 of them have already been used to represent 20 natural amino acids. Moreover, there are in theory an unlimited number of unnatural amino acids that can be incorporated into a protein sequence. Second, bioinformatics sequence representation lacks detailed chemistry. Up until now, most sequences are naturally occurring biopolymers and are stored and managed mainly in bioinformatics databases.

The current bioinformatics research still primarily focuses on the development of new tools for studying naturally occurring sequences. For example, recently Sboner et al.2 developed a tool for finding gene fusions." The focus is clearly on very large molecules, much larger than typical gustants and odorants. Unfortunately, it does not involve itself in coordinate chemistry, only the conventional groups associated with conventional valence chemistry. Coordinate chemistry is critical to the understanding of the chemical senses of biology.

Chen et al. also introduce NEMA that may be more useful in chemical sensing, "What is NEMA? NEMA stands for the newly enhanced Morgan algorithm. It includes a set of technologies for accurate perception of stereochemistry, canonicalization of molecular structures, conversion of the graph-based chemical structure into the canonical linear notation (the full NEMA name), and generation of NEMA keys from the full NEMA names for small and large molecules alike. NEMA offers a new method of stereochemical recognition that meets the industry's need for improved chemical representation of tetrahedral and geometric stereogenic centers. The NEMA method extends stereochemistry recognition to axial chirality, for example, allenes and atropisomers, such as hindered biaryls. It supports both two- and three-dimensional (2D and 3D) stereochemistry perception. They provide an example of a SCSR-enhanced V3000 molfile format. They also discuss problems that have already surfaced within competing formats such as InChI.

Chen et al. introduce an extension to the periodic table designed to provide a “home” for many amino acids (other than the commonly identified 20-26 amino-acids) not currently assigned short

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codes for purposes of computation and indexing. They label the new entries “pseudo atoms.” They do develop the need for explicit templates to support these files rather than the implicit files and templates inherent in the original and most recent Jmol formats.

The SCSR and NEMA concepts appear to be implemented using a Jmol compatible format that may be limited to only 4 decimal place precision (the same as Jmol) which may be found wanting in the future. However, the sample code presented indicates the entries are not restricted to the file format envisioned using the 80 column punch card style used much earlier in computation history.

There is no assertion by Accelrys or the RSC that the bond angles or bond lengths used to create a Jmol file are correct. The files are created using either measured relative locations of individual atoms in a molecule, but more often relative locations calculated using bond length and angle lookup tables of limited precision.

The Jmol file format is obsolete. It is based on the undelimited 80-column file format created in the punch-card era and initially used in for Fortran program computing. The format is described as F10.4 in Fortran. As currently defined, it can only accommodate 4 decimal place accuracy of position measured in Angstrom. The Jmol files do not generally include position information for the hydrogen atoms. This information is apparently added to the visualizer renderings based on standard distances. The number of hydrogens is deduced from the number of other bonds associated with a given atom.

**Figure 8.6.1-25** shows the Jmol file for tryptophan_6066 amino acid as of 5 May 2015. As noted in the caption, the file is seriously incomplete and relies upon the visualizer program to interpret the data and develop a feasible conformation based on only 2D information. It can be presumed the d-values for the distances between atoms calculated from this table are only projections of the actual distances involved.” The values 15 & 16 in ln 4 refer to the number of non-hydrogen atoms present and the number of bonds between the non-hydrogen atoms. The other items in ln 4 are largely ignored by the program at this time. No reference to a table of covalent radii for the atoms is cited.
After assuming a feasible conformation, the visualizer does appear to calculate rational distances between the atoms in a 3D space. However, as shown for some of the citrals in Section 8.6.xxx, the

\begin{verbatim}
Ln 1 limited to name of molecule, typically blank
Ln 2 reserved for information about source, typically blank
Ln 3 is for comments, typically left blank

15 16 0 0001 0 0 0 0 0 999 V2000
-1.7575 0.3126 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-1.2054 0.9256 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-0.3984 0.7541 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-0.1435 -0.0305 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-0.6284 -0.6979 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-0.1435 -1.3654 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0.6411 -1.1104 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0.6411 -0.2854 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
1.3556 0.1271 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
2.0701 -0.2854 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
2.0701 -1.1104 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
1.3556 -1.5229 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-1.4604 1.7103 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-2.2673 1.8818 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 0 0
-0.9083 2.3234 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 0 0
2 1 1 6
2 3 1 0
3 4 1 0
4 5 2 0
5 6 1 0
6 7 1 0
7 8 2 0
4 8 1 0
8 9 1 0
9 10 2 0
10 11 1 0
11 12 2 0
7 12 1 0
2 13 1 0
13 14 1 0
13 15 2 0
M END

Figure 8.6.1-25 J mol file for tryptophan_6066 in the RSC database ca May 2015. As a research tool, the file is seriously incomplete. All of the header lines are blank. 0999 in the count line indicates this variant of the file (V2000) can only contain up to 1000 atoms. The left-most column contains no list of atoms by name. They are shown in column 4 of the atom block (lines below the header and count line) instead. The Z column of the XYZdata file is all zeroes. There is no data in the field to the right dedicated to the charges associated with each atom of the molecule. The bond block (below the atom block) is required although little discussed in the J mol specification.

After assuming a feasible conformation, the visualizer does appear to calculate rational distances between the atoms in a 3D space. However, as shown for some of the citrals in Section 8.6.xxx, the
visualizer determines the feasible conformation of the molecules are straight hydrocarbons in 3D space rather than the partially cyclic forms described in most textbooks for the same molecules (and in their 2D representation by ChemSpider).

At this time, the distances given in Jmol are the best available. However, the reliance upon the visualizer to create the correct 3D conformation of a molecule must be questioned. Until the correct conformation is obtained, the d-values produced by the visualizer must be considered tentative. Chatterjee et al. (cited below) have provided all three of the XYZ coordinates for several citrals in their supplemental data. However, when truncated and reconfigured to the Jmol format, the DS-3.5 visualizer did not portray the molecules correctly. It appeared to change the tabular values and largely create a 3D rendition based on only the X & Y values it accepted.

The recommended Ln 2 in a Jmol file is:

```
IIPPPPPPPPPMMDDYYYYHmmddSSssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssssss
solution mimicking the olfactory epithelium (of proper pH particularly). Crystallography techniques may provide useful information but that information is usually limited to the material in the solid state. It is also normally limited to only simple organic compounds. It has been applied to a few very complex biologicals (ex., hemoglobin), but usually involves Herculean efforts by investigators. Chatterjee et al. shows in Section 8.6.1.6.5 that the dielectric constant of the solvent in which a odorant is dissolved plays a critical role in the actual conformation of a molecule.

The Jmol database does not define what dielectric constant is assumed for the solvent (if any) surrounding the molecules it displays.

8.6.1.6.4 Conformation of odorants—conventional leading edge technology

Further investigation of the question of conformation of odorants, particularly those involving what can be described as partial cyclic ring compounds, suggests the study of these compounds is at the leading edge of current chemical research. Section 8.6.2.6.2 addresses the complications related to the odorants found in citrus fruit.

Pihlasalo et al. have addressed the conformational problem of citral described in the previous section114.

"In this study, the conformational equilibria of citral were examined experimentally by nuclear magnetic resonance (NMR) spectroscopy and theoretically by density functional theory (DFT) calculations." "According to DFT, the most stable structure is an E-s-trans conformer which is 2.0 kJ mol⁻¹ more stable than the most stable Z-s-trans conformer, i.e. E-citral is slightly more stable than Z-citral."

Figure 8.6.1-27 shows their description of the four main conformers of citral. The double bonds between C7 and C8 are shown aligned vertically in the previous figure. "3,7-Dimethyl-2,6-octadienal, or citral, is a monoterpene, consisting of two geometrical isomers. The E-isomer is specifically referred to as geranial or citral A whilst the Z-isomer is referred to as neral or citral B." "Citral is an α,β-unsaturated aldehyde with an additional, isolated C=C double bond. However, the C=O bond can adopt either an s-cis or an s-trans orientation with respect to the conjugated C=C bond. The mobility about this bond, together with the three adjacent torsional angles, α, β and γ, defines the conformational behavior of citral but with only the former in mind, four main structures, E-s-trans (1), E-s-cis (2), Z-s-trans (3) and Z-s-cis (4), can be alluded to. Surprisingly, information on the conformational behavior of citral is sparse and only one report concerns NMR conformational studies wherein it was concluded that both Z and E-citral adopt s-trans conformations." "With limited exceptions experimentally and theoretically, to the best of our knowledge, the comprehensive conformational analysis of citral has not been published."

The depth of the analysis in the Pihlasalo et al. paper is significant and will not be addressed here. They did note their analysis resulted in 80 potential structures. Before proceeding, the number of structures was reduced to 24 by excluding similar structures and structures which had the torsional angles of opposite sign, i.e. mirror-image structures. Their Table 1 demonstrates that the four most prevalent conformers exhibit preferred torsion angles around the various C–C bonds. The four obtained minimum energy structures were determined at a defined level of theory. Their figure 2 is reproduced as Figure 8.6.1-28.

By noting the number of single C–C bonds in citral, four, it is clear that citral can exist in a variety of stereoisomers that are not mirror image enantiomers. Citral a 553578 (geranial), citral b 558878 (neral) are not exclusive isomers of citral, merely easily identified members of the family. A complete energy diagram of the molecule is needed to illustrate all of the potentially stable isometric forms. The dielectric constant of the medium in which citral is immersed is important and in the case of water, the pH also plays a significant role. It may be useful to define a citral c corresponding to its most stable configuration(s) when dissolved in water.
3 & 4 exhibit considerably lower d-values relative to the C7-C8 double bond than do 1 & 2. These structures were described earlier as xxx, xxx & xxx.

They note an important caveat when comparing papers by different authors, “Under the
experimental conditions applied here, E-citral to Z-citral interconversion was not observed based on integrated intensities of the $^1$H-NMR signals. But the inference for all $\alpha,\beta$-unsaturated carbonyl systems is clear: thus while the predominance of the s-trans conformation in this case is without question, s-cis conformations are also present in concert with analogous systems but their existence is less evident since they are not observable directly by NMR.”

Their conclusions include, “Optimization of citral conformations at the B3LYP/ TZVP level of theory revealed that a large number of conformations are nearly equally stable, i.e. there is equilibrium of many interconverting conformations. The most stable structure of all is an E-s-trans conformer which is 2.0 kJ mol$^{-1}$ more stable than the most stable Z-s-trans conformer, i.e. E-citral is slightly more stable than Z-citral. Furthermore, s-trans conformations were found to dominate over s-cis conformations. The amount of s-cis conformation present, however, is non-negligible.”

Their conclusions suggest additional footnotes are needed in ChemSpider when discussing the 3D conformation of citral a_553578 (geranial) and citral b_558878 (neral). Footnotes appear appropriate when discussing any of the $\alpha,\beta$-unsaturated aldehydes.

The Pihlasalo et al. paper includes an Appendix A that includes XYZ data for each of their four optimized representations in a Word file.

The Pihlasalo et al. data requires further discussion. Although the XYZ positions were given to 18 place accuracy, 14 places after the decimal point, no indication was given of the standard deviation associated with these values. The bond angles, assumed to be related to these calculations were only given to three-place precision (in whole degrees). It is likely that their XYZ values are only good to four decimal places. Without further justification, their XYZ positions can be considered to contain considerable “phantom precision.”

The Pihlasalo et al. data has been translated into separate *.mol files using the precise format provided by Accelrys (now Dassault Systems, Biovia) to support this work. [xxx however, DS 3.5 does not handle these files well. It tends to ignore the Z values and may change some of the X & Y values. [xxx give addresses if appropriate ] The format is limited to the 80 column line of the old IBM Card format used in the Fortran era. Atom positions are limited to four decimal accuracy when expressed in Angstrom.

The *.mol file format is limited to four decimal place precision. See Section 8.6.1.6.3.

### 8.6.1.6.5 Conformation of odorants depend on dielectric constant of epithelium

Citing R.G. Pearson. 1976 and also D. Sivanesan et al. 1999, Chatterjee et al. have noted$^{115}$, “It is well known that, the reactivity of a chemical species depends on the solvent associated around the molecules. “Generally, it is observed that, the solvent environment alters the charge distribution of a molecule and there is an increase in the dipole moment, compared to a gas phase calculation. Water enhances the intrinsic reactivity of polar molecules towards nucleophilic and electrophilic attack.” Chatterjee et al. did not name their different conformations of citral. It should be noted that Chatterjee et al. number their atoms in citral differently than Pihlasalo et al. Their analysis also shows the importance of the dielectric constant of the solvent when discussing the conformation of the citrals. At the high dielectric constant of water, the coiled forms of citral are the predominant form as opposed to the extended aliphatic form shown in the ChemSpider 3D representation of citral a_553578 (geranial) and particularly citral b_558878 (neral).

Thus, in olfaction, it is important that a solution representative of olfactory epithelium be employed in laboratory experiments when describing the actual conformation of the stimulating odorophores as well as the OR’s being stimulated. Table 1 of the Chatterjee et al. paper shows some fundamental parameters for citral in different dielectric environments. Their experiments only addressed dielectric constants up to 32.6. Their figure 2 shows the conformers of citral for the gas

phase and for dielectric constants of 1.6 (hexane), 15 (amyl alcohol) and 32 (methanol). For
dielectric constants of a solvent at 15 and 32, the citral occurs in its most coiled form. However,
water has a much higher dielectric constant, on the order of 80. It can be assumed that citral
occurs in it most coiled form within the mucosa and its d-value between the oxygen and the
isolated double bond adjacent to the two methyl groups is minimal. This corresponds to the Zs-cis
citral form labeled (4) in the paper of Pihlasalo et al. above.

The high dipole moment of citral in a water solvent suggests citral also exhibits a high dipole
potential as sensed during step 2 of the transduction process. See Section 8.6.5.

8.6.1.6.6 The future of conformal information for olfaction-crystallography

The science of crystallography offers much higher precision atomic positions within a molecule that
can be crystallized. The crystallization requirement appears to be met by virtually all of the liquid
crystalline structures of interest in olfaction, and gustation. Crystallography offers accurate bond
lengths, based on atomic positions, for a specific molecule. It does not depend on various tables
of average bond lengths, or calculations by various visualizers designed to provide “the best
available representations” of a given molecule (Section 8.6.10.1).

The use of extensive crystallographic data on odorants and their odorophores will provide for the
first time, precise conformations not based on various 1st order, 2nd order, and 3rd order
approximations as to their actual d-values. Such data should be isolated from the various “best
available representations based on computational biology such as the current Jmol, JSmol and
similar databases circa 2016.

Piane et al. described the state of crystallography related to proteins very clearly in 2016116.
“Nevertheless, the quantum-mechanical simulation of proteins is still in its early stages. The
first pioneeristic fully ab initio protein simulation dates back to 1998, in which the geometry
optimization of the isolated crambin molecule (642 atoms) was carried out at the
Hartree–Fock level (HF/4-21G) by van Alsenoy et al.” They described both the hardware used
and the performance obtained in the paper, “All calculations were run on a Cray Cascade
XC40 Supercomputer.” “However, it must be noted that 1000 optimizations steps on the
γ-chymotrypsin model on 1200 cores would cost about 3.6 million CPU hours, below the
average allocation of present day high performance computing project calls.”

8.6.1.7 Molecular Mechanics and electrical potentials TENT. TITLE/MOVE

[xxx it is suggested this should be a three level title discussing molecular mechanics, stereochemistry,
and electrical potentials and fields. ] Consider moving this up to 8.4.5 or 6 and combining with the
stereochemistry analogy.

8.6.1.7.1 Molecular mechanics—background

Molecular mechanics provides a starting point for understanding the major mechanism of olfaction
(as well as gustation).

“Molecular mechanics uses Newtonian mechanics to model molecular systems. The potential
energy of all systems in molecular mechanics is calculated using force fields. Molecular mechanics
can be used to study small molecules as well as large biological systems or material assemblies with
many thousands to millions of atoms.

All-atomistic molecular mechanics methods have the following properties:

116Piane, M. Corno, M. Orlando, R. et al. (2016) Elucidating the fundamental forces in protein crystal formation:
the case of crambin Chem Sci vol 7, pp 1496-1507
Each atom is simulated as a single particle. Each particle is assigned a radius (typically the van der Waals radius), polarizability, and a constant net charge (generally derived from quantum calculations and/or experiment). Bonded interactions are treated as “springs” with an equilibrium distance equal to the experimental or calculated bond length.

Variations on this theme are possible; for example, many simulations have historically used a “united-atom” representation in which methyl and methylene groups were represented as a single particle, and large protein systems are commonly simulated using a “bead” model that assigns two to four particles per amino acid.”

“The following functional abstraction, known as a potential function or force field in Chemistry, calculates the molecular system’s potential energy \( E \) in a given conformation as a sum of individual energy terms.

\[
E = E_{\text{covalent}} + E_{\text{noncovalent}}
\]

where the components of the covalent and noncovalent contributions are given by the following summations:

\[
E_{\text{covalent}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{dihedral}}
\]

\[
E_{\text{noncovalent}} = E_{\text{electrostatic}} + E_{\text{van der Waals}}
\]

The exact functional form of the potential function, or force field, depends on the particular simulation program being used.”

“The electrostatic terms are notoriously difficult to calculate well because they do not fall off rapidly with distance, and long-range electrostatic interactions are often important features of the system under study (especially for proteins). The QVBMM force field (implemented in STR3DI32) is unique in molecular mechanics as the only one to directly use all lone pair interactions in all of its energy calculations. The basic functional form is the Coulomb potential, which only falls off as \( r^{-1} \). A variety of methods are used to address this problem, the simplest being a cutoff radius similar to that used for the van der Waals terms. However, this introduces a sharp discontinuity between atoms inside and atoms outside the radius. Switching or scaling functions that modulate the apparent electrostatic energy are somewhat more accurate methods that multiply the calculated energy by a smoothly varying scaling factor from 0 to 1 at the outer and inner cutoff radii. Other more sophisticated but computationally intensive methods are known as particle mesh Ewald (PME) and the multipole algorithm.”

The above quotations should serve to highlight the difficulty of the purely theoretical and mathematical approach to addressing the energy field and the polarization of a specific complex molecule. Fortunately, it is not necessary to calculate the energy field or the net potential for purposes of understanding olfaction and gustation. It is only necessary to appreciate how changes in the field and potential arise.

Discussions relating to solvation and hydration in the context of molecular mechanics are equally difficult mathematically. However, these processes are of critical importance to the understanding of olfaction and gustation. Fortunately, only the practical and observed aspects of these subjects need be addressed in this work.

### 8.6.1.7.2 Molecular mechanics—application

All of the molecules of interest in olfaction and gustation exhibit an electrical polarization, that the above procedures attempt to evaluate. The magnitude of the polarization, its electrical potential in volts, is difficult to measure in the typical chemical environment. It is more convenient to describe its vectorial value, the polar moment (typically in volt–cm). However, in liquid crystal chemistry, the rotational aspect of the individual molecules is constrained and a measurement of the electrical potential transverse to the liquid crystal is straightforward on a bulk molecular basis.
The transverse potential of a typical phospholipid membrane is found to be in the range of 200 to 600 millivolts. This is a significant potential and forms a major part of the barrier preventing molecules from penetrating a lemma formed of a bilayer of two back-to-back phospholipid membranes.

If one of the phospholipid membranes becomes coordinately bound with another molecule, its apparent axial electrical potential changes due to the change in molecular mechanics of the overall structure. This change in electrical potential is the parameter that is sensed by the sensory neuron and used to eventually elicit sensations in the brain associated with olfaction and gustation.

Most of the subsequent discussion is aimed at describing how this change in electrical potential is brought about. The process typically involves two steps; a stereochemical selection process which determines which sensory neurons will react to a given odorophore, and a change in electrolytic potential describing the electrolytic intensity of the stimulant to the selected channel.

While the net change in electrical potential across the phospholipid membrane may be only a fraction of a millivolt, this is adequate for the sensory neurons to amplify and pass to the remainder of the neural system. The details of this process have been explored earlier (Section 8.6.1.3.1).

8.6.1.8 The stereochemistry of olfaction—bond lengths and angles

While understanding gustation required examining a variety of simple stereographic features of chemical structures, particularly related to the sugars, the situation is much more complex in olfaction. The structures of volatile organic compounds are much more complex, the list of pertinent anionic atoms is much broader and in some cases carbon can actually be replaced by silicon.

While it is necessary that odorants be volatile to aid transport through the air, it is mandatory that they be minimally soluble in mucosa for their sensing. Solution generally involves a state of hydration and it is the hydrated state that plays a critical role in olfaction. It is the hydrated state of a stimulant that is critically important in understanding how it is sensed.

The structures of chemicals can be subdivided into their constitution (connectivity), configuration and conformation. This is also true of the hydrated chemicals where different values for these properties apply than in the non-hydrated case. The hydrated state of many chemicals of interest vary significantly with temperature. In the following discussion, it will be important to rely upon the parameters of the various hydrated chemicals at physiological temperatures.

The constitution of a chemical can be described by a two-dimensional graph showing single, double and triple bonds or by a matrix defining the same features. While the matrix is convenient for computer manipulation, both the 2D graph and the matrix require significant supporting information (bond lengths and angles) when discussing the stereochemistry of the chemical. This information can be incorporated into three-dimensional graphs of the chemical defining its configuration. However, even this description may be incomplete because many chemicals exist in multiple configurations with different torsion angles around a bond. These configurations are described as individual conformations. All of these characteristics play a role in olfactory sensing.

A characteristic of major importance in olfaction appears to be the physical distance between certain species primarily the anionic species capable of sharing an electron-pair. Such species are capable of forming coordinate bonds with other molecules associated with the sensory receptors. These coordinate bonds are primarily low energy (~5 kcal/mole or 200 eV) hydrogen bonds.

The hydrogen bonds appear to be the lowest energy level of quantum-mechanical chemical bonds. Only the non-quantum-mechanical van der Wall forces occur within the energy continuum at lower energy levels.

Physical chemistry provides a set of standard bond lengths between different chemical species and a set of bond angles between species associated with a central atom. However, these values only apply to the simpler molecules. One soon encounters molecules with groups employing unique bond lengths and angles under nominal conditions (See March citation in Section 8.4.5). Even these lengths, and associated angles, may be altered when crowding occurs within a molecule. The bond

117Eliel, E. Wilen, S. & Doyle, M. (xxx Basic Organic Stereochemistry. NY: Wiley Interscience Chapter 1
lengths of even the coordinate bonds of hydration are critically important in olfactory sensing. While the standard bond lengths and angles are used here to elucidate the theory, more sophisticated values should be used in verification experiments. Such values are collecting based on the most recent computational mathematics procedures. As an example of the difference between the standard bond length and measured values, Eriks et al. have noted, "A distinctive feature of 1,2-diketones is the long C-C bond linking the carbonyls. This bond distance is about 1.54 Å, compared to 1.45 Å for the corresponding bond in 1,3-butadiene. The effect is attributed to repulsion between the somewhat polarized carbonyl carbon centers." JSmol gives the bond length between the two carbonyl carbons of the diketone 1,2-biacetyl as the much shorter 1.362 Ångstrom (a significant difference of about 12%).

In complex stimulants, it is important to define an equivalent bond length between a species and a nearby electronic feature, such as the apparent electronic center of a phenol structure (such as the X feature in the AH,B,X arrangement employed in gustatory sensing. In olfaction, it has been proposed that this feature may be centered on a hydrogen ion (Section 8.xxx).

An electronic feature of importance in olfaction may be as simple as the electron cloud associated with a double bond. It may be an aromatic ring structure, or another electron-pair sharing anion. It may also be an isolated double bond between two carbon atoms. Both a specific steric distance and a specific potential between the species and features are needed to satisfy the stereochemical requirements for the typical pair of coordinate bonds.

In gustation, a graph of sensation intensity versus a one-dimensional continuum describing the distance between specific species (the d-value) plays a critical role in receptor-stimulant coordinate bonding (Section 8.5.xxx). Such d-values appear to play a role in olfactory sensing. However, the presence of multiple olfactophores in/on a given stimulant suggest multiple d-values for a single molecule that contribute to the overall sensation elicited.

As in other sensory modalities, these multiple characteristics are processed independently and interpreted orthogonally in a multiple-dimension space that has not been defined to date. The interpretation process involves both the stage 2 signal processing inherent in the glomeruli and also within stage 4 signal manipulation.

[Table of angles here Combining Eliel Barrow Morrison & Boyd etc. ] Figure 8.6.1-29 See Standard Bond Lengths (Distances) figure five figures down.

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Bond lengths of organic compounds are influenced by a variety of nearby elements. A carbonyl bond is reported generally in the 1.203 to 1.22 Ångstrom range. Similar variations are found in the literature for nearly all chemical groups when associated with other groups. Except where specifically mentioned, Standard Bond Lengths will be used in the following discussions. Figure 8.6.1-29 summarizes these dimensions as used in manual calculations. The dimensions for OH--N and NH--O bonding are particularly hard to locate and have not been standardized at this time. The NH--O bond pattern at lower left has been described as a bifurcated hydrogen bond by Sletten & Kaale. The values involving sulphur are from Yoem et al. and their citations, Sutton and Wells. As Sutton illustrates, bond lengths between pairs of atoms are not fixed. They vary depending on the overall compound involved, generally in the third decimal place but occasionally in the second in complicated structures. They also vary with temperature. Values may also vary depending on the method of acquisition. Ab initio calculations are particularly suspect due to the assumptions included in the computer programs used to aid or perform these calculations. The table values below must be considered generic. More specific values may be obtained in the laboratory for molecules of interest.

Wikipedia provides a brief discussion relative to the variability of bond lengths and angles. It also includes a brief discussion of the effect of hybridization level for carbon, but not for the orbitals needed here, such as oxygen and nitrogen.

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124 Sutton, L. (1965) Tables of Interatomic Distances and Configuration in Molecules and Ions. London: The Chemical Society Special Publ #18


126 http://en.wikipedia.org/wiki/Bond_length
Recently, Franco et al. released a report focused on totally deuterated 1-octanol as an odorophore\textsuperscript{127}. The report leads this investigator to consider whether a deuterated hydroxyl bond might be of different length than a normal hydroxyl. Similarly, the deuterated hydroxyl might participate in a coordinated bond of different length than the normal hydroxyl. Finally, the length of the bond between the deuterated hydroxyl and the carbon atom might also differ from that of the normal hydroxyl.

Soper & Benmore\textsuperscript{128} have published on the deuterated bond lengths of deuterium oxide. They have found that, in the liquid state, the distance between oxygen and deuterium in a D\textsubscript{2}O molecule is 3\% shorter than the distance between oxygen and hydrogen in an H\textsubscript{2}O molecule. Conversely, hydrogen bonds—relatively weak bonds connecting the oxygen in one molecule with the hydrogen or the deuterium in another—are 4\% longer in heavy water than in light. These differences are less than 1\% in water vapor, where the molecules are isolated. “A four percent change in bond length is quite a bit,” comments Michael Rübhausen of the University of Hamburg in Germany. The researchers


probed the distances via beams of x-rays and beams of neutrons, and ran computer simulations to help interpret the data.

A three percent change in these bond lengths is significant, but the actual angular geometry of the bonds must be considered when discussing the d-value associated with a pair of deuterium coordinate bonds.

Wyatt has summarized a large variety of isomeric conditions important in olfaction in his Appendix A2. He addresses, constitutional isomers, including functional group isomers and positional isomers as well as stereoisomers, including chirality and enantiomers, diastereoisomers and the very important geometric isomers. Without recognizing the role of each of these isomers, olfaction cannot be understood in any depth. Constitutional isomers have the atoms connected in different ways, whereas stereoisomers have the same connectivity but differ in the arrangement of atoms in space.

Unfortunately, Wyatt's first paragraph reiterates the old positions that pheromone (in particular) involve proteins, and that the three-dimensional shape of a molecule is a controlling feature in olfaction. Neither of these is supported in this work.

It is obvious that a specific odorant can contain more than one odorophore. As a result, a given odorant may elicit a very complex sensation based on the stimulation of multiple sensory channels and generating different amplitude signals in those channels.

8.6.1.8.1 The stereo geometry of organic compounds

Olfaction is highly dependent on the field previously known as stereochemistry. With the advent of inexpensive computer power, the field is now known as computational chemistry. While computational chemistry has become a major tool of big pharma and protein research, in olfaction organic molecules limited to about 300 Daltons are of primary interest. Within this limit, a large variety of molecular geometries are found with the distances between pairs of atoms falling into relatively discrete distances due to the physical bond lengths described above and a small set of bond angles defined by a variety of packing and electrostatic charge distribution rules. For pairs of atoms and selected other electrostatic features associated with multiple carbon-carbon bonds and aromatic structures, defined in this work as orbitals (of interest in olfaction), the three-dimensional distance between them becomes significantly quantized. These quantized distances are at the core of the olfactory sensing mechanism. The quantized distances allow a finite number of olfactory receptors to be employed in the sensing of a wide variety of odorants.

The same geometric rules are used in the organic chemistry of the olfactory receptors as in the odorants of olfaction. By careful selection of the molecules associated with the olfactory receptors, they can form coordinate bonds with a wide variety of odorants, and particularly the individual odorophores within an odorant. When several olfactory receptors and odorophores form simultaneous coordinate bonds, the signals generated by the sensory neurons associated with the olfactory receptors can provide a very sophisticated representation of the stimulant. This representation will be described in detail in Section xxx related to the information extraction process utilized in the stage 4 engines of the CNS.

It will be shown that it is the stereo-geometry of the organic molecules (their conformal chemistry) relative to the orbitals defined in this work that is critically important in olfaction. The chemical groups defined in valence and covalent chemistry by human investigators, as a matter of convenience, and as an aid to understanding and cataloging chemical reactions, play no role in olfaction.

8.6.1.8.2 The carbonyl group is of major importance

The carbonyl group (C=O of the larger structure RR'C=O) appears to play a major role in olfaction. It may play a fundamental role as an odorophore by itself, due to its high degree of electrical polarization. Alternatively, it may play its role when in the hydrated state. It is also a component of the very important carboxylic group, characterizing the organic acids. It clearly plays a role in affecting other odorophores due to its high degree of polarization.
The polarization of the carbonyl group is one of the greatest in organic chemistry. It is so large that it is necessary to consider whether just this group alone is able to participate in a coordinate bond pair with a similar group forming a portion of a sensory receptor, and thereby generate a potential change across a phospholipid liquid crystal membrane adequate to elicit a sensation within the brain.

8.6.1.8.3 The steric characteristics of the carbonyl compounds

The carbonyl group, C=O largely determines the characteristics of the aldehydes and ketones, a large collection of compounds important in olfaction. The group is more fully defined by the aldehyde formula, RCHO and ketone formula, RR'CO. The simpler members of these families are soluble in water, presumably due to hydrogen bonding with the solvent.

The chemical interactions of the carbonyl group are complex.

The carbonyl group is polar and can form dimers through intermolecular dipole-dipole attraction. These are very weak bonds however and generally involve a large separation between the two parts of the dimer. In the case of the aldehydes, a pair of AH,B bonds can form. Alternately, the group can react with water to form a hydrated structure. The bond spacing associated with both the dipole-dipole and AH,B coordinate bonding arrangements is 1.22 Angstrom. The carbonyl group can also become hydrated and form an alcohol containing two hydroxyl groups. In this arrangement, the four bonds to the carbon are at angles of 109.5 degrees and the distance between the two oxygen orbitals is believed to be d = 2.34 Angstrom. This distance is the same as found in one of the forms of carboxylic acid, the principle acidophore. Figure 8.6.1-30 illustrates these potential situations.

The role of hydration is very significant among the ketones. The literature of hydration of the simplest ketone, acetone illustrates this molecule forms very complex clathrates (Fullerene like shells containing only a single acetone molecule) with formula like (CH₃)₂CO·17H₂O. Hydration of the carbonyl containing petroleum products appears to be quite complex and dependent on many conditions and the presence of contaminants.

Figure 8.6.1-30 Carbonyl bonding arrangements. Top: the polar character of the carbonyl group and its potential coordinate bonding to a similar structure by dipole-dipole bonding. Bottom: theoretical hydration of the carbonyl group in acetone and potential participation in a AH,B coordinate bond. The dipole moment of the carbonyl is 2.4 Debye.

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like methane\textsuperscript{130}. Toryanik has shown that at the dilute solutions of interest here, acetone does hydrate with one molecule of water that is itself coordinate bonded to seven other water molecules\textsuperscript{131}.

[\text{xxx are the following two sentences correct? 1.22 is intramolecular bond length}\]

These initial considerations suggest the carbonyl compounds are sensed by a receptor optimized for d-values of either 1.2-1.22 Ångstrom and can form an AH,B coordinate bond with the carbon and oxygen sites of the highly polar carbonyl or with a d-value of 2.34 Ångstrom and can form an AH,B coordinate bond with the two hydroxyl sites of the simply hydrated carbonyl.

It is interesting to consider the effect of changing the oxygen of acetone to a hydroxyl. This leaves the configuration nearly the same except the single C-O bond should be longer (1.43 Ångstrom versus 1.22 Ångstrom based on commonly accepted values). In the case of forming the AH,B bond after hydration, the relative bond length would remain 2.34 Ångstrom for both acetone and 2-propanol (isopropyl alcohol).

Youngentob et al. have provided data comparing the responses registered in the glomeruli maps of rats following exposure to acetone and to 2-propanol\textsuperscript{132} along with santalol and beta-pinene. They show a very high degree of similarity between the responses of the alcohol and acetone, suggesting the same receptor is sensitive to both chemicals. Unfortunately, their maps do not include any organic acids as stimulants. The bond length of 1.43 Ångstrom would suggest an acidic quality to the taste via the gustatory sensors, and possibly an equivalent to the acidic quality via the olfactory sensors. A bond spacing between the coordinate bonds of the hydrate would suggest a perceived sweetness associated with the alcohol. The MDS plots of Youngentob confirm the similarity of 2-propanol, acetone and santalol in olfactory space. However, the dimensions of their MDS plots are not readily associated with d-value axes. Figure 8.6.1-32 offers a pair of alternate axes based on conventional MDS theory. The set of axes may be rotated by any degree without changing the relative positions of the data points. Inclusion of a preferred chemical in their set of stimulants would have allowed the scale of the proposed axes to be calibrated more completely. It would also have established a potential d-value for pentadecane and beta-pinene.

Youngentob et al. did not discuss any potential hydration of their stimulants. The central carbon of 2-propanol is under stress. If it were to form a hydrogen bond with water, its configuration would be very similar to that of the hydrated carbonyl group shown above for acetone, with a d-value very

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{MDS analysis with alternate axes shown. The two alternate axes are based on the similarity of d-values among the chemicals along these axes. See text. Original from Youngentob et al., 2006.}
\end{figure}


There are two santalols listed in ChemSpider with very similar d-values. Alpha-santalol has $d=2.675$ Angstrom. Beta-santalol has $d=2.677$ Angstrom. These values would also stimulate the dulcal receptor centered at $d=2.757$ Angstrom. There are multiple configurations of pinene in ChemSpider. Beta-pinene is a very complex molecule devoid of any orbitals except for a single C=C bond. It is found in two optical isomers. It is considered toxic. It is virtually insoluble in pure water, suggesting it may go into solution in the olfactory mucosa due to the presence of other chemicals. It is easily oxidized (particularly in the presence of light) and may form a hydrogen bond with water.

It is possible the exposed C = O of the bitter receptor, phosphatidyl 3'-O-aminoacyl glycerol could provide the steric match to these stimulants. Otherwise a separate phosphatidyl compound exhibiting a carbonyl group with this dimension for $d$ is required to provide an efficient carbonyl receptor.

**8.6.1.8.4 The role of chirality in olfaction–carvone as example**

In the last lesson related to the $R,S$ system in a discussion of chirality, the Khan Academy notes that $(R)$ carvone smells like spearmint while $(S)$ carvone smells like caraway seed. They assert, without any citation to theory, “this is because of the chirality of the OR’s in the (human) nose.” This assertion if true would complicate the proposed d-value parameter of olfaction. The subject deserves further analysis.

Chirality implies not superimposable on mirror image. Generally applies to carbons not having a pair of like atoms attached to it.

To the extent they are correct in Chemspider, these two chemicals exhibit different d-values that can account for their difference in perceived odors. $(R)$-carvone exhibits d-values of 4.943, 4.461 & 2.951 Angstrom. $(+)-(S)$ carvone exhibits d-values of 5.347, 4.278 & 2.950 Angstrom.

*Figure 8.6.1-32* illustrates these two enantiomers. As calculated in the Jmol files of ChemSpider, the minimum energy configurations of these slightly non-planar structures differ significantly in the largest pair and the middle pair of their d-values.

The current (ca. 2015) Jmol files for the two carvone conformations are incomplete. They are both 2D files with the Z coordinates of XYZ space all equal to zero. “the resulting flat

**Figure 8.6.1-32** The most stable enantiomers of carvone reconstructed by the DS 3.5 visualizer. Their significant difference in d-values between the oxygen orbital and the double bond external to the cyclohexene ring are as calculated by the visualizer based on the 2D Jmol files. See text. The single bond at the bottom of the ring is rotatable under simpler conditions.
model will not be realistic. As a result, the visualizer used may attempt to represent the actual 3D conformation. As noted in the reference, “the result is a 3D model of the input 2D structure with a feasible conformation.” However, it may not accurately represent the actual structure! See Section 8.6.1.6.3.

The differences in values between the largest pair of d-values and the differences in values between the middle pair of d-values, presented by the DS 3.5 visualizer, can easily explain the difference in perceived odor without requiring separate chiral OR’s within the sensory apparatus, based on the hypothesis of this work.

The speaker in the Khan Academy presentation says, “the two enantiomers of carvone stimulate different receptors in the nose.” He does not say those different receptors must be chiral or must be enantiomeric to each other! In fact, they are different sensory receptor molecules associated with different OR channels capable of forming DACB with the carvones.

Thus, no role for chirality among the OR’s has been demonstrated based on the hypothesis of this work!

This discussion of chirality may indicate a method of further specifying the appropriate sensory molecule for a given OR where options are discussed in the sub-sections of Section 8.6.4. It is important when planning confirmation experiments that whether the chemicals used are racemic or have a specific optical activity should be noted.

8.6.2 Olfactory stimulant mapping leading to a hypothesis

The extremely wide range of chemicals that elicit the perception of odors in animals has made their categorization difficult. The lack of any unique monotonic perceptual scale has further complicated the problem. As a result, a wide variety of sophisticated statistical techniques have been employed in attempts to discover the fundamental properties of these chemicals that determine how they are perceived. In a nutshell, the answer is there are at least 23 determinants defining an odor. These determinants represent a wide variety of very specific molecular (and not merely geometric) structures within the field of chemistry.

Wikipedia includes a long list of chemicals and a nominal association with odor sources. Most of the associations list multiple sources for the individual chemical. The list is divided into major chemical groups (including amines) and presented in order of structural complexity. Geraniol is described as a rosy, flowery fragrance but its source is listed as geranium or lemon. These inconsistencies and the use of different names for the same chemical permeate the odor literature.

While the Wikipedia pages show a crude Fischer diagram corresponding to each of their aroma compounds classified by structure, they do not define what elements of those structures are critical to the defined aroma.

Davies provided an early odor map based on semantic descriptions of the major odors (fruity, cedar, minty, etc.). He used two likely parameters of the odor molecules, the measured cross-sectional area of the molecule and the free energy, $\Delta G$, of the molecule. The graph is rational. However, it overlooks the fact that most semantically defined odors contain a milieu of individual stimulants.

The olfactory community has had great difficulty on arriving at consistent names for even a top level categorization of odors. Breer et al. (1991, pg 102) used the top level names, fruity, floral, herbaceous and putrid.

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Acree has acted as steward of flavornet.org\textsuperscript{137}. This website provides a list of nearly 1000 substances with their CAS numbers, accumulated from many sources and using colloquial names for the perceived odorant/odorophore. It also provides a long list of odors and their potential odorants. The odor classes are not supported by detailed definitions. The odorant entries are frequently long lists of chemical names with no explanation of their specific functional role, similar to those of Kaiser for botanicals. The odor names are of little scientific value (5-oxydimethylfurfurole; perception, cardboard, crushed bug; 3-octen-2-one) except as a cross-check against similar lists. The odor label “fruit” is accompanied by at least 3 dozen chemical names. Similarly, the labels “green,” “herb,” “spice,” “sweet,” and “wood” are accompanied by about 25 chemical names. “Mint” is accompanied by about a dozen chemical names. Even “warm” appears in the list as an odor. In a separate listing, 25 odor classes are defined.

The stated focus of the site is on gas chromatography–olfactometry (GCO). It is important to note the stimulants are distributed in the gaseous phase but their olfactory performance requires they be dissolved in the mucosa. They define 25 odor classes, including “stone.” Some in the stone class appear to be associated with the large seeds of selected fruits. The lists on the site are cross-referenced in various tables.

In the perfume industry, the term top note, middle note and base note are used to describe the sensation elicited initially, after a short interval, and after about 30 minutes respectively by a stimulant. Various authors have described the effect due to the rapid evaporation of some of the odorant constituents. Alternately, the change in the dominance and longevity of an individual elicited sensation could be a complex result of the solubility of the odorants in the mucosa, and the solubility and volatility of the odorant and any solvent related to it in the stimulant. The result is a different level of adaptation in each of the OR channels stimulated, and subsequently different post stimulus adaptation profiles. A website provides a description of odors within these categories in considerable artistic detail\textsuperscript{138}.

The number of distinct odors is difficult to quantify. It is claimed that a well-trained nose can distinguish between more than 10,000 nuances of fragrance. Specialists generally speak of the “essential oils” creating various odors. Extraction of the individual essential oils frequently involves energetic processes (steam distillation) that may allow structural rearrangement before laboratory identification begins. An example could be the disrupting of the phenol ring of β-damascenone to form the straight chain geraniol. These factors suggest the sensation associated with a given odor is due to a mixture of a smaller group of unique odors. The challenge is to bound this group scientifically.

Aftelier, the perfume supplier, uses a very sophisticated fragrance wheel for teaching distributors and retail outlet employees in their commercial program. The inner ring of their wheel includes 14 segments with no obvious connection to the more common four major subdivisions. Michael Edwards, a consulting perfumer has prepared a simpler color wheel with only a casual relationship to the Aftelier fragrance wheel. Neither is based on a theoretical framework.

Doving has presented the results of several schemes at the next level of complexity. Figure 8.6.2-1 shows one based on the collected data of Wright & Michels\textsuperscript{139}. As a perspective, twenty-one odorants have been isolated from the flower. Few if any of the identified chemicals appear in this tree.

\begin{flushleft}
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\textsuperscript{138} http://www.ra2d.org/texts/youknow/perfume/families.asp
\end{flushleft}

\begin{flushleft}
\end{flushleft}
Lawless has performed a number of multidimensional studies on cheeses over the year[140]. They utilize conventional labels used in the food industry and are difficult to employ here. His plots do show tight grouping of his odors.

Carrasco & Ridout have provided multidimensional analysis data for humans based on a series of common mixtures of distinct odorants[141]. The data does not support analysis at the odorophore level.

Critchley has provided similar olfactory data to that of Kellekant using electrophysiological recording from area 13a from the caudal orbitofrontal cortex of rhesus monkeys[142]. They used the following stimulants:

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Odorants used in the olfactory discrimination task

<table>
<thead>
<tr>
<th>Odorant</th>
<th>Quality</th>
<th>Abbreviation</th>
<th>Supported in Section xxx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eugenol</td>
<td>Cloves</td>
<td>eu</td>
<td>Yes</td>
</tr>
<tr>
<td>Hexylamine</td>
<td>Rotten fish</td>
<td>hx</td>
<td></td>
</tr>
<tr>
<td>Phenylethanol</td>
<td>Floral</td>
<td>pe</td>
<td>Yes</td>
</tr>
<tr>
<td>Butyric acid</td>
<td>Putrid</td>
<td>bu</td>
<td>Yes</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Moth balls</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Caprylic acid</td>
<td>Goaty/burnt plastic</td>
<td>cp</td>
<td></td>
</tr>
<tr>
<td>Citral</td>
<td>Citrus/boiled sweets</td>
<td>ct</td>
<td></td>
</tr>
<tr>
<td>Amy1 acetate</td>
<td>Pear drops</td>
<td>aa</td>
<td></td>
</tr>
<tr>
<td>Vanillin</td>
<td>Vanilla</td>
<td>vn</td>
<td></td>
</tr>
</tbody>
</table>

The quality designations illustrate the typical differences of opinion among investigators (e.g., goaty/burnt plastic is an unusual designation). The significant number of different odorants among burnt plastics makes this a particularly poor scientific designation. Figure 8.6.2-2 shows their dendrogram for these materials. The small sample size (~38 neurons in the orbitofrontal lobe drawn from two monkeys) makes the material mostly illustrative. Except for naphthalene, the theory developed below will apply to all of these odorants, including the vanillin omitted from the dendrogram. Based on that theory, most of the odorants of Critchley & Rolls contain only a single odorophore, the ideal experimental condition. Vanillin contains several odorophores based on the theory proposed here.

![Dendrogram](image.png)

**Figure 8.6.2-2** A dendrogram of eight odorants recorded from rhesus monkeys based on 34 neurons (only 2.2% of those tested). The small number of neurons indicates the tree is illustrative but not statistically determinative. From Critchley & Rolls, 1996.

There has been a recent resurgence of activity related to multidimensional scaling in olfaction. In 2003, Mamlouk et al. applied multidimensional scaling to the data in the Aldrich Flavor and
Fragrances catalog. It contained 851 stimuli of primarily complex odors found in nature and 278 odor descriptors. Thus, their analysis was based on a database developed over a long period of time through consensus among many investigators. The analysis was totally computational-based. The descriptors are all based on behavioral experiments, typically by trained observers. The descriptors include a broad range of common names for odors described by specialists attempting to provide maximum differentiation between their labels in English (Figure 3). Mamlouk et al. used an unconventional criteria to determine the number of dimensions in their data set and concluded it contained on the order of 32 dimensions. Their graph plots the mean and standard deviation of the data set versus the number of dimensions used in the procedure on a logarithmic scale. On a linear scale, their 10% point would have occurred in the area of less than five dimensions. The number 32 is compatible with the number of glomeruli in the human anatomy but does not necessarily define the number of individual sensor channels present.

A study by Chrea et al. in 2004 shows how difficult it is to rely upon flavor and fragrance descriptors. They showed significantly different three-dimensional data sets for the same stimulants evaluated by native speakers of different languages and ethnic derivation. Their list of standardized odorant names is indecipherable by this investigator.

Wise et al. have prepared extensive dendrograms of flavors and fragrances in order to elucidate their underlying structures. Figure 3 of their paper shows the subtleties in organic structures that can lead to a variety of sophisticated fragrance descriptions, such as “compound 93 smells rosy with a ‘greener ozone-like smell with fruity top note’ and compound 94 smells like ‘rose, cinnamon, camomile spice and lilac.’” They spend considerable effort to set the perspective for their work and defining the definable in this area of research. Their dendrograms group a large number of chemicals into families with names of mixed semantic character followed by an even longer list of chemicals organized into a dendrogram with horizontal scale (and a different set of descriptive labels). They conclude, “Any given molecule will undoubtedly stimulate more than one type of receptor, perhaps several hundreds, with probabilities reminiscent of resonant circuits.” They close with a discussion of the relatively crude state of the scientific art related to olfaction.

8.6.2.1 Major structural groups involved in olfaction BRIEF

A successful theory of olfaction must be able to explain how all of the relevant chemical families stimulate the OR’s involved. These families begin with both linear and cyclic aliphatic as well as aromatic compounds. It also includes the aliphatic-aromatics, or arenes. The cyclic compounds can include both multifaceted and heterocyclic variants. Some of the multifaceted compounds involve fusion of more than two carbon positions, sometimes being described as structures with top hats. Alternately, they are frequently described as bicyclo and share three carbons between their rings. These geometry becomes quite complex.

At a fundamental level, the odorants and odorophores can be divided into three distinct sets; those based on aliphatics, those based on aromatic and those based on arenes (chemical combinations of aromatics and aliphatics). The volatility of these sets at room temperature and pressure (which is a function of their molecular weight) plays a significant role in their participation in olfaction. The arenes appear to be the most important and largest set of potential odorants. A single arene frequently exhibits multiple odorophores and can thereby contribute to very complex perceived scents. While a single arene can consist of multiple aliphatic arms associated with a single aromatic ring, such structures do not appear to play a major role in olfaction except in the case of the musks. Greater flexibility appears to be available in a single aliphatic-aromatic combination than in more complex arrangements.


8.6.2.1 Responses of non-cyclical organic homologs

Squire et al. have listed a broad set of organic families falling in this category in a pedagogical setting (page 602). However, they did not address the mechanisms used to sense these stimulants. The Mori team has presented extensive empirical material on the relative sensitivity of members of many homologous families based on action potential pulse counts. Imamura, Mataga & Mori explored several of these organic families extensively. Figure 8.6.2-3 presents their data showing the sensitivity of the olfactory system of a rabbit to the straight chain (normal or n—) carboxylic acid family as measured at a single mitral cell. Their goal was to record action potentials from the mitral cell layer of the main olfactory bulb (MOB). However, in some cases, their dye marks could only be localized to a mitral cell or a tufted cell. Therefore, their text frequently uses the expression mitral/tufted cell (MTL). The labeling should be restricted to “mitral cell.” Tufted cells are stage 2 analog signal processing neurons and do not generate action potentials.

Imamura et al. collected data at very low action potential rates, typically in the few pulses per second regime. The maximum rate of the neural system is typically in the 100-200 pulses per second regime with some specialized neurons reaching the 500 pulses/sec rate. They did achieve rates of ten pulses per second in some recordings (their figure 7).

Most of their mitral cell action potential data appears to have been collected extra-cellular, with amplitudes of a few millivolts recorded compared to peak amplitudes typically near 100 mV for intra-cellular recordings.

A profile of the proposed absorption spectra (a quantum-mechanical energy profile) of the test SSC/chemoreceptor is shown dotted.
Frame A shows the action potentials recorded at the mitral cell for n-butyric acid, (4) COOH, as a function of concentration. The few counts recorded per unit time is reflected in the vertical scale of frame B. A critical feature of this presentation is that this mitral cell did not respond to only one member of the carboxylic acid family. It responded with different pulse counts to a set of adjacent members of the family. The responses strongly suggest the response is not due to a stereochemical interaction (generally limited to a single member of the family) but to an energy range that includes the rearrangement energy associated with several members of the family. Here the term rearrangement energy refers to the energy required to excite the SSC of the chemoreceptor while the original stimulant participates in a chemical rearrangement within the molecule or in a chemical reaction resulting in a different molecule.

Figure 8.6.2-4 presents another aspect of their investigations. The responses of a set of mitral cells of a rabbit to normal fatty acids have been arranged in ascending order. "As an example, the bar shown in the 2nd row from the top indicates that they recorded 5 neurons that were activated by (2), (3) and (4) COOH but were not activated by other members of the n-fatty acids [(5)-(10) COOH]. Note that except 1 cell shown at the bottom and marked with an asterisk, all mitral cells are activated by subsets of fatty acids with equivalent ranges of hydrocarbon chain lengths." This mitral cell exhibited two independent ranges of sensitivity suggestive of a summation or a differencing in the stage 2 signal processing prior to the stage 3 mitral cell.

The responses shown in this figure do not indicate the strength of the response to the individual odors in their range.

Like the previous figure, this figure suggests individual chemoreceptor cells are sensitive to a range of rearrangement energies associated with the carboxylic acids and their SSC’s, rather than the stereochemistry of the odors.
The width of the individual bars varies because each is a function of the concentration of the stimulant applied at the SSC.

Figure 10 of Imamura et al. shows the response of a single set (of SSC/chemoreceptors to a series of both n-fatty acids and n-aldehydes. The overlap in the responses shows the sensitivity of the cells was to energy and not a specific stereo configuration of the stimulant molecule. The overlap also suggests the energy of activation of the n-fatty acid series members was very similar to the energy of activation of the n-aldehyde series. They found four cells of the set exhibited identical sensitivity to the appropriate members of both the n-fatty acid series and n-aldehyde series.

Imamura et al. examined the sensitivity to other organics, of 44 mitral cells sensitive to the n-fatty acid series. They noted, “Except for two cells (5%), none of the mitral/tufted cells showed facilitatory responses to any member of the n-alcohols. In addition, all members of the n-alkanes listed in (their) Table 2 were ineffective in activating any of the 44 MCL cells.

The n-alkane series with no oxygen ligand and the n-alcohols with only a hydroxyl ligand would be expected to exhibit a higher energy of activation than the molecules containing a carbonyl group or carboxyl group.

Imamura et al. did explore mitral cells that responded to the n-fatty acids as well as some simple n-alcohols. As might be expected, they found one cell that reacted to only (3)COOH and (4)COOH in the acid series but also responded to (3)CHO and (4)CHO. No other members of the n-fatty acids, n-aliphatic aldehydes, n-alcohols or n-alkanes they used elicited any response from this cell. This data supports the proposal that the SSC/chemoreceptors are energy sensitive, and shows the shorter chain length aldehyde family and acid family members overlap in stimulus energy.

They also showed a single cell sensitive to short acid and aldehyde molecules was also sensitive to ketones and esters of nominally the same (longer) side chain length. Their E4 ester exhibited the same peak stimulation as did their C4 n-chain stimulants. Their K4 ketone (with five carbons) showed the same nominal peak stimulation at their C4 n-chain stimulants.

Their figure 12 provides details of the spatial sensitivity of the MOB. The data allows for, but does not demonstrate, some signal...
summation/differencing by the tufted neurons prior to action potential pulse generation by the mitral cells.
Figure 8.6.2-5 provides additional confirmation of the proposition that the chemoreceptors and their associated SSC's for the carboxylic acid homologs are energy sensitive. In this figure: (IB)COOH = isobutyric acid, (IV)COOH = isovaleric acid, (MB)COOH = 2-methylbutyric acid, (Bz)COOH = benzoic acid, (PA)COOH = phenylacetic acid, (Ci)COOH = cinnamic acid, (Cr)COOH = crotonic acid.

The responses in frames A and C suggest the output of these mitral cells consist of the signals from two distinct chemoreceptor cells (although the lower set of responses in frame A might be from more than one chemoreceptor cell). Here again, the width of each set of bars suggests the responses are not due to a stereochemical controlled mechanism but to an energy controlled mechanism.

Reviewing the energy diagram for the stimulant/SSC/chemoreceptor combination in Figure xxx, it is clear that the energy associated with the stimulant that could be effectively transferred to the SSC must be greater than $E_a$ electron-volts and less than $E_b$ electron-volts. This set of limits effectively defines the range of fatty acids that can be sensed by a specific SSC/chemoreceptor combination.

This situation suggests the type of matrixing performed within either the stage 2 signal processing prior to stage 3 signal projection or the stage 4 signal processing subsequent to signal projection to a higher neural center. As an example, application of (C4)COOH or (C5)COOH would excite mitral cells A and C but not B. Alternately, application of (C6)COOH would only excite mitral cell C. This suggests a large set of SSC's in the rabbit, but not necessarily one for every individual stimulant. It would also suggest the genetic code generating a specific SSC's would not correlate with a specific stimulant.

Imamura, Mataga & Mori expanded their studies beyond the carboxylic acids in several ways. They repeated their experiments with a variety of simple aliphatic aldehydes, simple aliphatic alcohols, and simple alkanes. They incorporated limonene, a cyclic hydrocarbon similar to benzaldehyde that does not contain oxygen. It did not excite any of the mitral cells included in their report.

Their discussion section is quite extensive. Summarizing their conclusions:

- Single neurons in the dorsomedial region may respond not only to a range of carboxylic acids but also to a range of aldehydes.
For a specific mitral cell, “no member of the n-alcohol series and n-alkane series in (their) Table 2 was effective in generating an excitatory response.”

“Except for two cells (5%), none of the mitral/tufted cells showed facilitatory response to any member of the n-alcohols.”


“These results suggest that the carbonyl group of the odor molecules plays a key role in determining the tuning specificities of neurons in the fatty acid-sensitive region.”

“These results indicate that not only the primary odor molecules (n-fatty acids and n-aliphatic aldehydes) but also nonprimary odor molecules (ketones and esters) are effective in activating mitral/tufted cells in the dorsomedial region.”

Continuing to summarize, they found:

“. . . we observed a number of mitral/tufted cells in the ventral part of the MOB that were activated by subsets of n-aliphatic aldehyde and n-aliphatic alcohols. In contrast to the cells in the dorsomedial region, the majority of these cells were not activated by any member of the n-fatty acid odor molecules, so far as we have observed.”

The statements summarized above provide a powerful framework for exploring the SSC’s appropriate for use in combination with the chemoreceptor cells.

Wiberg have provided more extensive data on a series of enols (conjugated chains terminated by an oxygen on one end and a hydroxyl on the other)147. The data shows significant changes in energy and dipole moment as a function of chain length.

8.6.2.1.2 Roles of benzene, phenol and their derivatives

The olfactory modality involves sophisticated organic chemistry where the naming of compounds has long been more of an art than a science. Initially, many of the names were in some way associated with a product in the local community and associated with the local language. The goal here is to use traceable names to the greatest extent possible without the formality of using the IUPAC names. One approach is to use the designations employed in the activities of the Royal Chemical Society in assigning ascendent numbers to various molecules as they are entered into their Jmol database and illustrated in their ChemSpider HTML pages. These pages provide the complete IUPAC names of each molecule.

It is important to realize that benzene, its aldehyde and its alcohol, phenol, are all considered toxic to humans and frequently causing damage to the skin and to the internal organs when applied directly. Benzylaldehyde_235 is frequently described as a narcotic at high but less than damaging dosages. In spite of the danger from these chemicals themselves, they and their derivatives play a major role in olfaction. A myriad of chemicals with the prefixes benzyl, phenyl etc play major roles in the olfactory modality and the perfume industry.

146Johnson, B. Ong, J. & Leon, M. (2010) Glomerular activity patterns evoked by natural odor objects in the rat olfactory bulb are related to patterns evoked by major odorant components J Comp Neurol vol 518, pp 1542-1555

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The benzyl alcohol (phenol) is perceived as a sweet, acrid odor, according to the National Institute for Occupational Safety and Health. [Note: Phenol liquefies by mixing with about 8% water.]

The channel specific odorophore for this chemical is benzyl alcohol (phenol) itself. Caution: toxic at high concentrations.

The hydroxyl of simple benzene is so important, and its properties so unique, that it is given the name phenol. To this end, phenol is an aromatic ring with a hydroxyl group attached directly to it. The family of phenols becomes so large that a variety of subfamilies have developed a chemistry of their own. The methylphenols are named cresols. Phenols with two attached hydroxyl groups are called catechols and resorcinols depending on the relative positions of the hydroxyls. The presence of a carboxylic group attached directly to a phenol results in large families of specialized organic acids such as salicylic acid and hydroxybenzoic acid.

The benzyl and phenyl derivatives can be categorized coarsely by the location of a second orbital along the aliphatic chain combining with the initial benzyl or phenol. An orbital associated with the \( \alpha \), \( \beta \) or \( \gamma \), etc. carbon of the chain provides distinctly different properties to the molecule in the context of chemical sensing.

Of great interest in olfaction are a group of aliphatic-aromatic compounds, the arenes, that dominate the process of olfaction. It will be seen the physical distance between specific orbitals and the center of the electron cloud associated with the aromatic ring is a defining parameter, the d-value, in the DACB coupling of various odorophores with the olfactory receptors (OR) of the sensory neurons. The presence of a hydroxyl directly associated with the benzyl ring is not a fundamental requirement for an odorophore. As a result, it is important to recognize the benzyl ring rather than the phenol ring as the building block of most odorophores of olfaction.

In many cases, phenol derivatives involve disturbing the simple hydroxyl-phenol relationship by inserting other structures between the two moieties. There is a great tendency to continue referring to these derivatives as phenols (frequently using the adjective form phenyl- as a prefix and either -ol or -aldehyde as a suffix suggesting the presence of an oxygen atom at the end of the now aliphatic side chain. The side chains frequently include more than one oxygen atom or other orbital leading to considerable potential complexity with respect to olfaction.

The ability of the aromatic ring to provide electrons in the DACB relationship leads to the definition of a pseudo-diol as a molecule containing an aromatic ring and an oxygen atom capable of participating in a DACB relationship. Using this definition, the receptors of the OR can be defined as a family that includes pseudo-diols analogous to the family of diols forming the GR's of gustation.

The association of phenols with phosphatidyl triglycerides is not a common one. However, they are known. Brockerhoff studied them intensely during the 1960's\(^{148}\). Christie followed this early work\(^{149}\). A phosphatidyl phenol was available for purchase from Sigma in 2000. The possibility that these compounds are combined by esterification and used in vanishingly small amounts in the OR's of olfaction will be explored below.

8.6.2.1.3 Multicyclic, bicyclo, heterocyclic and other complex structures ADD

The complexity of the multicyclic compounds (with high molecular weights and limited volatility) make their applicability to olfaction limited, although some participation through mastication and retronasal sensing may be observed.


Following research into the nitro-benzoids, a separate family of non-nitro benzoids was developed. These include phantolide, tonalide, versalide and celestolide. These are totally synthetic as far as is known at this time. They involve at least one benzoid ring fused to a second typically five-sided ring. While initially described as musk-like (the purpose of their development, their one odorophore per species based on the hypothesis and corollaries of this work are all grouped around $d=3.72$ Angstrom, suggesting a floral, but not musk, scent.

A very prominent family of fused di-benzoids are naphthalene and its large number of derivatives. They nominally have the scent of mothballs. In many cases, their volatility is quite low. They exhibit one odorophore with a $d$-value near 2.661 Angstrom and probably have one or more nocentophores stimulating the nocent modality.

Another large family of important odorants involve the heterocyclic rings containing orbitals in place of one or more carbon atoms. The derivatives of these heterocyclic rings are as diverse as the all-carbon cyclic rings. The odorants exhibiting heterocyclic rings will not be explored in this work, except for cases noted elsewhere in the literature.

8.6.2.2 Analysis of the proposed “informational” framework of Beets

Beets has built on his own work and that of Amoore through the 1970's to develop his framework for understanding olfaction. While it begins with a thought experiment and is therefore largely conceptual, it does appear to play a role in preparing the foundation for the hypothesis developed here. The focus of Beet's analysis is on the range of perceived scents and not on the character of the actual odorants.

He writes in terms of the informational structure of human olfaction. By using a group consisting of both normosmias and those with specific anosmias, he is able to determine distinct groups of odorants and frequently a most significant odorant within each group. When speaking about the stage 5, cognitive function and an unexpressed concept of a saliency map, he says, "In short, the informational modality (framework) is assumed to be recognized in a complex pattern because of its spatial or spatiotemporal shape." He seems to be saying, an odorant stimulates one or more OR's depending on the odorophores present and these OR's generate a series of signals traveling by parallel paths to the saliency map where the pattern they generate is recognized (or learned) by the cognitive system and used to identify the original odorant. This constitutes a combinatorial arrangement with one pattern associated with each stimulant (odorant). From this framework, he develops several postulates:

1. A limited number of discrete informational (signaling) channels are involved in human olfaction and that all members of the human species depend upon the same set of channels for their olfactory function.

2. Stimulation of the periphery with a pure-i.e., structurally, configurationally, and chirally homogeneous-stimulant produces a complex pattern of information in which several or many modalities are represented on(by) various levels of intensity.

He says two symptoms are indicative of the existence of an informational framework, the frequent occurrence of a group of semantically similar descriptors in reports of odor evaluations and the occurrence of specific anosmia.

His logic cannot be developed further because his concept of structure does not include the concept of DACB coupling developed by the Shallenberger team and Kier in the context of gustation (Section 8.5.xxx). However, his concept is clearly compatible with a limited number of OR's and a combinatorial signal processing mechanism leading to a pattern presented to the cognitive stage for interpretation. That pattern involves individual signals with an intensity value associated with them.

Beets goes on to discuss stimulants of different order of effectiveness. He describes three broad categories of stimulants; "first, the term primary character is used for odors in which a single modality

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predominates strongly (a stimulant containing a single odorophore), the term compound character consists of a stimulant in which a few or even many modalities (odorophores) of which none clearly predominates, and the term background character refers to high informational complexity of odors in which most modalities (odorants or odorophores?) are represented in generally low intensities.” The words in parentheses have been added to show similarity to this work. He notes, “the compound character of an odor is said to be simple if the number of modalities (odorophores) is small and complex when it is high.” He does not go farther and define the transition value. Here simple is one odorophore and complex may include as many as (but seldom more than) a dozen odorophores within one odorant. As noted in connection with the VNO, some stimulants may contain both odorophores affecting the olfactory modality and vodorophores affecting the oskonyatory modality (Section 8.6.11.4).

Beets did note (page 103) the potential for an odorophore to exhibit a dipole potential of opposite polarity to that of an isomeric relative, thereby generating a different signal intensity at the output of a given OR.

The concepts expressed by Beets can be easily extended/expanded to be compatible with the more detailed framework provided in Section 8.6.2.8 and summarized earlier in Section 8.6.1.6.

In 1983, Meredith subscribed to a similar concept (page 202), “The olfactory system seems capable of responding to almost all molecules that can reach its receptors, including newly synthesized molecules that have never before been experienced. This all-embracing sensitivity argues that the main olfactory system exists as a general molecular analyzer rather than as a specific detector for particular chemical signals.”

8.6.2.3 Analysis of the 2008 Kreher et al. dendrogram

Kreher et al. have provided a conventional multidimensional analysis based on specific chemicals of multiple structural forms, as stimulants and both larval and adult forms of Drosophila as subjects. Unfortunately, their range of structural forms was limited and contained many complex chemicals that could stimulate multiple olfactory channels. They assert that they analyzed the full repertoire of olfactory sensors of Drosophila. Their conclusion surprised them somewhat: they concluded that five, at most six, receptors could account for the sensations elicited by over 80% of their stimulant set. They also showed that most of their stimulants elicited narrowband responses when measured by the action potential rates plotted against a continually changing order of stimulants chosen to produce smooth response functions. Their response indices showed both positive and negative values suggesting both summation and differencing within the stage 2 signal processing prior to stage 3 encoding. They generated an equation for their Response Index (RI) that except for two negative terms looked much like the visibility function of the vision modality. They described RI as involving a sum of individual responses of the form $aR_1 + bR_2 + cR_3 + \ldots$ and used a regression analysis program from SAS.

They identified their five most important genes leading to their five most important receptors as Or42a, Or45a, Or74a, Or82a and Or85c. At their high stimulus intensity level described as a 10^-2 dilution level, this set did not respond at all to their one organic alcohol. This finding could be appropriate. Pure alcohols do not stimulate the olfactory modality. The set appears to have responded poorly to their one terpene, their one aldehyde, and their group of aromatics. It responded strongly to their esters and alcohols. At a 10^-4 dilution level (apparently near threshold conditions), their data shows a different set of potentially primary receptors focused on Or7a, Or13a, Or24a, Or35a, Or42a, Or47a & Or85c.

While highly instructive, their data does not provide information relating to the human or higher mammalian olfactory system. It does suggest a smaller set of olfactory dimensions than Mamlouk.


et al. It does allow the construction of an initial response versus d-value graph parallel to that for gustation (Section 8.5.xxx).

8.6.2.3.1 The Kreher et al. olfactory dendrogram with overlay

Figure 8.6.2-6 shows the dendrogram provided by Kreher et al. in 2008 with additional annotation. The table on the right displays the multiple d-values for these chemicals as defined in Section 8.6.xxx.

All of the acetates exhibit precisely the same first order olfactophores based on the Electrolytic Theory of the Neuron implemented here. They should be grouped together. Isoamyl acetate is also known as isopentyl acetate. They both have the IUPAC name of simply pentyl acetate (C\textsubscript{7}H\textsubscript{14}O). Isoamyl acetate and pentyl acetate should occur at only one location in a dendrogram from a larger subject group. 2-heptanone is also known as methyl acetate, or methyl n-amyl ketone, with the molecular formula C\textsubscript{7}H\textsubscript{14}O. The geranyl acetate (C\textsubscript{10}H\textsubscript{16}O) has a conjugated structure that may result in additional olfactophores. The root structure is the carbonyl group that imparts a fruity sensation. Acetone, the simplest member of this family, elicits a fruity sensation (Rossiter, 1996).

The carbonyl group can be present at the end of a chain as an aldehyde, or in the middle of a chain as a ketone.

Cyclohexanone is a saturated six-membering except at the position supporting a ketone (carboxyl) group. Like the other ketones above, it exhibits an odor reminiscent of peardrop sweets and acetone. Acetone was unfortunately omitted from the stimulant set of Kreher et al. The acetone sensation is obviously due to its d = 1.22 carboxylophore which it shares with the other acetates above. Carbon dioxide is a nonpolar molecule exhibiting two carbonyl groups. In solution, it exhibits d = 1.22. The presence of two carbonyls may influence the intensity of its sweetness as an odor. It is suggested at this point that a d-value of 1.22 can be considered definitive for the basic “fruity” sensation (at least for the simpler stimulants).

The acetates exhibit two olfactophores, with d = 1.22 and d = 2.3\textsubscript{A} Angstrom. This combination of olfactophores is most closely associated with the stimulant, banana oil, but is also associated with several other fruit. It is suggested that this combination of d-values can be considered definitive for the sensation associated with banana oil, a subset of the fruity class.

Geranyl acetate is a carboxylic ester (d = 1.22 & 2.3) with a partially conjugated side chain. This feature may distort the intrinsic d-values. It is typically associated with a lemon or citrus sensation, a subset of the fruity class.

2,3 butanedione is a trans-di-carboxyl exhibiting both a carboxylophore (d = 1.22) and a dioneophore with d = 3.61. It is also labeled a vicinal di-ketone. The suffix-“dione” is indicative of a diketone. It is commonly the result of fermentation (associated with alcoholic beverages) and gives butter its characteristic flavor. It is frequently used in combination with acetoine (acetyl methyl carbinol, C\textsubscript{4}H\textsubscript{8}O\textsubscript{2}) in the preparation of the food product, margarine. It is suggested that this combination of d-values can be considered definitive for the sensation associated with butter, a subset of the fruity class.

Methyl salicylate exhibits three d-values, 1.22, 2.3 & 1.43 due to a hydroxol group and the two arms of a carboxylic ester. This chemical is definitive of the “mint” sensation, typically associated with oil of wintergreen--its trivial name. It is also a subset of the fruity class.

Propionic acid is the only simple carboxylic acid in the test set. It should exhibit only a resonant carboxylophore at d = 2.07. This chemical appears to be the first member of a large family of chemicals generally described as eliciting a rancid or pungent (alternately putrid) sensation. It is suggested that a d = 2.07 can be considered definitive for a “pungent” sensation.
Methyl eugenol is a ring structure with two C–O bonds, one is a simple hydroxyl group, the other is associated with a methyl group. These bonds would give \( d = 1.43 \) if not distorted by the methyl group. There may be an additional d-value associated with the oxygen atoms and the ring as a whole. It is typically associated with clove oil, a subset of the fruity class.

Breer et al. have associated methyl eugenol with the “herbaceous” categorization.

The alcohols all exhibit a single d-value of \( d = 2.7 \) due to their associated character when in solution. These chemicals are virtually odorless. This is a distinctly different situation than if they were considered to have a d-value of 1.43 that would be associated with a single C–O bond. Such a low d-value would suggest a pungent sensation.

No chemical in the Kreher stimulant set can be associated with the “floral” sensation. It is likely more complex chemical structures are required to elicit this sensation.

As a preliminary suggestion, it is suggested that d-values above 4.0 are not associated with individual olfactory sensations.

The above category definitions are compatible with a majority of the chemicals Laffort associated with the designations: fruity herbaceous and putrid (with exceptions involving the more complex chemicals that will be addressed later). Only one of Kreher’s chemicals fall into the floral category of Laffort, acetophenone.
All of the alcohols are involved in coordinate bonding with other alcohol or water molecules when in solution at $10^{-2}$ dilution. The bond arrangement is $O-H-O$ with $d = 2.7$ Angstrom. Molecules in this arrangement are known as associated liquids. This designation has a different meaning in the chemical laboratory and the oil industry (see Glossary). Mixing alcohol and water frequently creates a more slippery fluid. The coordinate mixture may be similar to the invert form of oil and water (which forms a remarkably effective lubricant).

The alcohols may also exhibit a C–O linkage with a $d = 1.43$ Angstrom (not shown in the figure) while the C=O linkage of the aldehyde, E2-hexenal may also show a linkage with a $d = 1.22$ Angstrom. This difference in the carbon-oxygen linkage would clearly separate the sensations generated by alcohols versus aldehydes. The alcohols do not have a clearly distinctive odor. Ethyl alcohol is characterized in the Merck Index as a pleasant odor and burning taste (an indication of a noxious chemical). Propyl alcohol is described as a stupefying odor.

The aromatics, shown in light blue are a mixed bag of cyclic chemicals. Two, acetophenone (ACP) and methyl salicylate, are aromatics with a simple side chains. Acetophenone has only a carbonyl group as an olfactophore. $d = 1.22$ Angstrom for this group. It elicits a sensation described as...
almond. Methyl salicylate exhibits a carboxylic ester giving it olfactophores with $d = 1.22$ and 2.3 Angstrom. It also exhibits a hydroxyl group attached directly to the ring, with a $d = 1.43$ Angstrom. It elicits a sensation associated with oil of wintergreen.

2-methylphenol (o-cresol) and 4-methylphenol (p-cresol) are both considered to have a mild smell of coal tar. They are not used in perfumery. They both exhibit a simple hydroxyl attached directly to the aromatic ring with a methyl group at the appropriate vicinal (adjacent) or opposing position. Their basic olfactophore is the C–O bond with $d = 1.43$.

Anisole and methyl eugenol both exhibit a short side chain consisting of an –O–CH$_3$ attached directly to the aromatic ring. This structure is an aromatic ether. Anisole thus has a $d = 1.43$ Angstrom. It elicits the sensation associated with the anise seed (a relatively equivocal term since the anise is a large botanical family). Methyl eugenol exhibits the same –O–CH$_3$ group attached directly to the aromatic ring and an additional hydroxyl at an adjacent position. It exhibits two first order $d$-values of $d = 1.43$ Angstrom. Both may exhibit other $d$-values related to the relationship of the oxygen to the ring structure as a group. It elicits the sensation associated with clove oil.

Benzaldehyde has a CHO group attached to a carbon of the aromatic ring. In the first order, $d = 1.22$ Angstrom. The material elicits a sensation associated with almonds.

The potential interaction of the oxygen atom with the resonant cyclic ring in these aromatic structures has not been explored. Such interaction may cause additional olfactophore structures with larger $d$-values contributing to the subtler aspects of the sensation they elicit. The radius of a six-carbon aromatic ring is nominally 1.39 Angstrom. The position of methyl groups attached to the ring can also change the electronic properties of the molecules (Morrison & Boyd, 2nd, pg 803).

In order to achieve solubility, virtually all of the aromatics (phenols) described here form hydrogen bonds with water. All of these bonds have a first order length between the oxygen atoms of the hydrogen bond of $d = 2.7$ Angstrom. These bond lengths are not currently shown in the figure.

8.6.2.3.2 The odorophores of insect species from Kreher et al.

As noted in the introductory paragraph on olfaction, there may be a connection between the olfactory modality in insects and in animals, and the response of both modalities to the excretions of plants. However, the similarities and differences between these functional capabilities have not been delineated to any significant degree.

The paper by Kreher et al. described their interpretation of the olfactory modality of insects from their perspective. Their investigations were behavioral. They initially noted they were dealing with “the olfactory system of Drosophila larva, which is morphologically and developmentally distinct from that of the adult.” They noted under the heading Conservation of Odor Space:

“The larval olfactory organ and the adult antenna have different developmental origins and markedly different morphology. They operate primarily in different milieu: larva burrow in food sources, whereas adults fly to food source and walk upon them.”

From their initial description, it appears the “larval dorsal organ, a dome of cuticle at the anterior end of the larva that is perforated by pores through which odors can pass” may be more similar to the organ of animals than the antenna structures in mature insects.

Their data has been considered in the development of the theory of olfaction presented here. This involved recognition that their stage 3 pulse rate measurements did not involve measurements at the actual axons of the sensory neurons.

Kreher et al. asserted that, “Of the 60 odor receptor genes of Drosophila, a subset was found to be expressed in the larva and 11 of these were demonstrated to encode functional odor receptors.”

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Thus, the number of genes did not correlate with the number of sensory receptors as expected based on this work. They employed the "empty neuron" laboratory approach wherein, "an in vivo expression system based on a mutant ORN (odor receptor neuron) of the fly that lacks an endogenous receptor. Based on their electrophysiology approach, they asserted that "the 11 identified genes represented less than half of the total larval odor receptor repertoire, however." Expression studies by others have shown that 25 (of the 60 genes) are expressed in the larval olfactory system and approximately half of these genes are also expressed in the adult olfactory organs.

Kreher et al. performed their tests using 26 diverse odorants, each examined at two concentrations, and CO₂. The conventional chemical families of the odorants were identified but no discussion of the effective structures associated with these odorants was provided. There was no effort to distinguish between odorants containing more than one odorophore. Their results were explored using "a 21-dimensional odor space." Their analytical results were well documented and displayed but as usual in this kind of analyses, the chemicals associated with various chemical families did not group together in the response histograms. They did provide a number of MDS analyses that provided relative Euclidian distances and angular distances between their odorant-pairs. These results were illustrated using conventional stick-diagrams for each chemical. However, their distances and angles did not relate to the 2D or 3D physical distances between atoms in the molecules but to the distances and angles derived from their 21-dimensional MDS presentations reduced to 3-dimensional presentations. These distances and angles represented the differences in spike rates measured in their electrophysiological records at dilutions of 10⁻² concentration (as described in their Experimental Procedures).

As shown in Figure 8.6.2-7, their Euclidian distances and Angles did not relate to the geometry of the chemical structures at all. Their angles do not relate to angles within their MDS spaces. In A, the values of $x_i$ and $y_i$ are pulse rates of each odorant for the $i$th receptor measured along a stage 3 neuron. In B, the symbols represent the normalized unit lengths defined in A. The use of the $\cos^{-1}$ conversion represents a non-linearization of the function and does not relate to the conventional calculation of an angle based on the sides of a triangle.

While an excellent and well documented study, their results provide little information on the mechanisms underlying the olfactory modality of insects. From their odor space results (figure 4), it is clear that the structure underlying the sensing of the acetates, butyrates and diones involved the underlying carbonophore and carboxylophore structures proposed in this work (Section 8.6.2.5) with a d-value of 2.7 Angstrom in a physical 3D space.

8.6.2.4 A simple floral categorization of elicited sensations

The d-values of the chemicals reported as fruity, herbaceous and pungent (putrid) appear to be easily calculated and classify those chemicals reasonably well into discreet bins. The florals appear more complex because they typically contain a cyclic ring, which may or may not be resonant. Kreher et al. included three cyclic ketones (carbonyls) in their data set.

Acetophenone is a complex aromatic carbonyl (ketone) that is generally associated with the odor of xoo (which is typically a fruit), but also cherry, honeysuckle, jasmine, and strawberry.

The odors associated with honeysuckle and jasmine are particularly effective at a long distance relative to almond and cherry. This difference may suggest a significant difference in their structure associated with higher volatility.
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Because of Wikipedia, etc., the statement that acetophenone is the simplest aromatic ketone appears frequently in the literature. It can be compared to the simplest cyclic ketone, cyclohexanone.

Cyclohexanone elicits a sensation related to peadrop sweets as well as acetone. Thus, cyclohexanone is the simplest cyclic ketone and acetophenone is the simplest aromatic (cyclic) ketone of interest in olfaction. The parent acyclic form is acetone. The parentage suggests the cyclic ketones are the foundation of the floral category of elicited sensations. Their d-values, beyond that of the carbonyl, are of considerable interest here.

Fenchone is a very complex chemical based on a highly modified monoterpene structure (including a top hat) with a single carbonyl group. It is reported to have an overall odor like camphore.

Looking first at the better studied resonant cyclic structure, phenol (ArOH) is considered fairly acid and minimally soluble in water at room temperatures (9.3g/100g @ 25°C). More complex structures within the family are even less soluble. To the extent they dissolve in water, the phenols ionize to form soluble anions. The phenols ($K_a \sim 10^{-10}$) are much more acidic than the alcohols but less acidic than the carboxylic acids.

The structure of interest here is the ion (ArO$^-$). By itself, this structure exhibits a carbonyl oxygen. The oxygen is associated with a negative potential and the ring is also associated with a negative dipole potential (resulting in a net dipole moment if the potential values are different). The Kolbe reaction describes how this polar material interacts with the polar CO$_2$ to form salicylic acid (o-hydroxybenzoic acid).

Among the aromatic structures of interest, there appears to be a significant division between the esters and ethers. The simplest ether, anisole, has a nominal C–O bond length of 1.43 Ångstrom and an additional potential d-value marginally greater than 1.43 but less than the C–O bond length plus the radius of the Ar ring, 1.39 Ångstrom, or 2.42 Ångstrom maximum.

The simplest ester, acetophenone has a carboxyl group bond length of 1.22 Ångstrom and a potential second d-value of the distance from the oxygen to the effective center of the aromatic ring (nominally $1.53 + 1.22 \cos 60 + 1.39 = 3.53$ Ångstrom maximum.

### 8.6.2.4.1 Analysis of more complex floral structures

[xxx rationalize the Rossiter material further chg title to “more complex floral structures”.

Rossiter has presented a variety of structures that have a significant rose odor. They are drastically different from those presented by Wise et al.

Figure 3 of Cheng et al. illustrates that subtle stereographic changes in a complex molecule can have significant effects on the perceived odor$^{154}$. The changes are similar to those shown in formulas for Syn- and Anti-anisaldehyde oxime in taste as described by Shellenberger. The Cheng et al. paper is analyzed in Section 8.6.2.10.2.

### 8.6.2.4.2 Concordance between hypothesis and the Kafka papers

Kafka presented an extensive study during the early 1970’s on the sensitivity of the chemical sensors of the migratory locust, locusta migratoria$^{155}$. Excellent data was provided of both a qualitative and quantitative nature. However, it was limited by the instrumentation of that day and the histology

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The summary and briefer paper of 1971 are very supportive of this work although in many cases the terminology was appropriate for the time period but archaic now. The conclusions drawn in the 1971 paper can easily be interpreted as applying to the DACB concept and the "overlay groups" of this work. He notes that "covalent bindings are not involved in the transducer mechanism for these odor molecules." When discussing the interaction between stimulant and OR, he describes "Dipole interactions mostly occur by mutual alignment of the interacting partners." He also notes, "Hydrogen bonds could be involved in this binding process..." He even speculates on the role of the carbonyl group acting as a proton "acceptor", or the hydroxy group as a proton "donor." [His bold-face text.] He also notes the fact that stereoisomers need not elicit similar responses.

His results were restricted by the confabulation in the data due to the use of multiple odorophore odorants rather than SOO's.

Kafka has prepared maps showing the relative selectivity of individual olfactory sensory neurons to large numbers (~370) of related chemicals. A feature of the material is its focus on individual chemical families and how they stimulate a selected neural sensory receptor. The summary notes, he investigated two distinct olfactory channels associated with a single olfactory pit (and there were apparently only two distinct olfactory receptor types in each pit of locusta migratoria).

1. Kafka employed 370 different chemical stimulants.
2. The precision of the stimulus was determined with an accuracy of 25% (0.4 log units)
3. The cells reacted either to oxygen-organic (reaction group 1), or to nitrogen-organic compounds (reaction group 2) with increased impulse frequency (reaction quantity). Cells of both types were found side by side in one pit organ.
4. With a proper choice of stimulus quality and quantity it was possible to elicit similar cell reactions.
5. The average stimulus quantity (No) necessary to produce a reaction of 30 impulses/second was determined for (only) cells of reaction group 1.
6. Compound which excite cells on one reaction group often inhibit those of the other reaction group. Unbranched amines with a chain-length of 4 C-atoms showed the strongest inhibitory effect on cells of reaction group 1.
7. From simultaneous recordings of the reactions of neighboring cells it was concluded that: The locus of the specificity, and therefore also of the interacting partners (acceptors) is the membrane region of the dendrite.
8. From the determination of the threshold values it was concluded that the cell's excitation is triggered by single molecular effects and not by mass effects. The properties of single molecules must therefore be considered to describe the specificity.
9. From the effectiveness of compounds which were systematically altered in constitution and configuration it was concluded that the properties necessary to interpret the specificity are of sub-molecular order. The steric conformation of the odor molecule is of secondary importance for the specificity.
10. (This comment employed terminology that can lead to confusion at the present time).

The presence of only two types of OR in a single pit suggests the two OR's were an organic acid sensitive channel (nominally OR 1) and a second dulcal channel (nominally OR 2). He noted that one channel was sensitive to acetates and the other channel was sensitive to amines. These two channels by analogy with mammals are able to support the locating of organic foods associated with both fresh and decaying plant matter.
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The sketch of the “olfactory pit” of the migrating locust in Figure 8.6.2-8 looks very similar to the gustatory taste bud of mammals (Section 8.5.1). As Kafka noted, a single pit appears to contain receptors for different signaling channels of olfaction. However, the similarity does raise the question as to whether the olfactory pit is in fact a gustatory pit in analogy to the mammalian histology. The mammalian olfactory epithelium does not appear to support a “pit” configuration and the individual sensory receptors appear to be located in isolation (Section 8.6.1.3). Kafka did not indicate precisely where his analog signals were measured or where his pulse signals (See Section 8.6.7.3) were recorded relative to the neural circuitry within the olfactory pit. He did cite the earlier electron microscope work of Steinbrecht. Potential sites for the intracellular analog probing of the stage 1 sensory axon and the intra- or inter-cellular probing of the stage 3 signal projection neuron(s) are shown. The area marked by parallel lines by Kafka is the potential site of stage 2 matrixing that could create both summing and differing signaling channels.

Steinbrecht quoted earlier research, “Axons of adjacent sensory cells—for example, of multineuron sense organs or groups of campaniform sensilla—may anastomose and form one axon, at least in insects. In the meantime, high resolution electron microscopy revealed the widespread occurrence of extremely thin axons, thus warning against the general acceptance of the axon fusion hypothesis. In sensory nerves of the cat and the pike, Gasser (1955,1956) observed neurites of 0.2 μ diameter, which of course are invisible with the light microscope.” and then asserts “In the two nerves studied, each antennal sense cell is individually connected with the brain by its own axon.”

To add precision to the literature, Steinbrecht noted, “While the present study was in progress, two of the above quoted claims of axon fusion (Rowell, 1961; Stiirckow, 1962) have been corrected by their authors. In electron micrographs of the nerves in question enough axons have now been observed to account for all the sensilla, most of them measuring less than 1 μ in diameter (Rowell, 1964; Stiirckow, Adams & Wilcox, 1967).”

The Steinbrecht paper is quite detailed. It notes, “All axons are of the non-myelinated type. The thicker fibres (diameter > 0.5 μ) are each ensheathed by glia cell processes which form envelopes of one or few loosely wrapped layers. The thin fibres are packed in bundles of 10—100 naked axons with a common glial sheath. The naked axons are separated only by the extracellular gap. There are no glial membranes between them.” This is a common method of pseudo-myelinating projection neurons within the mammalian cerebrum (Section 10.10.1). The pseudo-myelination by oligodendrocytes can increase the pulse train velocity along the neuron dramatically.

[xxx critically important paragraph]
The Steinbrecht paper also notes a critically important fact. “A special class of fused axons are the so-called multicellular giant fibres: many cell bodies contribute to the cytoplasm of one giant axon by fusion of their processes. The cell bodies may be distributed over the whole length or situated at one end of the giant axon. The former situation is the rule in ventral cord giant fibres of annelids (Stough, 1926; Nicol, 1948a) and crustaceans (Johnson, 1924; Holmes, 1942); . . . .” These multicellular fibres are the special fibers of locomotion found among many species and were the source of the giant fibers used by Hodgkin & Huxley to explore the electrical properties of the neuron during the 1940’s. As noted in Section xxx, Hodgkin & Huxley made a variety of what are now known to be protocol errors that led them to a variety of interpretive concepts that are not sustainable. Their theory of the neuron is falsified because of these problems. See Section xxx for a complete review of this situation.

