SORBONNE UNIVERSITÉ

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Sparse Gaussian Graphical Models for Structured Biological Networks

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Contents

Context

Complex networks in biology

Complex networks are omnipresent in biology.

- **Molecular Networks** Gene regulatory networks, protein-protein interaction networks, and metabolic pathways describe how genes, proteins, and metabolites coordinate cellular functions.

- **Cellular Networks** Signaling networks mediate communication within and between cells, orchestrating processes such as growth, differentiation, and immune response.

Data: Gene expression matrix

$$X \in \mathbb{R}^{n \times p}$$

n samples, p genes

X_{kj} = expression of gene j in sample k

Goal: Infer gene regulatory network

- Nodes = genes (p nodes)
- Edges = direct interactions

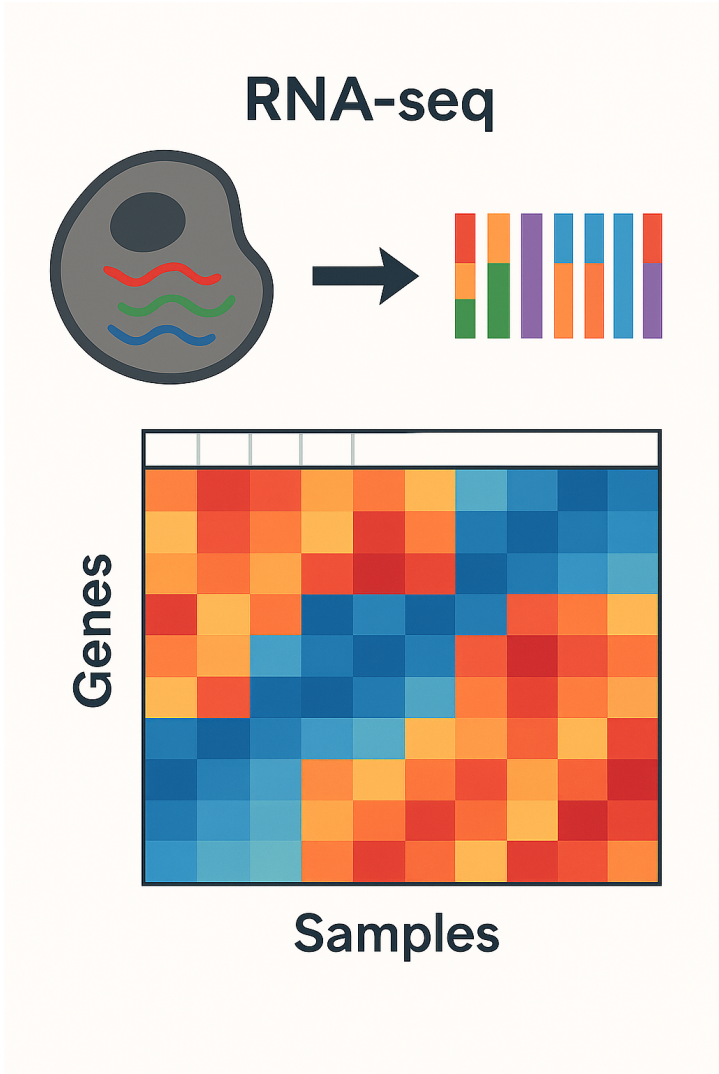


Figure: Gene expression matrix: rows = genes, columns = samples

Correlation Networks: A Naive Approach

Simple idea: Connect genes with high correlation

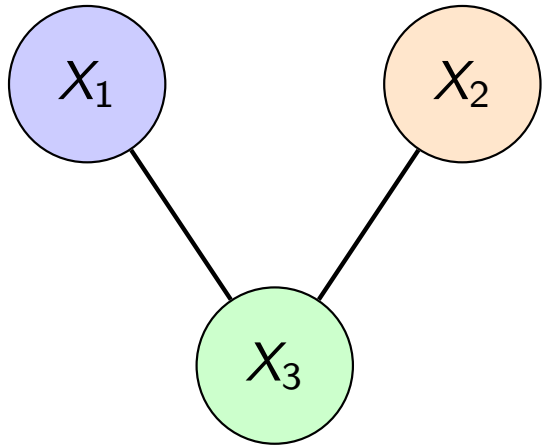
$$\text{Edge } (i,j) \Leftrightarrow |\text{corr}(X_i, X_j)| > \tau$$

Limitation: Correlation $\neq$ Direct interaction

- Captures indirect dependencies
- Cannot distinguish direct effects

Better approach: Conditional independence networks

Example:



