Excerpts from

The NEURONS and NEURAL SYSTEM: a 21st CENTURY PARADIGM

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

A Table of Contents and an index are located at the end of this paper.

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

James T. Fulton
Neural Concepts
jtfulton@neuronresearch.net

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8 Stage 1 & 2, Signal Generating & Processing Neurons

"Science is made up with facts as a house is made from stones. But a collection of facts is no more a science than a pile of stones is a house."
—Poincare, Hypotheses in Physics (1952)

"In order to understand any part of nature, one must have both experimental data and a theory for interpreting the data and predicting new data."
—Shepherd, Outline of a Theory of Olfaction, 2005

“One of the great challenges of neuroscience is to understand the rules by which sensory input is translated into behavioral output”
—Kreher et al., Translation of sensory input... (2008)

This Part provides an overview of chemical sensing and contains or leads to in depth vision & hearing sensing discussions

8.1 Introduction

The sensory neurons of animals serve disparate purposes but exhibit a remarkable uniformity at the morphological, cytological and electrophysiological level. This material will focus on the mammals. The visual and auditory modalities are focused on sensing of the distant external environment. The olfactory and gustatory modalities are focused on the near and even nearer external environments. The remainder of the external sensory modalities typically (with the exception of radiant heat) involve physical contact with the source of the stimulation.

Adopting Poincare’s above thesis, the goal of this chapter is to show how our collection of facts describe an architecturally identifiable structure of complexity and beauty.

All of the external sensory neurons employ the same internal circuitry consisting of a two-stage active electrolytic amplifier. Although they exhibit minor differences in adaptation time constants because of their connection to the sources of electrical energy, their main difference is in the form of the stage 0 elements between the sensory neuron and its environment.

The signal processing (stage 2) neurons immediately behind the sensory neurons vary more widely than do the sensory neurons, primarily in whether they are present at all. The retina and the olfactory modalities employ significant signal processing immediately adjacent to the sensory neurons. The auditory and gustatory modalities on the contrary, avoid stage 2 signal processing adjacent to the sensory neurons and employ stage 3 signal projection channels between the sensory neurons and more distant signal processing elements that may be considered part of the divergent stage 2 signal processing or of the convergent stage 4 signal manipulation elements of the modality architecture.

When discussing the sensory neurons in a consistent lexical context, there is a problem with the use
of the terms cilia and microvilli. Elsaesser & Paysan wrote an elaborate paper addressing this duality without defining their terms and coming to any conclusion about the correct terminology. They did provide over one hundred citations. The term cillum is from the Latin for eyelash and generally is considered a rigid structure. Unfortunately, villium also comes from the Latin and colloquially refers to curly hair. These terms are often used interchangeably in the literature. In this work, the goal is to use cillum and cilia when referring to structures emanating from the dendritic structure of a sensory neuron that are “rigid” or must maintain a column like character. The rigid structures are typically filled with rigid liquid crystalline proteins participating in a piezoelectric transduction process. The photoreceptors maintain a column-like structure for optimal optical efficiency. Villium and villi will be used when referring to structures emanating from the dendritic structure of a sensory neuron that are not rigid and need not maintain a column-like structure. These structures are typically filled with a fluid like material and reticul that are flexible in character. At the cytological level, the protein filled cilia transfer their signal to a first amplification stage within the soma of the neuron whereas, the microvilli of sensory neurons have been modified to create an active electrolytic device between their outer lemma and their inner reticulum. In this work, the visual, olfactory and gustatory sensory neurons exhibit microvilli; the auditory and many of the somatosensory sensory neurons exhibit cilia that are sensitive to dynamic loadings and motions.

All of the sensory modalities appear to employ the same type of signaling and present a nearly identical interface to the saliency map within the CNS. However, the sensory modalities employ fundamentally different initial steps in the transduction process.

The visual and auditory modalities (frequently labeled the major modalities) both employ the wave equations of Maxwell to define the critical processes in step 1 of the transduction process and the quantum-mechanical equations of the 20th Century to describe the interaction of the stimulus with the respective sensory receptors in order to produce an electrical signal within the sensory neurons.

The gustatory, olfactory and oskonatory modalities (frequently labeled the minor modalities along with the somatosensory modality) all employ the rules of coordinate chemistry (as opposed to the more widely understood valence chemistry) to describe how a stimulus interacts with the chemical sensory receptors. The subject of coordinate chemistry is addressed in Section 8.4.4.4.

Gardiner & Martin, writing in Kandel et al., 2000, assert “Sensory systems have a common plan” and use similar neural codes for the properties of modality, location, intensity and timing of physical stimuli. It will be confirmed here that the signaling architecture, methodologies and techniques within the different sensory modalities are essentially identical. While the visual and auditory modalities are very well understood and interpreted (especially employing the Electrolytic Theory of the Neuron) the modalities employing chemo– thermo– and mechanico–receptors are less well understood. The literature of these modalities at the electrophysiological level is relatively thin. As a result, this work will hypothesize in these areas based on the similarity to the more studied modalities. Only additional laboratory work, based on these hypotheses will allow confirmation or refutation of these hypotheses.

One area supporting the theory and the comparability of the sensory modalities is the adaptation characteristic of the sensory neurons.

2.1 Introduction

The signal generating neurons have the basic task of converting some source of energy into an electrical signal that can be processed and interpreted by the remainder of the neural system prior to taking some responsive action (when appropriate). An initial list of the sensory neurons generally includes those associated with seeing, hearing, touch, taste and smell. Less frequently, the sensory neurons associated with orientation are added to this list. Each of these broad designations can

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usually be subdivided into several additional descriptors. As an example, the photoreceptors of sight (the visual system) are further divided into spectrally sensitive types. The neurons associated with touch are frequently subdivided into those sensing relative motion and those sensing temperature. These subdivisions of a given modality are sometimes described as qualities within a modality. Shepherd has provided a table of sensory modalities, that he credits to Ganong (1985), that shows some of these groupings. His listing speaks of the form of incident energy when he generally means the source of the incident energy. The listing by Shepherd only includes a mixture of generic names for the types of sensory cells.

Feducci, editing Torrey’s 5th Edition, provides a brief introduction to the evolution of the sensory neurons.

Shepherd also provided an interpretation (pg 208) of a figure by Bodian (1967) that will be expanded upon here. The caricatures for the modalities other than vision do not allow for signal processing within the neural system supporting that modality. However, it is readily shown that most individual sensory neurons are not connected to the brain by a unique and exclusive neural circuit. Stage 2 signal processing is an effective method of economizing on neural circuitry and is found in nearly every sensing modality.

This work will postulate that the excitation energy is quantum-mechanical in form for most, if not all, of the sensory modalities. This prediction is made based on the impulse response reported for a range of these modalities. The result of the postulate is confirmation of the “law of specific nerve energies” attributed to J. Muller in the 1830’s. However, the modern interpretation of that law is quite different. The next section will calculate the minimum energy required to excite any sensory neuron and create a free electron within the signaling system. Later sections will show that this minimum energy is a critical design parameter within the overall neural system. It defines the technology available to support different sensory modalities. As a guide, these technologies involve the photoelectric, piezoelectric and electrostenolytic effects. These effects are all quantum-mechanical in nature. Both the piezoelectric and electrostenolytic effects appear to be used in multiple implementations that show striking morphologic differences.

The conversion of the input stimulus to a free electron is known as a transduction. It does not rely upon the release or transport of any protein within the neural system. All signaling is performed by the transport of fundamental electrical charges (or the propagation of energy resulting from the motion of such fundamental charges). The last caveat will be discussed in Section 9.1. This chapter will establish a framework for understanding and discussing the functional performance of these sensory neurons. It will also link the functional performance to the morphology of the neurons. Because the available information is so extensive, the features of the visual system will frequently be used as an exemplar of the general situation.

Most of the sensory neurons rely upon the photoelectric, piezoelectric or thermolectric effect to generate their electrical signals (sometimes aided by auxiliary molecular materials). The smell and taste sensory neurons remain in the least understood at present. They probably rely upon the secretion of an enzyme that reacts with the external molecules carried in the air or saliva within the local morphological structure of the neuron to generate an electrical stimulus.

The neurosecretory role of most (if not all) sensory neurons is not generally appreciated. Without this secretory capability, most neurons interfacing with the motor and glandular modalities would not be functional. This secretory role is be stressed in Section 2.7 and in Section 4.6.5.

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2Feducci, xxx Torrey’s 5th Ed. pg 449
This work does not support the putative chemical-gate structure of neural operation. Nor does it support the concept of a chemically based synapse between neurons. As a result, the term neurotransmitter is not used in this work except to show how that concept compares to the more rational electrolytic proposal. For those trained in the chemical approach, it is important to note that no transfer of heavy metal ions through the lemma of a neuron has never been observed by relatively direct means. The reported observations have all relied on electronic circuitry involving the flow of electrons to support the putative flow of heavy ions. This work will rely upon a companion work5 to provide an extensive review of the literature in these areas.

The companion work also develops a complete physiological explanation for the operation of the synapses. This operation is also electrolytic and does not involve any chemical transport across the synaptic gap. An entirely different operating rational is provided for the materials previously labeled neurotransmitters. They are in fact neuro-effectors and neuro-inhibitors. However, their action relates to the electrical power supplies of the neurons and not the transfer of signals across the synapse.

If the reader finds it difficult to embrace the electrolytic character of the neural system, it may help to recall that the underlying mechanisms only became known to man during the late 1950's and 1960's. Theories developed before that time (and reiterated up to the present6) relied upon an inadequate technological base. While those early workers would look upon the ideas presented here as magic (just like they would the liquid-crystal-based display of a hand-held calculator or cell phone), they are well known to the current college graduate in chemistry, physics, and electronics.

xxx of the sensory neurons. It is clear that all sensory neurons respond while exhibiting several different time constants. They all exhibit the same short term excitation/de-excitation (E/D) characteristic, they all exhibit a band limiting mechanism corresponding to a time constant of a few tenths of a second, and they all exhibit a very long term effect measured in hours to days. Each type of sensory neuron appears to use a slightly different means of overcoming the long term effect. These mechanisms will be discussed in the individual sensory neuron sections.

8.1.1 Important background

Before beginning, it is critically important to define the term receptor. Cavallito has documented the origins of this term in chemoreceptor research and notes its foundation in pharmacology7. He notes the great difficulty over the years in arriving at a definition of the term receptor within the pharmacological context.

In pharmacology, the concept of a receptor logically revolves about the activity of an exogenic substance introduced into the blood stream. It is assumed the target of that substance contains a specific receiving site on its surface. That site has been defined as a receptor. The concept does not relate to external stimulation of a sensory neuron. Among the sensory modalities (limited to external stimulation for the moment), a distinct mechanism, transduction, is designed to create an electrical signal in response to an external stimulant. This mechanism takes place at a specific input area of the sensory neurons related to the cilia or villi of the input (typically labeled dendritic) portion of the sensory neuron. Because of its sensitivity to extraneous stimulation, this input area is frequently isolated from the blood stream.

In the sensory modalities, a receptor is the site of transduction of an external stimulant (a first messenger) into an internal electrical signal (an internal messenger) within the neural system. The site of sensory neuron receptors is limited to the external interface of the cilia or villi. The site is typically isolated from the effects of pharmacological substances in the blood stream.

It is also important to place the concept of the Structure-Activity Relationship (SAR) in context with

5Fulton, J. (2004) PBV and BV


the broader field of scientific research. The SAR concept originated long ago when it was virtually impossible to understand the physiological operation of the biological systems within a species. In other fields, it is considered the “black box” approach to science. Introduce an input into the black box and see what the result is. The S in SAR originally stood for stimulant (which was typically described by a trivial name). As chemistry has developed, the stimulants have been described more completely by their chemical structure, and more recently by their electronic structure as well. Similarly, with advances, the activity resulting from these chemical structures have been divided into both the principle activity and various side effects. While the SAR approach to pharmacology still has its place, a great deal more is known about the internal operation of the biological system. Instrumentation has taken great leaps forward in laboratory investigations and treating the system as a black box is no longer appropriate. Section 8.4.1.4 will describe the current place of SAR in chemoreceptor research. Section 8.6.7 will explicitly show the initial steps in subdividing the SAR concept into a series of intermediate relationships applicable to the olfactory modality. The same subdivision is inherent in the discussions of other modalities.

This work is specifically designed to replace the SAR concept with a concatenated description of each individual step in the operation of the neural system. An associated goal is to show the detailed characteristics and transduction performance of the sensory neuron receptors of each sensory modality.

8.1.1.1 Genetics of the sensory neurons

As will become clear in this chapter, the discussions between the advocates of a labeled-line theory of sensory signal identification and those advocating an across-nerve approach involving multiple neurons is largely irrelevant. All individual sensory signaling paths (invariable of stage 3 type when delivering signals to stage 4) can be traced back through stage 2 to a single sensory neuron or set of sensory neurons. On the other hand, the stage 4 signal manipulation function is charged with interpreting the pattern of signals it receives from groups of stage 3 neurons. Both the inputs to stage 4 and the outputs of stage 4 consist of signals exhibiting a coherence in either time or space relative to the environment that can be described as an across nerve format. Terminology is important; there is no possibility of a cross-nerve hypothesis since it is a single signaling channel. The necessary terminology is the cross-nerve hypothesis (associated with a group of neurons within one nerve). Using the term fiber in place of nerve is poor practice. Erickson has addressed this terminology problem in an historical but less than precise manner.

8.1.1.2 Genetics of the sensory neurons

Genetics plays a significant role in understanding the stimulant sensing complex associated with the sensory neurons of the neural system. Early work led to the conclusion that the DNA code was nothing but a transcription for all of the proteins in the animal body, with much associated junk code. It is now becoming clear that much of that junk code is extremely important for defining and/or controlling many other processes and materials in the body. This realization has opened new avenues of research in the 21st Century. However, the resultant “deluge” of information has not found its way into an organized structure (a comprehensive theory) where it can be used effectively. Also gaining acceptance is the realization that a single gene may influence many portions of the physiological system, and not control only the genesis of a specific receptor molecule/ligand.

The term stimulant sensing complex (SSC) is used primarily in the chemical sensing and genetics community. It seldom appears in the vision and hearing communities. The abbreviation SSC is frequently used without detailed definition. It generally describes a stimulant sensing complex in the conceptual literature. It needs clearer definition. In olfaction, an SSC is occasionally defined as a complex containing an odor-receptor protein (ORP) or an odor-binding-protein (OBP), and occasionally both. Sometimes the OBP is described as mediating the binding between the ORP and the odorant. Other times the OBP is defined as the ORP.

It is important to note that proteins play a minor role as stimulants in chemical sensing. Most proteins are considered odorless, although their decay products are frequently highly stimulating odorants. As noted by Ache & Carr (page 111), the chemical families commonly considered gustants among aquatic invertebrates include the low molecular weight organic compounds, such as nucleotides, amines, amino acids, and organic acids. Similar assertions can be made concerning molluscs and many fish. Based on these findings and the importance of the proposed DACB of this hypothesis,

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it is likely that the chemical receptors of animals are generally not proteins but members of one or more of these same chemical families. The hypothesis of this work is that virtually all sensory receptors of external chemical sensory modalities are amino acids esterified to the lipids found in the outer cell wall of sensory receptor neurons.

For the last quarter of the 20th Century, the SSC’s were generally assumed to be limited to proteins. However, recent work has suggested the actual receptor molecules may be lipids created by mitochondria based on instructions in the DNA code. The non-protein lipid-based odor receptors will be labeled olfactory receptors (OR) and the non-protein lipid based taste receptors will be labeled gustatory receptors (GR).

SSC appears in many quotations taken from the literature. Except in referring to these quotations, SSC will be replaced with more definitive labels in this work. In all cases, an SSC will include all of the chemical species and processes directly supporting the transduction process. In chemical sensing, it will include any olfactory receptor, OR, and any mediating OBP present, or the equivalent gustatory receptor (GR) and any mediating gustatory binding protein (GBP) present.

Such a complex invariably contains a substrate. This substrate may support an associated, an enclosed, or an embedded receptor site. It may also support an enzyme facilitating/mediating the efficient operation of the receptor site, and it may be supported by a fluid environment, as in the oral and nasal cavities.

The lemma is characteristically a phospholipid, the receptors vary by modality; vision employs a retinoid receptor (Rhodoneine), hearing employs a lipid-based piezoelectric material (xxx), while both gustation and olfaction employ receptors that are themselves modified phospholipid complexes. In at least the case of electrostenolytics, the SSC appears to be supported by an enzyme (protein) facilitating the selection of the active material (glutamate) from the fluid milieu of the organism surrounding the neuron.

Genetics has remained an observational science until recently. Modern genetics is becoming a predictive science. However, predictions based on detailed knowledge of the genetic code are at an early stage. Although progress has occurred at an amazing rate, understanding the code still involves great amounts of “junk code” and “pseudogenes”. Attempts to employ “genetic medicine” remain in the experimental state. On the other hand, great success has been achieved using genetically modified (knockout) mice.

The connection between genetics and biology remains largely inferential. Investigators have not had conceptual (intellectual rather than animal) models adequate to the task. As a result, investigators frequently find “what they are looking for.” In the case of vision, they have routinely found three genes representing the putative three chromophores of vision, based on the conventional wisdom, when it can be shown (Section 8.1.2.x) that Mammalia, including Homo Sapien, exhibits four chromophores. Investigators have routinely not found the gene associated with the ultraviolet chromophore or the putative “rod” chromophore.

In the case of chemoreception, the problem has been more awkward. Until now, no satisfactory model describing a finite set of chemophores or chemical receptors, has arisen. Therefore, the investigators have assigned genes on virtually every chromosome to the chemoreception process based largely on the fact they code for what are described as G-protein coupled receptors (GPCR). Johnston et al.9 have made an extremely important observation about GPCRs as of 2012;

GPCR protomers, when reconstituted into nanodiscs, can signal to G proteins."

In essence, the unequivocal evidence linking GPCR's to transduction has yet to appear.

GPCR's are discussed in greater detail in Section 3.2.4. As noted in that section, defined above, and developed in the following portions of this chapter, the sensory receptors known and defined in detail are not proteins.

GPCR's consist of three subunits; the α-subunit, which contains the guanine-nucleotide-binding site, and the β- and γ-subunits which function as a heterodimer. Heterodimer in the field of biology is broader term than in organic chemistry. The two subunits may vary in number, location and definition of the individual amino acids. In most cases, the precise molecular structure of the subunits of the heterodimer have not been elucidated. Hence, what precisely they code for is not known at this time.

Strotmann has provided a paper describing "a unique subfamily of olfactory receptors" that illustrated the state of the art in 2001. It asserts each gene of the genetic code specifies a unique olfactory receptor that is a protein. However, they did not proceed to identify any specific receptor and demonstrate that it was a protein. Strotmann identified "five OR37 gene subtypes in the mouse, comprising four functional genes and one pseudogene.” He also noted regarding other genes, "The transcription orientation of four genes is identical, only the first gene in the cluster is positioned in opposite orientation." He did not address the function of the pseudogene or the functionality of a gene positioned in opposite orientation, or provide any reference.

It appears Strotmann did not consider the possibility that the olfactory receptors need not be genetically defined. There is a major literature suggesting the olfactory receptors may not be encoded by DNA (Section 8.4).

Terminology is a problem for an outsider attempting to understand the genetics literature. Figure 8.1.1-1 provides an overview of that terminology. [XXX add text, no figure box called]

The following figures describe the conceptual state of genetics prior to the discovery in the later part of the 1990's that DNA also coded "instructions" besides proteins. This has opened up an entirely new area of genetic research and requires a review and reinterpretation of much of the previous literature. This is particularly true with respect to the "receptors" of the sensory neurons. With rare exception in the case of unexplored receptors, the sensory receptors are not proteins. The figures are shown to provide a level of traceability. The complete caption for each figure and the defense of that caption will be found in the cited author's paper. Figure 8.1.1-1 from Lancet et al. shows the location of an odor receptor cluster relative to chromosome 17. No actual olfactory receptor has been located based on this coding sequence.

Figure 8.1.1-2 provides more detail relative to

Figure 8.1.1-1 A scheme depicting the cluster of olfactory receptor (OR) genes on human chromosome 17, at chromosomal band p13.3. See text. From Lancet et al., 1993.

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an OR cluster as proposed by Johnson\textsuperscript{12}. He accompanies this figure with the assertion (page 14) that; “Most newly translated proteins must be modified and translocated to an appropriate cellular or extracellular locus before they are ready to assume their biologic functions.” Such a broad statement without further details of how all of these changes are accomplished throw doubt on the original assertion that the actual beginning substrate was even a protein. His following discussion is entirely conceptual and dominated by possible rather than demonstrated steps. His discussion focuses on the chemical receptors and is not obviously appropriate for the visual and auditory receptors that clearly do not bind to the incident energy in a chemical union. It will be shown below that even in the case of the chemical receptors, they do not bind in the valence chemistry sense. As is well documented, no “reaction” occurs between the stimulant and receptor and no residue is produced. These facts are in conflict with much of Johnson’s subsequent discussion on pages 19 and 20. All of his discussion relies upon concepts generally associated with the also conceptual chemical theory of the neuron.

\textsuperscript{12}Johnson, L. ed. (1998) Essential Medical Physiology, 2\textsuperscript{nd} Ed. NY: Lippincott-Raven Page 15
Margolis et al. have provided extensive material on the olfactory marker protein(s), Olf-1\(^{13}\). Their wording is careful. “We propose that Olf-1 is a novel olfactory-specific trans-acting factor responsible for directing the expression of genes containing the Olf-1 motif in olfactory neurons. Thus it may play a role in regulating the expression of genes associated with neuronal turnover and olfactory transduction.” Olf-1 may not result in the creation of a protein acting as a stimulant sensing complex (SSC).

For those seeking a broader background in genetics, the lectures of Wolfe on the internet in 2005 are recommended\(^{14}\). [xxx not a strong source]

8.1.1.2.1 Genetics of vision EMPTY


\(^{14}\)Wolfe, J. (2005) [http://www.ucl.ac.uk/~ucbhjow/b241/lectures.html](http://www.ucl.ac.uk/~ucbhjow/b241/lectures.html)
8.1.1.2.3 Genetics of chemoreception

The genetics of chemoreception is in considerable disarray due to the publicity associated with a Nobel Prize awarded to Buck and Axel in the late 1990's. In 2003, Fain provided several assertions that appear unsubstantiated. He asserted there were about 1000 olfactory receptors (OR's) based on identified genes in humans numbering on the order of 900. As in other early assertions, it appears these genes have no other function than to code for OR proteins. Fain relates them to a very large family of G protein-coupled receptors (the conventional wisdom of the day). In fact, these genes must encode every detail of the neurons of the olfactory modality, not just the OR's.

Mombaerts has provided an extensive review of the literature relating the genes believed to relate to the ligands and molecules of the odorant receptors (OR). He noted in 2004, based on the conventional understanding of the genome, “Nearly all receptor genes have now been identified as the result of genome sequencing, but few receptor-ligand interactions have been characterized.” While discussing G-protein coupled receptors (GPCR), he concludes, “The Holy Grail of olfaction is within sight, but there is a long way to go—more than half of mouse and human non-chemosensory GPCRs have known ligands, but the vast majority of chemo-sensory GPCRs remain orphans.”

Matching the GPCR’s and their heterodimer peptides analytically is difficult in the extreme. Mombaerts suggests an alternative (page 273) is to isolate an OR that responds to a given stimulant, clone that OR, and demonstrate the cloned OR confers the requisite sensitivity to a sensory cell.

Zozulya et al. have provided a first cut of the entire repertoire of human olfactory receptors, described as stimulant sensing complexes (SSC) or odor binding proteins (OBP) in this work. The repertoire was the result of a data mining operation. Their strategy was to look for full-length, functional candidate odorant receptor genes was based on the high overall sequence similarity and presence of a number of conserved sequence motifs in all known mammalian odorant receptors as well as the absence of introns in their coding sequences.

Zozulya et al. noted,

“Each receptor recognizes multiple odorants, and each odorant binds to multiple receptors to generate specific activation patterns for each of a vast number of distinct smells.

The genes encoding ORs are devoid of introns within their coding regions. Mammalian OR genes are typically organized in clusters of ten or more members and located on many chromosomes. The repertoire of human OR (hOR) genes contains a large fraction of pseudogenes, suggesting that olfaction became less important in the course of primate evolution. Recent studies indicate that some 70% of all hOR genes may be pseudogenes, compared with fewer than 5% in rodents or lower primates.”

The following quotation provides an indication of their search for human olfactory receptors (hOR):

As a result of the search described above, 347 putative full-length OR genes have been identified in the human genome. This number includes all the previously known, annotated hOR sequences extracted from the public databases. It is feasible that a small number of full-length hORs escaped detection because of frameshifts or other sequencing or assembly errors in the corresponding HTGS entries. We are continuing routine searches using updated versions of genomic sequences to identify such cases. Because of the very high occurrence of OR pseudogenes in humans and the presence of ORs in highly variable parts of human genome, it is also possible that some polymorphic members of this gene family exist in the human population in both intact and defective allelic forms. A small subset of identified OR,
ORFs was discarded because of such defects as partial deletions of TM1 or TM7 regions. The argument can be made that these OR genes could encode functional receptors. In addition, it was hypothesized that odorant reception may also be mediated by receptors of a completely different class, such as guanylate cyclases. These caveats notwithstanding, we estimate that we have identified at least 90-95% of all full-length prototypical ORs in the human genome.
There is no indication in the paper that Zozulya et al. looked for any receptor that was not a protein. Ronnett and Moon have provided additional information concerning the genes believed to support olfaction.

The inferential matching of genes to specific proteins believed to be found in the sensory neurons and assumed to relate to the sensory receptors remains in a primitive state. No data, or even sophisticated description, has appeared in the literature showing any specific protein participating in the actual transduction process. Kreher et al. provided a valuable paper in 2008 involving the olfactory modality of insects. While valuable as background, the paper was based entirely on behavioral studies of a non-animal making correlation to mammals difficult. The paper relies upon many inferences (Section 8.6.1.1.7)

8.1.1.2.4 Role of “Holes” in Genetics

Stewart has shown an interesting hydrogen bonding relationship between the nucleic pairsin DNA. It stresses the multiple hydrogen-bond nature of the relationship between both thymine and adenine and between cytosine and guanine. As a result, these base pairs have almost identical stereographic shapes. The presence of multiple hydrogen bonds at every base pair along the DNA molecule offers a great deal on hole mobility along the molecule.

8.1.1.3 Transduction, neurotransmitters vs chemical signals

The term transduction has not made a successful transition from the physical sciences into the biological sciences. In their book of 2002, Gompertz et al., review the definitions of the term found in the 2nd Edition of the Oxford English Dictionary. The dictionary notes, the only use of the term in the biological sciences related to external excitation relates to the visual modality, and a lament in the Journal of the Acoustical Society of America of 1947 that the mechanism has not been used in the theory of the hearing modality.

As is shown in this work, all of the external sensory modalities of the nervous system employ transduction of the stimulus into an electrical signal by one mechanism or another.

The lack of an adequate understanding of transduction in the neural system has led to the proliferation of alternate concepts relating a “first messenger” to a “second messenger” of chemical character. These second messengers are all ancillary to the fundamental transduction mechanism.

[xxx most of this section belongs in Chap 2 or 3 ]

The biology community has drawn up a list of “chemical signals,” materials associated with communications between cells and larger components of the body. Communications is used here in the broadest possible sense. Figure 8.1.1-4 shows such a list from one author. It is interesting to note this list does not include many of the “chemical signals” generally associated with the nervous system. It is also interesting that nitric oxide is shown originating in endothelium, rather more explicitly as originating from the neural tissue in said endothelium. [xxx glutamic acid, etc. ]
It is common in the biological community to bridge between chemical signaling agents and the more specific term neurotransmitter. This is frequently done without any formal definitions. In 1993, Hucho provided a remarkable discussion of general principles and nomenclature related to the neuroreceptors. The paper is remarkably frank and skillfully worded. His opening sentences are enlightening, “Concepts evolve, and so did the receptor concept. Concepts are based on observations, on special experimental data that are generalized when somebody overlooks enough of them and is wise enough to see the general principle in the flood of numbers, plots and descriptions.” These sentences illuminate the fact that much of the framework of the neurosciences is based on concepts deeply rooted in philosophy and logic rather than rigorous application of the scientific method. Facts, plots and descriptions are relegated to secondary position behind “insights” that may be heavily weighted in the direction of the investigators prior training. These insights frequently take on a first order or linear tone in spite of the plots.

Hucho proceeds to a definition of a receptor common in the fourth quarter of the 20th Century, “Receptors are proteins interacting with extracellular physiological signals and converting them into intracellular effects. Neurotransmitter receptors are integral membrane proteins; their physiological signals are neurotransmitters and neuromodulators.” No citations of any kind are given to defend these assertions. He goes on to find difficulty with this definition. “For example, many of the neuropeptides discussed in this chapter have not been classified as transmitters by the criteria summarized below... On the other hand, it tacitly includes the so-called orphan receptors.

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receptors discovered by reverse genetics (the art of ‘pulling out’ clones with consensus probes homologous to sequences of well-known members of receptor families and superfamilies). Orphan receptors are proteins (actually in most cases just DNA sequence) for which the endogenous ligand, the physiological signal, has not yet been found.

