

Graph theory workshop

DR SARAH MORGAN, SEM91@CAM.AC.UK

BRAIN MAPPING UNIT, PSYCHIATRY DEPARTMENT

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Outline

Introduction to graph theory/network neuroscience

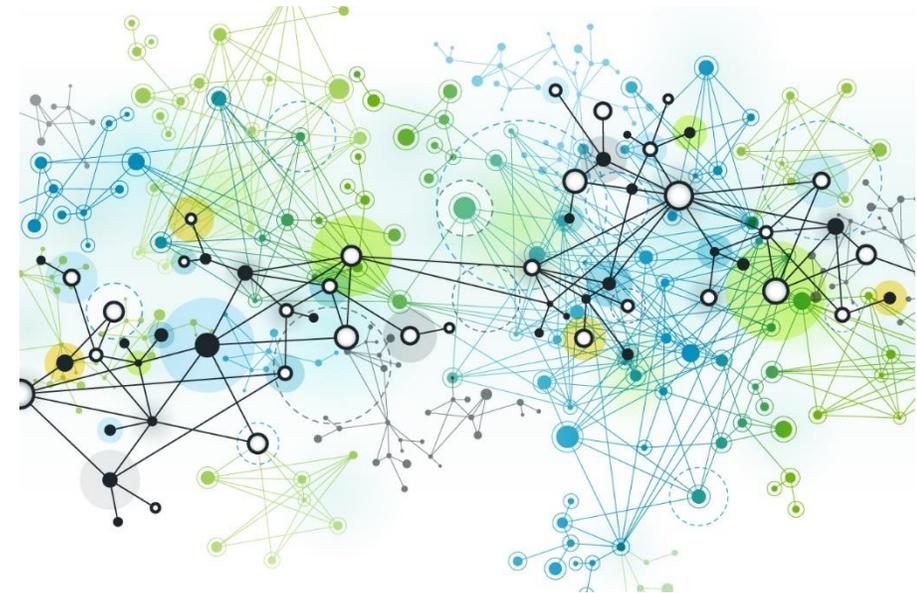
Exercise 1: Basic graph theoretical analysis of an fMRI brain network using the Brain Connectivity Toolbox

Exercise 2: Null models

Going further...novel graph theoretical approaches

Tips for brain network visualisation

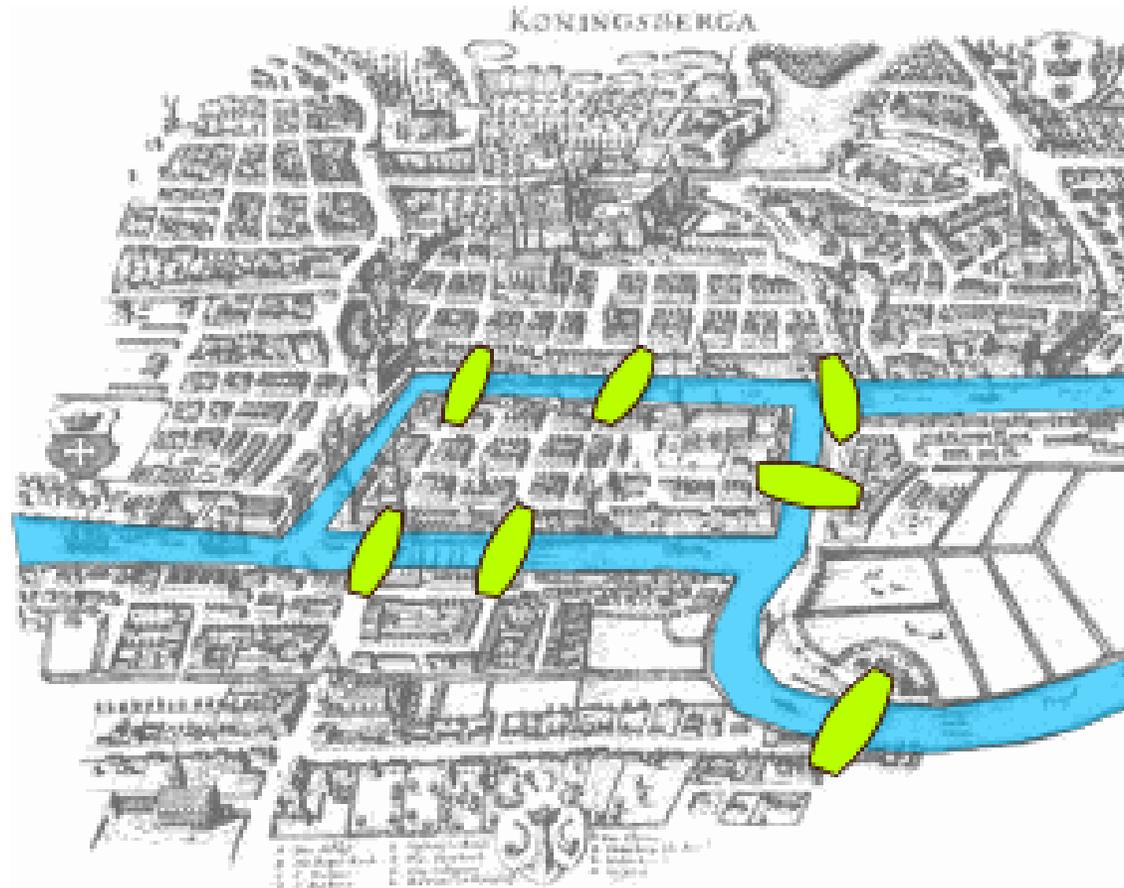
Q&A



What is graph theory?



