

Graph theory workshop

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Outline

Introduction to graph theory/network neuroscience

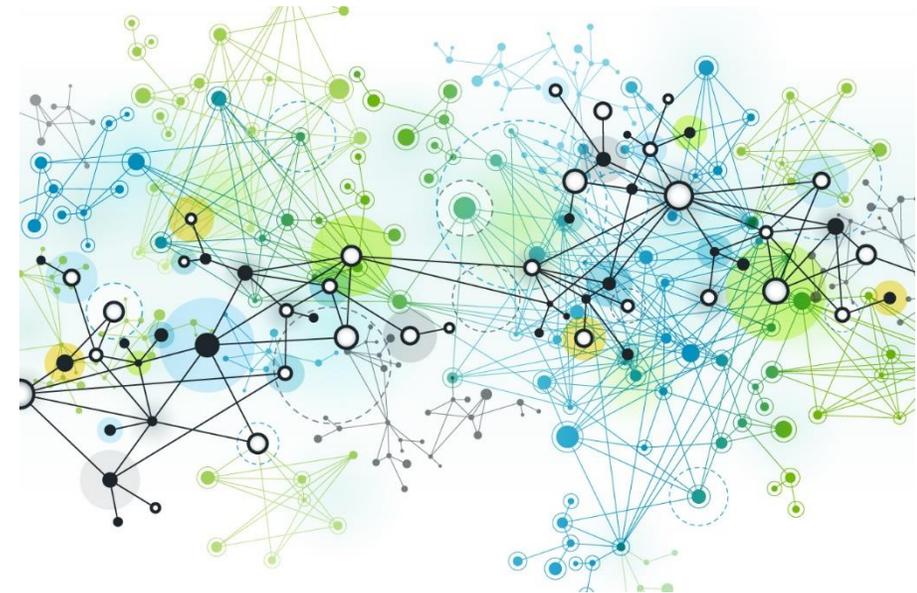
Exercise 1: Basic graph theoretical analysis of an fMRI brain network using the Brain Connectivity Toolbox

Exercise 2: Null models

Going further...novel graph theoretical approaches

Tips for brain network visualisation

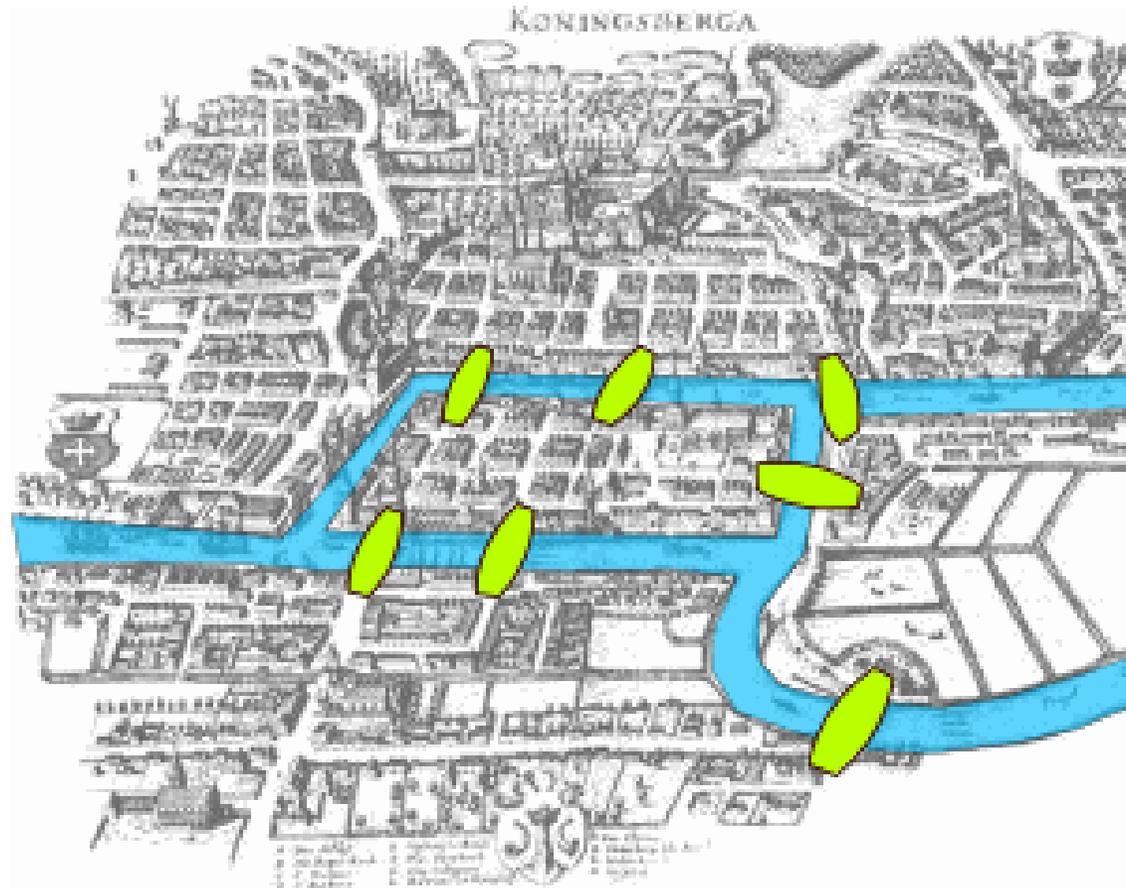
Q&A



What is graph theory?



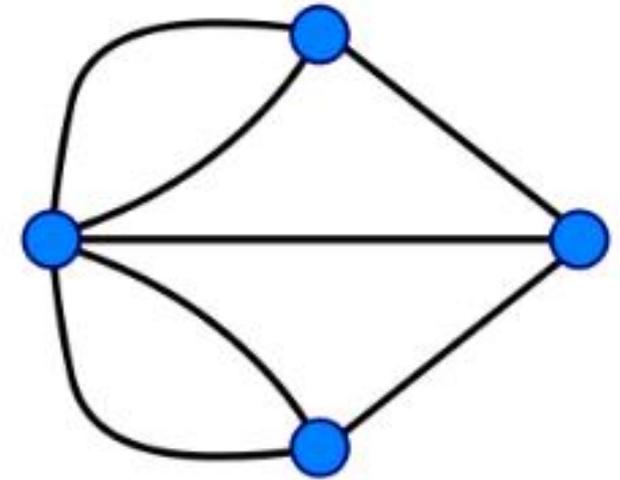
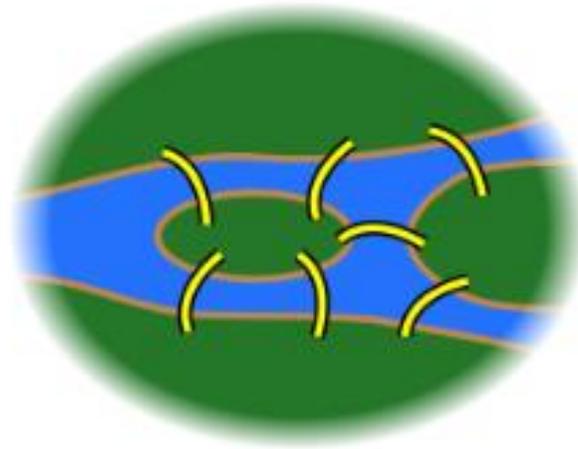
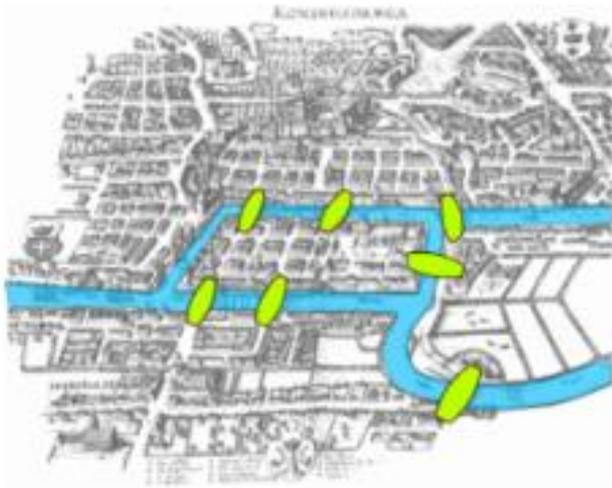
Seven Bridges of Königsberg



Can you walk through the city crossing all bridges only once?

In 1736, Euler used graph theory to show this is not possible.

