Sparse factor model for gene co-expression networks

Anne Blum, Magalie Houee, Aldons J. Lusis, Sandrine Lagarrigue, David Causeur

Sparse factor model for gene co-expression networks

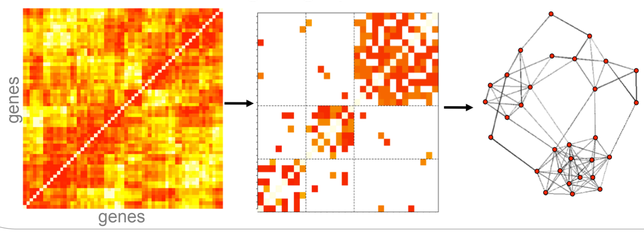
Y. Blum (1), **M. Houée** (2), **AJ. Lusis** (1), **S. Lagarrigue** (3), **D. Causeur** (2)

(1) Department of Medicine/Division of Cardiology, David Geffen School of Medicine, UCLA, Los Angeles, CA USA, (2) Agrocampus Ouest- Applied Mathematics Department, Rennes, France, (3). Agrocampus Ouest - UMR PEGASE INRA, Agrocampus Ouest, Rennes, France

Gene co-expression network

Network construction (for undirected graphical models)

1. Choose a measure L of the link between 2 genes
2. Decision rule: is L(y_i, y_j) different from 0 ?
3. Visualization through a graph



Measure of the link

Linear measures

• Pearson correlation: $corr(y_i, y_j) = \frac{Cov(y_i, y_j)}{\sqrt{Var(y_i)Var(y_j)}}$
simple and intuitive
→ **Co-expression networks**

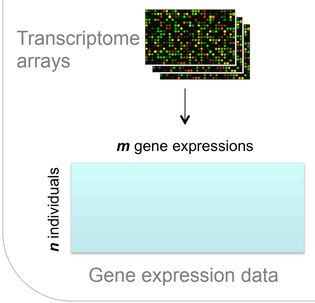
• Partial correlation: $corr(y_i, y_j | y_{\setminus i,j})$
→ Gaussian Graphical Model (GGM)

Non-linear measures

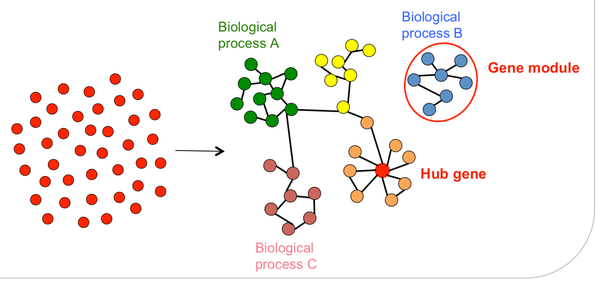
• Mutual information MI:
$MI(x,y) = \sum_{i=1}^{r}\sum_{j=1}^{r} P(x=i, y=i) log \frac{P(x=i,y=j)}{P(x=i)P(y=j)}$
→ Information-theory-based methods

Challenges

High dimension: n<<m



Sparsity assumption:
within a set of genes, only a few are interacting
(Tegner et al 2003)



Sparse factor model

Factor model

Key idea: to structure the dependence for correlation estimation (less parameters to estimate).

Y dataset with n rows (individuals) and m columns (genes).
Y ~ $N_m(\mu, \Sigma)$
Correlations between genes are described by a small number **q of factors containing a common dependence:**

Specific variability (uniqueness) — Common variability

$$\Sigma = \Psi + BB'$$

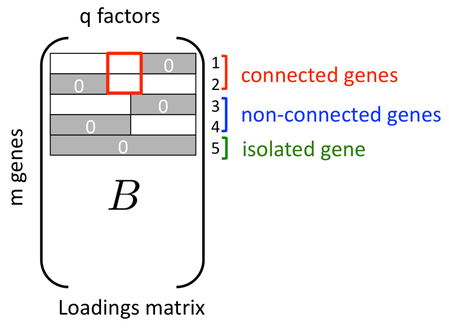
where Ψ is a diagonal matrix and B represents the m x q matrix of loadings

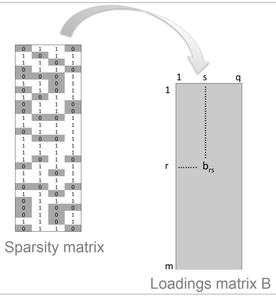
Estimation of the parameters

Estimation of Ψ and B: **EM algorithm** (Rubin & Thayer 1982)
Deviance:
$\mathcal{D}(\Psi, B) \propto \log\det(\Psi + BB') + \text{trace}[S(\Psi + BB')^{-1}]$
→ Calculate and minimize the expectation of $\mathcal{D}(\Psi, B; Z)$

Sparse adapted model

The topology of the network can be deduced from the loadings matrix B:





Adapted EM algorithm

M-step: minimizing the expected deviance under sparsity constrains:

$\mathcal{D}(\Psi, B; Z) + \lambda' R' vec(B)$ *Lagrange multiplier approach*

where λ is the vector of Lagrange multipliers and R the constraints matrix deduced from the sparsity matrix.

