Statistical Inference with Multi-layered Graphical Models

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Joint work with George Michailidis

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  - *Extending methods to spatial models;*
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 - *The statistics of artificial intelligence: theory and interpretability.*

- Estimation of graphs from high-dimensional data is of importance for biological processes, financial systems or social interactions;

- Nodes in such data can have a natural hierarchical structure, e.g. Genes affecting proteins affecting metabolites, or macroeconomic indicators like interest rates or price indices affecting stock prices;

- There are within layer and between-layer connections in such structures.
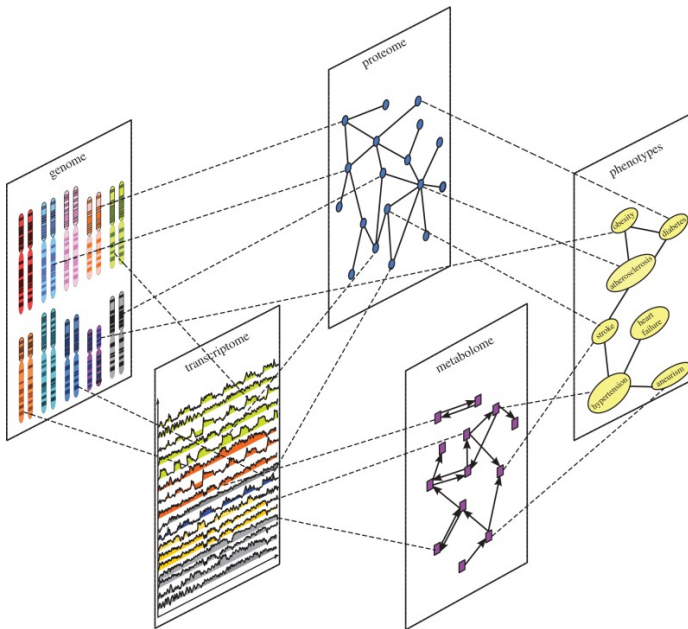
Source: Gligorijević and Pržulj (2015)

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

Liver   Kidney   Lungs
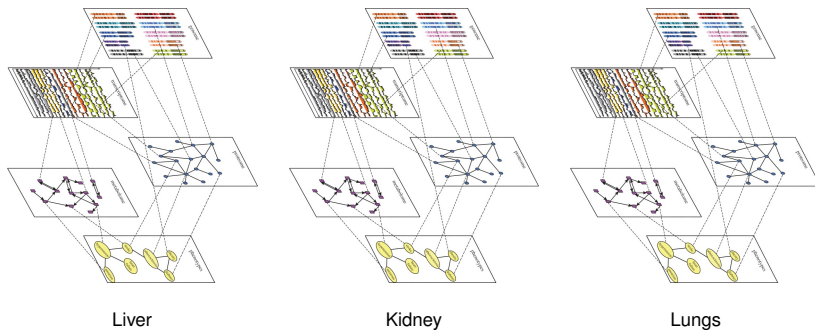
Statistical inference for hierarchical graphical models.

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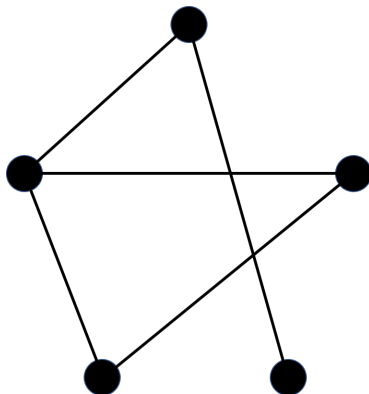
Specifically, we perform *joint estimation and hypothesis testing* for all the connections in these structures.
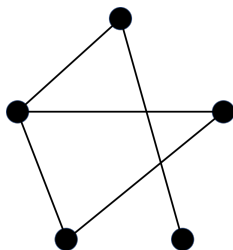
Table of contents

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

Non-zero entries in the precision matrix $\Omega_x = \Sigma_x^{-1}$ gives edges of the network.

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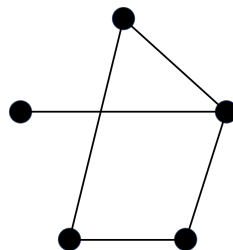Multiple testing and error control: Drton and Perlman (2007).

$$\mathbb{X}^k = (X_1^k, \ldots, X_p^k)^T \sim \mathcal{N}_p(0, \Sigma_x^k); \quad \Omega_x^k = (\Sigma_x^k)^{-1}$$
$$k = 1, 2, \ldots, K$$
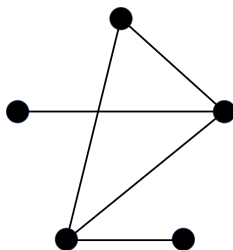
$k = 1$ $k = 2$ $k = 3$