Seven Bridges of Königsberg



1990s and early 2000s...advent of Network Science



Digital revolution → ability to map complex networks

A realisation of the universality of network characteristics (e.g. scale free → simple model, from growth + preferential attachment, Barabasi-Albert model)

Emergence of Scaling in Random Networks

Albert-László Barabási* and Réka Albert

Systems as diverse as genetic networks or the World Wide Web are best described as networks with complex topology. A common property of many large networks is that the vertex connectivities follow a scale-free power-law distribution. This feature was found to be a consequence of two generic mechanisms: (i) networks expand continuously by the addition of new vertices, and (ii) new vertices attach preferentially to sites that are already well connected. A model based on these two ingredients reproduces the observed stationary scale-free distributions, which indicates that the development of large networks is governed by robust self-organizing phenomena that go beyond the particulars of the individual systems.

The inability of contemporary science to describe systems composed of nonidentical elements that have diverse and nonlocal inter-

actions currently limits advances in many disciplines, ranging from molecular biology to computer science (*1*). The difficulty of describing these systems lies partly in their topology: Many of them form rather complex networks whose vertices are the elements of the system and whose edges represent the interactions between them. For example, liv-

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Network Science in 2020



Network Science Society- www.netscisociety.net/

Annual NetSci conference (Rome, July 2020), including Network Neuroscience Satellite



Cambridge Networks' Network- join our mailing list- www.cnn.group.cam.ac.uk

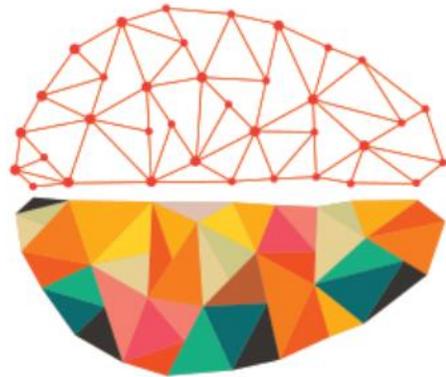
Bi-annual Cambridge Networks day (last one was August 2019, expect another in 2021)



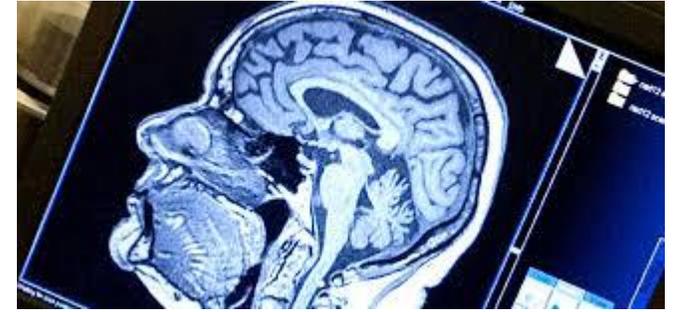
Network Neuroscience

“Understanding the brain represents one of the most profound and pressing scientific challenges of the 21st century. As brain data have increased in volume and complexity, the tools and methods of network science have become indispensable for mapping and modeling brain structure and function, for bridging scales of organization, and for integrating across empirical and computational methodologies.”

Sporns, Network Neuroscience, 2017



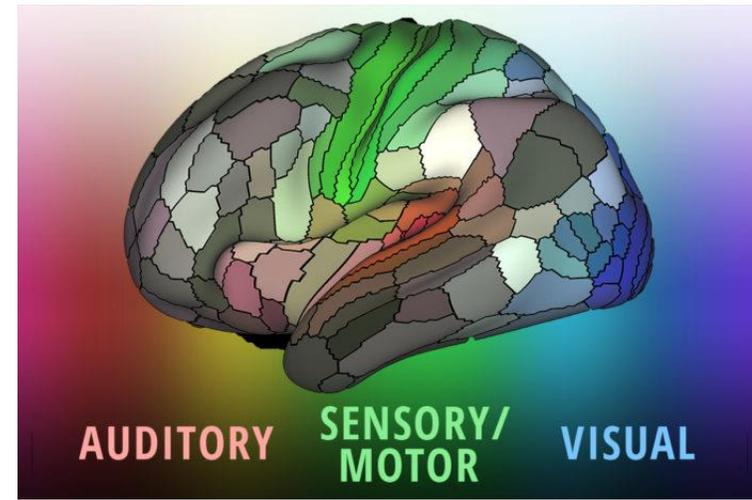
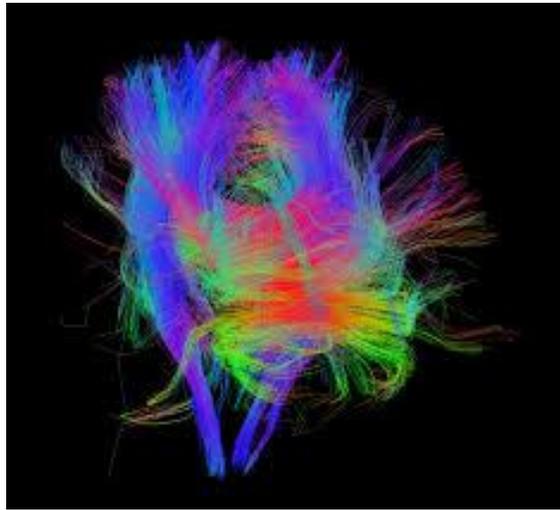
How do you construct a brain network?



Structural brain networks

DTI

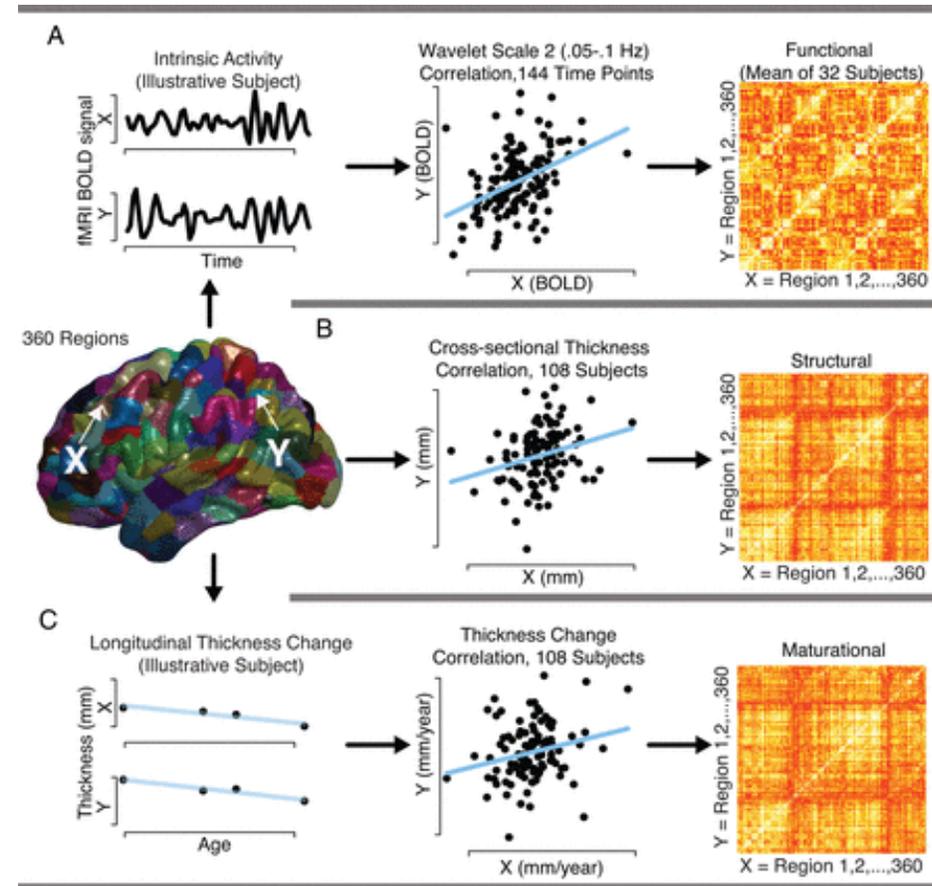
- Use the diffusion of water molecules to generate contrast in MR images
- Nodes are brain regions
- Estimate tracts between brain regions by assuming that the direction of greatest diffusivity is aligned to the local orientation of the white matter fibres
- Edges are often weighted by number of streamlines (or streamline density, or FA)



