Population Inference for Functional Brain Connectivity

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1 Functional Connectivity
   • Motivation
     • Existing Approaches to Network Inference

2 Our Approach: Population Inference for Networks
   • Two-Level Network Model
   • Estimation Procedure: $R^3$

3 Results
   • Simulations
   • Case Studies
Functional Neuroimaging

Molecular fMRI

Light sheet microscopy

fMRI, fNIRS

EEG, MEG

ECoG

Calcium imaging
Functional Neuroimaging in Humans

Observe macroscopic neural activity over time.

- Voxels (fMRI)
- Sensors (EEG/MEG)
- Electrodes (ECoG)
Functional Connectivity

How does the brain communicate (connect) at a systems level?

Functional Connectivity: Estimated relationships between brain regions.
Objective: Population Inference for Functional Connectivity

Are two population groups different? And how?

Patient Group

Healthy Group
Objective: Population Inference for Functional Connectivity
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Anatomy of Existing Procedures

Step 0: Standard fMRI pre-processing & Parcellation.

Step 1: Estimate brain networks for each subject.

Step 2: Summarize network via network metrics for each subject.

Step 3: Use standard statistical inferential methods to test population effects.

Brain Connectivity Toolbox
[ Sporns, 2005; Bullmore and Sporns, Nat. Rev. Neurosci., 2011; Rubinov and Sporns, 2009]

Focus: Functional MRI.
Anatomy of Existing Procedures

**Step 0:** Standard fMRI pre-processing & Parcellation.
- Parcellation: reduces fMRI volume to regions of interest (ROIs).
  - Anatomical or Functionally derived Atlases.

![Brain parcellation image](image_url)

**Step 1:** Estimate brain networks for each subject.

**Step 2:** Summarize network via *network metrics* for each subject.

**Step 3:** Use standard statistical inferential methods to test population effects.
Anatomy of Existing Procedures

Step 0: Standard fMRI pre-processing & Parcellation.

Step 1: Estimate brain networks for each subject.

- Correlation Networks.
- Markov Networks (partial correlations).
- Causal / Directed Networks.
- Dynamic Networks.

Step 2: Summarize network via network metrics for each subject.

Step 3: Use standard statistical inferential methods to test population effects.
Anatomy of Existing Procedures

Step 0: Standard fMRI pre-processing & Parcellation.
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Markov Network

An *undirected graphical model* that characterizes conditional dependence (direct) relationships.

- *Edge*: Two brain regions are **conditionally dependent**.
- *No edge*: Two brain regions are **conditionally independent**.

\[ A \perp B \mid C \]

Step 2: Summarize network via *network metrics* for each subject.
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Step 0: Standard fMRI pre-processing & Parcellation.
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### Kronecker Gaussian Graphical Model

\[ X_i \sim N_{p,T}(0, \Theta_i^{-1} \otimes \Omega^{-1}) \]

- \( \Omega^{-1} \) a temporal covariance.
- \( \Theta_i \) subject-specific functional connectivity.

### One-Step Estimator

\[
\max_{\Theta_i} \log |\Theta_i| - \text{tr}(X_i^T \hat{\Omega} X_i \Theta_i) - \lambda \|\Theta_i\|_1
\]

Step 2: Summarize network via network metrics for each subject.
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Anatomy of Existing Procedures

Step 0: Standard fMRI pre-processing & Parcellation.
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Step 3: Use standard statistical inferential methods to test population effects.
  - T-tests, linear regression models, permutation null distributions, multiple testing, etc.
A Simulation Test

Simulation:
- Markov Networks.
- Testing for edge presence or absence.
A Simulation Test
A Simulation Test
A Simulation Test

Apply 10% FDR correction

<table>
<thead>
<tr>
<th></th>
<th>Power</th>
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<tr>
<td>$R^3$</td>
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<td>Stand.</td>
<td>28%</td>
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What went wrong?

Networks are estimated from neural data!

- Imperfect network estimates can derail inference.
- Must account for network estimation process to control false positives & have good statistical power.
What went wrong?

Incorrect estimates of network metric mean and variance!

   - Variability in networks between subjects.
   - Variability of network estimates within subjects.

2. Challenge II: Biased Mean - Graph Selection Errors.
   - Errors at the subject level can create biases that propagate and confound inference at the population level.
   - False positive edges more likely between two nodes with many common neighbors.
What went wrong?

Challenge I: Two-Levels of Network Variability

Between Subject Variability:

3 Control Subjects from UCLA ABIDE Data Set
What went wrong?

Challenge I: Two-Levels of Network Variability

Network Variability within a Single Subject:

3 Estimated Networks after Resampling - Control Subject from UCLA ABIDE Data Set
What went wrong?

Challenge I: Two-Levels of Network Variability

Classical Two-Sample T-test:

\[ T = \frac{\hat{\mu}_A - \hat{\mu}_B}{\sqrt{\frac{\hat{\sigma}^2_A}{n_A} + \frac{\hat{\sigma}^2_B}{n_B}}} \]

Two-level Two-Sample T-test:

\[ T = \frac{\hat{\mu}_A - \hat{\mu}_B}{\sqrt{\left(\frac{\hat{\sigma}^2_{w,A}}{n_{w,A}} + \frac{\hat{\sigma}^2_{b,A}}{n_A}\right) + \left(\frac{\hat{\sigma}^2_{w,B}}{n_{w,B}} + \frac{\hat{\sigma}^2_{b,B}}{n_B}\right)}} \]
What went wrong?

Challenge II: Biased Network Metrics

- Errors from biased subject-level networks propagate and confound inference at the population level.
- Graph selection errors are not uniform for highly correlated data.

Toy Example of Network Estimation Errors for Markov Networks.
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Our Solution

* **Model**: Two-Level Network Models.

