

## Outline:

- “Static” Connectivity
  - Seed-based Correlation
  - Spatial ICA
  - Graph Theory
    - Parcellation
    - Community Detection
      - Distance/Hierarchical Clustering
      - Modularity Optimisation
      - Infomap
- “Dynamic” Connectivity
  - Sliding Window Correlation
  - Co-Activation Patterns
  - Temporal ICA/TFMS

## Synopsis

Connectivity in resting-state fMRI can be evaluated through a variety of different methods. These include methods for static functional connectivity, such as seed-correlation, spatial independent component analysis, and graph theoretical approaches. In addition, dynamic functional connectivity can be assessed using methods such as sliding window correlation, time-frequency analysis, co-activation patterns and temporal independence component analysis.

## Highlights

Connectivity in resting state fMRI can be assessed using a large number of different approaches, including static and dynamic methods

While most of these methods present a fairly consistent picture of the brain’s intrinsic connectivity, specific features and interpretations can depend on the particular constraints or assumptions of the chosen connectivity method

## Target Audience

Trainees and scientists looking to learn a bit more about how measures of connectivity are derived from resting state functional MRI.

## Objectives

To discuss various methods for measuring connectivity in resting state fMRI data. First we will cover *static* connectivity, including methods such as seed-based correlation, spatial independent component analysis (s-ICA), and graph theoretical approaches. Then we will briefly discuss *dynamic* connectivity, assessed by sliding window correlation, co-activation patterns, time-frequency analysis and temporal ICA (t-ICA).

## Static Measures of Connectivity

### *Seed-based Correlation*

In seed-based correlation, connectivity is defined from a reference waveform derived from the time-series data in some “seed” region. Once this reference is defined, a voxel-wise

correlation between the reference and the time-course for every voxel in the image is performed, to get correlation maps, which are subsequently thresholded at some significance value. Voxels surviving the thresholding define the connectivity map for that seed.

Seeds can be derived from single voxels (Biswal 1995), or regions of interest (ROI) (Lowe 1998), where in the latter case the reference waveform is typically the average time-course across the ROI. The location of these seeds are often chosen *a priori* based on structural (Lowe 1998) or functional information (Fox 2005), or are defined from task-based fMRI experiments (Biswal 1995). To get connectivity information about more than one system, multiple distinct seeds need to be used in the correlation analysis.

Generally speaking, seed-based correlation is equivalent to a general linear model (GLM) analysis on task-based fMRI data (Joel 2011), where a seed-derived time-course takes the place of the GLM model regressor, and the correlation coefficient corresponds to the GLM regression coefficient.

### *Spatial ICA*

Spatial independent component analysis (s-ICA) is quite distinct from seed-based correlation, in that s-ICA tries to solve the blind source separation problem (Hyvarinen 2000) by decomposing the space-time data into a linear mixture of spatial “sources” (McKeown, 1998; Beckmann 2004), each with an associated time-course. Here, the spatial sources can be represented as coefficient or statistical parametric maps, and are analogous to the correlation maps derived from seed-correlation.

While the data model in s-ICA is linear, just like the seed-correlation or GLM models, in this case both the spatial maps and the connectivity time-courses are unknown, and the solution to both sets of unknowns is defined by choosing the decomposition that maximizes the statistical independence between the different spatial sources. Two of the most popular choices in fMRI are the mutual information-based *infomax* principle (Bell 1995), or maximizing non-Gaussianity via *negentropy* (Hyvarinen 1999). Interestingly, it has been suggested that these s-ICA algorithms used in fMRI are actually more selective for spatial sparsity, rather than statistical independence (Daubechies 2009).

Unlike seed-correlation, s-ICA estimates the connectivity maps from multiple systems simultaneously. However, one input that is required is the dimensionality, or number of sources, and while this is at most the number of time-points in the data, it is typically much less. The dimensionality can be chosen *a priori* (McKeown 1998), or by maximizing Bayesian model evidence or using the Bayesian information criterion (Beckmann 2004).