Glasser et al, 2016

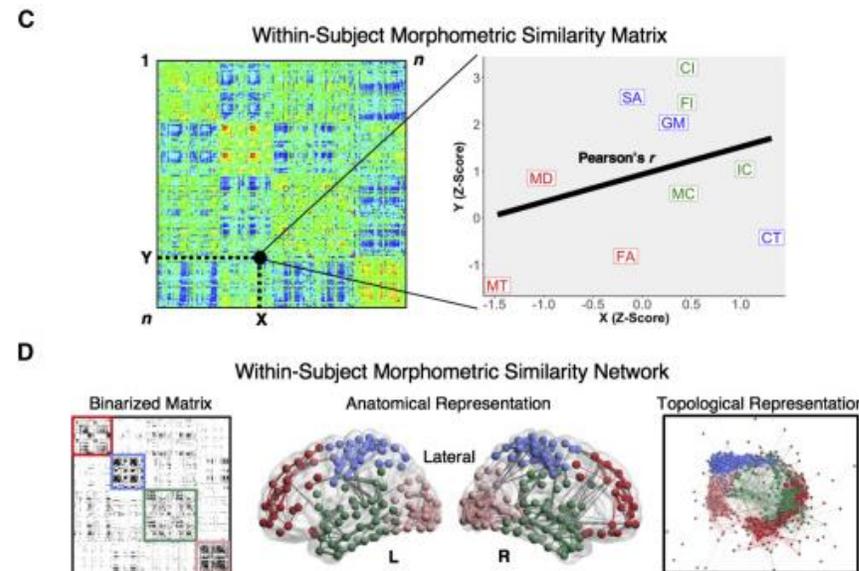
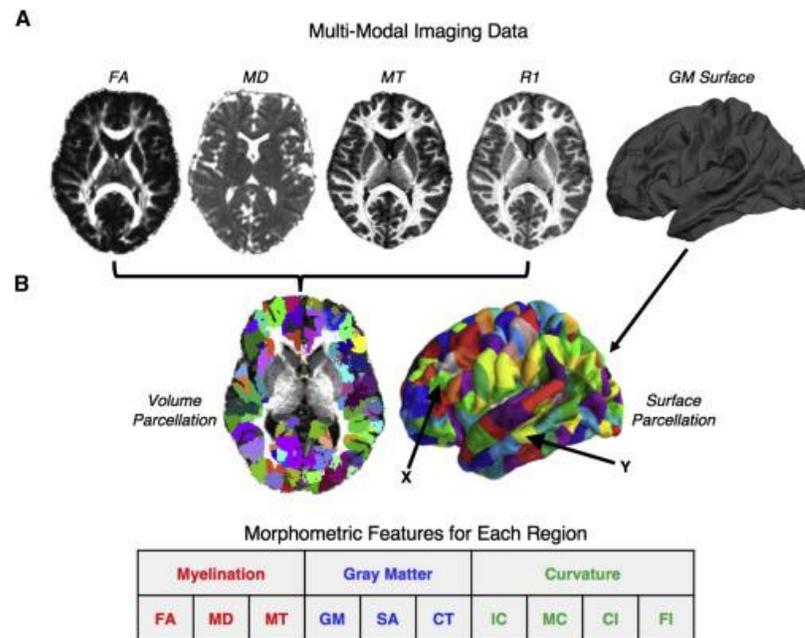
Structural covariance networks

- Creates a single network per group
- Nodes correspond to brain regions
- Edges represent cross-correlations of morphological metrics between pairs of regions taken across subjects
- For a review, see Alexander-Bloch et al *Nature Reviews Neuroscience* volume 14, pages 322–336 (2013)



Morphometric similarity networks

- A new way to construct a single structural network per subject from a T1w image
- Correlate 5-10 structural measures across regions within a single subject (Seidlitz et al, Neuron, 97, 231-247, 2018)

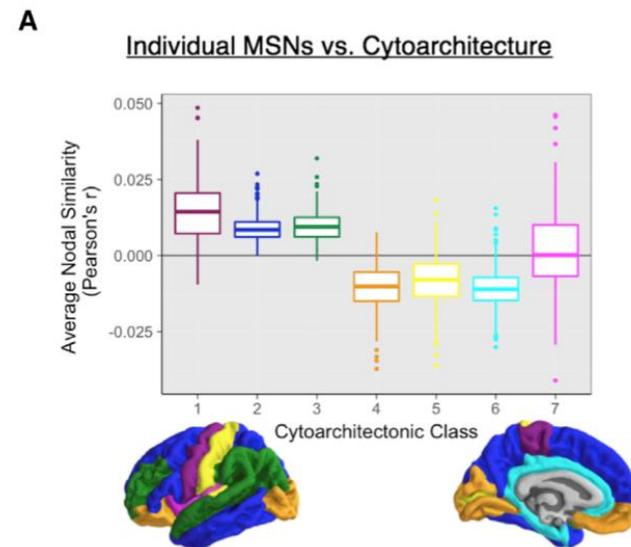
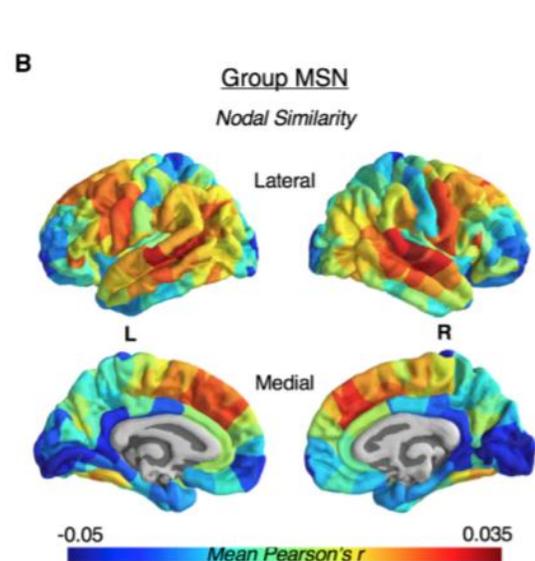


Seidlitz et al, Neuron, 2018

What is morphometric similarity?

Seidlitz et al, Neuron 2018 key points:

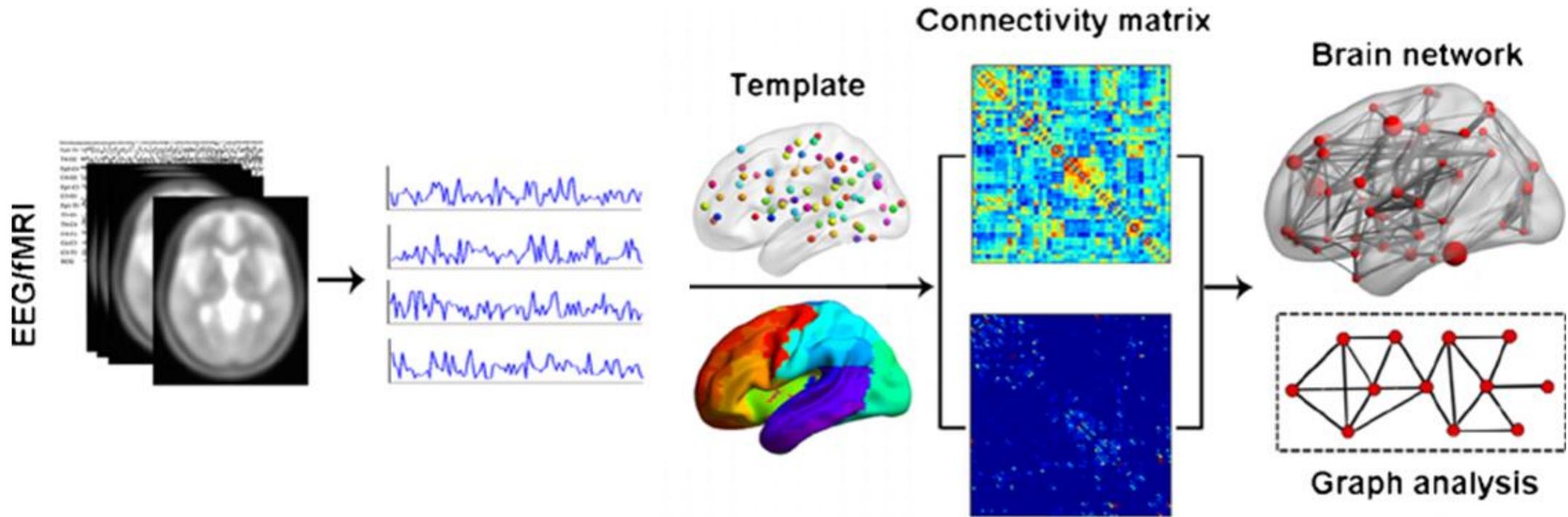
1. Can generate individual structural matrices (unlike structural covariance approach)
2. Macaque MSNs map onto connectivity derived from tract tracing
3. Morphometric similarity captures known cortical cytoarchitecture and related gene expression
4. MSN degree could explain about 40% of between subject variance in IQ



