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.

2. 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 two key contributions to ORN response: 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 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 132-134).

3. 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 to better explain how the embedding is enacted, and why we use t-SNE (versus PCA) to quantify the capability of the ORN repertoire to encode diverse odorants (lines 158-165). We added a new panel A to Figure 2 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 362-364).

4. 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 compressed sensing (CS) was too terse. We changed the first panel of Figure 3 to make it more intuitive, removing the unnecessary equations and replacing them with a simple graphic. We also added text to describe more fully the general compressed sensing framework (lines 209-218; lines 223-229).

   We have explained the details for the decoding tolerance precisely in the Methods, explaining our choice for this tolerance, and noting that our results are robust to particular choices in the tolerance.

5. 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. Given that the adaptation time for the adaptation mechanisms we discuss is on the order of 250ms , the background of odor needs not to be strictly static. If it evolved on a slower time scale it would be enough. We chose to simplify the presentation so that one of these odors is on a much slower timescale, effectively static. This may be conceivable if the foreground and background arise from spatially separated sources: e.g. a lawn may release a background “grass odor” everywhere, while a flower in that lawn releases a foreground “flower odor” localized in plumes streaming from the 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 mention this in lines 254-255.

6. 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.

7. 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 have rewritten the text describing the model to provide more explanation and have added a step in the derivation of the former equation (1) (now equation 2) to make the derivation clearer. We have added paragraphs explaining the origin of Weber’s Law from the model, and two panels

to Figure 1 to further illustrate the properties of the model and the Weber Law adaptation (lines 95-116; lines 126-144; Fig. 1F-1G).

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?

   This was not clear. Variability in ORN responses is dominated by the variability in the dissociation constants. The lower bound in free energy controls the level of spontaneous activity of the ORNs (firing rate in clean air) , which is known to vary across the ORN repertoire (Hallem and Carlson 2004). The upper bound in free energy determines the maximum amount of adaptation an ORN can do before its response starts to saturate. Without having this bound the neuron would be able to adapt over an infinite range of background odor concentrations. We added text in our description of the model to make these points clearer (lines 111-114).

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

   We have rewritten the end of the abstract to make it clearer for a general audience.

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.

2. 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 A_a 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.

   We have rewritten large parts of the paper to make this clearer. Please see responses to Reviewer 1's questions #3, 4, 7, 8.

3. 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.

4. 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 β in front of $A_a(t)$ in equation 2? How precise does the adaptation have to be for this to work?

Thank you for this suggestion. This comment (and Reviewer #1 Comment 6) suggests a need to investigate how much we can break Weber scaling and still maintain combinatorial codes. We have now extended the section on odor coding to address this issue (lines 172-178, 190-207). We have introduced in our model a new parameter β that allows us to gradually break the Weber-Fechner's scaling. When $\beta = 0$ Weber's law is strictly satisfied and when $\beta = 1$ there is no adaptation. Increasing β away from zero introduces a dependency of the adapted state on the background odor concentration. We added two panels in Figure 2 illustrating this.

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 phrase referred to the findings of Martelli et al (2011), and of a recent work from Aravi Samuel's lab, Si et al (2019), which recently showed that ORNs filters in larvae are stereotyped. But we agree with the reviewer that besides this general rule there are some odor-receptor combinations for which this general rule breaks down: e.g. super-sustained responses (Montague et al). We amended the text to tone down our phrase (line 121-122).

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

   We have changed the text describing the equations to clarify this connection (lines 101-104; lines 113-116).

3. 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 implemented divisive normalization following Olsen's paper. This is a rather simple model in which all glomeruli affect all other glomeruli. It is possible that a more complex model of divisive normalization where each glomeruli only inhibit a subset of glomeruli (via local interneurons) would contribute more. We noted this in the text (lines 318-325).

4. 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).

   While our model is a competitive binding model, it does not enact odorant-odorant antagonism, which is unique to the models in Singh et al (2019) and Reddy et al (2018). Odorant-odorant antagonism refers to the possibility that multiple odorants in a mixture can cause the overall response to reduce compared to the response to isolated odorants. This can occur in their model since activation is a second step after binding, and activation efficacy depends on odorant

identity. In our model, activation is independent of binding, and does not depend on odor identity. Both those papers consider mammalian olfactory receptors, which are GPCRs forming part of a cAMP-dependent pathway, where ion channel activation takes place in two steps: first, binding and second, activation. In our model, the receptor complex can activate spontaneously without any odor binding. In Figure 3—supplement figure 3, we do consider what happens when there are multiple binding sites on the receptor complex. Again, while binding is competitive for each binding site, odorants in mixtures do not mutually antagonize.

5. 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.

   It is appropriate to mention findings regarding the role of calcium channels in adaptation. We noted that in line 380-381.

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). Following the reviewer's advice we added a metric for clustering – the silhouette score – in the new extended section on odor coding, where we discuss relaxing Weber's Law (Fig. 2 caption D-E, Methods lines 469-480).

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 in the receptors stimulated by the background and foreground odor?

   Indeed, due to the response combinatorics (Fig. 1C), distinct odors are virtually guaranteed to stimulate overlapping receptors, though to differing degrees. We have included a dose response curve (Fig. 1G) that shows that, due to these overlaps, there are background-dependent shifts in the dose-response curves to foreground.