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."

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Neural Concepts

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August 1, 2016

[xxx remnants after 8.7 of material from Section 8.6]

8 Stage 1, Signal Generating [1]

"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

This Part provides detailed discussion of the sensory receptors related to Oskonation & chem sensing in Stage 4

8.6.11 Extension of the olfactory processes to the VNO and oskonation

Scalia & Winans[2] provided the first review of the distinct oskonatory modality in 1976, with citations to the earlier work beginning in 1970.

The hypothesis and corollaries developed for the chemical senses appear to be applicable to the subsidiary olfactory modality defined here as the oskon modality (Greek, to sniff). As noted in **Section 8.6.1.3**, it has only been in recent decades that the presence of this modality in humans has been well established. In fact, a situation known as Jacobson's puzzle has developed (Brennan & Keverne, pg 970) concerning how the function of the identified oskon modality differs from that of the main olfactory modality. The puzzle emanates from the chemical theory of the neuron which is not supported here. A premise of that theoretical development is that major urinary proteins (MUP's) play a role in the VNO.

Figure 8.6.11-1 shows the organization of the oskonation modality, using the old terminology as reported recently by Brennan & Keverne. They provide a overview of its operation from their

[1]August 1, 2016

[2]Scalia, F. & Winans, S. (1976) New perspectives on the morphology of the olfactory system: olfactory and vomeronasal pathways in animals *In* Doty, R. *ed*. Mammalian Olfaction, Reproductive Processes and Behavior. NY: Academic Press Chapter 2

perspective. Note all of the schematic exists within the electrical circuits of the neural system until the release of endocrine substances by the medial hypothalamus. The oskonation modality largely parallels the olfactory modality (**Section 8.6.7.1**) but does not necessarily intersect with it. They discuss different circuit options between the vomeronasal epithelium and the stage 2 signal processing circuits. The label "Main olfactory system" refers primarily to the area of the central nervous system dealing with the chemical senses and not just olfaction. As an example, they note, "Although both the main (MOB) and auxiliary (AOB) olfactory bulbs project to the amygdala, they terminate in adjacent, non overlapping areas (Scalia & Winans, 1975)."

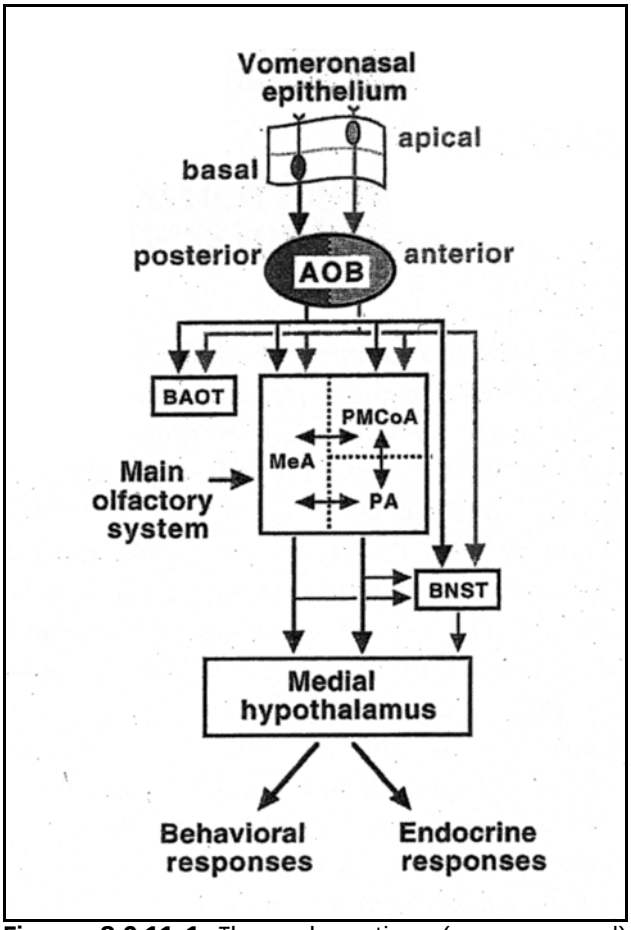

Figure 8.6.11-1 The oskonation (vomeronasal) modality of Brennan & Keverne. See the original paper for details related to the labeling. From Brennan & Keverne, 2003.

8.6.11.1 The role of the oskonatory (VNO) modality

The role of the oskon modality is different from that of olfaction. Where olfaction is designed to analyze a great range of stimulant mixtures and report their properties to the higher cognitive centers of the neural system, the oskon modality is more focused. It's purpose is to recognize only a very specific range of stimulants to the exclusion of virtually all others. When encountering such a select signal mixture, it is designed to cause a set of actions not well recognized by the organism, or the scientific community at this time. These actions generally relate to the propagation of the species.

Johnston has noted that in hamsters, both the olfactory and oskonatory modalities must be intact for males to successfully mate[3].

A challenge with regard to the oskonatory modality is that its stimulants may not be recognizable by the conscious executive of the target animal. It may not be perceived and reported as a declaratory memory. It may only be perceived within the nonconscious executive and be acted upon via the limbic system. Because of this situation, it may be difficult to isolate primary oskonatory vodorophores except based on their molecular structure (with d-values greater than 8.5 Angstrom). Many chemicals described as pheromones in the literature may actually contain both vodorophores and odorophores. Such chemicals as muscone_10483, civetone_4475121 and exaltone_9980 may or may not contain actual vodorophores while exhibiting distinctive odorophores, 4.289, 5.132 and 5.146 Angstrom respectively. The later two are recognizable by humans via the "musk" channel of olfaction.

A chemical frequently discussed in the pheromone literature is musk tebetine_60681. This chemical is of plant origin, even though it is frequently described as a pheromone among animals. It does exhibit a d-value of 5.211 Angstrom between a pair of nitrogen orbitals, a d-value of 7.434 Angstrom between a pair of oxygen orbitals and is clearly perceived as an odorant among humans. It may or may not exhibit a definitive vodorophore when in solution.

8.6.11.2 State of research in species specific signaling–Oskonation

[3]Johnston, R. (1983) Chemical signals and reproductive behavior *In* Vandenbergh, J. *ed*. (1983) Pheromones and Reproduction in Mammals NY: Academic Press Chap 1

4 Neurons & the Nervous System

Research in the field of species specific communications via volatile chemicals in the air has slowed to a crawl in the last two decades because of the conceptual framework initiated in the 1950's. That framework defined a pheremon (*pherein*, Greek, to carry plus *hormon*, Greek to excite or stimulate) and little else regarding what was known as the auxiliary olfactory modality;

Karlson & Luscher wrote in 1959, "During the past few decades, investigations have been made into various active substances which, though they resemble hormones in some respects, cannot be included among them. For example, the sexual attractants of butterflies are, like hormones, produced and secreted by special glands; minute amounts cause a specific reaction in the receptor organ (the antenna of the male), which eventually leads to a state of copulative readiness. Unlike hormones, however, the substance is not secreted into the blood but outside the body; it does not serve humoral correlation within the organism but communication between individuals[4]."

In a brief followup, they clarified their position;

"It was our aim to introduce, for a class of substances, a scientific term of international usefulness. Based on a clear definition, it should be a short word easily pronounced in many languages. This is not the case with 'pheromone'. It must be admitted that the derivation of 'pheromone' from hormone is questionable. We would therefore not insist on it ; but we regard the ending 'mone' as a proper suffix which is used in hormone, gamone, termone and pheromone[5]."

It is now clear that the materials in question do not have the chemical structure of hormones (typically enzymes) but are generally aliphatic alcohols or aldehydes, and arene alcohols or aldehydes. It is also clear that these chemicals with molecular weights in the 200 to 500 range are not supported by or otherwise associated with any protein material, even a simple peptide or dipeptide. Furthermore, the volatile material propagated between members of the same species is not employed as an enzyme (noted by xxx. It is used to stimulate the creation of an electrical signal by the exterior sensory neurons of the neural system in the same manner as any other odorant.

Because of the failure of the underlying framework, the activity in the genetic community has also slowed significantly. Attempts to explicitly identify genes creating protein based pheremones have not been successful[6]. Quoting Lancet et al. under the title, "Some open questions" in 1993, "These questions remained unsettled for a long time, because continuous efforts failed to discover olfactory receptor proteins and their genes[7]."

[xxx review wording based on modification to Wyatt's interpretations]
Based on the above background, more recent laboratory investigations confirming the character of the chemicals employed in communications between members of the same species (conspecifics), and the hypothesis and corollaries presented here, the conceptual framework based on pheremones is dismissed as faulty (falsified). No attempt is made to modify or redirect this falsified framework.

An entirely new and different framework is presented to describe the operation (oskonation) of the auxiliary olfactory modality based on the Electrolytic Theory of the Neuron. It includes a more complete vocabulary necessary to support discussions within the framework, and laboratory results supporting that framework. The framework is based on the d-value parameter drawn from the structural chemistry of the chemicals, but does not rely upon the conventionally defined chemical groups that form that structure. Following the terminology developed for the olfactory modality, an alternate set of names are suggested here to describe the processes involving the vomeronasal

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[4]Karlson, P. & Lüscher, M. (1959) 'Pheromones': a New Term for a Class of Biologically Active Substances Letters to Nature, *Nature* vol 183, pp 55 - 56 doi:10.1038/183055a0

[5]Karlson, P. & Lüscher, M. (1959) The Proposed Biological Term 'Pheromone, Letters to Nature, *Nature* vol 183 27 June 1959.

[6]Chadwick, D. Marsh, J. & Goode, J. *eds*. (1993) The molecular basis of smell and taste transduction. CIBA Foundation Symposium 179. NY: John Wiley & Sons pp 43, 64 & 73

[7]Lancet, D. Ben-Arie, N. et al. (1993) Olfactory receptors: transduction, diversity, human psychophysics and genome analysis *In* Chadwick, D. Marsh, J. & Goode, J. *eds*. (1993) The molecular basis of smell and taste transduction. CIBA Foundation Symposium 179. NY: John Wiley & Sons pp 132-133

portion of the neural system;

> **Oskon–** (from the Greek, to sniff)– To sense specific volatile chemicals released by members of the same species (conspecifics).
>
> **Oskonation–** (from the Greek, the act of sniffing)– The global title for the operation of the external chemical sensing portion of the neural system devoted to conspecific communications.
>
> **Oskonatory–** (adjective form of oskonation)
>
> **Vodorant–** (modification of odorant)– A volatile chemical of less than 500 mol wt. designed to stimulate the sensory receptors of the vomeronasal receptors of a conspecific.
>
> **Vodorophore–** (modification of odorophore)– A structural arrangement within a vodorant capable of forming a DACB couple with a vomeronasal receptor (VR) and exhibiting a d-value greater than 8.5 Angstrom (est.).
>
> **Vomer–** a thin flat bone dividing the two chambers of the nasal cavity and supporting the vomer epithelium containing the oskonatory modality receptors, VR's.

A vodorant must contain at least one vodorophore with a d-value greater than the threshold value of approximately 8.5 Angstrom. It may also contain one or more odorophores. A vodorophore can have any of the configurations found in odorophores but must have a d-value greater than the threshold value of approximately 8.5 Angstrom.

Several vodorants have been identified empirically. They are specific stereomeres of aliphatic alcohols in some insects and in mice. At least one found in humans and porcine animals has been identified as a fused multi-cyclic carbohydrate with a d-value of xxx.10.016 Angstrom.

[xxx modify wording here]
The term pheromone was never developed sufficiently to separate it into the two components, a vodorant and an included more specific vodorophore. **Section 8.6.11.4** will expand on this shortcoming.

It is important to note that various pheremones may contain both odorophores and vodorophores. In general, the human can perceive the odorophores via its conventional olfactory modality. The human may not be able to perceive vodorophores (of his or other species) that only affect the oskonatory modality passing signals up the limbic neural system.

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With the d-value based hypothesis of this work, the Jacobson puzzle is easily resolved and the need for MUP's is deprecated. The VNO is clearly a portion of the oskonatory modality, historically considered a subsidiary to the olfactory modality and relies on the same fundamental operating mechanisms. Only molecules of sufficiently low molecular weight (below 500) to exhibit adequate volatility at exothermic animal temperatures are employed. This requirement effectively eliminates proteins from participating in VNO modality operation. The oskonatory modality effectively extends the d-value range of the olfactory modality to greater than 11.0 Angstrom to accommodate the additional requirement for a means of detecting odorophores associated with individual animal species. In this regard, the OR 10 channel defined tentatively in the above material can be dual labeled the OR 10/VR 1 channel pending additional investigation. The limited data available suggests the presence of VR 2, VR 3 and probably a VR 4 as a minimum.