- Basic idea:
  - instead of defining seed-based inputs for correlation
  - we try and solve a data decomposition problem
  - the model is linear, just like the seed correlation/GLM model
  - but now both spatial maps and time-courses are unknown
  - the solution, in spatial ICA, is defined by choosing the decomposition that maximizes the independence between the output spatial map (Bell; Hyvaarian)
- Algorithm/Parameter choices
  - dimensionality
  - independence metric (MI, non-gaussianity, infomax)

- intuitively, kurtosis/negentropy maximizes the non-Gaussianity (CLT)
- Maps and Time-Courses
  - like seed correlation, the ICA decomposition produces spatial maps that are associated with a single time-course
  - unlike seed correlation, these maps are not defined by the time-courses
  - to highlight how remarkable this is, consider that PCA-dimensionality reduction is often performed and the ICA algorithms don't even see any time-courses (the temporal modes are generated afterwards, from the mixing matrix)
- Sparsity vs. Independence?
  - some arguments that spatial ICA actually selects for spatial sparsity, rather than spatial independence (Daubechies)

### *Graph-Theory*

Broadly speaking, if seed-correlation and s-ICA are considered voxel-based linear models, graph theoretical approaches are based on more explicit network models that describe the data as a collection of spatial nodes, and edges that reflect the connectivity between nodes (Bullmore 2009). Typically, the nodes are defined through a parcellation, which is essentially a binning of the brain's voxels into different parcels (nodes). Edges are formed by taking the representative time-course from each node and evaluating its connectivity with every other node in the network. Connectivity (edge strength) can be defined using full correlation (Eguiluz 2005), partial correlation (Salvador 2005), or one of many other connectivity metrics such as mutual information (Smith 2011). Typically, the network is summarized using a symmetric network or association matrix, where each row/column corresponds to a node, and the entries in the matrix represent the edge strengths.

A number of different analysis procedures can be performed on the network matrices to identify various network features. This includes computing node degree (how many connections a node has), small-worldness (Milgram 1967), community detection through modularity maximization (Sporns 2016), the InfoMap algorithm (Rosvall 2008), or hierarchical clustering (Girvan 2002).

The results of a network analysis can depend on an appropriate parcellation of the brain (Smith 2013). Parcellations can be derived from prior information or structural boundaries, but are more commonly defined through data-driven approaches such as k-means (Flandin 2002) or spectral clustering (Craddock 2012). Network nodes can also be defined through ICA (Smith 2015), although in this case the nodes are often not single, contiguous parcels.

- Basic idea:
  - if seed and ICA approaches are linear models, these approaches are based on graphical models
  - parcellate the brain into some spatial partitioning (voxels, regions, etc), which form the nodes of the "network" (not to be confused with resting state networks)
  - form edges by taking the representative time-course from each node and correlating (or evaluating partial correlations) with the time-course from every other node
  - network can be summarized using a network matrix

- identify functional networks by detecting communities of nodes based on some clustering metric
- Community metrics
  - euclidean distance or hierarchical clustering
  - modularity (Sporns)
  - Infomap
- Parcellation
  - hard parcellations (k-means, spectral, hierarchical)
  - ICA-based (Smith)
  - Correct and appropriate parcellations can make or break a network analysis

### Dynamic Measures of Connectivity

In static functional connectivity, the metrics of connectivity are assumed to be fixed over time. In contrast, dynamic functional connectivity identifies connectivity-related features that vary over time, aiming to capturing dynamics that reflect changes in neural activity (Hutchison 2013). Most commonly, dynamic connectivity has been assessed using sliding-window correlation (Chang 2010), in which conventional connectivity analyses are performed within each window, and then the time-evolution of these connectivity measures are evaluated as the window slides over the duration of the dataset. Other methods for evaluating dynamic connectivity include co-activation patterns (Liu 2013), time-frequency analysis (Chang 2010), and temporal ICA (Smith 2012).