True: $X_1 - X_3 - X_2$
But: $\text{corr}(X_1, X_2) \neq 0$

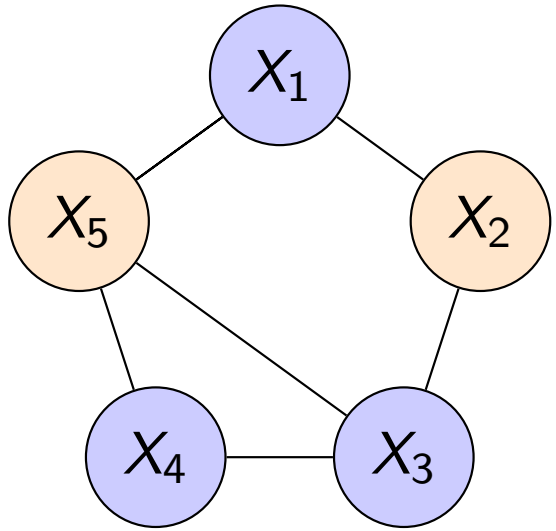
Undirected Graphical Models

conditional independence graph

An Undirected Graphical Model: represents $X = (X_1, ..., X_p)$ as graph $G = (V, E)$, where

- Nodes V = variables;
- Edges E = the pairwise relationships.

Example:



$X_2 \perp\!\!\!\perp X_5 \mid X_{\setminus\{2,5\}}$

Adjacency Matrix:

$$A_{ij} = \begin{cases} 1 & \text{if } (i,j) \in E \\ 0 & \text{otherwise} \end{cases}$$

This is called conditional independence graph, when

$$\text{No edge } (i,j) \Leftrightarrow X_i \perp\!\!\!\perp X_j \mid X_{\setminus\{i,j\}}$$

Gaussian Graphical Models

Gaussian Graphical Models (GGMs)

- **GGM Definition**: A conditional independence graph where

$$X \sim \mathcal{N}(\nu, \Sigma)$$

- **Precision matrix**:

$$K = \Sigma^{-1} \quad \text{(encodes conditional dependencies)}$$

Key Relationship:

$$X_i \perp\!\!\!\perp X_j \mid X_{\setminus\{i,j\}} \Leftrightarrow \operatorname{corr}(X_i, X_j \mid X_{\setminus\{i,j\}}) = 0$$
$$\Leftrightarrow K_{ij} = 0$$

(Missing edge $\Leftrightarrow$ Zero in K $\Leftrightarrow$ Conditional independence)

Application: Gene Regulatory Networks

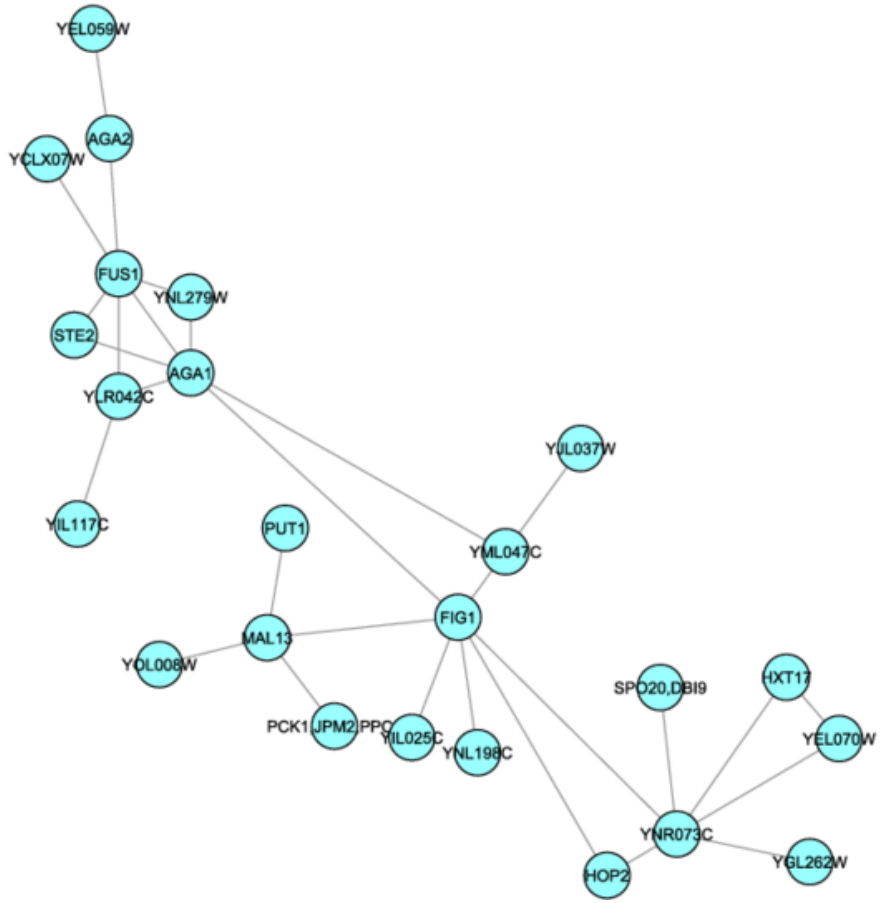


Figure: Iconix Microarray Data (Banerjee et al. (2008)).