Like other olfactory sensory neurons (and the sensory neurons in general) the vomeronasal receptors, VR, are known to be continually replaced from basal stem cells.

Brennan & Keverne note, "Because the VNO is a blind-ended, mucus-filled tube, the VR's are isolated from the airstream that passes through the nasal cavity during normal respiration." This feature may prevent the vodorophores stimulating this organ from escaping as readily as the odorophores of olfaction.
It appears the vodorophores are a subset of the odorophores of olfaction. While a number of chemicals have been identified as potential vodorants, their distinct properties have not been previously identified.

The source of human (and probably most animals) pheromones appear to be the apocrine glands, and potentially sebaceous glands, associated with the hair follicles in specific area of the body (Wyatt, pg 284). Specifics of the human pheromones are treated primarily form the behavior aspect in Wyatt's chapter 13, particularly with respect to the levels of specific anosmia reported.

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Doty edited a volume in 1976 that focuses mainly on the behavioral aspects of mammals attributed to pheromone related activity[8]. It included a brief review of early attempts to utilize specific chemicals in threshold experiments, including a few now identified as pheromones, in Chapter 15.

Vandenbergh has edited a volume on "Pheromones and Reproduction in Mammals" that is quite comprehensive but only in the area of behavior[9]. It is extremely limited in the area of chemistry. However, it does include a chapter on the organization of the exterior chemical sensing modalities that will be addressed in later chapters of this work.

8.6.11.3 Terminology related to the VNO–Oskonation

The terminology associated with the VNO has not evolved to an adequate level. The original concept was that the chemical passed between members of the same species to identify each other were proteins and that because they generated a response in the receiving animal, they were described as hormones. Thus, the name pheromone was developed from the Greek based on phero, to carry, plus hor(mone). ***It is now clear that most of the chemicals involved are not proteins, do not act as conventional hormones and the designation is inappropriate.*** It is now known that many of these agents are in fact aliphatic alcohols and many more complex agents may be arenes, made up of benzyl rings and aliphatic side chains containing a variety of orbitals including hydroxyls, aldehydes or C=C bonds.

Wyatt has prepared the current "bible" on pheromones (vodorants) from the behavioral perspective[10]. He has only touched on the chemistry of these substances and has virtually completely ignored the chemistry of the sensory receptors. His only comment concerning the character of the receptors is perfunctory and in the appendix A2 on isomeric chemistry, "and pheromones are detected by receptors, both of which are proteins, . . " In his broader discussion, he never establishes that the pheromones are proteins and shows that most of them are not (albeit they may be found in association with proteins, generally in the urine). He also makes the perfunctory statement that pheromones recognize their substrates by shape in three-dimensions. Unfortunately he does not demonstrate that assertion either. This work shows it is not the 3D shape, but a specific distance between pairs of orbitals on the exposed surface of both the receptor and the stimulant.

Wyatt's section 9.2.1 infers that OR's employ proteins in their transduction process(es) but never identifies a single specific protein. He relies entirely on inferences drawn by the genetics community during the 1990's.

Wyatt has provided a clearer understanding of the character and role of the pheromones in his definition. He defines a broad class of chemicals used in animal communications as semiochemical. He specifically omitted any suggestion that they were proteins when he says, "Pheromones are a subclass of semiochemicals, used for communication within the species (intraspecific chemical signals). Pheromones were originally defined as 'substances secreted to the outside by an individual and received by a second individual of the same species in which they release a specific reaction, for instance a definite behavior [releaser pheromone] or developmental process[primer pheromone]' (Karlson & Luscher 1959)" He interjected, "The word pheromone comes from the Greek *pherein*, to carry or transfer, and *hormon*, to excite or stimulate." Finally he contrasted pheromones and hormones by saying, "The action of pheromones *between* individuals is contrasted with the action of hormones as internal signals within an individual organism."

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[8]Doty, R. (1976) Mammalian Olfaction, Preroductive Processes, and Behavior. NY: Academic Press

[9]Vandenbergh, J. *ed*. (1983) Pheromones and Reproduction in Mammals NY: Academic Press

[10]Wyatt, T. (2003) Pheromones and Animal Behavior. London: Cambridge Univ. Press

Wyatt has provided a two-page aid to understanding the structural notation related to organic chemistry, his Appendix A1. He should have provided a citation to a more complete guide to the IUPAC rules. His five-page guide to isometric chemistry (Appendix A2) is more complete and useful, although his treatment of *L*– and *D*–carvone can be questioned. The current Jmol model for R-(-)-carvone_388655 (also known as L-carvone or L(-)-carvone) places the aliphatic ligand out of the plane of the ring and places the C=C bond associated with the aliphatic ligand on the same side of the ring as the carbonyl oxygen. The result is the d-values of carvone may differ significantly (d = 4.899 & 2.937 Angstrom for the R-(-)-carvone), which accounts for the different scents of its isomers.

Figure 8.6.11-2 provides a broader definition of the pheromone based on more recent research. Wyatt recognizes the terms in the figure using less precise terminology (multi-component pheromone) in his table 1.1 and section 2.6. He notes that to be effective a mixture of individual odorophores must be present to satisfy a combinatorial requirement within the cognitive stage of a target species. Such a combinatorial requirement may even extend to requiring multiple pheromones.

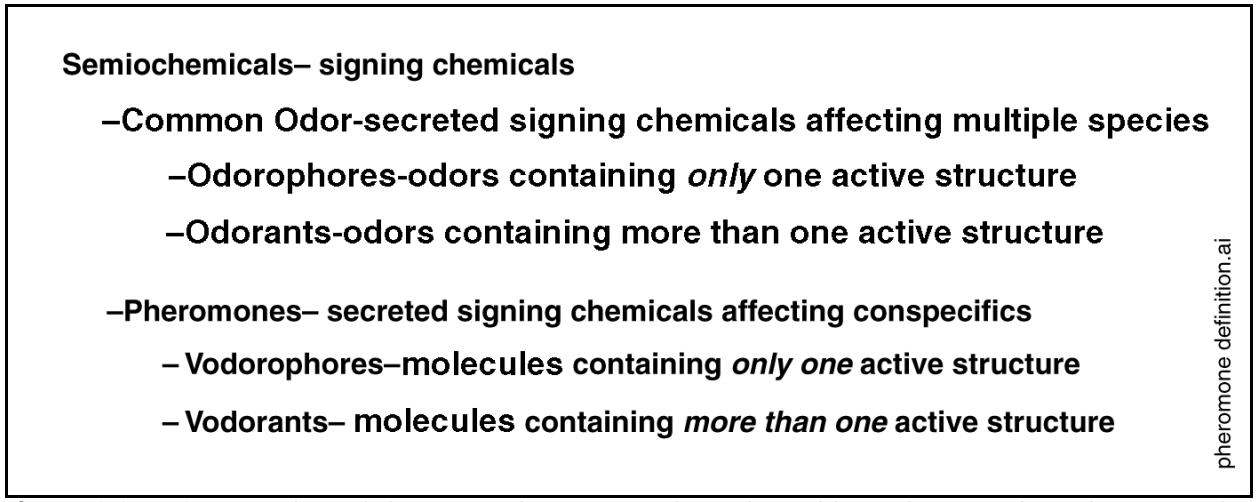

Figure 8.6.11-2 Expansion of the term pheromone based on this work. A vodorophore can be considered a minimal pheromone for the applicable VR channel. An individual vodorophore can also be considered a "singular" vodorant.

A sub class of vodorants are the mixed vodorants, those containing at least one vodorophore affecting conspecifics and one odorophore affecting a broader cohort. Wyatt describes a pheromone acting between individuals of different species as *allelochemicals* but this term has not gained traction in the literature. He also defined two peripheral situations of general interest. Predators can use the pheromone of a species as guides to the prey. In this case the pheromone is defined as a *kairomone* of the predators. Animals of one species can emit signals that benefit themselves at the expense of other species, such as attracting them to the predators location. In this case the deceitful or propaganda pheromones are known as an *allomone* of the originating species.

Wyatt also explores what appear as vodorophores in a conspecific situation may only appear as odorophores to other species. He notes the humanly perceived scent of male goats during the breeding season (page 37). He also notes the role of simple odorants as perceived by humans may be significant vodorants to social insects (page 114).

Many vodorophores may not be perceivable as scents to the conspecific as they only stimulate the oskonatory modality. If Meredith and Scalia & Winans are correct, the oskonatory neural paths may not connect to the stage 4 saliency map and thus may not be accessible to the stage 5 cognitive centers.

8.6.11.4 Suggested d-value graph of the oskonation modality

Currently the range of d-values associated with oskonation is between d = 8.5 and 11.63 Angstrom Based on several potential chemistries, it appears this range is associated with nine (9) distinct vodor receptors (VR). The VR's are separated by approximately 0.9 Angstrom with respect to the d-value parameter.

Figure 8.6.11-3 suggests the d-value graph applicable to the oskonation modality and the VNO based on the limited data available concerning the VR's and stimulants of this modality. The graph follows the format of the olfactory modality developed in **Section 8.6.2.8.1**. The d-values associated with some of the animals discussed below, and obtained from Jmol files, are shown in the figure to establish context. It shows two human vodorophores nestled close to d = 10.0 Angstrom and testosterone_5791 at 10.878 Angstrom. It also shows two mouse vodorophores at d = 8.989 and 11.160 Angstrom. The human vodorophore, Δ 4-16 Androsteronene also has an odorophore at d = 2.942 Angstrom. It can stimulate OR 2 of the olfactory modality. Some of the androsteroid compounds have been described by Beets (1982, page 102) but more current structures are available in Jmol files on ChemSpider.

The recognition of the vodorant of elephant and 140 species of moth force the preliminary definition of VR 4 at this time. Additional VR's cannot be ruled out. In fact, **Section 8.6.11.9** shows vodorophores among the moths extending to d = 16.3 Angstrom which are probably associated with a VR 9.

There are many aliphatic organic acids that can form C=C bonds farther from the oxygen atoms of the carboxylic acid group and thereby result in d-values greater than 12 Angstrom. As in the formation of acetates, the esterification of these organic acids with phosphatidic acid is straight forward and could easily result in a region of VR cells on the outer surface of the sensory neuron cilia with a range of d-values. Similarly, the potential for fused multi-cyclic rings, with more than four rings, is almost endless. Whether they will be found to be useful as pheromones is the question.