Seidlitz et al, Neuron, 2018

Functional brain networks

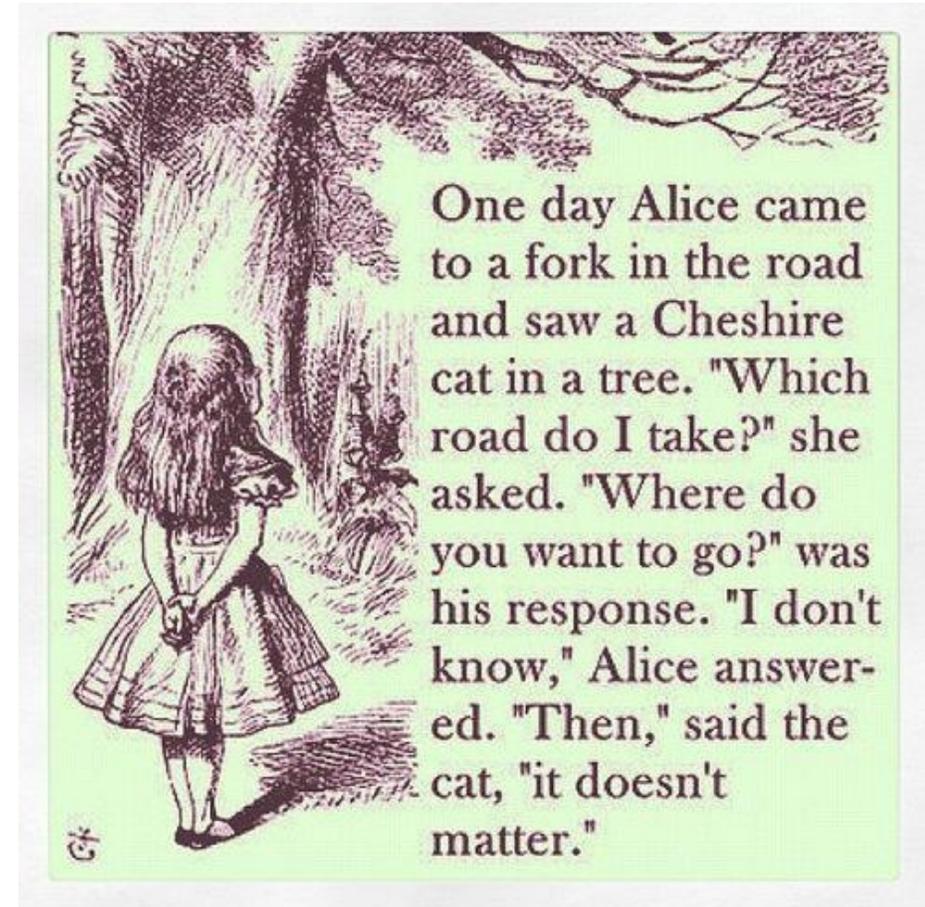
Functional brain networks:



Adapted from Cao et al, Molecular Neurobiology, 2014

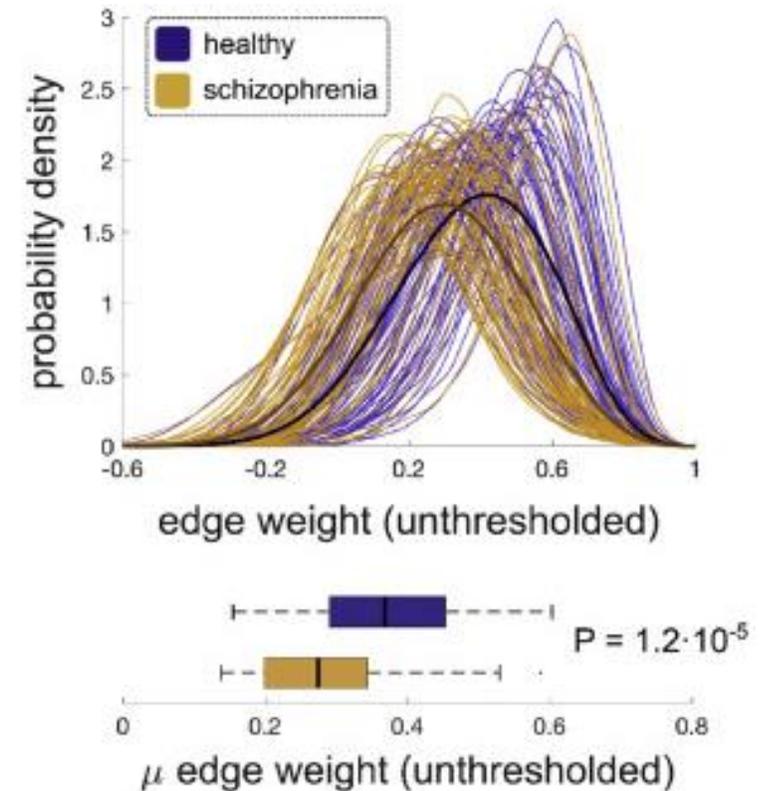
fMRI- notes about pre-processing:

- Different pre-processing steps will often affect higher order graph theory results
- Whether to perform global signal regression (GSR) is controversial- (Murphy and Fox, NeuroImage, 154, 169-173, 2017)
- There are no 'right' or easy answers ("Different processing approaches reveal complimentary insights about brain function"), but you need to bear these issues in mind when interpreting your results



Mean fMRI also often varies between subject group:

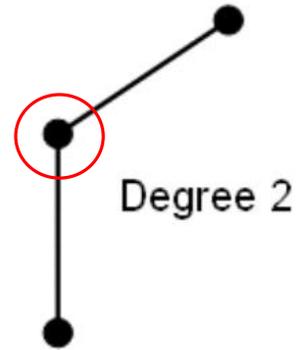
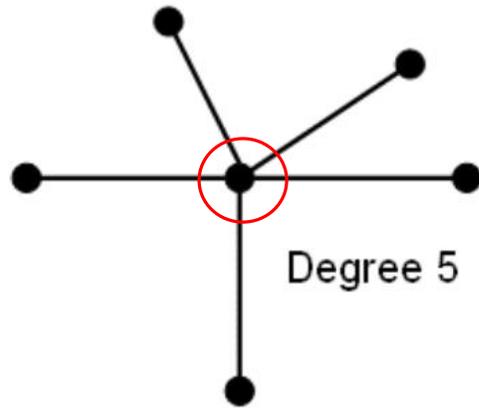
- Mean fMRI correlation often varies between subject group and can play a strong role in determining graph theory metrics (van den Heuvel et al, NeuroImage, 152, 437-449, 2017)
- Best to start by plotting the correlation distributions, and getting to know your data as well as possible!



