Order in Odors: A Power Law Structures the Encoding of Stimulus Identity and Intensity

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Odorant molecules are detected through the combinatorial activation of ensembles of olfactory sensory neurons. By capitalizing on the numerical simplicity of the *Drosophila* larval brain, Si et al. (2019) uncover principles constraining the representation of the quality and intensity of olfactory stimuli.

That "the brain knows what the nose smells" should come as no surprise to anyone who has been enchanted by a lavender field in Provence or succumbed to the attraction of freshly baked pastries. Yet the banality of our daily olfactory experiences does not diminish the incredible feat that our nervous system achieves every time it computes the identity and intensity of an odor (for review, see Wilson, 2013). Odors are detected by a repertoire of olfactory sensory neurons (OSNs) that range from tens to millions of cells. Each OSN has a receptive field defined by the odorant receptor (OR) it expresses. Each OSN expresses a single OR. The relatively low specificity of the OR family has two functional consequences: each odorant ligand ("odorant" hereafter) binds multiple receptors; multiple odorants bind the same receptor with not necessarily the same affinity. Accordingly, odors are represented by the combinatorial activation of subsets of OSNs with overlapping receptive fields. While the existence of a population code across the OSNs accounts for our ability to discriminate between thousands of odors, it does not explain how the identity (nature) and the intensity (strength) of an olfactory stimulus are represented independently of each other. To address this question, one would seek to monitor the activity of the full ensemble of OSNs in an animal stimulated by a large panel of odors. While the exhaustiveness of such an experiment might deter most, Samuel and colleagues successfully accomplished this technical *tour de force* in a recent study (Si et al., 2019).

To measure the activity of an entire set of OSNs, Si et al. (2019) capitalized on the miniature olfactory system of the *Drosophila melanogaster* larva. The nose of the larva is composed of a pair of bilaterally symmetric organs that host 21 OSNs. While the receptive field of individual ORs expressed at the larval stage has been investigated (Kreher et al., 2008), little is known about the population activity emerging from the simultaneous stimulation of multiple OSNs (Asahina et al., 2009). Si et al. took advantage of the transparency of the larva to image the function of its peripheral olfactory system by expressing the genetically encoded calcium indicator GCaMP. To stimulate the olfactory system of the same larva by odor pulses with controlled temporal and intensity profiles, the team employed microfluidics to develop a new olfactometer—a high-precision odor-delivery device. Next, Si et al. assembled a collection of 34 odorants representative of the chemicals emitted by fruits commonly found in the larva's habitat. Equipped with this new olfactometer and odor collection, the team imaged the activity of the OSN ensemble stimulated by pulses of waterborne odors with a dilution spanning five orders of magnitude, from very weak concentrations (10^{-8}) that hardly activated any OSNs to high concentrations (10^{-4}) that tended to saturate most OSNs. Combined with an ingenious technique to anatomically identify individual OSNs, the functional imaging experiments yielded a dataset with unprecedented depth of coverage, thereby permitting calculation of the dose-response curve of a complete set of OSNs for 34 odorants.

Big data often give rise to disproportionally small insight. By contrast, Si et al. fully exploited their big dataset to delineate principles structuring odor representations in the peripheral olfactory system of the larva. First, they found that the OSN dynamics (reported by GCaMP) follows a standard dose response independent of the nature of the odor. This "activation function" can be accurately modeled as a sigmoid (S-shape curve; Figure 1A). Upon normalization of the activation functions, the location of the function's threshold (inflection point denoted as K in Figure 1A) represents the unique free parameter of the model. This parameter, called "sensitivity," is given by the affinity of an OR for a particular odorant, which determines the range over which an OSN is sensitive to changes in the concentration of this odorant (blue box in the center panel of Figure 1A). Next, Si et al. inspected the statistical properties of the distribution of sensitivities observed for all OR-odorant pairs. This mean-field approach revealed that the odor-receptor sensitivities are distributed according to a power law—a relationship reminiscent of Stevens' law where the perceived intensity of a stimulus (ψ) grows as a power law with the stimulus intensity (C): $\psi \propto C^{\alpha}$, where α is a constant. The implication of this statistical property is profound: on average, relative changes in the concentration of any odorant produce the same relative changes in neural activity across the entire repertoire of OSNs. Equivalently, the average OSN activity scales as a power-law function of the concentration of an odorant—a statistical observation previously reported for adult fly OSNs (Stevens, 2016) and reestablished by Si et al. for the larval OSNs.

