Extracting correlations between pathways and microarray data

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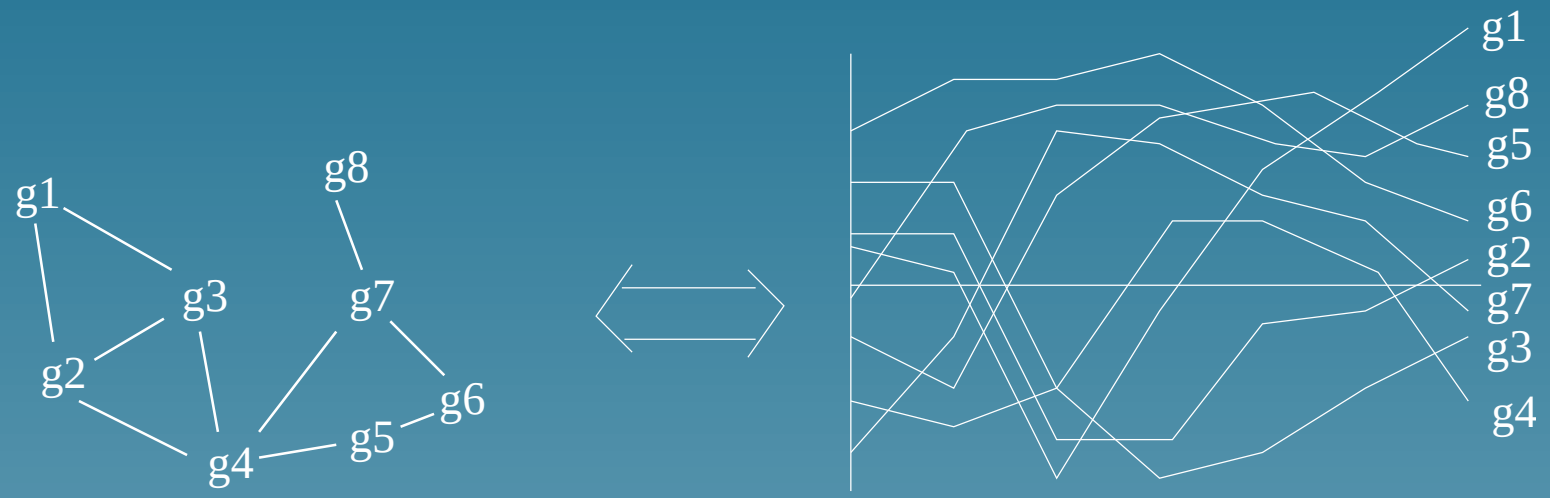
Outline

1. Problem formulation
2. An approach using kernel methods
3. Experimental results

Part 1

Problem formulation

The problem



Gene network

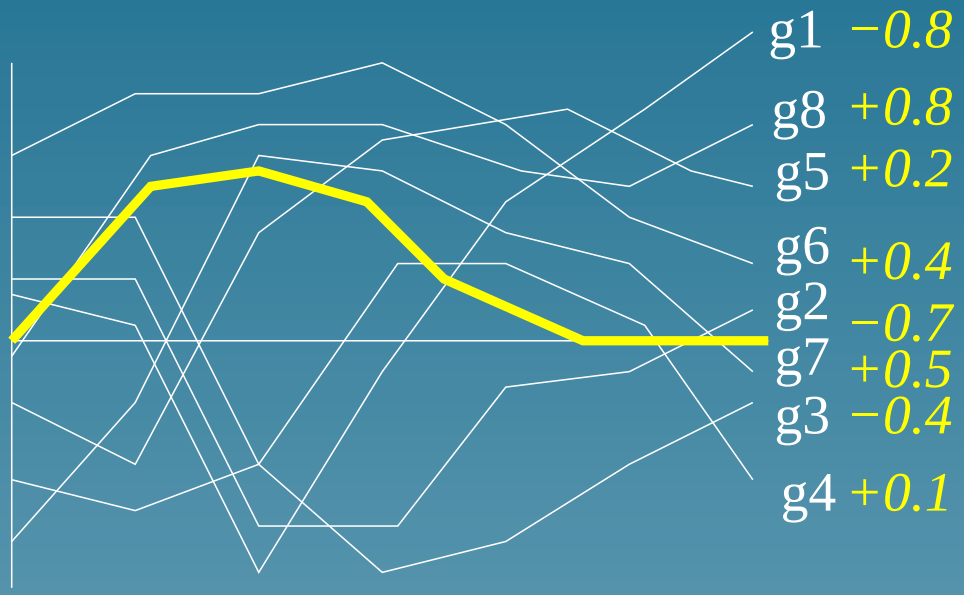
Expression profiles

Are there "correlations"?

What is a correlation?

