Kernel methods in computational biology: Three examples

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Ecole Polytechnique, June 16, 2003.

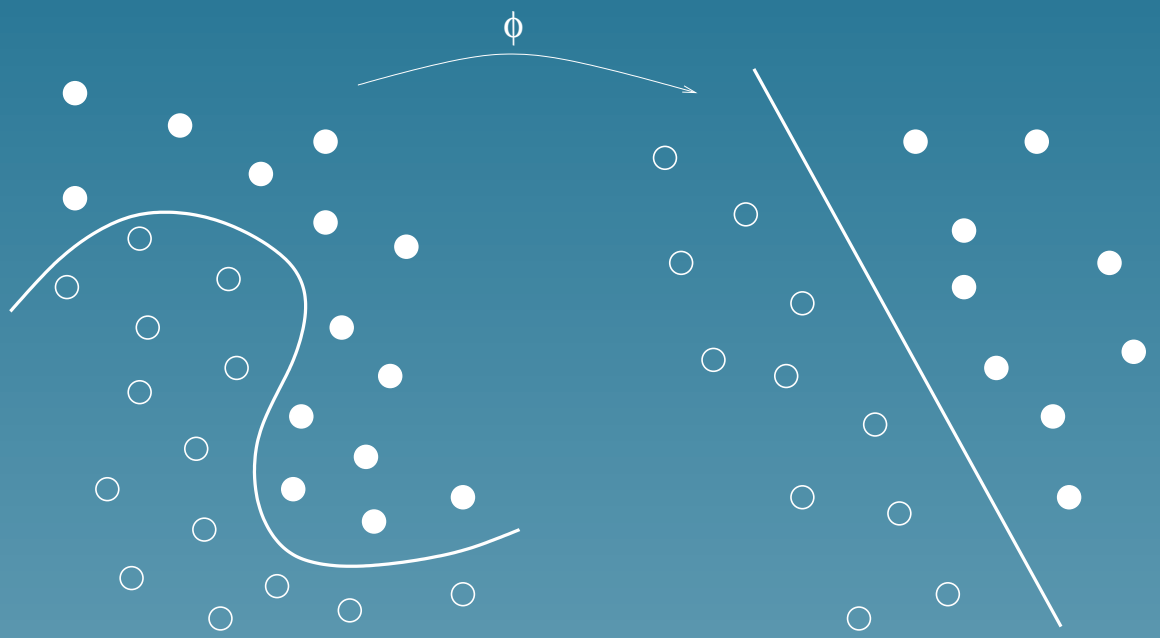
Outline

1. SVM and kernel methods
2. Gene function prediction from phylogenetic profiles
3. Remote protein homology detection
4. Detection of active metabolic pathways from gene expression data

Part 1

SVM and kernel methods

Support vector machines



- Objects to classify x mapped to a feature space
- Largest margin separating hyperplan in the feature space

The kernel trick

- Implicit definition of $x \longrightarrow \Phi(x)$ through the kernel:

$$K(x, y) \stackrel{def}{=} < \Phi(x), \Phi(y) >$$

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$$K(x,y) \stackrel{def}{=} < \Phi(x), \Phi(y) >$$

- Simple kernels can represent complex Φ
- For a given kernel, not only SVM but also clustering, PCA, ICA... possible in the feature space $=$ kernel methods

Part 2

Gene function prediction from phylogenetic profiles

(ISMB 02)

Mini introduction

- Genes are small parts of the DNA which encode proteins.
- About 6,000 genes in the baker yeast, 30,000 in human
- The sequences of the genes are (almost) known (sequencing projets)
- Next big challenge: understand their functions

Phylogenetic profile

- The phylogenetic profile of a gene is a vector of bits which indicates the presence (1) or absence (0) of the gene in every fully sequenced genome.

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

- Can be estimated *in silico* by sequence similarity search

From profile to function

- Genes are likely to be transmitted together during evolution when they participate:
  - ⋆ to a common structural complex,
  - ⋆ to a common pathway.
- Consequently genes with similar phylogenetic profiles are likely to have similar functions
- How to infer the function from the profile?

Naive approach

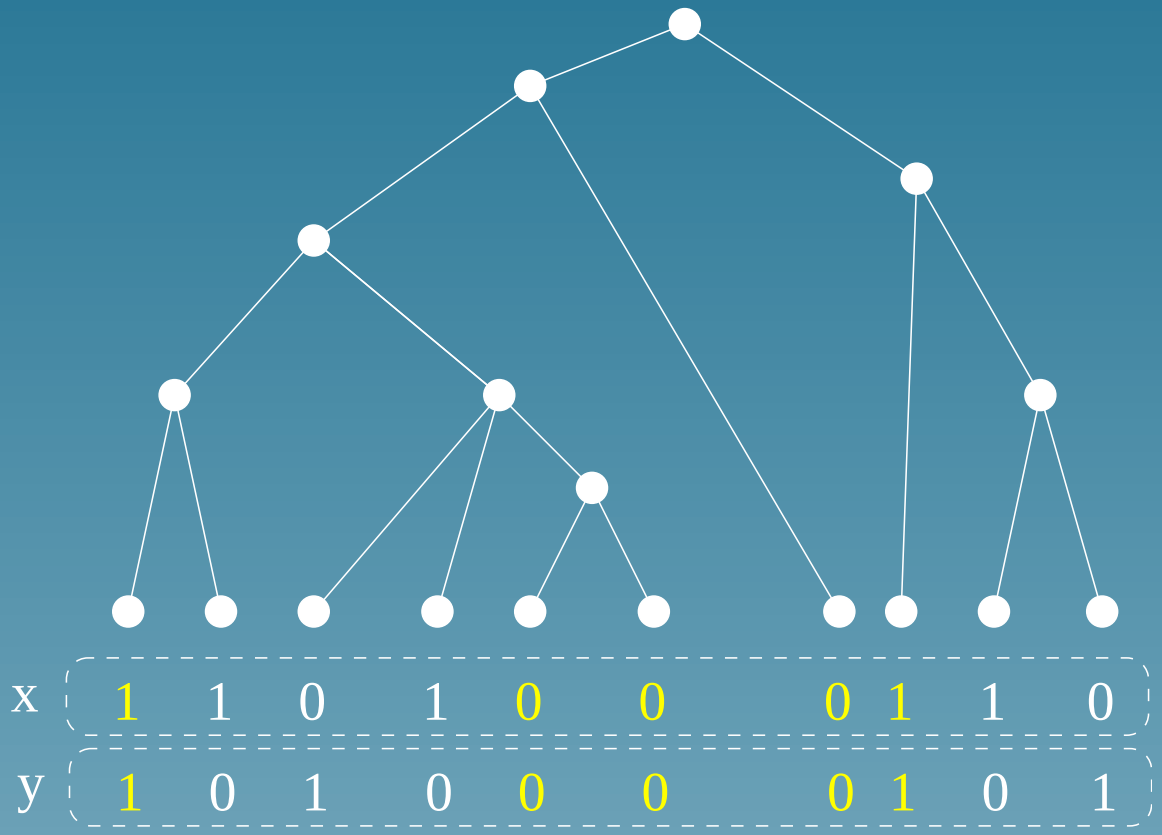
- Count the number of bits in common:

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

$$s(x, y) = 5$$

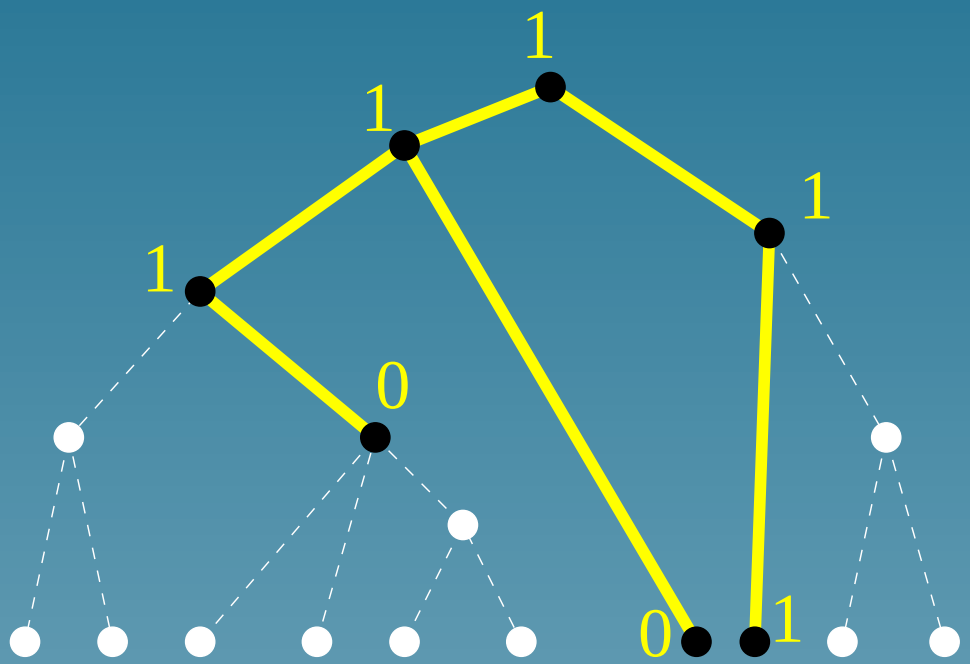
- Cluster or use k-NN for gene function prediction with this similarity measure (Pellegrini et al., 1999)

