

Statistical Inference with Multi-layered Graphical Models

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Joint work with George Michailidis

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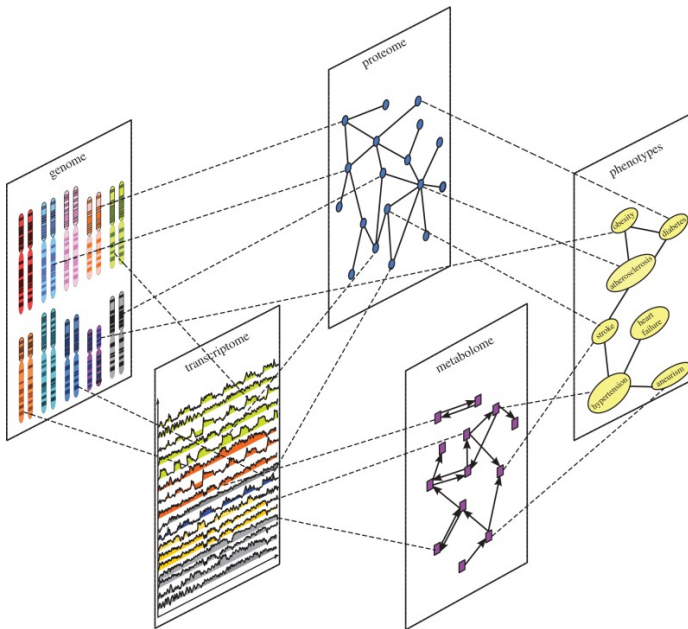
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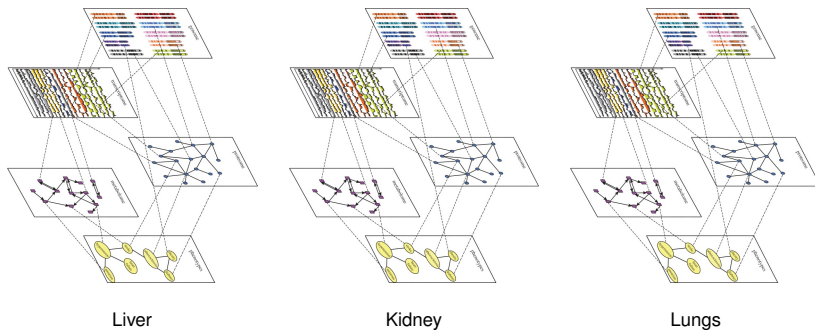
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 - *Extending methods to spatial models;*
 - *Uncertainty quantification in complex high-dimensional systems: causal models, tensor models.*
 - *The statistics of artificial intelligence: theory and interpretability.*

- 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;



Statistical inference for hierarchical graphical models.

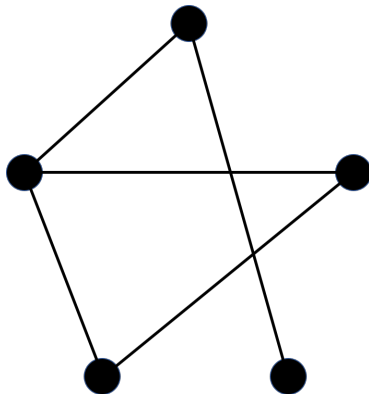
In this work we propose a general statistical framework based on graphical models for *horizontal* (i.e. across conditions or subtypes) *and vertical* (i.e. across different layers containing data on molecular compartments) *integration of information* in data from such complex biological structures.

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

- 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**

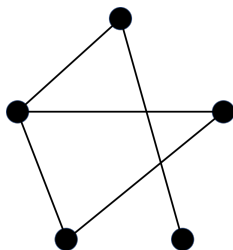
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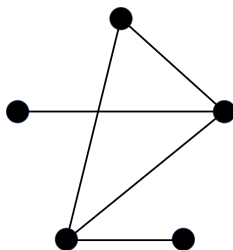


Sparse estimation of Ω_x : [Meinshausen and Bühlmann \(2006\)](#)
Multiple testing and error control: [Drton and Perlman \(2007\)](#).