Application: US Senate Voting Patterns

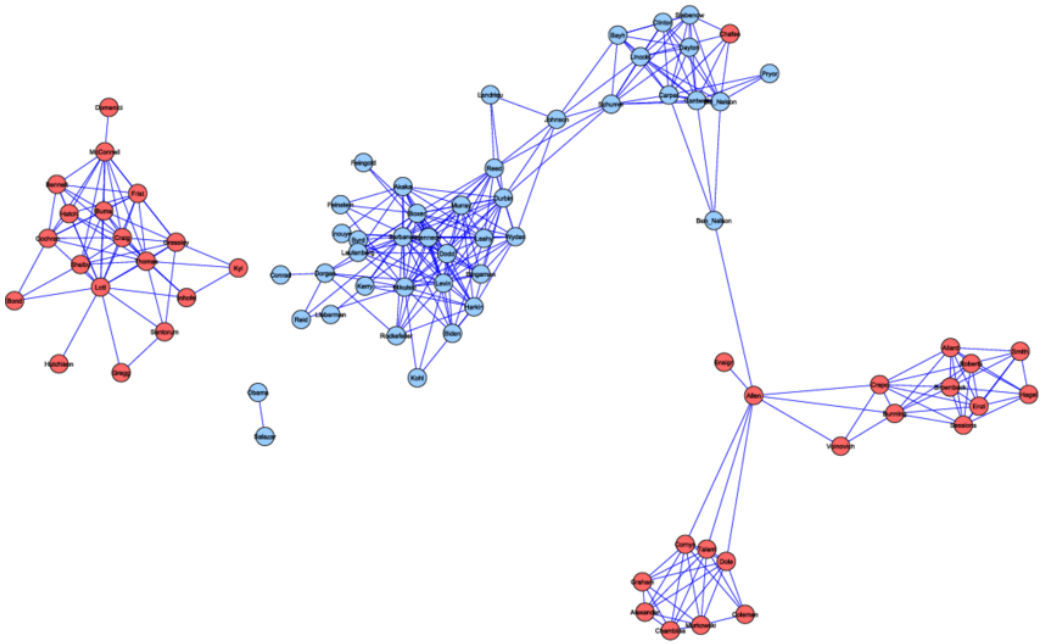


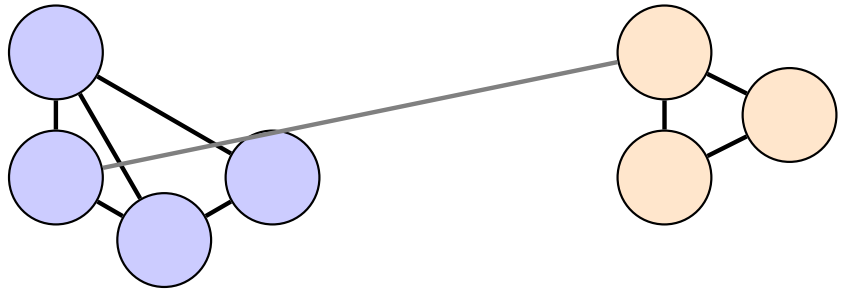
Figure: Graph structure of the US Senate (109th Congress, 2004–2006)(Banerjee et al. (2008)).

Beyond Sparsity: Modular Structure in Gene Networks

Sparse precision matrix identifies direct interactions

Biological networks exhibit modular organization:

- Genes cluster into functional modules
- Dense connections within modules
- Sparse connections between modules



$\Rightarrow$ **Block structure** in precision matrix

Setup

Data

- n samples $\times$ p biological variables matrix:

$$X \in \mathbb{R}^{n \times p}, \quad X_i \sim \mathcal{N}(0, K^{-1}) \text{ i.i.d.}$$

Assumptions

- **Sparsity**: few biological interactions
- **Clustering**: functional variable groups

Goal

Reconstruct biological network with cluster structure

Inference of GGM in the Literature

Maximum Likelihood Estimation (MLE)

Standard Approach

The log-likelihood for precision matrix $K \succ 0$:

$$\mathcal{L}(K) = \frac{n}{2} (\log \det K - \operatorname{tr}(SK))$$

where S is the sample covariance.

MLE solution: $\widehat{K}_{\text{MLE}} = S^{-1}$

Why MLE Fails in High Dimensions ($p \gg n$)

- × **Non-identifiability**: S singular when $p > n$
- × **No structure exploitation**: Ignores sparsity

$\Rightarrow$ **Need for regularization**

1. Graphical Lasso (Glasso)

Friedman et al. (2008)

Penalized Likelihood

$$\widehat{K} = \underset{K \succ 0}{\arg\max} \quad \mathcal{L}(K) - \rho \sum_{i \neq j} |K_{ij}|$$

Key features:

- ℓ_1 **penalty** encourages sparsity
- **Uniform penalization**: same ρ for all edges
- **Efficient optimization**: block coordinate descent

Limitation:

- $\times$ Assumes homogeneous sparsity
- $\times$ All edges penalized equally

2. SiMoNe (Ambroise et al., 2008)

Objective: Estimate the precision matrix K and the clustering $Z = (Z_1, \ldots, Z_p)$.

