Joint network inference with the consensual LASSO

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Joint work with Matthieu Vignes, Nathalie Viguerie and Magali San Cristobal



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consensus Lasso

Outline

1 Short overview on network inference with GGM

2 Inference with multiple samples

3 Simulations



Transcriptomic data



DNA transcripted into mRNA to produce proteins



Transcriptomic data



DNA transcripted into mRNA to produce proteins

transcriptomic data: measure of the quantity of mRNA corresponding to a given gene in given cells (blood, muscle...) of a living organism

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Systems biology



Some genes' expressions **activate** or **repress** other genes' expressions \Rightarrow understanding the whole cascade helps to comprehend the global functioning of living organisms¹

¹Picture taken from: Abdollahi A *et al.*, *PNAS* 2007, **104**:12890-12895. © 2007 by National Academy of Sciences



Model framework

Data: large scale gene expression data

individuals

$$n \simeq 30/50$$

$$\begin{cases}
X = \begin{pmatrix}
\cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & X_i^j & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot
\end{cases}$$

variables (genes expression), $p \simeq 10^{3/4}$

What we want to obtain: a graph/network with

- nodes: genes;
- edges: strong links between gene expressions.



Advantages of inferring a network from large scale transcription data

over raw data: focuses on the strongest direct relationships: irrelevant or indirect relations are removed (more robust) and the data are easier to visualize and understand (track transcription relations).



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 - Expression data are **analyzed all together** and not by pairs (**systems model**).



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- over raw data: focuses on the strongest direct relationships: irrelevant or indirect relations are removed (more robust) and the data are easier to visualize and understand (track transcription relations).
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over bibliographic network: can handle interactions with yet unknown (not annotated) genes and deal with data collected in a particular condition.



Using *correlations*: relevance network [Butte and Kohane, 1999, Butte and Kohane, 2000]

First (naive) approach: calculate correlations between expressions for all pairs of genes, threshold the smallest ones and build the network.















Partial correlation in the Gaussian framework

 $(X_i)_{i=1,...,n}$ are **i.i.d. Gaussian random variables** $\mathcal{N}(0, \Sigma)$ (gene expression); then

 $j \longleftrightarrow j'$ (genes j and j' are linked) $\Leftrightarrow \mathbb{C}\mathrm{or}\left(X^{j}, X^{j'}| (X^{k})_{k \neq j, j'}\right) > 0$



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If (concentration matrix) $S = \Sigma^{-1}$,

$$\mathbb{C}\mathbf{or}\left(X^{j}, X^{j'}| (X^{k})_{k\neq j, j'}\right) = -\frac{S_{jj'}}{\sqrt{S_{jj}S_{j'j'}}}$$

 \Rightarrow Estimate Σ^{-1} to unravel the graph structure



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 \Rightarrow Estimate Σ^{-1} to unravel the graph structure

Problem: Σ : *p*-dimensional matrix and $n \ll p \Rightarrow (\widehat{\Sigma}^n)^{-1}$ is a **poor** estimate of *S*)!



Graphical Gaussian Model

- seminal work: [Schäfer and Strimmer, 2005a, Schäfer and Strimmer, 2005b] (with shrinkage and a proposal for a Bayesian test of significance)
 - estimate Σ^{-1} by $(\widehat{\Sigma}^n + \lambda \mathbb{I})^{-1}$
 - use a Bayesian test to test which coefficients are significantly non zero.

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 $\forall j$, estimate the linear model:

$$X^{j} = \beta_{j}^{\mathsf{T}} X^{-j} + \epsilon$$
 ; $\arg \max_{(\beta_{jj'})_{j'}} (\log \mathrm{ML}_{j})$

because $\beta_{jj'} = -\frac{S_{jj'}}{S_{jj}}$.

