CHAPTER 6

Molecules to Perception

Outside your body awaits a multiverse of airborne chemicals. They spark a vast range of different odor qualities and behavioral meanings and are strikingly diverse in molecular structure. After registration by the nose, it is up to the brain to do something with all that information. But what is happening here? Unlike colors and sounds, the connection between stimulus structures with odor qualities is far from evident. We have seen that the stimulus did not readily explain odor. So how does your nose know that the molecule of cis-3-hexen-ol smells of freshly cut green grass, or that the chemical group of esters smells fruity? How does your brain decide whether it got its perceptual interpretation of these chemicals right?

The answer to these questions depends on what we think our sensory systems do when they scan a stimulus for information. The notion of perception we have come to rely on is the idea that our brain conducts an efficient extrapolation process, whereby our sensory systems get to the observable nature of things. Perception as extrapolation conveys the assumption that our senses operate by filtering information from contingent and variable scenarios to

detect stable patterns of the world encoded by its physical features. Neural representation, in this context, is an act in which the brain re-presents previously encountered, learned patterns to categorize the currently presented information. In this scenario, sensory perception functions as an information funnel, denoting a process capable of selecting features in a vast environment of distractions and successfully extracting the significant bits. But what are the significant bits? And how does the sensory system represent them?

Here, trouble starts for olfaction. It is not entirely clear. That is not to say that we lack the data. To the contrary, we know an awful lot about the minute details of the stimulus by now. Keen chemists can blow your mind with knowledge about the structural features of odorants. Big companies like Firmenich and Givaudan amass large databases with detailed molecular descriptions to aid in their search for new synthetic fragrances and flavors. An ångström in difference here, an added carbon atom there, and what about this hydroxyl group that donates its electrons to a benzene ring? Knowing such details is so meaningful that it is impossible to get access to these well-guarded and proprietary research databases.

The Missing Link

We do not understand what the olfactory system does in detail with all those features, how the brain makes sense of them as scents. That is astonishing because over the past three decades, we have discovered a lot about the biological foundations of olfaction (Chapter 2). Of course, you sometimes encounter comments about how little we know of olfaction (perhaps the odd sentence in this book has fallen victim to a similar sentiment). But if you think about it, we know a fair amount about the sense of smell today. It is just that we also have come to realize how little we understand

of what we know. It is not that the principal components are unfamiliar. To date there may be more structural data than we can make sense of. We can study the molecular specifics of the stimulus in all its chemical glory. We know about the structure of the pathway where this information is processed, including the vast number of receptors and the signal projections to the bulb and cortex. All the bits and pieces are in place. Only the principles of the olfactory cascade remain in debate. What is missing?

Missing is the connective principle, the topology that undergirds the process of perception and integrates its information at different levels. The stimulus, in one form or another, is the source from which our sensory system extracts information. Unclear is how the olfactory stimulus communicates its message. The general pointer to stimulus topology (it's the chemicals!) distracts from really thinking this answer through. Odor chemistry is mind-bogglingly complex, and the physical stimulus of smell still has no comprehensive classification. This, we now know, is not a result of the seemingly subjective nature of odor, but the molecular complexity of the olfactory stimulus.

The neuroscientist Charlie Greer at Yale reminded us of the root of the problem: "One of the most difficult things is that we don't understand *the chemistry of the system.* We still don't understand what a ligand is and how it interacts. That is in stark contrast to the physiology of the somatosensory system, where we understand hot receptors and cold receptors and pressure receptors at an extremely detailed level. Or the visual system. Or the auditory system. In many ways, these systems are, at least in my view, comparatively simple compared to the olfactory system."

Talk about stimulus input is ambiguous. Even in vision we are already talking about two different things. One is the distal object, a thing perceived in the distance (like a line projected on the screen). Another is the causal stimulus, meaning the photons hitting your retina. That they are different kinds of objects is evident.

Photons do not have lines or edges. They do not have shape or length. They do not have any of the properties we routinely assign to visual objects. Instead, they act as surface reflections that our visual system uses as a *measure of* distal objects. Our ability to see distal things as spatial connects to the fact that the causal stimulus behaves spatially in its interaction with the visual system (Chapter 5). Visible objects appear spatial to us because spatial dimensions (like distance and size) are determinate of the information that our system extracts from their surface reflections.

So how does the stimulus behave in its interaction with the olfactory system? We won't find an answer by looking at odorants in isolation. We don't even use this approach in models of the visual system, Stuart Firestein emphasized: "We don't worry about the physics of photons for the most part. There is a whole lot of work on photons done by particle physicists. Are they waves? Are they particles? Vision scientists worried very little about that. They were interested in optics, that's about it. But only because they had to set up an optics table to *deliver* the stimulus."

The reason chemistry dominates olfaction is a matter of historical convenience. The twentieth century was the time when chemistry was the best option to study odor, experimentally. This paradigm somehow survived.

"We have this common trope in the field, from molecules to perception," Firestein observed. For decades, the assumption was that there are rules that link chemical input to mental output. Today, olfactory information is still analyzed as encoded in stimulus structure, while the rest of the story, including the receptors, amounts to filling in the molecular details of the biological apparatus. By tracing how the receptors project their input to the brain, we arrive at a more or less linear model of the wiring of the system (like edge detection in vision). This model, however, is valid only if the receptors respond to odor chemistry as chemists model it. That is not the case.

Receptor biology is governed by its own rules. "The trouble with the idea to connect molecules with perception is that it goes from chemistry to psychophysics," Firestein noted. "What's been left out all these years? Biology!" Twenty-five years after the discovery of the olfactory receptors, and a century of stimulus chemistry, the question we ought to be asking is: How does the system work? "Now we have to put biology back in," Firestein argued before pointing out: "But when we put the biology back in . . . *It doesn't fit.* It doesn't fit that nice story of chemical structure to psychophysical perception. There's lots of other stuff going on instead."

The previous chapter revealed that odor processing is not about the distal stimulus as an external object, but a topology as created by the sensory system. This chapter examines why there is a big difference between the chemistry of the stimulus and the topology of its neural representation. Attention now turns to how biology reads chemistry.

The Common Trope

Chemistry presented a plausible starting point for initial scientific interest in olfactory biology. "This is the way olfaction has gone for a long time," Firestein observed. "Because it is called the chemical sense, right? All the molecules we smell are, for the most part, organic compounds. And you know," he shrugged, "there is a whole field called organic chemistry. Naturally, you expect them to take the lead on this. They name these things, they have extracted them, synthesized them. They run that chemical show. It's perfectly reasonable to rely on organic chemists to organize and classify the chemicals that they spend all their time working on. Which we [neuroscientists] don't because we just use them."

Neuroscience did not need to start from scratch. Odor chemistry was already in place when biologists entered the field. "You don't have to believe that this is the final answer," Gordon

Shepherd replied, "but it is definitely a tool for a much deeper understanding. It's almost a list of how to represent the input. To me, the simplest idea—since this is the idea of how the study of most senses occurs—is that you need to know where you are in the field of the sensory input in order then to stimulate the different parts of it. Just like the visual field. And then to know where to go in your system in the brain."