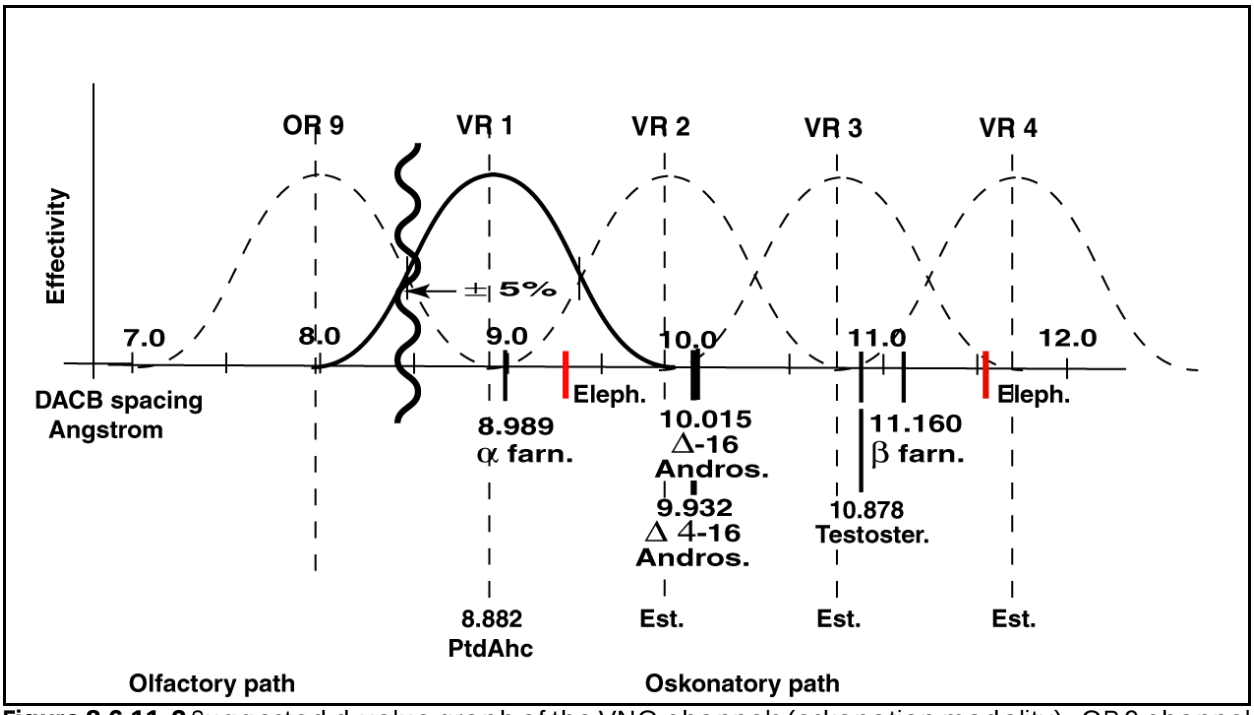

Figure 8.6.11-3 Suggested d-value graph of the VNO channels (oskonation modality). OR 9 channel of olfaction is shown for orientation. Dividing line between the modalities is shows as a wiggle. The receptor for VR 1 is believed to be PtdAhc, the ester of phosphatic acid and N-Acetyl-hydro-cadavarine [xxx an amino acid?]. The receptors for VR 2, 3 & 4 are unknown at this time. The two human vodorophores, Δ-16 androsteronene and Δ 4-16 androsteronene have nearly identical d-values as shown. Δ4-16 also exhibits an odorophore with d = 2.932 Angstrom, exciting OR 2. The two mouse vodorophores α-farnesene and b- farnesene, are also shown. The vodorophores marked Eleph. are shared between the elephant and 140 species of moth. See text.

To place the above graph in context, **Figure 8.6.11-4** shows an extended graph of the total external chemical senses space, through VR 3, based on their d-values. It can be compared to the earlier figure in **Section 8.6.1**. No unique maximum d-value for the VR's has been determined. It appears the rat may exhibit at least 4 VR's beyond the 9 OR's, based on the work of Johnson, Loeb and

colleagues. **Section 8.6.11.9** suggests this graph can be extended up to a potential VR10 based on data collected among the insects. Byers has explored a wide range of insect families and concluded there may be as many as 20 V channels.

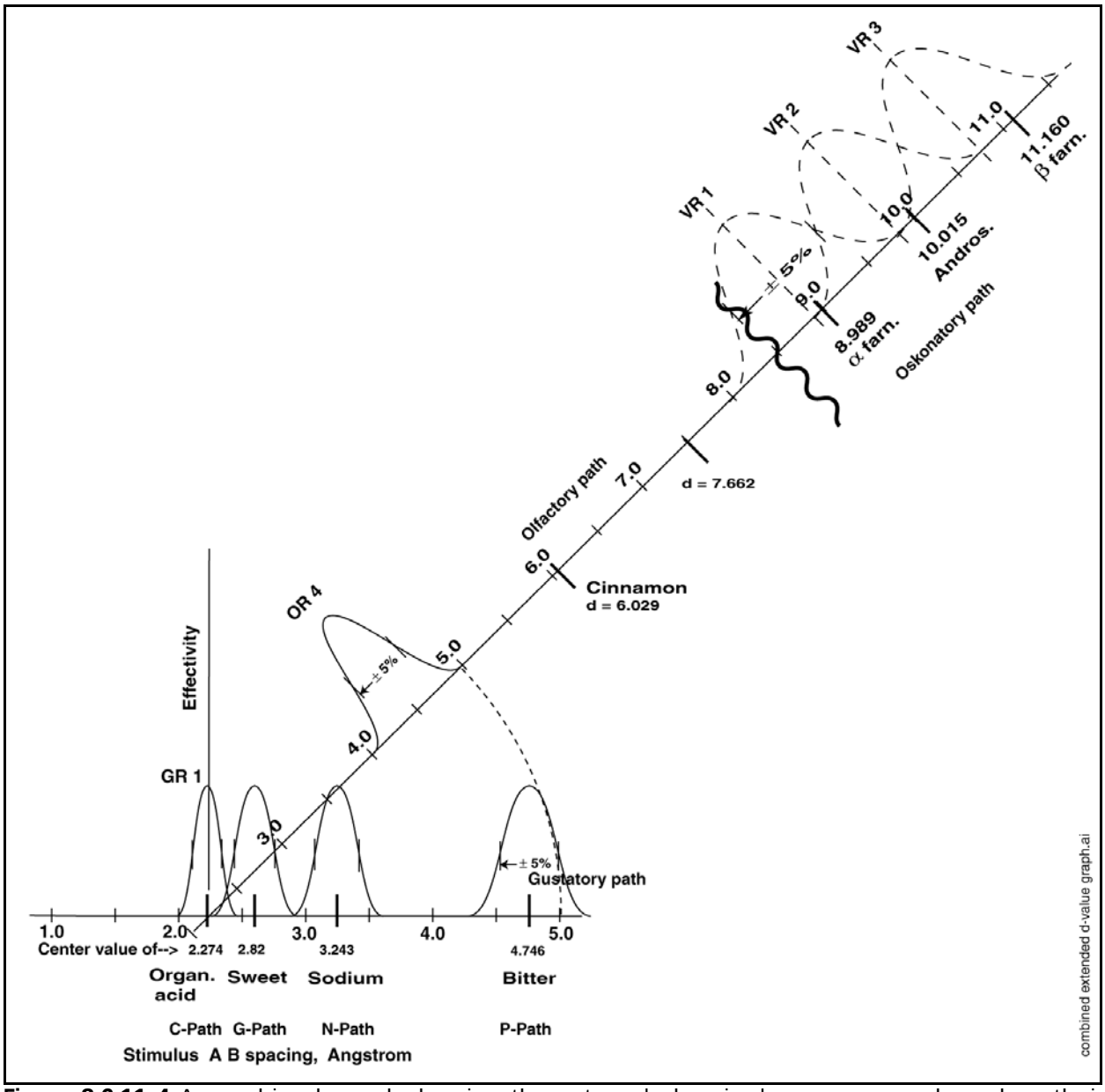

Figure 8.6.11-4 A combined graph showing the external chemical senses space based on their common parameter, their d-values. The 45 degree rotation of the combined olfactory/oskonatory axis is arbitrary for purposes of illustration. The estimated transition from olfaction to oskonation is shown at 8.5 Angstrom. The estimated effectivity characteristics of the first three oskonatory receptor channels (VR 1 to VR 3) are shown as dashed lines. The d-values for the odorophores, α-farnesene_4444849, β-farnesene_4444850 and androsterenone_5254715 are shown.

As in the earlier graph, the GR 1gustatory receptor and the OR 1 olfactory receptor are common with a d-value of 2.274 Angstrom. Only the unrotated GR 1 is shown explicitly. OR 4 is shown as exemplary of the olfactory receptor effectivity characteristics (based on the assumed ±5% width criteria. The previously labeled OR 10 is shown as VR 1 of the oskonatory modality. The estimated effectivity characteristic and center d-values for the VR's are shown dashed. The d-values for several recognized vodorophores are also indicated.

The labels, VR 1, VR 2, etc. used here refer to esters of phosphatidic acid and not to the two proteins labeled VR1 & VR2 of genetics. The series used here appears to include at least four members at this time, all esters of phosphatidic acid. In opposition to the assertion by Wyatt (page179) the VR's proposed here are very closely related to the OR's of the previous discussions in **Section 8.6**. In fact, the OR's and VR's can be considered a single family of chemicals where the designation changes depending on the species. Wyatt addresses these changes in role in his section 9.3.2.

8.6.11.4.1 The role of unsaturated fatty acids in oskonation

[xxx section may be out of place]
Section 8.5.4.10 suggests that some of the unsaturated fatty acids can be perceived as vodorophores. As an example, oleic acid_393217 contains one double bond and along with the two orbitals of the carboxylic acid group. It exhibits d-values of 10.759, 11.735 and 2.079 Angstrom. Linoleic acid_4444105 exhibits two double bonds along with the two orbitols of the carboxylic acid group and its d-values are 10.739, 11.711, 2.078, 11.777, 10.892 and 3.257 Angstrom. The d-values below 3.0 Angstrom will be perceived as acidic within the gustatory and olfactory modalities. However, the values above 10.0 Angstrom can be perceived as vodorophores stimulating channel VR 1, VR 2 and higher receptors.

[xxx example below exhibits too low a d-value. Change to oleic acid per the above paragraph]

8.6.11.4.2 The active VR structures as esters of organic acids

In developing the physical details of the oskonatory modality, the option appeared that the receptor ligands active in transduction might be long chain aliphatic carboxylic acids as suggested by **Figure 8.6.11-5**. This molecule is only used for illustration. Its d-value is much too short for oskonation. As discussed above, the lowest d-value of a vodorophore is about 8.5 Angstrom among animals.

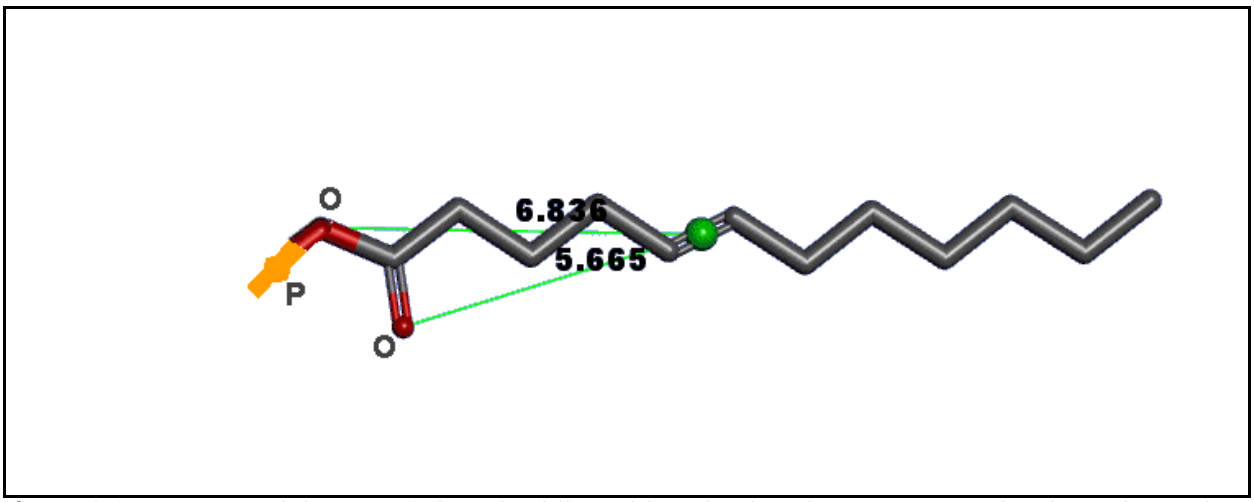

Figure 8.6.11-5 Potential ester of phosphatidic acid active in oskonatory transduction. The moiety is unsaturated (5E)-dodecanoic (or lauric) acid_4471802. An (E) or *trans*– double bond is shown at position 5. The potential DACB bonding is shown to have d-values of either 5.665 or 6.836 Angstrom. An alternate arrangement would employ a (Z) or *cis*– bend beginning at position 6. See text.

This ligand would be esterified to phosphatidic acid at the hydroxyl ligand of the acid as shown. The result is a triphosphoglyceride with one of the glycerides perpendicular to the other two in order to lie in the plane of the liquid crystalline material formed as the surface of a local region of the sensory receptor neuron cilia.. The resultant form is very similar structurally to the sphingolipids but without a nitrogen atom. This form is found at maximum concentration in nerve and brain cells of animals (Lehninger, 1970, upper right of pg 198). The active glyceride is shown in the (E) form. The choice between a (Z) and (E) form may be determined by the optimum packaging requirement of the liquid crystal on the cilia surface.