- Joint estimation of $\{\Omega_x^k\}$: Guo et al. (2011); Ma and Michailidis (2016)

- Difference and similarity testing with FDR control: Liu (2017)

Multi-Layered Gaussian Graphical models

$\mathbb{E} = (E_1, \ldots, E_q)^T \sim \mathcal{N}_q(0, \Sigma_y);$

$\mathbb{F} = (F_1, \ldots, F_r)^T \sim \mathcal{N}_r(0, \Sigma_z);$

$\Omega_y = (\Sigma_y)^{-1}, \Omega_z = (\Sigma_z)^{-1}$

$\mathbb{Y} = \mathbb{X}^T \mathbf{B} + \mathbb{E},$

$\mathbb{Z} = \mathbb{Y}^T \mathbf{C} + \mathbb{F}.$

- $\Omega_x, \Omega_y, \Omega_z$ give undirected within-layer edges, while $\mathbf{B}$, $\mathbf{C}$ gives directed between-layer edges.

- Sparse estimation of the components: Lin et al. (2016).

- Testing: **??**

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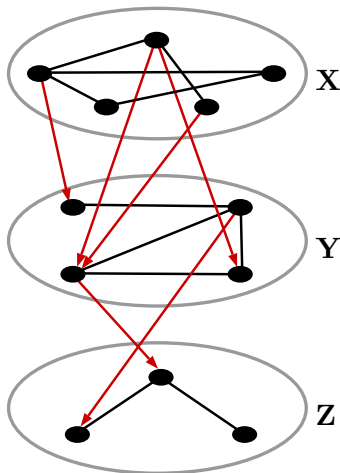$\mathbb{E} = (E_1, \ldots, E_q)^T \sim \mathcal{N}_q(0, \Sigma_y);$
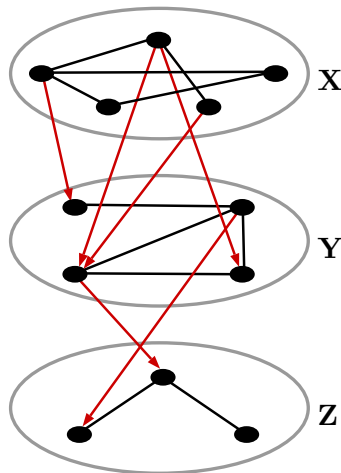
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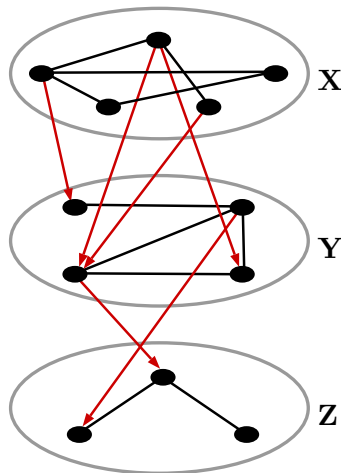
$$\mathbb{Z}^k = (\mathbb{Y}^k)^T \mathbf{C}^k + \mathbb{F}^k; \quad k = 1, 2, \ldots, K$$

Multiple Multi-layered Gaussian Graphical models

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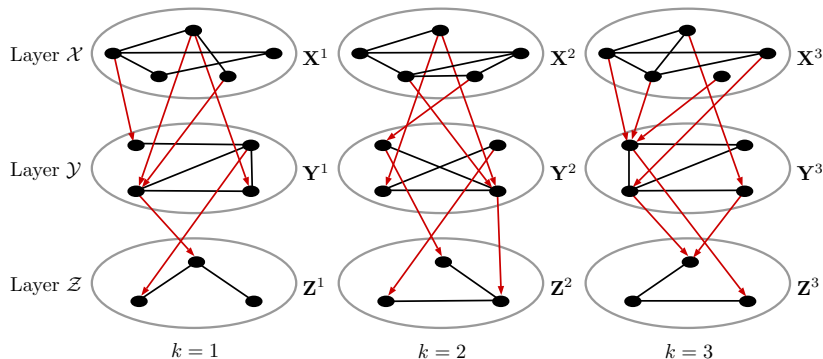
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What we do

- We decompose the multi-layer problem into a series of two layer problems.

- We estimate $\{\Omega_x^k, \Omega_y^k, \mathbf{B}^k\}$ jointly for all k from a single model;
  - Incorporate structural informartion using group sparsity,
  - Propose alternating block algorithm to compute solutions,
  - Derive convergence properties of solutions.

