# An Empirical Study of Continuous Connectivity Degree Sequence Equivalents

MICCAI 2016

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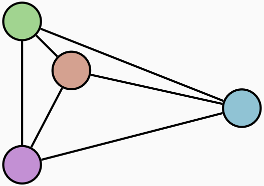
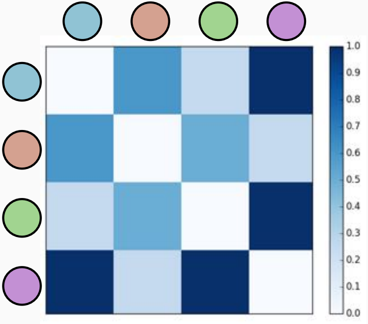
# Unfortunate Timing

## Spoiler Alert

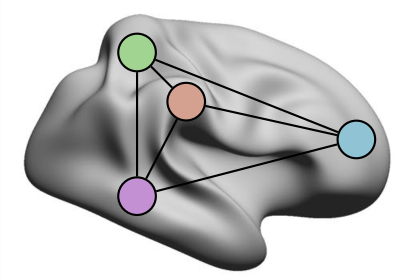
The results of this paper have a different focus from the main conference talk, but since they're based on the same model, the first half of the talks are very similar.

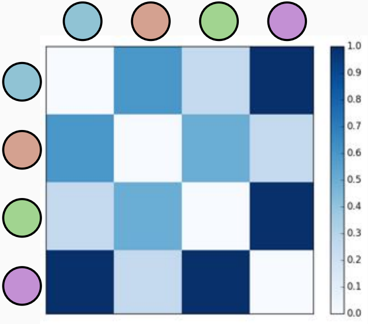
Network model



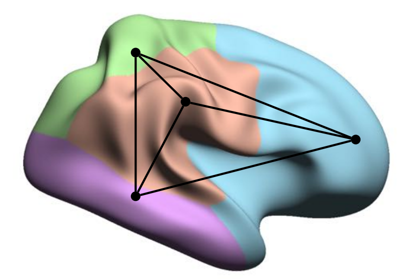


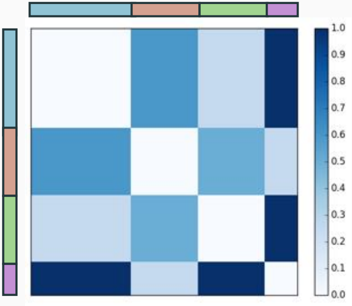
Brain Network model

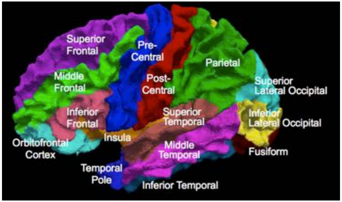




## Regional Connectivity model





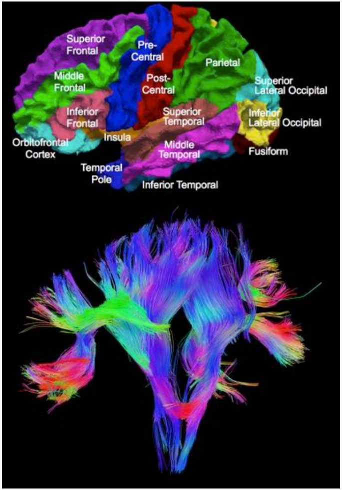



Standard Connectomics Pipeline:

1. Parcellate Cortex

Images from IGC-INI for the Freesurfer documentation (top), and Human Connectome Project (bottom).

# Standard Connectomics




Standard Connectomics Pipeline:

1. Parcellate Cortex
2. Fit tracks

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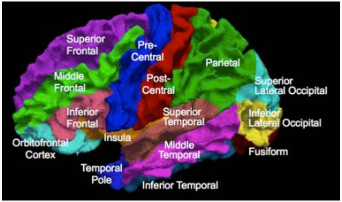


$$Adj^n = \begin{bmatrix} Adj^n_{11} & Adj^n_{12} & \cdots \\ Adj^n_{21} & Adj^n_{22} & \cdots \\ \vdots & \vdots & \ddots \end{bmatrix}$$

$$Adj^n_{ij} = \underbrace{|\{(x,y) : x \in E_i, y \in E_j\}|}_{\text{No. of tracks from i to j}}$$

