Modeling Genetic and Metabolic CellularNetworks

From Molecules to Cells and Organisms

Peter Schuster

Institut für Theoretische Chemie der Universität Wien, Austria

Seminar Lecture

Santa Fe Institute, 18.04.2005

Web-Page for further information:

http://www.tbi.univie.ac.at/~pks

1. What is computational systems biology?
2. Genabolic networks
3. Genomes and cellular networks
4. Forward and inverse problems
5. Reverse engineering – A simple example
6. Activation and silencing of genes
7. MiniCellSim – A simulation tool
8. Evolution of genabolic networks

1. **What is computational systems biology?**
2. Genabolic networks
3. Genomes and cellular networks
4. Forward and inverse problems
5. Reverse engineering – A simple example
6. Activation and silencing of genes
7. MiniCellSim – A simulation tool
8. Evolution of genabolic networks

Structural biology

Sequence ⇒ Structure ⇒ Function

Systems biology

Genome ⇒ Proteome ⇒ Dynamics of cells and organisms

Structural biology

Sequence ⇒ Structure ⇒ Function

Systems biology

Genome ⇒ Proteome ⇒ Dynamics of cells and organisms

Goals:

1. Large scale computer simulations of genetic regulatory and metabolic reaction networks.

Structural biology

Sequence ⇒ Structure ⇒ Function

Systems biology

Genome ⇒ Proteome ⇒ Dynamics of cells and organisms

Goals:

1. Large scale computer simulations of genetic regulatory and metabolic reaction networks.

2. Understanding the dynamics of cells and organisms including regulation through signal transmission in highly heterogeneous spatial structures.

Structural biology

Sequence ⇒ Structure ⇒ Function

Systems biology

Genome ⇒ Proteome ⇒ Dynamics of cells and organisms

Goals:

1. Large scale computer simulations of genetic regulatory and metabolic reaction networks.
2. Understanding the dynamics of cells and organisms including regulation through signal transmission in highly heterogeneous spatial structures.
3. Design of genetic and metabolic model systems, which allow for **optimization** through **evolution** and which provide explanations for the unique properties of living cells and organisms like **robustness**, **homeostasis**, and **adaptation** to environmental changes.

Structural biology

Sequence ⇒ Structure ⇒ Function

Systems biology

Genome ⇒ Proteome ⇒ Dynamics of cells and organisms

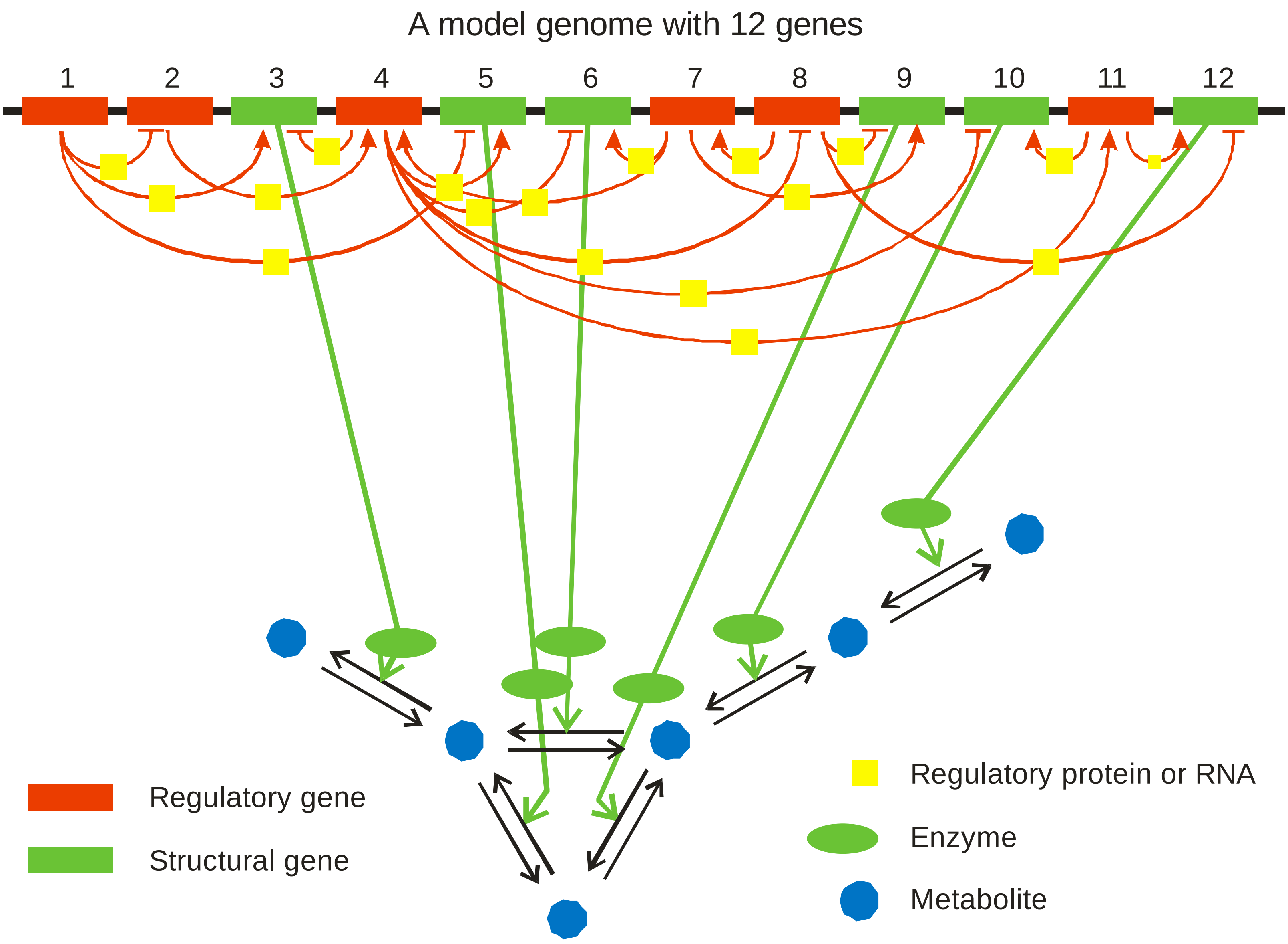
Goals:

1. Large scale computer simulations of genetic regulatory and metabolic reaction networks.

2. Understanding the dynamics of cells and organisms including regulation through signal transmission in highly heterogeneous spatial structures.

3. Design of genetic and metabolic model systems, which allow for **optimization** through **evolution** and which provide explanations for the unique properties of living cells and organisms like **robustness**, **homeostasis**, and **adaptation** to environmental changes.

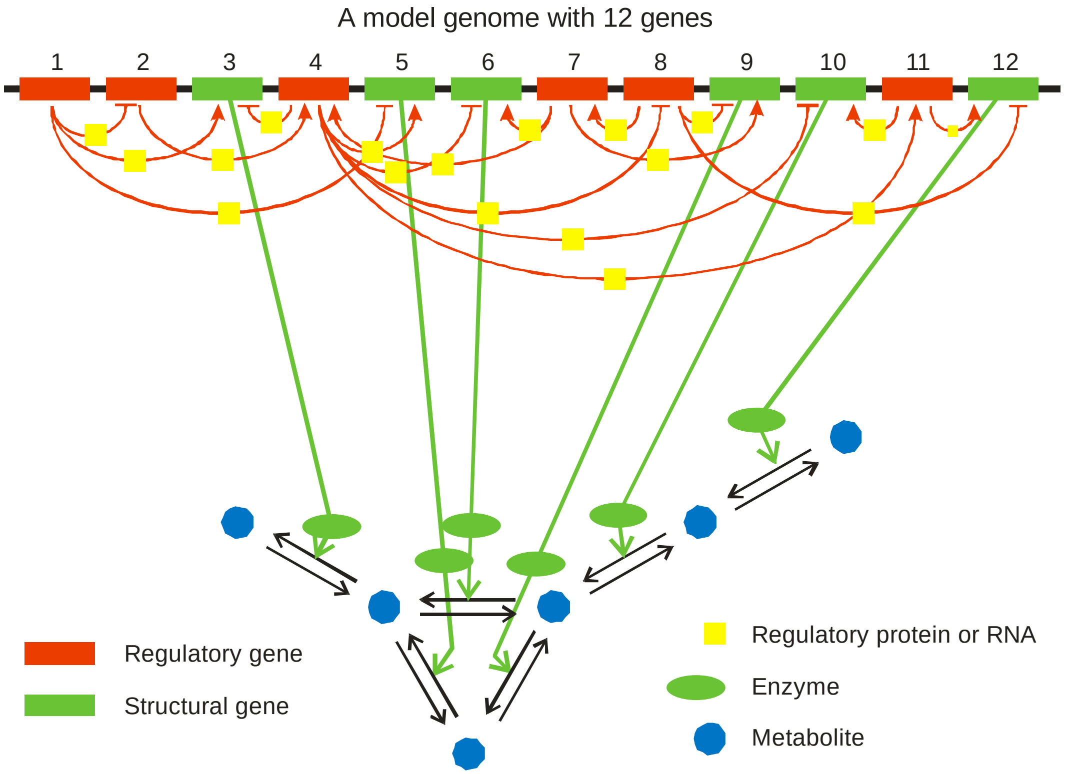
1. What is computational systems biology?
2. **Genabolic networks**
3. Genomes and cellular networks
4. Forward and inverse problems
5. Reverse engineering – A simple example
6. Activation and silencing of genes
7. MiniCellSim – A simulation tool
8. Evolution of genabolic networks


A model genome with 12 genes

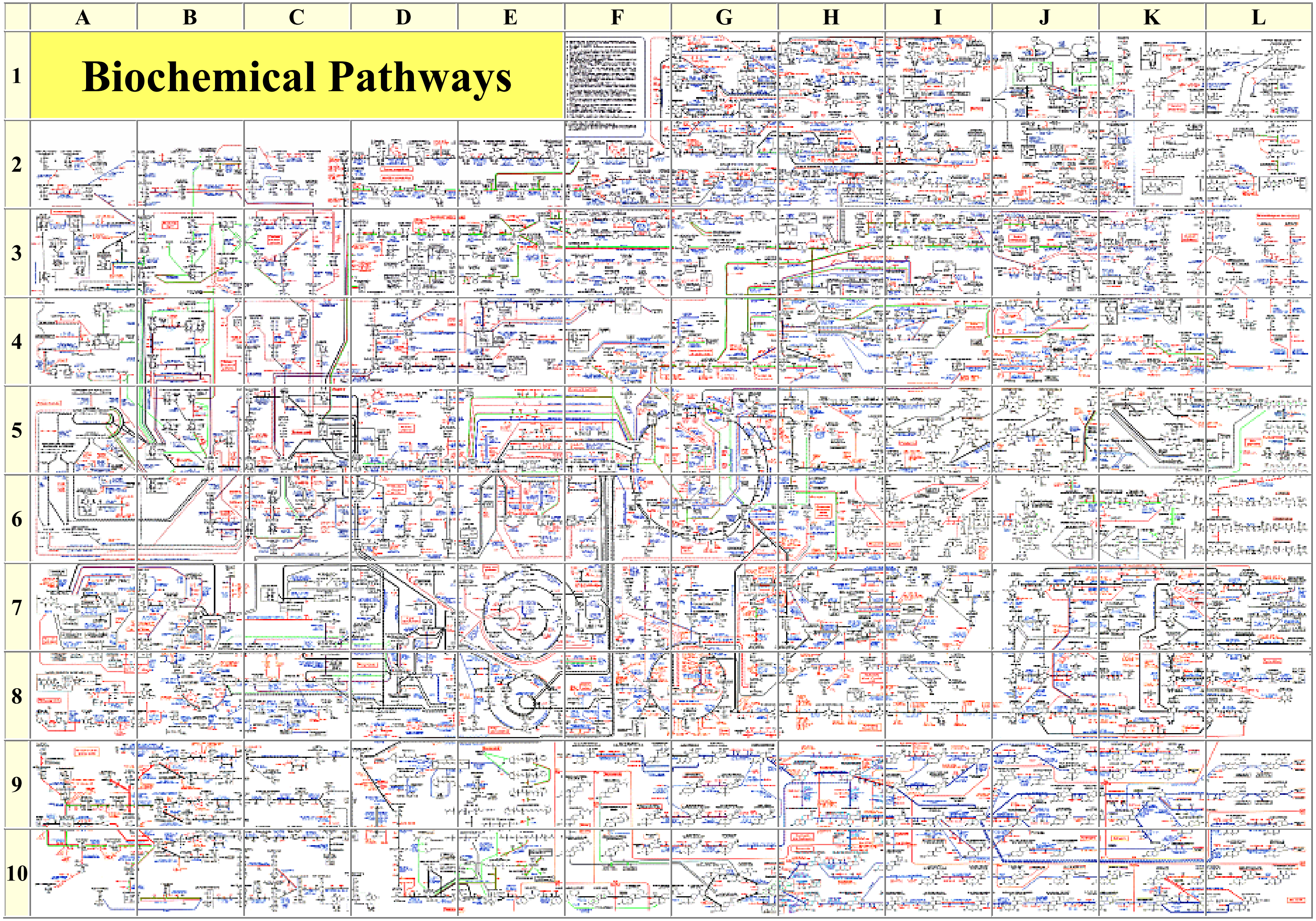
Sketch of a genetic and metabolic network

Genetic regulatory network

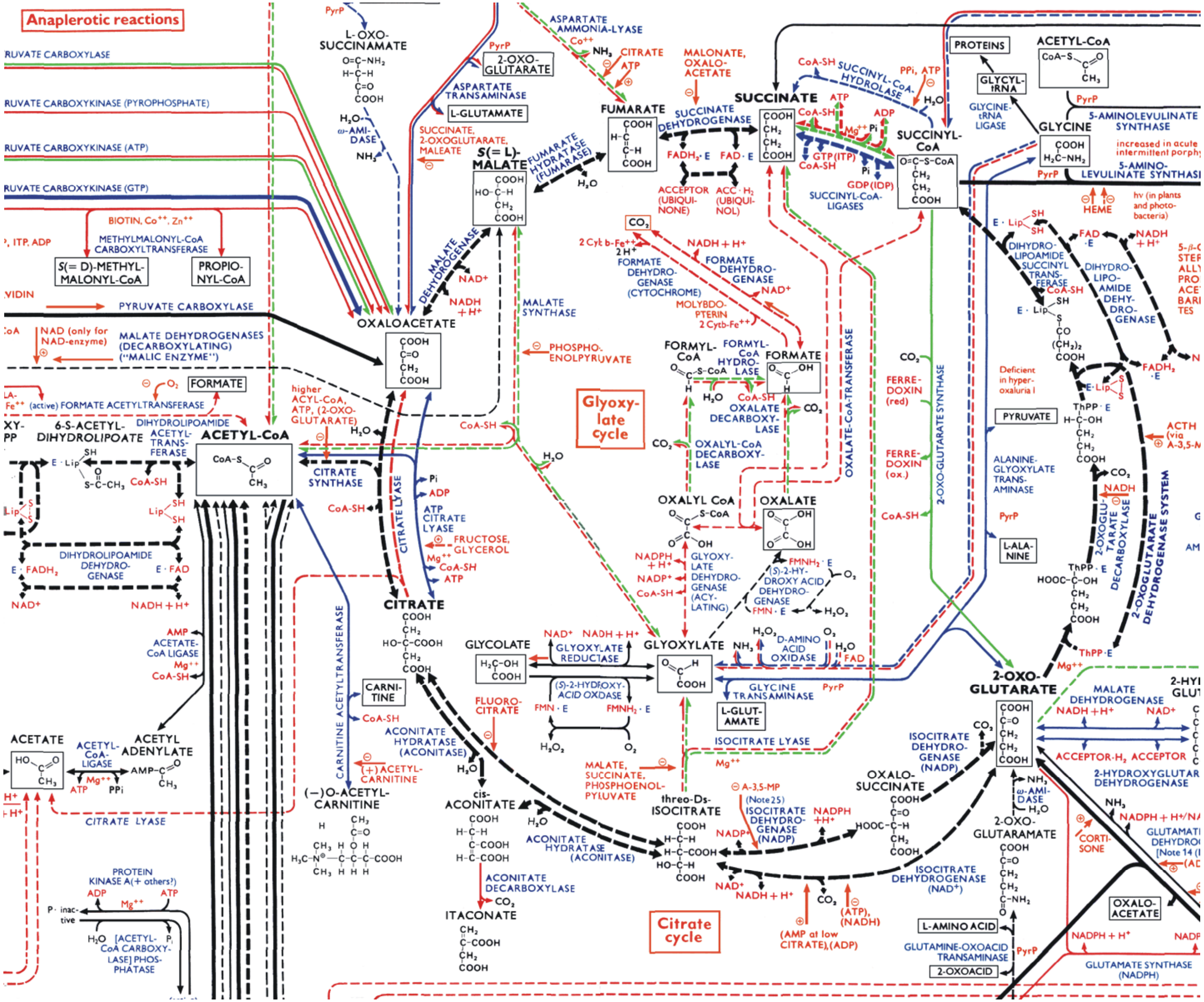
Metabolic network



Proposal of a new name: **Gen**etic and met**abolic network**

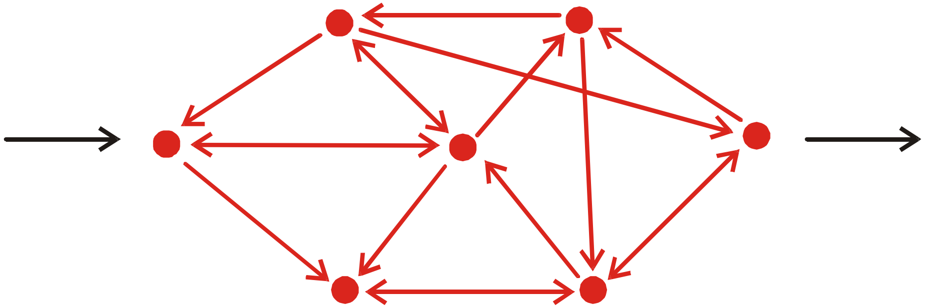


The reaction network of cellular metabolism published by Boehringer-Ingelheim.



