Differential Connectivity Analysis
A framework for identifying differences in high-dimensional networks

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Why Networks?

Art work by Nancy Rubin
Networks in Biology: Gene Regulatory Interactions

A Gene Regulatory Network

INPUT signal A
- receptor proteins
  - cascade of interacting kinase proteins or other molecules
  - active transcription factor A

INPUT signal B
- receptor proteins
  - inactive transcription factor A
  - inhibitory factor
  - inactive transcription factor B
  - active transcription factor B

OUTPUT mRNA
- DNA
  - cis-regulatory DNA sequence elements
  - RNA polymerase
  - target gene

OUTPUT protein
- cell functions
- feedbacks
Networks in Biology: Protein-Protein Interaction
Networks in Biology: Metabolic Reactions

DMAPP $\rightarrow$ IPP $\rightarrow$ GPP $\rightarrow$ Squalene $\rightarrow$ Lanosterol
Networks in Biology: Neural Circuits
1- Understanding interactions among components of biological systems:
   ▶ gene regulatory interactions, protein-protein interactions
   ▶ brain functional and structural connectivity

2- Changes in networks related to complex diseases
⇒ Differential network biology
   ▶ Early / more accurate diagnosis
   ▶ Delineating disease mechanisms & new therapies

Ideker & Krogan (2012) Mol Sys Bio
Networks in Biology

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Networks in Biology

1- Understanding interactions among components of biological systems:
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2- Changes in networks related to complex diseases ⇒ Differential network biology\(^1\)
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In practice, condition-specific networks are often estimated.

Differential Network Biology

Ideker & Krogan (2012) Mol Sys Bio
In practice, condition-specific networks are often estimated.
Estimating Condition-Specific Networks

Using marginal association, e.g. correlation

Correlation: measures the strength of (linear) association between two variables (e.g. brain regions)

Using conditional associations, e.g. partial correlation

Partial Correlation: measures the strength of (linear) association between two variables, after adjusting for other variables

If $X$ is Gaussian, the inverse covariance matrix $\Omega = \Sigma^{-1}$ characterizes conditional dependences $j \leftrightarrow k \iff \Omega_{jk} \neq 0$

$\Omega \sim \begin{bmatrix} - \times \times \\ - \times 0 \\ - 0 - \\ 0 - \times \end{bmatrix}$
Using marginal association, e.g. correlation

If \( X_i \) is Gaussian, the inverse covariance matrix \( \Omega = \Sigma^{-1} \) characterizes conditional dependences.

\[ \Omega \sim \begin{bmatrix} - & - & - & 0 \\ - & - & 0 & - \\ - & 0 & - & - \\ 0 & - & - & - \end{bmatrix} \]
Estimating Condition-Specific Networks

1. Using *marginal* association, e.g. *correlation*
   - **Correlation**: measures the strength of (linear) association between two variables (e.g. brain regions) $X_i$ & $X_j$
Estimating Condition-Specific Networks

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\[ j \perp k \iff \Omega_{jk} \neq 0 \]
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$$\Omega \sim \begin{bmatrix} - & \times & \times \\ \times & - & 0 \\ \times & 0 & - \end{bmatrix}$$
Conditional Independence Graphs (CIGs)

Nodes: variables (genes, etc)
Edges: connect variables that are conditionally dependent
\[ X_j \perp \perp X_k \mid \text{ne}(X_j) \quad \forall k \notin \text{ne}(X_j) \]

For normal \[ X \]
\[ X_j \perp \perp X_k \mid \text{rest} \iff \Omega_{j,k} = 0 \]
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For normal \( X \),

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Learning Condition-Specific Genetic Networks

Estimation of CIG given iid observations on $d$ variables$^2$
Learning Condition-Specific Genetic Networks

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Estimation of CIG given iid observations on $d$ variables\(^2\)

$X_{n\times d}$

\(^2\)Graphical lasso (glasso), Neighborhood selection, CLIME, etc
Learning Condition-Specific Genetic Networks