Penalized Likelihood

$$\underset{K \succ 0}{\text{maximize}} \quad \mathcal{L}(K) - \|\rho_{\mathbf{Z}}(K)\|_{\ell_1} + \text{const}$$

Adaptive penalty term:

$$\rho_{\mathbf{Z}_i, \mathbf{Z}_j}(K_{ij}) = \begin{cases} \sum_{q,\ell} Z_{iq} Z_{j\ell} \dfrac{|K_{ij}|}{\lambda_{q\ell}} & \text{if } i \neq j, \\ \dfrac{|K_{ii}|}{\lambda_0} & \text{if } i = j. \end{cases}$$

$\rightsquigarrow$ Optimization performed via a variational EM algorithm.

3. BAGUS (Gan et al., 2019)

Objective: Estimate the precision matrix K and A.

$$A_{ij} \overset{iid}{\sim} \mathcal{B}(\eta),$$
$$K_{ij} \mid A_{ij} \sim (1 - A_{ij})\, g_{\lambda_0} + A_{ij}\, g_{\lambda_1}$$

Penalized Log-Likelihood

$$\mathcal{L}(K) - \sum_{i<j} \text{pen}_{SS}(K_{ij}) - \sum_{i} \tau |K_{ii}|$$

Spike-and-slab penalty:

$$\text{pen}_{SS}(K_{ij}) = -\log\left[\frac{\eta}{2v_1} e^{-\frac{|K_{ij}|}{v_1}} + \frac{1-\eta}{2v_0} e^{-\frac{|K_{ij}|}{v_0}}\right]$$

- $\rightsquigarrow$ Penalization adapts to edge probability via A_{ij}.
- $\rightsquigarrow$ EM algorithm and block coordinate descent are used to infer K.

Our procedure

Limitations of existing approaches:

- Most methods do not provide **guarantees** on the inferred graph structure (e.g., no control over false positives).
- Only SiMoNE handles **clustering**, but with no guarantee.

Our Aim:

- **Graph inference:** Estimate the conditional independence graph A while controlling the False Discovery Rate (FDR), i.e., the proportion of errors among the discovered edges.

- **Clustering:** Recover the latent group structure underlying the variables.

Stochastic Block Model (SBM) for Binary Graphs

- Each node belongs to one of Q latent groups.

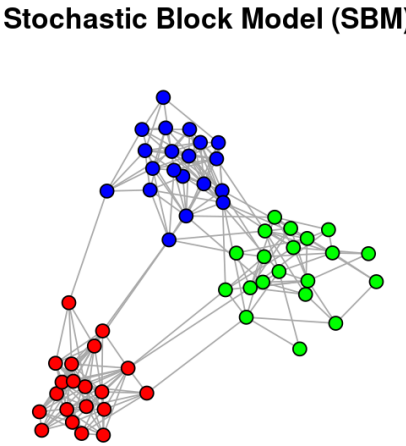
$$Z_1, \ldots, Z_p \overset{i.i.d.}{\sim} \mathcal{M}(1, \pi)$$

- Conditionally on Z, the variables A_{ij} are independent Bernoulli variables with parameters characterized by latent groups:

$$A_{ij} \mid (Z_i = q, Z_j = \ell) \sim \text{Bernoulli}(\omega_{q\ell})$$

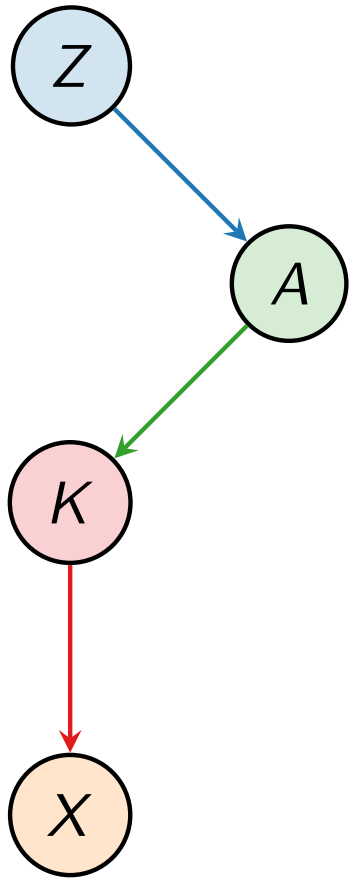
Example:

- $Q = 3$, $\pi = (0.4, 0.3, 0.3)$
- $\omega = \begin{pmatrix} 0.5 & 0.01 & 0.01 \\ 0.01 & 0.4 & 0.05 \\ 0.01 & 0.05 & 0.3 \end{pmatrix}$



Complete Hierarchical Model

- **Group Membership**
  $Z_i \sim \mathcal{M}(1, \pi)$
- **Connections**
  $A_{ij}|Z \sim \mathcal{B}(\omega_{Z_i Z_j})$
- **Precision Matrix**
  $$\begin{cases} K_{ii} \sim \mathcal{E}(\mu) \\ K_{ij}|A_{i,j} \sim (1 - A_{ij})\text{Laplace}(\lambda_0) + A_{ij}\mathcal{N}(0, \sigma^2) \end{cases}$$
- **Observed Data**
  $X|K \sim \mathcal{N}(0, K^{-1})$



