

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 1 peer reviewer, and the evaluation has been overseen by a Reviewing Editor and Catherine Dulac as the Senior Editor. The following individuals involved in review of your submission have agreed to reveal their identity: Fred Rieke (Reviewer #1, RE).

Please aim to submit the revised version within two months.

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

This is a revision of a paper describing a modeling approach to explore the role of front-end adaptation in olfactory coding. The paper is interesting, and contains a number of nice analyses that provide insight into the interaction between adaptation and coding. The revisions have made the paper easier to understand, but there are still several issues that are not as clear as they need to be. These, and some smaller points, are detailed below. In general (as detailed below), for each analysis I think it is essential that each of the steps involved in going from the modeled responses to a completed piece of analysis need to be clear to a non-expert reader.

We thank the reviewer for carefully reading our revised manuscript and for providing useful suggestions on how to improve it.

1. t-SNE analysis.

The comparison of t-SNE to PCA (first paragraph of the section starting at the bottom of page 5) is helpful. Can you build on the end of this paragraph to explain how t-SNE works, and, critically, to define the axes of Figures 2B,C? It is quite important that a reader is comfortable with what is being plotted here.

We have expanded our description of t-SNE as suggested. t-SNE only preserves local distances but not global distances. Thus, while it is a useful tool to cluster objects by similarity, the distances between clusters in the t-SNE projection are not necessarily meaningful because global distances are not preserved. We now mention this both in the main text and in the caption. We also explain in the main text that we use t-SNE primarily as a visualization method. To more rigorously quantify how well representations of odor identity are preserved, we calculate the mutual information (MI) between novel foreground odors and ORN responses in the 50-dimensional space. We also provide a short explanation of what MI is in the main text.

2. CS analysis.

The description of the sparseness constraint added to the paper is helpful. What is still not clear, however, is how the stimulus itself is estimated (I can guess, but it should be stated explicitly). Related to this point, the signal perturbation (Ds) is defined only in the Methods but needed to interpret the main text (lines 234-235). It should also be clearer (e.g. around line 240) that you are decoding discrete odor identity, not concentration (assuming that is correct).

We added explicit description of how the stimulus is estimated in the main text together with details about the definition of the signal perturbation. We also state clearly in the main text that the result is an estimate of the magnitude of each signal component and therefore both the identity and the intensity of the signal are estimated.

3. Decoding time-varying stimuli.

Several aspects of the analysis described in the paragraph starting on line 246 are not clear. Were odors randomly assigned to each whiff? And was the entire time course decoded, or was each whiff treated as a discrete event? In general, the description of this analysis needs to be considerably more detailed. Is there an intuitive argument as to why the longer time scales of adaptation are helpful that could be added to the paragraph starting on line 256?

We have revised the text at the location indicated in the review to address the reviewer's concerns. Note that we hold the adaptation timescale at 250 ms, but vary the memory timescale (longer ones are more helpful). We also added a phrase in the following paragraph to provide intuition as to why longer time scales of memory are useful.

4. Tests of primacy coding.

The text suggests that the background odors may interfere with primacy coding in the absence of front-end adaptation. The analysis presented in Figure 4 then shows that primacy sets are maintained in the presence of front-end adaptation. But there is not a test, unless I missed it, of the initial suggestion that primacy sets are not maintained without front-end adaptation. This test is needed to interpret this section.

We have now added on Figure 4c, the results for the non-adaptive case, showing that in absence of front-end adaptation, primacy sets are not well maintained, particularly when the primacy order is small.

5. Interplay of front-end adaptation and divisive normalization.

Figure 5 suggests that these two forms of gain control may play quite different roles in coding discrete odor categories (aversive, appetitive) and odor identity. This is quite interesting. I would consider swapping the order of presentation so you start with a discussion of odor identity (that flows more naturally from the previous sections). The differences between the present results and those of Olsen et al. should also, at a minimum, get discussed in more detail.

This is an interesting observation. We have rewritten this part of the text as suggested and have mentioned in the main text the interesting observation made by the reviewer. We have also expanded the comparison of our results with those of Olsen et al.

Reviewer #1 (Minor Comments):

lines 55-56: it's not clear what to make of phosphorylation here if the timescales are so different - consider deleting.

We rephrased this to mention other types of adaptation, but removed the explicit implication of the role of phosphorylation sites.

lines 202-203: mechanistically, it seems that the minimum background at which adaptation begins is set by spontaneous channel opening. If that is correct, it is not hard to envision models in which the onset of adaptation is independent of beta. Could you be more specific in this paragraph about the extent to which the conclusion about small deviations from WF behavior being beneficial depends on specifics of the model?

We added a phrase to emphasize that this effect is more general than our specific model.

lines 212-216: my understanding has always been that combinatorics (i.e. a single odorant molecule activating multiple receptors) helps resolve the problem of dimensionality. Hence I felt that the setup for this section was confusing because it raised an issue that I thought was resolved, or at least less of an issue than implied here.

Combinatorics does imply that many odors can be encoded within ORN responses, but does not necessarily state how the odorants could be decoded from the ORN responses. CS gives a framework in which combinatorics and sparsity allow one to decode both odor identity (which odorants comprise odor) and individual odorant intensities. We edited the first sentence of this section to make this clearer.

line 223: there is some repetition in the paragraph starting on this line (e.g. there are two, slightly different, versions of the cost function).

We simplified the text.