A comparative study of Gaussian Graphical Model approaches for genomic data

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The inference of networks of dependencies by Gaussian Graphical models on high-throughput data is an open issue in modern molecular biology. In this paper we provide a comparative study of three methods to obtain small sample and high dimension estimates of partial correlation coefficients: the Moore-Penrose pseudoinverse (PINV), residual correlation (RCM) and covariance-regularized method ($\ell_2\ell_1$). We first compare them on simulated datasets and we find that PINV is less stable in terms of AUC performance when the number of variables changes. The two regularized methods have comparable performances but $\ell_2\ell_1$ is much faster than RCM. Finally, we present the results of an application of $\ell_2\ell_1$ for the inference of a gene network for isoprenoid biosynthesis pathways in Arabidopsis thaliana.

INTRODUCTION

One of the aims of systems biology is to provide quantitative models for the study of complex interaction patterns among genes and their products that are the result of many biological processes in the cell, such as biochemical interactions and regulatory activities. In this framework, graphical models [1] have been exploited as useful stochastic tools to investigate and describe the conditional independence structure between random variables. In particular, the Graphical Gaussian Models (GGM) use the partial correlation estimates as a measure of conditional independence between any two variables [2]. Unfortunately, the application of GGMs classical theory is still a hard task. The genomic data are typically characterized by a huge number of genes $p$ with respect to the small number of available samples $n$. This makes unreliable the application of the classical GGMs theory to the small sample setting case. In recent years, several methods have been proposed to overcome this problem by reducing the numbers of genes or gene lists in order to reach the $n > p$ regime [3]. Other solutions have been also proposed [4–6] to circumvent the problem of computing full partial correlation coefficients by using only zero and first order coefficients. However, these approaches do not take into account all multigene effects on each pair of variables. A more sophisticated way to adapt GGMs to the $n < p$ case is to find regularized estimates for the covariance matrix [7–9] and its inverse. Once regularized estimates of partial correlation are available, heuristic searches can be used to find an optimal graphical model. A fundamental assumption to perform these quantitative methods is the sparsity of biological networks: only a few edges are supposed to be present in the gene regulatory networks, so that reliable estimates of the graphical model can be inferred also in small sample case [5]. A regularized GGM method based on a Stein-type shrinkage has been applied to genomic data [10] and the network selection has been based on false discovery rate multiple testing. In Ref. [11] the same procedure to select the network has been adopted, with a Moore-Penrose pseudoinverse method to obtain the concentration matrix. Finally, the authors in Ref. [12] have suggested an attractive and simple approach based on lasso-type regression to select among the partial correlations the nonzero values, paving the way to a number of analysis and novel algorithms based on lasso

GAUSSIAN NETWORKS FROM MICROARRAY DATA

Let $X = (X_1, \ldots, X_p) \in \mathbb{R}^p$ be a random vector distributed according a multivariate normal distribution $\mathcal{N} (\mu, \Sigma)$. The interaction structure between these variables can be described by means of a graph $G = (V, E)$, where $V$ is the vertex set and $E$ is the edge set. If vertices of $V$ are identified with the random variables $X_1, \ldots, X_p$, then the edges of $E$ can represent the conditional dependence between the vertices. In other words, the absence of an edge between the $i$–th and $j$–th vertex means a conditional
independence between the associated variables $X_i$ and $X_j$. In this study, we shall consider only undirected Gaussian graphs $G$ with pairwise Markov property, such that for all $(i, j) \notin E$ one has

$$X_i \perp X_j \mid X_{V \setminus \{i,j\}}, \quad i,j=1,\ldots,p,$$

i.e. $X_i$ and $X_j$ are conditionally independent being fixed all other variables $X_{V \setminus \{i,j\}}$. Since $X$ follows a $p$--variate normal distribution, the condition (1) turns out to be $\rho_{ij \setminus \{i,j\}} = 0$, where $\rho_{ij \setminus \{i,j\}}$ is the partial correlation coefficient between the $i$--th and $j$--th variable, being fixed all other variables. It has been shown [1] that partial correlation matrix elements are related to the precision matrix (or inverse covariance matrix) $\Theta = \Sigma^{-1}$, as:

$$\rho_{ij \setminus \{i,j\}} = -\frac{\theta_{ij}}{\sqrt{\theta_{ii}\theta_{jj}}} \quad i \neq j,$$

where $\theta_{ij}$ are elements of $\Omega$. In general, when the number of observations $n$ is greater than the number of variables $p$, it is straightforward to evaluate $\theta_{ij}$ in Eq. (2) by inverting the sample covariance matrix. Unfortunately, a typical genomic dataset is characterized by $n < p$, so that the sample covariance matrix becomes not invertible [4]. For this reason, in order to estimate the partial correlation matrix one needs alternative methods to overcome the problem, like regularization methods, ridge regression or pseudoinverse.

