Received: 7 November 2021 | Revised: 20 December 2021 | Accepted: 21 December 2021

DOI: 10.1002/bies.202100263

BioEssays

PROBLEMS & PARADIGMS

Prospects & Overviews

The sorption/chromatography hypothesis of olfactory discrimination: The rise, fall, and rebirth of a Phoenix

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Funding information
National Science Foundation (USA)

Abstract

Herein, I discuss the enduring mystery of the receptor layout in the vertebrate olfactory system. Since the awarding of the 2004 Nobel Prize to Axel and Buck for their discovery of the gene family that encodes olfactory receptors, our field has enjoyed a golden era. Despite this Renaissance, an answer to one of the most fundamental questions for any sensory system—what is the anatomical logic of its receptor array?—eludes us, still, for olfaction! Indeed, the only widely debated hypothesis, finding its origins in the musing of another Nobel laureate Sir Edgar Adrian, has it that the vertebrate nose organizes its receptors according to the “sorptive” properties of their ligands. This idea, known as the “sorption” or “chromatography” hypothesis, enjoys considerable support despite being controversial. Here, I review the history of the hypothesis—its rises and falls—and discuss the latest data and future prospects for this perennial idea whose history I liken to the mythical Phoenix.

KEYWORDS

coding, computational-fluid dynamics, electroolfactogram, mucosa, odor-discrimination, receptors, zones

INTRODUCTION

The Phoenix, mythical bird of Greek and Egyptian provenance, is a universal symbol of renewal. According to legend, this magnificent and peerless bird dies in an act of self-immolation after a lifespan of perhaps a 1000 years only to rise again from its own ashes. Like a Phoenix, some scientific hypotheses also seem to experience repeated phases of decline and renewal. The topic of this essay is one such case that has either been known as the “sorption” or “chromatographic” hypothesis of olfaction, though I will use the former moniker, mostly, for efficiency’s sake. Sorption, in the context used here, refers to a few qualities of odorants including water/mucus solubility, polarity, and other whole-molecule physical characteristics effecting their movement through the nasal cavity.[1,2]

It is not my purpose to exhaustively review the literature on this topic, especially given the excellent reviews that already exist.[3,4] Rather, I will emphasize key studies which support or fail to support the primary claims that together form the core of the sorption hypothesis. In addition, I have biased my selection of citations toward newer studies. Finally, I offer a critique of the current status of the hypothesis and comment on its future prospects.

The sorption hypothesis has its origin in the mind (and research) of no lesser a figure than Edgar Douglas Adrian, a Nobel Laureate and British Lord. Adrian won the 1932 prize, along with Charles Sherrington, for the discovery of the all-or-none nature and temporal discharge characteristics of neurons. Later in Adrian’s career he turned to studies of olfaction which is where our story begins. Already by Adrian’s time the logical layout of three of the five human sense organs had been apprehended.[5] The retina was understood—in the simplest terms anyway—to be a spatial array of receptors which formed a representation of the visual scene that was projected to the visual areas of the brain. Likewise, the skin everywhere was understood to contain touch receptors which mapped mechanical stimuli onto a facsimile of the body in the cortex commonly referred to today as a homunculus. Finally, the cochlea was known to contain a linearly arrayed representation of audible frequencies that could be used by the auditory

https://doi.org/10.1002/bies.202100263

cortex to decode complex sounds. In each case, *spatial patterns* spread across two-dimensional sensory surfaces seemed to be the defining feature encoding sensory information. By contrast, olfaction remained the most mysterious of all the senses when Adrian started his studies on the topic. It is clear from several of his papers that he was eager to bring the system to heel by drawing an analogy between olfaction and the other better known sensory systems, particularly vision, linking them together on the basis of spatial patterns of activation.[5–7] He wrote, "We recognize a sight not because a particular receptor is stimulated but because a particular pattern of activity is aroused, and it is reasonable to conclude that we recognize a smell in the same way."[6] And, based on his electrophysiological recordings (in rabbit) from the olfactory bulb which are a readout of olfactory receptor activity preserving spatial relationships, he suggested a basis for the differential patterns of olfactory bulb discharge that he observed for ester versus hydrocarbon odorants: "…nothing more recondite than solubility in water…"[7] Thus was born the idea that odorant discrimination may be based on spatial patterns of odorant sorption across the olfactory mucosa imposed by airflow and water or, more correctly, mucus solubility. Nearly three-quarters of a century later we are still debating not only the details but also the very existence of the sorption model of odorant discrimination. Given some of the confusion in the literature about what has and has not been established concerning the hypothesis, I will take the somewhat pedantic tack of analyzing the hypothesis claim by claim. Perhaps the most lucid and comprehensive description of the sorption hypothesis was provide by Schoenfeld and Cleland in a pair of complementary reviews.[3,4] The claims enumerated here are derived from statements found in those reviews though I have often reworded them for the sake of clarity or brevity.