What if data from 2 related subpopulations (e.g. normal/cancer)?
Learning Condition-Specific Genetic Networks

Methods for **joint estimation of multiple graphical models**

\[ X_{n \times d} \]

Learning Condition-Specific Genetic Networks

What if we have > 2 subpopulations?

\[ X_{n \times d} \]
Learning Condition-Specific Genetic Networks

What if we have > 2 subpopulations with complex relationships?
Learning Condition-Specific Genetic Networks
LASICH: general framework by considering “networks” of subpopulations

\[ X_{nxd} \]
Learning Condition-Specific Genetic Networks

LASICH: general framework by considering “networks” of subpopulations

\[ X_{nxd} \]

\[^4\] Saegusa & S. (2016), Elec J Stat
Learning Condition-Specific Genetic Networks

LASICH: general framework by considering “networks” of subpopulations

\[
X^{(1)}(n_{1} \times d) \quad X^{(2)}(n_{2} \times d) \quad X^{(3)}(n_{3} \times d)
\]

\[G_{S} \quad G_{V}^{(1)} \quad G_{V}^{(2)} \quad G_{V}^{(3)}\]

\[4\text{Saegusa & S. (2016), Elec J Stat}\]
Consider $K$ (sub)populations, with $n_1, \ldots, n_K$ observations of $d$ variables in each group.
Learning Condition-Specific Genetic Networks

- Consider $K$ (sub)populations, with $n_1, \ldots, n_K$ observations of $d$ variables in each group.
- If $n_k \gg d$, can estimate $\hat{\Omega}^k = (S^k)^{-1}$, where $S^k$ is the empirical covariance matrix in population $k$.
Learning Condition-Specific Genetic Networks

- Consider $K$ (sub)populations, with $n_1, \ldots, n_K$ observations of $d$ variables in each group
- If $n_k \gg d$, can estimate $\hat{\Omega}^k = (S^k)^{-1}$, where $S^k$ is the empirical covariance matrix in population $k$
- When $n_k \ll d$, can use penalized estimation to separately estimate $\Omega^k$
  \[
  \hat{\Omega}^k = \min_{\Omega^k} \text{loss}(\Omega^k) + \lambda \text{pen}(\Omega^k)
  \]

  ▶ A natural choice for $\text{loss}(\Omega^k)$ is the negative log-likelihood
  ▶ Lasso penalty $\text{pen}(\Omega^k) = \sum_{i \neq j} |\Omega_{ij}^k|$ gives sparse estimates (glasso)
  ▶ $\lambda$ is a tuning parameter that controls the sparsity level
    ★ small $\lambda \Rightarrow$ many edges
    ★ large $\lambda \Rightarrow$ fewer edges
LASICH: Joint Estimation of Condition-Specific Networks

- **Idea:** improve estimation of $\Omega_{ij}^{(k)}$’s by **borrowing information** across (similar) populations, while **learning group-specific edges**
LASICH: Joint Estimation of Condition-Specific Networks

Idea: improve estimation of $\Omega_{ij}^{(k)}$’s by borrowing information across (similar) populations, while learning group-specific edges

$$\min_{\Omega^1, \ldots, \Omega^K} \sum_{k=1}^{K} \text{loss}(\Omega_k) + \lambda_1 \sum_{k=1}^{K} \text{pen}_1(\Omega_k) + \lambda_2 \text{pen}_2(\Omega^1, \ldots, \Omega^K)$$
**LASICH: Joint Estimation of Condition-Specific Networks**

- **Idea:** improve estimation of $\Omega_{ij}^{(k)}$’s by **borrowing information** across (similar) populations, while **learning group-specific edges**

$$
\min_{\Omega^1,\ldots,\Omega^K} \sum_{k=1}^{K} \text{loss}(\Omega^k) + \lambda_1 \sum_{k=1}^{K} \text{pen}_1(\Omega^k) + \lambda_2 \text{pen}_2(\Omega^1, \ldots, \Omega^K)
$$