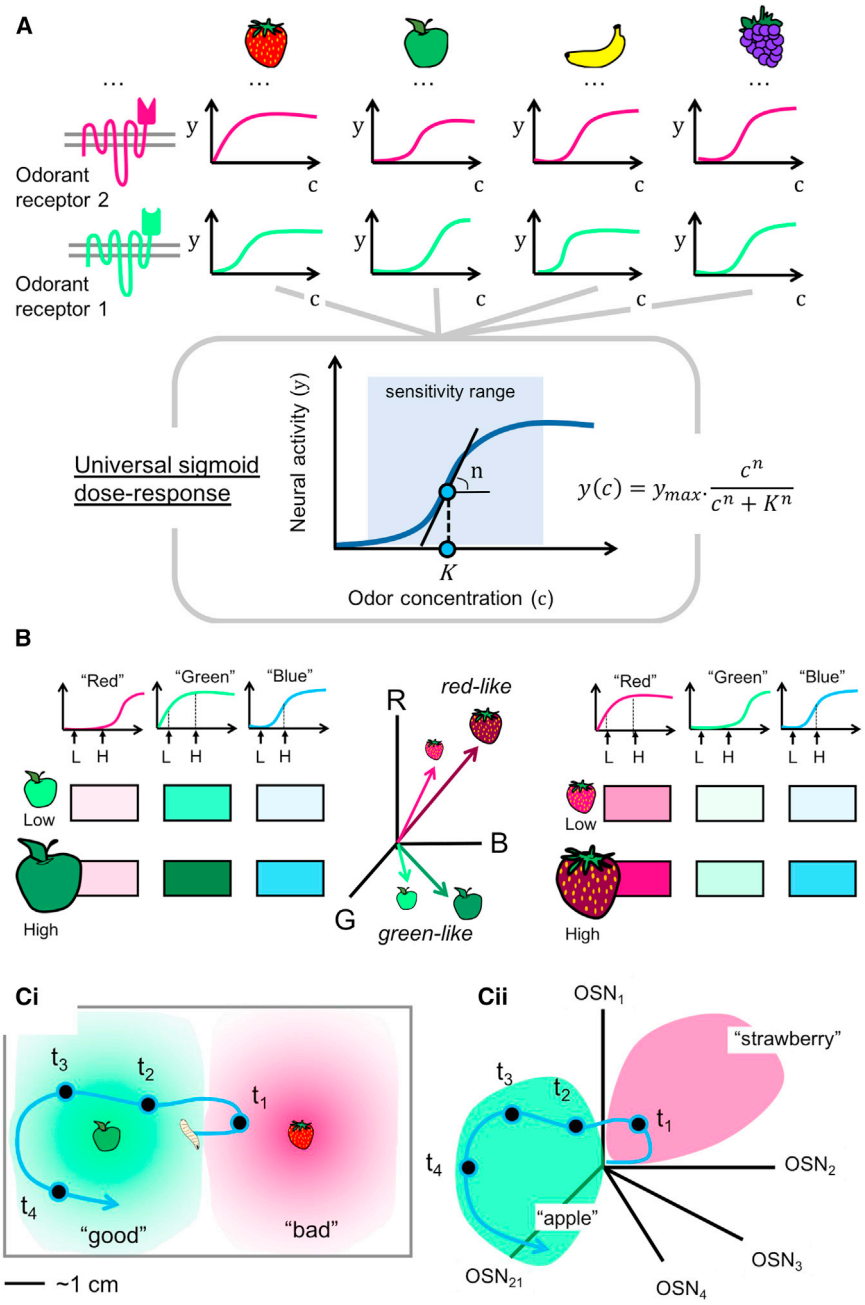

Figure 1. Encoding of Odors by the Peripheral Olfactory System of the Larva

(A) The same odorant receptor (OR) is bound by multiple odorant ligands (symbolized by different fruits). The dose response of any odor-receptor pair can be described by a sigmoid function where the threshold ("sensitivity," K) is a free parameter and the steepness of the curve (n) is a constant.

(B) Illustrative representation of "odors" as colors following a fictive RGB code in which a triplet of sensors respond to the intensity of an odor. The tuning (dose-response) curve of each sensor is odor dependent. According to this model, changes in the concentration (low versus high) of an odor (apple versus strawberry) lead to changes in colors that qualitatively maintain the same "hue" (identity) across an intensity range.

(C) Olfactory behavior upon Pavlovian conditioning where the "apple" odor is positively reinforced with food and the "strawberry" odor is negatively reinforced with the absence of food. (Ci) A trained larva is introduced in an arena with the apple odor on the left side and the strawberry odor on the right side. Shortly after having detected that it is heading toward the strawberry odor ("bad"), the larva turns around and ascends the apple odor gradient ("good"). (Cii) Hypothetical temporal trajectory of the olfactory stimulation experienced by the larva in (Ci) in the neural space spanned by the activity of the 21 OSNs. The apple and strawberry odors are predicted to form two different subspaces (colored manifolds) in the OSN space.