The sheer number of receptors complicated that idea. Richard Axel noted: "If you have a thousand different cells, and an odor activates one hundred receptors, the number of possible combinations is greater than the number of atoms in the universe! So that's a big number, a very big number. This immediately gave you the power you needed to recognize as many molecules as you would ever wish to recognize in your entire existence." That revelation inevitably altered ideas about odor coding.

"It appeared that biology was now possible to do," Firestein remarked. "The idea initially was to try and get the biology and the receptors to fit into what we already thought was going on based on the chemistry and the psychophysics. And the biology should just fit neatly in there. It doesn't work out that way as it turns out. But it's reasonable to think that way or to start that way."

Still, the stimulus remains at the center of olfactory theories. Can modern olfaction, with access to receptor biology, continue to build on structure-odor rules? Comparing past with present insights reveals a hidden shift in ontology.

Over the past couple of years, several articles tried solving structure-odor rules (SORs) with big data.[1] These studies advanced computational models of the olfactory stimulus, utilizing artificial intelligence to mine for clear correlations between chemistry and psychophysics. This approach also marks the arrival of a new generation in the olfactory community.

Testing new tools on old problems, Andreas Keller found, was a no-brainer: "There are these things that are just obvious that

should be tried." His collaborator Pablo Meyer agreed: "There's just a couple of obvious things to do. I mean, why not do it?" Joel Mainland thought that tools such as machine learning fueled a generational shift that also mirrored an epistemic break with tradition: from explanation to prediction. Machine learning constituted "a new set of techniques that the field has not absorbed yet."

Computational perspectives promised to crack the code in the nose with more sophisticated techniques, more data, and better data processing tools. Rick Gerkin, from a neuroinformatics view, said: "You can answer a little question here and there, but to answer questions like 'What is the dimensionality of olfactory perceptual space?' and 'How many odors are there?' you need to have large data sets, and large data sets take a long time to collect, they take a lot of money, and most labs doing olfaction and olfactory psychophysics are smaller labs that can't answer those questions."

One central problem with these new computational studies were the data. Leslie Vosshall remarked, "most of the theoretical work [in olfaction] has been based on [this] single thirty-year-old data set. Why has no one done an update?" This old data set is the *Atlas of Odor Character Profiles* (Chapter 3). Andrew Dravnieks, Vosshall continued, compiled "a great list in the early '80s, for use in the northeast of the United States, for people who are baby boomers. But so many of the words on that list have no frame of reference for the people who come to our studies." She added, "Any of these lists . . . they are perishable, highly culturally biased lists, that will work for some specific period in history, for a specific target audience."

Another problem with Dravnieks's *Atlas* is that its psychophysics was insufficient in methodology. Dravnieks had picked those descriptions himself. Computational studies mapping the semantics of "odor quality space" via Dravnieks's verbal descriptors lacked practical experiments involving human psychophysics. In a sense, they had mapped the odor quality space of Dravnieks.

Computational SORs faced the same problem as old SORs: they black-boxed the biology of the system. What if they had real psychophysics data?

A 2017 publication in *Science* by Andreas Keller, Leslie Vosshall, and Pablo Meyer provided just that.[2] This study is notable for several reasons. First, it used concrete, new psychophysical data on human odor responses, taken from an extensive study published prior in 2016 (also by Keller and Vosshall).[3] Second, this data set was massive. The value of human data collection in olfaction cannot be overemphasized. Keller and Vosshall tested forty-nine test subjects, who sniffed and assessed the quality of no fewer than 476 molecules (using nineteen semantic descriptors as well as ratings of odor intensity and pleasantness). Keller and Vosshall tested a wide range of odorants on an unusually large number of participants (for the underfunded field of olfaction, that is). "And it's incredibly boring work," Keller laughed. "You give people a molecule and ask how it smells. You can't do anything less exciting. It's like descriptive science in its purest form. But it is needed. So we bit the apple, and we tested it."

Third, the article is notable because it represented a modern take on scientific collaboration as crowdsourcing. The 2017 *Science* paper put this 2016 psychophysical data set into use with machine-learning algorithms mining for SORs. The study setup was as follows: It started with a public call for participants as part of the DREAM Challenges (an online open crowdsourcing platform for researchers to pose a scientific challenge for others to participate in). The challenge was straightforward enough: find an algorithm accounting for two data sets, one a list of the chemical features and the other the results of the 2016 psychophysics study. An additional, smaller set with chemical data was given to the participants afterward, allowing them to test and adjust their algorithms before submitting the final version for evaluation. Keller laughed: "So this is the challenge: I collected a data set, and we split it in

two and gave half to the people. And we were like: This is how these odors smell, predict for us how these other odors smell." Results of the two winning algorithms were published, but the algorithms themselves were not. The winners were Yuanfang Guan, a computational bioinformatician who had won several challenges regardless of the topic utilizing algorithm fitting; and Rick Gerkin, of whom we just heard. It is worth highlighting that Keller et al.'s 2017 article has been the most successful approach to big data in olfaction thus far; it constitutes a benchmark for similar proposals in the future.

Still, an algorithm is not an explanation. The article "Predicting Human Olfactory Perception from Chemical Features of Odor Molecules" provided a strong case of data mining and confirmation of a number of existing hypotheses on relevant structural features. But, at 0.3, its correlation was not sufficiently high. The DREAM Challenges project did not crack the code in the nose.

Its publication attracted the interest of science writers, like Ed Yong, partly for its big data appeal.[4] The study also evoked cautious critique from olfactory experts such as, for instance, Avery Gilbert. Gilbert's concerns did not target this particular study but applied to computational approaches to olfaction more generally. He identified the absence of psychological theory. Verbal descriptors constitute an arbitrary measure to account for the mechanisms of perceptual categorization. Gilbert's review exposed how disunited the field still is, with computational neuroscientists modeling the sense of smell in a manner markedly separate from that of cognitive psychology.

Gilbert emphasized that the olfactory space remains unknown: "So if one wants to predict what molecules might smell of sandalwood or citrus, one would have to retest all 476 molecules on another forty-nine sensory panelists using the new list of descriptors, then rerun the computer models on the new data set."[5] Why even these nineteen descriptors? Vosshall replied: "The reason our paper

used nineteen was just that we didn't find most of the other 127 descriptors applied to the molecules we were using. I'm sure you could use others." The remaining problem, in Gilbert's view, "is that words that are useful in an olfactory lexicon occur at different levels of cognitive categorization." In response, Keller and Meyer emphasized not to view their 2017 work beyond its objectives. It aimed to provide and demonstrate the application of computational tools for odorant design, not for a systems theoretical account of olfactory processing. And so they did just that.

