Sparse Gaussian graphical models for biological network inference

Julien Chiquet

Statistique et Génome, UMR CNRS 8071 - Université d’Évry Val-d’Essonne
Invited researcher at Statistique et Génome, UMR INRA 518 - AgroParisTech

NetBio – September the 12th, 2013
Outline

Introduction

Statistical framework: sparse GGM

GGM with latent structure

Inferring Multiple Graphical Structures

Multiattribute GGM
What the reconstructed networks are expected to be\(^1\) (1)

**Regulatory networks**

- relationships between gene and their products
- inhibition/activation
- impossible to recover at large scale
- always incomplete

\(^1\) and are presumably *wrongly* assumed to be
What the reconstructed networks are expected to be (2)

Regulatory networks

Figure: Regulatory network identified in mammalian cells: highly structured
What the reconstructed networks are expected to be (3)

Protein-Protein interaction networks

Figure: Yeast PPI network: do not be mislead by the representation, trust stat!
What the reconstructed networks are expected to be (3)
Protein-Protein interaction networks

Figure: Yeast PPI network: do not be mislead by the representation, trust stat!
What the reconstructed networks are expected to be (3)

Protein-Protein interaction networks

Figure: Yeast PPI network: do not be mislead by the representation, trust stat!
Why caring about network inference?

*Unraveling significant interactions at large scale* is impossible “manually”.

**Exploratory research**

- point out important molecules/pathways in an organism,
- giving further insight about the regulatory mechanisms,
- elucidation of gene/protein functions,

⇒ It helps at *formulating a hypothesis* for further wet lab experiment.
Why caring about network inference?

*Unraveling significant interactions at large scale* is impossible “manually”.

May plausibly help to understand the mechanisms of complex diseases or treatments.

- pointing important molecules/pathways in a organism,
- giving further insight about the regulatory mechanisms,
- elucidation of gene/protein functions,

⇝ It helps at formulating a hypothesis for further wet lab experiment.

Does not (and I do not think it will in close future) reconstruct a trustful regulatory network at large scale.
How is this measured?

Microarray technology: parallel measurement of many biological features

Focus e.g. on \textit{transcription}, looking toward \textit{gene regulatory networks}

DNA \rightarrow \text{transcription} \rightarrow RNA \rightarrow \text{TF}

Matrix of features $n \ll p$

Expression levels of $p$ probes are simultaneously monitored for $n$ individuals

$X = \begin{pmatrix}
  x_1^1 & x_1^2 & x_1^3 & \ldots & x_1^p \\
  \vdots & \vdots & \vdots & \ddots & \vdots \\
  x_n^1 & x_n^2 & x_n^3 & \ldots & x_n^p
\end{pmatrix}$
How is this measured?
Next Generation Sequencing: parallel measurement of even many more biological features

Focus e.g. on transcription, looking toward gene regulatory networks

Matrix of features $n \ll p$

Expression counts are extracted from small repeated sequences and monitored for $n$ individuals

$$X = \begin{pmatrix} k_1^1 & k_1^2 & k_1^3 & \ldots & k_1^p \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ k_n^1 & k_n^2 & k_n^2 & \ldots & k_n^p \end{pmatrix}$$
Summary of the problem at hand

1. Nodes (genes) are fixed
   - restricted to a set of interest (e.g., TF/target or via DA)
   Q: what if we missed some relevant actors?

2. Edges (regulations) are inferred
   - based upon statistical concepts
   Q: biological relevance?

Main statistical challenges

1. Ultra high dimensionality ($n \ll p$),
2. Heterogeneity of the data (noise, many techniques/signals/scales).

\[ \Rightarrow \text{Omic data is hopefully structured in many ways.} \]
Summary of the problem at hand

Inference

\[ \approx 10s/1000s \text{ assays} \]
\[ \approx 1000/100,000s \text{ features} \]

1. **Nodes (genes)** are fixed
   - restricted to a set of interest (e.g., TF/target or via DA)
   
   **Q:** what if we missed some relevant actors?

2. **Edges (regulations)** are inferred
   - based upon statistical concepts

   **Q:** biological relevance?

Main statistical challenges

1. **Ultra high dimensionality** \((n < p)\),
2. Heterogeneity of the data (noise, many techniques/signals/scales).

\[ \Rightarrow \text{Omic data is hopefully structured in many ways.} \]
Summary of the problem at hand

1. Nodes (genes) are fixed
   - restricted to a set of interest (e.g., TF/target or via DA)
   Q: what if we missed some relevant actors?

