Support vector machines, Kernel methods, and Applications in bioinformatics

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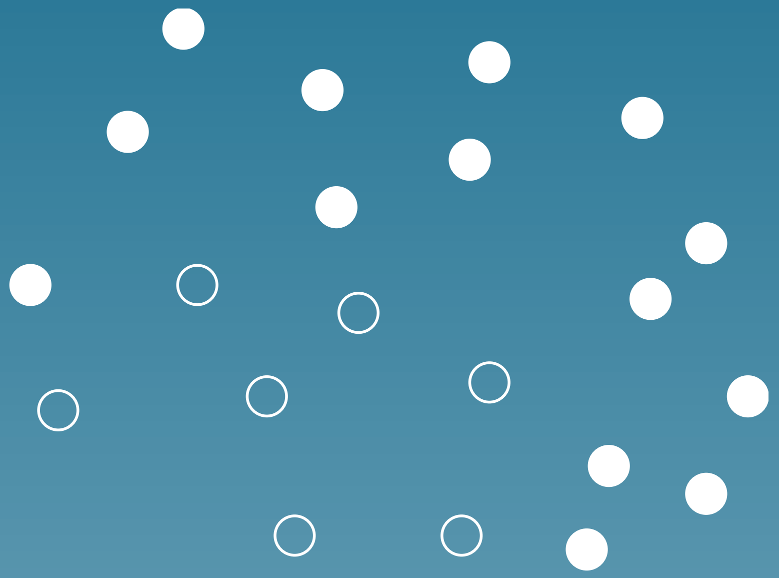
Overview

1. Support Vector Machines and kernel methods
2. Application: Gene function prediction from phylogenetic profile
3. Application: Protein remote homology detection
4. Application: Extracting pathway activity from gene expression data

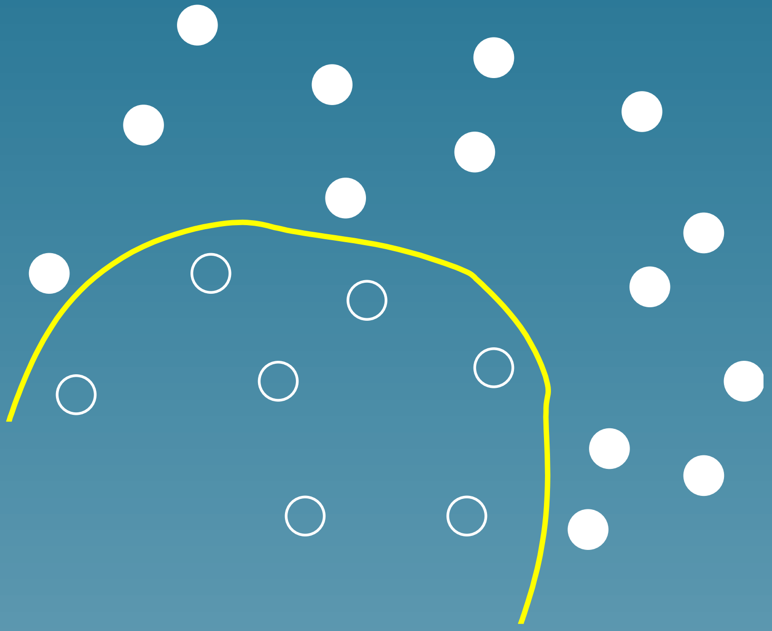
Partie 1

Support Vector Machines (SVM) and Kernel Methods

The pattern recognition problem

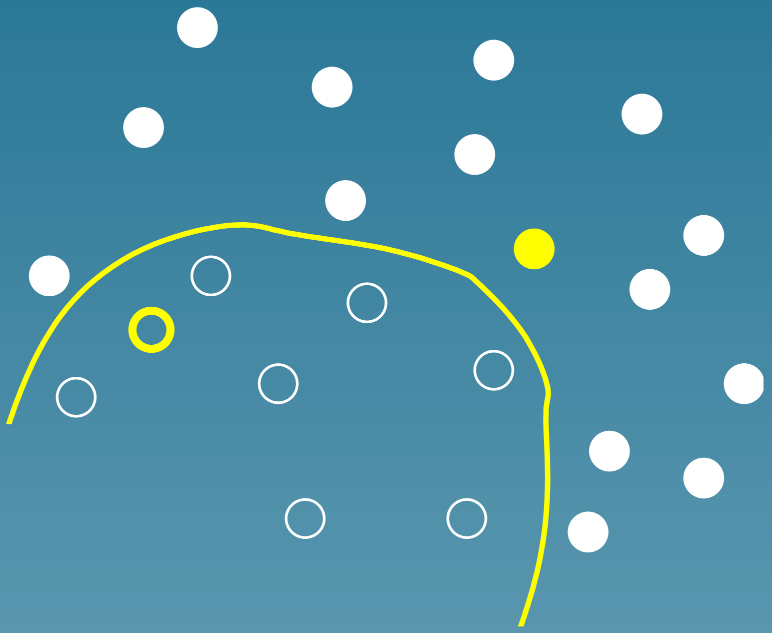


The pattern recognition problem



- Learn from labelled examples a discrimination rule

The pattern recognition problem

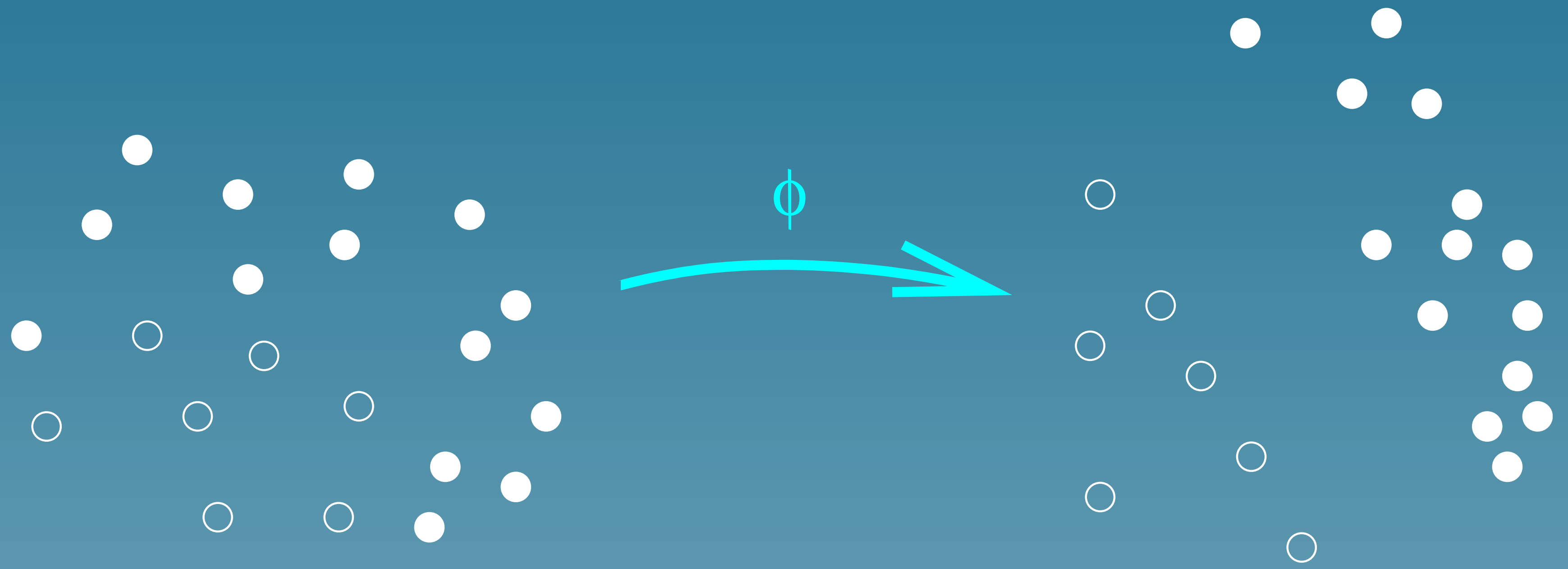


- Learn from labelled examples a discrimination rule
- Use it to predict the class of new points

Pattern recognition examples

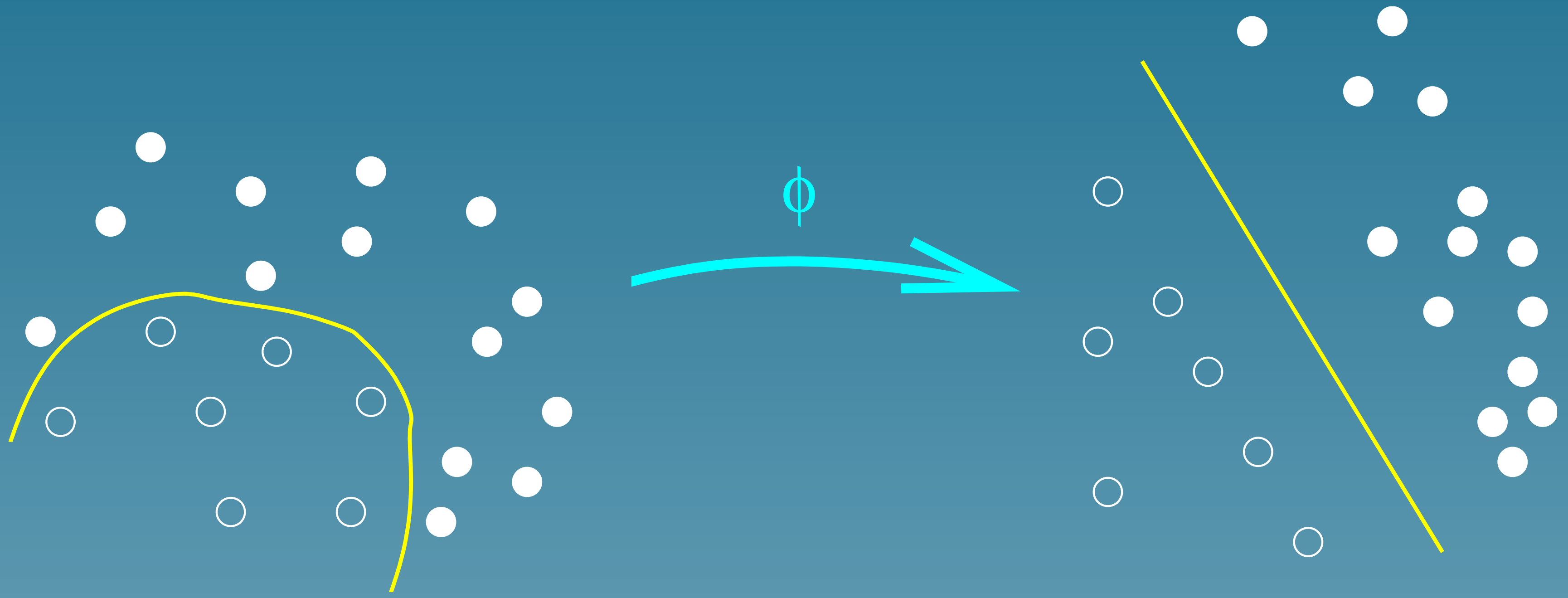
- Medical diagnosis (e.g., from microarrays)
- Drugability/activity of chemical compouds
- Gene function, structure, localization
- Protein interactions

Support Vector Machines for pattern recognition



- Object x represented by the vector $\Phi(\vec{x})$ (feature space)

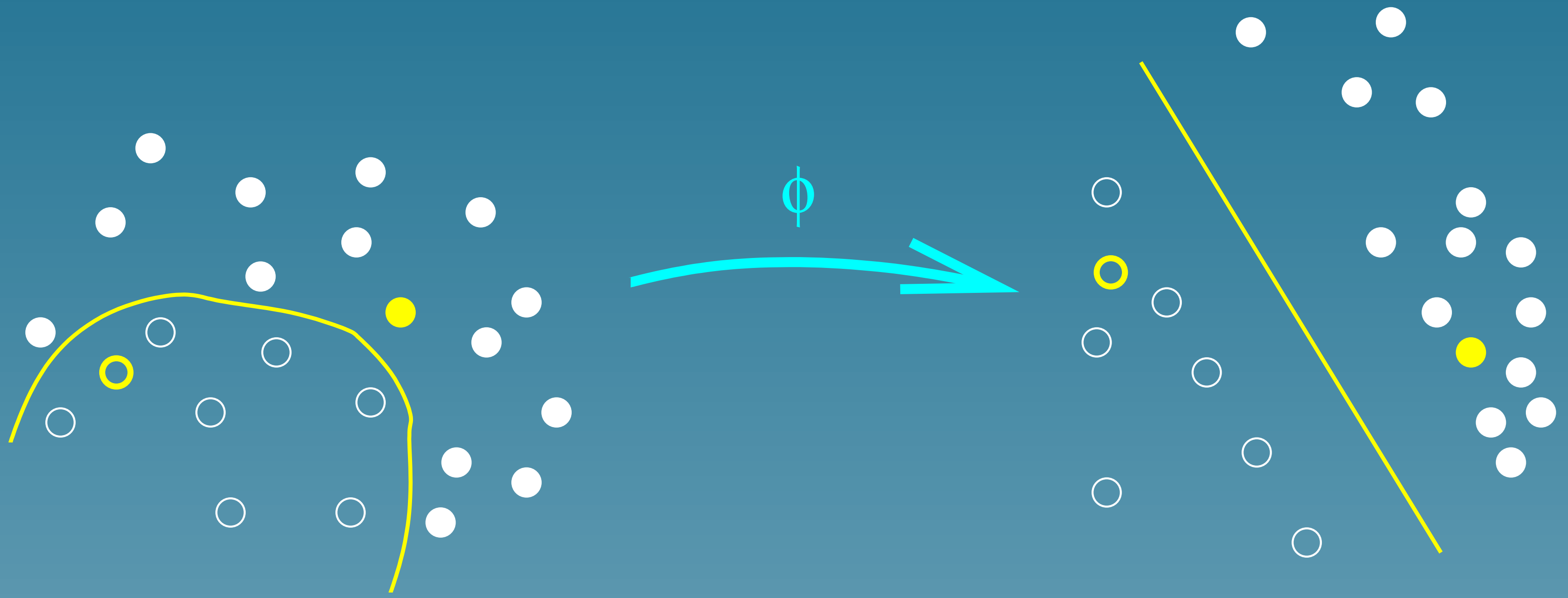
Support Vector Machines for pattern recognition



- Object x represented by the vector $\Phi(\vec{x})$ (feature space)

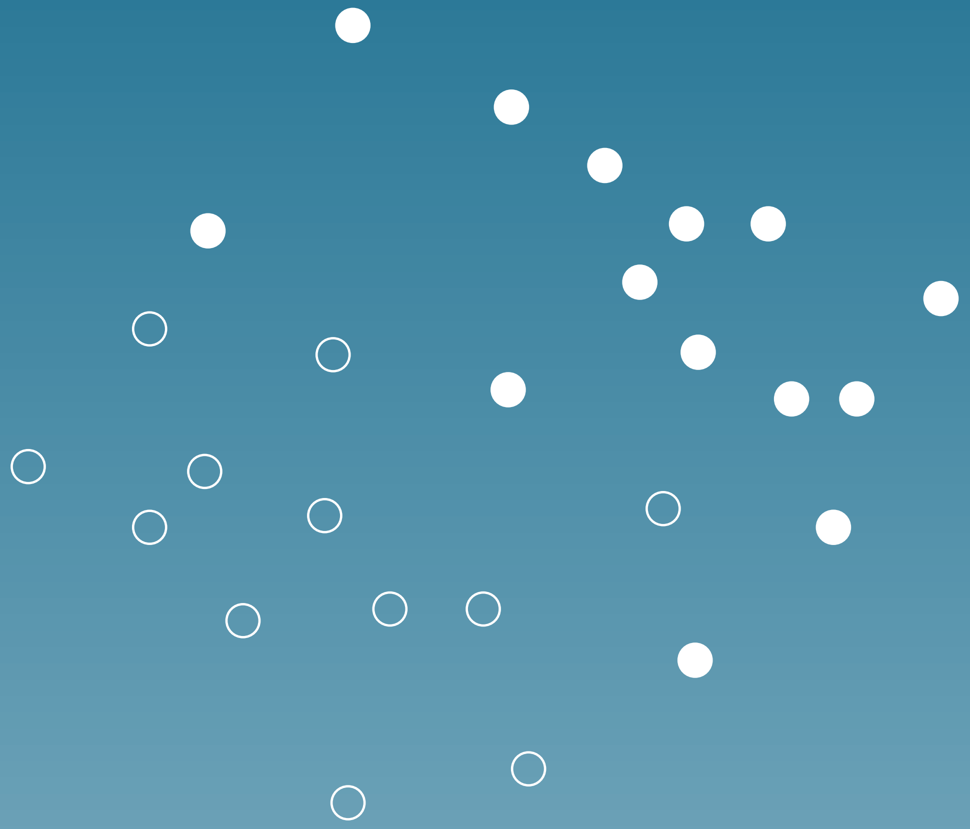
- Linear separation in the feature space

