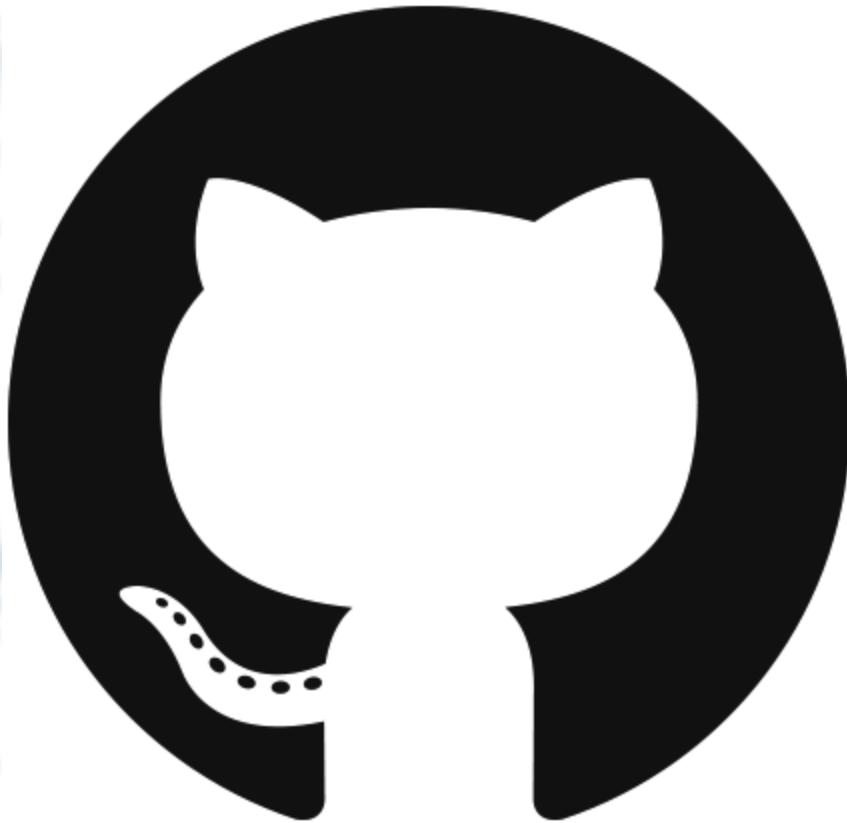


bpedigo@jhu.edu



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

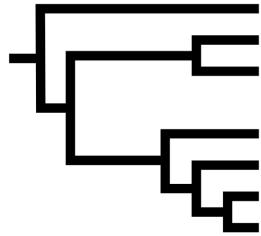


Connectomics is useful...

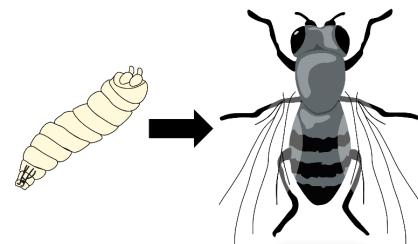
TODO: (3) plot of "connectome prevalence over time"

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

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



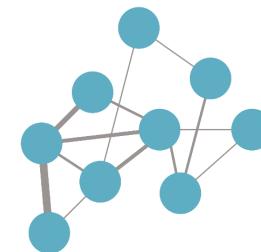
Evolution



Development



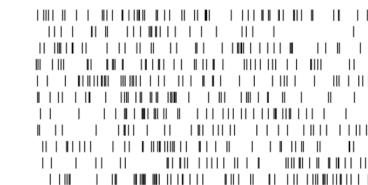
Genome



Connectome



Behavior



Activity

Connectome ↔ memory

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

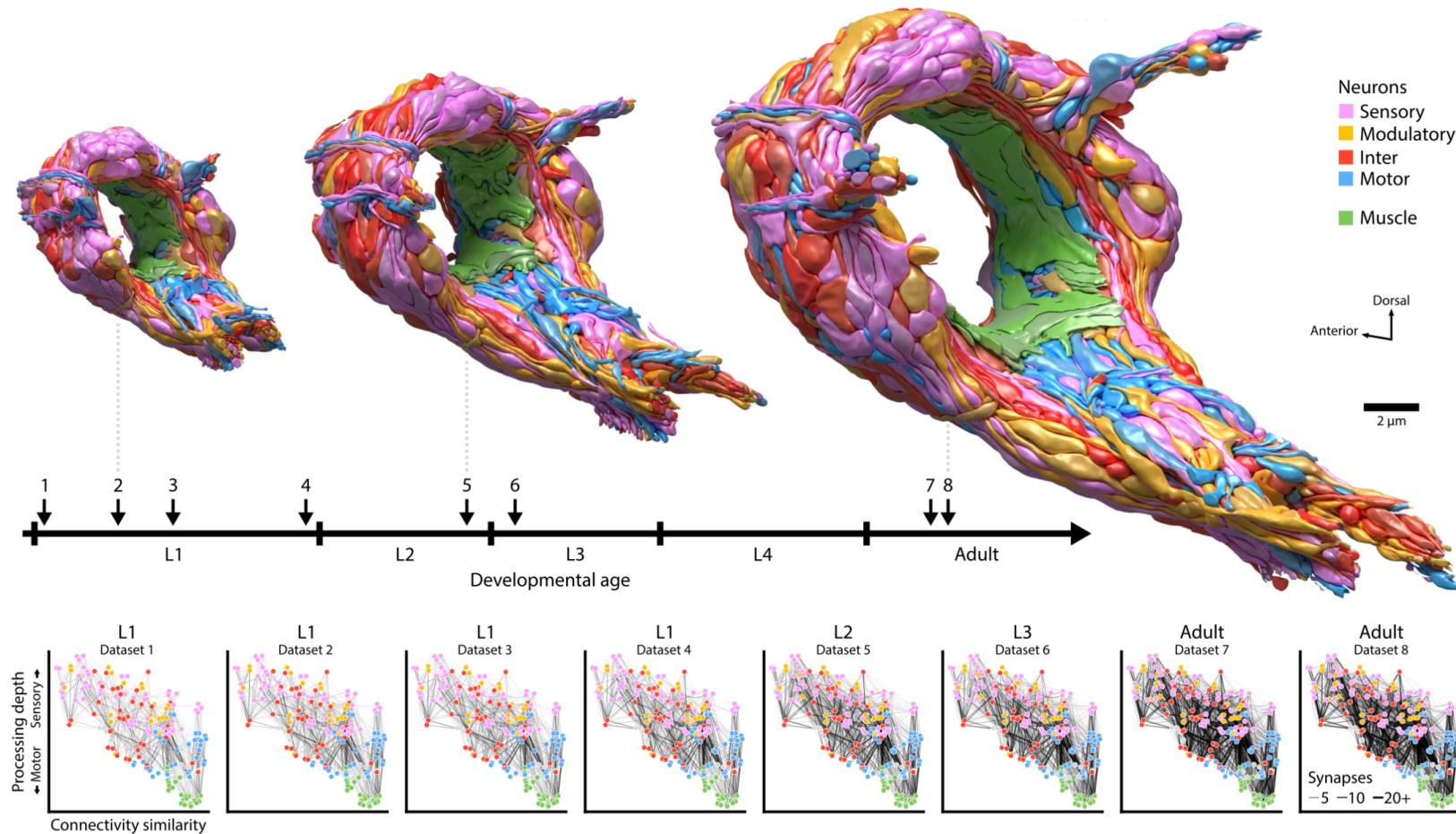
Emphasis added

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

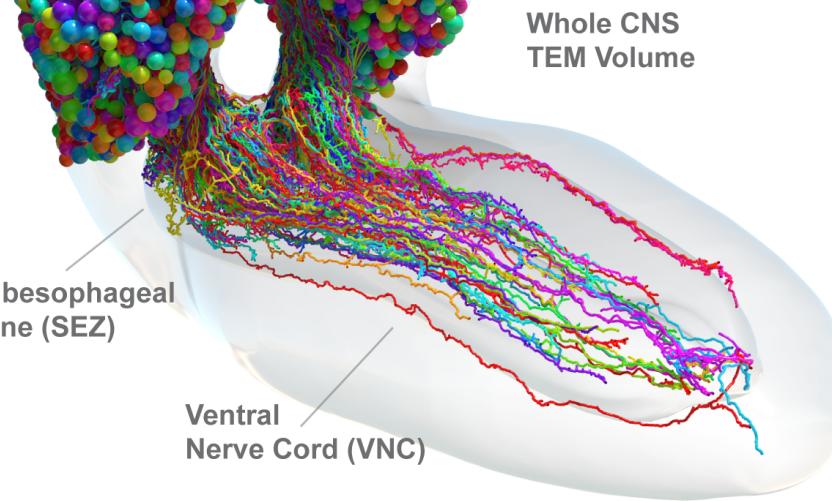


But it is methodologically hard to compare connectomes!

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

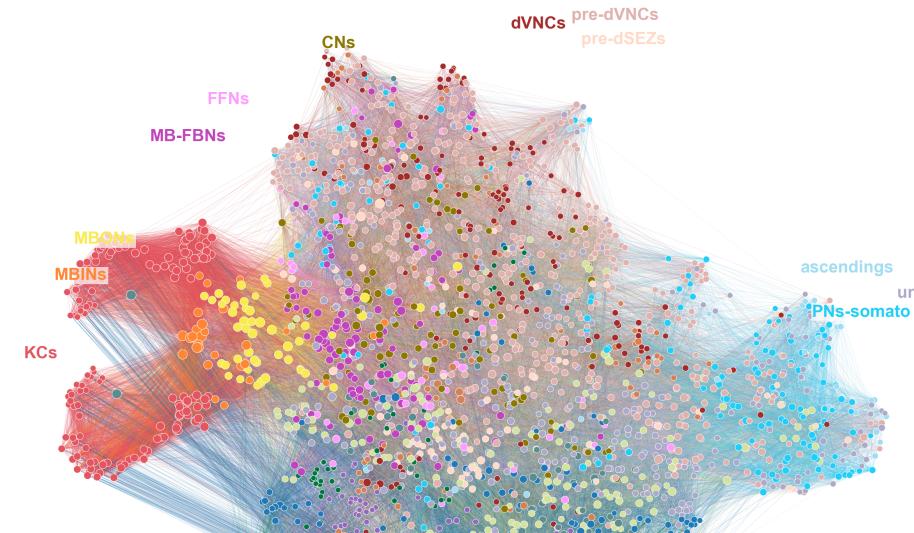
Outline for today

- 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



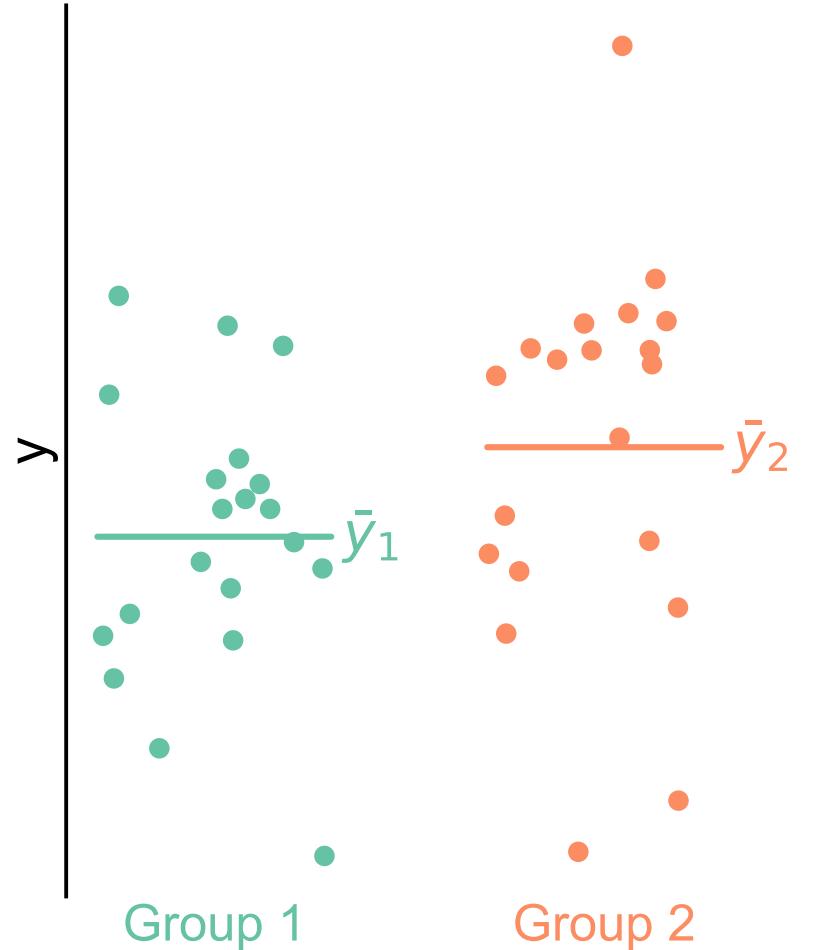
~3k neurons, ~550K synapses
Both hemispheres