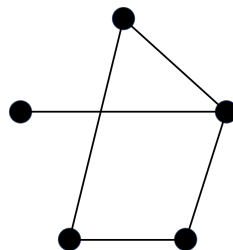
$$\mathbb{X}^k = (X_1^k, \dots, X_p^k)^T \sim \mathcal{N}_p(0, \Sigma_x^k); \quad \Omega_x^k = (\Sigma_x^k)^{-1}$$
$$k = 1, 2, \dots, K$$



$k = 1$



$k = 2$



$k = 3$

- 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

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

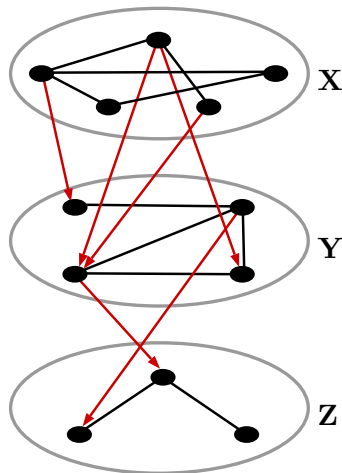
$$\mathbb{F} = (F_1, \dots, F_r)^T \sim \mathcal{N}_r(0, \Sigma_z);$$

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

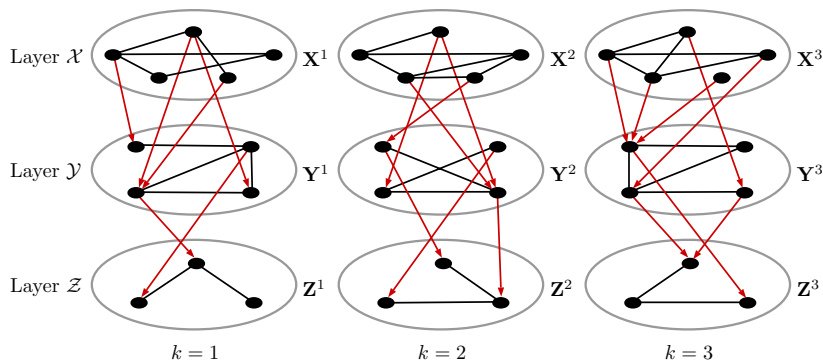
$$\mathbb{Y} = \mathbb{X}^T \mathbf{B} + \mathbb{E},$$

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

- $\Omega_x, \Omega_y, \Omega_z$ 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: ??



Multiple Multi-layered Gaussian Graphical models



$$\mathbb{E}^k = (E_1^k, \dots, E_q^k)^T \sim \mathcal{N}_q(0, \Sigma_y^k); \quad \Omega_y^k = (\Sigma_y^k)^{-1}$$

$$\mathbb{F}^k = (F_1^k, \dots, F_r^k)^T \sim \mathcal{N}_r(0, \Sigma_z^k); \quad \Omega_z^k = (\Sigma_z^k)^{-1}$$

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

$$\mathbb{Z}^k = (\mathbb{Y}^k)^T \mathbf{C}^k + \mathbb{F}^k; \quad k = 1, 2, \dots, K$$

- 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 information 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 $\mathbf{b}_i^k, i \in \{1, 2, \dots, p\}$ and derive its asymptotic distribution;
 - For $K = 2$, propose a test for row-wise differences $\mathbf{b}_i^1 - \mathbf{b}_i^2$;
 - Perform multiple testing for elementwise differences $b_{ij}^1 = b_{ij}^2, j = 1, 2, \dots, q$ within a row.
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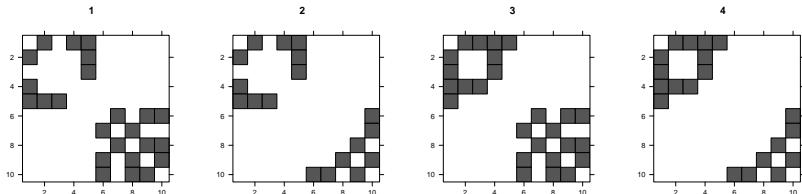
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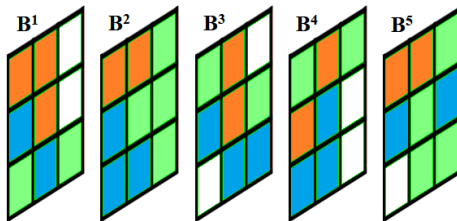
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Group structures in X-network is denoted by $\mathcal{G}_x = \{\mathcal{G}_{x,ii'} : i \neq i', 1 \leq i, i' \leq p\}$. Each $\mathcal{G}_{x,ii'}$ is a partition of $\{1, \dots, K\}$ denoting grouping over k for the $(i, i')^{\text{th}}$ elements of the X-precision matrices.



