Extracting active metabolic pathways from gene expression data

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Overview

1. Problem Formulation

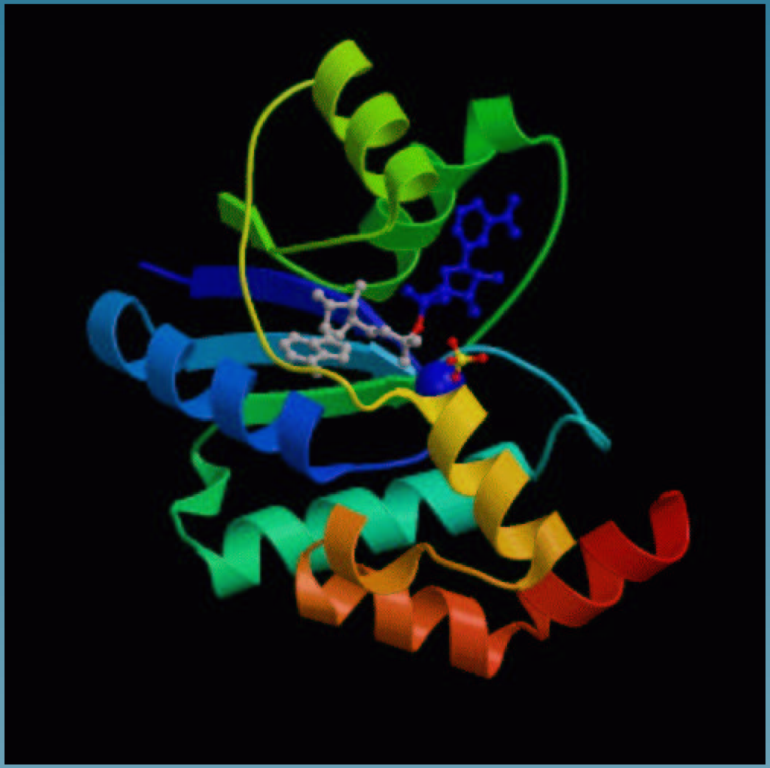
2. An approach using RKHS

3. Experimental results

Part 1

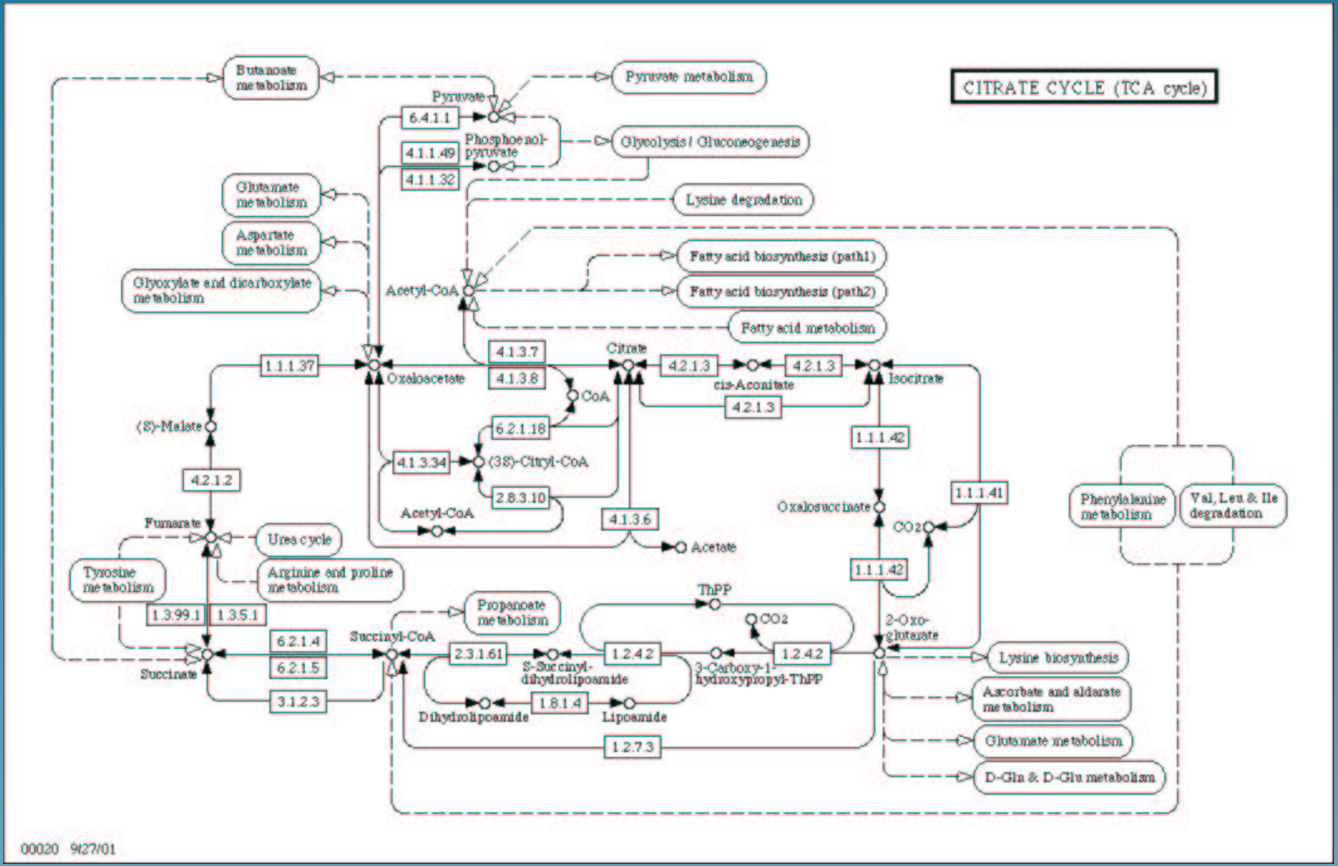
Problem formulation

Genes encode proteins which can catalyse chemical reations



