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May R. Berenbaum, Editor-in-Chief
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Regarding PNAS MS# 2019-22489

Dear PNAS Editors,

Our submission of a Brief Report titled '*Modelling the emergence of whisker barrels*' was rejected last week after comments received from two reviewers were considered. Reviewer 1 was very positive about the paper, whereas Reviewer 2 had concerns. The conclusion of Reviewer 2, "this study seems better suited to a more specialized journal", was repeated in the Editor's summary note, and thus we assume that the decision to reject was based largely on the comments of Reviewer 2. We appreciate and respect the Editor's decision given the comments provided. However, we contend that the comments of Reviewer 2 reveal their failure to grasp the central theory and key claims that were developed in the article. This lack of understanding was actually pointed out by Reviewer 2 (e.g., point 3 below) who conceded that they had difficulties in understanding the mathematical expressions in our manuscript.

Importantly, Reviewer 2 incorrectly compares the model we propose with "a classic chemospecificity" model. Our model was designed specifically to show that the assumption of pre-organised center points inherent in the classic chemospecificity models are not necessary to explain cortical map formation. Reviewer 2 also objects that "[immediate adjacency] does [not] seem like a biologically natural or desirable constraint" — we are lost for words to express our concerns about this objection — are there any more fundamentally natural constraints for a model of biological pattern formation than the constraint that cells should communicate only locally? Alan Turing would be turning in his grave!

We are of course aware of our responsibility as authors to make the claims of an article clear for our intended audience. However the deeply insightful comments provided by Reviewer 1 demonstrate that the paper is presented clearly, certainly with respect to the basic aspects that have led to confusion for Reviewer 2. Note that Reviewer 1, whose comments evidence a very clear understanding of the theoretical and technical aspects of the work, reached a much more positive conclusion: "I have a few questions about the paper, but otherwise, found it enjoyable and interesting to read."

With these points in mind, we write to request the opportunity to submit a revised version of the article, as well as a full rebuttal to the comments of Reviewers 1 and 2. To aid your decision, we reproduce below the comments of Reviewer 2 (unedited), together with a brief outline of the basis for our rebuttal to these comments, should this opportunity be granted. We hope you will agree that it is clear from our responses below that the critical comments of Reviewer 2 can be easily and rapidly addressed in a revision. Also, if you choose to allow us to re-submit, we hope you will consider using another reviewer who is familiar with this type of work.

We sincerely appreciate the time and effort of the Editors and Reviewers that has already gone into evaluating our article, and we note that it is very unusual for us to contest decisions of this nature, but we feel strongly that the decision to reject in this particular case was influenced by a fundamentally flawed interpretation of the work.

Reviewer #2 comments:

This study models the development of somatotopically organized afferent projections to rodent cortical whisker barrels. The basic question addressed is whether "barrel maps can emerge in a system with reaction-diffusion dynamics, under the guidance of signalling gradients, and in the absence of pre-defined centers". The simulation approach is an extension to a 2D sheet of the 1D model published by Karbowski and Ermentrout in 2004. The model is a relatively simple mathematical formulation based on parameters such as densities of axonal branches and synapses (connections), 'flux' of axonal branching, which interact with multiple "molecular signaling fields". I have a few specific concerns.

1) Various assumptions are made, such as the "assumption that axon branching decreases when synaptogenesis increases, and vice versa, i.e., that axon branches are required for synaptic connections to form. On multiple readings of this sentence I still don't see how the first clause implies the second.

We agree that this sentence could be easily clarified, and we note that it describes an assumption of the *original* model, not of our extension to it, hence addressing this will result in a very minor edit.

2) "We speculate that a projection interacts with a given ephrin field in the cortical subplate with a strength determined by the concentration of a similar molecule at its thalamic origin, i.e., the putative barreloid center. As such, two orthogonal linear thalamic gradients were defined, from which 41 pairs of γ values were sampled, at the coordinates of 41 barreloid centers." This seems to be a statement of what's needed for a classical chemospecificity dual gradient. If that's the assumption, why is it notable that an orderly map is achieved?

The premise of the article is to evaluate whether pre-existing center-points are required for the formation of cortical barrels. Classical chemospecificity models essentially assume center-points, i.e., conditions in the target tissue that instruct pre-identified afferents to stop growing. Our model provides a fundamentally different account. An orderly map forms because afferents *compete* with one another to follow signalling gradients, and because they do so with different strengths. Consider, for simplicity, that according to classic chemospecificity models, simulated afferents growing in isolation will find their targets just as they would if growing altogether. But according to our model, axons growing in isolation (and hence not competing with one another) will instead continue to migrate away from the center until a boundary is encountered. Simply put, ours is a model of competitive growth, not chemospecificity. Appreciating the distinction between pre-organised versus emergent centers is crucial to appreciating the importance of the results described in the article. This comment by Reviewer 2 suggests a basic failure to appreciate this important distinction. Re-emphasising this distinction is a minor revision.

This error by Reviewer 2 aside, the formation of an orderly map is only one half of the major result that we report in the article. The emergence of realistic barrel patterning is instead the key result, and we want to highlight here that none of Reviewer 2's comments acknowledge or contest this key finding.

3) "We emphasize that the formulation of the model is entirely local; the simulation permits information to be communicated from a given cortical grid cell only to those immediately adjacent (via diffusion)." It is unclear how this constraint of immediate adjacency stems from the equations. But neither does this seem like a biologically natural or desirable constraint.

We cannot see where this objection stems from. The description of this constraint is perfectly clear in the equations, which include only one spatial operator (\nabla in Equation 2), integration of which requires each cell to communicate only with its immediate neighbours. If Reviewer 2 cannot see this, then they are lacking some of the expertise required to properly evaluate the work, and we suggest that their confidence in making an overall recommendation should be tempered accordingly.

More importantly, all pattern formation, and arguably all biological processes, self-organize from local interactions between simpler processes. To object to our modelling approach on the grounds that enforcing local interactions is not "a biologically natural or desirable constraint" is to deny everything that has been learnt about pattern formation in natural systems since Turing introduced the reaction-diffusion formalism in 1952. We trust that on re-reading Reviewer 2's objection here, the Editors must agree that it is not to be taken seriously as a proposed weakness in our approach to modelling pattern formation in the developing cortex. The fact that some scientists still do not understand that local interactions are a necessary constraint for a model to be capable of demonstrating true self-organization, is a strong argument for publishing demonstrations of true self-organization like ours, in journals like PNAS that reach such a broad audience of scientists.

4) The conclusion that "the present results confirm that somatotopic map formation does not require the pre-specification of centerpoints by as yet undetermined additional developmental mechanisms" strikes this

reviewer as neither fully convincing on the one hand, nor terribly surprising either. Altogether, this study seems better suited to a more specialized journal.

Reviewer 2 is not *convinced* by our demonstration that pre-existing center-points are unnecessary for cortical map formation because they have failed to first appreciate that our model is absolutely not a center-point model (point 2). It follows that Reviewer 2 is also not *surprised* by our results because they do not understand that pattern formation in natural systems is a complex emergent property of local interactions (point 3). We feel that some very minor tweaks to the article to re-emphasise these points will ensure that the general audience of PNAS will not misinterpret the basic premise of the research as Reviewer 2 has, and as such we contend that this important and fundamental result about pattern formation in the developing brain is ideally suited to the broad readership of PNAS.

We look forward to hearing your decision about whether to permit a revision and resubmission of '*Modelling the emergence of whisker barrels*' to be considered for publication as a Brief Report in PNAS.

Sincerely,

Sebastian James
Leah Krubitzer
Stuart Wilson