Joint Estimation and Inference for Multiple Multi-layered Gaussian Graphical Models

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IISA-2017 Conference, Hyderabad, India
December 28, 2017

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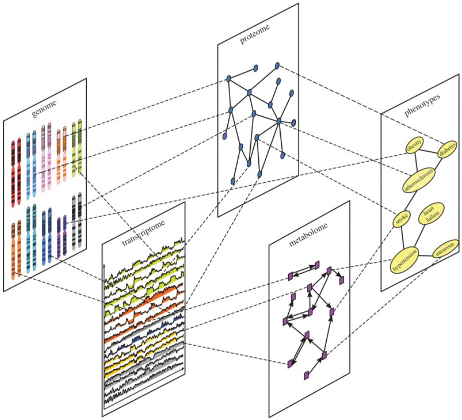
Summary

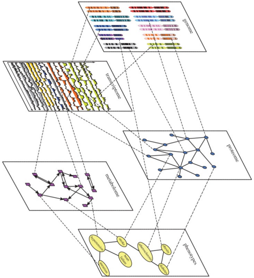
- Biological processes in the body have a natural hierarchical structure, e.g. **Gene > Protein > Metabolite**;
- There are within layer and between-layer connections in this structure.



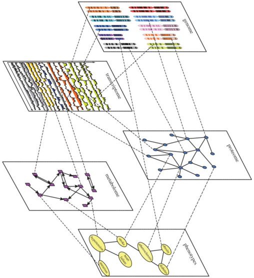
Source: Gligorijević and Pržulj (2015)

Summary

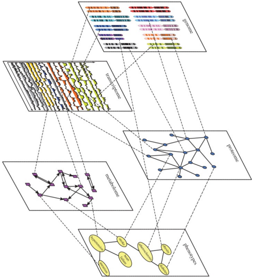
These connections can be different inside different organs, experimental conditions, or for different subtypes of the same disease;



Liver



Kidney



Lungs

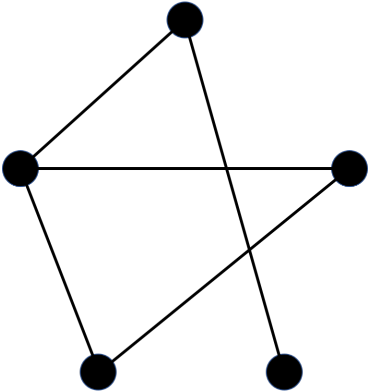
What we do

In this work we propose a general statistical framework based on graphical models for horizontal (i.e. across conditions or subtypes) and vertical (i.e. across different layers containing data on molecular compartments) integration of information in data from such complex biological structures.

Specifically, we perform *joint estimation and hypothesis testing* for all the connections in these structures.

Gaussian Graphical models

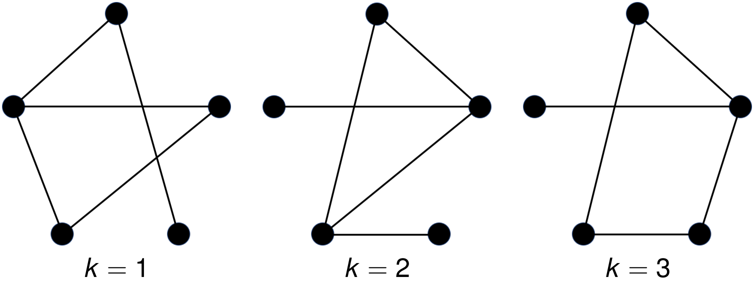
$$\mathbb{X} = (X_1, \ldots, X_p)^T \sim \mathcal{N}_p(0, \Sigma_x); \quad \Omega_x = \Sigma_x^{-1}$$



Sparse estimation of Ω_x: Meinshausen and Bühlmann (2006)
Multiple testing and error control: Drton and Perlman (2007).

