**Comparative evaluation of
network reconstruction methods
in high dimensional settings.**

Henrique Bolfarine

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PARA
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Abstract

BOLFARINE, H. **Comparative evaluation of network reconstruction methods in high dimensional settings**. 2017. Dissertation (masters) - Institute of Mathematics and Statistics, São Paulo, 2017.

In the past years, several network reconstruction methods modeled as Gaussian Graphical Model in high dimensional settings were proposed. In this work we will analyze three different methods, the Graphical Lasso (**GLasso**), Graphical Ridge (**GGMridge**) and a novel method called **LPC**, or Local Partial Correlation. The evaluation will be performed in high dimensional data generated from different simulated random graph structures (*Erdős-Renyi*, *Barabási-Albert*, *Watts-Strogatz*), using *Receiver Operating Characteristic* or ROC curve. We will also apply the methods in the reconstruction of genetic co-expression network for the differentially expressed genes in cervical cancer tumors.

Keywords: Network Reconstruction, Graphical Model, Gaussian Graphical Model, **GLasso**, **GGMridge**, **LPC**, Partial correlation.

Resumo

BOLFARINE, H. **Comparação de métodos de reconstrução de redes em alta dimensão.** 2017. Dissertação Mestrado - Instituto de Matemática e Estatística, São Paulo, 2017.

Vários métodos têm sido propostos para a reconstrução de redes em alta dimensão, que é tratada como um Modelo Gráfico Gaussiano. Neste trabalho vamos analisar três métodos diferentes, o método *Graphical Lasso* (**GLasso**), *Graphical Ridge* (**GGMridge**) e um novo método chamado **LPC**, ou Correlação Parcial Local. A avaliação será realizada em dados de alta dimensão, gerados a partir de diferentes estruturas, a partir de grafos aleatórios (*Erdős-Renyi*, *Barabási-Albert*, *Watts-Strogatz*), usando Receptor de Operação Característica, ou curva ROC. Aplicaremos também os métodos apresentados, na reconstrução da rede de co-expressão gênica para tumores de câncer cervical.

Palavras-chave: Reconstrução de redes, Modelos Gráficos, Modelos Gráficos Gaussianos, **GLasso**, **GGMridge**, **LPC**, correlação parcial.

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Abbreviation

GGM	Gaussian Graphical Models
GLasso	Graphical Lasso Algorithm
GGMridge	Graphical Ridge Algorithm
LPC	Local Partial Correlation method
<i>OLS</i>	Ordinary Least Squares
ROC	Receiver Operating Characteristic

List of Symbols

$\doteq$	Defined as
$\propto$	Proportional to
$\gg$	Way greater than
$ A $	The cardinality of set A
$\mathcal{N}$	Gaussian distribution
$\mathcal{U}$	Uniform distribution
$\mathbf{R}$	Correlation matrix
$\mathbf{K}$	Precision matrix
$\mathbf{P}$	Partial Correlation matrix

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Chapter 1

Introduction

1.1 About this work

In the past years the problem of estimating network structures hidden among variables has increased in attention, especially due available massive data sets from different scientific areas (Meinshausen and Bühlmann, 2010). In this context, Graphical Models (Lauritzen, 1996), emerged as a powerful framework for it's ability to encode conditional dependencies and for it's convenience in representing distributions over a graph structure that we can analyse further on.

Although this dissertation is not a rigorous work of bioinformatics, the gene co-expression problem inspires it. This means that the gene expressions are studied through the network perspective. The genes of interest are the nodes and their relations are direct or undirected edges (Schäfer and Strimmer, 2005). This relations are commonly identified using Pearson and Spearman correlations but, due to the characteristics of the variables, this often leads to spurious associations from unknown outside sources. Another problem is that, although there's a growing amount of data available, the sample size, usually, is still very small (on the order of tens) compared to the number of variables analyzed that are in the order of thousands (Castelo and Roverato, 2006). Data with this characteristics are known as *high dimensional* (Giraud, 2014). This implies that important associations are often hidden in hundreds, even thousands, of unimportant variables that don't affect the workings of the overall network. For this high dimensional problem we need a clear and acute filter which will help us manage the information, build a parsimonious model and find relevant associations. To address this issue we use the Graphical Models known as Gaussian Graphical Models

(**GGM**) (Lauritzen, 1996) (Whittaker, 2009), in which, by assuming that the data has gaussian distribution, a series of interesting properties emerges. For example, the Partial correlation matrix plays a key role, regarded as the strength of the an association between every two genes forming an edge in the network.

We analysed three different methods for estimating the network structure from a **GGM**, each with a different approach to the high dimensional problem. The first, and most known, is the Graphical Lasso, or **GLasso** (Friedman *et al.*, 2008), largely based on the optimization method by Banerjee *et al.* (2008), which applied the ideias from Meinshausen and Bühlmann (2006), using the ℓ_1 restriction (or ℓ_1 norm¹) in the estimates of the Precision matrix, which is the inverse of the Covariance matrix. Since then, other authors worked on the same problem trying to improve the methods performance((Witten *et al.*, 2011) (Mazumder and Hastie, 2012). In our study we used the plain **GLasso** algorithm provided by the authors in their web page². The second method analysed is less known, but proposes an interesting alternative to the Graphical Lasso. Developed by Ha and Sun (2014) based on the work of Schäfer and Strimmer (2005), it estimates the Partial correlation matrix using ℓ_2 penalty and then perform statistical tests based on empirical distributions. We applied the algorithm called **GGMridge**, provided by the authors³. Finally, we will present a method which estimates the Partial correlation neighborhood of two variables, that where selected using Pearson correlation, to learn the network structure, known as Local Partial Correlation or **LPC** (Thomas *et al.*, 2012). We evaluated the three methods performances using simulation studies in which we applied high dimensional data originated from different random graph structures. We have chosen the well-known *Erdős-Rényi* model (Erdos and Rényi, 1960), the *Watts-Strogatz* network, which model social interactions (Watts and Strogatz, 1998), and the *Barabási-Albert* network (Barabási and Albert, 1999), which models biological interactions, among others. The idea is to test if random generated networks, with different structures affects the methods performance. We analyzed the methods using the *Receiver Operating Characteristic* or ROC curve, which is a diagnostic test for binary classifiers. We also applied the methods to the data from (Zhai *et al.*, 2007), which has genes with chro-

¹The definition of this norm and the ℓ_2 norm can be viewed in the Appendix A.1.1.

²statweb.stanford.edu/~tibs/glasso/

³cran.r-project.org/web/packages/GGMridge/GGMridge.pdf

mosomal expression of tumorous cervical cells. The 1268 genes used in the reconstruction, have chromosomal aberration which where identified by *Mine et al. (2013)*.

1.2 Organization of the dissertation

We organized the work as follows, in chapter 2, we briefly reviewed some basic concepts in Statistics, Graph Theory, and regularization. In chapter 3 we will present core concepts of Graphical Models and **GGM**. In chapter 4 we present the chosen methods used in our study; **GLasso**, **GGMridge**, and **LPC**. In chapter 5, we present the methods applied in random graphs and Covariance matrices simulation, and the results and evaluation of the comparison. Finally, in chapter 6, we applied the methods presented in 4, in the cervical tumor data, and compared the results between methods.

Chapter 2

Basic Concepts

2.1 Introduction

In this chapter we will present some important concepts that will be useful throughout this work. We will begin presenting the Multivariate Gaussian Distribution and some of its properties, next we will define Conditional Independence in 2.3, Pearson Correlation (2.4.1) and Partial Correlation (2.4.2). Later on, in 2.5, we will present some basic concepts of Graph Theory that will be useful in understanding the ideas presented in chapters 3 and 4. Finally we will introduce some basic concepts of regularization in 2.6, that will be an important tool applied in the methods presented in chapter 4. For the readers already familiar with these topics we suggest skipping this chapter.

2.2 Multivariate Gaussian distribution

The Multivariate Gaussian Distribution plays a pivotal role in this dissertation. It has several properties that makes it an ideal model for gene expression (Schäfer and Strimmer, 2005), which is the main application discussed in chapter 6, among other natural phenomena. It is an easy generalization of the univariate Gaussian distribution, and it is defined by its first and second moments. It has the property that zero correlation implies independence and pairwise independence implies in total independence. The Multivariate Gaussian Distribution is defined formally in Mardia *et al.* (1980).

2.2.1 Definition

The random vector $X_V = (X_1, \dots, X_p)^T$, indexed by the set $V = \{1, 2, \dots, p\}$ has p -variate Gaussian distribution, where $\mu \in \mathbb{R}^p$ is the mean vector and Σ is a $p \times p$ dimensional Covariance matrix, that is represented by $X_V \sim \mathcal{N}_V(\mu, \Sigma)$. The density of the Multivariate Gaussian Distribution, given Σ is non-singular (this means that Σ has an inverse), is given by

$$f(\mathbf{x}) = \frac{\exp\left(-\frac{1}{2}(\mathbf{x} - \mu)^T \Sigma^{-1}(\mathbf{x} - \mu)\right)}{\sqrt{(2\pi)^p \det(\Sigma)}}, \quad \mathbf{x} = (x_1, x_2, \dots, x_p). \quad (2.1)$$

where $\det(\Sigma)$ is the determinant of Σ . The first and second moments of Multivariate Gaussian distribution are $E(X_V) = \mu$ and $Var(X_V) = \Sigma$.

For our means, it will be instructive to examine the conditional distribution of a variable X_i , $i \in V$, given the rest $X_{V_{-i}}$, with $V_{-i} \doteq V \setminus \{i\}$, and $X_V \sim \mathcal{N}_V(\mu, \Sigma)$. In this situation the role of the Precision matrix ([Dempster, 1969](#)),

$$\mathbf{K} = \Sigma^{-1}, \quad (2.2)$$

will become explicit, allowing us to better understand the methods presented in chapter 4. Suppose $X_V \sim \mathcal{N}_V(\mathbf{0}, \Sigma)$, where $\mu = \mathbf{0}$, and $V = \{1, 2, \dots, p\}$, has Gaussian distribution and we partition X_V as $X_V = (X_i, X_{V_{-i}}^T)^T$ then, the conditional distribution of X_i given $X_{V_{-i}}$ is in the form

$$X_i | X_{V_{-i}} \sim \mathcal{N}\left(X_{V_{-i}} \Sigma_{V_{-i}V_{-i}}^{-1} \Sigma_{V_{-i}i}, \Sigma_{ii} - \Sigma_{i,V_{-i}} \Sigma_{V_{-i}V_{-i}}^{-1} \Sigma_{V_{-i}i}\right), \quad (2.3)$$

with Σ as,

$$\Sigma = \begin{pmatrix} \Sigma_{ii} & \Sigma_{iV_{-i}} \\ \Sigma_{V_{-i}i} & \Sigma_{V_{-i}V_{-i}} \end{pmatrix}, \quad (2.4)$$

where $\Sigma_{iV_{-i}}$, and $\Sigma_{V_{-i}i}$ are $1 \times |V_{-i}|$ and $|V_{-i}| \times 1$ sized vectors and $\Sigma_{V_{-i}V_{-i}}$ is a $|V_{-i}| \times |V_{-i}|$ matrix, where $|A|$ is the cardinality of the set A . From [2.2](#), and $\Sigma \mathbf{K} = \mathbf{I}$, where $\mathbf{I}$ is the

identity matrix, and partitioning $\mathbf{K}$ as (2.4) we have

$$\begin{pmatrix} \Sigma_{ii} & \Sigma_{iV_{-i}} \\ \Sigma_{V_{-i}i} & \Sigma_{V_{-i}V_{-i}} \end{pmatrix} \begin{pmatrix} \kappa_{ii} & \kappa_{iV_{-i}} \\ \kappa_{V_{-i}i} & \mathbf{K}_{V_{-i}V_{-i}} \end{pmatrix} = \begin{pmatrix} 1 & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{V_{-i}V_{-i}} \end{pmatrix}, \quad (2.5)$$

which we obtain

$$-\frac{\kappa_{V_{-i}i}}{\kappa_{ii}} = \Sigma_{V_{-i}V_{-i}}\Sigma_{V_{-i}i}, \quad \kappa_{ii}^{-1} = \Sigma_{ii} - \Sigma_{iV_{-i}}\Sigma_{V_{-i}V_{-i}}\Sigma_{V_{-i}i} \quad (2.6)$$

From the properties (2.5) and (2.6) we have the following decomposition, which can be viewed as a linear regression between X_i and $X_{V_{-i}}$,

$$X_i = X_{V_{-i}}^T \beta^i + \epsilon_i, \quad (2.7)$$

where

$$\beta^i = -\frac{\kappa_{V_{-i}i}}{\kappa_{ii}}, \quad \epsilon_i \sim \mathcal{N}(0, \kappa_{ii}^{-1}). \quad (2.8)$$

From (2.7) and (2.8) we can observe that the elements of the Precision matrix affects directly the relation between X_i , and $X_{V_{-i}}$. Next we will present definitions that will relate these results with the concept of Conditional Independence.

2.3 Conditional Independence

Conditional Independence is a general form of independence, where X and Y are jointly distributed random variables, where $f(x, y) = f(x)f(y)$. It appears in a number of applications, it is the basis of a subject in Computer Sciences, known as Causality (Pearl, 2009), it appears in some Stochastic Processes (Brémaud, 2013), in Bayesian Statistics (Schervish, 2012), and as will see, plays a central role in Graphical Models.

2.3.1 Definition

Let X , Y and Z be random variables with a joint probability distribution. The variables X and Y are said to be Conditionally Independent given Z , that we denote as $X \perp\!\!\!\perp Y|Z$, if

$$f_{XY|Z}(x, y|z) = f_{X|Z}(x|z)f_{Y|Z}(y|z), \quad \text{whenever } f_Z(z) > 0. \quad (2.9)$$

In other words if we know the value Y , that doesn't provide additional information about X given we know Z . We can write (2.9) in other ways (Lauritzen, 1996) that is useful in some applications, when the following densities and variables, X , Y , and Z are well defined, we have that,

$$X \perp\!\!\!\perp Y|Z \iff f_{XYZ}(x, y, z) = f_{XY}(x, z)f_{YZ}(y, z)/f_Z(z), \quad (2.10)$$

$$X \perp\!\!\!\perp Y|Z \iff f_{X|YZ}(x|y, z) = f_{X|Z}(x|z), \quad (2.11)$$

$$X \perp\!\!\!\perp Y|Z \iff f_{XZ|Y}(x, z|y) = f_{X|Z}(x|z)f_{Z|Y}(z|y), \quad (2.12)$$

$$X \perp\!\!\!\perp Y|Z \iff f_{XYZ}(x, y, z) = h(x, z)k(y, z), \text{ for some } h, k \quad (2.13)$$

$$X \perp\!\!\!\perp Y|Z \iff f_{XYZ}(x, y, z) = f_{X|Z}(x|z)f_{YZ}(y, z). \quad (2.14)$$

Marginal independence, or independence can be obtained by conditional independence. It is as a particular case of (2.9) and it is denoted by $X \perp\!\!\!\perp Y|\emptyset$. In this case $\emptyset$ represents the absence of a variable,

$$X \perp\!\!\!\perp Y|\emptyset \iff f_{X|Y}(x|y) = f_X(x), \quad \text{whenever } f_Y(y) > 0.$$

Some properties emerge from (2.9) and the relations above, that relates conditional independence in situations where we have more variables, or even sets of variables.