Figure 8.6.2-9 shows one of his maps focused on stimulation of a single olfactory receptor by hexanoic acid_8552 and a wide variety of its aliphatic derivatives. The molecules bounded by the darkest box are all unsaturated carboxylic acids derived from hexanoic acid; From the top, they are (2E)-2-hexenoic acid_445834, (3E)-3-hexenoic acid_445835 and 2-oxohexanoic acid_140384.
The molecules within the heaviest box all include the proposed OR 1 (acidic) channel stimulating odorophore with $d=2.076$ Angstrom (as do all of the other molecules in that vertical column). The molecules within the next heaviest horizontal box all include the proposed OR 2 (dulcal) stimulating odorophore with $d=2.703$ Angstrom. The precision of the $N_0$ values is 0.4 log units. See text. From Kafka, 1971.

The molecules within the heaviest box all include multiple odorophores, including the odorophore with $d=2.076$ Angstrom, stimulating the proposed OR 1 (acidic) channel. The moderately and very active boxes in the vertical column only exhibit a single odorophore stimulating the proposed OR 1 channel with a $d$-value of 2.069, 3.232 & 4.063 Angstrom as well as the azeotropic value of 2.703 Angstrom.

The molecules within the next heaviest horizontal box all include the proposed OR 2 (dulcal) stimulating odorophore with $d=2.703$ Angstrom. The molecule at the intersection of the row with $d=2.709$ Angstrom and the column with $d=2.076$ Angstrom, (E)-3-hexenoic acid 445835, appears to stimulate both the OR 1 and OR 2 channels with $d$-values of 2.069, 3.232 & 4.063 Angstrom as well as the azeotropic value of 2.703 Angstrom.

The above figure provides a good qualitative perspective on the OR used in the investigation. However, more quantitative data is needed to draw conclusions about the effectivity profile(s) of the OR(s). The bracketing of the molecules by Kafka has been described more completely by adding the level of stimulation from his Table 1, described by the calculated parameter ($N_0$) to the upper left of the figure. $N_0$ describes the number of molecules required to enter the olfactory pit during the nominal stimulus interval through the aperture of the pit (described by Kafka as 15 square microns) in order to achieve a pulse rate of 30 pulses/second at the stage 3 signal projection neuron. This is a crude calculation at best because the response is not conformal to the stimulus interval.
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*(Section 8.6.7.3.7)*. Kafka optimistically attributes a precision of 25% (0.4 log units) to these calculations.

Using his calculated values for $N_0$, it is important to note that only three molecules stimulate his OR to the 30 pulse per second criteria, with all others being only 10%, 1%, 0.1% or less effective. It is also important to note that each of his most important stimulants exhibited multiple odorophores based on the hypothesis of this work. This situation illustrates the necessity of comparing these intensities with the effectiveness of the proposed OR's using a logarithmic presentation. It also suggests the critical need to employ single odorophore odorants, SOO, that do not form azeotropes in future stimulation experiments.

In the absence of the exclusive use of SOO stimulants, attempts to define the effectivity profile of a specific OR type are needlessly confounded by the number of odorophores present.

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By plotting the d-values for the molecules within the heaviest box as in Figure 8.6.2-10, some idea of the effectivity of the sensory receptor of the migratory locust used in these experiments compared to the proposed OR 1 and OR 2 channel receptors can be obtained. If the effectivity of the sensory receptor of the migratory locust was much wider than ±5% of the central value of its distribution, it is possible that the OR might have a central value near 2.791 Ångstrom (equivalent to a widened version of the proposed OR 2).

All of the molecules included in the bottom dashed box include either the odorophore with a d-value of approximately 2.076 or 2.703 Ångstrom and are thus able to stimulate either the widened OR 1 or the widened OR 2 channel. It is not clear, based on this work, why the hexanedioic acid (a.k.a adipic acid 191) is excluded from the bottom dashed box. More analysis is needed. Its exclusion can be understood if the odorant is self-suppressing (inhibiting) within the stage 3 channel being interrogated. That is if the stage 3 pulse data was collected from an OR1 minus OR 2 differencing channel (stage 2) because of its combination of odorophores.

The odorophores of hydroxyhexanoic acid 90191, shown at the top of the central column, exhibits the same nominal d-values (2.073, 2.812 & 3.315 Ångstrom) as the molecules in the heaviest box. It is not obvious why Kafka indicates this molecule did not stimulate his OR. It should be about as effective as both of the molecules below it, 2-methylhexanoic acid 19450 and hexanoic acid 8552.
All of the molecules included in the azeotrope box exhibit a d-value near 2.709 Angstrom along with other odorophores. This fact would suggest that the OR of the migrating locust was near OR 2 to the exclusion of stimulation by the three primary odorophores. The fact that hexanoic acid_8552 was very effective in stimulating the OR appears significant. This molecule exhibits the d-value of a saturated carboxylic acid, d=2.073 Angstrom. This value would suggest that the migratory locust OR under study was equivalent to the proposed OR 1 of this work. However, if the acid is converted to an azeotrope in solution as asserted here, it would also exhibit a second d-value at 2.703 Angstrom that could also stimulate the OR 2 or either of these channels if their effectivity profiles were wider.

The English language paper by Kafka discussed the magnitude of the differences between his boxes in his Table 1. The differences required to elicit a pulse rate of 30 impulses/second were in powers...
of ten (logarithmic) with those causing only slight response having \( N_0 \) values in the \( 10^7 \) to \( 10^{10} \) range and those not effective in the \( >10^{10} \) range. When the \( d \)-values of his molecules are plotted in the above figure, the question arises as to whether the effectivity scale should be linear (as drawn) or logarithmic. His figure reviewed in Section 8.6.7.3 would suggest the choice of a logarithmic scale may be preferred. It also suggests his boxing in the earlier figure was based on logarithmic differences rather than algebraic differences.

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This work does not support his description of “inhibiting” with reference to the stage 1 neural sensory receptor(s). However, if there was a stage 2 differencing circuit prior to where he measured either the analog or pulse circuits to assemble his figure, the results are consistent with this work. Such nodes are present in the mammalian gustatory taste bud but apparently not in the channels of the olfactory modality prior to the glomeruli.

The two amines shown in the upper right box of Kafka’s map, (±)-sec-butylamine_23255 and n-butylamine_7716 when present as azeotropes exhibit \( d \)-values of 3.14 Angstrom and thus stimulate the OR 2 channel. To be effective in inhibiting the stimulation of the OR 1 channel, a stage 2 differencing circuit subtracting the OR 2 signal from the OR 1 signal received from the stage 2 sensory neurons. n-hexylamine_7811, shown directly below n-butylamine_7716 when hydrated should exhibit the same \( d \)-value of 3.14 Angstrom and affect the OR 2 channel in the same way.

Kafka present a set of histograms showing the relative performance of homologous members of a given chemical family in figure 4. However, they are limited in utility by their portrayal as a function of carbon number and the tremendous compression of the logarithmic ordinate. The number of carbon atoms in a molecule plays essentially no role in olfaction. The generally much smaller number of carbon atoms contributing to the spatial relationship between the orbitals in an overlay group is of much greater importance.

A program designed to repeat Kafka’s protocol using non azeotrope forming SOO stimuli (and a much more careful interpretation of the stage 3 responses to those stimuli versus time, could provide much more precise descriptions of the effectivity profiles of the sensory receptors of insects and mammals. Relying upon the hypothesis of this work, a much narrower list of stimulants could be employed, with only a few carefully selected outlier SOO’s to demonstrate the adequacy of the hypothesis.

The use of azeotrope forming molecules among the selected outliers could provide valuable markers along the \( d \)-value dimension for calibration purposes.

### 8.6.2.5 Adoption of the AH,B concept to carbohydrate olfaction EXPAND

The AH,B, and potentially the AH,B,X concepts discussed above offer a clear explanation of the phenomenon of olfaction. The challenge is to organize the odorophores into functional groups that identify their underlying mechanism of operation. More than a dozen, out of an estimated two dozen, chemical structures have been identified as parent or fundamental odorophores.
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These fall into the following commonly identified and major chemical classes:

1. aliphatics,
   & citrus aliphatics (generally planar with a CH(CH3)2 terminal structure)
2. aromatics,
3. arenes (aliphatic-aromatics),
   & true phenols (frequently associated with flowers-OH attached to the benzene ring)
   & pseudo-phenols (inserting an aliphatic chain between the benzene ring and the OH
   & conjugated aliphatic aromatics
   & ether and ketones forming the aliphatic structures
   & very complex molecules combining the above structures.
4. fused ring structures;
5. amine variants of these classes, and
6. nitro variants of some of these classes

While these class designations are useful for identification, particularly at the odorant level, they do not suggest the actual structure of the ligands forming the odorophores of olfaction. These ligands frequently represent an “overlay” chemical structure independent of the commonly identified moieties.

By examining these classes in the context of the theory of gustation already presented, a useful theory of the olfaction modality can be obtained (including any extensions of the theory required by the special circumstances involving the more complex volatile chemicals.

Because of the rapidly expanding complexity of the above structures, it is common to find multiple odorophores within the structure of a single odorant molecule. Some of the odorophores have no logical connection to any of the commonly recognized moieties forming the odorant. They relate only to structural features created within the odorants.

A unique feature of the hydroxyl group was highlighted by DuBois et al. The hydroxyl group can act as either the AH or the B element in the AH,B coordinate chemical bond. A single hydroxyl group can act as either a hydrogen bond donor (via the hydrogen atom) or acceptor (via the unpaired electrons of the oxygen atom). Thus two hydroxyl groups of a molecule can provide both the AH structure and the B structure, as they frequently do in the sugars.

The aromatics and their variants introduce the π-cloud of the benzene ring as a source of paired electrons that can participate in a coordinate bond AH,B relationship. The clearest example of this relationship is found in the chemical, ferrocene where a single iron atom is coordinately bonded to two benzene rings via the π-cloud rather than a specific hydrogen or carbon atom.

The citrals and their variants introduce the π-cloud of a pair of double bonded carbons as a source of paired electrons that can also participate in a coordinate bond AH,B relationship.

The fused-ring structures introduce additional flexibility into the π-cloud concept that will not be explored here.

While the electrons form a cloud that is clearly displaced from the plane of the atoms of the aromatic rings, this has not been considered in the calculations of bond lengths related to the aromatic rings. The center of the electronic field of the cloud will be considered co-located with

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the centroid of the atoms forming the aromatic ring based on their atomic weights.

Frequently, only the hydrated or dimer forms of commonly defined chemical structures are effective as odorophores. Thus, their textbook chemical description may be misleading.

An arene has frequently been described using as many as five different names. An attempt will be made to use names here that reflect the critical structure of the odorophore as simply as possible. This may involve using some apparently unconventional names that differ from the recommended IUPAC names. However, graphics will be used to ensure clarity of the concept.

### 8.6.2.5.1 AH,B values for the aliphatic odorophores

Three major chemical classes of aliphatic odorophores have been identified. They all involve a carbonyl oxygen atom, simple aldehydes, vicinal di-carbonyls and the esters. These structures are generally planar in the vicinity of the odorophore making calculation of the distance, the d-value or valence, between the active elements straightforward.

In theory, a carbonyl oxygen and its associated carbon are so polar that they can participate in a coordinate bond pairing with a d-value or valence of approximately 1.22. However, it appears that the simple carbonyl structures, like acetone and formaldehyde, become hydrated in order to achieve sufficient solubility in mucosa to participate in olfaction. The result is a d = 2.34 for these hydrated carbonyl structures.

While the polar character of the carbonyl group is very important in organic chemistry, the ability of a carbonyl group to create an odorophore with d = 1.22 appears minimal. A more interesting case is the trans-di-carbonyl suggested by chemicals such as 2,3 butanedione. Such a structure exhibits a high valence of d = 3.61.

The aliphatic esters, derived from a carboxylic acid, exhibit a valence of d = 2.26. Figure 8.6.2-11(A) illustrates these three structures.

[xxx rework based on the notes in BLASS based on the data of Johnson & Leon.]

### 8.6.2.5.2 AH,B values for the aromatic odorophores

The definition of an aromatic odorophore is very important in organic chemistry, yet a carbonyl group containing a carbon atom external to the ring (in which case the structure becomes an arene) or consisting of multiple fused ring structures (where at least two carbon atoms are shared between the rings). Based on this restriction, the aromatic odorophores are limited to phenol (the hydroxide of benzene), a few ethers of multiple resonant ring structures, and the amines and nitrois of benzene. The amines and nitrois will be discussed separately below.

The fundamental aromatic odorophore is phenol. Although toxic when alone, the odorophore can exist as one of multiple odorophores in many nontoxic arenes. The odorophore of phenol consists of the hydroxyl group, AH, and the π-cloud of the benzene ring, B. While the chemical formula for phenol is C₆H₅OH, the odorophore can be described using the notation, Ar–C–OH where the distance from the center of the aromatic ring to the carbon associated with the hydroxyl is 1.391 Angstrom and the distance associated with the single carbon-oxygen bond is 1.399 Angstrom (based on the Jmol...
The valence of this combination is \( d = 2.791 \), assuming the effective center of the \( \pi \)-cloud is coaxial with the geometric center of the benzene ring. Multiple hydroxides of benzene are available, suggesting the potential for multiple odorophore sites associated with individual molecules.

8.6.2.5.3 The C=C bond as a full capability “orbital”

To fully realize the potential for odorophores among the complex chemistry of the natural odorants, it is necessary to consider the properties of the \( \pi \)-bond associated with two carbons, most simply but imprecisely expressed as the C=C bond. As in the case of the benzyl ring, there are effectively two unpaired electrons associated with this bond. These electrons can act exactly like the unpaired electrons of the more conventional orbitals, oxygen, nitrogen, sulfur and phosphorous. As a result, it is necessary to consider one of the atom-based orbitals paired with a C=C bond participating in a DACB relationship. In addition, it is important to consider a benzyl ring paired with a C=C bond participating in a DACB relationship. Finally, it is important to take one additional step and consider two C=C bonds acting as the the two “orbitals” in one-half of a DACB relationship with a receptor.

These additional combinations of “orbitals” bring an additional universe of odorophores to the olfactory modality. In general, these additional options exist d-values that overlay those of the simpler odorophores discussed previously. However, when combined with the other odorophores associated with a given odorant, they introduce an even larger set of odorophore combinations that can be perceived as a specific scent. This potential will be described in greater detail in subsequent sections.

As in the previous subsection, the configuration of the C=C bond (or more formally the \( \pi \)-bond between two carbon atoms) and a benzyl ring can be described using the notation, Ar–C–C–\( \pi \) where the distance of the \( \pi \)-bond beyond the last carbon is one half that between the two carbons forming the \( \pi \)-bond.

On the other hand, Morrison & Boyd [xxx??] have noted that a more appropriate terminology might be to consider the aromatic attached to a carbonyl group as Ar=C-C=O. This conjugated condition could also be shown as Ar=-C=-C=-O where the left-most carbon is a member of the ring. In this case, the charge cloud is shared and the the two groups would not support a DACB relationship.

A particularly important potential is associated with the unsaturated straight chain carboxylic acids. When an acid with only one C=C bond is esterified with phosphatidic acid via the hydroxyl group of the carboxylic ligand, the remaining carbonyl oxygen can pair with the unsaturated C=C bond to form the receptor of an OR. By employing a group of unsaturated straight chain carboxylic acids, with the C=C bond at different carbon numbers, a family of phosphatidyl-enals can be formed that are candidates for the oskonatory modality VR’s (Section 8.6.11).
8.6.2.5.4 \( A_H, B \) values for the simple chelate arene (aromatic) odorophores

Ferrocene is a molecule containing two planar cyclopentadienyl groups sharing one Ferrous ion (no oxygen or hydroxyl ligands). Its formula is \( \text{C}_5\text{H}_5\text{Fe} \), sometimes written as \( \text{FeCp}_2 \). As expected for a symmetric and uncharged species, ferrocene is soluble in normal organic solvents, such as benzene, but is insoluble in water. Ferrocene is an air-stable orange solid that readily sublimes. The carbon-carbon bond distances in ferrocene are 1.40 Å within the five-membered rings, and the Fe-Cp bond distances are 2.04 Å.

Nickelocene is a very similar compound but appears a bright green and exhibits a different spacing between the nickel and Cp ligands. There are small differences in ring spacing and charge distribution, whereas the odor of these two molecules is radically different: ferrocene smells spicy-camphoraceous; nickelocene smells oily-chemical.

**Figure 8.6.2-12** illustrates these compounds. Each of the Cp ligands is capable of sharing a pair of electrons with another molecule in a coordinate bond arrangement. Based on the spacing between the two cyclopentadienyl groups, these molecules are capable of forming a dual antiparallel coordinate bond (DACB) with an olfactory receptor resulting in the noted olfactory perception in the absence of any oxygen or hydroxyl group(s).

The ability of the two ligands of the metalocenes to form dual antiparallel coordinate bonds with a sensory receptor, where the spacing between the two Cp ligands result in different olfactory perception is good validation of the theory of olfaction presented in this work versus the vibrational or odotope hypotheses put forth by Turin, as well as others (Section 8.6.1.1).

The explicit location of the available unshared electron-pair within each ligand of the metalocenes has not been found in the literature. However, based on the symmetry of the molecules, their electrostatic location can be assumed to be along the central axis of each of the planar ligands. Assuming the shareable charge is located, the potential value of the ferrocene molecule would be 4.08 Ångstrom. To date, Section 8.6.2.8 has not identified a specific sensory receptor molecule matching this number and generating a perception of “spicy-camphoraceous.”

8.6.2.5.5 \( A_H, B \) values for the arene (aliphatic aromatic) odorophores

The arenes contain the majority of the odorophores. The class is large, and includes many subtle variations resulting in multiple potential odorophores within a single molecule. Some of these odorophores may be hindered by stereochemical considerations. Members of this class will be discussed based on the character of the electron pair sharing species present and their distance relative to the centroid of the aromatic ring. The simplest family of this class are; the aromatic ethers. The first member, with the oxygen forming the ether immediately adjacent to the aromatic ring exhibits a valence equal to that of the phenols, \( d = 2.791 \) Ångstrom. The odorophore can be described as \( \text{Ar} + \text{C} - \text{O} \). The next member is the aliphatic ether (or hydroxyl) of toluene, methylbenzene. The isomers of this configuration are not all planar and multiple valence values can be calculated for methylbenzene ether. The next member is ethylbenzene. The odorophore can be described as \( \text{Ar} + \text{C} - \text{C} - \text{O} \). Longer aliphatic ethers may be effective odorophores but their structures, and elicited sensations have not been broadly explored.
discussed in the literature. Two ethylbenzene forms that have been discussed are the allyl benzene ether (aka, 2-phenylallyl ether) and allyl benzene alcohol (aka, 2-phenylallyl alcohol). Both elicit the sensation associated with roses.

An aliphatic aldehyde can be substituted into the benzene ring. One of the simplest, with a CHO group attached to the ring is acetophenone. It has a valence of \( d = 3.619 \) Angstrom. The odorophore can be described as \( \text{Ar}+\text{C}–\text{C}=\text{O} \), but the comment of Morrison & Boyd may apply (Section 8.6.2.5.3).

An aliphatic acid can also be substituted into the benzene ring. This structure introduces two oxygen atoms into the molecule that involve a special geometry. The two oxygen atoms constitute an aliphatic odorophore by themselves as defined above. They may also define one or more additional odorophores in conjunction with the \( \pi \)-cloud of the aromatic ring. The valence of this (these) odorophores have not been defined.

Upon esterification, the arene acid defines an odorophore based on the oxygen of the ester and the \( \pi \)-cloud of the aromatic ring. The calculated valence of this odorophore is \( d = \) xxx based on standard bond lengths that do not consider the possible impact of the adjacent carbonyl oxygen. The carbonyl oxygen, in conjunction with the aromatic ring may also constitute an odorophore with a valence of \( 3.68 \) Angstrom based on standard bond lengths. Longer homologs of the basic acid benzene structure will exhibit higher valence values.

Some of the arene odorophores also contain an aliphatic chain that does not contain any electron sharing elements or features. These chains appear to add structural strength to the molecules. These modified molecules are frequently found in the structural molecules of cell walls.

The odorophore structures described for the arenes frequently appear in combination. As discussed later, such combinations have the ability to interact with multiple receptor sites and the resulting elicited sensation may be quite complex, since the sensation also results from the relative intensity of the individual odorophore interactions with the receptors. As an example, a common odorant, salicylaldehyde contains both the hydroxyl group of a phenol and a minimal aliphatic aldehyde, CHO. It has the ability to excite two potential receptors and create a distinct sensation. Methylsalicylate, an ester, is even more complex. It is totally planar except for the methyl group. It exhibits the phenol odorophore as well as the odorophores associated with the ester group and the aromatic ring. It is noted for eliciting the oil of wintergreen sensation.

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**Figure 8.6.2-13** describes a family of cinnamon odorants based on the Electrolytic Coordinate Chemistry hypothesis. The central member, cinnamyl alcohol, exhibits \( d \)-values of 6.029 Angstrom and 3.019 Angstrom suggesting two distinct odorophores within this odorant. All of the molecules shown exhibit a \( d \)-value within \(+6.7\%\) and \(-9.8\%\) of the central value of 6.029 Angstrom between the atomic orbital and the aromatic ring, suggesting an OR for this series of odorophores within a \( d \)-value near or slightly below 6.029 Angstrom. The left pair exhibit a second \( d \)-value between the atomic orbital and the \( \pi \)-covalent bond near 2.5 Angstrom suggesting a separate OR in this area. The right three members exhibit a similar second \( d \)-value grouped around 3.015 to 3.087 Angstrom suggesting an OR in this region. Cinnamyl acetate also exhibits an additional pair of \( d \)-values at 7.662 and 4.434 Angstrom suggestive of OR’s near these values and quite likely independent of the OR’s near 6.029, 2.5 and \(-3.05\) Angstrom. Cinnamyl acetate is frequently described as a “spicy cinnamon” which is also suggestive of a second odorophore of high \( d \)-value.
The cinnamyl acetate (ChemSpider 4445319) can be extended to incorporate a second phenyl moiety (ChemSpider 4521380) that would be shown directly above the cinnamyl acetate. The resultant di-phenyl nearly retains its primary d-values (now 6.074 and 7.610 Angstrom) but adds additional primary values of 3.925 and 5.245 Angstrom. The second of these additional values would suggest a potential flowery or rose-like perception in humans. These primary odorophores are supported by a variety of lower d-value odorophores.

The label cinnamyl phenylacetate is used here as a convenience name for the diphenyl. It is listed by ChemSpider using the name, Benzeneacetic acid, 3-phenyl-2-propenyl ester without any association to the cinnamons. Its systematic name is even less suggestive of its familial properties associated with olfaction, (2E)-3-Phenyl-2-propen-1-yl phenylacetate. Cinnamyl phenylacetate (CAS 7492-65-1) is described as eliciting a “deep chrysanthemum-like odor” by the Food and Agriculture Organization of the United Nations\(^\text{158}\). It is also known by the label cinnamyl phenyl acetate in the literature.

acetate among others.

The perceptual descriptor, “deep chrysanthemum-like” has not been encountered frequently in the olfactory literature although a similar expression, deep purple chrysanthemum” is frequently encountered in the fashion and gardening repertoire. It is likely to be a compound perception due to multiple odorophores like umami in gustation.

Cinnamyl phenylacetate is an obvious example of an odorant containing multiple discreet odorophores, Figure 8.6.2-14, not unlike mono-sodium glutamate among the gustants. When associated with the lower phenyl, the two oxygen orbitals exhibit d-values related to the γ-carbon and the ε-carbon. The d-value of 6.074 Ångstrom is very typical of the chemicals eliciting a perception of cinnamon very similar to that of the mono phenyl, cinnamyl acetate (d = 6.072 Ångstrom). The d-value of 7.610 Ångstrom, associated with the ε-carbon, has been associated with the perception of xxx.

The simultaneous availability of DACB relationships with these oxygen orbitals and the other phenyl suggest odorophores associated with the β-carbons (xxx).

When forming DACB relationships with the π-bonds of the aliphatic covalent bonds, this chemical exhibits a series of shorter d-values that will be discussed below.

Figure 8.6.2-14 Cinnamyl phenylacetate using a convenience name. See text. Designations using greek letters are shown relative to both of the phenyl rings, using apostrophes for the secondary ring.
Figure 8.6.2-15 shows the information associated with the above figures presented on a preliminary d-value perceptual space combining the gustatory and olfactory modalities (before any folding of the d-value line into individual modality spaces for information extraction by the neural system).

Pending further analysis, the nominal d-value of the OR most susceptible to stimulation by the cinnamons will be taken as $d = 6.029$ Å, the value of the simplest odorophore of the family, cinnamyl alcohol. Many of the common homologs of cinnamyl alcohol exhibit similar odorophore d-values (within 5-10% of the nominal value) related to the $\gamma$-carbon of the aliphatic chain and the centroid of the primary phenyl ring. However, these chemicals generally exhibit multiple odorophores as shown. Some of them exhibit a higher d-value associated with the $\varepsilon$-carbon. All exhibit lower d-values associated with the capability of the molecules to form DACB relationships between the oxygen orbitals and the $\pi$-bonds of the covalent carbon links of the aliphatic chains. These tend to group around d-values of 3.0 or less. Such a grouping is shared with the potential odorophores of eugenol, the primary chemical of the clove, with d-values of 2.805, 2.869, and 3.009 Å. This grouping strongly suggests an OR with a d-value between 2.85 and 3.09 Å. The figure also illustrates a few outliers in the $d = 4.34$ to 5.603 Å range that can provide additional odorophores not associated directly with the cinnamons.

The cinnamons as a chemical family provide strong support for the Electrolytic Hypothesis of Olfaction presented in Section 8.6.1.

The preliminary d-value perceptual space template can also display the principle odorophores associated with the flowery odorants and other major odorants described in Section 8.6.2.
The perception associated with roses is often used as a reference in perfumery. However, the definition of this term is difficult. The essential oils of roses is not a simple mixture, even among a single breed of rose. Wikipedia notes, “two major species of rose are cultivated for the production of rose oil:

• *Rosa damascena*, the damask rose, which is widely grown in Bulgaria, Turkey, Russia, Pakistan, India, Uzbekistan, Iran and China
• *Rosa centifolia*, the cabbage rose, which is more commonly grown in Morocco, France and Egypt

Bulgaria produces about 70% of all rose oil in the world. Other significant producers are Morocco, Iran and Turkey.

The most common chemical compounds present in rose oil are:

citronellol, geraniol, nerol, linalool, phenyl ethyl alcohol, famesol, steaoptene, α-pinene, β-pinene, α-terpinene, limonene, p-cymene, camphene, β-caryophyllene, neral, citronellyl acetate, geranyl acetate, neryl acetate, eugenol, methyl eugenol, rose oxide, α-damascenone, β-damascone, benzaldehyde, benzyl alcohol, rhodinyl acetate and phenyl ethyl formate.

The key flavor compounds that contribute to the distinctive scent of rose oil, however, are β-damascenone, β-damascone, β-ionone, and cis-rose oxide. β-damascenone presence and quantity is considered as the marker for the quality of rose oil. Even though these compounds exist in less than 1% (quantity) of rose oil, they make up for slightly more than 90% of the odor content due to their low odor detection thresholds.”

**Figure 8.6.2-16** shows the d-values for some of these components overlaid onto the template.

• β-ionone (ChemSpider 553581) exhibits a d-value of 4.772 Angstrom for the single oxygen associated with the γ-carbon and the double bond of the ring and 2.473 Angstrom based on that oxygen and the π-bond of the aliphatic chain. It exhibits a d-value of 2.360 Angstrom between its two double bonds.
• β-damascone (ChemSpider 1299471) exhibits a d-value of 3.051 Angstrom for the single oxygen associated with the α-carbon and the double bond in the ring and 2.542 Angstrom based on that oxygen and the π-bond of the aliphatic chain. It exhibits a d-value of 3.594 Angstrom between the two double bonds.
• β-damascenone (ChemSpider 4517997) is a more complex molecule. It exhibits a d-value of 3.069 Angstrom for the single oxygen associated with the α-carbon and the closest double bond of the ring and 2.388 Angstrom based on the oxygen associated with the α-carbon and the π-bond of the aliphatic chain.

At the same time, it exhibits a d-value of 5.020 Angstrom for the single oxygen associated with the α-carbon and the farthest double bond of the ring. Simultaneously, it exhibits additional d-values of 2.191, 3.548 & 5.727 Angstrom.

• cis-rose oxide (ChemSpider 1361574) is an arene with a heterocyclic ring containing oxygen and one double bond in its aliphatic arm. It exhibits a single d-value of 2.657 Angstrom based on these two features. This single d-value would suggest nominally equal stimulation of channels 1 and 2 of the olfactory modality until more precise effectivity profiles of these channels are obtained.

These values can be compared to the d-values of the simpler structures of 2-phenylallyl alcohol (xxx Angstrom for the γ-carbon), 2-phenylallyl ester (xxx? 5.065 Angstrom for the γ-carbon), phenyl ethanol_7131 (3.672 Angstrom between the oxygen at the α-carbon and the resonant ring), and that are also reported frequently as eliciting a perception of “rose.” [xxx coordinate with Section 8.6.11.1 re the tomato]
To the extent the chemicals shown in the figure are perceived as “rose” scented, phenylethanol only exhibits one DACB candidate odorophore with $d = 3.697$ Angstrom suggesting this odorophore is the fundamental odorophore associated with “rose.” However, the Food and Agriculture Organization of the United Nations describes 1-phenylethanol (ChemSpider 7131) as a colorless to pale yellow liquid or white solid with a mild floral odor. Relying upon these conditions, it becomes likely that the true perception of “rose” involves a combination of two odorophores, one related to the O-phenol DACB and one related to the O-$\pi$ bond DACB.

**8.6.2.5.6 AH,B values for the amine and amino acid odorophores**

Some amines and amino acids are of low enough mol. wt. to stimulate the olfactory modality. Most amines are poisonous or at least irritants.

The amines play a role in olfaction, primarily related to the pungent category of sensations. The amines are generally associated with rotting flesh and fecal matter.

The amines of interest are relatively simple and consist primarily of terminal amine groups on carbohydrate chains or associated with heterocyclic chemicals with nitrogen as a member of the ring.

Understanding the potential mechanism of amine sensing is difficult based on the anhydrous aliphatic formulas alone. However, the lower molecular weight amines are highly soluble in water and readily form hydrogen bonds with the water. The result is an azeotrope with a very clearly
defined odorophore. The d-value of the azeotropes of amines may be difficult to define with precision because the amines are found in primary, secondary and tertiary form. For purposes of this discussion, an amine can form a coordinate linkage, N-H-O-H. This linkage has a value of d = 2.82 between the nitrogen and the oxygen. Conceivably, the amine can also form a coordinate linkage of N-H-O with a d = 3.14 between the nitrogen and oxygen. The N-H bond is much shorter than the N-H bond. The amines also readily form intermolecular bonds of the form N-H-O-H with a d = 2.87 Angstrom. These values are estimates from Section 8.6.1.8 and not based on specific Jmol files.

The fact that both 1,4 butanediamine_13837702 (a.k.a. putrescine) and 1,5 pentanediamine_13866593 (a.k.a. cadaverine) are reported to elicit the same perceived odor is likely due to their formation of intermolecular bonds with the above d-values. These reports are in spite of the fact the length of the molecules is different and the d-values between the two nitrogen orbitals are significantly different, putrescine exhibits a d-value of 6.222 Angstrom, exciting OR 6 and cadaverine also exhibits a d-value of 7.425 Angstrom exciting OR 8.

These molecules demonstrate the ability of the OR 2 channel of humans to perceive a fetid odor at high concentrations, while perceiving a sweet odor at low concentrations. Assuming only OR 2 exhibits this property, the perceived odors of these two molecules are (with channel numbers in parenthesis),

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Low Concentration</th>
<th>High Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadaverine</td>
<td>Sweet-Citral (2,8)</td>
<td>Fetid-Citral (2,8)</td>
</tr>
<tr>
<td>Putrescine</td>
<td>Sweet-Cinal (2,6)</td>
<td>Fetid-Cinal (2,6)</td>
</tr>
</tbody>
</table>

The simplest aromatic amine is C₆H₇N or aniline_5889. It is also known as aminobenzene (and occasionally phenylamine. While this chemical can exhibit a d-value due to the nitrogen and the aromatic ring of 2.727 Angstrom, it can easily form a hydrogen bond with water that introduces additional odorophores. The family is highly poisonous and readily passes through the skin.

The amine group and the carboxylic acid group in amino acids are also positioned to form a coordinate bond pair with a receptor. For the pair within L-serine_5736 using the nitrogen and the carbonyl oxygen, the value of d = 3.470 Angstrom based on the Jmol file. For the pair using the nitrogen and the hydroxyl oxygen, the value of d = 2.846 Angstrom.

### 8.6.2.5.7 The complexity of the odorants of citrus

The citrus fruits have been studied intensely because of their economic value. Both extensive genetic studies based on DNA and other studies assuming a high degree of hybridization among a small set of original species have been reported. Botanically, the citrus fruits (Sapindales Rutaceae Citrus) can be divided into a number of species. As usual, different investigators adopt different phylogenetic notation than other investigators.

Carbonell-Caballero et al. have provided an exhaustive genetic analysis of the very broad family of citrus. They performed an analysis on 34 different citrus genotypes resulting in a set of cladograms based on different criteria. Their analysis did not address the subject of hybridization within and among the group. The common names of the fruit shown in Table 1 show a remarkably good correlation with their scientific names. A few oddities do appear in their cladograms of figure 3 & 4. The “Chinese box orange” is not a member of the Citrus genus. The Marsh grapefruit, Citrus paradisi, was the only grapefruit included in the study. The three Australian limes are of a separate genus than Citrus and a couple of other named limes appear out of place in the cladograms. The Rangspur lime specifically appears to be an actual lemon of Citrus limon (limon actually designating the lemons).

Interestingly, many of the species of specific interest are considered some of the earliest hybrids by

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The hybridization either occurring naturally or during ancient human times. The common ancestor appears to be the pomelo (Citrus maxima). Before the pomelo was the citron (Citrus medica), a fruit relished for the rind and not the pulp. It assumes many shapes, more like a squash than a typical citrus fruit. Citrus fruit are most often described in terms of their flavor rather than their taste or scent alone. The pomelo was hybridized (note the x between the botanical names) into the bitter orange (Citrus x aurantium) and the sweet orange (Citrus x sinensis). The mandarin, also known as the mandarin, Citrus reticulata, is characterized by its sweet taste. Citrus x sinensis appears to be a hybrid between the pomelo and the mandarin based on molecular markers.

The grapefruit (Citrus x paradisi) is known for its bitter to semisweet taste. The grapefruit has been recognized as a “natural hybrid” dating back many centuries if not millennia. The lemon (Citrus limon) is known for its sour taste. The lime (Citrus latifolia and Citrus aurantifolia) exhibit a more bitter taste. The ultimate scent associated with these fruits depends on both their primary and other odorophores.

A problem of olfactory nomenclature becomes evident when it becomes necessary to differentiate between “sweet” and “sour” oranges. Sweet and sour are terms closely associated with gustation and only secondarily with olfaction. Sweet is specifically associated with the glycol channel receptors (GR 2) and sour with the acidic channel receptors (GR 1) of gustation.

In olfaction, it is useful to adopt different words to describe the scents associated with the limal, OR 2, and citral, OR 8, channels or resort to compound expressions like “sweet smelling” and “sour smelling” to highlight their difference from the gustatory labels. Unfortunately, the loose terminology is deeply ingrained into the English language and culture. For now, a sweet smelling orange may be differentiated from a sour smelling orange by their scent as well as their perceived taste. Sweet smelling does not require the presence of a simple sugar or a glycol.

Subject to further investigation as to the role of the major odorants in the oranges, it is likely that the variation between sweet smelling and sour smelling oranges is probably determined by the ratio of citronellal to limonene concentration in the mucosa.

Ruberto, writing in Jackson & Linskens, provides considerable information concerning the chemical constituents (over 100) and dominant odorants of the essential oils of the citrus fruit. While they stress the importance of the structural foundation of the odorants as monoterpenes and their oxygenated derivatives, it is their capability to form DACB linkages that is their primary structural feature related to taste and smell. They do note the major role of limonene in these fruits, ranging from 90% of the essential oils in grapefruit, to 50-65% limonene plus about 10% each of β-pinene and γ-terpinene. Other essential oils contributing to the perceived scent include linalool and linalyl acetate. Many of these oils are odorants containing multiple odorophores. The relevance of these percentages is open to review because of their difference in effectivity in olfaction.

Citronellal is found as the essential oil in the eucalyptus tree, a species that shares the climate zones favored by citrus trees. Citronellal and neral exhibit the same structure except for the presence of one additional double bond in neral (that introduces an additional odorophore) as described below.

There are significant differences between the essential oils of the citrus fruit. Various sources disagree on the olfactory dominance of the odorants in oranges, grapefruit and limes. Based primarily on empirical investigations lacking a null hypothesis, authors have made sweeping statements that are

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difficult to defend.

The "citral" as chemicals found within the citrus fruit suffer from label confusion and specific accession numbers are important in defining what chemical is being discussed. Figure 8.6.2-17 shows the 2D configuration of selected chemicals from this group, including the "grapefruit mercaptan." There are several isomers of grapefruit mercaptan that will be explored in Section 8.6.6.5. They exhibit d-values from 4.636 to 4.9 Ångstrom in the Jmol files of ChemSpider. 2-[(1R)-4-Methyl-3-cyclohexen-1-yl]-2-propanethiol_21163535 (a.k.a., grapefruit mercaptan) appears to be dominant in grapefruit with a d = 4.873 Ångstrom. The grapefruit mercaptan lacks any common orbital, and uses sulfur and a C=C bond to support a DACB with the appropriate OR. The d-value of 4.873 Ångstrom is quite different from limonene and citronellal and suggests it may stimulate both the OR 5 and OR 4 olfactory channels.

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While limonene_20939 and citronellal_7506 have been widely discussed as common elements of the scent of citrus fruit, it appears their roles are more specialized.

Limonene_20939 contains no oxygen orbital and relies entirely upon two C=C bonds to provide a DACB with the appropriate OR.

Limonene, and several related odorants introduce an additional mode of odorophore/receptor interaction. The mode does not involve coordinate bond pairing involving the hydrogen bonding of atoms of oxygen or nitrogen alone. The replacement of one of these species by the π-cloud associated with a aromatic ring or the π-cloud associated with a carbon-carbon double bond results in an equally effective coordinate bond pairing with an appropriate receptor. Limonene (C_{10}H_{16}) offers no odorophore based exclusively on the conventional oxygen and nitrogen orbitals. However, the two C=C double bonds of limonene exhibit a d-value capable of exciting the proposed PtdHis OR at d = 4.467 Ångstrom.

There is an additional complication in the multiple configurations of limonene. (±)-Limonene_20939
exhibits a d = 4.303. (R)-(±)-Limonene_389747 exhibits a d = 4.597. Both excite the OR of channel 4. There is a question of the accuracy of these d-values at the detail level. The current conformational rules used in documentation within the Jmol archive and in rendering within the DS 3.5 program apparently do not differentiate between the potential angles of the oxygen in the aldehyde with respect to the remainder of the various aliphatic structures, including those of the chemicals with the prefix “citr,” including citral a (geranial_553578), citral b (neral_558878) and citronellal. Similar comments can be made regarding the non-aldehydes, citronellol et al.

The limonenes, with a d-value ranging from 4.303 to 4.9, appear to be dominant in lemons and limes, citronellal, with a d-value on the order of 7.102, appears to be dominant in oranges. The mercaptans, due to the introduction of a sulfide group in place of a double bond associated with the H₂C group of the limonenes, appears to be the dominant odorophore of grapefruit.

An inconsistency yet to be resolved is related to citronellal in this figure and its representation below as a straight aliphatic chain hydrocarbon. They are described here as aliphatic because of a failure to close their incipient ring structure. Using the straight chain representation, a d-value of 7.402 can be calculated rather than the expected value closer to 5.5 Ångstrom in analogy to citral b (neral). Citral b_558878 is shown in a coiled form in both its 2D and 3D configurations in ChemSpider. However, citronellal_7506 is shown in a coiled form in 2D and a straight form in 3D within ChemSpider. This situation has been brought to the attention of the ChemSpider archivist (26 and 28 February, 2015). This may or may not be an effective effort as it appears ChemSpider depends on graduate students at various universities to look into these kinds of problems, gratis.

In discussions with the various sources of Jmol files and their rendering, it has been made clear that this relatively new field is being archived but not curated as a convenience to researchers. However, it is only a convenience to the original submitter if the records are not correct and/or consistent.

The 2D structures of the alcohols, geraniol and nerol are shown differently in the Merck Index, 8th Ed. of 1968. They are shown in the earlier straight line aliphatic form similar to that shown for citronellal 7506 in its current 3D rendition in ChemSpider. Accurate three-dimensional representations of these molecules are needed to calculate precise d-values for these materials and draw specific conclusions regarding the perceived odor of these chemicals.

There is also confusion over specific structures assigned to a specific label. Citral b_558878 and citronellal_7506 have the same aliphatic form except for one change in angle of the final carbonyl oxygen relative to the backbone and one less double bond in citronellal. Based on laboratory evidence, citral b (neral) appears to stimulate the musk channel of OR 5 while citronellal is expected to stimulate the citral channel of OR 8. It is critically important to specify the angle between the carbonyl oxygen group and the vertical C–C bond of these chemicals in order to calculate their specific d-values.

Limonene appears to be the primary odorophore of the lemons and limes, and therefore appears to be the primary odorants stimulating the PtdHis OR of channel 4. The mercaptans of grapefruit appear to stimulate both the OR of channels 4 and 5. Geranial, citronellol, citronellol et al. appear to be the primary odorophores of the oranges and stimulate OR 8.

The channel labels developed in this work recognize these differences. Channel 4 is labeled the limal channel and channel 8 is labeled the citral channel.

So-called sweet oranges appear to stimulate channel 4 (limal) more than other oranges.

The chemical historically labeled citral occurs as two non-conjugated terpene isomers, the E-isomer (or citral a_553578) is geranial, the Z-isomer (or citral b_558878) is neral. Both exhibit a complex aliphatic structure resembling part of a cyclic ring in 3D rendering. They both exhibit two C=C bonds and offer two different d-values relative to the single carbonyl oxygen (and potentially the d-value of the two double bonds supporting their own DACB).
The only way to explain their performance using the AH,B coordinate bond pair concept is to look to the carbonyl oxygen, and the nearby double-bonded carbons as contributing an electron pair. While this arrangement is suggested in the analyses of Shallenberger & Acree, it is not discussed in detail. To complete the set of odorophores associated with each form, the centroid of the double bonds can be used.

Considering the carbonyl oxygen and the centroid of its closest carbon double bond, a d-value of 2.96 Angstrom can be calculated. This value would suggest these two citrals could each form a DACB with the OR of channel 2 and be perceived sweet at reasonable concentrations, and potentially as fetid at high concentrations. This proposed perception appears compatible with experimental evidence.

While an odorophore with a d-value of 2.96 is the same in geranial and neral, they may be perceived as of different intensity relative to the DACB involving the carbonyl oxygen. The odorophore at d = 2.96 is not shared with limonene even though it and geranial are often described as eliciting the same lemon sensation. They would be expected to elicit different perceptions of “sweetness.”

Geranial and neral exhibit additional potential electronic configurations known as carbanions as discussed in Morrison & Boyd (pages 852). They are virtually insoluble in water and the oxygen atom may need to be hydrated when participating in olfaction. These conditions suggest these additional electronic configurations may play a role in taste as well as smell. The α-hydrogen may act as an inorganic acid and act more as an irritant than an odorophore/gustaphore.

Beets, in Theimer, reviews additional molecules related to those in the above figure (pages 92-93) relying upon 2D “Lewis structures.” The cause of the differences in the perceived scent of all of these molecules are identifiable in 3D space using the hypothesis and corollaries of this work. Beets goes on to review a variety of more complex enantiomers.

While the odorants of the citrus fruit are all described as terpenoids, this designation is based on their derivation from the terpinoid building block of organic chemistry. They are significantly modified for the purposes of olfaction. Aldehyde forms are widely used compounds in perfumes and pharmaceutical preparations. The main disadvantage of these molecules is their intrinsic instability and propensity to oxidation (forming acids). This inconvenience, together with their high volatility, in the case of low molecular weight molecules used in the perfumery field, for instance, makes the use of aldehydes less appealing for some applications. The lack of an aromatic chemical ring in these odorants separates them from the floral odorants.

Limonene is found in two “mirror image isomers (enantiomers)” when shown in two dimensions. When shown in three dimensions, using the available Jmol files (not from ChemSpider) and the DS3.5 viewer, the situation is more complicated, Figure 8.6.2-18. Enantiomers have identical properties except for two, the way they affect polarized light and how they affect the olfactory modality. The (r)-(+) enantiomer of limonene elicits the perception of a pleasing citrus scent and the other (s)-(−)-
the perception of a pine forest (possibly combined with a citrus scent according to some subjects). These chemicals contain neither oxygen nor nitrogen atoms. Yet they elicit strong and distinct olfactory responses. These chemicals belong to a class where the odorophore is formed by at least one double carbon-carbon bond providing an electron in the coordinate bond pair relationship. Limonene relies on two double carbon-carbon bonds to form its odorophore. The d-value for this chemical can only be formed by the distance between the two double bonds.

![Figure 8.6.2-18](image)

Figure 8.6.2-18 The isomers of limonene, perceived as either a citrus or a pine forest. The d-values vary from those in the adjacent figures. They are created from Jmol files but not Jmol files from the ChemSpider site. The nominal d-values between the two C=C bonds (green spheres) in each molecule are shown.

Koster made the most specific delineations between several enantiomers. “Even enantiomers like R-(—)-carvone (spearmint) and S-(+)-carvone (caraway) or S-(—)-limonene and R-(+)-limonene (the R-(+)- being more orange-like than the other) can be distinguished (Laska & Teubner, 1999). Laska & Teubner expanded on Koster’s remarks and provided statistical data on ten pairs of enantiomers. Their figure 1, reproduced as Figure 8.6.2-19 is revealing.

![Figure 8.6.2-19](image)

Figure 8.6.2-19: Performance of 20 subjects in discriminating 10 pairs of enantiomers. Each data point represents the percentage (means ± SD) of correct choices from 10 decisions per odor pair and subject. The figures immediately above the abscissa indicate the number of subjects that failed to perform significantly above chance in the corresponding task. From Laska & Teubner, 1999.

They conclude in their discussion, “Whereas almost all subjects had few difficulties in distinguishing the (+)- and the (-)-forms of α-pinene, carvone and limonene, most panelists failed to discriminate between the antipodes of β-citronellol, menthol, fenchone, rose oxide, camphor, α-terpineol and 2-butanol.

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2-butanol when presented at equal concentrations.” The detailed structural differences between these “pairs” must be examined to interpret these results completely. To the extent they are 3D mirror images, they should have the same d-value and be equally effective as stimuli. However, there may be a marginal difference in their ability to stereochemically combine with the same OR. They did note in the discussion the frequent incongruity between this data and the earlier verbal descriptions by many investigators going back 30 years or more. They further conclude, “A final aspect of the present study is the finding that no generalizable conclusions can be drawn from our data as to odor structure–activity relationships which would allow us to predict whether or not a given pair of enantiomers can be olfactorily discriminated.”

Laska & Teubner continue to note the fact recognized by others, “Our finding that the antipodes of α-pinene were also discriminable despite their lack of a propenyl group, on the other hand, illustrates that the presence or absence of a certain functional group at the chiral carbon atom is not a sufficient predictor of enantio-selectivity. Similarly, membership of a certain chemical class is not a predictor of whether or not the antipodes of a substance are discriminable as, for example, carvone, fenchone and camphor are all carbonyl compounds but differ significantly in their discriminability.” The presence or absence of a group defined in valence chemistry is irrelevant in the coordinate chemistry of olfaction.

8.6.2.5.8 The citrus odorophores in 3 dimensions ADD

Before reviewing this section, please review Section 8.6.1.6.3 regarding the adequacy of the Royal Society of Chemistry (RSC) Jmol Library. The rapid growth of the description of the conformation of organic and biological molecules has shed deepening shadows over the current ability of the chemistry community to calculate descriptions of odorants and odorophores to the precision required by olfaction analyses. As a result, the Jmol and JSmol files supported by the RSC are used here as illustrative and showing relative d-value relationships, but cannot be depended upon to provide precise d-values.

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3D representations of the odorants of citrus are not readily available. In fact, the 3D representations available from ChemSpider do not agree with the 2D representations of the conformation of the same molecules from the same source. The generic form of the odorants shown in most papers and texts suggest the partial ring structures of citral α 553578 (geraniol), citral β 558878 (neral) and citronella 7506 maintain the same conformation as the closed ring forms shown in [Figure 8.6.2-29]. However, the typical computerized visualizer program has been programmed to select a feasible configuration for these chemicals (based on their programmers instructions). No attempt has been made by the programmer, or by the RSC staff associated with the Jmol file archive, to ascertain or display the actual conformation of these molecules under biological conditions (particularly at the correct pH). The number of individual C–C bonds about which rotation is possible, suggests a wide variety of possible conformations in the absence of detailed information about the lowest energy state for each molecule.

The same problem exists in ascertaining the specific conformation of the amino-acids hydrolyzed with phosphatidic acid to form the active OR of the sensory neurons.

For the purposes of this work, the extrapolation of the conventional 2D Fisher diagrams shown in [Figure 8.6.2-29] to their 3D equivalent have been assumed.

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As noted by Talapatra & Talapatra165 in their post-graduate level book, conformational analysis involves the interpretation or prediction of the physical (including spectral) properties, thermodynamic stabilities, and reactivities of substances in terms of the conformation or conformations of their molecules. The analytical difficulty grows rapidly with the complexity of organic chemicals. They discuss only a few chemicals with the complexity of an odorant.

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Kaiser frequently describes the alcohol form rather than the aldehyde form in many of his examples, thus he speaks of nerol (his 11) rather than Citrol B (neral). Similarly, Kaiser describes geraniol (his 6) rather than Citrol A (geranial). He also defines a similar compound linalool (his 8) showing a partial β-ionone ring, along with many others. These descriptions provide insight into a variety of homologous families. Boelens illustrates the problems in the literature of being precise with regard to scents166:

“Nerol and geraniol possess mild and sweet odors, slightly reminiscent of rose flowers. The odor character of nerol is fresher than that of geraniol. They both possess the rose-like note of geranium oil.”

Should their primary scent be associated with the rose or the geranium?? How is “fresh” defined? Or is fresh just taught to new perfumers by comparing examples?

The “best available” Jmol files for nerol 558917 and geraniol 13849989 both appear to be calculated and not from crystallography. They are both shown as planar aliphatic alcohols with only slightly different conformations. They both exhibit a d-value of 4.95 Angstrom between their two

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double bonds. They both exhibit a d-value of 3.013 Ångstrom between the oxygen and the nearest double bond. The d-values between the oxygen and the most distant double bond are 7.315 Ångstrom for nerol and 7.035 Ångstrom for geraniol. This last parameter defines their distinguishing perceived odor. The difference relates to channel 8, the citral channel. These parameters differ significantly from those expected based on the above semantic definitions.

The alcohols, Citrol A and B also exist as mirror images like limonene. They are also odorants with three potential odorophores each.

8.6.2.6 Other odorants and odorophores by chemical structure

There are a wide variety of odorants that extend beyond the simple aliphatics and arenes.

Jasmine is considered an absolute and not an essential oil as the petals of the flower are much too delicate and would be destroyed by the distillation process used in creating essential oils.

An absolute oil is essentially the same as an essential oil except for the processing method. An essential oil is nominally extracted by steam distillation. An absolute oil is extracted by a milder process. The term is in common use.

The major constituents of the absolute oil of Jasmine include methyl anthranilate, indole, benzyl alcohol, linalool, and skatole.

- Indole is a multicyclic compound of a benzyl and heterocyclic pyrrole ring and recognized by the FAO as “Unpleasant odor at high concentration, odor becomes floral at higher dilutions.”
- Skatole is also described by the IUPAC as 3-methyl-IH-indole. Skatole is recognized by the FAO using too many words; “Mothball, putrid, decayed, faecal odour, jasmine-like or fruity upon dilution.”
- Methyl anthranilate is an aniline (benzylamine) combined with a methylated carboxylic acid (systemic name methyl 2-aminobenzoate) providing multiple odorophores. The FAO describes it ambiguously as having a “Grape-like or orange aroma.”
- Benzyl alcohol (IUPAC-pheylmethanol, chemspider 13860335) is described ambiguously by the FAO as “slightly pungent, faint aromatic, fruity odor.”

Wintergreen is a large group of plants that exhibit one predominant odorant, methyl salicylate, which is typically described as an organic ester. The FAO describes methyl salicylate as “with a characteristic wintergreen odor.” Methyl salicylate is a compound odorant very similar to the aniline variant (methyl anthranilate) found in jasmine oil. Methyl salicylate has one hydroxyl associated directly with the benzyl ring and two hydroxyls associated with the alpha-carbon of the aliphatic chain.

8.6.2.6.1 The nitrobenzenes and nitrophenols BREF

Complex derivatives of the nitrobenzenes and nitrophenols play a significant role in olfaction. However, their simpler forms are toxic and frequently skin irritants. The structural characteristics of the derivatives related to olfaction have not been explored in detail. They frequently exhibit multiple AH,B structures and may exhibit multiple AH,B,X structures. (M & B pg 323 as a start). They are frequently involved in complex aromatic-aliphatic molecules. The nitro-group is typically resonant and analogous to the carboxylic acid group.

Nitrobenzene is a water-insoluble pale yellow oil with an almond-like odor. It is toxic in high
concentrations and readily absorbed through the skin. It is used mainly as an intermediary in industry. Mononitrotoluene, a nitro compound derivative of toluene (or alternatively a methyl derivative of nitrobenzene) is described as having a “characteristic odor.” 4-nitrophenol is a serious respiratory irritant so its odor is not normally described.

### 8.6.2.6.2 Musk related macrocyclic and nitrobenzoid odorants

The major work edited by Theimer in 1982 provides extensive information on the musks (three chapters) from the perspective of the manufacturing chemist in the fragrance industry. Within the work, it becomes clear that the musks are divided into two major groups; those based on animal sources consisting of macrocyclic compounds (typically 14-19 carbons in a single large ring) with at least one orbital that is predominantly oxygen but occasionally nitrogen, and those based on plant sources consisting of much simpler, primarily single ring benzoic compounds with multiple additions. The Theimer text is replete with comments about musk-like odors without any qualification or quantification of what constitutes a musk odor. The evaluations are entirely qualitative based on experienced perfumers using their accepted jargon. There was no assurance that the animal and plant “musks” were in any way related from a chemical perspective. Beets, in chapter 3, defined seven classes of musk based on structure (pages 107-117). The definitions were not complete or unique. The chemical complexities involve were great. If the d-values of this work are used instead of tracking chemical groups, the chemistry explored is much more interpretable.

#### Musks of animal origin

[xxx words on the macrocyclic musks]

**Figure 8.6.2-21** shows a typical animal-based musk, the sixteen carbon muscone. It makes up 0.5-2% of the material extracted from the musk deer odorant gland. The simplicity of the structure suggests the centroid-orbital distance \(d = 4.289\) Å must be significant based on the proposed hypothesis. Lacking any carbon-carbon double bonds, it is not clear that the ring can contribute to a DACB relationship with an OR. [xxx ]

Cyclopentadecanone_9980 (exaltone), civetone_4475121 (civettone) and muscone are the only macrocyclic musks considered commercially important by Mookherjee & Wilson.

Various Fischer diagram representations of muscone (page 438 in Mookherjee & Wilson in Theimer) and similar chemicals suggest there may be more than one configuration for some of these chemicals with the oxygen orbital located inside, outside or orthogonal to the main ring. (9) of Mookherjee & Wilson shows a double bond associated with a chemical ring (5-cis-cyclooctadecen-1-one) similar to that illustrated.

Similar chemicals have been studied but not in the last decade. There has been recent patent...
activity. Jmol files of these chemicals such as (3S)-3-methylcyclohexadecan-1-one and (E/Z)-cyclohexadec-5-en-1-one (Ambretone®, Musk TM II®) and were not located as of 2013.

Civetone_4475121, the chemical name for a commercial odorant named civettone, is nominally symmetrical as it has seven carbons on each side of the macrocyclic structure between the C=O carbonyl group and a C=C. It exhibits a d-value of 5.132 Angstrom between the ring centroid and the oxygen and a d-value of 9.087 Angstrom between the C=O and the C=C double bond. It represents 2-5% of the material removed from the civet odorant gland.

Cyclopentadecanone_9980 exhibits a single d-value of 5.146 Angstrom between the carbonyl oxygen and the centroid of the macrocyclic ring.

Mookherjee & Wilson quoted Stoll from 1936 on the existing knowledge regarding animal musk compounds:

1. The musk odor is confined to a very specific ring size (15-17 members).
2. The basic ring structure must contain at least 14 and less than 19 members, at least one C=O or NH group.
3. A second C=O group completely destroys the odor. (This is in apparent conflict with observations of Hill and Carothers on the cyclic anhydrides.)
4. The substitution of one ring member by an oxygen atom increases the odor intensity and displaces it toward that of ambergris.
5. Substitution of two or more ring members by oxygen atoms decreases the odor intensity and renders the tonality coarser.
6. If the ring contains two heterocyclic atoms in addition to two C=O groups, the compounds have a faintly sweet odor resembling musk and stronger than that of diketones.
7. The lactones are the most interesting compounds in the series.
8. Exaltolide gives by far the best odor.
9. Only pure ambrettolide is of equal quality to exaltolide.

Table IV in chapter 12 by Mookherjee & Wilson, reproduced here in abbreviated form as Figure 8.6.2-22 shows the variation in the perceived odor for this family of structures for the ketone, lactone, carbonate and anhydride forms versus the number of atoms in the ring. For 15 atoms in the ring, all of these variants are described as musk to some degree or other. Except for the ketones, these variants all result in the formation of a heterocyclic ring (one or more oxygen atoms substituted into the ring). The figure provides a quick indication of the efficacy of the DACB coupling to the OR as a function of the number of atoms in the ring and the type of addition to the ring.
Mookherjee & Wilson noted the difficulty in defining the perceived odor associated with the term "musk." They discussed the subject for several pages (480-487) and including, "If a perfumer is asked to define the general odor characteristic of the macrocyclic musks without using the term "musk," a typical list of descriptors often will include sweet, animal, seedy-dry-powdery and floral." These terms help relate the d-value of the macrocyclics to simpler odorants. How olfactory sweetness compares to or differs from gustatory sweetness was not described.

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**Musks of plant origin**

Ham & Jurs have performed an extensive study of musk and similar non-musk benzoid-based compounds using pattern recognition techniques. They also cited an earlier comprehensive study
of musks by Wood (1968 — 1970, 1982a, b). The musks can become very complex molecules. Their work was restricted to monocyclic benzenoids and relied upon the stereochemical parameters of the compounds. When examining 71 monocyclic benzenoid compounds (38 musks and 33 non-musks), they required 13 molecular structure descriptors to achieve 100% certainty in their separation of the compounds into their respective classes. They provide statistical values for how many were properly assigned based on 10 through 12 descriptors. A set of 29 other compounds were predicted based on these descriptors. It would appear difficult to design a protein receptor that could provide the necessary conjugate molecular pocket to satisfy these 13 descriptors.

Figure 8.6.2-23 shows the chemical complexity of the nitro-containing musks Ham & Jurs focused on. Their attention was directed toward the distance between one orbital and one carbon atom (required in their hypothesis) rather than between two orbitals or one orbital and the resonant aromatic ring.

Figure 8.6.2-24 shows a modification of their figure 3. They illustrate a feature of the two chemicals shown, a relationship between one oxygen of a nitro group and an arbitrary carbon of a distant methyl group. Without demonstrating they have a common perceived scent. The upper chemical is a member of the extensive testosterone family (some of which are mammalian hormones, but not known as pheromones) while the lower is a simple member of the nitro-benzoid family (found generally among plants but widely used in perfumery to emulate a mammalian musk). As developed here, it is the d-value of 5.211 Angstrom that is the common feature of all musks (whether natural or man-made, and whether of mammalian or plant origin). It identifies the primary odorophore of the musks. The secondary odorophore of the musks typically exhibits a d-value near 2.757 Angstrom, the center value of the PtdTrp OR acceptance range in step one of the transduction process (Section 8.6.2.8.1). Note the presence of these common relationships in all of the musks illustrated in the previous figure. The other ligands provide tertiary and higher odorophores with different d-values that contribute to the subtle differences in perceived scent between these chemicals.

Ham & Jurs describe several relationships between orbitals (figure 1) that suggest they were on the same track as proposed here but they did not pursue those relationships far enough. However, their figure 3 describes their pursuit in greater detail. They relied upon their early three-dimensional pattern matching software to categorize their molecules. The major problem with the Ham & Jurs approach is that it attempts to match only the structural patterns found in typical Fischer diagrams of the zig-zag type to account for out of plane conditions. They do not attempt to match the electronic features of the chemicals not represented in these figures. Figure 8.6.2-24 shows a modification of their figure 3. They illustrate a feature of the two chemicals shown, a relationship between one oxygen of a nitro group and an arbitrary carbon of a distant methyl group. Without demonstrating they have a common perceived scent. The upper chemical is a member of the extensive testosterone family (some of which are mammalian hormones, but not known as pheromones) while the lower is a simple member of the nitro-benzoid family (found generally among plants but widely used in perfumery to emulate a mammalian musk). As developed here, it is the d-value of 5.211 Angstrom that is the common feature of all musks (whether natural or man-made, and whether of mammalian or plant origin). It identifies the primary odorophore of the musks. The secondary odorophore of the musks typically exhibits a d-value near 2.757 Angstrom, the center value of the PtdTrp OR acceptance range in step one of the transduction process (Section 8.6.2.8.1). Note the presence of these common relationships in all of the musks illustrated in the previous figure. The other ligands provide tertiary and higher odorophores with different d-values that contribute to the subtle differences in perceived scent between these chemicals.

There is no suggestion in the Ham & Jurs paper that the testosterone family member shown in the figure exhibits any distinct scent. Based on the hypothesis of this work, i.e., lacking a second orbital or a benzyl ring, it would not be expected to have a distinctive scent. Therefore no alternative is shown on the left. However, many of the other testosterone family members do contain a second carbonyl or hydroxyl oxygen and can be expected to stimulate a distinctive perception.
In the context of this work, musk tebetine (spelled variously in the literature) approaches a minimal configuration, a dinitrobenzene with a d-value between the two nitrogens of 5.211 Angstrom. "Nitrobenzene is a yellow, oily liquid (above 42F), with a pungent odor like paste shoe polish."

It may be useful to note the similar structure of the simpler benzoic musks to the structure of picric acid in gustation. Where the picric acids tend to exhibit simple oxygen orbitals as additions to one or more cyclic structures, the benzoic musks tend to exhibit nitro groups as orbital additions to one or more cyclic structures. There are a group of plant-based musks that do not contain nitro groups. These odorants tend to have an oxygen orbital associated with the alpha-carbon of the aliphatic moiety of an arene. There is no current evidence that these compounds qualify as true musks except based on psychophysical experiments and their use in the fragrance industry.

Beets addressed some second order structural arrangements in nitro-benzenoids that affected their effectiveness.

**Synthetic Musks**

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Wood addressed a series of non-nitro benzoamides (page 514) that were perceived as musky or musk-like. Other than ambral, they tend to be bicyclic or tricyclic in character. The four that have achieved commercial success all exhibit the characteristic structure of an orbital associated with the alpha carbon of a benzoic ring (Figure 8.6.2-25). In addition, they exhibit various secondary rings that would impact the dipole potential of the overall chemical. They may or may not introduce significant secondary d-values.

![Figure 8.6.2-25 Four synthetic odorants producing a musk perception. They exhibit near identical minimum d-values. Rotating celestolide by 60 degrees demonstrates its common odorophore structure. The structures are nominally planar except for the CH₃ groups. Some commercial products drop the e from the end of the scientific names. The numbers following the parenthetic refer to those of Wood. Most Jmol files show the oxygen atoms rotated into the left-most position relative to the alpha-carbon. Modified from Wood, 1982.](image)

**D-value of the musks REOUTLINE**

A quantifiable descriptor for the musks has not been defined previously. Based on the above paragraphs, it can be questioned whether the musks are a homogeneous group from the olfactory perspective. Based on the hypothesis of this work, they exhibit marginally to significantly different minimum d-values. The first identified animal-based musk, muscone 10483, exhibits a \(d = 4.289\) angstrom while other animal-based musks tend to cluster around a minimum d-value of 5.14 angstrom. The plant-based musks tend to cluster around a minimum d-value of 5.2 angstrom. The major synthetic musks cluster about a minimum d-value of 3.72 Angstrom. The d-value for muscone may be an outlier due to the Jmol file used (the ChemSpider Jmol shows muscone 10483 as a planar molecule while the NCBI site of the NIH shows multiple conformers and the carboxyl oxygen out of plane). The synthetic may be adequate commercial representations of the musks but not actually be good scientific representations of the true musks. Wood noted that Theimer and Davies proposed (page 531) the term meta-musks for the synthetics and ortho-musks for the natural products.

Looking at a large spreadsheet of the musks, several features become obvious.
• Terminology remains a problem with many different spellings used for the same chemical by different authors. The synthetic “musk ambrette” is distinct from the natural ambrette seed and its essential oil, ambrettolic acid. Ambrettolic oil is a simple carboxylic acid with a long aliphatic chain including one C=C bond. Its structural configuration is not settled in the literature (ChemSpider shows it perfectly straight).

• The true (ortho-) macrocyclic musks, as well as the synthetic (meta-) nitrobenzoids, all exhibit a d-value in the range of 5.024 to 5.211. There are several potential phosphatidic acid esters that form OR’s compatible with this range, PtdGln (d = 5.294), PtdArg (d = 5.351) and PtdTyr (d = 5.534). The lower range value is within 10% of the central value of PtdTyr. It is within 5% of the central value for PtdGln. At this point, PtdGln can be considered the primary OR for the musks.

• The structure of the true (ortho-) macrocyclic musk, muscone, needs further analysis. The conformation illustrated by ChemSpider exhibits an unexpected d = 4.289 Angstrom.

The non-nitro benzoids described as musk-like require further analysis to uncover the source of their musk-like perception. They all exhibit a d-value near 3.72 Angstrom between their alpha-oxygen and their benzyl ring. However, they may also exhibit a d-value associated with their second ring structure.

Wood, in the last chapter of musk analyses in Theimer (page 528), discusses the structure-odor correlation ca. 1982. He reviewed many of the previous theories, generally from the 1960’s but including the pattern matching theories of Brugger and Jurs (1977), found wanting.

The Brugger & Jurs paper of 1977 described a methodology for teaching a primitive computer program of the time to examine a large number of chemical structures and segregate them into groups in an attempt to isolate a specific group by a multi-dimensional “decision surface” between it and the other groups. They used no experimental data because of the difficulty of generating the necessary set of parameters for each group. Instead, they relied upon the primitive ability of a computer to develop a three-dimensional description of a large number of chemicals based on tracing their Fischer diagrams into the computer along with a list of bond lengths, angles, etc. They conclude that pattern recognition can be used to isolate groups of chemicals with similar characteristics, but not efficiently.

In 2007, Hadaruga et al. reported on some quantitative structure-odor relationships (QSOR) of a few nitro-benzoid musks. While their introduction repeated the conventional teaching related to the role of proteins, their analyses did not depend on any of these teachings. The focus was on the nitrobenzoid musks of plant or synthetic origin. Their figure 2 is a good summary of the animal-based, plant-based and synthetic musks discussed above. Their figure 4 shows clearly that the most significant ligands of their nitrobenzoid molecules were the nitro group and the ring itself (with some importance associated with the aliphatic group addition between the nitro groups and some importance associated with the group at the one location (most often another nitro group). While their analyses did not focus on the nitro groups associated with the benzoid ring, they did focus on the distance between the R-groups of positions 2 and 6 opposite to the two typical nitro groups. Their statistical results are interesting. They found the optimum distance between these two groups to be “about 5 Angstrom” in excellent analogy to the d-values between the nitro groups of this hypothesis. However, their approach appears to lead nowhere from a theoretical perspective. The groups at positions 2 and 6 primarily impact the second step in transduction (electrostatic measurement) and not the first step (selection).

### 8.6.2.6.3 Selected organic odorants with sulfur as an orbital

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Mussinan & Keelan have edited the papers of a symposium on sulfur in food flavors, where a flavor results from stimulation by both gustants and odorants. While focused on foods rather than chemistry, they do provide some comprehensive lists of volatiles related to certain foods, some of which are odorants. They report a series of “character impact” sulfur compounds related to specific foods (page 2) shown here in Figure 8.6.2-26. However, the list is generic with respect to chemistry although references are provided. In the text, they do discuss the strength of propyl propane thiosulfonate as having a powerful and distinct odor of freshly cut onion. “Since the threshold of this compound (1.5 ppb) is several hundred times lower than its concentration (0.5 ppm), it undoubtedly makes a significant contribution to the overall onion flavor.” This molecule is unusual in that it contains two sulfur atoms sharing a single bond with one of the sulfur atoms sharing a double bond with each of two oxygen atoms (a special form of a sulfanyl group). It exhibits d-values of 2.477, 2.948 & 2.956 Å, the first stimulating the OR1 (acid) channel and the last two stimulating the OR2 (dulcal) channel. Besides the perception of an acidic odor, the Dulcal channel may be reporting an odor midway between the sweet and fetid odors associated with that channel.

Because of their diameter, the sulfur atoms introduce a bond length to their nearest neighbor that is greater than associated with oxygen and nitrogen. The result is different d-values for molecules containing these atoms compared to their oxygen and nitrogen analogs.

The addition of d-values to this figure provides additional room for discussion concerning the need for further definition of the dipole potential associated with these materials (Section 8.6.5).

The d-values can be interpreted using the figure in (Section 8.6.2.8.) The musk-like odor of the potato, particularly from the skin, is supported by the d-value provided in this figure.

Integrating the designations of others, it appears that in some cases, the subtleties of a perceived odor may not be obtained from just one odorophore, although this list does appear to be very informative pedagogically.

They also note the minute quantities of sulfur compounds found in many foods makes their analysis and quantization a challenging problem.” Further, “When attempting to analyze for sulfur constituents, the possibility of artifact formation must be carefully considered. Many sulfur compounds are thermally unstable. Therefore, it’s not surprising that the high temperature typically encountered in the inlet of a gas chromatograph can lead to artifact formation.”

The other papers do describe various methods of determining the presence of volatile sulfur compounds by gas chromatography and an “odor unit.” The paper on the volatiles of muskmelon will be addressed in Section 8.6.8.3.

8.6.2.6.4 Organic odorophores lacking oxygen and nitrogen—The sulfanes

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There are a series of odorants that include carbon hydrogen and sulfur, but no oxygen or nitrogen, yet stimulate the olfactory modality resulting in very distinctive scents.

Diallyltrisulfane_15481, commonly known as garlic oil, has a formula of $C_6H_{10}S_3$ and contains no oxygen, nitrogen or benzyl rings. It does incorporate two $C=C$ bonds and is a symmetrical planar aliphatic molecule. The three sulfur atoms are located in a chain in the center of the molecule. As a result, the molecule exhibits three d-values that are each duplicated at 3.345, 5.074 & 6.724 Angstrom, along with a d-value of 11.221 Angstrom. As will be shown below, the low d-values allow the molecule to form DACB couplings with OR’s #3-floral, 5-musk and 7-spice. When combined vectorially in latter stage processing, the intensity signals from these stimulations result in a very well known perception of garlic.

There are several lesser known isomers of diallytlisulfane with ChemSpider numbers of 4509624, 4509725, 20120960, and 20120974 that all can stimulate the olfactory modality but with different d-values and therefore different perceived scents according to the hypothesis of this work.

### 8.6.2.6.5 Compounds eliciting a perception of “woody”

The molecules eliciting a woody perception tend to be very complex. They probably, but not necessarily, follow the hypothesis of this work. Additional corollaries may be required.

Leffingwell has addressed the structure of both the natural santalols, derived from sandalwood, and in some similar odorants from campholenic aldehyde in some detail but not necessarily in the detail needed to resolve their odorophores\(^{172}\). The 3D relationship between the single oxygen orbital and the two $C=C$ bonds in the two Jmol representations for natural santalol appear to be identical in one pair of his isomers (beta-santalol) even though one is labeled odorless. Leffingwell’s goal was to demonstrate that chirality plays a role in olfactory transduction. This chirality is consistent with the hypothesis presented in this work but not definitive in its own right.

Leffingwell has described the odorants associated with sandalwood, and agarwood in some detail based on an assumption that chirality is a critical feature of these materials\(^{173}\). While sandalwood involves individual rings, often with top hats on the rings, agarwood and patchouli involve multiple fused rings. The rings are often fused at obtuse angles as in patchoulenol_9130391 from a tropical plant. All typically exhibit one oxygen orbital and frequently, but not necessarily in the case of molecules with a top hat on the ring, one or more $C=C$ bonds. (+)-(Z)-\(\alpha\)-santalol_16736011 exhibits a single top hat carbon bonding to two carbons on opposite sides of an aliphatic hexane structure. It also contains a hydroxyl group and a $C=C$ bond resulting in a d-value of 2.736 Angstrom. Based on its chemistry and the hypothesis of this work, this molecule is a SOO describing the “woody-sandal” odor. “Woody” has not been previously defined scientifically in the literature. Based on a review of that literature using the hypothesis presented here, it appears the perception of “woody” is most definitively defined based on the d-value of 2.736 Angstrom of santalol_16736011. It primarily stimulates the dulcal (OR 2) channel of olfaction. This molecule may be considered the defining molecule for the perception of a woody odor.

What is identified by Leffingwell as the “gold standard” for sandalwood, (+)-(Z)-\(\beta\)-santalol_16736012, appears to be a misnomer. The molecule clearly incorporates multiple odorophores. It has a single top hat carbon bonding to two carbons on opposite sides of an aliphatic hexane structure. It also contains a carbonyl oxygen, a hydroxyl group and a $C=C$ bond. This santalol is not an SOO. Leffingwell describes the perception of his “gold standard” as “it adds a urinaceous, animalic, sandalwood tonality to the oil.”

Among the patchouli family and based on this work, the defining member appears to be (+)-norpatchoulenol_10005248. This very complex molecule exhibits only one $C=C$ bond and only one hydroxyl group, resulting in a d-value of 3.922 Angstrom. However, the discussion in Leffingwell suggests confirmation of the purity of the samples and more organoleptic evaluation may be


At this time, (+)-norpatchoulol \_1005248 would appear to stimulate OR 3 (floral) and OR 4 (limal) about equally.

At the time of Leffingwell, the odor associated with agarwood remained due to a mixture of chemicals.

**8.6.2.7 Additional odorophore ligands and their step 1 selection by the OR's**

The active role of the $\pi$-bonds of C=C groups in olfaction leads to additional ligands not recognized within the conventional groups of organic chemistry.

With the identification of the benzyl ring and the $\pi$-bond of C=C as effective orbitals alongside oxygen, nitrogen, sulfur and phosphorus, it is possible to form 21 different pairs of orbitals that can participate in a DACB relationship with an olfactory receptor. To be effective in olfaction, the distance between these orbitals must exceed the minimum d-value of the OR 1 channel and not exceed the maximum d-value of the OR 9 channel.

The shape of the effectiveness characteristic of a given OR is yet to be determined. Based on other sensory modality receptors, it is likely that these characteristics will have an exponential rather than a Gaussian shape. This results in a very much more rapid fall in effectiveness with distance from the central d-value.

For d-values above the maximum for the OR 9 channel, the orbital pair may stimulate the oskionatory modality. Based on this criteria, two adjacent $\pi$-bonds in a straight chain aliphatic compound do not qualify as an odorophore, but two $\pi$-bonds separated by at least one pair of carbon atoms in the same configuration does qualify ($d \approx 2.101$ Angstrom).

To be effective, each of the orbitals of the above potential odorophores must be near enough to the surface of the molecule to support a hydrogen bond with the appropriate OR.

With the putative ±5% variation in d-value associated with each OR and the nominal spacing of the OR’s given in Section 8.6.xxx of this work, any of the orbital pairs meeting the above criteria will stimulate at least one of the OR’s. Under steady-state conditions, the total perceived scent at the output of stage 1 will result from the intensity with which each of the pairs stimulates a specific OR. Under more dynamic conditions, the perceived scent may change with time leading to initial note, intermediate note and trailing note in the language of the perfumer.

**8.6.2.7.1 Polynuclear aromatics sharing pairs of carbons-naphthalene et al.**

The structure of polynuclear aromatic compounds (like naphthalene) present an additional class of orbitals of interest in olfaction. The molecule is dinuclear (or bicyclic) with each ring maintaining its resonance structure and dislocated electrons forming a cloud like that of benzene. These polynuclear aromatics occupy a recognized configuration within the hypothesis and corollaries of this work.

As in all aromatic ring structures, the position of the electrons in the cloud associated with each ring at any one time is given by probabilities. At quantum mechanical time intervals, the electron cloud resembles a donut located above and below the plane of each ring and centered on the geometrical center of the ring. At time intervals commensurate with molecular binding however, the probability distribution for each ring is commensurate with the center of each of the probabilistic clouds. Thus, naphthalene exhibits two benzene structures with their electronic structures separated by a distance of 2.419 Angstroms. This distance, the d-value of the molecule, is compatible with a DACB binding to an appropriate olfactory receptor as developed in Section 8.6. Until additional information is gathered, the DACB has a 50/50 chance of binding to either the OR 1 or OR 2 channel of olfaction.

Naphthalene consists of only one pair of electron clouds and provides only one odorophore. Higher levels of polynuclear aromatic compounds consist of three or more electron clouds separated by 2.419 Angstrom, 4.838 Angstrom and multiples of 2.419 Angstrom when aligned, thereby providing multiple odorophores capable of forming DACB with a variety of olfactory receptors. When
The tendency of the polynuclear aromatics to combine with other ligands through substitution means they frequently retain their basic odorophores while potentially adding additional odorophores.

8.6.2.7.2 Polynuclear aromatics sharing three carbons—camphor et al.

Camphor and similar compounds involve ring structures sharing three carbons. They are frequently shown as a six-member ring structure with a top hat. An alternate representation shows camphor as consisting of two five-member rings sharing three carbons. One of the five-member rings of camphor includes a substituted carbonyl oxygen. While camphor is clearly perceived as aromatic, it is usually shown structurally as totally saturated without any "orbital" as defined in Section 8.4.1.1 except the single oxygen. However, it is recognized that the solvation of camphor is an important step\textsuperscript{174}. The six-member ring of camphor is not planar, but boat shaped like in the sugars. The two five-member rings are also significantly twisted out of any plane. These features suggest π-bond formation and resonance are not likely features of these compounds.

Little information has been found on the electronic state of camphor that would relate to a role as an odorant. With the toxicity of camphor and its perception of coolness suggests it may be acting as a noxious substance rather than an odorant. This could be in spite of its wide use in the orient since ancient times for a wide variety of applications.

The studies of the solvation of camphor by Kongsted et al. have surfaced the very different results associated with solvents of different polarity. Results related to water as the solvent were not located.

8.6.2.7.3 More complex compounds with top hats—the bornyls\textsuperscript{EDIT}

The expression "top hat" is frequently used to describe a cyclic hexane or an aromatic where an additional "out-of-plane" carbon is bonded to two opposing carbons of the ring. The out of plane carbon may be associated with additional chemical groups. Cyclic hexanes of this type are frequently described as bicyclo-pentanes where three carbons are shared between the two ring structures.

Boden et al. have described and compared multiple complex forms including a top hat in their US Patent #5,366,959 of November 1994. While the patent does not reveal the key question of how a top hat structure can contribute to a perceived odor, it does provide a variety of other

odorophores in conjunction with the top hat. Figure 8.6.2-28 presents a condensation of pages 1 & 2 of the “description” of the prior art. The Haworth diagrams are not adequate for calculating the d-values of these multiple odorophore odorants (assuming the top hat structure contributes to the formation of the odorophores). The structure to the left of the oxygen atom is typically described as a bornyl group. In the absence of the aliphatic structure beyond the oxygen, the molecule is described as borneol (Merck Index).

A common molecule exhibiting a more complex top hat than santalol is borneol 58234 (bornyl alcohol). It has a variety of commercial uses and molecular variants. Camphor 2441 is bornyl aldehyde. Bornyl molecules appear to be more nocents than odorants. The Merck Index describes the perception of borneol in less than precise language as “Peculiar peppery odor and burning taste somewhat resembling that of mint.” Both camphor and borneol are considered toxic at the current time. The bornyl ligand is not known to exhibit any delocalized electrons and does not exhibit any C=C bonds.

The essential oils of chrysanthemum have been reported as borneol 58234, chrysanthenone and bornyl acetate 83962. Borneol is a hydroxide found in nutmeg (Section 8.5.4.8.9). Alternately, it can be described as a hexane ring with a one carbon top hat connecting to opposite sides of a hexane ring along with two methyl groups. It exhibits no obvious AHB candidates. Chrysanthenone is defined in ChemSpider as 2-pipen-7-one 390901 (an unsaturated form of bornyl aldehyde). It exhibits a d-value of 3.625 Angstrom for the π-bond–oxygen pair. ChemSpider also suggests an alternate form, xxx 9964047, with a potentially different d-value. Bornyl acetate 83062 is even more complex and contains two oxygen orbitals but no covalent carbon bonds in the ring structures according to ChemSpider.

“A” is the generic form Boden et al. sought to patent and “B” illustrates the two specific configurations they define. Both cases involve a hydrogen and an ethyl with one at the R1 position and the other at the R2 position. Based on the hypothesis of this work, the groups at R1 and R2 are not functionally important unless they contain an orbital atom. As defined by Boden et al., the specified groups primarily impact the secondary features of the molecule such as volatility, solubility, etc. of the overall molecule.

The other illustrated forms exhibit a variety of d-values that can only be measured using 3D representations of the molecules. However, it is clear that a variety of d-values are found among these otherwise chemically similar molecules. For illustrative purposes and ignoring the bornyl structure, they can be described as containing DACB’s defined by a 2-carbon separation between the orbitals in all cases except the 3-carbon separation for D, H & J. Structure “K” exhibits a 1-carbon separation and two higher order separations depending on the character of the group Y1. Because of the potential for cis- or trans- arrangements between the two orbitals, a 3D model of the molecule must be used to determine the correct d-value. The 2-carbon separation DACB typically stimulates the (dulcal) channel #2. The 3-carbon separation DACB typically stimulates the (floral) channel #3 and/or the (limal) channel #4 depending on the specific molecular conformation.
Structure “C” is described as representing the cedarwood aroma, US patent 3,354,225.

Structure “D” of the description is fundamentally different than the structure “A” of the patent.

Structure “E” is described as representing a woody aroma, US patent 4,698,180.

Structure “F” can exhibit several different d–values depending on the conformation of the molecule, US patent 4,715,981.

Structure “G” does not include a top hat. It is similar, but not identical, to Ambercore 32818234. As shown, its functional group can be described as a 2-carbon DACB, US patent 5,194,423.
Structures “H,” US patent 4,544,775, and “J,” US patent 4,900,718, both exhibit a 3-carbon DACB structure but of different conformation.

Structure “J” is described as having an aroma defined using up to 6 common labels along with three labels applicable to its topnotes.

Structure “K” incorporates a C=C bond due to the C₄-C₅ alkylene structure designated Y₁. This double bond can act as an additional electrophobic orbital. The d-value of the DACB associated with this C=C bond in collaboration with the oxygen and hydroxyl group depends on the specific alkylene employed. The “K” structure exhibits a DACB with one-carbon between the orbitals as well as the above undefined DACB(s) involving the C=C bond.

8.6.2.7.4 Compounds eliciting a perception of “urine”

Androstenone includes a large family of similar compounds including androstenone_5254715. Androstenone stimulates a strong perception of an unpleasant, sweaty, urinous smell, a woody smell, or even a pleasant floral smell depending on the subject. It is a multi-cyclic structure containing only one aldehyde and only one C=C bond far removed from it. The literature generally considers androstenone an odorant in humans and many other closely related mammals (noted particularly with regard to the pig family)175. (3a,5a)-Androst-16-en-3-ol_92136, one member of this family, exhibits a d = 8.884 Angstrom and qualifies as a vodorophore (See definition in Section 8.6.11.1).

These odorophores will be considered distinct in this study in that they stimulate a high numbered OR 10 but that OR is located in the oskonation modality rather than the olfactory modality and can be labeled VR 1. See Figures 8.6.2-24 and 8.6.2-26.

The question of whether there is a vomeronasal epithelium (containing sensory neurons) remains controversial in humans. Such tissue may be vestigial. Many human subjects do not react to the androstenones in any significant manner. Other subjects are quite sensitive to these chemicals. The porcine mammals react to them in an undeniable physical manner.

Androstadienone, also known as androsta-4,16-dien-3-one_83932 is another member of this family but contains a second C=C bond much closer to the aldehyde oxygen. The vodorophore portion has a larger d-value at d = 9.854 Angstrom.

8.6.2.7.5 Selected heterocyclic compounds

Ache & Carr have discussed a wide range of pyridines and their role in the gustation of crayfish. xxx Figure 8.6.2-29 illustrates a variety of pyridine molecules known to affect the chemoreceptors of crayfish176.

Figure 8.6.2-29 Effectiveness of 12 pyridines in stimulating the chemoreceptors of crayfish. The effectiveness of the substances decreases from left to right in each row. See text. From Hatt & Schmiedel-Jacob, 1984.


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Deiters & Martin have described a large number of heterocyclic molecules (with up to 85 carbons)\textsuperscript{177},

**8.6.2.8 Potential chemistry of the OR's of olfaction**

The ability to define the chemistry of the four GR's of gustation from the literature as amino acids, or their derivatives esterified to phosphatidic acid suggests the same framework might apply to the olfactory modality. This suggestion is supported by the apparent use of PtdSer as GR 1 of gustation and OR 1 of olfaction.

A set of amino acids suitable for esterification with phosphatidic acid is available to form the olfactory receptors at least up through a seventh channel, OR 7, with a possible challenge at OR 6. The structural length of the 22 common amino acids do not readily support a DACB mode of sensory operation at d-values greater than 6.705 Angstrom. There is a potential for OR 8 to employ a diaminohexanoic acid (Dha) as the ligand esterified with phosphatidic acid to create PtdDha, achieving a d-value of 7.184 Angstrom.

As will be shown later, the olfactory channels appear to end with OR 9 and a tenth channel initially considered to represent OR 10 appears to be more properly labeled VR 1 of the vomeronasal organ (to be labeled the sensory portion of the oskonatory modality in Section 8.6.11).

To date four VR channels have been recognized with d-values in the range of 8.882 Angstrom to about 12.0 Angstrom. The possibility has arisen that the VR channels may employ any of a large group of aliphatic carboxylic acids as the moiety to esterify with phosphatidic acid, thereby forming a series of oskonatory receptors, VR 1 through VR 4, on the cilia of the sensory neurons that could extend back to include OR 6, OR 8 and OR 9. All of these receptors would employ a DACB coupling with their odorophores and vodorophores employing a single oxygen orbital and a C=C bond along the aliphatic chain at the appropriate distance from the oxygen atom. In this configuration the complete esterified phosphatidyl ester would be nominally defined as a quadriglyceride. Its head would incorporate any carboxylic acid long enough to satisfy the requirement for a C=C link at sufficient distance from the oxygen atom not involved in the esterification process. This configuration offers the possibility of a single carboxylic acid being used for all of the VR's and the OR's enumerated above. In that case, all of the receptors would employ different geometric isomers of the same organic acid. Wyatt, has described the geometric isomer as a particular form of diastereoisomer in his Appendix A2.

The stepping of the C=C bond down the aliphatic chain of a carboxylic acid would provide an equal step distance between the d-values of the receptors.

**8.6.2.8.1 Tentative d-value space for olfaction**

The material in this chapter was prepared during the initial analysis of the d-value as a primary parameter in olfaction. The OR 2 channel defined in this and following sections of Chapter 8 will generally assign PtdTrp with a d-value of 2.747 Angstrom to the active chemical receptor associated with the OR 2 channel sensory neuron receptor. In some places, the OR 2 channel chemical receptor may be shown as PtdTyr, with a d-value of 2.791 Angstrom based on a possible symmetry among the even number OR channel chemical receptors. See Section 8.6.4.1.3 for this rationale. In the absence of specific empirical data, this situation cannot be resolved. PtdTrp, with d-value equal to 2.757 Angstrom, will continue to be used in the bulk of Section 8.6. There is little impact on the material in this work based on this choice.