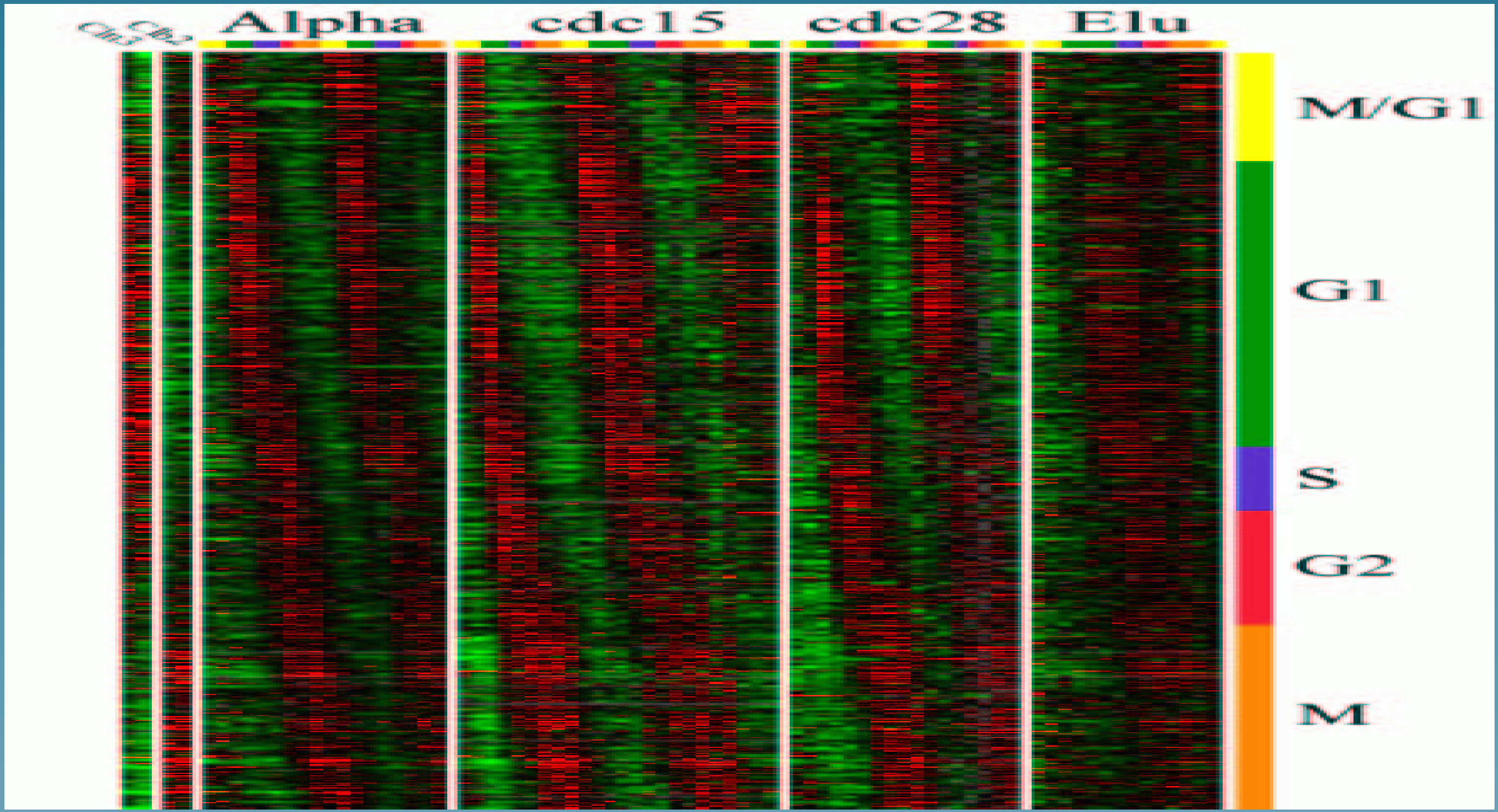
Nicotinamide Mononucleotide Adenylyltransferase With Bound Nad+

Chemical reactions are often parts of pathways



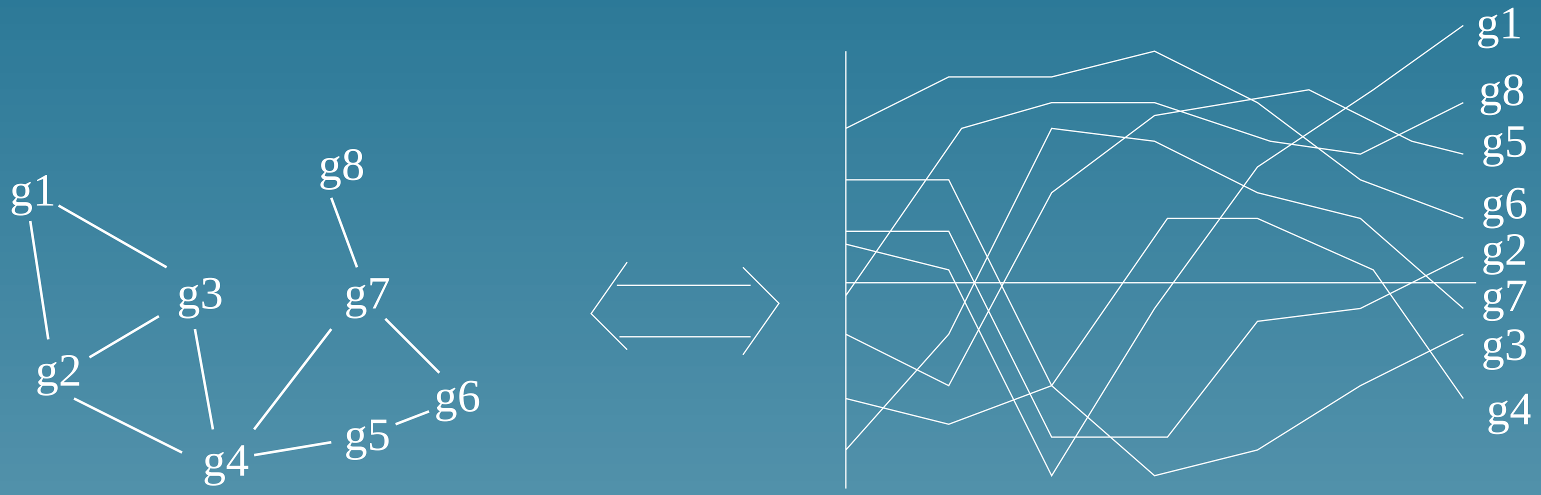
From http://www.genome.ad.jp/kegg/pathway

Microarray technology monitors RNA quantity



(From Spellman et al., 1998)