- *Symmetry*: $X \perp\!\!\!\perp Y|Z \implies Y \perp\!\!\!\perp X|Z$.
- *Decomposition*: $X \perp\!\!\!\perp YW|Z \implies X \perp\!\!\!\perp Y|Z$.
- *Weak Union*: $X \perp\!\!\!\perp YW|Z \implies X \perp\!\!\!\perp Y|ZW$.
- *Contraction*: $X \perp\!\!\!\perp Y|Z \ \& \ X \perp\!\!\!\perp W|ZY \implies X \perp\!\!\!\perp YW|Z$.

- *Intersection:* $X \perp\!\!\!\perp W|ZY \quad \& \quad X \perp\!\!\!\perp Y|ZW \implies X \perp\!\!\!\perp YW|Z$.

The meaning of this properties are found in [Pearl \(2009\)](#) and in [Lauritzen \(1996\)](#), where there is an extensive study is this properties (Graphoid Theory), and their proofs all can be obtained from (2.9), and from the forms; (2.10),(2.11), (2.12), (2.13), and (2.14).

2.4 Partial correlation

Partial correlation notion, as will see later on, will help us find if the variables are conditionally independent to each other. This is only valid in certain conditions, that will explore, to build a structure that will explicit the relations seen between the variables in 2.3. To understand Partial correlation we will start with the Pearson correlation.

2.4.1 Definition - (Pearson correlation)

Pearson correlation coefficient, or known only as correlation, is a measure of linear dependence between two variables, X and Y defined as

$$\rho(X, Y) = \frac{Cov(X, Y)}{\sqrt{Var(X)Var(Y)}}. \quad (2.15)$$

From the Cauchy-Schwartz inequality we can see that $|\rho(X, Y)| \leq 1$. If $\rho(X, Y) = 1$, then we have a total positive linear correlation, when it is $\rho(X, Y) = 0$, then there's no linear correlation, and if $\rho(X, Y) = -1$, then we have a negative linear correlation. It's easily seen that from (2.15), $\rho(X, X) = 1$, and $\rho(X, Y) = \rho(Y, X)$. From the multivariate perspective, if we have $X_1, \dots, X_p$ random variables, then the Correlation matrix is given as follows

$$\rho(X_1, \dots, X_p) = \begin{pmatrix} \rho(X_1, X_1) & \cdots & \rho(X_1, X_p) \\ \vdots & \ddots & \vdots \\ \rho(X_p, X_1) & \cdots & \rho(X_p, X_p) \end{pmatrix}. \quad (2.16)$$

2.4.2 Definition - (Partial Correlation)

Given a set of random variables, Partial Correlation measures the degree of association between two random variables given the rest. Let X_V be random vector, indexed by $V = \{1, \dots, p\}$, the Partial Correlation between X_i and X_j with $i, j \in V$, given $X_{-ij} \doteq X_{V_{-ij}}$, where $V_{-ij} \doteq V \setminus \{i, j\}$, is the Pearson Correlation between the residuals ϵ_i and ϵ_j from the regression between X_i and X_j against X_{-ij} . That is

$$X_i = \alpha_i + X_{-ij}\beta_i + \epsilon_i, \quad X_j = \alpha_j + X_{-ij}\beta_j + \epsilon_j. \quad (2.17)$$

From (2.17), we obtain $\hat{X}_i$ and $\hat{X}_j$, and residuals

$$e_i = X_i - \hat{X}_i, \text{ and } e_j = X_j - \hat{X}_j, \quad (2.18)$$

which gives us the Partial correlation in the form

$$\rho(X_i, X_j | X_{V_{-ij}}) = \rho(e_i, e_j) = \rho(X_i - \hat{X}_i, X_j - \hat{X}_j). \quad (2.19)$$

Let $\rho_{ij.V_{-ij}} \doteq \rho(X_i, X_j | X_{V_{-ij}})$, if $\rho_{ij.V_{-ij}} \approx 0$ we have that X_i and X_j are not correlated given the rest of the variables X_{-ij} . From (2.19) we have that

$$\rho_{ij.X_{-ij}} = \frac{\rho_{ij} - \rho_{ij.V_{-ij}}}{\sqrt{(1 - \rho_{i.V_{-ij}}^2)(1 - \rho_{j.V_{-ij}}^2)}}, \quad (2.20)$$

where $\rho_{ij} = \rho(X_i, X_j)$, and $\rho_{i.V_{-ij}} = \rho(X_i, X_{-ij})$, the proof of (2.20) is found in [Takahashi \(2008\)](#). Another approach for calculating Partial Correlation, when the variables are distributed as 2.2.1, is the *inverse method* which consists in inverting the correlation matrix $\mathbf{R} = \{\rho_{ij}\}$, when is non-singular. We define $\mathbf{Q} = \mathbf{R}^{-1}$ and the Partial correlation as $\mathbf{P} = \{\rho_{ij.X_{-ij}}\}$, from the inverse method we have that $\rho_{ij.V_{-ij}}$ is in the form

$$\rho_{ij.V_{-ij}} = -\frac{q_{ij}}{\sqrt{q_{ii}q_{jj}}}, \text{ for } \mathbf{Q} = \{q_{ij}\}. \quad (2.21)$$

The demonstration of the equivalence between (2.20) and (2.21), is given in [Thomas](#)

(2012). The elements of (2.20) are tested for the hypothesis $\rho_{ij.V_{-ij}} = 0$, where the p -values of the test are obtained by the equation

$$\hat{t}_{ij} = \sqrt{n-2-p} \cdot \frac{\hat{\rho}_{ij.V_{-ij}}}{\sqrt{1 - \hat{\rho}_{ij.V_{-ij}}^2}}, \quad (2.22)$$

We have that (2.22) has *t-Student* distribution with $n-2-p$ degrees of freedom (Giraud, 2014). This procedure only makes sense when we have that the sample size n is larger than $|V| = p$. Later, in chapter 3, we will discuss the relation between the Precision matrix of the Multivariate Gaussian distribution with Partial correlation and Conditional Independence.

2.5 Graphs

Graph Theory, in mathematics, models pairwise relations between objects. It translates these relations to analysable visual structures. In this section we will review the basics of Graph Theory, for a deeper analysis we suggest (Bollobás, 2013).

2.5.1 Definition - (Graph)

We define a *graph* as pair $\mathcal{G} = (V, E)$, where V is the finite set of vertices or nodes, and the set E is the set of edges, with $V \times V \subseteq E$. A graph is *directed* if we have that for all $i, j \in V$, if the ordered pair $(i, j) \in E$ then $(j, i) \notin E$. In this case we represent this relation as an arrow between i and j , as in Figure 2.1a. If the graph is said to be *undirected* then, for all $i, j \in V$ we have that, if the ordered pair $(i, j) \in E$ then $(j, i) \in E$, in this case we represent this relation as $\{i, j\} \in E$. This relation is represented visually as a line between i and j , as in Figure 2.1b.

2.5.2 Definition - (Sub-graph and Complete Graph)

For a subset $U \subseteq V$, we have that U induces a sub-graph $\mathcal{G}_U = (U, E_U)$, where $E_U = E \cap (U \times U)$, is the edge set obtained keeping both end points in U . A graph is *complete* if all nodes are joined by an arrow or line as in Figure 2.1b.

Figure 2.1: (a) *Directed graph.* (b) *Undirected complete graph.*

2.5.3 Definition - (Parent, Child, and Neighbor)

If there's an arrow pointing from i to j , then i is a *parent* of j , the set of all parents of a node is denoted as $\mathbf{pa}(j)$. If j is *child* of i , then there's an arrow pointing from j to i , the set of all children of a node, denoted by $\mathbf{ch}(i)$. If there's a line between two nodes i and j , then they are *adjacent* or *neighbors*. The set of all neighbors or the *neighborhood* of a node i , denoted by $\mathbf{ne}(i)$. In Figure 2.1a we have that the parents of node 2 is the set $\mathbf{pa}(2) = \{1, 3\}$, the set of children of node 1 is $\mathbf{ch}(1) = \{2, 3\}$. In Figure 2.1b the neighborhood of node 2 is given by $\mathbf{ne}(2) = \{1, 3, 4, 5\}$.

Figure 2.2: *Undirected graph with the 4 maximal cliques indicated.*

2.5.4 Definition - (Cliques and Degree)

A *clique*¹ is complete sub-graph $\mathcal{G}_C$ of $\mathcal{G}$, with $C \subseteq V$, it said to be *maximal* if it is not contained in other clique. In Figure 2.2 from (Hastie *et al.*, 2015), we have that the set

¹From the french *clique* means "gang".

of all maximal cliques $\mathcal{C}$ is given by $\mathcal{C} = \{\{1, 2, 3\}, \{3, 4, 5\}, \{4, 6\}, \{5, 7\}\}$. The *degree* of a node is defined as the number of edges incident to it, or the number of nodes that are in it's neighborhood, that is $\mathbf{deg}(i) = |\mathbf{ne}(i)|$. In Figure 2.2, node 3 has degree $\mathbf{deg}(3) = 4$.

2.5.5 Graph density

In graph theory, a *dense graph* is a graph in which the number of edges is close to the maximal amount of edges, or a complete graph as in 2.5.2. The opposite, is a graph with only a few edges, known as a *sparse graph*. We define the graph density as

$$D = \frac{2|E|}{|V|(|V| - 1)}. \quad (2.23)$$

where $|E|$ is the cardinality edge set, and $|V|$ the cardinality of the node set. In our simulations we will generate graphs with density of $D \leq 0.05$. The idea is to approximate the graphs with real world applications, where the networks are sparse as in gene-expression (Albert, 2005), and social phenomena (Watts and Strogatz, 1998).

2.5.6 Adjacency Graph

An *adjacency matrix* $\mathbf{A}_{\mathcal{G}}$ is a square matrix with elements $\{0, 1\}$ tused for representing a finite graph $\mathcal{G}$. If the matrix element is 1, it indicates that there is an edge between two nodes. For a undirect graph with no loops, which is an edge that connects a node to itself, the matrix is symmetric with zeros on the diagonal. For a given graph $\mathcal{G}$ we have that $\mathbf{A}_{\mathcal{G}} = \{a_{ij}\}$ is the adjacency matrix with elements defined as,

$$a_{ij} = \begin{cases} 1 & \text{if } \{i, j\} \in E, \text{ and } i, j \in V, \\ 0 & \text{otherwise .} \end{cases} \quad (2.24)$$

Where $a_{ii} = 0$, $a_{ij} = a_{ji}$. In Figure 2.3, we have the graph $\mathcal{G}$ on the left with nodes $V = \{1, 2, 3, 4\}$, and edge set $E = \{\{1, 2\}, \{1, 3\}, \{1, 4\}, \{2, 4\}\}$, we can see that from (2.24), we have the adjacency matrix $\mathbf{A}_{\mathcal{G}}$ of $\mathcal{G}$ on the right of the picture.

Figure 2.3: Graph $\mathcal{G}$, with its adjacency matrix $\mathbf{A}_G$.

In chapter 5, we will apply simulation methods, to generate adjacency matrices for random graph structures.

2.6 Regularization

Regularization in Statistics and Machine learning, refers to the process of introducing additional information in a model in order to prevent overfitting, to induce sparsity in the model, among other uses (Abu-Mostafa *et al.*, 2012). In our case, as we will see later on, inducing sparsity by constraining the parametric space lowering the variance and selecting variables that are relevant to the model will be our interest. We will present two of the most known methods for the case where we have a Linear Model (Friedman *et al.*, 2001). The first technic is known as the **Ridge** regression, introduced by Hoerl and Kennard (1970), the second technic is the **Lasso**, introduced by Tibshirani (1996). For the sake of simplicity we will present the methods applied to OLS^2 in a case with two variables.

2.6.1 Ridge Regression

From the OLS method we have the following expression

$$\arg \min_{\boldsymbol{\beta}} \|\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}\|_2^2 = \arg \min_{\boldsymbol{\beta}} \left\{ \sum_{i=1}^n \left(y_i - \beta_0 - \sum_{j=1}^p \beta_j x_{ij} \right)^2 \right\}, \quad (2.25)$$

²Ordinary Least Squares, A.1.2.

Figure 2.4: Ridge Regression (dashed) and the Lasso regression (dotted).

The **Ridge** method adds an ℓ_2 restriction to the value of the parameters (β_1, β_2) in the form

$$\|\boldsymbol{\beta}\|_2^2 = \sum_{j=1}^p \beta_j^2 \leq t, \quad t > 0. \quad (2.26)$$

From the restriction (2.26), we have that (2.25) is rewritten as

$$\arg \min_{\boldsymbol{\beta}} \left\{ \sum_{i=1}^n \left(y_i - \beta_0 - \sum_{j=1}^p \beta_j x_{ij} \right)^2 + \lambda_r \sum_{j=1}^p \beta_j^2 \right\}, \quad \lambda_r > 0. \quad (2.27)$$

Where λ_r is the **Ridge** restriction coefficient. There is a two-way relation between λ_r in (2.27), and t in (2.26). When λ_r increases, there is more restriction in the parameters so t decreases, on the other hand when λ_r decreases, we have less restriction, so t increases.

2.6.2 Lasso

The **Lasso** regression is similar to the **Ridge** method, but instead of the ℓ_2 restriction, we impose the ℓ_1 norm, so, for the *OLS* in (2.25), we have the following restriction

$$\|\boldsymbol{\beta}\|_1 = \sum_{j=1}^p |\beta_j| \leq t, \quad t > 0, \quad (2.28)$$

which gives us the following expression

$$\arg \min_{\beta} \left\{ \sum_{i=1}^n \left(y_i - \beta_0 - \sum_{j=1}^p \beta_j x_{ij} \right)^2 + \lambda_L \sum_{i=1}^p |\beta_j| \right\}, \quad \lambda_L > 0.$$

Where λ_L is the **Lasso** coefficient. In Figure 2.4, the **Lasso** restriction is the diamond shaped (dotted), and we observe that it restrict the values of β_1 and β_2 , so that the value of $\hat{\beta}_2$ (square-shaped dot) is zero. Both methods have their benefits and their drawbacks. The **Ridge** regression reduces parameters variability and return better predictions for the model. In the other hand it doesn't do variable selection. Contrary to the **Ridge**, the **Lasso** does variable selection, but we are not able to calculate *p-values* for the chosen parameters, this means we can't perform hypothesis testing. In chapter 4 we will apply regularization in different methods, mainly for reconstruction of Networks.

