Why only nine (9) olfactory sensory receptors in mammals (or humans)!

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Abstract:

A new and detailed hypothesis of olfactory sensing among the mammals is presented. The chemistry of olfaction (smell) is based on the rules of coordinate chemistry rather than the more widely understood rules of valence and covalent chemistry. The hypothesis is eminently successful in describing the perceived scents resulting from a wide variety of odorants.

The animal olfactory modality requires only nine olfactory sensory receptors (OR) to couple with, and identify about two dozen odorophores that occur, frequently in combination, within a constellation of thousands of odorants. These sensory receptors are identified based on their fundamental parameter, the distance (d-value) between two identified orbitals (selected atoms and specific structural arrangements of organic chemistry) capable of forming dual antiparallel coordinated bonds (DACB) shared with their stimulating odorophores.

The nine olfactory receptors are positioned along the same d-value line as the four gustatory receptors and the undefined number of oskonatory receptors (generally associated with the vomeronasal area of the nasal morphology). The centroids of the first four olfactory receptor responses occur at nearly the same d-values as the centroids of the previously defined gustatory receptors and may share a common set of receptor ligands.

The analog potentials emanating from the olfactory sensory neurons are processed as independent signaling channels within the neural system. The central nervous system treats these independent signaling channels as orthogonal. The CNS evaluates (perceives a given odorant) using the analog value of the individual sensory potentials associated with each of the vectors in a nine-dimensional orthogonal coordinate space. As a result, the olfactory modality of humans is able to identify more than 4000 (2^{12}) odorants depending on the signal-to-noise performance of the neural signals generated by the stimulus intensity of the odorants.

Each of the signaling channels of olfaction is given a unique label directly traceable to the coordinate chemistry associated with that channel. These labels overcome the frequently whimsical and/or otherwise imprecise labels dominating psychophysical experiments related to olfaction.

The sensory neurons of the olfactory modality exhibit an odor-constancy property similar to the color-constancy encountered in the visual modality. As a result experimental results are influenced by both the absolute intensity and relative intensity of the odorants employed. [361 words]

This paper is a condensation of over 300 pages of text and graphics describing the stage 1 (signal detection) and stage 2 (signal processing) operations associated with the olfactory modality of mammals in "The Neuron and Neural System[1]." The material includes an even larger number of citations to substantive laboratory research. Where references are made in this paper to Section numbers beginning with 8, they are to specific chapters and sections of that work.

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[1]Fulton, J. (2012) The Neuron and Neural System. available on line in its entirety at http://neuronresearch.net/neuron/ Chapter 8–olfaction

2 The Neuron & Neural System

This condensation resulted from the preparation of the above book starting with a blank sheet of paper by an analyst with a great deal of experience (over 50 years) in a wide variety of technologies. No preconceived hypothesis was relied upon. The physiological facts available from the scientific literature had to support the evolving hypotheses. At each step, the strict interpretation of the Scientific Method was employed. A hypothesis had to be stated and then efforts were made to falsify it. Only after passing this test could the hypothesis be used as the basis of a more sophisticated hypothesis.

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A thesis is presented describing the detailed operation of the olfactory modality based on an extension of the framework defining the four sensory receptors of the gustatory modality. The thesis employs the dual antiparallel coordinate bonding mechanism (DACB) defined for the gustatory modality during the 1960's. The thesis delineates between an odorant and its constituent odorophore(s). It shows that odorophores only conform to the functional groups of conventional valence and covalent chemistry in the simplest cases.

It is shown that the functional groups of valence and covalent chemistry are not important or relevant to olfaction. Olfaction depends on the physical spacing between a variety of orbitals that frequently span multiple functional groups. In many cases, particularly for inorganic molecules, these orbital configurations are only present in the hydrated form of the molecules when dissolved in the mucosa.

Both the preferred implementation of the olfactory receptors (OR), using a family of amino acids attached to a lipid by dehydration, and a closely related implementation of the OR's employing a family of unsaturated aliphatic carboxylic acids require only nine distinct channels to sense all of the odorophores associated with olfaction in humans, and probably all other mammals.

The thesis expands on the above framework by employing the dipole potential of the odorophore to provide further delineation of the perceived intensity of similar odorophores of different aliphatic chain length or molecular complexity.

The thesis replaces the earlier, 1991, genetic code-based hypothesis calling for upward of 1000 individual receptors in olfaction. It is compatible with a reinterpreted hypothesis of 1999 employing a combinatorial framework requiring a lessor, but undefined, number of individual receptors

The role of the proteins described as relevant to the olfactory modality by and expressed through the genetic code is relegated to that of a mitochondrial template or an enzyme mediating the odorophore-receptor binding process.

The thesis separates the sensation generated at the output of the individual types of sensory neurons from the perception of the individual odorophores within the central nervous system. The thesis is based on the concept that individual sensory channels are treated as mathematically orthogonal within all sensory channels of the neural system. The complete percept developed within the olfactory modality for an arbitrary odorant is a vector of specific intensity formed of up to nominally 23 individual vector components.

The spatial complexity of some odorants is beyond the description of the mechanisms and technology presented in this paper. The challenge is in determining the odorophores and their d-values developed below for these odorants. Three exemplars are menthol, camphor and eucalyptus. These materials may be more irritants to the nasal tissue (nocidents) than odorants (containing odorophores).

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 (nearly a standard) in psychophysical testing related to olfaction.

Keywords: olfaction, smell, coordinate chemistry, d-value, Electrolytic theory of the neuron

1. Introduction

Before undertaking any analysis of olfaction, it would be wise to review the introductory comments of Turin

& Yoshii in a recent handbook[2]. The comments provide a valuable perspective on how much of the literature has evolved and why the behavioral labels appear so whimsical. This work will argue that the title of their paper no longer represents a modern perspective.

The thesis presented here builds on extension of a successful description of the operation of the gustatory modality that relies upon a more detailed description of the odorophore(s) within an odorant. These odorophores are identified by their ability to form dual antiparallel coordinate chemical bonds with specific phospholipid molecules forming regions of the external lemma of the cilia of sensory receptor neurons. The phospholipid receptor molecules are derivatives of the phospholipids found on the remainder of the outer lemma of all neurons. In the simpler cases, they are the same phospholipids that have been long identified in the gustatory modality of the sensory neural system by biochemists.

Odorants are environmentally defined by their low vapor pressure, allowing them to become airborne easily, and their solubility in the mucosa of the nose (essentially water). The first characteristic limits their molecular weight, with rare exceptions, to below 300 Daltons (only a few odorants based on multicyclic organic molecules approach this molecular weight). A few heavier molecules are able to stimulate the olfactory modality when carried into the oral cavity in conjunction with foods. It is generally required that the mouth be closed during psychophysical experiments to insure the quality and repeatability of the olfactory data acquired.

1.1 Historical Background

The above paper by Turin & Yoshii reviews a long list of subsequently depracated theories of olfaction, suggesting that only two remain standing; the fragments of molecular shape or *odotope* approach and the *molecular vibration* approach (the latter depending on the tunneling phenomenon of semiconductor physics). None of their annotated approaches appears viable at this time or has progressed beyond the conceptual stage. . Their Section VI struggles with the question of how many receptors are required for olfaction (a few dozen or thousands). Their Section VII summarizes the remaining difficulties associated with their two stated conceptual approaches.

Before 2000, there was great debate about the number of glomeruli relative to the number of chemoreceptor neuron types. In 1991, Buck and Axel proposed the olfactory modality depended on a large number of sensory receptors (~1000 in the case of mammals)[3]. These sensory receptors were described as proteins defined by the genes of the genetic code. The mechanism of the odorant/ protein receptor binding process was not described, nor was the character of the actual odorants defined. A much simpler and more easily realized approach relies upon a greater understanding of the character of odorants. As a first step in moving to such an understanding, Malnic, Hirono, Sato and Buck proposed an alternate framework in 1999 They envisioned but did not define a combinatorial process to account for the perception of a large number of odorants by a much smaller but undefined number of sensory receptors in 1999[4].

In 2004, de Gennes provided a highly conceptual description of a potential organization of the olfactory modality[5]. The paper more resembled philosophical discussions of the 18th and 19th Centuries than a scientific discussion of the early 21st 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

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[2]Turin, L. & Yoshii, F. (2003) Structure-odor relationships: a modern perspective *In* Doty, R. *ed*. Handbook of Olfaction and Gustation. NY: Marcel Dekker pp 275-279

[3]Buck, L. & Axel, (1991) A novel multigene family may encode odorant receptors: a molecule basis for odor recognition *Cell* vol 65, pp 175-187

[4]Malnic, B. Hirono, J. Sato, T. & Buck, L. (1999) Combinatorial receptor codes for odors *Cell* vol 96, pp 713-723

[5]De Gennes, P-G. (2004) Organization of a primitive memory: Olfaction *PNAS* vol 101, no 44, pp 15778-15781

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 olfactory stimulants (over 100,000) when;
• the nine signal paths associated with the nine types of sensory neurons are statistically independent, and
• analog signal processing is employed).

Two caveats apply to the above statement. First, there is a significant difference between a stimulus with a chemically recognized name, and referred to in this work as an odorant, and the presence of one or more structural arrangements within that odorant capable of participating in a DACB and described as an odorophore. The structure of an odorophore is unrelated to any chemical arrangement or group that has been previously identified in valent and/or covalent chemistry. The susceptibility to forming a DACB is dependent entirely on the odorophores coordinate chemistry. Second, there may be more than nine sensory receptor types within the chemical sensing range of a mammal when the oskonatory channels are also considered. These channels, typically associated with the vomeronasal membrane located morphologically on the surface of the vomeronasal structure within the nose. The region of oskonatory sensitivity may be adjacent to the epithelium membrane of olfaction from a histological perspective. The presence of a distinct oskonatory function in humans remains an open question.

1.2 Technical Background

Investigators studying olfaction have failed for many decades to present a satisfactory explanation of the operation of the olfactory system because they have failed to recognize the chemistry involved. Chemistry can be subdivided into four major classes based on the type of bonds employed between the atoms and molecules,
• **valence chemistry–** typically associated with the bonds between atoms in inorganic compounds,
• **covalent chemistry–** typically associated with the bonds between atoms in "organic compounds,
• **conformal chemistry**– describing the intricate geometry of primarily organic molecules, and
• **coordinate chemistry–** typically associated with bonds between ligands and molecules of organic chemistry involving oxygen, nitrogen, sulfur among the various ligands.

Until about 2000, the subject of coordinate chemistry rarely appeared in undergraduate chemistry texts under that title. If discussed earlier, it was considered a variant of the covalent bond, usually described as a dative covalent bond or coordinate double bond. The result is generally an ionic pair of ligands. In the case of interest here, the chemistry involves a hydroxyl group where the hydrogen is shared between the oxygen and another atom of a distinctly different ligand. The result is typically a non-ionic bond that is very weak from an energy perspective.

As of 2007, Johnson & Leon were unable to explain the operation of the olfactory modality based on their examination of a wide variety of valent and covalent structures[6]. See their figure 1 (also reproduced in

[6]Johnson, B. & Leon, M. (2007c) Chemotopic odorant coding in a mammalian olfactory system. *J Comp Neurol* vol 503(1), pp 1–34 (*Manuscript available from NIH Public Access*)

Section 8.6.7.3.4 of this author's underlying work.

The literature of olfaction available at the end of the 20th Century was both large and contradictory. There was no rational theory or functional description of the olfactory modality. However, the prior work of this author in developing the theory, physiology and operation of the visual, auditory and gustatory modalities contributed a very viable foundation. At the start, neither the nature or scope of the olfactory receptors or the relevant features of a given odorant were known. As a result, it was necessary to perform a highly technical analysis to define both the character of the odorants and olfactory receptors of olfaction.

> The iterative process involving both the stimuli of olfaction and the interaction of the stimuli with potential OR's has resulted in an extended hypothesis that is highly consistent internally and exhibiting the precision approaching that of a die-cut picture puzzle. This statement can be criticized as containing too much hyperbole, but compared to any alternate hypothesis, it is self-evident.
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> The complete hypothesis includes extensions to accommodate diastereoisomers (**Section 8.6.6.7**) and other special situation that are not addressed in this paper.