Support Vector Machines for pattern recognition

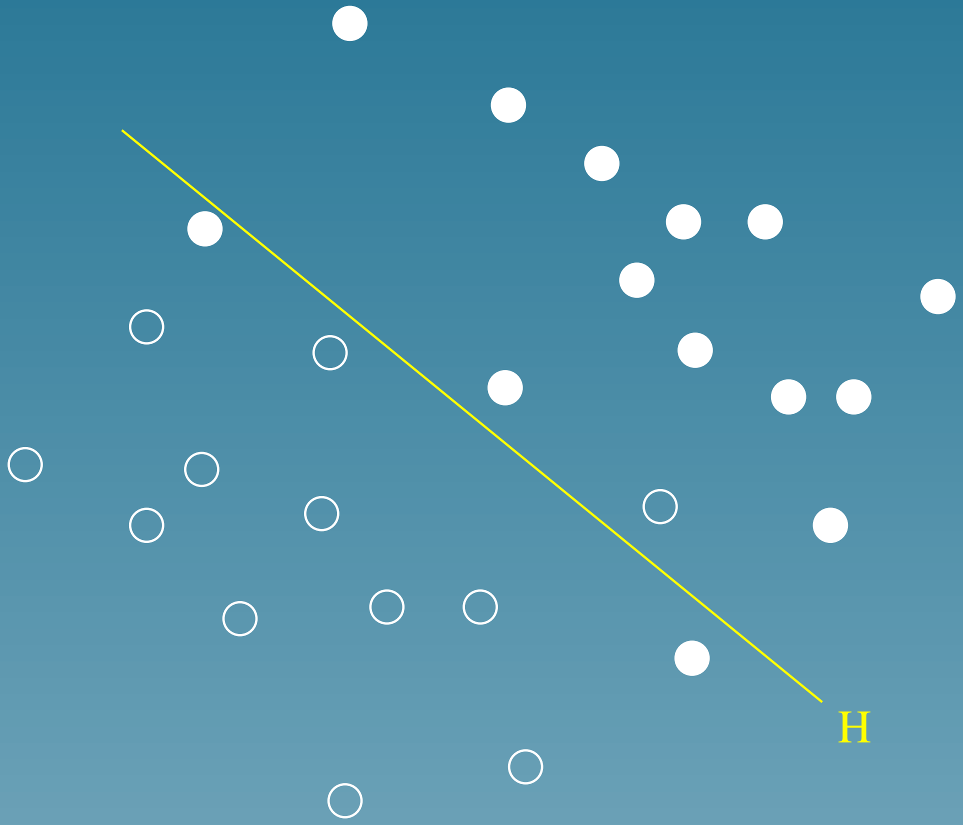


- Object x represented by the vector $\Phi(\vec{x})$ (feature space)
- Linear separation with large margin in the feature space

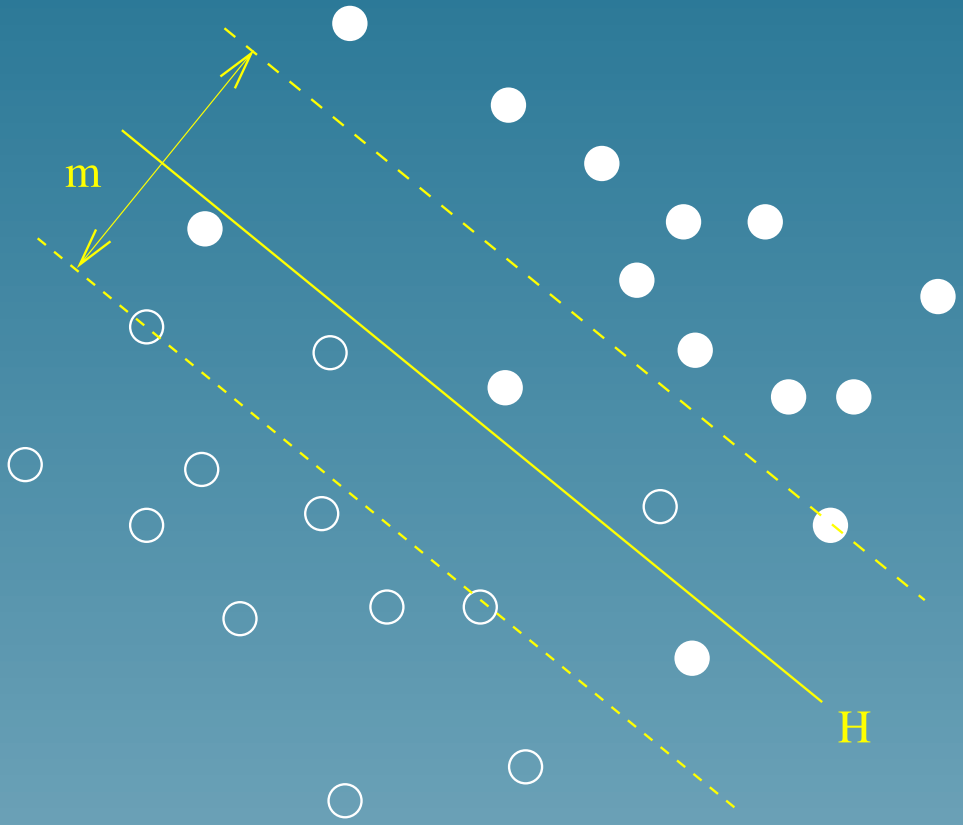
Large margin separation



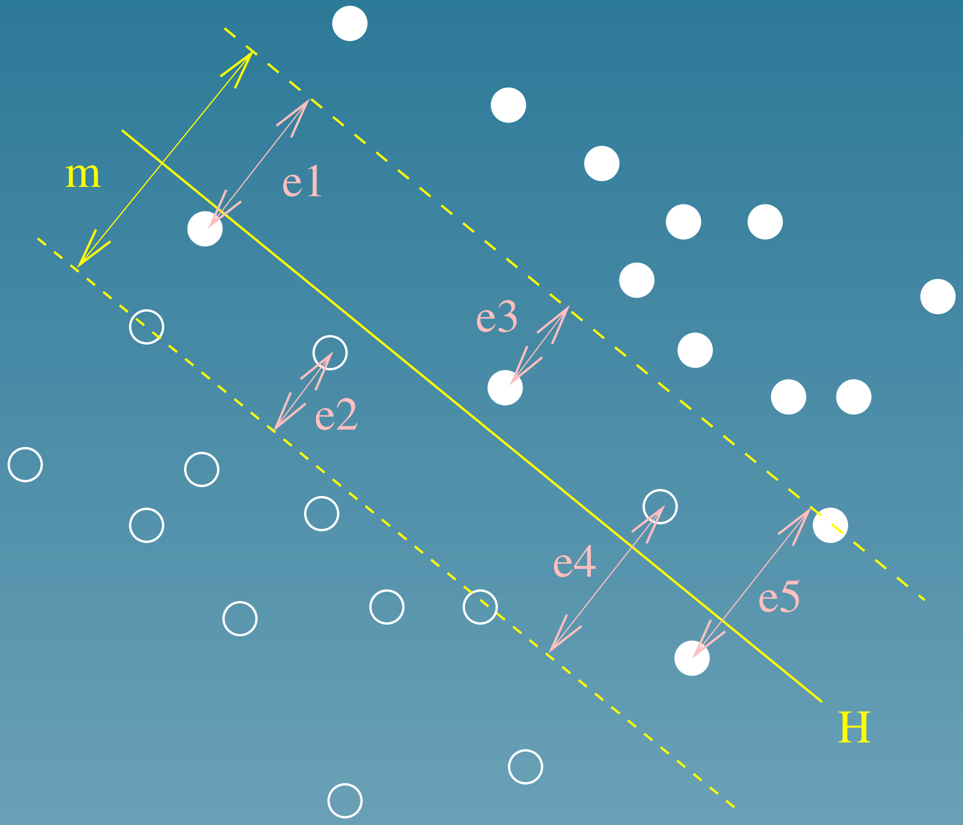
Large margin separation



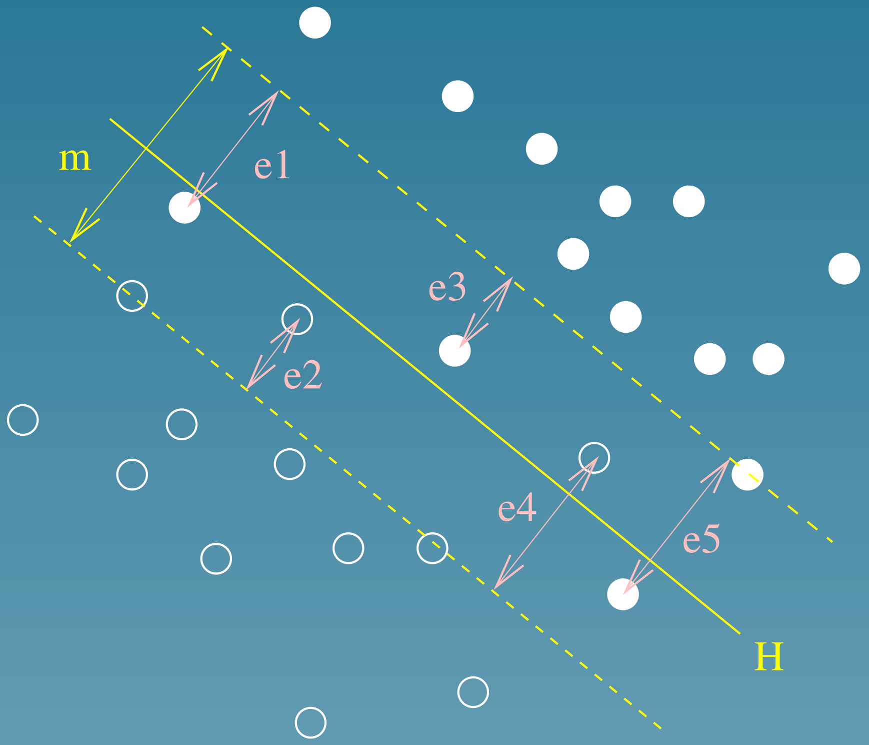
Large margin separation



Large margin separation



Large margin separation



$$\min_{H,m}\left\{\frac{1}{m^2}+C\sum_i e_i\right\}$$

Dual formulation

The classification of a new point x is the sign of:

$$f(x) = \sum_i \alpha_i K(x, x_i) + b,$$

where α_i solves:

$$\begin{cases} \max_{\vec{\alpha}} \sum_{i=1}^{n} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{n} \alpha_i \alpha_j y_i y_j K(x_i, x_j) \\ \forall i = 1, \ldots, n \quad 0 \leq \alpha_i \leq C \\ \sum_{i=1}^{n} \alpha_i y_i = 0 \end{cases}$$

with the notation:

$$K(x, x') = \Phi(\vec{x}).\Phi(\vec{x}')$$

The kernel trick for SVM

- The separation can be found without knowing $\Phi(x)$. Only the kernel matters:

$$K(x,y) = \Phi(\vec{x}).\Phi(\vec{y})$$

- Simple kernels $K(x,y)$ can correspond to complex $\vec{\Phi}$
- SVM work with any sort of data as soon as a kernel is defined

Kernel examples

- Linear :

$$K(x, x') = x.x'$$

- Polynomial :

$$K(x, x') = (x.x' + c)^d$$

- Gaussian RBf :

$$K(x, x') = \exp\left(\frac{||x - x'||^2}{2\sigma^2}\right)$$

Kernels

For any set $\mathcal{X}$, a function $K : \mathcal{X} \times \mathcal{X} \to \mathbb{R}$ is a kernel iff:

- it is symetric :

$$K(x, y) = K(y, x),$$

- it is positive semi-definite:

$$\sum_{i,j} a_i a_j K(x_i, x_j) \geq 0$$

for all $a_i \in \mathbb{R}$ and $x_i \in \mathcal{X}$

Advantages of SVM

- Works well on real-world applications
- Large dimensions, noise OK (?)
- Can be applied to any kind of data as soon as a kernel is available

Examples: SVM in bioinformatics

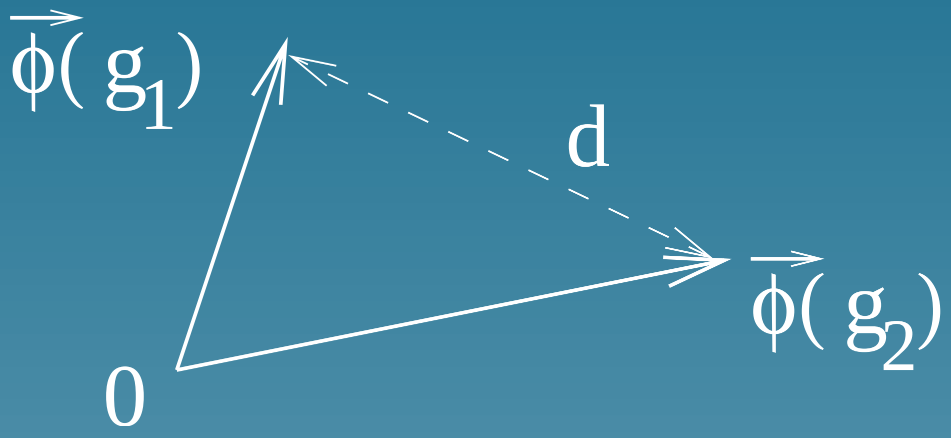
- Gene functional classification from microarry: Brown et al. (2000), Pavlidis et al. (2001)
- Tissue classification from microarray: Mukherje et al. (1999), Furey et al. (2000), Guyon et al. (2001)
- Protein family prediction from sequence: Jaakkoola et al. (1998)
- Protein secondary structure prediction: Hua et al. (2001)
- Protein subcellular localization prediction from sequence: Hua et al. (2001)

Kernel methods

Let $K(x, y)$ be a given kernel. Then is it possible to perform other linear algorithms implicitly in the feature space such as:

- Compute the distance between points
- Principal component analysis (PCA)
- Canonical correlation analysis (CCA)

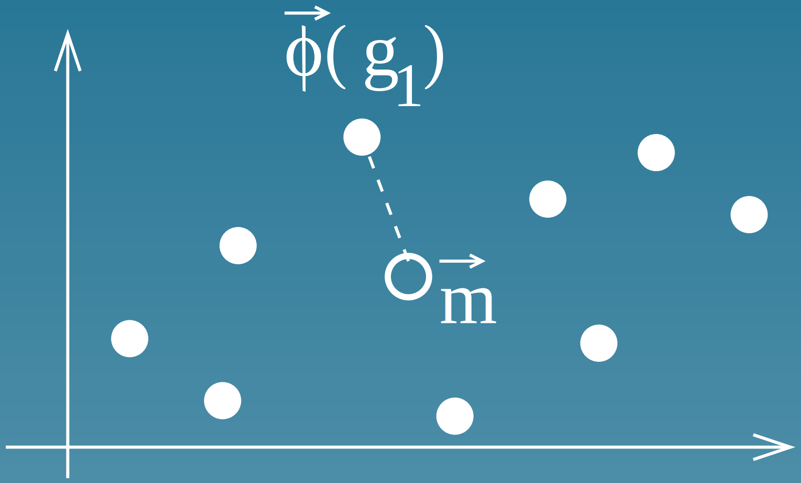
Compute the distance between objects



$$
\begin{aligned}
d(g_1,g_2)^2 &= \|\vec{\Phi}(g_1) - \vec{\Phi}(g_2)\|^2 \\
&= \left(\vec{\Phi}(g_1) - \vec{\Phi}(g_2)\right).\left(\vec{\Phi}(g_1) - \vec{\Phi}(g_2)\right) \\
&= \vec{\Phi}(g_1).\vec{\Phi}(g_1) + \vec{\Phi}(g_2).\vec{\Phi}(g_2) - 2\vec{\Phi}(g_1).\vec{\Phi}(g_2)
\end{aligned}
$$

$$d(g_1,g_2)^2 = K(g_1,g_1) + K(g_2,g_2) - 2K(g_1,g_2)$$

Distance to the center of mass

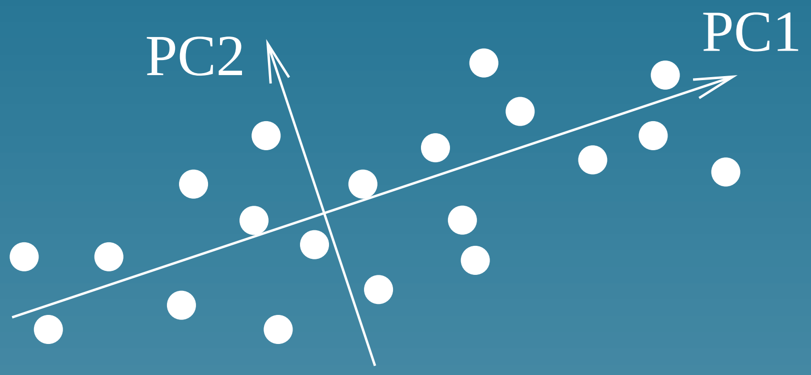


Center of mass: $\vec{m} = \frac{1}{N}\sum_{i=1}^{N} \vec{\Phi}(g_i)$, hence:

$$\|\vec{\Phi}(g_1) - \vec{m}\|^2 = \vec{\Phi}(g_1).\vec{\Phi}(g_1) - 2\vec{\Phi}(g_1).\vec{m} + \vec{m}.\vec{m}$$

$$= K(g_1, g_1) - \frac{2}{N}\sum_{i=1}^{N} K(g_1, g_i) + \frac{1}{N^2}\sum_{i,j=1}^{N} K(g_i, g_j)$$