Two potential d-values are shown. The third one between the two oxygen atoms will be considered

trivial in this discussion. In the (E) configuration, the d-value between the oxygen of the ester changes in equal steps as the double bond is moved along the chain. In the case of the d-value of the carbonyl oxygen, the d-value approaches an asymptote at low values.

By inspection, stepping the double bond along the chain would define a series of VR's of either equal or asymptotic d-value spacing, **Figure 8.6.11-6**. Although the resulting d-values would be different from those based on the amino acids defined earlier within both the gustatory and olfactory modalities, they provide a compatible and alternate set. Laboratory investigation will be required to resolve the true nature of the active VR ligands at location (3) of the triphosphoglycerides. The protocol for such investigations must be carefully designed since the dodecen-, tetradecen- and hexadecen- forms of these acids are commonly found in the (1) and (2) positions of the triphophoglycerides of the sensory neuron lemma.

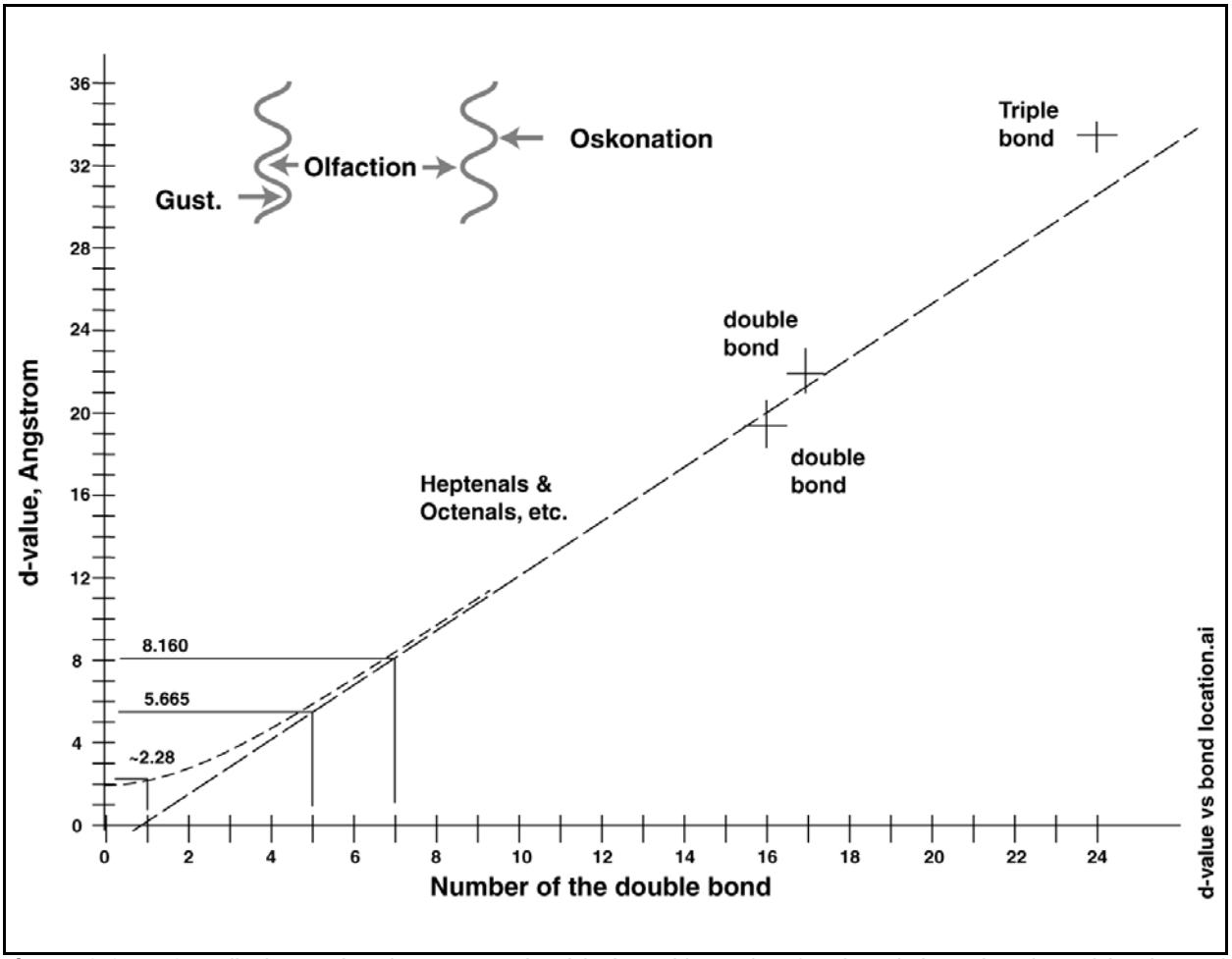

Figure 8.6.11-6 Preliminary d-value versus double bond location for the triphosphoglycerides based on an unsaturated aliphatic chain containing a carbonyl oxygen. Distances from the carbonyl oxygen to the center of the unsaturated (E) bond. Short dashed line is from data calculated using Jmol from ChemSpider files. Long dashed line is asymptotic projection incorporating data from the moth (crosses) as reported by Byers, also employing Jmol files from ChemSpider. The off-axis location of the carbonyl oxygen is only significant at short distances between the carbonyl and the double bond. Approximate regions of each modality are indicated along the top.

The variation of the crosses from moth data about the asymptote may be periodic and due to the different angular orientation of the even and odd (E) double bonds. In the case of the (Z) form, the d-values remain nominally the same but the packing configuration of the moiety on the surface of the cilia would be changed.

n-dodecanoic acid is used in the above example to establish the points along the short dashed

section.. However, the natural biological configuration can employ linear aliphatic molecules, like pentacosane (a 25 carbon molecule), to reach the desired maximum d-value within the oskonatory modality receptor space (**Section 8.6.11**).

Figure 8.6.11-7 shows an alternate set of olfactory receptors based on the carboxylic acid family esterified to the phosphatidic acid to form a family of triglyceride receptors relying upon a carbonyl oxygen and a double bond for the DACB pair.

While the family provides a plausible set of d-values at greater than d = 6.0 Angstrom, it does not support lower d-values in a way that agrees with known odorophore d-values. The series would need to be truncated at that value in favor of a different set of OR receptors at lower d-values. This subset could use the amino acids defined earlier in the preferred set of OR's.

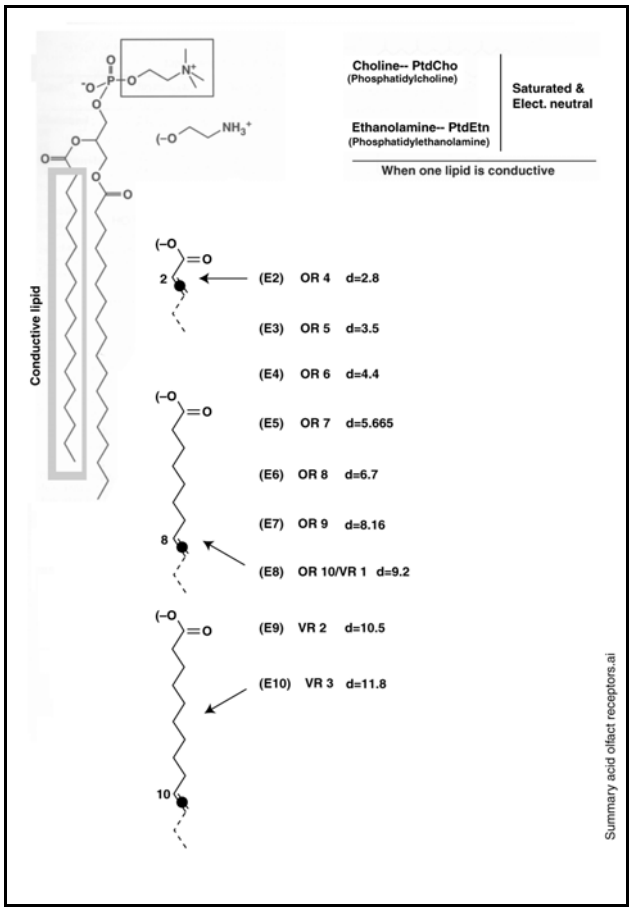

Figure 8.6.11-7 Alternate set of OR's based on a family of unsaturated carboxylic acids. The suggested OR's below OR 8 do not fit the available data for known odorophores and suggest the series is not realistic for use in olfaction.

8.6.11.5 The vodorants of the mouse

A set of potential vodorants of the mouse are shown in **Figure 8.6.11-8.**

Wikipedia has considerable material on the farnesene family but only in the context of botany (May, 2013). The opening paragraphs appear well prepared.

"The term farnesene refers to a set of six closely related chemical compounds which all are sesquiterpenes. α-Farnesene and ß-farnesene are isomers, differing by the location of one double bond. α-Farnesene is 3,7,11-trimethyl-1,3,6,10-dodecatetraene and ß-farnesene is 7,11-dimethyl-3-methylene-1,6,10-dodecatriene. The alpha form can exist as four stereoisomers that differ about the geometry of two of its three internal double bonds (the stereoisomers of the third internal double bond are identical). The beta isomer exists as two stereoisomers about the geometry of its central double bond.

Two of the α-farnesene stereoisomers are reported to occur in nature. (E,E)-α-Farnesene is the most common isomer. It is found in the coating of apples, and other fruits, and it is responsible for the characteristic green apple odour. Its oxidation by air gives compounds that are damaging to the fruit. The oxidation products injure cell membranes which eventually causes cell death in the outermost cell layers of the fruit, resulting in a storage disorder known as scald. (Z,E)-α-Farnesene has been isolated from the oil of perilla. Both isomers are also insect semiochemicals; they act as alarm pheromones (vodorophores) in termites or food attractants for the apple tree pest, the codling moth. α-Farnesene is also the chief compound contributing to the scent of gardenia, making up ~65% of the headspace constituents.

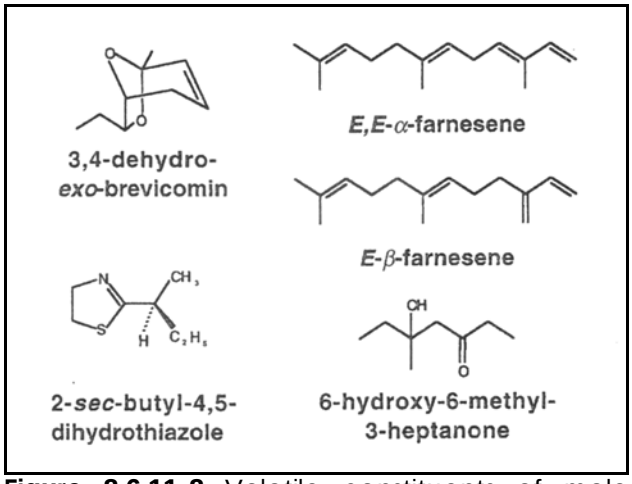

Figure 8.6.11-8 Volatile constituents of male mouse urine that are reported (probably erroneously) to be bound to the major urinary proteins and are likely to signal male gender identity. Without such binding, they are potential vodorants. From Brennan & Keverne, 2003.

ß-Farnesene has one naturally occurring isomer. The E isomer is a constituent of various essential oils. It is also released by aphids as an alarm pheremone (vodorant) upon death to warn away other aphids. Several plants, including potato species, have been shown to synthesize this pheromone (vodorant) as a natural insect repellent."

(E-E)-α-farnesene_4444849 (also CAS number · 502-61-4) is shown quite differently using DS3.5 and the Jmol file from ChemSpider, **Figure 8.6.11-9**. Its most important features are its very large d-values of 8.989 and 8.080 Angstrom. The higher value is compatible with OR 10 (or potentially relabeled as VR 1). The lower value is compatible with OR 9 as currently depicted.

(E)-beta-farnesene_4444850 (described as CAS number 18794-84-8) appears to vary only marginally in the previous figure. In this figure, the d-values have increased significantly over the values for (E-E)-α-farnesene; to the degree they suggest additional vomeronasal receptors, VR 2 supporting a d ~9.359 Angstrom and a potential VR-3 or VR 4 supporting a d ~ 11.160.

