Molecular Evolution and Control: System Biology Approach

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一、**The Present and Future of Biology**

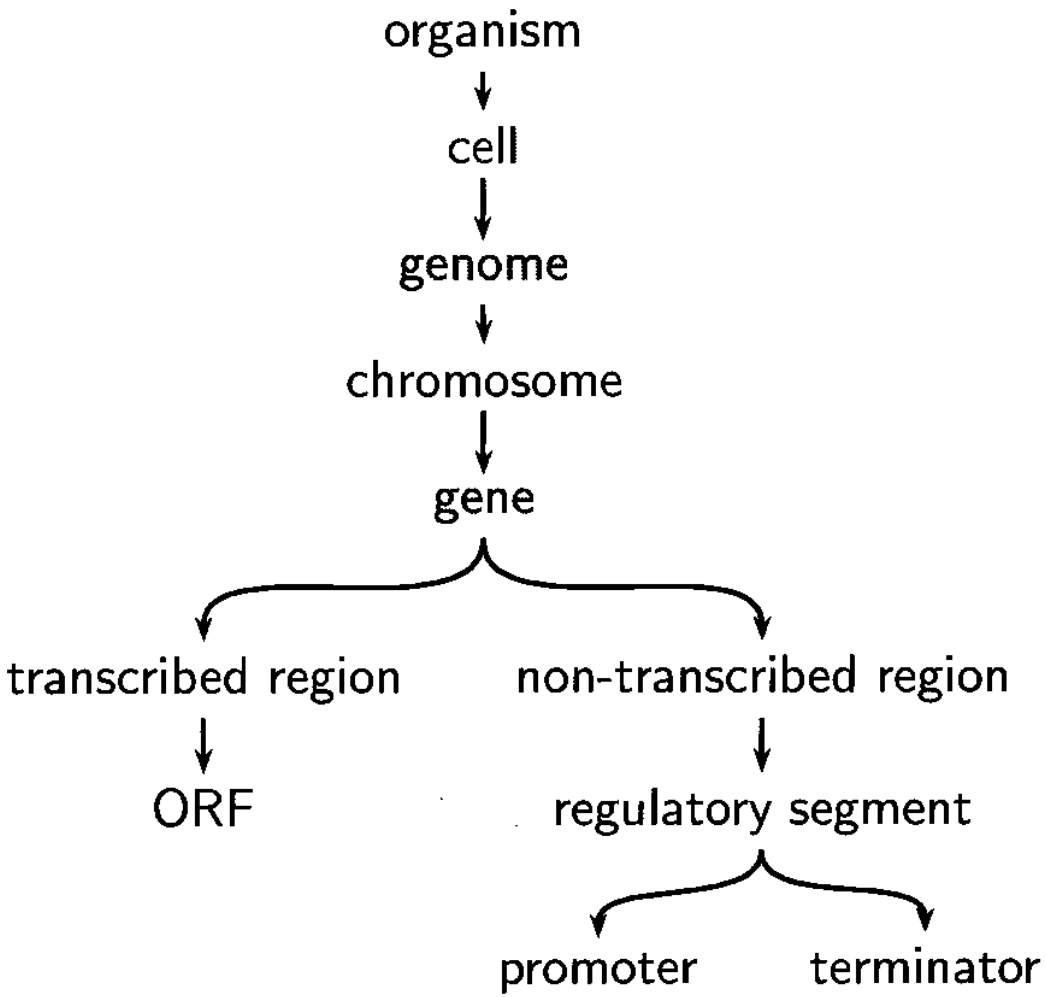
二、**Gene Regulation and Network**

三、**Gene Evolution and Control**

四、**System Control of Bio-molecular System**

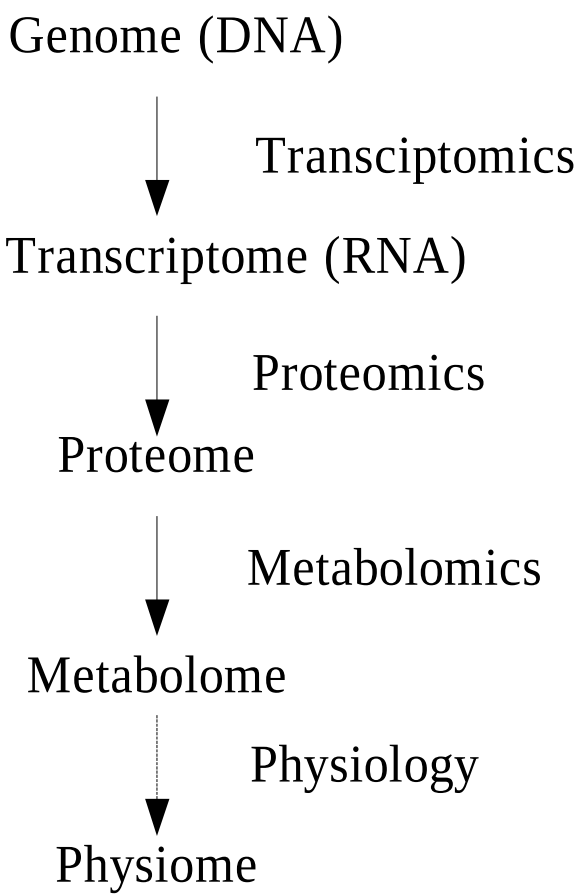
一、The Present and Future of Biology

a. Reductionism

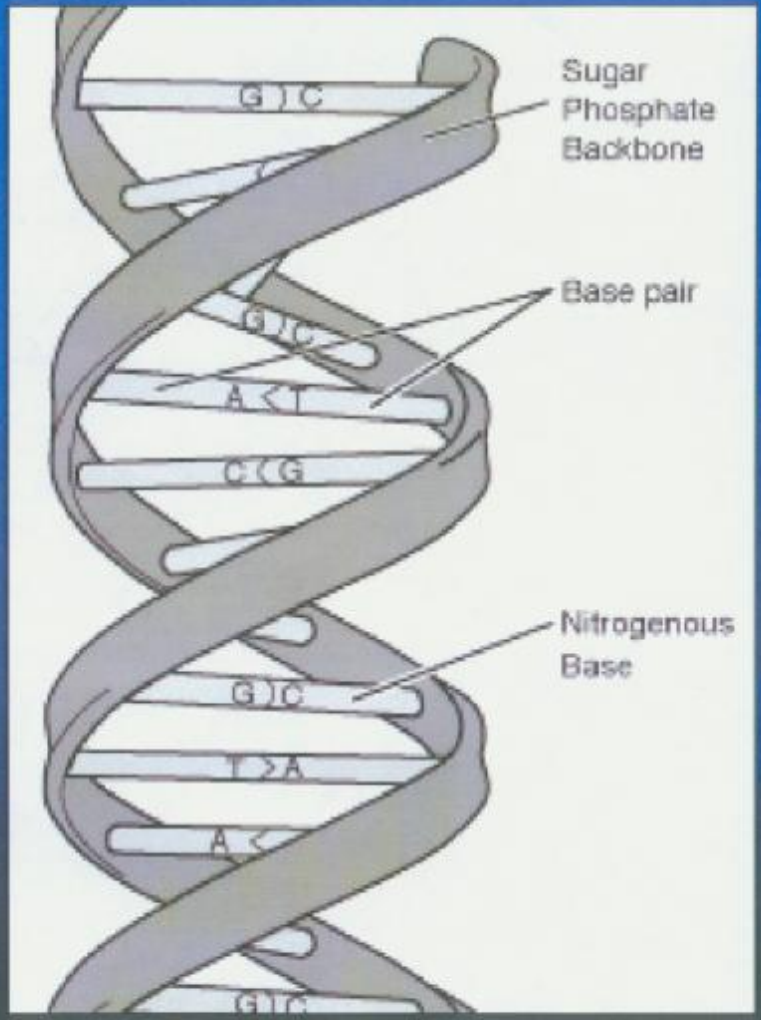


b. Integration and Reconstruction

• System-level understanding of a biological system

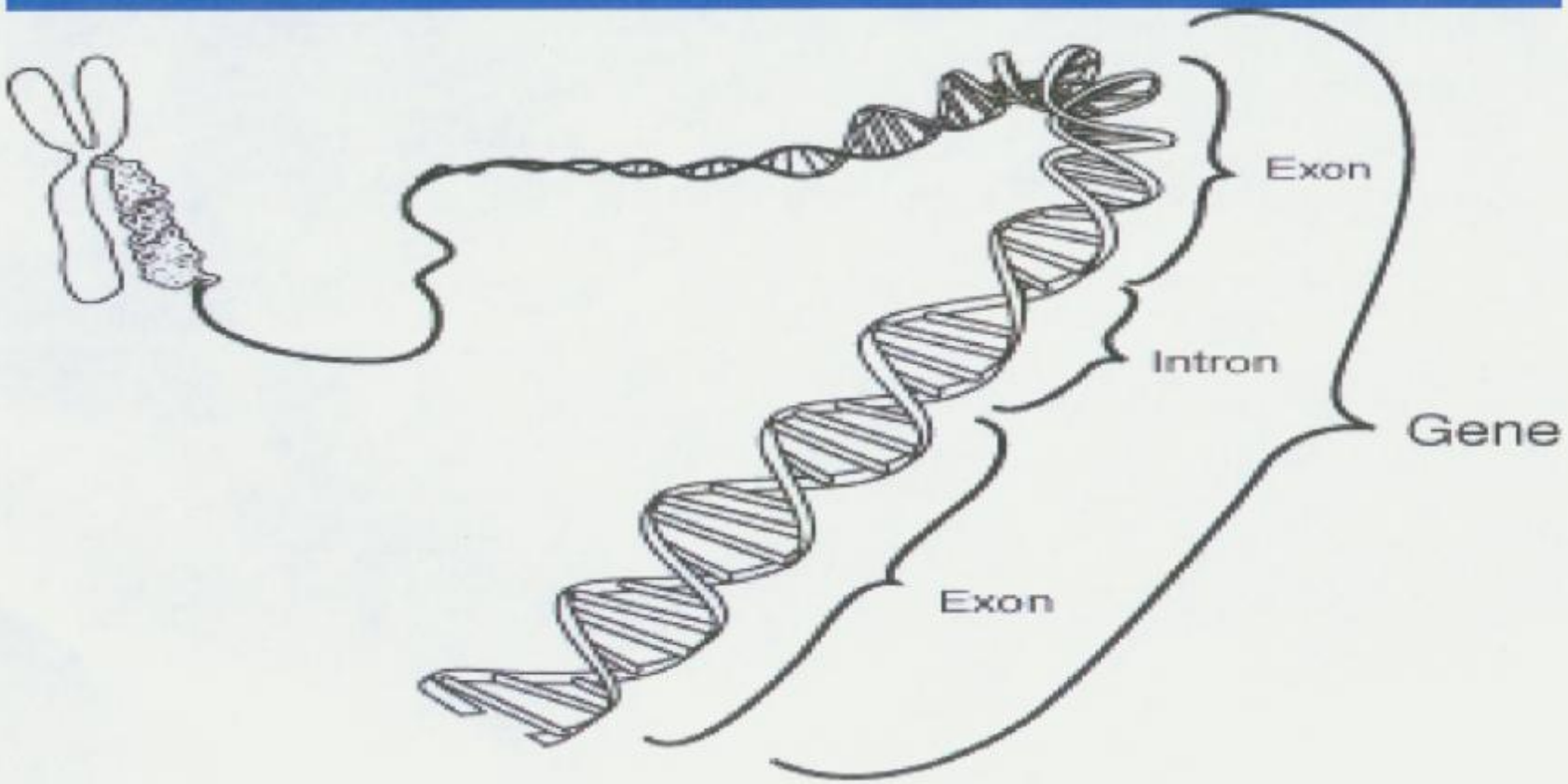