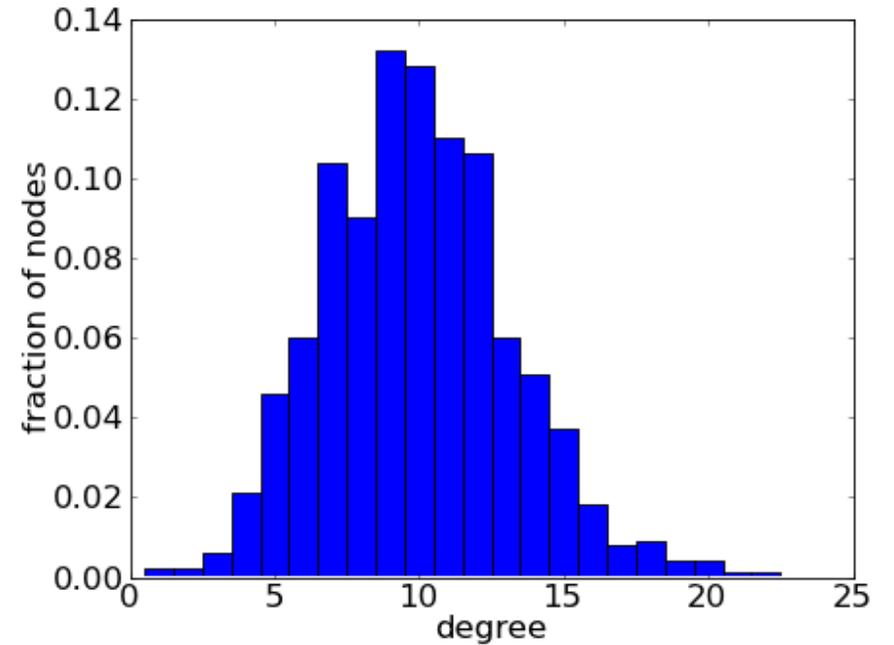
Vasa et al, 2018

How to characterise a graph

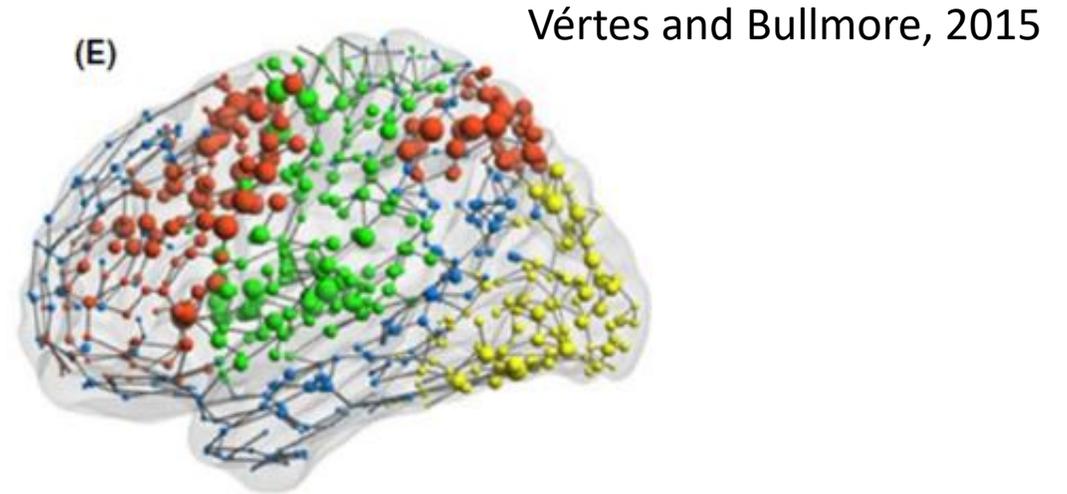
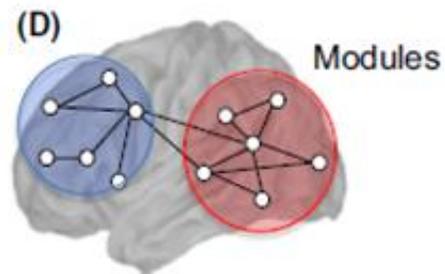
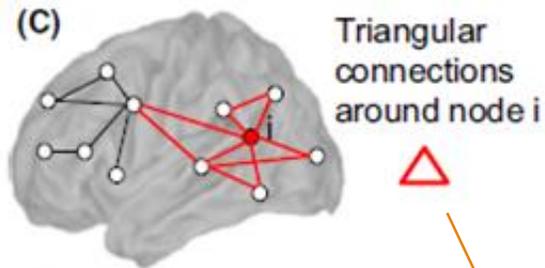
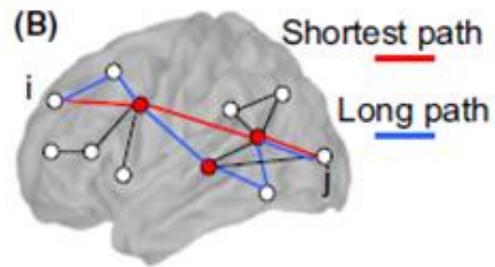
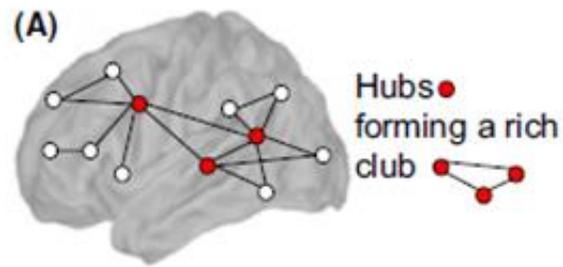
Degree:



Degree distribution:



How to characterise a graph



Clustering coefficient- what fraction of your neighbours are connected?

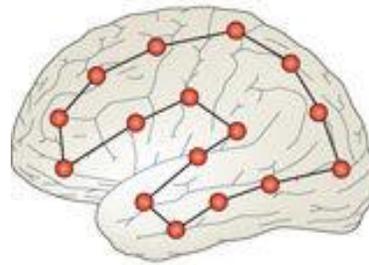
$$C_i = \frac{2 n_i}{k_i (k_i - 1)}$$

Economic trade-off

Brain networks have been shown to make an economic trade-off:

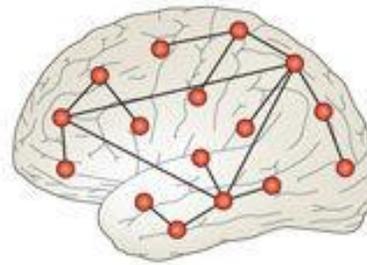
- Long distance edges are expensive to create and maintain
- But they have useful topological benefits

Lattice topology

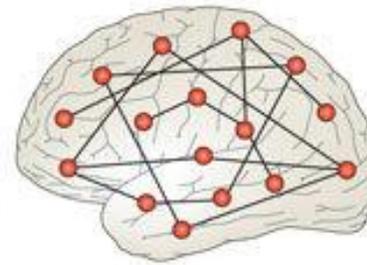


- Low efficiency
- High clustering
- Low cost

Complex topology



Random topology



- High efficiency
- Low clustering
- High cost

Are graph theory and connectomics useful?

Not the full story, but...

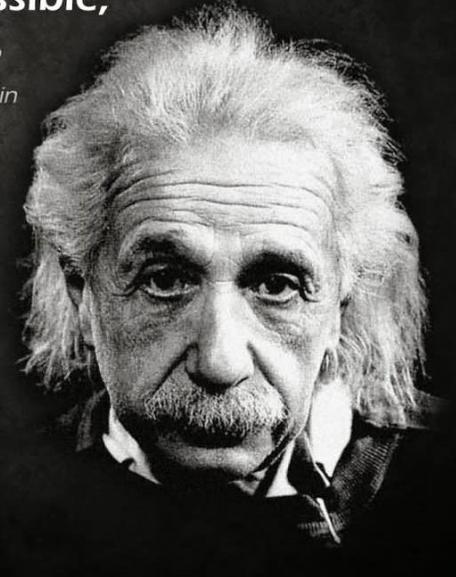
'A useful, simplified abstraction that allows to formally address critical questions, e.g.:

- How does brain network structure constrain function?
- What are the general organizational principles of brain networks?
- What developmental processes can give rise to networks that look and function like the brain?'