- Devise a full pairwise testing procedure for rows of $\mathbf{B}^k$;
  - Propose a debiasing method for estimates of individual rows of $\mathbf{B}^k$, say $\mathbf{b}_i^k, i \in \{1, 2, \ldots, p\}$ and derive its asymptotic distribution;
  - For $K = 2$, propose a test for row-wise differences $\mathbf{b}_i^1 - \mathbf{b}_i^2$;
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Linear model: $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$, with $\mathbf{X} \in \mathbb{R}^{n \times p}, \boldsymbol{\beta} \in \mathbb{R}^p, \boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I})$ with $\sigma > 0$;

Lasso: $\widehat{\boldsymbol{\beta}} = \operatorname{argmin}_{\boldsymbol{\beta}} \|\mathbf{y} - \mathbf{X}\boldsymbol{\beta}\|^2/n + \lambda\|\boldsymbol{\beta}\|_1$;

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Group lasso:
$$\widehat{\boldsymbol{\beta}} = \operatorname*{argmin}_{\boldsymbol{\beta}} \frac{1}{n} \|\mathbf{y} - \mathbf{X}\boldsymbol{\beta}\|^2 + \lambda \sum_{g \in \mathcal{G}} \|\boldsymbol{\beta}_g\|$$

where $\mathcal{G}$ is a *partition* of $\{1, 2, \ldots, p\}$.

Example: $p = 7, \mathcal{G} = \{[1, 2], [3, 4], [5, 6, 7]\}$. Then

$$\sum_{g \in \mathcal{G}} \|\boldsymbol{\beta}_g\| = \sqrt{\beta_1^2 + \beta_2^2} + \sqrt{\beta_3^2 + \beta_4^2} + \sqrt{\beta_5^2 + \beta_6^2 + \beta_7^2}$$

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.

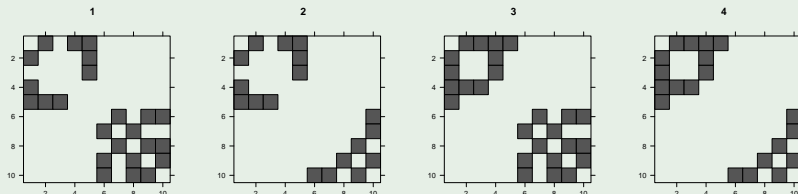Define $\mathcal{G}_y = \{\mathcal{G}_{y,jj'} : j \neq j', 1 \leq j, j' \leq q\}$ similarly.

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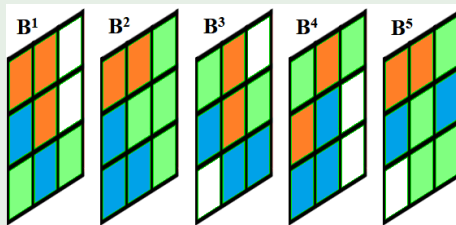Define $\mathcal{G}_y = \{\mathcal{G}_{y,jj'} : j \neq j', 1 \leq j, j' \leq q\}$ similarly.

Example

For i, i' in the upper block, $\mathcal{G}_{x,ii'} = \{[1, 2], [3, 4]\}$, otherwise it is $\{[1, 3], [2, 4]\}$.

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 $1 \leq h_i \leq p, 1 \leq h_j \leq q, 1 \leq h_k \leq K$.

Example

1. *Estimate neighborhood coefficients* of each X-node, say $\zeta_i = (\zeta_i^1, \ldots, \zeta_i^K)$ using the group sparsity information $\mathcal{G}_x$:

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

2. *Recover precision matrices* as MLE over the restricted supports:

$$\widehat{E}_x^k = \{(i, i') : 1 \leq i < i' \leq p, \widehat{\zeta}_{ii'}^k \neq 0 \text{ OR } \widehat{\zeta}_{i'i}^k \neq 0\},$$

$$\widehat{\Omega}_x^k = \underset{\Omega_x^k \in \mathbb{S}_+(\widehat{E}_x^k)}{\operatorname{argmin}} \left\{ \operatorname{Tr}(\widehat{\mathbf{S}}_x^k \Omega_x^k) - \log \det(\Omega_x^k) \right\}.$$

Joint Structural Estimation Method (JSEM)
Ma and Michailidis (2016)

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

2. *Recover precision matrices* as MLE over the restricted supports:

$$\widehat{E}_x^k = \{(i, i') : 1 \leq i < i' \leq p, \widehat{\zeta}_{ii'}^k \neq 0 \text{ OR } \widehat{\zeta}_{i'i}^k \neq 0\},$$

$$\widehat{\Omega}_x^k = \underset{\Omega_x^k \in \mathbb{S}_+(\widehat{E}_x^k)}{\operatorname{argmin}} \left\{ \operatorname{Tr}(\widehat{\mathbf{S}}_x^k \Omega_x^k) - \log \det(\Omega_x^k) \right\}.$$

