Complex Brain Networks

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Outline

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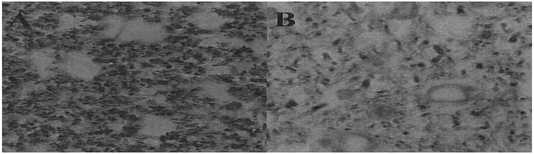
Connectivity: why do we care?

Clinical measurements:

- **White + grey matter connectivity** is thought to form the substrate for many different neurological and psychiatric disorders.
- **Modern MRI techniques** allows in-vivo measurements specific to different connections

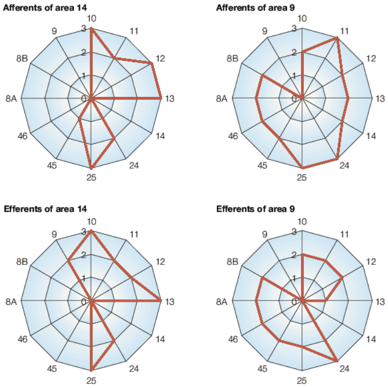
Example:

- Axonal degeneration/demyelination in Multiple Sclerosis (Evangelou *et al.* **2000**)



left: Control **right**: MS

Connections constrain function

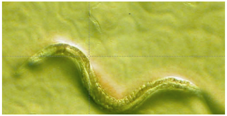


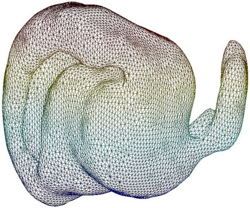
Passingham *et al.*, NNR (2002)

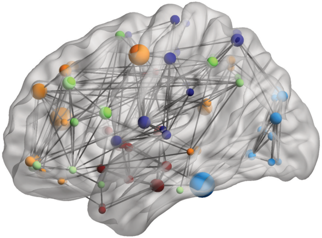
- The operations performed by an area are determined by its connectivity.
- Different regions have distinct **connectivity fingerprints**.
- Understanding regional connectivity is essential for understanding systems neuroscience.

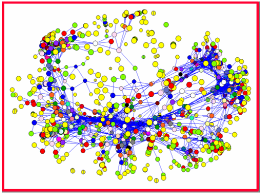
Networks in Neuroscience

Brain connectivity and its emergent dynamics are organized across multiple spatiotemporal scales









Investigating Brain Connectivity

Sacrificial tracer studies carried out on primates represent the **gold standard**

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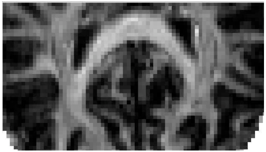
Diffusion-weighted MR imaging obtains similar pictures *in vivo* for humans



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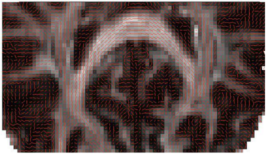
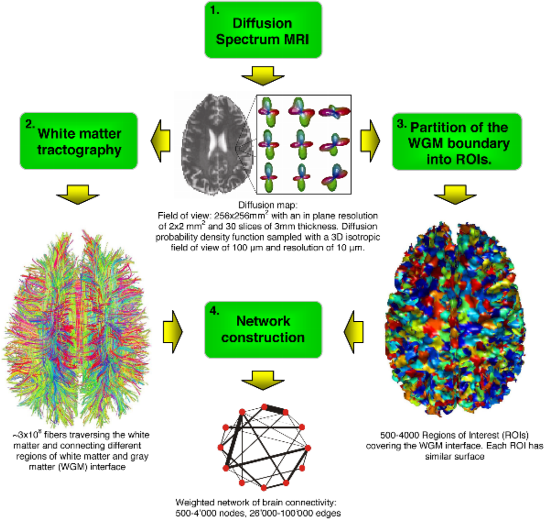


Tractography algorithms construct a vector field describing the connectivity structure

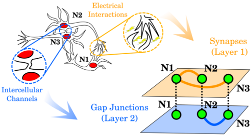
From MRI to Complex Brain Network



Hagmann *et al.*, PLOS One (2007)

Multilayered Neural Connectivity

- *C. elegans* electrical versus chemical connections (**Nicosia & Latora, 2015; Kleineberg *et al.*, 2016; Bentley *et al.*, 2016**)



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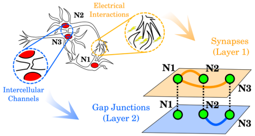
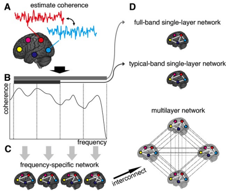
- *C. elegans* electrical versus chemical connections (**Nicosia & Latora, 2015; Kleineberg *et al.*, 2016; Bentley *et al.*, 2016**)

- Scale dependent connectivity e.g. different frequency bands (**Domenico *et al.*, 2016; Brookes *et al.*, 2016**)





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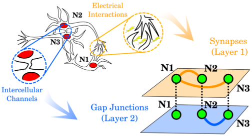

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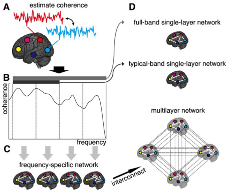
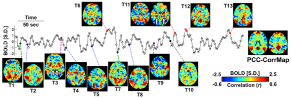
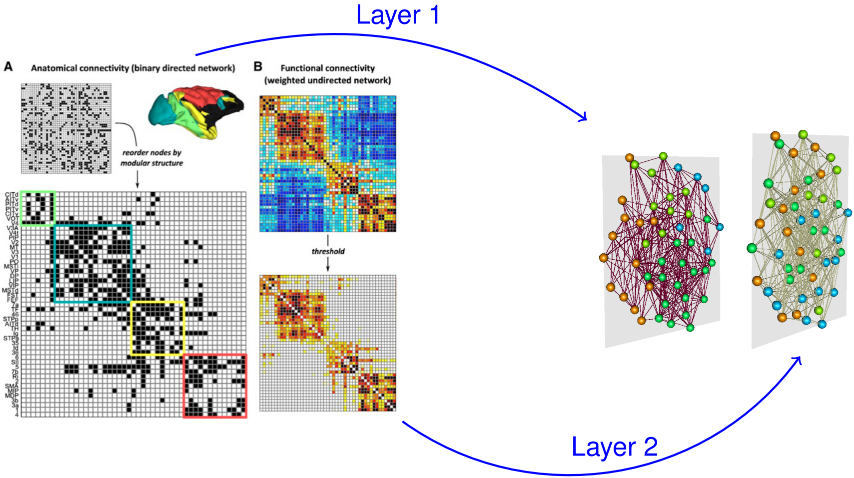