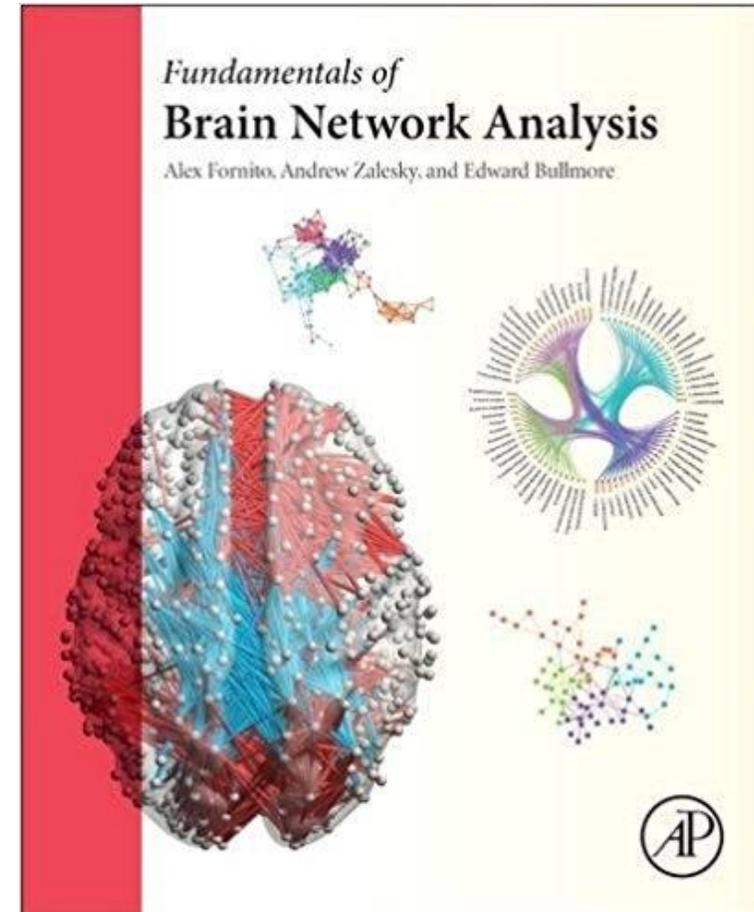
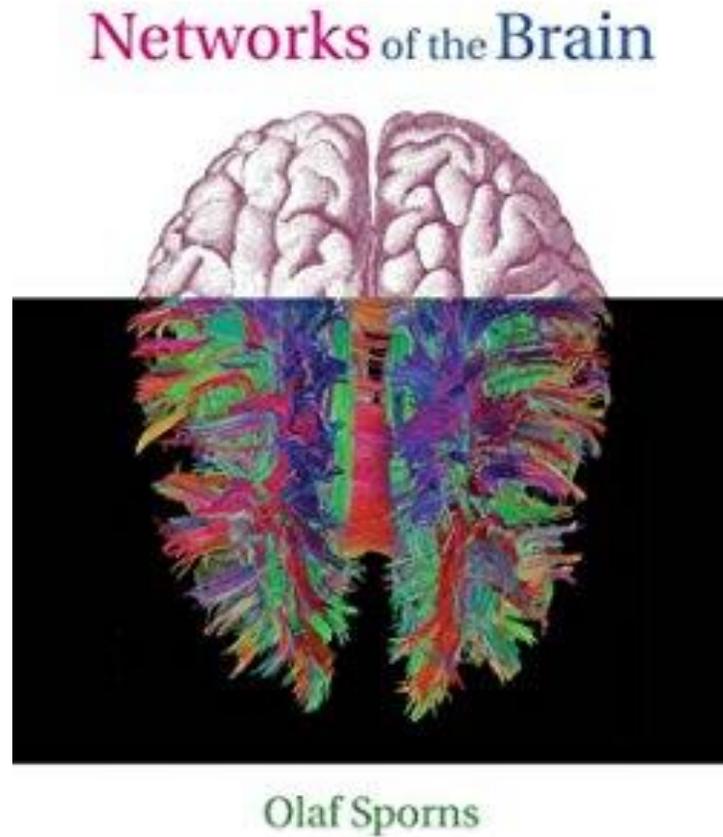
Always important to match methods to the question you're interested in!

**Everything
should be made
as simple as possible,
but not simpler.**

Albert Einstein



Network Neuroscience- Books



Toolboxes for graph theoretical analysis:

Today we will use Matlab, with the Brain Connectivity Toolbox (BCT), which can be downloaded online at: <https://sites.google.com/site/bctnet/>

Another helpful Matlab toolbox is the BGL:
<http://www.mathworks.com/matlabcentral/fileexchange/10922>

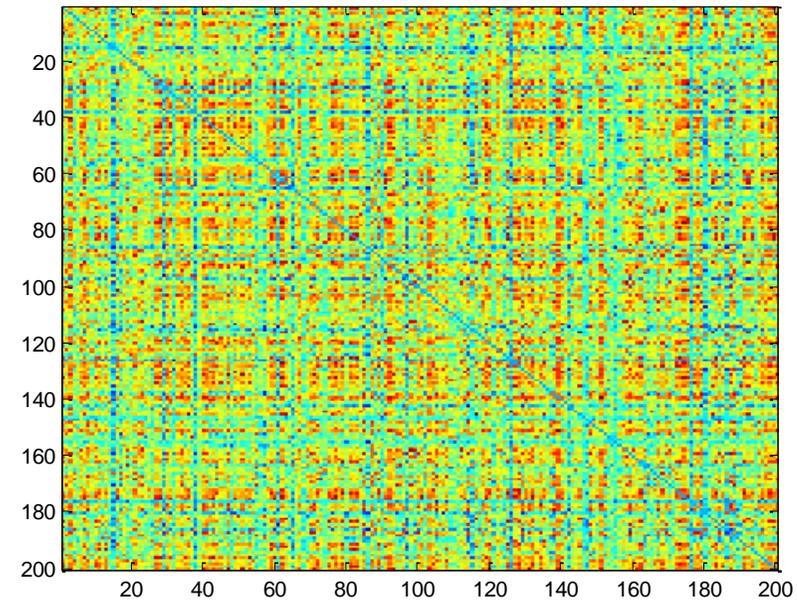
There are other options available, e.g. NetworkX in Python:
<https://networkx.github.io/>



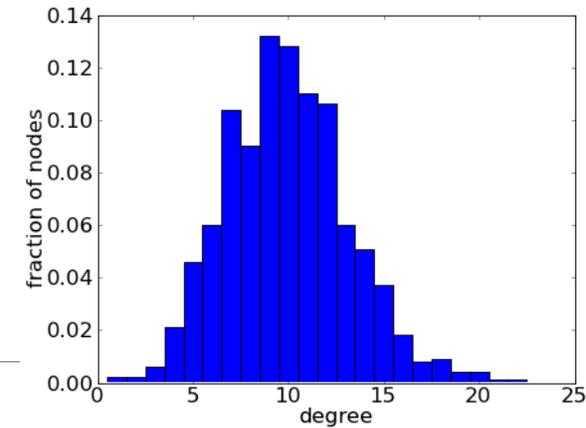
Exercise 1- characterising a brain network

- a) Open Matlab and load the file 'matrix.mat' (this is an fMRI correlation matrix, with 200 brain regions)
- b) Try plotting the matrix using the command: `imagesc(matrix)`. What do you notice about it?

https://figshare.com/articles/Materials_for_CBU_graph_theory_workshop/11766924/2



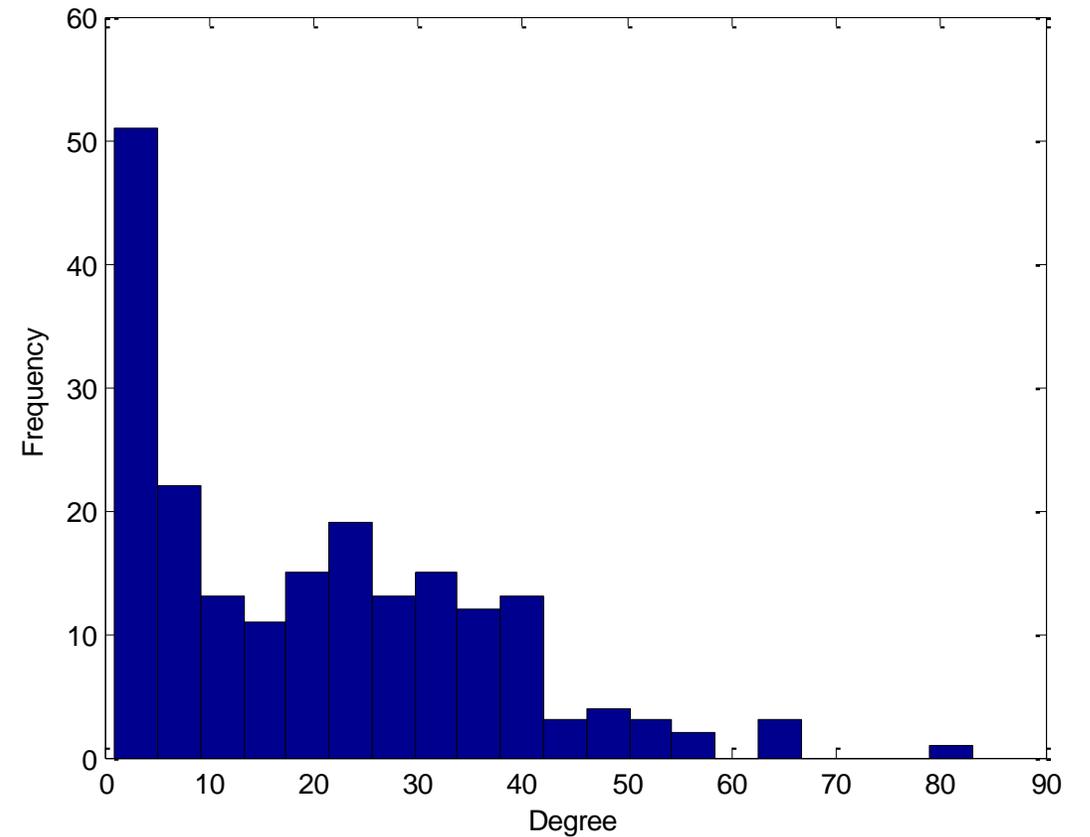
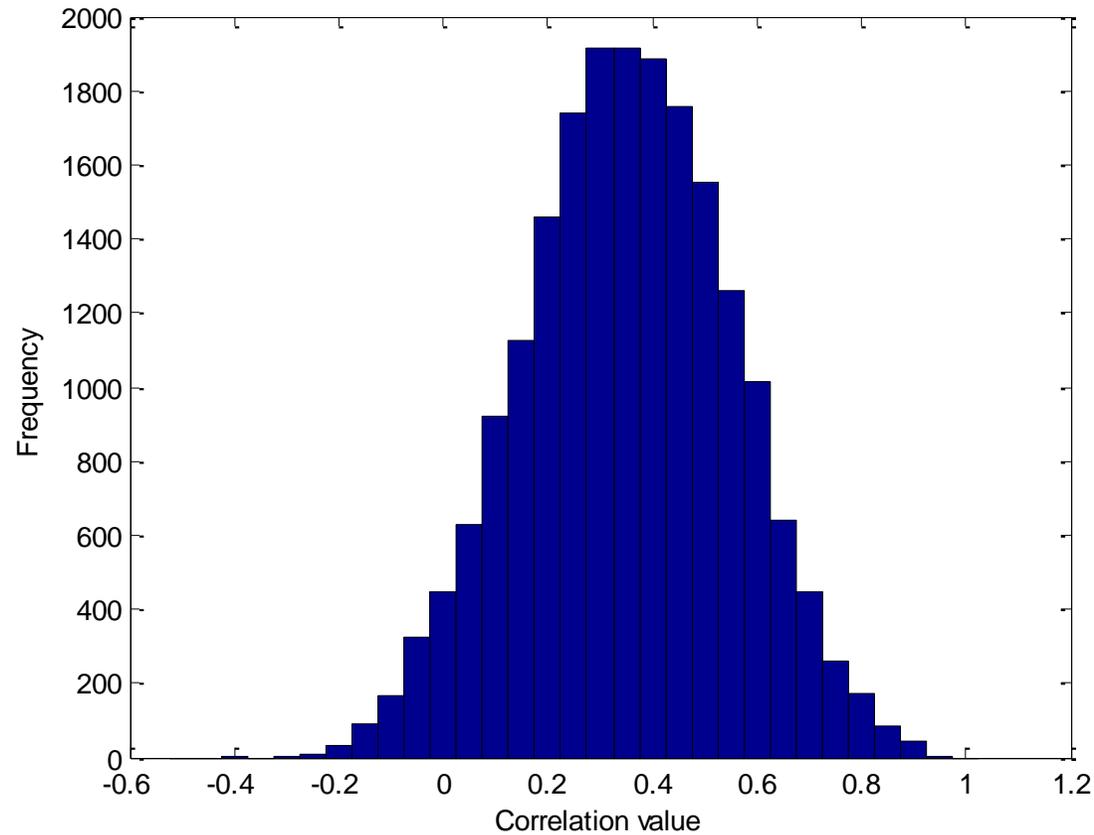
Exercise 1- characterising a brain network



