Kernel methods in computational and systems biology

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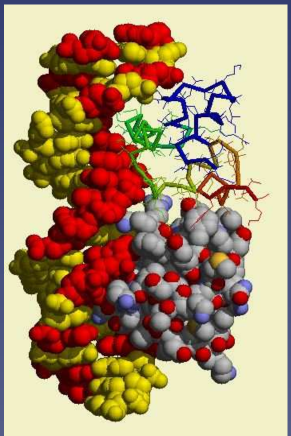
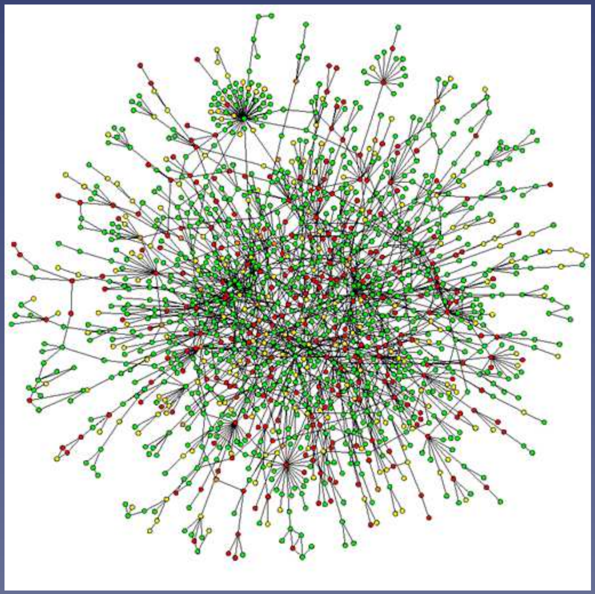
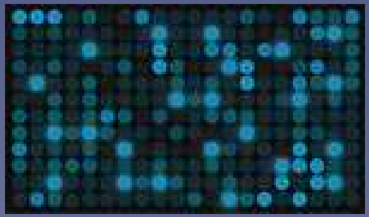
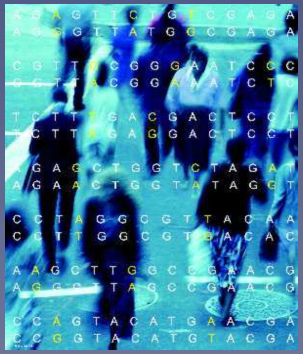
The age of data in biology









And many more...

Motivations

Develop a theoretical framework and algorithms in order to

- represent and integrate biological data
- model and conceptualize living systems
- infer properties of living systems

Biological data are often

- structured and heterogeneous : sequences, 3D structures, graphs, networks, expression profiles, phylogenetic trees, SNP, ...

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- structured and heterogeneous : sequences, 3D structures, graphs, networks, expression profiles, phylogenetic trees, SNP, ...
- in large quantities $(10^6$ gene sequences)
- in large dimension $(10^5 \sim 10^6$ spots on DNA chips)

A possible solution: kernel methods

Kernel methods (partially) overcome these issues:

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- Kernels for structured data
- Operations on kernels to integrate heterogeneous data
- Regularisation in order to deal with large dimensions
- Statistical framework for the processing of large datasets

What is a kernel?

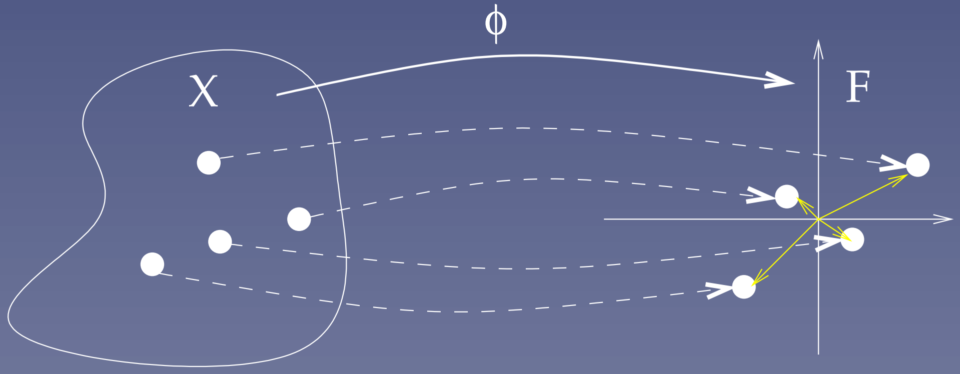
- Let $\mathcal{X}$ be a set to be analyzed (e.g., gene sequences or protein structures)
- A kernel on $\mathcal{X}$ is a measure of similarity $K(x, x')$ between elements of $\mathcal{X}$ (that is symmetric and positive definite).
- Example: a kernel for finite-length sequences

$$K(aatcga, cgaagtagccc) = 0.4$$

Geometric interpretation as inner product

If K is a kernel on $\mathcal{X}$, then $\mathcal{X}$ can be mapped to a Hilbert space $\mathcal{H}$ through $\Phi : \mathcal{X} \rightarrow \mathcal{H}$ in such a way that:

$$\forall \left(\mathbf{x}, \mathbf{x}'\right) \in \mathcal{X}^2, \quad K\left(\mathbf{x}, \mathbf{x}'\right) = \left\langle \Phi\left(\mathbf{x}\right), \Phi\left(\mathbf{x}'\right)\right\rangle_{\mathcal{H}}.$$



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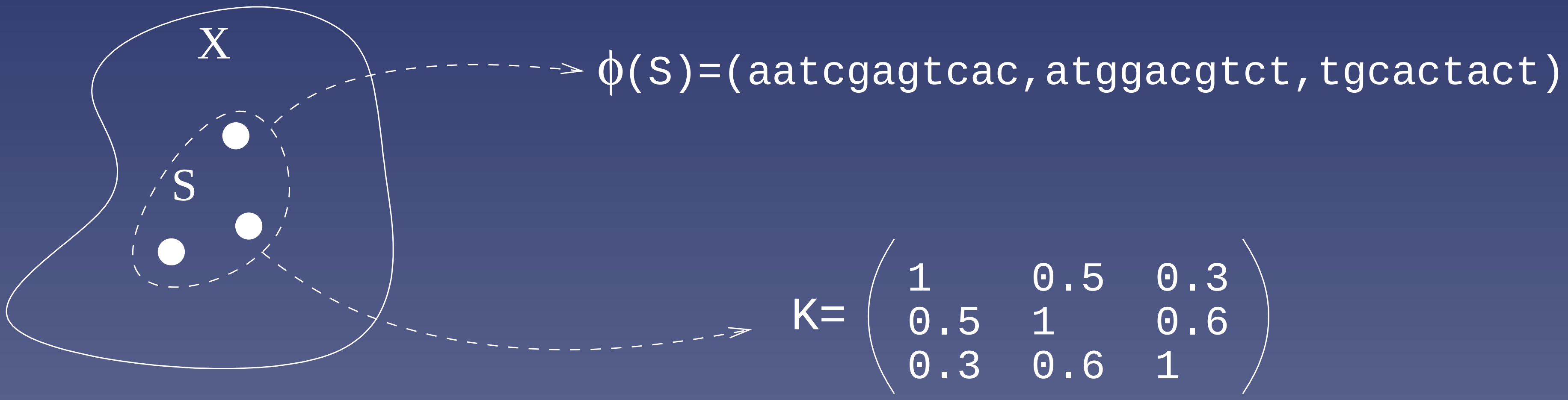
- "Simples kernels" can correspond to "complex" mappings
- Objets are not necessarily vectors!