The Watson-Crick Structure for DNA

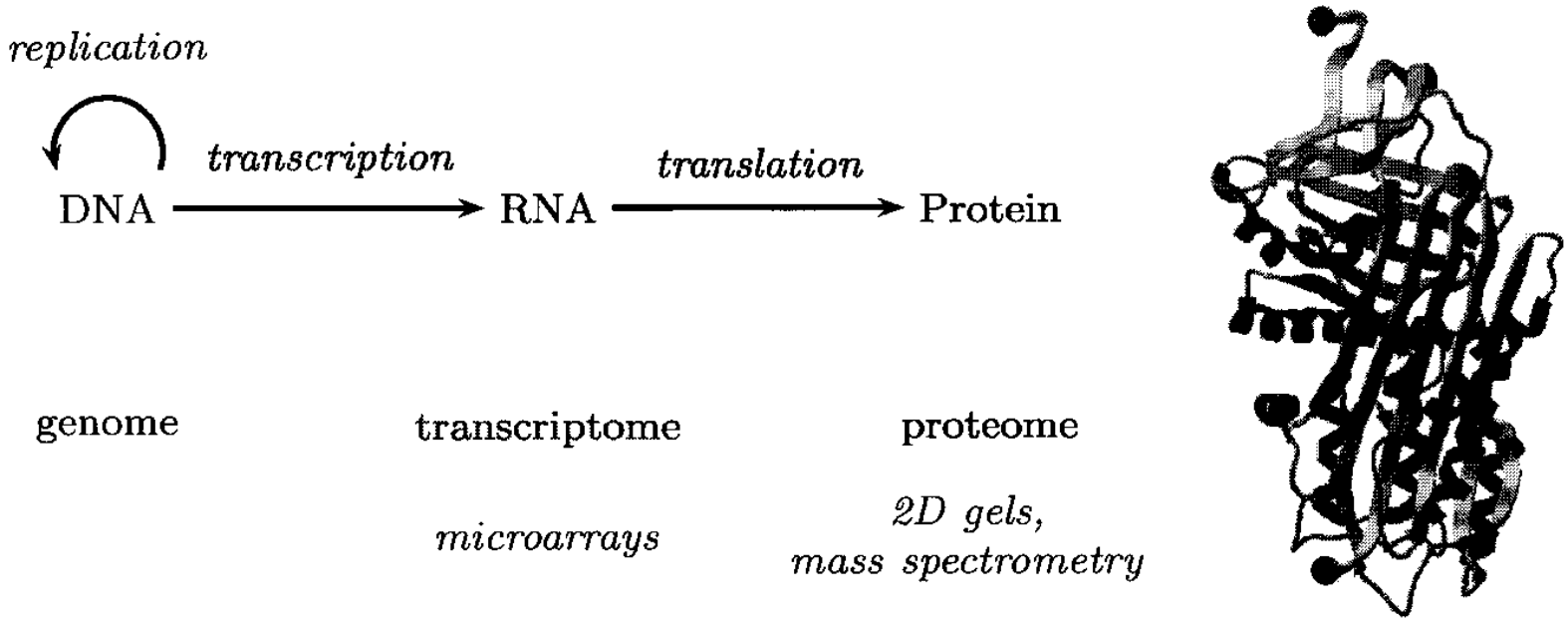


cDNA Microarray

- DNA



Genomics, Transcriptomics, Proteomics

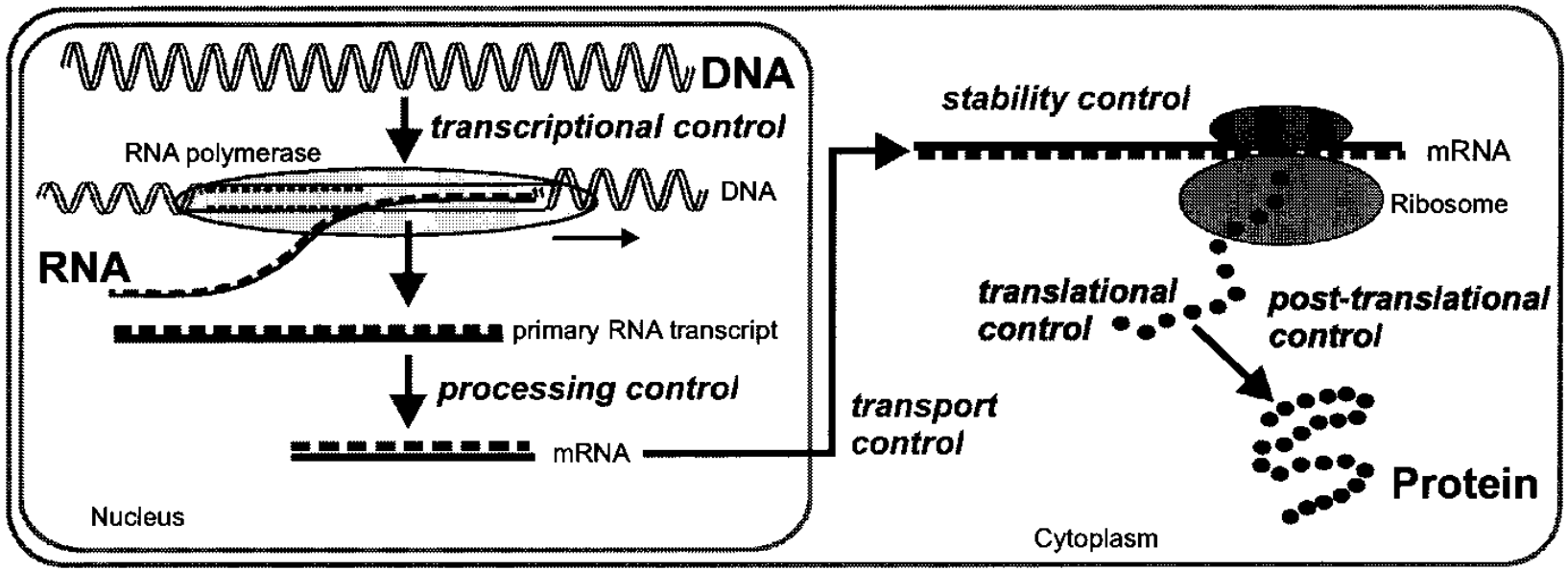


▷ Gene Expression:

- ✘ ... a *dynamic process*.
- ✘ ... an *information-fusion* problem.

O.Wolkenhauer (2001): Information Fusion in Genomics: Qualitative vs Quantitative. In *Data Fusion and Perception*. Della Riccia et.al. (eds), Springer. K.S.Sidhu, et al. (2001): *Bioinformatic Assessment of Mass Spectrometric Chemical Derivatisation Techniques for Proteome Database Searching*. *Proteomics*. 