**Partial correlation matrix estimation**

In order to describe the three methods that we shall investigate, let us consider the $n \times p$ matrix $X = (X_1, X_2, \ldots, X_p)$, where each $\{X_i\} \in \mathbb{R}^n$, with $n < p$. Let us indicate $S$ as the estimate of the covariance matrix $\Sigma$ and $\hat{\Theta}$ as the estimate of inverse covariance matrix $\Sigma^{-1}$.

**Pseudoinverse method (PINV)**

The precision matrix $\hat{\Theta}$ can be obtained as pseudoinverse of $S$, by using the Singular Value Decomposition (SVD). Indeed, a singular value decomposition of a $m \times q$ matrix $M$, is $M = UA\Lambda V^*$, where $U$ is a $m \times m$ unitary matrix, $\Lambda$ is $m \times q$ diagonal matrix with nonnegative real numbers on the diagonal and $V^*$ is a $q \times q$ unitary matrix (transpose conjugate of $V$). Then, the pseudoinverse of $M$ is $M^+ = V\Lambda^+U^*$, where $\Lambda^+$ is obtained by replacing each diagonal element with its reciprocal and then transposing the matrix.

**Covariance-regularized method ($\ell_{2C}$)**

Let us consider a log likelihood function with a $\ell_2$ penalization [9]:

$$L(\Theta) = \log \det \Theta - \text{Tr}(S\Theta) - \lambda \|\Theta\|_F^2,$$

with $\lambda > 0$ and $\|\Theta\|_F^2 = \text{tr}(\Theta^\top \Theta)$. The maximization of Eq. (3) with respect to $\Theta$ is equivalent to solve the following equation

$$\hat{\Theta}^{-1} - 2\lambda \hat{\Theta} = S. \quad (4)$$

Consequently, the problem turns out to be an eigenvalue problem, therefore the eigenvalues $\theta_i$ of $\hat{\Theta}$ can be evaluated as function of the eigenvalues $s_i$ of $S$:

$$\theta_i^\pm = \frac{s_i}{4\lambda} \pm \frac{\sqrt{s_i^2 + 8\lambda}}{4\lambda} \quad (5)$$

Since $\Theta$ must be positive definite, the correct value of $\theta_i$ is $\theta_i^+$ then, for the spectral theorem the precision matrix $\hat{\Theta}$ is given by

$$\hat{\Theta} = \sum_{i=1}^q \theta_i^+ u_i u_i^\top. \quad (6)$$

Finally, in order to estimate the parameter $\lambda$ that maximizes the penalized log-likelihood function in Eq. (3), we carry out 20 random splits of the data set in training and validation sets and then we evaluate the log-likelihood over the validation set.
Finally, the partition the columns into disjoint groups $G_k$, where index $k$ indicates the $k$–th column chosen as “central” in each group. Then the off-diagonal terms are set $\theta_\ell k = \theta$ if $i \in G_k$, otherwise $\theta_\ell k = 0$. In the cliques pattern, the precision matrix is partitioned as done in hubs and the off-diagonal terms $\theta_ij$ are set to $\theta$ if $i, j \in G_k$, with $i \neq j$. The positive definiteness for each configuration, is guaranteed by the diagonal entries which are selected in order to keep $\Theta_{\text{th}}$ diagonally dominant.

