Universal front-end gain control aids robust combinatorial coding in naturalistic environments

Nirag Kadakia[a] **and Thierry Emonet**[a,b]

[a]Department of Molecular, Cellular, and Developmental Biology; [b]Department of Physics, Yale University, New Haven, CT 06511

This manuscript was compiled on October 2, 2018

Please provide an abstract of no more than 250 words in a single paragraph. Abstracts should explain to the general reader the major contributions of the article. References in the abstract must be cited in full within the abstract itself and cited in the text.Please provide an abstract of no more than 250 words in a single paragraph. Abstracts should explain to the general reader the major contributions of the article. References in the abstract must be cited in full within the abstract itself and cited in the text.Please provide an abstract of no more than 250 words in a single paragraph. Abstracts should explain to the general reader the major contributions of the article. References in the abstract must be cited in full within the abstract itself and cited in the text.Please provide an abstract of no more than 250 words in a single paragraph. Abstracts should explain to the general reader the major contributions of the article. References in the abstract must be cited in full within the abstract itself and cited in the text.Please provide an abstract of no more than 250 words in a single paragraph. Abstracts should explain to the general reader the major contributions of the article. References in the abstract must be cited in full within the abstract itself and cited in the text.Please provide an abstract of no more than 250 words in a single paragraph. Abstracts should explain to the general reader the major contributions of the article.

Odor coding | Drosophila olfaction | Sensory systems | Weber's Law | Olfactory receptor neurons

Animals identify and discriminate odors using olfactory receptors (Ors) expressed in olfactory receptor neurons (ORNs) (1, 2). Individual ORNs, which typically express a single Or (2), respond to many odorants, while individual odorants activate many distinct ORNs (3–6). Odors are thus believed to be encoded by the combinatorial patterns of activity they elicit in the sensing periphery (3–5, 7–9), patterns then decoded downstream into behavioral response (10). Such a combinatorial coding strategy would be compromised in natural environments, where ethologically-relevant odors are often mixed with background ones (11) and intensity can vary widely and rapidly as odors are carried by the wind (12–16). How are odors recognized reliably despite these confounds? In *Drosophila melanogaster*, OR-odorant dose response curves exhibit similar Hill coefficients but distinct power-law distributed activation thresholds (4, 16, 17), which together with inhibitory odorants enhance coding capacity (4, 17, 18). In antennal lobe (AL) glomeruli, mutual lateral inhibition normalizes population response, helping to maintain the invariance of activity patterns (19, 20). Further downstream, sparse connectivity to the mushroom body (MB) helps maintain neural representations of odors, and facilitates compressed sensing decoding schemes (21–23). Finally, temporal features of neural response may contribute to concentration-invariant representations of odor identity (24–27).

Here we examine how adaptation at the very front-end of the insect olfactory circuit contributes to the fidelity of odor encoding. Our theoretical study is motivated by the recent discovery of invariances in the response dynamics of ORNs expressing the co-receptor Orco (16, 28–30). While for some Or-odor combinations, ORN response can exhibit large differences, such as super-sustained responses (31), for many Or-odor combinations the deconvolution of stimulus dynamics from neuron responses produces highly stereotyped filters (32), insensitive to odor concentration, enabling ORNs to maintain response time independent of odor intensity (16, 17, 32). These properties stem in part from an apparently universal mechanism of ORN adaptation: gain varies inversely with mean odor concentration according to Weber-Fechner's Law of psychophysics (16, 29, 30, 33, 34). This relatively fast adaptation (~ 250 ms) can be traced to feedback mechanisms in odor transduction, upstream of ORN firing (16, 29, 30, 35), and the generality of the scaling law suggests it may be mediated not by odor- or OR-dependent differences, but by the highly conserved Orco co-receptor (28, 36–38).

While in a single channel system such as *E. coli* chemotaxis, adaptive feedback via Weber-Fechner's Law robustly maintains sensitivity over concentration changes (39), the implication for a multiple-channel system – which combines information from several sensors with overlapping receptive fields – is less straightforward. Here we combine a biophysical model of universal ORN adaptive response and neural firing with various sparse signal decoding frameworks to explore how ORN adaptation affects combinatorial coding and decoding of odor signals spanning varying degrees of intensity, molecular complexity, and temporal structure. We find that this adaptive mechanism promotes the accurate discrimination of weak odor signals from strong backgrounds of varying molecular complexity, both in static odor environments and in fluctuating ones. We also investigate our framework in the context of the primacy coding hypothesis – that odors are encoded entirely by the few earliest responding ORNs (27, 40), finding that primacy coding is both consistent with and enhanced by front-end adaptation. Together, our results suggest that despite the broad overlap of ORN tuning curves, a mechanism of front-end adaptation, when endowed with universal Weber-

Significance Statement

In insect olfaction, odors are believed to be encoded by the distinct spatiotemporal patterns of activity they elicit in sensing neurons. Here, we investigate how these patterns would be maintained in naturalistic environments, where odor concentrations can vary rapidly, and where ethologically-relevant odors often mix with nuisance backgrounds. Here, we show that a single, robust mechanism of response adaptation, Weber's Law of perceived difference, which was recently observed in *Drosophila*, may play a vital role in maintaining these odor codes. While Weber's Law is known to maintain sensitivity in single-channel systems such as bacterial chemotaxis, here we illustrate its general applicability to multi-channels systems in which responses may be broad and highly overlapping.

Please provide details of author contributions here.

Please declare any conflict of interest here.

[1]A.O.(Author One) and A.T. (Author Two) contributed equally to this work (remove if not applicable).