CLAIM I: ODORANTS MOVING THROUGH THE NASAL CAVITY BECOME DISTRIBUTED IN DIFFERENT PATTERNS ACROSS THE OLFACTORY MUCOSA BASED ON THEIR SORPTIVENESS

Adrian's speculations about odorant sorption led to further elaborations of the idea by contemporaries.[8,9] However, it took a full generation before major progress was made on the hypothesis by Maxwell Mozell. It is doubtful that anyone has done more to advance the sorption hypothesis than Mozell, the PhD student of Adrian's PhD student Carl Pfaffman (the latter a seminal contributor to chemosensory science in his own right). In a pair of papers appearing 6 months apart in *Nature* and *Science* in 1964, Mozell demonstrated in frog olfactory mucosa that different spatiotemporal responses arose depending on the odorant used as a stimulus and that direction of airflow altered the pattern of response consistent with a role for sorption.[10,11] Perhaps as important as his scientific findings, Mozell suggested a comparison between the workings of the vertebrate olfactory system discriminating odorants to a gas chromatograph, an analogy which crystalized thinking about this potential mode of olfactory discrimination. Though his contributions to chemosensory science extend well beyond the sorption hypothesis, he spent a significant portion of the next four decades advancing what he referred to as the chromatographic model of olfaction (viz. sorption hypothesis).

Beyond the experiments already mentioned, how strong is the evidence for chromatographic-like separation of odorants as they move across the olfactory mucosa in the normal course of odorant investigation? There have been a few different types of evidence both direct and indirect to support this claim of the model: First, in both frog and rodent, the spatiotemporal patterns of mucosal responses have been shown to vary by odorant and, importantly, by airflow direction across the mucosa suggesting chromatographic-like separation of odorants.[2,10–12] Second, when the nasal cavity of a frog was substituted for a chromatographic column, different odorants evidenced markedly different retention times. And, critically, a given odorant's retention time passing through the frog nasal cavity correlated with its retention time passing through a polar carbowax chromatography column.[13] Third, and perhaps the most direct evidence of all, tritiated odorants were found to distribute themselves along the airflow path of the frog nasal cavity in gradients that accord with their sorptive qualities.[1] Fourth, computational fluid dynamics (CFD) simulations have more recently been able to model the chromatographic effects of odorants moving through the nasal cavity of humans and several nonhuman vertebrates.[14–16] These models consistently reveal sorption patterns that vary by odorant across the nasal mucosa even among animals as small as the mouse.[17,18]

Thus, the existing data—and first principles—should dispel any doubts that chromatographic-like effects are at play as odorant-laden air is passed through the nasal cavity either in normal respiration or during sniffing. As recognized by Mozell early on, and as should be self-evident, a chromatographic effect is not a biological adaptation but rather an inevitable physical–chemical process occurring wherever molecules interact with a surface they are moving by.[19]

CLAIM II: SORPTION PATTERNS CREATED BY THE CHROMATOGRAPHIC-LIKE EFFECT OCCURRING IN THE NASAL CAVITY AS ODORANTS PASS THROUGH ARE DETECTABLE BY THE OLFACTORY SYSTEM