1. O.Wolkenhauer, Y.Cai, A.Doig and C.J.T.Dodson (2002): Information Theoretic Analysis of Protein Sequences shows that Amino Acids Self Cluster. Submitted to *Journal of Theoretical Biology*.

Gene Expression and Regulation in Eucaryotes



... dynamic feedback-regulated processes:

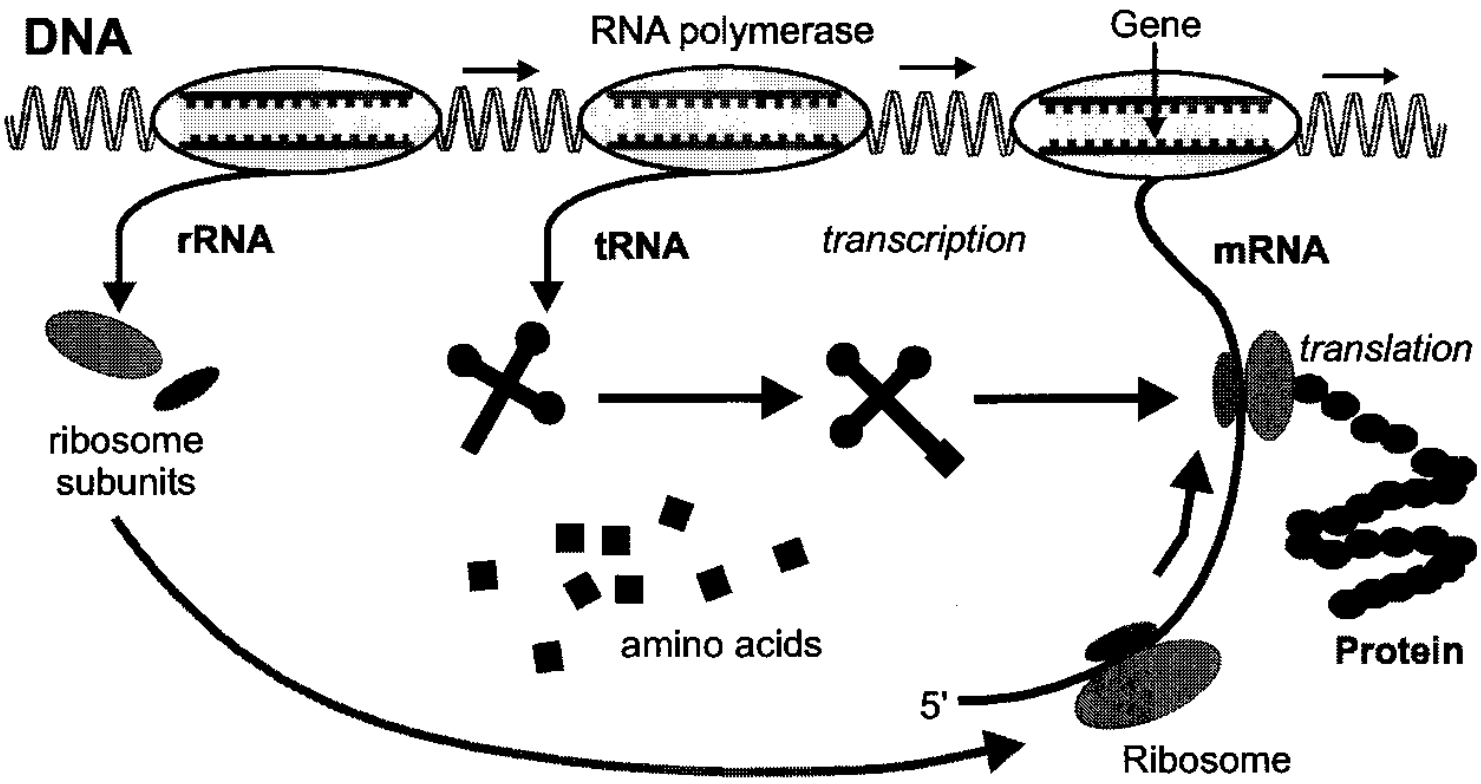
Shift of focus from molecular characterization to understanding integrated cellular systems

二、Gene Regulation and Network

1. Gene regulation Signal Detection

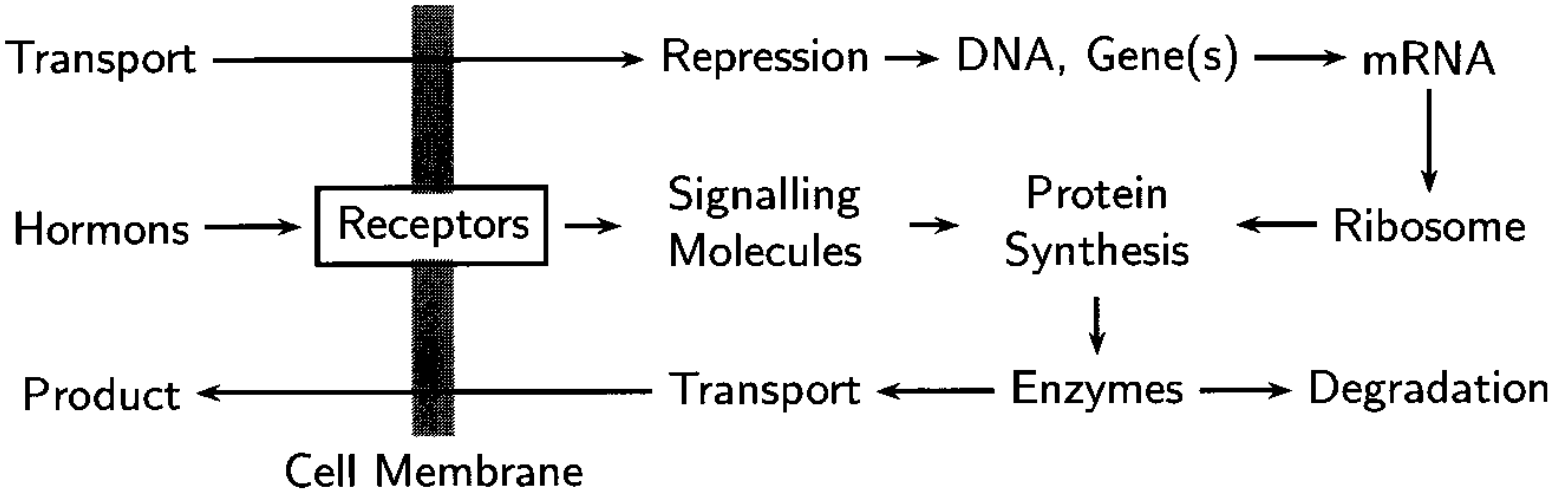
2. Microarray and Gene Expression Network

