A modified graphical gaussian model approach for genetic regulatory networks

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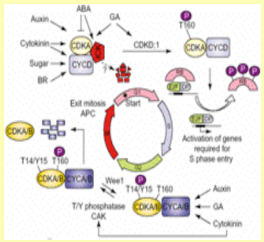
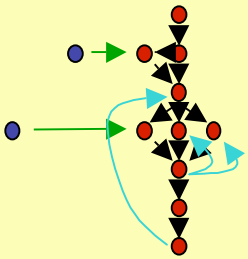
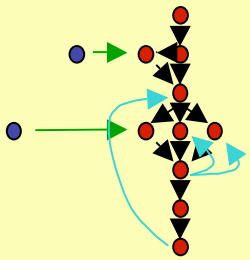
Introduction

biological scenarios





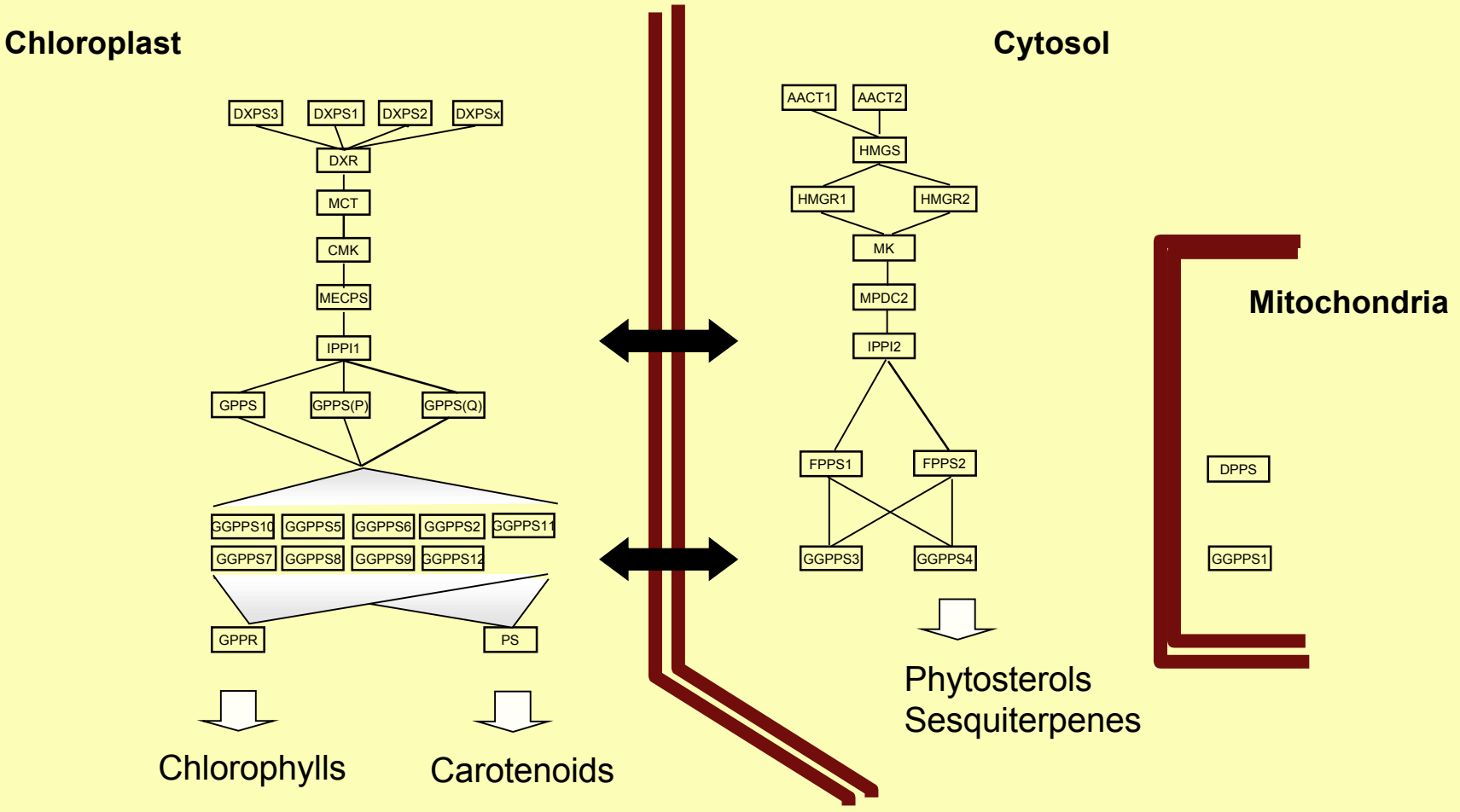
modified GGMs



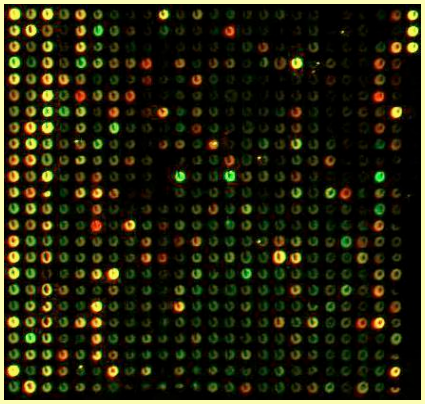
graphical gaussian models
(GGMs)

Biological scenarios

Isoprenoid pathways



Genetic regulation

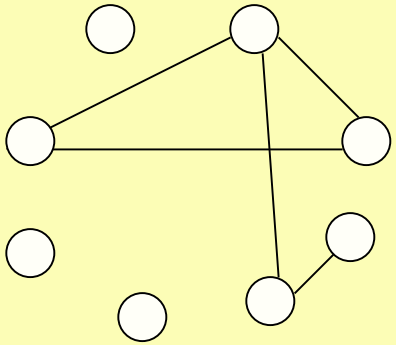


118 observations

39 genes

… signals …

graphical model to estimate conditional dependence between genes



Graphical Gaussian Models

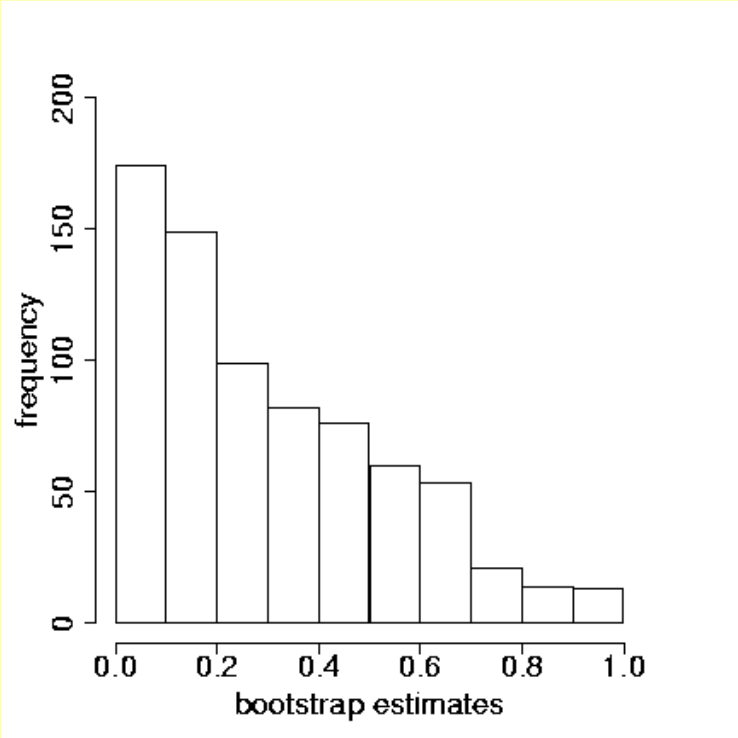
- undirected
- random variables follow a multivariate normal distribution
- log likelihood:

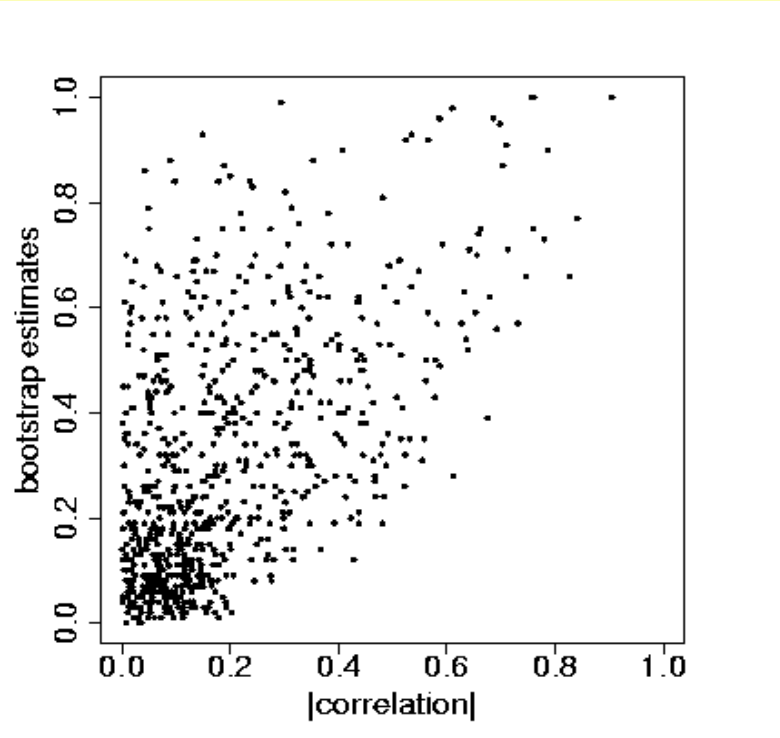
$$l(\mu, \Omega) = -\frac{N}{2}(q \ln(2\pi) + \ln|\Omega| + tr(\Omega S) + (\bar{y} - \mu)' \Omega (\bar{y} - \mu))$$

for a sample of N observations $y^1,\ldots,y^N$ with
sample mean $\bar{y}$, sample covariance matrix S
and precision matrix $\Omega = \Sigma^{-1}$

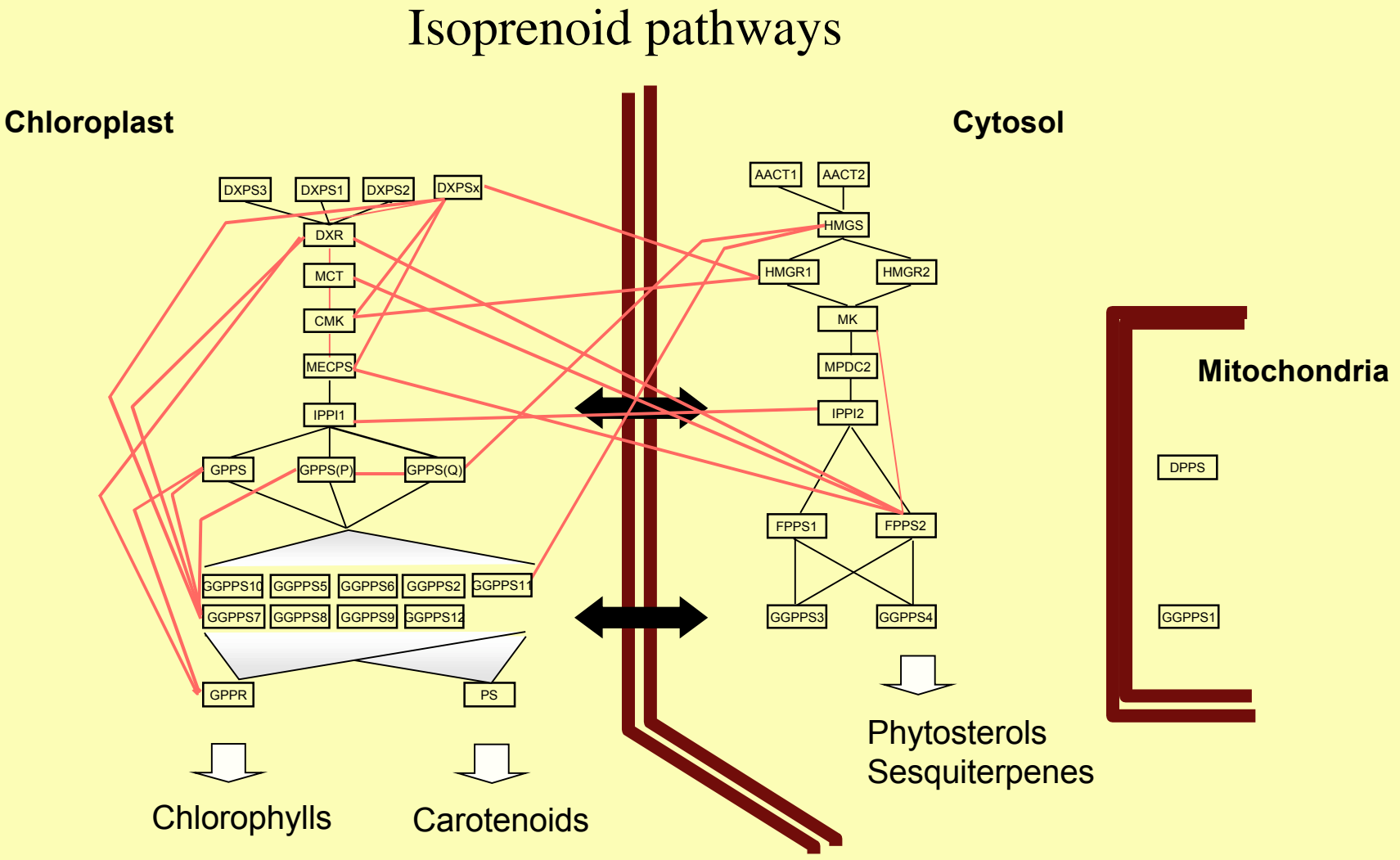
- partial correlation coefficient $\rho_{ijlrest}$ for gene pair ij

Bootstrapping and pairwise correlation





Application to isoprenoid pathways



Problems

- matrix inversion rank-sensitive
- genes ↑ ⇒ exponentially increasing number of models

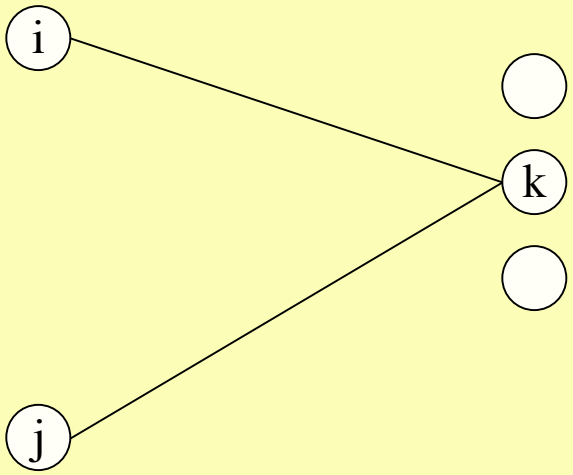
  ⇒ difficult to interpret
- how to interpret high partial correlation accompanied with low pairwise correlation
- efficient procedure for attaching new genes needed

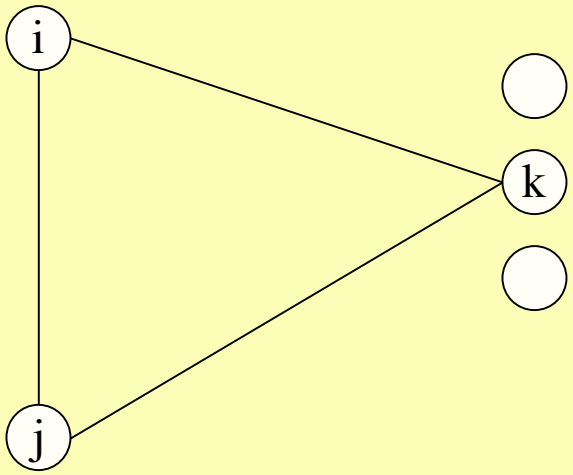
Outline for modified GGM approach

For each pair of genes i,j:

- take pairwise correlation into account
- fit GGMs with gene triples i,j,k for all remaining genes k to study the partial correlation
- combine GGMs and pairwise correlation for inference on edge ij
- 3 methods that differ with respect to statistical framework and computational costs