Sparsity using LASSO penalization


Sparsity matrix

Inference on the sparsity

L_1- regularization

$$\min_{\Psi,B} \mathcal{D}(\Psi, B) + \lambda \sum_{k=1}^{m}\sum_{i=1}^{q} |b_{ki}|$$

λ chosen by minimization of BIC

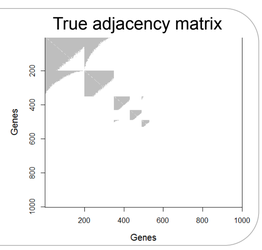
$$BIC(\lambda) = \mathcal{D}(\hat{\Psi}_\lambda, \hat{B}_\lambda) + 2\#\{(k,i),\ \hat{b}_{\lambda,ki} \neq 0\}$$

Comparison study

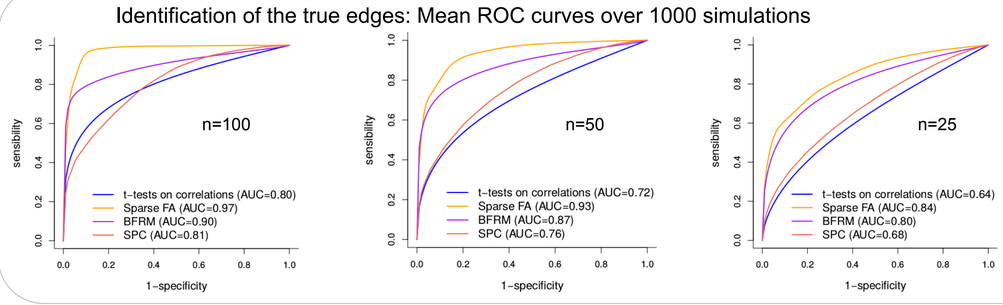
Comparable approaches:

- **SPC:** Sparse Principal Components (Witten et al, *Biostatistics* 2009)
- **BFRM:** Bayesian Factor Regression Model (West, *Bayesian Statistics* 2003)

Simulations
1000 datasets simulated from this true correlation structure (using n=10000)
5 modules: m_1=200 genes, m_2=150, m_3=80, m_4=60, m_5=40

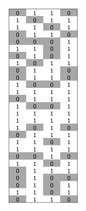


Identification of the true edges: Mean ROC curves over 1000 simulations



⇒ **Better estimation of the network**

Sparsity using biological knowledge


Sparsity matrix

Inference on the sparsity

Biological information:
- Gene Ontology
- Transcription factors,
- eQTL regulation
- ...

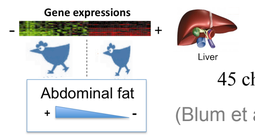
GO biological processes

	Term 1	Term 2	Term 3	...	Term X
gene 1	0	1	1	...	0
gene 2	1	0	0	...	0
gene 3	0	0	1	...	1
⋮	⋮	⋮	⋮	⋮	⋮
gene X	1	0	0	...	0

Example of biological constrain matrix

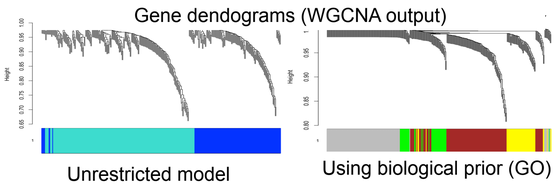
Example of application

Gene expression dataset:
~ 400 hepatic genes expression correlated with adiposity



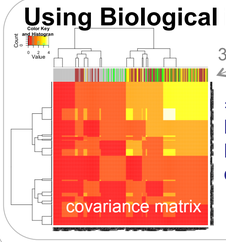
45 chickens
(Blum et al, 2010)

Gene modules detection using WGCNA (Horvath et al 2008)



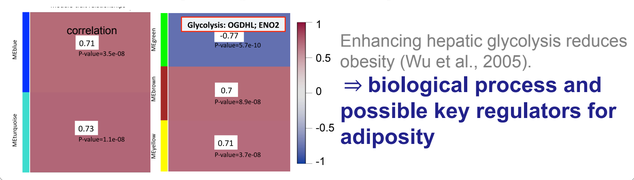
⇒ **a more precise structure is revealed**

Using Biological information only



⇒ **the model account both for biological knowledge and expression intensity**

Module-adiposity relationship



Enhancing hepatic glycolysis reduces obesity (Wu et al., 2005).
⇒ **biological process and possible key regulators for adiposity**

⇒ **New biological insight in gene module detection**

FANET sparse Factor Analysis for Network modeling R package

emfas.ccdlasso: this function proposes a LASSO-regularized EM algorithm using a cyclic coordinate descent algorithm to fit a sparse factor model for correlation


```
INPUT
data: gene expression dataset (rows=genes)

USAGE
emfas.ccdlasso(data, maxnbf=10, min.err = 1e-06,
max.iter = 100)

maxnbf: maximum number of factors in the model
min.err: stopping criterion value for iterations in ccd algorithm
max.iter: stopping criterion value for iterations in ccd algorithm

OUTPUT
Slasso: estimated correlation matrix
```

FANET sparse Factor Analysis for Network modeling R package

SparseEmfaBio: this function uses the biological constraines matrix to introduce sparsity in the factor model for correlation.

biomat: constructed by the user or by using the function `Construct.BioMatrix` (uses `biomaRt` R package)

```
INPUT
data: gene expression dataset (rows=genes)
biomat: biological constrain matrix

USAGE
SparseEmfaBio(data,biomat, min.err = 1e-06)

min.err: Stopping criterion value for iterations

OUTPUT
Sbio: estimated correlation matrix
```

References

More about Factor Analysis for expression data:
• Blum Y, et al. A Factor Model to Analyze Heterogeneity in Gene Expression. BMC Bioinformatics, 2010, 11:368.
• C. Friguet, et al. A factor model approach to multiple testing under dependence. Journal of the American Statistical Association, 104(488):1406–1415, 2009.
WGCNA R package:
P. Langfelder and S. Horvath. Wgcna: an r package for weighted correlation network analysis. BMC bioinformatics, 9(1):559, 2008.

R package `FANet` and tutorial

yuna-blum.com/links/FANet