Gene Expression and Regulation in Bacteria



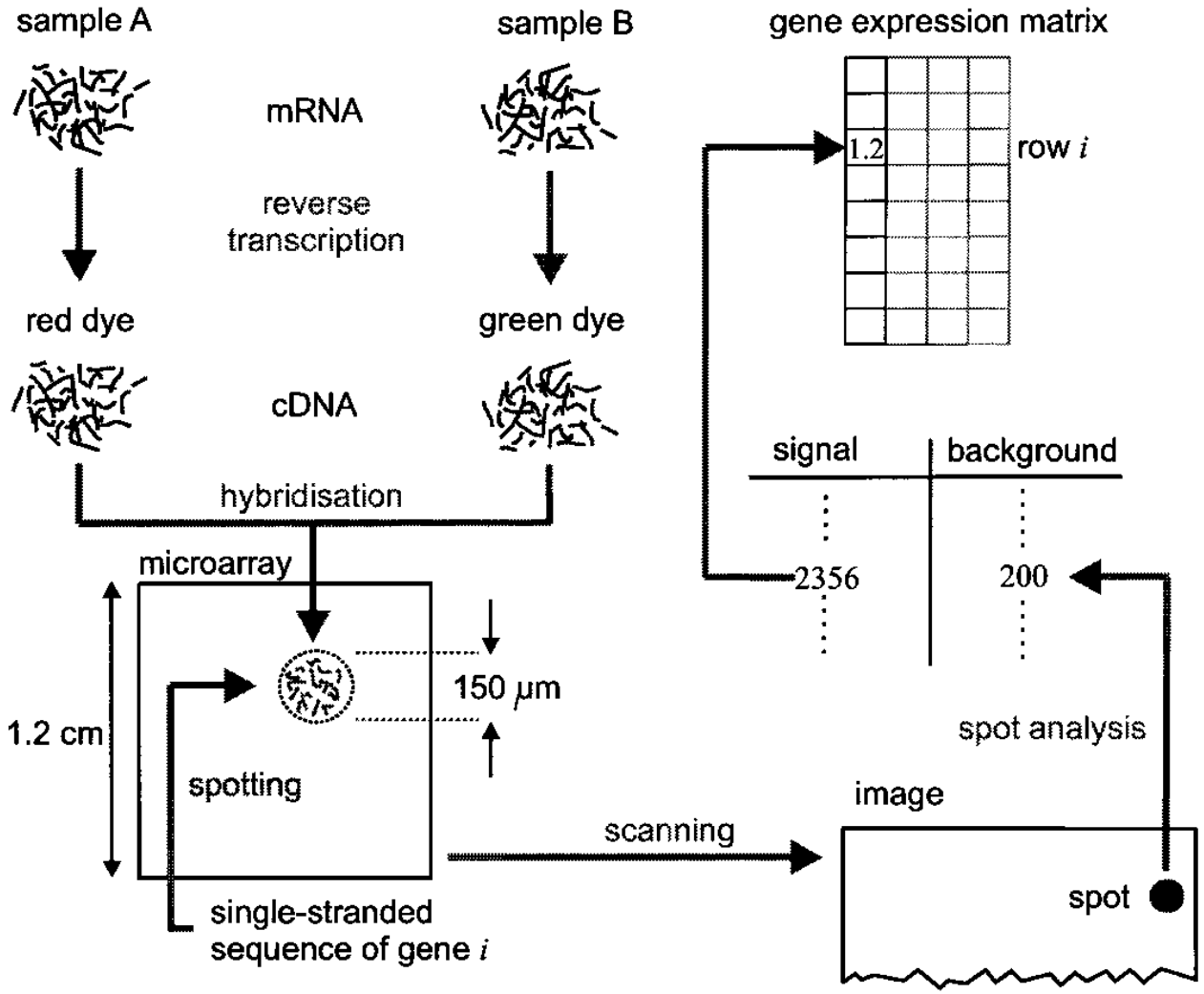
mRNA is unstable and is hence a basis for regulation of gene expression.

Gene Regulation



O.Wolkenhauer and W.Kolch (2002): Mathematical Systems Biology: Genomic Cybernetics. In *Emerging Computational Metaphors*, R. Paton (ed.) In press.