Frequentist approach

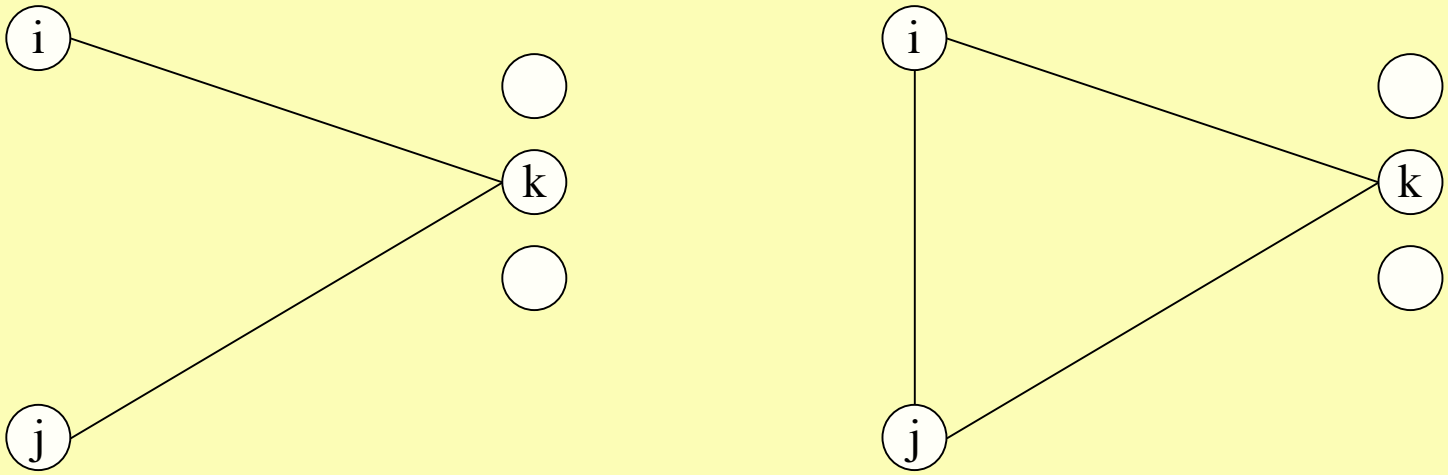




Focus on genepair ij

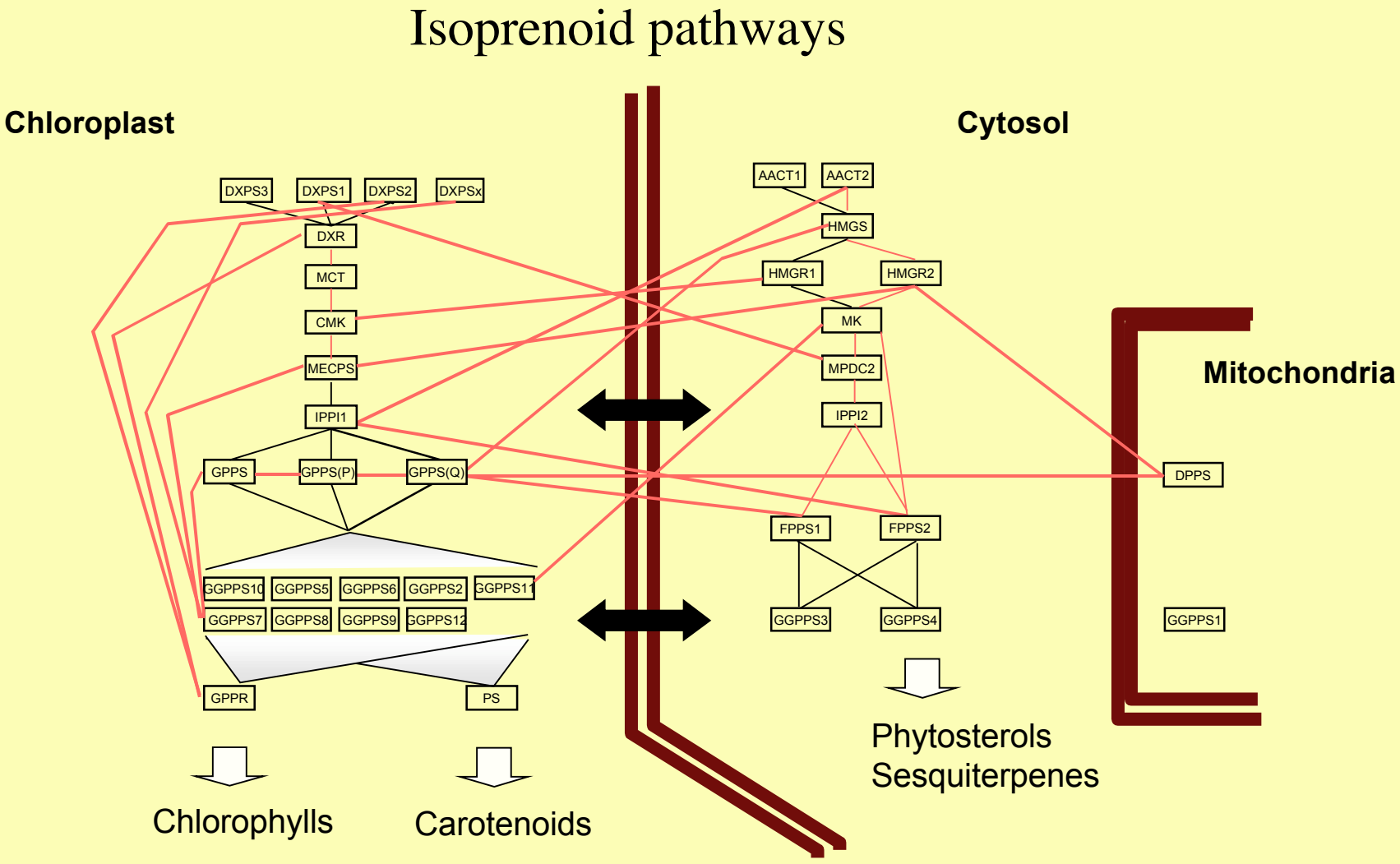
- $p_{ij|k}$ is p-value from deviance test $\delta_{ij|k} \neq 0$ versus $\delta_{ij|k} = 0$

Frequentist approach (cont'd)

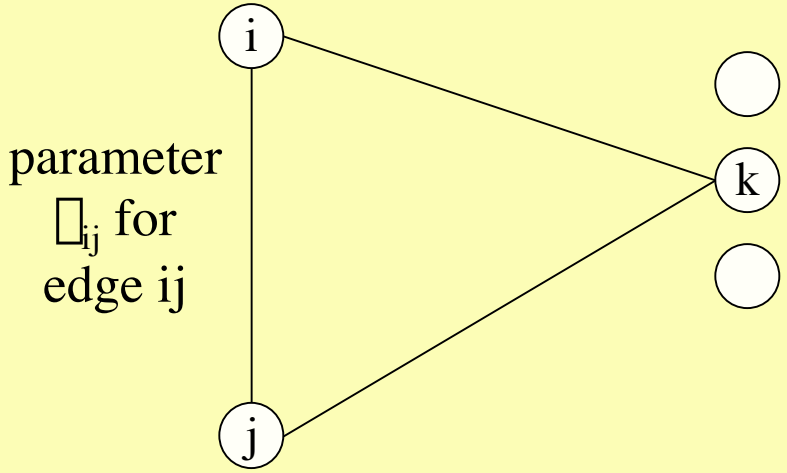


1) Form $p_{ij,max}$ = max ($p_{ij|k}$ for all genes $k \neq i,j$)
2) Adjust $p_{ij,max}$ according to Bonferroni-Holm or FDR
3) If the adjusted value $p_{ij,max} < 0.05$, draw edge between i and j

Application to isoprenoid pathway



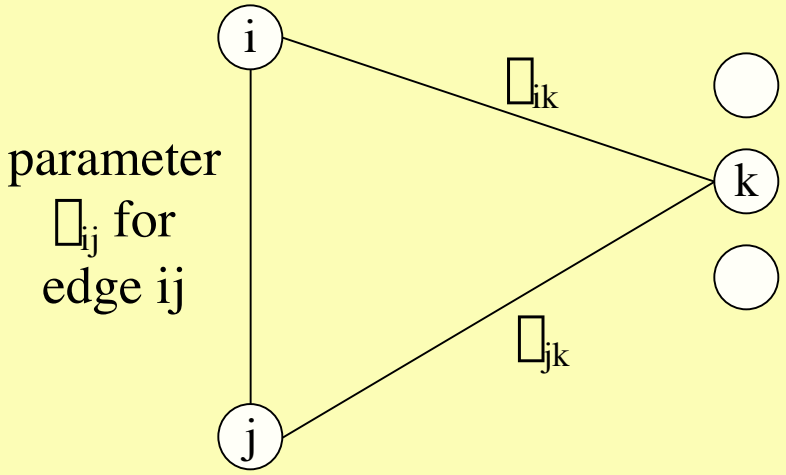
Likelihood approach with parameters θ



Estimate $\theta = \{\theta_{ij}$ for all i,j$\}$ in a maximum likelihood approach