Data representation with kernels



ϕ(S)=(aatcgagtcac,atggacgtct,tgcactact)

$$K=\begin{pmatrix} 1 & 0.5 & 0.3 \\ 0.5 & 1 & 0.6 \\ 0.3 & 0.6 & 1 \end{pmatrix}$$

- Each data set is a matrix
- Kernel methods process these matrices

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- Local alignment kernel for sequences (*Bioinformatics 04*)
- Kernel for sets of points (*NIPS'04*)

Applications

- Signal peptide detection in protein sequences

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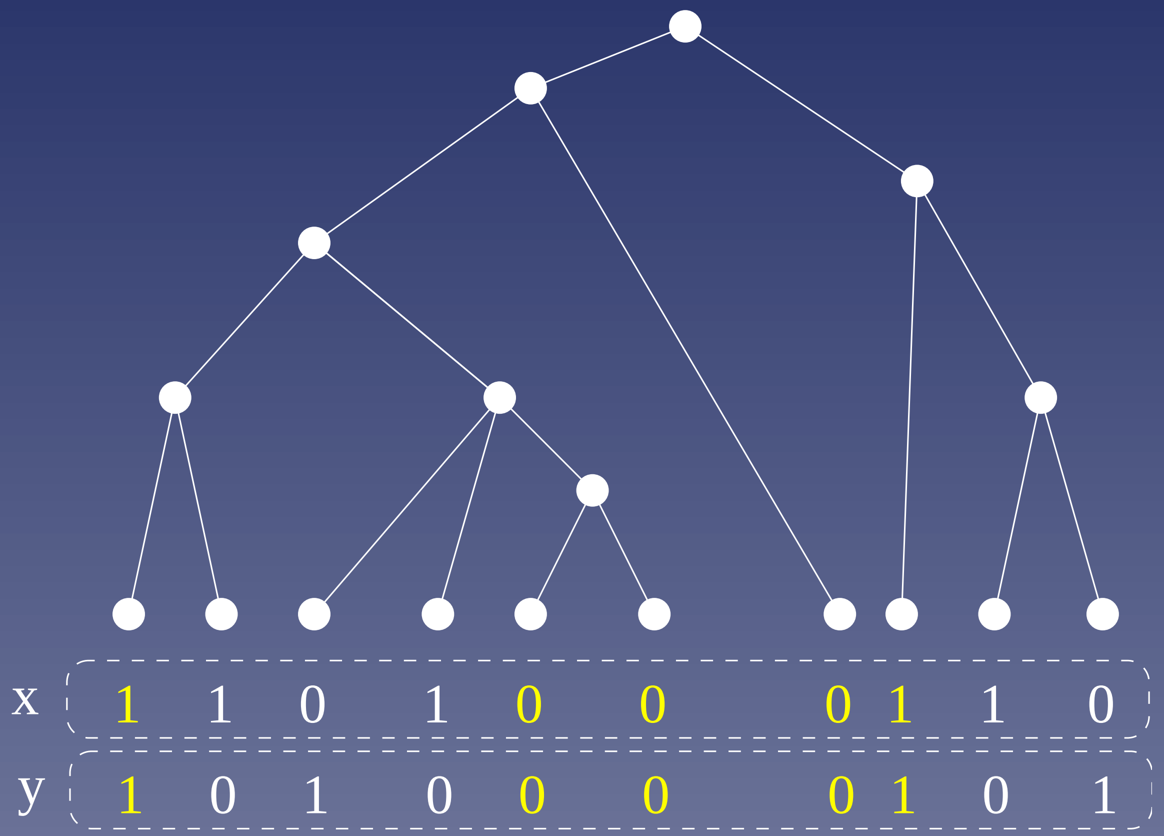
- Gene function prediction
- Virtual screening of small molecules
- Homology detection between gene sequences

Example 1: Phylogenetic profiles (*ISMB 02*)

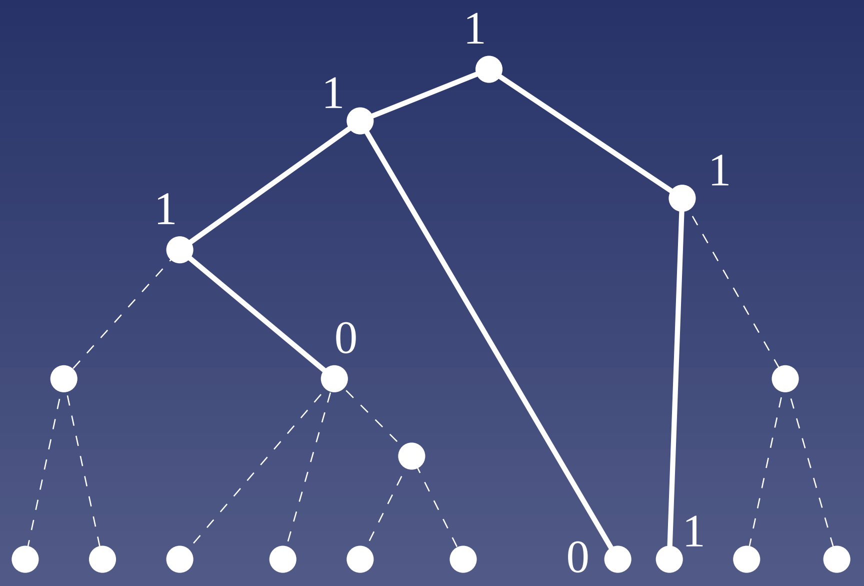
Gene	human	yeast	. . .	HIV	E. coli
YAL001C	1	1	. . .	0	0
YAB002W	0	0	. . .	0	1
⋮	⋮	⋮	⋮	⋮	⋮

- Computed *in silico*
- Useful to infer gene function

How to compare two profiles?