DNA Microarray Production



Streptomyces Microarray

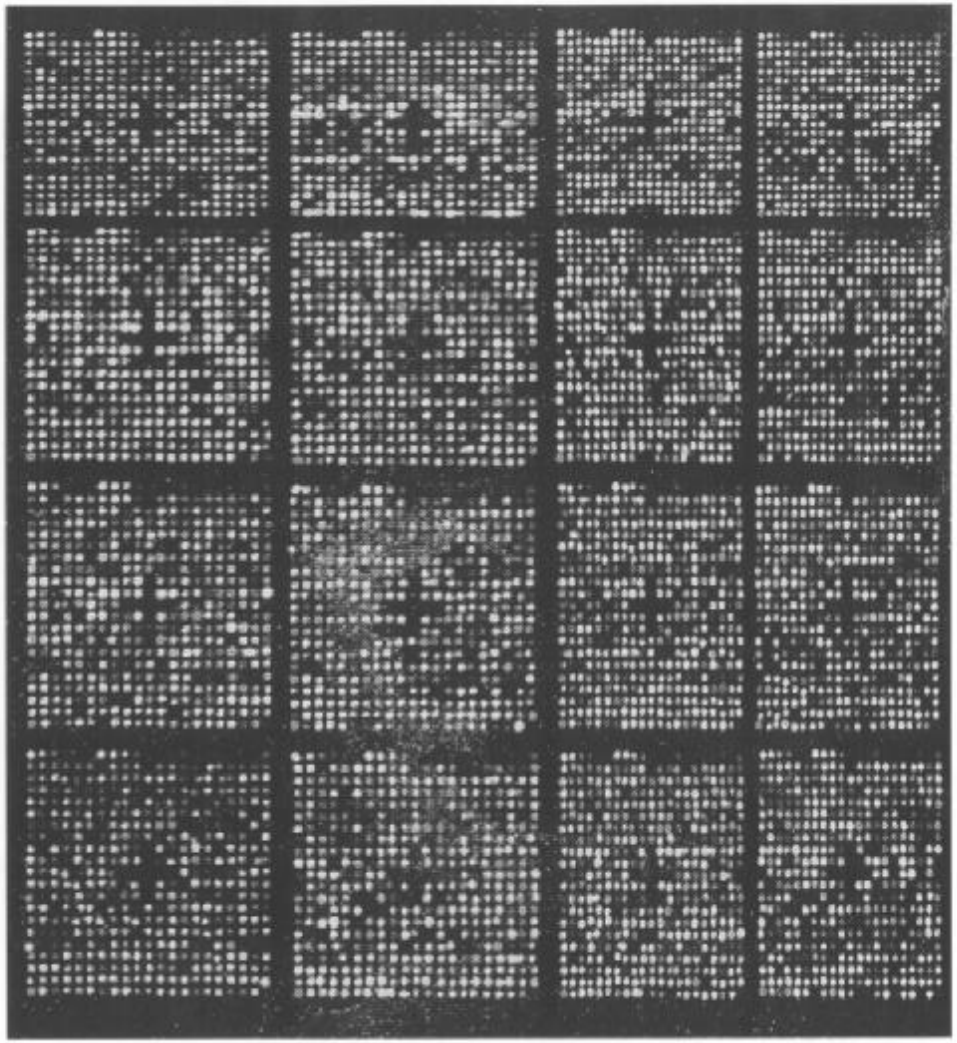
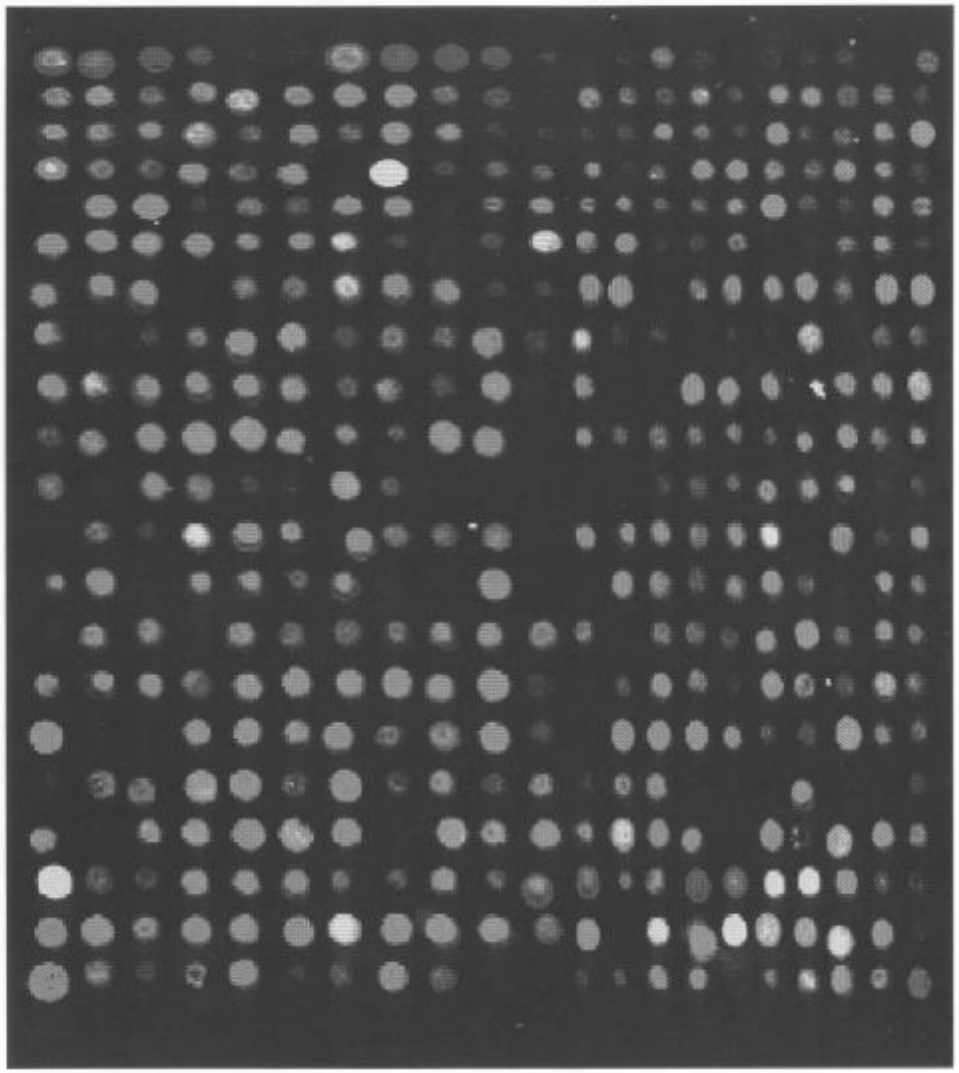


Image Analysis: Spotfinding



Gene Network Modelling

$$x_{t+1}^i = \gamma^i \cdot \phi\left(\sum_{j=1}^{n} s^{j,i} x_t^j + \sum_{r=1}^{m} g^{j,i} u_t^r + b^i\right) \underbrace{-\lambda_i x_t^i}_{degredation}$$

where

- x_t^i is the expression level of the ith gene at time t,
- u_t^r the kth external input at time instance t,
- $\phi(\cdot)$ is called *activation function*, $\phi(z) = 1/(1+\exp(-z))$,
- γ^i denotes the rate constant of gene i,
- u_t^r denotes the r-th external input at time instance t,
- $g^{r,i}$ describes the influence of the r-th external input on gene i,
- b_i is the basal expression of gene i,
- λ_i is the degradation constant of the i-th gene expression product.

Gene Network Modelling

Further simplifications:

$$x_{t+1}^i = \sum_{j=1}^{n} s^{j,i} x_t^j + \sum_{r=1}^{m} g^{j,i} u_t^r \ .$$

Ignoring inputs to the network:

$$x_{t+1}^i = \sum_{j=1}^{n} s^{j,i} x_t^j \ .$$

Regulation Signal Detection of Yeast Cell Cycle by Microarray Data

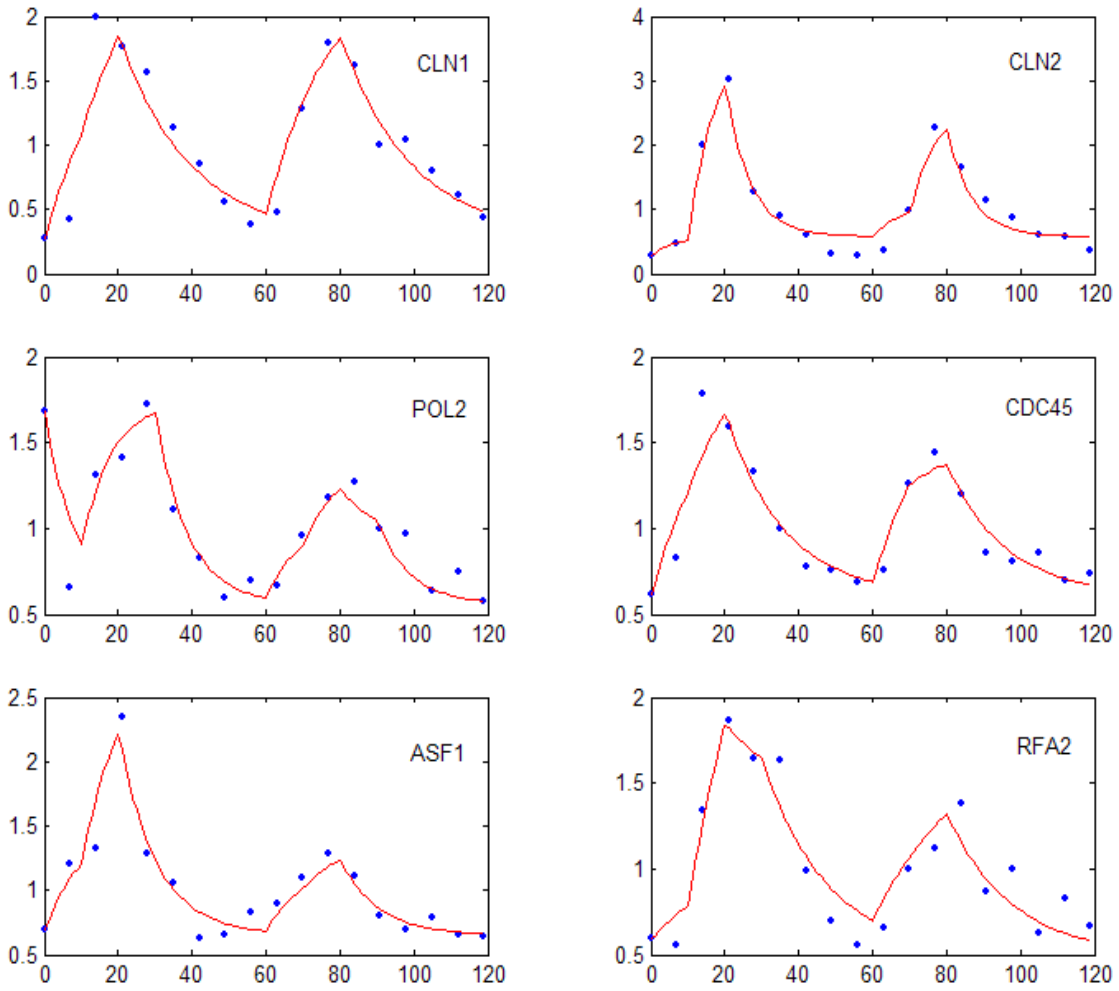
The dynamic of the ith gene is described by the following equation