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<td>$\mathbf{X}^{(i)} \sim \text{Network Model}(\Theta_i)$</td>
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<td>Subject-Level fMRI $\sim$ Subject-Specific Network Model</td>
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Population Network Model for Inference

Subject-Level Model

\[ X^{(i)} \sim \text{Network Model} (\Theta_i) \]

Subject-Level fMRI \( \sim \) Subject-Specific Network Model

Population-Level Model

\[ \mathbb{E} (\text{link} [f(\Theta_i)]) = Z\beta \]

Network Metrics \( f(\Theta_i) \) follow a Generalized Linear Model.
Population Network Model for Inference

Subject-Level Model

\[ X^{(i)} \sim \text{Network Model}(\Theta_i) \]
Subject-Level fMRI \sim \text{Subject-Specific Network Model}

Population-Level Model

\[ \mathbb{E}(\text{link } [f(\Theta_i)]) = Z\beta \]

Network Metrics \((f(\Theta_i))\) follow a Generalized Linear Model.

Population-Level Hypotheses

\[ \mathcal{H}_0 : \beta = 0 \quad \text{vs.} \quad \mathcal{H}_1 : \beta \neq 0 \]
Population Post Selection Inference

Problems:

- Two-level statistical model.
- Network estimation requires a selection procedure.
- Theory, statistics, and inference for standard multi-level models (e.g. random effects) no longer holds.
Population Post Selection Inference

Problems:

- Two-level statistical model.
- Network estimation requires a selection procedure.
- Theory, statistics, and inference for standard multi-level models (e.g. random effects) no longer holds.

Our problem belongs to a larger framework:

Population Post Selection Inference (popPSI)

A two-level problem with:

- Subject Level: A selection procedure used to estimate parameters.
- Population Level: Inference conducted on population level parameters.
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Our Approach: $R^3$

$R^3$ Procedure:

- **Resampling.** Bootstrapping to estimate subject network variability.

- **Random Effects.** Correct test statistics that account for two-levels of variability.

- **Random Penalization.** Improves errors associated with graph selection.
Our Approach: $R^3$

Challenge I Solution (Two-Levels of Network Variability):

Resampling + Random Effects

Specific Example: Inference for Edges.

- Beta-Binomial Model:

$$Y^{(i,*b)} | \mu_i \sim Binom(B, \mu_i)$$
$$\mu_i \sim Beta(\pi_g, \rho_g)$$

Edge Indicator: $Y^{(i)}_{(l,k)} = I(\theta^{(i)}_{(l,k)} \neq 0)$.

- Idea: Without resampling, no way to estimate edge variability.
- Estimation: Method of moments.

General Solution: Mixed Effects Models (GLMMs).
Our Approach: $R^3$

Challenge II Solution (Biased Network Metrics):

Resampling + Random Penalization

- Idea: Decorrelate data via randomization.
- Randomly Penalized Gaussian Graphical Models:

$$\max_{\Theta_i} \log |\Theta_i| - \text{tr}(\hat{\Sigma}_i^b \Theta_i) - \|W^b_\lambda \circ \Theta_i\|_1$$

- Random (symmetric) weight matrix, $W^b_\lambda$, centered around $\lambda$.
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Simulation Studies

Simulation: Markov Networks - Inference on edges - Two-Group Population.

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Simulation Studies

Simulation: Markov Networks - Inference on Subnetwork Density - Continuous Covariate (i.e. symptom severity) in Population.

- $T = p, p = 50$
- Single covariate
- High SNR
  - $(\beta = 1, \nu^2 = .1)$
Simulation: Markov Networks - Inference on Subnetwork Density - Continuous Covariate (i.e. symptom severity) in Population.
Simulation Studies

Simulation: Markov Networks - Inference on Subnetwork Density - Continuous Covariate (i.e. symptom severity) in Population.
Simulation Studies

Summary

- Random Effects Test Statistics:
  - Improved Statistical Power.
  - Improved Type I Error control.

- Random Penalization:
  - Improved Statistical Power.
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3. Results
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Brain regions that process color have more connections to those that process numbers and letters in synesthetes than controls.
Case Study: Color-Sequence Synesthesia

Are there different node clustering patterns between the two groups?
Case Study: Neurofibromatosis Type I

NF1 is a genetic disorder with a number of neurological symptoms.

NF1 physical symptoms

- Café au lait spots
- Lisch nodules
- NF1 lesions

Functional MRI Study:
- Resting-state study.
- 30 NF1 patients, 30 age-matched healthy controls.
Case Study: Neurofibromatosis Type I

Edge-Level Differences:

Controls have more anterior-posterior connections than NF1 patients.
Case Study: Neurofibromatosis Type I

Clustering Differences:

NF1 patients show more lateralized, atrophied modular clustering than controls.
Case Study: Autism Spectrum Disorder

Hypothesis: ASD Hyper- or Hypo-Connectivity in Salience Network?

Data: ABIDE UCLA and UM subjects - resting state fMRI.

Finding: Higher ADOS scores = Fewer connections between frontoparietal & limbic / ventral attention subnetworks.
Case Study: Autism Spectrum Disorder

Hypothesis: ASD Hyper- or Hypo-Connectivity in Salience Network?

Data: ABIDE UCLA and UM subjects - resting state fMRI.

Finding: Higher ADOS scores = Fewer connections from ACC (p-value = 0.0021) & PCC (p-value = 0.0045), members of the salience network.
Summary & Discussion Points

Inference for Brain Connectivity.

Main Message
- Brain / Neural Networks are estimated quantities.
- Failure to account for network estimation leads to incorrect inference!

Discussion
  - Lots of open statistical questions!
- Studies in different types of neural / brain connectivity.
MoNet: Markov Network Toolbox for Functional Connectivity

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References


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