CFD modeling of odorant sorption patterns in the nasal cavities of several species, while providing clear evidence of a chromatographic-like effect, also document that the concentration gradients created are quite small, in the nanomole$^{(\text{m2-s})}$ range.[17,18] For these spatial patterns to play a role in odorant discrimination it is obviously a necessary condition that the olfactory system be able to detect them. In Mozell's original studies of frog, he recorded summated multiunit discharges from branches of the olfactory nerve that sampled olfactory mucosal activity emanating from areas either near the internal nares or near the external nares.[10,11] Water soluble odorants produced markedly higher amplitude responses in upstream parts (nearer the beginning of the airpath) of the mucosa no matter the direction of artificially produced "sniffs." Indeed, given the magnitude of these differences it is only reasonable to conclude that they could influence perceptual outcomes provided there exists an appropriate central neural module to decode them. More recently, John Scott's laboratory—major proponents of the sorption hypothesis—has shown similar results in the rat using the electroolfactogram (EOG), a summated recording of olfactory receptor neuron (ORN) generator potentials.[2] In rat nasal cavity, CFD has documented a medially positioned air channel with higher flow velocities and a shorter airflow path with a laterally positioned channel with lower flow velocity and a longer flow path.[20] Analogous to Mozell's studies, medial olfactory mucosa tends to produce greater responses to water soluble odorant than lateral mucosa in experimental subjects in which sniffing is artificially controlled.[2,17] As was the case for Mozell's evidence, given the magnitude of the sorption gradient in rodents, it is reasonable to assume that if there was a central circuit to decode these signals, chromatographic separation of odorants could be perceived. This conclusion is further supported by recent evidence that rodents may possess far lower behavioral thresholds, at least for some odorants, than previously appreciated.[21,22] Thus, the nanomolar-range differences found across sorption patterns may not represent a particular detection challenge.

Weakening this claim of the sorption hypothesis is the lack of a recognized central mechanism for decoding the chromatographic signal. Intriguingly, rodent olfactory bulbs have an intrabulbar associational system which connects homologous glomeruli (i.e., innervated by olfactory sensory neurons expressing the same receptor gene) from the medial and lateral passages of the nasal cavity. In addition, there is an interbulbar commissural system that reciprocally connects homologous regions of the two bulb: medial to medial, lateral to lateral. It has been speculated that these systems may be involved in contrast enhancement, a signal-averaging operation or even signal intensity discrimination.[4,23] However, the function of these system remains unknown so any role played by them in decoding a chromatographic signal is merely speculative at this point.

Of course, the most direct evidence for the use of odorant sorption patterns in perception would be behavioral. Sniffing is the olfactory version of active stimulus investigation which has been likened to “whisking” in rodents and visual saccades in humans, and many other species.[3,24] Airflow velocity has a major influence on sorption patterns because it has an inverse relationship with duration of odorant–mucosal interactions. Thus, in principal, an animal could reduce the upstream depletion of mucus-soluble odorants by increasing sniff velocity. Conversely, increasing the duration of odorant–mucus interactions by decreasing sniff velocity could improve perception of poorly sorbed odorants, giving the molecules more time to pass into solution from the air phase. Given this situation, subjects making discriminations among odorants of different mucus solubilities might be expected to alter their sniffing strategy depending on odorant.[3,4] The details of the evidence for and against odorant sorption-dependent sniffing modulation will be discussed below in reference to another claim of the sorption hypothesis. Let it suffice, at this point, to state that the preponderance of evidence hews against the existence of sorption-dependent sniffing modulation.

Taken together, the evidence that sorption patterns created by the chromatographic-like effect occurring in the nasal cavity during odorant sampling are detectable by the olfactory system is mixed. The concentration gradients created by sorption would be potentially detectable but no central circuit has yet been discovered to process such a signal and animals do not seem to modulate sniffing based on an odorant's sorption profile.

CLAIM III: OLFACTORY SENSORY NEURONS EXPRESSING A PARTICULAR TYPE OF OLFACTORY RECEPTOR GENE ARE POSITIONED IN THE NASAL CAVITY TO FACILITATE DISCRIMINATION OF ODORANT SORPTION PATTERNS

One might have reasonably expected that Buck's and Axel's (1991) Nobel Prize winning discover of the giant family of G-protein coupled olfactory receptor genes would have sounded a death knell for the sorption hypothesis.[25] After all, the discovery of over 1000 different odorant receptors, in the mouse, serves as existential proof that the odorant code must be based predominantly on specific chemical moieties rather than spatiotemporal patterns across the receptor sheet as suggested earlier by Adrian and championed by Mozell (and acolytes). However, it was not long before additional evidence concerning the distribution of receptors across the olfactory mucosa made matters less clear. As is now known, olfactory receptors are not distributed uniformly across the olfactory mucosa but reside in one of perhaps four or five specific zones, though the exact number and function of these compartments remain in debate (Figure 1).[26–29] An olfactory mucosa made up of circumscribed zones of like-functioning receptors across which the olfactory airstream moves is precisely the set-up that a sorption mechanism might need.[2–4] In such a model, upstream zones would contain the mucus soluble odorant receptors (Zone 1 in Figure 1). And, as odorants moved downstream through the olfactory passages they would encounter zones filled with receptors tuned to ever more insoluble odorants (Zone 4 in Figure 1).[2–4] In this way, mucus soluble odorants would be sorbed onto upstream mucosa where their receptors are housed and mucus insoluble odorants would move downstream to meet their receptors.