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$$X^{j} = \beta_{j}^{\mathsf{T}} X^{-j} + \epsilon$$
; arg min $\sum_{(\beta_{jj'})_{j'}} \sum_{i=1} \left(X_{ij} - \beta_{j}^{\mathsf{T}} X_{i}^{-j} \right)^{2}$

because
$$eta_{jj'}=-rac{S_{jj'}}{S_{jj}}.$$

Graphical Gaussian Model

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- estimate Σ^{-1} by $(\widehat{\Sigma}^n + \lambda \mathbb{I})^{-1}$
- use a Bayesian test to test which coefficients are significantly non zero.
- sparse approaches:

[Meinshausen and Bühlmann, 2006, Friedman et al., 2008]:

 $\forall j$, estimate the linear model:

$$X^{j} = \beta_{j}^{\mathsf{T}} X^{-j} + \epsilon \qquad ; \qquad \arg\min_{(\beta_{ij'})_{j'}} \sum_{i=1}^{n} \left(X_{ij} - \beta_{j}^{\mathsf{T}} X_{i}^{-j} \right)^{2} + \lambda ||\beta_{j}||_{L^{1}}$$

with $\|\beta_j\|_{L^1} = \sum_{j'} |\beta_{jj'}|$ L^1 penalty yields to $\beta_{jj'} = 0$ for most j' (variable selection)

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Motivation for multiple networks inference

Pan-European project Diogenes² (with Nathalie Viguerie, INSERM): gene expressions (lipid tissues) from 204 obese women **before** and **after** a low-calorie diet (LCD).



- Assumption: A common functioning exists regardless the condition;
- Which genes are linked independently from/depending on the condition?



12/30

²http://www.diogenes-eu.org/; see also [Viguerie et al., 2012] < = >

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consensus Lasso

Naive approach: independent estimations

Notations: *p* genes measured in *k* samples, each corresponding to a specific condition: $(X_j^c)_{j=1,...,p} \sim \mathcal{N}(0, \Sigma^c)$, for c = 1, ..., k. For c = 1, ..., k, n_c independent observations $(X_{ii}^c)_{i=1,...,n_c}$ and $\sum_c n_c = n$.

Independent inference

Estimation $\forall c = 1, \dots, k$ and $\forall j = 1, \dots, p$,

$$X_j^c = \mathbf{X}_{ij}^c \beta_j^c + \epsilon_j^c$$

are estimated (independently) by maximizing pseudo-likelihood:

$$\mathcal{L}(S|\mathbf{X}) = \sum_{c=1}^{k} \sum_{j=1}^{p} \sum_{i=1}^{n_c} \log \mathbb{P}\left(X_{ij}^c | \mathbf{X}_{i, \setminus j}^c, S_j^c\right)$$

Problem: previous estimation does not use the fact that the different networks should be somehow alike!

Previous proposals

[Chiquet et al., 2011] replace Σ^c by Σ^c = ¹/₂Σ^c + ¹/₂Σ^c and add a sparse penalty;



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- [Chiquet et al., 2011] LASSO and Group-LASSO type penalties to force identical or sign-coherent edges between conditions:

$$\sum_{jj'} \sqrt{\sum_c (S^c_{jj'})^2} \quad \text{or} \ \sum_{jj'} \left[\sqrt{\sum_c (S^c_{jj'})^2_+} + \sqrt{\sum_c (S^c_{jj'})^2_-} \right]$$

 $\Rightarrow S^c_{jj'} = 0 \; \forall \, c$ for most entries OR $S^c_{jj'}$ can only be of a given sign (positive or negative) whatever c



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- [Danaher et al., 2013] add the penalty ∑_{c≠c'} ||S^c S^{c'}||_{L1} ⇒ very strong consistency between conditions (sparse penalty over the inferred networks identical values for concentration matrix entries);



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- [Danaher et al., 2013] add the penalty ∑_{c≠c'} ||S^c S^{c'}||_{L1} ⇒ very strong consistency between conditions (sparse penalty over the inferred networks identical values for concentration matrix entries);
- [Mohan et al., 2012] add a group-LASSO like penalty ∑_{c≠c'} ∑_j ||S_j^c - S_j^{c'} ||_{L²} that focuses on differences due to a few number of nodes only.



