Maggot brain, mirror image? A statistical analysis of bilateral symmetry in an insect brain connectome

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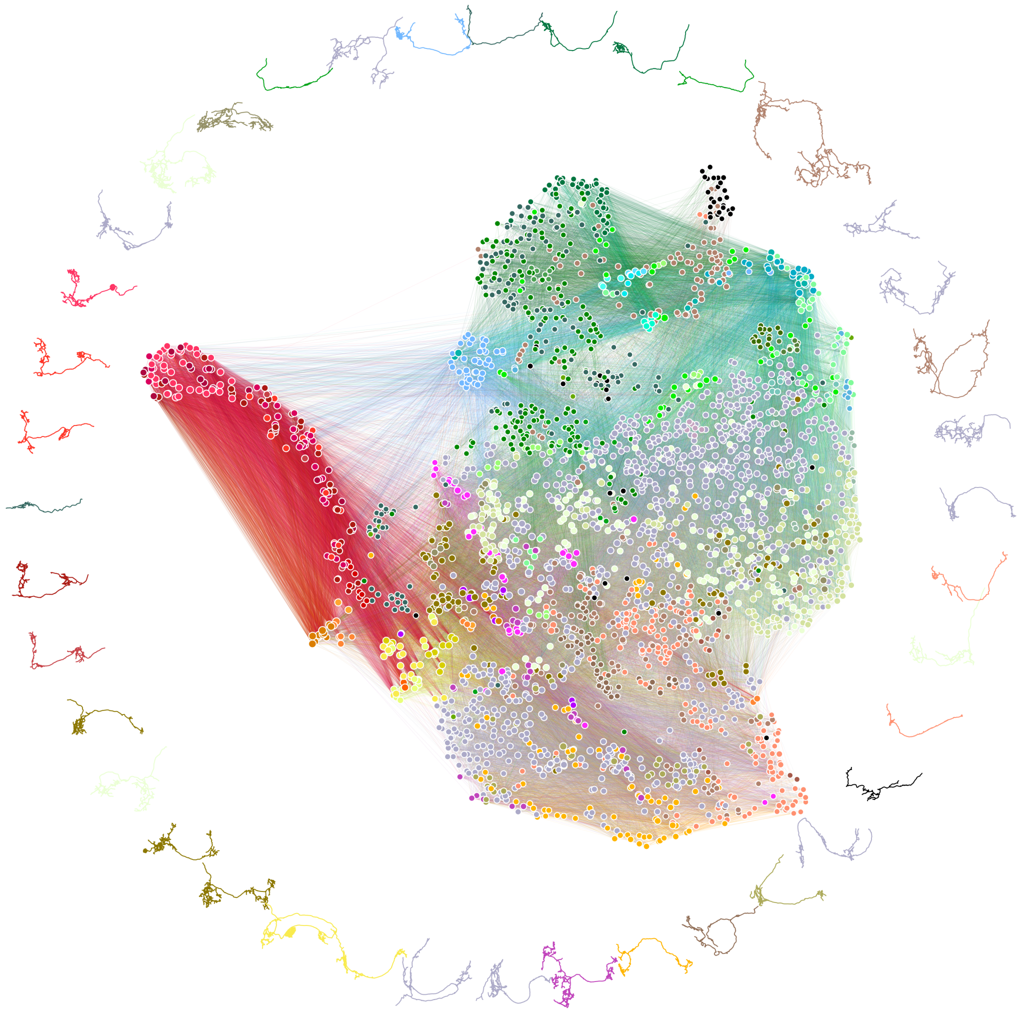


Many connectomics questions require comparison

For instance,

- Understand connectomes across evolution [1]
- Understand connectomes across development [2]
- Understand links between genetics and connectivity [3]

[1] Bartsotti + Correia et al. *Curr. Op. Neurobiology* (2021)