What is not used in the naive approach



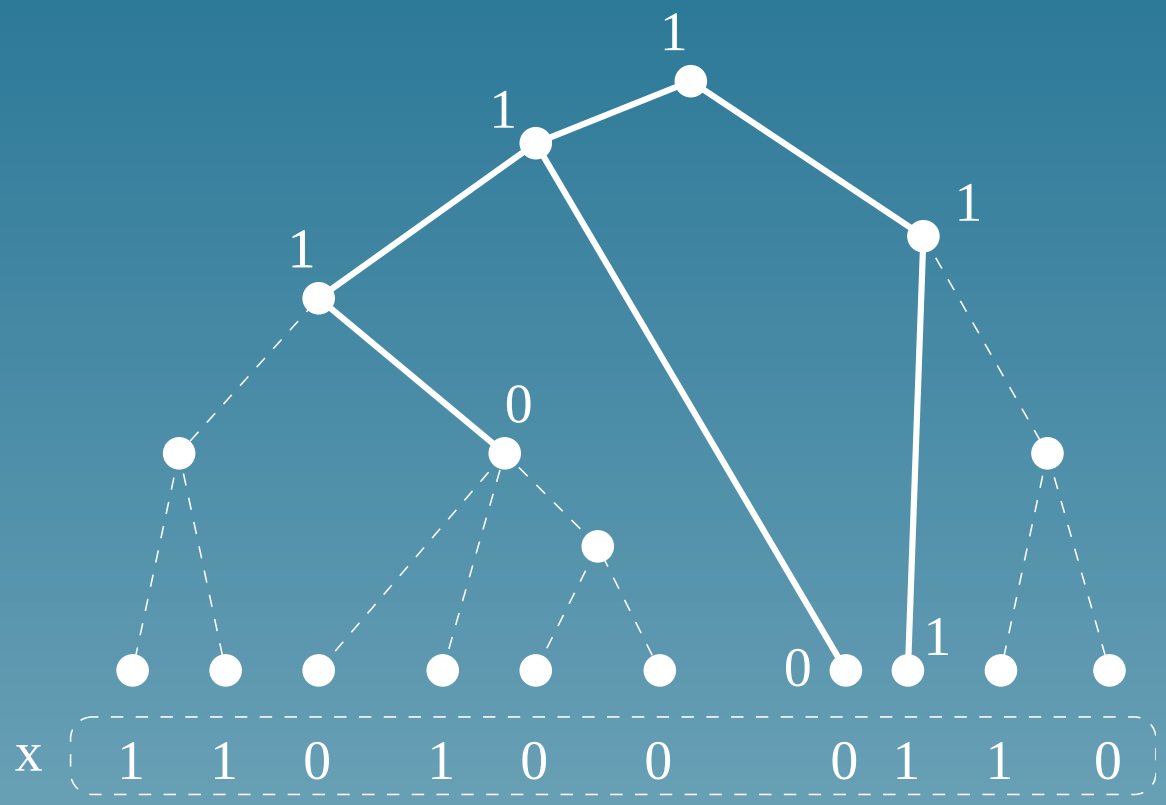
The knowledge of the phylogenetic tree.

Evolution pattern



A possible pattern of transmission during evolution defined by a rooted subtree with nodes labeled 0 or 1.

Evolution patterns and phylogenetic profiles



Is it the true story? We don't know, but...

Probabilistic model of gene transmission

- The phylogenetic tree as a tree graphical model
- Simplified model:
  - $\star$ $P(1) = 1 - P(0) = 0.9$, at the root,
  - $\star$ Along each branch transmission follows the transition matrix:

$$\begin{pmatrix} 0.9 & 0.1 \\ 0.1 & 0.9 \end{pmatrix}$$

Probabilistic assignment of evolution pattern

For a phylogenetic profile x and an evolution pattern e:

- $P(e)$ quantifies how "natural" the pattern is
- $P(x|e)$ quantifies how likely the pattern e is the "true history" of the profile x

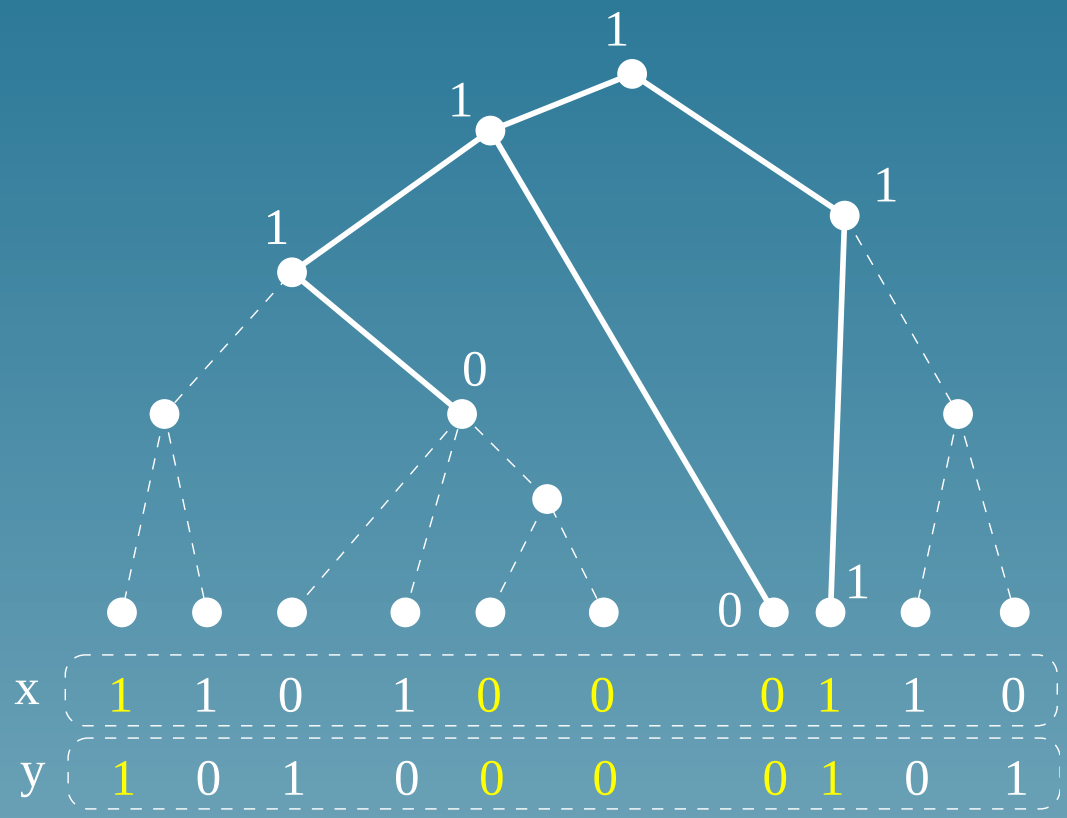
Representation of a profile in terms of evolution patterns

- Consider all possible evolution patterns $(e_1, \ldots, e_N)$, and represent each gene x by the vector:

$$\Phi(x) = \begin{pmatrix} \sqrt{P(e_1)}P(x|e_1) \\ \vdots \\ \sqrt{P(e_N)}P(x|e_N) \end{pmatrix}$$

- Comparing $\Phi(x)$ and $\Phi(y)$ gives a precise idea of which evolution patterns are shared or not by x and y.

Comparing two profiles through evolution patterns



Tree kernel

- Kernel methods (SVM, kernel-PCA, kernel-clustering...) only require the computation of the kernel function:

$$K(x, y) = \Phi(x).\Phi(y).$$

- In our case we obtain the tree kernel:

$$K(x, y) = \sum_{e} P(e)P(x|e)P(y|e),$$

where the sum is over all possible evolution patterns.

Kernel computation: trick 1

- For any given pattern e, the term:

$$\alpha(e) = P(e)P(x|e)P(y|e)$$

  can be factorized and computed recursively by working up the tree from the leaves

- Classical trick for computing likelihood with tree graphical models, cf. Felsenstein's algorithm

Kernel computation: trick 2

- The sum

$$\sum_{e} \alpha(e)$$

over all subtrees can also be factorized and computed recursively by working up the tree from the leaves

- Similar in spirit to the Context Tree Weighting algorithm (Willems et al., 1995).

Combining tricks

- Both tricks can be combined
- $K(x, y)$ can be computed by two post-order traversals of the tree
- The complexity is linear with the length of the profile.

Gene function prediction with SVM

- Profiles for 2465 genes of *S. Cerevisiae* were computed by BLAST search (cf Pavlidis et al. 2001), using 24 genomes.
- Consensus phylogenetic tree (cf. Liberles et al. 2002) with simplified probabilistic model of gene transmission
- SVM trained to predict all functional classes of the MIPS catalog with at least 10 genes (cross-validation)
- Comparison of the tree kernel with the naive kernel

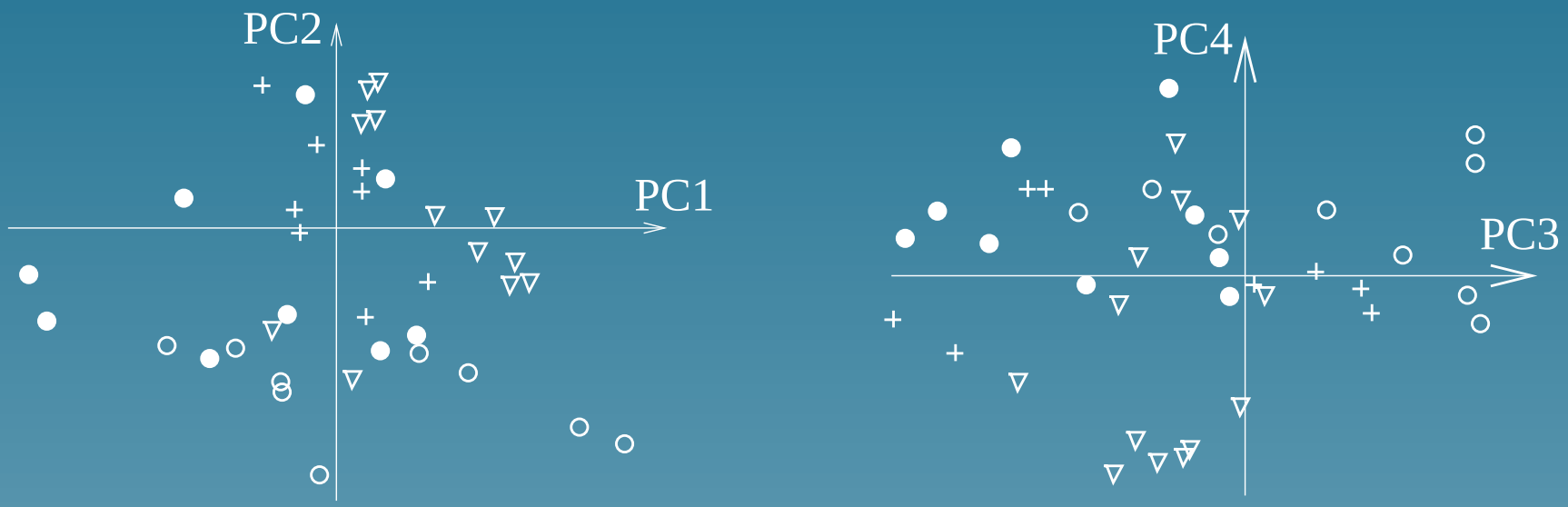
Results (ROC 50)