$$L(\theta) = \sum_{g \in G} L(\theta \mid g)P(g)$$

EM algorithm



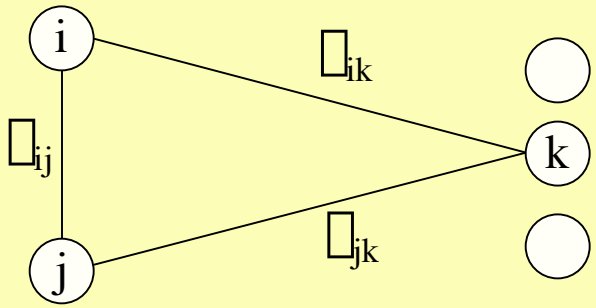
$$Q(\theta \mid \theta^t) = \sum_{g \in G} L(\theta \mid g) P(g \mid \theta^t, y) \quad \text{to be maximized}$$

$$\downarrow$$

$$\theta_{ij}^{t+1} = \prod_{k \neq i,j} \frac{\sum_{g \mid g_{ij}=1} \theta_{ik}^{t\, g_{ik}} (1-\theta_{ik}^t)^{1-g_{ik}} \theta_{jk}^{t\, g_{jk}} (1-\theta_{jk}^t)^{1-g_{jk}} \cdot L(\theta_g, \theta_g)}{\sum_{g} \theta_{ik}^{t\, g_{ik}} (1-\theta_{ik}^t)^{1-g_{ik}} \theta_{jk}^{t\, g_{jk}} (1-\theta_{jk}^t)^{1-g_{jk}} \cdot L(\theta_g, \theta_g)}$$

Simplification

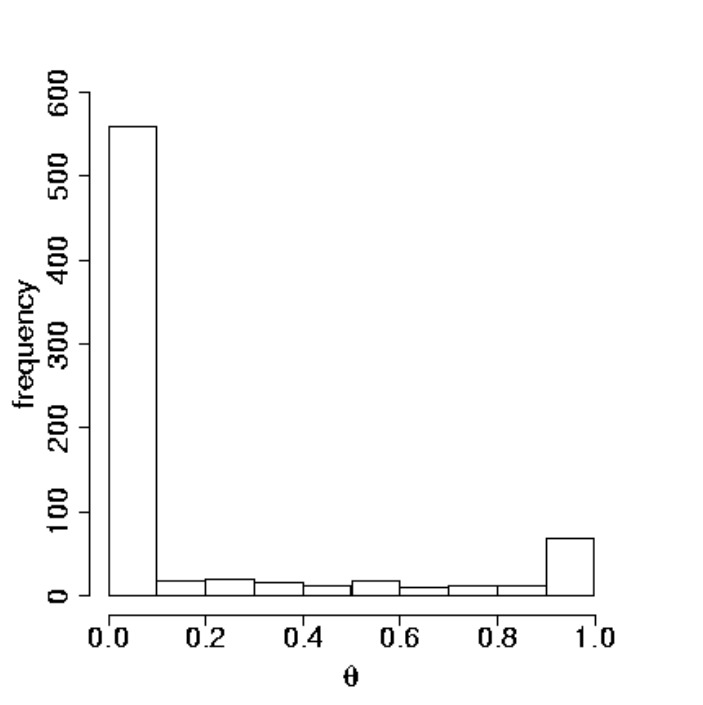
$$\theta_{ij}^{t+1} = \sum_{k \neq i,j} \frac{\sum_{g \mid g_{ij}=1} \theta_{ik}^{t\,g_{ik}} (1-\theta_{ik}^{t})^{1-g_{ik}} \theta_{jk}^{t\,g_{jk}} (1-\theta_{jk}^{t})^{1-g_{jk}} \cdot L(\beta_g, \sigma_g)}{\sum_{g} \theta_{ik}^{t\,g_{ik}} (1-\theta_{ik}^{t})^{1-g_{ik}} \theta_{jk}^{t\,g_{jk}} (1-\theta_{jk}^{t})^{1-g_{jk}} \cdot L(\beta_g, \sigma_g)}$$

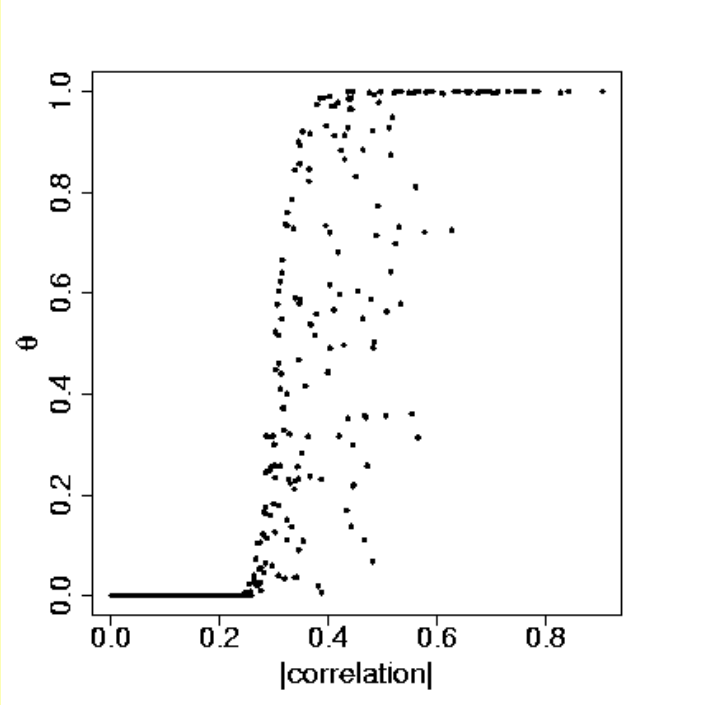


not all GGMs with i,j,k considered

$$\theta_{ij}^{t+1} = \sum_{k \neq i,j} \theta_{ik}^{t}\theta_{jk}^{t} \cdot P(\beta_{ij|k} > 0 \mid y) + (1 - \theta_{ik}^{t}\theta_{jk}^{t}) \cdot P(\beta_{ij} > 0 \mid y)$$

Distribution of θ_{ij}

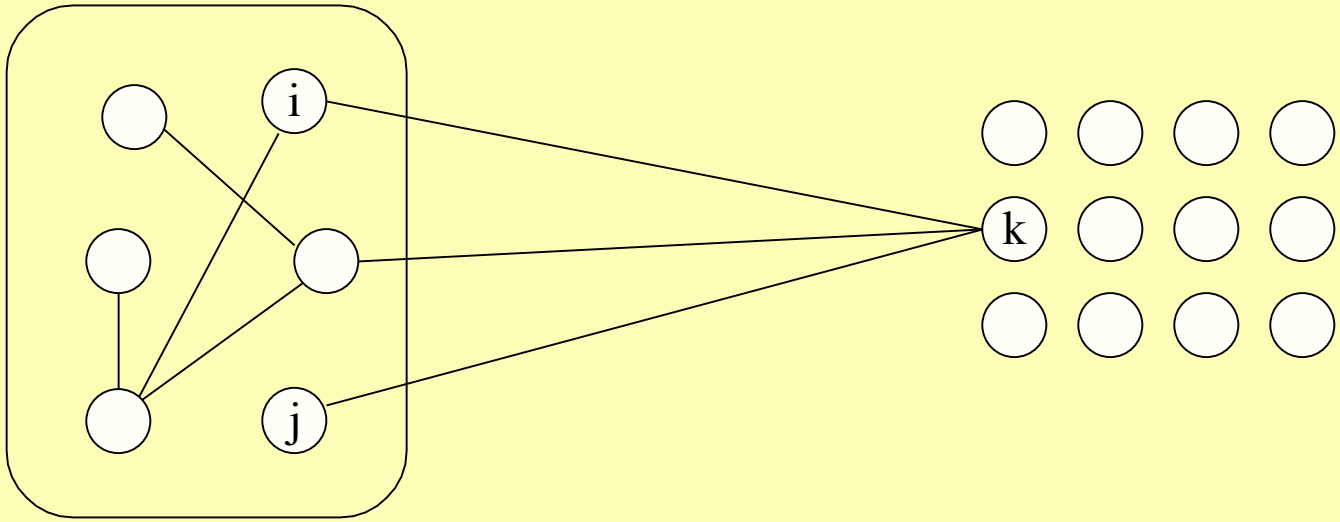




Conclusions

- GGM of gene triples used to look whether correlation between two genes can be “explained” by a third one
- frequentist approach simple, can be applied to many genes
- approach with □-parameters requires iteration, tested for up to 70 genes
- a large set of additional genes can be attached to constructed network

