

Analysis and inference of gene networks from genomic data



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Thanks

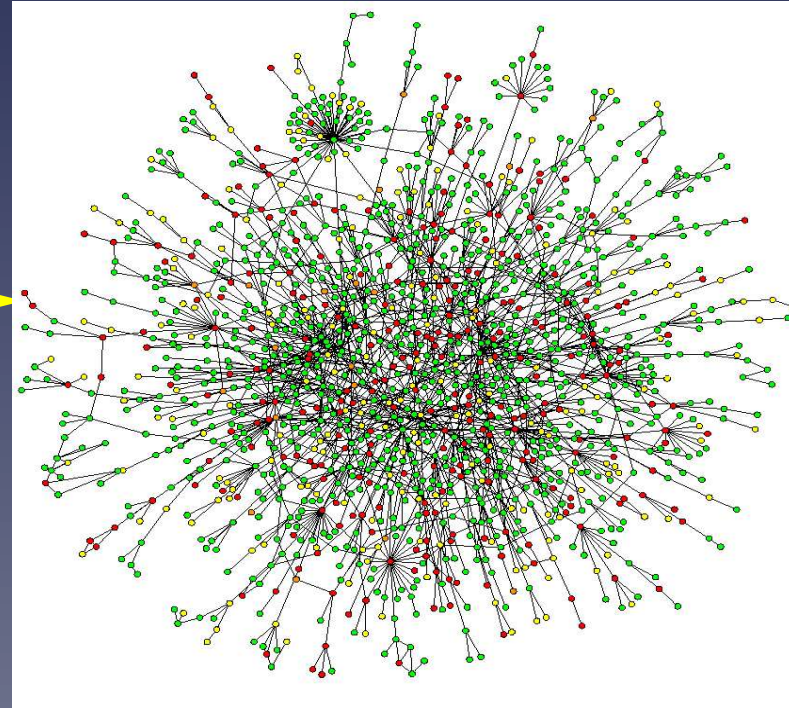
- Y. Yamanishi (Kyoto University)
- Computational biology at the Ecole des Mines



Motivations

- Many heterogeneous data **about genes** : sequences, expression, evolution, structures, etc...
- More and more data **between genes**: interactome, pathways, regulation etc...
- **Goal**: propose a **formalism** and **algorithms** to **compare** these data, and to **infer** gene networks from high-throughput genomic data.

Example 2: Gene network inference



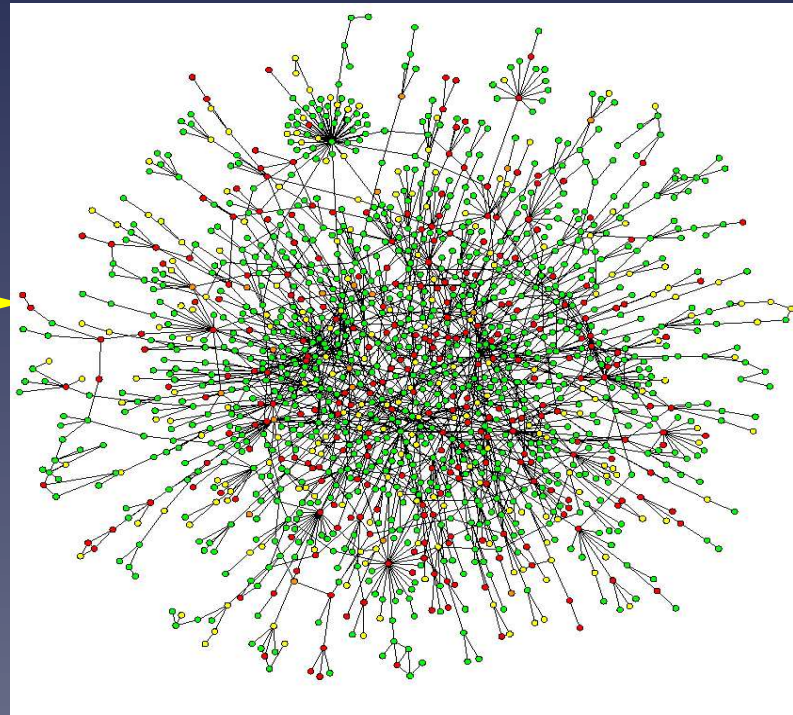
Outline

- 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

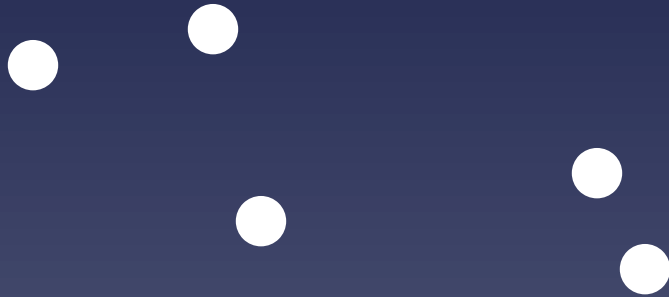
The problem



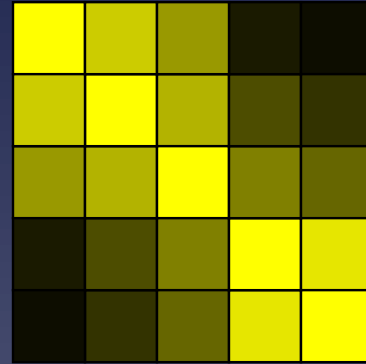
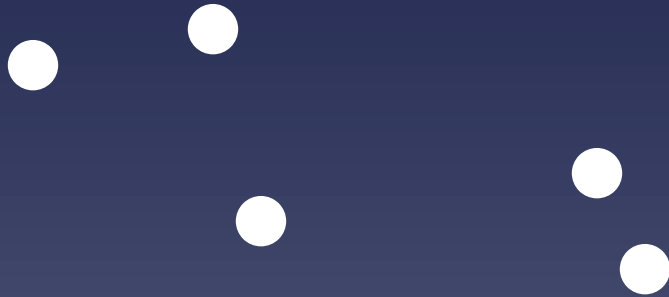
Related approaches

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

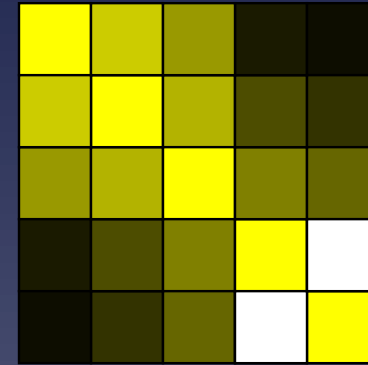
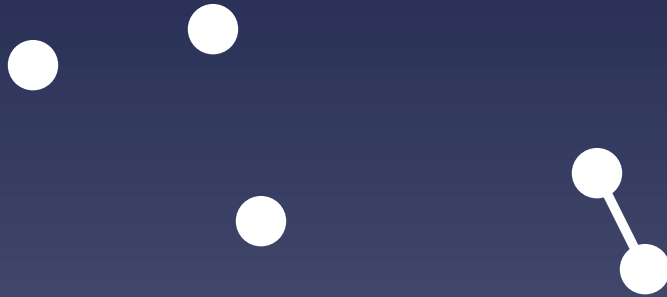
Network inference : the direct approach



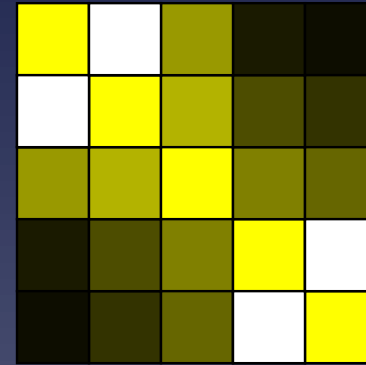
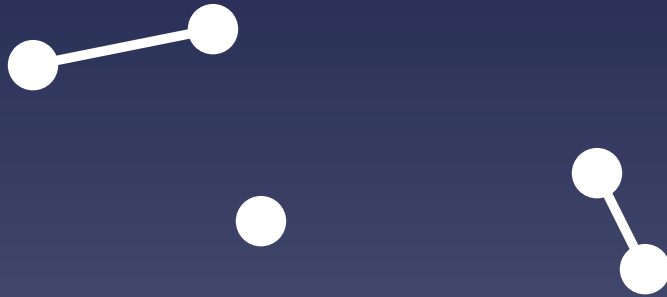
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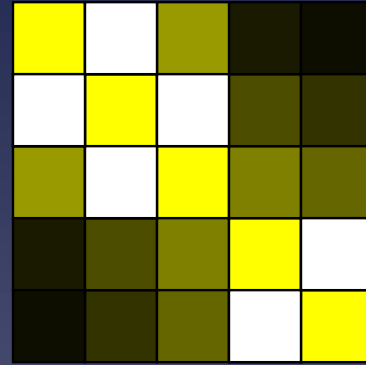
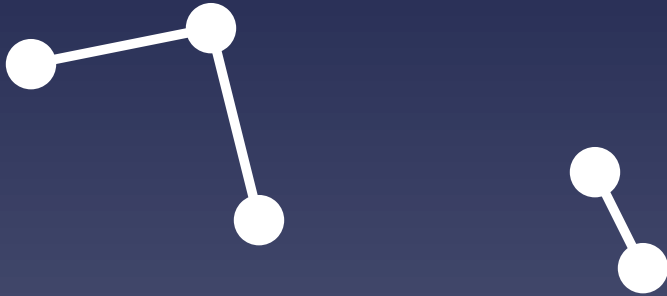
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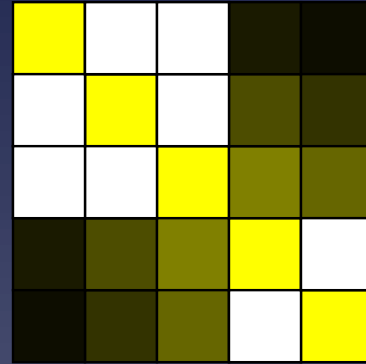
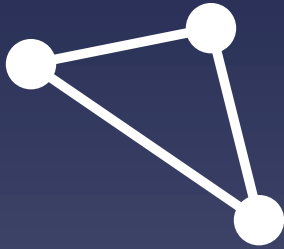
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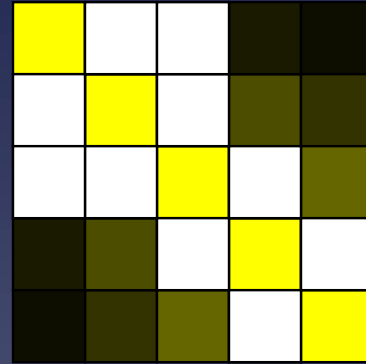
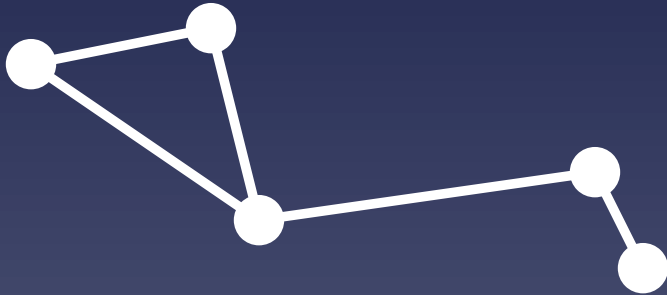
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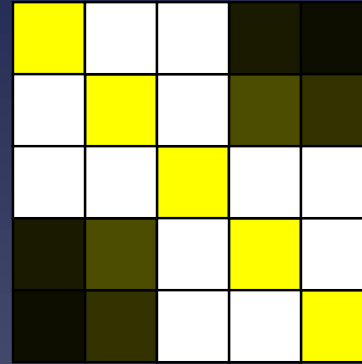
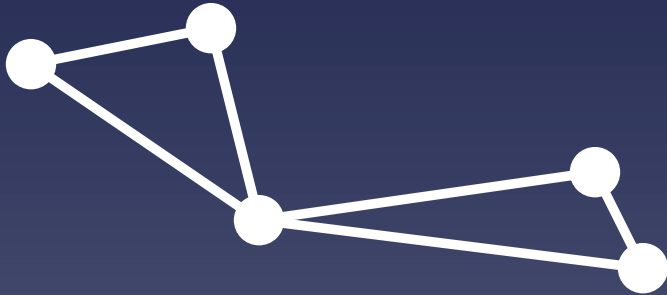
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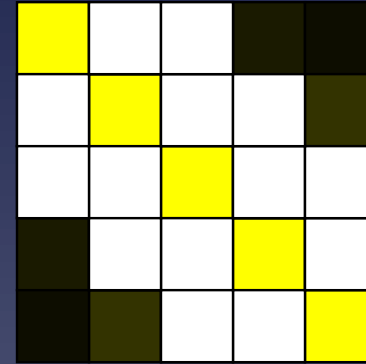
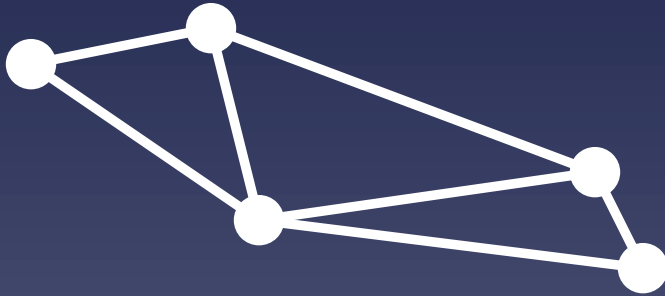
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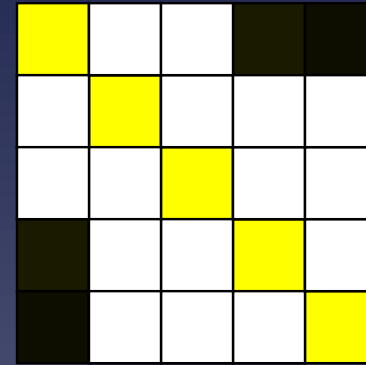
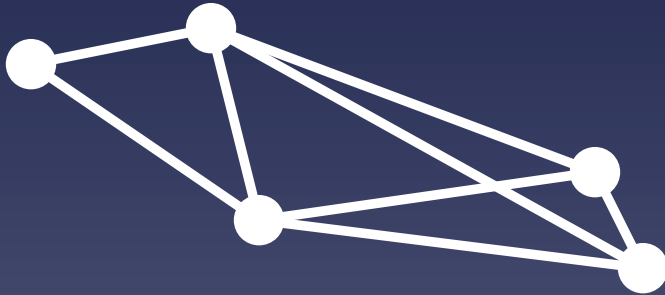
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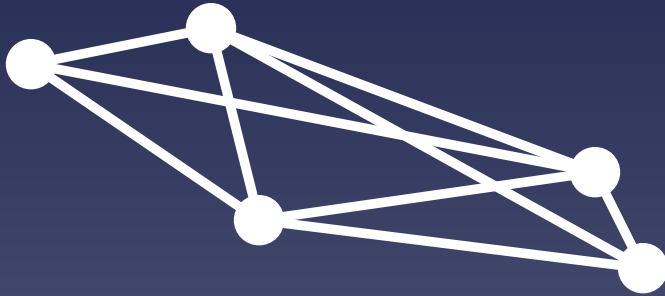
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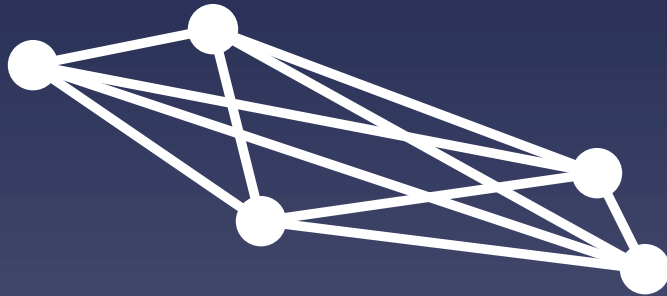