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%*

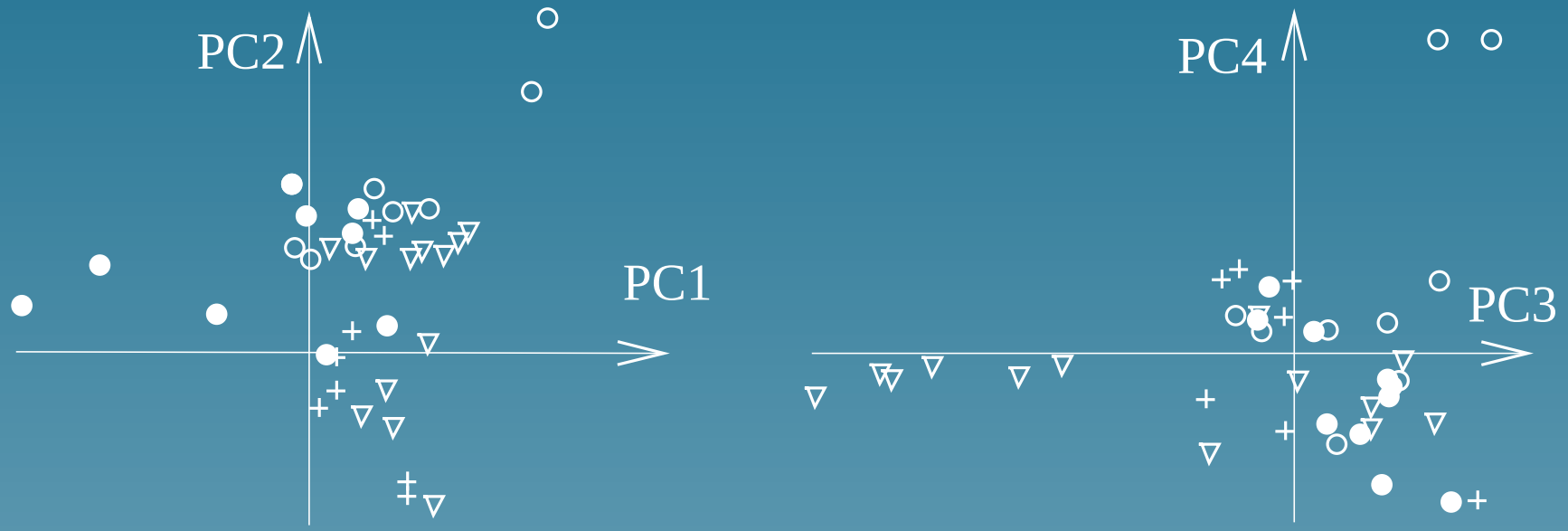
A insight into the feature space

- PCA can be performed implicitly in the feature space with a kernel function: kernel-PCA (Scholkopf et al. 1999)
- Projecting the genes on the first principal components gives an idea of the shape of the features space

Naive kernel PCA



Tree kernel PCA



- Amino−acid transporters
- Fermentation
- ABC transporters
- C−compound, carbonhydrate transport

Extensions

- $X_1, \ldots, X_n$ discrete r.v.
- $I_1, \ldots, I_v \subset \{1, \ldots, n\}$ a family of subsets
- Interpolated kernel:

$$K(x, y) = \frac{1}{v} \sum_{i=1}^{v} p(x_{I_i}) p(y_{I_i}) \times p(x_{I_i^c}) \delta(x_{I_i^c}, x_{I_i^c})$$

Property 1

This kernel interpolates between the diagonal kernel:

$$K_{diag}(x, y) = p(x)\delta(x, y)$$

and the product kernel:

$$K_{prod}(x, y) = p(x)p(y).$$

Property 2

Two objects x and y get closer in the feature space when they share rare common subparts:

$$K(x,y) = K_{prod}(x,y) \times \frac{1}{v} \sum_{i=1}^{v} \frac{\delta(x_{I_i}, y_{I_i})}{p(x_{I_i})}$$

Linear-time implementations

- iid r.v., all possible subsets (*PSB 02*):

Linear-time implementations

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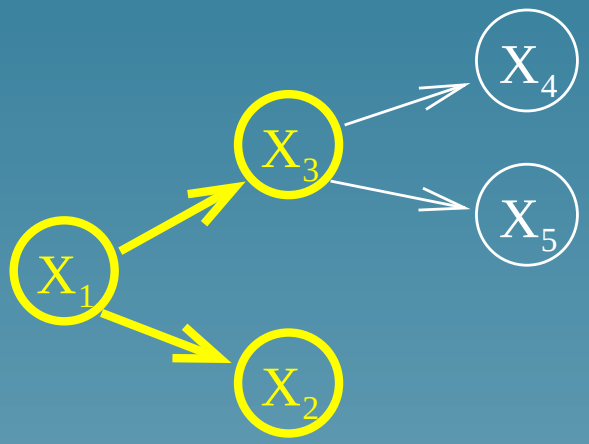
- Markov model, common blocks

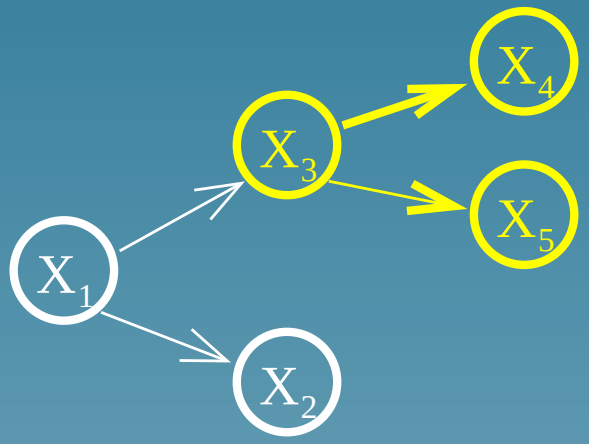
Linear-time implementations

- Tree graphical model, common rooted subtrees



Linear-time implementations

- Tree graphical model, common subtrees



Part 2

Remote protein homology detection

(with S. Hiroto, N. Ueda, T. Akutsu, preprint 2003)

Motivations

- Develop a kernel for strings adapted to protein / DNA sequences
- Several methods have been adopted in bioinformatics to measure the similarity between sequences... but are not valid kernels
- How to mimic them?

Local alignment

- For two strings x and y, a local alignment π with gaps is:

- The score is:

$$s(x, y, \pi) = s(E, E) + s(F, F) + s(G, G) + s(I, I) - s(gaps)$$

Smith-Waterman (SW) score

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

- Computed by dynamic programming
- Not a kernel in general

Convolution kernels (Haussler 99)

- Let K_1 and K_2 be two kernels for strings
- Their convolution is the following valid kernel:

$$K_1 \star K_2(x, y) = \sum_{x_1 x_2 = x, y_1 y_2 = y} K_1(x_1, y_1) K_2(x_2, y_2)$$

3 basic kernels

- For the unaligned parts: $K_0(x, y) = 1$.

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- For aligned residues:

$$K_a^{(\beta)}(x, y) = \begin{cases} 0 & \text{if } |x| \neq 1 \text{ or } |y| \neq 1, \\ \exp\left(\beta s(x, y)\right) & \text{otherwise} \end{cases}$$

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- For gaps:

$$K_g^{(\beta)}(x, y) = \exp\left[\beta\left(g(|x|) + g(|y|)\right)\right]$$

Combining the kernels

- Detecting local alignments of exactly n residues:

$$K^{(\beta)}_{(n)}(x,y) = K_0 \star \left(K^{(\beta)}_a \star K^{(\beta)}_g \right)^{(n-1)} \star K^{(\beta)}_a \star K_0.$$

Combining the kernels

- Detecting local alignments of exactly n residues:

$$K_{(n)}^{(\beta)}(x,y) = K_0 \star \left(K_a^{(\beta)} \star K_g^{(\beta)}\right)^{(n-1)} \star K_a^{(\beta)} \star K_0.$$

- Considering all possible local alignments:

$$K_{LA}^{(\beta)} = \sum_{i=0}^{\infty} K_{(i)}^{(\beta)}.$$

Properties

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

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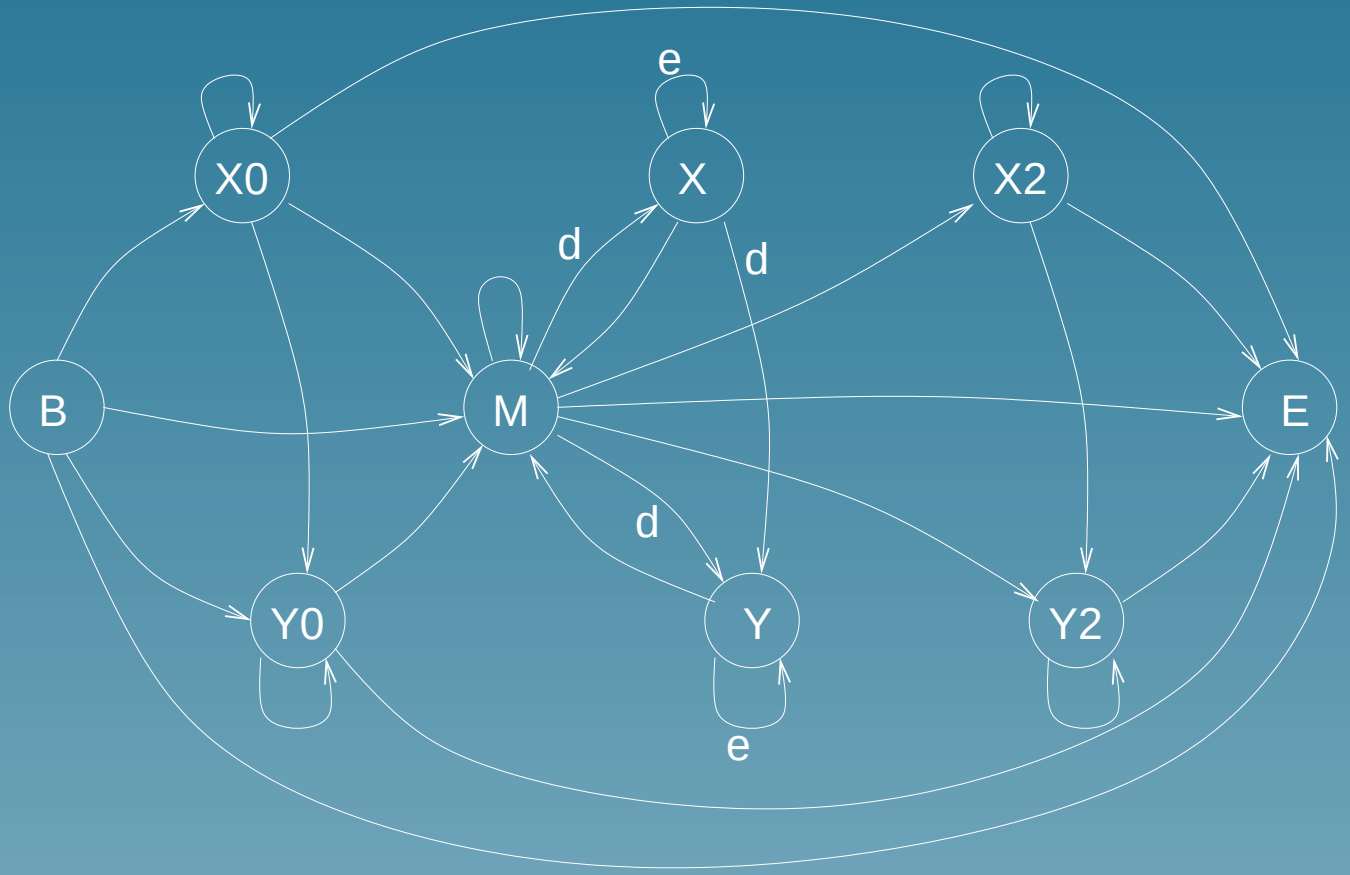
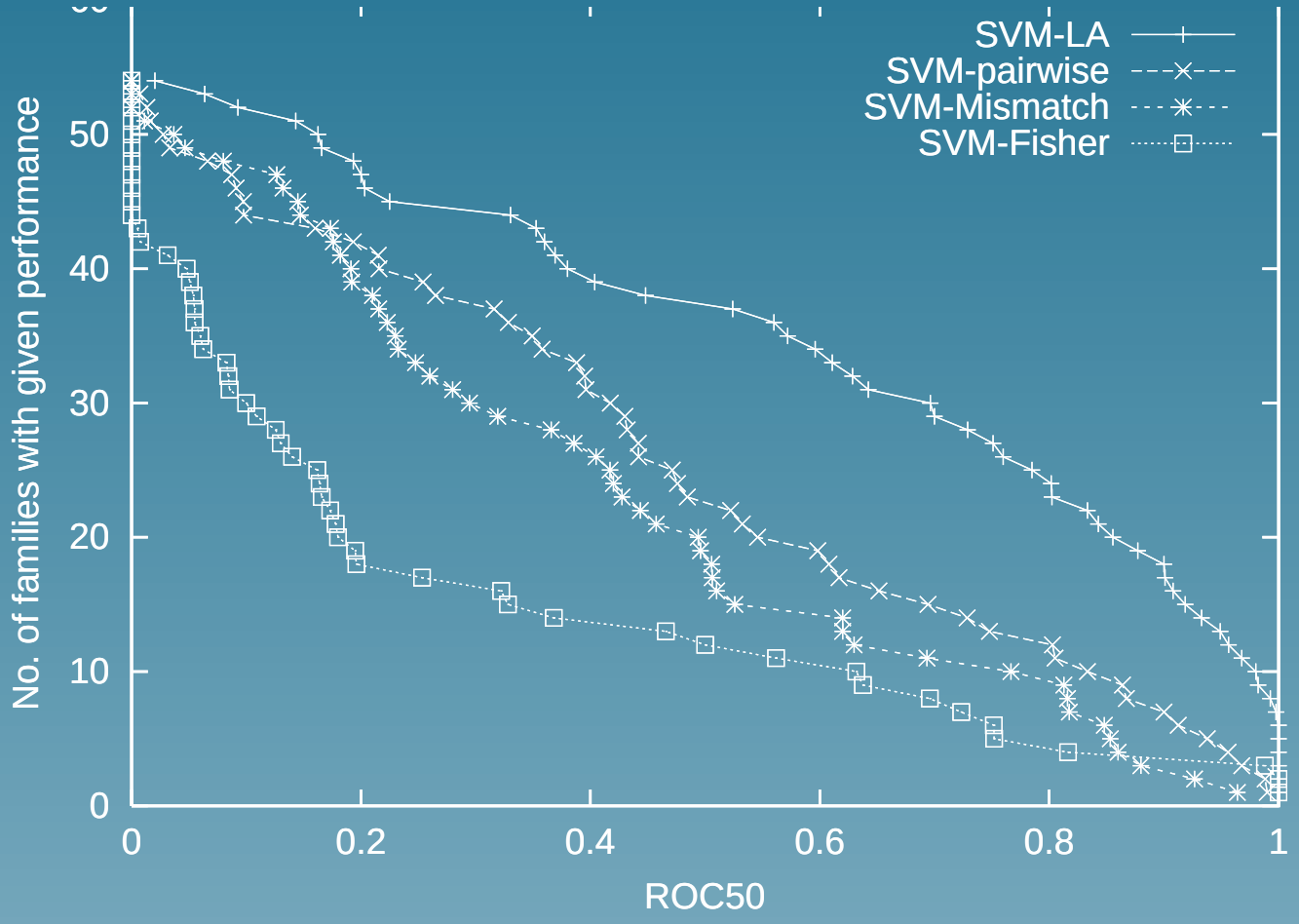
$$\lim_{\beta \to +\infty} \frac{1}{\beta} \ln K_{LA}^{(\beta)}(x,y) = SW(x,y).$$

Kernel computation



SCOP superfamily recognition benchmark

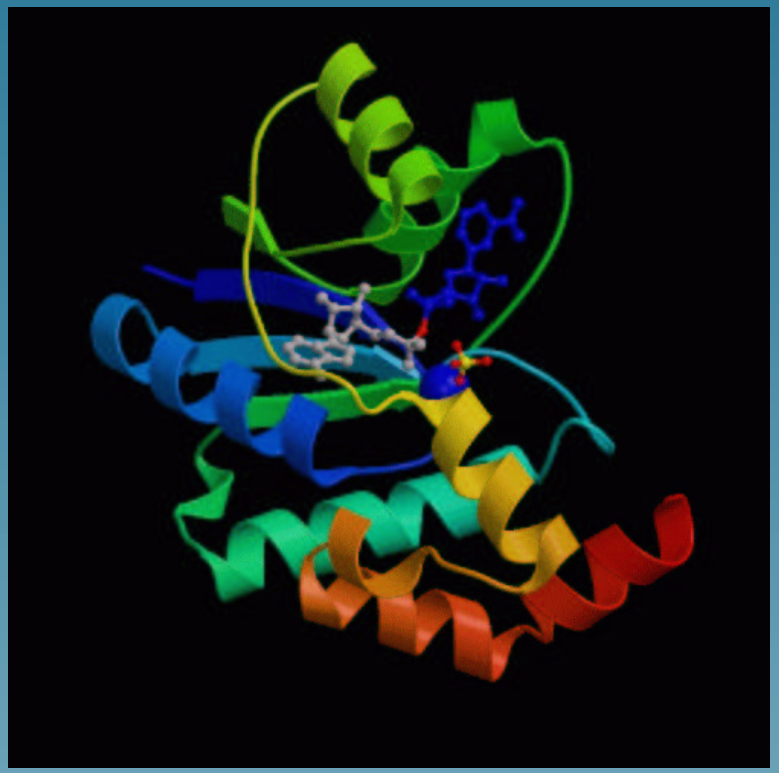


Part 3

Detection of active metabolic pathways from gene expression data

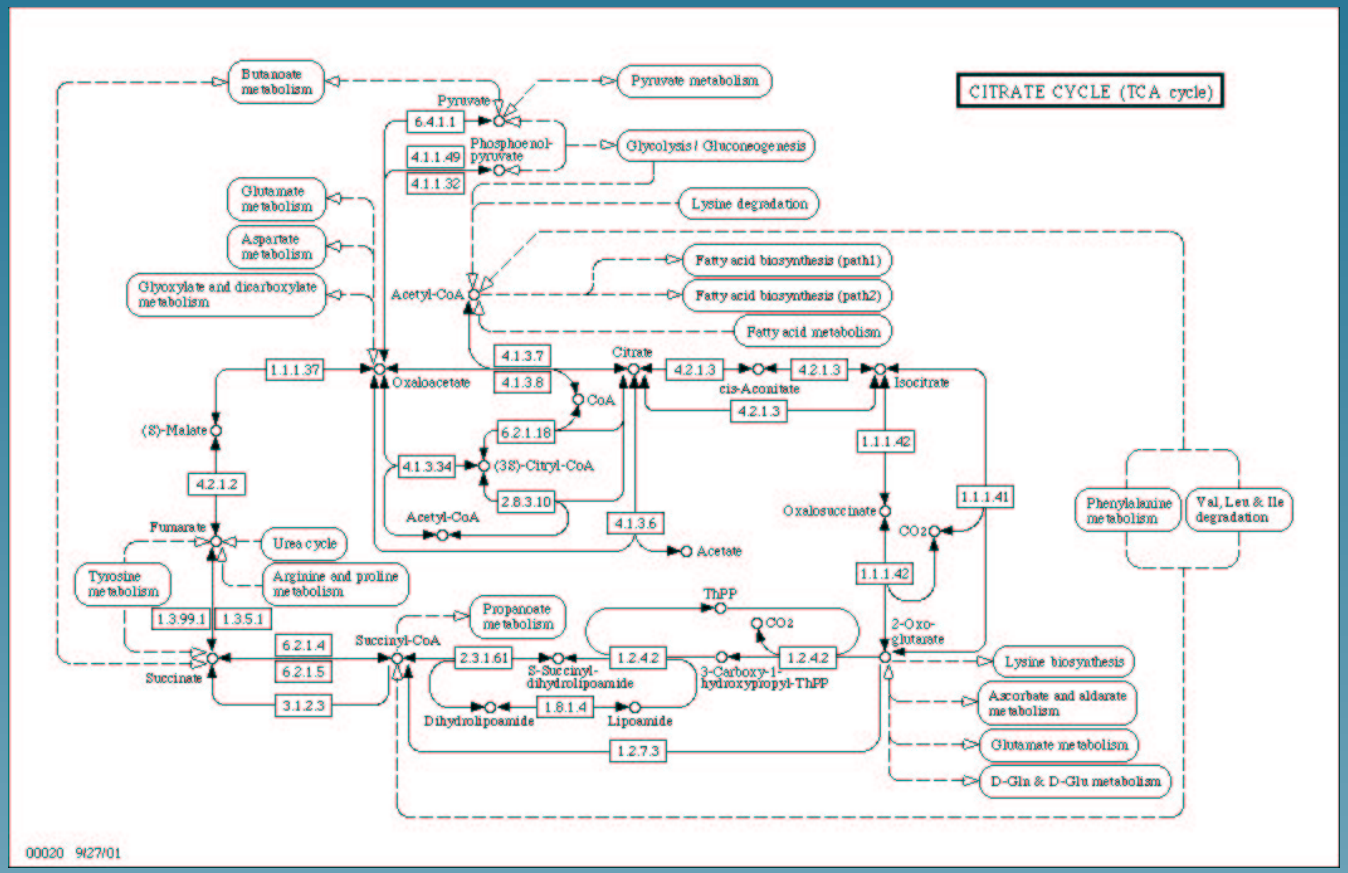
(NIPS 02)