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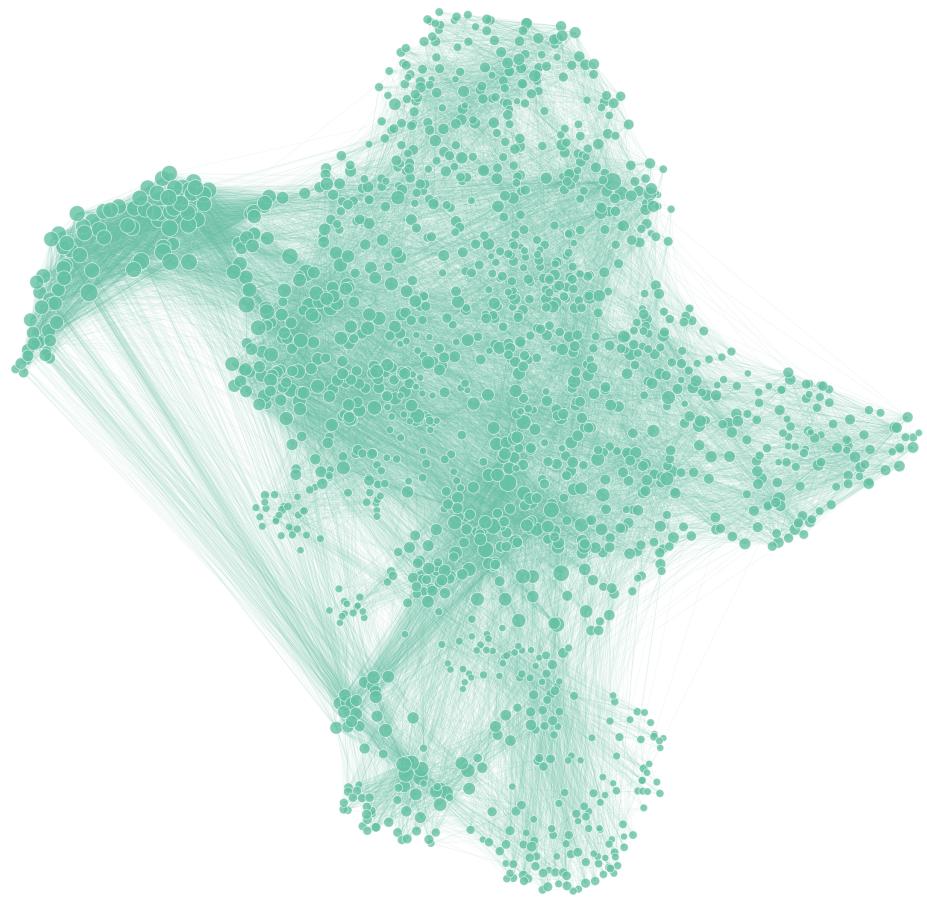
Are the ` left `
`and right `
`sides of this connectome <p> </p> different?`

<div class="columns"> <div>

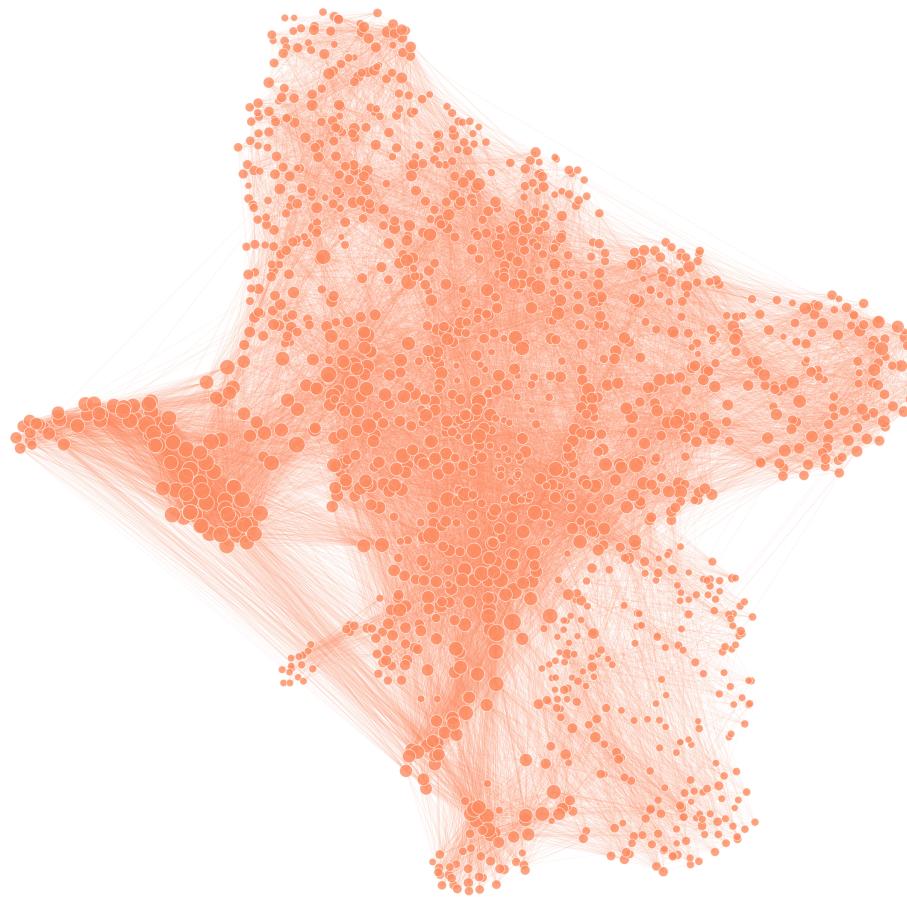


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- Known as two-sample testing
- $Y^{(1)} \sim F^{(1)}$, $Y^{(2)} \sim F^{(2)}$
- $H_0 : F^{(1)} = F^{(2)}$



Left



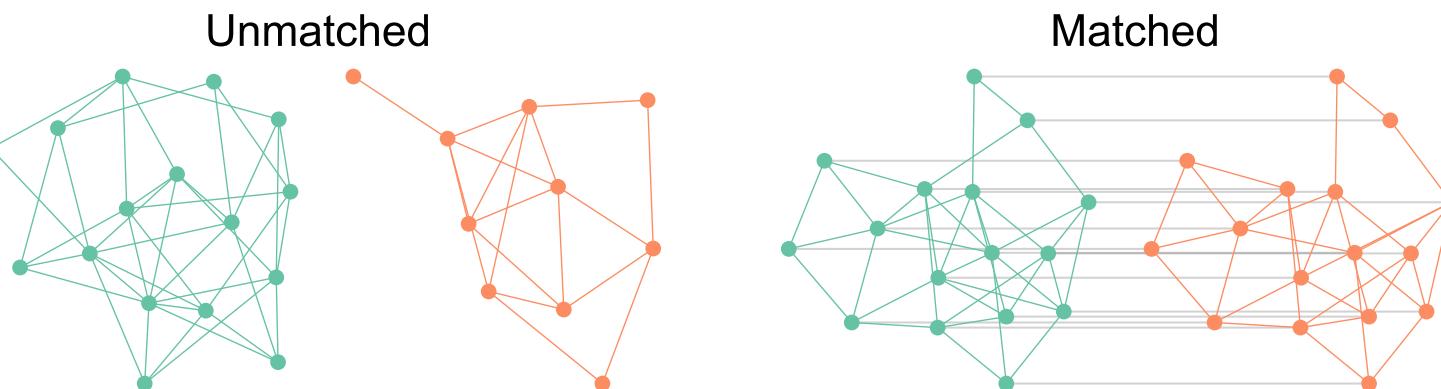
Right

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- Want a two-network-sample test!
- $A^{(L)} \sim F^{(L)}$, $A^{(R)} \sim F^{(R)}$

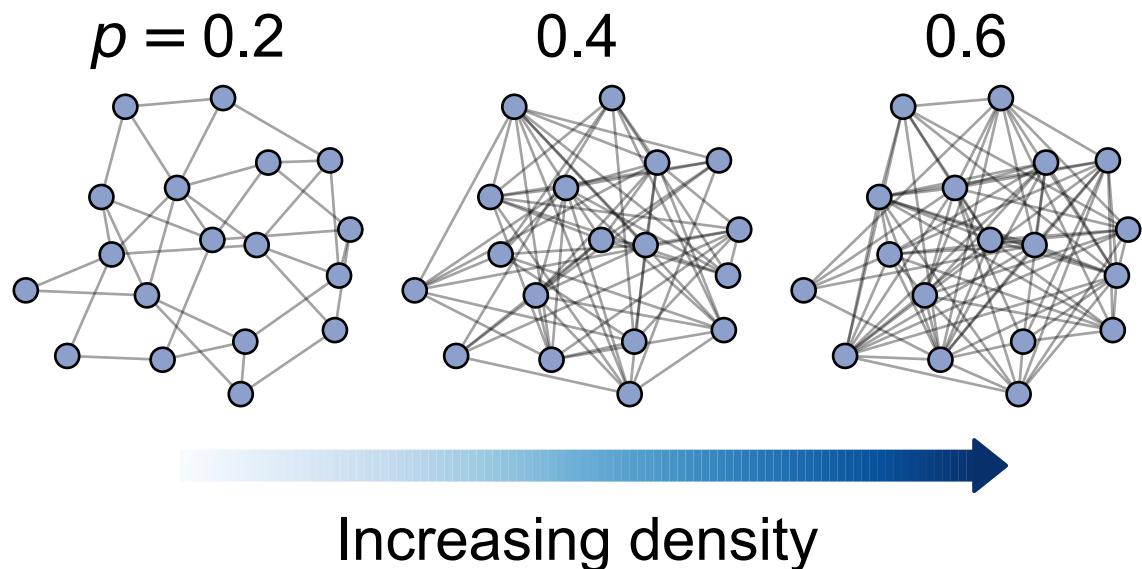
Assumptions

- 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

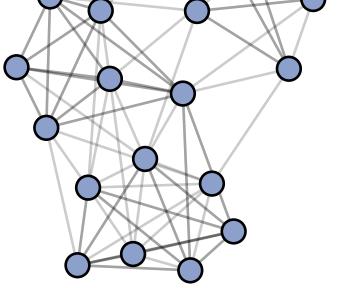


Erdos-Renyi model

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

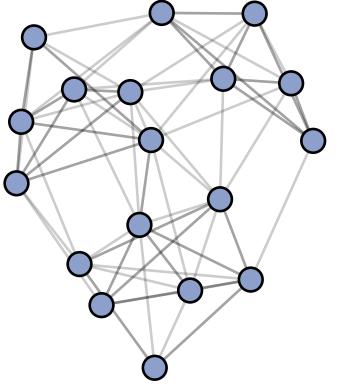


Left



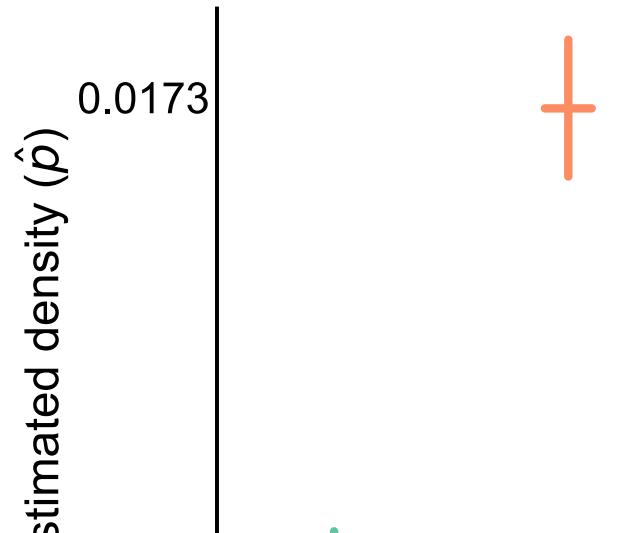
$$p = \frac{\# \text{ edges}}{\# \text{ potential edges}}$$