The following material will first describe the technology required to understand the mechanism of olfaction. It will then summarize the resulting physiology and chemistry of the olfactory receptors as they are coupled to the olfactory sensory neurons. After that summary, a similar summary will be presented describing the physical chemistry of the wide variety of odorants, and more fundamental odorophores found within the chemistry of those odorants. During the later discussion, a set of preferred odorophores and odorants will be described that optimally and uniquely couple to the OR's defined in the earlier discussion.

> When discussing the odorophores of olfaction, and particularly those 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 R,S 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. In this work, the molecular structures presented in both 2D and 3D will be based on the unique chemical numbers assigned by the Royal Chemical Society unless specifically noted otherwise. These number refer to specific conformations of a chemical rather than just the common names alone. Even the data in the Royal Chemical Society database, Jmol, contains inconsistencies that are difficult to discover.

1.2.1 Character of the dual coordinate bond used in chemical sensing

Pairs of coordinate bonds between two ligands are crucial to the operation of the chemical sensory receptors of mammalian olfaction and gustation. The coordinate bonds within each pair of bonds are normally parallel to each other and pointing in opposite directions (described as a dual antiparallel coordinate bond (DACB). It is the distance between the bonds that is the determining parameter related to each pair. Without recognizing this parameter, the distance or d-value, it is impossible to explain the operation of the sensory receptors of olfaction, gustation and oskonation (perception of individual species and/or sexes within a species).

The character of the DACB was first explored by Shallenberger and various colleagues during the late 1960's[7,8]. The work was seminal with respect to perception of sweetness associated with the sugars. The binding process proposed here is an extension of the DACB mechanism defined by Shallenberger and associates at that time. This extension has been elucidated in the related paper on "Why only four primary gustatory sensory paths?"[9]

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[7]Shallenberger, R. & Acree. T. (1967) Molecular theory of sweet taste Nature vol 216, pp 480-482

[8]Shallenberger, R. & Acree, T. (1971) Chemical structure of compounds and their sweet and bitter taste *In* Beidler, L. *ed*. Taste: Handbook of Sensory Physiology, Vol IV, Part 2, Chap 12

[9]Fulton, J. (2012) The Neuron and Neural System. available on line in its entirety at http://neuronresearch.net/neuron/ Chapter 8–olfaction

6 The Neuron & Neural System

The above mechanism does not involve proteins in the receptor/odorophore binding process or in the subsequent dipole measurement that comprise the two-step olfactory transduction process. While the presence of proteins in the sensory receptor neurons is beyond dispute, their precise role remains unclear. The identified proteins may play many roles. The most important roles would be to either act as a template in the mitochondrial generation of the specific phospholipid employed as the receptor in that sensory neuron or to act as an odorophore binding protein (OBP) in mediating the transduction process between an odorophore and an sensory neuron odor receptor (OR). Moon & Ronnett addressed these options in 2003[10].

The resulting detailed functional description of the olfactory modality largely supersedes the 1991 concept of Buck and Axel. The detailed functional description is compatible with a reinterpretation, and expansion, of the 1999 concept of Malnic, Hirono, Sato & Buck (involving a combinatorial mechanism to greatly reduce the required number of OR's)..

The current revolution in our understanding of the olfactory system came from the Johnson & Leon team using radiographic techniques to analyze the olfactory bulb[11]. The largest documented number of apparently redundant pairs of glomeruli is currently 27 in the rat (24 in the human) and logic would suggest the maximum number is probably less than 32 based on combinatorial mathematics.

Shallenberger, in cooperation with Acree and with Kier described the unique coordinate chemistry exhibited by the natural sugars using the notation AH,B where initially A = an oxygen atom of a hydroxyl group, H = a hydrogen atom of the same hydroxyl group, and B = an oxygen atom. Beets (1978, pg 188) suggested this concept could be extended to include all of the organic taste stimulants. Later, it was shown the AH,B notation could apply to a broader range of situations. In general,
• AH = a moiety capable of sharing additional pairs of electrons while closely associated with hydrogen. The AH moiety may be OH, NH, NH_2 or even CH in halogenated compounds.
• B = a moiety capable of sharing additional pairs of electrons. The B moiety may be O, N, an unsaturated C=C bond, or even the π-bonding cloud of the benzene ring.

This notation was later expanded to AH,B,X to account for the properties associated with a variety of artificial sweetners, some of very great potency. In 2000, Eggers, Acree & Shallenberger provided a review of their work over a 30 year span[12].

The AH,B.X notation and subject matter will be addressed in a subsequent paper. The goal of this paper is to follow Beets and expand the AH,B concept of coordinate chemistry to account for the gustatory properties of all stimulants leading to the perception of the four qualities listed above.

Figure 1.2.1-1 shows the basic coordination chemistry Shallenberger originally proposed as the mechanism resulting in excitation of the "sweet" sensory neuron. At the minimum, AH represents a hydroxyl group and B represents a neighboring hydroxyl oxygen atom. Shallenberger initially focused on the distance between B and H, of about 3 Angstrom, rather than the distance between B and A, of about 2.6 Angstrom (both values within ±7%). For the situation to be symmetrical, the axes of the two bonds need to be parallel, and the distance should be between B and the axis of AH. It will be the distance in three-dimensional space, or the d-value in Angstrom, between the A of the AH and the B that is of primary interest in a particular instance. This value is very close to 2.82 Angstrom. In this work, the analog and continuous d-value of the DACB arrangement between gustaphore and receptor. can be considered the equivalent to the cardinal value known

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[10]Moon, C. & Ronnett, G. (2003) Molecular neurobiology of olfactory transduction *In* Doty, R. *ed*. Handbook of Olfaction and Gustation. NY: Marcel Dekker Chapter 4 pg 76

[11]Johnson, B. Arguello S. & Leon, M. (2007) Odorants with multiple oxygen-containing functional groups and other odorants with high water solubility preferentially activate posterior olfactory bulb glomeruli *J Comp Neurol* vol 502, pp 468-482

[12]Eggers, S. Acree, T. & Shallenberger, R. (2000) Sweetness chemoreception theory and sweetness transduction *Food Chem* vol 68(1), pp 45-49

as the *"valence"* in valence and covalent chemistry.

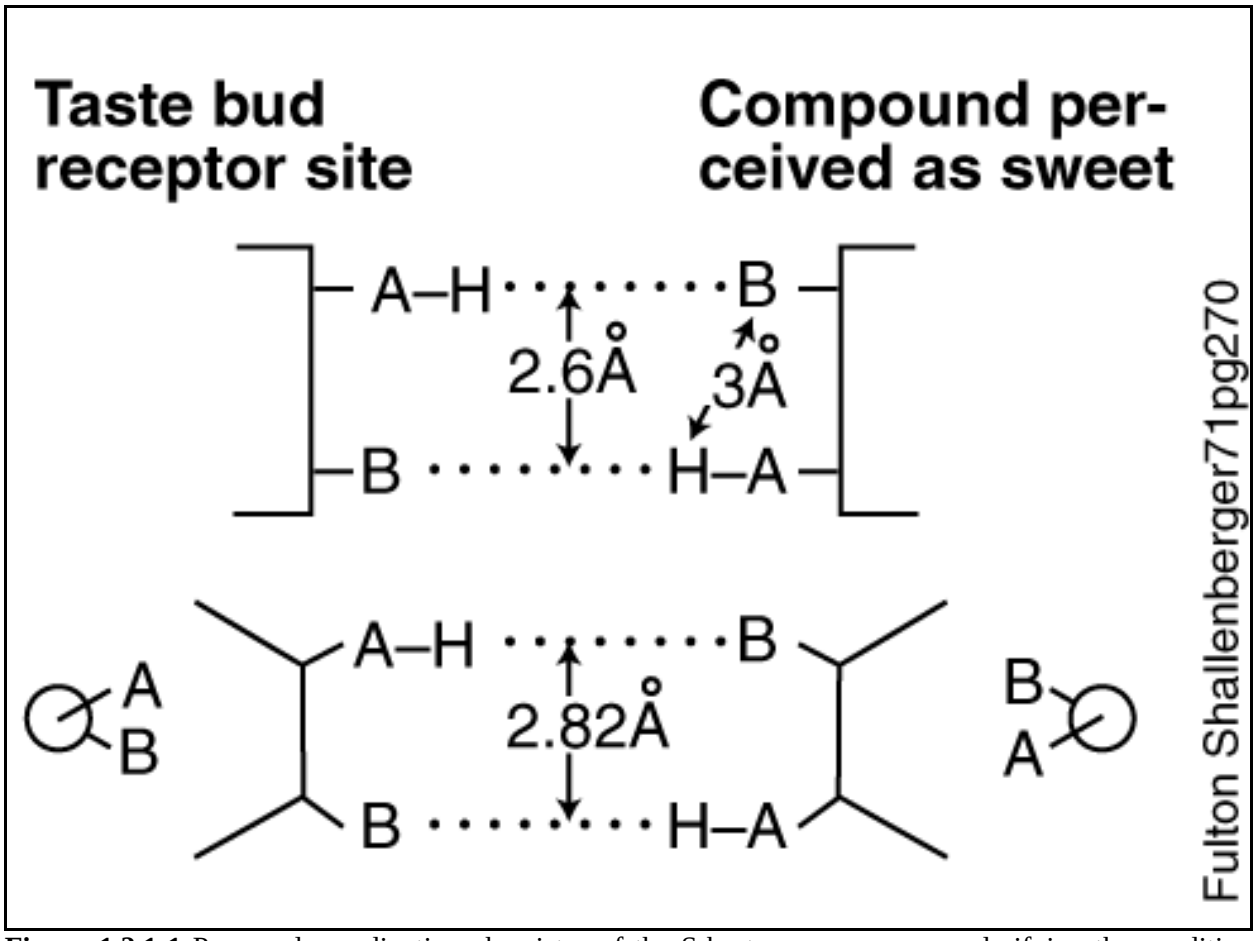

Figure 1.2.1-1 Proposed coordination chemistry of the S-best sensory neurons clarifying the condition described by Shallenberger. In the simplest case, all A's & B's are hydroxyl oxygen and H's are hydroxyl hydrogen. Top; as viewed in two-dimensional space. Bottom; as viewed in three-dimensional space. His original text did not differentiate between the distance between AH and B. His later writings referred to the H,B distance as 3 Angstrom. Both numerics are ±7%. Modified from Shallenberger & Acree, 1971.

Until the advent of nearly free computer time on quite capable personal computers and the ability to analyze large three-dimensional molecular structures (supported by the pharmaceutical industry), it was very difficult to determine the actual distances between atoms in molecules with precision. With the support of the Jmol activity by the Royal Chemical Society and other organizations, it is now possible to determine these distances to at least two-decimal places to the right of the decimal in Angstrom. Currently, the third digit to the right is questionable because of the inadequate tabulation of the requisite structures that form the fundamental data base. Many of the values given in the various databases available have been submitted by individual investigators using early 3D computational programs of questionable accuracy and adequacy. The curators of these data bases claim insufficient funds to cross check the submitted values. This work has relied upon the ChemSpider database of the Royal Chemical Society. It has also been necessary to be highly selective in choosing a rendering program for these molecules. This paper relies upon the Discover Suite 3.5 program by Accelyrs (DS 3.5) to provide a consistent rendering of all the appropriate molecules.

In the following material, many chemical names will be followed by an underscore followed by the chemical number assigned to that chemical by the Royal Chemical Society (RCS). This is done to

eliminate confusion as much as possible because of the frequent use of alternate names and or configurations for a given chemical by different investigators. Unfortunately, some of the 2D and 3D conformations for a specific ChemSpider number in their archive are quite different. This situation must be resolved.

The d-values rendered by manipulating the options in the DS 3.5 program based on the parameters in Jmol from the RCS appear to be continually evolving as advances are made in the algorithm used to render the secondary and tertiary interactions among the atoms of a molecule. The changes are appearing in the third decimal place to the right of the decimal point. Some of the changes may be due to variations in rounding protocols.

Fenaroli's Handbook of Flavor ingredients[13] provides 2D figures for a great variety of both gustants and odorants. However, these 2D forms are of limited utility in defining the perceived odor of odorants and odorophores that rely on their 3D conformation and d-value for their effectivity. The perceived tastes and scents in this work have been assembled from the literature over a long period of time and show little organization relatable to a theoretical or functional framework.