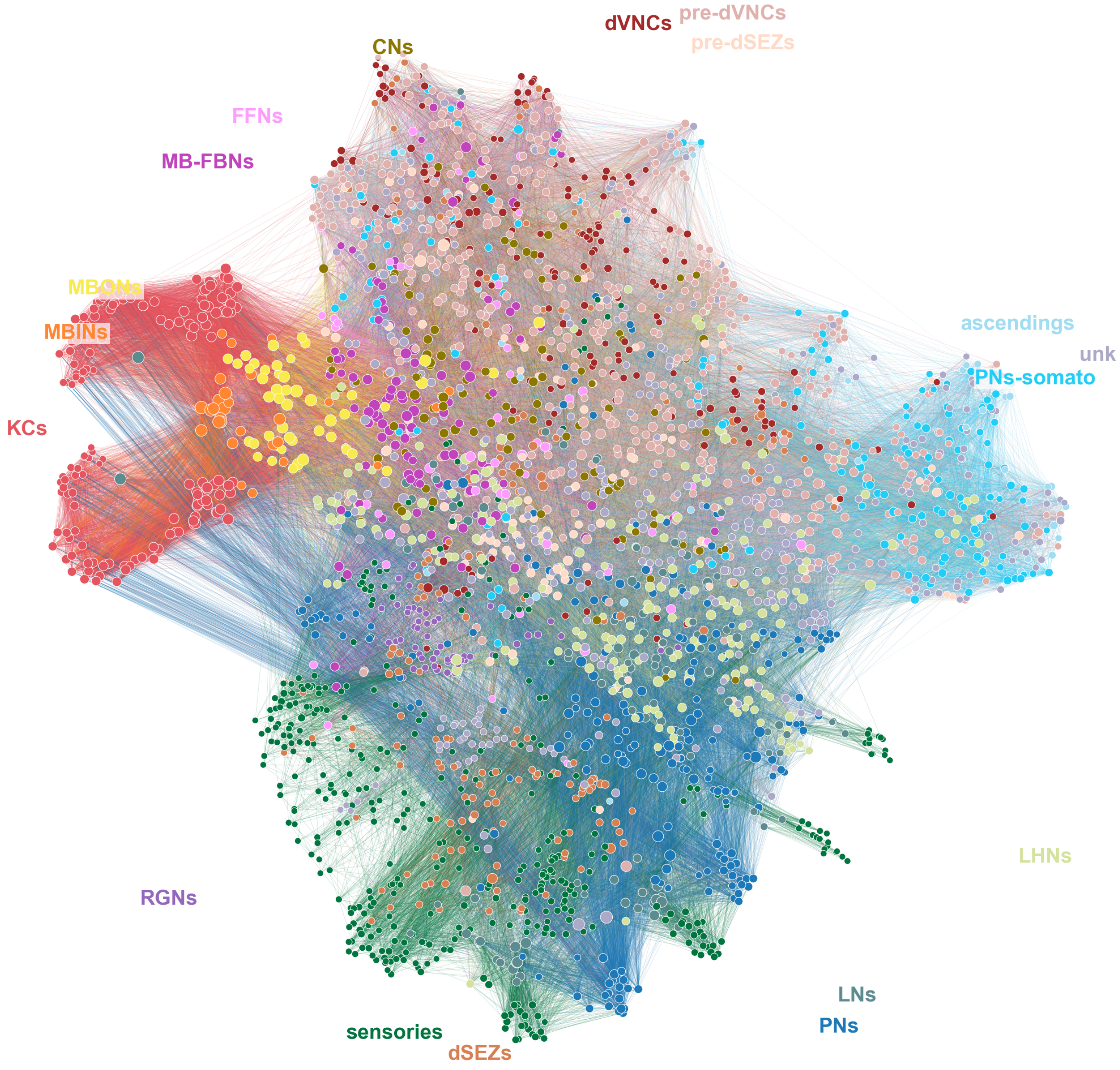
[2] Witvliet et al. *Nature* (2021)

[3] Valdes-Aleman et al. *Neuron* (2021)

Larval *Drosophila* brain connectome

See Michael Windings's talk, 11 AM (EST) Dec 2nd

- ~3000 neurons, ~544K synapses
- Both hemispheres of the brain reconstructed

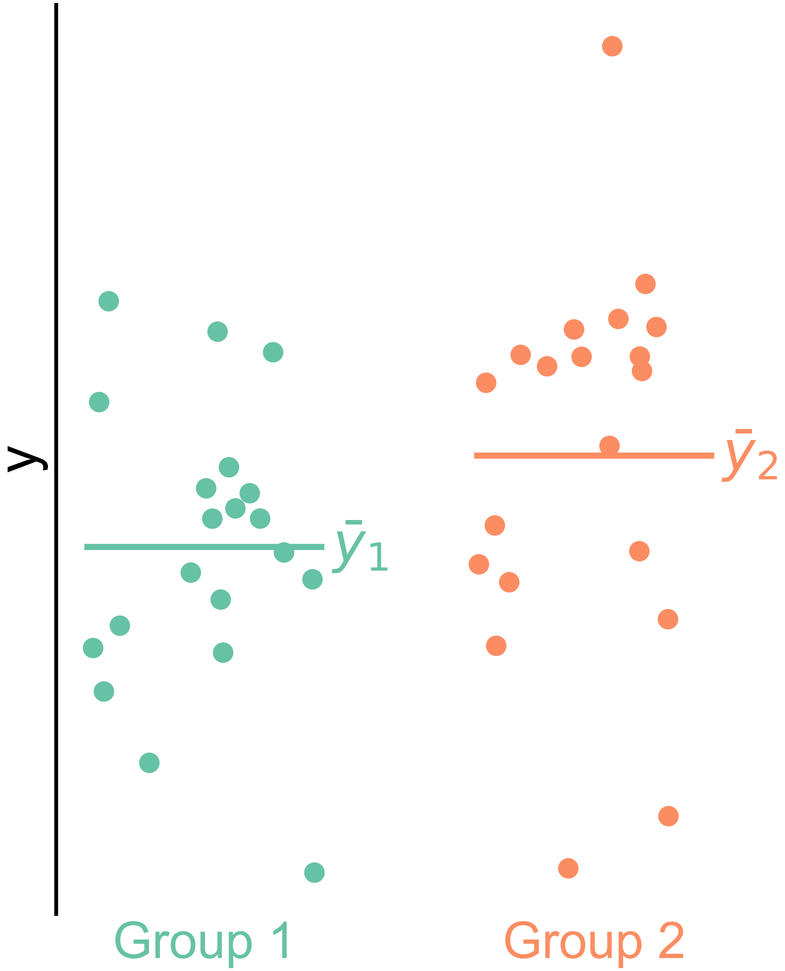


Winding et al. “The complete connectome of an insect brain.” In prep (2021)

Are the left and right sides of this connectome *the same*?

