**IMAGING THE LIVING BRAIN:**

**Reductionism revisited in times of dynamical systems**

Withstanding contemporary fashion in the philosophy of science, this paper outlines an argument in favor of reductionist explanations of sensory perception via molecular mechanisms in neurobiology. It explores in depth the recent application of new real-time molecular imaging techniques to mixture coding in olfaction. Seemingly emergent psychological expressions of odor, irreducible to the physical structure of the stimulus, are linked back to underlying molecular mechanisms at the receptor level. This paper explicates the necessity to rethink the reductionist conceptualizations of material causes in parallel with advances in experimental methodology.

1. ***Frankly, what’s so wrong with Reductionism? Considerations from Neuroscience***

Imagine studying an entire brain in action, live stream in all its complex interactive signaling, down to the single-cell level. Can we now look at the interrelated dynamics that fixed-tissue brain slices didn't cover, or where previous imaging techniques failed in resolution? Might this present the final nail in the coffin for reductionist accounts in the life sciences?

Champions of a process philosophy of biology seem to suggest as much (e.g., Dupré 1993; 2012). These proponents have correctly highlighted the dynamical nature of biological entities such as proteins and cells, their interactions, including context-sensitive behaviors and effects. Function, anti-reductionists emphasize, is determined by context, not parts. Many biological interactions paint a rather promiscuous picture of structure-function relationships. And often we find that biological processes are governed top-down instead of bottom up. In order to understand how biological entities operate, we ought to be mapping the network of spatial and temporal relations between parts, for they seem more important than parts themselves. Such highly dynamic picture has had many scholars in the Philosophies of Biology and Mind convinced that reductionism is untenable in modern biology and neuroscience.

Biology, we are repeatedly told, is complex, contextual, intertwined, interrelated, entrenched – and therefore irreducible to some basic parts and principles. Most recently, Nicholson (2019, 110) proclaimed: “single-molecule studies are yielding results not anticipated by the use of population-averaged methods. These results are bringing about a radical shift in how we think about the cell, replacing a mechanical, neatly ordered, rigid picture with one that is inherently stochastic, more plastic, and less predictable. What we are witnessing, in effect, is a *conceptual revolution being triggered by a methodological revolution* (emphasis added).*”* The rise of modern techniques that investigate cell behavior in context, in action, and in combination, thus may sound like another case against causal-mechanistic explanations in the reductionist corner. Yet the opposite is the case. There is a conceptual revolution that follows a methodological revolution. But it’s one that leads us to revisit the value of reductionism.

New techniques and methodologies regularly lead to fundamental changes in science. This has been transparent especially in neuroscience (Bickle 2006). Revolutionary discoveries in the 1950s hinged on new experimental techniques, especially tool refinement of single-cell recordings in research on the somatosensory and visual processing (Shepherd 2009). By the 1970s and 80s, however, the revolutionary developments of mid-twentieth century neuroscience came to a hold. Progress in both theory development and experimental discovery stagnated. In his landmark book *Vision*, David Marr (1982; Ch. 1) remarked: “But somewhere underneath, something was going wrong. The initial discoveries of the 1950s and 1960s were not being followed by equally dramatic discoveries in the 1970s. No neurophysiologists had recorded new and clear high-level correlates of perception.”

Marr famously contended that reductionist approaches had failed, as electrophysiological work on single-cell recordings could not account for a global theory of the brain as an integrated system of neuronal interaction, leading him to advance a computational framework (Bickle 2015). Since the 1980s, neuroscience grew divided into two methodological camps: computational modelers next to the molecular and cellular bench workers. This development carried deep disciplinary consequences. Marr’s proposal reinvigorated the field. Still, it also increasingly sidelined molecular explanations in favor of models that ignored the material conditions of cellular responses. This methodological schism mirrors distinct conceptual foundations by which to study how the brain works and how to assign mental phenomena their material, particularly their molecular and cellular basis. Proponents of computational models believe that predictions via simulations, such as neural networks and machine learning algorithms, are the way forward to propel theorizing in modern neuroscience. In comparison, bench scientists insist that we need to gain access to the minute elemental machinery that undergirds neural processing to arrive at real explanations of the brain.

For a while, it seemed that computational methods gained widespread prominence, with research on the molecular means merely filling in the details. The resulting, frequently derogatory image of molecular bench work as handmaiden to the higher-level theorists now requires a serious update, though. Could recent developments in new genetic and high-resolution imaging techniques reverse Marr’s original verdict?

Advanced methods in neuroscience require us to revisit the reductionist approach to perceptual and cognitive processes. Techniques for targeted interventions have provided insights into many details of the molecular and cellular mechanisms responsible for cognitive phenomena. Such lower-level, molecular insights start to change our theoretical understanding of some seemingly higher-level, mental phenomena entirely (Bickle and Barwich forthcoming).

