Supervised Gene Network Inference

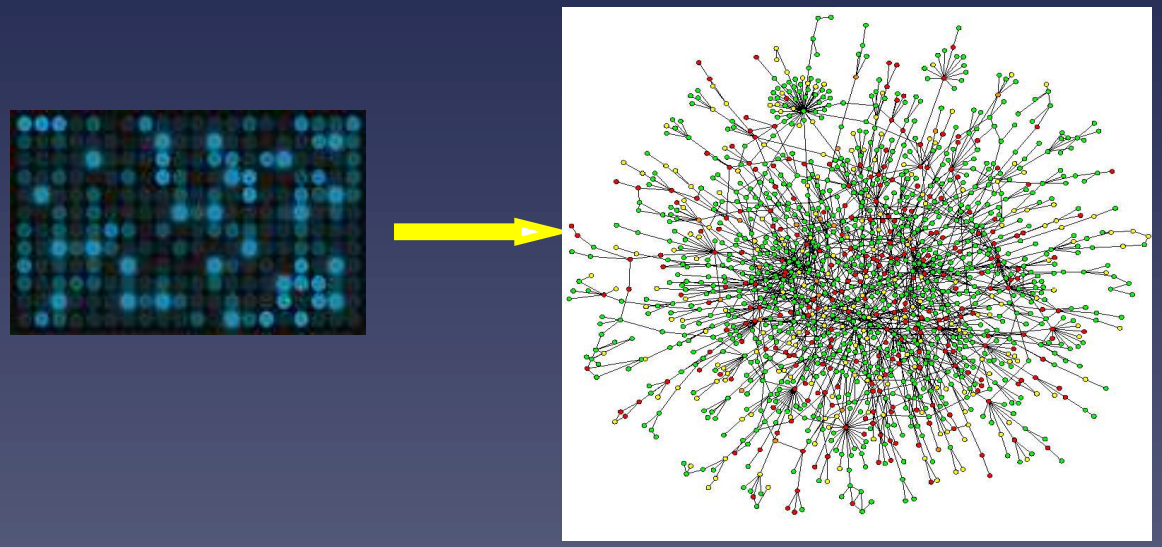
Jean-Philippe Vert
Ecole des Mines de Paris
Computational Biology group
Jean-Philippe.Vert@mines.org

Institute for Genomics and Bioinformatics, UC Irvine, August 18th, 2005

Thanks

- Yoshihiro Yamanishi
- Computational biology at the Ecole des Mines

Motivations: systems biology



- Gene expression
- Sequence
- Protein structure
- Protein localization, etc...

- Regulatory network
- Signaling pathways
- Metabolic pathways
- Interaction network, etc...

Outline

- A direct approach to network inference
- Supervised network inference
- Extraction of pathway activity
- Learning from several heterogeneous data

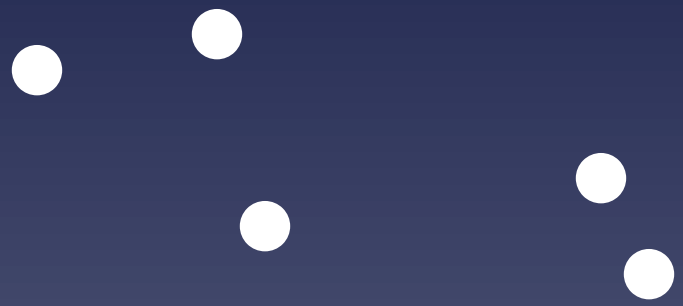
Part 1

A direct approach to network inference

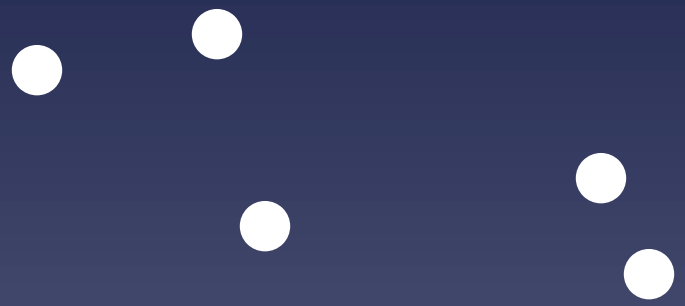
Related approaches

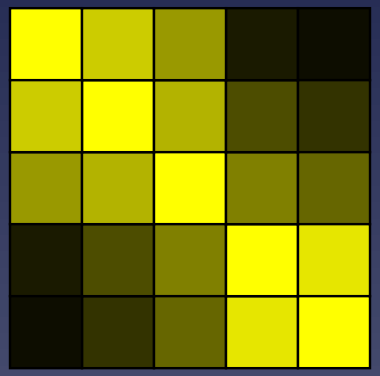
- Bayesian nets for regulatory networks (Friedman et al. 2000)
- Boolean networks (Akutsu, 2000)
- Nearest neighbors method (Marcotte et al, 1999)