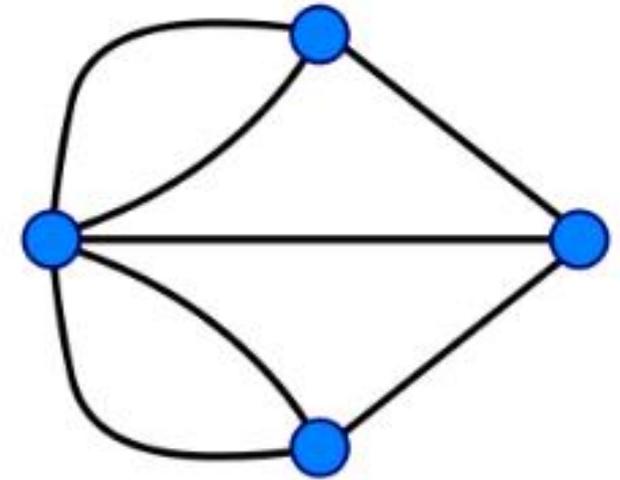
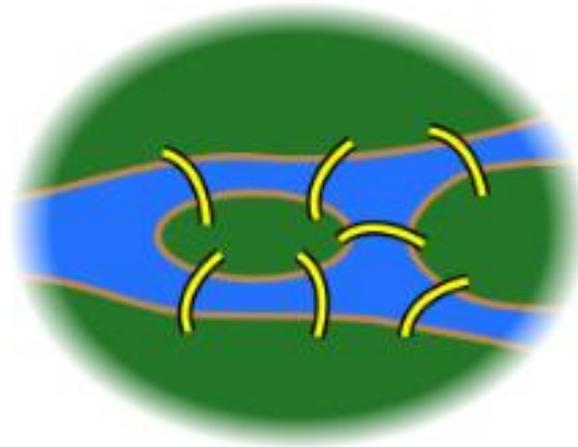
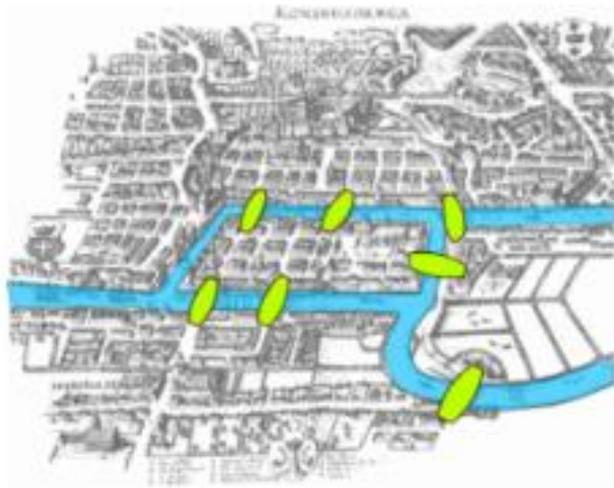
Seven Bridges of Königsberg



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-

Department of Physics, University of Notre Dame, Notre Dame, IN 46556, USA.

*To whom correspondence should be addressed. E-mail: alb@nd.edu

Network Science in 2018



Network Science Society- www.netscisociety.net/

Annual NetSci conference (Paris, June 2018), including Network Neuroscience Satellite



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

Annual Cambridge Networks day normally in May/June, watch this space!!

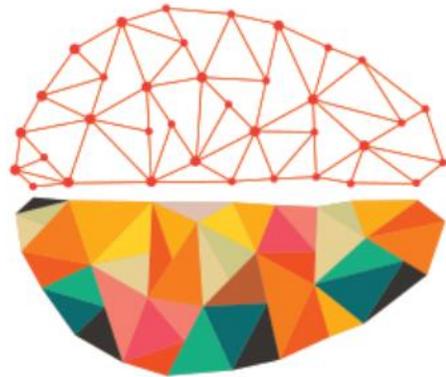
And this year the International Conference on Complex Networks and their Applications is also coming to Cambridge... <http://complexnetworks.org/> (10-13 December)



Network Neuroscience

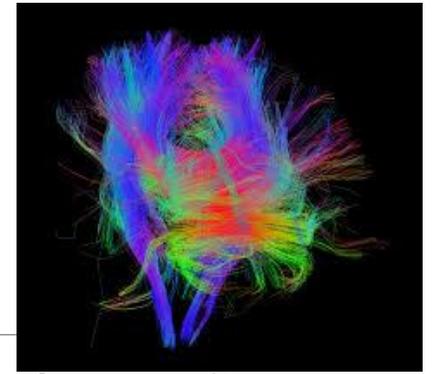
“Understanding the brain represents one of the most profound and pressing scientific challenges of the 21st century. As brain data have increased in volume and complexity, the tools and methods of network science have become indispensable for mapping and modeling brain structure and function, for bridging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

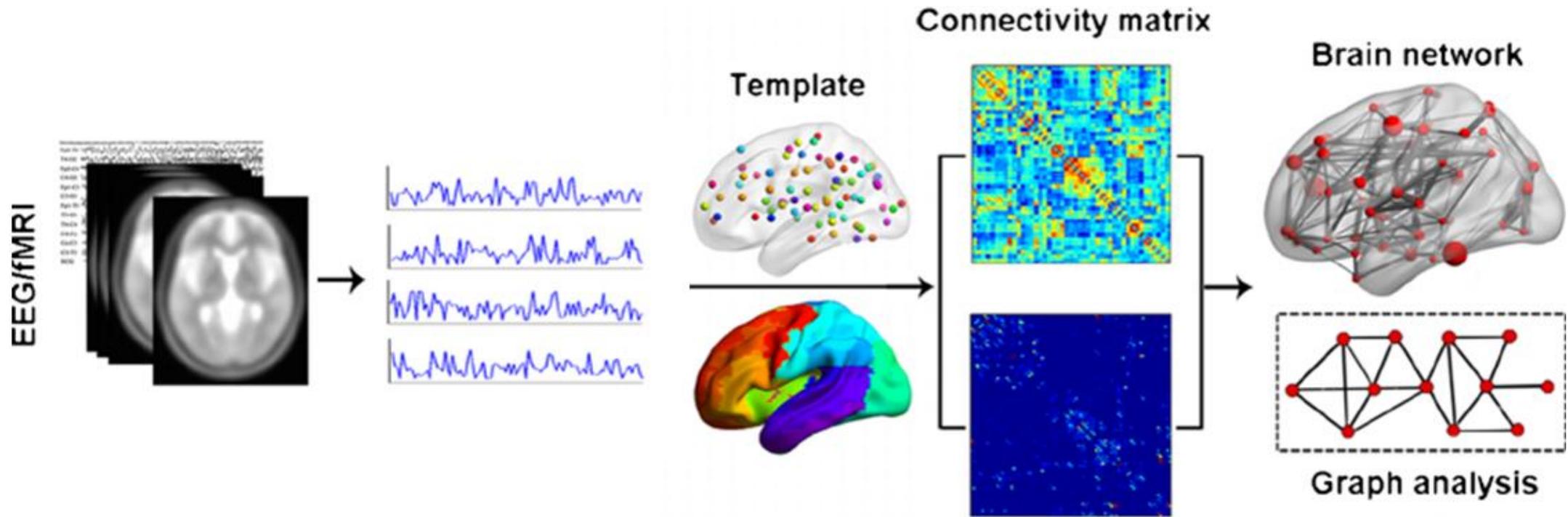


DTI networks- measure tracts between brain regions. Often weighted by number of streamlines (or FA)