- $\text{loss}(\Omega^k)$ is the negative log-likelihood for population $k$
- Lasso penalty $\text{pen}_1(\Omega^k) = \sum_{i\neq j} |\Omega_{ij}^k|$ encourages sparsity
- $\text{pen}_2(\Omega^1, \ldots, \Omega^K)$ encourages **similarity** among $\Omega^k$’s: $\Omega_{ij}^{(k)} \approx \Omega_{ij}^{(k')}$ if populations $k$ and $k'$ are related (LASICH uses a Laplacian penalty)
Example: Gene Networks of Breast Cancer Subtypes
Genomic subtypes of breast cancer identified by array-comparative genomic hybridization display distinct molecular and clinical characteristics.
Genomic subtypes of breast cancer identified by array-comparative genomic hybridization display distinct molecular and clinical characteristics.
Example: Gene Networks of Breast Cancer Subtypes

![Graph showing survival rates of different breast cancer subtypes over time with legends for Amplifier, Basal-complex, 17q12, Luminal-simple, Luminal-complex, and Mixed subtypes. The log-rank p-value is 0.0006.]
Example: Gene Networks of Breast Cancer Subtypes

- Luminal Simple
- Luminal Complex
  - GLasso
  - Guo et al.
  - FGL
  - LASICH
- Basal Complex
A Few Comments

- With high probability, networks are correctly estimated
- With high probability, partial correlations and their signs are correctly estimated
- LASICH also works if subtype memberships are unknown
Differential Connectivity Analysis

Suppose we obtain the following network estimates:

Normal:
- Node 1 connected to Node 2
- Node 1 connected to Node 3

Cancer:
- Node 2 connected to Node 3

Q: Does this mean that the two networks are really different?
A: Probably, but not necessarily!

Need to account for variability in network estimation.

≡ Differential Connectivity Analysis
Differential Connectivity Analysis

Suppose we obtain the following network estimates

Q: Does this mean that the two networks are really different?
Differential Connectivity Analysis

Suppose we obtain the following network estimates

\[
\begin{array}{ccc}
\text{Normal} & \text{Cancer} \\
1 \quad 2 \quad 3 & 2 \quad 1 \quad 3
\end{array}
\]

Q: Does this mean that the two networks are really different?
A: Probably
Differential Connectivity Analysis

Suppose we obtain the following network estimates:

Q: Does this mean that the two networks are really different?
A: Probably, but not necessarily!
Differential Connectivity Analysis

Suppose we obtain the following network estimates

```
Network I
1
2
3
```

```
Network II
1
2
3
```

Q: Does this mean that the two networks are really different?
A: Probably, but not necessarily!

- Need to account for variability in network estimation
Differential Connectivity Analysis

Suppose we obtain the following network estimates:

Q: Does this mean that the two networks are really different?
A: Probably, but not necessarily!

- Need to account for variability in network estimation

Need inference for differential connectivity ≡ Differential Connectivity Analysis
Differential Connectivity Analysis

Suppose we obtain the following network estimates:

**Normal**

[Diagram of a network with nodes 1, 2, and 3 connected in a triangle]

**Cancer**

[Diagram of a network with nodes 1, 2, and 3 connected in a line]

Q: Can we assess whether two networks are different by testing if $\Omega_I = \Omega_{II}$?

A: It depends...

$\Omega_I \neq \Omega_{II}$ does not imply differentially connected nodes/edges!

Schott (07); Li & Chen (12); Srivastava & Yanagihara (10); Cai et al (13); Xia et al. (15); etc
Differential Connectivity Analysis

Suppose we obtain the following network estimates

<table>
<thead>
<tr>
<th>Normal</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Q: Can we assess whether two networks are different by testing if $\Omega^I = \Omega^{II}$?

Schott (07); Li & Chen (12); Srivastava & Yanagihara (10); Cai et al (13); Xia et al. (15); etc...
Differential Connectivity Analysis

Suppose we obtain the following network estimates

Normal

2

1

3

Cancer

2

1

3

Q: Can we assess whether two networks are different by testing if $\Omega_I = \Omega_{II}$?