Figure 8.6.2-30 provides a tentative d-value graph for the olfactory receptors (OR's) critical to the first step (selection) in the two-step transduction process.

The figure provides a set of suggested olfactory labels related to the specific or primary OR channel. The labels suggest the perception of the simplest member of the group of odorophores stimulating
the particular OR. Eight channels have been firmly identified in this draft graph but at least two additional channels are being investigated. One, OR 10 appears to be found in the vomeronasal epithelium and belong to the oskonatory (vomeronasal) modality. The oskonatory modality and its d-value space is developed further in Section 8.6.11.

The effectivity characteristic of the OR 10 channel may be narrower than the nominal olfactory channel. In addition, the precise chemical structure of the receptor may be species specific in order to achieve its primary role, sexual attraction within the species. Alternately, the OR’s of the vomeronasal modality may employ the more sophisticated A,H,B,X sensing mechanism found in the super-sweet and super-picric stimulants of gustation. The result is a secondary criteria in step 1, selection, of the transduction process that effectively provides a narrower effectivity characteristic.

Most odorants incorporate multiple odorophores. The primary and secondary (or multiple subsidiary) OR channels stimulated by the odorant give the overall perception of the odorant (based only in step one of transduction- the complete perception requires consideration of both the first and second steps in transduction). In the case of floral, the secondary odorophores differentiate the group into subgroups, rose, jasmine, “green floral,” “white floral,” etc.

As an example, the natural macrocyclic musk known as civetone exhibits a primary odorophore with d = 5.132 Angstrom without any secondary odorophore. The synthetic nitro-benzoid musk known as musk tebetine exhibits a primary odorophore with d = 5.211 Angstrom and two secondary odorophores of 2.730 and 2.764 Angstroms. The more complex odorants frequently incorporate additional odorophores that lead to more complex perceptions within the multi-dimensional olfactory space discussed in Section xxx.

Musk tebetine illustrates a well known feature of olfaction; odorophores stimulating the PtdTyr receptor of the OR 2 channel are perceived as pleasant at low concentrations but fetid at high concentrations.

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One of the particularly obnoxious odorants suggest the need for an additional channel; cadaverine (d = 7.425 Angstrom) suggests the need for an eighth and/or ninth channel or that its stimulation of
the seventh channel is particularly effective (Section 8.6.2.5.6).

The semantic labels shown are arbitrary, and involve difficult choices because of the frequency these labels appear in the marketing and academic literature. They can be compared with those of Amoore in 1969 and referred to by Wise et al in 2000, and with the less definitive labels of Rossiter in 1996 based on frequency of occurrence of a term in the literature. Since the Amoore labels were presented in an arbitrary order, they have been reordered here for convenience. Note the absence of any label related to citrus or fruity. The draft OR channel numbers, along with selected information concerning the oskonyatory (vomeronasal) modality have been added to this list, for completeness.

Amoore (1952 & 1969) This work (2012) Single odorophore odorant (SOO)Channel

<table>
<thead>
<tr>
<th>Olfactory modality</th>
<th>Single odorophore odorant (SOO)</th>
<th>Channel</th>
</tr>
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<tbody>
<tr>
<td>pungent (fomic acid)</td>
<td>Acetic acid (2.276)</td>
<td>OR 1</td>
</tr>
<tr>
<td>floral (phenylethyl-methylethyl carbinol d = 4.026)</td>
<td>Skatole (2.721)</td>
<td>OR 2</td>
</tr>
<tr>
<td>dulcal (d = 2.757)</td>
<td>Skatole (2.721)</td>
<td>OR 2</td>
</tr>
<tr>
<td>floral (d = 3.508)</td>
<td>Benzyl alcohol (3.647)</td>
<td>OR 3</td>
</tr>
<tr>
<td>limal (d = 4.467)</td>
<td>Limonene (4.303)</td>
<td>OR 4</td>
</tr>
<tr>
<td>musky (pentadecanolactone)</td>
<td>Musk d = 5.294</td>
<td>OR 5</td>
</tr>
<tr>
<td>musk (d = 5.294)</td>
<td>Acetone (5.132)</td>
<td>OR 5</td>
</tr>
<tr>
<td>Cinnamon (6.075)</td>
<td>Cinnamyl alcohol (6.159)</td>
<td>OR 6</td>
</tr>
<tr>
<td>Spice (d = 6.705)</td>
<td>1-hexen-6-ol (6.793)</td>
<td>OR 7</td>
</tr>
<tr>
<td>Citral (d = 7.184)</td>
<td>Citronellal (7.192)</td>
<td>OR 8</td>
</tr>
<tr>
<td>Putrid (d = 8.02)</td>
<td>6-heptenal (8.022)</td>
<td>OR 9</td>
</tr>
<tr>
<td>Putrid (d = 8.02)</td>
<td>(May stimulate multiple channels)</td>
<td></td>
</tr>
<tr>
<td>ethereal (ethylene dichloride)</td>
<td>(inadequate precision in definition)</td>
<td></td>
</tr>
<tr>
<td>minty (menthone d = 2.662)</td>
<td>(nocent modality stimulant)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oskonyatory (Vomeronasal) modality</th>
<th>Pheromone (d = 8.882) androsteneone (8.884)</th>
<th>VR 1 (OR 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putrid (d = 8.02)</td>
<td>6-heptenal (8.022)</td>
<td>VR 2 (OR 11)</td>
</tr>
<tr>
<td>Putrid (d = 8.02)</td>
<td>6-heptenal (8.022)</td>
<td>VR 2 (OR 11)</td>
</tr>
<tr>
<td>[xxx. Chk value of 8.884 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In 1964, Amoore gave an even larger comparison of labels used by at least nine investigators over the years. Several conclusions can be drawn regarding this table; fruity is equated with citrus, phenolic is equated with carboxylic, ethereal is equated to ethers but the examples shown are not ethers, the musky of Amoore is analogous to sweaty of others of the time period (based on Chemspider) mol file, and there is virtually no statistical correlation between the names provided by different investigators. The confusion is uncommon for a scientific discipline and is due to two facts; the lack of a satisfactory null hypothesis throughout the 20th Century and the failure to realize that most individual odorants incorporate multiple odorophores (a level of definition only achieved through an adequate hypothesis). The table provided columns for established primary odorants and probable primary odors (with only one entry in each, isovaleric acid and sweaty). Sweaty is an appropriate name for the perceived scent due to stimulation of the OR 1(acidic) channel at a specific intensity level. Any carboxylic acid of ten carbons or less can contribute to this perception at room temperature. Phenylethyl methylethyl carbinol 20475013 (known as PEME carbinol) has a d = 4.026 and could stimulate either OR 3 (floral) or OR 4 (citral) and possibly both.

The butyl mercaptan ((CH₃)₂CSH) of Amoore is an imitant when hydrated, stimulating the nocent modality rather than the olfactory modality. It would not be considered putrid under the hypothesis of this work.

Wise et al. defined an objective adjective in olfaction on that of Thiboud who based "his objective description 'on the olfactory note of the raw material' (p. 255). Unfortunately, his olfactory notes were based more on fragrances, and at best simple molecular odorants, rather than fundamental odorophores. Wise et al. went on to note that one chemical and its three derivatives each offered different scents, 'Derivatives of phenylalll alcohol (91) smell rosy, but with other notes: compound 92 smells rosy with 'a lilac and spicy shadow,' compound 93 smells rosy with a 'greener, ozone-like smell with fruity top note; and compound 94 smells like 'rose, cinnamon, carnation, spice and lilac.' Clearly, these chemicals exhibit more than one odorophore. Wise et al. makes an interesting intellectual read. However, it does not come to any substantive conclusions concerning the primary
odorants or odorophores of olfaction.

This work will not attempt to demonstrate any correlation between the primary odorants (containing only one odorophore) of this work with any other list of “primary” odorants.

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[xxx moved from 8.6.2.3 was in wrong place, terminology not defined and missing other receptors]

**Figure 8.6.2-31** shows the proposed sensory receptors for the olfactory modality based on the Electrolytic Theory of the Neuron. [xxx add words.

The fact that the proposed individual OR moieties alternate between an aliphatic and arene form is noted (except for OR 8). The significance of this observed relationship (if any) is unknown. The exception for OR 8 may be due to inadequate analysis of the potential moieties for use in this OR.

The precise number of olfactory receptor channels remains tentative because of the lack of multidimensional analyses related to this modality.

The olfactory modality appears to share the organic acid receptor with the gustatory modality.

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The floral receptor is able to form a coordinate bond pair with a wide variety of carbohydrate chemicals. It is described here as having $d = 2.27$ using standard bond lengths. Eliel et al have described the precise bond lengths and angles for methyl formate (pages 391-392). The result is $d = 2.257$ Ångstrom. They have also shown that the formamides and acetamides ($d = 2.259$ Ångstrom) can also form a coordinate bond pair with this receptor.

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[xxx edit or reconfigure]

Specifying the requirements on a receptor for coordinate pair bonding with an aromatic $\alpha$-ether, an aromatic $\alpha$-ester and an aromatic $\gamma$-ether may be difficult. It is unlikely a phospholipid will contain a simple phenol [xxx??]. It can be assumed that the $\pi$-bond cloud is centered on the center of the phenol ring. However, the radius of a phenol is very nearly the same as the bond length of a conjugated carbon bond. It may be possible to consider the receptor as replacing the phenol ring by an equivalent electron pair located at 1.39 Ångstrom from the ring carbon leading to the side chain. This distance would be only slightly shorter than the standard C–O bond length and could be matched by an appropriate C–C–O bond angle.

The phenol and the $\alpha$-carbon are planar with the carbon bond and the radius of the phenol forming a straight line.
Figure 8.6.2-31 Summary: sensory receptors of olfactory modality MISPLACED based on the Electrolytic Theory of the Neuron and a coordinate chemistry mechanism.
Figure 8.6.2-32 shows the initial version of such a graph based on their figure 4. Frame A shows an initial gustatory taste space as a function of the d-value of the AH,B coordinate bonding. Frame B shows a similar olfactory odor space as a function of the d-value of the AH,B bonding. The calculated values of the olfactophores are "slide rule accurate" and based on the common textbook values for the bond lengths. The graph assumes that a single chemical can exhibit multiple olfactophores just as monosodium glutamate does in taste space. In this case, the four chemicals shown all exhibit a carbonylophore with a nominal d = 1.22 Angstrom.
According to Kreher et al., ethyl acetate and ethyl butyrate both exhibit both the carbonylophore and a non-resonant carboxylophore with d = 2.27. It will be assumed that these two chemicals smell very similar and any difference is due to secondary theoretical considerations (probably involving crowding). 2,3 Butanedione (a cis-di-carboxyl) exhibits both a carboxylophore and a dioneophore with d = 3.61. These d-values all arise from considering the carbonyl group as forming an AHB coordinate bond with a receptor that does not involve hydration of the carbonyl. As an initial hypothesis, it will be suggested that all of these chemicals exhibit an odor sensation characteristic of acetone, with a secondary sensation related to the other two olfactophores. Their specific characteristics are yet to be determined.

The odor space includes a potential nonresonant carboxylophore at d = 2.34 Angstrom due to a simple carboxylic acid olfactophore.

The supplemental material provided with the Kreher et al. paper does group all of the acetates in one area of a large dendrogram, with ethyl acetate and ethyl butyrate adjacent to each other and propyl acetate very near. The more complex geranyl acetate, a terpene derivative is more distant.

In 1998, Johnson et al. presented a slightly different picture using the d-values obtained from Jmol structures available in 2013. They explored the four similar chemicals ethyl acetate, 8525, ethyl butyrate, 7475, isoamyl acetate, 29016 and isoamyl butyrate, 7507 (the numerics correspond to their designation in ChemSpider) using deoxyglucose uptake in rats. Their assertion was that the four chemicals formed a quad where the members were differentiated by the presence of one or both of the specific butyrate or isoamyl groups and these features were significant in differentiating between these stimulants. The 1998 paper did not quantify the difference in perception between these four chemicals, and they did not show their deoxyglucose uptake profiles were statistically significant. After considerable statistical calculation, they did show the difference in carbon number played a significant role however (as would be expected based on their apparent dipole potential).

All of these compounds exhibit a d-value of 2.08 Angstrom and an angle between the two oxygen atoms of 115 degrees except ethyl butyrate at d = 2.28 Angstrom and 120 degrees. They developed the theme that the two isoamyl groups were significant in determining the perceived smell of these forms. Based on this work, the four chemicals stimulate the same organic acid receptor channel centered at 2.276 Angstrom but to a different degree based on their dipole potentials (where the presence of the isoamyl and/or butyrate groups play a significant role). However, the presence or absence of these structural groups is insignificant per se.

The 1998 paper was an early one and it did not recognize the redundancy within the glomeruli demonstrated in their later work. The areas 1 & 2 of the 1998 paper correspond to the two areas labeled 9 in Figure 8.6.7.13 of Section 8.6.7.3.3 overlaying the borders between the I/J and I/I regions of the original Johnson & Leon graphic.

8.6.2.8.2 OR responses to amino acids and other stimulants in catfish

Caprio and colleagues have explored the sensitivity of catfish to amino acids as olfactory stimulants.

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The work was clearly exploratory based on the arbitrary selection of their amino acids. Valentincic et al. studied the learned discrimination capability of a group of catfish (Ictalurus and Ameiurus) to a group of L-amino acids. L-serine was one of their chosen amino acid stimulants.

Nikonov & Caprio investigated the responses to a mixed group of stimulants in the olfactory bulb of the catfish.

Nikonov & Caprio prepared a series of papers on the response to amino acids of OR's of catfish. There approach was conventional and assumed the OR's were transmembrane G-proteins. In the first paper, they selected four amino acids based on their structure. They apparently were mistaken or there was an error in translation. They indicate they used monosodium glutamate as an amino acid instead of glutamic acid (GLU) as the acidic amino acid, arginine (Arg) as a representative basic amino acid, alanine (Ala) as a representative neutral amino acid and methionine (Met) as a typical long chain amino acid using stimulant concentrations between $10^{-6}$ and $10^{-4}$ M. They recorded signals from 327 olfactory bulb units. Unfortunately, none of these amino acids formed dimers with the proposed amino acids of the receptors proposed in the above section.

Nikonov et al. in a 2007 paper recorded stage 1 generator potentials from OR's of the catfish (Ictalurus punctatus) at relatively low concentrations as determined from the shape of the generator potentials.

In a second paper, Nikonov et al. recorded forebrain responses to olfactory stimulation. They recorded stage 3 action potentials in the forebrain and demodulated them to recover the analog waveforms. These waveforms were faithful reconstructions of the stage 1 generator waveforms recorded in the earlier paper.

As a group, these papers did not show the amino acids employed were closely related to the receptors of the OR's in catfish.

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8.6.2.9 Summary odorophore architecture of this work

As an introduction, the following points will be stressed,

- The odorophores of mammalian olfaction (and oskonation), including humans, do not rely upon the chemistry groups of conventional chemistry. They are defined exclusively by the overlay groups defined by their capability of forming DACB. For complex molecules, the number of independent overlay groups within a given molecule, or odorant, expands exponentially.

- The overlay groups are fundamentally three-dimensional in character and their precise d-values must be determined in 3D space. The most common and arguably most important overlay groups involve two oxygen orbitals resulting in a \(-\text{diol}\) or \(-\text{dione}\) conformation separated by a nominal number of effective carbon atoms. A mixture of the two oxygen orbital types (one supporting a double bond and the other supporting only a single bond of ordinary valence chemistry, such as in the case of the carboxylic acids), is also common.

- The d-values of a given molecule (odorant) related to olfaction (and oskonation) must be calculated when solvated by the mucosa. Theoretical calculations of the d-values of a molecule based on the minimum potential energy conformation in a 3D representation of the molecule are not adequate. In many cases, the actual molecule may be present in a non minimal potential energy conformation.

- The use of “standard” bond lengths in computational chemistry may lead to eminious values. Proper calculations must depend on precise bond lengths associated with the conformation in question (which may be impacted by crowding).

At the current time, many of the overlay groups calculated from various databases (including the Jmol and JSmol databases of the Royal Society of Chemistry) are not adequately curated to ensure visualization based on these databases provide sufficiently precise d-values. However, this work is forced to rely upon such d-values at this time. The Jmol files are no longer available in 3D based on the cancellation of their internet security certification based on the “Cessation of Activity” as of 15 October 2015.

It has also become apparent that many of the d-values calculated from the Jmol and JSmol files (based on average molecular bond lengths) of the RSC differs significantly from the measured bond lengths of crystallography.

- - - - -

Based on the Electrolytic Theory of the Neuron and the application of the DACB to olfaction, oskonation and gustation, the very large range of odorants can be categorized into only a few basic chemical structures and their derivatives. As generally happens in organic chemistry, the number of derivatives is very large. The basic chemical structures of olfaction begin with the unsaturated aliphatics, the aromatics and the aromatic-aliphatics. The aromatic-aliphatics are not limited to the arenes formed from only hydrocarbons. The addition of one or more orbitals containing unpaired electrons in their outer shell, oxygen, nitrogen, sulfur and phosphorous, expand the members of each of these derivative groups immensely. The further expansion of the odorants to include fused homocyclic and heterocyclic molecules expands the number of odorants greatly.

The ability of ring structures to accommodate multiple aliphatic side chains further increases the number of potential odorants.

The only constraint on the total number of odorants is that each candidate must contain at least two sites capable of forming hydrogen bonds with the two sites on the sensory neural receptors of similar d-value, must be sufficiently soluble in the olfactory mucosa, and must be sufficiently volatile to travel between the source and the olfactory epithelium.

Each pair of sites within an odorant capable of forming DACB’s with the sensory receptors qualifies as a distinct odorophore. As a result, each odorant may contain from one to a very large number (well above 12) of odorophores. As a result, the perceived odor of a single odorant may be the
result of a complex multidimensional representation within the stage 4 saliency map of the neural system.

[xxx? covered below?]

The following few figures will omit orbitals other than oxygen, the fused aromatic rings, rings containing other than six members, and the heterocyclic rings in the interest of simplicity. All of these conformations do produce viable odorophores and odorants.

Figure 8.6.2-33 provides a flow diagram for generating a wide range of odorant molecules or azeotropic compounds, beginning with the cyclic and aliphatic hydrocarbons. The labels shown are not exclusive and frequently overlap with each other because of the rapid increase in the options provided by organic chemistry. Both the cyclic and non-cyclic aliphatic hydrocarbons are fundamentally odorless. However, their desaturation and or incorporation of orbital atoms can lead to significant odors.

The aromatic label applies to all resonant ring structures whether 5, 6, 7 or more sided (as long as they satisfy Huckel’s rule).

The aromatic group includes a very large number of structures incorporating either a hydroxyl or amidic group attached to a member of the ring. Absent these groups, the aromatics tend to be noncents. With the hydroxyl group, they form the very important phenol structure. From an olfactory perspective, there is a significant difference between an arene exhibiting a hydroxyl group separate from any other side chain joined to the ring via esterification and an arene with only an esterified side chain. Labeling becomes awkward in this area and some expansion of the IUPAC naming rules may be needed (the use of allyl over the years appears to be a particular problem in olfaction). Based on the description in this paragraph, there is a substantial difference in perceived odor between a benzene aliphatic ester (no stand-alone hydroxyl group) and a phenol aliphatic ester. See benzyl ether, anisole_7238, and phenol ether, guaiacol_447, in the next figure.

The figure demonstrates there are at least six paths to the creation of an odorant containing at least one odorant. Any path resulting in two sites capable of a DACB in one molecule is a legitimate path to an odorant. In general, several of these paths may be employed simultaneously to create an odorant containing multiple odorophores. A single odorophore odorant (SOO) is preferred in olfactory research because it leads to the simplest perceived odor. Such an odor is perceived by stimulation of only one of the n-dimensional coordinates of the saliency map dedicated to olfaction.

The arenes must include one additional C=C bond or orbital in order to exhibit a perceived odor.

Fused aromatic structures can exhibit an odor as long as at least two electrophobic sources are present in the overall structure. Both homologous and heterologous structures are included in this group (thus opening the group to a broad range of nitrogen-based, and even sulfur-based odorants not discussed further in this work except in specific cases).

Among the lighter molecular weight substituted hydrocarbons containing one orbital, their coordinate chemical interaction with water to form an azeotrope introduces a significant odorophore.
8.6.2.9.1 Aromatics and arenes as odorants

Figure 8.6.2-34 shows an initial segment of the aromatic and arene family tree (but limited to six-sided aromatic structures). The figure allows for a wide range of additional ligands to occur. When R = CH₃, the labels given below the molecules apply. The figure contains a number next to each molecule indicating the number of potential DACB's associated with that molecule when R = CH₃. Where the number is one, the molecule can be considered a single odorophore odorant (SOO).

As noted in the indented paragraph, Acetophenone is described as a methyl benzyl ketone in this work since it does not exhibit an OH group indicative of a phenol derivative from the olfactory perspective. The presence of an OH group attached to the benzene ring is significant in olfaction; it increases the number of odorophores within an odorant substantially.

The figure highlights a variety of relationships among the aromatics and arenes.

1. Benzene alone does not exhibit the capability of forming a DACB. It would not be expected to be an odorant exhibiting even a single odorophore. However, it is considered a significant nocent and to be highly toxic when ingested. It can be used to form a variety of bicyclic and heterocyclic
compounds as well as arenes. In general, the arenes are not toxic and form the bulk of the aromatics associated with hedonic odors. Exceptions include some of the simplest arenes, benzyl hydroxide_971 (phenol), benzaldehyde_235 and isopropenylbenzene_7129, which are discussed in the following sub-section.

2. As R becomes more complex the number of orbitals can grow without limit, indicating the potential for a very large number of odorophores within a single odorant. Whether the individual odorophores are equally effective in step one of olfaction is a more complicated question.

3. As the arrows below anisole_7238 indicate, the derivatives of the arenes can include more than one aliphatic side chain, each of which can contain orbitals affecting the perceived odor of the molecule.

4. As the arrows below anisole_7238 also show, the location of a given moiety on either side of the ring can cause changes in the d-values of the various odorophores, thereby changing the perceived odor of two chemicals with the identical molecular weight and apparently the same grouping.

5. The mere fact that a molecule becomes non-planar can change its d-values and cause it to have a distinguishing odor compared to its otherwise similar partner.

6. Stick, or stick and ball representations of these molecules on paper do not show their true 3D character and can not be relied upon for calculating d-values using standard bond length tables.

7. As in the case of most of the illustrated molecules, one or more rotatable bonds are present. The Jmol figures are believed to show the minimum energy situation for these bonds but there is no confirmation of this condition or how it is demonstrated. Some of the d-values obtained from the Jmol files may require modification if not confirmed in the future.

Note, the CHO group is indicative of the aldehyde, and not just the C=O relationship. Thus, the aldehyde of benzene is given as C6H5CHO. By structure, it can be considered a benzyl carbonyl. This structure, and that of isopropenylbenzene, are discussed more fully in the next sub-section.
The two allyl structures shown in the lower center exhibit significantly different steric relationships with the rest of their molecules and will exhibit different d-values related to the C=C group. Similarly, the 2-(allyloxy)phenol_63937 will exhibit different d-values than eugenol_13876103 even though the active chemical groups present are identical. The allyl radical is CH2–CH=CH2. The molecule labeled 2-phenylallyl alcohol_72356 (a.k.a. 2-phenyl-2-propen-1-ol_72356) exhibits a still different set of d-values. In accordance with the above indented note, it is more appropriately labeled a...
benzene derivative. since it does not contain a hydroxyl group attached to the benzene ring.

Vanillylamide 314326 in row 4 exhibits twelve distinct odorophores due to the presence of four orbitals and the electrophilic aromatic ring. The use of this molecule in olfactory research is clearly counter-indicated.

Figure 8.6.2-35 shows the architecture of these families by name in the context of this work. Some of the labels are taken from the empirical literature and may not be simple odorants (those labeled as “oil of ---” particularly). The simplest odorants are based on the benzene chemical group, with derivations to the phenols, phenol ethers and aliphatic phenol ethers. Closely related groups are also shown for continuity. It appears the aliphatic benzyl alcohols and ethers are the parent of many of the most important floral odorophores. The structural groups suggest more scientifically relevant names for several of the groups. Carbonyl cyclohexene is shown because of its very close association with the other resonant ring carbohydrates and its terpenoid structure. Alcohols are named by a multitude of systems. Here, a resonant ring structure without a hydroxyl attached directly to it is considered a benzene and not a phenol. Such structures do not exhibit the d-value of a phenol. For purposes of this analysis, the position of various oxygen and nitrogen atoms will be described relative to the resonant ring, thus an α-oxygen is attached directly to the ring. A γ-oxygen is two carbons removed from the ring. An ester (of carboxylic acid) represents a special configuration in the context of aliphatic-aromatics. Its correct d-value may depend on the presence of other nearby groups.
The high volatility of the benzene derivatives, compared to the phenol derivatives, helps explain their role in blooming flowers. A large variety of derivatives of the florals shown in the shaded area provide the profusion of odorophores among the flowering plants.

A variety of flowering plants seek to attract insects that thrive on decomposing protein by releasing an odorant with similar d-value. These constitute putrid florals from an olfactory perspective. The result is a fundamental division of the florals into hedonic and putrid classes. Putrescine, (1,4 butanediamine) and cadaverine (1,5 pentanediamine) are two aliphatic amines that are produced by the breakdown of amino acids in living and dead organisms and both are toxic in large doses.

The aliphatic odorophores, shown on the right, are a relatively small family. They are divided into two categories based on their formation of an overlay group.

The first three are basically odorless when present in saturated form. However, they do not exist in
their simplest chemical form in the presence of water. In the process of solvation, they become hydrated and thereby form azeotropes. These azeotropes exhibit two sites capable of forming DACB’s and are therefore odorophores. With additional desaturation, they form odorants exhibiting multiple odorophores.

The second pair contain two oxygen orbitals and form odorophores without further desaturation or hydration. In the case of the di-carbonyls, they exhibit one or more odorophores. Depending on their conformation, they may form multiple distinct odorophores.

The lower molecular weight aliphatic carboxylic acid exhibit high volatility and high solubility, even if their ionization coefficient is quite low in mucosa. They can act as effective odorants. The lower molecular weight esters of these acids also appear to play a role in olfaction as do a few di-carbonyls, particularly those exhibiting vicinal carbons. However, these materials lose their volatility with increasing molecular weight, limiting their role to the area of olfaction.

The number of amine odorophore families shown at lower left is relatively small. However, their role is considerable, based particularly on their formation in the process of cooking. Many odorophores are formed that exhibit significant volatility and solubility.

8.6.2.9.1xxx Overview of perceived odorant families in humans OPTIONAL

The following figure presents an overview that is in development and not to be relied upon. Its purpose is to show how many of the chemicals on the left and their families may exhibit multiple odorophores of different strength that stimulate more than one of the olfactory channels shown in the lower portion of the figure. The examples are not necessarily complete or cross-checked from every angle for accuracy.

[XXX what is X stand for in the figure?? ]

**Figure 8.6.2-36** is an expansion of the figure showing d-values of the OR’s to show how the more common odorants stimulate those OR’s. The upper bars describe the various odorophores within specific families of odorants showing various molecules based on their efficiency in stimulating a specific olfactory channel; Primary, Secondary, Tertiary, Quartenary, etc. Multiple primary stimulants may be present because of the presence of multiple molecules within a family. In the case of garlic_15481, the symbol X is used to indicate two primary odorophores at the indicated d-value.
Figure 8.6.2-36 DRAFT The family relationships between a wide range of odorants showing Primary, Secondary, Tertiary, etc. relationships. The OR moiety for channel 6, at 6.075 Ångstrom, Ptd--- remains undefined. It could be provided by a different structural arrangement and exposure of PtdHis. The Ptd--- labels for channels 8 & 10 are tentative and do not describe “common” amino acids esterified to phosphatidic acid. The Ptd--- label for channel 9 remains undefined. Any OR of channel 10 or higher can be considered a vodorophore receptor, VR, of a new series as shown. See text.
While the figure is primarily illustrative, it does highlight a variety of important facts that need to be correlated with current practice in the perfume manufacturing and marketing communities.

1. A rose-like scent is subsidiary to the more general floral scent (shared by the roses and most other flowers of pleasant fragrance).

2. The differences in scent between roses and jasmines are in their secondary and tertiary odorophores.
   
   The poorly defined difference between “green florals” and “white florals” is probably related to their secondary odorophores.

3. At low intensity levels, the dulcal odorants are considered pleasant, appear as significant odorophores in the jasmine family of flowers, and are frequently incorporated into commercially viable perfumes.

4. The OR sensitive to the cinnamon (d-value nominally 6.0 Angstrom) has not been defined. It is likely an ester of a derivative of an amino acid (like inositol in gustation).

5. There are likely to be one or more additional OR’s with d-values of ~7.5, 8.2 and higher.
   
   The contribution of these OR’s to the total perception of odors is probably small.

6. The lemons and limes of citrus fruit are dominated by limonene, an odorant with only one odorophore, that primarily affects the limal channel, OR 4 due to its d = 4.303 Angstrom.

   Other citrus odorants have primaries at d = 2.687 Angstrom, that act as secondaries to the dominant odorophore of limonene, with their own secondaries at 5.537, 7.102 and 7.259 Angstrom as well as a primary at 7.102 Angstrom that acts as a secondary to limonene.

Limonene is the only common natural odorant that both dominates the scent of the citrus family and is the predominant stimulus of the PtdHis olfactory channel, thereby suggesting that channel be labeled the citral channel.

7. The natural mammalian musks have a primary odorophore with d = 5.1 Angstrom. The value shown at 4.289 Angstrom is believed to be due to the conformation chosen to create the J mol file used by ChemSpider.

8. There is a natural odorant that is frequently considered a plant based equivalent of the mammalian musk, 2-hydroxy-5-methoxybenzaldehyde exhibiting odorophores with d-values of 5.25, 5.60 and/or 6.035 Angstrom. The d = 5.25 value might qualify as an adequate substitute for the mammalian musk but would exhibit additional elements in its scent not shared with the mammalian musk.

9. Four synthetic non-nitro benzoids, phantolide et al., are very aromatic but not musk-like based on the hypothesis of this work.

10. The OR channels labeled cinnamon and spice respond to relatively large odorophores of limited volatility. The sensing of these odorophores usually requires relatively high air temperatures, or grinding or mastication of the source materials, and frequently involves retro-nasal application to the sensory receptors.

   The reduced effectiveness with increased d-value, driven by molecular weight, suggests only a few, if any, undefined OR channels exist at d-values greater than 8.0 Angstrom.

11. Garlic oil is shown as exhibiting three odorophores (marked with X’s) that appear to stimulate OR3, OR 5 and OR 7. There is no way at present to distinguish any primary odorophore. Further analysis of the scents generated by its isomers in psychophysical experiments may clarify this situation.

12. The single odorophores of two separate putrid flowers are shown at d = 6.222 and 7.425
The highest d-value may couple with OR 8 and may define the need for an OR 9.

The remaining questions are what are the moieties esterified to phosphatidic acid with d-values near 6.075, 7.4 and 8.2 Ångstrom?

A minor amino acid with one more methylene group (C7H16N2O2) than lysine (C6H14N2O2) would exhibit a d-value in the region 7.4 to 8.2 Ångstrom. There are multiple candidates in this area. (3S)-3,7-heptanoic acid is a good candidate with a d = 7.184 Ångstrom. N-acetyl-N-hydroxycađaverine is another candidate with d = 8.297 Ångstrom. It has a backbone of five CH2 groups and a slightly rearranged amino group. To minimize the naming problem, the first chemical esterified with phosphatidic acid will be labeled PtdDha and the second PtdAhc. Italics will be used to indicate they are not simple amino acids.

Other conformations of these and similar structures may provide preferred d-values.

Identifying the OR with a d-value near 6.075 remains to be accomplished. There are many possibilities, another derivative of PtdHis or of the amino acid esters nearby on the d-value line. Histidine itself does offer a DACB coupling capability with a d = 6.315 Ångstrom that could be employed if the ester exposed this structure to the mucosa instead of the structure with a d = 4.467 Ångstrom.

Ache & Carr have explored an unusual amino acid (using a broad definition), taurine (C2H7NO3S) that is ubiquitous in many marine invertebrates. The family is more formally named the amino sulfonic acids. This molecule is rich in oxygen both in hydroxyl and aldehyde conformation, and includes an amine group. However, it does not exhibit a carboxylic acid group.

8.6.2.9.2 A multi-dimensional display of olfactory perception space

Section 8.6.6 develops a complete multi-dimensional space applicable to the olfactory modality. The result is a space analogous to the color space of Munsell in vision. See Sections 17.3.1.2 and 17.3.5.2 of the author's work “Processes in Biological Vision” for discussions of the Munsell Color Space. It is clear from the one-dimensional d-value line that the olfactory perception space originates from nine distinct OR-fed (stage 1) neural signaling channels. While such a space is not easily envisioned graphically, the space can be initially portrayed by a series of zeros and ones with each OR (and associated centered d-value) described by a single one within a string of zeros in what appears to be a binary code.

8.6.2.9.3 The hedonistic flowers

The hedonistic flowers form an immense group where nearly every flower exhibits a multitude of odorants and most of those odorants incorporate multiple odorophores. These odorophores are not limited to stimulating the OR 3 (floral) channels. In many of the flowers, the concentration of odorants varies over the life of the flower. From the observer’s perspective, her perception (at least for flowers stimulating OR 2) varies with the intensity of the odorophore presented to her olfactory epithelium. In addition, the sensory neurons of stage 1 are frequently at different levels of adaptation (thus leading to transient differences in the perceived “smell” with time. As a result,

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characterizing a particular flower of a particular species of plant becomes extremely difficult.

Figure 8.6.2-37 illustrates what appears to be the most important chemical structure related to the hedonistic flowers. 2-phenylallyl alcohol (2-phenyl-2-propen-1-ol) is the simplest member of this structure and is frequently associated with the basic perceptual odor of the rose.

From the perspective of olfaction, the formal name should probably be 2-benzyl-2-propen-1-ol since the molecule does not contain the hydroxyl ligand attached directly to the benzyl ring that qualifies it as a phenol (See Section 8.6.2.1.2).

The molecule exhibits three distinct odorophores with d-values of 2.852, 3.270 & 3.972 Ångstrom based on the JSmol files of late 2015 and DS 4.1 visualizer. These odorophores stimulate the receptors of OR 2, OR 3 & OR 4 channels. The ratio between the perceived stimulant intensities is yet to be determined. Removing the oxygen atom, the structure would revert to a hydrocarbon arene with only the odorophore at d=3.270 Ångstrom and stimulating only the OR 3 (floral) channel.

The molecule on the right indicates the natural extension of this framework. R can represent significantly long unsaturated aliphatics or a variety of compounds incorporating at least one additional orbital. Additional orbitals or C=C bonds considerably increase the number of odorophores as indicated in Figure 8.6.2.9-xxx. These theoretically introduce additional “notes” in the perceived odor of the botanical species.

The additional ability of the basic framework of the hedonic flowers to combine with multiple aliphatic side chains to form very complex compounds appears to account for much of the variety in the various odorants of the hedonistic flowers.

In accordance with the hypothesis of this work, many of the odorants found in hedonistic flowers exhibit a multitude of odorophores satisfying the DACB criteria and present various stimulus intensities to the observers nose. The result is an almost endless variety of 9-ary space codes describing different sensory situations.

Figure 8.6.2-37 illustrates two of the most common variants of odorophores associated with the hedonistic flowers. The aromatic ether and the aromatic γ-alcohol are commonly found among roses. They can exhibit additional d-values if the R group contains additional orbitals or unsaturated C=C bonds.
8.6.2.9.4 The citrus fruits

When discussing the odorophores of the citrus fruits, most of the structural configurations in the literature must be ignored in favor of the more detailed terminology adopted recently. The RS and/or E,Z nomenclature (and potentially the use of + and – signs as well) must be employed to provide adequate definition of what is being discussed with regard to olfaction. See section 8.6.2.5.7.

In the last lesson related to the RS system, the Khan Academy notes that (R) carvone smells like spearmint while (S) carvone smells like caraway seed. They assert, without any citation to theory, this is because of the chirality of the OR’s in the (human) nose. See Section 8.6.1.8.4.

The citrus fruits exhibit a wide ranging set of odorants that are largely shared between the lemons, limes and oranges. These fruits exhibit at least two SOO’s, limonene_20939 at the lower end of the d-value spectrum and stimulating the limal, OR 4, channel, and citronellal_7506 near the higher end stimulating the citral, OR 8, channel.

The grapefruit odorants are fundamentally separate from those of other citrus in their employing a selection of sulfur-based odorants in addition to potential limal and citral channel stimulants. So-called “grapefruit mercaptan_21163535”(C 10H18S) is considered the principle odorant of grapefruit.

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The structure of the molecule is quite similar to that of limonene.

The molecules known as citral have not been adequately characterized for purposes of olfaction. Due to the four points of rotation about C–C bonds, the family contains a large number of isomers. Citral a (geranial) is typically associated with the high d-value case stimulating OR 8. Citral b (neral) is typically associated with the low d-value case stimulating OR 4. Neither geranial nor neral is typically found in isolated form, but mixed with a wide variety of isomers of citral. Most of these isomers are not enantiomers (mirror image isomers) but stereoisomers (exhibiting different conformations). The stereoisomers typically exist at different energy minimums, with different d-values corresponding to their precise conformation. Characterizing the odor of citrus fruit is particularly difficult because of the wide range of d-values associated with a given mixture of citral isomers and other odorants.

8.6.2.9.5 The putrid flowers

There are seven well known flowers with a very strong objectionable odor, generally considered to be putrid. One of the most prominent because of its size is Titan Arum (Amorphophallus titanum). Another is the Western Skunk Cabbage (Lysichiton americanus). A third is the Carrion Flower (Stapelia gigantea) which has many nicknames and isn’t very large. A fourth is the Dead Horse Arum Lily (Helicodiceros muscivorus); this species actually generates heat for purposes of raising the volatility of its odorants. The principle odorants of these plants are disulfides and trisulfides with d-values in the 2.080 region with one potentially at d = 3.397 due to the distances between the sulfur atoms. Only if the methane groups exhibit a significant charge polarization would they exhibit higher d-values. It is common to suggest these di- and tri-sulfides parallel the odorophores of putrescine and cadaverine of protein degradation. However, their structure and d-values are entirely different.

Both putrescine (with d = 6.222 Angstrom) and cadaverine (with d = 7.425 Angstrom) are simple straight chain aliphatics with no C=C bonds and terminating in two NH2 groups (diamines). They are found in stale urine and are frequently associated with decomposing protein material.

At least putrescine may have achieved an unearned reputation. Beets has noted, “In 1968, Amoore and his co-workers observed that a few of their panel members did not report the odor of putrescine (1,4-diaminobutane) to be offensive and were unable to perceive the odor of dilute solutions of this amine.” He went on, “Recently (Amoore, 1975; Amoore et al., 1975), this phenomenon has been studied in detail. The offensive odor of putrescine was found to be entirely due to the presence of traces of the cyclic Schiff base 1-pyrroline.” This information is consistent with the d-values of these materials reported here. Putrescine cannot be expected to have an offensive scent with a d-value of 6.222 Angstrom. However, the description of the Schiff base 1-pyrroline is not adequate to establish a specific d-value. It may be a generic label given the time period. The pyrrole family, beginning with the highly aromatic pyrrole with two double bonds, is subject to rapid deterioration when exposed to air into more complex compounds of undetermined d-value.

The above odorants are generally based on sulfides, sulfanes and sulfanilamides but not thiols (mercaptans). Thiols, incorporating the group -SH appear to more effectively stimulate the nocent modality like hydrochloric acid, a homolog, through hydration. In onions, the sulfenic acids, RSH-OH, based on sulfanilamide are of the same structure and are imitantsnot odorophores. The chemical stimulant in onions is a complex multi-ring hydrocarbon closely related to picric acid. Because of that feature, it is more properly described as a gustant than odorant.

The d-values of putrescine and cadaverine introduce a need for more definition in the widths of the effectivity characteristic for OR 6 through OR 8 and the potential need for an OR 9. These two

chemicals exhibit only one odorophore each and none at a low d-value that would suggest they are associated with the neural channel of OR 1. However, they may help define a pungent axis between OR 1 and the higher numbered OR’s mentioned. In this case, the axis would extend from the purely acidic perception to the purely putrid perception (suggesting the OR 1 should be labeled acidic rather than pungent).

[xxx and OR 8 or OR 9 should be labeled the putrid channel.

**8.6.2.9.6 Odorophores of overlay ligands (structural arrangements)**

While conventional chemical groups do not play a determining role in olfaction, equivalent overlay groups do play such a role. **Figure 8.6.2-38** presents a description of these overlay configurations for discussion purposes. The figure is intended to show discrete and non-overlapping categories. To achieve this objective, each term should be used in its narrowest definition, with no implied adjectives or alternatives. The major categories are not named structural groups but structural arrangements irrespective of the conventional groups present. A few group names appear under major categories 2 and 3 because of their simplicity.

Category 1 is generally recognized as including chemicals with no intrinsic odor. Category 2 includes several chemical categories that may be unexpected because they have been so widely used in behavioral research. These are the simplest forms of these chemicals. Some of the chemicals in these categories may actually be nocents rather than odorants. They typically exhibit astringent properties and are perceived as “cooling” but do not exhibit a perceivable smell. The chemicals in category 3 are the first that are described as odorants under this hypothesis and its corollaries by virtue of the presence of two orbitals. This category is limited to orbitals containing one of the four atoms, oxygen, nitrogen, sulfur and phosphorus. The most common chemicals are the organic acids and the acetates. Many of the open chain chemicals are quite twisted in their geometrical configuration (that must be considered in 3D space). It also includes a variety of non-aromatic closed chains with two substituted orbitals (example, xxx).

Many of the closed chain compounds of category 3, such as the sugars, do not exhibit sufficient volatility to be considered odorophores or odorants. When brought into solution in the oral cavity, they are readily perceived as gustaphores.

Category 4 includes a wide range of chemicals that are perceived as odorless although they contain one orbital but not the required two.

Category 5 introduces the first large group of odorants, most of which contain a single odorophore. While potentially considered aromatic by the behaviorist investigator, they are not aromatic from the chemist’s perspective. The most easily identified members are the alcohols (the -enols) and aldehydes containing a double bond between two carbons in their aliphatic chain.

Category 6 expands the odorant repertoire significantly. Since the aromatic hydrocarbons are orbitals in the context of this work, only one additional orbital is required to form an odorophore. The simplest of this group, although also a nocent, is phenol, an aromatic with a substituted hydroxyl group. The more complex phenols appear in category 7 and are less noxious. An interesting subcategory is naphthalene, a simple aromatic ring fused with a second aromatic ring that exhibits two distinct orbitals and qualifies as a single odorophore.

Polarized three-, four-, five- and seven-member rings are included in this category along with the conventional six-member aromatic rings. The criterion is that they must satisfy Huckel’s Rule.

Category 7 includes the arenes (homocyclic aromatic-aliphatics) containing one additional orbital. This is a very large category containing many of the odorophores found in the essential oils of flowers, fruits and other botanicals. The second orbital can be located virtually anywhere along the aliphatic side chain with the distance of the second orbital from the aromatic ring determining the OR channel stimulated. The second orbital can be located farther than the delta carbon but such chemicals begin to stimulate the oskonatory rather than the olfactory modality.

The individual arene can contain multiple substituted orbitals or multiple aliphatic side chains. The result is additional odorophores if a substituted orbital is also present or the individual chains contain additional orbitals. Such arenes introduce category 8. They contain multiple odorophores and must
be treated as odorants. As odorants, category 8 chemicals introduce an additional degree of complexity in behavioral experiments and glomeruli mapping activities.

Categories 9 and 10 will not be developed here in detail. Category 9 consists of rings that contain one or more atoms other than carbon, but limited in this case to the atomic orbitals defined in this work. While the presence of these atoms may disturb or destroy the resonance of the parent rings, they generally do not. Many of these heterocyclic rings are considered aromatic by the chemist because of the continued resonances. Morrison & Boyd, 2nd Edition (page 1073) illustrates more than a dozen heterocyclic compounds with many containing two or more hetero-atoms in a ring. Whether the individual orbitals or the heterocyclic ring as an orbital are dominant in forming DACB connections requires more analysis of the experimental record. Morrison & Boyd (page 1083) shows picoline with the methyl group associated with the resonant ring rather than a specific atom of the ring (which is not supported in the current ChemSpider rendition showing the methyl group associated with a single carbon). The behaviorist also reports aromatic perceptions, even from a single ring incorporating only a single orbital. Most heterocyclic rings containing two orbitals but no other substitutions or aliphatic extensions are perceived as aromatic and therefore odorants or odorophores depending on the specific DACB configurations supported.

Such heterocyclic rings are capable of forming all of the categories of compounds described in categories 6, 7 & 8 for the homocyclic aromatics. The effective d-values of these compounds, and therefore their perceived odors, depend on the dominance of their overlay ligands.
### Figure 8.6.2-38

Overlay ligands (structural arrangements) affecting olfaction ADD. Less than a dozen categories of chemicals are required to accommodate all of the odorants of olfaction. However, the categories and subcategories beginning with 7 contain large numbers of individual chemicals. See text.

<table>
<thead>
<tr>
<th>Category</th>
<th>No Intrinsic Odor</th>
<th>Single d-value dependent odorophore</th>
<th>Odorants with multiple d-value odorophores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Saturated hydrocarbons</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Saturated hydrocarbons + 1 orbital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(subject to impurities at the ppm level)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldehydes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Saturated hydrocarbons + 2 (atomic) orbitals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open chain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closed chain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Unsaturated hydrocarbons with 1 orbital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Unsaturated hydrocarbons with 2 orbitals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Homocyclic aromatic hydrocarbons + 1 orbital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital at substitution position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital a second fused homocyclic aromatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Homocyclic aromatic-aliphatics (arenes) + 1 orbital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital attached to alpha carbon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital attached to beta carbon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital attached to gamma carbon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbital attached to delta carbon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Homocyclic aromatic-aliphatics + 2 orbitals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a new level of olfactory complexity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Heterocyclic chains (with or without substitution)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Heterocyclic aliphatics (with or without add'tl orbitals)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.6.2.9.7 A preferred odorophore wheel

[xxx duplicates Section in 8.6.6.5 shorten this text and refer to that section for details]

The orthogonal 9-dimensional space described above can be shown graphically, but with a loss in orthogonality and somewhat more difficulty in describing complex situations. Figure 8.6.2-39 (left) shows a “olfactory wheel” (analogous to a compass rose) describing a set of preferred odorophores useful in exploring the olfactory perceptual space. It is proposed that each of the preferred odorophores shown only stimulate one of the identified OR channels.

Figure 8.6.2-39 A olfactory wheel & set of preferred odorophores UPDATE. Left: It is proposed that each of the odorants shown contain only one odorophore that stimulates only the associated OR channel. ChemSpider lists two distinct cinnamyl alcohols. Note the accession number used here.

Right; The proposed response to a psychophysical experiment reporting the intensity of the perceived response (on a scale of 0 to 5) to a single standardized concentration of a preferred odorophore. See text.

[xxx need more analysis to define the OR 7 preferred odorophore

While not fully identified at this time, the OR 9 channel with a maximum effectivity at a d-value near 8.0 Angstrom could be ideally stimulated by 6-heptenal 4446441, a nominally straight chain hydrocarbon with one C=C double bond at a distance of 8.022 Angstrom from the oxygen orbital. While 6-heptenal has a molecular weight of only 112 Da, with a vapor pressure of 4.885 mm/Hg at 25 C, its length may contribute a degree of fragility to this molecule. Many of the odorants stimulating the OR 9 channel have molecular weights in the region of 250 or higher and appear to be more rigid in their configuration. If there are odorophores within larger molecules with d-values exceeding nine Angstrom and justifying additional OR channels, they have not appeared as part of this analysis.

The related straight chain aldehyde, heptanal, is said to exhibit a strong odor (presumably in pure, and not a hydrated, form). If correct, a further corollary to the hypothesis employed here is needed to account for the simple aldehydes and alcohols exhibiting a scent under some conditions. This could include a charge distribution sharing between the two carbons farthest from the oxygen with the character of a C=C double bond as in 6-heptenal. However, it is more likely to result from hydration of these chemicals prior to olfactory transduction.

On the (right), a modified wheel is shown reporting the intensity of the perceived response to a single
The expected response to a more complex odorant (or mixture of odorants—a fragrance) would be shown by an arrow along each radial proportional to the perceived response to each of the odorophores (measured separately) by the individual OR channel. The scale of 0 to 5 is arbitrary and may be either linear (when examining short ranges) or logarithmic (when examining large ranges) in practice.

The use of this olfactory wheel and set of preferred odorophores can provide a very useful protocol for a group of psychophysical experiments that initially identifies traceably the perceived names of various scents created by stimulation of various combinations of OR's. If these identifications are performed by experienced perfumers, the protocol can then be used in reverse to identify odorants with a precision not previously achieved.

The olfactory wheel cannot be used to perform vector manipulations to provide a composite vector of a given odorant; the observed vector values must be replotted into an orthogonal 9-dimension space to allow such summation to be meaningful. Some of the more obscure labels for common scents can probably be rationalized by this process. Woody and cardboard as scents are probably analogous to the color brown in color vision. Brown can be considered a yellow or orange at low chromatic saturation. By collecting data on a wide range of odorants in 9-dimensional space, they can be compared to their predicted vector in 9-dimensional space. However, many of these vectors cannot be plotted on the two-dimensional olfactory wheel. The names found on the periphery of the Aftelier “Natural perfume Ring” do not represent a traceable relationship with the scents in 9-dimensional olfactory space.

8.6.2.9.8 Cross-reference of proposed OR channels and commercial perfume names

The nine OR channel names of the above analysis can be correlated to a degree with the 14 names of the inner ring of the “Natural Perfume Ring” of Aftelier. Aftelier makes no claim that their names are associated with any underlying chemical structures or mechanisms. The order of names around their ring appears to be arbitrary and will be reordered here. The primary odor label of “pungent” (associated with OR 1) has little place in a wheel designed to support commercial sales of perfumes. Similarly, the primary odor label of “putrid” (associated with OR 9) has little place in the wheel.

<table>
<thead>
<tr>
<th>Olfactory channel</th>
<th>Primary odor label</th>
<th>Aligned with on Aftelier wheel</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 1</td>
<td>pungent (Lewis acids)</td>
<td>not generally applicable to perfumes</td>
</tr>
<tr>
<td>OR 2</td>
<td>dulcal</td>
<td>Sweet at low concentrations (~five locations)</td>
</tr>
<tr>
<td>OR 3</td>
<td>floral</td>
<td>floral</td>
</tr>
<tr>
<td>OR 4</td>
<td>limal</td>
<td>Citrus (limonene)</td>
</tr>
<tr>
<td>OR 5</td>
<td>musk</td>
<td>animalic, rich, musk</td>
</tr>
<tr>
<td>OR 6</td>
<td>cinnamon</td>
<td>spicy, sweet, cinnamon</td>
</tr>
<tr>
<td>OR 7</td>
<td>spice</td>
<td>spicy</td>
</tr>
<tr>
<td>OR 8</td>
<td>citral</td>
<td>Citrus (citronella)</td>
</tr>
<tr>
<td>OR 9</td>
<td>putrid</td>
<td>not generally applicable to perfumes</td>
</tr>
</tbody>
</table>

Olfactory channel | Primary odor label       | Aligned with on Oskon wheel       |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 10/VR 1</td>
<td>pheromone</td>
<td>no explicit alignment</td>
</tr>
</tbody>
</table>

[xxx need to introduce VR 1 or provide hyperlink]
Among the common designations for citrus, the primary odorophore of Grapefruit has a d-value of 4.9 Ångstrom and appears on the musk side of the limal/musk sensitivity overlap area on the sensitivity function versus d-value graph.

The extended names in the right column show how the equivalent names in the middle column are reached on the Aftelier wheel. The additional names on the Aftelier chart appear to be completely semantic based on psychophysical experiments where a list of names to select from was provided.

8.6.2.10 Analysis of recent empirical papers on olfaction

Several papers have attempted to develop a set of empirical rules defining the performance of the olfactory modality using only a few chemical families based on their groups according to valence chemistry. Several of these papers are discussed below. They are also discussed as a group in Section 8.6.3.1.5. [xxx combine this material with the later section —]

Decalin, C10H18, plays a role in both the Gorbachov & Rossiter and the Cheng et al. papers discussed below. It consists of two fused cyclohexane rings without further decoration. The transform is nominally planar while the cis-form exhibits a distinctive twist between the two hexane rings along their juncture. Decalin does exhibit an aromatic odor because of the separation between the resonant charges of the two rings. The difference in the distance for the trans and cis forms explains the difference in perceived odor. Trans-decalin_10265270 exhibits a d = 2.556 Ångstrom. Cis-decalin_10179239 exhibits a d = 2.447 Ångstrom. The similar d-values ensure that both molecules are perceived as a combination of acidic and dulcal, thereby defining the character of the perception of an “aromatic odor.” Both can be considered to be single odorophore odorants (SOO). The perception of a difference in odor between them may help further define the precise sensitivity functions of the acidic and dulcal channels of olfaction.

While the Dimoglo et al. paper recommends the rules related to the active ambergris fragments (AAF) of Gorbachov & Rossiter be deprecated in favor of their activity fragment rules, FA1 and FA2, these are not fundamental rules but empirical guides. Both should sets of rules should be deprecated in favor of the fundamental criteria for any odorant developed in this work; that it be able to form a DACB with one or more OR’s with a d-value in the range of 1.8 and 8.5 Ångstrom. This fundamental requirement incorporates the ability of the molecule to exhibit an external pair of orbital sites that are capable of supporting a DACB. It also incorporates the requirement that the chemical be sufficiently volatile to reach the olfactory epithelium. Lacking this fundamental capability, the chemical will be odorless. See Section 8.6.1.6 for additional discussion concerning the fundamental requirement and various alternatives for satisfying it.

8.6.2.10.1 Analysis of the Gorbachov & Rossiter paper of 1999

Gorbachov & Rossiter proceeded from Rossiter’s 1996 paper to push the structure activity relationship (SAR) concept into the arena of structural features not directly related to chemical groups. They still based their analyses primarily on conventional chemical groups but selecting specific sets (typically three) of carbon atoms from individual locations within one or more chemical groups.

Unfortunately, their work preceded the development of the Jmol files. Their chemical diagrams, although clear to a practicing chemist are not named or provided with any kind of identifying code. They used a software package described as “Cerius2 version 3 software from Molecular Simulations Inc.” and a “forcefield described as eff95_950_1.01 cited in a 1991 paper. Molecular Simulations was merged into Accelrys in 2001. Accelrys markets Discover Studio visualizer version 3.5 (DS 3.5). It appears to be a much more advanced visualizer when coupled with the Jmol files of the Royal Chemical Society.

They initially assert a premise that their work has identified the trans-decalin structure as key to the odor of the ambergris family of odorants. However, they quickly note that cis-decalin structures

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sometimes exhibit a woody odor that they associated with the trans-decalin structure. They then note that many “woody” stimulants do not contain any decalin structure. These observations argue against (falsify) their opening hypothesis. Later, they note that their structure 5, timberol, and structure 9, ambercore, also exhibit perceived odors similar to the ambergris family. These two structures do not exhibit the AAF molecular set (active ambergris fragment) that they profess to be key structures of their odorants. In their discussion, they also assert, “The AAF correctly describes the presence (or absence) of the ambergris odor for all of the 181 compounds investigated.” However, their criteria is not a theoretical one. It consists of statistical limits determined by examining their data set.

Their ambercore structure (9) does not agree with the current structure for this material given by ambercore_32818234 in the Jmol files. Their timberol structure (5) is not present in the Jmol files under that name. It is a registered trademark for CAS #70788-30-6. The Jmol file for this CAS # is 104315. Timberol_104315 is a single odorophore odorant (SOO), see definition in Section 8.6.1.2. Timberol_104315 exhibits a d-value of 5.437 Ångstrom. Ambercore is not an SOO. It exhibits d-values of 5.148 and 5.718 Ångstrom and a lower value typical of a phenol structure (with an oxygen atom connected directly to a benzylring). These d-values suggest the ambergris family primarily stimulate the “musk” channel of this work (centroid at 5.294 Ångstrom) and potentially the “cinnamon” channel as well (centroid at d = 6.075 Ångstrom).

Karanal (5-butan-2-yl-2-(2,4-dimethyl-1-cyclohex-3-enyl)-5-methyl-1,3-dioxane), named for Karen Rossiter, is known to consist of 8 pairs of enantiomers. In a search of the online literature, Karanal has a CAS # 117933-89-8. The Jmol file for this chemical is 10660411 and will be described as Karanal_10660411 in this work. Karanal_10660411 exhibits d-values of 4.840 and 5.063 Ångstrom. Based on this work, Karanal stimulates the low d-value side of channel 5, musk, and stimulates channels 4, limal, and 5, musk approximately equally.

Gorbachov & Rossiter settled on an empirical requirement for odorous members of their ambergris family. The requirement for their osmophore (equivalent to the odorophore of this work) is:

1. the presence of an oxygen atom and three carbon atoms (four carbons in early discussions).
2. the presence of a hydrogen atom, H(sub-alpha), attached to one of the carbons, labeled C(sub-alpha).
3. other requirements related to the effective atomic charges on the atoms not described.
4. potentially other requirements related to chirality, etc., not described.

They described such an osmophore as a active ambergris fragment (AAF). They do not define the nominal distances between these atoms in 3D space but provide a variety of values that are expected to converge on a set of nominal values. They do not consider the potential charge contribution of a double bond or of a benzyl ring in their model. Their figure 5 describes their nominal distances between AAF atoms without direct reference to a specific molecule. The numbers are not relevant to this work. Their figure 6 illustrates their selected carbon atoms for four different chemicals in simple 2D stick form. Figure 8 shows their method is fundamentally to find the distance between various atoms in a complex molecule and see if the distances between the oxygen atom and any three carbon atoms approximate the nominal values for their convergent set.

They do not propose a new hypothesis at the end of their paper beyond what can be gleaned from figure 5. Neither Gorbachov nor Rossiter published on this subject during the next 15 years.

Figure 8.6.2-40 compares the hypotheses of Gorbachov & Rossiter and the hypotheses of this work.

In the top half of the figure, the important olfactory properties of trans-Timberol_104315 and its cis-partner(s) are shown as defined via the SAR hypothesis and via the electrotylic hypothesis of this work. The SAR hypothesis is entirely empirical. Gorbachov & Rossiter attempted to ascertain a pattern of atoms requisite to stimulate an unspecified OR or OR’s of the olfactory modality. No explanation was given on why their chosen atoms were relevant to olfaction. Immediately below the trans-Timberol_104315 is the equivalent pattern according to the electrolytic hypothesis. The critical d-value of 5.437 Ångstrom is shown as the distance in 3D space between the oxygen atom free of any coordination involvement and the charge available due to the resonant structure of the benzyl group. When brought into proximity to the channel 5 OR, “musk,” the two chemical ligands are able to form a DACB, thereby completing step 1 of the transduction process of olfaction.
In the bottom half, the trans- and cis- structures of xxx are shown. ADD my molecule(s) below the figure. The upper-left rendition of the molecule exhibits the distances between their proposed
critical distances. Below the labels is the same molecule shown with only the distance between the oxygen atom and the centroid of the electrical charge due to resonance in the benzyl structure. \( [\text{xxx describe which channel the d-value relates to.} \) On the right is shown an isomer of that on the left with the oxygen now located in the equatorial position. \( [\text{xxx show my projected structure with its d-value.} \)

The electrolytic hypothesis of this work provides a much simpler yet more precise explanation of the perceived odor of both the Timberol’s and the two isomers in the lower half of the figure.

### 8.6.2.10.2 Analysis of the Dimoglo et al paper of 2001

Dimoglo et al. offered another paper involving the electronic-topological method (ETM)\(^\text{193}\). They establish a solid framework in their methods section on which to base discussions. These discussions find fault with much of the AAF (active ambergris fragment) hypotheses developed by Gorbachov & Rossiter at the end of their paper. Unfortunately it does not provide any short common names for any of the chemicals such as xxx described in Gorbachov & Rossiter. Dimoglo et al. attempt to use a set of chemical structures where approximately 50% generate a perception of ambergris and the rest do not. They expanded their previously defined activity fragment (FA1) and subdivide it into two parts, an FA1a and FA1b. Their basic approach is to continue to seek a solution based on structural distances in 3D space between certain atoms and groups. Their approach is fundamentally empirical and statistical. They are looking for patterns among their statistics. The approach is to determine a set of probabilistic criteria in which certain designated structural distances must fall. Their focus is on a large group of decalin and non-decalin structures. In general, their FA1 and FA2 criteria surfaces the need for an additional activity fragment which they define as FA2. They noted, “It appeared, however, that in the case of non-decalin systems FA1 did not allow activity to be predicted unambiguously... Observations such as these have led to further SOR investigations on mixed series containing decalin- and non-decalin-type systems.”

Their results and assertions show certain preferred 3D distances between their atoms, generally a single oxygen atom and a single hydrogen atom along with a variety of carbon containing groups. Of course, the natural bond lengths and bond angles of organic chemistry make it likely that many distances will cluster around certain values. All of their investigations involved a major constituent perceived as ambergris or geometrically similar to such a constituent. Even with their new FA2 criteria, they continue to find inconsistencies and note, “However simultaneous coexistence of the musk fragment and FA2 in a molecule and correlation of the corresponding notes in the molecule’s odor is a very complex question and the subject for further theoretical and experimental studies.”

In closing their paper, they mentioned two subjects; they did mention the term hydrogen bond acceptor (only once) and they suggested that the olfactory receptors were protein based (but without any support).

### 8.6.2.10.3 Analysis of the Cheng, Nu, Mao & Wang paper of 2009–EMPTY

Cheng et al. provide a good review of the state of olfactory theory in 2009. However, their empirical approach does not lead to a useful hypothesis. Initially, they introduce two historical hypotheses of olfaction, the recognition and the vibrational theories. They note two variants of the recognition hypothesis; “The first is that of Ohloff. The second is the electronic-topological method. The second is that described by Gorbachov & Rossiter, above.” An alternate formulation of the empirical approach was introduced by Vlad et al. in 1983. It involved an “ambergris triangle.” The Vlad et al. triangle involved bonds between an oxygen atom and two hydrogen atoms. Their triangle involved bond lengths drastically greater than those of conventional structural chemistry. This situation suggests the triangles do not exist as illustrated but involve other intermediate structures between the atoms described. This is confirmed in structure I of Cheng et al. They also noted the lack of relevance, and frequent violation of the “decalin rule.” Cheng et al. did not discuss the vibrational hypothesis further.

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They concluded their introduction by asserting, “Based on the above introduction, there is a need to find new, more correct rules which relate the chemical structure and ambergris odor. In this paper, we shall present the results of a study of structural, stereochemical and electronic features of some typical ambergris odorant molecules based on quantum chemical calculation method.” They then note without benefit of a block diagram or schematic model of their subject matter that, “Molecule’s odor is influenced by many factors, such as structural and stereochemical features, functional groups, and electronic properties etc. Nevertheless, many investigations show that no single molecular property is sufficient to determine the odor of a molecule. Odor quality is multidimensional, but it is evident that odor is exclusively associated with volatile molecules. The highest molecular weight found so far for an odorant is 294.” They proceed to discuss multiple concepts in highly general terms of little consequence to the technical literature. They do note correctly, “However, the presence of a functional group is not necessarily a prerequisite for odor. Even alkanes can have pronounced odors.” Two even stronger statements can be made:

1. **there is no prerequisite for a functional group to be present** and
2. **saturated alkanes are odorless but unsaturated alkanes with two double bonds can exhibit an odor**.

Alkanes are frequently reported to exhibit an odor due to the difficulty of acquiring material at purities below the parts per million to parts per billion level.

Cheng et al. exhibit two molecules on page 3 that appear quite similar from a chemical group perspective but are uniquely and significantly different from a coordinate chemistry perspective. The distances between the single oxygen atom and the two carbon double bonds are dramatic. They conclude correctly, “In some sense, the olfactory character of an organic compound is somehow a function of the spatial arrangement of the molecule, and that is further influenced by its electronic and hydrophobic properties.” They then enter into a discussion of electronic states centered on HOMO and LOMO calculations that is largely irrelevant. Without a knowledge of the sensitivity characteristic of the OR, it is irrelevant to speak of the energy of the stimulant in the first step of transduction. The energy they calculated may impact the dipole potential of the molecule that is important in the second step of transduction.

It is unfortunate that they then quote Vlad et al., “As Vlad suggested, the analysis based on structural and stereochemical features only (bond lengths and angles, distances between specific atomic groups, etc.) is not enough to establish features of origin of ambergris odor.” In fact the bond lengths and angles are the dominant factor in step one of the transduction process.

Cheng et al. introduced an alternate “new ambergris triangle,” structure III of Cheng et al., that also involved bonds of drastically different length than encountered in structural chemistry; the lengths also suggest the presence of intermediary atoms. The molecules illustrated suggest both Vlad et al. and Cheng et al. are veering away from the conventional valence chemistry toward a coordinate chemistry independent of the chemical groups present. Their optimizations illustrated in figure 4 are basically irrelevant without describing their interaction with the appropriate OR. They conclude, “Therefore, our ‘new ambergris triangle’ rule seems applicable only to the tricyclic ethers.” They further conclude with respect to these structures, “Table 2 shows that there is no positive connection between odor intensity and isomer’s total energy. That is to say, it is not sure that the odor intensity of the lowest energy isomer is the strongest among all different isomers.”

Their hypothesis does not relate to the vast multitude of olfactory stimulants and is not completely satisfactory when limiting the stimulants to the ambergris family!

### 8.6.2.10.4 Extending the 1985 paper of Hoffmann & Pauluth—OR spectral sensitivity

Hoffmann & Pauluth offered data on a range of nine terpineols associated with the olfactory perceptions associated with ambergris (Section 8.6.1.1). The information was spotty and from early experiments. However, it offers the chance to develop a protocol for evaluating the spectral sensitivity of various OR’s based on their d-values. The goal would be to establish a protocol insuring consistent and equal stimulation by a series of chemicals when measured at the surface of the olfactory epithelium. The intensity of all of the stimulations should be controlled to insure the experiments occurred under odor-constancy conditions (similar to the color-constancy conditions of vision when the stimuli are all within the photopic range of intensity). The temporal conditions need to also be carefully controlled to limit the auxiliary “notes” and other perceptions frequently associated with olfactory organoleptic experiments. The washout procedures need to be carefully
developed. Finally, the odor evaluation subjects need to be constrained as to the terms they can use to describe an odorant. It is suggested they be constrained to use the labels associated with the nine OR channels of this work, or an equally constrained alternate list. If any alcohol is used as a dilutant, it must be insured that the contaminants in the alcohol (at the parts per billion level) are eliminated.

Hoffmann & Pauluth explored about nine terpineols and described their fabrication procedures for the more obscure members of their set. Their nomenclature was explicit but needs to be compared to the more recent structural nomenclature. Their table 2 gave a wordy description of each of the nine without providing any citations or constraining the language used. In a few cases, they provided single word perceptual labels in conjunction with a given chemical. The easily identified chemicals are shown below with their 3D Jmol numbers.

<table>
<thead>
<tr>
<th>Jmol #</th>
<th>H &amp; P name</th>
<th>H &amp; P scent</th>
<th>d-value</th>
<th>scent from d-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8418</td>
<td>cis-β-terpineol</td>
<td>hyacynths</td>
<td>5.031</td>
<td>musk</td>
</tr>
<tr>
<td>390927</td>
<td>α-terpineol</td>
<td>lilac</td>
<td>5.152</td>
<td>musk</td>
</tr>
<tr>
<td>391434</td>
<td>trans-β-terpineol</td>
<td>no evaluation</td>
<td>5.583</td>
<td>musk/cinn</td>
</tr>
<tr>
<td>10186979</td>
<td>trans-β-terpineol</td>
<td>no evaluation</td>
<td>5.583</td>
<td>musk/cinn</td>
</tr>
<tr>
<td>13850142</td>
<td>trans-β-terpineol</td>
<td>no evaluation</td>
<td>4.585</td>
<td>lima1</td>
</tr>
<tr>
<td>13850142</td>
<td>trans-β-terpineol</td>
<td>no evaluation</td>
<td>4.585</td>
<td>lima1</td>
</tr>
</tbody>
</table>

Their hyacynths and lilac both stimulate the low end of the musk (channel 5) sensitivity function.

All of the terpineols described by Hoffmann & Pauluth appear to represent single odorophore odorants (SOO) consisting of one oxygen orbital and one double-bonded pair of carbon atoms. These elements are incorporated in a single structure containing a cyclic aliphatic ring structure, typically cyclohexane.

**Figure 8.6.2-41** shows where the above terpineols would appear along the d-value axis of the olfactory sensitivity graph. By following a rigorous test protocol, it should be possible to determine a more precise width of the individual channel sensitivity functions where test subjects would be asked to compare pairs of terpinols under the conditions identified above. For example, the subjects could be asked:

1. Which of the pair 8418 and 390927 (hyacynths and lilac) is perceived as more lima1?
2. Which of the pair 8418 and 390927 (hyacynths and lilac) is perceived as more musk?
3. Describe the perception of 391434 using only the terms, floral, lima1 & musk?

A question not yet resolved in this work is illustrated by the dashed line associated with cis-β-terpineol 8418 and similar molecules where one or more of the orbitals are located at a position that can vary depending on the rotation around a single carbon bond (generally between two carbon atoms). The two extreme cases are labeled conformational isomers. The d-value of 5.031 Angstrom is the one measured for the molecule in the Jmol library. However, by rotating the groups attached to C11 about the C9-C11 bond, the larger d-value of ~5.875 Angstrom is measured. The question becomes:

4. How is the variation in orbital location associated with rotation about a C–C bond accounted for during organoleptic evaluations and in the Jmol documentation?

Is one form of such conformational isomers favored because of hinderance in the majority of cases? Alternately, is the preferred form of conformational isomers determined by energy considerations? (M&B,1971, pp 96-101) Gorbachov & Rossiter note, “It is generally accepted that the conformation of a molecule responsible for triggering an odor response does not necessarily have to correspond to any of the theoretical minimum energy conformations. This phenomenon is also well accepted in drug-receptor interactions.” Conformational isomers have also been labeled conformers, conformational enantiomers and conformational diastereomers (M&B,1971, page 217).

Pending the obtaining of clarity regarding this question, this work will assume that the conformation shown in the Jmol file provided by the Royal Society of Chemistry for a particular molecule is the predominant conformational isomer. See Section 8.6.1.6. The RSC is only beginning to act as a curator for Jmol files. Many of the current underlying Jmol data files are incomplete 2D representations of
8.6.2.11 Fischer diagrams with d-values of important chemical forms REFER.

Although extremely difficult to ascertain individual chemical structures that are fundamental to a given sensation, Figure 8.6.2-42 provides a montage of key structures.
Montage of major chemical structures in olfaction. Calculated by me from a table of "standard bond lengths" that is inadequate. Amines and amino acids are shown at the lower right.
Although this figure is limited in its scope, it does offer a hypothesis concerning the fundamental chemical structures associated with the major elicited sensations. Many of even these simple molecules exhibit multiple d-values, that can potentially stimulate multiple sensory receptors in order to elicit subtle, or shaded, sensations.

- \( d = 1.22 \text{ Å} \); fundamentally fruity sensation.
- \( d = 1.22 \text{ Å} \) and \( 2.3 \text{ Å} \); fundamentally banana oil.
- \( d = 1.22 \text{ Å} \) and \( 3.61 \text{ Å} \); fundamentally buttery.
- \( d = 1.43 \text{ Å} \); fundamentally clove oil.
- \( d = 1.97 \text{ Å} \) or \( 2.82 \text{ Å} \); fundamental pungent sensation based on amines– A wide range of amine based compounds exhibit a pungent odor when in hydrated form. A number of straight saturated chain diamines also elicit the sensation of rotting flesh.
- \( d = 2.34 \text{ Å} \); fundamental pungent sensation of carbohydrates– An elicited sensation due to a nonresonant carboxylate ion. This sensation may be shared with the similar gustatory sensation, may share the same sensory receptor, or be due exclusively to the gustatory modality.
- \( d = 2.703 \text{ Å} \); the distance between two oxygen atoms in a “hydrogen bond. Fundamentally odorless but may be incorporated into a DACB.
- \( d = 2.82 \text{ Å} \); fundamental odor of the aromatic \( \alpha \)-ether and associated with the sensation elicited by clove, anise and licorice.
- \( d = 3.61 \text{ Å} \); fundamental odor of the diketone and associated with the sensation elicited by butter. xxx
- \( d = 3.647 \text{ Å} \); fundamental odor of the phenyl/2 carbon aliphatic alcohol with the perceived sensation of xxx.
- \( d = 5.065 \text{ Å} \); fundamental odor of the aromatic \( \gamma \)-ether and associated with the sensation elicited by the rose, along with jasmine.
- \( d = 5.603 \text{ Å} \); fundamental odor of the xxx and associated with the sensation elicited by cinnamon.

[xxx update this whole section]
- \( d = 2.42 \text{ Å} \); fundamentally
- \( d = 3.53 \text{ Å} \); fundamentally jasmine.

Specifying the simplest structure responsible for the sensation associated with roses is particularly difficult. The sensation appears to be due to a mixture of “essential oil.” Many of these essential oils appear to be complex derivatives of citral, the fundamental chemical associated with the scent of citrus fruit. It has many isomers. Citral A (geranial) is a straight chain unsaturated aldehyde, an E-isomer. Citral B (neral) is a Z-isomer. Many fold to nearly form a ring structure. Wise looked at several variant that are potential derivatives of citral. They were 2-phenylallyl alcohol and several of its esters. All contained a carbonyl group at the first carbon of the side chain. [xxx check]

- \( d = 5.07 \text{ Å} \); fundamentally rose.
- \( d = 6.0 \text{ Å} \); tentative top of the olfactory range of d-values.

The figure and the number of identified d-values leading to distinguishable sensations appears to be compatible with Amoore’s earlier suggestion of seven fundamental odorous channels but differs in the character of the structural groups responsible for these sensations. The fundamental characteristic is not the interconnection of the atoms in a molecule but the spacing between certain specific atoms of these molecules that are capable of supporting coordinate bonding (and
without involving any chemical reactions at energies exceeding 50 kcal/mole). The reliance on a distinct set of d-values to define individual olfactory sensation channels, insures that significantly different chemical families can exhibit the same odorophores (such as those eliciting a musk sensation).

**Figure 8.6.2-43** shows a one-dimensional olfactory (odor) space summarizing the discussion in this section. [xxx replace and edit]

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**8.6.3 The transduction mechanism in olfaction**
The scenario developed in Section 8.6.2, based on the hypothesis of this work, readily describes the broad capability of the olfactory modality and is totally compatible with the conceptual ideas of combinatorial chemical sensing currently gaining traction within the neuroscience community and the perfume industry. It shows there are not likely to be more than a dozen, probably fewer than nine, unique olfactory channels (beginning with this number of discrete OR types) employed in reporting the character of the odorants applied to the olfactory modality.

While the genetic community may identify thousands of genes involved in creating the individual OR channels, most of these genes are concerned with the detailed creation and operation of the sensory neurons supporting the phosphatidyl moieties performing odorophore selection and not in defining those moieties.

There is no evidence that any of the moieties contributing to step 1 selection as part of the transduction process are proteins or protein derivatives.

There is no creditable evidence of odorophores “reacting” with the OR’s and resulting in a residue of such a reaction appearing in the mucosa. Similarly, there is no creditable evidence that any odorophore passes through the outer lemma of the sensory neurons as part of the transduction process. The odorophores participate in a DACB coupling with the OR’s that is subject to spontaneous decoupling at body temperature due to the low energy of the coordinate chemical arrangement employed.

The role of the inorganic acids is highlighted by its absence from this work, while the role of the organic acids is prominent. An argument can be made that the inorganic acids are damaging to the olfactory system and their presence is a function of the nociceptor system. This would be defensible if the adaptation characteristic reported by Ekman et al. (Section 8.6.7.xxx) for hydrogen sulfide was not so conventional. It may be the inorganic acids are sensed by the olfactory system when the anion of the acid is complexed (similar to the way sodium is complexed prior to sensing in the gustatory system). The sulfide ion offers a variety of possibilities for such hydration. Alternately, Hydrogen sulfide does form a coordinated bond structure with itself when in liquid form or in solution. Section 8.6.3.4.4 discusses this possibility.

With the knowledge gained by the analysis of odors in Section 8.6.2 and the performance of the other sensory modalities earlier in this chapter, it is appropriate to develop a hypothesis concerning transduction in the olfactory modality. The gustatory modality hypothesis has shown that coordinate chemistry between the stimulants and the sensory receptors plays a major role in taste and this has led to a detailed description of the chemical structure of the individual sensory receptors of gustation. It appears coordinate chemistry also plays a key role in the olfactory transduction process, and there is some evidence that the sensory receptors for the sugars (PtdGal) and the carboxylic acids, (PtdSer) (Section 8.5.1) are found in both the oral cavity and the nasal cavity. The challenge is to resolve the number of sensory channels and the characteristics and potential chemical formulas of the other sensory receptors supporting these channels.

Olfactory transduction need only address chemicals that have sufficient volatility in air to reach the olfactory epithelium. This criteria excludes virtually all inorganic (non hydrocarbon) substances. An interesting exception is carbon dioxide. It is believed to require hydration (to form carbonic acid) within the mucosa in order to become an odorant. A similar requirement may apply to hydrogen sulfide. The vast majority of odorants are carbohydrates.

The available dendrograms of olfaction suggest approximately a dozen independent sensory channels with interpolation providing a very large number of identifiable odors by a highly trained specialist (with less than 100 identifiable by the typical subject). The analysis of the chemical structures of major odorants show approximately a dozen likely odorophores. This section will attempt to identify the most probable sensory receptors supporting the sensory neurons of these channels.

It is recognized that the olfactory modality and the gustation modality cooperate to support a very large number of individually recognizable sensations by a trained subject.
Because of the anecdotal information that metal ions play a role in the olfactory transduction process, several potential transduction mechanisms were examined employing the metals, copper, magnesium and zinc in coordinate chemistry configurations. While reasonable, these mechanisms did not define a simple and direct method of coupling these configurations to the lemma of the sensory neuron cilia. They also did not offer the variety of coordinate chemistry configurations with the d-values needed to support all of the fundamental chemical structures found in the major classes of odorants.

The complexity of the structure of many odorophores is such that it is appropriate to define a first order theory of olfaction followed by the elements of an extension to a second order theory. The first order theory is designed to elucidate the theory and show how it accounts for a large portion of the empirical database. The second order theory will explore specific cases that do not appear to conform to the first order theory at the detail level.

This work will exclude poly-cyclic (multi-cyclic) molecules because of the difficulty of visualizing their dipole moment; the critical parameter of odorophores based on the Electrolytic Theory of Olfaction. The calculation of the dipole moment of poly-cyclic molecules requires complex computer calculations using programs that may not have been optimized (or of adequate precision) for calculating this parameter. Such programs frequently employ simplifying assumptions that are not always stated explicitly.

Getchell et al. have provided an interesting figure (pg 662) showing a poly-cyclic molecule, a top-hat molecule and three molecules involving a mono-cyclic ring that all elicit a musty sensation. “Each of the compounds has on one side of the molecule, either a methoxy group, or a methyl group and a hydroxy group very close together.” They exhibit a threshold sensitivity for humans in the few parts per trillion range, some of the lowest ever measured. The description of the odorophore of the mono-cyclic molecules is straightforward based on this work. They note, an informal observation is that 10–20% of people have a specific anosmia for the poly-cyclic compound, suggesting it may be a primary odor (stimulate a distinct receptor in the context of this work).

It appears that the implementation of a system of sensory receptors coupled to phosphatidic acid offered the highest potential for defining the actual olfactory transduction mechanism. The initial investigation considered the formation of coordinate dimers between simple molecules attached to the phosphatidic acid that were the same as the fundamental members of each class of odorants. This method assured the necessary structural spacing between the active receptor structures and the odorant structures. In searching the empirical literature of the olfactory (and gustatory) sensory neurons, some alternate phosphatidyl molecules were located that were known to populate the olfactory epithelium and offer the required d-valued structures, i.e., the potential to support at least two coordinate bonds, with the necessary spacing to interface with the individual odorophore, with the individual stimulant.

The analyses of Section 8.6.3 suggest as many as ten sensory receptors may be required to satisfy the olfactory sensory requirement without examining stimulants with odorophores having d-values above 4.0. The actual number of sensory channels described here may be statistical, based on the limited multi-dimensional scaling data available.

The following analysis is intended to define potential sensory receptors without regard to all of the potential limitations on a given chemistry related to specific physiological conditions. The dipole moments of the defined phospholipids are generally unknown at this time, as are the changes in dipole potential associated with achieving the coordinated condition.

8.6.3.1 Historical Background

The term SSC (stimulant sensing complex) will be used in this section for historical reasons as a synonym for the complete olfactory receptor (OR) cell.

No specific transduction mechanism has been defined during the last 100 years for either the olfactory or gustatory modalities. Price noted the early spectrographic work of Ash in 1968 based
on rabbit olfactory mucosa. Ash reported the presence of ascorbic acid as a potential chemoreceptor. No additional evidence appeared to support or extend the Ash work. Most subsequent work has focused on the proposal that the chemoreceptors are protein based.

Price explored the potential for proteins to form the stimulant sensing complexes in his work and by reviewing the literature, without defining any specific SSC. He closed in 1981 by noting, “It is clear that studies of olfactory receptor proteins in vertebrates are at a very primitive stage. The problem of how to identify a receptor protein in extracts deserves special attention.” Rhein & Cagan echoed the same position in the same volume, “The molecular basis of the initial steps of olfactory sensation has been an enigma to scientists for decades.” “Biochemical studies of the mechanisms underlying olfaction have received relatively little attention.”

Murphy outlined a series of possible mechanisms in 1988 without recognizing any quantum-mechanical possibilities. The list is obsolete.

A major problem with the current state of olfaction research is that no actual detailed mechanism of transduction has been defined in the literature. Schild & Restrepo confirmed this fact in a review as recently as 1998. “The morphology of olfactory receptor terminals was first described by Schultze 140 years ago. How ORN’s function, however, has remained a riddle that still is not completely solved.” They go on, “However, a comprehensive review of cellular studies of olfactory transduction focused on electrophysiological and biophysical aspects is lacking.” They conclude their introduction, “More importantly, the comprehensive review of the literature makes a compelling argument that olfactory receptors are more complicated than heretofore imagined and reveals the limitation in our knowledge of the complexity of the mechanisms underlying olfactory transduction.” They note in their final summary, “little is known about the mechanisms of olfactory transduction on ORNs in situ.”

This work will attempt to explain many of the complexities of transduction alluded to by Schild & Restrepo. It will develop a dual criteria model of olfactory transduction compatible with the known characteristic of the receptor neurons in other sensory modalities. The criteria require specific steric properties and specific energy bands to be occupied before a specific odor receptor can influence its associated odor receptor neuron. The odor receptor will remain an SSC in this proposal, rather than the narrower concept restricted to protein-based OBP’s.

In 1991, Breer et al. asserted, “The presently favored concept of olfactory signal transduction is based on the assumption that odor molecules interact with hitherto unknown receptor proteins and activate reaction cascades via G proteins.” The situation remains much the same today. However, a reinterpretation and expansion of the concepts developed in a paper by Malnic, Hiroi, Sato & Buck offers a better hypothesis leading to a clear understanding of olfaction. The paper is discussed in Section 8.6.3.1.2 below and the reinterpretation is compatible with the bulk of the hypotheses in this Section 8.6.

The receptor proteins (if any) remain unknown and the method by which signal amplification is achieved via a “cascade” remains undefined. At that time, it was expected that the genetic code would lead to simple descriptions of the sensory receptor proteins. That has not happened and the euphoria related to the genetic code has subsided with the realization that the majority of both the

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architectural framework and the content of the “code” remains undeciphered. Writing in the same volume, Spielman et al. have described at least ten separate potential mechanisms (or points of attack by stimulants) that could explain the transduction process just for the bitter taste channel(s). None are developed beyond the conceptual stage.

Silver & Finger, writing in Getchell et al. have summarized the various theories of olfaction that have been developed previously. They cite Lancet as a recent review. No significant new theory of transduction has appeared since that time. All theories up to this time have relied upon the archaic chemical theory of the neuron.

After reviewing the appropriate history, a different approach will be presented in the following sections.

Amoore addressed the “Central Problem of Odor Research” in his 1970 book. The book is as comprehensive as possible for that time. He asserted, “I have established convincing experimental proof that the odorous qualities of a compound is largely determined by the size and shape of its molecules and by their electronic affinities.” (Italics added). This assertion remains true today. Today, more advanced techniques can be used to identify and demonstrate these relationships.

His page 15 figure from Moulton and Tucker of 1964 is quite useful and his Table 40 showing the various names used by multiple investigators to refer to the same stimulant is instructive. As noted below, the entries in the columns labeled “Reputed specific anosmias” are largely fanciful based on the hypothesis of this work. The only entry in the “Established primary odorant” column is reasonable but any simple carboxylic acid of adequate volatility meets the requirement as well as isovaleric acid does. The labels “oily,” “metallic” and “burnt” remain undefined within the context of this hypothesis. Table 40 was updated as table IV in Amoore, 1982, page 54 (with a revision date of 8–1978).

Squire et al. have identified a large number of organic chemical families that are sensed by the external chemical receptors (2003, pg 602) but did not include any cyclic families. However, no framework was provided explaining how these materials were sensed except to introduce putative odor-binding proteins (OBP). These OBP’s include those sensing the complex proteins known as pheromones. The premise is that these OBP’s are soluble in aqueous solution and aid the transport of the hydrophobic molecule to the active elements of the chemoreceptors. They only referenced one 1981 source as evidence that the binding materials were proteins.

Price commented on the character of the SSC’s. “It is intellectually attractive to suppose that the receptor protein concept, so widely applicable to stimulations of cells by chemicals, applies to odorant stimulation of olfactory receptor cells. There are alternative hypotheses in which the site of initial interaction is envisioned to be the lipid portion of the cell membrane.” Dodd & Persaud, writing in the same monograph noted with respect to air-breathing vertebrates, “We believe that olfactory neurons employ some combination of the molecular mechanisms that are found in other receptor systems.”

Price also noted in 1981, there were very few experimentalists in chemical sensing compared to vision, “much of the experimental work is unrepeated, and the amount of reliable data is so minute that it is not possible to offer support for any particularly olfactory mechanism.”

Margolis & Getchell provided an extensive work in 1988 that is now quite dated. They discussed...
the SSC's under the simple name olfactory receptors attached to sensory neurons. They summarized the literature to that date and noted the olfactory receptors “are presumed to be proteins capable of binding the odorant stereospecifically and of undergoing changes, giving rise to transduction events.”

Turin has explored many exotic explanations for odor transduction including differentiation based on energy (or wavenumber)\(^{203}\). His report on differences in smell between isotopes of the same substance is instructive. Turin & Yoshii have provided a current perspective on the problems in defining the parameters sensed in olfaction\(^{204}\). They even introduce the perceived difference between carbon-based and silicon-based stimulants. They lean toward a relatively small number of SSC’s detecting specific properties of molecules rather than the one stimulant-one receptor concept. They also elaborate on “The puzzle of odorant intensity.” They also support the concept of metallic ligands as critical aspects of SSC’s. They conclude in 2003, “The fact that after several decades of experimental investigations, the basic mechanism by which odors are detected remains open to question shows that there is much work to be done.” [xxx used in earlier section also ]

Xxx writing in Finger et al. show the concept of one molecular stimulant-one receptor is not a viable concept since stereoisomers of carvone exhibit decidedly different perceptions\(^ {205}\).

This work will combine the thoughts of Price, Dodd & Persaud and Turin & Yoshii, while reaching farther a field for reliable data. This reaching includes recognizing the efforts taken in mammalian systems to prevent the visual and hearing sensory neurons from coming into contact with oxygen, and high levels of sodium. The toxicity of sodium ion to the sensory portion of the phonoreceptors is well documented and extreme measures are taken to prevent the high-sodium content perilymph from mixing with the protective endolymph within the cochlea. It will also note the ability of sodium to greatly accentuate both the sensed taste and perceived flavors of many other stimulants. Based on these and other criteria, the mechanisms of transduction in chemoreception will be subdivided as follows;

1. A mechanism based on the ability of the sodium ion to attack at least specialized regions of the plasma membrane of the microtubules. The resulting transfer of charge through the membrane results in a depolarization of the pedicle voltage for that cell. This has the effect of enhancing the potential change caused by any other stimulant affecting that cell.