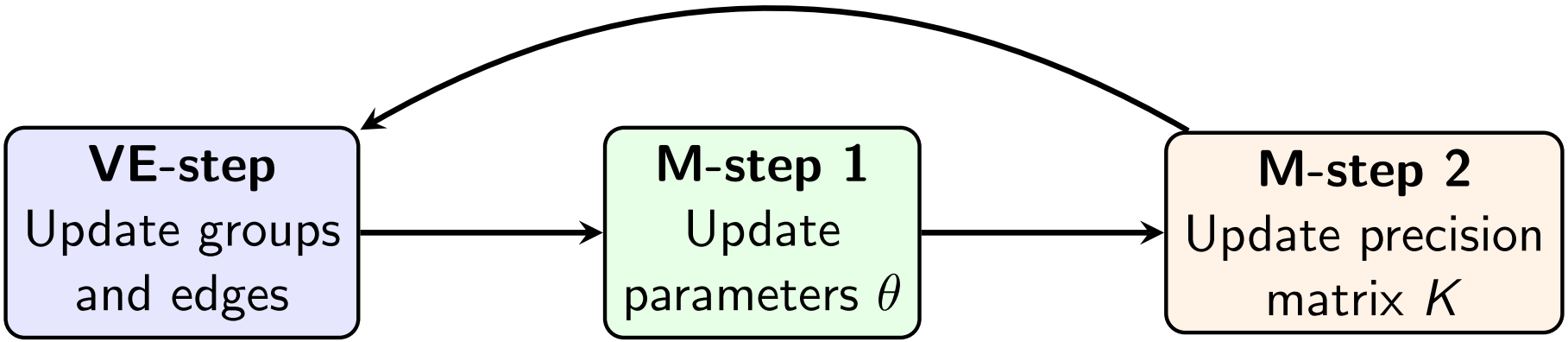
- Latent groups
- Network structure
- Spike-and-slab
- Observed data

Model Inference: Variational EM Approach

Challenge: Complex latent structure

- Precision matrix K
- Model parameters $\theta = (\pi, \omega, \sigma, \lambda_0)$
- Latent modules Z and edges A

Solution: Variational EM algorithm



VE-step: Updating Latent Structure

- **Edge probabilities** $\rho_{q\ell}^{i,j}$

$$\rho_{q\ell}^{i,j} = \mathbb{P}(A_{ij} = 1 \mid K_{i,j}, Z_i = q, Z_j = \ell)$$

Probability of connection given modules and precision

- **Group assignments** $\tau_{i,q}$
Fixed-point equation:

$$\widehat{\tau}_{i,q} = C_i \widehat{\pi}_q \exp\left(\sum_{j \neq i} \sum_{l=1}^{Q} \widehat{\tau}_{j,l} \, \widehat{d}_{q,l}^{i,j} \right)$$

Estimating the Precision Matrix K

Cluster-adaptive penalization

Key idea: Adaptive penalization based on module membership

For each gene i, solve:

$$\widehat{\beta}_i = \arg\min_{\beta} \frac{1}{2n}\|X_i - X_{-i}\beta\|^2 + \sum_{j\neq i}\left[\frac{p_{ij}}{2\sigma^2}\beta_j^2 + \frac{1-p_{ij}}{\lambda_0}|\beta_j|\right]$$

where:

$$p_{ij} = \sum_{q,\ell} \tau_{i,q}\tau_{j,\ell}\rho_{q\ell}^{i,j}$$

(edge probability weighted by module membership)

Interpretation: Higher connection probability $\Longrightarrow$ lower penalty

Graph inference with FDR Control

Edge probability:

$$\ell_{ij} = \mathbb{P}(A_{ij} = 0 \mid \widehat{Z}_i, \widehat{Z}_j, \widehat{K}_{ij}) = \frac{(1 - \widehat{\omega}_{\widehat{Z}_i \widehat{Z}_j})\, g_{\widehat{\lambda}_0}(\widehat{K}_{ij})}{(1 - \widehat{\omega}_{\widehat{Z}_i \widehat{Z}_j})\, g_{\widehat{\lambda}_0}(\widehat{K}_{ij}) + \widehat{\omega}_{\widehat{Z}_i \widehat{Z}_j}\, \phi(\widehat{K}_{ij}; 0, \widehat{\sigma}^2)}.$$

FDR control procedure:

1. Sort ℓ-values: $\ell_{(1)} \leq \ell_{(2)} \leq \cdots \leq \ell_{(m)}$
2. Find largest k such that: $\frac{1}{k} \sum_{r=1}^{k} \ell_{(r)} \leq \alpha$
3. Select edges with $\ell_{ij} \leq \ell_{(k)}$

Output : a final adjacency matrix $\widehat{A}$ with **FDR-controlled support recovery**.