Genes encode proteins which can catalyse chemical reations



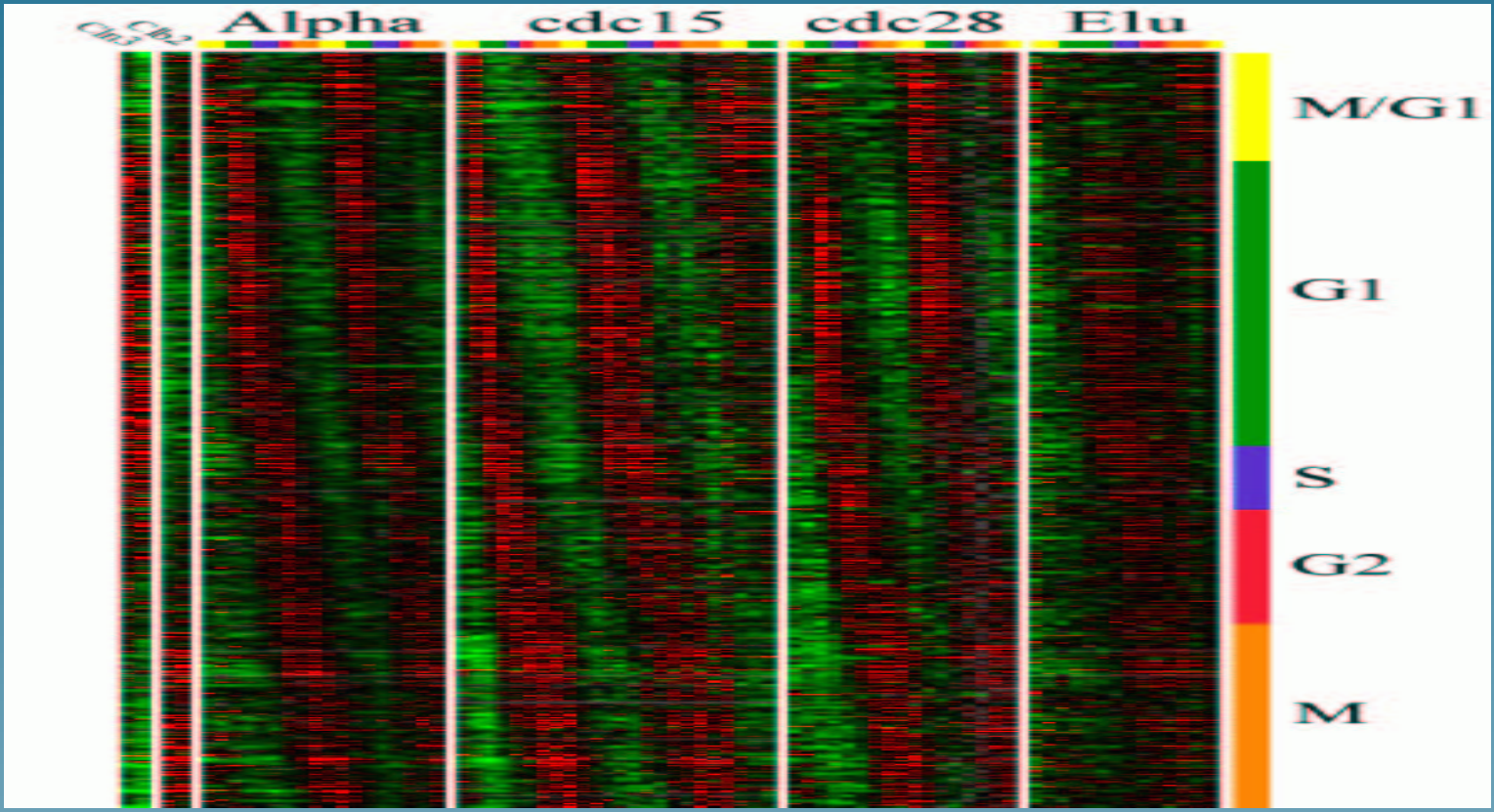
Nicotinamide Mononucleotide Adenylyltransferase With Bound Nad+

Chemical reactions are often parts of pathways



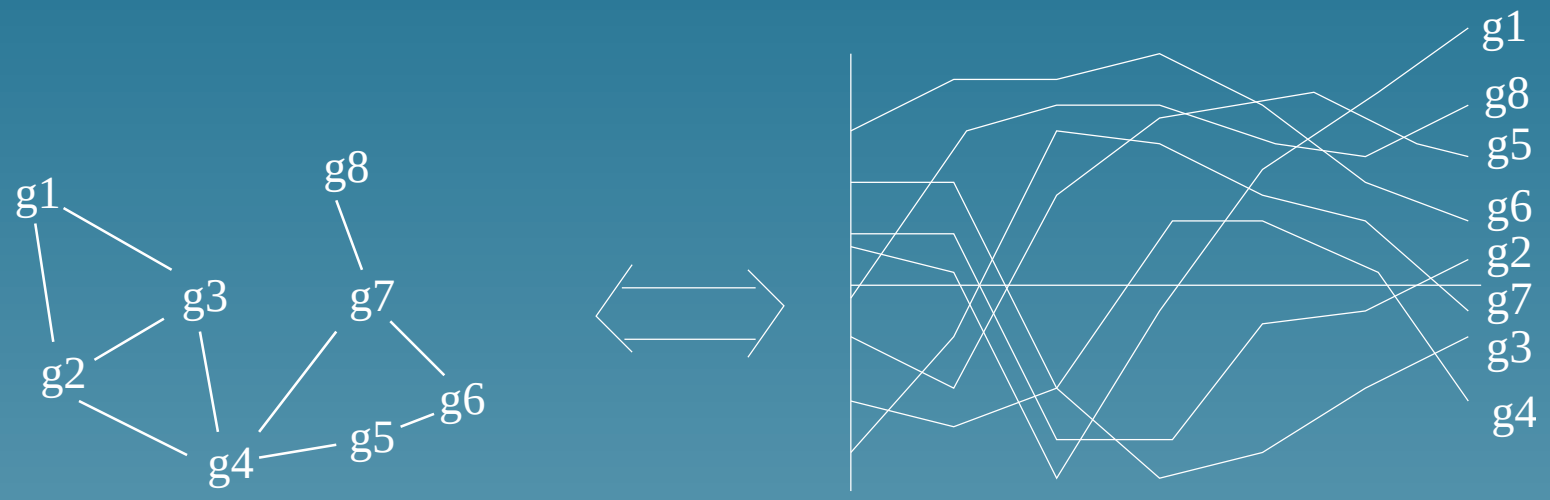
From http://www.genome.ad.jp/kegg/pathway

Microarray technology monitors RNA quantity



(From Spellman et al., 1998)

Comparing gene expression and protein network

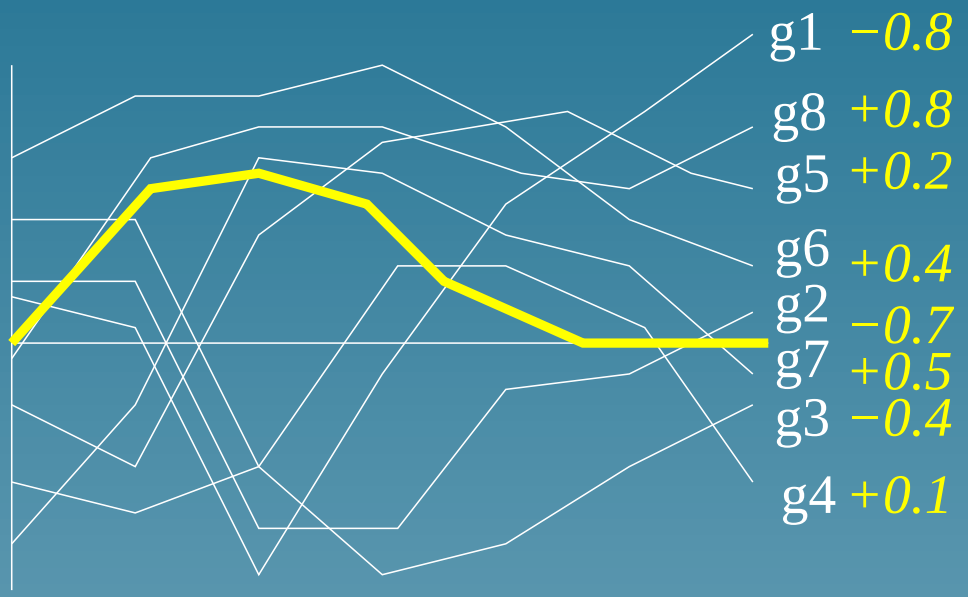


Gene network

Expression profiles

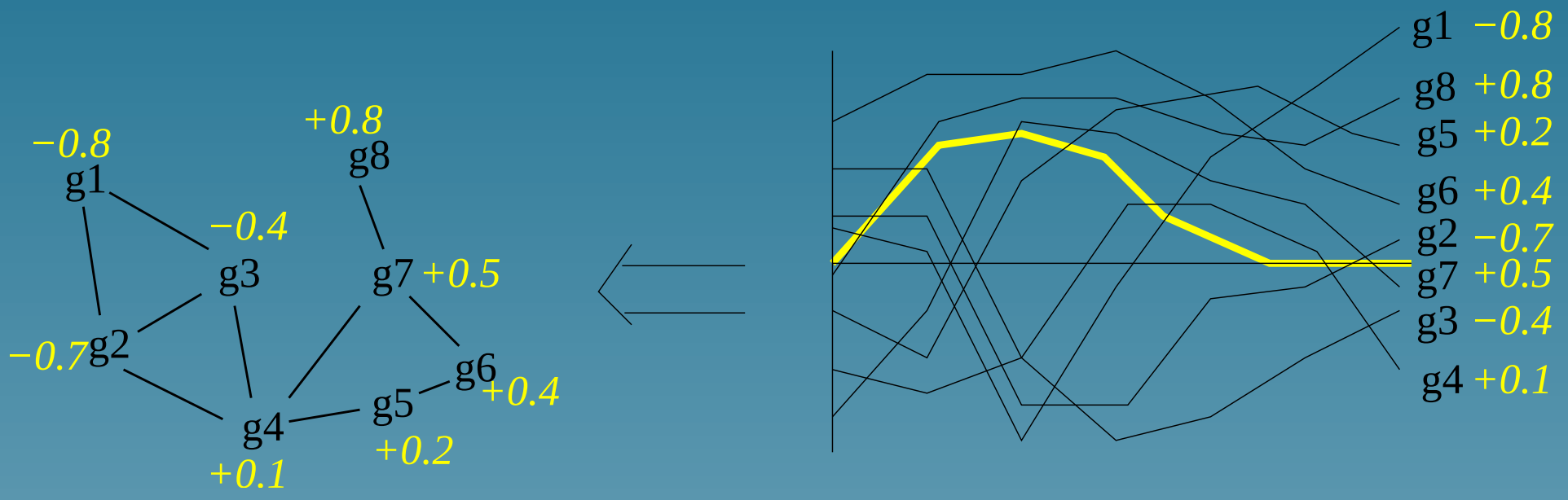
Are there "correlations"?