The citric acid or Krebs cycle (enlarged from previous slide).

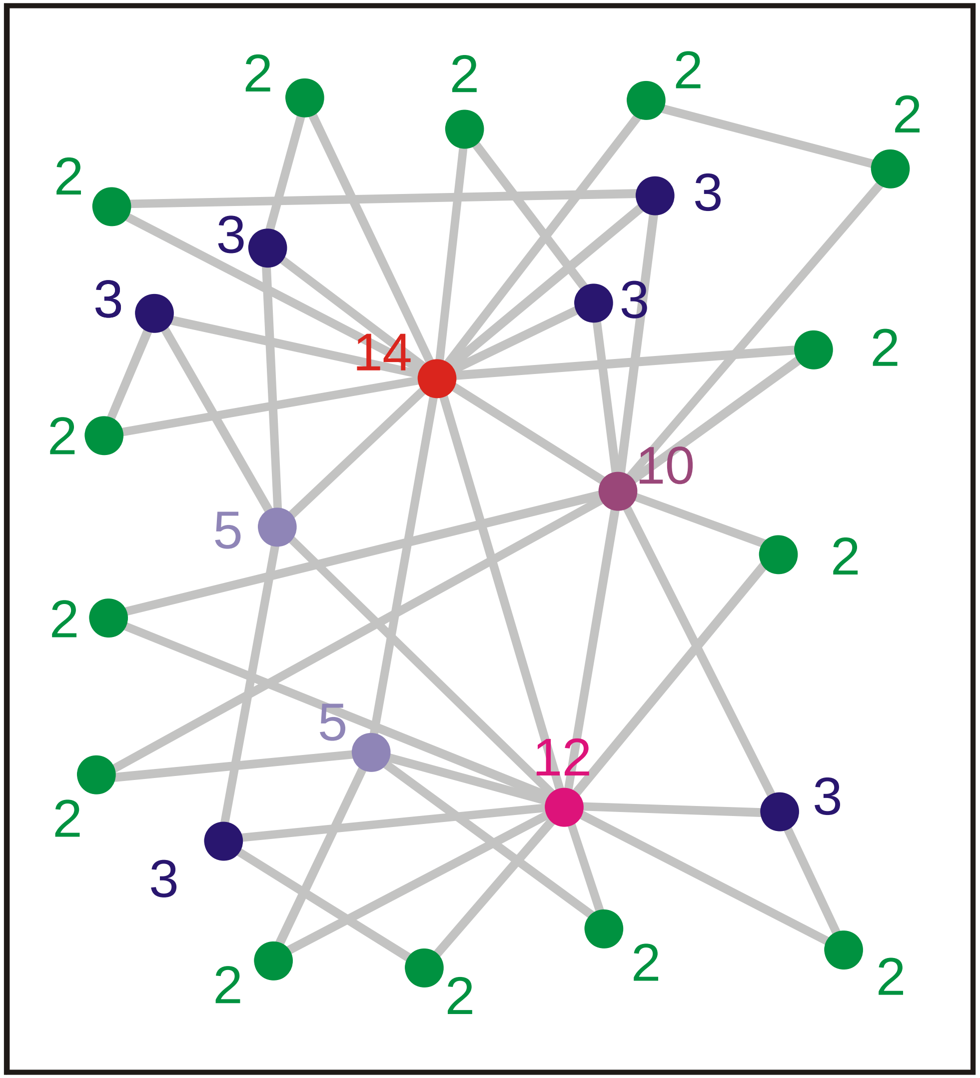
Linear chain



Network

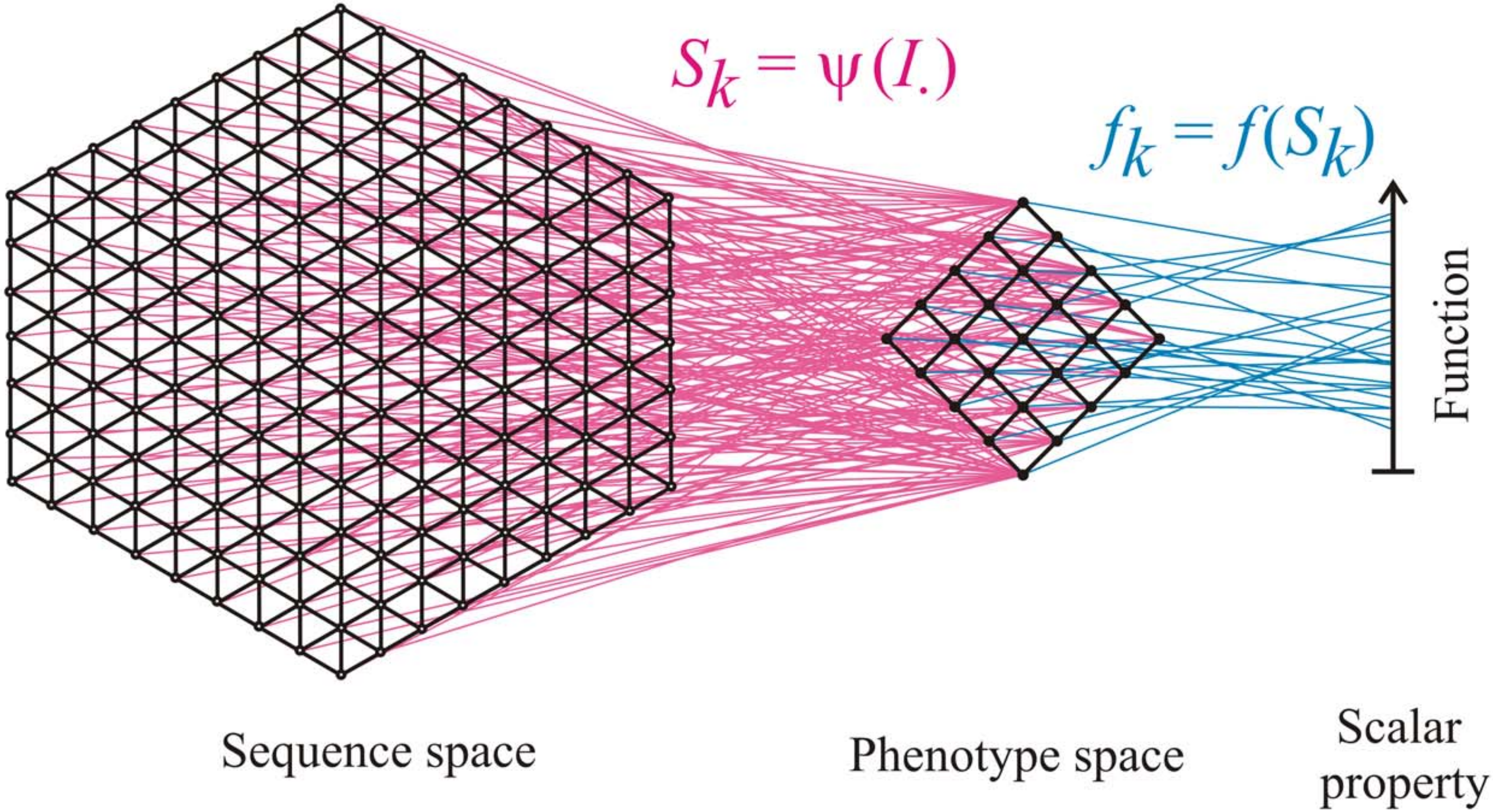
Processing of information in cascades and networks

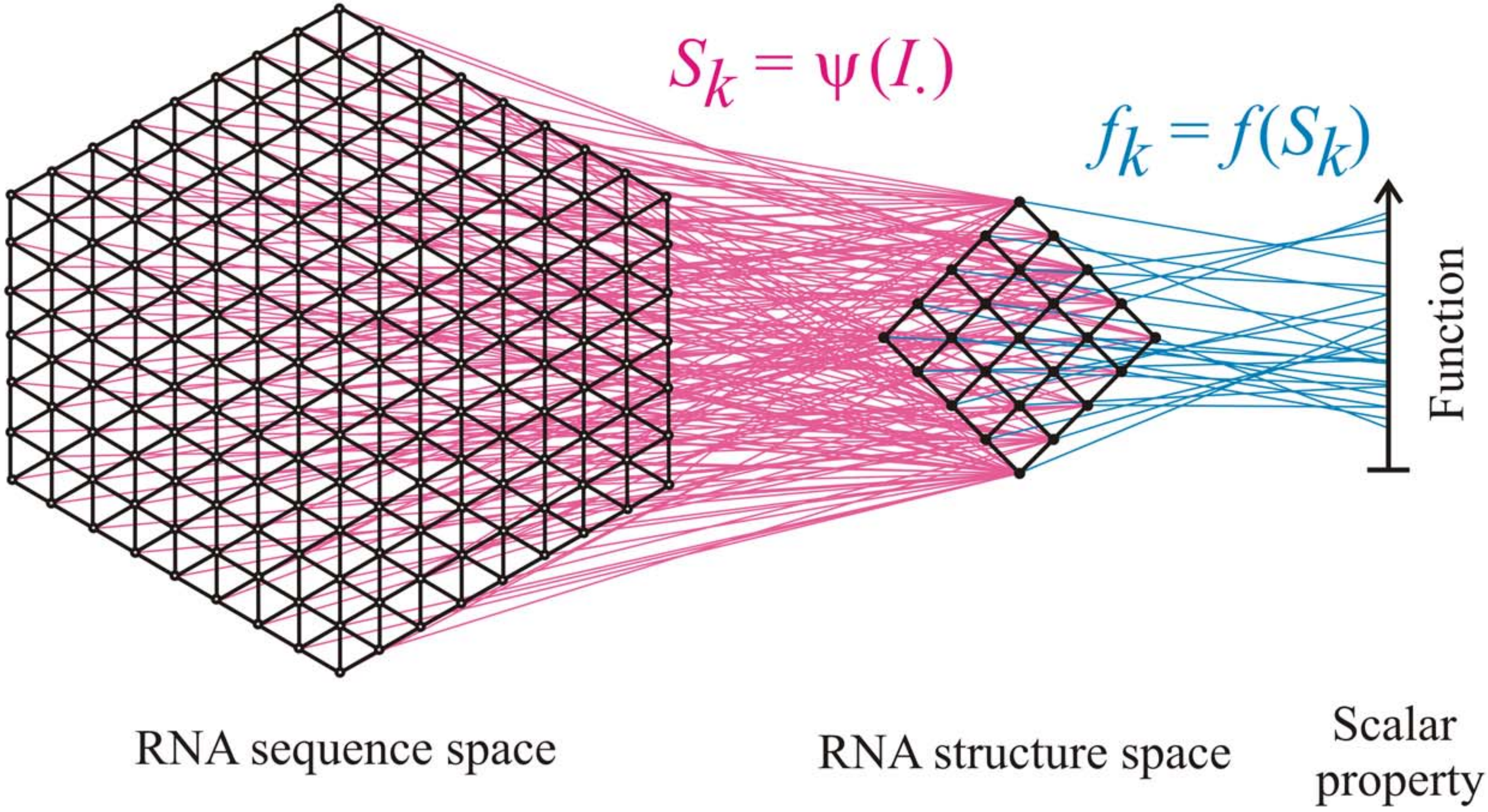
links	# nodes
2	14
3	6
5	2
10	1
12	1
14	1

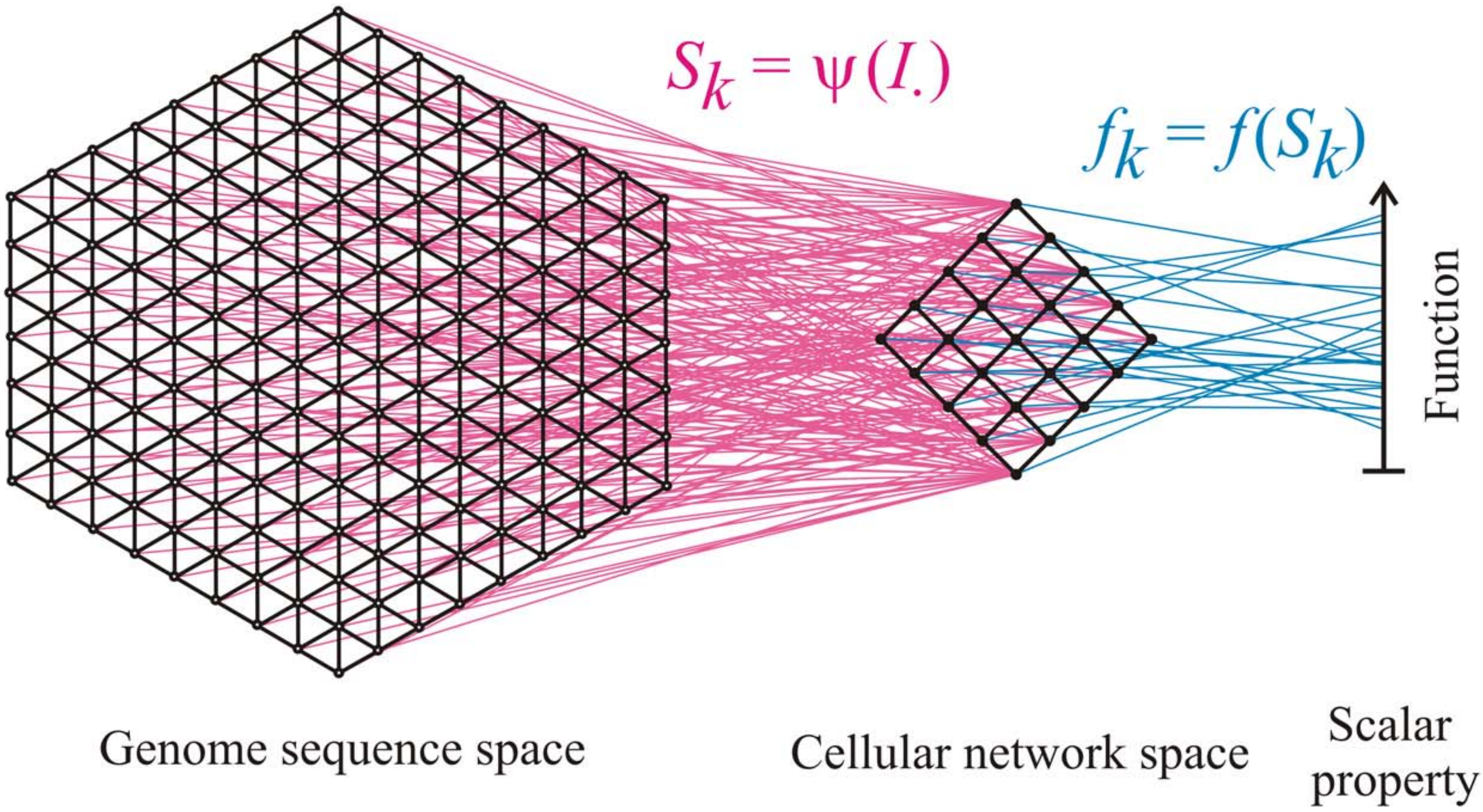


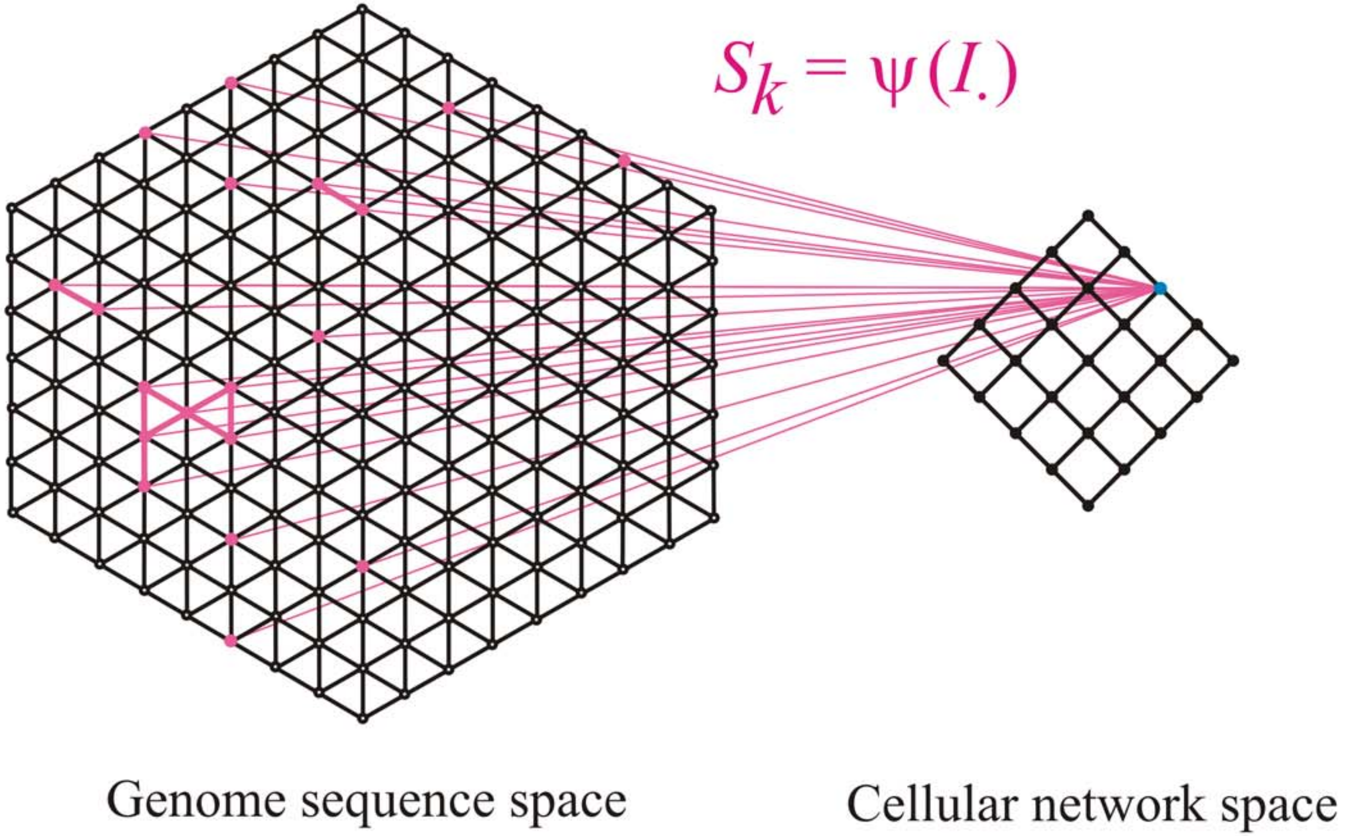
Analysis of nodes and links in a step by step evolved network