A: It depends...

$\Omega_{IJK} \neq \Omega_{IIJK}$ does not imply differentially connected nodes/edges!

Schott (07); Li & Chen (12); Srivastava & Yanagihara (10); Cai et al (13); Xia et al. (15); etc
Differential Connectivity Analysis

Suppose we obtain the following network estimates

\[
\begin{align*}
\text{Normal} & \\
\begin{array}{c}
2 \\
3
\end{array} & \begin{array}{c}
1 \\
2 \\
3
\end{array} \\
\text{Cancer} & \\
\begin{array}{c}
2 \\
3
\end{array} & \begin{array}{c}
1
\end{array}
\end{align*}
\]

Q: Can we assess whether two networks are different by testing if \( \Omega^I = \Omega^{II} \)?
A: It depends...

\[\Omega^I \neq \Omega^{II} \quad (\Sigma^I \neq \Sigma^{II}) \] gives a valid **global** test of network equality\(^5\)

---

\(^5\) Schott (07); Li & Chen (12); Srivastava & Yanagihara (10); Cai et al (13); Xia et al. (15); etc
Differential Connectivity Analysis

Suppose we obtain the following network estimates

Q: Can we assess whether two networks are different by testing if $\Omega^I = \Omega^{II}$?
A: It depends...

$\nabla \Omega^I \neq \Omega^{II} (\Sigma^I \neq \Sigma^{II})$ gives a valid global test of network equality$^5$

$\nabla \Omega^I_{jk} \neq \Omega^{II}_{jk} (\Sigma^I_{jk} \neq \Sigma^{II}_{jk})$ does not imply differentially connected nodes/edges!

---

$^5$Schott (07); Li & Chen (12); Srivastava & Yanagihara (10); Cai et al (13); Xia et al. (15); etc
A Toy Example

Node 3 is not connected node 1 in treatments but the interaction between 1 and 2 is the same in both populations.

Let $\Omega_N = \begin{bmatrix} 1 & 0 \\ 0.5 & 0 \\ 0.5 \\ 1 & 0 \\ 0.5 & 0 & 1 \end{bmatrix}$; then $\Omega_C = \begin{bmatrix} 1 \\ 2 \end{bmatrix}$.

$\Omega_{N12} \neq \Omega_{C12} \Rightarrow$ rejecting $H_0 : \Omega_{Njk} = \Omega_{Cjk}$ may give false discoveries!

Can still test $H_0 : \text{supp} \Omega_{Njk} = \text{supp} \Omega_{Cjk} \equiv$ differential connectivity!

▶ Testing qualitative interactions – difficult, especially in high dimensions.
Node 3 is **not** connected node 1 in treatments but the interaction between 1 and 2 is the same in both populations.

Let

$$\Omega^N = \begin{bmatrix} 1 & 0.5 & 0.5 \\ 0.5 & 1 & 0 \\ 0.5 & 0 & 1 \end{bmatrix};$$
Node 3 is not connected node 1 in treatments but the interaction between 1 and 2 is the same in both populations.

Let

\[ \Omega^N = \begin{bmatrix} 1 & 0.5 & 0.5 \\ 0.5 & 1 & 0 \\ 0.5 & 0 & 1 \end{bmatrix}; \quad \text{then} \quad \Omega^C = \begin{bmatrix} 1 & 1/\sqrt{3} & 0 \\ 1/\sqrt{3} & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}. \]
A Toy Example

Node 3 is not connected node 1 in treatments but the interaction between 1 and 2 is the same in both populations.