Structure-odor rules, as the go-to strategy in modeling olfaction, are not theory-free tools. Trouble arises from the viewpoint of wet-lab neuroscience. Biology is not data to derive from an algorithm. Biological organization is the *explanandum* (the thing to be explained), whereas algorithms may aid in the derivation of the *explanans* (explanations).

Firestein thus considered these new tools heuristics, not explanations: "There's potentially valuable information in there. I think these machine-learning studies are good leads." So, he cautioned: "They are published like final results, but they're not final results. They're loaded with artifacts. There are all sorts of false positives." It would be imprudent to rule out structure-odor breakthroughs via machine learning, but it has not worked as yet. Why this is the case matters profoundly.

Prevalent in recent computational models is the treatment of biology as a proxy, as a stand-in connecting the chemistry of the stimulus with the perception of the human subject. Mainland argued that this is feasible: "If you want to go study one receptor really carefully and figure out how that receptor responds to an odor, that's great. But it's really a huge pain to do. Instead, use these methods, like [the DREAM Challenges], where you take a molecule and learn what features correspond to perception. In theory, if you have enough data, you'll learn exactly what Stuart is learning. You're using a different set of features, but you could

eventually infer everything that he can infer." Mainland paused. "Would you eventually want to know what the receptors are doing? Absolutely. Is it possible that we can figure this out without ever looking at receptors? Yes, it's possible. We don't need to know what the receptors are doing to figure out how to map structure to percept. The current models are basically doing that. And they work relatively well. They're noisy, but they work. You don't have to know every single step along the way to make the jump. It can be a black box."

Keller agreed: "I think about it as a triangle thing: the molecules and stimuli, then you have the pattern of activated receptors, and then you have the percept. You could predict from the physiochemical features what receptors it activates, and then you could predict from what receptors are activated what the perceived odor percept is. You just cut out that middleman and move over to black box off the receptors."

Gerkin went a step further: "We already know these receptors. We know about how many receptors there are. We broadly know how some of them are tuned, and we know something about how they interact in the bulb. But my point is that you can throw all that in the garbage. You can develop a theory of olfactory perception without knowing any of that. My hypothesis is that you can use psychophysics and make measurements to make strong predictions about the grand perceptual space, what the shape of the space is, and how stimuli mix in that space." This optimism may be premature. But is it misguided?

Black-boxing the receptors is bound to fail. Even the most powerful tool cannot avoid the problem of theory-ladenness, the consequences borne from the selection of premises and evaluative criteria. Consider an alternative example. Imagine using strictly morphological criteria for inferences about the mechanism of heredity. The resulting model would be based on correlation, not causation. SORs, structure-odor rules, whether gained by classical

chemistry or big data, similarly circumvents the biology of the system, the causal grounds of feature selection, and integration by the olfactory system. Modeling SORs, with whatever technique, offers a *lead* to a hypothesis but not the actual mechanism. SORs do not equal the principles of stimulus processing and perception.

It is vital to make this difference clear. Stimulus chemistry is often framed as coextensive to odor coding. Yong's astute article about the DREAM Challenges project, "Scientists Stink at Reverse-Engineering Smells," is a good example. If you read carefully, you find one notion missing: receptors. What is omitted in most popular accounts that introduce the challenge of modeling olfaction are the receptors interacting with the chemical stimuli, the receptors determining what features get selected. But these receptors are the key to understanding how the olfactory system turns molecular features into neural patterns of information. Back to our alternative example of heredity: what gets taken for a solution here is a morphological description without the mechanism of transmission that determines the units of transmission.

Mainland raised the critical issue: "The only case where it matters [to include biology] is when you get something out of the biology that's not in the things that we're using." Do we have sufficient reason to think that knowledge of biology would lead to a different model of the stimulus in odor coding?

Indeed, we have.

The Black Box of Biology

It all starts with the receptors. Their importance for theories of odor coding cannot be exaggerated. Chapter 2 detailed that olfactory receptors are G-protein coupled receptors (GPCRs), situated on the cilia of the olfactory sensory neurons in the nasal epithelium. Cell distribution in the epithelium is random (although rough gene expression zones in the epithelium exist).[6] These cells

continuously change as receptors die and renew. The olfactory system has a constant turnover of sensory cells. (The epithelium is the only part of your body exposing nerve cells to the outer world: a fantastic target for infections. If your epithelium did not renew itself routinely, you would be unable to smell anything after two or three colds.)

For Greer, that is what distinguishes olfaction: "This is the only central nervous system, mind you, where populations of sensory neurons die on a regular basis and are replaced by new populations of sensory neurons—who then correctly send out their axon to the right part of the olfactory bulb to converge with other similar axons." The fact that the system rewires regularly shapes how it interacts with an irregular, unpredictable stimulus. The interface with which the nose scans for odors is under constant construction. And that is not the only notable feature.

Olfactory receptors, as the interface of the olfactory system, actively structure stimulus input—so much so that subsequent theorizing about the neural representation of odors must begin with knowledge of the receptors and their binding behavior, similar to input models in vision or audition (Chapter 5). While all sensory cells are selective, however, olfactory receptors stand out for a couple of reasons.

First, there is stimulus-receptor affordance, the things the system can do with the properties of the physical stimulus. Color vision deals with a low-dimensional stimulus: electromagnetic wavelength. Color receptors, cones, are dedicated to specific chunks of the visible light spectrum. These receptors operate in an additive and subtractive fashion in combination with each other. This results in a straightforward stimulus-quality model; say:

$a = n$

"Red light" has a wavelength spectrum from about 390 to 700 nanometers.

Such a model further allows for well-defined feature calculations of color combinations:

$x - y = z$
"White light" minus "green light" results in "pink."

While odor receptors are tuned to specific features and act in a combinatorial fashion, this is where similarities end. The physical characteristics of odorants are considerably different from visual input and do not afford the same kind of calculations. The olfactory stimulus is multidimensional in its molecular makeup. Stimulus-receptor space in olfaction is not defined by accumulative combination, as in vision or audition.

Aldehydes, specifically chain aldehydes, present an excellent example to illustrate this difference. Chain aldehydes come in different lengths of carbon chains. (These organic compounds are popular materials in perfumery; indeed, Chanel No. 5 was the first perfume that consisted almost exclusively of synthetics, namely a string of different aldehydes.) Aldehydes of different lengths have different smells. The C8 aldehyde is perceived as fatty, the C10 aldehyde as citrusy, and aldehydes with longer chains come off as floral. Unlike for colors and wavelengths, however, no accumulative model links the number of carbon atoms to odor quality. Besides, it is impossible to apply chemical explanations of aldehydes to other chain odorants—say, alcohols with different carbon chain lengths (ranging from four-carbon butanol's clinical smell to six-carbon hexanol's green note, to eight-carbon octanol's aromatic odor).

Odor coding does not afford a predictive stimulus-response model in the manner of "for any odorant with a carbon chain the model holds that a chain of C8 + another C = results in a cherry scent." That is just not how it works. The essential difference between the low-dimensional stimulus in vision, or audition, and the high-dimensional stimulus in olfaction is that an additive scale does not capture the coding of the latter.