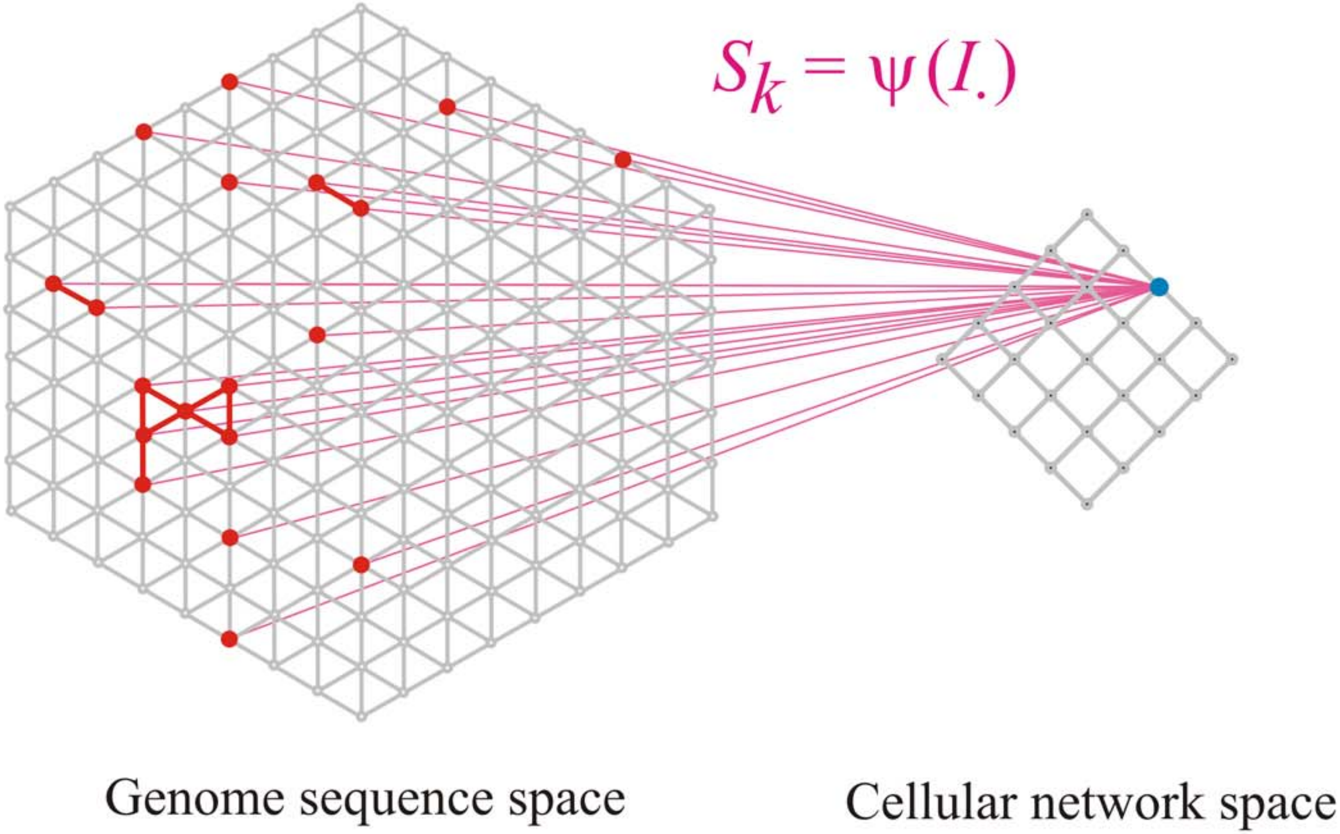
1. What is computational systems biology?
2. Genabolic networks
3. **Genomes and cellular networks**
4. Forward and inverse problems
5. Reverse engineering – A simple example
6. Activation and silencing of genes
7. MiniCellSim – A simulation tool
8. Evolution of genabolic networks

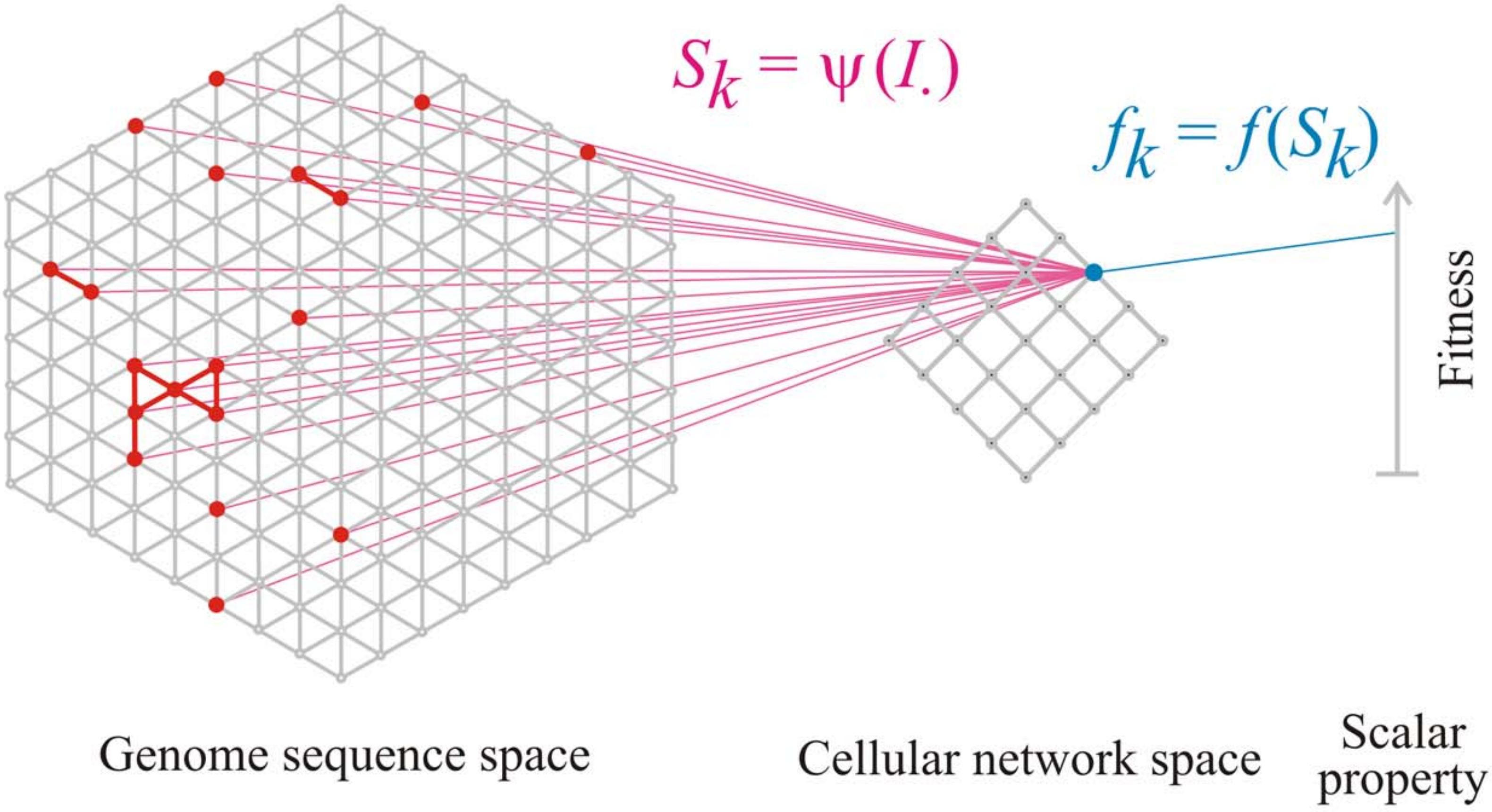

$S_k = \psi(I.)$
$f_k = f(S_k)$
Function
Sequence space
Phenotype space
Scalar property


$S_k = \psi(I.)$
$f_k = f(S_k)$
Function
RNA sequence space
RNA structure space
Scalar property


$S_k = \psi(I.)$
$f_k = f(S_k)$
Function
Genome sequence space
Cellular network space
Scalar property


$S_k = \psi(I.)$
Genome sequence space
Cellular network space


$S_k = \psi(I.)$
Genome sequence space
Cellular network space


$S_k = \psi(I_\cdot)$
$f_k = f(S_k)$
Fitness
Genome sequence space
Cellular network space
Scalar property

1. What is computational systems biology?
2. Genabolic networks
3. Genomes and cellular networks
4. **Forward and inverse problems**
5. Reverse engineering – A simple example
6. Activation and silencing of genes
7. MiniCellSim – A simulation tool
8. Evolution of genabolic networks

GUAUCGAAAUACGUAGCGUAUGGGGAUGCUGGACGGUCCCAUCGGUACUCCA

RNA sequence

RNA folding:

Structural biology, spectroscopy of biomolecules, understanding **molecular function**

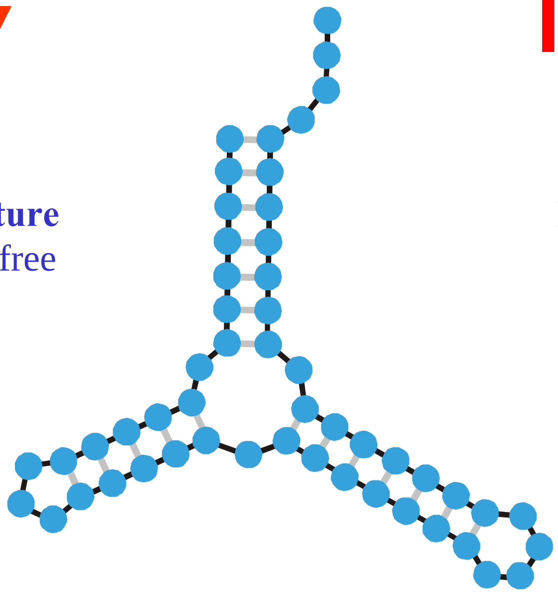
Iterative determination of a sequence for the given secondary structure

Inverse Folding Algorithm

RNA sequence that forms the structure as minimum free energy structure

Inverse folding of RNA:

Biotechnology, **design of biomolecules** with predefined structures and functions



RNA structure of minimal free energy

RNA structure

Sequence, structure, and design through inverse folding

Kinetic differential equations

$$\frac{dx}{dt} = f(x;k);\ x=(x_1,\ldots,x_n);\ k=(k_1,\ldots,k_m)$$

Reaction diffusion equations

$$\frac{\partial x}{\partial t} = D\,\nabla^2 x + f(x;k)$$

Parameter set

$k_j(T, p, pH, I, \ldots);\ j=1,2,\ldots,m$

General conditions: T , p , pH , I , ...

Initial conditions: $x(0)$

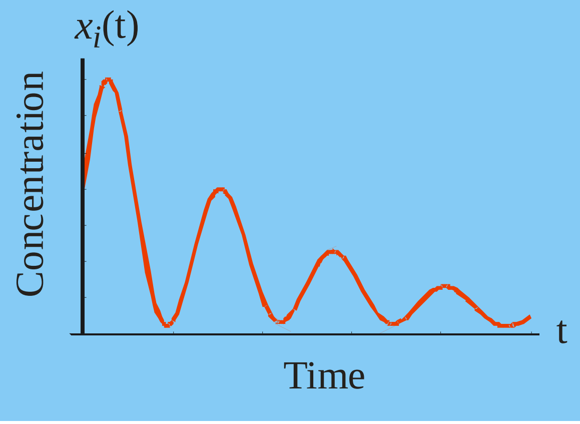
Boundary conditions:

boundary ... $\boldsymbol{S}$, normal unit vector ... $\hat{\boldsymbol{u}}$

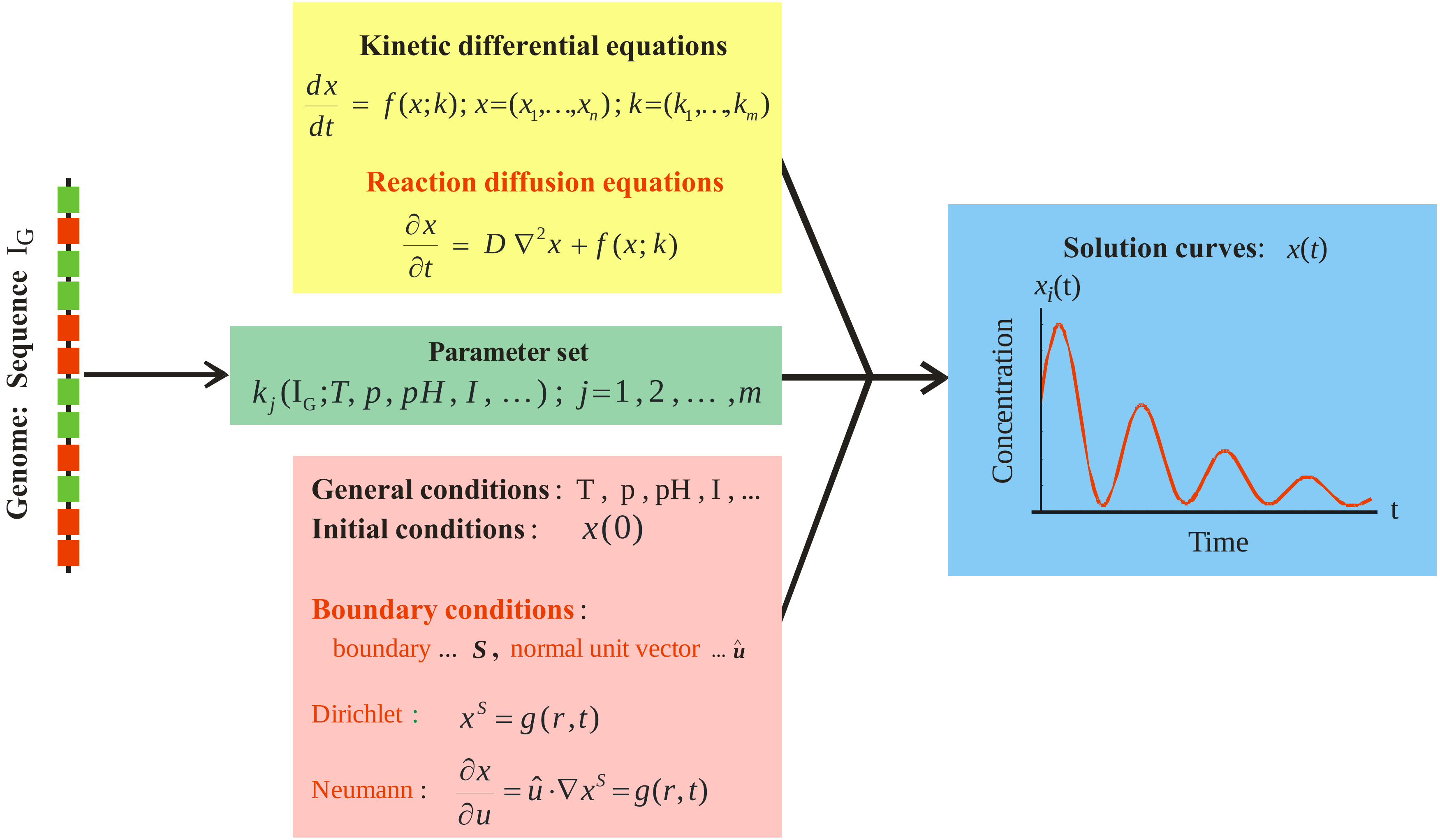
Dirichlet : $x^S = g(r,t)$

Neumann : $\dfrac{\partial x}{\partial u} = \hat{u}\cdot\nabla x^S = g(r,t)$

Solution curves: $x(t)$



The forward problem of chemical reaction kinetics (Level I)



Genome: Sequence I_G

Kinetic differential equations

$$\frac{dx}{dt} = f(x;k);\ x=(x_1,\ldots,x_n);\ k=(k_1,\ldots,k_m)$$

Reaction diffusion equations

$$\frac{\partial x}{\partial t} = D\,\nabla^2 x + f(x;k)$$

Parameter set

$$k_j(I_G;T,p,pH,I,\ldots);\ j=1,2,\ldots,m$$

General conditions : T , p , pH , I , ...

