An introduction to graph analysis and modeling
Topology Inference

MSc in Statistics for Smart Data – ENSAI

Autumn semester 2017

http://julien.cremeriefamily.info

Introduction

first two courses: Analysis of an existing, observed network

- $\rightsquigarrow$ basic characterization
- $\rightsquigarrow$ find an underlying organization (clustering)

Today: reconstruct (infer) a network from external data

Become familiar with

- Gaussian graphical models,
- sparse inference methods (ℓ_1-regularization *a.k.a* the Lasso).

Canonical example: Genomic data

We consider examples from life science, but everything said extends to

- Sociology, Astrophysics, Stock exchange, Insurance data, ...
- ...any multivariate data.

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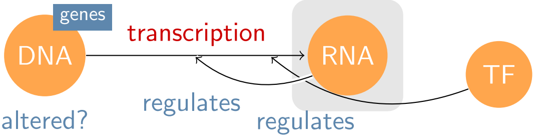
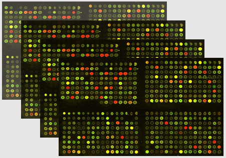
Omic: parallel measurement of many biological features

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



signal processing



Matrix of features $n \ll p$

Expression levels of p probes are simultaneously monitored for n individuals

pretreatment

$$\mathbf{X} = \begin{pmatrix} x_1^1 & x_1^2 & x_1^3 & \dots & x_1^p \\ \vdots & & & & \\ x_n^1 & x_n^2 & x_1^2 & \dots & x_n^p \end{pmatrix}$$

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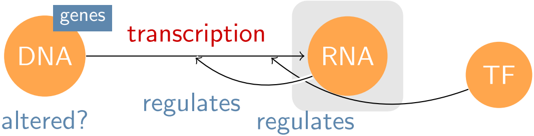
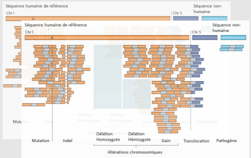


assembling



Matrix of features $n \lll p$

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

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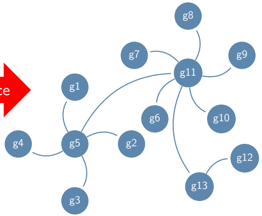
$$\mathbf{X} = \begin{pmatrix} k_1^1 & k_1^2 & k_1^3 & \dots & k_1^p \\ \vdots & & & & \\ k_n^1 & k_n^2 & k_1^2 & \dots & k_n^p \end{pmatrix}$$

Network inference: a challenging problem

$\approx$ 10s/1,000s assays

$\approx$ 1,000s/1,000,000s features

Inference



1. Nodes are fixed
   - restricted to a set of interest
2. Edges (interactions) are inferred
   - based upon statistical concepts

Statistical question

1. Variable selection (which edges?)

Main statistical challenges

1. (Ultra) High dimensionality ($n < p$, $n \lll p$)
2. Heterogeneity/structure of the data

Outline

1. Network and data modeling
   - Statistical dependence
   - Gaussian Graphical models
2. Network Inference
   - Inducing sparsity for edge selection
   - Limitations and extensions of sparse GGM
   - Example: plasmodium data set

Outline

References

- Graphical Models in Applied Multivariate Statistics, Joe Whittaker
- Graphical Models, S. Lauritzen

Outline

Modeling relationship between variables

Independence

Definition (Independence of events)

Two events A and B are independent if and only if

$$\mathbb{P}(A, B) = \mathbb{P}(A)\mathbb{P}(B),$$

which is usually denoted by $A \perp\!\!\!\perp B$. Equivalently,

- $A \perp\!\!\!\perp B \Leftrightarrow \mathbb{P}(A|B) = \mathbb{P}(A)$,
- $A \perp\!\!\!\perp B \Leftrightarrow \mathbb{P}(A|B) = \mathbb{P}(A|B^c)$

Example (class vs party)

	party	
class	Labour	Tory
working	0.42	0.28
bourgeoisie	0.06	0.24

	party	
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Table: Joint probability (left) vs. conditional probability (right)

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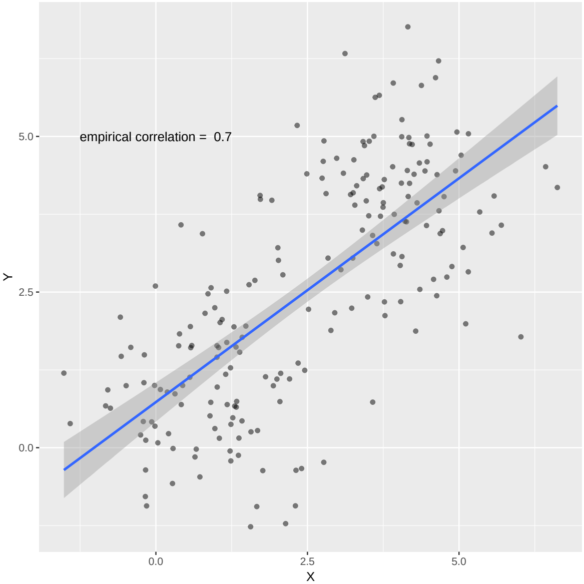
Limits of correlation for network reconstruction



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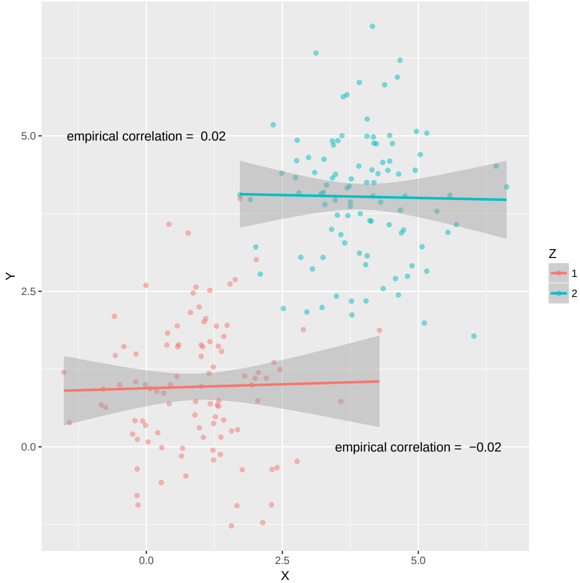

Modeling relationships between variables (2)

Conditional independence

Generalizing to more than two events requires strong assumptions (mutual independence). Better handle with

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Example (Does QI depends on weight?)