Standard Connectomics Pipeline:

1. Parcellate Cortex
2. Fit tracks
3. Construct networks

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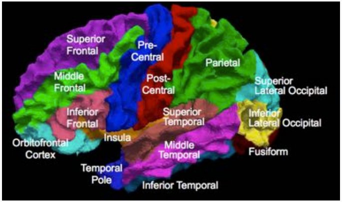
# Standard Connectomics




- Clustering Coefficients
- Path length and centrality
- Degree distributions

Standard Connectomics Pipeline:

1. Parcellate Cortex
2. Fit tracks
3. Construct networks
4. Measure network statistics

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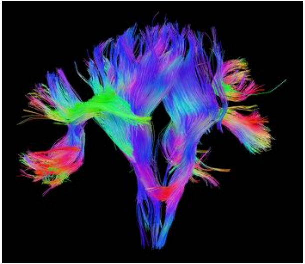
# Some Known Problems



Three important problems:

1. Tracks have noise.

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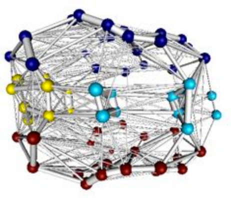

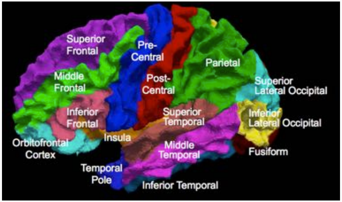


Three important problems:

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2. Nodes are atomic; but brain regions are not.

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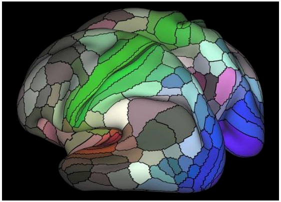

Three important problems:

1. Tracks have noise.
2. Nodes are atomic; but brain regions are not.
3. There is no agreed upon standard parcellation.

# Choice of Parcellation Problems

Choice of Parcellation Matters!

- Clustering Coefficients [Z+10, L+16]
- Path length/centrality [Z+10, RG+12, L+16]
- Degree distributions [Z+10, RG+12, L+16]

# Choice of Parcellation Problems

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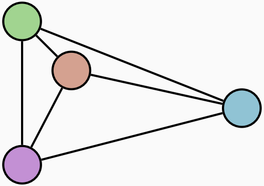
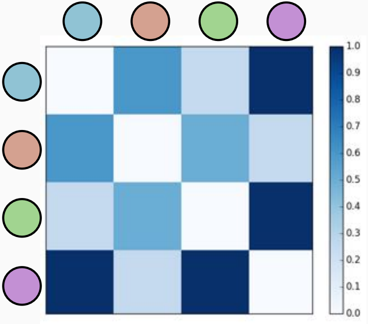
There may not even be a best parcellation [dRVdH13].

So what can we do?