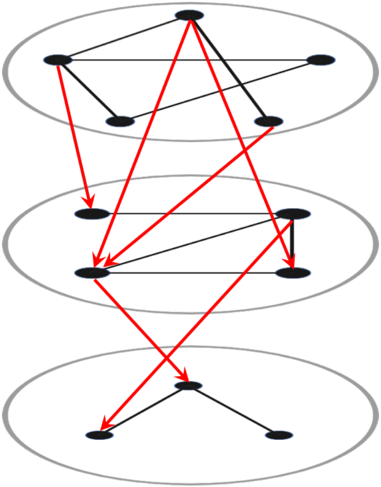
Multiple Gaussian Graphical models

$$\mathbb{X}^k = (X_1^k, \ldots, X_p^k)^T \sim \mathcal{N}_p(0, \Sigma_x^k); \quad \Omega_x^k = (\Sigma_x^k)^{-1}$$
$$k = 1, 2, \ldots, K$$



- Joint estimation of $\{\Omega_x^k\}$: Guo et al. (2011); Ma and Michailidis (2016)
- Difference and similarity testing with FDR control: Liu (2017+)

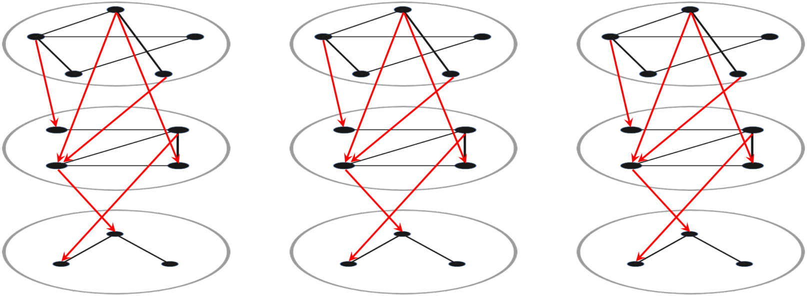
$$\mathbb{E} = (E_1, \ldots, E_q)^T \sim \mathcal{N}_p(0, \Sigma_y);$$
$$\Omega_y = (\Sigma_y)^{-1}$$
$$\mathbb{Y} = \mathbb{X}\mathbf{B} + \mathbb{E}$$



- Ω_x, Ω_y give undirected within-layer edges, while **B** gives directed between-layer edges.
- Sparse estimation of $(\Omega_y, \Omega_x, \mathbf{B})$: Lin et al. (2016).

Multiple Multi-layered Gaussian Graphical models

$$\mathbb{E}^k = (E_1^k, \ldots, E_q^k)^T \sim \mathcal{N}_p(0, \Sigma_y^k); \quad \Omega_y^k = (\Sigma_y^k)^{-1}$$
$$\mathbb{Y}^k = \mathbb{X}^k \mathbf{B}^k + \mathbb{E}^k; \quad k = 1, 2, \ldots, K$$



$k = 1$ $\quad$ $k = 2$ $\quad$ $k = 3$

- We estimate $\{\Omega_x^k, \Omega_y^k, \mathbf{B}^k\}$ jointly for all k from a single model;
- For $K = 2$ and $i \in \{1, 2, \ldots, p\}$, we also provide a global test for $\mathbf{b}_i^1 = \mathbf{b}_i^2$, and do multiple testing for $b_{ij}^1 = b_{ij}^2, j = 1, 2, \ldots, q$.