Greer contrasted receptor coding in olfaction with the auditory system: "I guess you could argue that, because the basilar membrane is a continuum in response to high-frequency versus low-frequency tones, there is an opportunity for a combinatorial code there as well. As you play a chord of music, you're going to be stimulating different parts of it, and that will lead to the perception of the music. But I don't think it has the open endpoints that we have in the olfactory system." In the coding of the olfactory stimulus, there is no transience in the range of one key feature. "There's a continuum of tones that you can see putting on a map," Firestein added. "In olfaction, you don't see that kind of continuum. There's no continuum between aldehydes and ketones. Or any other kind of chemical group or classification."

Any model that aims to map perceptual odor space onto stimulus space must begin with the fact that odor coding is not linear or accumulative. Odor receptors deal with several thousand different molecular parameters in no particular order of continuity or scale. Therefore, there is no uniform way to carve the physical space of odorants "at its joints" like visible wavelengths or audible frequencies. Olfactory receptors make sense of about five thousand molecular parameters, including stereochemical configuration, molecular weight, hydrophobicity, functional groups, polarity, basicity, and so forth. This is what is meant by high-dimensional stimulus space.

Odor receptors determine the range of chemical features translated into a signal. But they do not split up the stimulus into uniform, regular chunks (as do the visual cones). You will not end up with a receptor group for one chemical property—say, carbon chains—and another group for polar surface areas. Instead, receptors pick out different features. Moreover, they vary in their range of features (next to feature combinations). Say you have a receptor responding to the polar surface area of a ring structure—but only structures of a certain size, not the polar surface areas of ring

structures in general. Now multiply such combinatorics several hundred times, up to the thousands! Chemical features distinguish stimulus space. But these features are not carved up uniformly across the receptors. And so this mosaic coding allows for some degree of data fitting when it comes to structure-odor rules. It does not support the predictability of SORs.

If the receptive range of cones to wavelengths defines color, why don't we define odor by the receptive behavior of the olfactory receptors? Neurobiologists agree that odor percept formation builds on receptor patterns.[7] What remains unquestioned is whether receptor patterns indeed match traditional odor chemistry. Could the study of receptor behavior overthrow the premise of stimulus-response models?

The answer is yes. Two recent studies by the Firestein lab, in 2016 and 2018, tested a deceptively simple question: Would the receptors classify the stimulus differently than a chemist would?[8] Chemists group odorants according to significant chemical groups and functions. Firestein's team measured receptor responses instead (an approach known as medicinal chemistry in pharmacology). The idea behind the experiments was simple, yet no one had considered it. "It was Zita who came up with this idea," Firestein said, crediting his former postdoctoral researcher Zita Peterlin. "I think, in her mind, she sees these chemical structures like no one else. A bit like in the movie *A Beautiful Mind*. She sees patterns in these molecules that others do not."

Erwan Poivet, who continued Peterlin's project after she left for Firmenich, summarized the idea: "Organic chemistry will rely on stuff like: What's the functional group of your molecule? What is its size? What is its length? How many double bonds, is it polar, or is it a-polar? All these different features. And that will be the way chemists classify the molecule. But maybe this is not relevant at all for biological systems, such as the olfactory system. Maybe your receptors don't care about there being an acid or an ester. Let's say

you have an aldehyde and alcohol. Chemically they're pretty different. But for olfaction, you still have oxygen in both of them with a double bond. Maybe that's what the receptor is tuned to. Maybe it doesn't care if you have a hydrogen or another carbon."

The Firestein lab threw a range of molecules at a mouse epithelium. They recorded and analyzed the receptor responses to check whether the stimulus preferences in receptor behavior matched the stimulus classification in organic chemistry. The answer was no. The olfactory receptors did not match stimulus chemistry as a trained chemist would. What that means is that the receptors follow their own rules. Without the details of receptor biology, SORs and big data are left with force fitting.

Figure 6.1 shows the differences in how chemists and receptors group the chemical similarity of odorants. At the top of the figure, you see how odorants 3 and 5 are most similar according to the principles of organic chemistry, subsequently followed by odorants 6, 2, 1, and, last, odorant 4. At the bottom, you see how odorants 5 and 6 are most similar according to the receptors. Meanwhile, odorants 1 and 2 form a similarity group, independently of odorants 5 and 6; and odorants 3 and 4 are closer to the group of odorants 5 and 6 than odorants 1 and 2. "We chose to look at molecules that, if you look at their chemistry, were quite different," Poivet explained. "We looked at cyclic molecules with benzene or heteroaromatic rings to see if we can find something to relate them. And the way they were classified by chemistry was very different from the way we can classify these molecules after we force them into neurons."

The real experiment was more sophisticated than the above suggests. Poivet laughed: "We had olfactory sensory neurons in a petri dish. And we inoculated [introducing a substance into the tissue], one by one, all these odorants. Every time we have a neuron that responds, we can follow its calcium sensor GCaMP [a fluorescent protein highly sensitive to calcium activity in cell activation]. We found that there were cells that respond only to one

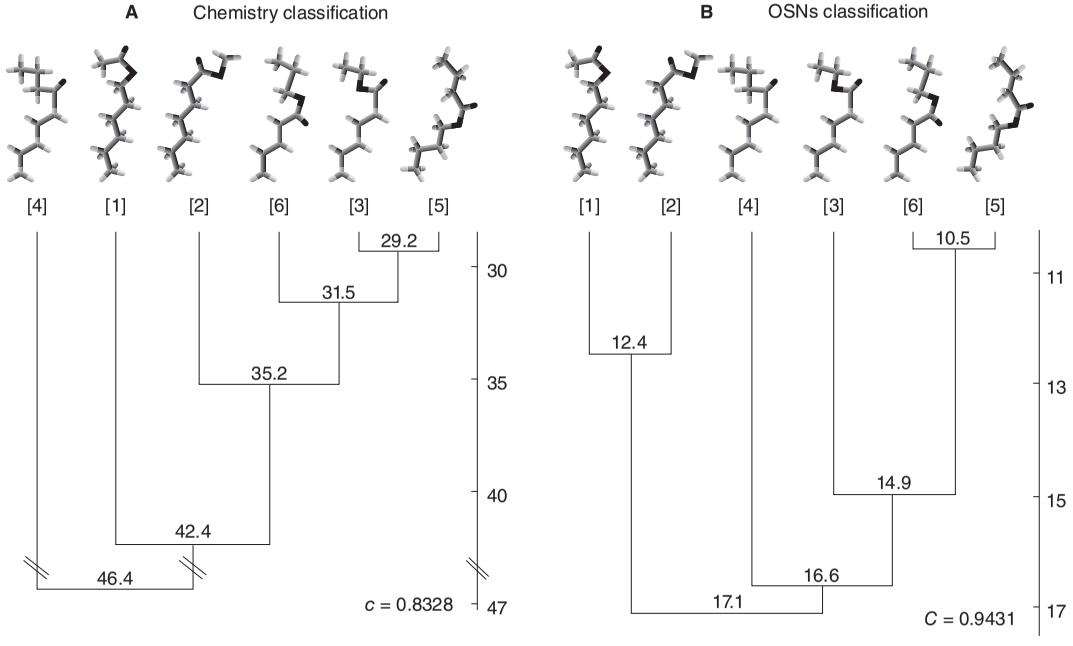

Figure 6-1 Hierarchical clustering analysis of tested esters. Comparison of odorant similarity. The left tree shows how analytic chemistry grades the chemical similarity between ketones. The right tree shows us how the olfactory receptors determine chemical similarity. These classifications differ significantly in their classification of chemical similarity (explanations in text). Source: Reformatted from Poivet et al., "Functional Odor Classification through a Medical Chemistry Approach," *Science Advances* 4, no. 2 (2018), fig. 3 CC BY-NC.