Structural covariance networks- creates a single network per group. Nodes correspond to brain regions and the edges represent cross-correlations of morphological metrics between pairs of regions taken across subjects

Morphometric Similarity Networks (MSNs)- a new way to construct a single structural network per subject. Correlate 5-10 structural measures across regions within a single subject (Seidlitz et al, Neuron, 97, 231-247, 2018)

Functional brain networks:



Adapted from Cao et al, Molecular Neurobiology, 2014

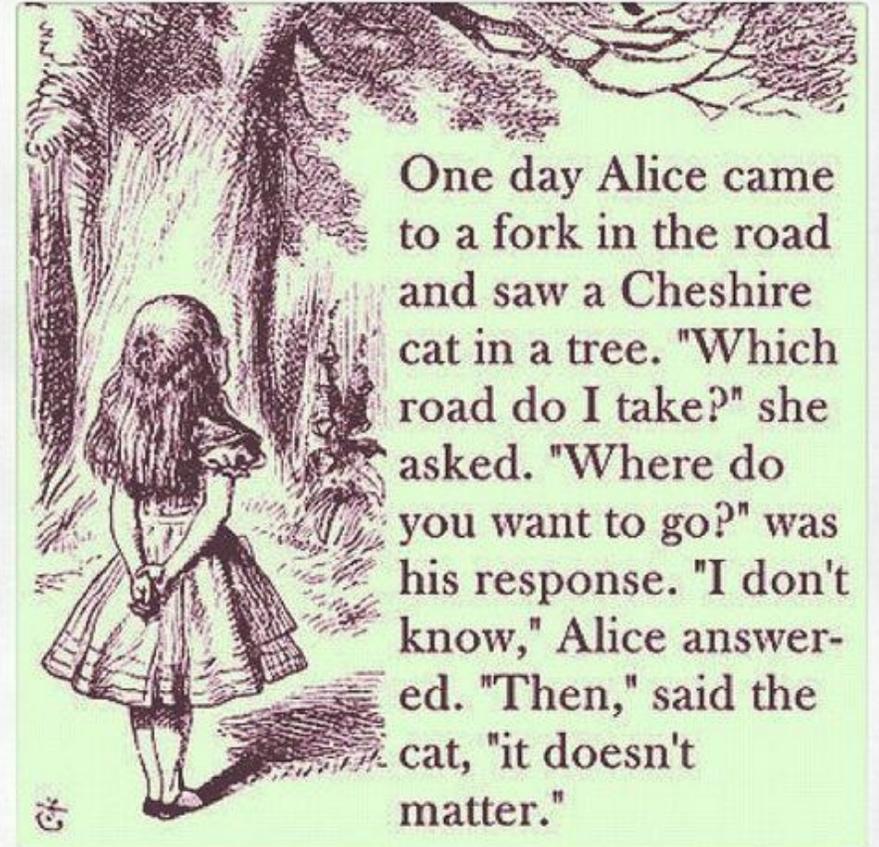
fMRI- a note about pre-processing:

Different pre-processing steps will often affect higher order GT results

Whether to perform global signal regression (GSR) is controversial- (Murphy and Fox, NeuroImage, 154, 169-173, 2017)

Mean fMRI correlation often varies between subject group and can play a strong role in determining metrics like global efficiency (van den Heuvel et al, NeuroImage, 152, 437-449, 2017)

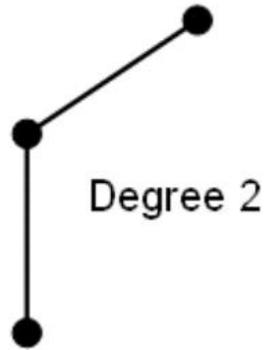
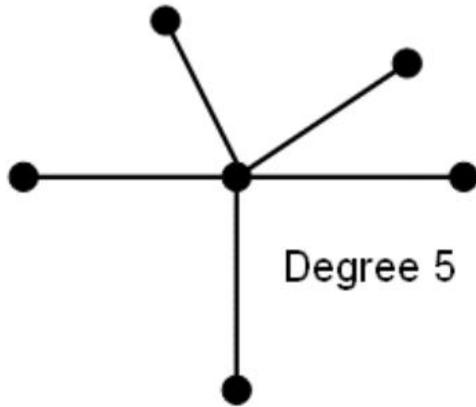
There are no 'right' or easy answers ("Different processing approaches reveal complimentary insights about brain function"), but you need to bear these issues in mind when interpreting your results



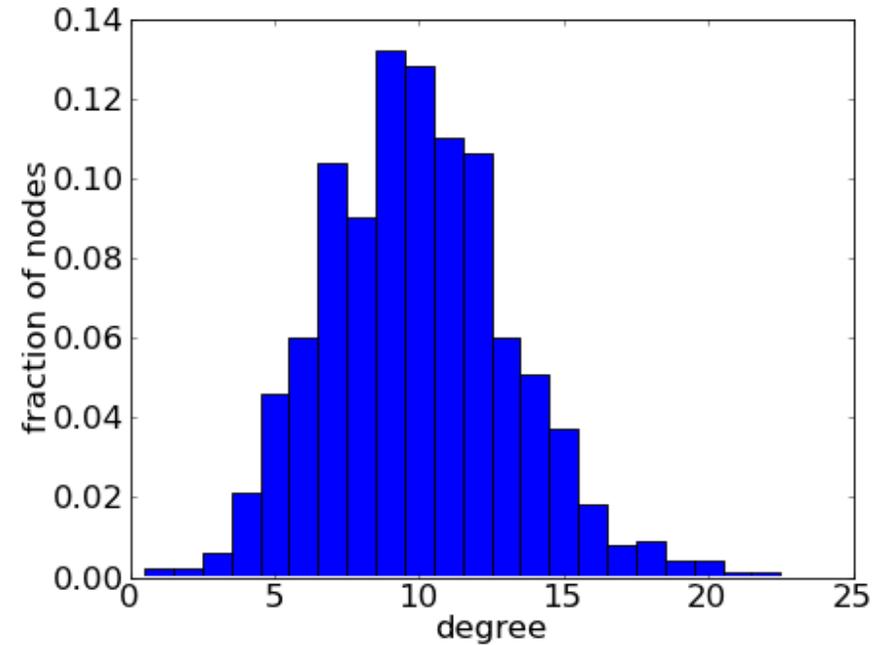
One day Alice came to a fork in the road and saw a Cheshire cat in a tree. "Which road do I take?" she asked. "Where do you want to go?" was his response. "I don't know," Alice answered. "Then," said the cat, "it doesn't matter."