2. Edges (regulations) are inferred
   - based upon statistical concepts
   Q: biological relevance?

Main statistical challenges

1. high dimensionality,
2. Heterogeneity of the data (noise, many techniques/signals/scales).

⇝ Omic data is hopefully structured in many ways.
Summary of the problem at hand

1. Nodes (genes) are fixed
   - restricted to a set of interest (e.g., TF/target or via DA)
   Q: what if we missed some relevant actors?

2. Edges (regulations) are inferred
   - based upon statistical concepts
   Q: biological relevance?

Main statistical challenges

1. high dimensionality
2. Heterogeneity of the data (noise, many techniques/signals/scales).

→ Omic data is hopefully **structured** in many ways.
Outline

Introduction

Statistical framework: sparse GGM

GGM with latent structure

Inferring Multiple Graphical Structures

Multiattribute GGM
Gaussian Graphical Model: canonical settings

Microarrays in comparable Gaussian conditions

Profiles of a set $\mathcal{P} = \{1, \ldots, p\}$ of genes is described by $X \in \mathbb{R}^p$ such as

1. $X \sim \mathcal{N}(\mu, \Sigma)$, with $\Theta = \Sigma^{-1}$ the precision matrix.
2. a sample $(X^1, \ldots, X^n)$ of chips stacked in an $n \times p$ data matrix $X$.

Conditional independence structure

$(i, j) \notin E \iff X_i \perp \perp X_j \mid X\{i,j\} \iff \Theta_{ij} = 0$.

Graphical interpretation

$G = (\mathcal{P}, E)$

$X_1 \perp \perp X_2 \mid X_3 \perp \perp X_4 \mid X_5 \perp \perp X_6 \perp \perp X_7$

$\Rightarrow$ “Covariance” selection

The data

Stacking $(X^1, \ldots, X^n)$, we met the usual individual/variable table $X$

$\begin{pmatrix}
    x_{11} & x_{12} & x_{13} & \ldots & x_{1p} \\
    \vdots  & \vdots  & \vdots  & \ddots & \vdots \\
    x_{n1} & x_{n2} & x_{n3} & \ldots & x_{np}
\end{pmatrix}$
Gaussian Graphical Model: canonical settings

Microarrays in comparable Gaussian conditions

Profiles of a set $\mathcal{P} = \{1, \ldots, p\}$ of genes is described by $X \in \mathbb{R}^p$ such as

1. $X \sim \mathcal{N}(\mu, \Sigma)$, with $\Theta = \Sigma^{-1}$ the precision matrix.
2. a sample $(X^1, \ldots, X^n)$ of chips stacked in an $n \times p$ data matrix $X$.

Conditional independence structure

$$(i, j) \notin \mathcal{E} \iff X_i \independent X_j | X_{\{i,j\}} \iff \Theta_{ij} = 0.$$ 

Graphical interpretation

$$\mathcal{G} = (\mathcal{P}, \mathcal{E})$$

$\implies$ “Covariance” selection
Gene expression $X_i$ is linearly explained by the other genes:

$$X_i | X_{\setminus i} = - \sum_{j \neq i} \frac{\Theta_{ij}}{\Theta_{ii}} X_j + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, \sigma_i), \quad \varepsilon_i \perp X$$

Conditional on its neighborhood, other profiles do not give additional insights

$$X_i | X_{\setminus i} = \sum_{j \in \text{neighbors}(i)} \beta_j X_j + \varepsilon_i \quad \text{with} \quad \beta_j = -\frac{\Theta_{ij}}{\Theta_{ii}}.$$
Gaussian Graphical Model and Linear Regression

Linear regression viewpoint

Gene expression $X_i$ is linearly explained by the other genes':

$$X_i | X \setminus_i = - \sum_{j \neq i} \frac{\Theta_{ij}}{\Theta_{ii}} X_j + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, \sigma_i), \quad \varepsilon_i \perp X$$

Conditional on its neighborhood, other profiles do not give additional insights:

$$X_i | X \setminus_i = \sum_{j \in \text{neighbors}(i)} \beta_j X_j + \varepsilon_i$$

with $\beta_j = -\Theta_{ij} / \Theta_{ii}$.