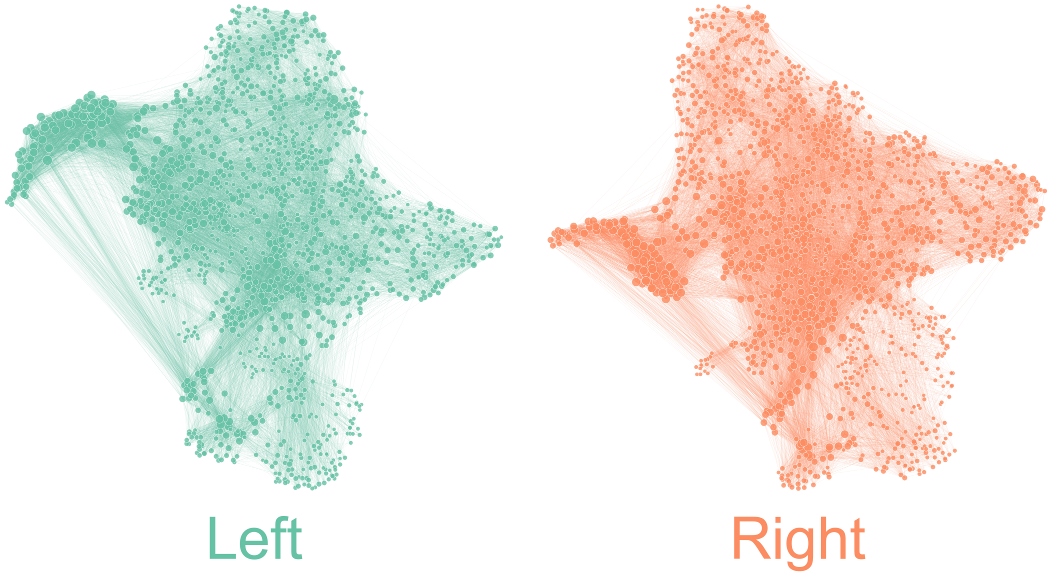
Are these populations the same?

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



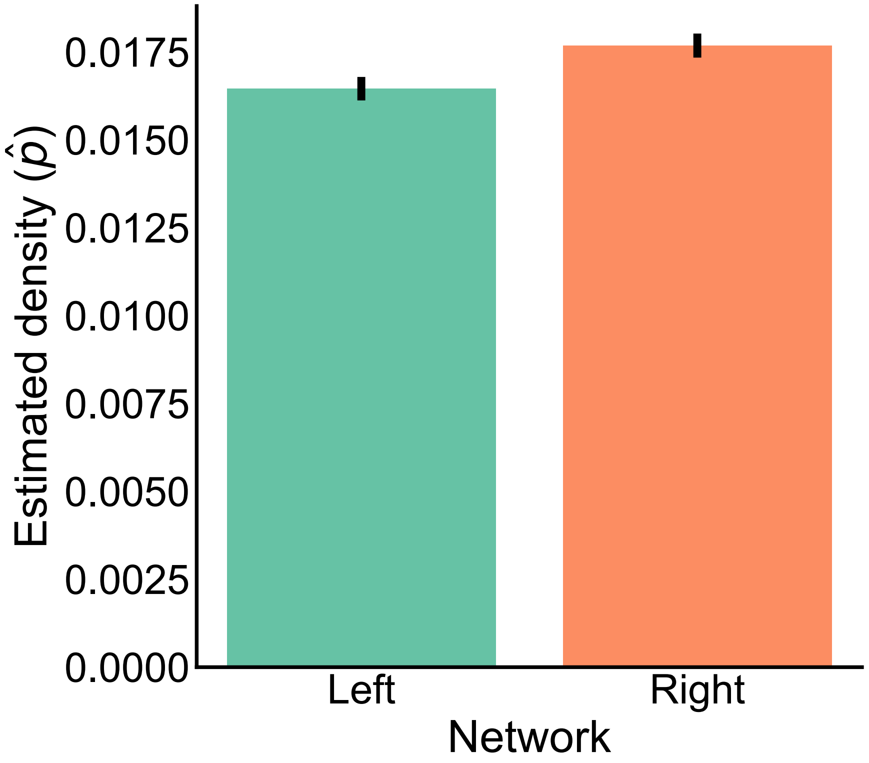
Are these two *networks* the same?

- Want a two-network-sample test!
- For simplicity (for now), consider networks to be *directed, unweighted*.
- For simplicity (for now), consider the left → left and right → right (ipsilateral) connections only.
- $A^{(L)} \sim F^{(L)}$, $A^{(R)} \sim F^{(R)}$
- $H_0 : F^{(L)} = F^{(R)}$
  $H_A : F^{(L)} \neq F^{(R)}$