Finally he notes, “The molecular definition given here is different from a more biological receptor concept that names cellular entities like the rods and cones of the retina ‘photoreceptors’ and the cells of the muscle spindle ‘stretch receptors’.” Later on page 65 in the same volume, Otto notes, As discussed in Chapter 1, the term ‘receptor’ is differently and sometimes confusingly used in different contexts. In the field of signal transduction, the term ‘receptor’ stands for a protein structure, which activates a subsequent effector system while it is activated by binding an agonistic ligand. In the context of binding studies, this term has a much more general sense. There it is synonymously used for the term ‘binding site’. Very often the terminology is mixed, thus bearing the danger of losing the awareness for the definition of binding specificity.”

These citations highlight the considerable confusion found in the literature when terms are not precisely defined in the preparation of a published report. Hucho proceeds to note his text is based on concepts used in, and aimed at, the pharmacology community.

In fact, Hucho is far off track. None of the external sensory receptors of the neural system involved in transduction are proteins. This work will develop the details related to the chemistry of each external sensory receptor in turn. His concept of a transmembrane receptor is far too elementary to be useful. It will be compared to a more detailed description of individual receptors in Section 8.5.3.1.

In the pharmacology community, the high concentration of a substance near a neuron leads to its definition as a neurotransmitter or neuromodulator, even as in the case of GABA, the material is actually a residue (a waste product) of a reaction. In this case, the conceptual receptors known as GABA$_A$ and GABA$_B$ are actually the receptors for glutamate, which reacts electrosynaptically to form GABA with the release of both CO$_2$ and GABA into the surrounding neural matrix. Functionally, it is not obvious that two receptors are required in this instance.

The host of defined receptor sites for glutamate is in even greater disarray. The TIPS (Trends in Pharmacological Sciences) prepares an ongoing summary of receptor nomenclature. As of 1993, this summary described eight (or nine) receptor sites for glutamate without defining the precise purpose of any of them. The 1993 supplement opens with a significant statement, “NO FORMAL system for the rational classification of receptor exists.” [Capitals in original] “Receptors are subtyped on the basis of different pharmacological profiles rather than on distinct second-messenger/signal-transduction pathways or primary structures.”

The “second messenger” concept has become the ultimate crutch in neuroscience. It arose in the 1950’s based on research related to the liver by Earl Sutherland and his colleagues. It has been adopted by many research communities to provide a logical (if not scientific) explanation of nearly any transduction process. Figure 8.1.1-5, from Siegel et al., shows the extremes to which it is carried. An unspecified stimulant (the first messenger) elicits a second messenger (from an abbreviated selection of possibilities) after multiple unspecified processing steps by a series of proteins. The ultimate target is identified without regard to, or definition of, these intervening steps. The paradox associated with the conceptual hypothesis of the “second messenger” has been explored by Lichtstein & Rodbard[23]. While making significant assertions about the inadequacy of the concept in their paper, no followup discussions ensued at that time.

Brezina & Weiss readdressed the subject ten years later[24], “Neurons and other cells are regulated by a great multiplicity of neurotransmitters, modulators, hormones and other chemical messengers, which, through complex networks of extensively diverging and converging pathways, exert a multiplicity of effects. How do we analyze the functioning of such a complex network?” Unfortunately, their paper introduced even greater topological complexity by considering matrices of conceptual transmitters and introducing co-

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transmitters. They ultimately passed the questions they asked along to later investigators. They were unable to add preciseness to the overall discussion.

The above material takes on a Bayesian character. By philosophically limiting the range of phenomena considered (receptors are proteins, they create second messengers via other proteins) the empirical results are necessarily interpreted within that limited range. The likelihood that receptors of neurologically active stimuli could be other than proteins is eliminated in advance. Unfortunately, the data shows otherwise. First, most neuroreceptors related to chemoreception are actually specialized phospholipids integral to the lemma of the neurons. The initial visual receptors are carotenoids physically separate from any protein. Only the auditory receptors contain proteins, or protein-like materials, that are used as piezoelectric devices. Second, the transduction processes of the neural system do not involve any chemical process generating metabolic products. The laboratory community has clearly demonstrated that no experimental procedure has ever isolated a metabolic process directly traceable to transduction.

A major problem with texts and papers up through the turn of the Century has been their lack of attention to the types of quantum chemistry employed in the sensory modalities. The field of coordination chemistry is typically missing from the index to these materials (Siegel, 1999, 2006).

Figure 8.1.1-6 provides a comparison of the historical chemical approach to neural sensing and the approach of the Electrolytic Theory of the Neuron. The historical approach is based primarily on logic and largely preconceived ideas. The electrolytic approach is based heavily on the observed performance characteristics of the neural system, architecture and tissue. The electrolytic approach provides a deterministic, modality specific description of the sensory process. It is based on a single “second messenger,” the electron, considered as a current that can be amplified, summed, differenced, exponentiated and interpreted. The signals related to the initial transduction current are transmitted over labeled-line neural paths. Probing of these paths electronically elicits signals that can be related (deterministically) back to the source stimulus.

An important feature of the Electrolytic theory of the Neuron is that steps defined in this theory are readily quantifiable using conventional laboratory equipment. Much of the predicted performance has already been demonstrated in the laboratory by other investigators. The level of match between the predicted and measured performance is remarkable, regardless of the sensory modality involved. A second important feature is the laboratory data demonstrating that the synapse is electrically reversible, a difficult phenomenon to explain based on the unidirectional assumption of the chemical approach.

**Figure 8.1.1-5** The generalization of the “second messenger” concept. The concept can be used to explain anything. It has no physical foundation. PI; a variety (two are listed) of metabolic products of phosphatidylinositol, a phospholipid. AA; metabolic products (four are listed) of arachidonic acid, an unsaturated fatty acid. From Duman & Nestler in Siegel et al. 6th Ed. 1999.
The chemical theory of the neuron has been notoriously poor at providing any quantifiable explanations of sensory operation. This chapter will develop contiguous, detailed and mathematically quantifiable models of each of the sensory modalities, usually involving multiple parallel channels to the range of colors, scents and tastes discernible by the human. The model of each of these modalities will begin with a metric physically related to the stimulants unique to that sensory mechanism. The description of the gustatory modality will include a metric related to the various stimulants for the first time. The individual models will explain how the time constants related to that modality are independent of any chemical kinetics (except for the electrostenolytic process providing electricity to the sensory neurons. These models will also be contiguous with those in the following chapters related to signal projection and signal interpretation leading to cognition by the mind.

As a specific example, proponents of the chemical theory have described a pseudo-type 2 lemma of the sensory neurons that contains very complex proteins of the GPCR class or alternately proteins introducing pores into the membrane. These pores are apparently in some way analogous to the type 4 lemma responsible for moving large molecules through the cell wall. However, in this case, the pores are responsible for moving charged alkali and alkali-earth ions through the lemma. No satisfactory explanation has surfaced to date as to how the pores or GPCR proteins accomplish the transduction process.

The assertion that the mechanism of transduction is mediated by proteins is based entirely on the fact that only the protein transcription aspects of the DNA code are understood at this time. The protein transcription portion involves less than 2 percent of the total DNA code. No explanation has appeared to date as to how lipoproteins are defined within the DNA code or are created in response to DNA code instructions!!!

### 8.1.1.4 Chemicals of major importance in the chemical theory of the neuron

Johnson has discussed the importance of G-proteins and the “second messenger” concept. Most
authors discussing the second messenger concept rely on the chemical cyclic AMP (or cyclic adenosine monophosphate) to fill this role.

However, Takeuchi et al. have noted there are many sensory neurons that do not contain cAMP. In some cases they assign the second messenger role to another chemical, InsP$_3$. Inositol 1,4,5-triphosphate. Inositol and its ability to complex with sodium, and potentially other alkali and alkali-earth ions, is of major importance in the gustatory modality (Section 8.5.4).

The role of GABA in the chemical theory is that of a distinct neuroinhibitor (neurotransmitter) affecting the sensitivity of neurons to excitation. Soon after its discovery in the brain in the 1950's, one of the principles noted, "GABA probably was a metabolic wastebasket". The Electrolytic Theory of the Neuron provides its true and unique role, as the end product of the electroneutral process powering all neurons. In this process, it is an end-product that is recycled via a portion of the citric cycle. It presence in excess in the neural matrix does in fact inhibit the operation of the nearby neurons.

### 8.1.1.5 A redefinition of the "messengers" of the neural system

The literature has been less than substantive when discussing the so-called 1st and 2nd messengers. Very little concerning the 1st messengers appears in the literature and the use of the term 2nd messenger is inconsistent. The term messenger appears to have entered the neural literature via attempts to explain what appears to be chemical communications between non-neural cells. It has been used in the neural literature in a largely conceptual context for years. A 1st messenger has been associated with any external medium impacting a neuron. A second messenger has been described as any agent found within a neuron, resulting from transduction of the 1st messenger, and supporting subsequent signaling within that neuron. A wide range of chemicals have been defined as 2nd messengers based primarily on their presence in the internal chemistry of the neuron, regardless of its measured role in signaling. Based on these presences, elaborate conceptual reactions have been defined to explain the importance of these chemicals in the signaling process.

Lichtstein & Rodbard revisited the 2nd messenger concept in 1987. After suggesting there are a very large number of uncharacterized specific signals called “1st messengers,” they noted only a handful of 2nd messengers had been proposed. Based on this situation they said, “Even allowing for the discovery of a large number of additional second messengers, there remains a paradox in terms of information-transfer within the cell: how can so many specific signals produce so many effects through so few relatively nonspecific intermediates?” They offer no rational solution to the stated paradox after considering multiple options based on the chemical theory of the neuron. Their only figure is a conceptual block diagram focused on hormones as the 1st messengers. The paper brings little new to the discussion of 2nd messengers. Brezina & Weiss addressed the subject again in 1997 with similar inconsequential results. The Electrolytic Theory of the Neuron offers a clearer and more detailed description of these “messengers.”

The Electrolytic Theory of the Neuron redefines the 1st messengers narrowly as external stimulants that are transduced by the sensory neurons into electrical signals that are subsequently relayed to the central nervous system (CNS). It defines a set of chemicals, the neuro-facilitators and the neuro-inhibitors, that provide electrical power to the neurons and/or reduce the power available to the neurons. It also defines a set of neuro-modulators, typically hormones, that change the operating characteristics of the neurons, independent of the powers supplies, and thereby impact the electrical signals passed to the CNS.

The only 2nd messenger recognized by the Electrolytic Theory of the Neuron is the electron. It exists in three operational forms:
1. a free electron moving within the conduction band of a medium,
2. an electron moving within the valence band of a semiconducting medium (and not considered free)

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3. a free electron on the surface of an insulating material that participates in the electro-magnetic propagation of a signal along that insulating surface.

Some of these mechanisms may be foreign to the experience of the reader. However, they are well known mechanisms in semiconductor physics and electro-magnetism.

The 2nd messenger of this theory (the electron in one of its forms defined above), created by the stage 1 transduction mechanism, is used exclusively for signaling between the stage 1 and stage 7 neurons.

As noted in Section 2.6.1.1, the Electrolytic Theory of the Neuron recognizes that the original designations of currents in a neuron by Huxley and Hodgkin were euphemisms. Their label “sodium current” did not assert the current consisted of sodium ions, it referred to a conventional current entering through the lemma of a single compartment neuron. Likewise, their label “potassium current” referred to a conventional current flowing out of the lemma of the neuron. The inward current label was based on the higher concentration of sodium ions in the matrix surrounding the neuron. The outward current label was based on the higher concentration of the potassium ions within the neuron compartment. It has been repeatedly shown that the lemma of the neurons is impervious to both of these ions in their fundamental form. As in any electrolytic or electrical device, the primary current is in fact the electron current (flowing in opposite direction to the “conventional” current defined erroneously by Benjamin Franklin based on a conceptual positively charged particle).

The Electrolytic Theory of the Neuron recognizes the multi-compartment (and three-terminal) character of the neural portion of the neuron cell. As a result, two currents are recognized relating to the axoplasm. The first is the polarizing current of electrons entering the axoplasm of the neuron from the electrostenolytic power source on the outer surface of the axolemma. The second is the depolarizing current of electrons passing out of the axoplasm and into the podaplasma under the control of the voltage between the dendroplasm and the podaplasma.

A 3rd messenger can be defined as the substance(s) (typically but not exclusively hormones under most definitions of hormones) released by stage 7 neuron-affecters in order to influence muscle, neuronal and potentially other types of tissue.

8.1.1.6 Ultimate detection thresholds for the sensory neurons

Block has provided an evocative discussion of the potential sensitivity of the sensory neurons from a fundamental noise perspective that appears to be on track. He even speculates on the threshold performance of poorly defined sensors such as magnetoreceptors and gravitational receptors.

8.1.2 Comparative anatomy and histology in neuroscience

Johnson has provided a comprehensive clinical text including useful background on the neural

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An organism incorporates a variety of sensory neurons that support communications within its neural system. There are other means of communications within the organism that will not be addressed here, specifically chemical communication between cells and hormonal communications between the central nervous system and the extremities of the organism. Many authors have attempted to describe and organize a list of the sensory receptors of the neural system. The following list attempts to order them relative to their approximate importance to the human neural system.

**NEURAL RECEPTORS OF THE EXTERNAL ENVIRONMENT**
- Photoreceptors of vision.
- Phonoreceptors of hearing.
- Vestibular-receptors of spatial orientation.
- Chemoreceptors of olfaction and gustation.
- Odor-receptors of olfaction.
- Taste-receptors of gustation.
- Somatosensory neurons—heat, cold, pressure & physical damage.

**NEURAL RECEPTORS OF THE INTERNAL ENVIRONMENT**
- Kinesthetic receptors of spatial positioning and activity.
- Chemoreceptors of vascular system.
- Pressure receptors of the vascular system.
- Temperature receptors primarily of the vascular system.

The majority of the sensory neurons employ quantum-mechanical sensing mechanisms. These mechanisms are readily identified by the unique excitation/de-excitation (E/D) response function associated with these mechanisms. For convenience, this same E/D function (or equation) will be described as the photoexcitation/de-excitation equation (P/D) in vision, as the phonoexcitation/de-excitation equation (P/D) in hearing, and as the chemoexcitation/de-excitation equation (C/D) in olfaction and gustation.

The sensory receptors of vision and the external chemical environment will be seen to employ external transduction mechanisms that couple energy into the neural system by a quantum-mechanical mechanism. The sensory receptors of hearing and kinesthetics employ internal transduction mechanisms that deliver electrical charge to the neural system as a result of quantum-mechanical mechanisms, namely the piezo-electric effect.

Material reported in the fundamental research arena of the biological cell must be read very carefully to insure its relevance. As an example, the early paper of Bangham et al. have reported on a very professionally performed set of experiments on artificial phospholipid membranes using a material only described as ovolecithin. Ovolecithin is generally described as lecithin obtained from egg yolks. While they stress the non-porosity of artificial lemma to cations, compared to anions, the control of the purity of the presumed bilayer membrane is open to further review.

**8.1.2.1 Areas of specialized lemma in sensory neurons**

In the evolution of this work, it has been appropriate to define the plasma membrane forming the lemma of neural cells, and three specialized forms of plasma membrane. With the extension of this work to include olfaction and gustation, it is appropriate to define a fourth form.

**Plasma membrane**—The outer membrane completely surrounding a cell and consisting of a double wall membrane of two leaves. Each leaf usually consists of a liquid crystalline film of biological phospho-glycerides. The cell is usually divided by internal membranes into at least three distinct functional sections in neurons. These sections are associated with the morphologically defined axons, dendrites and podites. These sections of the membrane may show further specialization. The character of the membrane is also divided into four functional types.

The **type 1 plasmalemma** consists of a molecularly symmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular and electron flow (it is a very good

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The type 2 plasmalemma consists of a molecularly asymmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular flow but acts as an electrical diode with respect to electron flow.

The type 3 plasmalemma consists of a liquid crystalline bilayer with many embedded proteins providing a transport path through the membrane.

The type 4 plasmalemma consists of a molecularly asymmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular flow but acts as an electrical diode with respect to electron flow and incorporates an external structure subject to chemical attack.

The type 5 plasmalemma consists of a continuous liquid crystalline bilayer of axoplasm that is impervious to transverse molecular flow but acts as an electrical conductor with respect to electron flow and incorporates an external structure acting as a receptor site for neuro-affector agent precursors. Upon formation of the neuro-affector agent, it is held at the receptor site until released under neural control (subject to a change in the axoplasm potential).

Type 1 membrane is the classical membrane that is impervious to molecular as well as electron flow. Type 3 membrane supports the commonly conjectured but not demonstrated flow of large molecules through the cell wall. Types 2 is an asymmetrical bilayer membrane supporting the electrosalenolytic process providing negative electrical bias to the plasma of all cells relative to the surrounding matrix. Type 4 membrane is a more specialized version of a type 2 membrane where the outer leaf of the bilayer has been specialized to support olfaction and gustation.

Any time two type 2 plasmalemma are juxtaposed between plasmas of appropriate electrical potential, an active electrolytic device can be formed.

8.1.2.2 The transduction mechanism of sensory neurons

Squire et al. have provided a complex, and largely conceptual, table comparing the transduction mechanisms employed by the different sensory modalities based on the conventional chemical theory of the neural system. It was modified from Shepherd (1994) and focuses on the “second messenger” concept to explain how transduction is accomplished. Their figure 23.18 shows how truly conceptual the 2nd messenger actually is. The table hypothesizes a large number of proteins identified as G-protein-coupled receptor (GPCR) families as a primary participants in the transduction process. Their method of participation is largely unspecified. The table also includes a large number of question marks in place of pertinent information. Interestingly, it does not include the hearing modality. It will not be referred to subsequently in this work. The Electrolytic Theory of the Neuron provides a much simpler, more deterministic, and more compact table. It eliminates all of the largely conceptual, and frequently stochastic chemical processes previously associated with the neural system.

Summarizing the work to follow, the transduction process employed by the various sensory modalities can be described using Figure 8.1.2-1. The steps in these processes are much fewer using the Electrolytic Theory of the Neuron. [xxx put brief version of this in Chapter 1 ]

[xxx elaborate on my table ]
8.1.2.3 Uniqueness of the transduction mechanism of sensory neurons

The transduction mechanism employs a process not previously presented in textbooks and journals of physical chemistry. The process differs from first and second order chemical reactions and from consecutive reactions and conventional chain reactions.

The excitation/de-excitation mechanism of the sensory neurons employs what can be considered a chain reaction with replacement of the original reactants within a closed loop under the control of a stimulating event. The energy associated with this stimulating event may be derived from photons, phonons, odors and mechanical work.

The mechanism typically employs a quantum-mechanical transition that is reversible under very controlled conditions. In the case of vision, the mechanism frequently involves a resonant oxygen molecular structure that can be described using many names, an enol structure, a conjugated oxygen structure, or a hybrid alcohol/aldehyde structure. The chromophores associated with the photoreceptors of vision, the Rhodones, exhibit this structure.

It will be important to differentiate between the stimulants and their internal constituents. In olfaction, these are called odorants and odorophores respectively. When speaking across odorant
boundaries, the odorophores are described globally as olfactophores. Similar terminology is used in gustation but the use of gustaphore in both an individual and global context can be confusing. The individual odorophores and gustaphores of a particular stimulant, as a group, are described as the determinants of the stimulant in some papers.

The molecular structure supporting transduction within a given modality are in intimate contact with the respective sensory neurons. These structures can be considered energy processing complexes (EPC’s). In the case of the chemoreceptors, they can be described as stimulant sensing complexes (SSC’s). The overall transduction mechanism in a given modality can be described as either an EPC/photoreceptor, an EPC/phonoreceptor or an SSC/chemoreceptor. The EPC/phonoreceptors are very similar to the combination used in other mechanoreceptors. The mechanoreceptors will not be discussed in detail in this work.

The precise nature of the energy band gap found in the EPC’s is unusual. The width of the bandgap is much wider than normally associated with a single molecular species (as measured by flame chromatography as an example). It can be associated with a bulk crystalline material but is more appropriately associated with a single layer liquid crystalline structure in sensory processes. It is proposed that all of the EPC’s of photo-detection and chemodetection involve liquid crystalline surface layers.

All of the transduction mechanisms of the sensory neurons appear to conform to a single excitation/de-excitation equation. In the following sections, this equation will be labeled the P/D Equation for both photo and phono detection and the C/D Equation for chemo-detection.

8.1.2.4 Sensory neuron regeneration

The literature is controversial concerning sensory neuron regeneration. There are reports of regeneration of the sensory neurons of smell following laceration and possible regeneration of both olfactory and visual neurons on a routine basis. There is a conventional view that the sensory neurons of hearing are not replaced, and that damage to the cilia of hair cells is permanent. The question is difficult to resolve because of the static character of most histological investigations. In the case of hearing, it will be shown that the piezoelectric material within each cilium is replaced but the outer lemma of the cilium is not replaced. The catastrophic failure occurs when the cilium becomes bent over. The bud-like photoreceptor cells frequently found near the root of mature cells could be immature or replacement cells or they could be cells stunted during neurogenesis.

8.1.3 Isolation of neurons at stage boundaries

The literature contains many statements asserting that an analog stage 1 or stage 2 neuron produces action potentials. This is frequently due to a procedural error in an experiment. The investigator fails to recognize that the orthodromic phasic stage 3 neuron is directly coupled to the preceding neuron. Lowenstein has provided direct evidence of this problem in Figure 8.1.3-1. The experiment concerned a Pacinian corpuscle or touch receptor. The artwork is only a sketch but the description in the paper is clear. The circuit to the left of the Node of Ranvier was unmyelinated and operating in a stage 1 analog mode and the circuit to the right was myelinated and operating in a stage 3 phasic mode. More precisely, the myelin sheath begins with the first axon segment propagating an action potential, typically beginning at the arrow. The output was recorded at a point to the left of the arrow. When the circuit was disturbed at the arrow, the stage 1 portion to the left continued to produce generator potentials normally. Quoting Lowenstein,

“By micro-dissection technics it has been shown that removal of the connective tissue lamellae from the unmyelinated nerve ending in a pacinian corpuscle does not abolish the generator potential. when the first node of Ranvier is blocked by pressure or narcotics, the generator potential is unaffected but conducted impulses are abolished.”


8.1.4 Sensory modalities addressed in this chapter

The neural system supports a variety of sensory modalities; typically described as 11 that generate conscious perceptions and a host of others that do not. There are three major external modalities operating with the source at a distance, vision, hearing & smell. The sensory channels of the vestibule also sense less obvious external sources related to the organism in inertial space and the direction of the gravity field. Two modalities operate with the source nominally in contact with the organism, taste and touch. There are also a wide variety of internal modalities, generally sensing the chemical homeostasis of the organism itself.

This chapter will focus on the external sensory modalities, including the sense of touch. Pribram, ’91 has treated the tactile modality in considerable detail. His material can be related to the neural circuits of this work without difficulty. The internal sensory modalities, such as sensing oxygen content of the blood, will not be addressed here because of their range of functions and sparse information about their operation, and sometimes even location. The sensing of pain will be addressed less completely because the database is so fragmentary. However, it appears there are independent pain channels based primarily on the fact that the perception of pain frequently suggests the absence of an adaptation mechanism (a feature of all other sensory channels).

The sensory modalities of vision and hearing will be addressed in summary form here because of their
extensive treatment in other materials\textsuperscript{33,34} by this author.

Many graphs will be presented within the context of each sensory modality that exhibit a familial relationship to those in the earlier record. However, they usually differ in their degree of calibration (with scales provided here in nearly every case) and frequently in the number of orthogonal axes employed (a concept not usually described in mathematical terms). As an example of the earlier situation, McGinley et al. (Section 8.6.5.5) have provided three polar charts (frequently called radar charts, spider charts or C-scan charts) as examples for the gustatory, olfactory and nociceptor modalities under different labels. They are totally uncalibrated and no specific relationship between the axes is defined. They assert their scales are objective but do not claim they are quantitative. The meaning of the central shaded area on each chart is not discussed. Their odor chart appears based more on the lexicon of the English language than on the science of olfaction. The major labels appear undefendable.

8.1.5 A conceptual flow diagram of the neural system focused on sensory modalities

Shepherd has presented a very high level conceptual flow diagram relating a variety of sensory modalities, some CNS engines and some behavioral responses. It is reproduced as Figure 8.1.3-3.


\textsuperscript{34}Fulton, J. (2008) Hearing: A 21\textsuperscript{st} Century Paradigm. Bloomington, Indiana: Trafford and \url{www.neuronresearch.net/hearing}
8.2 The photoreceptor neurons of vision BRIEF

In the short term, this section will rely upon the complete discussion of the stage 1 sensory processes, chapter 12 as discussed in "Processes in Biological Vision," 2004, http://neuronresearch.net/vision/pdf/12Primary.pdf

The notes below are only here to save them for later incorporation into a complete Section.

[xxx Lam noted in 1978, that he was unable to identify any chemical neurotransmitter (of the half dozen known at that time, present in or released by the photoreceptors of the vertebrate retina]. In conclusion, our chemical studies so far indicate that none of the known putative transmitters

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appears to be a likely candidate for the photoreceptor transmitter. Conversely, Lam provided good data on the specific activities and the concentrations of certain amino acids in the retina. Subsequently, Sarthy & Lam provided tentative identification of chemical neurotransmitters in the Newt. They also reported a close association between these amino acids and the retinal neurons of goldfish.

The 1998 medical physiology text of Johnson discusses the organization of the retina in significant detail while taking the entirely opposite position of the majority of the vision community. He asserts that the fovea is dominated by cone cells providing color vision and the periphery is dominated by rods supporting only monochrome vision. He does not explain how human eyes employ monochrome materials in almost all printed text and read it well using only cones, whereas reading chromatic text (letters in one color with a background of another) is frequently quite difficult.

In 2013, the Journal of Neuroscience prepared a special edition of papers by only four groups, essentially a swan song for a few of the senior Dons of the genetic specialty within the visual research field. The work paints many scenarios related to long term evolution but presents few testable/factual hypotheses. Many inferences are made between the genetic code and the presumed operation of the visual system over the eons of evolution. In one paper, the existence of four distinct photoreceptors ranging from the UV to long wavelengths is supported. However, of the four photoreceptors shown schematically, and all presumed to be rhodopsins, two are structurally identical and the cis-form of all four cannot be related to the spectrum of the individual chromophores. In fact, one of the authors recognizes the spectra he relates to the photoreceptors does not relate to the actual measured absorption of the photoreceptors. No recognition of the resonant character of the photoreceptors, and the unique spectra due to this resonance, is present on the surface of the opsin disks.

Friedlander & Tootle have provided a comprehensive discussion of the development of the eyes and visual system, circa 1990. Interestingly, they do not address the Canal of Cloquet connecting the tissue forming the lens to the source of nutrition associated with the blind spot and the cardiovascular flow supported by the "optic nerve." This is a major prenatal morphological structure frequently shown in cross sections of the human eye. It is totally reabsorbed after the completion of lens formation.

They have provided an explicit descriptions of alpha, beta and gamma ganglion cells on morphological grounds and the W, X & Y signals from the ganglion cells on electrophysiological grounds of the cat retina with several references to more detailed discussions. "The initial definition of X- and Y-cells was based on, respectively, linear or nonlinear summation of the visual input to the cells." Their Figure 6 attempts to define these cells functionally based on their response to individual square pulses applied to the center channel of presumed center-surround neural channels. In some cases the stimulation was by parametric (electrical) means at the optic chiasm.

2.2.3.2 The pseudo-two-terminal biological transistor of the photoreceptor cell

[xxx lost paragraph from section 2.2.3.1 about a three-terminal biological transistor and its Figure 8.2.1-1]
In the absence of electrical access to the region between the membranes, the two-membrane laminate has limited (but very important) application as an amplifier. **Figure 8.2.1-2(A) and (B)** illustrate this situation. Here again, the symbol “A” above the base region signifies an active biological semiconductor device. Note that if the collector is made negative with respect to the emitter, the bias requirements for “transistor action” is still obtained. The emitter to base region is forward biased and the collector to base region is reverse biased.

If the Activa is fabricated without explicit electrical contact to the base, it is still possible to obtain transistor action by exciting the Activa by other means. If quantum-mechanical energy of sufficient strength (not intensity) is applied to the region of the device near the emitter-base junction, free charges of opposite sign can be generated in the base region. The charge of higher mobility will impact the operation of the device more significantly. Solving the equations applying to the current in such a device, it can be shown that the base current must be equated to the collector current minus the emitter current. Solving for the collector current, \( I_{out} = \frac{I_{free}}{\alpha} \) or the output current is typically 50-100 times the current generated by the incident energy. In specially produced man-made transistors, this amplification factor can be as high as 5,000. Devices of this type are excellent photon detectors and can also be used as mechanical impact detectors, ionization gauges, etc.

Frame (C) shows the output current as a function of a fictional input potential that cannot be measured, \( V_{in} \). The input current remains equal to the output current.

The transfer characteristic of such an Activa to energetic stimulation is given by the equation above and is independent of the collector-to-emitter potential.

### 8.2.1 Recent mapping of the signal paths of the brain

**Figure 8.2.1-2** shows a recent diffusion type fMRI of the female human brain designed to show the signal paths between major engines. Not the paucity of signal paths between the left and right occipital lobes in this image. This paucity, accompanied by the extensive signaling between the individual occipital lobes and the diencephalon supports the propositions of this work that the TRN plays a major role in the stage 4 information extraction in human vision.