- Time varying functional networks (**Mucha *et al.* 2010; Bassett *et al.*, 2011; Calhoun *et al.*, 2014**)



Outline

2-Layer Structure-Function Multiplex



- Both networks define a multiplex structure in which the SC level shapes or imposes constraints on the FC level

Mathematical Representation

- A multiplex $\mathcal{M}$ of N nodes and M layers can be represented by a set of **M adjacency matrices**

$$A^{[\alpha]} \text{ for } \alpha = 1, \dots M$$

- That is

$$A_{ij}^{[\alpha]} = \begin{cases} 1 & \text{if node } i \text{ and node } j \text{ are connected in layer } \alpha \\ 0 & \text{otherwise} \end{cases}$$

Basic Multiplex Measures

- It follows that a multiplex is fully specified by the vector

$$\mathbf{A} = [A^{[1]}, A^{[2]}, \ldots, A^{[M]}]$$

- The **degree vector** naturally extends the notion of network degree to the multiplex setting

$$\mathbf{k}(i) = [\sum a_{ij}^{[1]}, \sum a_{ij}^{[2]}, \ldots, \sum a_{ij}^{[M]}]$$

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Basic Multiplex Measures

- **Total overlap** measures the total of pairs of nodes connected at the same time by a link in any two layers.

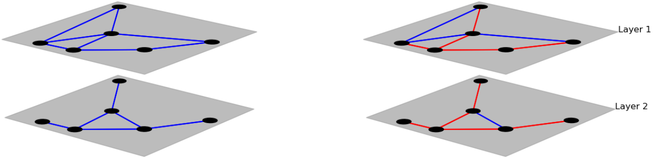
$$\mathcal{O}^{\alpha,\alpha'} = \sum_{i<j} a_{ij}^{[\alpha]} a_{ij}^{[\alpha']}$$

Basic Multiplex Measures

- **Total overlap** measures the total of pairs of nodes connected at the same time by a link in any two layers.

$$\mathcal{O}^{\alpha,\alpha'} = \sum_{i<j} a_{ij}^{[\alpha]} a_{ij}^{[\alpha']}$$

- Measures **similarity between structural & functional networks**



Structure-Function Duplex: Layer 1

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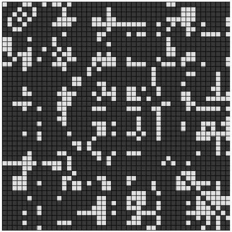


- We choose the structural network (layer 1) to be the known **cortical network of the Macaque monkey**
  - 47 brain regions (nodes) which are linked by 505 directed fibres (edges)
  - Binary connectivity matrix, i.e. $A_{ij}^{[1]} = 1$ if brain region i projects to brain region j

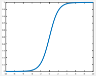
Structure-Function Duplex: Layer 2

- Activity in each cortical region is modelled as a Wilson-Cowan node

$$\frac{du_i}{dt} = -u_i + f\left(c_1 u_i - c_2 v_i + P + \sum w_{ij}^{[1]} u_j\right)$$
$$\frac{dv_i}{dt} = -v_i + f\left(c_3 u_i - c_4 v_i + Q\right) \qquad i = 1, \dots 47$$

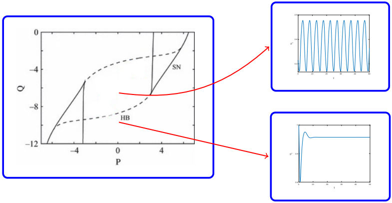
- Parameters: $c_1 = c_2 = c_3 = 10, c_4 = -2$ as in (**Hlinka & Coombes, 2012**)
- The firing rate function is taken to be sigmoidal

$$f(x) = 1/(1 + \exp(-x))$$



Structure-Function Duplex: Layer 2

- The model supports **transition between trivial steady state dynamics and oscillatory neural-like behaviour** as P, Q are varied



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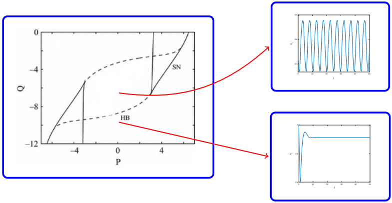
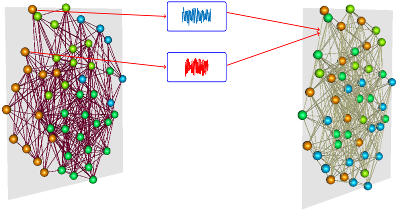




- The functional layer is derived by calculating the **Pearson's correlation between the time series of each cortical area**

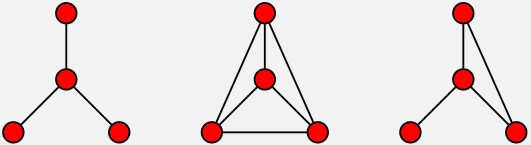
- The functional layer is binarised to have the same number of links as the structural layer

Clustering

- Recall that the **local clustering coefficient** accounts for the number of triangles in a network and is given by the ratio

$$C_i = \frac{\#\Delta s}{\#\text{two-paths}} = \frac{|\Delta|}{|P_2|}$$

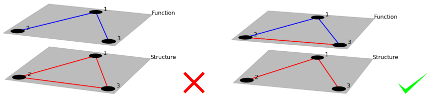
- e.g.



