Markov Network Toolbox (MoNeT) for Functional Connectivity Estimation and Multi-Subject Inference

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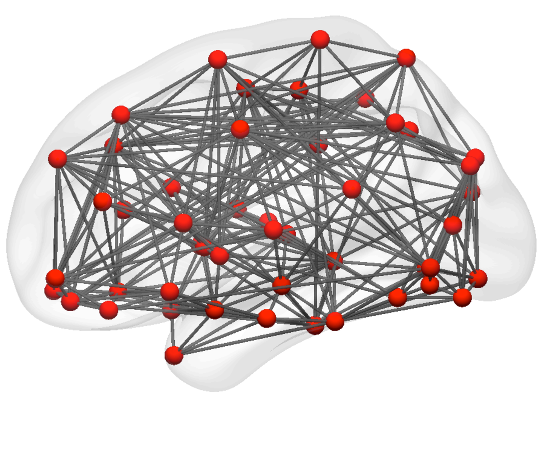
Introduction

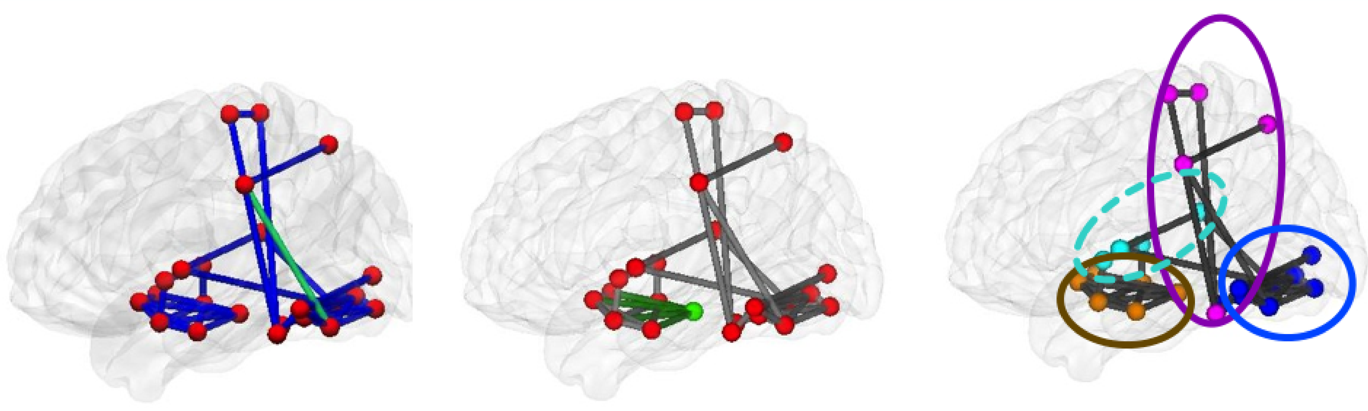
Functional MRI activation studies compare activation patterns across groups by accounting for all sources of variability including intra-subject and inter-subject variability using random effects test statistics. Recent interest in studying the networks of brain activation has led to a plethora of studies comparing edges, nodes, and community network structures across groups. Unfortunately current approaches to testing network features ignore the fact that network estimates are not fixed, but highly variable due to both intra-subject and inter-subject variability, as well as graph selection variability in high dimensions.

- We provide new statistical techniques to compare features of multi-subject networks based on resampling and random effects methods (R^3).
- Markov Network Toolbox (MoNeT) for functional connectivity estimation currently implements high dimensional statistical methods to provide functional connectivity models for multi-subject fMRI data. R^3 approaches will soon be supported in MoNeT.
- We demonstrate the efficacy of our novel methods on the Autism Brain Imaging Data Exchange (ABIDE) dataset and on colored-sequence synesthesia.