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41Frontpiece (2013) Special Section in Science, vol 342, page 577
Figure 8.2.1-2 2013 plan view of cranial signal transfer using MRI techniques. From Wedeen et al., Science, 2013.
Figure 8.2.1-3 shows a similar lack of direct connection between the two halves of the occipital lobes from Park & Friston⁴².

8.2.2 Recent development of a 2nd order set of parameters for the retinines, the rhodonines()

The field of x-ray crystallography has recently explored the molecular parameters of some of the retinines (retinol, etc.) leading to a better understanding of the potential peaks in the spectral responses of the retinines (the rhodonines) particularly for the long wavelength chromophore, rhodonine(5). The more precise structural characteristics of rhodonine(5) suggest a shorter wavelength peak than developed in the 1st order calculations based on Platt and used earlier in this work. The current value of 610 nm, rather than 625 nm is consistent with the measured and suggested wavelengths of Thornton (Section 5.xxx).

8.2.3 Recent In-depth analysis of the New Chromaticity Diagram

In March 2014, Necas-Niessner & Necas-Niessner⁴³ prepared a detailed analysis of my New Chromaticity Diagram. The result was a detailed colloquy between the parties leading to a clarification of many of the equations and text associated with the original text in “Processes in Biological Vision”

8.2.4 Recent showing that opsins/rhodopsin is not used in Insect vision

A major finding has occurred relevant to the sensory neurons of the visual modality. The detailed examination of the sensory neuron receptors of Insecta and some types of Mollusca eyes do not employ an opsin substrate. The receptor molecules, rhodonines, are deposited directly on the vili extending from the dendrites of the sensory neuron. This finding can be compared directly with the sensory neuron receptors of Chordata.

These clarifications should be introduced into the material forming Section 8.2.


8.3 The phonoreceptor and neurons of hearing & the vestibular system BRIEF

In the short term, this section will rely upon the complete discussion of the stage 1 sensory processes, chapter 5 as discussed in “Hearing: A 21st Century Paradigm,” 2008, published by Trafford and available from bookstores or online at the following site, also available as individual chapters online, http://neuronresearch.net/hearing/pdf/5Generation.pdf.

The material in the remainder of this section are notes to be included in a final rewrite of this chapter. Carpenter & Sutin show a particularly useful graphic of the labyrinth.

Figure 8.3.1-1 shows the middle and inner ear from a pneumatic/mechanical perspective.

This representation makes it clear that the round window is primarily a pressure relief port that responds to any pressure applied at the oval window. Similarly, the eustachian tube is a pressure relief port that responds to any pressure introduced into the middle ear by the motion of the tympanic membrane. [xxx appears in Ganong, page 106. Copy to ear book as well. I added words only to section 4.2.2.5.

8.3.1 The Auditory modality

8.3.1.xxx The electrophysiology of the neurons of the auditory system [xxx awaiting consolidation into new section 8.5]

The 1998 description of the auditory neuron by Geisler, Figure 8.3.1-2, approaches the actual situation. This work extends his concept by detailing how the variable impedance \( (G_{ap} + DG\sin \omega t) \) is controlled, how the impedance, \( R_{bas} \), is implemented and where the power source \( E_{EP} \) is located.

Figure 8.3.1-2 Early alternate representations of the auditory sensory neuron. UPDATE.

\[\text{Figure 8.3.1-1 Pneumatic/mechanical representation of the transmission of vibrations from the outer to inner ear. From Churchill, 1972.}\]

\[\text{Figure 8.3.1-2 Early alternate representations of the auditory sensory neuron. UPDATE.}\]

8.3.2 The vestibular modality

The role of the vestibular system, that is usually associated morphologically with the hearing modality, plays marginally different roles among the aquatic, terrestrial and flying families of animals. Thus care must be taken to differentiate these different roles.

While the operating principles of the vestibular modality have long been conceptualized, the actual operation of the elements of this modality have only been understood in detail since the appearance of the man-made strap-down inertial platforms of the late 1980's and particularly with the variants of the strap-down inertial platforms using the combination of lasers and fiber optics in the 1990's.

8.3.2.1 Background relating to the physiology of the vestibular system

The role of the vestibular modality is to provide a truly inertial frame of reference in support of the saliency map formed to reflect the external world to the brain of an animal. The saliency map prepares a three-dimensional representation of the external environment, and the various appendages and surfaces of the animal within that framework. It is the vestibular system that determines the orientation of that representation within the inertial environment. It does this in an almost identical manner to that used in modern light-beam based inertial platforms used in high performance aircraft and military systems. The only significant difference is in the use of acoustic signals in a fluid environment instead of electromagnetic signals in a fiber optic environment.

The vestibular modality creates what is generally described as a biased inertial framework. In the case of man-made inertial systems, the bias signal is generally drawn from a magnetic compass providing a reference to true North. The bias is established when the system is stationary on the earth's surface and not located near the North or South pole since these locations give a very poorly defined reference.

For biological systems, the primary bias signal is drawn from the local gravity vector. There are some indications that a secondary bias signal may be drawn from the magnetic vector used in man-made compasses as well. Alternately, a secondary signal may be derived via the visual system interpreting some feature of the position of the sun in reference to the local environment. This secondary reference would make it much easier to understand the migratory habits of many species.

The inertial system low frequency filters the bias signals to provide a very stable reference that is not affected by short term rotations and displacements of the body (man-made or biological) associated with the inertial reference.

The defined biological inertial framework is head-centered (more precisely vestibular system location centered) rather than body-centered. Being a gravity biased head-centered framework in the general case, the vestibular modality accommodates rapid movements of the head by measuring the angular and linear movements of the vestibular modality associated with these head movements and inserting the necessary signals into the saliency map.

The above framework is easily confirmed in the process of arising from bed. When lying in a bed, the system bias is acquired through the gravitational pressures on the sensory neurons of the somatosensory modality. When one first opens its eyes, the subject is clearly aware of where the walls, floor and ceiling of the bedroom are located within the inertial framework. As(she) arises, the head is typically rotated through 90 degrees in one plane, but the perception of the walls, ceiling and floor remain in their previously perceived inertial locations. It is clear the head has rotated relative to the inertial framework of the vestibular modality. And the saliency map reflects these changes. It should also be clear that the saliency map continues to reflect a complete spherical framework. The subject continues to reflect where the wall behind his head is located, even though it is not within his visual purview. It does remain within his acoustic purview as demonstrated by the proper representation within the saliency map of the presence of a ticking clock on that wall.

The presence of specific body parts within the established inertial framework is provided via the somatosensory neural system after adequate learning as a baby (and with additional training related to particular sports- including the extension of the perceived body parts associated with a racket, a gun or other paraphernalia required in that sport).

The overall role of the vestibular modality can be summarized as providing a long term stable 3D representation of the exterior environment relative to the location of the physical location of the...
modality along with the ability to sense short term variations in location (both angular and displacement) of the vestibular modality.

8.3.2.2 The physiology of the vestibular system

The nominal physiology of the vestibular modality consists of three circular cylindrical tubes arranged perpendicular to each other in a 3D space and generally labeled the labyrinth of the vestibular system. The tubes are typically described as fluid filled but the contents may in fact constitute a liquid crystalline material. Each tube is also formed of two concentric tubes with the inner cylinder filled with endolymph. The outer tube is filled with perilymph. Whether the endo lymph and perilymph are fluids or liquid crystalline materials is critically important in the physiology of the system. Liquids obey a specific set of physical laws that involve a high degree of dispersion as a function of frequency for acoustic signals moving through the fluid. Liquid crystalline materials obey a distinctly separate set of physical laws where acoustic energy is propagated with negligible dispersion as a function of frequency. Acoustic energy propagating within a liquid crystalline environment can be much more easily directed/constrained compared to the same energy propagated within a curved cylindrical enclosure.

In either case, the acoustic energy propagating within the curve cylindrical tubes of the vestibular modality are easily sensed by sensory neurons located in ampulla at the swollen ends of the tubes. The sensory neurons are closely related to those used within the auditory modality. The sensed signals are directly related to short term angular displacements of the vestibular modality due to the motions of the head.

Figure 8.3.2-1 presents a simplified sketch of the above elements prepared by Robert Demarest45. The figure illustrates the three cristae ampullae associated with angular displacement sensing, but only two of the macula associated with linear displacement, the macula utriculi and the macula sacculi. Noback describes the two macula as being “gravity organs” orthogonal to each other with “the long axis of the macula in the utriculi is oriented in the horizontal plane, and that of the macula in the sacculi is in a vertical plane.” It is more likely that the macula are sensitive to movement parallel to the hairs of the sensory neurons rather than to the morphological dimensions of the macula. Calling the organs, inertially sensitive would be a more informative terminology. They are typically insensitive to the static forces of gravity due to their presence within the gelatinous endolymph. As in any liquid crystal, the endolymph acts as a low viscosity fluid at low acoustic frequencies but acts like a solid at higher frequencies. Thus, the combination of otoliths and hair cells are allowed to relax in the absence of high frequency stimulation and react with maximum signal output when stimulated by high frequency (or impulse type) acoustic energy.

When discussing the vestibular modality, Noback offers the largely gratuitous and unsupported assertion that “the ear is considered a more efficient energy converter than the eye.” In fact, the photoreceptor neurons are virtually perfect in terms of efficiency. Both modalities appear to offer quantum noise limited performance over considerable sectors of their performance, although this is easier to demonstrate in the visual case.

Noback has noted the saccular and utricular elements of the vestibular modality may not be as efficient in humans as in other species. It may even be the case that the human physiology lacks an effective lateral motion sensory capability compared to the vertical and fore and aft capability. He asserts that the utricle generates neural signals associated with vertical motion (gravity) leaving one to assume the saccule is associated with motions in the horizontal plane (based on the assumption that the hair cells respond to bending rather than axial stimulation. It is possible the single saccule has sensory neurons associated with two orthogonal walls and thereby generates signals related to both lateral and fore and aft motions.

The macula of frame C shows the presence of otoliths associated with the hairs of the sensory neurons. It is these otoliths moving as a small seismic mass that stimulate the associated hair cells to generate the linear displacement signals.

It is important to note there are two independent sets of sacculae and utricles, one set associated with each vestibule, cochlea and ear. Molavi has discussed the orientation of these structures more fully as part of a PhD Thesis in 2004\(^{46}\). A lecture from 2003 is still present on the Internet\(^{47}\). While it is basically a set of cartoons used to teach elementary physiology of the vestibular modality and its connection to eye movements to first year medical students, it does contain significant information. It assumes the hair cells are stimulated by bending forces. It notes the membranous labyrinths are not aligned with, and perpendicular to, the sagittal plane; they are at 45 degrees to the sagittal plane.


\(^{47}\)Angelaki, xxx (2003)
http://thalamus.wustl.edu/Neural_Systems_03/sys_web_2003/Angelaki_eyemovement.PDF
plane. Such an orientation may allow sensing of signals in two aspects of the horizontal plane much like the V-tail of the Beechcraft Bonanza airplane of the 1950-60's allowed control of both vertical and horizontal motion using only that V-shaped tail structure. The signals from each ear would be processed differentially (summed and differenced) to separate the applied inertial forces. Within the discussion, they note the prevalence of nausea, leading to frequent vomiting when the visual cues and the vestibular cues are in conflict when presented to the stage 4 saliency map for delivery to the stage 5 cognitive neural system.
Goldberg has presented a lecture of vestibular anatomy for medical students that while introductory makes many points supported here. Figure 8.3.2-2 describes the anatomical orientation of the vestibular modalities in the human.

Whereas most investigators suggest each semi-circular canal is less than 360 degrees in total angle, Goldberg in later figures suggests each canal completes a full circle with the sensory neuron placed within the endoplasm and accessible to bidirectional motion of the endolymph. Additional documentation is needed in this area.

When discussing the connection between pointing of the eyes and the vestibular modality, Goldberg describes the pairing of and response of the the “vertical canals” as follows;

“Left anterior and right posterior canals (LARP): rotation in the vertical plane skewed 45° anteriorly to the left.”

“Right anterior and left posterior canals (RALP): rotation in the vertical plane skewed 45° anteriorly to the right.”

While pedagogically useful at an introductory level, this view is oversimplified. Combined with the statement that “the three semicircular canals lie in 3 orthogonal planes” implies that pairs of canals are merely operated in parallel. The conclusion can be drawn that these parallel arrangements provide a degree of redundancy in case of injury or disease. Experience with strap-down gyros of the type represented by the vestibular system, show that signals extracted from the different sources can be processed in much more sophisticated ways. Thus differential signals can be derived from each pair of cristae ampullae, thereby providing much more precise angular measurements in each of the three rotational vectors than obtainable by just using the sources associated with two nominally parallel canals.

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The Goldberg lecture points out that the signals generated within the vestibular modality are all analog (tonic) signals and not initially action potentials. The otolithic organs (saccule and utricle sensory neurons) propagate to the “Superior nucleus.”

As illustrated by Goldberg, the elements of the labyrinth, saccules and utricles are all connected to the eighth cranial nerve. Goldberg also defines the target areas for the neurons within this nerve.

Goldberg also develops the phenomenology relating the visual and vestibular modalities to each other. However, he does not provide significant information on the histology and physiology resulting in this phenomenology. He discusses the origin of nausea and vomiting as caused by conflicts between the vestibular modality and the visual modality.

In the 20th Century it was common to associate bending of all hair cells with neural stimulation rather than the current view that the auditory hair cells are stimulated by axial forces. See Section 8.3.1.xxx. At least some of the vestibular hair cells appear to be stimulated primarily by bending, those associated with the semicircular canals.

Noback has noted that the otoliths are embedded in a gelatinous mass (by definition a liquid crystalline material and not a fluid) labeled the endolymph. This is the same liquid crystalline material that is employed within the cochlear duct of the Organ of Corti of hearing.

8.3.2.2.1 Features of the endolymph as a liquid crystal

The term “gel” is the historical and common name for the scientifically defined liquid crystalline state of matter. These materials exhibit essentially zero structural rigidity at zero acoustic frequency and will take the shape of any container in which they are found, as would any liquid. However, when stimulated by a sudden impulse, they are known to “ring” at a high frequency, like any very structurally rigid material. The ringing frequently has a time constant expressed in seconds indicative of their high ratio of rigidity to attenuation. The endolymph is now generally recognized to be a liquid crystalline material.

When discussing the “optokinetic signal” from the semicircular canals, Goldberg notes,

“The vestibular system is imperfect
1. The cupula habituates in 5 seconds.
2. The brainstem and cerebellum extend this time to roughly 25 seconds, after which there is no further response to head acceleration.
3. The vestibular system is a poor transducer of very slow (<0.1Hz) rotation.”

Statements 1 and 3 are precisely as expected of a vestibular modality employing a liquid crystalline medium that exhibits very low structural rigidity at low acoustic frequencies (habituates in 5 seconds) but acts as a solid at higher frequencies (above a few Hertz rotational frequency).

8.3.2.2.2 The veracity of the Epley procedure of medicine

In his introductory pedagogical lecture, Goldberg notes a procedure used to treat “Benign positional vertigo: debris from the otoconia in the utricle float into the posterior canal, causing interference with cupula function, brought out by motion in the plane of the affected posterior canal. This can be treated by the Epley maneuver, that rotates the head to float the debris away.” The assumption underlying this statement and treatment is that the otoconia debris exhibits a significant difference in density from the endolymph (as generally required) and that the endolymph has a viscosity similar to that of water (which is contrary to the common wisdom). Goldberg has noted the endolymph is a gel and not a low viscosity liquid.

While the Epley procedure itself is benign, its effectiveness is difficult to demonstrate and it may fit more properly in the long list of “feel better” treatments continuing to be present in medical practice.

8.4 The chemoreceptor neurons of taste, smell and discomfort

Response of a medical doctor specializing in pain management to the reading of the draft material in sections 8.4, 8.5 & 8.6,

“My gut response: PHENOMENAL!!!
The concepts and the observation are truly astounding in their simplicity and almost intuitive basis once the numbers are put together. The fact that taste and smell can be saturated but rather quickly recover matches precisely with the manner in which coordinate bonds can be made and broken.

Chemoreception in its broadest sense involves the sensing of both external stimuli and internal stimuli. The internal chemoreceptors are focused in three regimes, those designed to sense the chemistry of the blood, the chemistry of the inhaled gases, and the chemistry of the ingested substances. The external chemoreceptors are focused in three regimes, those designed to sense distant stimuli and generally related to olfaction (smell), those designed to sense nearby chemical stimuli and generally related to gustation (taste), and a third category involving those designed to sense and react quickly to levels in the previous two channels that could cause damage to the organism (usually described as nocioreceptors).

This section, and Sections 8.5 & 8.6, will be limited to the external chemical sensory neurons associated with olfaction, gustation and pain due to chemical stimulation. The internal chemical sensory neurons, such as those associated with the enteric system, and with O2-level and CO2-level sensing, will be addressed superficially in Section 8.9.

Laffort has defined three modalities to the area of external chemoreception.

1. Olfaction or the sense of smell, characterized by a very acute ability to differentiate the most subtle molecular structures and to detect them at very low concentrations. It could be said that this is an analytical sense.
2. Gustation or the sense of taste, characterized by overall perception of four fundamental tastes; sweet, salty, acidic and bitter. It could be said that this in an integrative sense.
3. Common chemical sensitivity or trigeminal sensitivity (conveyed by the trigeminal nerve), characterized by perception of irritating, stinging and suffocating stimuli.

This last modality is frequently described as the nocent modality. It utilizes nocioreceptors that are frequently mixed in with the sensory neurons of the other modalities. Doty & Cometto-Muniz describe the capabilities of the chemical nocioreceptors embedded in the broader nocent modality and compare their performance with that of the olfactory receptors, Section 8.8.1. Their protocol was not based on any stated null hypothesis and did not include hydrochloric acid in the stimulant set.

This work will add a subdivision of olfaction to Laffort’s list; oskonaton, the detection of odorants by the vomeronasal facility originating in conspecifics (other animals of the same species). Figure 8.4.1 attempts to place these sensory modalities into context. While the first line of sensory modalities were well developed during the evolution of marine animals, the transition to a terrestrial environment expanded the requirements to sense the external environment, including the distant environments related to food acquisition as well as species identification. The modalities of gustation, olfaction and pheromone detection are shown stepwise to suggest their development (or expansion) over time. The development of the sensory receptors of these modalities occurred within the epidemis that already supported a variety of sensory neurons related to the nocent modality of somatosensing.

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While the majority of external sensory modalities involve sensing the location of a sensory signal location on the surface of the organism, or the direction to a remote source, the chemical modalities do not support such location capabilities. This difference will be found of considerable benefit to the research scientist attempting to understand the differences between stimulants affecting the chemical sensing modalities and those affecting the nocent modality of somatosensing.

A critical delineation is needed between the attractant and irritant roles supported by the chemicals affecting the chemical senses.

As part of their discussion, Doty & Cometto-Muniz (pg 982) did note the seminal work of von Skramlik in 1925. Skramlik noted the unique difference between the gustatory and olfactory modalities and the chemical portion of the nocent modality.

The gustatory and olfactory modalities do not track the sensing location within the oral and nasal cavities, whereas the nocent modality does track the sensing location. This feature provides a valuable criteria for determining what chemicals are effective within the gustatory and olfactory modalities and what chemicals are primarily irritants sensed by the nocent modality.

This criteria clearly determines that the inorganic (Bronsted) acids, and most other inorganic compounds, are primarily irritants to the epidermis and its specialized tissue, the mucosa.
Kobal et al.\textsuperscript{51}, among others, confirmed this distinction between olfaction and nociception in 1989. This distinction will be developed further in \textbf{Sections 8.6.6.2}.

It appears that attractants are primarily designed to indicate a source of food for foraging animals. The irritants appear designed to drive away foragers. In the case of the flowers and many plants, the attractants serve a second function; to attract pollen distributors.

Cagan & Kare noted in 1981\textsuperscript{52}, “The infrequency of evident scientific interest in and concern for taste and olfaction in recent years stands in striking contrast to the earlier appreciation of the importance of these senses.” Relative to research in the visual and auditory senses, the statement appears to remain true today.

Amoore described the scope of chemical sense research, with a focus on olfaction in 1970\textsuperscript{53} using the illustrative graphic, \textbf{Figure 8.4.1-2}. Unfortunately, the state of the art at that time did not provide an adequate null hypothesis and the biological sciences community did not explore the four pillars of the main span adequately.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure8.4.1-2.png}
\caption{Exploring the chemical senses—the Bay Bridge analogy. Many of the steps along this chain have not been explored in a structured and detailed manner. From Amoore, 1969.}
\end{figure}

This work will follow the definition of McClintock as it relates to the chemical sensing modalities\textsuperscript{54},

“Molecular biology is a thoroughly reductionist approach that seeks to understand the whole by completely understanding the component parts.”

However, it will not follow the guidance of Glendinning et al. in the first paragraph of Chapter 13 of that same text. The chemical sensing systems will be seen to employ a very limited set of transduction techniques, and only a small number of individual receptors supported by those techniques, followed by a combinatorial signal processing function resulting in a myriad of unique


Documenting the human sensations of smell and taste have been difficult because investigations have been largely limited to psychophysical experiments. Neurophysical data has been available primarily from lower species. Finger, Silver & Restrepo have edited a recent volume with a provocative title but virtually no information concerning the physiology of the olfactory and gustatory systems and only the most conceptual neurological material. At best, they provide a long list of genes where various investigators have “provided evidence of involvement in olfactory transduction (page 187).” The volume does not appear to have been edited critically for consistency. Their introduction (Chapter 1) makes a number of key assertions:

- “Most animals have chemoreceptors for monitoring internal as well as external chemical conditions.”
- “Humans, being air-breathing vertebrates, have a passageway connecting the nose and mouth.”
- “Our language does not always make a clear distinction between stimulation of the gustatory and the olfactory receptor cells.”
- “Taste is used colloquially to describe any chemical sensation produced by food in the mouth.”

Several expressions are shown in strikeout and call for explanation. Many aquatic air breathing vertebrates (Cetacea as an example) do not have a passageway connecting the nose and mouth. From a scientific perspective, sensation is a perception developed within the CNS. A sensation within the CNS is not directly associated exclusively with the insertion of food in the mouth. It may result from a chemical reaction within the oral cavity. It appears to also include an olfactory and frequently a somatosensory component. Taste is usually associated with both the gustatory modality and elements of the somatosensory modality (involving temperature, chemical overload, texture, etc.) Expanding, our language does not always distinguish between stimulation of the gustatory, olfactory and somatosensory receptor cells.

They went on:

- “Chemical stimuli play an important role in behaviors such as feeding, territorial recognition, and sexual or social activities.”
- “Thus, the diverse chemosensory functions all occur in a single cell in single cell animals.”
- “In metazoan forms, the different chemosensory functions are usually divided into distinct sensory modalities.”

The insertion of the phrase “in single cell animals” is justified here by their following sentence, where the word chemosensory has been inserted for clarity.

After noting, “All taxonomic groups of tetrapod vertebrates have at least two major divisions of the nasal chemosensory organs, the main olfactory system and the vomeronasal system,” and the paucity of data, Johnston has provided a chapter 5 exploring whether the human has a vomeronasal organ, without drawing a firm conclusion. “In humans, current evidence supports the existence of a pocket in the nasal cavity which is in a position where one would expect to see a vomeronasal organ if there were one. Anatomical evidence, however, does not show convincingly that this pocket has any sensory cells with axons, nor that any cells in this region make connection with the olfactory bulb or other part of the brain (page 121).” Personal experience would suggest otherwise. Schwanzel-Fukuda & Pfaff have explained the source of this controversy (Section 8.4.3.2.1). Takagi went so far as to illustrate the dual olfactory system of the monkey and other small mammals. Monti-Bloch et al. have provided a review of these organs showing the location of the vomeronasal organ in humans, its ontogeny, generator waveforms and some discussion of human pheromones.

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Doty edited a handbook of olfaction and gustation in 2003 that provides both academic and clinical material. It offers considerably more detailed information than Finger et al. It focuses on anatomy and the chemicals of olfaction but does not address the neurophysiology of olfaction or gustation at a significant level. Doty reviews many of the earlier theories of olfaction and gustation and generally finds them wanting. On the other hand, Doty does not converge on one specific theory or model that is able to describe chemical sensing. Doty also provides a Chapter 47 discussing the chemical sensing aspects of the somatosensory modality. Again, it does not converge on a most likely theory or model. Turin & Yoshii (page 276) provide a conventional and obviously inadequate definition of an odorant: “The general requirements for an odorant are that it should be volatile, hydrophobic, and have a molecular weight less than approximately 300 daltons.” Their subsequent paragraph is philosophical in character. This work will demonstrate; the odorant should be volatile (in order to reach the nasal tissue, by sufficiently soluble to dissolve in a water based mucosa, have a molecular weight less than approximately 300 daltons to be able to travel a significant distance in the air, and most importantly must contain one or more odorophores to which the target nasal tissue is sensitive. These odorophores typically involve an overlay group (defined below) with a specific distance between specific atomic species developed more clearly in the following sections 8.5 & 8.6 of this work.

Turin & Yoshii (page 280) suggest there are only two currently viable theories of olfaction, one based on molecular structure (odotopes) and one based on “vibration theory.” Neither is shown to be viable in the general case. The remainder of their chapter is very useful, especially the discussion of small differences between odorants and non-odorants. The hard molecular weight limit of “less than 300” is a useful criteria.

Based on the thinness of the database and the character of the sensory neurons of vision and hearing, the premises of this work can be stated as:

1. The sensory neurons of taste and smell, as well as the chemical sensing neurons of the somatosensory modality, while distinct types, follow the cytology and electrolytic circuitry of the visual and hearing sensory neurons.

2. The major difference between the sensory neurons of taste, smell and chemically induced pain compared to those of vision and hearing relate to the electrolytic structure in and around the fine dendritic structure of the cells of the cells.

3. The low energy levels related to taste and smell leads to the proposal that the taste and smell sensory neurons operate in the amplification mode similar to the hearing sensory neurons.

4. The absence of any reaction products following sensing leads to the proposal that the transduction process in taste and smell sensory neurons relies upon coordinate chemistry rather than reaction chemistry (valence or covalence chemistry).

5. The signal flow between the taste and smell sensory neurons and the CNS exhibits the same architecture as that of vision and hearing. The olfactory signal flow is similar to that of vision (independent of the spinal column). The gustatory signal flow is similar to that of hearing (signals proceed to the CNS via the lower brain stem).

This introductory material will not explore the somatosensory modality further. See Section 8.8 for more discussion of this modality.

The following material will demonstrate these postulates to the extent possible within the available database. It will demonstrate the likelihood that two sensory channels, that for the organic acids and that for acid chemicals (bitter in taste, pungent in smell) appear in both the oral and nasal cavities of mammals.

The expansion of the chemical realm considered important in chemical sensing to include coordinate bond chemistry as well as valence and covalent bond chemistry is the key to understanding the subject. This expansion includes the examination of so-called associated liquids, where a specific chemical is found mostly or exclusively in a coordinated bond state with the solvent, typically water. This designation applies to chemicals commonly present in solid, liquid and gaseous states at biological temperatures, such as the presence of hydrated sodium ions stimulating the Na-sensory path and the presence of hydrated hydrogen sulfide in stimulating both the picric-

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The path of gustation and the path of olfaction.

The alcohols also form associated liquids with water. However, the pure alcohols are considered tasteless in pure form and when mixed with water. The resulting coordinated structures do not stimulate any known sensory neuron receptors.

The interplay of the perceptions related to gustation and olfaction have not been clearly developed. While it is widely recognized that the perceptions developed within the olfactory modality play a major role in determining the overall perceived flavor of a food rather than just its perceived taste, the literature in this area is largely that of the social sciences and the food product development laboratory.

A challenge to science presented by the food packaging industry was noted in a recent Wall Street Journal review: “Wine Spectator Magazine recently included a description of an inexpensive wine as, Ripe black cherry, wild strawberry, chocolate liqueur and red licorice notes are underscore by graphite and spice accents in this light-bodied, tangy red. Floral finish.” As a group, these terms have no meaning within a scientific description of a flavor, taste or smell.

8.4.1 Brief summary of the literature & glossary EXPAND

A conference in 1971 among the leaders in chemical sensing research summarized the poor level of understanding of the mechanisms of taste and smell at that time. The roundtable discussion held at the end of the conference (pp 254-259) was quite revealing concerning the participants' perception of major improvements in understanding in the decades to follow. Henning (page 239) speculated on the general criteria for the receptor processes in gustation and olfaction at that time. Little confirmatory work has appeared supporting those speculations. Cagan (page 243) also provided some general speculation but did not support his propositions with vigor.

Teeter & Cagan have provided some interesting parameters relating to the operation of the physiology of the external chemical sensory neurons. Although they attempt to correlate these parameters with the conventional wisdom of the day, the parameters tell a quite different story when related to the Electrolytic Theory of the Neuron of this work. They discuss conceptually five different potential gated pore mechanisms without demonstrating, or documenting, the function of any of them.

Michael Mann, of the University of Nebraska Medical Center, has provided an on-line source of introductory information about taste and smell, but without any in-depth presentation of the mechanisms involved. It follows the conventional conceptual view that has evolved over many years. While his data is valuable, the framework developed here is quite different.