Consider the events $A =$ "having low QI", $B =$ "having low weight".

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Example (Does QI depends on weight?)

Consider the events $A =$ "having low QI", $B =$ "having low weight". Estimating[1] $\mathbb{P}(A, B)$, $\mathbb{P}(A)$ and $\mathbb{P}(B)$ in a sample would lead to

$$\mathbb{P}(A, B) \neq \mathbb{P}(A)\mathbb{P}(B)$$

Modeling relationships between variables (2)

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Example (Does QI depends on weight?)

Consider the events $A =$ "having low QI", $B =$ "having low weight". But in fact, introducing $C =$ "having a given age",

$$\mathbb{P}(A, B|C) = \mathbb{P}(A|C)\mathbb{P}(B|C)$$

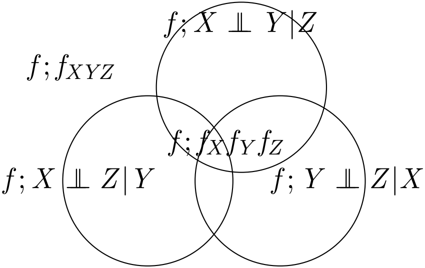
(Conditional) independence of random vectors

A "natural" generalization

Definition

Consider 3 random variables X, Y, Z with distribution f_X, f_Y, f_Z, jointly f_{XY}, f_{XYZ}. Then,

- X and Y are independent iif $f_{XY}(x, y) = f_X(x) f_Y(y)$;
- X and Y are conditionally independent on Z, $z : f_Z(z) > 0$ iif $f_{XY|Z}(x, y; z) = f_{X|Z}(x; z) f_{Y|Z}(y; z)$.



Outline

Graphical models

Definition

A graphical model gives a graphical (intuitive) representation of the dependence structure of a probability distribution, by linking

1. a random vector (or a set of random variables.) $X = \{X_1, \dots, X_p\}$ with distribution $\mathbb{P}$,

2. a graph $\mathcal{G} = (\mathcal{P}, \mathcal{E})$ where
   - $\mathcal{P} = \{1, \dots, p\}$ is the set of nodes associated to each variable,
   - $\mathcal{E}$ is a set of edges describing the dependence relationship of $X \sim \mathbb{P}$.

Definition

The conditional independence graph of a random vector X is the undirected graph $\mathcal{G} = \{\mathcal{P}, \mathcal{E}\}$ with the set of node $\mathcal{P} = \{1, \dots, p\}$ and where

$$(i, j) \notin \mathcal{E} \Leftrightarrow X_i \perp X_j | \mathcal{P} \backslash \{i, j\}.$$

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Conditional Independence Graphs

An example

Let X_1, X_2, X_3, X_4 be four random variables with joint probability density function $f_X(x) = \exp(u + x_1 + x_1 x_2 + x_2 x_3 x_4)$ with u a given constant.

Apply the factorization property

$$
\begin{aligned}
f_X(x) &= \exp(u + x_1 + x_1 x_2 + x_2 x_3 x_4) \\
&= \exp(u) \ \cdot \ \exp(x_1 + x_1 x_2) \ \cdot \ \exp(x_2 x_3 x_4)
\end{aligned}
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Graphical representation

$\mathcal{G} = (\mathcal{P}, \mathcal{E})$ such as $\mathcal{P} = \{1, 2, 3, 4\}$ and

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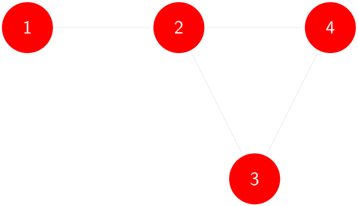

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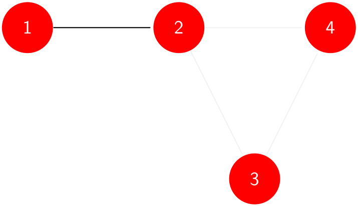

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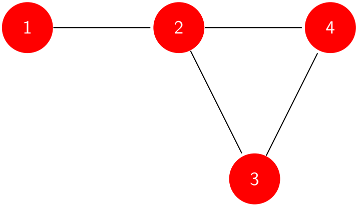
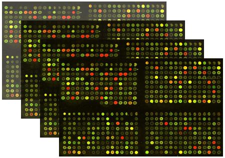


The Gaussian case

The data



Inference

$$\mathbf{X} = \begin{pmatrix} x_1^1 & x_1^2 & x_1^3 & \dots & x_1^p \\ \vdots & & & & \\ x_n^1 & x_n^2 & x_1^2 & \dots & x_n^p \end{pmatrix}$$

Assuming $f_X(\mathbf{X})$ multivariate Gaussian

Greatly simplifies the inference:

- ⇝ naturally links independence and conditional independence to the covariance and partial covariance,
- ⇝ gives a straightforward interpretation to the graphical modeling previously considered.

Why Gaussianity helps?