“Phylogenetic” kernel



x	1	1	0	1	0	0	0	1	1	0
y	1	0	1	0	0	0	0	1	0	1

$$K(x,y) = \sum_e P(e)P(x|e)P(y|e),$$

Gene function prediction (ROC 50)

Functional class	Naive kernel	Tree kernel	Difference
Amino-acid transporters	0.74	0.81	**+ 9%**
Fermentation	0.68	0.73	**+ 7%**
ABC transporters	0.64	0.87	**+ 36%**
C-compound transport	0.59	0.68	**+ 15%**
Amino-acid biosynthesis	0.37	0.46	**+ 24%**
Amino-acid metabolism	0.35	0.32	- *9%*
Tricarboxylic-acid pathway	0.33	0.48	**+ 45%**
Transport Facilitation	0.33	0.28	- *15%*

Example 2: Local alignment kernel (*Bioinfo. 04*)

- The Smith-Waterman local alignment score:

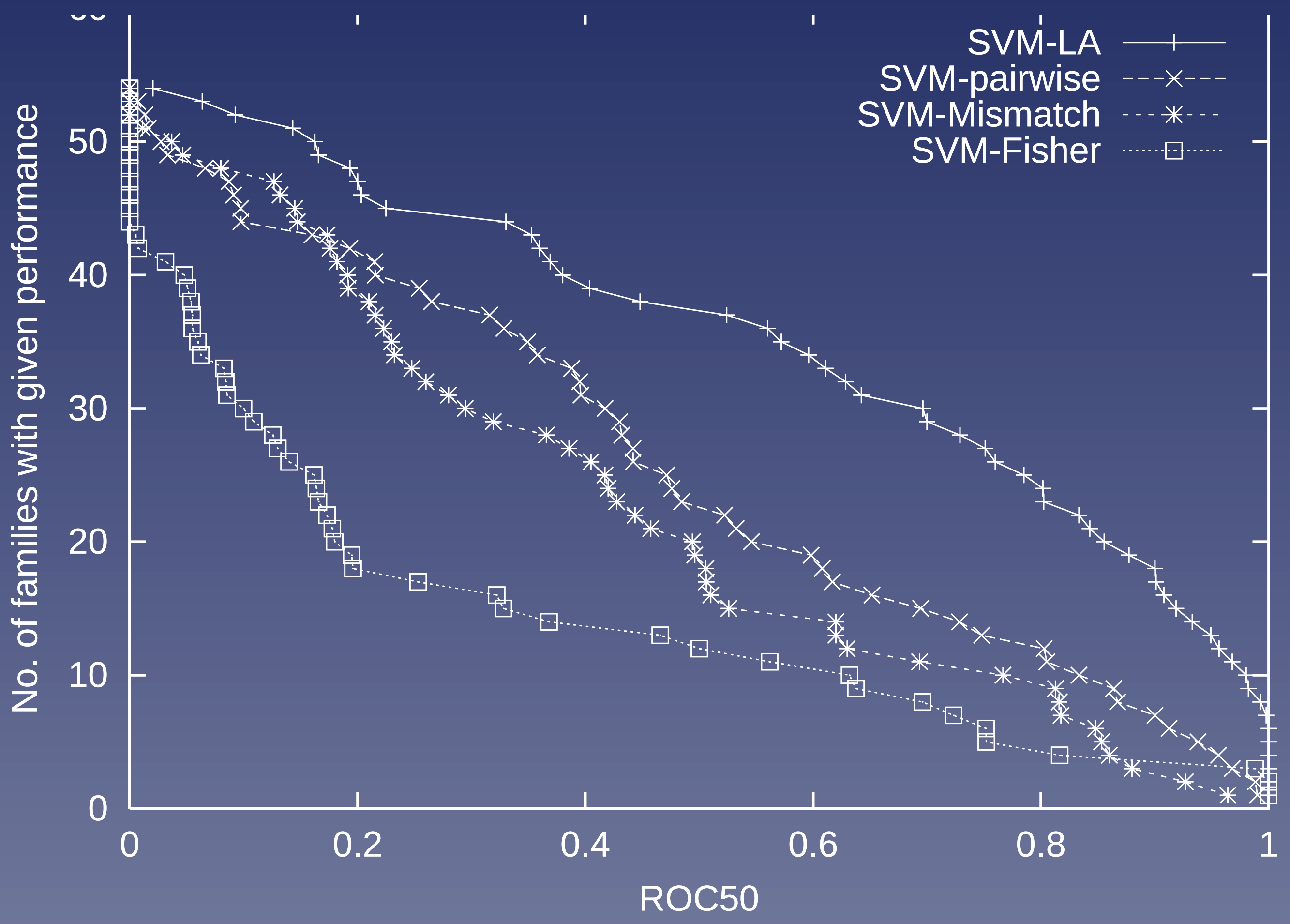
$$SW(x,y) = \max_{\pi \in \Pi(x,y)} s(x,y,\pi)$$

is a widely-used measure of similarity between biological sequences, but... it is not a kernel

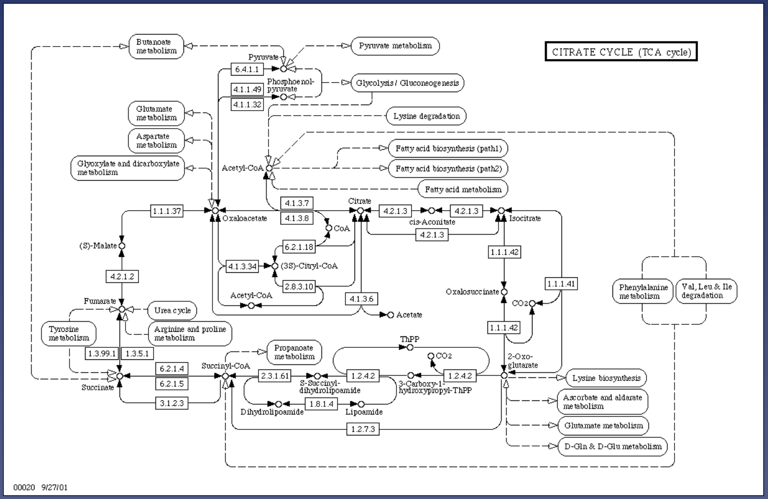
- The following local alignment kernel is valid:

$$K_{LA}^{(\beta)}(x,y) = \sum_{\pi \in \Pi(x,y)} \exp\left(\beta s(x,y,\pi)\right),$$