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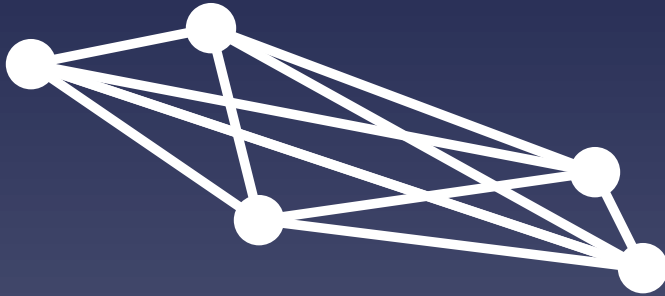
Yellow	White	White	White	Black
White	Yellow	White	White	White
White	White	Yellow	White	White
White	White	White	Yellow	White
Black	White	White	White	Yellow

Network inference : the direct approach



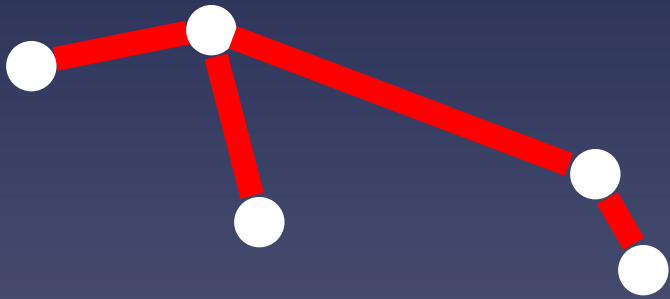
1	0	0	0	0	0
0	1	0	0	0	0
0	0	1	0	0	0
0	0	0	1	0	0
0	0	0	0	1	0
0	0	0	0	0	1

Network inference : the direct approach

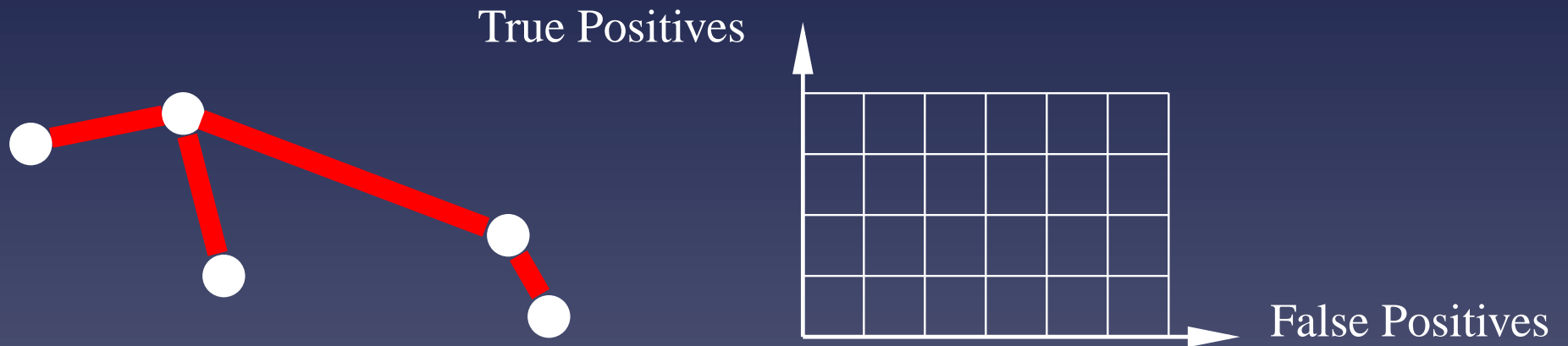


1	0	0	0	0
0	1	0	0	0
0	0	1	0	0
0	0	0	1	0
0	0	0	0	1

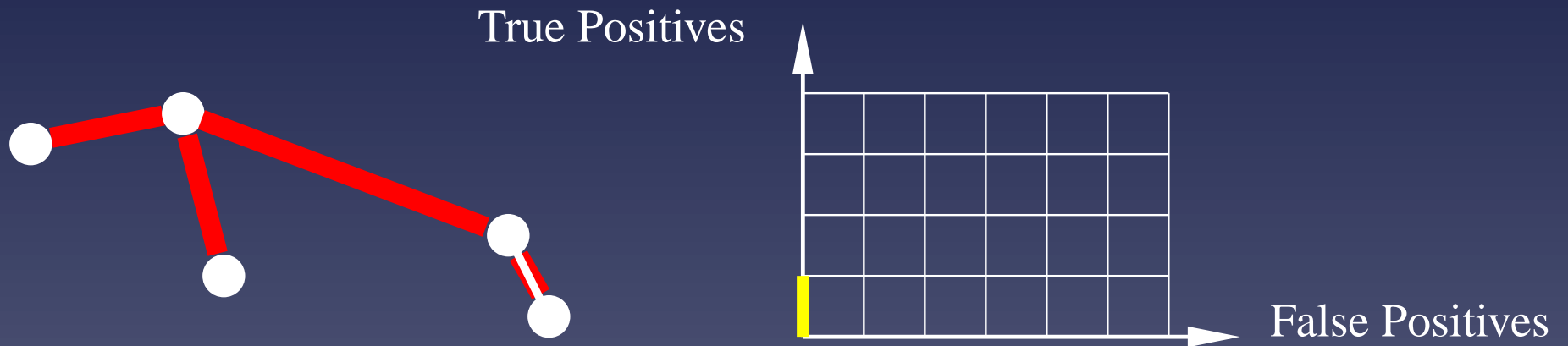
Evaluation of the performance : the ROC curve