Consensus LASSO

Proposal

Infer multiple networks by forcing them toward a consensual network: i.e., explicitly **keeping the differences** between conditions under control but **with a** L^2 **penalty** (allow for more differences than Group-LASSO type penalties).

Original optimization:

$$\max_{(\beta_{jk}^{c})_{k\neq j,c=1,\dots,C}} \sum_{c} \left(\log \mathrm{ML}_{j}^{c} - \lambda \sum_{k\neq j} |\beta_{jk}^{c}| \right).$$



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[Ambroise et al., 2009, Chiquet et al., 2011]: is equivalent to minimize p problems having dimension k(p-1):

$$\frac{1}{2}\beta_j^T\widehat{\Sigma}_{\backslash j\backslash j}\beta_j + \beta_j^T\widehat{\Sigma}_{j\backslash j} + \lambda \|\beta_j\|_{L^1}, \qquad \beta_j = (\beta_j^1, \dots, \beta_j^k)$$

with $\widehat{\Sigma}_{i/i}$: block diagonal matrix $\mathbb{D}iag(\widehat{\Sigma}_{i/i}^1, \dots, \widehat{\Sigma}_{i/i}^k)$ and similarly for $\widehat{\Sigma}_{i/i}$

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Add a constraint to force inference toward a "consensus" β^{cons}

$$\frac{1}{2}\beta_j^T \widehat{\Sigma}_{\langle j \rangle j} \beta_j + \beta_j^T \widehat{\Sigma}_{j \langle j \rangle} + \lambda \|\beta_j\|_{L^1} + \mu \sum_c w_c \|\beta_j^c - \beta_j^{\text{cons}}\|_{L^2}^2$$

with:

- w_c : real number used to weight the conditions ($w_c = 1$ or $w_c = \frac{1}{\sqrt{n_c}}$);
- μ regularization parameter;
- β^{cons}_i whatever you want...?

Choice of a consensus: set one...

Typical case:

- a prior network is known (e.g., from bibliography);
- with no prior information, use a fixed prior corresponding to (e.g.) global inference

 \Rightarrow given (and fixed) β^{cons}



Choice of a consensus: set one...

Typical case:

- a prior network is known (e.g., from bibliography);
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 \Rightarrow given (and fixed) β^{cons}

Proposition

Using a fixed β_j^{cons} , the optimization problem is equivalent to minimizing the *p* following standard quadratic problem in $\mathbb{R}^{k(p-1)}$ with *L*₁-penalty:

$$\frac{1}{2}\beta_j^T B^1(\mu)\beta_j + \beta_j^T B^2(\mu) + \lambda ||\beta_j||_{L^1},$$

where

- $B^{1}(\mu) = \widehat{\Sigma}_{\forall\forall j} + 2\mu \mathbb{I}_{k(p-1)}$, with $\mathbb{I}_{k(p-1)}$ the k(p-1)-identity matrix
- $B^2(\mu) = \widehat{\Sigma}_{j,j} 2\mu \mathbb{I}_{k(p-1)}\beta^{\text{cons}}$ with $\beta^{\text{cons}} = \left((\beta_j^{\text{cons}})^T, \dots, (\beta_j^{\text{cons}})^T \right)^T$

16/30

Choice of a consensus: adapt one during training...

Derive the consensus from the condition-specific estimates:

$$\beta_j^{\rm cons} = \sum_c \frac{n_c}{n} \beta_j^c$$



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Choice of a consensus: adapt one during training...

Derive the consensus from the condition-specific estimates:

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Proposition

Using $\beta_j^{\text{cons}} = \sum_{c=1}^k \frac{n_c}{n} \beta_j^c$, the optimization problem is equivalent to minimizing the following standard quadratic problem with L_1 -penalty:

$$\frac{1}{2}\beta_j^T S_j(\mu)\beta_j + \beta_j^T \widehat{\Sigma}_{j\setminus j} + \lambda \|\beta_j\|_{L^1}$$

where $S_j(\mu) = \widehat{\Sigma}_{\forall\forall\forall} + 2\mu A^T(\mu)A(\mu)$ where $A(\mu)$ is a $[k(p-1) \times k(p-1)]$ -matrix that does not depend on *j*.