[2]To whom correspondence should be addressed. E-mail: author.twoemail.com

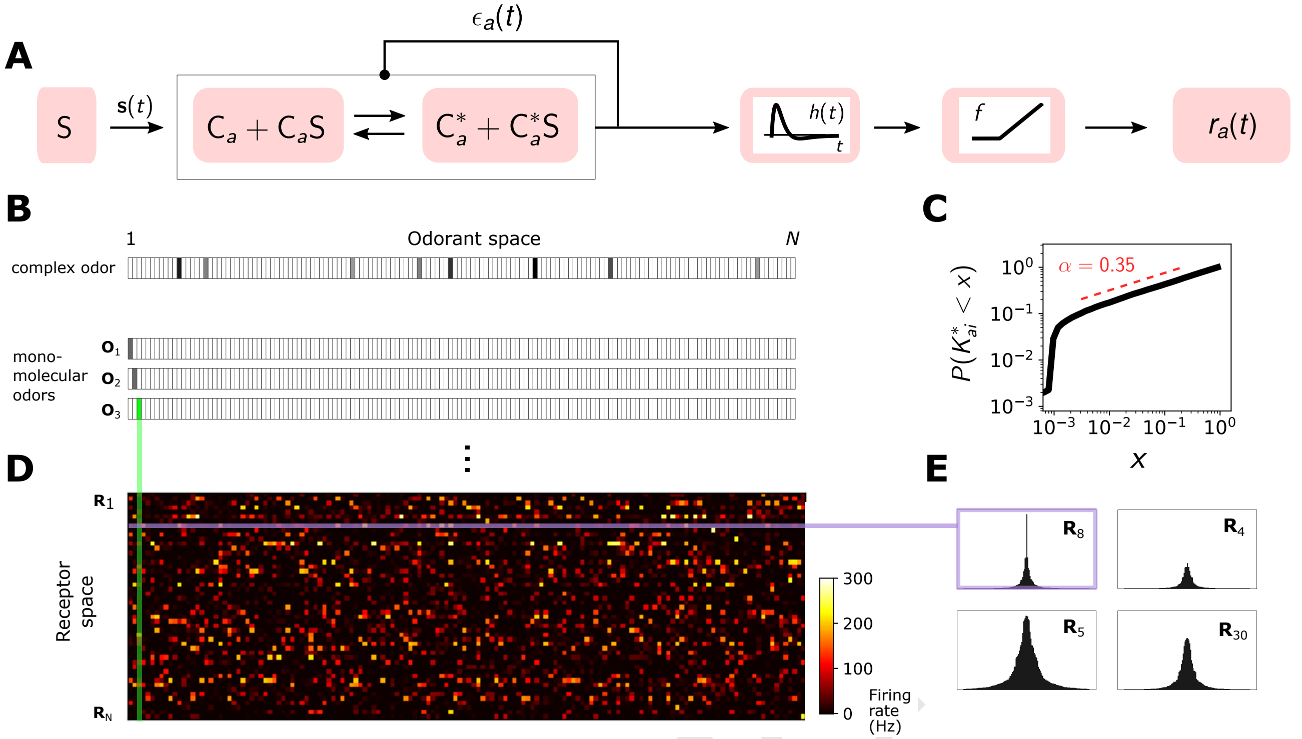

Fig. 1. A Odor binding model. Or/Orco complexes C_a bind odorant molecules s_i comprising stimuli S. These complexes can stochastically switch between inactive and active states, where the steady-state active fraction is determined by the complex free energy $\epsilon_a(t)$. The activity feeds back on to the free energies with timescale τ to pull the activity to a baseline level A_{a0}. ORN firing rates $r_a(t)$ are generated by passing $A_a(t)$ through a linear temporal filter $h(t)$ and a nonlinear thresholding function f. **B** Odor mixtures are represented by real-valued N-dimensional vectors **s**, whose components s_i are the concentrations of the individual molecular constituents of s. **C** Active binding constants are distributed as a power-law with coefficient $\alpha = 0.35$ (17). **D** The maximal firing response of 50 ORNs to the 150-possible monomolecular odors $\mathbf{s} = s_i$, for the power-law K_{ai}^* distribution in C. **E** Representative ORN tuning curves, generated by ordering the responses within a single row of the response matrix in D. A diversity of response, mimicking that of (4), arises from both the distribution of odorant binding constants K_{ai}^* and the distribution of receptor free energies ϵ_a.

Fechner scaling via the co-receptor Orco, may play a vital role in preserving representations of odor identity in naturalistic odor landscapes.

Results

Model of ORN sensing repertoire. We consider a repertoire of $M = 50$ ORN types modeled using a simple extension of a minimal model of odor-to-ORN firing (16) that reproduces the Weber-Fechner adaptation and firing rate dynamics measured in individual *Drosophila* ORNs in response to Gaussian and naturalistic signals. Within ORNs of type $a = 1, ..., M$, Or-Orco complexes form non-selective cation channels (Fig. 1a) that stochastically switch between active and inactive states, while simultaneously binding to odorants i with dissociation constants, K_{ia}^* and K_{ia}, respectively (16, 35). Assuming these processes are faster than other reactions in the signaling pathway, the quasi-steady state active fraction A_a of channels in ORNs of type a is (Methods):

$$A_a(t) = \left(1 + e^{\epsilon_a(t)} \frac{1 + \sum_i^N s_i(t)/K_{ai}}{1 + \sum_i^N s_i(t)/K_{ai}^*}\right)^{-1}. \quad [1]$$