Joint Structural Estimation Method (JSEM)
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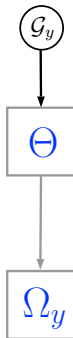
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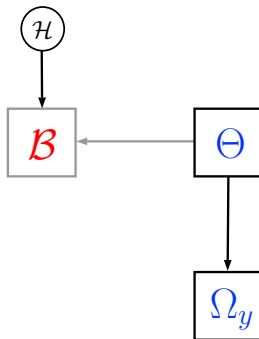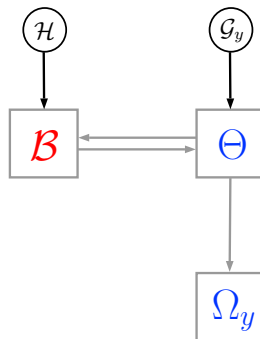
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Solution: Iterate!

Our testing methodology only requires *generic* estimates that satisfy the following convergence rates:

$$\|\widehat{\zeta}^k - \zeta_0^k\|_1 \leq O\left(\sqrt{\frac{\log p}{n}}\right)$$

$$\|\widehat{\mathbf{B}}^k - \mathbf{B}_0^k\|_1 \leq O\left(\sqrt{\frac{\log(pq)}{n}}\right)$$

$$\|\widehat{\Omega}_y^k - \Omega_{y0}^k\|_\infty \leq O\left(\sqrt{\frac{\log(pq)}{n}}\right)$$

The estimation procedure gives one suitable set of estimates.
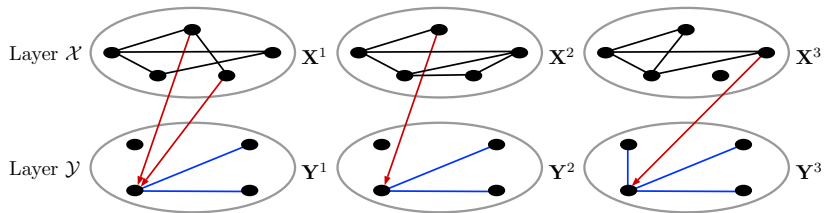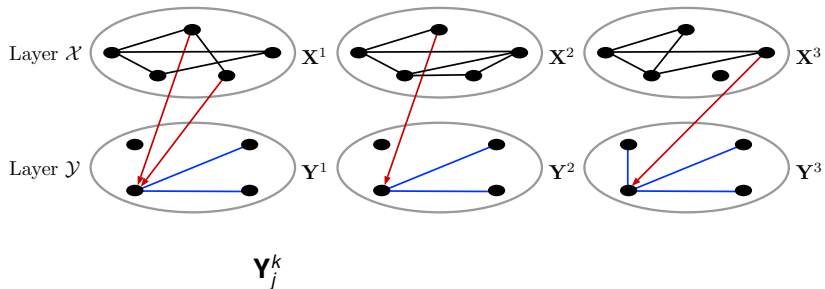
The objective function

$$\mathbf{Y}_j^k \quad - \quad \mathbf{E}_{-j}^k \boldsymbol{\theta}_j^k$$

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Joint Multiple Multi-Level Estimation (JMMLE)

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1. Solve for $\{\mathcal{B}, \Theta\}$:

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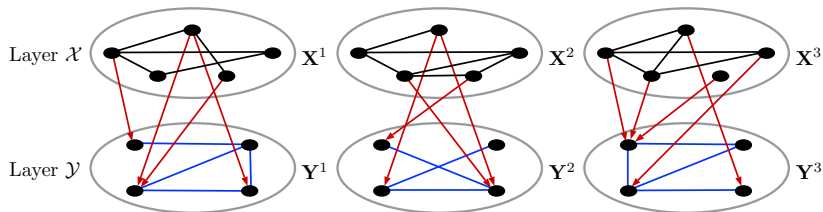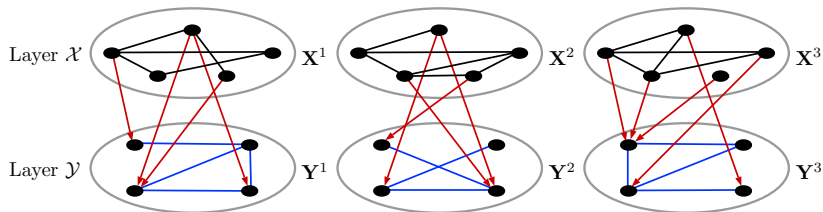
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$$\{\widehat{\mathcal{B}}, \widehat{\Theta}\} = \underset{\mathcal{B}, \Theta}{\operatorname{argmin}} \{f(\mathcal{Y}, \mathcal{X}, \mathcal{B}, \Theta) + P(\mathcal{B}) + Q(\Theta)\}$$