**Residual correlation method (RCM)**

We consider a regression model for the variables $X_i$ and $X_j$ as

$$X_i = \langle \beta_{(i)}, X \rangle_{\text{th}, i} + b_i$$

$$X_j = \langle \beta_{(j)}, X \rangle_{\text{th}, j} + b_j$$

(7)

where $\{\beta_{(i)}\}$ is the regression coefficient vector in $p - 2$ dimensions referred to the $i$–th gene; $X_i$ is the $i$–th column of the matrix $X$ and $X_{\text{th}, i}$ is $X$ without the $i$–th and $j$–th columns. The Regularized Least Square (RLS) [15] method evaluates the regression models (7) by solving

$$\min_{\beta \in \mathbb{R}^{p-2}} \frac{1}{n} \|X_i - \beta_{(i)} X_{\text{th}, i}\|^2 + \lambda \|\beta_{(i)}\|^2.$$  

(8)

Now, if $\hat{X}_i$ and $\hat{X}_j$ are the RLS estimates of $X_i$ and $X_j$, one can evaluate the residual vectors $r_i = \hat{X}_i - X_i$ and $r_j = \hat{X}_j - X_j$. This allows to evaluate the partial correlation coefficients $\rho_{ij|p-2}$ between the $i$–th and $j$–th variable being fixed all other $p - 2$ variables as the Pearson correlation $r_{irj}$ between the residuals, i.e.

$$\rho_{ij|p-2} = r_{irj} = \frac{\text{cov}(r_i, r_j)}{\sqrt{\text{var}(r_i) \cdot \text{var}(r_j)}}.$$  

(9)

Finally, the $\lambda > 0$ parameter has been chosen by minimizing the Leave-One-Out cross validation errors.

**COMPARATIVE STUDY OF ACCURACY**

**Data generation**

Datasets with different numbers of variables and observations have been used in order to investigate the performances of the methods, i.e. $p = \{50, 200, 400\}$ and $n = \{20, 200, 500\}$. Each dataset $X$ has been generated from a multivariate gaussian distribution with zero mean and covariance $\Sigma_{\text{th}} = \Theta_{\text{th}}^{-1}$. The structure of the precision matrix $\Theta_{\text{th}}$ presents the following patterns [13]: random, hubs and cliques and it has approximately $p$ non vanishing entries out of the $p(p - 1)/2$ off-diagonal elements, except for clique configuration where the entries are approximately $2p$.

In the random pattern, the off–diagonal terms of $\Theta_{\text{th}}$ are set randomly to a fixed value $\theta \neq 0$. In the hubs configuration, we partition the columns into disjoint groups $G_k$, where index $k$ indicates the $k$–th column chosen as “central” in each group. Then the off-diagonal terms are set $\theta_{ik} = \theta$ if $i \in G_k$, otherwise $\theta_{ik} = 0$. In the cliques pattern, the precision matrix is partitioned as done in hubs and the off–diagonal terms $\theta_{ij}$ are set to $\theta$ if $i, j \in G_k$, with $i \neq j$. The positive definiteness for each configuration, is guaranteed by the diagonal entries which are selected in order to keep $\Theta_{\text{th}}$ diagonally dominant.

| n  | $\ell_2C$ AUC | $\ell_2C$ AUC std | $\ell_2C$ T (s) | PINV AUC | PINV AUC std | PINV T (s) | RCM AUC | RCM AUC std | RCM T (s) |
|----|---------------|--------------------|-----------------|----------|---------------|----------|---------|-------------|---------|
| r  | 500           | 0.998              | 0.0001          | 38.86    | 0.987         | 0.0006   | 0.161   | 0.999       | 0.0001  |
| h  | 500           | 1.000              | 0.0000          | 83.74    | 0.999         | 0.0000   | 0.164   | 1.000       | 0.0000  |
| c  | 500           | 0.995              | 0.0002          | 84.95    | 0.963         | 0.0014   | 0.164   | 0.996       | 0.0002  |

TABLE I: AUC, AUC standard error and timing performances for $p = 400$. Left part: $\ell_2C$ method. Center part: PINV. Right part: RCM. Indices $r$, $h$ and $c$ stand for random, hubs and clique pattern, respectively.
In order to compare the performances of the three methods, we have used this procedure: (I) For each data generation pattern, draw a random dataset $X$ from $\mathcal{N}(0, \Sigma_n)$; (II) Evaluate $S$ and $\Theta_{exp}$ in the case of PINV and $\ell_{2C}$, hence find $\rho_{exp}$ from Eq. (2); in the case of RCM use Eq. (9) for the evaluation of $\rho_{exp}$; (III) For each method, evaluate the AUC performance, as follows. Since the edges in our simulated dataset have the same strength and we know the label edge and non edge for each element, the elements of $\rho_{exp}$ can be divided in two sets: $\rho_{exp}$ for the edge elements and $\rho_{exp}$ for the non edge ones. The AUC measures the performances of the three methods in terms of accuracy of classification of edge and non edges by using the relative $\rho_{exp}$ values.

