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Sparse factor model for gene co-expression networks

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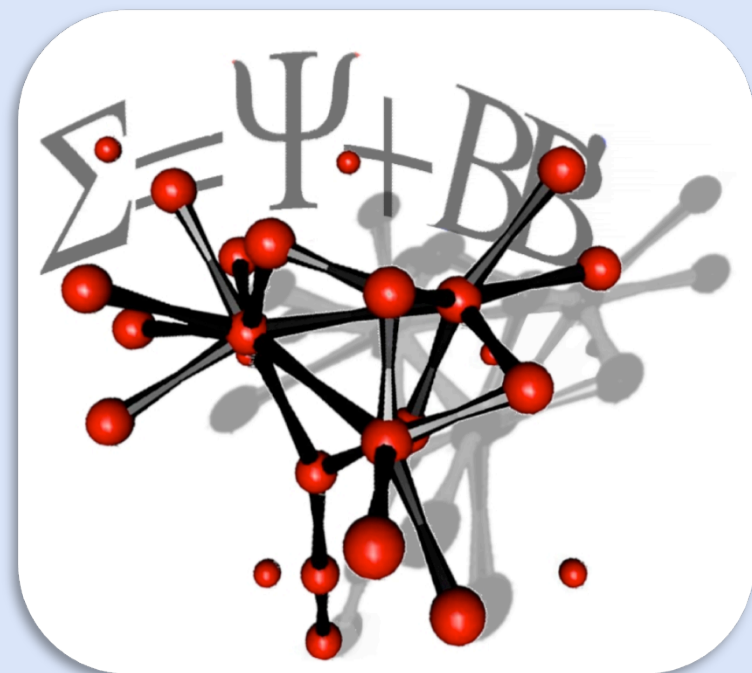
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Sparse factor model for gene co-expression networks

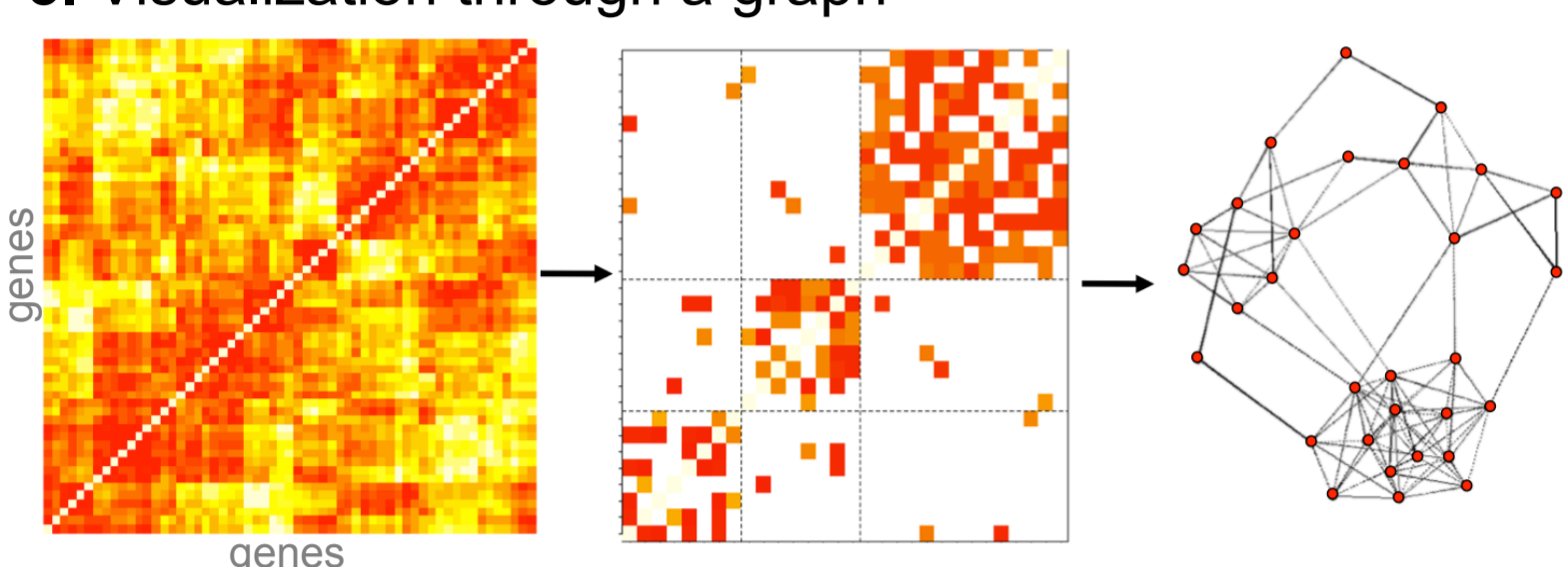
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Gene co-expression network