Example: nearest neighbors method

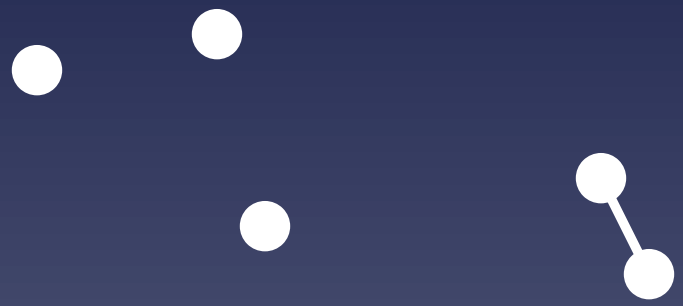


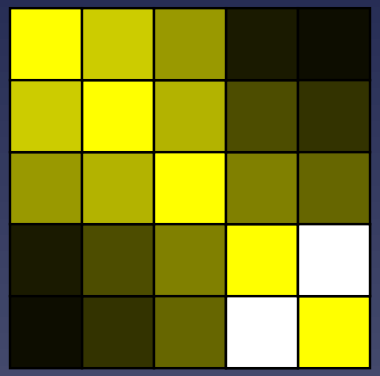
Example: nearest neighbors method



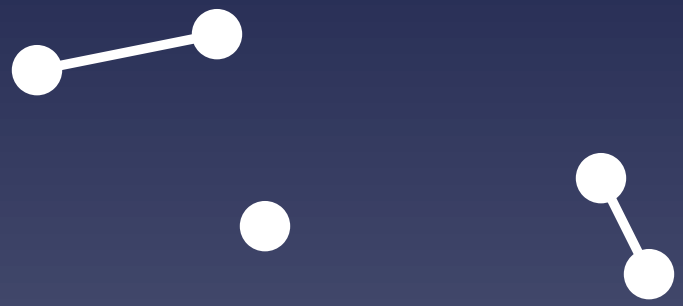


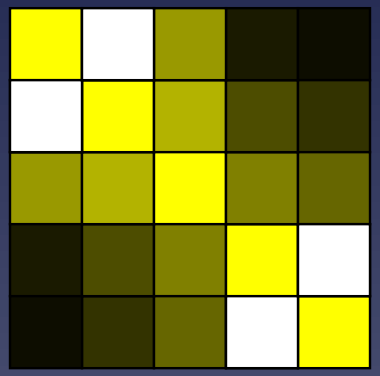
Example: nearest neighbors method



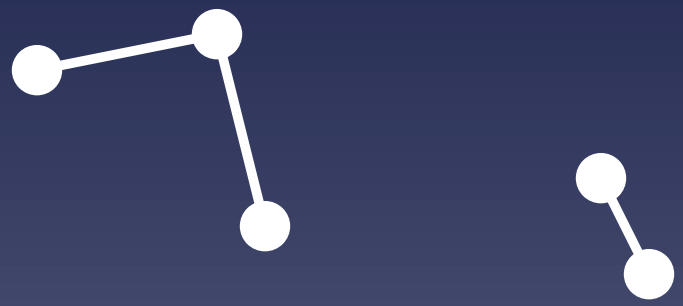


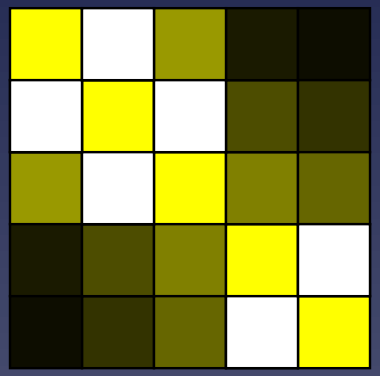
Example: nearest neighbors method



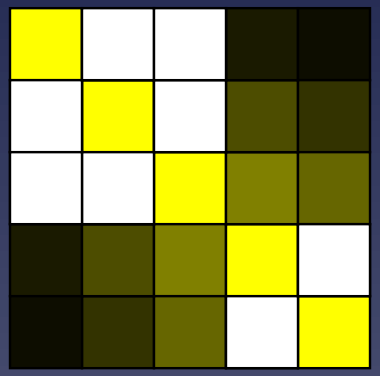


Example: nearest neighbors method

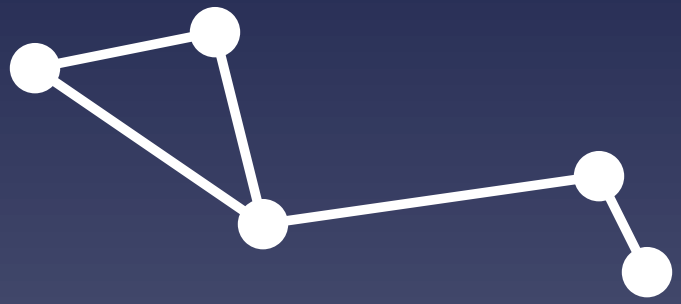


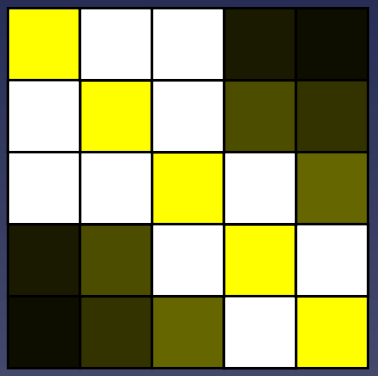


Example: nearest neighbors method

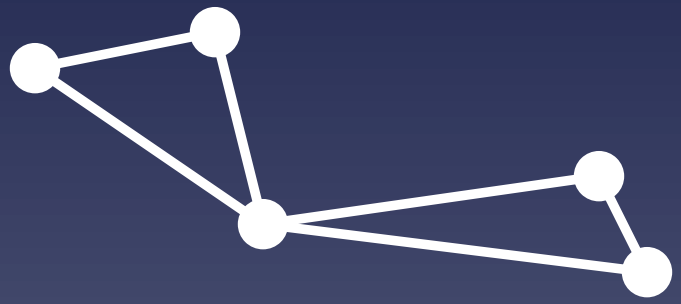


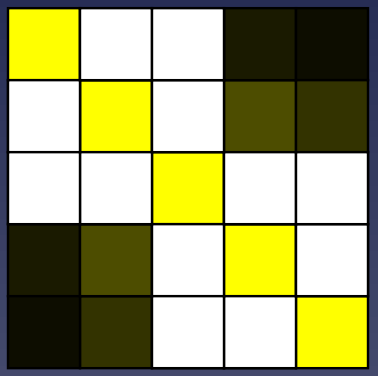
Example: nearest neighbors method



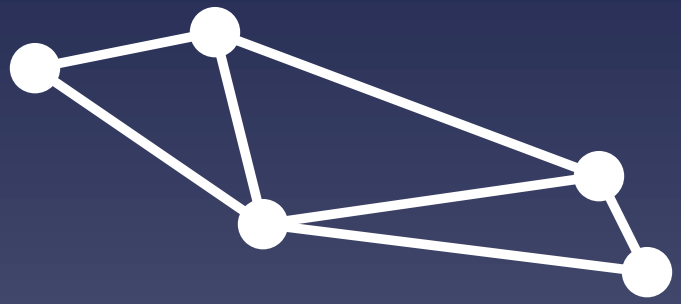


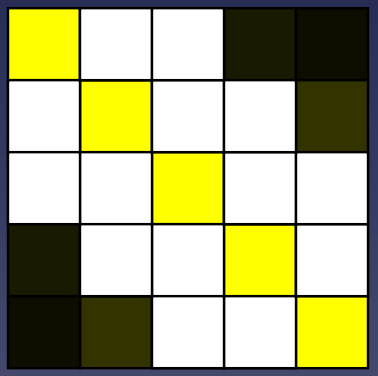
Example: nearest neighbors method



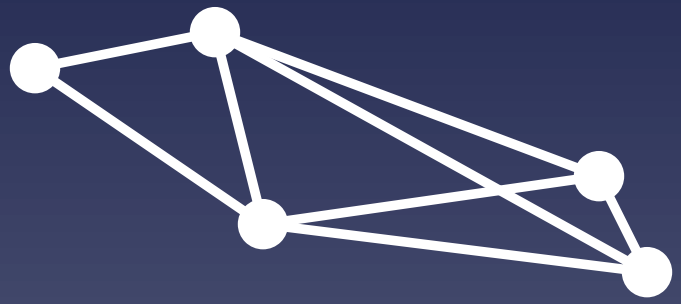


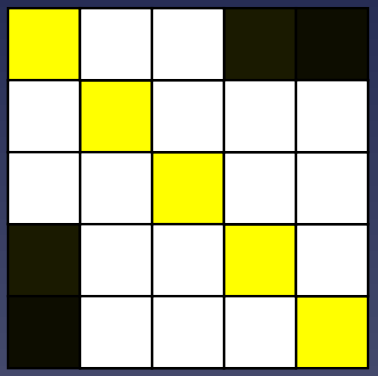
Example: nearest neighbors method



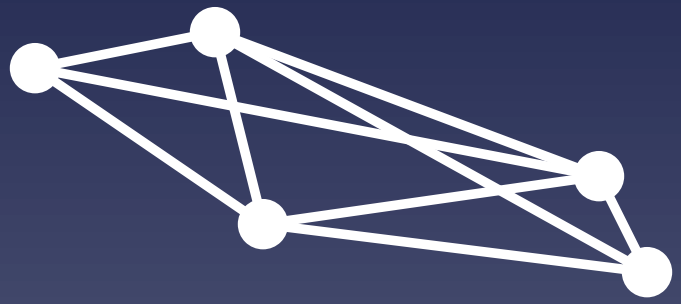


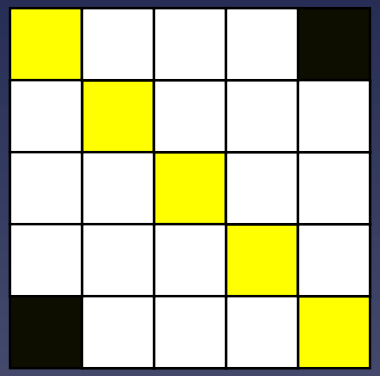
Example: nearest neighbors method



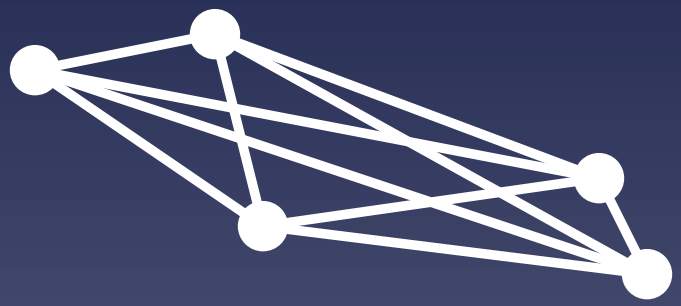


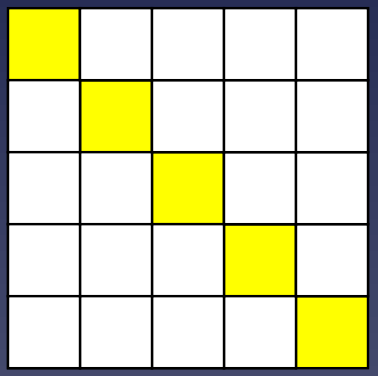
Example: nearest neighbors method



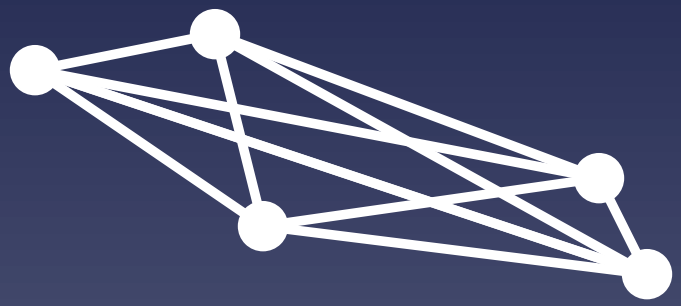


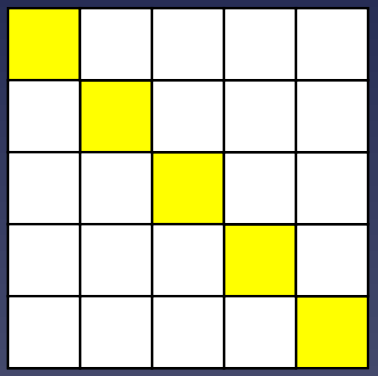
Example: nearest neighbors method



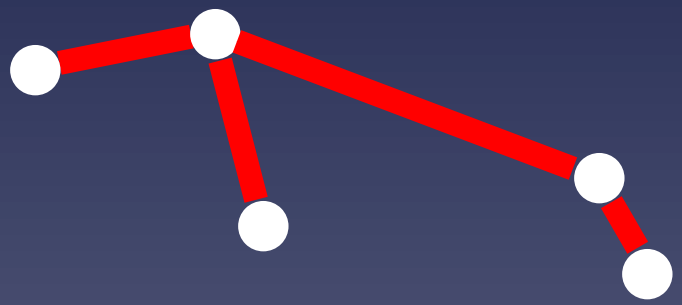


Example: nearest neighbors method

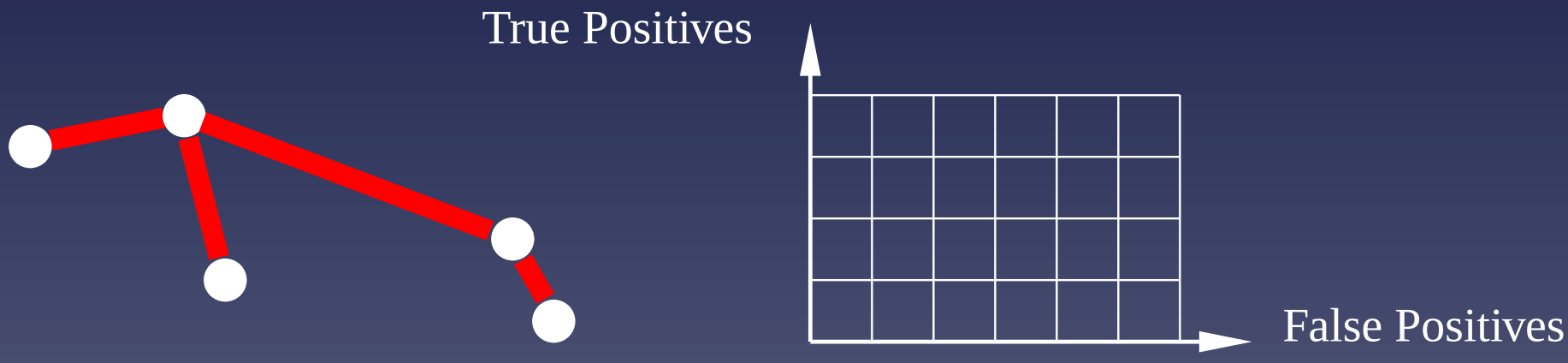




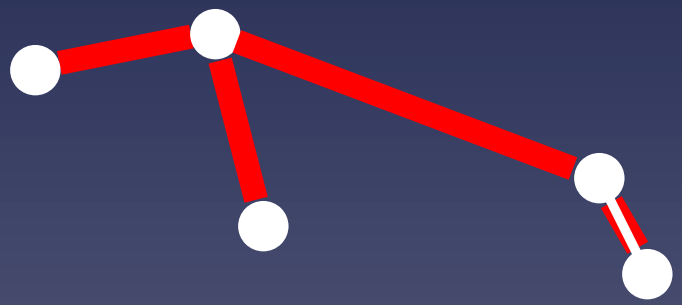
Evaluation of the performance : the ROC curve

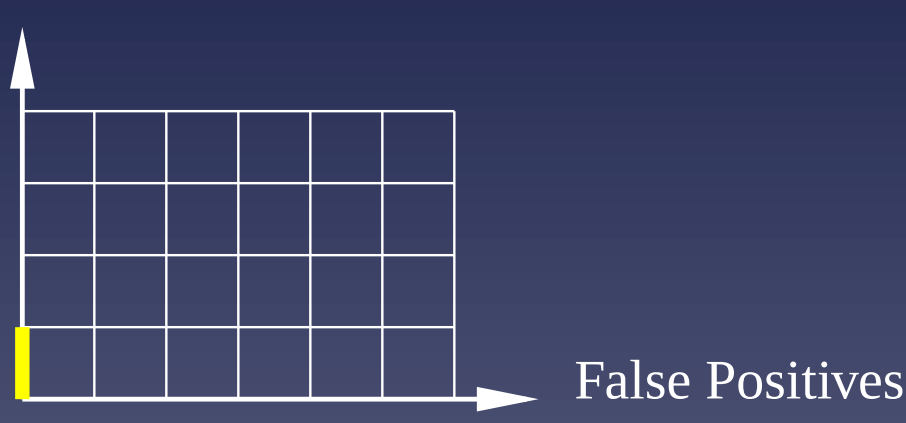


Evaluation of the performance : the ROC curve

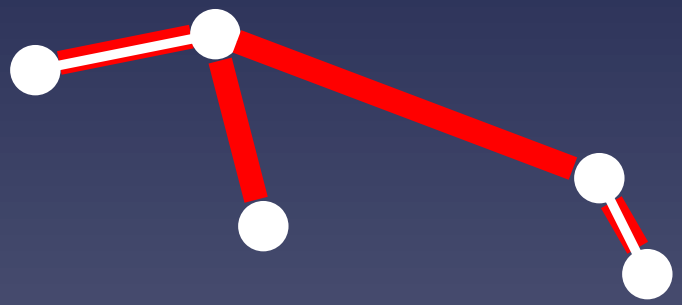


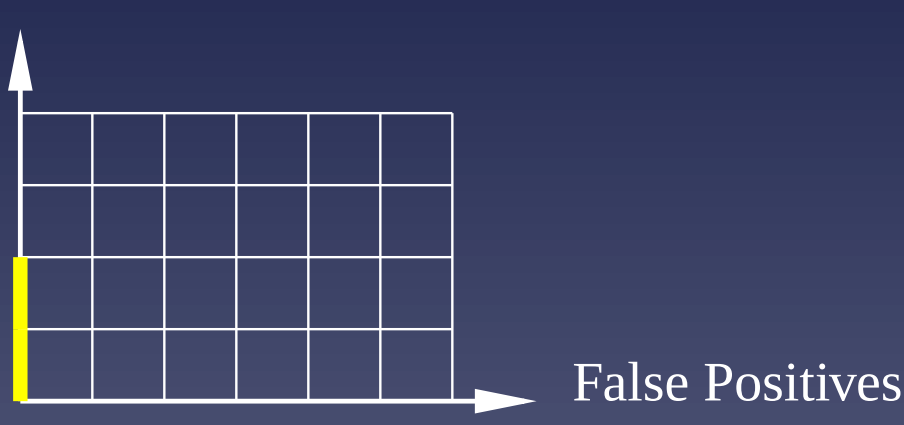
Evaluation of the performance : the ROC curve



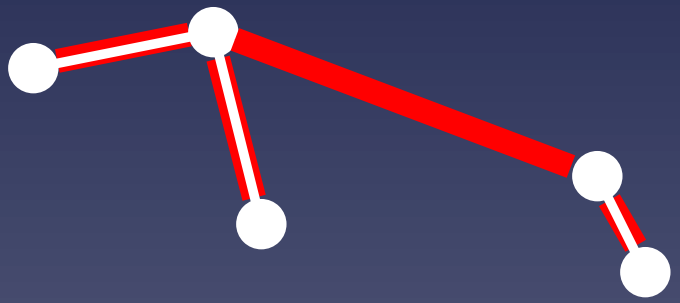


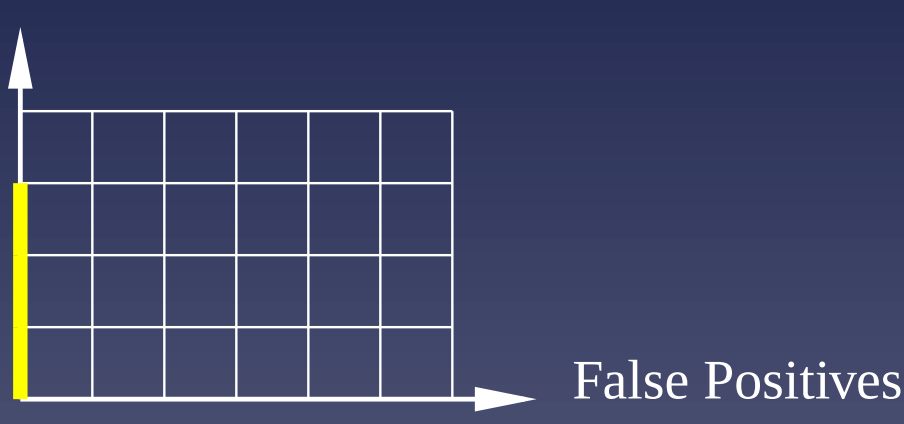
Evaluation of the performance : the ROC curve



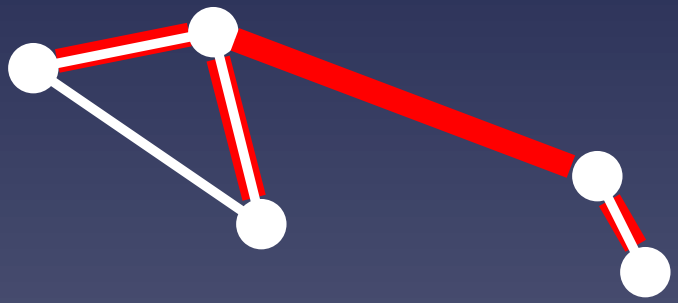


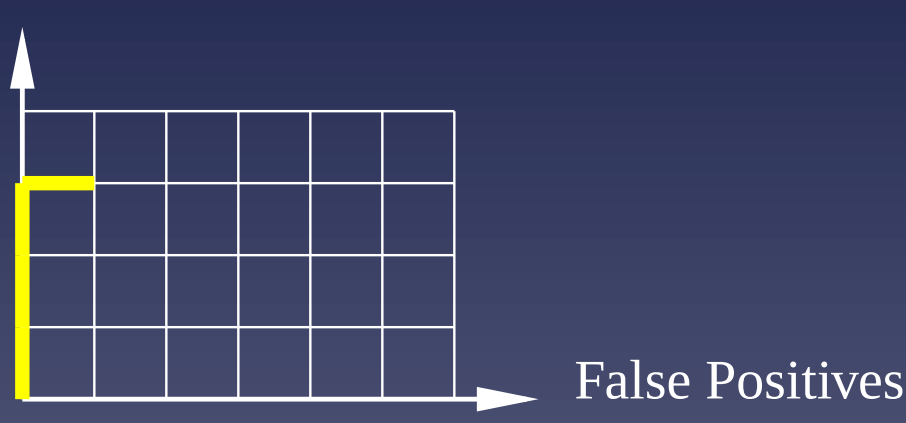
Evaluation of the performance : the ROC curve



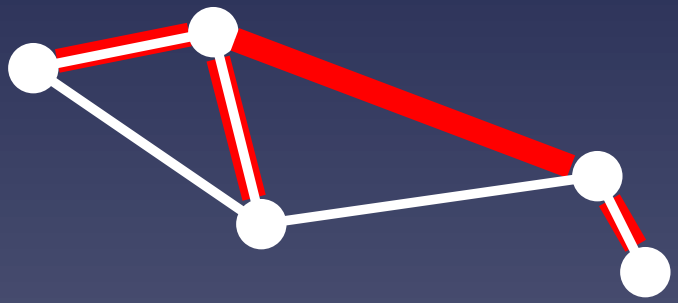


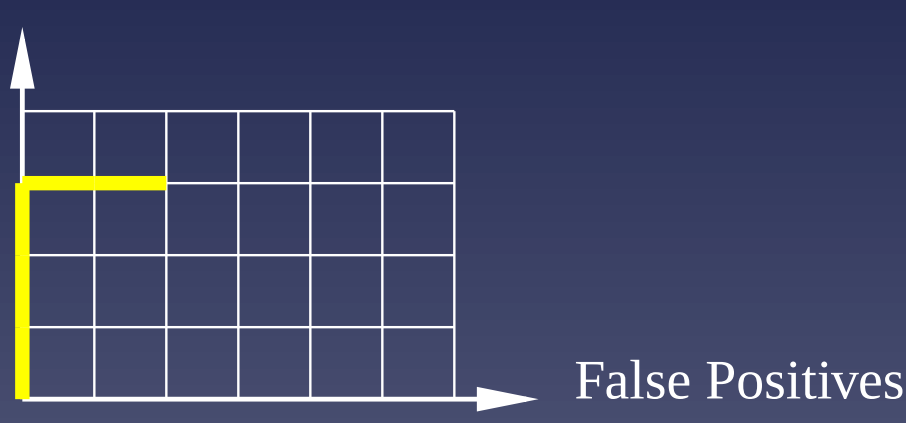
Evaluation of the performance : the ROC curve