Principal component analysis

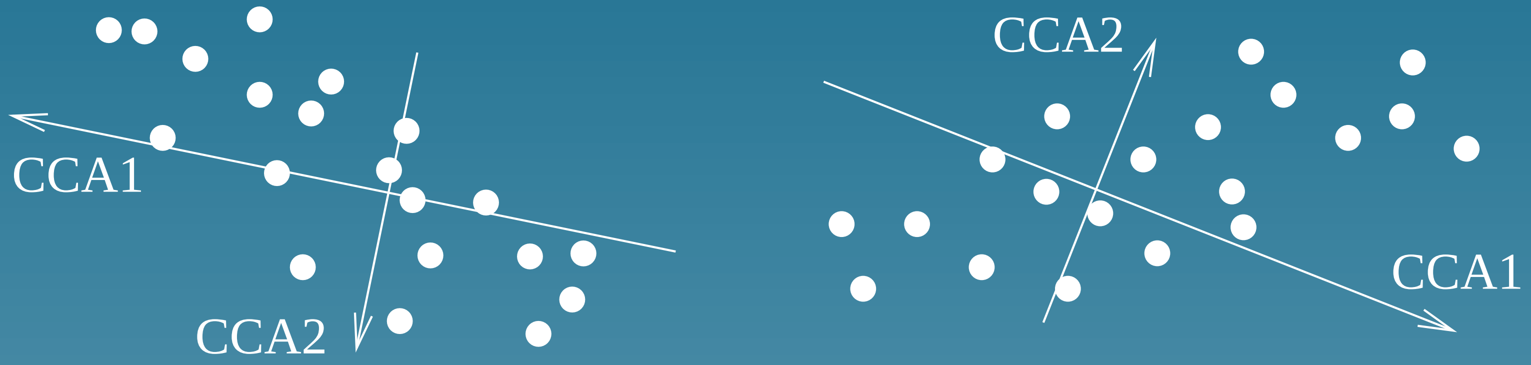


It is equivalent to find the eigenvectors of

$$\begin{aligned} K &= \left(\vec{\Phi}(g_i).\vec{\Phi}(g_j)\right)_{i,j=1\ldots N} \\ &= \left(K(g_i, g_j)\right)_{i,j=1\ldots N} \end{aligned}$$

Useful to project the objects on small-dimensional spaces (feature extraction).

Canonical correlation analysis



K_1 and K_2 are two kernels for the same objects. CCA can be performed by solving the following generalized eigenvalue problem:

$$\begin{pmatrix} 0 & K_1K_2 \\ K_2K_1 & 0 \end{pmatrix} \vec{\xi} = \rho \begin{pmatrix} K_1^2 & 0 \\ 0 & K_2^2 \end{pmatrix} \vec{\xi}$$

Useful to find correlations between different representations of the same objects (ex: genes, ...)

Part 2

Application: Gene functional prediction from phylogenetic profiles

(*ISMB 2002*)

Definition

- 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 measure the similarity between profiles?

Naive approach

- Count the number of bits in common:

$$\begin{array}{ccccccccccc} x & 1 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 1 & 0 \\ y & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 1 \end{array}$$

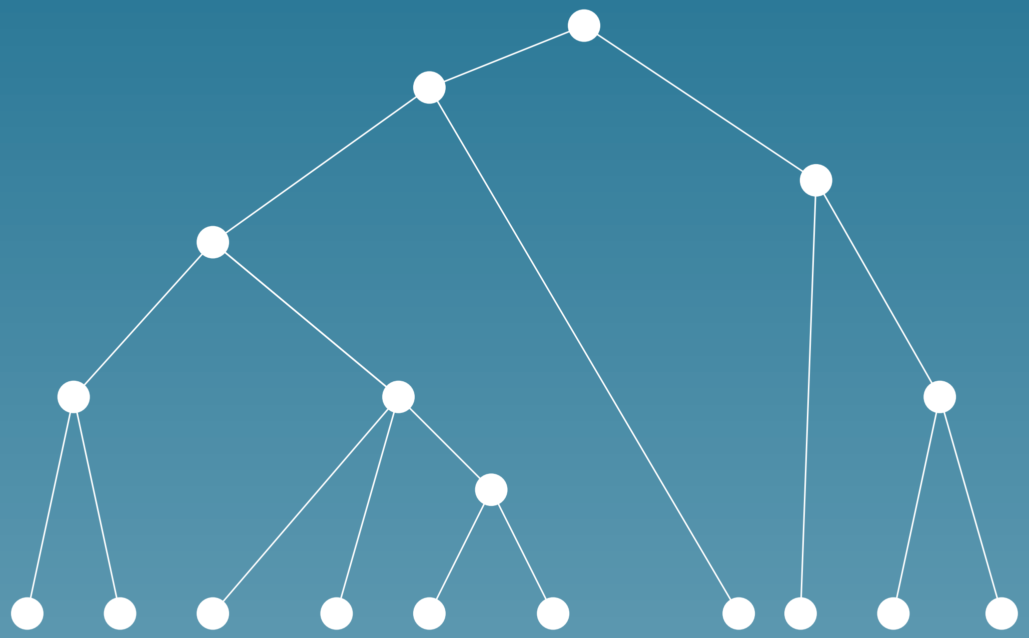
$$s(x, y) = 5$$

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

Limitations of the naive approach

- The set of sequenced organisms has a strong influence on the similarity score (e.g., eukaryotes are under-represented)
- A more detailed understanding of when two proteins were transmitted together or not during evolution could be useful

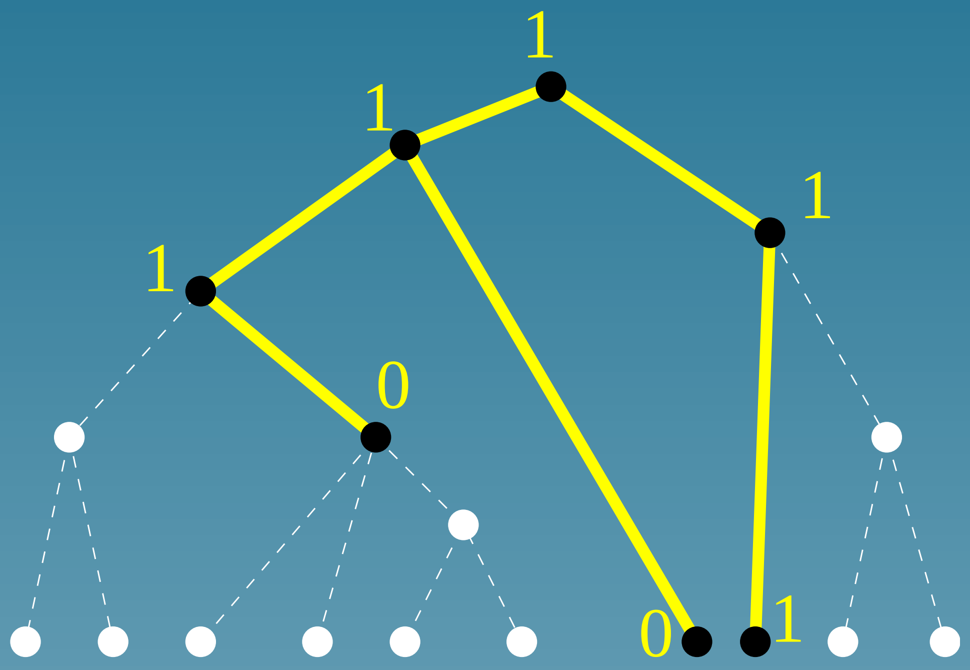
What is not used in the naive approach



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

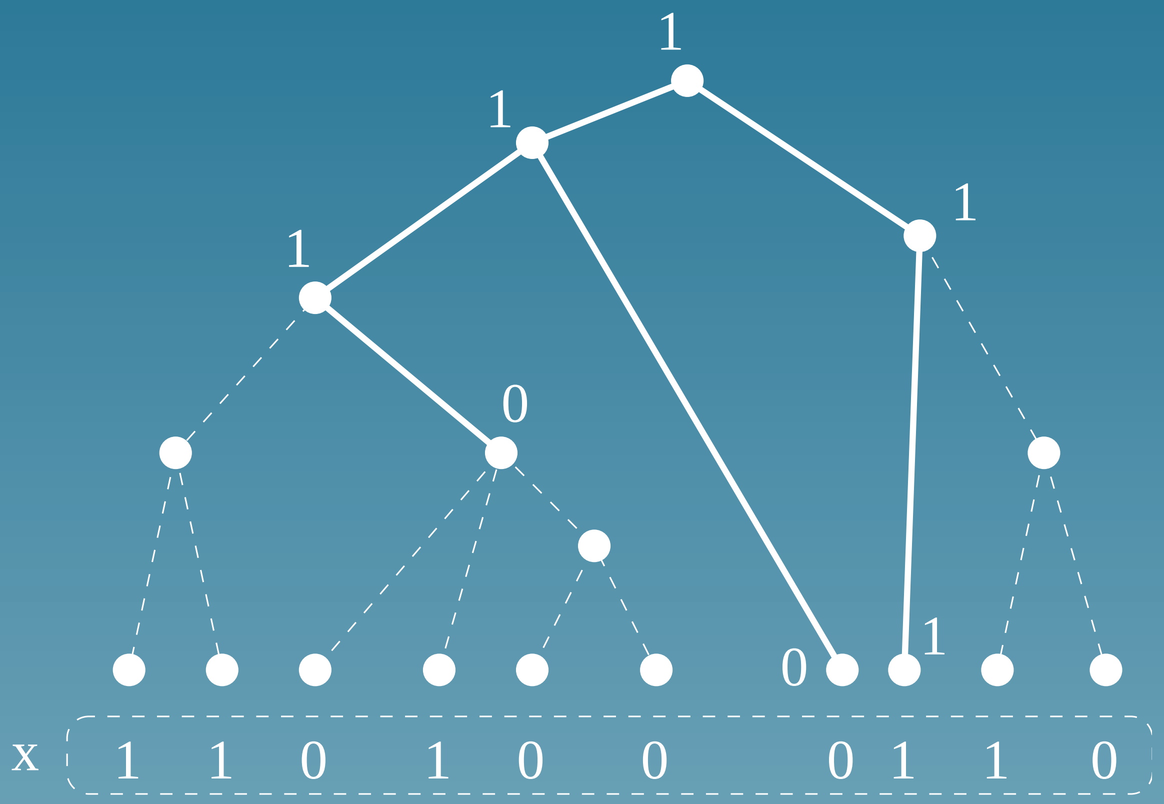
The knowledge of the phylogenetic tree.

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:

  ⋆ $P(1) = 1 - P(0) = 0.9$, at the root,

  ⋆ 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

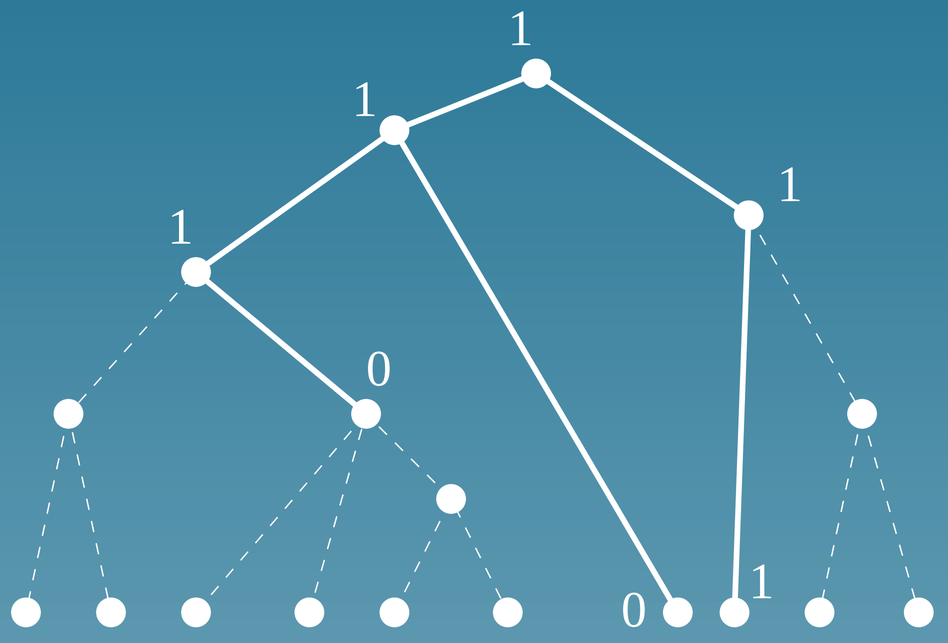
- Consider all possible evolution patterns $(e_1, \ldots, e_N)$, and represent each gene x by the vector:

$$\Phi(x) = \left(\begin{array}{c} \sqrt{P(e_1)} P(x|e_1) \\ \vdots \\ \sqrt{P(e_N)} P(x|e_N) \end{array} \right)$$

- The corresponding kernel is:

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

Comparing two profiles through evolution patterns



x 1 1 0 1 0 0 0 1 1 0

y 1 0 1 0 0 0 0 1 0 1

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

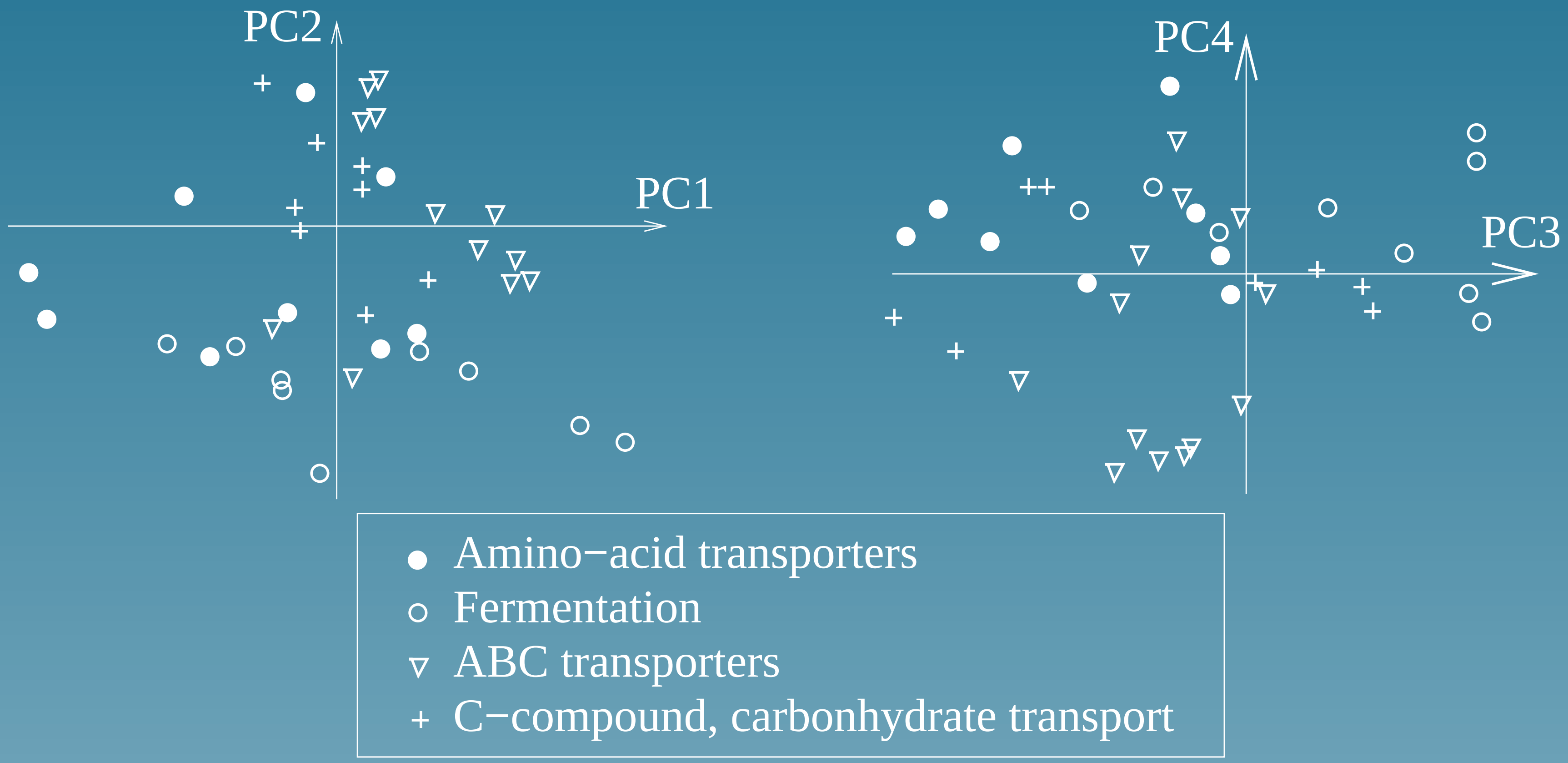
Results (ROC 50)

