National Institute for Theory and Mathematics in Biology
Funded by the U.S. National Science Foundation and the Simons Foundation

Inferring Brain Wiring Rules

Ryan Lee, Tingyu Zhao, Bingjie Hao, Istvan Kovacs

The availability of brain data across a wide range of organisms is currently experiencing an unprecedented boom. These advances present exciting opportunities for computational research, with the potential for theoretical frameworks to act as synergistic guiding forces in experimental design. A key question we aim to address is how to formulate genetic wiring rules in brains, which govern the emergent synaptic network patterns.

Biological question: The *C. elegans* nervous system is an ideal model to test new mathematics, due to the abundance of experimental data and the ease of generating new observations. Yet, a successful model for explaining or predicting *C. elegans* wiring rules remains elusive, despite evidence suggesting minimal individual variability. This gap underscores the need for new mathematical models and computational frameworks that integrate connectome, contactome, and transcriptome information. The resulting frameworks are expected to be broadly applicable, including to the recently fully mapped *Drosophila* connectome.

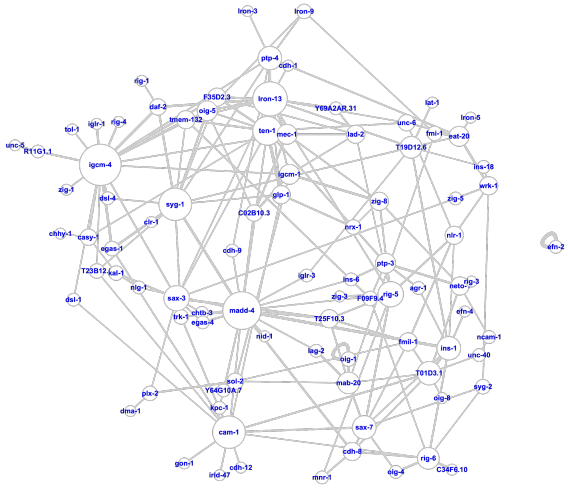

Figure 1: the top 179 predicted rules behind chemical synapses in *C. elegans*. Node sizes are proportional to node degrees and edges are weighted by rule *z*-scores.

New mathematics: Modern low-dimensional embedding techniques such as UMAP and t-SNE are typically used to position neurons in a predefined low-dimensional space, ensuring that nearby data points correspond to neurons forming synapses. Here, we address the inverse problem: instead of determining neuron locations, we assume they are known, with each dimension representing the expression of a specific gene. Our goal is to learn the structure of the genetic space itself so that neurons closely aligned in this space are the ones most likely to form connections in the brain. To achieve this, we develop a Spatial Connectome Model to infer wiring rules, followed by randomization of the connectome and genetic information to identify significant patterns. For the first time, we allow nonlinear and higher-order hypergraph wiring rules, requiring innovative tools to navigate the curse of dimensionality of the genetic space. This framework is applied to both gap junctions and chemical synapses (see Figure 1), producing wiring rules between the genetic factors involved that can be directly tested in ongoing and future experiments. Additionally, these inferred rules enable computational predictions of synapses that may be sensitive to the loss of specific genes, providing experimentally testable hypotheses.

Reference: https://www.biorxiv.org/content/10.1101/2024.07.08.602367v2. This research was supported in part by grants from the NSF (DMS-2235451) and Simons Foundation (MP-TMPS-00005320).