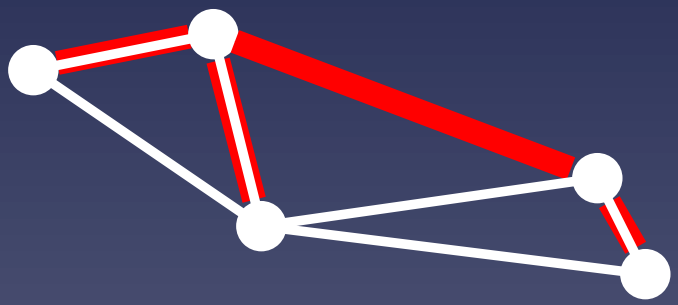


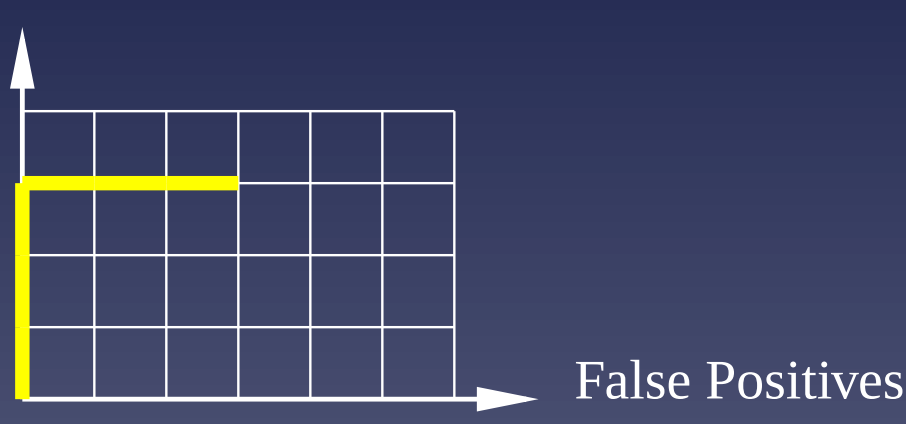
Evaluation of the performance : the ROC curve



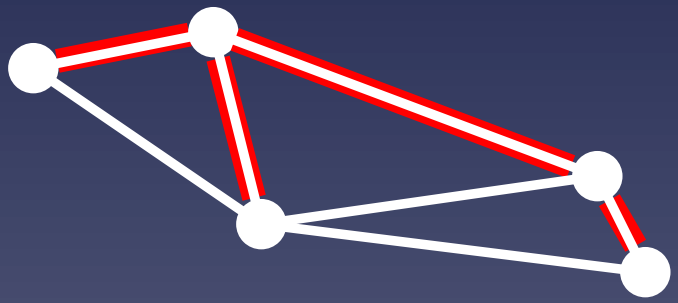


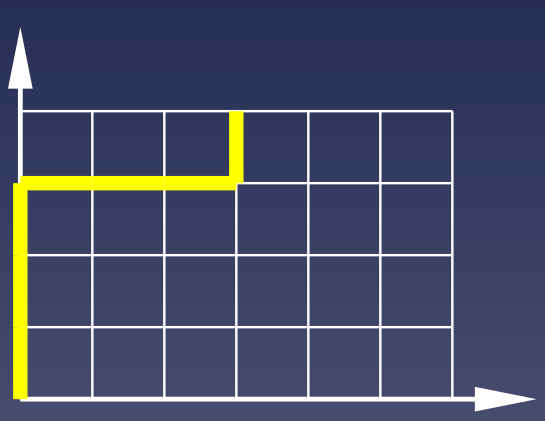
Evaluation of the performance : the ROC curve



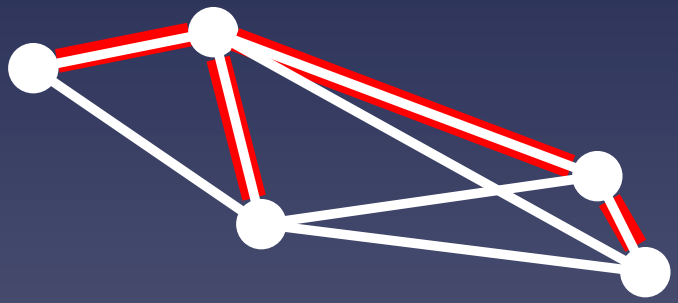


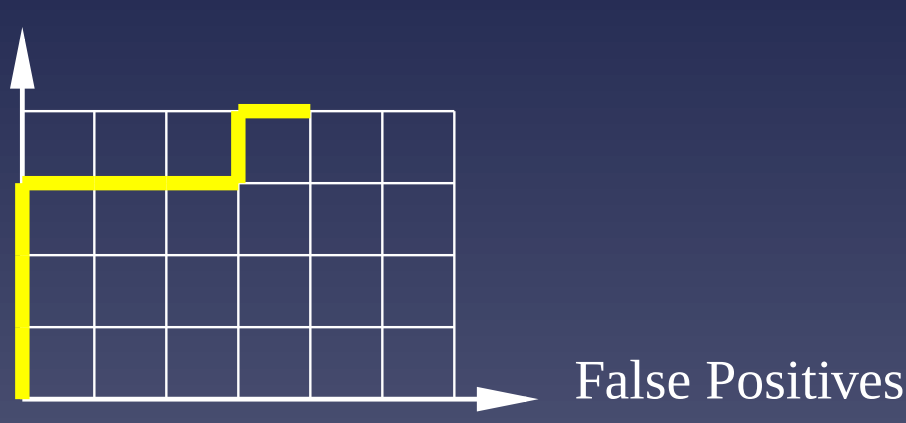
Evaluation of the performance : the ROC curve



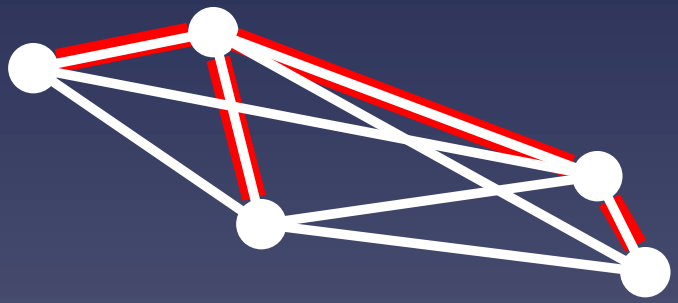


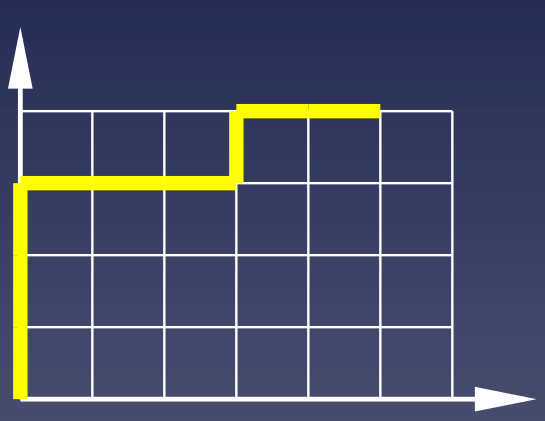
Evaluation of the performance : the ROC curve



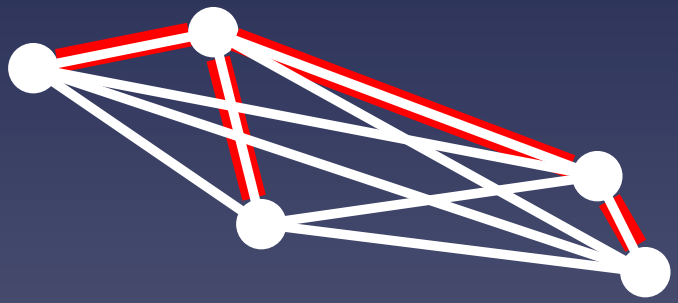


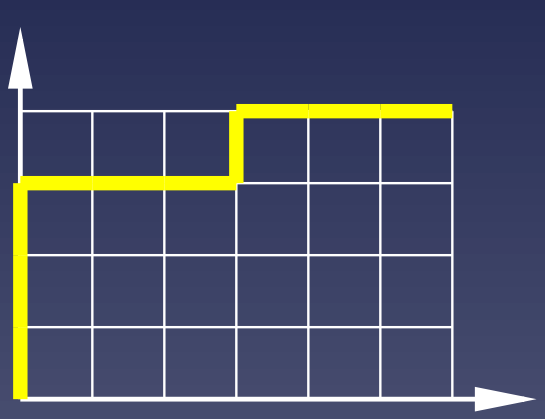
Evaluation of the performance : the ROC curve





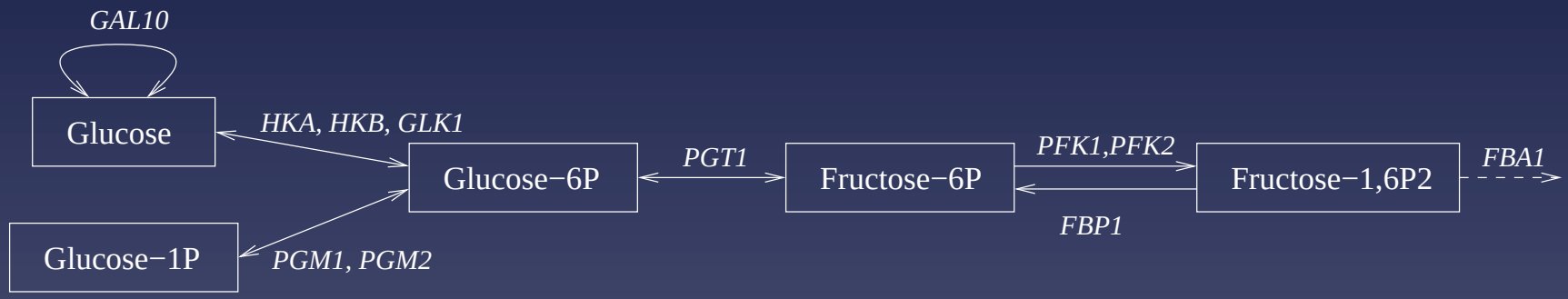
Evaluation of the performance : the ROC curve

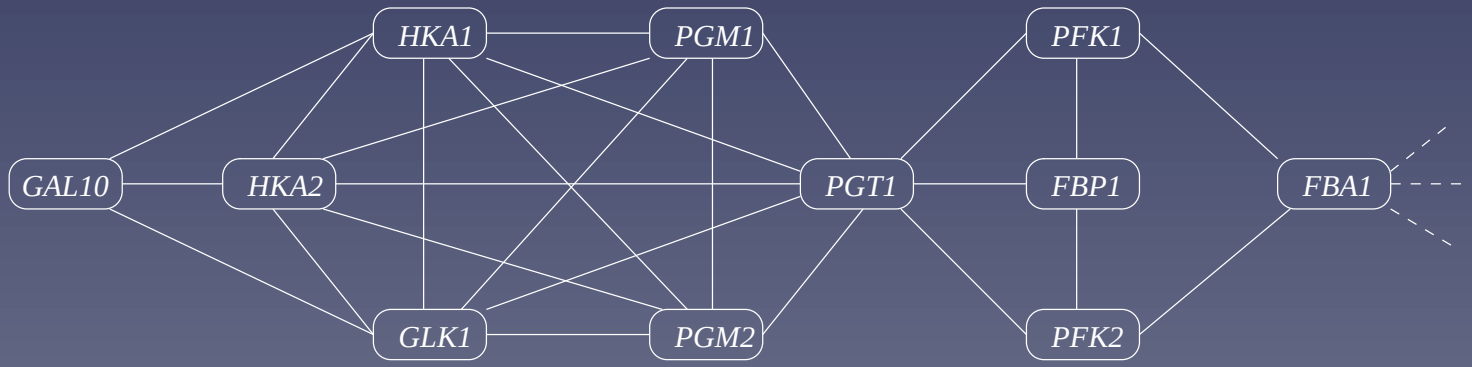




$$ROC = 21/24 = 87,5\%$$

Application: the metabolic gene network

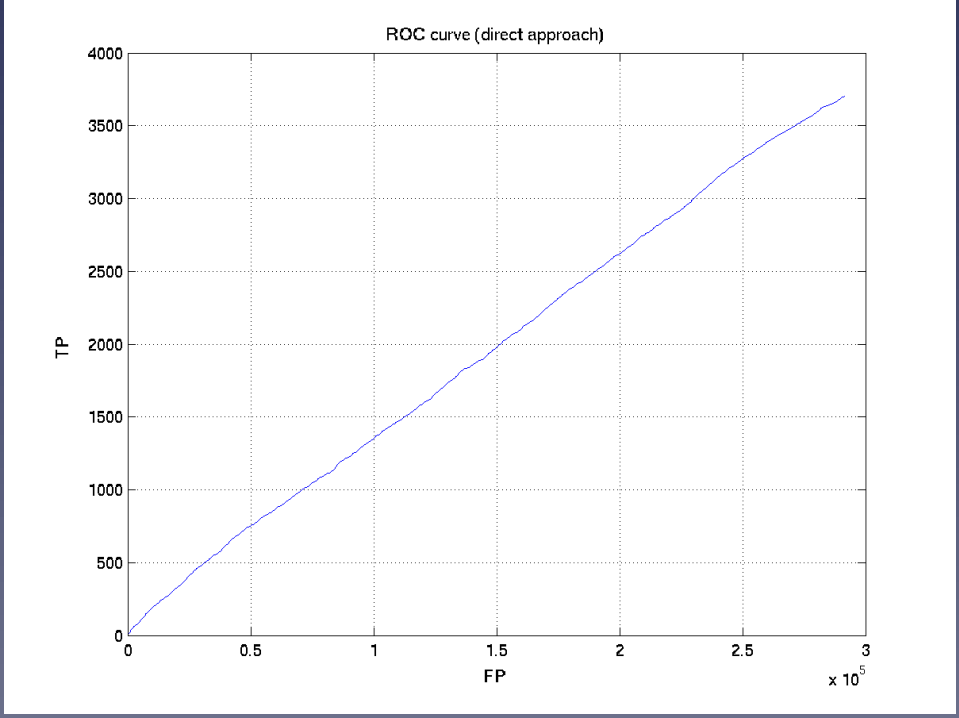




Link two genes when they can catalyze two successive reactions

Performance of metabolic network reconstruction

The metabolic network of the yeast involves 769 genes. Each gene is represented by 157 expression measurements. (ROC=0.52)



What is wrong?

- What similarity measure between profiles should be use?