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:

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

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

3. Continue till convergence.

Non-asymptotic error bounds for $\widehat{\beta}$

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

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

$$\|\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0\| \leq \frac{12\sqrt{s_\beta}\lambda_n}{\psi^*}$$

$$\sum_{h \in \mathcal{H}} \|\beta^{[h]} - \beta_0^{[h]}\| \leq \frac{48 s_\beta \lambda_n}{\psi^*}$$

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 $\boldsymbol{\beta}_0$ (the true $\boldsymbol{\beta}$) 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 $n \to \infty$,

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

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

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

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

Debiased estimators (Zhang and Zhang, 2014)

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$$\hat{\beta}_j^{(\text{deb})} = \hat{\beta}_j + \frac{\mathbf{z}_j^T(\mathbf{y} - \mathbf{X}\widehat{\boldsymbol{\beta}})}{\mathbf{z}^T\mathbf{x}_j},$$

where $\mathbf{z}_j$ is the vector of residuals from the ℓ_1-penalized regression of $\mathbf{x}_j$ on $\mathbf{X}_{-j}$.

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The debiasing factor for the jth coefficient is obtained by taking residuals from the regularized regression and scale them using the *projection of $\mathbf{x}_j$ onto a space approximately orthogonal to it*.

- We propose a debiased estimator for $\mathbf{b}_i^k$ that makes use of already computed model quantities, and establish asymptotic properties of its scaled version,

- We assume $K = 2$, and propose an asymptotic test for detecting differential effects of a variable in the upper layer, i.e. testing for the null hypothesis $H0 : \mathbf{b}_{0i}^1 = \mathbf{b}_{0i}^2$,

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- We are interested in testing if the effect of variable i in the X-data has any downstream effect. For this we use the ith rows of the estimates $\widehat{\mathbf{B}}^k$.

- We debias these row vectors using the neighborhood coefficients in the X-network computed previously using JSEM:

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

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

Result

Assume we have 'good enough' estimators:

$$\|\widehat{\zeta}^k - \zeta_0^k\|_1 = O\left(\sqrt{\frac{\log p}{n}}\right)$$

$$\|\widehat{\mathbf{B}}^k - \mathbf{B}_0^k\|_1 = O\left(\sqrt{\frac{\log(pq)}{n}}\right)$$

$$\left\|\widehat{\Omega}_y^k - \Omega_y^k\right\|_\infty = O\left(\sqrt{\frac{\log pq}{n}}\right)$$

Define $\widehat{s}_i^k = \sqrt{\|\mathbf{X}_i^k - \mathbf{X}_{-i}^k \widehat{\zeta}_i^k\|^2/n}$, and $m_i^k = \sqrt{n} t_i^k / \widehat{s}_i^k$. and:

$$\widehat{\Omega}_y = \text{diag}(\widehat{\Omega}_y^1, \ldots, \widehat{\Omega}_y^K), \quad \mathbf{M}_i = \text{diag}(m_i^1, \ldots, m_i^K)$$

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Then under mild conditions, for sample size satisfying
$\log p = o(n^{1/2}), \log q = o(n^{1/2})$ we have $\widehat{\Omega}_y^{1/2} \mathbf{M}_i (\widehat{\mathbf{C}}_i - \mathbf{D}_i) \sim \mathcal{N}_{Kq}(\mathbf{0}, \mathbf{I}) + o_P(1)$.

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$$D_i = (\widehat{\mathbf{c}}_i^1 - \widehat{\mathbf{c}}_i^2)^T \left(\frac{\widehat{\Sigma}_y^1}{(m_i^1)^2} + \frac{\widehat{\Sigma}_y^2}{(m_i^2)^2} \right)^{-1} (\widehat{\mathbf{c}}_i^1 - \widehat{\mathbf{c}}_i^2)$$

where $\widehat{\Sigma}_y^k = (\widehat{\Omega}_y^k)^{-1}, k = 1, 2$.