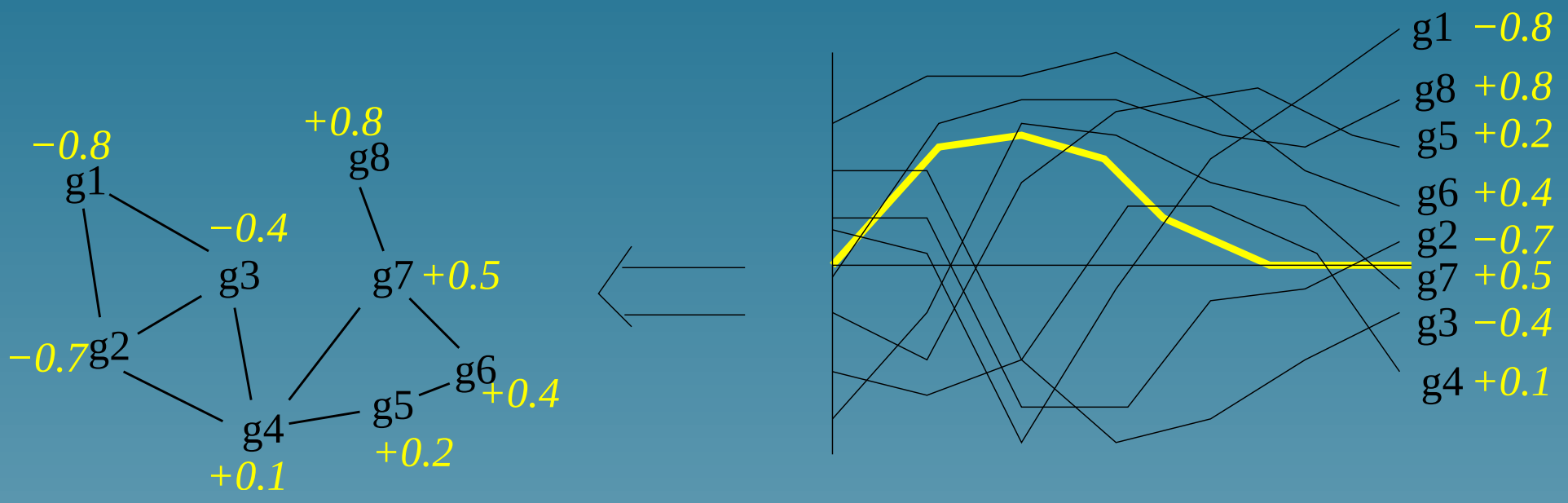
- "Patterns" of expression shared by genes closed to each others on the network
- Examples:
  - ⋆ Activation of a pathway: enzymes which catalyze successive reactions might share a particular expression pattern
  - ⋆ Formation of a protein complex: the co-expression of several genes closed to each other on a protein interaction network is required.

Pattern of expression



- An expression pattern is a particular expression profile.
- The correlation between a pattern and a gene expression profile quantifies how each gene shares the profile.

Smoothness of a pattern



- A pattern whose correlation varies smoothly with respect to the graph topology is an interesting pattern.

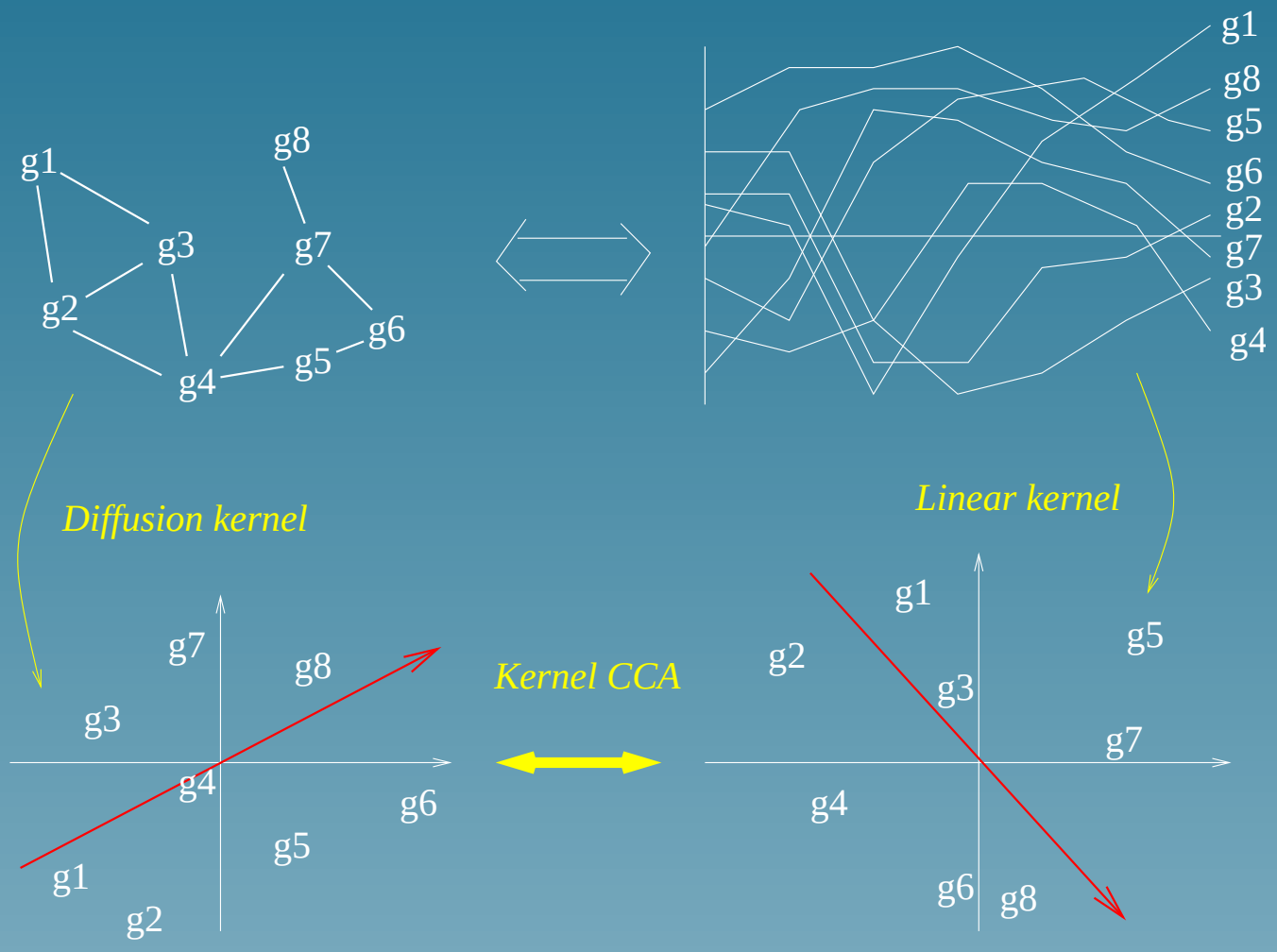
Part 2

An approach using kernel methods

Overview

- We have developped an algorithm to extract expression patterns smooth with respect to a network topology
- Based on recent developments in the field of kernel methods (SVM...)
- Input: a gene network and a set of expression profiles
- Output: a set of interesting expression patterns, and the groups of genes which share it or not