$s_i(t)$ are the time-dependent concentrations of the individual monomolecular components of the odor signal $\mathbf{s}(\mathbf{t})$ at time t, and $N = 150$ is the size of the molecular odorant space (Fig. 1b). Inward currents elicited by activating Or-Orco channels eventually result in a negative feedback onto $A_a(t)$ (16, 30, 35):

$$\tau \frac{d\epsilon_a(t)}{dt} = A_{a0} - A_a(t). \quad [2]$$

Here τ is the adaptation time and $\epsilon_a(t)$ is the free energy change due to modifications of the Or-Orco complexes by the adaptation mechanism, which is limited to the finite range $\epsilon_{\mathrm{L},a} < \epsilon_a(t) < \epsilon_{\mathrm{H},a}$ (16). Firing rate is minimally modeled by filtering the activity $A_a(t)$ with the double exponential filter $h(t)$ and rectifying nonlinearity f (Methods and (16)):

$$r_a(t) = f\left(h \otimes A_a(t)\right). \quad [3]$$

Here, $\otimes$ represents convolution. When deconvolved from stimulus dynamics, the shapes of the temporal kernels of *Drosophila* ORNs that express Orco are largely receptor and odor independent (16, 17, 32). Moreover, adaptation is not intrinsic to the receptor (35). Accordingly, τ, $h(t)$ and f are assumed independent of receptor and odorant identities.

We assume that the lower cutoffs $\epsilon_{\mathrm{L},a}$ are receptor-dependent and choose them from a normal distribution. This variability ensures that ORNs are activated above quiescence (around 5 Hz) at distinct stimulus levels (16). Diversity among odor-ORN responses mainly arises from the distribution of chemical dissociation constants. For simplicity we only consider agonists, i.e. $K_{ia}^* > K_{ia}$ but the analysis can easily be extended to include inhibitory odorants, which increases coding capacity (18). We choose the dissociation constants from a power law distribution ($\alpha = 0.35$) recently found across ORN-odor pairs in *Drosophila* larvae (Fig. 1c). For a handful of ORNs we choose a very small value for one of the K_{ai}^* to

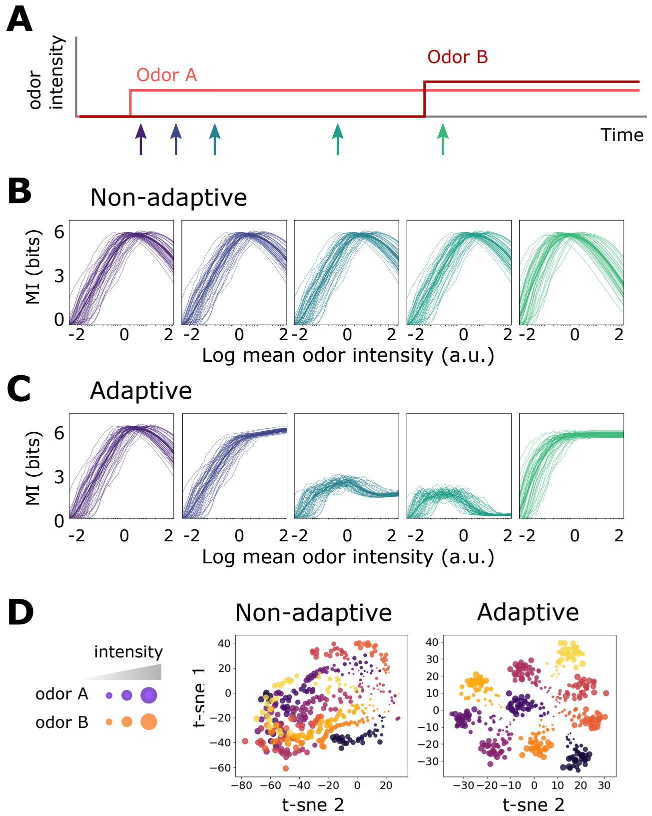

Fig. 2. Front-end adaptation maintains information capacity and representations of odor identity across changes in intensity. **A** Step of odor A is followed by a step of odor B at a later time t_B, where $t_B \gg \tau$. Odor A and B have similar intensities. **B** Evolution of mutual information (MI) between odor signals and ORN response, in the non-adaptive system, as a function of relative odor concentration. Thin lines are the MI contained in individual ORNs; heavy line is the average. MI is plotted at times of order of τ following t_A (purple; purple-blue), right before t_B (blue-green), and shortly after t_B (green). **C** Same as (B), for the adaptive system. **D** Abstract representation of ORN responses in reduced dimensions.

mimic high responders to private odorants relevant to innate responses. We checked that adding these private odors does not affect the general findings.

While this phenomenological model could be extended to include further details – e.g. we could relax the quasi-steady-state assumption in Eq. 1 and use a more complex model for the firing rate (16) – this minimally-parameterized form captures the key dynamical properties of Orco-expressing ORNs relevant to our study: receptor-independent adaptation (35) with universal Weber-Fechner scaling (16, 17, 29, 30) that maintains response time independent of mean stimulus intensity (16, 32), and diversity of the tuning curves (4) and temporal firing patterns (24–26) in response to panels of monomolecular odorants (Fig. 1d-1e).

Concentration-invariant preservation of coding capacity. To investigate how front-end adaptation affects encoding capacity, we calculate the mutual information (MI) between odor signal $\mathbf{s} = \mathbf{s}_A + \mathbf{s}_B$ and response $\mathbf{r}$ as a function of signal intensity, with and without adaptation. A step of odor A, $\mathbf{s}_A$, turns on at time t_A and a step of odor B, $\mathbf{s}_B$ turns on at some later time t_B (Fig. 2a). Both odors have similar intensities. In the non-adaptive case, MI peaks around the region of maximum sensitivity ($\sim 10^2$ a.u.) after t_A (Fig. 2b). The adaptive system mimics the non-adaptive system at t_A, before adaptation has kicked in (Fig. 2c). In time, adaptation causes the sensitivity to decrease, and the mutual information peak shifts to higher concentrations. Eventually, all ORNS are firing at adapted baseline and mutual information is mostly eliminated. However, having now adjusted its regime of maximum sensitivity to the presence of odor A, the system can respond appropriately to odor B: the MI at t_B is nearly 6 bits across 3 decades of concentration.