$C_i = \{0, 0, 0, 0\}$ $C_i = \{1, 1, 1, 1\}$ $C_i = \{1, 0, 1, \frac{1}{3}\}$

Multiplex Clustering

- A number of different extensions are possible
- Here we employ the approach in (Battiston *et al.* 2015) in that we exclude intra-layer Δs
- That is



arXiv:1307.6780v2 [physics.soc-ph] 17 Feb 2015

Structure of Triadic Relations in Multiplex Networks

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Recent advances in the study of networked systems have highlighted that our interconnected world is composed of networks that are coupled to each other through different "layers" that each represent one of the many possible subsystems or types of interactions. Nevertheless, it is traditional to aggregate multilayer data into a single weighted network in order to take advantage of existing tools. This is admittedly convenient, but it is also extremely problematic, as important information can be lost as a result. It is therefore important to develop multilayer generalizations of network concepts. In this paper, we analyze triadic relations and generalize the idea of transitivity to multiplex networks. We focus on triadic relations (which yield the simplest type of transitivity) and thus generalize the concept and computation of clustering coefficients to multiplex networks. We show how the layered structure of such networks introduces a new degree of freedom that has a fundamental effect on transitivity. We compute multiplex clustering coefficients for several real multiplex networks and illustrate why generalizing standard network concepts to multiplex networks must be done with great care. We also derive analytical expressions for our clustering coefficients in a family of random multiplex networks. Our analysis illustrates that social networks have a strong tendency to promote redundancy by closing triads at every layer and that they thereby have a different type of multiplex transitivity from transportation networks, which do not exhibit such a tendency. These insights are invisible if one only studies aggregated networks.

The computation of triadic relations—that is, relationships between triplets of nodes—using a clustering coefficient is one of the central ideas in network theory. Triadic relations are the smallest structural patterns that produce transitivity in a network, and counting them and analyzing them is thus crucial to have a proper understanding of clustering in networks. To measure transitivity in a network, one computes a clustering coefficient by comparing the number of connected triples of nodes to the number of triangles. In the present paper, we generalize the ideas of triadic relations and transitivity to multiplex networks, in which entities are connected to each other via multiple types of edges. To do this, we take into account the many possible types of cycles that can occur in multiplex networks, and we show that different types of real networks have different types of clustering patterns that cannot be detected using traditional measures of transitivity in networks. Our results thus suggest that clustering mechanisms are likely to be very different in different types of networks, as we have demonstrated for social and transportation networks.

The quantitative study of networks is fundamental for investigations of complex systems throughout the biological, social, information, engineering, and physical sciences [1–3]. The broad applicability of networks, and their success in providing insights into the structure and function of both natural and designed systems, has generated considerable excitement across myriad scientific disciplines. Numerous tools have been developed to study networks, and the realization that several common features arise in a diverse variety of networks has facilitated the development of theoretical tools to study them. For example, many networks constructed from empirical data have heavy-tailed degree distributions, satisfy the small-world property, and/or possess modular structures; and such structural features can have important implications for information diffusion, robustness against component failure, and more.

Multiplex Clustering

- **Multiplex clustering**

$$C(i)=\frac{\sum_{\alpha}\sum_{\alpha\neq\alpha'}\sum_{j\neq i,m\neq i}\left(a_{ij}^{[\alpha]}a_{jm}^{[\alpha']}a_{mi}^{[\alpha]}\right)}{(M-1)\sum_{\alpha}k_i^{[\alpha]}(k_i^{[\alpha]}-1)}$$

Here M is the number of layers and $k_i^{[\alpha]}$ is the degree of node i in layer α

- Or in the case of a **two-layer network**

$$C(i)=\frac{\sum_{j\neq i,m\neq i}\left(a_{ij}^{[1]}a_{jm}^{[2]}a_{mi}^{[1]}+a_{ij}^{[2]}a_{jm}^{[1]}a_{mi}^{[2]}\right)}{k_i^{[1]}(k_i^{[1]}-1)+k_i^{[2]}(k_i^{[2]}-1)}=\frac{\left(A^{[1]}A^{[2]}A^{[1]}+A^{[2]}A^{[1]}A^{[2]}\right)_{ii}}{k_i^{[1]}(k_i^{[1]}-1)+k_i^{[2]}(k_i^{[2]}-1)}$$

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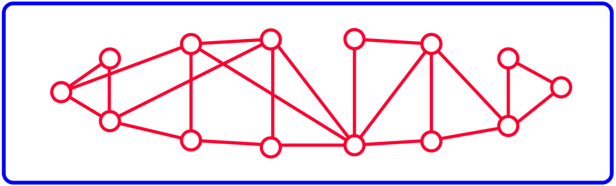
- Or in the case of a **two-layer network**

$$C(i) = \frac{\sum_{j\neq i, m\neq i} \left(a_{ij}^{[1]} a_{jm}^{[2]} a_{mi}^{[1]} + a_{ij}^{[2]} a_{jm}^{[1]} a_{mi}^{[2]} \right)}{k_i^{[1]}(k_i^{[1]}-1)+k_i^{[2]}(k_i^{[2]}-1)} = \frac{\left(A^{[1]}A^{[2]}A^{[1]} + A^{[2]}A^{[1]}A^{[2]} \right)_{ii}}{k_i^{[1]}(k_i^{[1]}-1)+k_i^{[2]}(k_i^{[2]}-1)}$$

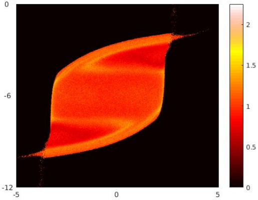
Random Surrogates

- All multiplex (and network) measures are normalised
- More specifically
  - the structural layer is rewired by swapping edge pairs (or triples!)