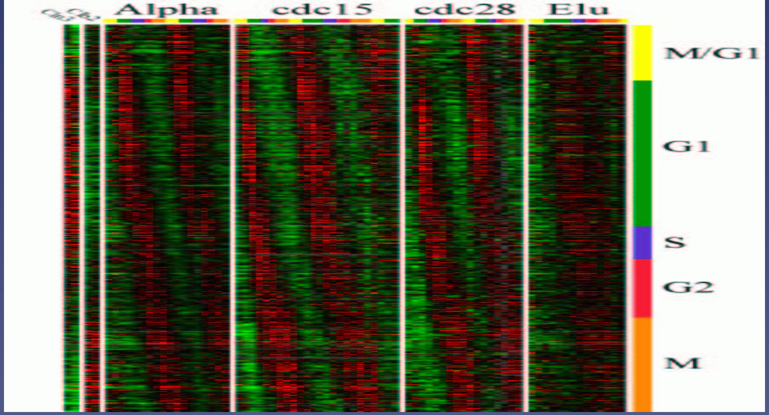
Empirical evaluation



Comparison of heterogeneous data (NIPS’02)



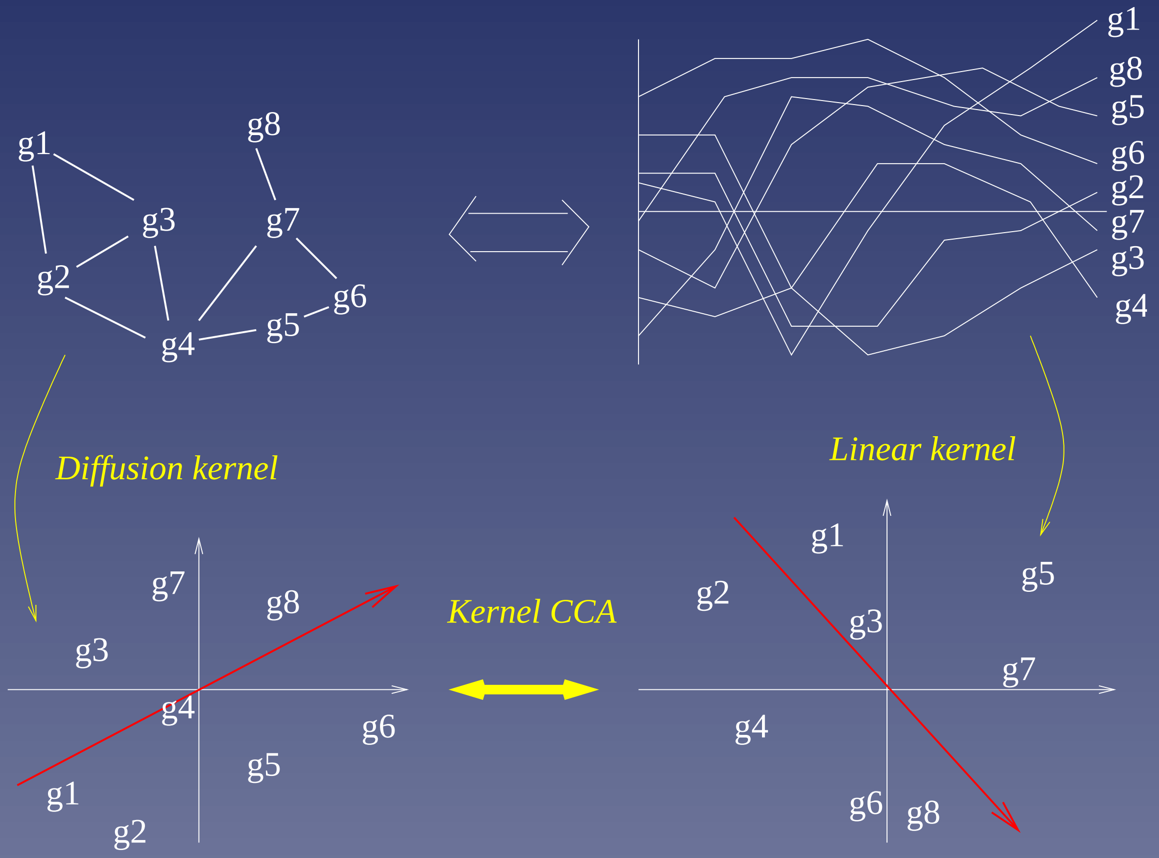
VS



Detecting pathway activity? Data and graph denoising?

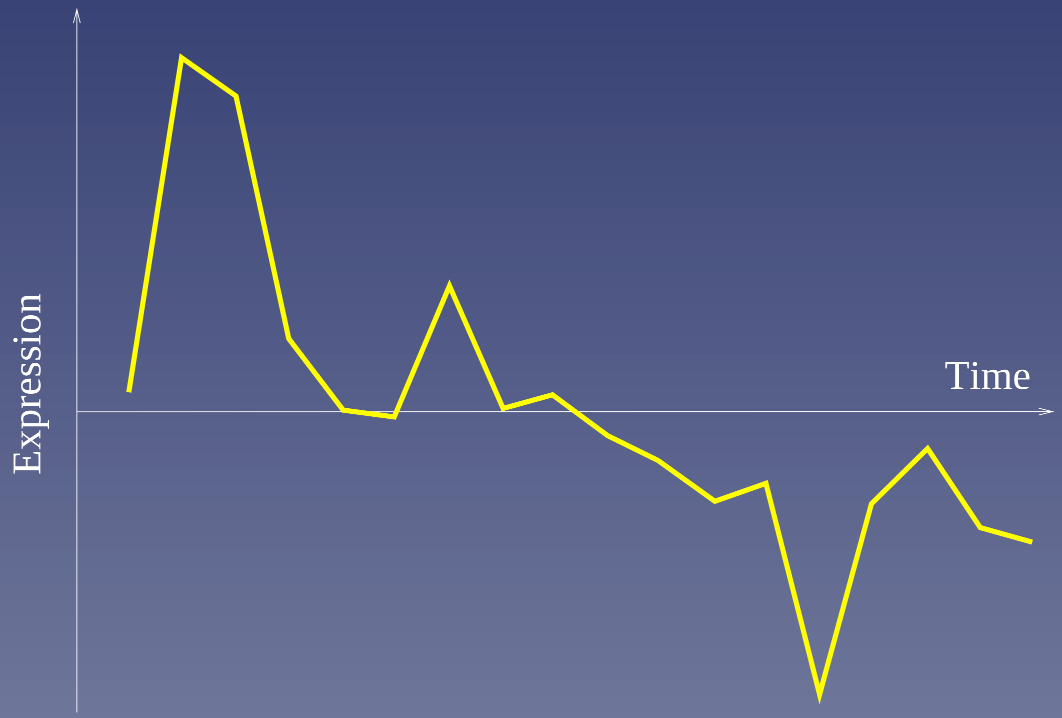
Network reconstruction?