molecule, cells that respond to two molecules, cells that respond to every molecule. It was a pretty good mix of everything! We looked for some patterns. Although they were all ketones [in the 2016 study; the 2018 study added esters], they differed by the number of carbons in their cycle, also polarity and, more interestingly, the polar surface area of the ring." (The polar surface area is the sum of the surfaces of polar atoms, such as nitrogen, oxygens, and hydrogens.)

It turned out that the olfactory receptors could not care less what analytic chemistry dictated. "The way [ketones] would be classified by organic chemistry," Poivet argued, "would be the size of the ring as a first way to separate them, and then the composition of the ring as a second way. Do we have a nitrogen, or an oxygen, or a sulfur atom? And that would be your subfamily in the big family of a five- or six-carbon cycle group." The receptors had other preferences. "In olfaction, the classification we have was very, very different. The size does not matter at all. Neither does the cycle composition. What mattered was actually the polar surface area. This is where you have the electric charge in the three-dimensionality of your cycle, which actually accounts for the fact that the neuron will accept the odorant as a ligand or not."

In less technical terms, Poivet and Firestein's study had two notable findings. First, they found that the priority and hierarchy of features by which chemists and receptors determine chemical similarity differed. Some features that classical chemistry highlighted were of little interest to the receptors. Chemists and receptors had a different idea of what defined odorants as structurally similar. Second, the receptors responded to chemical features that hadn't even been predicted, or were even on the radar, of previous SORs and big data studies.

Poivet nodded: "The pattern we found was that if you have an olfactory receptor that accepts the lowest polar surface area of the molecules, and also a molecule with a larger polar surface area,

your receptor will accept, at least for these cyclic molecules, all the molecules with a polar surface area in between. No matter their size, like if these are bigger in their cycle or not. That was pretty interesting because—just with organic chemistry—you couldn't have predicted this!"

How biology makes sense of chemical similarity, therefore, diverges from the ideals of chemists. This changes how we should arrive at a theory of smell perception. Just like in cryptography, you have to have the right key to break the code. Everything else is word salad, regardless of whether it yields a few sentences that might make sense. To understand what a neural signal represents hinges on knowledge about what stimulus features the signal encodes. Consider an analogy. When physicists define the term "gravity" it matters whether they interpret it according to the framework of Newton or after Einstein. Both theories describe gravity as a field. But Newton saw gravity as a force on top of absolute time and space (as separate notions), whereas Einstein defined gravity as a curvature of spacetime. When you now model chemical similarity in olfaction, think of this as a similar paradigm shift.

Consequently, two principles of receptor-stimulus interactions ought to center in olfaction theory: first, the combinatorics afforded by the multidimensional stimulus, and second, chemical similarity according to receptor behavior. These two features highlight why odor biology is not a black box linking stimulus chemistry to perception. But there is another noticeable characteristic of olfactory receptors, one that ultimately shapes the neural representation of odor.

The Blind Homunculus

The brain represents what it is shown by the receptors. It does not "see" the configuration of external odorants but deals only with signals from the epithelium. Informational units, the signaling

pieces that perform a coding function in perceptual object formation, thus are determined by the mechanisms and patterns of receptor interaction, not the chemotopy of the distal stimulus.

Two fundamental mechanisms shape the signal that reaches the brain: *combinatorial coding* and *inhibition.* Combinatorial coding splits the information of the physical stimulus into several independent signals. Inhibition means that some parts of a stimulus can block the activity of another (such that the receptor pattern of a blended mixture is not a simple addition of activation signals by its components). These mechanisms, taken together, render the notion of chemotopy (as the neural representation of external stimulus topology) untenable.

The consequences of combinatorial coding for signal transmission and neural representation is twofold. First, the signal is underdetermined because it is crosscutting and overlapping. Several odorants interact with a receptor (and vice versa).[9] Moreover, different molecular features can activate a receptor. What the activity of a receptor represents, therefore, is not indicative of a specific property or microstructure. Second, the signal is further ambiguous because the binding preferences of receptors are uneven. Not only do code receptors exist for multiple bits of chemistry, but they also have different tuning ranges in their combinatorics. Each receptor type responds to a particular range of features. Some of these receptors are broadly tuned, interacting with a vast number of various features and odorants. Others are highly specific, responding to a smaller number of parameters. You have to know the behavior of a receptor for an idea about the kind of information and scope it signals.

At the receptor level, the external signal gets thoroughly scrambled. Say receptor type R1 detects a specific functional group of odorants, while another receptor type, R2, only recognizes chain structures of a definite length (that is, four to six carbon atoms). At this point, the informational content of the olfactory stimulus

is split into numerous bits and pieces across the receptor sheet. All this activity is mixed together on a single spatial plane.

Combinatorial coding has significant implications for the coding of mixtures. It entails that different odorants, in combination and under more natural conditions, could overlap in the receptors they activate. That's important when you look at mixture perception. Firestein explained: "You put the mixture on [expose the tissue to the stimulus], and you see a whole bunch of cells light up. Then you put each odor on separately, and you look at what cells light up. Of course, if you add up the numbers individually to the number that you see by the mixture, it's less." Firestein thus warned about the limitations of monomolecular stimuli. "Everything we usually do is monomolecular. Dissociate the cells [separate them from vessels and cell aggregations], put this odor on, and see what you'll find lighting up. Put another odor on, you see some other stuff. But that's very unnatural because everything we smell in the world is a blend of a few things up to hundreds of things."

A general theory of odor coding should be built on the principles of mixture perception. For one thing, stimulus information at the receptor level is no longer linked to individual odorants (as discrete external objects). Cell activation in the epithelium appears as a spatially distributed pattern. Activation patterns are randomly distributed and overlapping. What we end up with is a field of feature combinations, where the information of one stimulus (odorant O1) is not topologically discrete from the activity induced by other odorants (say, O2 and O3) encountered in parallel with O1. Distal stimulus topology ends up scrambled on a single plane, such that the interpretation of olfactory signals is contingent upon the mechanisms of the sensory system, not the external configuration of the stimulus.