- c) Using the script 'exercise_1.m', plot the correlation distribution for the correlation matrix.
- d) Then threshold and binarise the matrix at 10% density (see if you can understand exactly what the code is doing and why! We often binarise networks to remove weak 'noisy' correlations)
- e) Plot the degree distribution of the network. Remember the degree distribution is $P(k)$, i.e. the probability that a node has degree k (see figure at the top of this slide).
- f) Using the BCT toolbox, calculate the mean shortest path length, L , and the clustering coefficient, C , for your thresholded, binarized network. *Hint: the BCT function to calculate clustering coefficient begins with: 'clustering_coef_...'. The function to calculate the average shortest path length is 'charpath.m'. But be warned- charpath.m doesn't take the input you might expect. Read the documentation carefully!*

Extension: What do you think are the pros/cons of binarizing a network vs using the fully weighted version?

Exercise 1- characterising a brain network



Exercise 1- characterising a brain network

```
degree=sum(matrix_thresh);  
figure  
hist(degree,20) % plots the correlation distribution  
xlabel('Degree')  
ylabel('Frequency')
```

Code to calculate C and L:

```
C=mean(clustering_coef_bu(matrix_thresh));
```

```
L = charpath(distance_bin(matrix_thresh));
```

```
C=0.49, L=2.93
```

Null network models

How do we interpret our results? Are our values for C and/or L particularly unusual?

To answer these questions, we need to have a benchmark.

Null network models can help.



Erdos-Renyi networks

There are lots of possible null models!

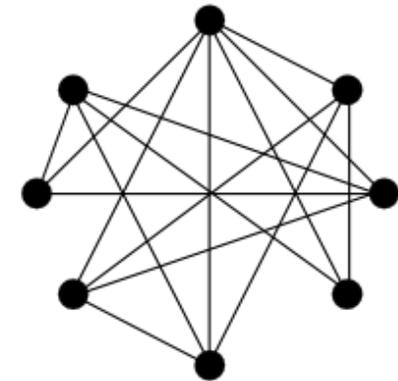
e.g. Erdos-Renyi graph: $G(n,p)$

- n =number of nodes
- p =probability of adding an edge between any two nodes
- Each possible edge is included with probability p

Or preserve the degree distribution

- Often preferred if you want to check your result isn't simply driven by the degree distribution
- Can select an algorithm which keeps the network connected

Small ER network



Exercise 2: null network models

- a) Read the BCT's section on null networks-<https://sites.google.com/site/bctnet/null>
- b) We want to assess whether the C and λ we obtained earlier are higher or lower than we would expect in random networks. Select the appropriate null network model from the BCT (preserving degree distribution) and use it to generate 100 null networks in Matlab
- c) Calculate the mean C and L for each of these null networks (C_r and L_r)
- d) Networks with $\sigma = \frac{C/C_r}{L/L_r} > 1$ are often defined as small-world (high clustering and short path length). Is our brain network small-world? You can learn more about small-world networks here: https://mathinsight.org/small_world_network

Exercise 2

```
randmatrix=cell(1,100);  
for ind=1:100  
    [R,eff] = randmio_und_connected(matrix_thresh, 10);  
    randmatrix{1,ind}=R;  
end  
for ind=1:100  
    C_rand(ind)=mean(clustering_coef_bu(randmatrix{1,ind}));  
    L_rand(ind)=charpath(distance_bin(randmatrix{1,ind}));  
end
```

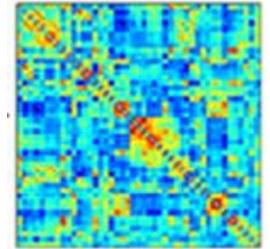
```
mean(C_rand) % = 0.25  
mean(L_rand) % = 2.3
```

$$\sigma = \frac{0.49/0.25}{2.9/2.3} = 1.6, \quad > 1$$

Going further...more novel graph theory
approaches

Network based statistics

- One approach to go beyond regional degree is Network Based Statistics (NBS)
- NBS is a method to control the family wise error rate when performing mass-univariate testing at every edge in a graph (e.g. to test for case-control differences)
- It exploits the interconnections between regions (the fact that edges are not independent of each other) to give a large increase in power
- A NBS toolbox is available online-
<https://sites.google.com/site/bctnet/comparison/nbs>



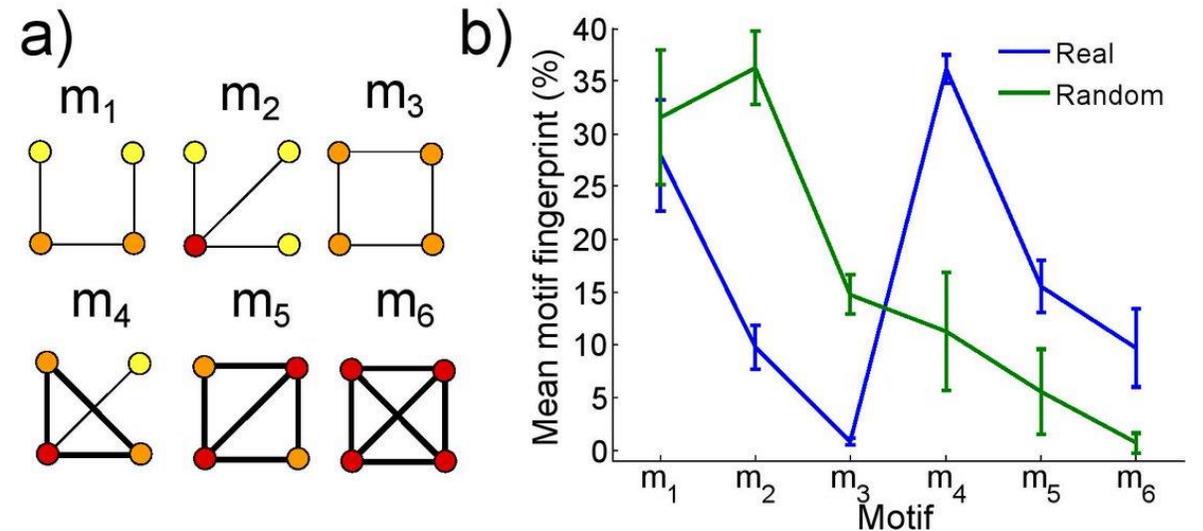
(a) FDR ($q = 10\%$)