Case of 2 variables or size-2 random vector

Definitions (Let X, Y be two real random variables.)

$$\mathrm{cov}(X, Y) = \mathbb{E}\Big[\big(X - \mathbb{E}(X)\big)\big(Y - \mathbb{E}(Y)\big)\Big] = \mathbb{E}(XY) - \mathbb{E}(X)\mathbb{E}(Y).$$

$$\rho_{XY} = \mathrm{cor}(X, Y) = \frac{\mathrm{cov}(X, Y)}{\sqrt{\mathbb{V}(X) \ \cdot \ \mathbb{V}(Y)}}.$$

Proposition

- $\mathrm{cov}(X, X) = \mathbb{V}(X) = \mathbb{E}[(X - \mathbb{E}X)(Y - \mathbb{E}Y)]$,
- $\mathrm{cov}(X + Y, Z) = \mathrm{cov}(X, Z) + \mathrm{cov}(X, Z)$,
- $\mathbb{V}(X + Y) = \mathbb{V}(X) + \mathbb{V}(Y) + \mathrm{cov}(X, Y)$.
- $X \perp\!\!\!\perp Y \Rightarrow \mathrm{cov}(X, Y) = 0$.
- $X \perp\!\!\!\perp Y \Leftrightarrow \mathrm{cov}(X, Y) = 0$ *when* X, Y *are Gaussian.*

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The bivariate Gaussian distribution

The Covariance Matrix

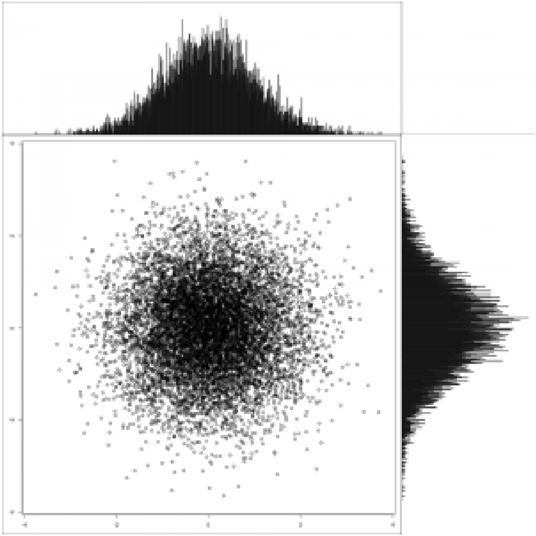
Let

$$X \sim \mathcal{N}(\mathbf{0}, \mathbf{\Sigma}),$$

with unit variance and $\rho_{XY} = 0$

$$\mathbf{\Sigma} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}.$$

The shape of the 2-D distribution evolves accordingly.



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Let

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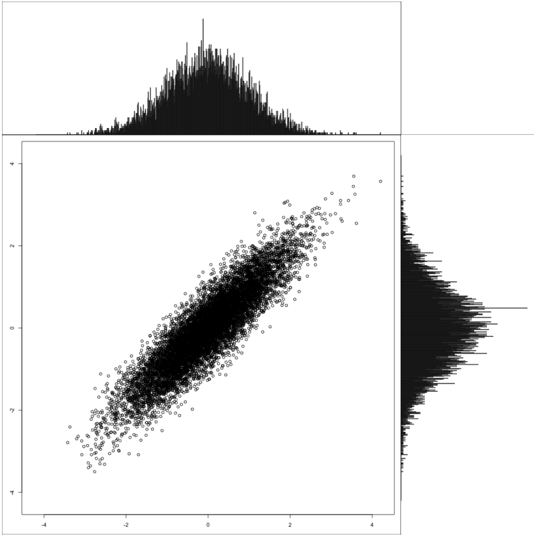

Generalization: multivariate Gaussian vector

Now need partial covariance and partial correlation

Let X, Y, Z be real random variables.

Definitions

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$$\rho_{XY|Z} = \frac{\rho_{XY} - \rho_{XZ}\rho_{YZ}}{\sqrt{1-\rho^2_{XZ}}\sqrt{1-\rho^2_{YZ}}}.$$

$\rightsquigarrow$ Give the interaction between X and Y once removed the effect of Z.

Proposition

When X, Y, Z are jointly Gaussian, then

$$\mathrm{cov}(X, Y|Z) = 0 \Leftrightarrow \mathrm{cor}(X, Y|Z) = 0 \Leftrightarrow X \perp Y|Z.$$

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Gaussian Graphical Model: canonical settings

Experiments in comparable Gaussian conditions

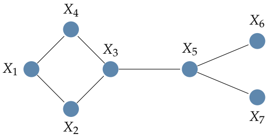
1. $X \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, with $\boldsymbol{\Omega} = \boldsymbol{\Sigma}^{-1}$ the precision matrix.
2. a sample $(X^1, \dots, X^n)$ of exp. stacked in an $n \times p$ data matrix $\mathbf{X}$.

Conditional independence structure

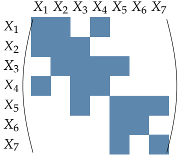
$$(i, j) \notin \mathcal{E} \Leftrightarrow X_i \perp\!\!\!\perp X_j | X_{\setminus \{i,j\}} \Leftrightarrow \Omega_{ij} = 0.$$

Graphical interpretation

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



$\boldsymbol{\Theta}$



$\rightsquigarrow$ "Covariance" selection

Gaussian vector and linear regression (I)

Proposition (Gaussian vector and conditioning)

$$Z = \begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix} \sim \mathcal{N}(\mathbf{0}, \mathbf{\Sigma}), \quad \mathbf{\Sigma} = \begin{pmatrix} \mathbf{\Sigma}_{11} & \mathbf{\Sigma}_{12} \\ \mathbf{\Sigma}_{21} & \mathbf{\Sigma}_{22} \end{pmatrix}, \quad \mathbf{\Omega} = \mathbf{\Sigma}^{-1} = \begin{pmatrix} \mathbf{\Omega}_{11} & \mathbf{\Omega}_{12} \\ \mathbf{\Omega}_{21} & \mathbf{\Omega}_{22} \end{pmatrix}.$$

Then,

$$Z_2 | Z_1 = \mathbf{z} \sim \mathcal{N}\left(-\mathbf{\Omega}_{22}^{-1}\mathbf{\Omega}_{21}\mathbf{z}, \mathbf{\Omega}_{22}^{-1}\right)$$

and

$$\mathbf{\Omega}_{22}^{-1} = \mathbf{\Sigma}_{22} - \mathbf{\Sigma}_{21}\mathbf{\Sigma}_{11}^{-1}\mathbf{\Sigma}_{12}.$$

Corollary

Partial correlations are related to the inverse of the covariance matrix:

$$\mathrm{cor}(Z_i, Z_j | Z_k, k \neq i, j) = -\frac{\Omega_{ij}}{\sqrt{\Omega_{ii}\Omega_{jj}}}$$