Comparing gene expression and protein network

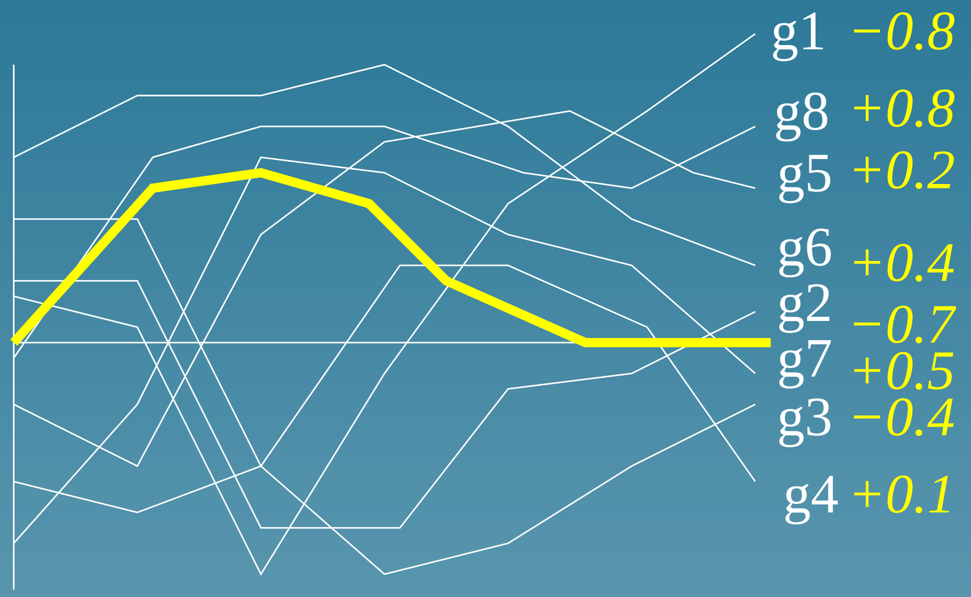


Gene network

Expression profiles

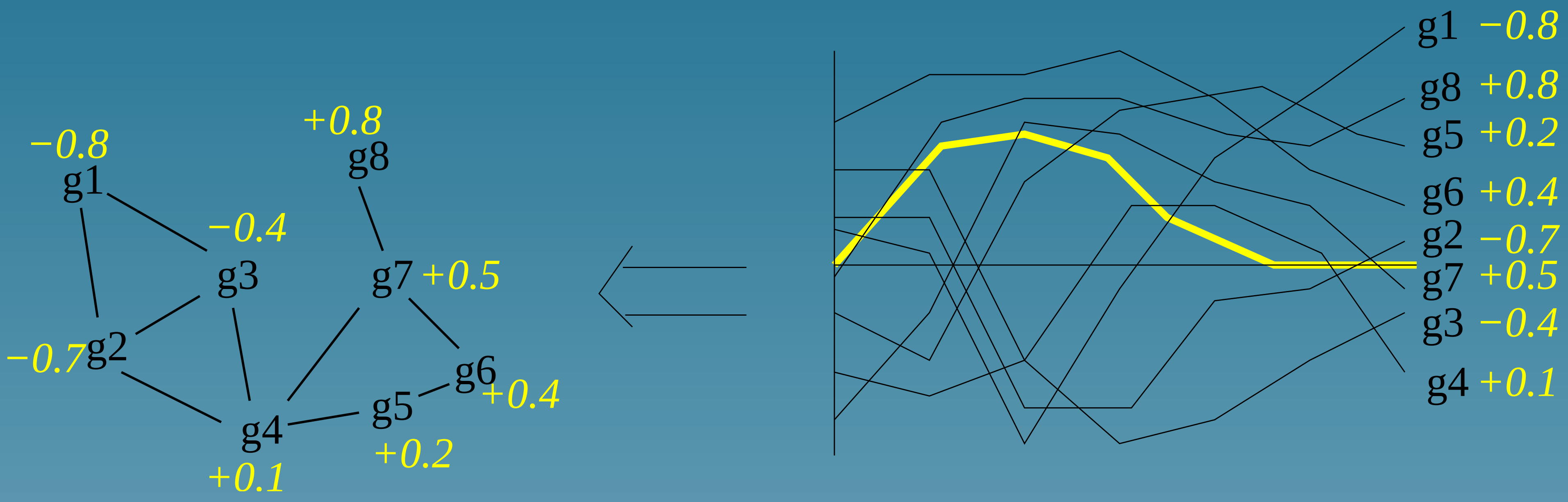
Are there “correlations”?

Pattern of expression



- In yellow: a candidate pattern , and tbe 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

Part 3

An approach using RKHS

Kernels and RKHS

- A kernel $K(x,y)$ on the set of genes $\mathcal{X}$ is a symetric positive definite function
- A kernel defines a Hilbert space on the set of functions:

$$H = \text{span}\{K(x,.), x \in \mathcal{X}\} \subset \{f : \mathcal{X} \to \mathbb{R}\}$$

  called reproducible kernel Hilbert space (RKHS).
- The norm $||f||_H$ can have useful interpretation for particular kernels

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

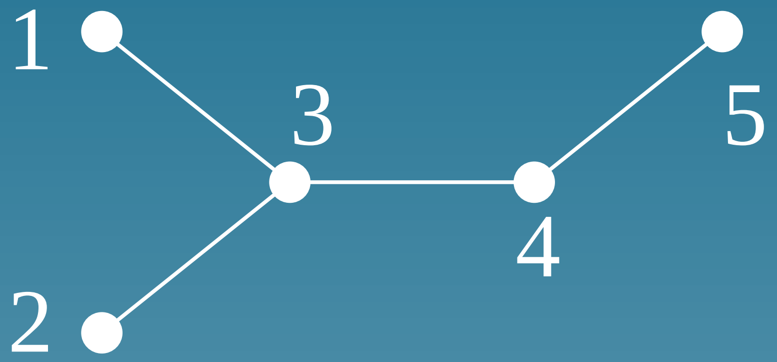
- Let $K_2(x,y)$ be the diffusion kernel obtained from the gene network, with RKHS H_2.

- 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 $f : \mathcal{X} \rightarrow \mathbb{R}$, the larger the function:

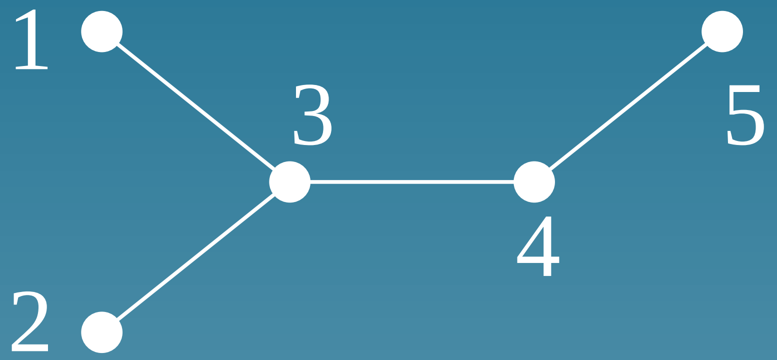
$$\frac{||f||_{H_1}}{||f||_{L_2}}$$

Diffusion kernel (Kondor and Lafferty, 2002)



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

Diffusion kernel (Kondor and Lafferty, 2002)



$$K = \exp(-L) = \begin{pmatrix} 0.49 & 0.12 & 0.23 & 0.10 & 0.03 \\ 0.12 & 0.49 & 0.23 & 0.10 & 0.03 \\ 0.23 & 0.23 & 0.24 & 0.17 & 0.10 \\ 0.10 & 0.10 & 0.17 & 0.31 & 0.30 \\ 0.03 & 0.03 & 0.10 & 0.30 & 0.52 \end{pmatrix}$$

