

January 08, 2018

Dear Editors,

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 *Neuron*.

Recent studies have theorized that the statistical features of odor-receptor interactions are tuned to optimize coding capacity. These works, which have not yet incorporated front-end adaptation, advance our understanding of how animals encode odors at fixed concentrations, in the absence of background odors.

Our primary conceptual advance is that front-end adaptation within olfactory receptor neurons (ORNs) significantly aids odor encoding and decoding when odors mix with backgrounds and fluctuate rapidly. We find that ORN adaptation enhances the impact of known downstream neural transformations, in the antennal lobe (Olsen et al, *Neuron* 2010) and mushroom body (Litwin-Kumar et al, *Neuron* 2017), which help maintain neural representations of odor identity. Thus, ORN adaptation promotes odor recognition, as it reduces information loss before these downstream transformations are enacted. Indeed, we find that for some classification tasks, regulation within individual neurons can be just as important as connectivity between them.

We show that these enhancements directly emerge from two key properties of ORN adaptation recently characterized experimentally in *Drosophila melanogaster*, by us and others: a) adaptation arises from olfactory ion channel self-feedback, but is not intrinsic to the identity of the particular receptor involved (Nagel & Wilson, *Nat Neuro* 2011), and b) receptor gain scales inversely with mean concentration –Weber’s Law of psychophysics (Gorur-Shandilya et al, *eLife* 2017; Cao et al, *PNAS* 2016).

Our results are robust. They require no odor- or ORN-specific parameter tuning. They hold for various decoding schemes, whether reconstructing exact odor signals or learning associations among odors. They also extend the recently-proposed primacy coding hypothesis, which posits that odors are encoded by the set of earliest responding glomeruli (Wilson et al, *Nat Comm* 2017).

Our study is of interest to the broad readership of *Neuron*: Weber’s Law exists in vision, touch, and audition. and is viewed as a mechanism to maintain sensitivity across signal intensities. Here we suggest a new way of thinking about it. In a multi-channel sensory system, it helps preserve combinatorial codes, which are signatures of signal identity.

As potential reviewers you may want to consider: Venkatesh Murthy (MCB Harvard; vmurthy@fas.harvard.edu), Dmitry Rinberg (NYU; dmitry.rinberg@nyulangone.org), and Rachel I. Wilson (Harvard Medical School; rachel_wilson@hms.harvard.edu) Because of potential conflicts of interests, we request that our manuscript not be reviewed by Aurel Lazar, Dong-Gen Luo, or Yuhai Tu.

Thank you kindly for your consideration.

Sincerely yours,



Thierry Emonet

Associate Professor of Molecular, Cellular and Developmental Biology & Physics