Objective & Motivation

Objectives: Two Group Comparisons of Graph Topological Features



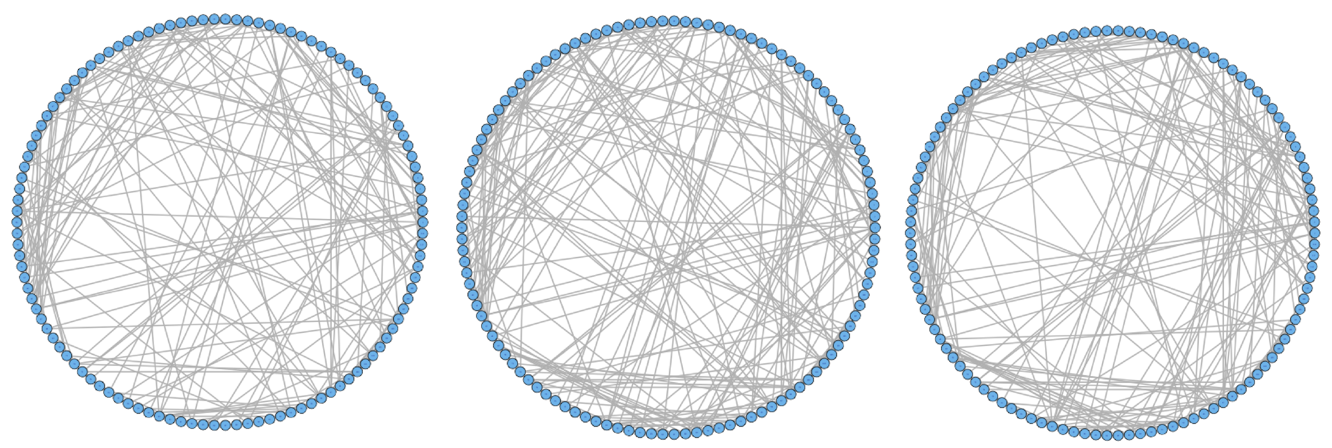
Edge Level
Does a specific edge or functional connection have a stronger presence in a diseased group ?

Node Level
Does a node have denser connections in the control group ?

Community Level
Does a node show differential community allegiances between diseased and control groups ?

Variability in Multi-Subject Networks Pose a Challenge to Inference

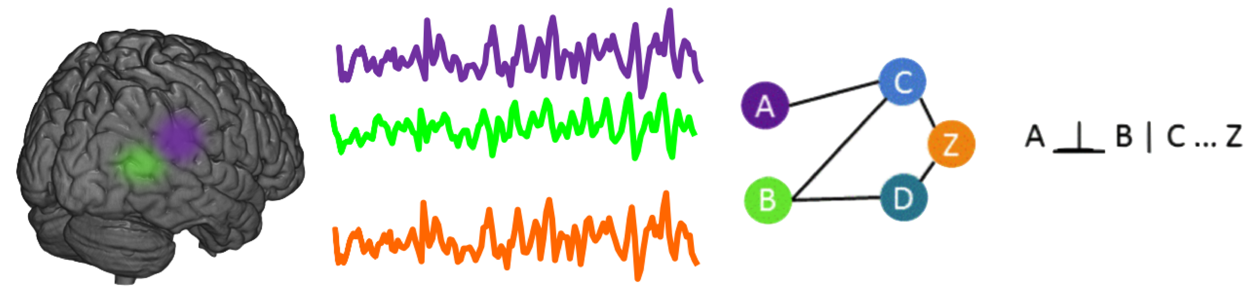
- Subject networks are estimated from noisy neuroimaging data.
- **Each subject network in neuroimaging is not fixed, but a highly variable estimated quantity.**
- In addition to inter-subject variability, each subject network possesses intra-subject variability as well.
- Any hypothesis test to obtain p-values on network features should account for all sources of uncertainty, otherwise the p-value for each network feature will be incorrect and misleading.



(a) Autism Subject 1 (b) Autism Subject 2 (c) Autism Subject 3

Markov Network subject variability in ABIDE [1].

Markov Networks for Functional Connectivity



Edges in Markov Networks indicate direct relationships between two regions of interest. Indirect edges that might have occurred in simple correlation networks are eliminated.

- Markov Networks produce reliable and biologically interpretable edges in network models.[2, 3]
- In high dimensions, when the number of brain regions is large, if true graph structure is sparse (i.e. assuming not all brain regions have direct functional connections), we can estimate the network despite limited number of fMRI time points.

Graphical Model Estimation and Model Selection.