Graphical Interpretation

Local Markov property conditioning on the neighborhood

Global Markov property conditioning on a separating node
Gold standard penalized approaches
Use $\ell_1$ for both regularizing and promoting sparsity

Penalized likelihood (Banerjee et al., Yuan and Lin, 2008)

$$\hat{\Theta}_\lambda = \arg \max_{\Theta \in S_+} \ell(\Theta; X) - \lambda \|\Theta\|_1$$

- symmetric, positive-definite
- solved by the “Graphical-Lasso” ($O(p^3)$, Friedman et al., 2007).

Neighborhood Selection (Meinshausen & Bühlman, 2006)

$$\hat{\beta}^{(i)} = \arg \min_{\beta \in \mathbb{R}^{p-1}} \frac{1}{n} \|X_i - X_{\setminus i}\beta\|_2^2 + \lambda \|\beta\|_1$$

CLIME – Pseudo-likelihood (Cai et al., 2011; Yuan, 2010)

$$\hat{\Theta} = \arg \min_{\Theta} \|\Theta\|_1 \text{ subjected to } \|n^{-1}X^tX\Theta - I\|_{\infty} \leq \lambda$$
Gold standard penalized approaches
Use $\ell_1$ for both regularizing and promoting sparsity

Penalized likelihood (Banerjee et al., Yuan and Lin, 2008)

$$\hat{\Theta}_\lambda = \arg \max_{\Theta \in S_+} \ell(\Theta; X) - \lambda \|\Theta\|_1$$

Neighborhood Selection (Meinshausen & Bühlman, 2006)

$$\hat{\beta}^{(i)} = \arg \min_{\beta \in \mathbb{R}^{p-1}} \frac{1}{n} \left\| X_i - X_{\setminus i} \beta \right\|^2_2 + \lambda \|\beta\|_1$$

- not symmetric, not positive-definite
+ $p$ Lasso solved with Lars-like algorithms ($O(npd)$ for $d$ neighbors).

CLIME – Pseudo-likelihood (Cai et al., 2011; Yuan, 2010)

$$\hat{\Theta} = \arg \min_{\Theta} \|\Theta\|_1 \text{ subjected to } \left\| n^{-1} X^t X \Theta - I \right\|_\infty \leq \lambda$$
Gold standard penalized approaches
Use $\ell_1$ for both regularizing and promoting sparsity

Penalized likelihood (Banerjee et al., Yuan and Lin, 2008)

$$\hat{\Theta}_\lambda = \arg \max_{\Theta \in \mathbb{S}_+} \ell(\Theta; X) - \lambda \|\Theta\|_1$$

Neighborhood Selection (Meinshausen & Bühlman, 2006)

$$\hat{\beta}^{(i)}(\beta) = \arg \min_{\beta \in \mathbb{R}^{p-1}} \frac{1}{n} \|X_i - X_{\setminus i} \beta\|_2^2 + \lambda \|\beta\|_1$$

CLIME – Pseudo-likelihood (Cai et al., 2011; Yuan, 2010)

$$\hat{\Theta} = \arg \min_{\Theta} \|\Theta\|_1 \text{ subjected to } \|n^{-1}X^tX\Theta - \mathbf{I}\|_\infty \leq \lambda$$

- not positive-definite
+ $p$ linear programs easily distributed ($O(p^2d)$ for $d$ neighbors).
Gold standard penalized approaches

Use $\ell_1$ for both regularizing and promoting *sparsity*

Penalized likelihood (Banerjee *et al.*, Yuan and Lin, 2008)

$$
\hat{\Theta}_\lambda = \arg \max_{\Theta \in \mathbb{S}_+} \ell(\Theta; X) - \lambda \| \Theta \|_1
$$

Variants and recent improvements

'13 NIPS submissions

- Use square-root Lasso in place of Lasso for tuning insensitive property package
- Solve CLIME for $p = 10^6$ (on 400 cores).