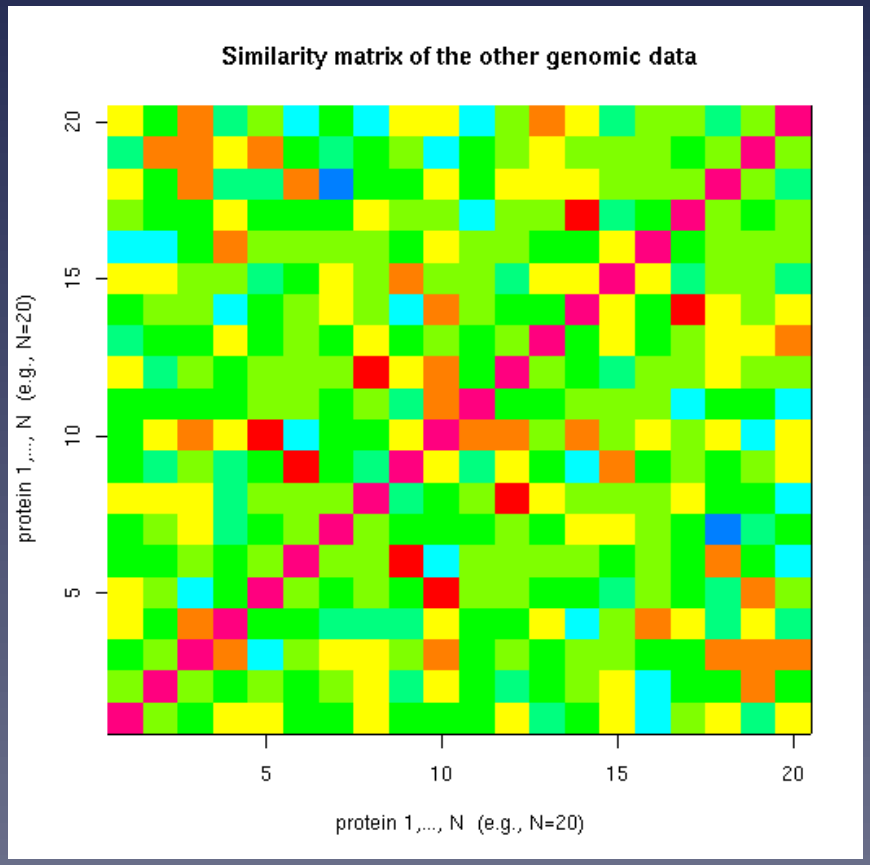
What is wrong?

- What similarity measure between profiles should be use?
- Which network are we expecting to recover?