# Continuum Graphs

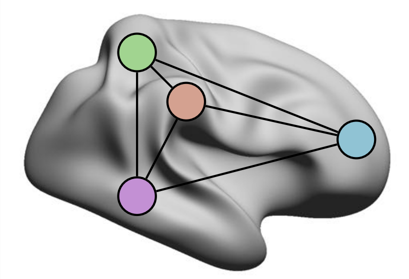
## Standard network Model

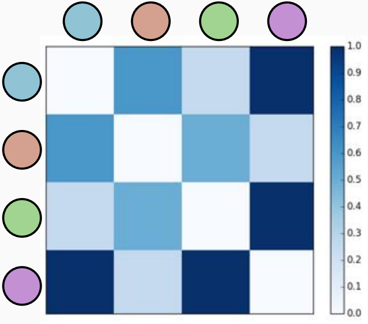




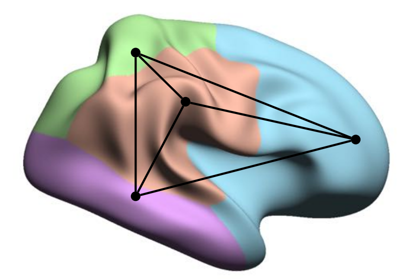
# Continuum Graphs

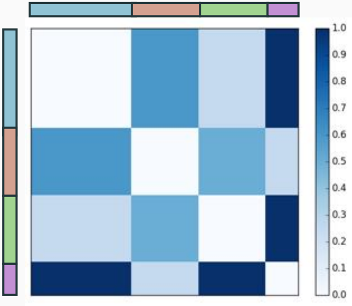
## Brain Network Model





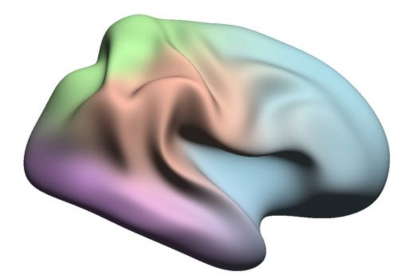
## Regional Connectivity Model

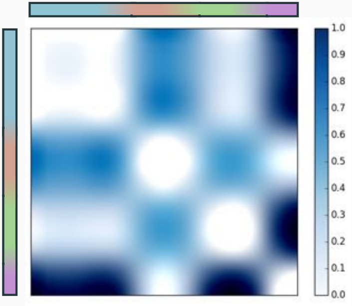




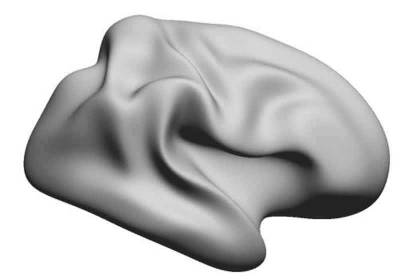
# Continuum Graphs

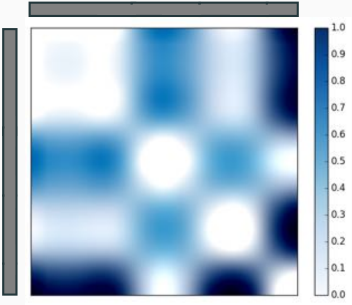
## Relaxed Regional Connectivity Model





Coordinate-based Connectivity Model?





[Poisson] Point Processes:

- Random process with point pattern realizations.
- Described by an intensity function $\lambda$ : Domain $\to \mathbb{R}^+$, the asymptotic rate of events (point obs.).
- [Poisson] Events occur independently, and for any region $R \subset$ Domain, $P(\text{obs. } N \text{ events}) = Poisson(\int_R \lambda(x)dx)$.

In our context:

- Events are obs. track endpoint pairs.
- Domain $= \Omega \times \Omega$, where $\Omega \sim S^2 \cup S^2$ is the cortical surface.

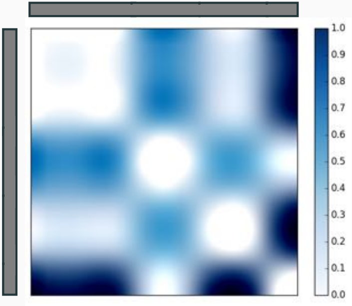
# Point Process Connectomics

In our context:

- Events are obs. track endpoint pairs.
- Domain $= \Omega \times \Omega$, where $\Omega \sim S^2 \cup S^2$ is the cortical surface.
- We assume that pairs of track endpoints appear ind. with some asymptotic rate $\lambda$ over the connectivity domain $\Omega \times \Omega$.

# Continuous Connectivity

$$\lambda : \Omega \times \Omega \to \mathbb{R}^+$$



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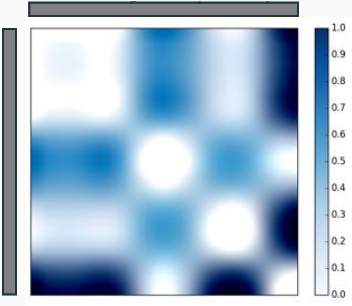



**Choice:** We will approximate $\lambda$ by Kernel Density Estimation (KDE).

Procedure:

1. Recover the cortical surfaces (each hemisphere $\sim S^2$)
2. Register the surfaces.
3. Define a kernel $K(p, x)$ on $S^2$.
4. Convolve each set of endpoints with the product kernel $\kappa = K(p, x)K(q, y)$ on $S^2 \times S^2$.
5. Sum the convolved kernels to form $\hat{\lambda}$.