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:

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

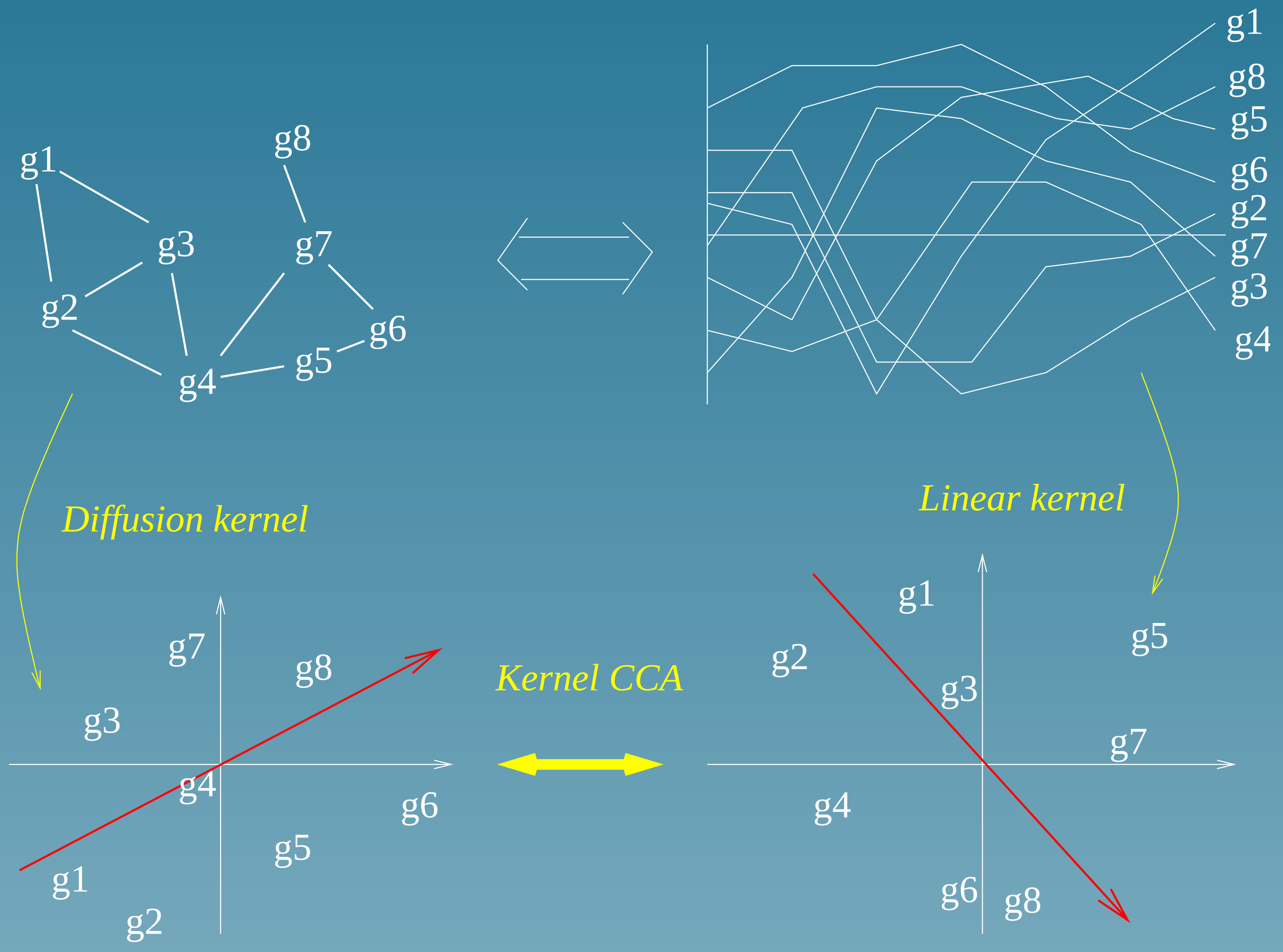
where the parameter δ controls the trade-off between relevance/smoothness on the one hand, correlation on the other hand.

