

Tools for comparative connectomics: case studies from two sides of a larval Drosophila brain

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Benjamin D. Pedigo

(he/him)

[NeuroData lab](#)

Johns Hopkins University - Biomedical Engineering

 bpedigo@jhu.edu

 [@bdpedigo \(Github\)](#)

 [@bpedigod \(Twitter\)](#)

 bpedigo.github.io

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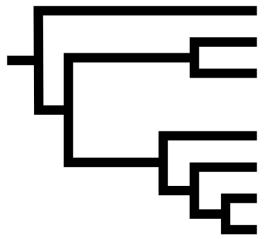
These slides at:

Connectomics is useful...

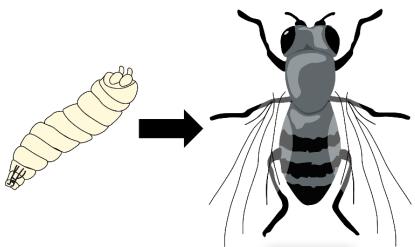
TODO: (3) plot of "connectome prevalence over time"

TODO: (4) highlight one example fly result (? maybe central complex)

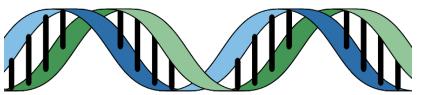
Many stated goals of connectomics are to link connectome to other properties



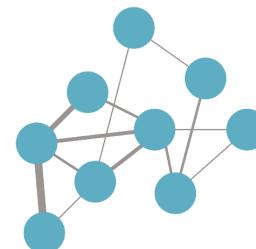
Evolution



Development



Genome



Connectome



Behavior



Activity

Connectome \leftrightarrow memory

...the acquisition of wiring diagrams across multiple individuals will yield insights into how experiences shape neural connections.

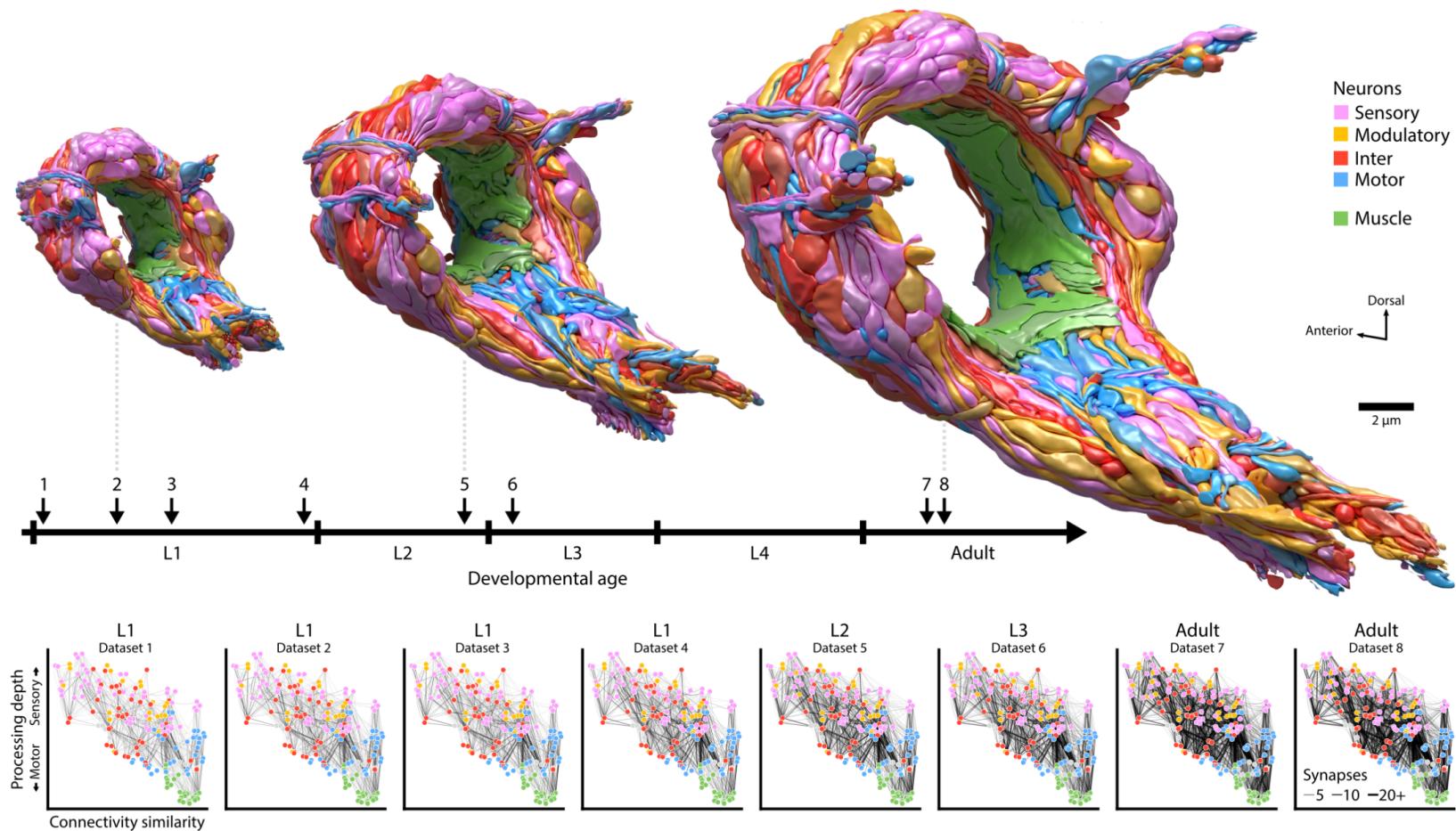
Emphasis added

Connectome ↔ evolution

Comparative connectomics of [...] **species across the phylogenetic tree** can infer the archetypal neural architecture of each bauplan and identify any circuits that possibly converged onto a shared and potentially optimal, structure.

Emphasis added

Connectome ↔ development



But it is methodologically hard to compare connectomes!

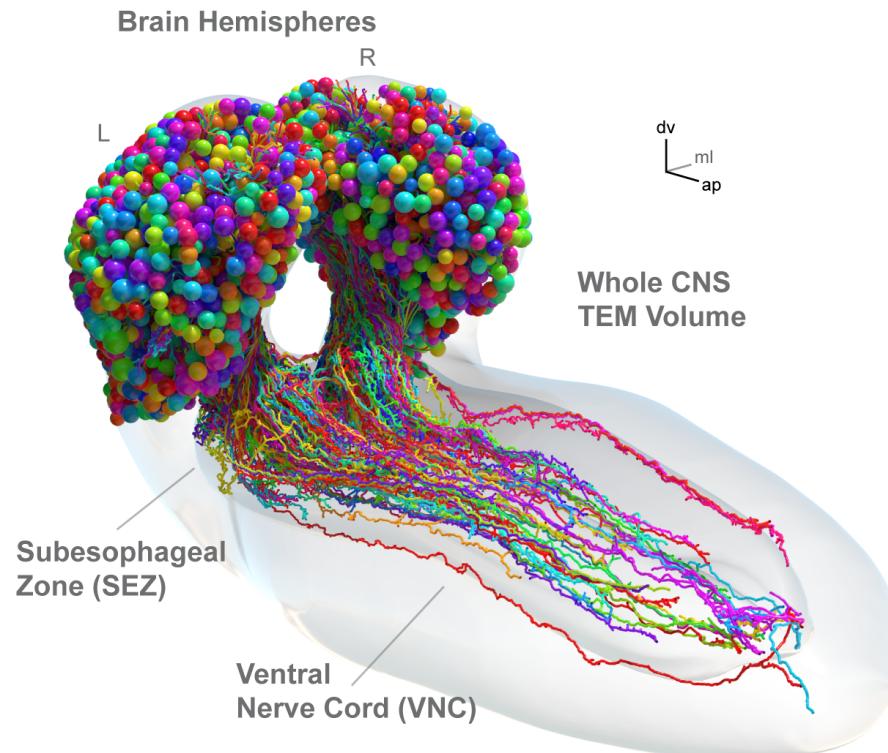
- Data are networks
 - Data are networks with rich attributes
- Data are noisy
 - "Developmental noise"
 - "Experimental noise"
- Data are big (and getting bigger)

Outline for today

- Describe larval connectome dataset
- Show how connectome comparison can be framed as network hypothesis testing
- Show how we can use automated tools for predicting the correspondence of neurons across datasets
- Mention extensions to use/combine/extend these tools