[13] Burdock, G. (2010) Fenaroli's Handbook of Flavor Ingredients, Sixth Edition. Boca Roton, Fl: CRC Press

In reviewing the potential analog between an organic acid gustaphore and its receptor, the planar structure associated with the carboxyl group could form a similar DACB with a receptor as shown in **Figure 1.2.1-2** (**Figure 8.5.4-6** of underlying document). In this case, any organic acid can be considered the acid tasting substance on the right and a similar structure can represent the receptor on the left. In this case, the d-value is calculated as 2.268 Angstrom for the non-resonant forms of the carboxyl groups. An alternate case, assuming resonance between the carboxyl bonds, would have a d-value of 2.07 Angstrom. The non-resonant condition will be used in this paper. The non-resonant value is very close to the value of the carboxyl group of serine by DS 3.5.

Almenningen et al. have provided detailed dimensions for the monomer and specifically the dimer of formic acid shown here[14]. They provide statistical limits on their parameters after reviewing the earlier work of others. Their statistics may be influenced by the presence of the hydrate of formic acid, methanediol. Interestingly, the so-called hydrogen bond is measured from the centers of the two oxygen atoms.

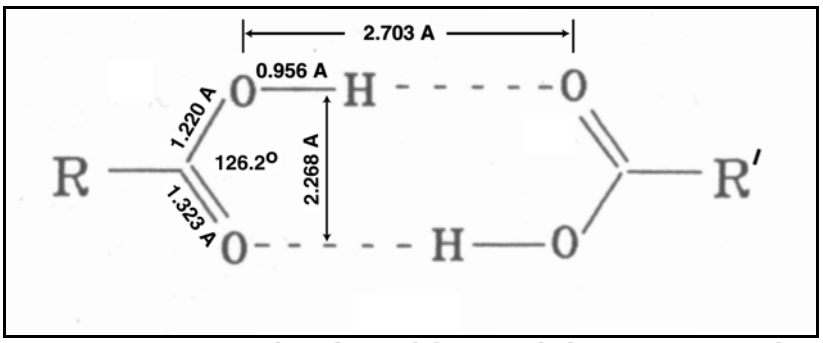

Figure 1.2.1-2 1; A carboxylic acid dimer with dimensions. R and R' are hydrogen for a formic acid dimer. 2; In gustation, R is the serine portion of phosphatidyl serine acting as the receptor and R' is any organic acidophore. When R and R' are more complex, the nominal d-value may vary at the margin due to the more complex rules of molecular geometry.

The hydrogen bond in each leg of such a dimer typically has an energy of 2-10 kCal/mole. This low energy illustrates the ease with which the bond can be broken following the transduction process.

As suggested by the difference in bond lengths relating to the left carbon, resonance does not appear to play a role in this structure. However, more analysis may be warranted. Valla has described nine different coordinate bonding arrangements for the carboxylic acid group, three that involve two bonding paths[15].

Because of the carboxyl group in their intrinsic structure, all amino acids can coordinate with the proposed acid sensory receptor and stimulate the acid sensory channel to a degree. Boudreau (page 130) reviewed the relative intensity of these sensations in several species.

Figure 1.2.1-3 shows the challenge in interpreting the literature for just one of the chemicals of interest, serine. The question that arises is whether to use the d-value for the gas phase or the solution phase for serine. Almenningen et al. provide a *measured* value for the gas phase very close to the *calculated* value for the aliphatic carbonyl ester. The recent value of 2.276 Angstrom provided by the Jmol program of the RCS will be used here. This value is for L-serine_5736. This chemical has been described even more precisely as L-(-)-Serine_5736 with a d-value of 2.277 Angstrom on Feb. 10, 2015. It is different than the d- value for serinol_61591. The value of 2.276 may be within the probable error of the d-value of 2.26(8) in the figure. Minor differences in d-value may be observed depending on the R ligand and whether it is connected to the amino acid by a single coordinate bond or a DACB. In the case of an R different from the dimer situation, some variation in the resulting spacing may be encountered in order to achieve a DACB.

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[14]Almenningen, A. Bastiansen, O. & Motzfeldt, T. (1969) A reinvestigation of the structure of monomer and dimer formic acid by gas electron diffraction technique *Acta Chem Scand* vol 23(8), pp 2848-2864

[15]Valla, V. & Bakola-Christianopoulou, M. (2007) Chemical aspects of organotin derivatives of beta-diketones, quinonoids, steroids and some currently used drugs: A review of the literature with emphasis on the medicinal potential of organotins *Synth React Inorganic, Metal-Organic, and Nano-Metal Chem* vol 37, pp 507–525,

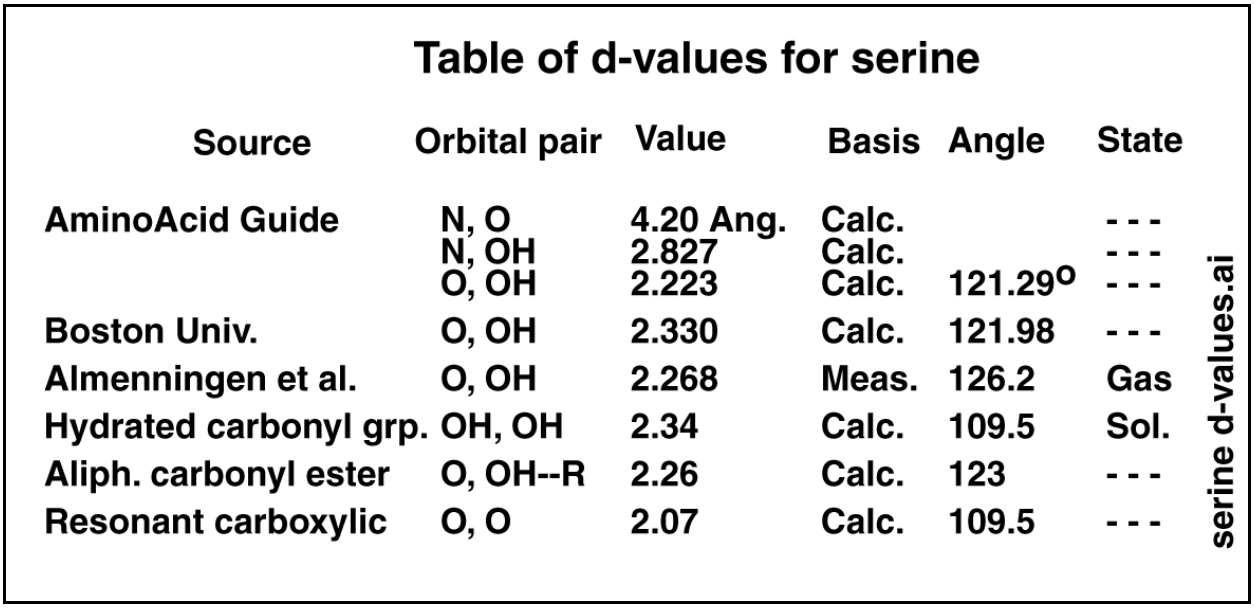

Table of d-values for serine

Source	Orbital pair	Value	Basis	Angle	State
AminoAcid Guide	N, O	4.20 Ang.	Calc.		- - -
	N, OH	2.827	Calc.		- - -
	O, OH	2.223	Calc.	121.29°	- - -
Boston Univ.	O, OH	2.330	Calc.	121.98	- - -
Almenningen et al.	O, OH	2.268	Meas.	126.2	Gas
Hydrated carbonyl grp.	OH, OH	2.34	Calc.	109.5	Sol.
Aliph. carbonyl ester	O, OH--R	2.26	Calc.	123	- - -
Resonant carboxylic	O, O	2.07	Calc.	109.5	- - -

serine d-values.ai

Figure 1.2.1-3 Selected d-values for serine from the literature up to January, 2015. The most pertinent values involve the orbital pair, O,OH. The measured value of Almenningen et al. for serine in the gas phase and the value for the aliphatic carbonyl ester appear to be the most relevant at 2.26(8) Angstrom but differ marginally from the value of 2.276 Angstrom used elsewhere in this work. See text.

In relating their AH,B structure to the sugars, Shallenberger (1982)[16] noted the structure associated with the O-3 and O-4 oxygen atoms of a saccharide appeared in the vast majority of the sweeter sugars. This structure is best described as a 1-2 *cis*-glycol. In the case of glucose, they showed that only OH-4 and OH-3 were the logical choice for a primary AH,B relationship. Using a galactose, they were able to further establish that OH-4 was AH and the only remaining possibility for B is O-3.

> The labels cis– and trans– are used in this paper as simplifications of the actual situation in cyclic compounds. The term trans– is consistent with two oxygen atoms oriented perpendicular to the plane of the molecule and pointing in opposite directions. The term cis– is consistent with two adjacent oxygen atoms in the equatorial plane of the molecule. Shallenberger & Acree have discussed this situation briefly.

Looking more closely at the chemistry that can result in a d-value of 2.6 to 2.82 Angstrom in a sugar, it is found that the two oxygen atoms must be separated by two carbon atoms connected by single bond, within at least a portion of a six-member ring structure. Furthermore, the oxygen atoms must be present in a *cis*– configuration.

Both the acidophore configuration (one carbon and two oxygens) and the glycophore configuration (two carbons and two oxygens) can be considered diols or diol derivatives. Whether a hydrogen is associated with the B oxygen or not is not relevant. The B oxygen is able to coordinate bond with a hydrogen in either case. It is useful to consider the possibility of a third diol consisting of three carbons and two oxygen atoms. A common arrangement of this form found among many bitter stimulants exhibits a d-value of 4.746 Angstrom.

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[16]Shallenberger, R. (1982) Advanced Sugar Chemistry. Westport, CT: AVI Publishing Chapter 10 pp 265-275

1.2.2 The d-value of the DACB used in gustation, olfaction and oskonation

Figure 1.2.2-1 shows how the chemical sensing mechanism is divided between three categories supporting gustation, olfaction and oskonation based on the following values for the d-value. As noted in the caption, there is a difference in definition in the table. The names and associated d-values in the gustation column are based on the potential DACB formation of the individual odorophores. The names and associated d-values in the olfaction and oskonation columns are associated with the sensory receptors, each of which may be able to form DACB's with ligands exhibiting a d-value within a range of d-values centered on the value in the left most column. Specific chemicals most likely forming the sensory olfactory receptors (OR) and oskonatory receptors (historically defined as vomeronasal receptors (VR)) will be defined below.