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

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



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

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

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

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

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

Joint Structural Estimation Method (JSEM)

Ma and Michailidis (2016)

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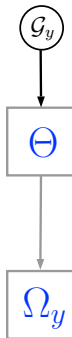
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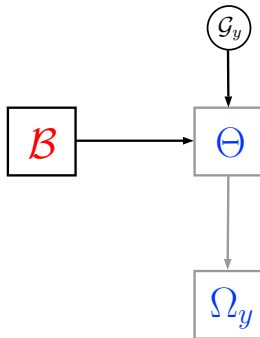
Joint Structural Estimation Method (JSEM)
Ma and Michailidis (2016)

Estimate Y-layer precision matrices by first estimating neighborhood coefficients of each Y-node, say $\Theta_j = (\theta_j^1, \dots, \theta_j^K)$ and then refitting.

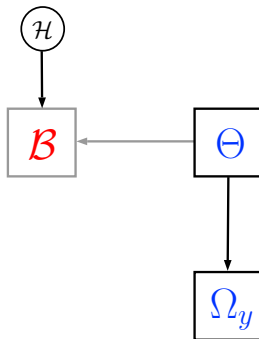
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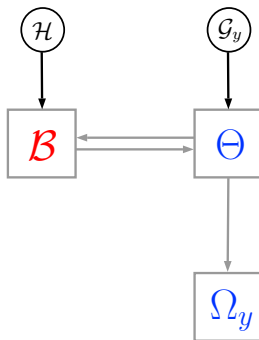
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Solution: Iterate!

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

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

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

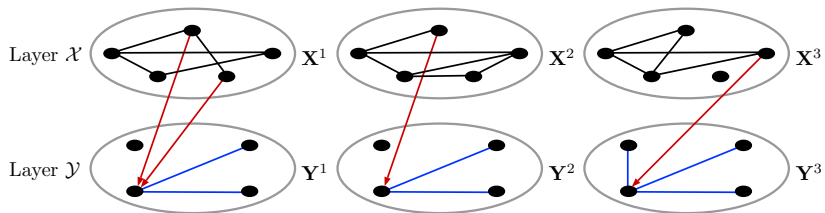
$$\|\hat{\Omega}_y^k - \Omega_{y0}^k\|_\infty \leq O\left(\sqrt{\frac{\log(pq)}{n}}\right)$$

The estimation procedure gives one suitable set of estimates.

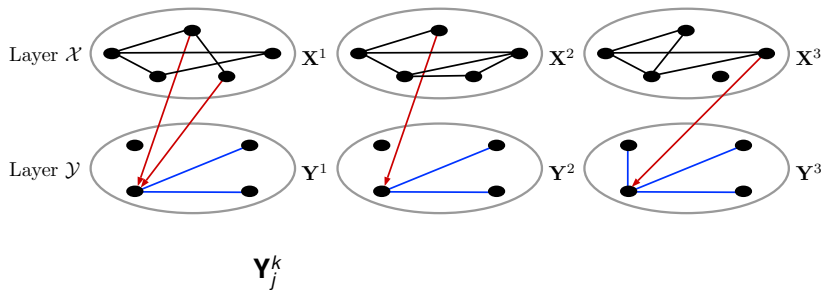
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The objective function

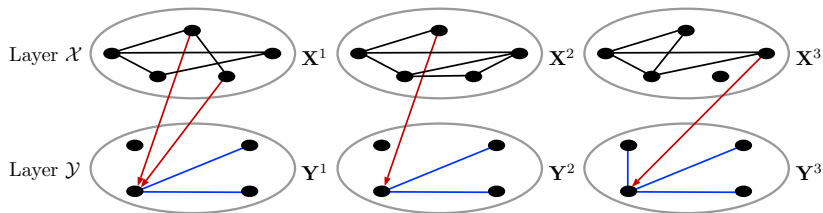
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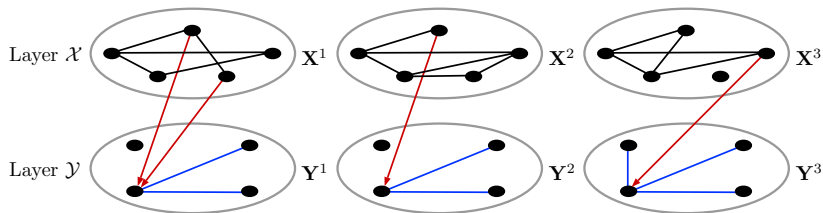