Right



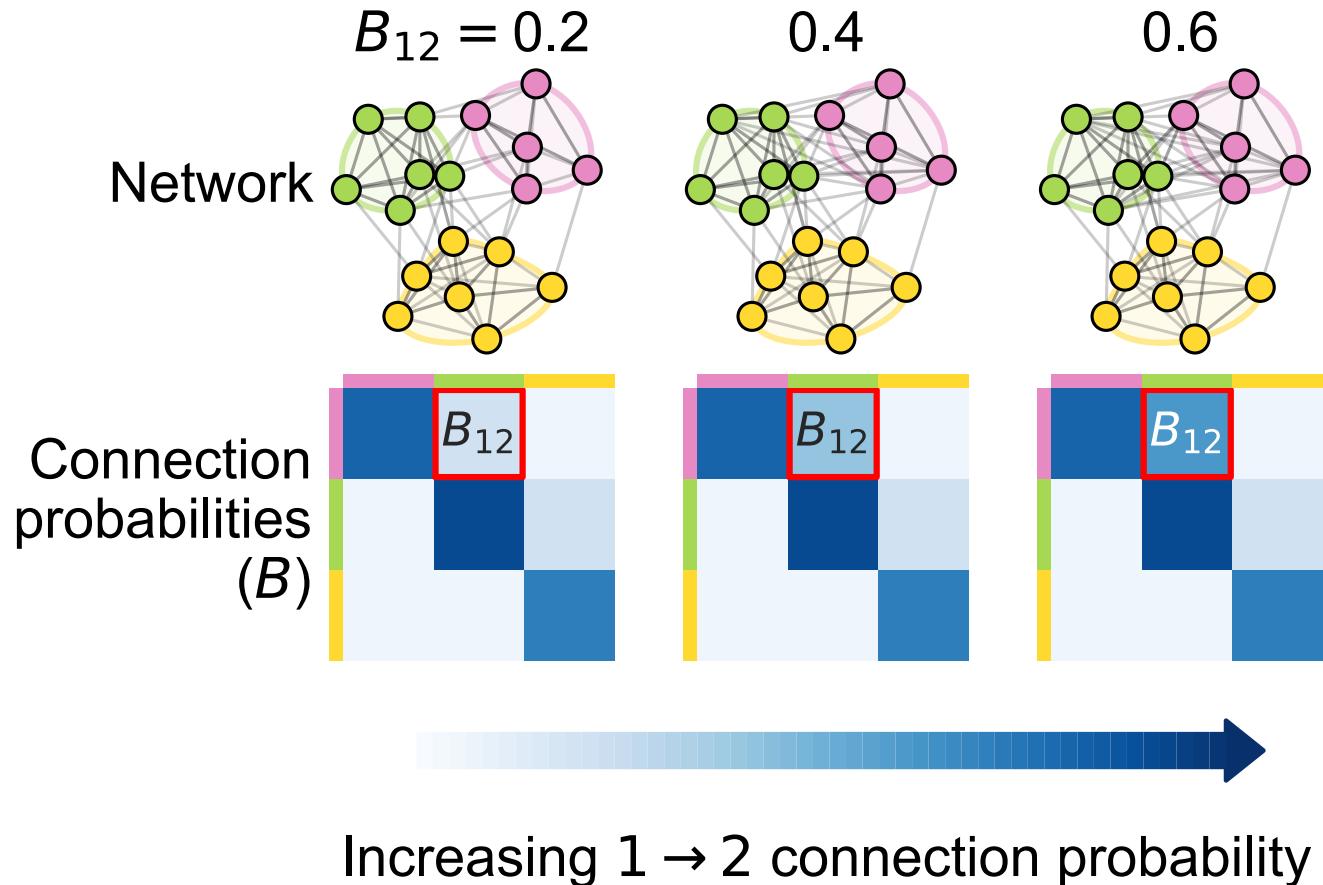
$$\begin{aligned} H_0: p^{(L)} &= p^{(R)} \\ H_A: p^{(L)} &\neq p^{(R)} \end{aligned}$$

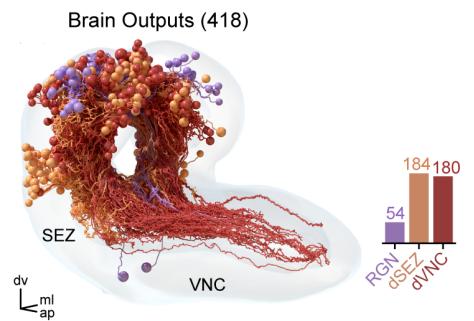
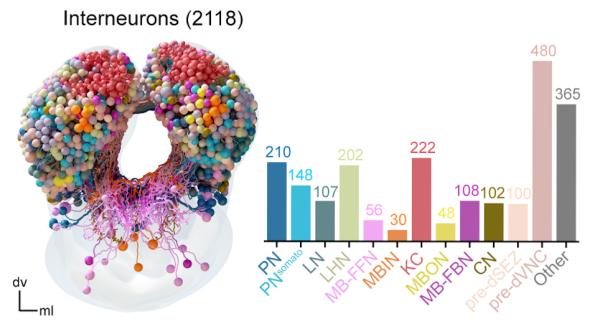
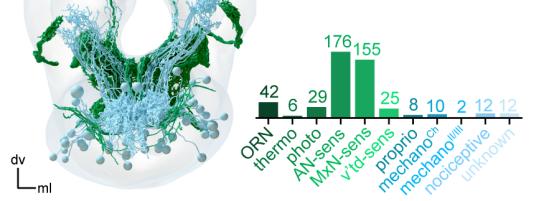
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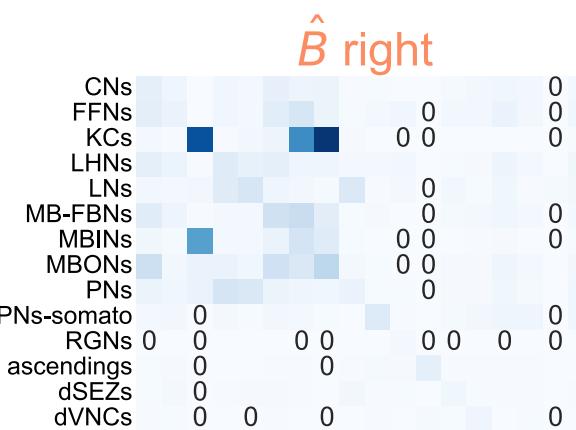
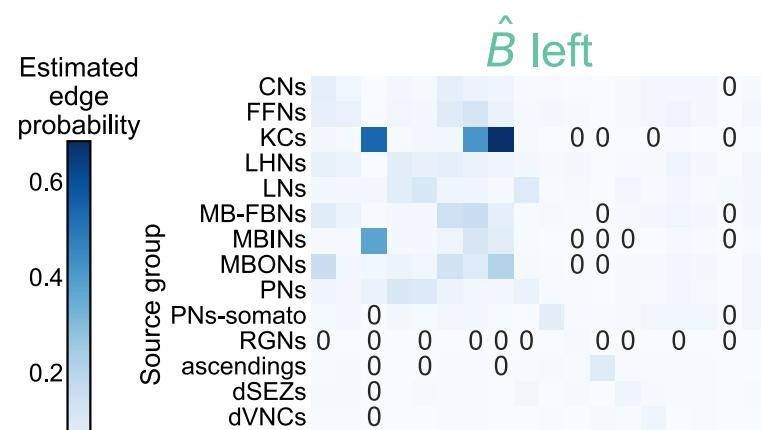
Stochastic block model

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



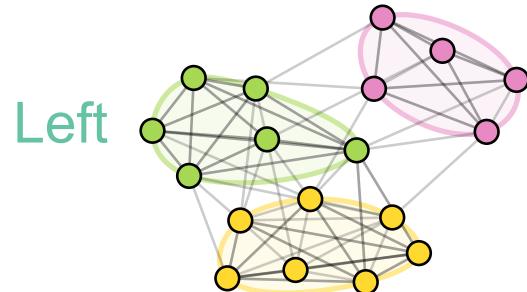


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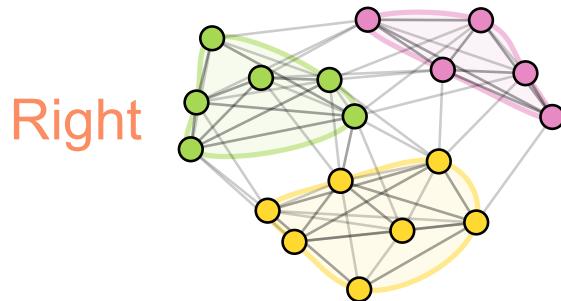