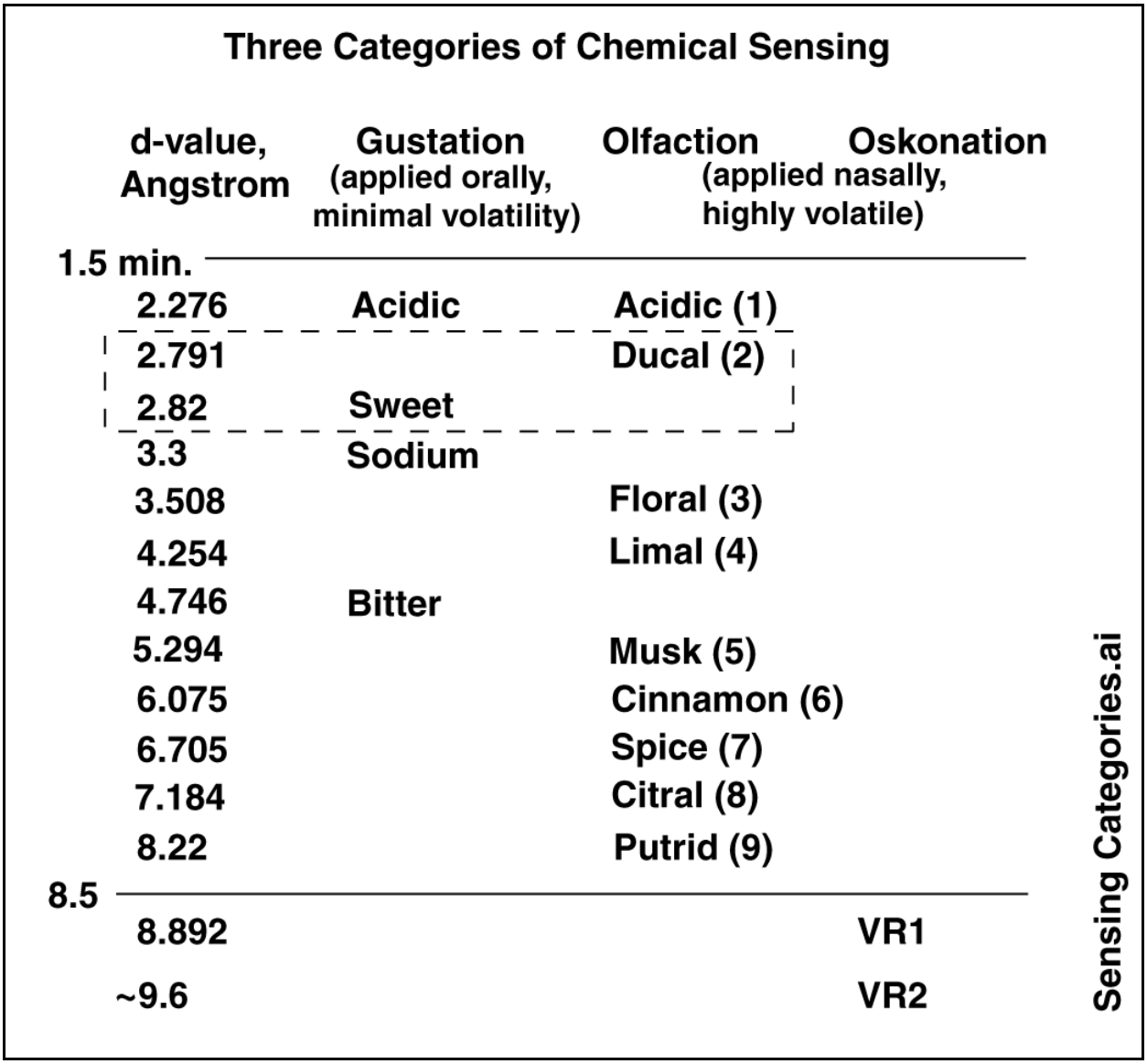

Figure 1.2.2-1 Division of chemical sensing modalities into channels. The d-values shown are for the centroid of the sensory receptor for the olfactory and oskonatory channels. The d-values shown for the gustatory channels are based on the predominant chemistry stimulating that channel. There is no umami channel, the perceived sensation is the result of a combination of the perceptions via the sweet and sodium channels of the gustatory modality. Additional oskonatory channels are available to mammals other than humans at higher d-values than shown. The perception by humans of the two oskonatory channels listed is the subject of argument.

A serious attempt has been made to harmonize the labels used in the above table with that of the literature. However, the literature is famously inconsistent. The gustatory label sweet and the olfactory label ducal may both apply to the same sensory chemical receptor (note dashed box). The chemicals stimulating the ducal channel are known to elicit a perception of sweet at low stimulus intensity and fetid at high stimulus intensity. Similarly, the olfactory label bitter may excite both the Limal and Musk sensory receptors with near equal effectiveness.

Olfaction, and to a degree gustation, exhibit a phenomenon similar to color constancy in vision. For stimulant levels above a threshold, the perceived sensation of a stimulant remains fixed (smell constancy). Below this threshold, applicable to each individual sensory channel, the perceived sensation may vary uncontrollably due to the difference in the signal produced by the stage 1 sensory neurons with stimulation intensity. The perceived sensation may even change for a single odorophore when its stimulus intensity is below the normal operating range of the sensory neurons. As an example, the perception of ducal (d = 2.757 Angstrom) ranges from sweet at low stimulation intensity to fetid at high intensities. Olfactory channel nine appears to most frequently generate a perception of putrid in humans. However these labels have not been arrived at through statistically adequate psychophysical experiments.

> The above paragraph provides an explanation for the variation in perceived taste, odor and their combination, flavor, encountered by many taste and smell connoisseurs. The perception changes on a time scale measured in seconds. The change give rise to a variety of semantic expressions related to “notes,” “highlights,” etc.

This paper will describe the mechanism and processes involved in mammalian olfaction and illustrate the structure of the applicable classes of odorophores found within odorants (stimulant) based on a dual antiparallel coordinate bond (DACB) feature, similar to that found in the coordinate chemistry of the sugars..

The generally accepted number of odorants that can be distinguished by a trained human using a sequential differential test basis, is on the order of 10,000 to 100,000. This could be accomplished using a fully populated combinatorial array of only 13 to 17 sensory receptor types (and associated sensory channels) relying upon a binary pulse code. Using an analog amplitude code in each distinct sensory channel, the number of sensory receptor types required would be even smaller, on the order of 8 to 12. This work demonstrates the number of individual channels in mammalian olfaction is nine.

1.3 Physiological framework used in this presentation

To relate this presentation to the neural system of mammals, and humans, it is necessary (if not mandatory) to develop a framework or top level block diagram of the neural system. **Figure 1.3.1-1** presents a complete block diagram of the combined olfactory and oskonatory (vomeronasal) modalities in the context of the overall neural system. As indicated in the caption, only a small portion of this diagram will be discussed in this presentation. Blocks #1, 2, 4 & 5 are critically involved in understanding the operations of the olfactory modality. Block #3 (representing stage 3) plays a significant role in determining the number of discriminatable odors achieved by humans but involves techniques and mechanisms not otherwise involved in this presentation.

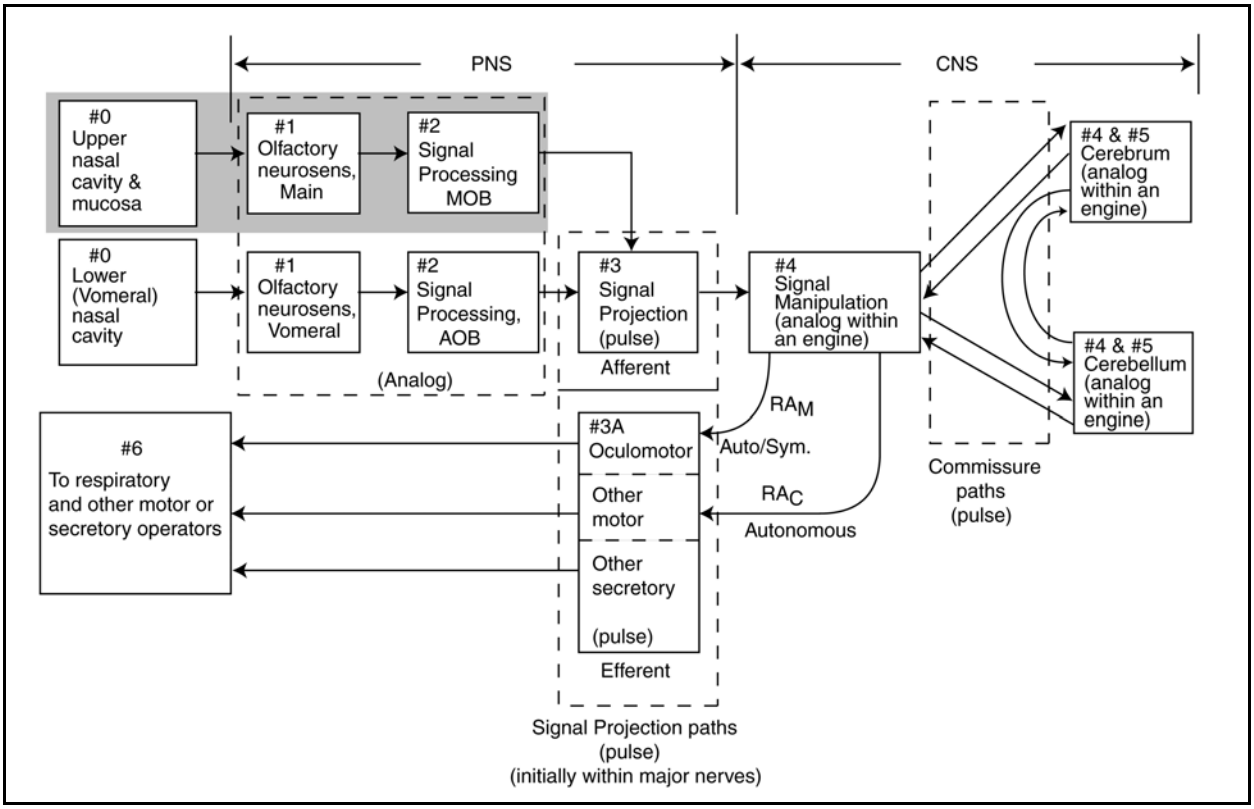

Figure 1.3.1-1 Top level block diagram of the olfactory and oskonatory modalities embedded in the overall neural system. Only a few blocks of this diagram will be addressed in this exposition. Only blocks #1, 2 (within grey box), 4 & 5 will be addressed explicitly. Block #3 plays an important role in determining the maximum number of discriminatable odors in humans, but the details of its operations are beyond the scope of this presentation. MOB & AOB; main and auxiliary olfactory bulbs of morphology.

2. Summary presentation of olfactory modality and its operation

The biosciences community has not been able to offer a satisfactory model and/or framework for how odors are perceived for nearly a century. The problem has been their attempt to use the rules of conventional (valence and covalent) chemistry. The actual chemistry involved is a combination of conformal and coordinate chemistry as described below. The actual transduction process involves two distinct steps; stereo-chemical selection via coordinate chemistry and intensity measurement via dipole potential (not dipole moment) measurement.

2.1 The chemistry of transduction in olfaction

After formulating the DACB portion of the hypothesis of this work, a large variety of plant and commercially prepared odorants were examined to ascertain their potential d-values. A table of these values can be found in sheet 1 of the following file;
http://neuronresearch.net/smell/pdf/TablePreferredDescriptors.xls#Sheet1!A1 The values are shown in columns approximating the individual channels proposed in the hypothesis.

It was clear from the above file that only a finite number of olfactory sensory receptors (OR) were required to sense the unique d-value parameter associated with this large list. Following the methodology developed in **Section 8.5** on gustation, it was also clear that there was likely some commonality between the OR's of olfaction and the GR's of gustation. This was particularly likely in the case of the first channel in each modality which appeared focused on the perception of organic acids. It was only slightly less likely in the

case of the second channel in each modality which appeared focused on the perception of ducal odorophores. This category is broader than the conventional designation of "sweet" and recognizes the perception of both sweet and fetid by this channel depending on the intensity of the stimulation by the ducal stimulants. Based on these similarities and the limited extent that various d-values could be found in nature due to the conformal rules of organic chemistry, it was found that a series of OR's consisting of about nine channels could be defined with centroidal d-values between 2.276 and 8.5 Angstrom. The lower limit was set by the minimal distance between two oxygen atoms when shared by a single carbon in an organic acid. The upper limit was set by the change in the perceived character of various stimulants between that of odorants and chemicals that have come to be known as pheromones. The proposed pheromones are generally mislabeled based on the assumption that they were (are) proteins. In this work, they will be described as vodorants because of their similarity to odorants. The sensing of vodorants and their vodorophores will be via vodorophore sensory receptor neurons (VR). In this work, the pheromones actively stimulate the sensory receptors of a totally separate oskonatory modality; the oskonatory modality is involved in the chemical sensing of pheromones released primarily by other (conspecific) members of the same genus or species of animals. The oskonatory modality is discussed further in **Section 8.6.11**. It is not discussed further in this paper.

2.1.1 The hypothetical set of OR's and their d-values in biological olfaction

The following paragraphs will summarize the features, parameters and labeling of the proposed family of OR's supporting olfaction (at least in humans but believed to apply to all animals employing an olfactory modality).

2.1.1.1 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). This measurement is performed by the first electrolytic amplifier within the sensory neuron (**Section 8.6.5**).

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.

2.1.1.2 Proposed spectral response of the OR's plotted on a d-value

Figure 2.1.1-1 provides a proposed (ca. 2015) d-value graph for the olfactory receptors (OR's) critical to the first step (selection) in the two-step transduction process. The figure is from **Section 8.6.2.8.1**.

The figure provides a set of suggested olfactory labels related to the individual OR channels. 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. Identification of the ninth channel is currently hampered by the few odorants in the literature that are candidates for exciting an OR with a peak sensitivity near d= 8.2 Angstrom. The active portion of an OR 9 has been identified as Ptd*Ahc*. It is described below in conjunction with Ptd*Dha*. The oskonatory modality and its d-value space is developed further in **Section 8.6.11**.

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 on step one of transduction– the complete perception requires consideration of both the first and second steps in transduction). In the case of an odorant with a primary odorophore stimulating the floral channel, the secondary odorophores may support the differentiation of the group into subgroups such as those semantically

labeled, rose, jasmine, “green floral,” “white floral,” etc.

