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

1. 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.

We are happy that the reviewer found the paper of general interest and we thank her/him for providing many constructive comments to improve the paper.

1. 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.

Our use of the wording “response dynamics” was confusing because it did not distinguish between the two main steps of the ORN response discussed in the paper: 1) odor-receptor binding and activation of the OR-Orco complex (equation 2); 2) signal transduction and adaptation (equations 3-4). Because odor-binding and activation is nonlinear, variability in Step 1 introduces variability in the dynamic response of the ORN, even though the filter used for the firing rate is assumed the same for all ORNs. We edited the text in the area indicated by the reviewer to make clear that it is the signal transduction and adaptation dynamics that exhibit a surprising degree of invariance with respect to odor-receptor identity, not the odor binding and ion channel activation (lines 143-149).

1. 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.

We rewrote portion of the text and added new paragraphs to better explain why we use dimensionality reduction to quantify the capability of the ORN repertoire to encode diverse odorants, and the effect of adaptation on this process (lines 194-209). We now also explain why we use t-SNE instead of PCA to do so (lines 194-209). Finally, we added a new panel A to the figure to better introduce our approach and to help the reader interpret the other panels in the figure.

The later discussion about response dynamics is intended to draw parallels between our clustering results in Figure 2 and previous published results in which time traces of spiking activity were projected to a 3-dimensional space. In both cases, responses cluster by odor identity. In these studies the authors used the entire time trace, while here we consider the response at a single time. We amended the text in the Discussion to clarify this (lines 522-526).

1. 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.

Indeed, our discussion of CS was too terse. We changed the first panel of the figure to make it more intuitive. We also added several paragraphs to describe why the coding task might benefit from CS given what we know about the receptor anatomy (lines 299-309), what compressed sensing is and why it is useful as a decoding scheme (lines 316-327), and how it can be enacted mathematically in odor decoding (lines 328-343). We didn’t add many mathematical details, rather just the main point (CS permits the estimation of a high-dimensional stimulus vector from a low-dimensional vector of responses, when the signal is sparse). Originally, we had included the metric for assessing decoding accuracy in the Figure caption, but instead put it in the *Methods* to explain why it was chosen as such.

1. Discrimination in complex 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.

We are concerned with the detection of novel odors amid odors already present, thereby assuming that backgrounds odors have persisted for some time beforehand. This would be the case for example if in a lawn of grass that releases one odor everywhere there was a flower of interest to some insect. Downwind from the flower there would be a background “grass odor” everywhere because the sources are distributed over a large area, but the “flower odor” would be a foreground odor localized in plumes streaming from flower. Of course there are other cases where one odor of interest fluctuates on the same timescale as another nuisance odor. Then the distinction between foreground and background is lost. In our framework these would be considered both foreground odors.

The role of short term memory is to limit the amount of information utilized from the past. We now discuss this briefly in the pertinent section in *Results/Front-end adaptation enhances odor decoding in complex environments*. Mathematically, the activation energies integrate in time, so they could be shaped by information from long ago. This would require an artificially large amount of neuronal capacity. The main point is simply to see how far back background odors should be retained. We find that a memory timescale on the order of the ORN adaptation time (250 ms) seems sufficient.

1. 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.

Indeed. Thank you for the suggestion. Please see response to Reviewer 2 comment #4.

1. 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.

We agree on both points. We added restructured the first section of the Results, adding details motivating where previous Eq. 1 came from (Lines 100-123). First, the definition of receptor active fraction is presented, and then we discuss in words how one can get the final closed-form expression for active fraction (formerly Eq. 1). The explicit Boltzmann factors that go into this formula are listed in the SI, rather than adding these technicalities to the main text. We give some details on the responses to step currents of different magnitudes (as are typically used in experiments), and the dynamics of these responses in terms of the equations (lines 134-140)

Next, we discuss what are the required ingredients in the feedback dynamics to permit Weber’s Law (lines 150-162). We also draw and discuss the general shape of the active fraction for neurons in different states (e.g. unadapted, adapted) (Fig. 1F-G; lines 163-179). This will help intuit how affects the activate fraction curves for elevated signal concentrations, and how confounds between background and foreground odors affect these dose-responses.

**Reviewer #1 (Minor concerns):**

1. 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?

The lower bounds on free energies allow the adaptation to enable for different receptors at different signal magnitudes, as has been observed experimentally. If this did not occur, for all stimuli levels, the steady state ORN firing rate would jump, discreetly, from 0 Hz to 30 Hz once the odor is strong enough. In fact, for sufficiently low firing rates, for many ORNs, the steady state firing rises with signal intensity, until at certain point where it remains fixed at 30 Hz.