2. A mechanism based on the ability of a non-protein-based stimulant-binding complexes (SSC) to participate in a quantum-mechanical energy transfer between the stimulant and the electrolytic elements of the microtubules of a sensory neuron. The SSC must be present in a liquid crystalline coating of the microtubules. Many of these materials are lipids.

3. A mechanism based on the ability of a protein-based stimulant-binding complexes (SSC), otherwise known as odor-binding proteins (OBP) to participate in a quantum-mechanical energy transfer between the stimulant and the electrolytic elements of the microtubules of a sensory neuron. The SSC (ne OBP) must be present in a liquid crystalline coating of the microtubules.

In both the protein-based and the non-protein-based SSC’s, it is necessary that the molecules involved to form a liquid crystalline coating on at least parts of the microtubules. The liquid crystalline character is necessary to support the broadening of the energy bands associated with the SSC to widths effective in exchanging energy with a broad range of stimulants and transferring the energy to the neural system.

The ability of sodium ions, at culinary concentrations, to enhance the sensed signal due to other stimulants is well recognized and a strong support for this proposition. The proposition can be tested

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by examining the generator waveform of a chemoreceptor known to be sensitive to a stimulant other than NaCl, when NaCl is applied. The response will not follow the C/D Equation if the proposition is correct. This proposition does not preclude a conventional SSC focused on NaCl.

Macleod provided Figure 8.6.3-1 showing the relative threshold sensitivities of a broad group of organic molecules. The threshold range is on the order of the full dynamic range of the visual system.

His paper includes an extensive review of the perceived character of an odor compared to the structural character of the molecules associated with that odor. It highlights the difficulty in obtaining a simple stereographic explanation for odors, but offers no alternative.

In his synopsis, Macleod has provided a well-worded summary of the problems in understanding the sensing of odors. He notes, "...it seems unlikely that one unified theory could pertain. The problem that is usually most difficult for such theorists to explain is that many compounds of widely different structures can possess very similar aromas." He presented many structural examples. His rare list of odor thresholds is shown in Figure 8.6.3-2. The range of 10^7 in thresholds is remarkable. It is similar to the overall dynamic range of the visual modality. In both cases, it appears the instantaneous dynamic range is about 200. However through the same adaptation mechanism, the overall dynamic range of the modality becomes huge.

This work will expand on Macleod's thesis in a stepwise manner, with structure playing the critical role.

The subject of threshold sensitivity will be addressed more completely in Section 8.6.3.6.

Revial et al. provided a framework that may be useful in understanding the transduction mechanism. They suggest an interesting association of properties for detecting chemical groups. "It is proposed that a group is due to a number of types of acceptor sites sharing some common, steric and energetic properties."

The examples below suggest the designation OBP is probably too restrictive. Analysis shows that the vast majority of potential odor or stimulant binding molecules are not proteins. The expression stimulant sensing complex (SSC) will be used in this work, with the OBP's as a sub-classification. The SSC's are present in such minute quantities, they may remain undetected empirically until unique procedures are developed.

The genetic community has identified a very large number of genes relating to the external chemoreceptors and have been inferring connections between these genes and various odor receptors associated with individual stimulants (odorants) without data confirming a one-to-one

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relationship. Approximately 1000 genes have been identified in mice and over 350 in humans. The data collection and entry into databases is rapidly exceeding the limited knowledge of how the chemoreceptor modalities operate.

8.6.3.1.1 Efforts to fix the number of sensory receptor channels

There have been multiple teams of researchers seeking to explain the operation of the olfactory modality from different perspectives for a very long time. The two most recent schools have encompassed the genetic school and the histological school. A separate school assuming all sensory receptors employed or depended on proteins in the sensing process has also arisen based primarily on the early geneticists claim that the genetic code only defined proteins. The progress related to each of these schools will be reviewed below.

8.6.3.1.2 Efforts to characterize SSC’s based on genetics

Glusman et al. claim to have documented the entire human olfactory genome. However, they have not determined the relationship between the genome and the actual operation of elements of the olfactory modality. They have asserted that olfactory related genes occur throughout the genome.

Zozulya et al. claim to have identified all of the functional human odorant receptor genes through data mining and subsequent physical cloning in their 2001 paper.

“Background: The mammalian olfactory apparatus is able to recognize and distinguish thousands of structurally diverse volatile chemicals. This chemosensory function is mediated by a very large family of seven-transmembrane olfactory (odorant) receptors encoded by approximately 1,000 genes, the majority of which are believed to be pseudogenes in humans.

Results: The strategy of our sequence database mining for full-length, functional candidate odorant receptor genes was based on the high overall sequence similarity and presence of a number of conserved sequence motifs in all known mammalian odorant receptors as well as the absence of introns in their coding sequences. We report here the identification and physical cloning of 347 putative human full-length odorant receptor genes. Comparative sequence analysis of the predicted gene products allowed us to identify and define a number of consensus sequence motifs and structural features of this vast family of receptors. A new nomenclature for human odorant receptors based on their chromosomal localization and phylogenetic analysis is proposed. We believe that these sequences represent the essentially complete repertoire of functional human odorant receptors.

Conclusions: The identification and cloning of all functional human odorant receptor genes is an important initial step in understanding receptor-ligand specificity and combinatorial encoding of odorant stimuli in human olfaction.”

The beauty of the mapping they performed and developed using packaged computer programs is beyond question. However, they fail to provide any mechanism as to how these proteins sense the vast array of predominantly non-protein odors, or how to distinguish effective from pseudogenes. See the quote of the well known researcher, Svante Paabo in his 2015 book, and several related comments in Section 1.2.5.1.1.

Turin & Yoshii have directly addressed the question of “Why are there so many receptors?” in their 2003 paper (page 288). This work will show there are less than a few dozen (phospholipid based receptors) in human olfaction (rather than a nominal 1000 enzyme based receptors).

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Mombaerts has presented a comprehensive and well referenced review of the research relating the genes to potential SSC's in two papers. The reviews were based entirely, and intrinsically, on the chemical theory of the neuron. The papers built on an earlier paper also heavily influenced by early genetic theory. The baseline assumption is that the genetic code specifies the precise protein used as the SSC for a particular stimulant. The concept that the code might be instructing the mitochondria of the cell to manufacture a non-protein SSC (such as a sophisticated phosphatidyl complex such as found in the lemma of cilia) is not addressed in the paper. Neither is the possibility that the SSC's are self-assembling based on the presence of the required constituents in the mucosa.

In the first paper (2004a), Mombaerts reviews the entire field of potential genes, and potential ligands for both odorant and taste receptors, but without a detailed analysis of the cytology and/or potential electrolytics involved. He also provides many definitions of various processes and chemical features. He asserts that “~1000 odorant receptors are dedicated to the conventional sense of smell” in mice. He also describes a large class of transduction and amplification supporting G-protein-coupled receptors (GPCRs) generally invoked in the (canonical/conceptual) chemical theory of the neuron. No specifics are provided as to how the transduction processes operate or how the GPCRs support signal amplification. He closes by citing Reed, “The Holy Grail of olfaction is within sight, but there is a long way to go—more than half of mouse and human non-chemosensory GPCRs have known ligands, but the vast majority of chemo-sensory GPCRs remain orphans.”

The Reed review is beautifully written but is based heavily on inferences and sites a variety of problems with the largely conceptual formation of the chemo-sensory neurons. It appears to follow the original hypotheses of Buck and Axel (1991). As frequently noted, this hypothesis is “Based upon the assumption derived from biochemical evidence that odorant signal transduction involved G proteins, the thus G protein-coupled receptors, a very large gene family of closely related olfactory-specific seven transmembrane spanning domain receptor was identified by polymerase chain reaction (PCR) (Buck and Axel, 1991 etc.). This hypothesis remains un confirmed.”

The Moon & Ronnett paper reviews the background for odorant receptors as protein based and finds it is primarily indirect. They also noted the convergence of axons from similar olfactory receptors onto specific glomeruli within the olfactory bulb. They also noted, “Malnic, Hirono, Sato & Buck (1999) performed single cell PCR on ORNs whose odorant responses had been determined to demonstrate that a combinatorial code exists for odorant perception.” Such a code, involving only 32 receptor types and 32 related glomeruli each with only an on and off state, can define $2^{32} = 4,294,967,296$ individual odorophores. The nominal upper limit on the number of genes identified by Buck & Axel required to encompass human olfaction was approximately 1028. A much smaller number of glomeruli with only binary outputs can define a large number of sensed states. Glomeruli with ten binary output signals can define 1028 individual sensed chemicals. As seen in Section 8.6.7, rats exhibit close to 20 independent output channels with potentially $2^{20} = 1,049,576$ individually perceived odorophores using only a binary signal from each channel. Section 8.6.7.3.3 points to a total of 9 independent sensory channels in the human olfactory modality. Such a modality could

209 Mombaerts, P. (2004a) Genes and ligands for odorant, vomeronasal and taste receptors Nat Rev Neurosci vol 5, pp 263-278


provide 512 independent combinatorial values to the higher engines of perception utilizing only a simple on/off code. If a more complex code employing the output from analog sources is employed, the number of output channels of the glomeruli would be multiplied by the number two raised to the number of identifiable signal levels associated with each individual channel. The result could easily reach 16,000. It could probably reach 128,000 perceived odors in experiments involving sensing the minimum perceived difference between pairs of odorants.

In 2004, de Gennes provided a highly conceptual description of a potential organization of the olfactory modality\textsuperscript{215}. The paper more resembled philosophical discussions of the 18\textsuperscript{th} and 19\textsuperscript{th} Centuries than a scientific discussion of the early 21\textsuperscript{st} Century. “The nasal epithelium is pictured as containing N (~300 or more types of detector cells” in mammals. The paper is fundamentally a parametric analysis based on a large group of arbitrary assumptions about the physiology of the olfactory modality. One assumption was a bulk density of $10^7$ neurons/cm$^3$ in the storage area (SA). He associates a gain factor at a synapse that involves more output spikes than input spikes. Although titled as a discussion of primitive memory, he did not identify the form or location of said memory, except that it was orthodromic to the piriform cortex. The piriform cortex was not further identified. He did not address the form of code used in signaling between the epithelium and subsequent engines of the olfactory modality. De Gennes introduced the subject of “spin glasses,” fundamentally a concept in magnetic materials, without further discussion. As such, it can only be considered an extraneous distraction. He also introduces his concept of a “flare.” He also asserts that each storage area of memory accepts inputs from only one type of emitter (output generator) in the piriform cortex. His bibliography consists of nine citations primarily to text books on neuroscience. One exception was a citation to Buck and associates (2001).

As noted above, Buck and her associates changed from the assumption of individual sensory receptors for every identifiable stimulant (more than 400) to a “combinatorial approach” like used in vision and taste but apparently de Gennes did not get the memo. The use of a combinatorial approach allows a small number of sensory receptor types (nine, see discussion below) to be used to perceive a wide range of individual stimulants (over 100,000 when analog signal processing is employed).

This potential use of analog intensity values within the neural system (common in other sensory modalities) also makes it much easier to account for the well recognized tendency of the perceived odor of an odorant to change with concentration.

The principle requirement in the case of the Malnic et al. paper is to recognize they were trying to achieve a definitive matrix between their odorants and their olfactory receptors, rather than a matrix of the odorophores within their odorants and the olfactory receptors. The distinction is very critical. The odorophore of an alcohol is totally different from that of an organic acid, regardless of the length of the aliphatic backbone. Some of their odorants contained multiple odorophores based on this work. What they describe as slight changes in their odorants described in their Discussion were in fact major changes in the odorophores present. The description of odor coding beyond the nose in their Discussion is worthy of reinterpretation based on the assumption that each type of OR and glomeruli only senses one type of odorophore. It will be shown in this work that the perception of a complex odorant is based on a multidimensional representation similar to that commonly identified in gustation. In that representation, every receptor/gglomeruli channel is treated as independent and the resulting representation is an orthogonal set of dimensions. The value associated with each dimension is a representation of the dipole potential of the specific odorant containing the unique odorophore.

It is proposed here that a reinterpretation of the Malnic, Hirono, Sato & Buck (1999) paper (introducing the concept of an odorophore within an odorant and a dipole potential associated with each odorant when bound to a receptor by a specific odorophore) supercedes all of the extrapolations of the Buck & Axel (1991) paper found in the literature, and particularly the pedagogical literature. Such an interpretation of that document is compatible with the work presented below. The caricatures in Moon & Ronnett related to transduction can be ignored under the proposed reinterpretation and more complete hypothesis of this work.

Buck has held the bully-pulpit in olfaction since the 1991 paper but she has not been able to develop a theory of olfaction or demonstrate a one-to-one connection between here concept of one OR per stimulant. An opening line in her 2000 paper suggests her continuing struggle at that time, “How does the olfactory system organize the signals provided by 1000 OR’s and 200 VR’s?” She offered no solution to this dilemma. On page 615, she began to cross the Rubicon by exploring the possibility that a combinatorial process was involved requiring fewer OR’s. “However, different odorants were detected by different combinations of OR’s, indicating that the OR family is used in a combinatorial fashion to encode the identities of different odorants.” She also noted the stage 2 signal processing role of the olfactory bulb in that paper. Her figure 4A shows a matrix for four organic acids and four alcohols detected by various combinations of 14 OR’s. She also associates the flowery labels of the olfactory community with each of these stimulants. The organic acids are generally associated with a rancid odor while the alcohols are generally associated with a perfume like odor. Her attention remained on the functional groups within the chemical structure of each odorant rather than on the the odorophores defined in this work. Beginning in 2004, she began to focus on the concept of a combinatorial transduction process that might alleviate the need for thousands of individual OR’s. Her assertion in the second paper, “OR’s are used in a combinatorial manner to detect odorants and encode their identities.” is completely compatible with the hypothesis of this work although She has not yet recognized the difference between a stimulant and its (potentially multiple) internal odorophores. Her focus remains on genetics and protein chemistry instead of (non-protein) molecular chemistry and computational chemistry.

In the second paper (2004b), Mombaerts explores the few SSC per sensory neuron concept and narrows that concept even further to the single SSC-single neuron hypothesis. Finding that hypothesis difficult to defend in totality, he reverts to an oligogenic approach (the few SSC’s per neuron hypothesis).

The premise of this work is that the SSC’s and their connection to the sensory neurons do not involve exclusively proteins.

If the sensory channels rely upon self-assembly of the SSC’s, or if the SSC’s are metal complexes of simple peptides, and if the actual sensory neuron lemma must be tailored, a large collection of genes would be required to create all of the conditions and constituents required to generate a single SSC neuron combination. As Mombaerts noted, approximately 1000 genes have been associated with the olfactory transduction process even though less than fifty distinct odotope sensing channels have been identified by Johnson, Leon et al. in mice (the most studied animal of olfaction).

Sanz et al. have presented recent data on a claimed OR that is genetically-based, and references to other similar work. They provide citations to most of the other current genetically-based OR investigations. They note in their introduction, “the link between odor quality of odorants and their detection by ORs is still lacking. Laing et al. (2003) suggested that odorants that share a common quality could reflect activation of a common receptor type. However, working with homologous

oxygenated aliphatic molecules, they did not find a common quality to each of the odorants that had the same molecular feature and concluded that identification of the odorants occurs via a combinatorial mechanism involving several types of receptors.”

They describe their use of the term odotope as follows.

“odotope” is formed by “odo,” which refers to odor, and “tope,” which refers to topology, describing how spatial features are connected to each other. In this way, odotope meaning joins “pharmacophore” meaning: the pharmacophore approach assumes that all the active molecules bind in a common manner to the same target site. The official International Union of Pure and Applied Chemistry definition from 1998 precises: “a pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response” and “the pharmacophore can be considered as the largest common denominator shared by a set of active molecules.” More recent definitions enhance the crucial role of the spatial arrangement of structural features for a particular biological activity. The odotope so appears as the spatial arrangement of chemical features that is recognized by at least one OR, and is linked to an odorant activity.

Sanz et al. expressed their putative OR using very complex procedures involving introducing their selected gene into a portion of the bovine rhodopsin chromosome and expressing it in human embryo kidney cells. However a majority of the work reported was computational modeling.

Their main conclusion: “In summary, the findings reported here provide a new insight in the understanding of the relationships between odorants, ORs and odor quality. It has especially been shown for the first time by a 3D-QSAR approach that ligands of an OR, OR1G1, have to be divided in 2 groups in order to find satisfactory models, suggesting 2 modes of interaction of odorants with this receptor. This result is in agreement with another study (Sell 2006) reporting that it would be difficult to design a model for a typical ligand for OR1G1.”

More recently, Keller provided a well spoken but largely conjectural “commentary” focused on the potential evolution of the olfactory modality from a genetic perspective as of 2012219. This remains an area of exploratory research. He claimed that individual mammalian species exhibit a very large number of “pseudogenes” relative to the number of “intact genes.” He made the important observation, “It has been a challenge to identify directed evolutionary processes that shaped the chemosensory receptor gene repertoires in the background of the variability resulting from undirected effects of genomic drift.” He noted the continual lack of a defined one-to-one relationship between the chemoreceptor genes and specific OR ligands, even in the more specialized and heavily studied VR’s of the mouse.

8.6.3.1.3 Efforts to histologically characterize the receptors

Several groups have attempted to describe the phospholipid content of the olfactory sensory neurons. They typically find the content to be 46%PtdCho, 26%PtdEtn, 8%PtdIns & 7%PtdSer220. The problem is these numbers apply to the vast areas of the sensory neuron lemma and not to the specific receptor portion of the cilia that is relevant to transduction. A more focused investigation is needed involving only the cilia. PtdIns & PtdSer have been recognized as critical to the gustatory receptor function. They may also be important in olfaction as discussed below. However, a variety of phospholipids present at sub-one-percent levels in total lemma extracts may be critically important to transduction in the olfactory modality.

The literature notes the high level of Zn2+ in the olfactory mucosa along with an equally high level of the amino acids associated with the dipeptide carnosine. It also notes the high efficiency of carnosine as a chelating agent. Thus, the presence of carnosine and Zn2+ as separate chemical elements is highly unlikely. Coordinate chemistry would suggest these materials are present as a


metal complex, Zn(II)carnosine. Such metal complexes are generally very complicated steric structures. The character of the metal complexes also suggest they exhibit a multitude of electronic configurations. Many of them are used as “indicator dyes” in the laboratory. The potential role of zinc complexes in a coordinate chemistry mechanism can not be ignored in olfactory research.

Lack of information on the chemistry of the receptor lemma areas is a significant impediment to further olfactory empirical research.

8.6.3.1.4 Efforts to characterize the receptors as proteins

There is a major problem in assuming the odor receptors are proteins. The bond energies of the proteins, typically with a saturated carbon backbone, are much higher than the energy levels associated with the vibrational states of the typical odorants. Thus, a more unsaturated molecule (or ligand as a minimum) is needed to support energy transfer in the 0.6 to 4.0 electron volt range. As a result, finding bonds with the appropriate energy differences within a given protein is demanding.

Many of the functional requirements lead away from proteins as receptors because of their large molecular weight where most of that molecular weight is non-functional. This results in a potential loss in capture cross section and a reduction in the specific sensitivity of the molecule as an OR.

A putative change in the color of the mucosa is the only reported change related to olfaction. This change in color is potentially related to the change in electronic state of the SSC’s. This would suggest the SSC’s have some of the properties of indicator dyes (and may or may not be conjugated with a protein). The microtubules (dendrites) of the olfactory neurons have been reported to exhibit a rougher surface than typical cilia. This may be indicative of the surface chemistry associated with these histological structures.

The absence of a major chemical reaction in olfaction also suggests the energy change sensed as part of the transduction process is well below the one to two electron-volt (23-46 kcal/mole) level. Chemical bond breaking generally requires at least 50 kcal/mole. It is also the energy level generally associated with protein rearrangement. It is well below the energy associated with charge transfer within, or along the backbone of a protein.

The absence of a major chemical reaction in olfaction suggests the energy level involved in transduction may be much smaller. Such a small energy change could induce a voltage in the base-emitter circuit of the first Activator on the order of a few millivolts as found in the auditory sensory neurons.

The challenge is to find the mechanism that can employ a low energy level change, that does not involve a chemical reaction, but can cause an electrolytic signal within the sensory neuron.

No stimulant sensing complex (SSC) has been identified outside of this work to date, although several have been suggested based on various criteria. Historically, the perception has grown within the research community that the SSC’s are probably specialized proteins. Price has discussed the probability that the SSC’s are proteins. He opens his discussion with, “It is intellectually attractive to suppose that the receptor protein concept, so widely applicable to stimulation of cells by chemicals, applies to odorant stimulation of olfactory receptor cells. There are alternative hypotheses in which the site of initial interaction is envisioned to be the lipid portion of the cell membrane.” This work will not limit the potential SSC’s without a more precise list of requirements.

221- - - (1975) Handbook of Chemistry and Physics, 56th Ed. CRC Press pp F236-F242

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Lancet proposed the following criteria for any protein to qualify as an SSC, or more specifically an olfactory receptor molecule:

1. tissue specificity
2. enrichment in the olfactory cilia
3. glycosylation
4. transmembrane disposition (integral membrane protein)
5. correct bilayer concentration (major component of membrane)
6. diversity (sequence heterogeneity)
7. specific recognition by function-modulating reagents (antibodies, lectins)
8. interaction with transductive proteins
9. reconstitution of odorant modulation of enzymatic activities

This is a very broad conceptual shopping list. Only a few of the elements relate to specific functional requirements. Some characteristics appear to be out of proportion to the task (#5). Others appear to be unrelated to the task (#3, #7). Still others are dependent on preconceived ideas (#1, #4, #5, #8).

A more functionally oriented list might be:

1. diversity with respect to steric form
2. tendency to aggregate in or on the surface of a dendroplasm
3. maximum sensitivity in transduction
4. high stimulant capture cross section
5. XXX

Most of the previous attempts to meet these requirements have been based on conventional kinetic and thermodynamic considerations involving chemical reaction chemistry.

8.6.3.2 Lipids win the lipid versus protein sensory receptor debate

8xx.4.4.6 A phosphatidyl dipeptide receptor hypothesis of olfaction

Phosphatidylserine (PtdSer) is a leading candidate for the receptor of the acid channel of gustation. It provides a unique spacing of its coordinate orbitals compatible with all carboxylic acids, 2.34 Angstrom. Since the lower members of the carboxylic acid family, through caproic acid, are reasonably volatile, it is possible that the olfactory modality employs this same receptor component for producing the irritating to distinctly unpleasant sensation produced by these agents. It is interesting to note the spacing of the other proposed gustatory receptors and see if they could also contribute to olfaction. As shown in the one-dimensional gustatory response graph, PtdSer has a nominal spacing of 2.34 Angstrom, PtdGal, 2.6 Angstrom; PtdIns, 3.3 Angstrom and PtdAsn, 4.84 Angstrom. These same receptors could be used in olfaction. They could be supported by additional or alternate receptors.

A phosphatidyl carnosine offers a unique similarity to Phosphatidyl serine but appears to offer a sensitivity peaking near 2.15 Angstrom because of the unusual spacing of the planar peptide linkage –NHCO–. The C–N bond length is unusually short in the peptide linkage, only 1.32 Angstrom compared to the normal 1.47 Angstrom C–N bond, suggesting about a 50% double-bond character (Morrison & Boyd, pg 1107). This results in a distance between two of the oxygen orbitals of 2.0 to 2.15 Angstrom, conveniently located between the PtdSer and the PtdGal receptor values.

It is not clear how carnosine, or a methylated variant, anserine, would couple to a phosphatidyl substrate. However, a dipeptide of serine and β-alanine would give the same steric structure as carnosine but be terminated by an OH that is easily esterfied to the phosphatidic acid substrate, resulting in phosphatidylserinealanine (PtdSerAla). Figure 8.6.3-3 shows the dipeptide ready to be

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It is interesting to note, carnosine and PtdSerAla involves a dipeptide that has been rearranged so it cannot form longer proteins. This introduces the question is a dipeptide that cannot expand into a tripeptide still a protein?

The above discussion provides a solution to a long running debate; whether receptor molecules are lipid based or protein based. Farbman has framed this debate. Taking a broader perspective, the sensory neuron requires specialized neurolemma areas to support the electrolytic transduction and amplification process. This specialized area consists of specific phospholipids exhibiting electrical properties compatible with electrical contact between the SSC’s and the base region of the Activa formed by the neural input structure. The polar end of the phospholipid molecules are specifically tailored interface with the SSC molecules. The SSC molecules are metal-complexes containing multiple simple peptides (oligoproteins). Thus olfactory transduction requires the presence of both lipids and proteins at the input portion of the olfactory sensory neurons.

Weissmann has provided the background required to appreciate the structure of the candidate phospholipids. Vogel et al. have demonstrated the conductivity of the typical phospholipid is sufficient to allow the measurement of a finite potential between its two ends when present as a monolayer film.

8.6.3.1.5 Potential olfactory transduction processes based on energy states

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8.6.3.1.5 Potential olfactory transduction processes based on energy states

[xxx material below may belong in history section above. It offers no real baseline applicable to the Electrolytic Theory The material may relate better to STEP TWO than STEP ONE ]

The potential for the olfactory and gustatory modalities to share receptors designed to sense organic acids suggests that the olfactory modality depends on sensing absolute steric distances to create distinct sensations of smell. The distance between two orbitals capable of sharing electron-pairs in what is known as an AH,B configuration appears to be the critical dimension. In the case of the organic acids, d = 2.34 Angstrom in the aciophore.

Ohloff et al. has described a triaxial rule for identifying a compound that will elicit the sensation associated with ambergris. The concept is similar to the AH,B concept of Shallenberger & Acree in gustation but it only requires the presence of one oxygen orbital and two hydrogen atoms. The concept relies upon energy calculations rather than stereochemistry. Ohloff used a trans-decaline molecule as his template. This molecule consists of two fused cyclohexanes that are not odorants without additional substituents. The rule involves a pair of substituents pointed axially in one
direction and a third pointing in the opposite direction. One of the pair must contain an oxygen or have an oxygen attached to it. The Vlad team has pointed out the inadequacy of the initial Ohloff triaxial rule.

Gorbachev et al., writing in English, have described the more detailed concept of the Vlad team. They employed a quantum-chemical calculation to explore the energy fields of a large number of odorants (not just odorophores) associated with ambergris. Ambergris is a common name for a mixture of odorants taken from the sperm whale. The primary odorant is ambrein, a decalin with a long aliphatic chain terminating in a hexane ring. Ambroxan is a simpler decalin with a fused heterocyclic pyrrole.

Gorbachev et al. focused on an oxygen atom and two hydrogens in a specific steric geometry (the ambergris triangle) account for the ambergris odor. They note, “It should be stressed that the 1s functions of the hydrogen atoms appearing in the “ambergris triangle” have the same sign in the acceptor MO and that one of these hydrogen atoms is always negatively charged. In addition, it was established that the charge density within the triangle remains approximately constant and equal to \( \sigma = -0.1 \text{ e/Å}^2 \).” They go on, “all molecules having an ambergris-type odor have a free MO (an acceptor MO) located in the energy range from 0.2233 to 0.2556 au and characterized by large absolute values for the coefficients of the AO’s of axial, tertiary, and allyl hydrogen atoms, which are also adjacent to oxygen atoms (see Fig.).”

Rossiter (1996) has noted Vlad’s comment concerning the charge on the H hydrogen, “The negative charge on the hydrogen atom furthest away from the oxygen atom is somewhat surprising. However Vlad does comment that ‘this statement is not very strong in view of the approximations used in the calculations.’”

While similar to the concept of Shallenberger for the sugars in gustation, no explanation was given as to how this geometry interfaces with the olfactory receptors. The analysis focused on hydrogen as the second constituent instead of the oxygen, as in the case of Shallenberger. No complete transduction mechanism has been offered by either Ohloff or the Vlad team.

Kovatcheva et al. (2004) have performed an extensive computer-aided analysis on a large number of ambrein derivatives to develop the applicability of the ambergris triangle.

Cheng et al. (2009) have provided a more precise derivation of the ambergris triangle based on:
• a broader range of constituents of ambergris,
• some tricyclic ethers and modern HOMO-LUMO calculations. It is shown in (B). The difference in values between the two are substantial. The Cheng et al. triangle generally applies to distances associated with a single substituent and other atoms adjacent to that structure. The Cheng et al. values appear inconsistent with the trans-decaline structure of Ohloff and current Standard Bond

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Length values. Neither of these “pragmatic” approaches appears to offer a general solution to describing the functional characteristics of a molecule associated with the ambergris odor. This work offers an alternate interpretation of the odorophores associated with ambergris that does not employ energy calculations of the type suggested by Ohloff et al., by Gorbachev et al., by Kovatcheva et al., or by Cheng et al. The alternative generally asserts the lone oxygen is in a DACB relationship with either the phenyl ring of ambrein or with the double carbon bond found in many of the odorants of ambergris. Ambrein exhibits a number of odorophores based on the electrolytic hypothesis proposed here.

8.6.3.2 Potential mechanisms of olfactory transduction

There are no comprehensive descriptions of the cytology of olfactory sensory neurons and their operation at the mechanism level in the current literature. Most of the available literature of olfactory transduction has focused on operational considerations, i.e., what was the neurophysical or psychophysical results of stimulation by a particular chemical. Remarkably, no discussion has been found in the literature describing an actual reaction associated with olfactory transduction; no reaction chemistry, no steric rearrangement chemistry, no electronic rearrangement and no decomposition chemistry. While the mechanism involved frequently involves very small quantities of material, it would be expected that some residues that were not in the original stimulant would be identified in the mucosa of laboratory animals. This absence suggests the olfactory mechanism does not involve any chemical reaction or rearrangement.

This work has the advantage of calling on the previously documented configuration and performance of other sensory neurons. The similarities of these sister sensory neurons provides valuable insight into the potential configuration of the olfactory sensory neurons.

Looking at the olfactory literature globally, and the generic sensory neuron of this work, it is possible to propose a olfactory sensory neuron histology, cytology and fundamental transduction mechanism compatible with both. The literature supports a method of operation that is different from the general assumption related to odor binding. The common procedure of “washing out” the stimulus and its neurological effect is incompatible with the conventional concept of “odor binding” where odorophores either react chemically with the receptor or pass through a lemma into the interior of the sensory neuron. Similarly, the generator waveforms recorded neurologically indicate the action of the odor stimulants is short term in character and not associated with a long term chemical “binding.”

Doty provided one of the few conceptual descriptions of the physiology of the olfactory sensory neuron in 1976. He provided both a coarse drawing of the cytology of the neuron as well as a conceptual view of its physiology shared with a broad audience of associated investigators. No detailed discussion of the contiguous steps illustrated in his schematic providing an end-to-end description of the output generator potential as a function of the application of the odorant has ever appeared. Figure 8.6.3-5 compares the electrolytic theory of this work with the largely conceptual model based on the chemical theory developed by many contributors over the years. This work does provide a contiguous description of the creation of the generator potential as a function of the application of the odorant (including the complete transient response of the sensory neuron). It includes both functional and mathematical descriptions of each process in the overall contiguous process. Notice the significantly lower number of steps involved in the electrolytic approach. Not illustrated in Doty’s drawing is the axon as it courses from the dendroplasm/axoplasm interface at the lower surface of the olfactory knob to the axon pedicle. It is likely that the dendroplasm/axoplasm interface occurs at the olfactory knob and the upper extension of the neuron beyond the soma actually encloses the axon. In that case the dendrite is totally enclosed within the olfactory knob (and the olfactory knob is a three terminal device in the language of circuit theory). The knob can be considered a three-terminal circuit with the signals from the cilia summed at the input terminal of the 2nd Activa amplifier, the poditic terminal at the point located by the asterisk, and the output terminal sending its signal down the axon to the pedicle of the axon. Only detailed electrophysiological measurements of the potentials within the lemma of the sensory neuron can demonstrate this point. However, electrophysiology measurements of the electrical
fields surrounding the neuron (like those available for visual sensory neurons) can point to the precise location of the poditic terminal.

As shown in Section 8.6.xxx, the voltage output at the pedicle of the axon is an analog waveform in olfaction, with a time course varying significantly with the application of the odorant. To the extent it is associated with an action potential generation, the so-called initial segment of the axon in Doty’s figure does not exist.

The “receptor potential” Doty associates with the response of an undefined membrane has been measured in other sensory modalities and found to be an analog potential at the output of the 1st Activa (the adaptation amplifier) formed between the external lemma and the reticular lemma within the dendritic structure of the neuron. It is this potential that forms the electrical input to the 2nd Activa (the distribution amplifier) of the neuron. The 2nd Activa is primarily an impedance reducing amplifier to insure its output signal is not dissipated too quickly during analog projection to the olfactory bulb. Its output is an electrical waveform. The detailed electrical operation of the sensory neuron is the same as it is in all external sensory receptor neurons (Section 8.6.5.xxx).
Doty provided his set of “Emerging First Principles of olfactory transduction” in 1976 (page 72). The set must be carefully reviewed as to applicability in the light of the Electrolytic Theory of the Neuron and the more detailed information accumulated since that time. The set was not accompanied by any contiguous description of the olfactory sensory neuron and relied upon a great deal of undemonstrated conventional wisdom.

8.6.3.2.1 Basic requirements of olfactory receptors

Schild & Restrepo reviewed the overall olfactory transduction state of the art in 1998 focused on its electrophysiology and biophysical aspects. They summarized many of the measured parameters associated with the sensory neurons but maintained the conventional chemical theory viewpoint when discussing the underlying theory. What they did not stress was that most of their data was obtained parametrically and only applied to the axonal aspects of the overall sensory neuron. As a result, most of the data contained in the review applies to the neuron itself and not the transduction process. That data will be addressed in Section 8.xxx. They review the diversity of transduction mechanisms in the literature under five subheadings. They are all chemically-based and focused on cAMP. No detailed mechanism is described or proposed. They do note the reported densities of cAMP channels through the cilia remain in the 205-2,400 channels/sq. micron region. These calculations remain anachronistic as no images of these purported channels have appeared in all of the neural literature.

Turin has updated an early theory based on a potential indirect tunneling mechanism at the quantum-mechanical level. It has been ignored by many in the community. Rinaldi discussed its ramifications and capabilities in 2007. Loosely quoted, he said, “Among various alternative possibilities that have been proposed, the most controversial is the so-called ‘vibration theory of olfaction’. First introduced in the 1930s, it states that the smell of a molecule is determined by intramolecular vibrations (apparently referring to the resonance between the two oxygen atoms of a carboxylic acid) rather than by the shape of the molecule. In 1996, Luca Turin, revitalized the theory by suggesting that the transduction of molecular vibrations into receptor activation could be mediated by inelastic electron tunneling... Turin's idea did not receive much attention until 2003, after science writer Chandler Burr wrote a book about Turin, his 'heretical' theory and how the established scientific community purportedly ignored it (Burr, 2003). Suddenly, the discussion about the vibration theory of smell was immersed in a harsh controversy about the correctness of scientific practice (Solomon, 2006).

The above ideas and some additional ideas introduced by Adkins & Phillips have not produced a rational explanation of olfactory transduction.

The studies of Russell et al. have suggested that PtdIns and PtdSer may play a role in olfactory receptors similar to that they play in gustatory receptors. It is worth noting that the inositols are significant odorants and PtdSer is the receptor for organic acids, whether they are delivered to the mouth or are airborne.

While the olfactory modality appears to involve ten to less than thirty independent sensory channels, based on the number of glomeruli in stage 2 signal processing, identification of two of the receptors involved in those channels suggests the path to identifying the others. Tailored phosphatidyl compounds on the surface of the cilia appear to form the receptors.

8.6.3.2.2 Confirmation of the excitation/de-excitation equation for olfaction

Dodd & Squirrel have provided a modified figure from Gesteland, 1971, showing the currents flowing in and around the typical ORN. Unfortunately, the Gesteland experiments employed a very early and low spatial resolution electrical probe. The resulting current flow map was of lesser quality to similar plots for the visual sensory neurons (Section xxx). A figure adapted from Morrison (Fulton...
Morrison90.wpd in taste and smell art) in that section shows how the stage 1 sensory neuron of olfaction can be described as a multiport electrolytic circuit, including identification of the poditic terminal.

Takeuchi & Kurahashi have provided a valuable paper related to the E/D equation\textsuperscript{233}. Their paper demonstrates that the transient response of transduction is represented by the same E/D equation as the other sensory modalities (Section 8.7). They also demonstrated the same isolated olfactory sensory neuron exhibited the same E/D response when excited by a odorophore or by short wavelength light.

In this study the activity of transduction channels in the olfactory cilia was recorded in cells that retained their abilities of responding to odorants that have been reported to produce InsP\textsubscript{3} (instead of producing cAMP, and therefore tentatively termed “InsP\textsubscript{3} odorants”). InsP\textsubscript{3} is an abbreviated label for inositol 1,4,5-triphosphate. It is a widely found chemical that is able to participate in a considerable family of biochemicals. It is most significantly found in combination with the phospholipids as the receptor material PtdIns on the dendrites of the sensory neurons.

The two InsP\textsubscript{3} odorants were Lilial and lyral. Lilial (from the flower, Lily of the Valley) is a fragrance ingredient formally known as Butylphenyl Methylpropional. Lyral is a trade name for a synthetic fragrance resembling Lilial, 4-hydroxymethylpentylcyclohexene carboxaldehyde. Both are used in cosmetics but also known as a skin irritant frequently causing dermatitis. Based on the electrolytic theory of this work, they are both xxx odorophores. The light was only described as the UV component from a Xenon lamp.

Their figures 6(A) and 6(D) clearly show the change in the response with stimulus intensity typically associated with the E/D response for Lilial and for UV light. Their figures 7(A) and 7(B) clearly show the change in the response with stimulus intensity typically associated with the E/D response for Lyral and for UV light. Many other figures are shown that can all be interpreted as caused by the coordinate bonding of these odorophores to PtdIns. The rest of their text is of no interest here. Takeuchi & Kurahashi took care not to induce adaptation in their experiments.

Leinders-Zufall et al. addressed the question of adaptation in olfaction\textsuperscript{234}. They note, “The mechanisms underlying odor adaptation in olfactory receptor neurons (ORNs) are fundamental for a complete understanding of the sense of smell. Like sensory neurons of other modalities, vertebrate ORNs adapt to ambient conditions by time dependent modification in the sensitivity to a given stimulus.” After reviewing a variety of chemical hypotheses related to adaptation, they conclude, “These varied findings make further investigations necessary.” Their figure 1 provides good data confirming the applicability of the E/D Equation to both sustained and short exposure to cineole by a selected ORN. They note a brief delay before the beginning of the E/D response that varies with stimulus intensity. They provide what they label a desensitization time constant as a function of the stimulant exposure time. They illustrate a 27.7 second decay characteristic using the symbol, $\tau$, that erroneously suggests a time constant. These two response segments constitute the signal response, the generator potential, of the ORN and are not directly related to the adaptation mechanism. The actual time constants of the E/D response can be obtained by curve fitting the E/D equation to the recorded responses.

Kleene has provided a recent paper based on the conventional 20\textdegree{} Century wisdom relative to olfaction and a set of caricatures\textsuperscript{235}. The paper incorporates data from Takeuchi & Kurahashi but provides little new information.


\textsuperscript{234}Leinders-Zufall, T. Ma, M. & Zufall, F. (1999) Impaired odor adaptation in olfactory receptor neurons after inhibition of Ca\textsuperscript{2+}/Calmodulin kinase II J Neurosci vol 19, RC19, pp 1–6

8.6.3.3 **Proposed two-step transduction process**

After reviewing the history of olfactory research, it is concluded that the only viable explanation for transduction in olfaction is to follow the methodology found in gustation. It is proposed that olfactory transduction involves a two-step process, a first step focused on the selection of those odorophores capable of a DACB coupling to individual moieties esterified to the phosphatidic acids of the outer lemma of the sensory neuron dendrites (step 1) followed by the measurement of the dipole potential associated with that odorophore (step 2). The esterified moieties are labeled the OR's of the olfaction modality. The final neural signal exhibits an intensity that is proportional to the probability of the DACB coupling between the odorophore and a specific OR and the amplitude of the dipole potential of the odorophore. This protocol is similar to the two-step process involved in the rate of reaction of first order chemical reactions.

8.6.3.3.1 **Complex structures not addressed by the proposed theory**

Naphthalene, a fusion of two benzene rings without further additions or substitutions forms the beginning of a more complex family of odorants. The material is considered a resonance hybrid of three different valence bond structures. Its odorophore(s) must be associated with the complex \( \pi \)-cloud of the material.

An additional class of odorants not addressed in the current theory contains complex molecules with structures incorporating three-dimensional structures beyond the simple boat and chair structures. Figure 8.6.3-6 shows a selection of chemical forms of interest. The variations among these three suggest the difficulty of sensing all of the available fragrant non-electrolytes.

Figure 8.6.3-6 A composite of fragrant non-electrolyte structures EDIT. May want to remove menthol from this set.

It is likely that more detailed energy density calculations within the physical environs of the molecule will be required to define the electronic site providing the second coordinate bond site along with the oxygen.

8.6.3.3.2 **Fats and their breakdown residues**

The literature related to the role of fats in olfaction is thin and primarily empirical. It is primarily
focused on the food industry. As noted by Gilbertson & Kim, “Fat has long been assumed to present only textural cues to receptors in the oral cavity.” It is important to differentiate between the fats and the fatty acids of chemistry. The fats are generally separated into two major types, the saturated and unsaturated. The unsaturated fats are predominant because of the ability of one saturated fat to be modified into a great many different unsaturated fats. As the authors note, the unsaturated fats can typically be separated into cis- and trans- variants with significantly different chemical properties. The Gilbertson & Kim paper attempts to develop an explanation for the chemoreception of fats but at a superficial level.

The fundamental fats exhibit a variety of acetate structures. However, as the molecular weight of the fats increases, they become less and less soluble and therefore less likely to stimulate any chemoreceptor. However, during cooking (at least boiling), these molecules are frequently modified significantly through hydrolysis and many of the resulting residues exhibit a much lower molecular weight and significant ability to stimulate the chemoreceptors. The principle residues are glycerols and a variety of organic acids. Both residue types are capable of stimulating both gustatory and olfactory sensory receptors based on the hypothesis of this work.

8.6.3.3.3 Hydrogen sulfide and other inorganics requiring hydration

As shown in Section 8.5.xxx, the inorganic sodium ion can act like other gustaphores after forming a coordinate complex with water molecules. It appears that CO2 and H2S may do the same thing.

The chemistry of sulphur is quite complex. It is known to form a variety of covalent type and coordinate type bonds. Its ability to participate in sp3d2 hybridization structures provides a limitless range of possibilities for forming an odorophore. Henon et al. have noted, “A theoretical study of dipole moment functions (DMF) of hydrogen sulfide (H2S) molecule is a particular challenging task for ab initio electronic structure calculations in view of further studies of intensities anomalies observed in infrared high resolution spectra.” They note that others have obtained theoretical values that differ from the experimental results by factors of two.

While the solubility of hydrogen sulfide in water is relatively low, the human sensitivity to hydrogen sulfide is significant:

- 0.00047 ppm is the recognition threshold, the concentration at which 50% of humans can detect the characteristic odor of hydrogen sulfide,[13] normally described as resembling "a rotten egg".
- Less than 10 ppm has an exposure limit of 8 hours per day.
- 10–20 ppm is the borderline concentration for eye irritation.
- 50–100 ppm leads to eye damage.
- At 100–150 ppm the olfactory nerve is paralyzed after a few inhalations, and the sense of smell disappears, often together with a awareness of danger.[14][15]
- 320–530 ppm leads to pulmonary edema with the possibility of death.

The olfactory system adapts rapidly to hydrogen sulfide making its continued presence at moderate concentrations even more dangerous. Safety instrumentation is required to support workers handling H2S on a continuing basis.

Dos Ramosa, M. & McCabea report, “The system water + hydrogen sulphide has been studied extensively and a large amount of experimental data is available, which has been recently reviewed by Carroll et al., Chapoy et al., and Koschel et al.” They also discuss the significant effect

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of the presence of salt on the solubility of H₂S in H₂O.

Hydrogen sulfide itself is not an acid. It is moderately soluble in water (261 volumes in 100 volumes at 20°C). When dissolved in water, it forms the very feeble hydrosulphuric acid with only 0.0007 (0.07 percent) of the substance ionized to form:

\[ H_2S \rightarrow H^+ + HS^- \]

The question of the moment is, how does H₂S or HS⁻ stimulate the olfactory sensory receptors? Stimulation is probably not based on its ionized form in solution. Alternately, does it only affect separate nocioreceptors? The un-ionized material is able to form coordinate bonds much like water itself. Figure 8.6.3-7 shows the two molecules when coordinately bonded. The variation in bond angles and lengths is due to the out of plane arrangement of individual groups. The potential for mixed bonding between these chemicals should not be overlooked. The ability of fragments of these coordinated structures to form coordinate bond pairs with sensory receptors appears quite reasonable, although there is no reason to believe water alone can act as an odorophore.

The S—H bond is particularly long (~2.6 Angstrom) and therefore weak in hydrogen sulfide. This weakness is frequently cited as the reason this molecule is a gas while water is a liquid at biological temperatures. The S—H bond is nominally 1.33 Angstrom and the angle HSH is nominally 92.2 degrees (Section 8.6.1).

The simplest odorophore of hydrogen sulfide, based on the coordinate-bond-pair requirement developed above, appears to be a non-ionized structure consisting of two molecules of H₂S in a coordinate bond relationship. This relationship provides two atoms able to support covalent bond sharing and the requisite hydrogen able to support hydrogen bonding with a suitable sensory receptor. If planar, such a structure would exhibit a d = 3.94. If the two sulfur atoms were out of plane or the available bonding cites were rotated, the effective d-value would be higher. Further analysis is needed to confirm or modify the d = 3.94 Angstrom value.

One of the many alternate odorophores of hydrogen sulfide in water could be between one molecule of H₂S and one molecule of H₂O via a hydrogen bond. This arrangement would be expected to have a somewhat lower d = value. However, a structure of one H₂S molecule and two H₂O molecules creates a potential dual coordinate bond with a d-value of 4.485 Angstrom in the simple case of a 90 degree angle between the H—S bonds and aligned S—H and H—O bonds. This value is only 5.5% below the nominal 4.746 Angstrom d-value for picric acid. For a 92.1 degree angle, the difference is less (~1.4%). More precise bond angles might improve this match. H₂S•2(H₂O) is an effective stimulant of the (unnamed xxx) path of olfaction. It is also an effective stimulant of the picric path of gustation.

An additional potential odorant would couple two more water molecules to the sulfur atom via hydrogen bonds. The resulting hydrated configuration could offer up to four odorophores per molecule of H₂S. The angles between the covalent and coordinate bonds may equilibrate at 109 degrees (tetrahedral conformation) instead of the planar version shown at 92.1 degrees. At 109 degrees, the expected d-value would be about 5.14 Angstrom or ~8% higher than 4.746 Angstrom.
The dipole moment of hydrogen sulfide is 0.97 Debye (about one-half the 1.84 Debye of water). No value for the dipole potential along the dipole axis (bisecting the H–S–H angle) has been located in the literature. The dipole potential of the hydrated H₂S structure is not currently available.

The very distinctive odor of rotten egg associated with hydrogen sulfide may imply a unique sensory receptor sensitive to a d-value of 3.94. No other common stimulant is represented by this value. However, the microphore of gustation has a d-value of about 4.2. There may be a connection between the sensory receptors of these two stimulants. More rigorous determination of both of these d-values is needed at biological temperatures.

Lacking additional data, the odorophore of the stimulant hydrogen sulfide, is suggested to consist of two molecules of H₂S in a coordinate bond configuration capable of supporting a dual coordinate bond with a sensory receptor with a d-value of 3.94. The olfactory sensory receptor and sensory neuron is proposed to be the same as that used within the gustatory modality, but physically appearing in the nasal cavity and connected neurologically to the olfactory circuits of the CNS.

8.6.4 FIRST STEP in the transduction process—selection

Initially, an approach was pursued matching each odorant to a separate OR as expounded in the Nobel Laureate presentation of Axel & Buck of 1991. However, this approach appeared highly illogical based on the fact that all other major sensory modalities employ a combinatorial concept where a small number of receptors can be used to sense a very large number of stimulants using a multiple dimension perception space. The initial approach was abandoned. Buck has sense abandoned their original approach in favor of a combinatorial approach.

The approach presented here involves a two-step transduction process where the initial step (selection) employs a DACB relationship between the individual odorophores of an odorant and any of up to nine OR’s. Some of the potential DACB relationships may be prevented by steric considerations.

Two interesting findings play a significant role in directing the search for the OR's of olfaction; the likelihood that PtdSer is present as a GR in gustation and as an OR in olfaction and the likelihood that an ester of phosphatidic acid and tryptophan (PtdTrp) can form an ideal dimer with skatole, thereby suggesting that PtdTrp is the OR for skatole and other members of the indole family in olfaction.

These findings suggest multiple members of the amino acid family might esterify with Ptd in order to perform as individual OR’s. The following sub-sections explores this possibility in detail. In some cases, multiple possibilities exist for the OR channel molecule involved in transduction. Section 8.6.4.1 will discuss the potential for aliphatic molecules to esterify with Ptd. Section 8.6.4.2 will discuss the potential for arenes to be involved in the esterification process. Laboratory verification of the proposed OR molecules participating in DACB is required to resolve these possibilities.

It is important to note that comments and reference chemicals cited as standards for identifying specific olfactory channels have not been reviewed for medical appropriateness. This section and the following subsections are totally academic analyses. Do not employ any of these reference chemicals in animal or human experiments without reviewing them with your institutions ethical practices committee.

There is insufficient data to establish the width of the sensitivity function of each OR moiety at the a 50% probability level. Similarly, there is insufficient data to describe the capture range of a given odorophore to form a DACB with a receptor exhibiting a sensitivity function represented by a unit impulse function. For the purposes of the following subsections, the 50% probability values for each OR will be taken as ±5% of the central value established by the nominal d-value of the proposed OR.

It will be assumed in the following discussion that each OR employs a moiety that only exhibits one d-value compatible with forming a DACB of interest in olfaction. However, it can form this DACB with the appropriate structure within a wide range of odorants.
There is a tendency to associate histamine with the amino acids because of their similar suffix. However, histamine is not an amino acid. It is a pyrimidine with two nitrogen substituents and an aliphatic chain with another nitrogen singly bonded to the beta-carbon.

When attempting to define a primary set of odorophores, the early work of Beets in Theimer, 1982, should be reviewed. While unsuccessful, his analyses provide valuable background.

The following discussion will describe nine olfactory receptor channels using semantic channel descriptors developed earlier in this research. While in conflict with many individual papers in the literature, the labels used here are based on significant theoretical evidence associating them with their channel assignments.

The following labels with block letters following the prefix Ptd indicate the combining of one of the 20-25 common amino acids, using their conventional labels, with the lipid Ptd. Labels with italic letters following the prefix Ptd indicate the combining of one of the uncommon amino acids (there are about 150 of these, Lehninger, pg 26, 1972) or a modified amino acid, with the lipid Ptd. Many researchers assume there are less than 25 essential amino acids because of their prior education. The essential amino acids (from a nutrition perspective) are also known as the indispensable amino acids because they cannot be created de novo within the human body and must be ingested. The website, “About Education,” provided a useful summary in 2015 of the amino acids in their human role.

The essential amino acids for all people are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Several other amino acids are conditionally essential amino acids, meaning they are required at some stages of growth or by some people who cannot synthesize them, either because of genetics or a medical condition. In addition to the essential amino acids, babies and growing children also need arginine, cysteine and tyrosine. Individuals with phenylketonuria (PKU) need tyrosine and also must limit their intake of phenylalanine. Certain populations need arginine, cysteine, glycine, glutamine, histidine, proline, serine and tyrosine because they either cannot synthesize them or are unable to make enough to meet the needs of their metabolism.

The last sentences may be useful in determining why some older adults, particularly women report considerable loss in their ability to perceive odors. Many of the amino acids listed are incorporated into the proposed sensory neuron receptors of this work. With age, one or more of these critical components of the sensory receptor neurons may not be produced within the human system or successfully absorbed from food.

Ache & Carr have explored an unusual amino acid (using a broad definition), taurine (C2H7NO3S) that is ubiquitous in many marine invertebrates (See Section 8.6.4).

see comment in section 8.6.4.1 below  
[xxx where is summary olfactory receptors?  Currently in Figure 8.6.2-6 in Kreher analysis section  ]

Following the initial analyses of this section, an interesting feature of the proposed OR's can be seen in the Summary of olfactory receptors, [Figure 8.6.xxx ]. The proposed OR's consist of two interdigitated groups of amino acid based phospholipids. The OR's associated with the odd number sensory channels (based on their d-values) are essentially straight aliphatic chain amino acids, or in the case of channel 3 a simple modification of such an amino acid. The OR's associated with the even number channels are essentially aldehydes consisting of a simple phenol with an attached aliphatic side chain consisting of a simple amino acid. The identified "simple amino acids" are among the 20 to 30 amino acids identified by earlier investigators as present in protein chemistry. However, no reason to limit the amino acid to this group when they are associated with non-protein lipids in olfaction. The larger list of all known amino acids is currently on the order of 150. In the case

239http://chemistry.about.com/od/lecturenoteslab1/a/Essential-Amino-Acids.htm
of channels 8 & 9, the OR’s proposed do not contain simple amino acids or complete phenyl rings. However, the number of potential chemicals meeting the requirements for an OR attached to a lipid is very large. Many of these chemicals may be amino acids outside of the 20 to 30 identified above. The chemical proposed for the channel 8 OR, diaminoheptanoic acid, incorporates a partial phenyl ring and exhibits a d-value very similar to that if the ring had been completed.

Efforts were made to associate the proposed OR’s with conventional carbon chemistry by identifying an OR sensitive to specific arenes with an orbital at the α, β, γ, δ, ε locations etc. This approach did not appear to offer the desired generalized environment. Efforts were also made to form the required OR’s using a single long aliphatic chain carboxylic acid hydrolyzed to the phosphatidyl acid lipid and a single C=C bond placed at increasing distance from the remaining oxygen orbital of the aliphatic structure. This configuration appears to offer some potential for explaining the operation of the VR’s of the oskotony modality (associated with the vomeronasal region of the mammalian nose) but did not match the requirements of the olfactory modality at low d-values. See Section 8.6.11, and specifically Section 8.6.11.4.

The most satisfactory solution to identifying the OR’s of olfaction was achieved by recognizing three long known facts;

- The chemistry of the sugars involves coordinate chemistry and frequently involves pairs of coordinate bonds between ligands.
- Coordinate chemistry does not involve a “reaction” generating identifiable “residues.”
- A variety of amino acids had been identified as present in the olfactory epithelium (but without any known purpose).
- The outer bilayer of the lemma of a cell, particularly a neuron, consists of either phosphatidylcholine (PtdCho) or phosphatidylethanolamine (PtdEtn). The non lipid moiety in these chemicals are closely related to the amino acids.

Exploring a set of chemicals incorporating the above technologies resulted in a set of sensory neurons incorporating OR’s in specialized areas of their exterior lemma compatible with forming a dual antiparallel coordinate bond (DACB) with a great many odorants.

No empirical results have been located researching the potential connections between various amino acids and Ptd to form the chemical receptor portion of olfactory sensory neurons. However, mining the known list of common amino acids based on their d-values provides a list of likely candidates. Up through about OR 6, there are multiple candidates for most channels. The candidates are primarily aliphatic amino acids with only a few arene candidates. For OR 7 through 9, there are few candidates among the 20-25 common amino acids but a variety of lesser known candidates.

Section 8.6.1.8.4 has developed the relevance of chirality to the olfaction modality. It suggests an additional means of delineating between those molecules suggested as alternates for use in a specific OR channel below. All of the amino acids exhibit optical activity and are chiral except for glycine (M&B, pg 1100). While both positive and negative rotation of the plane of polarization is introduced by the amino acids in a polarimeter, only those introducing l- (levorotation) polarization are found in biological proteins. In other biological uses, both l- & d- (dextrorotation) polarizations are found. It is common to use the notation (+) & (-) instead of d– & l- for clarity and to avoid confusion with other alphabetical notations.

It does not appear that chirality plays a role in olfaction or gustation since they are based on the coordinated chemistry of the molecules involved, and specifically their d-values in Angstrom between various orbitals. The minimum energy configuration of the molecule within the pH of the surrounding matrix appears to be more important as it appears to determine the preferred orientation of the groups of the molecule associated with a single carbon–carbon bond that is otherwise free to rotate.

An interesting relationship appears in some listings; the potential that the odd numbered OR’s might employ aliphatic ligands and the even numbered OR’s might employ arene ligands. This interdigitation may be key to the ability of the OR’s to provide a more even spacing between the
d-values of the receptors and/or the desired level of overlap between their efficiency profiles. No theoretical preference has been uncovered favoring either of these approaches. Section 8.6.4.1 will examine the potential aliphatic ligands combined with Ptd.

8.6.4.1 Potential OR's based on aliphatic amino acids

This section will examine the potential aliphatic ligands that could combine with Ptd to provide a complete family of OR’s. The next fourth level section will consider other alternatives.

8.6.4.1.1 PtdSer– Potential OR for channel 1, organic (Lewis) acids

d = 2.276 Ångstrom

The ultimate goal in specifying the OR for the organic acids in olfaction is to determine the d-value for the carboxylic group in the ester of serine and phosphatidic acid when present in a water-based solvent. The problem is complicated by the old literature versus modern 3D representations of serine. Older material suggests the carboxylic group in serine may be hydrated to give a C–(OH)₂ configuration, or it may be resonant to give a HO–=C–=OH configuration, or it may be present in the O=C–OH configuration. Current chemical computation programs, including various Jmol files, present the carboxylic acid group in the latter (non-resonant) configuration with an angle between the two oxygen--carbon bonds as 120.021 degrees, the C–OH bond length of 1.43 Ångstrom and C=O bond length of 1.220 Ångstrom without any caveat as to the solute state if any. The result is a d = 2.276 Ångstrom between the two oxygen orbitals. Earlier literature gives a variety of similar but different values, with differences between the values in introductory texts and advanced organic chemistry texts. One Jmol file describes citric acid as consisting of three carboxylic acid groups, in a HO–C–O configuration with each group exhibiting a d-value of 2.21 Ångstrom and an angle of 120 degrees. The Klee papers of an earlier decade give the d = 2.268 Ångstrom as a common odorophore value for the carboxylic acid groups in tomato, including malic acid. However, a more recent value based on DS3.5 and the ChemSpider Jmol file for malic acid_510 gives d = 2.276 Ångstrom.

While not critical, because the DACB relationship between the OR and an odorophore assumes the two structures are both in the same state of solvation, the d-value used here will be 2.276 Ångstrom on the assumption this is the effective value in the aqueous state. This is the value appearing in most 3D representations based on the Jmol files of 2013. If incorrect, the d-value of both the OR and the carboxylic acid based odorophore will be assumed to change proportionately.

The channel specific odorophore for this carboxylic acid channel are the one- through six-carbon carboxylic acids. Acids of higher carbon number appear to lack the necessary volatility to be considered effective odorants.

8.6.4.1.2 Ptd4Hi– Potential OR for channel 3, the dulcals

8.6.4.1.3 Ptd4Hi– Potential OR for channel 3, the florals

The most likely molecule used by the channel 3 (floral) sensory receptor is Ptd4Hi, a variant of the amino acid, (–)-histidine_6038, with a d-value of 3.508 Ångstrom. No other candidate for this sensory receptor molecule has been identified.

8.6.4.1.4 PtdHis– Potential OR for channel 4, the limals
8.6.4.1.5 PtdGln– Potential OR for channel 5, the musks

[xxx three potential alternates total]

8.6.4.1.6 Ptd??– Potential OR for channel 6, the cinnamons

8.6.4.1.7 PtdLys– Potential OR for channel 7, the spices

8.6.4.1.8 PtdDha– Potential OR for channel 8, the citrals

8.6.4.1.9 Ptd Ahc - Potential OR for channel 9, the putrids

8.6.4.2 Potential arene-based OR's (ased on an aromatic ring and at least one additional orbital)

As noted in Section xxx, tryptophan appears to be an ideal receptor chemical to esterify with phosphatidic acid to create an olfactory receptor, phosphatidyl tryptophan (PtdTrp), with a d = 2.757 Angstrom. This OR would be well suited to link to a range of odorophores exhibiting the benzyl ring esterified to a longer aliphatic chain. It is particularly amenable to linking with methyl eugenol and the related methyl salicylate and methyl anthranilate.

PtdSer and PtdTrp provide effective OR's for odorophores in the region of d = 2.276 and d = 2.757 Angstrom. The challenge is to identify additional chemicals that can esterify with phosphatidic acid to form additional OR's with higher nominal d-values, particularly near 3.75, 5.5, 6.25 and 7.6 Angstrom.

[xxx bring in appen N showing attempts to show a dipeptide, or even an organo-metallic compound could be an OR were repeatedly found to be negative]

The common role of the phosphatidic ester of serine in both gustation and olfaction, and the likelihood that the phosphatidic ester of tryptophan is also an OR provides a strong suggestion that other OR's might also be based on esters of other amino acids. There are a vast number of chemicals that might provide such d-values. However, it is worth exploring other amino acids that are readily available in the mammalian system that could satisfy these requirements. The following discussion is based entirely on speculation at this time. There is no known empirical data supporting the following proposals.

There are fourteen “essential” amino acids containing orbitals or benzyl rings outside their fundamental amino group. Ten are aliphatic and four include aromatic ring structures. Two of the aliphatic group are sulfur-based and two are negatively charged (aspartic and glutamic acids). With serine and tryptophan already identified, and these four candidates appearing to be outside the candidate group, there remain eight candidate “essential” amino acids available to satisfy the four requirements remaining. Beyond this group are the large number of minor amino acids.

While serine is typically grouped with the amino acids with nonpolar R groups, and tryptophan is typically grouped with the amino acids with uncharged polar R groups, there are three amino acids labeled positively charged (basic) at pH values in the range of 6 to 7. They are, lysine, arginine and histidine. While these amino acids are considered odorless before esterification, they do exhibit a variety of orbital pairs and orbital/phenyl combinations compatible with the d-values of a variety of documented odorophores:

• arginine–5.351/7.432/7.533 and 8.838
• histidine–4.467/4.548/6.298 and 6.315
• lysine–6.705/7.495/8.557.

These three amino acids, along with serine and tryptophan are reported to be perceived as slightly sweet when in the D- isomer form by Kier in 1972.

Arginine and lysine are aliphatic in character. However, histidine is more complex and incorporates a heterocyclic imidazole ring. A problem arises when the potential acceptance ranges of these amino acids are considered. Figure 8.6.4-1 shows that before esterification, their potential acceptance ranges overlap and they exhibit multiple potential acceptance ranges. Further analysis is required to ascertain their acceptance ranges after esterification with phosphatidic acid and whether either of three situations are acceptable.

• Can a useful OR have two acceptance ranges?
• Can the stereographic situation for the esterified amino acid eliminate one or more of the potential acceptance ranges from practical use?
• Is it for two OR's to exhibit common acceptance ranges?

[xxx For the moment, it will be assumed that each of the positively charged (basic) amino acids only exhibit a single effective acceptance range after esterification via the hydroxyl group within the carboxyl group; with PtdArg having a d = 7.6 Ångstrom, PtdHis having a d = 6.3 Ångstrom and PtdLys having a d = 8.6 Ångstrom.

This leaves a requirement for two other OR's with d-values near 3.75 and 5.5 Ångstrom. There are only a few other major amino acids with the potential to provide the desired d-values. Tyrosine is of particular interest. It is in the uncharged polar group and exhibits a potential d-value of 5.534 Ångstrom between the aldehyde oxygen remaining after esterification at the hydroxyl group within the carboxyl group.

Glutamine might be a candidate for the last open requirement. It exhibits a d-value of 3.441 Ångstrom between the aldehyde oxygen remaining after esterification. However, 3.441 is nine percent below the target value of 3.75.]

As noted for PtdSer, the esterification process typically involves a hydroxyl group of the amino acid not associated with the carboxylic acid group. However, esterification involving the hydroxyl group within the carboxylic acid group is probably possible within the enzymatic regime of the mammalian biological system.
The two thio-amino acids were examined but neither offered a d-value in the remaining range required. Similarly, the two negatively charged amino acids were examined but only exhibited d-values in the 3.441 Å range due to the nitrogen and the aldehyde oxygen of the primary amino acid structure.

Failing to locate an appropriate amino acid with a d-value of about 3.75 Å, other alternatives need examination. As in the case of the special iso form of leucine found in gustation, a special iso form of arginine appears likely to provide a d-value near that desired. Alternately, an arginine derivative with one less methyl group would appear to be a candidate. The rare amino acid, 4-hydroxylysine exhibits a potentially acceptable d-value of 3.508 Å. When esterified with phosphatidic acid, it could be described by the shorthand of Ptd4Hi.

8.6.4.2.1 Recent experiments with amino acids as dimer stimulants

Work reported since 1997 have shown the ability of many species to discriminate between a subset of the common amino acids. However, the discrimination has failed for other amino acids. This situation offers support for the proposed OR receptors of this work where a similar situation is found. Only some of the OR receptors can be associated with amino acids esterified to phosphatidic acid. As noted, some OR channels cannot easily be associated with common amino acids, although they might be associated with some of the rarer amino acids. It is reasonable to posit that the amino acids that are sensed by many species are each forming a dimer between the stimulant amino acid and the OR channel amino acid. In this case, the amino acid stimulant is the perfect primary stimulant for activating the corresponding OR channel.

8.6.4.2.1 Background

This group of chemicals is very large and contains a variety of odorophores associated with the spices as well as many flowers. Some of the structural differences are quite subtle and these differences frequently play a larger role in odorophore intensity discrimination (STEP TWO in transduction) than in odorophore selection.

If the benzene ring has a hydroxyl group attached directly to it, the result is given the special name phenol.

Morrison & Boyd have provided Figure 8.6.4-2 illustrating some of the subtle differences between major chemicals extracted from the essential oils of a variety of spices. These chemicals can stimulate OR’s sensitive to aromatic rings with attached oxygen orbitals as well as other OR channels. These chemicals are primarily selected by the phenol channel in STEP ONE and modulate the intensity of that channel through the mechanism of STEP TWO of transduction. This modulation is due to their varying dipole potential brought to the OR once attached to it via the DACB relationship. Vanillin is also selected by the phenyl-alpha-carbon OR. Note the different locations of the double carbon bonds among these chemicals. These double bonds can also stimulate specific OR’s sensitive to the

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d-values generated by the various oxygen orbitals and these double bonds. As a general rule, these chemicals are not simple odorants (containing only a single odorophore) but act as compound odorants (containing more than one distinct odorophore). However, this feature may be subtle. In the case of the phenol esters, the d-value between the aromatic ring and the ester oxygen is only 2% different from that of the phenol hydroxyl d-value. This difference is well within the nominal ±5% capture tolerance of the DACB relationship for a specific OR.

By forming a heterocyclic ring of two oxygen atoms and three carbon atoms, safrole has introduced a different dipole potential than eugenol (along with some potential change in the precise d-values associated with the two oxygen orbitals).

![Figure 8.6.4-2](image)

**Figure 8.6.4-2** Several odorophores found in the essential oils of the spices. All are phenols with additional modifications. These modifications are primarily recognized as leading to different intensities within the stimulated odorophore channel. Notice only thymol is a simple phenol with additional non-orbital containing aliphatic elements added. Eugenol and isoeugenol are methyl esters of phenol with an additional non-orbital containing aliphatic chain. Eugenol and safrole are very closely related. See text. From Morrison & Boyd, 1971.
This figure clearly illustrates it is not the chemical groups that determine the smell of an odorant (or taste of a gustant). It is the d-value associated with the individual odorophores forming potential DACB relationships with the receptors (not illustrated in this figure). Figure 8.6.4-3 introduces several additional critically significant parameters.

First, there are questions related to nomenclature;

- As frequently noted, using a Fischer diagram to identify a chemical structure is inadequate when discussing their participation in olfaction and gustation.
- Because of the profusion of acceptable names for the same chemical, it is critically important that an accession number related to an accepted database be cited in academic research reports.
- Because of the frequent presence of multiple forms related to a specific chemical name, it is critically important that an accession number related to an accepted database be cited in academic research reports.

As illustrated, there is more than one isoeugenol, and each isoeugenol is associated with a different [xxx primary, defining, fundamental, distinguishing, transcendent, leading, dominant, predominant, ranking etc. ] [xxx secondary, Etc.] perceived odor.

Second, there are a subtle list of housekeeping aspects that suggest great care must be taken when using Jmol packages.

- The Jmol packages renumber the atoms within a structure essentially uncontrolled (vis. the trans–versus o– variants of isoeugenol from the same database, ChemSpider) and no relationship to previous rules on the numbering the constituents of chemical structures.

The numbering of Jmol packages causes many cardinal numbers to be omitted. As shown, there is no carbon numbered C1 in anisole, there are no carbons numbered C9 and C10 in eugenol_13876103. Alternately, there is no C1 and C2 carbons identified in the o-iso-eugenol shown.

- While illustrating a resonant structure, the Jmol programs do not normally treat the benzene ring as resonant. Instead, they provide different lengths for the single and double bonds, resulting in three different diameters for the structure depending on the atoms referenced, even though the structure illustrated are all shown as planar.

It is critically important that the benzene ring be treated as resonant in olfaction, and that the decoupled cloud of electrons be associated with a definable centroid. In the analyses in this section, the distance from the centroid to the carbon(s) supporting the aliphatic chain(s) is very important.

The figure can be considered an exemplar for various families of arene-based odorants and “essential oils.” The arenes are by far the largest group of olfactory stimulants in mammals. The figure shows the primary odorophore of the family is found among all members of the family and that a set of secondary odorophores provide additional dimensions to the overall olfactory experience. As in the case of gustation, these additional dimensions appear as neural signal amplitudes at the nodes of a multi-dimensional olfactory space. In the case of olfaction, the number of dimensions in this space will be shown to be in the range of 20 to 32. The actual value is consistent with the number of non-repeated glomeruli in the olfactory bulb (the stage 2 signal processing center of the olfactory modality). The bulb exhibits almost a duplicate organization serving more than one purpose as discussed in the sections applicable to stage 2 signal processing.

The chemicals illustrated are primarily associated with seeds, as opposed to flowers, and typically exhibit limited volatility. They frequently excite the OR’s via the retronasal path.

The tables of d-values have been arranged to compare similar distances in common rows. Note the relatively small differences in the d-values associated with the [xxx dominant, primary etc odorophore defining the dominant perceived odor (smell)]. The significantly larger differences between the secondary and primary d-values indicate the odorant acts as a dual odorophore stimulating two distinct OR’s. The results are significant differences in perceived smells among these family members. In more complex molecules, tertiary mechanisms and their d-values may further differentiate
members of a family. Note the 30% spread among the secondary odorophores of \( o -i s o e u g e n o l \), suggesting two distinct secondary odorophores. As a result, \( o -i s o e u g e n o l \) exhibits three distinct odorophores. No description of its perceived odor was found via cursory search of the literature.

Many similar sets of figures can be produced for the phenyl structures dominating the perceptions of olfaction. One similar set begins with anisole, followed by anethole and hydromethyl anethole and various isomers. The perceived smell of many of these constituents have not been documented in an orderly index. A comparison of the calculated odorophores of trans-iso Eugenol and the isomers of hydroxymethyl anethole, and their perceived smells can be used to demonstrate the value of the hypothesis presented here.

Another set of figures can be produced for the phenyl structures dominating the perceptions associated with flowers. The odorants in this group typically rely upon a primary odorophore where one of the orbitals is associated with the alpha carbon of the aliphatic chain (and not with the phenyl ring directly). Thus, phenyl ethanol is the first member of the odorophores associated with the term flowery.

The cinnamons are a separate family where the lowest order odorophore is associated with the beta-carbon and the phenyl ring (with \( d \approx 5.603 \)). Some of the cinnamons rely upon a gamma-carbon and phenyl ring to form their lowest order odorophore (with \( d \approx 6.07 \)).

In most cases, the perceived scent is the result of a mixture of essential oils and each of the essential oils associated with a specific flower is a compound odorant exhibiting multiple odorophores. This level of combinatorial matrixing leads to a great number of perceivable scents with less than 32 OR’s in a typical mammalian species. A majority of these OR’s are identified in this section along with the simplest channel specific odorophore for each of these OR’s and its associated neural channel.

If the orbital attached directly to the benzene is the amino group, the result is known as an aniline.
8.6.4.1.3 PtdTyr– Potential OR for channel 2, the dulcals

The major candidate for the channel 2 sensory receptor molecule is the amino acid, (–)-tryptophan, with a d-value of 2.757 Å (based on a 3D reconstruction of a 2D Jmol file by the DS 3.5 visualizer). When combined with phosphatidic acid, the resultant molecule is phosphatidyltryptophan (PtdTrp). PtdTrp only exhibits a potential DACB site, between the 6-sided ring and the nitrogen in a 5-sided heterocyclic ring where the two rings share a C=C structure.

An earlier candidate for this sensory molecule was PtdTyr, based on the amino acid tyrosine. Three different tyrosines are included in the ChemSpider files; tyrosine contains only a 2D data file and no author name, DL-tyrosine contains a 3D file and author name, and D-tyrosine contains a 3D file and author’s name. Tyrosine has the hydrogen atom in front of the plane of the molecule, D-tyrosine has the hydrogen atom behind the plane of the molecule, and DL-tyrosine ignores the hydrogen atom entirely. The complexity of the tyrosine molecule suggests some steric hindrance would be required to ensure the OR was only sensitive to a range of d-values around 2.791 Å.

A continuing problem. Examining the three Jmol files for tyrosine, a commonly encountered problem is recognized. The 2D file for tyrosine gives a d-value of 2.791 Å for the hydroxyl oxygen to phenol ring distance while the other two 3D files give a value of 2.70 Å for the same distance. None of the data sets allows traceability to the actual bond length measured or assumed in the calculations.

8.6.4.1.4 PtdHis– Potential OR for channel 4, the limals

The major candidate for the channel 4 sensory receptor molecule is the amino acid, (–)-histidine, with a d-value of 4.254 Å (based on the 3D Jmol file). When combined with phosphatidic acid, the resultant molecule is phosphatidylhistidine (PtdHis). An earlier candidate for this sensory receptor molecule was identified as PtdPhe, formed from the amino acid, phenylalanine. Phenylalanine exhibits a d-value of about 4.488 Å.

8.6.4.1.5 PtdCaa– Potential OR for channel 6, the cinnamones

The channel six OR is predominantly used to sense a limited range of odorophores associated primarily with the family of plant odors found in the genus Cinnamomum. These odorants are α,β carbonyl compounds (cinnamylaldehyde) that have employed nucleophilic additions to form cinnamyl acetate (ChemSpider 4445319) and cinnamyl phenylacetate (4521380) with d-values near 6.075 Å and two cinnamyl alcohols (21105870 & 13871718) with d-values near 6.025 Å. It appears likely, the potential OR is formed by the nucleophilic addition of an amino acid to cinnamylaldehyde. The original amino acid is likely to be glycine (M&B, pg 727).

The cinnamyl's are α,β unsaturated carbonyl compounds, specifically a phenyl-1,2-carbonyl. Their characteristic property is a double bond between the two carbons at the α,β positions in an aliphatic string attached to a aromatic ring.

The proposed OR consists of a cinnamyl compound combined with an amino acid group to form a cinnamyl amino acid (Caa) that can hydrolyze with the Ptd molecule without changing its d-value of 6.075 Å. The resulting OR will be labeled PtdCaa.

There are a great many possible chemical combinations that could satisfy the above conditions. Great care is required in describing these possibilities using common names in the absence of IUPAC.
approved names. Figure 8.6.4-4 shows a simple potential compound that may not be chemically realizable but meets the stated requirement.

[xxx a toluate (chemspider 4521380) is a toluene connected to something by its single methyl group. Toluene is a benzyl ring with one methyl group attached. M&B pg 370 ]

[xxx the previous pix was copied as a placeholder while having keyboard problems on upstairs computer]

<table>
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<th>A-B ID</th>
<th>d-value</th>
<th>A-B ID</th>
<th>d-value</th>
<th>Spread</th>
<th>A-B ID</th>
<th>d-value</th>
<th>Spread</th>
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<th>d-value</th>
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<td>Cloves</td>
<td>Nutmeg</td>
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8.6.4.4 Options in the defined receptors of olfaction and gustation

A nominal set of receptors has been defined for both the gustatory and olfactory modalities in the absence of any relevant experimental database. However, the chemistry associated with these nominations is sufficiently complex to support a variety of other choices, pending experimental verification.

It is noteworthy that the amino acid described here as the ligand in the OR 2 receptor, PtdTrp, is a candidate to replace galactose as the ligand in the GR 2 receptor of gustation if a d-value of 2.757 Ångstrom is acceptable as a replacement for a value of 2.82 Ångstrom. This change would replace a member of the cyclohexane alcohol family by an amino acid, leading to a more complete set of GR’s based on amino acids. It would also make the active ligand in GR 2 and OR 2 identical.

Similarly, the ligand of GR 3, muco-inositol is a candidate to replace Ptd4Hi defined above as the ligand in OR 3 if a d-value of 3.32 Ångstrom is acceptable as a replacement for the value of 3.508 Ångstrom associated with Ptd4Hi. If satisfactory, this and the change to GR 2 would result in the first three OR’s being identical to the first three GR’s. This would appear to greatly simplify the evolutionary task of populating the olfactory modality with suitable receptors among the chordates (vertebrates).

8.6.5 SECOND STEP in transduction—Electrostatic measurement EXPAND
Simple changes to a complex compound, unrelated to the specific pair of coordinate bonding pair associated with the first order theory, can cause qualitative changes in the perceived sensation. In several cases, these changes can be accounted for by changes in the actual bond lengths within the coordinate bonding pair due to these nearby structural changes.

8.6.5.1 Background EMPTY
8.6.5.1.1 Bond stretching, crowding or other lesser known techniques

As early as 1900, Jaubert wrote:

"The phenolic OH is essentially odorless until its H is replaced by an alkyl or acyl group; as in the following examples:

HOC₆H₄OH (para-oxybenzaldehyde) = little odor.
HOC₆H₄OCH₃ (anisic aldehyde) = odor.
HOC₆H₃OH (protocatechuic aldehyde) = little odor.
HOC₆H₃OCH₃ (vanillin) = odor.
HOC₆H₃OCH₂C₆H₄OH (piperonal) - odor.

More recently, Wise et al have examined a series of chemicals with a similar odorophore between a phenolic ring and the nearest oxygen atom to that ring²⁴⁵. Their philosophical position was reviewed in Section 8.6.1.1.

Figure 8.6.5-1 shows several of the more complicated odorants Wise et al. focused on.

While commonly addressed as phenols in this time, the molecules shown do not exhibit the OH group of a true phenol. They are more properly addressed as benzyls or as phenol derivatives. The molecules of Jaubert contain the necessary OH group (in addition to other structures) attached directly to a resonant carbon ring to qualify as phenols.

Like the case of monosodium glutamate in gustation, there are clear examples of the fact that one chemical may stimulate multiple olfactory sensory channels. The figure shows how an incremental change in the structure of a chemical can result in incremental changes in the perceived sensations. These changes involve major changes in the applicable semantics.

Structure 91 and 93 have the same structure in the region of the phenol yet are described as eliciting different sensations. Some of this change may be due to the stretching of the phenol-ester bond. The caption provides the details of these rosy smelling compounds. The complexity of the professional descriptions of the respective odors is commensurate with the number of odorophores of the molecules.

²⁴⁴Jaubert, G-F. (1900) Artificial odorant materials Science vol 9(279), pp 190+ (with critique by Bogert on page 710-711)

Except for structure 95, the caption quotes Wise et al. who appear to be quoting Frater & Lamparsky (1991). 91 obviously exhibits one olfactophore associated with the C–OH relationship with a d = 1.43 Ångström. It also appears to exhibit an olfactophore associated with the oxygen atom and the resonant ring, which may also be affected by the double bond to the methyl group. 95 exhibits a very similar structure except the side chain is extended by two single bond carbons and the double bond is rearranged. While 91 is described as smelling like a rose, 95 is described as smelling like hyacinth. 93 is similar to 91 except the oxygen of the hydroxyl group has been incorporated into an ester with a four carbon structure with one carbon-carbon double bond. While 91 is described as “rosy with other notes,” 93 is described more specifically as “rosy with a ‘greener ozone-like smell.”

Modified from Wise et al., 2000.

Figure 8.6.5-1 Incremental changes in related complex olfactory stimulants. “Derivatives of 2-phenylallyl alcohol (91) smell rosy but with other notes: compound 92 smells rosy with “a lilac and spicy shadow,” compound 93 smells rosy with a ‘greener ozone-like smell with fruity top note’ and compound 94 smells like ‘rose, cinnamon, carnation spice and lilac.’” 95 is Cinnamyl alcohol, (2E)-3-phenylprop-2-en-1-ol. It is also known as 3-phenylallyl alcohol. “It has the odor of hyacinth.”

Modified from Wise et al., 2000.
with fruity top note’. 91, 95 and 93 involve only one oxygen atom in a single side chain attached in the same way to one phenol ring.

92 introduces an additional complex structure beyond the terminal hydrogen associated with the hydroxyl in 91 and 95 with a carbon chain intermediate in length between 91 (rosy) and 95 (hyacinth, generally extracted from cinnamon wood). It is said to “smell rosy with a lilac and spicy shadow’,.” 92 includes a carbonyl group with a $d = 1.22$ Angstrom and several opportunities to associate with other molecules like itself or with water. Either of these associations would provide a hydrogen bond and $d = 2.7$ Angstrom. Listing all of the possible olfactophores of this molecule and their $d$-values becomes a challenge shared with other molecules of this complexity. Frater & Lamparsky appear to be trying to gain more information from 94, that is the same as 92 except for the replacement of the carbon at the center of the trio of oxygen atoms. 94 and 92 retain their rosy and lilac characteristics, while 94 has gained a secondary label of carnation spice.

These structural changes do not affect the odorophore as defined in the first order theory using Standard Bond Lengths. However, it is known that actual bond lengths are affected by the complexity of the electron-pair sharing atoms due to their other bonds or the crowding of the bonds by adjacent moieties. It appears the oxygen to phenolic bond is changed in length in these examples, resulting in a change in the probability of coordinate bonding pairs forming with the sensory receptor. This change in probability can change the net elicited sensation. Additional research is needed to explain these effects and confirm or modify the second order effect proposed here.

Wise et al. describe the sensation elicited by each of these chemicals through the nose of a trained perfumer (Section 8.6.1.1). As an example, “compound 93 smells rosy with a ‘greener ozone-like smell with fruity top note’ and compound 94 smells like ‘rose, cinnamon, carnation spice and lilac’.”

The analogy between the external chemical receptors and the photoreceptors suggests strongly that the chemical receptors also utilize a quantum-mechanical transduction mechanism. The multidimensional scaling analyses strongly suggest the transduction mechanism utilizes between three and six unique transduction channels (analogous to the multiple channels in the visual system).
The degree of steric specificity needed in animals can be gleaned from the examples illustrated by Schneider 246, Figure 8.6.5-2. Bombycol is believed to be an important pheromone of the silk worm moth, Bombyx mori. While its stereomers may aid in identifying a specific individual, it is probably important that the olfactory system properly classify all of these variants as originating from a source of the same species. On the other hand, Schneider measured a threshold sensitivity to the 10-trans 12-cis variant at least five orders of magnitude higher than for any of the other molecules.

Nandi has explored the steric acceptance of the enantiomeric odorant molecules carvone and camphor by various peptide motifs 247. The computational protocol is complex. He investigated the interaction profile of “the enantiomeric pairs of these materials with four peptides composed of five residues. The chiral peptide structures are H-Leu-His-Thr-Pro-Met-OH (designated as Peptide 1), H-Met-Ala-Tyr-Asp-Arg-OH (designated as Peptide 2), H-Tyr-Val-Ala-Ile-Cys-OH (designated as Peptide 3) and H-Phe-Ser-Thr-Cys-Ser-OH (designated as Peptide 4) respectively. Although these sequences are observed in OR, they are used in the present work only as different helical chiral mimics of the receptor segments, which can be used to observe the discrimination of intermolecular interaction and no more.” His model shows that “the enantiomers of carvone have distinctly different interaction profile with all peptides considered, but the enantiomers of camphor do not exhibit any significant enantio-difference. This parallels the experimental fact that the enantiomers of carvone have different smells, while those of camphor cannot be discriminated by olfaction.”

8.6.5.1.2 Dipole potential change versus odorant molecular weight

The work of Imamura et al. suggests that the total molecular weight of the molecule beyond the portion involved in the coordinate bond pairing portion may affect the dipole potential of the overall odophore/receptor structure. Such a change would change the generator potential of the sensory neuron as a function of this parameter.

First order theory of the dipole moments of aliphatic chain alcohols suggests they all have the same value based on the terminal group. Smythe & Walls have documented the growth in understanding of this parameter and the fact that systematic differences are encountered with chain length. 248 “The ethyl esters of the monobasic fatty acids show a slight decrease in moment with increase in the size of the molecule analogous to the decrease in ionization constant.” Smyth & Walls gave specific numerical values for these dipole moment differences. These differences are more than adequate to affect the output signal of the sensory neurons.

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246 Schneider, xxx (1963) xxx


Tekins et al. have expanded the database in this area using computational methods\textsuperscript{249}.

8.6.5.2 The proposed configuration of the olfactory sensory neuron

8.6.5.2.1 Circuit description of the olfactory sensory neuron

With the exception of one simple two-terminal circuit applicable to chemoreception in general proposed by Kurihara et al., no circuit diagram of the olfactory sensory neuron could be found in the literature\textsuperscript{250}. Their circuit diagram contains no capacitors or active elements and does not address the detailed operation of the olfactory sensory neuron. Figure 8.6.5-3 shows the proposed sensory neuron of olfaction based on the common functional circuit elements found in other sensory modalities. The circuit is amenable to direct quantum-mechanical stimulation of the base region of the first Activa (as in photoreception) or to the application of an electrical potential to the base electrode (as in phonoreception). Because of the expected low energy of stimulation, the figure adopts the configuration used in hearing.

In the case of phonoreception, the first Activa is biased into the operating range required by a conventional amplifier. The circuit is capable of accepting electrical signals in the tenths of a millivolt to ten millivolt range. Such a range appears compatible with the energy levels involved in the odor reception scheme suggested by Turin.


In hearing an AC electrical potential is created between the plates of a capacitor by piezo-electric action. In the case of olfaction, it is proposed a similar AC electrical potential is created between the plates of a capacitor by dielectric polarization due to an electronic rearrangement of the dielectric. The dielectric is formed by a stimulant sensing complex, SSC. This rearrangement is temporary and caused by the temporary presence of a stimulant in steric coupling with the SSC.

The proposed configuration creates a quantum-mechanical shift in the electronic state of the SSC every time an appropriate stimulant couples with the SSC. This coupling at the molecular level would be a low probability event unless the SSC was present in a liquid crystalline form on the surface of the input structure of the sensory neuron. It is proposed that the SSC is present in such a form and is located on the surface of a specialized section of the dendroplasm of the sensory neuron. It is this specialized section that creates the Activa just as it does in other modalities.

It is further proposed that the SSC is present in a liquid crystalline form where part of the crystalline configuration forms the dielectric of a capacitor between the electrolyte of the mucosa and the base region of the Activa within the sensory neuron.

Indicator dyes are characterized by their multiple electronic configurations. Each of these configurations exhibits a moment. The change in configuration can be described by a transition dipole moment. A non-zero transition dipole moment change in a material forming the dielectric of a capacitor will result in a change in the potential between the electrodes of that capacitor. The concept is discussed briefly in Adamson251. Maron & Lando go into the subject of dipole moments, and the various spectra related to molecular structure252. They provide a pedagogical energy.


diagram. For molecules of more than three atoms, the complexity of the spectra becomes quite high. However, the change in polarization associated with the vibration-rotation spectra are of interest here. The energies of interest are in the millivolt range and the associated wavelengths are in the near-infra-red range.