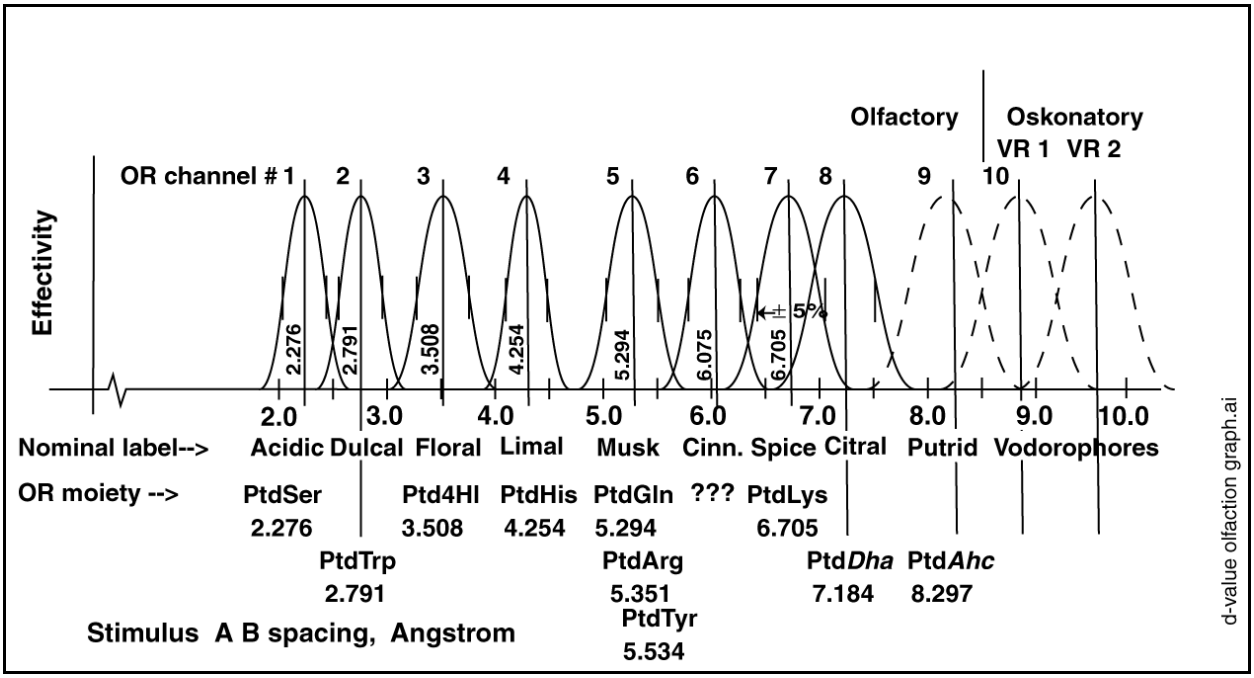

Figure 2.1.1-1 Tentative d-value graph for the olfactory receptors, OR’s. The effectivity axis may be linear or logarithmic. The width of the acceptance range of each OR is only approximated for illustration (based on the linear assumption). OR 10 is considered to be located on the vomeronasal epithelium and support the oskonatory modality rather than the olfactory modality. It may be considered VR 1 of a new series of oskonation receptors, VR’s.

As an example, the natural macrocyclic musk known as civetone exhibits a primary odorophore with d = 5.132 Angstrom without any secondary odorophore. It stimulates OR 5 alone. The synthetic nitro-benzoid musk known as musk tebetine exhibits a primary odorophore with d= 5.211 Angstrom (stimulating OR 5) and two secondary odorophore of 2.730 and 2.764 Angstroms (stimulating OR 2). The more complex odorants frequently incorporate additional odorophores that lead to more complex perceptions within the multi-dimensional olfactory space discussed in **Section 2.3**.

Musk tebetine illustrates a well known feature of olfaction; odorophores stimulating the PtdTrp receptor of the OR 2 channel are perceived as pleasant at low concentrations but fetid at high concentrations.

One of the particularly obnoxious odorants suggest the need for an additional channel; cadaverine (d = 7.425) suggests the need for a ninth channel or that its stimulation of the eighth channel is particularly effective. Cadaverine is frequently perceived as pleasant at low intensities becoming obnoxious at high intensities. Hept-6-enal_4446441 (a.k.a 6-heptenal_4446441 with d =8.023 Angstrom) may be an effective stimulant of the nominal OR 9.

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. See **Section 2.1.2.1** below.

In the figure, the spectral sensitivity of each OR is shown as a symmetrical function with a width of ±5% of the central value at a half-amplitude point. This width is arbitrary but appears reasonable. It provides a crossover between adjacent OR channels near the half-amplitude points.

This graphic and the accompanying tables show why the number of OR's is limited to nine. In most mammals, the receptors with d-values above 8.5 are considered to be vomeronasal receptors (VR), thereby limiting the range available to the OR's. while it is conceivable that other OR's could be inserted between the specified OR's, this appears unlikely. There are only a few simple amino acids available that are not used in the suggested set of this work.

Two of the available amino acids, PtdArg and PtdTyr, are shown as potential alternatives to PtdGln because they exhibit very similar d-values. The are not good candidates for expanding the number of channels beyond nine. While channel 10 could be considered an olfactory channel in humans, this would be an arbitrary description.

The number of VR's in the insect world may extend up to 20 based on the studies of Byers and others (**Section 8.6.11.9**).

2.1.1.3 The semantic labeling of the olfactory channels

Relating the various proposed OR's to the d-value line brings order to a previously unordered list. The naming of the resultant OR channels is difficult because many of the potential labels have been used inconsistently in the literature. In this work, the channels are labeled and the labels justified as follows.

The OR 1 channel is typically associated with the ***acidic*** perception (frequently described anecdotally as sourness). It shares both the acidic perception and the receptor, PtdSer, with the GR 1 channel of gustation. The preferred odorophore for this channel is acetic acid_171. It is preferred over the simpler, but more toxic, formic acid.

The OR 2 channel, ***ducal***, shares its range of perceptions with GR 2, ranging from sweet to sickly sweet to obnoxious depending on concentration. Unexpectedly, skatole_6480 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_7131 is the preferred odorophore for this channel

The OR 4 channel is labeled ***limal*** because of its close association with limonene_20939, 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_4475121.

The OR 6 channel is labeled ***cinnamon*** because of its dominant perception resulting from the primary odorophore, cinnamyl alcohol_21105870.

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_63156.

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_7506.

The OR 9 channel ***putrid*** because of its association with the putrid flowers, although this designation may be criticized based on the limited purification processes use to isolate the odorophores of these flowers. The preferred odorophore for this channel is 6-heptenal_4446441 with d =8.023 Angstrom (alternately 6-octenal_212236302) with d = 7.948 Angstrom could be used).

2.1.1.4 The presence of the proposed OR's in the olfactory epithelium

The figure shows the most likely modified phospholipid used to create the OR in each channel of the olfactory modality. The common amino acids associated with each of these OR's are known to be present

on the surface of the olfactory epithelium but their purpose there has not previously been elucidated.

2.1.2 The hypothetical set of odorants and odorophores used in biological olfaction

The number of odorants perceived by humans is unlimited. However, the number of odorophores is finite and the number of OR channels needed to sense all of these odorophores is even more limited. Only nine odor receptors (OR) are required to sense the complete set of odorants and odorophores. Any molecule exhibiting a d-value of more than about 1.5 Angstrom and less than about 8.5 Angstrom between pairs of orbitals, and capable of a DACB will be perceived (if the stimulus intensity is appropriate). This perception is achieved regardless of the presence or arrangement of any chemical groups (based on valence and covalent chemistry) within the molecule. *The conventional chemical groups play no role in the coordinate chemistry of olfaction*. The major orbitals in order of importance are an oxygen atom, the benzyl ring, a double bond between two carbon atoms, a nitrogen atom, a sulfur atom and a variety of unusual chemical structures beyond the scope of this paper.

A common molecular arrangement within an odorant consists of a benzyl ring with a side chain containing a single hydroxyl group, a carbonyl oxygen or a C=C link. Phenol is the simplest combination of a benzyl ring and a hydroxyl group (d-value is 2.61 Angstrom). However, it is too caustic and toxic to be commonly used in olfactory research. The 3D distance between the orbitals determines the d-value of the structure and its perceived odor. Moving the carbonyl oxygen or the C=C link further from the benzyl ring is a common way of modifying the perceived odor of the odorant. Thus, a long unsaturated aliphatic side chain aromatic molecule can exhibit a wide variety of perceived odors depending on the position of the C=C link in the unsaturated side chain. Similarly, changing the distance between the carbonyl oxygen and the C=C link can change the perceived odor of an unsaturated aliphatic molecule (without a benzyl ring being present). **Section 8.6.11.9.1** describes several molecules of a long chain hydrocarbon with only a single carbonyl atom but various locations for the C=C bond..

The presence of a second side chain, can change the d-value of the benzyl ring–second orbital combination because of the eccentricity of the charge center introduced into the benzyl ring relative to its geometric center.

As noted earlier, some odorophores forming a DACB with the channel 2 OR will be perceived as sweet or putrid depending on the concentration of the applied stimulus.

2.1.2.1 The proposed family of single channel odorants

As in the case of gustation, there are a great many odorants that can stimulate the olfactory modality. Many of these odorants exhibit more than one odorophore. This introduces a difficulty when performing psychophysical experiments in olfaction. To avoid the confusion that can arise using arbitrary odorants in various experiments, it is proposed that a set of odorants be chosen where each odorant exhibits only one odorophore. These can be designated as single channel odorants (SCO) according to the following definitions used in **Section 8.6.7.1**

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 channel 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)–** An odorant containing only a single odorophore with a d-value between ~1.5 Angstrom and 8.5 Angstrom, and therefore able to target only an individual OR (or two OR's within their overlap area if any). 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.

An SCO may be capable of one or more additional DACB at d-values greater than ~8.5 Angstrom. But these DACB's would b associated with the oskonatory modality and constitute VR's totally unrelated to the single odorophore of the SCO. Androsta-4,16-dien-3-one_83932 is such a vodorant. It exhibits two d-values affecting the chemical senses. The d = 9.932 Angstrom structure stimulates the VR 2 channel of the oskonatory modality, while the d = 2.942 Angstrom structure stimulates the OR 2 dulcal channel of the olfactory modality.

A preferred list of SCO's will contain only one preferred odorophore (possibly in multiple copies). **Figure 2.1.2-1** presents the preferred list of SCO's at this time. The values are compared to a similar set of odorants (not necessarily SCO's by Amoore. 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, fruity or sweet in the data set of Amoore. The proposed OR channel numbers, along with selected information concerning the oskonatory (vomeronasal) modality have been added to this list, for completeness.

Amoore (1952 & 1969)	Proposed OR's (2015)	Single Channel Odorant (SCO)	Channel
Olfactory modality			
pungent (formic acid)	acidic (d = 2.276)	acetic acid (2.276)	OR 1
	dulcal (d = 2.791)	skatole (2.721)	OR 2
floral (phenylethyl-methylethyl carbinol d=4.026)	floral (d = 3.508)	benzyl alcohol (3.647)	OR 3
	Limal (d = 4.254)	limonene (4.303)	OR 4
musky (pentadecanolactone)	musk (d = 5.294)	civetone (5.132)	OR 5
	Cinnamon (6.075)	cinnamyl alcohol (6.159)	OR 6
	Spice (d = 6.705)	1-hexen-6-ol (6.793)	OR 7
	Citral (d = 7.184)	citronellal (7.192)	OR 8
putrid (butyl mercaptan)	Putrid (d ~ 8.2)	6-heptenal (8.023)	OR 9
ethereal (ethylene dichloride) (inadequate precision in def.)			
minty (menthone d = 2.662) (may excite multiple chan's)			
camphorous (camphor) (nocent modality stimulant)			
Oskonatory (Vomeronasal) modality			
	Unlabeled (d~8.89)	androstenone (8.884)	VR 1 (OR 10)
	Unlabeled (d~9.7)	D-16 androsteronene (10.015)	VR 2 (OR 11)

Preferred SCO odorants.ai

Figure 2.1.2-1 The preferred list of single channel odorants (SCO) as of 2015. Each Single Channel Odorant (SCO) contains only one odorophore and that odorophore is well matched to the respective olfactory receptor. The left column from Amoore is provided to suggest some of the problems with alternate odorants that have been used in experiments and their potential problems. Camphor acts more as an irritant to nasal tissue than it does an olfactory stimulant.