See R package `huge, fastclime, flare, QUIC`.
Practical implications of theoretical results

Selection consistency (Ravikumar, Wainwright, 2009-2012)

Denote $d = \max_{j \in \mathcal{P}}(\text{degree}_j)$. Consistency for an appropriate $\lambda$ and

- $n \approx \mathcal{O}(d^2 \log(p))$ for the graphical Lasso and Clime.
- $n \approx \mathcal{O}(d \log(p))$ for neighborhood selection (sharp).

(Irrepresentability) conditions are not strictly comparable...

Ultra high-dimension phenomenon (Verzelen, 2011)

Minimax risk for sparse regression with $d$-sparse models: useless when

$$\frac{d \log(p/d)}{n} \geq 1/2,$$

(e.g., $n = 50$, $p = 200$, $d \geq 8$).

Good news! when $n$ is small, we don’t need to solve huge problems because they can’t but fail.
Practical implications of theoretical results

Selection consistency (Ravikumar, Wainwright, 2009-2012)

Denote $d = \max_{j \in \mathcal{P}}(\text{degree}_j)$. Consistency for an appropriate $\lambda$ and

$\blacktriangleright \ n \approx O\left(d^2 \log(p)\right)$ for the graphical Lasso and Clime.

$\blacktriangleright \ n \approx O\left(d \log(p)\right)$ for neighborhood selection (sharp).

(Irrepresentability) conditions are not strictly comparable...

Ultra high-dimension phenomenon (Verzelen, 2011)

Minimax risk for sparse regression with $d$-sparse models: useless when

$$\frac{d \log(p/d)}{n} \geq 1/2, \quad (\text{e.g., } n = 50, p = 200, d \geq 8).$$

**Good news! when $n$ is small, we don’t need to solve huge problems because they can’t but fail.**
Model selection

Cross-validation

Optimal in terms of **prediction**, not in terms of selection

Information based criteria

Since, $\text{df}(\hat{\beta}^{\text{lasso}}) = \left\| \hat{\beta}^{\text{lasso}} \right\|_0$ (Zou, Hastie, 2008)

- Straightforward application of BIC/AIC
- Adaptation for the sparse high dimensional problem (eBIC, AICc, ...),
- GGMS elect (Girault *et al.*, ’12) selects among a family of candidates.

Stability selection (Meinshausen and Bühlman, 2010, Bach 2008)

Keep edges frequently selected on a range of $\lambda$ after sub-samplings

+ Selecting “the” right $\lambda$ is not a problem anymore
+ Works well for network inference (see Haury *et al.* 2012).
Limitations towards biological network inference

- Sparse GGM
  - very solid statistical and computational framework
  - extend to non strictly normal distribution (NGS)

  - competitive to other inference methods
  - performances remain questionable on real data, as for other methods

Idea: try to take into account biological/data features

1. structure of the network (organization of biological mechanisms)
2. sample heterogeneity (patient heterogeneity)
3. horizontal integration (use multiple data and platforms)

Illustration on cancer data sets.
Outline

Introduction

Statistical framework: sparse GGM

GGM with latent structure

Inferring Multiple Graphical Structures

Multiattribute GGM
Handling with the data structure and scarcity

By introducing some prior

Priors should be biologically grounded

1. no too many genes effectively interact: \textit{sparsity},
2. networks are organized: \textit{latent clustering}. 
Structured regularization

SIMoNe: Statistical Inference for MOdular NEtworks

\[
\arg \max_{\Theta, Z} \ell(\Theta; X) - \lambda \| P_Z \star \Theta \|_{\ell_1},
\]

where \( P_Z \) is a matrix of weights depending on a underlying latent structure \( Z \) (depicted through a stochastic block model).

\( \rightsquigarrow \) Cluster-driven inference via an EM-like strategy.


Chiquet et al., SIMoNe R-package (needs updates...), Note Bioinformatics, 2009.
Structured regularization
“Bayesian” interpretation of $\ell_1$ regularization

Laplacian prior on $\Theta$ depends on the clustering $Z$

$$P(\Theta|Z) \propto \prod_{i,j} \exp \left\{ -\lambda \cdot P_{ij}^Z \cdot |\Theta_{ij}| \right\}. $$

$P_Z$ summarizes prior information on the position of edges
How to come up with a latent clustering?