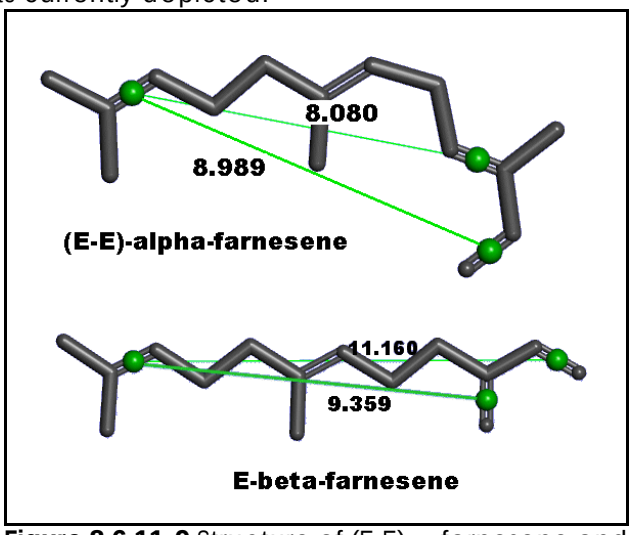

Figure 8.6.11-9 Structure of (E-E)-α-farnesene and E-β-farnesene from DS3.5 and the Jmol file from ChemSpider. The higher d-value clearly corresponds to a vodorophore stimulating VR 1 (OR 10) and the lower value may stimulate either OR 9 or OR 10 (pending additional research relative to the effectivity characteristics of those OR's).

- - - -

Based on the size and complexity of the other molecules in the figure from Brennan & Keverne, only the farnesenes appear to have high enough d-values to contain vodorophores.

- - - - -

Brennnan & Keverne suggest the transduction mechanism associated with the pheromones and their associated VR's differ from that of the olfactory modality on highly conceptual grounds related to the chemical theory of the neuron not supported here. They suggest these chemicals do not possess cyclic nucleotide gated ion channels and do not respond to cyclic nucleotide injection.

Based on the hypothesis and corollaries of this work derived from the Electrolytic Theory of the Neuron, the transduction mechanism is the same. Only the receptor portion of the outer lemma of the sensory neurons differ in different OR and VR channels.

Based on the hypothesis and its corollaries, the pheromones are not related to any particular set of proteins in any required manner, although they may be found along with a variety of proteins in the urine of animals.

- - - -

The number of VR channels and the intensity measuring capability of the sensory neurons supporting the oskonatory modality suggest a large number of animal species could be provided relatively individual vodorophore combinations to aid species selection and mating responses.

- - - -

Brennan & Keverne support the position that only one vomeronasal receptor is associated with a given sensory neuron (page 972). They support their position with several citations.

8.6.11.6 The vodorophores of human and porcine mammals

The androgens have been described as vodorophores for both humans and porcine mammals during the last few decades. Like the farnesenes, the androgens form a large family. ChemSpider lists twelve members with the same skeletal form and nearly identical molecular weight. These twelve all consist of only one oxygen orbital and one C=C bond at the extreme opposite end of the nominally planar molecule (except for a few hydrogens and carbons out of plane). **Figure 8.6.11-10** shows the 3D representation of one of these family members with a molecular weight of 272 and known colloquially as androsterenone_5254715.

Another member of this family is known as androsta-4,16-dien-3-one_83932. It has a similarly high d = 9.932 Angstrom and would be expected to stimulate the VR 2 channel. In addition, because of a C=C adjacent to the carbonyl, it also exhibits a d-value of 2.942 Angstrom that will represent a OR 2 channel odorophore in olfaction. It is known to be sexually stimulative in humans. It is proposed it stimulates the same VR in humans as androsterenone_5254715.

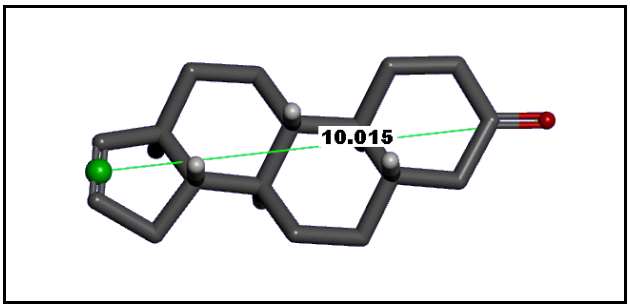

Figure 8.6.11-10 (5α)-androst-16-en-3-one; proposed vodorophore of human/porcine mammals. The d-value of 10.015 Angstrom suggests it stimulates VR 2 of the oskonation modality.

- - - - -

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

- - - - -

Wikipedia contains a montage of the many steroid families closely related to the 19 carbon androgens[11].

The androgens provide a useful extension of the archaic term pheromone into two distinct categories. The term pheromon is replaced by vodorant in this work since no hormonal action is involved and the suffix mone is inappropriate). Based on current knowledge, androsterenone_5254715 is a vodorophore. It exhibits only one d-value. On the other hand, androsta-4,16-dien-3-one_83932 is a vodorant. It exhibits two d-values affecting the chemical senses. The d = 9.932 Angstrom structure stimulates the VR 2 channel of the oskonatory modality, while the d = 2.942 Angstrom structure stimulates the OR 2 channel of the olfactory modality.

Refering to Androstenone ((5a-androst-16-en-3-one_5254715), Wikipedia also notes,

"Depending upon the (human) subject, it is reported to be an unpleasant, sweaty, urinous smell, a woody smell, or even a pleasant floral smell.

There are two different genotypes that allow an individual to smell androstenone. The first genotype, which consists of two fully functional copies of the gene, is the RT/RT allele, and the second is the RT/WM allele. The OR7D4 receptor[4] has two non-synonymous single nucleotide polymorphisms, which cause the gene to have two amino acid substitutions, which in turn cause the receptor to act differently. Those in possession of the two proper genes, (RT/RT) for OR7D4 tend to describe the odor for the steroid as the odor of stale urine. Those with only one gene (RT/WM) typically described the odor as weak or were not able to detect it. They can also find the smell 'pleasant', 'sweet' or 'similar to vanilla'.

In small amounts, the odor is hardly detectable by most people. This may be due to a polymorphism in the receptor gene that codes for the androstenone receptor.[12] However, the ability to detect the odor varies greatly. It has been shown that the odor can be detected by people down to levels of 0.2 parts per billion to 0.2 parts in 100 million. Several groups report, however, that some individuals who initially cannot smell androstenone can learn to smell it by repeated exposures to it.[multiple citations are provided]

[11] http://en.wikipedia.org/wiki/File:Steroidogenesis.svg

Wyatt does cite a paper by Gower (1990) that highlights the similarity between civetone and the putative human pheromones based on 16-androstenes. Using Gower's 2D representation, civetone and 5α-androst-16-en-3-one are identical vodorophores in the context of this work. However, using the more expanded terminology of the current day and Jmol representations, significant differences appear. **Figure 8.6.11-11** shows an expanded and annotated version. Minor wrinkles in the planarity of these materials appear to create marginally different d-values that appear to be significant.

Civetone_4475121 is a macrocyclic carbohydrate rather than a fused multicyclic carbohydrate. However, its d-value is nominally the same as the other members of the 16-androstene family. Thus, civetone is an excellent example of the fact the chemical structure of a molecule does not describe its role in olfaction.

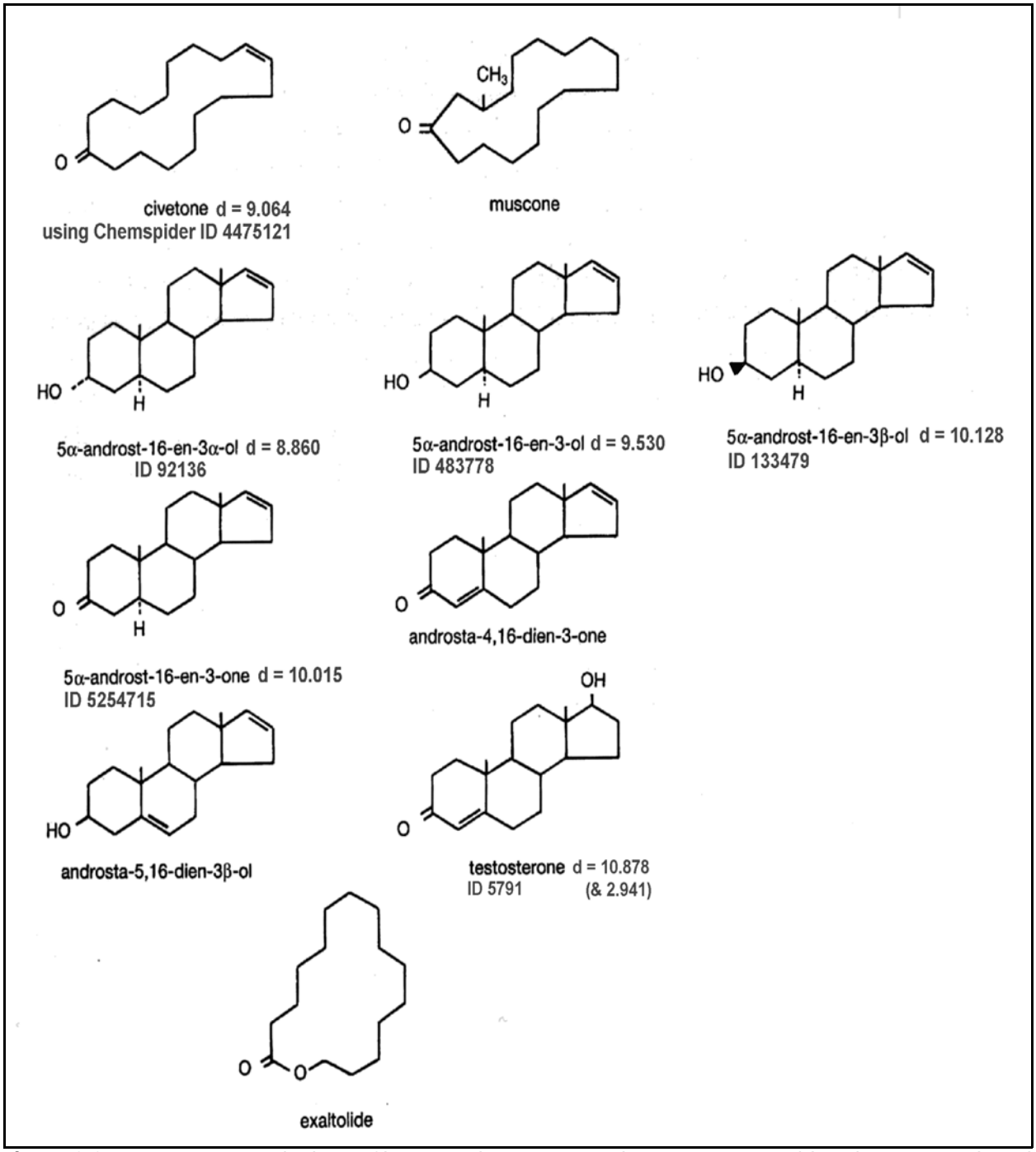

Figure 8.6.11-11 An expanded set of human pheromones. Those structures with only one C=C bond are vodorophores, the others are vodorants. Most recent representations show the right-most pentagon as equilateral. The second row shows the three variants; the 3α, 3 and 3β versions. Muscone and Exaltolide are not members of the 16-androstene family. Testosterone is not a member of the 16-androstene family because of the missing C=C bond at upper right (in favor of a hydroxyl group) Expanded from Gower, 1990.

In the expanded figure, civetone_4475121 appears to be better matched to 5α-androst-16-en-3α-ol_92136. These two chemicals would be expected to stimulate VR 1 in humans. whereas 5α-androst-16-en-3-one would appear to stimulate VR 2.

It is instructive to note that testosterone is different from the other members of the adrosterone family in having two oxygen orbitals instead of the typical one oxygen orbital and a double bond at the extreme opposite end of the molecule. Testosterone_5791 is a vodorant containing one odorophore and one vodorophore. The d-values are 2.941 and 10.878 Angstrom. This appears to be a common pattern among vodorants. The low d-value odorophore stimulates the OR 2 channel of olfaction (mildly) and the high d-value vodorophore stimulates one of the VR channels (in this case, probably VR 3 but possibly a VR 4.

Exaltolide_9980 and other macrocyclic molecules probably require the use of the Huckel Rule, and other more advanced theories of chemistry, to explain their role in olfaction and oskonation. See **Section 8.6.2.6.2**.