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

$$D_i = (\widehat{\mathbf{c}}_i^1 - \widehat{\mathbf{c}}_i^2)^T \left(\frac{\widehat{\Sigma}_y^1}{(m_i^1)^2} + \frac{\widehat{\Sigma}_y^2}{(m_i^2)^2} \right)^{-1} (\widehat{\mathbf{c}}_i^1 - \widehat{\mathbf{c}}_i^2)$$

where $\widehat{\Sigma}_y^k = (\widehat{\Omega}_y^k)^{-1}, k = 1, 2.$

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

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

$$d_{ij} = \frac{\widehat{c}_{ij}^1 - \widetilde{c}_{ij}^2}{\sqrt{\hat{\sigma}_{jj}^1/(m_i^1)^2 + \hat{\sigma}_{jj}^2/(m_i^2)^2}}$$

2. Obtain the threshold

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

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Based on the FDR control procedure, we can perform *within-row thresholding* in the matrices $\widehat{\mathbf{B}}^k$ to tackle group misspecification.

$$\hat{\tau}_i^k := \inf \left\{ \tau \in \mathbb{R} : 1 - \Phi(\tau) \leq \frac{\beta}{2q} \max \left(\sum_{j \in \mathcal{I}_q} \mathbb{I}(|\sqrt{\hat{\omega}_{jj}^k} m_i^k \hat{c}_{ij}^k| \geq \tau), 1 \right) \right\}$$

$$\hat{b}_{ij}^{k,\text{thr}} = \hat{b}_{ij}^k \mathbb{I} \left(|\sqrt{\hat{\omega}_{jj}^k} m_i^k \hat{c}_{ij}^k| \geq \hat{\tau}_i^k \right)$$

Even without group misspecification, this helps identify directed edges between layers that have high nonzero values.

1. Multiple multi-level graphical models

2. Model formulation

3. Joint Multiple Multi-Level Estimation

4. Hypothesis testing in multi-layer models

5. **Numerical experiments**

6. Future work

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 $\mathbf{Y}^k = \mathbf{X}^k \mathbf{B}^k + \mathbf{E}^k$;
- 50 Replications.
- Tuning parameters:

$$\gamma_n \in \{0.3, 0.4, ..., 1\} \sqrt{\frac{\log q}{n}}, \lambda_n \in \{0.4, 0.6, ..., 1.8\} \sqrt{\frac{\log p}{n}}$$

1 True positive Rate-

$$\text{TPR}(\widehat{\mathcal{B}}) = \frac{1}{K} \sum_{k=1}^{K} \frac{|\operatorname{supp}(\widehat{\mathbf{B}}^k) \cup \operatorname{supp}(\mathbf{B}_0^k)|}{|\operatorname{supp}(\mathbf{B}_0^k)|}$$

2 True negatives-

$$\text{TNR}(\widehat{\mathcal{B}}) = \frac{1}{K} \sum_{k=1}^{K} \frac{|\operatorname{supp}^c(\widehat{\mathbf{B}}^k) \cup \operatorname{supp}^c(\mathbf{B}_0^k)|}{|\operatorname{supp}^c(\mathbf{B}_0^k)|}$$

3 Relative error in Frobenius norm-

$$\text{RF}(\widehat{\mathcal{B}}) = \frac{1}{K} \sum_{k=1}^{K} \frac{\|\widehat{\mathbf{B}}^k - \mathbf{B}_0^k\|_F}{\|\mathbf{B}_0^k\|_F}$$

4 Matthews correlation coefficient (MCC).

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

Results

(π_x, π_y)	(p, q, n)	Method	TPR	TNR	MCC	RF
$(5/p, 5/q)$	(60,30,100)	JMMLE	**0.97(0.02)**	0.99(0.003)	**0.96(0.014)**	0.24(0.033)
		Separate	0.96(0.018)	0.99(0.004)	0.93(0.014)	0.22(0.029)
	(30,60,100)	JMMLE	0.97(0.013)	0.99(0.002)	**0.96(0.008)**	0.27(0.024)
		Separate	0.99(0.009)	0.99(0.003)	0.93(0.017)	0.18(0.021)
	(200,200,150)	JMMLE	0.98(0.011)	**1.0(0)**	**0.99(0.005)**	**0.16(0.025)**
		Separate	0.99(0.001)	0.99 (0.001)	0.88(0.009)	0.18(0.007)
	(300,300,150)	JMMLE	**1.0(0.001)**	**1.0(0)**	**0.99(0.001)**	**0.14 (0.015)**
		Separate	1.0(0.001)	0.99(0.001)	0.84(0.01)	0.21(0.007)
$(30/p, 30/q)$	(200,200,100)	JMMLE	**0.97(0.017)**	**1.0(0)**	**0.98(0.008)**	**0.21(0.032)**
		Separate	0.32(0.01)	0.99(0.001)	0.49(0.009)	0.85(0.06)
	(200,200,200)	JMMLE	**0.99(0.006)**	**1.0(0)**	**0.99(0.007)**	**0.13(0.016)**
		Separate	0.97(0.004)	0.98(0.001)	0.93(0.002)	0.19(0.07)

Table of outputs for estimation of regression matrices, giving empirical mean and standard deviation (in brackets) of each evaluation metric over 50 replications.