$$\frac{dx_i(t)}{dt} = l_i x_i(t) + g_i(t) \qquad (1)$$

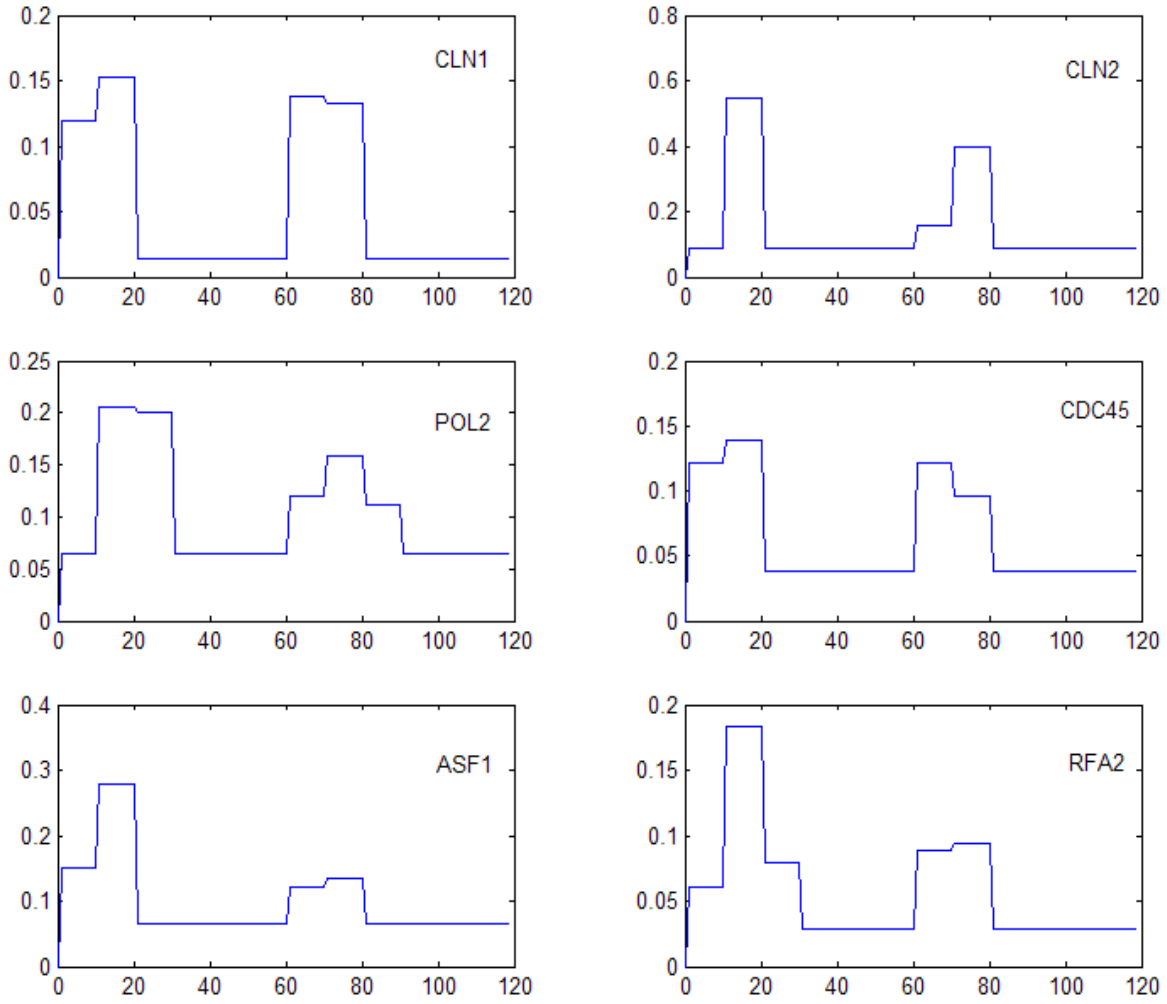
where l_i denotes the characteristic of gene $x_i(t)$, which is related to half life, and the regulation signal $g_i(t)$ is expressed by the following function

$$g_i(t) = \sum_{j=1}^{n} a_{ij} u(t - t_j) \qquad (2)$$

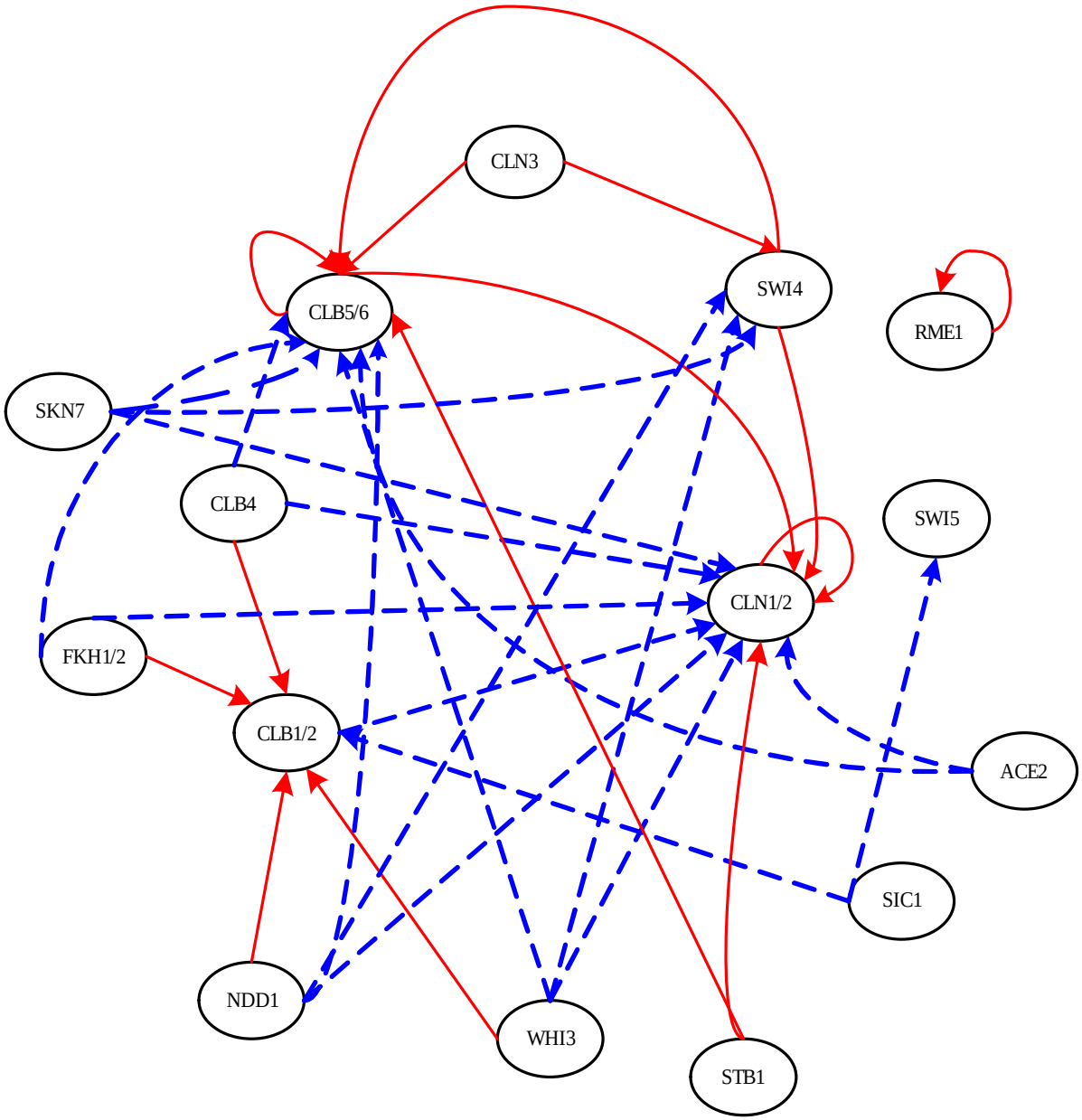
After l_i and a_{ij} are estimated, then the regulation signal $g_i(t)$ of the ith gene is obtained as $g_i(t)$ is seen to match the onset and ceasing of experiment results.