Drosophila larvae are capable of associative learning (Gerber and Stocker, 2007). Upon Pavlovian conditioning, larvae form olfactory memory specific to the identity of the reinforced odor but generalizable across concentrations. The attraction level of an odor that is innately weakly attractive can dramatically increase when paired with food. Conversely, an attractive odor can elicit aversive responses when paired with the absence of food. While the power-law relationship to the overall activity level of the OSNs does not explain the ability of larvae to discriminate between the identity of distinct odors, it suggests a mechanism conferring concentration invariance to the peripheral representation of odor qualities. By applying a dimensionality reduction technique (PCA) to the distribution of sensitivities and the time course of the ensemble of OSN activities, Si et al. demonstrate that distinct odors define different directions in the space spanned by the population of larval OSNs. By analogy to the visual system, where the red, green, and blue channels can encode a plethora of colors, consider the representation of odors by a triplet of sensors with sigmoid dose responses. In this synesthetic thought experiment, illustrated in Figure 1B, an "odor" would activate the three sensory channels at different levels, but the resulting hue would remain qualitatively independent of the stimulus intensity. The encoding of real odors is obviously more complex, since it takes place in a neural space with 21 dimensions (Figure 1C)—one dimension per OSN. As was found for the second-order olfactory neurons (projection neurons) of the locust (Stopfer et al., 2003), stimulating the larval olfactory system with a pulse of odor resulted in a temporal trajectory in the OSN space. The trajectories elicited by different concentrations of the same odor form a manifold (subspace). Discriminable odors are expected to define distinct manifolds. To determine what "the nose is smelling," the task of the olfactory circuit downstream of the OSNs might be to delineate the manifold on which the peripheral olfactory system evolves (Figure 1Cii). How this computation is achieved mechanistically remains unclear, but the inhibitory feedback created by the local interneurons in the larval antennal lobe (equivalent of the olfactory bulb; Berck et al., 2016) might

play an important role by normalizing olfactory representations across concentrations (Asahina et al., 2009; Wilson, 2013).

The study by Si et al. proposes several principles that unify the combinatorial coding of odors by primary sensory neurons. It also brings about many questions related to the physiology and the collective function of OSNs. What is the origin of the sigmoid shape of the dose-response function that describes virtually any odorant-receptor pair (Figure 1A)? This property might not be fully determined by the olfactory transduction cascade mediated by the OR for the following reasons. First, the spike dynamics appears to be largely conserved across OSNs of the adult fly while the olfactory transduction dynamics can vary considerably (Nagel and Wilson, 2011). Second, the OSN activity elicited by behaviorally relevant patterns of odor stimulation are strikingly similar to those produced by the optogenetic activation of the same OSN with equivalent light patterns (Schulze et al., 2015). The similarity between the odorant-driven and optogenetics-driven OSN firing activities suggest that features pertaining to the dynamical representation of olfactory stimuli are conditioned by the spiking machinery of the OSN. Are combinatorial OSN activation patterns the only determinants of behavioral responses? Besides their excitatory effects, odors can also inhibit the activity of OSNs (Wilson, 2013). In larvae with a single functional OSN controlled by optogenetics, OSN inhibition has been shown to promote near-deterministic stops and turning maneuvers (Schulze et al., 2015). While the prevalence of OSN inhibition could not be determined with GCaMP, the numerical simplicity and molecular tractability of the larval olfactory system is likely to be advantageous to elucidate this question in future work. Considering that the dose responses observed for fly ORs are similar to those reported for vertebrate and human ORs, it is a safe bet that computational principles underpinning the peripheral encoding of odors are common between the miniature brain of a larva and its larger vertebrate counterparts.

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Looking into the Brain of Buridan's Ass

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To survive, animals must maximize the minimum—take care of the least satisfied among their basic needs. In this issue of *Neuron*, a study by Juechems et al. (2019) illustrates that this core principle might shape the way medial prefrontal regions of the human brain drive and valuate sequential choices between different types of reward.

The famous character of Buridan's story is a donkey, who ends up dying from both thirst and hunger, because he was placed exactly midway between a stack of hay and a pail of water and therefore could not reach a decision. In fact, this situation had already been mocked by Aristotle as a ridiculous paradox, which in Ancient Greece featured not a donkey but "a man, being just as hungry as thirsty, and placed in between food and drink." For Aristotle, it was obvious that the man would be able to choose which reward to consume first and hence would survive the dilemma. Yet he did not explain *how* the human brain can make such a choice. A recent study by Juechems and colleagues provides