The chemicals labeled putrid in the larger work (**Section 8.6.6.3**), putrescine and cadaverine, are both primary odorants (with only one odorophore each) and necessarily also single channel odorants (SCO). However, they may not be ideal SCO's because their d-values differ significantly from the central d-value of any suggested or identified OR.

The 19 carbon androgen family stimulating the various VR's of the oskonatory modality is very large. Only examples of single channel vodorants are shown in the above figure for VR 1 and VR 2. There are many competing chemical alternatives and many different conformations among the alternatives . It is absolutely necessary to include their ChemSpider number when discussing any member of this family to avoid confusion. As noted earlier, most members of the androgen family are not proteins. They are predominantly multi-ring cyclic carbohydrates. They are also not hormones. Their action with regard to the animal body is not that assoicated with common hormones. The extension -one has become permanently associated with these non-protein, non-hormone, carbohydrates.

2.1.3 Composite graph showing hypothetical OR's stimulated by selected odorants

Figure 2.1.3-1 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 effectivity characteristics of each channel remain subject to further verification.

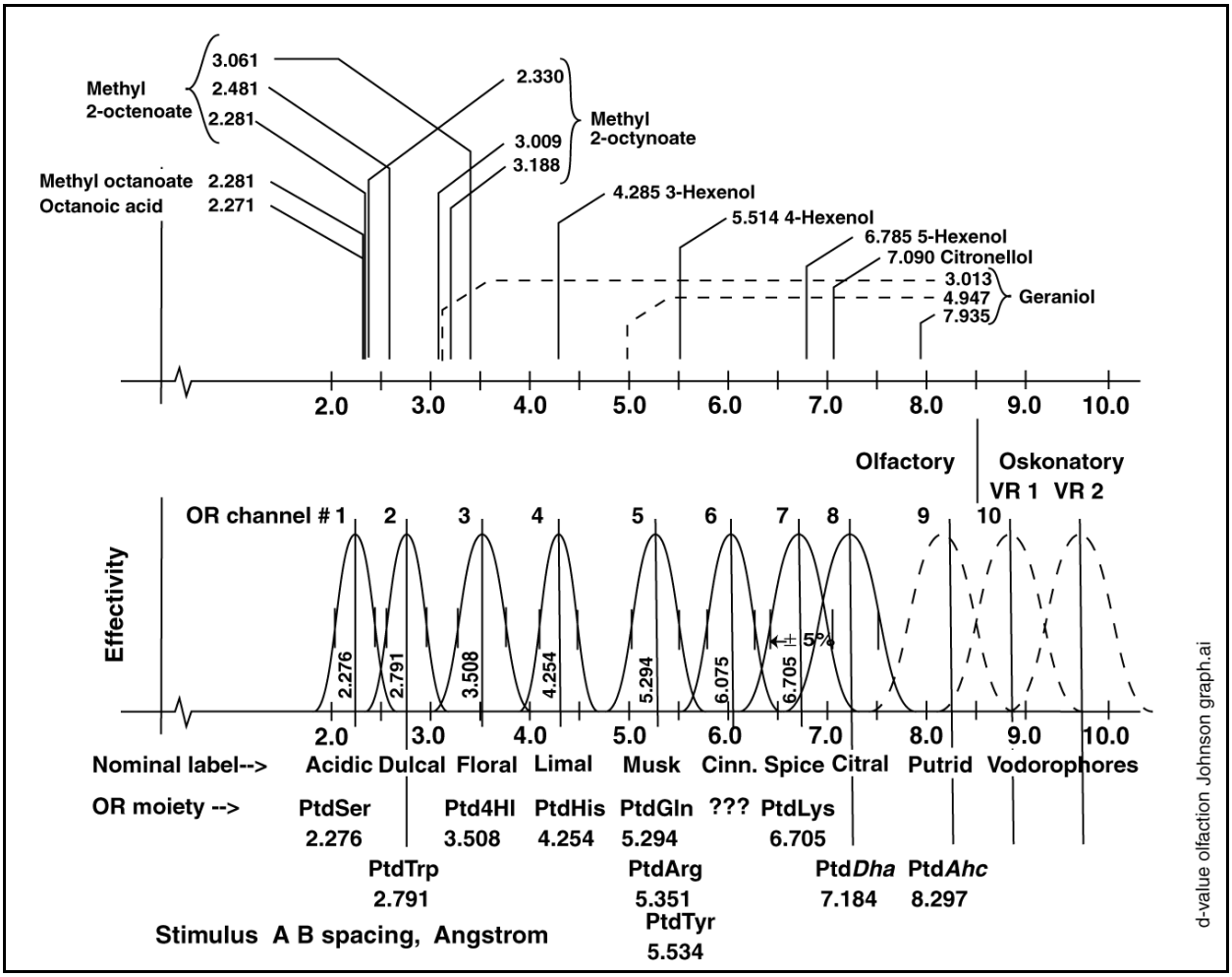

Figure 2.1.3-1 Stimulation of the OR channels by selected stimulants from the Johnson et al., 2007 paper. These chemical participate in step 1 (selection) in the transduction process and and stimulate the OR channels listed. The OR channels and their center d-values can be compared to the locations in the glomeruli reported by Johnson et al., 2007.

The nominal channel labels below the d-value scale are heavily influenced by the major odorophores associated with each channel. The limal channel is closely associated with limonene_20939 while the citral channel is closely associated with the citronellal_7506 of the sweet orange. Interestingly, the musk channel is also closely associated with the dominant odorophore in grapefruit, grapefruit mercaptan_21163535 with d=4.9 Angstrom. This coincidence is worthy of further investigation.

2.1.4 Laboratory confirmation of the above hypothetical data sets

The material presented above is internally consistent to a remarkable degree but it requires experimental verification. Verification at the stage 1 output level is currently extremely difficult histologically. Identification at the input to the stage 2 engines of signal processing is considerably easier via BOLD MRI techniques. The team led by Johnson & Leon has provided excellent verification using these techniques although in some cases they used less than optimum odorants (relative to the preferred odorants and odorophores defined above). The use of single channel odorants (SCO) will hopefully be used in their future experiments.

As indicated by Johnson et al., 2007 (pages 5-6), humans 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. The feature is based on coordinate chemistry. 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 employed within the context of the hypothesis of this work.

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 2.1.4-1** from Johnson et al. showing the areas of the glomeruli of rats responding to these stimulations based on [^{14} 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.

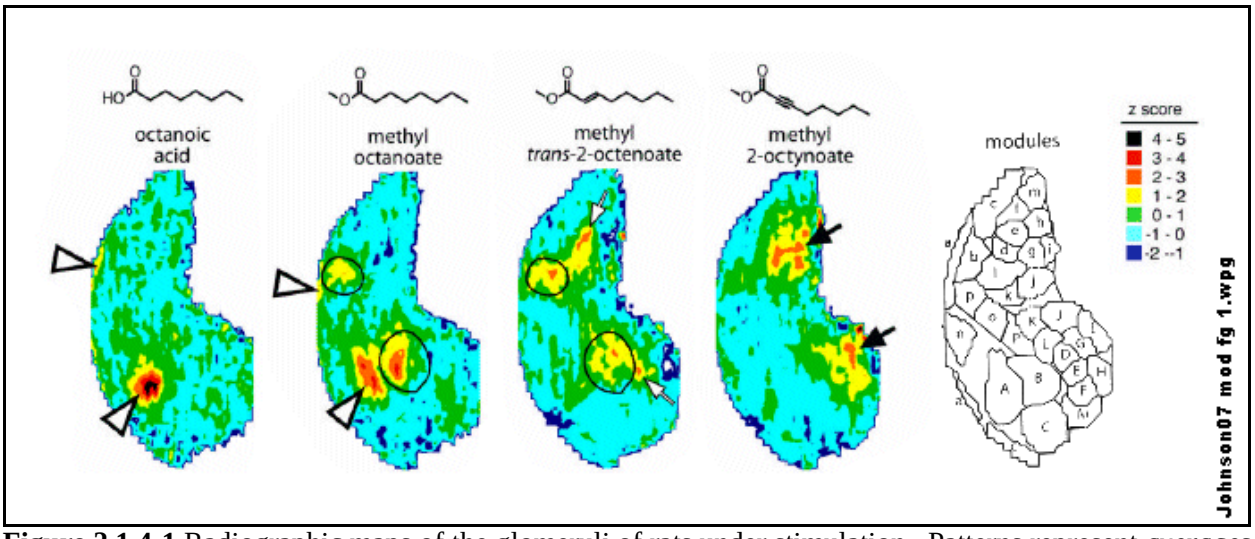

Figure 2.1.4-1 Radiographic maps of the glomeruli of rats under stimulation. Patterns represent *averages* of z-score *standardized* data matrices from *several* rats exposed to the same odorant condition. The arrows point to equivalent areas in the upper and lower halves of the glomeruli. The z-scores may be dependent on uncontrolled variables. 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 lower case 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[17] 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[18]. 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[19], 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 date. 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 5. Beyond OR 5, 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 acetate 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

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[17]Johnson, B. Ho, S. Xu, Z. et al. (2002) Functional mapping of the rat olfactory bulb using diverse odorants reveals modular responses to functional groups and hydro-carbon structural features, *J Comp Neurol* 449 (2002) 180–194

[18]Johnson, B. Woo, C. & Leon, M. (1998) Spatial coding of odorant features in the glomerular layer of the rat olfactory bulb *J Comp Neurol* vol 393, pp 457–471

[19]Johnson, B. & Leon, M. (1996) Spatial distribution of [^{14}C]2-Deoxyglucose uptake in the glomerular layer of the rat Olfactory bulb following early odor preference learning *J Comp Neurol* vol 376, pp 557-566

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." The word "must" was italicized by this investigator to aid the discussion. If one is familiar with the extensive use of lookup tables by other sensory modalities, the use of a lookup table in cognition related to olfaction does not appear unexpected. This mechanism provides a simple answer to the relationship between an odor intensity map presented by the stage 4 saliency map and the reported scent generated by stage 5 cognition.

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[20]. Their figure 3 demonstrates the same hydrocarbons purchased from three reputable sources can not 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 a 2007 paper[21] 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/I.

In a majority of their papers, the Johnson team describes their odorants using straight chain representations of their aliphatic chemicals. Failure to describe the folding of the molecule, as in the case of citronellol and citronellal may have led them away from uncovering the true character of the odorophores within their odorants based on their d-value.

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

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[20]Ho, S. Johnson, B. & Leon, M. (2006) Long hydrocarbon chains serve as unique molecular features recognized by ventral glomeruli of the rat olfactory bulb *J Comp Neurol* vol 498, pp 16–30

[21]Johnson, B. Ong, J. Lee, K. Ho, S. Arguello, S. & Leon, M. (2007) Effects of double and triple bonds on the spatial representations of odorants in the rat olfactory bulb *J Comp Neurol* vol 500(4), pp 720–733

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).

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 a 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 3 and 4 in accordance with this hypothesis. 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 carboxyl 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, and 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 l, p, L & P. The expansion into l, p, L & 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 2.1.4-2**. 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 l, 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**).