Initial conditions : $x(0)$

Boundary conditions :

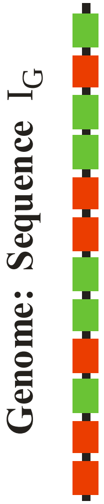
boundary ... $\boldsymbol{S}$, normal unit vector ... $\hat{\boldsymbol{u}}$

Dirichlet : $x^S = g(r,t)$

Neumann : $\dfrac{\partial x}{\partial u} = \hat{u}\cdot\nabla x^S = g(r,t)$

Solution curves: $x(t)$

The forward problem of cellular reaction kinetics (Level I)



Parameter set

$$k_j(\mathrm{I_G};T, p, pH, I, \dots);\ j=1, 2, \dots, m$$

Kinetic differential equations

$$\frac{dx}{dt} = f(x;k);\ x=(x_1,\dots,x_n);\ k=(k_1,\dots,k_m)$$

Reaction diffusion equations

$$\frac{\partial x}{\partial t} = D\,\nabla^2 x + f(x;k)$$

General conditions : T , p , pH , I , ...

Initial conditions : $x(0)$

Boundary conditions :

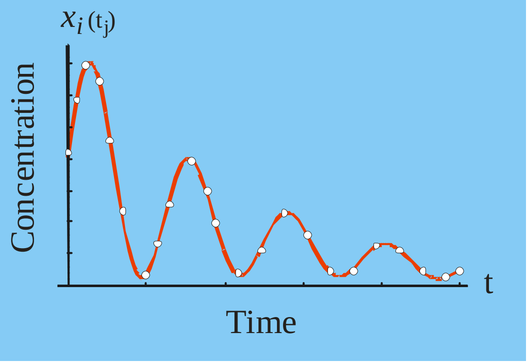
boundary ... ***S*** , normal unit vector... $\hat{\boldsymbol{u}}$

Dirichlet : $x^S = g(r,t)$

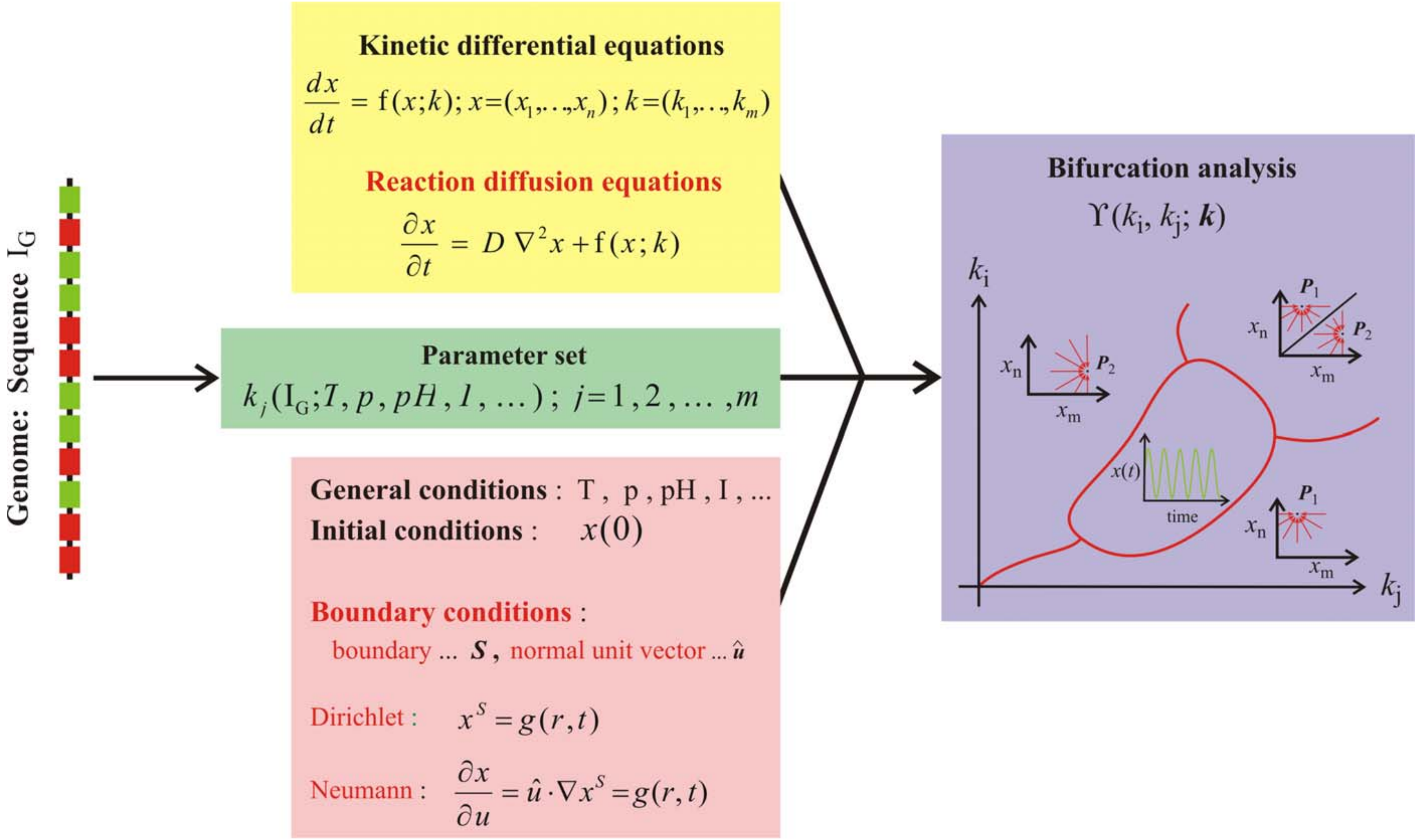
Neumann: $\frac{\partial x}{\partial u} = \hat{u}\cdot\nabla x^S = g(r,t)$

Data from measurements

$x(t_j);\ j = 1, 2, \dots, N$



The inverse problem of cellular reaction kinetics (Level I)



Kinetic differential equations

$$\frac{dx}{dt} = \mathrm{f}(x;k);\ x=(x_1,\ldots,x_n);\ k=(k_1,\ldots,k_m)$$

Reaction diffusion equations

$$\frac{\partial x}{\partial t} = D\,\nabla^2 x + \mathrm{f}(x;k)$$

Parameter set

$$k_j(\mathrm{I_G}; T, p, pH, I, \ldots);\ j=1,2,\ldots,m$$

General conditions : T , p , pH , I , ...

Initial conditions : $x(0)$

Boundary conditions :

boundary ... $\boldsymbol{S}$, normal unit vector ... $\hat{\boldsymbol{u}}$

Dirichlet : $x^S = g(r,t)$

Neumann : $\frac{\partial x}{\partial u} = \hat{u}\cdot\nabla x^S = g(r,t)$

Bifurcation analysis

$\Upsilon(k_i, k_j; \boldsymbol{k})$

The forward problem of bifurcation analysis in cellular dynamics (Level II)

Genome: Sequence I_G

Parameter set

$$k_j(I_G; T, p, pH, I, \ldots)\ ;\ j=1,2,\ldots,m$$

Kinetic differential equations

$$\frac{dx}{dt} = f(x;k);\ x=(x_1,\ldots,x_n);\ k=(k_1,\ldots,k_m)$$

Reaction diffusion equations

$$\frac{\partial x}{\partial t} = D\,\nabla^2 x + f(x;k)$$

General conditions : T , p , pH , I , ...

Initial conditions : $x(0)$

Boundary conditions :

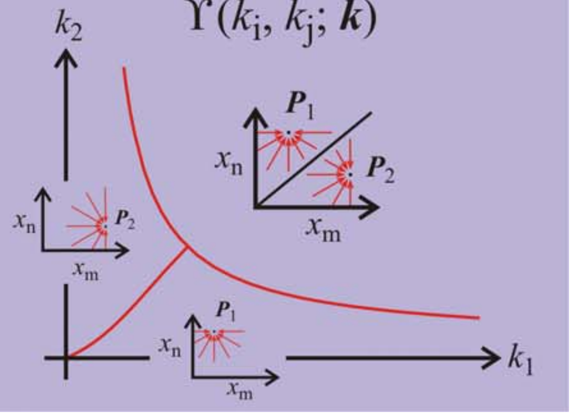
boundary ... $\boldsymbol{S}$, normal unit vector ... $\hat{\boldsymbol{u}}$

Dirichlet : $x^S = g(r,t)$

Neumann : $\dfrac{\partial x}{\partial u} = \hat{u}\cdot\nabla x^S = g(r,t)$

Bifurcation pattern

$\Upsilon(k_i, k_j; \boldsymbol{k})$



The inverse problem of bifurcation analysis in cellular dynamics (Level II)

1. What is computational systems biology?
2. Genabolic networks
3. Genomes and cellular networks
4. Forward and inverse problems
5. **Reverse engineering – A simple example**
6. Activation and silencing of genes
7. MiniCellSim – A simulation tool
8. Evolution of genabolic networks

$$* \xrightarrow{r} \mathbf{A}$$

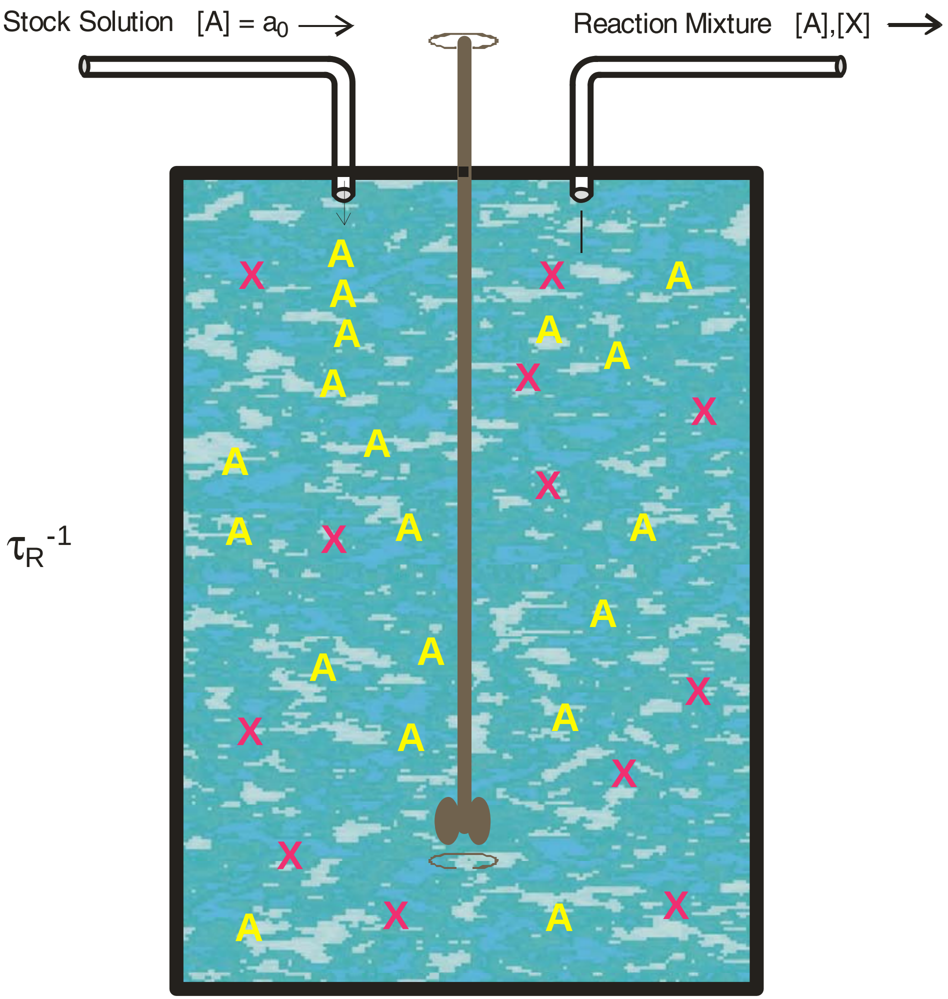
$$\mathbf{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathbf{X}$$

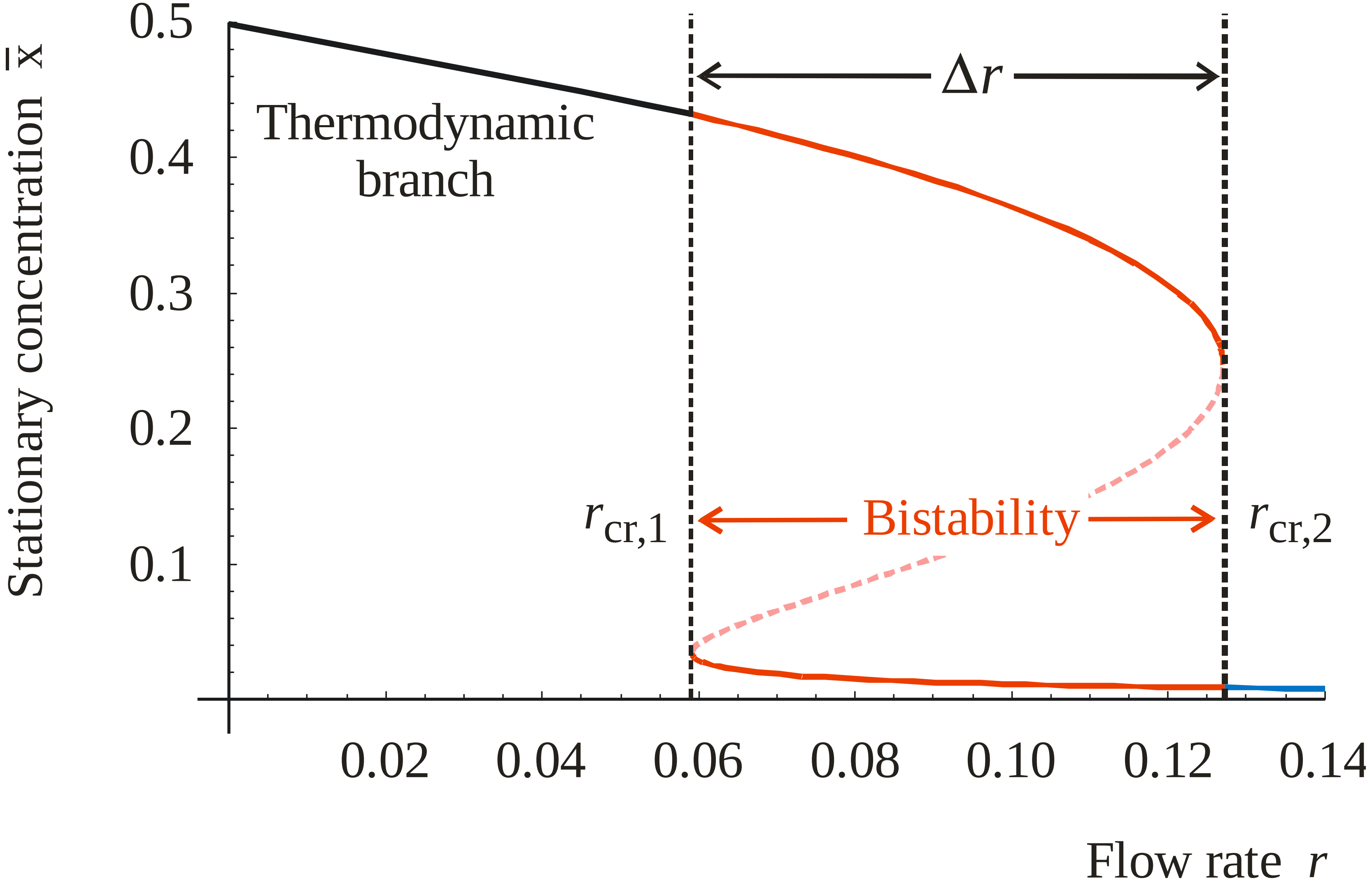
$$\mathbf{A} + 2\,\mathbf{X} \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3\mathbf{X}$$

$$\mathbf{A} \xrightarrow{r} 0$$

$$\mathbf{X} \xrightarrow{r} 0$$

Flow rate $r = \tau_R^{-1}$




Stationary concentration $\bar{x}$
0.5
0.4
0.3
0.2
0.1
Thermodynamic branch
Δr
$r_{\mathrm{cr},1}$
Bistability
$r_{\mathrm{cr},2}$
0.02
0.04
0.06
0.08
0.10
0.12
0.14
Flow rate r

$$* \xrightarrow{r} \mathbf{A}$$

$$\mathbf{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathbf{X}$$

$$\mathbf{A} + 2\,\mathbf{X} \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3\mathbf{X}$$

$$\mathbf{A} \xrightarrow{r} 0$$

$$\mathbf{X} \xrightarrow{r} 0$$

Kinetic differential equations:

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = \frac{\mathrm{d}a}{\mathrm{d}t} = r\,(a_0 - a) - (k_1 + k_3 x^2)\,a + (k_2 + k_4 x^2)\,x$$

$$\frac{\mathrm{d}[\mathrm{X}]}{\mathrm{d}t} = \frac{\mathrm{d}x}{\mathrm{d}t} = -r\,x + (k_1 + k_3 x^2)\,a - (k_2 + k_4 x^2)\,x$$

$$* \xrightarrow{r} \mathbf{A}$$

$$\mathbf{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathbf{X}$$

$$\mathbf{A} + 2\,\mathbf{X} \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3\mathbf{X}$$

$$\mathbf{A} \xrightarrow{r} 0$$

$$\mathbf{X} \xrightarrow{r} 0$$

Kinetic differential equations:

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = \frac{\mathrm{d}a}{\mathrm{d}t} = r\,(a_0 - a) - (k_1 + k_3 x^2)\,a + (k_2 + k_4 x^2)\,x$$

$$\frac{\mathrm{d}[\mathrm{X}]}{\mathrm{d}t} = \frac{\mathrm{d}x}{\mathrm{d}t} = -r\,x + (k_1 + k_3 x^2)\,a - (k_2 + k_4 x^2)\,x$$