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

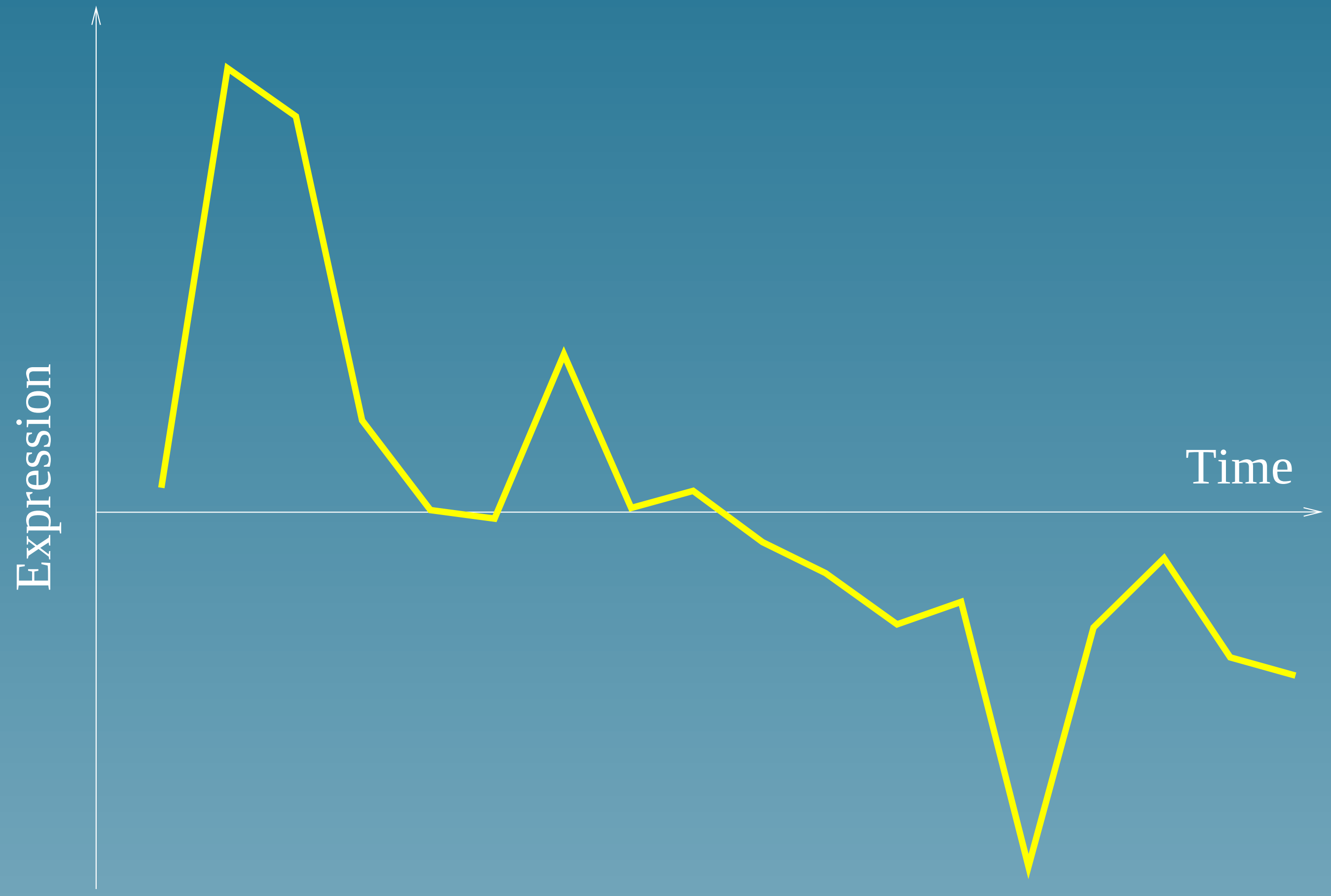
Part 4

Experimental results

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

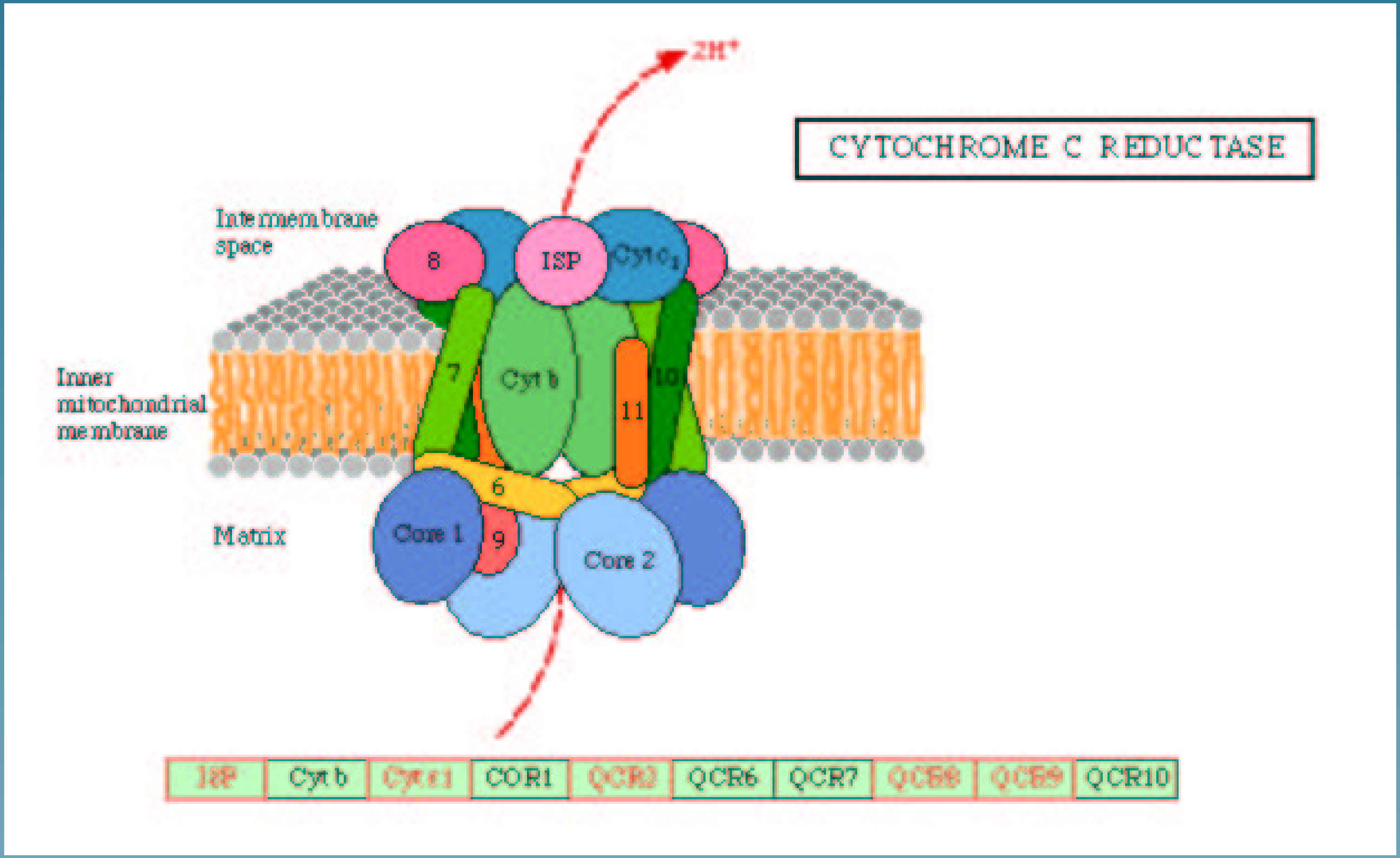


Related metabolic pathways