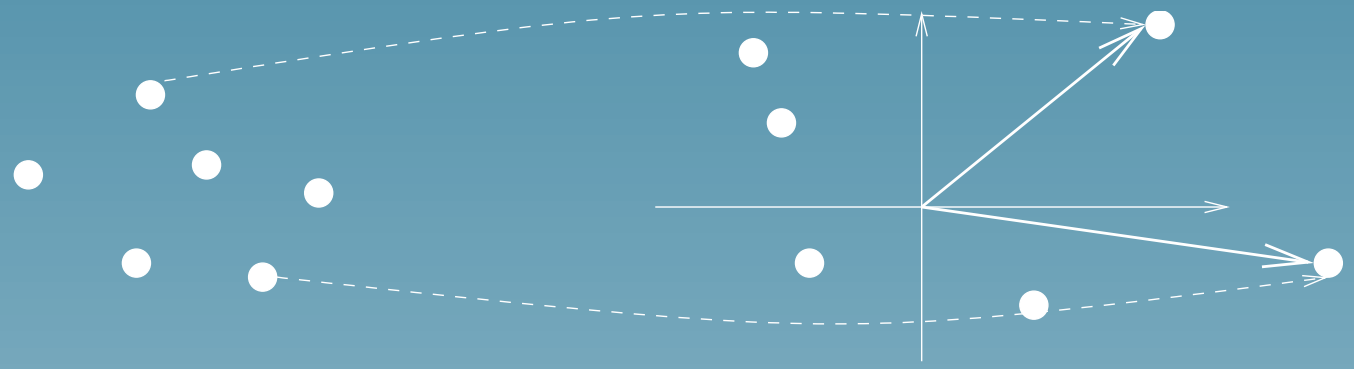
The idea


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

Kernel

For any mapping $\Phi(.)$ from the set of genes to a Euclidean space $\mathbb{R}^n$, the kernel $K(g, g')$ between two genes is the inner product between their images:

$$K(g, g') = \Phi(g).\Phi(g').$$



Diffusion kernel (Kondor and Lafferty, 2002)

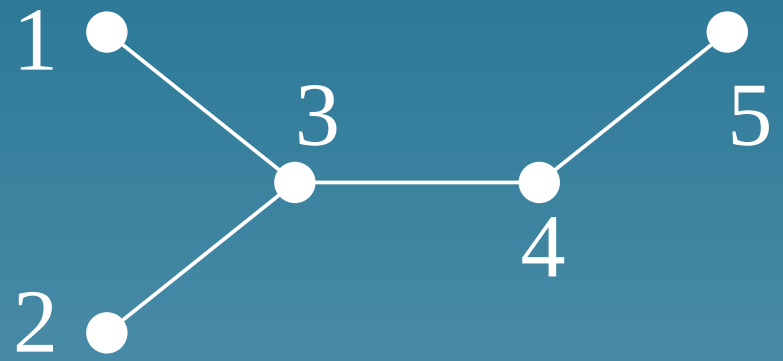
- For a given graph, there is a natural mapping Φ to a (high dimensional) Euclidean space which conserves the topology of the graph.

- The corresponding kernel $K(g, g')$ between any two genes can be computed by:

$$K = \exp(D - A),$$

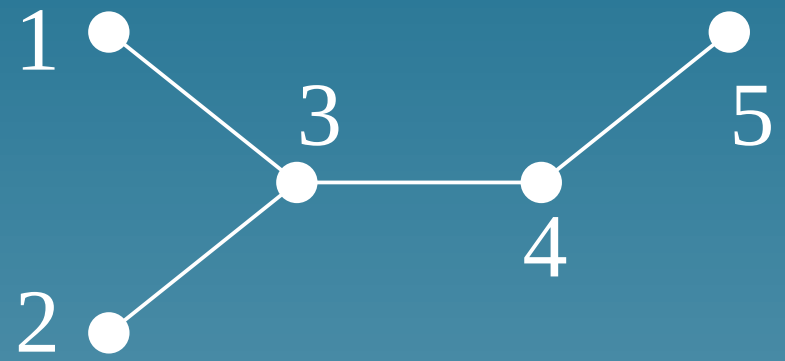
where A is the adjacency matrix and D the degree diagonal matrix

Example of a diffusion kernel (1)



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

Example of a graph kernel (2)



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

Expression kernel

- Expression profiles are vectors
- The inner product between two profiles is a valid kernel

Kernel CCA (Bach and Jordan, 2002)

- Let K_1 be the graph kernel, and K_2 be the expression kernel (corresponding to mapping the genes to two Euclidean spaces)
- Finding directions with large correlations is equivalent to solving the generalized eigenvalue problem:

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

Part 3

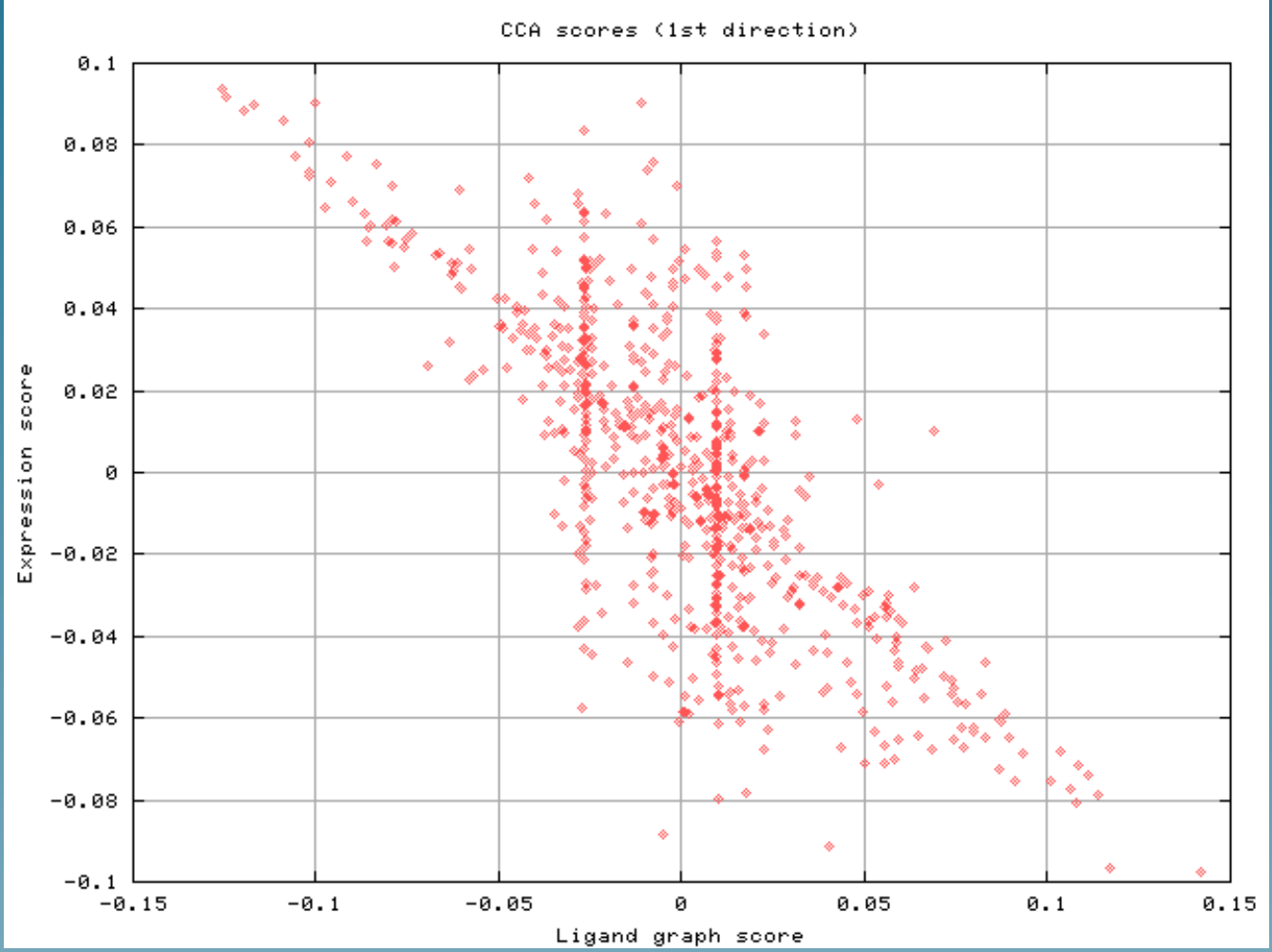
Experimental results

Data

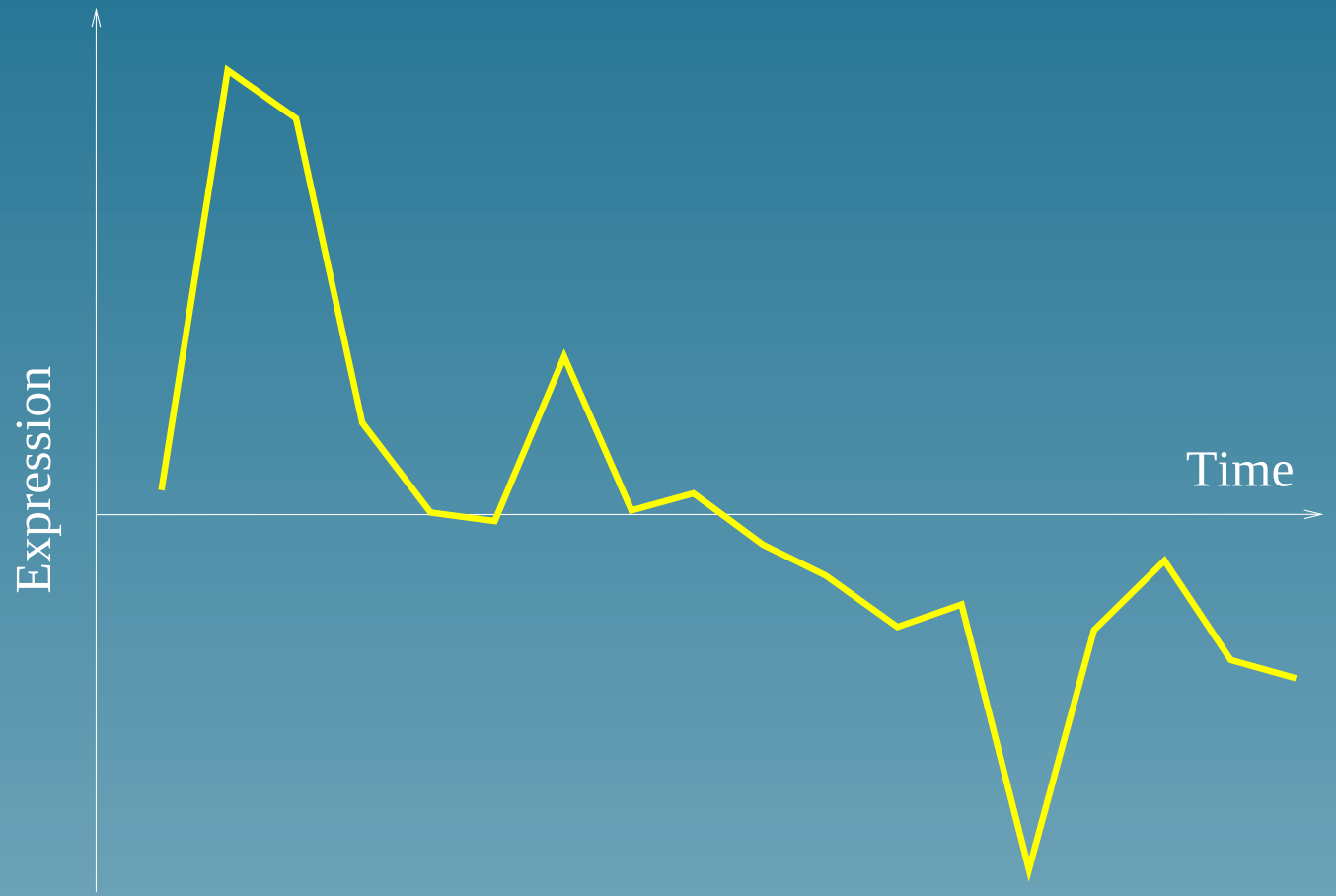
- Gene network: genes are linked if they are known to catalyse two successive reactions (data available in Kyoto University's KEGG database, `www.genome.ad.jp`)