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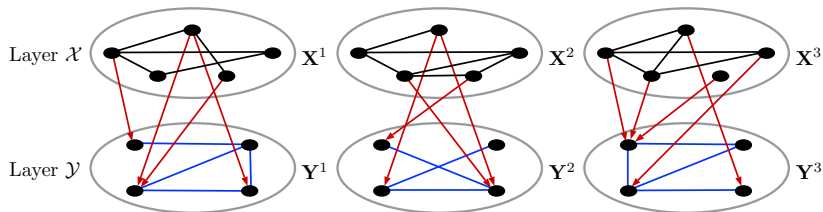
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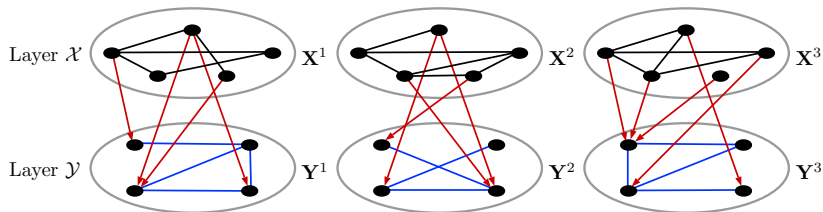
$$\mathbf{Y}_j^k = \mathbf{E}_{-j}^k \boldsymbol{\theta}_j^k - \mathbf{X}^k \mathbf{B}_j^k$$

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$$\sum_{k=1}^K \frac{1}{n_k} \sum_{j=1}^q \left\| \mathbf{Y}_j^k - (\mathbf{Y}_{-j}^k - \mathbf{X}^k \mathbf{B}_{-j}^k) \boldsymbol{\theta}_j^k - \mathbf{X}^k \mathbf{B}_j^k \right\|^2$$

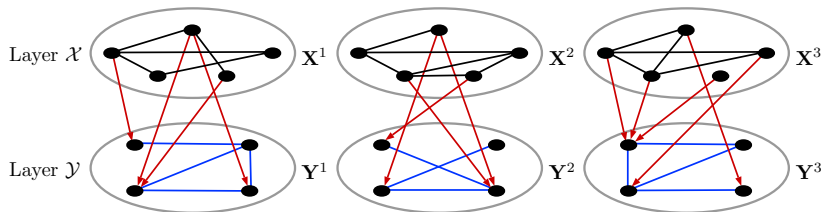
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$$+ \lambda_n \sum_{h \in \mathcal{H}} \|\mathbf{B}^{[h]}\| + \gamma_n \sum_{j' \neq j, g \in \mathcal{G}_{jj'}} \|\boldsymbol{\theta}_{jj'}^{[g]}\|$$

Joint Multiple Multi-Level Estimation (JMMLE)

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

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- 2 Recover \mathbf{Y} -precision matrices as MLE over the restricted supports:

$$\hat{E}_y^k = \{(j, j') : 1 \leq j < j' \leq q, \hat{\theta}_{jj'}^k \neq 0 \text{ OR } \hat{\theta}_{j'j}^k \neq 0\},$$

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

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

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:

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

- 3 Continue till convergence.

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

$$\|\hat{\beta} - \beta_0\|_1 \leq \frac{48\sqrt{|h_{\max}|}\mathbf{s}_{\beta}\lambda_n}{\psi^*}$$

$$\|\hat{\beta} - \beta_0\| \leq \frac{12\sqrt{\mathbf{s}_{\beta}}\lambda_n}{\psi^*}$$

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

with ψ^*, \mathbb{R}_0 being constants, and $\beta = (\text{vec}(\mathbf{B}^1)^T, \dots, \text{vec}(\mathbf{B}^K)^T)^T$, $|h_{\max}|$ the maximum group size in β_0 (the true β) and \mathbf{s}_{β} the sparsity of β_0 .