Θ- Partial Covariance, Σ- Covariance

- High dimensional graphs Θ can be estimated by eliminating edges attributed to noise. A popular method is to achieve this is to penalize the maximum likelihood as in the *graphical lasso* algorithm [4].
- The penalty or regularization parameter λ determines the number of edges and is found using model selection methods such as Stability Selection [5] or StARS [6].

$$\hat{\Theta}(\lambda) = \arg\min_{\Theta \succ 0} \left(-\log\left(\det \Theta\right) + \mathrm{Tr}\left(\hat{\Sigma}\Theta\right) + \lambda\|\Theta\|_1\right) \quad \text{(Graphical Lasso)}$$

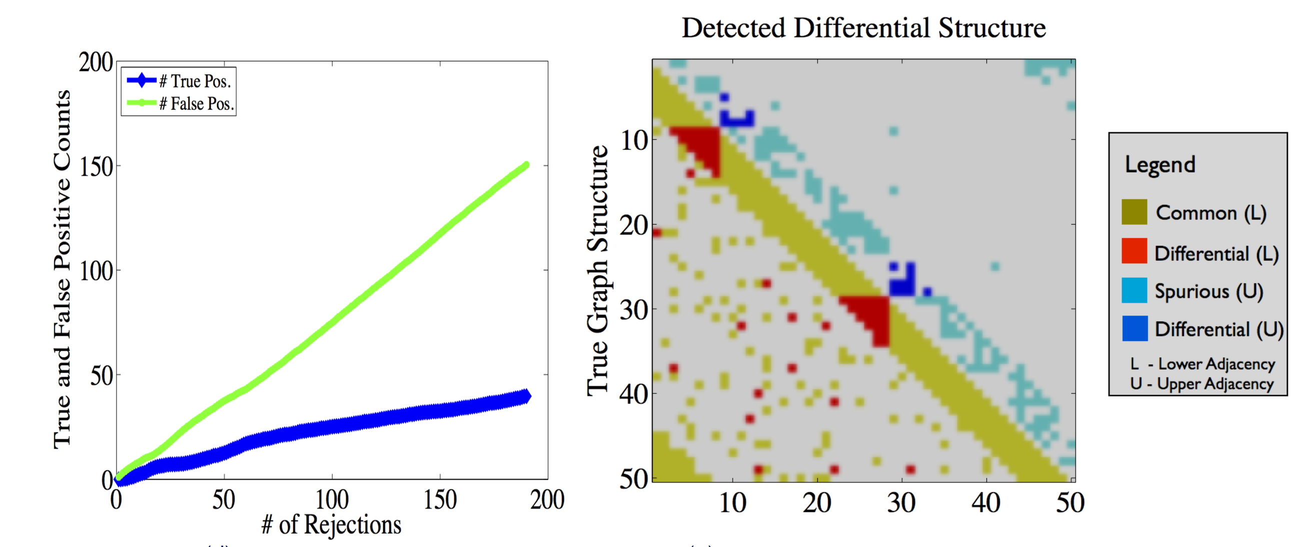
Motivation: The standard hypothesis testing framework is inadequate.

The goal is to find differences in edge structure between two groups.

A Simple Two-Sample Test Fails to Account for all Sources of Uncertainty in Multi-Subject Data

- We simulated data assuming known network structure for two groups of subjects, 20 subjects per group. We then perform the following standard approach to network comparisons.
  - Estimate Markov networks from simulated data per subject,
  - Test for mutually exclusive differential edges using a simple two-sample z test.
  - Apply multiple testing procedures to find differential edges.
- **Results**: Given the true differential edges (red) between the groups, most of the detected differences were spurious and were actually common to both groups!
- **Problem**: A regular two-sample test only accounts for inter-subject variability. Does not account for intra-subject network variability or graph selection variability in Markov Networks.

We use the standard approach to find such differential edges between two groups of simulated data, below.



(d) Small World Graph (e) Small World Graph, 83% FDP

Results of simple two-sample tests to identify differential edges.