Adding credence to these ideas was the discovery that olfactory receptors expressed within a zone limited to the dorsomedial recess of the rodent nasal cavity—the most upstream portion—are particularly sensitive to water soluble odorants (Zone 1 in Figure 1).[30–33] Moreover, EOG recordings and receptor synapse imaging from the olfactory bulbs of rodents have repeatedly confirmed a hot spot for mucus soluble odorants in the dorsomedial zone and its bulbar targets.[2,18,34] Finally, Scott et al., in a heroic effort correlating the CFD-simulated sorption profiles of scores of odorants with their measured EOG responses in the dorsomedial and dorsolateral passages of the olfactory mucosa, have provided extensive evidence for sorption-tuned responses. However, their use of unnaturally long artificial “sniffs” and the large variability in their results raises questions about the generalizability of their data to the intact animal.[2]

This corpus notwithstanding, there has been little direct evidence that olfactory receptor genes are positioned in the nasal cavity to

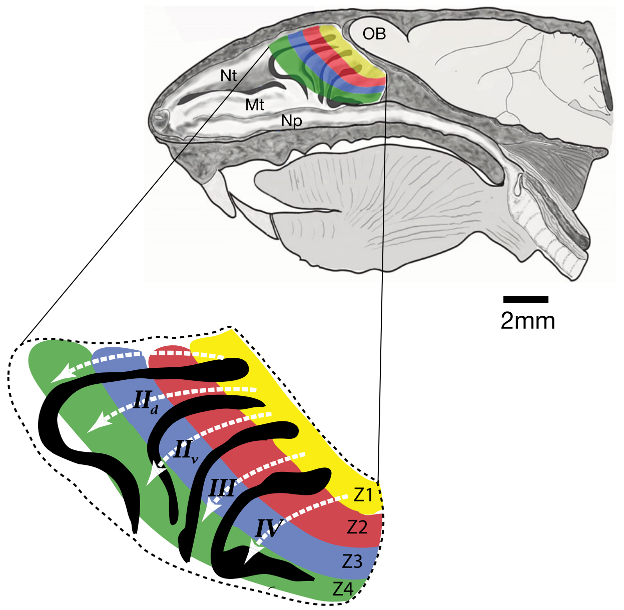

FIGURE 1 Drawing of midsagittal view of adult mouse head illustrating the medial aspect of endoturbinates with magnified area inset (dorsal up; rostral left). Colored stripes, which collectively are coextensive with olfactory mucosa, illustrate idealized boundaries of olfactory receptor zones (Z1–Z4).[26,27] White arrows illustrate idealized airpaths through the turbinates. Note that this depiction assumes a lack of overlap of olfactory receptor zones and airpaths perpendicular to their long axis consistent with the sorption hypothesis. See text and Figures 2 and 3 for realistic assessment of zone layout and airpaths endoturbinates are labeled with Roman numerals; d, dorsal; v, ventral; Mt, maxilloturbinate; Np, nasopharynx; Nt, nasoturbinate; Ob, olfactory bulb; (redrawn with permission)[45]

facilitate discrimination of odorant sorption patterns. First, the significance of receptor placement for mucus soluble odorants in the dorsomedial zone is unclear. This area, which may have an independent function compared to the rest of the olfactory mucosa, houses virtually all of the phylogenetically older fish and amphibian so-called "Class I" receptors.[35,36] But the dorsomedial zone also contains the far more numerous Class II receptors thought to have expanded their number with the vertebrate radiation onto dry land.[32,36] Given this history, it has been proposed that Class I receptor restriction to the dorsomedial zone may be explained by evolutionary contingency rather than by a sorption mechanism.[17] In this speculative but parsimonious scenario, olfactory receptor subfamilies with mucus-soluble ligands would have evolved first in aquatic and semiterrestrial vertebrates. Subsequently, olfactory receptor subfamilies with insoluble ligands grew in number through selection, driving nasal cavity expansion radially, as fully terrestrial vertebrates occupied xeric environments where such receptors could confer an adaptive advantage.[17] It is hard to conceive of an experiment that would distinguish between evolutionary contingency and sorption mechanism as the cause of the spatial restriction of Class I receptors. Worth noting, however, is that even in the dorsomedial zone, Class II receptors outnumber Class I receptors foiling any simple scheme relating receptor class, ligand specificity, and position in nasal cavity.