Outline

- $\mathcal{Y} = \{\mathbf{Y}^1, \ldots, \mathbf{Y}^k\}, \mathcal{X} = \{\mathbf{X}^1, \ldots, \mathbf{X}^k\}, \mathcal{B} = \{\mathbf{B}^1, \ldots, \mathbf{B}^k\}$;
- Group structures in X-network is denoted by

$$\mathcal{G}_x = \{\mathcal{G}_{x,ii'} : i \neq i', 1 \leq i, i' \leq p\}$$

  Each $\mathcal{G}_{x,ii'}$ is a partition of $\{1, \ldots, K\}$ denoting grouping over k for the $(i, i')^{\text{th}}$ elements of the X-precision matrices. For example, for $K = 5$,

$$\mathcal{G}_{x,12} = \{(1,2),(3),(4,5)\}; \quad \mathcal{G}_{x,13} = \{(1),(2,3),(4,5)\}$$

- Define $\mathcal{G}_y = \{\mathcal{G}_{y,jj'} : j \neq j', 1 \leq j, j' \leq q\}$ similarly.
- Group structures in $\mathcal{B}$ is denoted by $\mathcal{H}$, with each $h \in \mathcal{H}$ being a collection of 3-tuples (h_i, h_j, h_k) so that $1 \leq h_i \leq p, 1 \leq h_j \leq q, 1 \leq h_k \leq K$.

Neighborhood selection

- **For single GGM**: Estimate neighboring edges for each node, then refit.

$$\hat{\zeta}_i = \underset{\zeta_i}{\text{argmin}} \left\{ \frac{1}{n} \|\mathbf{X}_i - \mathbf{X}_{-i}\zeta_i\|^2 + \nu_n \sum_{i' \neq i} |\zeta_{ii'}| \right\};$$

$$\hat{\Omega}_x = \underset{\Omega_x \in \cup_i \text{support}(\zeta_i)}{\text{argmin}} \{ \text{Tr}(\mathbf{S}_x \Omega_x) + \log\det(\Omega_x) \}$$

Can do this because $\zeta_{ii'} = -\omega_{ii'}/\omega_{ii}$, so zeros of the precision matrix and neighborhood matrix are same.

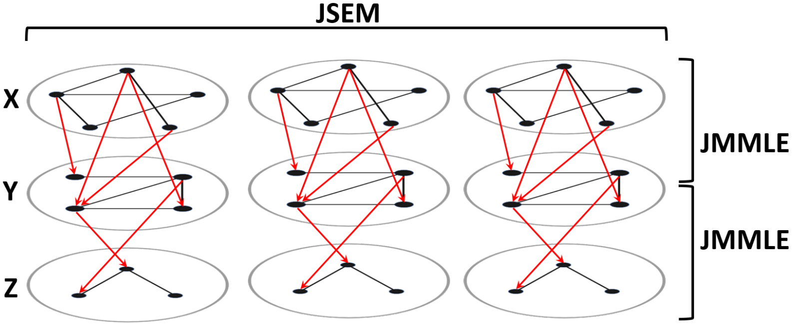
- **For multiple GGM**: Incorporate penalty across different k (JSEM: Ma and Michailidis (2016)).

$$\hat{\zeta}_i = \underset{\zeta_i}{\text{argmin}} \left\{ \sum_{k=1}^{K} \frac{1}{n_k} \|\mathbf{X}_i^k - \mathbf{X}_{-i}^k \zeta_i^k\|^2 + \nu_n \sum_{i' \neq i, g \in \mathcal{G}_{x,ii'}} \|\zeta_{ii'}^{[g]}\| \right\};$$

$$\hat{\Omega}_x^k = \underset{\Omega_x^k \in \cup_i \text{support}(\zeta_i^k)}{\text{argmin}} \left\{ \text{Tr}(\mathbf{S}_x^k \Omega_x^k) + \log\det(\Omega_x^k) \right\};$$

Joint Multiple Multi-Level Estimation (JMMLE)

We decompose the multi-layer problem into a series of two layer problems. For within-layer connections in the topmost layer, we use JSEM. For other connections we use JMMLE.