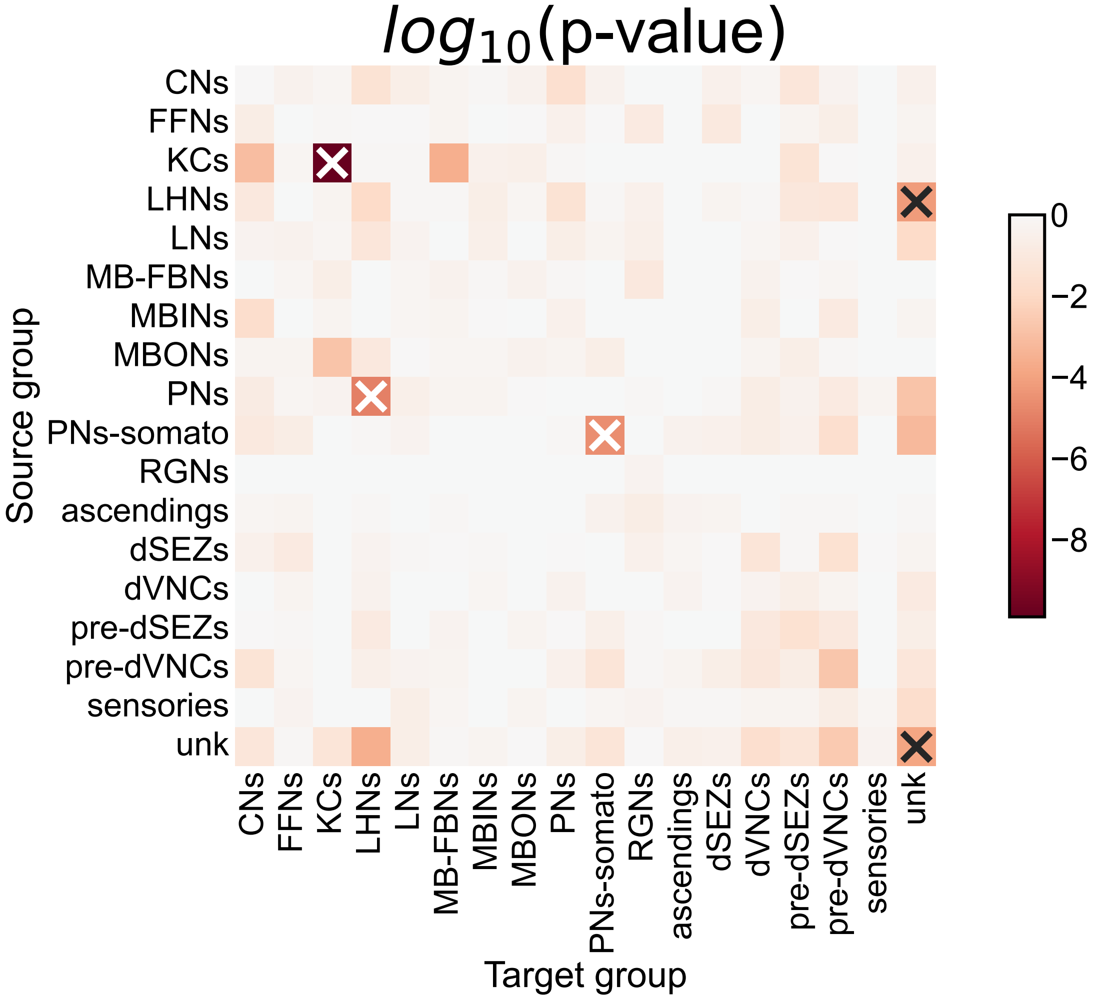
Density-based testing: Erdos-Renyi (ER) model

- Connections independent, same connection probability p for all edges
- $P[i \to j] = p$
- Compare probabilities:
  $H_0 : p^{(L)} = p^{(R)}$
  $H_A : p^{(L)} \neq p^{(R)}$
- **p-value** $< 10^{-23}$
- Is this a difference we care about?



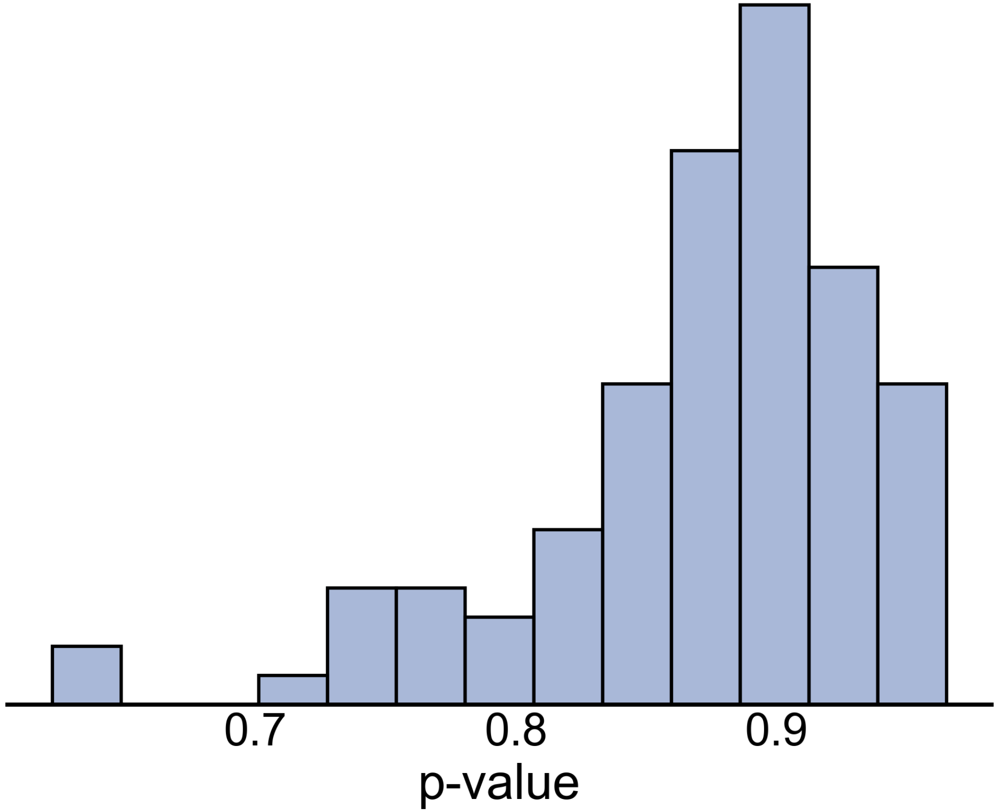
Group-based testing: stochastic block model (SBM)