Modeling at two levels



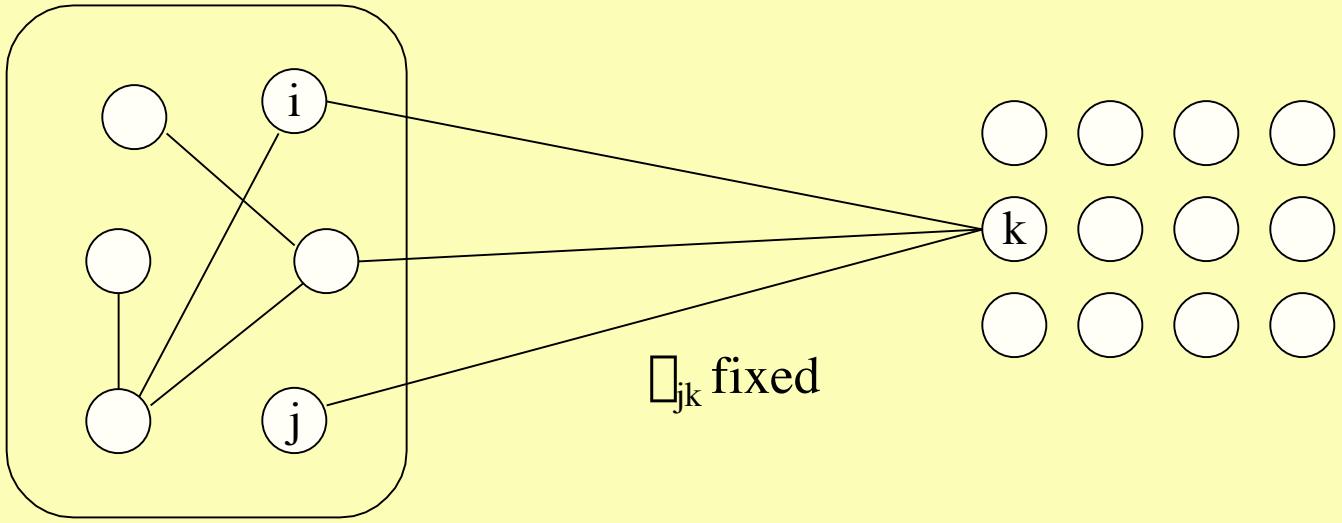
genetic network

- small number <100
- model edges

attach additional genes

- possibly 1000s
- which one “explain” edges?

Attaching additional genes

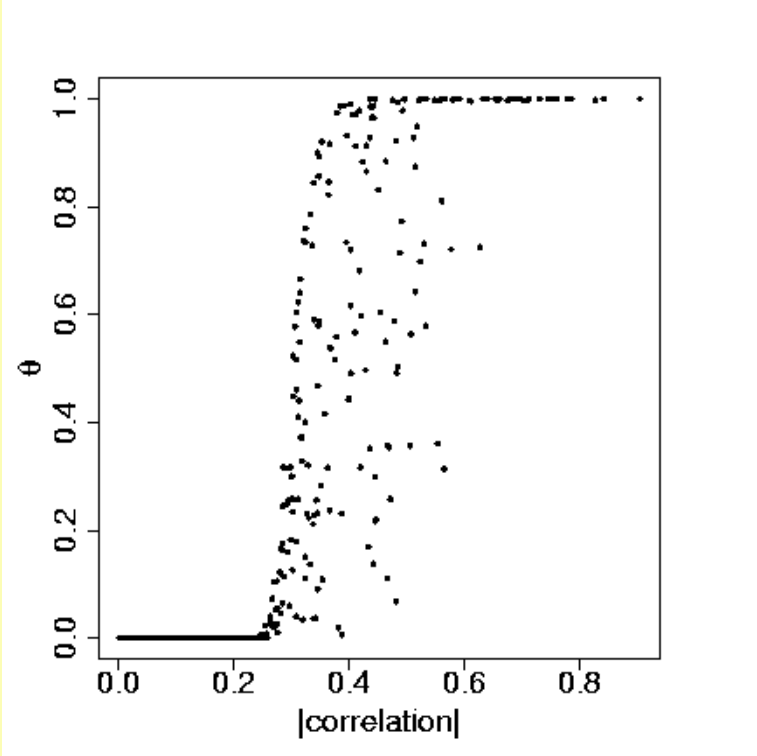


For additional genes k

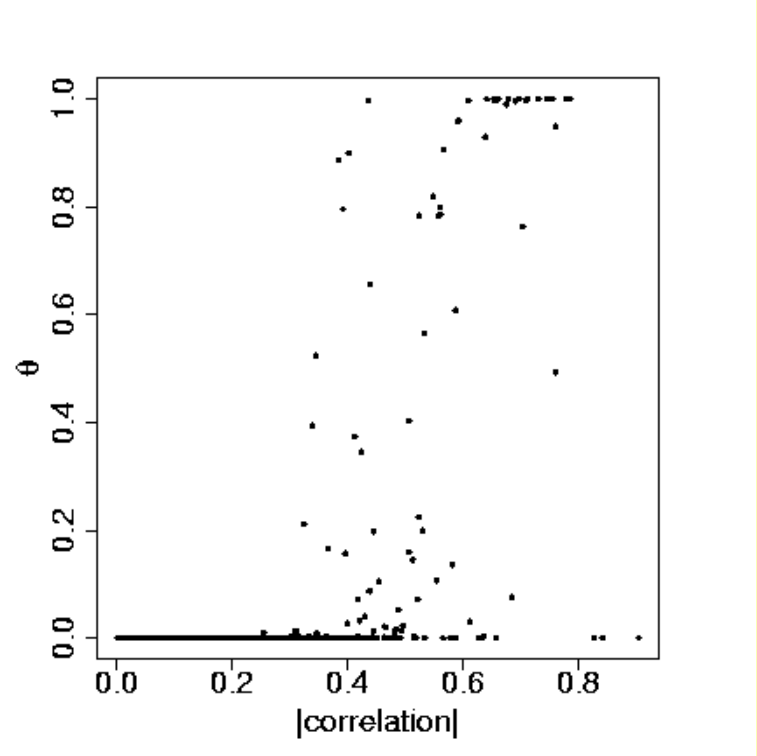
- include in computation of θ_{ij} but keep θ_{ik} and θ_{jk} fixed
- θ_{ij} decreases
- count how often k decreases θ_{ij}, validate