Group-based testing

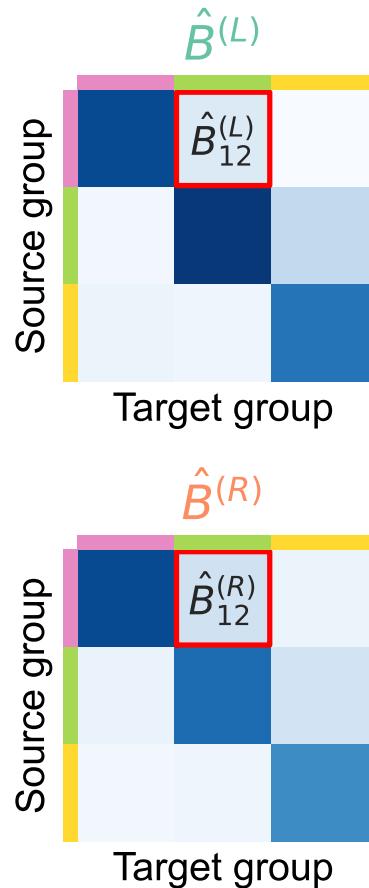
Group neurons



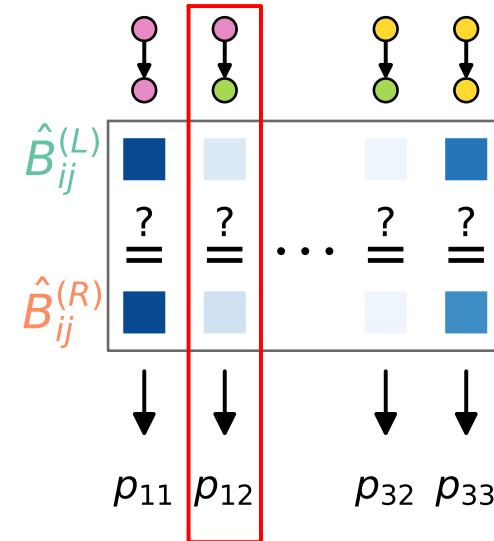
Right



Estimate group connection probabilities

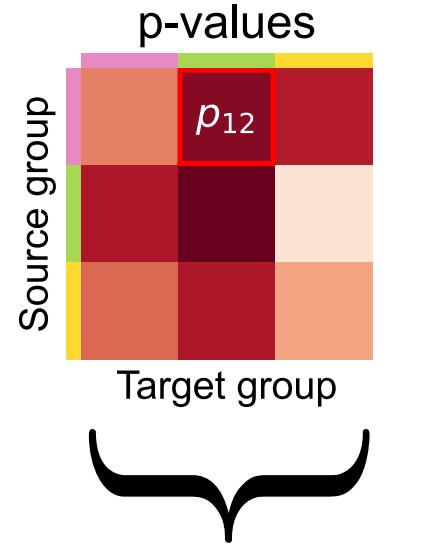


Compare probabilities, compute p-values



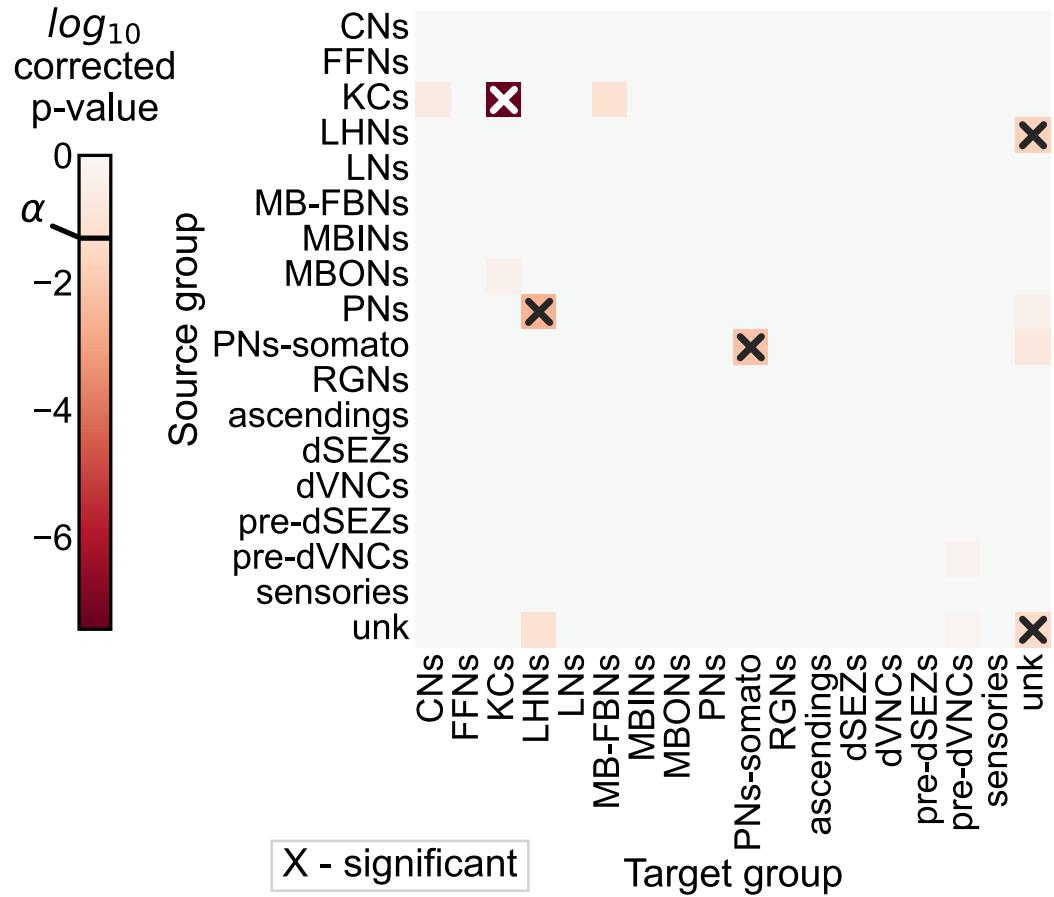
$$\begin{aligned} H_0: B_{ij}^{(L)} &= B_{ij}^{(R)} \\ H_A: B_{ij}^{(L)} &\neq B_{ij}^{(R)} \end{aligned}$$

Combine p-values for overall test



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

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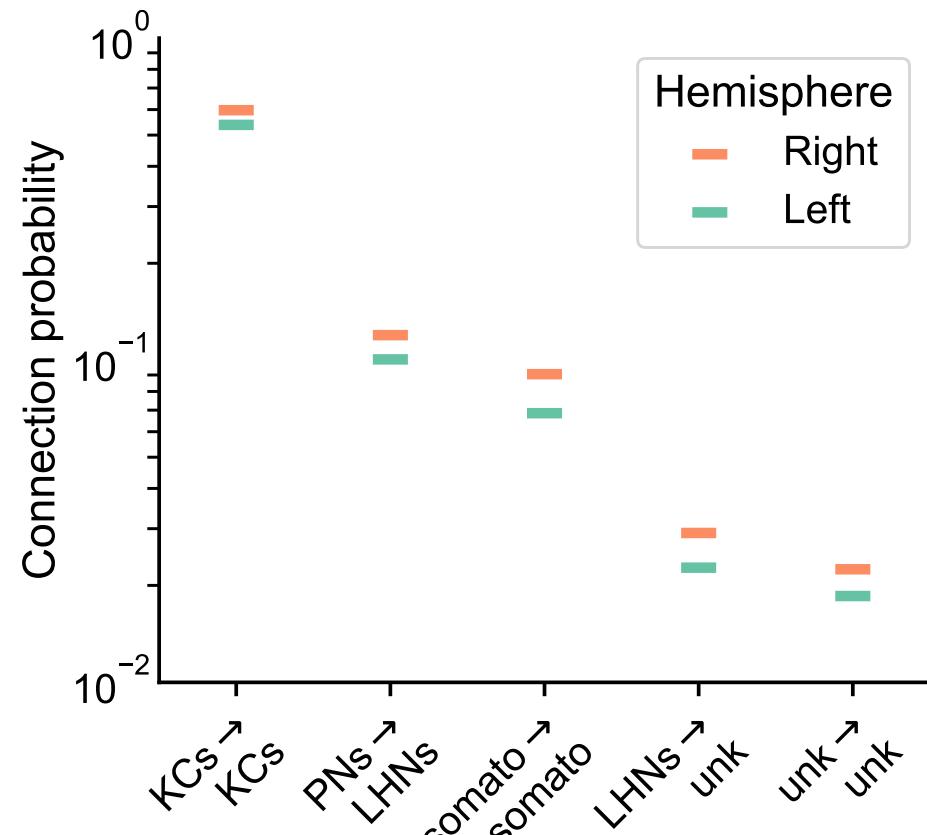
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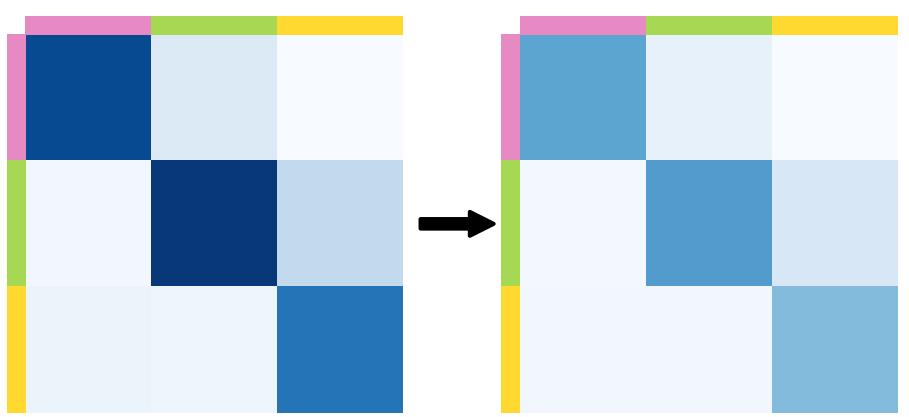
- After multiple comparison, find 5 group-to-group connections which are significantly different
- Combine (uncorrected) p-values (like a meta-analysis), leads to p-value for overall

- 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, $\frac{p^{(L)}}{p^{(R)}}$

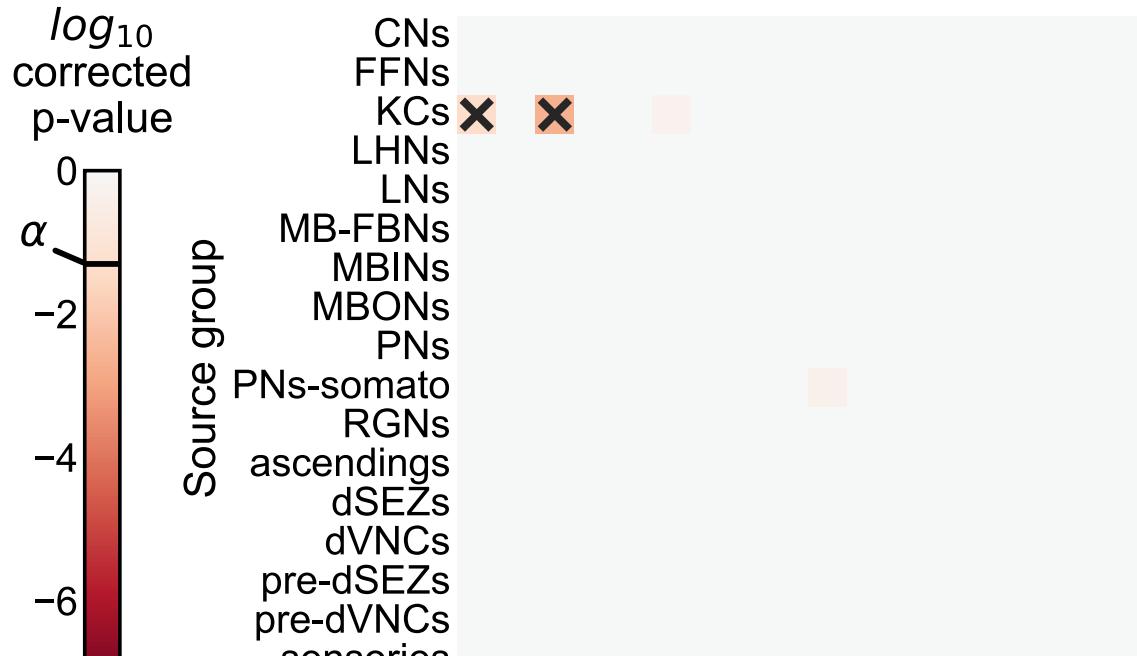
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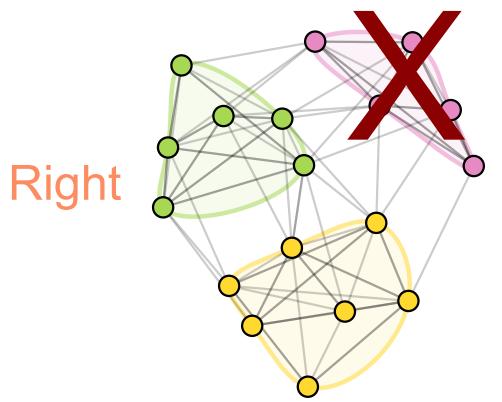


$$\begin{aligned}
 H_0: B^{(L)} &= cB^{(R)} \\
 H_A: B^{(L)} &\neq cB^{(R)}
 \end{aligned}$$

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Remove Kenyon cells



Re-run all tests

Density

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

Group connection

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

Density-adjusted
group connection

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

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- Density test:

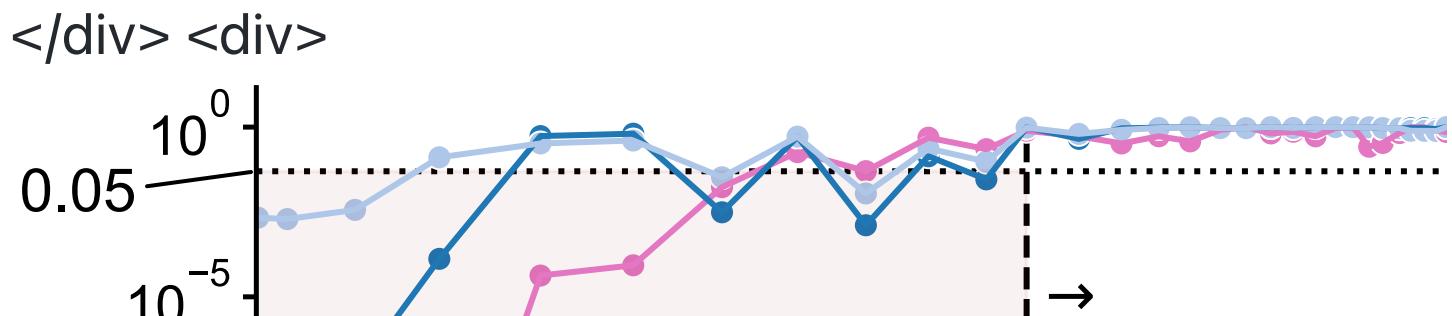
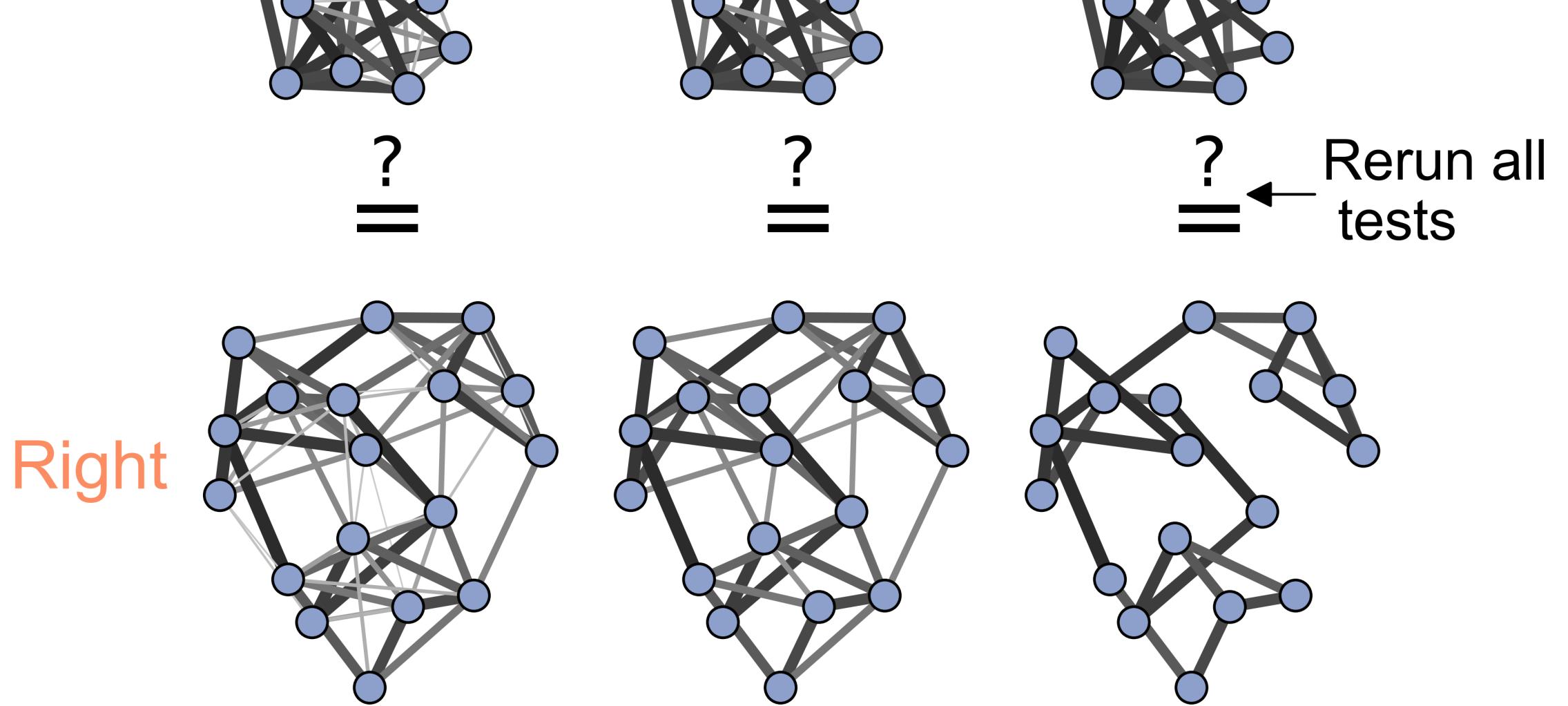
$$p < 10^{-26}$$