Gaussian vector and linear regression (II)

Consider the linear model

$$Y = X^{\intercal}\boldsymbol{\beta} + \varepsilon, \quad \varepsilon \sim \mathcal{N}(0, \sigma). \tag{1}$$

Other interpretation for the regression coefficients

If $(X^T, Y)^T \sim \mathcal{N}(\mathbf{0}, \mathbf{\Sigma})$ with a block-wise decomposion of $\mathbf{\Sigma}$ and $\mathbf{\Omega} = \mathbf{\Sigma}^{-1}$ then by condition $Y|X$ we get

$$Y = \sum_{j=1}^{p} X_j \mathrm{cor}(X_j, Y|X_k, k \neq j) \sqrt{\frac{(\mathbf{\Omega}_{XX})_{jj}}{\omega_{YY}}} + \varepsilon, \quad \varepsilon \sim \mathcal{N}(0, 1/\omega_{YY}). \tag{2}$$

By comparing (1) to (2) then β_j is related to the partial correlation between X_j and Y, i.e. describes effect of X_j on Y once effect of other predictors have been removed.

Gaussian Graphical Model and Linear Regression

Linear regression viewpoint

Variable X_i is linearly explained by the other variables:

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

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

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

$\leadsto$ "Neighborhood" selection

Outline

References

- Habilitation, J. Chiquet, Chapter 2
  https://tel.archives-ouvertes.fr/tel-01288976/

- The Element of Statistical Learning Hastie, Tibshirani, Friedman, chapter 17.

Some families of methods for network reconstruction

Test-based methods

- Tests the nullity of each entries
- Combinatorial problem when $p > 30 \ldots$

Bayesian methods

- Compute the posterior probability of each edge
- Usually more computationally demanding
- For special graphs, computation gets easier

Sparsity-inducing regularization methods

- induce sparsity with the ℓ_1-norm penalization
- Use results from convex optimization
- Versatile and computationally efficient

Outline

Inference: maximum likelihood estimator

The natural approach for parametric statistics

Let $X \sim f_X(x; \mathbf{\Omega})$, where $\mathbf{\Omega}$ are the model parameters.

Maximum likelihood estimator

$$\hat{\mathbf{\Omega}} = \arg\max_{\mathbf{\Omega}} \ell(\mathbf{\Omega}; \mathbf{X})$$

where ℓ is the log likelihood, a function of the parameters:

$$\ell(\mathbf{\Omega}; \mathbf{X}) = \log \prod_{i=1}^{n} f_X(\mathbf{x}_i; \mathbf{\Omega}),$$

where $\mathbf{x}_i$ is the ith row of $\mathbf{X}$.

- This a convex optimization problem,
- We just need to detect non zero coefficients in $\mathbf{\Omega}$

The multivariate Gaussian log-likelihood

Let $\mathbf{S} = n^{-1}\mathbf{X}^\intercal\mathbf{X}$ be the empirical variance-covariance matrix: $\mathbf{S}$ is a sufficient statistic of $\mathbf{\Omega}$.

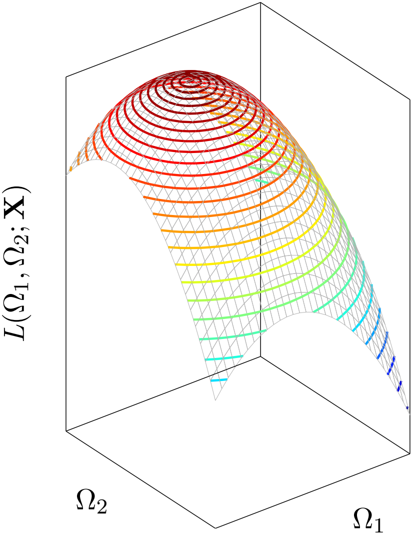
The log-likelihood

$$\ell(\mathbf{\Omega}; \mathbf{S}) = \frac{n}{2} \log\det(\mathbf{\Omega}) - \frac{n}{2} \mathrm{Trace}(\mathbf{S}\mathbf{\Omega}) + \frac{n}{2} \log(2\pi).$$

- $\rightsquigarrow$ The MLE $= \mathbf{S}^{-1}$ of $\mathbf{\Omega}$ is not defined for $n < p$ and never sparse.
- $\rightsquigarrow$ The need for regularization is huge.

A Geometric View of Shrinkage

Constrained Optimization



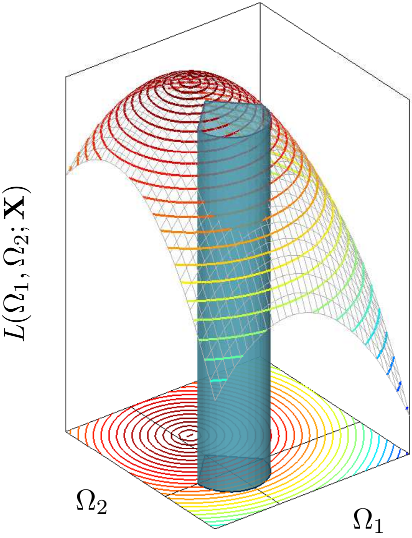
We basically want to solve a problem of the form

$$\underset{\Omega_1, \Omega_2}{\text{maximize}}\, \ell(\Omega_1, \Omega_2; \mathbf{X})$$

where ℓ is typically a concave likelihood function.

A Geometric View of Shrinkage

Constrained Optimization



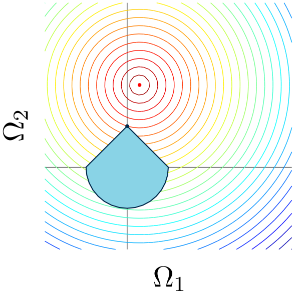
$$\begin{cases} \underset{\Omega_1,\Omega_2}{\text{maximize}} & \ell(\Omega_1, \Omega_2; \mathbf{X}) \\ \text{s.t.} & \Omega(\Omega_1, \Omega_2) \leq c \end{cases},$$

where Ω defines a domain that *constrains* $\boldsymbol{\beta}$.

How shall we define Ω ?