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\Omega_N = \begin{bmatrix} 1 & 0.5 & 0.5 \\ 0.5 & 1 & 0 \\ 0.5 & 0 & 1 \end{bmatrix}; \quad \text{then} \quad \Omega_C = \begin{bmatrix} 1 & 1/\sqrt{3} & 0 \\ 1/\sqrt{3} & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}.
\]

\[
\times \quad \Omega_N^{12} \neq \Omega_C^{12} \implies \text{rejecting } H_0 : \Omega_N^{jk} = \Omega_C^{jk} \text{ may give false discoveries!}
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A Toy Example

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\[ \times \Omega^N_{12} \neq \Omega^C_{12} \Rightarrow \text{rejecting } H_0 : \Omega^N_{jk} = \Omega^C_{jk} \text{ may give false discoveries!} \]

\[ \checkmark \text{Can still test } H_0 : \text{supp}(\Omega^N_{jk}) = \text{supp}(\Omega^C_{jk}) \equiv \text{differential connectivity!} \]
A Toy Example

Node 3 is not connected to node 1 in treatments, but the interaction between 1 and 2 is the same in both populations.

Let

\[
\Omega^N = \begin{bmatrix}
1 & 0.5 & 0.5 \\
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\( \checkmark \) Can still test \( H_0 : \text{supp}(\Omega^N_{jk}) = \text{supp}(\Omega^C_{jk}) \equiv \) differential connectivity!

- Testing qualitative interactions – difficult, especially in high dimensions.
A New Framework for Testing Differential Connectivity

We utilize the Markov property of CIGs, by focusing on the common neighborhood of each node $j$ in the two networks: $ne_j^0 = ne_j^I \cap ne_j^{II}$.

Key Obs 1: Under the null ($H_0: ne_j^I = ne_j^{II}$), $X_j \perp \perp X_k \mid ne_0^j$ for any $k \not\in ne_0^j$.

Key Obs 2: Under the alternative ($H_0: ne_j^I \neq ne_j^{II}$), $X_j / \perp \perp X_k \mid ne_0^j$ for some $k \not\in ne_0^j$. 
We utilize the **Markov property** of CIGs, by focusing on the **common neighborhood** of each node \( j \) in the two networks: \( ne_j^0 = ne_j^I \cap ne_j^{II} \).

**Key Obs 1**: Under the null \( (H_0 : ne_j^I = ne_j^{II}) \), \( X_j \perp \perp X_k \mid ne_j^0 \) for any \( k \notin ne_j^0 \).
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Key Obs 2: Under the alternative \( (H_0 : ne_j^I \neq ne_j^II) \), \( X_j \perp \perp X_k \mid ne_j^0 \) for some \( k \notin ne_j^0 \).
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Key Obs 2: Under the alternative ($H_0 : ne_j^I \neq ne_j^{II}$), $X_j \not\perp \not\perp X_k \mid ne_j^0$ for some $k \notin ne_j^0$. 
A New Framework for Testing Differential Connectivity

We utilize the Markov property of CIGs, by focusing on the common neighborhood of each node $j$ in the two networks: $ne_j^0 = ne_j^I \cap ne_j^\parallel$.

Key Obs 2: Under the alternative ($H_0 : ne_j^I \neq ne_j^\parallel$), $X_j \perp \perp X_k \mid ne_j^0$ for some $k \notin ne_j^0$.
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We utilize the Markov property of CIGs, by focusing on the common neighborhood of each node $j$ in the two networks: $ne_j^0 = ne_j^I \cap ne_j^II$.

Key Obs 1: Under the null ($H_0 : ne_j^I = ne_j^II$), $X_j \perp \perp X_k \mid ne_j^0$ for any $k \notin ne_j^0$.

Key Obs 2: Under the alternative ($H_0 : ne_j^I \neq ne_j^II$), $X_j \not\perp \not\perp X_k \mid ne_j^0$ for some $k \notin ne_j^0$. 

![Diagram of two network graphs with nodes and edges highlighted to illustrate the concept of common neighborhood and conditional independence.]
A New Framework for Testing Differential Connectivity

We utilize the Markov property of CIGs, by focusing on the common neighborhood of each node $j$ in the two networks: $ne_j^0 = ne_j^I \cap ne_j^{II}$.

