Improving Gaussian Graphical Model inference by modeling the graph structure

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Outline

Data

Biological data :

- gene expression data
- or quantitative amounts of proteins

p = number of entities (genes, proteins)
n = number of repeating observations

Aim : infer the direct links between entities $\Leftrightarrow$ infer a graph:
- nodes = entities (genes, proteins)
- edge = direct relation between two entities

- regulations between genes
- protein-protein interactions

Gaussian Graphical model (GGM)

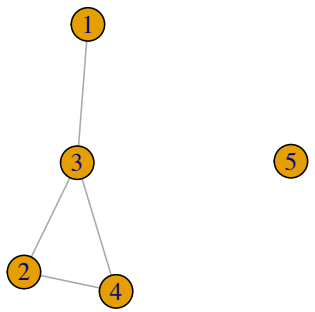
random variables $Y_1, \ldots, Y_p$: expression of the p genes or proteins

Assumption GGM : $(Y_1, \ldots Y_p) \sim \mathcal{N}(0, \Sigma)$

Direct links

Denote $\Omega = \Sigma^{-1} = (w_{ij})_{1 \leq i,j \leq p}$: precision matrix

$$i \sim j \text{ (edge between } i \text{ and } j) \Leftrightarrow \text{corr}(Y_i, Y_j | (Y_k)_{k \neq i,j}) \neq 0$$
$$\Leftrightarrow \omega_{ij} \neq 0$$



Graph inference in GGM

Inference of the graph edges based on a n-sample of $(Y_1, \dots Y_p)$
High-dimensional setting : $p \gg n$

Literature:

- infer the precision matrix Ω (glasso)
- infer the neighboors of each node (Meinshausen Bühlmann)
- multiple-testing approach $H_{0,ij} : w_{ij} = 0$ against $H_{1,ij} : w_{ij} \neq 0$

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Inference is difficult:

- lack of power
- graph inferred can be different according to the method
- in general, no control on the inferred graph

Multiple-testing approach

$$H_{0,ij} : \underbrace{w_{ij} = 0}_{i \nsim j} \quad \text{against} \quad H_{1,ij} : \underbrace{w_{ij} \neq 0}_{i \sim j}$$

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Test statistics ?

- if $p \ll n$: natural test statistics based on the inverse of the sample covariance matrix $\widehat{\Sigma}$

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- in high-dimensional setting :
  Ref: Liu et al 2013, Ren et al 2015, Jankova et al 2018
  - estimators for the entries of the precision matrix w_{ij}
  - based on different modifications of initial Lasso-regularized estimators
  - proved to be asymptotically normal a sparcity condition
  - enables the construction of test statistics to test $H_{0,ij}$

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Simultaneous tests: test $H_{0,ij}$ for all pairs of variables (i, j).
$\hookrightarrow$ multiple testing problem

Aim

Inference of the graph : detect significant edges

- with control on the inferred graph in term of False Discovery Rate (FDR: proportion of errors among the discovered edges)
  - (Bonferroni)
  - Benjamini and Hochberg
  - Liu et al 2013: asymtotic FDR control under sparcity assumption

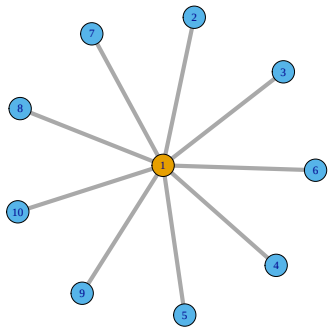
Aim

Inference of the graph : detect significant edges

- with control on the inferred graph in term of False Discovery Rate (FDR: proportion of errors among the discovered edges)
  - (Bonferroni)
  - Benjamini and Hochberg
  - Liu et al 2013: asymtotic FDR control under sparcity assumption
- with high ability to detect true edges
  - multiple testing literature : *Ref: Efron & al, 2001, Efron, 2004, Sun & Cai, 2007, Cai & Sun, 2009, Sun & Cai, 2009*
  - incorporating some latent dependence structure may allow more detections

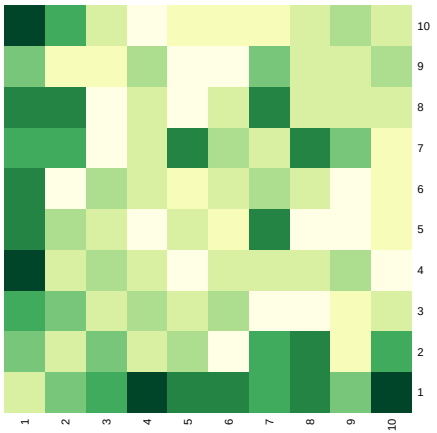
incorporating some latent structure ?