An excellent example of this is a current study concerning the receptor mechanism behind odor coding (Xu et al. 2019, 2020). The study was conducted with a recent invention by the Hillman lab at Columbia: SCAPE (Swept, Confocally-Aligned Planar Excitation microscopy), a tool for 3-dimensional, rapid live-stream imaging of small living, freely moving organisms (e.g., C. elegans, drosophila) and intact brain tissues of larger animals (e.g., mice). This example will demonstrate the potential of theoretical revolutions embodied by such modern real-time molecular imagining tools.

Cellular mechanisms no longer provide the mere details to supply higher-level computational models of physiological processes but constitute the material foundation from which to derive better neuroscientific theories and models. We will see that, contrary to Nicholson et al.’s judgment, modeling of dynamical systems in neurobiology cannot proceed without a revised and detailed conception of reductionism, which yields mechanistic explanations as contingent on ongoing updates of molecular dynamics.

The paper proceeds as follows. Section 2 begins with an introduction to the case study and an outline of what first presents itself as a clear case of emergence in smell perception. The failure of previous reductionist explanations is shown to reside in a misconceptualization of the key causal elements involved. In support of this analysis is a recent, yet unpublished study of the receptor mechanism that was made possible only with the invention of SCAPE microscopy. Section 3 concludes by making explicit the implications that such new real time imaging tools have for the advancement of reductionist explanations, and how theorizing about causal element and interactive levels neuroscience is essentially driven by methodological innovation.

1. ***How Biology perceives Chemistry***
   1. *Where Molecular Science meets Perfumery*

Say you want to invent a machine that can detect the slightest change of chemical concentration in an ever-changing environment. This machine would need to be fast, adaptive, sensitive, and widely tuned. Your nose is precisely such an instrument. Today we know that small airborne molecules, called odorants, cause smells. Odors are numerous, and their molecular basis is intriguingly complex. Smelly molecules come from a variety of sources and are of immense structural diversity. In fact, your nose is constantly surrounded by several hundreds of such odorants. It allows you to filter specific odor notes and detect differences resonating with minimal variances of elements in your surroundings. And it does so with striking precision (Shepherd 2004). The olfactory system displays an impressive capacity for chemical detection. Recent estimates suggest that, for example, humans can distinguish one trillion odor stimuli (Bushdid et al. 2014). Although olfactory neuroscience has advanced spectacularly over the past three decades, we still do not understand in satisfying detail how the brain makes sense of scents (Wilson and Stevenson 2010; Shepherd 2012; Barwich 2020). We do not entirely know how sensory biology turns chemical features into odors, and why musk molecules smell musky.

Confronted with the staggering complexity of fragrance chemistry and the notorious irregularity of stimulus responses in olfactory psychophysics, smell perception seems to present an ideal case to argue against any kind of ontological or methodological reductionism. However, the opposite is the case, as we'll soon see. The fundamental rationale behind my claim is straightforward. In demonstrating that insight into the cellular mechanisms of the sensory system can explain the psychological functions and phenomenological expressions of odor – including their irregular expression, I am arguing that it is indeed the molecular level that determines how physical features give rise to qualitative experience. This claim first needs some backup on olfactory research and its challenges.

What makes smell a particularly compelling subject to examine is that it scrupulously defies any naive physicalist notion of the stimulus. Contrary to what some philosophers of mind have assumed (Lycan 2000; Young 2016), smells are not just simply explained by the molecular structure of their chemical stimulus (Barwich 2014, 2018, 2019, 2020). Structure-odor relations are highly irregular. Similar chemical structures can give rise to entirely different odors, and various structures can fall under the same qualitative category (Rossiter 1996; Sell 2006; Barwich 2015). You can see this in Figure 1, showing notably different musk odorants.



*Figure 1 (from Barwich 2020): Four classes of musk odorants different in structure and chief chemical features.*

Next to the unpredictability of odor from individual odorants, there further is the challenge of understanding mixture perception. Outside the laboratory, we do not get to smell monomolecular solutions presented in a vial. We encounter odors as heterogeneous plumes, containing several hundreds of different volatiles. Consider the aroma of coffee. Coffee aroma comprises about four hundred odorants, none of which smells of coffee on their own. So, the perceptual whole is larger than the sum of its molecular parts. It is this challenge of mixture perception that will provide us with a strong case ***for*** – not against – reductionism.

Mixtures behave unpredictably. Perfumers have known this for centuries. They create formulas as an expression of the precise proportions and measures in the design of a fragrance. Behind these formulas is acquired material expertise, including a lot of trial and error. Because chemicals do not behave additively in mixtures. The master perfumer Christophe Laudamiel, creator of *Polo Blue*, explained (quoted in Barwich 2020, emphasis added):

*"When you have a formula, the formula often is****complex****. (…) In your formula, you have****hidden things that have a certain function****. Your formula behaves in some way. When you're going to 'massage' this formula, add something or remove something… during your development, all of a sudden, there is a note in that formula – that sticks out, that you haven't seen before. In the formula, there's wood, vanilla, and citrus. It was all fine and nice, then you put something else in, and all of a sudden you see only the vanilla with the citrus. Or now you see the vanilla, the citrus, and the lilies, and it smells disgusting. Although it was there before, it was not the prominent thing in the smell. Even if I tell you it's in there, you don't see it. But then, I change something in the formula, and that thing sticks out. It might be an ingredient, or it might be an effect. When it's an effect, it's a nightmare because you don't know where it's from! What is it? Is that coffee, lemon, vanilla? You don't know because you've never had this scent together, and so you never know what it smells like alone."*

Perfumers routinely experience such puzzling interactions in mixing fragrant materials. Sometimes, individual odorants do not seem to have any effect on the overall quality of the mixture, no matter how much stuff you add. At other times, minute amounts of an individual odorant may change the scent of a mix entirely, often in a way that resembles none of the qualitative features of its components (Ellena 2012).