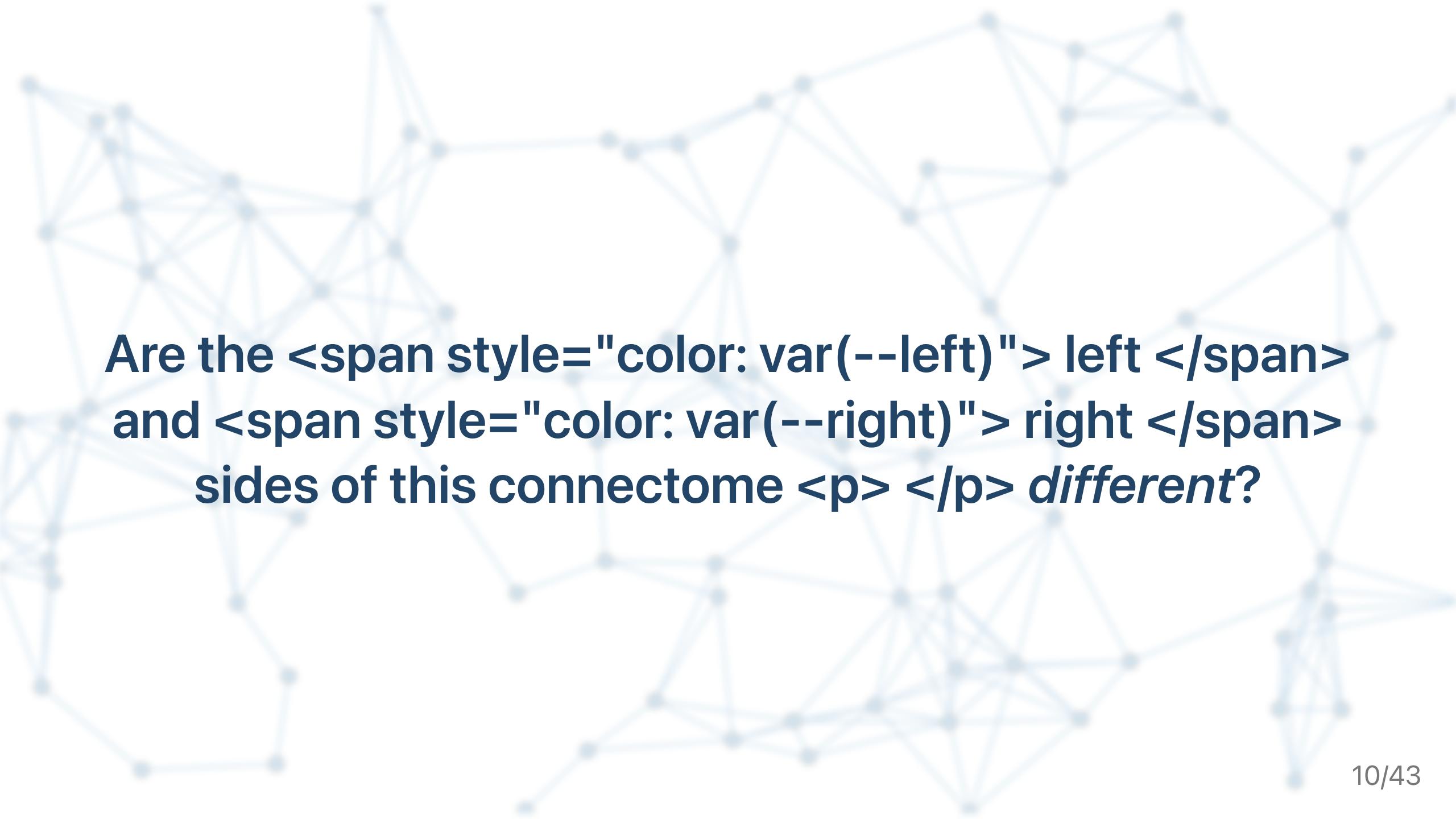
Larval *Drosophila* brain connectome

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~3k neurons, ~550K synapses

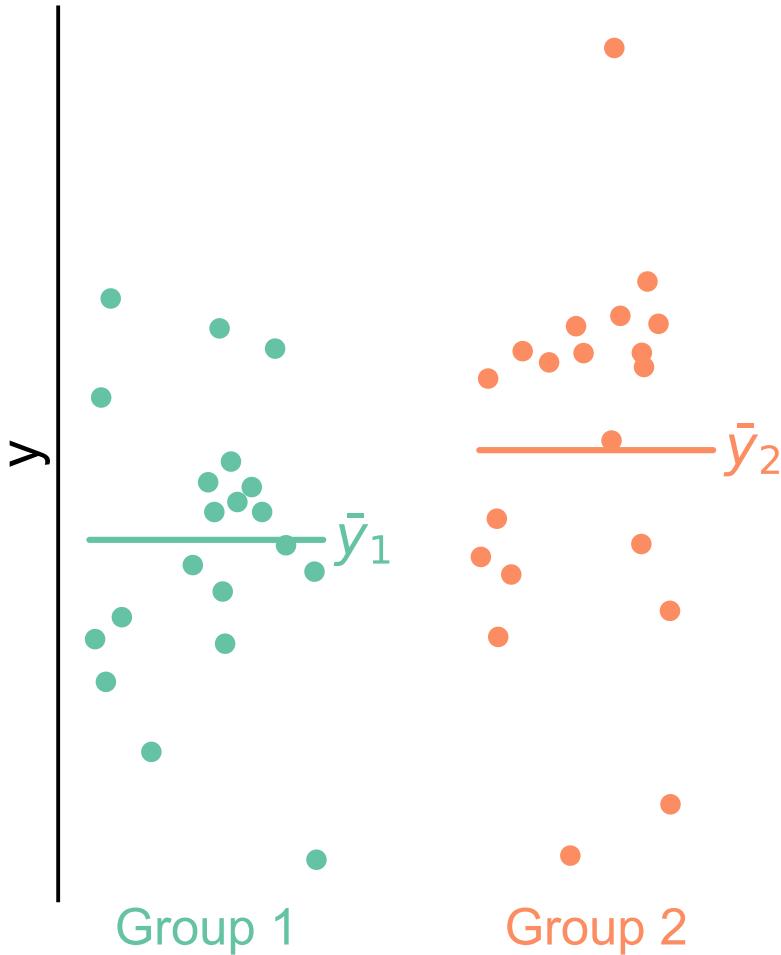
Both hemispheres



Are the `` left `` and `` right `` sides of this connectome `<p> </p>` different?

Are these populations different?

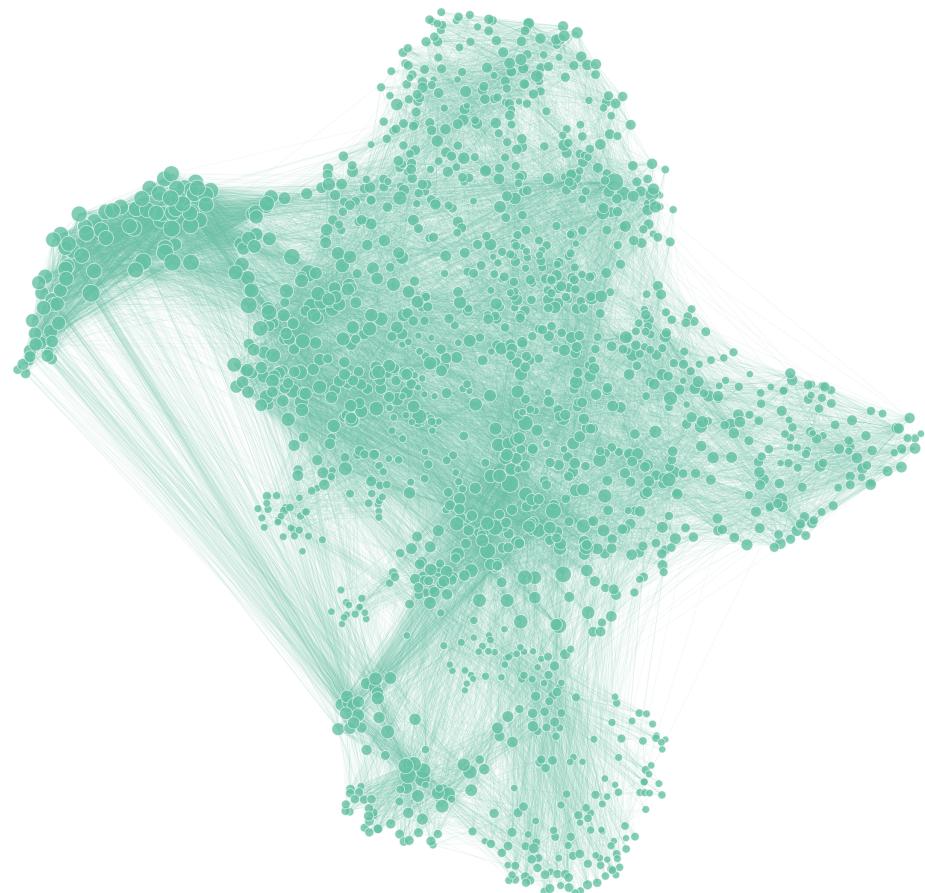
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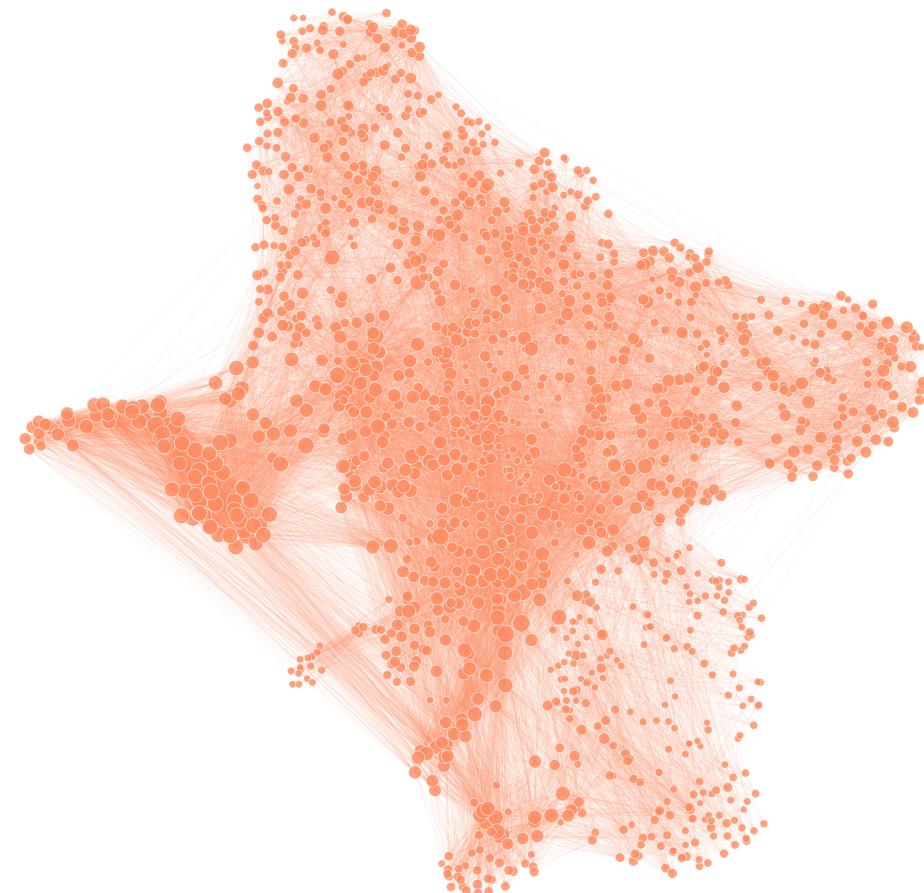
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Are these two *networks* different?

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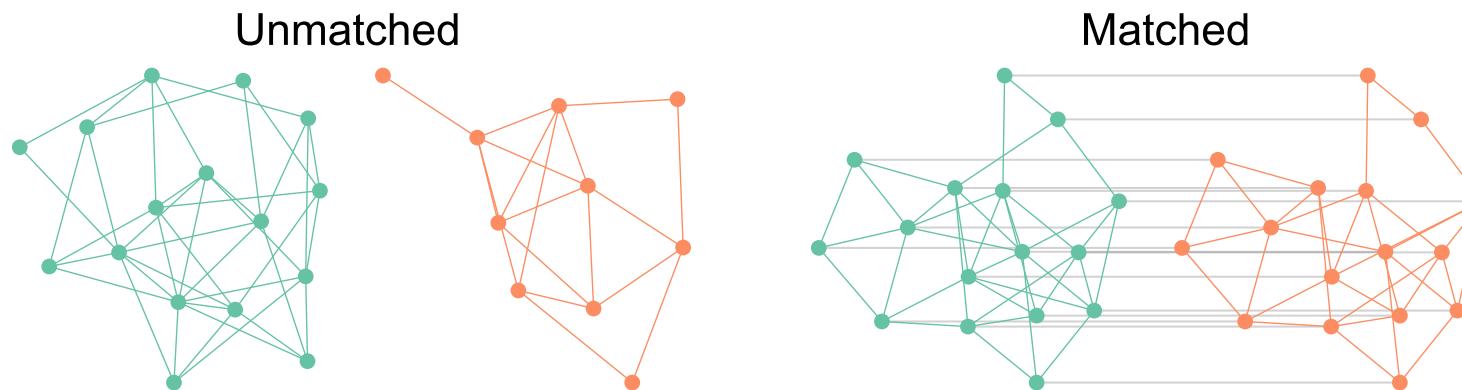
Left



Right

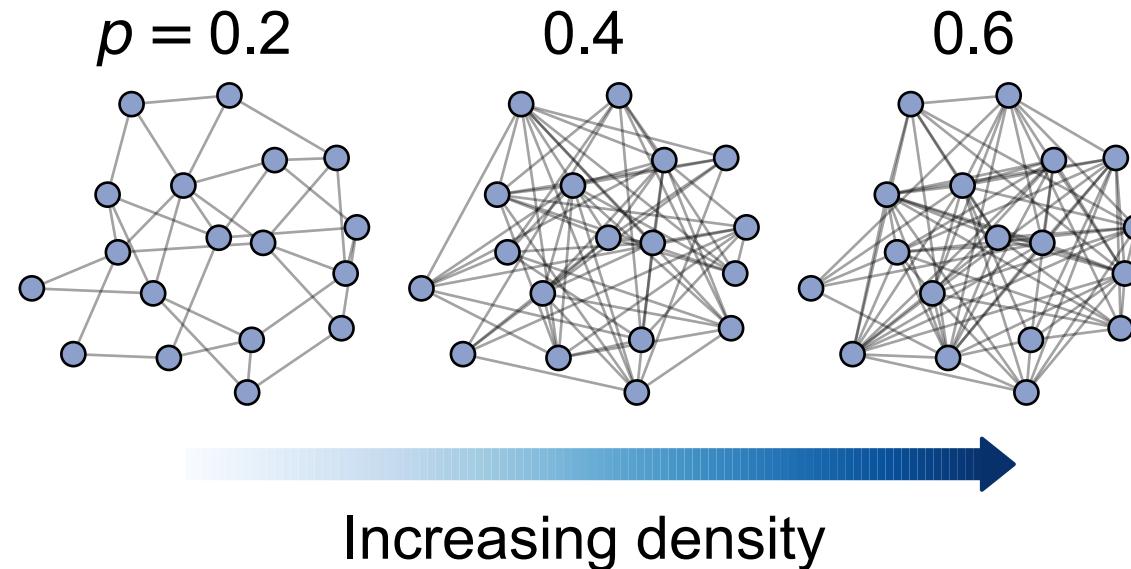
Assumptions

- We know the direction of synapses, so network is *directed*.
- For simplicity (for now), consider networks to be *unweighted*.
- For simplicity (for now), consider the ` left → left ` and ` right → right ` (*ipsilateral*) connections only.
- Not going to assume any nodes are matched