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%*

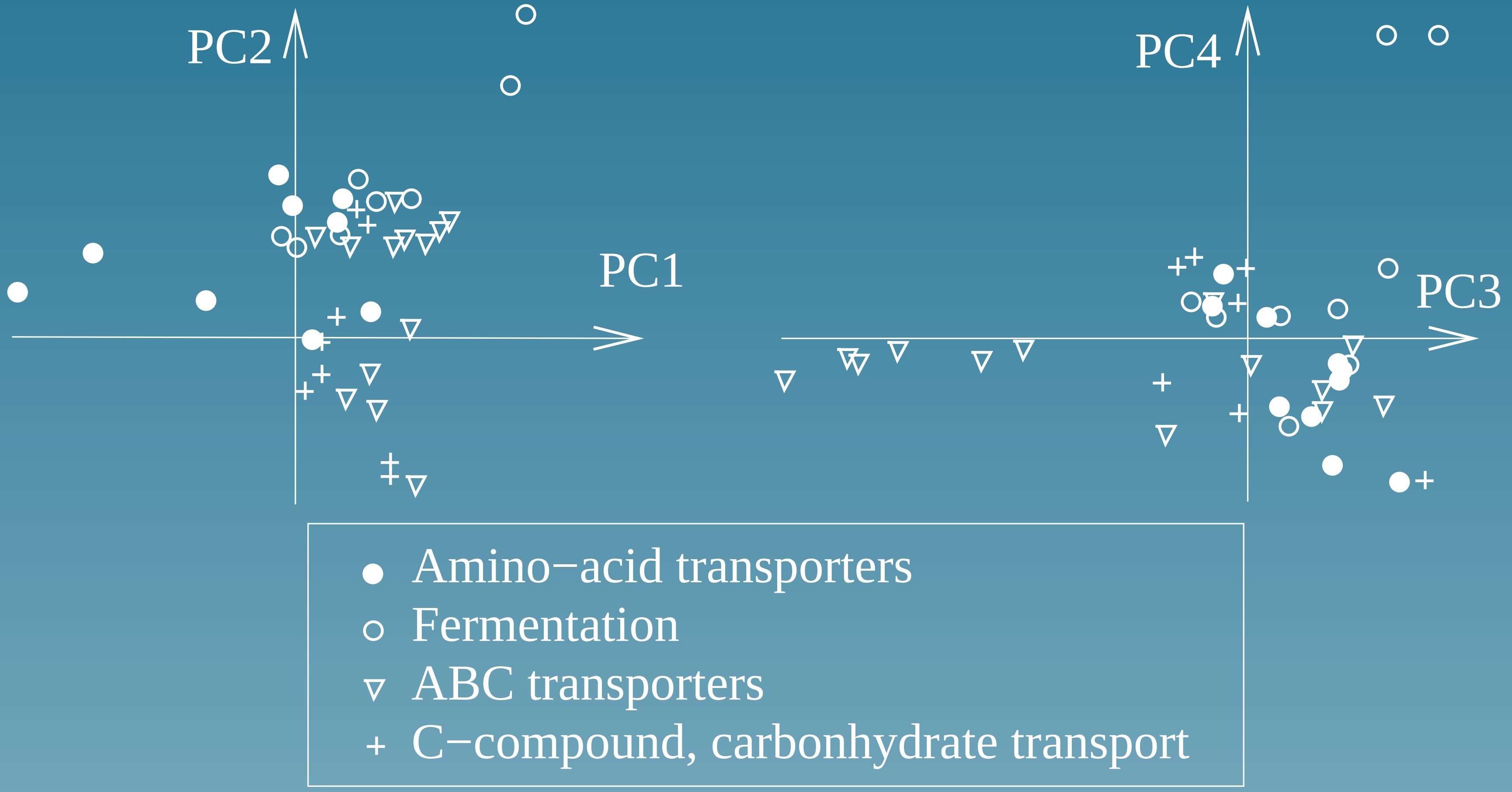
A insight into the feature space

- 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



Part 3

Local alignment kernel for strings

(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?

Related work

- Spectrum kernel (Leslie et al.):

$$K(x_1 \ldots x_m, y_1 \ldots y_n) = \sum_{i=1}^{m-k} \sum_{j=1}^{n-k} \delta(x_i \ldots x_{i+k}, y_j \ldots y_{j+k}).$$

Related work

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- Fisher kernel (Jaakkola et al.): given a statistical model $\left(p_\theta, \theta \in \Theta \subset \mathbb{R}^d\right)$:

$$\phi(x) = \nabla_\theta \log p_\theta(x)$$

  and use the Fisher information matrix.

Local alignment

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

```
ABCD EF---G-HI JKL
     ||   |  |
 MNO EEPORGS-I TUVWX
```

- 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:

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

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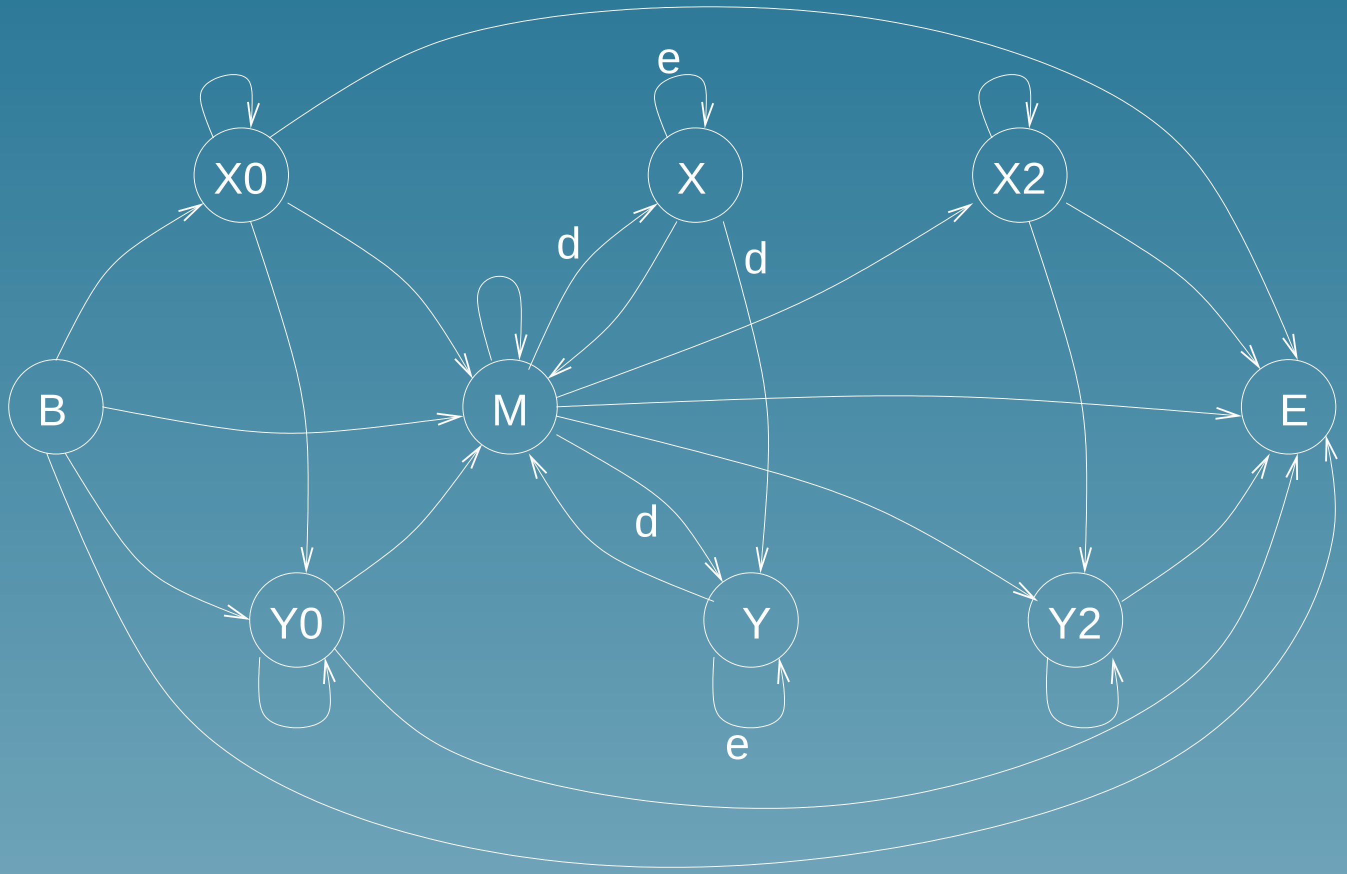
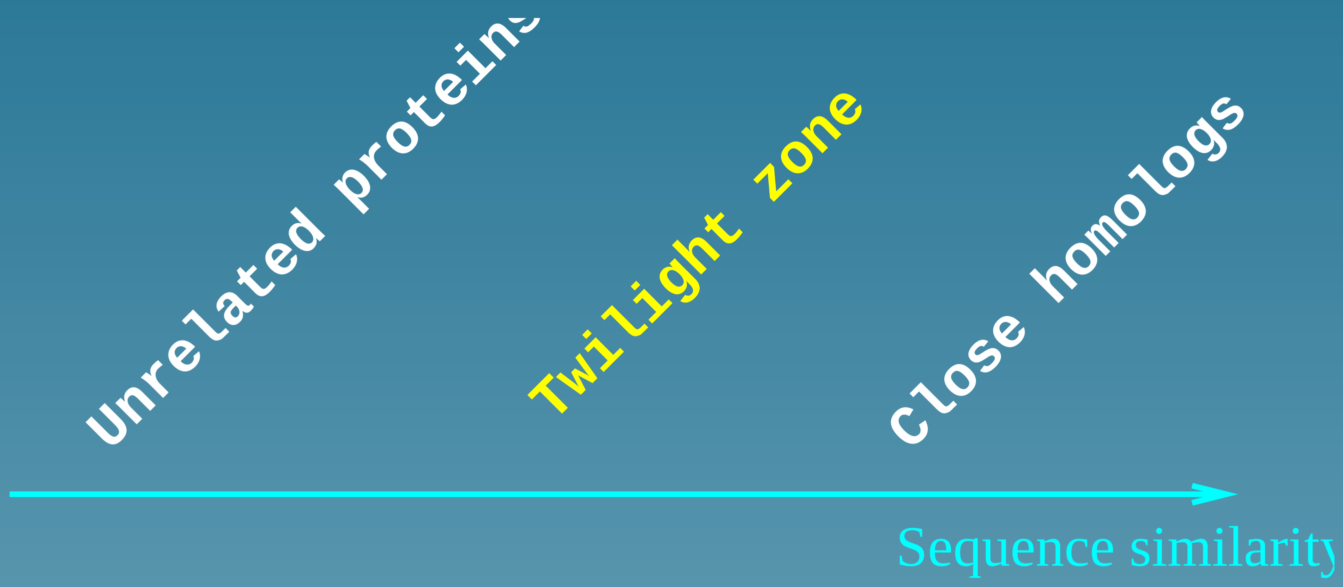
$$K_{LA}^{(\beta)}(x,y) = \sum_{\pi \in \Pi(x,y)} \exp\left(\beta s(x,y,\pi)\right),$$

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

Kernel computation

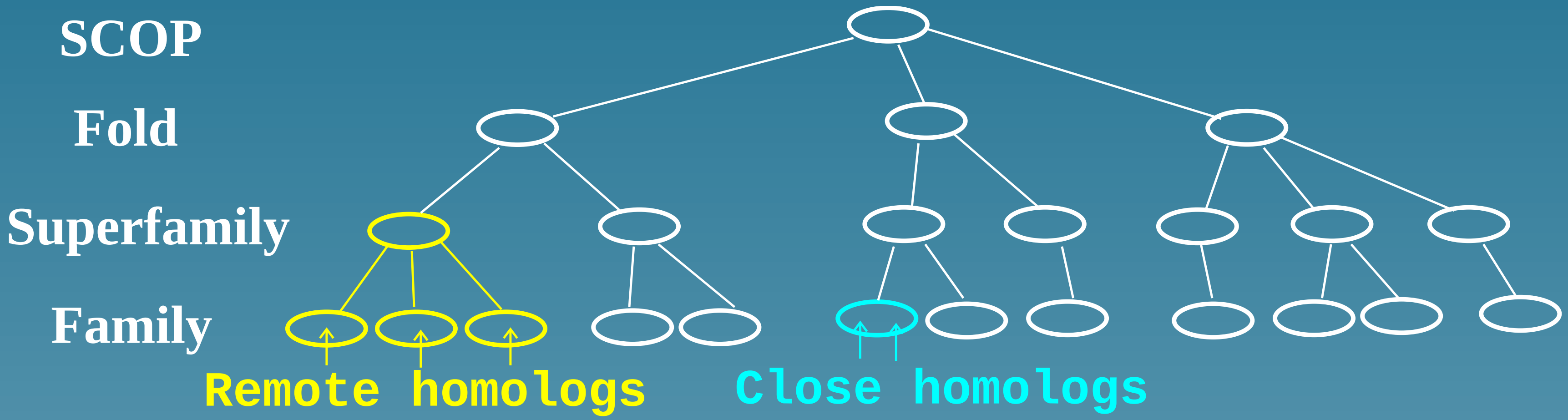


Application: remote homology detection



- Same structure/function but sequence diverged
- Remote homology can not be found by direct sequence similarity

SCOP database



SCOP

Fold

Superfamily

Family

Remote homologs

Close homologs

A benchmark experiment

- Can we predict the superfamily of a domain if we have not seen any member of its family before?

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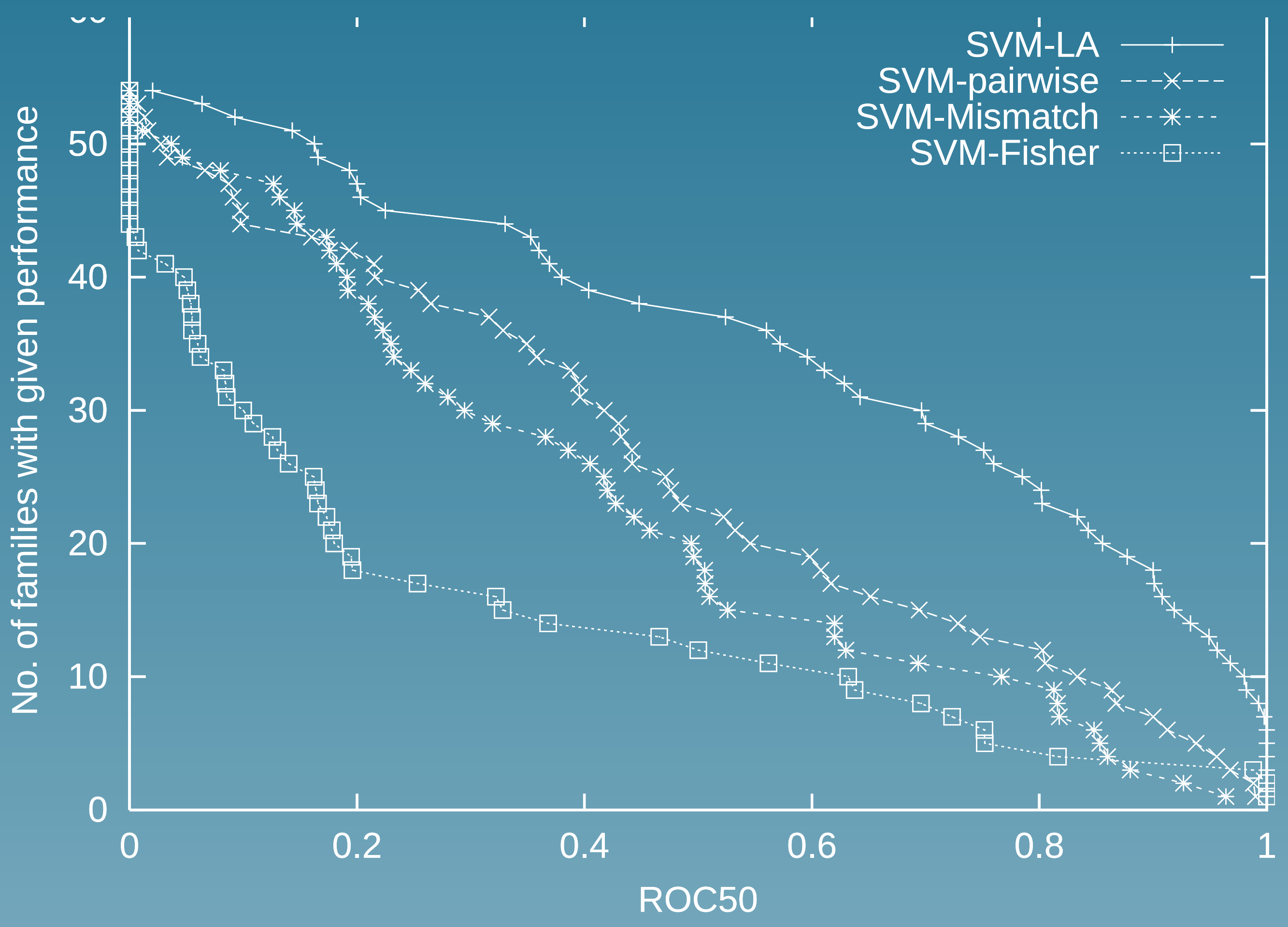
A benchmark experiment