We expect that preservation of information capacity helps maintain odor identity. We visualize this by projecting the 50-dimensional ORN response $\mathbf{r}$ to a lower two-dimensional space using t-distributed stochastic neighbor embedding (t-SNE) (41). Testing this both for a smaller (Fig. **??**) and larger (Supporting Information) odor repertoire, odors cluster by identity in the adaptive system, while in the non-adaptive system, representations mix among their identity and concentration. This suggests that universal front-end adaptative feedback helps preserves odor identities within the ensemble of ORN response.

Front-end adaptation enhances odor discrimination in complex environments. How well does the preservation of coding capacity translate to better signal reconstruction? One potentially complicating factor is the disparity between sensor dimension and stimulus dimension: while *Drosophila* only express $\sim$ 60 olfactory receptor genes (42), the space of odorants is far greater (23). However, many naturally-occurring odors are comprised of a small subset of odorants, which is suggestive as mathematical results in compressed sensing guarantee their reconstruction, assuming a sufficiently random response (23, 43–45). There is no direct evidence that a compressed decoding framework is implemented in the *Drosophila* olfactory circuit (46). Here we used this framework as a mathematical tool to quantify how front-end adaptation potentially affects odor decoding. We later verify our conclusions with other classification techniques that make use of the known architecture of the olfactory system.

To incorporate the linear framework of compressed sensing, we treat the nonlinear odor encoding exactly but approximate the decoding to first order. We first examine how foreground odors are recognized when mixed with background odors, quantifying decoding accuracy as the percentage of odors correctly decoded within some tolerance (Methods; Fig. 3a). Without adaptation, detection accuracy for concentrations is maintained within the range of receptor sensitivity, for a simple, weak background. However, accuracy is virtually eliminated as background complexity and intensity rise (Fig. 3b). The range of the sensitivity is higher in the adaptive system, and it is substantially more robust across changes in molecular complexity and intensity of the background odors (Fig. 3c).

In realistic odor environments, the concentration and duration of individual odor whiffs vary widely (14), and we wondered how well a front-end adaptation mechanism with a single timescale τ could promote whiff detection in such environments. As inputs to our coding/decoding framework we apply a naturalistic stimulus intensity recorded using a photo-ionization detector (16) (Fig. 3d) to which we randomly assign sparse identities from the N-dimensional odorant space. To mimic background confounds, we combine these signals with static odor backgrounds, and then calculate the percentage of decoded whiffs (purple bars in Fig. 3d). We also assume a finite length of short-term memory: detected odor signals are only retained τ_{F} seconds in the immediate past (Methods). Without ORN adaptation, sufficiently strong backgrounds eliminate the ability to reconstruct the identity of individual odor whiffs, irrespective of the complexity of either the foreground or background odor (Fig. 3e, green lines). In the adaptive system, this is substantially mitigated (red lines in Fig. 3e), as long as the memory duration τ_{F} is on the same