# Recovery of the Intensity Function

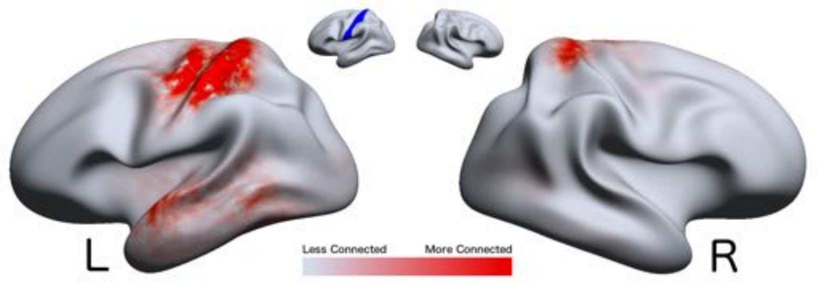
The spherical heat kernel (expressed in truncated spherical harmonic form) [Chu06], turned into a product kernel:

$$f(p, x, \sigma) = \sum_{h=0}^{H} \frac{2h+1}{4\pi} \exp\{-\sigma(h^2 + h)\} P_h^0(p \cdot x)$$

$$K_\sigma(p, x) = \begin{cases} f(p, x, \sigma) & \text{if } p, x \text{ are on same hemi.} \\ 0 & \text{otherwise} \end{cases}$$

$$\kappa_\sigma((p, q), (x, y)) = K_\sigma(p, x) K_\sigma(q, y) \text{ kernel for domain: } \Omega \times \Omega$$

# Pretty Pictures




A marginal connectivity $M(y) = \int_{E_i} \lambda(x, y)dx$ to the Left post-central gyrus for one subject. Red denotes higher connectivity regions with the blue region.

### Marginal connectivity

For any $E \subset \Omega$, define the marginal connectivity as

$$M_E(x) = \int_E \lambda(x, y) dy$$

It can be shown that if $\lambda(x, y)$ is continuous, then $M_E(x)$ is also continuous.

# Degree Equivalents

Continuous Conn.

$$\lambda : \Omega \times \Omega \to \mathbb{R}^+$$

Marginal Conn.

$$M(x) = M_\Omega(x) = \int_\Omega \lambda(x, y) dy$$

Discrete Networks, $V = \{v_i\}_i^K$

$$e : V \times V \to \mathbb{R}^+$$

Discrete Degree

$$deg(x) = \sum_{y \in V} e(x, y)$$

# Choosing $\sigma$

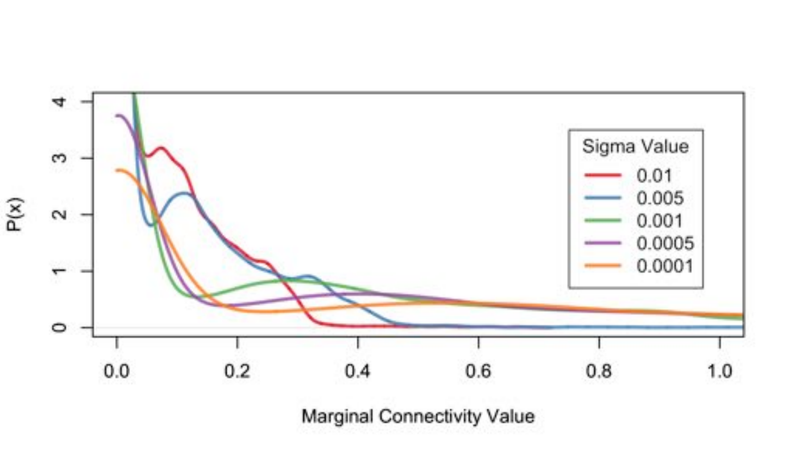
$$\kappa((p,q)|D) = \sum_{(x_i,y_i)\in D} K_\sigma(x_i,p)K_\sigma(y_i,q)$$

$$= \sum_h^H \sum_k^H \Bigg[ \underbrace{\left(\frac{2h+1}{4\pi}\right)\left(\frac{2k+1}{4\pi}\right)\exp\{-\sigma(h^2+h+k^2+k)\}}_{\text{Independent of } D,\ \text{evaluated every iteration}}$$

$$\times \underbrace{\sum_{(x_i,y_i)\in D} P_h^0(x_i\cdot p)P_k^0(y_i\cdot q)}_{\text{Independent of } \sigma,\ \text{evaluated } \textbf{once}} \Bigg]$$

Naive evaluation takes $O(n|D|)$ time for $n$ choices of $\sigma$. This formulation runs in $O(n+|D|)$.