Biological expertise

- Build $\mathbf{Z}$ from prior biological information
  - transcription factors vs. regulatees,
  - number of potential binding sites,
  - KEGG pathways, . . .

- Build the weight matrix from $\mathbf{Z}$.

Inference: Erdős-Rényi Mixture for Networks
(Daudin et al., 2008; Latouche et al., 2011)

- Equivalent to the Stochastic Bloc Model (SBM);
- Spread the nodes into $Q$ classes;
- Connexion probabilities depend upon node classes:
  \[ \Pr(i \leftrightarrow j | i \in \text{class } q, j \in \text{class } \ell) = \pi_{q\ell}. \]

- Build $P_{\mathbf{Z}} \propto 1 - \pi_{q\ell}$. 
Learning scheme

Suppose you want to recover a clustered network:

Target Adjacency Matrix

Target Network
Learning scheme

Start with microarray data
Learning scheme

- Inference without prior
- Data
- Adjacency Matrix corresponding to $G^*$
Learning scheme

- Penalty matrix $P_z$
- Decreasing transformation
- Adjacency matrix corresponding to $G^*$
- Inference without prior
- Connectivity matrix $\pi Z$
- Mixer

Data

SIMoNE
Learning scheme

Inference with clustered prior

Data + Mixer

Penalty matrix $P_Z$

Decreasing transformation

Connectivity matrix $\pi_Z$

Adjacency Matrix corresponding to $G^*$

Adjacency Matrix corresponding to $G^*_Z$
Illustration on breast Cancer
Prediction of the outcome of preoperative chemotherapy

Hess et al.

Data set
133 patients classified as
1. pathologic complete response,
2. residual disease,
according to a signature of 26 genes (small network).

Figure: Pooling the data, Neighborhood Selection
Data set

1. pathologic complete response,
2. residual disease,

according to a signature of 26 genes (small network).

Figure: Pooling the data, SIMoNE with clustering
Outline

Introduction

Statistical framework: sparse GGM

GGM with latent structure

Inferring Multiple Graphical Structures

Multiattribute GGM
Handling the scarcity of data

Merge several experimental conditions

condition 1

condition 2

condition 3

Multiple inference of GGM

$$\arg \max_{\Theta^{(c)}, c=1, \ldots, C} \sum_{c=1}^{C} \ell(\Theta^{(c)}; S^{(c)}) - \lambda \text{ pen}_1(\Theta^{(c)}).$$
Handling the scarcity of data

Inferring each graph \textit{independently} does not help

**condition 1**

\[
(X_{1}^{(1)}, \ldots, X_{n_1}^{(1)})
\]

**condition 2**

\[
(X_{1}^{(2)}, \ldots, X_{n_2}^{(2)})
\]

**condition 3**

\[
(X_{1}^{(3)}, \ldots, X_{n_3}^{(3)})
\]

Multiple inference of GGM

\[
\sum_{c=1}^{C} \ell(\Theta(c); S(c)) - \lambda \text{pen} \ell_1(\Theta(c))
\]
Handling the scarcity of data

By pooling all the available data (like we just have with Hess’ data set)

condition 1

condition 2

condition 3

\[(X_1, \ldots, X_n), \, n = n_1 + n_2 + n_3.\]

Multiple inference of GGM
Handling the scarcity of data

By breaking the separability

condition 1

\[(X^{(1)}_1, \ldots, X^{(1)}_{n_1})\]

inference

condition 2

\[(X^{(2)}_1, \ldots, X^{(2)}_{n_2})\]

inference

condition 3

\[(X^{(3)}_1, \ldots, X^{(3)}_{n_3})\]

inference

Multiple inference of GGM

\[\arg\max_{\Theta} \sum_{c=1}^{C} \ell(\Theta(c); S(c)) - \lambda \text{pen} \ell_1(\Theta(c))\]
Handling the scarcity of data