A Geometric View of Shrinkage

Constrained Optimization



$$\left\{\begin{array}{ll}\underset{\Omega_1,\Omega_2}{\text{maximize}} & \ell(\Omega_1,\Omega_2;\mathbf{X}) \\ \text{s.t.} & \Omega(\Omega_1,\Omega_2) \leq c\end{array}\right. ,$$

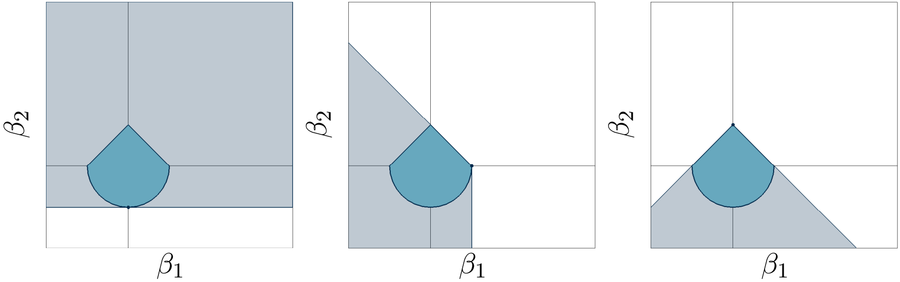
where Ω defines a domain that *constrains* $\boldsymbol{\beta}$.

How shall we define Ω ?

A Geometric View of Sparsity

Dual and Polar Cones

Generalizes normals



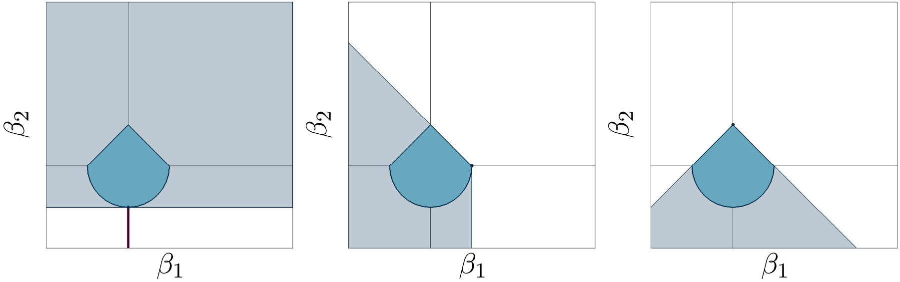
Let C be a convex set,

- $C^\star(x_0) = \left\{y | y^T(x - x_0) \geq 0, x \in C\right\}$ is the dual cone in x_0,
- $N_C(x_0) = \left\{y | y^T(x - x_0) \leq 0, x \in C\right\}$ is the polar (or normal) cone,

A Geometric View of Sparsity

Dual and Polar Cones

Generalizes normals



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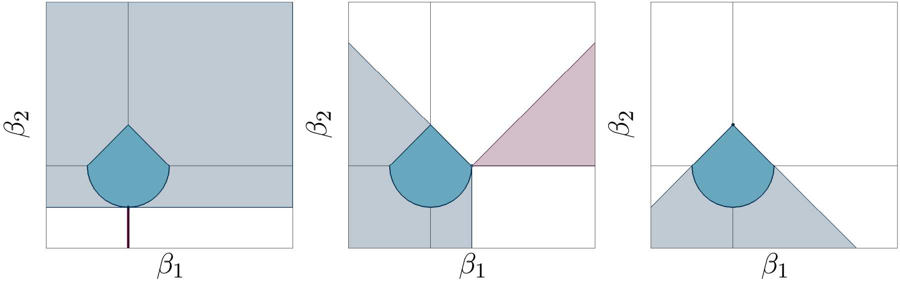

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A Geometric View of Sparsity

Dual and Polar Cones

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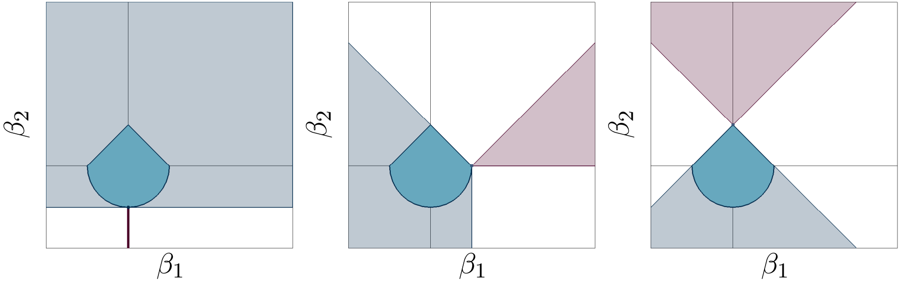

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Shape of cones $\Rightarrow$ sparsity pattern

The Lasso

Least Absolute Shrinkage and Selection Operator

Idea

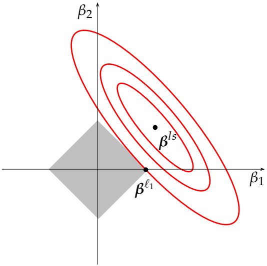
Suggest an admissible set that induces sparsity (force several entries to exactly zero in $\hat{\boldsymbol{\beta}}$).

Lasso as a regularization problem

The Lasso estimate of $\boldsymbol{\beta}$ is the solution to

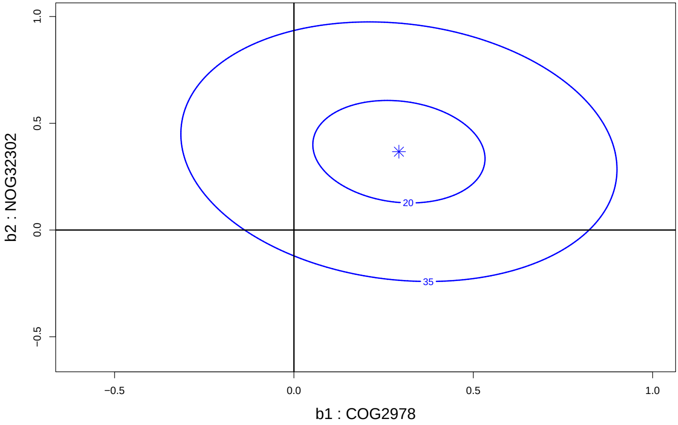
$$\hat{\boldsymbol{\theta}}^{\text{lasso}} = \arg\min_{\boldsymbol{\theta}} -\ell(\boldsymbol{\theta}), \quad \text{s.t. } \sum_{j=1}^{p} |\Omega_j| \leq s,$$

where s is a shrinkage factor.