# Degree Equivalents




Estimated density of sampled marginal connectivity functions.

# Degree Equivalents

## Consistency and Asymptotic Normality

Assume the true connectivity function $\lambda$ is continuous, and let $\hat{\lambda}$ be function recovered by the previously described KDE.

Then $\hat{\lambda}$ is a special case of the class of manifold KDE described by Henry and Rodriguez [HR09]. The error function

$$Err(\lambda, \hat{\lambda}) = |\lambda - \hat{\lambda}|$$

converges almost surely to zero everywhere (it is **consistent**), and obeys a central limit theorem (asymptotically a vanishing normal distribution).

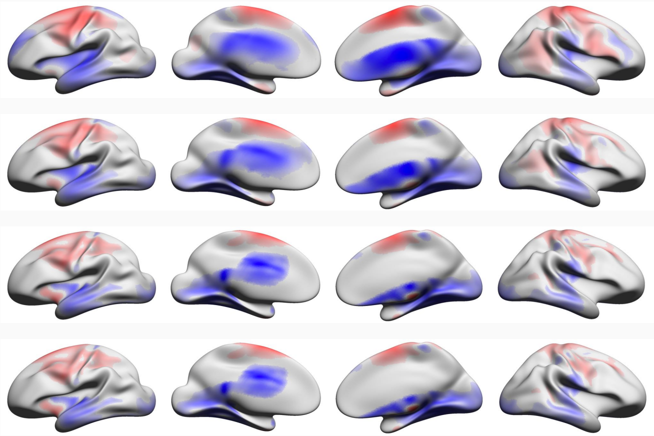
Moreover, the integral of this error is also asymptotically normal.

Procedure:

1. Recover the cortical surfaces (each hemisphere $\sim S^2$)
2. Register the surfaces.
3. Recover tractographies using both DTI and CSD local models.
4. Estimate $\hat{\lambda}_{DTI}$ and $\hat{\lambda}_{CSD}$.
5. Test point-wise differences between $\hat{\lambda}_{DTI}$ and $\hat{\lambda}_{CSD}$ using a $t-$test.

# Degree Equivalents

Red is DTI, Blue is CSD.



$\sigma = 0.01$

$\sigma = 0.005$

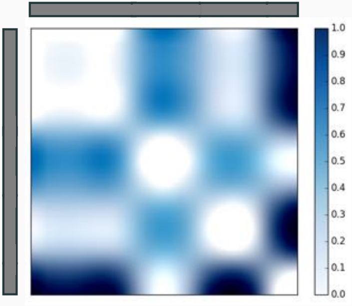
$\sigma = 0.001$

$\sigma = 0.0005$

# Other Applications

# Continuum to Discrete

$$\lambda : \Omega \times \Omega \to \mathbb{R}^+$$



# Continuum to Discrete

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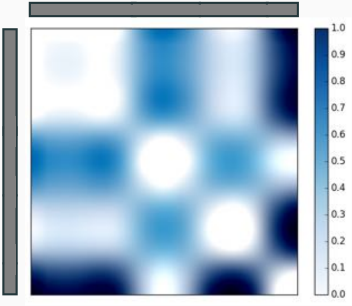
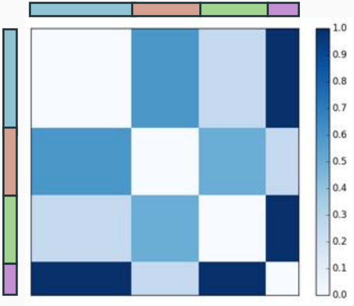
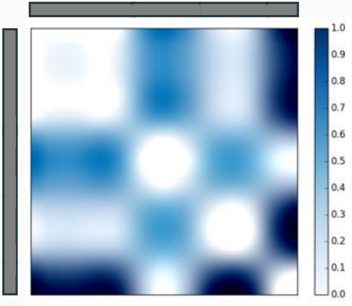


