EliApps YALE UNIVERSITY

Nirag Kadakia <nirag.kadakia@yale.edu>

Fwd: eLife decision: 17-01-2019-ADV-eLife-45293

2 messages

Thierry Emonet <thierry.emonet@yale.edu> Thu, Feb 28, 2019 at 8:07 AM
To: "Kadakia, Nirag" <nirag.kadakia@yale.edu>

Good reviews!
T
http://emonet.biology.yale.edu

---------- Forwarded message ---------
From: <editorial@elifesciences.org>
Date: Thu, Feb 28, 2019 at 7:21 AM
Subject: eLife decision: 17-01-2019-ADV-eLife-45293
To: <thierry.emonet@yale.edu>

Dear Dr Emonet,

Thank you for submitting your article "Front-end Weber-Fechner gain control enhances the fidelity of combinatorial odor coding" for consideration by eLife. Your article has been reviewed by 3 peer reviewers, and the evaluation has been overseen by Fred Rieke as the Reviewing Editor and Catherine Dulac as the Senior Editor. The following individuals involved in review of your submission have agreed to reveal their identity: Katherine I. Nagel (Reviewer #2).

The reviewers have discussed the reviews with one another and the Reviewing Editor has drafted this decision to help you prepare a revised submission. Please aim to submit the revised version within two months.

The reviewers agreed that the work was of potential interest. They also agreed, however, that the presentation needs to be improved considerably. To be considered further, the paper needs to be revised carefully considering eLife's broad readership. This includes unpacking details about technical aspects of the work - such as embedding and compressed sensing - and explaining the key mathematical concepts of the model in words and (better) in schematic figures. The terseness with which the results were presented made evaluating the work difficult. The individual reviews below contain specific suggestions and comments that should help identify where such changes are needed, but we would also encourage the authors to ask for comments from several non-olfactory colleagues, particularly about accessibility.

Individual reviews follow:

Reviewer #1 (General assessment and major comments (Required)):

This paper investigates the impact of Weber adaptation in olfactory receptor neurons on olfactory coding using a model based on past experimental work (described in the paper this one is linked too). The central question should be of general interest, and the approach taken in the paper seems appropriate. I struggled, however, with the way the work is presented and this left me unsure about the conclusions reached. I am not an expert in olfaction, but I suspect these struggles will be shared by many other potential readers.

Response dynamics: I was quite confused about the importance of differences in response dynamics of different ORNs. In places the text appears to state that differences in dynamics are small (e.g. intro, right column of page 1), and in others that they are important (page 3, left column). Some of this may originate from responses of a single cell to multiple odors vs responses of different cells. Nonetheless, the present version of the paper is confusing in this regard.

Figure 2 and embedding: The embedding process used in the analysis illustrated in Figure 2 is not explained in any detail - meaning that I could not interpret Figure 2. Later in the Discussion (page 6, right column) this figure is referred to with respect to response dynamics - this was particularly unclear. This figure is critical to the paper, so must be explained in more detail.

Figure 3: The use of compressed sensing in the decoding analysis in this figure is unclear. Related to this point, it's not clear how an appropriate tolerance is chosen (page 4, top of right column). The approach to decoding needs to be described in considerable more detail.

Discrimination in complex odor environments: it is not clear here why the background should be represented as static. I would have thought it would be subject to many of the same properties that make the signal dynamic. The role/importance of short term memory is also unclear.

It would be interesting to see how important ORN-specific adaptation is for the results presented, as compared to a mechanism that acted universally across all ORN responses.

Equation 1: The origin of this equation could get explained in more detail.

Equation 2: This form of feedback, and particularly its relation to Weber adaptation, should get explained more.

Reviewer #1 (Minor Comments):

Page 3, left column: Variability in ORN responses appears to originate from the distribution of lower bounds to the free energy differences and from the distribution of dissociated constants. It is not clear why both are needed, and how much each contributes to the diversity of ORN responses.

Why do you assume changes in free energy are bounded by an upper and lower limit?

Abstract, last sentence: This is pretty technical, and I think could be stated more simply.

Reviewer #2 (General assessment and major comments (Required)):

This manuscript asks how adaptation in olfactory receptor neurons (ORNs) impacts the ability of an olfactory system to encode odor identities reliably. There is a broad consensus in the field that odors are encoded by the combinatorial activity of an array of receptors, each composed of an odor-specific receptor and a common co-receptor. At least one form of adaptation, in which the sensitivity of olfactory receptor neurons is adjusted based on the activation level of the receptor complex, is present within ORNs, likely acting at the level of feedback onto the orco co-receptor. This study uses theoretical approaches to ask how this form of adaptation impacts decoding of odor identity, using three different models of odor decoding: compressed sensing, primacy coding, and a biologically-inspired Kenyon cell model. The manuscript builds on a previous paper from the same group that developed a formulation for ORN adaptation based on a 2-state receptor model. The broad finding of the study is that front-end adaptation improves odor identity decoding using a variety of models. Overall I think this study addresses an important question and does so in a thorough way, making use of very reasonable models for both odor encoding and decoding, and providing a nice overview of the state of the field. However, I think some elements of the exposition could be made more accessible for less mathematically-inclined readers, and that some additional simulations would help pinpoint the reason why front-end adaptation improves encoding.

Major concerns:

1) The manuscript is written for a highly quantitative audience and assumes a background familiar with the various models (receptor model, compressed sensing, t-SNE) they employ. I think the paper could be made more accessible by unpacking some of the mathematical formulae in the main text.

