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November 9, 2018

Dear Editor,

We are pleased to submit the manuscript “**Front-end Weber-Fechner gain control enhances the fidelity of combinatorial odor coding**” by N. Kadakia and T. Emonet for consideration in PNAS.

We address a key question in olfaction: *How do animals perceive odors uniquely in different environmental conditions*? Distinct odors activate unique sets of olfactory receptor neurons (ORNs), suggesting that odors are encoded by the particular combination ORNs they excite – a “combinatorial code” for odor identity. But these codes may scramble with environmental changes, such as intensity fluctuations and background odors. Here we show that an adaptive scaling law recently identified in *Drosophila* ORNs contributes significantly to preserving these codes. Our work is significant in that:

1. Weber Law found – but not know implications.
2. Previous works in temporal coding
3. It has been shown that mutual inhibition between *Drosophila* projection neurons normalizes ORN responses, preventing saturation and boosting weaker signals. Our work shows that adaptation within individual ORNs themselves may play an even greater role in maintaining these codes. This implicates the importance of regulation at the very front-end of the olfactory circuit, before neural signals are mixed downstream.
4. The Weber-Fechner law allows sensory systems to retain sensitivity by adjusting responses to the environment. This is straightforward for a single channel system (one receptor). But the 60 olfactory receptors in *Drosophila* respond to many of the same compounds, with different affinities, so adjusting all ORN responses for optimal sensitivity may require a precise balancing act. Our work shows that such fine-tuning is not necessary – a single adaptive mechanism, completely insensitive to particular odor identity is highly adept at maintaining coding fidelity. Crucially, adaptation arises via ion channel self-feedback – depending on channel activity, but not on intrinsic ORN- or odor-specific properties.
5. We show that this mechanism boosts the coding fidelity of various
6. Multiple decoding schemes – just as robust. Primacy coding

Previous works have shown that spatio-temporal patterns of activity in projection neurons segregate, in low-dimensional projections, by odor identity.

1. Laurent and Stopfer [1] have shown that spatio-temporal patterns of activity in the projection neurons (PNs) could represent independently odor identity and intensity. However, no *mechanism* was provided for this decomposition, which they attributed to computation in the antennal lobe (AL). Our work suggests that such decomposition already occurs in the ORNs (compare our Fig.3C with Fig.3B in [1]). We show that ORN response dynamics depend on odor identity and are independent of odor intensity, which can be separately encoded in the response magnitude.

In this paper we address a key, much-debated question in olfaction: what information about odor stimuli is encoded in temporal patterns of neural activity? Odors activate distinct sets of olfactory receptor neurons (ORNs) depending on the affinity of the odorant receptors for the odorant molecules. These *spatial* representations are accompanied by diverse *temporal* patterns of activity which have been observed at different levels of the olfactory system (ORNs, glomeruli and higher brain regions). However the origin and function of these temporal patterns is currently unclear.

Here we show in detail that odors have *intrinsic dynamics* that depend on odor *identity* and that determine the response dynamics of ORNs in *Drosophila*, suggesting a single response function can be associated with a single ORN and mediates the response to a large number of different odors. Second we show that the adaptation capabilities of ORNs provide a *mechanism* by which individual ORNs can explicitly encode information about stimulus dynamics independently of stimulus and background intensity. These findings enable us to *predict* the response of an ORN to different odors solely from measurements of the time-dependent stimulus. Moreover, a single ORN can separate stimuli from four different odors regardless of their concentration. Hence in addition to providing a clear explanation for the origin of the temporal patterns of activity in the olfactory periphery, our findings open an important question for future behavioral studies: Whether odor-specific dynamics represent an additional dimension of the odor space that animals use in discrimination and navigation.

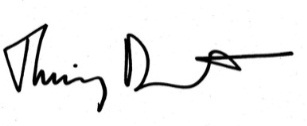
In the following we summarize why our study represents a major conceptual advance over previous work.