Shepherd published a book in 2012 attempting to provide an overview of the sensory mechanisms and information extraction engines associated with “flavor.” It was written for the popular press or as an initial introduction for biology students. Figure 8.4.1-3 shows his rendition of the major signaling channels and information extraction engines of the human. The labels will not all be defined here; most of the labels should be familiar to the reader of this work. They will be defined when addressed in later sections.

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Accompanying this flow diagram was a more structured block diagram shown in Figure 8.4.1-4. These two diagrams are generally compatible with this work but exhibit differences in the details (Ex., 1) under taste, umami is shown to be a composite of the salty, sour and sweet channels of human taste in this work and not a distinct sensory channel, 2) the complexity of the auditory modality and olfaction modality are not given adequate treatment in Shepherd's rendition).
Before continuing, the next section will introduce the alternate framework of this work.

8.4.1.1 A fundamental change in approach to external chemical sensing

The often repeated foundation statement by Morrison & Boyd⁶⁴, along with many others has been, "The basis of organic chemistry, is the structural theory." Structure has generally referred to how individual or groups of atoms (or ligands) are combined into larger groups (or moieties). This process has generally related to the valence electrons of the various ligands and moieties. This framework does not serve the subject of external chemical sensing well. An alternate framework is more appropriate.

The alternate framework involves the lesser known coordinate chemistry (rather than valence and

covalent chemistry) of specific “orbitals” that are present in a synthetic or overlay structure within a given moiety that is unrelated to the more obvious valence-based chemical structure. The orbitals of coordinate chemistry of interest in external chemical sensing are illustrated in Figure 8.4.1-5.

Row B shows the conventional representations of the benzene ring flanking the configuration of interest in chemical sensing; the ring exhibits a set of unpaired electrons that can be shared through hydrogen bonding with other structures.

Row A shows a similar representation of an anion of cyclopentadienyl exhibiting a similar set of unpaired electrons that can be shared.

Row C shows a similar representation of a cation of cycloheptatrienyl (the tropylium ion) exhibiting a similar set of unpaired electrons that can be shared.

In most of the above cases the unpaired set of electrons are assumed to be located at the geometric center of the structure. This assumption is particularly important in chemical sensing as developed below with regard to the dual antiparallel coordinate bond (DACB) of chemical sensing (Section 8.4.8 for a preview and Sections 8.5 and 8.6 for detailed development). The above structures all satisfy Hückel’s Rule discussed in more detail in Section 8.4.15.2.

There is an additional ring structure of interest in chemical sensing, the macrocyclic ring with carbon numbers rising above 20. Their role appears to be primarily among the pheromones of oskonation (Section 8.6.11). Understanding their participation in external chemical sensing may also require application of Hückel’s Rule.

Row D shows the double bond and triple bond of conventional valence chemistry and their representation of interest in coordinate chemistry. In the general case, the unpaired electrons are assumed to occupy a region centered between the two atoms.

Rows E and F show the notation describing the unpaired electrons of nitrogen, oxygen, phosphorus and sulfur. These unpaired electrons are present even in the case of these atoms being valence bonded to other entities. The locus of the unpaired electrons is assumed to be at the center of the atom.

The radius of the “cloud” representing the location of the unpaired electrons is critically important in determining the length of the hydrogen bonds in which they participate. These radii are specific to the particular atomic structure.

All of the above structures play a major role in the coordinate chemistry of external chemical sensing (with the exception of phosphorous playing a minor or insignificant role). The role is totally independent of the concurrent valence chemistry of these entities.

It is the distance (the d-value) in 3D space between any pair of these orbitals when present in a given molecule that determines how they are perceived within the gustatory, olfactory or oskonatory modalities of a biological subject. In the context of the hypothesis and corollaries of this work, each pair of orbitals can be considered to be connected by an “overlay ligand” within a moiety that need not have any relationship to the ligand forms and rules of conventional valence chemistry.

The structural path between any pair of orbitals will be defined as the overlay group in this
work to differentiate that structure from the conventional description of chemical groups forming the molecule.

8.4.1.2 Recent chemoreception literature

Squire et al. have discussed the information extracted by the gustatory modality. This information related to a chemical stimuli involves quality, intensity and hedonic value (where hedonic value refers to the perceived pleasantness or unpleasantness of a taste sensation). They suggest the hedonic value is based on genetic, physiologic and experiential factors. The last factor can be heavily culturally-based. They also note the three factors are interrelated in developing a perceived flavor.

Moncrieff provided a broad text on these sensory modalities from the human perspective in 196765. His chapters 4 (Olfaction) and 5 (Gustation) followed by chapters 11 (taste and constitution) and 15 (flavour and food) provide a broad outline of the problem. Dodd & Squirrell provided a considerable amount of histological data and some performance data related to olfaction in 198066. Shepherd provided an overview of the problem in 198867.

Lawless & Lee68 attempted to describe the scheme leading to the concept of flavor as shown in Figure 8.4.1-6. The concept, based on sensations and not histology provides independent “irritation” channels that could be associated with putative nociceptors. It could also be expanded to include pungency and astringent sensory channels within the nociceptors. Hofmann et al. have provided some cursory conceptual material related to these modalities69. At the histological level, nociceptors remain largely notional although clinical and physiological data is accumulating (Section 8.8).

References:


Noble has presented a broader description of flavor and uses the term flavonoid. He considers perceived “flavor” to consist of taste, smell and nocent and/or tactile components. He discusses astringency in some detail beginning with the phenol based flavonoid, flavan-3-ol in its monomer, dimer and trimer forms.

This work will only consider “flavor” as a perception based on the combined sensations of taste, smell, texture, temperature and occasionally pain as presented to the saliency map. Teranishi has noted, “We can not adequately express, define, or explain our taste and smell sensations.” After alluding to sight and hearing, he goes on, “. . .but we cannot adequately define flavor either qualitatively or quantitatively.”

It is extremely difficult to definitively separate the sensations generated by the gustatory and olfactory modalities. Lim & Lawless have provided an interesting study of the qualitative difference in sensations for the same chemicals depending on whether the nasal passages are closed off.

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Such differences may reduce the accuracy of much of the data in the journal literature.

Besides the four historical primary tastes, and possibly umami, the terms pungency (associated with peppers), a cooling sensation, a tingling sensation, and an astringent sensation may be included in the description of a flavor. Whether these sensations are the result of the gustatory sensory channels or mechanoreceptor channels is frequently discussed. See Section 8.6.11.

The field of flavor science has mushroomed since the 1980’s, with many important texts and papers supporting the commercial preparation and storage of foods. The contribution of these works to the understanding of the transduction of stimulants ultimately into sensations has been largely lacking in these works.

Sensing associated with taste and smell has been under intense investigation ever since Axel & Buck were awarded a Nobel Prize in 2004 for their work reported in 1991\(^{73}\). The real breakthroughs came beginning in 1995, particularly with the autoradiographic work of the Bret Johnson & Michele Leon team at the University of California, Irvine (discussed in Section 8.6.3).

The taste and smell modalities are known to involve three distinct regions, the olfactory epithelium in the upper nasal cavities, the vomeronasal organ in the lower nasal cavities and the gustatory surfaces of the oral cavity.

Hudspeth & Tanaka provided a brief review that only touched on the chemical senses, taste and olfaction\(^{74}\). They note the classical concept suggests the taste sensations of sweetness, sourness, saltyness and bitternes. They quickly note the sensitivity of the human system to fat as well. Many alternates to this brief listing have been proposed. Nearly a century ago, Ikeda suggested an additional axis to the taste map involving glutamate (ormore specifically monosodium glutamate)\(^{75}\). He named the sensation associated with glutamate umami. Sugimoto & Ninomiya have provided a review of more recent work related to umami\(^{76}\). Axel & Buck suggested a very large number of independent olfactory sensortypes. They inferred several relationships between the olfactory system and over 1000 genes (see Section 8.6.3.1.2 for her recent change in focus to a combinatorial approach reducing the number of OR’s required in olfaction).

Pfaffman et al. showed that a single neural channel exhibits responses from a wide variety of taste stimuli\(^{77}\). The effects were compared between a variety of rodents. An important confirmation involved the sensitivity to both chloride ion and quinine among other substances. The simplest conclusion was that the chloride ion concentration was not in a class by itself. In fact they found no correlation between the response to NaCl and NH₄Cl. They also noted a correlation between fructose and both NaCl and NH₄Cl in the squirrel monkey but not the hamster.

Pfaffman et al. reported relative sweetness for the sugars at equal molar concentrations in the following order; sucrose \(>\) fructose \(>\) maltose \(>\) lactose \(>\) dextrose \(>\) galactose. Note that sucrose, maltose and lactose are disaccharides before their hydrolysis. Before hydrolysis, all are reducing sugars except sucrose. There was no indication that the subject could identify the specific sugars listed in this sequence.

It is a major protocol error in taste research to use equal molarities of various mono and multisaccharides without recognizing the number of glycophore present in each of these stimulants and adjusting their molarities accordingly. Except for its availability in the food industry, the use of sucrose, instead of glucose, as a standard in taste research is a most unfortunate choice.

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\(^{76}\)Sugimoto, K. & Ninomiya, Y. (2005) Introductory remarks on umami research: candidate receptors and signal transduction mechanisms on umami Chem Senses vol 30(suppl 1) pp i21-i22

The situation at different concentrations is more complicated. For NaCl, it is reported to taste sweet at very low concentrations, then salty sweet, and then pure salty at a concentration of 0.2 M. “KCl is reported as sweet, bitter, bitter-salty and then salty, bitter and sour as concentrations increases.” They use a term “side bands” but do not define it explicitly.

Pfaffman et al. also noted the nominal 7-day turnover of sense cells in the taste buds.

The responses in the squirrel monkey were subject to prior adaptation, or pre-adaptation, commonly labeled priming in the psychological literature.

Kaissling & Thorson provided Figure 8.4.1-7 describing the olfactory sensillum of a moth as they understood it. Their early paper is important. It asserts that one molecule of bombykol (a pheromone of the moth, Bombyx mori, is sufficient to cause a perceived neural response in that species. They also provided a passive electrical circuit overlay to this figure.

Squire et al. (2003, pg 613) have provided a similar image but stress the difference in color/contrast between the individual cells within a given taste bud. They also note the typical bud contains not a few, but typically 50-150 chemoreceptor neurons.

Shepherd has provided a recent paper describing the olfactory process in the same context as will be developed in this work. He describes the sensory signals as being processed initially in the olfactory bulb, being passed through the thalamus, and generating complex signals (involving the high level concept of flavors) associated with the correlation and interpretation processes of stage 4 and 5. Unfortunately, his paper does not develop any theory of the transduction process at the detailed level in olfaction.

Shepherd has introduced a postulate that requires additional discussion. He melds the perception of flavor with the ability of an animal to enunciate that perception. From that perspective, he implies that the human species, because it is most highly developed in the enunciation area, necessarily has the most highly developed flavor perception (2005, pg i5). This position appears undefendable in the context of this work. He repeated it in a 2012 text. See Section 8.6.7.6.

Stevenson has recently published a book on flavor that is from the perspective of the food industry. His chapter 2 does recognize and discuss the relationship of flavor relative to taste, smell and nocent receptor channels but only in a global context. In his chapter 1, he addresses the same subjects as in chapter 2 and does note the role of the retronasal pathway from the mouth. He does not discuss

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the chemistry of the detectable volatile chemicals. The listing is largely without merit from a chemical viewpoint as discussed briefly in Section 8.4.1.3.2.

Stevenson did attempt to define a theory of flavor (chapter 6) based on his superficial study of the empirical record that he documented in his book. He did provide some useful categorization of the hedonic aspects of flavor (chapter 5). Ancillary to his main subject, he did provide data on the energy content of various fundamental food elements; fats at 38 KJ/g, carbohydrates and proteins (both at 17 KJ/g) and ethanol at 30 KJ/g. He notes ethanol is not normally consumed for its energy content. Among the carbohydrates, he identifies the simple (various sugars) and the complex (primarily the starches).

He did note the general requirement for multiple odorophores to generate a precise perception of a specific odor.

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Multi-dimensional scaling (MDS) has been applied to taste. Hellekant et al. have provided a broad paper developing a multi-dimensional space for taste in 20 rhesus monkeys using 26 stimulants including those related to umami. They also provide an unusual cluster analysis that relates to the individual subjects rather than a broad list of chemicals.

They used the program, SYSTAT vers 5.2 for Macintosh to present their cluster and MDS analyses. It begins with data in a spreadsheet. The cluster and MDS programs used to prepare their spreadsheets were not specified.

Rather than dissolve their stimulants in distilled water, they used an artificial saliva (which contained many of their stimuli in small amounts). Their figures 3 (related to the anterior tongue) & 8 (related to the posterior tongue) show the variation in sensitivity among their subjects to their chemicals. The need for large statistical samples in gustatory sensor research is obvious. Selected samples can provide very erroneous insights. Sensitivity was described in terms of the number of action potentials within five seconds over a given nerve. It is difficult to ascertain any average subject from figure 8. Figure 3 suggests distinctly different sensitivity groups within their subjects. These figures were ignored in the overall paper. They discuss the performance of monkey compared to humans and chimpanzee but not to orangutan. See Section 8.6 for further discussion.

The task of this section is to put this material into the framework of the overall neural system.

Johnson & Leon have provided a summary of their extensive experimental work that is also consistent with this work.

The loss of the perception of taste (ageusic) and the loss of the perception of smell (anosmia) are ancient ones. However, they have not been studied comprehensively. Henkin has written extensively on the problems. Farbman has also written in generalities on the subject, including some medical correlations. Personal experience suggests a deficiency in the metal complexes (particularly involving zinc) lead to anosmia. Magnesium may also play a role in olfaction. Turin has explored the role of zinc in olfaction in developing his inelastic electron tunneling hypothesis. Physical trauma to the head frequently causes shearing of the fasciculated neurons passing through the cribriform.

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DeSimone discussed the difficulty of assigning a single transduction mechanism to the chemostimulus-sensitive transduction neurons. Achieving sensitivity to non-polar and both positively and negatively charged polar materials in one sensory neuron configuration is difficult and probably impossible. DeSimone discusses these problems in the context of his understanding of the applicable 1981 technology. The neural system appears to take a different path. The following discussion will develop different sensory neuron configurations to account for the different character of the stimuli based on the available laboratory evidence. Farbman discusses the individually identified chemosensitive sensory neurons of the very simple nematode, Caenorhabditis elegans as an introduction to the sensory neurons of other species. He cites the report of Sengupta & Carlson (Chapter 3 of the same work). The two groups agree that individual chemosensitive neurons of the worm respond to a range of similar chemical stimuli. They report a large group of genes (on the order of 550) involved in encoding specific sensory neurons with a much smaller set of morphologically identifiable sensory neurons. They do not discuss the transduction mechanism per se. They do note, “Genetic and structural data implicate the cilia (microvilli) as the location of the primary signal transduction events in sensory signaling.” Farbman describes only four distinct sensory neurons behind the chemosensory pore of C. elegans optimally sensing 11 different substances.

Doty et al. have released a second edition of the Handbook of Olfaction and Gustation. It is nearly devoid of physiological data and lacks any discussion of the actual signaling occurring within the chemical sensing modalities. The signaling pathways are limited to simple block diagrams and the coding discussion is based on conventional psychophysical observations (not the coding of the information within the neural system. Under the title, Structure-Odor relationships, Turin & Yoshii introduce the subtitle, “The puzzle of odorant intensity” (page 289).

8.4.1.2.1 Recent advances in fMRI—xxx
Shepherd has recently reviewed the state of the art in fMRI and MRI based on work carried out at Yale University. xxx add from 2012 book, pgs 76-77.

8.4.1.2.2 Recent advances in atomic force microscopy (AFM)—where are the pores?
The atomic force microscope (AFM) appeared on the biological scene during the 1990’s but its performance was limited and data gathering was slow. The recent introduction of the Fast-AFM technique has changed its range of application significantly.

Figure 8.4.1-8 provides a framework for discussing the capabilities of the Fast-AFM technique.

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The resolutions being achieved in the laboratory are on the order of 1-5 nm at frame capture rates on the order of 0.01 seconds. These parameters should allow the recording of any pores or gates in the external lemma of a neuron without great difficulty. However, no such observations and reports have been found in the neuroscience literature to date, ca. October, 2015.

The precision and the frame rate of current Fast-AFM techniques appear to be adequate to reflect the opening and closing of “sodium ion channels” and other conceptual descriptions related to neural processes. To date, no such verification of these techniques has occurred. Slade should be contacted if an investigator is interested in documenting a pore or gate as proposed in many studies other than this work.

8.4.1.2.3 The BIG QUESTION, what is the physical shape of a molecule in the biological environment?

The exact dimensions of a molecule are critically important to the understanding of the transduction process in chemical sensing, particularly gustation, olfaction and oskation. It also offers additional details concerning documentation of the spectral performance of the visual modality chromophores (specifically 2nd order values beyond the available 1st order values developed in this theory before 2016.

The widespread growth in computer capability has resulted in the development of ab initio molecular modeling and a wider use of x-ray crystallography. Unfortunately, the documentation associated with the results of this usage in molecular modeling has not kept up with rational requirements. Currently, for molecules that have been investigated by x-ray crystallography, that technique offers much superior and precise values for the parameters of a specific molecule. Unfortunately, x-ray crystallography requires a much higher level of computational sophistication and care in experimental protocol development than does molecular modeling.

Several databases have arisen to accumulate the results of molecular modeling. These files are seldom well documented; they do not specify the methodology used in the computation and frequently rely upon a two dimensional model based upon questionable chemical bond lengths, angles, etc. that are seldom consistent.

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

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

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

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

The XYZ file format most frequently used with J mol files is designed to accommodate a number of variants as defined by the Jmol.org. A major problem arises when incomplete data sets from undefined sources are incorporated into the database without significant curation. See Section 8.6.1.6.3 for a broader discussion on this situation.

In the immediate future, the molecular parameters of a given molecule (particularly their r-value) are best determined by x-ray crystallography. Unfortunately, only a few molecules of interest in chemical sensing have been studied to date. As a result, the best available molecular parameters from molecular modeling must of necessity be used since they are at least available. These best available parameters can only provide a relative set of d-values.

### 8.4.1.3 The problem of defining terms

In 2008, Erickson prepared a review of the gustatory research field spanning his long career. He complained loudly about the lax scientific approach taken in this field, a subject he has addressed many times. He was most concerned about the lack of definitions related to the “basic tastes.” He notes specifically the lack of clear definitions of the terms sweet, sour, salty, bitter etc. After presenting a 17 page paper followed by 16 pages of critique by 18 senior members of the community and a 9 page response, the community remained without a set of definitions of these terms. It is clear that the basic problem is the origination of the scientific concepts of taste in the world of human psychophysics and little actual human electrophysiology related to that world. Virtually all of the electrophysiology is on lower mammals, particularly rats.

Erickson can be easily criticized for raising a set of fundamental philosophical questions related to science in general and a lack of a set of definitions in particular. However, in doing so, he owes his audience his best shot at providing a framework for resolving most of those problems. He did not do that.

While Erickson makes many strong points that should be considered by any young researcher entering the field, he does not converge on a solution to these problems. Nor does he provide a set of working definitions for the parameters of gustation or olfaction.

The distinction between bitter and sour is often poor. In this work, a stimulant is perceived as sour if it contains an organic acid ligand (a diol with only one carbon between the two orbital oxygen atoms. It is only reported as bitter if it incorporates three carbons between the oxygen and hydroxyl group of a diol ligand.

Many have noted the ambiguity associated with the terms basic tastes and primary tastes in the taste literature (Breslin, page 429). The literature is not clear when the terms are applied to one or more stimuli (stage 0), when they are applied to a sensory channel (stage 1), or when they are applied to a perceived condition (stage 5). Taste is primarily a (stage 5) perception based on

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A major problem in olfactory research is the significant separation between the term aromatic as used in perfumery and general language, and the term aromatic as it is now used in organic chemistry. In perfumery, the term denotes a sensation while in chemistry, it is a chemical containing a benzene ring (with its \( \pi \)-cloud of electrons).

### 8.4.1.3.1 Subordinate components of a sensory stimulation?

Because of the interconnections between the nasal and oral cavities, a perceived flavor can be caused by the interaction of a perceived taste and a perceived odor. These perceptions can in turn be caused by the application of multiple tastants and multiple odorants being applied to the sensory channels of the organism. Each tastant molecule can actually contain multiple gustaphores, as can each odorant molecule exhibit multiple odorophores. The gustaphores, and possibly some as yet unidentified odorophores, can exist in one of two forms. The 2-point form describes the number of hydrogen bonds shared between each “regular” gustaphore or odorophore and the corresponding gustatory receptor (GR) or olfactory receptor (OR). As will be seen later, the distance between the two hydrogen bonds of the 2-point binding (the d-value) determines what gustaphore(s) or odorophore(s) binds with which of the GRs or ORs. The 3-point form describes the character of a “super” gustaphore, and potentially a “super” odorophore that binds to its respective receptor at two points but in addition, influences the electrostatic field of the receptor via a third point of association (not necessarily involving a bond). In both cases, the primary 2-point binding, applies a potential to the receptor associated with the stage 1 sensory neuron that causes a different net potential to be applied to the intensity meter that is different from the quiescent potential associated with the receptor.

The d-value defined above determines which channel of the multiple “place” channels is called upon to deliver the potential information to the Central Nervous System via the stage 2 signal processing engines. Figure 8.4.1-9 illustrates these relationships. The figure specifically differentiates between a perceived flavor and a perceived irritant. Irritants affect the nociceptors of the neural system rather than the chemical sensory modalities. This differentiation is in agreement with the terminology of Bryant & Silver\(^\text{93}\) although not necessarily with their overall thesis. They appear to treat all olfactory stimulants (including the alcohols and organic acids) as irritants whereas most investigators propose irritants only affect the nociceptor system.

This work separates the chemical sensory channels (flavor related) from the nociceptor, temperature and somatosensory channels. These latter sensory channels may contribute to the overall experience of ingesting food but they do not contribute to the perceived flavor of that food. Unfortunately, the long employed reference stimulant HCl falls into the class of inorganic acid irritants rather than gustaphores. This work also treats the salts of the alkali earths as astringents rather than natrophores.

As shown in the figure, a perceived taste or a perceived odor can be generated by \( m \) out of a potential \( n \) stimulants. Each stimulant is a specific molecular form. Furthermore, each of these stimulants can be created from \( m \) out of \( n \) potential ligands (–phores). In the simpler cases, these ligands are represented by well recognized functional groups of conventional chemistry. However, the groups do not participate in valence or covalent bonding. All bonding related to gustation and olfaction involve coordinate bonds. These coordinate bonds are formed in addition to any valence or covalent bonds already present in the stimulant or receptor molecules.

The above description should demonstrate that the idea of using mono-molecular odorants in laboratory investigations is not generally the appropriate protocol. It is important to employ mono-molecules containing only a single odorophore. Mono-sodium glutamate is the classic example of a mono molecule consisting of three distinct odorophores.

fiber codes recently, but apparently without a clear model of the olfactory modality in mind. His figure 9.9 is clear and compatible with this work, but the text and caption are less definitive. A question yet to be resolved precisely is whether the various olfactory channel receptors overlap to the degree that a specific odorophore can excite multiple signaling channels at the output of stage 1. He ends by offering "a new concept," cross-label coding. In developing that concept, he notes the different molecular features of a pheromone are encoded through interactions within and between the two to four glomeruli that comprise the MGC in moths (i.e., each pheromone contains multiple distinct odorophores). He also asserts that most moth "pheromones" are actually mixtures of two distinct molecules, A & B (pheromones or odorants). After further discussion (and many citations), he established there are different signals on the stage 1 output labeled lines compared to the signals on the stage 2 output labeled lines (after the glomeruli). He then brings the term odotopes into the discussion without definition and proceeds to suggest the glomeruli perform parallel distributed processing that may involve some stage 1 signal differencing, in order to arrive at a combinatorial code for a specific pheromone or mix of pheromones. See Section 8.6.7.

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The term pheromone is used to identify a specific type of odorant which is secreted by an individual organism and received by a second individual of the same species, in which they cause a specific reaction. To be called a pheromone, the point of reception is usually in an auxiliary olfactory sensory area known as the (stage 1) vomeronasal area. However, it should be noted that it may be found within the normal olfactory sensory area, and that animals of another species may sense this pheromone as a normal odorant generating no unique response. No matter what area they stimulate, a pheromone, the stage 1 sensory area employs a distinct set of olfactory receptors associated with a distinct set of "place" labeled channels proceeding to a separate stage 2 signal processing area before propagation to the higher engines of the CNS. The framework defined above varies slightly, and is more specific, than the earlier description of the pheromone/vomeronasal system by xxx in Finger et al. of 2000. XXX did not provide for multiple

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possible odorophores within his individual pheromone molecule.

### 8.4.1.3.2 The perceived flavor, a mixture of gustation and olfaction

When presented via the saliency map, the elements of gustation and olfaction, sometimes accompanied by the perceptions of texture, can be perceived as a unitary perception, described generally as flavor.

The volatiles involved in olfaction are presented in two ways. They can be sniffed through the nostrils (orthonasal olfaction), or, when food containing volatiles are chewed and swallowed, volatiles can be forced up behind the palate into the nasal cavity from the back (retronasal olfaction). Orthonasal olfaction is commonly associated with “smell” alone. Retronasal olfaction is more difficult to isolate and is more frequently considered an integral element of “flavor.”

The Klee team at the University of Florida have been studying the steps necessary to bring back the total flavor of tomatoes basically lost during the 1970’s effort to develop the optimal hybrid tomato. Their extensive investigations involving the statistics of the social sciences begins with the frequently caveat, “Furthermore, the chemical composition of a food in itself tells us very little about whether or not that food will be liked. Clearly, alternative approaches are needed to elucidate flavor chemistry.” In expanding on this situation, they note the chemical structures of their compounds do not relate directly to whether they are gustaphore or odorophores or not. They began by investigating 68 chemicals before reducing their candidate chemicals that they investigated or knew were present in their data set to 28, Table 1. They did not organize these chemicals into any framework that might identify them as gustaphores, odorophores or agonists/antagonists to either of these gustaphores. One of their major findings was, “This result indicates that volatiles previously predicted to be the most important contributors to tomato flavor based on odor units have no significant impact on consumer liking.” Their concluding remark showed they had not achieved their goal, “Our data illustrate the challenge of understanding flavor, and consumer preferences in particular, in a natural product.” “Previous concepts of the most important volatile contributors to human food preferences based on odor units must be reevaluated.” In an early 2013 paper, they identified six stimulants as contributing to the desirable flavor of the tomato. At least two of these, geranial and methylsalicylate, will be shown to be odorophores of general interest in Section 8.6. Most of their candidates are not normally related to the desirable odorophores found in foods or flowers. In a second 2013 paper, they claim they have identified at least six volatiles involved in olfaction (odorants) related to the tomato that contribute to the perceived taste of the tomato. But their listing is a mixture, including one sugar and at least on likely odorant, geranial. The value of these papers can only be determined after the description of the olfactory modality in Section 8.6 is completed. That analysis will determine the odorophores present in the stimulants they have annotated and show it is not the commonly identified chemical moieties that underly perceived smell and/or flavor but very specific structural ligands frequently crossing the boundaries between conventional moieties.

Stevenson has addressed the characteristic food flavors based on their major chemical group (page 8). This listing is superficial and should not be relied upon. As an example, he describes the alcohols as a group, with menthol as an example, as exhibiting the flavor of peppermint. Clearly, no chemist would describe the alcohols as perceived as having the flavor of peppermint and just as clearly, menthol is not a simple alcohol it is a phenol. Attempting to provide a corrected version of Stevenson’s Table 1.1 is a major undertaking at the academic level and scope of this work. Suffice to say the alcohols can be considered to start with the saturated alcohols (that all have a slightly dulcal, or sweet, character due to their hydration and formation of an azeotrope), proceed to the unsaturated alcohols that can have virtually any perceived odor depending on the presence of double bonds in addition to the hydroxyl group, and then proceeding to the very large family of aromatic alcohols known as the phenols in their simplest form. His suggestion that all esters taste like banana based on his example of isoamyl acetate cannot be taken seriously, etc. His approach does not recognize the critically important d-value of the various constituents of the “essential oil of peppermint.” Similarly, he chooses the (five-sided) gamma decalactone as his example for

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a very large group of 3, 4, 5, 6 & 7 sided ring structures with a variety of side-chains containing an unspecified number of carbon atoms, double bonds and/or orbitals. [xxx see Fulton Stevenson09pg8.wpg for markup of his page 8]

In chapter 6, Stevenson does attempt to describe a theory of flavour based on his “functional approach.” He notes the separate psychological perspective and the biological perspective. Under each, he discusses the first aspect as the locating, identifying and selecting of food and the second aspect as the process of “harm detection in the mouth.” He discusses the second aspect using the same subtitles as the first. The overall discussion is highly subjective.

8.4.1.3.3 Is the bitter tasting CaCl₂ a salt from the gustatory perspective?

The definition of a “salty” flavor obscures a major problem in gustation that involves the solvation of inorganic “salts.” The problem also occurs in olfaction where the solvation of various inorganic gases are involved. Salt is a very ancient term used in many languages around the world to define the common salt, NaCl. However, the technical community defines salt as the residue of a reaction between an acid and a base. By this definition, CaCl₂ and MgCl₂ are salts, yet it is generally recognized they taste bitter, more like quinone than table salt.

