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Michael Eisen, Ph.D.
Editor-in-Chief, *eLife*

Dear Dr. Eisen,

We are pleased to resubmit our manuscript after several months of making extensive improvements to address the high-quality concerns of the reviewers. This work is not under consideration elsewhere. This work addresses a question of fundamental and timely importance to the neuroscience community: as theoretical models of computation become increasingly complex, how can we properly interrogate these models – their parameterizations, their degeneracies, scientific hypotheses generated by inspecting these models, and explanations of neural data generated by fitting these models to the wealth of data from modern recording techniques?

The reviewers to the first submission found substantial merit in the work, both in its motivation and execution. They also appropriately pointed out the need for an improved explanation of emergent property inference (EPI), extensive comparisons to state-of-the-art alternative approaches, and greater depth in the scientific analyses. In the revised manuscript, we show the results of nearly a year of work to speak to these requests, in what we (and the community) now find to be a much more thorough and persuasive set of findings.

In terms of exposition, we have ovehauled the motivation and presentation of our approach. We explain that EPI is motivated by an incongruity between the practice of theoretical neuroscience and statistical inference techniques: the focus on emergent properties vs. data. Through this lens, we offer a more clearly written explanation of EPI, which is far more intuitive and less technical and saves such details for Methods. We have tested this narrative on colleagues and peers and have seen significantly positive response.

Also, the revised manuscript includes a thorough methodological comparison of EPI to modern likelihood-free inference techniques, including the method SNPE. SNPE was cosubmitted alongside the first version of this manuscript, and that work has now been published by eLife (Goncalves et al. 2020). This comparison serves to prove two important points: a) EPI can scale to higher dimensions than alternative techniques, and b) EPI is the only inference technique that can precisely condition on emergent properties. Goncalves et al. 2020 was originally cosubmitted with this manuscript, and in the intervening months we have taken considerable effort and time to address important issues pointed out by the reviewers. While the two studies share the same high-level goals, they differ in the class of models and phenomena they target: Goncalves et al has a particular focus on models of ion-channels, cellular processes and biophysically detailed models of neural networks. On the other hand, this manuscript was motivated by the need to analyze circuit and systems-level models of neural dynamics, with a particular focus on cortical and recurrent neural network models. Futhermore, these methods differ meaningfully in their mathematical foundations.

Finally, we have clarified the manner in which models of primary visual cortex and superior colliculus are analyzed with EPI. This revised manuscript focuses on producing scientific insight from the rich parametric structure captured and quantified by deep probability distributions through EPI. Not only are these novel insights obtained in a way that emphasizes the methodological capabilities of EPI, we now provide clear scientific background, motivation, and takeaways for each model

Please do not hesitate to contact us if we can provide any further information. We would welcome the opportunity for our work to be reviewed by the same scholars as was the previous submission. Thank you for the consideration.

Sincerely,

John P. Cunningham