How to characterise a graph

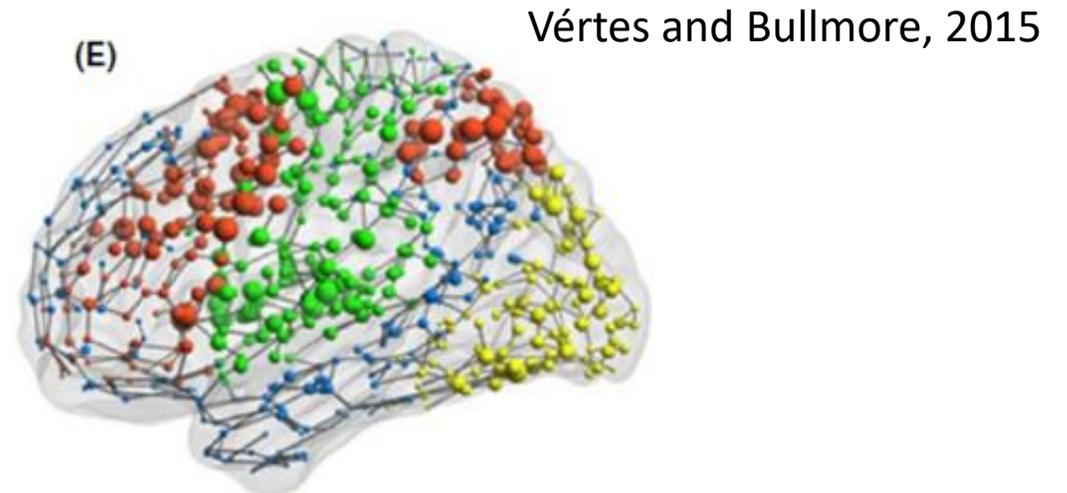
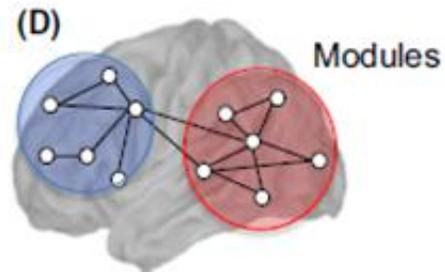
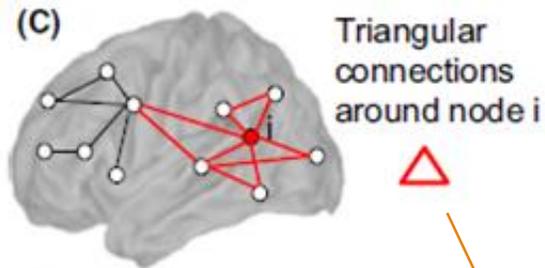
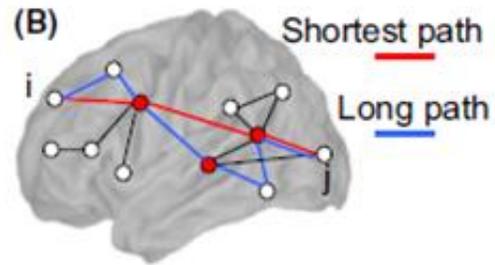
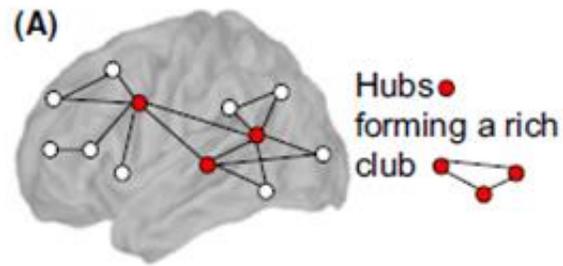
Degree:



Degree distribution:



How to characterise a graph



Clustering coefficient- what fraction of your neighbours are connected?

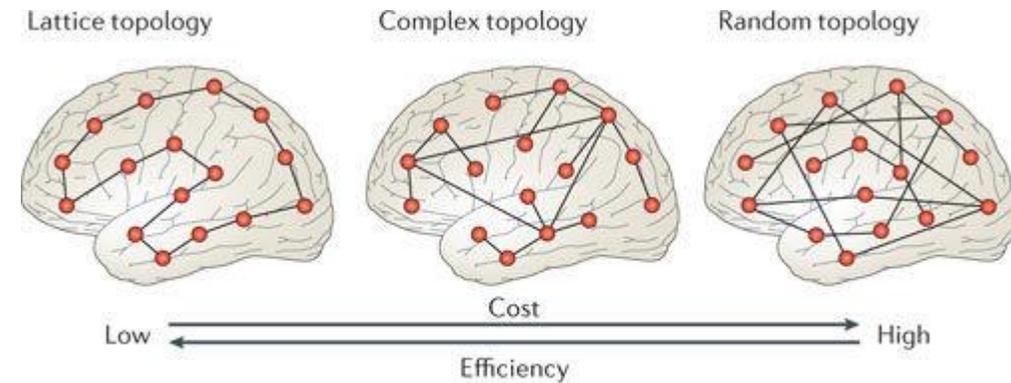
$$C_i = \frac{2 n_i}{k_i (k_i - 1)}$$

Some key results:

Brain networks make economic trade-off

Links to the molecular/cellular level, e.g. associations between network topology and local gene expressions (Wolf et al, 2011), fMRI hubs have been located in regions with high rates of glucose metabolism measured by PET (Tomasi et al, 2013)

Network control principles predict neuron function in the C.elegans connectome (Yan et al, 2017, non-NI)



Nature Reviews | **Neuroscience**

Bullmore and Sporns, 2012

Are graph theory and connectomics useful?

Not the full story, but...