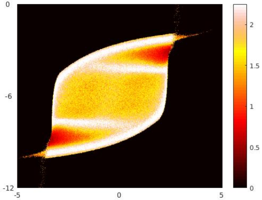


  - 100 functional layers are constructed and their average used for normalisation
- e.g. clustering: $C/\langle C_{\text{rand}} \rangle$

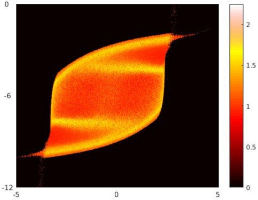
Results: Multiplex Measures



(a) standard clustering



(b) global overlap



(c) multiplex clustering

- Single versus multiplex measures as a function of the basal activation parameters P, Q
- Dark regions correspond to **non-oscillatory regions of parameter space**

Structure-Function Clustering

- We consider **two variations** of the standard multiplex clustering

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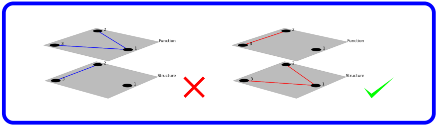
  - Structural tuples closed by a functional edge

$$\frac{\left(A^{[1]}A^{[2]}A^{[1]} + A^{[2]}A^{[1]}A^{[2]}\right)_{ii}}{k_i^{[1]}(k_i^{[1]}-1) + k_i^{[2]}(k_i^{[2]}-1)}$$



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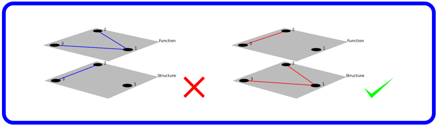
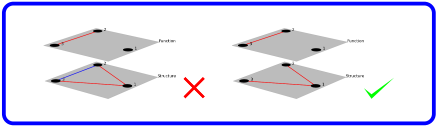


  - In the absence of a structural edge
    - $\#\Delta_{\mathrm{SF}} = \sum a_{ij}^{[1]} a_{jm}^{[2]} a_{mi}^{[1]} (1 - a_{jm}^{[1]})$
    - **How to count $\#$ two-paths now?**



Structure-Function Clustering

Note that structure-function clustering is given by

$$C_{\mathrm{SF}}(i) = \frac{|\Delta_{\mathrm{SF}}|}{|P_2^{[1]}| - |\Delta^{[1]}|} = \frac{\sum a_{ij}^{[1]} a_{jm}^{[2]} a_{mi}^{[1]} (1 - a_{jm}^{[1]})}{\sum a_{ij}^{[1]} a_{mi}^{[1]} - \sum a_{ij}^{[1]} a_{jm}^{[1]} a_{mi}^{[1]}}$$

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and recalling the definition for standard CC we get

$$1 - C_i = 1 - \frac{\sum_j \sum_{m, m \neq j} a_{ij} a_{jm} a_{mi}}{\sum_j \sum_{m, m \neq j} a_{ij} a_{mi}} = \frac{\sum_j \sum_{m, m \neq j} a_{ij} a_{mi} - \sum_j \sum_{m, m \neq j} a_{ij} a_{jm} a_{mi}}{\sum_j \sum_m a_{ij} a_{mi} - \sum_j \left(a_{ij}\right)^2}$$

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so that

$$|P_2^{[1]}| - |\Delta^{[1]}| = \left(\sum \sum a_{ij}^{[1]} a_{mi}^{[1]} - \sum \left(a_{ij}^{[1]}\right)^2 \right) (1 - c_i^{[1]}) = k_i^{[1]} (k_i^{[1]} - 1)(1 - c_i^{[1]})$$

Structure-Function Clustering

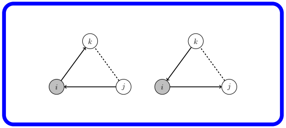
- This results in the following **structure-function clustering coefficient**

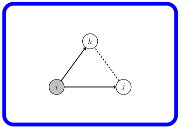
$$\widetilde{C}_i = \frac{\left(A^{[1]}(A^{[2]} \circ (E - A^{[1]}))A^{[1]}\right)_{ii}}{k_i^{[1]}(k_i^{[1]} - 1)(1 - c_i^{[1]})}$$

$\circ$ denotes element wise multiplication & $c_i^{[1]}$ clustering of node i in layer 1

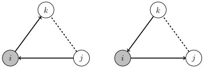
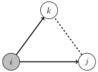
Structure-Function Clustering

- **Specific 'motifs' of interest**
  - **Cycles:** nodes that communicate indirectly
  - **outward:** nodes that receive a common drive



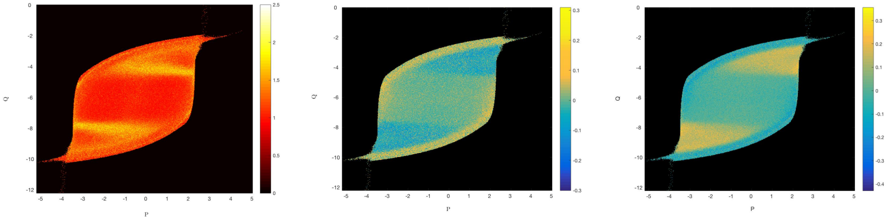


Specific Motifs of Interest

Patterns	Graphs	Structure-Function Clustering
Cycle		$\widetilde{C}^{\text{cyc}}(i) = \frac{\left(A^{[1]}\left(A^{[2]}\circ\left(E-A^{[1]}\right)\circ\left(E-A^{[1]T}\right)\right)A^{[1]}\right)_{ii}}{\left(k_{\text{in}}^{[1]}(i)k_{\text{out}}^{[1]}(i)-(A^{[1]})^2_{ii}\right)\left(1-c^{[1]}_{\text{cyc}}(i)\right)}$
Out		$\widetilde{C}^{\text{out}}(i) = \frac{\left(A^{[1]}\left(A^{[2]}\circ\left(E-A^{[1]}\right)\circ\left(E-A^{[1]T}\right)\right)A^{[1]T}\right)_{ii}}{k_{\text{out}}^{[1]}(i)\left(k_{\text{out}}^{[1]}(i)-1\right)\left(1-c^{[1]}_{\text{out}}(i)\right)}$
Both	All graphs above	$\widetilde{C}^{\text{both}}(i) = \frac{\left(A^{[1]}\left(A^{[2]}\circ\left(E-A^{[1]}\right)\circ\left(E-A^{[1]T}\right)\right)\left(A^{[1]}+0.5A^{[1]T}\right)\right)_{ii}}{\left(k_{\text{in}}^{[1]}(i)k_{\text{out}}^{[1]}(i)-(A^{[1]})^2_{ii}+0.5k_{\text{out}}^{[1]}(k_{\text{out}}^{[1]}-1)\right)\left(1-c^{[1]}_{\text{both}}(i)\right)}$