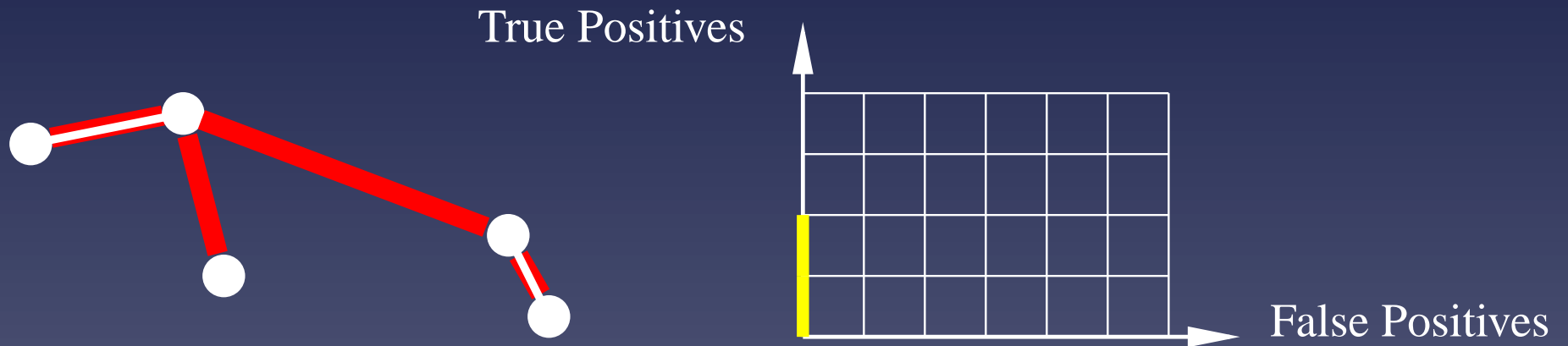
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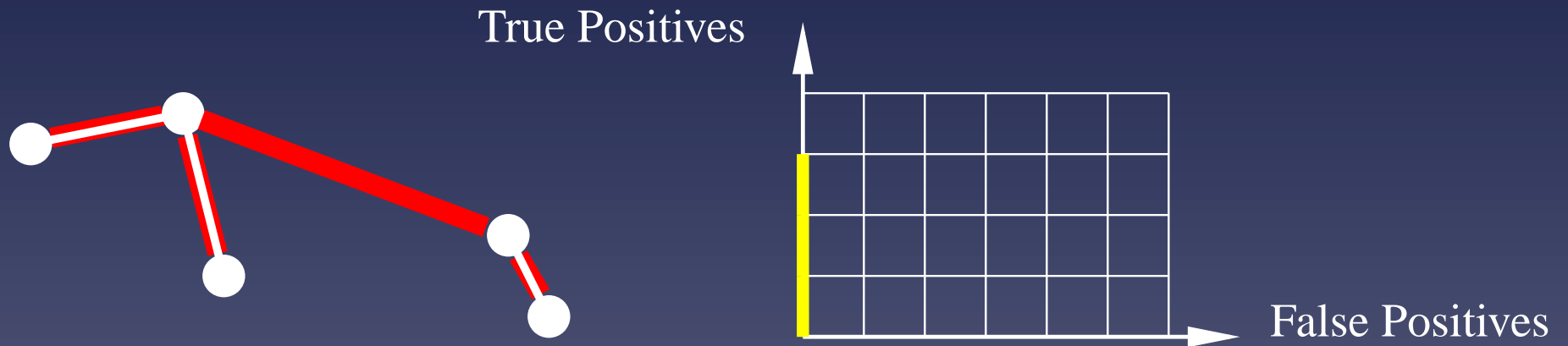
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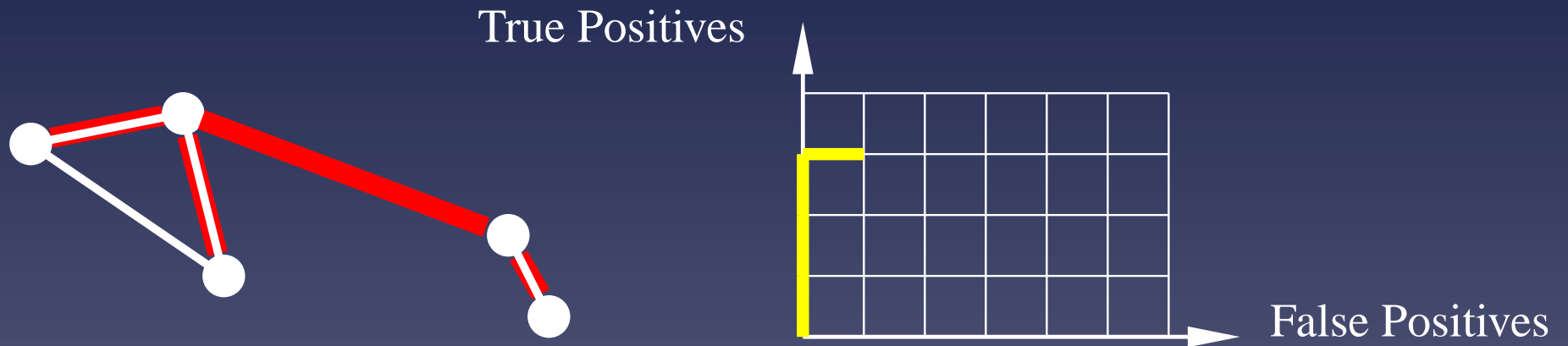
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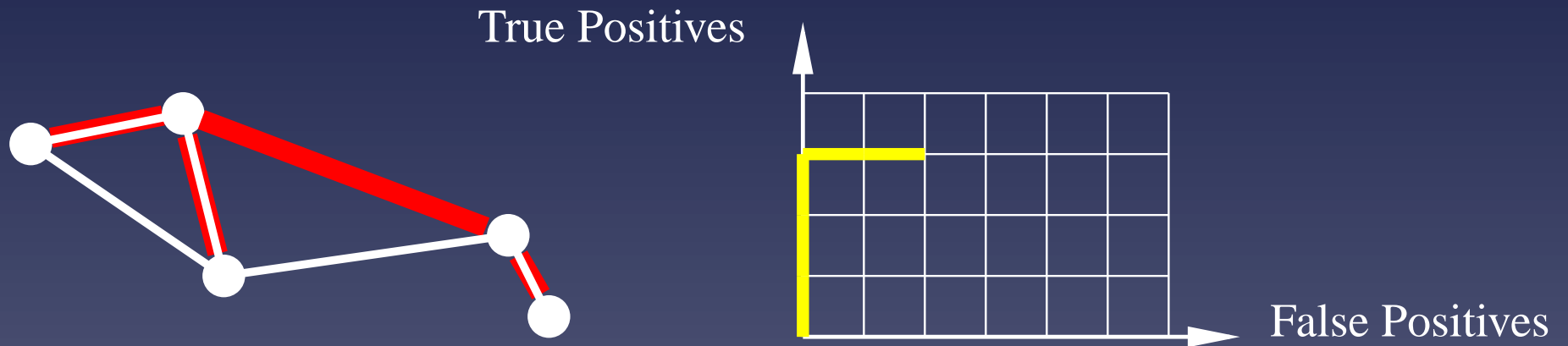
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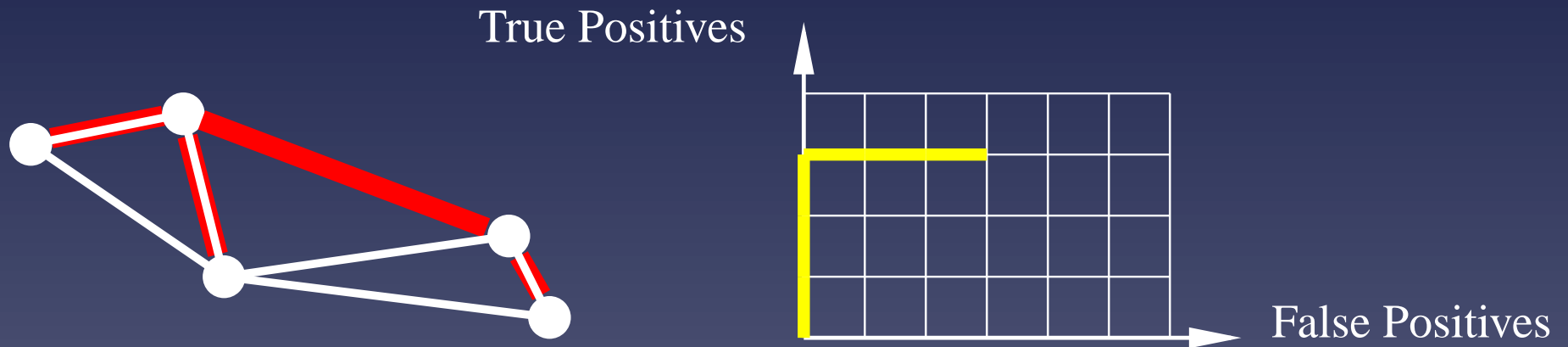
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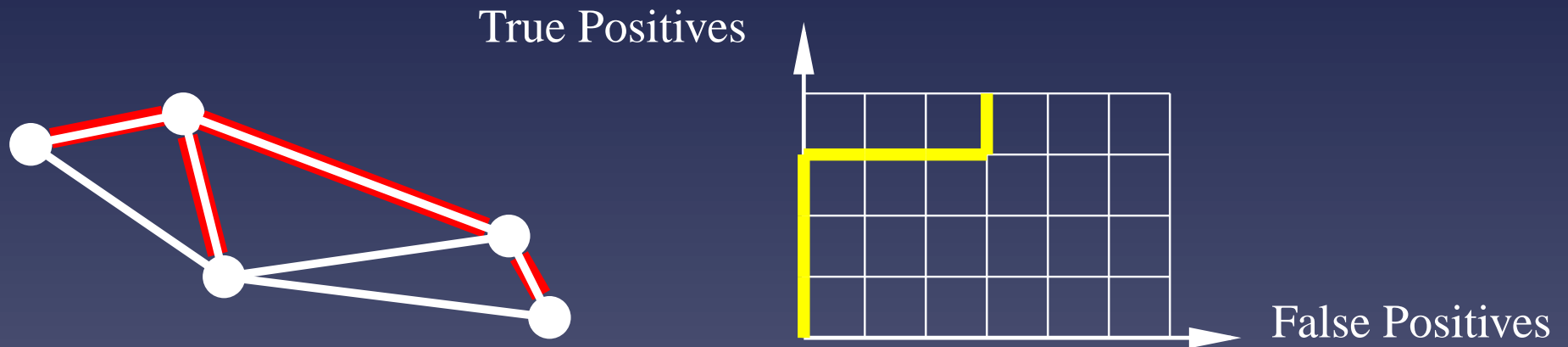
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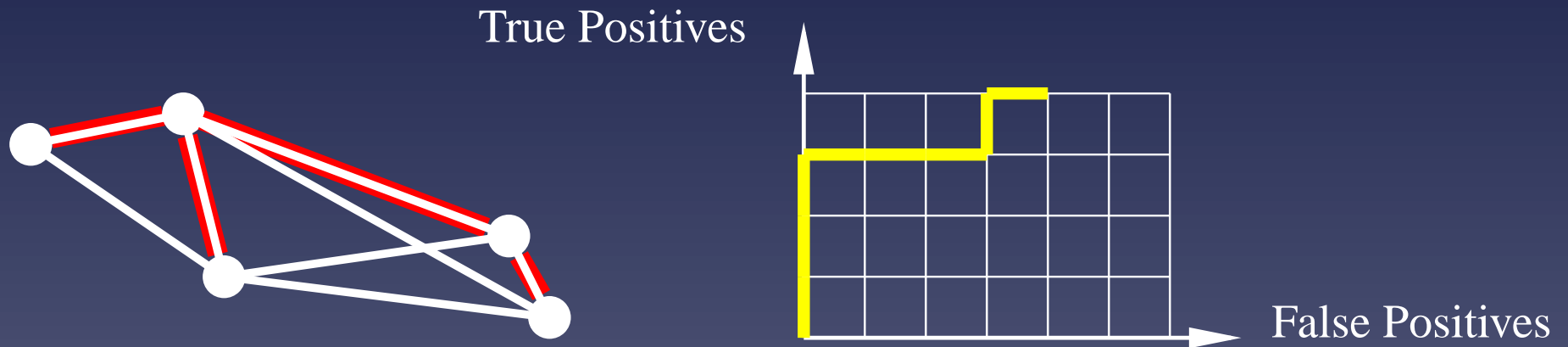
Evaluation of the performance : the ROC curve



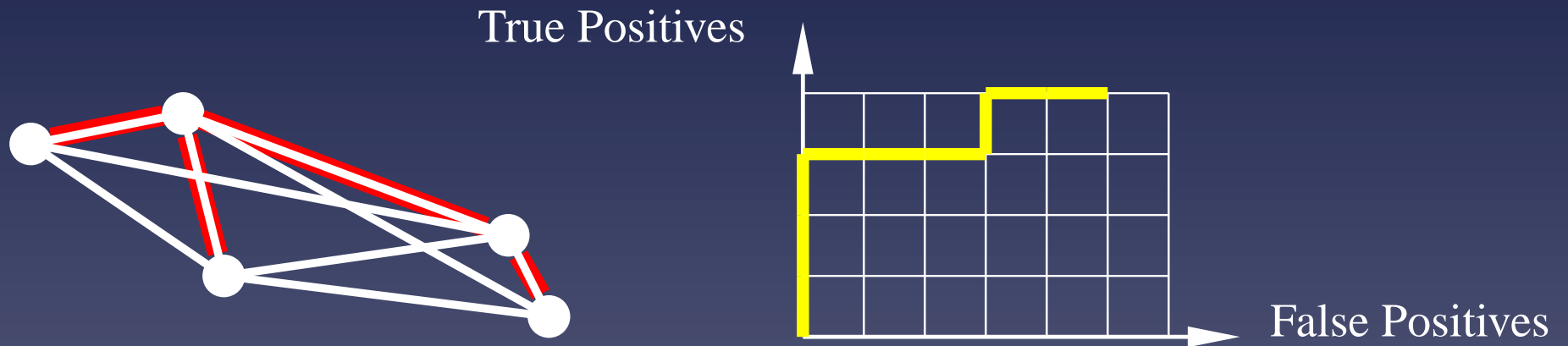
Evaluation of the performance : the ROC curve



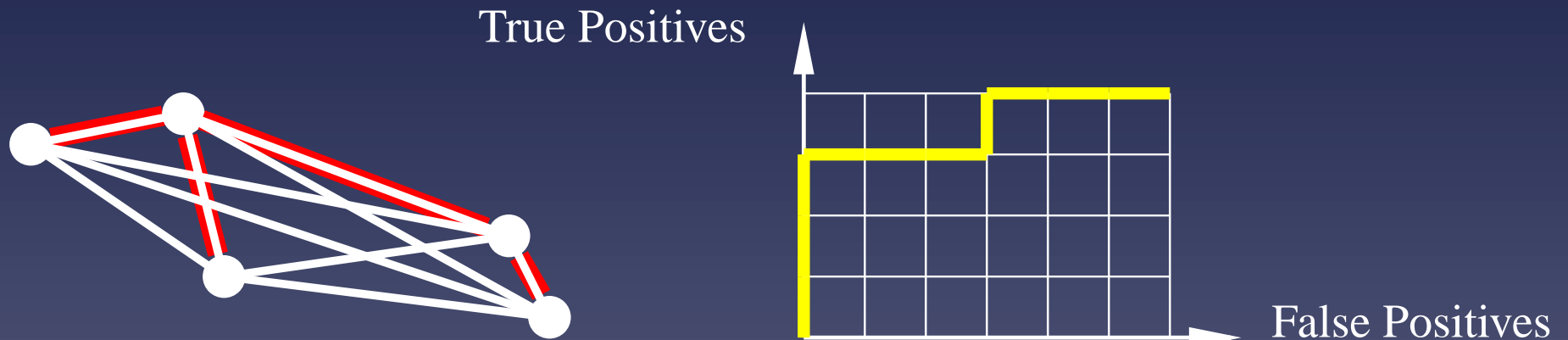
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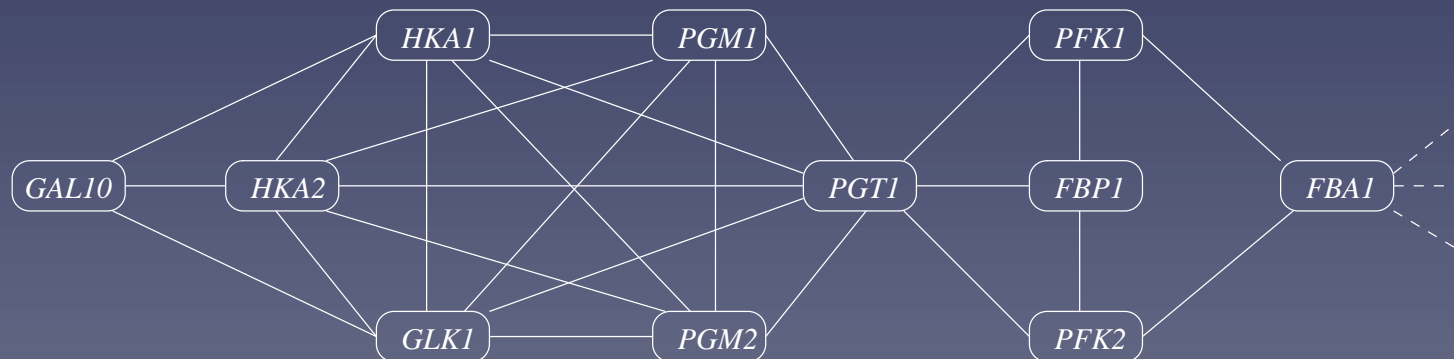
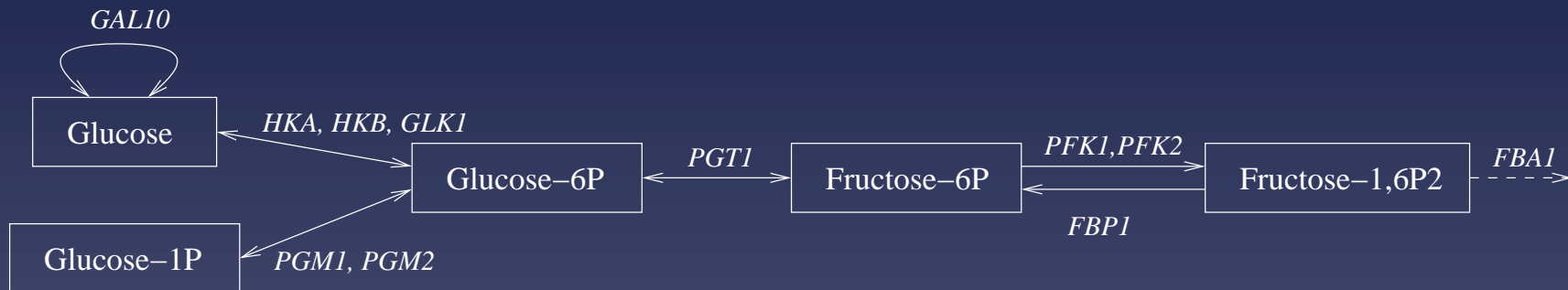