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

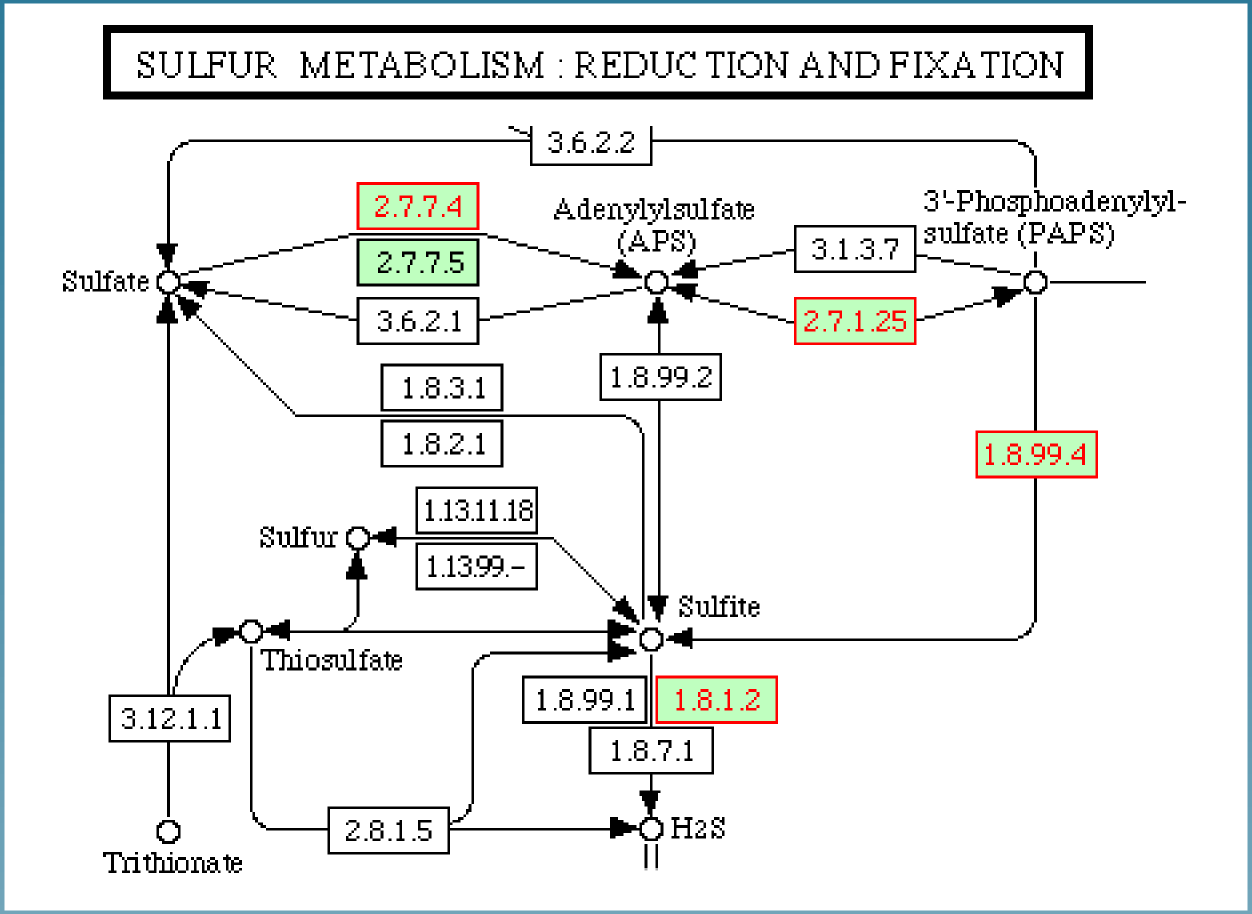
- Oxidative phosphorylation (10 genes)
- Citrate cycle (7)
- Purine metabolism (6)
- Glycerolipid metabolism (6)
- Sulfur metabolism (5)
- Selenoaminoacid metabolism (4) , etc...