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:** $corr(y_i, y_j | y_{i,j})$

→ Gaussian Graphical Model (GGM)

Non-linear measures

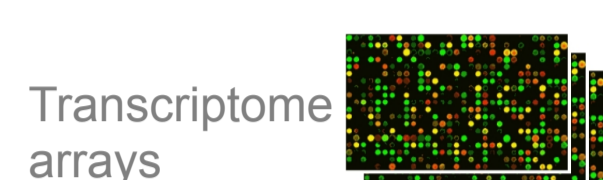
• **Mutual information MI:**

$MI(x, y) = \sum_{i=1}^I \sum_{j=1}^J P(x=i, y=j) \log \frac{P(x=i, y=j)}{P(x=i)P(y=j)}$

→ Information-theory-based methods

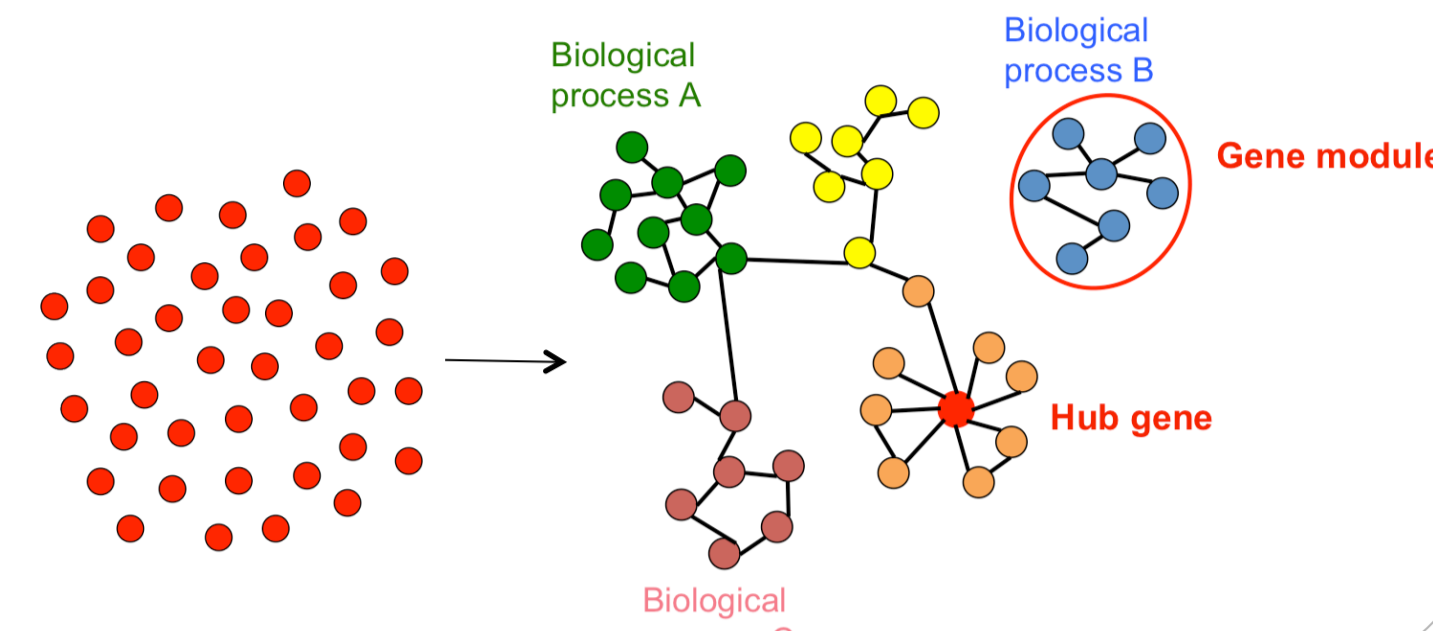
Challenges

High dimension: $n \ll m$



Gene expression data

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).