This work will develop the fact the archaic name “salty” as used in gustation really applies to the sensation resulting to stimulation by the complex Na⁺(H₂O)ₙ, where n is typically six. This is the gustaphore that will be described in this work as a “natrophore.” The sodium ion carries a plus one valence and is typically shown in column 1a of the periodic table. The critical aspects of this structure when it acts as a gustatory stimulant are the distance in Angstrom between the pairs of oxygen atoms complexed to the sodium ion, and the ability of these oxygen atoms to coordination bond to the sensory receptors.

The salts of CaCl₂ and MgCl₂ are technically salts. Their cations typically carry a plus two valence and are typically shown in column 2a of the periodic table. However, when placed in solution, the cations can form a variety of complexes with the water through coordinate bonding. Most commonly, the magnesium atom is surrounded by six oxygen atoms (Mg[OH₂]₆). The critical aspects of these structures when they act as gustatory stimulants are the distances between the Magnesium ion and the coordinate bonded oxygen (2.07 Angstrom), and the pairs of oxygen atoms (2.9 Angstrom, the oxygen atoms are in contact with each other) complexed to the cations of these salts, and the ability of these oxygen atoms to coordination bond to the sensory receptors. These distances are different from those of table salt and result in the bitterness of these chemicals. Their bitter taste confirms their classification as picrophores, rather than natrophores. See Section 8.5.4.6 for more details.

Katz et al. have reported on the coordination chemistry of the calcium, magnesium beryllium and zinc ions.

“Salty” is an archaic term that is misleading and should be discarded from the technical literature of academia and the food industries. It is not used in this work, except in quotations from old literature.

8.4.1.4 Brief Glossary

The following definitions of these gustatory/olfactory terms are provided only for discussion purposes by an outsider. They are subject to continual review and revision. This section will be dissolved in favor of separate glossaries for gustation (Section 8.5.xxx) and olfaction (Section 8.6.xxx) as the work matures.

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[http://pubs.acs.org/doi/abs/10.1021/ja953943j](http://pubs.acs.org/doi/abs/10.1021/ja953943j)

Basic tastes doctrine - A loosely defined proposal dating from the early 1900's that the gustatory modality can only perceive a limited set of independent or "basic" tastes.

Basic tastes - (ne primary tastes) The major groupings of perceptual responses to human psychophysical taste studies as defined by multidimensional analyses of large scale studies involving the widest possible range of stimulants and subjects, and providing adequate statistical precision. Based on the number of basic functions resulting from these studies, the basic taste space exhibits three orthogonal dimensions suggesting these dimensions are presented to the cognitive functions of the brain as independent parameters and the pattern of these parameters is used to define specific tastes based on learning (including some pre-wired memory in infants). By considering the basic tastes as limits of the multidimensional taste space, all tastes can be represented within this space.

Benzene - used as a suffix to describe a benzene ring combined with and any other moiety.

Pheny l- used as a prefix to describe any benzene ring of the form C₆H₅ combined by only one bond with another single moiety.

Taste - (noun) A semantic descriptor of a perceived sensation derived principally from the gustatory modality.

Sweet - A basic taste perception closely associated with the quest for food and commonly associated with a wide range of sugars and sugar like substances.

Sour - A basic taste perception closely associated with the desire to avoid ingestion of toxic substances and commonly associated with a range of acidic chemicals.

Salty - A basic taste perception closely associated with the desire to maintain an appropriate homeostatic condition with respect to the salinity of the fluids of the body, and necessarily associated with the fundamental saline solution of biology.

Bitter - A basic taste perception closely associated with limiting the ingestion of a variety of complex chemicals that are not easily processed by the digestive system.

The correlation between these perceptual responses and the electrophysiological signals emanating from individual sensory neurons has been demonstrated when the neurons have been stimulated by the principle chemicals associated with each of these perceived classes.

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A variety of terms appear in the olfactory and gustatory literature that are not common to most of the neural literature. Some of these are described here. For a more extensive glossary, see the online glossary, http://neuronresearch.net/glossary.pdf

Ab initio - From the beginning.

Ageusic - Lacking a sense of taste.

Aliphatic compounds – Molecules containing hydrogen and carbon not in aromatic rings, although they may contain alicylic (non-aromatic) rings.

Allosteric – of, relating to, or being a change in the shape and activity of a protein (as an enzyme) that results from combination with another substance at a point other than the chemically active site.

Amiloride - A potassium-sparing organic diuretic (mol wt. = 229.6) used in the management of hypertension and congestive heart failure.

Ampholytes - Molecules that exist in solution partly as neutral molecules and partly as positive and negative ions.
**Anomeric carbon** - (or anomeric center)-

1. A carbon atom attached to two oxygen atoms by single bonds. Typically found in cyclic monosaccharides.

2. An anomeric carbon is the new stereo-center created in forming the cyclic structure of a monosaccharide.

3. The reducing carbon of a sugar; C-1 of an aldose, C-2 of a 2-ketose.

4. An example of an anomeric carbon is that carbon in a monosaccharide (like glucose) about which rotation occurs. The anomeric carbon can be determined by the carbon (C) attached to two oxygen (O) atoms joined by single bonds. This rotation brings about two distinct configurations, α and β -anomers. Carbohydrates can then change spontaneously between the α and β configurations: a process known as mutarotation.

**Anosmic** - Lacking a sense of smell. Specific anosmia, lacking sensitivity to a specific stimulant.

**Apoptosis** - The death of a cell due to internal mechanisms and events. "Cell death from within." See also necrosis.

**Chorda tympani** - A part of one of three cranial nerves, a branch of the facial nerve (the seventh cranial nerve) that serves the taste buds in the front of the tongue, runs through the middle ear, and carries taste messages to the brain. It branches from the facial nerve inside the facial canal, just before the facial nerve exits the skull via the stylomastoid foramen.

**Confocal microscopy** - The technique of using a pinhole aperture in the return path (and often in the illumination path as well) of the microscope to limit the field of view in both depth and cross-section. Important in scattered light rejection. The pinhole in the return path is frequently called a "lyot stop in optics texts. Scanning of the restricted field is frequently employed to recover a useful field of view.

**CLSM** - Confocal laser-scanning microscopy.

**Dipolar ion** - A species bearing no net charge but exhibiting a large dipole or multi-pole moment. A dipolar ion is typically a super-polar molecule surrounded by an intense electrostatic field.

**Dipole electrostatic Potential** - (DEP) The electrostatic potential along the major electrostatic axis of the molecule. See also MEP.

**Equatorial** - (requires expansion) Used to describe atoms of a ring structure lying in the plane of the ring. Now subdivided into three clearer definitions with respect to their neighbors; equatorial in planar rings and equatorial-trans- or equatorial-cis- in puckered rings.

**Fascicle** - Small bundles of neurons, below the level of a nerve.

**Flavor** - A perception based on sensations of taste, smell, texture, temperature and occasionally pain as presented to the saliency map.

**Flavorant** - An additive known to affect the perceived response to a gustatory stimulant. See flavor.

**Glomerulus** - A small convoluted or intertwined mass (as of organisms, nerve fibers, or capillaries). In neurology, a neuropil.

**Haworth projection** - A projection where the sugar ring is represented as a flat polygon, commonly a pentagon or a hexagon, instead of in proper geometrical conformation like a chair. The advantages of the Haworth projection are that it is easy to draw, and it is very easy to see whether substituent groups on the ring are on the "top" or the "bottom" of the ring (cis or trans).

**Heterodimer** -

a. (reserved)

b. A protein composed of two polypeptide chains differing in composition in the order, number, or kind of their amino acid residues.

**Homologous** -

a: having the same relative position, value, or structure: as (1) : exhibiting biological homology (2)
: having the same or allelic genes with genetic loci usually arranged in the same order <homologous chromosomes>.
b: belonging to or consisting of a chemical series whose members exhibit homology.

**Inositol** – (Ins) A primary candidate family for a ligand of the sensory receptor for hydrated sodium sensing in gustation. Muco-inositol form is the primary candidate within the family. It offers two receptor sites that share a common hydroxyl group. Formally, the inositols are cyclitols, cyclic polyhydroxyalkanes, and sweet alcohols but not sugar alcohols (a trivial name). They can be obtained by de-oxygenating a monosaccharide ring but they are no longer saccharides.

**InsP3** – (or IP3) Inositol 1,4,5-triphosphate, a proposed second messenger that causes the release of calcium from certain intracellular organelles.

**Isoelectric point** – The pH level at which the number of amino acids or peptides exhibiting positive charges is equal to the number exhibiting negative charges. As a result, no migration of these particles will occur under the influence of an electrical field.

**Kinetics, chemical** – A branch of physical chemistry which involves the rates and mechanisms of chemical reactions.

  1. Simplest, the long term average output-input relationship in a chemical reaction.
  2. Typical, the average output-input relationship in a chemical reaction.
  3. Advanced, the output-input relationship showing all transient elements of a chemical reaction.

**MEP** – Molecular electrostatic potential. A broader term than the dipole electrostatic potential.

**Miraculin** – A natural tetrameric glycoprotein. While it does not generate a sweet sensation itself, if applied to the tongue, it will make ordinary sour foods, such as citrus taste sweet for up to one hour. Gymnemic acid can reverse the sweet taste caused by miraculin, as it can the taste of sucrose.

**Mitral** –
1. Relating to or resembling a miter worn by certain ecclesiastics.
2. Relating to a mitral valve.

**Motif** – A distinctive usually recurrent molecular sequence (as of amino acids or base pairs) or structural elements (as of secondary protein structures). A simple protein motif consisting of two alpha helices.


**Necrosis** – The death of a cell due to external mechanisms and events. “Cell death from without.” See also apoptosis.

**Neural response functions** – A term used to describe the variation in sensitivity of individual types of sensory neurons within the multidimensional taste space. Apparently a bell-shaped function exhibiting little overlap with the functions of the adjoining types of sensory neurons sampling the complete space.

**Neuropil** – An intertwining of a mass of axons and neurites forming large numbers of synapses.

**Neurotrophins** – Soluble proteins believed to support cell growth.

**Odor map (or odor image)** – The representation of the odor/taste environment in the saliency map of stage 4 and accessible by the stage 5 cognitive portion of the brain.

**Odotope** – The common molecular substructure (functional group) responsible for interaction with a given stimulant sensing complex.

**Olfactophore** – A particular stimulant sensing complex associated with a chemoreceptor. Analogous to a chromophore in vision. Used differently here than suggested by Ham & Jurs, 1985.

**Parosmia** – A perverted olfactory perception.

**Parametric measurement** – A measurement made while the circuit is being stimulated abnormally,
as in patch-clamp experiments or in the global application of pharmaceuticals to the surface of a cell.

**Parametric stimulation** - The artificial excitation of a neuron by electrical means not associated with the neurite terminals via a synapse.

**Pheromone** - A substance secreted to the outside of an individual and received by a second individual of the same species in which they cause a specific reaction, for example, a definite behavior or developmental process. Vertebrate pheromones remain largely operationally defined and are not identified chemically with a few exception.

**Peptides** - Simple proteins consisting of only a few amino acid units.

**Piriform cortex** - (sometimes prepiriform) An area in the anterior temporal lobe of each cerebral hemisphere forming part of the olfactory cortex, receiving nerve impulses from the olfactory receptors via the olfactory bulb without the prior involvement of the thalamus as in other sensory systems. It is not part of the neocortex but is a three-layered palaeocortex. Also spelt pyriform cortex, an etymologically incorrect but common form. From Coleman, A. (2001) A Dictionary of Psychology.

**Placode** - A platelike structure, like the hard toothlike scales of sharks, skates, and rays.

**Pseudogenes** - Genomic DNA sequences similar to normal genes but non-functional; they are regarded as defunct relatives of functional genes. See [www.pseudogene.org](http://www.pseudogene.org)

**QHCl** - Quinine hydrochloride, a complicated molecule consisting of two fused aromatic rings, quinoline, the bicyclic quinuclidine, and a OH and a –O– separated by 5 carbons on the fused aromatic. The OH is separated by four carbons from a N in one of the rings.

**Reducing sugars** - Sugars which contain a free aldehyde (sometimes keto/alcohol) group and reduce indicators such as Cupric ion (Cu²⁺) complexes to the Cuprous form (Cu⁺). The reducing agent in these reactions is the open-chain form of the aldose or ketose. The reducing end of a sugar is the one containing a free aldehyde or keto group.

**Umami** - A putative taste sensation resulting from stimulation by monosodium glutamate.

**Vomeronasal organ** - Also known as Jacobson’s organ. Reported in the literature to provide specialized intra-species communications via pheromones.

### 8.4.1.5 Overview of chemoreception problem

Henning has provided a simple description of the basic requirements of chemoreception. He lists:

1. The graded transduction of a chemical into an electrical signal;
2. Some amplification should be allowed for;
3. The process should be fast enough to generate a potential within a few 100 ms;
4. The mechanism proposed must meet modest specificity requirements.”

As Henning notes, “Most of the existing theories on odor and taste satisfy only part of these criteria.”

Focusing on the ligand-receptor aspect of transduction, he has reiterated the five basic questions of Scatchard and added two of his own,

1. How many? (binding sites).
3. Where?
4. Why? (Forces involved) and
5. What of it?

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6. What are the kinetics of binding and dissociation?
7. Is there interaction among binding sites?

Such simple questions may obscure the complexity of the problem. Rossiter has taken a different philosophical path and asked five different questions.

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

These appear to be the more important questions. It is the goal of this work to discover and present substantive first order answers to all of these questions.

Kare and on occasion others, have noted an important fact, “Many illustrations of olfaction and taste have been given using the insect system as examples. Frogs eat flies, yet man does not relish them. Butterflies chemically attract one another but have no apparent chemical effect on me. Synthetic sweeteners, appealing to many humans, are offensive to many species. All the evidence supports the conclusion that species live in different sensory worlds, which may or may not overlap.” Care is called for in the field of comparative physiology.

In the same 1971 discussion, Kare asked for estimates of how long it would take to achieve a general understanding of the gustation and olfaction modalities. The responses ran from five to fifty years. Clearly such an understanding did not occur in the first forty years. It is hoped this presentation will achieve most of the requirement at the end of forty years.

8.4.1.5.1 Problems in representations of cyclic carbon rings

Figure 8.4.1-10 describes a variety of chemical representations found in the chemical literature. Most have arisen spontaneously, with only a few being given formal names. Most attempt to represent three-dimensional structures on a two-dimensional (paper) surface. The result is necessarily an approximation that is typically inadequate when discussing gustation and olfaction.
The major problem is the tendency to approximate the 109.5 degree bond angles associated with carbon by using a simple equal-angle hexagon to represent six carbon rings. The Newman representation correctly uses a 120 degree rotation because of the projection employed. The actual angles in three-dimensional space are shown in the left-most representation as 109.5 degrees. The Haworth representation makes no attempt to represent the bond angles associated with the H– and OH– moieties. The conformation representation tries to highlight the puckering of the ring but typically suggests the angle between the peripheral moieties are 120 degrees. Only a true three-dimensional representation, or the Jmol representation shown rotating on a monitor can properly represent a cyclic compound.

Unfortunately, the Jmol representations are prepared using open source software at present. No major organization has taken ownership or responsibility for the software. As a result, only a smattering of molecules are available in this representation, primarily large proteins and very simple molecules of mol. wt. under 100. Many of these simpler molecules are appearing on Wikipedia.

In Section 8.4.1.1 with Benzene being the prototypical example. Quoting Morrison & Boyd liberally, “Aromatic compounds are cyclic—generally containing five-, six-, or seven-membered rings—and when examined by physical methods, they are found to have flat (or nearly flat) molecules.” “From a theoretical standpoint, to be aromatic a compound must have a molecule that contains cyclic clouds of delocalized π electrons above and below the plane of the molecule; furthermore, the π clouds must contain a total of \((4n + 2)\) π electrons.” Italics and emphasis in the original. The formula gives all even numbers except multiples of four. Huckel’s numbers are seen to be 2, 6, 10, 14, 18, 22 etc., a relatively dense set of numbers. Three- and four-membered rings satisfying Huckel’s numbers are known but they tend to exhibit considerable angle strain that affects their properties.
8.4.1.5.3 Appearance of new 3D tools for computational chemistry

As noted above, the precise distance between the various orbitals is critical information in the study of chemoreception. With the advent of the high capability personal computer, several 3D molecular modeling (rendering) programs have appeared. Unfortunately, the current regime for qualifying the files placed in the various data banks and for qualifying the performance of the various visualization programs is extremely limited. Even the nomenclature used to describe a specific chemical is in a major state of confusion; the confusion is so extensive that Wikipedia has begun placing green check marks next to filing codes used to identify a specific chemical in different data bases. Because of these and other current limitations, the admonition by Angel Herraez is critical, “it is the responsibility of the user to confirm the accuracy of any rendering.”

A currently popular 3D visualizer is the result of an informal consortium of academics, Jmol. Jmol does not appear to properly render aliphatic-aromatics, asymmetrical cyclic molecules critical to the understanding of olfaction.

It is not clear that Jmol is ready for use in chemical sensing where the precision of the bond lengths and angles shown in the rendering can be questioned. Three digit accuracy in the final bond lengths and angular measurements are critically important. A preferred visualizer at present are the free and paid versions of Discovery Suite 3.5 (DS3.5) from Accelyrs, but its documentation is minimal. Section 8.4.5 will address this situation in greater detail.

8.4.1.5.4 Dipole potentials defined

The units of the dipole potential may not be well known.

Dipole moments have a dimension of charge × distance (esu – cm). Since the charge is of the order of 1 ×10⁻¹⁰ esu and the distances are of the order of 1 Ångstrom (10⁻⁸ cm) the order of magnitude for dipole moments is μ = 10⁻¹⁰ ×10⁻⁸ esu-cm = 10⁻¹₈ esu-cm. Dipole moment is expressed in Debye defined as 1 Debye (D) = 10⁻¹₈ esu-cm. A molecule with one positive and one negative charge separated by 1 Ångstrom would have a dipole moment of 4.80 D (charge of one electron = 4.80 × 10⁻¹⁰ esu). In SI system the unit of dipole moment is Cm (coulomb × meter) where, 1D = 3.334 × 10⁻³⁰ Cm⁻¹

The dipole moment is usually found from the dielectric constant of the material. For suitable (typically amphiphilic) substances, the dipole potential can also be found using a variant of the Langmuir (trough) Apparatus. Burdick & Jackson (now a division of Honeywell) has presented a tabulation of the dipole moments of a variety of organic materials. [xxx may not be available now except in my file] See also Section 8.6.3.4.

8.4.1.6 Selection of experiment participants

The variation in the sensitivity of individuals of the same species and the variation among the norms of different species are well known in research on the chemical senses. Perfumers and wine merchants actively seek good “noses.” Even young subjects exhibit significant shortcomings in their ability to sense and/or perceive tastes and odors. It appears vitally important that subjects be screened for their range of sensitivity before being allowed to contribute to a data pool that is to be summed to avoid biasing the data.

8.4.1.7 Stimulant & gustaphore concentration versus intrinsic sensitivity

Many laboratory investigations have been performed using constant molar concentrations of chemicals when many of the individual chemicals may incorporate multiple gustaphores, may hydrolyze in solution or in the case of sugars, may muta-rotate in solution.

Similarly, the absolute sensitivity of the gustatory system in particular may exhibit enormous
differences between the gustatory receptor (GR) channels. Skramlik has asserted the sensitivity of the human tongue to strychnine is one hundred thousand times higher than to sugar\textsuperscript{[107].}

### 8.4.1.8 Attempts to establish a structure-odor or structure-response relationships

The chemoreception research field has suffered from a lack of an adequate model of the neurophysiological system involved. As a result, it has followed an approach long used in pharmacology.

Beets provided a clear description of the SAR (structure-activity relationship) developed in the field of pharmacology and applied to the field of olfaction\textsuperscript{[108].} The early work was primarily in the industrial development of synthetic structures mimicking natural pheromones (primarily musks). These are primarily multi-fused-ring structures. Thus, the field started by attacking one of the most complex areas of organic chemistry. Hansch, writing in 1973\textsuperscript{[109]}, recognized the extreme complexity of the task based on the staggering complexity of the biological system and noted that “any search for quantitative relationships between biological response and molecular structure, by means of classical methods of kinetic and thermodynamic is impossible.” Based on his premise, he opens with, “The correlation of chemical structure with biological response produced by a set of related drugs is an impossible problem. Nevertheless, it is so important and so fascinating that, countless investigators have spent their careers on it and countless more will continue to do so.” This situation remains true today. However, better tools offer alternate paths to solutions in the sensory transduction area (devoid of kinetics).

Two books were found encompassing the SAR approach to chemoreceptor exploration and published in the last 30 years. According to Dodd\textsuperscript{[110]}, the purpose of a SAR study is to correlate the biological effects of a chemical, e.g., its taste, with the molecular properties of the stimulant. The definition was followed by a 1-2 page conceptual illustration. Two years later, Beets spent 10-12 pages expanding on his interpretation of a SAR but did not offer a concise definition of the subject. After warming to his subject, he defined a set of properties, $S_n$, of a chemical structure, $S$, as encompassing all relevant features of $S$ that have been recognized by man. “When the structure of an unknown molecular species is drawn on a sheet of paper with complete indications of configurational details, all the properties, chemical, physical and physiological, which the species will have are at the same time irrevocably and fully defined.” This is clearly an inadequate Bayesian approach to science. A scientist in this position “doesn’t know what he doesn’t know.” He then defines a similar set of activities, $C_n$, related to the field of chemoreception and apparently associated with the larger set of sensations, $C$, presented to the cognitive elements of the brain (but more commonly associated with the motor responses used by the brain to describe these sensations). Avoiding the use of specific mathematical concepts, Beets appears to define a direct relationship as an exclusive path between a specific element of the structural set $S_n$ and a specific element of the activity set $C_n$. He defines an indirect relationship as one where one activity, $C_n$, can be correlated with other activities in the set $C$, presumably in a traceable response to an element of $S$.

The SAR approach has been described as pragmatic, without a close association with any theory.

In a 1996 review, Rossiter also employed two concepts to aid in organizing her olfactory research, the chemical structure-odor relationship (SOR) and the chemical structure-activity relationship (SAR). She reviewed odor properties of various chemicals in the perfume industry and noted, “In an attempt to predict such properties, chemists have been searching for correlations between molecular structure and odor for more than six decades. The fruits of this research are a wide and

\textsuperscript{[107]}

\textsuperscript{[108]}

\textsuperscript{[109]}

\textsuperscript{[110]}
varied collection of postulated structure-odor relationships (SORs)." Rossiter described her attempts to move from the SOR regime to the SAR regime and even to a quantitative structure-activity relationship (Q SAR). She noted the rapid conversion of both SOR and SAR studies to computerized methods but did not describe her precise understanding of the SAR methodology. The editors of "Current Computer-Aided Drug Design recently addressed QSAR in 2015."111 The paper is well structured, however, the quotation from Dirac is taken out of context. The quotation from both W. Edward Deming and Ronald Fischer however are right on target when addressed to any experimentalist or observer of biological behavior.

At the conclusion of the theory development section of this work, a significant amount of discussion will look at the framework defined by the theory and how it can solidify the concepts of the SOR and SAR in gustation (Section 8.5.5.1.1) and more completely in olfaction (Section 8.6.7.4.1).

8.4.2 The stimuli processed by the chemical sensors

The major chemical sensors of the neural system consist of the olfactory and gustatory modalities. They are very closely related and their perceived information, smells and flavors are closely related. Many investigators believe the olfactory subsystem is the dominant modality. Odorous chemicals must be volatile (mol. wt. below 300-400), minimally water-soluble and lipid-soluble to be sensed by the olfactory modality. Tastable chemicals need to be soluble in saliva at pH = 7.0. The sugars are not odorous but dissolve freely in water and are sensed by the gustatory system. The sugars are not soluble in non-polar solvents.

A key feature highlighted in the following discussions is that the stimulants are present not only in solution, but frequently in a hydrated state. when hydrated, it is the stereochemistry of their hydrated state which is important in chemical sensing.

Squire et al. (2003, pg 607) has discussed the various terminologies in use to describe chemical stimulants. “The distinguishing features of an odor molecule have been called determinants or, alternately, epitopes.” The term epitope is drawn from immunology and implies a variety of features not necessarily relevant to the sensory modalities. “Theoretical studies suggest that odor ligands commonly comprise three or four determinants, which interact with two to six receptor sites.”

The assertion, there are three or four determinants, which interact with two to six receptor sites,” is quite compatible with some of the results of multidimensional scaling applied to gustation (Section 8.6.3 xxx). However, multidimensional analysis leads to a much larger number of statistically independent dimensions in olfaction (Section 8.4.4.3 xxx).

The chemical receptors react to a wide range of ionic, primarily inorganic, materials and non-ionic, primarily organic, materials. The difference between these large classes suggest the chemical receptors may utilize at least two distinct transduction mechanisms.

[xxx edit overall to show sugar is detected by stereoisomerism or by energy. ]

The perceived tastes of the sugars have been studied in detail. However, the chemical differences between the sugars causing these perceived differences are very subtle differences in stereoisomerism. These differences suggest a stereoscopic approach to transduction. However, the ease of transition between the different isomers of the sugars suggest this is not a reliable detection criteria. Other mechanisms relating to the reducing powers of the sugars must be considered.

On the other hand, many of the ionic materials are quite capable of interacting directly with at least selective sections of the membranes forming the neurites of the receptor cells.

A complication of understanding the olfactory modality is the requirement to use individual purified chemicals in the laboratory. Natural stimulants contain large numbers of molecules contributing to their odors as shown in Squire et al. (page 650) for the jasmine flower from Mori & Yoshihara (1995). Twenty one individual chemicals are shown. Only two are described as peculiar to the jasmine.

8.4.2.1 The sensitivity of the gustatory receptor neurons

The sensitivity of the gustatory neurons varies significantly with the duration of the applied stimulation,

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the chemical character of the stimulant, any recent prior stimulant and other stimulants applied simultaneously. Eyzaguirre & Fidone provided the following summary related to these parameters.

The perceived taste associated with a given stimulant also varies with its applied concentration. A weak concentration of NaCl (9-20 mM) is perceived as sweet by humans. However, if the concentration of NaCl is raised above 30 mM, a very definite salty sensation will result.

An alkaline stimulant (other than a salt) is only sensed at pH values above 10. The sensory neurons responding to an alkaline stimulant are believed to be sensitive to a variety of stimulants. Surprisingly, the taste receptors responding to acid have a very high threshold, the presence of a sour stimulant is not recognized until the pH of the solution falls to less than 4. It must fall to a pH of less than 3.5 before a definite sensation of sourness is perceived. Figure 8.4.2-2 places these numbers in context.

Organic acids frequently provoke a sensation that is a mixture of two independent sensations. Citric acid, for example, elicits a sensation that is a mixture of sweet and sour. Picric acid evokes a sensation that is a mixture of bitter and sour.

The appreciation of sourness depends very much on the rate of application of the acidic substance and on the secretion of saliva. Saliva has a buffering capacity, which tends to neutralize the acid applied to the tongue.

The sweetness of the sugars is particularly hard to quantify because they are non-electrolytes. The sweetest of all natural sugars is fructose, followed by sucrose, glucose and others—lactose being among the least sweet of all sugars. The artificial sweetener, trade-named saccharin is considered 700 more sweet than sucrose.

For test purposes, the bitter taste is evoked by the application of quinine salts.

Distilled water is sensed by the tongue since its introduction invariably changes the pH of the existing solution.

Mixing of stimulants can result in unexpected perceptions. Eyzaguirre & Fidone suggest individual stimulants are perceived separately. However, masking is a commonly observed effect. Masking suggests certain sensations are subtracted from each other within the neural channels projecting the taste sensations to the brain. Eyzaguirre & Fidone discuss both inhibitory and excitatory signals within the olfactory bulb.

Eyzaguirre & Fidone provide a graph (page 147) showing the action potentials of a single neural path generated by NaCl as a function of concentration. Their figures on page 150 show the graded generator potential of an olfactory sensory neuron as well as a combination of generator potential and action potential stream resulting from stimulation with butyl alcohol. The generator waveforms shown are negative going, have an amplitude of a few millivolts, and are identical to those expected from the Excitation/De-excitation Equation of photoreception (ref. xxx). Because of the necessity for the stimulants to diffuse through the mucosa or saliva, the electrophysical chemical receptor responses tend to be measured in seconds. The figure on page 150 from Ottoson, 1956, shows a total rise time of 1 1/3 seconds and a tail of about two seconds to the 1/e point. The delay from time of stimulant application was not shown.

The literature is unclear about the responses of individual chemoreceptor neurons to ionic material. Figure 8.4.2-2 shows the receptor potentials of a single neuron to a series of salts containing other positive ions than sodium. The common constituent is the chlorine ion.

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112 Beidler, L. (1961) Taste receptor stimulation *Prog biophy biophys chem* vol 12 pp 107-151
There is similar confusion concerning the response of specific neurons to non-ionic material. There are many reports discussing different sets of stimuli and the field of organics and biologicals that act as stimulants is very large. Leinders-Zufall (1998) provided data on four individual cells to a group of six organics.