Graph to infer



from

Matrice with test statistics for each pairs of variables (i, j)



- learning the graph structure (nodes clustering)
- incorporating it in the multiple-testing procedure

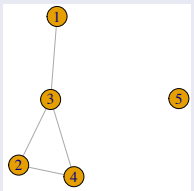
learning the graph structure ?

$\hookrightarrow$ modeling the graph structure through the adjacency matrix A

Adjacency matrix A of a graph

$A = (A_{ij})_{1 \leq i,j \leq p}$ with

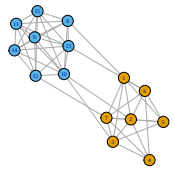
$$A_{ij} = \begin{cases} 1 & \text{if there is an edge between i and j} : i \sim j \\ 0 & \text{otherwise} : i \nsim j \end{cases}$$



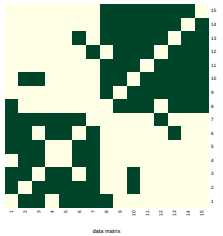
$$\begin{pmatrix} 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 \\ 1 & 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$\hookrightarrow$ random graph model on A

- random graph model on A : stochastic block model SBM

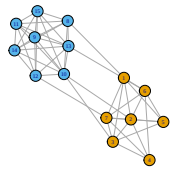


$\Longleftrightarrow$



Graph to infer $A \in \{0,1\}^{p \times p}$

- random graph model on A : stochastic block model SBM



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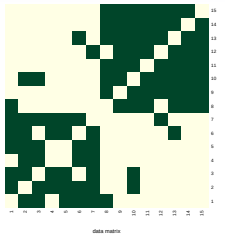


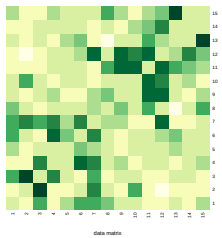
Graph to infer $A \in \{0,1\}^{p \times p}$

- Or A is unknown $\rightarrow$ NSBM model : Noisy SBM

$X =$ Noisy version of A

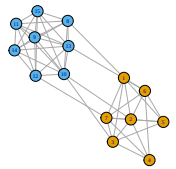
Observed: X : (p, p) matrix

with X_{ij}: test statistic



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

- random graph model on A : stochastic block model SBM



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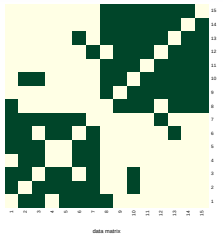

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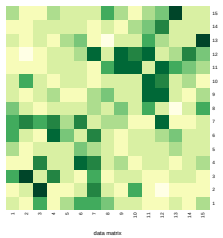

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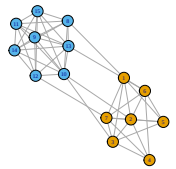
- Estimation of the parameters of the model (nodes clustering)

- random graph model on A : stochastic block model SBM



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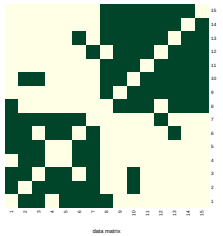

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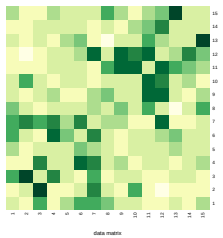


$X \in \mathbb{R}^{p \times p}$

- Estimation of the parameters of the model (nodes clustering)
- Multiple-testing procedure incorporating the estimated parameters

$$H_{0,ij} : \underbrace{A_{ij} = 0}_{i \nsim j} \quad \text{against} \quad H_{1,ij} : \underbrace{A_{ij} = 1}_{i \sim j}$$