Related genes

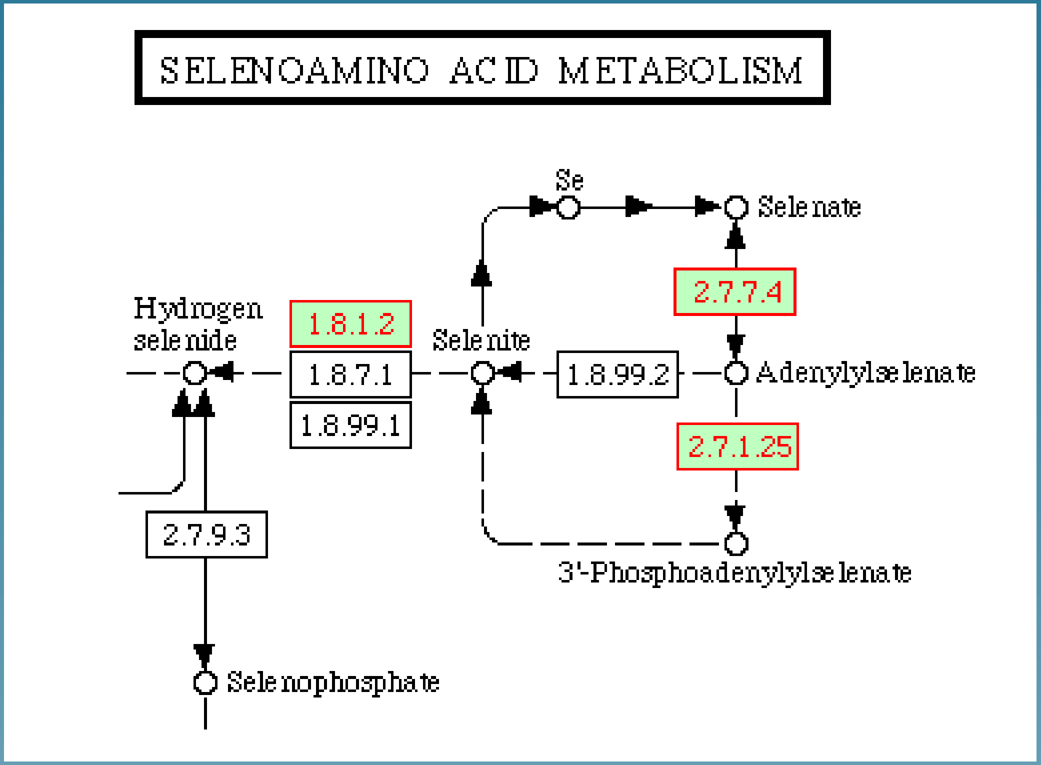


ISP	Cyt b	Cyt c1	COR1	QCR2	QCR6	QCR7	QCR8	QCR9	QCR10

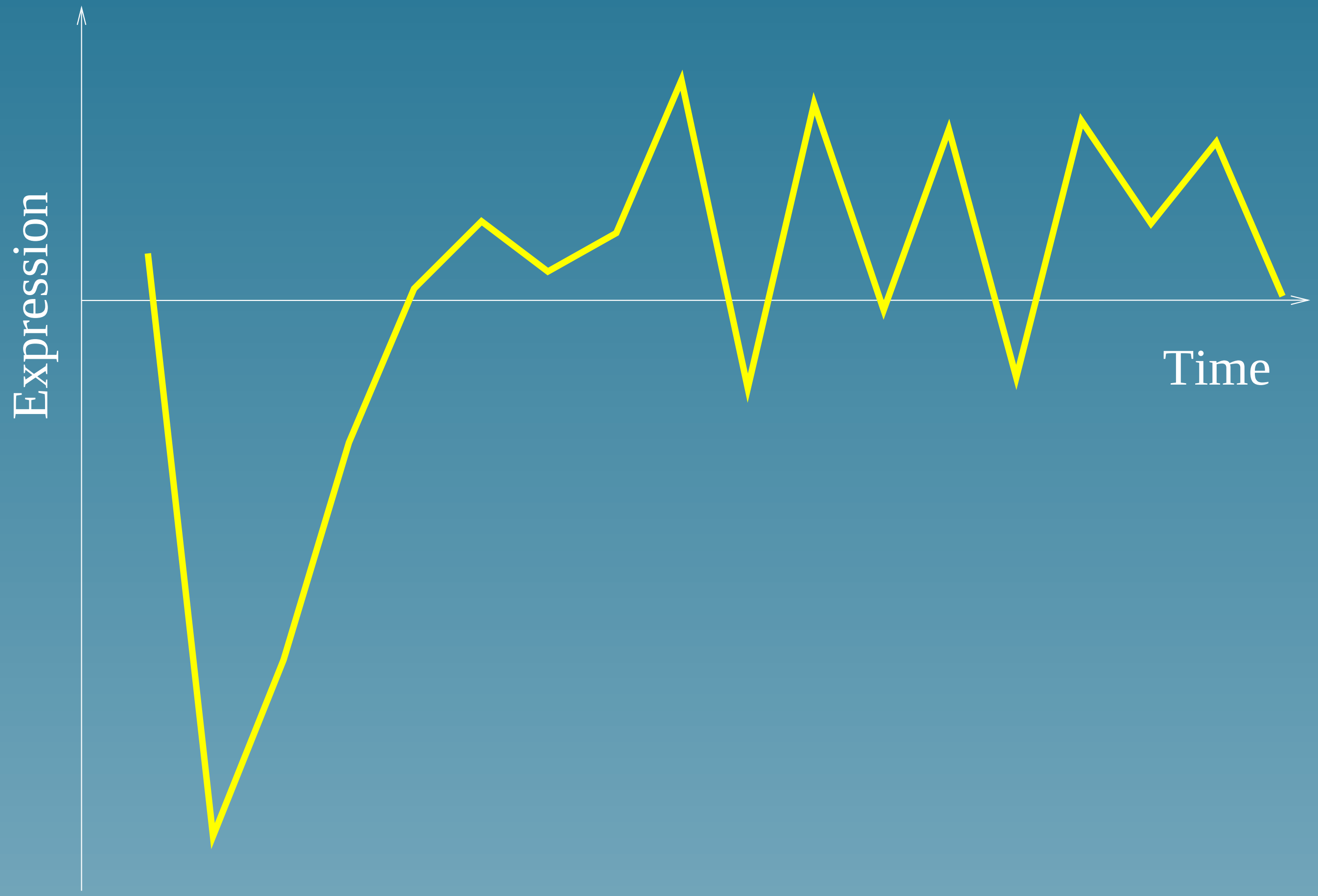
Related genes



Related genes



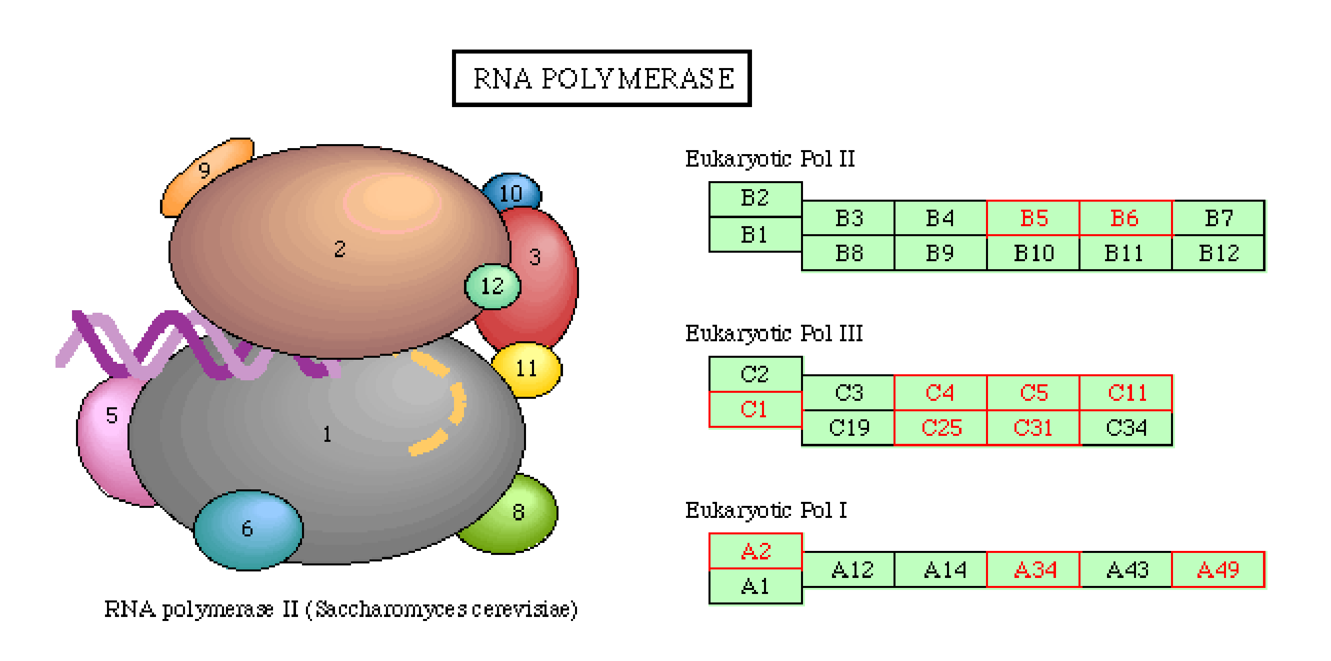
Opposite pattern



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

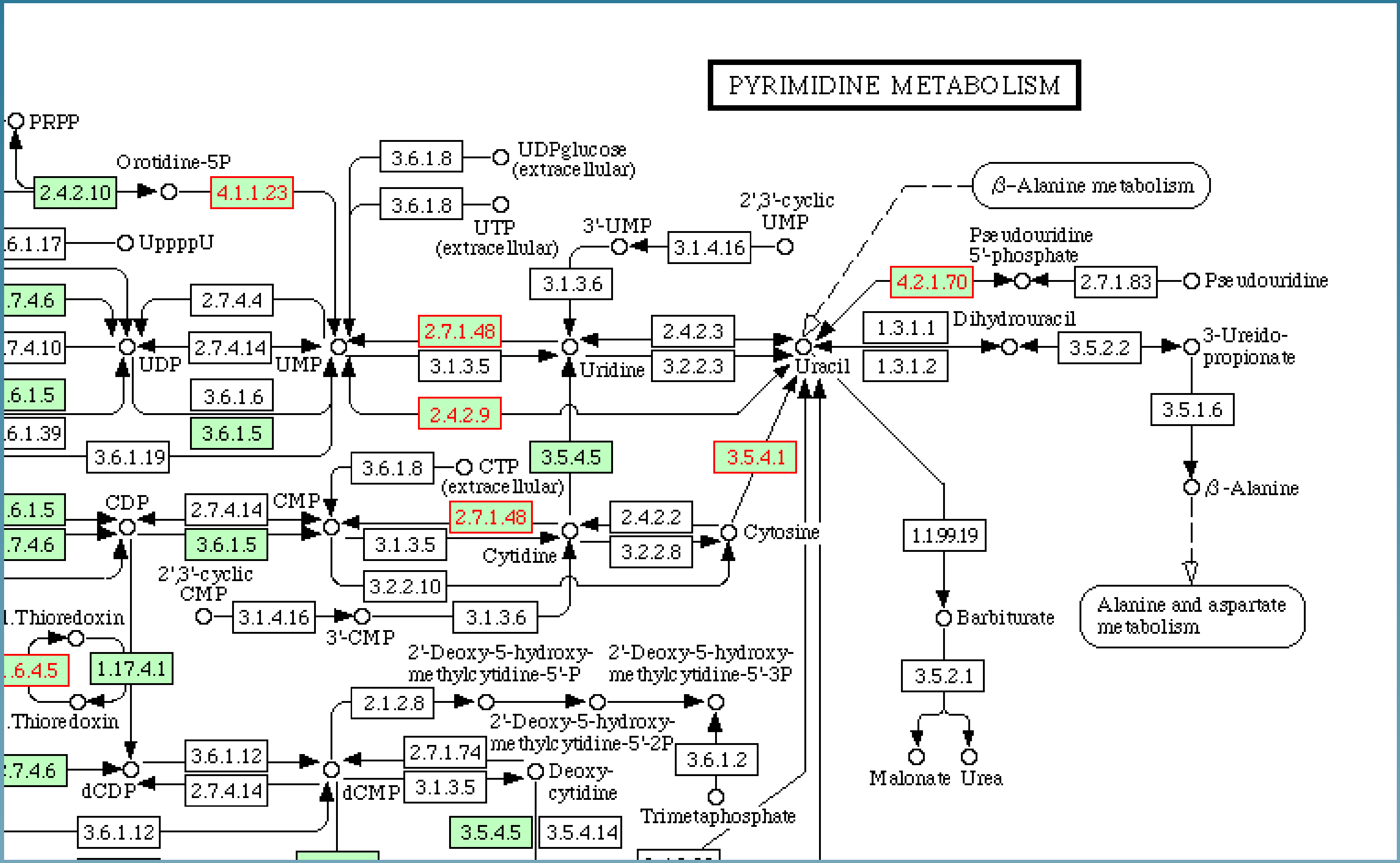
Eukaryotic Pol III

C2	C3	C4	C5	C11
C1	C19	C25	C31	C34