Evaluation of the performance : the ROC curve



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

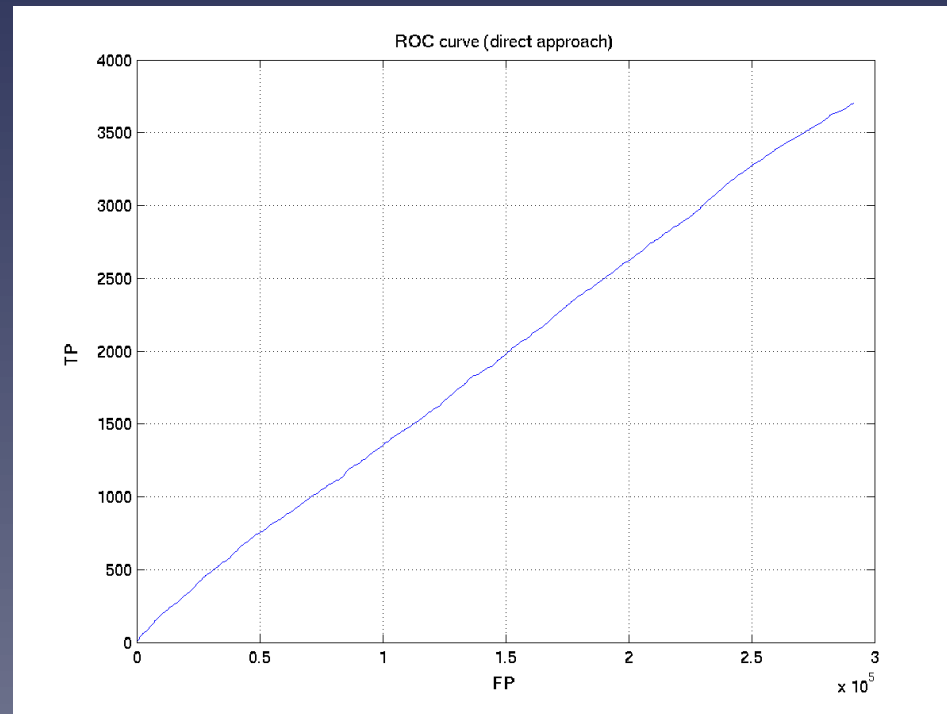
Application: the metabolic gene network



Link two genes when they can **catalyze two successive reactions**

Evaluation of the direct approach

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



Shortcuts of the direct approach

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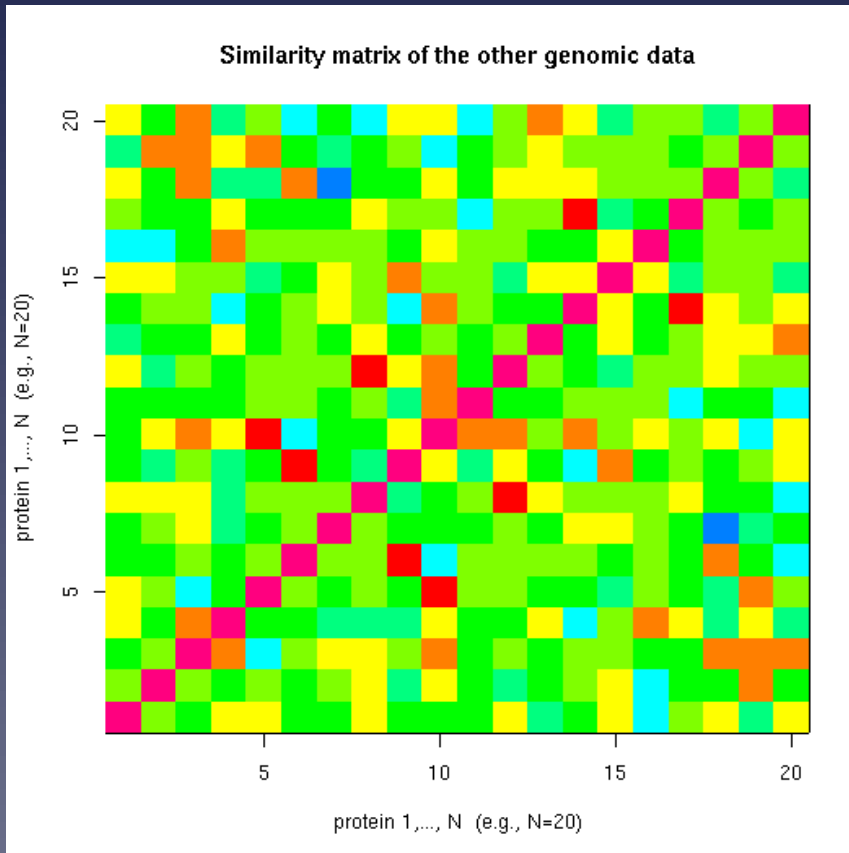
Shortcuts of the direct approach

- What **similarity measure** between profiles should be use?
- **Which network** are we expecting to recover?
- How to use **prior knowledge** about the network to be recovered?

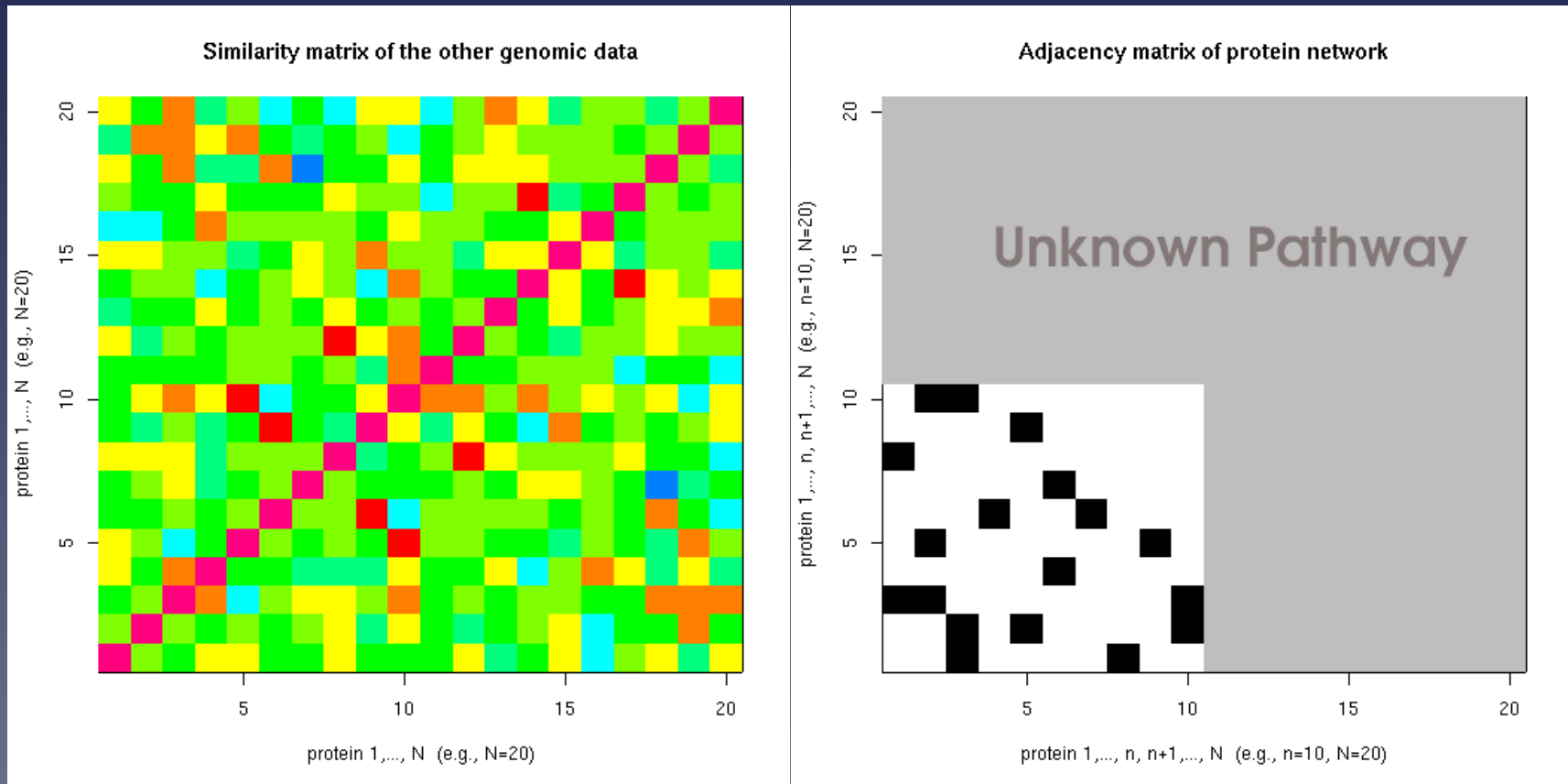
Part 2

Supervised network inference

The supervised gene inference problem



The supervised gene inference problem



The idea in a nutshell

- Use the known network to “learn” a more relevant measure of similarity

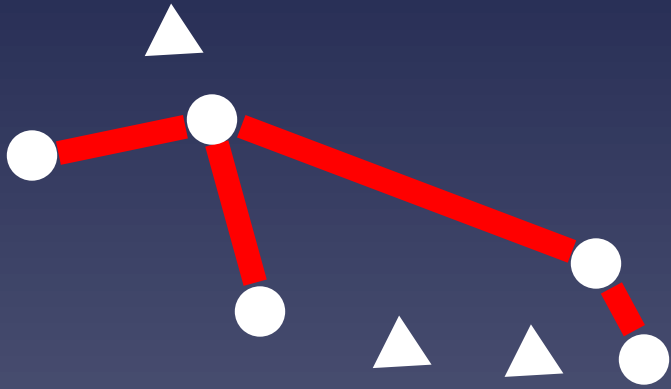
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- Use the known network to “learn” a more relevant measure of similarity
- For example, map the genes expression profiles to a different space, where the natural distance better fits the known network

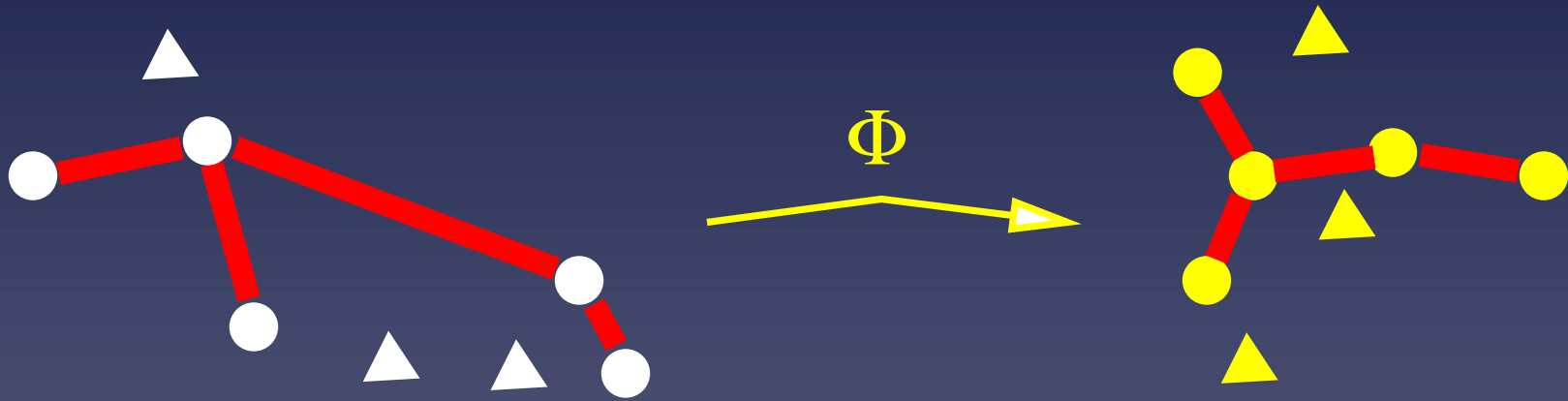
The idea in a nutshell

- Use the known network to “learn” a **more relevant measure of similarity**
- For example, map the genes expression profiles to a **different space**, where the natural distance better fits the known network
- Then apply the direct strategy **in the second space**