8.6.11.7 The vodorophores of the elephant

Wyatt has described a pheromone (vodorant) that contains two distinct vodorophores that are shared between the elephant (*Elephas maximus*) and 140 species of moth! The vodorant is (Z)-7-dodecen-1-yl acetate, a primary linear aliphatic aldehyde with a cis condition at carbon 7. Current Jmol files (specifically 4515862/CAS14959-85-5) show the carbonyl oxygen interchanged with the methyl group of Wyatt's figure. One vodorophore has d = 9.277 Angstrom and the other has d = 11.552 Angstrom. His source was Rasmussen et al. 1997. In another Jmol file, 4515862, the d-values are given as 10.468 and 9.292.

The Rasmussen et al. reports are quite detailed[12,13,14]. The second 1996 paper compares the pheromones of African and Asian ephants. Rasmussen et al. used both natural material matching that from moths, and totally synthetic material containing no protein, to stimulate elephants under a variety of ecological conditions.

Denhard et al. report a totally different set of pheromones affecting the Asian elephants[15]. They investigated 5α-androst-2-en-17-one and the corresponding alcohol, 5α-androst-2-en-17β-ol. The first compound is typically considered a human pheromone. "The present findings of two unsaturated androgens in the elephant with either a 17-oxo- or 17-hydroxy-group were surprising, because 2-en unsaturated 17-oxo and 17-hydroxy androgens have not been demonstrated elsewhere except for a report of 5α-androst-2-en-17-one in human axillary bacterial isolates (Gower et al., 1997)." They continued, "The demonstration of one keto- and one hydroxy-steroid parallels the situation in pig species in which three steroidal compounds with either a 3-oxo- or a 3-hydroxy-group (5α-androst-16-en-3-one, 5α-androst-16-en-3α-ol and 5α-androst-16-en-3β-ol; Patterson, 1968a,b) contribute to the boar pheromone and have been shown to stimulate both sexual behaviour and oxytocin release in females (Mattioli et al., 1986; Claus and Schams, 1990)."

Rasmussen et al. (1997) close with the remark, "That (Z)-7-dodecen-1-yl acetate is the major component of the Asian elephant urinary sex pheromone is indeed an unexpected finding of fundamental importance to the field of mammalian chemical communication." They did not determine where or how the pheromone originated.

8.6.11.8 The vodorophores of other mammalian species EMPTY

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[12]Rasmussen, L. Lee, T. Roelofs, W. et al. (1996) Insect pheromone in elephants *Nature* vol 379 pp 684

[13]Rasmussen, L. Hall-Martin, & Hess (1996) Chemical profiles of male African elephants, *Loxodonta africana*: physiological and Ecological implications *J Mammalogy* vol 77(2), pp 422-439

[14]Rasmussen, L. Lee, T Zhang, A.. Roelofs, W. et al. (1997) Purification, identification, concentration and bioactivity of (Z)-7-dodecen-1-yl acetate: sex pheromone of the female Asian elephant, *Elephas maximus Chem Sense* vol 22, pp 417-437

[15]Dehnhard, M. Heistermann, M. Göritz, F. et al. (2001) Demonstration of 2-unsaturated C_{19}-steroids in the urine of female Asian elephants, *Elephas maximus*, and their dependence on ovarian activity *Reproduction* vol 121, pp 475–484

8.6.11.8.1 A single pheromone in rabbit isolated by Schaal et al.

Schaal et al. have reported on the pheromones of rabbit, *Oryctolagus cuniculus*[16]. Their premise was that there was only one pheromone within the conspecifics of this species related to the mother/offspring relationship.

Schaal et al. described their criteria for identifying a pheromone unequivocally , "Although there is a long-standing semantic debate about the definition of a pheromone in mammals, we used the most restrictive meaning of the concept. Thus, five operational criteria were considered to assess whether 2-methylbut-2-enal (2MB2) can qualify as a pheromone:
1. chemical simplicity of the signal; unambiguous,
2. morphologically invariant, and functionally obvious behavioural response of the receiver;
3. high selectivity of stimulus–response coupling;
4. species specificity of reception; and
5. unconditional stimulus–response coupling.

A sixth criterion has been added by us that relates to the species specificity of emission of the odour cue."

They took pains to demonstrate that 2-methylbut-2-enal_9912 was the pheromone in rabbit's milk to the exclusion of 150 other volatiles. While they recognize the frequent presence of multiple pheromones to achieve maximum effectivity in many species, they show that in rabbit only the one pheromone is controlling and the only one present (to a high degree of probability). "It is noteworthy that this single compound accounts fully for the activity of the complex mixture of volatiles carried in milk. This situation contrasts with the great majority of the putative pheromones known in mammals, which are most often composed of mixtures that lose their releasing power after fractionation."

"The generality of 2MB2 activity was assessed in pups from other rabbit strains and breeds including angora, castor, chinchilla, laghmere, butterfly and Belgian hare. 2MB2 assays elicited searching–grasping in more than 80% of those pups (Fig. 4b), showing that genotype has no effect on its releasing power.

"At the systems level, the pheromone–behaviour coupling will permit the explanation of the chemosensory subsystem mediating its detection. It should then help in deciphering the specificity of
the activity pattern elicited in these chemosensory pathways from peripheral to higher-order neural levels." They offered no support for these assertions at the time of the paper.

The hypothesis and corollaries presented here cannot account for the pheromone properties of their single and simple carbohydrate with a formula of C_5H_8O and a d = 2.539 Angstrom. It only qualifies as a stimulant to the acidic channel, OR 1, of olfaction and GR 1 of gustation. It is suggested that 2MB2 is not a pheremone (vodorophore) but a common element in milk among animals. It represents both a gustaphore and odorophore based on its d-value. When combined with the presence of lactose, that stimulates the channel 2 OR and GR 2, the mixture found in milk is very attractive to the newborn. The pups were attracted to milk, not any species specific vodorant.

8.6.11.8.2 A single pheromone in cat (feline)

Wkipedia provides a nice popular discussion of cat pheromones with citations. They note the chemical labeled felinine_144304 and a series of degradation products they describe as putative pheromones. "Felinine then slowly degrades into the volatile MMB." The MMB's are small mercaptons with a d-value of about 5.167 Angstrom, which should smell like musk. However, felinine has two d-values of 9.248 and 10.337 Angstrom, among a larger set, which are more likely to represent pheromones. They would be expected to stimulate VR 1 and VR 2.

There are also about a dozen low d-value substances that are known as feline facial pheromones. These chemicals are usually incorporated into commercial catnip. These substances cause felines

[16]Schaal, B. Coureaud, G. Langlois, D. et al. (2003) Chemical and behavioural characterization of the rabbit mammary pheromone Letters to *Nature* vol 424, pp 68-72

a great deal of pleasure for a period of a few minutes, followed by a refractory period lasting 20 minutes to 2 hours. These chemicals are all based on a fused 6-member hetrocyclic ring and 5-member homocyclic ring. Most of the fused rings contain two oxygen atoms in nearby positions. One typically in the hetrocyclic ring and the other a carbonyl oxygen. These low d-value chemical structures do not qualify as pheremones (vodorophores) but basically very attractive odorophores and possibly gustaphores.

8.6.11.9 The vodorophores of insect species Empty

8.6.11.9.1 pheromones of the moths

The pheromones of the moths has been extensively studied and cataloged. Byers[17,18] has provided material based on the earlier work of Arn that is extensive (The Pherolist). Byer provides considerable information on the occurrence of multiple pheromones (which may contain multiple vodorophores in many cases). His investigations involved mining a large database of moth data provided by the Pherolist of Arn[19]. This list appears to have disappeared from the academic database and research along the lines of Arn appear to have been terminated. The list included 2931 combinations of 377 unique chemical names of sex pheromone attractants used by 1572 moth species in 619 genre and 49 families. The word protein does not appear in the Byers papers. All of the pheromones were aldehydes, alcohols, acetates, epoxides or methyl-branched and similar hydrocarbons. As the number of species grew over time, their use of multiple pheromones appears to have also grown. They appear to have been used in a combinatorial arrangement as the total number did not expand linearly with the number of species. Byers notes the total estimated number of moths is 185,000.

As will be noted below, many of the vodorants contain multiple vodorophores and this fact must be incorporated into any calculation of the total number of combinations available. Up to eight pheromones were found to be employed in a single species, although less than 0.5% of the population used a combination of more than six pheromones. 45% of the species employed only one pheromone. Aliphatic chains of up to 25 carbons in length were found to be present among the moth population. The extracted data would strongly suggest oskonatory modality employed up to eight vodorophore sensory receptors.

The database was searched using a second computer program that allowed queries to be changed in order to search many combinations of pheromones and pheromone characteristics. The most common pheromones (vodorants) are shown in **Figure 8.6.11-12**, although using a stick figure representation rather than a more informative 3D presentation. The molecule is not a straight chain based on its Jmol file but twists about 60 degrees at the first double bond. The longest d-value in this figure is 16.352 Angstrom for (E,E,Z)-10,12,14-hexadecatrienal based on its 3D configuration. The vodorophore would extend over 14 carbons between the carbonyl oxygen and the farthest double bond. This vodorophore would probably stimulate VR xxx based on a linear extrapolation of the VR family shown in earlier figures with an abscissa labeled d-value. The vodorant also exhibits vodorophores of d = 14.685 and 13.128 Angstrom along with a variety of odorophores with shorter d-values formed by the various double-bond pairs.

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[17]Byers, J. (2006) Pheromone component patterns of moth evolution revealed by computer analysis of the Pherolist *J Anim Ecol* vol 75(2), pages 399–407

[18]http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2656.2006.01060.x/full

[19]Arn, H. (2001) *The Pherolist* Originally available at http://www.pherolist.slu.se/index.html Ostensibly available through the WorldCat at http://www.worldcat.org/title/pherolist/oclc/044364835