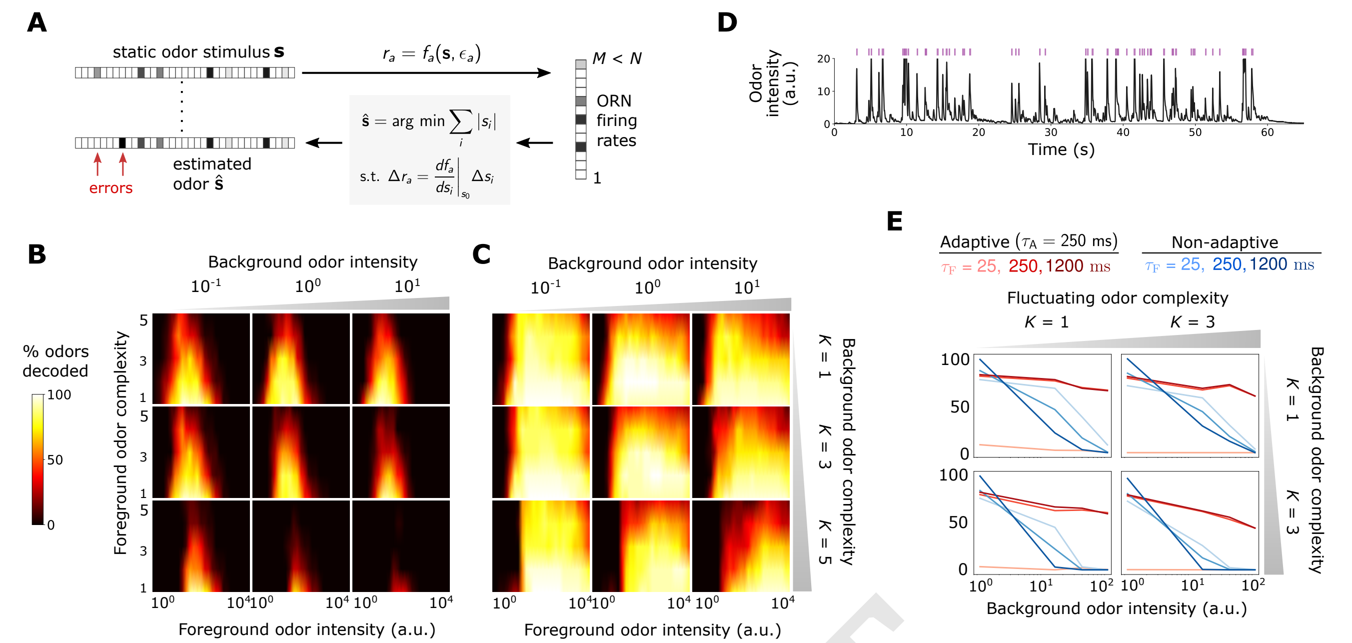

Fig. 3. Front-end adaptation promotes accurate sparse odor decoding in static and naturalistic odor environments. **A** Odor stimuli produce ORN responses via odor-binding and activation and firing machinery, as described by Eqs. 1-3. Odors are then decoded using compressed sensing by linearizing around a background s_0 and minimizing the constrained L_1 norm of the odor signal (Methods). Odors are assumed sparse, exhibiting K nonzero components, $K \ll N$. **B** Decoding accuracy of foreground odors in the presence of background odors, without front-end adaptation. Individual heatmaps show the decoding accuracy of the foreground odor as a function of its intensity and complexity; plots are arrayed by background odor intensity (column-wise) and complexity (row-wise). Odors are considered accurately decoded if the sparse components are estimated within 25% of their true values and the zero components (not in the odor mixture) are estimated below 10% of s_0. **C** Same as (B), for the adaptive system. **D** Recorded trace of naturalistic odor signal; whiffs (signal > 5 a.u.) demarcated by purple bars. This signal is added to static backgrounds of different intensities and complexities, which is then decoded in time (Methods). **E** Individual plots show the percent of accurately decoded odor whiffs as a function of background odor intensity, for the non-adaptive (blue) and adaptive (red) systems, for different t_F (line shades). Plots are arrayed by the complexity of the naturalistic signal (column-wise) and the complexity of the background odor (row-wise)

order as the adaptation timescale τ (darker red lines).

Front-end adaptation enhances primacy coding. The primacy coding hypothesis posits that odor identity is encoded by the set (but not temporal order) of the p earliest responding glomeruli/ORN types, known as primacy set of order p (27). If the activation order of ORNs were invariant to the strength of an odor step or pulse, primacy sets would in principle form concentration-invariant representation of odor identity.

Though our coding framework uses the full ORN ensemble in signal reconstruction, some of these ORN responses may contain redundant information, and a smaller primacy subset may suffice. To examine this relationship, we apply our model to a sigmoidal stimulus that rises to half-max in 50 ms, calculating decoding accuracy in time. Since ORNs activate sequentially, the primacy set is defined by the ORN subset active when the odor is accurately decoded. For simple odors, a limited set of earliest responding neurons fully accounts for the odor identity ($K = 1, 3, 5$ plots in Fig. 4a), in agreement with primacy coding. As expected for more complex odor mixtures, the full repertoire is required for accurate decoding ($K = 7, 9$ plots in Fig. 4a). Primacy coding also predicts that for stronger stimuli, responses occur earlier in time, since the primacy set is realized quicker, which our framework replicates (SI).

Beyond mere consistency, however, front-end adaptation might also enhance primacy coding in different environmental conditions, such as background odors, which could scramble primacy sets. To investigate this, we calculated the primacy sets for 1000 sparse odor mixtures atop various static backgrounds. We find that primacy sets for these mixtures are preserved across different background concentrations, for all but the smallest primacy orders (Fig. 4c). This suggests that front-end adaptation may play a central role in reinforcing primacy codes across differing environmental conditions.

Contribution of front-end adaptation for odor recognition within the *Drosophila* olfactory circuit. Signal transformations in the sensing periphery are propagated through the remainder of the olfactory circuit, where they are ultimately translated to behavioral response. How does front-end adaptation interact with these subsequent neural transformations? ORNs expressing the same OR converge to a unique AL glomerulus, where they receive lateral inhibition from other glomeruli (19, 47). This inhibition implements a type of divisive gain control (20), normalizing the activity of output projections neurons, which then synapse onto a large number of Kenyon cells (KCs) in the mushroom body. To investigate how odor representations are affected by interactions between front-end ORN adaptation and this lateral inhibition and synaptic divergence, we extended our ORN encoding model by adding uniglomerular connections from ORNs to the antennal lobe, followed by sparse, divergent connections to 2500 KCs (21, 22, 48). Inhibition was modeled via divisive normalization, with parameters chosen according to experiment (20). We quantified decoding accuracy by training and testing a binary classifier on the KC activity output of sparse odors of distinct intensity and identity, randomly categorized as appetitive or aversive. Odor signals of the same identity but differing intensity were assigned the same valence. We trained the classifier on $N_{\rm ID}$ sparse odor identities at intensities chosen randomly over 4 orders of magnitude, then tested the classifier accuracy on the same odor identities but of differing concentrations.

Classification accuracy degrades to chance level as $N_{\rm ID}$

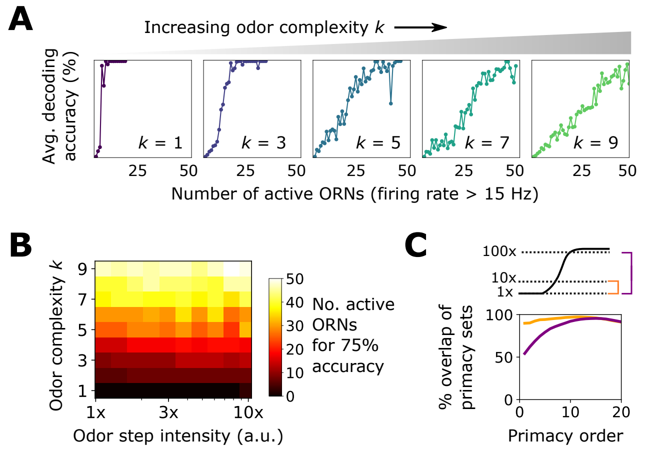

Fig. 4. **A** Decoding accuracy as a function of the number of active ORNs (firing rate > 15 Hz), for different odor complexities. The primacy set consists of those ORNs required to be active for accurate decoding; the set size grows with odor complexity. **B** Number of active ORNs required to fully decode odor signals of varying odor intensity and complexity. **C** Primacy sets for a step signal in the presence of different background intensities are almost identical for all but the smallest primacy orders ($p \gtrsim 5$). Yellow: overlap of the primacy sets for step signal when placed atop a weak (1x) vs. a medium (10x) background; purple: overlap of primacy sets for step signal atop weak vs. strong (100x) backgrounds.