Another important distinction in the debate over the existence of a sorption mechanism is relevant here: Even if it could be shown that olfactory receptor position was driven by natural selection to take advantage of the constraints of sorption (i.e., receptors with mucus-soluble ligands positioned upstream in the air path and the converse) this would provide necessary but not sufficient evidence of a sorption mechanism of discrimination. Claiming that natural selection has placed olfactory receptors with mucus soluble ligands upstream in the nasal airpath where they can avoid sorption-driven depletion is a much simpler proposition than claiming a sorption-based odorant discrimination mechanism, the latter requiring a central decoder mechanism, as already noted.

CLAIM IV: THROUGH MODULATION OF SNIFFING BEHAVIOR, ODORANTS CAN BE DIRECTED TO THE LOCATION IN THE NASAL CAVITY WHERE THEIR MOST RESPONSIVE OLFACTORY RECEPTOR NEURONS RESIDE

This claim, linked conceptually to the sorption hypothesis, does not actually require a mechanism of sorption-based quality-coding to exist. It only requires there to be regional specificity of olfactory receptor types based on the mucus solubility of their ligands. Succinctly expressed, "… animals could adjust their sniffing to direct particular odotopes to the most responsive ORNs, particularly when such ORNs are positioned in areas not well matched for the intrinsic sorptiveness of the odorant".[3] One prediction of this claim is that animals should sniff at higher velocities when investigating mucus soluble odorants to reduce their upstream sorption and should sniff at lower velocities when investigating insoluble odorants to increase time for odorant–mucosa interactions.

The preponderance of evidence augurs against the validity of this claim, though admittedly the literature on this point is not fulsome. Youngentob et al. did not find any systematic variation in rat sniffing behavior when they compared responses to moderately mucus soluble isoamyl acetate to highly mucus soluble pyridine.[37] In a more recent study, also using odorants that varied in mucus solubility, rats failed modulate sniff flow rate during odor discrimination tasks.[24] Finally, in a study using noninvasive plethysmography, rats did not alter sniff flow rate during discrimination tests when the sorptiveness of odorant targets was systematically altered.[38] However, Rojas-Líbano and Kay, monitoring respiratory activity through diaphragm electromyography, found sniffing was modulated when rats were detecting "high-sorption" versus "low-sorption" targets.[39] However, the effect size found in this latter study was quite small (explaining ≈13% of the variance in sniffing). And, more importantly, the experimental design was confounded by marked differences in the difficulty of detecting the low-sorption compared with the high-sorption odorants selected for study.

In addition to the mostly negative studies reviewed above, there are also abundant CFD simulations showing what may be obvious: more molecules are brought into the nasal cavity and deposited during sniff-