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We utilize the Markov property of CIGs, by focusing on the common neighborhood of each node $j$ in the two networks: $\text{ne}_j^0 = \text{ne}_j^I \cap \text{ne}_j^{II}$.

Key Obs 1: Under the null ($H_0 : \text{ne}_j^I = \text{ne}_j^{II}$), $X_j \perp \perp X_k$ for all $k \notin \text{ne}_j^0$.

Key Obs 2: Under the alternative ($H_0 : \text{ne}_j^I \neq \text{ne}_j^{II}$), $X_j \nmid X_k$ for some $k \notin \text{ne}_j^0$.
A New Framework for Testing Differential Connectivity

Step 1: Estimate the joint neighborhood of each node,

\[ \text{ne}_{0j} = \text{ne}_{Ij} \cap \text{ne}_{IIj} \]
A New Framework for Testing Differential Connectivity

Step 1: Estimate the joint neighborhood of each node, $ne_j^0 = ne_j^I \cap ne_j^{II}$
A New Framework for Testing Differential Connectivity

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◊ Need to estimate a superset of $ne_j^0$
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A New Framework for Testing Differential Connectivity

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♦ Need to estimate a superset of $ne_j^0$
A New Framework for Testing Differential Connectivity

Step 1: Estimate the joint neighborhood of each node, $ne_j^0 = ne_j^I \cap ne_j^{II}$

- Need to estimate a superset of $ne_j^0$
A New Framework for Testing Differential Connectivity

Step 2: For every $k \not\in t^{0j}$, test whether $X_j \perp \perp X_k | t^{0j}$, which is equivalent to $H_0, jk : \beta_{jk} = 0$ in node-wise regression.

- Test for regularized regression to find differentially connected edges.
- Score-based test (e.g., SKAT) to find differentially connected nodes.

Challenge: $t^{0j}$ is estimated from data — double peaking.

- LEPD (Zhang & Zhang, 2014; van de Geer et al, 2014; GraceI (Zhao & S., 2016)
- Liu et al (2007), etc.
A New Framework for Testing Differential Connectivity

Step 2: For every $k \notin ne_j^0$, test whether $X_j \perp X_k | ne_j^0$
Step 2: For every $k \notin \overline{ne}_j^0$, test whether $X_j \perp X_k \mid \overline{ne}_j^0$

✓ $H_{0,jk} : X_j \perp X_k \mid \overline{ne}_j^0$ is equivalent to $H_{0,jk} : \beta_k^j = 0$ in node-wise regression
A New Framework for Testing Differential Connectivity

Step 2: For every $k \notin \tilde{e}_j^0$, test whether $X_j \perp X_k \mid \tilde{e}_j^0$

$\checkmark \quad H_{0,jk} : X_j \perp X_k \mid \tilde{e}_j^0$ is equivalent to $H_{0,jk} : \beta_{jk} = 0$ in node-wise regression

- Test for regularized regression find differentially connected edges$^6$

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$^7$LEPD (Zhang & Zhang, 2014; van de Geer et al, 2014); Gracel (Zhao & S., 2016)
A New Framework for Testing Differential Connectivity

Step 2: For every $k \notin \ne_j^0$, test whether $X_j \perp X_k \mid \ne_j^0$

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- Test for regularized regression find differentially connected edges\(^6\)
- Score-based test (e.g. SKAT) find differentially connected nodes\(^7\)

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\(^7\) LEPD (Zhang & Zhang, 2014; van de Geer et al, 2014); Gracel (Zhao & S., 2016)

\(^8\) Liu et al (2007), etc
A New Framework for Testing Differential Connectivity

Step 2: For every \( k \notin \bar{ne}_j^0 \), test whether \( X_j \perp \perp X_k \mid \bar{ne}_j^0 \)

\[ H_{0,jk} : X_j \perp \perp X_k \mid \bar{ne}_j^0 \text{ is equivalent to } H_{0,jk} : \beta_j^k = 0 \text{ in node-wise regression} \]

- Test for regularized regression find differentially connected edges\(^6\)
- Score-based test (e.g. SKAT) find differentially connected nodes\(^7\)

✗ Challenge: \( \bar{ne}_j^0 \) is estimated from data — double peeking\(^8\)!