becomes very large (Fig. 5a). When acting alone, either divisive normalization or ORN adaptation can help, although the effect of ORN adaptation is stronger. When both are active, accuracy improves further, suggesting that these distinct adaptive transformations may act jointly at different stages of neural processing in preserving representations of odor identity. Interestingly, if we train the classifier to distinguish odors by their distinct identity, rather than valence, we find that the benefits conferred by divisive normalization do not appear until N_{ID} is substantial, with accuracy below 65% for $N_{ID} > 50$ (Fig. 5b). On the other hand, with ORN adaptation accuracy remains above 85% for more than 1000 odor identities, strongly implicating front-end adaptation as a key player in maintaining odor identity representations, before they are further processed downstream.

Discussion

We investigate the theoretical implications of observed universal input gain control in *Drosophila* olfactory receptor neurons. We argue that such gain control, obeying the Weber-Fechner Law of psychophysics, plays a central role in preserving neural representations of odor identity at the front-end of the olfactory pathway. Our conclusions rely on both a compressed sensing scheme that fully reconstructs odor signals from neural response, as well as classification algorithms that categorize odors by identity or valence. We find that input gain control acting on a single timescale of ~ 250 ms enhances the coding capacity of ensemble ORN response, helping maintain representations of odor identity independent of intensity (Figs. 1 and 2). It acts jointly with normalization in the antennal lobe to aid the discrimination of naturalistic, dynamic odor signals from static backgrounds, implicating the importance of signal transformations at multiple steps in the olfactory circuit (Figs. 3 and 5). We also study our model in the context of primacy coding – that signals are encoded by the earliest activating glomeruli – finding that front-end adaptation enhances primacy coding by maintaining primacy sets amid background confounds (Fig. 4).

LIMITATIONS OF THIS WORK

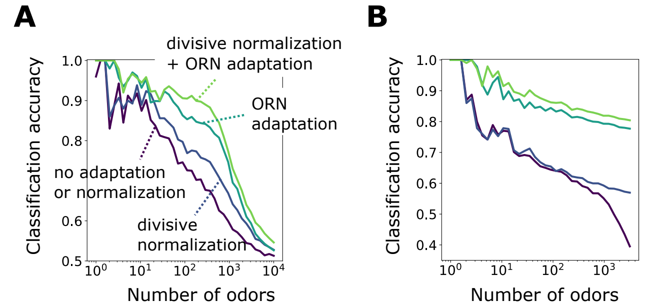

Fig. 5. **A** Accuracy of binary classification by odor valence, as a function of the number of distinct odor identities classified by the trained network (concentrations span 4 orders of magnitude), in systems with only ORN adaptation, only divisive normalization, both or neither. **B** Same as (A) but now classifying odors by identity.

LIMITATIONS OF THIS WORK
LIMITATIONS OF THIS WORK
LIMITATIONS OF THIS WORK
LIMITATIONS OF THIS WORK
LIMITATIONS OF THIS WORK

Previous studies in the *Drosophila* olfactory circuit have characterized the impact of various response characteristics in maintaining combinatorial codes. Lateral inhibition helps tame saturation and boost weak signals (20). ORNs exhibiting both excitatory and inhibitory responses to odorants can increase coding capacity by exploiting response bidirectionality (18). In vertebrates, G-protein-coupled chemoreceptors rather than Orco-coupled cation channels, antagonism among odorants may help maintain response sparsity (49). Finally, in both vertebrates and insects, the degree of connectivity to either the olfactory bulb or mushroom body (each KC receives connections from only ∼6 AL glomeruli) may be precisely tuned to optimize the system's capacity to learn associations (22). Our results show that a number of these downstream features are enhanced front-end dynamic adaptation.

Other studies in insect olfaction have implicated the unique temporal patterns of neural response as signatures of odor identity (24–26, 50). ORN and projection neuron time traces form distinct trajectories in low-dimensional projections, and cluster by odor identity, much as we have found here (Fig. 2b). In our framework, temporal coding is implicit. Because the strength of ORN feedback onto receptor complex activation depends on an ORN's unique response characteristics, odor signals are naturally formatted into temporal patterns that are both odor- and ORN-specific – despite the universality of τ. Further, the short forgetting timescales, $\tau_{\mathrm{F}} \sim \tau \sim 250$ ms, suggest that only brief time windows are needed for accurate odor identification, consistent with previous findings (24).

In living systems, sensory adaptation ensures that responses remain in regimes of maximum sensitivity, increasing their effective dynamic range (51–54). Doing so requires matching sensory response to attributes of the environment, either by adapting to specific stimuli or to stimuli statistics (51). In a single-channel system such as bacterial chemotaxis, information capacity is increased by matching the midpoint of the nonlinear dose-response curve, where sensitivity is highest, to mean ligand concentration (55). This is enacted in a robust and dynamic way, through a feedback loop from the activity output of the pathway onto proteins dictating receptor sensitivity (39, 56). We hypothesize that an analogous feedback loop exists in olfactory receptor neurons, from Orco-mediated Or channel activity onto the free energy of receptor activation (16). This mechanism appears to act identically across ORNs, and because olfactory tuning curves are highly overlapping, raises questions about its efficacy in complex environments: adaptation to one odor could adversely affect identification of a new odor if the latter excites some but not all of the same ORNs. Our results show that this general feedback, operating at a single timescale, does help to preserve combinatorial representations of odor identity, despite these broad overlaps.