- Group connection test:

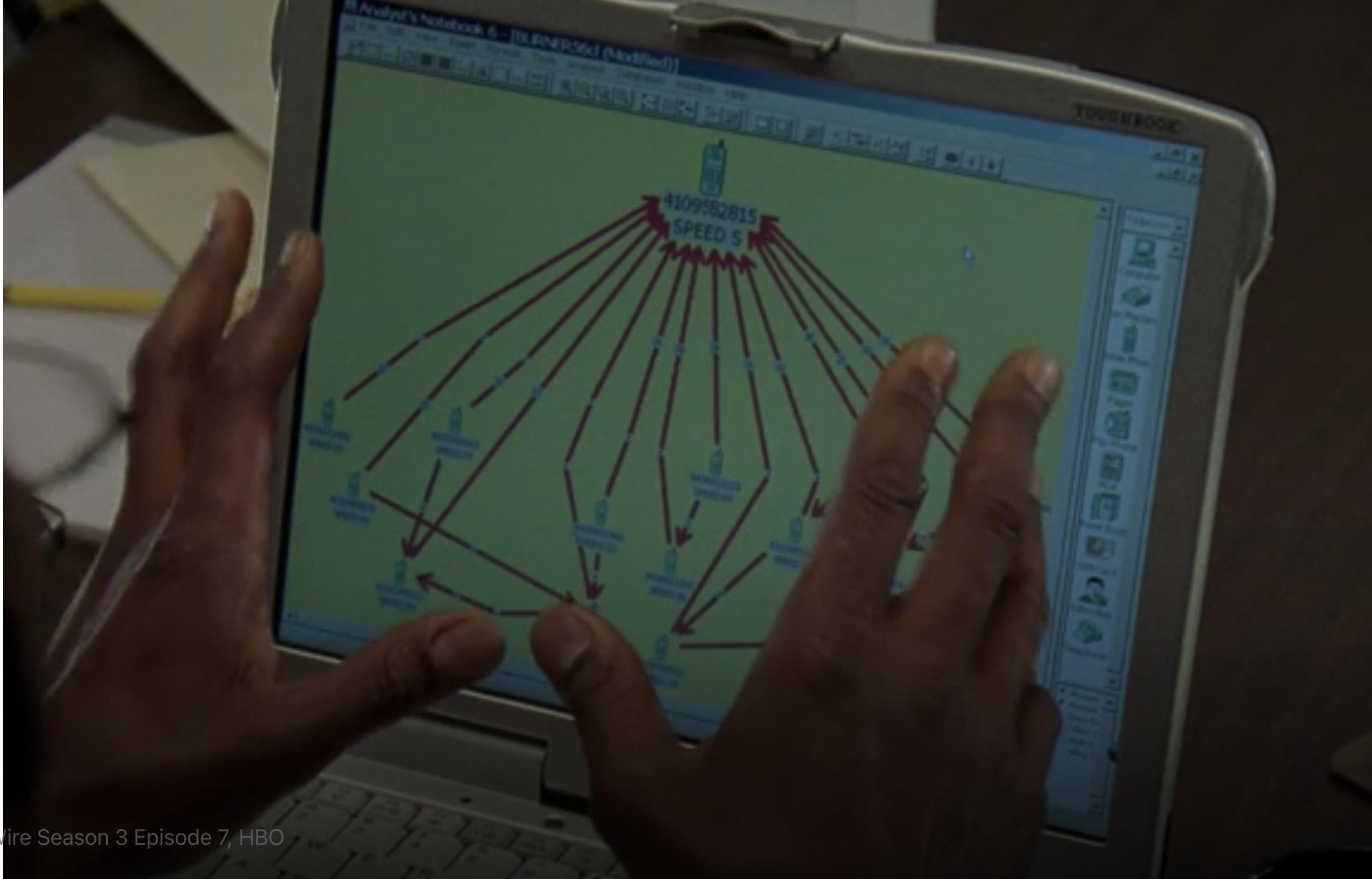
$$p \approx 0.003$$

To sum up...

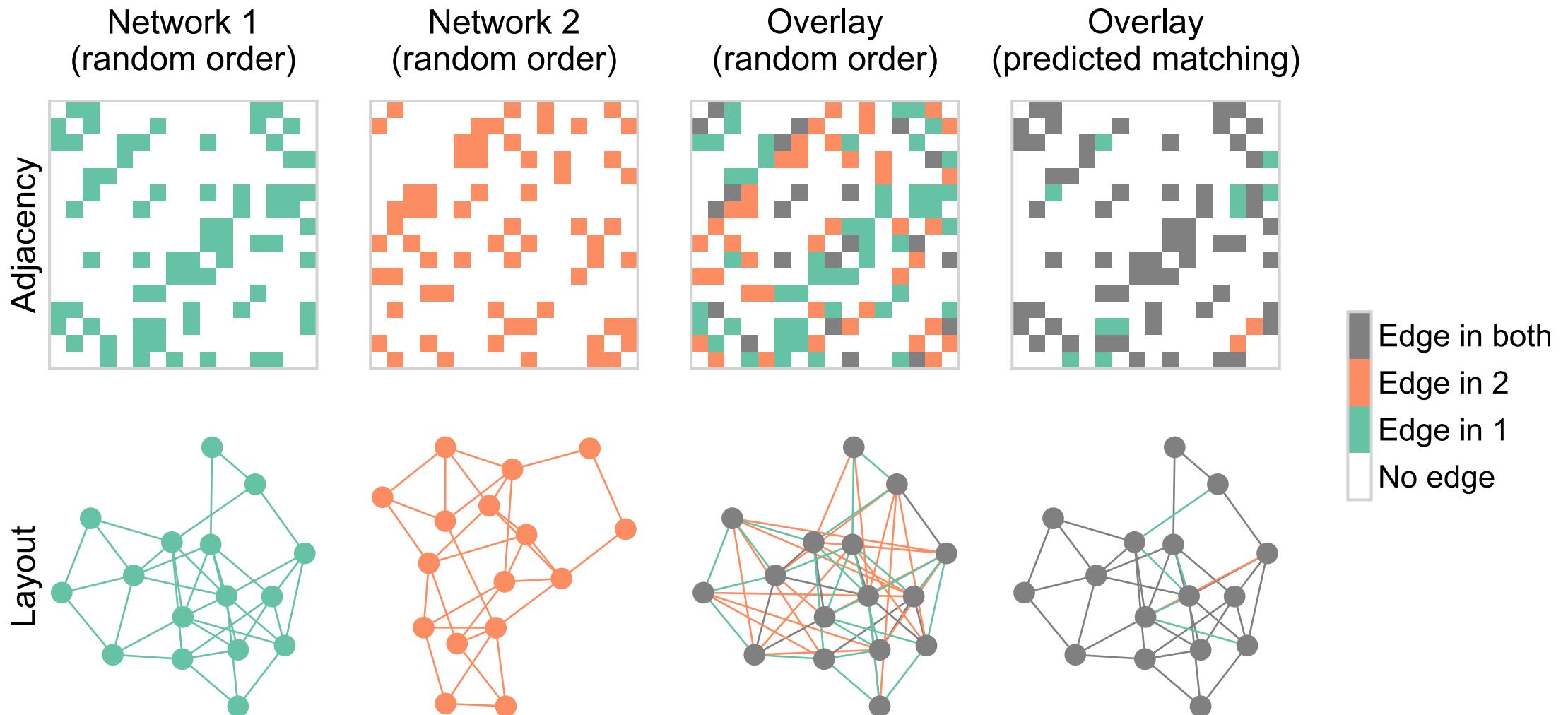
Model	H_0 (vs. $H_A \neq$)	KCs	p-value	Interpretation
ER	$p^{(L)} = p^{(R)}$	+	$< 10^{-23}$	Reject densities the same
SBM	$B^{(L)} = B^{(R)}$	+	$< 10^{-7}$	Reject group connection probabilities the same
aSBM	$B^{(L)} = cB^{(R)}$	+	≈ 0.002	Reject above even after accounting for density
ER	$p^{(L)} = p^{(R)}$	-	$< 10^{-26}$	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)



Matching neurons



What is graph matching?



How do we measure network overlap?

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

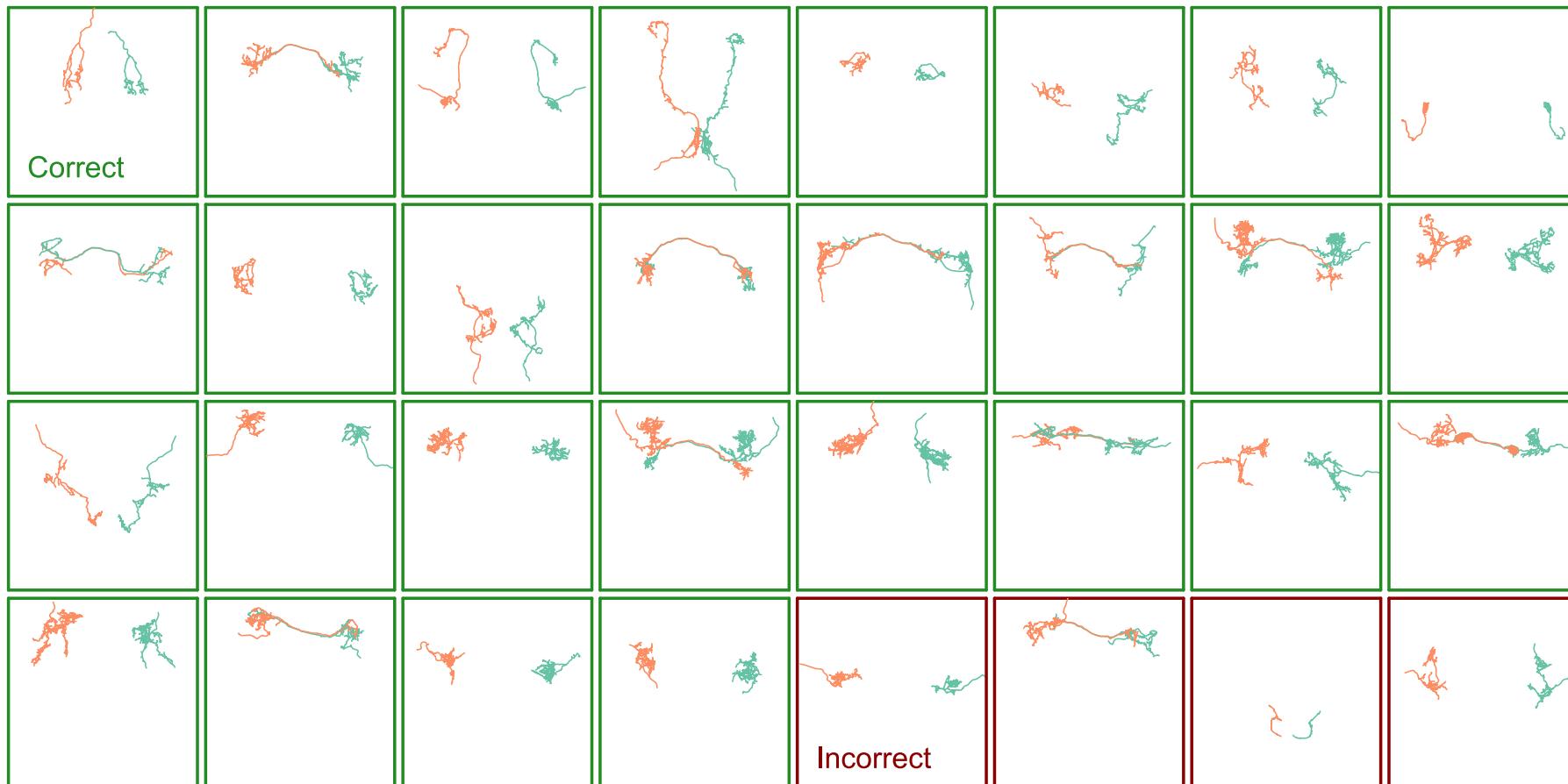
where \mathcal{P} is the set of permutation matrices