- Microarray data: 18 measures for all genes (6,000) of the budding yeast S. Cerevisiae by Spellman et al. (public data), corresponding to a cell cyle after release of alpha factor.

1st CCA scores



Upper left expression



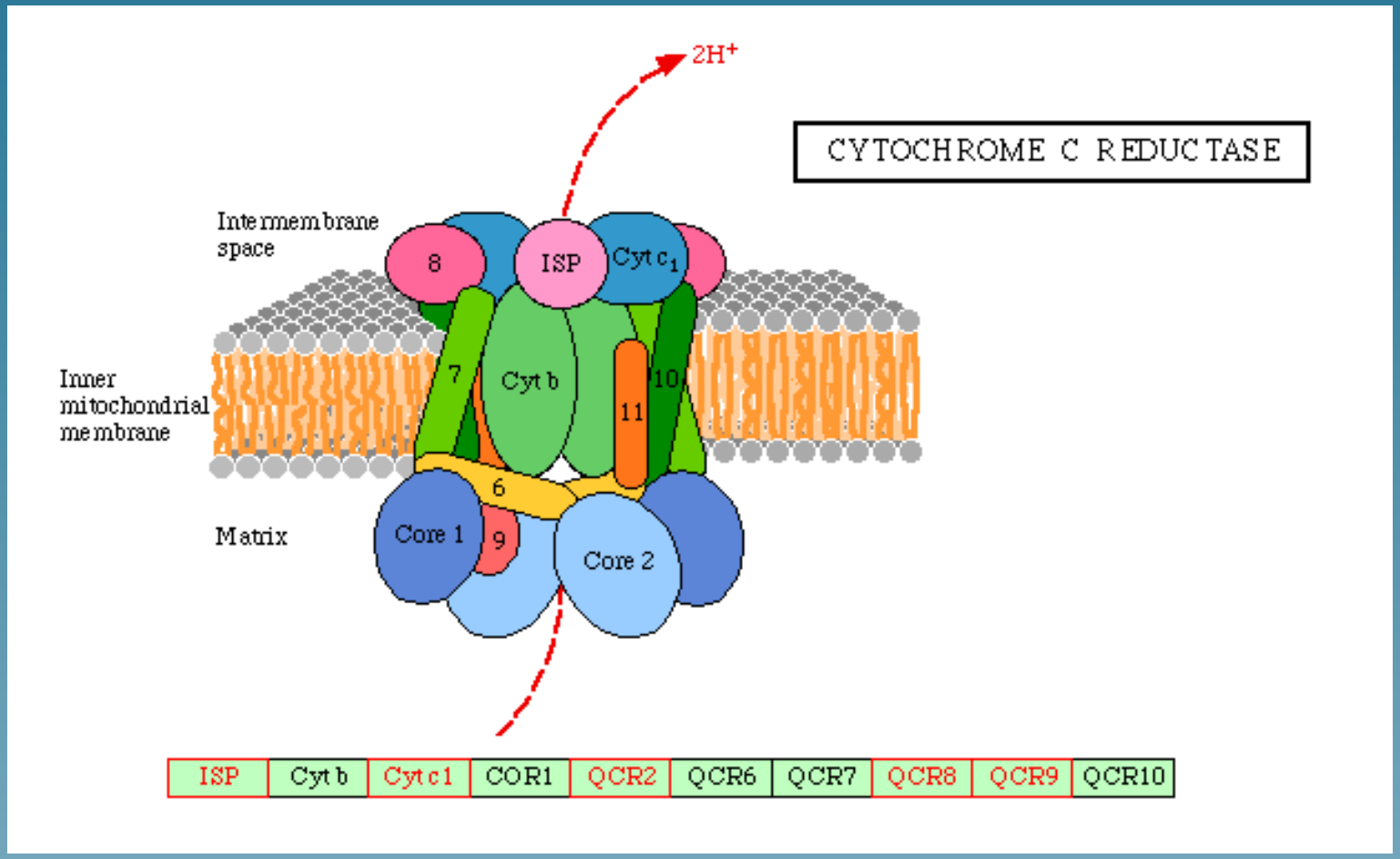
Average expression of the 50 genes with highest $s_2 - s_1$.