Such phenomena are not whims of a precocious sense but suggest a computational basis of odor images instead. For example, you can create the odor image of "potato chips" with three key odorants: methanethiol ("rotten cabbage"), methional smells ("potato"), and 2-ethyl-3,5-dimethylpyrazine ("toast"). Crucially, the synthesis of a complex aroma from a few key volatiles does not imply a deflationary explanation that reduces smell to a few physical parameters of the stimulus. The critical finding here is that the configural odor image of "potato chip" does not just depend on the set of ingredients. What profoundly matters is the *ratio*in which the three key odorants are put together (Rochelle et al. 2017). This effect gives an indication of what has been missing in simple physicalist models of olfaction: the *mechanism* of odor coding. That mechanism centers around receptor behavior, not chemicals.

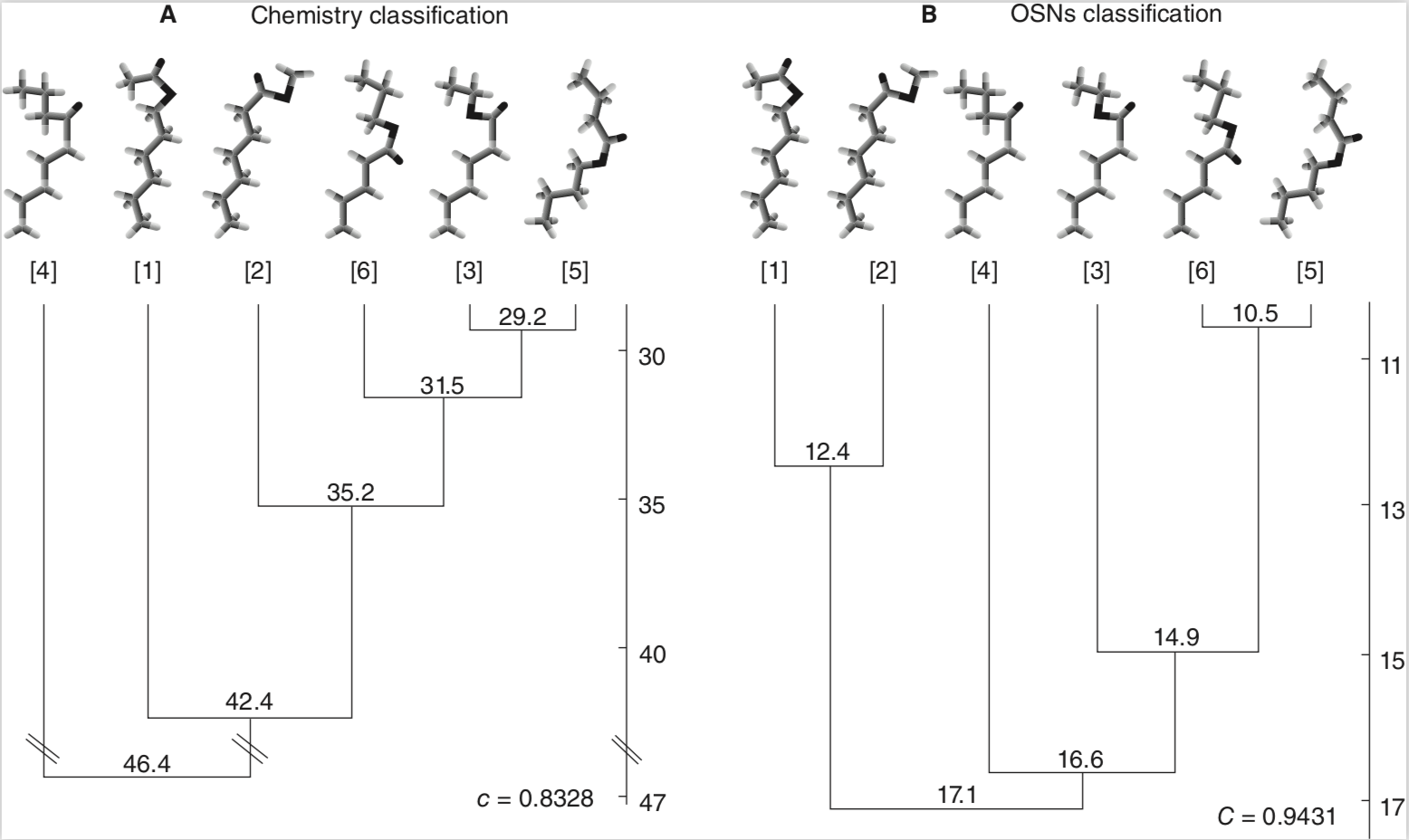
This insight brings us to the critical empirical hypothesis to advance a reductionist picture of olfaction. The reason why previous reductionist explanation of olfaction has failed is not that odor quality, especially in mixtures, is an emergent property in the strong sense (meaning that it cannot be accounted for by causal-mechanistic principles). Reductionist explanations were simply framed around the wrong element. We have focused on the chemical stimulus instead of the receptors. Because smells are an inherently computational feature of the sensory system, so much so that molecular mechanisms can account for their characteristics. That also means we have to recognize the real basis of computation: the coding principles at the receptor level.