We combine sparse neighborhood selection in the Y-network with sparse estimation of $\{\mathbf{B}^k\}$.
Take $\Theta_j = (\boldsymbol{\theta}_j^1, \ldots, \boldsymbol{\theta}_j^K), \Theta = \{\Theta_j\}_{j=1}^q$.

$$\{\hat{\mathcal{B}}, \hat{\Theta}\} = \underset{\mathcal{B}, \Theta}{\text{argmin}} \left\{ \sum_{k=1}^K \frac{1}{n_k} \sum_{j=1}^q \left\| \mathbf{Y}_j^k - (\mathbf{Y}_{-j}^k - \mathbf{X}^k \mathbf{B}_{-j}^k) \theta_j^k - \mathbf{X}^k \mathbf{B}_j^k \right\|^2 \right.$$

$$\left. + \lambda_n \sum_{h \in \mathcal{H}} \|\mathbf{B}^{[h]}\| + \gamma_n \sum_{j' \neq j, g \in \mathcal{G}_{jj'}} \|\boldsymbol{\theta}_{jj'}^{[g]}\| \right\}$$

$$\hat{\Omega}_y^k = \underset{\Omega_y^k \in \cup_i \text{support}(\boldsymbol{\theta}_i^k)}{\text{argmin}} \left\{ \text{Tr}(\mathbf{S}_y^k \Omega_y^k) + \log\det(\Omega_y^k) \right\} \quad k = 1, 2, \ldots, K$$

$$\{\hat{\mathcal{B}}, \hat{\Theta}\} = \operatorname*{argmin}_{\mathcal{B},\Theta} \{f(\mathcal{Y}, \mathcal{X}, \mathcal{B}, \Theta) + P(\mathcal{B}) + Q(\Theta)\}$$

The objective function is biconvex, so we solve the above by the following alternating iterative algorithm:

1. Start with initial estimates of $\mathcal{B}$ and Θ, say $\mathcal{B}^{(0)}, \Theta^{(0)}$.
2. Iterate:

$$\mathcal{B}^{(t+1)} = \operatorname*{argmin}_{\mathcal{B}} \left\{ f(\mathcal{Y}, \mathcal{X}, \mathcal{B}, \Theta^{(t)}) + Q(\mathcal{B}) \right\}$$
$$\Theta^{(t+1)} = \operatorname*{argmin}_{\Theta} \left\{ f(\mathcal{Y}, \mathcal{X}, \mathcal{B}^{(t+1)}, \Theta) + P(\Theta) \right\}$$

3. Continue till convergence.

The two subproblems

$$\hat{\mathcal{B}} = \underset{\mathcal{B}}{\text{argmin}} \left\{ \sum_{k=K}^{q} \frac{1}{n_k} \sum_{j=1}^{q} \left\| \mathbf{Y}_j^k - (\mathbf{Y}_{-j}^k - \mathbf{X}^k \mathbf{B}_{-j}^k) \hat{\boldsymbol{\theta}}_j^k - \mathbf{X}^k \mathbf{B}_j^k \right\|^2 + \lambda_n \sum_{h \in \mathcal{H}} \| \mathbf{B}^{[h]} \| \right\}$$

$$= \underset{\mathcal{B}}{\text{argmin}} \left\{ \sum_{k=1}^{K} \frac{1}{n_k} \| (\mathbf{Y}^k - \mathbf{X}^k \mathbf{B}^k) \mathbf{T}^k \|_F^2 + + \lambda_n \sum_{h \in \mathcal{H}} \| \mathbf{B}^{[h]} \| \right\}$$

where $t_{jj}^k = 1, t_{jj'}^k = -\theta_{jj'}^k$.

$$\hat{\Theta} = \underset{\Theta}{\text{argmin}} \left\{ \sum_{k=K}^{q} \frac{1}{n_k} \sum_{j=1}^{q} \left\| \mathbf{Y}_j^k - (\mathbf{Y}_{-j}^k - \mathbf{X}^k \hat{\mathbf{B}}_{-j}^k) \boldsymbol{\theta}_j^k - \mathbf{X}^k \hat{\mathbf{B}}_j^k \right\|^2 + \gamma_n \sum_{j' \neq j, g \in \mathcal{G}_{jj'}} \| \boldsymbol{\theta}_{jj'}^{[g]} \| \right\}$$