Erdos-Renyi model

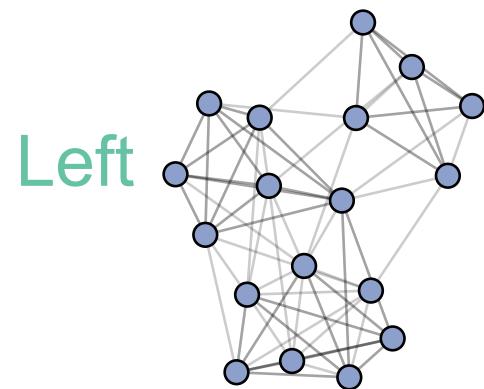
- All edges are independent
- All edges generated with the same probability, p



We detect a difference in density

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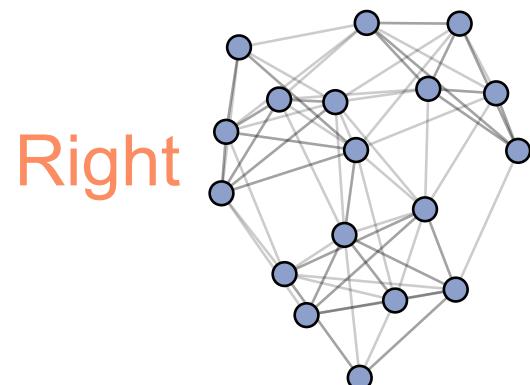
Compute global
connection density



Left

Compare ER
models

$$p = \frac{\text{\# edges}}{\text{\# potential edges}}$$



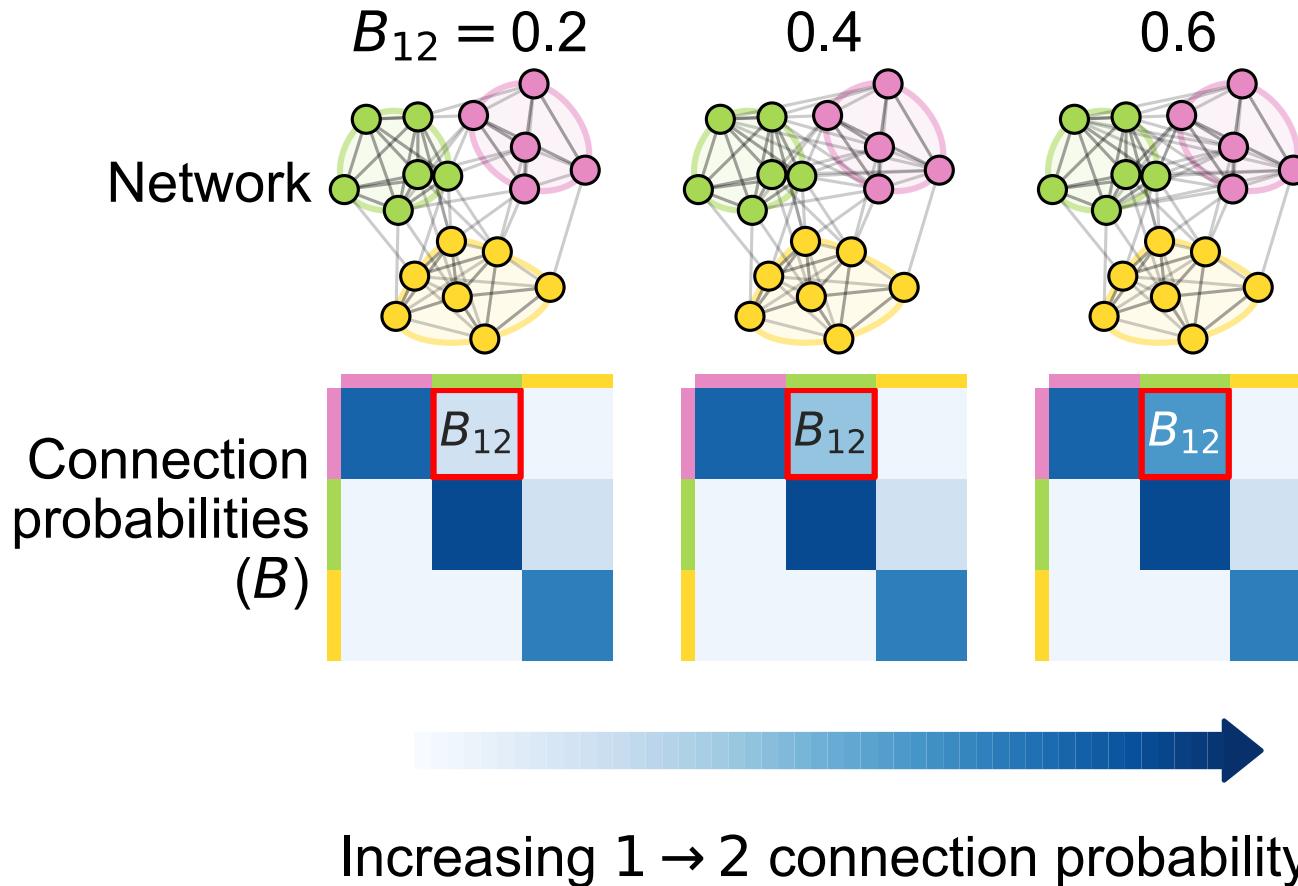
Right

$$\begin{aligned} H_0: p^{(L)} &= p^{(R)} \\ H_A: p^{(L)} &\neq p^{(R)} \end{aligned}$$

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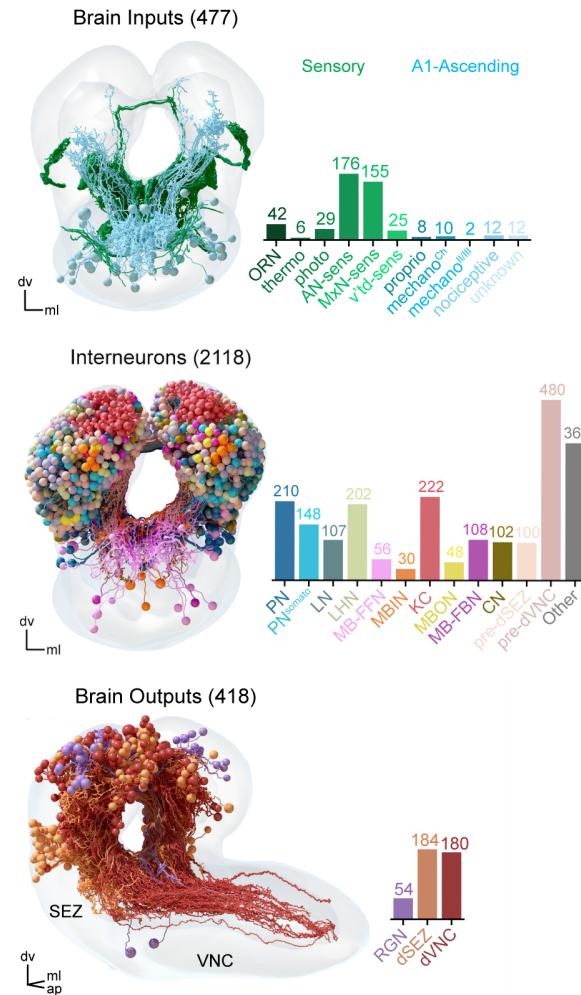
Stochastic block model

- Edge probabilities are a function of a neuron's group



Connection probabilities between groups

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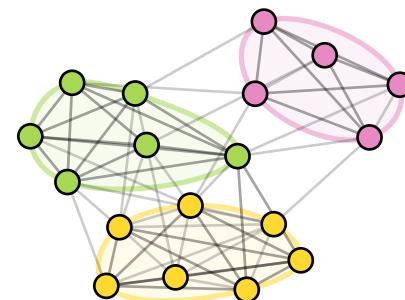


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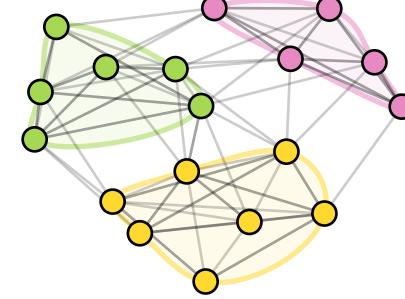
Group-based testing

Group neurons

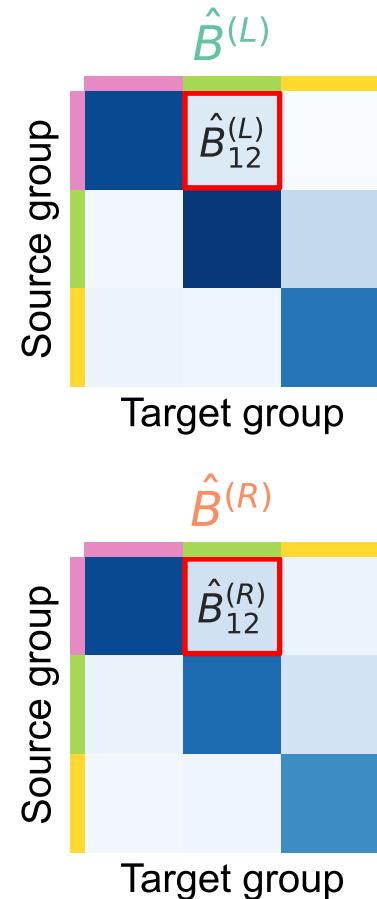
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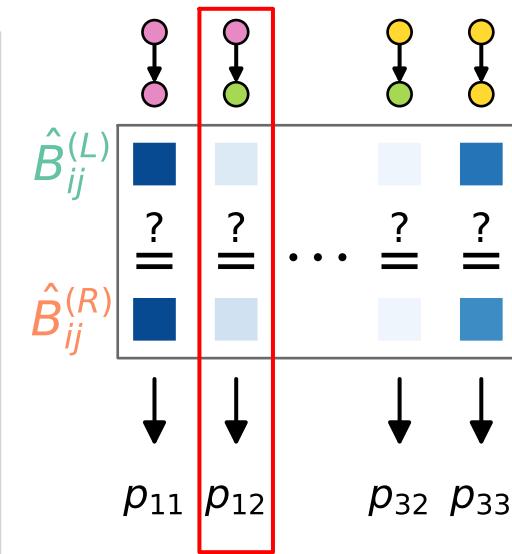
Right



Estimate group connection probabilities

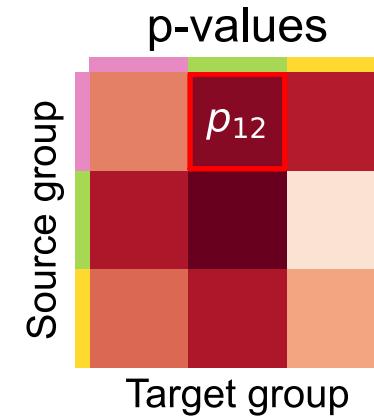


Compare probabilities, compute p-values



$$H_0: \hat{B}_{ij}^{(L)} = \hat{B}_{ij}^{(R)}$$
$$H_A: \hat{B}_{ij}^{(L)} \neq \hat{B}_{ij}^{(R)}$$