Consequently, the brain cannot identify single odorants in a mixture by their combined receptor activation patterns. Consider

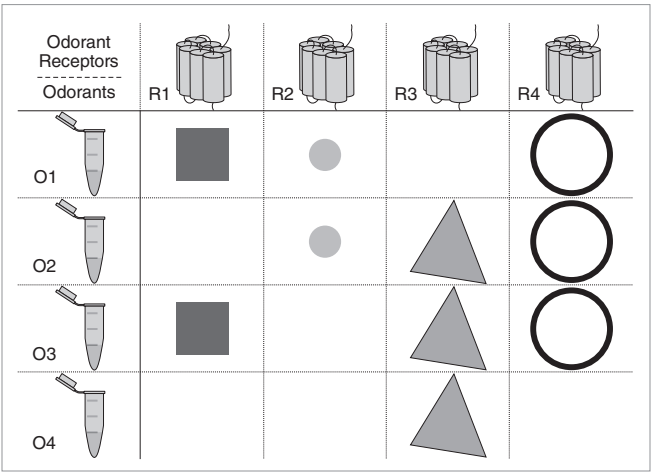

Figure 6-2 Hypothetical example of combinatorial odor coding at the receptor sheet. A mixture containing both odorants O1 and O2 overlaps in its receptor (R) coding with a mixture that consists of odorants O1 and O3. Likewise, a mixture containing both odorants O2 and O3 overlaps with a mixture involving odorants O1 and O4. Source: © Ann-Sophie Barwich.

the following hypothetical example. Imagine a receptor activation pattern R1-R2-R3-R4. In principle, this pattern could be caused by different sets of molecules as a consequence of combinatorial overlap. Figure 6.2 shows what this might look like. Effectively, in mixture recognition, it is not possible for the receptors to unambiguously determine the individual components.

This poses an intriguing challenge. How does the brain really know what kinds of things it encounters? Think about it by comparing the underlying issue to the story of *Flatland*.[10] Flatland is a fictional world, a two-dimensional place with two-dimensional beings. One day, Flatland's inhabitants see a three-dimensional object moving through its two-dimensional plane. Such an encounter with a three-dimensional object appears as a two-dimensional pattern on the plane. Now think about this plane as the receptor

sheet and your brain as a Flatlander observing the receptor patterns. Suppose a spherical object like a ball moving through Flatland. It would start as a small point that grows into a circle, increasing in size before it turns back into a small point until it vanishes. Now assume the pattern of another object moving through, a spinning top. It starts out as the same! Just by looking at the plane, it is impossible to tell whether the two-dimensional patterns of Flatland are a representation of a sphere or a spinning top. A similar case holds for olfaction, in which receptor patterns, forming an odor object, can be caused by a set of different odorants. Different odorants can generate the same mixture pattern.

Hold on a minute, you may say. Sure, receptor combinatorics implies that some mixtures have overlapping activation patterns. Still, in principle, odorants involved in mixture patterns could be determined by excluding double activations on the receptor sheet. It is a bit more complicated, perhaps, but possible. Some ambiguity in these patterns would remain, but we could derive a general theory of odor coding from individual odorants rather than having to deal with mixtures. Notwithstanding the challenge for the brain, making sense of scrambled receptor data does not stop here, because odorants in a mix might also block each other.

This type of stimulus inhibition at the receptor level is unheard of in the other senses. It might be unique to olfaction. It is not known to happen in vision or audition. It is not known in taste or touch or any other sensory modality, as far as we can tell. "I don't know of any other sensory system that does this." Firestein sounded excited. "Green photons activate green cones, but they don't inhibit blue cones or red cones. There's color opponency and all that, but that's upstairs, right?" He pointed to his head. At the receptor level, "there'd be no mechanism for that. You can get a red photon at a high enough luminosity to activate a green cone a little bit. But they don't block; there's no inhibition."

Could there be inhibitory processing right at the first step of odor coding? A recent study by the Firestein lab indicated just that.[11] As the majority of olfactory research shifted its focus toward the big questions in central processing, the Firestein lab continued to probe the receptors. Firestein did not think that the relevant functions were sufficiently understood. "So we got interested in blends," Firestein said. But how could researchers determine if odorants blocked each other, instead of merely overlapping in their receptor activation (as a result of combinatorial coding)? Whatever mixture you throw at the epithelium, "it's less than you would get out of a simple mixture." Firestein explained. "Because there are some receptors that are seeing both or all three of those features, so you're double counting."

The answer arrived in the form of a spectacular new microscope, SCAPE.[12] SCAPE stands for swept, confocally-aligned planar excitation. Firestein laughed, "anything for a catchy acronym. Essentially, it's based on a light sheet kind of microscopy. But it's a rapid scanning light sheet so that you can record many cells in a volume of tissue and very rapidly—quite an improvement really."

SCAPE opened a new window of experimental opportunities, amassing terabytes of data. It made it possible to scan an entire living, moving fly—for example, researchers can puff some odors at it while looking at its brain *in action.* Tissue samples larger than flies and larvae, like sections of the brains of mice, can also be scanned. The novelty of SCAPE was that it allowed scanning an entire intact tissue section while also recording single cell activity, both at an incredibly high speed and with high resolution.

"We took a hemisected preparation," Firestein detailed. "So we have the [mouse] head in a dish, perfusion in and out, and we can image a large swath of the olfactory epithelium at a depth. We can get down to a volume, down to a depth of about 180 or so microns. But we can also do it at the single-cell level. So you can also, when you want it, get single-cell resolution. It's like a combination of

doing single cells and EOG [electrooculography]." With SCAPE, one can determine which cells react specifically to what odor to distinguish the patterns. And all that can be done in intact and active tissue, not in dissociated cells or fixed brains cut into slices. Firestein noted: "The obvious thing to do with this would be blends or mixtures to see the code." The data, collected by Firestein's graduate student Lu Xu, are beautiful. You can now look at a tissue section and see how the entire preparation responds to a stimulus.

The findings yielded two major surprises. The first surprise was that odorants acted as both agonists and antagonists. "Apparently, in the mixture, one of the components is acting not only as an agonist but also as an antagonist at one or another receptor," Firestein said. This means that an odorant O1 can modulate receptor activity such that cells, activated by other odorants, say O2 or O3, show reduced activity or no activity at all when presented with a mixture containing both O1 and O2 or O1 and O3. Moreover, this odorant O1 does not act as an antagonist per se, but only acts in combination with specific other odorants (which may act as antagonists to different odorants as well). Antagonism, therefore, depends on the particular combination of an odorant with other odorants in a mix and is not a feature of the odorant per se. Firestein confirmed: "We've done a couple of mixtures now, and we've never found an odor that acts only as an agonist or only as an antagonist."

