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 valid concerns of the reviewers. The reviewers indicated the need for an improved explanation of emergent property inference (EPI), comparisons to state-of-the-art alternative approaches, and greater depth and quality in the scientific analyses. In the revised manuscript, 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.

The revised manuscript includes a thorough methodological comparison of EPI to modern likelihood-free inference techniques, including the method SNPE of the cosubmitted manuscript which 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.

Finally, we have re-approached 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

Goncalves et al. 2020 was originally cosubmitted with this manuscript, and we have taken considerable effort and time to address important issues pointed out by the reviewers, while the cosubmission has been published. We are very supportive of this work, and recognize its publication date. While the two studies share the same high-level goals, they differ in the class of models and phenomena they target: Goncalves et al was motivated by the need to constrain, adjust and select mechanistic models of neural dynamics by experimental data, with 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 which produce mathematical criteria or “emergent properties”, with a particular focus on cortical and recurrent neural network models. Futhermore, these methods differ greatly in their mathematical foundations, making the methodological comparison a highly valuable contribution to neuroscience and machine learning. We hope that if this manuscript is accepted, there is an opportunity for a highlight piece summarizing the contributions of the two works published at *eLife*.

Please do not hesitate to contact us if we can provide any further information.

Sincerely,

John P. Cunningham

on behalf of all authors.