### References

- Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, 34(4), 537–541.
- Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *NeuroImage*, 7(2), 119–132.
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27), 9673–9678.
- Joel, S. E., Caffo, B. S., van Zijl, P. C. M., & Pekar, J. J. (2011). On the relationship between seed-based and ICA-based measures of functional connectivity. *Magnetic Resonance in Medicine*, 66(3), 644–657.
- Hyvärinen, A., & Oja, E. (2000). Independent component analysis: algorithms and applications. *Neural Networks*, 13(4-5), 411–430.
- McKeown, M. J., & Sejnowski, T. J. (1998). Independent component analysis of fMRI data: examining the assumptions. *Human Brain Mapping*, 6(5-6), 368–372.
- Beckmann, C. F., & Smith, S. M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging*, 23(2), 137–152.
- Bell, A. J., & Sejnowski, T. J. (1995). An information-maximization approach to blind separation and blind deconvolution. *Neural Computation*, 7(6), 1129–1159.
- Hyvärinen, A. (1999). Fast and robust fixed-point algorithms for independent component analysis. *IEEE Transactions on Neural Networks*, 10(3), 626–634.

Daubechies, I., Roussos, E., Takerkart, S., Benharrosh, M., Golden, C., D'Ardenne, K., et al. (2009). Independent component analysis for brain fMRI does not select for independence. *Proceedings of the National Academy of Sciences*, 106(26), 10415–10422.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, 10(3), 186–198.

Eguíluz, V. M., Chialvo, D. R., Cecchi, G. A., Baliki, M., & Apkarian, A. V. (2005). Scale-free brain functional networks. *Physical Review Letters*, 94(1), 018102.

Salvador, R., Suckling, J., Coleman, M. R., Pickard, J. D., Menon, D., & Bullmore, E. (2005). Neurophysiological architecture of functional magnetic resonance images of human brain. *Cerebral Cortex*, 15(9), 1332–1342.

Smith, S. M., Miller, K. L., Salimi-Khorshidi, G., Webster, M., Beckmann, C. F., Nichols, T. E., et al. (2011). Network modelling methods for FMRI. *NeuroImage*, 54(2), 875–891.

Milgram, S. (1967). The small world problem. *Psychology Today* 1, 61–67

Sporns, O., & Betzel, R. F. (2016). Modular Brain Networks. *Annual Review of Psychology*, 67, 613–640.

Rosvall, M., & Bergstrom, C. T. (2008). Maps of random walks on complex networks reveal community structure. *Proceedings of the National Academy of Sciences*, 105(4), 1118–1123.

Girvan, M., & Newman, M. E. J. (2002). Community structure in social and biological networks. *Proceedings of the National Academy of Sciences of the United States of America*, 99(12), 7821–7826.

Smith, S. M., Vidaurre, D., Beckmann, C. F., Glasser, M. F., Jenkinson, M., Miller, K. L., et al. (2013). Functional connectomics from resting-state fMRI. *NeuroImage*, 17(12), 666–682.

Flandin, G., Kherif, F., Pennec, X., Malandain, G., Ayache, N., Poline, J.-B., et al. (2002). Improved detection sensitivity in functional MRI data using a brain parcelling technique. *MICCAI* 2488, 467–474.

Craddock, R. C., James, G. A., Holtzheimer, P. E., Hu, X. P., & Mayberg, H. S. (2012). A whole brain fMRI atlas generated via spatially constrained spectral clustering. *Human Brain Mapping*, 33(8), 1914–1928.

Smith, S. M., Nichols, T. E., Vidaurre, D., Winkler, A. M., Behrens, T. E. J., Glasser, M. F., et al. (2015). A positive-negative mode of population covariation links brain connectivity, demographics and behavior. *Nature Neuroscience*, 18(11), 1565–1567.

Hutchison, R. M., Womelsdorf, T., Allen, E. A., Bandettini, P. A., Calhoun, V. D., Corbetta, M., et al. (2013). Dynamic functional connectivity: Promise, issues, and interpretations. *NeuroImage*, 80, 360–378.

Chang, C., & Glover, G. H. (2010). Time-frequency dynamics of resting-state brain connectivity measured with fMRI. *NeuroImage*, 50(1), 81–98.

Liu, X., & Duyn, J. H. (2013). Time-varying functional network information extracted from brief instances of spontaneous brain activity. *Proceedings of the National Academy of Sciences*, 110(11), 4392–4397.

Smith, S. M., Miller, K. L., Moeller, S., Xu, J., Auerbach, E. J., Woolrich, M. W., et al. (2012). Temporally-independent functional modes of spontaneous brain activity. *Proceedings of the National Academy of Sciences*, 109(8), 3131–3136.