17/30

Common framework

Objective function can be decomposed into:

convex part
$$C(\beta_j) = \frac{1}{2}\beta_j^T Q_j^1(\mu) + \beta_j^T Q_j^2(\mu)$$

 L^1 -norm penalty $\mathcal{P}(\beta_j) = ||\beta_j||_{L^1}$



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optimization by "active set" [Osborne et al., 2000, Chiquet et al., 2011]

1: repeat(λ given)

2: Given \mathcal{A} and $\beta_{jj'}$ st: $\beta_{jj'} \neq 0, \forall j' \in \mathcal{A}$, solve (over *h*) the **smooth** minimization problem restricted to \mathcal{A}

 $C(\beta_j + h) + \lambda \mathcal{P}(\beta_j + h) \implies \beta_j \leftarrow \beta_j + h$



4: until

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 $C(\beta_j + h) + \lambda \mathcal{P}(\beta_j + h) \implies \beta_j \leftarrow \beta_j + h$

3: Update \mathcal{A} by adding most violating variables, i.e., variables st:

abs
$$\left|\partial C(\beta_j) + \lambda \partial \mathcal{P}(\beta_j)\right| > 0$$

with $[\partial \mathcal{P}(\beta_j)]_{j'} \in [-1, 1]$ if $j' \notin \mathcal{A}$ 4: until

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4: until all conditions satisfied i.e. $abs \left|\partial C(\beta_j) + \lambda \partial \mathcal{P}(\beta_j)\right| > 0 \rightarrow d \mathcal{P}(\beta_j) = 0$

Common framework

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$$C(\beta_j) = \frac{1}{2}\beta_j^T Q_j^1(\mu) + \beta_j^T Q_j^2(\mu)$$

 L^1 -norm penalty $\mathcal{P}(\beta_j) = ||\beta_j||_{L^1}$

optimization by "active set" [Osborne et al., 2000, Chiquet et al., 2011] Repeat:

- 1: repeat(λ given)
- 2: Given \mathcal{A} and $\beta_{jj'}$ st: $\beta_{jj'} \neq 0$, $\forall j' \in \mathcal{A}$, solve (over *h*) the **smooth** minimization problem restricted to \mathcal{A} large λ

$$C(\beta_j + h) + \lambda \mathcal{P}(\beta_j + h) \implies \beta_j \leftarrow \beta_j + h$$

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$$\left|\partial C(\beta_j) + \lambda \partial \mathcal{P}(\beta_j)\right| > 0$$

with $[\partial \mathcal{P}(\beta_j)]_{j'} \in [-1, 1]$ if $j' \notin \mathcal{A}$ 4: **until all conditions satisfied** i.e. abs $|\partial C(\beta_j) + \lambda \partial \mathcal{P}(\beta_j)| > 0$ \Rightarrow as prior \ge $2 < \infty$ Nathalie Villa-Vialaneix (INRA. Unité MIA-T) consensus Lasso Toulouse. April 23th, 2014 18 / 30.

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small λ

Bootstrap estimation ~ BOLASSO [Bach, 2008]

subsample n observations with replacement





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Bootstrap estimation ~ BOLASSO [Bach, 2008] subsample *n* observations with replacement





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Bootstrap estimation \simeq BOLASSO [Bach, 2008] subsample n observations with replacement Х х Х cLasso estimation for varying λ , $(\beta_{ii'}^{\lambda,b})_{jj'}$

threshold

keep the first T_1 largest coefficients





Frequency table (1,2) (1,3) ... (j,j') ... 130 25 ... 120 ...





 \rightarrow Keep the T_2 most frequent pairs



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Simulation

Simulated data

Expression data with known co-expression network

- original network (scale free) taken from http://www.comp-sys-bio.org/AGN/data.html (100 nodes, ~ 200 edges, loops removed);
- rewire a ratio r of the edges to generate k "children" networks (sharing approximately 100(1 – 2r)% of their edges);

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- rewire a ratio r of the edges to generate k "children" networks (sharing approximately 100(1 – 2r)% of their edges);
- generate "expression data" with a random Gaussian process from each chid:
 - use the Laplacian of the graph to generate a putative concentration matrix;
 - use edge colors in the original network to set the edge sign;
 - · correct the obtained matrix to make it positive;
 - invert to obtain a covariance matrix...;
 - ... which is used in a random Gaussian process to generate expression data (with noise).