Pattern of expression



- In yellow: a candidate pattern , and the correlation coefficient with each gene profile

Pattern smoothness



- The correlation function with interesting patterns should vary smoothly on the graph

Pattern relevance

- Interesting patterns involve many genes
- The projection of profiles onto an interesting pattern should capture a lot of variations among profiles
- Relevant patterns can be found by PCA

Problem

Find patterns of expression which are simultaneously

- smooth
- relevant

From kernels to RKHS

- To each kernel K is associated a reproducing kernel Hilbert space (RKHS), subset of $\mathbb{R}^{\mathcal{X}}$, defined as the completion of:

$$span\left\{K(x,.), x \in \mathcal{X}\right\}.$$

- The norm of a function $f = \sum_i a_i K(x_i,.)$ in the RKHS is:

$$||f||_{\mathcal{H}} = \sum_{i,j} a_i a_j K(x_i, x_j).$$

Pattern relevance

- Let $e(x)$ the profile of gene x
- Let $K_1(x, y) = e(x).e(y)$ be the linear kernel, with RKHS H_1.
- The norm $||.||_{H_1}$ is a relevance functional: the relevance of $f \in H_1$ increases when the following decreases:

$$\frac{||f||_{H_1}}{||f||_{L_2}}$$

Pattern smoothness

- Let $K_2(x, y)$ be the diffusion kernel obtained from the gene network, with RKHS H_2.
- It can be considered as a discretized version of a Gaussian kernel (solving the heat equation with the graph Laplacian)
- The norm $||.||_{H_2}$ is a smoothness functional: the smoother a function $f : \mathcal{X} \to \mathbb{R}$, the larger the function:

$$\frac{||f||_{H_1}}{||f||_{L_2}}$$

Problem reformulation

Find a linear function f_1 and a function f_2 such that:

- f_1 be relevant : $||f_1||_{L^2}/||f_1||_{H_1}$ be large
- f_2 be smooth : $||f_2||_{L^2}/||f_2||_{H_2}$ be large
- f_1 and f_2 be correlated :

$$\frac{f_1.f_2}{||f_1||_{L^2}||f_2||_{L^2}}$$

be large

Problem reformulation (2)

The three goals can be combined in the following problem:

$$\max_{f_1, f_2} \frac{f_1 . f_2}{\left(||f_1||^2_{L^2} + \delta ||f_1||^2_{H_1} \right)^{\frac{1}{2}} \left(||f_2||^2_{L^2} + \delta ||f_2||^2_{H_2} \right)^{\frac{1}{2}}}$$

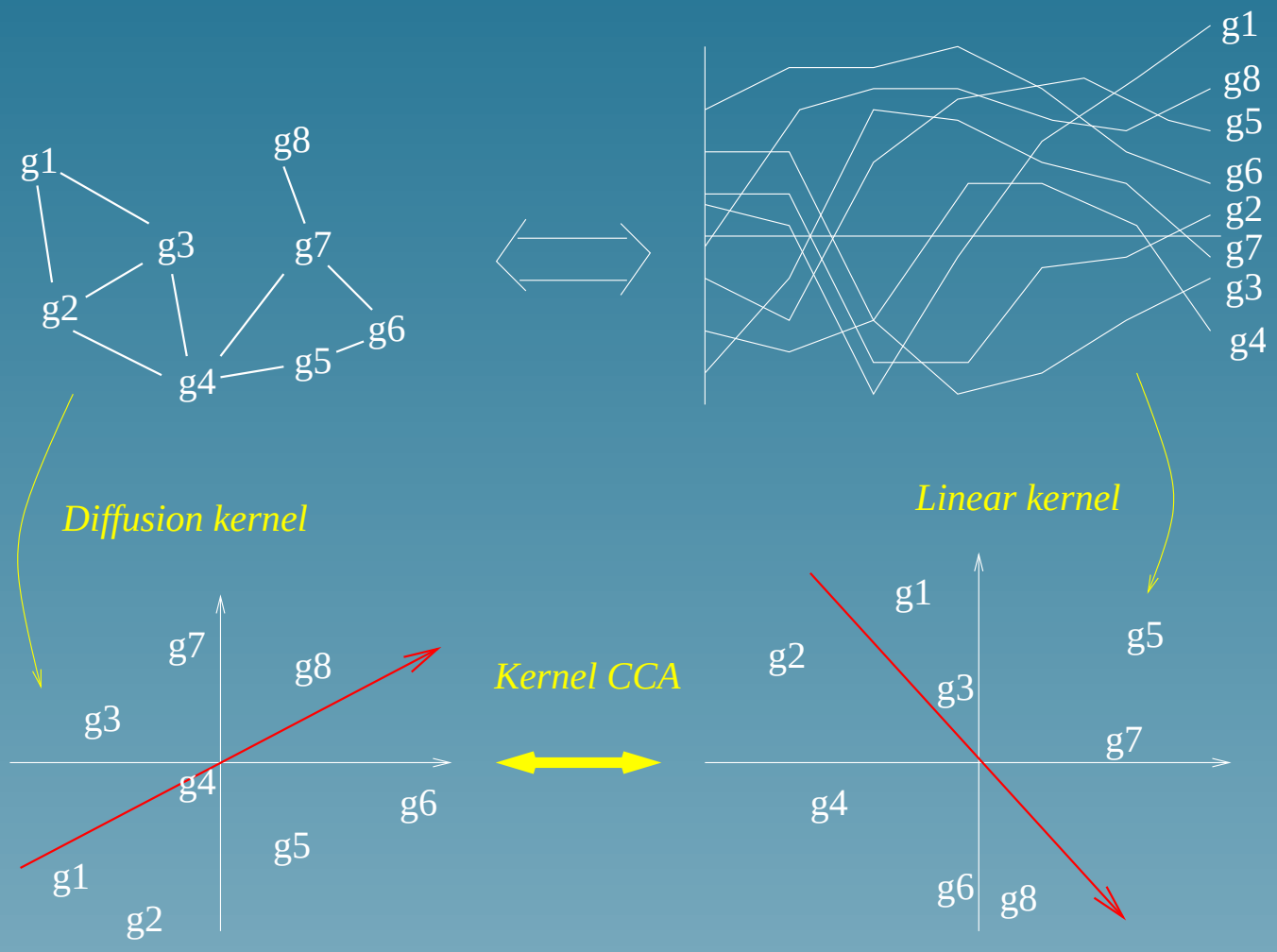
where the parameter δ controls the trade-off between relevance/smoothness on the one hand, correlation on the other hand.

Solving the problem

This formultation is equivalent to a generalized form of CCA (Kernel-CCA, Bach and Jordan, 2002), which is equivalent to the following generalized eigenvector problem

$$\begin{pmatrix} 0 & K_1K_2 \\ K_2K_1 & 0 \end{pmatrix} \begin{pmatrix} \alpha \\ \beta \end{pmatrix} = \rho \begin{pmatrix} K_1^2 + \delta K_1 & 0 \\ 0 & K_2^2 + \delta K_2 \end{pmatrix} \begin{pmatrix} \alpha \\ \beta \end{pmatrix}$$

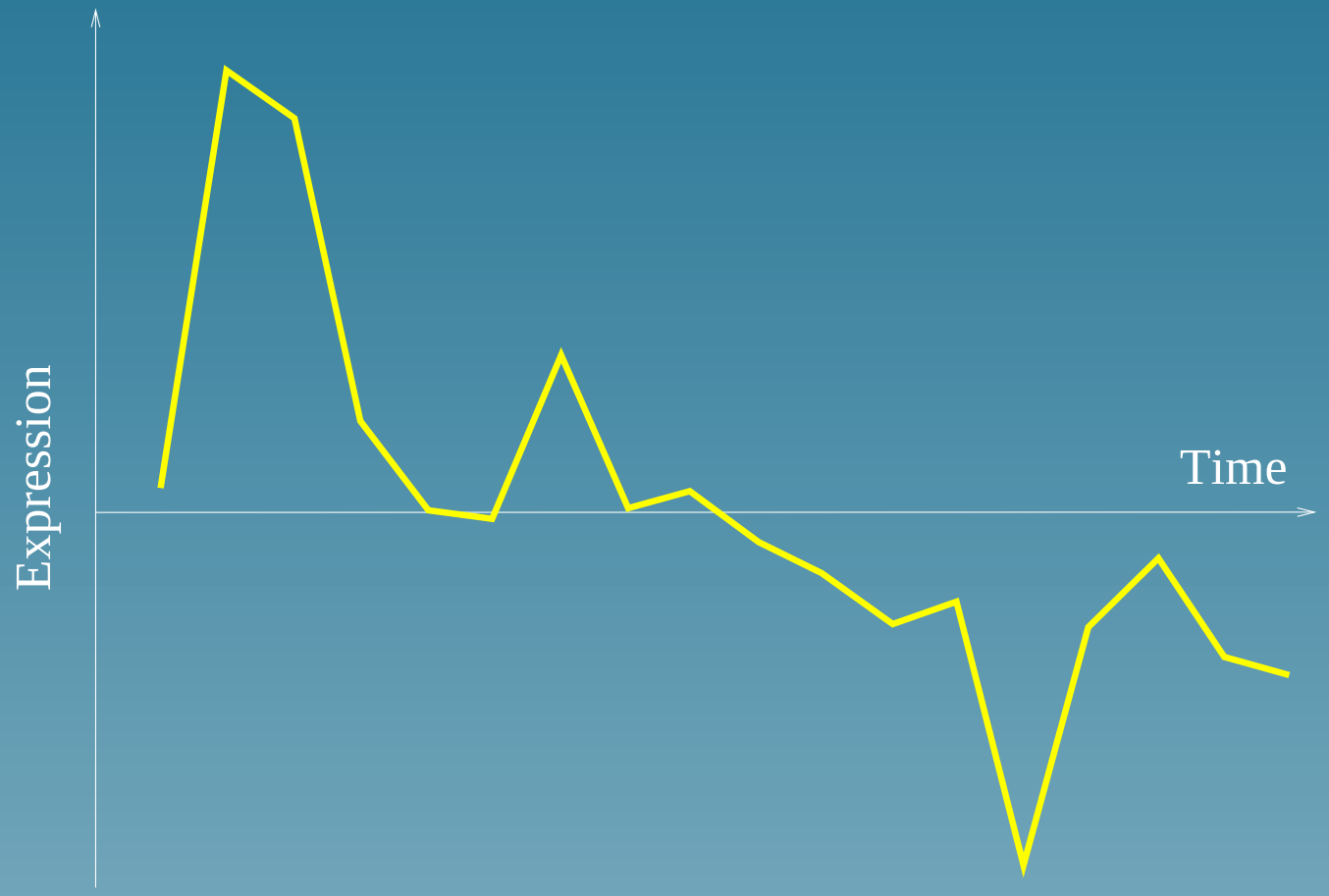
Summary


g1
g8
g3
g7
g2
g6
g4
g5
g1
g8
g5
g6
g2
g7
g3
g4
Diffusion kernel
Linear kernel
Kernel CCA
g7
g8
g3
g4
g6
g5
g1
g2
g1
g5
g2
g3
g7
g4
g6
g8