Chapter 3

Graphical Models

3.1 Introduction

In the past decades, Graphical Models emerged as an interesting alternative for understanding complex phenomena in different applied fields. It is useful for understanding the joint distribution of an entire set of random variables and helps explicit conditional dependencies notions, representing them as lines between them. To better understand these dependencies we can use a simple example ([Giraud, 2014](#)). When it snows in Paris, the Parisians experience long traffic jams, at the same time a large number of snowmen “appears” in the city parks. We can presume that there’s a strong correlation between the size of the traffic jam, and the number of snowmen in the parks. But it’s known that snowmen don’t cause traffic jams and vice-versa. In fact, this dependency is due to the fact that both events have the same cause, the snow. We can represent this relation in the form of a diagram, or graph, as in Figure (3.1).

Figure 3.1: *Snowing causes both the traffic jams and snowmen in the parks.*

From the facts presented, we can presume that conditionally to the snow, that is, if we set aside the snow factor, the traffic jams and the snowmen at the park are likely not to be associated. To better understand these conditional relations, in this chapter, we will present

the two most known Graphical Models, the *Directed Acyclic Graphs*, or **DAG** model, also known as *Bayesian Networks* and the *Undirected Graphical models*, in which we will focus in the case where the variables are Gaussian (**GGM**). In this chapter we will present the basics of the two models and then concentrate in the **GGM**.

3.2 Direct Acyclic Graphical Models - DAG

A **DAG** is a direct graph $\mathcal{G} = (V, E)$, where V is a set of nodes and E an edge set of ordered pairs $E \subseteq V \times V$, with the properties as seen in 2.5.1. It is acyclic, that is, it has no loops. In Figure 2.1a, from chapter 2, we have a cyclic graph. In a **DAG** each variables corresponds to a random variable $X_V = (X_1, \dots, X_p)$, indexed by the set of vertices $V = \{1, \dots, p\}$. A **DAG** has the property that is overall density is obtained trough the graph structure. It factorizes following Conditional Independence rules 2.3, between the node X_i , with $i \in V$, and the rest of it's parents¹, which gives us the following definition.

3.2.1 Factorization - DAG

Let $\mathcal{G} = (V, E)$ be a **DAG**. If the distribution of the random variables X_V is a Graphical Model according to $\mathcal{G}$, with f a positive density, then f factors as

$$f(x_1, x_2, \dots, x_p) = \prod_{i=1}^p f(x_i | x_{\text{pa}(i)}). \quad (3.1)$$

Applying 3.1 to the graph structure in Figure 3.2, which is a **DAG** with nine variables, we have the following factorization,

$$\begin{aligned} f(x_1, x_2, \dots, x_9) &= f(x_1)f(x_2)f(x_3|x_1)f(x_4|x_2)f(x_5|x_2) \\ &\times f(x_6|x_3, x_4, x_5)f(x_7)f(x_8|x_6)f(x_9|x_7, x_8). \end{aligned}$$

Another way to interpret the relation between random variables in a **DAG**, is to view it under the perspective of *Direct Markov property* (Ganguly, 2014), which states that every

¹Definition given in 2.5.3.

Figure 3.2: Example of a **DAG**.

variable is conditionally independent of its non-descendants as in (3.2), where the descendants of a node i , are the nodes that are reached from i by following some sequence of arrows (i included), that we denote by $\mathbf{de}(i)$. For example, in Figure 3.2 the descendants of the node with index 4 is $\mathbf{de}(4) = \{6, 8, 9\}$.

$$X_i \perp\!\!\!\perp X_{V \setminus \mathbf{de}(i)} | X_{\mathbf{pa}(i)}, \quad i \in V. \quad (3.2)$$

So in a **DAG**, the relation between factorization and conditional independence is embedded in the graph structure. The **DAG** model is also known as *Bayesian Networks*, although it necessarily adopts a Bayesian statistics framework (Wasserman, 2013). In general **DAG** are harder to interpret in to make inference on (Hastie *et al.*, 2015). For more information about **DAG** we suggest Pearl (2009).

3.3 Undirected Graphical Models

An *Undirected Graphical Model*, also known as *Markov Random Field*, is a graph structure $\mathcal{G} = (V, E)$, with random variables as nodes with undirected edges, as seen in 2.5.1. In this model we can also factorize the density given the graph structure, but differently from the **DAG** model the Undirected Graphical model factorizes over the set of maximal cliques $\mathcal{C}$,

as seen in 2.5.4, and instead of using densities f , as in 3.1, it uses positive functions ψ_C , with $C \in \mathcal{C}$, known as *potentials*. The factorization is given as follows.

3.3.1 Factorization - (Undirect Graphical Models)

A probability density function f over an undirected graph structure $\mathcal{G} = (V, E)$ is given by

$$f(x_1, x_2, \dots, x_p) = \frac{1}{Z} \prod_{C \in \mathcal{C}} \psi_C(x_C), \quad (3.3)$$

where $x_C \doteq (x_i, i \in C)$, and Z is the normalizing constant known as the *partition function*, which is given by

$$Z = \sum_{x \in \mathcal{X}} \prod_{C \in \mathcal{C}} \psi_C(x_C).$$

where the set $\mathcal{X}$ is the set which the random variables $X_1, X_2, \dots, X_p$ are defined. The undirected graph in Figure 5.2, with random variables $(X_1, X_2, \dots, X_7)$ as nodes, factors as (3.3), and the set of maximal cliques $\mathcal{C} = \{\{1, 2, 3\}, \{4, 5, 6\}, \{3, 4\}, \{2, 5\}, \{5, 7\}\}$ resulting in the joint density

$$f(x_1, x_2, \dots, x_p) \propto \psi_{123}(x_1, x_2, x_3) \psi_{456}(x_4, x_5, x_6) \psi_{34}(x_3, x_4) \psi_{25}(x_2, x_5) \psi_{57}(x_5, x_7), \quad (3.4)$$

for some choice of potential function $\{\psi_{123}, \psi_{456}, \psi_{34}, \psi_{25}, \psi_{57}\}$.

Figure 3.3: *Undirected graphical model*

Next will present an important property that unites the concept of graphical models and factorization to the conditional independence between the variables.

3.4 The Markov Properties

The Markov property relates the structure of the graph with conditional independence properties. In an Undirected Graphical Models, conditional independence are relations between separated subsets of the nodes in the graph. From these separations we have three Markov properties. The first is the *Pairwise Markov Property*, that states that for any pair of non-adjacent nodes, they are conditionally independent to the each other given the rest. The second is the *Local Markov Property*, where a node is conditionally independent to its non-neighborhood given it's neighborhood. And the last is the *Global Markov property* which relates conditional independence between sets separated by a given set. For a given finite graph $\mathcal{G} = (V, E)$, with joint distribution X_V . We define these properties as follows.

3.4.1 Pairwise Markov Property (PM)

For any non-adjacent $i, j \in V$, that is $\{i, j\} \in E$, we have that

$$X_i \perp\!\!\!\perp X_j | X_{V \setminus \{i, j\}}. \quad (3.5)$$

3.4.2 Local Markov Property (LM)

For any node $i \in V$, we have that

$$X_i \perp\!\!\!\perp X_{V \setminus \text{cl}(i)} | X_{\text{ne}(i)}, \quad (3.6)$$

where $\text{ne}(i)$ is the neighborhood of i , as seen 2.5.3, and $\text{cl}(i)$ is the closure of i , defined as $\text{cl}(i) = \text{ne}(i) \cup \{i\}$.

3.4.3 Global Markov Property (GM)

For any disjoint subsets U, B, S of V , such that S separates U from B , then

$$X_A \perp\!\!\!\perp X_B | X_S. \quad (3.7)$$

These properties are not equivalent. The *Global Markov property* implies in the *Local Markov property*, that in turn, implies in the *Pairwise Markov Property*, so

$$(\mathbf{GM}) \implies (\mathbf{LM}) \implies (\mathbf{PM}). \quad (3.8)$$

If we have a positive density $f(x_1, x_2, \dots, x_p) > 0$, then there is an equivalence between $(\mathbf{GM})$, $(\mathbf{LM})$, and $(\mathbf{PM})$, so we have that

$$(\mathbf{GM}) \iff (\mathbf{LM}) \iff (\mathbf{PM}) \quad (3.9)$$

These properties and examples of equivalence are largely discussed in Lauritzen (1996).

Contrary to the DAG, where there is clear equivalence between factorization and the Markov Property (3.2), in the case of Undirected Graphical Models this property is only possible by the Hammersley-Clifford theorem², where it is shown that a Gibbs random field satisfies every Markov property as seen in 3.4, and is represented by a Gibbs measure for an appropriate (locally defined) energy function, then we can apply the factorization defined in (3.3). The inverse is also true, with the factorization represented as $(\mathbf{F})$, that gives us the relation in 3.10.

$$(\mathbf{F}) \iff (\mathbf{GM}) \iff (\mathbf{LM}) \iff (\mathbf{PM}). \quad (3.10)$$

3.5 Gaussian Graphical Models

Gaussian Graphical Models, or **GGM**, are Graphical Models where the variables associated to the graph structure are Gaussian, as seen in 2.2.1, this fact provides an useful framework for representing network structures, which allows Conditional Independence identification among the variables. In a **GGM**, X_V , has p -dimensional Gaussian distribution, with non-singular Covariance matrix Σ . The vector X_V , indexed by the set $V = \{1, \dots, p\}$, models a graph structure $\mathcal{G} = (V, E)$. From the Gaussian distribution properties in 2.2.1, it is known that zero Partial correlation, as seen in 2.4.2, between variables X_i and X_j with

²Hammersley, J. M., Clifford, P. (1971), "Markov Fields on Finite Graphs and Lattices", unpublished, available at <http://www.statslab.cam.ac.uk/~grg/books/hammfest/hamm-cliff.pdf>.

$i, j \in V$ is equivalent to conditional independence of the variables given the rest of the variables in $X_{V_{-ij}}$, where $V_{-ij} = V \setminus \{i, j\}$. We presented in (2.21), a relation between the correlation matrix $\mathbf{R}$, and the Partial correlation matrix $\mathbf{P}$, this relation is easily extended (Thomas, 2012) to the elements of the Precision matrix $\mathbf{K} = \mathbf{\Sigma}^{-1}$ in the form

$$\rho_{ij.V_{-ij}} = -\frac{\kappa_{ij}}{\sqrt{\kappa_{ii}\kappa_{jj}}}, \quad \mathbf{K} = \{\kappa_{ij}\}, \quad i, j \in V. \quad (3.11)$$

From the the Multivariate Gaussian properties, the density in 2.2.1 can be rewritten as

$$f(\mathbf{x}) = \exp\left(\boldsymbol{\alpha} + \boldsymbol{\beta}^T \mathbf{x} - \frac{\mathbf{x}^T \mathbf{K} \mathbf{x}}{2}\right), \quad \mathbf{x} = (x_1, x_2, \dots, x_p), \quad (3.12)$$

where $\boldsymbol{\alpha}$ is the normalizing constant, and $\boldsymbol{\beta}^T \mathbf{x} = \mathbf{\Sigma}^{-1} \boldsymbol{\mu}$. We can observe that if the elements of the Precision matrix are zero, κ_{ij} , we can factorize (3.12) in to a form $f(x_i, x_j, \mathbf{x}_{-ij}) = h(x_i, \mathbf{x}_{-ij})k(x_j, \mathbf{x}_{-ij})$, for $i \in V$ and $\mathbf{x}_{-ij} \doteq \mathbf{x}_{V_{-ij}}$. From 2.13, we have that X_i and X_j are conditionally independent give the rest. This gives us the following relation between the Precision matrix, the Partial correlation and Conditional Independence,

$$\kappa_{ij} = 0 \Leftrightarrow \rho_{ij.V_{-ij}} = 0 \Leftrightarrow X_i \perp\!\!\!\perp X_j | X_{V_{-ij}}, \quad i, j \in V. \quad (3.13)$$

From the relation in (3.13), we can estimate the graph structure, trough the Partial correlation or Precision matrix. An easy way is to use the *OLS* estimate of $\mathbf{\Sigma}$, for the case we have $X_V \sim \mathcal{N}_V(\mathbf{0}, \mathbf{\Sigma})$, this estimate is in the form

$$\hat{\mathbf{\Sigma}} = \frac{1}{n} \mathbf{X}^T \mathbf{X}, \quad (3.14)$$

where $\mathbf{X}$ is a $n \times p$ dimensional data matrix. From (3.14) we estimate the Precision matrix $\hat{\mathbf{K}}$, that in turn, from (3.11) gives us Partial Correlation matrix estimation

$$\hat{\mathbf{P}} = -\mathbf{scale}(\hat{\mathbf{K}}), \quad (3.15)$$

where $\mathbf{scale}(A) = \text{diag}(A)^{-1/2} A \text{diag}(A)^{-1/2}$, with A a square matrix, and $\text{diag}(A)$ is the square empty matrix with the diagonal of A in its diagonal.

In Figure 3.4a we have a graph structure with $|V| = 20$ nodes with its adjacency matrix, represented as a heat-map, in Figure 3.4b. From this adjacency matrix we generated a Covariance matrix, using a procedure that will present in chapter 5, in which we generated a sample of size $n = 200$, $\hat{\mathbf{P}}$ is estimated using (3.15). We can observe clearly, that the graph structure in Figure 3.4a is “printed” in the Partial correlation estimate, making the reconstruction of the network possible.

Figure 3.4: (a) GGM graph structure. (b) Adjacency Matrix

Figure 3.5: (a) Estimate $\hat{\mathbf{P}}$. (b) Estimate $\tilde{\mathbf{P}}$.