$$= \underset{\Theta}{\text{argmin}} \left\{ \sum_{k=K}^{q} \frac{1}{n_k} \sum_{j=1}^{q} \| \hat{\mathbf{E}}_j^k - \hat{\mathbf{E}}_{-j}^k \boldsymbol{\theta}_j^k \|^2 + \gamma_n \sum_{j' \neq j, g \in \mathcal{G}_{jj'}} \| \boldsymbol{\theta}_{jj'}^{[g]} \| \right\}$$

where $\hat{\mathbf{E}}^k = \mathbf{Y}^k - \mathbf{X}^k \hat{\mathbf{B}}^k$.

Non-asymptotic error bounds for $\hat{\mathcal{B}}$

For $\lambda_n \geq 4\sqrt{|h_{\max}|}\mathbb{R}_0\sqrt{\frac{\log(pq)}{n}}$, the following hold with probability approaching 1 as $n \to \infty$,

$$\|\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0\|_1 \leq \frac{48\sqrt{|h_{\max}|}s_\beta\lambda_n}{\psi^*}$$

$$\|\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0\| \leq \frac{12\sqrt{s}_\beta\lambda_n}{\psi^*}$$

$$\sum_{h \in \mathcal{H}} \|\boldsymbol{\beta}^{[h]} - \boldsymbol{\beta}_0^{[h]}\| \leq \frac{48 s_\beta \lambda_n}{\psi^*}$$

with $\psi^*, \mathbb{R}_0$ being constants, and $\boldsymbol{\beta} = (\text{vec}(\mathbf{B}^1)^T, \ldots, \text{vec}(\mathbf{B}^K)^T)^T$, $|h_{\max}|$ the maximum group size in $\boldsymbol{\beta}_0$ and s_β the sparsity of $\boldsymbol{\beta}_0$.

For $\gamma_n = 4\sqrt{|g_{\max}|}\mathbb{Q}_0\sqrt{\frac{\log(pq)}{n}}$, the following hold with probability approaching 1 as $n \to \infty$,

$$\|\hat{\Theta}_j - \Theta_{0,j}\|_F \leq \frac{12\sqrt{s_j}\gamma_n}{\psi}$$

$$\sum_{j \neq j', g \in \mathcal{G}_y^{jj'}} \|\hat{\boldsymbol{\theta}}_{jj'}^{[g]} - \boldsymbol{\theta}_{0,jj'}^{[g]}\| \leq \frac{48 s_j \gamma_n}{\psi}$$

$$\left|\text{support}(\hat{\Theta}_j)\right| \leq \frac{128 s_j}{\psi}$$

$$\frac{1}{K}\sum_{k=1}^{K} \|\hat{\Omega}_y^k - \Omega_y^k\|_F \leq O\left(\frac{\sqrt{S}\gamma_n}{\sqrt{K}}\right)$$

with $\psi, \mathbb{Q}_0$ being constants, $|g_{\max}|$ the maximum group size in Θ_0, s_j the sparsity of Θ_j and $S = \sum_j s_j$.

Outline

1. Formulation of multiple multi-level graphical models
2. Model formulation, computation and theory
3. **Hypothesis testing**
4. Simulation studies

- Consider the case $K = 2$, and suppose we are interested in testing if the effect of variable i in the X-data is different across the two populations.
- For this we use the i^{th} rows of the estimates $\hat{\mathbf{B}}^1$ and $\hat{\mathbf{B}}^2$.
- We debias these row vectors using the neighborhood coefficients in the X-network computed previously using JSEM: In this setup, define the desparsified estimate of $\mathbf{b}_i^k$ as

$$\hat{\mathbf{c}}_i^k = \hat{\mathbf{b}}_i^k + \frac{1}{n t_i^k} \left(\mathbf{X}_i^k - \mathbf{X}_{-i}^k \hat{\zeta}_i^k \right)^T (\mathbf{Y}^k - \mathbf{X}^k \hat{\mathbf{B}}^k)$$

for $k = 1, 2$, where $t_i^k := (\mathbf{X}_i^k - \mathbf{X}_{-i}^k \hat{\zeta}_i^k)^T \mathbf{X}_{-i}^k / n$.