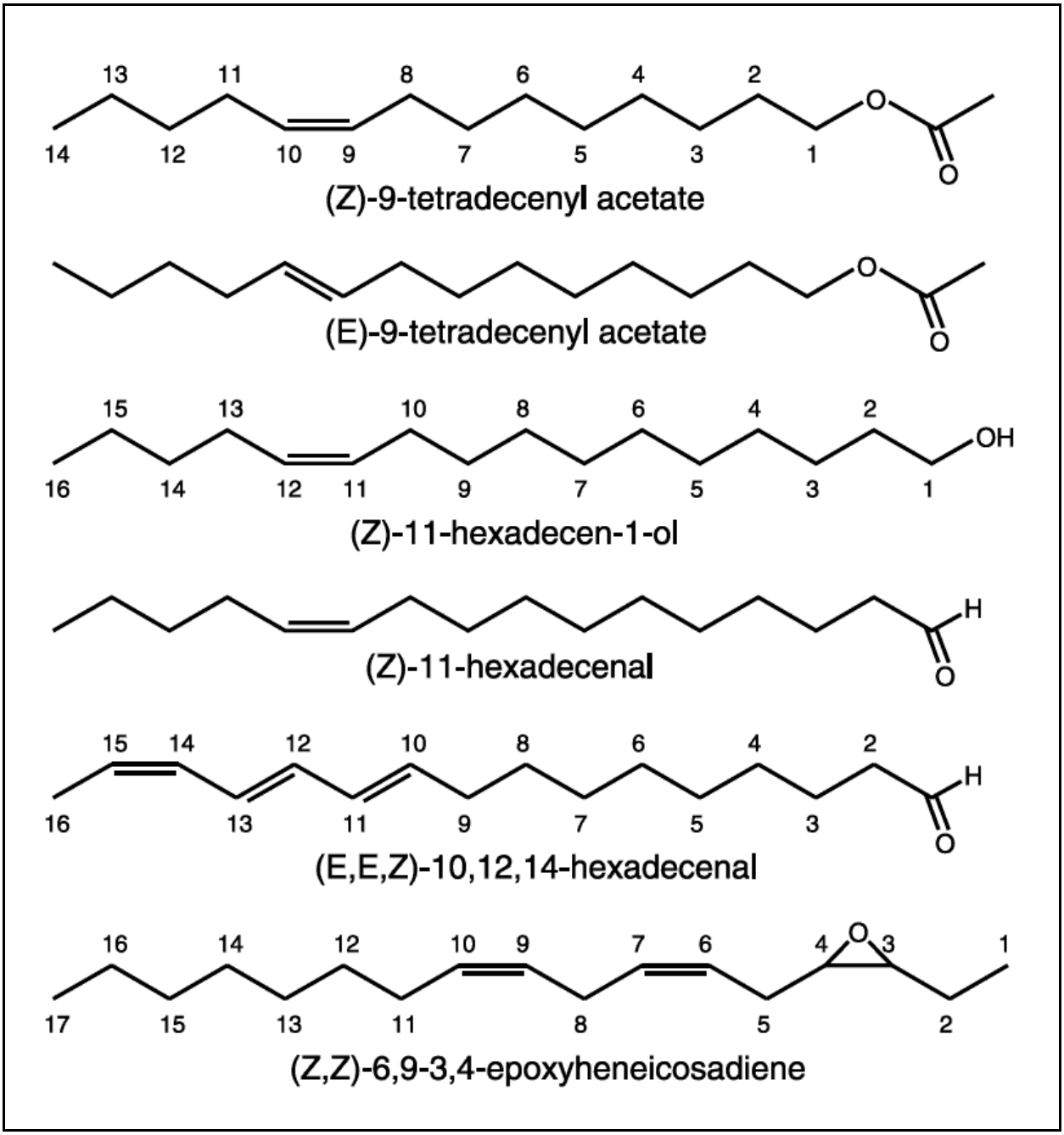

Figure 8.6.11-12 Examples of moth pheromone components: (Z)-9-tetradecenyl acetate or Z9-14:Ac in commonly used abbreviated form (the most common component used by 199 species) (E)-9-tetradecenyl acetate or E9-14:Ac (component of 17 species) (Z)-11-hexadecen-1-ol or Z11-16:OH (most common alcohol, used by 50 species) (Z)-11-hexadecenal or Z11-16:Al (most common aldehyde, used by 119 species) (E,E,Z)-10,12,14-hexadecatrienal or E10E12Z14-16:Al (used by tobacco hornworm, *Manduca sexta*) and (Z,Z)-6,9–3,4-epoxyheneicosadiene or Z6Z9-3,4epo-21:Hy (epoxide hydrocarbon used by 14 species). Data compiled from Pherolist: Arn et al. 1992; Arn 2001 by Byers, 2006.

A second database is available addressing the pheromones of all insects[20].

Section 8.6.7.11 discusses the commonality of certain moth pheromones and at least a female pheromone of the Asian elephant, *Elephas maximus*. The moths consist of "140 Lepidopteran species in 13 families (Am et al, 1992). The precise structure and d-values of the shared vodorophores may be in question. They are shown differently based on stick diagrams in Rasmussen et al. and the more recent 3D representations in the Jmol files of ChemSpider. The low number of carbons involved put this vodorophore outside the range of the Byers study.

Byers provides three dimensional graphs showing;
- the number of instances versus number of carbon atoms, and either
- the type of carbon structure,
- the various Z,E permutations available,
- the number of species in each of 12 moth families and
- the using epoxide components.

No work has been done by this author to identify the molecular structure of VR's beyond 12 carbons. A potential 12-carbon phosphatidyl lauric acid has been examined briefly.

Kasang has provided similar information concerning the moth, Bombyx mori[21]. The focus was on unsaturated long chain aliphatic alcohol molecules. By using tritiated hydrogen stimuli, they were able to determine the moth was able to sense as little as 10^8 labeled molecules of stimulant. Interestingly, they divided their stimulants into esters, alcohols and acids. It is not clear whether they employed any stimulants relatable to the picric class of stimulants, but apparently not. He draws his conclusions from a series of negative results. While he speaks of esters and acids, the only conformations he addresses are unsaturated alcohols with a double bond at the 10-carbon and 10,12-carbon (bombykol_392860, d = 2.405, 13.198 and 15.600 Angstrom) positions of aliphatic alcohols, **Figure 8.6.11-13**.

The IUPAC names for these molecules have changed since 1970. The molecule in the lower frame is nominally described as a (10E)-10-Hexadecadien-1-ol and the upper molecule is nominally described as (10E, 12E)-10,12-Hexadecadien-1-ol or bombykol without reference to their tritiation. The section to the left of the double bond is frequently shown differently in various representations but plays little role in oskonation or olfaction.

The two higher d-values would correspond to stimulants affecting the VR 5/6 and VR 8 channels as described in the following figure. The 10,12-carbon form is described as 10^3 more active than the simpler 10-carbon alcohol. This description is compatible with the predicted effectivites from the figure. Kasang's conceptual drawing of the exposed surface of the antennae is not sufficiently detailed to represent the actual process involved.

A molecule exhibiting three orbitals or other resonant structures necessarily exhibits three d-values. In this case, the lowest d-value indicates this molecule also exhibits a odorophore stimulating OR 1/ 2 of the olfactory modality as well as the oskonatory receptors.

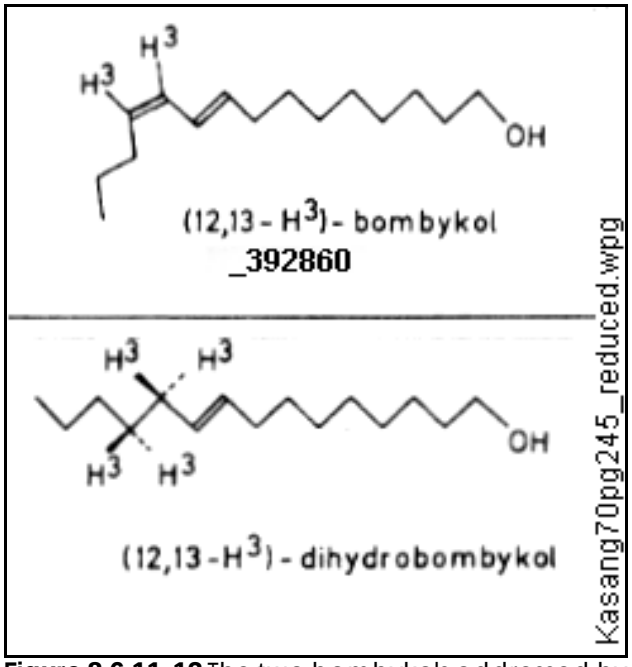

Figure 8.6.11-13 The two bombykols addressed by Kasang (1970) shown tritiated. Modified from Kasang, 1970.

[20]El-Sayed, A.(2005) The Pherobase: Database of Insect Pheromones and Semiochemicals. Available at: www.pherobase.com

[21]Kasang, G. (1970) Bombykol reception and metabolism on the antennae of the silkmoth *Bombyx mori In* Ohloff, G. & Thomas, A. eds. Gustation & Olfaction NY: Academic Press. pp 345-349

This is a frequent complication when allowing humans to describe the perceived odor of a pheromone. While it exhibits vodorophores that humans can not perceive, it also frequently exhibits an odorophore that the human can perceive.

8.6.11.9.2 Extending the vodorophore effectivity space

Figure 8.6.11-14 shows an extended family of VR effectivities based on the additional data available on moth pheromones. The spacings between the VR channels are arbitrarily taken as equal and the effectivities have been assumed to exhibit the same dispersion regardless of center line d-value. The VR 9 effectivity is based on a suggested VR formed of phosphatidic acid and the 16 carbon acetate that is described as (E,E,Z)-10,12,14-hexadecatrienal or E10E12Z14-16:Al (used by tobacco hornworm, *Manduca sexta*) after the esterification. The suffix A1 is used to indicate how many species of moth use this particular aldehyde or which species uses it. The aldehyde is numbered _9032691 in ChemSpider. The result is labeled PtdE10E12Z14 in the figure. Based on the moth data,

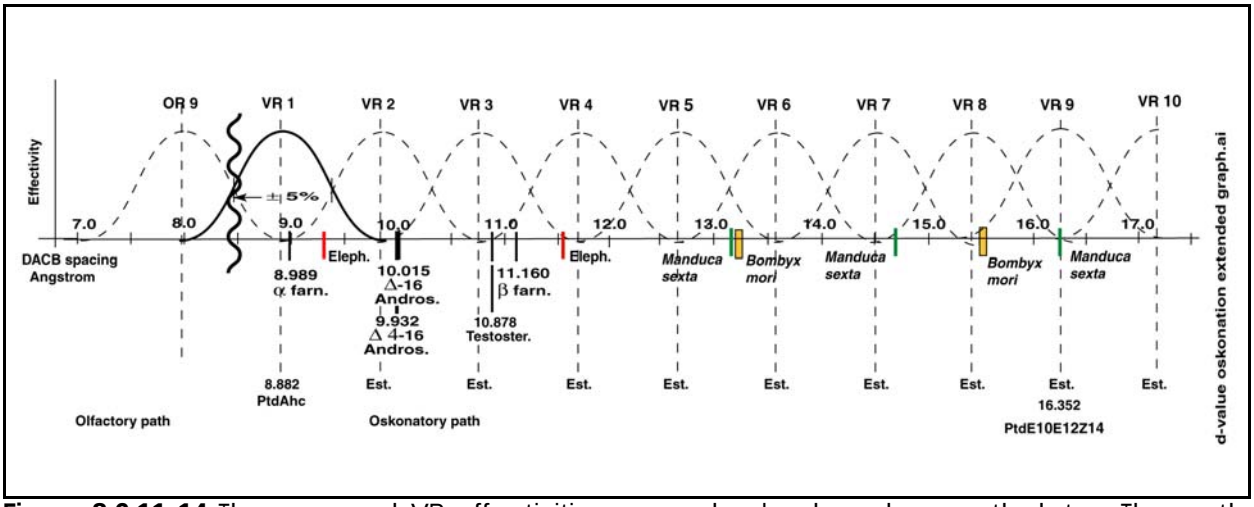

Figure 8.6.11-14 The proposed VR effectivities versus d-value based on moth data. The moth, *Manduca sexta* exhibits three vodorophores at d = 13.128, 14.685 & 16.352 Angstrom. The silk moth, *Bombyx mori* exhibits two vodorphores at d = 13.198 and 15.600 Angstrom with the latter more effective. The effectivities are shown as of constant width regardless of center values. The center line values of the VR's are based on a linear expansion of the scale for VR's 1 through 3 and the odorophores defined in this work.

PtdE10E12Z14 actually exhibits three vodorophores with d-values of 16.352 (Z14), 14.685(E12) and 13.128(E10) Angstrom as shown. As in the case of odorophores, many vodorophores can form DACBs with the defined vodorophore receptors. Because of the minimum strain in the DACB relationship, they are maximally effected in the first step of the transduction process.

The ultimate extent of this figure is expected to be related to a form of pentacosane based on Byers. However, pentacosane has been used to identify a large variety of chemicals exhibiting many different ligands and configurations. n-pentacosane_11900, $C_{25}H_{52}$, is a straight aliphatic hydrocarbon of 25 carbons and no double bonds or other orbitals. It is probable that Byers should have identified his pentacosane more specifically. A search of ChemSpider for chemical with the same straight aliphatic structure produces _137222, _454764 and _454992; all with multiple methyl groups but no orbitals. A search of C25H48O produces several pentacosanes with two orbitals;

(16E)-16-Pentacosen-2-one_17223790 (one double bond & one oxygen, d = 19.301 Angstrom)
17-pentacosenal_20169710 (one double bond & one oxygen, d = 21.884 Angstrom)
24-Pentacosyn-1-ol_28678708 (a triple carbon bond & one hydroxyl, maximum d-value for 25C, d = 33.622 Angstrom)

In the worst case, _28678708 would require the figure be extended to d = 33.622 and a final of about VR 29. Byers suggests a d-value this extreme would only be found rarely, but a pentacosane is reported to be employed by *Lymantriidae*. Further analysis of the Pherolist appears warranted.

Each moth species is expected to exhibit a different combination of vodorophores spread among multiple vodorants. Byers reports 45% with one vodorant, 36% with two, 12% with three, 5% with four 1% with five and $\leq$0.5% for $\geq$six. The number of of vodorophores per vodorant appears to vary between one and six with a few odorophores present in more convoluted structures.