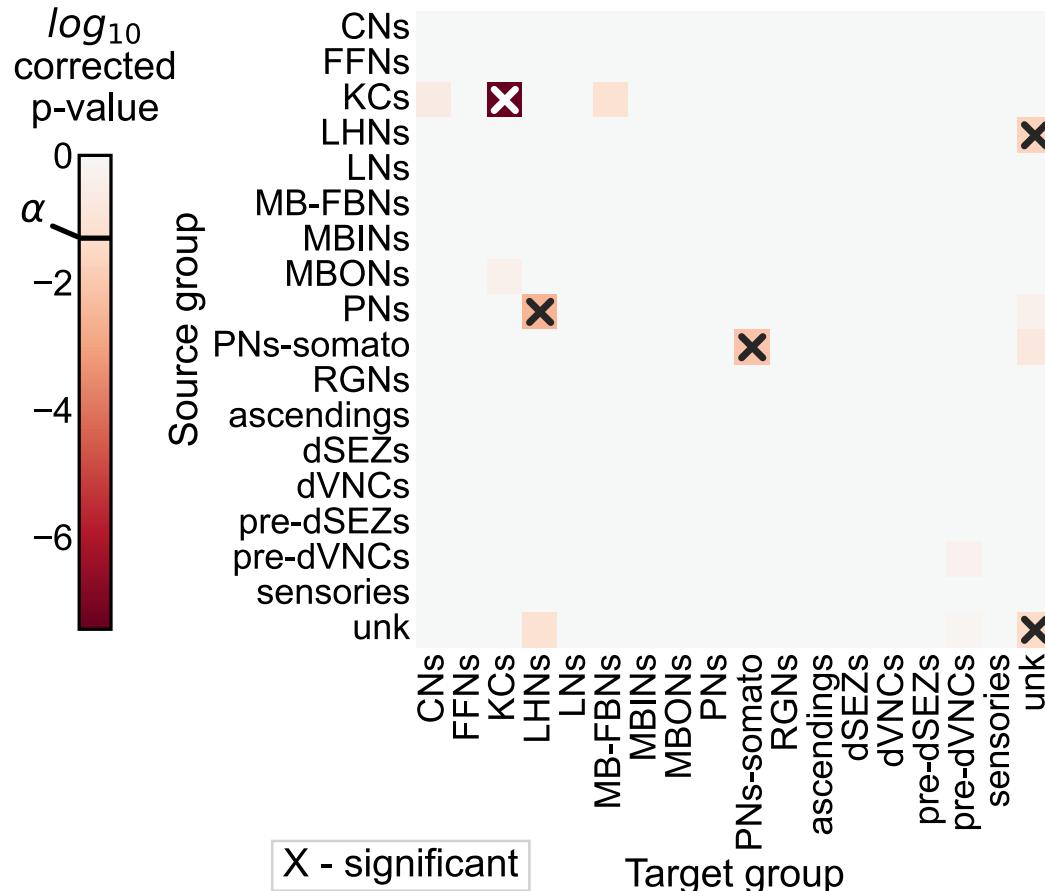
Combine p-values for overall test



$$H_0: \hat{B}^{(L)} = \hat{B}^{(R)}$$
$$H_A: \hat{B}^{(L)} \neq \hat{B}^{(R)}$$

Detect a difference in group connection probabilities

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- After multiple comparison, find 5 group-to-group connections which are significantly

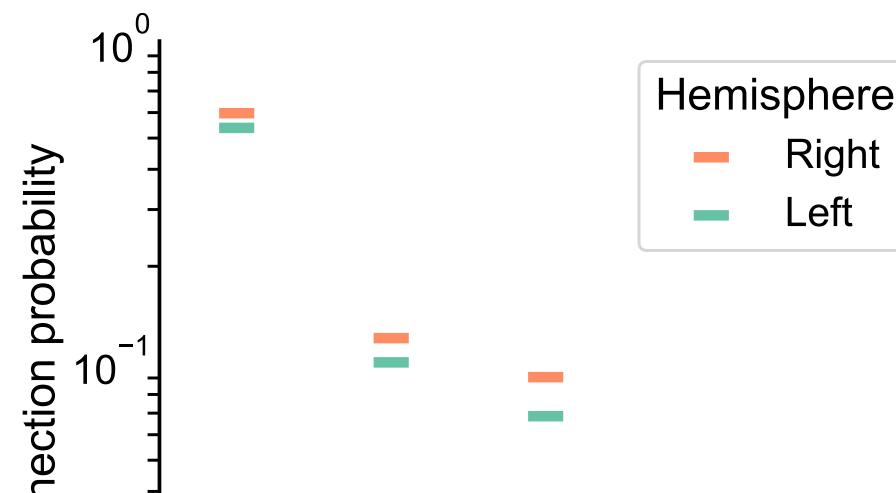
Should we be surprised?

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- Already saw that even the overall densities were different
- For all significant comparisons, probabilities on the right hemisphere were higher
- Maybe the right is just a "scaled up" version of the left?
 - $H_0 : B^{(L)} = cB^{(R)}$

where c is a density-adjusting constant, $\frac{p^{(L)}}{p^{(R)}}$

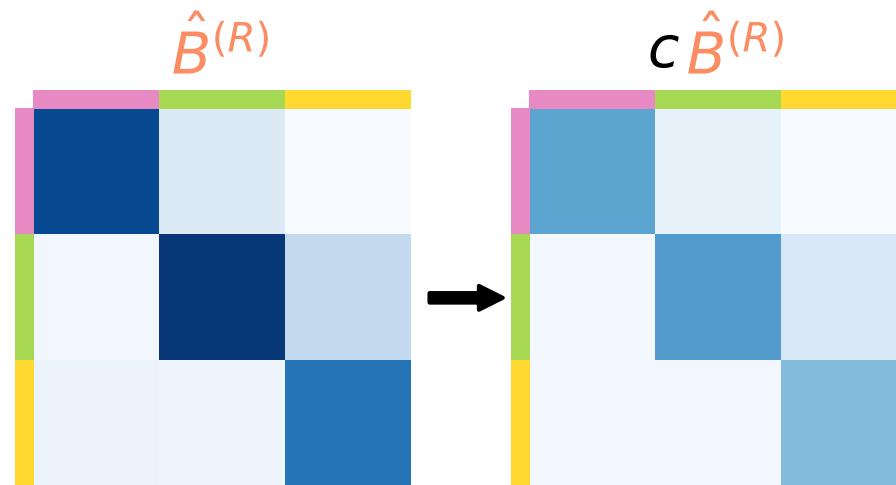
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After adjusting for density, differences are in KCs

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Scale connection probabilities
to match densities



$$\begin{aligned} H_0: B^{(L)} &= cB^{(R)} \\ H_A: B^{(L)} &\neq cB^{(R)} \end{aligned}$$

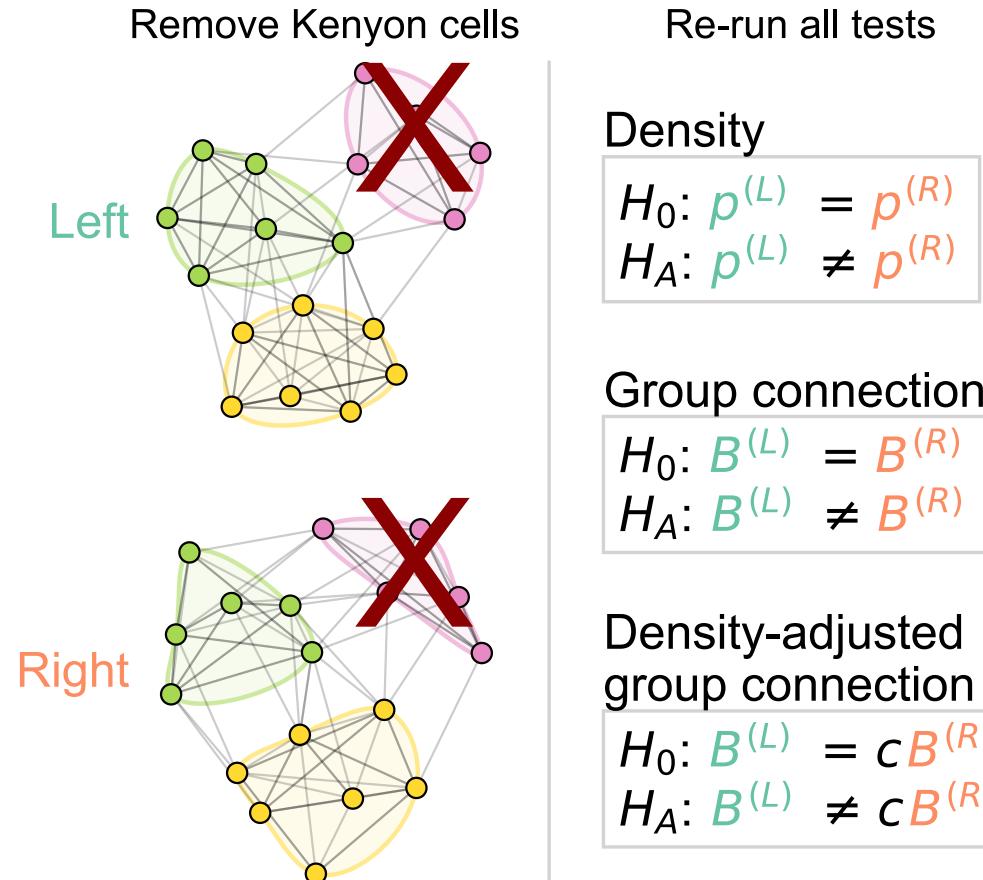
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\log_{10}
corrected
p-value

CNs
FFNs
KCs

When we remove KCs...

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- Density test:

To sum up...

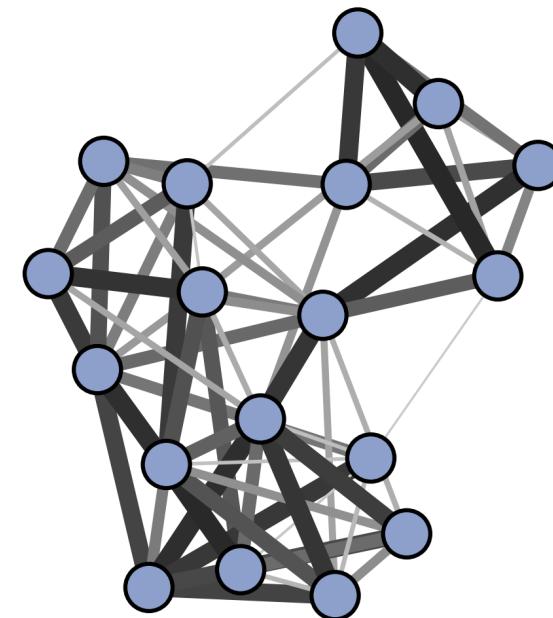
Model	H_0 (vs. $H_A \neq$)	KCs	p-value	Interpretation
ER	$p^{(L)} = p^{(R)}$	+	$< 10^{-23}$	Reject densities the same
SBM	$B^{(L)} = B^{(R)}$	+	$< 10^{-7}$	Reject group connection probabilities the same
aSBM	$B^{(L)} = cB^{(R)}$	+	≈ 0.002	Reject above even after accounting for density
ER	$p^{(L)} = p^{(R)}$	-	$< 10^{-26}$	Reject densities the same (w/o KCs)
SBM	$B^{(L)} = B^{(R)}$	-	≈ 0.003	Reject group connection probabilities the same (w/o KCs)
aSBM	$B^{(L)} = cB^{(R)}$	-	≈ 0.43	Don't reject above after density adjustment (w/o KCs)

Examining the effect of edge weights

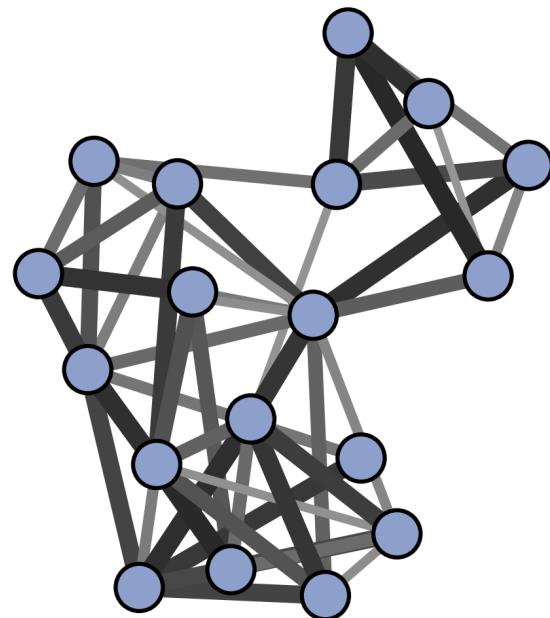
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Increasing edge weight threshold