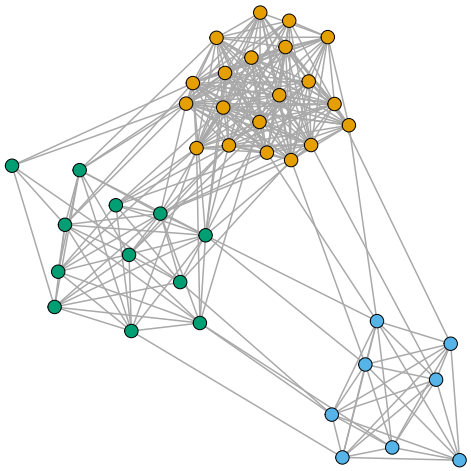
Outline

SBM

Stochastic Block Model - SBM

- Each node belongs to one of Q latent groups.
  Latent variables $Z_1, \ldots, Z_p$ i.i.d. with values $\{1, \ldots, Q\}$ and probability $\pi_q = \mathbb{P}(Z_1 = q)$
- Conditionally on Z, the variables A_{ij} are independent Bernoulli variables with parameters characterized by latent groups :

$$A_{ij}|(Z_i = q, Z_j = l) \sim Bernoulli(\gamma_{q,l})$$



Model

Noisy Stochastic Block Model - NSBM

NSBM

- The true underlying binary graph A is a SBM
  - with Q groups
  - connectivity parameters $\gamma = (\gamma_{q,l})_{1 \leq q,l \leq Q}$
  - group proportions $\pi = (\pi_q)_{1 \leq q \leq Q}$
  - latent variables $Z_i \in \{1, \ldots, Q\}$ for $i = 1, \ldots, p$
- Conditionally on A and Z, the observations X_{ij} are independent with

$$X_{ij}|Z, A \sim \begin{cases} \mathcal{N}(0, \sigma_0^2) & \text{if } A_{i,j} = 0 \quad (\text{if } i \nsim j) \\ \mathcal{N}(\mu_{ql}, \sigma_{ql}^2) & \text{if } A_{i,j} = 1 \quad (\text{if } i \sim j), Z_i = q, Z_j = l \end{cases}$$

NSBM model

Mixture model :

Observations : $X = (X_{ij})_{1 \leq i,j \leq p}$

Latent variables : Z, A

Unknown parameters : $\theta = (\pi, \gamma, \mu, \sigma)$

with $\pi = (\pi_q), \gamma = (\gamma_{ql}), \mu = (\mu_{ql}), \sigma = (\sigma_{ql})$ $q, l \in \{1, \dots Q\}$

we suppose that σ_0 is known ($\sigma_0 = 1$)

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- Estimate the parameters θ and make clustering (recover the latent groups = estimate Z)
- Estimate $A \in \{0,1\}^{pxp} \Leftrightarrow$ infer the graph G by using $\hat{\theta}$ and $\hat{Z}$

Multiple testing :

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Estimation and clustering

NSBM = mixture model with latent variables $\rightarrow$ MLE can not be computed

- Variational Expectation Maximization (VEM) algorithm to estimate $\hat{\theta}$
  + MAP rule to estimate Z
  + model selection to select the number of groups Q

- ICL_{ex} : Integrated complete-data log likelihood
  baysesian framework
  greedy algorithm for optimization in Z
  automatic estimation of the number of groups Q

Estimation and clustering

ref: Côme and Latouche, 2015 in SBM model

- Start from a initial partition of the nodes in Q_{up} groups (Q_{up} large)
- For each node : move the node from its group to another group ?
- Criteria : integrated complete-data log likelihood ICL_{ex}
- Some groups become empty
- At the end, we obtain a clustering of the nodes $\hat{Z}$ and an estimation of the number of groups $\hat{Q}$

Estimation and clustering

Integrated complete-data log likelihood ICL_{ex}:

$$ICL_{ex}(Z, A) := \log p(X, A, Z)$$
$$= \log \left(\int_{\pi,\gamma,\mu,\sigma} p(X, A, Z|\pi, \gamma, \mu, \sigma) p(\pi, \gamma, \mu, \sigma) d(\pi, \gamma, \mu, \sigma) \right)$$

- Bayesian framework
- all the parameters in $\theta = (\pi, \gamma, \mu, \sigma)$ are integrated out
- conjugate priors for π, γ, μ, σ

$\Rightarrow$ analytical expression of ICL_{ex}, which involves the number of nodes in group q, the number of edges between groups q and l...