8.6.11.9.3 A typical VR among the moths, *Lepidoptera*

It is proposed that the sensory receptors (VR's) of the oskonatory modality are formed as in gustation and olfaction by the esterification of a typically aliphatic organic acid and phosphatidic acid. **Figure 8.6.11-15** shows this esterification for (9E)-tetradecanoic acid [xxx expand diagram to show (10E)-hexadecanoic acid to match Byers (E)-10 hexadecenal in figure1]. After esterification, it exhibit a vodorophore receptor site with a d = 10.6311 Angstrom exposed to the surrounding environment. Adopting this value for one of the VR channels would suggest a minor realignment to support a center line of VR 3 at d=10.631 Angstrom versus the estimated value of 10.750 shown in the earlier figure.

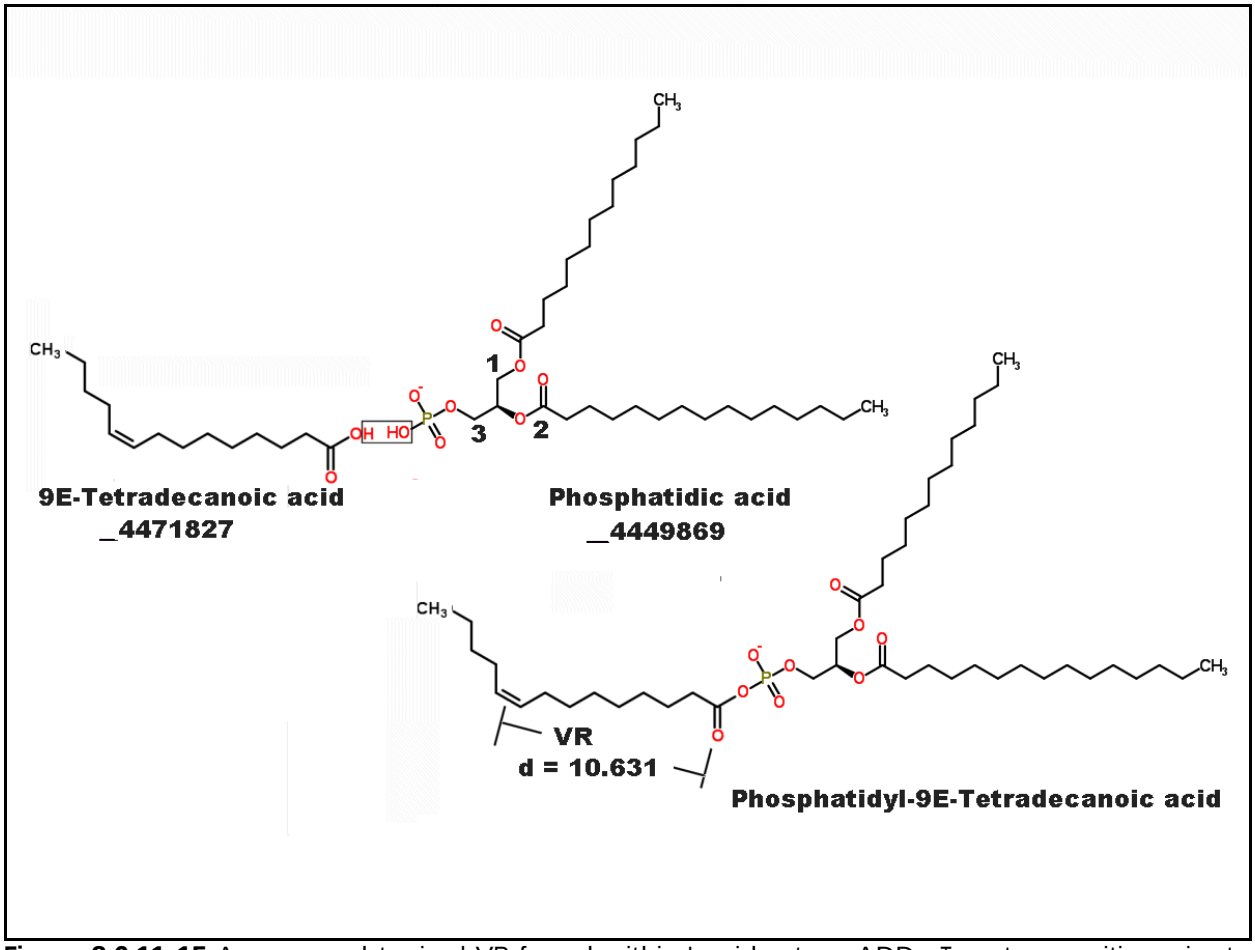

Figure 8.6.11-15 A proposed typical VR found within Lepidoptera ADD. Top; two moities prior to esterification. Phosphatidic acid_4449869 is for illustration only. Usually leg 1 or 2 contains a double bond when found in neural cell lemma. Bottom; resulting vodorophore receptor as found within the mucosa of the vomeronasal region (or alternate name used in insect taxonomy). See text.

The esterification of a phosphatidic acid and an aliphatic acid of progressively longer distance between its carbonyl oxygen and the location of a single double bond appears to be an attractive method of implementing the VR's of a oskonatory modality.

8.6.11.9.4 Coding of pheromones among the moths, *Lepidoptera*

Byers has described the taxonomy of the moths of *Lepidoptera* (an *Order* title shared with butterflies) in some detail, including how many of each species employs a specific number of vodorants (pheromones). However, there is another aspect of the pheromones not explored in the earlier work. Each vodorant can contain multiple vodorophores (or a mixture of odorophores and

vodorophores). This added complexity introduces an additional dimension into the discussion of the coding of the pheromones in order to facilitate the identification of conspecifics in the environment by other moths. Byers has addressed the expansion of the pheromone family used by the moths as the moth families under *Lepidoptera* have expanded. He notes the apparent use of combinatorial encoding by the moths to minimize the number of pheromones required. However, it is the presence of multiple vodorophores in a given pheromone (vodorant) that has been overlooked.

Using the lock and key analogy frequently invoked in discussions of stereochemistry, two situations arise; the conventional discussion of pheromone coding suggests a broad range of grooved keys with only one notch and fitting only a specific one tumbler lock, while the more extensive situation suggests each grooved key may exhibit multiple notches and each lock may contain multiple tumblers. The latter situation allows a single grooved and notched key to fit
- only a subset of locks with the same groove pattern and
- only a more specific subset of grooved locks exhibiting the matching notch/tumbler pattern.

This additional degree of complexity greatly expands the number of individual and discrete matches that are possible.

There is no requirement that every insect have a complete set of VR's, it need only have the VR's shared with its conspecifics. But the overall set is needed to accommodate an understanding of the vodorophore modality.

It may also be important to differentiate between molecules with different E,Z transition patterns as the position and direction of these transitions introduces additional structural differentiations within a given stimulant (key) and/or VR (lock). The difference between 9E-tetradecanoic acid_4471827 and 9Z-tetradecanoic acid_4444564 is small, d = 10.631 and d = 10.636 but for shorter molecules (particularly within the odorophore range), the difference can be significant.

Figures 3 and 4 of Byers (plotted to different scales) suggests the average number of vodorants per species within a family rises exponentially with the number of species in the family. It is proposed that including the variation in vodorophores within each vodorant will cause the resulting relationship to become even more exponential in character. Byers addresses the use of a square root function in figure 4 (**Figure 8.6.11-16**), a frequent approximation to an exponential function in the psychophysical experimental community.

Figure 5(a) of Byers shows the moths seldom use carbon chain lengths of less than 11 carbons within their pheromones. This provides a clear delineation between the odorant regime and the vodorant regime (at least among the moths). Figure 5(b) shows a preponderance of epoxide based vodorants for carbon chain lengths exceeding 18 carbons. Figure 5(c) shows the distribution between aldehydes, alcohols and acetates among the components of their pheromones. Based on this work such a distinction by chemical group is unimportant. It is the number and d-values of vodorophores (virtual group overlays) within each of these chemical labels that is important.

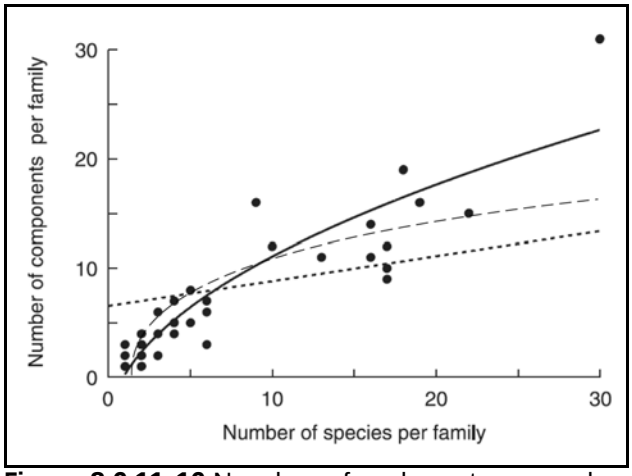

Figure 8.6.11-16 Number of vodorants vs number of moth species in a family. The exponential (dashed line) has been added to Byers' linear and square root fitting options as a more likely theoretical option. See original caption for details. From Byers, 2006.

Figures 6 & 7 continue his analysis along the lines of figure 5 and leading to the multidimensional plots of figures 8, 9 & 10 where the number of carbons below 10 and greater than 18 have been omitted.

They note the lower volatility of the longer carbon chains and the likelihood that they are only employed among conspecifics in close proximity to each other. only two species were identified using 23 carbon chains (of the epoxide form) and only one species using 24 and 25 carbon chains.

8.6.11.10 Potential hyper-sensitivity of vodorophores in VNO

The high sensitivity to vodorophores by the VR may be due to either of two factors. First, the enclosed environment of the VNO suggests that vodorophores that enter the VNO may not be removed following stimulation by normal respiration. This offers the potential for the vodorophore to recouple with the VR and thereby cause an accentuated perceived response via an iterative DACB coupling procedure. The result would be an apparent time constant associated with the perception much longer than typically encountered for odorophores. Second, there is a real possibility that the vodorophores and the VR's may form an AH,B,X relationship that results in a super-sensitivity like that encountered in a variety of gustatory channels (and possibly, although not encountered in this work, some olfactory channels). This AH,B,X relationship would greatly increase the intensity of the perceived scent compared to that normally generated by step 2 of the transduction process.,

8.6.11.11 The predicted schematic diagram of the VR modality sensory receptor neuron

It is expected that upon further investigation the sensory receptors of the oskonatory modality will exhibit the same electrolytic architecture within the cell as those of the olfactory and gustatory modality. They may exhibit different time constants due to the sensitivity of these circuits to their electrostenolytic supply processes and other parenchyma (surrounding matrix).

8.6.11.12 The treatment of VR outputs by the stage 2 and higher engines of the neural system

Brennan & Keverne have sketched the paths supporting stage 2 and higher operation of the oskonatory modality (pp 972-976), again relying upon the archaic chemical theory of the neuron. However, the neural traffic flow indicated is still applicable.

Meredith has provided some early block diagrams of all of the exterior chemical sensing modalities[22]. His discussion includes several additional external chemical sensing modalities; the trigeminal modality (page 203) and the septal modality (page 202) and the nervus terminalis in particular. The material is sketchy. The septal modality may be a portion of the olfactory modality. His discussion of the oskonatory modality (page 204) is more substantive. His signal path maps are quite complex and just defining the terms requires a full page of fine print. One of his assertions may highlight problems in understanding the oskonatory modality. He notes the very limited number of neurons leaving the auxiliary olfactory (oskonatory) bulb and the fact they may pass directly to the limbic system thereby denying the cognitive engines any access to those signals via stage 4 signal processing and the saliency map. Scalia & Winans, writing somewhat earlier, provided more detailed information suggesting the same conclusions[23]. "The observation that the main olfactory pathway and the vomeronasal pathway share no channels in common from their beginnings in the nasal mucosa to their terminals in the pyriform lobe ha been taken as a starting pint for an hypothesis that two separate olfactory systems exist."

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[22]Meredith, M. (1983) Sensory physology of pheromone communications *In* Vandenbergh, J. *ed*. (1983) Pheromones and Reproduction in Mammals NY: Academic Press Chapter 8

[23]Scalia, F. & Winans, S. (1976) New perspectives on the morphology of the olfactory system: olfactory and vomeronasal pathways in animals *In* Doty, R. *ed*. Mammalian Olfaction, Reproductive Processes and Behavior. NY: Academic Press Chapter 2

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