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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

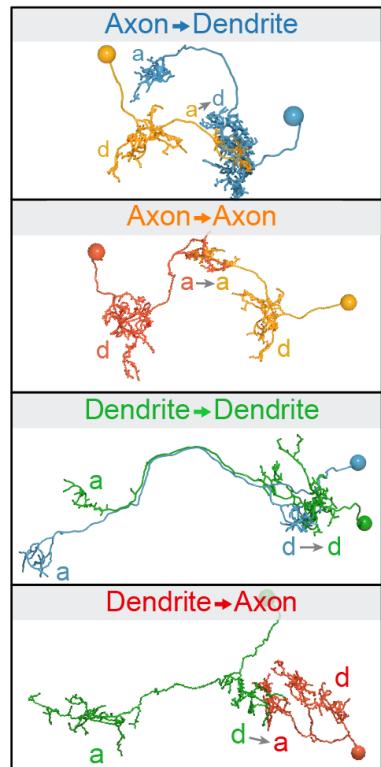
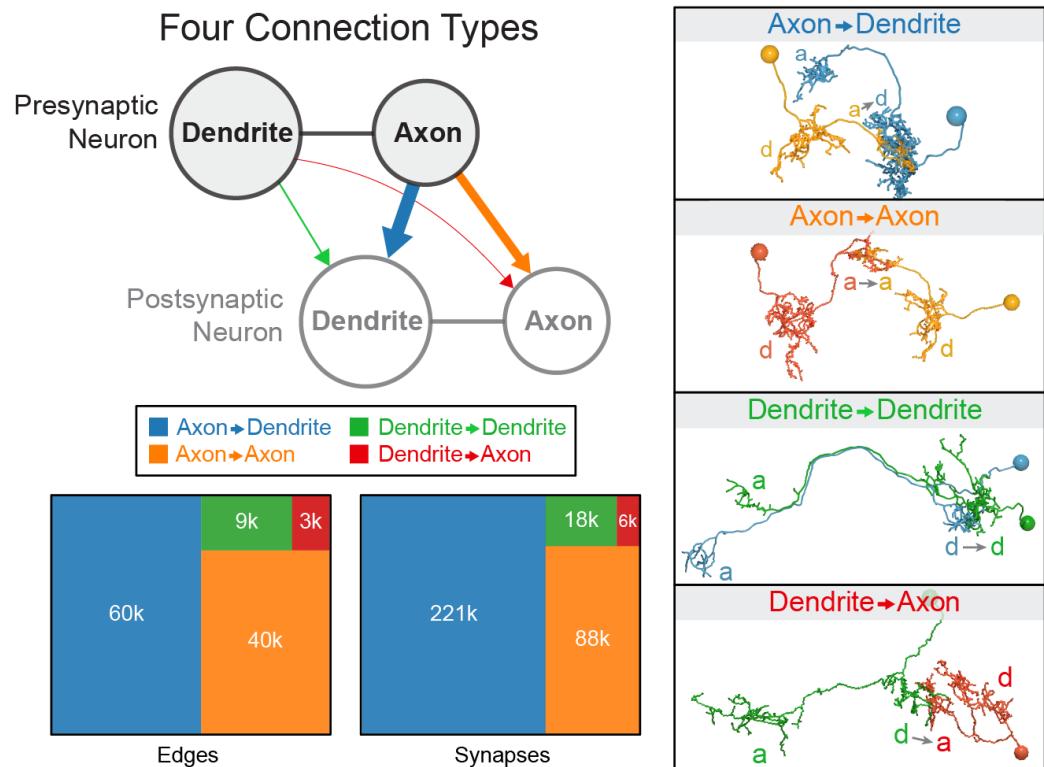


With "vanilla" graph matching: ~80% correct (according to expert annotator)

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

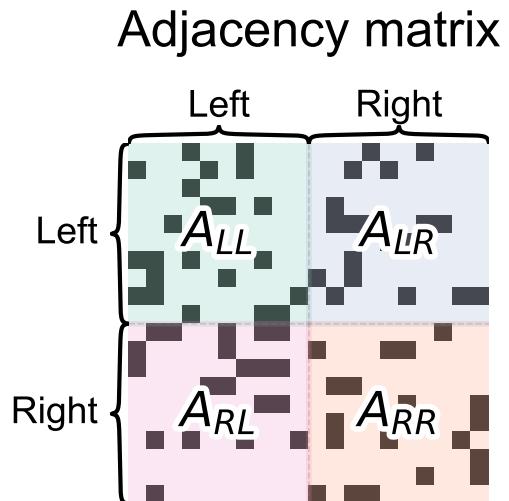
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Thus far, we've not used the contralateral connections

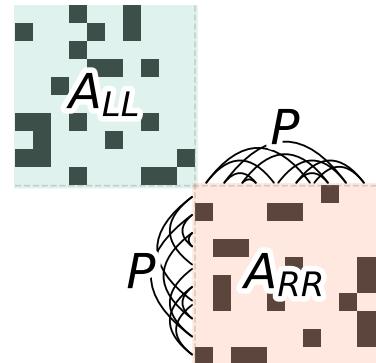
These are about 1/3 of the edges in the brain!

From graph matching to bisected graph matching

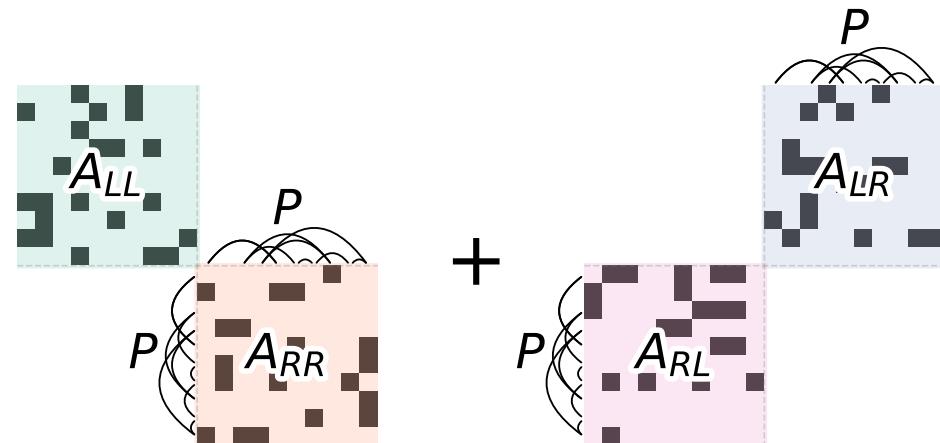


Ipsilateral \rightarrow A_{LL}, A_{RR}
Contralateral \rightarrow A_{LR}, A_{RL}

Graph matching (GM)



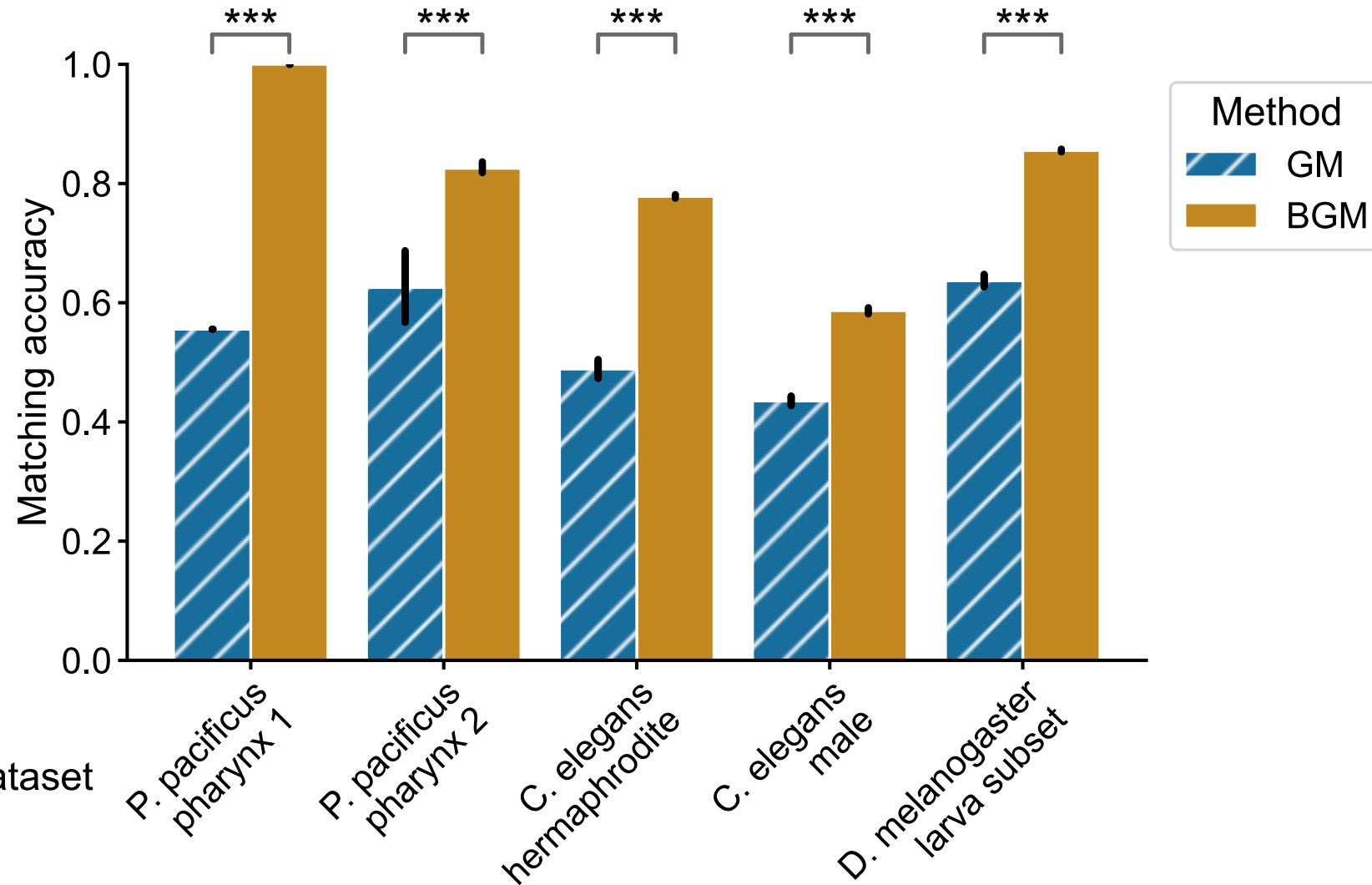
Bisected graph matching (BGM)