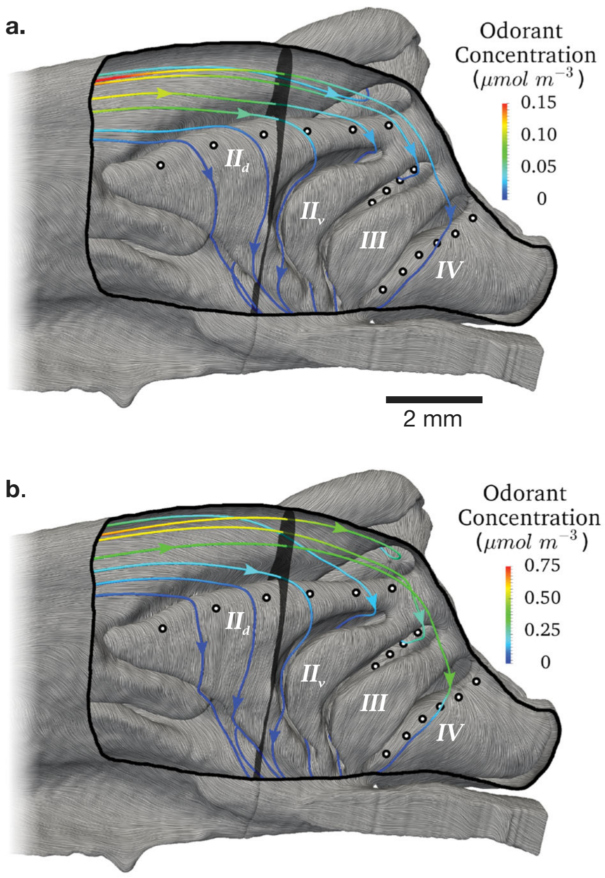

FIGURE 2 Midsagittal view of computational fluid dynamics (CFD) simulation of steady inspiration through olfactory recess of mouse (oriented as in Figure 1). The septum has been digitally removed (black line bounded area) to expose medial aspect of turbinates. Airpaths (arrows) from volumetric streamlines are colored according to acetophenone concentration, a mucus soluble odorant. (A) Simulation of respiration-typical flow rate. (B) Simulation of sniffing-typical flow rate. Black-bordered white circles depict electrophysiological recording locations discussed elsewhere.[17] Note: (1) airpaths through olfactory recess are complex and often askew with respect to one another; (2) sniffing does not change airpaths it only increases odorant concentrations (redrawn with permission)[18]

ing than during slow inspiration, no matter an odorant's sorptiveness (Figure 2).[17] Thus, a prospective smeller would do well to sniff with equal vigor toward any novel stimulus in order to maximize detection. In this context, sniffing can be construed as a ubiquitous appetitive behavior among mammals that is maximally deployed whenever a novel object is encountered. Supporting this view is the observation that sniffing is displayed toward novel objects with normal parameters even in rodents made anosmic by removal of the olfactory bulbs.[40]

Considered together, the evidence is rather paltry that sniffs act like olfactory "saccades" guiding odorants toward highly selective receptors for their ligands as has been provocatively proposed.[3] At a conceptual level, this proposal may also require further clarification: given that most natural "odor objects" consist of complex mixtures, often possessing components with different sorptive characteristics, it is hard to conceive of a sorption-influenced sniffing strategy that would advantage one odorant component without disadvantaging another rendering the strategy futile.[41] However, this criticism would be nullified if natural odorant sources tended to emit component signals with correlated chemical structures.

THE RISE OF A PHOENIX: THE CURRENT PROSPECTS FOR THE SORPTION HYPOTHESIS

It is difficult to judge the recent status of the sorption hypothesis. On the one hand, there have been very few negative critiques of the idea over its long history, perhaps because of the eminence of some of its proponents. On the other hand, there have been only a handful of studies in the last decade that even mention the hypothesis (PubMed search October 20, 2021). One gets the impression, from talking with colleagues, that most practicing chemosensory scientists regard the sorption hypothesis as a rather quaint notion, one belonging to an era gone by. In this backdrop comes a pair of very recent studies shedding new light on the model. Segura et al. have deposited a manuscript on a preprint service that, while awaiting the imprimatur of publication, represents a *tour de force* analysis of gene spatial distribution in the olfactory mucosa.[42] Through the use of high resolution 3D transcriptomic analysis and machine learning algorithms the authors were able to map, in mouse, the expression patterns of 17 628 genes across the nasal cavity including ≈98% of the annotated olfactory receptor genes. Among other discoveries, the authors mathematically defined five olfactory receptor expression zones and used them to decompose the expression patterns of all the genes included in their study. Importantly, they correlated gene expression patterns with published data on known olfactory receptor ligands providing evidence that olfactory receptors are positioned in the olfactory mucosa at locations more likely to be reached by their cognate ligands based on mucus solubility. These data represent perhaps the strongest evidence for the sorption hypothesis since Mozell substituted a frog's nasal cavity for a chromatographic column back before the first hand-held mobile phone had been invented!

However, in another recent paper, Zapiec and Mombaerts developed a "multiplex method" to map the distribution of olfactory receptors across the olfactory mucosa.[43] They used three-color fluorescence in situ hybridization with 3D reconstruction to classify the expression areas of 68 olfactory receptor types in the mouse. The receptors that they examined mapped to *nine* expression zones! Importantly, the zones were observed to be "highly overlapping and strikingly complex" and might be greater than nine in number according to the authors. Without ever mentioning the sorption hypothesis, the authors concluded that receptor zones were part of a mechanism for limiting gene choice by a given olfactory receptor cell.