Estimation and clustering

Greedy Algorithm:

- For each node i^*, we evaluate the variation $\Delta_{g \to h}$ of ICL_{ex} if i^* moves from its group g to a new group h.
- $\Delta_{g \to h}$ can be evaluated in a computationally efficient way

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  $\hookrightarrow$ *we estimate the posterior probability that there is an edge between i and j*
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Output : node clustering $\hat{Z}$, number of groups $\hat{Q}$, estimator $\hat{\theta}$

Graph inference

Aim : infer the adjacency matrix $A \in \{0,1\}^{pxp} \Leftrightarrow$ infer graph edges

Simultaneous test of : $H_{0,ij} : \underbrace{A_{ij} = 0}_{i \nsim j}$ against $H_{1,ij} : \underbrace{A_{ij} = 1}_{i \sim j}$

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ℓ-values. (also called the local FDR. Efron, 2001)

$$\ell_{ij}(X, Z; \theta) = \mathbb{P}_\theta(A_{ij} = 0 \mid X, Z)$$

- $\ell_{ij}(X, Z; \theta)$ calculated in the NSBM with Bayes formula
- Reject $H_{0,ij}$ when $\ell_{ij}(X, Z; \theta) \leq t$
- Control of the **FDR** : proportion of errors among the discovered edges
  $\hookrightarrow$ threshold t such that the **FDR** is controlled at level α.

Graph inference

- Threshold t such that the **MFDR** is controlled at level α.

$$\text{MFDR}_\theta(t) = \frac{\mathbb{E}[\text{nb of falsely detected edges}]}{\mathbb{E}[\text{nb of detected edges}]}$$

$\text{MFDR}_\theta(t)$ explicitly calculated

- Choose largest threshold t such that $\text{MFDR}_\theta(t) \leq \alpha$
- $t = t_\theta(\alpha)$ generalized inverse of MFDR_θ en α.

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qvalues. (Storey, 2003)

$$q_{ij}(X, Z; \theta) = \text{MFDR}_\theta(\ell_{ij}(X, Z; \theta))$$

- Decision rule : Reject $H_{0,ij}$ provided that

$$q_{ij}(X, Z; \theta) \leq \alpha$$

Algorithm 1: Estimation and Graph inference in NSBM

Input: X, level α

Apply greedy algorithm to get $\widehat{\theta}$ and $\widehat{Z}$

Compute the q-values $q_{ij}(X, \widehat{Z}, \widehat{\theta})$

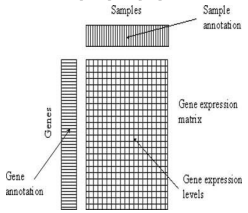
Output: Infer a graph

$$\widehat{A_{ij}} = \mathbb{1}\{q_{ij}(X, \widehat{Z}, \widehat{\theta}) \leq \alpha\}$$

Outline

Our Procedure

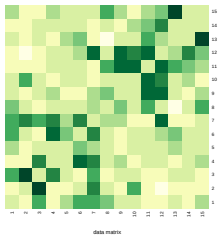
Gene expression data



p genes
n samples

SILGGM package

Test Statistics X_{ij}



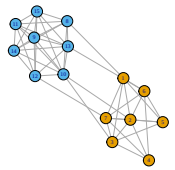
$X \in \mathbb{R}^{pxp}$

Algorithm 1

parameters: $\hat{\theta}$

clustering: $\hat{Z}$

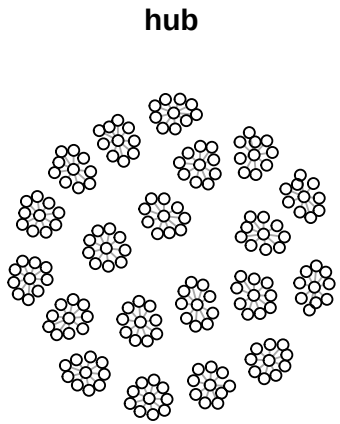
graph: $\hat{A} \Leftrightarrow \hat{G}$