- $c_{\#}^{[1]}(i)$ with $\{\#\} \in \{\text{cyc}, \text{out}, \text{both}\}$ denotes directed clustering (**Fagiolo, 2007**) of node *i* in layer 1

Results: SF Clustering



(a) $\widetilde{C}^{\,\text{both}} / \langle \widetilde{C}^{\,\text{both}}_{\text{rand}} \rangle$ (b) $\widetilde{C}^{\,\text{both}} / \langle \widetilde{C}^{\,\text{both}}_{\text{rand}} \rangle - \widetilde{C}^{\,\text{cyc}} / \langle \widetilde{C}^{\,\text{cyc}}_{\text{rand}} \rangle$ (c) $\widetilde{C}^{\,\text{both}} / \langle \widetilde{C}^{\,\text{both}}_{\text{rand}} \rangle - \widetilde{C}^{\,\text{out}} / \langle \widetilde{C}^{\,\text{out}}_{\text{rand}} \rangle$

- Multiplex clustering corresponding to neurologically relevant patterns
- Distinct regions of parameter space exist in which clustering is dominated either by common drive or by indirect functional connectivity

Weighted Clustering Coefficient

- In the previous experiments networks where thresholded in order to obtain binary connectivity matrices
- Next we consider **weighted clustering coefficients**
- Multiple definitions exist but we consider here the following definition due to Grindrod-Zhang-Horvath (**Kalna & Higham, 2007**):

$$C_{\mathrm{w}}(i) = \frac{\sum_j \sum_{k,k\neq j} w_{ij} w_{jk} w_{ki}}{\sum_j \sum_{k,k\neq j} w_{ij} w_{ki}} = \frac{\left(W^3\right)_{ii}}{k_w(i)^2 - \left(W^2\right)_{ii}}$$

- Here, $k_w(i)$ is the weighted degree of node i
- The weights are assumed to lie in $[0, 1]$

Extension to Weighted Multiplexes

Similar to before we have that

$$C_{\mathrm{wm}}(i) = \frac{\sum_{\alpha} \sum_{\alpha' \neq \alpha} \sum_{j,m} \left(w_{ij}^{[\alpha]} w_{jm}^{[\alpha']} w_{mi}^{\alpha]} \right)}{(M-1) \sum_{\alpha} \sum_{j \neq m} \left(w_{ij}^{[\alpha]} w_{mi}^{[\alpha]} \right)}$$

or

$$C_{\mathrm{wm}}(i) = \frac{\sum_{\alpha} \sum_{\alpha' \neq \alpha} \left(W^{[\alpha]} W^{[\alpha']} W^{[\alpha]} \right)_{ii}}{(M-1) \sum_{\alpha} \left(k_{\mathrm{w}}^{[\alpha]}(i)^2 - \left(W^{[\alpha]2} \right)_{ii} \right)}$$

Here $k_{\mathrm{w}}^{[\alpha]}$ denotes the weighted degree

Extension to Weighted Multiplexes

And for structure-function clustering:

$$C_{\mathrm{wsf}}(i) = \frac{\left(W^{[1]}\left(W^{[2]} \circ \left(I - W^{[1]}\right)\right)W^{[1]}\right)_{ii}}{\left(k_{\mathrm{w}}^{[1]}(i)k_{\mathrm{w}}^{[1]}(i) - \left(W^{[1]2}\right)_{ii}\right)\left(1 - c_{\mathrm{w}}^{[1]}(i)\right)}$$

• Here $k_{\mathrm{w}}^{[1]}(i)$ denotes the weighted degree and $c_{\mathrm{w}}^{[1]}(i)$ the weighted clustering due to Grindrod-Zhang-Horvath for the ith node in the structural layer

• Note that the above formulation is easily extended to undirected structural networks

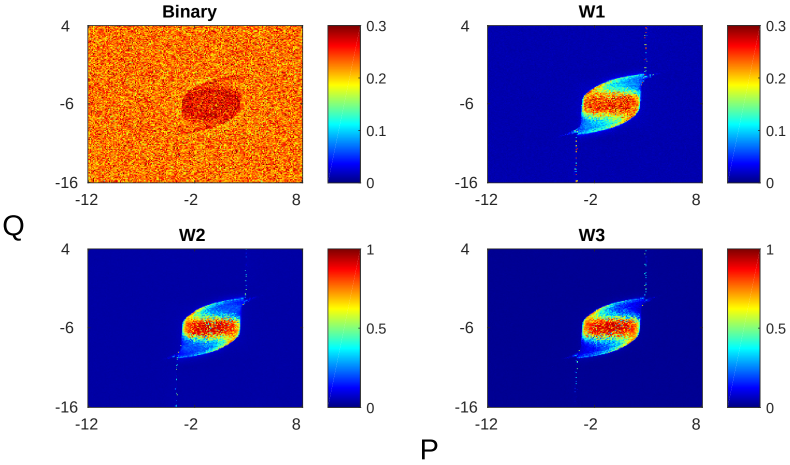
Extension to Weighted Multiplexes

In our experiments to date

- we have structural topology (i.e. layer 1 is binarised)
- functional layer is either
  - binary ($A^{[2]}$ is thresholded to have the same number of links as layer 1)
  - weighted in one of three ways:
    - $W^{[2]} = abs(C). * A^{[2]}$
    - $W^{[2]} = abs(C)$
    - $W^{[2]} = abs(C). * (C > 0)$

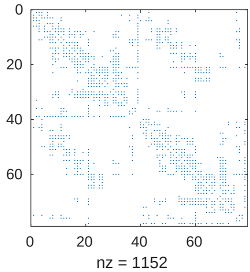
Here C is the correlation matrix and I am using Matlab notation (*i.e.* '$.*$' means element-wise multiplication, etc.).