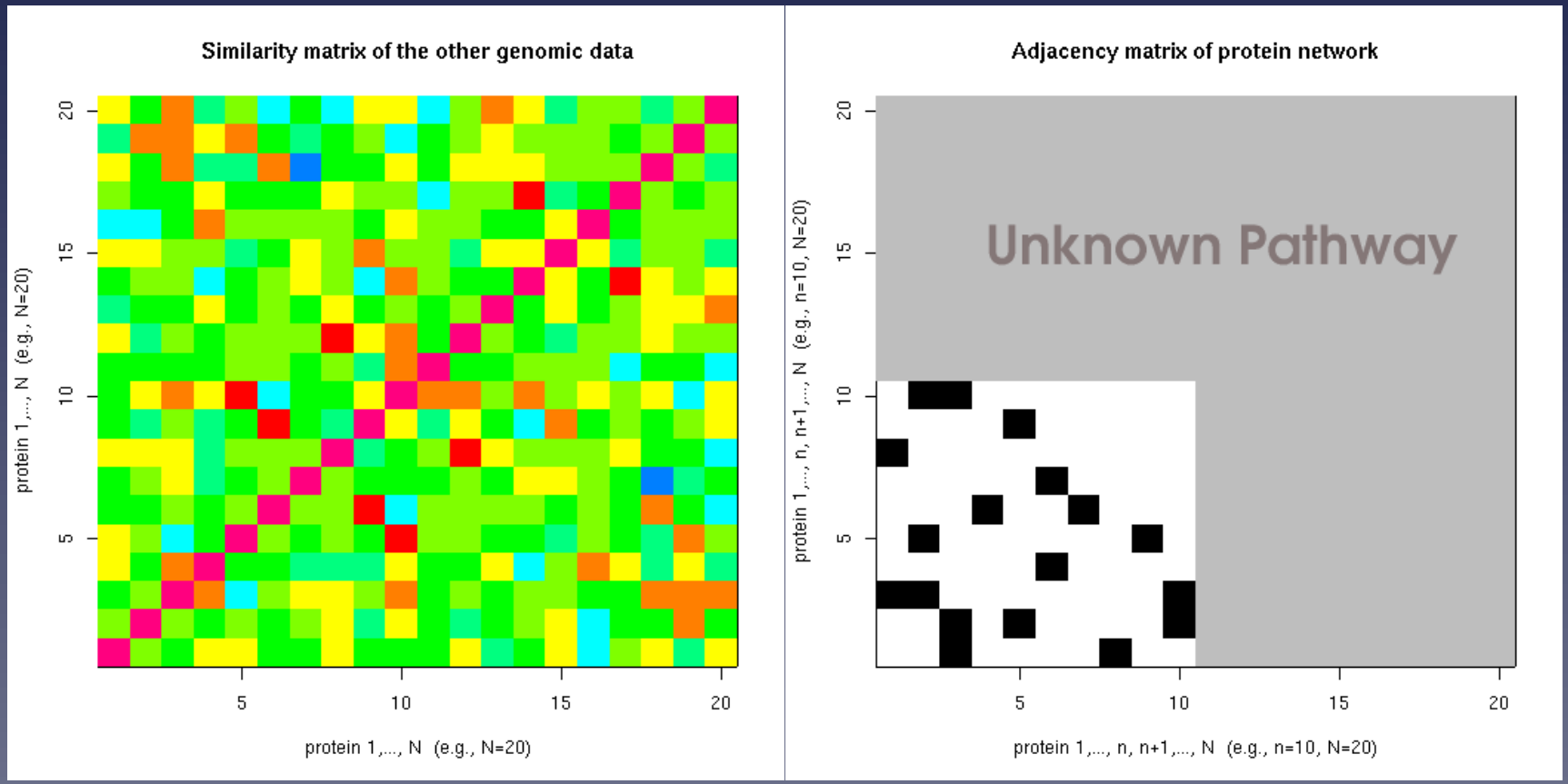
Part 2

Supervised network inference

The supervised gene inference problem

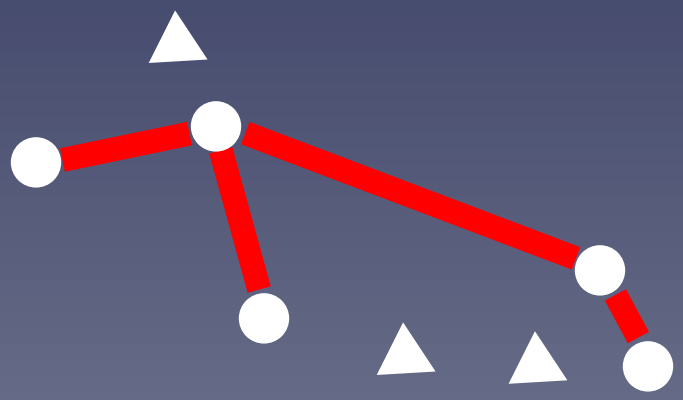


The supervised gene inference problem



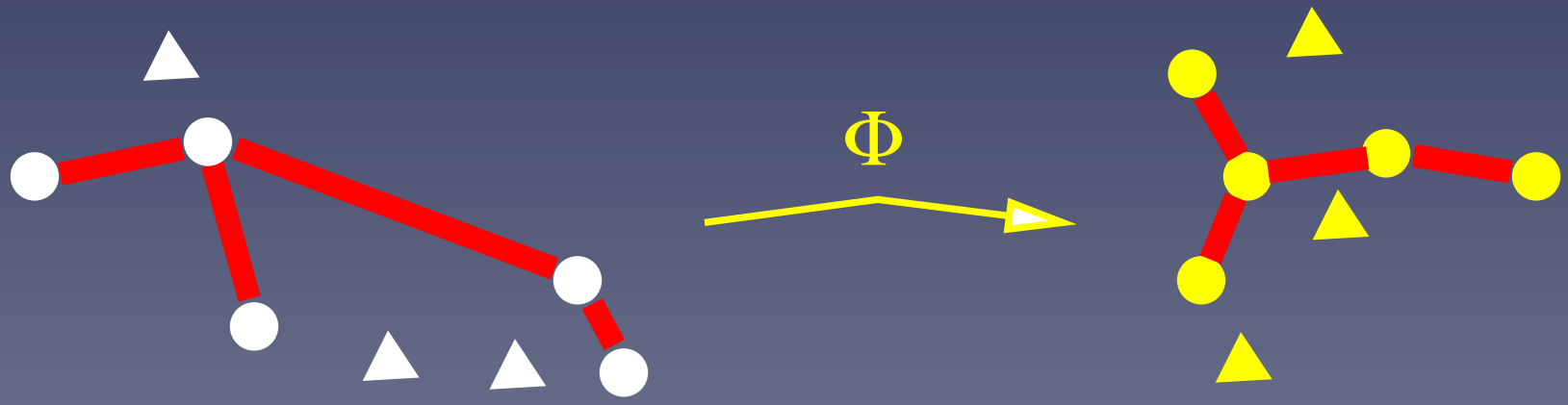
The main idea

Supervised graph inference
through
distance metric learning



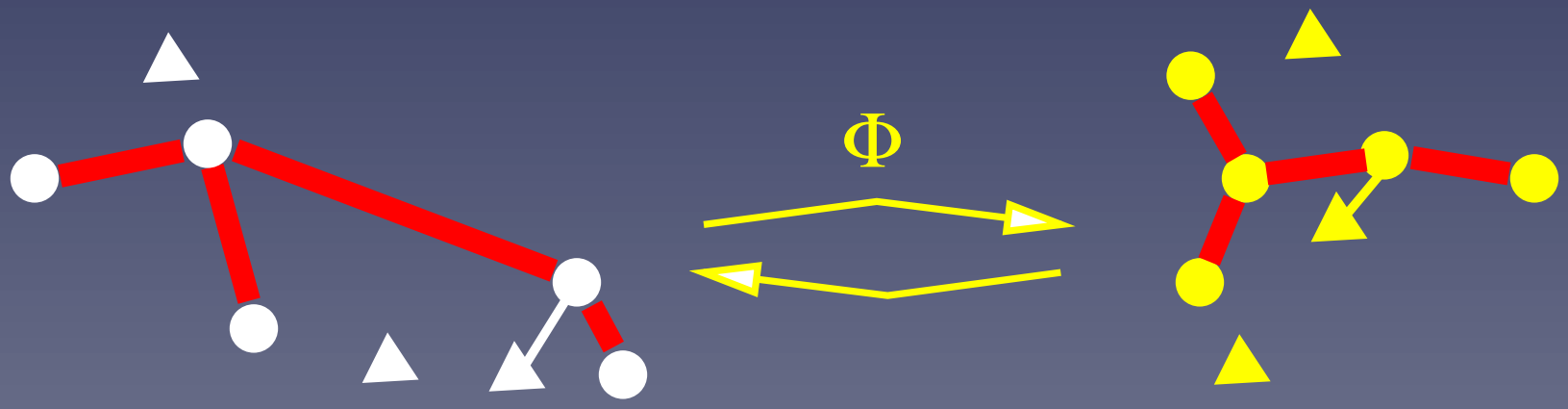
The main idea

Supervised graph inference
through
distance metric learning



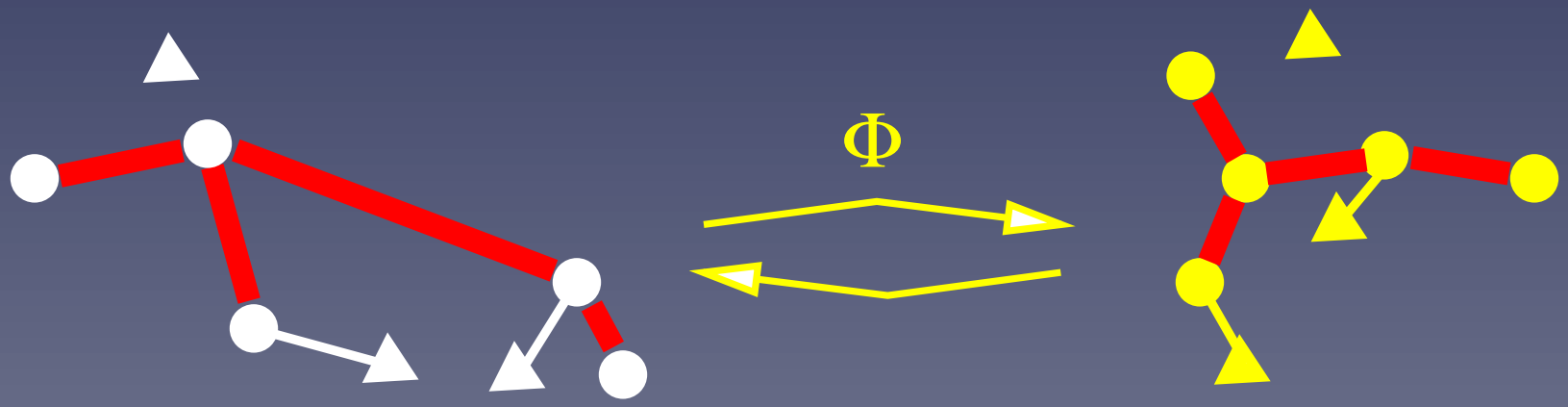
The main idea

Supervised graph inference
through
distance metric learning



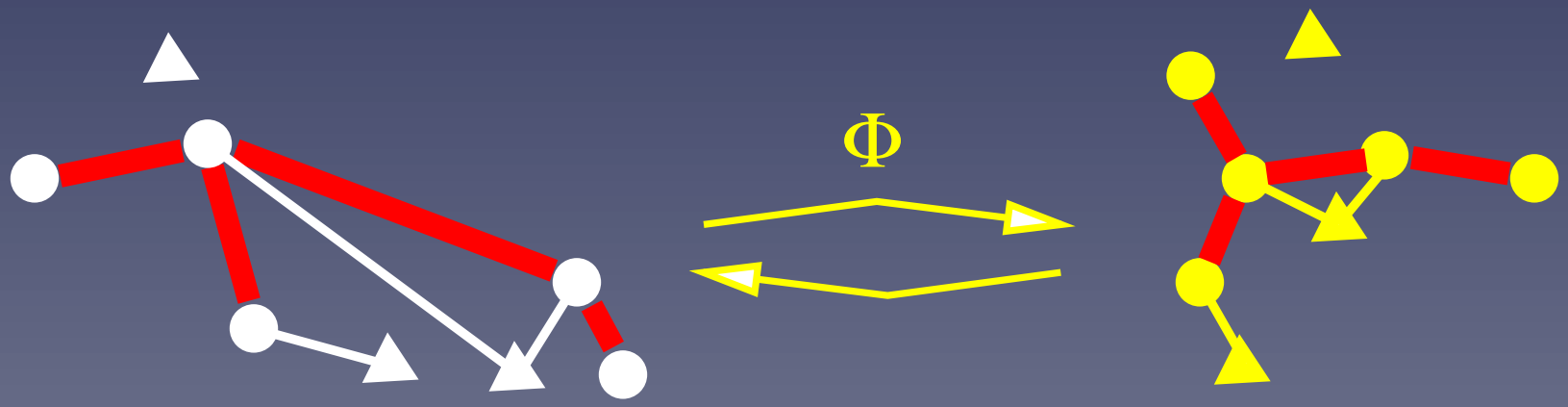
The main idea

Supervised graph inference
through
distance metric learning



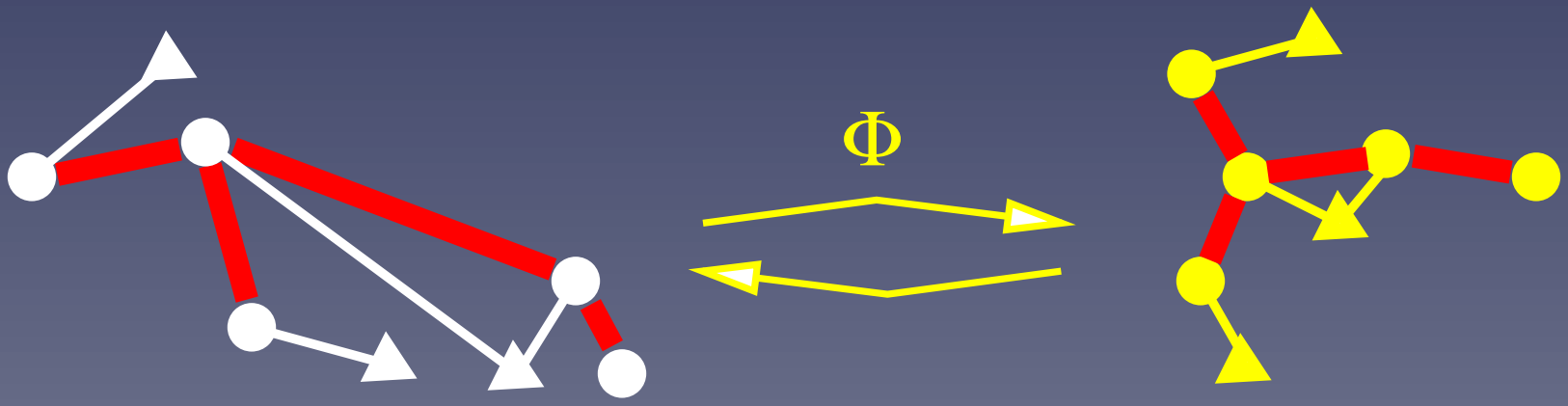
The main idea

Supervised graph inference
through
distance metric learning



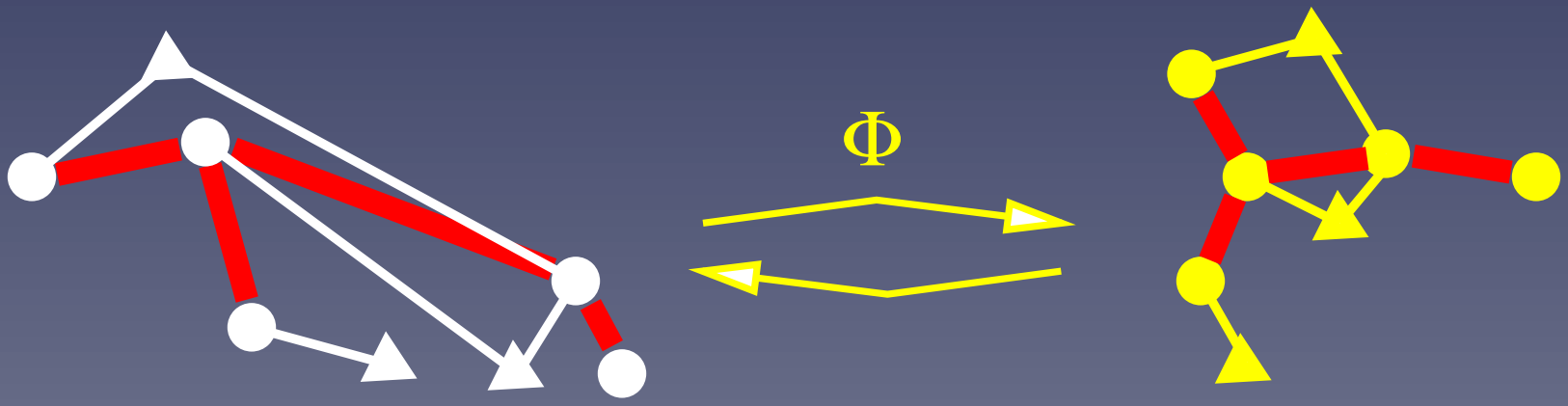
The main idea

Supervised graph inference
through
distance metric learning



The main idea

Supervised graph inference
through
distance metric learning



Learning the mapping Φ

- Let $x \in \mathbb{R}^p$ be an expression profile

Learning the mapping Φ

- Let $x \in \mathbb{R}^p$ be an expression profile
- Let us consider linear mappings:

$$\Phi(x) = (f_1(x), \ldots, f_d(x))' \in \mathbb{R}^d$$

made of linear features $f_i(x) = w_i^\top x$

Learning the mapping Φ

- Let $x \in \mathbb{R}^p$ be an expression profile
- Let us consider linear mappings:

$$\Phi(x) = (f_1(x), \ldots, f_d(x))' \in \mathbb{R}^d$$

made of linear features $f_i(x) = w_i^\top x$

- A feature $f : \mathbb{R}^p \to \mathbb{R}$ is "good" if connected genes in the known network have similar value.

"Good" features

- A "good" feature $f(x) = w^\top x$ should minimize:

$$R(f) = \frac{\sum_{i \sim j} (f(x_i) - f(x_j))^2}{\sum_{i=1}^{n} f(x_i)^2}$$

"Good" features

- A "good" feature $f(x) = w^\top x$ should minimize:

$$R(f) = \frac{\sum_{i \sim j} (f(x_i) - f(x_j))^2}{\sum_{i=1}^n f(x_i)^2}$$

- Regularisation: for statistical reasons, it is safer to minimize:

$$\min_{f(x)=w^\top x} \frac{\sum_{i \sim j} (f(x_i) - f(x_j))^2 + \lambda ||w||^2}{\sum_{i=1}^n f(x_i)^2}$$

Influence of λ

- $\lambda \to +\infty$: PCA
  - ⋆ Useful for noisy, high-dimensional data.
  - ⋆ Used in spectral clustering. The graph does not play any role (unsupervised)
- $\lambda \to 0$: second smallest eigenvector of the graph
  - ⋆ Useful to embed the graph in a Euclidean space (used in graph partitioning)
  - ⋆ Sensitive to noise. Mapping of points outside of the graph unstable (overfitting)

Extracting successive features

- Successive features to form Φ can be obtained by:

$$w_i = \underset{w \perp \{w_1,\ldots,w_{i-1}\},\, \hat{\mathrm{var}}(f_w)=1}{\arg\min} \left\{ \sum_{i \sim j} \left(f_w(x_i) - f_w(x_j)\right)^2 + \lambda ||w||^2 \right\}.$$

Extracting successive features

- Successive features to form Φ can be obtained by:

$$w_i = \underset{w \perp \{w_1,\ldots,w_{i-1}\}, \hat{\mathrm{var}}(f_w)=1}{\arg\min} \left\{ \sum_{i \sim j} \left(f_w(x_i) - f_w(x_j)\right)^2 + \lambda ||w||^2 \right\}.$$

- Generalizes Principal Component Analysis (PCA)

Extension to non-linear features

- In order to allow nonlinear features, we need to replace:
  - ⋆ $||w||^2$ by $||f||^2$
  - ⋆ $w_i \perp w_j$ by $f_i \perp f_j$
- We need to work in a Hilbert space of (nonlinear) functions that generalizes the linear case

Positive definite kernels

Let $\mathcal{X}$ be a set endowed with a symmetric positive definite kernel $k : \mathcal{X}^2 \to \mathbb{R}$, i.e.,

$$\sum_{i=1}^{n}\sum_{j=1}^{n} c_i c_j k(x_i, x_j) \geq 0$$

for any $n \geq 0, (x_1, \ldots, x_n) \in \mathcal{X}$ and $(a_1, \ldots, a_n) \in \mathbb{R}$

Examples:

- $k(x, y) = x \cdot y$ for $\mathcal{X} = \mathbb{R}^d$
- $k(x, y) = \exp(-||x - y||^2/(2\sigma^2))$ for $\mathcal{X} = \mathbb{R}^d$

Reproducing kernel Hilbert space

- A p.d. kernel defines a Hilbert space of functions $f : \mathcal{X} \to \mathbb{R}$ obtained by completing the span of $\{k(x, \cdot), x \in \mathcal{X}\}$
- The norm of a function $f(x) = \sum_{i=1}^{n} c_i k(x_i, x)$ is:

$$||f||_k^2 = \sum_{i,j=1}^{n} c_i c_j k(x_i, x_j).$$

- This space is called the reproducing kernel Hilbert space (RKHS)

Example: linear RKHS

For $\mathcal{X} = \mathbb{R}^d$ and $k(x, y) = x \cdot y$, we have:

- $f(x) = \sum_{i=1}^{n} c_i x_i \cdot x = f_w(x)$ with $w = \sum_{i=1}^{n} c_i x_i$.
- $||f||_k^2 = \sum_{i,j=1}^{n} c_i c_j x_i \cdot x_j = ||w||^2$
- If $f(x) = w \cdot x$ and $g(x) = v \cdot x$ then:

$$< f, g >_k = w \cdot v$$

Graph-driven feature extraction in RKHS

- For a general set $\mathcal{X}$ endowed with a p.d. kernel k we therefore have the following graph-driven feature extractor:

$$f_i = \underset{f \perp \{f_1,\ldots,f_{i-1}\}, \hat{\mathsf{var}}(f)=1}{\arg\min} \left\{ \sum_{i \sim j} (f(x_i) - f(x_j))^2 + \lambda ||f||_k^2 \right\}.$$

- The values at the minima (the spectrum) quantifies how much the graph fits the data

Solving the problem

- By the representer theorem, f_i can be expanded as:

$$f_i(x) = \sum_{j=1}^{n} \alpha_{i,j} k(x_i, x).$$

- This shows that

$$\begin{aligned} < f_i, f_j >_k &= \alpha_i^\top K \alpha_j \\ ||f_i||_k^2 &= \alpha_i^\top K \alpha_i \end{aligned} \tag{1}$$

Solving the problem (cont.)

- The problem can then be rewritten:

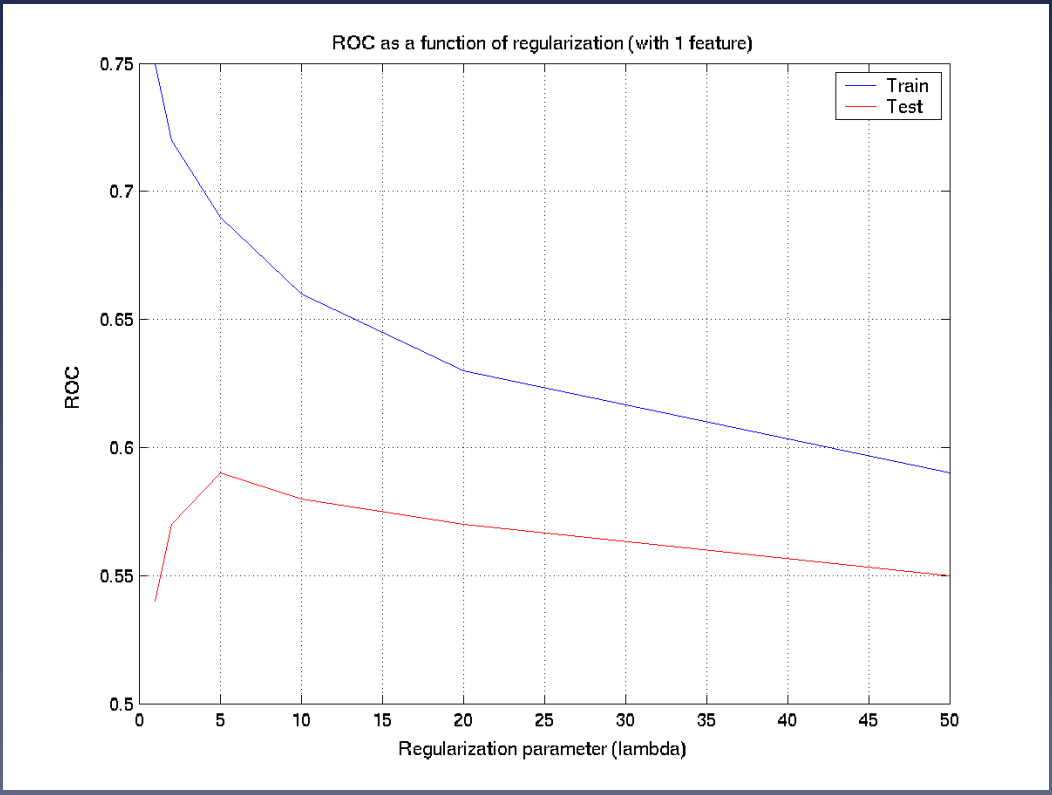
$$\alpha_i = \underset{\alpha\in\mathbb{R}^n, \alpha K_V \alpha_1 = \ldots = \alpha K_V \alpha_{i-1} = 0}{\arg\min} \left\{ \frac{\alpha^\top K_V L K_V \alpha + \lambda \alpha^\top K_V \alpha}{\alpha^\top K_V^2 \alpha} \right\}$$

  where K_V is the centered $n \times n$ Gram matrix and L is the Laplacian of the graph

- It is equivalent to solving the generalized eigenvalue problem:

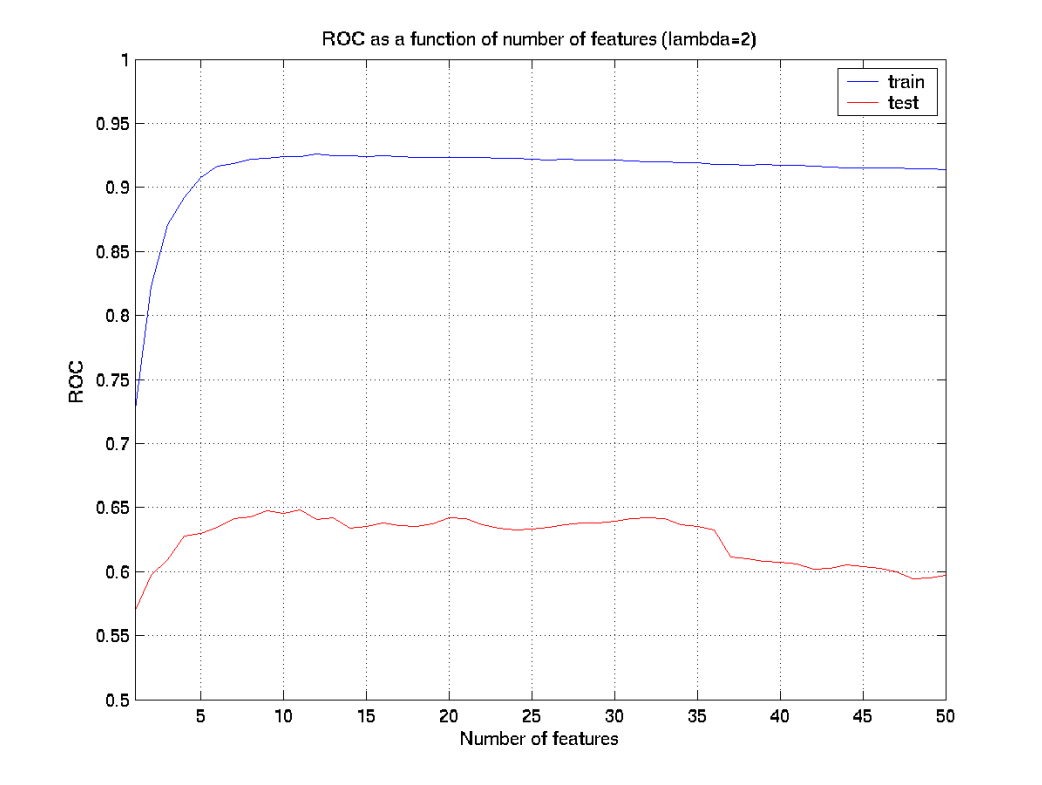
$$(L K_V + \lambda I)\alpha = \mu K_V \alpha.$$

Evaluation of the supervised approach: effect of λ



Metabolic network, 10-fold cross-validation, 1 feature

Evaluation of the supervised approach: number of features ($\lambda = 2$)



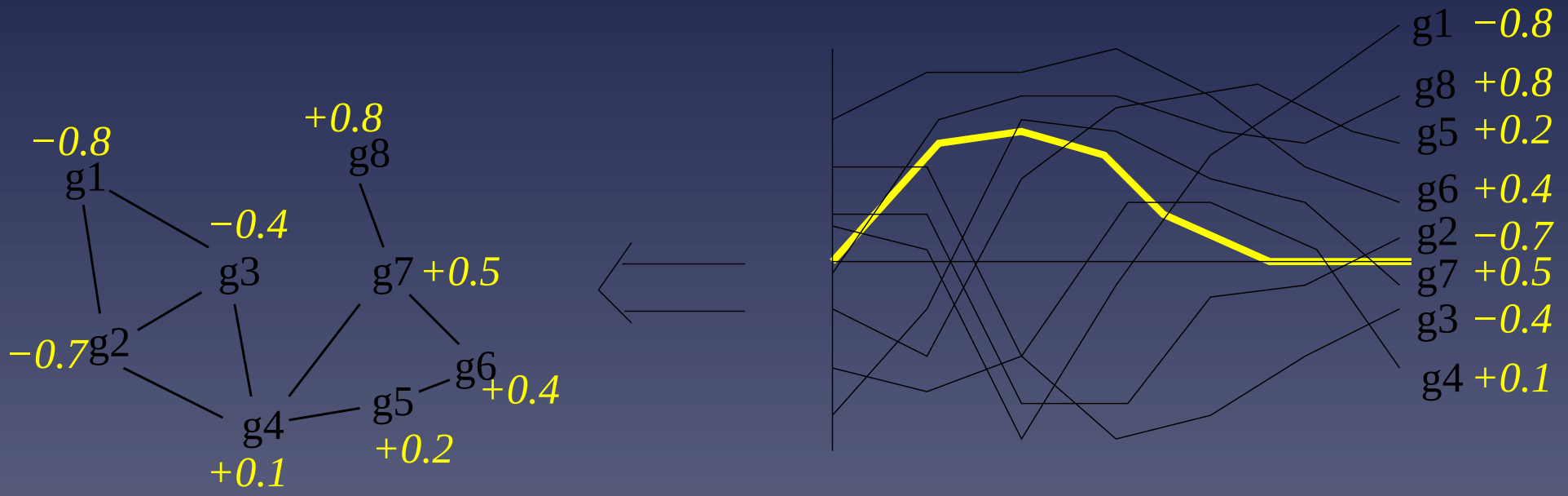
Part 3

Extraction of pathway activity

The idea

- The previous approach is a way to extract features from gene expression data: $f(x) = w^\top x$.
- These features are smooth on the graph: connected nodes tend to have similar values
- This is way to detect "correlations" between gene expression data and metabolic network : typical activity patterns of typical pathways

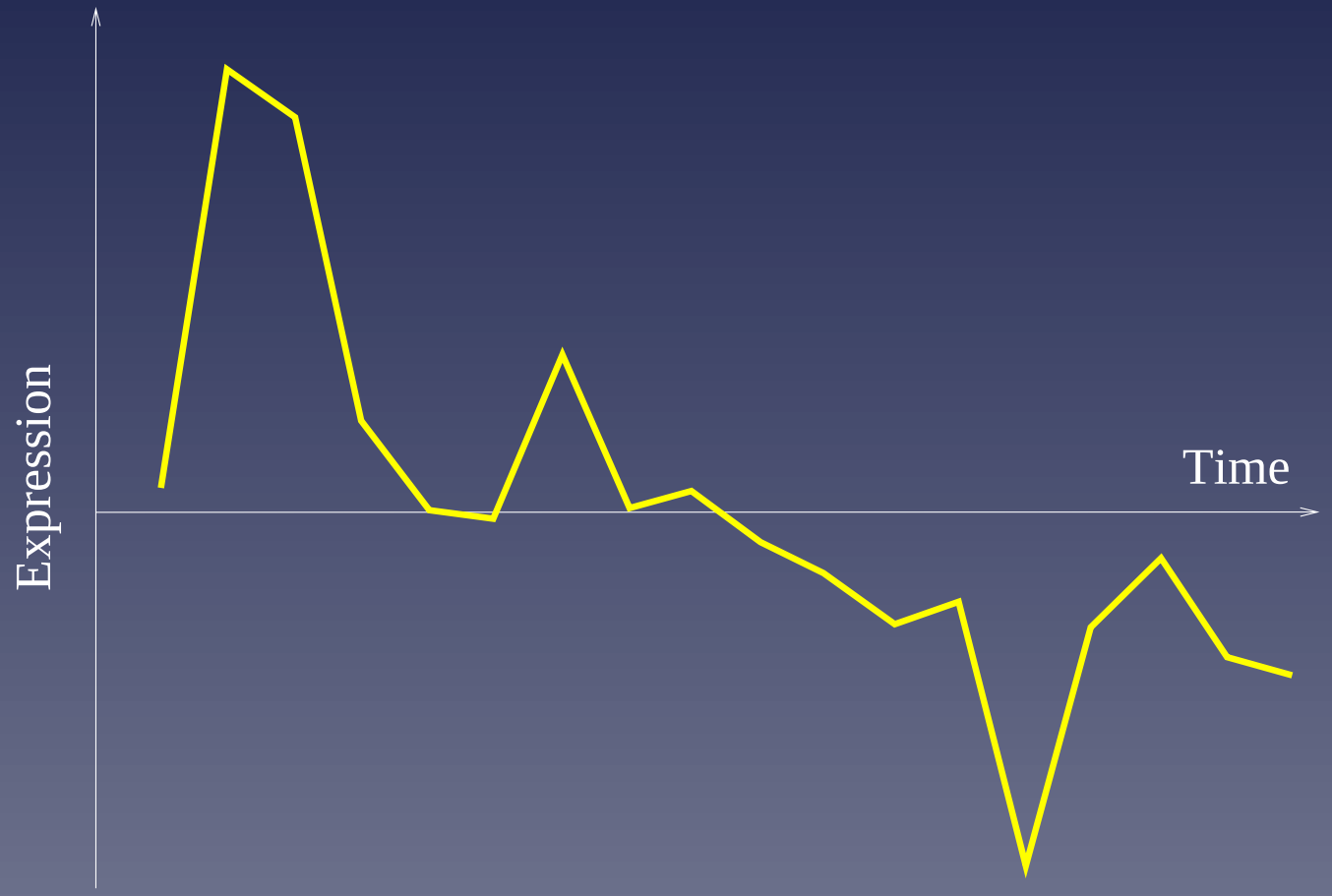
Illustration



Experiment

- Gene network: two genes are linked if the catalyze successive reactions in the KEGG database (669 yeast genes)
- Expression profiles: 18 time series measures for the 6,000 genes of yeast, during two cell cycles

First pattern of expression

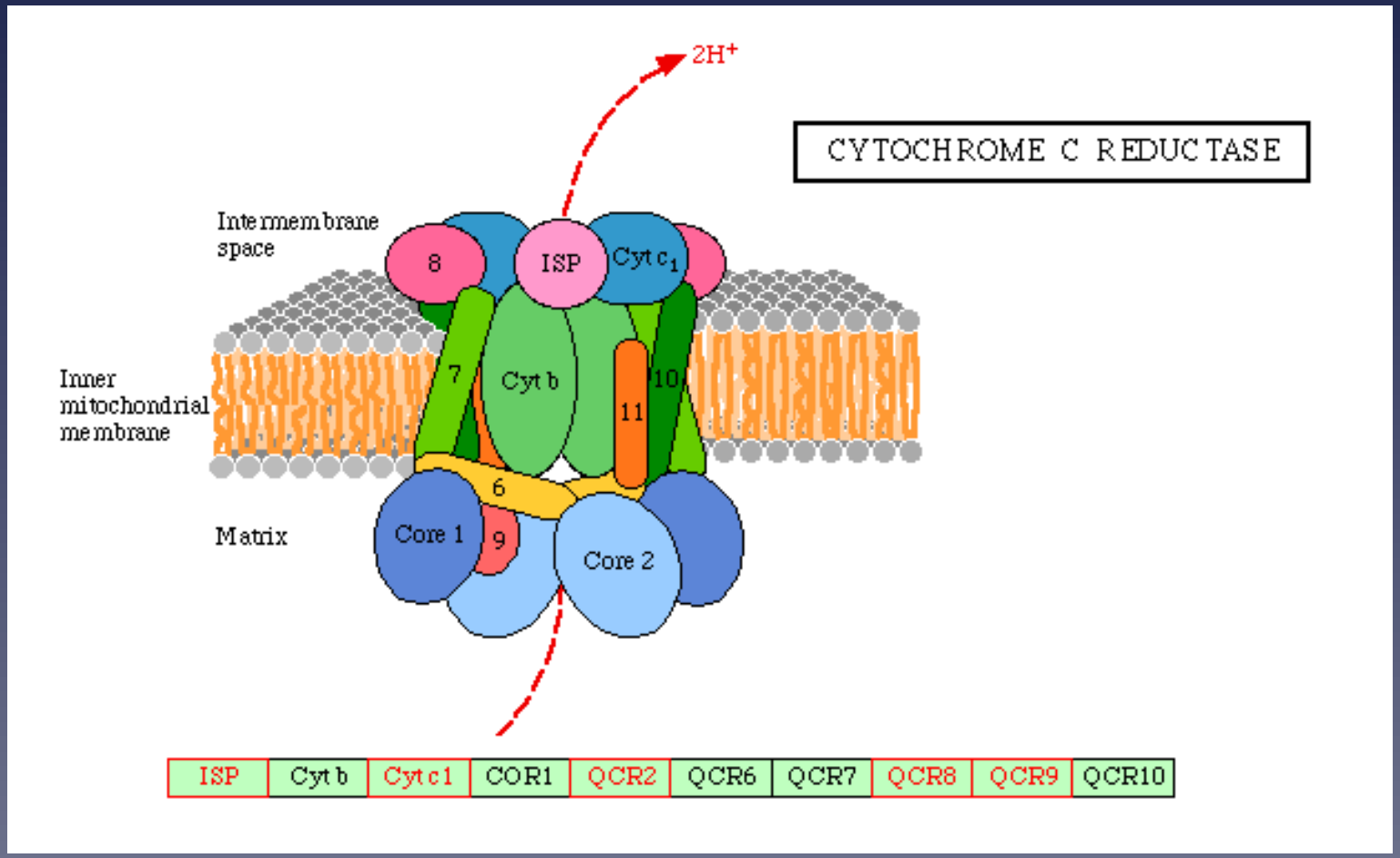


Related metabolic pathways

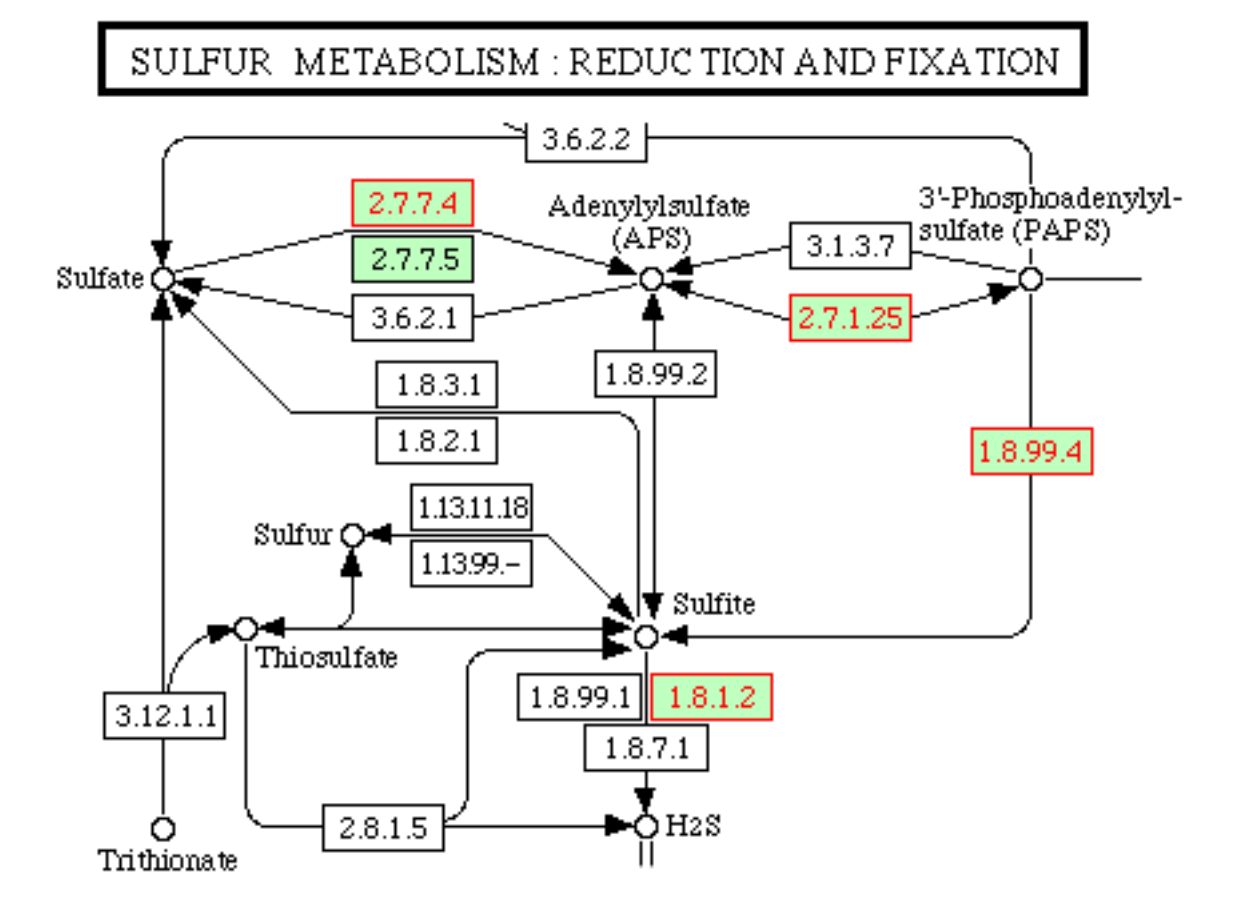
50 genes with highest $s_2 - s_1$ belong to:

- Oxidative phosphorylation (10 genes)
- Citrate cycle (7)
- Purine metabolism (6)
- Glycerolipid metabolism (6)
- Sulfur metabolism (5), etc...