The importance of this latter study to a sorption mechanism should be obvious: for the sorption pattern of odorants to carry any useful information to the CNS there would have to be restrictive zones of receptors positioned perpendicular to the direction of the respiratory airstream, that is, simultaneously comparing upstream to downstream odorant stimulation (Figure 1). High numbers of zones (compared to

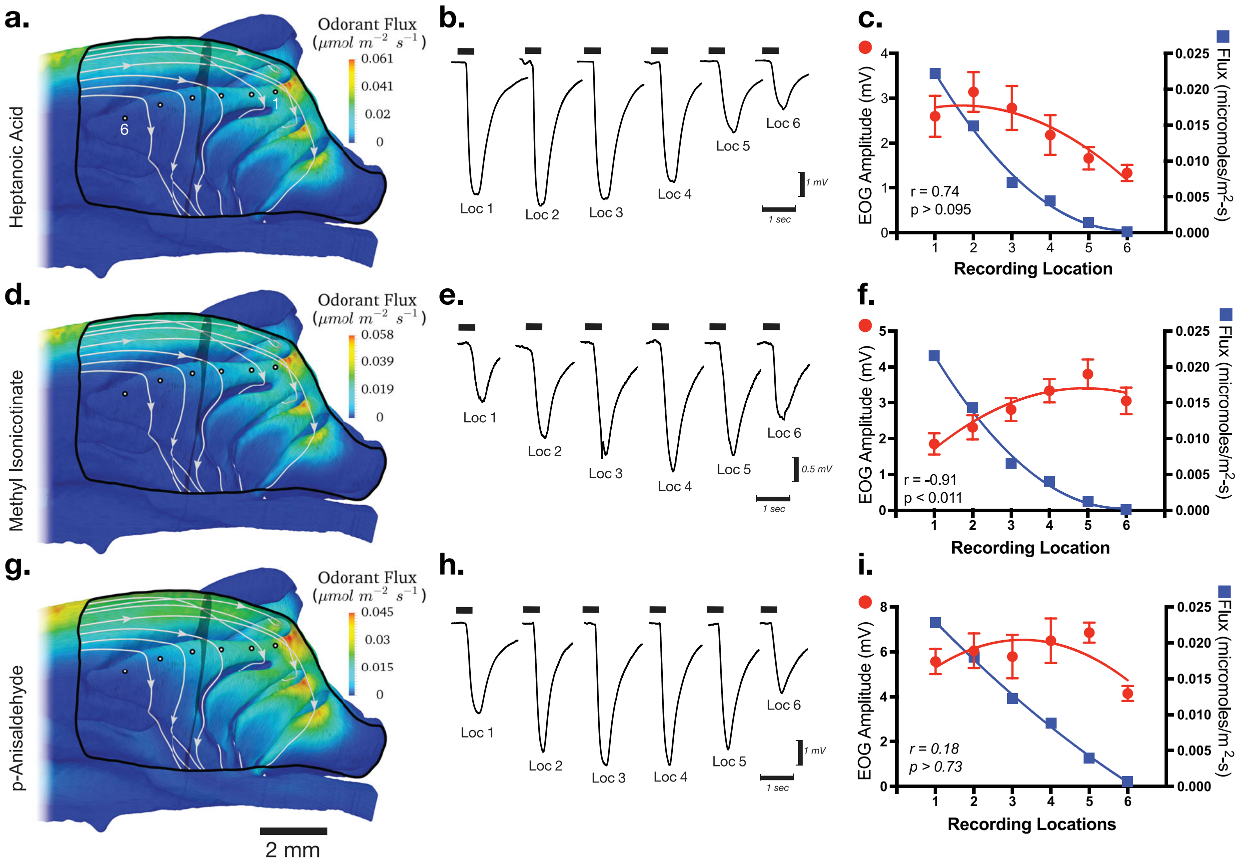

FIGURE 3 CFD simulations of odorant sorption compared to EOG mapping in mouse. Panels A, D, G contain airflow paths and odorant deposition (flux) patterns for three odorants with contrasting EOG response profiles (orientation as in Figures 1 and 2). The septum has been digitally removed (black line bounded area) to expose medial turbinates. Flow patterns are illustrated with streamlines calculated from the CFD solution (sniffing typical flow rates). The EOG recording locations on endoturbinate II_d are shown as black-outlined white circles. Location 1 is caudal-most (right) and location 6 is rostral-most (left). Panels B, E, H contain sample raw EOG traces from individual animals at each of the standard recording locations in response to 0.1% concentration of odorant. The thick horizontal segments above the traces show when the stimulus was turned on. Panels C, F, I show mean (± SEM; $n \geq 9$ mice per odorant; red lines and symbols) EOG amplitudes at different recording locations. Odorants and recording locations are the same as panels A, D, G. For comparison to the EOG responses, odorant flux values were extracted from the CFD simulations of odorant deposition at the recording locations and are plotted in blue (right vertical axes). Note: (1) ordinates have different scales to account for the different odor intensities; (2) no consistent relationship was observed between sorption patterns and EOG response patterns in contradiction to sorption hypothesis. Pearson-*r* correlations and *p*-values are shown for each graph (figure copied from previous open-source publication of author).[18] CFD, computational fluid dynamics; EOG, electroolfactogram; SEM, standard error of the mean

previous estimates) with high overlap and complex form all militate against the extraction of chromatographic data from odorant sorption patterns. Perhaps this is why recent odorant response mapping using the EOG have failed to show any discontinuities in the maps of odorant responses or any correlation between empirically measured response gradients and CFD simulations of odorant sorption patterns (Figure 3).[17,18]

CONCLUSIONS

The labyrinthine passages and complex flow streams of the typical vertebrate nasal cavity are as seemingly unlike the linear column and unidirectional flow of a chemist's chromatography machine as one could imagine. Nevertheless, the idea that the olfactory systems of some species may use sorption patterns as a mode of odorant discrimination lives on 80 years after its conception, though it has faced cycles of rise and decline. Although the recent unpublished data from Segura et al. stir the ashes of this Phoenix, the following issues will have to be addressed before rebirth is assured:[42]