Model Selection: Parameters and Number of Clusters

Parameter Selection (λ_0, σ):

- Test discrete grid of values
- Select combination minimizing BIC:

$$\text{BIC}_{\lambda_0,\sigma} = -2 \cdot \text{pseudoLik}(K) + \log(n) \cdot \|\widehat{K}\|_0$$

where $\|\widehat{K}\|_0$ = number of non-zero edges

Number of Clusters (Q):

- Choose Q minimizing cluster BIC:

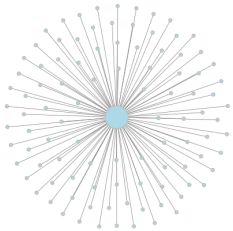
$$\text{BIC}_Q = -2 \cdot \text{pseudoLik}(K) + \underbrace{(Q-1)\log(p) + \frac{Q(Q+1)}{2}\log\left(\frac{p(p-1)}{2}\right)}_{\text{cluster complexity penalty}}$$

Simulations Experiments

Generated Network Structures

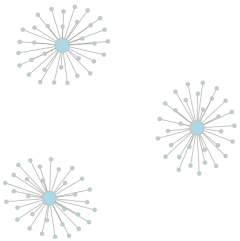
Three distinct topological configurations

- Single central hub



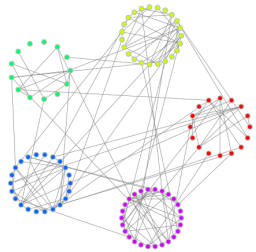
(a) 1-Hub Network

- 3 hubs



(b) 3-Hub Network

- 5 communities
- $w_{\text{in}} = 0.1,\ w_{\text{out}} = 0.01$



(c) SBM 5 Communities

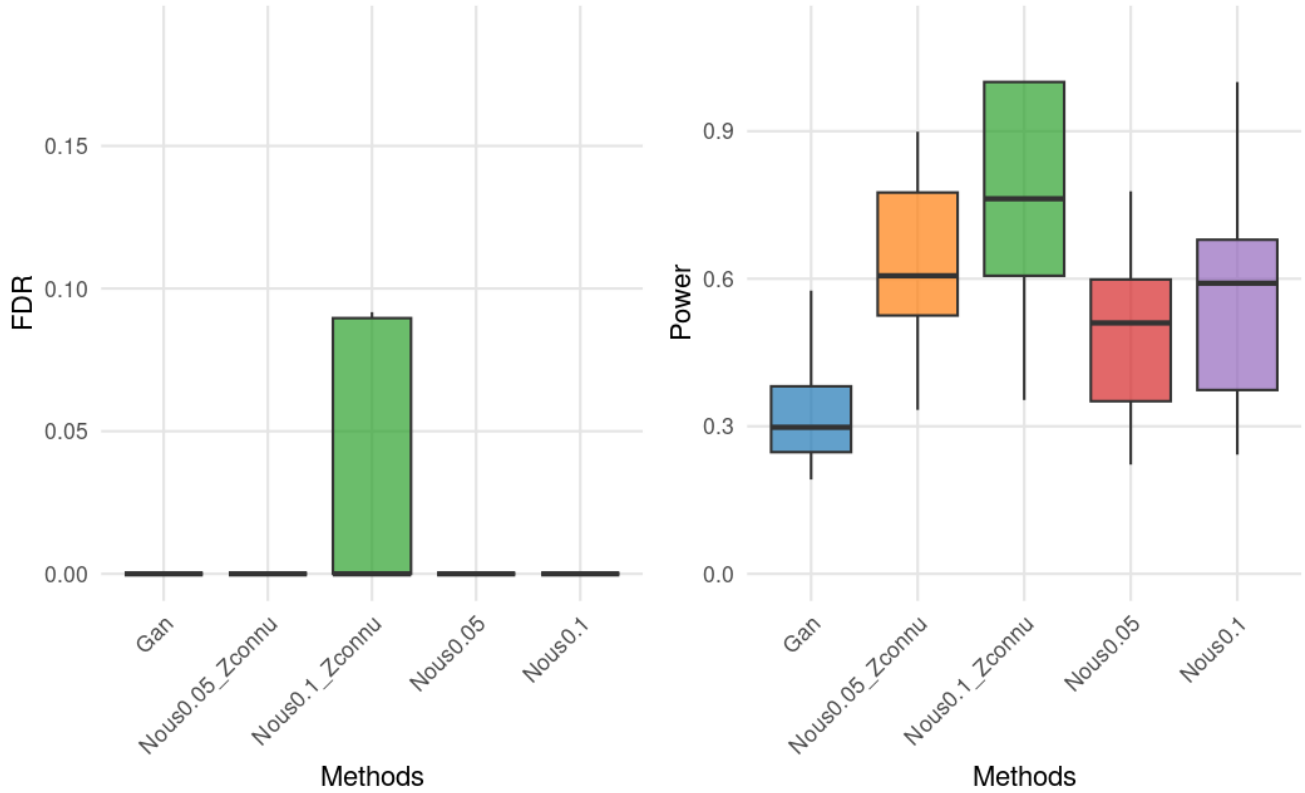
Simulation parameters: $n = 100,\ p = 100$

SBM (5 blocks)