Attaching genes from other pathways

without additional genes



with additional genes

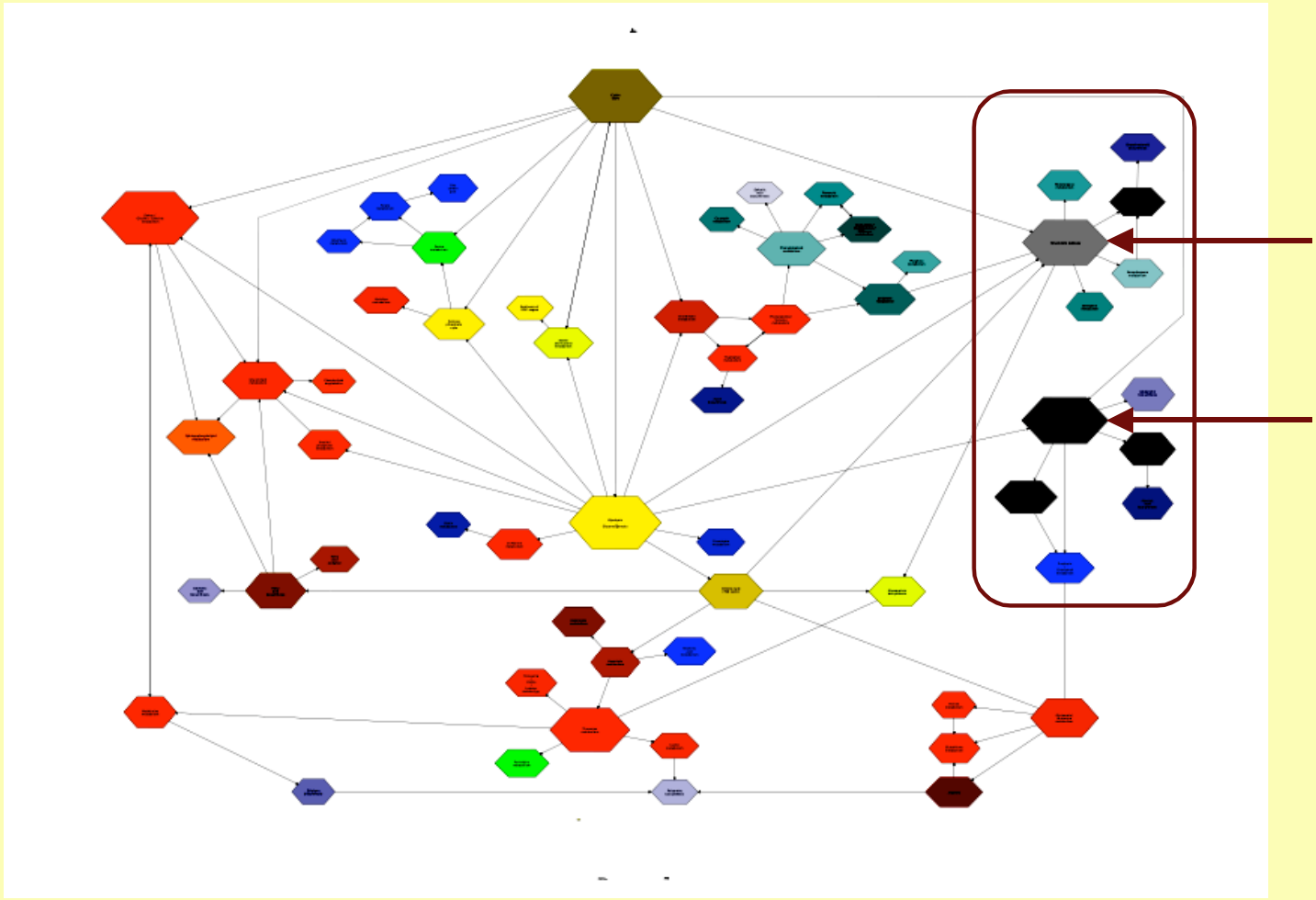


Attaching genes from other pathways

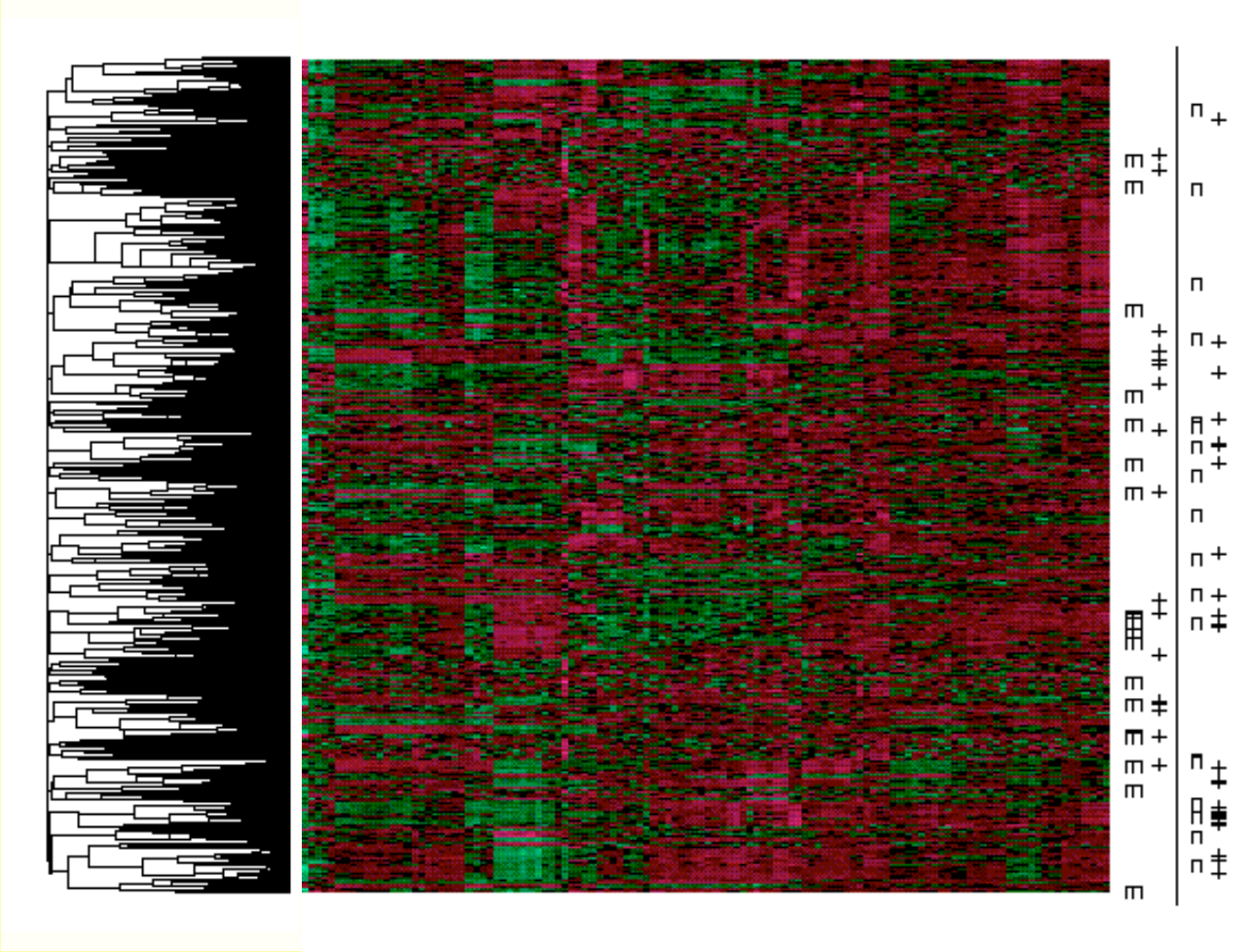
both pathways	chloroplast	cytoplasm
carotenoid*	carotenoid*	tocopherol*
tocopherol*	onecarbonpool	phytosterol*
calvin cycle	chlorophyll*	
chlorophyll*	calvin cycle	
abscisic acid*		
onecarbonpool		
phytosterol*		

