

We thank the reviewers for their analysis, appreciative words, and suggestions. Owing to space constraints our reply below does not address the points that can be easily addressed by amending our manuscript.

Reviewer 1

1. ' $P(s)$ ': Unfortunately the Reviewer's comment is truncated; we aren't fully sure if we are interpreting ' $P(s)$ ' correctly. We assume it to be the empirical frequency distribution of the sample activity, equivalent to n moment constraints. This constraint is one of those used in step 2. of the protocol (lines 27–56), to be compared with the other constraints. We may add that using the empirical frequencies as constraints at the sample level is questionable: activities with zero frequencies lead to zeroes in the maximum-entropy distribution, and these are unreasonable because the sample size is much smaller than the state-space size. This indicates that maximum-entropy is used beyond its range of validity. The approach at the population level + marginalization cures this problem.

2. *Puzzling finds in the literature*: We apologize for having forgotten to discuss this; this oversight can be easily fixed.

Reviewer 2

1. *Comparison with other frameworks and long intro*: We respectfully acknowledge the Reviewer's personal stand on the 'results vs introduction' point. Our opinion is that at times it is important to focus on the problem and the principles of the method purported to solve it, leaving more detailed results till later. The reason is this: if the method is misapplied, the results are actually irrelevant or even misleading – and yet they may *appear* interesting, risking to steal our focus from the principles. What's worse is that the results themselves may not reveal, or may even conceal, that the method was misapplied. We think that this has happened in many uses of the maximum-entropy method in neuroscience.

The modicum of results we presented is meant to bring to light this possible misapplication. We called this a 'dilemma' because we do not wish to advertise the newly derived equations as the final solution to the problem. At this stage we consider a careful description of the problem critical, and a comparison with more advanced methods still premature.

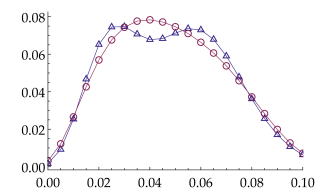
Also, we would like to reach a broader audience than the one specifically interested in 'cooperativity'. Our primary goal is to raise awareness about this possible pitfall of the maximum-entropy method, and to show a possible solution. We fear that focusing on further results specific to cooperativity would conceal the wider bearing of our message.

2. *Effect of firing rates and correlations*: The empirical correlations determine (rather than affect) the result; see the protocol 1–3, lines 27–56. Firing rates surely affect the results, but they do so through the intermediary of the correlations. The question about the effect of firing rates actually brings us back to an analysis of the initial problem: do we want a measure of 'cooperativity' that is invariant under firing-rate changes? do the principles behind the maximum-entropy method provide this? from this point of view, are we misapplying the method?

3. *Bayesian approaches and sampling*: The literature indeed offers fully Bayesian approaches, which we also prefer. But maximum-entropy methods still abound in the neuroscientific literature, and maybe they can be reasonably motivated. Our goal is to point out the subtlety in applying these methods. The literature we have explored makes very little use of the basic sampling formulae presented in our paper. This is surprising: such formulae are surely essential even in a very basic analysis of the data.

Reviewer 3

1. *Whether it matters in practice*: We agree with the Reviewer that pointing out the circumstances where the difference matters would be useful. For instance, the thinner right tail of the population-level distribution observed by the Reviewer indicates that higher-order correlations observed in the data are important (this is the question Schneidman et al. were addressing in their research, which popularized maximum-entropy in neuroscience). Note that a more entropic distribution is not necessarily more correct (after all, we could just use a uniform distribution otherwise). Application of the method with higher-order constraints can show more interesting differences between sample- and population-level distributions, e.g. a bimodality not observed in the empirical frequencies, as in the plot on the right (bimodal distribution = population-level). This also leads to different conclusion about the relative importance of the correlations.



But we believe that *even if the differences were negligible, the results of the paper would still matter*: the point is that we could not have known about the presence or absence of differences, if we had not faced the whole problem and derived a formula showing that the difference were negligible.

2. *Unnecessarily principled*: Regarding our motivation for emphasizing principles, we kindly ask the Reviewer to read our reply 1. to Reviewer 2 above. Possibly the writing could be improved on our part to make the paper flow more smoothly, without sacrificing the more philosophical discussion?