Inhibitory effects in olfactory mixture perception have been known as perceptual phenomena in psychophysical tests.[13] These effects had not been linked to a mechanism, however. Was inhibition an effect arising at the periphery and/or by central processing? There had been some earlier reports on inhibitory effects at the receptor level in olfaction.[14] What surprised everyone now was the sheer amount of inhibition. Inhibition was not a phenomenon affecting only the odd one or two receptors. "It's pretty widespread!" Firestein emphasized. "We find that in a mixture of three

odors—when you look at the three odors, and then you look at the mixture—we can see as much as 20 to 25 percent inhibition. It's a lot of inhibition that goes on. If you look, for example, at a cell that you see is dominantly activated by citral, and then you look at those cells in the mixture, you find that as many as 20 percent of them are being inhibited."

There was a second surprise, with even more enormous implications. Results further indicated *enhancement* effects, next to inhibition in mixture coding. Enhancement means that some cells, which showed little to no response to any of the individual odorants, suddenly responded actively to a mixture of these odorants. Firestein knew this was important. At first, he admitted: "I can't quite make sense of that part yet." The study continued while this book was in progress. Shortly before manuscript submission, Firestein emailed that they had linked the effect to an explanation: allosteric interaction. This mechanism—roughly!—states that a ligand (like an odorant) binds to a specific site at the receptor (the allosteric site) and thereby alters that receptor's activity. In other words: odorants *modulate* how an effector binds other odorants. As an example, a receptor R1 does not bind a given odorant O1 administered individually. If this odorant O1 is presented in a mix with odorant O2, however, then odorant O2 attaches to the allosteric site of the receptor to modulate its activity such that it now binds odorant O1. Lu Xu and Firestein tried different variations of mixtures, with mixtures that contained components in equal as well as unequal concentration. The enhancement effect remained robust.

Allosteric interaction had been well known in pharmacology, yet it had never been observed in GPCRs. Xu et al. had an answer to this puzzle: "That it has gone undiscovered in other Class A GPCRs [one of the six GPCR classes, grouped by sequence homology and functional similarity] is perhaps not surprising since they comprise a much smaller family of receptors than the olfactory

receptors and there is much less variation between them."[15] The size and genetic diversity of olfactory GPCRs, and their range of structurally diverse ligands, indeed makes them an excellent model to study other GPCRs, a subject of great relevance in pharmacology and drug design.

But what is the function of such inhibitory and enhancement effects specifically in odor coding? Xu et al. suggested that it serves discrimination and identification of complex blends. Consider the effects of combinatorial coding in olfaction: "Making conservative estimates that any given odor molecule can activate three–five receptors at a medium level of concentration, then a blend of just ten odors could occupy as many as fifty receptors, more than 10 percent of the family of human receptors. This will result in fewer differences between two blends of ten similar compounds." So you'd end up with indiscriminate odor activity in comparisons of more complex mixtures (which often contain dozens, even hundreds, of odorants). Patterns of odor activity become less and less distinct; this is also because receptors have overlapping sensitivities. How can the brain differentiate between different complex mixtures given these enormous levels of receptor activation and pattern overlap? You need to reduce receptor activity to refine discrimination of different mixture combinations. Inhibition and enhancement mechanisms serve this purpose.

Ultimately, this finding manifests a paradigm shift for a theory of odor coding. It shows that the receptor code in mixtures is fundamentally different from receptor codes of monomolecular stimuli. The idea of a linear, additive combinatorial model of odor coding, like that in vision or audition, breaks down completely. You cannot crack the olfactory code without understanding receptor behavior.

Odor coding modeled on the combinatorial scheme is, to a sufficient degree, underdetermined. Different odorant blends may end up with the same receptor representation, meaning spatial distri-

bution of odor signals cannot disambiguate olfactory identity in mixtures. Compare the idea with a familiar notion in the philosophy of science: the "underdetermination of scientific theory by evidence" (proposed by the French physicist Pierre Duhem, extended by the American philosopher Willard Van Orman Quine).[16] This notion states that different, even incompatible, theories can accommodate the same sets of observations. The same observational data, thus, can be read wholly differently depending on the interpretational framework. For example, the fact that the sun rises in the east to set down in the west is compatible with both geocentric and heliocentric models of the universe: same data, different models. We have now seen that a similar principle characterizes the combinatorial coding of odors at the receptor sheet. So how does the brain know what really happens outside the nose? How can the nose accurately tell which odorants it encounters? And what could possibly be the function of such indeterminate coding?

Without a model starting from receptor behavior, we cannot understand how the brain makes sense of smell—what it signals and represents via its neural activity patterns. Xu et al. thus noted that their findings about receptor coding carry further implications for central processing. They observed that the brain recognizes smells via pattern recognition, not combinatorial coding and topographic mapping: "Together with the recent work in piriform cortex suggesting a lack of topographical representation, there is abundant motivation to consider alternative coding strategies that also account for the presence of receptor modulation at the first step of olfactory discrimination." The next two chapters will unravel the details of this claim to propose such an alternative.

For now, let's conclude that mixtures yield effects that are not predictable from models that determine odor coding via individual components. While the precise mechanisms underpinning these effects remain part of the ongoing inquiry, we saw that a general theory of olfaction must start from receptor responses to the

stimulus, not chemical topology defined by traditional chemistry. Steven Munger replied: "What the brain is eventually going to see may be completely unrelated to what that individual component would have done."

Where Molecular Science Meets Perfumery

The olfactory system evolved to evaluate odors in context, not in isolation. That is the first crucial step to understanding the mechanisms of odor coding, which continue in central processing. Molecular clouds are not discrete, separable objects since odorants also mix with their environmental background. The nose thus measures odors in relation to each other and as part of an olfactory landscape. That implies two tasks: the assessment of complex mixtures with each other (same or different), and the evaluation of components as part of a complex mix (including salience, and figure-ground segregation). The fact that the nose can detect individual volatiles with remarkable precision in this context does not mean that that is its central computational principle.

Mixture perception is where molecular science pairs with knowledge in perfumery. Olfactory receptors show significant suppression and enhancement effects in mixture coding. These molecular effects, while surprising to scientists, have been a long and well-known perceptual phenomenon among perfumers.

Consider the toilet revolution. (Yes, you read that right.) The Bill and Melinda Gates Foundation recently joined forces with Firmenich, the biggest fragrance producer in the world, to find a solution to the stench of public toilets in rural areas with low or no water resources.[17] Water-free toilets are a problem in sanitation: what neutralizes a lot of the stink is water. Without water, public toilets turn into chambers of olfactory torture, containing an unbearably condensed combination of feces, urine, body odor, food, and smoke. Forget waterboarding, really. Naturally, people prefer

to defecate on fields in the fresh air, resulting in a disease threat and potential source of communal infections. To facilitate behavioral change, Firmenich and the Gates Foundation worked together to make the odor of these toilets more appealing.