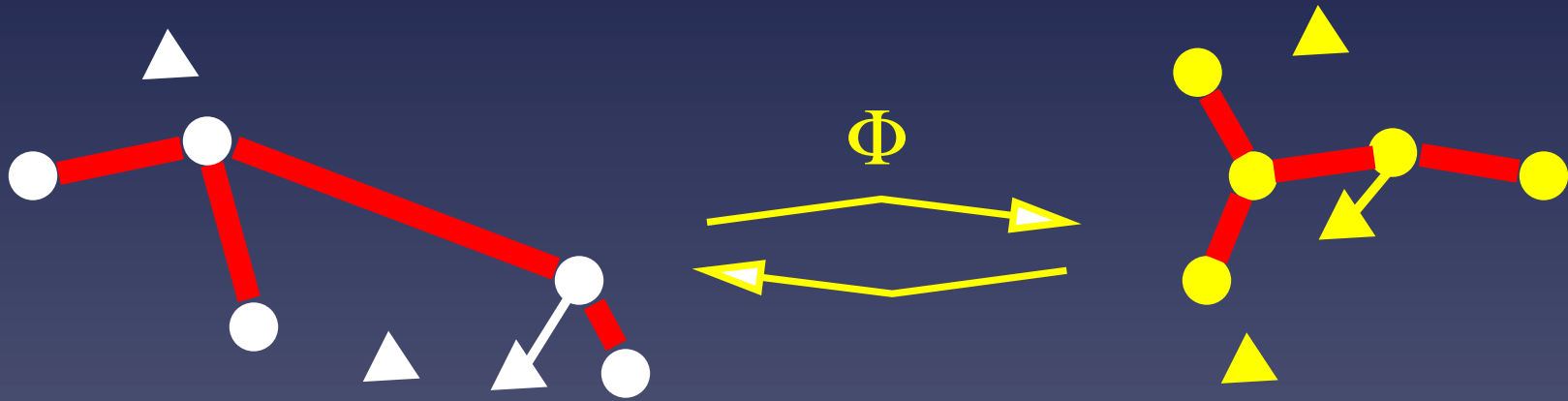
Illustration



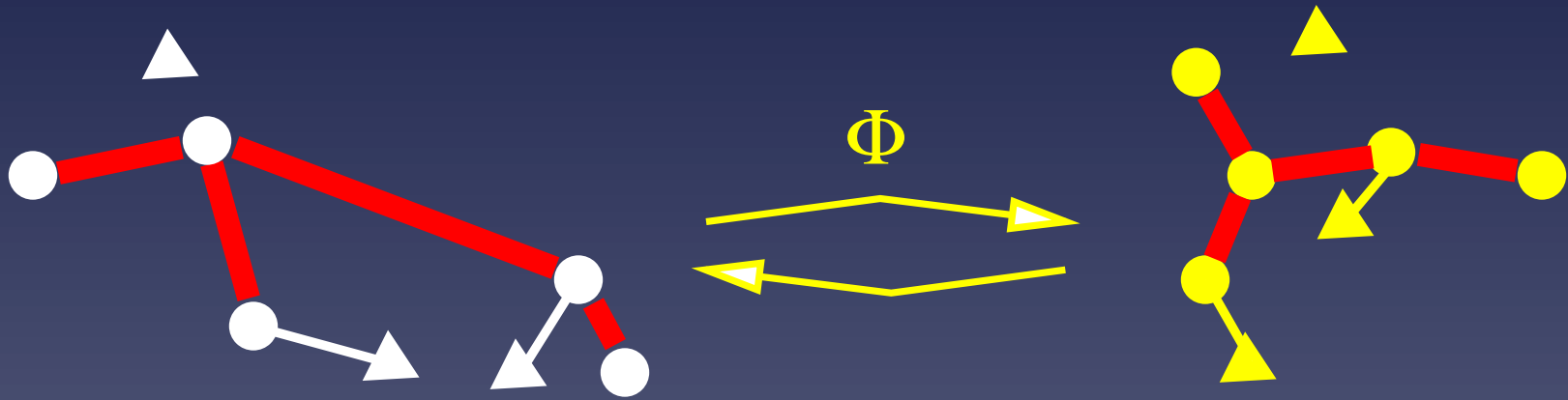
Illustration



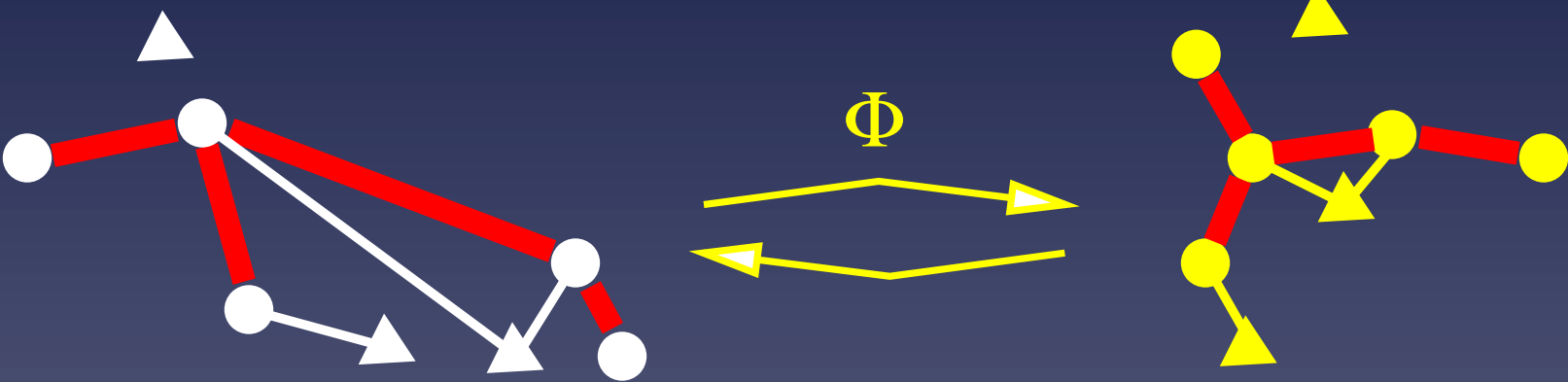
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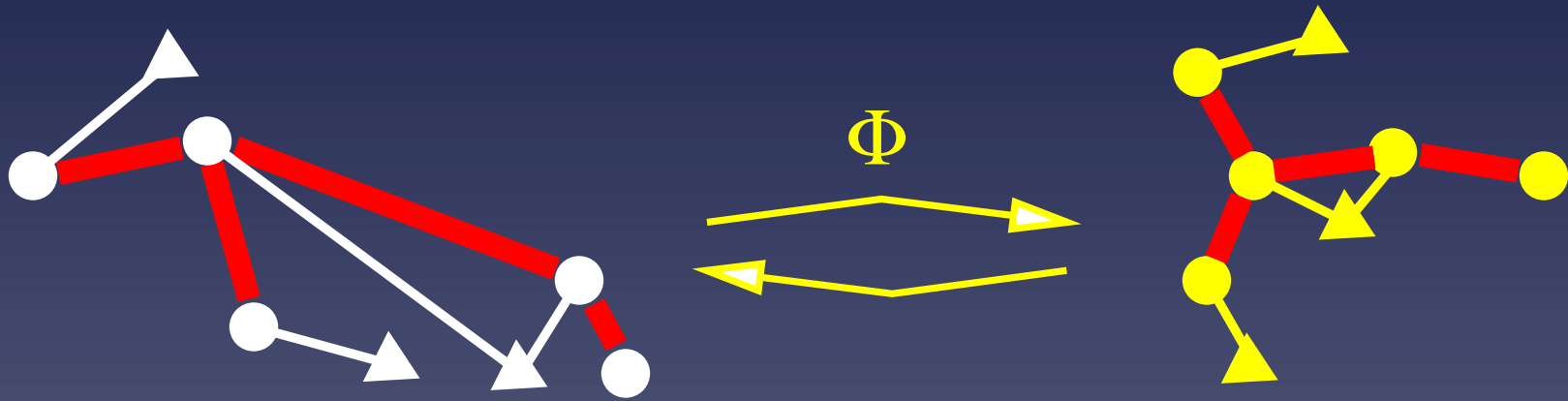
Illustration



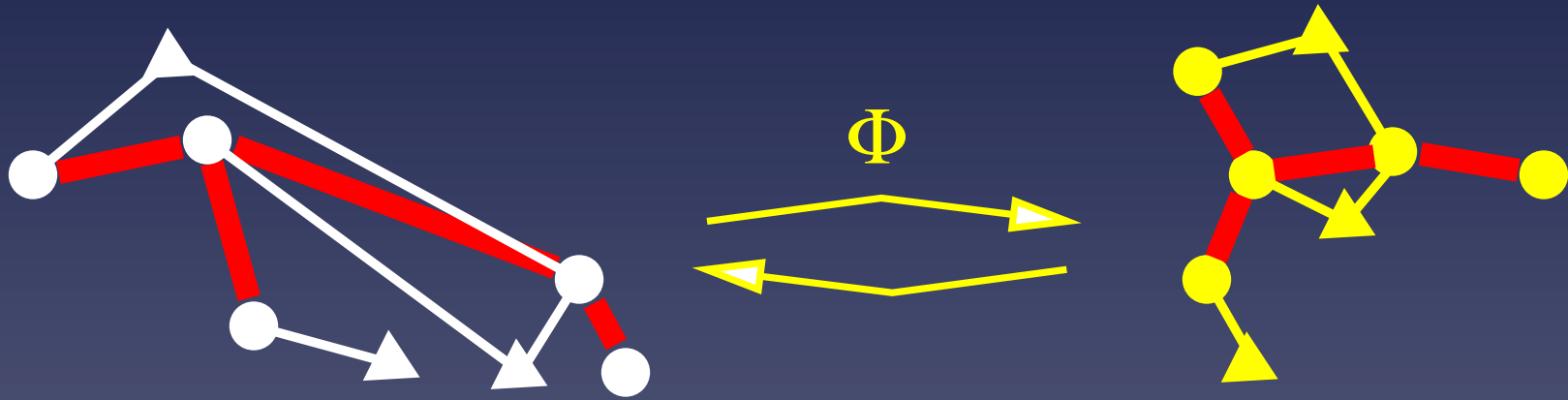
Illustration



Illustration



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Learning the mapping Φ

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

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

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

“Good” features

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

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

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- If the data are centered ($\sum_i x_i = 0$), then this is equivalent to minimizing:

$$R'(f) = \frac{\sum_{(i,j) \in E} (f(x_i) - f(x_j))^2}{\sum_{i=1}^n f(x_i)^2}.$$

Regularization

For statistical reasons (particularly in large dimension), it is safer to minimize:

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

Influence of λ

- $\lambda \rightarrow +\infty$: PCA
 - ★ Useful for noisy, high-dimensional data.
 - ★ Used in spectral clustering. The graph does not play any role (unsupervised)
- $\lambda \rightarrow 0$: 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:

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

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- Each features satisfies $w = \sum_i \alpha_i x_i$ (Representer theorem)

Solving the problem

- The problem can then be rewritten:

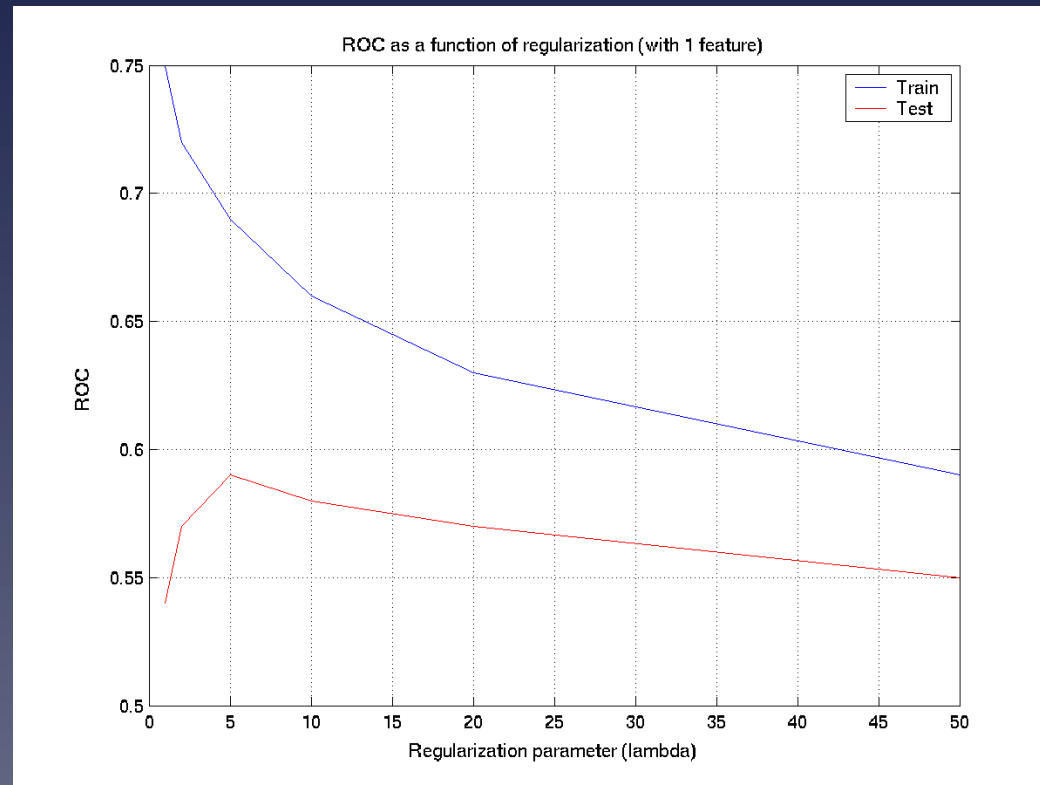
$$\alpha_i = \arg \min_{\alpha \in \mathbb{R}^n, \alpha K_V \alpha_1 = \dots = \alpha K_V \alpha_{i-1} = 0} \left\{ \frac{\alpha^\top K_V L K_V \alpha + \lambda \alpha^\top K_V \alpha}{\alpha^\top K_V^2 \alpha} \right\}$$

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

- It is equivalent to solving the generalized eigenvalue problem:

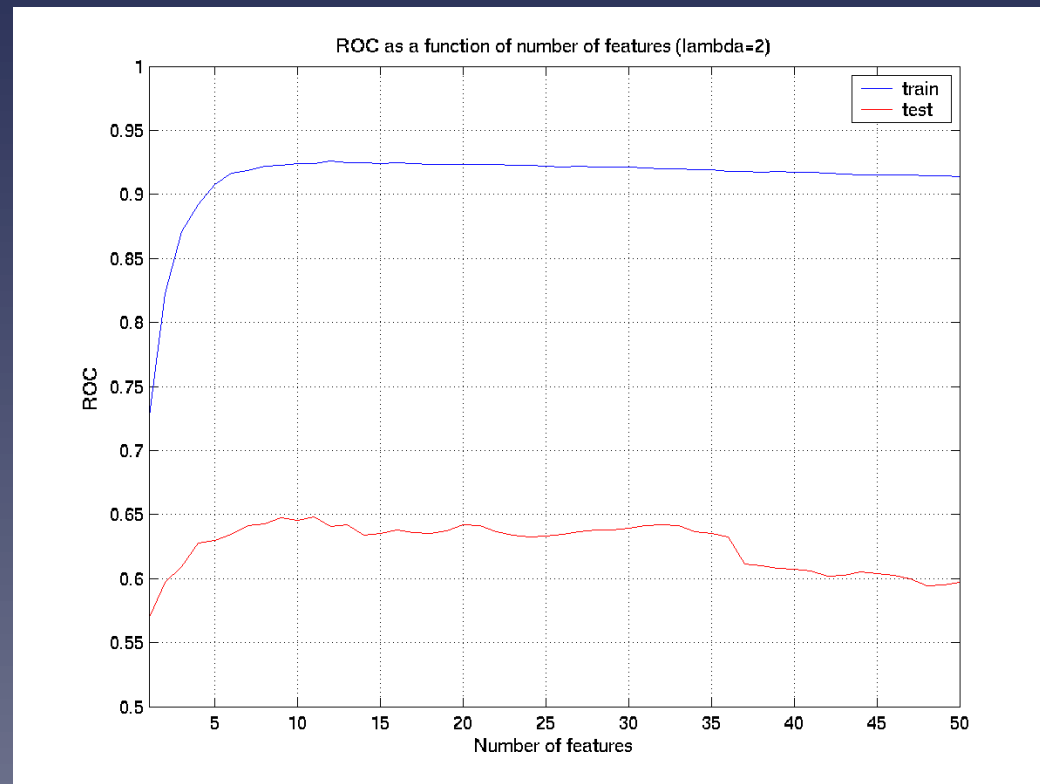
$$(LK_V + \lambda I)\alpha = \mu K_V \alpha.$$