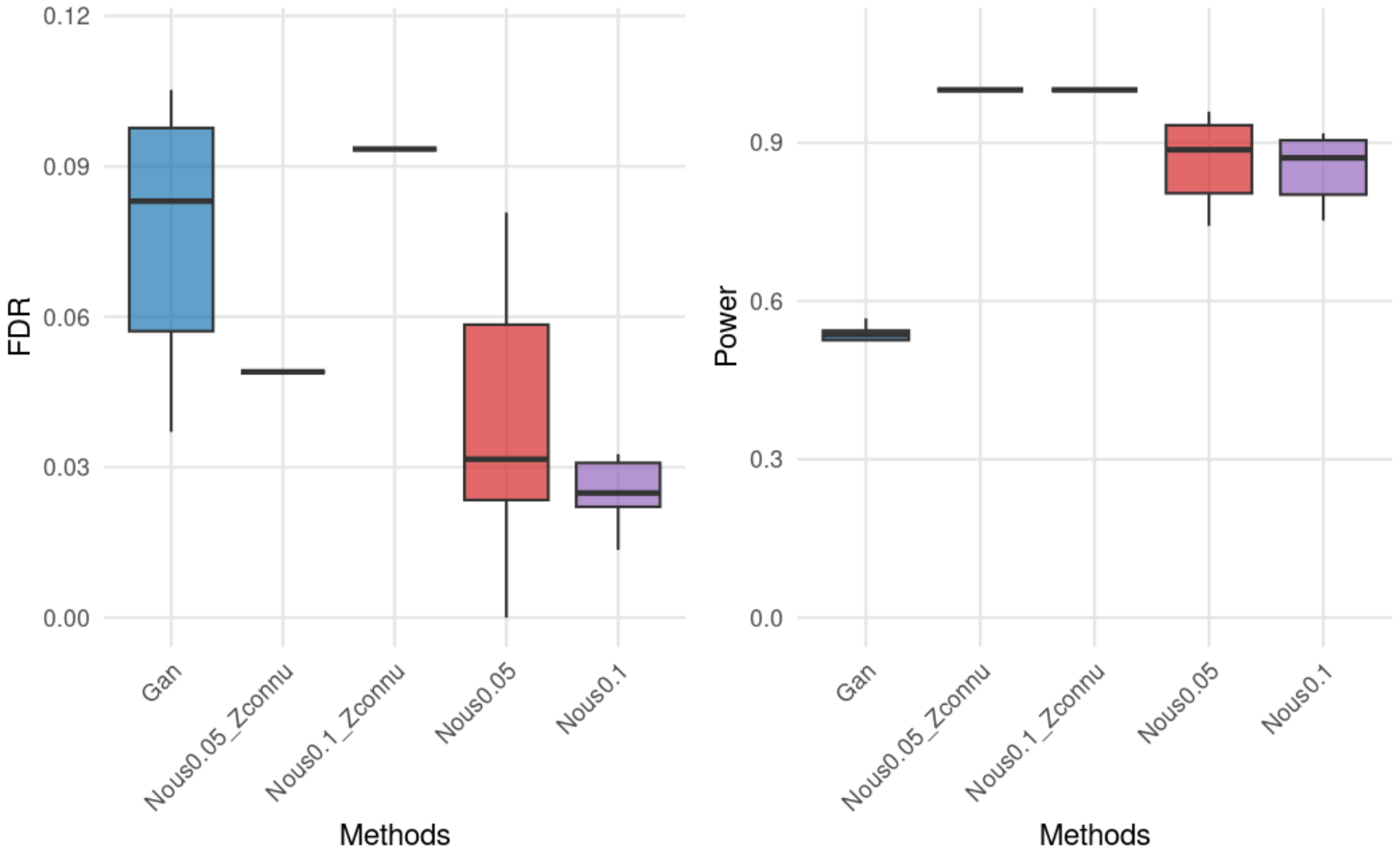
Evaluation metrics:

- **FDR (False Discovery Rate)**
- **Power (True Positive Rate)**

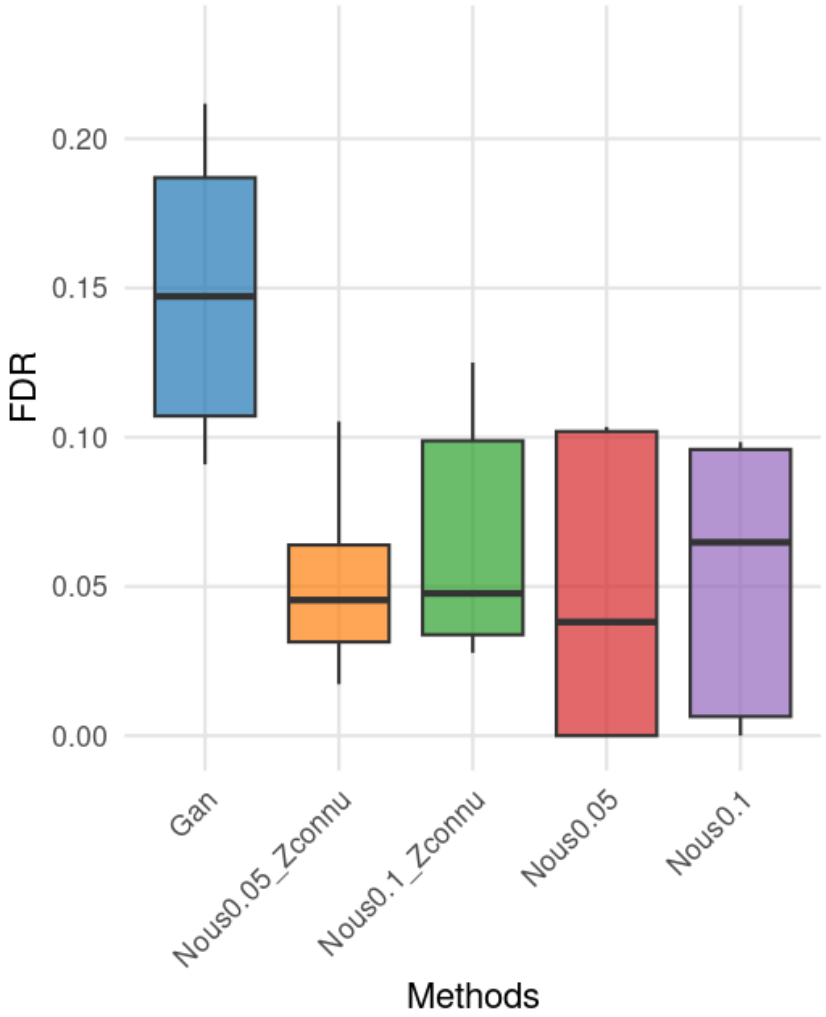
1-hub topology

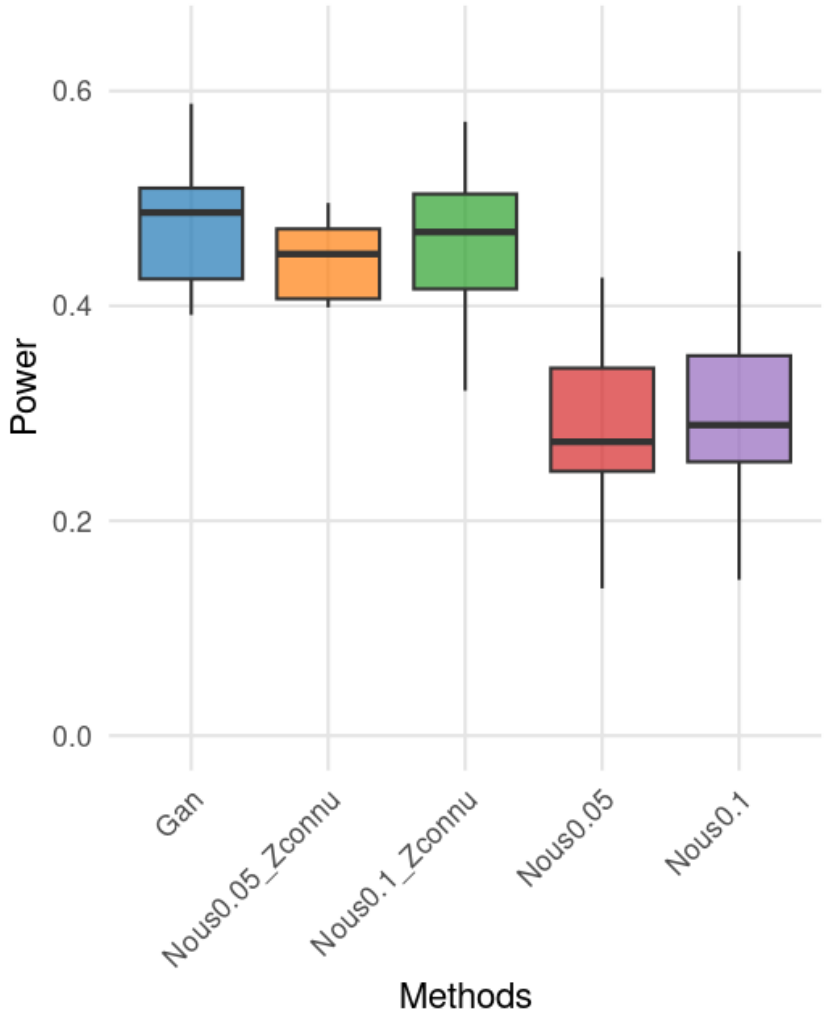


3-hub topology



SBM (5 blocks)


FDR
0.20
0.15
0.10
0.05
0.00
Gan
Nous0.05_Zconnu
Nous0.1_Zconnu
Nous0.05
Nous0.1
Methods


Power
0.6
0.4
0.2
0.0
Gan
Nous0.05_Zconnu
Nous0.1_Zconnu
Nous0.05
Nous0.1
Methods

Take-home messages

- We proposed a method for graph inference in Gaussian Graphical Models (GGMs), with control over the False Discovery Rate (FDR).
- This method also allows inference of a clustering structure among the variables.
- The method still needs to be applied to various datasets, including real-world data.

Références

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