TABLE II: AUC, AUC standard error and timing performances for $p = 200$. Left part: $\ell_{2C}$ method. Center part: PINV. Right part: RCM. Indices $r$, $h$ and $c$ stand for random, hubs and clique pattern, respectively.

| \(n\) | $\ell_{2C}$ | PINV | RCM |
|---|---|---|---|
| | AUC | AUC std | T (s) | AUC | AUC std | T (s) | AUC | AUC std | T (s) |
| $r$ 500 | 0.999 | 0.0001 | 5.807 | 0.999 | 0.0001 | 0.0377 | 0.999 | 0.0001 | 807 |
| $h$ 500 | 1.000 | 0.0000 | 10.655 | 1.000 | 0.0000 | 0.0376 | 1.000 | 0.0000 | 450 |
| $c$ 500 | 0.996 | 0.0002 | 10.821 | 0.999 | 0.0001 | 0.0439 | 0.999 | 0.0000 | 436 |
| $r$ 200 | 0.986 | 0.0003 | 5.592 | 0.703 | 0.0067 | 0.0310 | 0.999 | 0.0007 | 861 |
| $h$ 200 | 1.000 | 0.0000 | 10.425 | 0.748 | 0.0124 | 0.0309 | 0.999 | 0.0003 | 856 |
| $c$ 200 | 0.944 | 0.0010 | 10.529 | 0.612 | 0.0064 | 0.0336 | 0.950 | 0.0008 | 1028 |
| $r$ 20 | 0.784 | 0.0016 | 6.150 | 0.880 | 0.0048 | 0.0187 | 0.871 | 0.0046 | 24.5 |
| $h$ 20 | 0.999 | 0.0001 | 10.574 | 0.999 | 0.0002 | 0.0182 | 0.999 | 0.0001 | 27.9 |
| $c$ 20 | 0.669 | 0.0016 | 10.545 | 0.649 | 0.0017 | 0.0189 | 0.654 | 0.0017 | 25.3 |

RESULTS

In order to investigate whether the transcriptional regulation is at the basis of the crosstalk between the cytosolic and the plastidial pathways, Laule et al. [19] have studied this interaction by identifying

APPLICATION TO BIOLOGICAL PATHWAYS

Isoprenoids play various important roles in plants, functioning as membrane components, photosynthetic pigments, hormones and plant defence compounds. They are synthesized through condensation of the five-carbon intermediates isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). In higher plants, IPP and DMAPP are synthesized through two different routes that take place in two distinct cellular compartments. The cytosolic pathway, also called MVA (mevalonate) pathway, provides the precursors for sterols, ubiquinone and sesquiterpenes [17]. An alternative pathway, called MEP/DOXP (2-C-methyl-D-erythritol 4-phosphate / 1-deoxy-D-xylulose 5-phosphate), is located in the chloroplast and is used for the synthesis of isoprene, carotenoids, abscisic acid, chlorophylls and plastoquinone [18]. Although this subcellular compartmentation allows both pathways to operate independently, there are several evidences that they can interact in some conditions [19]. Inhibition of the MVA pathway in A. thaliana leads to an increase of carotenoids and chlorophylls levels, demonstrating that its decreased functioning can be partially compensated for by the MEP/DOXP pathway. Inversely, inhibition of the MEP/DOXP pathway in seedlings causes the reduction of levels in carotenoids and chlorophylls, indicating a unidirectional transport of isoprenoid intermediates from the chloroplast to the cytosol. In order to investigate whether the transcriptional regulation is at the basis of the crosstalk between the cytosolic and the plastidial pathways, Laule et al. [19] have studied this interaction by identifying
the genes with expression levels changed as a response to the inhibition. They have shown that the inhibitor mediated changes in metabolite levels are not reflected in changes in gene expression levels, suggesting that alterations in the flux through the two isoprenoid pathways are not transcriptionally regulated. In order to clarify the interaction between both pathways at the transcriptional level, Wille et al. [4] have explored the structural relationship between genes on the basis of their expression levels under different experimental conditions. This study aims to infer the regulatory network of the genes in the isoprenoid pathways by incorporating the expression levels of 795 genes from other 56 metabolic pathways. Moving beyond the one-gene approach, the authors have found various connections between genes in the two different pathways, suggesting the existence of a crosstalk at the transcriptional level.