Adaptation and masking are particularly important mechanisms in the olfactory modality.

8.4.2.1.1 Synopsis of the Chemical Theory of the Neuron

There are a variety of current chemical theories of the neuron. Ham & Jurs suggested the following in 1985\[113\];

Perhaps the best mechanism is that proposed by Dodd and co-workers (Dodd and Squirrell, 1980; Dodd and Persaud, 1981) which explains all of the known features of olfaction and has precedence in other areas of biochemistry. According to this mechanism, olfaction is based on the interaction of molecules with membrane proteins. The odorant molecules act as allosteric regulators of enzyme activity. That is, the interaction of the odorant with the receptor involves the binding of the odorant molecule to the receptor and the change in the conformation of the receptor to accommodate the molecule. Therefore, the size, shape and electronic properties of the molecule are important in determining its nature as an odorant.

The Dodd and Squirrell theory, labeled the Allosteric Membrane Enzyme (AME) Hypothesis, was expressed in 1985 using narrative in less than one page, and using no figures. They developed it during 1978-1985.

"1. Binding sites for odorants. These may be proteins or phospholipids and may exhibit different degrees of selectivity to different odorants, with possibly high binding specificity to some odorants of biological significance, such as pheromones.

2. Receptor potential. This is brought about by ligand-initiated conformational change in an ion-gating protein, by any of the following mechanisms: (a) modulation of membrane fluidity, with consequent alteration in membrane phospholipid-protein interactions; (b) direct ligand induced conformational change of an allosteric protomer of a membrane enzyme with intrinsic ion-gating properties, such as Na⁺, K⁺-ATPase or Ca²⁺-ATPase; or modulation of a second messengersystem through an enzyme cascade system or through non-covalent binding or covalent chemical modification of the protein. In the latter mechanisms it is not necessary for the binding protein to be part of an oligomeric transducer complex. Additional degrees of freedom are open if it is not, and the ligand-protein complex may diffuse on or off the transducer molecule, allowing several receptors to share the same transducer. This may allow cooperative interactions between clusters of binding proteins.

3. Intensity coding. The fraction of sites occupied will mainly determine the magnitude of the receptor potential.

4. Quality coding. The degree of response of different primary neurons to identical stimuli may be determined by either membrane phospholipid composition or by relative distribution of receptor proteins. With the former, little difference may be expected for many congenic odorants, while with the latter, greater differences may be expected."

The mechanisms of transduction and chemical to electrical conversion are largely speculative in the Dodd & Squirrell (1980) paper. While the conventional wisdom, based primarily on long-standing

pedagogy, is proteins play a major role in chemoreceptor transduction, the literature is virtually
devoid of any data or plausible mechanisms involving proteins in transduction (particularly in the last
twenty years).

This work will introduce the question, “Can a dipeptide that has been modified to the point it
cannot participate in a longer peptide chain be considered a protein? (Section 8.xxx)”

Turin & Yoshii have summarized the current “plausible theories of odor detection” based on the
conventional chemistry theory of the neuron114. They describe two classes of theories: shape-based
theories and vibration theories. They suggest the shape-based theories are converging on the
“across neuron pattern” concept with individual patterns defined as odotopes. They note the
demise of the vibrational theories in the 1980’s only to be resurrected recently based on a potential
“inelastic electron tunneling spectroscopy” approach. This approach defines a series of energy
levels associated with individual sensory neurons that provide piecewise coverage of the desired
energy range. This approach is largely conceptual at this time. Turin has described it in depth115.
Turin & Yoshii describe the difficulties with these theories (pp 289-292). They note the apparent role
of zinc (and potentially other metallic ions) in olfaction and gustation. They conclude in 2003, “The
fact that after several decades of experimental investigations, the basic mechanism by which odors
are detected remains open to question shows that there is much work to be done.”

In summary, explanations of the operation of the chemoreceptors based on the chemical theory
of the neuron suffer from;
1. A lack of specificity below the conceptual level.
2. No explanation of how the chemistry of the mucosa and saliva remain unchanged during and
   after stimulation.
3. No explanation of how chemical species return to the external surround after passing through the
   sensory neuron wall in order to cause a sensible change in the neural system.
4. No explanation of how a second messenger is generated without any chemical reaction
   involving enough energy to break a single chemical reaction bond.
5. No definitive description of any protein employed in transduction (resulting in an electrical signal
   at the pedicel of a sensory neuron).

Parsimony suggests the eight processes conceptualized by Van der Heijden (page 70) for the
transduction process under the Chemical Theory of the Neuron is less likely than the two step
transduction process (selection and measurement) involved in the Electrolytic Theory of the Neuron.

Wright has made an interesting observation that appears to apply to both the gustatory and
olfactory villi/cilia. “The olfactory cilia are one micron in (outside) diameter and one to three
hundred long... It is difficult to imagine any chemical transformation going on in a pipe of these
dimensions, so the primary process of stimulation must be a physical one not involving making or
breaking of chemical bonds116.”

8.4.2.1.2 Electrolytic Theory of the Neuron & chemoreception

The photoreceptor neurons and the phonoreceptor neurons of the Electrolytic Theory of the Neuron
provide a logical foundation for the proposed chemical receptor, or chemoreceptor, neurons. Squire et al. have noted the “dendritic” extremity of the olfactory neuron is virtually identical to the
equivalent structure of the photoreceptor neuron117. However, their wording appears to misinterpret
their source, Dodd & Squirrell. Dodd and Squirrell provide a more detailed view that provides more
explicit terminology. They describe a conventional cilia emerging from the “knob” of the
chemoreceptor, as the base of a chalice, that then subdivides into the individual microtubules (or

of Olfaction and Gustation. NY: Marcel Dekker pg 279-282

773-791


Press page 601
dendrites in many texts) forming the staves of the chalice. Referencing a review by Steinbrecht (1969), Dodd & Squirrell note, “The proximal portion of the cilia has a diameter of about 0.25 μm and a normal 9(2) + 2 axonemal structure, but after a few μm there is a distinct narrowing of the cilia to a diameter of about 0.15 μm diameter and from here on the cilium gradually tapers to about 0.06 mm in diameter.

The above description surfaces two important features of neural cilia.

Neural cilia fall into two distinct classes, those formed of nominally solid protein in long extruded rods and those formed as fluid filled tubes supporting the flow of electrical currents toward the axoplasm of the neuron. The latter structures are frequently labeled villi.

9(2) +2 refers to the cylindrical arrangement of 9 pairs (sometimes sporadic triples) of microtubules encircling 2 central microtubules within, and near the base of, a neural cilium of the villi type. This level of detail can only be seen with electron-microscopy.

Diameters considerably below 0.5 micron are obviously challenging for a light microscope.

The gradual tapering of the distal part of the cilium is accompanied by a progressive reduction in the number of microfilaments (microtubules); thus any cross-section through the mucus shows cilia with varying numbers of microfilaments according to the point at which each has been cut.” They also note the difficulty in measuring the microtubules. “Lengths are likely to be underestimated.” Lengths vary from about 5-10 μm in humans to 80-200 μm in frogs. They also note, “Olfactory cilia are unlike the respiratory cilia of the surrounding tissues which maintain a constant diameter and retain a 9(2) + 2 structure of microfilaments throughout their length.”

While Squire et al. note the microtubules contain no other organelles, Dodd & Squirrell note the microtubules are covered with “a large number of particles in the membranes of the olfactory cilia compared to corresponding respiratory cilia, in bovines. It is postulated that these particles might represent olfactory receptor sites.”

The terminal elements of the olfactory neuron is analogous to those of the photoreceptor cell with the disk stack removed. This analogy provides significant clues to the transduction mechanism of the olfactory system used to sense organic chemicals. The photoreceptor microtubule elements are sensitive to quantum-mechanical shocks greater than 2.34 electron-volts.

**Figure 8.4.2-3** compares the proposed schematic of the chemoreceptor neuron compared to a micrograph of a human olfactory neuron. Morrison & Costanze suggest the belt-like complex just below, or girdling, the knob (arrows) provides connection between adjacent neurons. In fact, the connections represent the connection to a reservoir of glutamic acid shared by adjacent cells and providing electrical power to the sensory neurons. The proposed chemoreceptor is based on the photoreceptor with the disks and associated apparatus removed. Relating this proposal is difficult because of the limited empirical database available. In-vivo chemoreceptor neuron investigations are particularly difficult.

Dodd & Squirrell note, “Despite the generally held belief that nerve cells in adult vertebrates are unable to be regenerated, there is a continuous process of cell renewal in the olfactory epithelium, with the basal cells acting as stem cells.” They reference Moulton (1975) who observed a turnover rate of about 29 days in mouse.

Teeter et al. have provided a very useful summary of the empirical database leading to the

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They note the frequent assumption that morphologically light and dark cells, as well as basal cells in some species, might employ different transduction mechanisms. Pfaffman et al. also describe the analog character of the chemoreceptor neuron responses. Kaissling and Thorson have provided one of the few detailed histological descriptions of the chemoreceptors which are frequently found enclosed within a “hair wall” in the olfactory modality or a taste bud in the gustatory modality. Their figure 5 associates the names outer segment and inner segment with the histology of the chemoreceptor (with the soma of the cell associated with the inner segment). The electrical overlay in that figure clearly shows the histologically bipolar cell exhibits more than just two electrical terminals. The overlay does not assume any active electrolytic device within the cell to provide electrical amplification. Nor does the overlay show any electrical output projecting along the axon. By extension, their electrical overlay is compatible with that shown in the figure shown here.

8.4.3 Architecture of the external chemoreceptor modalities

Two schools of thought have arisen concerning the architecture of the external chemoreceptors. One school has drawn analogies with the immune system. The other has drawn analogies with the visual and hearing systems.

The immune analogy supporters drew three conclusions (Hildebrand & Shepherd, 1997):

(a) There is likely to be a large family of receptor molecules (100-1000 members).
(b) An olfactory receptor is likely to have a variable region of odor binding and a constant region for second-messenger transduction.
(c) The receptor is likely to belong to the GPCR superfamily.

The analogy has supported the presumption of a large family of protein-based odor-binding protein (OBP) receptors despite a paucity of evidence to support the presumption at this time. It also supports the description of the stimulant as a ligand whose set of determinants constitutes an olfactophore. A problem with this analogy is the failure of many stimulants to cause the production of cAMP within the chemoreceptor neuron (relying upon the chemical theory of the neuron). This fact has required the development of an alternate theory involving selective activation of either cAMP or IP3 (Inositol 1,4,5-triphosphate).

The vision analogy supporters drew similar but divergent conclusions:

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(a) There is likely to be a more modest number of receptor molecules capable of sensing a variety of molecules.
(b) Each receptor neuron supports only one or a few stimulant sensing complexes (SSC) that may or may not be protein-based OBPs.
(c) The SSC is sensitive to the determinants of a given stimulant rather than the overall structure of the stimulant.
(d) Stage 2 signal processing within the peripheral neural system and stage 4 signal feature extraction within the CNS extracts the pattern information needed to describe a specific stimulant or stimulant set.

This work will rationalize these estimates. The Electrolytic Theory of Chemical Sensing shows that the gustation modality employs only four sensory receptor types (Section 8.5) while the olfaction modality employs less than 23 sensory receptor types, with about 15 accounting for most of the olfactory responses (Section 8.6). Two of the sensory receptor types appear in both the gustation and olfaction modalities; the type sensitive to organic acids and the type sensitive to bitter substances. The individual sensory receptor is sensitive to a specific molecular geometry and employs coordinate bonding rather than reaction chemistry to perform transduction.

Simon & Roper have described a significant difference between the olfactory and gustatory modalities common to many species; “Two patterns of central organization are apparent in every animal in which olfaction and gustation are highly developed. In the first instance receptors are densely distributed in large localized sheets of epithelium and extend their axons to discrete, concentrated synaptic areas, glomerular neuropil. In the second instance, the axons project into organized centers that are less compact and nonglomerular. This delineation of distinctive central organization constitutes the most rigorous criterion for defining the separateness of the two senses.”

8.4.3.1 Top level architecture of the olfactory modality

Only a few investigators have offered schematics of the olfactory modality. Most of these have been incomplete and often anecdotally based. In this work, the top level architecture will be developed first to show how it fits into the framework of the overall neural system. Then, the architecture of the peripheral portion of the modality will be developed before developing the architecture of the sensory neurons.

One paper must be mentioned because of its novelty. Zou et al. presented a paper in 2001 that they felt duty-bound to retract in 2008. It purported to define an overall neural path from the olfactory sensory neurons to the CNS using what they described as a trans-neuronal tracer to travel that path. While a plausible result under the conceptual chemical theory of the neuron, such a trans-neuronal tracer traveling the length of the neural path is not compatible with the Electrolytic Theory of the Neuron.

Figure 8.4.3-1 shows the top level architecture of the olfactory modality employed in this work. It focuses on the mammalian orders as the fish and birds appear to employ different architectures and/or naming conventions. This figure is compatible with the overall six stage neural system of mammals. It is augmented by the motor system acting as a seventh stage in order to create a recognizable response, whether auditory or skeletal-muscular in form.

The figure is based on the nominal sensory modality architecture discussed in Section xxx. The figure differs primarily in the identification of two distinct initial signaling channels associated with the main olfactory channel and an auxiliary channel known as the vomeral olfactory channel. The main channel is associated with the olfactory mucosa located in the upper nasal passages immediately below the main olfactory bulb within the cranium. The sensory neurons of the main channel pass through the cribiform plate of the ethmoid bone to reach the main olfactory bulb. The sensory neurons of the vomeral channel take a separate path to reach the auxiliary olfactory bulb.

The vomeral channel can be considered analogous to the foveal channel of the visual modality. It is a high precision channel used to identify, with high chemical resolution, stimulants (pheromones) arising from other members of the same species, particularly members of that species of the opposite


sex.

In the context of this work, both the stage 2 main olfactory bulb and auxiliary olfactory bulbs are considered parts of the peripheral nervous system based on their function. They are concerned with signal manipulation leading to a compaction of the information derived from the sensory neurons prior to the projection of that information to the stage 4 circuits of the CNS, all of which are located within the cranium.

The olfactory signal paths leading to the higher cortical centers have not been agreed upon by the histologists working in the field. Some assert the initial point of arrival of the signals is via the pons. Others assert the initial arrival point is at the inner surface of the temporal lobe (the uncus) of the cerebral cortex. Still others suggest paths centering on the thalamic reticular nucleus (TRN), the nominal arrival point for all sensory modality signals after initially passing via the brainstem (in the general region of the pons). The major path of olfactory signals appears associated with the fifth maxillary nerve as illustrated by Pansky (1988) in Section 8.6. Noback has provided several artistic representations of the signaling paths of the olfactory modality. His text makes it clear that several questions remained open concerning the signaling paths. Noback clearly differentiates graphically between the fifth nerve and the olfactory tract (page 5). The uncus, TRN, thalamus and other proposed structures based on morphology are very close together in most species. Noback shows paths potentially proceeding to each of these bodies (pages 222-225). It requires additional physiological research to define the precise functional areas associated with these signal paths. Better understanding of the functional relationships should lead to more clarity in the morphological/histological understanding as well.

Noback has also highlighted the bi-olfactory circuitry connecting the two main olfactory bulbs. These connections imply at least a crude directional sensing capability associated with the olfactory modality in many mammals.

Figure 8.4.3-1 Top level block diagram of mammalian olfactory modality ADD. The block diagram follows the architecture of other sensory modalities. It does exhibit a dual input structure, main and vomeral channels, similar to the visual modality.

The olfactory modality plays a more important role in the limbic system than other sensory modalities. Thus, its contribution to both the emotional as well as the cognitive activities of the brain must be considered. As a result, the outputs of both the limbic and cerebral subsystems of the CNS are extensive. At the most basic level, the motor outputs related to respiration (supporting sniffing) and to pointing (orientation relative to the surroundings) are clearly important. The other outputs related to olfaction are more diffuse, but no less important.

8.4.3.2 Expanded architecture of the olfactory modality

Figure 8.4.3-2, from Graziadei, provides a comprehensive block diagram of the olfactory modality noting the three distinct function sensory structures: the olfactory epithelium, the septal organ, and the vomeronasal organ, while discussing the developmental aspects of this modality. He has described this as a simplified scheme of connections. A number of his functional elements have no orthodromic path to the primary CNS elements. Two points are of interest when he shows the "pyriform cortex" passing its output primarily to the mediodorsal thalamus on its way to the neocortex. First, the pyriform cortex is normally considered part of the neocortex. His reference to the neocortex may more properly be labeled prefrontal cortex. Second, the mediodorsal thalamus probably represents the TRN surrounding the thalamus acting in its role of a supervisor and routing control center. This discussion will suggest the primary functional path is from the olfactory epithelium through the olfactory bulb, to the pyriform cortex via the TRN and to the prefrontal cortex via the TRN again. It will suggest the vomeronasal organ supports a separate path involving less computational capability via the accessory olfactory bulb, the corticomedial amygdala, and the hypothalamus to the prefrontal cortex.

Many of the locations mentioned above fall outside the annotation provided by Brodmann. The septum is in area 25 and the pyriform cortex is generally in area 28. Note the septum (aka septal area or septal region) and the septal organ are separate entities in Graziadei. Most of the elements, other than the olfactory bulbs and sensory organs, are found within the limbic system.

Note the lack of a direct path from the olfactory bulbs to the thalamus or TRN. Merging of sensory data in a first pass through the TRN, before stage 4 information extraction, is a primary responsibility of the TRN. The olfactory signals do not contain spatial information about the external environment. Therefore, the stage 2 signals need not pass through the TRN on the way to stage 4 signal manipulation. Following stage 4 information extraction, they do pass through the TRN and mediodorsal thalamus before insertion into the saliency map and cognition by the prefrontal lobes of the neocortex.

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Figure 8.4.3-2 Schematic of the mammalian olfactory modality shown with incomplete paths. Graziadei describes it as highly simplified. This text offers additional comments on this figure. From Graziadei, 1990.
Pansky notes “the area of the olfactory receptor cells in man are located in a small 2.5 sq. cm patch high up in each nostril. The total number of receptor cells is about 100 million in man. Using these coarse numbers, the diameter of the olfactory receptor neurons is approximately the same diameter as the photoreceptors. Each cell is embedded in a matrix of supporting (sustentacular) cells (page 279). The neurite portions of these receptor cells are embedded in the odor-absorbing secretion coating the mucosa.”

Dodd & Squirell (1980) provided Figure 8.4.3-4 showing the variations in olfactory system among different vertebrates. The difference between the olfactory sensitivity of dogs (German shepherd) and humans is clearly due to the difference in surface area of the olfactory epithelia, not the sensitivity of individual chemoreceptors.
The axons of the receptor cells are unmyelinated and very fine. Noback provides a summary of the peripheral neural system in rabbit. "There are approximately 50,000,000 receptor cells per nostril, and 45,000 mitral cells, 150,000 tufted cells, and 2,000 glomeruli in each olfactory bulb." Mori et al. give the number of glomeruli as 3,000. In the rabbit, up to 25,000 axons converge on each glomeruli, the major stage 2 signal processing centers. A single glomeruli typically contacts about 24 of the 48000 mitral cells. The other neurons mentioned are found near the glomeruli in a structure reminiscent of the retina of vision. The axons do not branch until they enter the glomeruli of the olfactory bulb. Each axon makes 15 to 40 synapses with the orthodromic neurons within the olfactory bulb. As noted below, the mitral neurons are the stage 3 ganglion cells that project phasic signals to the CNS.
Dodd & Squirrel (1980) have stressed the high level of convergence leading to the glomeruli. Figure 8.4.3-5 suggests the complex structure of the neuritic tree(s) of a neuron required to achieve such high degree of convergence. The labeling has been modified to suggest the basal neuritic tree is poditic in order to provide a differencing capability within the input structure of this neuron. This figure from Cajal will be discussed further in Section XXX.

8.4.3.2.1 The vomeronasal organ and auxiliary olfactory bulb

Like the vision and hearing modalities, the olfaction modality has a specialized high performance sensing and signal processing channel (although it may be vestigial in humans126). The vomeronasal organ (VNO) is analogous to the foveola in vision. The VNO is also known as Jacobson’s Organ. The literature suggests the VNO forms in the early human fetus and then regresses in the neonate127. The VNO is a specialized olfactory epithelium, with a specialized stage 2 signal processor in the auxiliary olfactory bulb (AOB), and a distinct stage 4 signal processing area (the xxx).

A problem in interpreting the human VNO is the fact the major cranial nerves were defined before the role of the VNO emerged. Schwanzel-Fukuda & Pfaff have noted the nerve associated with the VNO is now called the terminal nerve or zeroeth cranial nerve128.

The literature suggests the SSC’s of the VNO may be very specific to certain protein stimulants. They may allow the identification of specific members of a species via proteins in its urine.

McLean & Shipley have described the AOB and compared the neural schematics leading from the MOB and the AOB to the CNS129. They note the AOB appears to project neurons directly to the amygdala.

8.4.3.2.2 Afferent neural paths to the main olfactory bulb

McLean & Shipley have also described the afferent neurons projecting to the olfactory bulbs. Nickell & Shipley have discussed the commissural and centrifugal connections between the two main olfactory bulbs130.

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8.4.3.2.3 Schematic of the human main olfactory bulb

Johnson has provided the best conceptual schematic of the peripheral elements of the olfactory modality in humans (omitting any auxiliary olfactory bulb) in Figure 8.4.3-6. The figure is similar to a simpler ones in Pansky and in Imamua et al. showing only summation within the glomeruli. Note, there is no correlation between the glomeruli labeled A through D and the groups of ORN, labeled A through D, passing along an individual fascicle. The ORN within each group are drawn using different symbology to aid in tracing their axons to the apical dendritic trees within a given glomeruli. The poditic (basal dendritic) trees are shown synapsing only with the axons of granule cells. Shepherd provided a similar conceptual schematic in 2004 (page 167).

Yokoi et al. have provided a simpler, yet still conceptual, schematic of the ORN and glomeruli that has been reproduced widely in introductory texts. It is characterized by bidirectional flow at the synapses of the basal dendritic trees of the mitral/tufted cells with granule cells. Such signaling is not supported in this work.

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Figure 8.4.3-6 Neuronal schematic of the main olfactory bulb. The organization closely follows that of the visual retina. Four glomeruli are shown, each receiving three of the approximately 25,000 chemoreceptors that would converge on it. Two types of stage 3 neurons, mitral cells (mc) and tufted cells (tc) have their apical dendrites in the glomeruli, about 100 per glomerulus. Basal dendrites of these cells are located in deeper layers of the olfactory bulb. Their axons project to the brain along the olfactory tract. The periglomerular cells (pgc) of the external plexiform layer forms reciprocal synapses with a given glomerulus and spreads lateral inhibition to surrounding glomeruli. The granule cells (gc) form reciprocal synapses with the basal dendrites of the stage 3 neurons. From Johnson, 1988.
The mitral and tufted cells correspond to the ganglion cells of the retina and most other peripheral neural tissue. In fact, Gershon labeled the type 1 ganglion neurons of the enteric system mitral neurons. Griff et al have expanded on the similarity of mitral and tufted neurons, "Mitral cells differ from tufted cells by the location of their cell bodies, the distribution of their lateral dendrites, and their cortical and subcortical projections." Though these anatomic differences are well known, physiological differences between these neurons are less well understood. They are clearly similar cells with only subtle differences in functional assignments. Yokoi et al and Wilson group these two types in their discussions as mitral/tufted cells. Nagayama et al. explored the operational differences between these two cell types. Xxx was it significant? Note most investigators combine mitral/tufted category. See Section 8.9.2 for the topography of enteric system neurons.

8.4.3.3 Top level architecture of the gustatory modality

Spector & Travers have developed a top level model of the gustatory system that is a simplified version of that being presented here. They note,"This neural coding process involves at least three stages. They define a first stage that is conceptually the same as stage 1 of this work, a "stimulus interacts with the receptors and triggers related transduction events in taste bud cells." Not mentioned explicitly in their formulation is the signal processing achieved in the peripheral gustatory system, stage 2 of this work, before forwarding the signal to the central nervous system. Their second stage corresponds to stage 3 of this work. It "involves the activation of afferent fibers that transmit the peripheral signal to the brain." Their third stage conceptualizes the combined stages 4 & 5 of this work. "It represents the processing of the peripheral signal that occurs in the central nervous system (CNS)." This work separates this processing into the information extraction function in stage 4 and the cognition related to processing that information in a more global context combining all sensory modalities in stage 5.

Their presentation is extensive and valuable. However, it consists of "a critical review of the published data" (supported by an extensive bibliography including their earlier laboratory work). They note specifically on page 144 a condition overcome by this work, "The lack of an identifiable continuum along which the physical features of the stimulus vary systematically... poses a challenge to the experimental study of quality coding in the taste system." They also highlighted a variety of unsolved problems with their semantic framework for gustation relying heavily on recent activity in the field of genetics. Their entire dissertation only included one block diagram of the gustatory system. In their conclusion, they lament a continuing problem also addressed in the following chapters of this work. "For all of the behavioral and electrophysiological work that has been conducted to date, it is revealing that definitive evidence distinguishing various models of neural coding of taste quality remains to be seen."

Figure 8.4.3-7 has been expanded from that of Spector & Travers to incorporate these additional features. Their figure is based primarily on traffic analysis within the neural system of the rodent. It begins with cranial nerves VII, IX and X. It is likely that the signals ascending from the parabrachial nucleus pass through the control function of the thalamic reticular nucleus on the way to both the VPN and the amygdala/hypothalamus. Squire et al. (2003, pg 635) has described the projection of the gustatory signals to the CNS, including projections to elements of the thalamus. The means by which signals from the limbic system are passed to the prefrontal cortex remains unclear. However,
Spector & Travers do suggest signals from the gustatory neurons of primates are recorded from the orbitofrontal cortex area of what this work calls the prefrontal cortex.

The Spector & Travers paper is comprehensive but contains a wide range of puzzles and paradoxes. These challenges will be discussed below as appropriate. They use the term tuning in a very broad manner to describe the selectivity of sensory neurons to inadequately described classes of stimuli. The stimuli were the conventional; sucrose, NaCl, HCl and quinine-HCl. The stereochemical and quantum-mechanical properties of these substances was not developed.

Figure 8.4.3-7 Top level architecture of the gustatory modality of the rodent. Only ascending pathways are shown. CT(VII); chorda tympani branch of the facial nerve. GSP(VII); greater superficial branch of the facial nerve. LT(IX); lingual-tonsillar branch of the glossopharyngeal nerve. SLN(X); superior laryngeal branch of the vagus nerve. The mechanism for collecting information from the limbic system on the left for presentation to stage 5 is unclear. See text. Modified from Spector & Travers, 2005.
Noback has presented an alternate, and less complete graphical description of the gustatory modality in Figure 8.4.3-8. It shows a clear path from the peripheral neural elements of the gustatory system to the thalamus and on to the medial surface of the parietal lobe of the cerebral cortex.

8.4.3.4 The path of stimulants to the external chemoreceptors

The gross path of stimulants to the external chemoreceptors is the same. The stimulant is brought into contact with the fluid environment surrounding the microtubules of the outer segment of the neuron. At the detail level, the paths for the olfactory and gustatory receptors are different. The chemical content of the mucus and saliva are fundamentally different. The saliva is charged with beginning the digestion process and it includes a variety of enzymes not relevant to gustation. Whereas the mucus of the olfactory surface is nominally continuous and surrounding all of the chemoreceptors, the saliva transports the stimulants to semi-enclosed taste buds that tend to isolate the (potentially different) fluid environments of different types of chemoreceptors. Johnson has provided the concentration of the major electrolytes of saliva (page 446-449) as a function of flow. Figure 8.4.3-9 shows the artificial saliva used by Hellekant.
In either the gustative or olfactory situation, the stimulant is required to diffuse from the air/fluid environment through the fluid, to the exposed elements of the chemoreceptors. The diffusion rates through the fluid environment may be significant to the concentration of the stimulant at the chemoreceptors as a function of time.

Bradley & Beidler have listed all of the “major” proteins and peptides (60 out of at least 200) they have found in the saliva of the human and the mouse. They did not rank these materials by importance or function.

### 8.4.3.5 Common elements of the chemoreception modalities

Figure 8.4.3-10 presents a composite dendrogram of the chemoreception modalities. It is drawn to highlight the fact that it is the combination of the sensations of taste and smell, as well as other modalities that combine to create a flavor experience. It also highlights the likelihood that the same acidophore receptors are probably used in both the gustatory and olfactory modalities. The diagram emphasizes the presence of significant stage 2 signal processing in the olfactory modality signal paths but virtually none in the gustatory paths. [Incorporate features from the draft figure dendrogram proposal.ai]

Besides sharing the organic acid receptors, the two modalities employ essentially identical sensory neurons, varying only in the specific molecule used to form the receptor of transduction (Sections 8.xxx & 8.xxx). These molecules are used to interface with the gustaphores and olfactophores appropriate to the individual sensory channels illustrated. Most of the groups designated on the right consist of large numbers of molecules providing different gustatory and olfactory stimulants. Many stimulants incorporate more than one odorophore or gustaphore.

The generator waveforms of the sensory neurons exhibit different time constants due to the properties of the neural matrices in which they reside.

