Reproducing Whole-Brain Connectome Using a Developmental Model

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How is connectivity understood?

While the biological mechanisms of neuronal identity and targetted axon guidance are well-studied, there is open opportunity for the big data generated about the brain to be leveraged toward computational models of brain development. This work replicates brain connectivity data using a biologically plausible developmental model [1], with the goal of explaining the regularities in the observed structure using a simpler developmental model.

How do neurons know where to connect?

- How could a chemical encoding represent the connectome weights?
- Learn vector representations ("barcodes") at the spatial level
- The barcodes model the transcription profile, or *identity* of each region
- The connectivity weight between one region and another is produced using the two barcodes
- Thus: homophilic wiring rules; "birds of a feather flock together"
- This work relies on the Genetic Connectome Model (GCM) [1]:
- If V is the number of regions, D is the number of coordinates in the barcode, and $X \in \mathcal{R}^{V \times D}$ is the matrix of barcodes, then the GCM model defines an association matrix $O \in \mathcal{R}^{D \times D}$ used to produce the connectivity matrix $M \in \mathcal{R}^{V \times V}$ as follows:

$$M = \mathcal{H}(XOX^\top)$$

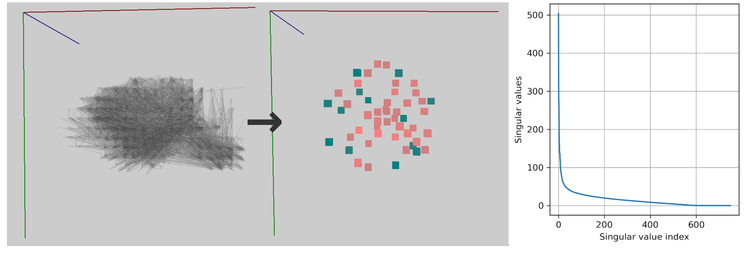
- The nonlinearity $\mathcal{H}$ is the Heaviside step function
- Without $\mathcal{H}$, the resulting linear equations are solvable by singular value decomposition (SVD):

$$X = U$$

$$O = \Sigma V^\top U$$

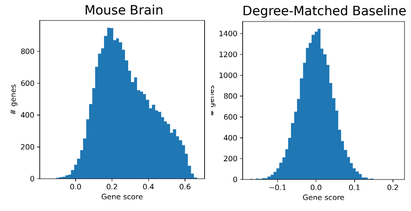
- Given the standard decomposition $M = U\Sigma V^\top$

How much information is needed to encode the mouse connectome?



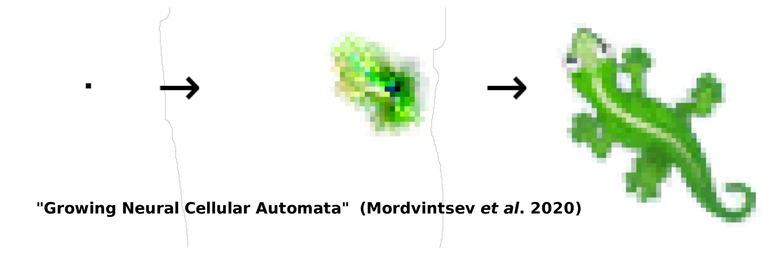
- Allen Brain Atlas *Mouse Brain Connectivity* [2, 3]
- Processed to produce voxel-based connectome (left)
- Approximation formed using truncated SVD to create barcodes
- One coordinate of the barcodes constitutes a spatial profile (center)
- A significant part of the connectome is expressible with just a few coordinates, evidenced by the singular value distribution (right)

Do the barcodes correspond with gene expressions?



- Allen Brain Atlas *ISH Dataset* [4] containing nearly 20,000 genes
- Barcodes are tested for correspondence with genetic expression data
- The first 16 coordinates are evaluated as a population code
- **Gene scores** indicate cross-validated predictivity of the genetics from the barcodes using a linear model
- GCM fit to the mouse brain data has high gene scores
- GCM fit to a degree-matched random graph has noise-level scores

Future Work: Can we do better?



- Encode the recipe rather than the result
- Turing patterns [5]
- Neural cellular automata [6] used to model the parallel, distributed process of developmental pattern formation

Conclusion: Development constrains connectivity

- Connectivity matrix with over one million entries reduced to spatial variables, "barcodes," which efficiently encode the connectivity using drastically fewer variables
- The barcodes are correlated with genetic expression in the mouse brain, providing computational evidence for the role of gene expression patterns in driving the development of connectivity

[1] Dániel L. Barabási, Taliesin Beynon, Ádám Katona, and Nicolas Perez-Nieves. Complex computation from developmental priors. 14(1):2226. Number: 1 Publisher: Nature Publishing Group.

[2] Joseph E. Knox, Kameron Decker Harris, Nile Graddis, Jennifer D. Whitesell, Hongkui Zeng, Julie A. Harris, Eric Shea-Brown, and Stefan Mihalas. High resolution data-driven model of the mouse connectome. Pages: 293019 Section: New Results.

[3] Allen Institute for Brain Science. Allen Mouse Brain Atlas [Mouse Brain Connectivity]. Available from mouse.brain-map.org.

[4] Ed S. Lein et al. Genome-wide atlas of gene expression in the adult mouse brain. 445(7124):168–176. Publisher: Nature Publishing Group.

[5] Alan Turing. The chemical basis of morphogenesis. 237(641):37–72.

[6] Alexander Mordvintsev, Ettore Randazzo, Eyvind Niklasson, and Michael Levin. Growing neural cellular automata. 5(2):e23.

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