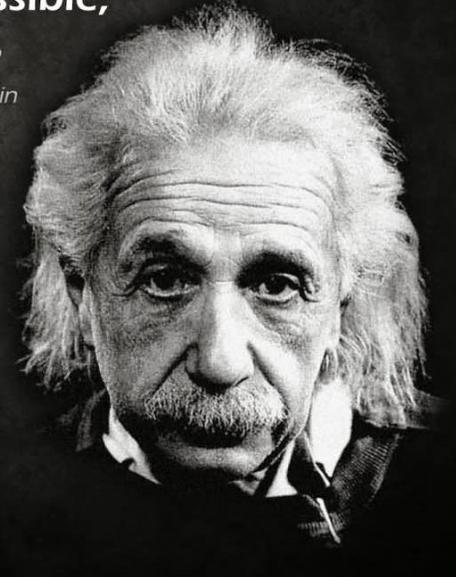
‘A useful, simplified abstraction that allows to formally address critical questions, e.g.:

- 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!

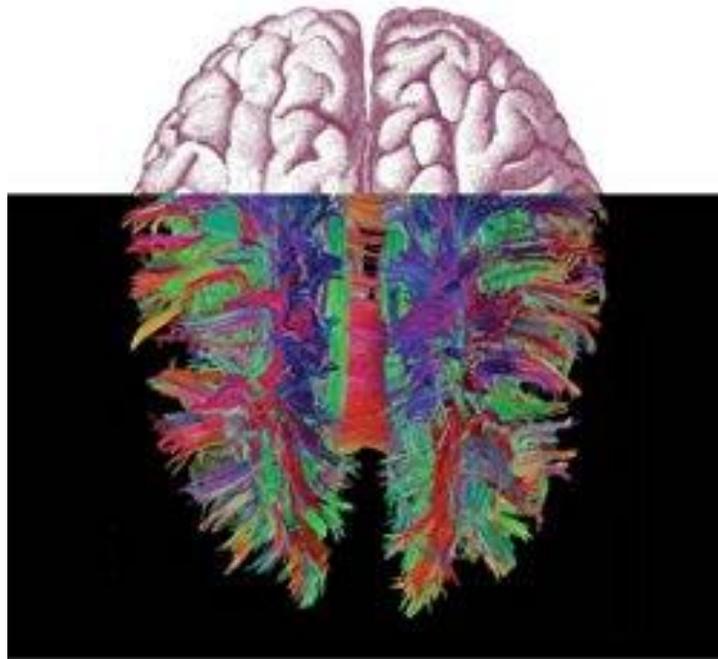
**Everything
should be made
as simple as possible,
but not simpler.**

Albert Einstein



Network Neuroscience- Books

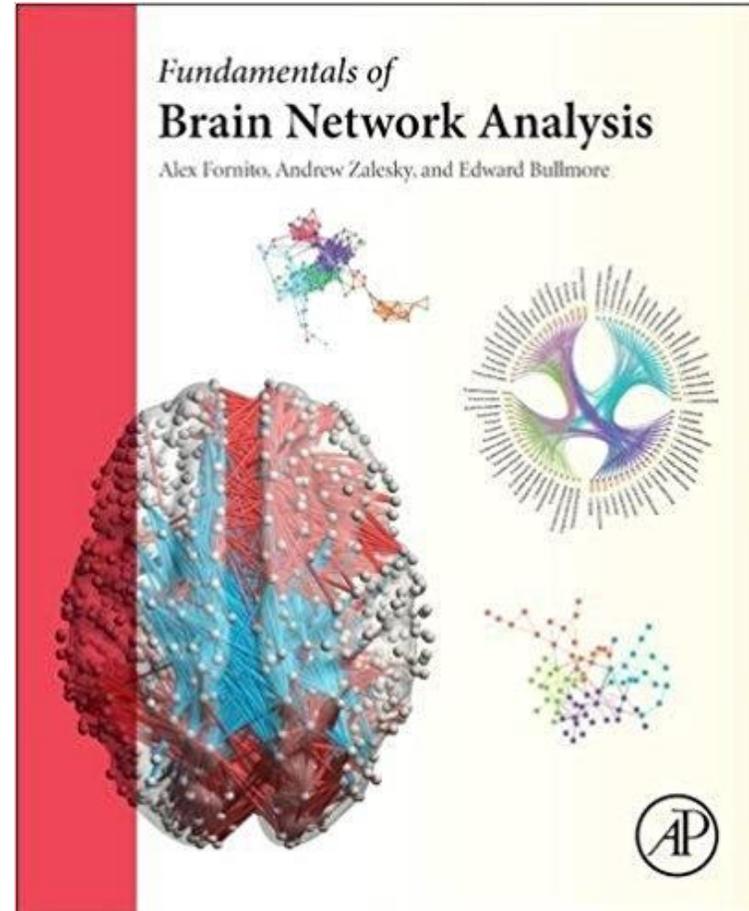
Networks of the Brain



Olaf Sporns

Fundamentals of Brain Network Analysis

Alex Fornito, Andrew Zalesky, and Edward Bullmore



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/>

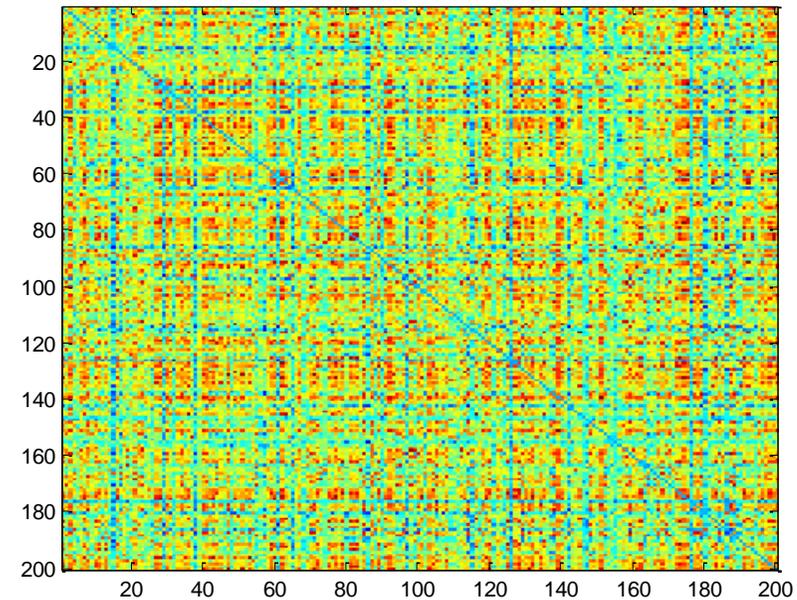
Another helpful Matlab toolbox is the BGL:
<http://www.mathworks.com/matlabcentral/fileexchange/10922>