This theory and the available data confirm there are four independent sensory channels in the gustatory modality. Signals from these channels encounter little signal processing until they reach stage 4. The olfactory data base is inadequate to determine the precise number of sensory channels in olfaction; however, the number is surely less than nine (as opposed to some

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**Figure 8.4.3-9** Artificial saliva used by Hellekant et al., 1997.

### Table

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<tr>
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<td>33.3 mg/l</td>
</tr>
</tbody>
</table>

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geneticist claiming nearly one thousand). The geneticists have based their assertion on a total gene count where the purpose of the individual genes is largely unknown.

A few chemicals that have previously been considered odorants (the inorganic acids in particular) are more properly described as nociophores (irritants to the nocioreceptors).

Laffort has addressed the subject of protein based receptors as recently as 1994. “Unfortunately, all attempts carried out to date have failed, at least as far as the isolation and identification of highly specific proteins are concerned.”

### 8.4.3.5.1 Binding sites on chemoreceptor membranes

Cuatrecasas and Hollenberg have provided the definition of a binding site (quoted in Brown et al., 1977):

“By definition, a binding site on a membrane surface can be called a “receptor” only if it exhibits the following seven characteristics.

1. exhibit steric specificity,
2. pharmacological specificity,
3. and target-cell specificity.
4. must bind to the putative receptor when the ligand is present at physiological concentration,
5. and it must be possible to saturate the available receptors on the membrane.
6. The binding must be reversible.
7. The most crucial test is that the interaction of the ligand with the receptor must elicit a physiological response.

Pogni et al. have also provided some background material and parametric data. They obtained the EPR spectra of several copper complexes including those formed with histidine and glycine. They explored di-tri- and tetra-peptides of these materials with the different amino acids in different relative positions.

### 8.4.3.5.2 The analog output of stage 1 chemoreception neurons

Bryant & Silver have discussed briefly the analog signals that are produced at the output of the stage 1 sensory neurons in chemoreception. They described these signals in rats and humans as “slow electrical potentials.” In the common framework of this work, they are described as analog generator potentials to differentiate them from pulse mode action potentials. The figure below will describe these generator potentials as recorded in the rabbit. They are characteristic of all stage 1 sensory neurons in all sensory modalities in all mammals.

### 8.4.3.5.3 Transduction response of chemoreception

The sensory neurons of the chemoreceptor modalities (in both mammals, reptiles and insects) show the same transduction characteristic as do the quantum-mechanical sensory neurons of the visual and auditory modalities. This characteristic is shown in Figure 8.4.3-11. Boecke et al. made special efforts to use a continuously flowing air stream and probe the plasma of the sensory neurons of the

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The waveforms all exhibit a finite time delay \( t_{DA} \) associated with the attack portion of the waveform. The waveform exhibits a first order departure from the baseline when recorded using a well balanced oscilloscope probe of sufficient bandwidth. The shape of the waveform is critically dependent on the product of the intensity of the stimulus and the capture cross section of the individual sensory neurons. At high values of this product, the waveform exhibits an “overshoot” that is fundamental to the mechanism. Note the time delay \( t_{DD} \) associated with the decay characteristic after cessation of the stimulus. The value of \( t_{DD} \) is determined by the response level at termination of the stimulus. The decay characteristic following the decay delay is a first order decay with a time constant, \( \tau_D \). This time constant is intrinsic to the transduction process of the sensory neuron. It is typically a few tenths of a second.

Laboratory procedures frequently involve slow and poorly timed application of various stimulants to the chemical receptors, resulting in loss of detail concerning the intrinsic response of the sensory receptor neurons.

### 8.4.4 Global aspects of potential stimulant sensing chemistry

Beginning early in the 20th Century, investigators assumed the SSC’s of olfaction had to be protein based. Although this position has yet to be confirmed, the assumption is taught as fact to this day. Cohn and Edsall edited a major volume in 1943 describing the state of the art related to proteins, peptides and amino acids. It remains a valuable compendium to this day. After approximately 100 years of research, Ko and Park noted the following concerning the role of proteins in olfaction, “The recent progress in a study on the olfactory receptor genes is expected to allow for the identification of the unknown function of the receptor proteins in the near future.”

Infrequently, investigators have asserted the SSC’s could be lipids. However, this assertion has never become a viable option. It is possible the field of chemistry has not advanced sufficiently to understand the chemistry of the SSC’s. The field of coordinate chemistry (involving a metallic ion bonded to a non-carbon atom of an organic ligands) and the closely related organometallic chemistry (involving a metallic ion bonded to a carbon atom) are now maturing. They may hold the answer to the SSC problem.

This work will show that the transduction involved in chemoreception relies upon coordination chemistry (or coordination complex chemistry) involving the phospholipids of specialized regions of the sensory neuron lemma. While coordination chemistry plays a critical role in many stable compounds required by life (hemoglobin as an example), it plays a similar role in olfaction and gustation involving short lifetime coordination complexes. In his preamble, Lawrance notes, “What we can conclude is that metal coordination chemistry is a demanding field that will tax your skills as a scientist. Carbon chemistry is, by contrast, comparatively simple, in the sense that essentially all stable carbon compounds have four bonds around each carbon center. Metals, as a group, can exhibit coordination numbers from two to fourteen, and formal oxidation states that range from negative values to as high as eight.”

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143Boecke, XXX from ottoson in Beidler, pg 107

144Cohn, E. Edsall, J. eds. (1943) Proteins, Amino Acids and Peptides. NY: Reinhold


The coordination chemistries of the metalloproteins, metalloenzymes are well explored at this time. The coordination chemistry of the metallophospholipids is basically unexplored, particularly for the lighter metals of groups 1s and 2s. Most texts do not address the complexes of sodium and calcium. In the 2004 (2nd) edition of Comprehensive Coordination Chemistry, volume 3 contained a chapter on the coordination chemistry of the 1s and 2s elements that hardly addressed sodium and calcium.

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Oncley provided a comprehensive, but very early, discussion of the electric moment and relaxation times associated with many proteins, peptides, and amino acids that may play a role in olfaction. As noted below, many of the more complex biological molecules, such as hemoglobin, are best described in the coordinate chemistry context.

This section will develop the possibility that the SSC’s are metallic ions bonded to simple peptides instead of more complex proteins. Lehninger notes the reaction of CuSO₄ with either a peptide or a protein gives a purple complex of Cu²⁺ and the peptide, which can be measured quantitatively in a spectrophotometer. Others have noted, as described below, the spontaneous assembly of many zinc-based metal complexes.

The mucosa of animals is frequently noted for its distinct color. This color is suggestive of the presence of a Cu²⁺ or other transition element complex with a peptide. A peptide is a minimum molecular weight protein.

### 8.4.4.1 Chemical nomenclature and the IUPAC/IUBMB etc

As noted infrequently within this work, the rules of organic chemistry are exceedingly complex and become critically important as more sophisticated chemical mechanisms and procedures become involved in understanding the operation of the chemical senses. The IUPAC, and more recently the IUBMB, have continuously attempted to formulate rules adequate to the needs of a rapidly expanding science. These attempts have necessarily had to accommodate common terminology used for decades within the community. As a result, many exceptions to the formal IUPAC rules have been reluctantly accepted by the IUPAC by codicil or other corollaries. A dated but excellent perspective on the overall situation appears in March. The current definitions supported by IUPAC are cataloged.

### 8.4.4.2 Proteins as potential gustatory or olfactory receptors

The mention of protein to a biochemist usually invokes the image of large complex molecules of amino acids. However, the definition of a protein can be a broad one. A dipeptide, and even a single amino acid (a peptide) can be defined as a protein within some contexts. In this work a protein is a molecule larger than a single dipeptide.

Proteins are conventionally associated with the following tasks within an animal organism:
1. as structural elements,
2. as muscle tissue,
3. as chemical transporters,
4. as enzymes,
5. as hormones,

and related generally to chemical decomposition (both digestion and phagocytosis) and synthesis within the organism. While their role in sensory neural transduction has been conceptualized generally, such roles have not been previously defined at the detailed cytological and specific reaction levels. Such detailing is a major goal of this volume. Similarly, their role in neural system signaling and function has been described largely conceptually. Many of the commonly accepted roles of proteins within the neural system have never been demonstrated in the laboratory. Discussions relating to this situation will occur frequently throughout this volume.

The generation of large molecular weight proteins in accordance with the DNA code by mitochondria within a cell is generally considered the normal mode of protein production. Proteins are usually segregated into simple (containing only amino acid ligands) and conjugated proteins (those containing non-amino acid ligands). There are also small molecules of simple proteins consisting of only amino acids, such as the peptides. They typically contain less than a dozen amino acid units. Some peptides, such as the dipeptide carnosine (mol wt. 226), are not derived from proteins encoded by DNA. They are primarily ingested (or assembled from amino acids ingested) in food. Many other peptides do not derive from DNA encoded protein structures but are important biologically. The proteins and peptides as a group do not have the low excitation energy associated with taste and smell. However, more specific complex molecules incorporating these peptides may. The C–N bond of the peptide linkage cannot rotate freely, a property of supreme importance with respect to the three-dimensional conformation of polypeptide chains. This rigidity assures a higher degree of specificity in steric unions.

Isolating individual proteins from a neurological environment is a technical challenge because of the variety of proteins in that environment. If a protein of interest is present in an organelle, it is typically best to isolate the organelle in quantity before attempting to isolate the protein.

It appears a family of small chelating peptides, including carnosine and its N-methylated derivative, anserine (β-alanyl-N-methyl-L-histidine, mol wt. =240), may be part of the molecules acting as SSC's in olfaction. The larger family may include a variety of histidine derivatives. They appear to coordinate with the transition group metals, Cu, Zn, etc. easily. The combined molecules offer many unique properties.

Price has discussed “Olfactory Receptor Proteins” as SSC’s without demonstrating the proposition. His subtitle is more interesting, “Are olfactory receptor sites proteinaceous? Section xxx presents a plausible demonstration that the olfactory receptor sites are peptide-aceous but not necessarily proteinaceous.

This work has only uncovered one case were a sensory neuron receptor involves a protein in its fundamental transduction process. That case is in audition, not in vision, gustation or olfaction.

### 8.4.4.2.1 The role of histidine-containing dipeptides

A family of chemicals, based on the positively charge amino acid, histidine, were studied extensively in the last quarter of the 20th Century. The results of investigations of carnosine and anserine were predominantly negative with respect to the role of these chemicals in chemical sensing by the neural system. However, the study of the coordinate chemistry of these materials provides a good foundation for understanding how the actual sensory receptors of chemical sensing actually operate.

Trombley et al. observed, “In spite of the supportive evidence, the lack of a direct effect of carnosine on the afferent targets of carnosine-containing olfactory sensory neurons casts doubt on its status as a neurotransmitter. Discussions continued in 2000 concerning where carnosine is formed and released in the olfactory mucosa. Bakardjiev & Bauer note “Rats produce carnosine after stripping the neurons from the flat cell layer. The data suggest that this type of cell but not olfactory neurons

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They later conclude, “A century after the isolation of carnosine we have learned many details about carnosine and related dipeptides. Nevertheless, the biological functions of these peptides in different tissues remain obscure, and a unifying concept to answer this question has not yet emerged.”

De Marchis et al. have surveyed the role of carnosine in the cells of the neural system. Like others in 2000, De Marchis et al. conclude, “In the last decade, several studies have been performed to understand the biological functions played by carnosine-related dipeptides in the nervous system. Although many theories have been proposed about a wide range of properties that enable them to act as antioxidants, metal chelators, free radical scavengers, inhibitors of protein glycosylation, and neuromodulators, their precise physiological role remains unknown.” Ronnett & Moon stated in 2002, “Thus, in the absence of compelling functional studies the sum of these data does not support the role of carnosine as the neurotransmitter of the olfactory receptor neurons.”

Additional information on these and other studies of carnosine and anserine have been accumulated in Appendix N.

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8.4.4.3 Lipids as potential gustatory or olfactory receptors

The family of phospholipids, found in the bilayer walls of neurons, is gigantic. Weissmann & Claiborne provided a “bible” on this subject in 1975. Even this work does not go far enough to describe all of the features of the family.

Figure 8.4.4-1 describes the basic features of the phospholipids of interest. The family is based on the triglycerid framework of (a). The polar phosphate group of (b), along with two fatty acid groups, are added to form the generic arrangement in (c). The basic phospholipid is shown in more detail on the right. The two fatty acid chains need not be of the same length, nor need they both be saturated as shown by Chapman (Weissmann & Claiborne, page 22).

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154De Marchis, S. Modenal, C. Peretto, P. Migheli, A. Margois, F. & Fasolo, A. Carnosine-related dipeptides in neurons and glia Biochem (Moscow) vol 65(7), pp 824-833


A more complex level of non-saturation in a phospholipid is a "conjugated fatty acid" forming one leg of the two chains. This is a relatively rare form not recognized in many texts (Lehninger 1970, page 190). Cook has provided a long list of conjugated fatty acids along with a set of rules for describing
When found in a phospholipid, this feature contributes electrical conductivity along the length of the chain. Zhou et al. found increases of 3-4 orders of magnitude\textsuperscript{158}. As a result, when used in a neuron, this class of phospholipid exhibits a polar head attached to a conductive leg protruding through the bilayer of the membrane. The dipole moment of the polar head is effectively extended (without increasing the lever arm of the moment) to the electrolytic environments on each side of the bilayer. The precise geometric form of the conjugated fatty acids depend on their cis and trans configurations.

\textbf{Figure 8.4.4-2}, reproducing the Chapman figure, illustrates how multiple phospholipid molecules can exist adjacent to each other in a very small region of a single bilayer of a lemma. The kinks in the fatty acids are indicative of cis-double bonds along the chain. This is common in actual practice.

\textsuperscript{157}Cook, H. (1991) Fatty acid desaturation and chain elongation in eucaryotes \textit{In} Vance, D. & Vance, J. \textit{eds.} Biochemistry of Lipids, Lipoproteins and Membranes. 4\textsuperscript{th} Ed. NY: Elsevier Chapter 5

If the dipolar moment of the polar group was to change, due to a modification of the polar group, such as through a coordinate chemical arrangement with another substance in solution, the electrical potential at the other end of the phospholipid would change relative to the electrolytic environment of the polar group. This change can be sensed by the appropriate electrolytic amplifier. Bangham shows a similar situation (Weissmann & Claiborne, page 30) using a reconstituted "black lipid membrane" and involving a change of over 100 mV in potential. A similar response is shown for a portion of neural tissue from a frog (demonstrating its electrolytic conductivity).

Figure 8.4.4-2 Drawing showing the complexity of a real lemma. The size shown is about 30 x 30 Angstrom. It contains six cholesterol molecules, five phospholipid molecules of three different types, and four sphingolipid molecules of two different types. From Chapman, 1975.
In an excellent review, Bangham noted\textsuperscript{159}, “The tight and spatially oriented packing of phospholipids as a smectic mesophase or black lipid membrane gives rise to a plane or planes of fixed ions at a (two-dimensional) concentration equivalent to a bulk uni-univalent concentration of 5-10 mole/liter!” His earlier 1968 review contains a wealth of valuable information about phospholipid bilayer membranes and their electrical interaction with sodium in aqueous fluids\textsuperscript{160}.

8.4.4.3.1 The dipole potential and dipole moment of chemistry

When a molecule is formed, it exhibits an electrostatic field surrounding the individual atoms of the molecule. This field can be computed (using the Jmol algorithm) and measured (with difficulty). These fields are described by the individual electrostatic fields associated with each bond within the molecule.

The electrostatic features known as the bond moments and the dipole moments of the bonds and molecules play a major role in olfaction and gustation according to the Electrolytic Theory of the Neuron. The character of the valence or covalent bond between two atoms is determined by the electrostatic strengths of the two atoms involved. This strength is described by the effective charge associated with each atom and the effective distance between these effective charges, the product of these two features the bond potential and the electrostatic length of the bond is the bond moment.

When a molecule is formed by more than two atoms, the molecule exhibits a net dipole moment given by the vectorial sum of its individual bond moments. This vectorial summation describes the net electrostatic field associated with the molecule. This summation may be zero in the case of totally symmetrical molecules but frequently is not, as in the case of the resonant cyclic hydrocarbons.

The fields and calculated dipole moments of several molecules will be illustrated with the olfaction section of this chapter. The actual electrostatic field will be shown to play a major role in the “super” stimulants of gustation. It remains to be seen whether it plays a role in “super” stimulant of olfaction.

The property of interest in external chemical sensing is the net dipole potential relative to the ligand binding to the receptor when surrounded by the mucosa or oral cavity fluid.

An excellent review of bond and dipole moments is available online in 2012\textsuperscript{161}.

8.4.4.3.2 Dipole potential and moment of phospholipids in lemma

The dipole moments associated with the various polar groups in phospholipids have been indicated in Figure 10-3 of Lehninger (1970). However, no precise potentials or dipole moments are given. Sherer & Seelig give a value of 19 Debye for the dipole moment of phosphocholine. Klymchenko et al. have noted the absolute dipole potential for phosphatidylcholine bilayers are large relative to the input operating range of the common emitter circuit of the Activa developed here (~20 mV)\textsuperscript{162}. They suggest it is difficult to measure these with precision but values from $\psi_\alpha = -280$ to $-500$ mV appear in their work. Thus, only a small change in the dipole potential would be needed as a result of a coordinate chemistry arrangement to be sensed by the neural system. See Section 8.5.5.1.1 xxxx.

While dipole potentials are difficult to measure for molecules in solution, because the molecules are free to rotate randomly in the absence of an applied field, this is not the case for the phospholipids when in liquid crystalline form in a monolayer. In this case, the dipole potential is easily measured. However the presence of the phospholipid in a bilayer complicates the measurement procedurally.

\textsuperscript{159}Bangham, A. (1972) Lipid bilayers and biomembranes Annu Rev Biochem vol 41, pp 753-776

\textsuperscript{160}Bangham, A. (1968) Membrane models with phospholipids Prog Biophys Mol Biol vol 18, pp 29-95


Petrov & Sachs addressed the subject of dipoles in phospholipids from a mathematical perspective163. Their theme was, “in view of the well-established charge and dipolar asymmetry of the two leaflets of a native membrane, the theory of flexoelectricity (and curvature elasticity) is extended to take into account this asymmetry.” They defined the direction of the dipole moment incompletely as, “dipoles are regarded as positive if pointing inward toward the hydrophobic core.” It can be assumed they relied upon the common definition of a dipole moment, “the electric dipole moment points from the negative charge towards the positive charge, and has a magnitude equal to the strength of each charge times the separation between the charges.”

The dipole potential is most easily measured using the Langmuir film technique–floating a monolayer film of the material on a (typically) distilled water surface and measuring the potential difference between its upper and lower surfaces. The thin film must constitute a continuous liquid crystalline monolayer to provide the desired potential.

The dipole potential of a molecule is the vector summation of the dipole potential of each of its constituent asymmetrical chemical ligands. When a chemical entity is coordinately bound to another chemical entity, their net dipole potential can be calculated from their individual values. It is proposed that the change in dipole potential between the unbound and bound states of the phospholipids forming the receptors constitutes the principle parameter sensed in the transduction process of the olfactory and gustatory sensory neurons.

8.4.4.4 Coordination chemistry fundamentals

Coordination chemistry has been dominated by the study of compounds formed between metal ions and other neutral or negatively charged molecules. This is the coordinate chemistry of compounds fathered by Alfred Werner in the late 19th Century. It is frequently described as the coordinate chemistry of organo-metallic complexes. It specifically exempts compounds where the metal binds directly to carbon. The journal, Coordinate Chemistry, is dedicated to the Werner form of organo-metallic complexes. A broad synopsis of the field has been assembled in Appendix N of this work.

More important to this work is the coordinate chemistry of the hydrogen (or London) bond. The hydrogen bond is very weak and typically temporary, depending on the environment of the bonding materials. The temporary nature of these bonds is particularly relevant to the study of olfaction and gustation.

Reedijk has provided a tutorial review of the difference between the coordinate chemistry of Werner and that of London164. Unfortunately, the title of the paper is a bit ambiguous. He notes this fact in his introductory remarks, “This tutorial review is not meant to review hydrogen bonding in coordination compounds in full detail, but will rather focus on the influence that (intramolecular) hydrogen bonding may have on the coordination of ligands to metals and the stabilization of their molecular and lattice structure.” The paper describes the hydrogen (London) bond primarily in its role of stabilizing an organo-metallic complex of the Werner type. Reedijk does note the hydrogen bond only became recognized several decades after Werner promulgated his coordinate chemistry of the organo-metallic complex (and after Werner had received the Nobel Prize). The hydrogen bond concept was first noted in the literature around 1920. Reedijk is a true Don of organo-metallic chemistry but he does not address the DACB described in this work. This is unfortunate as his wisdom could provide a significant contribution. His figure 1 only addresses three potential forms (where he has taken pains to show a metal atom even in a non-coordinate bond environment). He does describe the high strength Z—H bond as the H bond donor group and the coordinate bond free but capable atom, B, as the non-coordinated donor atom in a ligand. The result is a structure described as Z—H---B. The---is very fragile compared to those of valence chemistry. His figure 12 shows a molecule commonly found among the channel 2 (ducal) stimuli described in Section 8.5.

The field of coordination chemistry based on the hydrogen (London) bond is vast and its details complicated. The coordinate chemistry of the hydrogen bond appears to be the foundation of the chemical sensing process. [The field as it might apply to gustation is addressed in Section 8.5 Similarly, its applicability to olfaction and oskoration is discussed in Section 8.6.


The so-called coordinate (dative) bond of conventional valence chemistry does not play a significant role in coordinate chemistry.

Bowman-James has discussed a broadening of the subject of coordinate chemistry recently. However, her focus was on very large scale heterocyclic molecules containing multiple amide or amine groups, as many as six nitrogen atoms and 24 or more carbons in the simpler cases. She did not discuss hydroxyl groups or other anions than nitrogen. She did seek to add additional precision to several terms used in coordinate chemistry and spoke of multiple hydrogen bonds associated with one molecule. However, she did not engage in the definition of the DACB so crucial to chemical sensing. Some of her recommended definitions are two restrictive for purposes of chemical sensing.

She noted that Werner had invoked, “a secondary valence for transition-metal compounds; ‘Even when they are saturated in the sense of the older theory of valence, the elementary atoms still possess sufficient chemical affinity to bind other seemingly also saturated atoms and groups of atoms under generation of clearly defined atomic bonds.’” “Therein was born the concept of a double valence for transition-metal ions, a primary valence, satisfying principles of neutrality, plus a secondary valence, providing a ‘coordination number’, often consisting of additional species beyond those necessary to satisfy the charge.”

She also noted, “where anion coordination is invoked, the definition of the term ‘ligand’ should be understood to refer to Lewis acid capability and the term ‘coordination’ refers to hydrogen bonds as opposed to coordinate covalent bonds.”

She closed with a description of her ligands wherein, “these ‘ligands’ will arrange according to common polyhedra around an anion ‘center’. By this description, she has not allowed for the presence of a common polyhedra around a cation center such as ionized sodium.

8.4.4.4.1 Coordinate chemistry of the transition elements

This work has not found the role of the coordinate chemistry of the metals, other than the alkaline and alkaline earth metals, significant in the first order theory of chemical sensing. The following material is included for its attention to coordinate chemistry.

The nomenclature of coordinate chemistry is necessarily complex. Lawrence has provided an introduction focused on the terminology involved. A brief description of the IUPAC rules on nomenclature is provided on Wikipedia. Basolo & Johnson have provided multiple pages of nomenclature related to these compounds. They differentiate between the primary valence (or oxidation state) of a metal ion and its secondary valence (or coordination number). “Every element tends to satisfy both its primary and secondary valence.” The primary valence tends to be satisfied with ionic bonds to other atoms. The secondary valence is frequently satisfied by more complex organic molecules attached to the “coordination sphere” of the metal ion. They discuss hemoglobin as an example of a metal in biology as an introduction to the field of bioinorganic chemistry (page 131).

Geometry

Structure in complexation chemistry is first described by its “coordination number”, the number of ligands attached to the metal (more specifically, the number of σ-type bonds between ligand(s) and the central atom). Usually one can count the ligands attached, but sometimes even the counting can become ambiguous. Coordination numbers are normally between two and nine, but large numbers of ligands are not uncommon for the lanthanides and actinides. The number of bonds depend on the size, charge, and electron configuration of the metal ion and the ligands. Metal ions may have more than one coordination number.

Typically the chemistry of complexes is dominated by interactions between s and p molecular orbitals.
of the ligands and the d orbitals of the metal ions. The s, p, and d orbitals of the metal can accommodate 18 electrons (see 18-Electron rule; for f-block elements, this extends to 32 electrons). The maximum coordination number for a certain metal is thus related to the electronic configuration of the metal ion (more specifically, the number of empty orbitals) and to the ratio of the size of the ligands and the metal ion. Large metals and small ligands lead to high coordination numbers, e.g. [Mo(CN)8]4-. Small metals with large ligands lead to low coordination numbers, e.g. Pt[P(CMe3)]2. Due to their large size, lanthanides, actinides, and early transition metals tend to have high coordination numbers.

Different ligand structural arrangements result from the coordination number. Most structures follow the points-on-a-sphere pattern (or, as if the central atom were in the middle of a polyhedron where the corners of that shape are the locations of the ligands), where orbital overlap (between ligand and metal orbitals) and ligand-ligand repulsions tend to lead to certain regular geometries.

Isomerism
The arrangement of the ligands is fixed for a given complex, but in some cases it is mutable by a reaction that forms another stable isomer. There exist many kinds of isomerism in coordination complexes, just as in many other compounds.

Geometric isomerism
Geometric isomerism occurs in octahedral and square planar complexes (but not tetrahedral). When two ligands are opposite each other they are said to be trans, when mutually adjacent, cis. When three identical ligands occupy one face of an octahedron, the isomer is said to be facial, or fac. If these three ligands and the metal ion are coplanar, the isomer is said to be meridional, or mer. For example, in an octahedral compound with three of one ligand and three of another, there are two geometric isomers: the mer in which each set of three same ligands is in a meridian and the fac in which each set of three is on a face of the octahedron.

Structural isomerism
Structural isomerism occurs when the bonds are themselves different. Linkage isomerism is only one of several types of structural isomerism in coordination complexes (as well as other classes of chemical compounds). Linkage isomerism occurs with ambidentate ligands which can bind in more than one place. For example, NO2 is an ambidentate ligand: it can bind to a metal at either the N atom or at an O atom.

Color
Metal complexes often have spectacular colors. These colors are caused by electronic transitions caused by the absorption of light. Most transitions that are related to colored metal complexes are either d-d transitions or charge transfer bands. In a d-d transition, an electron in a d orbital on the metal is excited by a photon to another d orbital of higher energy. A charge transfer band entails promotion of electron from a metal-based orbital into an empty ligand-based orbital (Metal-to-Ligand Charge Transfer or MLCT). The converse also occurs: excitation of an electron in a ligand-based orbital into an empty metal-based orbital (Ligand to Metal Charge Transfer or LMCT). These phenomena can be observed with the aid of electronic spectroscopy; also known as UV-Vis. For simple compounds with high symmetry, the d-d transitions can be assigned using Tanabe-Sugano diagrams. Increasingly, these assignments can be confirmed using computational chemistry.

Many organic coordination compounds occur naturally. For example, hemoglobin and myoglobin contain an iron center coordinated to the nitrogen atoms of a porphyrin ring; magnesium is the center of a chlorine ring in chlorophyll. The field of such inorganic compounds is known as bioinorganic chemistry.

Coordination number
There are many definitions of the term coordination number, but there is no one simple unambiguous definition that works in all cases. For simple monodentate and chelating ligands, the coordination number can be defined as the number of atoms or ligands directly bonded to the metal atom.

The total number of points of attachment to the central element is termed the coordination number and this can vary from 2 to as many as 16, but is usually 6. In simple terms, the coordination number of a complex is influenced by the relative sizes of the metal ion and the ligands and by electronic factors, such as charge which is dependent on the electronic configuration of the metal ion.

Coordination Number 4
Two different geometries are possible, as shown in Figure 8.4.4-3. The tetrahedron is the most common while the square planar is found almost exclusively with metal ions having a d8 electronic configuration.
configuration.

Tetrahedral
The chemistry of molecules centered around a tetrahedral C atom is covered in organic courses. Similar arrangements are found where the central atom is a metal. Replacing the carbon in a tetrahedron by a metal, such as cobalt, is quite common. There are large numbers of tetrahedral Cobalt(II) complexes known.

Square Planar
This is fairly rare and is included only because some extremely important molecules exist with this shape.

Additional definitions related to coordination chemistry and organometallic chemistry are available at http://www.ilpi.com/organomet/coordnum.html. These may not be sanctioned by any organization.

Garnovskii & Kharisov have edited a book on the fundamentals of coordination and organometallic chemistry169. They discuss the methods of direct synthesis of these types of compounds. However, they do not investigate such chemistry involving amino acids or involving specific metallic ions.

The coordinate chemistry of copper appears to be the most studied of the biologically active metal ions. The endogenous presence of trace amounts of both copper and zinc in the CNS and particularly in association with the olfactory neurons is well documented170,171. Spiro noted that measuring these trace elements in biological tissue has been extremely challenging until recently, even though among the transition elements, zinc is second only to iron in abundance (page 3).