1. A novel CNS module for decoding a sorption signal must be found or a plausible mechanism for decoding such a signal must be put forward based on known olfactory system architecture. The visual system, for example, is replete with specialized circuits for contrast enhancement, direction and orientation selectivity, color and motion processing, to name a few. Finding a similar module in the CNS, including, perhaps, in the olfactory bulbs, accessory olfactory

nucleus, or amygdala, that simultaneously compares outputs from upstream and downstream portions of the olfactory mucosa would be strong evidence in support of the sorption hypothesis.

2. Olfactory receptor zone number and layout must be clarified. Estimates of olfactory zone number currently range from four to nine depending on the study, though most authors admit to uncertainty in their estimates.[26–29,42,43] Critically, the layout of receptor zones must be compared quantitatively to actual airflow patterns ascertained by high quality CFD simulations (cf. Figures 1 and 2). Although the study of Segura et al. is suggestive of a sorption mechanism, these authors report a correlation between odorant mucus solubilities and gradient indices of olfactory receptor distributions along anatomical axes (e.g., rostrocaudal), not along airflow paths.[42] Comparing receptor distributions to actual airflow paths will be especially important given recent studies suggest that airflow through the rodent nasal cavity is far more complex than previously thought and does not follow anatomical axes (Figures 2 and 3).[17,18]
3. Although there are empirical and theoretical reasons to expect maximal sniffing in the presence of any novel object, as noted above, more research is needed on the nexus between sniffing parameters and odorant sorption. The current data clearly favor the lack of a relationship between these two factors, casting doubt on the sorption hypothesis. But the data are mixed on this point and the issue has been understudied.
4. Finally, through the use of computational and conceptual models, it could be determined whether sorption patterns are capable of providing useful information in the aid of odorant discrimination. Recent studies have shown that the sorption pattern of relatively insoluble odorants are spatially uniform and nearly indistinguishable while those of relatively soluble odorants are spatially heterogenous but also nearly identical in form (Figure 3).[2,17,18] Thus, it is unclear whether odorant sorption patterns, even if decodable by the CNS, would provide enough information to be useful in odorant discrimination. Ironically, Adrian may have been prescient, on this point since nearer to the end of his career he came to doubt the importance of his olfactory sorption idea on the grounds it may convey too little information.[44]

ACKNOWLEDGMENT

This work was supported by grant IOS-1655113, National Science Foundation (USA) NSF.gov.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Coppola, D. M. (2022). The sorption/chromatography hypothesis of olfactory discrimination: The rise, fall, and rebirth of a Phoenix. *BioEssays*, e2100263. https://doi.org/10.1002/bies.202100263