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

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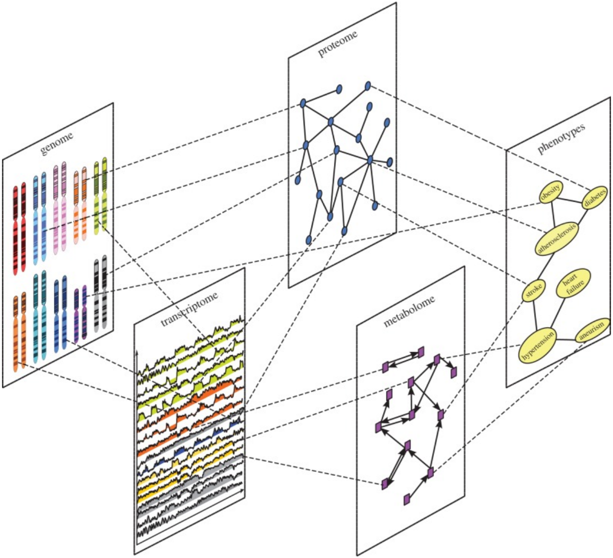
Summary

- 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;
- These connections can be different inside different organs, experimental conditions, or for different subtypes of the same disease;
- We design a framework for *joint estimation and hypothesis testing* for all the connections in these complex biological structure.

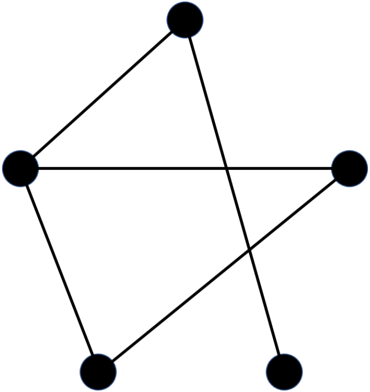
Schematic of data integration



(Source: Gligorijević and Pržulj (2015))

Outline

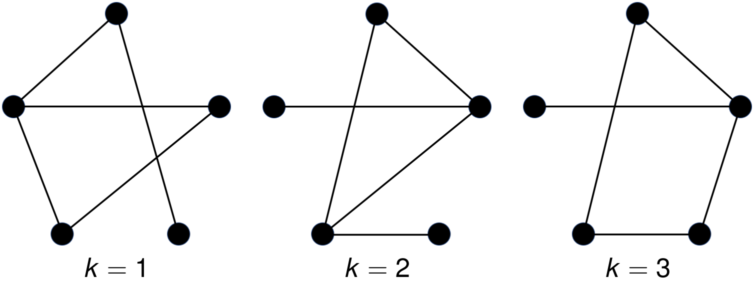
$$\mathbb{X} = (X_1, \ldots, X_p)^T \sim \mathcal{N}_p(0, \Sigma_x); \quad \Omega_x = \Sigma_x^{-1}$$



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

Multiple Gaussian Graphical models

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



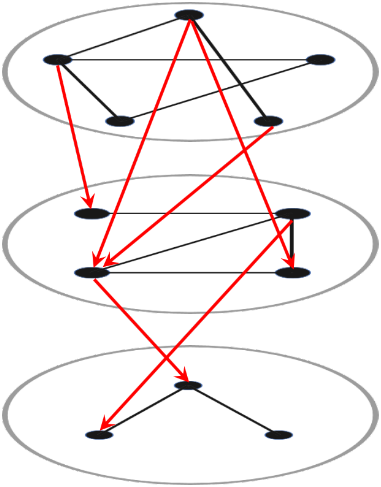
- Joint estimation of $\{\Omega_x^k\}$:
- Difference and similarity testing with FDR control: Liu (2017+)

Multi-Layered Gaussian Graphical models

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

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

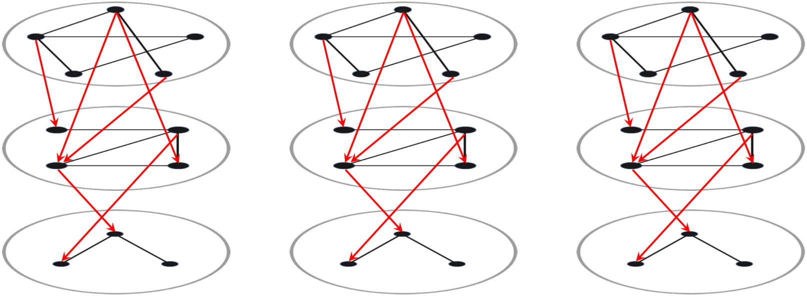
$\mathbb{Y} = \mathbb{X}\mathbf{B} + \mathbb{E}$



- 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

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



$k = 1$ $k = 2$ $k = 3$

- 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

Notations

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

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

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

  Can do this because $\zeta_{ii'} = -\omega_{ii'}/\omega_{ii}$.

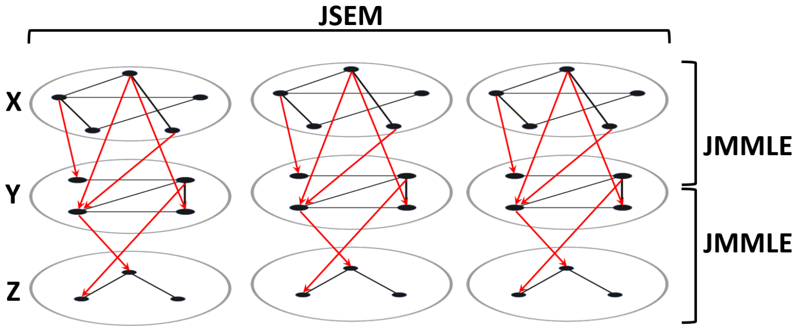
- **For multiple GGM**: Incorporate penalty across different k (JSEM: Ma and Michailidis (2016)).

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

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

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.



The JMMLE estimator

We combine sparse neighborhood selection in the Y-network with sparse estimation of $\{\mathbf{B}^k\}$.

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

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

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

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

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.

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

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

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

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

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 $\boldsymbol{\beta}_0$.

Error bounds for $\widehat{\Theta}, \widehat{\Omega}$

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

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

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

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

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

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

- 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 $\widehat{\mathbf{B}}^1$ and $\widehat{\mathbf{B}}^2$.
- 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

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

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

Assume we have 'good enough' estimators:

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

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

Also define

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

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

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

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

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

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

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

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

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

References

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THANK YOU!

Questions?