By breaking the separability

condition 1

\[(X_1^{(1)}, \ldots, X_{n_1}^{(1)})\]

inference

condition 2

\[(X_1^{(2)}, \ldots, X_{n_2}^{(2)})\]

inference

condition 3

\[(X_1^{(3)}, \ldots, X_{n_3}^{(3)})\]

inference

Multiple inference of GGM

\[
\arg \max_{\Theta^{(c)}, c=1\ldots,C} \sum_{c=1}^{C} \ell(\Theta^{(c)}; S^{(c)}) - \lambda \text{ pen}_{\ell_1}(\Theta^{(c)}).
\]
Break the separability

Joint the optimization problem by either modifying

$$\arg \max_{\Theta^{(c)}, c=1,...,C} \sum_{c=1}^{C} \tilde{\ell}(\Theta^{(c)}; \tilde{S}^{(c)}) - \lambda \text{pen}_{\ell_1}(\Theta^{(c)}).$$

1. the fitting term
2. the regularization term
A multitask approach  
Chiquet, Grandvalet, Ambroise, Statistics and Computing 2010/11

Break the separability

Joint the optimization problem by either modifying

$$\arg \max_{\Theta^{(c)}, c=1,..., C} \sum_{c=1}^{C} \tilde{\ell}(\Theta^{(c)}; \tilde{S}^{(c)}) - \lambda \text{pen} \ell_1(\Theta^{(c)}).$$

1. the fitting term
2. the regularization term

Intertwined-Lasso

- $\overline{S} = \frac{1}{n} \sum_{t=1}^{T} n_t S^{(t)}$ is the “pooled-tasks” covariance matrix.
- $\tilde{S}^{(t)} = \alpha S^{(t)} + (1 - \alpha) \overline{S}$ is a mixture between specific and pooled covariance matrices.
A multitask approach
Chiquet, Grandvalet, Ambroise, Statistics and Computing 2010/11

Break the separability

Joint the optimization problem by either modifying

$$\arg \max_{\Theta^{(c)}, c=1\ldots,C} \sum_{c=1}^{C} \tilde{\ell}(\Theta^{(c)}; \tilde{S}^{(c)}) - \lambda \text{ pen}_{\ell_1}(\Theta^{(c)}).$$

1. the fitting term
2. the regularization term

Sparsity with grouping effect

- Group-Lasso (Yuan and Lin 2006, Grandvalet and Canu, 1998),
- Cooperative-Lasso (Chiquet et al, AoAS, 2012),
Grouping effects induced

Potential groups

Group-Lasso

Cooperative-Lasso

Group(s) induced by edges (1, 2)
Grouping effects induced

**Recent works**

- Use Fused-Lasso, sparse group-Lasso
- Adapted several time to the **Graphical Lasso framework**
  - See, e.g. D. Witten’s team works.
  - The multitask/neighborhood selection’s approach remains competitive.

- Promising manuscript (Mohan et al. arXiv, 2013)
  - Networks differences are only due to **perturbations at the node level**.
  - For instance, a hub is encouraged to be shared across tasks.
Revisiting the Hess et al. data set

**Figure:** Cooperative-Lasso applied on the two sets of patients (PCR/noPCR). Bold edges are different in the finally selection graph.
Application: ER status in Breast cancer

Dataset: 466 patients with breast cancer provided by Guedj et al.,

Objective: identify changes in regulatory mechanisms

- $\text{ER}^+ / \text{ER}^-$: breast cancer growth stimulated by estrogen hormones,
- $\text{ER}^+$ tackled with anti-hormonal therapies,
- $\text{ER}^-$ found clinically more aggressive.

Application: ER status in Breast cancer
Network inference with cooperative-Lasso on 200 candidate genes (partial view)

Figure: The dashed black edges are inferred only under the ER- condition and the solid black edges are only predicted under the ER+ condition. Gray are common to both conditions.
Application: ER status in Breast cancer
Network inference with the cooperative-Lasso fits known anti-apoptotic mechanisms

Figure: Most edges are supported by the literature (except two)
Outline

Introduction

Statistical framework: sparse GGM

GGM with latent structure

Inferring Multiple Graphical Structures

Multiaattribute GGM
Why Multi-attribute Networks?
Joint work with E. Kolaczyk (Boston) and C. Ambroise (Évry)

Data integration

- Omic technologies can profile cells at different levels: DNA, RNA, protein, chromosomal, and functional.
- multiple molecular profiles combined on the same set of biological samples can be synergistic.