Experimental expression profile of genes in yeast cell cycle



The regulation signals during the Dictyostelium development


CLN3
SWI4
RME1
CLB5/6
SKN7
CLB4
SWI5
CLN1/2
FKH1/2
CLB1/2
ACE2
SIC1
NDD1
WHI3
STB1

Applications of Microarrays

1. Identification of members of specific pathways/networks
2. Identification of links between different sets of genes
3. Discovery and modelling of regulatory pathways
4. Response analysis (e.g. metabolic engineering)
5. Identification of new drug targets
6. Diagnostic tool: e.g. different human cancers

✔ Whole genome analysis

✔ Time series analysis

✘ Lack of resolution

✘ Post-translational modification

三、Evolution and Control

1.Assume a trait P can be controlled by a dynamic diffusion gradient as follows

$$\frac{\partial y}{\partial t} + D\frac{d^2 y}{dx^2} - ry(x) = 0$$

$P = X_T$ with the condition $y(x_T) = T$

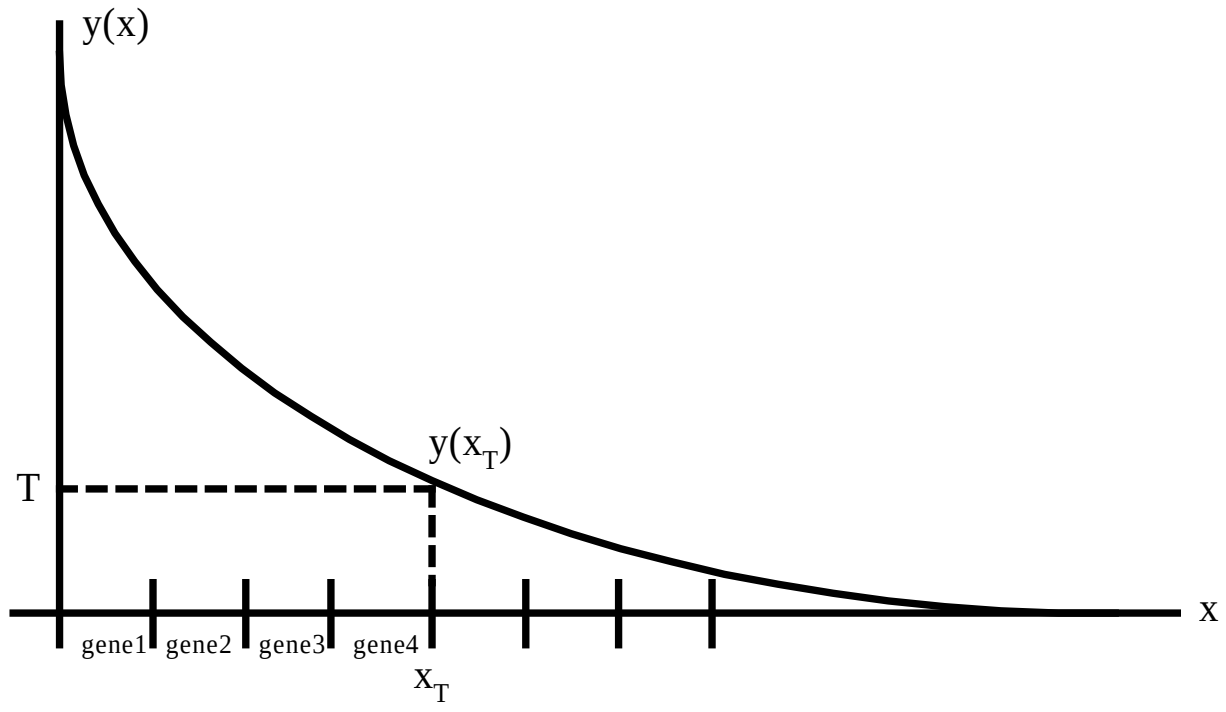
At steady state, i.e.

$$D\frac{d^2 y}{dx^2} - ry(x) = 0$$

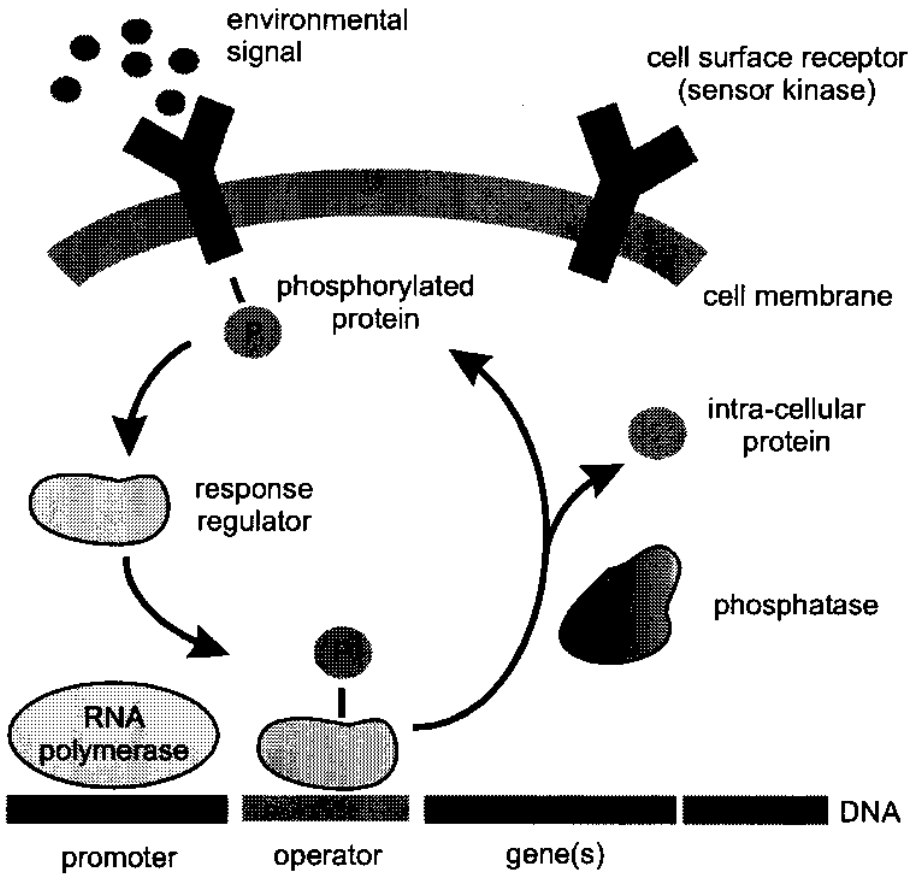
$$y(x) = S\exp\left[-\sqrt{\frac{r}{D}}x\right]$$