Next to social impact, this work has fundamental research implications. It finally presents a link to connect perceptual effects to a molecular basis on which to model olfactory coding. Matt Rogers, involved in this project, said: "This project is a development of malodor counteractants, which are receptor antagonists—molecules that block the receptors from the malodors that were identified and put in the latrines in Africa. We delivered this list of antagonists to the perfumer, who was supposed to build a fragrance with this antagonist molecule."

What perfumers know, and molecular science has started to explore, is that many perceptual effects in olfaction link to the blending of odor (Chapter 3). Some odorants act as antagonists that suppress the perception of other odorants in mixtures. What turns an odorant into an antagonist, however, often depends on its combination with other odorants in a mixture. The sensory system does not "sum up" its stimulus; it often relies on principles that come to light only in mixture coding.

This intersection of molecular with perceptual expertise is also an opportunity for psychology to reenter discussion. Psychological theorizing can contribute in the formulation of computational principles that correlate odor coding at the molecular level with observable perceptual effects (Chapter 9). Marion Frank, at the University of Connecticut, argued: "The field should look at the olfactory system as it operates in more natural situations. Namely, what it is doing with as many as three–four distinct chemicals, at once, each of which changes in intensity over time." Frank's number is not arbitrary, but links to the Laing limit (named after a series of studies by David Laing in the late 1980s).[18] Laing discovered a limit to how many individual notes a person, trained and untrained,

could identify at once in a complex mixture, a perceptual "cap." The Laing limit kicks in usually at three individual notes for untrained noses, and about three to five in the case of expert noses, indicating a general limit to sensory processing, not an absence of training. This gives us the first fundamental clue to odor coding. It builds on pattern recognition, and this pattern recognition is not determined by the coding of individual odorants but by how the system handles them in combination.

The nose *samples*—and the brain *measures* mixtures. This idea of measurement comes into play in two ways already at the periphery.

First, there is the calibration of the system. For the brain to act as an environmental measure it needs a background against which to evaluate change, detect novelty, and recognize saliency. Remarkably, your olfactory system does all that without being distracted by the present odorous background. That's because your nose habituates and adapts quickly to odorants, although not at equal speed. This uneven adaptation of odor receptors exacerbates the scientific study of mixtures. At the same time, uneven adaptation is a determinative mechanism in mixture perception.

Some mixture components are suppressed as a result of selective adaptation after a period of time so that nonadapted elements appear more prominent.[19] Consequently, the same mixture is perceived differently the longer people smell it. Plus, adaptation rates between people differ. Thomas Hettinger argued that selective adaptation explains how our system is tuned to perceiving odors as part of mixtures. "We take, say, three components of the mixture, and then we add a fourth component. So we take the three components, we sniff [this mixture] a few times; we 'adapt out' some of that background. Then we immediately sniff the mixture with four components. The fourth component is perceived above the background of the other three components. You can show that you can extract out information about individual components of a

mixture." He emphasized: "A combination of mixture suppression and selective adaptation allows you to recognize the components in mixtures." Mixture coding is where chemistry meets psychology via biology. Frank agreed: "Combined studies of the well-known psychophysical phenomena of 'mixture suppression' and 'selective adaptation' bring experimental control over the natural workings of the olfactory system."

Second, there is the computational scaling of olfactory information, starting at the receptors. Such scaling involves a measurement of "how much" and "in what proportion." To evaluate the disposition of chemical information in context, the olfactory system breaks apart the sampled information into multiple pieces before reconstructing an odor image. That image, we know now, is not the sum of its molecular parts. How does the brain compute the odor image of a mixture from its multiple, different individual components? Again, the clue lies in mixture coding.

The computation of odor images concerns the ratio in which the system detects odorants in mixtures. Recent studies suggest that the olfactory system weighs the ratio of odorants as a form of pattern detection. Hettinger and Frank analyzed concentration measures, using the concept of the odor activity value (OAV).[20] In this, they worked parallel with the chemist Vicente Ferreira at the University of Zaragoza.[21] Frank explained: "This concept is defined as the ratio of odorant concentration to its threshold value. With a modest number of assumptions, it was concluded that the ratio of the identification probabilities (P1 / P2) is approximately equal to the ratio of the odor activity values (OAV1 / OAV2). This transformation is important because it helps to establish the contribution of components in flavor and fragrance mixtures that are often described by odor activity values."

Does odorant ratio determine odor images? Terry Acree provided further experimental proof. His lab recreated the aroma of "potato chips" using only three key odorants.[22] Acree's synthesis

of a complex aroma from a handful of key odorants does not lead to a deflationary explanation of odor, reducing odor quality to a few physical parameters. None of the key odorants on their own smelled of potato chips: methanethiol smells of rotten cabbage, methional smells of potato, and 2-ethyl-3,5-dimethylpyrazine smells of toast. The crucial discovery was that the configural image of "potato chip" did not depend simply on the list of ingredients but was linked to the ratio in which the three key odorants were put together.

Calibration and scaling are integral to measurement. They are also central to olfactory coding, linking perceptual effects to a molecular cause. The primacy of proportion and ratio in mixture composition is another phenomenon known from perfumery (Chapter 9) as well as biology—Steven Munger noted: "Complex mixtures of chemicals are very precise not just in their chemical composition but with the ratios of those components. The olfactory system needs to pull them apart so that it can recognize the individual components—but do it in such a way that key aspects of the mixture are retained in the pattern of output to the brain. The pattern is encoded by the nervous system in such a way that the animal can make an appropriate behavioral response."

The upshot is that it may not merely be the "what" but the "in what relation" that underpins the coding and computation of odor quality. What neural mechanisms allow the olfactory brain to receive input and operate in this manner, to sample and measure then represent and map the variable composition of its chemical environment?

Topology in Neural Representation

Receptor coding showed that the brain does not model the olfactory stimulus like an analytical chemist would model a molecule. We need to go beyond stimulus chemotopy to understand the

neural representation of odor. Studies on the mechanisms of mixture coding in this chapter paint a complex picture. But the brain has to have some idea of what reaches the nose. Receptor patterns are not the sole or final answer. By some measure, the brain arranges this vast mosaic of receptor activity. Beyond the receptors, however, neural activity encoding mixtures does not furnish us with transparent stimulus-response maps. The olfactory stimulus cannot be captured on an additive scale since its coding and computation is not additive, not in the bulb (Chapter 7) and even less so in the olfactory cortex (Chapter 8). From the brain's point of view, the same receptor activations (the brain's observations) can be generated by multiple distal objects (the physical stimulus).

How the brain interprets receptor patterns turns into an intriguing puzzle. The question no longer is how the brain knows that, say, cis-3-hexen-ol smells of freshly cut green grass. Instead, it is how the brain assigns meaning to overlapping, nondiscrete receptor activity in response to odorants. So how does the brain organize the scrambled receptor activity into neural assemblies and perceptual images? By which principles does the brain make sense of mosaic data from the receptor sheet? These questions lead us to the olfactory brain in the next two chapters.

Pandora's box has been opened.