# Responses to reviewer comments

Since receiving reviewer feedback, we have carefully reviewed every point of the paper and have made several corrections. Although these corrections did not change the main conclusions of the paper, the values of various measurements have changed. Most of these changes were instigated by internal reviews in addition to the feedback received from reviewers. Here is a summary of changes and corrections:

1. **Mean responses are now subtracted within each training and testing dataset.** We changed the way signals were binned and the way the mean response was subtracted in cross-validation. In the previous submission, the mean responses were subtracted before the signals were split for cross-validation. We realized that this approach could introduce artificial correlations in subsets of data and bias the estimates of the hyperparameters.
2. **Figure 3 and Supp. Figures 1 and 2 now use boxplots.**  In the previous submission, histograms were used.
3. **Estimators** *C*factor**,** *C*sparse**, and** *C*sparse+lowrank**have been modified.** Since the original submission, we tested several alternative variations of the estimators and found them to perform slightly better than the ones suggested in the original submission. These changes did not change the main conclusions of the paper but altered some properties of the estimates such as the sparseness of the connectivity between cells and the rank of the latent component. These changes are reflected in Figures 4, 5, and 6.

## Reviewer #1.

***Comment 1.*** *I think several parts of the paper could be written more succinctly. For example the presentation of K-fold cross-validation is fairly standard and could be omitted or at least moved in the methods section. The abstract could also be compressed into a single more compact paragraph.  Overall the main message of the paper could be delivered more briefly.*

In the revised manuscript, we removed the equations defining the cross-validation loss and the relative cross-validation loss. Other changes, too numerous to list in detail, were made to shorten the paper by 3 pages.

***Comment 2.*** *For readers unfamiliar with the relationship between partial correlations, precision matrices, and covariance matrices, it might be worth expanding the text around eqs (3-4) a bit.*

In the revised manuscript, we reference a textbook (Whittaker, 2009) that derives and explains in detail the notion of pairwise partial correlations and their relationship to the precision matrix. Since these are well-established concepts, we believe it is sufficient to provide these pointers along with a simple definition of partial correlations found in the Introduction.

***Comment 3.*** *I didn't find Fig 4G-I very interpretable or helpful.  The authors should try to improve these panels, or drop them.*

We agree that drawing quantitative conclusions from the 3D connectivity plots depicted in Fig. 4G-I. Yet, these plots convey visually what the paper sets to achieve: effective representation of functional connectivity in cortical microcircuits. Plot 4G is meant shows that even with only ~10% connectivity of 300 cells, the connectivity appears dense. Panels H and I show visually what panel F shows more abstractly: just how different graphs of connectivity are inferred by two methods.

Based on these considerations, we decided to keep panels 4G-I intact.

***Comment 3.*** *The authors select the best sparsity and rank hyper parameters by cross-validation.  It would be nice to see how sharply peaked the corresponding objective function is.  For example, Fig 5 is hard to interpret if we don't know how sharply the obtained degree and latent rank are constrained by the observed data.*

We have examined plots of cross-validated loss as a function of the hyperparameters of the sparse+latent estimator or of the resulting sparsity of the functional connectivity graphs. These functions were never sharp peaked. We do not defend the point that the obtained sparsity values and latent ranks are fundamental properties of the datasets. Indeed, with longer recordings or with more cells included in the analysis the connectivity becomes denser and the latent ranks increase (e.g. Fig. 5C). Larger sample sizes allow discovering more significant terms in the estimate. We have described this point in the Results section referring to Figure 5 A-C.

***Comment 4.*** *Fig 6: the definition/interpretation of "normalized connectivity" was a bit hard to understand.  Could the authors clarify this a bit?*

We have added a more explicit definition of the “normalized connectivity” in the text on pp 10-11.

***Comment 5.*** *The authors argue in the discussion that inference of conditional dependencies between two neurons requires the observation of all the interacting neurons. This is intuitive but I was wondering to what extent the latent + sparse model can also account for unobserved units as suggested in [49] for gaussian graphical models. This could also be interesting to test either in the simulated or the real data by deliberately leaving some neurons out.*

This important point applies in idealized conditions. Indeed, in a system of linearly interacting variables most of which are observed and only a few are latent, given a sufficiently large sample, the spase+latent model would likely uncover the correct number of latent variables. However, in neural populatio recordings, removing a few neurons from the recording does not translate into increased numbers and influence of latent units. Indeed the opposite occurs: larger populations produce larger numbers of latent units (Figure 5A). Larger populations provide more data from which more factors can be inferred. Additionally, larger populations interact with larger numbers of latent units. Therefore, intuitions that apply to simple systems such those described in theoretical papers break down in studies of the neocortex. However, repeating the analysis on various subsets of the recorded neurons can be useful to demonstrate that the recovered sparse pairwise interactions are robust, or at least more robust than the partial interactions computed without regularization. We have performed this analysis by believe these findings to be trivial and did not include them in the paper.