- *Fig (d) shows that spurious edge differences overwhelm true edge differences very quickly.*
- *Fig (e) shows that 83% of the estimated differential structure (Upper) is a false difference compared to the true graph structure (Lower) .*

Results Using Novel Statistical Framework to Account for all Sources of Uncertainty in Multi-Subject Network Estimates

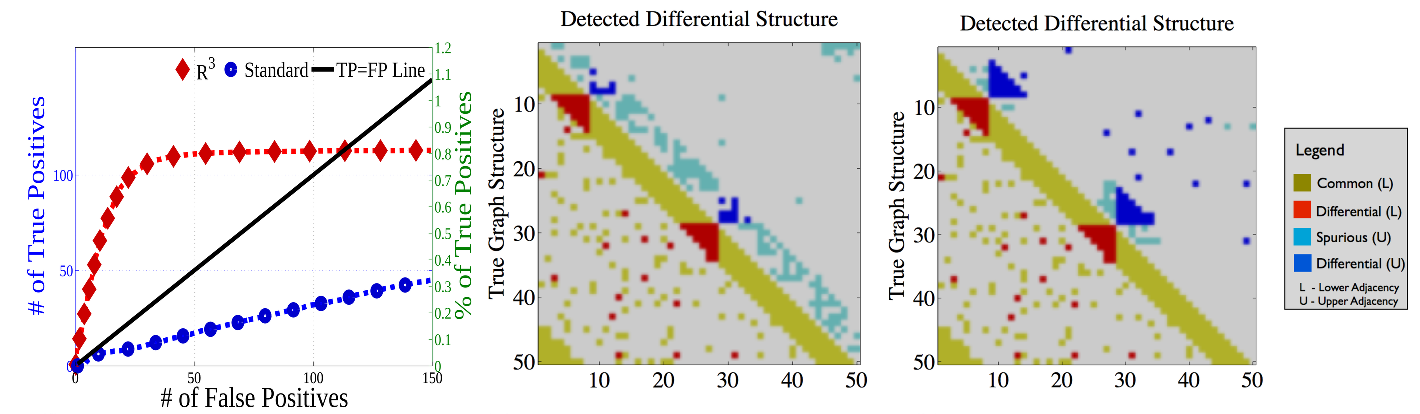
R^3 - Resampling & Random Penalization & Random Effects [7, 8].

Resampling: Repeatedly bootstrap the fMRI time series for each subject and aggregate the results across bootstraps to estimate intra-subject variability of the network.
Random Penalization: In high dimensions and for select network features such as edges, randomize sparse penalty parameter for each resample to reduce graph selection bias and variability
Random Effects: Instead of standard tests, compute a random effects test statistic for every network feature such that it incorporates both intra-subject variance and inter-subject variance

Edge Level Example

Differential Testing for Mutually Exclusive Edges (Simulation Example)

- We simulated fMRI data for two distinct populations such that the true underlying network was small world.
- Figs (g),(h) reveal that R^3 more effectively eliminates spurious differences.



(f) True Positive Counts (Y-Axis), False Positive Counts(X-Axis) (g) Estimated Differences (Upper), Standard Inference (h) Estimated Differences (Upper), R^3 Inference

The R^3 approach is almost 4 times better than standard hypothesis testing in terms of identifying true differences with false discovery control. Each subject has 50 nodes, 400 observations, with 20 subjects per group. Similar results hold for 100 node networks.

Differential Testing for Mutually Exclusive Edges (R^3) in ABIDE Suggest Common Patterns in ASD Literature

- **Fewer long-range connections in ASD**
- **Fewer bilateral connections in ASD**