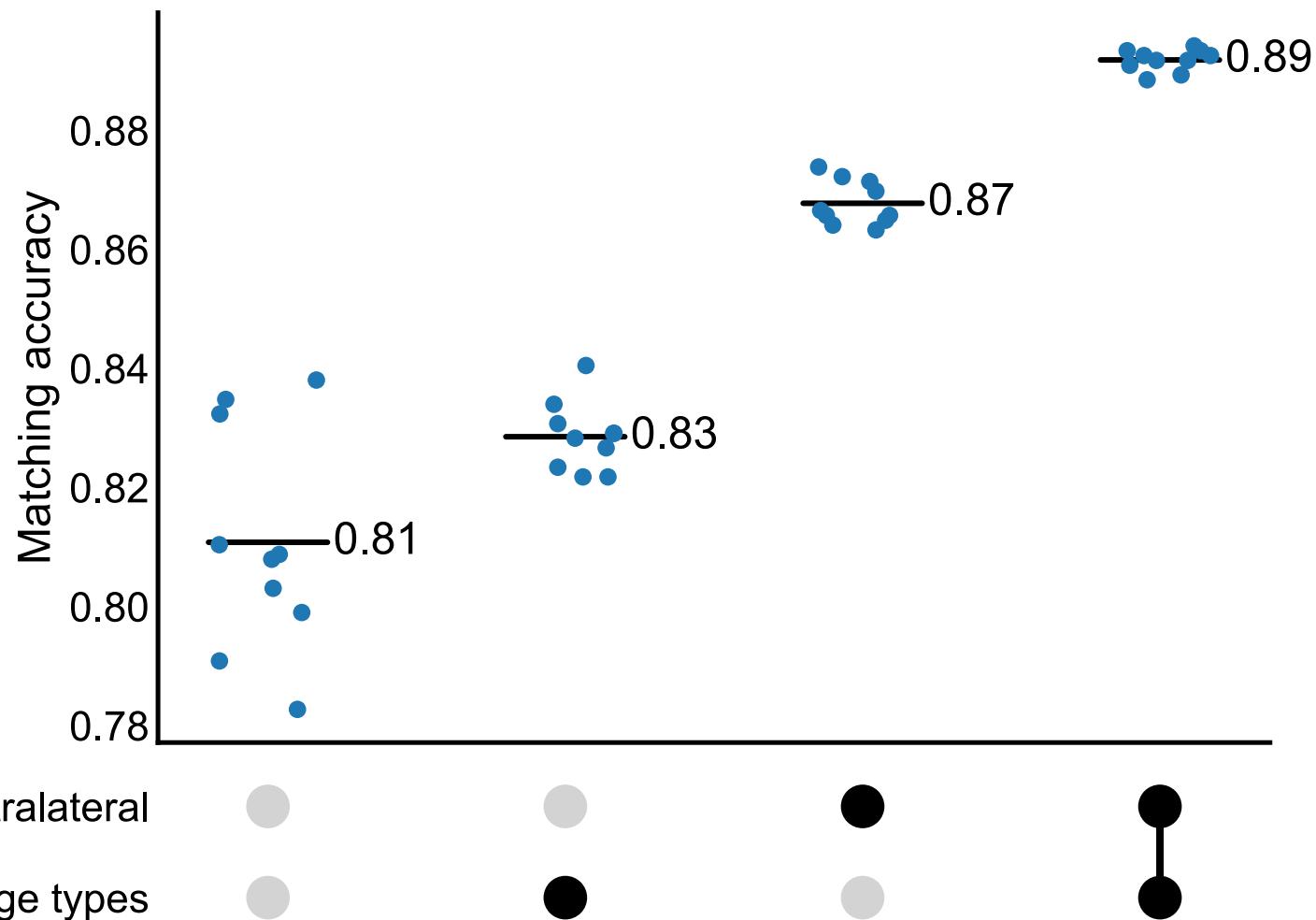
$$\min_P \| A_{LL} - P A_{RR} P^T \|_F^2$$

$$\min_P \| A_{LL} - P A_{RR} P^T \|_F^2 + \| A_{LR} P^T - P A_{RL} \|_F^2$$

Contralateral connections are helpful!



Performance improvement on the full brain

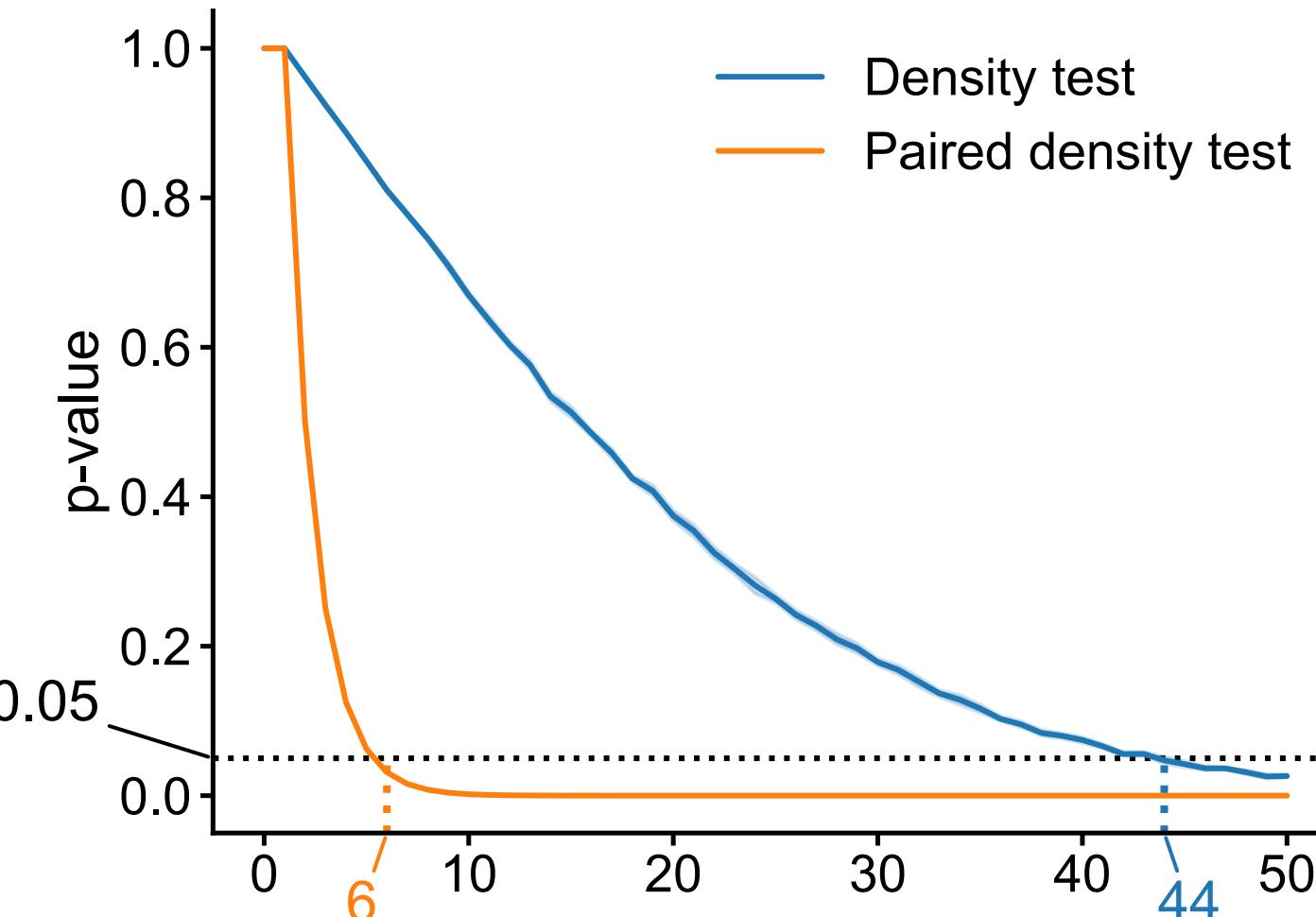


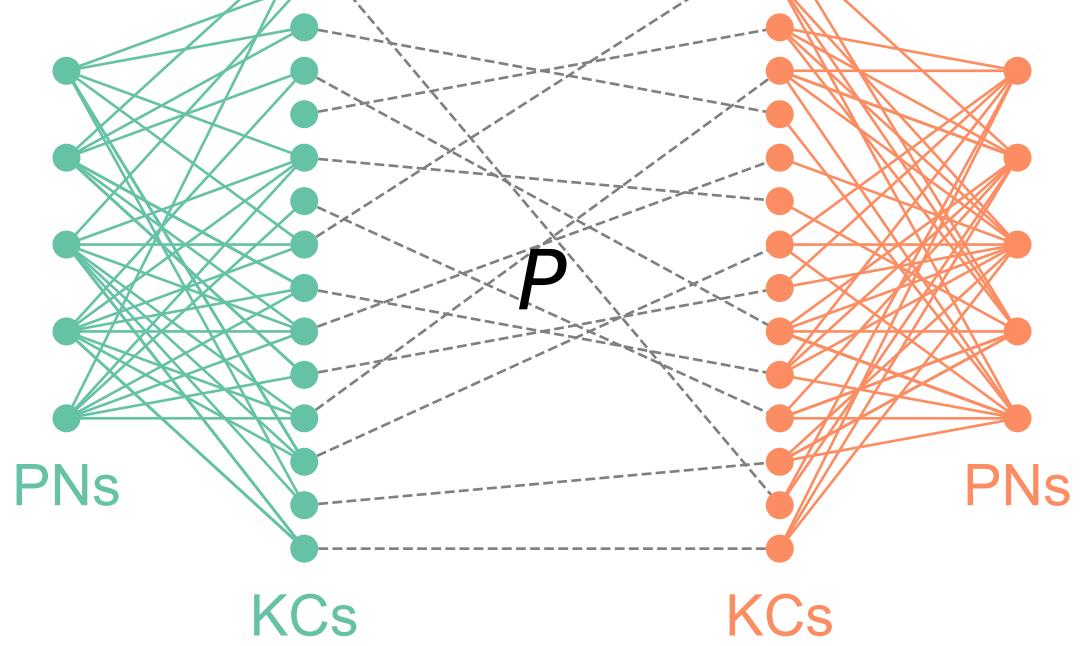
Extensions and ongoing work

```
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```

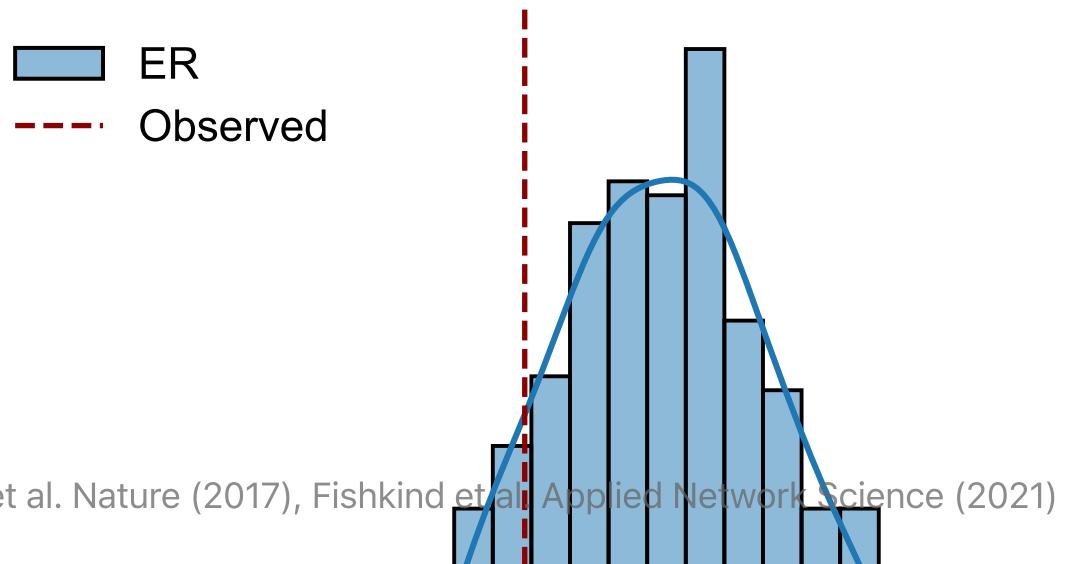
- Generate an Erdos-Renyi network (A)
- Perturb a copy of it (B)
- Test for differences between A and B