Evaluation of the supervised approach: effect of λ



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

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



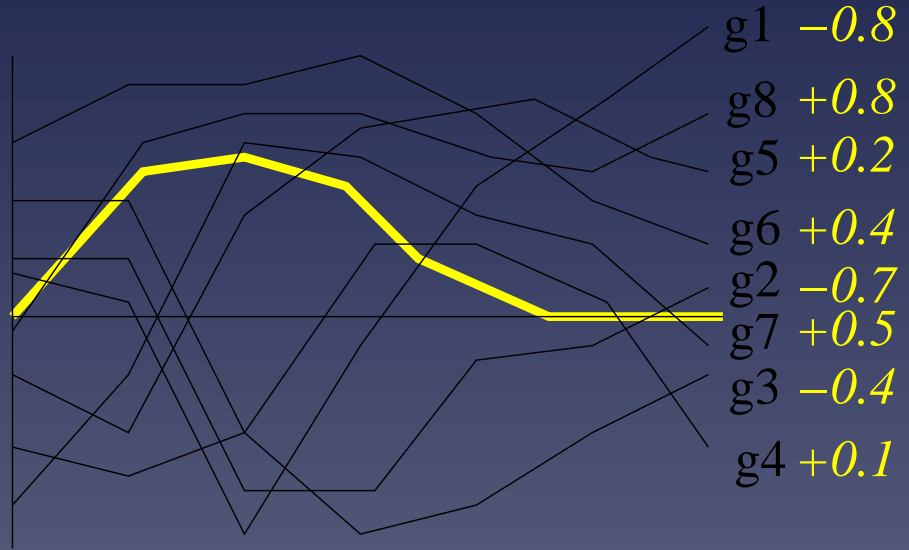
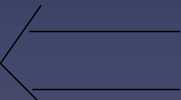
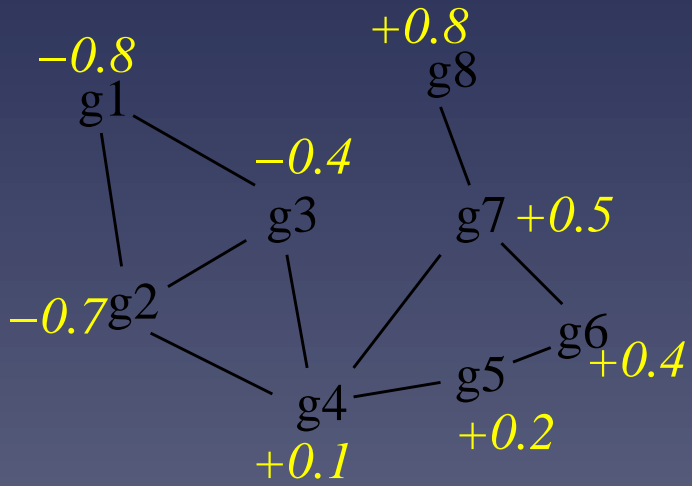
Part 3

Extraction of pathway activity

The idea

- The previous approach is a way to extract features from gene expression data: $f(x) = w^T x$.
- 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**

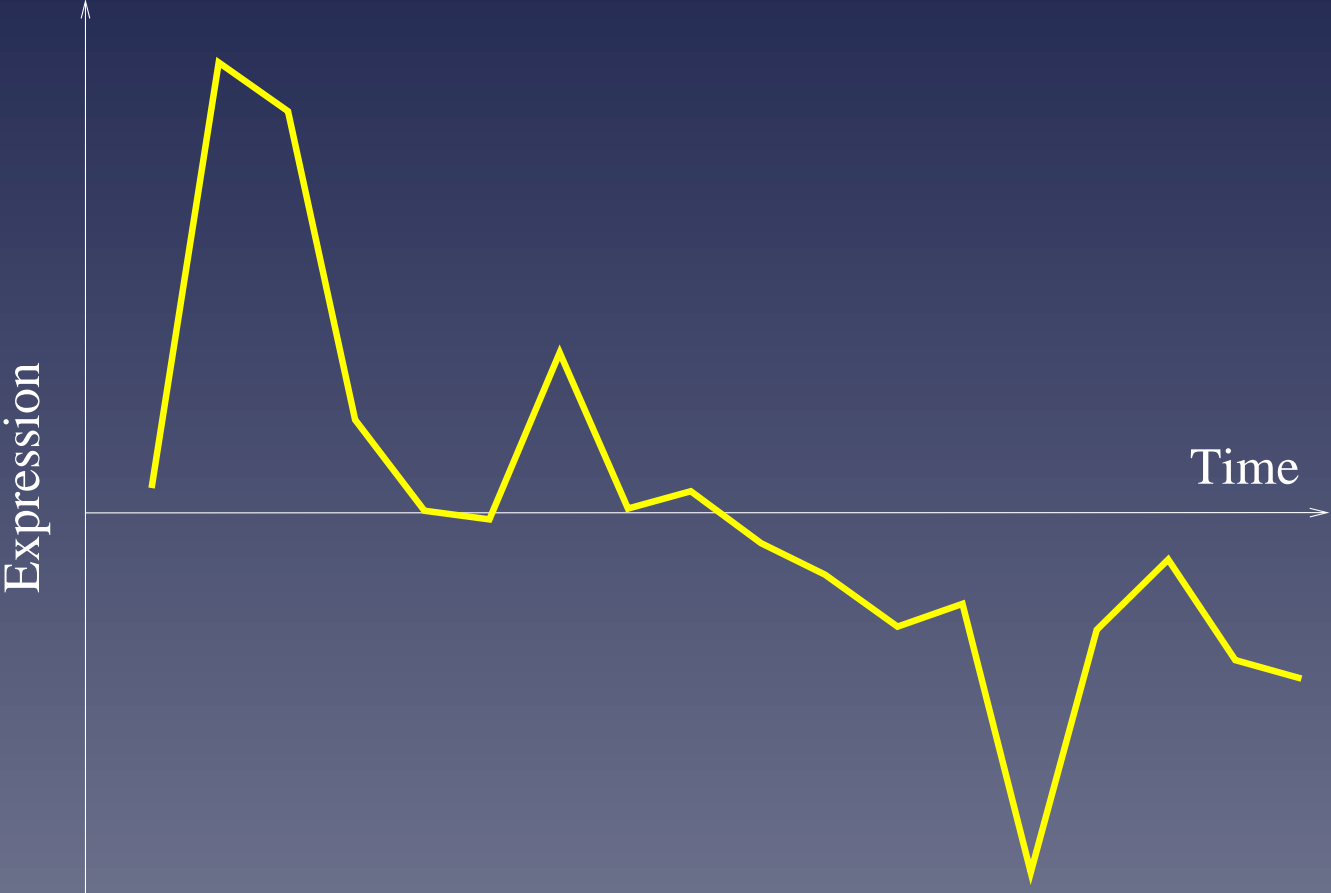
Illustration



Experiment

- **Gene network:** two genes are linked if they 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

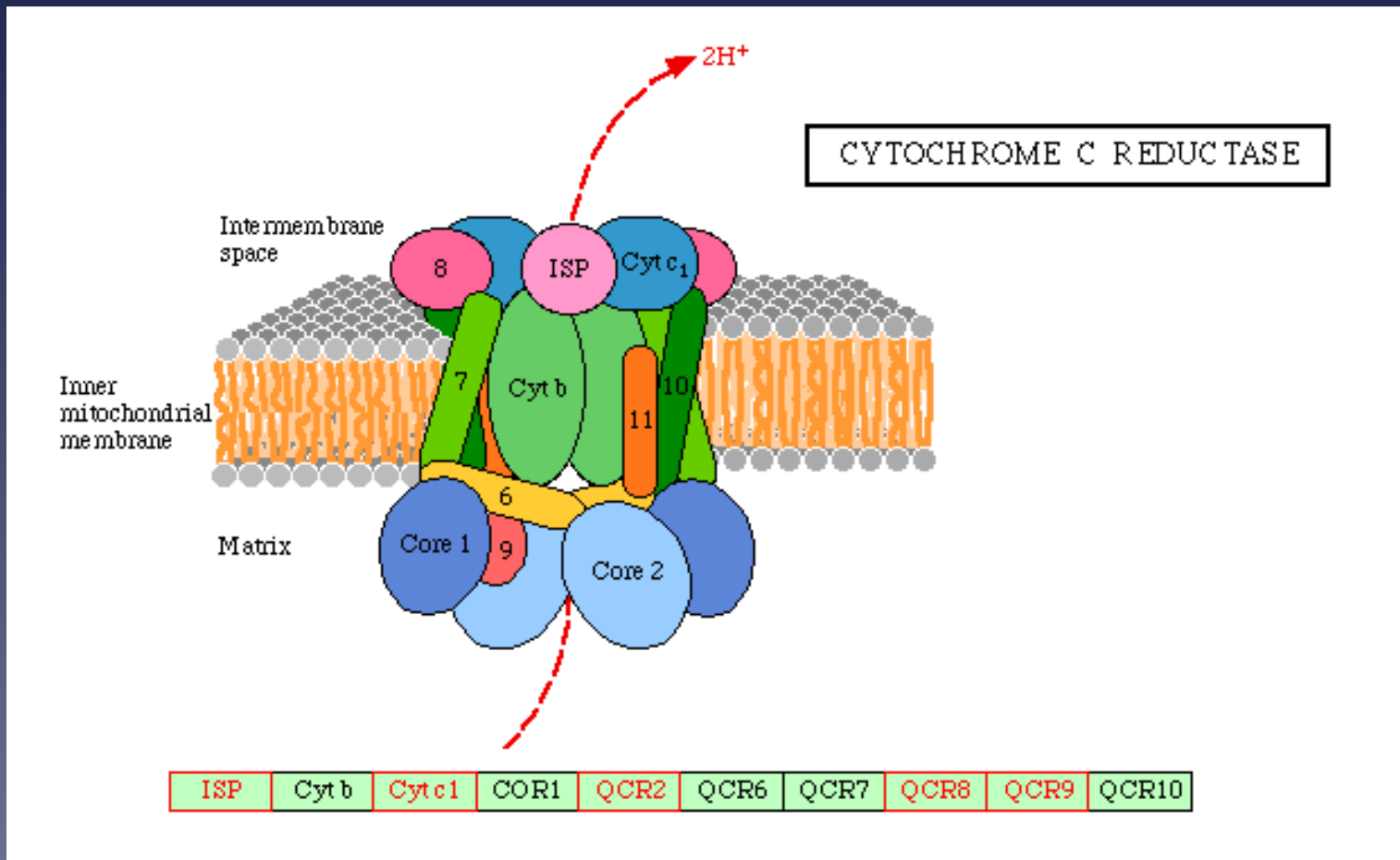


Related metabolic pathways

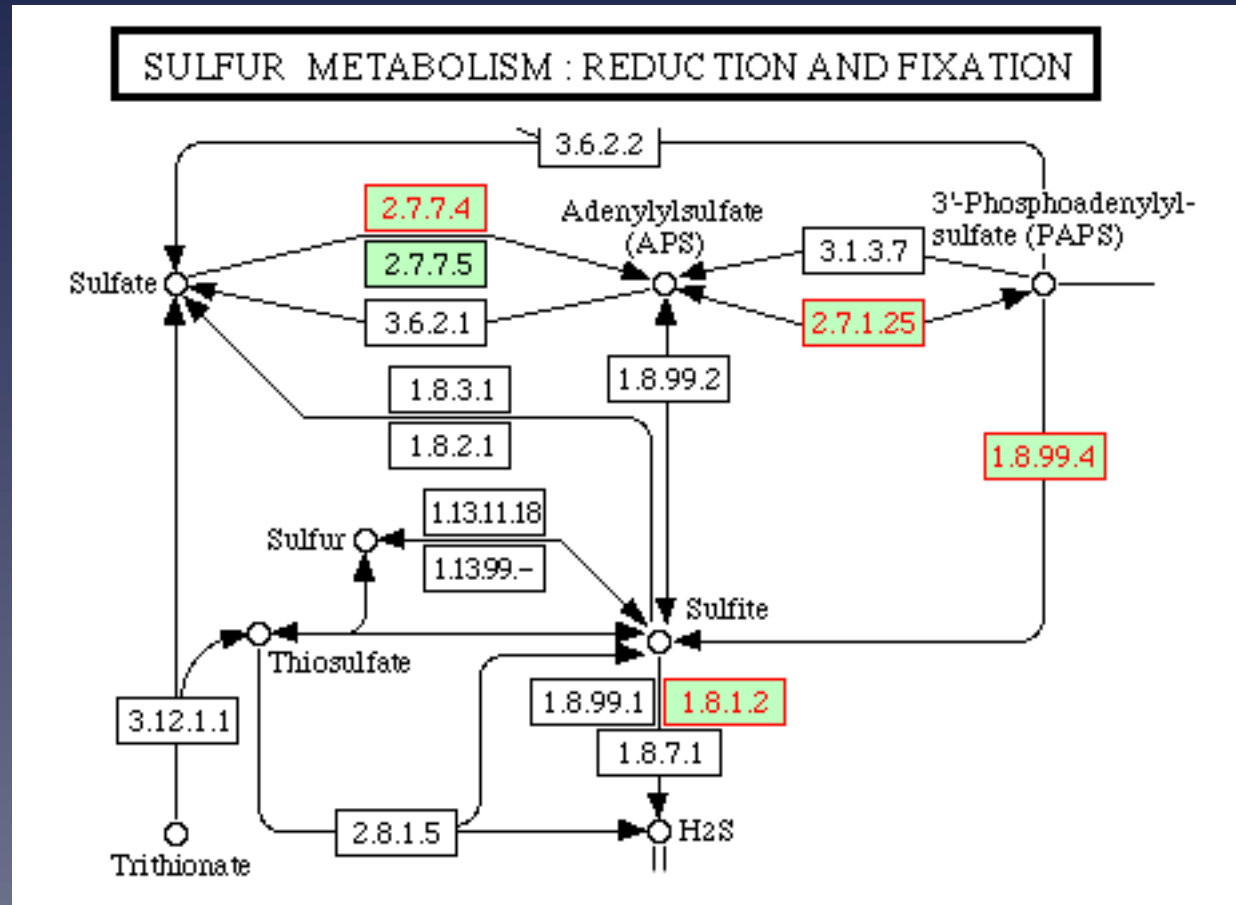
50 genes with highest $s_2 - s_1$ belong to:

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

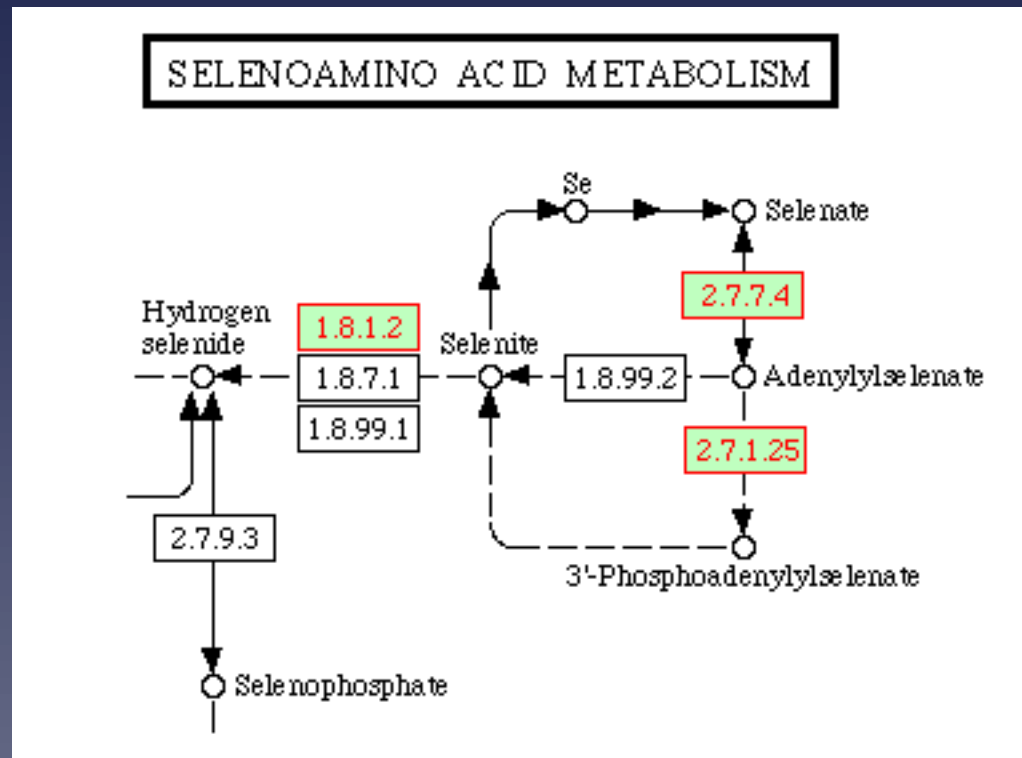
Related genes



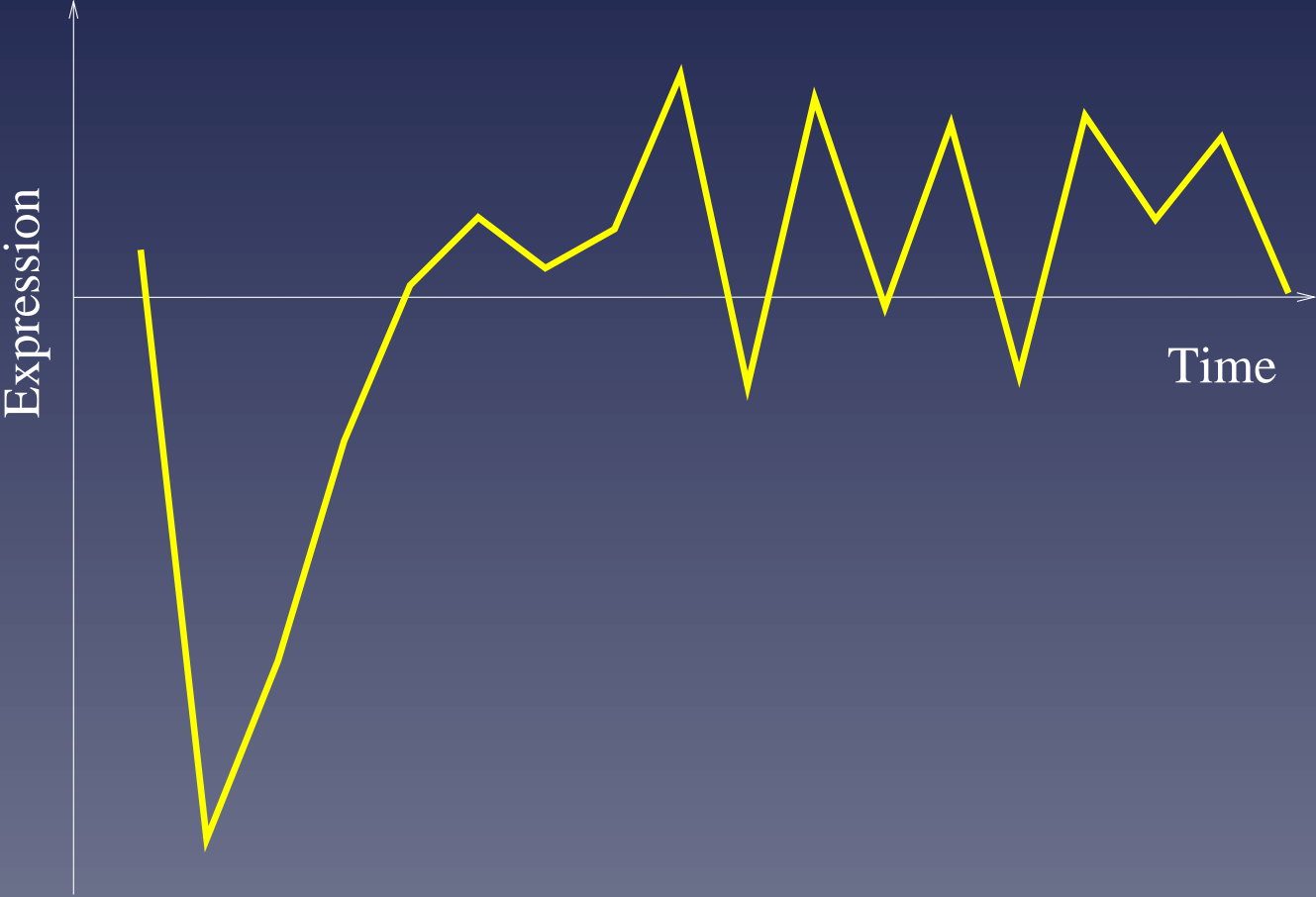
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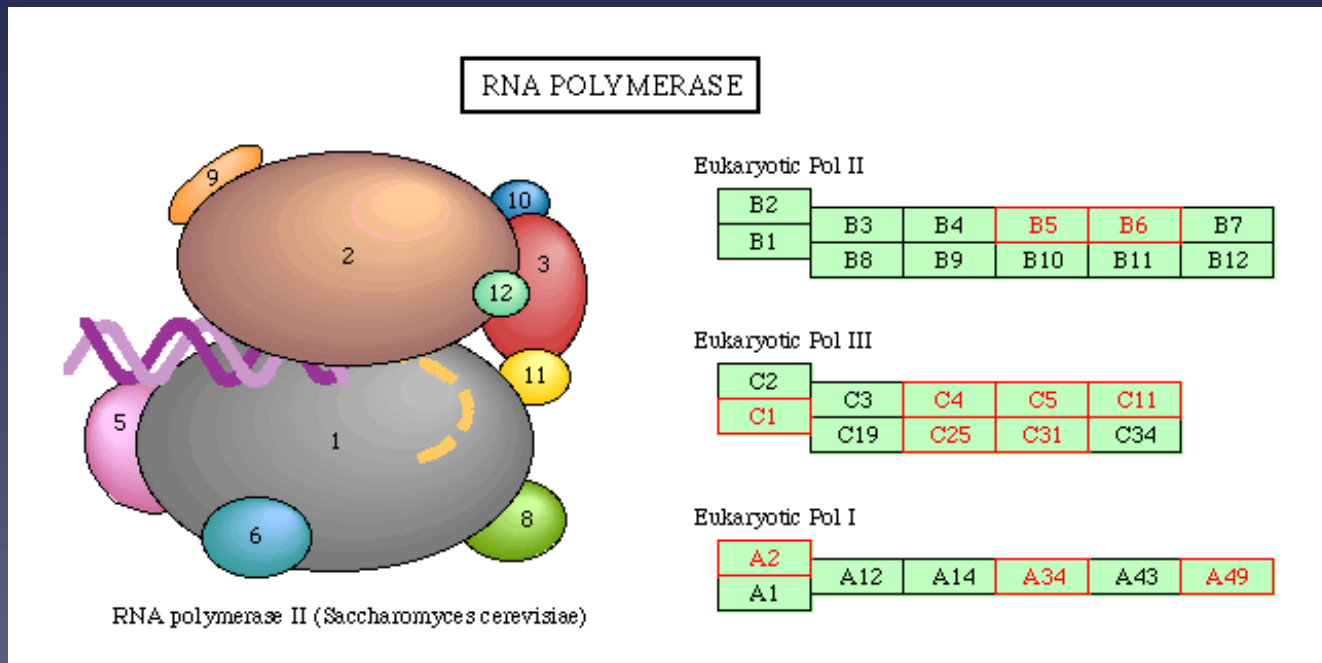
Opposite pattern