Is there sufficient reason to think that knowledge of the receptors and their binding behavior would affect or alter our understanding of the stimulus and its associated mechanism of odor coding? Indeed, there is. This question necessitates two replies. The first and shorter answer concerns single odorant coding. The second and longer one relates to mixture coding.

* 1. *Short Answer: Biology does not follow the Rules of Analytic Chemistry*

Odor coding involves about 5000 relevant molecular parameters (Vosshall and Keller 2016). The olfactory stimulus is high-dimensional, unlike the low-dimensional stimulus in vision or audition. That is what made stimulus-response models in olfaction such a tease. The rise of Big Data seemed to promise an answer to this mindboggling structural complexity. Recent studies appealed to machine learning to tackle the principles of chemical similarity that underlie the olfactory stimulus (Koulakov et al. 2011; Keller et al. 2017). These studies correlate essentially two datasets: verbal descriptors of odor quality on the one hand, and molecular descriptors of odorants on the other. Nevertheless, even the most successful study today yields merely a weak positive value of 0.3 (Keller et al. 2017).

All these machine-learning accounts have one critical thing in common: they lack any notion of the receptors. This omission rests on an implicit but significant assumption; namely, that the receptors distinguish odorants by the same features that a chemist considers as causally relevant in the classification of their chemical similarity. That assumption constitutes a clear and testable empirical hypothesis. However, it was applied to olfaction only recently (Poivet et al. 2016, 2018). It turns out that the olfactory receptors couldn't care less about what the principles of analytic chemistry prescribe. You can see the results of a study by the Firestein lab at Columbia in Figure 2, where tested the receptive range of receptor responses to a number of ketones. The chemical classification differs profoundly in its arrangement from the organization of similarity in ketones by the receptors.



*Figure 2 (modified after Poivet et al. 2016 in Barwich 2020): Comparison between the classification of ketone molecules regarding their chemical similarity according to the principles of organic chemistry (left) and receptor binding behavior (right).*

A direct comparison explains this difference. As a chemist, you follow a specific and hierarchical catalog of features defining chemical similarity. You'd first (i) separate different ketones by the size of the ring; then (ii) by the composition of the ring; before (iii) deciding on a sub-family by looking for the presence of a nitrogen, oxygen, or sulfur atom; etc. Meanwhile, in testing the receptor responses, ring size did not matter at all; neither did cycle composition (Poivet et al. 2016). What did matter was a feature that the machine learning algorithms in previous studies hadn't even come up with, namely the polar surface area (i.e., the electric charge in the 3-dimensionality of the cycle). Basically, the polar surface area determines whether the neuron will accept the odorant as a ligand.

Such difference between chemical and biological models points at the real mistake in previous reductionist explanations: we had operated with the wrong causal elements. To understand which chemical features are causally relevant, and in what order and combination, requires knowledge about the receptors concerning their binding behavior and mechanisms. That this is much more complicated than merely replacing odor chemistry with receptor chemistry for stimulus-odor models can be seen next.

* 1. *Longer Answer: Receptor Mechanisms determine the Signal, not the Stimulus*

A just published study (Xu et al. 2020), may overthrow the received model of receptor coding. It highlights the need to derive our explanations of olfaction from wet-lab research on the sensory system, instead of black-boxing biological processes under odor-structure correlations. Receptor biology is not merely "filling in the details" of computational models; it is the basis on which to develop and advance computational models of olfaction and other perceptual processes (Barwich 2019). It also is the basis on which to revise reductionist understanding of sensory effects. At this point, the explanatory potential of novel molecular neuroimaging techniques finally comes into play.

The chief reason why hardly anyone tried to examine the molecular mechanisms of mixture perception in olfaction is that it looked almost impossible to do. Odor coding at the receptor level is combinatorial (Malnic et al. 1999). That is to say that one odorant can interact with a number of different receptors. And one receptor can detect a variety of odorants by various chemical features. Therefore, to study mixture coding, you would need a tool that could measure a significant proportion of receptor neurons in the epithelium (which contains about 100 million cells) while, at the same time, also allow for single-cell analysis.