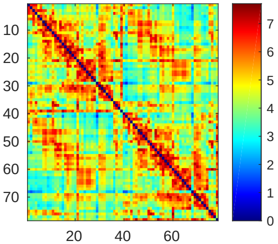
Extension to Weighted Multiplexes: Macaque Brain



- Structure-function clustering on the Macaque brain (unnormalised)

Human Brain

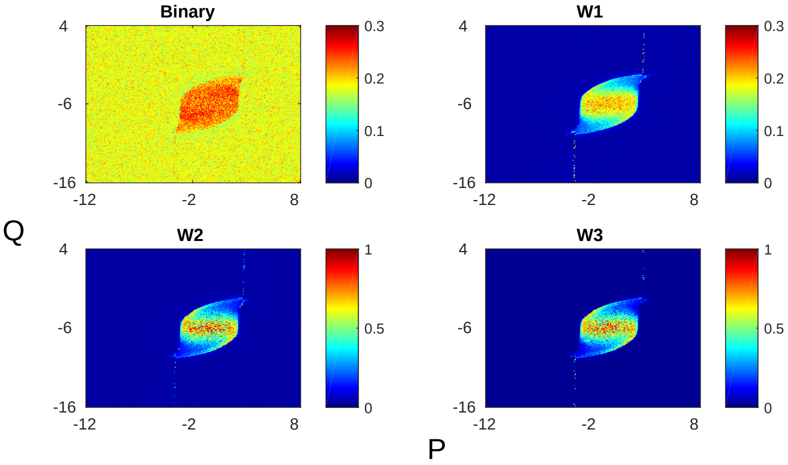




We have repeated the above analysis on a healthy human brain obtained from the Human Connectome Project:

- $N = 78, m =$ (thresholded to retain $\approx$ 35% of connections)
- considered the same 4 cases as before (1 binary, 3 weighted)

Extension to Weighted Multiplexes: Human Brain



- Structure-Function clustering on the human brain (unnormalised)

Future work

- Weighted structure/function (*i.e.* no topology)
- How to normalise the structural network
- Weighted null models
- MEG/EEG data (89 healthy patients currently)
  - 2-layer (structure-function – both weighted)
  - 5-layer multiplex (different frequency bands)
  - 5-layer temporal multiplex
  - structure-function temporal multiplex
  - healthy Vs diseased study

Outline

The Brain as a Spatial Network

- Spatial aspect of brain networks important for a number of reasons:
  - Brain regions that are spatially close have a larger probability of being connected than remote regions
  - **wiring costs are distant dependent**

- A number of neurological conditions are accompanied by alterations in both gross anatomy and structural connectivity

Relation between surface morphology and brain connectivity unclear

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The Brain as a Spatial Network - Motivation

- To date white matter connectivity studies dominate
- Recent evidence suggests **grey** + **white** matter deficiencies are important
- It has been hypothesised grey matter connectivity can be inferred via **cortical folding**

PNAS

Intrinsic gray-matter connectivity of the brain in adults with autism spectrum disorder

Christine Ecker[a,1,2], Lisa Ronan[b,1], Yue Feng[a], Eileen Daly[a], Clodagh Murphy[a], Cedric E. Ginestet[c], Michael Brammer[c], Paul C. Fletcher[b], Edward T. Bullmore[b], John Suckling[b], Simon Baron-Cohen[d], Steve Williams[c], Eva Loth[a], MRC AIMS Consortium[3], and Declan G. M. Murphy[a]

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Edited by Alex Martin, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, and accepted by the Editorial Board May 15, 2013 (received for review January 3, 2013)

Autism spectrum disorders (ASD) are a group of neurodevelopmental conditions that are accompanied by atypical brain connectivity. So far, in vivo evidence for atypical structural brain connectivity in ASD has mainly been based on neuroimaging studies of cortical white matter. However, genetic studies suggest that abnormal connectivity in ASD may also affect neural connections within the cortical gray matter. Such intrinsic gray-matter connections are inherently more difficult to describe in vivo but may be inferred from a variety of surface-based geometric features that can be measured using magnetic resonance imaging. Here, we present a neuroimaging study that examines the intrinsic cortico-cortical connectivity of the brain in ASD using measures of "cortical separation distances" to assess the global and local intrinsic "wiring costs" of the cortex (i.e., estimated length of horizontal connections required to wire the cortex within the cortical sheet). In a sample of 68 adults with ASD and matched controls, we observed significantly reduced intrinsic wiring costs of cortex in ASD, both globally and locally. Differences in global and local wiring cost were predominantly observed in fronto-temporal regions and also significantly predicted the severity of social and repetitive symptoms (respectively). Our study confirms that atypical cortico-cortical "connectivity" in ASD is not restricted to the development of white-matter connections but may also affect the intrinsic gray-matter architecture (and connectivity) within the cortical sheet. Thus, the atypical connectivity of the brain in ASD is complex, affecting both gray and white matter, and forms part of the core neural substrates underlying autistic symptoms.

brain structure | gyrification | morphometry

Autism spectrum disorders (ASDs) are a group of neurodevelopmental conditions characterized by impaired social communication, social reciprocity, and repetitive/stereotypic behavior (1). There is consensus that ASD is accompanied by developmental differences in brain anatomy and connectivity (2). However, the specific neurobiological substrate of ASD remains elusive.