$Y \sim N_m(\mu, \Sigma)$

Correlations between genes are described by a small number **q** of factors containing a common dependence:

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

where Ψ is a diagonal matrix and B represents the $m \times q$ matrix of loadings

Estimation of the parameters

Estimation of Ψ and B: **EM algorithm** (Rubin & Thayer 1982)

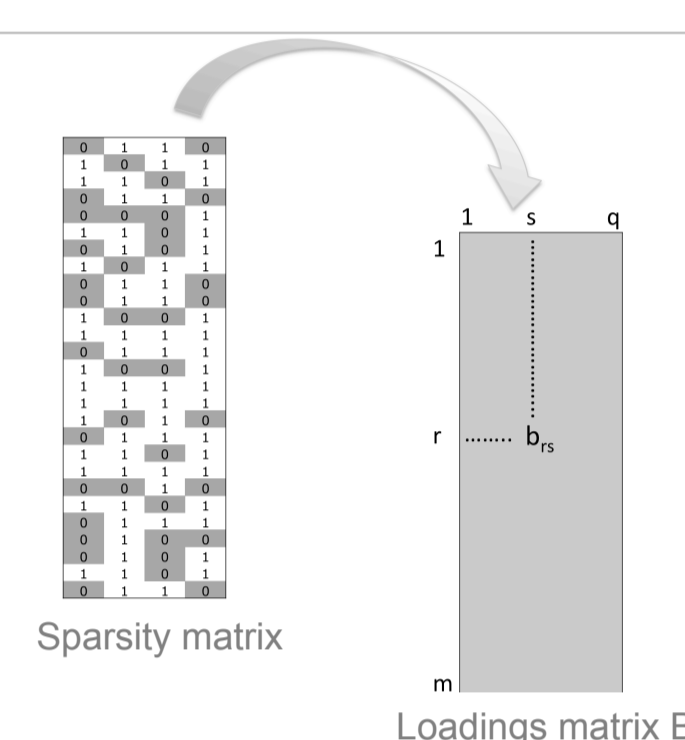
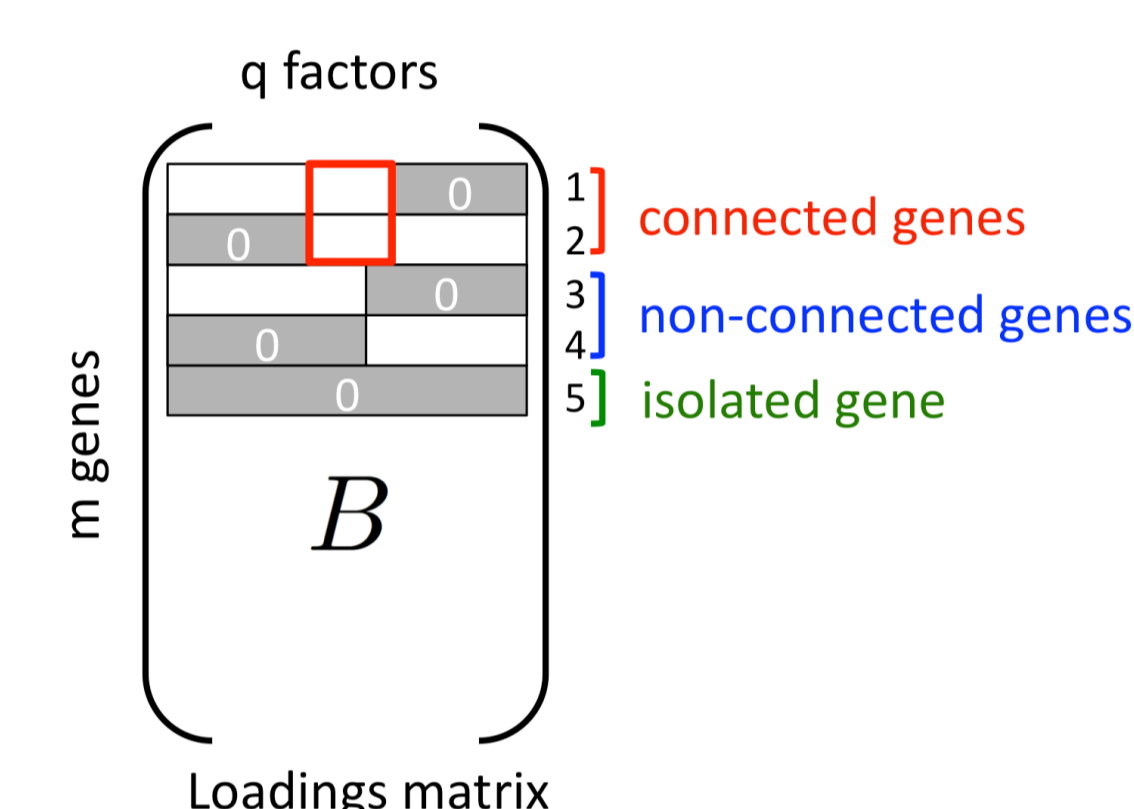
Deviance:

$$D(\Psi, B) \propto \log \det(\Psi + BB') + \text{trace}[S(\Psi + BB')^{-1}]$$

→ Calculate and minimize the expectation of $D(\Psi, B; Z)$

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 constraints:

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

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

Sparsity using LASSO penalization

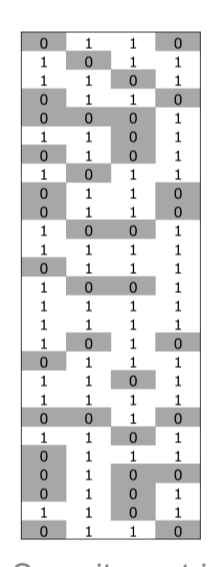
Inference on the sparsity

L₁- regularization

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

λ chosen by minimization of BIC

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



Comparison study

Comparable approaches:

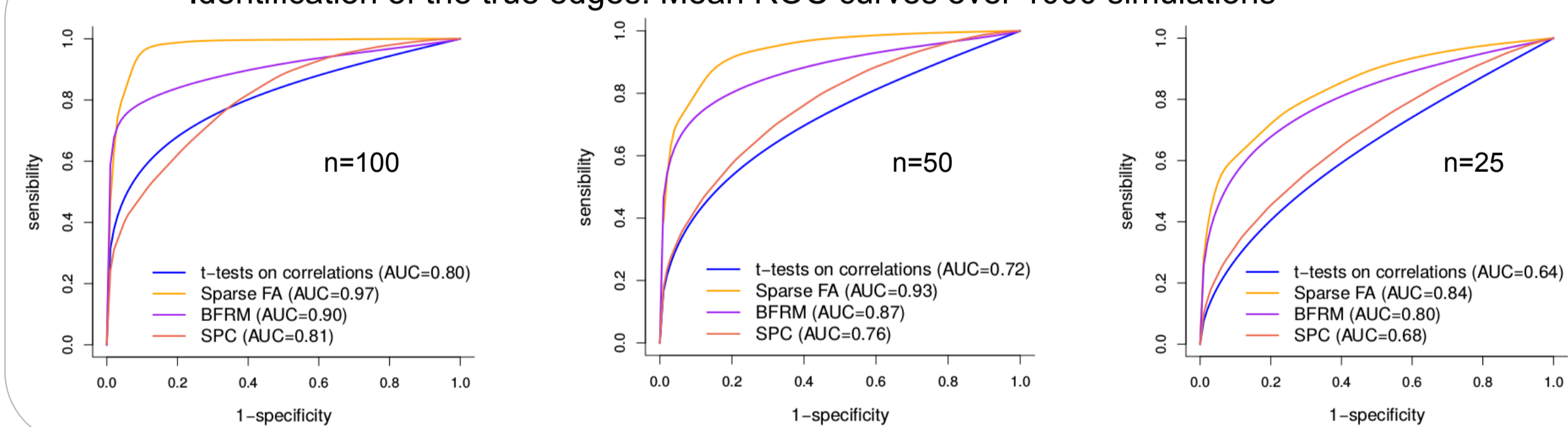
- **SPC:** Sparse Principal Components (Witten et al, *Biostatistics* 2009)
- **BFRM:** Bayesian Factor Regression Model (West, *Bayesian Statistics* 2003)