Spiro has edited several volumes on metal ions in biology including an entire volume on copper proteins172. The latter included detailed information and structural diagrams on a number of copper proteins. He notes, “Metal ions are essential to life as we know it. This fact has long been recognized, and the list of essential ‘trace elements’ has grown steadily over the years. . . Vast stretches of this terra incognita remain uncharted.” He develops the importance of electron transitions between the various d orbitals (page 34).

8.4.4.4.2 Coordinate chemistry of the hydrogen bond and non-metallic atoms

The hydrogen bond is a critical element in the modalities involving chemical sensing. The hydrogen bond is a critical element in the dual antiparallel coordinate bond (DACB) defined and discussed extensively in Sections 8.5 & 8.6. Wells described the variability of the hydrogen bond among a wide variety of chemical groups173. The hydrogen bond (London bond) length varies between the gaseous, liquid and solid states for a given molecule. In some cases, multiple London bonds of different lengths are observed within a given molecule in a particular state. When dissolved, the bond lengths also vary with the dielectric constant of the solvent. Wells also notes the difference in hydrogen bond lengths measured using X-ray versus neutron diffraction techniques.

Wells also provides important background information relating to oxygen, a principle element in the hydrogen bond phenomenon. The three different hybridizations of oxygen account for many of the
special structures involving oxygen. Similar information is provided for nitrogen and for sulfur, although these are less important in chemical sensing.

The 1984 Chart 1.1 of Wells on “the complete structural chemistry of a substance” can be expanded considerably for the purposes of chemical sensing. It does not include the coordinate chemistry of the species.

8.4.4.5 Nomenclature and the pharmacology community–HCl

It is appropriate to remind the reader that the pharmacology community uses several abbreviations that are misleading at the detailed level in chemistry. Specifically, the labeling of a compound as codein-HCl or similar terminology suggests that HCl is present in the compound loosely bound to the other component. Such labeling is merely a short-hand to indicate the chloride salt of a base (while avoiding the formal change in the name of the component derived from the base).

For example, the reaction of pyridine (C₅H₅N) with hydrochloric acid (HCl) yields pyridine hydrochloride (C₅H₅N•HCl). Even though this style of formula is often used for denoting the hydrochlorides, the dot incorrectly implies that the two molecules are weakly bonded together; rather, what is present is the salt C₅H₅N⁺Cl⁻ with the correct chemical name pyridinium chloride.

8.4.5 Limitations on available visualization tools

Computational chemistry is a burgeoning new field based on the availability of high power computers, even on the desktop. However, the tools used with these computers is having difficulty keeping up with the empirical and theoretical aspects of biochemistry. To cope with this problem, a number of data banks have been established to collect the data spewing from a variety of academic, and to some extent commercial, sources. The major current (2013) problems in this field are two-fold; the data bases are being filled with unverified files (such as .mol and .pdb), even at the national databases such as NIH (pers. communications). Second, the visualization tools used to interpret these files are not adequately documented, or even maintained. Some of these tools have been made available by small (one-man) organizations (OpenAstexViewer), some by informal academic associations (Jmol) and others by fully staffed commercial organizations with a reputation to protect (Accelyrs). Whatever the team, the visualizer programs suffer from a major lack of documentation describing the capabilities and limitations of their programs.

The little known Astex visualizer has some superior features related to color rendition but little else to recommend it.

The current visualization programs provide strikingly different representations based on the same underlying file, Figure 8.4.5-1. The upper 3D representation shows a totally planar structure for denatonium while the lower representation shows a non-planar structure more complex than that in the upper frame and previous figure. Note the four bonds to O13. This representation differs significantly from the Fischer diagram in the center of the figure. DS3.5 describes the bond between C7 and N12 as “aromatic.” It does not describe the bond between O13 and N1. The distances between the atoms of these three denatonium moiety representations vary drastically.
Figure 8.4.5-1 Alternate structures for the denatonium family given by different visualizer programs. The programs are unable to provide consistent representations of this family, including the specific CAS 1674-99-3. See text.
Similarly, Figure 8.4.5-2 provides two totally different representations of amiloride (DB00594 from the Canadian Data Bank), both showing the molecule as planar. The left frame using the Jmol visualizer suggests the lower two outer nitrogen atoms have a spacing of 2.86 Angstrom. The right frame using the DS3.5 visualizer shows the same molecule, from the same Jmol file. In this case, the two lower outer nitrogen atoms have a spacing of 4.723 Angstrom. Simple hand calculations using accepted bond lengths strongly suggests the Jmol visualizer should not be relied upon even though the underlying file may be correct, as represented by the DS3.5 visualizer.

At the current time, it is mandatory that every representation provided by a visualizer be checked manually for reasonableness. It is similarly necessary to qualify every data file adopted from an exterior source.

The visualizers typically use a file that represents the average position of each atom in a molecule over a long time interval. The individual “snapshots” used in the averaging are known as conformers or conformers. It is frequently useful to examine the range covered by the conformers applicable to a given data file, particularly for larger molecules, and particularly proteins. See Section 8.5.9.6.

The currently most capable, and readily available, of these is Jmol, an open-source program building on the earlier programs. It has been used most extensively in protein and other large molecule explorations. Until quite recently these programs as a group could not render hydrogen bonds properly. With the advent of Jmol version 12.0 in 2010, Jmol can now render hydrogen bonds (hbond) adequately.

Visualizer version 3.5 from the Discovery Studio of Accelrys Software, Inc. is another program available in a free and supported version. It is quite powerful but apparently poorly documented in the free version.

The focus here is on small molecules as opposed to very large proteins, etc.

Jmol and Visualizer rely upon data files developed in a molecule building program. There are several data bases focused on these files that are proprietary and several that are freely available. In most cases, the programs are supported by individuals or small groups (frequently within larger organizations) which limits their speed of development, debugging and documentation. It is difficult...
to find a comprehensive tutorial or manual for J mol, Visualizer or many of the other modeling and rendering programs.

Where feasible, (either the needed molecule has already been entered by others or this author has added specific molecules, into the J mol library. There are a variety of libraries being assembled but it is difficult to determine the precision of the molecules included. J mol offers the option of accessing several of these libraries with little effort.

The best estimate of the d-values based on J mol will be determined and used in the following analyses. The goal is to identify the J mol values in some specific way, possibly using italic type xxx.

PubChem is providing 3D molecular structures using its own 3D viewer that is quite primitive as of 2012.

As far as can be determined, only a few viewers will allow measurement of the distance between an atom and the centroid of a phenol or other ring structure, or to the center of a covalent bond. In some cases, the measurements offered are difficult to implement from the keyboard and may be less than precise. Thus, many of the d-values of interest in gustation, and olfaction, must be calculated using the bond distances and angles taken from the 3D images.

The J mol rendering program is totally dependent on the data base file (either .pdb used for large proteins or the simpler .xyz file format frequently used for simpler molecules). The file formats do not include any temperature data nor identification of the author, although there is some movement toward establishing ownership to some of the models produced. The atom positions are given relative to a three dimensional coordinate system that generally does not account for rotation of the ligands around a single bond, or other more sophisticated concepts. The bond lengths displayed frequently vary from those shown in Figure 8.6.1-9 of this chapter (which are admittedly drawn from a variety of investigators using technology of the last half of the 20th Century).

As an example, the distance from O4 to O5 of glucose-D-alpha varies from 2.88 Angstrom (www.edinformatics.com),
3.412 Angstrom using DS Visualizer,
4.14 Angstrom (http://www.biotopics.co.uk/JmolApplet/glucosejdisplay.html ), to
4.23 Angstrom (using J mol version 13.0.8 installed on my Windows XP machine and calling an unknown source file.

In fact, the O5 oxygen is attached to a methyl group connected to C5 and able to rotate about its single bond as shown in an appropriate MEP representation (recognizing the noted rotation). Neither of the cited locations render the MEP potential for their molecules. In that sense, they are both obsolete. Figure 8.4.5-3 from some class notes from the University of Texas clearly shows the MEP field of two molecules due to their thermally induced rotation along with their dipole moment and Fischer Diagram174. While nominally planar, the formaldehyde molecule exhibits a cylindrical MEP when free to rotate. Using the C =O bond length of 1.22 Angstrom and the dipole moment of 2.4 Debye, the dipole potential can be calculated as 1.96 electrostatic units (esu. See next section for the definitions of these terms).

Using J mol v. 13.0.8, and citric acid from PubChem, the carboxyl groups show 2.27

174(Class notes) http://www.utdallas.edu/~biewerm/10-alcohols.pdf
Angstrom and 123.1 degrees between the oxygen atoms while similar renderings give 2.21 and 120 degrees.

The bond lengths in these renderings depend on the molecule building program used. Each employs one or more subsidiary structure optimization routines after building a specific molecule. There are a variety of these with most builder programs offering a choice of routines to employ. In ArgusLab for instance, the author notes that following optimization using the PM3 routine, “The bond length should be 1.391 angstroms. The experimental value is 1.399 angstroms. PM3 does a pretty good job with molecules like benzene.” A difference of one part in one hundred is only marginally adequate for developing the theory of chemoreception.

Because of these and other current limitations, the admonition by Angel Herraez is critical, “it is the responsibility of the user to confirm the accuracy of any rendering.” In the case of the citric acid shown on his site, the angle between the two oxygen atoms is given as 120 degrees where most textbooks give the angle as 109.5 degrees. The NYU rendering of the carboxylic acid group of leucine gives 122.05 degrees but shows the hydroxyl group as =O–H and the single oxygen as –O. The distance between the two oxygen atoms is the expected 2.337 Angstrom. Many renderings do not show the double bond associated with the one oxygen atom but do give the bond lengths as different between the doubly bonded oxygen and the singly bonded hydroxyl group.

This rendering problem is a major one. It can be overlooked in pedagogy at the students peril, but not in academic research.

Herraez has provided a valuable set of links to sources of molecules and other tabulations, http://biomodel.uah.es/Jmol/manual/en/inicio.htm. It includes sources of smaller molecules. Many of the links are obsolete or not maintained adequately. Many have been moved to http://archive.org and their internal options are no longer functional. Most employ early Jmol versions or Chime.

The 2011 supplement to the Herraez book notes the maturation of the latest version of Jmol and notes,

“Jmol now uses by default somewhat reduced van der Waals radii and in ball and stick mode atoms are rendered at 23% of it.” “There is also a small difference in radii used when the model comes from a non-pdb format, or a pdb format with or without hydrogens.”

MEP mapping has only become available in Jmol with version 10.9.63. Coordinate bonding has only been available in Jmol beginning with version 12 (early in 2010) and there are currently very few examples of its use available. No examples of hydrated molecules involving coordinate chemistry have been located on the Internet as of this writing. Version 13 of Jmol has just been released (late 2012).

Jmol does not appear to properly render aliphatic-aromatics, asymmetrical cyclic molecules critical to the understanding of olfaction.

It is not clear that Jmol is ready for use in chemical sensing where the precision of the bond lengths and angles shown in the rendering can be questioned. Three digit accuracy in the final bond lengths and angular measurements are critically important.

Figure 8.4.5-4 illustrates another problem in determining the best d-values for use here. While it is conventional to consider the bond structure between the two oxygen atoms as a straight line, it clearly is not at the detailed level. Quoting Chaplin, “It should be noted that the two water molecules are not restricted to perpendicular planes and only a small proportion of hydrogen bonds are likely to have this average structure.”

---

The Jmol program gives d-values based on the numerics added into its parameter files. There is currently no traceability of these values to the underlying chemistry (such as cited below in March). Thus, its values are not necessarily the same as those found elsewhere in the literature. Adding to the problem is the sensitivity of these calculations to temperature, state of solvation, and Brownian motion.

Finally, as the sophistication of the analyses increase, it is important to recognize that bond lengths vary significantly depending on the actual “bond type” (1s, 1s2, etc.) involved, defined by the quantum-mechanical structure of the specific orbital. Only texts in advanced organic chemistry typically address these questions\(^{176}\). March provides specific bond lengths for a variety of typical compounds, and caveats these values are chemically specific. They also note the precise values of interest are frequently obtained by x-ray diffraction for solids, electron diffraction for gases and only with difficulty by spectroscopic methods for other materials. They do note the d-values for a given bond type typically varies by less than one percent.

March also introduces an additional level of sophistication regarding the bond energies of organic reactions (pp 24-27), noting the average bond energies, \(E\), may vary significantly from the dissociation energy, \(D\).

March only briefly addresses coordinate bonding (pg 76), as appropriate to his time period.

Saccharine and Acesulfame K.

He offers to prepare additional Jmol representations on request.

Angel Herraez is very active in modeling molecules with Jmol. See http://biomodel.uah.es/en/model3/index.htm for a set of biological bilayers with and without surface water. The difference between the palmitic and oleic strands can be seen. Little focus was placed on the head-groups but the illustrated group appears to be phosphatidyl ethanolamine (PtdEth)

8.4.5.1 Investigation of various molecule builder programs

A molecule builder program is needed to tailor some of the molecular structures appearing in olfaction. Several builders have been examined cursorily. A major problem in using the results prepared using these programs by anonymous investigators is the ease with which individual bondlengths, bond types and bond angles can be changed (not necessarily in unison). This makes it easy to describe irrational molecule configurations without any indication of such changes in the data base files.

ArgusLab. Development activity related to this program appears to have stopped around 2004, version 4.0.1 (although the author, Mark Thompson, is still active in the field). No concise tutorial is available. A fairly large and convenient template repertoire is presented. The program offers a variety of (obscure to this investigator) optimization routines. It also offers stereo viewing using red-blue lenses, but not split screen stereo.

The program does not appear to present the two amino acids, glutamic and aspartic acid in their complete ionized form. This is critical to understanding the role of these two amino acids in powering the neural system. The complete forms are usually shown with two carboxylic acid groups. Upon removal of one of the hydrogens from a OH group, the glutamate or aspartate ion is shown with the appropriate negative charge.

The one carboxylic acid group is shown as resonant with one resonant bond length at 1.42 Angstrom, the other at 1.23 Angstrom and an angle of 116.03 degrees instead of the more commonly used 1.27 Angstrom for both and 109.5 degrees. It uses 1.27 for the double bond instead of the more common 1.22 Angstrom.

ArgusLab appears to hang if it is closed without first saving any molecular design in progress. The program appears unusable as currently implemented.

DS Visualizer vers 3.5 from Discovery Studio, Accelrys Software, Inc. A very large scale program available as a free version or a supported and licensed version. Like all of these programs, it takes several hours to figure out how it operates. As an example, the program offers over 3000 sample molecules but no obvious way to alphabetize or search the list of molecules. The list appears to contain a great variety of very specialized “orphan molecules” but no sugars and practically no amino acids or alcohols. The program is written primarily in Perl. It offers split screen stereo viewing but not viewing with red-blue glasses.

Using Windows Explorer to peruse the files supporting the program under Discovery Studio 3.5 /share/fragments, there are significant lists of allose sugars and various fragments of amino acids, alcohols, organic acids, rings and groups. All are in the .mol format except for the amino acid fragments and carbohydrate fragments that are in the .mol2 format. Clicking on one of these files in Windows Explorer will initialize DS Visualizer and display the molecule in the graphics windows. Fragmentary tutorials are presented but they are brief and not supported by lists of hot-keys etc. There is a 30 page tutorial addressing DS Visualizer 3.1 in German.

The method of selecting atoms for measurement is obscure. Looking at a tutorial on the Internet for version 3.1, the following is found:

One or more atoms, bonds, or molecules can be selected using the Selection tool. To select one item, left-click on it. To select more than one item, press [Shift] and left-click simultaneously. An entire molecule, or parts of it can be selected by holding down the left mouse button and dragging the selection tool around the display or pressing [Ctrl]A.

Glutamic acid is presented as a dual carboxylic acid amino acid. The two acid groups are not shown as resonant and the bond lengths appear correct. The double bond is shown as 1.22 Angstrom and the single bond is 1.43 Angstrom.

For alpha-D-Glucose, DS Visualizer shows the methyl group at C6 as in the plane of the ring and O4 in the axial position. Bond lengths are given to six place precision in the data table view. On the screen, they are given to 4 place precision. O2-O3 is given as 2.742 Angstrom for alpha-D-glucose. O3-O4 is given as 2.744 Angstrom for alpha-D-galactose. These are the two oxygen atom pairs forming the odorophore in these sugars.

8.4.6 Extending the three-point lock & key concept of stereochemistry

The following material will extend the framework of coordinate chemistry to incorporate the AH,B concept of coordinate chemical bond pairs (generally associated with Shallenberger) and the extension of that concept to the AH,B,X, or three-point, concept (generally associated with Kier). The AH,B,X concept involves the original coordinate bond pair to hold an additional element of the stimulant in a specific physical position relative to the sensory receptor moiety, so that it impacts the overall electrical dipole potential of the receptor moiety. The location of X was labeled the dispersion point by Kier (1972). These concepts are readily described using the key and lock analogy of stereochemistry. In the AH,B concept, two parameters are critically important. First, the distance between the AH (typically an hydroxyl ligand, OH) and the B (typically an oxygen ligand) elements of the stimulant. Second the magnitude of the dipole potential of the stimulant molecule. The first parameter corresponds to the distance between the tumbler of the lock, or the notch on the key. The second corresponds to the depth of the notch in the key and the corresponding critical length of the tumbler in the lock. The first parameter is critically important in determining what stimulants will coordinate with sensory receptor molecule of a specific sensory channel, and the second parameter determines the strength of the signal generated in the selected signal receptor channel.

The extended AH,B,X concept is almost exactly analogous to the (anti-theft) lock and key system used on many modern automobiles. In this analog, the parameters analogous to the AH,B concept must be satisfied, but an additional parameter must be satisfied. An additional electrical potential of specified amplitude must be applied to an additional element of the lock, usually provided by a resistor mounted in or on the key. [xxx need a figure or reference to later figure ]

These same lock and key concepts are used in both gustation and olfaction.

8.4.7 A shorthand to describe odorophores and gustaphores by Janssen

The molecular structure of tastants and odorants become very complex and unwieldy at the detailed level. Janssen has used a shorthand to describe the structure of various pharmacological preparations in a SAR context, based on a simple model of a chemical structure where each pair of shared electrons is indicated by a line between the two atoms. In his application, he sought to define more complex functional groups by alternate simplified designations. Thus, he defined the structure of a complex containing \( \text{Ar} = \text{benzene or an isosteric aromatic ring; } N = \text{ basic nitrogen and } C = \text{ carbon as} \)

\[ \text{Ar-C==C-C-N=C} \]

Janssen also defined a moiety as \( \text{AA'} = \text{isosteric aromatic fused ring structure (the rings share at least two carbons).} \)

In the following discussion, it will be useful to describe the gustophores and odorophores of a given substance using this notation. It will become clear that a typical gustadant and odorant incorporate multiple gustophores and odorophores each requiring a description of the defined form. More importantly, an adequate description of a gustophore or odorophore requires specification of its conformation, not just its constitution. Both the bond lengths between atoms and other entities as

well as the bond angles associated with adjacent bonds are required. Furthermore, the association of hydrogen with some of these structures is a critical feature. Describing the required features frequently requires a true three-dimensional approach that goes beyond the conventional diagrams.

The symbology will be extended beyond that of Janssen, along the lines of that associated with Shallenberger & Acree (Section 8.5.3)

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 center, or even the \( \pi \)-bonding cloud of the benzene ring.

X = a moiety capable of influencing the electronic energy density in a region of a receptor when brought into close proximity to that region.

Even this terminology will be extended to include sulfur (and rarely phosphorus) in these sets.

In many situations, 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. In this work, the d-value can be considered the valence of the odorophore/receptor interaction. This use of the term is feasible because the conventional usage describing the state of oxidation of an atom plays a negligible role in olfaction.

**Figure 8.4.7-1** illustrates the expanded concept.

1. The distance between the left-most oxygen and the nominal center of the \( \pi \)-cloud associated with the aromatic ring is of interest, AH–C+Ar. Note the distance to the center of the ring is beyond the first carbon from the AH moiety and is accounted for in this notation by the plus symbol.
2. The distance between the NH\_2 group and the center of the aromatic ring is of interest, AH–C–C–C+Ar. Note the distance to the center of the ring is beyond the third carbon from the AH moiety and is accounted for in this notation by the plus symbol.
3. The distance from the A of the AH of the carboxyl group, specifically the OH group, to the center of the aromatic ring is of interest, AH–C–C–C–C+Ar.
4. The distance from the A of the AH of the carboxyl group, specifically the OH group, to the O of the same carboxyl is of interest AH–C–B.

All of the distances are calculated as the direct path (the hypotenuse of a triangle) between the two end points in three-dimensional space. Each of the resulting distances relate to a distinctly separate gustophore of tyrosine. Only some of these distances may be relevant to the gustatory modality of a specific species. That species may only have receptors sensitive to a subset of these distances. Some of the potential gustophores may also include structural features that interfere with an adequate stereochemical bonding between the gustophore and the sensory neuron receptor.

The centroid of the \( \pi \)-cloud of the aromatic ring is assumed to be well defined at the geometric center of the ring in this presentation. In fact, it may not be well centered due to the presence of ancillary ligands. Defining the electronic field of fused rings and more complex structures will require additional investigation.

The literature reports additional situations where only a double bond between two carbon atoms can be considered an unsaturated center able to act as a moiety of type X. A fully conjugated carbon chain is also presumed to be capable of acting as a moiety of type X.

**8.4.7.1 Initial definition of one-dimensional taste and smell spaces**

The calculated distance-values, d-values, associated with a series of gustatants and/or odorants can be plotted on a linear graph. Such a graph will be valuable later in developing various multi-dimensional interpretations of taste and the
Taste and smell spaces of various orders have been used in the past to define various primary classes of gustatant and odorants. However, the typical gustatant and odorant is represented by a group of gustophores or odorophores. These groups can be directly related to various chemical geometries within the overall molecule. It is these chemical geometries (frequently described only by their d-values) that constitute the only classes of interest here.

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

### 8.4.7.2 Complex structural groups within chemical stimulants

Such odorants as musk are much too complex to be considered primary odorants or belonging to a primary class of odorants.

The simplest potential odorophore appears to be the highly polar carbonyl group. In its simplest form it could form a coordinate bond pair with the oxygen acting as $B$ and the carbon and an associated hydrogen acting as $AH$. Beets (1978, pp 187-188) has suggested a variety of alternate configurations depending on the specific conditions of the sensory receptors.

The first two members of subclasses of this class are formaldehyde and acetone. Another first member is phenol of the primary class, aromatic alcohols. The other classes will be defined below. More complex odorophores within a class take on much more complex conformations.

Odorophores are characterized by their structural conformation, not just their configuration. Changing the conformation of an odorophore can change the intensity of the elicited sensation significantly.

Hydrogen bonds play a major role in the stimulant-receptor relationship. However, intramolecular hydrogen bonds are largely irrelevant to the chemoreception mechanism. It is the intermolecular hydrogen bonds that are significant.

### 8.4.8 An overview of the external chemical sensory receptors

It has long been a challenge of the bioscience community to define a single parameter that could describe the performance of the external chemical receptors. This work has discovered and documented that parameter. It involves an extension of a concept employed in taste research related to both natural and artificial sugars since the 1960's and developed by Shallenberger and colleagues. By extending this concept, involving a dual antiparallel coordinate bond (DACB) between a stimulant and its receptor, such a long sought parameter is obtained. The parameter describes the perpendicular distance between the two antiparallel bonds defined above (typically in Angstroms for convenience). The single dimension d-value parameter describes the position of all stimulants to and all receptors of the external chemical senses.

Transduction within the external chemical senses involves a two-step process, first, a selective process that isolates a large group of unitary stimulants as coupling with only one of the receptors in each family shown in the following figure and second, a measurement process that determines the dipole potential (not the dipole moment) of each unitary stimulant. The term unitary stimulant is used to differentiate simple stimulants from those stimulants containing more than one ligand where each of these ligands can stimulate a different receptor/channel of one of the sensory modalities of the neural system.

### 8.4.8.1 A modality delineating chemical senses framework

It is useful to visualize the relationship between the external chemical sensory channels (at least with respect to the mammals). This is easily done by describing the step 1 transduction mechanism (the selection process prior to the step 2 measurement mechanism).
**Figure 8.4.8-1** summarizes the organization of the external chemical sensing modalities into three distinct modalities, the gustatory, the olfactory, and the oskonatory. The oskonatory modality is associated with intra-species communication and the sensory receptors found on the vomeronasal epithelium. Many of the terms in this figure will be addressed in detail in the appropriate sections of this chapter.

It will be shown that the olfactory modality only employs nine distinct olfactory receptors (OR's) and related olfactory channels communicating with the stage 2 glomeruli and higher order signal processing engines.

The number of oskonatory (vomeronasal) receptors (VR's) remains undetermined at this time but four have been tentatively identified as noted. The approximate d-values are targets based on extension of the OR's d-values. The values in parenthesis are the calculated d-values of the identified active ligands.

It appears the gustatory and olfactory modalities share the first sensory receptor channel, GR 1/OR 1. The GR 2 and OR 2 channels appear to overlap considerably at the receptor level. However, the character of the coupling stimulants are quite different. The gustants of the GR 2 channel are dominated by non-volatile sugars. The olfactants of the OR-2 channel are dominated by highly volatile arenes.

**Figure 8.4.8-2** provides a graphical equivalent of the above tabular representation. While each of the nodes in the above table represents an orthogonal sensory channel, the same unfolded d-value line can be refolded at only a few points to provide a pedagogical framework. This framework indicates clearly why there are only nine olfactory receptor channels based on the hypothesis of this work. **Section 8.6.2** provides a broader discussion of the underlying framework for this figure. While **Section 8.6.xxx** will describe an alternate spacing of the olfactory receptors, the extent of the d-values between the gustatory and oskonatory modalities is distinctly limited. The figure also indicates there are only four gustatory channels in agreement with the historical understanding. **Section 8.5.4** will show definitively that the frequently proposed “umami” channel is based on the perception obtained by combining two sensory channels, the hydrated-sodium channel (GR 3) and the glucol (or sugar) channel (GR 2), as indicated in the primary example of a “umami gustant,” mono-sodium glutamate.
As the analyses underlying this work were developed, attempts were made to identify likely chemicals that could esterify with phosphatidic acid, resulting in a reasonably viable receptor moiety. Following completion of the examination of all three external chemical sensory modalities, it became obvious that certain changes to that list as shown in the figure were feasible and might result in a simpler evolutionary development of the modalities. As an example, it is likely that tryptophan, an amino acid, could replace galactose, a sugar, as GR2. As a result, all of the olfactory receptors sensing organic odorants would be based on amino acids.

In the case of OR3 and GR3, the modified amino acid designated as 4Hi and used in Ptd4Hi could replace the cyclohexane alcohol muco-inositol in PtdIns. This would leave all of the identified GR and OR receptors (up through either OR5 or OR7) employing amino acid based ligands. However, it would result in GR3 being slightly less well matched to the hydrated sodium gustaphore based on their d-values.

No ligand for OR6 and OR8 were identified during the initial analyses of the olfactory modality. It was clear that none of the remaining twenty-two common amino acids had a sufficiently high d-value to match the requirement without modification. However, in the analyses associated with the osmonatory modality, it became clear that an unsaturated set of dodecenoic acids could be esterified with phosphatidic acid to form an adequate set (although not necessarily the real set) of VR’s. The dodecenals and shorter octenals, etc., with less than six carbons between the double bond and the carbonyl oxygen do not offer a good match to the desired d-values (Section 8.6.11.4.1).

Further harmonization of the GR and OR receptors is likely as additional experimental verification of the hypothesis presented here is undertaken.

8.4.8.2 Comparing the active ligands of the sensory receptors of chemical

In sections 8.5 (Gustation) and 8.6 (Olfaction), the detailed chemistry of several different sets of potential sensory receptors are defined. It is possible, based on these two distinct studies, to suggest a simpler and more logical set of sensory receptor ligands when these two studies are examined after the fact. Such an analysis will be found at the end of the Olfaction study (Section 8.6.12).

[See Part 1b for all Sections of 8.5 xxx This comment is probably obsolete!].

8.4.9 The Excitation/de-excitation equation of chemical sensory receptors EMPTY

Figure 8.4.9-1 shows the progressive change in both the delay and amplitude portions of the E/D
response of frog as reported by Getchell\textsuperscript{179}. Note the increasing delay before the response departs the baseline, and the reduction of the slope of the leading edge as the stimulus concentration (intensity) is reduced. Note also the constant time constant of the decay characteristic regardless of the intensity of a short interval stimulus. These are precisely as predicted by the E/D Equation. Note also the symmetry of the response to stimulation by benzaldehyde at very low intensities. This symmetry is characteristic of the Hodgkin Condition where the response exhibits only one time constant defining a Poisson equation.

Figure 8.4.9-1 The E/D performance of an olfactory receptor of frog as a function of stimulus intensity. Stimulant; benzaldehyde at levels equivalent to those on the left. Control; moist air delivered through a parallel delivery tube. Arrow indicates change in response at the termination of the stimulus (plus delay associated with the transduction mechanism). Unmarked bars along top edge designate stimulus interval. See Text. From Getchell, 1974.

\textsuperscript{179}Getchell, T (1974) Electrogenic sources of slow voltage transients recorded from frog olfactory epithelium 
\textit{J Neurophysiol} vol 37(6), pp 1115-1130
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