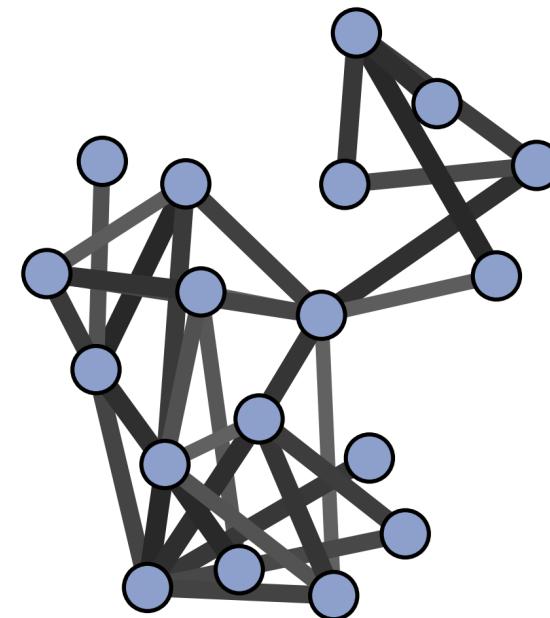
Left



3



3



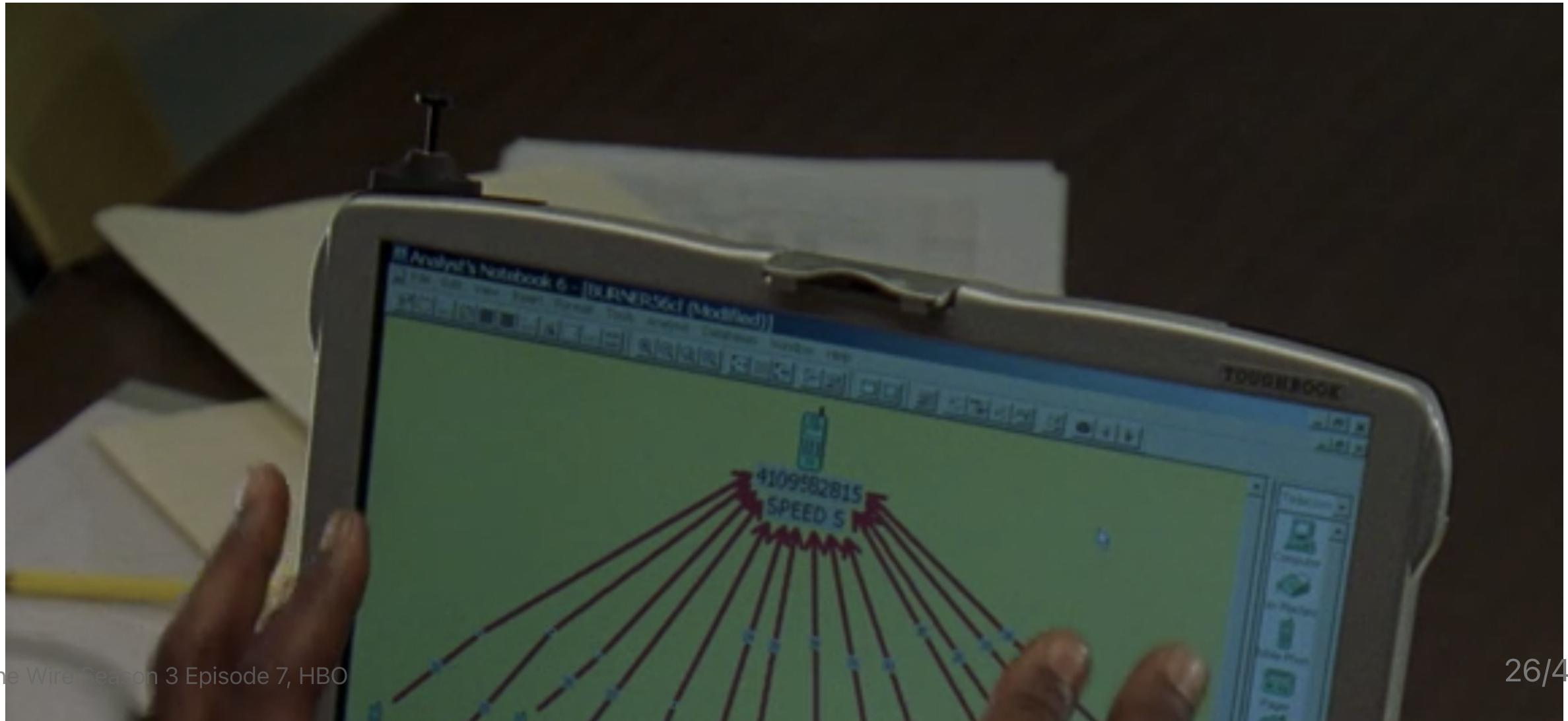
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Borun all

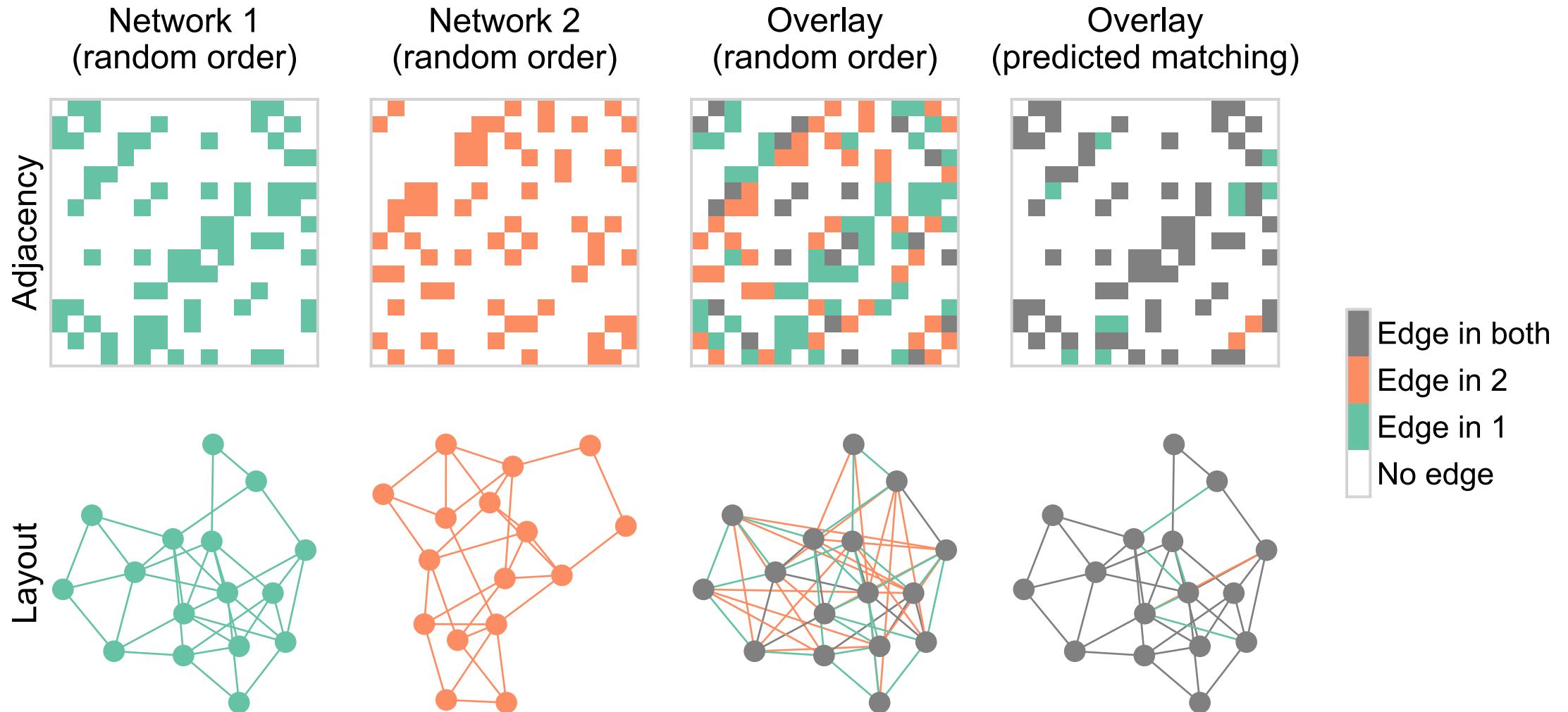
Matching neurons

Can we use networks structure to predict this pairing?

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What is graph matching?



How do we measure network overlap?

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$$\min_{P \in \mathcal{P}} \|A - \underbrace{PBP^T}_{\text{distance between adj. mats.}}\|_F^2$$

reordered B

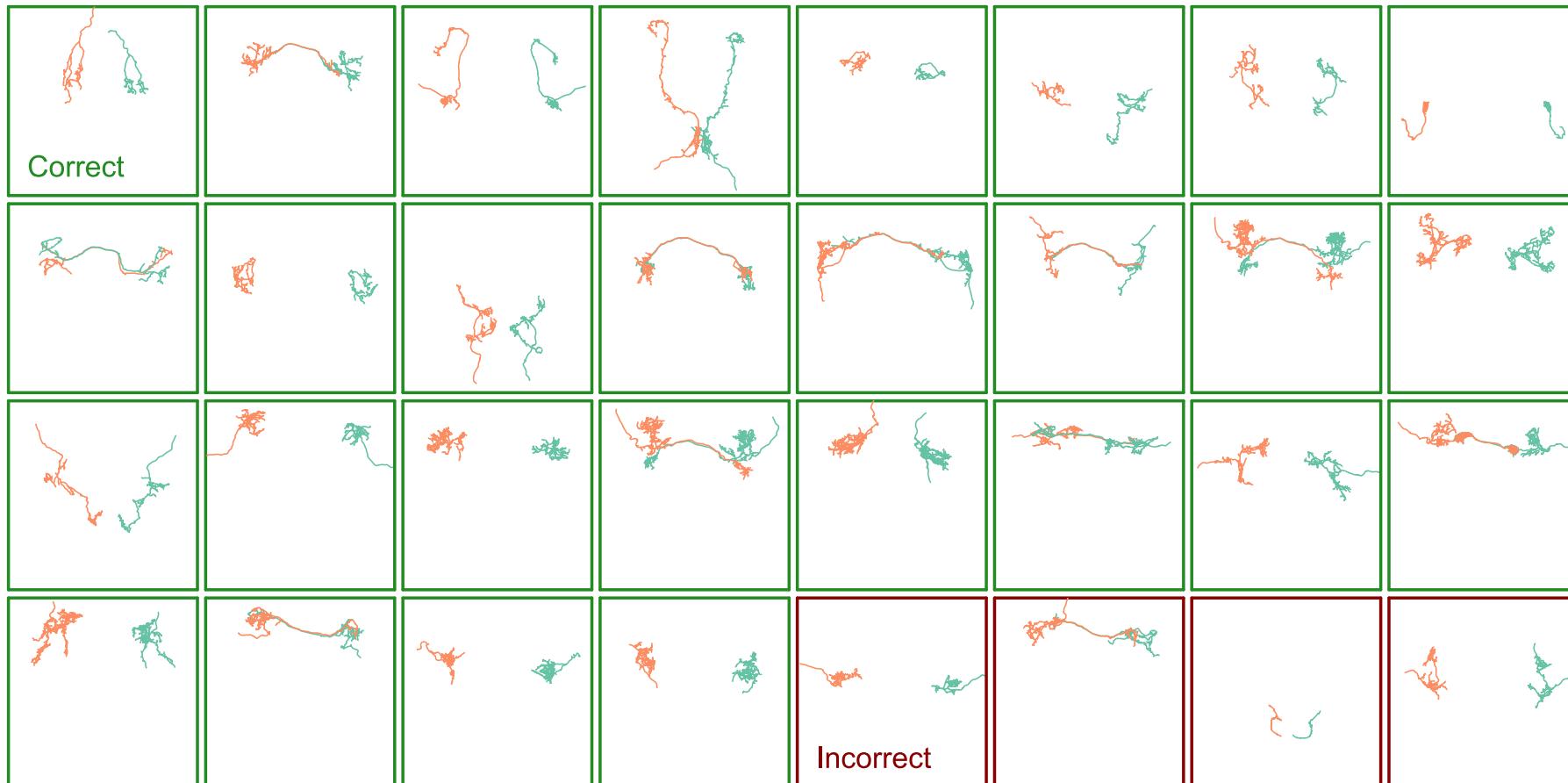
where \mathcal{P} is the set of permutation matrices