This tool arrived in 2015 when Elisabeth Hillman, professor of biomedical engineering at Columbia University, introduced the new device of SCAPE in *Nature Photonics*(Bouchard et al. 2015). SCAPE stands for Swept, Confocally-Aligned Planar Excitation microscopy. It is a hybrid between light-sheet and confocal scanning microscopy. One of the clear advantages of SCAPE is its *speed.* There are no physical translations or data transformations between lenses required because the scanning mirror's illuminating plane is collecting the reflection as it sweeps (Figure 3). The scanning speed exceeds 2-photon microscopy and further supports observing spontaneous cell activity since there is no pre-selection of tissue sections required. Another advantage is the *resolution* of this technique, which tops contemporary light-sheet microscopy. Current penetration goes down to layer 5 neurons within layers 1 and 2 of the cortex in awake and behaving mice.

SCAPE allows for 3-dimensional, rapid live-stream imaging of small living, even freely moving organisms next to *intact* brain tissue of larger animals (e.g., mice). This tool images living tissue in as fast as 0.1 seconds, and its high resolution allows for single-cell analysis in full brain scans. So, you can puff an odor at a fruit fly, a pheromone at a moth, or record activity across the epithelium or olfactory bulb of a mouse to see its network of nerve cells responding, almost in real time and right down to the individual nerve cell. Alternatively, you can look at the muscular contractions of freely moving larvae to study its proprioceptive dynamics (Vaadia et al 2019). So SCAPE allows you to investigate blood flow as well as neural action. The technique presented an obvious opportunity to test for mixture coding in olfaction where you could scan a larger sample of epithelium tissue while simultaneously examine activation at the single cellular level.

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*Figure 3 (Bouchard et al. 2015): SCAPE’s scanning set up with a rapidly moving mirror such that it can capture the reflected light in one sweep and without the need for a second mirror (and data translation).*

A collaborative study by the Firestein and the Hillman lab set out to do that. "We took a hemisected preparation," Firestein reported (quoted in Barwich 2020). "So we have the [mouse] head in a dish, perfusion in and out, and we can image almost the *entire*olfactory epithelium at a depth. We can get down to a volume, down to a depth of about 180 or so microns. *Really far in*. But we can also do it at the *single cell*level. So you can sweep across, see activity over large swaths of the epithelium. You can also, when you want it, get single cell resolution. It's like a combination of doing single cells and EOG."

It was possible to analyze which cells reacted specifically to what odorant, and to distinguish the various patterns of cell-clusters. Firestein added: "The obvious thing to do with this would be blends or mixtures to see the code." Indeed, a question that lured somewhat in the background was whether there might even be something more to ligand-receptor interactions in olfaction than combinatorial coding.

Xu et al. (2020) analyzed ~10,000 olfactory receptor cells via genetic tools that target calcium-dependent activity (GCaMP6f mice). The results were surprising. Up to 38% of cells responding to a mixture differed from the collection of cells responding to the individual odorants in such mixture. Why was that unexpected?

A certain amount of difference in activity was predicted under combinatorial coding, as some odorants might overlap in receptor activation (Figure 4). What really was astonishing was (1) the *sheer number of cells* that differed in their activity, and (2) the observation that cell activity did not just show suppression effects (by >30%), but also*enhanced activation* (by >30%). This effect did not fit into the received model of olfactory coding. A closer look at this study will help to make this claim explicit.



*Figure 4: Hypothetical schema of how a mixture containing different odorants can overlap in receptor activation on the epithelium, where activation patterns are randomly distributed and may overlap.*

The study design involved the testing of two mixtures (of three odorants in each set). Odorants were chosen on the basis that they are chemically as well as perceptually dissimilar. In combination, these odorants yielded a configural odor image, meaning the mixtures produced a quality different than their elemental components. (The Firestein lab consulted the perfumer Laudamiel about mixture composition.) Additionally, odor set 2 was tested in equal concentration, odor set 1 in unequal concentration.

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*Figure 5 (modified after Xu et al. 2019): Averaged heat maps of olfactory sensory neurons responding to odor sets (monomolecular, binary and tripartite mixtures), showing significant suppression and enhancement effects.*

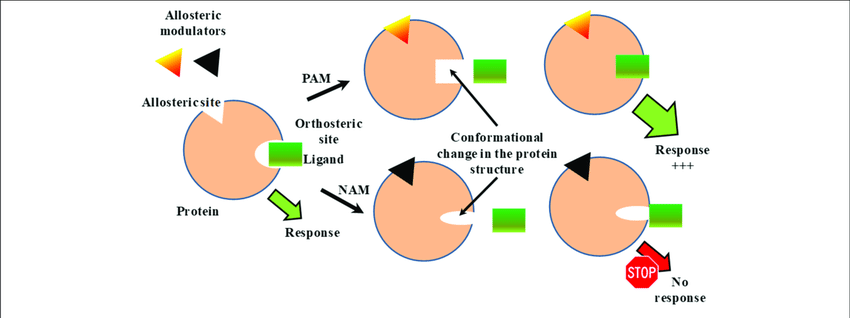
Figure 5 (left, B) details the suppression effects (odor set 2) with a heat map of peak responses in averaged cells. The first (circled) row shows a strong modulation effect. Here, individual cells reacting to a binary mixture differ substantially in their responsiveness to the overall blend containing all three odorants. Specifically, you see an absence of single cell activity or notably diminished responsiveness of individual cells in the tripartite set. Matching the responses of the tripartite set to the binary mixture suggested that Isoraldeine (asterisk) acted as the primary inhibitor instead of Dartanol (triangle). You can also detect individual cells being silent in the tripartite mix that are active in at least one of the two binary mixtures. Such modulation is not an outcome of combinatorial coding but inhibition.