---

\(^6\)LEPD (Zhang & Zhang, 2014; van de Geer et al, 2014); GraceI (Zhao & S., 2016)

\(^7\)Leeb & Potscher (2008); Berk et al (2013); Lee et al (2015)

\(^8\)Liu et al (2007), etc

Example: Neighborhood Estimation with the Lasso

Two options:

1. **Sample splitting**
   - Estimate $\mathbf{X}_j$ using half of the data and test $\mathbf{X}_j$ using the other
   - w.h.p. $t_{ne0} \supseteq ne0$, but this may not be satisfied in small samples!
   - Potentially lower power

2. **Naive lasso neighborhood selection approach**
   - Use the full data for estimation and testing!
   - w.h.p. $t_{ne0} \supseteq ne0$
   - w.h.p. $t_{ne0}$ is a deterministic set

Meinshausen & Buhlmann (2006)
Zhao & S. (2018+)
Example: Neighborhood Estimation with the Lasso

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---

10 Meinshausen & Buhlmann (2006)
Example: Neighborhood Estimation with the Lasso

Two options:

1. Sample splitting
   - Estimate $n^0_j$ using half of the data and test $X_j \perp X_k \mid \overline{n^0_j}$ using the other
   - w.h.p. $\overline{n^0_j} \supseteq n^0_j$, but this may not be satisfied in small samples!
   - Potentially lower power

2. Naive lasso neighborhood selection approach\textsuperscript{9}!
   - Use the full data for estimation and testing!
   - w.h.p. $\overline{n^0_j} \supseteq n^0_j$

\textsuperscript{10} Meinshausen & Buhlmann (2006)
Two options:

1. **Sample splitting**
   - Estimate \( n_{ej}^0 \) using half of the data and test \( X_j \perp X_k \mid \tilde{n}_{ej}^0 \) using the other
   - w.h.p. \( \tilde{n}_{ej}^0 \supseteq n_{ej}^0 \), but this may not be satisfied in small samples!
   - Potentially lower power

2. **Naive lasso neighborhood selection approach**\(^9\):
   - Use the full data for estimation and testing!
   - w.h.p. \( \tilde{n}_{ej}^0 \supseteq n_{ej}^0 \)
   - w.h.p. \( \tilde{n}_{ej}^0 \) is a deterministic set\(^{10}\)

---

\(^9\) Meinshausen & Buhlmann (2006)

\(^{10}\) Zhao & S. (2018+)
Some Intuition
Some Intuition
Some Intuition

Population

Sample 1

Sample 2
Some Intuition
Key Assumption
Key Assumption

\[ \lambda \sqrt{q^*} \]

\[ \sqrt{\log(p)/n} \]

Gap in Signal Strength

\[ \hat{n}e \]

\[ n^* \]

\[ n^* \]
Power Analysis

Type-I error & Power for nodes with \( k \) differentially connected edges (\( P_k \)) — \( d = 200 \)
Power Analysis

Type-I error & Power for nodes with $k$ differentially connected edges ($P_k$) — $d = 200$

$n = 100$

- split.SKAT
- split.GraceI
- naive.SKAT
- naive.GraceI

$n = 200$

$n = 400$

$n = 800$
Power Analysis

Type-I error & Power for nodes with \( k \) differentially connected edges (\( P_k \)) — \( d = 200 \)

- \( n = 100 \)
- \( n = 200 \)
- \( n = 400 \)
- \( n = 800 \)
Differential Connectivity in Breast Cancer Subtypes

- $d = 358$ cancer-related genes
- $n^I = 117$ $ER-$ and $n^{II} = 407$ $ER+$ samples from TCGA
Differential Connectivity in Breast Cancer Subtypes

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Summary

- Changes in biological networks can provide important insight into biological systems and disease mechanisms.