Steady states:

$$\bar{x}^3 (k_3 + k_4) - \bar{x}^2 k_3 a_0 + \bar{x}(k_1 + k_2 + r) - k_1 a_0 = 0$$

$$* \xrightarrow{r} \mathbf{A}$$

$$\mathbf{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathbf{X}$$

$$\mathbf{A} + 2\,\mathbf{X} \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3\mathbf{X}$$

$$\mathbf{A} \xrightarrow{r} 0$$

$$\mathbf{X} \xrightarrow{r} 0$$

Kinetic differential equations:

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = \frac{\mathrm{d}a}{\mathrm{d}t} = r\,(a_0 - a) - (k_1 + k_3 x^2)\,a + (k_2 + k_4 x^2)\,x$$

$$\frac{\mathrm{d}[\mathrm{X}]}{\mathrm{d}t} = \frac{\mathrm{d}x}{\mathrm{d}t} = -r\,x + (k_1 + k_3 x^2)\,a - (k_2 + k_4 x^2)\,x$$

Steady states:

$$\bar{x}^3 (k_3 + k_4) - \bar{x}^2 k_3 a_0 + \bar{x}(k_1 + k_2 + r) - k_1 a_0 = 0$$

$$k_1 = k_2 = \alpha,\; k_3 = k_4 = 1: \quad 2\bar{x}^3 - \bar{x}^2 a_0 + \bar{x}(r + 2\alpha) - \alpha a_0 = 0$$

$$* \xrightarrow{r} \mathbf{A}$$

$$\mathbf{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathbf{X}$$

$$\mathbf{A} + 2\,\mathbf{X} \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3\mathbf{X}$$

$$\mathbf{A} \xrightarrow{r} 0$$

$$\mathbf{X} \xrightarrow{r} 0$$

Kinetic differential equations:

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = \frac{\mathrm{d}a}{\mathrm{d}t} = r\,(a_0 - a) - (k_1 + k_3 x^2)\,a + (k_2 + k_4 x^2)\,x$$

$$\frac{\mathrm{d}[\mathrm{X}]}{\mathrm{d}t} = \frac{\mathrm{d}x}{\mathrm{d}t} = -\,r\,x + (k_1 + k_3 x^2)\,a - (k_2 + k_4 x^2)\,x$$

Steady states:

$$\bar{x}^3 (k_3 + k_4) - \bar{x}^2 k_3 a_0 + \bar{x}(k_1 + k_2 + r) - k_1 a_0 = 0$$

$$k_1 = k_2 = \alpha,\ k_3 = k_4 = 1:\quad 2\bar{x}^3 - \bar{x}^2 a_0 + \bar{x}(r + 2\alpha) - \alpha a_0 = 0$$

Polynomial discriminant of the cubic equation:

$$216\,\mathrm{D} = r^3 + r^2\left(6\alpha - \frac{a_0^{\,2}}{8}\right) + r\,(12\alpha^2 - 5\alpha\,a_0^{\,2}) + 8\alpha^3 + 4\alpha^2 a_0^{\,2} + \frac{\alpha\,a_0^{\,4}}{2} = 0$$

$$* \xrightarrow{r} \mathbf{A}$$

$$\mathbf{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathbf{X}$$

$$\mathbf{A} + 2\,\mathbf{X} \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3\mathbf{X}$$

$$\mathbf{A} \xrightarrow{r} 0$$

$$\mathbf{X} \xrightarrow{r} 0$$

Kinetic differential equations:

$$\frac{\mathrm{d[A]}}{\mathrm{dt}} = \frac{\mathrm{d}a}{\mathrm{dt}} = r\,(a_0 - a) - (k_1 + k_3 x^2)\,a + (k_2 + k_4 x^2)\,x$$

$$\frac{\mathrm{d[X]}}{\mathrm{dt}} = \frac{\mathrm{d}x}{\mathrm{dt}} = -\,r\,x + (k_1 + k_3 x^2)\,a - (k_2 + k_4 x^2)\,x$$

Steady states:

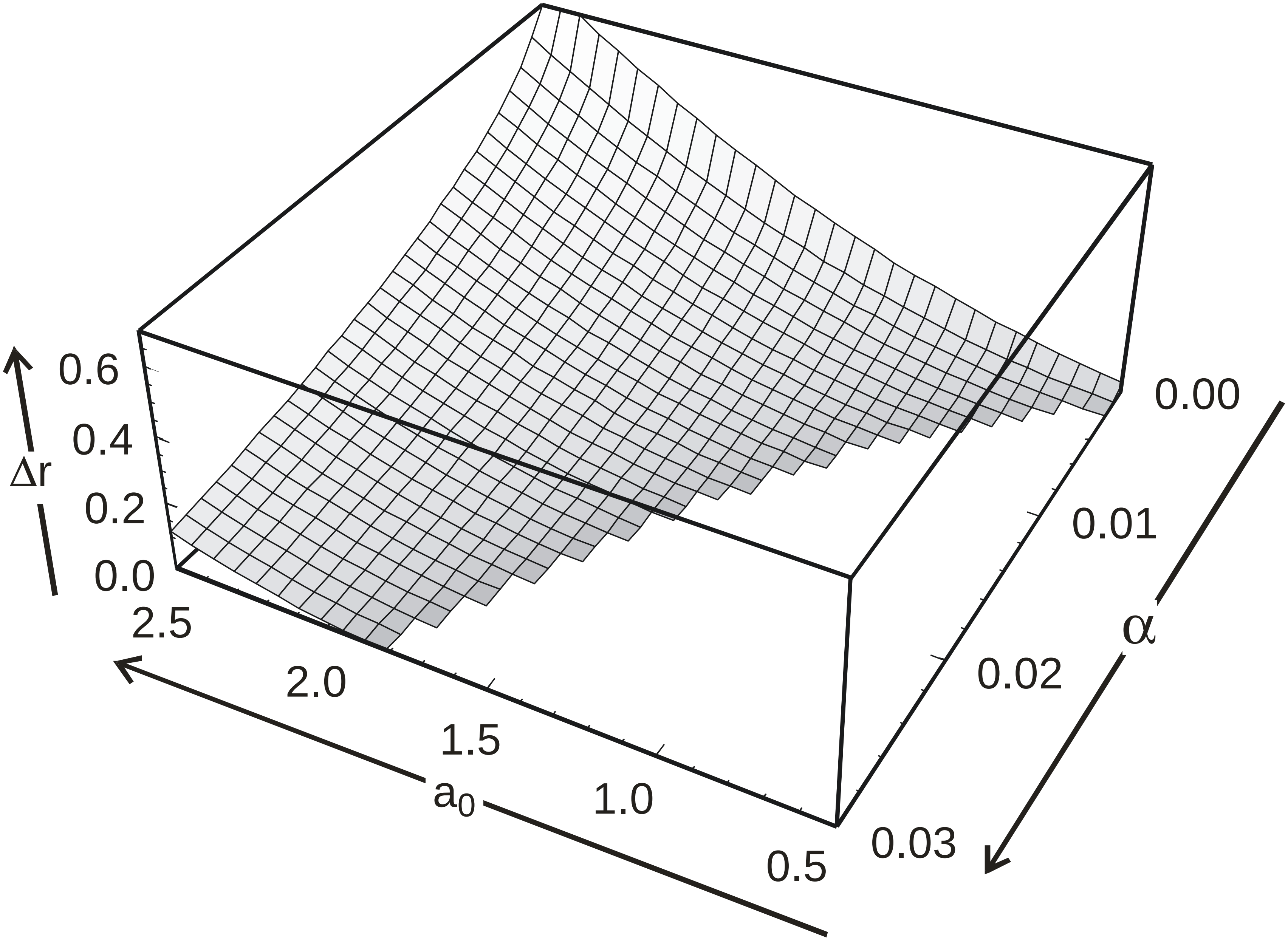
$$\bar{x}^3(k_3+k_4) - \bar{x}^2 k_3 a_0 + \bar{x}(k_1+k_2+r) - k_1 a_0 = 0$$

$$k_1 = k_2 = \alpha,\ k_3 = k_4 = 1: \quad 2\bar{x}^3 - \bar{x}^2 a_0 + \bar{x}(r + 2\alpha) - \alpha a_0 = 0$$

Polynomial discriminant of the cubic equation:

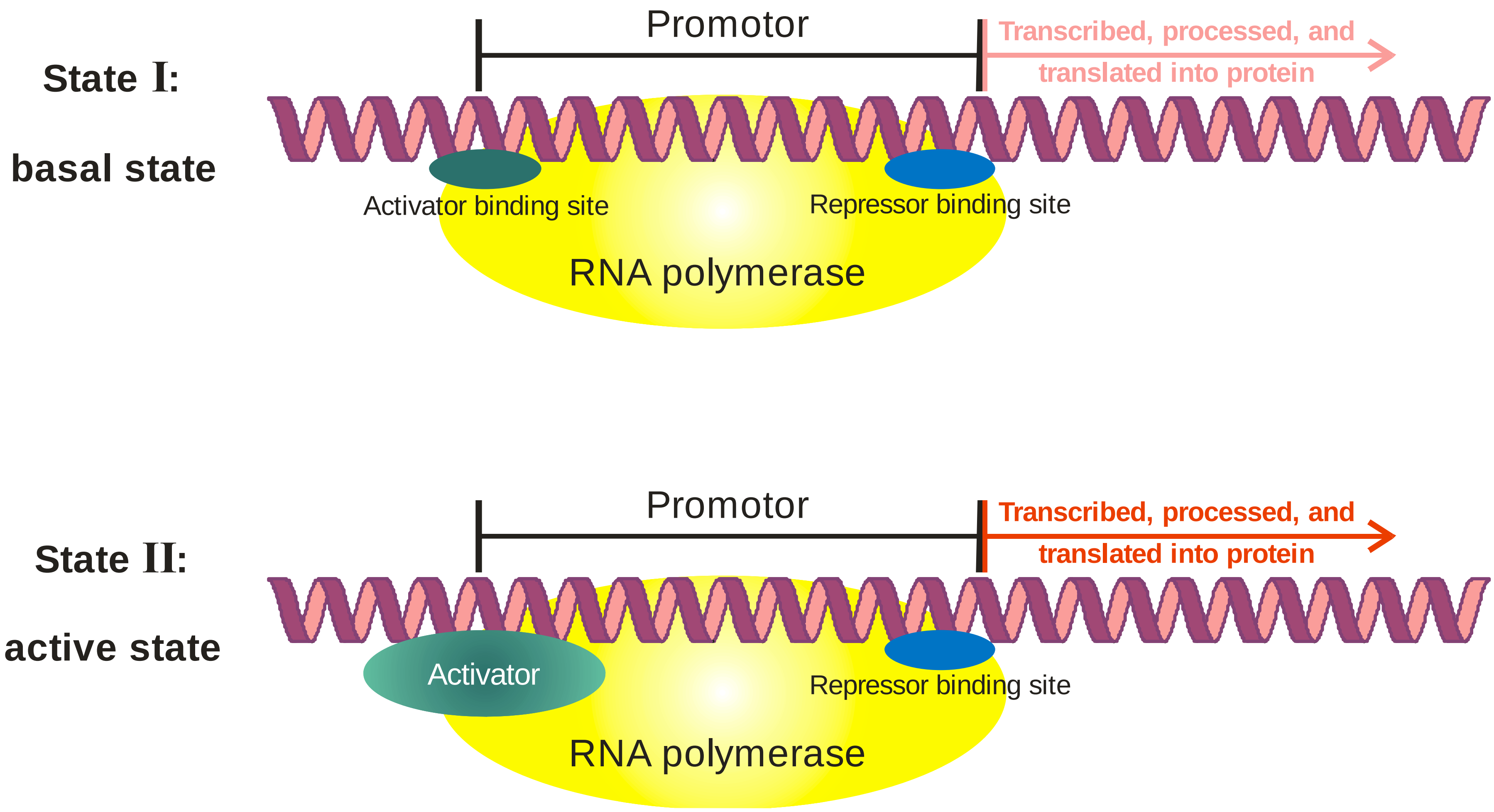
$$216\,\mathrm{D} = r^3 + r^2\left(6\alpha - \frac{a_0^{\,2}}{8}\right) + r\,(12\alpha^2 - 5\alpha\,a_0^{\,2}) + 8\alpha^3 + 4\alpha^2 a_0^{\,2} + \frac{\alpha\,a_0^{\,4}}{2} = 0$$

D < 0: 3 roots r_1, r_2, and r_3, 2 are positive $\Rightarrow$ $\mathbf{\Delta r} = r_1 - r_2$



Range of hysteresis as a function of the parameters a_0 and α

1. What is computational systems biology
2. Genabolic networks
3. Genomes and cellular networks
4. Forward and inverse problems
5. Reverse engineering – A simple example
6. **Activation and silencing of genes**
7. MiniCellSim – A simulation tool
8. Evolution of genabolic networks



State I:

basal state

Promotor

Transcribed, processed, and translated into protein

Activator binding site

Repressor binding site

RNA polymerase

State II:

active state

Promotor

Transcribed, processed, and translated into protein

Activator

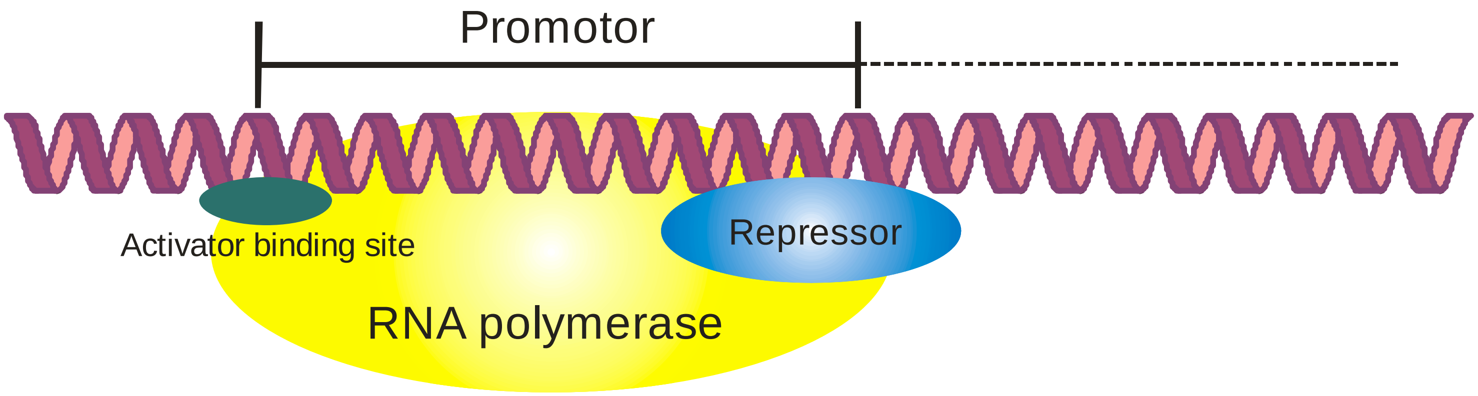
Repressor binding site

RNA polymerase

Active states of gene regulation

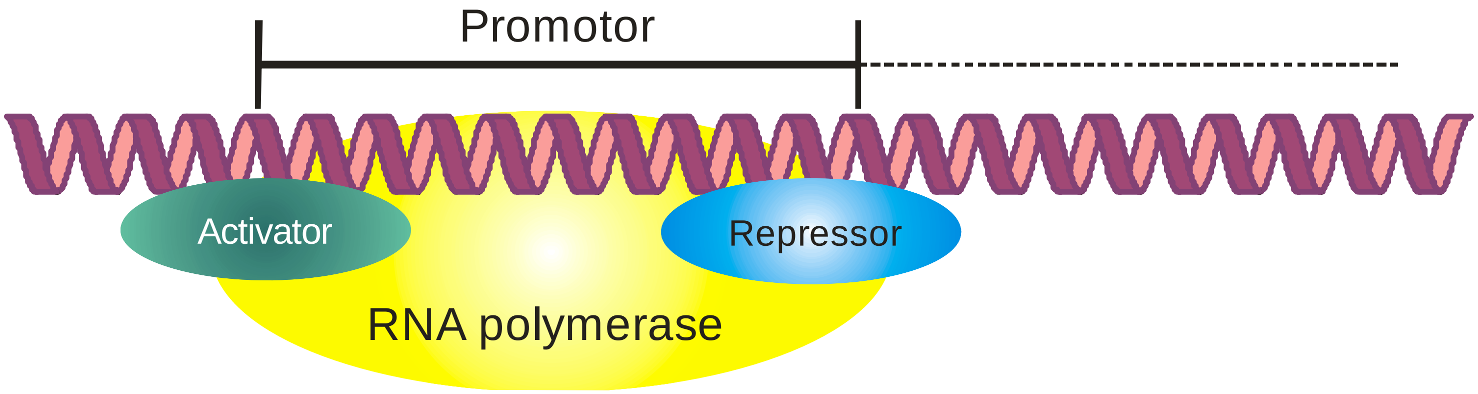
State III:

inactive state



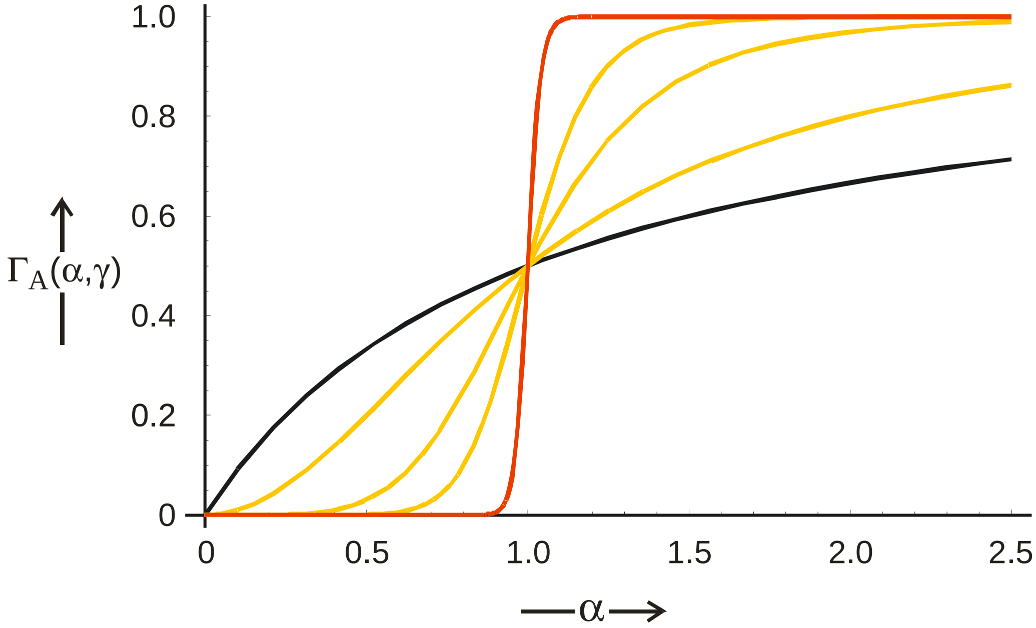
State III:

inactive state

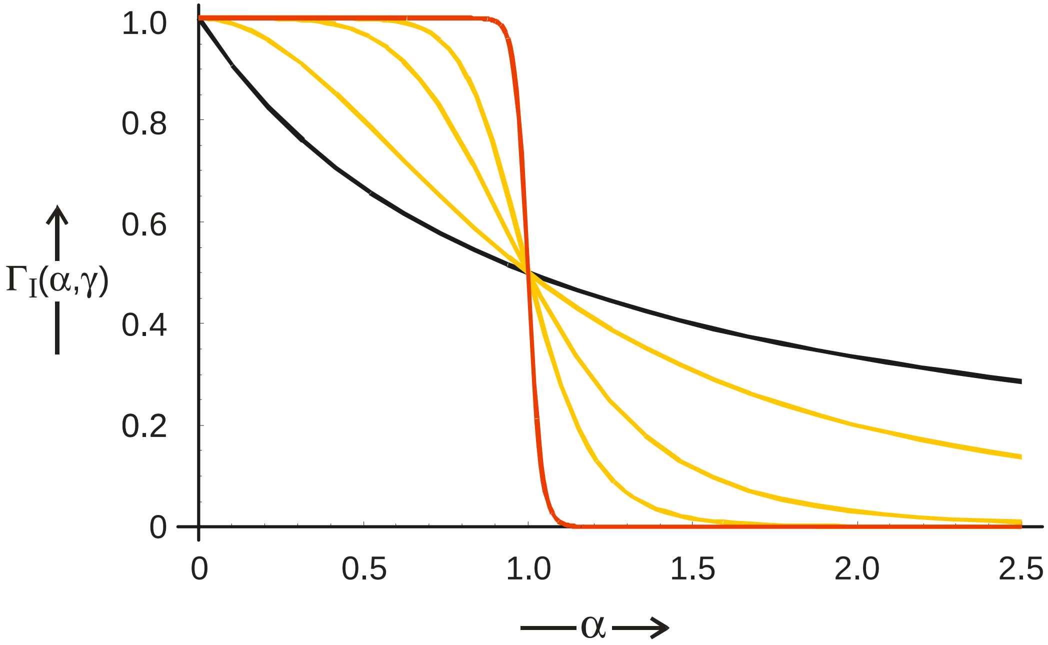


Inactive states of gene regulation

$$\Gamma_A(\alpha) = \frac{\alpha^\gamma}{\kappa^\gamma + \alpha^\gamma}$$



$$\Gamma_I(\alpha) = \frac{\kappa^\gamma}{\kappa^\gamma + \alpha^\gamma}$$



Gene activity for cooperative
binding of activator and inhibitor

$$\begin{tikzcd}
& A + G + H \arrow[dr, shift left] \arrow[dl, shift left] & \\
C + H \arrow[ur, shift left, "K_1"] \arrow[dr, shift left] & K = K_1K_3 = K_2K_4 & A + F \arrow[ul, shift left, "K_2"'] \arrow[dl, shift left, "K_4"] \\
& M \arrow[ul, shift left, "K_3"] \arrow[ur, shift left] &
\end{tikzcd}$$

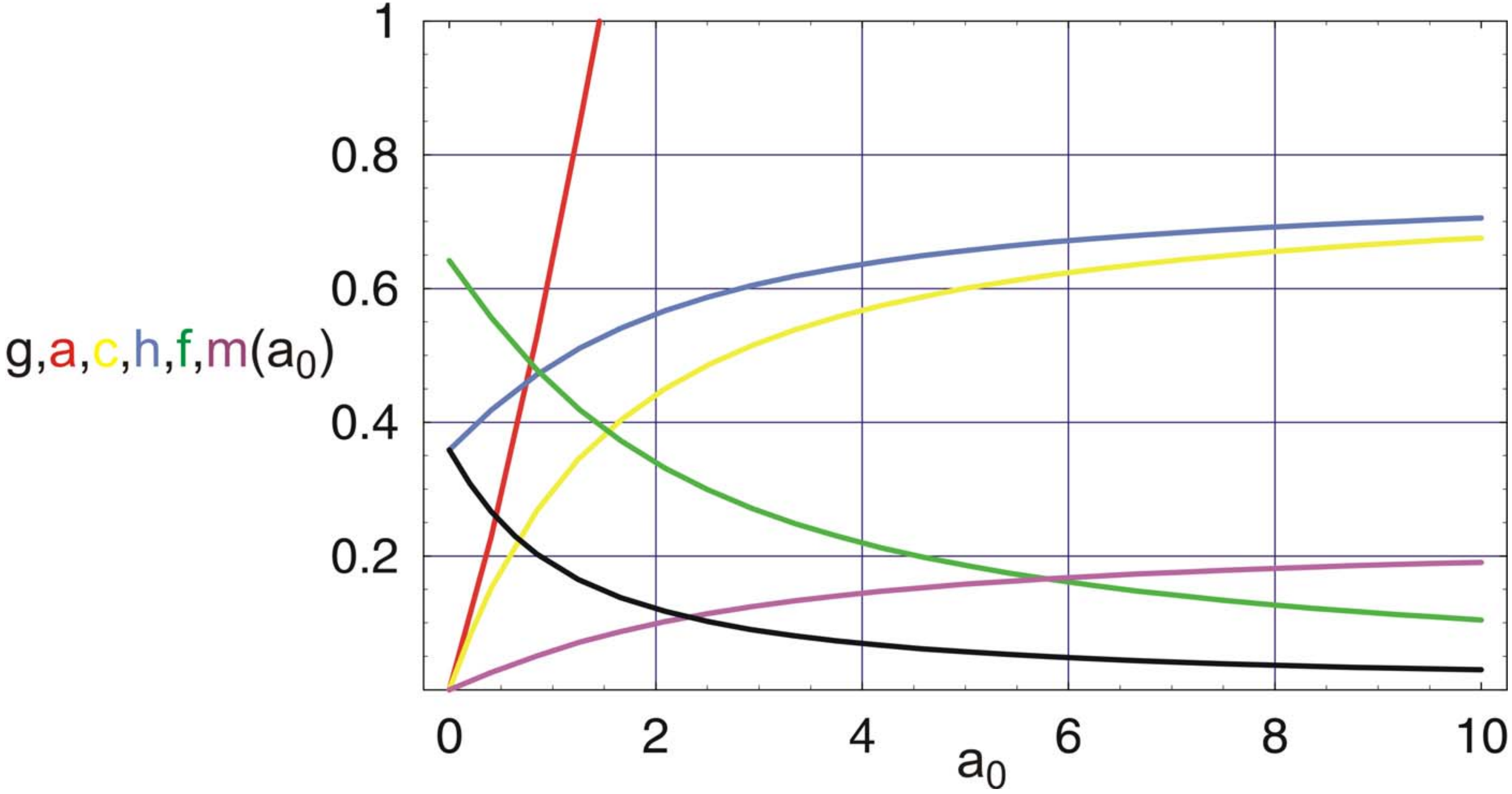
Computation of $g(a_0, \mathrm{h}_0, \mathrm{g}_0)$

$$4(1+K_1 g)(1+K_2 g) K g (g-g_0) = 2(1+K_2 g) K_1 g A(g) + 2(1+K_1 g) K_2 g H(g) + A(g) H(g)$$

$$A(g) = -(1+K_1 g)(1+K_2 g) - K g (h_0 - a_0) + D(g)$$

$$H(g) = -(1+K_1 g)(1+K_2 g) - K g (a_0 - h_0) + D(g)$$

$$D(g) = \sqrt{(1+K_1 g)^2 (1+K_2 g)^2 + 2(1+K_1 g)(1+K_2 g) K g (a_0 + h_0) + K^2 g^2 (a_0 - h_0)^2}$$

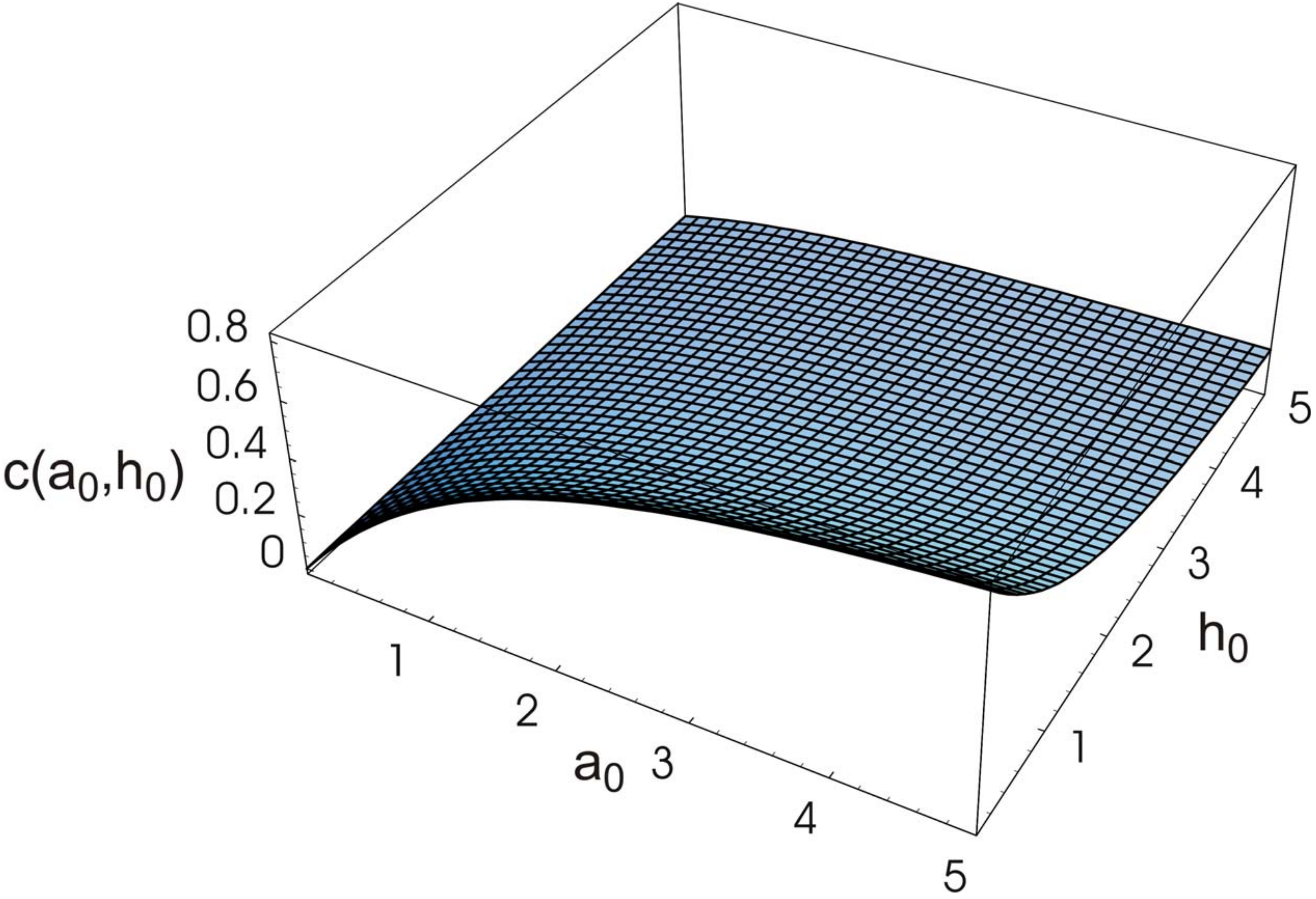

g,a,c,h,f,m(a_0)
1
0.8
0.6
0.4
0.2
0
2
4
6
8
10
a_0

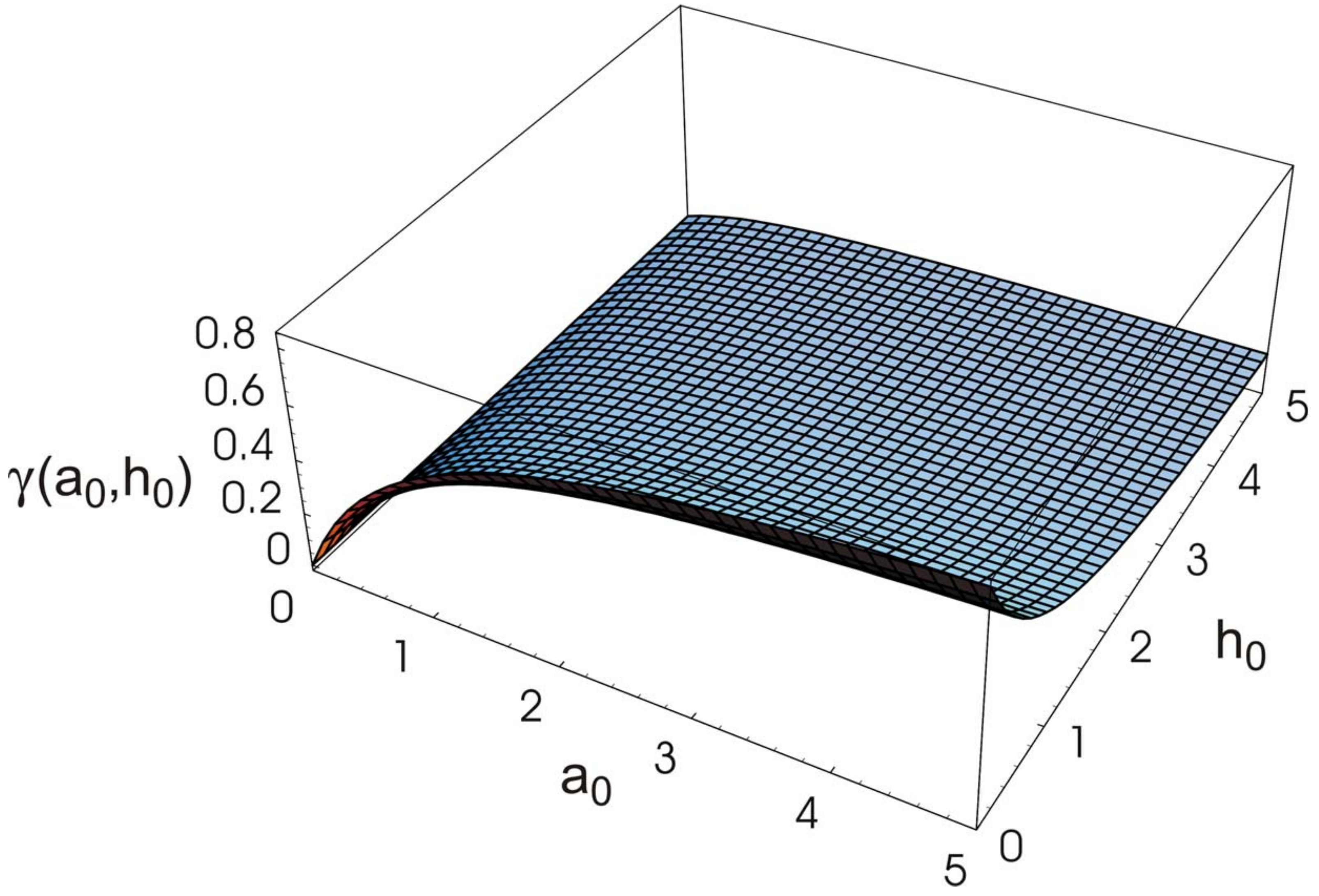
$$\Gamma_A(a) = \frac{a^\gamma}{\kappa^\gamma + a^\gamma}\ , \Gamma_I(h) = \frac{\kappa^\gamma}{\kappa^\gamma + h^\gamma}$$