- Can we predict the superfamily of a domain if we have not seen any member of its family before?
- During learning: remove a family and learn the difference between the superfamily and the rest
- Then, use the model to test each domain of the family removed

SCOP superfamily recognition benchmark

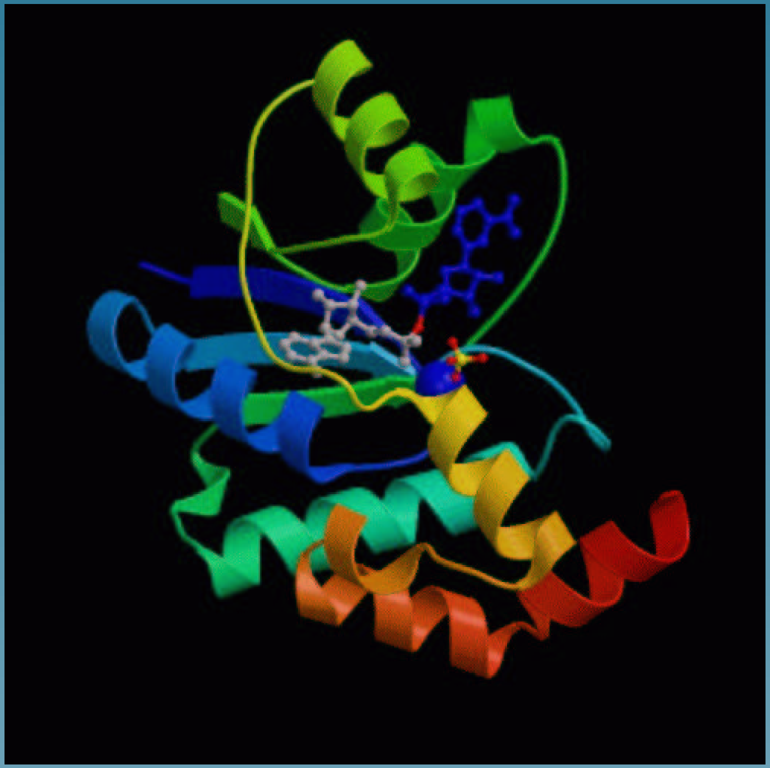


Part 4

Detecting pathway activity from microarray data

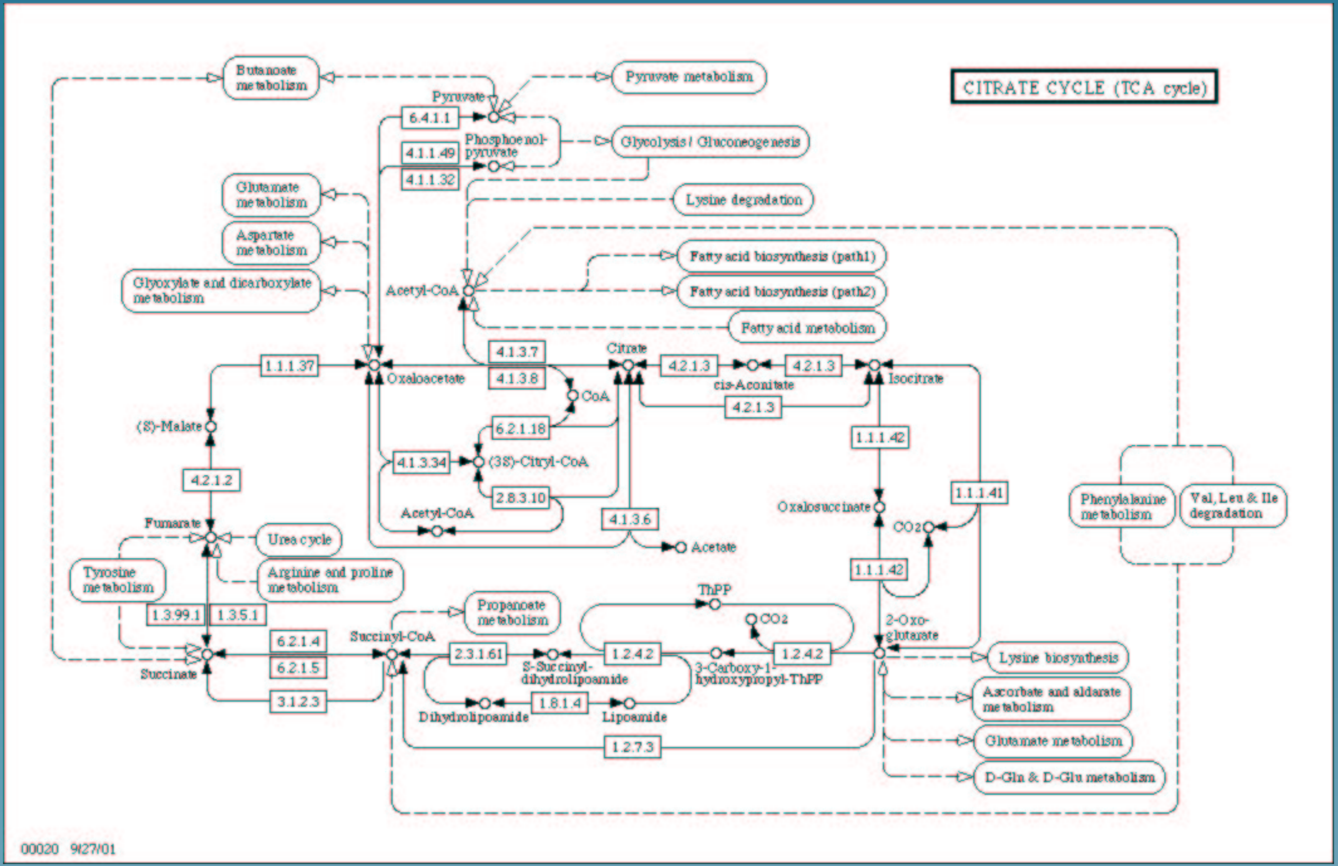
(with M. Kanehisa, *ECCB 2003*)

Genes encode proteins which can catalyse chemical reations



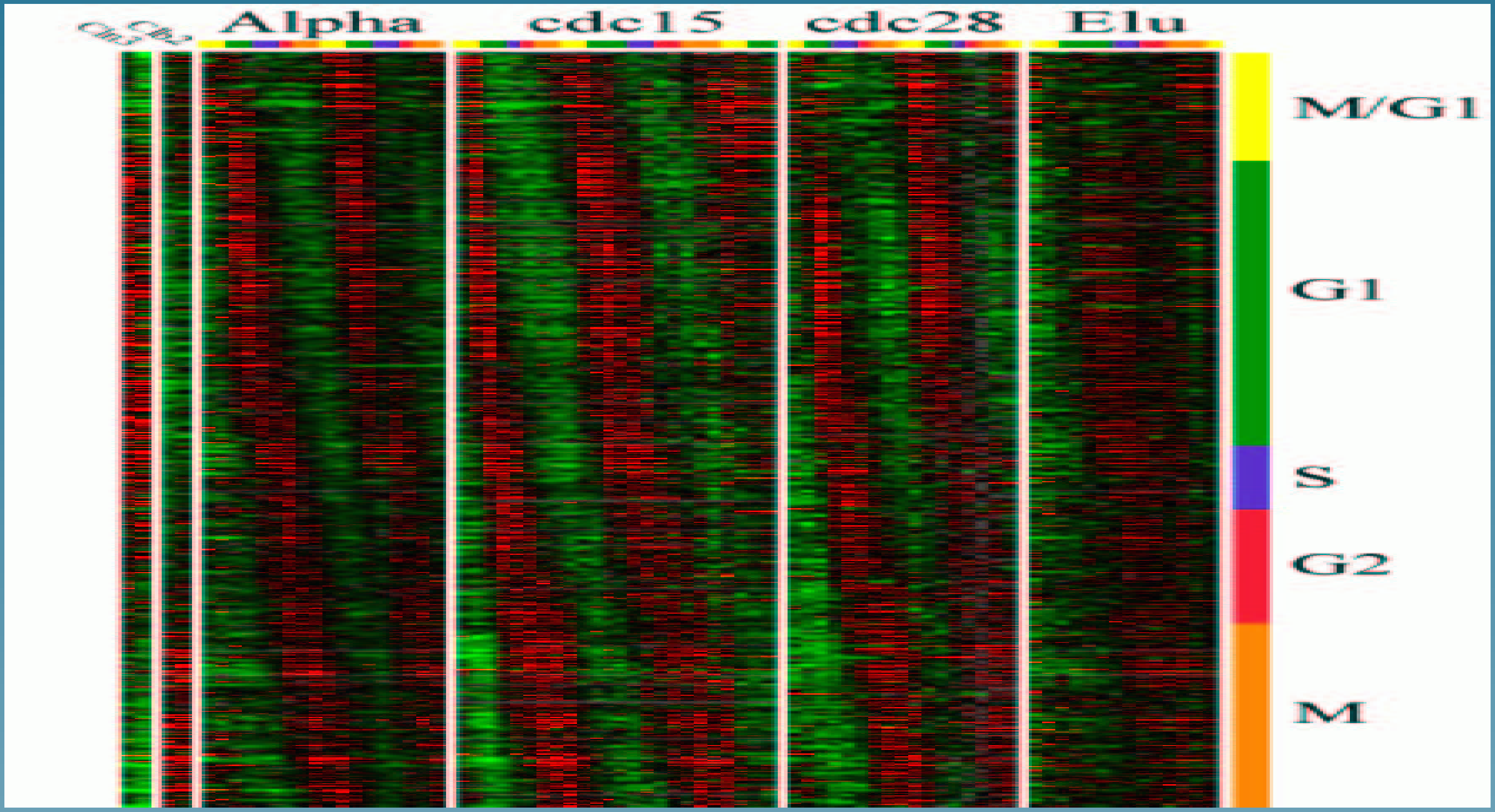
Nicotinamide Mononucleotide Adenylyltransferase With Bound Nad+

Chemical reactions are often parts of pathways



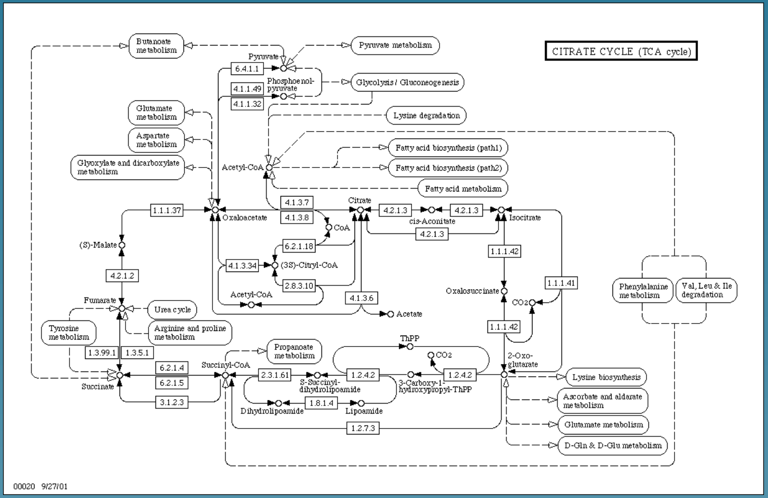
From http://www.genome.ad.jp/kegg/pathway

Microarray technology monitors mRNA quantity

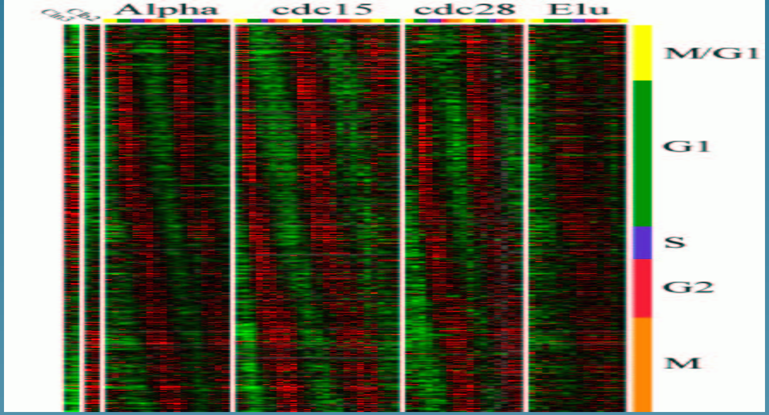


(From Spellman et al., 1998)

Comparing gene expression and pathway databases

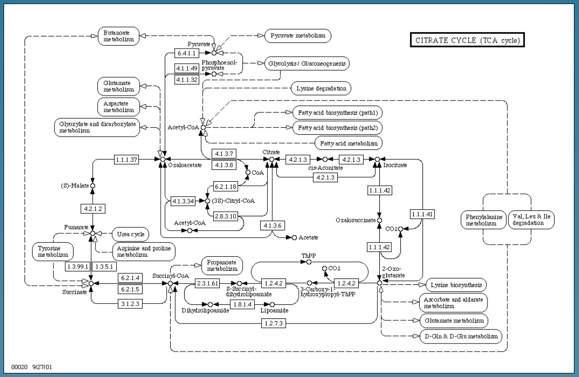


VS

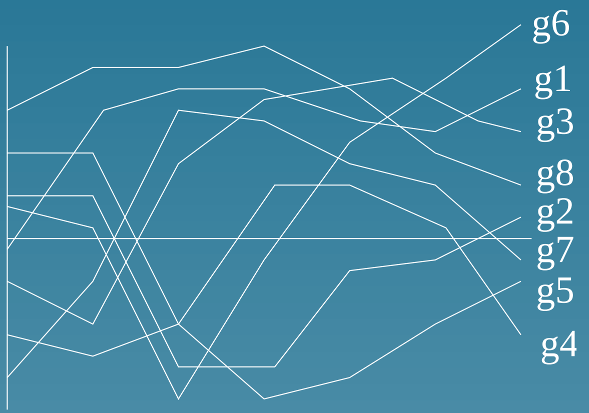


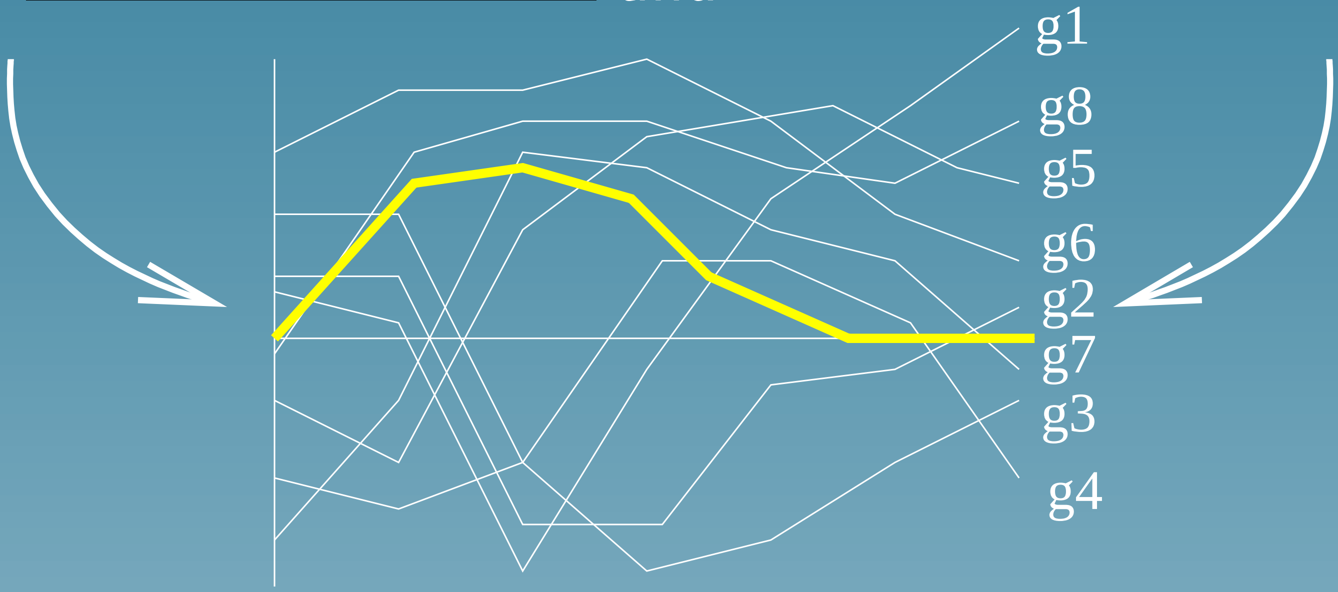
Detect active pathways? Denoise expression data?
Denoise pathway database? Find new pathways?
Are there "correlations"?