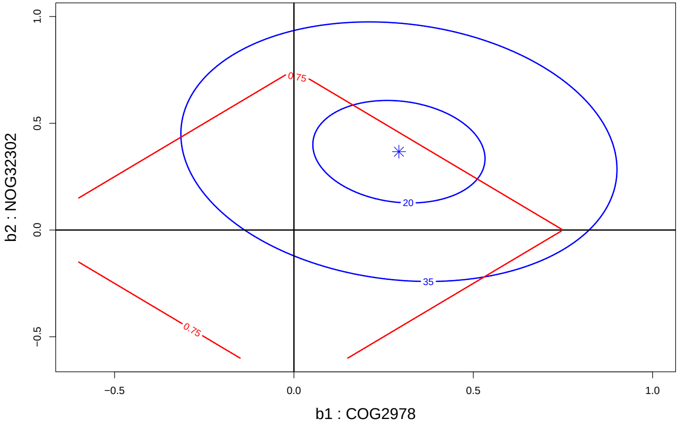
Insights: 2-dimensional example with the square loss

$$\sum_{i=1}^{n}(y_i - x_i^1\Omega_1 - x_i^2\Omega_2)^2, \qquad \text{no constraints}$$



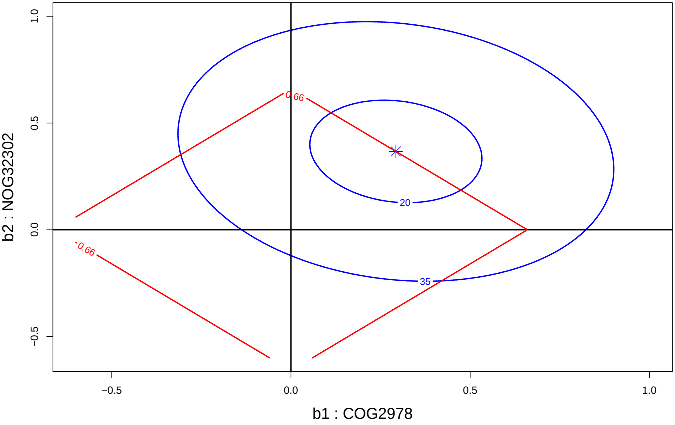
Insights: 2-dimensional example with the square loss

$$\sum_{i=1}^{n}(y_i - x_i^1\Omega_1 - x_i^2\Omega_2)^2, \qquad \text{s.t. } |\Omega_1| + |\Omega_2| < 0.75$$



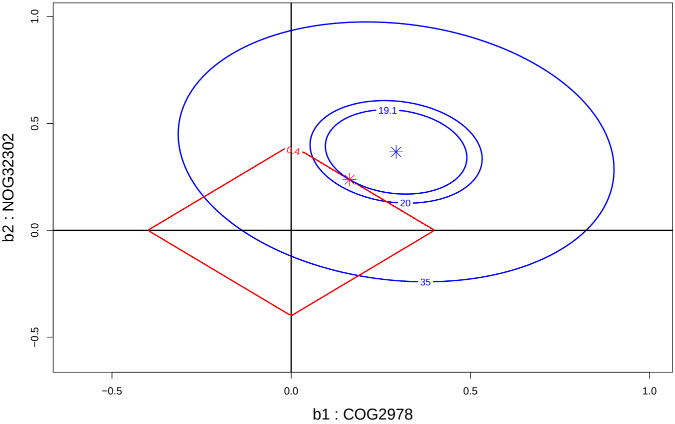
Insights: 2-dimensional example with the square loss

$$\sum_{i=1}^{n}(y_i - x_i^1\Omega_1 - x_i^2\Omega_2)^2, \qquad \text{s.t. } |\Omega_1| + |\Omega_2| < 0.66$$



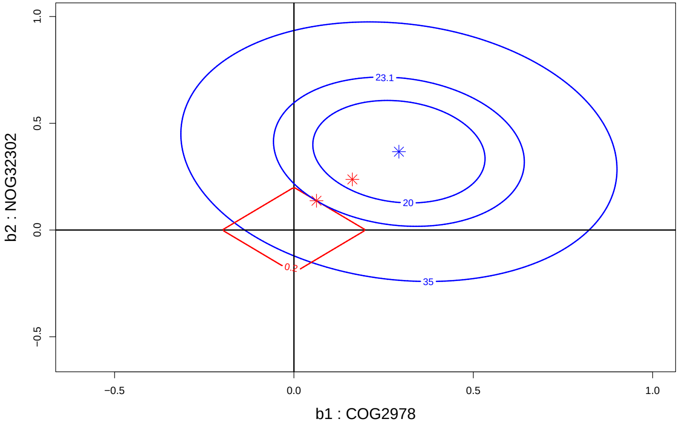
Insights: 2-dimensional example with the square loss

$$\sum_{i=1}^{n}(y_i - x_i^1\Omega_1 - x_i^2\Omega_2)^2, \qquad \text{s.t. } |\Omega_1| + |\Omega_2| < 0.4$$