```
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```

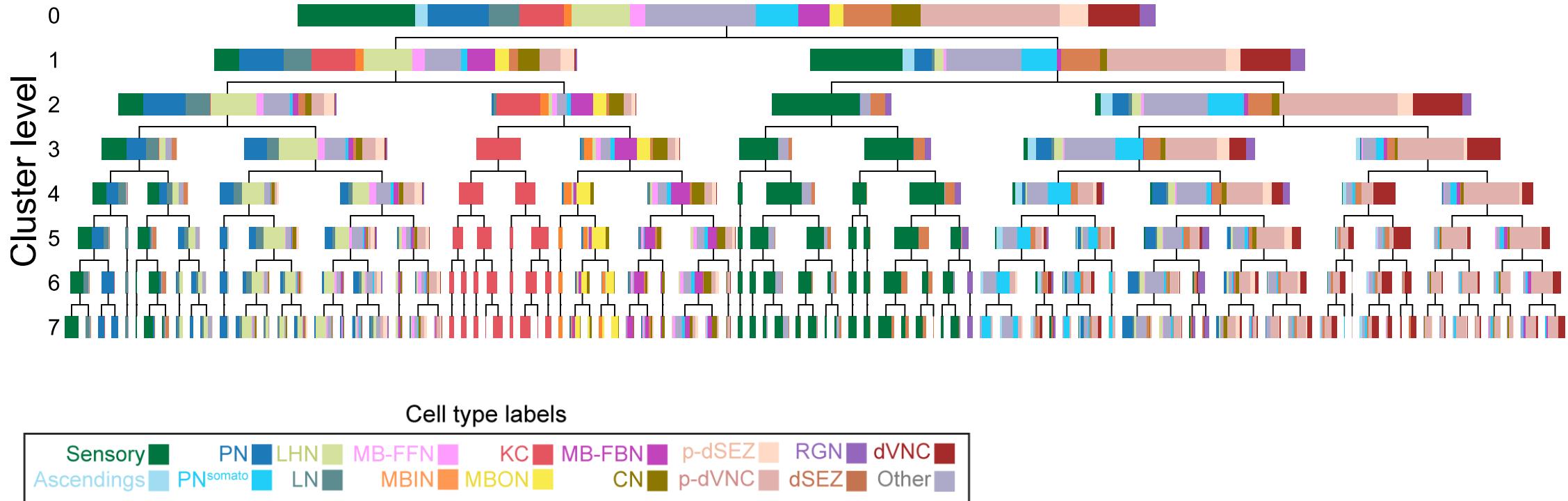




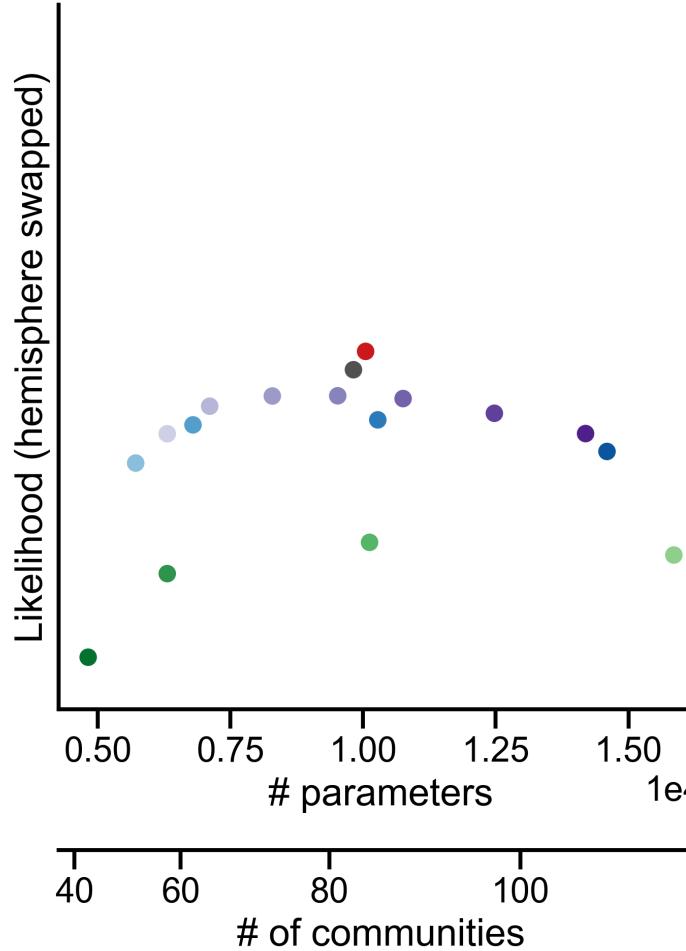
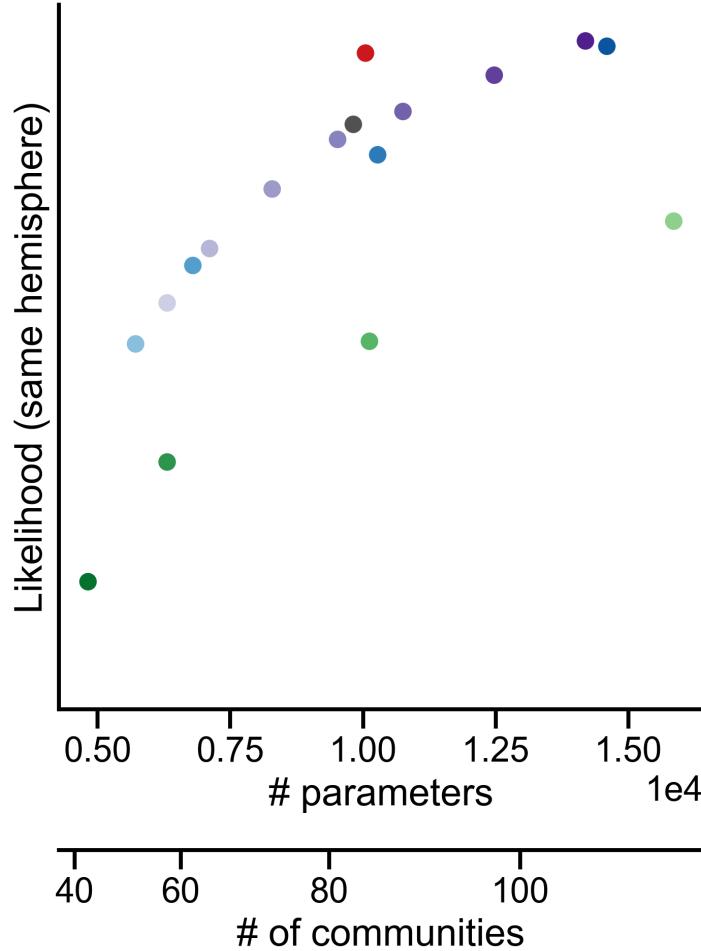
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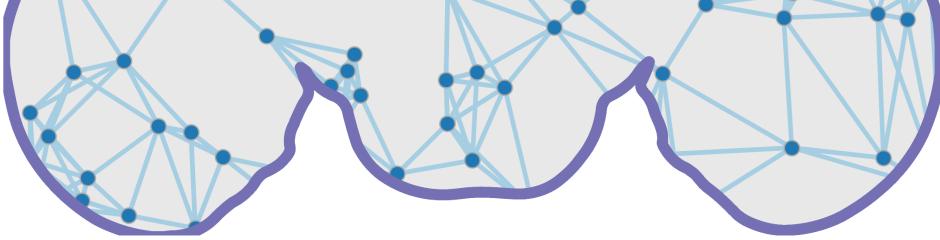
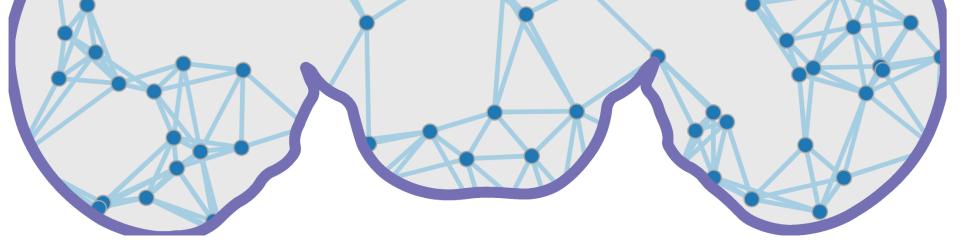


Hierarchical clustering of neurons by connectivity



Using pairs and models to evaluate cell type groupings

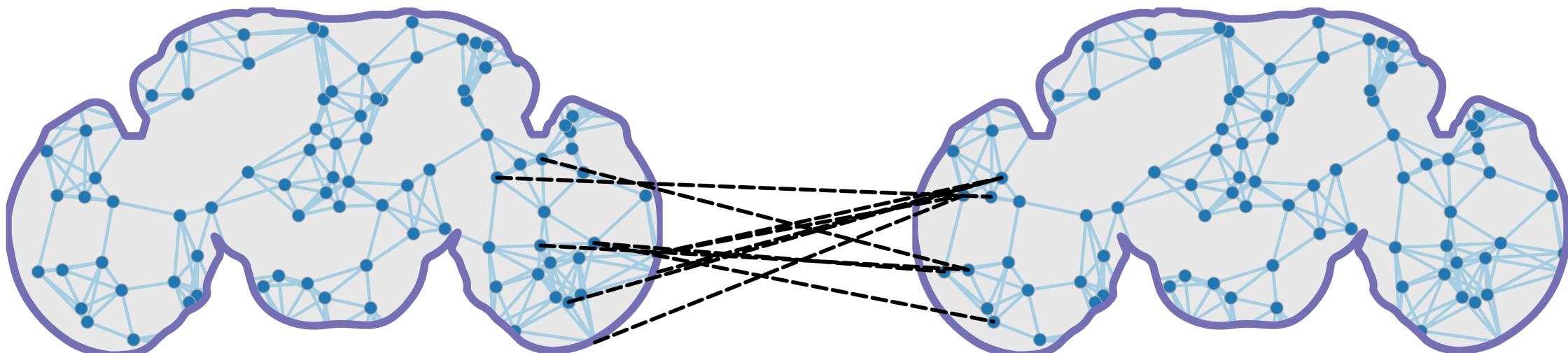




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- Model-based network comparison enables testing (and refining) hypotheses about connectomes
 - We proposed a few tests, but just the beginning!

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github.com/microsoft/graspologic



downloads 139k Stars 260 contributors 49

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Model-based testing

github.com/neurodata/bilateral-connectome

JB jupyter book

Improved matching

Eric Bridgeford

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Ali

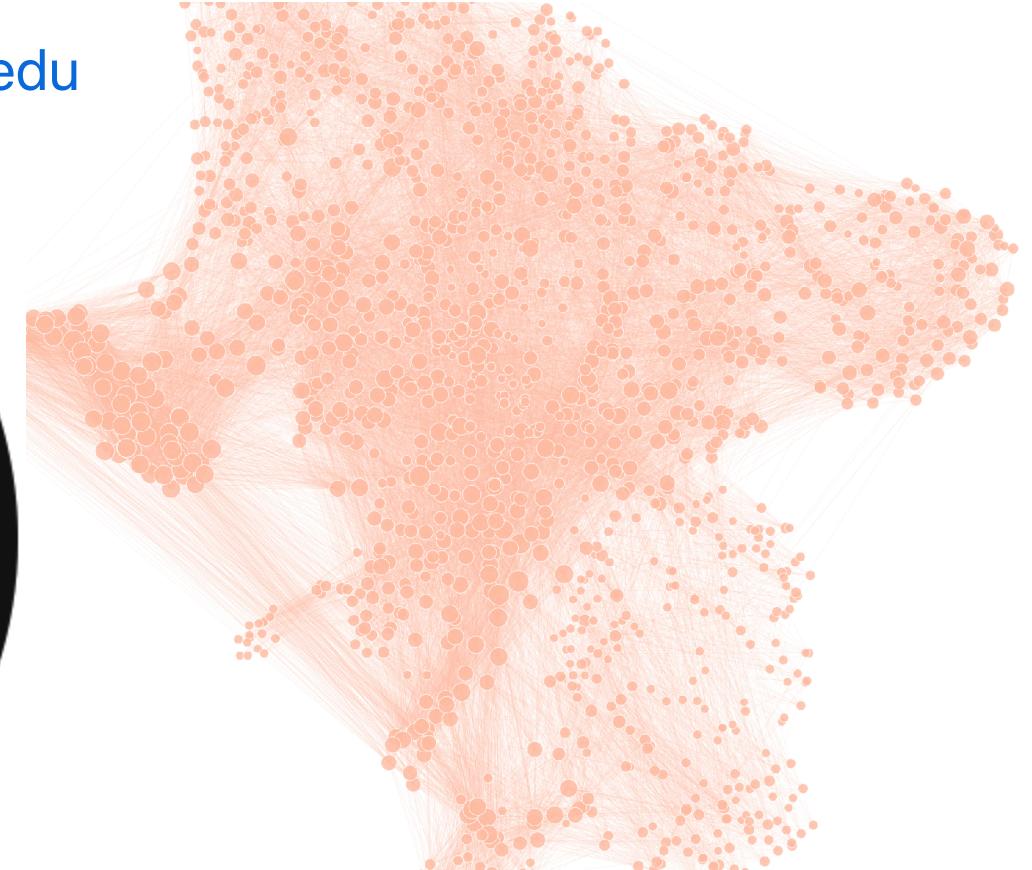
Saad-Eldin

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bpedigo@jhu.edu



Right