Using kernel-CCA

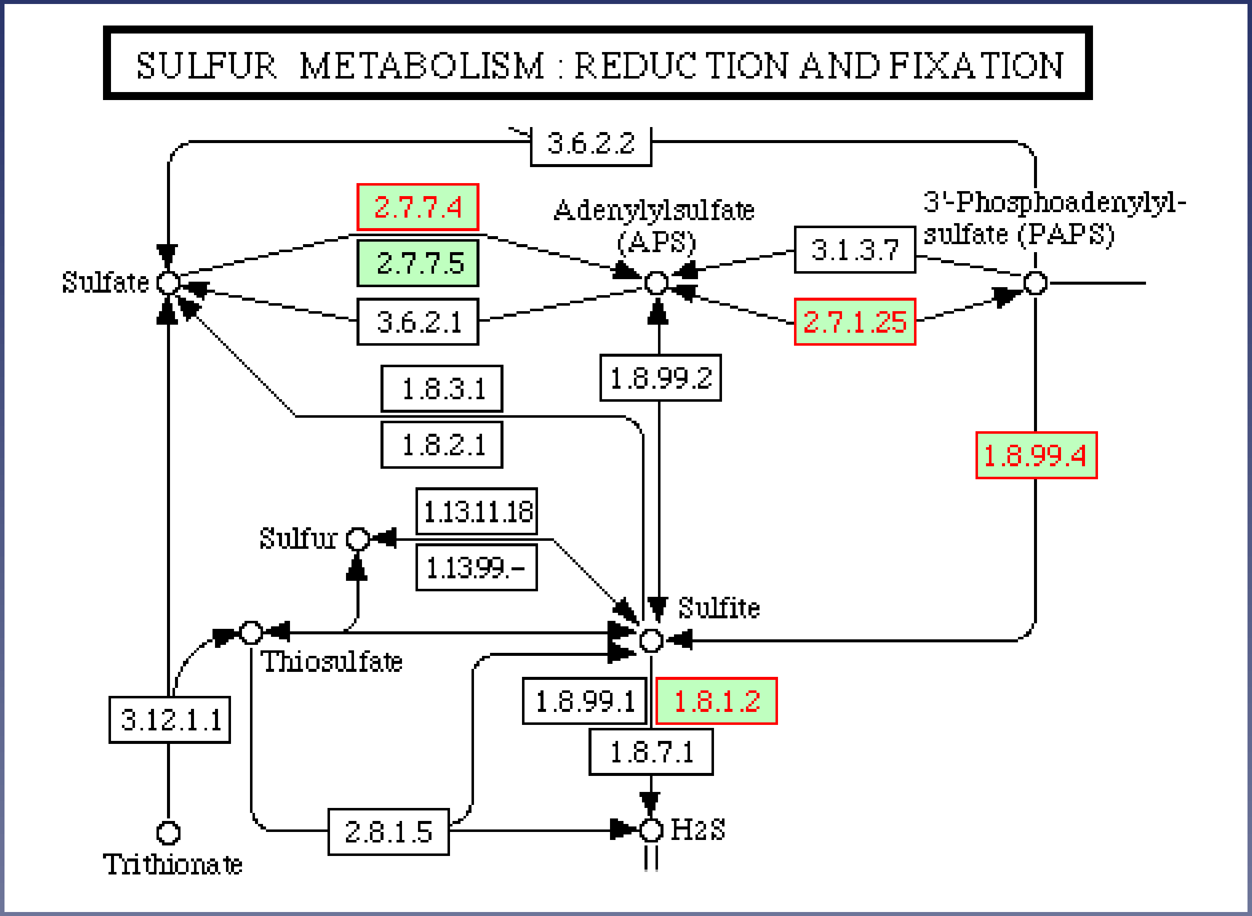


Example (*ECCB'03*)