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

$$\begin{aligned}\|\hat{\Theta}_j - \Theta_{0,j}\|_F &\leq \frac{12\sqrt{s_j}\gamma_n}{\psi} \\ \sum_{j \neq j', g \in \mathcal{G}_y^{jj'}} \|\hat{\theta}_{jj'}^{[g]} - \theta_{0,jj'}^{[g]}\| &\leq \frac{48s_j\gamma_n}{\psi} \\ \frac{1}{K} \sum_{k=1}^K \|\hat{\Omega}_y^k - \Omega_y^k\|_F &\leq O\left(\frac{\sqrt{S}\gamma_n}{\sqrt{K}}\right)\end{aligned}$$

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- 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

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The debiasing factor for the j^{th} 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}_j^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 $H_0 : \mathbf{b}_{0i}^1 = \mathbf{b}_{0i}^2$,
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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 i^{th} rows of the estimates $\hat{\mathbf{B}}^k$.
- We debias these row vectors using the neighborhood coefficients in the X-network computed previously using JSEM:

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

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

Result

Assume we have 'good enough' estimators:

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

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

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

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

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

$$\hat{\mathbf{C}}_i = \text{vec}(\hat{\mathbf{c}}_i^1, \dots, \hat{\mathbf{c}}_i^K)^T, \quad \mathbf{D}_i = \text{vec}(\mathbf{b}_{0i}^1, \dots, \mathbf{b}_{0i}^K)^T$$

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

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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

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

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

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

Besides controlling the type-I error at a specified level, the above testing procedure maintains rate optimal power, i.e. asymptotic power goes to 1 when $\|\mathbf{b}_{0i}^1 - \mathbf{b}_{0i}^2\| \geq O(n^{-1/2})$.

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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 $j = 1, \dots, q$:

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- 2 Obtain the threshold

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

- 3 For $j = 1, \dots, q$, reject H_0^{jj} if $|d_{ij}| \geq \hat{\tau}$.

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

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

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**

- Number of categories (K) = 5;
- Structured $\{\Omega_x\}, \{\Omega_y\}, \mathcal{B}$;
- Groups in \mathcal{B}, Ω_x are non-zero with probability $5/p$, and their elements come from $\text{Unif}[-1, -0.5] \cup [0.5, 1]$;
- Groups in Ω_y are non-zero with probability $5/q$, and their elements come from $\text{Unif}[-1, -0.5] \cup [0.5, 1]$;
- 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:

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

- 1 True positive Rate-

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

- 2 True negatives-

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

- 3 Relative error in Frobenius norm-

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

- 4 Matthews correlation coefficient (MCC).

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

(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.

(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.

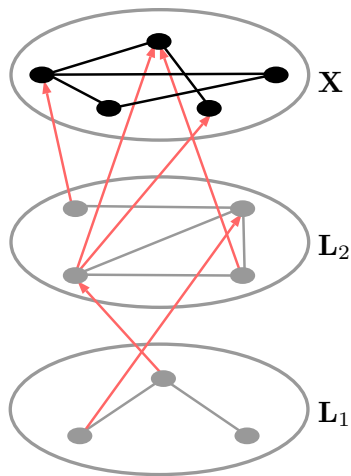
- Set $K = 2$, then randomly assign each element of \mathbf{B}_0^1 as non-zero w.p. π , then draw their values from $\text{Unif}\{[-1, -0.5] \cup [0.5, 1]\}$ independently.
- Generate a matrix of differences \mathbf{D} , where $(\mathbf{D})_{ij}$ takes values $-1, 1, 0$ w.p. $0.1, 0.1$ and 0.8 , respectively. 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.

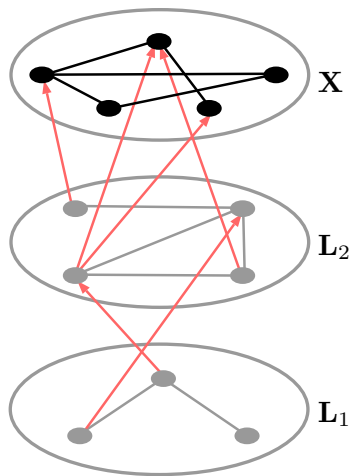
- Beyond pairwise testing: global and simultaneous tests for $K > 2$;
- Multi-level estimation and testing for model assumptions other than structured sparsity;
- Testing for complex high-dimensional models;
- Non-gaussian data;
- **Graphical models with non-linear interactions.**