Simulation

An example with k = 2, r = 5%



³actually the **parent network**. My co-author wisely noted that the mistake was unforgivable for a feminist... $\langle \Box \rangle \langle \partial \rangle$

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consensus Lasso



Choice for T_2 Data: r = 0.05, k = 2 and $n_1 = n_2 = 20$ 100 bootstrap samples, $\mu = 1$, $T_1 = 250$ or 500



Dots correspond to best $F = 2 \times \frac{\text{precision} \times \text{recall}}{\text{precision} + \text{recall}}$ \Rightarrow Best *F* corresponds to selecting a number of edges approximately equal to the number of edges in the original network.



consensus Lasso

23/30

Choice for T_1 and μ

	μ	<i>T</i> ₁	% of improvement		
	0.1/1	$\{250, 300, 500\}$	of bootstrapping		
network sizes	rewired edges: 5%				
20-20	1	500	30.69		
20-30	0.1	500	11.87		
30-30	1	300	20.15		
50-50	1	300	14.36		
20-20-20-20-20	1	500	86.04		
30-30-30-30	0.1	500	42.67		
network sizes	rewired edges: 20%				
20-20	0.1	300	-17.86		
20-30	0.1	300	-18.35		
30-30	1	500	-7.97		
50-50	0.1	300	-7.83		
20-20-20-20-20	0.1	500	10.27		
30-30-30-30	1	500	13.48		

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24 / 30

Comparison with other approaches

Method compared (direct and bootstrap approaches)

- independant Graphical LASSO estimation gLasso
- methods implementated in the R package simone and described in [Chiquet et al., 2011]: intertwinned LASSO iLasso, cooperative LASSO coopLasso and group LASSO groupLasso
- fused graphical LASSO as described in [Danaher et al., 2013] as implemented in the R package fgLasso



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- consensus Lasso with
 - fixed prior (the mother network) cLasso(p)
 - fixed prior (average over the conditions of independant estimations) cLasso(2)
 - adaptative estimation of the prior cLasso(m)



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Parameters set to: $T_1 = 500, B = 100, \mu = 1$



Selected results (best F)

rewired edges: 5% - conditions: 2 - sample size: 2 × 30

direct version Method groupLasso coopLasso gLasso iLasso 0.28 0.35 0.32 0.35 Method fgLasso cLasso(m) cLasso(p) cLasso(2) 0.32 0.31 0.86 0.30

bootstrap version

Method	gLasso	iLasso	groupLasso	coopLasso
	0.31	0.34	0.36	0.34
Method	fgLasso	cLasso(m)	cLasso(p)	cLasso(2)
	0.36	0.37	0.86	0.35

Conclusions

- bootstraping improves results (except for iLasso and for large r)
- joint inference improves results
- using a good prior is (as expected) very efficient
- adaptive approch for cLasso is better than naive approach



26/30

Real data

204 obese women ; expression of 221 genes before and after a LCD $\mu = 1$; $T_1 = 1000$ (target density: 4%)

Distribution of the number of times an edge is selected over 100 bootstrap samples







Networks



densities about 1.3% - some interactions (both shared and specific) make sense to the biologist



Thank you for your attention...

Programs available in the R package **therese** (on R-Forge)⁴. Joint work with





Magali SanCristobal (GenPhySe, INRA Toulouse) Matthieu Vignes (MIAT, INRA Toulouse)



Nathalie Viguerie (I2MC, INSERM Toulouse)



⁴https://r-forge.r-project.org/projects/therese=pkg= > +

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consensus Lasso



Questions?



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consensus Lasso

Toulouse, April 23th, 2014 30 / 30

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Simulation

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