Upper left genes

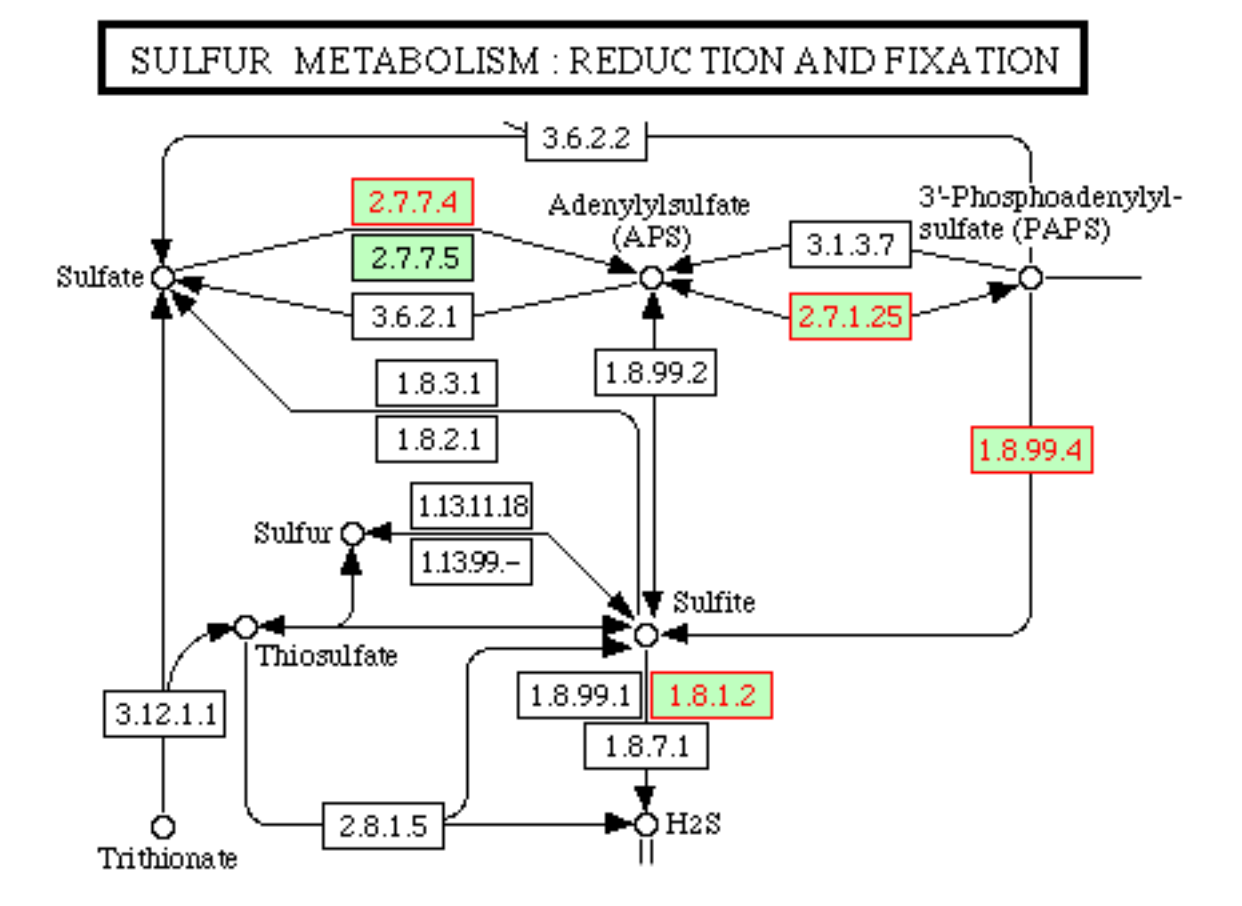
50 genes with highest $s_2 - s_1$ belong to:

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

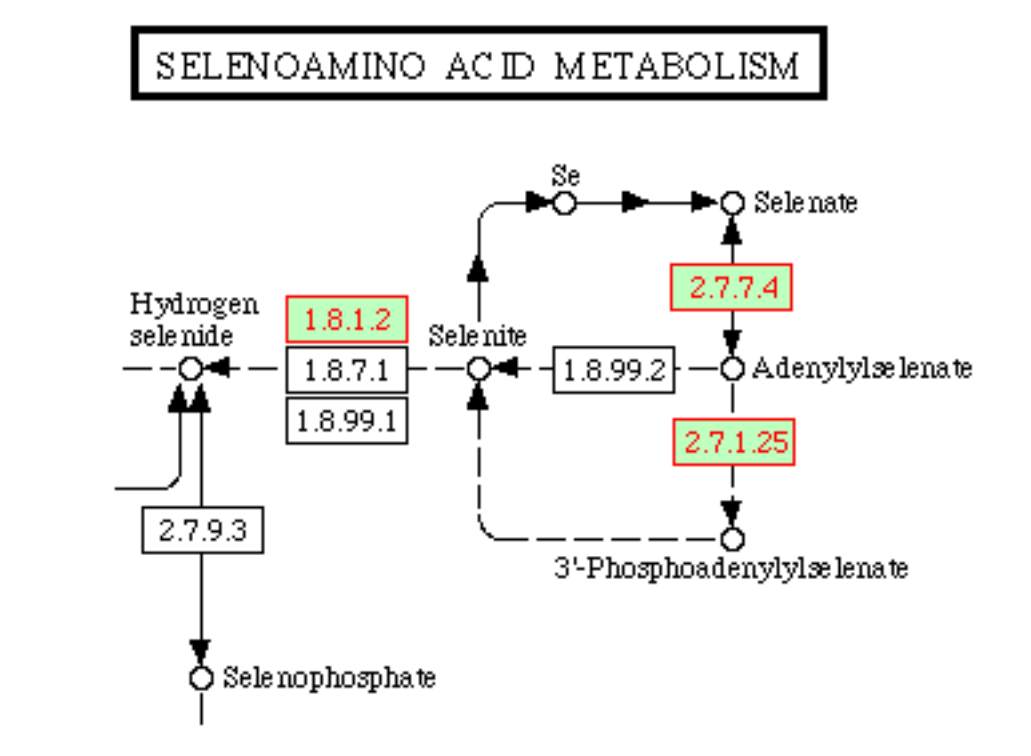
Upper left genes



Upper left genes



Upper left genes



Lower right expression

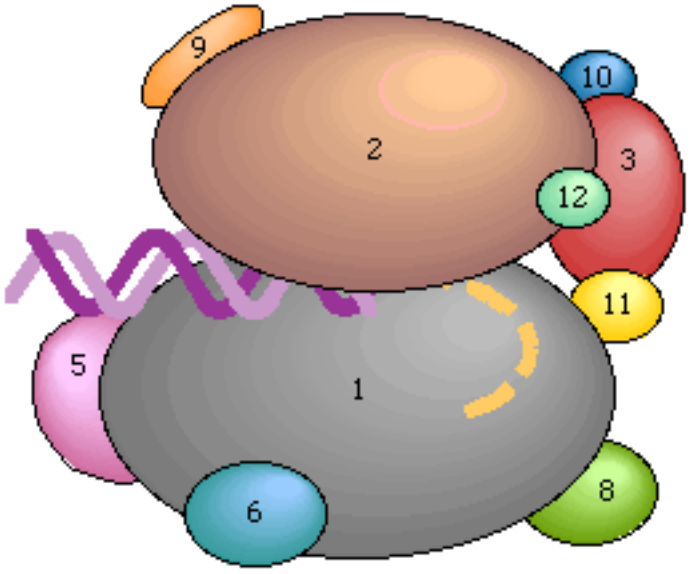
Average expression of the 50 genes with highest $s_2 - s_1$.

Lower right 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...

Lower right genes

RNA POLYMERASE



RNA polymerase II (Saccharomyces cerevisiae)