Data

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

First pattern of expression

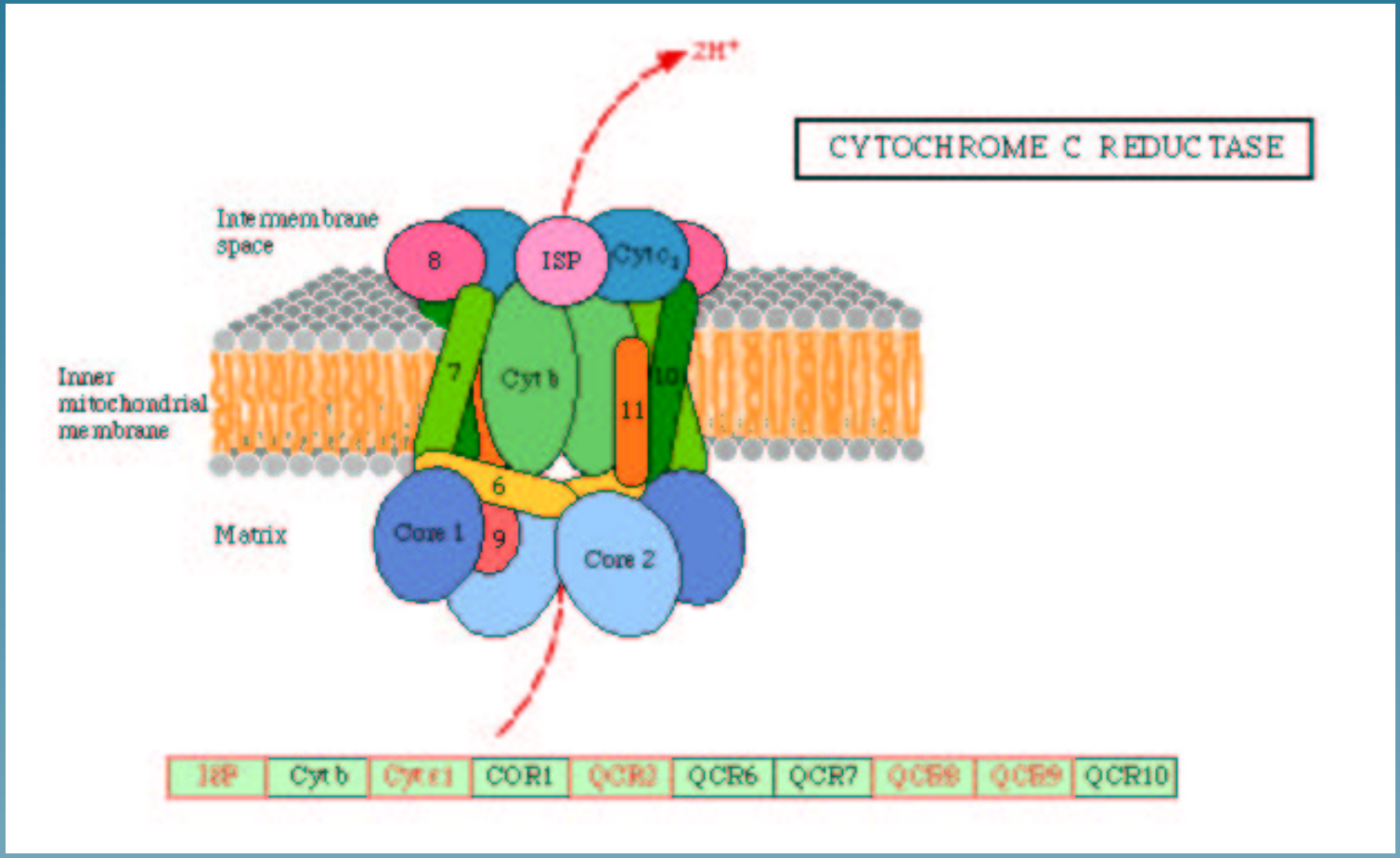


Related metabolic pathways

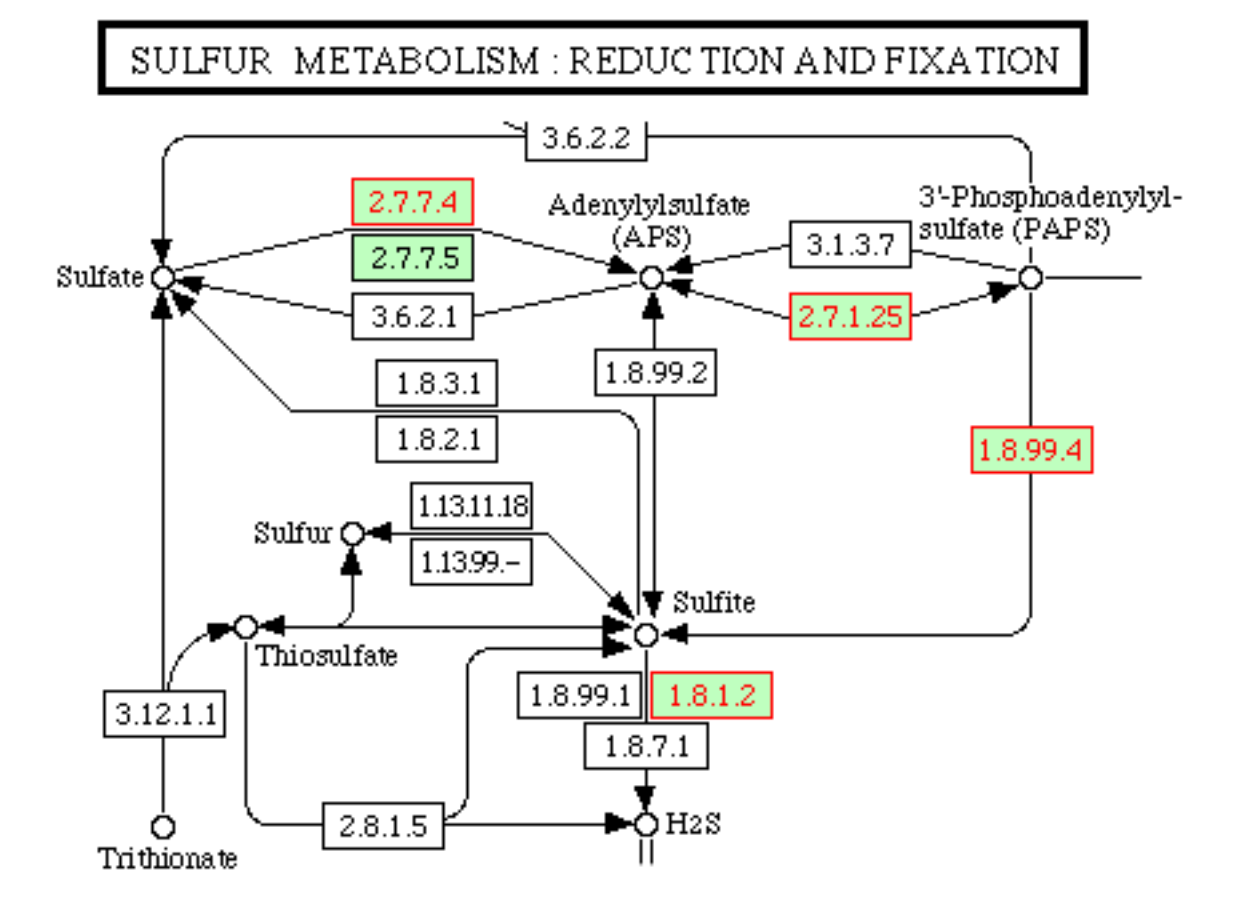
50 genes with highest $s_2 - s_1$ belong to:

- Oxidative phosphorylation (10 genes)
- Citrate cycle (7)
- Purine metabolism (6)
- Glycerolipid metabolism (6)
- Sulfur metabolism (5)
- Selenoaminoacid metabolism (4) , etc...