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



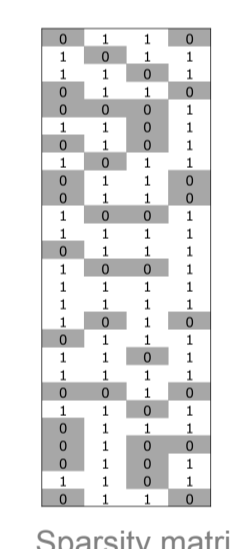
⇒ **Better estimation of the network**

Sparsity using biological knowledge

Inference on the sparsity

Biological information:

- Gene Ontology
- Transcription factors,
- eQTL regulation
- ...



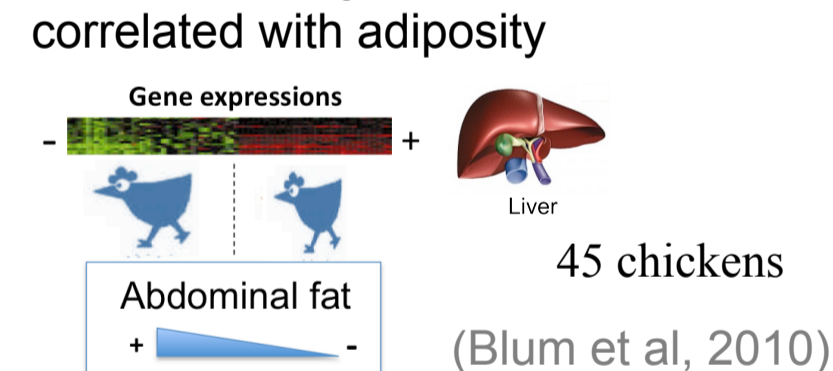
	Term 1	Term 2	Term 3	...	Term X
gene 1	0	1	1	...	0
gene 2	1	0	0	...	0
gene 3	0	0	1	...	1
...
gene X	1	0	0	...	0

Example of biological constrain matrix

Example of application

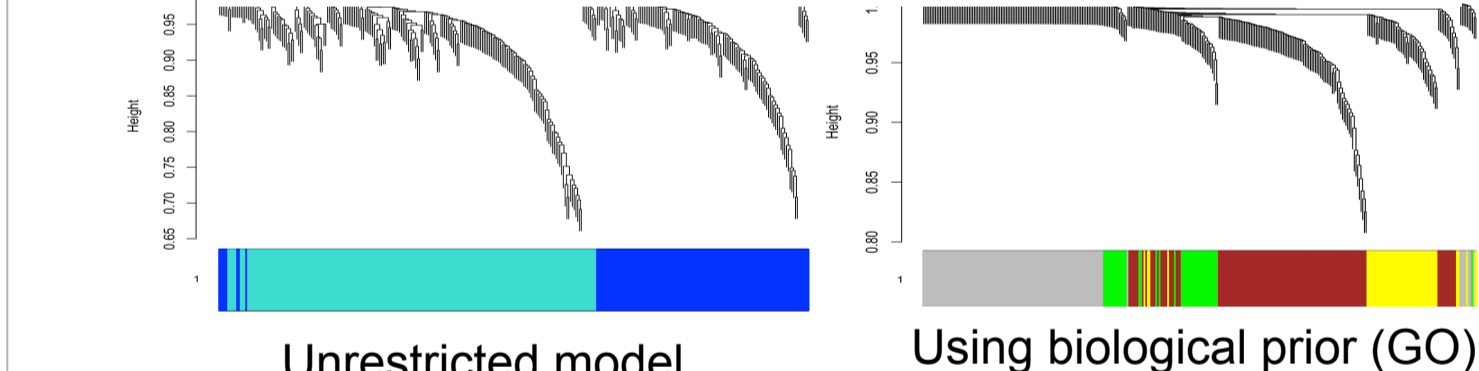
Gene expression dataset:

~ 400 hepatic genes expression correlated with adiposity



Gene modules detection using WGCNA (Horvath et al 2008)

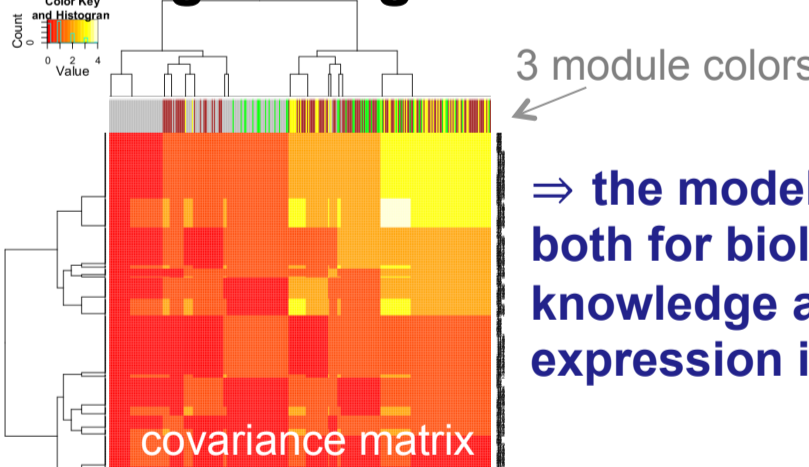
Gene dendrograms (WGCNA output)



⇒ **a more precise structure is revealed**

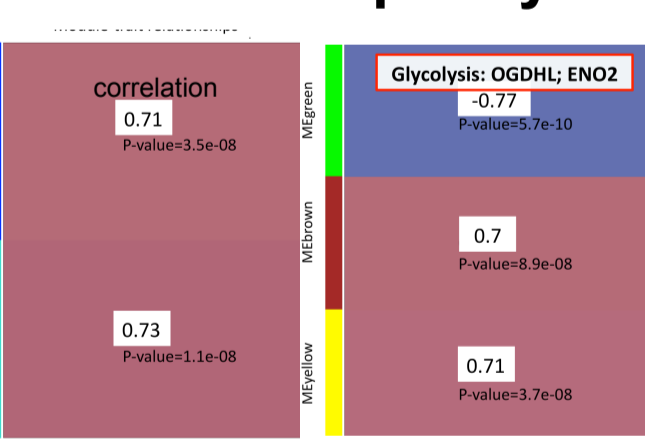
Using Biological information only

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



Module-adiposity relationship

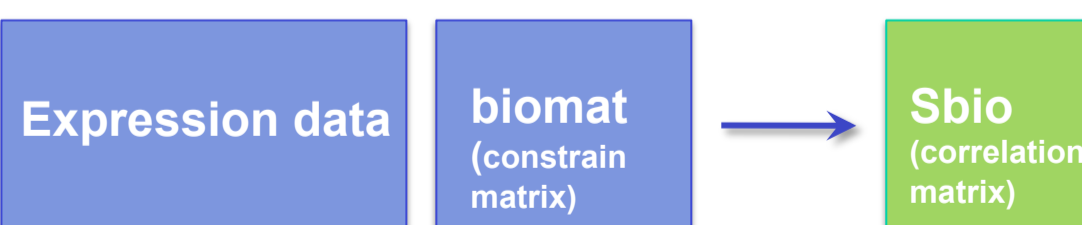
Enhancing hepatic glycolysis reduces obesity (Wu et al., 2005).
 ⇒ **biological process and possible key regulators for adiposity**



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

FANET sparse Factor Analysis for Network modeling R package

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



biomat: constructed by the user or by using the function `Construct.BioMatrix` (uses `biomat` 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