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

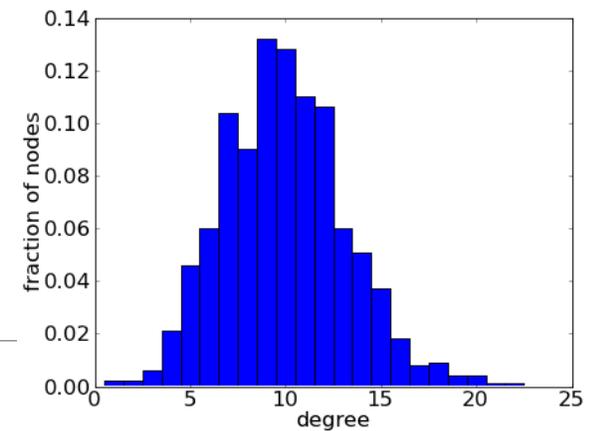


Exercise 1- characterising a brain network

- 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?



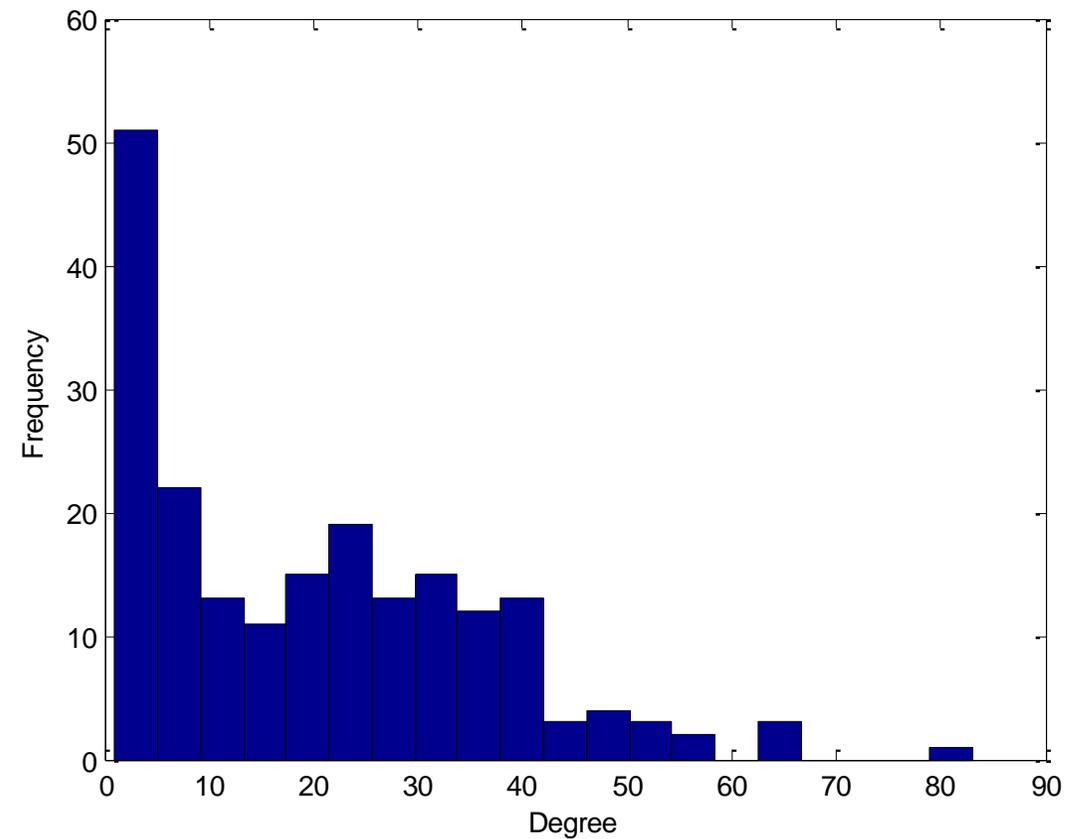
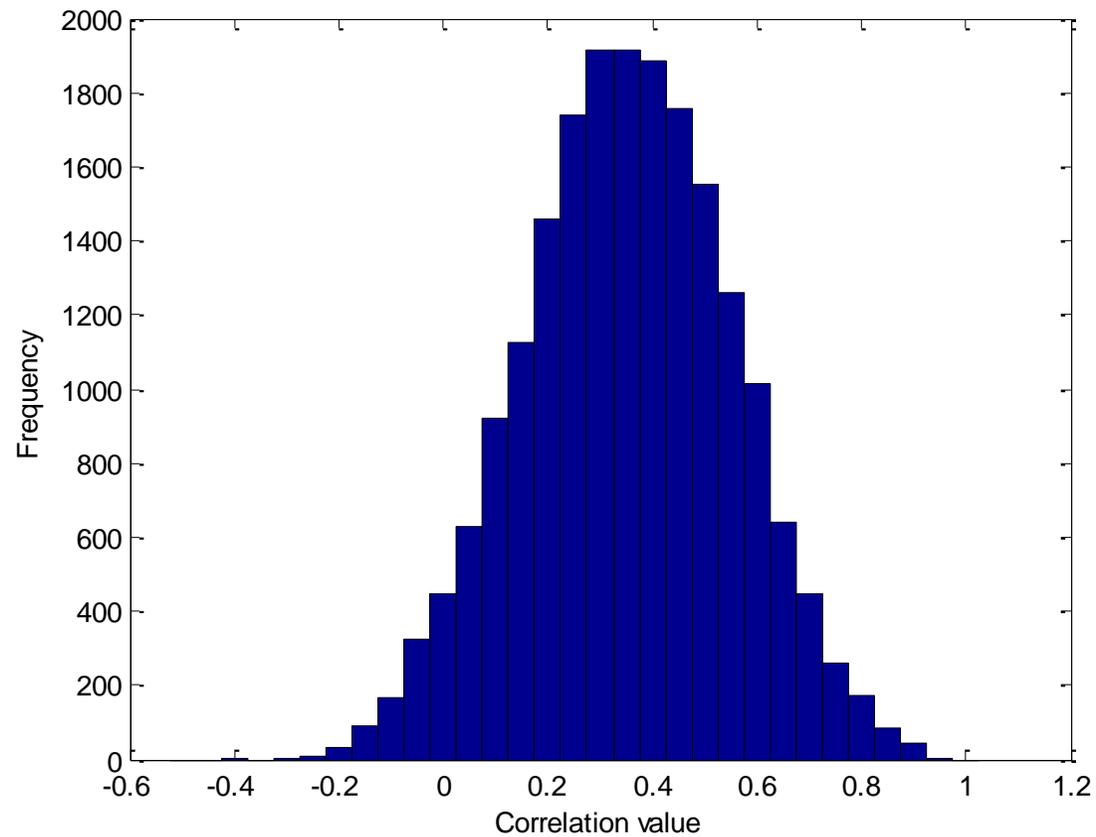
Exercise 1- characterising a brain network