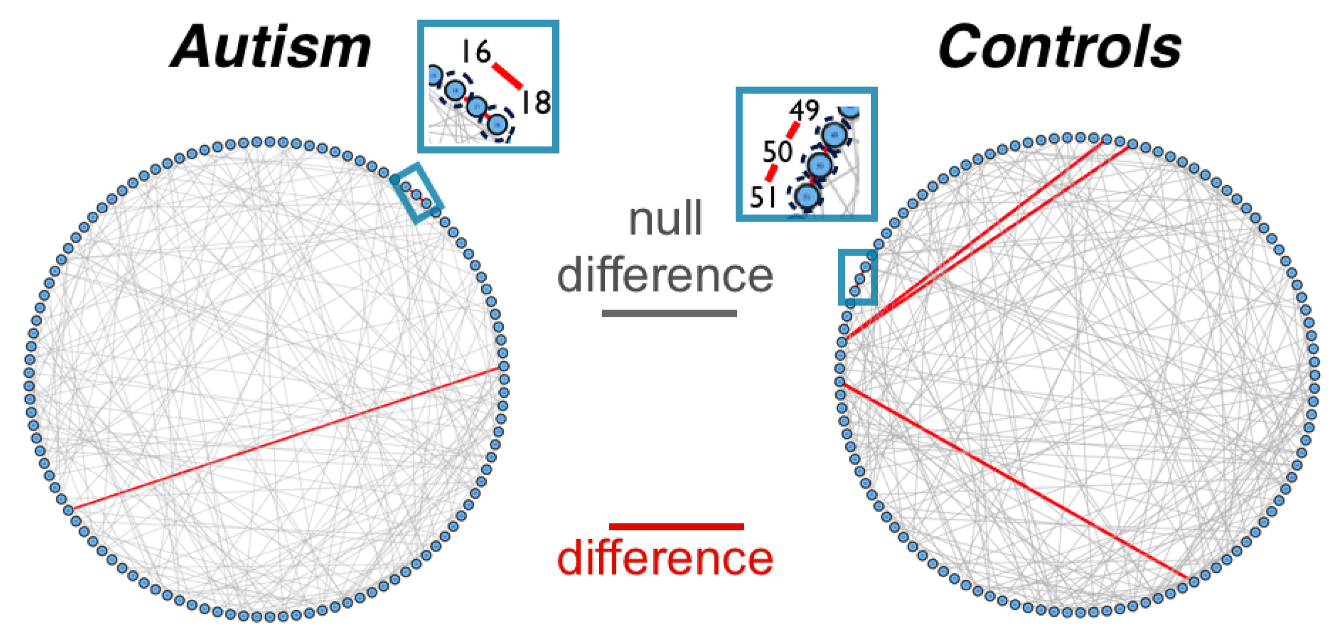
List of edges differentially present in ASD

	ROI	ROI	Raw P-value
1.	Left frontal pole (16)	Left insula (18)	.0016
2.	Left caudate (2)	Left subcallosal cortex (68)	.0102

- **IFG edges not present in ASD**
- **Fusiform edge not present in ASD**

List of edges differentially present in Controls

	ROI	ROI	Raw P-value
3.	Right IFG, po.(27)	Right po. supra-marginal(55)	.0012
4.	Left sup. parietal (50)	Right sup. parietal (51)	.0028
5.	Right IFG, pt(25)	Right posterior supramarginal (55)	.0067
6.	Right post. central (49)	Left superior parietal (50)	.0076
7.	Left lateral occipital cortex(58)	Superior right fusiform (95)	.0098



Circular graphs of ASD and control groups with 113 regions of interest (blue nodes) from the Harvard-Oxford Atlas and 235 edges tested. *Individual subject graphs were estimated for 41 autistic subjects and 32 control subjects using our randomized inference procedure. Preliminary analysis of resting state data from the ABIDE dataset revealed 7 differential edges with an estimated direct FDR of 26%.*

Community Level Example

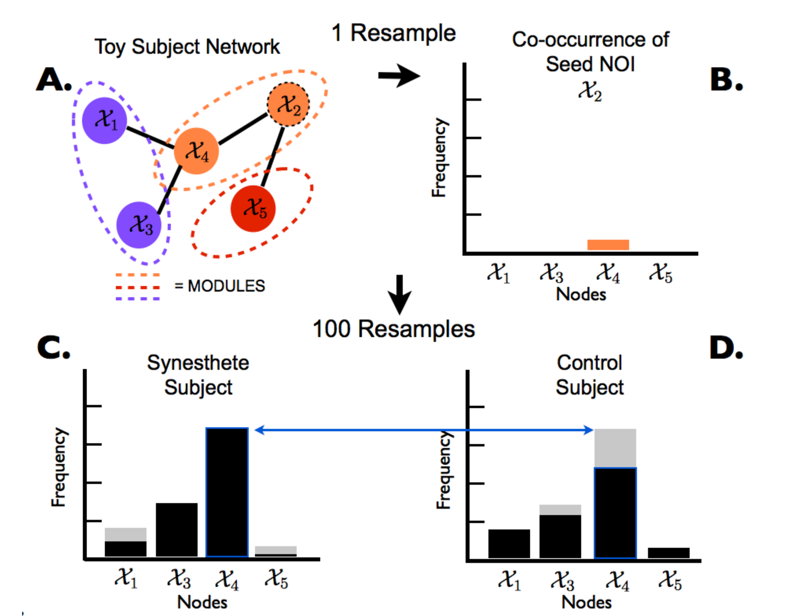
Differential Testing of Modularity Patterns