Results

(π_x, π_y)	(p, q, n)	Method	TPR	TNR	MCC	RF
$(5/p, 5/q)$	(60,30,100)	JMMLE	0.76(0.018)	0.90(0.006)	**0.61(0.024)**	**0.32(0.008)**
		Separate	0.77(0.031)	0.92(0.007)	0.56(0.03)	0.51(0.017)
		JSEM	0.24(0.013)	0.8(0.003)	0.05(0.015)	1.03(0.002)
	(30,60,100)	JMMLE	0.7(0.018)	**0.94(0.002)**	0.55(0.018)	**0.3(0.005)**
		Separate	0.76(0.041)	0.89(0.015)	0.59(0.039)	0.49(0.014)
		JSEM	0.13(0.005)	0.9(0.001)	0.03(0.007)	1.04(0.001)
	(200,200,150)	JMMLE	0.68(0.017)	**0.98(0)**	0.48(0.013)	**0.26(0.002)**
		Separate	0.78(0.019)	0.97(0.001)	0.55(0.012)	0.6(0.007)
		JSEM	0.05(0.002)	0.97(0)	0.02(0.002)	1.01(0)
	(300,300,150)	JMMLE	0.**71(0.014)**	**0.98(0)**	0.44(0.008)	**0.25(0.002)**
		Separate	0.71(0.017)	0.98(0.001)	0.51(0.011)	0.59(0.005)
		JSEM	0.04(0.002)	0.98(0)	0.02(0.002)	1.01(0)
$(30/p, 30/q)$	(200,200,100)	JMMLE	**0.77(0.016)**	**0.98(0)**	**0.46(0.013)**	**0.31(0.003)**
		Separate	0.57(0.027)	0.44(0.007)	0.04(0.008)	0.84(0.002)
		JSEM	0.05(0.002)	0.97(0)	0.01(0.002)	1.01(0)
	(200,200,200)	JMMLE	0.76(0.018)	**0.98(0)**	**0.55(0.015)**	**0.27(0.004)**
		Separate	0.73(0.023)	0.94(0.003)	0.39(0.017)	0.62(0.011)
		JSEM	0.05(0.002)	0.97(0)	0.03(0.003)	1.01(0)

Table of outputs for estimation of lower layer precision matrices over 50 replications.

- Set $K = 2$, then randomly assign each element of $\mathbf{B}_0^1$ as non-zero w.p. π, then draw their values from Unif$\{[-1, -0.5] \cup [0.5, 1]\}$ independently.
- Generate a matrix of differences $\mathbf{D}$, where $(\mathbf{D})_{ij}$ takes values –1, 1, 0 w.p. 0.1, 0.1 and 0.8, respectively. Finally set $\mathbf{B}_0^2 = \mathbf{B}_0^1 + \mathbf{D}$.
- Identical sparsity structures for the pairs of X- and Y-precision matrices.
- Type-I error set at 0.05, FDR controlled at 0.2.
- Empirical sizes of global tests are calculated from estimators obtained from a separate set of data generated by setting all elements of $\mathbf{D}$ to 0.

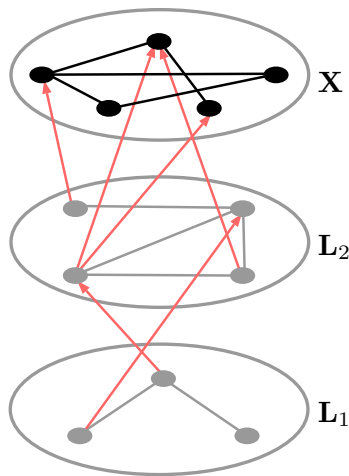| (π_x, π_y)	(p, q)	n	Global test		Simultaneous tests	
			Power	Size	Power	FDR
$(5/p, 5/q)$	(60,30)	100	0.977 (0.018)	0.058 (0.035)	0.937 (0.021)	0.237 (0.028)
		200	0.987 (0.016)	0.046 (0.032)	0.968 (0.013)	0.218 (0.032)
	(30,60)	100	0.985 (0.018)	0.097 (0.069)	0.925 (0.022)	0.24 (0.034)
		200	0.990 (0.02)	0.119 (0.059)	0.958 (0.024)	0.245 (0.041)
	(200,200)	150	0.987 (0.005)	0.004 (0.004)	0.841 (0.13)	0.213 (0.007)
	(300,300)	150	0.988 (0.002)	0.002 (0.003)	0.546 (0.035)	0.347 (0.017)
		300	0.998 (0.003)	0.000 (0.001)	0.989 (0.003)	0.117 (0.006)
$(30/p, 30/q)$	(200,200)	100	0.994 (0.005)	0.262 (0.06)	0.479 (0.01)	0.557 (0.006)
		200	0.998 (0.004)	0.020 (0.01)	0.962 (0.003)	0.266 (0.007)
		300	0.999 (0.002)	0.011 (0.008)	0.990 (0.004)	0.185 (0.009)

Table of outputs for hypothesis testing.

