Integrating analyses across scales of nervous systems: from micro to macro

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Graph Theoretic Models of Brain Networks

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<th>Sources of Research Support</th>
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<td>1. Medical Research Council</td>
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Integrative approaches to the connectome

• Analogy and reductionism

• Analogical or comparative connectomics
  – Modules
  – Rich clubs
  – Generative modeling
  – Economical principles

• Reductionist connectomics
  – Cytoarchitectonics
  – Myelination
  – Gene expression

• Conclusions
The central challenge is biological validation of human MRI networks

- Macro scale networks $\sim 10^{-2}$ m, cm
- Noisy data not measured in SI units
- No gold standard for human brain networks
- No agreed biophysical explanation for functional connectivity or structural covariance
- What do these results mean in terms that other neuroscientists can understand and respect?
The multi-scale organization of brain anatomy

Macro $10^{-2}$ m
- MRI, fMRI, DWI

Meso $10^{-4}$ m
- Tract tracing

Micro $10^{-6}$ m
- Electron microscopy

Molecular
- Gene expression

Lichtman & Denk (2011)
Analogical or reductionist: two strategies for integration across scales

**Analogical**
Make an informative comparison between human MRI networks and more precisely known nervous systems in other species

**Reductionist**
Link human MRI network organization to human cellular or genomic biology
Graph theoretical analysis is generalisable to connectomes across all species

Modular community structure of human MRI networks

Mesoscale connectomics of mammalian cortex is driven by advances in tract-tracing technology

Multiple tract-tracing experiments for estimation of anatomical connectivity and wiring cost in the mouse connectome

The mouse connectome has a community structure comprising functionally specialised hierarchical modules.
C elegans and Drosophila connectomes also have a community structure of functionally specialised modules

Human DTI macro scale networks have a high cost, highly integrative rich club

van den Heuvel, Kahn, Goni, Sporns (2012) *Proc Natl Acad Sci USA*
The *C. elegans* micro scale connectome has a high cost, highly integrative rich club

Towlson et al (2013) *J Neurosci*
A generative model that optimises wiring cost is not sufficient to recapitulate the human DTI macro network.

\[ P(u, v) = E(u, v)^\eta \times K(u, v)^\gamma \]

- Probability of connection between nodes \( u \) and \( v \)
- Euclidean distance between nodes
- Topological relationship between nodes

Optimising distance parameter only

Optimising distance and topology parameters

Betzel et al (2016) *NeuroImage*
A generative model that minimizes wiring cost is not sufficient to recapitulate the mouse tract-tracing meso network.

Rubinov, Ypma et al (2015) *Proc Natl Acad Sci USA*
Analogical or comparative analysis across scales and species will often be conditioned by methodological differences

Contemporary tract tracing indicates that weight of anatomical connectivity varies over 5 orders of magnitude and connection density >60% in the macaque cortex.

Whereas human MRI networks will often have connectivity in range (-1,1) and thresholded density ~ 15%.

Markov et al (2012) *Cereb Cortex*
Markov et al (2013) *Science*
Comparative connectomics suggests some universal principles of brain network organization

Economical principle of a trade-off between minimization of biological costs versus maximisation of the integrative capacity of the network

Macro network nodal topology was reductionistically linked to local cytoarchitectonics in macaque

Scholtens et al (2014) *J Neurosci*
MRI network connectivity was sometimes linked to local cytoarchitectonics in human

Structural covariance network hubs have faster rates of adolescent cortical shrinkage and myelination ($\Delta MT$).

Whitaker, Vertes et al (2016) *Proc Natl Acad Sci USA*
Mouse brain regions that are anatomically connected share similar gene transcriptional profiles

A) Parcellated mouse isocortex
B) Anatomical connectivity matrix
C) Gene co-expression matrix

Mouse connectome topology and gene expression: connected hubs co-express genes for oxidative metabolism

Fulcher & Fornito (2016) Proc Natl Acad Sci USA
Partial least squares revisited

PLS is a multivariate technique that identifies a few components that maximise the covariance between a set of response variables and a larger set of collinear predictor variables.

\[ O(10) \text{ nodal topology metrics} \quad O(10^4) \text{ mRNA measurements} \]

\[ O(10^2) \text{ regions} \quad O(10^2) \text{ regions} \]

Response variables, \( Y \)  
Predictor variables, \( X \)

McIntosh & Bookstein (1996) *NeuroImage*
Statistically independent and spatially patterned gene expression profiles predict different network properties

Genes strongly predictive of inter-modal degree and long connection distance are enriched for oxidative metabolism

Conclusions

• Biological validation of human MRI networks can be addressed by analogical (comparative) or reductionist strategies

• Analogically, many aspects of MRI network topology have been recapitulated in more certainly known brain networks

• Reductionistically, we are entering an exciting phase of being increasingly able to link MRI network topology to cellular organization, myelination and gene expression

• A common theme emerging from both analogical and reductionist analyses is the economical principle that more integrative elements of network topology are more biologically expensive
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