Inhibitory effects in mixture perception are well known from psychophysical tests (e.g., Cain 1974; Laing 1984; Kay et al. 2005) and link back to the phenomena described in the quote by Laudamiel earlier in this paper. What had been missing thus far was a link of these perceptual effects to a molecular mechanism. Another observation of the Firestein-Hillman study was that odorants in mixtures could act *both*antagonistic and agonistic. Whether an odorant acted as an antagonist or agonist was not a property of the odorant per se, but mixture dependent. This effect mirrors perfumers' descriptions of unpredictable perceptual outcomes in mixture combinations.

Figure 5 (right, A) unveils the second, even more puzzling effect not following from combinatorics alone. Here, responses to odor set 1 show a more extensive response of cells to the tripartite mixture than to the monomolecular or binary mixtures combined. Some cells not activated by any of the monomolecular or binary mixtures did respond to the tripartite blend. That finding was entirely unexpected and eluded an explanation at first.

What could this mean? Both inhibition and enhancement effects point at the presence of two principal and hitherto unconceived molecular mechanisms at the periphery. Inhibition effects indicated a mixture-dependent agonism/antagonism (*some* inhibition results are concentration effects, but not all).

But what of enhancement? Xu et al. (2019, 2020) suggested an explanation via a causal mechanism associated with other molecular interactions, one that has hitherto been unknown to occur at the sensory periphery: allosteric interaction (Figure 6). Briefly, a ligand binds to a specific site at the receptor (the allosteric site) and, in turn, modifies that receptor's activity. On this account, odorants can *modulate* how an effector binds other odorants. Say, a receptor R1 does not interact with a given odorant O1 (when administered individually). This changes when this odorant O1 gets presented in a mix with another, specific odorant O2. Then odorant O2 attaches to the allosteric site of the receptor, modulating its activity, such that the receptor R1 receptor now binds odorant O1.



*Figure 6 (Vavers 2019): Model of allosteric interaction in receptor binding. PAM = positive allosteric modulation; NAM = negative allosteric modulation.*

How could this mechanism revolutionize our understanding of odor coding? It suggests that combinatorial coding is not the principal mechanism that serves discrimination and identification of odors in complex blends. Simply evaluate the effects of combinatorial coding. Firestein (quoted in Barwich 2020) explained: "Making conservative estimates that any given odor molecule can activate 3-5 receptors at a medium level of concentration, then a blend of just 10 odors could occupy as many as 50 receptors, more than 10% of the family of human receptors. This will result in fewer differences between two blends of 10 similar compounds." In effect, in mixture perception, combinatorial receptor activity and signal patterns become less distinct and smear into each other. So how would the brain know what the nose is detecting? What's needed is a reduction of activity that results in a sparser and thus differentiated signal. Inhibition and enhancement mechanisms serve the purpose of signal discrimination and differentiation.

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*Figure 6 (from Xu et al. 2019): Comparison between the received combinatorial model and the new model of sparse coding at the receptor level.*

1. ***Reductionism Revisited: Implications for “Higher-Level” Theorizing***

What these most recent insights into the molecular mechanism of odor coding exemplify is that the visible hallmarks of biological processes (with all their contextuality, unpredictability, irregularity, functional promiscuity) are fundamentally accountable down to their molecular and cellular causes. The appearance of emergence and irreducibility of these phenomena to essential material factors is a consequence of the misidentification of the principal elements and the misframing of the causal mechanisms responsible. Thus, it is time to reconsider currently fashionable anti-reductionist reasoning in the Philosophies of Biology and Neuroscience, which rested primarily on the conceptual interpretation of noticeable irregularities in biology. Such theoretical analysis of empirical phenomena, however, remains contingent upon the conditions of the methodologies that underpin our understanding of elements, levels, and interaction. New technologies have the real potential to overthrow that understanding.

The case of SCAPE has shown that new imaging tools, paired with genetic techniques, allow for a targeted investigation of *what* *previous technologies had required to study and therefore see as different causal levels,* such as the behavior of individual cells versus cell populations. The response of cells in the context of other cells as a population *can now be modeled on one causal plane and integrated into a causal mechanistic explanation.*

This methodological shift has substantial theoretical implications. It requires a rethinking of what constitutes the principal elements and interaction. An observed "surplus" in effects (often subsumed under the proxy of "emergence") does not necessarily signify a failure of reductionism but is pointing at a previous misguided conceptualization instead. We should not forget that the principal elements and their analysis are not an empirical given; their discovery constitutes the real purpose of the inquiry. Hence, we must acknowledge the difference between the reductionist program and the concepts currently employed in reductionist models. The latter ought to be modified according to knowledge derived from current technologies, not method-detached theory and conceptualization.