downstream pathways marked by *

Attaching genes from other pathways



Hierarchical clustering

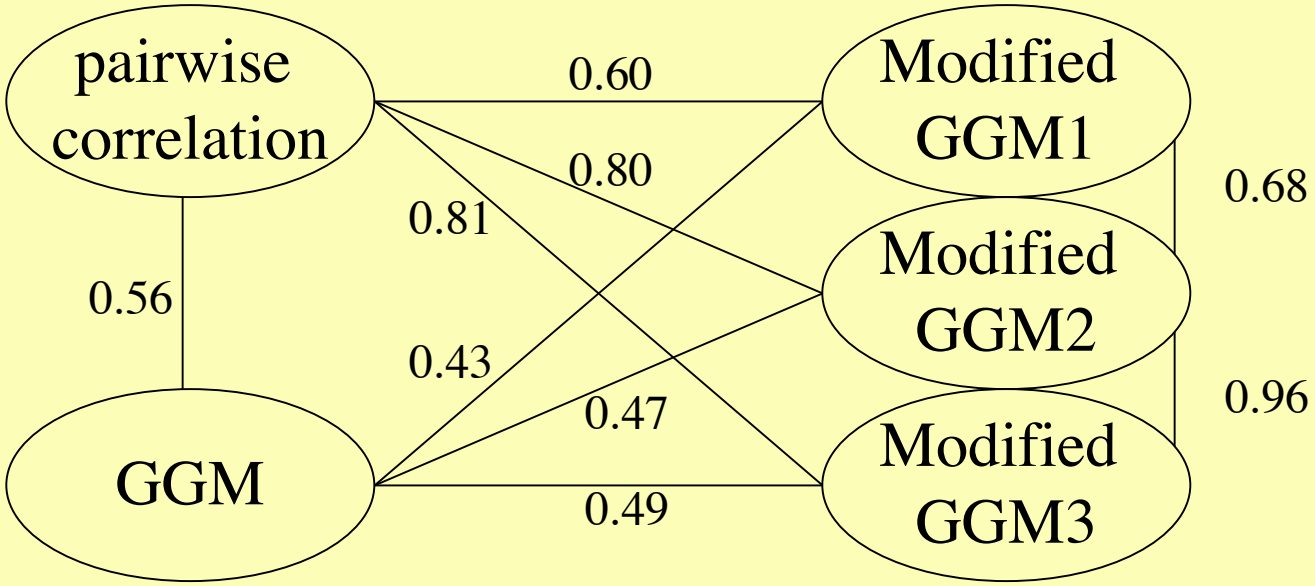


Conclusions

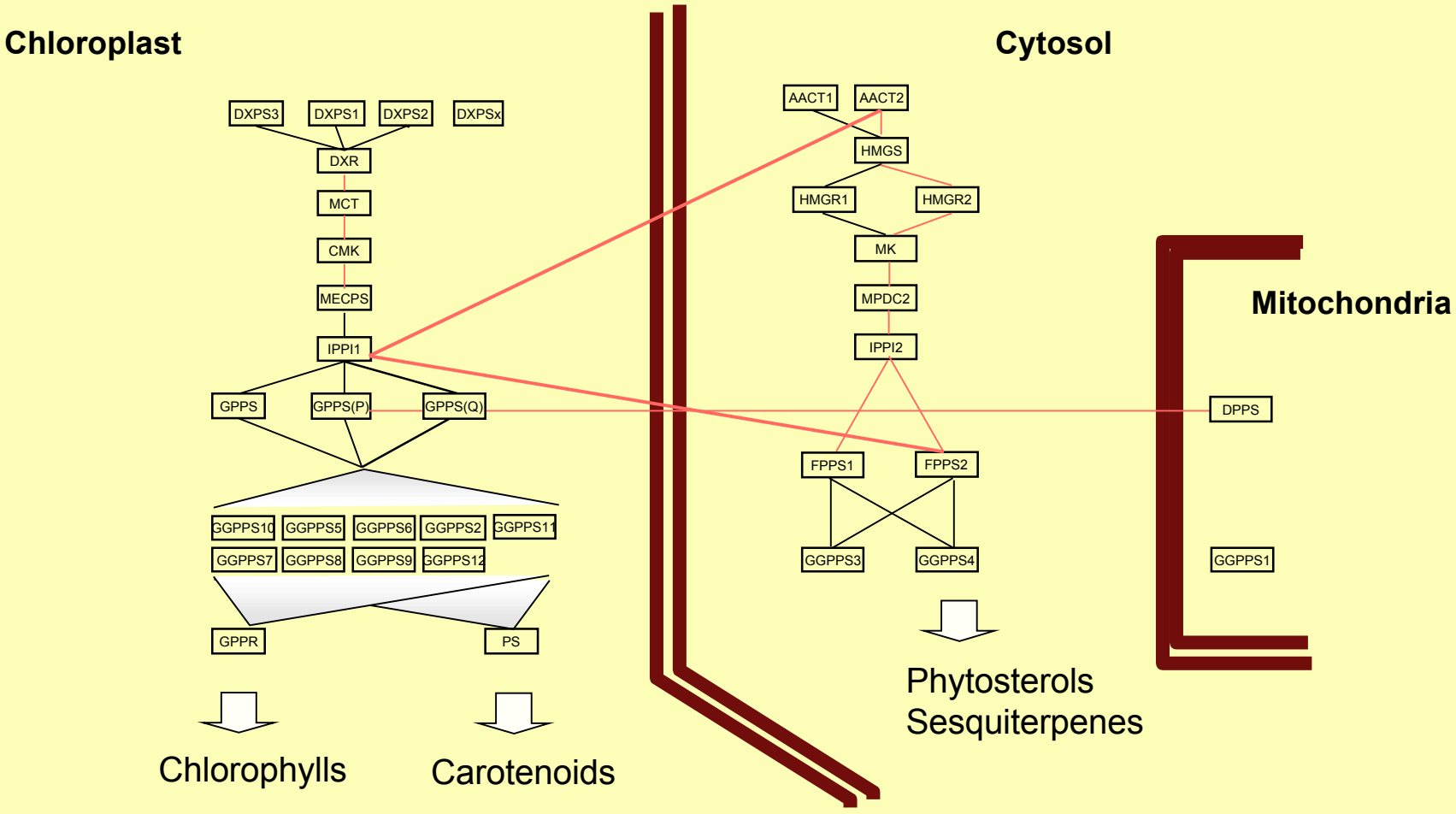
Modified GGMs

- model dependence between genes
- combine GGMs and pairwise correlation for inference on edge ij
- different statistical design, computational cost
- additional genes can be fitted into the model
- similarities in expression patterns between groups of genes can be identified (also verified in yeast data)