(b) NBS ($p = 0.037$)

Motif analysis:

- Network motifs have been described as the 'building blocks' of complex networks (Alon et al, Science 2002)
- By counting the occurrence of each possible motif, you can create a motif fingerprint for your network
- Flexible approach to studying local connectivity patterns
- E.g. Sporns and Kotter, PLoS Biol, 2004 suggested that brain networks maximize both the number and the diversity of functional motifs, while the repertoire of structural motifs remains small
- The FANMOD tool allows for fast motif detection- <http://theinf1.informatik.uni-jena.de/motifs/>



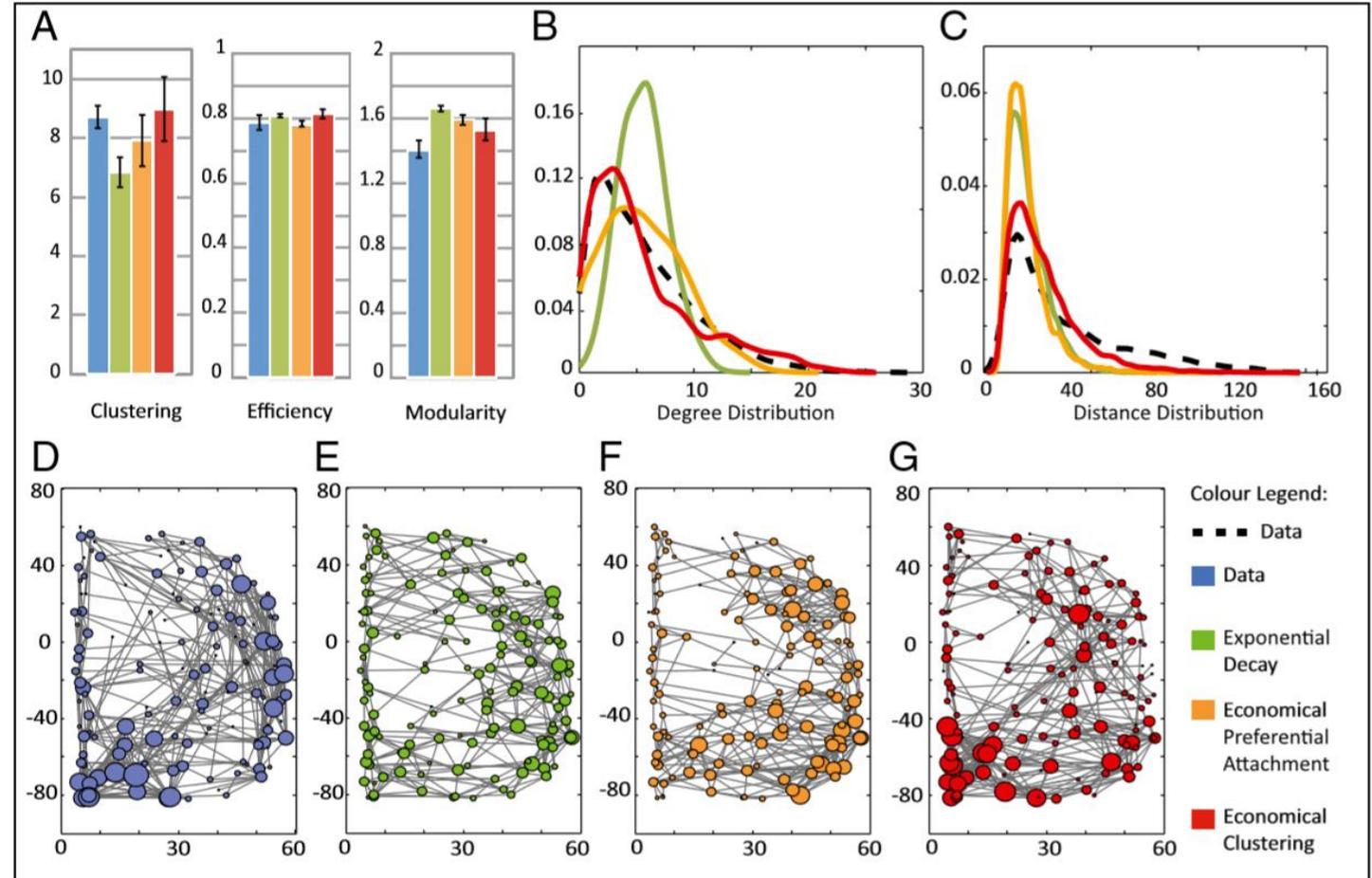
Morgan et al, Network Neuroscience, 2018

Generative models

What are the organisational principles underlying brain networks?

Vértes et al, PNAS 2012 showed you can use a simple function to generate networks with brain-like topologies:

$$P_{i,j} \propto (k_{i,j})^\gamma (d_{i,j})^{-\eta}$$

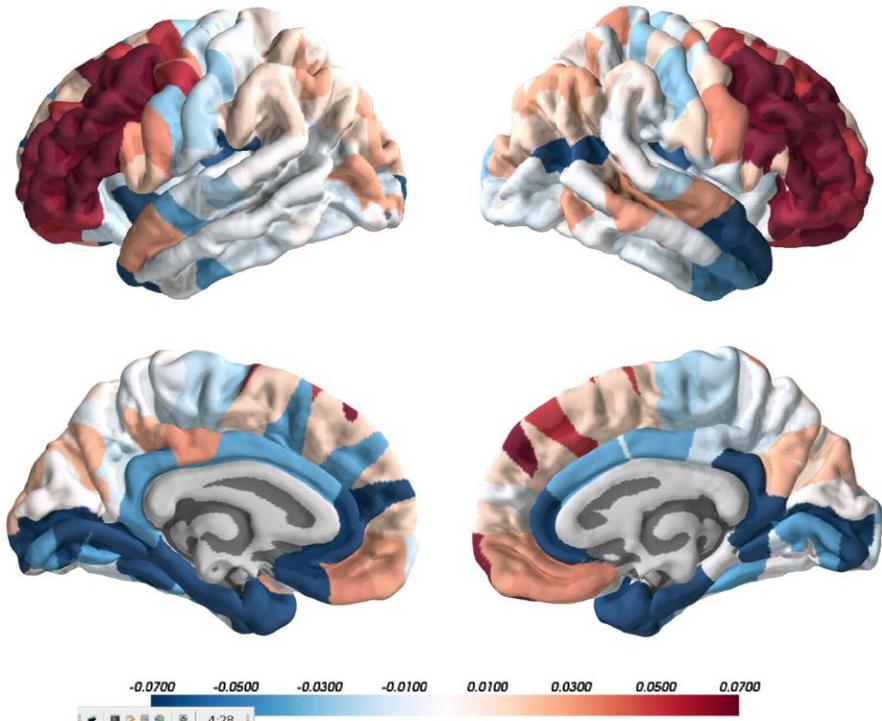


How to visualise a brain network?

To plot regional values:

<https://github.com/WhitakerLab/BrainsForPublication>

(open project, feel free to contribute!)



To plot the whole network:

<https://www.nitrc.org/projects/bnv/>

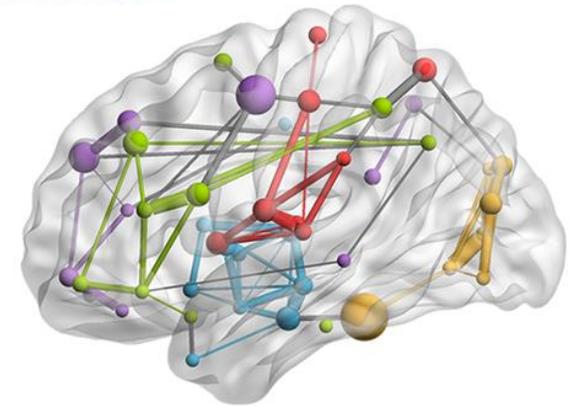
BrainNet Viewer

Please cite:

Xia M, Wang J, He Y (2013) BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. PLoS ONE 8: e68910.

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Any questions?

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