For example, it would be helpful to show a plot of the activation function Aa as a function of odor concentration (equation 1) for some of their sample model neurons, in both the unadapted and adapted state.

In addition, the discussion of compressed sensing is highly...compressed. If the authors could describe this in an intuitive or graphical way in the main Results it would help readers understand what this is and how it works.

Using a KC-inspired model to decode odor identity will probably be the most intuitive decoding scheme for many biologists. Here this decoding scheme is presented last but perhaps it might go earlier in the manuscript.

2) One possible interpretation of the results in Figs. 2 and 3 is that in the non-adaptive system, high background odor concentrations cause the receptors to saturate, preventing them from encoding anything about the target odor, or at least massively compressing their dynamic range. This would mean that sensitivity adaptation is important (the activation curve needs to shift with increasing odor concentration), but not the precise form of the adaptation. Could the authors perform additional simulations to address this? For example: (1) What is the state of the receptors (distribution of activation levels) in the adapted versus un-adapted system in high background odor (prior to target odor presentation) vs background+target? (2) How do the results in figures 2 and 3 differ if the adaptation is not exact? That is, what if there is some factor ß in front of Aa(t) in equation 2? How precise does the adaptation have to be for this to work?

Minor concerns:

p. 4, 1st paragraph "When de-convolved from stimulus dynamics, the shapes of the temporal kernals of Drosophila ORNS that express orco are largely receptor- and odor-independent." I am not sure I entirely buy this although I don't think it is critical to the conclusions of the paper.

p. 4, 2nd paragraph: can you clarify the relationship between free energy and Kd?

Fig. 5b: I am not sure I understand why the divisive normalization model is contributing so little to the classification of odor identity. This seems at odds with the results of simulations in Olsen et al. 2010 and also Zhu...Friedrich 2013. Is this because the decoding model is different? Can the authors provide any insight into why the normalization contributes very little in this case?

Discussion, 1st paragraph: "odorant-odorant antagonism" is this implicitly included in your model because there is only one binding site on the model receptor? (I am thinking of the competitive binding model in Singh et al. (https://www.biorxiv.org/content/10.1101/311514v3).

p. 7, 1st paragraph: is it worth mentioning here the findings from Cao 2016 suggesting that orco-mediated adaptation relies on intracellular calcium (Fig. 6c)? A similar Ca-mediated adaptation is observed in vertebrate olfactory receptors (e.g. Leinder-Zufall et a. 1999) and of course in photoreceptors (e.g. Fain et al. 1989), which might say something about the generality of this mechanism and form of adaptation.

Reviewer #3 (General assessment and major comments (Required)):

The authors describe a receptor type-independent adaptation mechanism at the level of the olfactory sensory neurons (OSNs) that maintains odor capacity in natural conditions. They proposed that adaptation or gain control follows the Weber-Fechner Law of psychophysics (previously shown by the same group) and suggest that in a biological context it may be driven by Orco co-receptor activity in a non-receptor specific manner. The model results show that this kind of adaptation can aid concentration-invariant coding, discrimination (even in the presence of background odors) as well as it agrees with the novel hypothesis of primacy coding. The topic discussed in the article is relevant and the results are convincing, it is worth publishing; and I have no major concerns just some minor concerns.

Reviewer #3 (Minor Comments):

1) What does the 2-dimensional embedded representation mean from a biological point of view? Why 2D? If it is just to demonstrate clustering, maybe is worth assessing a metric for the clustering (such as intracluster vs extra cluster distances).
2) Adaptation of specific receptors enables maximum sensitivity of the system of given odors (well described in the article). It would be a good idea to describe an issue of a potential overlap overlap in the receptors stimulated by the background and foreground odor?

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* We will look forward to hearing from you with a revised article with tracked changes, and a response letter (uploaded as an editable file) describing the changes made in response to the decision and review comments.

* If source manuscript files have not already been provided, we will need them at the revision stage; further details are here: https://submit.elifesciences.org/html/elife_author_instructions.html#revised

* If your study includes bench research, please include a Key Resources Table within your resubmission. This is designed to highlight genetically modified organisms and strains, cell lines, reagents, and software that are essential to reproduce the results presented (but it is not designed to be a comprehensive list of all the materials and resources used). You should download the following template, which includes notes on completion as well as an example table: https://cdn.elifesciences.org/author-guide/key_resources_table.xlsx. For relevant submissions, the completed table should be incorporated within your article file at the very beginning of the Materials and Methods section (examples in published articles are available at https://elifesciences.org/articles/32586#s4 and https://elifesciences.org/articles/31023#s4).

* If your work involved the use of cell lines, please indicate in the Materials and Methods section of your manuscript if their identity has been authenticated, state the authentication method (such as STR profiling), and report the mycoplasma contamination testing status. Please consult our Journal Policies for further details: https://submit.elifesciences.org/html/elife_author_instructions.html#policies

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Best wishes,

Fred Rieke
Reviewing Editor

Catherine Dulac
Senior Editor

Nirag Kadakia <nirag.kadakia@yale.edu> Thu, Feb 28, 2019 at 9:52 AM
To: Thierry Emonet <thierry.emonet@yale.edu>

This is encouraging! It appears we have to adapt the paper for eLife (it was written for the PNAS layout), and that should help respond to the reviewers concerns. But I am pleased that the suggested revisions are straighforward and doable.

The 2nd reviewer (likely Kathy) suggested some changes, but nothing too major and it should be straightforward.

I mentioned to you in December that I am going on a trip with Bijal -- the trip is March 6-17. So I will begin working on this as soon as I return.

The turnaround was quite timely too, which is nice.

Nirag
[Quoted text hidden]