A useful first step

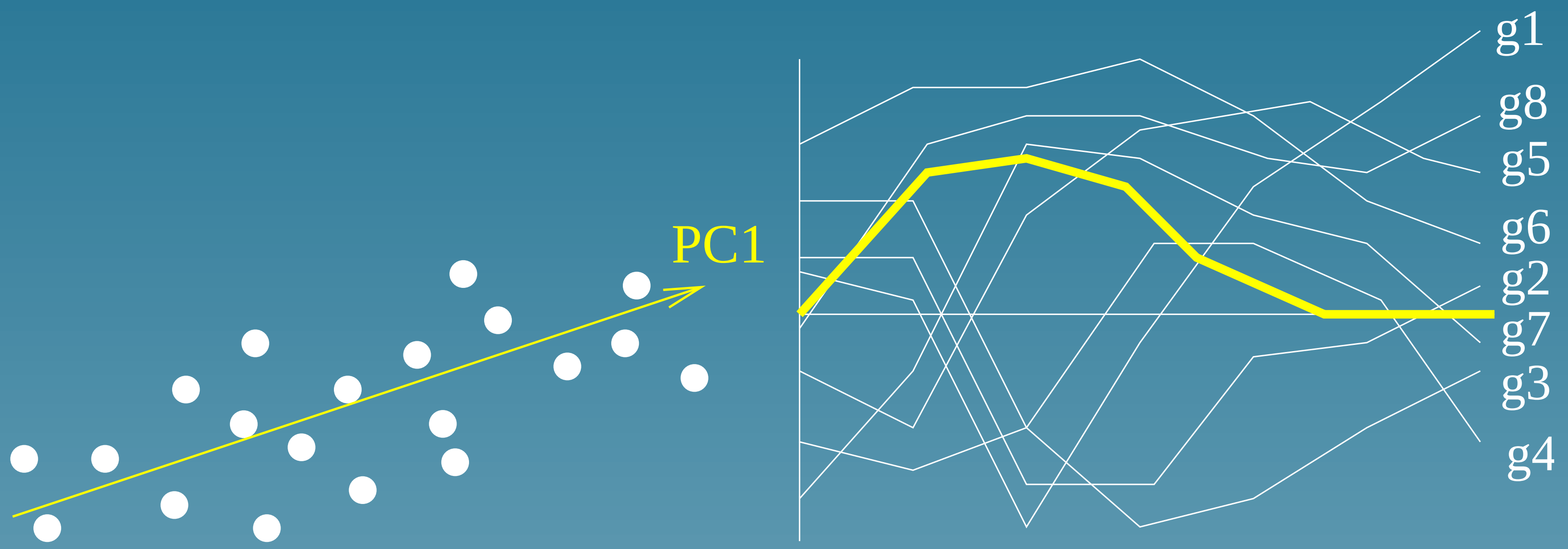


and





Using microarray only



PCA finds the directions (*profiles*) explaining the largest amount of variations among expression profiles.

PCA formulation

- Let $f_v(i)$ be the projection of the i-th profile onto v.

- The amount of variation captured by f_v is:

$$h_1(v) = \sum_{i=1}^{N} f_v(i)^2$$

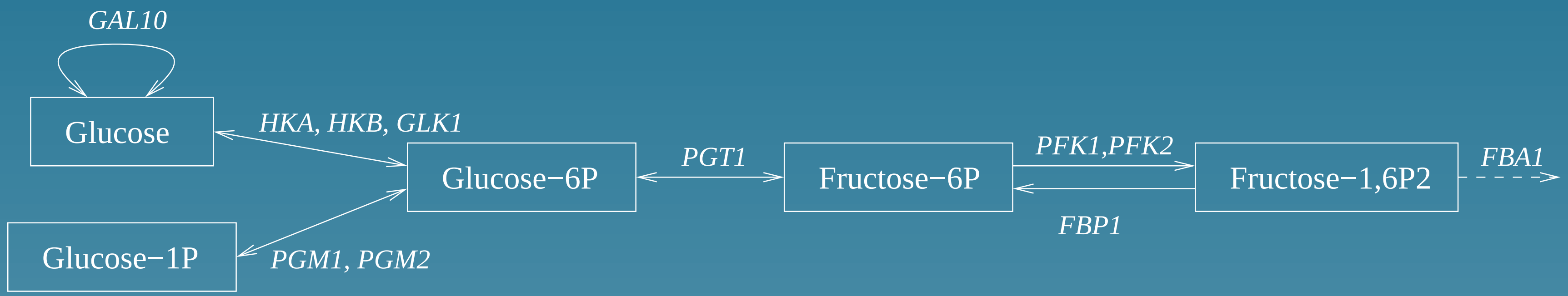
- PCA finds an orthonormal basis by solving successively:

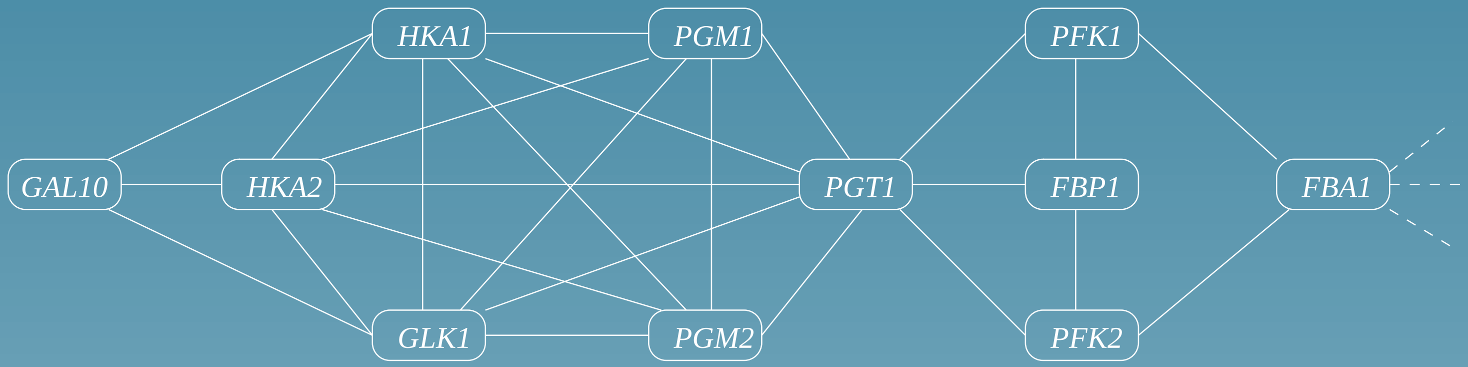
$$\max_v h_1(v)$$

Issues with PCA

- PCA is useful if there is a small number of strong signal
- In concrete applications, we observe a noisy superposition of many events
- Using a prior knowledge of metabolic networks can help denoising the information detected by PCA

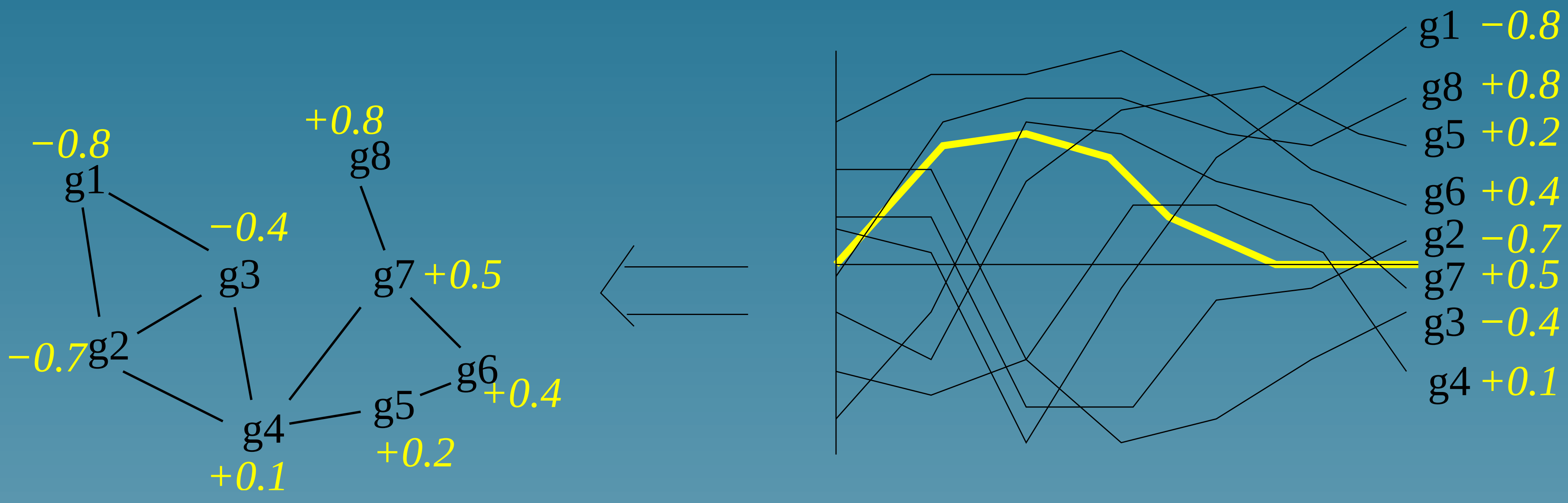
The metabolic gene network





Link two genes when they can catalyze two successive reactions

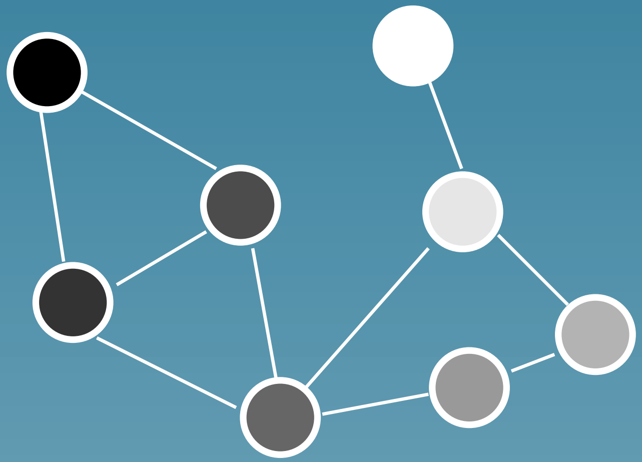
Mapping f_v to the metabolic gene network



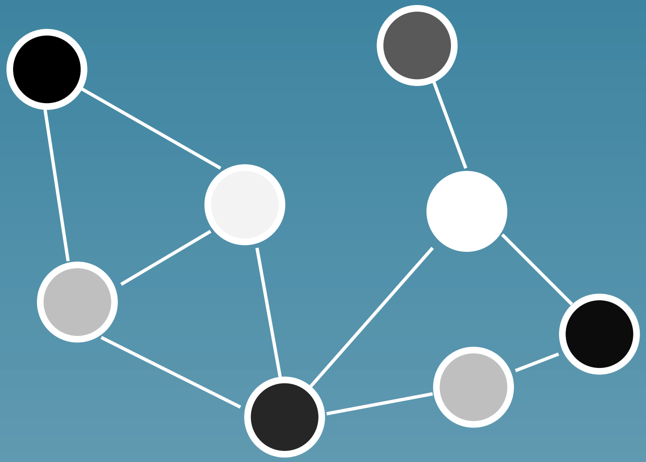
Does it look interesting or not?

Important hypothesis

If v is related to a metabolic activity, then f_v should vary ”smoothly” on the graph

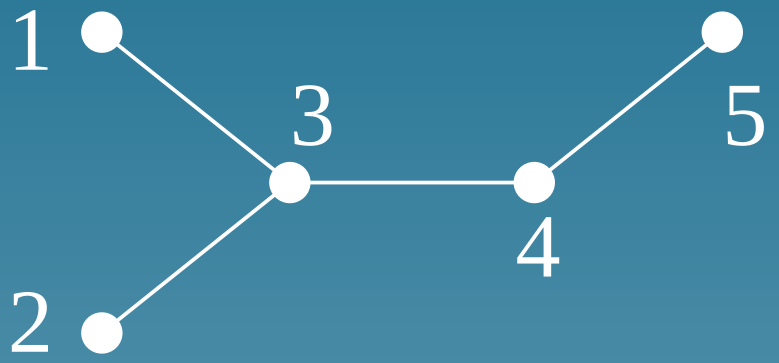


Smooth



Rugged

Graph Laplacian $L = D - A$

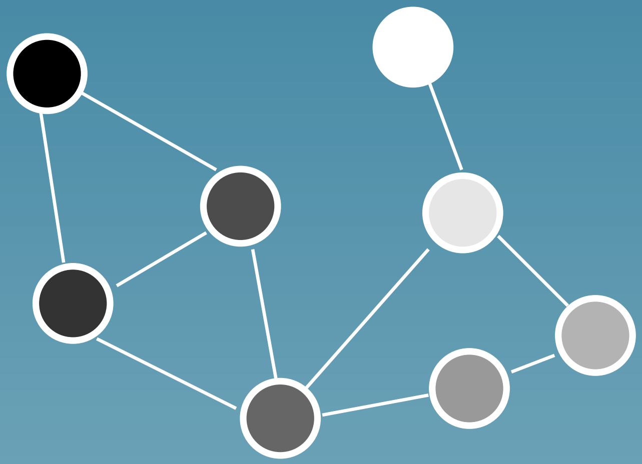


$$L = \begin{pmatrix} -1 & 0 & 1 & 0 & 0 \\ 0 & -1 & 1 & 0 & 0 \\ 1 & 1 & -3 & 1 & 0 \\ 0 & 0 & 1 & -2 & 1 \\ 0 & 0 & 0 & 1 & -1 \end{pmatrix}$$

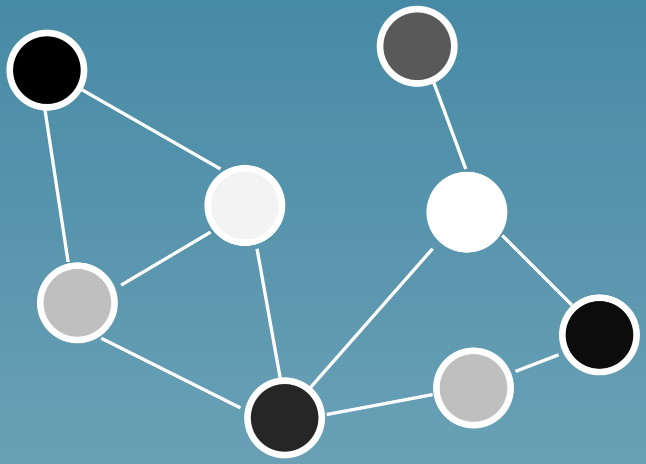
Smoothness quantification

$$h_2(f) = \frac{f^\top \exp(-\beta L) f}{f^\top f}$$

is large when f is smooth



h(f) = 2.5



h(f) = 34.2

Motivation

For a candidate profile v,

- $h_1(f_v)$ is large when v captures a lot of natural variation among profiles
- $h_2(f_v)$ is large when f_v is smooth on the graph

Try to maximize both terms in the same time

Problem reformulation

Find a function f_v and a function f_2 such that:

- $h_1(f_v)$ be large
- $h_2(f_2)$ be large
- $corr(f_v, f_2)$ be large

by solving:

$$\max_{(f_v, f_2)} corr(f_v, f_2) \times \frac{h_1(f_v)}{h_1(f_v) + \delta} \times \frac{h_2(f_2)}{h_2(f_2) + \delta}$$

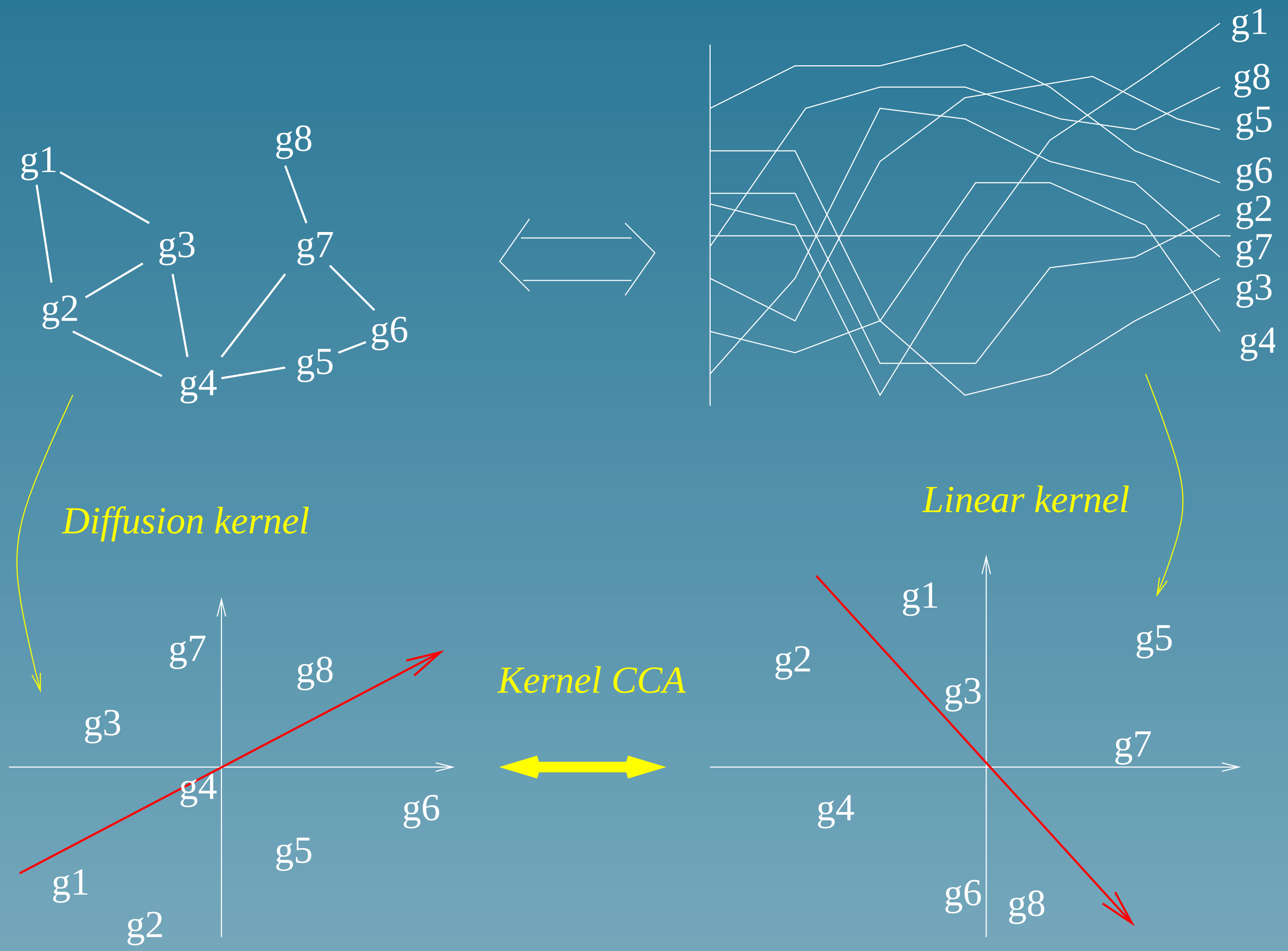
Solving the problem

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

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

where $[K_1]_{i,j} = e_i^\top e_j$ and $K_2 = \exp(-L)$.
Then, $f_v = K_1\alpha$ and $f_2 = K_2\beta$.