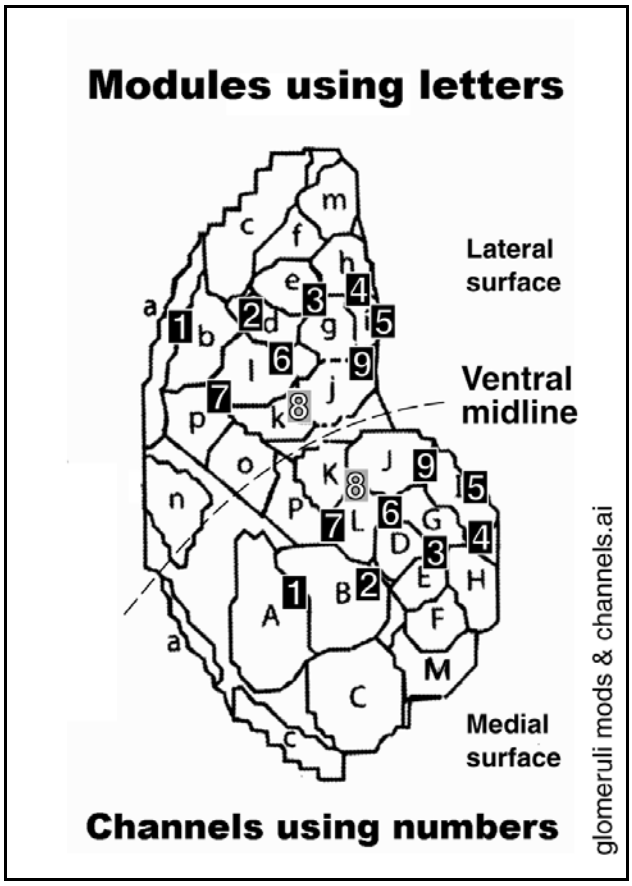

Figure 2.1.4-2 A redrawn module map of the rat glomeruli based on the receptor channels of olfaction. The boundaries of the letter areas are determined by a complex calculation. The numbers locate the centroids of the signaling channels as they appear on the surface of the anatomically standardized rat 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 2.1.4-3 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.

OR Channel	Center d-value	Preferred stimulant	d-value Angstrom	Hot spot module	Johnson stimulant	d-value Angstrom
1	2.276 Ang.	Acetic acid	2.277	A/B	Octanoic acid	2.277
2	2.791	Skatole*	2.721	B/D	Cyclo-octadiene	2.696
3	3.508	Benzaldehyde	3.635	E/G		
4	4.254	Limonene**	4.597	H/I		
5	5.294	Exaltone***	5.146	I		
6	6.075	Cinn. alcohol	6.029	G/L		
7	6.705	1-Hexen-6-ol	6.785	L/P	5-Hexen-1-ol	6.785
8	7.184	Citronellal****	7.090	K/J	Citronellol	7.090
9	8.22	6-Heptenal	8.017	I/J		

* A nitrogen/ring odorophore

** A oxygen & nitrogen free odorophore

*** A circular configuration of cyclopentadecanone_9980

**** Citronellal preferred over citronellol as stimulant

Preferred odorant_hot spot modules.ai

Figure 2.1.4-3 OR channels, preferred stimulants & hot spot locations. 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[22]. 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.

2.1.5 An alternate implementation of OR's based on the same hypothesis

An alternate implementation of the OR's employing an unsaturated set of aliphatic carboxylic acids has been explored as an alternate to the above OR set involving amino acids as a critical feature. **Section 8.6.11** of the underlying work describes this alternative in detail. This alternative gives a slightly less satisfactory sensing capability relative to the organic (Lewis) acids. It becomes more satisfactory at high d-values and may be the preferred implementation among the VR's of the oskonatory modality. The use of the alternate implementation would still require no more than 9 independent sensory channels to satisfy the olfactory modality requirement to sense odorants with d-values in the 1.5 to 8.5 Angstrom range.

2.2 The neural mechanisms of transduction in olfaction

[22]Johnson, B. & Leon, M. (2000) Modular representations of odorants in the glomerular layer of the rat Olfactory bulb and the effects of stimulus concentration *J Comp Neurol* vol 422, pp 496–509

The mechanism of transduction is the same in all of the olfactory channels, as it is in gustation and oskonation. Transduction involves the formation of a DACB between the specific odorophore of an odorant and its target OR. This process results in an electrostatic change in the OR that is transferred to its attached sensory neuron. The sensory neuron measures this change in electrostatic potential and produces a "standardized" output signal at the pedicle of its axon. The signal is standardized in the sense that its base (DC) level in the absence of stimulation is adjusted to a common value, and the output amplitude is adjusted based on the adaptation level of the neuron (based on prior stimulation). These neural adjustments are beyond the scope of this paper but are discussed in the underlying text (**Section 8.6.3.2**).

2.2.1 Transduction in the acidic channel of the olfactory modality as an exemplar

It appears that the transduction mechanism used in channel 1 of the gustatory modality for non-volatile acids is the same as used in channel 1 of the olfactory modality for volatile acids.

> 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 ducal odorophore of smell.

Figure 2.2.1-1 Top illustrates the evolution of this mechanism (**Section 8.6.2.5**). The conventional molecule forming the external bilayer of the typical biological cell wall is shown above the horizontal line. It consists of the chemical known as choline hydrolyzed to phosphatidic acid to form phosphatidylcholine (PtdCho). Some researchers have asserted the outer bilayer of the cell wall is phosphatidyl ethanolamine (PtdEth) instead of PtdCho. Replacing choline in the box by Ethanolamine makes no difference in this case. Whether the long chain lipid is conductive in this case is immaterial.

Immediately below the horizontal line is the phospholipid proposed to be present as the channel 1 OR. It is derived from the hydrolysis of the same phosphatidic acid and a second amino acid, serine, to form phosphatidylserine (PtdSer). PtdSer exhibits a d-value of d = 2.276 Angstrom. This is the same d-value as exhibited by Lewis (organic) acids. It is proposed that the Lewis acids individually form a DACB easily with PtdSer, thereby changing the dipole potential of the lipid sensed by the electrical circuitry of the sensory neuron.

2.2.2 The transduction in channels 2 through 6 of the olfactory modality

Figure 2.2.2-1 Bottom illustrates this mechanism for the proposed nine OR's. Channels 3, 8 & 9 employ minimally modified amino acids. Additional research may uncover amino acids that can be used to avoid even these minimally modified moieties.

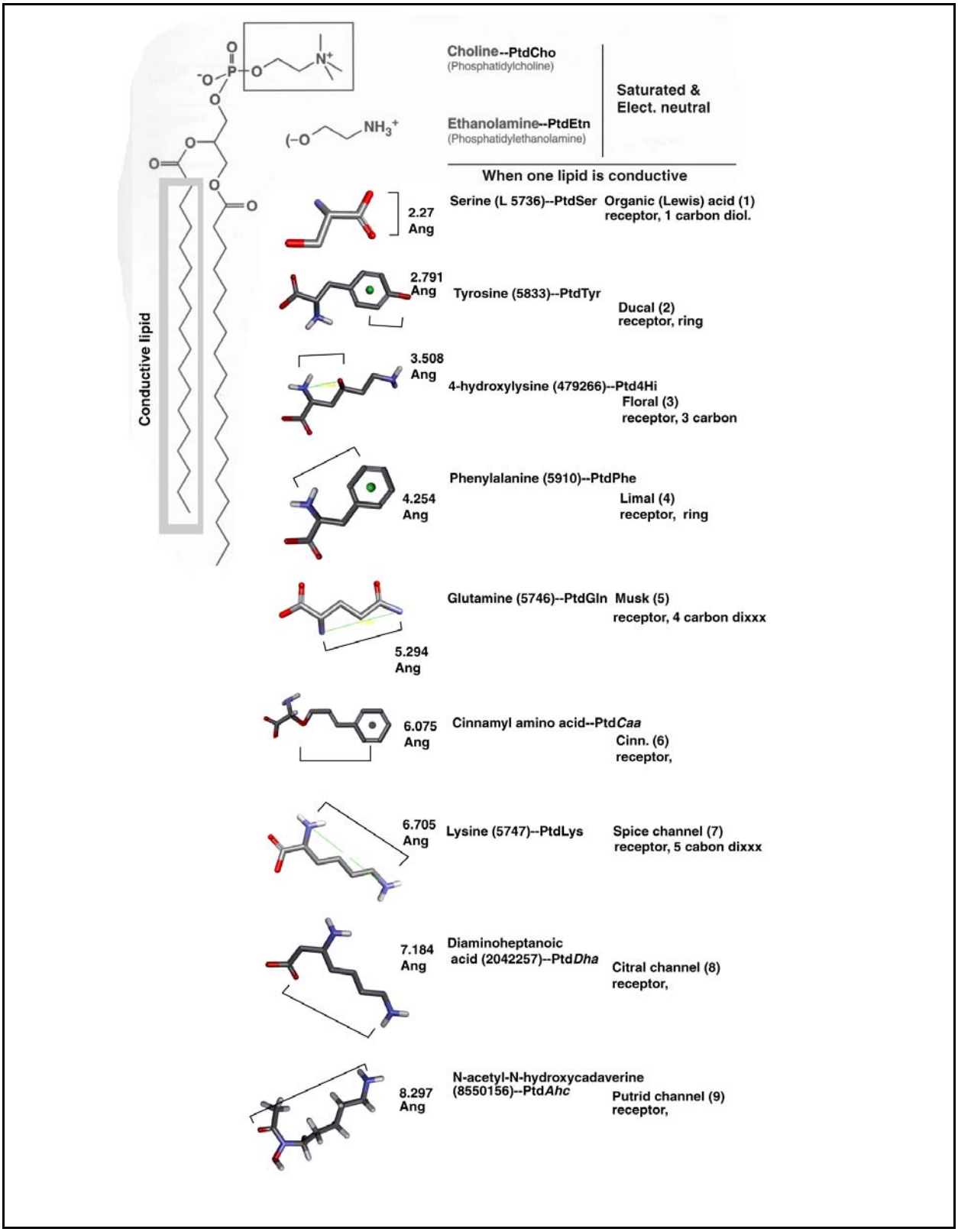

Figure 2.2.2-1 Abbreviated summary: sensory receptors of olfactory modality based on the Electrolytic Theory of the Neuron, the assumption of an amino acid component associated with each OR and a coordinate chemistry mechanism. See text.

2.3 The interpretation of the olfactory signals within stage 4 of the CNS

The perception of an odorant relies upon the information processing (extraction) function of stage 4 in the portion of the neural system dedicated to the olfactory modality. See the flow diagram in **Section 1.3**. Each of the channels arriving at stage 4 originate in the output of the glomeruli of stage 2, signal processing. The signals are converted from analog form to pulse coded form and then decoded back to analog form by the stage 3, signal projection, on an individual channel basis. The process of encoding/decoding may degrade the quality of the analog signal marginally, but potentially noticeably. The operation of the stage 3 circuits are beyond the scope of this paper but may be found in the text, "The Neuron and Neural System" cited elsewhere in this papeer and available on the internet site in their entirety.

The orthogonality of the signals received over the individual stage 3 channels at stage 4 is not impacted by the potential reduction in the signal-to-noise ratio associated with the analog amplitude of the signals.

2.3.1 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 2.3.1-1**. 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.

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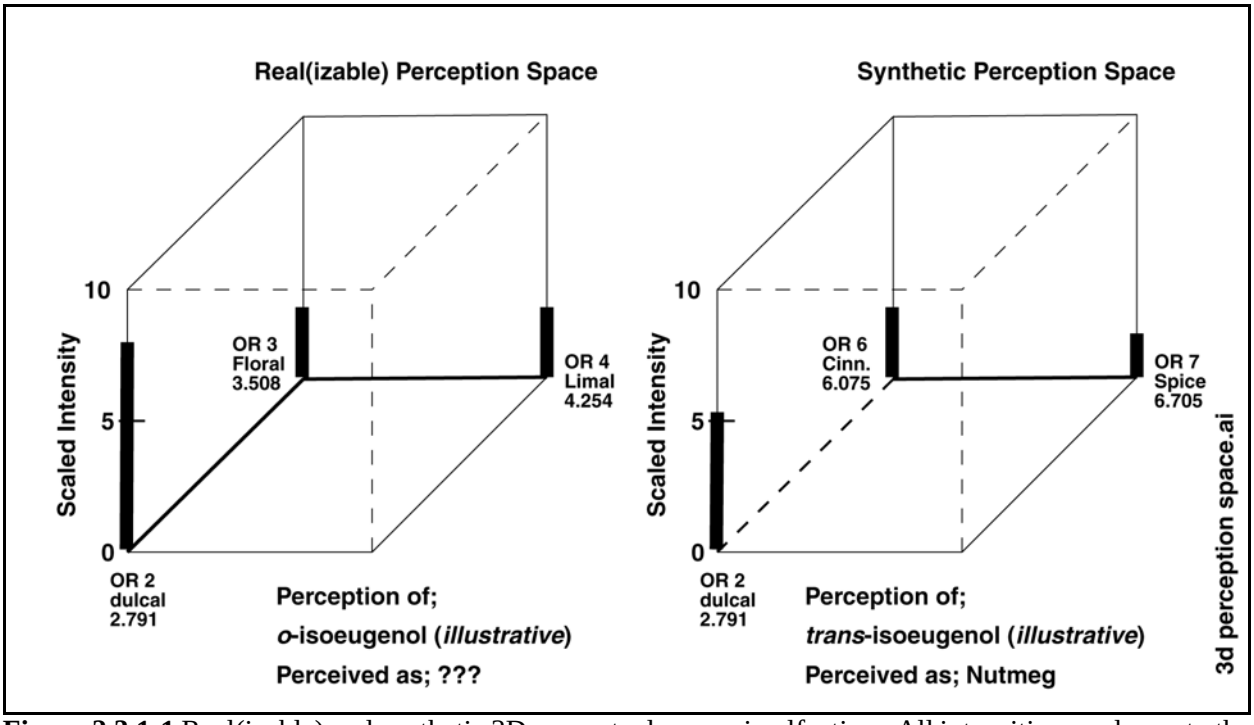

Figure 2.3.1-1 Real(izable) and synthetic 3D perceptual spaces in olfaction. All intensities are drawn to the same scale. Left–real perception space; Heavy axes represent the d-value line. Vertical bars represent the response of the odorophores of o-isoeugenol by the three OR channels (assuming the three 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*-isoeugenol 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. The literature is inconsistent regarding the perceived scent of *o*-isoeugenol. In the right frame, a similar molecule, *trans*-isoeugenol 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 hetrocyclic 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.