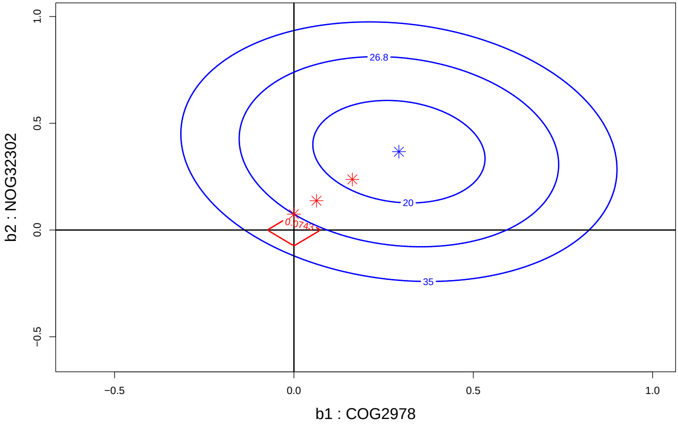
Insights: 2-dimensional example with the square loss

$$\sum_{i=1}^{n}(y_i - x_i^1\Omega_1 - x_i^2\Omega_2)^2, \qquad \text{s.t. } |\Omega_1| + |\Omega_2| < 0.2$$



Insights: 2-dimensional example with the square loss

$$\sum_{i=1}^{n}(y_i - x_i^1\Omega_1 - x_i^2\Omega_2)^2, \qquad \text{s.t. } |\Omega_1| + |\Omega_2| < 0.0743$$



Application to GGM

A penalized likelihood approach

$$\hat{\mathbf{\Theta}}_\lambda = \arg\max_{\mathbf{\Theta}\in\mathbb{S}_+} \ell(\mathbf{\Theta};\mathbf{X}) - \lambda \mathrm{pen}_{\ell_1}(\mathbf{\Theta})$$

where

- ℓ is the model log-likelihood,
- pen_{ℓ_1} is a penalty function tuned by $\lambda > 0$.
  1. *regularization* (needed when $n \ll p$),
  2. *selection* (sparsity induced by the ℓ_1-norm).

Gold standard penalized approaches

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

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

+ symmetric, positive-definite
– solved by the "Graphical-Lasso" ($\mathcal{O}(p^3)$, *Friedman et al, 2007*).
- R-packages **glasso**, **quic**, **huge**.

Neighborhood Selection (Meinshausen & Bülhman, 2006)

– not symmetric, not positive-definite
+ p Lasso solved with Lars-like algorithms ($\mathcal{O}(npd)$ for d neighbors).
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Neighborhood Selection (Meinshausen & Bülhman, 2006)

For variable j, solve $\hat{\boldsymbol{\beta}}_j = \arg\min_{\boldsymbol{\beta}\in\mathbb{R}^{p-1}} \frac{1}{2}\|\mathbf{X}_j - \mathbf{X}_{\backslash j}\boldsymbol{\beta}\|_2^2 + \lambda\|\boldsymbol{\beta}\|_{\ell_1}.$

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Neighborhood Selection (Meinshausen & Bülhman, 2006)

$$\hat{\mathbf{B}}^{\text{ns}} = \arg\min_{\mathbf{B}\in\mathbb{R}^{p\times p},\mathrm{diag}(\mathbf{B})=\mathbf{0}_p} \frac{1}{2}\mathrm{tr}(\mathbf{B}^\top\mathbf{S}_n\mathbf{B}) - \mathrm{tr}(\mathbf{B}^\top\mathbf{S}_n) + \lambda\|\mathbf{B}\|_{\ell_1}.$$

− not symmetric, not positive-definite
+ p Lasso solved with Lars-like algorithms ($\mathcal{O}(npd)$ for d neighbors).
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Outline

Practical implications of theoretical results

Selection consistency (Ravikumar, Wainwright, 2009-2012)

Denote $d = \max_{j\in\mathcal{P}}(\mathrm{degree_j})$. Consistency for an appropriate λ 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

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

Good news! when n is small, we don't need to solve huge problems because they can't but fail.

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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

- GGMSelect (Girault *et al*, '12) selects among a family of candidates.
- Adapt IC to sparse high dimensional problems, e.g.

$$\text{EBIC}_\gamma(\widehat{\boldsymbol{\Omega}}_\lambda) = -2\text{loglik}(\widehat{\boldsymbol{\Omega}}_\lambda; \mathbf{X}) + |\mathcal{E}_\lambda|(\log(n) + 4\gamma \log(p)),$$

Resampling/subsampling

Keep edges frequently selected on an range of λ after sub-samplings

- Stability Selection (Meinshausen and Bühlman, 2010, Bach 2008)
- Stability approach to Regularization Selection (StaRS) (Liu, 2010).

Outline

The plasmodium data

```r
library(Matrix)
load("plasmodium_expression.Rdata")
dim(Y)
```

```
## [1] 3490   46
```

```r
head(Y)[, 1:5]
```

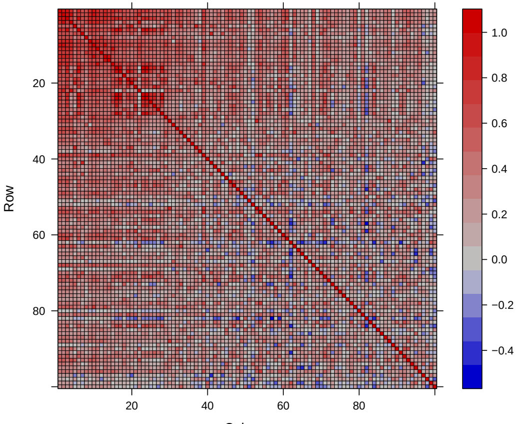
```
##                TP1    TP2    TP3    TP4    TP5
## MAL13P1.100 0.4510 0.6532 1.0760 0.5515 0.4238
## MAL13P1.102 1.5320 1.8920 0.8803 1.0300 0.9328
## MAL13P1.103 0.5218 0.5213 0.5328 0.3719 0.3258
## MAL13P1.105 0.5515 0.5527 0.8627 0.4541 0.4299
## MAL13P1.107 0.5630 0.4463 1.0760 0.4035 0.2082
## MAL13P1.112 0.5390 0.5393 0.5642 0.5326 0.4469
```

The plasmodium data

Gene to Gene empirical covariance

Covariance between the 100 most variable genes.

```
genes.subset <- order(apply(Y,1,var))[1:100]
image(Matrix(cor(t(Y[genes.subset, ]))), userRaster=TRUE)
```



Network between the genes I

Sparse Estimation

Regulatory network between the 100 most variable genes.