Comparison of different methods



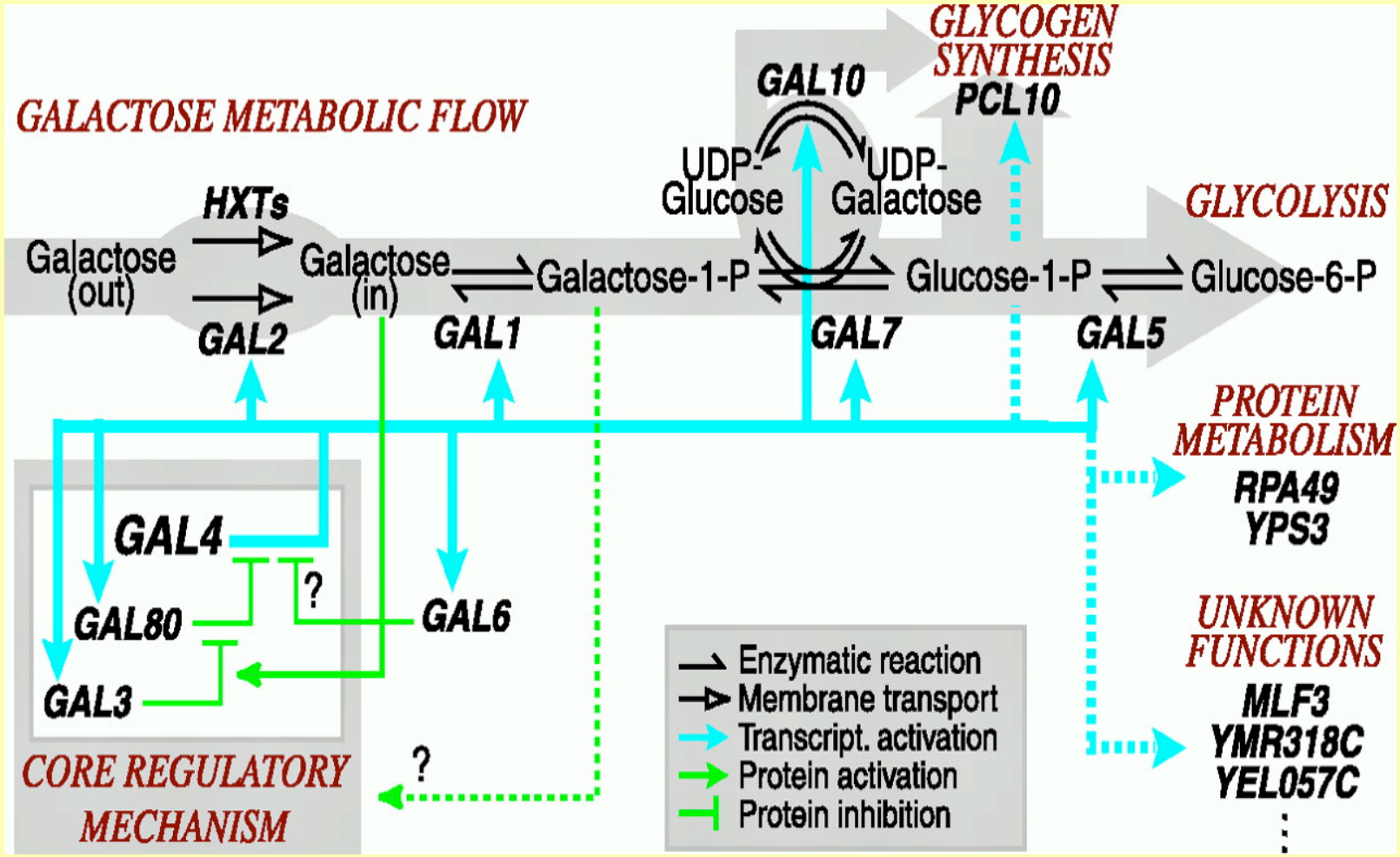
Consistent results



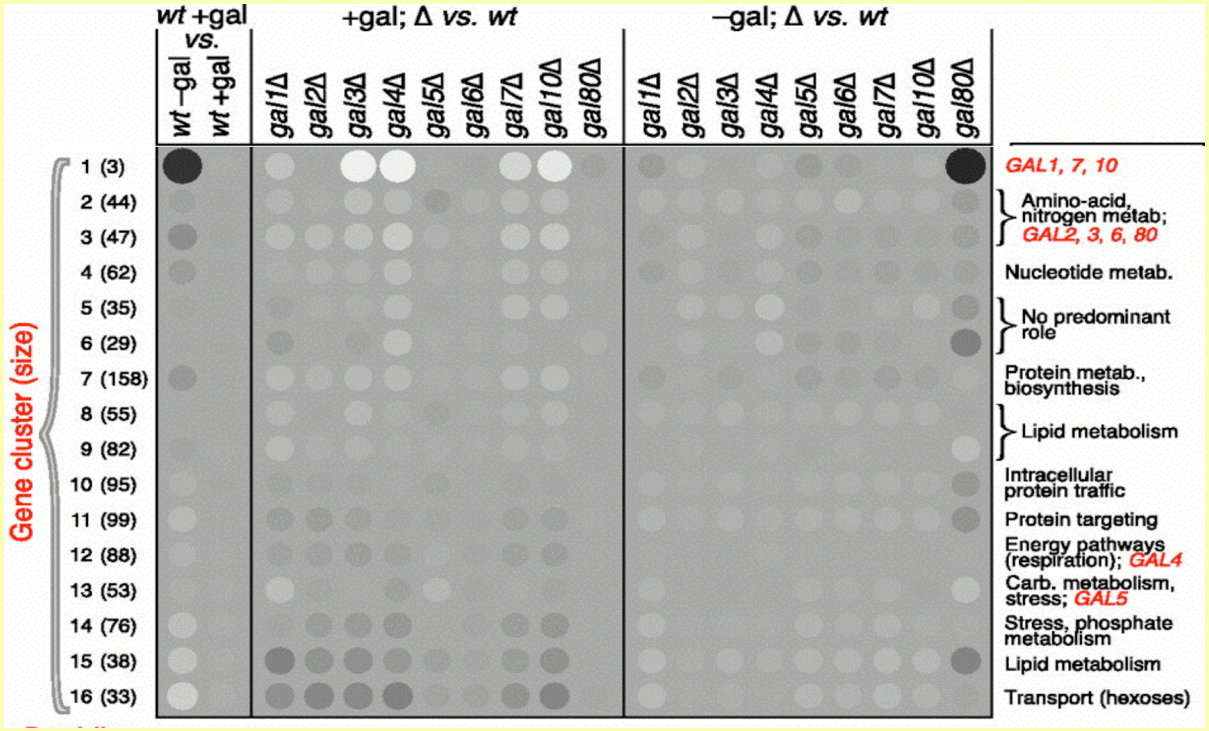
Acknowledgments

- Peter Buehlmann
- Stefan Bleuler, Amela Prelic, Eckhard Zitzler
- Philip Zimmermann, Lars Hennig, Willi Gruissem

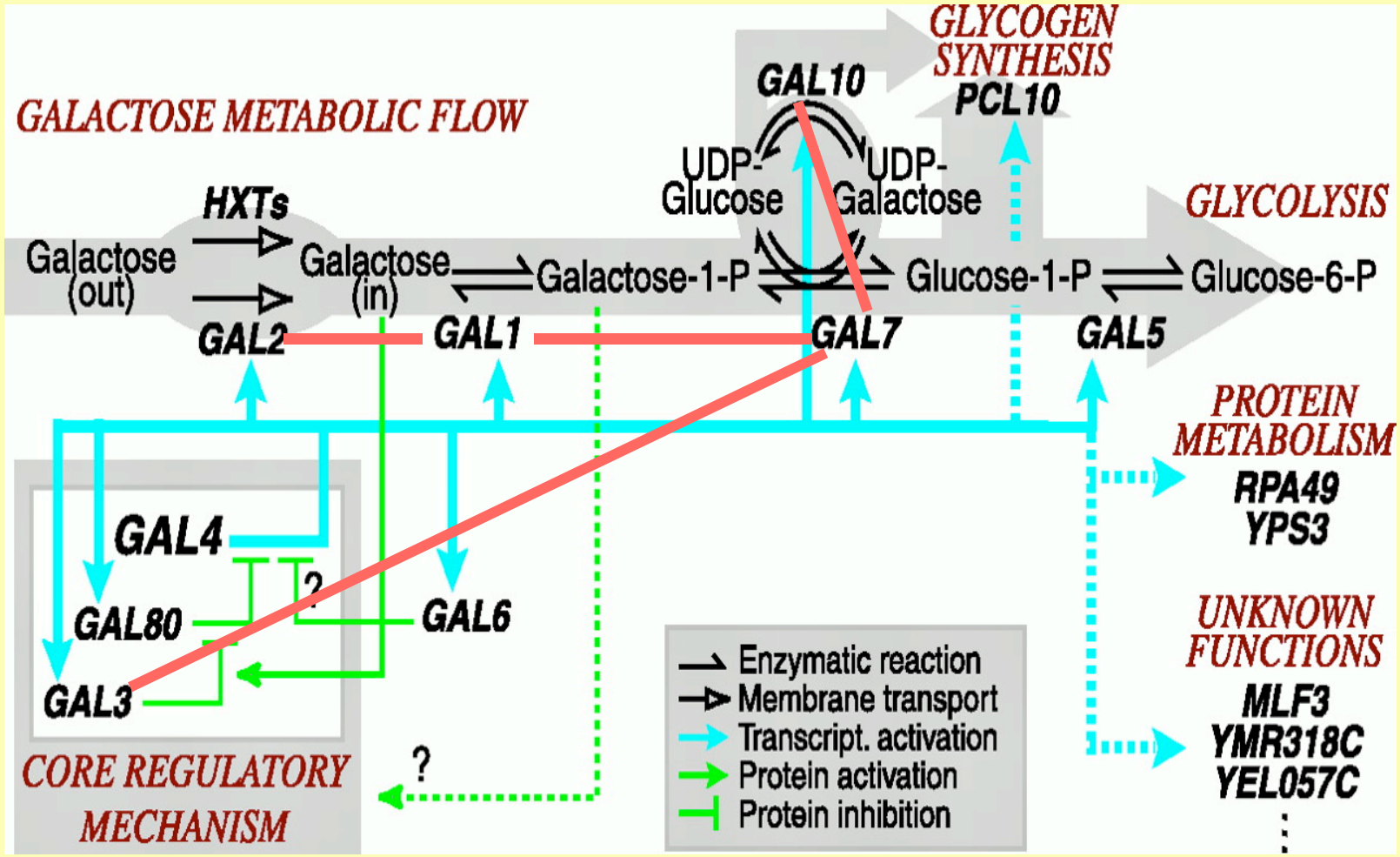
Galactose pathway in yeast



Galactose pathway in yeast



Network for galactose pathway



Network for galactose pathway

Genes that attached to network

GCY1 ←
FAR1
YDR010C
YEL057C ←
YPL066W
YOR121C
MLF3 ←

YLL058W
YJL212C
PCL10 ←
LYS1
YBR139W
YCR059C

$$l(\theta,\Sigma) = -\frac{N}{2}(q\ln(2\pi) + \ln|\Sigma| + tr(\Sigma S) + (\bar{y}-\theta)'\Sigma(\bar{y}-\theta))$$

$$L(\theta) = \sum_{g \in G} L(\theta \mid g)P(g)$$

$$Q(\theta \mid \theta^t) = \sum_{g \in G} L(\theta \mid g)P(g \mid \theta^t, y)$$

$$\theta_{ij}^{t+1} = \sum_{k \neq i,j} \theta_{ik}^t \theta_{jk}^t \cdot P(\theta_{ij|k} > 0 \mid y) + (1-\theta_{ik}^t\theta_{jk}^t) \cdot P(\theta_{ij} > 0 \mid y)$$

$$\theta_{ij}^{t+1} = \sum_{k \neq i,j} \frac{\sum_{g \mid g_{ij}=1} \theta_{ik}^{t\,g_{ik}}(1-\theta_{ik}^t)^{1-g_{ik}}\theta_{jk}^{t\,g_{jk}}(1-\theta_{jk}^t)^{1-g_{jk}} \cdot L(\theta_g, \Sigma_g)}{\sum_g \theta_{ik}^{t\,g_{ik}}(1-\theta_{ik}^t)^{1-g_{ik}}\theta_{jk}^{t\,g_{jk}}(1-\theta_{jk}^t)^{1-g_{jk}} \cdot L(\theta_g, \Sigma_g)}$$