For the case that $n < p$, we have that data is known as high dimensional, that means that $\mathbf{P}$ can't be estimated using (3.15), due to the fact that $\hat{\Sigma}$ is a singular matrix. If we wish to estimate $\mathbf{P}$ in this case we have to use other means. In Figure 3.5b, we have an estimate $\tilde{\mathbf{P}}$, from the same data as used for the estimate on Figure 3.5a, but with sample size reduced

to $n = 10$. The estimate $\tilde{\mathbf{P}}$ could only be obtained using the generalized inverse³ of $\hat{\Sigma}$. We can observe in Figure 3.5b that estimates in $\tilde{\mathbf{P}}$ are different from the ones in Figure 3.5a, the values are larger than those from Figure 3.5b. In fact if we reduce the sample size of n in relation to p , even if $n > p$, the Partial Correlation spread will increase, as in the plot presented Figure 3.6. When $n < 10$ we have the generalized inverse.

Figure 3.6: *Spread of the Partial Correlation estimates in relation to the sample size.*

Using the generalized inverse is not the only method for estimating $\mathbf{P}$ in high dimensional cases, in fact this method is not very precise since there's no unicity in generalized inverses. Over the years many methods were developed, examples include Schäfer and Strimmer (2005), Banerjee *et al.* (2008), and Peng *et al.* (2009). In the next chapter we will present three of these methods, the *Graphical Lasso*, or **GLasso**, the method known as **GGMridge**, and the **LPC** method.

³The generalized inverse is defined in A.2.1.

Chapter 4

Methods

4.1 Introduction

We will briefly present the methods evaluated in chapters 5 and 6. We will start with the **GLasso**, and present its relation to the regularized log-likelihood function, next we will present the **GGMrige** and discuss some aspects of its regularization method, and finally we will present the **LPC** method, that selects the neighborhood of a given variable based on it's correlation.

4.2 GLasso

The **GLasso** method has its roots on the work of Meinshausen and Bühlmann (2006), in which Gaussian Graphical Models are estimated by fitting a ℓ_1 penalty for the elements of the Precision matrix $\mathbf{K}$ to increase its sparsity. Before we continue it will be useful to present the log-likelihood function for $\mathbf{K}$. Suppose $\mathbf{X}$ is a $n \times p$ dimensional data matrix with distribution X_V , as seen in section 3.5, and Precision matrix $\mathbf{K}$, it is known (Friedman *et al.*, 2001), that the log-likelihood $\mathcal{L}(\mathbf{X}; \mathbf{K})$, is in the form

$$\mathcal{L}(\mathbf{X}; \mathbf{K}) = \log \det(\mathbf{K}) - \text{tr}(\mathbf{S}\mathbf{K}), \quad (4.1)$$

where $\det(A)$ is the determinant of A , $\text{tr}(A)$ is it's trace, and $\mathbf{S} = n^{-1} \sum_{k=1}^n \mathbf{X}^{(k)} \mathbf{X}^{(k)T}$, where $\mathbf{X}^{(k)}$, $k \in \{1, \dots, n\}$ are the lines of $\mathbf{X}$, is the empirical covariance matrix. The maximum likelihood estimates (**MLE**) of (4.1) converges to $\mathbf{K}$ as n goes to infinity (Hastie *et al.*, 2015),

but, in practice, several applications have much more variables than samples, $n \ll p$, which implies that $\mathbf{S}$ is rank degenerated and makes the **MLE** method unapliable. [Banerjee et al. \(2008\)](#) approached this problem by solving the penalized log-likelihood

$$\mathcal{L}(\mathbf{X}; \mathbf{K}) = \log \det(\mathbf{K}) - \text{tr}(\mathbf{SK}) - \lambda \|\mathbf{K}\|_1 \quad (4.2)$$

showing that it is convex, and performing optimized methods in a block coordinate fashion ([Banerjee et al., 2008](#)). The **GLasso** method approaches 4.2 by giving the exact maximizer of the penalized log-likelihood in the form

$$\mathbf{K}^{-1} - \mathbf{S} - \lambda \text{Sign}(\mathbf{K}) = 0. \quad (4.3)$$

In (4.3) we have the sub gradient notation ([Friedman et al., 2001](#)) for the operator $\text{Sign}(\cdot)$, defined as $\text{Sign}(\kappa_{ij}) = \text{sign}(\kappa_{ij})$ if $\kappa_{ij} \neq 0$, else if $\kappa_{ij} = 0$, then $\text{Sign}(\kappa_{ij}) \in [-1, 1]$. From the properties of the precision matrix, $\mathbf{W} = \mathbf{K}^{-1}$, and the partition

$$\begin{pmatrix} W_{11} & w_{12} \\ w_{21} & w_{22} \end{pmatrix} \begin{pmatrix} \mathbf{K}_{11} & \kappa_{12} \\ \kappa_{21} & \kappa_{22} \end{pmatrix} = \begin{pmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{0} & 1 \end{pmatrix},$$

we have that (4.3) can be rewritten

$$W_{11} + s_{12} + \lambda \text{Sign}(\beta) = 0, \quad (4.4)$$

where $w_{11}\beta = -W_{11}\kappa_{12}$, as derived in (2.8). In [Friedman et al. \(2008\)](#), estimating the system (4.4) is equivalent to estimating equations for the LASSO regression (2.28). The algorithm applies coordinate descent methods ([Friedman et al., 2007](#)) to recursively solve (4.4). The procedure is explained in detail in [Friedman et al. \(2001\)](#), we present the algorithm of the **GLasso** method in Algorithm 1. There are other ways to update $\hat{\beta}_j$ ([Banerjee et al., 2008](#)), but the coordinate descent is the most intuitive to understand. The method updates as follows,

$$\hat{\beta}_j \leftarrow S(s_{12(j)} - \sum_{k \neq j} w_{11(kj)} \hat{\beta}_k, \lambda_L) / w_{11(j)} \quad (4.5)$$

Algorithm 1 GLasso

procedure

Initialize $\mathbf{W} = \mathbf{S} + \lambda_L \mathbf{I}$, (the diagonal of $\mathbf{W}$ doesn't change);

for $j = 1, 2, \dots, p, 1, \dots$ until convergence **do**

1. Partition $\mathbf{W}$ into **part 1**: all but the j th row and column and

part 2: the j th row and column;

2. Solve $\mathbf{W}_{11}\beta - s_{12} + \lambda_L \text{Sign}(\beta) = 0$, using (4.5);

3. Update $w_{12} = \mathbf{W}_{11}\hat{\beta}$;

end for

Solve, for $\hat{\kappa}_{12} = -\hat{\beta}\hat{\theta}_{22}$ where $1/\hat{\kappa}_{22} = w_{22} - w_{12}^T\hat{\beta}$.

end procedure

for $j = 1, 2, \dots, p-1, 1, 2, \dots, p-1, 1, 2, \dots$, where $s_{12(j)}$ are the elements of the vector s_{12} , $w_{11(j)}$ are elements of the partitioned matrix $\mathbf{W}_{11}$ and S , is the soft threshold operator

$$S(x, t) = \text{sign}(x)(|x| - t)_+.$$

The coordinate descent method makes the method solve sparse problem with 1000 nodes in less than a minute, and can work easily with different values of λ_L . But, there are some drawbacks, the method doesn't estimate correctly the Partial correlations, it "learns" the structure, and there's a need to apply cross validation methods to select the best coefficient λ_L . In [Bien *et al.* \(2011\)](#) there is an example of cross-validation for estimating Covariance matrix, but can also be applied for $\mathbf{K}$.

4.3 GGMridge

Contrary to the **GLasso** method seen in [4.2](#), that tries to "learn" the graph structure, the **GGMridge** ([Ha and Sun, 2014](#)) estimates the original network by identifying the zero elements of the Partial correlation matrix, and re-estimates the remaining non-zero values. The idea behind this procedure is to obtain not only the network structure but the true Partial correlation values, that in the gene co-expression perspective measures the strength of the expression between any two genes.

The method basically consists of three stages, in the first stage we obtain a penalized estimation of the Partial correlation matrix using a Ridge “*ad-hoc*” solution (Hoerl and Kennard, 1970). Next it uses a threshold $\alpha_r \in (0, 1)$ to select the non-zero elements based on mixture distributions related to the hypothesis test of the elements that were estimated. Finally it re-estimates the Partial correlation of the remaining non-zero elements. The **GGMridge** method is largely based on the work of Schäfer and Strimmer (2005), but instead of using the Ridge “*ad-hoc*” solution based on generalized inverse of the empirical Covariance matrix $\mathbf{S}$, to guarantee that in high dimensional settings $\mathbf{S}$ would be non-singular.

The method starts by obtaining the estimate of the Partial correlation matrix $\tilde{\mathbf{P}}_{\lambda_r}$ from the empirical Covariance matrix $\mathbf{S}$, obtained from X_V as seen in 2.2.1 (centered in zero, with spread 1), with $n < p$, in the form

$$\tilde{\mathbf{P}}_{\lambda_r} = -\mathbf{scale}((\mathbf{S} + \lambda_r \mathbf{I}_p)^{-1}), \quad (4.6)$$

where the operator **scale** is as defined in (3.15). In (4.6), the **scale** function is applied to $(\mathbf{S} + \lambda_r \mathbf{I}_p)^{-1}$, which is an estimate of the precision matrix $\tilde{\mathbf{K}}_{\lambda_r}$, where $\lambda_r > 0$ is known as the ridge coefficient (actually this “*ad-hoc*” solution is not the minimization of the log-likelihood function, with ℓ^2 penalty, a formal solution for this minimization is seen in Warton (2008)), which can be obtained by cross-validation¹, and $\mathbf{I}_p$ is a $p \times p$ identity matrix. The elements $\{\tilde{\rho}_{ij}^{\lambda_r}\} = \tilde{\mathbf{P}}_{\lambda_r}$ are tested using the Fisher z – *transformation*

$$\psi(\tilde{\rho}_{ij}^{\lambda_r}) = \frac{1}{2} \log \left\{ (1 + \tilde{\rho}_{ij}^{\lambda_r}) / (1 - \tilde{\rho}_{ij}^{\lambda_r}) \right\}, \quad i, j \in V, \text{ with } i \neq j. \quad (4.7)$$

From (4.7), follows a mixture distribution of $f_0(\psi)$, with $\psi \doteq \psi(\tilde{\rho}_{ij}^{\lambda_r})$, and alternative distribution $f_a(\psi)$, where $H_0 : \rho_{ij}^{\lambda_r} = 0$, $H_a : \rho_{ij}^{\lambda_r} \neq 0$. Due to assumption of sparsity of the original $\mathbf{P}$ we assume that the mixture

$$f(\psi) = \eta_0 f_0(\psi) + \eta_a f_a(\psi), \quad (4.8)$$

have the majority of observations around H_0 , so we have that $\eta_0 \gg \eta_a$, with $\eta_0 + \eta_a = 1$. We

¹See supplementary B from (Ha and Sun, 2014).

estimate the distribution of (4.8) using Efron's central matching method (Efron, 2004) where $f_0(\psi)$ has gaussian distribution $\mathcal{N}(\mu_0, \sigma_0)$, and $f_a(\psi)$ is left unknown. Both distributions are matched at their central parts (Ha and Sun, 2014) then, using polynomial Poisson regression, we estimate $f(\psi)$. From this distribution we have the p -values, and the selected non-zero estimates through a threshold α_r (that can be learned by cross validation along λ_r^2), used in a false discovery rate test (Benjamini and Hochberg, 1995).

This process generates a Partial correlation graph structure where each variable X_i with $i \in V$, has a neighborhood of non-zero elements $\mathbf{ne}_i \subset V$. From the properties of the partitioned distribution seen in chapter 2, in (2.3), (2.6), (2.7) and (2.8), the estimates of the precision matrix $\mathbf{K}$ are

$$\hat{\kappa}_{ii} = \frac{(n - |\mathbf{ne}_i|)}{\|X_i - \mathbf{X}_{\mathbf{ne}_i} \hat{\beta}^{i, \mathbf{ne}_i}\|_2^2} \quad \text{and} \quad \tilde{\kappa}_{ij} = -\hat{\kappa}_{ii} \hat{\beta}^{i, \mathbf{ne}_i}_j. \quad (4.9)$$

Based on the sparsity assumption we have that $|\mathbf{ne}_i| < n$, with $\hat{\beta}^{i, \mathbf{ne}_i} = (\mathbf{X}_{\mathbf{ne}_i}^T \mathbf{X}_{\mathbf{ne}_i})^{-1} \mathbf{X}_{\mathbf{ne}_i}^T X_i$, where $\mathbf{X}_{\mathbf{ne}_i}$ is a $|\mathbf{ne}_i| \times n$ submatrix of the data matrix $\mathbf{X}$. Since the solution is not symmetric to the elements off-diagonal (4.9), we have that the final estimate is

$$\hat{\kappa}_{ij} = \hat{\kappa}_{ji} = \text{sign}(\hat{\beta}_j^{i, \mathbf{ne}_i}) \sqrt{|\tilde{\kappa}_{ij} \tilde{\kappa}_{ji}|} \quad \text{for } i \neq j, \quad (4.10)$$

with $\hat{\beta}_j^{i, \mathbf{ne}_i}$ elements of the vector $\hat{\beta}^{i, \mathbf{ne}_i}$. To better understand the method, we have the **GGMridge** represented in Algorithm 2 in simpler way that presented in Ha and Sun (2014).

4.4 Local Partial Correlation (LPC)

As seen in section 3.5, it is known, in multivariate models, when n is smaller than p , that most statistical methods are compromised. A popular strategy in bioinformatics, where this problem is common, is to compute the standard Pearson correlation between any two genes to

²This method is explained in the supplementary materials of Ha and Sun (2014), Section B.

Algorithm 2 GGMridge

procedure1. $\tilde{\mathbf{P}}_{\lambda_r} = -\text{scale}((\mathbf{S} + \lambda_r \mathbf{I}_p)^{-1});$ 2. Test $H_0 : \rho_{ij}^{\lambda_r} = 0$, $H_a : \rho_{ij}^{\lambda_r} \neq 0$ with

$$\psi(\tilde{\rho}_{ij}^{\lambda_r}) = 1/2 \log\{(1 + \tilde{\rho}_{ij}^{\lambda_r})/(1 - \tilde{\rho}_{ij}^{\lambda_r})\}, \text{ for } \{\tilde{\rho}_{ij}^{\lambda_r}\} = \tilde{\mathbf{P}}_{\lambda_r};$$

Estimate *p-values* from $f(\psi) = \eta_0 f_0(\psi) + \eta_a f_a(\psi)$ as in (Ha and Sun, 2014);3. If the *p-values* for $\rho_{ij}^{\lambda_r}$ for $i < j$, is less than α_r define a neighborhood $\mathbf{\hat{n}e}_i$ for X_i ;4. $\hat{\beta}^{i, \mathbf{\hat{n}e}_i} = (\mathbf{X}_{\mathbf{\hat{n}e}_i}^T \mathbf{X}_{\mathbf{\hat{n}e}_i})^{-1} \mathbf{X}_{\mathbf{\hat{n}e}_i} X_i$, for $i \in V$;5. Estimate $\kappa_{ii} = (n - |\mathbf{\hat{n}e}_i|) / \|\mathbf{X}_{\mathbf{\hat{n}e}_i} \hat{\beta}^{i, \mathbf{\hat{n}e}_i}\|_2^2$ and $\tilde{\kappa}_{ij} = -\hat{\kappa}_{ii} \hat{\beta}^{i, \mathbf{\hat{n}e}_i}$;6. Estimate $\hat{\kappa}_{ij} = \hat{\kappa}_{ji} = \text{sign}(\hat{\beta}_j^{i, \mathbf{\hat{n}e}_i}) \sqrt{|\tilde{\kappa}_{ij} \tilde{\kappa}_{ij}|}$ for $i \neq j$;7. Return $\hat{\mathbf{P}} = -\text{scale}((\hat{\mathbf{K}}))$.**end procedure**

learn a network structure, called “relavance network”, where a missing edge denotes marginal independence. However, high correlation may indicate different interactions between genes (Schafer and Strimmer, 2005).