1. Laurent and Stopfer [1] have shown that spatio-temporal patterns of activity in the projection neurons (PNs) could represent independently odor identity and intensity. However, no *mechanism* was provided for this decomposition, which they attributed to computation in the antennal lobe (AL). Our work suggests that such decomposition already occurs in the ORNs (compare our Fig.3C with Fig.3B in [1]). We show that ORN response dynamics depend on odor identity and are independent of odor intensity, which can be separately encoded in the response magnitude.
2. Raman and Stopfer [2] have shown that the diversity of ORN response dynamics was necessary to produce spatio-temporal patterns of neural activity in the AL. But again the origin of these different dynamics remained unclear. The current belief is that they are due to differences in the *kinetics of the interaction* between odorant molecules and odorant receptors [3]. Our measurements of ORN and stimulus dynamics over a large range of concentrations show that stimulus dynamics are a major determinant of ORN response. In our data, kinetics of interaction plays only a marginal role in shaping ORN response.
3. In a recent study [4] we showed that a mixture of excitatory and inhibitory odorants not only affected the amplitude of ORN response but also its temporal aspect due to differences in physicochemical properties of the odor molecules. However, how the temporal dynamics of the stimulus affected ORN dynamics and possibly odor coding was unclear. Our current manuscript provides the following three major conceptual advances over [4]:
   1. We identify a *mechanism* by which ORNs dynamics can encode odor-specific dynamics independently of their intensity. This mechanism relies on adaptation capabilities of ORNs and on the odor-dependent difference in stimulus dynamics.
   2. We show that measurements of odor stimuli can be used to predict the exact time-dependent response of an ORN to different odor types. To our knowledge no model has managed to *predict* the response of an ORN to *different* odors, including the model proposed in [3]. This model also provides an explanation (Supp. Fig. 8) for the observations made in [4].
   3. We show for the first time that diverse stimulus dynamics are present in *natural conditions* and can determine ORN response to plumes of odors. In nature different odor types could be more difficult to track than others, and different strategies might be used by animals to track different odors.
4. Our findings also provide a possible explanation for how a fly can discriminate between odors without a combinatorial map [6].

We suggest the following possible reviewers: Larry Abbott (Columbia University; [lfabbott@columbia.edu](mailto:lfabbott@columbia.edu)), Vikas Bhandawat (Duke University; [bhandawat@gmail.com](mailto:bhandawat@gmail.com)), Mark Stopfer (NIH; [stopferm@mail.nih.gov](mailto:stopferm@mail.nih.gov)), Scott Waddell (U Mass Med School; [scott.waddell@umassmed.edu](mailto:scott.waddell@umassmed.edu)), and Rachel I. Wilson (Harvard Medical School; [rachel\_wilson@hms.harvard.edu](mailto:rachel_wilson@hms.harvard.edu)). Because of conflicts of interests we request that it not be reviewed by R. Axel, A. Lazar, and L. Vosshall.

Thanks very much for your consideration.

Sincerely yours,



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**References:**

1. Stopfer, M., Jayaraman, V. & Laurent, G. Intensity versus identity coding in an olfactory system. Neuron 39, 991-1004 (2003).

2. Raman, B., Joseph, J., Tang, J. & Stopfer, M. Temporally diverse firing patterns in olfactory receptor neurons underlie spatiotemporal neural codes for odors. J Neurosci 30, 1994-2006 (2010).

3. Nagel, K.I. & Wilson, R.I. Biophysical mechanisms underlying olfactory receptor neuron dynamics. Nat Neurosci 14, 208-216 (2011).

4. Su, C.Y., Martelli, C., Emonet, T. & Carlson, J.R. Temporal coding of odor mixtures in an olfactory receptor neuron. Proc Natl Acad Sci U S A 108, 5075-5080 (2011).

5. Olsen, S.R., Bhandawat, V. & Wilson, R.I. Divisive normalization in olfactory population codes. Neuron 66, 47-299 (2010). S.R. Olsen & R.I. Wilson. Lateral presynaptic inhibition mediates gain control in an olfactory circuit. Nature 452:956-60 (2008)

6. DasGupta, S. & Waddell, S. Learned Odor Discrimination in Drosophila without Combinatorial Odor Maps in the Antennal Lobe. Curr Biol 18, 1668-1674 (2008).