Petersen & Cone have provided an excellent paper discussing many aspects of the dipole moment of proteins, particularly rhodopsin, the disk protein associated with vision\textsuperscript{253}. It forms a good tutorial as well as providing valuable protocols and experimental data. They provide a footnote; “the dipole moment, $\mu$, is in Debyes (D), where 1 D = $10^{-18}$ statcoulomb-cm. Thus an electron and a proton separated by 1 Angstrom produce a dipole moment of 4.8 D. In other words, 1 charge-Å = 4.8 D.” They show that most small proteins separate into two classes based on their dipole moment and their molecular weight, those with values of $\mu/W$ of 5 x $10^{-3}$ D/Dalton and a second group with $\mu/W$ clustered about 20 x $10^{-3}$ D/Dalton. Rhodopsin with a dipole moment of 720 Debye and a molecular weight of 35,000 ± 2000 Daltons, has a $\mu/W$ value of 20 x $10^{-3}$. Gerber et al. note that the proteins with the larger dipole moments all tend to aggregate and suggest that the dipole moments aid in the aggregation process. This ability of the protein to aggregate is crucially important in the formation of the outer disks of visual sensory neurons. Aggregation may play a similar role in forming the SSC’s of olfaction. The change in the dipole moment of rhodopsin upon saturating illumination is only 25 D (5 charge-Å) or about 3%.

Petersen & Cone give precise data on the dielectric constant of rhodopsin solutions and its change with applied frequency in a standard test cell. In the in-vivo situation, a value for the aggregated material is believed to be necessary.

Many complex organo-metallic compounds exhibit a dipole moment in the 2-5 Debye range\textsuperscript{254}. More comprehensive general lists are available but they tend to be old\textsuperscript{255}. Following further isolation of the chemistry of interest, a more detailed search may uncover the desired values for their dipole moments. The lower molecular weight of these organo-metallic materials (the molecular weight of copper tartrate is only 329 Daltons, give them much higher $\mu/W$ values than those of proteins. Nominal static $\mu/W$ values for the organo-metallics are in the 2–6 x $10^{-3}$ range. The transition dipole moment may be much larger relatively because of the small size of the molecules.

Takashima has provided excellent background on the dipole moment\textsuperscript{256}. An on-line calculator for calculating the dipole moment of arbitrary proteins is available\textsuperscript{257}. However, the structure of the protein must be known in detail.

Two technical challenges arise in attempting to define a steric mechanism of transduction. First, the capture cross-section of the transduction mechanism must be as large as possible. Second, the transition dipole moment must be as large as possible and it must be optimally sensed. Forming the SSC’s into a liquid crystalline structure is one method of increasing capture cross-section and potentially increasing the efficiency of sensing the net transition dipole moment.

**Figure 8.6.5-4** shows the circuit along with its cytological equivalent. Frame A shows the cytological layout of the proposed typical olfactory sensory neuron. All plasmalemma are electrically insulating bilayer membranes, except for specialized sections that are semiconducting. These specialized
sections are active participants in forming active semiconductor devices, Activa, or in supporting the electrostenolytic process electrically powering the cell. All of the sensory neuron except for its axon is located within the olfactory epithelium and its mucosa. The body of the sensory neuron peripheral to the soma is arbitrarily defined as the dendrite portion. That portion between the soma and the olfactory bulb is arbitrarily described as the axon.
Figure 8.6.5-4 Proposed cytological and electrolytic description of the olfactory sensory neuron ADD & MODIFY. MODIFY frame A to show stimulation. Modify B & C to show dipole potential rather than change in capacitance.
The bulbous extreme end of the dendrite is labeled the knob. Its internal structure is not reported in the literature. Multiple individual microtubules emanate from the knob. These function as dendritic spines with multiple sensitive areas typically associated with synapses in non-sensory neurons. In the sensory neurons, these areas are modified to support transduction.

Only the microtubules (cilium) lie in the mucosa. The number of microtubules emanating from the dendritic knob varies from species to species, from as few as four to as many as thirty. The typical length of the microtubules is about 50 microns in mammals. The microtubules are splayed into a planar surface within the thick mucosa.

The three horizontal arrows in the dendroplasm indicate where the multilayer sandwich to their left actually extend up into the individual cilium of the neuron. The character of these layers changes from insulating to semiconducting at multiple points along each cilium just as they do in the microtubules of the visual sensory neurons. The two insets, A1 & A2, illustrate how the transduction mechanism may appear at one point along the length of the cilium. Inset A1 shows an Activa (black rectangle) supported by its electrostenolytic supply (E.S.1) and the transduction element consisting of an SDC forming the dielectric of a capacitor, C, with its outer conducting surface formed by the mucosa. Inset A2 shows an alternate configuration where an auxiliary electrostenolytic source (E.S.0) appears on the outer surface of the capacitor. This source provides an electrical bias to the capacitor that may provide a higher sensitivity to the overall circuit as discussed in Section xxx.

The dashed arrows associated with each electrostenolytic supply show the direction of electron charge flowing into or out of the respective plasmas. The “conventional charge” defined erroneously by Benjamin Franklin flows in the opposite direction.

Charges from each of the Activa in each cilium are introduced into the dendroplasm and generate a potential between the dendroplasm and the podaplasma. This causes the Activa shown between the dendroplasm and the axoplasm to transfer approximately 200 times as much charge to the axoplasm. This additional charge passes through impedance associated with E.S. (4) and generates the output voltage at the synapses shown.

The sensory neuron delivers a tonic generator waveform at the remote glomeruli by diffusion. Because of the length of the axon required to pass through the cribriform plate and the low rate of signal propagation by diffusion, the bandwidth of the olfactory sensory neurons is necessarily low.

Frame B shows the same circuit configuration as in Frame A. The transduction element is shown connected between the diode leading to the first Activa input and the electrostenolytic potential shared with the collector terminal (axoplasm). There is only limited information defining how this element is electrostatically connected. The dashed box shows an alternate configuration where the transduction element is shown connected between the diode and the common ground connection. Similarly, only limited data is available as to whether this element represents a capacitor or an intrinsic dipole potential, either of which can be changed by the presence of a stimulant. The most likely scenario is that the transducer represents a dipole potential that can vary with the coordinate bonding of a stimulant to that element.

Frame C shows the same circuit configuration as in Frame B but redrawn to illustrate the commonness of the circuit. It is described as a PNP type asymmetric differential pair in conventional electronic engineering terms. The left (or first) Activa is base driven and the right (or distribution) Activa is emitter driven. The left Activa provides a high impedance input and a gain of nominally 200:1. The right Activa provides a low impedance output at 1:1 gain. Hence, the axoplasm appears as a voltage source capable of providing the same amplitude signal to multiple synapses leading to multiple distinct orthodromic neurites. It also shows a change in the molecular dipole associated with the transduction element without specifying whether this molecular dipole introduces a change in capacitance or a change in dipole potential.

Frame A1 is expanded in Figure 8.6.5-5 to show the operation of the microtubules (cilium) at the molecular level. Lowe & Gold have shown that odorant sensitivity and the odorant-evoked inward...
transduction current are uniformly distributed along the cilia. Based on this premise, Gold has asserted, “Thus, all components of the transduction mechanism must be present in the cilia.” Lowe & Gold also showed that the latency of the transduction current is independent of the region of the cilia that are stimulated. This implies that current is generated at the site of odorant binding.

The figure starts with the two bilayer membranes separated by only a thin layer of water crystallized into a hydronium liquid crystal by the confined quarters. The two bilayers are both present as liquid crystals. They are formed of insulating lipids except in the shaded areas. The insulating lipids are phosphoglycerides with fully saturated nonpolar tails (typically PtdEtn). In the shaded areas, at least one of the tails is not saturated and is conductive like the polar head. These phosphoglycerides are typically from the family of globosides. They are typically associated with neurons and exhibit more complex polar heads and unsaturated tails. It is proposed these globosides constitute semiconducting electrolytic materials. The complex heads provide the steric arrangement required to accommodate either the electrostenolytic process or the OR mechanism shown. The more detailed discussion of these materials appears in [Section 5.2.4.1].

The shaded area on the left constitutes a first Activa. The semiconducting lipid of the dendrolemma constitutes a region of P-type electronic material. The semiconducting lipid of the reticulum also constitutes a region of P-type material. The region of hydronium between them is an N-type electronic material. The sandwich forms an active electrolytic PNP transistor device, an Activa. The polar head of the dendrolemma facing the mucosa provides a steric site suitable for accommodating the electrostenolytic power supply providing ~150 mV to the Activa collector as shown (See Section xxx). The polar head of the reticulum facing the dendroplasm passes the electron current directly into the dendroplasm as shown by the dashed arrow. The magnitude of this current is controlled by the bulk potential of the hydronium N-type material.

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The N-type material of the Activa is connected to an adjacent P-type region on the right, again formed of a semiconducting globoside. The junction of the P and N materials forms a PN diode junction and an electrical connection to the stimulus sensing complex, SSC. The diode is forward biased and acts like a "low" impedance electrical conductor. The polar head of the globoside forming the semiconducting dendrolemma is sterically selected to support a steric coupling with the SSC in liquid crystalline form. The polar head also constitutes one plate of a capacitor, C\text{p}, with the SSC as the dielectric. The other plate is formed by the interface between the SSC and the mucosa.

The SSC may or may not exhibit a dipole moment in the absence of an odor stimulant (horizontal bar inside left half of SSC). However, in the presence of a sterically appropriate odor stimulant, it is a zwitterion and will exhibit a dipole moment as shown by the inclined bar on the right. This second dipole moment is due to a quantum-mechanical change in the configuration of the SSC molecule(s). This change in dipole moment between the absence and presence of a stimulant causes a change in the dielectric properties and the resultant voltage on the capacitor, C\text{p}. The change in voltage is passed through the forward biased PN junction to the base of the Activa. This voltage controls the amplitude of the current passing through the Activa.

The change in the dipole moment of the SSC acts to repel the stimulant from its steric coupling with the SSC. Thus, the presence of the stimulant in a steric relationship is only temporary. The resultant voltage change at the Activa is also temporary. The stimulant molecule is free to go without encountering any chemical change in character.

The waveform at lower left shows the current waveform entering the dendroplasm resulting from a group of stimulant molecules coupling and uncoupling from the SSC within a time period short with respect to the time constant of the overall quantum-mechanical-electrolytic circuit. The
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Vogel et al. have demonstrated the conductivity of the typical phospholipid is sufficient to allow the measurement of a finite potential between its two ends when present as a monolayer film. They have measured the potential across phosphatidyl choline and phosphatidylethanolamine when in the single layer liquid crystalline state. These potentials are found when the liquid crystalline film has reached an equivalent molecular cross-sectional area of 40 sq Angstrom for these materials. The potential is given as 555 mV for PtdEtn and 669 mV for PtdCho at 18-19°C with the hydrophobic surface negative. These are large voltages relative to the input dynamic range of the first Activa of the sensory neuron. With the nominal gain of 200x for the Activa and a sensitivity of about 0.1 to 1.0 mV for the following circuitry, a change in the quiescent potential of the phosphatidyl moiety of the sensory receptor of less than five microvolts. Such a small change is not currently measurable in the laboratory, but the presence of such changes are indicated by the psychophysical data of Imamura et al. for changes in the potential due to coordinate coupling of the receptors with alcohols and carboxylic acids of different chain lengths (Section 8.6.2.3).

Mathematical form of this waveform, including its latency, $\Delta$, are developed in Section xxx.

Many empiricists have attempted to graphically conceptualize the transduction mechanism of olfaction. See Ache reproduced in Schild & Restrepo (page 455), as an example. The chemical neuron approach is much more complex, usually employing arrows and symbolism, and has not shown itself amenable to verification or deterministic calculations.

The above figure provides a closed form, verifiable and deterministic model of olfactory transduction. It employs no putative pores or channel passing complexes under the control of undefined protein processes.

8.6.5.2.2 Circuit parameters of the olfactory sensory neuron

Schild & Restrepo have included considerable parametric data (with citations) on the axonal portion of the olfactory sensory neurons. Statements like "whole cell capacitance" presume a two terminal structure for the neurons. Under the Electrolytic Theory of the Neuron, this label should be modified to the whole axoplasm capacitance as it was obtained by injecting charge into the axon and measuring the resulting voltage rise. Values in the 2-10 pF range are consistent with the sensory neurons of other modalities. They report a wide range of axon resting potentials, undoubtedly because of the lack of control of the dendrite environment while investigators made these measurements. A value of ~70 mV would be expected and falls near the middle of the range quoted. They report an average time constant of the axoplasm of ~60 ms, giving a first order RC filter corner frequency of ~16 Hz. While lower than in other modalities, these values are consistent with the extended length of the axon required to pass through the cribiform bone. Measured time constants in some species have been as long as 100 ms. They did note an important point, the delay displayed in their generator potentials of figure 4 are proportional to the amplitude of the stimulus (page 433). Unfortunately, they have continued to repeat the reports based on conclusions improperly drawn the work of Gesteland in 1971. That assertion was that sensory neurons exhibit action potentials (beginning on page 434). Schild & Restrepo note, "These reports were discussed controversially, see Getchell." Gesteland was very clear that his measurements were extracellular, and in fact of the crudest kind. His measurements were made between the two sides of the olfactory epithelium. Because of his technique (his figure 1), he actually measured generator waveforms of opposite polarity to that at the axon of a cell "and with action potentials spikes superimposed" (page 144).

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He was measuring the complement of the generator waveform at the collector of the first Activa instead of at the collector of the second Activa (the normal axon potential [See Section xxx]). It is now known his current path in figure 1 requires changing to reflect the documented role of the poditic terminal (Section xxx).

Gesteland does provide several parameters supporting the neural model developed here. [xxx review gesteland 1971]

Additional data showing such action potentials has not appeared subsequently. It appears Gesteland relied upon data collected extracellularly. It exhibits low amplitude action potentials riding on top of generator waveforms. The combined waveform is easily explained as due to capacitive coupling under the Electrolytic Theory of the Neuron. Schild & Restrepo show generator waveforms on page 444 that are free of action potential features.

Schild & Restrepo reproduce a figure from Kurahashi\(^\text{265}\) that may represent the diode characteristic of the axon load, Figure 8.6.5-6. If so, the load diode had a reverse cutoff current (I\(_0\)) of –25 pA. Unfortunately as noted in the original caption, the current traces shown on the left were arbitrarily shifted. The nominal horizontal axis of each waveform does not correspond to zero current. The holding voltage would have been accompanied by a holding current that is not shown explicitly, but can be seen on the right.

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**Figure 8.6.5-6** Odorant induced currents at various holding potentials from a newt ADD, *Cynops pyrrhogaster*. Current traces were arbitrarily shifted. See text. Modified from Kurahashi, 1989

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\(^{265}\) Kurahashi, T. (1989) Activation by odorants of cation-selective conductance in the olfactory receptor cell isolated for the newt *J Physiol (Lond.*)* Vol 419, pp 177-192
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8.6.5.2.3 Analog waveforms generated by ORN’s

The literature provides many analog generator waveforms from olfactory receptor neurons (Schild & Restrepo, page 443-444). These waveforms exhibit a latency as a function of stimulus intensity that is not compatible with experiments involving the putative photoexcitation of cAMP. This latency as a function of intensity is characteristic of the excitation/de-excitation mechanism proposed in this work. Farbman has provided a very clear patch-clamp recording from the olfactory cilium of a frog (page 110). The change in amplitude of up to 20 mV suggests the recording was from the axoplasm of the sensory neuron. The variation in the amplitude of the signal over time suggests some logarithmic compression due to the current to voltage conversion but no sign of hard saturation or of action potential generation.

8.6.5.2.4 Action potentials generated parametrically in ORN’s

There have been several assertions concerning phasic action potentials emanating from ORN’s. Gesteland (page 789) has reviewed the only way action potentials can be recorded from ORN’s. They do not occur in-vivo without human electrical intervention. Getchell later confirmed Gesteland’s position (page xxx).

8.6.5.3 Threshold sensitivity of the olfactory modality

Figure 8.6.5-7 [xxx Need commentary about how and where is threshold established. ] [xxx discuss purity of materials available to the investigator]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Threshold (ppm)</th>
<th>Compound</th>
<th>Threshold (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octanol</td>
<td>3</td>
<td>Acetic acid</td>
<td>82</td>
</tr>
<tr>
<td>Nicotine</td>
<td>5</td>
<td>Diethylamine</td>
<td>108</td>
</tr>
<tr>
<td>Heptanol</td>
<td>7</td>
<td>Cyclohexanone</td>
<td>112</td>
</tr>
<tr>
<td>Hexanol</td>
<td>8</td>
<td>Benzaldehyde</td>
<td>125</td>
</tr>
<tr>
<td>Octanoic acid</td>
<td>9</td>
<td>Benzyl acetate</td>
<td>132</td>
</tr>
<tr>
<td>Heptanoic acid</td>
<td>11</td>
<td>Valeric acid</td>
<td>139</td>
</tr>
<tr>
<td>Hexanoic acid</td>
<td>16</td>
<td>Formic acid</td>
<td>145</td>
</tr>
<tr>
<td>α-Terpineol</td>
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<td>Butanol</td>
<td>112</td>
</tr>
<tr>
<td>l-Carvone</td>
<td>23</td>
<td>Amyl acetate</td>
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</tr>
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<td>Menthol</td>
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<td>d-Carvone</td>
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<tr>
<td>Pentanol</td>
<td>59</td>
<td>Methanol</td>
<td>3020</td>
</tr>
</tbody>
</table>

Figure 8.6.5-7 Electrophysiological thresholds obtained for the rat ADD measured at the ethmmoid nerve From Bryant & Silver, 2000.

[xxx Address sensitivity to pheromones, probably based on increased dedicated surface area. ]
[xxx address the expansion of the flow model of xxx using phi, psi etc. ]
8.6.5.3.1 Human sensitivity versus odorant intensity

Randebrock has provided extensive data on the slope of the response versus intensity characteristic of the human nose\textsuperscript{266}. The data shows the conventional break in the response between a low slope region and the higher slope region typical of the wide dynamic range region described as the photopic regime in vision. The slopes varied in integral multiples of one-half power as also commonly found in the operation of other sensory modalities.

8.6.5.3.2 Similarity of vision EPC’s to chemical SSC’s

[xxx needs editing. Especially water and copper parts.
[xxx expand figure to combine vision and olfactory scales Note narrower acceptance range in olfaction]

Section 8.2.xxx defined the energy processing complexes of vision in detail. Their performance can be displayed in the same form as the SSC’s supporting the normal homologs presented above. Figure 8.6.5-8 shows the energy processing complexes (EPC’s) of vision, the Rhodonines, plotted as a function of their energy bands. The half-amplitude edges of these bands are defined with respect to their Helmholtz-Boltzmann statistics. They are shown as dotted white boxes in the figure. They are known with good precision. The bar widths have been expanded horizontally (the black bars) by 200\% to suggest the broader limits of threshold sensitivity. In this form, the bars show a degree of overlap similar to that in [Figure 8.6.3-xxx]. The amplitude spectra of the Rhodonines are shown below the bar graph for reference. The shape of these absorption spectra are obviously not Gaussian.

![Figure 8.6.5-8](image_url)

A bar graph describing the energy bands of the Rhodonines. Dotted boxes; absorption bands based on half-amplitude limits. Black bars; broader absorption bands suggestive of limiting sensitivity. Gray column; range of minimum excitation energy of the first Activa within each sensory neuron. One electron volt equals 23,060 calories/mole. Also shown for reference; the amplitude spectra of the Rhodonines of Vision (including the ultra-violet spectra in magenta). Dotted red line is half-amplitude line.

\textsuperscript{266}Randebrock, R. (1971) Molecular theory of odor with the a-helix as potential perceptor In Ohloff, G. & Thomas, A. eds. Gustation and Olfaction. NY: Academic Press pp 111-125
In many organic reactions, there is only a narrow range of reaction energies (usually associated with temperature in the laboratory) that will result in formation of the desired product. This is the case for the ESP’s and SSC’s. The lower limits of the bars appear to conform to the conventional energy of activation, \(E_{\text{act}}\) of physical chemistry\(^{267}\). However, \(E_{\text{act}}\) is used in an equation of the form \(\alpha(\lambda) = 1/(1+\exp(E_{\text{act}}/KT))\) rather than in the simpler exponential form associated with a first order reaction. Note also that the upper limits of the bars introduce another determinant on these reactions. They conform to an upper limit on the energy of activation for these materials as defined by Helmholtz-Boltzmann statistics. As in the cases reported by Imamura et al., higher energies (normally associated with shorter chain organic n-homologs acting as stimulants) will not result in an excitation.

The Rhodonines are the resonant form of retinol/retinal that are the EPC’s of mammalian vision when present in the retina in the liquid-crystalline form. Their absorption band gaps are very narrow, typically less than one electron volt (less than 23,060 calories/mole). In the case of the long wavelength EPC, Rhodoline(5), an additional mechanism is employed. A 2-exciton mechanism is used to accumulate the energy from two photons into a sufficiently large packet to excite the base material of the Activa within the long wavelength photoreceptors. Such a 2-exciton mechanism cannot be eliminated from consideration among the SSC’s of chemoreception at this time.

The excitation of a free charge in the base of an Activa appears to involve the excitation of the liquid crystalline form of water, called hydronium in this work. This activation energy (gray column) is in the range of 2.2 to 2.34 electron volts (50 to 54 kcal/mole). Minton has explored the polymerized forms of water in detail\(^{268}\). He called them anomalous water rather than hydronium. Figure 8.6.5-9 shows the two structural forms favored by water as it polymerizes. Form (I) is described as the tridymite structure. Form (II) looks similar to the graphite form of carbon. Both of these forms can be extended into a liquid crystalline configuration.

Copper[tartrate] is a similarly complex molecule that can exist in many states. Its lowest excitation energy is quite low based on the fact that it reacts with glucose in solution to form gluconic acid. In a separate reaction, glucose can be converted to gluconic acid with the only catalyst present being Br\(_2\). Br\(_2\) has a bond dissociation energy of only 46 Kcal/Mole (1.994 electron volts). The reaction does not occur in the presence of I\(_2\) with a bond dissociation energy of 36 Kcal/Mole (1.56 eV).

8.6.5.4 Labeled olfactory neurons versus stimulants

Figure 8.6.5-10 is an interpretation of some data from Buck\(^{269}\) presented by Smith in 2008\(^{270}\). The data actually originated in Malnick et al\(^{271}\). The discussion by Smith is that of a behavioral scientist. He does note the sensitivity of the experiments to many variables (page 227). The question of the purity of the alcohols used also arises. These chemicals lack a recognized odorophore and are usually considered odorless. However, even a 1% impurity in the chemicals used in the experiments can


result in the perception of an odor related to the impurity due to its low threshold. Thus the trend among the alcohols based on chain length is questionable. While the trend for the organic acids may be a result of their difference in dipole potential, it is more likely due to other factors, both technical and experimental. The source of the mouse signals was not specified in detail. No information was presented on the statistical relevance of the data, nor any indication of the signal processing associated with the axons accessed.

The descriptors in the right column appear to be primarily anecdotal based on several different investigators (sweety is probably a typographical error for sweaty). The annotation applicable to the acids is reasonably consistent with the later findings of this work. The labels associated with the alcohols is much less consistent, even recognizing the intent is to show a trend with molecular weight or number of methylene units.

8.6.5.5 The sensory neuron transfer function & odor units in olfactometry

The field of odor quantification has moved ahead faster in the environmental control field than in academia. There are now many commercial recording olfactometers in the field operating twenty-four hours per day in networks. The networks typically provide consolidated maps of various odor profiles over areas encompassing several square miles.

McGinley et al. have provided a tutorial on “Odor Basics, Understanding and Using Odor
Testing. It was to be used in conjunction with the fielding of one brand olfactometer. Some of the graphics in this section, and in the summary of Section 8.6.2.9.5, are equivalent to but different from theirs.

Odotech, Inc. offers an olfactometer arranged to support a multimember panel of subjects simultaneously. Quoting the website of Odotech.com, “When measuring odor with an olfactometer, panelists are exposed to the odor sample via the dilution unit of the olfactometer. Initially, the odor is highly diluted, all panelists indicate that they cannot smell it. The operator then increases the concentration by diluting the sample a little less with pure air in a given, accurate ratio, and the panelists respond. The operator keeps reducing the odor sample dilution until half of the panelists indicate that they can smell the odor, but the other half still cannot. By definition, the point at which 50% of the panelists cannot smell the odor but 50% can, is called the PERCEPTION THRESHOLD and is equal to 1 odor unit per cubic meter. Amoore has provided some statistics on the range of this threshold among 443 humans (Section 8.6.1.1). His one-sigma variation in this quantity was ±1.7 odor units.

Also, be aware that there are established analysis methods (i.e. EN 13725 and ASTM E679-04) that guide the approach.

8.6.5.5.1 The (natural) logarithmic character of olfactory reporting

It is generally accepted that the overall performance of the olfactory modality operates under logarithmic signaling conditions. McGinley et al. provided a simple graphic suggesting the perceived intensity of a odorant as a function of concentration was a straight line on log-log graph paper and attribute this relationship to Stevens who popularized it in the 1960's (although it was promulgated as Weber’s Law, particularly in the visual and auditory sciences since 1834). Unfortunately, they did not address the shape of the graph as it approaches threshold or as it reaches saturation within the sensory neurons. Figure 8.6.5-11 addresses these additional features.

Based on this work, all of the amplification associated with a given sensory modality occurs within the stage 1 sensory neurons (except for the potential for extraneous and limited signal amplification within stage 3 due to specific sets of parameters chosen for other purposes). Thus, the transfer function of the sensory neurons correctly represents the transfer function of the whole olfactory modality when discussing stimulation by individual preferred odorophores.

The input characteristic of the Activa forming the first amplifier in a stage 1 sensory neuron is known to be logarithmic from waveforms recorded in the visual and auditory modalities. However, it’s dynamic range is limited. It exhibits a saturation at about 15 millivolts relative to its quiescent voltage level. The Activa attempts to amplify the analog input signal (the measured dipole potential) linearly but its output is voltage limited to less than 150 millivolts maximum.

Figure 8.6.5-11 Transfer function of the sensory neurons of olfaction. Step one of the odor unit scale is taken as the threshold where 50% of the subjects report detection (not recognition) of an odorophore. The absolute concentration scale, but not the odor unit scale, moves to the left under sustained stimulation. The slope is taken as 1.0 pending more detailed measurements. See text.


Actual measurements of the analog potentials of the olfactory sensory neurons are needed to establish these parameters more precisely.

The first Activa also functions as the adaptation amplifier. For any sustained stimulation affecting a specific OR channel, the amplification factor, and therefore the absolute output potential at the pedicle of the axon, will be reduced with time for a constant concentration of the stimulant. The concentration scale is effectively moved to the left with time. The reduction can be significant, emulating a temporary specific anosmia in that channel. The move can be significant, resulting in an effective dynamic range for an individual OR channel, consisting of multiple sensory receptors, on the order of one million to one (20 odor steps).

8.6.5.5.2 Establishing a quantitative scale, the odor unit

McGinley et al. defined a threshold for a given chemical based on the criteria that 50% of six to eight subjects occupying seats at a common manifold olfactometer could perceive the presence of a substance while the others did not. This value was defined as one odor unit. They then increased the concentration of the chemical in the air provided to the subjects by factors of two until they recognized and offered an identification of a perceived odor. Note the test is one of detection and not the recognition of a specific odorant. As noted in McGinley et al., the “concentration” can be calculated in terms of mass or number of molecules per unit volume but the precise effective volume is generally unknown. It is common to report this volume as one cubic meter.

A table in McGinley et al. (their figure 2) provides an estimate of the difference between the detection threshold and the recognition threshold for an unspecified odorant is at least one but less than two odor units (a factor of two to four).
8.6.6 The multi-dimensional olfactory perception space

The definition of the number of independent neural channels associated with olfaction and the recognition that transduction involves a two-step process opens the door to describing the performance of the olfactory modality more precisely and how those results can best be documented.

Based on Section 8.6.2.8, nine distinct olfactory sensory receptor channels can be identified in human olfaction.

By reviewing the large empirical data base, it is possible to identify the nominal d-values for the center of these channels and begin to determine the profile of each of these channels relative to the central value.

As in gustatory research, many statistical methods have been applied to the olfactory modality in order to determine the fundamental mechanisms and processes involved. These have included cluster analyses, a variety of principle component analysis (PCA) procedures and a variety of multi-dimensional scaling (MDS) procedures. The most useful procedure appears to employ a cluster analysis initially in order to uncover the major features of the data set followed by a more detailed MDS analysis to quantify the data more precisely and employ the rotation of axes theorems applicable to that procedure. Section 8.6.3.3 has offered a draft of the distribution of sensory receptor channels based on this procedure and the available database. The draft is amenable to improvement. Once the candidate receptor molecules have been identified, their most precise d-values can be obtained from crystallography. This science offers precisions of at least three digits after the decimal point, when measuring in Angstrom.

Based on the discussions in this section and earlier, this work will provide a set of preferred odorophores (Section 8.6.7). These preferred odorophores are chemical stimulants containing only one odorophore and believed to have d-values well matched to the center d-values of the individual sensory receptor channels. However, additional laboratory activity should provide much more focused statistical analyses on the olfactory mechanisms leading to a more mature set of preferred odorants containing only one odorophore. With a more mature set of preferred odorants, it should be possible to extend the various statistical analyses to define the effectivity profiles of the individual channels and support the determination of the dipole potentials of a much wider set of odorophores. These dipole potentials are critically important to understanding the precise operation of step 2 in the transduction process.

To avoid additional complexity due to the dynamics of the adaptation process associated with all sensory neurons, this section will restrict stimuli concentrations to no more than 100 times the threshold sensitivity of the particular OR channel.

Like all of the sensory modalities investigated here, the individual OR channels are treated as statistically independent by the higher signal processing (stage 4) and cognitive (stage 5) engines of the neural system. The result of this treatment is that the channels are all considered orthogonal to each other.

Because of the great confusion in the semantic labeling of perfumes, fragrances and odorants in the marketplace, it may be best to restrict technical discussions to the use of a tabulation such as that developed below instead of a subjective set of arbitrary descriptors. Where any channel is only stimulated by a single odorophore, it may be possible to associate a meaningful semantic descriptor with the associated perceived response.

Practical implementation of this tabulation may be some time in the future. To be used with precision, it is first necessary to document the effectivity profile of the olfactory sensory receptor for each sensory channel. Simultaneously, the specific mean d-value for each odorophore of a large number of odorant, preferably 500 odorants, must be determined (and probably the d-value effectivity spectrum for each of these odorophores).

As part of the qualification of this tabulation process, it may also be possible to verify the exponent of the Steven’s Equation for each channel of the olfactory space. With the Steven’s Equation...
Using PCA techniques focused on a 1-dimensional space

Yeshurun et al. have reported the use of the Principle Component Analysis (PCA) technique by ordering a large number of odorants according to a single criteria\textsuperscript{274}. They note their approach is different; they investigate the perceptual response and attempt to work backward to the molecules generating that response. Their first component reflected a span that they described as “perceived pleasantness,” and used pleasantness for short. They note this dimension has also been labeled as perceptual valence or hedonic tone. They describe their pleasantness scale as extending from fragrant to sickening. For some reason, the term fragrant was replaced by light in the bottom paragraph of page 331 but used in figure 22.10A to describe the principle component loading factor.

They cite and rely on the chemicals in the Atlas of Odor Character Profiles of 1985 by Dravnieks as a starting point\textsuperscript{275}. This old report lists chemicals by their names and principle chemical groups but not by their odorophores.

They assert their first dimension incorporates 32% of their variance, and the first ten accounted for approximately 70% of the variance. They proceeded to identify the major features of the molecules associated with their PC loadings using conventional chemical labels; atomic van der Waals volumes, the Xu index, a pleasantness connectivity index, the number of non-H atoms, etc. Their figure 22.12B attempts to relate their predicted perceptual PC1 to the actual perceptual PC1. The graph shows a great deal of dispersion and little sign that the linear line of regression is relevant, although they suggest it is a modest but significant prediction of PC1 (odorant pleasantness) based on physicochemical attributes. In their 2009 conclusion, they note, “Although the neuroanatomy of the olfactory system is well described and the molecular mechanism of olfactory transduction are well understood, overall coding of olfaction remains a mystery, ... whereby an olfactory percept cannot be predicted from an olfactory stimulus structure.”

It does not appear that starting from the perceptual quality of a set of odorants is effective in determining the fundamental features of the stimulating odorants.

A fundamental problem in their work and the chemicals selected by Dravnieks is that their odorants were not directly related to fundamental odorophores as defined in this work. As a result, the inclusion of odorants containing multiple odorophores led to less precision in their statistical results.

Figure 2 of Johnson & Leon provide an excellent example of the use of 2D PCA in gustation, olfaction and flavor. On the other hand, it deals in various fruits and vegetables; a level far above that of the essential oils, individual odorants and far from individual odorophores.

Defining the n-dimensional (orthogonal) perceptual space of olfaction

The n-dimensional sensory and perceptual space of olfaction cannot be effectively described using a three-dimensional graphic space. As defined here, the olfactory sensory and perceptual spaces involve nine sensory channels; an intensity value associated with each channel and frequently with time as an additional dimension. Unless steps are taken to standardize the concentration of the stimulants (as is done in order to display the chromatic attributes of the visual modality) the intensity


values for each odorophore must be normalized with respect to the stimulant (not among the group of responses). And unless steady state conditions are insured, time must be carried as a parameter in any perceptual space. If steady state conditions are insured and a commitment to equalized concentrations is instituted (preferably at 200-500 times threshold to avoid saturation problems), it is possible to display three sensory channel signals at three nodes of the remaining two dimensional surface of the available 3D graphic space, Figure 8.6.6-1. This can be accomplished in two ways: by using three adjacent nodes along the d-value coordinate (in which the perceptual space shall be defined as real, alternately realizable), or by using three nodes that are not adjacent along the d-value coordinate (in which the perceptual space shall be defined as synthetic). Synthetic perceptual spaces may be useful to describe certain families of fragrances or odorants but the mathematical manipulation of the scaled values may be limited. Real perceptual spaces provide greater computational capabilities but may not be able to illustrate all of the features of a given fragrance or odorant.

---

Figure 8.6.6-1 Realizable and synthetic 3D perceptual spaces in olfaction. All intensities are drawn to the same scale. Left—real perception space; Heavy axes represent the d-value line. Vertical bars represent the response of the odorophores of o-isoegenol by the three OR channels (assuming the three odorophores of o-eugenol near d = 2.757 Å are each as effective as the individual odorophores stimulating the OR 3 and OR 4 channels. Right—synthetic perception space; Dashed line between OR 2 and OR 6 is not in d-value space. One of three odorophores is not as effective at stimulating the OR 2 channel as in left frame. The odorophore stimulating the OR 7 channel is less effective than the OR 6 channel odorophore. See text.

In this figure, the relative effectiveness of the odorophores in stimulating the appropriate channels varies. In the left frame, o-isoegenol exhibits three odorophores essentially equally exciting the OR 2 receptors. Simultaneously, a fourth odorophore (of the same molecule) is stimulating the OR 3 channel and a fifth is stimulating the OR 4 channel. In the right frame, a similar molecule, trans-isoegenol exhibits a similar set of three odorophores stimulating the OR 2 channel but one more weakly. The OR 6 odorophore is stronger than the odorophore stimulating the OR 7 channel. The axis between the OR 2 and OR 6 is not congruent with the d-value axis but the axis between OR 6 and OR 7 is.

---
As shown in other sections, the d-values of the odorophores of a given odorant are seldom associated with a realizable (contiguous) perceptual space. While o-isoeugenol can be represented in a contiguous (and therefore realizable 3D space as noted above, this is unusual. As also noted above, trans-isoeugenol is only presentable in a synthetic 3D space. In both cases, the first three odorophores result from DACB pairings between a benzyl ring and the immediately adjacent orbitals. The fourth and fifth are both associated with an oxygen orbital paired with a C=C bond along the aliphatic chain of the arene. The value of 6.486 Å is most closely associated with the spice channel, OR 7, and 6.045 Å is most closely associated with the cinnamon channel, OR 6. When combined with the stimulation of the OR 2 channel, trans-eugenol is perceived as a spicy (possibly acidic) cinnamon, labeled nutmeg in the vernacular. o-isoeugenol, by stimulating a different series of channels results in a different perceived scent, a limal (possibly acidic) floral (not identified to date from the literature).

The mints generally contain methyl salicylate in some abundance. They are generally characterized by the odorophores of this chemical with d-values stimulating the OR 2 and OR 3 channels. There appears to be a good chance that methyl salicylate can close it partial ring by hydrogen bonding. If it did, it would become a multicyclic heterocyclic structure not significantly different than naphthalene, a “cooling” nociphore with which it is frequently associated in psychophysical experiments (or the author’s experience).

Providing one further example;

- looking at only a few of the essential oils of the roses, and
- using the putative effectivity characteristics used in the figures of this work,

...to be described as a rose scent, stimulation of OR 2 and OR 3 are generally minimized, the stimulation of OR 3 is prominent and the stimulation of OR 5 and OR 6 are minimized. Thus a rose scent is dominated by stimulation of the OR 3 floral channel. This dominance can be augmented by employing multiple odorants containing odorophores focused on stimulating the OR 3 channel.

The methodology used to identify nutmeg and rose provides a means of assigning a scientifically traceable description of an odorant or fragrance back to its most effective individual odorophores.

How well this methodology can relate to the perfume industry labeling (which does not generally include acidic, dulcal, putrid or pheromone labels in their vernacular) of “five standard families” noted in Wikipedia, the seven notes that were considered fundamental around 1900, the eleven notes in the Edwards Fragrance Wheel of 1983 or the widely distributed 14 notes of the inner circle of the Aftelier Fragrance Wheel cannot be determined at this time. The designations incorporated into these wheels are clearly disparate and make no claim to a scientific underpinning.

The scents described above are those that would be predicted based on the outputs of the stimulated stage one sensory receptors under steady state conditions and low odorant concentrations (on the order of 200-500 times threshold). Stage 2 through 4 signal processing and information extraction may result in different cognitive, stage 5, perceptions. This subject will be discussed in later chapters xxx on the performance of the human olfactory modality.

[xxx edit below here   ]

As shown in Section xxx,

Step 1, the selection process, initially leads to the description of the nominal 9-dimension space by a set of binary values. However, due to the effectivity of the selection process, each of the actual set of values range from 1.0 to zero.

Step 2 of the transduction process, measurement, also provides a multiplier applicable to each of the set of values. It also introduces a dynamic range limitation on the overall intensity level representing each of the set of values. For purposes of discussion, the intensity multiplier will have a
A value of 1 to 100 where the value of 1 is the minimum "noise" associated with the measurement. Therefore, each value in the set will be represented by a signal from 0.0 to 100 with a noise floor, or threshold, value of 1.0.

Although an MDS analysis can be performed on a data set of any number of dimensions, it is generally not practical to represent more than three orthogonal dimensions graphically in a given figure. Therefore, the solution is to represent a subset of the complete set of data in a three-dimensional or two-dimensional representation. These representations will only incorporate the one-dimensional d-value parameter if the nodes of the selected channels are adjacent to each other along the unfolded d-value line.

Although not demonstrated at this time for olfaction, the perceived intensity of the scent resulting from stimulation of the OR 1 and OR 8 channels simultaneously can be considered the mean of the perceived intensity of the two individual intensities or as is more likely, the root of the sum of the squares (RSS) of the individual perceived intensities and be located at a position proportional to the difference in intensity between the mean value and the difference in distance between the two nodes. The result is a two-dimensional representation of the OR 1/8 arc extending from the acidic node to the putrid node as illustrated in Figure xxx. Such an arc is similar to the "pungent" label frequently found in the literature. However, this arc does not include stimulants related to the acidic-fetid arc defined as between the OR 1 and OR 2 channels. A different label must be adopted for the axis defined by these two nodes.

It is possible and practical to define a 3-dimensional perceptual space (3D perceptual) with up to three orthogonal nodes as found in the visual modality (assuming the wavelength interval between short and ultraviolet is ignored). This situation is illustrated in Figure xxx for the OR 1 (acidic), OR 2 (dulcal) and OR 3 (floral) nodes. The effective intensity and location of the scent resulting from three primary odorants (odorants of only one odorophore each) or one odorant of multiple odorophores. The intensity of the perceived scent is then given by the RSS of the individual intensities, and its location is taken as the xxx of the OR 1/2/3 (or acidic/dulcal/floral) space as shown in Figure xxx(C).

8.6.6.2.1 A multi-dimensional display of olfactory perception space

It is clear from the one-dimensional d-value line that the olfactory perception space originates from nine distinct OR-fed (stage 1) neural signaling channels. While such a space is not easily envisioned graphically, the space can be initially portrayed by a series of zeros and ones with each OR (and associated center d-value) described by a single one within a string of zeros in what appears to be a binary code;
### 240 Neurons & the Nervous System

<table>
<thead>
<tr>
<th>Olfactory channel</th>
<th>Olfactory chan. label</th>
<th>d-value (^3) centroid</th>
<th>Primary node (^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 1</td>
<td>Acidic (Lewis acids)</td>
<td>2.276</td>
<td>1000000000</td>
</tr>
<tr>
<td>OR 2</td>
<td>dulcal (skatole)</td>
<td>2.757</td>
<td>0100000000</td>
</tr>
<tr>
<td>OR 3</td>
<td>floral</td>
<td>3.508</td>
<td>0010000000</td>
</tr>
<tr>
<td>OR 4</td>
<td>limal</td>
<td>4.467</td>
<td>0001000000</td>
</tr>
<tr>
<td>OR 5</td>
<td>musk</td>
<td>5.294</td>
<td>0000100000</td>
</tr>
<tr>
<td>OR 6</td>
<td>cinnamon</td>
<td>6.075</td>
<td>0000010000</td>
</tr>
<tr>
<td>OR 7</td>
<td>spice</td>
<td>6.705</td>
<td>0000001000</td>
</tr>
<tr>
<td>OR 8</td>
<td>citral</td>
<td>7.184</td>
<td>0000000100</td>
</tr>
<tr>
<td>OR 9</td>
<td>putrid</td>
<td>8.297</td>
<td>0000000010</td>
</tr>
</tbody>
</table>

1) Effective 1 Mar 2015

2) Each of the digits in the binary code can be considered a node in an 9-dimension space (with 000000000 representing no stimulation of the olfactory modality).

Expanding on this arrangement, a perception of various scents without regard to relative channel amplitudes would typically be;

<table>
<thead>
<tr>
<th>Common perception</th>
<th>Olfactory channels*</th>
<th>Typical odorophore</th>
<th>Nodes in a 9-ary space**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buttery (rancid)</td>
<td>1</td>
<td>butyric acid</td>
<td>1000000000</td>
</tr>
<tr>
<td>Dulcal</td>
<td>2</td>
<td>skatole_6480</td>
<td>0100000000</td>
</tr>
<tr>
<td>Rose-like</td>
<td>3 &amp; 1</td>
<td>β-damascene_1299471</td>
<td>1010000000</td>
</tr>
<tr>
<td>Wintergreen</td>
<td>3 &amp; 2</td>
<td>methyl salicylate_13876103</td>
<td>0110000000</td>
</tr>
<tr>
<td>Jasmine-like</td>
<td>3 &amp; 2</td>
<td>???</td>
<td>0110000000</td>
</tr>
<tr>
<td>Citrus</td>
<td>4</td>
<td>limonene_20939</td>
<td>0001000000</td>
</tr>
<tr>
<td>Musk, natural</td>
<td>5</td>
<td>natural_130483</td>
<td>0000100000</td>
</tr>
<tr>
<td>Musk, synthetic</td>
<td>5 &amp; 2</td>
<td>musk ketone_60681</td>
<td>0100100000</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>6</td>
<td>cinnamyl alcohol_13871718</td>
<td>0000010000</td>
</tr>
<tr>
<td>Spice (clove)</td>
<td>7 &amp; 2</td>
<td>methyl eugenol_13876103</td>
<td>0100001000</td>
</tr>
<tr>
<td>Spice (nutmeg)</td>
<td>7 &amp; 6</td>
<td>trans-iso Eugenol_21106129</td>
<td>0000011000</td>
</tr>
</tbody>
</table>

* primary channel is in bold face type.
** node labels designate axes stimulated; they are not binary codes.
***cinnamyl alcohol_13871718 (3-Phenyl-1-propanol) is an SOO and is not the same as cinnamyl alcohol_21105870

[xxx update above and below ]

This tabulation develops several facts.
- Simple Lewis acids only stimulate OR 1 (PtdSer).
- The indoles only stimulate OR 2 (PtdTrp).
- The perception of citrus is due totally to limonene exciting OR 4 (PtdHis), with other odorophores contributing secondary “highlights,” “notes,” etc.
- The natural musk, a large macrocyclic aldehyde only stimulates OR 5 (PtdGln).
- The cinnamons stimulate a variety of OR’s besides OR 6.
- The spices, clove, nutmeg etc. typically stimulate OR 7 and several other OR’s depending on the
variety of the spice.
• To date, OR 8 has not been defined. It is potentially PtdDha as defined earlier.
• To date, OR 9 (if any) has not been defined although two cinnamon’s point to the existence of OR’s 8 and 9.
• OR 10 is currently defined as PtdAhc, and associated with the vomeronasal, rather than the olfactory modality.

This scenario suggests that \(2^9 = 512\) independent odorophores can be perceived strictly on the basis of the report of the stimulation of one or more individual OR channels based on only on step 1 of the transduction process (and without regard to the degree of stimulation or any adaptation by the sensory system). It is not claimed that the animal can identify a specific odorant based on the unique perception at this stage. It is also impossible to assert at this stage whether the overall array is fully populated or sparse.

As noted earlier, the amplitude of the signal delivered to the higher stage 4 information extraction engines depends on;
• the effectivity of the DACB coupling of a particular odorophore to its target OR,
• the measured dipole potential of that odorophore, and
• the state of adaptation of the sensory neurons associated with that OR channel.

If the d-value of the individual odorophore(s) associated with an odorant are different from the nominal d-value of the odorophore, the effectivity of the DACB coupling will be reduced from a relative value of 1.000.

Each of the resulting effective digit amplitudes resulting from step 1 (selection) can be multiplied by the dipole potential (an analog value) of the individual odorophore as measured by the coupled OR. Based on other studies in the visual and hearing modalities, the typical sensory neuron has a dynamic range, defined as a maximum signal amplitude divided by a noise level, of typically 200:1. Thus, without considering adaptation, the typical OR can report an analog signal to the stage 2 (signal processing) and higher stage neural engines that is between zero and 200 x the effective digit amplitude. This reported signal is key; it means each of the OR channels (up to 512 in a fully populated sensory array as defined above) can report a signal amplitude of up to 200 discernable signal levels (assuming the olfactory system is noise limited at the OR sensory neuron. The result it the theoretical capacity of identifying \(512 \times 200 = 102,400\) unique signal levels at the input to the stage 4 information extraction engines. As in the visual perception space first defined by Munsell (Section xxx of xxx) during the early 20th Century, the dynamic range of the olfactory modality is probably not uniform across the perception space and a reduced number of unique signal levels is probably present (more compatible with the frequently estimated 10,000 perceivable odors, Section 8.6.2).

The contours of the multidimensional perception space can be explored effectively using a carefully selected group of odorants containing only one preferred odorophore capable of DACB binding with each OR type. For example, using 6-phenyl-2-hexanone_24711 instead of cinamyl acetate_4445319 (which eliminates the oxygen embedded in the aliphatic chain of the latter) to provide a stimulant to only the potential OR 8 (PtdDha defined above) with a peak sensitivity near 7.184 Angstrom.

Such an exploration must recognize that the reported perceptions will be a function of the relative stimuli concentrations. This requirement is particularly well documented with respect to the indoles. At low relative concentrations, the indoles are used to add a specific pleasant note to the perception of jasmine in perfumery; whereas, at a significantly higher relative concentration, the indoles contribute a fetid odor to the same chemical mixture.

It is important to note the mammalian olfactory modality of the neural system, like all sensory modalities, was not designed to report absolute signal levels. However, it can report very small differences between two stimulants compared over a short time interval and at stimulant levels that do not introduce the automatic adaptation function built into the stage 1 sensory neurons.

Section 8.6.6.6.1 extends the above concept to replace the ones in the above line of code describing the nodes of olfaction with intensity values ranging from 0 to 5 on an analog scale (that is probably logarithmic with regard to stimulus intensity.

A description of a particular odorant by a string such as 023406700 is reminiscent of the descriptors used in the three-dimensional Munsell Color Space. Here, the digits define a location in 9-ary space that does not fall along the d-value line. In vision, such a stimulant is labeled non-spectral since the
value cannot be described by a single wavelength along the spectral range produced by a prism. In the olfactory case, they may be labeled non-baseline, referring to the d-value axis as the baseline.

For more complicated odorants (or mixtures of odorants), a tabular representation may be preferable to the above representations. Figure 8.6.6-2 suggests such a tabulation based on either the potency values (where the perceived aromas are kept constant in a given comparison) or the perceived human responses (where the applied potencies are kept constant in a given comparison).

<table>
<thead>
<tr>
<th>Odorant with ID number</th>
<th>Check one box below</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potency values</td>
</tr>
<tr>
<td></td>
<td>Perceived aroma scores</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Label</th>
<th>Acidic</th>
<th>Dukal</th>
<th>Floral</th>
<th>Limal</th>
<th>Musk</th>
<th>Cital</th>
<th>Spice</th>
<th>Cital</th>
<th>Purid</th>
<th>Effective value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>RMS</td>
</tr>
<tr>
<td>Intensity</td>
<td>x</td>
<td>y</td>
<td>z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$\sqrt{\sum/n}$</td>
</tr>
</tbody>
</table>

The right-most column is labeled RMS, for root-mean-squares, a common mathematical treatment for obtaining the effective amplitude of orthogonal functions that are varying sinusoidally. It is based on the concept that the powers among several sinusoidal stimuli add linearly. This concept can be extended by the Fourier Theorem to include any summation of periodic stimuli.

The olfactory modality senses quantum mechanical parameters and not power (or any quantity related to power). Because of the exponential character of the signal processing channels of chemical sensing, an RSS calculation, root-sum-squares, may be more appropriate (oversmall dynamic ranges) where the taking of the mean of the sum of the squares is omitted.

8.6.6.2.2 Using a synthetic axis in MDS analyses- Lawless & colleagues

Lawless has made a career of studying the olfactory modality via psychophysical tests. Lawless & Glatter performed a study of odors using MDS techniques in the course of developing the practical use of MDS. Figure 8.6.6-3. The composite figure is useful because of the chemical names used at bottom left to define various scents in their view. Unfortunately, they used essential oils instead of pure chemicals in some cases. Many of the names used are synonyms used in the field and not sufficiently explicit to evaluate (e.g., dimyrcetol and dihydromyrcetol). Dihydroterpineol is available.

in several isomers. The alpha version is described as, “DIHYDROTERPINEOL. Nature-identical. Odor: intensely pine-woody; coniferous connotation, somewhat lime note. Flavor: mild woody ...” by The Good Scent Company. Its simple formula (a benzyl with a hydroxyl attached to the alpha carbon) suggests a $d \sim 3.6$ Ångstrom stimulating both the floral and limal channels. This stimulation of both floral (OR 3) and limal (OR 4) may be the combination that is frequently defined as woody. Many of the compounds are not included in ChemSpider at this time.

Lawless & Glatter did not attempt to define their axes in the detail desired here. They described their process, “These data were analyzed as similarity estimates by the SYSTAT (Macintosh Version 3.2) MDS module for nonmetric multidimensional scaling, using the option for minimizing Kruskal’s stress Formula 1 in two dimensional solutions.” They also noted the frame on the right was from a “first sort” of the data from the previous study involving about 80 people. Their Kruskal stress values (background in Section 8.5.2.3) were near 0.04 for the full group and within the 0.04 to 0.17 range when they subdivided the full group. On examination, it appears that dimension 1 relates to the olfactory channel stimulated and dimension 2 may relate to the perceived intensity of the stimulants used. If so, -1.7 on dimension 1 corresponds to a $d$-value of 7.184 Ångstrom (OR 8), -0.5 corresponds to a $d$-value of 4.467 Ångstrom (OR 4) and +1.3 corresponds to 3.6 Ångstrom (midway between OR 3 and OR 4) as projected onto a synthetic axis running from OR3/OR4 to OR 8. Dimension 2 corresponds to a perceived intensity where the values between -0.5 and +1 indicate similar intensities and the values between -1.0 and -1.5 suggest a less intense perception. These less intense woody perceptions are usually associated with the exotic woods as opposed to the strong perceptions associated with pine oils. Interestingly, their plot differentiates between the lime oils (C and F) and the other citrus oils (A, B, D & E) although their tabular listing did not. It thereby confirms the separation between the limal and citral channels predicted here based on the hypothesis. The separation is most clear in the 1989 sort involving the full group and a Kruskal stress value of xxx. In other respects, their textual description agrees with the interpretation given here based on the $d$-values of the OR channels. No detailed information was given about the concentrations of the stimuli except they were from jars containing a perfumer’s blotter dipped to the depth of one centimeter in the labeled fragrance and then allowed to equilibrate for one hour.

The extraction of true axes from initial MDS analyses has become a high art in recent times. Several software packages are available under the labels promax rotation, varimax rotation, etc. In the current situation only extraction techniques maintaining orthogonality is useful. An introductory discussion by J. D. Brown of the University of Hawai’i at Manoa appears particularly helpful. A lecture by A. Ainsworth of California State University (Northridge) is very useful. See also Section 8.5.2.3.1

Lawless also prepared a set of dendrograms that are worthy of study if one has an adequate null hypothesis. Lacking such a hypothesis, the dendrograms are primarily pretty. Lawless did explore several rotations of the MDS axes to uncover interesting relationships or trends toward such relationships. Associating the d-values of the pure chemicals in the stimulant set with their locations within the dendrograms does surface additional relationships.

Jellinek commented constructively on the results of the 1989 paper at the same time as the appearance of the 1990 paper. He performed several regression analyses on the Lawless data and concluded that there was an anomaly near the mid-range of the best fitting linear regression. No conclusions were drawn.

A question arises concerning the chemical labeled limonene used by Lawless. Additional analysis is needed to determine why limonene (presumed to be limonene_20939 with d = 4.303 Angstrom) continues to appear with the citral channel (OR 8, d = 7.184 Angstrom) odorants instead of with the limal channel (OR 4, d = 4.467 Angstrom) odorants in the MDS analyses.

The 1995 paper by Lawless and colleagues on sorting cheeses advanced the use of MDS analyses but did not employ analytic chemicals as part of the stimulus set.

[xxx edit/rewrite Figure as presented belongs in gustatory section, 8.5.xxx ]

Figure 8.6.6-4 presents a graphic of the one-dimensional data of the previous figure in a three-dimensional perceptual space shared with the gustatory modality. The olfactory data set is incomplete and receptors at d-values higher than 4.2 are known to exist. The two spaces share the acido-receptor at d = 2.04 Angstrom. The initial 3D perceptual space appropriately represents the olfactory sensory receptors as recorded at the sensory neurons of stage 1. It is proposed that the intermediate stage 2 through 4 signal processing has the requirement to recreate this perceptual space for inclusion in the saliency map. Following the normal mode of operation, the stage 5 cognition treats the signals from each class of receptors independently and interprets them in an n-dimensional space where n is between 10 and 23. This graphic does not portray the perceived n-dimensional olfactory space. The higher number of dimensions provides a much greater texture to the perceptual space.

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279 Ainsworth, A. (xxx) Factor Analysis  www.csun.edu/.../Psy524%20lecture_21FA_cont.ppt

If confirmed, the d-value spacing between the acido-receptor at 2.07 angstrom and the aminophore-receptor at 1.97 Angstrom is indicative of the potential narrowness of the stereochemical selection process among the variety of receptors employed in olfaction.

The pheromones (species and sex specific odorophores) are processed separately from the remainder of the odorophores, via the vomeronasal organ and tract, and appear to be perceived in a separate olfactory space.

The vomeronasal reception process is addressed in Section xxx of this work. Brennan & Keverne have addressed this subject recently in a handbook281.

8.6.6.2.3 Recognizing intermediate values in MDS and other analyses

The above development of a 3D perceptual space does not adequately treat two important features of the representation. It is well known that changing the concentration of certain odorophores changes their perceived scent significantly (with indole and skatole being good examples) even though they appear to only be stimulating the OR 2 channel. Similarly, changing the relative concentration of two stimulants to different OR channels can result in significantly different perceived scents. These two situations call for the definition of terms to aid in quantifying these effects.

The second example suggests a “relative concentration arc” between two nodes of a 3D perceptual space and following a direct line between the two OR channels. While the arc between OR 4 and OR 5 might be labeled the limal-musk arc. The midpoint of such an arc might be perceived as something totally different from its two end labels, as is the midpoint of the green-red arc of vision that is perceived as bright yellow.

The first example suggests an “intensity arc” associated with the pleasant (hedonistic) scent of skatole at low concentrations and the repugnant scent at high concentrations. A similar situation occurs in vision where at high intensity the midpoint of the red green arc appears as saturated yellow while at lower intensity for both of the principle components, the result becomes distinctly different “brown.”

When two or three nodes of the data set are selected for representation, the various axes correspond to what are generally called arcs, spectra, or similar terms in olfaction. However, these arcs will be much more precisely defined and probably will not conform to the marketing oriented arcs of the perfume trade. As an example, odorants and odorophores will only be described as putrid if they excite the OR 8 channel and acidic if they excite the OR 1 channel. The resulting arc would be the acidic-putrid arc defined as a diagonal in the 9-dimension space extending from the centroid of the OR 1 channel (d=2.2xx) to the centroid of the OR 8 (d=xxx) channel.

The axis between these two nodes does not include the d-value line but can be given relative values as desired.

8.6.6.2 Defining an odorant in n-dimensional (orthogonal) perceptual space

8.6.6.3 Separating stimulants to the olfactory and nocent modalities - trigeminal nerve

There is a need, before exploring the multidimensional space of olfaction, to distinguish between stimulants that primarily affect the olfactory modality from those that primarily affect the nocent modality.

Getchell & Getchell have provided an anatomical sketch attempting to describe this difference in Figure 8.6.6-5.

Doty and Cometto-Muniz (page 984) have discussed the challenge of identifying pure odorants that affect the olfactory modality but not the trigeminal nerve, i.e., the nocent modality. There has long been evidence that the olfactory and gustation modalities share their perceptions at the output of stage 4, resulting in the perceptions of flavors. Similar evidence has been accepted with regard to olfaction and nocent modalities sharing perceptions at the level of the saliency map at the output of stage 4 (Doty and Cometto-Muniz, page 982). They noted the work of von Skramlik in 1925. He used his knowledge of the sensory modalities in an unusual way. He noted that the olfactory modality (with signals processed through the olfactory bulb) was entirely insensitive to source direction or receptor location within the nasal and oral cavities whereas the nocent modality (with signals processed through the trigeminal nerve path) was source direction and receptor location sensitive. Based on this difference he separated a long list of stimulants into categories that they reproduced as follows:

“Among ‘pure’ odorants were -
A. anethole, caninene (juniper), eugenol, geraniol, indole, limonene, phenyl ethyl alcohol, pinene, skatol, and terpineol.

Examples of ‘impure’ odorants were one that produced -
1. smell + sour sensations (acetic acid, butyric acid, propionic acid, and valeric acid);
2. smell + sweet sensations (bromoform, chloroform, ethyl chloride, iodoform, nitrobenzol);
3. smell + cool sensations (camphor, eucalyptol, menthol, phenol, safrol);
4. smell + warm sensations (ethanol, pentanol, propanol); and
5. smell + painful or prickly sensations (acetone, acetic acid, ammonia, bromine, chlorine, formic acid, iodine, nicotine, pyridine, SO2, thiophene, toluol and xylol).”

Figure 8.6.6-5 Location and innervation of the human olfactory mucosa ADD. A; focusing on the trigeminal nerve (n. V), and its ethmoidal branch. B; focusing on the olfactory sensory neurons. C; note the intrinsic presence of the olfactory sensory neurons in the outer layer of the epithelium whereas only the dendrites of the extrinsic trigeminal nerve neurons are found in this outer layer. From Getchell & Getchell, 1991.
With rare exceptions, this set of classifications appears quite useful. His pure odorants are those typically associated with olfaction and accounted for in the presented hypothesis, although many incorporate multiple odorophores. His smell + sour sensations (1.) are those shared between the olfaction and gustation modalities (not with the nocent modality) because of their carboxylic acid groups stimulates the PtdSer receptors used in both the olfactory and gustatory modalities. Both of these categories are accounted for under the presented hypothesis without additional corollaries.

The rest are a variety of inorganics, simple alcohols, and chemicals known to cause significant stimulation of the nocent modality and frequently leading to localized damage of the mucosa and epidermis at high concentrations. Some of these exhibit odorophores under the presented hypothesis but some would require the incorporation of additional corollaries to qualify as odorants under this regimen.

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Based on the hypothesis and corollaries of this work, von Skramlik’s 1925 categorization can be expanded to include three categories,

A. Pure odorants and gustants, exclusively non-localizable stimuli as above.
B. Mixed odorants and gustants (due to the shared PtdSer receptors of these two modalities) category 1 above
C. Mixed odorants and/or gustants also exhibiting nocent capabilities
   some chemicals in categories 2, 3, 4 & 5 above
   methyl salicylate as well as phenol being a good example from category 3
D. Pure nocents, exclusively localizable stimulants
   most chemicals from categories 2, 3, 4 & 5 above
   the alcohols being examples of this category

Category D includes a variety of minor as well as major irritants. The minor irritants include the simple aliphatic alcohols. Major irritants, verging on the destructive include phenol. Current examples of the pure nocents would also include the inorganic acids (hydrochloric acid) as major irritants at significant concentrations and a variety of astringents (including the alkali-earth salts) which may be considered minor or major irritants based on concentration and recognized properties.

[xxx edit and point to 8.8.2.1.1 ]

The cool and warm nocents play a major role based on their concentrations. “Cool” nocents used in foods and odorants are generally at low enough concentrations to contribute to a hedonistic sensation. At higher concentrations, they may be overwhelming and considered major irritants. Among the “hot” nocents, capsaicin is the most prominent. Based on concentration, it ranges from the pepperspray used by Police to a common constituent in “Mexican” and other equatorial country foods. The citation in Wikipedia says “Pure capsaicin is a volatile, hydrophobic, colorless, odorless, crystalline to waxy compound.” Rowland et al. have discussed capsaicin in considerable detail and repeat the claim that it is odorless and flavorless. These descriptions appear to be in conflict with its chemical structure as shown in Figure 8.6.6-6. However, the nocent channel stimulation may be so great as to overwhelm any olfactory perception(s).

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The molecule exhibits a variety of d-values compatible with olfaction (without considering those associated with the nitrogen orbital); likely stimulating OR 5, OR 6, OR 7 and OR 8 as a minimum. The two oxygen orbitals associated with the ring may also act as odorophores affecting OR 2 and OR 3. The potential scents associated with these odorophores may be overwhelmed by the major irritating capability of the chemical.

A clear example of the mixed odorants and nocents would be methyl salicylate which exhibits definitive odorophores affecting OR 2 and OR 3 but also stimulates a cool response via the nocent modality. In general, the “mints,” and probably the multicyclic and more saturated (non benzylic) rings appear to fit into this category (naphthalene, which may affect OR 1 and OR 2 in a minor way.).

In the absence of any clear case of hydration, the aliphatic alcohols appear to fit into the pure nocent (nocant) category.

Applying the above framework to the senses of the oral and nasal cavities, the olfactory, vomeronasal and gustatory modalities are concerned with pure sensations of the types described without providing any information concerning the location of the stimuli. The nocent modality and nociceptors do provide information about the location of the stimulus.

Note the chemicals labeled putrid in this work (putrescine and cadaverine) are both primary odorants (with only one odorophore each) and necessarily also single odorophore odorants (SOO). However, they may not be ideal SOO because their d-values differ significantly from the central d-value of any identified OR.

While the natural chemicals from the flowers frequently labeled putrid, Titan Adrumxxx, cabbage and other plants exhibit non-primary odorants with odorophores at d-values of .xxx. These chemicals do not include any odorophores stimulating OR 8 and cannot be considered to be contributing to a perceived putrid scent, although they can be considered to contribute to a dulcal scent.

8.6.6.3.1 Trigeminal neuron responses to cyclical and non-cyclical organic homologs

While the natural chemicals from the flowers frequently labeled putrid, Titan Adrumxxx, cabbage and other plants exhibit non-primary odorants with odorophores at d-values of .xxx. These chemicals do not include any odorophores stimulating OR 8 and cannot be considered to be contributing to a perceived putrid scent, although they can be considered to contribute to a dulcal scent.
Doty & Cometto-Muniz have provided extensive statistically precise information on the threshold sensitivity of the trigeminal sensory paths to a wide variety of organic homologs\textsuperscript{283}. Doty indexed discussions of the trigeminal nerve under “Part III: Other Chemosensory Systems” and not as part of the discussions of olfaction or gustation.

Noback, in his extensive study of the neural paths and signaling performance of the neural system strongly suggests the trigeminal nerve (n. V) is heavily involved in the nocent modality (pain, temperature, touch, and proprioception). It is described as conveying neural signals from the anterior portion of the tongue but there is no suggestion that these are gustatory signals.

It is likely that camphor and camphorous stimulants impact the trigeminal neurons rather than the olfactory sensory neurons much like hydrochloric acid does and many other irritants do.

**8.6.6.4 Verification of the olfactory modality hypothesis by MDS**

The identification of odorophores capable of only stimulating one of the defined OR’s of olfaction, the SCO’s specified in the table of Section 8.6.2.6.5, [xxx confirm sec #] provides a useful method of verifying large pieces of the sensory hypothesis presented here. If these odorophores are used as samples in a multi-dimensional scaling investigation, the degree in which the MDS analysis supports the order of OR’s defined here will provide a clear verification or falsification of all or parts of the hypothesis.

The presence of the channels and the relative correctness of both their order and relative spacing can be determined in the psychophysics laboratory using the single channel odorophores, SCO’s. The resulting data can be plotted using the one dimensional d-value axis only. Attempting to plot the results in the folded orthogonal n-dimensional representation is beyond the capability of the MDS software programs available. However, the relative spacing between the SCO’s will provide the data necessary to plot either realizable or synthetic odorant perception spaces.

**8.6.6.5 Use of the olfactory modality hypothesis & the MDS framework**

Following confirmation of the orthogonal framework of the Olfactory Hypothesis using MDS techniques, and distinguishing between putative stimuli of the olfactory and nocent modalities developed in Section 8.6.6.2, the framework can be a valuable tool in confirming;

**8.6.6.5.1 The musks in a calibrated MDS space**

Schiffman & Dackis have provided an important paper showing an MDS space containing 14 musks that is consistent with this work\textsuperscript{284}. Their abstract noted, “The multidimensional space achieved arranges the macrocyclic and nitro musks in separate regions of the space. Multidimensional scaling of confusabilities and similarities proved to be a more stable means of characterizing the differences between the 14 musks than ratings on adjective scales.” They specifically noted, “The results indicate that a wide range of structurally unrelated compounds have musk odors: steroids, macrocyclic ketones, indanes, tetrahydro napthenes, acetophenones, etc.” However, each of these materials employ one of a few overlay moieties that do conform to the hypothesis and corollaries of this work. They used a screened set of naive evaluators, sniff bottles, and made an initial attempt to avoid adaptation among the evaluators during the trials.

They utilized the ALSCAL MDS procedure that was new at that time. It provides more discrimination between the evaluators as well as the stimulants. “The similarity among the subjects is remarkable. All the subjects fall within the first quadrant indicating that there are no aberrant subjects with negative weights. Also, the subjects fall along a 45° angle between the dimensions; this means that individual subjects weight the individual dimensions in nearly equal ways. The subjects are all clustered approximately equidistant from the origin, indicating that the common space equally


represents each individual’s data.” “It is important to note here that dimensions are mathematical artifacts of the procedure and are not necessarily meaningful in themselves unless meaning is found and assigned to them. The significant aspect is simply the arrangement of the stimuli with experimental measures of similarity represented as distances between points in a space. Here the spatial arrangement in Fig. 2 is virtually identical over individual subjects.” “None of the subjects who took part in the experiment were anosmic to any of the individual stimuli. This conclusion is drawn from the similarity of the individual subject’s spaces as well as from verbal report.”

The problem of using semantic labels was addressed and highlighted the long recognized problem, “The semantic differential ratings were widely distributed over subjects on every scale for every adjective. The distributions of the ratings are shown in the histograms in Fig. 4.”

“The arrangement in Fig. 2 reveals some trends with regard to chemical structure. The macrocyclic musks (labeled [MI in Fig. 2) are located in the upper and right portions of the space. The nitro musks (labeled [N]) are located toward the left. An exception to this is musk alpha which is the only stimulus which contains bromine groups.”

8.6.6.5.2 Verification of the olfactory modality hypothesis by MDS

- the presence of various odorophores among the many odorants, based on theoretical calculations,
- differentiating between the various odorants associated with specific fragrances and,
- separating the various fragrances associated with individual botanically labeled flowers, seeds, etc.

A preliminary spreadsheet showing these differences is available from the author of this work (at least in the 2013-2020 time period).

8.6.6.6 Defining other (non-orthogonal) perceptual spaces of olfaction

While orthogonality is a critical aspect of understanding the underlying operation of the olfactory modality, less precise non-orthogonal representations may be important in pedagogy and field applications of olfactometry. A frequent example are the various odor wheels used in the commercial field (and frequently without adequate background in pedagogy).

McGinley et al. have defined a variety of characterization spaces for the gustatory and olfactory modalities using arbitrary semantic descriptors. They did not provide any theoretical framework for their presentations as it was designed as a commercial users guide. Their graphs involved non-orthogonal spaces; one histogram and three “wheels” of the type P (or plan-position-indicator, PPI) scan variety (but without any specific representations between the radials). Their gustatory wheel has four radials representing Sour, Sweet, Salty and Bitter at 90 degree intervals. They present both an odor description wheel and a sensation descriptor wheel of eight equally spaced radials. They also present an “odor descriptor” histogram.

Their sensation descriptor wheel appears to apply more to the nocent modality than to olfaction.

Their odor descriptor wheel is reproduced in Figure 8.6.6-7. While totally lacking in theoretical framework, it can be argued it provides a logical organization of major chemical groups based on the perceptions of olfaction although the distinction between medicinal and chemical might be questioned (Why is ammonia listed as a medicinal and not a chemical? Why is menthol listed as a medicinal?).

Ammonia is a poor label to use in olfaction experiments. The chemical named ammonia, NH₃, is a strong irritant (an astringent) and is sensed by the nocent modality. When dissolved in water, it forms ammonium hydroxide. As a 10% solution, it remains a "pungent" irritant that irritates the eyes and nasal passages. At 25% solution (also known as ammonia water or Spirit of Harshorn) it is a serious astringent like ammonia itself. The odor of dissolved ammonia is probably associated with hydrated ammonia hydroxide. These materials are difficult to control as they are temperature and pH sensitive. They corrode several metals found in conventional piping. At very low concentrations it is found in waste products, including urine.

Chlorine exhibits properties similar to those of ammonia. Its primary role is as an astringent reported by the nocent modality and should not be used as an identifier in the olfactory modality. Neither ammonia or chlorine exhibits a stable and readily identifiable odorophore.

[xxx edit ]

The framework of this hypothesis will offer a similar but different nine-radial wheel in Section 8.6.6.5.1. That wheel will recognize the change in character of the perceived response as a function of the
intensity along a given radial.

8.6.6.6.1 The nine radial perception wheel of this work

This section extends the concept developed in Section 8.6.6.2.1. The theoretical framework developed here results in a different wheel than that of McGinley et al. The 9-dimension orthogonal space of MDS can be shown non-orthogonally, but with somewhat more difficulty in describing complex situations. Figure 8.6.6-8 (left) shows a “olfactory wheel” (analogous to a compass rose) describing the set of nine individual OR channels and their labels. It also shows a set of preferred odorophores useful in exploring the olfactory perceptual space. It is proposed that each of the preferred odorophores shown only stimulate one of the identified OR channels.

This wheel represents the d-value dimension shown as a circle beginning at OR 1 (2.276 Angstrom) and proceeding linearly around the circumference to OR 9 at about 8.0 Angstrom. There is a discontinuity between OR 9 and OR 1 in this representation.

While an obscure fact to the layman, it is well known to the perfumer that skatole has a sweet perception at low concentrations but a fetid perception at high concentrations.

While not fully identified at this time, the OR 9 channel with a maximum effectiveness at a d-value near 8.0 Angstrom could be ideally stimulated by 6-heptenal 4446441, a nominally straight chain hydrocarbon with one C=C double bond at a distance of 8.022 Angstrom from the oxygen orbital. While 6-heptenal has a molecular weight of only 112 Da, with a vapor pressure of 4.885 mm/Hg at 25 C, its length may contribute a degree of fragility to this molecule. Many of the odorants stimulating
the OR 9 channel have molecular weights in the region of 250 or higher and appear to be more rigid in their configuration. If there are odorophores within larger molecules with d-values exceeding nine Angstrom and justifying additional OR channels, they have not appeared as part of this analysis.

The related straight chain aldehyde, heptanal, is said to exhibit a strong odor (presumably in pure, and not a hydrated, form). If correct, a further corollary to the hypothesis employed here is needed to account for the simple aldehydes and alcohols exhibiting a scent under some conditions. This could include a charge distribution sharing between the two carbons farthest from the oxygen with the character of a C=C double bond as in 6-heptenal. However, it is more likely to result from hydration of these chemicals prior to olfactory transduction.

On the (right), a modified wheel is shown reporting the intensity of the perceived response to a single standardized concentration of a preferred odorophore (that does not stimulate any other OR). The expected response to a more complex odorant (or mixture of odorants—a fragrance) would be shown by an arrow along each radial proportional to the perceived response to each of the odorophores (measured separately) by the individual OR channel. The scale of 0 to 5 is arbitrary and may be either linear or logarithmic in practice. The perceived odor may change significantly along a radial (sweet near threshold vs fetid at high concentrations in the case of the dulcal radial, OR 2 channel). This variation is detailed in Section 8.6.7.1.1.

The use of a well founded olfactory wheel and set of preferred odorophores can provide a very useful protocol for a group of psychophysical experiments that initially identifies traceably the perceived names of various scents created by stimulation of various combinations of OR's. If these identifications are performed by experienced perfumers, the protocol can then be used in reverse to identify odorants with a precision not achieved earlier.

McGinley et al. have suggested an analogy between a piano and the radials of the olfactory wheel. They suggest stimulating multiple keys at one time will cause perception of a chord; not unlike stimulating multiple radials and causing a specific perception. The elementary analogy cannot be taken to far because the olfactory wheel radials are not harmonically related, and the olfactory wheel does not repeat itself at octave intervals like the similar auditory wheel of Section 8.4.xxx.

The olfactory wheel cannot be used to perform vector manipulations to provide a composite vector of a given odorant; the observed vector values must be replotted into an orthogonal 9-dimension space to allow such summation to be meaningful. Some of the more obscure labels for common scents can probably be rationalized by this process. Woody and cardboard as scents are probably analogous to the color brown in color vision. Brown can be considered a yellow or orange at low chromatic saturation. By collecting data on a wide range of odorants in 9-dimensional space, they can be compared to their predicted vector in 9-dimensional space. However, many of these vectors cannot be plotted on the two-dimensional olfactory wheel. The names found on the periphery of the Aftelier “Natural perfume Ring” do not represent a traceable relationship with the scents in 9-dimensional olfactory space.

When reinterpreted in an orthogonal 9-ary space, a given stimulant provides new insights. A description of a particular odorant by a string such as 023400000 is reminiscent of the descriptors used in the three-dimensional Munsell Color Space. Here, the digits define a location in 9-ary space that does not fall along the d-value line. In vision, such a stimulant is labeled non-spectral since the value cannot be described by a single wavelength along the spectral range produced by a prism. In the olfactory case, they may be labeled non-baseline, referring to the d-value axis as the baseline.

8.6.6.7 Extending the corollaries to cover diastereoisomers

With the semantics use in perfumery offering such imprecise and seriously overlapping descriptions of various odorants, it is necessary to employ the d-values associated with individual odorants to organize the actual inventory of odorants. Unfortunately, in the more complex thiols, their conformation can vary beyond the form(s) currently documented in Jmol. Thus, only one d-value is typically available from Jmol even though four different values may be present if the diastereoisomers involve conformational isomerism (M & B 2nd, 1971, pg 98). As noted in Goeke, these racemic diastereoisomers may be difficult to isolate unless there are additional (generally aliphatic) ligands associated with the orbital of interest in the molecule. Lacking such structures, the diastereoisomers may be interconvertible conformational isomers that cannot be isolated by conventional chemical means. With such structures, they are considered non-interconvertible at
biological temperatures and represent configurational diastereoisomers. Goeke introduces a limitation on understanding the geometries involved by suggesting the distances between the orbitals of the odorants generally stay in the range of 2–4 Ångstrom. To at least 9 Ångstrom is needed to understand all of the perceived odor differences.

Goeke has provided an extensive review of the sulfur-containing odorants based on the conventional knowledge of the time. The report includes 325 structures incorporating sulfur, a few only intermediaries, the results of many syntheses but no original psychophysical experimental results by Goeke were included. Many tabulations of groups of sulfur containing molecules are presented along with long semantic labels but little analyses of why they are perceived as they are. No theoretical framework of olfaction is described. To the extent the descriptive labels are statistically reliable, the Goeke paper is a goldmine for extending the hypothesis and corollaries of this work. His abstract notes, “Sulfur-containing compounds are some of the strongest odorants. The perception of their odors often depends on their concentration as well as on their chemical, diastereo- and enantiomeric purity. Even if present only in trace amounts, they may change the overall olfactory impressions of fragrant mixtures, which makes the art of composing perfumes both difficult as well as rewarding.” and “With regard to fragrance chemistry, the article gives a review of the particular odor properties, structure-odor correlations, biological significance and of the biochemical generation of sulfur-containing odorants.” His text begins with, “It is the overlapping domain of character impacting sulfurs in foods with perfumery that is reviewed in this article.” His figure 1 lists 21 structures of all types containing a sulfur atom and implies that each is the primary source of perceived odor associated with a simple semantic label (generally a food). Figure 2 extends these structures to include an additional 20 with more complicated semantic labels. Goeke and others are beginning to recognize the importance of the distance between pairs of orbitals in olfaction. “The strongest and most typical cassis or buchu odorants are those having a free tertiary mercapto-group in a 2–4 Ångstrom distance to a carbonyl group.” In addition, he notes, “The steric bulk around the mercapto-group is of importance, since primary or secondary mercapto ketones are not very potent or lose their cassis character.” This comment suggests an additional corollary to the hypothesis of this work may be needed to account for the importance of this structural feature.

Figure 8.6.6-9 repeats his Table I and provides significant additional information supporting the need for such a corollary. Note the Lewis diagrams associated with these four different configurations are only marginally different but their perceived odors (scents) are quite different. Note also the high concentration of the materials in water. Ohloff and Sundt have provided more information concerning the scents associated with these diastereoisomers, “who favored the trans-over the cis-compound”. The language of the quotation suggests and the structural diagrams confirm the paper is old. They may not have recognized there were four diastereoisomers to examine. These configurational diastereoisomers exhibit d-values of 2.978, 3.141 & 3.175 Ångstrom. This range is between the center value of the effectivity characteristic for OR 2 and OR 3 and strongly suggests that some of these structures couple with both channels to a certain degree, and that the resulting pattern described in the saliency map reflects this dual stimulation. ChemSpider lists two additional diastereoisomers with d-values of 3.198 & 3.342 Ångstrom. Goeke may have omitted these because they complicate the discussion. The d = 3.342 Ångstrom value is much closer to the center of the OR 3 channel characteristic and the associated diastereoisomer may be described as much more floral than dulcal.


It appears that Goeke chose to begin his atom numbering from a different carbon than does the Royal Society of Chemistry at this time. His text did not define the suffixes a, b, a' and b'.

The ability to isolate these diastereoisomers in the laboratory confirms they are configurational isomers and not conformers (at least at room temperatures). Sulfur containing chemicals are typically delicate and can degrade on exposure to air, actinic light or elevated temperatures. As a minimum an odorophore will be degraded back to a racemic mixture of odorophores. These sensitivities and the ability of sulfur to hydrogen bond are widely documented.

The small differences in the d-values of these configurations stress the degree of overlap between the effectivity characteristics of the OR 2 (dulcal) and OR 3 (floral) channel receptors. They also strongly suggest it is the relative amplitude of the intensities of these odorophores that establish an identifying pattern in the saliency map of stage 4 neural processing of the olfactory modality. This intensity remains the product of a variety of individual parameters.

Goeke introduced his further discussion of the diastereoisomer properties of some thiols with the comment, “The astonishing results are summarized in Table II together with the results reported for terpineol, which nicely demonstrates the olfactory impact of the mercapto-group.” Figure 8.6.6-10 repeats his Table II and provides additional background for creating such a corollary. Goeke discussed the inconsistencies in the literature related to these variants on page 250 and described the differences as astonishing.” There may be a problem to this day with the nomenclature. ChemSpider describes the center-most structure of (59) as the (R) version and a specific common name of Grapefruit mercaptan. This name and the accompanying parameters are better associated with the left-most form of (59) in the figure. (59) has the common name of 1-p-menthene-8-thiol in Goeke (now p-menthen-8-thiol, ID = 4932553 in ChemSpider). ChemSpider describes three configurations of (59) with d-values of 4.633, 4.636 and 4.873 Angstrom. The two lower values are

![Chemical structures](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Sensory evaluation (0.1% in water)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R) Goeke</td>
<td>(1S,4S)-a</td>
</tr>
<tr>
<td>ChemSpider</td>
<td>(2S,5S)</td>
</tr>
<tr>
<td>d-value, Ang.</td>
<td>3.141</td>
</tr>
<tr>
<td>(1S,4R)-b</td>
<td>(2S,5R)</td>
</tr>
<tr>
<td>5324597</td>
<td>5324598</td>
</tr>
<tr>
<td>(1R,4R)-a'</td>
<td>(2R,5R)</td>
</tr>
<tr>
<td>5324596</td>
<td>5324595</td>
</tr>
<tr>
<td>(1R,4S)-b'</td>
<td>(2R,5S)</td>
</tr>
<tr>
<td>2.978</td>
<td>3.175</td>
</tr>
</tbody>
</table>

Figure 8.6.6-9 Sensory evaluation of menthanone derivatives. The R/S nomenclature of Goeke appears different from that currently used by ChemSpider as shown along with the accession number used by ChemSpider for each configuration. The d-value calculated from the Jmol file for each accession number is also added. The two chemicals on the right are solids at room temperature. See text. Modified from Table I, Goeke, 2002.

---

associated with a sulfur perpendicular to the plane of the ring, configurations 4932553 and 9052835 respectively. The higher value is associated with configuration 21163535 and has a sulfur near 120 degrees relative to the ring and the C=C bond within that ring. The differences in semantic descriptions is not compatible with the common d-values. (73) has the common name of terpineol. Three variants are given in ChemSpider, generally with the structures switched from those shown in the Goeke figure. All three exhibit a d-value of 4.456 Å to three digit accuracy (odorophores stimulating receptor OR 4). Therefore, the difference in semantic descriptions of their perceived odor may be due to other causes (possibly involving different laboratories). The descriptor, "reminiscent of cold pipe" is unusual; it more likely applies to the cutting and lubricating oils used in pipe manufacture. It may relate to a cold pipe used in smoking.

Figure 8.6.6-10 Olfactory properties of (59) and (73, terpineol). (59) is 1-p-menthene-8-thio. Note; the double bond in the ring forms an "orbital" and is significant. The underscore numbers shown are only suggestive. There are many forms of these chemicals recorded in ChemSpider. The descriptor "cold pipe" appears to be a semantic outlier. It may apply to a smoking pipe as opposed to a water pipe. See text. Expanded from Table II of Goeke, 2002.

Because the various configurations of (59) all have the sulfur at about 110 degrees from the plane of the hexenyl ring, their d-values are nominally the same and the semantic descriptors justify Goeke’s assertion that the difference in the descriptors was “astonishing.” A more precise test protocol may have been needed. The descriptors shown here are not consistent with the channel names adopted in this work. The d-values for the two right most configurations of (73) are equally close. However Terpineol_390927 exhibits a larger d-value. The 3D values shown in Chemspider ca. 2015 show different rotations about the #1 bond that places them at different orientations rather than just on othersides of the plane of the benzyl group. The d-values in parenthesis were obtained at an earlier time and possibly using a different archive and/or rendering software. All five configurations can stimulate either the channel 4 (Limal) and/or channel 5 (Musk) OR depending on the precise width of the sensitivity functions for these two OR’s. Without very careful instructions prior to the psychophysical tests, the chemicals shown could be expected to be described inconsistently as the labels from Goeke indicate.

Table III continues to expand on the criticality of the conformation of the molecules. However, most of the molecules in this table exhibit multiple odorophores and are therefore odorants. The descriptors overlap so significantly that it appears they were drawn up in a room of specific anosmics. Subsequent tables are also critical but focuses on semantic labels that also lack the needed precision.

Table V is devoted to the volatile aliphatic sulfur compounds associated with passionfruit. Their semantic descriptions are wide ranging. A majority of them exhibit one of only two pairs of odorophores described in this work, S-C-C-C=O and S-C-C-C-O-R or S-C=C-C=O and
S-C=C–C–O–R where R may be hydrogen.

Goeke provides many more important relationships but does not dwell on any framework to explain their performance. He concludes, “Sulfur-containing compounds are some of the strongest odorants so far known. Their odors often depend on their concentrations and, above all, their chemical, diastereo and enantiomeric purity. Even if present only in trace amounts, they may change the overall olfactory impressions of fragrant mixtures, which makes the art of composing perfumes both difficult as well as rewarding.”

Goeke’s tables, to the extent the descriptions are statistically relevant and independent indicate many of the arene based thiols are configurational diastereoisomers that are not interconvertible, at least prior to cooking.

Figure 8.6.6-11 shows how the various thiols of Tables II and III would appear on a d-value baseline associated with the nominal effectiveness characteristics of the OR 3 and 4 channels used here.

![Figure 8.6.6-11](image)

The stimulants are shown at equal intensity (amplitude below the baseline). The effectiveness characteristics are shown with a nominal width (about ±5.0%). The net intensity at the output of the OR sensory receptor neurons cannot be ascertained from this graph because of the number of variables still not specified. It appears clear that most of these odorophores cited stimulate multiple OR channels resulting in a olfactory pattern at the stage 4 saliency map of more than one dimension (Section 8.6.xxx). The position of the stimulants relative to the OR’s makes it difficult to rationalize or substantiate the “astonishing” semantic descriptors Goeke gleaned from the literature.

The very low human threshold to thiols with d-values in the proposed notch between OR 2 and 3...
suggest the signal processing occurring within stages 2 through 4 of the neural system may treat this region as in the visual system with respect to the perceived color of yellow (or yellow-orange). As here, there is no receptor with peak sensitivity in the wavelength region associated with yellow. Instead the neural system employs two data streams, one representing the logarithmic sum of the medium wavelength and long wavelength sensory neuron responses and the second representing the logarithmic difference between the medium and long wavelength responses. Yellow is the perceived color when the sum (intensity) channel is near maximum but the difference (chromatic) channel is near a minimum.

In his Section 4, Goeke asserts, “The most obvious occurrence of sulfur-containing compounds in flowers is related to those which are bat-pollinated, such as quite a number of nocturnal blooming white cacti, exhibiting intense vegetable- or garlic-like odors. Usually, this olfactory stimulus is supported by conspicuous structures of the flowers that give acoustic guidance for their echo-locating guests.”

The community would be well served by one laboratory repeating many of the psychophysical experiments reported in Goeke using higher purity chemicals, with confirmation by a second laboratory. In both cases, the subjects should be characterized with respect to their specific anosmias if any (both related to step 1, selection, and step 2, measurement of odorophore intensity). Such experiments could effectively employ a shorter list of possible descriptive labels. If these tests were to be followed by an MDS analyses, it would be useful to include the appropriate “preferred odorophores” for the channels of interest in the cohort of stimulants. These preferred odorophores are identified in Section 8.6.2.9.