***Comment 6.*** *It would also be interesting to repeat the analysis but conditioning on a specific stimulus each time. In this case, I'd expect that the latent part will be smaller for each stimulus (since the common input will be restricted to a specific stimulus). But it would be interesting whether the sparse part will remain more or less unchanged, something that will be more indicative of actual anatomical connectivity.*

We have compared the structure of regularized estimates conditioned on the stimulus. In agreement with previous studies (reviewed in the Introduction), we found that the correlation structure changed significantly between stimulus conditions. We have examined several changes in the sparse and low-rank components induced by the stimulus. However, our findings are too preliminary to be included in this paper. We plan to include this analysis in future publications.

***Comment 7.*** *In the papers where the low rank + sparse matrix decomposition method is discussed [49,50], a convex framework is proposed where the l\_1 and the nuclear norm of the matrix are penalized. The authors do cross-validation over all possible values instead of using the nuclear norm, which can reduce shrinkage but leads to a non-convex problem. Is there a specific reason for doing so? (In fact the optimization here would also be computationally more efficient since the low rank part is always a positive semidefinite matrix and thus its nuclear norm would be equal to just the trace.) Similarly, for l\_1 regularization the authors first determine the non-zero pattern with l\_1 regularization and then do an unregularized regression restricted to that set to find the correlation values. Why is that so?*

Our initial motivation was to uncover models that described the data most succinctly. We found that using convex optimization methods to uncover the structure (support) of the model, followed by the refitting of the non-zero parameters produced much sparser estimates with relatively little cost in performance. We performed additional tests and found that the convex models with refitting indeed slightly but consistently outperformed the sparser models with refitting. To be consistent with the principles proposed in our paper, in the revised manuscript, we used the L1-penalized versions of the sparse and sparse+latent estimators without refitting. The resulting estimates yielded many more latent units (see Fig. 5). The main conclusions of the paper did not change.

***Comment 8:*** *The link to the matlab code appears to be broken.*

The MATLAB code and the data to reproduce our results can found at https://github.com/atlab/cov-est.

## Reviewer #2

***Comment 1.*** *The correlation models differ in the number of parameters, and therefore the merits of different models in predicting the correlation structure of the data might need to be weighted by them. However, while comparing the models presented, the number of parameters is not taken into account. I think that this is quite important, and therefore, using a method such as Akaike information criterion or similar might add some generality to the interpretation of the results of the present manuscript.*

Many approaches have been devised for variable selection. We used nested cross-validation to choose the optimal values of the hyperparameters, which, in turn, determine the number of free parameters in the estimates. We agree that the Akaike information criterion or other selection criteria could be used as well. We note, however, that cross-validation is more general and makes fewer assumptions about the data generating process. Indeed in the limit of large sample sizes, the two approaches have been proven to be equivalent (See Arlot (2010) *A survey of cross-validation procedures for model selection*). Cross-validation is the preferred method whenever computationally feasible. In the revised manuscript, we explicitly state these points in the Discussion section.

***Comment 2****. In the first part of the paper, data are generated through simulations using a multivariate Gaussian model. However, this model cannot fully represent the structure of the mouse visual cortex data that is modeled later. I think it would be interesting to reproduce Fig. 1 (rows 5 and 6) with a spiking generative model, such a correlated Poisson population, with different correlation structures. For instance, as a factor model, one could consider a Poisson model of independent neurons plus one or more mother spike trains that are summed up to the uncorrelated Poisson spike trains. This kind of analysis would be interesting to understand whether the reported results are robust against non-negativity of the firing rates and against large departures from Gaussianity (e.g. occurring at low firing rates).*

Indeed, establishing the correspondence between partial correlations and conditional dependencies in non-Gaussian distributions is an interesting problem (See e.g. Baba et. al. (2004) Partial correlation and conditional correlation as measures of condition dependence, *Australian and New Zealand Journal of Statistics*). A project of this type would be too large in scope to be included in this paper. In our paper we propose since some representations outperform others in cross-validated tests, they deserve greater interest than conventional correlations and demonstrate examples of such results.

***Comment 3.*** *Finally, although the authors make predictions about the functional connectivity that is present in mouse visual cortex, a comparison with what it is known anatomically in cortex is not present.*

In the revised manuscript, we have provided three references to studies of the dependency between the synaptic connectivity and the physical distance between the cells and the differences in their stimulus preference. We do not provide a more quantitative comparison because we cannot claim that the functional connections arise predominantly from monosynaptic anatomical connections.