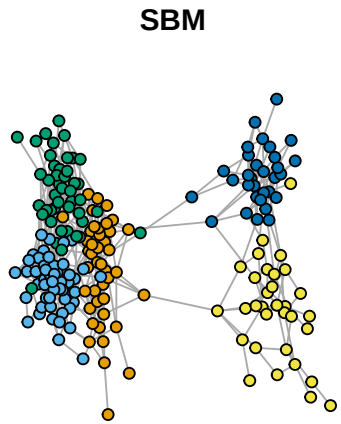


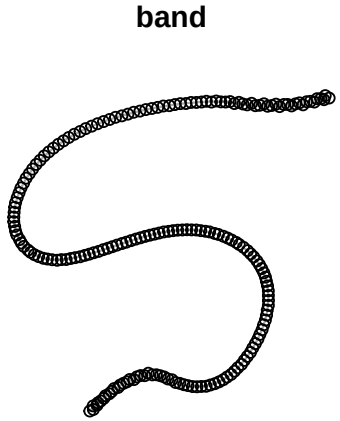
Outline

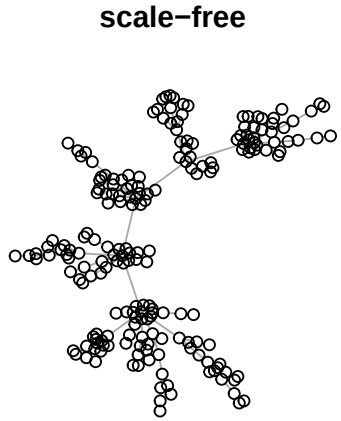
Simulations

- Different graph structures:









Simulations

- Different GGM inference methods:
  - test statistics provided by the package SILGGM : without and with our procedure
  - Glasso procedure
  - Meinshausen and Bühlmann procedure

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- Estimation of the FDP and the power with 200 Simulations

FDP = proportion of errors among the edges declared significant

TDP (power)= the proportion of edges declared significant among the true edges

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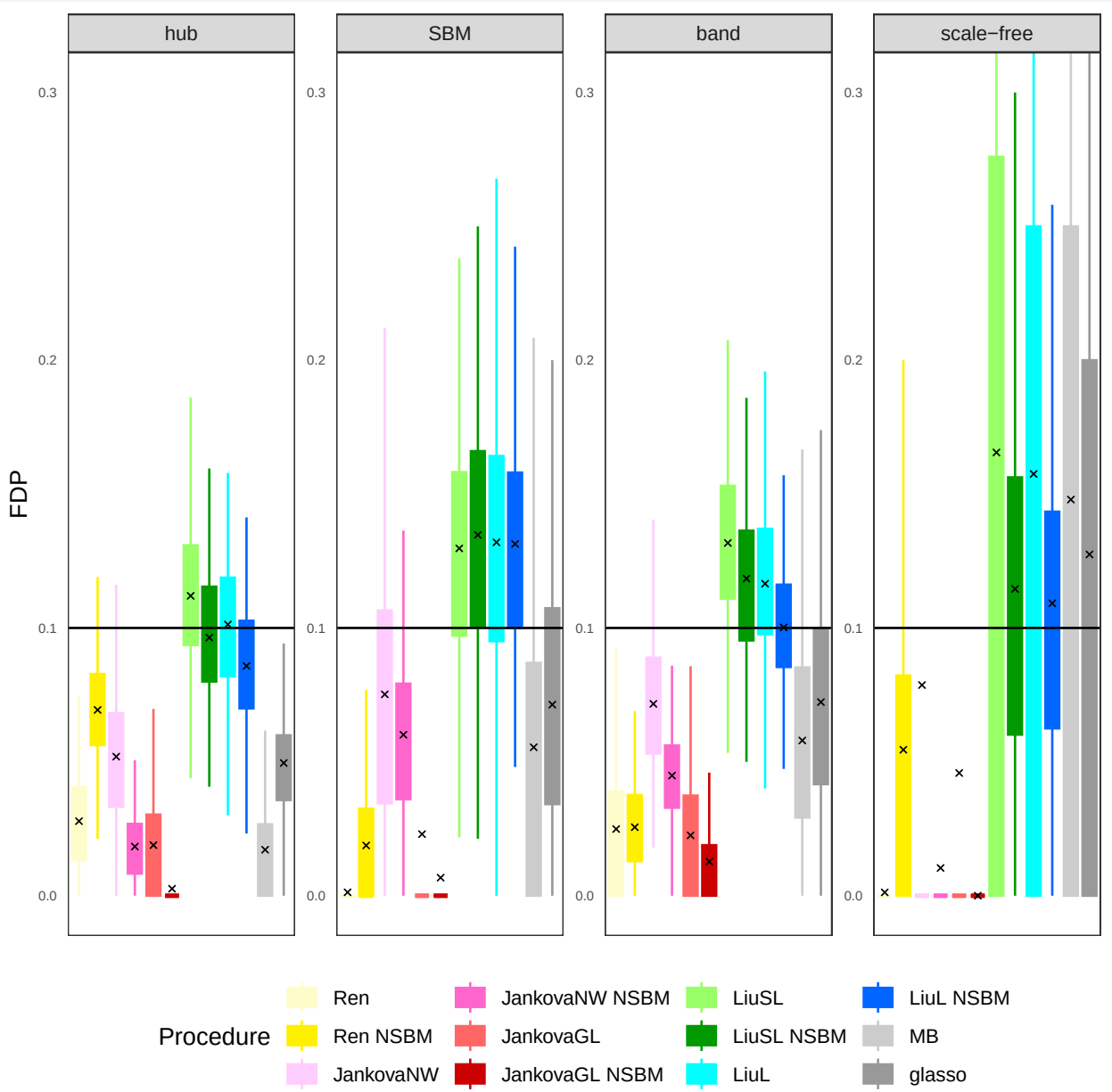
- Estimation of the FDP and the power with 200 Simulations