- Beyond pairwise testing: global and simultaneous tests for $K > 2$;

- Multi-level estimation and testing for model assumptions other than structured sparsity;

- Hypothesis testing for complex high-dimensional models;

- Non-gaussian data;

- **Graphical models with non-linear interactions**.

- Take the multi-layer structure as a *generative model*.

- Only the top layer is observed, other layers are composed of latent variables.

Graphical models with non-linear interactions

- Take the multi-layer structure as a *generative model*.

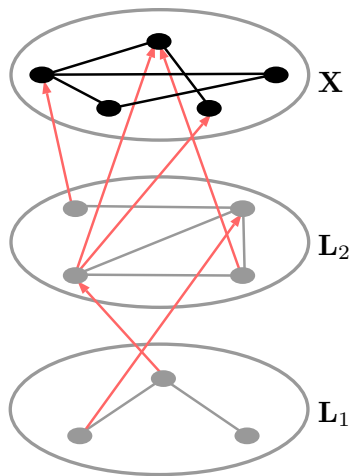- Only the top layer is observed, other layers are composed of latent variables.

$$\mathbb{L}_1 = (L_{11}, \ldots, L_{1r})^T \sim \mathcal{N}_r(0, \Sigma_1);$$
$$\mathbb{L}_2 = \phi(\mathbb{L}_1^T \mathbf{B}) + \mathbb{E},$$
$$\mathbb{X} = \phi(\mathbb{L}_2^T \mathbf{C}) + \mathbb{F},$$
$$\mathbb{E} = (E_1, \ldots, E_q)^T \sim \mathcal{N}_q(0, \Sigma_2);$$
$$\mathbb{F} = (F_1, \ldots, F_p)^T \sim \mathcal{N}_p(0, \Sigma_x).$$

where ϕ is a known activation function.

- Non-linear generalization of a factor model.

- A general version: $\mathbb{L}_2 = f_1(\mathbb{L}_1) + \mathbb{E}$ etc. for unknown function f_1, has been proposed as Deep Latent Gaussian Model (Rezende et al., 2014).

- The choice $\phi(\mathbb{L}^T\mathbf{B}) \equiv \phi(\mathbb{L})^T\mathbf{B}$ corresponds to Non-linear Gaussian belief networks (Frey and Hinton, 1999).

Incorporate *sparse* estimation of the model parameters to model non-linear interactions.
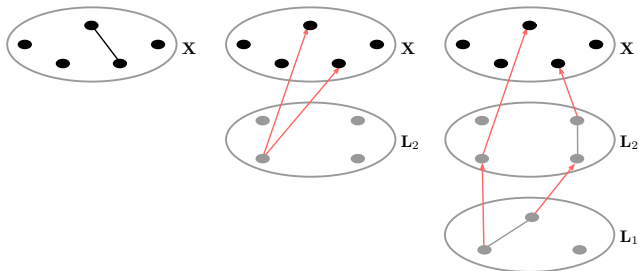
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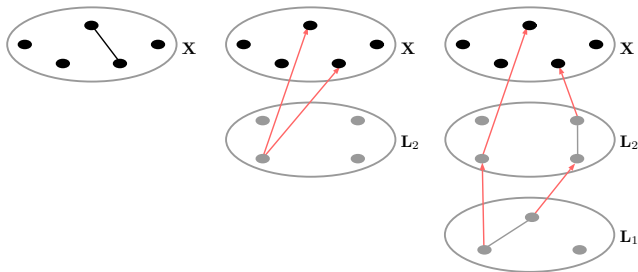
- Monte-Carlo Sequential EM, backpropagation
- Theoretical properties of estimates

- We proposed a general framework to model data in *complex hierarchical structures*, with a focus on multi-level biological Omics datasets;

- We provide an *estimation algorithm* and *testing methodology* for the parameters involved, with theoretical results ensuring the validity of the methods;

- The general nature of the work leaves many *directions for future developments*.

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Preprint available at: https://arxiv.org/abs/1803.03348

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Guo, J., Levina, E., Michailidis, G., and Zhu, J. (2011). Joint estimation of multiple graphical models. *Biometrika*, 98(1):1–15.

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Liu, W. (2017). Structural similarity and difference testing on multiple sparse Gaussian graphical models. *Ann. Statist.*, 45(6):2680–2707.

Ma, J. and Michailidis, G. (2016). Joint Structural Estimation of Multiple Graphical Models. *J. Mach. Learn. Res.*, 17:5777–5824.

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THANK YOU!