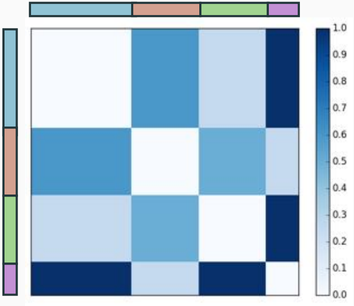

$$\mathcal{G} : \{E_k\}_{k=1}^{K} \times \{E_k\}_{k=1}^{K} \to \mathbb{R}^+$$



# Continuum to Discrete

$$\lambda : \Omega \times \Omega \to \mathbb{R}^+ \qquad \mathcal{G} : \{E_k\}_{k=1}^K \times \{E_k\}_{k=1}^K \to \mathbb{R}^+$$




Def: $\mathcal{G}(E_i, E_j) = \iint_{E_i \times E_j} \lambda(x, y) dx dy$

$= \mathbb{E}[\text{No. of obs. tracks from } E_i \text{ to } E_j]$

# Comparison of Parcellation Sets

Criteria for choosing a parcellation:

$$\ell_2(P) = \sum_{(E_i,E_j)\in P} \iint_{E_i \times E_j} \left[Adj_{ij} - \lambda(x,y)\right]^2 dxdy$$

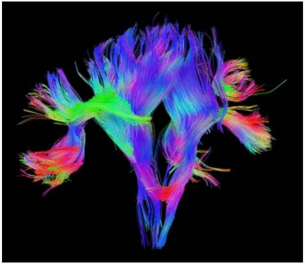
$$\ell_{like}(P) = \sum_{(E_i,E_j)\in P} \log \mathcal{L}(Adj_{ij})$$

$$\begin{aligned} AIC(P) &= \ell_{like} - \#\text{ of parameters} \\ &= \ell_{like} - |P|^2 \end{aligned}$$

# Parcellation Choice

Preliminary results:

| Type | DK | Destrieux | DKT31 |
|---|---|---|---|
| $\ell_2(P)$ | $1.0517 \times 10^{-5}$ | $\mathbf{1.0257 \times 10^{-5}}$ | $1.1262 \times 10^{-5}$ |
| $\ell_{like}(P)$ | **85256.0** | 357292.9 | 88434.9 |
| $AIC(P)$ | **175068.1** | 736341.9 | 185234.3 |



Three important problems:

1. Tracks have noise.
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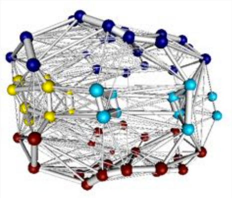

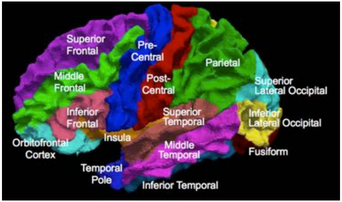


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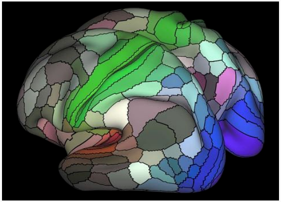

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# References


- Moo K Chung, *Heat kernel smoothing on unit sphere*, Biomedical Imaging: Nano to Macro, 2006. 3rd IEEE International Symposium on, IEEE, 2006, pp. 992–995.
- Marcel A de Reus and Martijn P Van den Heuvel, *The parcellation-based connectome*, NeuroImage **80** (2013), 397–404.
- Guillermo Henry and Daniela Rodriguez, *Kernel density estimation on riemannian manifolds: Asymptotic results*, Journal of Mathematical Imaging and Vision **34** (2009), no. 3, 235–239.
- Anton Lord et al., *Brain parcellation choice affects disease-related topology differences*, Psychiatry Research: Neuroimaging **249** (2016), 12–19.
- Rafael Romero-Garcia et al., *Effects of network resolution on topological properties of human neocortex*, Neuroimage **59** (2012), no. 4, 3522–3532.
- Andrew Zalesky et al., *Whole-brain anatomical networks: does the choice of nodes matter?*, NeuroImage **50** (2010), no. 3

Thank you!

Questions?

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