Inspired by the bioinformatics simple approach came the idea to select “local” partial correlations. What we mean by “locally selected” is that for each Pearson correlated pair chosen through a threshold in it’s *p-values*, we have a neighborhood of nonzero elements. If this neighborhood has more variables than samples, we select fractions of the n highest Pearson correlations, and build a Partial correlation submatrix, that is further tested if the elements are non-zero, which indicates if an edge is present between this pair, which is called this method local Partial correlation or **LPC** (Thomas *et al.*, 2012). In Figure 4.1 we can observe the neighborhood selected with the Pearson correlation (traced), and then the fraction of this neighborhood being locally selected by the highest correlation values (dark dots), which are the values used for calculating the Partial correlation between X_i and X_j .

So, for a multivariate Gaussian distribution X_V , as in 2.2.1, for a sample with size n , with $p = |V|$ variables, and $n < p$. The method starts by calculating $\rho_{ij} = \rho(X_i, X_j)$, for every $i, j \in V$, which is the Pearson correlation defined in 2.4.1. For each $\hat{\rho}_{ij}$, we perform a hypothesis test $H_0 : \rho_{ij} = 0$ versus $H_a : \rho_{ij} \neq 0$, where the *p-values* $\mathbf{p}_{ij}$, obtained trough squared *t-statistics* as seen in (2.22). If $\mathbf{p}_{ij}$ is small, there is an indication that there might

Figure 4.1: *Neighborhood selection with LPC.*

be an interaction between X_i and X_j , if $\mathbf{pv}_{ij}$ is high then there might be no interactions. We then consider a threshold $\alpha_{\hat{\rho}} \in [0, 1]$ to select which values of $\hat{\rho}_{ij}$ that are to be further analyzed. From this selection, we construct a new matrix $\tilde{\mathbf{R}}$ such that each row and column is filled with the elements

$$\tilde{\mathbf{R}} = \{\tilde{r}_{ij}\}, \quad \tilde{r}_{ij} = \begin{cases} \hat{\rho}_{ij}, & \text{if } \mathbf{pv}_{ij} < \alpha_{\hat{\rho}}, \quad \text{for all } i, j \in V, \\ 0, & \text{otherwise.} \end{cases} \quad (4.11)$$

For a fixed $i, j \in V$ such that $\tilde{r}_{ij} \neq 0$, we will define the local neighborhood of X_i and X_j as the subsets of V . So, for each $k \in V \setminus \{i\}$ and $l \in V \setminus \{j\}$, with $\tilde{r}_{ik} \neq 0$ we have the subsets

$$\hat{\mathbf{ne}}_i^{local} = \{k \in V \setminus \{i\}; \tilde{r}_{ik} \neq 0\}, \quad \text{and} \quad \hat{\mathbf{ne}}_j^{local} = \{l \in V \setminus \{j\}; \tilde{r}_{jl} \neq 0\}. \quad (4.12)$$

For a fixed pair $\{i, j\} \in V$ with conditions (4.12), we have the local neighborhood of the pair defined as

$$\hat{\mathbf{ne}}_{ij}^{local} = \{\hat{\mathbf{ne}}_i^{local} \cup \hat{\mathbf{ne}}_j^{local}\} \setminus \{i, j\}.$$

If $|\hat{\mathbf{ne}}_{ij}^{local}| > n$, we select the $\lfloor n/2 \rfloor$ (where $\lfloor n/2 \rfloor$ is the greatest integer function), highest correlations associated with $\{i, j\}$, and the local neighborhood associated with this correlations, $\hat{\mathbf{ne}}_{ij}^{LPC} \subset \hat{\mathbf{ne}}_{ij}^{local}$, where

$$\hat{\mathbf{ne}}_{ij}^{LPC} = \{k \in \hat{\mathbf{ne}}_{ij}^{local}; \tilde{r}_{\{i,j\}k}^{(1)}, \dots, \tilde{r}_{\{i,j\}k}^{(\lfloor n/2 \rfloor)}\}, \quad (4.13)$$

where $\tilde{r}_{\{i,j\}k}^{(m)}$, are the sorted correlation values from $m = 1, \dots, \lfloor n/2 \rfloor$. From 4.13, we determine a local correlation submatrix $\tilde{\mathbf{R}}^{LPC}$ of $\tilde{\mathbf{R}}$, with elements $\hat{\mathbf{R}}^{LPC} = \{\hat{\rho}_{kl}^{LPC}\}$, with the variables indexed by the set $\hat{\mathbf{ne}}_{ij}^{LPC} \cup \{i, j\}$, in the form

$$\hat{\rho}_{kl}^{LPC} = \rho(X_{\{i,j\}}, X_{\hat{\mathbf{ne}}_{ij}^{LPC}}), \quad \text{with } k, l \in \hat{\mathbf{ne}}_{ij}^{LPC} \cup \{i, j\}.$$

From the properties of the Partial correlation matrix seen in (2.21), we define the matrix $\hat{\mathbf{Q}}_{LPC} = (\hat{\mathbf{R}}^{local})^{-1}$, which gives us the local Partial correlation, or **LPC** estimate, of X_i and X_j , in the form

$$\hat{\rho}_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}} = -\frac{q_{ij}^{LPC}}{\sqrt{q_{ii}^{LPC} q_{jj}^{LPC}}}, \quad \text{with } \hat{\mathbf{Q}} = \{q_{ij}^{LPC}\}.$$

To test the hypothesis $H_0 : \rho_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}} = 0$ versus $H_a : \rho_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}} \neq 0$, that is, to test if there is an edge between X_i and X_j we apply the *z-transformation*,

$$\psi(\hat{\rho}_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}}) = \frac{1}{2} \log\{(1 + \hat{\rho}_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}})/(1 - \hat{\rho}_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}})\}, \quad (4.14)$$

for significance level of α_{LPC} the null hypothesis is rejected if

$$\sqrt{n - |\hat{\mathbf{ne}}_{ij}^{LPC}|} - 3 \cdot |\psi(\hat{\rho}_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}})| > \Phi^{-1}(1 - \alpha_{LPC}/2), \quad (4.15)$$

where Φ is the cumulative Gaussian distribution $\mathcal{N}(0, 1)$. For more information about the test, we suggest [Kendall *et al.* \(1946\)](#).

In Algorithm 3, we have the routine for implementing the **LPC** method, and in B.1.1 we have the R implementation used in the simulations in 5.5, in chapter 5. We can observe from the passages shown in this section, that the **LPC** method is simple to understand and to implement. But there is a major drawback, that the time the method takes to complete the routine increases exponentially if the number of variables increases. To overcome this problem, we applied parallelization of some of the routines in the method, using the R package **doParallel**,³ to try improve its performance.

³<https://cran.r-project.org/web/packages/doParallel/index.html>.

Algorithm 3 LPC

procedure

1. Estimate $\hat{\rho}_{ij} = \rho(X_i, X_j)$, for every $i, j \in V$;
2. Calculate the *p-values* $\mathbf{pv}_{ij}$ for every ρ_{ij} ;
3. Initialize $\tilde{\mathbf{R}} = \{\tilde{r}_{ij}\}$ an empty matrix, given a threshold $\alpha_{\hat{\rho}}$;

$$\tilde{r}_{ij} = \begin{cases} \hat{\rho}_{ij}, & \text{if } \mathbf{pv}_{ij} < \alpha_{\hat{\rho}}, \text{ for all } i, j \in V, \\ 0, & \text{otherwise.} \end{cases}$$

for every pair $i, j \in V$, and $\tilde{r}_{ij} \neq 0$ **do**

1. Define $\hat{\mathbf{ne}}_i^{local} = \{k \in V \setminus \{i\}; \tilde{r}_{ik} \neq 0\}$ and $\hat{\mathbf{ne}}_j^{local} = \{l \in V \setminus \{j\}; \tilde{r}_{jl} \neq 0\}$;
2. Define $\hat{\mathbf{ne}}_{ij}^{local} = \{\hat{\mathbf{ne}}_i^{local} \cup \hat{\mathbf{ne}}_j^{local}\} \setminus \{i, j\}$;
3. if $|\hat{\mathbf{ne}}_{ij}^{local}| > n$, define $\hat{\mathbf{ne}}_{ij}^{LPC} = \{k \in \hat{\mathbf{ne}}_{ij}^{local}; \tilde{r}_{\{i,j\}k}^{(1)}, \dots, \tilde{r}_{\{i,j\}k}^{(\lfloor n/2 \rfloor)}\}$;
4. $\hat{\rho}_{kl}^{LPC} = \rho(X_{\{i,j\}}, X_{\hat{\mathbf{ne}}_{ij}^{LPC}})$, with $k, l \in \hat{\mathbf{ne}}_{ij}^{LPC} \cup \{i, j\}$;
5. $\hat{\mathbf{Q}}_{LPC} = (\hat{\mathbf{R}}^{local})^{-1}$;
6. $\hat{\rho}_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}} = -q_{ij}^{LPC} / \sqrt{q_{ii}^{LPC} q_{jj}^{LPC}}$, with $\hat{\mathbf{Q}} = \{q_{ij}^{LPC}\}$;
7. Test $H_0 : \rho_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}} = 0$ versus $H_a : \rho_{ij.\hat{\mathbf{ne}}_{ij}^{LPC}} \neq 0$ with (4.15) and (4.15).

end for

end procedure

Chapter 5

Simulation

5.1 Introduction

In this chapter we will implement and evaluate the methods presented in chapter 4. The idea is to reconstruct different network structures and compare the results using ROC curves. The networks were generated using *Random Graph* models (Bollobás, 1998). They are random because there's an underlying probability distribution that generates the graph. We have chosen three known models, the *Erdős-Rényi*, the *Watts-Strogatz*, and the *Barabási-Albert* (Figures 5.1a, 5.1b, 5.1c). The models are generated using random processes that will be further explained in 5.2. For each model we will generate a Covariance matrix from the graph's adjacency matrix (seen in section 2.5.6) next, we simulate a high dimensional sample from a multivariate Gaussian distribution. The details of this transformation are given in section 5.3. The results of the comparison are given 5.5.

Figure 5.1: *Simulated graph structures.*

5.2 Graph structures

5.2.1 Erdős-Rényi

The *Erdős-Rényi* model, first introduced by [Erdos and Rényi \(1960\)](#), is a random graph with well-known properties ([Bollobás, 1998](#)). The set of edges are distributed equally and independently across the node set with fixed probability. The graph $\mathcal{G}_{ER} = (V, E)$ is obtained by starting with a node set $V = \{1, \dots, p\}$, in which we connect any two nodes with an edge with probability p_{ER} . We will apply this method to generate in [5.3](#), a Covariance matrix from the adjacency matrix $\mathbf{A}_{\mathcal{G}_{ER}}$, in order to perform the comparisons in [5.5](#). In [Algorithm 4](#), we have a simple method for generating $\mathbf{A}_{\mathcal{G}_{ER}}$.

Algorithm 4 Erdős-Rényi

procedure

 Initialize $\mathbf{A}_{\mathcal{G}_{ER}} = \{a_{ij}\}$, empty matrix and p_{ER} ;

 for $i < j$, for all $i, j \in V$: do

 1. $p_{ij} \sim \mathcal{U}(0, 1)$;

 2. $a_{ij} = \begin{cases} 1, & \text{if } p_{ij} < p_{ER}, \\ 0, & \text{otherwise;} \end{cases}$;

end for

 $\mathbf{A}_{\mathcal{G}_{ER}} = \mathbf{A}_{\mathcal{G}_{ER}} + \mathbf{A}_{\mathcal{G}_{ER}}^T$;

end procedure

Although the *Erdős-Rényi* model is relevant due it's simplicity and known properties, it fails to capture networks seen in real world applications. Mainly by the fact that the probability of finding nodes with large degree, in this process, are practically null. We have chosen this model because it is a standard structure used to evaluate methods of network reconstruction in several publications such as [Ha and Sun \(2014\)](#), [Schäfer and Strimmer \(2005\)](#), and [Cai et al. \(2016\)](#), and others. Also, it will be useful to compare the performances of the selected methods in this work with other methods in similar situations.

5.2.2 Watts-Strogatz model

The *Watts-Strogatz* model, introduced by Watts and Strogatz (1998), based on the idea of modeling social interactions and other networks in real world applications. Its name comes from the Watts-Strogatz phenomena, or popularly known as six degrees of separation (Travers and Milgram, 1967). The process behind the *Watts-Strogatz* network is to begin with a lattice with connected neighbors in to a certain degree, and increase the amount of disorder by “rewiring” the edges with probability p_{SW} , and reconnecting it to other edges in the network with equal probability. For this method, in the network simulation, we used the well-known R¹ package **Igraph** (Csardi and Nepusz, 2006), used mainly for graph applications. The *Watts-Strogatz* has interesting properties (Watts and Strogatz, 1998), but still, doesn’t form as much nodes with a lot of connections as we see in real world networks. Nevertheless we applied the methods to this random graph in order to evaluate their performances under this structure.

