

From: cody.walters@us.nature.com
Subject: CONFIDENTIAL: Invitation to review Nature Communications manuscript NCOMMS-25-65811-T
Date: 8 September 2025 at 19:54
To: alexander_bates@hms.harvard.edu



Dear Dr. Bates,

We hope you will be interested in reviewing a manuscript for Nature Communications. The manuscript is entitled "Dissecting origins of wiring specificity in dense reconstructions of neural tissue" and the abstract is appended below. Your expert opinion on this work would be most valued.

To provide a timely decision for the authors, we would kindly ask you to return your comments within 14 days. If you would like to assist, but would need more time to review the manuscript, please do not hesitate to let me know.

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Nature Communications is committed to facilitate training in peer review and to ensure that everyone involved in our peer-review process is appropriately recognised. We have therefore started an initiative to allow and encourage established referees to involve one early-career researcher in our peer-review process. If you participate in this initiative, you will remain the primary contact and you will submit the final report, but the review that you compile together will be considered a co-review, meaning that both of you receive recognition for your contributions. We will send instructions to your co-reviewer and ensure that their referee activity is logged on our systems so that they are recognised for their review activity. **If you would like to participate, please reply to this email with the name and contact details of the researcher you'd like to co-review with within two working days of accepting this invitation.** We cannot accept the addition of a co-reviewer after submission of the report and reserve the right to exclude the suggested co-reviewer if a conflict of interest is detected. Please note that if you are co-reviewing this paper with an early-career researcher, you will have to decide together on whether you want to opt-in or opt-out of being named within the Reviewer Recognition statement of the published paper.

If you are unable to review on this occasion, we would appreciate any suggestions for alternative reviewers with a similar expertise to yours - perhaps someone from your own research group? We strive to achieve a **diverse demographic representation** among our reviewers and we would welcome suggestions from under-represented groups.

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To accept or decline our invitation, please use the following link:

<https://mts-ncomms.nature.com/cgi-bin/main.plex?el=A7S5CYW4A2VkJV4J4A9ftdrUJHZhBn7GHhGjKRaUwOfQZ>

From there, follow the link to manuscript NCOMMS-25-65811-T, where you will be able to view general manuscript information followed by instructions on how to proceed.

On a case by case basis, we may ask you to comment on concerns raised by the other reviewers after we have received all reports. The purpose of this consultation is to improve the feedback provided to the authors.

For information on our peer review policies, see [here](#).

Thank you in advance for your help. Please don't hesitate to email me if you have any questions.

Best regards,

Cody J. Walters, Ph.D.
Senior Editor, Nature Communications

Please keep this information confidential.

Marcel Oberlaender, Philipp Harth, Daniel Udvary, Jan Boelts, Jakob Macke, Daniel Baum, and Hans-Christian Hege

****ABSTRACT****

What are the origins of the highly specific wiring patterns that are formed by the neurons in the brain? To address this question, we introduce a method to predict the empirically observed wiring diagram – the connectome – at synaptic resolution based on dense electron-microscopic reconstructions of neural tissue. Our method generates the connectome based on the morphological properties of the neurons in combination with synaptic specificity models, whose parameters capture how neurons wire conditional on their subcellular, cellular and cell type properties. We employ simulation-based Bayesian inference to identify all values for these parameters that can generate the observed connectome. Finally, for each synapse in a dense reconstruction, our method provides quantitative measures to reveal which synaptic specificity models are necessary, sufficient and best-suited to generate it. The output of our method are experimentally testable predictions of wiring preferences from subcellular to cell type levels that could account for each synapse in dense reconstructions. We demonstrate our method on dense datasets from mouse primary visual and human temporal cortex. Strikingly, this demonstration shows that just three assumptions, with nearly the same synaptic specificity values, predict the connectivity in both datasets. Our method is openly accessible as a computational framework that includes a comprehensive workflow for the analysis of wiring specificity, and which provides users with full flexibility to define and test their hypotheses. Our method sets the stage to uncover the principles by which neural networks are organized, and to compare these principles across brain areas, species and time points.

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