Graphical models with non-linear interactions



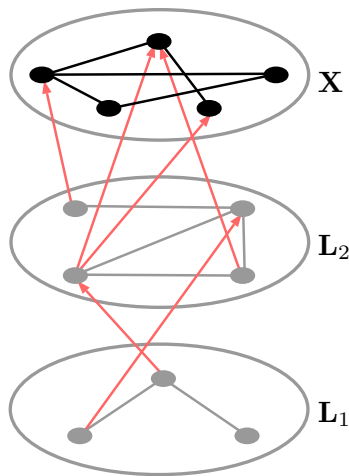
Graphical models with non-linear interactions

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



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



Graphical models with non-linear interactions

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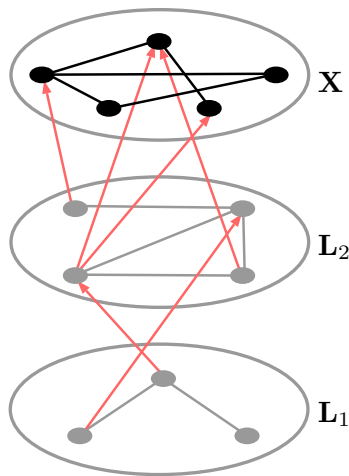
$$\mathbb{L}_1 = (L_{11}, \dots, L_{1r})^T \sim \mathcal{N}_r(\mathbf{0}, \Sigma_1);$$

$$\mathbb{L}_2 = \phi(\mathbb{L}_1^T \mathbf{B}) + \mathbb{E},$$

$$\mathbb{X} = \phi(\mathbb{L}_2^T \mathbf{C}) + \mathbb{F},$$

$$\mathbb{E} = (E_1, \dots, E_q)^T \sim \mathcal{N}_q(\mathbf{0}, \Sigma_2);$$

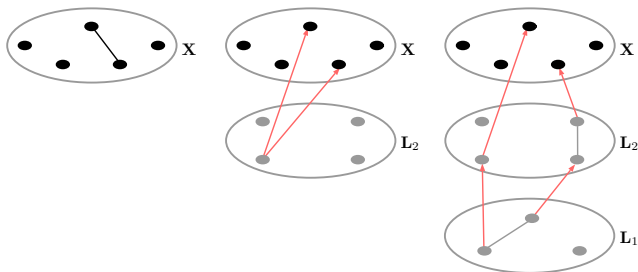
$$\mathbb{F} = (F_1, \dots, F_p)^T \sim \mathcal{N}_p(\mathbf{0}, \Sigma_x).$$



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.



- Monte-Carlo Sequential EM, backpropagation
- Theoretical properties of estimates

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

- Drton, M. and Perlman, M. D. (2007). Multiple Testing and Error Control in Gaussian Graphical Model Selection. *Statist. Sci.*, 22(3):430–449.
- Frey, B. J. and Hinton, G. E. (1999). Variational learning in nonlinear Gaussian belief networks. *Neural Comput.*, 11(1):193–213.
- Gligorijević, V. and Pržulj, N. (2015). Methods for biological data integration: perspectives and challenges. *J. R. Soc. Interface*, 12(112):20150571.
- Guo, J., Levina, E., Michailidis, G., and Zhu, J. (2011). Joint estimation of multiple graphical models. *Biometrika*, 98(1):1–15.
- Lin, J., Basu, S., Banerjee, M., and Michailidis, G. (2016). Penalized Maximum Likelihood Estimation of Multi-layered Gaussian Graphical Models. *J. Mach. Learn. Res.*, 17:5097–5147.
- 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.
- Meinshausen, N. and Bühlmann, P. (2006). High dimensional graphs and variable selection with the \tilde{A} lasso. *Ann. Statist.*, 34(3):1436–1462.
- Rezende, D. J., Mohamed, S., and Wierstra, D. (2014). Stochastic Backpropagation and Approximate Inference in Deep Generative Models. In *ICML Proceedings*, volume 32, pages 1278–1286.
- Zhang, C.-H. and Zhang, S. S. (2014). Confidence Intervals for Low Dimensional Parameters in High Dimensional Linear Models. *J. R. Statist. Soc. B*, 76:217–242.

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- Gligorijević, V. and Pržulj, N. (2015). Methods for biological data integration: perspectives and challenges. *J. R. Soc. Interface*, 12(112):20150571.
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- 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!