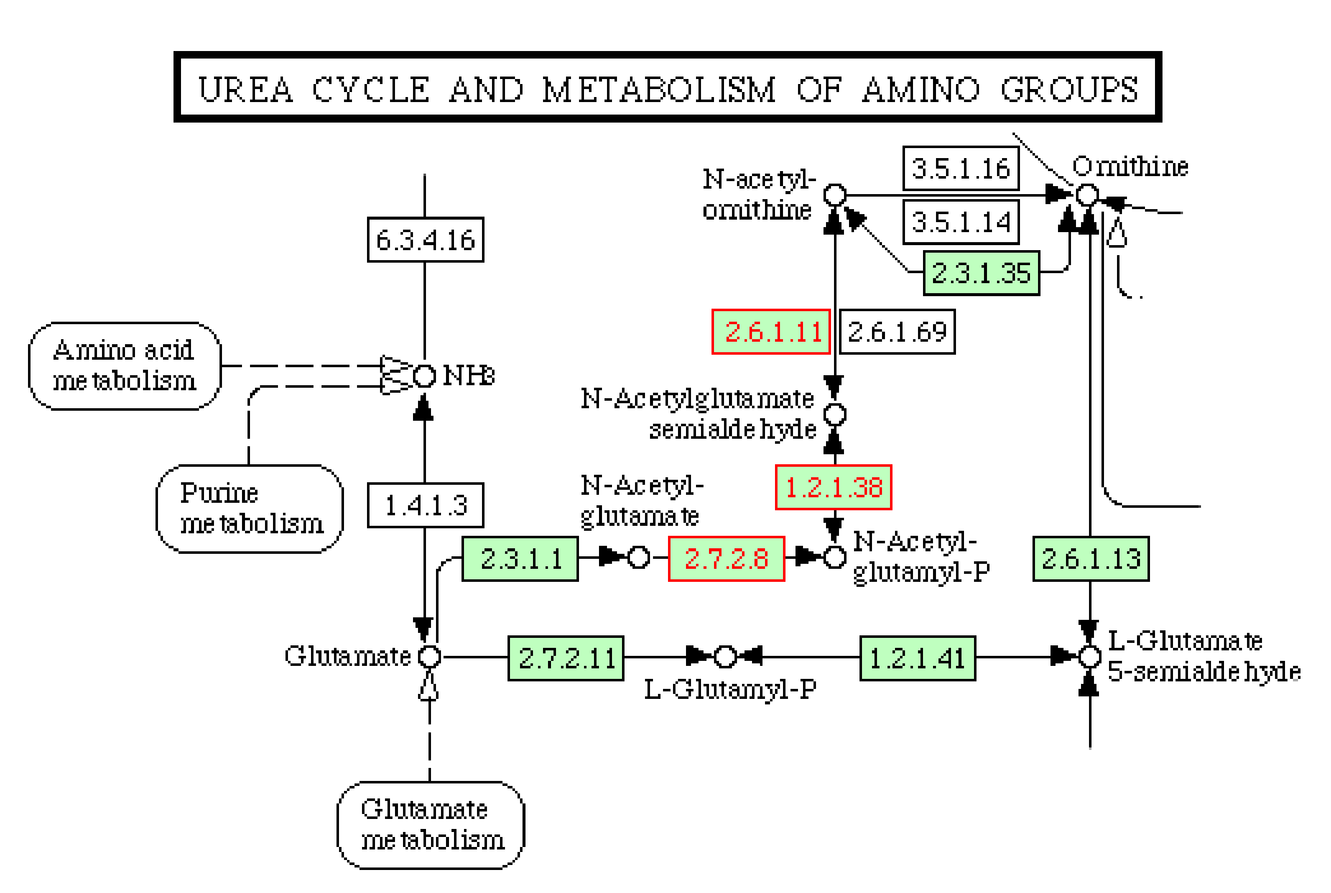
Eukaryotic Pol I

A2	A12	A14	A34	A43	A49
A1					

Related genes



Related genes



Conclusion

Conclusion

- Heterogeneous data can be integrated with kernels
- The approach can be generalized (non-linear kernel for gene expression, string kernels...)

Workshop

Kernel Methods in Bioinformatics

Harnack-Haus, Berlin, April 14, 2003

`http://cg.ensmp.fr/vert/kmb03`