Comparison of the metabolic network vs cell cycle gene expression in yeast



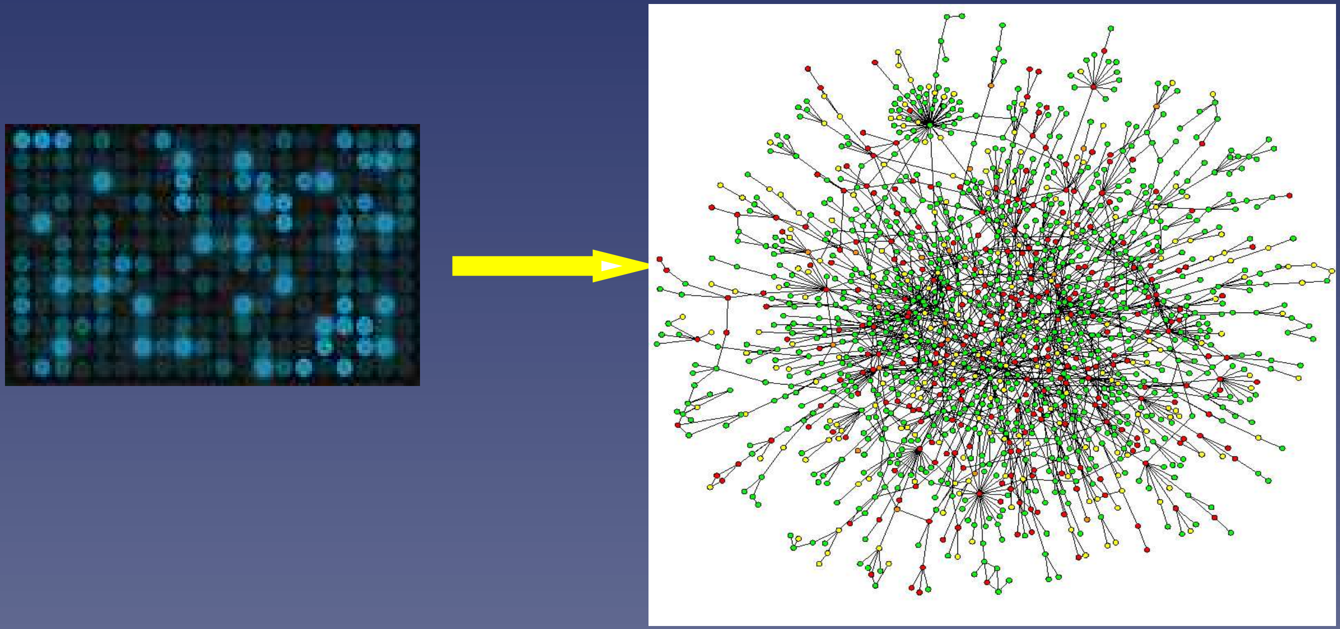
Correlated pathways



Extensions

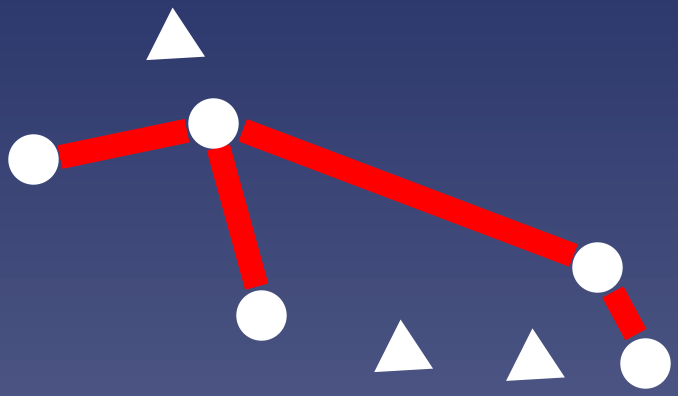
- Feature extraction for gene supervised classification (*NIPS'02*)
- Feature extraction for gene clusteing and operon detection (*ISMB'03*)

Supervised graph inference



Bayesian networks (Friedman et al., 2001), dynamical systems (Akutsu, 2000), nearest neigbor joinging method (Marcotte et al., 1999)...

Graph learning through metric learning



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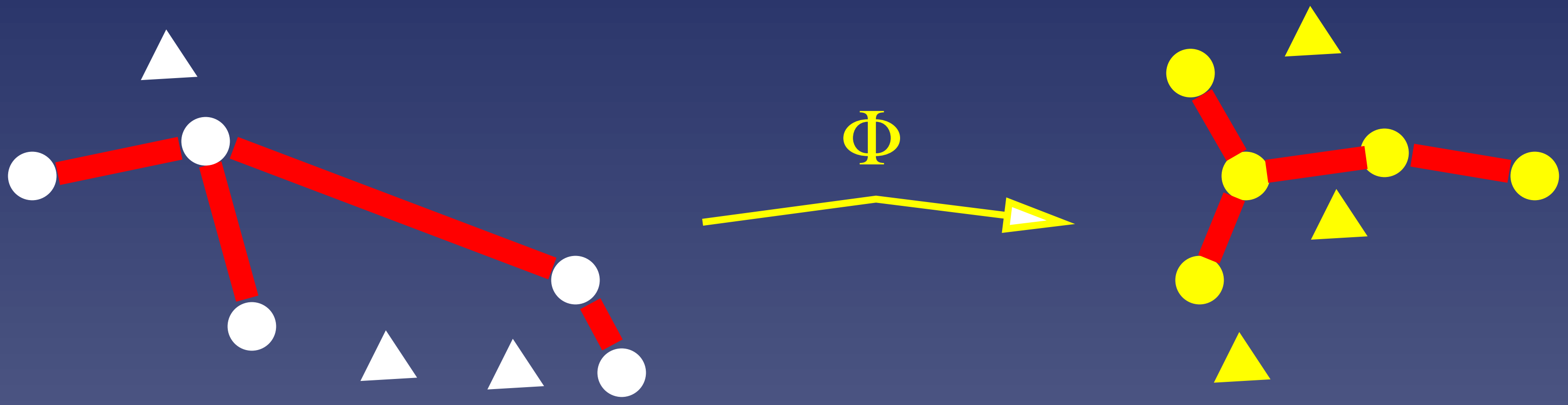

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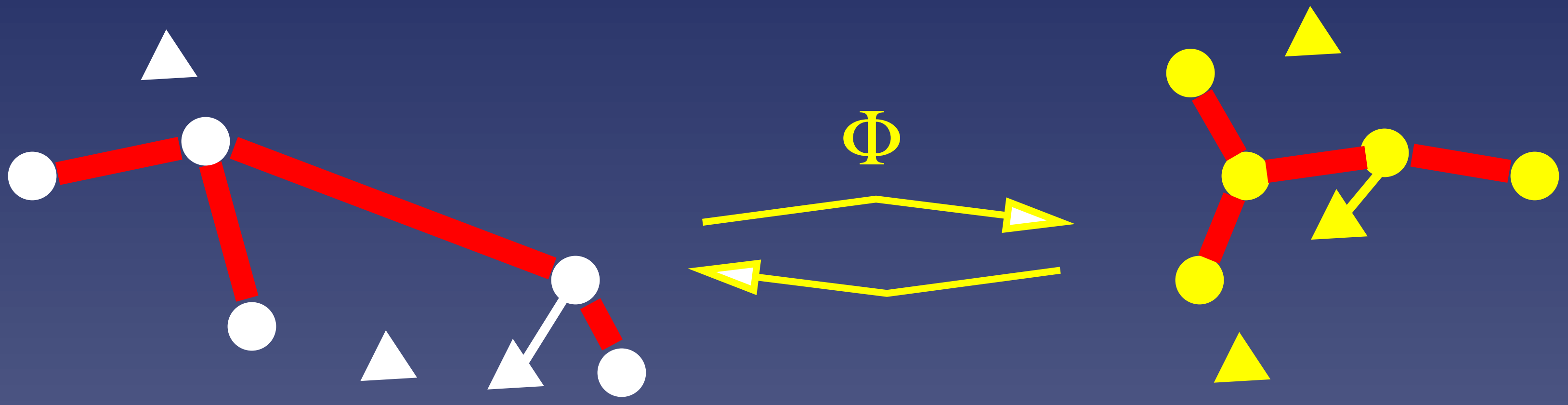