Neuroimaging evidence suggests that ASD is accompanied by anatomical differences in several large-scale neurocognitive networks (3), which typically include the cerebellum (4), the amygdala–hippocampal complex (5), fronto-temporal regions (6), and the caudate nuclei (7). These gross-anatomical abnormalities are likely to reflect differences in the cytoarchitectonic make-up of individual brain regions in ASD, as can be observed in postmortem studies. For instance, individuals with ASD may have a reduced size, but increased number, of minicolumns (8), which could underpin differences in cortical surface area (9, 10). Also, individuals with ASD may have an excess number of neurons in some brain regions (11), which in turn may affect measures of cortical thickness (9, 12). Therefore, different morphometric features of the cortical surface provide proxy measures of various aspects of local gray-matter architecture. However, currently there is a lack of imaging markers that can be used to explore gray-matter neuroanatomy as a connected neural system.

The development of such biomarkers is important because increasing evidence suggests that ASD is accompanied by atypical structural "brain connectivity" within the wider neural systems mediating autistic symptoms and traits (13–15). So far, the notion of abnormal anatomical connectivity in ASD is mainly based on neuroimaging studies examining white-matter differences using voxel-based morphometry (e.g., ref. 6) or diffusion tensor imaging (DTI) (e.g., refs. 16 and 17)). However, genetic and molecular studies suggest that abnormal neural connectivity in ASD may not be restricted to white-matter connectivity of the brain but also affect direct synaptic connections within cortical gray matter. For example, many of the genes and/or copy number variants (CNVs) associated with ASD encode for genes involved in cell adhesion, synaptogenesis, and maturation (reviewed in refs. 5, 6, and 18). One would therefore expect that ASD is also associated with differences in local cortico-cortical circuits that do not communicate via white matter (i.e., those "intrinsic" to the cortical sheet).

Such intrinsic cortico-cortical connections have been well described in histological studies and generally denote connections running parallel to the cortical surface (Fig. 1A). As such, intrinsic connections are confined to the cortical gray matter and should be distinguished from extrinsic connections that pass through white matter and terminate in other cortical regions (e.g., U-fibers or interhemispheric connections) (19). For example, Lewis et al. (20) reported the existence of excitatory intrinsic long-range axon collaterals in the prefrontal cortex, which can extend up to 4–5 millimeters along the cortical surface (see also ref. 21). Intrinsic connections have also been documented in other regions of the brain (e.g., visual, motor, and somatosensory cortices) (22) and may include components of the inhibitory cortical circuitry (e.g., wide-arbor basket cells) (23). Intrinsic connections are therefore an integral part of the horizontal (i.e., lateral) gray-matter architecture of the cortex, and their development has therefore been closely related to a variety of surface-based geometric features, including surface area (10), cortical separation distances (24), and Gaussian curvature (25). These measures are also known as

Author contributions: C.E., E.T.B., J.S., S.B.-C., S.W., M.A.C., and D.G.M.M. designed research; C.E., E.D., E.L., M.A.C., and D.G.M.M. performed research; L.R. and M.A.C. contributed new reagents/analytic tools; C.E., L.R., Y.F., E.D., C.E.G., M.B., and P.C.F. analyzed data; and C.E., L.R., C.M., P.C.F., M.A.C., and D.G.M.M. wrote the paper.

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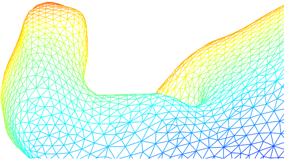
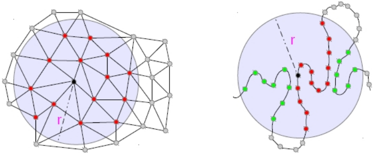
Neural Network Structure - Setup



(a) Δtion



(b) Connectivity Rules

- Network construction:
  - Construct **minimally connected network**, $\mathcal{G}_0$, via a triangulation
  - Additional links added between vertex pairs, v_i and v_j, if they are sufficiently close as measured by
    - (a) **Euclidean distance**, i.e. $||v_i - v_j||_2 < r$; **and**
    - (b) **path-length**, $d(v_i, v_j)$, measured on $\mathcal{G}_0$

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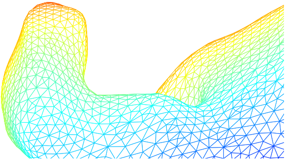

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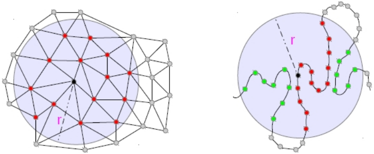

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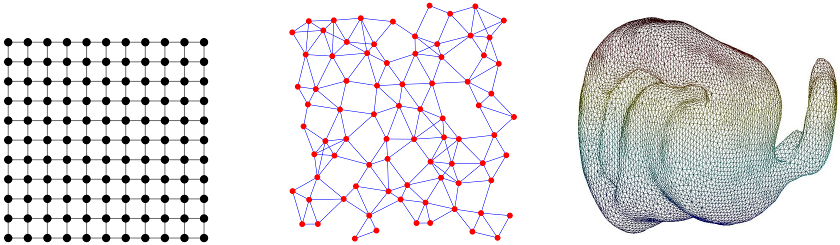
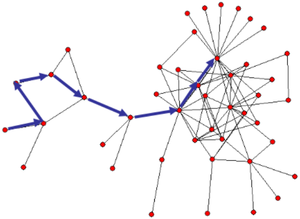


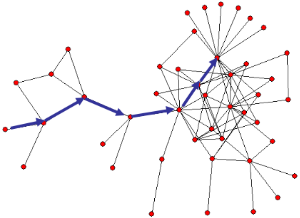
(a) Lattice graph (b) Random network (c) Rat cortex

- Use a simple cellular automata model to compare spreading dynamics on a lattice, random graph and rat brain ($N \approx 9600$)
- Activity spreads according to the following simple rules:
  - nodes are in one of two states: active ($x_i = 1$) or inactive ($x_i = 0$);
  - an inactive node becomes active if it is connected to at least m active nodes (active nodes remain active)