Eukaryotic Pol II

B2	B3	B4	B5	B6	B7
B1	B8	B9	B10	B11	B12

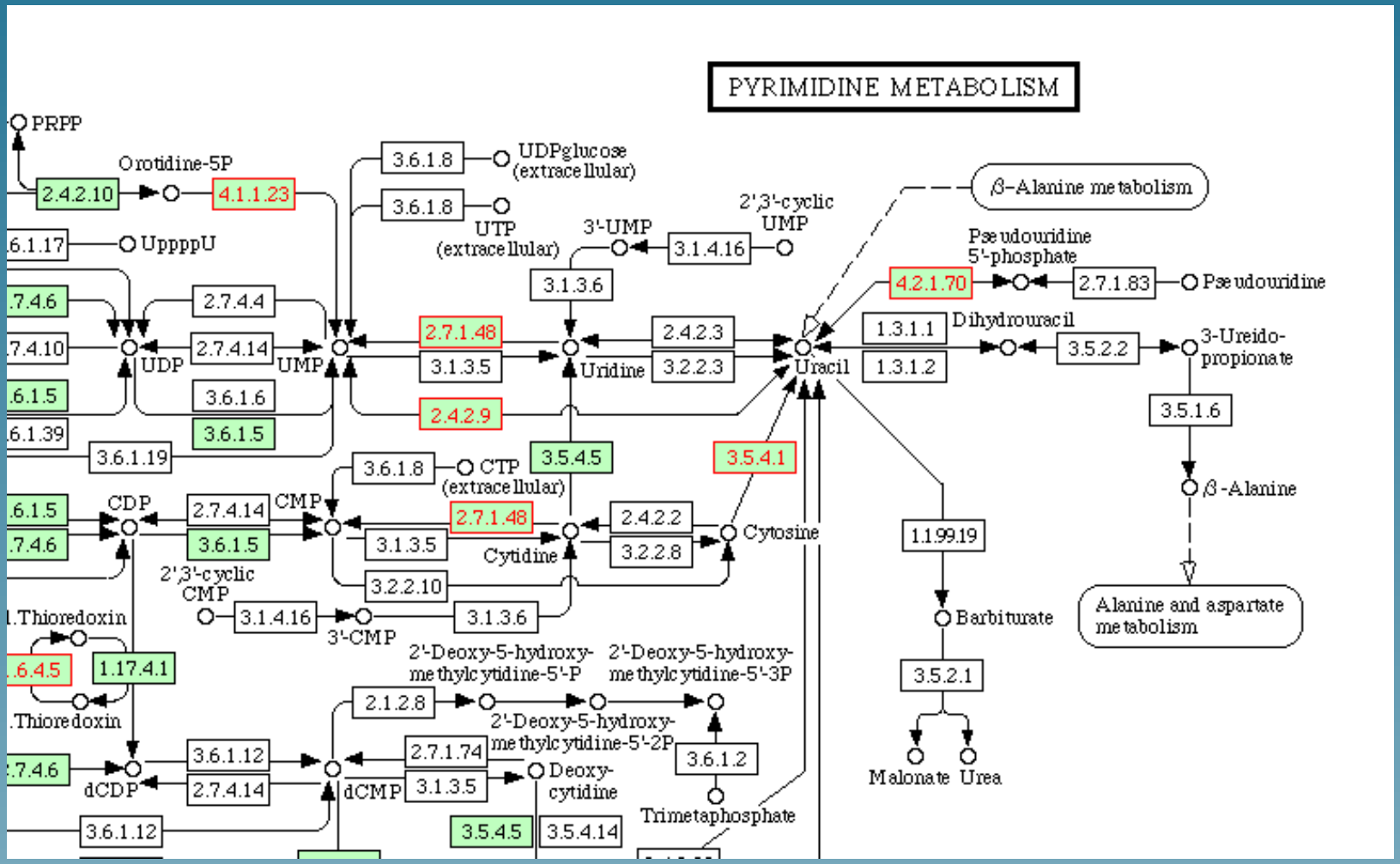
Eukaryotic Pol III

C2	C3	C4	C5	C11
C1	C19	C25	C31	C34

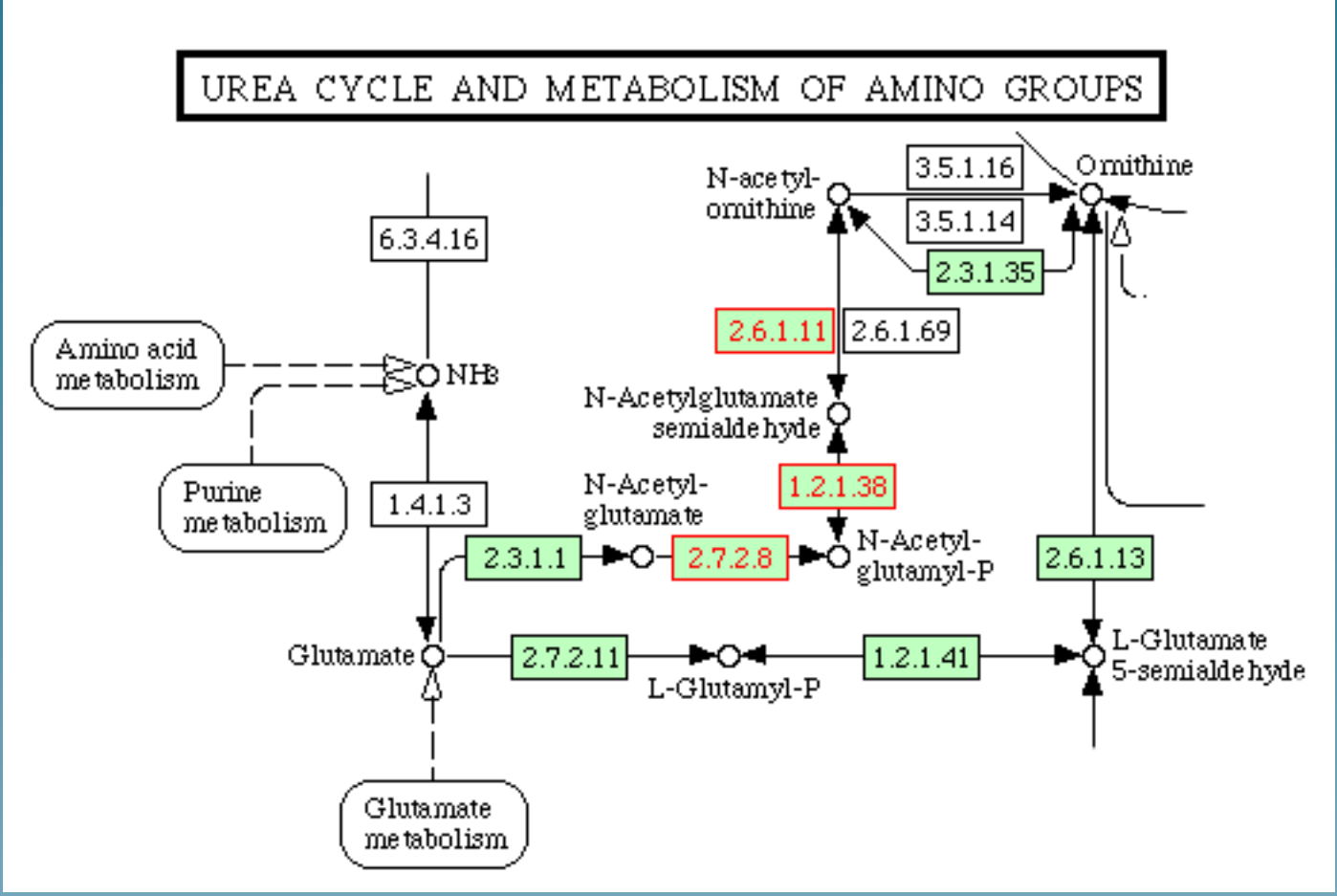
Eukaryotic Pol I

A2	A12	A14	A34	A43	A49
A1					

Lower right genes



Lower right genes



Conclusion

Conclusion

- A method to extract correlations between microarray data and a gene network
- Accepts noise and errors in the data
- Can be generalized to other types of information by using other kernels (e.g., string kernels to find correlations with sequences)
- More details: "Graph-driven feature extraction from microarray data", J.-P. Vert and M. Kanehisa, Preprint June 2002.