8.6.6.7.1 Onions, raw and cooked

Widder et al. have investigated the aroma arising from onions in some detail. When raw, they highlight 3-Mercapto-2-methylpentan-1-ol, that was present as two diastereoisomers, as the major odorant based on mass spectrscopy and $^1$H NMR measurements. It exhibits a $d = 4.379$ Angstrom based on the Jmol file of ChemSpider. “The results show that the flavor quality is strongly dependent on the concentration of the compounds. At high concentrations (1 ppm, $10^{-3}$g/L) 3-mercapto-2-methylpentanol causes a very strong and unpleasant odor, which was described as sulfuret, burnt gum-like, sweaty, and onionlike. At lower concentrations (0.5 ppb, $5 \times 10^{-7}$g/L) a very pleasant broth-like, slightly sweaty, onion-like, and leek-like flavor quality could be perceived. The odor threshold of the racemic mixture in water is 0.15 ppb.”

A second component, 3-mercapto-2-methylpentanal that may have been present in two distinct isomers, played a significant role after cooking. It exhibits a $d = 4.308$ Angstrom based on the Jmol file of ChemSpider. “The sensory impression of 3-mercapto-2-methylpentanal also depends on its concentration. In low amounts (5 ppb) it has a very pleasant meaty and roasty flavor profile, whereas at high concentration (1 ppm) its flavor quality was mainly described as sulfuretic, pungent, and meaty. The odor threshold of 3-mercapto-2-methylpentanal is 0.95 ppb.”

Both of these molecules are odorophores and appear on the low d-value side of the limal (OR 4) channel effecitvity characteristic. They would be undistinguishable from each other and other OR 4 channel stimulants in the absence of additional odorophores stimulating other channels. To distinguish onions from grapefruit and other odorant sources, it is probably necessary to recognize additional odorants and/or odorophores.

The resulting bouquet would result in a more complex scent pattern in the stage 4 saliency map. Goeke’s work suggests that many of the molecules of interest exist as racemic mixtures where each component may exhibit a different d-value. As a result, the mixtures are actually semiochemical bouquets containing more than one odorant and/or odorophore. ChemSpider does not currently
support a group of racemic forms adequately to allow determination of their individual d-values easily.

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8.6.7 1st order olfactory labels & odorophores-underlying chemistry

Olfactory research has been impeded greatly by the lack of either of two classifications. The first is a set of unique and non-conflicting labels for perceived scents that are traceable to the underlying physiology and chemistry. The second is a set of readily available odorophores (only stimulating one olfactory channel) that can be used to establish the linkage between the individual OR’s and OR channels and the perceived scents. This work has established the framework for, and identified the members of each of the above classifications. The task at this time is to verify the correctness of these classifications and standardize the names of the perceived scents of human olfaction.

With the framework provided by this hypothesis and its corollaries, SOR/SAR studies can now be undertaken with a much higher probability of producing important results.

8.6.7.1 Proposed set of preferred human odorophores and receptors

[xxx duplicates other preferred odorophore lists]

In prior experiments, investigators have employed a myriad of odorants, many of which supported multiple odorophores, thus stimulating multiple receptors of the human olfactory system. To avoid confusion in future data and data analysis, it is necessary to insure odorants are used that only stimulate a single olfactory sensory neural channel. Figure 8.6.7-1 suggests a fundamental set of these odorants. Where necessary, the next homolog of the recommended chemical may be used but care should be taken not to introduce additional odorophores into a single odorant of a set.

**Figure 8.6.7-1** Proposed fundamental set of human odorophores and candidate receptor molecules.

---

**Figure 8.6.7-2** provides a summary chart showing the identified and proposed fundamental odorophores and gustaphores of chemical sensing and the proposed phospholipid receptors conforming to the Electrolytic Theory of the Neuron. The CLASS designations are meant to conform to conventional usage in the food and fragrance industries. They can be subdivided within the commercial community. However, the Descriptors provided here form a more specific scientific subclassification of these designations.

It is interesting to note the term FLORAL subdivides and is associated with both hedonic flowers and putrid flowers.

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**Figure 8.6.7-2** Proposed fundamental set of human odorophores and candidate receptor molecules.
### Figure 8.6.7.2

A summary of fundamental odorophores and gustaphores with their proposed phospholipid receptors. ADD. TURN ON PAGE. See text.

<table>
<thead>
<tr>
<th>ODOROPHORES/RECEPTORS</th>
<th>CARBONYLS</th>
<th>HERBS</th>
<th>SPICES</th>
<th>FLORAL</th>
<th>ACID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>di-CARBONYLS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SIMPLE</td>
<td>CITRUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td></td>
<td></td>
<td></td>
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<td>Label</td>
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<td></td>
</tr>
<tr>
<td>Typical source</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,3 butane-dione</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2,27</td>
<td>1.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptor</td>
<td>PtdScn</td>
<td>PtdAce</td>
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<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GUSTAPHORES/RECEPTORS</th>
<th>SALTY</th>
<th>SWEET</th>
<th>BITTER</th>
<th>ACID</th>
<th>FECAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Sodium Icn</td>
<td>Glucola</td>
<td>Picrophores</td>
<td>Rancid Oils &amp; Fats</td>
<td>Indexes</td>
</tr>
<tr>
<td>Family</td>
<td>OH-Na-HO</td>
<td>OCOOH</td>
<td>OCOOH</td>
<td>R-COOH</td>
<td>Phenol - N or Phenyl-pyrole</td>
</tr>
<tr>
<td>Label</td>
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<td></td>
<td></td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrated sodium</td>
<td>all sweeteners</td>
<td>Lewis acids</td>
<td>aged Butter</td>
<td>feces</td>
</tr>
<tr>
<td></td>
<td>salt in saliva</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>d-value</td>
<td>3.3</td>
<td>2.5</td>
<td>4.7</td>
<td>2.34</td>
<td>2.757</td>
</tr>
<tr>
<td>Receptor</td>
<td>PtdIns</td>
<td>PtdGal</td>
<td>PtdDg</td>
<td>PtdSer</td>
<td>PtdTrp</td>
</tr>
</tbody>
</table>
Family describes, in very simplified notation, the chemical notation defining the fundamental odorophore or gustaphore eliciting the CLASS or more specifically the Descriptor sensation. The auxiliary descriptors assigned to the Essential oils are primarily illustrative. The distribution of odorants (and odorophores) between parts of plants requires further analysis. The designation CH₃Ar denotes a toluene.

The notation Ar denotes a benzene. The notation HO•Ar denotes a phenol. The symbols following Ar are descriptive of an aliphatic moiety. The OR following Ar does not include OH. The designation +π denotes an X relationship involving a π-bond between two carbons within the AH,B,X concept. Ring positions are not shown in this notation.

Morrison & Boyd [xxx??] have noted that a more appropriate terminology might be to consider the aromatic attached to a carbonyl group as Ar=C=C=O. This conjugated condition could also be shown as Ar=C=C=O where the left-most carbon is a member of the ring. In this case, the two groups would not support a DACB relationship.

A more appropriate definition of the families requires a three-dimensional representation (as used in earlier detailed definitions) to appreciate the stereochemical relationships involved.

A great many odorants and gustants involve multiple odorophores that make their elicited sensation more complex than that of a fundamental stimulant.

Monosodium glutamate is the ideal example of a complex gustant. It exhibits the hydrated sodium ion, the 1,2 equatorial-trans-glycol gustaphore, and the carboxylic acid gustaphores. It does not exhibit a unique umami gustaphore.

Where convenient, a Label is provided describing the primary chemical families most closely associated with the Descriptors. A typical stimulant is shown to provide an easy association with each Descriptor.

A d-value is shown for the chemical structure of each Family derived from its three-dimensional representation. As noted in earlier sections (Sections 8.5.xxx & 8.6.xxx), the signals generated by each sensory channel are treated as independent (and mathematically orthogonal) parameters in taste and odor space. As a result, taste space requires at least three-dimensions for its graphic representation. The odor space is much more complicated and in theory requires more than ten dimensions to describe it graphically at the sensory level. The number of dimensions required to represent odor space following stage 2 signal processing (orthodromic to the glomeruli) is yet to be defined.

Based on d-values, it appears the same receptor, PtdSer, may be employed to capture the carboxylic acid odorophore of smell and the carboxylic acid gustaphore of taste. In a more limited context, it appears the sweet receptor, PtdGal, may be used to capture the sweet gustaphore of taste and the phenol odorophore of smell. Phenol is not generally used as a pleasant odorant because of its toxicity. However, the more complex members of its family predominate among the hedonic odorophores in the botanical world.

No empirical work has yet defined a receptor associated with a chemical sensory neuron. However, the presence of a wide variety of amino acids and phospholipids associated with the dendrites of the sensory neurons is widely reported. These are typically present in trace amounts compared to the principle structural phospholipids, PtdCho and PtdEtn. However, only trace amounts are required. Future exploration needs to focus on these trace amounts while ignoring the presence of PtdCho and PtdEtn.
The proposed receptor phospholipids are generally formed of esters of phosphatidic acid and a sugar, sugar alcohol, amino acid, or variants thereof. The phosphatidyl serine (PtdSer) is believed to form DACB couple with carboxylic acids and therefore perform as the acid receptor in both gustation and olfaction. In some cases, the hydroxyl group of the amino acid participates in the esterification. In other cases, the hydroxyl of the carboxylic acid group participates. These cases are indicated by adding an asterisk to the shorthand designation.

<table>
<thead>
<tr>
<th>DESIGNATION</th>
<th>ACTIVE PORTION OF RECEPTOR</th>
<th>FAMILY of Act. Portion</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR 1</td>
<td>PtdSer# Serine, used as carboxylic acid receptor</td>
<td>Amino acids</td>
</tr>
<tr>
<td>GR 2</td>
<td>PtdGal Galactose, used as glucophore receptor</td>
<td>Sugars</td>
</tr>
<tr>
<td>GR 3</td>
<td>PtdIns Inositol, used as natraphore receptor</td>
<td>Sugars</td>
</tr>
<tr>
<td>GR 4</td>
<td>PtdAsn* Asparagine, used as micophore receptor</td>
<td>Amino acids</td>
</tr>
<tr>
<td>PtdGcn</td>
<td>Gluconic acid, used as ester receptor</td>
<td>Sugars</td>
</tr>
<tr>
<td>OR 1</td>
<td>PtdSer# Serine, used as carboxylic acid receptor</td>
<td>Amino acids</td>
</tr>
<tr>
<td>PtdTrp*</td>
<td>Tryptophan, used as indole/skatole receptor</td>
<td>Amino acids</td>
</tr>
<tr>
<td>PtdTyr*</td>
<td>Tyrosine, used as a simple phenol receptor, d = 5.534</td>
<td>Amino acids</td>
</tr>
<tr>
<td></td>
<td>Used as phenyl-orbital receptor, d = 2.8</td>
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</tr>
<tr>
<td></td>
<td>Used as phenyl-α-carbon receptor, d = 3.65</td>
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<td>Used as phenyl-β-carbon receptor, d = 6.075</td>
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<td>Used as phenyl-δ-carbon receptor, d = 6.435</td>
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<td>&amp; more</td>
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</tbody>
</table>

# A phospholipid receptor shared between the gustatory and olfactory channels, d = 2.276 Angstrom.

The above table of receptors satisfy the neural requirements for perceiving the large majority of all gustaphores, odorants & some odorants discussed in the literature (alone or in combination). Other sensory channel receptors (potentially up to 25 more) have yet to be defined. The majority of these OR’s are based on esters of phosphatidic acid and a sugar or an amino acid.
Providing unique channel labels and preferred odorophores

It is difficult to correlate the colloquial labels used in psychophysical testing in the area of behavioral science. However, the modified table of Masuda & Mihara reproduced above can provide some support. Reading left to right, the columns of that chart show how various chemical families stimulate a series of OR channels based on the step 1 transduction process. Reading down from row to row defines the effect of the dipole potential of the chemicals within a family on the intensity of the perceived signal and therefore the perceived scent and reported semantic label.

A basic feature of the step 2 evaluation is that the character of the perceived scent is highly dependent on stimulant concentration at the olfactory epithelium.

As an example, the OR 2 sensory channel reports a “sweet” sensation at low concentrations near threshold whereas the same channel reports an obnoxious sensation at high concentrations. This range of responses is well documented for indole and skatole in the case of OR 2. These chemicals are found in the sweet smell of jasmine and rose at low concentrations as well as the obnoxious odor of feces at high concentrations. Placing a label on the OR 2 channel is difficult when it is associated with such a wide range of scents; the term sweetness might be appropriate if it is recognized that a lack of sweetness leads to an offensive (fetid) perception. Alternately, the term dulcal is compatible with a range of sweet to sickly-sweet to fetid.

The OR 1 channel is typically associated with the perception of sourness. It shares both the perception, sourness, and the receptor, PtdSer, with the GR 1 channel of gustation. The preferred odorophore for this channel is acetic acid. It is preferred over the simpler, but more toxic, formic acid.

The OR 2 channel shares its range of perceptions with GR 2, ranging from sweet to sickly sweet to obnoxious depending on concentration. Unexpectedly, skatole at low concentrations represents the preferred odorophore for this channel.

The OR 3 channel is labeled floral because of its close association with the hedonic flowers. 1-phenylethanol is the preferred odorophore for this channel.

The OR 4 channel is labeled limal because of its close association with limonene, a preferred odorophore associated with limes and lemons (as well as sour oranges).

The OR 5 channel is labeled musk because of its preferred odorophore, the macrocyclic animal musk, civetone.

The OR 6 channel is labeled cinnamon because of its dominant perception resulting from the primary odorophore, cinnamyl alcohol.

The OR 7 channel is labeled spice because of its general association with a variety of spices that stimulate this channel. The preferred odorophore is 1-hexen-6-ol.

The OR 8 channel is labeled citral because of its close association with various citrus but particularly the “sweet” orange. The preferred odorophore of this channel is citronellal.

The OR 9 channel is putrid because of its association with the putrid flowers, although this designation may be criticized based on the limited purification processes used to isolate the odorophores of these flowers. The preferred odorophore for this channel is 6-heptenal (alternately 6-octenal). [xxx confirm that 4446441 is straight version with d =8.017 Angstrom ]

8.6.7.1.1 Channel perception versus stimulant concentration

Many odorants are known to be perceived differently with changes in their concentration upon application to the olfactory epithelium. This change is primarily related to stage 5 cognition after all of the prior operations of the olfactory modality. A particularly well documented case is that of indole; indole is a significant odorant produced by flowers and is perceived as sweet at the normally encountered low concentration levels. At much higher concentrations, it is considered the epitome
of fetid odors. Figure 8.6.7-3 provides a framework for defining the variation in perceived scent for each individual channel of the olfactory modality based on the results of both steps 1 and 2 of transduction. Such variation in intensity of stimulation (step 2) on a channel-by-channel basis (step 1) provides for a wide variation in perceived scents when multiple channels are stimulated simultaneously. This result is in line with the combinatorial signal processing proposed here and becoming the accepted conception of olfactory modality operation within the community. The figure shows several labels in lighter type related to low concentration levels. The semantic literature has suggested the labels shown based on totally empirical observations by subjects who have not been presented any theory-based framework (Section 8.6.2.5.8). The labels must be considered anecdotal in character. The labels shown as derived from the Jmol and/or JSmol files in the ChemSpider PDB of 2015 are based on the d-value parameter developed in this work. The difference between the semantic and Jmol labels appears to be due to an inadequate definition of the limal and citral channels during the early semantic work (also Section 8.6.2.5.8). In the future, more precise labels are anticipated based on crystallographic studies of liquid-crystals of specific molecules, preferably single odorophore odorants (SOO).

<table>
<thead>
<tr>
<th>High conc. (Sweaty)</th>
<th>Fetid</th>
<th>Lemon</th>
<th>Musky</th>
<th>Chemical solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel</td>
<td>Acidic</td>
<td>Dulcal</td>
<td>Floral</td>
<td>Limal</td>
</tr>
<tr>
<td>#</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Low conc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic literature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jmol/JSmol files</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Future crystallog.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 8.6.7-3 Perceived scent by channel as a function of odorophore concentration. Many of the labels in smaller type are highly anecdotal. These values are subject to modification over time. The table requires a series of tailored psychophysical experiments to complete. See text. It may be necessary to describe intermediate concentration level. Channel #1 is shared with the gustatory modality, at least in most mammals.

The protocol used to complete the above table needs to be carefully constructed. It needs to recognize the difference between detection and recognition. Detection of an odorophore is generally associated with the threshold value in the literature. The recognition of a specific scent associated with that odorophore generally occurs at five to ten times the threshold concentration. This level will be defined as the low concentration recognition level. As noted for all sensory neurons documented so far, they perform a logarithmic conversion that effectively compresses the output signal range but maintains the information content of the signal. They also adapt rapidly to accommodate a major change in stimulus concentration. This requires that the concentration level be increased in steps of under 200:1 to avoid adaptation. But the total signal range allowed before saturation in the transduction process is more typically 1000:1 or more. Thus the concentration range should be raised in steps no greater than 100:1 after allowing equilibration at a specific level for at least ten seconds. The result should be a stair-step pattern not unlike that used by Avenet & Lindeman (1989) in exploring the taste cells (Section 8.6.1.1). Note the adaptation process underway near the end of each 30 second interval in their representations. The subject should report his/her
perception of the scent after between five and ten seconds exposure from a very select list of terms that only includes perceptions expected for that individual channel. Complex terms such as “woody,” should be reserved for later tests involving odorants stimulating more than one odorophore channel. The total range covered should exceed at least 1000 times the low concentration recognition level.

At high concentrations, the acidic channel appears to be perceived as sweaty based on Amoore and comments by Beets concerning the Amoore papers. Their comments would suggest the different dipole potentials among their chemicals would account for the difference in the perceptual intensities among the acids.

Johnson & Leon, 2000, quote Arctander regarding the affect of concentration on the perceived odor for several chemicals. “Humans report that low concentrations of pentanal evoke a dry-fruity or nutty odor, whereas high concentrations evoke a more acrid and pungent odor. Humans also report that aliphatic ketones similar to 2-hexanone smell ethereal, spicy, or fruity at low concentration but have more pungent, ‘chemical,’ or solvent-like odors at high concentrations.” As usual, these are very wordy semantic descriptions but they suggest the scope of the changes. It is likely that pentanal_7772 and 2-hexanone_11095 were present in a hydrated form since neither exhibits an odorophore as isolated molecules based on the hypothesis of this work.

A question arises concerning the label for the OR 1 channel. Should it be called pungent as more general than acidic and thereby allow the use of the term acidic at one point in the intensity spectrum for the channel and “sweaty” for a different point along the intensity spectrum? Is sweaty properly described as acidic or just pungent? A common definition of pungent is commonly taken as a sharp, acrid sensation. Thus pungent is related to the scent, a response, and not the form of the stimulating chemical. A range of chemicals, such as the acetates stimulate OR channel 1 but are not acids (although they still exhibit the overlay moiety of the carboxyl group. Expanding the chosen term to other semantic terms, acidophore appears easier to say than pungenophore, pungenophore or pungophore. An additional option is to choose between carboxyl and acidic, since it is the carboxyl overlay moiety that is determinative. Carboxophore is also semantically easy. It would also clearly eliminate the inorganic acids as stimulants to this channel.

Kolor explored the scents and flavors of several mercaptons and noted, “It is well recognized in the flavor industry that variations in the concentration of certain chemicals can have a dramatic effect on their flavor characteristics. Ethyl 3-mercapto propionate, which has a flavor threshold in water of 0.2 ppm, is a very good example of this phenomenon. At low concentration levels it has a very pleasant, fruity, grapey character, while at higher concentrations its aroma takes a skunky or foxy, animal-like aroma.” This chemical has d-values of 2.280, 4.457 and 5.242 Angstrom, stimulating the OR 1, 4 & 5 channels respectively. It is hard to associate his position with the above figure since so many OR channels could have been stimulated in a given trial. Its perceived scent may be transitioning along several different paths. It may be transitioning from a perception of geranium to lemon within channel 4. It may be transitioning from geranium to musky within channel 5. Alternately, it may be transitioning from the limal characteristic of OR 4 being dominant to the musk characteristic of OR 5 as the concentration is increased. Clearly a more precise association of geranium with a sensory channel is required in this area.

8.6.7.2 Proposed dendrogram & “smell space” for large human populations

From a structure perspective, it is appropriate to separate the odorants into separate major groups;

1. aliphatic structures
2. aromatic structures (derived from benzene)
3. fused aromatic structures

Each of these major groups introduce different electronic and/or quantum mechanical mechanisms into the olfaction process. The aliphatic-aromatics, or arenes, are considered aromatics in this


grouping because the $\pi$-cloud of the benzene ring plays a major operational role in defining the associated odorophores.

Within these major groups, several families can be defined based on their well recognized chemical structures. A variety of oxygen-based and nitrogen-based groups play major and distinct roles. These can generally be organized by the lowest molecular weight members of the group first. As the molecular weight of a chemical increases within a major group, the number of odorophores in the chemical generally grows.

The lowest molecular weight member of some of these families are odorants that are decidedly toxic and cannot be readily used in human behavioral experiments.

At a point, the typical chemical incorporates features of several families of the major groups defined above. The description of these chemicals requires a matrix approach, and the number of odorophores present in a specific chemical tends to grow.

The theory developed here has not addressed the fused aromatics. Hence the following material will not include them, even though they are very important odorants.

Since a degree of solubility is required in both gustation and olfaction, the opportunity for hydration through coordinate bonding is always present. In many cases, the properties of simple molecules and ions cannot be explained without recognizing their hydrated state. The hydration of the sodium ion is a prime example. Hydration of the carbonyl group is frequently important.

Olfaction is primarily a process involving organic chemistry. However, it is dependent on the phenomenon of coordinate chemical bonding. The capability is shared among a small variety of “inorganics.” For purposes of olfaction, molecules containing the atoms of oxygen, nitrogen, sulfur and phosphorous will be considered as organics if they can share their non covalently bonded electron-pairs with the bio-organic molecules of the sensory neuron receptors.

The dendrogram (sometimes cladogram) is ideally used for material involving continual bifurcation into two new materials and little or no recombination among the individual materials appearing farther up the tree. It is not well suited for representing materials resulting from the recombination of multidimensional material (crossbreeding among different species, and even orders or classes of animals as an example). Its only utility in olfaction is in going back to an unfolded graph of d-values and ordering a group of chemicals that stimulate the same two adjacent OR's through identical step 1 selection but different step 2 intensity parameters in a “real” perceived intensity versus d-value space. Alternately an ordering of chemicals that stimulate two non-adjacent OR's through identical step 1 selection but different step 2 intensity parameters in a synthetic perceived intensity versus d-value space (as described when discussing the multidimensional spaces of MDS in Section 8.6.6).

The failure of the dendrogram to adequately handle material formed by interaction of elements from a multidimensional space surfaces another important fact.

The bifurcation of a species into two new species is much more than a morphological event. It is primarily an event related to the basic DNA. Generally after the first bifurcation, and certainly after additional bifurcations, the resulting species can no longer interbreed (regardless of their morphology).

From Wikipedia: A hybrid animal is one with parentage of two separate species, differentiating it from crossbred animals, which have parentage of the same species. Hybrids are usually, but not always, sterile.

One of the most ancient types of hybrid animal is the mule, a cross between a female horse and a male donkey or ass. The tiger is a hybrid cross between a male lion and female tiger. The yattle is a cross between a cow and a yak. Other crosses include the tigon (between a female lion and male tiger) and yakalo (between a yak and buffalo). The Incas recognized that hybrids of Lama glama (llama) and Lama pacos (alpaca) resulted in a hybrid with none of the advantages of either parent.
Figure 8.6.7-4 illustrates two dendrograms (A & B); one employing a real d-value scale (A) and one a synthetic proportional scale (B). Frame can be used in two ways. First, the lower primary odorophore can be assigned to OR 1 and its perceived scent established. Then, the upper primary odorophore can be assigned to OR 9, ignoring the equation shown next to the upper primary odorophore) and its perceived scent established. Then the remaining primary odorophores can be used as stimulants and their perceived scents established, thereby establishing the entire spectrum of perceived scents for the set of primary odorophores (and their known d-values) for a given set of odorophore concentrations.

Second, the d-value scale can be expanded to range from a selected primary odorophore to an adjacent primary odorophore (using the equation shown next to the upper primary odorophore) established in the above test sequence. The perceived scent of the two primary odorophores are also available from the above test sequence. Then a family of odorants, each exhibiting only the two selected primary odorophores, but exhibiting different dipole potentials can be used to establish the perceived scent of each of these chemicals. The goal is to order the samples according to their perceived scent (not their intensity). If at least some of the dipole potentials are known, the scale between the two primary odorophores can be calibrated as linear or given by some other function.

Frame (C) can be used to evaluate a family of odorants with a single odorophore (or a pair of
odorophores) but different dipole potentials. Pelosi, Pasqualetto & Lorenzi\textsuperscript{292} have provided a paper describing a family of ten thiazoles exhibiting only one odorophore but with a variety of different dipole potentials. The family should provide a good example of the use of this graph based on a real dipole potential scale (assuming the purity of their samples was sufficiently good). The samples all exhibit a nominal $d = 2.457$ Ångstrom but drastically different dipolar potentials based on their structure. The olfactory threshold of the family vary by a factor of one million to one. The simplest member of the family, a thiazole with two simple aliphatic side chains, had the lowest threshold by a factor of 100:1. The two members with the lowest threshold both were perceived as bell pepper-like. The members with considerably higher thresholds were perceived generally as rubber-like. The family included two isomers with a difference of 150:1 in threshold. Pelosi, Pasqualetto & Lorenzi focused on the mass spectrometric measurements of their materials but did not show that those measurements were descriptive of the odorants. While their abstract says eight carbon atoms must be attached to the thiazole ring for optimum perceived bell pepper scent, their text suggests seven or eight.

Detailed experiment protocols for these frames must be developed by the laboratory investigator.

**Figure 8.6.7-5** - - - In this figure, the notation $Ar^+$ or $+Ar$ will be used to describe the vector distance between the center of the aromatic ring and the carbon forming the terminal point of the aliphatic side chain of interest.

<table>
<thead>
<tr>
<th>Class</th>
<th>Basic Odorant</th>
<th>Odorophore</th>
<th>d-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Res. aliphatic acids</td>
<td>$\text{ROO}$</td>
<td>$O=\overset{\sim}{C}=O$</td>
<td>2.07</td>
</tr>
<tr>
<td>Aliphatics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliphatic carbonal ester</td>
<td>$\text{RCOOR}'$</td>
<td>$O=\overset{\sim}{C}=O$</td>
<td>2.26</td>
</tr>
<tr>
<td>Hydra. aliphatic acids</td>
<td>$\text{RCOOH+H}_2\text{O}$</td>
<td>$\overset{\sim}{O}=\overset{\sim}{C}=\overset{\sim}{O}$</td>
<td>2.34</td>
</tr>
<tr>
<td>Hydra. aliphatic alcohol</td>
<td>$\overset{\sim}{O}=\overset{\sim}{H}=-\overset{\sim}{O}_2$</td>
<td>$-$</td>
<td></td>
</tr>
<tr>
<td>trans-di-carbonyl</td>
<td>$\text{RCOCOR}'$</td>
<td>$O=\overset{\sim}{C}=\overset{\sim}{O}$</td>
<td>3.61</td>
</tr>
<tr>
<td>Aromatics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatic $\alpha$-alcohol</td>
<td>$\text{Phenol}$</td>
<td>$Ar^+C-OH$</td>
<td>2.82</td>
</tr>
<tr>
<td>Aromatic $\alpha$-ketone</td>
<td>$\text{Menthone}$</td>
<td>$Ar^+C=O$</td>
<td>?</td>
</tr>
<tr>
<td>Aromatic carboxylic ester</td>
<td>$\text{ArCOOR}'$</td>
<td>$Ar^+C=O &amp;$</td>
<td>3.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$Ar^+C-O &amp;$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$O=\overset{\sim}{C}=O$</td>
<td>2.26</td>
</tr>
<tr>
<td>Aromatic $\gamma$-ether or alcohol</td>
<td>$2\text{-phenyl-ethanol}$</td>
<td>$Ar^+C-C-OR$</td>
<td>5.07</td>
</tr>
<tr>
<td>Amines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydra. ammonia or pri. amine</td>
<td>$\text{RN}_2\text{H}_2\text{O}$</td>
<td>$N-\overset{\sim}{H}=O$</td>
<td>2.82</td>
</tr>
<tr>
<td>Amino acids, alcohol</td>
<td></td>
<td>$\overset{\sim}{O}=\overset{\sim}{C}=\overset{\sim}{N}$</td>
<td>2.25</td>
</tr>
<tr>
<td>carboxyl</td>
<td></td>
<td>$\overset{\sim}{O}=\overset{\sim}{C}=\overset{\sim}{N}$</td>
<td>2.18</td>
</tr>
</tbody>
</table>

**Figure 8.6.7-5** INCOMPLETE A comparison of “basic” odorants with Wise et al., figure 5. The primaries of Wise are actually reference odorants from Amoore (1969). See text.
Figure 8.6.7-6 illustrates the general situation in olfactory chemistry that contributes to problems in defining families of odorophores. Beyond a small molecular weight, members of a family tend to take on additional chemical groups from outside the immediate homologous series (especially among the arenes). The result are odorants that are no longer homologous with their parent and frequently exhibit multiple odorophores.

Groups of arenes frequently appear to be homologs globally but are clearly heterologs at the detailed level.

While the figure portrays this feature as continuous, it is clearly stepwise in character. A second complication is that many of the family protologs are either caustic or at least toxic. Thus experiments utilizing the protolog of a family may not be feasible. Boeckh has shown that the lower molecular weight members of a homologous series tend to be less stimulative based on the odorant concentration in air. Optimum sensitivity in the case of fatty acids occurs at a chain length of six carbons.

Figure 8.6.7-6 The character of homologous and heterologous odorants ADD.

8.6.7.2.1 Correlation with the empirical database- a set of SCO’s

Amoore provided two important contributions to the olfactory puzzle in 1969. He attempted to correlate the various names given to sensations (in English) with each other and with potential odorophores. He also collected and analyzed data on anosmia in humans. By detailing the failed olfactory sensory channels, the proposed semantic terms in the above figure can be confirmed.


| Table II of Amoore, and accepting alternate chemical names for some of the entries, several classes of odorophores can be drawn from his census of earlier investigators. Using his numbers, Figure 8.6.7-7 shows a set of classes that appears reasonable.

<table>
<thead>
<tr>
<th>Amoore's line number</th>
<th>Consensus semantic</th>
<th>Primary odorant</th>
<th>Primary odorophore</th>
<th>Primary d-value</th>
<th>d-value assoc. with anosmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Spicy</td>
<td>Salicylic aldehyde</td>
<td>Ar+O=C=O</td>
<td>3.68</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Minty</td>
<td>Menthone</td>
<td>Ar+C=O</td>
<td>2.61</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Citrous</td>
<td>Citral A</td>
<td>O=C–C+π</td>
<td>2.96</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>Floral</td>
<td>2-phenylethanol</td>
<td>Ar+O=C–OR</td>
<td>5.07</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>Fragrant</td>
<td>(undefined)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Musk</td>
<td>Macrocyclic musks (4)</td>
<td>O=C....C=C</td>
<td>5.13, OR 5</td>
<td>Yes</td>
</tr>
<tr>
<td>23</td>
<td>Burnt</td>
<td>(undefined)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Fecal</td>
<td>Indole (high concen.)</td>
<td>Ar–N</td>
<td>2.74, OR 2</td>
<td>Yes</td>
</tr>
<tr>
<td>33</td>
<td>Acid</td>
<td>Acetic acid</td>
<td>O=C–C=O</td>
<td>2.27, OR 1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrated carbonyl</td>
<td>HO–C–OH</td>
<td>2.34</td>
<td></td>
</tr>
</tbody>
</table>

Salicylic aldehyde is shown with two odorophores. The second correspondsto phenol by itself, more specifically benzene hydroxide. While toxic and caustic, phenol appears to form the base for a variety of, but not all, aromatic compounds eliciting sensations related to organic flowers and fruits.

This work has not explored the electronic structure of fused-aromatic or fused-cyclic structures. Indole appears to be the protolog and skatole being the second member of the family, both elicitings a sensation of fecal matter. Both exhibit a aromatic ring fused to a heterocyclic pyrrole ring with nitrogen substituted into the pyrrole ring (Momson & Boyd, pg 1081). The heterocyclic ring exhibits aromatic properties. As a result, these chemicals exhibit two \( \pi \) -clouds that are technically able to share electrons but also interact due to their shared C–C arrangement.

All of the classes identified in this table were found lacking in specific groups of anosmics, providing supporting evidence for the existence of these classes of independent olfactory sensory channels. Amoore described his identification of individual anosmics as of limited statistical value, but he did attempt to establish that each subject was not anosmial to more than one of the chemicals in his listings. This would suggest his subjects could be thought of as a group of “knock-out” humans with
individual defects of one underlying cause or another.

The above figure would suggest a multi-dimensional space of not less than ten dimensions, but probably not more than the nominally twenty dimensions suggested by the number of glomeruli in the human olfactory bulb. The additional channels are used to sense fused- aromatic structures and some amine structures (although some of the latter d-values may overlap the d-values of the above figures and be sensed by the same sensory receptor). It may also include one or more pheromone receptors in any human auxiliary olfactory bulb (Section 8.4.3).

As noted in Section 8.6.4.2, an alternate set of preferred odorophores can be created using a group of amino acids that are known to stimulate various OR channels and may in fact form a dimer with the same putative amino acid used as the esterified receptor of the OR.

All of the identified primary odorants employ odorophores with distinctly different d-values and each is separately identifiable by a properly configured sensory channel neuron receptors. Such identification does require the individual receptors to exhibit a narrow d-value acceptance range as discussed earlier (Section 8.xxx).

A full investigation, using a statistically adequate number of subjects, by multi-dimensional scaling (MDS) of the proposed primary odorants should provide significant information about the dimensionality of human olfaction.

### Effect of conjugation on the d-value

Figure 8.6.7-8 from Tieman et al. (2007) illustrates the effect of conjugation of a set of planar phenylaldehydes. In all cases, the d-value is taken from the centroid of the electron cloud of the aromatic group and the single orbital present as calculated by DS3.5 using the .mol files from ChemSpider.com. Note the ridiculous nature of three different naming conventions for three clearly related pseudo-diols. By a strict reading, none of these are phenols (with a hydroxyl attached directly to the aromatic ring). The label cinnamaldehyde is obviously a common name, not a scientific name. The label 2-phenylacetalddehyde while widely used does not appear to the systemic name for this chemical. The systemic names are notoriously difficult to pronounce or to comprehend. The only way to accurately identify these chemicals is using one of the many assigned numeric codes. However, these are currently highly inconsistent. The ChemSpider codes are shown because they have the advantage of coming from a single managed source.

A point to note is the asymmetry of these structures relative to a line drawn from the center of the ring structure through the orbital. The length of this dimension (equal to the defined d-value) can only be determined by measuring all of the actual individual bond angles and bond lengths. The use of an equivalent bond length corresponding to a conjugated carbon chain suggesting a one and one-half bond value between pairs of carbons, C=—C=—C configuration, is probably not wise.

Kaiser has recently produced a beautiful book.
on the “Meaningful Scents around the World295.” The work includes a listing of all of the chemicals obtained from each of their gas chromatography analyses of the material collected in their adsorption traps acquired in situ, frequently within the canopy of the rainforest or other difficult locations to reach. Unfortunately, it only addresses natural (botanical) odorants but the color photography is excellent. It is a unique resource from at least two perspectives. It provides a single consistent numerical listing of 232 chemicals accompanied by their Zig-Zag (Lewis Diagram) version of a Fischer Diagram. The index provides a formal listing of these diagrams based on their systematic (IUPAC) chemical names. More constraining is the absence of any 3D structural representations of these molecules that would allow determination of the $d$-values of each compound and thereby a specification of each odorophore within a given odorant. With time, it should be possible to analyses the major odorants more completely and associate their individual odorophores with the perceived olfactory names provided based on psycho-physical experiments.

Kaiser also provides selective mass spectrometry information, but he does not relate that information directly to the olfaction mechanism.

8.6.7.3 Overview of the complete olfactory modality–stage 2 and higher ADD

Before summarizing the operation of the olfactory modality, it is important to have some understanding of the overall modality. This section will provide a brief overview of the material appearing in detail in subsequent chapters. Dawson et al. provided textual material on olfaction with several conceptual schematics in 1988296. By analogy with other modalities, their figure 1 suggests that their glomeruli are primarily sites of stage 2 signal summation and their tufted and mitral cells are equivalent to the stage 3 encoding neurons of the visual modality. The material in Margolis & Getchell does not support the grand title of that work. Schab & Crowder have edited a book containing considerable discussion of the later stages of olfaction but lacking a detailed schematic model297. They provide considerable information resulting from psychophysical experiments, clinical observations and surgical interventions (lobotomies in particular).

Laing, Doty & Breipohl have edited a volume presenting brief discussions on the architecture of the overall olfactory modality in the context of the total neural system298. Figure 8.6.7-9 reproduces Fig 3 of the paper by Shiley & Reyes in that volume. It portrays the major signal flow paths of the modality. They provide some additional detail in their fig 4. They did not address the vomeronasal and auxiliary olfactory bulb.


8.6.7.3.1 The morphology of the olfactory modality in the CNS

Shiley & Reyes accompanied the above figure with a good discussion of the morphology of the olfactory modality within the CNS. They specifically noted the complexity of the anterior olfactory nucleus (AON) that is now recognized to be a distinct cortical structure containing a significant amount of white matter running through it, much like between the two major portions of the thalamus.

Figure 8.6.7-9 Major efferent connections of the olfactory system ca 1993. OE; olfactory epithelium. MOB; main olfactory bulb. AON; anterior olfactory nucleus. From Shipley & Reyes, 1991.
8.6.7.3.2 Interconnection of the neurons of stages 1 and 2

[xxx add other historical papers]

Mark A. Johnson et al. have written on the form and interconnection of the sensory neurons and the neurons of the glomeruli from a largely genetic perspective. The material includes a variety of imagery, however, the paper is largely textual and conceptual, suggesting how things must be rather than how they are. They speak of a third group of receptors that they describe as belonging to a distinct olfactory modality beyond the primary and vomeronasal subsystems.

They discuss a variety of genes that are expressed in mice by creating receptors on the surface of both the cilia of dendrites and the axons of olfactory sensory neurons, OSN. The paper attempts to organize considerable material from other sources into a coherent scenario. They describe the specialized receptors as trace amine-associated receptors, TAARS and make the conventional assertion, “TAARs belong to a distinct and evolutionarily conserved family of G protein-coupled receptors that are distantly related to biogenic amine receptors and not related to ORs.” It discusses highly volatile and aversive amines “such as 2-phenylethylamine, a carnivore odor that repels rodents, and isoamylamine, a leucine metabolite that is avoided by mice.” They make many global statements that appear to lack detailed support, “Here, we show that TAAR OSNs are similar to OR OSNs in some regards, but also have some unexpected and unique features. Like ORs, TAARs are localized to cilia, where they can detect odors, and also to axons. TAAR OSNs project to discrete glomeruli, but the OSNs expressing each TAAR form four to six glomeruli per bulb, whereas OR OSNs converge on only two glomeruli per bulb. Most of the TAAR glomeruli are confined to a specific region in the dorsal OB. Surprisingly, TAAR OSNs express the olfactory cell adhesion molecule (OCAM), which is predominantly expressed in OSNs that project to the ventrolateral OB.”

The two aversive amines mentioned do not appear to be particularly aversive to humans. The phenylethylamine has one odorophore with a d-value of 5.104 Å that is perceived as musk-like by humans and presumably rodents. Isoamylamine, more formally known as isopentylamine, is a an irritant to the skin and mucous membrane and therefore a noxious chemical affecting the nocent modality (probably in place of the role suggested by MA Johnson et al.). It exhibits no odorophore in the context of the hypothesis of this work. It is possible it may become hydrated within the mucosa at very low concentrations.

No information is provided on the chemical character of their receptors (other than they are putative members of the G-protein family) or the operating mechanisms associated with the OSN.

Much of the material suggests to this reader that they are working with genes that support creation of cell elements unrelated to the chemo-receptor role. Many passages are typically indirect, “The high levels of dendritic expression strongly support the proposed role for TAARs as bona fide receptors for volatile amines in the environment.”

8.6.7.3.3 Areas of the glomeruli responding to particular odorophores

Brett A. Johnson et al. explored the effects of double and triple bonds of selected odorants, primarily acetates but including octanoic acid, in the glomeruli of rats in 2007. Their results are important and they took major precautions in developing their protocols in the absence of a theoretical framework. As expected, their discussions are couched in the framework of functional chemical groups rather than the “overlay moieties” of this work. Their wording occasionally points in the direction of multiple hydrogen bonds as a requirement for some of their intermediate conclusions.

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The Johnson et al. paper is based on the more detailed 2006 work of Ho et al\(^\text{301}\). of the Johnson group. They, have explored the role of the triple bond, C=C, in olfaction. Their figure 1 shows the progression of the position of maximum signal in the glomeruli with progression from a single bonded to double bonded to triple bonded odorant. The triple bonded methyl 2-octynoate\_7801 stimulated the glomeruli of the rat at the interface between areas d & g and D & G of the anatomically standardized contour charts used by the Johnson group. The primary odorophore appears to be the carbonyl ester that appears in all three of their odorants. However, the progression with level of bonding does indicate the importance of the multiple bond relationship to the carbonyl oxygen in forming a new odorophore. For the carbonyl oxygen to C=C odorophore, the d-value is 2.654\text{ Å} compared to the 2.180\text{ Å} of the carbonyl oxygen to oxygen odorophore. The 2.180 Ångstrom odorophore primarily stimulates the acidic channel via OR 1 while the 2.654 Ångstrom odorophore stimulates the dulcal channel via OR 2. The paper also reported on 1,7-octadiyne\_63287 which is a linear aliphatic chemical containing two triple bonds but no other orbitals. It has a d-value of 7.262 Ångstrom and would be expected to stimulate the citral channel via OR 8 most strongly. The 2007 paper of Johnson et al. supported the Ho work (of the same laboratory) asserting, “These data suggest that the olfactory system may recognize the triple bond in these molecules as a distinct molecular feature.”

**Problem**—The d-values shown in the above paragraph were obtained using DS 3.5 visualizer and the most recent Jmol file (Mar 2015) for methyl 2-octynoate\_7801. They differ from the values in the following figure obtained with the same visualizer program but an earlier version of the Jmol file downloaded in the July 2014 time period. Manual calculations using the bond lengths in the most recent Jmol file and displayed in the DS 3.5 visualizer give a d-value of between 2.997 and 3.001 Ångstrom before rounding. The differences in value do not appear to change the stimulated OR channel based on the analysis presented here.

All of their chemicals are described by their CAS numbers. The purity of the best chemicals available are at best marginally adequate when exploring their performance at the ppm or ppb level. Their discussion is a gold mine of information. However, their Conclusions section is quite brief. The results may not be statistically precise due to several factors;

1. the number of animals examined
2. the involved concatenation of statistical calculations used to arrive at their factor analyses
3. their practice of superimposing their maps of the glomeruli to achieve standardization
4. the purity of the chemicals available.

However, these papers continue to move the empirical database forward.

Table 1 of Johnson et al. continues to accumulate lengthy semantic descriptions of perceived odors (scents) that exhibit little organization and even add new contributions, like “‘wet’ seashore” coupled with sweet rosy and refreshing.

Their radiographic technique for recording activity in the glomeruli necessarily requires long stimulation intervals (45 minutes), with the resulting adaptation profile of the sensory neurons reducing the signal arriving at the glomeruli over time.

**Figure 8.6.7-10** shows the d-values for octanoic acid and the three methyl octanoate forms used. Each form includes a carboxyl overlay moiety as an odorophore with a d-value between 2.277 and 2.330 Ångstrom. These moieties all stimulate the OR 1 receptor. Octanoic acid and methyl octanoate only excite this olfactory channel. The two unsaturated carbon bonds introduce additional odorophores. The double bond in methyl 2-octenoate exhibits two additional odorophores at d = 2.461 and 3.061 Ångstrom. The triple bond in methyl 2-octynoate exhibits two additional odorophores at d = 3.099 and 3.188 Ångstrom.

Three variants of methyl octanoate and their d-values. A; octanoic acid_370. B; saturated methyl octanoate_7800. C; methyl 2-octenoate_4516683. The bond at position 2 is a double bond. D; methyl 2-octynoate_7801. The bond at position 2 is a triple bond. Note the systematic differences in the d-values. See text.
Figure 8.6.7-11 illustrates how the above odorophores stimulate the proposed OR channels based on the d-value graph of Section 8.6.2.8.1. The actual effectiveness characteristics of each channel remain subject to further verification.

As indicated by Johnson et al., 2007 (pages 5-6), human perceive different odors associated with the order of the chemical bond at certain locations in a molecule, and their mathematical manipulations led to the following assertion, “These data suggest that the olfactory system may recognize the triple bond in these molecules as a distinct molecular feature.” They did not indicate how this difference was recognized within the olfactory modality. Here, their difference in d-values in the region of OR 2 and OR 3 would clearly lead to different perceived odors based on stage 2 combinatorial signaling.
It is clear that octanoic acid and its derivative molecules all stimulate the OR 1 channel. It is likely that both methyl 2-octenoate and methyl 2-octynoate also stimulate both the OR 2 and OR 3 channels to varying degrees. This information can be compared to Figure 8.6.7-12 from Johnson et al., showing the areas of the glomeruli of rats responding to these stimulations based on \([^{14}\text{C}]\)2-deoxyglucose uptake experiments. Earlier papers have described the symmetry of the two olfactory glomeruli and beginning with the 2000 paper, they note, “The arrays from the left and right bulb of a given rat were averaged. These average arrays then were subjected to different transformations depending on the analysis to be performed.”

The modules frame on the right originated in the Johnson et al., 2002 study. By overlaying the other maps with this frame, it can be seen which module of the glomeruli is most affected by a given stimulant.

![Radiographic maps of the glomeruli of rats under stimulation](image)

**Figure 8.6.7-12** Radiographic maps of the glomeruli of rats under stimulation ADD. Patterns represent averages of z-score standardized data matrices from several rats exposed to the same odorant condition. See text. Modified figure 1 from Johnson et al., 2007.

The module labeled with upper case A overlays the hot spot related to octanoic acid quite well, suggesting this module is the focus of OR 1 channel activity in the glomeruli (As noted by Johnson et al., the modules labeled with lower case letters in the glomeruli are paired with modules in the lower half labeled with upper case letters). Thus the two open arrows point to A and a respectively. While A appears to reflect considerable activity, a is largely out of the plane of the radiographic recording film. Note regions a and c also appear along the bottom of the figure as well as at upper left.

The appearance of lowercase a and c regions at two different places in their module map suggests a better understanding of the derivation of the map is desirable. This is particularly true in the light of their 2002 paper\(^{302}\) showing two distinctly different maps (Figure 8, frames C & D). They discuss the history and merits of both variants after noting their (ventral center) variant was a redraw of an earlier one and the other (dorsal center) variant has been used by a competing group of researchers. The ventral center variant of 2002 does not incorporate the n, o, p & P modules of the 2007 variant. The dorsal center variant also lacks these more recent module designations.

They then explain how their module boundaries were determined. The details of this complex

graphic/mathematical process is described in a 1998 paper. This paper also shows the process of moving from the morphology of the glomeruli shown in Section 8.6.1.4 to their module map. In that paper, they clearly embrace the combinatorial approach to olfaction, “In conclusion, the present results are consistent with a combinatorial mechanism of olfactory coding wherein unitary responses of olfactory receptors to odorant features would produce spatial patterns of bulbar activity that are characteristic for a given odorant.” The 1998 paper relies upon an even earlier 1996 paper, including a discussion of two early experiments helping to define their eventual protocols. It also defines the straight edges along the rostral and caudal sides of the module maps. The width of the maps is approximately 3 mm in the Wistar rats employed.

The 2002 paper also discusses the distortions inherent in a 2D representation of a 3D object and the limitations on the accuracy of the module boundaries due to the complexity of the statistical processing they employ (even to the point that some of the modules may be subject to the identification of sub-modules at a later day). The paper stresses their reliance upon the concept of functional groups as principle stimulants in olfaction but recognize that some stimulants do not contain any oxygen atoms and do not exhibit any identifiable functional groups previously associated with olfaction. Several statements are made about potential options to their concept that are compatible with the hypothesis and corollaries of this work. Their observation that increased carbon number support the activity in the glomeruli moving to more rostral points. A major limitation on their experiments and the resulting analyses is the limited maximum number of carbons in the chemicals they explored (figure 1). This limited them to OR channels 1 to about 6. Beyond OR 6, the actual site of activity moves back in a caudal direction based on this work. On page 183, they describe the perceived scents of a variety of acetates without developing why they smell so differently. They also fail to note that these acetates share their properties with the carboxylic acids from which the aceta structure is derived by esterification. This may be because they draw the esterification oxygen in row four of figure 1A on the opposite side of the carbonyl oxygen from the hydroxyl oxygen of the carboxylic acids in the first row. As in the case of the 2007 paper, the 2002 paper remains a goldmine of information awaiting a re-analysis based on a more comprehensive theory such as presented in this work.

At the end of page 187, the 2002 paper employs “exclusive or” logic to uniquely identify a given stimulant from its module pattern in the glomeruli. This method does not rely on any understanding of the underlying mechanism and was not employed beyond modules c/C. They also noted certain anomalies with regard to the i/I modules. Their Table 2 provides some interesting correlations of chemicals with similar perceived odors based on their z-score correlation statistics but no explanation of why. They begin to close their discussion on page 192 with the statement, “There is no evidence that animals perceive separately the individual functional groups (or other molecular features) that comprise any individual odorant. That is, although we can classify odorants as ketones or acids by looking at the spatial activity patterns, there is little evidence that the olfactory system uses this classification to generate odor perceptions.” This statement is very strong as long as one considers functional groups to be the foundation of olfaction. It loses importance if the investigator is open to considering “overlay moieties” as the foundation of olfaction. They also make the statement that, “Any simple relationship between bulbar spatial activity patterns and odor perception would be somewhat surprising, given the further processing that must occur in olfactory cortical areas, where the tidy segregation of activity into glomerular modules is further divided into distributed patches.”

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Johnson and colleagues examined the intensity distributions associated with the 2-DG radiograms of a wide list of low molecular weight volatile molecules in order to determine their map. The intent appears to have been to identify the perimeter of the area responding to different chemical groups. In their 2002 paper, they noted, “all 14 of the carboxylic acids we had studied previously (Fig. 1A) activated glomeruli in the anterior, dorsal part of the bulb, which we have labeled module “a” (Fig. 2). Every acid also activated a corresponding dorsomedial module ‘A’.” When comparing the data in their Fig. 2 and with later material in the 2007 paper, it is clear that the “hot spot” associated with a specific type of stimulant moves about within the area of a and A, suggesting the perimeters define a mesa-like area lacking a distinct centroid. This situation can be expected due to the amount of statistical calculation and the relatively small number of stimulants and the few subjects employed to define each module. It is also seen in module b/B that they associate with the aldehydes. The aldehydes they illustrate in 2002 did not fit well within their b/B module and several exhibit no significant hot spot. This is to be expected based on the hypothesis of this work. A saturated aldehyde does not qualify as an odorophore in the context of this hypothesis and corollaries. Like the aldehydes, the alcohols they illustrate in Fig. 2, do not exhibit hot spots within the b/B modules. Saturated alcohols are recognized in most disciplines as being odorless and should not exhibit any hot spots when sufficiently pure. Highly volatile impurities at the level of parts per thousand in solution can cause vapors at the ppb or ppm level and be significant in determining the perceived odor of an alcohol.

Ho, Johnson & Leon demonstrated the difficulty of working with the saturated hydrocarbons in 2006. Their figure 3 demonstrates the same hydrocarbons purchased from three reputable sources cannot be relied upon in olfaction studies, particularly those employing the 2-DG technique. They also show the mapping of 99.8% pentadecane is entirely different from the three samples of 99% pure pentadecane. The hypothesis and corollaries of this work indicate no d-value supporting an odorophore in the alcohols. In figure 5, they showed the variation in glomeruli mapping at various concentrations for heptane. Although the caption says the patterns track the concentration “with higher concentrations producing a higher level of activation,” the imagery at 7500 ppm does not support this statement. Their conclusion is succinct, “Indeed, the glomerular responses were systematic enough to allow us to pick out anomalies that were based on odorant contaminants, rather than the target odorant.”

Johnson et al. in the 2007 paper extended their analyses to octanoic acid and its derivatives (many that were not saturated, Fig 1) and a series of hexenols (Fig. 2). Unfortunately they did not employ a similar series of unsaturated decanols; use of the unsaturated decanols would have aided in defining the module pairs beyond the letters i/l.

Methyl octanoate reflects stimulation of module A and B (as well as a and b) suggesting these modules are the focus of activity associated with the OR 1 channel. The difference in the activity level between the maps for octanoic acid and for methyl octanoate needs further analysis to determine if relevant. As noted in the caption, the maps represent averaged z-scores presented in a standardized manner and collected from several (a small number) of rats. Johnson et al. have distinguished these activities by open arrows and circular perimeters.

Methyl trans-2-octenoate shows a progressively different area of activity (with considerably less activity in modules A and a and somewhat less in B and b). Modules b, d, e & i show activity (along with B, D & E and some activity in I and H). This map suggests that methyl trans-2-octenoate is stimulating the OR 1 channel as well as either or both OR 2 & 3 channels (both as predicted by the previous figure).

Methyl 2-octynoate shows major activity continuing to move to the right, into modules D, E, G & H as well as d, e, g & h (solid arrows pointing to G and g). This activity is consistent with the predicted activity in OR 2 channel and more stimulation of the OR 3 channel as predicted in the above figure. While the d-values of methyl 2-octynoate would indicate continued stimulation of OR 1 channel, the relative z-scores of Johnson et al. do not indicate as much stimulation (although modules A and b are shown in green (any activity in module a is out of plane and difficult to read).

---

[xxx probably combine with material above supporting figure 8.6.7-12]

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---

As noted by Johnson et al (upper two frames of figure 5) and as predicted here based on the marginal changes in d-values, the trans and cis variants of a given derivative of an odorant show minimal differences in perceived scents by humans and in their radiograms from rats. Their figure 5 does support the extension of the above analyses to OR channels xxx and xxx in accordance with this hypothesis. ADD WORDS Their figure 8 shows the marginal changes in affected glomeruli areas due to greater differences in structural arrangement of the overlay moieties. It continues to support the assertion that the trans and cis configurations introduce marginal changes in the stimulated areas.

Their figure 8 confirms the relative insignificance of the trans and cis variants (when they occur removed from the carbonyl oxygen) among another family of molecules ranging from geraniol (with trans double bonds at positions 2 and 6) and trans, cis-2,6-nonadienal. Geraniol exhibits two odorophores, corresponding to d-values of 3.013 and 7.935 Angstrom. The material would be predicted to stimulate OR 2 and 3 (due to the double bond at position 2), and OR 9 (due to the double bond at position 6). It would not be expected to stimulate the OR 1 channel since it does not contain the carbonyl functional group. OR 2 & 3 remain associated with modules D, E and d, e as predicted earlier and OR 9 begins to associate with modules j and J (near the J / L and j / l transitions). Nerol, with a cis bond at the 2 position causes activity in the glomeruli nearly identical to that of geraniol in modules D, E, d & e. Less activity is indicated in modules j and J than for geraniol but this may not be statistically relevant.

The acetates of both geraniol and nerol exhibit greater activity in modules D, E, d & e as expected by the two odorophores now present related to the ester oxygen and the carbonyl oxygen paired with the double bond at position 2. Activity in modules j, l and J related to OR 9 is also evident in geranyl acetate.

In the case of their last two examples, trans,trans- and trans, cis-2,6-nonadienal, the closeness of the double bond at position 2 and the carbonyl oxygen result in reduced d-values of 2.460 & 6.923 and 2.460 & 6.916 respectively. As expected the low d-values cause these molecules to stimulate OR 1 primarily and potentially OR 2. The activity in the glomeruli is focused on b and B as predicted from above, moving into i, p, L and P. The expansion into i, p, L and P would suggest OR 7 and potentially OR 8 channel activity is focused in these modules of the glomeruli.

As a result of the above relationships, the module map of Johnson et al., 2002, can be redrawn roughly as shown in Figure 8.6.7-13. All of the OR channel numbers shown are based on the d-values taken from the d-values of the molecules used by Johnson et al., 2007, and the nominal OR channel centroids from this work. The Johnson and colleagues papers include only one stimulant associated with the OR 8 channel of this work. Its activity level was minimal in Fig. 3(A) of their 2007 paper and its hot spot is shown as 8 with a gray surround near the border between the K & L modules. The activity in the lateral region was dispersed in modules i, d & e. Johnson did not include any 8-octanol or 8-octanoate in the 2007 or 2007b papers to quantify channel 8. The 2000 paper focused on penta and hexa compounds. Geraniol is not a representative OR 9 stimulant because it also stimulates OR 5 and OR 2 & 3. The use of preferred stimulants based on the hypothesis would avoid those containing multiple odorophores (and generating multiple zones of activity) in favor of preferred odorophores (Section 8.6.6.5).
[xxx show table of stimulant and OR channel number versus module designation in the figure citronenol not strong enough as used to define OR channel 8 well.]

Figure 8.6.7-13 A redrawn module map of the rat glomeruli based on the receptor channels ADD of olfaction. The numbers locate the centroids of the signaling channels as they appear on the surface of the anatomically standardized rat glomeruli. The ventral midline is suggested by the addition of modules n, o & p to the most recent Johnson and colleagues' map of 2007.
Figure 8.6.7-14 summarizes the data used to establish the location of olfactory channel activity on the glomeruli module map. The preferred stimulants are optimized for the OR's defined in this work as of 2013. They each provide only a single odorophore, thereby minimizing the number of active sites within the glomeruli. The d-value of the preferred stimulant is as close to the maximum of the effectivity characteristic of the OR believed to form the OR for that channel. The stimulants listed for Johnson and colleagues are only representative of those they associated with a specific module. This work predicts that many of their stimulants stimulate more than one OR channel and result in more complex maps of glomeruli activity than desired.

<table>
<thead>
<tr>
<th>OR Channel</th>
<th>Center d-value</th>
<th>Preferred stimulant</th>
<th>d-value Angstrom</th>
<th>Hot spot module</th>
<th>Johnson stimulant</th>
<th>d-value Angstrom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.276 Ang.</td>
<td>Acetic acid</td>
<td>2.277</td>
<td>A/B</td>
<td>Octanoic acid</td>
<td>2.277</td>
</tr>
<tr>
<td>2</td>
<td>2.791</td>
<td>Skatole*</td>
<td>2.721</td>
<td>B/D</td>
<td>Cyclo-octadiene</td>
<td>2.696</td>
</tr>
<tr>
<td>3</td>
<td>3.508</td>
<td>Benzaldehyde</td>
<td>3.635</td>
<td>E/G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.254</td>
<td>Limonene**</td>
<td>4.597</td>
<td>H/I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5.294</td>
<td>Exaltone***</td>
<td>5.146</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6.075</td>
<td>Cinn. alcohol</td>
<td>6.029</td>
<td>G/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6.705</td>
<td>1-Hexen-6-ol</td>
<td>6.785</td>
<td>L/P</td>
<td>5-Hexen-1-ol</td>
<td>6.785</td>
</tr>
<tr>
<td>8</td>
<td>7.184</td>
<td>Citronellal****</td>
<td>7.090</td>
<td>K/J</td>
<td>Citronellol</td>
<td>7.090</td>
</tr>
<tr>
<td>9</td>
<td>8.22</td>
<td>6-Heptenal</td>
<td>8.017</td>
<td>I/J</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A nitrogen/ring odorophore
** A oxygen & nitrogen free odorophore
*** A circular configuration of cyclopentadecane 9980
**** Citronellal preferred over citronellol as stimulant

Figure 8.6.7-14 OR channels, preferred stimulants & hot spot locations ADD. The hot spot modules are based on the 2002 map of Johnson & colleagues. No statistical analysis was performed as part of this work. Thus the locations taken from the previous graph are illustrative and frequently appear to be near borders of the modules defined by Johnson & colleagues. The stimulants listed for the Johnson activity are only representative. Any pure carboxylic acid with a saturated hydrocarbon structure can be used to characterize OR channel 1. See text.

The change in local signal intensity in the glomeruli with changes in stimulant concentration were explored by Johnson & Leon in 2000, but only for low d-value materials. The work was primarily exploratory, but they offered a series of plausible hypotheses where inconsistencies arose. At high concentrations (~250 ppm), they observed some signals in modules c/C and f/F from materials without an obvious odorophore, suggesting again that additional corollaries to the hypothesis of this work may be needed.

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The reason for the duplication between the two halves of the glomeruli spanning the ventral median remains unclear. Since the olfactory modality does not collect or preserve any spatial organization relative to the exterior environment, several possibilities are presented. The simplest is to suggest that the two sets of modules function differently, one set performing global summations and the other set performing global differencing related to the individual OR channels. Demonstrating this possibility requires more data, regarding either the cytology of the involved neurons (are the differencing neurons bistratified) or the character of the stage 3 encoded signaling from the glomeruli (are there pulse streams that increase and decrease their pulse rate about a nominal continuous pulse rate).

If either of these observations confirm a differencing mechanism, the explanation of how higher level olfaction is performed in stages 4 and 5 can be described more fully in analogy to the visual modality. Yokoi et al., as well as others (see Section xxx regarding stage 3 encoding), have recorded differencing signals at the output of the stage 3 mitral cells. Unfortunately, it is extremely difficult to record the individual analog waveforms applied to the very small diameter bi-stratified neurites of an encoding mitral neuron.

In a second paper during 2007, Johnson et al suggest there is no evidence for combinatorial encoding. However, without a theoretical framework, it is difficult to support such an assertion. The assertion was based on their earlier assertions related to conventional functional groups. In the cited paper, they noted,

“Earlier experiments mapping odorant-evoked 2-DG uptake or optical signals in the olfactory bulb suggested that individual odorant functional groups might be represented in particular glomular clusters, modules, or domains in the olfactory bulb (Leon and Johnson, 2003; Mori et al., 2006)," and “More recent work with a larger number of combinations of hydrocarbon structures and functional groups has indicated that this simple notion does not generalize to all combinations. Instead, odorant functional groups and hydrocarbon structures in many cases appear to interact to produce new features that are recognized by new sets of receptors and glomeruli that are not predictable from the responses to the individual elements (Johnson et al., 2005b). In other cases, structural elements such as unsaturated bonds (Johnson et al., 2007) and hydrocarbon branching (Johnson et al., 2005b) appear to disrupt the recognition of functional group-related features. The position of a functional group within an aliphatic hydrocarbon structure also can influence which glomular modules are activated (Johnson et al., 2005a).”

These are rational positions. However, they have not placed the material in an adequate framework addressing the DACB relationship between a mix of orbitals larger than they speculate upon. They also failed to cite molecules containing two orbitals with distances between them of more than 7.5 Angstrom.

This work has shown that molecules containing multiple odorophores do stimulate multiple OR channels and do cause activity at multiple locations on the glomeruli map. These situations strongly support, almost demand, a combinatorial relationship within the neural system.

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The 2007 Johnson et al. paper included multiple principle component analyses (PCA) of the underlying data matrices used to develop their glomernul module map. These matrices were not discussed in any detail in the paper although the protocol for developing them was presented in textual form. These analyses found that there was one principle factor and two lesser factors in these maps that could provide more understanding of the underlying processes generating the maps. To attempt to determine these factors, a two-way ANOVA was performed.

The two-way ANOVA explored the significance of the bond type, the functional group and the interaction among the three factors. The discussion of the results of these analyses was limited to a few sentences scattered over several pages. The author’s asserted that the results were statistically significant but did not report what parameters the factors represented. The resulting 2D plots of pairs of the three factors did not produce any readily understandable relationships like those produced

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In 2009, Leon & Johnson presented a wide ranging review of their understanding of the glomeruli across many species. While including many citations, it necessarily did not include many underlying details supporting their positions. Only two conceptual figures and one brief MDS graph appeared in the paper. Interestingly, they did not answer the question posed by the title of their paper; Is there a space-time continuum in olfaction?

This work has clearly established there is a one dimensional continuum explaining the operation of the transduction process (the d-value line, Section 8.6.2.8.1 and Section 8.6.2.9 in the summary) and a separate temporal regime explaining the dynamics of the olfactory response (the E/D equation, Section 8.7). The number of variables related to the temporal response temporal response makes it difficult to describe in a single function. Therefore, combining the space response with the temporal response is feasible in a complex way but not in an easy one sentence manner.

Figure 2 of their paper cited figure 4C (lateral view) in one of their 2007 papers. The 2007 paper, labeled 2007c here is clearly attempting to resolve the many overlaps in the glomeruli activity maps produced by this team earlier. It is in considerable conflict with the summary description of the chemicals stimulating a given glomeruli area in their 2007a and b papers. As an example, their activity maps prior to the 2007c paper show the saturated carboxylic acid stimulants affecting areas a and A on their maps. However, the 2007c paper shows carboxylic acids as primarily affecting an area corresponding to area k and/or j (They only addressed the lateral half of their earlier complete map in the 2007c paper). The problem is they have not developed a functional model of the olfactory modality to explain their data. Based on their data, the saturated carboxylic acids stimulate area a (corresponding to OR 1) and only the unsaturated carboxylic acids with a double bond at carbon 7 or 8 stimulate areas k and/or j (corresponding to OR 8 or OR 9).

As developed in this paper, many of their stimulants are not primary odorants (i.e., odorophores) by themselves. They contain multiple odorophores stimulating different OR channels. In the case of the carboxylic acids, the saturated aliphatic carboxylic acids are odorophores affecting only the OR 1 channel. However, the unsaturated aliphatic carboxylic acids are not odorophores, they are odorants containing multiple odorophores. They all contain the odorophore stimulating OR 1 and generally exhibit two additional odorophores affecting either one or two additional OR channels, depending on the carbon atom number associated with a double or triple bond.

The above explanation resolves the difficulties displayed by the various figures by Johnson & Leon. Most of the olfactory stimulants are odorants exhibiting multiple odorophores. These odorophores excite multiple OR channels and hence cause multiple hot spots in the glomeruli maps.

Their discussion on page 2136 regarding “strong lateral inhibitory networks between glomeruli and mitral cells” is not well supported. They merely accept the undocumented concept of earlier investigators. A much simpler solution to achieving “response sharpening” is to allow the mitral neurons to be bi-stratified (as in many other sensory areas of the neural system) and perform signal differencing between their two input structures.

As noted earlier, their method of obtaining their maps is quite involved and employs multiple statistical methodologies. The results, while colorful, are not sufficiently precise that they can be reproduced and result in a single hot spot in the map for a single specific narrow set of chemicals. As shown in the previous figure and discussion, a map of the stimulated areas based on the OR’s is unique and not overlapping (from the point of view of the OR’s). If the stimulant contains multiple

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odorophores, as many of their odorants do, it should be expected that multiple areas of activity will be recorded in their statistical maps. An additional problem with figure 2 of 2007c is the fact the labeled classes are not chemically unique, in the absence of further definition, methyl esters and ethyl esters are clearly members of the class of aliphatic esters. Only detailed reading of their two categories of papers can illustrate the difficulty in classifying their stimulants based on their functional designations. "Very water soluble odorants" include many of the other classes in figure 2. As an example, at least the simplest five carboxylic acids are, like the alcohols, miscible in water, up to the point that the water is the minority constituent.

Falasconi et al, including Johnson & Leon apparently as consultants, performed a different cluster analysis that resulted in a different glomeruli map (their figure 7) than any of the prior maps by Johnson & Leon\textsuperscript{310}. They described their stimulant set, "To describe the present odorant set, we considered the using 50 different descriptors involving functional groups, hydrocarbon chain structures, and the presence of benzene rings. However, the final set of 21 descriptors was selected after eliminating chemical features that are correlated, to avoid the introduction of undesired statistical relationships, and including only those odorants in the database with 15 or more examples to maximize statistical consistency. The final list includes the following properties (left column, their list; right column, comments on that list):

<table>
<thead>
<tr>
<th>property</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>carboxylic acid,</td>
<td>A primary odorophore</td>
</tr>
<tr>
<td>alcohol (not phenol), primary alcohol,</td>
<td>Omit in favor of following labels</td>
</tr>
<tr>
<td>aliphatic (not alicyclic) secondary alcohol,</td>
<td>Aliphatic primary alcohol</td>
</tr>
<tr>
<td>ester (not lactone), aliphatic ester (not alicyclic),</td>
<td>Aliphatic ester</td>
</tr>
<tr>
<td>aromatic ester,</td>
<td>Aromatic ester, acyclic</td>
</tr>
<tr>
<td>aldehyde,</td>
<td>Omit</td>
</tr>
<tr>
<td>aliphatic aldehyde, aromatic aldehyde,</td>
<td>Aliphatic aldehyde</td>
</tr>
<tr>
<td>ether, ketone, aliphatic ketone (not alicyclic),</td>
<td>Aliphatic ketone</td>
</tr>
<tr>
<td>aliphatic or alicyclic with multiple O-containing functional groups, aliphatic or alicyclic hydrocarbon,</td>
<td></td>
</tr>
<tr>
<td>alkane, aromatic, aromatic with O-containing substituent,</td>
<td>Aromatic with O-containing substituent</td>
</tr>
<tr>
<td>alicyclic, polycyclic, and heterocyclic</td>
<td></td>
</tr>
</tbody>
</table>

This set appears excessively long with regard to their exploratory regime and incomplete with regard to the orbitals affecting olfaction (compare with Section 8.6.2.9.5). It contains a number of duplications and overlaps within the chemical regime addressed and that regime omits major groups of odorants not addressed by Johnson, Leon and colleagues (example; a wide range of aromatic-aliphatics (arenes)) of the flowers, macrocyclics, nitro-benzoids and the sulfanyls.

Falasconi et al. opened their Discussion section with a description of why their results might not agree with other similar 2-DG glomeruli maps. They did note, “Our data also support the notion of an identity code operating in the olfactory system, which underlies the first step in odorant perception. An identity code, in which specific olfactory receptor neurons play a critical role in mediating odor perception, would have to have differential responses among different olfactory receptor neurons.” This terminology appears to be consistent with and point toward the nine OR channels of this work.

The conclusion is that the calculation regime of both Falasconi et al. and the Johnson team, based only on stimulants frequently involving multiple odorophores, lacks sufficient precision to pin point the location on the glomeruli of the signals from a given OR. The purpose of introducing of fuzzy logic into the calculations of the Falasconi et al. team is unclear to this investigator. While a recognized empirical method of statistical analysis, it does not appear to advance our knowledge of the operation of the olfactory modality.

8.6.7.3.4 The 2007c paper of Johnson & Leon

The 2007c paper of Johnson & Leon is massive, 58 pages in the manuscript available on the NIH Public Access site (34 pages when typeset in J Comp Neurol) and 158 citations touching on all stages of olfaction. All of the paper cannot be discussed in detail here. However, many of the section titles employed suggest the tone and scope of the paper;

“All possible chemical features are not represented as unique modules”
“Gaps in chemotopic progressions involving homologous series”
“Possible causes of chemotopic progressions”
“Not all modules show chemotopic progressions”
“Possible consequences of chemotopic progressions”
“Not all continuously varying molecular properties are coded by progressions”
“Combinatorial coding of odorant molecular features”
“Limitations of mapping methods”
“Odorant confusion matrix”
“Correlations between rat glomerular 2DG patterns and human odor descriptions”
“When spatial organization is and when it is not a spatial code”
“What does the speed of olfaction tell us about odor coding?“
“Detailed descriptions of the specificities of glomerular modules”
“Conclusion”- One paragraph.

The last sentence in their conclusion is compatible with the indented assertion of this author above regarding the relationship between the spatial dimension and the temporal dimension in olfaction. “In contrast to the strong evidence supporting an olfactory spatial code, there is no evidence for a similarly close relationship between temporal patterning of olfactory responses and perception or discrimination.” This statement is based on their evaluation of the empirical record and not on any detailed analysis of the electrophysiological database.
Their analyses were all accomplished within the context of conventional valence and covalent chemistry as suggested by their figure 1, reproduced here as Figure 8.6.7-15.

The figure only addresses oxygen, and indirectly the double and triple bonds of carbon, as the only orbitals of concern in olfaction. No representation of the aromatic ring as an orbital is even suggested. No suggestion is offered as to how the various chemical configurations might be associated with an OR in transduction. Their conventional assertion, “Studies of olfactory coding must account for both the breadth of odorant chemical structures that are detected by animals and the subtle discriminations that are possible between closely related compounds. Because of this dual challenge, the research must involve a great number of odorants.” is questioned here. By focusing on the small number of independent OR channels, it is possible to explore the step one (selection) performance of the olfactory modality using only a dozen odorophores and predict the performance of a wide variety of other odorants.

Their Table 1 includes a list of papers examining different stimulus situations using the 2DG technique.
8.6.7.3.5 Additional material on module signals in glomeruli

The above material left areas of the Johnson & Leon glomeruli module map without association with the OR's of olfaction. In a 2003 paper, Leon & Johnson, figure 2, shows modules c/C, f/F, h & j being active using the same 2-DG uptake technique when stimulated by several ketone-ring structures. The figure also shows activity in c/C and f/F based on putative 2-hexanone stimulation. 2-hexanone is a simple saturated straight chain aldehyde with no recognized d-value based on DACB coupling. Such activity in c/C and f/F due to this material would suggest contamination in either the purchased chemical or in the test equipment. Leon & Johnson attributed the activity in these areas as due to the presence of a single carbonyl oxygen, based on their assumption that olfaction was based on recognized functional groups. They did not include the data from 2-hexanone in their analyses summarized in figure 3. The remainder of the paper speculated on possible explanations for the presence of the documented activity. The d-values of L-menthone_24636, L-carvone_388655 and 2-acetylpyridine_13648 based on the hypothesis of this work do not support activity in modules c/C, f/F, j & h. To the extent their data is reliable, Leon & Johnson did show that enantiomers of the three chemicals, excluding the simple aldehyde, exhibited the same distribution of activity in their module maps. The d-values of these three chemicals do support stimulation of the OR 2 (border region between b/B and d/D), OR 4 (border region between h/H and i/I) and OR 5 (i/I modules) channels.

“We noted that molecules without any oxygen moiety activated more ventral and caudal glomerular regions than were activated by medium-sized odorants containing oxygen atoms [citing Johnson et al., 2002].” They offered no theoretical foundations for the speculations in the 2003 paper. They concluded their paper with, “we have just begun to examine the extraordinarily wide range of odorant molecules and it is certainly possible that there are additional coding mechanisms that are involved in producing the perceptions of molecules that have yet to be studied.”

As noted earlier, the hypothesis and corollaries of this work may need extension to account for the ability of some complex chemical structures to stimulate the olfactory modality. Bicyclic ring structures with top-hats including a hetero-oxygen clearly fall in this category. The three chemicals examined by Leon & Johnson in the 2003 paper do not appear to fall into this category.

- - - -

In their 2010 paper, Johnson, Ong & Leon provide the 2-DG maps for a variety of common food stuffs as recorded in rats. They also provided a series of 2D graphs based on their PCA (MDS) calculations, but they did not identify any of the major axes in these figures. Without identifying the axes, they were unable to identify the plane represented in their figures and associated with the putative 9D space proposed in this work.

8.6.7.3.6 Summation & differencing at the mitral & tufted neurons

Meredith provided excellent data supporting the differencing of signals within the glomeruli of hamsters using histograms versus time." The paper included conceptual cartoons but is without any detailed circuit diagrams, instead relying on earlier papers speaking of dendro/dendro synapses supporting inhibition. They also suggest there are cells similar to the horizontal cells of the mammalian retina (stage 2 circuits) that are differencing signals from stage 1 cells separated by significant physical distances.

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Yokoi et al. have provided excellent early data on the output of mitral neurons of stage 3 in rabbits\textsuperscript{313}. Their data clearly supports differencing of the signals from “adjacent” glomeruli and the production of action potentials representing this differencing. They assert their probes were introduced into the medial portion of the exposed dorsal surface of the left main olfactory bulb.

Their model (caricatured in figure 6) assumes only summation at the dendritic inputs to the mitral cells from the olfactory receptor neurons (ORN) and inhibition by auxiliary neurons described as granule cells (GR). Allowing for bi-stratified mitral cells, as in this work and found throughout the neural system (Section xxx of xxx), supports the much simpler model of differencing within the mitral neurons themselves. Their concept of dendro-dendro synapses was common in that era but is not compatible with the well documented operation of three-terminal neurons (Section xxx).

All of their stimulants were saturated aliphatic aldehydes of various chain lengths. Typically, these materials change form when in solution; they become hydrated through hydrogen bonding. The transient performance of the neural signals in their figure 2A and probably 2B deserve closer examination, particularly those of (5)CHO, (6)CHO and (7)CHO.

Their test equipment and protocols allowed very short stimulus intervals (~2 sec). Their recordings were typically extracellularly with recorded action potential heights of only about 1.5 mV.

Wachowiak & Shipley prepared a major review on coding and synaptic processing within the glomeruli in 2006\textsuperscript{314}. The paper is worthy of careful study along with referral to the citations. They subdivide the neurons of the glomeruli into more types than just the glomeruli neurons connecting to the mitral cells as generally found in the literature. “These new findings show that the intrinsic neurons that comprise the glomerular network - ET, PG and SA cells - are more complex and physiologically diverse than previously suspected. Not surprisingly in view of this newly revealed complexity, less is known about their synaptic organization and even less about the functional roles that glomerular and possible sub-glomerular networks play in olfactory coding.” Their reference to spontaneous action potential generation is indicative of difference processing within the circuits of the glomeruli. They use primarily fanciful names for their neurons within and adjacent to the glomeruli. Without defining all of the circuits here, their conclusion also supports signal differencing. “The results show that a network comprised, minimally, of an ON→ET→SA→(distal glom)→PG→M circuit, serves to provide interglomerular lateral inhibition among the glomeruli (Fig. 4). Strong ON activation of a given glomerulus activates the ON→ET→SA→(distal glom)→PG→M circuit, which inhibits mitral cells - and thus glomerular throughput - in weakly activated glomeruli.” These are all analog circuits prior to encoding by the Mitral cells; the proper terminology is depressing (by subtraction) rather than inhibition in the analog context.

### 8.6.7.3.7 A detailed pulse record from stage 3 of the olfactory modality

Kafka\textsuperscript{315}, writing in Ohloff & Thomas in 1971 provided a very useful set of responses reproduced here as Figure 8.6.7-16. The histological diagram of the olfactory “pit organ” of the migratory locust, locusta migratoria, was not shown at sufficient detail or annotated sufficiently as to probe locations to be discussed here. However, the responses appear typical of the signaling channel of any olfactory sensory modality as described elsewhere in this work.

Kovats asked an important question during the discussion following this paper. He asked, “You observe a spike at a certain concentration, but I notice that as you lower the concentration the signal is delayed. Can this mean that the antennae concentrates the substance until sufficient is available for signal?” Kafka gives a plausible response for that time period.


However, he did not know the character of the sensory neurons, or the signaling code used among the stage 3 neurons, at that time. Based on this work, the delay is clear confirmation of the Excitation/De-excitation mechanism within any sensory neuron. First, the delay in the appearance of the signal at the pedicle of a sensory neuron increases as stimulation decreases.

Second, the first pulse of the stage 3 signal train is indicative of the time of occurrence of the stimulation (and includes the delay component as well as any travel delay within the neural system between the stage 1 and first stage 3 neuron. Third, the delay between the subsequent
The fact that the time of the initial pulse and the variation in pulse-to-pulse spacing during the initial rise in the analog response indicates the calculation of an average pulse rate over an extended interval misrepresents the information intrinsic in the response.

Both the analog and pulse waveforms indicate the washout process commonly used in gustatory experiments is totally ineffective at terminating either the stimulation or response of a specific OR. It is clear that, following cessation of presentation of stimulant at the aperture of the olfactory pit, the stimulant that entered the pit remained effective until the molecules evaporated from the mucosa due to a combination of their volatility, solubility and potentially other parameters.

Because of the difficulty of locating data on the pulse rate at stage 3 for various stimulant intensities, a paper by Ache & Carr is cited here. Ache & Carr have discussed a wide range of pyridines and their role in the gustation of crayfish316. Of specific interest is figure 5 showing the linearity of the average pulse rate at stage 3 versus the stimulus concentration applied to the stage 1 GR's when plotted using a linear ordinate and logarithmic abscissa.

8.6.7.4 Olfactory modality operation in the context of SOR/SAR studies

It is now possible to overcome Rossiter's main objection to SOR/SAR studies in 1996. She noted that without a theoretical framework recognizing both the quality (channel) and the intensity of an odorant "and good, precise, reproducible data, all SAR work is a waste of time" (Section 8.6.1.1).

This work has identified a one-dimensional continuum representing odor space. However, it has also recognized that the sensory system employs a quantification process to simplify the overall olfactory modality. This process recognizes that only specific odorophore structures are found sufficiently often to warrant individual sensory channels. This work has identified approximately nine distinct sensory channels, each with an identifiable candidate receptor and presumably a distinct sensation in response to stimulation of that receptor. The acceptance range of each receptor, in terms of the one-dimensional odor space, is finite but narrow. It appears to be on the order of ±5% of its central value to the half amplitude points. This range indicates that each receptor is capable of forming a DACB bond with a range of odorophores. Because of the character of step 1 (selection) of the transduction process, all odorophores stimulating a given channel will be reported as identical when represented in the saliency map of the organism. Only their effective intensity obtained in step 2 of the transduction process will be reported as a discrete amplitude function at the output of stage 1 (signal detection).

More importantly, and more pragmatically, this work has shown that proteins play no role in the olfactory process. The odorants are not proteins, the chemical portion of the transduction process does not rely upon proteins and the operation of the sensory neurons does not rely upon proteins. If proteins play any role in directing an odorophore to the appropriate OR, it has not become apparent from the data.

This work has also shown that the structure contemplated in the structure activity relationship (SAR) and the structure-odor relationship (SOR) and based on conventional chemistry practice does not play a significant role in olfaction. The structural arrangement of interest is an overlay on the molecular structure that ignores the conventional structural relationships.

Some of the olfactory receptors may support a three point coordinate bond arrangement, AH,B,X, similar to that found in gustation. However a significant change in signal intensity at the output of stage 1 would significantly change the perceived scent, at least as documented for the dulcal channel as noted above [Figure 8.6.7.3].

Additional laboratory investigation will be required to identify the specific sensations elicited by stimulation of each of the sensory channels. The results will furnish a unique receptor structure-sensation relationship (RSSR) that can be used as a building block to create an odorophore-sensation relationship (OSR). The odorophore set will be larger than the receptor set and the relationship is one of convergence. The odorophore set can be used to identify all odorants containing one or more of the odorophores. The relationship between the odorants set and odorophores set involves a nearly infinite set converging on a manageable but large set.

The one-dimensional odor space can be folded into a multidimensional space of nominally nine dimensions because the central nervous system treats each sensory channel of the olfactory modality as an independent, and therefore orthogonal source. While all odorophores must stimulate individual receptors, they may stimulate them with different intensities. The glomeruli appear to be designed to perform complex signal processing (addition and subtraction, but in either the linear or logarithmic regime) based on the relative stimulus intensities reported by each sensory channel. As in other modalities, the output of the glomeruli are distributed to multiple locations within the CNS, and some peripheral locations. Some of these alternate locations may cause motor responses before the cognitive element of the CNS is fully aware of a specific odorant.

8.6.7.4.1 SOR/SAR in context of the neurological map

The titles structure-activity relationship (SAR) and structure-odor relationship (SOR) have not been adequately defined for the purposes of this work. Here, the 1996 paper by Rossiter will be used as a jumping off point. In her definition of the SOR, she is clearly speaking of the structure of the stimulant and the perceived odor or scent. In her discussions of SAR, she is generally speaking of the biological activity associated with a structure, not its perceived odor. In the discussion, she focuses on the measurements of the size of molecules and ligands by Amoore. “The ultimate goal of any SAR study is the design of a novel compound with the desired biological activity.” In discussing the use of MDS analyses, she also notes, “This confirms the need to combine distance criteria and molecular shape in the development of three-dimensional SARs.”

She focuses more intently on a term QSAR, that appears to be defined as a quantitative structure-activity relationship (an equation or tabulation of dimensions). After discussing the subject further, she asserted, “This illustrates the need to combine osmophore and shape models with QSARs which take into account electronic properties such as electrostatic potential and transport properties such as log P and volatility.”

The terms SOR and SAR are commonly used in the perfume community and it will be difficult to introduce any alternate terminology. Figure 8.6.7-17 provides a clarification of the terms discussed above.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Specific definition/preferred definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOR/SSR</td>
<td>Structure-perceived odor relationship/Structure-scent relationship</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure-biological activity relationship</td>
</tr>
<tr>
<td>OOR/OSR</td>
<td>Odorophore-perceived odor relationship/Odorophore-scent relationship</td>
</tr>
<tr>
<td>OAR</td>
<td>Odorophore-biological activity relationship</td>
</tr>
<tr>
<td>AOR/ASR</td>
<td>Activity-perceived odor relationship/Activity-scent relationship</td>
</tr>
</tbody>
</table>

Figure 8.6.7-17 Clarification of the semantics of the terms SOR/SAR ADD. For clarity, the term odor is associated with the stimulant (odorant) and its odorophores. The perceived odor at stage 5 of the neural system is defined as the scent associated with an odor, odorant or odorophore. See text.
The editors of “Current Computer-Aided Drug Design addressed QSAR in 2015317. The paper is well structured and names many of the complex computer programs currently in use; however, the quotation from Dirac is taken out of context. While it may apply to very complex reactions and molecules in pharmacology (as well as his field of quantum mechanics), it does not apply to more fundamental areas of biological physiology where great strides have been made in solving equations applicable to problems unknown in Dirac’s time. The quotation from both W. Edward Deming and Ronald Fischer however are right on target when addressed to any experimentalist or observer of biological behavior. The field of electronics-based physiology is moving into a region that requires greater precision in the development of null hypotheses and the accumulation of data supporting or falsifying such hypotheses.

In the figure offered below, it is quickly recognized that additional descriptive terms may be required to more clearly delineate the processes occurring between the biological activity related to transduction by the OR’s and the perception of the information pattern presented to the stage 5 cognition engines by the stage 4 saliency map.

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Figure 8.6.7-18 describes the architecture of the olfactory modality in the context of the larger neural system. The olfactory modality shares its fundamental architecture with all other sensory modalities. Only the receptor portion of the stage 1 sensory neurons are unique to their modality. At a more detailed level, the stage 1, and possibly stage 2 portions of the figure are replicated to provide main and auxiliary morphological olfactory lobes. It is estimated there are 32 glomeruli in each human main olfactory bulb.

Figure 8.6.7-18 SAR/SAR as an overlay on the architecture of the olfactory modality. A given odorant can exhibit a range of odorophores. An individual olfactory receptor (OR) can form a DACB relationship with a range of odorophores having d-values within its range of effectivity. The glomeruli of stage 2 perform a sum and differencing operation on the information received from the sensory neurons. After encoding and decoding their output within stage 3, stage 4 has the responsibility of extracting the information relative to the original odorant(s) and placing that information into the saliency map that is accessible by the cognitive circuits of stage 5. The reporting of the perceived scents involves stages 6 and 7. The three letter labels on the left are defined in the text.
Among the boundless number of odorants, each can be distinguished by the multiple individual odorophores its structure provides. There is a great amount of convergence leading to the nominal 40 odorophores in the biological kingdom. This mapping defines the SOR structure of the odor environment.

The community has frequently used a set of abbreviations in classifying their odorants, etc. that are not always clearly defined. The terms used here are:

- **AOR**—biological activity and perceived odor relationship,
- **OAR**—Odor and biological activity relationship,
- **OOR**—Odorophore and perceived odor relationship,
- **OSR**—Odorophore-sensation relationship,
- **SAR**—Structure and perceived odor (activity) relationships,
- **SOR**—Structure and odorophore relationships,

where perceived odor and sensation are synonymous.

The SOR matrix contains a great deal of path crossing. The odorophores of a specific odorant are tailored to stimulate one of the sensory receptors of the target species. There appear to be cases where one odorant may contain two or more odorophores that stimulate the same sensory receptor. This occurs in both di- and tri-carboxylic acid structures as an example. It may also occur where both amine and carbonyl structures are present. The mapping of the odorophores onto the stage 1 sensory receptors constitutes the initial element of the odorophore-activity relationship, OAR. There is significant convergence but less crossing of paths when both the odorophores and the receptors are placed in d-value order. The complete OAR relationship requires additional knowledge of the stage 2 signal processing and stage 4 signal manipulation (information extraction) neural activities. These result in information being stored in the saliency map, along with ancillary information from other sensory modalities. The combined information in the saliency map allows the stage 5 cognition element to make an informed evaluation of the stimulant presented and call for appropriate stage 7 action.