5.2.3 Barabási-Albert model

The *Barabási-Albert* model, introduced by Barabási and Albert (1999), is based in two main premises, the first is that networks expands continuously by addition of new nodes, the second is that these new nodes attach preferentially to nodes that are already well connected. This means that the probability that a new node connects to existing nodes is not uniform, which allows nodes with high degree to emerge, or hubs, compared to 5.2.1 and 5.2.2. The size of the degrees k in a *Barabási-Albert* model distributed as *power law*; $P(k) \sim k^{-\gamma}$, where $2 < \gamma < 3$, is a parameter which indicates how long the tail of the power law’s distribution is (Barabási and Albert, 1999). We simulated the *Barabási-Albert* network using the preferential attachment principle as a random process. For a network with p nodes, we start with two connected nodes in a graph $\mathcal{G}_{SF} = (V, E)$, with $V = \{1, 2\}$ and $\{1, 2\} \in E$. We introduce the next node, 3, which connects with probability

$$p_j = \frac{\mathbf{deg}(j)}{\sum_{l \in V} \mathbf{deg}(l)}, \quad j \in V,$$

¹<https://cran.r-project.org>.

with the nodes in V , where $\mathbf{deg}(j)$ is the number of connections of node j . The process goes on, with $p - 3$ steps, generating a graph $\mathcal{G}_{SF}$ with *Barabási-Albert* network properties. In Algorithm 5 we have a procedure used for generating the adjacency matrix $\mathbf{A}_{\mathcal{G}_{SF}}$.

Algorithm 5 Barabási-Albert

procedure

Initialize empty matrix $\mathbf{A}_{\mathcal{G}_{ER}} = \{a_{ij}\}$;

Let $V = \{1, 2\}$, $\{1, 2\} \in E$, and $a_{12} = 1$;

for $i = 3, \dots, p$ **do**:

1. $p_j = \mathbf{deg}(j) / \sum_{k \in V} \mathbf{deg}(k)$, $j \in V$;

2. Select $j \in V$ with probability p_j ;

3. if $j < i$, $a_{ji} = 1$, else if $i < j$, $a_{ij} = 1$;

4. $i \in V$, and $\{i, j\} \in E$;

end for

$\mathbf{A}_{\mathcal{G}_{SF}} = \mathbf{A}_{\mathcal{G}_{SF}} + \mathbf{A}_{\mathcal{G}_{SF}}^T$;

end procedure

We felt that the *Barabási-Albert* model would be interesting in our evaluation, because it seems to appear in a number of real-world networks; the world-wide web, in business networks, transportation networks, gene expression (Albert, 2005), and so on. Another reason, is the network's property in forming hubs. Recently, the emergence of works with the intention to produce network reconstruction methods mainly applied to *Scale-free* or *Barabási-Albert* models, such as Peng *et al.* (2009), and Liu and Ihler (2011). A version in R for Algorithm 5, is found in the Appendix B.2.1.

5.3 Simulating the Graph structure

With the adjacency matrices generated by the processes described in 5.2.1, 5.2.2, and 5.2.3, we will transform $\mathbf{A}_{\mathcal{G}}$ in to a Covariance matrix Σ_{sim} , from which we will simulate random samples $X_V \sim \mathcal{N}_V(\mathbf{0}, \Sigma_{sim})$. The used method is described in Cai *et al.* (2016), in which it initially constructs a Precision matrix and then invert it to obtain the Covariance matrix. To construct the Precision matrix, first we need to attribute random values to the

non-zero elements of $\mathbf{A}_{\mathcal{G}}$, this process gives us the matrix Ω_1 ,

$$\Omega_1 = \begin{cases} \omega_{ij} = \omega_{ji} = u_{ij} \cdot \delta_{ij}, & \text{if } a_{ij} = 1 \text{ with } a_{ij} \in \mathbf{A}_{\mathcal{G}}, \\ 0, & \text{otherwise,} \end{cases} \quad (5.1)$$

where the variable u_{ij} , in (5.1) is a uniform random variable defined in the interval $(0.4, 0.8)$. The variable δ_{ij} is a discrete uniform distribution with values in $\{-1, 1\}$, this value will give us equal amounts of positive and negative values in the Precision matrix. The matrix Ω_1 has zeros in its diagonals, this means that is singular, to solve this problem we apply the following transformation

$$\Omega_2 = \Omega_1 + (|\lambda_{\min}(\Omega_1)| + 0.05)\mathbf{I}_p,$$

where $\lambda_{\min}(\Omega_1)$ is the minimum eigen value of Ω_1 , and $\mathbf{I}_p$ is a $p \times p$ identity matrix. This guarantees that Ω_2 is invertible. Next, we have Ω^{-1} , that is the matrix formed by the multiplication

$$\Omega^{-1} = \text{diag}(\mathbf{u})\Omega_2^{-1}\text{diag}(\mathbf{u}),$$

where $\text{diag}(\mathbf{u})$, which is a diagonal matrix formed by the p -dimensional vector, with uniform distribution $\mathbf{u} \sim \mathcal{U}_p(1, 5)$. Finally the Covariance matrix is obtained through $\Sigma_{sim} = \Omega^{-1}$ from which we simulate the multivariate normal distribution $X_V \sim \mathcal{N}_V(\mathbf{0}, \Sigma_{sim})$, with $n < p$. A routine for this transformation is found in the Appendix B.2.2.

5.4 ROC curve

The ROC curve or Receiver Operator Characteristic is a methodology used for the comparison of new diagnostic methods (Johnson and Johnson, 2005), usually binary classifiers. For our case, these classifiers are the methods presented in chapter 4, they are binary because it identifies if there is or not an edge between two nodes. The ROC curve describes the tradeoff between the *False Positive Fraction* $P(FP)$, which is the probability of the method erroneously identifies an edge, also known as *false positives* (FP), and the *True Positive Fraction* $P(TP)$, which is the probability of the method correctly identify an edge, or also known as *true positives* (TP). In the known literature, the fractions $P(TP)$ and $1 - P(FP)$,

are also referred as *sensitivity* and the *specificity* of the method. For our study the FP , and TP , is summarized by the sets

$$\begin{aligned} TP &= |\{\text{indetify an edge given } \exists \text{ an edge}\}|, \\ FP &= |\{\text{indetify an edge given } \nexists \text{ an edge}\}|. \end{aligned}$$

The probabilities $P(FP)$ and $P(TP)$ are given as

$$P(FP) = \frac{FP}{N}, \quad P(TP) = \frac{TP}{P}, \quad (5.2)$$

where N is the *condition negatives*, which is the number of non-edges in the original network we trying to learn, and P is the *condition positives*, that is the number of edges in the original network. These quantities rewritten in terms of the of the TP and FP , and from the *true negatives* (TN), and *false negatives* (FN) are defined as

$$\begin{aligned} TN &= |\{\text{indetify a non-edge given } \nexists \text{ an edge}\}|, \\ FN &= |\{\text{indetify a non-edge given } \exists \text{ an edge}\}|, \end{aligned}$$

which gives us $N = FP + TN$, and $P = TP + FN$. The ROC curve is defined as a set of points

$$\text{ROC}_\gamma = (P(FP_\gamma), P(TP_\gamma)), \quad \gamma \in \mathbb{R}, \quad (5.3)$$

where $P(FP_\gamma)$ and $P(TP_\gamma)$, are the fractions (5.2), where FP_γ and TP_γ where generated given a value γ . In our case γ will assume different regularization values in the different methods chosen. In the **GLasso** method, $\gamma = \lambda_L$, such that $\lambda_L \in \mathbb{R}_+$, in the **GGMridge** method we have the threshold $\gamma = \alpha_r$, which is the *p-value* used for selecting the edges in 4.3, (in step 3. of the Algorithm 2 in chapter 4), and in the **LPC** method we have two values for $\gamma = (\gamma_1, \gamma_2)$, $\gamma_1 = \alpha_{\hat{\rho}}$ which is the *p-value* used in (4.11), for selecting correlation values, and $\gamma_2 = \alpha_{LPC}$, for the hypothesis test of the Partial correlation estimates in (4.15), with $\alpha_{\hat{\rho}}, \alpha_{LPC} \in [0, 1]$.

A classifier has perfect learning capability if $P(TP_\gamma) = 1$, for all $P(FP_\gamma) \in [0, 1]$ (the

Figure 5.2: *Representation of a ROC curve.*

dotted line in Figure 5.2), and has no diagnostic capability if $P(TP_\gamma) = P(FP_\gamma)$ (the dashed line in Figure 5.2), for all $\gamma \in \mathbb{R}$. In this case, the classifier has the same capability of a random choice between edge and non-edge, with equal probability. A common way to compare two different classifiers is to compare the area under the ROC curve

$$A_{\text{ROC}} = \int_0^1 \text{ROC}_\gamma(\xi) d\xi. \quad (5.4)$$

The methods with higher A_{ROC} are the ones preferred. We can approximate the areas of the generated points (5.3), by interpolating the values, and then integrating it using different numerical methods. In Rosner (2015) an approximation using the trapezoidal rule² is used to achieve the value of the areas. In the next section we will construct ROC_γ curves using the methods from chapter 4, and use this procedure to evaluate and compare the generated areas.

5.5 Simulation Results

In this section we will present the results for the different simulation scenarios. We ran 300 simulations, generating 300 of each graph structure presented in 5.2, and took the average of

²The rule is seen in the Appendix A.3.1.

the values obtained through the ROC_γ curve, for γ seen in 5.4. We generated the samples from $(p = 50, n = 20)$, $(p = 100, n = 50)$, and $(p = 200, n = 50)$ using the procedure discussed in 5.3. Later we applied the trapezoidal rule (we used the R package known as **pracma**³), to the mean ROC_γ for each method and situation, using γ with values shown in Table 5.1. The results for the areas is observed in Table 5.5, the mean of the areas by method in Table 5.2, and the mean of the areas by network structure in Table 5.3. In Table 5.4 we have the sparsity (2.5.5) of the graphs. In Table 5.6, we have the ROC_γ curve of the areas of between the standard deviations. The ROC_γ curves properly, with only the averages of the curves, are in 5.5.2, The curves with the averages plus the standard deviation are in 5.5.3.

Method	γ
GGMridge	$\{0, 001, \dots, 1; \text{by } 0.005\}$
GLasso	$\{0, 0001, \dots, 40; \text{by } 0.1\}$
LPC	$\{0, 0001, \dots, 0.4; \text{by } 0.1\} \cup \{0.6, 0.7, 0.8, 0.9, 1\}$

Table 5.1: Used γ for ROC_γ curves.

Methods	GGMridge	GLasso	LPC
mean	0.8239	0.7516	0.7633

Table 5.2: Mean ROC_γ curves by method.

Structures	<i>Erdős-Rényi</i>	<i>Watts-Strogatz</i>	<i>Barabási-Albert</i>
mean	0.7975	0.7878	0.7541

Table 5.3: Mean ROC_γ curves by Structure.

variables, samples	<i>Erdős-Rényi</i>	<i>Watts-Strogatz</i>	<i>Barabási-Albert</i>
$p = 50, n = 20$	0.04	0.08	0.04
$p = 100, n = 50$	0.04	0.04	0.02
$p = 200, n = 50$	0.02	0.02	0.01

Table 5.4: Sparsity of the generated graphs.

³<https://cran.r-project.org/web/packages/pracma/index.html>

variables, samples	Graph model	GGMridge	GLasso	LPC
$p = 50, n = 20$	<i>Erdős-Rényi</i>	0.83	0.75	0.77
	<i>Watts-Strogatz</i>	0.78	0.69	0.72
	<i>Barabási-Albert</i>	0.76	0.73	0.72
$p = 100, n = 50$	<i>Erdős-Rényi</i>	0.86	0.78	0.78
	<i>Watts-Strogatz</i>	0.87	0.78	0.80
	<i>Barabási-Albert</i>	0.82	0.77	0.76
$p = 200, n = 50$	<i>Erdős-Rényi</i>	0.85	0.77	0.79
	<i>Watts-Strogatz</i>	0.86	0.77	0.80
	<i>Barabási-Albert</i>	0.77	0.72	0.73

Table 5.5: ROC_γ areas of the means.

variables, samples	Graph model	GGMridge	GLasso	LPC
$p = 50, n = 20$	<i>Erdős-Rényi</i>	0.13	0.13	0.14
	<i>Watts-Strogatz</i>	0.10	0.10	0.12
	<i>Barabási-Albert</i>	0.14	0.12	0.15
$p = 100, n = 50$	<i>Erdős-Rényi</i>	0.07	0.08	0.08
	<i>Watts-Strogatz</i>	0.07	0.09	0.07
	<i>Barabási-Albert</i>	0.10	0.12	0.11
$p = 200, n = 50$	<i>Erdős-Rényi</i>	0.05	0.05	0.05
	<i>Watts-Strogatz</i>	0.05	0.05	0.05
	<i>Barabási-Albert</i>	0.09	0.08	0.08

Table 5.6: Difference of ROC_γ areas of the standard deviations.

5.5.1 Analysis and Conclusion

The first thing we might notice in observing the plots in 5.5.2 and 5.5.3, is that the ROC_γ curve produced by the **GLasso** method, contrary to the other methods, doesn't go all the way to the point (1,1). Investigating this fact we conclude that the restriction coefficient λ_L , when it is in a certain small value ($\lambda_L \approx 0.0001$), doesn't generate the estimation that gives us a complete graph (2.5.2), it stops in a structure and stays in that particular result, no matter how close we approximate λ_L to zero. Although this might present some problems in generating the ROC_γ area, the results presented by the interpolation might in fact inflate the results for the **GLasso**, so we chosen to continue our analysis in this way. In the related literature, this problem also appears when the **GLasso** is evaluated as ROC_γ curve in Ha and Sun (2014) and (Peng *et al.*, 2009). Some use other measures related to FP , TP , TN , and FN , as seen in 5.4, like the Accuracy and False discovery rate as in (Wang *et al.*, 2012). Other fact we can observe clearly is that **GGMridge** method gives us

the biggest area under the curve in all cases and different scenarios. This is confirmed by the data in the Table 5.5. One might think that this method is the best of the three, but with further analysis we discovered that the form we used to generate the data for the ROC_γ might be contributing for this fact. We have generated curves by varying the value of α_r in other steps of the algorithm, the curves presented we generated before the false discovery test [Benjamini and Hochberg \(1995\)](#) was applied, and those with different results were generated by the test. The results of this change tend to produce lower values for the ROC_γ area from those found, and increases greatly the standard deviation of the method. Besides this fact, in overall, we can see that the **GGMridge** method has the highest value for the area of ROC_γ curve in any situation.

The values of **GLasso** and **LPC** are very competitive in all scenarios, in the *Barabási-Albert* the **GLasso** tends to be higher than the **LPC**, but, from the plots and values we can see that as the number of values increases the **LPC** method is approaching the **GLasso**, and even is bigger in the case of $(p = 200, n = 50)$. In the *Watts-Strogatz* network the **LPC** method performs better than the **GLasso** in all cases. And on the *Erdős-Rényi* the methods are very close in their performance. One fact that it is worth noticing is that in Figure 5.4, for $(p = 100, n = 50)$, the **LPC** produced a curve in which there's a drop in the method's performance between *sensitivity* with values in $(0.4, 0.7)$, and *1-specificity* with values in $(0.005, 0.2)$, this might due to the variation of the γ used for the method.