We saw this kind of conceptual turn exemplified with the case of odor coding. Receptor modulation explained several perceptual phenomena that were seemingly in favor of explanations evoking "higher-level emergence", instead of an anti-reductionist stance pointing to molecular, cellular mechanisms. Let's recap:

* First, there is the observation that, in biology, that *context can determine* and *alter function*. We saw indeed that irregularities in mixture perception, such as the perceptual suppression of components or configural "emergence", was rooted in two fundamental molecular mechanisms: (1) mixture dependent agonism and antagonism, next to (2) allosteric interaction.
* Second, receptors acted both *functionally promiscuous yet specific*. Odor receptors have different binding sites for different effects and modulations in ligand binding. (Receptor biology has come a long way since lock-and-key.)
* Third, odor mixtures seemed to give rise to *emergent* perceptual *qualities* (the whole is more than the sum of its parts). Configural perceptual images (as known from perfumery) can now be linked to the specifics of mixture-coding patterns as determined by receptor modulation.

What these points amount to is nothing short of the promise of a theoretical revolution, a revolution embodied by the methodological affordances of these new tools. Notably, the advancement of real time molecular imaging tools allows for a reconsideration of central concepts in the study of biology and neuroscience that further reductionist views because these tools allow *identifying the mismatch between natural conditions and the laboratory model* of a system's function. How we are able to frame the levels of investigation, hierarchy, and integration – to carve out the causal elements involved – does depend on the methods that determine what can be observed to interact at the same time. (Here, SCAPE is only one of several novel visualization techniques that may revolutionize our understanding of cellular mechanisms on a systems theoretical scale in this context. Other breakthrough procedures involve lattice light-sheet microscopy from Ed Boyden's lab at MIT (Chen et al. 2015).)

In the end, such tools deliver more than a detailed window into the brain; they contribute to a shift in disciplinary outlook and theory by closing the experimental gap between what currently appears as "higher-level observations" in contrast with the study of their "lower-level foundations." In fact, the frequently hidden conceptual shifts that are fueled by such technological developments invite us also to rethink the conceptual basis of talk about objectivity and subjectivity in the study of mental phenomena. Objectivity in perception, as the case of mixture coding in olfaction taught, must be framed around the causally determinative element, receptor mechanisms, not an input-output correlation of perception as inherited by pre-scientific ideas about the mind.