The upper bound is metabolic -- without it, the neuron could adapt to A0 irrespective of signal intensity, which would require more and more energy as the signal increases. We included this upper bound to remove this possibility, although it is not critical for our results.

We noted the metabolic origin of this in the text. (lines??)

Meanwhile, the distribution of Kd is based on experimental results in Si, Kanwal, et al Neuron 2019, which measures these in larvae. Both the distribution of Kd and the free energies play a role in the observed diversity, but both are predicated on prior experimental results.

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

Yes, that’s true. Amended.

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

1. 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.

We are happy that the reviewer found the paper to be relevant and thorough. We thank her for providing constructive comments to improve the paper.

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 as a function of odor concentration (Eq. 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.

Please see responses to Reviewer 1’s question #3, 4, 7, 8.

1. 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.

We were also somewhat on the fence in the ordering of the results. We opted for this presentation mainly because primacy coding and compressed sensing decoding are more easily interpretable and far more tractable computationally without the added machinery of the AL and MB connectivity. Further, primacy coding has been shown in projection neurons, one step away from ORNs, so we presented it before we discuss the AL-MB connectivity. We do note in the CS section that we will later investigate the implications of circuit mechanisms in later sections. For these reasons, we chose to keep the ordering as is.

1. 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 in front of Aa(t) in equation 2? How precise does the adaptation have to be for this to work?

This comment (and Reviewer #1 Comment 6) suggests a need to investigate how much we can break Weber scaling and still maintain combinatorial codes. This is an excellent point. We first note that a multiplicative factor on could be absorbed into redefinitions of and . This would still preserve Weber’s Law scaling (which follows from the integral feedback onto and the constancy of ), just to a different background level at possibly a different rate. The critical element in maintaining Weber’s law here is the constancy of , which we have now noted in the first Results section (lines 163-179).

Thus, we added a new section (Relaxing Weber-Fechner’s law reduces the benefit of front-end adaptation to odor coding) in which we broke Weber Law scaling weakly by allowing to be receptor-dependent, and to scale as ~log . We investigate the ramifications of this relaxation of Weber’s Law, and show the distribution of activity levels and t-SNE clustering in added panels in Fig. 2. Indeed, we attribute the effect of Weber’s Law, in part, to a prevention of receptor saturation as suggested by Reviewer 2.

**Reviewer #2 Minor Concerns:**

1. p. 4, 1st paragraph "When de-convolved from stimulus dynamics, the shapes of the temporal kernels 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.

This is one main conclusion of Martelli et al (2011), whose conclusions we accept here as is. However, it is not critical to the results we present here.

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

We have rewritten Eq. 2 (formerly Eq. 1) to explicitly show where *K* and *K*\* enter the free energy in the definition of *A*(t).

1. 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?

There may be a few reasons for the discrepancy. First, we decode the KC responses, not glomeruli, so it is possible that synaptic divergences may render divisive normalization less effective. Another distinction is that we use odor mixtures, containing several components, rather than single odorants. We noted this in the text. (lines 471-478)

1. 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>).

That effect is distinct. Odorant-odorant antagonism arises from the interplay of binding affinity and activation energy – ORNs may bind odorants readily but then activate weakly, or vice versa. This then would imply that some odorants in mixtures would occupy binding sites without leading to ORN activity, reducing the effect of other odorants in the mixture that bind less readily, but are more effective in leading to firing events. The model presented in both Reddy et al and Singh et al are not allosteric – receptor activation is a second kinetic step after binding. Our model treats binding and activation as distinct and independent, not sequential. For that reason, activation is independent of odorant identity. So odorants within mixtures do not mutually antagonize – more of either excitatory odorant in the mixture will increase firing rates. The two models are not inconsistent, since that work refers to mammalian olfaction, which relies on GPCRs, rather than insect olfaction.

1. 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.

We chose to focus on the generality with the *Drosophila* ORN repertoire, more than similarities between insect and mammalian olfaction, or other sensory modalities. However, since we do speculate on molecular mechanisms, we agree that it is appropriate to mention findings regarding the role of calcium channels in adaptation. We noted that in line 554.

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

1. 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.

We thank the reviewer for his/her time in reviewing the paper and positive feedback.

**Reviewer #3 Minor Concerns:**

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 intra-cluster vs extra-cluster distances).

We explained in the Results section what the projection means, and why 2D (just for ease of visualization). We added a metric for clustering – the silhouette score – in the added section in the Results, in which we discuss relaxing Weber’s Law.

1. 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 in the receptors stimulated by the background and foreground odor?

TODO