In Table 5.4 the sparsity of the graphs that were generated, we can see that in most cases the density is below 0.05, the only case this doesn't happen is in the *Watts-Strogatz* case for $p = 50$, this happens due the way the network was generated.

From the facts presented we can leave some ideas, and questions for further research;

- Perform the simulations for $p > 200$, in the order of thousands, and evaluate the results.
- Improve the **LPC** method performance.
- What is the right way to produce a ROC_γ curve for the **GGMridge** method?
- How the change in the γ used in the **LPC** method, changes its ROC_γ curve.

5.5.2 ROC curves - average values

Figure 5.3: ROC curves generated using Erdős-Rényi model with.

Figure 5.4: ROC curves generated using Watts-Strogatz model with.

Figure 5.5: ROC curves generated using Barabási-Albert model with.

5.5.3 ROC curves - average and standard deviation

Figure 5.6: ROC curves generated using Erdős-Rényi model, with standard deviation.

Figure 5.7: ROC curve generated using Watts-Strogatz model, with standard deviation.

Figure 5.8: ROC curve generated using Barabási-Albert model, with standard deviation.

Chapter 6

Application to Data

6.1 Introduction

Continuing with the chosen methods¹ evaluation. We applied them to a real-world scenario where the reconstructed network results is compared. Although in nature, we can observe different types of complex networks (Barabási and Albert, 1999), most of the methods have the *gene co-expression* application in mind (Ha and Sun, 2014) (Schaefer and Strimmer, 2005), so it is a natural choice for the evaluation.

Briefly, a *gene* is a segment of DNA (*deoxyribonucleic acid*), which is a double strand with a sequence of *nucleotides* or bases (there are four different bases; adenine (A), thymine (T), cytosine (C), and guanine (G), that only can form certain pairs²). These bases have all the instructions needed to direct the workings of all living systems. The gene encodes the instruction for the synthesis and regulation of proteins, that determine shape, structure and function of the cell. Although genes are essential in life management, they only comprise 2% of human genome, while the rest are non-code regions, with other functions (Schaefer, 2006). The human genome, contain estimated 19,000 – 20,000 genes (Ezkurdia *et al.*, 2014). It is assumed that the gene expression tend to portray the cell’s function. The aim of gene co-expression analysis is often to identify genes whose expression differs, in cells from a healthy tissue, from those with abnormal behaviors, such as tumorous tissues. By examining this differences, researchers aim to understand the disease development, and to identify what

¹Presented in chapter 4.

²The human genome, consists of some 3 billion base pairs (Schaefer, 2006).

genes are involved in such conditions.

The gene co-expression data, in most cases, is high dimensional. As we seen in chapters 3 and 4, dealing with this conditions, from a statistical point a view, is very challenging. We chosen a data set with this characteristics, and performed a simple analysis, in which we counted the nodes, which are the genes, and edges, which are the intensity of the expression between the genes, that where identified in common by the methods. The data used is the gene expression analysis provided by Zhai *et al.* (2007), which contains the expression of 21 tumor tissue from human Cervical Cancer samples (which is strongly associated with certain types of human papillomaviruses (HPV)), and 10 normal samples. The original data is obtained from the Gene Expression Omnibus³ repository, with access number GSE7803, using the Affymetrix U133A platform (the format the microarray where generated).

6.2 The Data and Methods

From the Zhai *et al.* (2007) data base, we have the expression of 25,387 genes, from these genes we selected 1,268 based on the work developed by Mine *et al.* (2013), which identified in the data, the *differently expressed genes* or DEG, that are genes with expression that differs from normal samples. The study used not only the Zhai *et al.* (2007) data base, but also 3 other data bases; Biewenga *et al.* (2008), Pyeon *et al.* (2007), and Scotto *et al.* (2008), all of them related to human Cervical Cancer. The study in Mine *et al.* (2013), aims to understand how these DEG are connected with the HPV virus capacity to induce genomic changes, that not only promote the appearance of tumors, but tumor growth.

In our study, we where only interested in recovering the network structure based on the available data. We didn't perform any data augmentation, by inserting data from the different studies used in Mine *et al.* (2013), because it would be necessary further statistical investigation of the data, and choosing the right method to bind them in a single structure. We also didn't perform any biological analysis, since this kind of analysis require a deeper knowledge biological systems.

In the next section we will compare the results obtained by the methods and present the

³<https://www.ncbi.nlm.nih.gov/geo/>

networks that were generated.

6.3 Results of the Application

We applied the data to the methods, with no treatment or normalization⁴, besides those that came from the experiment to reduce variance (Zhai *et al.*, 2007). Also we reconstructed the networks not using all the 1,268 genes identified by Mine *et al.* (2013), but we chosen the restriction coefficients of the methods that, returned approximately half this quantity, with tree times the number of edges⁵. The coefficients used and the results generated by the methods is seen in Table 6.1, and in Figure 6.1.

Method	Coefficients	number of nodes	number of edges
GGMridge	$\lambda_r = 1, \alpha_r = 0.01$	558	1876
GLasso	$\lambda_L = 0.6$	630	1942
LPC	$\alpha_{\hat{\rho}} = 0.1, \alpha_{LPC} = 0.02$	658	1774

Table 6.1: Results of the methods: number of nodes and edges.

(a) Number of nodes in common.

(b) Number of edges in common.

Figure 6.1

In Figure 6.1 we identified the number of genes and edges that the methods identified in common and presented the results as Venn diagrams, with the number of edges in Figure 6.1a and the number of edges in Figure 6.1b. The network images where done using the

⁴The **GGMridge** method performs the normalization of the data in all cases.

⁵This proportion was achieved informally by conversations with the bioinformatics community.

Cytoscape tool [Shannon *et al.* \(2003\)](#). The network reconstructed using only one method seen in 6.4.1. The **LPC** method in Figure (6.2), **GGMridge** in Figure (6.3), and **GLasso** in Figure 6.4. In Figure 6.5 we have the network reconstructed using **LPC** and **GLasso**, in Figure 6.6 we have **LPC** and **GGMridge**, and in Figure 6.7 we have **GLasso** and the **GGMridge**. Finally in Figure 6.8 we have the three methods represented together, with the nodes organized in a way as the Venn diagram in Figure 6.1a with the edges preserved. In Table 6.2 we have the minimum and the maximum degrees of the nodes by method. This degrees relates to the size of the nodes of the networks in the Figures. The smaller the size of the node the smaller the degree, and bigger the node also bigger the degree.

Method	min	max
GGMridge	1	35
GLasso	1	188
LPC	1	14
GLasso and LPC	3	165
GGMridge and LPC	1	35
GGMridge and GLasso	2	188
GGMridge , GLasso , and LPC	3	177

Table 6.2: *Maximum and minimum degrees of the methods.*

6.4 Analysis and Conclusion

The Venn diagrams in 6.1a and 6.1b gives us interesting information. We can see that the **LPC** and **GGMridge**, excluding the **GLasso**, share a large number of nodes, 343 in total. If we include the nodes also shared with the **GLasso** we have 670 common identifications, which is 81.9% of the jointly identified nodes. In Figure 6.6 this is easily seen. On the other hand, the edges are not proportionally shared as the nodes. Only 8.1% of the edges where identified in common. In the **GLasso** and **LPC** method this fact becomes more evident, although they share a fair amount of nodes, 54, the number of edges shared is significantly small, only 14. We can conclude that although the methods identify, jointly, a good amount nodes, the edges tend to form links inside each method. We can observe this fact in other perspective trough the degrees.

From the results in Table 6.2 we can see that the degrees of the methods translates to the Figures 6.2, 6.3, and 6.4. The **LPC** method has nodes with maximum degree 14, this means that the network is more scattered, with few nodes with high degree. In contrast, the network reconstructed by the **GLasso** has a maximum degree of 188, which means that it has identified a hub, this is seen in the network, where the nodes are concentrated around a group of nodes. The **GGMridge** method has maximum degree of 34, but as we see in Table 6.2, the method identified the node with largest degree from the **GLasso** method, this means that a node with a low degree in one method has high degree in the other. Other fact can observe is that the **GLasso** network is very distinctive from the other methods, since it formed more hubs, this result can also be seen in Figure 6.8. But as we seen, this hubs might not real hubs, since the other methods didn't recognize these hubs.

From the results obtained we can leave some questions, and future topics for research.

- Examine with more details the recovered structure from the methods, test if it has some topological form.
- Introduce Biological analysis to the results.
- Normalize the data, perform more tests before applying to the method.
- Make the same analysis with the compiled data, from the bases (Biewenga *et al.*, 2008), (Pyeon *et al.*, 2007), and (Scotto *et al.*, 2008). Try to find a way to fit this data without loss of information.
- Try the method to the entire genes, and analyze the results.
- Verify if the **GLasso** hubs, are real hubs.

6.4.1 Reconstructed Networks

Figure 6.2: *Reconstructed Network using LPC method. The nodes represent the genes (color in green), the links are the grey edges. The size of the nodes represent the degrees. The smallest node represent 1 degree the largest node represent 14 degrees. In total there are 658 identified nodes and 1774 edges. We can observe that we don't have major hubs and the edges seem evenly distributed, that is we have a large number of nodes with same degree.*

Figure 6.3: *Reconstructed Network using GGMridge method. The nodes generated are in green and the edges are in gray. The smallest size node represent 1 degree the largest node represent 35 degrees. In total there are 558 identified nodes and 1876 edges. The generated network appears to have more hubs and less nodes with same degree. We can see some concetration in some nodes.*

Figure 6.4: *Reconstructed Network using GLasso method. The nodes generated are in red and the edges are in gray. The smallest size node represent 1 degree the largest node represent 188 degrees. In total there are 630 identified nodes and 1942 edges. From the generated network we can observe the presence of hubs with large number of degrees and a large number of nodes with one degree.*

Figure 6.5: *Reconstructed Network with the GLasso and LPC method. The 277 red circles are the nodes identified only by the GLasso method, the 377 green parallelograms are the nodes identified by the LPC method, and the 281 yellow diamonds are the nodes identified by both the GLasso and LPC method. The largest node, identified by the GLasso has 165 degrees the smallest 3.*

Figure 6.6: *Reconstructed Network GGMridge and LPC method. The 60 gray inverted triangles are the nodes identified only by the GGMridge method, the 88 green parallelograms are the nodes identified by the LPC method, and the 570 blue hexagons are the nodes identified by both the GGMridge and LPC method. The largest node, identified by both GLasso and LPC has 35 degrees the smallest 1. We can observe that the methods have identified most of the nodes in common.*

Figure 6.7: Reconstructed Network **GGMridge** and **GLasso** method. The 298 red circles are the nodes identified only by the **GLasso** method, the 370 gray inverted triangles are the nodes identified by the **LPC** method, and the 260 orange triangles are the nodes identified by both the **GLasso** and **LPC** method. The largest node, identified by the **GLasso** has 188 degrees the smallest 3.

Figure 6.8: Comparison of the three methods; **GGMridge**, **GLasso**, and **LPC**. The 244 red circles are the nodes identified only by the **GLasso** method, the 27 gray inverted triangles are the nodes identified by the **GGMridge** method, and the 34 green parallelogram identified by the **LPC** method. The 33 orange triangles are the nodes identified by both the **GLasso** and **GGMridge** method. The 343 blue hexagons are the nodes identified by both the **GGMridge** and **LPC** method. The 54 yellow diamonds are the nodes identified by both the **GLasso** and **LPC** method, and The 227 light blue squares are the nodes identified by the three methods. We can see that most of the hubs are associated with the **GLasso** method, and most of the edges are between the **LPC** and **GGMridge** methods and the three methods.

Appendix A

Support Material

The subjects presented in this section are ordered as they appear in the text.

A.1 Chapter 1

A.1.1 Vector Norm

A vector norm is defined for a vector $\mathbf{x}^T = (x_1, x_2, \dots, x_n)$ with $\mathbf{x} \in \mathbb{R}^n$, as a function,

$$|| \cdot || : \mathbb{R}^n \longrightarrow \mathbb{R}.$$

The ℓ_1 norm is defined as

$$||\mathbf{x}||_1 = \sum_{i=1}^n |x_i|,$$

where $|\cdot|$ is the module of x_i .

The ℓ_2 norm is defined as,

$$||\mathbf{x}||_2 = \sqrt{\sum_{i=1}^n |x_i|^2}.$$

A.1.2 Ordinary Least Squares

In a linear regression, we want to find the model that best fits our samples in the form

$$y_i = \alpha + x_i\beta + \epsilon_i,$$

in which $i = 1, \dots, n$, is the number of samples and ϵ_i is the error term with distribution

$$\epsilon_i \sim N(0, \sigma^2), \text{ with } \sigma^2 \in \mathbb{R}^+ \text{ and } E(\epsilon_i, \epsilon_j) = 0.$$

We can generalize the problem for p variables introducing matrix notation.

$$\begin{cases} y_1 = \beta_0 + \beta_1 x_{11} + \epsilon_1, \\ \vdots \quad \quad \quad \vdots \quad \quad \quad \vdots \\ y_n = \beta_0 + \beta_1 x_{1n} + \epsilon_n, \end{cases}$$

Which give us the form $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$ where

$$\mathbf{Y} = \begin{pmatrix} y_1 \\ \vdots \\ y_n \end{pmatrix}, \quad \mathbf{X} = \begin{pmatrix} 1 & x_{11} \\ \vdots & \vdots \\ 1 & x_{1n} \end{pmatrix}, \quad \boldsymbol{\beta} = \begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix}, \quad \boldsymbol{\epsilon} = \begin{pmatrix} \epsilon_1 \\ \vdots \\ \epsilon_n \end{pmatrix}.$$

That gives us a **minimization** problem

$$\arg \min_{\boldsymbol{\beta}} \|\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}\|_2^2 = \arg \min_{\beta_0, \beta_1} ((\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})^\top (\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}))$$

where

$$\|\mathbf{x}\|_2^2 = \left(\sqrt{x_1^2 + \cdots + x_n^2} \right)^2 = \mathbf{x}^\top \mathbf{x},$$

is the L^2 norm of the vector $\mathbf{x}$, which gives us

$$\arg \min_{\boldsymbol{\beta}} ((\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})^\top (\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})) = \arg \min_{\beta_0, \beta_1} \left(\sum_{i=1}^n (y_i - \beta_0 - \beta_1 x_i)^2 \right)$$

We can rewrite the matrix term as

$$(\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})^\top (\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}) = \mathbf{Y}^\top \mathbf{Y} - 2\mathbf{Y}^\top \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\beta}^\top \mathbf{X}^\top \mathbf{X}\boldsymbol{\beta}.$$

We observe that we have a form of quadratic equation, which can be minimized using the partial derivative over the parameters to find the inflexion point which will be our minimum.

$$\begin{aligned} \frac{\partial RSS}{\partial \hat{\boldsymbol{\beta}}} &= -2\mathbf{X}^\top \mathbf{Y} + 2\mathbf{X}^\top \mathbf{X}\hat{\boldsymbol{\beta}} = \mathbf{0} \\ \Rightarrow \mathbf{X}^\top \mathbf{X}\hat{\boldsymbol{\beta}} &= \mathbf{X}^\top \mathbf{Y} \\ \hat{\boldsymbol{\beta}} &= (\mathbf{X}^\top \mathbf{X})^{-1} \mathbf{X}^\top \mathbf{Y} \end{aligned}$$

This process is known as *OLS* or **ordinary least squares**.