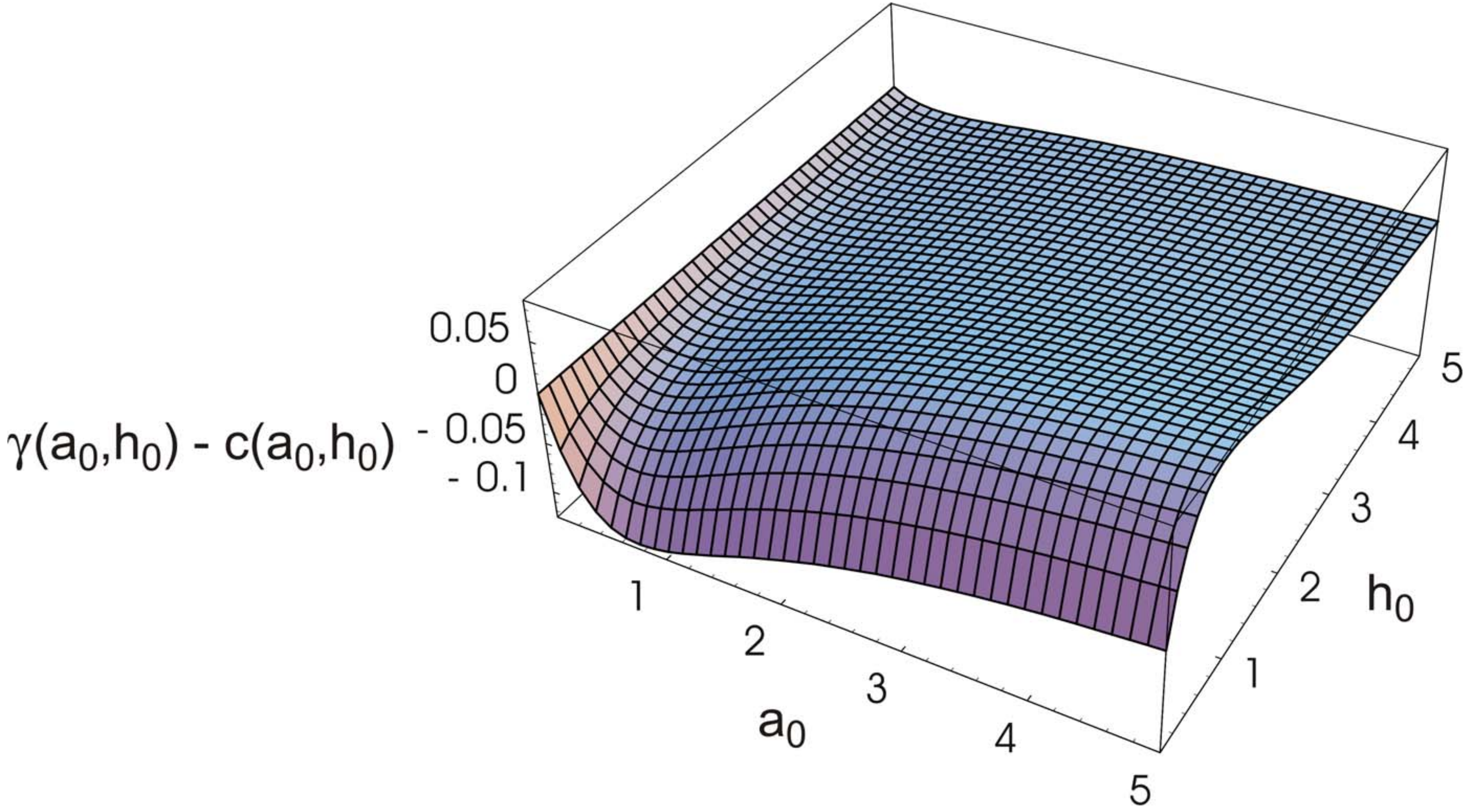
$$c(a) = \frac{K_1\, a\, g_0}{1 + K_1 a + K_2 h + K\, a\, h} \cong \frac{K_1\, g_0\, a_0}{1 + K_1 a_0} \cdot \frac{1}{1 + K_2 h_0}$$

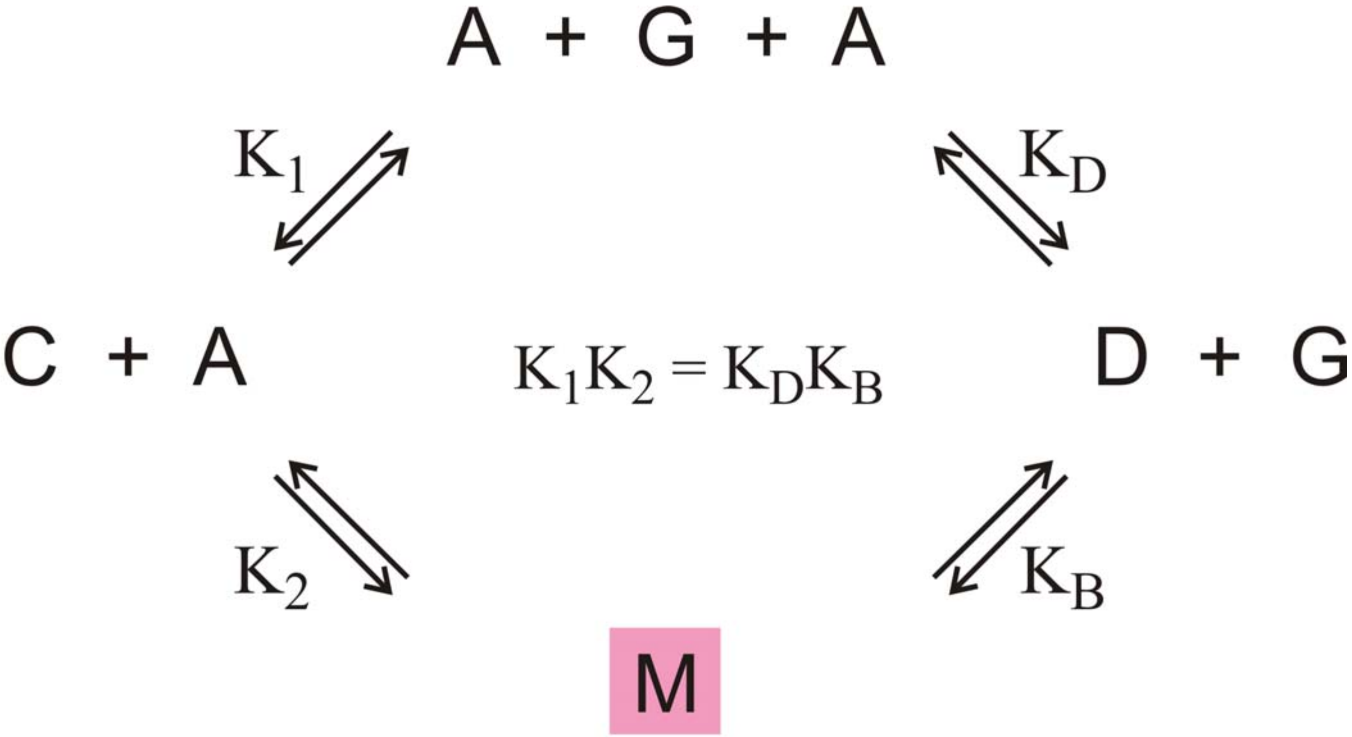
$$a \cong a_0\ ,\ h \cong h_0\ ; \quad K = K_1 K_2$$

Approximation through replacing free concentrations by total concentrations


0.8
0.6
0.4
c(a$_0$,h$_0$)
0.2
0
1
2
a$_0$
3
4
5
1
2
h$_0$
3
4
5


γ(a₀,h₀)
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
a₀
0
1
2
3
4
5
h₀


0.05
0
- 0.05
- 0.1
$\gamma(a_0,h_0) - c(a_0,h_0)$
1
2
3
4
5
a_0
1
2
3
4
5
h_0



$$D \equiv A_2$$

Activator dimer binding to regulatory unit

$$A + G + A \;\underset{}{\overset{K_D}{\rightleftarrows}}\; D + G \;\underset{K_B}{\rightleftarrows}\; \boxed{M}$$

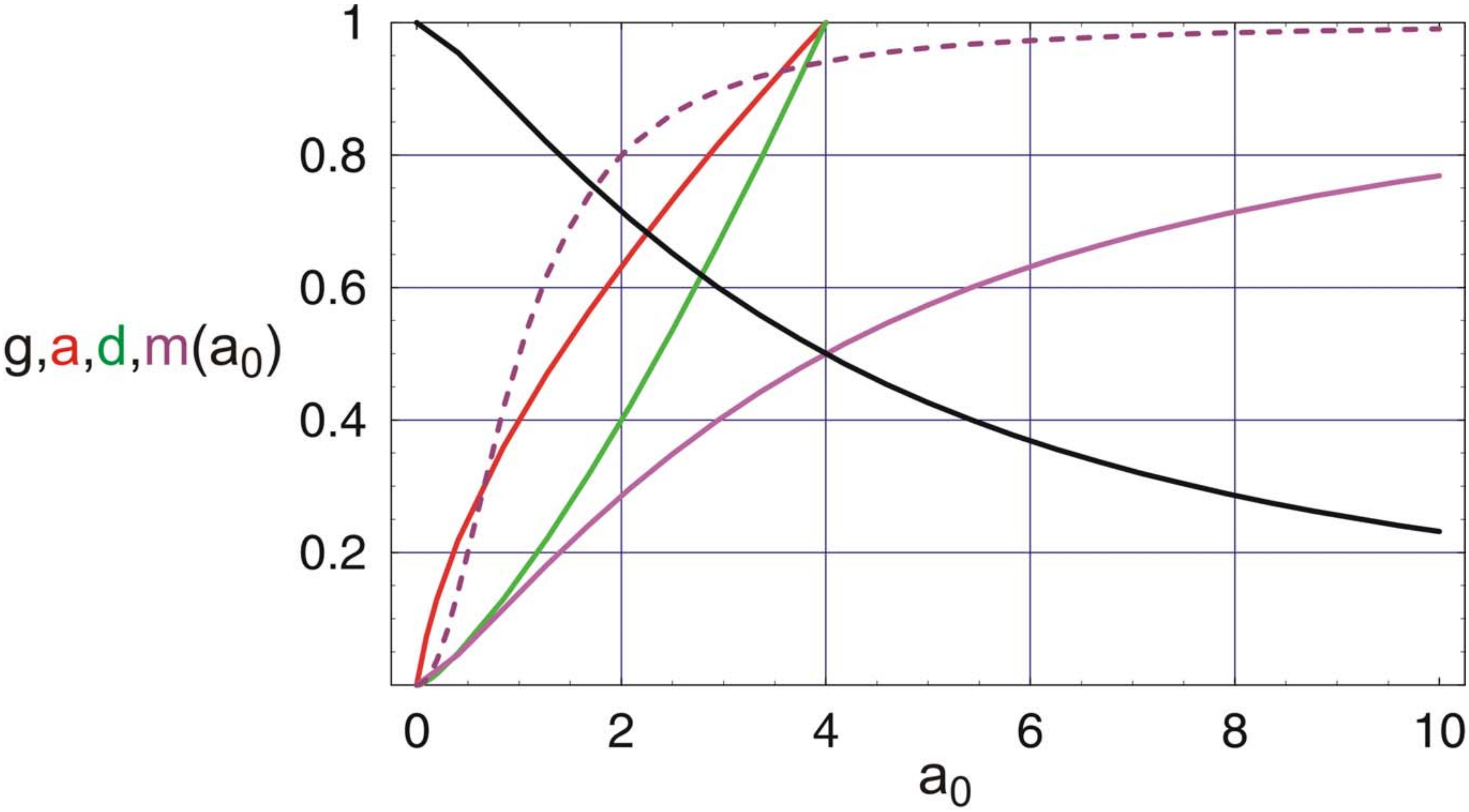
$$D \equiv A_2$$

Activator dimer binding to regulatory unit

$$a^4 + \frac{\kappa_D}{2} a^3 + \frac{\kappa_D}{2}\left(2\kappa_B + 2g_0 - a_0\right) a^2 + \frac{\kappa_D^{2}\kappa_B}{2} a + \frac{\kappa_D^{2}\kappa_B}{2} a_0 = 0$$

$$m = \frac{g_0 \, a^2}{\kappa_B \kappa_D + a^2} \cong \frac{g_0 \, a_0^2}{\kappa_B \kappa_D + a_0^2}$$

Approximation through replacing free concentration by total concentration



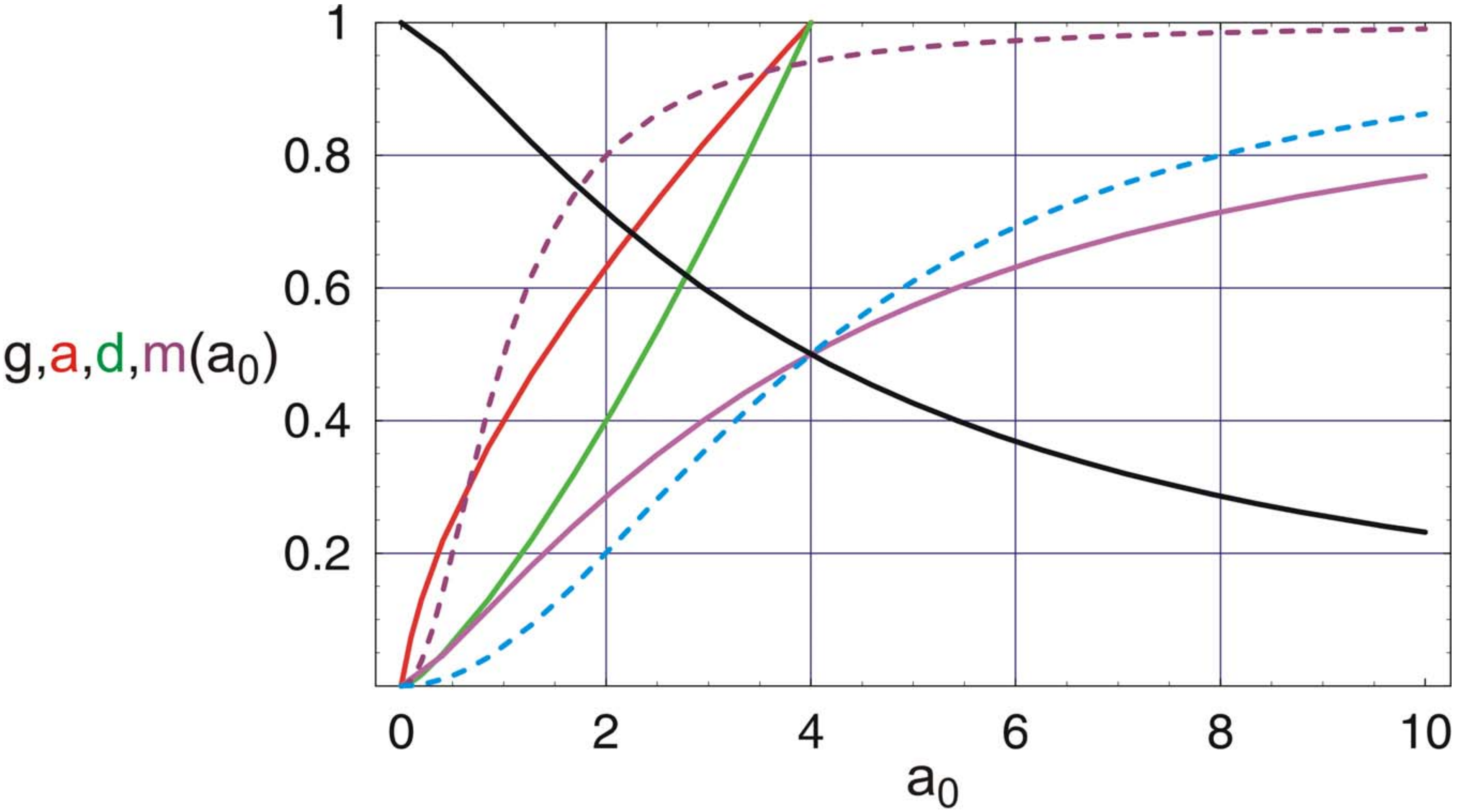
$K_D = 1, K_B = 1$

$$a^4 + \frac{\kappa_D}{2} a^3 + \frac{\kappa_D}{2}\left(2\kappa_B + 2g_0 - a_0\right) a^2 + \frac{\kappa_D{}^2 \kappa_B}{2} a + \frac{\kappa_D{}^2 \kappa_B}{2} a_0 = 0$$

$$m = \frac{g_0\ a^2}{\kappa_B \kappa_D + a^2} \cong \frac{g_0\ a_0{}^2}{\kappa_B \kappa_D + a_0{}^2}$$

$$m \cong \frac{g_0\ a_0{}^2}{(2\kappa_B + \sqrt{\kappa_B \kappa_D} + g_0)^2 + a_0{}^2}$$