Methods

1. Africa Couto, Mattias Alenius, and Barry J. Dickson. Molecular, anatomical, and functional organization of the drosophila olfactory system. *Current Biology*, 15(17), 2005.
2. Linda Buck and Richard Axel. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell*, 65(1):175–187, 1991.
3. Rainer W Friedrich and Sigrun I Korsching. Combinatorial and chemotopic odorant coding in the zebrafish olfactory bulb visualized by optical imaging. *Neuron*, 18(5):737–752, 1997.
4. Elissa Hallem and John Carlson. Coding of odors by a receptor repertoire. *Cell*, 125(1): 143–160, 2006.
5. Guirong Wang, Allison F. Carey, John R. Carlson, and Laurence J. Zwiebel. Molecular basis of odor coding in the malaria vector mosquito anopheles gambiae. *Proceedings of the National Academy of Sciences*, 107(9):4418–4423, 2010. ISSN 0027-8424.
6. Kiyomitsu Nara, Luis R Saraiva, Xiaolan Ye, and Linda B Buck. A large-scale analysis of odor coding in the olfactory epithelium. *Journal of Neuroscience*, 31(25):9179–9191, 2011.
7. Bettina Malnic, Junzo Hirono, Takaaki Sato, and Linda B Buck. Combinatorial receptor codes for odors. *Cell*, 96(5):713–723, 1999.
8. John G Hildebrand and Gordon M Shepherd. Mechanisms of olfactory discrimination: converging evidence for common principles across phyla. *Annual review of neuroscience*, 20(1): 595–631, 1997.
9. Marien de Bruyne, Kara Foster, and John R. Carlson. Odor coding in the drosophila antenna. *Neuron*, 30(2):537 – 552, 2001. ISSN 0896-6273.
10. Rachel I. Wilson. Early olfactory processing in *Drosophila*: mechanisms and principles. *Annual Review of Neuroscience*, 36(1):217–241, 2013.
11. M. Renou, V. Party, A. Rouyar, and S. Anton. Olfactory signal coding in an odor background. *Biosystems*, 136:35 – 45, 2015.
12. John Murlis. Odor plumes and how insects use them. *Annual Review of Entymology*, 37: 505–532, 1992.
13. MJ Weissburg. The fluid dynamical context of chemosensory behavior. *The Biological Bulletin*, 198(2):188–202, 2000. PMID: 10786940.
14. Antonio Celani, Emmanuel Villermaux, and Massimo Vergassola. Odor landscapes in turbulent environments. *Phys. Rev. X*, 4:041015, Oct 2014.
15. Ring T. Cardé and Mark A. Willis. Navigational strategies used by insects to find distant, wind-borne sources of odor. *Journal of Chemical Ecology*, 34(7):854–866, Jul 2008.
16. Srinivas Gorur-Shandilya, Mahmut Demir, Junjiajia Long, Damon A Clark, and Thierry Emonet. Olfactory receptor neurons use gain control and complementary kinetics to encode intermittent odorant stimuli. *eLife*, 6:e27670, jun 2017. ISSN 2050-084X.
17. Guangwei Si, Jessleen K Kanwal, Yu Hu, Christopher J Tabone, Jacob Baron, Matthew E Berck, Gaetan Vignoud, and Aravinthan DT Samuel. Invariances in a combinatorial olfactory receptor code. *bioRxiv*, page 208538, 2017.
18. Li-Hui Cao, Dong Yang, Wei Wu, Xiankun Zeng, Bi-Yang Jing, Meng-Tong Li, Shanshan Qin, Chao Tang, Yuhai Tu, and Dong-Gen Luo. Odor-evoked inhibition of olfactory sensory neurons drives olfactory perception in *Drosophila*. *Nature Communications*, 8(1):1357, 2017.
19. K. Asahina, M. Louis, S. Piccinotti, and L. Vosshall. A circuit supporting concentration-invariant odor perception in *Drosophila*. *Journal of Biology*, 8(1):9, 2009.
20. Shawn R. Olsen, Bhandawat Vikas, and Rachel I. Wilson. Divisive normalization in olfactory population codes. *Neuron*, 66:287–299, 2010.
21. S.J.C. Caron, Vanessa Ruta, L.F. Abbott, and Richard Axel. Random convergence of olfactory inputs in the *Drosophila* mushroom body. *Nature*, 497(4774):113–117, 2013.
22. Ashok Litwin-Kumar, Kameron Decker Harris, Richard Axel, Haim Sompolinsky, and L.F. Abbott. Optimal degrees of synaptic connectivity. *Neuron*, 93(5):1153 – 1164.e7, 2017. ISSN 0896-6273.
23. Kamesh Krishnamurthy, Ann M. Hermundstad, Thierry Mora, Aleksandra M. Walczak, and Vijay Balasubramanian. Disorder and the neural representation of complex odors: smelling in the real world. *bioRxiv*, doi:10.1101/160382, 2017. .
24. Stacy L. Brown, J. Joseph, and M. Stopfer. Encoding a temporally structured stimulus with a temporally structured neural representation. *Nature Neuroscience*, 8:1568–1576, 2005.
25. Baranidharan Raman, Joby Joseph, Jeff Tang, and Mark Stopfer. Temporally diverse firing patterns in olfactory receptor neurons underlie spatiotemporal neural codes for odors. *Journal of Neuroscience*, 30(6):1994–2006, 2010.
26. N. Gupta and M. Stopfer. A temporal channel for information in sparse sensory coding. *Neuron*, pages 2247–2256, 2014.
27. Christopher D. Wilson, Gabriela O. Serrano, Alexei A. Koulakov, and Dmitry Rinberg. A primacy code for odor identity. *Nature Communications*, 8(1):1477, 2017.