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The scents described above are those that would be predicted based on the outputs of the stimulated stage 1 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 is discussed in the chapters following #8 of "The Neuron and Neural System" concerning the performance of the human olfactory modality.

2.3.2 A 2D non-orthogonal representation of 9-ary space of human olfaction

An alternate to the orthogonal 9-ary space which is difficult to illustrate or envision is a two-dimensional representation as a 9 radial wheel (or rosette). This type of display is widely used in the perfume industry but with widely, and wildly, varying labels. **Figure 2.3.2-1** presents an alternate representation using the individual channel names developed in this work, along with the preferred single channel odorant (SCO) defined earlier below them. Formic acid has traditionally been used instead of acetic acid to stimulate OR 1. Both are SCO's.

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 ducal radial, OR 2 channel). This variation is detailed in **Section 8.6.7.1.1**.

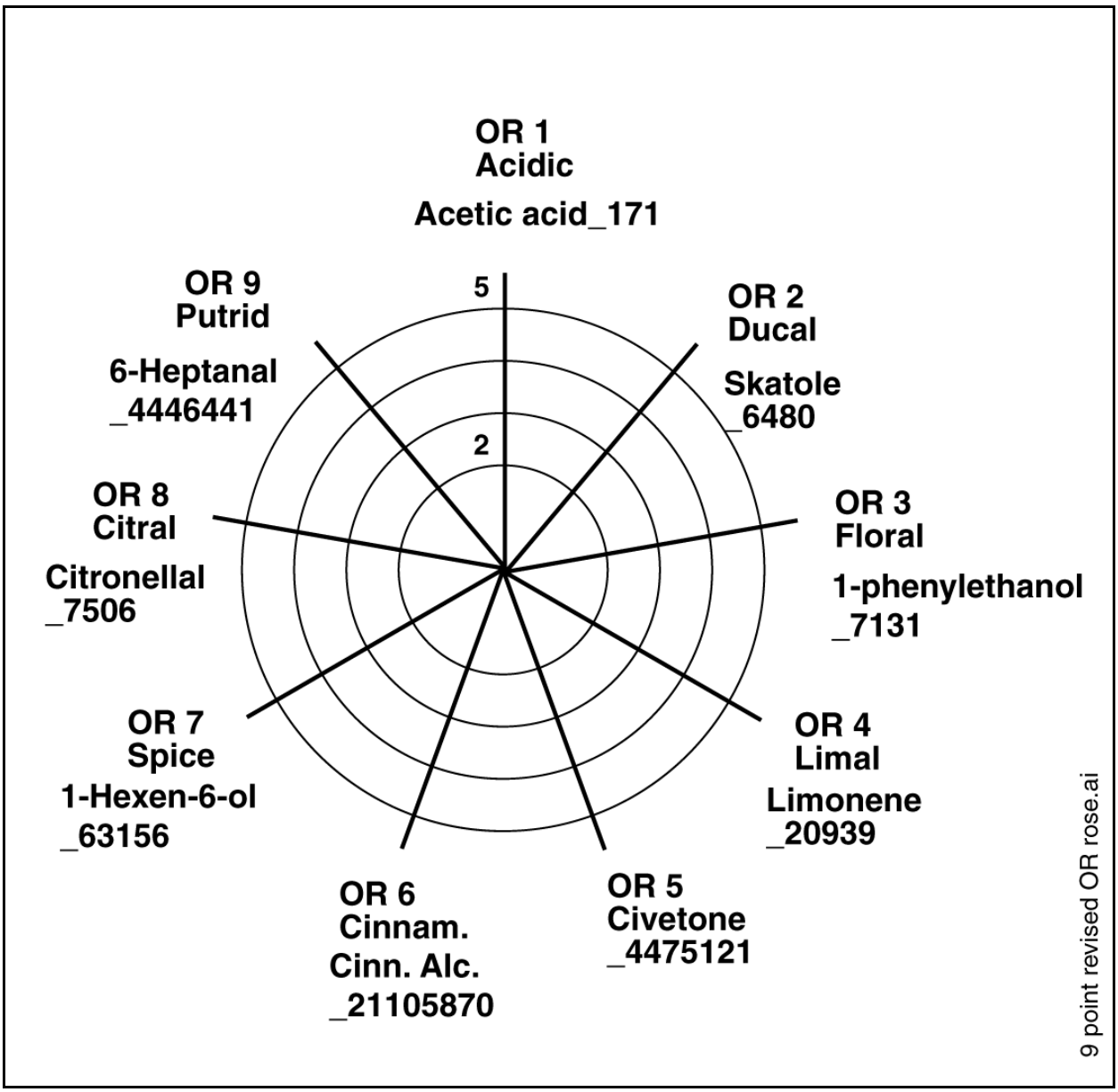

Figure 2.3.2-1 A 2D olfactory wheel & set of preferred single channel odorants (SCO's) followed by their ChemSpider numbers. ChemSpider lists two distinct cinnamyl alcohols. Note the accession number used here. Variations in the concentration of some of the SCO's may cause significantly different perceptions relative to this representation. The rings represent a 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 an SCO. See text.

2.3.3 The theoretical verses psychophysical estimates of odorants/odorophores

Over the years many workers in olfaction have made estimates of the number of distinct odors a human could perceive without employing any substantial scientific framework for a basis. The estimate was usually

limited to one digit precision and based on an extrapolation of a small set of differential detection experiments between pairs of odors. The protocol used in these experiments seldom sought to control the state of adaptation of the individual sensory channels or the channels as a group (although they frequently employed a "washout" step to normalize the database to a degree). The experiments did not identify a stimulus intensity assuring operation in a odor constancy regime, or quantify the results as a function of intensity. The fundamentally anecdotal conventional wisdom has been documented by Bushdid et al. as about 10,000 discriminable odors in their introduction to their calculations. There calculations suggest the number of discriminable odors actually exceeds one trillion odors (10^{12} odors)[23]. Their new estimate was not based on any physiological model of olfaction or any theory of the odor/OR (olfactory) transduction process. A critique of the Bushdid et al. paper is presented in **Section 8.6.8.5**. The critique questions the relevance of their calculations in the absence of any connection to a physiological model of the olfactory modality, any theory of the transduction mechanism involved and their assignment of parameters to the equations of combinatorial analysis. It also notes the highly skewed character of their list of chemicals used in their experiments. Omitting the sulfur and nitrogen containing chemicals because they are outside the theory presented in this and the accompanying work, their list is nearly devoid of chemicals stimulating the cinnamon, spice musk and putrid OR's of human olfaction. Their list is dominated by organic acids that all stimulate the OR's of channel one.

Determining the number of identifiable odors by a trained perfumer or other professional is complicated by the number of variables involved. The number is impacted by the signal-to-noise ratio of the signals perceived by the stage 5 cognition engines of the central nervous system. This signal to noise ratio is related to that introduced at the stage 1 sensory neurons as modified by the coding technique used in stage 3 neural signal projection. The use of single channel odorants is a necessity for obtaining repeatable results. While the intensity of such SCO's is readily controlled, the noise in the signal-to-noise calculation is more difficult to define. It requires evaluating the noise level of the sensory neurons, the adaptation state of those neurons, the thresholding generally employed as part of the analog signal to monopulse "action potential" signal conversion, the related sampling noise associated with the encoding/decoding process and any excess noise associated with the neurons of the stage 5 engines of cognition.

To compare the estimates from different perfumers, it is imperative that they be using SCO's when collecting the data on which their estimates are based and that their protocols be as identical as possible.

In the simplest model, the potential number of identifiable odors is controlled by the number of permutations available among the nine orthogonal sensory channels of olfaction *multiplied* by the analog amplitude discrimination capability of the stage 5 cognition engines. The number of permutations is directly determined by probability theory as $2^9 = 512$. The number of distinguishable analog levels is more difficult to estimate in the absence of experimentation designed to define this figure using individual odorophores (similar to the experiments performed by Munsell in the visual domain in the early 1900's. The probable range of discriminatable amplitude levels, without using differential sensing and requiring an odor constant intensity range, is between $2^3 = 8$ and $2^5 = 32$. Based on these values, a best estimate for the number of discriminatable odors under odor constant conditions is in the range of 4096 and 16384 (with a precision of one decimal at this time lacking experimental confirmation). This range is compatible with the conventional estimates in the region of 10,000 discriminable odors while the olfactory modality is operating within the odor constant regime.

The calculated range based on this work and the long standing professional estimates are comparable. Both deserve more careful experimentation based on a definitive protocol.

3 Conclusions

The following results apply to molecules of molecular weight below 300 Daltons.

Odorants (stimulants) of the olfactory modality are restricted to those chemicals with appropriate volatility

[23]Bushdid, 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

and solubility. They are further limited to those chemical structures, odorophores capable of forming a dual antiparallel coordinate bond with a spacing between the bonds, a d-value, compatible with one of the less than 27 identified sensory receptor channels. The simpler odorophores may only be effective when in a hydrated state.

The d-value of an odorophore is measured in three dimensional space and can not be ascertained from the typical two dimensional representation of a molecule (Fischer, Haworth or Newman). It is best determined from a Jmol or similar representation.

The odorophores of this work differ from Turin's odotopes which are based on identifiable functional groups. Here odorophores are characterized as ligands extending between and including two orbitals capable of forming dual antiparallel coordinate bonds with appropriate d-values.

Suitable odorants meeting the above criteria only qualify as effective odorants when they contain one or more odorophores capable of binding with the sensory receptors of the olfactory modality and presenting a dipole potential causing a change in the electrical output of the first (adaptation) amplifier of the sensory neurons, in accordance with the Electrolytic Theory of the Neuron.

Potential odorophores follow the fundamental coordinate bonding structure developed by Shallenburger and associated in the 1960's and employ the same set of atoms and related structures defined as orbitals at that time.

Although a favorite of psychophysical investigators, the aliphatic alcohols in pure form are odorless based on their chemical structure. However various impurities at the parts per million or lower level can imput a odor to these chemicals. The alcohols can also become hydrated in solution, resulting in a potential dual coordinate bond relationship. The majority of these hydrated do not generally bind with the sensory receptors because of their d-value.

The hydrated aliphatic organic acids form the simplest of the classes of odorophores. They are also the simplest form of gustaphores. This ability to stimulate both sensory modalities is unusual.

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Based on analogy with the gustatory modality, it is proposed that the sensory receptors of olfaction are phospholipids and not proteins as previously assumed generally. The only olfactory receptor explicitly identified at this time is that for the organic acids; phosphatidylserine (PtdSer). The serine portion of this structure forms a planar one carbon diol with a d-value of 2.1 Angstrom. PtdSer has long been known to occur in sensitive patches of the outer lemma of the cilia of the sensory neurons[24].

4 Acknowledgments

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[24]Lehninger, A. (1970) Biochemistry. NY: Worth Figure 10-3

Table of Contents 15 March 2015

List of Figures Mar 15, 2015

(Active) SUBJECT INDEX (using advanced indexing option)