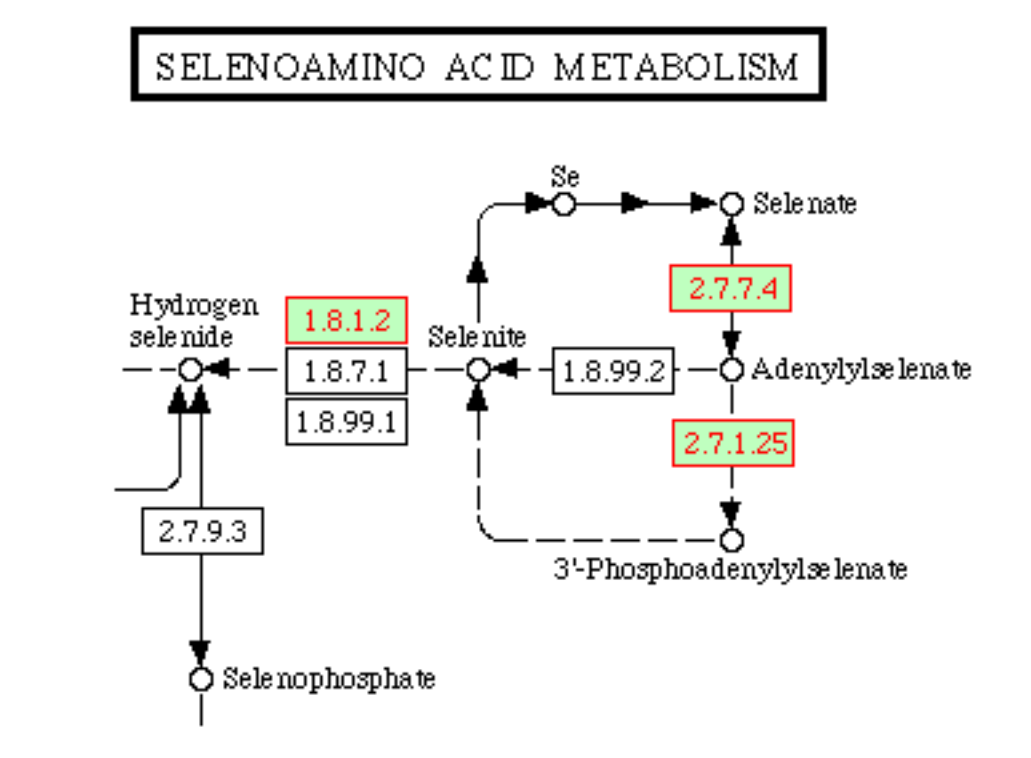
Related genes



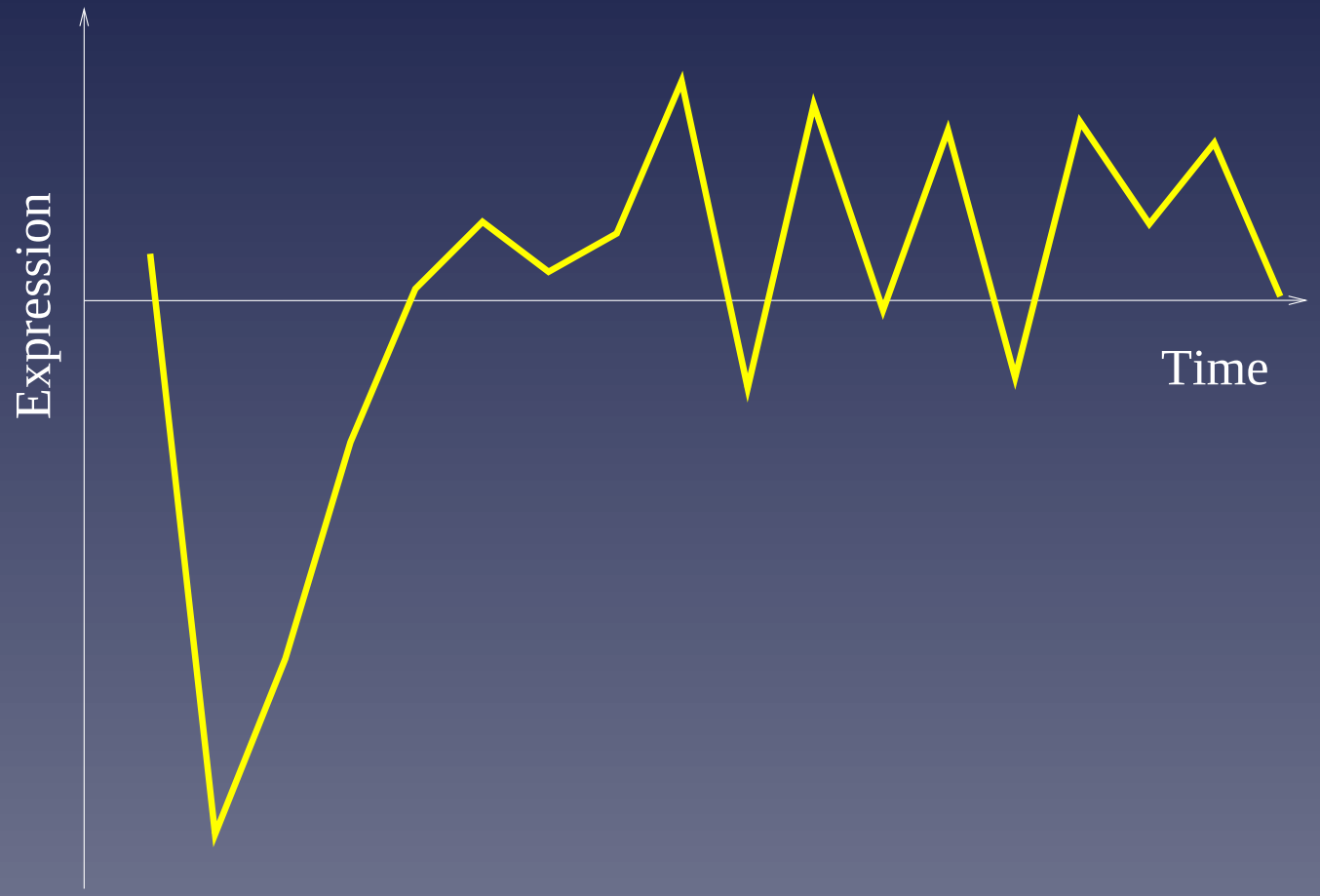
Related genes



Related genes



Opposite pattern

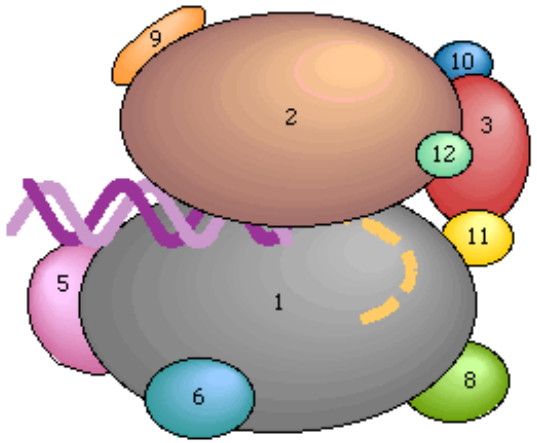


Related genes

- RNA polymerase (11 genes)
- Pyrimidine metabolism (10)
- Aminoacyl-tRNA biosynthesis (7)
- Urea cycle and metabolism of amino groups (3)
- Oxidative phosphorlation (3)
- ATP synthesis(3) , etc...

Related genes

RNA POLYMERASE



RNA polymerase II (Saccharomyces cerevisiae)