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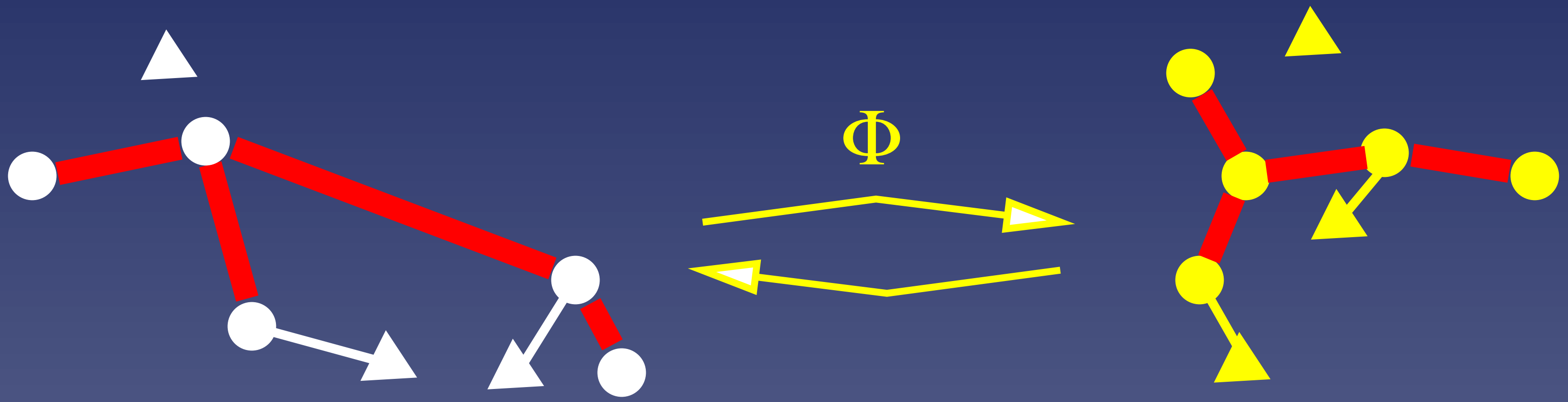

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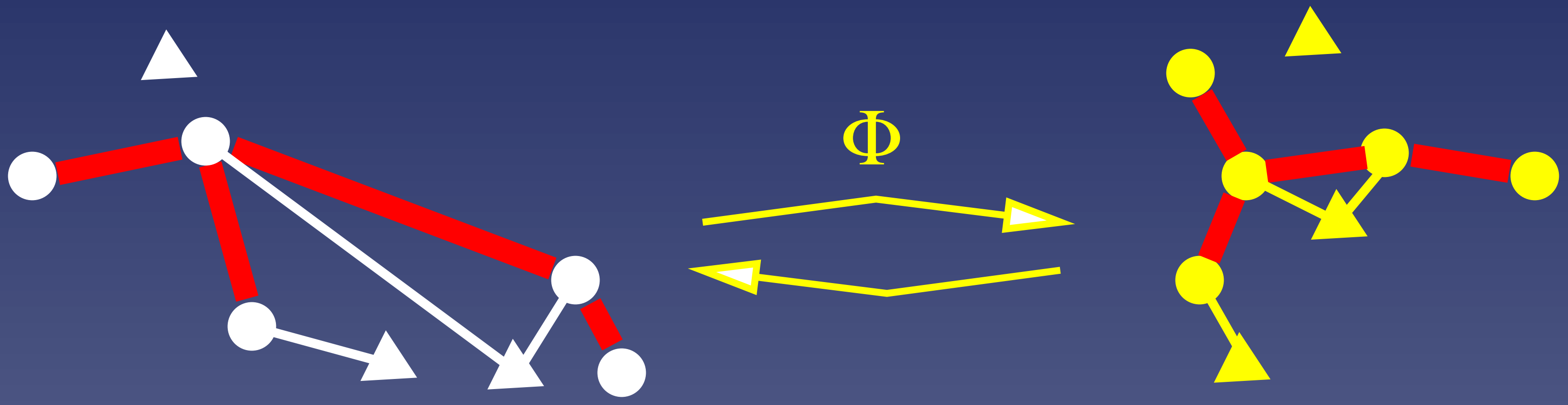

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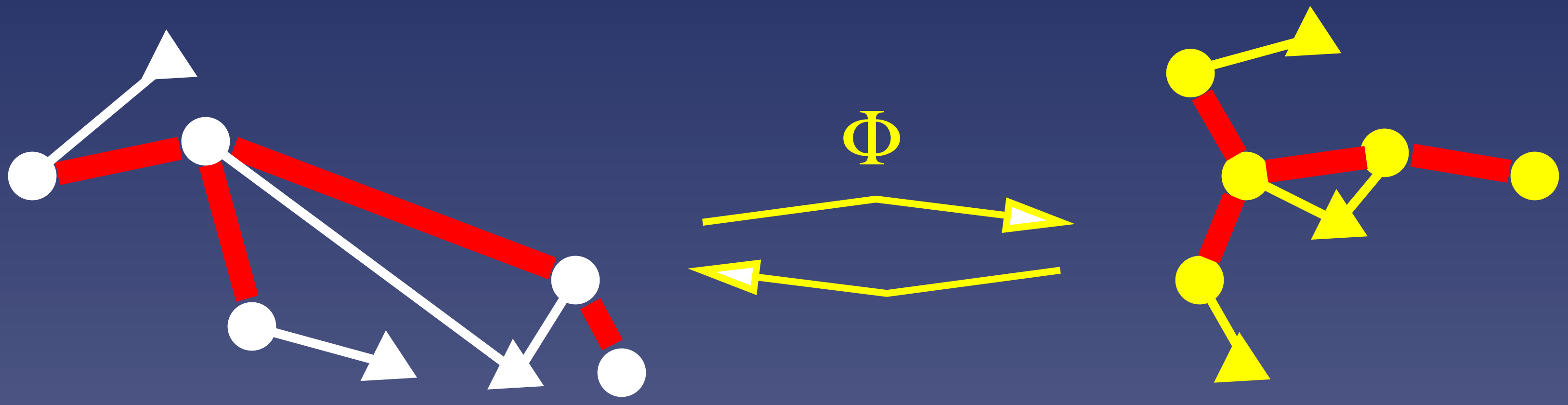