- 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 top of this slide).
- f) Using the BCT toolbox, calculate the mean shortest path length, L , and the clustering coefficient, C , for your network

Extension: Can you calculate the global efficiency of the original weighted correlation matrix? 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 us here



Erdos-Renyi networks

There are lots of possible null models!

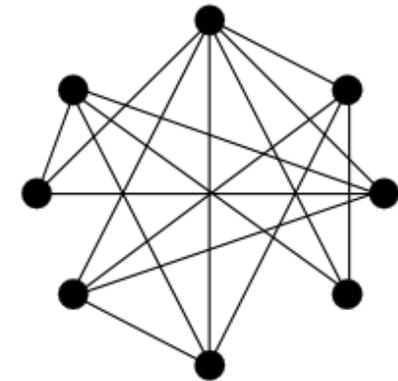
e.g. Erdos-Renyi graph: $G(n,p)$

- 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
```

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

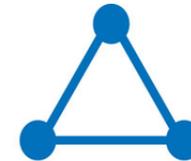
Going further...more novel graph theory
approaches

Network motifs

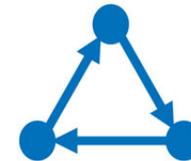
An alternative approach to characterising your network is to look for sub-graphs within the network, often called 'network motifs'

'Building blocks' of complex networks

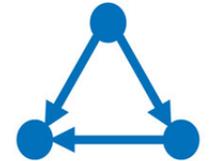
E.g. Sporns and Kotter, PLoS Biol, 2004 suggested that brain networks maximize both the number and the diversity of functional motifs, while the repertoire of structural motifs remains small (in neuroanatomical networks)



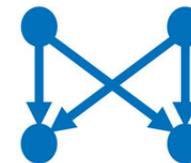
Triangle



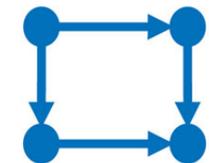
Feedback loop



Feed-forward loop



Bi-fan



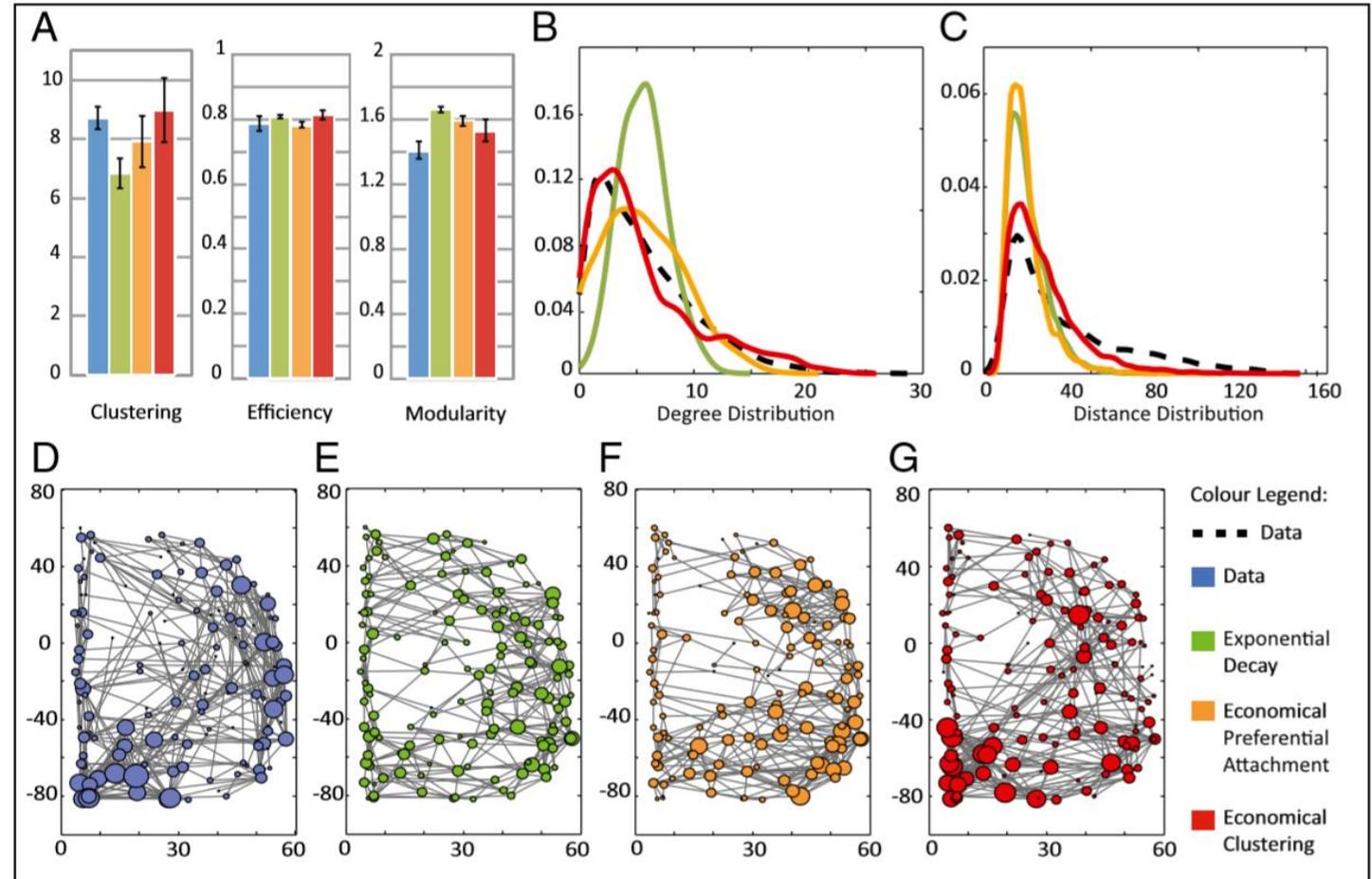
Biparallel

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:

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