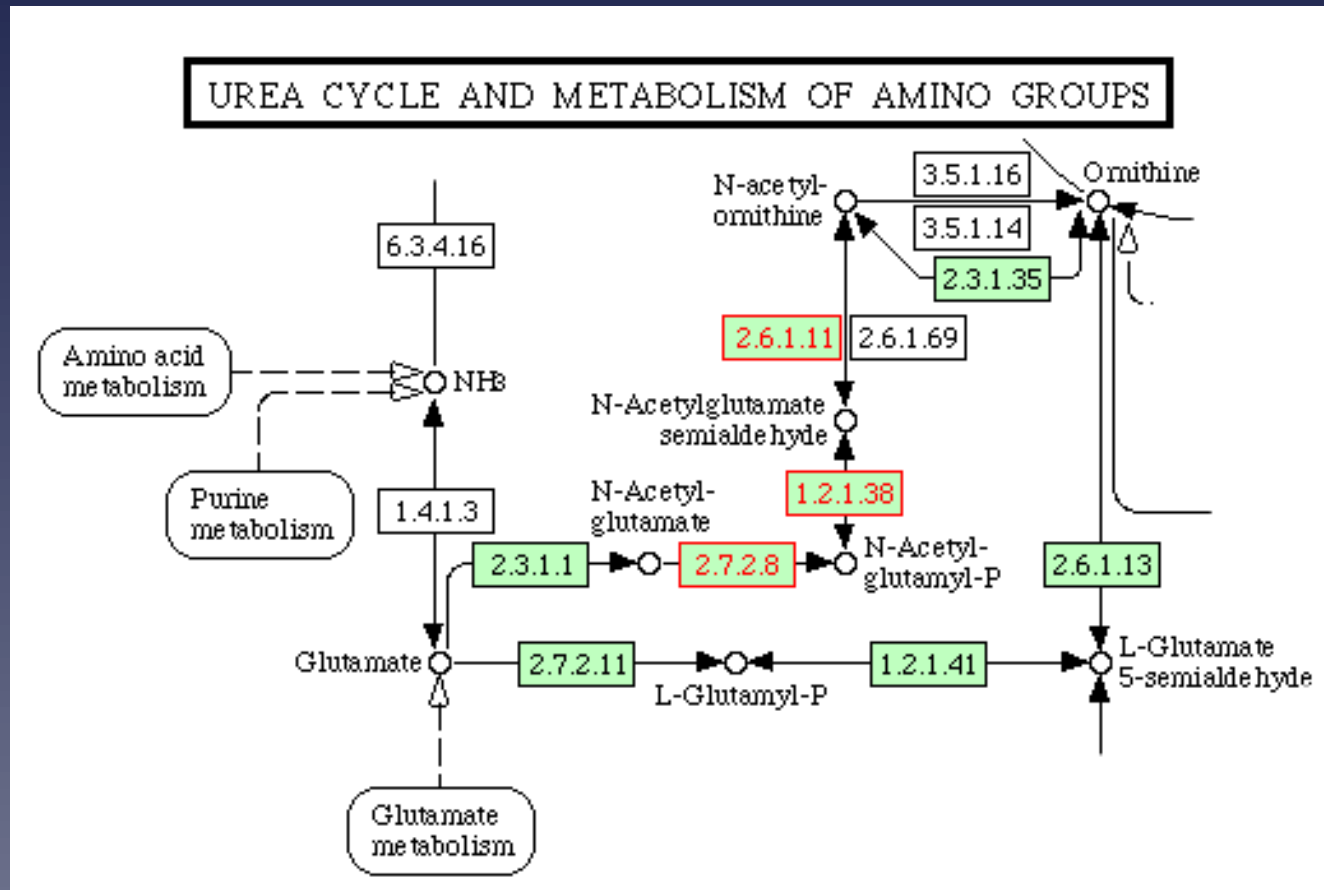
Related genes

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

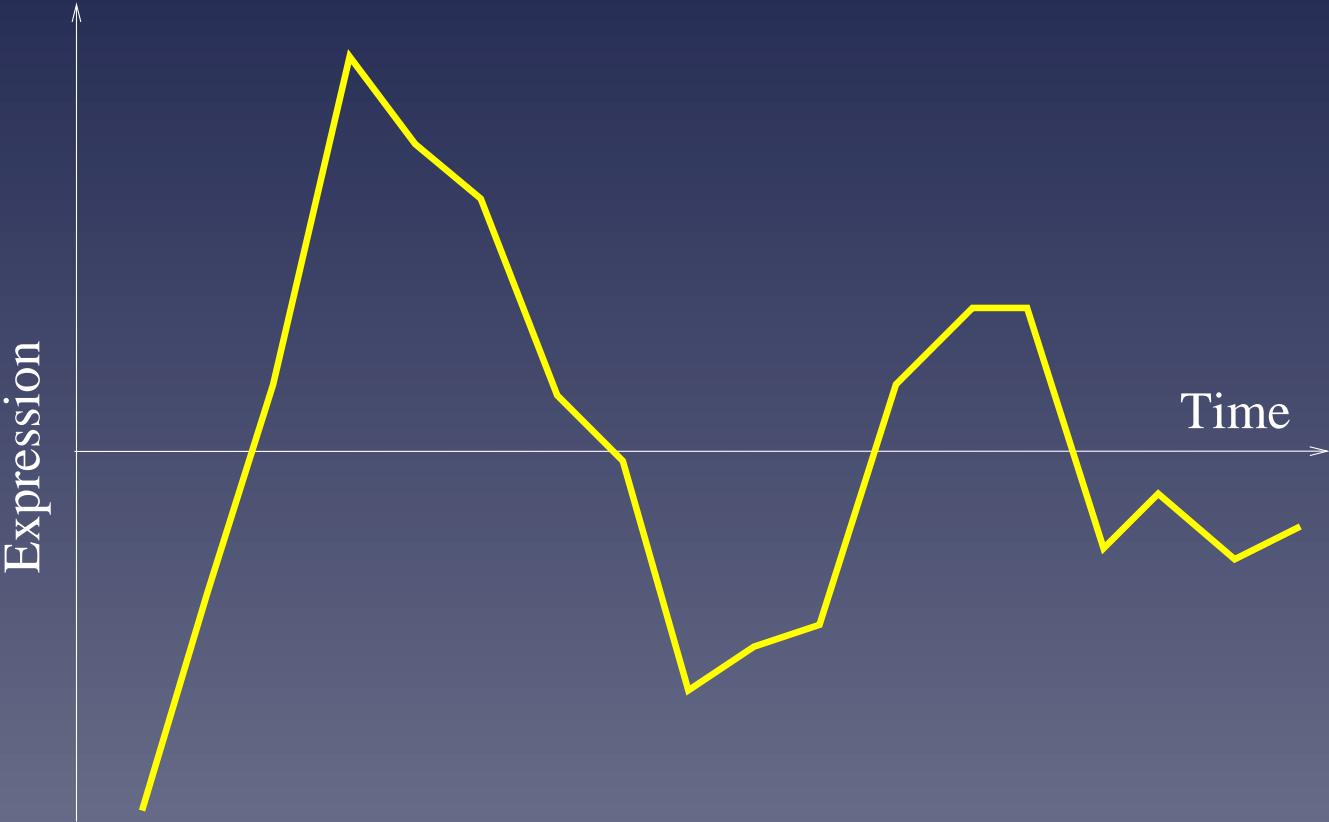
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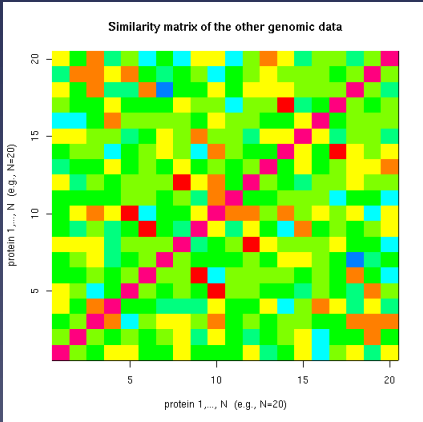
Second pattern



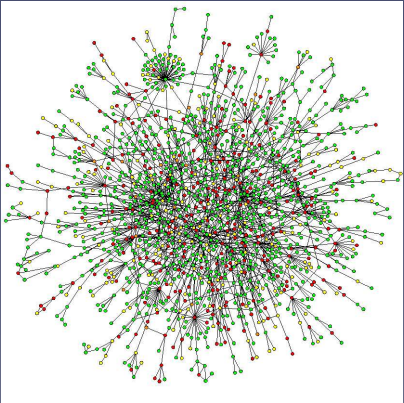
Part 4

Learning from several
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Summary of the process



Features



The “kernel trick”

- The matrix of similarity is $K_{i,j} = x_i^\top x_j$

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- The matrix of similarity is $K_{i,j} = x_i^\top x_j$
- However, more general measures are allowed: they simply must be **symetric positive definite**
- This enables **nonlinear** features, as well as features from other types of data, **as soon as a symetric p.d. function $K(x, y)$ is defined**

Kernels

Several kernels have been developed recently:

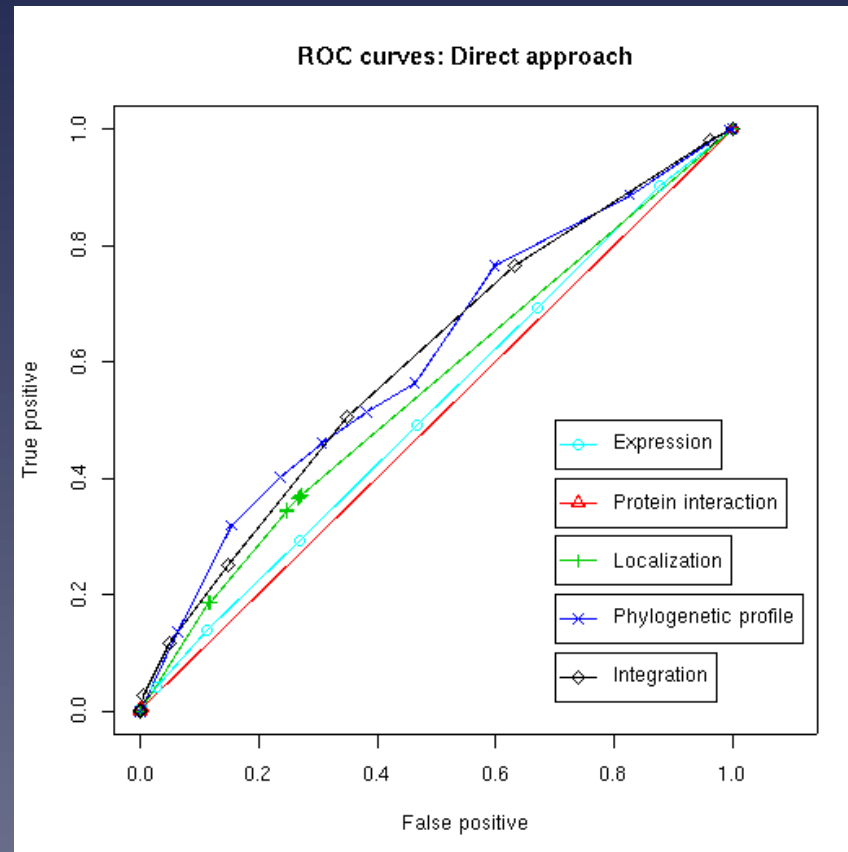
- for phylogenetic profiles (JPV. 2004)
- for gene sequences (Leslie et al. 2003, Saigo et al. 2004, ...)
- for nodes in a network (Kondor et al. 2000)

Learning from heterogeneous data

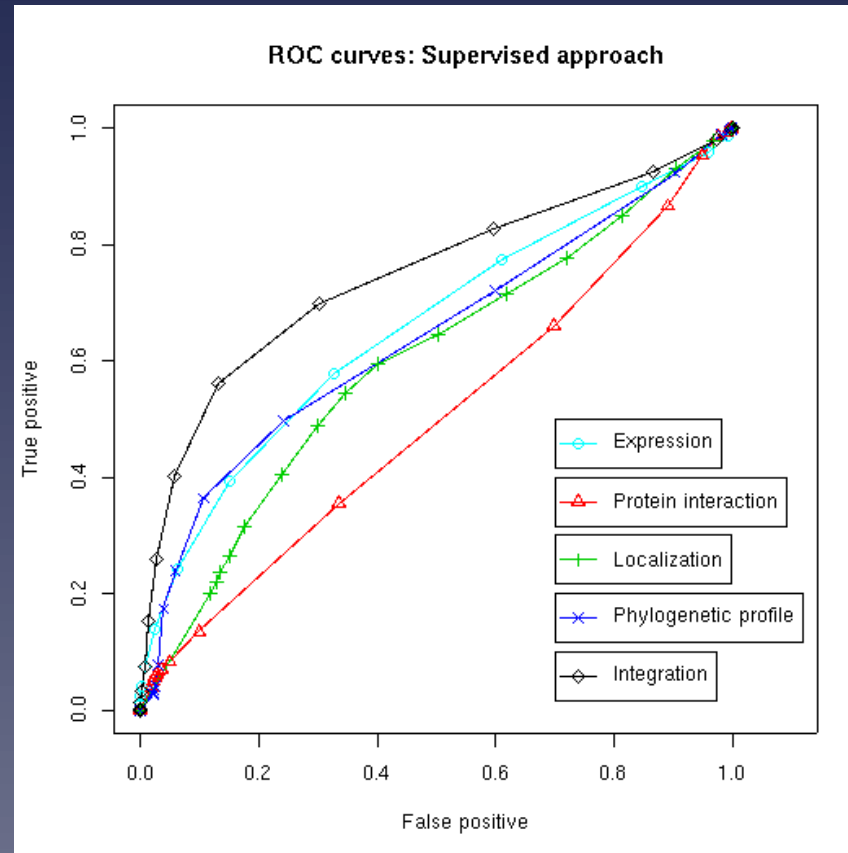
- Suppose several data are available about the genes, e.g., expression, localization, structure, predicted interaction etc...
- Each data can be represented by a **positive definite** similarity matrix K_1, \dots, K_p called **kernels**
- Kernel can be combined by various operations, e.g., addition:

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

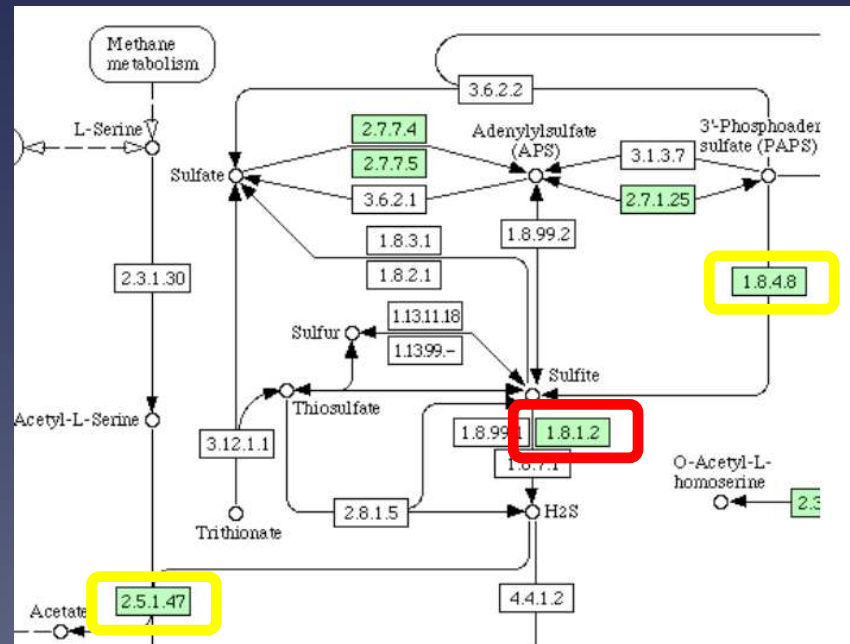
Learning from heterogeneous data (unsupervised)



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

- A new approach to **feature extractions** and **supervised network inference**, many possible variants and extensions
- Straightforward generalization to **any network** (e.g., interactome): **the same data can be used to infer different networks**
- Currently tested on **characterization of tumor cells** (with Institut Curie) and **metabolism of *P. falciparum*** (with Institut Pasteur).