Neural Network Structure - Statistics



Path



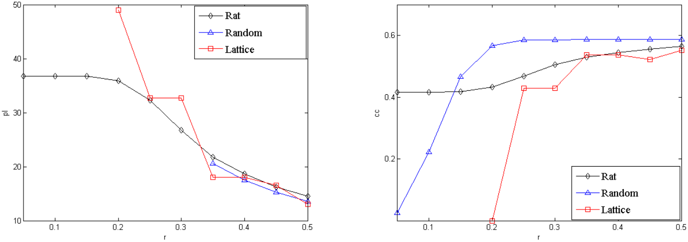
Shortest Path

The **average, or characteristic, path-length** is given by

$$\langle l \rangle = \frac{1}{n(n-1)} \sum_{i,j} a_{ij},$$

where the matrix A is the network adjacency matrix (i.e. $a_{ij} = 1$ if node $i \sim j$).

Neural Network Structure - Results



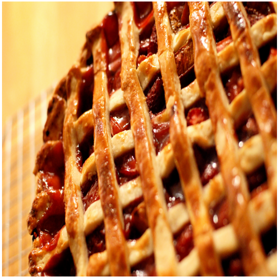
(a) Path-length

(b) Clustering coefficient

WS clustering for the geometric random graph approaches theoretical value:

$$1 - \frac{1}{\Gamma\left(\frac{3}{2}\right)\sqrt{\pi}}\left(\frac{3}{4}\right)^{\frac{3}{2}} \approx 0.58650$$

Neural network structure - Results



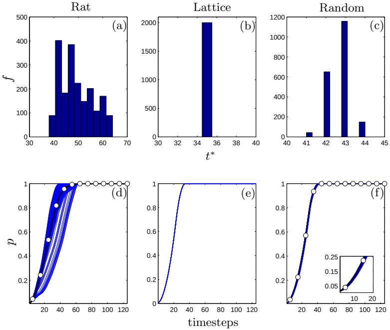
- Example spreading behaviour in the 3 different architectures
- Initial conditions comprised a small region of activation (1% of nodes) surrounding a randomly chosen node
- $m = 2, r = 0.35$ in all the above

Neural Network Structure - Results

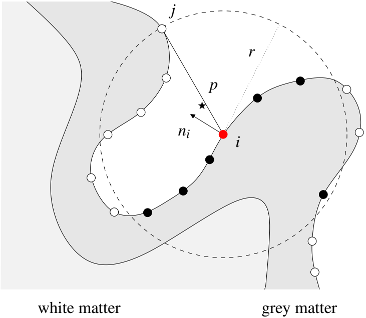
- Quantify via t^*: time to full activation
- **Significant** difference in:

  Average activation time

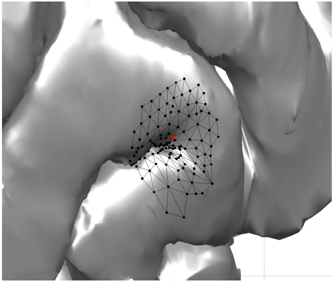
  Strong dependence on initial state



Extensions: the human brain



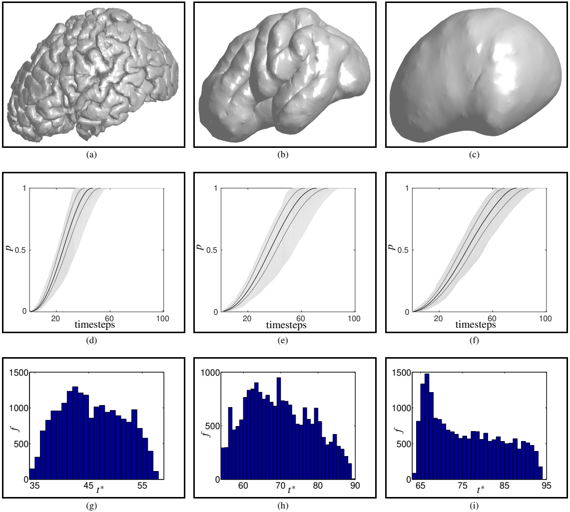
(a)



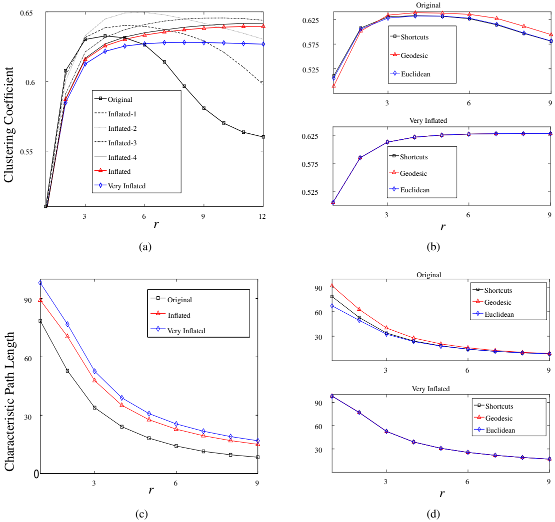
(b)

- The human brain is higly convoluted.
- We consider a simple model of grey matter connectivity that allows for short-cuts due to cortical folding. ($N \approx 150,000$)
- Again, we deploy a simple cellular automata model of neural activity

Extensions: the human brain



Extensions: human brain



- Clustering was maximised at $r = 4$mm
- Experimentally observed grey matter connections typically 4-5mm
- Grey matter connectivity maximises information processing abilities

Outline

Connecting it altogether

- **Multiplex brain betworks**:
  - Proposed duplex model of structure-function networks
  - Multiplex measures display emergent features not present in single layer represntation
  - Interesting behaviour found close to criticality and beyond...
  - Extensions to weighted networks and clinical data next

- **Spatial network properties**:
  - Combining different forms of neuroimaging data important
  - By not including spatial information we risk over-simplifying the resulting network models.

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