Assume we have 'good enough' estimators:

$$\|\hat{\zeta}^k - \zeta_0^k\|_1 = O\left(\sqrt{\frac{\log p}{n}}\right); \quad \|\hat{\mathbf{B}}^k - \mathbf{B}_0^k\|_1 = O\left(\sqrt{\frac{\log(pq)}{n}}\right)$$

$$\left\|(\hat{\Omega}_y^k)^{1/2} - (\Omega_y^k)^{1/2}\right\|_\infty = O\left(\sqrt{\frac{\log q}{n}}\right)$$

Also define

$$\hat{s}_i^k := \sqrt{\|\mathbf{X}_i^k - \mathbf{X}_{-i}^k \hat{\zeta}_i^k\|^2/n}; \quad m_i^k := \sqrt{n} t_i^k / \hat{s}_i^k$$

Then for sample size satisfying $n \gtrsim \log(pq), \log p = o(n^{1/2}), \log q = o(n^{1/2})$ we have

$$\begin{bmatrix} \hat{\Omega}_y^1 & \\ & \hat{\Omega}_y^2 \end{bmatrix}^{1/2} \begin{bmatrix} m_i^1(\hat{\mathbf{c}}_i^1 - \mathbf{b}_i^1) & \\ & m_i^2(\hat{\mathbf{c}}_i^2 - \mathbf{b}_i^2) \end{bmatrix} \sim \mathcal{N}_{2q}(\mathbf{0}, \mathbf{I}) + o_P(1)$$

Global test for $H_0 : \mathbf{b}_{0i}^1 = \mathbf{b}_{0i}^2$ at level $\alpha, 0 < \alpha < 1$

1. Obtain the debiased estimators $\hat{\mathbf{c}}_i^1, \hat{\mathbf{c}}_i^2$;
2. Calculate the test statistic

$$D_i = \left\| m_i^1 (\hat{\Omega}_y^1)^{1/2} \hat{\mathbf{c}}_i^1 - m_i^2 (\hat{\Omega}_y^2)^{1/2} \hat{\mathbf{c}}_i^2 \right\|^2$$

3. Reject H_0 if $D_i \geq \chi^2_{2q, 1-\alpha}$.

Simultaneous tests for $H_0^j : b_{0ij}^1 = b_{0ij}^2$ at level $\alpha, 0 < \alpha < 1$

1. Calculate the pairwise test statistics d_{ij} for $j = 1, \ldots, q$:

$$d_{ij} = \frac{\tau_{ij}^1 \hat{\mathbf{c}}_{ij}^1 - \tau_{ij}^2 \hat{\mathbf{c}}_{ij}^2}{1/m_i^1 + 1/m_i^2}$$

   where τ_{ij}^k is the $(i,j)^{\text{th}}$ element of $(\hat{\Omega}_y^k)^{1/2}, k = 1, 2$.

2. Obtain the threshold

$$\hat{\tau} = \inf \left\{ \tau \in \mathbb{R} : 1 - \Phi(\tau) \leq \frac{\alpha}{2q} \max \left(\sum_{j \in \mathcal{I}_q} \mathbb{I}(|d_{ij}| \geq \tau), 1 \right) \right\}$$