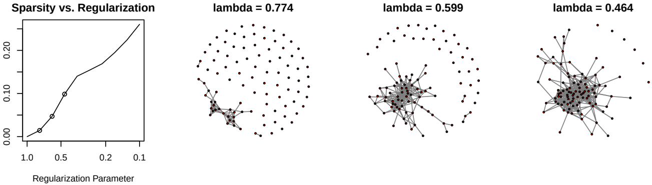
```
library(huge)
huge.out <- huge(as.matrix(t(Y[genes.subset, ])), method="glasso", cov.output=TRUE)

## Conducting the graphical lasso (glasso) with lossless screening....in progress:0%
Conducting the graphical lasso (glasso) with lossless screening....in progress:9%
Conducting the graphical lasso (glasso) with lossless screening....in progress:19%
Conducting the graphical lasso (glasso) with lossless screening....in progress:30%
Conducting the graphical lasso (glasso) with lossless screening....in progress:40%
Conducting the graphical lasso (glasso) with lossless screening....in progress:50%
Conducting the graphical lasso (glasso) with lossless screening....in progress:60%
Conducting the graphical lasso (glasso) with lossless screening....in progress:70%
Conducting the graphical lasso (glasso) with lossless screening....in progress:80%
Conducting the graphical lasso (glasso)....done.

plot(huge.out)
```

Network between the genes II

Sparse Estimation



Network between the genes I

Inverse covariance

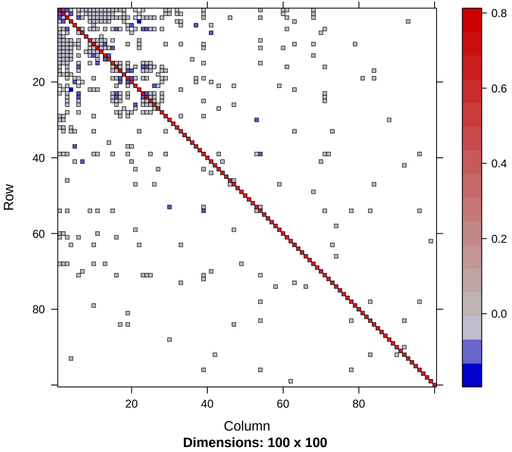
```
library(huge)
huge.out$df
```

```
##  [1]    0   71  233  488  693  763  836  963 1110 1289
```

```
image(Matrix(huge.out$icov[[3]]))
```

Network between the genes II

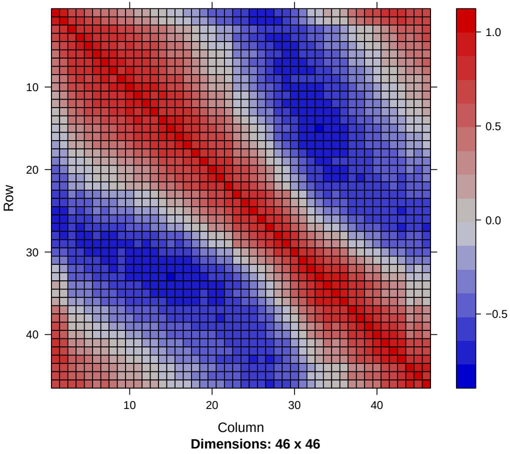
Inverse covariance



The plasmodium data

Covariance between conditions

```r
image(Matrix(cor(Y)))
```



Covariance structure between the conditions

Sparse Estimation

```
library(huge)
huge.out <- huge(as.matrix(Y), method="glasso", cov.output=TRUE)

## Conducting the graphical lasso (glasso) with lossless screening....in progress:0%
Conducting the graphical lasso (glasso) with lossless screening....in progress:9%
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Conducting the graphical lasso (glasso) with lossless screening....in progress:70%
Conducting the graphical lasso (glasso) with lossless screening....in progress:80%
Conducting the graphical lasso (glasso)....done.

sel.out  <- huge.select(huge.out)

## Conducting extended Bayesian information criterion (ebic) selection....done
```
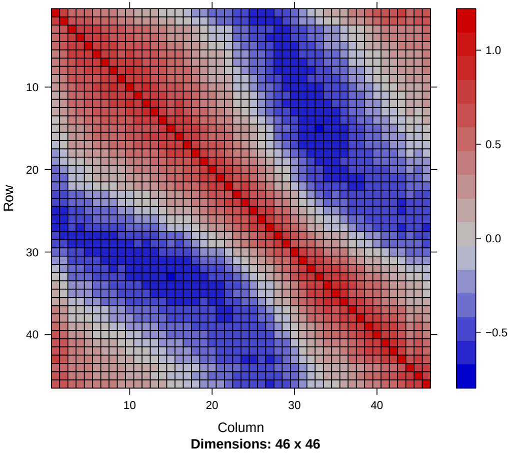

Covariance structure between the conditions

Sparse Estimation

```
image(sel.out$opt.cov)
```



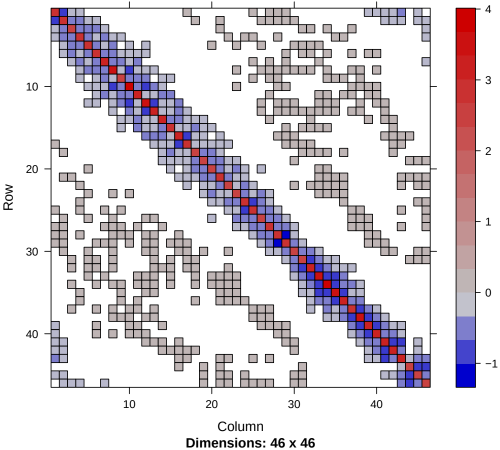
Covariance structure between the conditions I

Sparse Estimation of the inverse covariance

```
sum(abs(sel.out$opt.icov) != 0)

## [1] 760

ncol(sel.out$opt.icov) ** 2

## [1] 2116

image(sel.out$opt.icov)
```

Covariance structure between the conditions II

Sparse Estimation of the inverse covariance



Covariance structure between the conditions I

Associated network

```
plot(huge.out)
```

Covariance structure between the conditions II

Associated network