28. Mattias C. Larsson, Ana I. Domingos, Walton D. Jones, M.Eugenia Chiappe, Hubert Amrein, and Leslie B. Vosshall. Or83b encodes a broadly expressed odorant receptor essential for drosophila olfaction. *Neuron*, 43(5):703 – 714, 2004. ISSN 0896-6273.
29. Jon Cafaro. Multiple sites of adaptation lead to contrast encoding in the *Drosophila* olfactory system. *Physiological Reports*, 4(4):e12762, 2016.
30. Li-Hui Cao, Bi-Yang Jing, Dong Yang, Xiankun Zeng, Ying Shen, Yuhai Tu, and Dong-Gen Luo. Distinct signaling of *Drosophila* chemoreceptors in olfactory sensory neurons. *Proceedings of the National Academy of Sciences*, 113(7):E902–E911, 2016.
31. Shelby A Montague, Dennis Mathew, and John R Carlson. Similar odorants elicit different behavioral and physiological responses, some supersustained. *Journal of Neuroscience*, 31 (21):7891–7899, 2011.
32. Carlotta Martelli, John R. Carlson, and Thierry Emonet. Intensity invariant dynamics and odor-specific latencies in olfactory receptor neuron response. *Journal of Neuroscience*, 33 (15):6285–6297, 2013.
33. Ernst Heinrich Weber. *EH Weber on the tactile senses*. Psychology Press, 1996.
34. Gustav Theodor Fechner. *Elemente der psychophysik*. Breitkopf und Härtel, 1860.
35. KI Nagel and RI Wilson. Biophysical mechanisms underlying olfactory receptor neuron dynamics. *Nature Neuroscience*, 14:208–216, 2011.
36. Merid N Getahun, Shannon B Olsson, Sofia Lavista-Llanos, Bill S Hansson, and Dieter Wicher. Insect odorant response sensitivity is tuned by metabotropically autoregulated olfactory receptors. *PLoS One*, 8(3):e58889, 2013.
37. Merid N Getahun, Michael Thoma, Sofia Lavista-Llanos, Ian Keesey, Richard A Fandino, Markus Knaden, Dieter Wicher, Shannon B Olsson, and Bill S Hansson. Intracellular regulation of the insect chemoreceptor complex impacts odour localization in flying insects. *Journal of Experimental Biology*, 219(21):3428–3438, 2016.
38. J. A. Butterwick, J. del Mármol, K. H. Kim, M. A. Kahlson, J. A. Rogow, T. walz, and V. Ruta. Cryo-em structure of the insect olfactory receptor orco. *Nature*, 560:447–452, 2018.
39. U. Alon, M.G. Surette, Barkai N., and Stan Leibler. Robustness in bacterial chemotaxis. *Nature*, 397:168–171, 1999.
40. Hamza Giaffar, Dmitry Rinberg, and Alexei A. Koulakov. Primacy model and the evolution of the olfactory receptor repertoire. *biorxiv*, 2018. .
41. L.J.P. van der Maaten and G.E. Hinton. Visualizing high-dimensional data using t-sne. *Journal of Machine Learning Research*, 9:2579–2605, 2008.
42. Leslie B Vosshall, Allan M Wong, and Richard Axel. An olfactory sensory map in the fly brain. *Cell*, 102(2):147 – 159, 2000. ISSN 0092-8674.
43. David Donoho. Compressed sensing. *IEEE Transactions on Information Theory*, 52(4):1289–1306, 2006.
44. Emmanuel Candes, Justin Romberg, and Terence Tao. Robust uncertainy principles: Exact signal reconstruction from highly incomplete frequency information. *IEEE Transactions on Information Theory*, 52(2):489–509, 2006.
45. Surya Ganguli and Haim Sompolinsky. Compressed sensing, sparsity, and dimensionality in neuronal information processing and data analysis. *Annual Review of Neuroscience*, 35(1): 485–508, 2012.
46. C. Pehlevan, A. Genkin, and D. B. Chklovskii. A clustering neural network model of insect olfaction. In *2017 51st Asilomar Conference on Signals, Systems, and Computers*, pages 593–600, 2017.
47. Shawn R. Olsen and Rachel I. Wilson. Lateral presynaptic inhibition mediates gain control in an olfactory circuit. *Nature*, 452:952–960, 2008.
48. Alex C. Keene and Scott Waddell. *Drosophila* olfactory memory: single genes to complex neural circuits. *Nature Reviews Neuroscience*, 8:341–354, 2007.
49. Gautam Reddy, Joseph Zak, Massimo Vergassola, and Venkatesh N Murthy. Antagonism in olfactory receptor neurons and its implications for the perception of odor mixtures. *bioRxiv*, page 204354, 2017.
50. Nitin Gupta and Mark Stopfer. Insect olfactory coding and memory at multiple timescales. *Current Opinion in Neurobiology*, 21:768–773, 2011.
51. B. Wark, B. N. Lundstrom, and A. Fairhall. Sensory adaptation. *Current Opinion in Neurobiology*, 17(4):423–429, 2007.
52. Katherine I. Nagel and Allison J. Doupe. Temporal processing and adaptation in the songbird auditory forebrain. *Neuron*, 51(6):845 – 859, 2006. ISSN 0896-6273.
53. S. B. Laughlin. A simple coding procedure enhances a neuron's information capacity. *Zeitschrift für Naturforschung C*, 36(9-10):910–912, 1981.
54. M. DeWeese and A. Zador. Asymmetric dynamics in optimal variance adaptation. *Neural Computation*, 10:1179–1202, 1998.
55. Ilya Nemenman. Information theory and adaptation. In Michael E. Wall, editor, *Quantitative Biology: From Molecular to Cellular Systems*, chapter 4, pages 73–91. CRC Press, USA, 2012.
56. N. Barkai and S. Leibler. Robustness in simple biochemical networks. *Nature*, 387:913–917, 1997.