- A ***Community*** or module refers to groups of nodes that are more connected to each other than to nodes from other modules.
- ***Co-occurance frequency*** **measures how frequently two nodes belong to the same module after repeatedly perturbing the data**
- Modularity assignments can be highly variable to due within subject variability. Therefore, use resampling to reduce uncertainty in modularity assignments in every subject.
- Resampling + random effects node level test-statistic [9] detects nodes that reveal statistically significant differences in modularity allegiance.

(A) represents a toy network obtained after 1 resampling of the data, along with re-estimation and re-clustering of the network for a single synesthetic subject.

(B) illustrates the co-occurance when the seed node of interest (NOI) X2 co-occurs with node X4 in the orange module.

(C) & (D) aggregate co-occurance frequencies from 100 resamples for subjects in both groups.

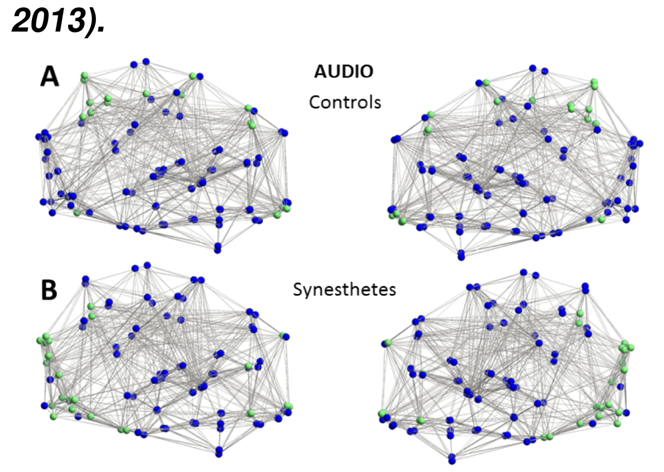


A summary of the modularity analysis procedure using an example toy network. (Reproduced from Tomson, et al. 2013)

Differential Nodes based on Community Patterns in Colored-sequence Synesthesia

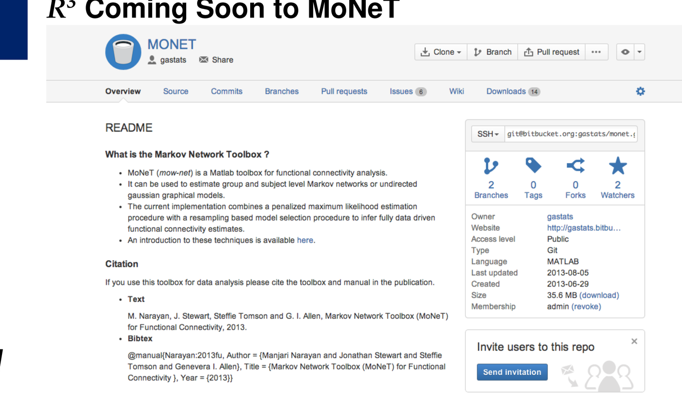
- Colored Sequence Synesthesia is a perceptual condition in which people automatically experience color upon hearing or seeing graphemes (numbers and letters).
- In the experiment 20 synesthetes and 19 controls listened to audio clips of graphemes from Sesame Street.
- Green nodes demonstrate differential modularity patterns between groups

Synesthetes utilize more visual regions than controls, while controls unite frontal and parietal regions significantly more often than synesthetes.(Tomson, et al. 2013).



Markov Network Toolbox (MoNeT)

www.bitbucket.org/gastats/monet
R^3 Coming Soon to MoNeT



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