The complete SAR is a concatenation of the SOR and the OAR and is frequently extended to incorporate the observable expressions presented by the stage 7 portion of the motor system (such as grimaces, words and hand motions when selection processes are utilized).

The convergence and divergence of signals described above introduces a significant amount of conflation (convolution in mathematical language) that is not easy to deconflate (deconvolve) in the psychophysical laboratory. However, by carefully selecting singular odorants (individual odorophores), it is possible to avoid the conflation and track individual responses to an odorophore through the complete olfactory modality to the point of perceived scent. When accompanied by adequate adaptation control, this use of singular odorants, is a critical requirement highlighted by Rossiter; the data must be precise and repeatable in another laboratory.

Neither of the terms, concatenation (suggesting a linkage of individual serial elements into a chain) or conflation (suggesting a summation of multiple parallel elements into a single chain) do justice to the complexity of the olfactory (or any other sensory) modality.

### 8.6.7.4.2 Resolving the labeled-line vs across-nerve-pattern dichotomy

Descriptions of how the different stimuli are initially sensed in the peripheral portion of the olfactory system has evolved along two separate paths, the labeled-line theory and the across-nerve-pattern theory. These two approaches are seldom precisely defined and may not be totally distinct. Several authors offer different interpretations of their meaning. The above figure should resolve the issue. All neural pathways are labeled lines where researchers are unable to read the labelson the schematic at this time. The labels are incorporated into the schematic portion of the genetic code. The fact that a neural path can be regenerated after severing (even in humans in specific cases) is evidence that the schematic exists. All neural lines are labeled, however, the information carried along these lines at a given time can be describe by a pattern. This pattern can be directly traced to, and be associated with, the structural character of the odorophores present (if not the individual odorant).

In the context of the figure, there are primary (receptor-related) labeled-lines and secondary (feature-related) labeled-lines. However, all neural paths between major neurological elements can
be considered labeled, even if investigators have yet to discover and/or label them from a science perspective. There is not sufficient information available to determine if any primary labeled-line extends to the central nervous system (CNS). As in the case of vision, it is probable that no primary labeled-line extends to the CNS. The signals on most of the feature lines are probably sums and differences of primary line signals.

Christensen & White provided a comprehensive overview of this subject from its introduction by Dethier in 1976. They note, “In the ‘labeled-line’ model, the sensory axons carrying information to the CNS are ‘absolutely restricted’ with respect to selectivity, whereas in an ‘across-fiber’ code, ‘each stimulus would produce a different and characteristic total response profile’ across the entire population of sensory neurons. While Dethier’s discussion focused on the modality of taste, the same principles can be applied to olfaction. Although these terms appear to represent useful concepts, their application to olfactory coding is not entirely straightforward.” They provided a simple schematic applicable to olfaction that captures the summation of inputs from sensory neurons associated with the same SSC’s but does not introduce any differing.

The term quality has been used as a parameter in chemoreceptor research for a long time. Its definition has seldom been precise and has changed frequently. Smith & Scott review the history of this term. In general, the quality of a stimulant was associated with its perception. The labeled-line hypotheses tend to require an individual SSC-sensory neuron type for each quality while the across-nerve pattern hypothesis tends to require an individual SSC-sensory neuron type for each stimulant determinant with the quality being represented by a pattern of neural responses.

Christensen & White go on to introduce a new hybrid term and concept; “Across-label coding.” In the discussion, they enumerate the multiple signaling paths related to a given stimulant in the moth. They develop the idea of combinatorial signal processing and subsequent projection. “Each glomerulus may serve as the locus for a distinct odorant input, and through parallel distributed processing, different odor stimuli are represented in distinct patterns of activity across partially overlapping subsets of glomeruli.” They go on to discuss potential stage 4 signal processing, including the possibility of the use of content addressable memory.

Shepherd (1988, page 23) illustrates the labeled-line theory showing one of four gustatory stimulants exciting each of four distinct sensory neurons that connect by individual neural pathways to individual brainstem neurons, and then notes “the first unit recordings from single fibers of the chorda tympani by Pfaffman in 1941 showed this could not be the case.” A more rational approach was the “across-fiber-pattern” theory. Pfaffman et al. (1976) suggested that, “in such a system, sensory quality does not depend simply on activation of some particular fiber group alone, but on the pattern of others active.” Spector and Travers defined these theories somewhat differently. “The labeled-line theory postulates that there are a few classes of neurons and that the activity in a given class generates a specific qualitative perception.” “The across-nerve pattern theory postulates that any given qualitative perception arises from patterns of activity in large ensembles of neurons.” They note the labeled-line model can be a special case of the across-nerve pattern theory where one particular neural path dominates a pattern of neural paths. They note, “the ability to definitively test the validity of various models of the neural coding of taste quality has been hampered by a nearly complete reliance on correlatve statistical procedures and a lack of available techniques that allow selective manipulation of putative classes of gustatory neurons.”

The labeled-line hypothesis related to a similar organization believed to exist in the immune system. The across-nerve-pattern hypothesis can be compared to the visual system where only four photoreceptor types can define ~100,000 colors. As in vision, it is difficult to define the limiting level of discrimination between stimulants. In vision, the human eye can discriminate between approximately 500 individual hues, along with a large number of saturation levels combined with an

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even larger number of illumination levels. The three-dimensional visual color space has been estimated to include 7.5 million discriminatable points.

[xxx coordinate this paragraph with the comments within the Shepherd paragraph above.]

Spector & Travers assert (page 178), “the labeled-line model must satisfy the very restrictive conditions that activity in a given unit type is both necessary and sufficient to generate a specified qualitative perception. Thus, the only definitive way to distinguish between the two theories is to selectively preclude groups of unit types, singly and in combination, from contributing to the overall taste-evoked signal.” While a clear condition, it only applies to these two theories. They also note, “The labeled-line theory is in essence a special case of the across-nerve pattern theory.”

Hildebrand & Shepherd gave a different definition of the labeled-line hypothesis in 1997, based on Shepherd (1985). “In general, it may be postulated that each glomerular unit constitutes a complex labeled-line, labeled structurally by the ORC `projecting to it and functionally by their collective MRR, i.e., the spectrum of odors that activate the subset and consequently its glomerular unit.”

Data is now available to resolve the labeled-line versus across-nerve-pattern dichotomy. Figure 8.6.7-19 from Doetsch explains the situation at the most basic level\[320\]. The same bundle of neurons within a single fiber (nerve) are shown. In frame A, the neurons are labeled by number. If the fiber emanates from sensory neurons, each is traceable to its source and can then be associated with a specific type of stimulus (and possible physical location in the visual and auditory modalities). In frame B, the same array of neurons is shown projecting information about the environment at a given time. A specific pattern of neurons is active. The individual neurons may be passing analog signals to a subsequent analog site or they may be projecting action potential pulse trains (phasic signals) to the next orthodromic stage. Both the labeled-line and across-nerve (fiber) designations are relevant. The descriptor, “across-neuron,” is inappropriate since a single neuron does not exhibit an internal structure that can support any pattern.

Although not usually discussed, the CNS always knows the specific source of each individual PNS nerve since the routing is controlled by the genetic code (unless surgical procedures have been used to reroute them). In this case, the neurons describing the letter four in frame B would be transmitting a set of signals generated by a difference in signal level traveling along those neurons due to the numeric “4” being projected on the retina. The “information” content of the message would be extracted in stage 4 of the CNS. In the case of olfaction or gustation, the pattern forming the letter “4” might describe a mixture of mono-sodium glutamate and quinine-HCl. That information would also be extracted in stage 4 of the CNS.

A single labeled-line originating in one retina can project useful information to the CNS, as when a distant flashing light at night is perceived by a sailor. Its location, period and color can be delivered to the brain over this single labeled-line. Alternately, the neurons in a given two-dimensional array can represent the three-dimensional gustatory space. The pattern in this two-dimensional array can project information about all of the important aspects of the given stimulus or group of stimuli at the instant the pattern was recorded.

The work of the Mori team and the Johnson & Leon team lead to a clearer understanding of the combinatorial character of the across-neuron pattern signal processing used in olfaction. The work of Christensen & White define the character of the resulting across-neuron patterns.

The evidence shows the SSC's of olfaction are not stimulant specific but determinant specific. As a result, the stage 1 output of the sensory neurons can be considered positive going analog waveforms that are determinant-labeled-lines. The determinants of olfaction are a large but finite set (on the order of 20-30 individual determinants). They are represented at the output of the glomeruli (within stage 2) as positive going electrolytic signals within the dendrites and podites of the ganglion neurons (consisting of both morphologically identified mitral and tufted cells). These outputs have been mapped by observing the rate of utilization of 2-DG as a function of position along the surface of the main olfactory bulb. These glomeruli outputs represent a monopolar positive-going across-neuron-pattern that describes a particular stimulant within the neural system.

The monopolar signals from the glomeruli are summed and differenced at the stage 2 input terminals of the Activa within the ganglion neurons of the main olfactory bulb. These signals are then used to encode the action potentials generated in the stage 3 output circuits of the ganglion neurons. If only summation occurs at a given ganglion neuron, the neuron is biased to produce a negligible pulse rate under quiescent conditions. As a result, its mono-directional output pulse rate is proportional to the sum of the signals applied to its dendritic input. The pulse rates from these summing ganglia represent a positive going across-neuron-pattern describing the intensity profile of the stimulant (or stimulants). This pattern can be considered a first order pattern.

If only differencing occurs at a given ganglion neuron, the neuron is biased to produce a nominal pulse rate under quiescent conditions. As a result, its bidirectional output pulse rate is proportional to the difference between the signals applied at its dendritic and poditic inputs. The resulting pulse rates from these differencing ganglia represent multiple bipolar across-neuron-pattern describing the differences between sets of stimulant determinants. These patterns can be considered second order patterns resulting from one or more simultaneous stimulants.

The combination of the first order mono-directional action potential rate pattern and the multiple second order bi-directional action potential rate patterns provide a complete neural description of the stimulants present at a given time. This combination of patterns appears at the axons of the stage 3 ganglion neurons and is projected to the CNS by these neurons.
The total number of ganglion neurons emanating from a MOB and forming the LOT is known approximately for only a few species. How many of these ganglion neurons produce summing outputs and how many produce differencing outputs is unknown. The work of Christensen & White must be greatly expanded to obtain meaningful numbers for the species of primary interest, humans, rats, rabbits, mice, etc.

While propagated to the CNS using pulse techniques, the actual across-neuron-patterns recovered at the stage 3 decoding neurons are analog maps. Thus the number of identifiable stimulants at the CNS depends on the signal-to-noise ratio of the stimulant signals at the output of the stage 1 sensory neurons. These ratios depend on the concentration, solubility and other parameters of the stimulants as much as on the sensitivity of the various SSC’s to the stimulants. At high signal-to-noise ratios, it has been estimated that the human can recognize approximately 100,000 stimulants on a sequential differential test basis. The number of individually identifiable stimulants that can be identified reliably under these conditions is probably much lower.

The forms of stage 2 signal processing and stage 3 encoding are very similar to that used in the visual modality, except the potential number of second order differencing channels is much higher. The sum of the number of first order and second order channels defines the multidimensional order of the system. The CNS has no difficulty in processing signals of high dimensional order as shown for the visual modality. In preparing the information obtained from stage 4 processing, a “place” is assigned to each dimension in the multiple bit word delivered to the saliency map. It is the olfactory portion of the saliency map that describes this aspect of the external environment. The analog value inserted in that place is compared to all of the values in all of the individual places (across all sensory modalities) to determine the external environment at a given moment (Section xxx re saliency map). The code used to populate the saliency map has not been identified at this time.

The labeled-line hypothesis in its pure form only applies to the olfactory modality with respect to the determinants of a stimulant and not the stimulant. Furthermore, the labeled-line hypothesis only applies as far as the end of the axons of the stage 1 sensory neurons. Beyond that point, the features of the across-neuron-pattern hypothesis dominate in the neural system.

8.6.7.4.3 Designing OAR/SOR/SAR experiments

The design of experiments of the OAR/SOR/SAR type requires that stable and repeatable conditions be attained. While the concept is one of a linear operating space, it must be recalled that all sensory neurons perform a linear stimulant to logarithmic generator potential conversion. It is the generator potential that is propagated through the neural system. All sensor neurons have a minimum operating level below which they are random noise limited (or at least impacted). To avoid this problem, it is appropriate to operate in the odorotopic regime (analogous to the photopic regime in vision). This is a region where the generator potential has a constant slope with respect to stimulus concentration greater than or equal to 1.0 when plotted on a log-log graph. Operating in this regime will avoid most of the “non-repeatable” problems found in the literature, particularly where multiple odorophores are presented at one time. Once the elicited sensations are understood, based on odorotopic conditions, elicited sensations under non-odorotopic conditions can be better understood.

Like other sensory modalities, the time constants of the sensory neurons are quite important. They are also asymmetrical. The major attack time constant is in the millisecond or less range. However, the signal decay characteristic at the pedicle of the sensory neuron axon is more complex. The first effective decay time constant is in the few seconds range. However, there is a second time constant associated with the adaptation mechanism. It is only important when stimulation near or above the odorotopic regime is employed. This time constant is typically in the few minutes range. Care must be taken to insure repeatable initial conditions as well as stimulation in the odorotopic regime. It should be noted, washing out the stimulant is effective at the receptor level but it may not be effective as the sensory neuron level if it follows a high concentration stimulation.

8.6.7.5 Stage 2 and later morphology of the olfactory modality

[move to later section of Chapter 8 ]

To aid in interpreting the olfactory modality, it is useful to have an overall signal flow diagram of olfaction. While writing on “flavor,” Shepherd has provided a useful rendition of the olfactory
modality showing signal flow as it relates to the cytoarchitecture of the brain in Figure 8.6.7-20. His concept of an image being formed prior to the information extraction engines of stage 4 is not supported here. Hence, the title to his figure has been replaced. It is generally recognized that the olfactory modality exhibits no capability to generate a spatial image relating to odors. The only image is an n-dimensional “image” describing the relative intensities of the signals generated in the nine independent (and therefore) orthogonal signaling channels created in stage 4 and presented to the cognition engines of stage 5 via the saliency map. It is also noted that the results associated with “lateral inhibitory microcircuits,” differencing, can be recorded in stage 3 pulse signaling circuits but the causal mechanism arises in stage 2 analog circuits.

In his 2012 book321, Shepherd reviewed a wide range of concepts seeking to resolve the labeled-line versus the across-fiber pattern. He inadvertently complicated his investigation by including umami as a fifth fundamental taste perception. He also defined a tastant like the gustant of this work without recognizing that such a tastant was not fundamental but generally contained multiple gustaphores. These assumptions made defining a single one dimensional independent parameter impossible. Failure to recognize the orthogonality of individual signals delivered over labeled-lines also caused an independent parameter (in this case the d-value of the DACB) to elude him. The orthogonality of the labeled-lines result in the folding of the d-value scale into a multi-dimensional olfactory space.

The gustant (tastant) of major focus in defining umami is mono-sodium glutamate. As shown in this work, Section 8.5.xxx contains three distinct gustaphores, the hydrated sodium ion, the dulcal moiety and the acetate moiety.

The individual labels in the graphic will be described and discussed later as each stage of the neural system is addressed. While Shepherd asserts in the title to one of his chapters that "A smell is like a face, this work would suggest it is more like a musical note played by a symphony of many instruments. It has no spatial aspect (either 2D or 3D; however, it has a complexity that can be expressed in a 9-dimensional space."
8.6.7.6 Stage 4 information extraction in olfaction

Only limited work at the detailed level has been reported for stage 4 of olfaction. It is known that afferents from the olfactory bulbs extend to the amygdaloid nucleus, the anterior perforated space and the primary olfactory cortex (generally described as the (pre-)piriform cortex, uncus region or area 28 (Noback page 222). Area 28 is on the medial surface of the temporal lobe.

Bekkers & Suzuki have looked at the role of the piriform cortex of stage 4 within the context of the olfactory modality from the conventional perspective (e.g. GABAergic neurons, etc.). While they discuss briefly the work of many and provide citations to that work, the paper is primarily an overview. All but the first figure are from other sources. Their figure 1 is quite unconventional is showing commissure from the lateral olfactory tract entering the anterior and posterior piriform cortex through the outer surface of the cerebral cortex rather than through the inner surface. Figure 1b can be further annotated based on this work and other similar investigations if a more conventional interpretation of the circuit paths are adopted. The conclusion does not provide much new information and primarily outlines work yet to be done. It includes a list of “Outstanding Questions.” Examples include:

- Do neurons in different layers (e.g., semilunar, superficial pyramidal, and deep pyramidal cells) perform different functions? Do the properties and functions of afferent and associational connections vary with laminar depth?

- Where are different aspects of the odor percept formed? If in higher order structures (such as the orbitofrontal cortex), what are the critical features of pre-processing performed by the PC?

In 2014, Olofsson et al. reported their results using VEP techniques (and limited results from fMRI experiments). They used the expression event-related potentials (ERP) rather than VEP. The clinical work was more exploratory than confirmatory. They summarized one significant problem with the olfactory modality, and probably the gustatory modality as well. While people can often tell two smells apart, “On one context a smell might be identified as a nice cheese, in another it might seem like the person standing next to us needs to wash their clothes.” This is an anecdotal case of a wide variety of unidentified odorants being present as opposed to the contextual situation associated with a single odorophore.

In a separate paper, Olofsson provided a review of useful data on the time to perceive a given odor. The discussion is long and the semantics avoids specificity in a number of critical situations. Based on his results, he proposes a simple conceptual model of olfaction involving detection, object processing, valence and edibility. The model is a mesh network. Valence is not defined in the paper but he does indicate it has a high/low character. Olofsson notes, “the valence-centered approach assumes that odor valence is determined by molecular stimulus features (Khan et al., 2007).” He also notes, “Evaluation of valence (rapidly choosing whether the odor is pleasant or unpleasant) were carried out at a slower speed of around 1100–1200 ms.” He does stress the “cascade” character of the steps leading to an olfactory perception in his discussion. However, the mesh character of Olofsson’s network makes it difficult to arrive at simple and unique time delays at or between stages of his graphic representation of the modality.

In 2012, Shepherd addressed the question of stage 4 information extraction in the cerebral cortex and quoted Wilson & Stevenson of 2006 extensively. The following material can be related to the

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Wilson & Stevenson asserted that adaptation to olfactory stimulation occurs within the CNS, stages 4 and beyond. This is contrary to the performance documented here for every external sensory modality. They offered no substantial documentation for this assertion. Adaptation is a primary function of the sensory receptor neurons of stage 1. The function is divided between the transduction mechanism on the surface of the neuritic structures of the neuron and the first A-type based amplifier, the adaptation amplifier, within each sensory neuron. See Sections 8.6.1 & 8.6.3 for the specifics related to the olfactory sensory neurons.

Shepherd summarized his text in Chapter 13 before even addressing the “Mouth Sense & Flavor” in Chapter 14, with the highly homocentric and seldom accepted assertion, “The main message of this book is that, despite the declining number of receptor genes, the brain processing mechanisms of the smell pathway, culminating in the neocortex, bestow a richer world of smell and flavor on humans than on other animals.” The italics are in the original text, page 111. As in other sensory modalities, the olfactory and certainly the combined gustatory, olfactory and osmoregulatory capabilities of many animals appear to exceed the human capabilities based on field observation. Beyond Chapter 14, Shepherd becomes more philosophical than scientific. On page 208, he tempers his position by noting, “The received wisdom (I have believed it myself) is that we (humans) are poor at describing our world of smells.”

8.6.7.7 Number of perceivable odors in humans

The subject of the number of perceivable odors will be addressed further in later chapters of this work. However, the framework for estimating this number is available from the hypotheses of this work. Figure 8.6.7-21 describes this framework. It recognizes there are an uncountable number of chemicals in the environment.

Historically, the molecules of the environment were definable and understandable based on the rules of valence and covalent chemistry. More recently, understanding the larger molecules of protein and biological chemistry have required knowledge of conformal chemistry, a more complex set of structural rules defining the bond lengths and bond angles allowed within a structural form. Even more recently, the conformal chemistry rules related to the folding of very large molecules has become important. This folding frequently determines the exposure of some atoms and groups of the molecule to additional chemical interactions with other molecules. These interactions include the relatively new field of coordinate chemical bonding. It is this coordinate chemical bonding that is crucial to the understanding of olfaction!

The dual antiparallel coordinate bond (DACB) is a critical feature of olfaction chemistry. While the number of definable chemicals in the environment is uncountable, the number of odorophores found within this universe of chemicals is distinctly limited based on the ensemble of rules described above.

However, there are only a finite number of different odorophores based on the DACB bond requirement of this hypothesis and the structural rules of organic chemistry. There appear to be at least hundreds of different fundamental structural arrangements meeting the requirement that they provide a d-value between about 1.8 and 8.5 Ångstrom, the sensitivity range of the identified human olfactory modality. The d-values of these fundamental structural arrangements are frequently perturbed by structural crowding and other phenomena. These secondary effects cause variations in the nominal d-value in the second and third values to the right of the decimal point. Thus, the total number of countable odorophores, based on the accuracy desired in the range of 100 to a few thousand. These odorophores all converge on nine identifiable types among the few million odor receptors (OR) of the olfactory epithelium involved in step 1 of the transduction process. All of these few million OR’s are accumulated into nine olfactory signaling channels by the glomeruli of stage 2 based on their common specific sensitivity. Since the nine channels are processed as statistically independent, they can represent $512 = 2^9$ distinct states based only on the presence or absence of a signal in a given channel. Each signaling channel provides an analog signal representing the median intensity resulting from the product of the intensity of the individual stimulus and the sensitivity profile of the OR at that d-value. The literature does not provide an adequate estimate of the maximum signal-to-noise of these channels. However, it appears to be limited by the encoding/decoding process of the stage 3 projection neurons. The figure uses an estimate of $64 =$
2⁶ for the maximum signal-to-RMS noise in each channel. Based on this framework, the human olfactory modality employs a perceived odor space of up to an estimated 32,768 states. As in the visual modality, some of these states may not be perceivable in practice. However, the estimate is consistent with the common wisdom among perfumers as to the maximum number of odors a trained human can perceive.

This framework provides a totally different value for the number of perceivable odors by humans than does the recent paper of Bushdid et al. discussed in Section 8.6.8.5.

8.6.8 Confirmation of the hypothesis and corollaries by specific papers

Up until the 1990's, most qualitative and quantitative analyses related to olfaction involved psychophysical experiments, and NMR and gas chromatography measurements followed by synthesis of the presumed chemical constituents of mixed odorants. Structural analysis based on this data was grossly unsuccessful in identifying the underlying structures responsible for any scents (perceived odors).

Bryant & Mezine presented an extensive family of complex molecules in an investigation of nocent stimulation of the trigeminal nerve of the rat. Probably all of the molecules quality as odorants that are relevant to this work. However, the molecules contain large numbers of individual odorophores. See Section 8.7.3.1.2.

8.6.8.1 Paper of Masuda & Mihara

Masuda & Mihara provided a paper describing the olfactory performance of the substituted alkylpyrazines that provides substantial support for the hypothesis developed here. Written in 1988, it explores the NMR properties of a group of materials and invokes a stereochemical model involving a "pocket" in the olfactory receptor, neither of which are appropriate to the task at hand. They do invoke hydrogen bonding in their interpretation and even two hydrogen bonds per molecule. However the bonds are not restricted to being antiparallel as utilized in the current hypothesis. They also describe a few distances between a hydroxyl group and a quaternary carbon in the seven Angstrom range. However, a quaternary carbon does not offer the capability of forming an additional hydrogen bond via coordinate chemistry.

Masuda & Mihara do provide a comprehensive table of odor thresholds for a series of alkylpyrazines as a function of the length of the hydrocarbon side chain as well as a variety of orbital-based ligands also attached to the basic ring. Each of their substances is defined by a CAS registry number for added precision; some of these numbers are no longer valid but the important numbers are. A spreadsheet has been prepared using these numbers and both Jmol files and the DS3.5 visualizer to determine the critical d-values associated with each molecule in their stimulant set.

Their Table II can be rearranged in multiple ways based on the hypothesis of this work in order to illustrate valuable structures. It is not obvious why the original column order was chosen. The columns of Figure 8.6.8-1 groups the substituted ligands by family and associated d-values. All of the compounds in the original first column exhibit only one major (or dominant) d-value, d = 2.732 Angstrom.

Quoting Pelosi et al. (1983), they noted the nitrogen farthest from an oxygen associated directly with the 6-member ring of a pyrazine was the only nitrogen of significance in the stimulus of an OR. They noted the ability of both the nitrogen and that oxygen to form hydrogen bonds with some other molecule(s). Those pyrazines showed a threshold of 0.02 to 0.002 ppb (parts per billion in water). They also described the threshold performance of one 5-sided thiazole, a heterocyclic ring with both a nitrogen and a sulfur atom in the ring. The value of 0.003 ppb was given.

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The rows differ by the alkyl hydrocarbon and indicate the difference in threshold sensitivity and
described by the columns. The columns of Masuda & Mihara have been rearranged with vertical bars added based on the
current best estimate of the effectiveness characteristic of each OR. The colloquial character of the
descriptions is obvious. Odors stimulating the same OR channels are assigned a variety of perceived
cents by reporters who may have exhibited significant specific anosmias. Modified from

Figure 8.6.8-1 Odor descriptions and thresholds of substituted pyrazines. The columns of Masuda & Mihara have been rearranged with vertical bars added based on the current best estimate of the effectiveness characteristic of each OR. The colloquial character of the odor descriptions is obvious. Odors stimulating the same OR channels are assigned a variety of perceived scents by reporters who may have exhibited significant specific anosmias. Modified from Masuda & Mihara, 1988.

The rows differ by the alkyl hydrocarbon and indicate the difference in threshold sensitivity and
perceived scent with changes in the dipole potential of each complete molecule. Note, all of the chemicals reported in this table incorporated more than one odorophores, with the exception of pyrazine itself.

The addition of a benzyl ring to the basic odorants based on sulfur or oxygen adds additional potential odorophores to the chemical. This is illustrated by the addition of the scent of cresol-like, phenol-like, and chemical to the descriptors in these columns. The d-values for the 2-phenoxypyrazine_413629 are 2.327, 2.733, 2.87, 3.756, 5.092 and 5.47 Angstrom. The d-values for 2-(phenylsulfanyl)pyrazine_460203 are 2.654, 2733, 3.204, 4.041, 5.567 and 5.636 Angstrom. These complex chemicals stimulate a variety of OR channels as indicated. However, their relative effectiveness in stimulating one channel versus another are unknown at this time. Masuda & Mihara asserted, “In general, the odor thresholds of 3-substituted 2-alkylpyrazines increase in the following order: OCH3, < OC2H5 < SCH3 < SC2H5 < OC6H5 < SC6H5. How they established such a sequence among such a mixed bag of apples and oranges is not clear.

The variation in the perceived scents associated with each set of parameters is indicative of the colloquial nature of the labels used in perfumery and the probable presence of specific anosmias among the untested reporters. The label “sweet” appears ubiquitously in the first two rows. The label “green” is ubiquitous in the first column. Masuda & Mihara did not describe how they qualified their human subjects as good/adequate odorant reporters or how they controlled the labels the reporters could use in their responses.

Figure 8.6.8-2 shows the difference in concept between the hydrogen bonding of Masuda & Mihara, based on the stereochemical pocket of the OR and the DACB relationship proposed in this work. Both frames show the same methoxypyrazine with an aliphatic side chain. The d-value for the DACB structure on the right (O to N6) is 3.646 Angstrom. The d-value for O to N3 is 2312 Angstrom and the d-value between the oxygen and the resonant ring is 2.393 Angstrom. The question of hydrophobicity doesn’t play a role in this proposal. The key feature is the DACB coupling. As a general rule, the proposed receptor molecules are polar and therefore hydrophilic amino acids.

Figure 8.6.8-2 Comparison of two concepts of odorophore/OR coupling. Left, conceptual coupling of Masuda & Mihara based on a pocket in the hydrophobic layer of the OR capable of establishing one or more hydrogen bonds with the odorophore. Right, the proposed DACB coupling between the odorophore and the two orbitals (shown as oxygen) of the OR. The perpendicular distance, d, between the two hydrogen bonds is the important parameter in this frame. The only other criteria is that the orbitals of the odorophore and the orbitals of the OR be on their external surfaces. There is no requirement that the two hydrogen bonds be in the same plane as the pyrazine ring. Modified from Masuda & Mihara, 1988.

8.6.8.2 Paper of Rossiter, 1996

The paper of Rossiter, 1996 becomes a rich source for mining based on the hypothesis and corollaries of this work. This section will provide a reinterpretation of her database in the context of the
hypothesis of this work. Initially, it is useful to discuss her text and structures associated with figure 40.

8.6.8.2.1 “Green” as a scent (perceived odor) related to OR4

Rossiter has noted in her text associated with figure 40 that the structures shown in Figure 8.6.8-3 are all perceived as “green” among investigators in the perfume industry. The figure has been modified to identify the “overlay moiety” associated with the DACB coupling of the individual structures to the appropriate OR channel of this work. Solid dots have been used to identify the centroids of the benzyl rings and the p-bonds of specific C=C bonds. The systemic name for form 66 is 3-Z-hexen-1-ol and filed in ChemSpider as 21105914. The systemic name for form 68 is 1,3,5-undecatriene_55707. Form 70 with R1 and R2 = H is simply phenylaldehyde_13876539. The d-values for form 70 do not change significantly if R1 and R2 are replaced by more complicated saturated hydrocarbons.

Structures 66, 68, 69 & 70 are all seen to have d-values grouped about the nominal center of the OR 4 (limal) channel at 4.467 Angstrom. Structure 66 has a d-value on the low d side of the nominal limal channel effectivity characteristic while structures 68, 69 & 70 are grouped on the high d side of the nominal channel. In the absence of significant overlap between the effectivity characteristics of the OR 3 and OR 5 with the OR 4 channel, these four structures would be expected to be perceived as identical (when presented at equal concentrations at the olfactory epithelium and in the absence of any difference in their dipole potentials).

Structure 67, as documented in Jmol and using the DS3.5 visualizer has significantly different d-values. When R = H, 2-methoxy pyrazine_17443 has a d-value between the oxygen and N in 3.646 Angstrom. The d-value to N is 2.313 Angstrom. When structure 67 has R = n-propyl, 2-methoxy-3-propylpyrazine_460429 has d-values of 3.625 and 2.315 Angstrom respectively. These values are nominally the same, as would be expected for any saturated hydrocarbon attached at location 3. They may impact the dipole potential of the molecule but do not introduce any additional orbitals. The various structures based on form 67 would be expected to be perceived as more floral via OR 3 than limal via OR 4.

If structure 67 is modified to 2-acetylpyrazine_28682 by placing the methyl carbon between the oxygen and the ring, the oxygen to N d-value becomes 4.704 Angstrom. This value and form exhibit almost the exact overlay moiety as in form 68 and is predicted to stimulate the scent of “green.”

Additional investigation appears warranted as to (1) whether the evidence is statistically precise to describe the perceived odor of this molecule as green (all evaluators were free of any specific
anosmia), (2) whether form 67 belongs in the green (limal) group of perceived odors or in the floral group and (3) whether it was adequately described (versus 2 acetylpyrazine_28682 with any one of the specified saturated hydrocarbon ligands or hydrogen at position 4).

Note the totally different structures of forms 66 through 70. Their individual ligands are almost totally different, yet they are perceived as green. This situation all but falsifies any putative olfactory theory based on conventional groups and/or ligands of ordinary chemistry. On the other hand, if form 67 is removed or slightly modified, the structures all exhibit a common overlay moiety of two orbitals separate in 3D space by a d-value of between 4.295 and 4.896 and stimulate the OR 4 channel of the olfactory modality. In addition, structure 69 contains neither oxygen or nitrogen but meets the specified criteria for forming a DACB coupling to OR 4 based on coordinate chemistry. This is excellent support for the hypothesis of this work.

In discussing the role of sulfur in olfaction, Rossiter quotes Boelens, “the cis carbon-carbon double bond in cis-3-hexenol (66) and cis-3-hexenyl acetate can be replaced by a sulfur atom with no significant effect on the odor profile. If this statement is statistically correct, the replacement should have the effect of increasing the d-value of (66) from 4.295 Angstrom to 5.164 (using 3-mercaptopropanol_79578 as an analog) [xxx check Boelens paper for a more appropriate chemical name for this chemical] putting it closer to the d-value of the other materials in the figure but probably pushing it into the effectivity characteristic of OR 5 instead of the OR 4 channel. This should result in a significantly different perceived odor.

This evidence plus that related to the perception of a pine forest and/or a lime suggests the dipole potential and the concentration of these chemicals would place them at different locations along the dulcal intensity continuum of [Figure 8.6.7-3].

In her discussions, she does note that structure 66, cis-hexen-1-ol, now known as (3Z)-Hex-3-en-1-ol_21105914, is a particularly simple molecule that is characteristic of and extracted from freshly cut grass. It has a d = 4.295 Angstrom, on the low d-value skirt side of the limal channel, OR 4 (and may stimulate the OR 3 channel as well). In the perfumer’s terminology, it is perceived as “green” and she notes its perception remains unsurpassable. The trans-version, 3-Hexenol_4447565 with d = 4.285 Angstrom is described as less sharp and more fatty. But its d-value is only marginally shorter than for the cis-variant. Its dipole potential may contribute to the difference in perceived odor.

8.6.8.2.2 The scent of the unsaturated alcohols & their d-values

Rossiter notes the systematic evaluation of the unsaturated alcohols by several investigators over the years that have established the change in perceived odor with chain length between the hydroxyl group and the double bond. As the double bond moves from the two-position, the scent changes from

“(2) fruity, fresh, and sweet, d = 3.006 Angstrom for trans version _12988 through
(3) leafy and grassy green, d = 4.285 Angstrom for trans version _447565, and then
(4) insect-green and vegetable-like green, d = 5.514 Angstrom for trans version _55301, to
(5) oily-fatty and herbal, d = 6.785 Angstrom for trans version _63156.”

The above set can be extended by looking at other unsaturated alcohols,

(6) ??? for 6-heptenal, d = 8.017 Angstrom for trans version _4446441, and
(7) ??? for 7-dodecen-1-yl acetate, d = 9.287 Angstrom for trans version _4509620
(8) ??? for 8 dodecen-1-yl acetate, d = 10.541 Angstrom for trans version _451607

While these multi-word labels do not agree with the single word labels used here for molecules of similar d-values, they do show a progression compatible with the effectivity characteristics of the appropriate OR channels. If the word vegetable-like green was changed to potato skin-like, and the term herbal was changed to spice, the underlined words would be quite closely matched to the labels used in this work. The counter option would be to change the label spice in this work to herbal for OR channel 7. Until the range of labels associated with OR 7 are determined, this choice can not be made.
As noted, the work of these previous investigators can be extended by looking at 6-heptenal and 7 dodecen-1-yl acetate etc. based on this work. The alcohols become more delicate as their length is extended. While trans-6-heptenal is generally described as putrid, a more specific label may require more careful study. The 7- and 8-dodecen-1-yl also extend over into the pheromone regime associated with oskoration (Section 8.6.11).

Hatanaka et al. have compared the straight-chain alcohols and aldehydes\textsuperscript{326}. They observed no difference in their scent (perceived odor) when they had the same unsaturated structure, except that they were 10 to 1000 times more potent.

Johnson et al. have explored the effects of double and triple bonds of selected odorants, primarily acetates but including octanoic acid, in the glomeruli of rats\textsuperscript{327}. The triple bonded 2-octynoate has a $d = 3.188$ Angstrom compared to 2-octenoate with $d = 3.061$ Angstrom. It therefore stimulates the OR 3 channel more strongly than 2-octenoate based on the hypothesis. Both stimulate channels OR 2 and OR 3. Their studies of the signals generated in the glomeruli due to these chemicals are discussed in Section 8.6.7.3, the overview of stage 2 operation of the olfactory modality.

As generally recognized, the saturated alcohols exhibit no odor, as justified by the lack of an odorophore based on this hypothesis. The unsaturated alcohols do exhibit an odorophore as described above, based on this hypothesis, and as described in Rosseter’s fully referenced paper.

The alcohols are frequently esterified with organic acids to form acetates. The result is a molecule that always exhibits the carboxyl group, resulting in an odorophore with a nominal $d$-value of 2.276 Angstrom. If the alcohol was saturated, it remains saturated and no additional odorophores are exhibited by the ester. If the alcohol was unsaturated, the ester continues to exhibit the odorophore characteristic of the alcohol plus an additional odorophore based on the unsaturated bond of the alcohol and the carbonyl oxygen of the acetate. This odorophore typically has a $d$-value marginally longer than that of the unsaturated bond and the original oxygen now forming the ester.

8.6.8.2.3 “Catty” as a scent (perceived odor)

Rosseter noted, “Grapefruit, passion-fruit, grape, melon, and blackcurrant odors are produced by certain sulfur compounds when present at very low concentrations. Indeed, volatile organic sulfur compounds are very important constituents for the flavor of food and beverages, not only in the area of fruit flavors but also, for example, in meat, bread, garlic, potato, beer, and coffee” (page3223) and “At high concentrations volatile organic sulfur compounds generally have the unpleasant odor that chemists usually associate with sulfur materials. This dependence of odor quality on concentration makes it very difficult to carry out structure-activity studies on this group of compounds.” The scope of the first sentence makes it very difficult to find a set of tasters (except novices) with a common background and no specific anosmia. The scope of the second shows the difficulty of preparing an adequate test protocol. She went on, “One small group of sulfur compounds which has been the focus of an SAR study is a series of four mercapto ketones and mercaptans (Figure 38). All four materials were perceived as having the “catty” note of blackcurrant bud oil, which has always been of interest for the flavorist and, more recently, for the perfumer.”

Figure 8.6.8-4 reproduces her figure 38 with additional annotation. It is a condensation of figure 1 in Polak et al\textsuperscript{328} and does not include their reference “catty” odorophore labeled a. The label catty scent was based on their association of it with the fresh urine of a tomcat. They did a sophisticated statistical analysis involving 10 different chemicals; all but one reference contained sulfur and seven of the ten contained a ketone arrangement. Unfortunately, their conclusions were only qualitative.


and offered little insight into the underlying character of their ten mostly sulfanyl chemicals. Their factor analysis diagrams did not assign labels or absolute scales to their two axes. "A particular rank order of similarity among the mercapto odorants is not evident from Figure 2A." Polak et al. did note the distance between the oxygen of the ketone and the sulfur tended to be between 2 and 4 Angstrom but varied considerably due to the different conformers associated with each molecule.

In the figure, the d-values are those obtained from the Jmol file offered by ChemSpider.

![Figure 8.6.8-4](image_url)

**Figure 8.6.8-4** A set of mercaptans (thiols) of different structural families. Letter labels and original names from Polak et al., 1988. Modified from Rossiter, 1996.

Except for structure i in the Polak paper, the structures all exhibited only one odorophore under the hypothesis of this work. Structures c and g did not exhibit any odorophore within the hypothesis and corollaries of this work, suggesting additional corollaries may be required to address the sulfanyl's and ever increasing molecular complexity.

Their range of mercaptans exhibited d-values suggesting stimulation of OR 2, 3 or 4 channels by individual mercaptans. They did note without further comment that tertiary thiols have threshold levels 300-3000 times lower than those of primary and secondary thiols.

### 8.6.8.2.4 The odorophore of grapefruit

Demole et al. have investigated the structure of the odorants of grapefruit in line with the above Rossiter comments and found an unexpected constituent. As they note, "1-p-Menthene-8-thiol (now p-menthene-8-thiol 4932553) is shown to be a potent character-donating constituent of grapefruit juice, in which it occurs at the ppb-level or below. A convenient synthesis is described for this thiophene-thiol, apparently the most powerful flavor compound ever found in nature." and "When adequately diluted, this novel, powerful flavor-impact compound displays a genuine, unmistakable aroma of fresh grapefruit juice (in which it naturally occurs at or below the ppb-level). The d-value of this odorophore is 4.633 Angstrom, well positioned to stimulate the limal (OR 4) channel of olfaction.

### 8.6.8.3 Paper of Wyllie et al., 1994, on muskmelon & related papers

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Wyllie et al. studied the aroma of muskmelon (Cucumis melo cv. Kakdimon) in considerable detail. Their lists of relevant volatiles are quite long, reminiscent of those of Kaiser. However, they did focus on seven peaks in their gas chromatography results that were also perceived as sensory responses to the most dilute extracts. Four of the seven involved sulfur compounds:

- S-methyl thiolbutanoate (systemic name, S-Methyl butanethioate_56225, d = 2.617 Angstrom),
- 3-(methylthio)propanal (systemic name, 3-(methylsulfanyl)Propanal_17597, d = 5.107 Angstrom),
- 3-(methylthio)propyl acetate (systemic name, 3-(methylsulfanyl)Propyl acetate_77128, d = 5.161 & 6.587 Angstrom) and
- tentatively dimethyltetrasulfide.

Many of their identified odorants are based on saturated esters of carboxylic acids (example: ethyl butanoate, a.k.a. ethyl butyrate_7475 with a d = 2.280 Angstrom). These typically stimulate the OR 1 (acidic) channel of olfaction, as well as the GR 1 (acidic) channel of gustation when the melon is ingested. The thioates typically have d = 2.6 Angstrom and stimulate the OR 2 (dulcal) channel. The molecules with d = 5.1 Angstrom typically stimulate the OR 5 (musk) channel and a value near 6.7 stimulates the OR 7 (spice) channel.

They focus their analyses on gas chromatography using a FID detector based on a technique introduced by Miranda-Lopez. Many of their identified odorants are based on saturated esters of carboxylic acids (example; ethyl butanoate, a.k.a. ethyl butyrate_7475 with a d = 2.280 Angstrom). These typically stimulate the OR 1 (acidic) channel of olfaction, as well as the GR 1 (acidic) channel of gustation when the melon is ingested. The thioates typically have d = 2.6 Angstrom and stimulate the OR 2 (dulcal) channel. The molecules with d = 5.1 Angstrom typically stimulate the OR 5 (musk) channel and a value near 6.7 stimulates the OR 7 (spice) channel.

The odor unit calculations are given to six digit accuracy!

While defining a range of odor units from 0.02 to 4093.18, they acknowledged significant inconsistencies in the ranking of the chemicals in the data compared to other sources. Like in Goeke, some of the list of descriptors appear “astonishing.” Limonene for example is labeled “stale/dirty socks” in Table II. In the later discussion (page 44) they note, “The identity of the dirty socks aroma is unknown.”

In gross outline, the paper by Wyllie et al. on the muskmelon is clearly consistent with the hypothesis and corollaries of this work. However, as noted in their conclusion, there are many inconsistencies in their results. Many of the inconsistencies appear tied to their homogenization of the melon pulp in a Waring brand kitchen blender. They assert, “Aroma volatiles of the Makdimon melon are dramatically altered by homogenizing the flesh prior to SDE.” They continually attribute actions to a lipooxygenase that they are unable to isolate. However, on page 37 they note, “These results are consistent with the finding of Lester that there is no lipooxygenase activity in the middle-mesocarp tissue from the netted muskmelon “Perilla.” A majority of the identified thio compounds stimulate the OR 5 (musk) channel of the olfactory modality and thereby justify the common name of the musk melon.

8.6.8.3.1 Paper of Miranda-Lopez et al. on wine odorants

Miranda-Lopez et al. reported on an effort to obtain quantifiable assays of wines harvested at different times within a vintage and during adjacent vintage years. After an important review of prior experiments by the community (including the names adopted by various investigators to describe their results), Miranda-Lopez et al. defined their program carefully. They employed a flame ionization detector (FID) attached to a gas chromatography olfactometer (GCO) and a method of recording a single human response to the effluent of the GCO and suggestive of its intensity. The intensity scale

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332Guadagni, D. Buttery, R. & Harris, J. (1966) xxx J Sci Food Agric vol 17, pp142-144
was linear and ran from zero to fifteen. They provided extensive data tables. Unfortunately, the
individually identified chemicals were associated with multiple varied semantic labels.

Typically, the only notable change between the different wine samples was some variation in
concentration in some compounds. The identified peaks had concentrations in the wine extract of
at least 1 mg/L; the minimum concentration the integrator could determine. “On average, only 20% of
the FID peaks from all 6 wines were odor-active under these test conditions.

They named their overall experiments Osme, and discussed some of their data output as osmegrams.
They discussed the lack of good conformity between their GCO peaks and the peak intensities
reported by their observer. “Those peaks probably represented the same compound: the retention
times for each peak were close and the descriptors were similar or identical. An explanation for the
multiple Osme peaks for one compound may be that panelists were more sensitive than the FID.
Panelists may have been detecting compounds which overlapped due to column overload.
Compounds that were difficult to volatilize may have overloaded the column creating peaks that
eluted over a longer period of time in lower concentrations. Possibly, panelists were able to detect
this overlapping as multiple Osme peaks.”

“Thus, FID results alone may provide an incomplete and/or misleading summary of the odor-active
compounds in the wine extract.” They also concluded, “LARGE differences were observed in
consensus Osme grams across maturities within the same vintage. In the consensus Osme gram certain
peaks appeared, disappeared, or changed in odor intensity dependent, among other factors on the
degree of grape ripeness.”

8.6.8.4 Paper of Sklar et al., 1986 on rat enzyme release

Sklar has provided a potentially useful categorization of odorants\textsuperscript{333}, Figure 8.6.8-5, based on the
quantity of an enzyme in frog olfactory cilia in response to many stimulants also categorized in human
olfaction. It is noteworthy that the reference used, ., is a relatively complex molecule containing at
least three distinct odorophores as opposed to limonene with only one (with d=4.303 Angstrom).
Citralva (now more commonly known as Geranonitrile_1267637) contains a triple-nitrogen-carbon
bond that is rare in odorants. Note also the negative percentages due to the presence of citralva
in all test samples (explanatory note b).

The introduction to the Sklar et al. paper is clear and concise, concluding with “In the present study
we provide a detailed characterization of odorant interactions with the olfactory adenylate cyclase.
We report that adenylate cyclase stimulation occurs primarily with fruity, floral, minty, and herbaceous
odorants, while putrid odorants fail to influence the olfactory adenylate cyclase.”

Sklar was also working with Pevsner et al\textsuperscript{334} on putative odorant binding proteins. The Pevsner paper
suggests where Sklar et al. were coming from.

The Sklar results begin, “Isolated olfactory cilia from the bullfrog R. catesbeiana contain high levels
of adenylate cyclase activity confirming the results of Pace et al.”

Below this point, italics have been added to both quotations and comments as appropriate by this
author.

“Many floral, fruity, herbaceous, and minty odorants are potent stimulators of the enzyme. Citralva,
a substituted terpenoid odorant having a fruity odor quality, is one of the most potent cyclase
stimulators. We have, therefore, arbitrarily assigned a standard value of 100% stimulation to the

\textsuperscript{333}Sklar, P. Anholts, R. & Snyder, S. (1986) The Odorant-sensitive Adenylate Cyclase of olfactory receptor cells
\textit{J Biol Chem} vol 261(33), pp 15538-15543

\textsuperscript{334}Pevsner, J. Sklar, P. & Snyder, S. (1986) Odorant-binding protein: Localization to nasal glands and secretions
\textit{PNAS} vol 83, pp 4942-4946
Neurons & the Nervous System

cyclase activity elicited by 100 μM citralva. Maximal stimulation by citralva corresponds to a 55% increase in activity over the GTP-stimulated basal level. Odorants structurally related to citralva, such as ceral, dimethyl acetal, and citronellal stimulate the enzyme to -69% and -56% of the citralva-stimulated level, respectively (Figure 8.6.8-5). Many odorants which are structurally unrelated to citralva, such as menthone, D-carvone, L-carvone, 3-hexylpyridine, 2-hexylpyridine, hedione, helional, and coniferan are also potent stimulators of the olfactory adenylate cyclase. We designate odorants that stimulate adenylate cyclase activity to greater than 50% of the citralva-stimulated level as potent cyclase stimulators. Those odorants that increase activity to less than 20% of the citralva-stimulated level are considered poor stimulators. Several fruity, floral, minty, and herbaceous odorants stimulate activity to an intermediate level. Examples include amyl salicylate (40%), dimethyloctanol (33%), eucalyptol (45%), eugenol (47%), and cinnamic aldehyde (34%). Interestingly, the classes of fruity, floral, minty, and herbaceous odorants also contain some non-stimulating odorants such as limonene, linalyl alcohol, lilial, and ethyl vanillin (Figure 8.6.8-5). The assertion in the last sentence strongly suggests the selected enzyme is not crucial to the perception of odorants. They did not indicate how their odorous classifications were determined.

They note, “To gain insight into the molecular parameters that determine the potency of an odorant as a cyclase stimulator, we investigated homologous series of structurally related odorants including the pyrazines, thiazoles, and pyridines. Stimulation of adenylate cyclase activity can be detected only when the parent compound, methoxypyrazine, thiazole, or pyridine has a hydrocarbon chain attached.” This assertion strongly suggests the important role of the dipole potential of the chemical, following selection by the OR, in determining its ultimate perception.

“In general, stimulation of adenylate cyclase is most apparent with odorants which are fruity, floral, minty, or herbaceous. Although many odorants from these groups stimulate adenylate cyclase activity, some exceptions are evident, including odorants like limonene, linalyl, and linalool which do not stimulate cyclase activity.” Limonene is an important reference odorant that does not stimulate significant adenylate cyclase activity.

“The inability of putrid odorants such as isovaleric acid and triethylamine to stimulate adenylate cyclase activity cannot be explained by adverse effects of these odorants on the enzyme, since these odorants do not significantly decrease the basal GTP-stimulated adenylate cyclase activity up to concentrations of 1 mM. Although we cannot fully exclude the possibility that stimulation by these odorants is below the level of detection in our assay, extracellular recordings from individual receptive units indicate that putrid odorants stimulate similarly sized populations of olfactory neurons as fruity, floral, minty, and herbaceous odorants. Putrid odorants are frequently polar, charged molecules, whereas hedonic odorants are mostly nonpolar.”

The following summarizes their discussion, “Activation of adenylate cyclase by odorants has been suggested to be the primary transduction mechanism in olfaction. However, currently there is no direct evidence linking odorant-stimulated enzyme activity to the generation of electrical activity within an olfactory receptor cell. Nonetheless, several lines of evidence suggest that odorant-stimulated adenylate cyclase activity is relevant to olfaction.” And, “The failure of certain groups of odorants to stimulate the olfactory adenylate cyclase suggests that at least one additional transduction mechanism is involved in olfaction.”

Assigning d-values to their odorants suggests their categorization was entirely based on semantic instructions to their test subjects. Limonene at d = 4.303 Angstrom and Citronellal at d = 7.09 Angstrom are clearly not in the same “fruity” category (Figure 8.6.7-11 in Section 8.6.7). In fact, they are used as principle odorophores for two distinct OR channels.
Sklar et al. also defined a broad list of nitrogen-based odorants as shown in Figure 8.6.8-6. The operation of these odorants follows the same pattern as for the oxygen-based odorants except for the differences in bond lengths involved.

**Table 7. Stimulation by Odorants of the GTP-Dependent Adenylate Cyclase in Frog Olfactory Cilia**

<table>
<thead>
<tr>
<th>Odorant</th>
<th>Stimulation (%)</th>
<th>Odorant</th>
<th>Stimulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>14 ± 8(3)</td>
<td>Purfuryl mercaptan</td>
<td>29 ± 9(3)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10 ± 7(3)</td>
<td>Triethylamine</td>
<td>4 ± 7(5)</td>
</tr>
<tr>
<td>Chloroform</td>
<td>5 ± 2(3)</td>
<td>Phenylethylamine</td>
<td>0 ± 7(2)</td>
</tr>
<tr>
<td>Butanol</td>
<td>4 ± 10(3)</td>
<td>Isobutyric acid</td>
<td>2 ± 7(2)</td>
</tr>
<tr>
<td>Pyridine</td>
<td>4 ± 22(4)</td>
<td>Pyrrolidine</td>
<td>4 ± 6(2)</td>
</tr>
<tr>
<td>Xylene</td>
<td>-2 ± 3(2)</td>
<td>Isovaleric acid</td>
<td>-6 ± 8(5)</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>-14 ± 33(3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fruity**
- Citralva* 100
- Citral dimethyl acetal* 69 ± 10(5)
- Citronellal 56 ± 5(3)
- β-Ionone 55 ± 5(3)
- Citronellyl acetate* 50 ± 9(4)
- Isoamyl acetate 19 ± 11(8)
- Limonene 5 ± 4(5)
- Lyral* -4 ± 6(2)

**Floral**
- Isomenthone 105 ± 10(3)
- L-Carvone 74 ± 31(6)
- Menthone 71 ± 3(4)
- Eucalyptol 45 ± 8(4)

**Minty**
- Hedion (MDHJ) 63 ± 4(3)
- Coniferal* 60 ± 20(2)
- Geraniol 58 ± 3(3)
- Helional 53 ± 6(5)
- Decanal 53 ± 8(2)
- Amylsaliclyte 40 ± 10(2)
- Dimethylstereol 33 ± 9(3)
- Acetophenone 30 ± 4(3)
- Phenylethyl alcohol 19 ± 4(3)
- Lilial* -1 ± 4(2)

<table>
<thead>
<tr>
<th>Odorant</th>
<th>(100 μM)</th>
<th>Odorant</th>
<th>(100 μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citralva</td>
<td>100</td>
<td>L-Carvone</td>
<td>105</td>
</tr>
<tr>
<td>Citral dimethyl acetal</td>
<td>69 ± 10(5)</td>
<td>Menthone</td>
<td>71 ± 3(4)</td>
</tr>
<tr>
<td>Citronellal</td>
<td>56 ± 5(3)</td>
<td>Eucalyptol</td>
<td>45 ± 8(4)</td>
</tr>
<tr>
<td>β-Ionone</td>
<td>55 ± 5(3)</td>
<td>Hedion (MDHJ)</td>
<td>63 ± 4(3)</td>
</tr>
<tr>
<td>Citronellyl acetate*</td>
<td>50 ± 9(4)</td>
<td>Coniferal*</td>
<td>60 ± 20(2)</td>
</tr>
<tr>
<td>Isoamyl acetate</td>
<td>19 ± 11(8)</td>
<td>Geraniol</td>
<td>58 ± 3(3)</td>
</tr>
<tr>
<td>Limonene</td>
<td>5 ± 4(5)</td>
<td>Helional</td>
<td>53 ± 6(5)</td>
</tr>
<tr>
<td>Lyral*</td>
<td>-4 ± 6(2)</td>
<td>Decanal</td>
<td>53 ± 8(2)</td>
</tr>
<tr>
<td>α-Carvone</td>
<td>74 ± 4(7)</td>
<td>Amylsaliclyte</td>
<td>40 ± 10(2)</td>
</tr>
<tr>
<td>Eugenol</td>
<td>47 ± 7(5)</td>
<td>Dimethylstereol</td>
<td>33 ± 9(3)</td>
</tr>
<tr>
<td>Cinnamic aldehyde</td>
<td>34 ± 5(4)</td>
<td>Acetophenone</td>
<td>30 ± 4(3)</td>
</tr>
<tr>
<td>Isoeugenol</td>
<td>31 ± 5(3)</td>
<td>α-Pinene</td>
<td>21 ± 12(3)</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>27 ± 4(4)</td>
<td>Phenylethyl alcohol</td>
<td>19 ± 4(3)</td>
</tr>
<tr>
<td>Ethyl vanilline</td>
<td>-3 ± 6(5)</td>
<td>Lilial*</td>
<td>-1 ± 4(2)</td>
</tr>
</tbody>
</table>

*From Sklar et al. (1986).
*Adenylate cyclase activity was measured as described in Sklar et al. (1986). Odorants were tested at 100 μM in the presence of 10 μM GTP. Data are expressed as a percentage of the activity observed in the presence of 100 μM citralva. Citralva stimulation was 17 and 22% of the stimulation by 2 μM forskolin and 10 μM GTP, respectively. Values are expressed as the mean ± S.E. of (n) experiments. From Sklar et al., 1986 as modified by Snyder in Margolis & Getchell, 1988.

**Figure 8.6.8-5** Stimulation of enzyme release by odorants. Odorants were tested at 100 μM in the presence of 10 μM GTP. Data are expressed as a percentage of the activity observed in the presence of 100 μM citralva. Citralva stimulation was 17 and 22% of the stimulation by 2 μM forskolin and 10 μM GTP, respectively. Values are expressed as the mean ± S.E. of (n) experiments. From Sklar et al., 1986 as modified by Snyder in Margolis & Getchell, 1988.
Figure 8.6.8-6: A variety of nitrogen and sulfur-based odorants. The stimulation levels and log $p^a$, are from Sklar et al., and of little interest in this work. The pyridines are heterocyclic compounds containing one nitrogen. The pyrazines are heterocyclic compounds containing two nitrogens. The values in parenthesis indicate the number of experiments used to calculate the mean and standard of error for each value. From Sklar, et al., 1986.

<table>
<thead>
<tr>
<th>Odorant</th>
<th>Stimulation</th>
<th>Log $p^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100 μM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methoxypyrazines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methoxypyrazine</td>
<td>$-5 \pm 5$ (8)</td>
<td>$-0.53$</td>
</tr>
<tr>
<td>2-Methyl-3-methoxypyrazine</td>
<td>$9 \pm 3$ (3)</td>
<td>$0.14$</td>
</tr>
<tr>
<td>2-Ethyl-3-methoxypyrazine</td>
<td>$20 \pm 8$ (5)</td>
<td>$0.68$</td>
</tr>
<tr>
<td>2-Isopropyl-3-methoxypyrazine</td>
<td>$36 \pm 8$ (5)</td>
<td>$1.00$</td>
</tr>
<tr>
<td>2-Isobutyl-3-methoxypyrazine</td>
<td>$53 \pm 4$ (10)</td>
<td>$1.62$</td>
</tr>
<tr>
<td><strong>Alkylpyrazines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Ethylpyrazine</td>
<td>$-7 \pm 8$ (2)</td>
<td>$0.74$</td>
</tr>
<tr>
<td>2,3-Dimethylpyrazine</td>
<td>$-6 \pm 8$ (3)</td>
<td>$0.87$</td>
</tr>
<tr>
<td>2,3,5-Trimethylpyrazine</td>
<td>$-3 \pm 1$ (3)</td>
<td>$1.53$</td>
</tr>
<tr>
<td>2-Ethyl-3-methylpyrazine</td>
<td>$-2 \pm 7$ (3)</td>
<td>$1.41$</td>
</tr>
<tr>
<td>Pyrazine</td>
<td>$0$</td>
<td>NC$^a$</td>
</tr>
<tr>
<td>2,3,5,6-Tetramethylpyrazine</td>
<td>$0 \pm 11$ (3)</td>
<td>$2.20$</td>
</tr>
<tr>
<td>2-Methylpyrazine</td>
<td>$7 \pm 6$ (3)</td>
<td>$0.20$</td>
</tr>
<tr>
<td>2,3-Diethyl-5-methylpyrazine</td>
<td>$16 \pm 9$ (3)</td>
<td>$2.61$</td>
</tr>
<tr>
<td><strong>Pyridines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridine</td>
<td>$4 \pm 10$ (4)</td>
<td>$0.66$</td>
</tr>
<tr>
<td>2-Hexylpyridine</td>
<td>$107 \pm 8$ (3)</td>
<td>$4.02$</td>
</tr>
<tr>
<td>3-Hexylpyridine</td>
<td>$118 \pm 10$ (3)</td>
<td>$4.02$</td>
</tr>
<tr>
<td><strong>Thiazoles</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazole</td>
<td>$-18$</td>
<td>NC</td>
</tr>
<tr>
<td>2-Acetylthiazole</td>
<td>$3 \pm 7$ (5)</td>
<td>$0.10$</td>
</tr>
<tr>
<td>2,4-Dimethyl-5-acetylthiazole</td>
<td>$14 \pm 6$ (2)</td>
<td>NC</td>
</tr>
<tr>
<td>2,4,5-Trimethylthiazole</td>
<td>$25 \pm 2$ (2)</td>
<td>NC</td>
</tr>
<tr>
<td>2-Isobutylthiazole</td>
<td>$59 \pm 5$ (4)</td>
<td>NC</td>
</tr>
</tbody>
</table>

$^a$ NC, not calculated.
8.6.8.5 Papers of Weiss et al. (2012) and Bushdid et al. (2014)

Weiss et al. and Bushdid et al. have presented recent papers that were primarily conceptual and based on their interpretation of the empirical (mostly psychophysical) literature.

The Weiss et al. group included professional perfumers. Based on the title of the paper, their goal was to define “an olfactory white” based on their understanding of a “visual white” that is not traceable to this work (Section xxx in Biological Vision). Visual white is not defined by a broad spectrum of sources stimulating the visual photoreceptors of stage 1 equally. Instead, visual white is a perception created when the difference signals of signal processing (stage 2) exhibit null values in all of these channels simultaneously, \( O = P = Q = 0 \).

Weiss et al. made no effort to select a group of single odorophore odorants (SOO) for use in their experiments. The rationale of Weiss et al. for their definition of olfactory white was stated as:

“Mixtures with Many Equal-Intensity Spanned Components Are Identified as Olfactory White. Visually, humans can discriminate easily between many different “whites,” but all these whites retain the color-gestalt identity of white. To determine whether odorant mixtures of \(~30\) spanned components similarly obtain a gestalt identity, we conducted an odor-identification experiment. Selecting from physicochemical space, we generated four versions of 40-component mixtures. To prevent any cognitive influences of the label “white,” we labeled these mixtures with the meaningless name “Laurax.” Each of the four versions of Laurax was assigned to three different participants from a group of 12. To acquaint themselves with the odor, each participant came to laboratory on three consecutive days, and every day repeatedly smelled and rated the applicability of 146 verbal descriptors (16) to only their version of Laurax. On the fourth day, test day, participants performed a four-alternative forced-choice identification task for 23 different, novel, but partially overlapping target odorant mixtures of 1, 4, 10, 20, 30, or 40 components, all selected to span physicochemical space. Each target mixture was provided with four alternative labels: Three labels were assigned by an expert perfumer (coauthor D.G., who was blinded to experimental aims and conditions) as optimal identifiers for each mixture (SI Appendix, Table S2), and the fourth label was “Laurax.”

Their focus on a gestalt definition of white is not consistent with the precise physiological definition of this work based on the stage 2 output signals of biological vision, \( O = P = Q = 0 \) (Section xxx of Biological Vision). Their concept is similar to that of using a broad spectral band photometer to determine not only the perceived intensity of the sum of all sources visible to the instrument but also the color of the measured light. A photometer fails notoriously at describing the color of the measured light (even in sequential A-B tests using a “white standard.”

They noted the coarse character of their normalization of intensity among odorants:

“All odorants were diluted with either mineral oil, 1,2-propanediol or deionized distilled water to a point of approximately equally perceived intensity. This perceived-intensity equation was conducted according to previously published methods. In brief, we identified the odorant with lowest perceived intensity, and first diluted all others to equal perceived intensity as estimated by experienced lab members (1). Next, 24 naïve subjects (10 women) smelled the odorants and rated their intensity. We then further diluted any odorant that was 2 or more standard deviations away from the mean intensity of the series, and repeated the process until we had no outliers. This process is suboptimal, but considering the natural variability in intensity perception, together with naïve subjects’ bias to identify “a difference”, the iterative nature of this procedure, any stricter criteria would generate an endless process.”

In translation,

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No equation was defined in association with the second sentence of the above paragraph. And, in the last statement, they did not quantify the accuracy of their numbers or provide error bars.

Bushdid et al.336 claimed that the human can discriminate over one billion stimuli compared with the generally accepted value of between 10,000 and 100,000 stimuli. They specifically noted, “The lay and scientific literature typically claims that humans can discriminate 10,000 odors, but this number has never been empirically validated.”

Their analyses proceeded without the benefit of any discussion of the physiology of the olfactory modality or any description of the transduction mechanism between potential odorants and the olfactory receptors of the olfactory modality. As a result, their model and analyses must be considered totally conceptual and probably ephemeral.

They began their analysis with the two equated terms on the left in Figure 8.6.8-7 but did not provide any citation or discussion of the limitations on the use of this equation. There are a variety of critical limitations that will be annotated below.

The equation has been expanded to show the additional equality on the right.337 This is a recognized equation for the number of observable results in a given set of discrete and stochastically independent events. The events (in this case the chemicals) must be independent from an olfactory perspective. It describes “the number of ways it is possible to choose from among the total number of C places in our list the N places where we write A?” As noted by de Mere during the 1650s, the sensitivity of this equation to proper interpretation of each term in the equation is extremely critical (Cramer page 42). The equation is particularly sensitive to the value of C.

![Figure 8.6.8-7](image)

**Figure 8.6.8-7** Equation of combinatorial analysis for discrete stochastically independent events.

It is clear that by raising the value of C by one unit, from 128 to 129 in this equation, the number of discriminable stimuli would be increased by a factor of 129 (to over 129 times 1.72 x 10¹² or over 200 trillion. By lowering the value from 128 to 127, the number would be reduced to 1.72 x 10¹² divided by 128 to give only 10¹⁰ discriminable stimuli (only 10 billion rather than 1.72 trillion). The interpretation of the value assigned to C is of utmost importance!

1. The equation only applies to discrete events, and not to analog values of one or more variables. In contrast, the olfactory modality, like all major sensory modalities, involves variable intensity stimuli and generates analog neural signals within the neural system. While Bushdid et al. did not address the question of variable intensity stimulation explicitly, they did recognize it implicitly. They recognized it by relying upon the work of Weiss et al who attempted to normalize the intensity of a large set of stimuli by establishing individual concentrations of each odorant (without providing evidence on the accuracy of their normalized results).

2. After defining their equations, they assign the number of stochastically independent events in their equations the value of 128, equal to their number of odorous molecules utilized (without regard to the total number of odorophores involved).

They provided a list of their 128 odorants and the solvents employed in the supplementary material to their paper. The list is a mixture of systemic and historical (common) chemical names accompanied by C. A. S. numbers but not the more precise ChemSpider numbers. A list reordered to show the structural grouping of the odorants and the sensory channel they stimulate, including

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336Bushdid, C. Magnasco, M. Vosshall, L. & Keller, A. (2014) Humans can discriminate more than 1 trillion olfactory stimuli *Science* vol 343, pp 1370-1372 and supplement

many Chemspider numbers and some d-values, is available\textsuperscript{338}. In this tabulation, the accession number from the original spreadsheet is maintained.

By merely extending their number of odorous molecules employed, they could have raised the claimed number of discriminable odorants arbitrarily and to astronomical levels. As noted above, minor changes in the value of C introduce tremendous changes in the total number of discriminable stimuli.

3. Bushdid et al. made no effort to demonstrate that the list of 128 chemicals they employed were in fact stochastically independent as used in olfaction. While their list did include at least 5 single odorophore odorants (SOO) as defined in this work (Section 8.6.2.8), it is equally obvious based on the theory of this work that a large number of their 128 chemicals are in fact statistically related (not independent) to other members in their list. As an example, all of the Lewis acids in their list are statistically related to the carboxylic odorophore and participate in the transduction process associated with sensory OR channel #1 of the olfactory modality. Their list includes at least nine odorants containing, as a minimum, one copy of the carboxylic acid odorophore structure. Recognizing just the commonality of odorophores in their list stimulating sensory channel #1 would reduce their value of C from 128 to 119. The number of odorants in their list containing at least one diol structure is at least eleven (limiting the number to odorants with systemic names for the moment). Any odorophore containing a diol structure will stimulate sensory channel #2. By recognizing the statistical dependence among these odorants, the value of C is reduced to 108 or less. This procedure can be continued until a value of C on the order of nine is reached.

4. As Bushdid et al. noted, their “Numbers are rounded for display but were computed with arbitrary precision using Mathematica.” They did not provide any estimate of the statistical error in their calculations based on the crudeness of the normalization process used by Weiss et al. or any statistical variations in their mixing or comparison processes.

5. They did not factor in the statistical accuracy associated with their statistical test procedure, except to eliminate subject #1 because he only marginally exceeded chance in his percentage of right versus wrong answers.

Based on the hypothesis developed above, it is mandatory that the mathematical modeling of the olfactory modality recognize the two-step transduction mechanism actually used in the neural system; the first step involves a discrete stereochemical selection process, and the second step involves an analog measurement of the change in electrostatic potential associated with the olfactory receptors between their quiescent and stimulated condition. In the case developed below, a more complex equation must be used than that introduced by Bushdid et al. The more appropriate equation employs both a discrete factor based on step one multiplied by a second factor based on the analog dynamic range characterized by the signal-to-noise ratio of the neural signals under the condition of odor constancy (equivalent to the color constancy of the visual modality.

Until the approach suggested by Bushdid, based on the experiments of Weiss et al., is modified to more closely represent the physiology of the olfactory modality, it can only be considered a mathematical exercise based on an ephemeral “what if” situation.

8.6.8.5.1 Choice of solvents

Bushdid employed three solvents in their experiments: 1,2 propanediol, mineral oil and distilled water. Distilled water is recognized as the ideal tasteless and odorless solvent. However, it is frequently necessary to employ water that has been multiply distilled to obtain adequate purity, particularly in order to remove residual Lewis acids. The distilling process typically results in a mixture of water and Lewis acids at a concentration far above the perceived odor threshold for this species. They did not define their mineral oil from an olfactory perspective.

Mineral oil has a C.A.S. number of 8042-47-5 but no Jmol designation and is not included in the ChemSpider database. Sigma-Aldrich offers a multitude of mineral oils (their analytical grade

product number is 330760) without describing their chemical properties other than refractive index, density, viscosity and specific gravity. While relatively benign, Sigma-Aldrich recommends it be kept in a sealed container and not be inhaled.

1,2-propanediol (228188) is a channel #2 (G-path or sweet) stimulating gustaphore based on the theory of this work (Section 8.5.xxx) with a d-value of 2.853 Angstrom. It is the simplest member of the diol (glycol) family and can be considered a single channel gustant affecting the gustatory modality. It exhibits a vapor pressure of 0.08 mmHg at 20°C and a vapor density of 2.62 (vs air). To the extent it is volatile and soluble, it is a channel #2 (dulcal) single odorophore odorant (SOO) in its own right and not ideally suited to be a benign solvent in olfactory experiments. The presence of this solvent can bias all of the results of Bushdid et al.

8.6.8.5.2 Reordering of the Bushdid et al. odorants by OR channel sensitivity

Bushdid et al. provided a spreadsheet describing their test odorants as supplemental data. As noted above, many of their test odorants contain more than one odorophore. Their list does include at least five SCO’s given a preferred status in this work (Section 8.6.xxx). A majority of their test odorants can be grouped according to their participation in step one of olfactory transduction and then ordered according to their molecular weight or their ability to affect the electrostatic potential of the OR with which they can be expected to form a DACB. Many of the more complex multiple odorophore odorants on their list will not be discussed in detail here. They frequently used a mixture of systemic and common names with C. A. S. numbers. These could generally be correlated with the more precise ChemSpider numbers in order to obtain likely d-values. However, this sometimes led to confusion.

[xxx provide URL address or other access point of revised list.

The revised list of their odorants, with ChemSpider/Jmol numbers and listed by OR channel they stimulate can be found at C://WhNeuron/Taste and Smell/Ref Papers/Fulton-mod-Bushdid-tableS1.xlsx. The list has been expanded to show the single odorophore odorants (SOO) recommended in this chapter as preferred SOO’s. The names of some chemicals have been expanded to show the ChemSpider preferred name in parentheses.

The revised list shows the disproportionate use of organic acids that all stimulate the OR 1 sensory channel in the experiments. Focusing only on,

• the diol chemicals, the diamides and the pyrazines
• chemicals incorporating at least one orbital atom (oxygen, nitrogen or sulfur and at least one phenyl) and
• aliphatic chemicals incorporating at least one orbital atom and at least one unsaturated C=C link
• arenes exhibiting the above requirements and
• excluding chemicals with complex structures (typically labeled top hat structures not treated in the hypothesis,

the revised list of about 128 chemicals consist of,

28 organic acids in the set that stimulate the OR 1 (acid) channel.
20 chemicals that stimulate the OR 2 (Dulcal) channel.
4 chemicals that stimulate the OR 3 (Floral) channel.
4 chemicals that stimulate the OR 4 (Limal) channel.
2 chemicals that stimulate the OR 5 (Musk) channel.
1 chemical that stimulates the OR 6 (Cinnamon) channel.
1 chemical that stimulates the OR 7 (Spice) channel.
1 chemical that stimulates the OR 8 (Citral) channel (based on a poor Jmol rendition).
0 chemical that stimulates the OR 9 (Putrid) channel.

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339 http://www.sciencemag.org/content/343/6177/1370/suppl/DC1
There are about 28 chemicals (odorants) in the original list that exhibit more than one odorophore. However, there is no way to determine which odorophore is dominant in each of these odorants. This work has not attempted to determine their dominance either.

There are also approximately 37 chemicals that contain no recognized odorophore or odorophore structures beyond the theory of this work. They are grouped under the heading "Not sorted by channel" at the bottom of the revised listing. Many of these are aliphatic alcohols or aldehydes exhibiting no odorophore based on this hypothesis. If any odor is perceived relative to these chemicals it is probably due to impurities at a level below 0.1% concentration. The presence of impurities below this level in commercially available reagent grade chemicals is well known problem within the perfume industry. Some of the sulfur compounds are marked as "no odorophore**) in the d-value column. The sulfur containing chemicals are frequently capable of complexing with other molecules and may actually exhibit an odorophore (See Sections 8.6.6.7 & 8.6.8).

The revised list and the above summary can be used to examine the chemical mixtures described in the supplemental table S2 of Bushdid et al. It becomes clear that most of the mixtures used are dominated by alcohols and aldehydes (17 of 128 or 13%) exhibiting no perceived odor and/or a large group of organic acids (28 of 128 or 21%) perceived as acidic in character. In addition 20 of 128 (16%) chemicals are perceived as dulcal in character. As a result, most of their mixtures of 10, 20 or 30 chemicals can be expected to be perceived as acidic with a mild sweetness. A caution must be noted regarding dulcal stimulants: in high concentrations (not likely when diluted in a mixture of at least 10 other chemicals), the perceived odor may be fetid (Section 8.6.7.1.1).

About 41 chemicals remain unsorted because they are excluded by the rules just described. They are not included in the hypothesis presented to date. Others exhibit very complex (typically top hat) structures that are not addressed in the hypothesis.

All of the 28 organic acids exhibit the same carboxylic acid odorophore and are stochastically dependent within the requirements of the equation presented by Bushdid et al. Similarly, many of the chemicals shown as stimulating OR 2 are diols, diamides or pyrazines. Each of these groups are stochastically dependent.

No effort has been made to prioritize the chemicals listed with respect to their effectiveness in forming a DACB bond with an OR channel in step one of the transduction process. Neither have they been prioritized with respect to the signal intensity they generate within the given OR channel. Such a prioritization would require detailed knowledge of the dipole potential of each odorant when in a DACB relationship with an OR. This information is not readily available at this time. The determination of the dipole potentials (not the dipole moments) under these conditions is a worthy doctoral or post doctoral investigation.

If the chemicals listed as combinatorial odorants in the revised spreadsheet are examined, it is seen that they exhibit multiple d-values and may stimulate multiple OR’s. They are poor candidates for use as SCO’s in the laboratory. Decanoic acid is in a class by itself. Two strikingly different chemicals exist under that name. Capric acid_2863 is a solid at room temperature with a low volatility. It was used in its undiluted form in the experiments of Bushdid et al., presumably to get a reliable response from the test subjects and probably after heating. Alternately, the subject may have perceived an odor due to an impurity in the available material. Decanoic acid_23877 is an unsaturated aliphatic acid with a very large d-value = 11.802 Angstrom. It appears to stimulate one of the VR’s in the oskatory modality rather than an OR in olfaction.

If the chemicals with common names ending with the extension “ol” are examined, it is quickly seen that the common names are frequently a problem. Here, the C.A.S. numbers were taken as the reference in order to acquire the appropriate ChemSpider number and calculate the d-value for the chemical.

As an example, the chemical named as phenyl ethanol is better described as phenylethyl alcohol based on the specified C.A.S. number of 60-12-8 (leading to the ChemSpider number of 5830). In the context of olfaction, this chemical is not a saturated alcohol. It is a combination of a hydroxyl group within an aliphatic chain and a phenol group. As a result, it exhibits a d-value of 5.294 Angstrom and can be expected to stimulate the Musk channel of olfaction (sensory channel #5) rather than the dulcal channel (sensory channel #2).

As a second example, 3-hexanol (C.A.S. 623-37-0 and ChemSpider 11678) is an unsaturated alcohol
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with a d-value of 4.299 suggesting that it is perceived as belonging among the sensory channel #4 (Limal) stimulants.

As a third example, eucalyptol (C.A.S 470-82-6) exhibits a very complex “hat” structure with a configuration not addressed in the theory of this work promulgated to date. It has been given two ChemSpider numbers, of 2656 and 21111689, that appear to be identical for purposes of olfaction.

The list has only been reordered to show how the majority of the chemicals in the Bushdid et al. list converge on only nine sensory OR’s and the resultant nine signaling channels. The order of the chemicals listed within a given sensory channel is arbitrary at this time. Some of the chemicals, like eucalyptol are not addressed with respect to olfaction by this theory. At this time, they can only be associated with a given sensory channel based on psychophysical experiment.

8.6.8.5.xxx Summary comments

Both the Weiss et al. and Bushdid et al. papers lack any significant relationship to the psychophysical system they were writing about.

The best that can be said about the Weiss et al. approach is that they were relying upon the Law of Large Numbers to achieve a Gaussian function with a suitably small standard deviation to describe their concept of olfactory white. This work has not defined any differencing circuits within the stage 2 signal processing of animal olfactory sensing that would lead to a definition of olfactory white within their conceptual space.

The analysis of Bushdid et al. does not appear to support their claim of over one trillion discriminable odorants by the human olfactory modality. Their list of test chemicals contains a great deal of redundancy at the odorophore level and their value of C = 128 is not supportable.

Their list of chemicals is dominated by the organic acids available in a well stocked general research laboratory but is nearly devoid of the chemicals found in a broader based perfumers laboratory. There are virtually no chemicals relating to the spices, cinnamons and musks which provide a major source of odors in the natural environment. The absence of any 2-phenylallyl esters and alcohols (associated with the fragrant flowering plants is particularly noted. They also omitted any of the putrid flowering plants affecting the channel nine OR of this work.

It is more likely that C = 9 or a nearby integer based on the physiological framework developed in this work. The more commonly suggested value of 10,000 discriminable odorants remains the most likely value. This estimate is compatible with the estimate of this work based on a combination of steps 1 & 2 of transduction (Section 8.6.7.6). Step 1 indicates a potential of $2^9 = 512$ perceived odors based on combinatorial analysis. Step 2 indicates a potential of between $2^3 = 8$ and $2^9 = 256$ identifiable analog levels associated with each sensory (and signaling) channel. When multiplied together, a value for the number of predicted perceived odorants is in the range of 4096 and 131,072. Under odor constant test conditions. As is well known in the literature, straying outside the odor constant regime can lead to dulcal channel stimulants being perceived within a continuum from sweet to fetid (Section 8.6.2.6 and 8.6.2.8). Bushdid et al. did not explore the non-odor constant regime.

The value of 256:1 for the signal to noise range of the sensory receptors is based on very sketchy estimates of the dynamic range of the sensory channels (not the transduction process) of the visual modality. This is a very difficult value to establish because of the dynamic capabilities of the sensory neurons and their receptors. It may be good policy to reduce the estimated maximum number of identifiable analog levels to $2^2 = 64$. The maximum number of discriminable odorants would then approach 32,768.

8.6.9 Aging in olfaction

The general loss of the ability to perceive odors is called Anosmia. Hyposmia is partial loss of smell. The loss of sensitivity relating to a limited range of odorants or olfactory channels has been called “specific anosmia.” There has long been informal debate on the causes of poor olfaction in the elderly. The discussion has usually centered around poor nutrition, and especially the lack of certain metals in the diet.
In analogy to the loss of accommodation in vision, a similar condition in olfaction can be called prosopanosmia, the loss of the sense of smell as a function of aging. Doty et al. have explored the effects of aging on olfaction. Figure 8.6.9-1 shows their data.

The very large ranges associated with the elderly is substantiated by personal experience. Among my peers, their level of olfactory sensing varies widely, apparently with their state of hydration as much as with any other single factor. Characteristically, women assert their loss of olfactory sensitivity more than men do in social discussions. The effect of taking one-a-day vitamin supplements appears limited if even observable. Based on the research presented here, it may be due to lack of one or more "essential" amino acids employed in OR production but is probably not due to lack of the chelatable metals in the diet. However, no systematic observations have been made involving amino acid intake.

The internet literature related to anosmia and prosopanosmia is unusually generic. One clear conclusion is "Fortunately, for most people, anosmia is a temporary nuisance caused by a severely stuffy nose from a cold. Once the cold runs its course, a person's sense of smell returns." This situation is most involved in a pneumatic blockage related to access to the olfactory endothelium by odorophores. This blockage is not likely to be odorophore, or channel, specific. Other frequently

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mentioned causes of anosmia include:

- Nasal polyps -- small noncancerous growths in the nose and sinuses that block the nasal passage.
- Injury to the nose and smell nerves from surgery or head trauma.
- Exposure to toxic chemicals, such as pesticides or solvents.
- Certain medications, including antibiotics, antidepressants, anti-inflammatory medication, heart medications, and others.
- Cocaine abuse.
- Old age. Like vision and hearing, your sense of smell can become weaker as you age. In fact, one's sense of smell is most keen between the ages of 30 and 60 and begins to decline after age 60.
- Certain medical conditions, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, nutritional deficiencies, congenital conditions, and hormonal disturbances.
- Radiation treatment of head and neck cancers.

The spectral breadth of the loss of chemical sensing seems to rule out any mechanism associated with one or more individual sensory channels.

The Anosmia Foundation reports, “In 22% of cases, no cause is ever found (an idiopathic condition).” The idiopathic condition is compatible with a slow onset of the condition due to aging and probably relates to an inappropriate nutrient condition within one or more engines of the olfactory modality within the CNS.

The Merck Manual suggests, “The following findings are of particular concern:

- Recent head injury
- Symptoms of nervous system dysfunction, such as weakness, trouble with balance, or difficulty seeing, speaking, or swallowing
- Sudden start of symptoms

Both sudden onset, especially following head injury is suggestive of damage to the neurons connecting the olfactory epithelium to the glomeruli of the olfactory lobe leading to the Central Nervous System (CNS). This condition seldom repairs itself.

A frequent comment in the literature is “Sometimes a person will regain his or her sense of smell spontaneously.” Such a situation suggests the problem is not organic, in the sense of irreparable physical failure. It is compatible with an imbalance in the delivery of nutrients to a variety of areas of the brain.

Kobal et al. provided the results of a large scale evaluation of the general population in 2000341. Hummel et al. provided a followup based on a larger cohort in 2007342. Neither paper addresses the potential cause of the abnormality.

### 8.6.9.1 Major failure modes associated with olfaction

The major failure modes, based on the above introductory remarks can be defined based on the top block diagram of Section 8.6.1.3 and the morphology of olfaction described there. This section will focus only on the main olfactory signaling chain and will omit those elements associated with the auxiliary (or vomeral) olfactory modality.

The major failure mode in olfaction is a temporary obstruction of the pathways within the nose (stage

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0) due to excess mucosa (having a cold) or other physical obstruction. Such a condition is frequently cited as the first stage in a more permanent loss in olfactory sensitivity. However, this relationship may be only anecdotal. Such blockages generally result in a hypoamosia across the complete range of odors.

### 8.6.9.1.1 Tumors and invasive trauma

Virtually any stage of the olfactory modality can be damaged by invasion of the neural space by tumors disturbing the function of various neural engines. These tumors are subject to identification by present clinical practices. Invasive trauma can also damage the modality and is readily identified by clinical practices.

### 8.6.9.1.2 Non-invasive trauma

Non-invasive trauma is becoming a more frequently cited cause of olfactory failure, either of the hyposmia type leading to eventual anosmia or of specific anosmia associated with signal generation (stage 1) or signal processing (stage 2). The predominant form of non-invasive trauma appears to involve damage to the axons of the signal generating neurons as they penetrate the cribiform plate. The relatively large olfactory bulb is not well braced to prevent motion of the LOB relative to the cribiform plate. The result can be significant severing of the axons of the stage 1 neurons. When occurring at a distance from the LOB, the damage is likely to lead to hyposmia initially. Specific anosmia is most likely if the damage occurs near the glomeruli of the LOB, where the axons have been sorted relative to their specific sensory receptor channels.

### 8.6.9.1.3 Chemical basis for anosmia

Medical science has long sought to explain most forms of anosmia as due to chemical abnormalities within the sensory neurons (stage 1) or more general problems elsewhere in the modality. However, the medical literature has failed to highlight a specific form of chemical imbalance. Specific anosmia is not readily assigned to stages 3, 4 and 5 because the engines of these stages are not generally related to specific sensory channels.

A great deal of investigation has related to heavy metal ions, in various chelated forms, mediating such anosmia, without significant results. It is often suggested that such heavy metal ions might affect individual olfactory channels (resulting in specific anosmia). The problem has been the lack of any comprehensive model of the olfactory modality. The model of this work has not found any logical requirement for or actual empirical evidence for such heavy metal ions being present in olfaction.

The literature has hypothesized a wide variety of chemical failures within the olfactory modality, again based on cartoons based on a conjectured chemical theory of the neuron. They have been unrelated to any contiguous model of the olfactory modality neural network.

### 8.6.9.1.4 Medical imaging techniques applied to anosmia

Medical imaging techniques are beginning to highlight anomalies in the operation of the various circuit paths and stage 4 & 5 engines of the olfactory modality. However, at the current time, the resolution of these techniques (currently 1-2mm in each of three orthogonal directions and encompassing about 8 million neurons per pixel) is far below that required to identify a failure mode involving a few hundred to a few thousand neurons. As a result, these techniques can only identify coarse signaling paths that may not be operating optimally.

### 8.6.10 Verification/falsification of the olfactory hypothesis

The olfactory hypothesis presented provides a very useful explanation of many different aspects of olfaction. However, it can and should be extended.

The problem of verification is complicated by the lack of specific descriptions and d-values for those descriptions) for a sufficiently large number of odorants. Several blogs exist that provide extensive anecdotal and semantic descriptions of the perceived odors of a variety of molecules by various
individuals (n =1 in their statistical data set).  

8.6.10.1 Perfecting the d-values of gustation and olfaction

Up to this point, d-values of only three digit precision have been defined (even where four digits are shown in most cases. The reason is the difficulty of locating adequate and consistent experimental results of higher precision.

Since the early 1990’s, with the rise of significant computer capabilities at nominal cost in the hands of investigators, the field of computational chemistry has blossomed. This field has exhibited at least two important features; first, the continued lack of a set of standard definitions of specific molecules at every more complex detailed levels, and second the ability of individual investigators to “build” molecules representing their understanding of the structure and properties of a molecule of given name in the literature. Two additional aspects of the field are its focus on large molecules (generally large proteins with weights of millions of Daltons) and the focus on the properties of molecules not in their solvated condition (generally incorporating parameters derived from x-ray crystallography of solid materials).

The challenge in this work is to determine the coordinate chemistry parameters of very small molecules (typically less than 300 Daltons) when in solution. This is far below the size of “small molecules” (800 Dalton molecular weight) typically defined in computational chemistry, and based on the earlier fields of pharmacology and bioc hemistry. The availability of coordinate chemistry parameters for the very small molecules appears to be very limited at this time.

Several important tools for the stereographic representation of molecules are currently available in the public marketplace. These include, ArgusLab version 4.0.1 of 2004, Jmol version 12 of 2012, and the Discovery Studio Visualizer, version 3.5 of 2012. These programs are able to accept molecular descriptions from a variety of sources, but most importantly the .pdb files deposited in the Protein Data Bank and two versions of molecular files, .mol and .mol2 accumulated from a variety of sources. The author of ArgusLab ceased active development of the program in 2004. A new package labeled the Virtual Molecular Model Kit (VMK) has recently appeared along with a monthly application oriented journal. This material is designed for educators. A promising but immature program after five years is Avogadro. An initial comparison of the Jmol files for Rhodonine(5) 4444397 gave different d-values of 11.181 Angstrom for the DS 3.5 visualizer and 10.684 Angstrom for Avogadro visualizer (a 5% difference, which is very large). Avogadro did not show the double bonds of retinal, nor did its tabulated bond lengths reflect the presence of double bonds. Avogadro is not a usable program as of July 2014.