A.2 Chapter 4

A.2.1 Generalized inverse

If A is a $m \times n$ matrix, then G is a *generalized inverse* of A if G is an $n \times m$ matrix with

$$AGA = A.$$

The Penrose conditions are used to define different generalized inverses for $A \in \mathbb{R}^{n \times m}$, and $G \in \mathbb{R}^{m \times n}$:

1. $AGA = A$;
2. $GAG = G$;
3. $(AG)^T = AG$;
4. $(GA)^T = GA$;

If G satisfies the first condition, then it is a generalized inverse of A . If it satisfies the first two conditions, then it is generalized inverse of A . If it satisfies all four conditions, then G is a *Moore-Penrose pseudoinverse* (Penrose, 1955) of A .

A.3 Chapter 5

A.3.1 Trapezoidal rule

The trapezoidal rule approximates the region under a function $f(x)$ as a trapezoid, resulting in its area. So we have that

$$\int_a^b f(x)dx \approx (b - a) \left[\frac{f(a) + f(b)}{2} \right].$$

For a Numerical implementation in a non-uniform grid we have

$$\int_a^b f(x)dx \approx \frac{1}{2} \sum_{k=1}^N (x_{k+1} - x_k)(f(x_{k+1}) + f(x_k)).$$

Appendix B

Algorithms

The subjects presented in this section are ordered as they appear in the text.

B.1 Chapter 4

B.1.1 Local Partial Correlation

```
# Require the following packages

library("parallel")
library("foreach")
library("doParallel")

#### Functions ####
#####
filter.rows <- function(x, rows, fun=sd){
  rows <- min(rows, nrow(x))
  val <- apply(x, 1, fun)
  sel.rows <- order(val, decreasing=TRUE)[1:rows]
  return(x[sel.rows, ])
}

just.filter <- function(x, percent, maxRows){
  res <- filter.rows(filter.prop(x, percent), maxRows)
  return(res)
}

# Get probability values for each correlation matrix.
cor.prob = function(X, dfr = nrow(X) - 2) {
  R = cor(X)
  above = row(R) < col(R)
  r2 = R[above]^2
  Fstat = r2 * dfr / (1 - r2)
  R[above] = 1 - pf(Fstat, 1, dfr) #Probability of the F distribution
  R
}
#####

#Function for calculating the LPC method

#if(print.lpc == T)
```

```

print(paste("alpha_", alpha))

nCores = detectCores() - 1
cl = makeCluster(nCores)
registerDoParallel(cl, cores = detectCores() - 1)

#-----
sampleNames <- toupper(names(data))
sampleNames <- gsub("[-.,;,-,|,/\\\\].*", "", sampleNames)
#-----
names(data) <- sampleNames
#-----

if (nLim != -1) {
  data <- just.filter(data, porc, nLim)
  if(print.lpc == T)
    print("filtering")
} else {
  if(print.lpc == T)
    print("NOT filtering")
}
dim(data)

# Transpose da data (pxn) to (nxp)
X=t(data)

# Number of variables.
p = ncol(X)

# Size of the sample.
n = nrow(X)

# Warning for thr case n >= p.
if(p <= n){
  print("nothing to do: n >= p.")
  return(FALSE)
}

# Calculate the sample covariance of the data, can we do this?
covX = cov(X)

# Calculates the sample corrilation of the data, can we do this?
corX = cor(X)

# Return the pvalue of the correlation matrix.
pvalcor = cor.prob(X)

# New empty matrix
matRoXY = matrix(0, ncol = p, nrow = p)
colnames(matRoXY) = colnames(X)

#Fill the matrix matRoXY with correlation from X
if (alpha==1) {
  for(i in 1:(p-1)) {
    for(j in (i+1):p) {
      matRoXY[i, j] = corX[i, j]
      matRoXY[j, i] = matRoXY[i, j]
    }
  }
} else {

```

```

for(i in 1:(p-1)) {
  for(j in (i+1):p) {
    matRoXY[i,j] = ifelse(pvalcor[i,j] < alpha, corX[i,j], 0)
    matRoXY[j,i] = matRoXY[i,j]
  }
}
}

# Puts zeros in the rest of the matrix where theres NA.
matRoXY[is.na(matRoXY)] = 0

# igraph function (transform into an adjacency graph?)
g1 = graph.adjacency(matRoXY, mode = ("undirected"), weighted = TRUE)

# Get the vertices of a igraph object g1, V()
# Change the vertices names to the sequence 1:p.
V(g1)$name = c(seq(1:p))

# Accessing edges ...
# Get edges from the object g1, list of the kind a->b.
edges = get.adjlist(g1)

# Function unlist transforms a list into a single vector
totEdg = unlist(edges)

# Generate a matrix with 99 in all positions, why?
Ap = matrix(99,ncol=ncol(X),nrow=ncol(X))

# Number of neighbors is equal to the size of the sample.
# I'm fixing the number of neighbors to the size of the sample.
nViz = n
t0 = Sys.time()

## foreach(), similar to lapply and loop function from doParallel
## Aply the function to all the elements of X.
lpcData = foreach(k = 1:ncol(X), .packages = c("igraph", "corpcor"), .combine = rbind) %dopar% {
  # for (k in 1:ncol(X)) {
  # k = 4

  #Get values from the list "edges"
  #Position where the elements is different from zero.
  vertices = edges[[k]]
  if(print.lpc == T){
    'print(k)
    #####print(vertices)
    #####print(length(vertices))
    #####print("-----")'
  }
  #Will pass to the line of the matrix
  if (length(vertices) > 0) { # (sum(!is.na(vertices))!=0)
    for (j in 1:length(vertices))
    {
      # print(j)
      # j = 4
      if(vertices[j] > k && matRoXY[k, vertices[j]] !=0)
      {
        i1 = as.character(k)
        j1 = as.character(vertices[j])

        # Get the neighbors of a node. The function receives the graph,

```

```

#the nodes that we want to find the
#neighbors and how far in the graph we want to search.
#(graph, order, nodes)
vizlist = graph.neighborhood(g1, 1, nodes = c(i1, j1), mode=c("all"))

#Sort the neighbors from the largest to the smallest
#unique(), remove redundancies
#GET THE COMMON NEIGHBORS
viz = sort(as.integer(unique(c(V(vizlist[[1]])$name,
V(vizlist[[2]])$name))),decreasing=TRUE))

# Downsizing the number of neighbors in case we have we still
# have more neighbors than observations, but aren't we using the number
# of the sample size as neighbors.

if(length(viz) >= nViz)
{

  # Get the biggest correlation from the two selected nodes.
  cor.maiores.i = sort(abs(matRoXY[viz, c(k)][-k]),
    decreasing = TRUE)[1:(nViz/2)]
  cor.maiores.j = sort(abs(matRoXY[viz, c(vertices[j])][-(vertices[j])]),
    decreasing = TRUE)[1:(nViz/2)]

  # Remove the zeros
  cor.maiores.i = cor.maiores.i[cor.maiores.i > 0]
  cor.maiores.j = cor.maiores.j[cor.maiores.j > 0]

  # Getting the n/2 biggest correlations.
  cor.maiores = sort(abs(unique(c(cor.maiores.j, cor.maiores.i))),
    decreasing = TRUE)[1:(nViz/2)]
  cor.maiores.i = cor.maiores.i[cor.maiores.i %in% cor.maiores]
  cor.maiores.j = cor.maiores.j[cor.maiores.j %in% cor.maiores]

  majI = cor.maiores.i[! is.na(cor.maiores.i)]
  majJ = cor.maiores.j[! is.na(cor.maiores.j)]

  #— valor absoluto - zero - erro?
  posicao.i = sapply(majI, function(valmajI)
    {which(abs(matRoXY[,c(k)]) == valmajI, useNames = TRUE)})
  posicao.i = unlist(posicao.i)

  posicao.j = sapply(majJ, function(valmajJ)
    {which(abs(matRoXY[,vertices[j]]) == valmajJ, useNames = TRUE)})
  posicao.j = unlist(posicao.j)

  if((length(posicao.i)==0) & (length(posicao.j)==0)) next

  if(length(posicao.j)==0){
    viz = sort(c(k, as.numeric(vertices[j])), posicao.i))
  } else {
    if (length(posicao.i)==0) viz <- sort(c(k, as.numeric(vertices[j])), posicao.j))
    else viz = unique(sort(c(k, as.numeric(vertices[j]), c(posicao.i, posicao.j))))
  }
}

lcl = length(viz)

# Neighbor covariance matrix
Csub = covX[viz, viz]

```

```

# dim(Csub)

# cor2pcor computes the pairwise partial correlation.
# Coefficients from either a correlation or a covariance matrix.
#-----

# Calculates the Partial correlation from a covariance matrix or corr matrix
corr.inv = cor2pcor(Csub)
rownames(corr.inv) = viz
colnames(corr.inv) = viz

# Performs the z-transformation test
p.value = 1-pnorm(abs(sqrt(n-(lcl-2)-3)*
                    log((1+corr.inv[i1,j1])/(1-corr.inv[i1,j1]))/2))

# right superior lpcData = partial correaltion
# left inferior lpcData = p-value
Ap[k,vertices[j]] = p.value
Ap[vertices[j],k] = corr.inv[i1,j1]

}
} # end loop

}
Ap[k,]
}

# Calculates the tome that the loop has taken.

ti <- Sys.time()
if(print.lpc == T)
  print(paste(as.numeric( round(ti-t0,2), units = "secs")/60,
    "min, _p=", p, "tempo/p=", round(as.numeric(ti-t0, units = "secs")/p,2), "s/node"))

colnames(lpcData) = rownames(data)
rownames(lpcData) = rownames(data)

if (save) {
  writeLpcFile(lpcData, porc, pGenes=p)
}

# Stop the parallelzation routine.
stopCluster(cl)

```

B.2 Chapter 5

B.2.1 Scale-free simulation

```

# Number of variables
p = 10

# Size of hubs
hubs = 2

# Generate vector with 1 to p.
vec = 1:p

# Transform vec to characters.
charac = as.character(vec)

```



```

# Generate combination of nodes and edges.
comb = combn(rev(charac),2)
col = data.frame(ed1 = rev(comb[2,]), ed2 = rev(comb[1,]), stringsAsFactors = F)
col$pair = ifelse(as.numeric(col$ed1)
< as.numeric(col$ed2), paste(col$ed1, col$ed2), paste(col$ed2, col$ed1))

col$edges = numeric((length(vec)*(length(vec)-1))/2)

# Generate Starting hubs.
vec.sel = 1:hubs
temp = combn(vec.sel,2)
temp2= data.frame(ed1 = temp[1,], ed2 = temp[2,])
col.sel = temp2[!duplicated(temp2$ed1),]
col.sel$pair.sel = ifelse(as.numeric(col.sel$ed1)
< as.numeric(col.sel$ed2), paste(col.sel$ed1, col.sel$ed2), paste(col.sel$ed2, col.sel$ed1))

col[col$pair %in% col.sel$pair.sel, "edges"] = 1
A = matrix(0, ncol = length(vec), nrow = length(vec))
A[upper.tri(A)] = col$edges

# Generate table edge.counts, that counts the number of edges and control
# the preferential attachment.
edges.count = data.frame(vec)
edges.count$E = numeric(length(vec))
edges.count$edges = numeric(length(vec))
edges.count[edges.count$vec %in% col.sel$ed1, "E"] = 1
edges.count[edges.count$vec %in% col.sel$ed2, "E"] =
edges.count[edges.count$vec %in% col.sel$ed2, "E"]+1

edges.count[edges.count$E != 0, "edges"] =
edges.count[edges.count$E != 0, "vec"]

edges.count$prob = edges.count$E/sum(edges.count$E)
prob = edges.count$prob

# Diffrence between sets
compl.vec = setdiff(vec, vec.sel)
compl.vec.temp = compl.vec

# Random Process that generates the preferential attachment.
for(i in compl.vec[1]:(compl.vec[1]+length(compl.vec)-1)){

  new.node = i
  samp.node = sample(edges.count$edges, 1, prob = edges.count$prob)
  new.pair =
  ifelse(new.node < samp.node, paste(new.node, samp.node), paste(samp.node, new.node))

  col[col$pair %in% new.pair, "edges"] = 1
  edges.count[edges.count$vec %in% new.node, "E"] = 1
  edges.count[edges.count$vec %in% new.node, "edges"] = new.node
  edges.count[edges.count$vec %in% samp.node, "E"] =
  edges.count[edges.count$vec %in% samp.node, "E"]+1

  edges.count$prob = edges.count$E/sum(edges.count$E)

}

# Resulting adjacency matrix.
A = matrix(0, ncol = length(vec), nrow = length(vec))

```

```
A[upper.tri(A)] = col$edges
A = A+t(A)
```

B.2.2 Matrix transformation

```
# Sample uniformly select between (0.4,0.8)
cov = runif(sum(A)/2, epsilon1, epsilon2)

# Sample {-1,1} with equal probability.
sign = sample(c(1,-1),size = sum(A)/2, replace = T, prob = c(prob1, prob.menos1))
cov = sign*cov
Omega = A
Omega[which(((upper.tri(A)) * (A!=0)) != 0)] = cov
Omega[lower.tri(A)] = 0
Omega = Omega + t(Omega)
Omega = Omega + (0.05 + abs(min(eigen(Omega)$values))) * diag(1, ncol(A), ncol(A))

# Matriz diagonal prp com uniformes
D = matrix(0,nrow = p,ncol = p)
diag(D) = runif(p,1,5)

# Convert precion matrix.
Sigma = D%*%solve(Omega)%*%D
```


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