The kernel point of view...



Diffusion kernel

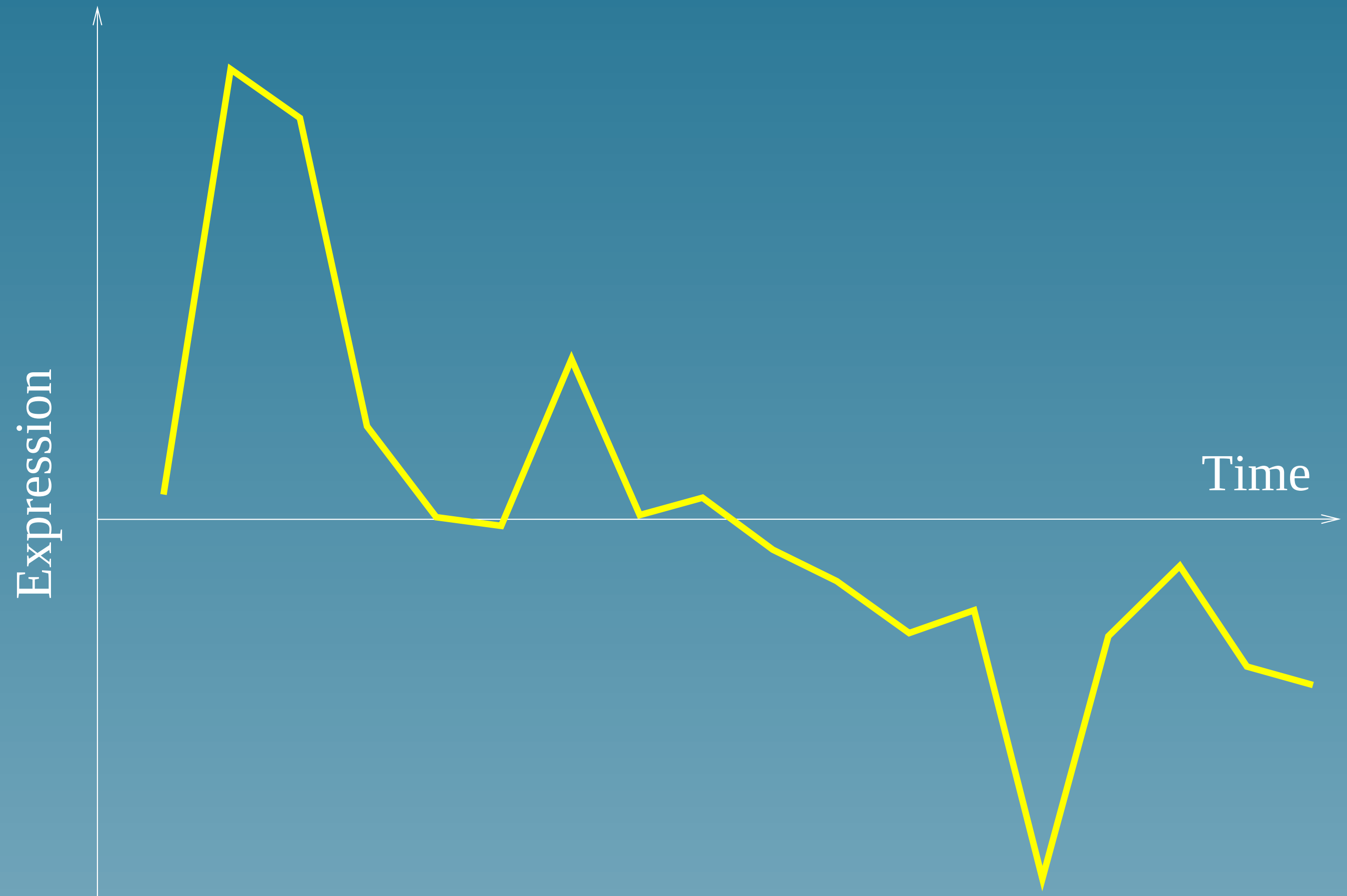
Linear kernel

Kernel CCA

Data

- 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

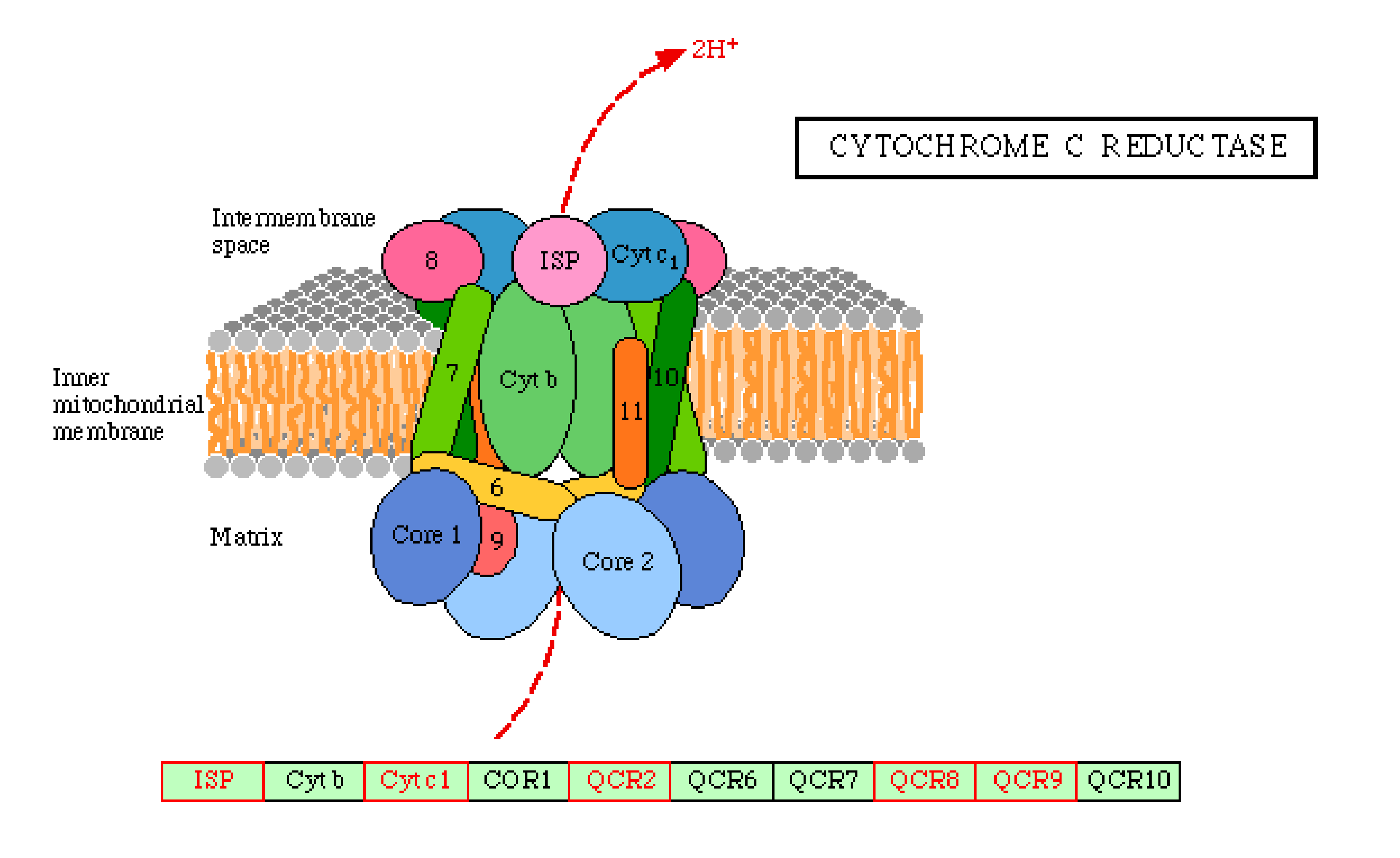


Related metabolic pathways

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)
- Selenoaminoacid metabolism (4) , etc...