Related genes



Related genes



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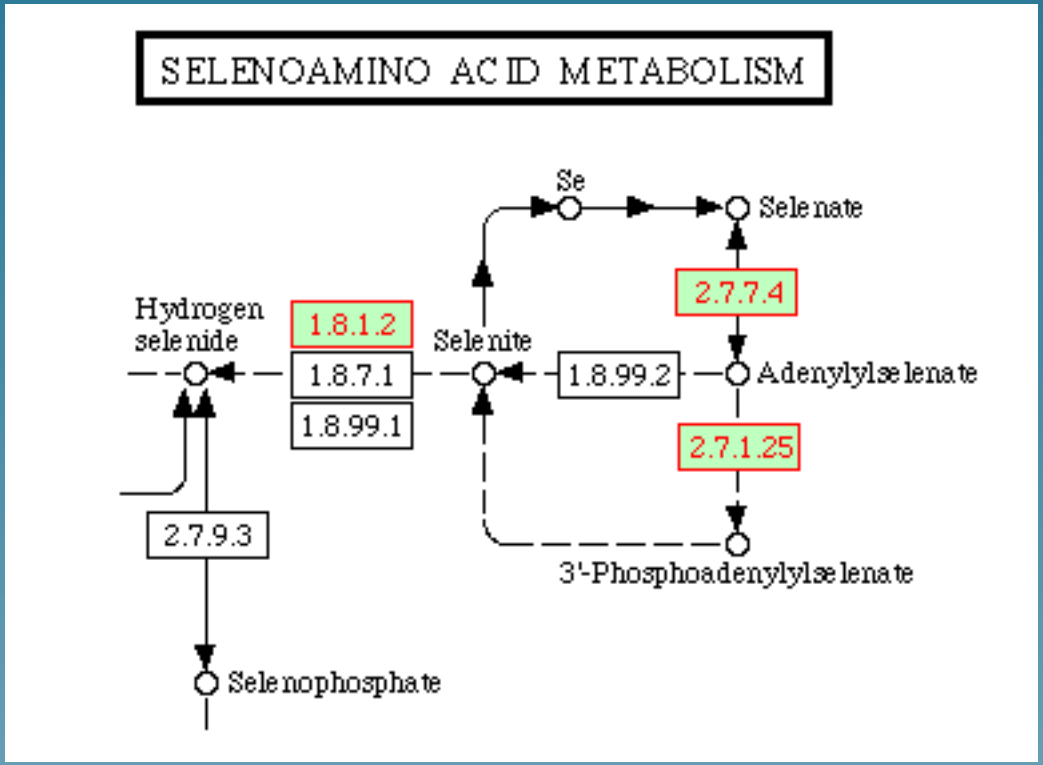


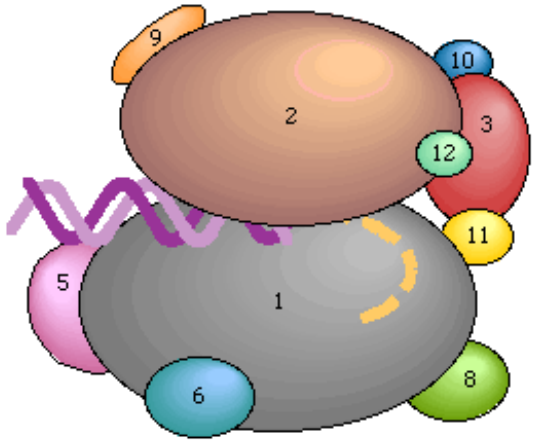
Opposite pattern

Related genes

- RNA polymerase (11 genes)
- Pyrimidine metabolism (10)
- Aminoacyl-tRNA biosynthesis (7)
- Urea cycle and metabolism of amino groups (3)
- Oxidative 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

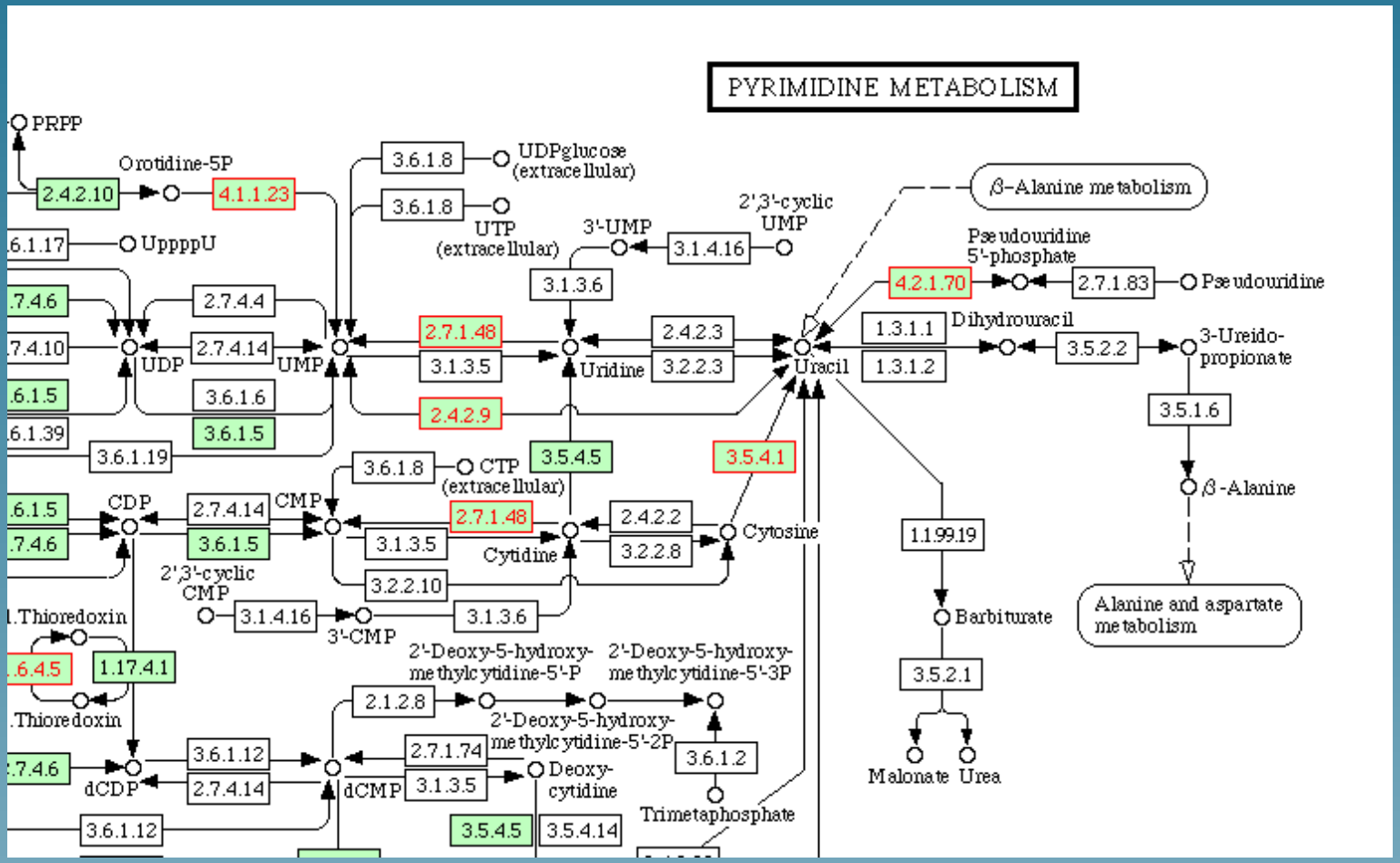
Eukaryotic Pol III

C2	C3	C4	C5	C11
C1	C19	C25	C31	C34

Eukaryotic Pol I

A2	A12	A14	A34	A43	A49
A1					

Related genes



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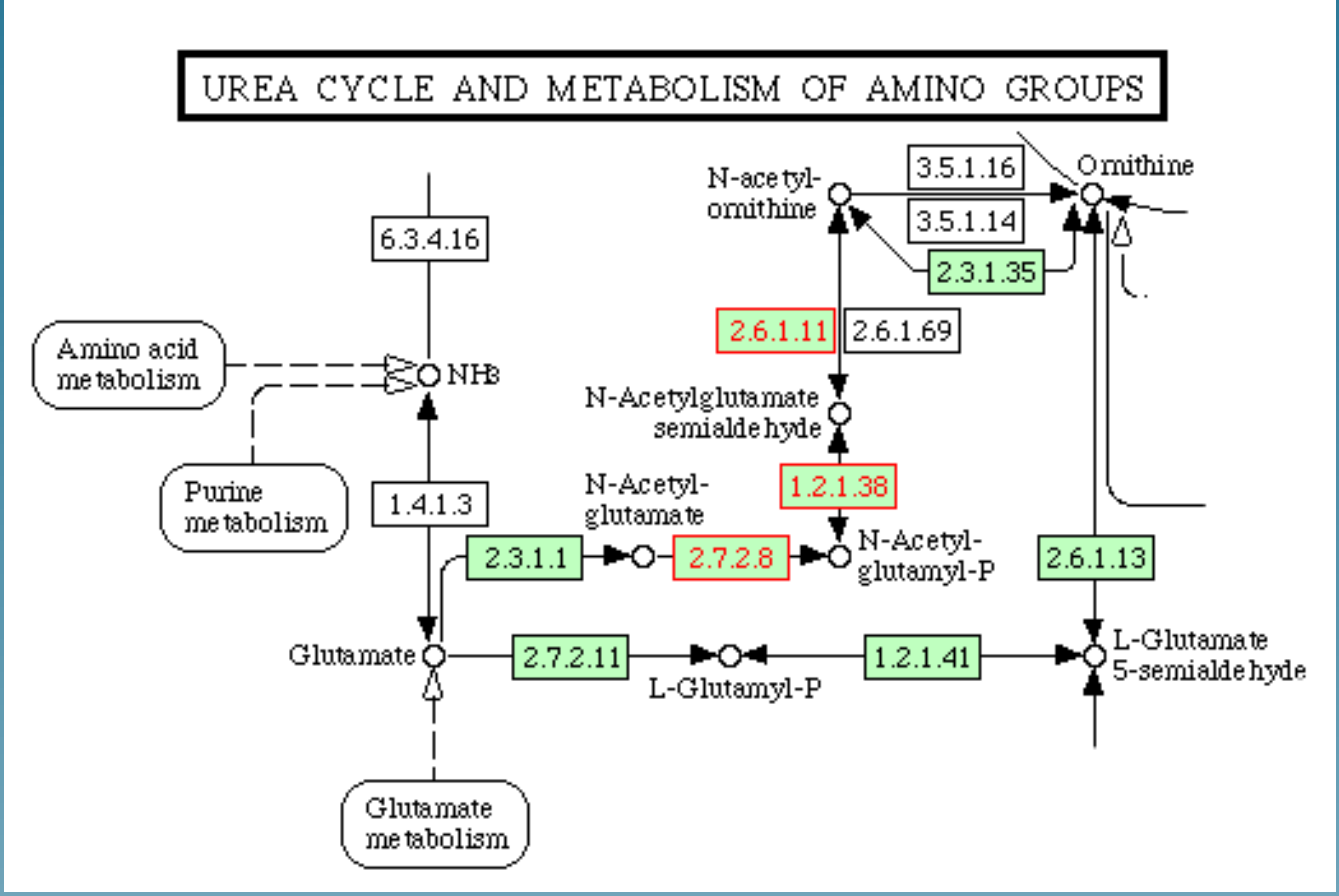

Extensions

- Can be used to extract features from expression profiles (preprint 2002)
- Can be generalized to more than 2 datasets and other kernels
- Can be used to extract clusters of genes (e.g., operon detection, *ISMB 03* with Y. Yamanishi, A. Nakaya and M. Kanehisa)

Conclusion

Conclusion

- Kernels offer a versatile framework to represent biological data
- Increasing library of kernels and kernel methods
- Encouraging results on real-world applications
- Candidate to play an important role in learning from heterogeneous data