TABLE III: AUC, AUC standard error and timing performances for $p = 50$. Left part: $\ell_{2C}$ method. Center part: PINV. Right part: RCM. Indices $r$, $h$ and $c$ stand for random, hubs and clique pattern, respectively.

| n  | $\ell_{2C}$ | PINV | RCM |
|----|-------------|------|-----|
|    | AUC        | AUC std | T (s) | AUC | AUC std | T (s) | AUC | AUC std | T (s) |
| r  | 500        | 0.999 | 0.0000 | 0.4401 | 1.000 | 0.0000 | 0.0152 | 1.000 | 0.0000 | 2.76  |
| h  | 500        | 1.000 | 0.0000 | 0.4506 | 1.000 | 0.0000 | 0.0061 | 1.000 | 0.0000 | 4.19  |
| c  | 500        | 0.999 | 0.0000 | 0.4184 | 1.000 | 0.0000 | 0.0065 | 1.000 | 0.0000 | 3.45  |
| r  | 200        | 0.996 | 0.0004 | 0.4206 | 0.997 | 0.0004 | 0.0038 | 0.998 | 0.0004 | 1.92  |
| h  | 200        | 1.000 | 0.0000 | 0.4266 | 1.000 | 0.0000 | 0.0030 | 1.000 | 0.0000 | 2.26  |
| c  | 200        | 0.976 | 0.0023 | 0.3971 | 0.985 | 0.0009 | 0.0036 | 0.978 | 0.0011 | 2.10  |
| r  | 20         | 0.821 | 0.0047 | 0.4106 | 0.654 | 0.0097 | 0.0024 | 0.815 | 0.0066 | 1.56  |
| h  | 20         | 1.000 | 0.0000 | 0.4174 | 0.542 | 0.0076 | 0.0019 | 0.866 | 0.0081 | 1.43  |
| c  | 20         | 0.675 | 0.0052 | 0.3776 | 0.574 | 0.0076 | 0.0022 | 0.666 | 0.0057 | 1.48  |

Results from the covariance-regularized method for A. thaliana isoprenoid pathways

We apply the $\ell_{2C}$ method to the publicly available data set from Ref. [4]. The selection of the graph is performed by computing the 95% bootstrap confidence interval of the statistics and the absence of an edge occurs when the zero is included in this interval. The data consist of expression measurements for 39 genes in the isoprenoid pathways and 795 in other 56 pathways assayed on 118 Affymetrix GeneChip microarrays. We are interested in the construction of a gene network in the two isoprenoid pathways in order to detect the effects of genes in the other pathways. In Fig. 1 we reproduce the inferred network with 44 edges. For each pathway we find a module with strongly interconnected and positively correlated genes. This suggests the reliability of our approach, the authors have found various connections between genes in the two different pathways, suggesting the existence of a crosstalk at the transcriptional level.
CONCLUSIONS

In this paper, we present a comparative study of three different methods to infer networks of dependencies by estimates of partial correlation coefficients in the typical situation when \( n < p \). In particular, we consider the Moore-Penrose pseudoinverse method (PINV), the residual correlation method (RCM) and a covariance-regularized method (\( \ell_2C \)). Firstly, we evaluate AUCs and timing performances on simulated datasets and we find that PINV presents some instability in AUC outcomes associated to the variable number variations. On the other hand, the two regularized methods show comparable performances with a sensible gain of time elapsing of \( \ell_2C \) with respect to RCM. Finally, we present the results of an application of \( \ell_2C \) for the inference of a gene network for isoprenoid pathways in *A. thaliana*. We find a negative partial correlation coefficient between HMGS and HDS, that are the two hubs in the two isoprenoid pathways. This means that they respond differently to the several tested experimental conditions and, together with the high connectivity of the two hubs, provides an evidence of cross-talk between genes in the plastidial and the cytosolic pathways. This evidence did not result from studies at level of single gene. Moreover, studies that infer this network by using only low-order partial correlation coefficients find more interactions between the two pathways with respect to the \( \ell_2C \) method. A reduced number of edges between the two pathways is plausible considering the different cell compartmentalization of the two isoprenoid biosynthesis pathways.

This work was supported by grants from Regione Puglia PO FESR 2007–2013 Progetto BISIMANE (Cod. n. 44).

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