Eukaryotic Pol II

B2	B3	B4	B5	B6	B7
B1	B8	B9	B10	B11	B12

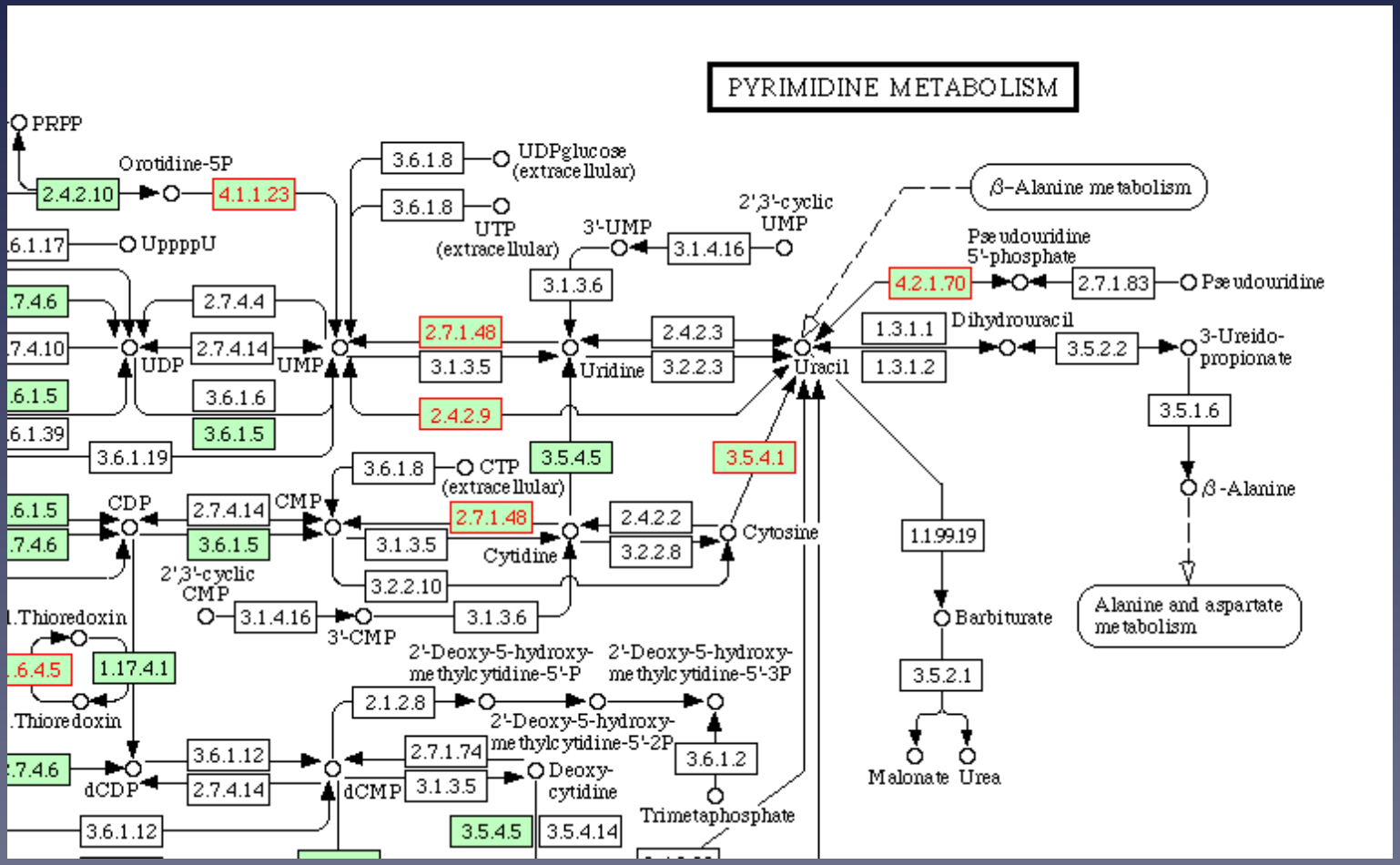
Eukaryotic Pol III

C2	C3	C4	C5	C11
C1	C19	C25	C31	C34

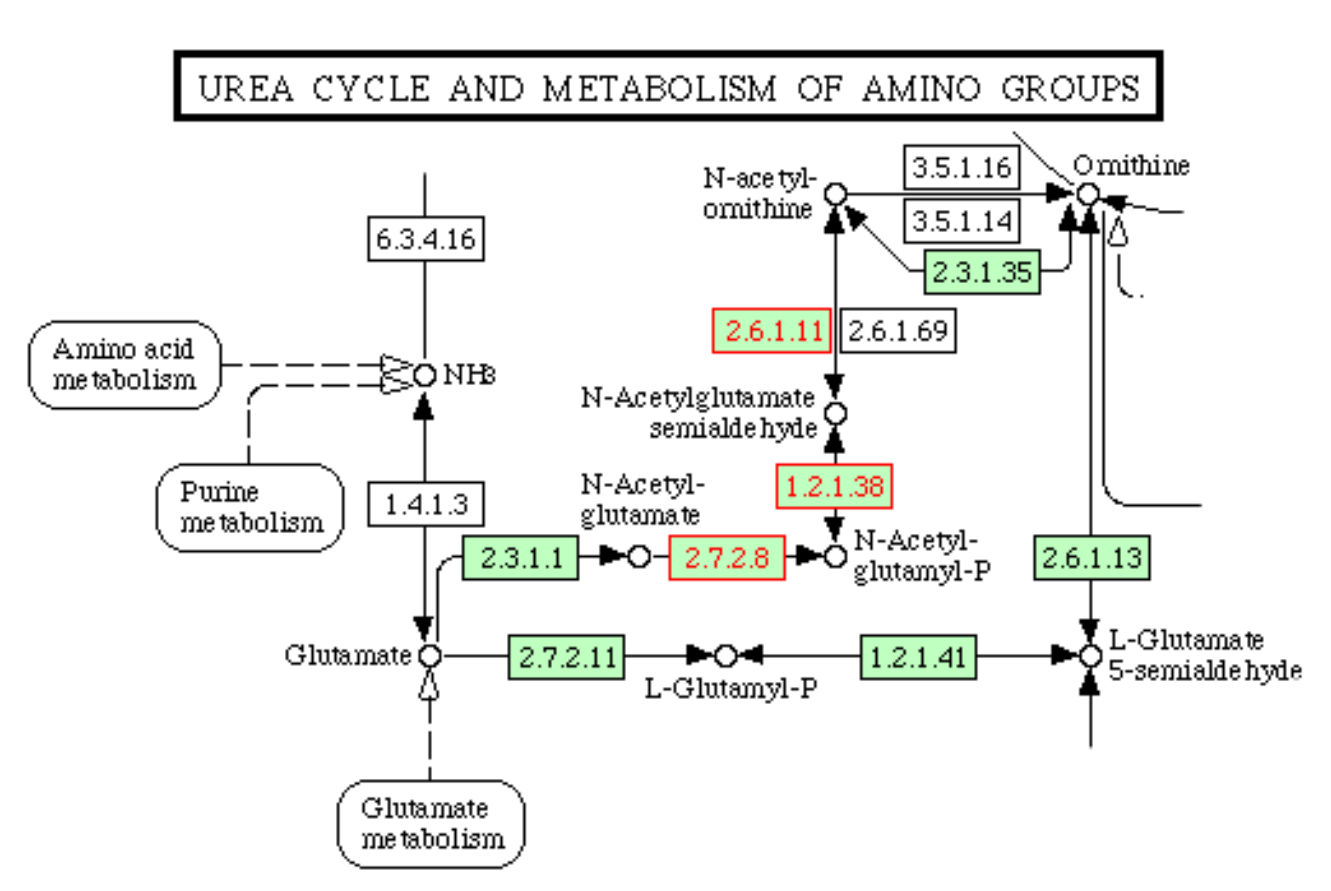
Eukaryotic Pol I

A2	A12	A14	A34	A43	A49
A1					

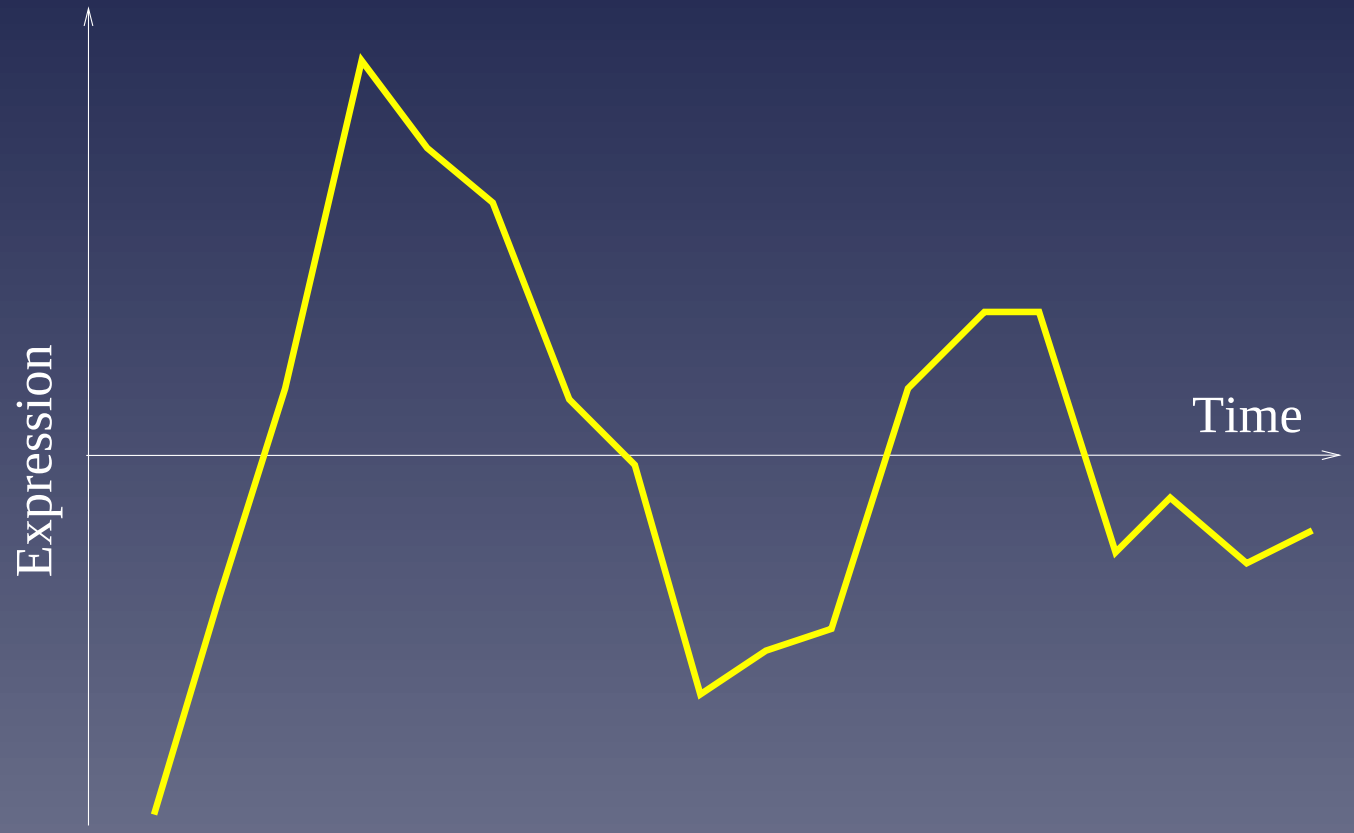
Related genes



Related genes



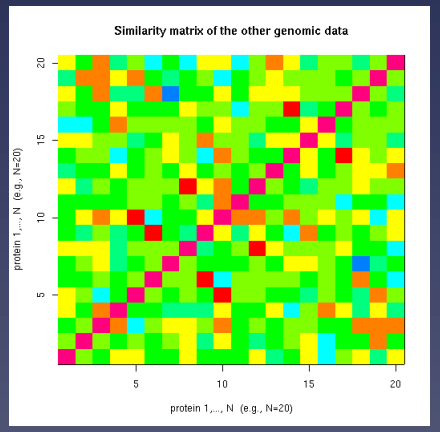
Second pattern

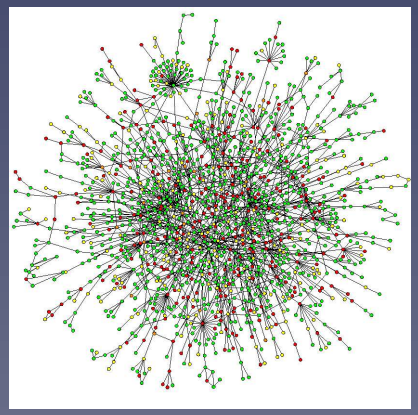


Part 4

Learning from several heterogeneous data

Summary of the process





Features

Kernels

Several similarity kernels have been developed recently:

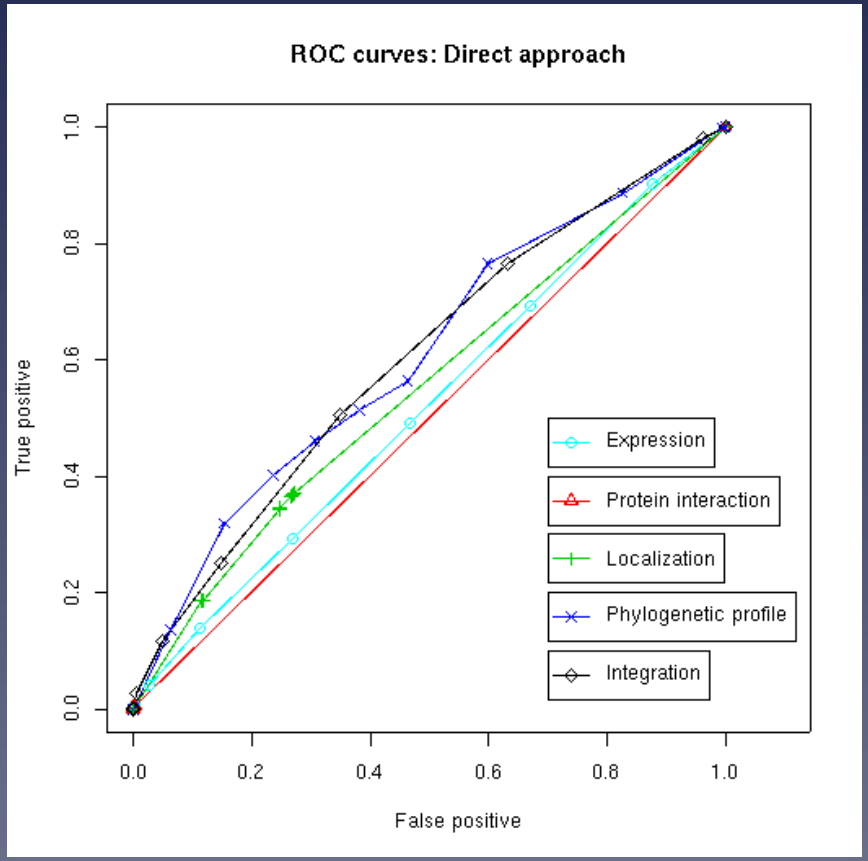
- for phylogenetic profiles (JPV. 2004)
- for gene sequences (Leslie et al. 2003, Saigo et al. 2004, ...)
- for nodes in a network (Kondor et al. 2000)

Learning from heterogeneous data

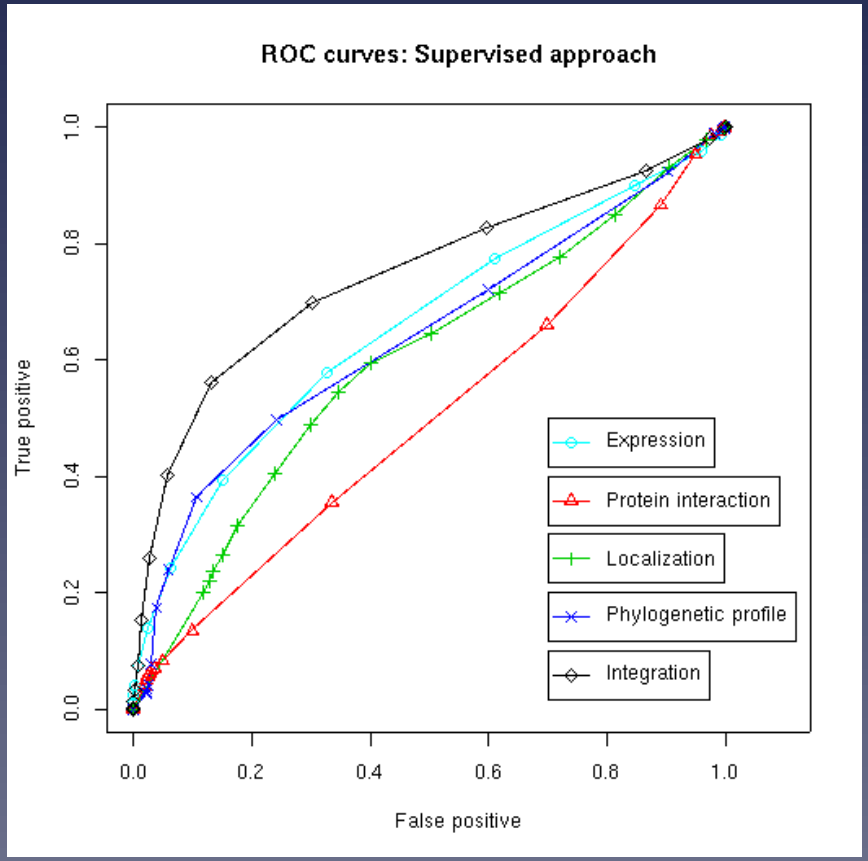
- Suppose several data are available about the genes, e.g., expression, localization, struture, predicted interaction etc...
- Each data can be represented by a positive definite similarity matrix $K_1, \ldots, K_p$
- Kernel can be combined by various operations, e.g., addition:

$$K = \sum_{i=1}^{p} K_i$$

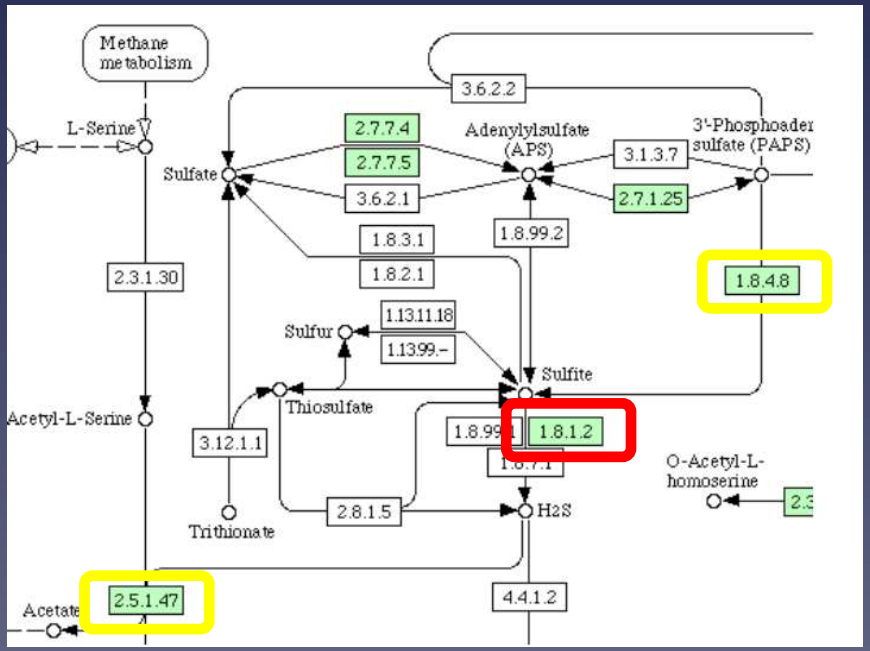
Learning from heterogeneous data (unsupervised)



Learning from heterogeneous data (supervised)



Application: missing enzyme prediction



The gene YJR137C was predicted in 09/2003 between $EC : 1.8.4.8$ and $EC : 2.5.1.47$. It was recently annotated as EC:1.8.1.2

Conclusion

Conclusion

1. Supervised inference is better than unsupervised

Conclusion

1. Supervised inference is better than unsupervised
2. Supervised graph inference can be performed by distance metric learning

Conclusion

1. Supervised inference is better than unsupervised
2. Supervised graph inference can be performed by distance metric learning
3. Data integration with kernels is simple and powerful

Conclusion

1. Supervised inference is better than unsupervised
2. Supervised graph inference can be performed by distance metric learning
3. Data integration with kernels is simple and powerful
4. Few assumptions about the network to infer (works well for the metabolic network and the protein interaction network)