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- Measures the number of edge disagreements for unweighted networks,
- Norm of edge disagreements for weighted networks

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Matching (by connectivity only) performs fairly well



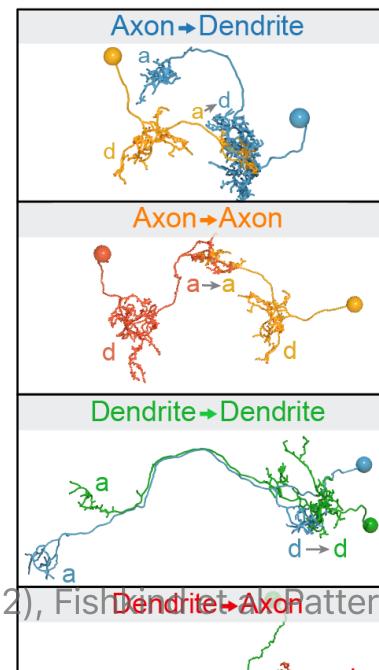
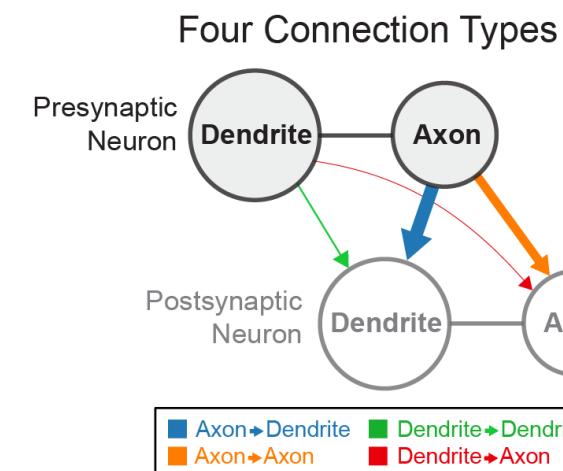
With "vanilla" graph matching: ~80% correct (according to expert annotator)

Many ways to try to improve on this...

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- Edge types allow for "multilayer" graph matching
- Partial knowledge of the matching (seeds)
- Morphology (e.g. NBLAST)

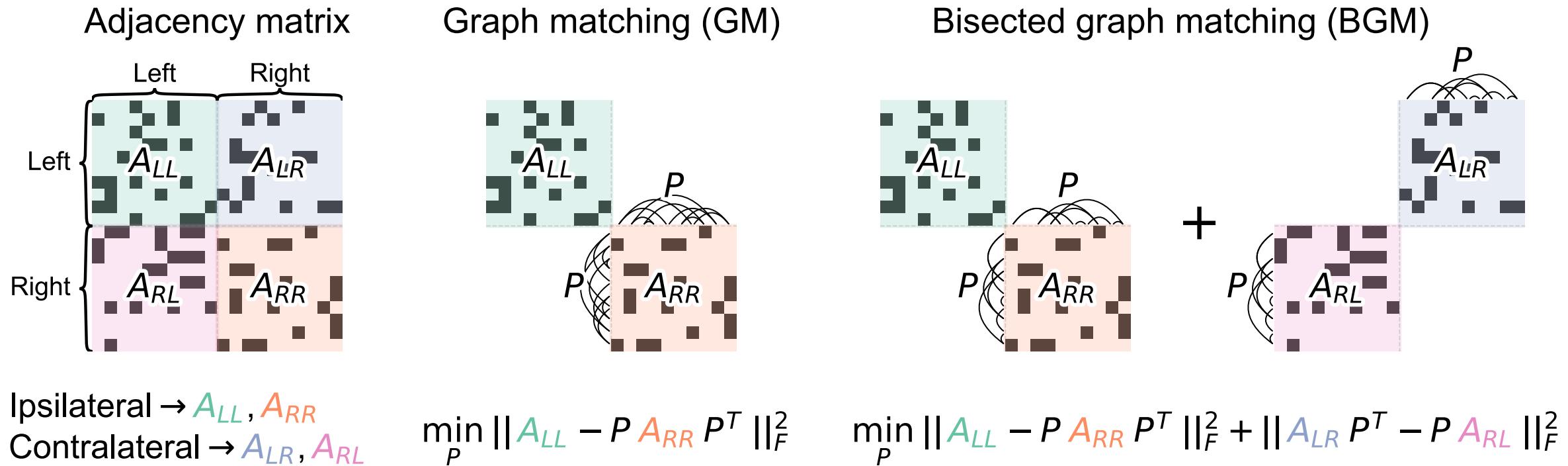
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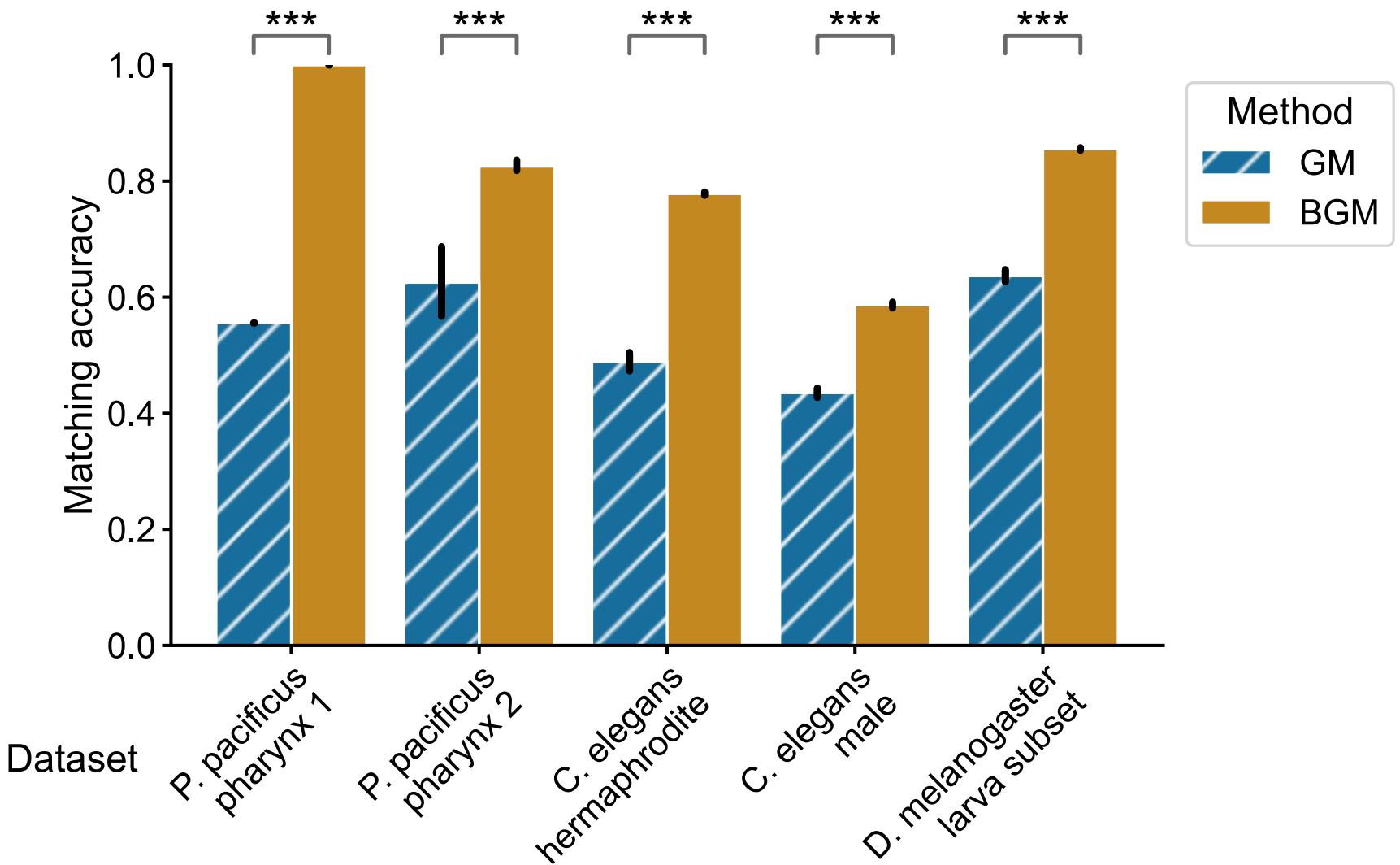
Thus far, we've not used the contralateral connections

These are about 1/3 of the edges in the brain!

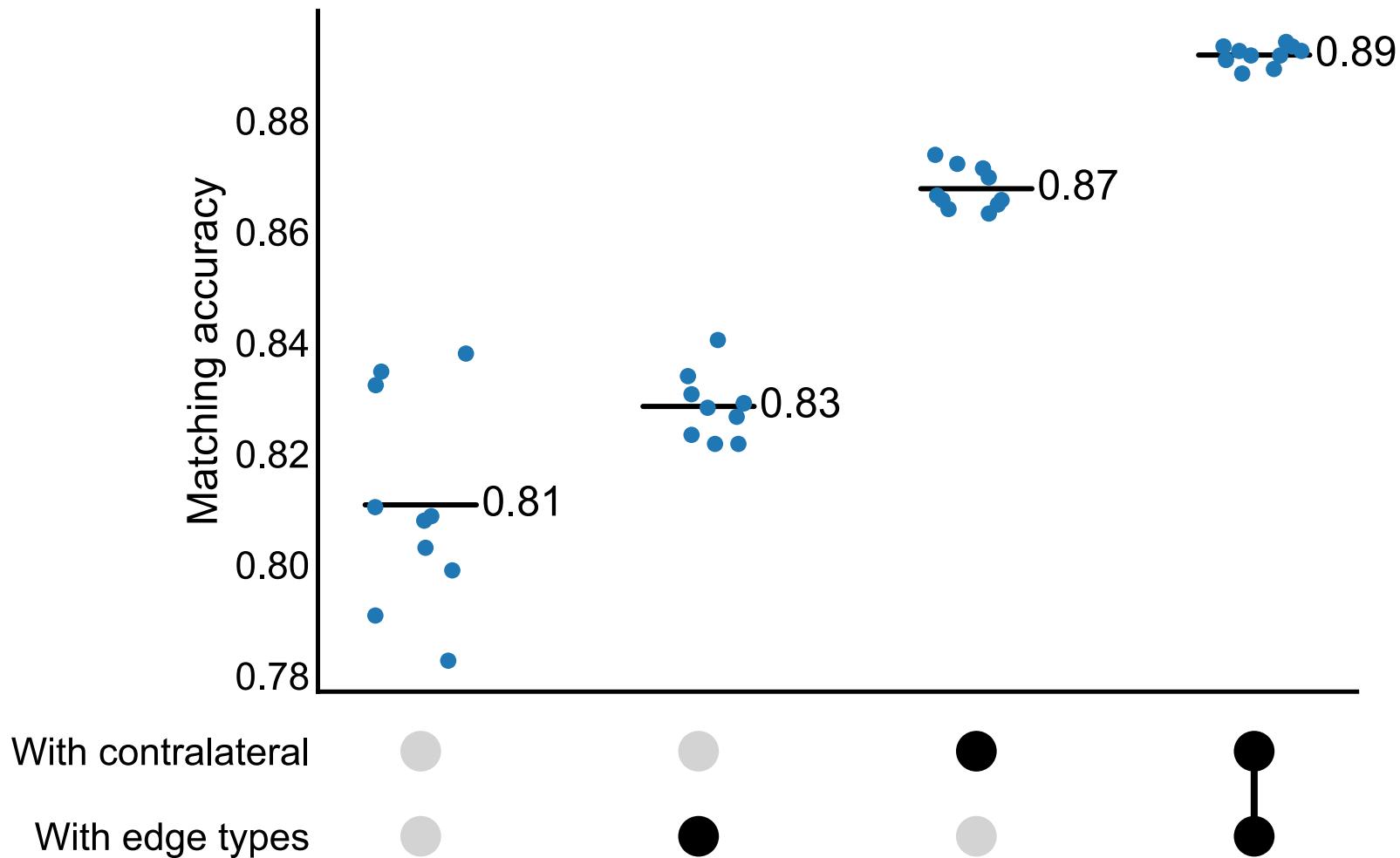
From graph matching to bisected graph matching



Contralateral connections are helpful!