Remark: *a close independent work of Kolar and Xing appeared late 2012...*
Multiattribute GGM

Consider e.g. some $p$ genes of interest and the $K = 2$ omic experiments

1. $X_{i1}$ is the expression profile of gene $i$ (transcriptomic data),
2. $X_{i2}$ is the corresponding protein concentration (proteomic data).

Define a block-wise precision matrix

- $X = (X_1, \ldots, X_p)^T \sim \mathcal{N}(\mathbf{0}, \Sigma)$ in $\mathbb{R}^{pK}$,
- $X_i = (X_{i1}, \ldots, X_{iK})^\top \in \mathbb{R}^K$.

$$\Theta = \Sigma^{-1} = \begin{bmatrix} \Theta_{11} & \Theta_{1p} \\ \vdots & \ddots \\ \Theta_{p1} & \Theta_{pp} \end{bmatrix}, \quad \Theta_{ij} \in \mathcal{M}_{K,K}, \forall (i,j) \in \mathcal{P}^2.$$

Graphical Interpretation

Define $\mathcal{G} = (\mathcal{P}, \mathcal{E})$ as the multivariate analogue of the conditional graph:

$$(i, j) \in \mathcal{E} \iff \Theta_{ij} \neq 0_{KK}.$$
Multiattribute GGM as Multivariate regression

Multivariate analysis viewpoint

Straightforward algebra and we have

\[ X_i \mid X_{\bar{i}} = x \sim \mathcal{N} \left( -\Theta_{ii}^{-1} \Theta_{i\bar{i}} x, \Theta_{ii}^{-1} \right) . \]

or equivalently, letting \( B_i^T = -\Theta_{ii}^{-1} \Theta_{i\bar{i}} \),

\[ X_i \mid X_{\bar{i}} = B_i^T X_{\bar{i}} + \epsilon_i, \quad \epsilon_i \sim \mathcal{N}(0, \Theta_{ii}^{-1}), \quad \epsilon_i \perp X. \]

Remembering the univariate case?

\[ X_i \mid X_{\bar{i}} = - \sum_{j \in \text{neighbors}(i)} \frac{\Theta_{ij}}{\Theta_{ii}} X_j + \epsilon_i, \quad \epsilon_i \sim \mathcal{N}(0, \Sigma_{ii}), \quad \epsilon_i \perp X. \]
So once the data set as been carefully reshaped...

The Data

\[
X = \begin{bmatrix}
  x^1 \\
  \vdots \\
  x^N
\end{bmatrix} = \begin{bmatrix}
  X_1 & \cdots & X_p
\end{bmatrix} =
\begin{bmatrix}
  x_1^1 & \cdots & x_1^p \\
  \vdots \\
  x_N^1 & \cdots & x_N^p
\end{bmatrix} =
\begin{bmatrix}
  x_{11} & x_{1K} & \cdots & x_{11} & x_{1K} & \cdots & x_{1pK} \\
  \vdots \\
  x_{N1} & x_{NK} & \cdots & x_{N1} & x_{NK} & \cdots & x_{NK}
\end{bmatrix},
\]

- \(x^n\), is a \(pK\)-size row vector containing the data related to the \(n\)th individual.
- \(X_i \in \mathcal{M}_{N,K}\) is \(N \times K\) block matrix containing the data related to the \(i\)th gene.
Multivariate Neighborhood selection

The penalized multivariate regression approach

For each node /gene, recover its neighborhood by solving

$$\arg\min_{B_i \in \mathcal{M}_{(p-1)K,K}} \frac{1}{2N} \left\| X_i - X_{\setminus i} B_i \right\|_F^2 + \lambda \Omega(B_i),$$

Choice of Penalty

Group-based penalty to activate the set of attributes simultaneously on a given link:

$$\Omega(B_i) = \sum_{j \in \mathcal{P} \setminus i} \| B_{ij} \|, \quad B_{ij} \in \mathcal{M}_{KK}$$

- $\| M \| = \| M \|_F = \left( \sum_{i,j} M_{ij}^2 \right)^{1/2}$, the Frobenius norm,
- $\| M \| = \| M \|_\infty = \max_{i,j} |M_{ij}|$, the sup norm (shared magnitude),
- $\| M \| = \| M \|_\star = \sum \text{eig}(M)$, the nuclear norm (rank penalty).
Simulation Study Design

Small study, set up as follows.