$$P = \sqrt{D/r}\,\ln(S/T)$$

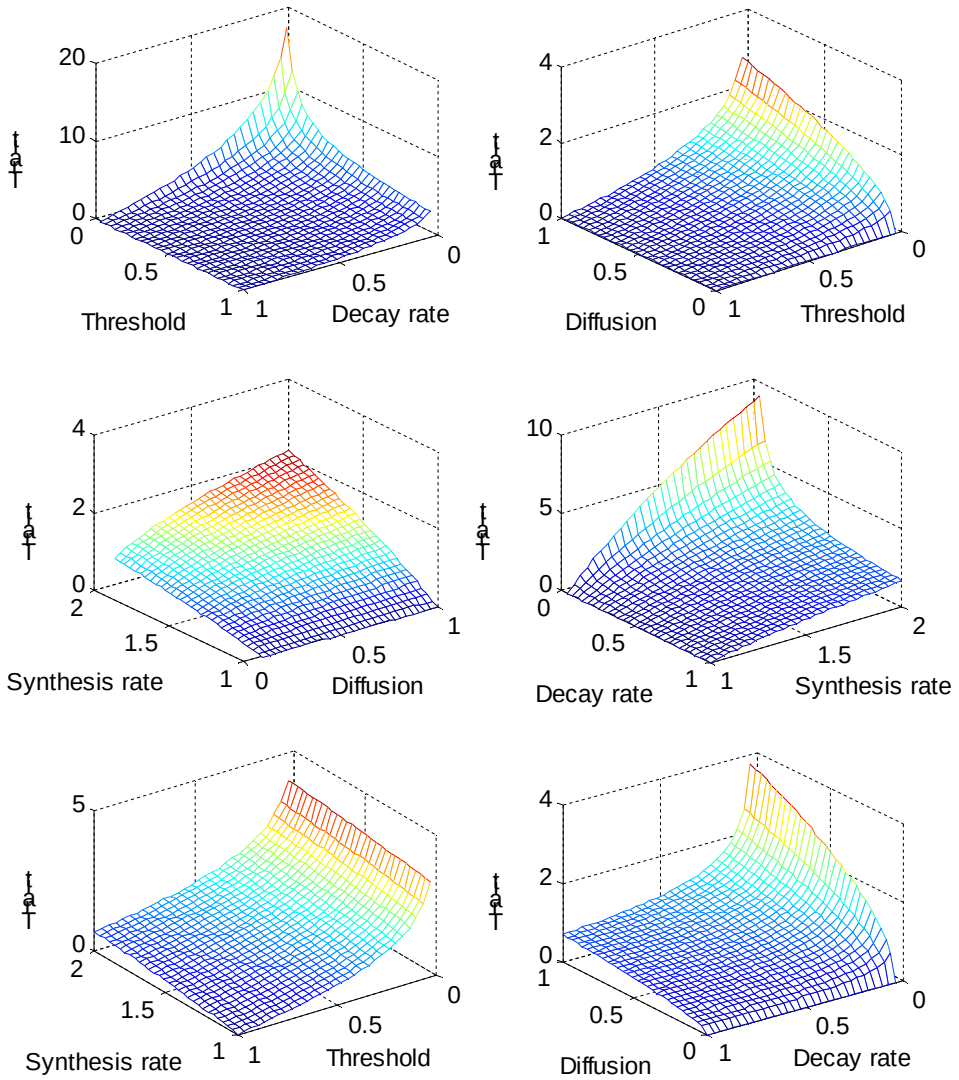
$$\left|\frac{\Delta P}{\Delta D}\right| + \left|\frac{\Delta P}{\Delta r}\right| + \left|\frac{\Delta P}{\Delta S}\right| < r$$



Intra- and Inter-Cellular Dynamics

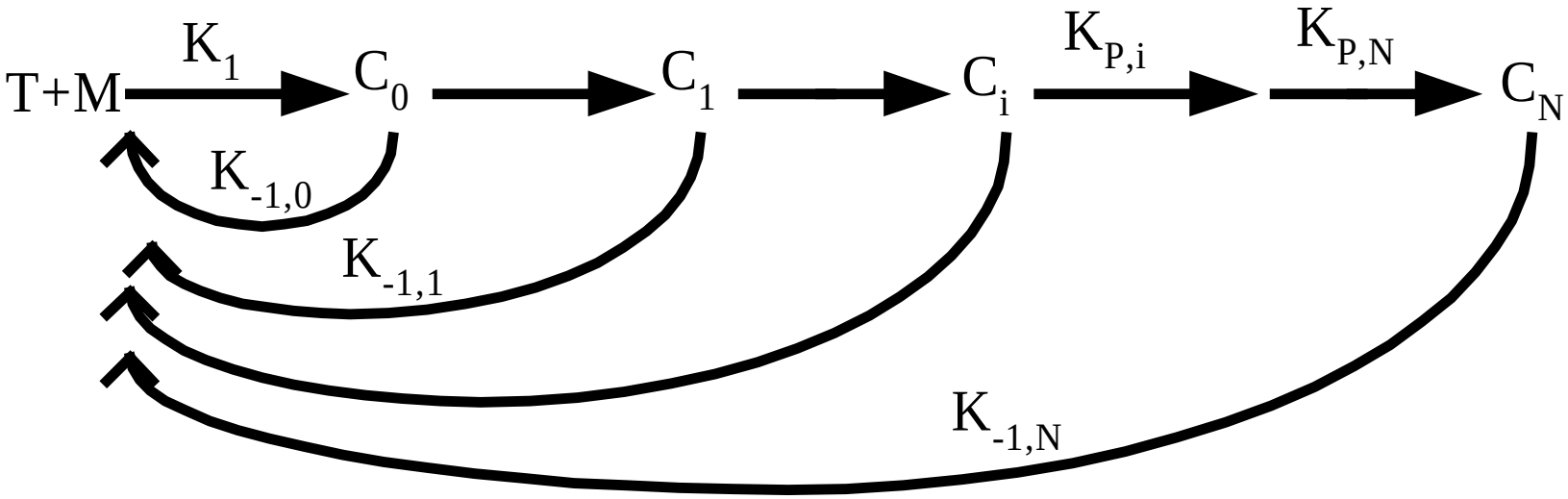


Downward, J. *Nature*, Vol. 411, 14 June 2001, 759-762. Kaneko, K. *J. Theor. Biology*, Vol. 199, No.3, August 1999, 243-256


20
10
0
0
0.5
1
1
Threshold
0.5
0
Decay rate
4
2
0
1
0.5
0
1
Diffusion
0.5
0
Threshold
4
2
0
2
1.5
1
1
Synthesis rate
0.5
0
Diffusion
10
5
0
0
0.5
1
1
Decay rate
1.5
2
Synthesis rate
5
0
2
1.5
1
1
Synthesis rate
0.5
0
Threshold
4
2
0
1
0.5
0
1
Diffusion
0.5
0
Decay rate

1. 地中海貧血症
2. 黒皮膚 $\dot{X} = F(x,q), Y = H(x)$

McKeithan Network



Kinetic Proofreading in T-cell Signal

$$\dot{T} = -k_1 TM + \sum_{i=0}^{N} k_{-1,i}\, C_i$$

$$\dot{M} = -k_1 TM + \sum_{i=0}^{M} k_{-1,i}\, C_i$$

$$\dot{C}_o = -k_1 TM - (k_{-1,0} + k_{p,0}) C_0$$

$$\vdots$$

$$\dot{C}_i = k_{p,i-1}\, C_{i-1} - (k_{-1,i} + k_{p,i}) C_i$$

$$\vdots$$

$$\dot{C}_N = k_{p,N-1} C_{N-1} - k_{-1,N}\, C_N$$

T: Concentration of T-cell receptor

M: Concentration of a peptide-major histocompatibility complex (MHC)

C_o : Initial ligand-receptor complex

C_i : Concentrations of various intermediate complexes

C_N : Concentration of final complex.

Systems Biology?

Genomics is the field of biological research, taking us from the DNA *sequence* of a gene to the *activity* of the product (usually a protein) for which it codes.

Gene Expression is the *process* by which information, coded in the DNA, is converted into proteins (hormones, enzymes, antibodies,...).

Systems Theory is a family of methodologies to formally represent *structure* and *dynamic behaviour*.

Systems Biology aims at a system-level understanding of the *organisation* and *control* of genetic pathways.

四、System control of Bio-molecular System

A system-level understanding of a biological system can be derived insight into four key properties.

1. **System structures: a. Network of gene interactions and Biochemical pathways.**

   b. Mechanisms (Interaction) of intracellular and multicellular structure.

2. **System dynamics: a. Metabolic analysis of system behaviors**

   b. Sensitivity analysis of system behaviors

   c. Dynamic analysis of system behaviors

3. **The Control Method: Mechanisms that systematically control the state of cell can be modulated to minimize malfunction and provide potential therapeutic targets for treatment of disease.**

4. **The Design Method: Strategies to modify and construct biological systems having desired properties can be derived based on definite design principles and simulations, instead of blind trial-and –error.**