Sketch of replies to N. Comp. reviews

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Reviewer 1

(1). First, I would like to direct attention to the paper by Amari, Nakahara, Wu and Sakai in Neural Computation 2003, which the authors also cited in this paper. In this paper, Amari et al showed that "weak higher-order interactions of almost all orders are required for realizing a widespread activity distribution." (Theorem 3). As shown in the case of pairwise model (Eq.3.19 in their paper), if the fixed moments are limited and do not have higher-order, a distribution will be concentrated when we increase the number of neurons.

The suggested ME model by this paper constrains a few moments as opposed to larger number of neurons, which can not result in the wide-spread distributions according to the above theory. In other words, I speculate that the bimodal structure is an artifact of constraining fewer number of moments for a model with such large number of neurons. This could happen even if we use up to all 65th moments. I would like to know how the authors think of Amari's paper in the light of the current manuscript.

We think that the arguments of Amari et al. (2003) do not apply to the inference in our manuscript, for several reasons:

i. We did perform the calculations with an increasing number of moments as sufficient statistics, eventually using the full sample distribution. As mentioned on p. 9 and shown in § 4, from about 5 moments upwards the final result doesn't change appreciably.

   Most important, as we discuss in §§ 6 and 7, our results are the same *without* using any sufficient statistics – that is, *no maximum-entropy* model at all – under a fully Bayesian nonparametric approach. In fact, the fully nonparametric approach leads to slightly wider distributions (we hope to publish these results soon).

ii. As N increases, the two peaks we infer do become more pronounced, as suggested by our Fig. 1. So our inference is not really in contradiction with Amari et al.. The results of that paper hold for the $N \to \infty$, and no explicit form for the limit-remainder is given. It is therefore unclear whether at $N = 10\,000$ we should already observe a delta. Our findings i., above, suggest that we should not. Limit-reminders such as '$\mathrm{O}(1/N^k)$' as given in Amari et al. do not help unless we know their precise form. As an extreme example, $\frac{10^{10}}{N}$ is $\mathrm{O}(1/N)$, and in this case the $1/N$ term cannot really be neglected unless $N \gg 10^{10}$.

iii. The results of Amari et al. assume that the probability of the neuronal activity factorizes over time. In our manuscript we assume, as explained in § 6, that our degree of belief is *exchangeable* under time-bin permutations, but this exchangeability *does not imply factorizability* over time, as is clear from de Finetti's theorem. So we are not sure whether Amari et al.'s results apply at all to our inference.

(2) [we can reply by applying to real data.]

(3) I was not satisfied with the section of the Bayes factor. The Bayes factor (Eq.10) was calculated for models with different dimensionality. Then, a larger model should better account for the data. How do you determine whether you include the higher-order or not, in other words how do you determine the significance of the delta? If the models have the same dimension, one may use heuristics, for example given by Kass and Raftery (JASA 1995). If you have nesting models, one may resort to chi-squared test? Just computing the BF without such a verification method, providing the quantity BF adds only marginally to the visual inspection of the distributions.

Let us emphasize, first of all, that the purpose of our paper is to make inferences about the total activity of the larger population, not to decide among different sufficient statistics or correlation orders. Section 4 is meant to show the implications of our method for that kind of discussions. In particular we numerically show that conclusions based on a sample and conclusions based on the larger population can be very different. Our method can bypass that difficulty, if one wants to use it for such comparisons.

There are many differing views on the questions of comparison, complexity, nesting, and 'penalization' of models. Our view is close to that expressed in several works, studies, and commentaries (e.g. Good 1985; Jones et al. 1986; Chatfield 1995; Copas et al. 1995; Draper 1995; Spiegelhalter et al. 1995; Raftery 1995; Gelman et al. 1995; Draper et al. 1996; Hoeting et al. 1999; Clyde et al. 1999; Browne & Draper 2006), and well-explained in MacKay (1992). We summarize this view below. According to it, the analysis in our § 4, based on the weight of evidence, is consistent and does not need any corrections.

Note in particular that we absolutely avoid speaking about 'significance', also as recommended by the American Statistical Association in their recent official statements (ASA 2016; 2019 especially § 2). We are simply calculating the evidence (Good 1950) $\mathrm{P}(D \mid M_i)$ for several hypotheses M_i based on data D. Evidence is a continuous quantity and

we are not setting any arbitrary thresholds. Multiplied by a pre-data probability, this evidence gives the post-data probability for each hypothesis. The pre-data probability will depend on the specific case, animal, brain region, and additional knowledge. If the evidence is $10^{35} : 1$ for the first hypothesis against the second, but our pre-data probability for the second is 10^{36} times that for the first, then the second hypothesis will have higher post-data probability. But there is still a continuum of cases, no dichotomy. No such dichotomy is necessary.

If a *choice* among two or more hypotheses has to be made for some purpose (say, hardware algorithm implementation in some automated device), such choice requires not only the probabilities $p(H_i \mid D)$, but also the gain/loss matrix for the various choices conditional on the various hypotheses. The choice is then made by maximization of the expected gain. Some gain matrices can even lead to choosing the hypothesis having *lower* posterior probability (this frequently happens in medical decision problems, see e.g. Sox et al. 2013).

(4) I enjoyed somewhat philosophical arguments regarding the interpretation of the ME distribution (P8 and Appendix). However, I was not sure how these are relevant to the paper if it is just an interpretation. Can we consider different outcomes arising the different interpretations? If the authors are preparing another manuscript in this direction, these arguments may better be used for that paper? (This is just a weak suggestion.)

Reviewer 2

2. The method requires that the measurements on n neurons are 'representative' of the full population of N neurons. The authors show one example, where they divide a dataset into two subsets of neurons with different statistics. They show that the extrapolations from these two subsets are significantly different. But this particular analysis is somewhat ad hoc. Are there any more systematic tests of procedures for understanding how sensitive this analysis is to choosing different subsets of neurons? Or different recoding periods?

3. In particular, correlations tend to be stronger between nearby neurons than far-away neurons. This should be a consistent pattern that shows up in most experimental datasets and which should lead to systematic biases in inferring the properties of populations, N, which are large enough to result in lower average correlation (see Nonnenmacher et al., PLoS CB 2017). Is there any way to take this dependence into account?

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