***References***

1. Barwich, Ann-Sophie. 2014. "A Sense So Rare: Measuring Olfactory Experiences and Making a Case for a Process Perspective on Sensory Perception." *Biological Theory* 9(3): 258-268.
2. Barwich, Ann-Sophie. 2015. "Bending Molecules or Bending the Rules? The Application of Theoretical Models in Fragrance Chemistry." *Perspectives on Science* 23(4): 443-465.
3. Barwich, Ann-Sophie. 2018. "How to be Rational about Empirical Success in Ongoing Science: The Case of the Quantum Nose and its Critics." Studies in History and Philosophy of Science 69: 40-51.
4. Barwich, Ann-Sophie. 2019. “A Critique of Odor Objects.” *Frontiers in Psychology.* doi: 10.3389/fpsyg.2019.01337
5. Barwich, Ann-Sophie. 2020. *Smellosophy: What the Nose tells the Brain.* Cambridge, MA: Harvard University Press.
6. Bickle, John, and Ann-Sophie Barwich. Forthcoming. “Molecules to Minds: Introduction to Cellular and Molecular Cognition.” In: *Mind, Cognition, and Neuroscience: A Philosophical Introduction*, ed. by Benjamin D. Young and Carolyn Dicey Jennings. London: Routledge.
7. Bickle, John. 2006. “Reducing Mind to Molecular Pathways: Explicating the Reductionism Implicit in Current Mainstream Neuroscience.” Synthese 152: 411-434.
8. Bickle, John. 2015. “Marr and Reductionism” *Topics in Cognitive Sciences* 7: 299-311.
9. Bouchard, Matthew B., Venkatakaushik Voleti, César S. Mendes, Clay Lacefield, Wesley B. Grueber, Richard S. Mann, Randy M. Bruno, and Elizabeth M.C. Hillman. 2015. "Swept confocally-aligned planar excitation (SCAPE) microscopy for high-speed volumetric imaging of behaving organisms." *Nature Photonics* 9(2): 113-119.
10. Bushdid, Caroline, Marcelo O. Magnasco, Leslie B. Vosshall, and Andreas Keller. 2014. "Humans can discriminate more than 1 trillion olfactory stimuli." *Science* 343(6177): 1370-1372.
11. Cain, W. S. 1974. “Odor Intensity - Mixtures and Masking.” B Psychonomic Soc 4:244-244.
12. Chen, Fei, Paul W. Tillberg, and Edward S. Boyden. 2015. "Expansion microscopy." Science 347(6221): 543-548.
13. Dupré, John. 1995. *The disorder of things: Metaphysical Foundations of the Disunity of Science.* Cambridge, MA: Harvard University Press.
14. Dupré, John. 2012. *Processes of Life: Essays in the Philosophy of Biology.* Oxford: Oxford University Press.
15. Ellena, Jean-Claude. 2012. *The Diary of a Nose: A Year in the Life of a Parfumeur.* London: Penguin UK.
16. Kay, L. M., T. Crk, and J. Thorngate. 2005. “A redefinition of odor mixture quality. Behav Neurosci 119:726-733.
17. Keller, Andreas, and Leslie B. Vosshall. 2016. "Olfactory perception of chemically diverse molecules." *BMC Neuroscience* 17(1): 55.
18. Keller, Andreas, Richard C. Gerkin, Yuanfang Guan, Amit Dhurandhar, Gabor Turu, Bence Szalai, Joel D. Mainland et al. 2017. "Predicting human olfactory perception from chemical features of odor molecules." *Science* 355(6327): 820-826.
19. Koulakov, Alexei, Brian E. Kolterman, Armen Enikolopov, and Dmitry Rinberg. 2011. "In search of the structure of human olfactory space." *Frontiers in Systems Neuroscience* 5: 65.
20. Laing, D. G., H. Panhuber, M. E. Willcox, and E. A. Pittman. 1984. “Quality and Intensity of Binary Odor Mixtures.” Physiol Behav 33:309-319.
21. Lycan, William. 2000. “The slighting of.” In: *Of Minds and Molecules: New Philosophical Perspectives on Chemistry*, ed. by Nalini Bhushan and Stuart Rosenfeld. New York: Oxford University Press, pp. 273-289.
22. Malnic, Bettina, Junzo Hirono, Takaaki Sato, and Linda B. Buck. 1999. "Combinatorial receptor codes for odors." *Cell* 96(5): 713-723.
23. Marr, David. 1982. *Vision: A Computational Investigation into the Human Representation and Processing of Visual Information.* New York, NY: W.H. Freeman and Company
24. Nicholson, Daniel J. 2019. “Is the Cell really a Machine?. Journal of Theoretical Biology 477(21): 108-126.
25. Poivet, Erwan, Zita Peterlin, Narmin Tahirova, Lu Xu, Clara Altomare, Anne Paria, Dong-Jing Zou, and Stuart Firestein. 2016. "Applying medicinal chemistry strategies to understand odorant discrimination." *Nature Communications* 7: 11157.
26. Poivet, Erwan, Narmin Tahirova, Zita Peterlin, Lu Xu, Dong-Jing Zou, Terry Acree, and Stuart Firestein. 2018. "Functional odor classification through a medicinal chemistry approach." Science Advances 4(2): eaao6086.
27. Rochelle, Madeleine M., Géraldine Julie Prévost, and Terry E. Acree. 2017. "Computing odor images." *Journal of Agricultural and Food Chemistry* 66(10): 2219-2225.
28. Rossiter, Karen J. 1996. "Structure-odor relationships." *Chemical Reviews* 96(8): 3201-3240.
29. Sell, Charles S. 2006. "On the unpredictability of odor." *Angewandte Chemie International Edition* 45(38): 6254-6261.
30. Shepherd, Gordon M. (2004). “The human sense of smell: are we better than we think?” *PLoS Biology* 2(5): e146.
31. Shepherd, Gordon M. 2009. *Creating Modern Neuroscience: The Revolutionary 1950s.* Oxford: Oxford University Press.
32. Shepherd, Gordon M. 2012. *Neurogastronomy: How the Brain creates Flavor and why it Matters.* New York: Columbia University Press.
33. Vaadia, Rebecca D., Wenze Li, Venkatakaushik Voleti, Aditi Singhania, Elizabeth MC Hillman, and Wesley B. Grueber. 2019. "Characterization of proprioceptive system dynamics in behaving Drosophila larvae using high-speed volumetric microscopy." *Current Biology* 29(6): 935-944.
34. Vavers, Edijs, Liga Zvejniece, Tangui Maurice, and Maija Dambrova. 2019. "Allosteric modulators of sigma-1 receptor: a review." *Frontiers in Pharmacology* 10. doi:10.3389/fphar.2019.00223
35. Wilson, Donald A., and Richard J. Stevenson. 2006. *Learning to Smell: Olfactory Perception from Neurobiology to Behavior.* Baltimore: Johns Hopkins University Press.
36. Xu, Lu, Wenze Li, Venkatakaushik Voleti, Elizabeth MC Hillman, and Stuart Firestein. "Widespread Receptor Driven Modulation in Peripheral Olfactory Coding." bioRxiv (2019): 760330.
37. Xu, Lu, Wenze Li, Venkatakaushik Voleti, Dong-Jing Zou, Elizabeth MC Hillman, and Stuart Firestein. 2020. "Widespread Receptor Driven Modulation in Peripheral Olfactory Coding." Science 368( 6487): eaaz5390.
38. Young, Benjamin D. 2016. "Smelling matter." *Philosophical Psychology* 29(4): 520-534.