Performance improvement on the full brain



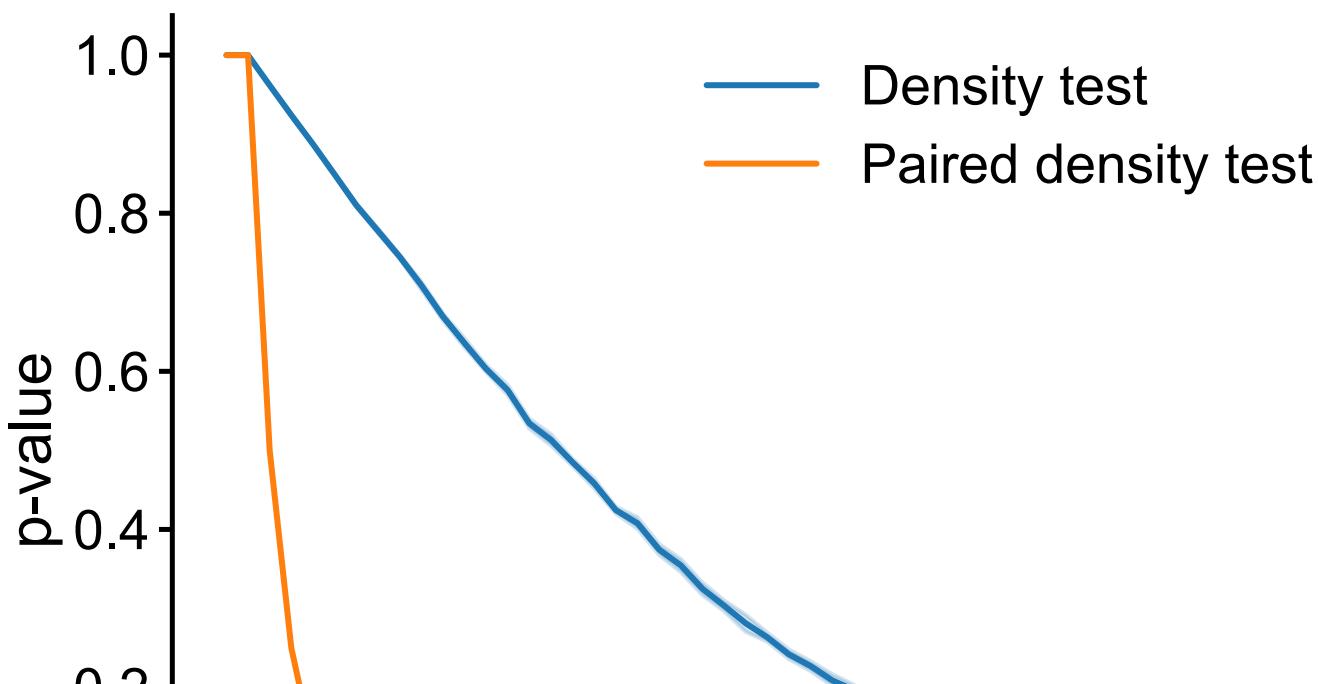
Extensions and ongoing work

Pairs facilitate more powerful tests

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- Generate an Erdos-Renyi network (A)
- Perturb a copy of it (B)
- Test for differences between A and B

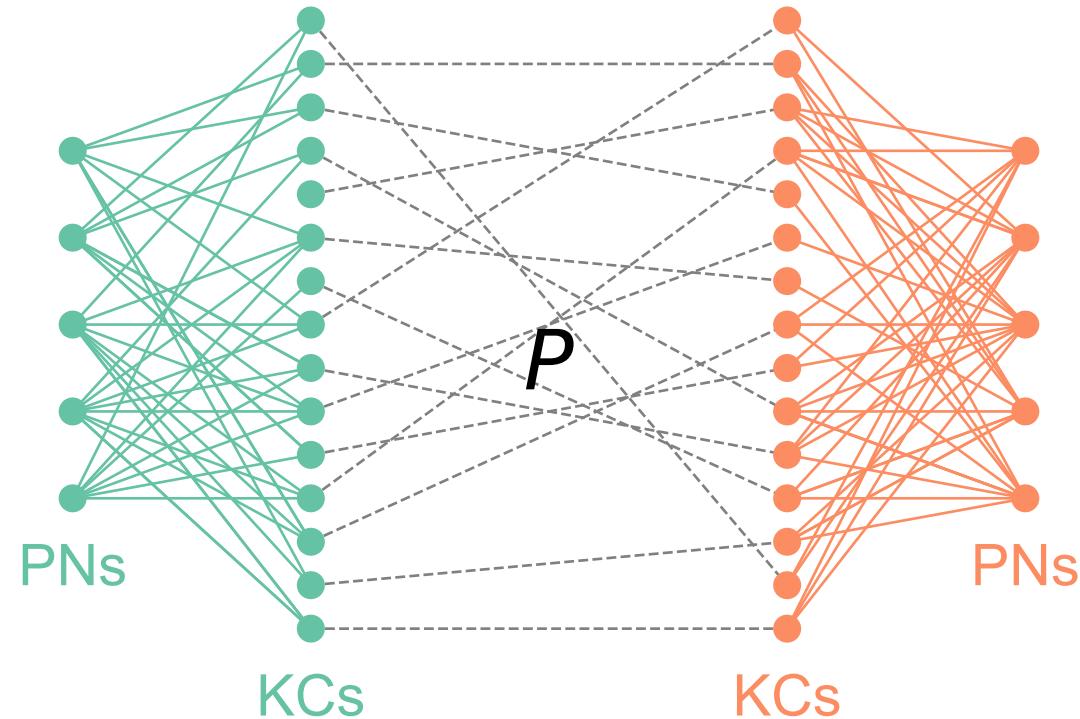
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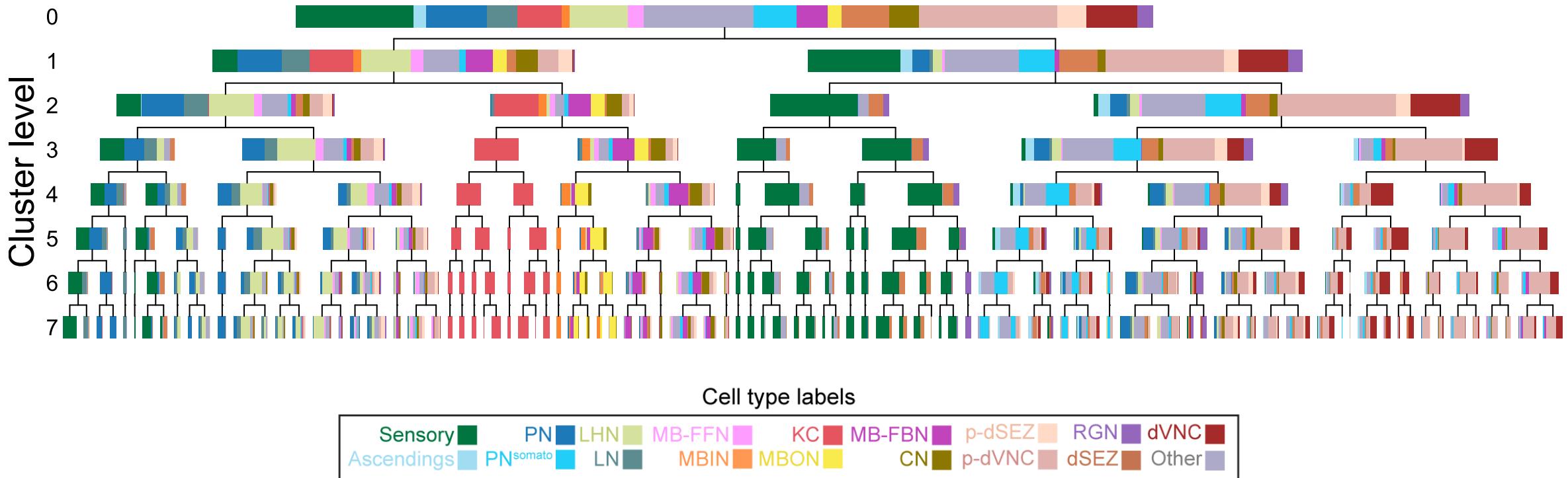
Testing for "stereotypy" at the edge level

Is matching stronger than expected under some model of independent networks?

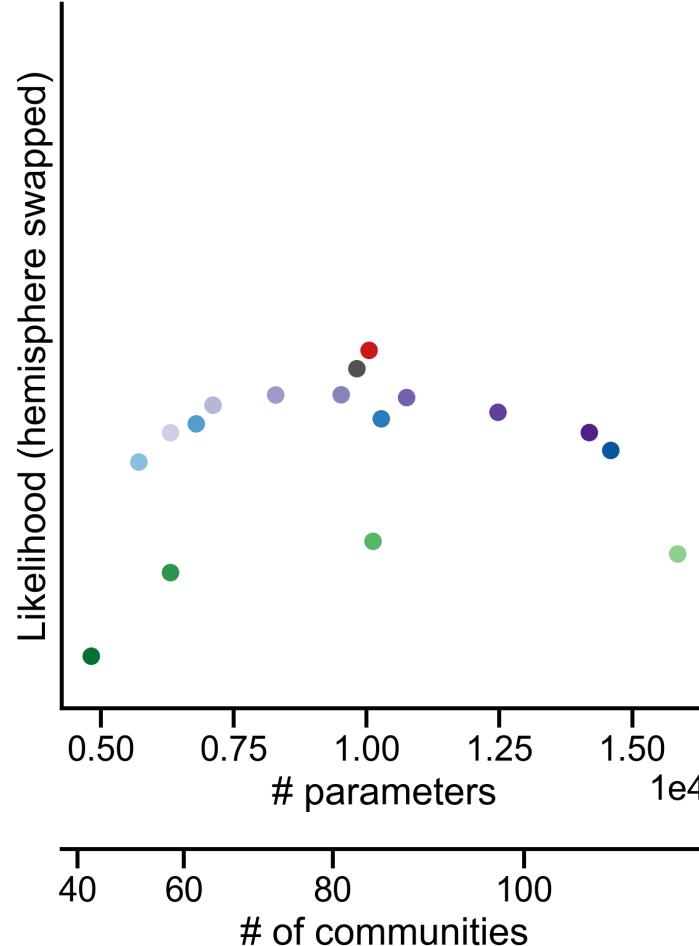
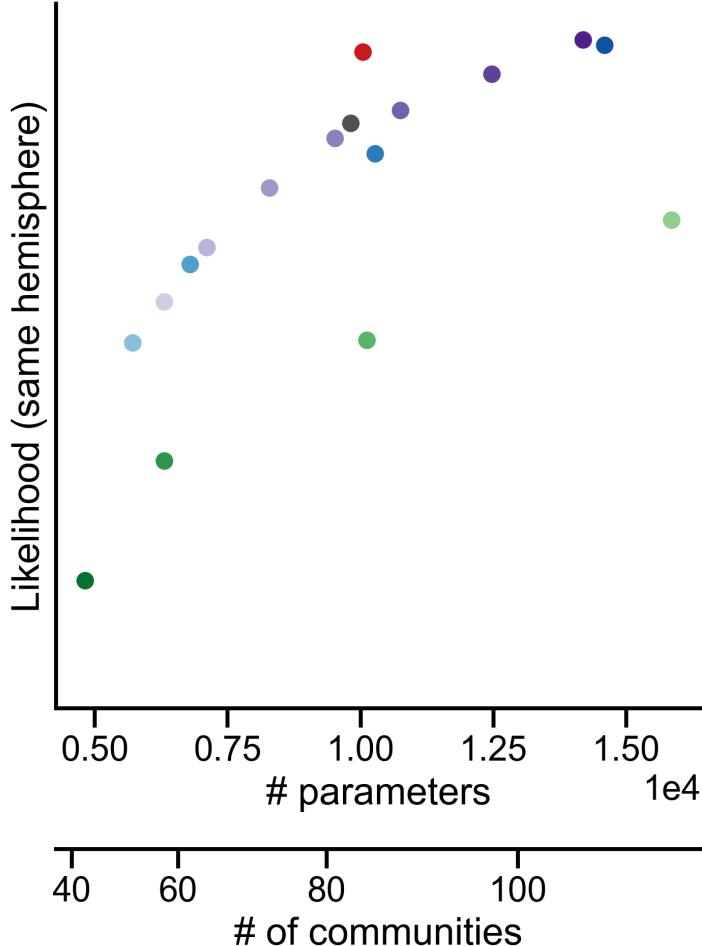
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Hierarchical clustering of neurons by connectivity