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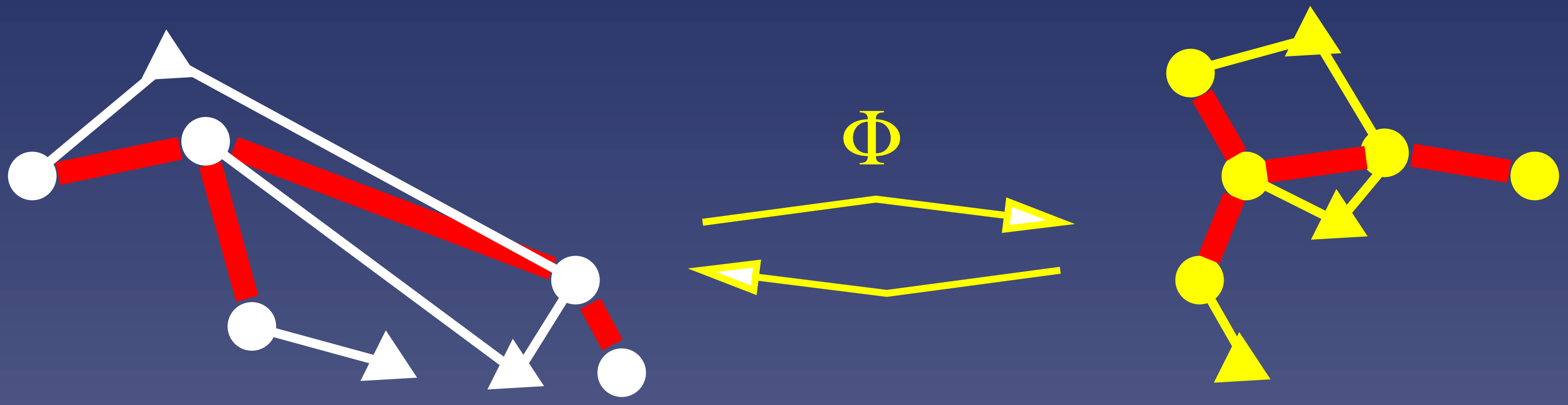
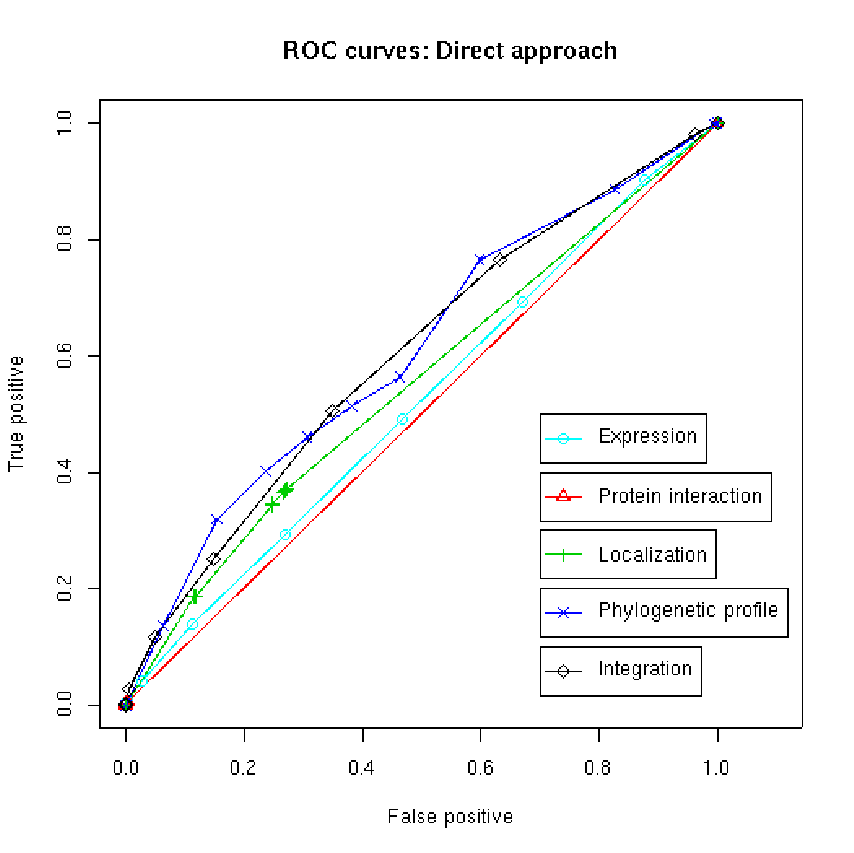
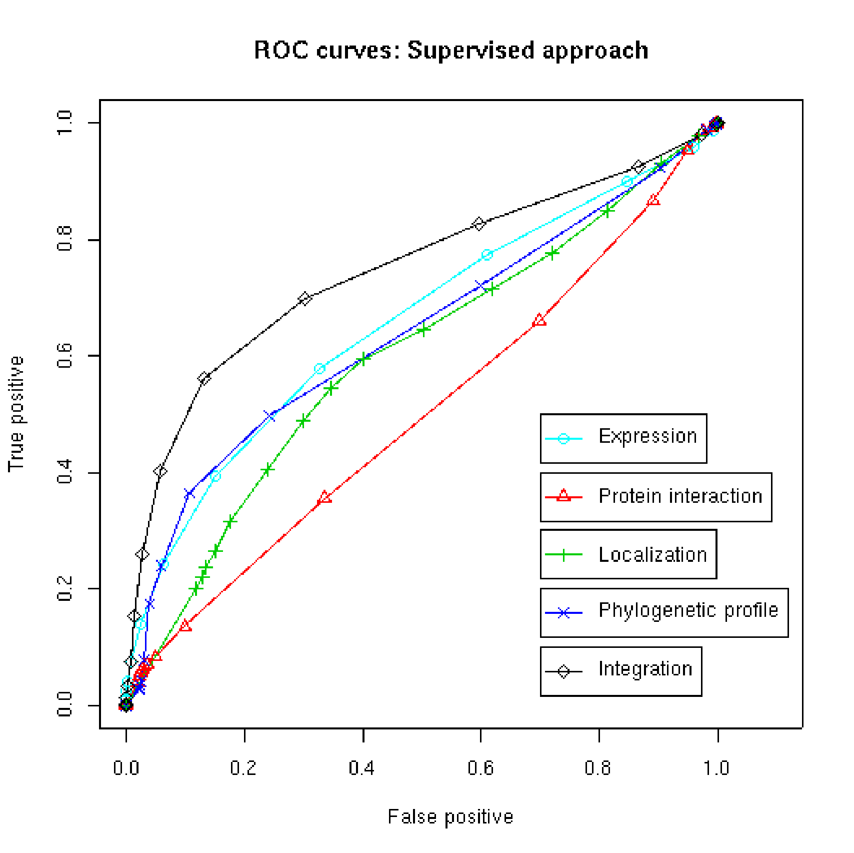


Unsupervised graph learning



Supervised graph learning



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- A strong and increasing demand to solve well-defined problems
- More and more possibilities to formulate new hypothesis/theories from results of data mining (e.g., scale-free properties...)
- An urgent need for an adapted mathematical framework to represent and integrate biological data (probabilistic? kernel methods? dynamic systems? operator algebra?...)
- How to transfer fundamental findings into applications, such as new therapies?

A challenge for the CAS-MPI Institute

- Seek a fast international recognition through an original and high-level research

- Strong collaboration with the CAS biological and medical facilities, and with the MPI excellence centers in computer science and mathematics

- Focus on a small number of well-defined applications, in collaboration with nearby CAS laboratories

- Keep a long-term theoretical goal

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