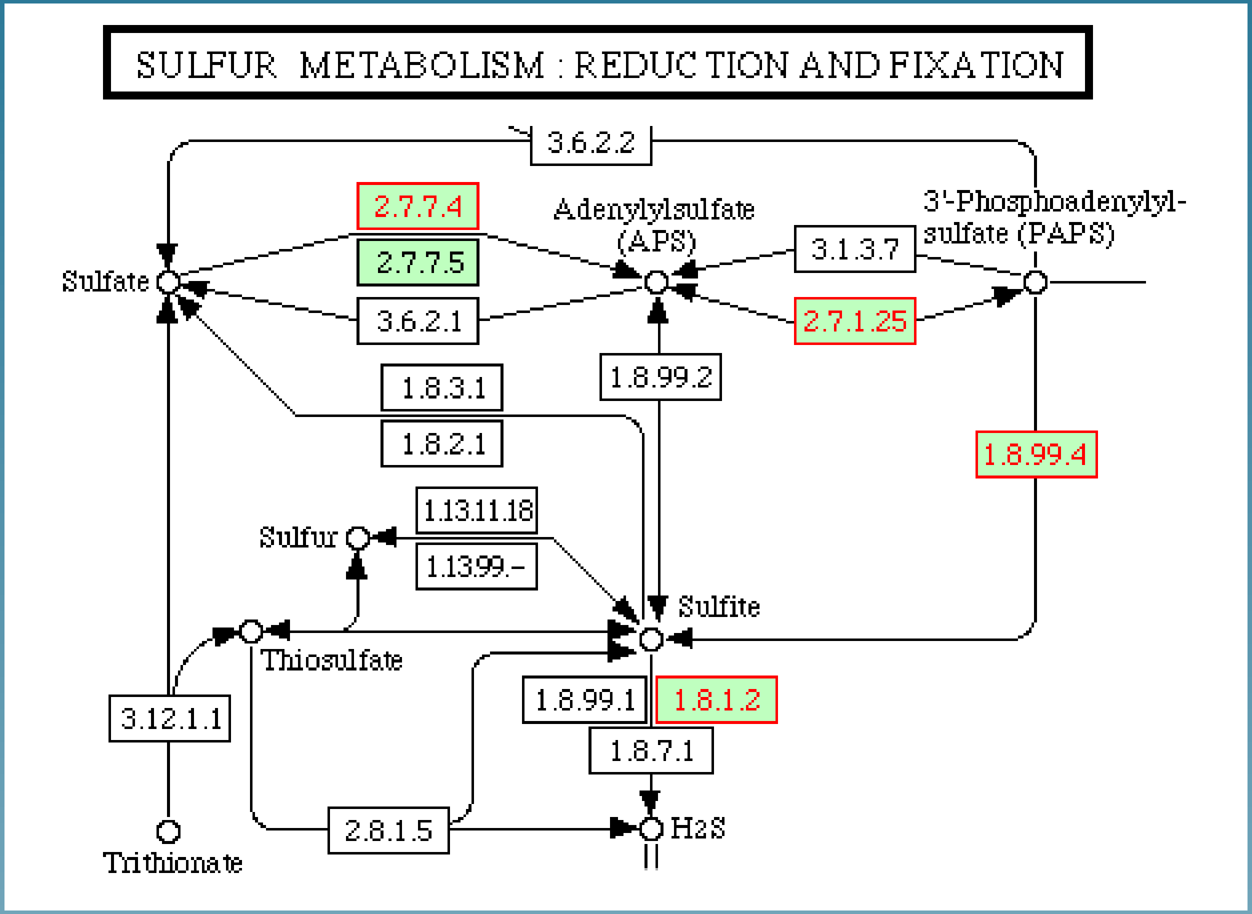
Related genes



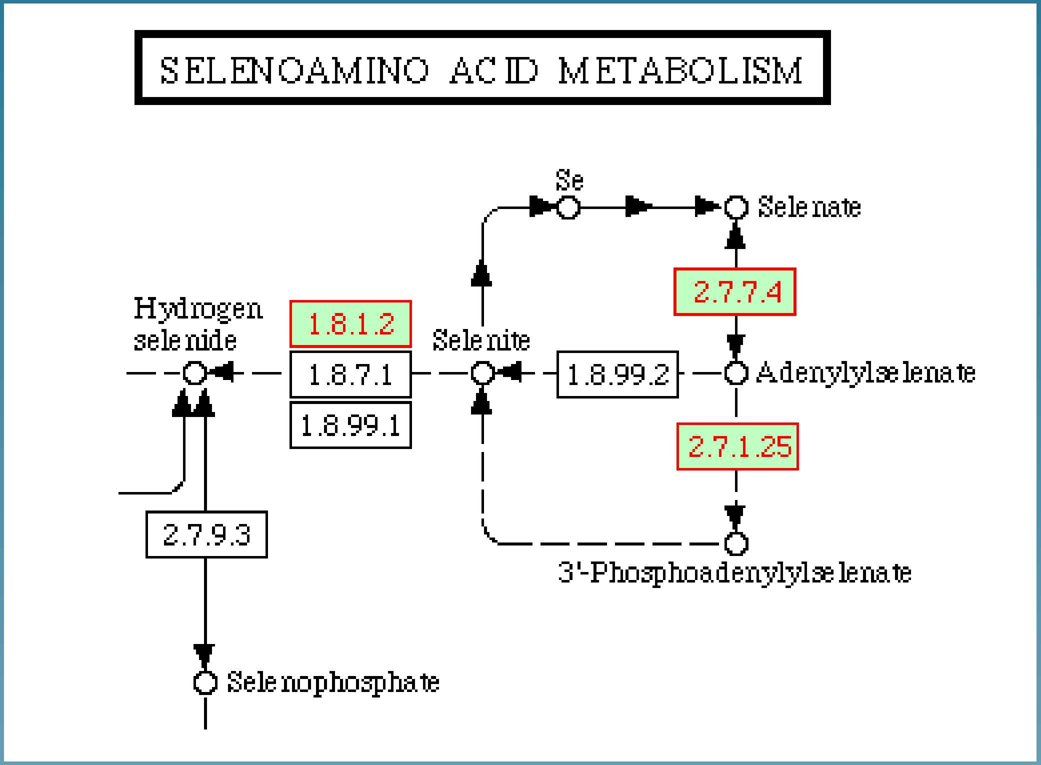
CYTOCHROME C REDUCTASE

ISP	Cyt b	Cyt c1	COR1	QCR2	QCR6	QCR7	QCR8	QCR9	QCR10

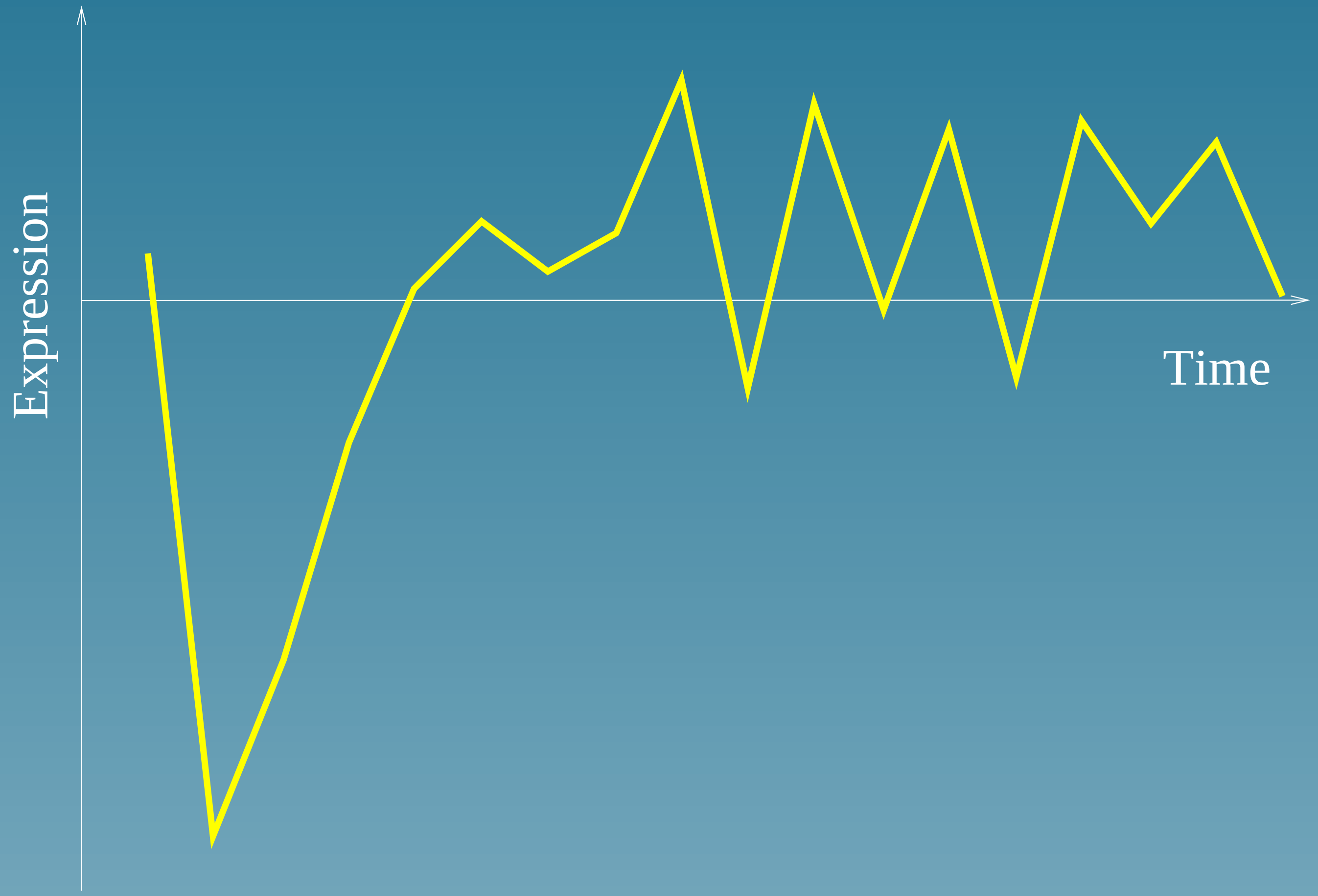
Related genes



Related genes



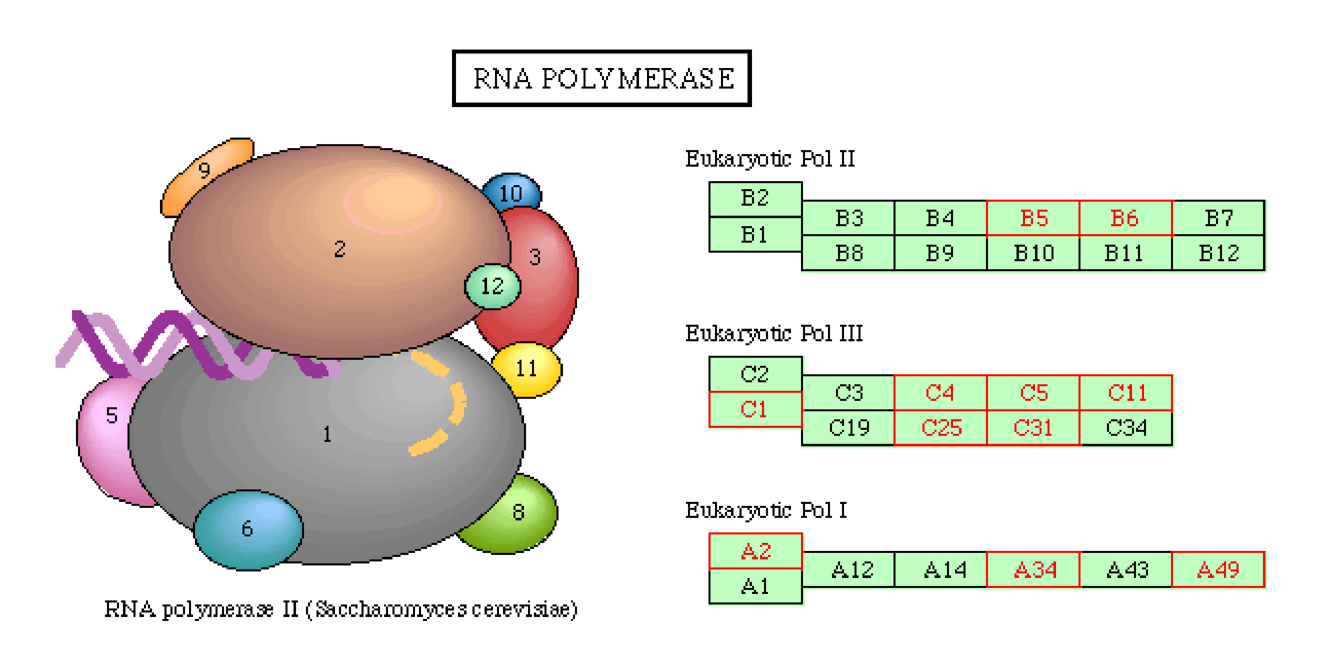
Opposite pattern



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

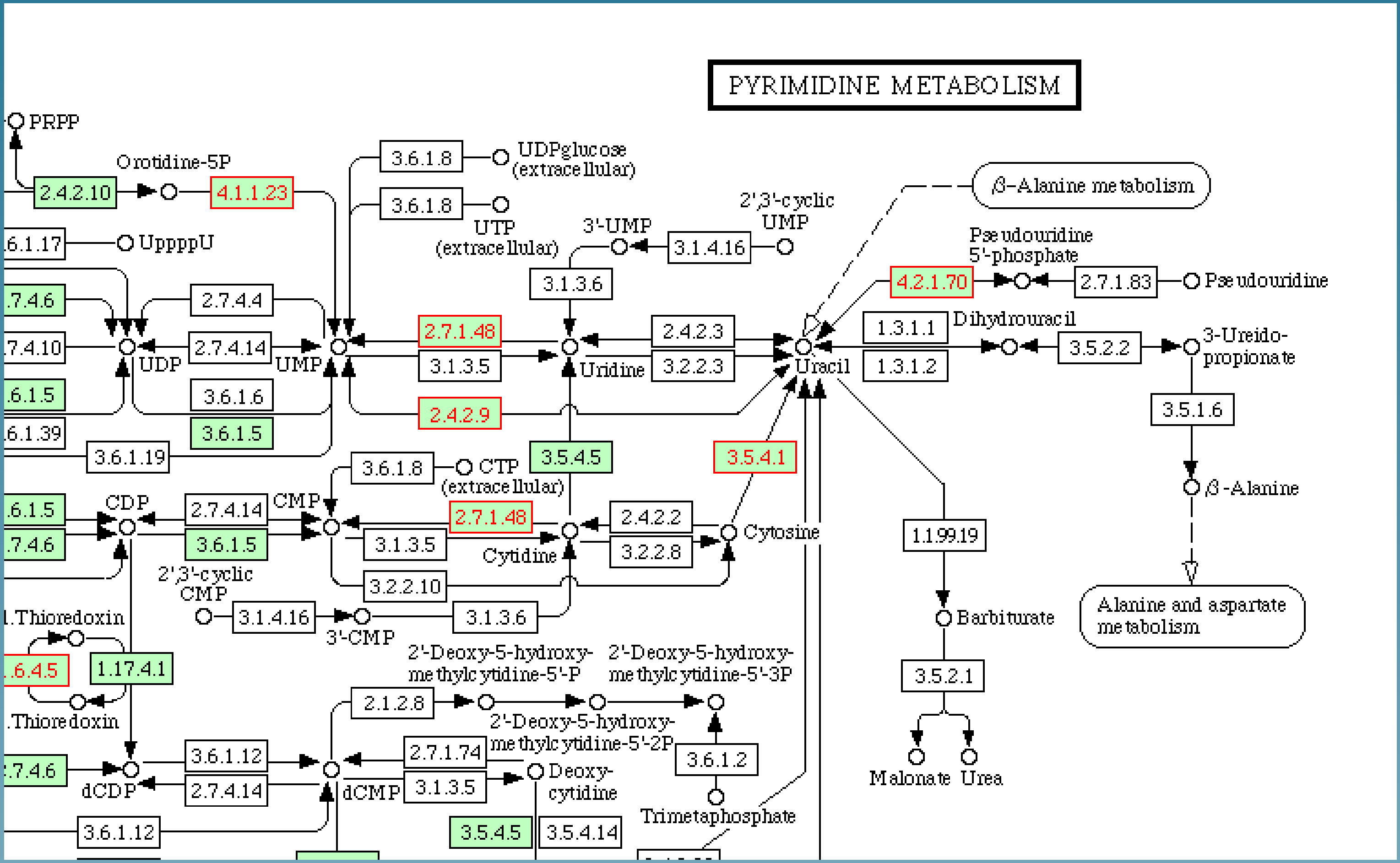
Eukaryotic Pol III

C2	C3	C4	C5	C11
C1	C19	C25	C31	C34

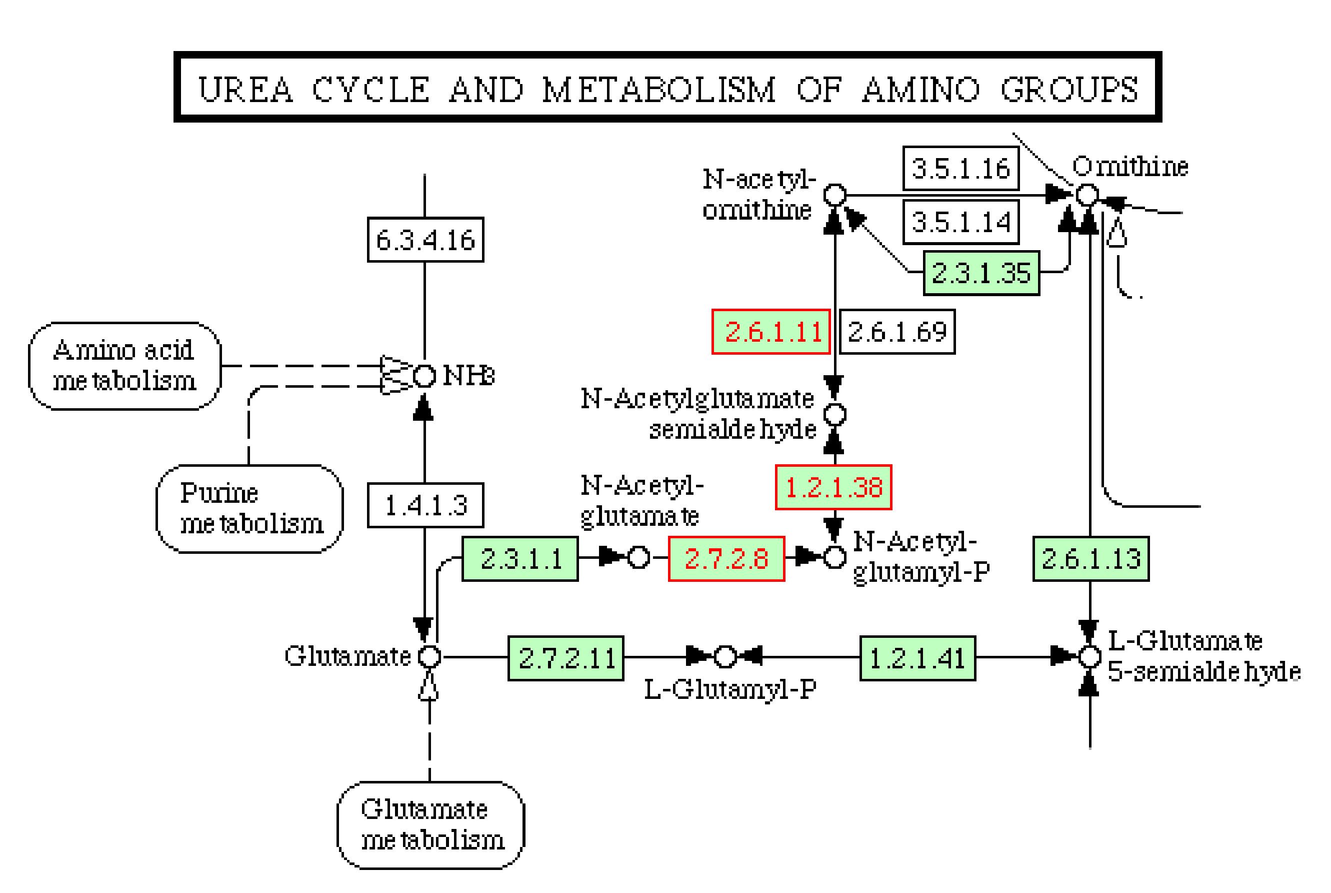
Eukaryotic Pol I

A2	A12	A14	A34	A43	A49
A1					

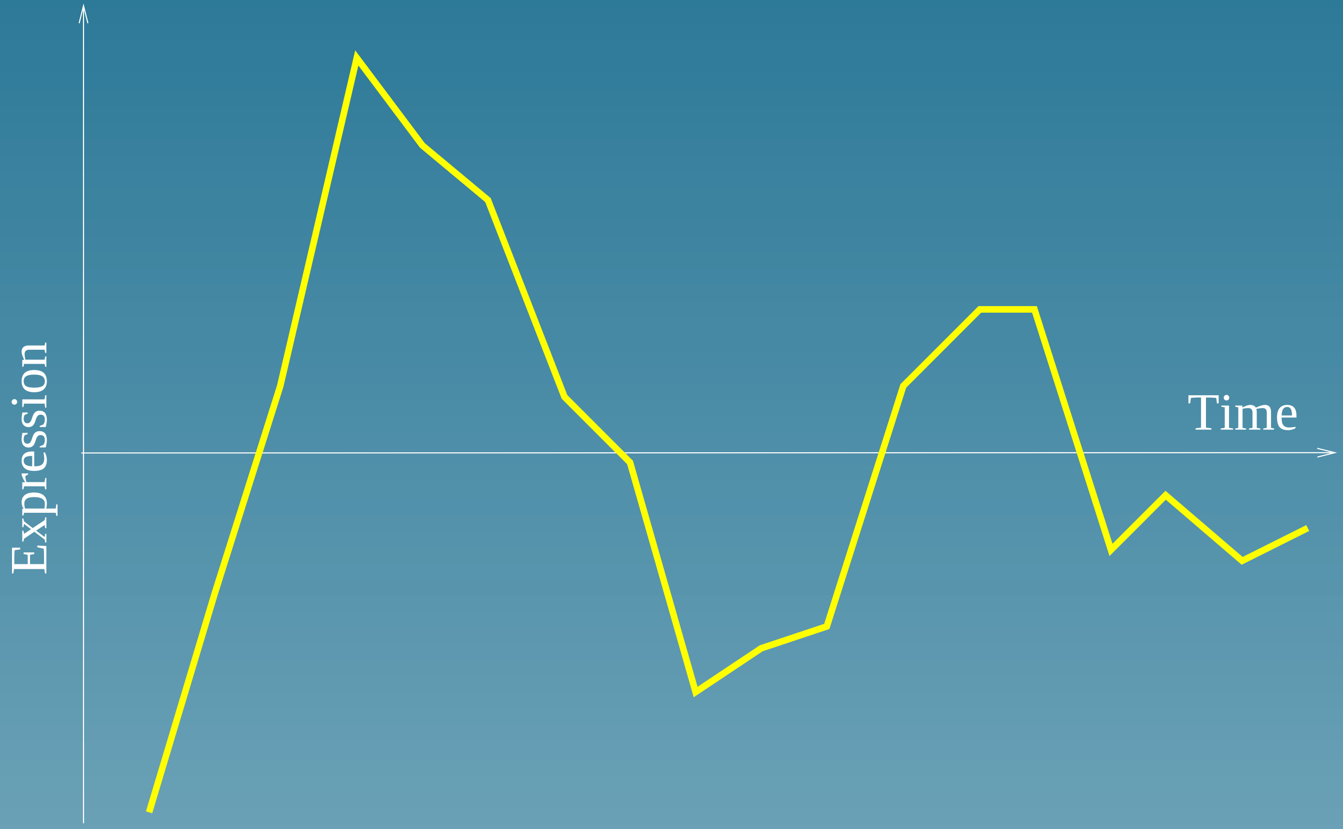
Related genes



Related genes



Second pattern



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
- SVM and kernel methods work well on real-life problems, in particular in high dimension and with noise
- Encouraging results on real-world applications
- Many opportunities in developping kernels for particular applications