1. Simulation of an Erdős-Renyi graph;
2. Expand the adjacency matrix to multivariate space
   \[ A = (A + I) \otimes I_{K \times K}; \]
3. Compute \( \Theta \) a positive definite approximation of \( A \) by replacing null and negative eigenvalues by a small constant
4. \( \Theta = \Theta + \gamma I \) with \( \gamma \) a parameter controlling the difficulty of the problem;
5. Draw an i.i.d. sample \( X \) of \( X \sim \mathcal{N}(0, \Sigma) \).
Simulation Results

Aggregation improves upon single-attribute methods for learning networks

Settings

- $K=2$ attributes
- $p = 20$ (small networks),
- 20 edges on average,
- vary $n$ from $p/2$ to $2p$,
- AUC averaged over 50 runs.
Simulation Results

Aggregation improves upon single-attribute methods for learning networks

Settings

- \( K=4 \) attributes
- \( p = 20 \) (small networks),
- 20 edges on average,
- vary \( n \) from \( p/2 \) to \( 2p \),
- AUC averaged over 50 runs.
Illustration on the NCI-60 data set
Molecular profile data on a panel of 60 diverse human cancer cell lines

1. **Protein**: reverse-phase lysate arrays (RPLA) for 92 antibodies;
2. **Gene**: Human Genome U95 affymetrix (∼ 9,000 genes).

⇝ consensus set with 91 protein and corresponding gene profiles.

Jaccard’s similarity index

\[ J(A, B) = \frac{|A \cap B|}{|A \cup B|} \]

⇝ multiattribute network shares a high Jaccard index with both uni attribute networks.
Illustration: Three Types of Regulatory Networks

- **multi attribute**
  - gene + protein
- **attribute 1**
  - gene
- **attribute 2**
  - protein
Illustration: Three Types of Regulatory Networks

- **Multi attribute**
  - gene + protein

- **Attribute 1 & 2**
  - gene AND protein

- **Attribute 1 | 2**
  - gene OR protein
Conclusion

Sparse Gaussian Graphical Model

Well established framework with a vast, growing literature

1. Nice modeling tool (conditional dependencies),
2. Good theoretical framework (which I have not much talked about),
3. Powerful algorithms (screening, first-order, homotopy)
   - that scale the dimension (large \( p \) large \( n \))
   - that allow resampling/parallelization (for robustness)

\( \Rightarrow \) Great tool for covariance estimation/selection in a reasonably high dimensional settings.

Still...  

- phenomena are quite complex: a biological interaction is not even well defined  
- more data is coming...

\( \Rightarrow \) Need for methods with data integration and to solve couple problems
Perspectives/Ongoing work
Joint network inference to the estimation of a related biological feature

Enhance network reconstruction by simultaneously identifying TF

Knowledge of TF is crucial to achieve good network reconstruction

Haury et al., BMC Bioinformatics, 2012.

⇝ With S. Robin, we are working on TF elucidation at large scale from transcriptomic data through penalized multivariate regression.

Couple differential analysis (DA) to network inference

Introducing network knowledge is of great benefit for DA


⇝ With P. Gutierrez and G. Rigaill we proposed fused-ANOVA, a penalized model for differential analysis

⇝ A unifying convex method is planed to be part of Trung Ha’s PhD Thesis (with Guillem and M-L Martin-Magnette).
Thanks

To you *for your patience* and for listening...

Co-authors

C. Ambroise  
PU, Évry

C. Charbonnier  
PhD, Inserm

M. Jeanmougin  
PhD, Curie

Y. Grandvalet  
DR, Compiègne

C. Matias  
DR, Évry

Co-Workers

S. Robin  
DR, AgroParis

E. Kolaczyk  
PU, Boston

P. Gutierrez  
M2, PhD?

G. Rigaill  
MCF, Évry