- Connection probability set by the source node's group (τ_i) and target node's group (τ_j)
- $P[i \rightarrow j] = B_{\tau_i, \tau_j}$
- Compare group-to-group connection probabilities:
  $H_0 : B^{(L)} = B^{(R)}$
  $H_A : B^{(L)} \neq B^{(R)}$
- **p-value** $< 10^{-4}$



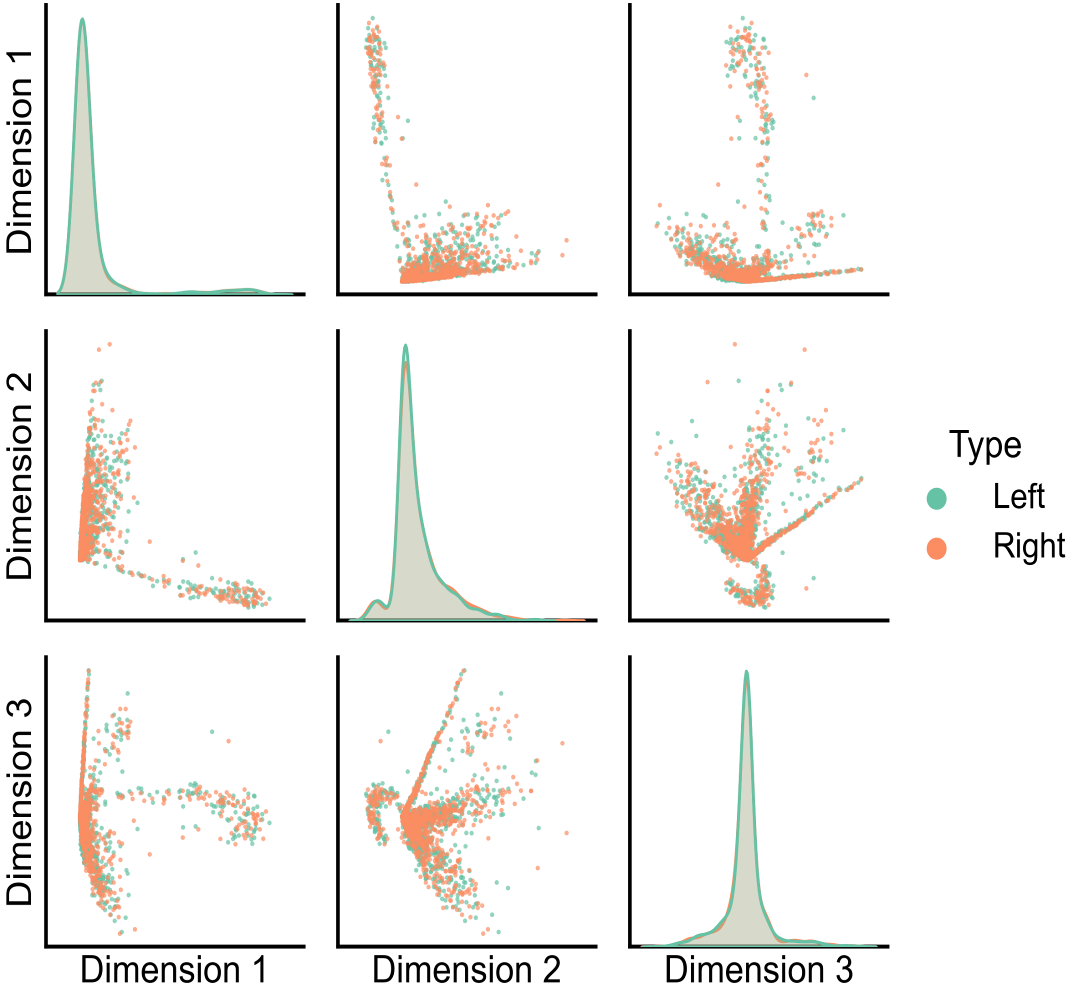
Adjusting for a difference in density

- Rejecting $B^{(L)} = B^{(R)}$ can be explained by the difference in density?
- New null hypothesis:
  $H_0 : B^{(L)} = cB^{(R)}$
  where c is a density-adjusting constant, $\frac{p^{(L)}}{p^{(R)}}$
- Randomly subsample edges from denser network, rerun test
- **p-values** > 0.6



More flexibility: Random dot product graph (RDPG)