  FDP = proportion of errors among the edges declared significant

  TDP (power)= the proportion of edges declared significant among the true edges

- $n = 100, p = 200, \alpha = 0.1$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SBM
band
scale−free
FDP
0.0
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0.2
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Procedure
Ren
Ren NSBM
JankovaNW
JankovaNW NSBM
JankovaGL
JankovaGL NSBM
LiuSL
LiuSL NSBM
LiuL
LiuL NSBM
MB
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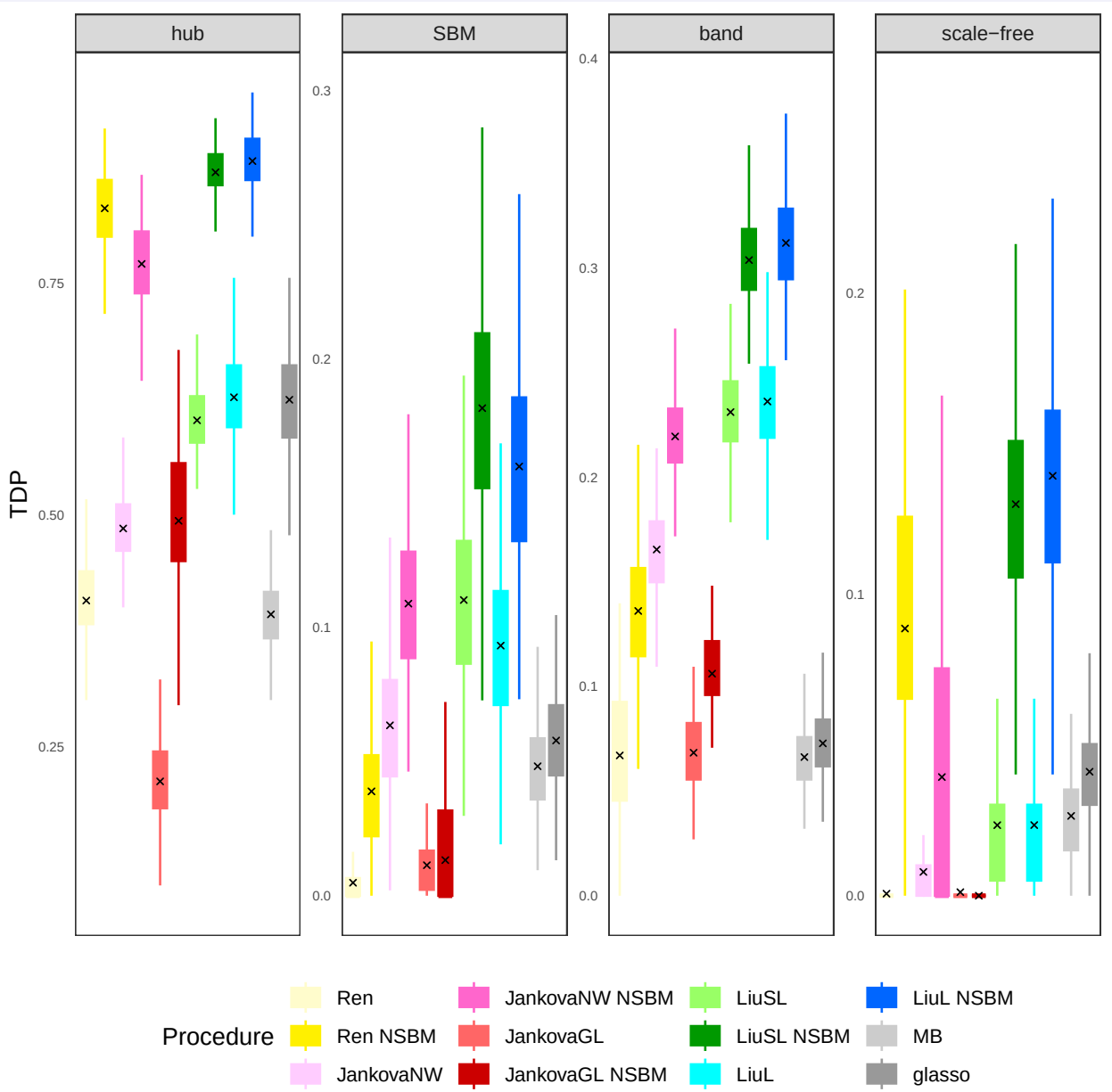
hub
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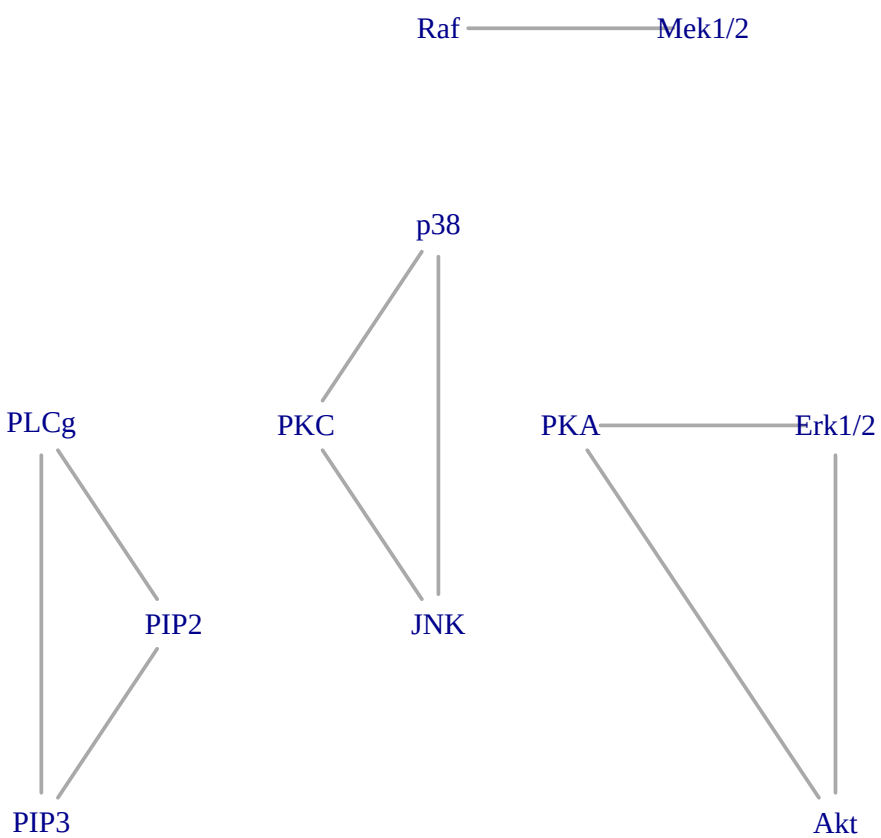
Procedure
Ren
Ren NSBM
JankovaNW
JankovaNW NSBM
JankovaGL
JankovaGL NSBM
LiuSL
LiuSL NSBM
LiuL
LiuL NSBM
MB
glasso

Real data

- flow cytometry data produced by Sachs et al.
- quantitative amounts of 11 proteins measured in 902 cells.

  - Inference with the full dataset (*LiuL*'s test statistics, $\alpha = 0.05$)



Real data

- Subsampling to test performance of our procedure

	n=10	
edge	LiuL	LiuL NSBM
Raf - Mek1/2	178	187
PLCg - PIP2	18	39
PLCg - PIP3	57	94
PIP2 - PIP3	114	147
Erk1/2 - Akt	178	185
Erk1/2 - PKA	14	43
Akt - PKA	44	79
PKC - p38	95	117
PKC - JNK	69	96
p38 - JNK	70	100

Number of times the 10 edges are detected over 200 simulations

Take-home message

- Inference in the NSBM :
  - faster alternative to the VEM algorithm
  - automatic selection of the number of groups
- Application to graph inference in GGM
  - use test statistics proposed in the literature on GGM as entries of our procedure
- Simulations
  - almost control in term of FDR on the inferred graph
  - increase in power
- Real dataset ?

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