The computational chemistry programs used to build the pdb files and to represent the molecules graphically rely upon a considerable variety of optimization programs. These programs do not always give the same distances and angles between the orbitals of the same molecule.

8.6.10.2 Isolating and identifying the OR’s of olfaction

The isolation and identification of the molecules forming the OR’s of olfaction appears to be straightforward under the proposed hypothesis. The task is to isolate at least the dendritic portions of the sensory neurons from the olfactory epithelium and then separate the ligands capable of participating in the DACB from the phosphatic acid portion of the molecule. This appears to involve a simple

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344https://www.youtube.com/watch?v=I4n5un-pizs

345Avogadro Program: http://avogadro.cc/wiki/Main_Page

346Avogadro Appraisal: http://www.jcheminf.com/content/4/1/17
hydolysis. The remaining mixture of (primarily) amino acids can be isolated and identified by chromatography techniques, respecting the fact the amino acids are highly sensitive to the pH of their environment (Lehninger, 1970, pp81-86). They can also be identified by electrophoresis. More recent advances in chromatography should be considered.

8.6.10.3 Recent laboratory investigations seeking channel tuning information

This section will review several post 2000 papers designed to complement the investigations of Johnson & Leon using different techniques. The techniques are viable and the investigations well designed. However, they each contain a serious problem. They all limit their selection of stimulants to a homologous series of saturated aliphatic aldehydes assumed to represent a broad selection of odorophores in the absence of any theory describing how or why they act as odorants or odorophores. In fact, based on the hypothesis of this work, the selected series offer neither a selection of odorants, a selection of SOO, or in fact a set of odorophores in the absence of the hydration. Hydration of the fundamental molecules produces a more complex configuration, that of azeotropes capable of forming only DABC's of a single d-value. A secondary problem is almost as serious; all of the chemicals used are difficult to obtain at purities in the parts per million to parts per billion range. In the absence of this level of purity, the results may reflect simultaneous stimulation of the sensory receptors by individual azeotropes in the presence of significant other undefined odorophores.

Shepherd et al. established that the signal intensity generated by their set of homologous saturated aliphatic aldehydes was not uniform and this fact is shown in his data. The other investigators discussed in the following sub-sections did not establish that their stimuli all exhibited the same solubility in the mucosa of their animals. They relied upon the nominal concentration of their stimuli when in vapor form.

As a result, the material in the following sections is addressed with respect to the information provided but does not rely upon the results provided.

Among the techniques available for identifying individual glomeruli, the optical imaging technique is the only one capable of clearly identifying individual glomeruli at this time. Meister & Bonhoeffer has taken pains to assure their optical experiments achieved the necessary resolution and achieved it at low and nominal stimulus levels. Kida et al. may have identified individual glomeruli using the very leading edge of current fMRI technology.

8.6.10.3.1 Investigations of Shepherd et al.

Shepherd and colleagues have presented several papers in the 2000-2015 era employing MRI techniques using very high intensity magnets to study the glomeruli of rats.

Figure 8.6.10-1 shows their schematic of the stage 1, 2 and 3 regions of the olfactory modality of the mouse modified from Shepherd et al347. The figure has been modified to reflect the Electrolytic Theory of the Neuron and the baseline established in this work. First, The processing stages of this work have been added along the left margin for clarity of discussion. Second, the interpretation of the Mitral/Tufted (M/T) neurons have been modified to reflect their bi-stratifed neurite structure. While these neurons are frequently portrayed as "pyramid" cells in two dimensional sketches, they are in fact conical in 3D representations. The apical input to the neuron can be shown to be the dendritic input shown here as arborized within the glomeruli to synapse with a large number of axons from the stage 1 sensory neurons. The dendrite passes a non-inverted sum of signals from all of the relevant synapses to the emitter terminal of the Activa (not shown) of the M/T neuron. Each M/T neuron also exhibits one or more poditic inputs (two are shown for each M/T) along the base of the conical M/T. These poditic inputs also project their coarse arborization to one or more glomeruli other than that of the associated dendritic structure where they are arborized to make contact with multiple sensory neuron axons. The podite is connected to the inverting input of the Activa within the M/T. Stage 2, the signal processing stage of the neural system, consists of both the synaptic activity within the

The histograms of Shepherd shown on the right appear initially to suggest the efficacy of the aldehyde/OR interaction within the stage 1 sensory receptor neurons. However, on closer examination of the source, they actually reflect the difference in signal intensity generated by the variable concentration of the aldehyde stimulants in the mucosa. As shown in the following discussion of Xu, (Shepherd) et al., All of the homologous saturated aliphatic aldehydes used by Xu et al. exhibited only one and the same actual odorophore capable of forming a DACB with the olfactory receptors. The histograms do not exhibit any vertical scale, however, the equivalent histogram in Xu et al. does. The range of amplitudes in their histogram is on the order of 7:1 (which is compatible with the appearance of the Shepherd, et al. histograms. Based on this information and assuming the individual histograms were normalized separately, the apparent channel of stimulation for these histograms can be assigned as shown; the signals generated by the OR 1 type sensory receptors of the A-Path channel would be expected to show the shape of the A histogram, the B histogram could be associated with OR 2 of the G-Path channel, and C histogram could be associated with OR 3 of the N-Path. The histogram labeled D reflects the stage 2 signal differencing performed by the Activa within the M/T neurons before action potential generation. The greater amplitude of the positive-going portion of the histogram suggests the signals may be better portrayed using a logarithmic vertical scale in order to portray the character of the negative-going portion of the biphase histogram. The use of a logarithmic scale is more compatible with the signaling known to occur in other sensory channels of the neural system (Section 9.xxx).

Shepherd et al. made note of the effect of differencing within the M/T neurons, resulting in an effective sharpening of the response functions at the output of the M/T neurons compared to the response functions associated with the stage 1 sensory receptors. This differencing occurs in the analog signaling domain and does not involve inhibition as the term is used in this work.
Figure 8.6.10-2 expands on the caricature of the M/T neuron (labeled D used by Shepherd et al.) and found frequently in the literature based on the chemical theory of the neuron. The signals accumulated (summed) by parallel synapses within glomeruli B (dedicated to a single sensory receptor and single associated signaling path) are applied to the emitter, e, of the Activa within the neuron via the apical dendrite. Similarly the signals accumulated from within glomeruli A & B (each dedicated to a different signaling channel) are delivered via the radial podites to a final summing point within the M/T neuron before being delivered to the base terminal of the Activa. The result is a net signal controlling the Activa and its analog output given by,

Net stimulation \[= \sum B - (\sum A + \sum C)\]

In the case of stage 3a encoding neurons, like the M/T, the internal biasing of the Activa is controlled by the resistor shown between the base terminal, b, and the ground terminal. In its quiescent state, no current (actually a minimal current) passes through the Activa via the collector to base path. Only when the net stimulation amplitude exceeds the stimulation threshold does the Activa become active. This threshold is set by the resistor shown connected to the collector, c, and the resistor shown connected to the base, b. When biased appropriately, the Activa exhibits a positive amplification factor for any signal exceeding the threshold. This condition leads to the generation of one or more monopulses (action potentials) at the collector (Section 9.xxx). These pulses are passed to the myelinated axon where they are propagated (not conducted) to orthodromic neurons. See Section 9.xxx. As discussed in Section 3.xxx, electrical power to the Activa is provided by the electrostenolytic conversion of glutamate (Glu) to GABA (+CO₂) on a specialized region of the outer lemma of the neuron as shown. The electrostenolytic process acts like a battery supplying a negative potential to the axoplasm of the neuron.

8.6.10.3.2 Investigations of Meister & Bonhoeffer

Meister & Bonhoeffer provided a paper in 2001 using optical techniques to study the glomeruli of rats. They also focused on the chain length in a homologous series of saturated aliphatic aldehydes in an effort to determine the tuning and topography of the glomeruli. They did not describe the source or purity of their chemicals. They did not discuss the azeotropic properties of their selected chemicals (Section 8.6.10.3.3). As noted when discussing the Xu et al. paper, the purity of the aldehydes is of paramount importance. They explored what they describe as “intrinsic optical signals; these signals appear to be due to differential light scattering as a function of glomerular expansion or contraction during stimulation of the appropriate sensory neurons. Their technique showed a spatial resolution on the order of 50 microns and a temporal resolution of about 2 seconds. As in any investigation employing a set of homologous saturated aliphatics varying in number of carbons, they encountered difficulties.

“Comparing the patterns of activity elicited by a given odorant at increasing concentrations, one finds that the response amplitude generally increases. In addition, there is a clear change in the response patterns. At low concentrations (dilutions D = 0.0001 or 0.001; see Materials and Methods), each of these odors can be identified by just

one or a few specific glomeruli that respond distinctly. With increasing concentration, many more glomeruli participate in the response with comparable amplitudes. The response patterns can still be distinguished but only by considering the entire ensemble of glomeruli. For example, to distinguish odors C6, C7, and C8 at high concentration (D = 0.1), it is clearly not sufficient to find the glomerulus with the strongest response. Instead, it becomes more revealing to identify which glomeruli in the set are not activated by the odor."

Their results in figure 5d suggest they may have encountered glomeruli reporting maximum response to saturated aliphatic aldehydes with carbon chain lengths of 6, 7, and 8. However, the responses at high concentration, from figure 5a are significantly broader and show little selectivity. Their data is of excellent quality. However, it fails to identify the specific odor path associated with each of the aldehydes or the width of the efficacy function of that path. Their discussion is useful but does not come to any unique assertions.

In their discussion, they use less than precise wording, "Over the past few years, a simple hypothesis has emerged for how olfactory bulb glomeruli are connected to the sensory periphery, summarized as “one glomerulus– one receptor.” It is thought that each glomerulus receives inputs from just one type of sensory neuron and that each sensory cell expresses just one type of olfactory receptor (Mori et al., 1998). In this picture, the glomerulus—more specifically its afferent input signal—interacts with the world of volatile chemicals through just one chemical binding site.” Use of the expression, “one glomerulus–one receptor type” would clarify this quotation.

They also note, “In nature, sniffs of saturated vapor occur infrequently, except for the rare occasion when an animal needs to swim across a pool of amyl acetate. Instead, rats are found to detect and discriminate odors at 10^{-6} of the saturated vapor (Passe and Walker, 1985), and given the difficulties of behavioral measurements, this is probably a conservative estimate. In our sample, the most sensitive glomeruli gave a half-maximal response to their preferred odorant already at 0.0002 of the saturated vapor concentration, and all glomeruli tested had a half-maximal response at <0.01 of saturated vapor. When we measured tuning curves at higher concentration, although still far from saturated vapor, they were significantly broader than the affinity spectra (Fig. 5d). This results simply because the olfactory response is compressed by saturation (Eq. 1), such that high-affinity and low-affinity ligands have the same effect.”

The closing sentence of Meister & Bonhoeffer can be better understood if they had a physiological or electrical model of the modality on which to base their conjectures. This work asserts that at low stimulus concentrations, the system is highly combinatorial and employs a 9-dimension orthogonal space where only one receptor channel needs to be stimulated to provide a meaningful perceived odor. The available coding space need not be sparse to achieve this perceived odor even though the loading of this code space may be sparse when a single well chosen (preferred SOO) odorant is employed.

8.6.10.3.3 Investigations of Xu et al.

Xu et al. provided a paper in 2003 using mice, a 7 Tesla MRI machine and a homologous series of saturated aliphatic aldehydes. They also supplemented their experiments with tests involving ethyl and amyl acetates (presumably ethyl acetate_8525, d = 2.080 Å, and n-pentyl acetate_11843, d = 2.082 Å, but potentially isoamyl acetate_29016, d = 2.087 Å). Their results provide 50 percentile iso-contours of the activity in their maps of glomeruli (a possibly higher degree of precision than the earlier works of Johnson & Leon (Section 8.6.7.3.4)). They prepared solutions of their odorants that were allowed to evaporate into their “extra-pure” air supply before being directed to the epithelium of the mice. While they state their intent was to normalize the stimulation associated with the odorants, the profile of their total signal was substantial as noted below.

It should be noted that the purity of the chemicals available from Sigma and used in the experiments of Xu et al. are not adequate for use in olfactory research. The sensory receptors of olfaction typically exhibit an output signal proportional to the natural logarithm of the

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stimulus intensity. A one percent impurity level can be quite significant in both radiographic and fMRI experiments related to the glomeruli.

The operation of the olfactory portion of the neural system addressed by Shepherd et al. can be precisely described without consideration of the granular cells present in the depiction in the original figure. This depiction was based on the very early morphological investigations illustrated in the Shepherd et al. paper, of Golgi (1875) and of Cajal (1911, using the Golgi method) using the primitive microscopes available to them at that time. These light microscopes were unable to resolve a great amount of detail resolved by current conventional light microscopes. However, it is noteworthy that even current light microscopes cannot resolve neuritic and axonal structures at the one micron diameter level. Estimates can be found in the literature suggesting that half of the neurons and their ramifications cannot be resolved without moving to the electron microscopic domain. As noted by Shepherd et al. in the caption to their figures, the granular neurons are not located in close proximity to the M/T. The sketches by Golgi and by Cajal do not clearly show either the axonal or dendritic structures of the granular cells synapsing with the dendritic or poditic inputs to the M/T as suggested by the model in figure 4 of Shepherd et al. This work does not support a bidirectional synapse under normal operating conditions. The synapse is a three terminal electrolytic device (an Activa) that can be biased to act as an effective diode passing current in either direction but not simultaneously. This work does not support a dendrodendritic synaptic model (or a dendrosomatic synapse) based on a morphological definition of the relevant neuron. Section 8.xxx provides a clearer definition of the internal structure of a neuron at the cellular level. Neither does this work support the suggested interpretation of an electron micrograph of Rall et al from 1966, a time when the character of the electron dense area between two neural lemmas was not appreciated (See Vardi, 1998).

Figure 8.6.10-2 from Xu et al. provides the supporting information for the above figure. While visually and intellectually attractive, the Xu et al. paper suffers a several shortcomings. Like the above Shepherd et al. paper, it,

- lacks a detailed physiological and/or electrolytic model of the olfactory modality,
- utilized a defective protocol due to inadequate knowledge of olfactory mechanisms, and
- was unable to exploit the laboratory effort expended.

Both the Shepherd et al. and Xu et al. papers relied upon the assumption that the length of the carbon chain of saturated aliphatic molecules was the dominant parameter determining the perceived odor or the action potential pulse rate in olfaction. Their findings do not support their fundamental assumption.

Frame (b) of the figure shows that, although the intent of Xu et al. and Shepherd et al. was to employ stimuli of equal intensity, this was not achieved. The total signals associated with each odorant were significantly different on a linear scale (range about 7:1). More importantly, they did not understand the functional character of their homologous series of saturated aliphatic aldehydes. While these aldehydes, butanal (nee butyraldehyde), pentanal, hexanal, heptanal and octanal all appear significantly different in their structural arrangement, they are in fact virtually identical in their olfactory performance. When solvated in the mucosa, they all are hydrated to form the same azeotrope, a single hydrogen bond between two oxygen atoms with a d-value of 2.703 Angstrom. Thus these odorants all exhibit the same odorophore and stimulate the same signaling channel (the G-Path) associated with the OR 2 receptor (PtdTyr). This fact is uniquely well illustrated in frame (c) of the figure. All of the five aldehydes primarily stimulate areas b and its complement I most strongly, with lesser stimulation of the adjacent areas a and its complement k & n (with a secondary area of signal significance, p.


The goal of experiments designed to populate frame (c) of this figure should be to show a diagonal formed of maximum activity (a function of the product of domain size and domain intensity), thus showing that the stimulants did in fact cause activity in different domains as a function of the variable feature in the left most column of the frame.

Xu et al. noted, “With the spatial resolution in this study, the major bulb layers could be readily separated. A given pixel (Voxel) likely contained several glomeruli, and possibly, a small amount of neighboring non-glomerular tissue.” FMRI gear with a magnetic strength of greater than 15 Tesla will be needed to resolve individual glomeruli. At this higher resolution, the domain map of Xu et al. will be modified significantly. It is important to note the designated domain areas on the left in frame (a) do not conform to the equivalent areas designated by Johnson & Leon in Figure 8.6.7-13 based on radiological studies.

A question arises regarding the results similar to frame (c) when using a homologous series of molecules varying in distance between two orbital sites that are also capable of forming azeotropes. Will the data display both a diagonal line related to the homologs supporting distinct DACB’s and a vertical line related to the common azeotropic DACB’s?

The homologous series of saturated aliphatic molecules based on the length of the carbon chain does not provide a set of odorophores stepping across the d-value range of olfaction. A homologous...
series of aliphatic molecules (such as X-hepten-1-ol and X-hepten-1-ol) based on the distance between a single oxygen atom and a single C=C bond in the carbon chain does provide a set of odorophores that steps across the d-value range of olfaction. As an example, 2-heptenol \(472863\) exhibits a d-value of 3.006 while 6-hepten-1-ol \(472863\) exhibits a d-value of 8.024 Angstrom. 2-heptenal is a special case because this aldehyde can be considered an \(\alpha,\beta\) unsaturated carbonyl compound that involves a conjugated arrangement. It may have special properties in conventional chemistry; for purposes of olfaction, its d-value remains relevant. See Section 8.6.7.3.3 for further discussion.

A major result of using the same odorophore, the azeotropic hydrogen bond to form the DACB with the PtdTyr receptor, is shown on the right of frame (a) the representations primarily reflect the difference in the intensity of the presented odorophore (along with differences intrinsic to the method of data analysis and the small data set employed by the investigators).

The Xu et al. paper presents an extensive discussion but makes few assertions concerning the results (while making a number of suggestions and drawing several indirect conclusions).

Their four statements in their results beginning at the foot of page 11030 are valuable (item #’s added), 1. All aldehydes activated significant portion of the glomerular layer. 2. The topography of the maps evolved regular with the carbon chain length. 3. The signal increased both in area and in intensity with carbon number, peaking at C7 (figure 2b).” Peaking at C7 is totally supported by their figure 2b showing the intensity of the stimuli relative to carbon number. The peak is not directly related to the carbon number of the aldehyde.

Their last strong statement is valuable. “4. A striking feature was that the main activity occurred in broad regions of the medial and lateral regions. The anterior lateral surface (fine black arrow in fig. 2a) was highly activated by all tested aldehydes.” Such a statement is totally justified by the presence of only one azeotropic odorophore for all of the saturated aliphatic aldehydes.

The important point is, the Xu et al. paper strongly supports the electrolytic hypothesis of olfaction developed in this work.

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The Xu et al. protocol calls for a great deal of manipulation of their data (apparently more than that used to reduce similar DG data by Johnson & Leon), even to the extent of slicing and dicing the data ala the slicing and dicing of inferior grade bonds that led to the recent financial collapse. They have not demonstrated that they were not processing noisy data where the signal to noise ratio was at least 5:1.

In their Fig 3c, they incorporate operators to indicate their geometric comparisons. Specifically the intersection operator \(\cap\) (Unicode: 22C2). It is typically used in an expression of the form \(X_1 \cap X_2\) to indicate the intersection of these two domains. The character is sometimes called "cap."

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It is important to note the “domains” identified by Xu et al. based on their fMRI technique are distinctly different than the “domains” identified by Johnson et al. using their DG-based radiological techniques. Figure 8.6.10-2 compares their nomenclature. The radiologically derived domains have been defined beginning in 2000 by Johnson & Leon (with improvements in 2002, up through 2007). The fMRI derived domains shown are from the Xu et al. paper of 2003. Their paper of 2000, using a 7 Tesla fMRI attempts to demonstrate repeatability of their data collection protocol. Their figure 1b is less than convincing in this respect. They discuss the issue based on both short exposure times of 0.6 minutes and 3.5 minute intervals between samples which they define as repeatable and longer exposure intervals where they encountered adaptation, habituation and other mechanisms. Similar variations resulting from short exposures are shown in fig. 5 for both isoamyl acetate and limonene.

Neither of these maps correspond to the voxel size of their investigations. Each domain is much larger than the voxels used and still much larger than the size of individual glomeruli. Kida et al. assert there are about 2000 glomeruli in each rat olfactory bulb whereas these maps include less than 50 domains.
As noted in Section 8.6.7.3.3, the domain maps of Johnson & Leon appear to straddle the actual points representing maximums in the individual signaling channels. The mathematical procedures of Xu et al. are similar but the data is not sufficient to demonstrate the same relationships for the Xu et al. domain maps.

To confirm the validity of their overall approach and protocol, some of the Xu et al. procedures were repeated using saturated aliphatic ethyl acetate and amyl (pentyl) acetate. These two molecules exhibit the same single odorophore with a d-value of 2.080 Angstrom and 2.082 Angstrom respectively. Both excite the OR 2 and the G-Path channel and their glomeruli maps would be expected to be quite similar. Their figure 4d confirms this is the case even though they did not demonstrate the equal concentration of these two molecules in the mucosa of the olfactory epithelium and they focused on only the values of their data when thresholded at the 50th percentile level. “Significant spatial correlations and overlap were noted (SCC = 0.44 and 72% overlap) between the two patterns (Fig. 4d). However, the absolute size and intensity appeared to vary in the two maps (Fig. 4b and c). It thus appeared that similar trends were found for ester patterns as for aldehydes (Fig. 2).” When the concentration of the two esters were equal, it would be expected that the maps would be even more similar.

Figure 8.6.10-4 Comparison of glomeruli domain nomenclature based on the technology employed. Left; the domain map based on fMRI data collection. V; ventral, M; medial, D; dorsal, L; lateral. Right; the domain map based on 2DG realiogical investigations. There is no recognizable commonality between these two representations.

Comparisons of the activity maps in Fig. 2a demonstrate several basic characteristics. All aldehydes activated significant portions of the glomerular layer. The topology of the maps evolved regularly with the carbon-chain length. The signal increased both in area and in intensity with carbon number, peaking at C7 (Fig. 2b). A striking feature was that the main activity occurred in broad regions of the medial and lateral regions. The anterior lateral surface (fine black arrow in Fig. 2a) was highly activated by all tested aldehydes, whereas the intensities in the medial and posterior lateral surface (thick black arrow and arrowhead, respectively, in Fig. 2a) increased most notably with carbon number. The difference in lateral and medial responses was observed in all animals (data not shown). In the dorsal region, shorter-chain aldehydes activated the anterior part, whereas longer carbon chains activated the posterior part (thick and fine white arrows, respectively, in Fig. 2a). In all maps, the activity in the medial side was located at more posterior regions than that in the lateral side.”

Xu et al. only make one reference to potential protein-based sensory receptors described elsewhere in the literature. In a later sentence in the same paragraph they do refer to tyrosine hydroxylase as playing a potential role in olfaction. This work does not support either of these statements in the context of olfaction. This work asserts that tyrosine when esterified with phosphatidic acid is probably the OR 2 receptor supporting the G-Path. The resulting PtdTyr is clearly not a protein. No evidence has been found at the detailed level of this work supporting any role for proteins in the stimulus sensing and/or signal generating role of stage 1, signal generation.

In 2002, Kida, Xu, Shulman & Hyder described the resolution achieved with their 7 Tesla, horizontal
bore fMRI when using the BOLD technique and iso-amyl acetate as the stimulant. They quote voxel sizes of 220 x 220 x 250 microns³, 110 x 110 x 250 microns³ and 110 x 110 x 125 microns³. The largest number in each set is the slice thickness they used. Taking a nominal neuron size of 10 x 10 x 10 microns³, their voxel sizes encompassed about 1500 neurons and multiples thereof. They assert, “We provide the first clear in vivo evidence of repeated and reproducible localization of activations from individual glomerulae in the rat olfactory bulb using high resolution fMRI.” The data and figures presented do not appear to demonstrate this assertion. In their discussion, the wording was more awkward, “Assuming a spheroidal glomerulus with 150 μm diameter (0.002 μL), the current fMRI spatial resolution (0.001–0.003 μL voxels) can contain the signal from a single glomerulus provided that values for center-of-mass of the unit and voxel coincide, otherwise partial-volume will still exist.” Elsewhere they note, “Although regional reproducibility can be seen by visual inspection, reproducibility of individual glomerulae is not always observed.” They cited no source supporting their assumption. Rubin & Katz made a similar size assumption in 1999. Meister & Bonhoeffer provided histograms of glomeruli size in the rat with a centroid at 150 μm. To resolve two adjacent discs, the pixel diameter (in a 2D representation) should be less than one-third the object diameter. The glomeruli of mice are nominally 35 microns in diameter. Kida et al. did identify individual glomeruli at low stimulus concentration in their figure 2d, the identified glomeruli were probably reporting signals in the OR1 (A-Path) channel due to the acetate odorophore with a d-value of 2.087 Angstrom. This odorophore was present in their SOO stimulant, iso-amyl acetate. Kida et al. documented this identification using a BOLD image-contrast technique. The identification used a different fMRI slice than typically used by other investigators. It can be expected the identified glomeruli represented the convergence of a few thousand axons from the stage 1 sensory neuron receptors.

8.6.11 Flavor as a perception melding multiple sensory modalities

Flavor is a high level perceptual concept involving a single perception developed from combining the gustatory, olfactory, somatosensory (frequently restricted to the oral cavity) and sometimes auditory and visual channels as presented in the saliency map. The perception of “Texas barbecue” is probably an example of this kind of sensory integration into a global perception (even to including a checkeredboard apron on an individual with a big silver belt buckle who is serving the product).

Stevenson has recently published a book on flavor that is from the perspective of the food industry. His chapter 2 does recognize and discuss the relationship of flavor relative to taste, smell and nocent receptor channels but only in a global context. In his chapter 1, he addresses the same subjects as in chapter 2 and does note the role of the retronasal pathway from the mouth. He does not discuss the chemistry of the detectable volatile chemicals. The listing is largely without merit from a chemical viewpoint as discussed briefly in Section 8.4.1.3.2. As an example, it uses menthol as an example of an alcohol, rather than as a phenol derivative.

8.6.11.1 Recent efforts to recover the previous flavour potential of the tomato

The Klee team at the University of Florida (Gainseville) has been attempting to determine why the

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desirable taste and flavor aspects of tomatoes was largely lost during the 1970s as part of the effort to improve the tomatoes color aspects and shipability as required in modern domestic commerce through gene modification (hybridization). Their work has been largely empirical, and in fact predominantly exploratory up to this point (Section 8.4.1.2.2). With the work developed in this Chapter, it may be possible to move their research closer to a bio-sciences, as opposed to a social sciences, foundation.

The problem is a common one observed by any traveler making frequent trips between the New York area and the Los Angeles area beginning in the 1970's. A simple hamburger with a beefsteak tomato slice on it was a thing of beauty in California but it had not taste. The same beefsteak tomato in New York was not as pretty but its taste was significantly more interesting. This investigator always attributed the problem to the soil preferred by citrus in arid California to the soil preferred by cranberries in the damp low lands of New Jersey.

While the Klee team and several others have been focused on changes related to the genetics of the tomato, the above anecdotal scenario suggests it may be more related to the local environment. Is the problem one of nature or nurture?

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A review of many of the papers from the Klee team and others suggests the flavor profile of the tomato does consist of distinct gustatory and olfactory aspects. From the gustatory perspective, the tomato exhibits several gustants containing one or more individual acidophores (d-value = 2.268 Angstrom). These include malic acid, citric acid, ascorbic acid, leucine and isoleucine amino acids. They also exhibit glycophores (d-value = 2.82 Angstrom) associated with glucose and fructose. From the olfaction perspective, primarily via the retronasal pathway, the principle odorophores are stimulating the rose or R-path (d-value = 5.065 Angstrom), 2-phenylethanol and 2-phenylacetaldehyde. [xxx check these values]

The Yeast Metabolome Database says “The aroma of pure 2-phenylacetaldehyde can be described as: honey-like, sweet, rose, green, grassy.” These qualitative descriptions are less than precise. Its primary quantitative feature is that it stimulates the R-path OR. In this work the R-path corresponds to the channel 5 OR, the Musk channel. Thus the genetically unmodified tomato elicits a perception of acidic GR 1, Sweet, GR/OR 2 and Musk OR 5. The relative strengths of the actual perceptions of these gustaphores/odorophores is currently unknown and would require laboratory confirmation.

Figure 8.6.11-1 shows the dendrogram developed by Mahieu et al to classify the 27 chemicals in a subset they investigated. Mahieu et al analyzed a very large data set based primarily on the conventional chemical groups within biochemistry and the current state of the art in plant genetics. They made no attempt to determine the underlying structure of these chemicals that contributed to their olfactory qualities. “The relationships among the various volatiles in this study was determined by clustering of the data derived from 74 introgression lines (ILs) derived from a cross between S. lycopersicum and S. pennelli, 89 ILs derived from a cross between S. lycopersicum and S. habrochaites, as well as the four parents of the two populations.” The result was a 27 member tree clustered into four major groups, those with a five carbon structure (C5, primarily aliphatic), those with a six-carbon structure (C6, primarily simple hexanes and their derivatives), those based on leucine or isoleucine (L/I, primarily simple isomerized aliphatic alcohols and aldehydes) and the “floral” structures (F, primarily aliphatic aromatics). Notice the mixed character of these labels. Some labels are based on simple stick diagram chemistry, some are based on a named amino acid and its derivative and one (F) is an abstract term suggesting the perceived smell of flowers.

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The diagram is interesting because it did isolate the most likely primary odorants of tomato. The benzyl alcohol (d=3.647 Angstrom) and aldehyde (d=3.625 Angstrom) are usually associated with the perceived smell of the florals, OR 3. The phenyl alcohol (d=5.065 Angstrom) and aldehyde (d=4.896 Angstrom) are usually associated with the perceived smell of roses and hyacinth/lilac respectively. These odorants are found in a wide range of roses, tomatoes and watermelons. They primarily stimulate the channel 5 OR (Musk) and possibly the channel 4 OR (Floral). The phenyl alcohol with a nominal d-value = 5.065 Angstrom was described earlier in Section 8.6.xxx. It most efficiently stimulates an OR defining the R-path of olfaction with a nominal d-value of 5.065 Angstrom through a conventional DACB coupling. It should be noted that the two identified benzyl moieties in the same cluster, while sharing a ring structure with the phenyl moieties, are not effective R-path odorophores. Their olfactory properties are not normally associated with roses, tomatoes or watermelons. [xxx]

Figure 8.6.11-2 shows an annotated version from Tieman et al. describing the likely paths taken to form several moieties of interest to the tomato research community under in-vivo conditions. While
shown in planar Fischer diagram form, these molecules are not planar. The lower path leads to 2-phenylacetonitrile (a.k.a. benzyl cyanide), a chemical not likely to be found within a tomato. The moiety at the top has been supplemented by one of its variants shown in inset. The reason is 1-nitro-2-phenylethane does not exhibit the appropriate d-value to qualify as an odorophore of interest here.

Figure 8.6.11-2 Proposed pathway for production of the volatile compounds 2-phenylacetaldehyde and 2-phenylethanol in plants. The insert at top left shows an alternate form of nitro-2-phenylethane. 2-phenylacetonitrile at lower right is also known as benzyl cyanide and is probably not important in olfaction. See text. Modified from Tieman et al., 2006.

Ater these “modifications,” the figure is interesting because all of the moieties derived from and including phenethylamine (CAS 64-04-0) exhibit virtually the same odorophore, the ligand incorporating the phenyl ring up to the first nitrogen or oxygen orbital along the aliphatic chain. The d-values of these moieties measured using the DS3.5 visualizer and Jmol files for these chemicals, are all within ±4 percent of the nominal R-path OR value of 5.065 Ångstrom. On the left, phenylalanine does not have a d-value appropriate to excitation of the R-path OR.

In summary, the Klee team has isolated the principle gustaphores and odorophores of the tomato, including several acidophores, several glycophores and at least two R-path odorophores. The relative intensity of the human perceptions of these chemicals has not been determined. These
intensities need to be determined before an aggressive program of taste optimization in tomato by genetic manipulation can be implemented efficiently. The R-path odorophores are members of a large family called phenethylamines that also include the 2-phenylallyl esters and alcohols well known in the perfume industry (Section 8.6.2).

8.6.11.2 Efforts by industry to categorize flavors

The commercial literature of wines is awash with efforts to organize the flavor sensations aroused by wines in particular but also other products. Figure 8.6.11-3 provides a well known “Aroma Wheel” attributed to Ann Noble, Emeritus of University of California-Davis.

Figure 8.6.11-3 An aroma wheel developed by an academic in coordination with industrial wine makers. Accredited to Noble.
Figure 8.6.11-4 shows a similar wheel used by Aromaster. Note the significant differences between these representations. Floral is subdivided into five categories in one and nine categories in the other. The common element is reduced to the fact that they both employ a three ring structure to group their various labels. Both representations attempt to display a multi-dimensional space (combining gustatory, olfactory, somatosensory, and to a degree oskatory sensations) on a 2-dimensional surface. The primary value of the labels are for non-academic pedagogical purposes.

Figure 8.6.11-4 An alternate aroma wheel as slightly higher resolution. Source is as labeled.
8.6.12 Reinterpreting the stimuli/response literature based on the hypothesis EMPTY

[xxx may want to move part of the following into the main text]

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The hypothesis is subject to further extension beyond that elucidated in Sections xxx, xxx & xxx. At this time, it specifically does not address the hydration of the aliphatic alcohols. Hydration may introduce a significant extension of the hypothesis, much as it did in the case of the hydration of sodium ion in the case of gustation.

8.6.12.1 Semantic descriptions of commercially named products

The Merck Index has long carried a listing of a wide variety of oils of commercial value, indexed as “Oil of . . .”. The data is technical with regard to the major constituents of the oils derived from plants (by volume) but it is unable to describe which are most effective with respect to olfaction. It also indicates the variation in sources for oils of the same name (Sumatra versus Borneo, etc.) as well as the frequently different genus and species of the source.

Many chemistry textbooks make casual associations between specific chemicals and their presence within the overall descriptor of “Oil of . . .”, but without quantifying their assertion in any way. Triller et al. have provided probably the most inclusive document using semantic names for both their (frequently trademarked) chemical names and a large list of perceived odors. The result is virtually uninterpretable by any researcher outside of their local group of investigators. See Section 8.6.12.5.

As shown in Sections 8.6.1.1.2 & 8.6.2.6, a more organized variation in commercial names is found among citrus fruit. This work has delineated the significant chemical differences between the odorants and odorophores of citrus. Lemons and sweet oranges are characterized by their limonene content, more conventional oranges are characterized by their citronella content and grapefruit are characterized by their mercaptan content. “Grapefruit mercaptan” appears to stimulate both the linal and musk channels of olfaction, thus providing the distinctive grapefruit flavor if not smell.

8.6.12.2 Reinterpreting the work of Kaiser

While collecting a broad range of data concerning the volatile chemicals associated with a vast array of botanical specimens, Kaiser offered no method of determining which of the volatiles were major odorants. Several facts can be extracted from his data following visual inspection.

1. A hybrid rose cannot be considered to be a rose in the context of olfactory research.
2. Pure-bred roses, based on a basically morphological taxonomy, vary widely in the relative concentration of the various volatiles they release into the air.
3. No correlation appears obvious between the concentration of a given chemical and the scent of a rose.
4. No correlation appears obvious between the names of the chemicals present and the scent of a particular rose. α-pinene and limonene are examples of this situation.
5. Chemicals commonly thought to be characteristic of the rose in olfaction typically vary by an order of magnitude in concentration among pure-bred roses. These chemicals include α-pinene, geraniol, limonene, linalool and 2-phenethyl alcohol.
6. A chemical that appears as an aldehyde in some roses may only appear as an alcohol in others while continuing to provide an odorophore stimulating the same OR of olfaction.
7. Example: Rosa alba maxima emits volatiles stimulating at least the citral, dulcal, floral, musk and

spice OR channels as shown in the following figure, although the degree of stimulation of each channel is unknown and may vary widely.

While \( \alpha \)-pinene occupies a prominent place in Kaiser's documentation (due to the ordering of names he adopted from their order of elution when using a specific analytical column, his page 213), the chemical contains no orbitals commonly found in olfaction but is a significant imitant at high concentrations and is likely to be reported by the nocent modality as such. This is likely to be true for many of the chemicals in his lists.

**Figure 8.6.12-1** shows a reformatting of the text of page 253 of Kaiser to place all of the data for an individual rose in one distinct column. It has also been extended to incorporate the d-values of most of the odorophores believed to be constituents of the most likely odorants, and the label of the primary OR associated with each of those individual odorophores. Only d-values and OR relationships for chemicals examined in the preparation of this work have been included here.

Many of the chemical names on Kaiser's lists are not those found on other similar listings.

It should be obvious that the term "rose-like" to describe a fragrance is not definitive. Every rose variety exhibits a selection of different odorants.
Eucalyptol is currently represented by eucalyptol 2656 and eucalyptol 21111689 in Chemspider although they have identical structures based on the DS3.5 visualizer and the Jmol files. The former has the designation (±) in front of its common name. The latter has the designation (1s,4s) preceding the systemic name for both.

The tabular data on pages 215-269 of Kaiser are worthy of a full scale data mining effort based on the hypothesis of this work. Such an effort should add additional knowledge about the odorants of lesser importance in a broad range of botanicals. However, the designations used by Kaiser may not be totally adequate as noted below.
8.6.12.3 Re-examining the step-one transduction framework

A distinction is made in the following statements between benzyl and phenol compounds based purely on their application in olfaction. Virtually any benzyl compound can exhibit one or more odorophores. One of the simplest is benzyl hydroxide (phenol). The next simplest group (but excluding the hydroxyl group attached directly to the ring) are the ethers of benzene. Other extremely important compounds contain a carbonyl group attached to the benzyl ring as either as a ketone. The expression phenyl, is frequently used to name such compounds to indicate the likely origin of the ketone. In this work, phenyl will not be used to describe a benzene ring with one hydrogen absent (C6H5). Instead the label benzyl will be used in its place to describe the current functional relationship. If the benzyl ring is modified to accommodate a hydroxyl group in addition to other side chains, it will be designated a phenyl (C6H4OH– ). This work will not concern itself with the formation of a given molecule in the chemistry laboratory.

The electrolytic hypothesis of olfaction within the broader electrolytic theory of the neuron provides a clear framework for the codification of odorants. The hypothesis is absolutely dependent on the rules of coordinate chemistry (as opposed to valence chemistry).

The theory clearly explains why saturated hydrocarbons, whether aliphatic or cyclic are basically odorless. Experiments finding odors related to these chemicals should be aware of contaminants at the level of parts-per-billion (PPB) that can account for the observed odor.

The theory clearly explains why unsaturated hydrocarbons C=C bonds and more complex hydrocarbons containing unsaturated (C=C) bonds and orbitals able to share pairs of electrons exhibit significant odorophores.

The theory clearly explains why the aromatics, and the arenes particularly, can support a wide range of odorophores. These unsaturated structures may remain hydrocarbons or include a variety of orbitals able to share unpaired electrons.

The theory clearly describes multiple family relationships among the aromatics and arenes. A hierarchy can be developed beginning with benzene, phenol, benzyl ethers and benzyl carbonyls.

- The first benzyl ether has the common name anisole (methyl benzyl ether).
- The first benzyl carbonyl has the common name benzaldehyde.
- A first combination of an aldehyde and a hydroxyl group with a benzyl group is labeled guaiacol_447 (2-methoxyphenol).

The theory clearly describes how arenes with multiple aliphatic arms containing unsaturated bonds or orbitals capable of sharing pairs of electrons create a geometrically expanding number of identifiable odorophores.

8.6.12.3.1 Aromatics and arenes as odorants

Figure 8.6.12-2 shows an initial segment of the aromatic and arene family tree. The figure allows for a wide range of additional ligands to occur. When R = CH3, the labels given below the molecules apply. The figure contains a number next to each molecule indicating the number of potential DACB's associated with that molecule when R = CH3. Where the number is one, the molecule can be considered a single odorophore odorant (SOO). SOO's are preferred for research investigations since they greatly simplify the data interpretation process. As noted in the indented paragraph, Acetophenone is described as a methyl benzyl ketone in this work since it does not exhibit a OH group indicative of a phenol derivative from the olfactory perspective. The presence of an OH group attached to the benzene ring is significant in olfaction; it increases the number of odorophores within an odorant substantially.

The figure highlights a variety of relationships among the aromatics and arenes.
1. Benzene does not exhibit the capability of forming a DACB. It would not be expected to be an odorant exhibiting even a single odorophore. However, it is considered a significant nocent and to be highly toxic when ingested. It can be used to form a variety of bicyclic and heterocyclic compounds as well as arenes. In general, the arenes are not toxic and form the bulk of the aromatics associated with hedonic odors. Exceptions include some of the simplest arenes, benzyl hydroxide_971 (phenol), benzaldehyde_235 and isoporpenylbenzene_7129, which are discussed in the following sub-section.

2. As R becomes more complex the number of orbitals can grow without limit, indicating the potential for a very large number of odorophores within a single odorant. Whether the individual odorophores are equally effective in step one of olfaction is a more complicated question.

3. As the arrows below anisole_7238 indicate, the derivatives of the arenes can include more than one aliphatic side chain, each of which can contain orbitals affecting the perceived odor of the molecule.

4. As the arrows below anisole_7238 also show, the location of a given moiety on either side of the ring can cause changes in the d-values of the various odorophores, thereby changing the perceived odor of two chemicals with the identical molecular weight and apparently the same grouping.

5. The mere fact that a molecule becomes non-planar can change its d-values and cause it to have a distinguishing odor compared to its otherwise similar partner.

6. Stick, or stick and ball representations of these molecules do not show their true 3D character and can not be relied upon for calculating d-values using standard bond length tables.

7. As in the case of most of the illustrated molecules, one or more rotatable bonds are present. The Jmol figures are believed to show the minimum energy situation for these bonds but there is no confirmation of this condition or how it is demonstrated. Some of the d-values obtained from the Jmol files may require modification if not confirmed in the future.

Note, the CHO group is indicative of the aldehyde, and not just the C=O relationship. Thus, the aldehyde of benzene is given as C6H5CHO. By structure, it can be considered a benzyl carbonyl. This structure, and that of isopropenylbenzene, are discussed more fully in the next sub-section.
The two allyl structures shown in the lower center exhibit significantly different steric relationships with the rest of their molecules and will exhibit different d-values related to the C=C group. Similarly, the 2-(allyloxy)phenol_63937 will exhibit different d-values than eugenol_13876103 even though the active chemical groups present are identical. The allyl radical is CH2=CH=CH2.
The two salicylic molecules on the right illustrate another family derivation. Salicylaldehyde shows its derivation from two of the primary olfactory types. The first parent is phenol. In the case shown, the R of its parent (acetophenone) has been replaced by H. It incorporates a hydroxyl group with the resulting 3 potential DACB relationships. It leads to a more complex methyl salicylate that introduces another chemical group. The inline oxygen of this group becomes another active orbital site. As a result, methyl salicylate exhibits six potential DACB relationships.

Finally, the conformation shown on the far right of row 4, 1-phenyl-1,2-propandione is an α-diketone. It exhibits three d-values of 2.549, 3.598 and 4.392 Angstrom based on the JSmol file of October 2015. The values are suspect as noted in Section 8.6.1.8. The right-most portion of the molecule is a diketone with a d-value of about 3.61 Angstrom based on a bond length between the two carbonyl carbon of 1.375 Angstrom (versus a similar value of 1.54 Angstrom for a similar molecule, a difference of 11%). The diketone portion contributes a “buttery” perception. This diketone structure appears in many floral odorants.

ChemSpider illustrates a large number of diones. They are frequently drawn in the trans-configuration in many 2D cases but displayed in the cis- form in 3D, because of crowding. (reminiscent of glycols).

Whereas the benzyl group, as a single resonant structure, only exhibits one source of available electrons, the slightly more saturated C6H8 group (1,3 cyclohexadiene) exhibits two other potential sources of electrons related to its two C=C bonds. The more saturated C6H10 (cyclohexene) only exhibits one source of electrons. The d-values of the odorophores of each overall molecule are dependent on the location of the center of the double bonds in each case.

Phenol (benzyl hydroxide) exhibits two distinct features capable of participating in a DACB; one source of electrons due to its resonant structure as well as a separate oxygen atom capable of sharing a pair of electrons. The distance between these two features is 2.90 Angstrom. However, phenol acts primarily as a nocent. It is very dangerous if swallowed.

Tables of “standard” bond lengths and bond angles cannot be relied upon to build structures in coordinate chemistry. There are too many secondary influences. Actual measured value for these features of a molecule are required. Currently, there is no obvious way to tell how a given molecule in a Jmol file from the Royal Society of Chemistry is developed. As a result, care must be taken to verify the precision of the d-values of a given molecule. See Section 8.6.1.6.

It appears the calculated d-values based on Jmol files and the various visualizer programs are only dependable to two decimal places. The third decimal value frequently changes between different instances calculated for the same molecule.

It is important to note the Jmol files and the DS 3.5 visualizer employ a computerized element numbering system that frequently differs from the textbook numbering systems of chemistry. No discussion of the rules employed by these programs has been unearthed.

Attempts have been made to characterize the arenes according to the position of the first orbital along the aliphatic chain. Material can be found discussing the orbital in place of the alpha, beta, gamma, delta and epsilon carbon positions. However, by the time the beta carbon position is addressed, the precise conformation of the molecule must be described in order to predict the d-value of the molecule. Absent a realistic d-value, the discussion flounders.

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358 [http://www.chemspider.com/Search.aspx?rid=c4a0a69a-e2d8-4065-9862-e4e87d25680c](http://www.chemspider.com/Search.aspx?rid=c4a0a69a-e2d8-4065-9862-e4e87d25680c)
8.6.12.3.2 Benzaldehyde & isopropenylbenzine as special cases

Benzaldehyde_235 and isopropenylbenzine_7129 appear to be special cases of arenes based on the benzyl ring. Both involve a side chain that is itself conjugated (-C=O and -C=C respectively). As a result, their combination appears to be totally conjugated and the presence and availability of electrons may be specialized. It is important to evaluate whether these two molecules exhibit one shared electron cloud, or two distinctly separate clouds that could support a DACB relationship with another molecule.

The question may be best resolved by considering the perceived odor of these two chemicals and estimating whether their perception is based primarily on olfaction or nocioreception? Benzaldehyde is considered a narcotic at high concentrations and is reported to cause contact dermatitis. Isopropenylbenzene is similarly labeled in the Merck Index.

The conformation of isopropenylbenzene_7129, may provide a source of electrons at a C=C location critically important in the odorants of many oils found among the roses. However, the molecule exhibits a rare conjugated bond sequence in connection with its resonant ring structure. This condition may leave the molecule without a potential DACB capability. The DS 4.1 visualizer shows only one electron cloud for α-methyl styrene_7129, an alternate name for isopropenylbenzene_7129. Thus, the molecule may be a nocent but not an odorant.

8.6.12.3.3 The unsaturated aliphatic hydrocarbons

Fully saturated aliphatic hydrocarbons (no orbitals) are intrinsically odor-free (except due to contaminants. However, if there are two unsaturated C=C bonds along the aliphatic chain, the molecule will exhibit an odorophore based on the distance between the double bonds. If there are three C=C bonds, the molecule will exhibit two potential odorophores.

The use of unsaturated aliphatic hydrocarbons with two double bonds may be useful in research as the location of one of the double bonds can be easily moved along the length of the aliphatic chain. This movement may allow greater delineation of the sensory efficacy of the OR channels with respect to the d-value parameter.

8.6.12.3.4 The unsaturated aliphatic alcohols

The limited effectiveness of alcohols as odorants has been known since at least 1900. The situation has not changed with time. What little odor is associated with alcohol may be due to its hydrated state, where the resulting O=H-O bonding exhibits a d = 2.70 Angstrom between the two oxygen atoms. The resulting solution could form a DACB with the OR 1 (acidic) sensory channel.

Laska & Teubner have provided the results of behavioral experiments involving a homologous series of alcohols and aldehydes. They did not discuss the precise chemistry of their test materials when in solution or in the mucosa, except they were purchased with a stated purity of better than 99 per cent. The materials were diluted with isoamyl acetate in an attempt to provide nominally equal strength odorants. Unfortunately, isoamyl acetate exhibits a distinct odor by itself, d = 2.087 Angstrom (based on this work), and may participate in other coordinate bonding with the aliphatic alcohols and aldehydes. Their results may be suspect. Leinders-Zufall et al. used n-amyl acetate as a stimulant in their 1999 experiments.

Figure 8.6.12-3 reproduces their Figure 1. The results are quite interesting. Note the large number of subjects who could not perform above chance level in this series of tests, particularly between adjacent pairs and next to adjacent pairs in the homologous series. Their data for the aldehydes is

similar but shows an even higher number of subjects (in some cases 15 out of 20) unable to exceed the chance threshold.

**Figure 8.6.12-3** Performance of 20 subjects in discriminating between members of a homologous series of aliphatic alcohols. Each data point represents percentage (means ±SD) of correct choices from 10 decisions per odor pair and subject. Filled symbols indicate odor pairs that were not discriminated above chance at the group level. The figures above the abscissa indicate the number of subjects that failed to perform above chance in the corresponding test. Names of substances are given in their Table 1. From Laska & Teubner, 1999.

Their discussion obviously claims successful discrimination in their experiments but does include the interesting observation, “However, the question arises of whether the performance of the human subjects shown in the present study was indeed based on the ability of the olfactory system to discern between odor qualities or whether other sensory systems or talents of the olfactory system may have been involved.”

[xxx how does my theory explain the above?? ]

It can be concluded that the olfactory modality does not incorporate an alcohol (d =1.43) receptor.

### 8.6.12.3.5 The unsaturated aliphatic carboxylic acids

In fully saturated aliphatic carboxylic acids, the molecule only exhibits the single odorophore associated with the non-resonant O–OH structure. However, if there is an unsaturated C=C bond along the aliphatic chain, the molecule exhibits two additional odorophores based on the distance between the double bond and each of the oxygen orbitals. If there are two C=C bonds, the pattern becomes more complex with a total of six potential odorophores present. **Section 8.6.11.9** reviewed many of these carboxylic acids.

The use of carboxylic acids containing only one C=C bond may be useful in research as the location of the double bond can be easily moved along the length of the aliphatic chain. This movement may allow greater delineation of the sensory efficacy of the OR channels with respect to the d-value.
parameter.

8.6.12.4 Examples of multiple odorophore odorants

Figure 8.6.12-4 will explore how well the hypothesis of this work performs in practice. It will do this initially by exploring the eugenol family and then comparing it to a more complex set of molecules by replacing the methyl group esterified to the benzyl ring with ethyl and propynyl groups. It will then explore molecules where the oxygen free aliphatic chain is modified by the addition of orbitals to that chain.

As one example of many, the designation eugenol, or even isoeugenol, is not adequate when participating in olfactory research. The family is large and multi-faceted. This table illustrates the problem. Each contains a set of odorophores that are not the same even though the chemicals have the same generic name.

No reliable scent has been found in the literature for isoeugenol or for o-isoeugenol and the other scents may not be statistically relevant. The label column is based on very informal usage among a variety of investigators. The labels should not be considered definitive. It does appear the perceived difference between nutmeg and clove is based on the fourth and fifth odorophores of their respective molecules. All four of the odorants exhibit similar first, second and third d-values.

anisole_7238 (methyl phenyl ether or more appropriately methyl benzyl ether) and ethyl phenyl ether_7391 (more appropriately ethyl benzyl ether) have only one odorophore and can be expected to be perceived quite similarly. The lower d-value for ethyl phenyl ether_7391 (more appropriately ethyl benzyl ether_7391 since it does not have an OH attached to the benzyl ring) is due to the longer aliphatic chain changing the length of the bond length between the oxygen orbital and the delocalized electrons of the phenyl ring. The effect is small as noted by comparing these two molecules with the nominally longer n-propyl phenyl ether_11655 (more appropriately n-propyl benzyl ether since it does not have an OH attached to the benzyl ring). 2-prooxyphenol can be considered the first member of an expanding family of homologs and isomers of the homologs (such as the eugenol family).

Ethyl vanillin (3-ethoxy-4-hydroxybenzaldehyde) is similar to ethyl phenyl ether and has an even finer
and more intense vanilla flavor than vanilla itself. Note how the first and second d-values remain nearly the same for all of the chemicals listed (within 0.2 Angstrom). The third d-value of the vanillins is significantly higher than for the other molecules, replacing stimulation of the OR 2 dulcal channel with stimulation of the O3 floral channel. Note also, that ethyl vanillin_8154 exhibits a more intense and finer odor than vanillin_13860434. It appears to do this by stimulating the OR 4 limal channel as well as the OR 3 floral channel.

The majority of the OH/benzyl, ether/benzyl and OH/ether odorophores predominantly stimulate the OR 2 (dulcal) channel. The =O/benzyl odorophore predominantly stimulates the OR 3 (floral) channel and the =O/OH odorophore predominantly stimulates the OR 5 (cinnamon) channel (as suggested by the bars along the bottom of the figure). The d-values in the other columns are mixed and/or too near the transition value between a pair of channels.

The binary code for step-one transduction for phenol_971 and for anisole_7238 is obviously 010000000. The binary code for the guaiacol_447 and its family members is 011000000. If one explores the channel stimulations due to vanillin_13860434, a first approximation to its binary code might be 0110101000. The exponents indicate the presence of multiple odorophores stimulating the designated channel. In the case of channel 2, the d-values of 2.813 and 2.865 Angstrom represent the two odorophores. In the case of channel 3, the d-values of 3.135 and 3.624 Angstrom represent the two odorophores. Ethyl vanillin_8154 can be approximated by 0110101000. Guaiacol_447 is clearly the parent of both the eugenol and vanillin families.

The above binary codes show that phenol and the members of the anisole family shown are all single odorophore odorants (SOO). The guaiacol family are the first to exhibit three odorophores all affecting the OR 2 channel.

The eugenol family molecules exhibit additional decoration associated with higher OR channels. The differences in perceived odor between members of this family are due to individual changes in the d-values of their odorophores. The vanillin family molecules exhibit additional decoration associated with still higher OR channels and exhibit similar variations in d-value among the family members.

[xxx numbering atoms in DS 3.5 is unconventional. ]

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8.6.12.5 Reinterpreting the work of Triller et al.

The 2008 paper focuses on the semantic definition (frequently trademarked names) of their odorants and semantic names of various perceived odors as defined within their investigating team. While the paper describes the 2D structure of many chemicals using stick diagrams (sometimes labeled structural diagrams), they do not address the physical distance between the orbitals as part of a series of overlay chemical groups. They do not report any d-values or similar parameters related to their stimulants. They do not take note of any C=C bonds or the resonances associated with benzyl rings.

Look first at their data for molecules they characterize as causing or not causing the perception of muguet (lily of the valley) and summarized in figure 2. They list eight odorants in their figure 2 that all exhibit a single common odorophore as defined in this work and perceived as exhibiting a muguet (lily of the valley) odor. It has the d-value of 6.038 Angstrom for the 3-(4-tert-butylphenyl)propanal form of Bourgeonal®_58364, (5). They indicate the test material consisted of about 4% of this more intense form of Bourgeonal and apparently 96% of the less intense p-isomer (6). Such an odorophore would stimulate the cinnamon channel (OR 6) of this work most intensely. An alternate name for this molecule, p-tert-Butyhydrocinamnic aldehyde indicates its cinamic character. The tri-methyl group associated with these molecules contains no orbitals and would only change the d-value marginally compared to the simpler arene without this group.

No essential oil associated with lillies of the valley could be found in the scientific or consumer literature.

ChemSpider lists three variants of Lilial® (7), 1266494 (2R), 1363748 (2S) and 199342, Lilial_199342 is
(2R)-2-Methyl-3-[4-(2-methyl-2-propanyl)phenyl]propanal_1266494 and (2S)-2-Methyl-3-[4-(2-methyl-2-propanyl)phenyl]propanal_1363748 both exhibit a d = 4.071 Angstrom due to their similar 3D structures. They would most effectively stimulate the OR 4 (limal) channel of this work. Floralozone® (8), 3-(2-Ethylphenyl)-2,2-dimethylpropanal_95150 exhibits d = 6.427 and like Lilial_199342, it stimulates the cinammal channel (OR OR 6) most strongly. The above molecules all exhibit a single odorophore.

Lyral® (9), 4-(4-Hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde_82714 displays a fundamentally different structure from a chemical group perspective and coordinate chemistry perspective. It exhibits three odorophores with d-values of 4.975, 6.574, and 10.890 Angstrom stimulating OR 4/5 (limal or musk), OR 6/7 (limal or spice & VR 3 (see Section 8.6.xxx). The d = 4.975 Angstrom value indicates it stimulates both the OR 4 and OR 5 channels but the relative intensity of each stimulation cannot be provided at this time. Figure 8.6.12-5 reproduces their figure 2 with additional notation added. The notation includes a more specific descriptor (beginning with an underline), an accession number on the ChemSpider archive of molecules. Some of the odorant molecules exhibit more than one odorophore. In that case, as for
Figure 8.6.12-5 Agonists for OR1D2 (OR 6) of the cinnal channel. OR1D2 was previously known as hOR17-4. Numerics beginning with an underline refer to ChemSpider archive numbers. d-values are shown for selected molecules discussed in this work. See text. Modified from Triller et al., 2008.
Triller et al. note, “We have now identified agonists containing no aldehyde but ketone, and alcohol or ether functions, i.e., 10 and 15, respectively, and are in the process of refining the binding-site model based on our results. (10) was identified as 4-[4-(1-Methylethyl)phenyl]butan-2-one_74634. It exhibits a single odorophore with a d = 6.069 Ångstrom. It would be expected to stimulate the OR 6 (cinnal) channel most strongly. Triller et al. indicate this molecule exhibits no perceived muguet odor. The triller et al. paper did not clearly identify their molecule (15). The structural diagram indicates it is a saturated six-sided heterocyclic ring containing oxygen with an attached hydroxyl group opposite to the oxygen. A reasonably similar planar molecule, Tetr hydro-2H-pyran-4-ol_67513, exhibits a d = 4.144 Ångstrom that would be expected to stimulate the OR 4 receptor and the limal channel more than the OR 6 receptor.

The use of chemical group names is superfluous when the coordinate chemistry and overlay groups defined in this work are employed to explain the mechanism of olfaction.

Their (16) and (17) would be expected to stimulate the OR 6 receptor. (17) is a multiple odorophore odorant (MOO) and would be expected to stimulate lower numbered receptors also due to the presence of additional odorophores. Some of these odorophores might be more effective as stimulants than that affecting OR 6.

To the extent muguet (lilly of the valley) is perceived upon the stimulation of only one sensory channel, that channel appears to be OR 6 (cinnal). However, some of their subjects may have indicated otherwise depending on how they interpreted the semantics of the protocols used. Based on this information, the receptor of OR 6 can be related to their receptor OR1D2 (formerly known as one of the human olfactory receptors, hOR17-4) to the extent OR1D2 is an actual receptor and not present in some other capacity. The conclusions of Triller et al. in this regard are tempered, “Our previous results could be interpreted as an indication that OR1D2 is, to some extent, a ‘muguet receptor’. This is probably because selection of Bourgeonal® analogues for screening biased the data set towards muguet materials. However, it is clear from our results (Fig. 2) that activation of OR1D2 does not guarantee that a substance possesses a muguet odor, since 9 of the 17 agonists have no element of muguet in their odor profile. Furthermore, it is evident that failure to activate OR1D2 does not mean that a compound will fail to elicit muguet character (Fig. 3). In other words, OR1D2 activation does not correlate directly with any specific percept (of their analysis, ed.).”

OR1D2 is a protein listed officially in the RCSB protein data bank (PDB) as 1D2 - P34982. It is described there as “Odorant receptor which may be involved in sperm chemotaxis. Bourgeonal is a strong chemoattractant for sperm in vitro and is shown to be a strong agonist for OR1D2 in vitro. May also function in olfactory reception.” The use of the terms may be and may also shows the limited verification of the role of this protein in olfaction. Triller et al. noted, “Since their discovery, however, mammalian olfactory receptors have proven exceedingly difficult to match to their cognate ligands. Numerous laboratories have faced puzzling difficulties in functionally expressing olfactory receptor proteins in both heterologous and homologous systems. In brief, the association between the identified gene and the functional sensory receptor molecule has not been made.

Muguet is the diminutive form of Old French mugue or muguete (?“musk”), from muscade, from Latin muscada, feminine of muscatus (?“muskly”). Its derivation from musk introduces an additional complication relative to this work since OR 5 is labeled the musk channel. The olfactory channel most influenced by the molecules studied in the triller et al. paper is labeled the cinnal channel associated with the olfactory receptor 6 (OR 6).

The molecules shown in the lower portion of their figure 2 appears to be a mixed bag. The label “Agonists which have no muguet character “ is probably over restrictive since they did not investigate the phenomenon of masking at all. As noted above, (10), 4-[4-(1-Methylethyl)phenyl]butan-2-one_74634 exhibits a single odorophore with a d = 6.069 Ångstrom that is very similar to that of (5). It should be in the upper portion of the figure except for the semantic descriptors of their test subjects.

Although the term “green” has been used over the years by different olfactory investigators,
its definition has never been satisfactory. To suggest it relates to the smell of new mown hay is less than helpful from a scientific perspective. What was the botanical source of the hay?

It is important to note the paper incorporates no definitions, or citations to such definitions, of the array of semantic terms used to describe perceived odors. (18) is actually labeled as musty, that is semantically very similar to musky or musk. (19) would also be expected to mimic (7) rather closely except for the fact it incorporates other odorophores that might be more effective than and mask the d=6.038 Angstrom odorophore. (20) and (21) have very similar structures to (7) respectively. It would be important to examine the 3D structure of these molecules in order to understand their efficacy. (23) should be more effective at stimulating OR 5 than OR 6 because of its shorter aliphatic chain. (24) on the other hand should be more effective at stimulating OR 7, because of its longer aliphatic chain. (25) was not identified in detail. However, it appears very similar to some of the citrals that stimulate the OR 8 receptor and the citral channel of human olfaction. As noted in Section 8.6.1.6.3, this molecule exists in multiple conformations that cannot be ascertained from the structural diagram shown.

Their figure 3 can be expanded without limit to illustrate molecules that do not stimulate a perception of muguet. Based on the hypothesis of this work, the simpler molecules, (2), (26), (12), (14) and (27) exhibit demonstrable reasons why they exhibit different d-values than required to stimulate OR 6. The primary messages to be drawn from their figure 3 are three. First, 2D structural diagrams are inadequate to support investigations related to olfaction. Second, the presence of multiple odorophores in one odorant molecule can obscure the target perception of the test protocol. Third, the use of semantic descriptors drawn from a totally subjective list of possibilities does not serve science well.

Beginning on page 868, Triller et al. follow an archaic train of thought regarding a stereoelectronic fit to explain molecular selection in the olfactory modality. In the second paragraph, they begin to consider specific anosmias that they defined as “the inability of a subject to perceive a given odor, while that subject is still capable of perceiving other odors. However, the exact meaning of the term is somewhat unclear and varies from user to user.” Their definition is compatible with the hypothesis of this work. Their discussion veers between studies of the olfactory modality and the oskornatory (VNO) modality. The material is extensive but leans heavily on semantics as in the earlier parts of the paper. They do not provide any analysis of a large number of structural diagrams related to their anosmia investigations, i.e., no theoretical aspects related to anosmia are discussed.

Triller et al. end their paper stressing the negative results of their work relative to improving the theoretical understanding of olfaction.

8.6.12.6 Reinterpreting the 2006 work of de Souza et al.

The Acree group presented a paper in 2006 based on the empirical and totally subjective school of aroma research361. The emphasis was apparently on the olfactory aspects of aroma based on the volatility of their test samples. The subjectivity was demonstrated by the repeated meeting of the test subjects in order to draw up a restricted list of ten odor categories out of 24 “reference standards” used in the Acree laboratory (their Table 1). These ten perceived odors would constitute their complete list of allowed responses in their evaluations of two forms of alcoholic beverages. “Cachaça is the typical Brazilian spirit produced from the distillation of fermented raw sugar cane juice, whereas rum, traditionally produced in Caribbean countries, is a spirit obtained by fermenting cooked sugar cane juice and molasses.”

A descriptive sensory analysis (DSA) was at the center of the empirical test procedure. This subjective testing was extensive in order to collect statistically sufficient information. Their figure 1 shows the ten labels allowed using a “spider” diagram (a typical ten radial plan position indicator (PPI) display in radar terminology).

The test phase involved 12 experienced subjects who were presented three samples at a time (where two were identical) and requested to identify the perceptually different sample.

The constituents of each beverage were identified objectively by gas chromatography-olfactory (GCO) and mass spectrometry. 25 odorants were identified in cachaca (with 5 labeled unknown based on GCO); 20 were identified in the rum (with two labeled unknown by GCO).

Figure 8.6.12-6 modifies their Table 4 to illustrate a variety of features of their work. The original row for eugenol has been divided into two rows to accommodate the complexity of the molecule. The row for \( \beta\)-damascenone_4517997 has also been divided into two rows for the same reason.

The feature of major interest is the overlay (chemical) groups defined by the physical distance between “orbitals” capable of participating in hydrogen bonding and not by the standardized chemical grouping of elements found in textbooks. The distance, between individual pairs of these orbitals in 3D representations is defined in this work, as a d-value. Section 8.4.1.1 describes these “orbitals. Sections 8.5.1 (related to gustation) or 8.6.1 (related to olfaction) describes how these orbitals are present in “overlay structures” within the field of coordinate chemistry. Section 8.5.3 goes into more detail on the development of the overlay group concept. Based on these definitions, most of the molecules addressed by de Souza et al. exhibit multiple overlay structures, each with its own d-value.

The vertical bars on the right highlight the rounding applied to the terms used to calculate the ratios of potency between the cachaca and the rum. These ratios are at best suggestive. To avoid potential confusion, the indices assigned by the RSC in their ChemSpider database have been added to the odorants employed and/or found in the two beverages. The asterisks indicate a few of the names used in the study were not found in the database except under alternate labels preferred by the IUPAC. A major finding are the d-values shown on the left. These values result from the development of d-value as a fundamental parameter in the olfactory characteristic of any odorant in this work (Section 8.6.2.8). The d-values of these odorants are taken from 3D representations of these molecules found in the ChemSpider Jmol files as of June 2016. These files are included in the ChemSpider Protein Data Base (PDB) maintained by the Royal Society for Chemistry. The most important conclusion is that most of the odorants used did not exhibit d-values that were single-valued, and therefore were not preferred odorophores.

The use of single-valued odorants containing only a single preferred odorophore in laboratory investigations make the data reduction task much easier. The use of such odorophores insure that the identified components of a particular odor consist of orthogonal components.
On the other hand, most of the odorants listed in the table were organic acids or derivatives of organic acids (typically butyrates). Three of the butyrates exhibited identical d-values and should have been identified by the same perceived odor under well-controlled test conditions. However, two were described as apple and one as melon using the constrained odor list.

The one single-valued odorant with a high d-value was described in the constrained list as floral when its d-value would suggest the disallowed label of musk.

Eugenol, 13876103 exhibits six overlay structures with the following d-values: 2.805, 2.869, 3.009, 4.335, 6.740, and 7.019 Å. The last two values do correspond to channel 7, spicy, of this work. However, 4-ethylguaiacol, 56245 does not exhibit a high d-value that can be associated with spicy. An unconstrained list of labels for this odorant would be more likely dulcal (perceived as either sweet or fetid depending on concentration). The lower four d-values of eugenol contribute to the dulcal, floral, and limal perceptions in olfaction.

8.6.12.6 A suggested conclusion for the de Souza et al. paper

de Souza et al. do not provide a conclusion section to their paper. In a suggested conclusion, this work would provide a significantly clearer difference between Brazilian cachaça and Caribbean rum. β-damascenone, 4517997 appears to be the dominant odorant in both beverages as one might expect. Its d-values suggest a dulcal (channel 2), a floral (channel 3) and a limal (channel 4) perception using the suggested labels of this work. The cachaça exhibits a significant spicy (channel

**Table 4. Potency Ratios of the Odorants Common to Rum and Cachaça**

<table>
<thead>
<tr>
<th>d-values from Jmol/JSmol</th>
<th>nominal channel</th>
<th>odorant</th>
<th>potency (Charm)</th>
<th>constrained odor</th>
<th>ratio C/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.805, 2.869, 3.009, 4.335</td>
<td>2, 3, 4, 5, 7, spicy</td>
<td>eugenol_13876103</td>
<td>6625</td>
<td>10</td>
<td>spicy</td>
</tr>
<tr>
<td>2.261, 3.872, 5.225</td>
<td></td>
<td>unknown 1</td>
<td>1327</td>
<td>10</td>
<td>cereal</td>
</tr>
<tr>
<td>2.418, 2.461, 4.586</td>
<td></td>
<td>ethyl phenyl acetate_13885245</td>
<td>702</td>
<td>10</td>
<td>fruity</td>
</tr>
<tr>
<td>2.713, 2.789, 2.805</td>
<td></td>
<td>24-nonadaleral_21711</td>
<td>675</td>
<td>10</td>
<td>floral</td>
</tr>
<tr>
<td>5.065</td>
<td>5, musk</td>
<td>phenyl ethyl alcohol_5830</td>
<td>3705</td>
<td>83</td>
<td>floral</td>
</tr>
<tr>
<td>2.280, 5.091, 5.014</td>
<td></td>
<td>2-phenylethyl acetate_21105987*</td>
<td>768</td>
<td>75</td>
<td>floral</td>
</tr>
<tr>
<td>2.280</td>
<td></td>
<td>ethyl isobutyrate_7065</td>
<td>1806</td>
<td>192</td>
<td>melon</td>
</tr>
<tr>
<td>2.399</td>
<td></td>
<td>diethyl acetal_23620752</td>
<td>5009</td>
<td>1035</td>
<td>fruity</td>
</tr>
<tr>
<td>2.191, 2.388, 3.069, 3.548, 5.020, 5.727</td>
<td>1, 2, 3, 5, 5, 6</td>
<td>β-damascenone_4517997</td>
<td>60974</td>
<td>15467</td>
<td>fruity/floral</td>
</tr>
<tr>
<td>2.280</td>
<td></td>
<td>ethyl 2-methylbutyrate_42253</td>
<td>1120</td>
<td>633</td>
<td>apple</td>
</tr>
<tr>
<td>2.280</td>
<td></td>
<td>ethyl butyrate (or butanoate)_7475</td>
<td>131</td>
<td>192</td>
<td>apple</td>
</tr>
<tr>
<td>2.813, 2.865, 3.624+3</td>
<td></td>
<td>vanilin_13860434</td>
<td>10</td>
<td>134</td>
<td>vanilla</td>
</tr>
<tr>
<td>2.290</td>
<td></td>
<td>β-methyl-γ-ocatrole_56625*</td>
<td>10</td>
<td>140</td>
<td>mould</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unknown 2</td>
<td>10</td>
<td>791</td>
<td>solvent</td>
</tr>
</tbody>
</table>

*Values of <10 were rounded up to 10 (a least detectable potency). Vertical bars indicate questionable ratios. * Chemical names have changed in IUPAC.

Figure 8.6.12-6 Potency ratios of cachaça and rum with d-values added to constituents. The eugenol line has been split into two lines because of the complexity of the molecule. The d-values are based on the ChemSpider PDB as of June 2016. The dominant molecules in the difference in aroma between cachaça and rum are eugenol, diethyl acetal and phenyl ethyl alcohol. See text. Modified from de Souza et al., 2006.
7) odorant, eugenol, that is present at an 11% potency level relative to β-damascenone and is not present in rum to any significant extent. Diethyl acetal appears in both beverages with about the same potency, 8%, relative to the β-damascenone component in both beverages. It adds an acidic (channel 1) perception to the beverages. Phenylethyl alcohol, present at a significant level (about 5% relative to the potency of β-damascenone) in cachaca but not in rum. This molecule stimulates channel 5, and contributes a perception of musk, in the olfactory system. These findings are in agreement with their figure 2 without the clutter associated with the other non-orthogonal odorants present. See Section 8.6.6.6 regarding the development of the spider (aka PPI) representation. The significant difference in the “unknown 1” component between the cachaca and the rum is noted. This is probably an artifact of the preparatory activities before GCO component separation activity. An additional conclusion can be drawn that eugenol is broken down during the cooking process used to prepare rum, thus eliminating the spicy odorophore, eugenol present in significant potency in cachaca.

How the presence of the few dominant molecules in these two beverages influences their overall aroma with respect to the categories and time dependent “notes” used in perfumery and beverages (Section 8.6.1.1) requires further evaluation in the laboratory.

8.6.12.6.2 Followup work related to de Souza et al. paper

The de Souza paper offers an opportunity to determine the principle olfactory channel stimulated by β-damascenone. β-damascenone exhibits four low d-values that support the stimulation of the acidic (1)dulcal (2) and floral (3) channels. The 3.069 Angstrom value straddles the yet to be defined adequately dulcal/floral transition region. It exhibits two higher d-values with the 5.727 Angstrom value straddling the yet to be defined adequately musk/cinnamal transition region.

It is important that any laboratory undertaking avoid confusion between

<table>
<thead>
<tr>
<th>Molecule</th>
<th>d-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-damascone</td>
<td>2.542, 3.051, 3.594</td>
</tr>
<tr>
<td>a-damascone</td>
<td>2.402, 3.610, 5.083</td>
</tr>
<tr>
<td>trans-damascone</td>
<td>2.388, 2.624, 3.846</td>
</tr>
</tbody>
</table>

and potentially other close relatives of these molecules.

By performing a triangle test between β-damascenone and the preferred single odorophore odorants proposed in this work (Section 8.6.2.9.7) at nominally equal potency, the specific olfactory channel and the relative potency of the odorophores at 2.191, 2.388, 3.069 & 3.548 Angstrom should be definable. A similar set of tests could define the relative potencies of the individual odorophores of eugenol. The results could be readily plotted on an odorwheel (or spider diagram) displaying only the nine orthogonal axes defined in this work. Such a display could employ linear radial scales in order to focus attention on the major odorants only. The other odorants in the de Souza et al. paper would be recognized as containing a group of dispersed low level odorophores essentially contributing background noise to the overall perceptual aroma.

The similarity between the odors of some roses and the odorophores of Brazilian cachaca and/or Caribbean rum is noted. See Section 8.6.2.5.5.

The same protocol could be used to evaluate the relative potencies of the odorophores of eugenol, no other orbitals associated with chemical sensing.

Following the suggested investigations, it may be possible to more clearly delineate the overlap in sensitivity between channels 2 and 3 in human olfaction by careful laboratory experimentation using a modification of the above protocols and other single odorophore odorants (SOO) with d-values near 3. Angstrom.

8.6.13 Re-examining the step–two transduction framework

The exploration of the step-two transduction framework has yet to begin since it was only recognized in the above discussions. Protocols for such exploration can be readily developed based on the material presented. The use of simple unsaturated alcohol homologs appears ideal for such studies.
They each typically only exhibit one odorophore and are liquids at biological temperatures (up through n-decyl alcohol).

8.6.14 An after the fact comparison of the ligands of GR and OR

Following completion of the detailed study of the gustatory and olfactory modalities, it is obvious that these studies converged on two distinct sets of amino acids ligands hydrolyzed to a long chain phospholipid found in the outer wall of all cells, but particularly the neural portion of the sensory neurons. Section 8.4.8 summarizes these findings prior to the following analysis. The selections were made based on the separate literatures available relating to these two modalities. Both sets involve a series of phospholipid amino acids with sensitivities varying in accordance with the d-value of their potential orbital pairs capable of forming a DACB with a selected set of gustaphores and/or odorophores. The first four receptors in the two modalities exhibit similar d-values and a common set of sensory receptor ligands might be employed successfully. Only active laboratory investigations can further qualify the veracity of this suggestion. Figure 8.6.14-1 shows the favored set of receptor ligands for each modality. In retrospect,
• it is clear that we do not, and can not, know the original design specifications for each modality or the preferred tradeoffs in performance between the two modalities, and
• it appears that future laboratory investigations should focus on what amino acids or their residues are found in the saliva and the mucosa. It is quite possible that a condensed list of amino acids hydrolyzed to the common phospholipid could be used as the chemical receptors in both the gustatory and olfactory modalities. Following a comprehensive search for the acids or their residues, a determination of their sensitivity to d-value in DACB formation needs to be determined before a final recommended list of receptors can be developed.

<table>
<thead>
<tr>
<th>Designation</th>
<th>Active Ligand</th>
<th>Used to detect</th>
<th>d-value centroid</th>
<th>d-value centroid</th>
<th>Designation</th>
<th>Active Ligand</th>
<th>Used to detect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GUSTATORY Modality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR 1</td>
<td>PtdSer# Serine</td>
<td>Acids</td>
<td>2.276</td>
<td>2.276</td>
<td>OR 1</td>
<td>PtdSer# Serine</td>
<td>Acids</td>
</tr>
<tr>
<td>GR 2</td>
<td>PtdGal Galactose</td>
<td>Sugars</td>
<td>2.82</td>
<td>2.791</td>
<td>OR 2</td>
<td>PtdTyr Tyrosine</td>
<td>Phen-orb.</td>
</tr>
<tr>
<td>GR 3</td>
<td>PtdIns mucinositol</td>
<td>Sodium</td>
<td>3.32</td>
<td>3.508</td>
<td>OR 3</td>
<td>PtdHis 4-Hydroxylysine</td>
<td>Phen-α</td>
</tr>
<tr>
<td>GR 4</td>
<td>PtdAsn Asparag.</td>
<td>Picrics</td>
<td>4.746</td>
<td>4.467</td>
<td>OR 4</td>
<td>PtdHis Histidine</td>
<td>Phen β</td>
</tr>
</tbody>
</table>

**Figure 8.6.14-1** Comparison of favored sensory receptor ligands for gustation and olfaction. Both studies defined serine as the amino acid hydrolyzed to phosphatidyl acid to form the lowest d-value sensory receptor. PtdGal & PtdTyr have sufficiently similar d-values that either could be used in both receptor channels, depending on the width of their sensitivity characteristics. Mucoinositol is known to be present in the olfactory epithelium and could be the common channel 3 receptor ligand. See text.

END 8.6.;

8.6.3.3.1 Potential sensory receptors for fruity stimulants based on ketones or aldehydes

The first proposed sensory receptor is acetoin, or its isomer acetaldo, when esterfied to phosphatidic acid (PtdAce). Figure 8.6.14-2 shows this moiety forming a coordinated double bond with acetone, the simplest of the ketones or aldehydes associated with the d = 1.22 stimulant family (nominally the simplest fruity odors). Each hydrogen bond is formed between an oxygen atom sharing an electron-pair and the polar carbon of the adjacent molecule. According to the polar potentials discussed in Section 8.6.3.1xxx, [before renumbering] [xxx the source of the hydrogens suggests hydration is required before the described coordinate bonding pair could be achieved.
The arrangement of the carbon and oxygen atoms of each carbonyl group is planar. The perspective shown foreshortens the length of the hydrogen bonds. The nominal distance between the active centers associated with each bond is 2.7 Angstrom.

An alternate situation recognizes the need for the acetone to become hydrolyzed in order to achieve any reasonable solubility in the mucosa. It also suggests the carbonyl of the phospholipid receptor also needs to be hydrolyzed to be effective within the mucosa.

Figure 8.6.14-2 Possible fruity odorophore-sensory receptor interface, $d = 1.22$ Angstrom. The spacing between the two coordinate bonds is 1.22 Angstrom.
8.6.3.3.3 The proposed sensory receptor for the resonant carboxylic group in solution, \( d = 2.07 \) EMPTY

8.6.3.3.4 The proposed sensory receptor for the alkyl esters, \( d = 2.3.4 \) EMPTY

A range of lactone related molecules appear to be candidates for the sensory receptor sensitive to \( d = 2.27 \) coordinate bond spacing. The simplest could be \( \alpha \)-D glucose 1-phosphatidic acid. Such a form relies upon part of the phosphonic acid structure for coordinate bonding and this may conflict with other requirements. More likely candidates appear to be D-gluconic acid or D-\( \delta \)-gluconolactone, which exist in equilibrium in solution and are found widely in the biological system. They are uronic acids, where only the hydroxyl group associated with the primary carbon is oxidized to a carbonyl group. Their esterification with phosphatidic acid provides the desired non resonant planar carboxylic acid moiety as shown in Figure 8.6.14-3. Phosphatidyl gluconic acid will be abbreviated PtdGln. When considering the closed ring form of D-\( \delta \)-gluconolactone, care must be taken to realize the hydrogen bond is with an available electron-pair. It does not require breaking the bond between the oxygen and the C-6 carbon.

8.6.3.3.5 The proposed sensory receptor for the aromatic \( \alpha \)-ethers and alcohols, \( d = 2.82 \) EMPTY

The literature of aromatic \( \alpha \)-ethers and alcohols in the olfactory and perfume literature is extensive. They are generally associated with the elicited sensations associated with clove, anise and licorice.

The logical receptor for these odorants would be an amino acid containing either the ester or the alcohol at the alpha position, esterified to a phosphatidic acid. Tyrosine appears to satisfy the requirements for the formation of such a receptor. Tyrosine is the substrate for many important neural system neuro-stimulants. Figure 8.6.14-4 shows the structural properties of such a suggested receptor. The planar shelf appears ideally suited to coordinate bond pairing with a wide variety of aromatic \( \alpha \)-ester or alcohol ligands.

A phosphatidyl ester of tyrosine, PtdTyr, makes a perfect candidate receptor for the phenols if the tyrosine is esterified via the carboxylic group. [xxx integrate into previous paragraph or drop]

8.6.3.3.6 The proposed sensory receptor for the diketones, \( d = 3.61 \)

The literature of diketones in the biological
environment is limited. However, Marchi-Artzner et al. have prepared amphiphilic lipids of the β-diketone variety (1,3-diketones), which they christen only ligand \( \textbf{L} \). These were used to prepare artificial bilayer lipid membranes\(^{362} \). Valla et al. have studied a wide range of mostly β-diketones and some quinone derivatives with the second ketone at either the ortho or para-positions\(^{363} \). Unless the o-quinone diketones (vicinal ketones, of the 1,2-diketone or 2,3-diketone variety—α-diketones) are positioned axially in opposite directions, they do not exhibit the potential d-value of interest here. Such an arrangement is the essence of the odor associated with fermentation due to the presence of 2,3-butanedione. This chemical is also widely used in margarine to elicit a buttery sensation and is a common result of fermentation. It can be prepared from butanedionic acid (succinic acid in the biochemistry community). [xxx duplicate of earlier]

Because of its wide use, it is obvious there is a sensory receptor signaling the presence of this odorophore but a ring structure in the receptor appears unlikely. \( \alpha \)-benzoquinone would not be likely to have the two carbonyl oxygen groups in opposing axial orientations in order to achieve the necessary d-value of 3.61.

The target is an 2,3 keto-butanol that can be esterified to phosphatidic acid to give the desired phosphatidyl diketone shown in Figure 8.6.14-5. It is possible a –diol (such as lactic acid) would be appropriate rather than a –dione but this would impact the d-spacing based on nominal bond lengths.

The term “buttery” is used loosely in both the taste and smell literature. Fresh butter has little to no odor but a distinctive taste. The taste is generally attributed to a carbonyl, probably associated with a high molecular weight glycerol butyrate. Rancid butter takes on a distinct odor believed to be due to the hydrolysis of glycerol butyrate to butyric acid and glycerol. The resulting odor is typical of carboxylic acids.

Theimer et al. have studied the trans- and cis-forms of various monocyclic ketones with useful

\[ \text{Figure 8.6.14-5 Proposed receptor for the fundamental “buttery” odorophore with } d = 3.61 \]

The actual ligand may be more complex. The ligand is planar. A stimulant would be present in a plane forward or rearward relative to the plane of the paper. See text.


They found the cis-stereomer is responsible for the intense urine odor. The trans-ketone has less than 1% of the odor strength of the cis-ketone. The major problem associated with their work was a complete lack of a null hypothesis and reliance upon a series of thought experiments based on their admitted lack of knowledge about how olfaction worked. As they noted in the first paragraph of their introduction, “Elucidation of the mechanism of olfaction remains for the future. Even the functioning of the olfactory cells, the first step in the perception of odors by animals, is still only a vaguely understood process.” As a result, their conclusions can at best be described as speculative. Their NMR analyses are largely extraneous.

8.6.3.3.8 The proposed sensory receptor for the aromatic gamma-ethers and gamma-alcohols, $d = 5.07$

2-phenylethanol appears to be the simplest member of a family eliciting a sensation typically associated with the rose, as well as other flowers such as hyacinth. Defining a receptor for this family of odorants, and specifically the $\gamma$-ether or $\gamma$-alcohol of phenol can involve a phenol substrate such as phenylalanine or tyrosine, or it can involve a non-phenol structure.

Phenylalanine and tyrosine are initial amino acids leading to a large family that includes ephedrine and epinephrine. Significant rearrangements of the basic amino acids are involved in some of the species in this family. Adding ethyl alcohol to phenylalanine and then esterification of the combination to phosphatidic acid via the carboxyl group offers the potential for an ideal $\gamma$-alcohol receptor. The receptor ligand would be very similar to dopamine but with oxygen replacing the nitrogen atom. It is possible dopamine could be the actual ligand. The resulting structure would perform similarly to the $\alpha$-alcohol receptor defined above based on tyrosine alone.

Figure 8.6.14-6(A) shows this potential form where the atom on the right could be either oxygen or nitrogen.

Describing a non-phenol phospholipid derivative with such a high d-value is challenging. Two candidates are the sugar L-sorbose, and a glycoside. Sorbose has a very similar stereographic geometry as 2-phenylethanol, suggesting they could form a coordinate bond pair easily.

Figure 8.6.14-6(B) shows a suggested coordinate bond pair between a phosphatidyl sorbose (PtdSor) and 2-phenylethanol (shown edge on to the conjugated ring). The bonds shown are representative. It is difficult to show the detailed arrangement lacking a three-dimensional presentation medium and the freedom of the CH$_2$OH groups to rotate about the single carbon-carbon bonds. The distance between the two coordinate bonds is nominally 5.07 Ångstrom. This bond spacing is compatible with coordinate bond pairs between the suggested phospholipid and each of the related “rose” odorants shown in the following section and labeled (91) through (94).

---

Figure 8.6.14-6 Possible aromatic $\gamma$-ether/alcohol receptor based on (A), dopamine or a sibling and (B), the sugar sorbose. The same odorophore is shown twice in the center of the image. The phenol rings are shown edge on in all cases. The distance between the coordinate bonds is $d = 5.07$ in both cases. See text.
8.6.3.9 PtdTrp– Potential sensory receptor for the indoles, $d = 2.757$

[xxx see also 8.6.3.4.1 edit text to match revised figure ]

The role of two indoles in olfaction have been explored. Although the amines, and particularly the fused ring nitrogen structures have not been examined in detail, it is worth noting that a phosphatidyl ester of tryptophan, PtdTrp, makes a perfect candidate receptor for the indoles.

Figure 8.6.14-7 shows an interesting situation. While the representation of skatole includes a charge center at the geometric centroid of the benzyl ring, the charge center of the benzyl ring of indole is displaced (note the different conjugated bond arrangement). [xxx check this out ] As a result, the nitrogen to benzyl ring centroid distance is quite different between these two members of a single family. However, the reason, the displacement of the center of charge in the indole allows the chemical to exhibit another odorophore based on the centroids of the pyrrole and benzyl rings of appropriate value. These two $d$-values are well within the expected sensitivity range of the presumed OR, the ester phosphatidyl tryptophan (ptdTrp).

Methyl anthranilate (ChemSpider13858096) exhibits a $d = 2.797$ Angstrom that is very close to that of skatole plus two other higher values associated with the alpha carbon of an aliphatic group attached to the benzyl ring.

![Figure 8.6.14-7 The special d-value situation of indole and skatole. Skatole exhibits a d-value between the nitrogen of the pyrrole ring and the centroid of the benzyl ring. Indole exhibits a higher nitrogen to benzyl ring centroid due to a displaced charge center. [xxx check this out ] However, the distance between the centroid of the pyrrole and the displaced center of the benzyl ring now exhibits an appropriate d-value to elicit a perception of fecal matter. Both figures prepared using DS3.5 from ChemSpider Jmol files, 2013.](image)
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