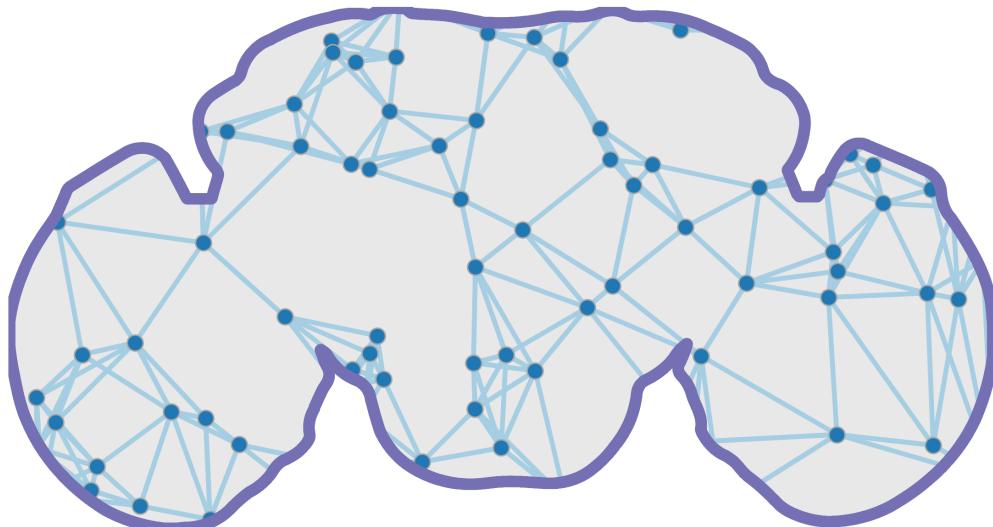
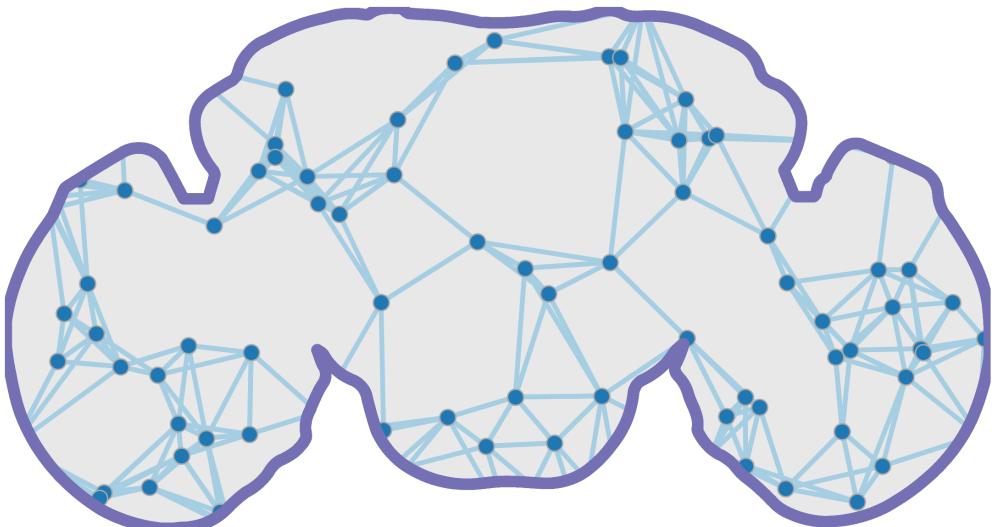


Using pairs and models to evaluate cell type groupings



Summary

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- Model-based network comparison enables testing (and refining) hypotheses about connectomes
 - We proposed a few tests, but just the beginning!

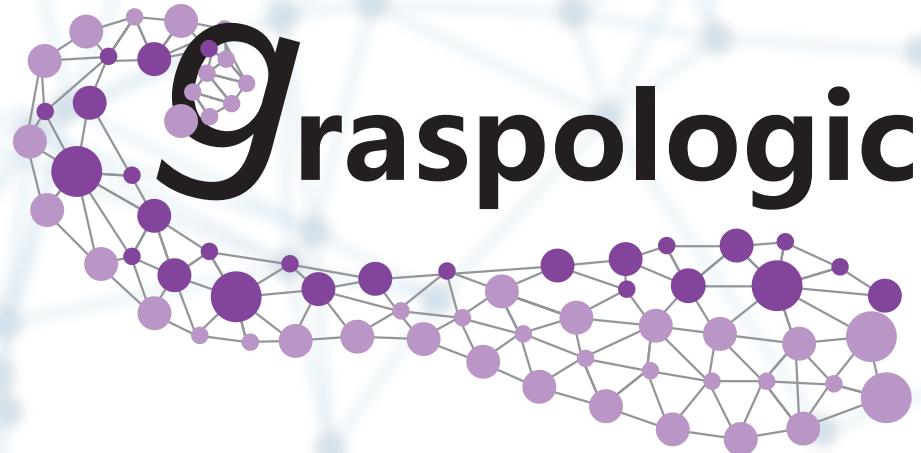
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How to use these (and other) tools?

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graspologic

github.com/microsoft/graspologic



downloads 139k

Stars 260

contributors 49

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Model-based testing

Acknowledgements

Team

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Michael Winding

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Mike Powell

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Questions?

Slides:

tinyurl.com/princeton-bilarva

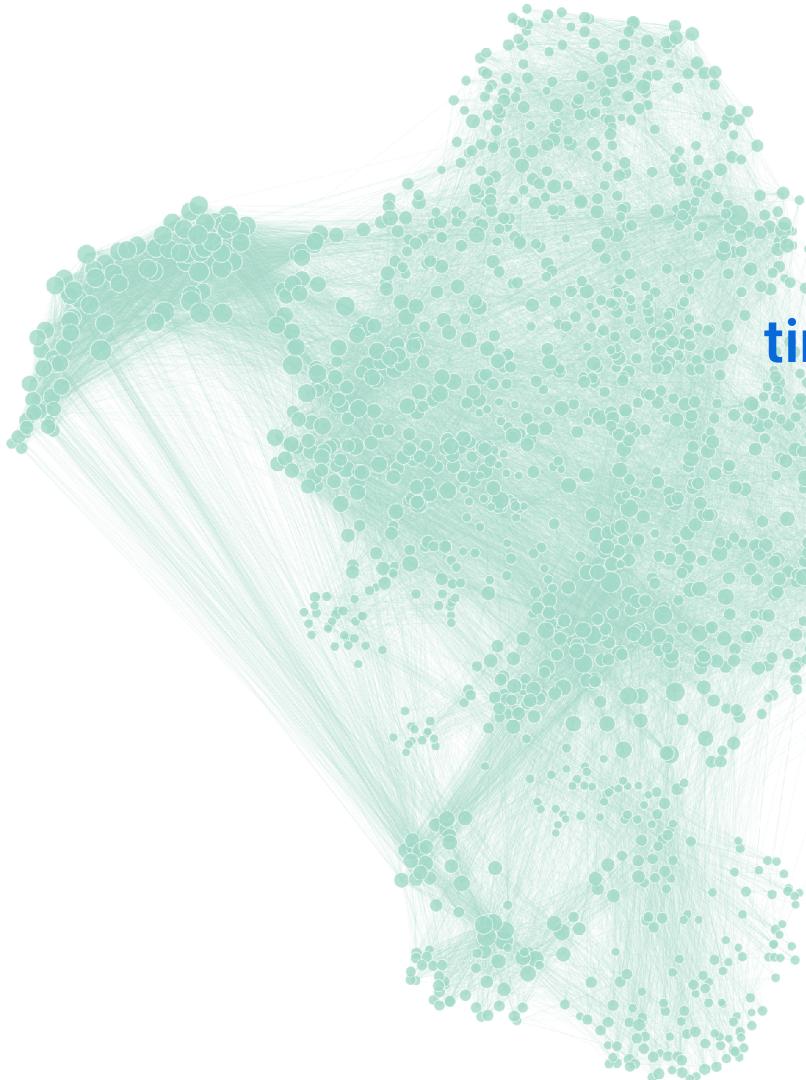
Benjamin D. Pedigo

✉ bpedigo@jhu.edu

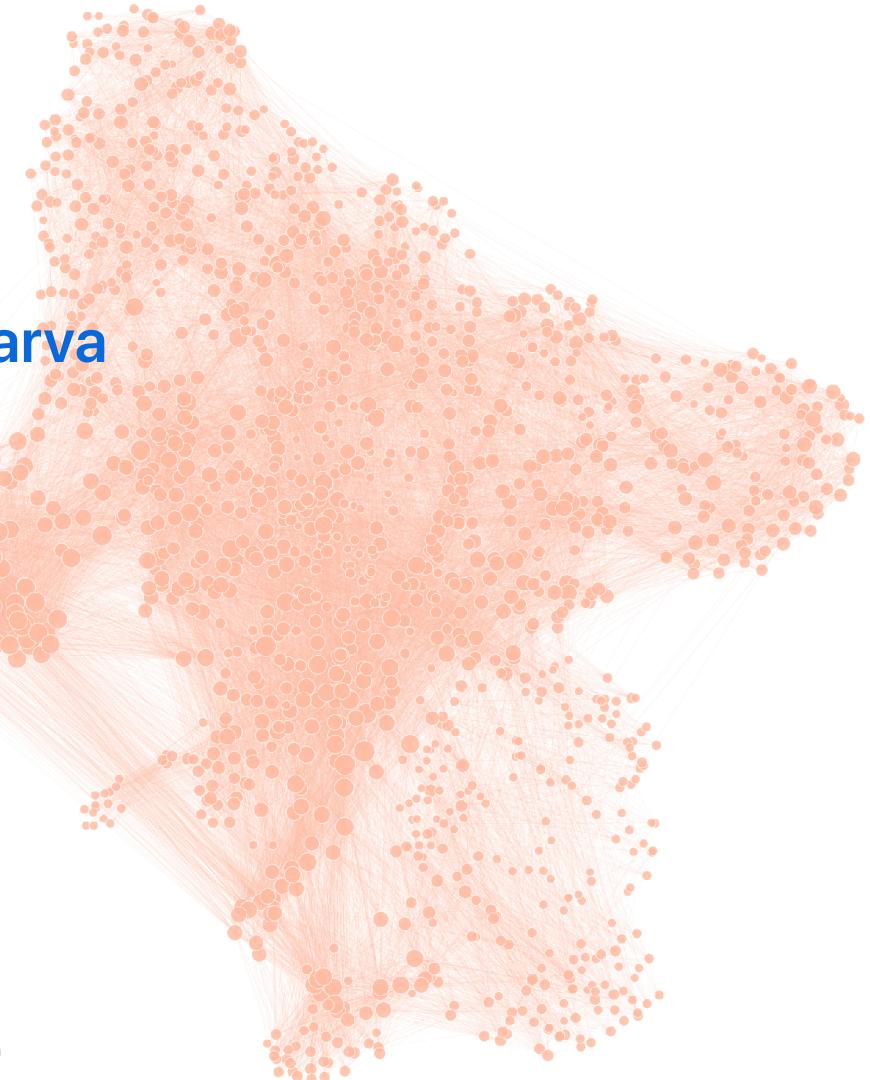
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Left



Right