3. For $j \in \mathcal{I}_q$, reject H_0^j if $|d_{ij}| \geq \hat{\tau}$.

Outline

Simulation setup

- Number of categories (K) = 5;
- Structured $\{\Omega_x\}, \{\Omega_y\}, \mathcal{B}$;
- Groups in $\mathcal{B}, \Omega_x$ are non-zero with probability $5/p$, and their elements come from Unif$(-1, -0.5) \cup (0.5, 1)$;
- Groups in Ω_y are non-zero with probability $5/q$, and their elements come from Unif$(-1, -0.5) \cup (0.5, 1)$;
- We generate size-n i.i.d. samples $\mathbf{X}^k$ from $\mathcal{N}_p(0, \Sigma_x^k)$, and $\mathbf{E}^k$ from $\mathcal{N}_p(0, \Sigma_y^k)$, then obtain $\mathbf{Y}^k = \mathbf{X}^k \mathbf{B}^k + \mathbf{E}^k$;
- 100 Replications.

Evaluation metrics

1. True positives-

$$\text{TP}(\hat{\mathcal{B}}) = \frac{\sum_k |\,\text{supp}(\hat{\mathbf{B}}^k) \cup \text{supp}(\mathbf{B}_0^k)|}{\sum_k |\,\text{supp}(\mathbf{B}_0^k)|}$$

2. True negatives-

$$\text{TN}(\hat{\mathcal{B}}) = \frac{\sum_k |\,\text{supp}^c(\hat{\mathbf{B}}^k) \cup \text{supp}^c(\mathbf{B}_0^k)|}{\sum_k |\,\text{supp}^c(\mathbf{B}_0^k)|}$$

3. Relative error in Frobenius norm-

$$\text{rel.Frob}(\hat{\mathcal{B}}) = \sum_{k=1}^{K} \frac{\|\hat{\mathbf{B}}^k - \mathbf{B}_0^k\|_F}{\|\mathbf{B}_0^k\|_F}$$

Same metrics are used for $\hat{\Theta}$.

Results

Setting 1: $n = 100, p = 60, q = 30, K = 5$						
Method	TP($\hat{\mathcal{B}}$)	TN($\hat{\mathcal{B}}$)	rel.Frob($\hat{\mathcal{B}}$)	TP($\hat{\Theta}$)	TN($\hat{\Theta}$)	rel.Frob($\hat{\Theta}$)
Joint (JMMLE)	0.999 (2e-3)	0.99 (0.01)	0.19 (0.02)	0.66 (0.06)	0.95 (0.01)	0.33 (0.02)
Separate	0.95 (0.02)	0.99 (2e-3)	0.27 (0.03)	0.89 (0.02)	0.63 (0.01)	0.77 (0.04)
Setting 2: $n = 100, p = 30, q = 60, K = 5$						
Method	TP($\hat{\mathcal{B}}$)	TN($\hat{\mathcal{B}}$)	rel.Frob($\hat{\mathcal{B}}$)	TP($\hat{\Theta}$)	TN($\hat{\Theta}$)	rel.Frob($\hat{\Theta}$)
Joint (JMMLE)	0.996 (4e-3)	0.99 (6e-3)	0.21 (0.01)	0.58 (0.04)	0.98 (3e-3)	0.32 (8e-3)
Separate	0.66 (0.04)	0.994 (1e-3)	0.59 (0.03)	0.62 (0.03)	0.81 (7e-3)	0.43 (0.01)
Setting 3: $n = 150, p = 200, q = 200, K = 5$						
Method	TP($\hat{\mathcal{B}}$)	TN($\hat{\mathcal{B}}$)	rel.Frob($\hat{\mathcal{B}}$)	TP($\hat{\Theta}$)	TN($\hat{\Theta}$)	rel.Frob($\hat{\Theta}$)
Joint (JMMLE)	1.00 (0)	1.00 (0)	0.12 (5e-3)	0.39 (0.04)	0.996 (2e-3)	0.30 (7e-3)
Separate	0.42 (0.03)	0.99 (1e-3)	0.48 (0.02)	0.41 (0.02)	0.73 (0.01)	0.44 (0.02)

Future work

- Larger simulation: effect of signal strength and sparsity;
- Real data application, application to personalized medicine;
- Mediation analysis.

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THANK YOU!

Questions?