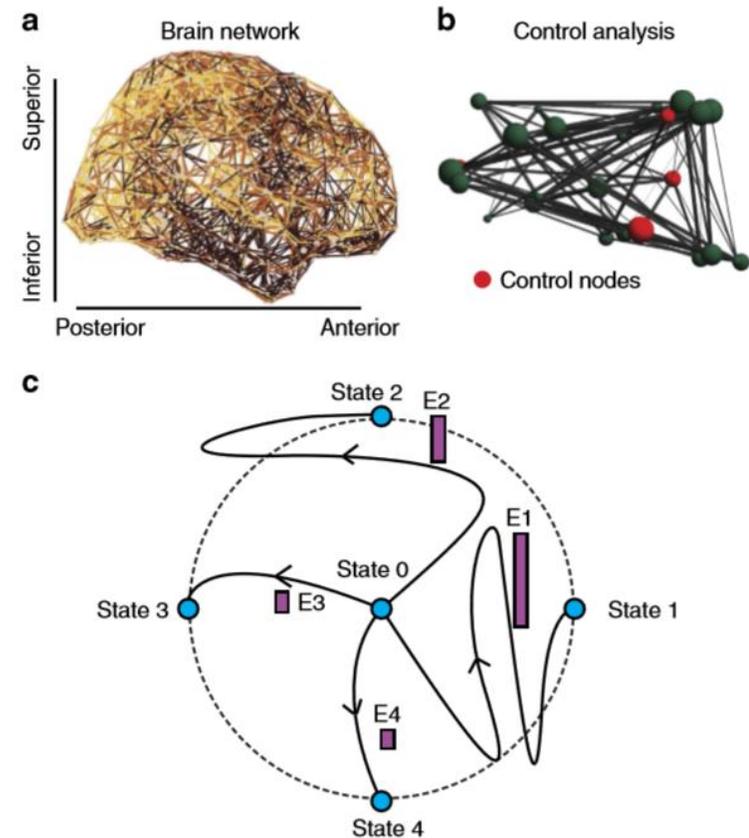


Controllability of brain networks

How can you control a brain network?

Some researchers use brain networks to try to identify control nodes, whose large-scale regional activity can move the brain into new trajectories that traverse diverse cognitive functions

Ultimately understanding which nodes have the most control over the rest of the network could be helpful in identifying targets to treat brain disorders



Wavelet despiking and probabilistic thresholding

<http://www.brainwavelet.org/>

Wavelet despiking is a new approach to analyse fMRI brain networks (Patel et al, NeuroImage, 95, 287-304, 2014). Removes motion artefacts in a principled, rigorous way- much better than scrubbing

It also outputs the 'degrees of freedom' for the time series- allowing you to calculate a p-value for the probability that each edge exists, and threshold probabilistically rather than at fixed density (see Patel and Bullmore, NeuroImage, 142, 14-26, 2016)

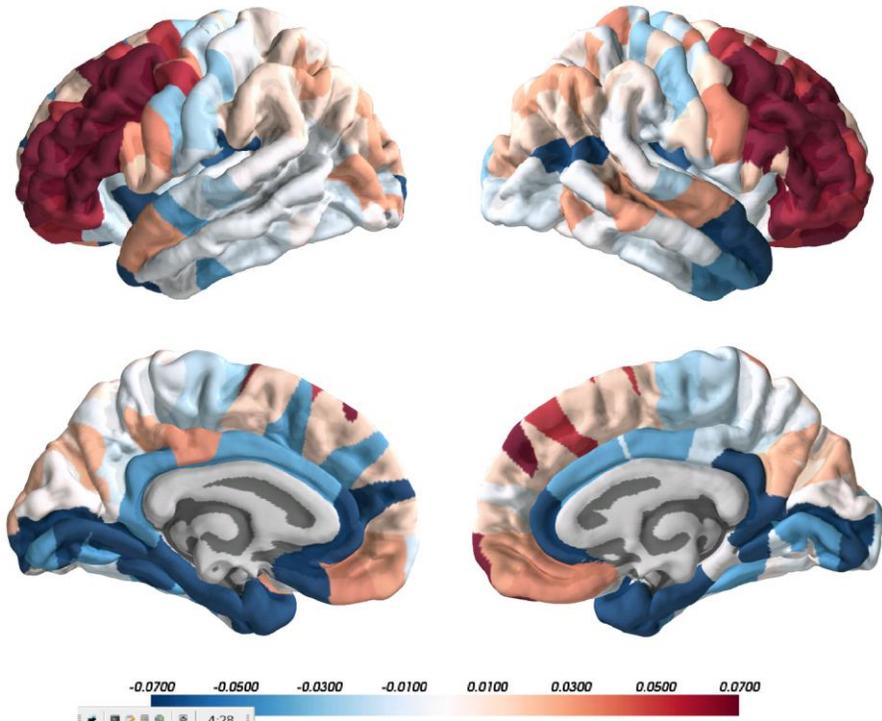


How to visualise your brain network?

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/>

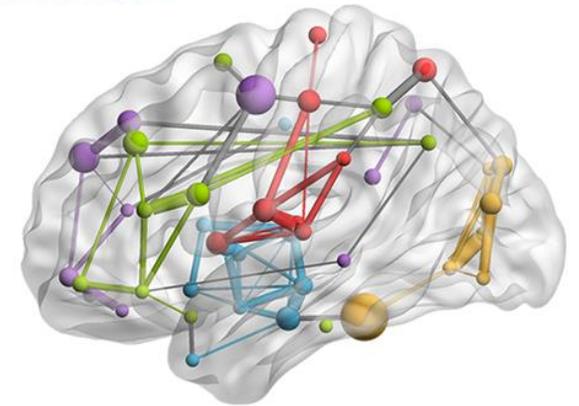
BrainNet Viewer

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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National Key Laboratory of Cognitive
Neuroscience and Learning,
Beijing Normal University.

Contact Information:
Mingrui Xia: mingruixia@gmail.com
Yong He: yong.h.he@gmail.com



Any questions?

(sem91@cam.ac.uk)