- Looking at values of $\Omega^I$ and $\Omega^{II}$ (or $\Sigma^I$ and $\Omega^{II}$)
  - OK if goal is global differences in two networks
  - Not OK if goal is identifying differentially connected nodes/edges

- Can test differences in the supports of $\Omega^I$ and $\Omega^{II}$

- Presented a general framework based on Markov property

- Can use various high-dimensional estimation and inference methods

★ Require a 'beta-min' condition!

- Extension to other distributions?
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Extension to other distributions?
Collaborators

▶ T. Saegusa, Univ. of Maryland
▶ S. Zhao, Google Research

Funding

▶ NSF: DMS, DMS/NIGMS
▶ NIH: NIGMS, NHLBI, BD2K

References:

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Thank You!
And a bit of advertising...

4th Annual Summer Institute in Statistics for Big Data (SISBID)

The Summer Institute for Big Data (SISBID) is designed to introduce biologists, quantitative scientists, and statisticians to modern statistical techniques for the analysis of biological big data.

Key Dates
- Modules: July 11-28
- Registration opens February 1, 2018.
Simulation Study

\[ D_1 = 1 \]
\[ D_2 = 2 \]
\[ D_3 = 1 \]

Simulated networks for each group
Simulation Study 1: Known Clusters

![Graph showing TP vs TP + FP for different methods with various lambda values.]

- **LASICH**: \( \lambda_2 = 0.01, 0.05, 0.1, 1 \)
- **FGL**: \( \lambda_2 = 0.05, 0.2, 0.4, 0.6 \)
- **GGL**: \( \lambda_2 = 0.05, 0.2, 0.4, 0.6 \)

Guo et al.
Simulation Study 2: Estimated Clusters

![Graph showing TP vs TP + FP for different methods and Rand Indices.

- LASICH (Rand Index .6)
- LASICH (Rand Index .7)
- LASICH (Rand Index .8)
- LASICH (Rand Index .9)
- glasso
- FGL
- GGL
- Guo et al.](attachment:image.png)
Testing for Differential Connectivity

Condition-specific network estimates are highly variable.

Sedaghat et al (2014), Cancer Informatics
Testing for Differential Connectivity

Condition-specific network estimates are **highly variable**\(^{11}\)

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Condition-specific network estimates are highly variable\textsuperscript{11}

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Testing for Differential Connectivity

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\textbf{# Common Edges in Cancer and Normal Networks}

\textit{P}<0.01

\textsuperscript{11}Sedaghat et al (2014), Cancer Informatics
A General Result for Testing Differential Connectivity

Theorem

Suppose the procedure used in the estimation step of DCA satisfies the following conditions for each $j$:

1. The estimated common neighborhood of $j$, $\text{ne}_0^j$, satisfies
   \[
   \lim_{n \to \infty} P\left(\text{ne}_0^j \supseteq \text{ne}_0^j\right) = 1 \quad \text{(coverage property)};
   \]

2. Either the data used to test hypotheses $H_0^{jk}$ are independent of the data used to estimate $\text{ne}_0^j$, or, the estimated common neighborhood $\text{ne}_0^j$ is deterministic with high probability.

Then if the inference procedure for testing $H_0^{jk} : \beta_j^k = 0$ is asymptotically valid, DCA asymptotically controls the type-I error rate.
A General Result for Testing Differential Connectivity

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Changes in Brain Connectivity in TBI

Brain imaging data from teenagers with concussion who remained symptomatic at 3-4 weeks post-injury – mild traumatic brain injury (TBI) compared to gender matched healthy controls.

CCN Lab (Olaf Sporns), Indiana University

Are there changes in brain connectivity associated with TBI?
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- $n^I = 25$ teenagers with concussion who remained symptomatic at 3-4 weeks post-injury – mild traumatic brain injury (TBI)
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- $d = 78$ ROIs
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