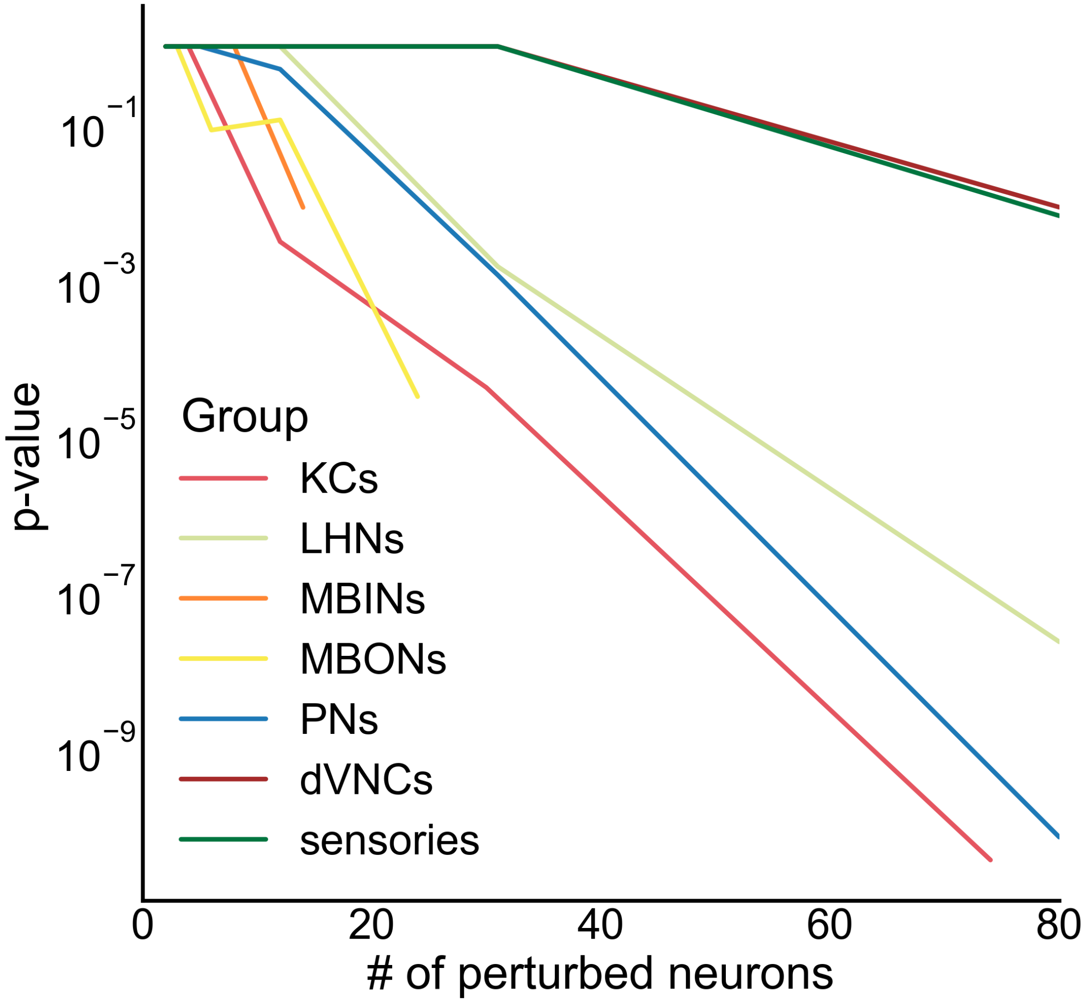
- Probability from dot product of source node's latent vector, target node's latent vector.
- $P[i \to j] = \langle x_i, y_j \rangle$
- $x_i^{(L)} \sim F^{(L)}$, $x_i^{(R)} \sim F^{(R)}$ in d dimensions
- Compare distributions of latent vectors:
  $H_0 : F^{(L)} = F^{(R)}$
  $H_A : F^{(L)} \neq F^{(R)}$
- **p-value** ≈ 1



Athreya et al. JMLR (2017), Tang et al. Bernoulli (2017)

Can we detect differences when we know they exist?

- Make two copies of right hemisphere network
- Apply some perturbation to one of them:
    - Ex: Shuffle edges incident to some number of nodes in some group
- Rerun the RDPG-based test for symmetry



To sum up...

Model	H_0 **(vs.** $H_A \neq$**)**	**p-value**	**Interpretation**
ER	$p^{(L)} = p^{(R)}$	$< 10^{-23}$	Reject densities the same
SBM	$B^{(L)} = B^{(R)}$	$< 10^{-4}$	Reject cell type connection probabilities the same
SBM	$B^{(L)} = cB^{(R)}$	≈ 0.7	Don't reject the above after density adjustment
RDPG	$F^{(L)} = F^{(R)}$	≈ 1	Don't reject latent distributions the same

The answer to this very simple question totally depends on how you frame it!

- Tests are sensitive to some alternatives and not others
- Difference you might not care about (e.g. density) need to be explicitly accounted for

Future work

- Many other tests
- Many other alternatives
- Roadmap for future principled comparisons of connectome networks!

graspologic:

github.com/microsoft/graspologic

downloads 79k

Stars 233

contributors 45

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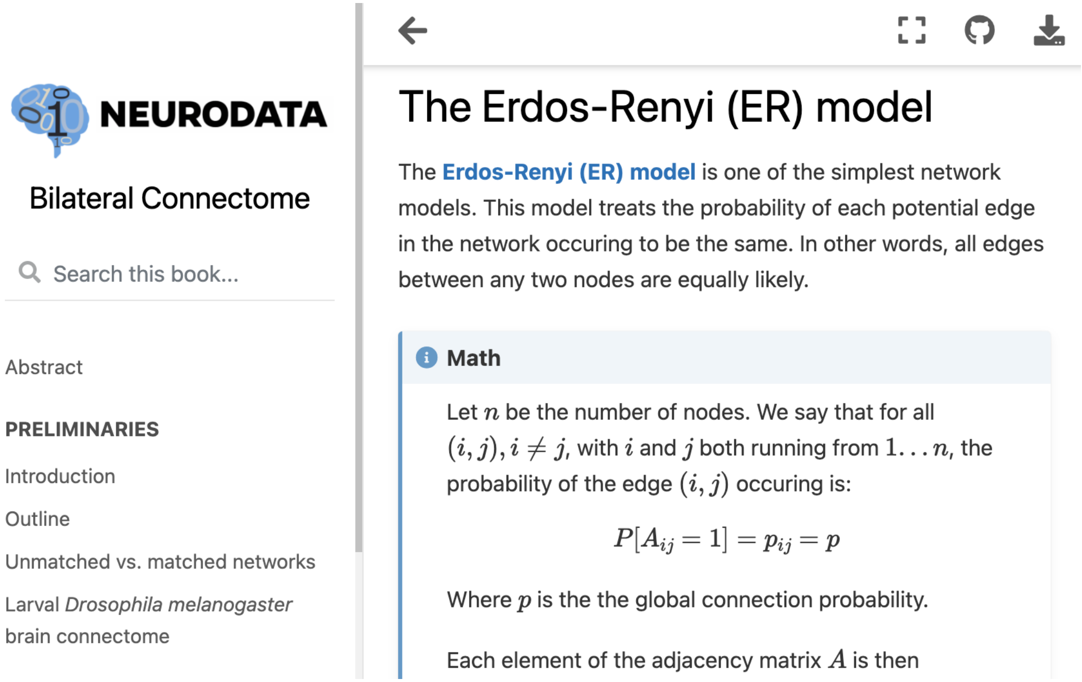
This work:

github.com/neurodata/bilateral-connectome



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Bilateral Connectome

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Abstract

PRELIMINARIES

Introduction

Outline

Unmatched vs. matched networks

Larval *Drosophila melanogaster* brain connectome

The Erdos-Renyi (ER) model

The **Erdos-Renyi (ER) model** is one of the simplest network models. This model treats the probability of each potential edge in the network occuring to be the same. In other words, all edges between any two nodes are equally likely.

Math

Let n be the number of nodes. We say that for all $(i, j), i \neq j$, with i and j both running from $1 \dots n$, the probability of the edge (i, j) occuring is:

$$P[A_{ij} = 1] = p_{ij} = p$$

Where p is the the global connection probability.

Each element of the adjacency matrix A is then

Chung, Pedigo et al. JMLR (2019)

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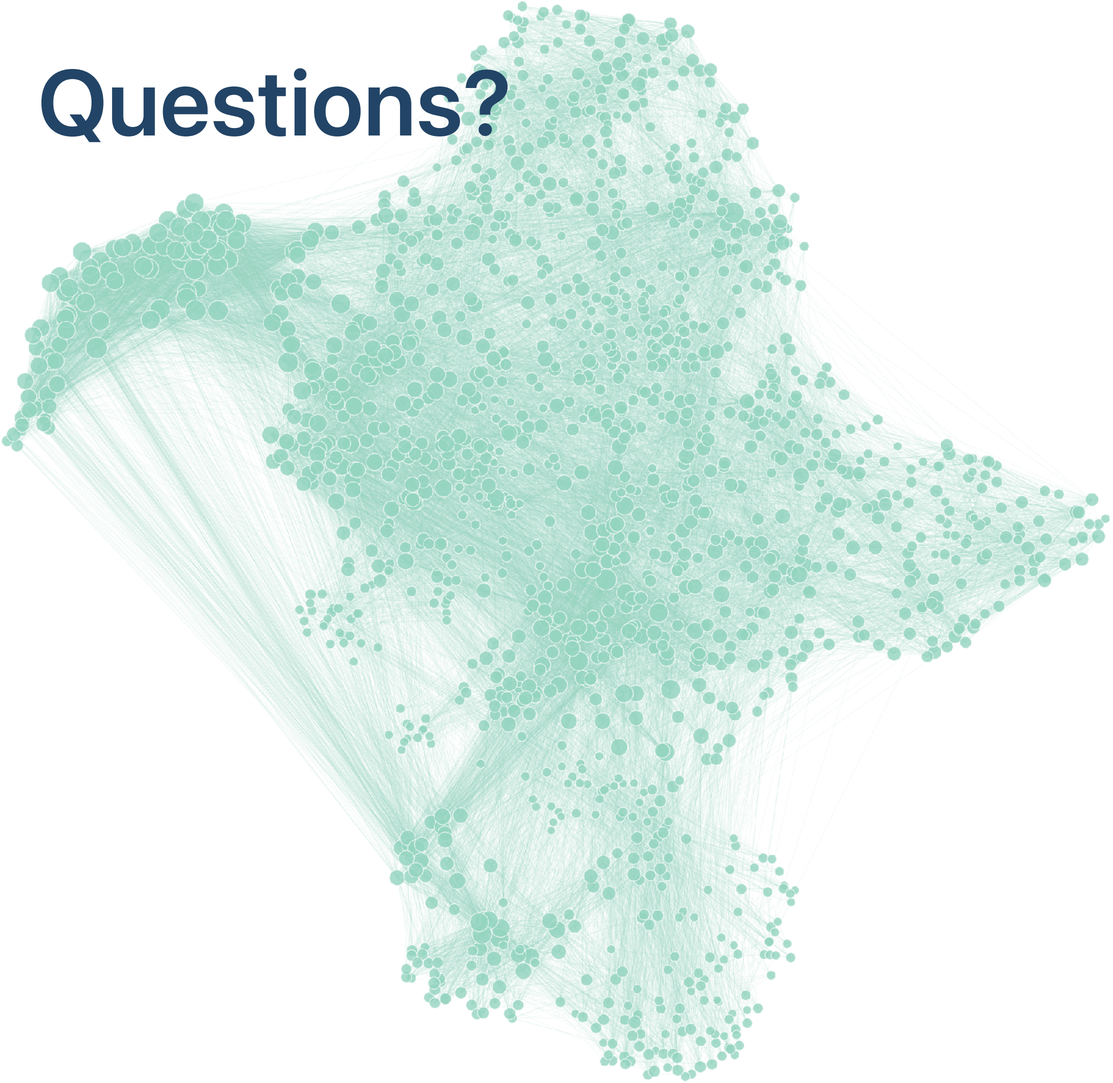
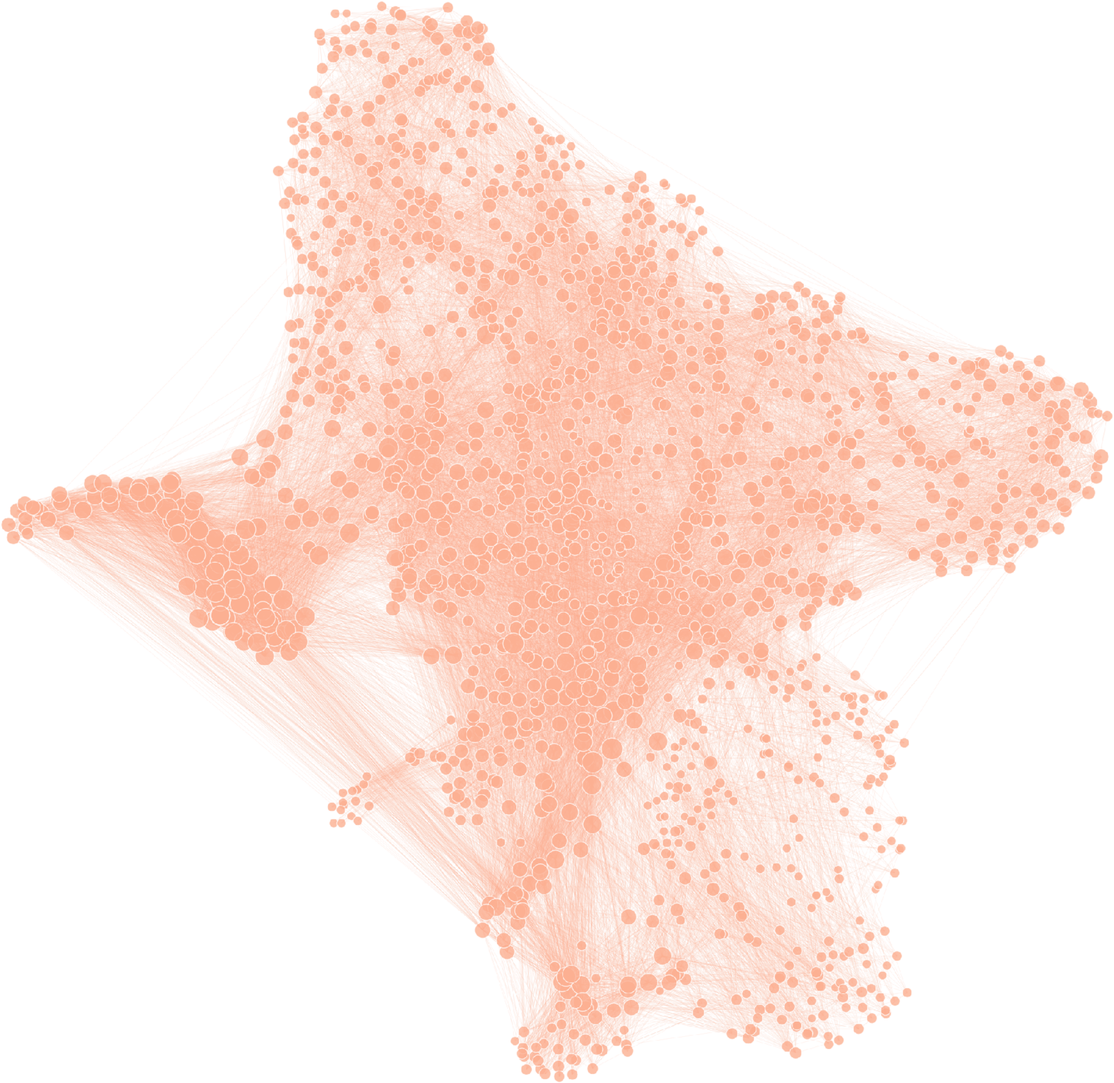
Questions?



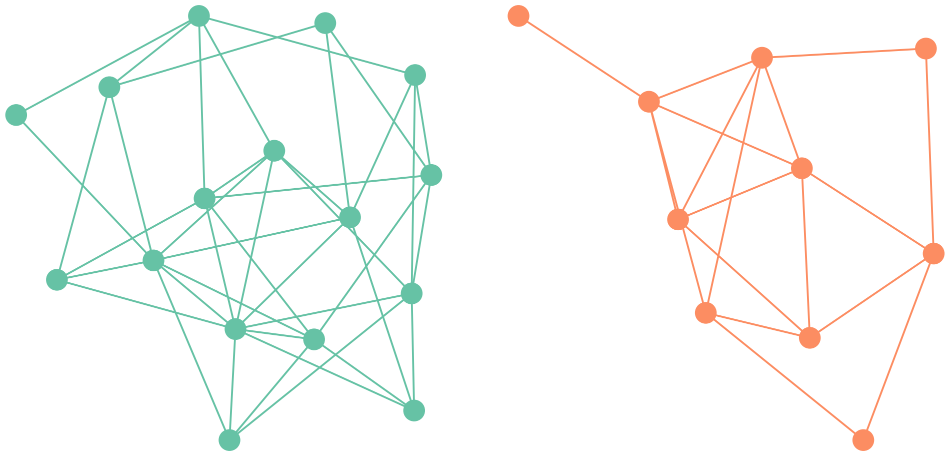
Left



Right

Appendix

Unmatched



Matched