Approximation through the point $m(a) = 0.5$



$K_D = 1, K_B = 1$

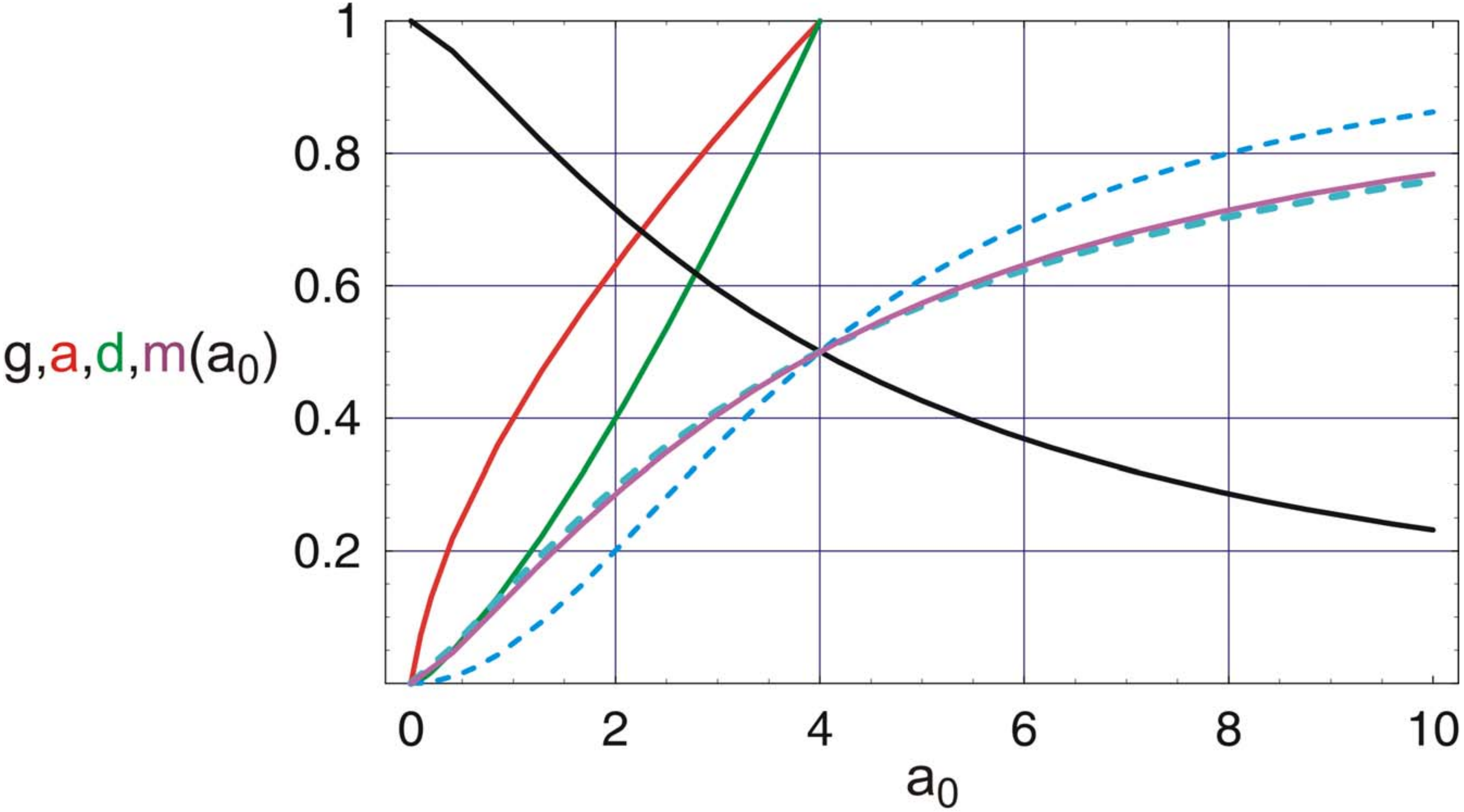
$$a^4 + \frac{\kappa_D}{2} a^3 + \frac{\kappa_D}{2}\left(2\kappa_B + 2g_0 - a_0\right) a^2 + \frac{\kappa_D{}^2 \kappa_B}{2}\, a + \frac{\kappa_D{}^2 \kappa_B}{2}\, a_0 = 0$$

$$m = \frac{g_0\, a^2}{\kappa_B \kappa_D + a^2} \cong \frac{g_0\, a_0{}^2}{\kappa_B \kappa_D + a_0{}^2}$$

$$m \cong \frac{g_0\, a_0{}^2}{(2\kappa_B + \sqrt{\kappa_B \kappa_D} + g_0)^2 + a_0{}^2}$$

$$m \cong \frac{g_0\, a_0{}^n}{(2\kappa_B + \sqrt{\kappa_B \kappa_D} + g_0)^n + a_0{}^n}\ ; \quad n = \frac{4\,(2\kappa_B + \sqrt{\kappa_B \kappa_D} + g_0)\, m'}{g_0}$$

Approximation through the point $m(a) = 0.5$ and tangent at this point



$K_D = 1, K_B = 1$

1. What is computational systems biology?
2. Genabolic networks
3. Genomes and cellular networks
4. Forward and inverse problems
5. Reverse engineering – A simple example
6. Activation and silencing of genes
7. **MiniCellSim – A simulation tool**
8. Evolution of genabolic networks

$$\mathbf{A} + \mathbf{B} \rightarrow \mathbf{X}$$
$$2\,\mathbf{X} \rightarrow \mathbf{Y}$$
$$\mathbf{Y} + \mathbf{X} \rightarrow \mathbf{D}$$

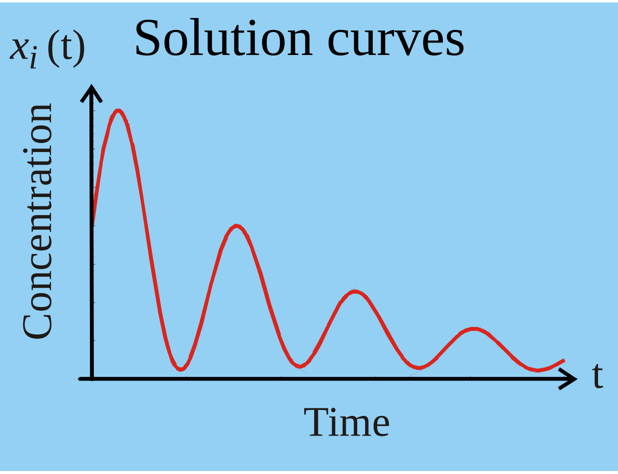
Stoichiometric equations

SBML – systems biology markup language

$$\frac{\mathrm{d}a}{\mathrm{dt}} = \frac{\mathrm{d}b}{\mathrm{dt}} = -k_1 a b$$
$$\frac{\mathrm{d}x}{\mathrm{dt}} = k_1 a b - k_2 x^2 - k_3 x y$$
$$\frac{\mathrm{d}y}{\mathrm{dt}} = k_2 x^2 - k_3 x y$$
$$\frac{\mathrm{d}d}{\mathrm{dt}} = k_3 x y$$

Kinetic differential equations

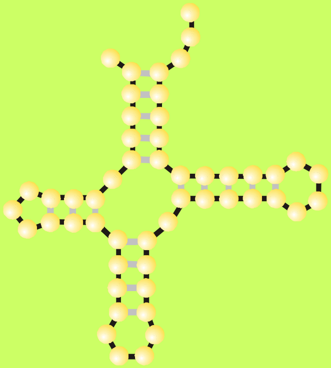
ODE Integration by means of *CVODE*


Solution curves

Sequences

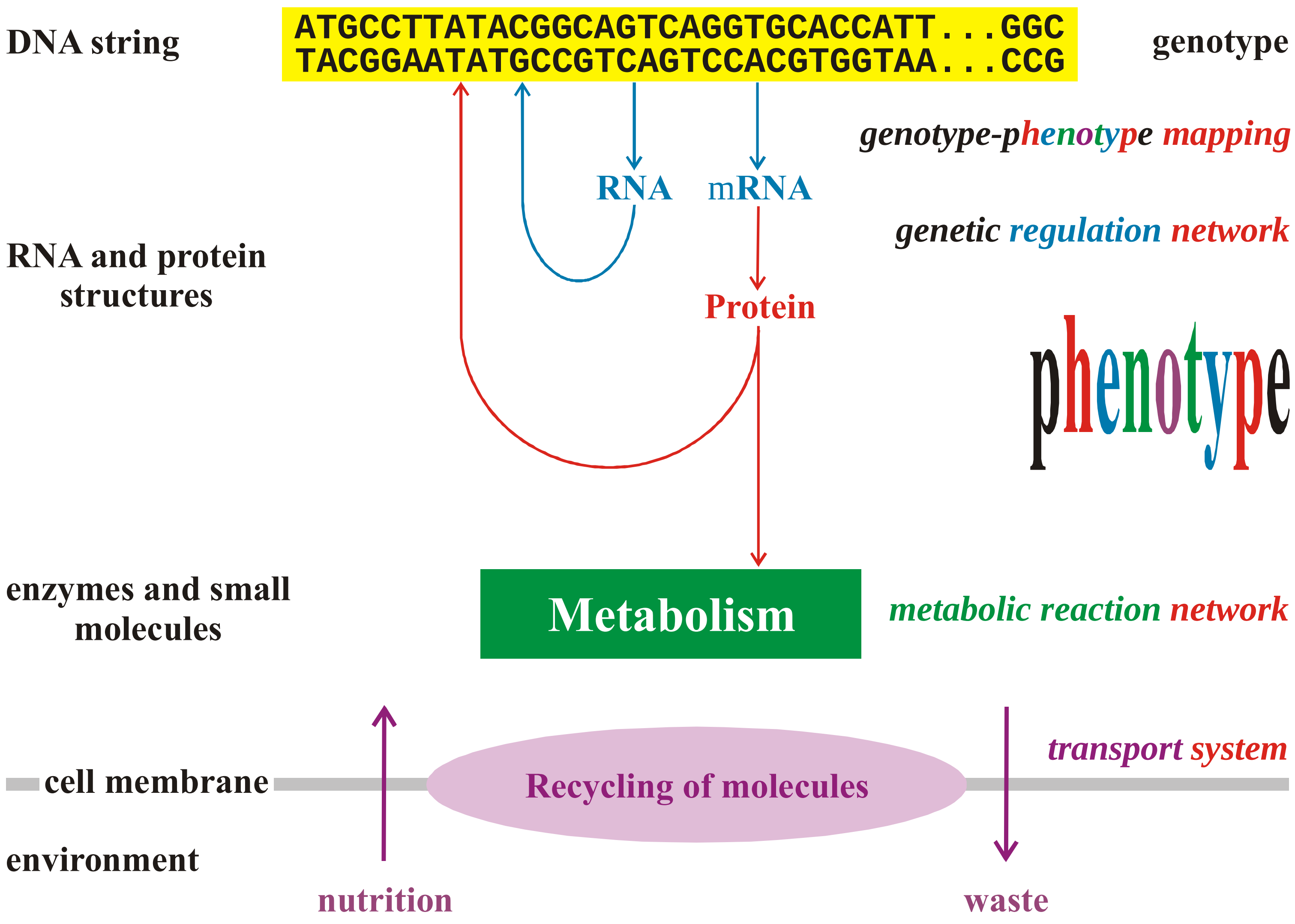
Vienna RNA Package

Structures and kinetic parameters



The elements of the simulation tool MiniCellSim

SBML: *Bioinformatics* **19**:524-531, 2003; *CVODE*: *Computers in Physics* **10**:138-143, 1996



DNA string

ATGCCTTATACGGCAGTCAGGTGCACCATT...GGC
TACGGAATATGCCGTCAGTCCACGTGGTAA...CCG

genotype

genotype-phenotype mapping

RNA **mRNA**

genetic regulation network

RNA and protein structures

Protein

phenotype

enzymes and small molecules

Metabolism

metabolic reaction network

transport system

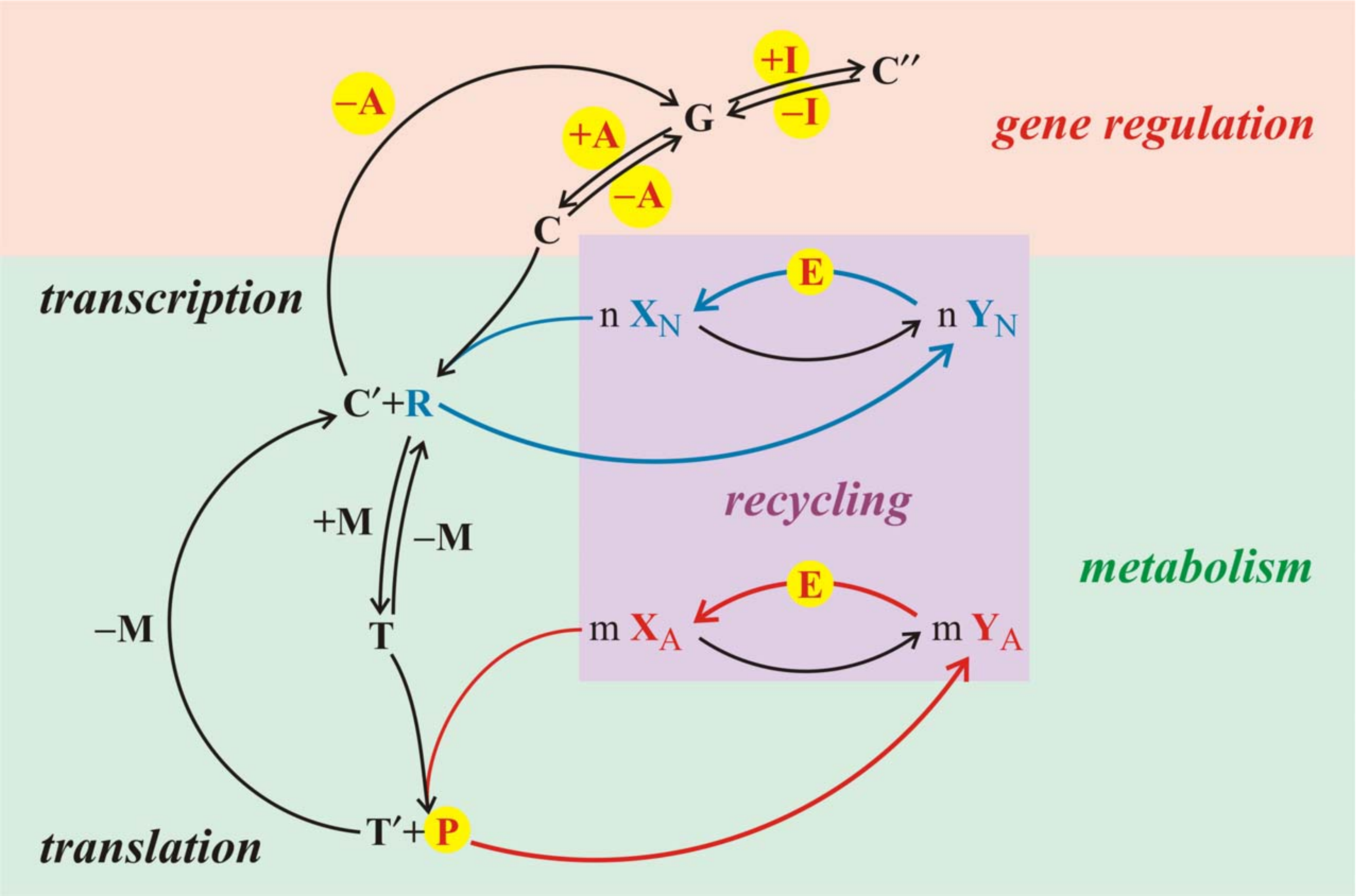
cell membrane

Recycling of molecules

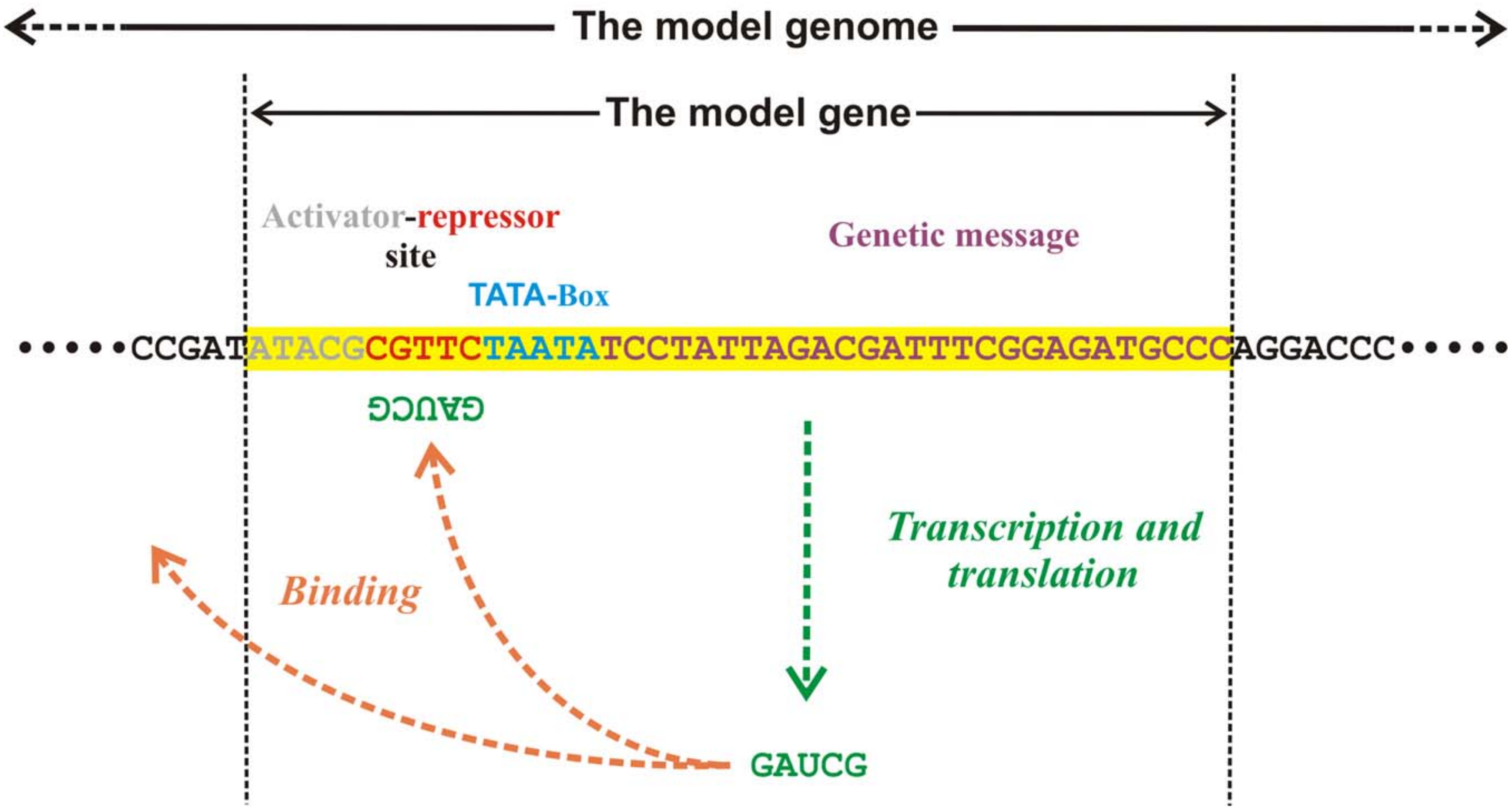
environment

nutrition **waste**

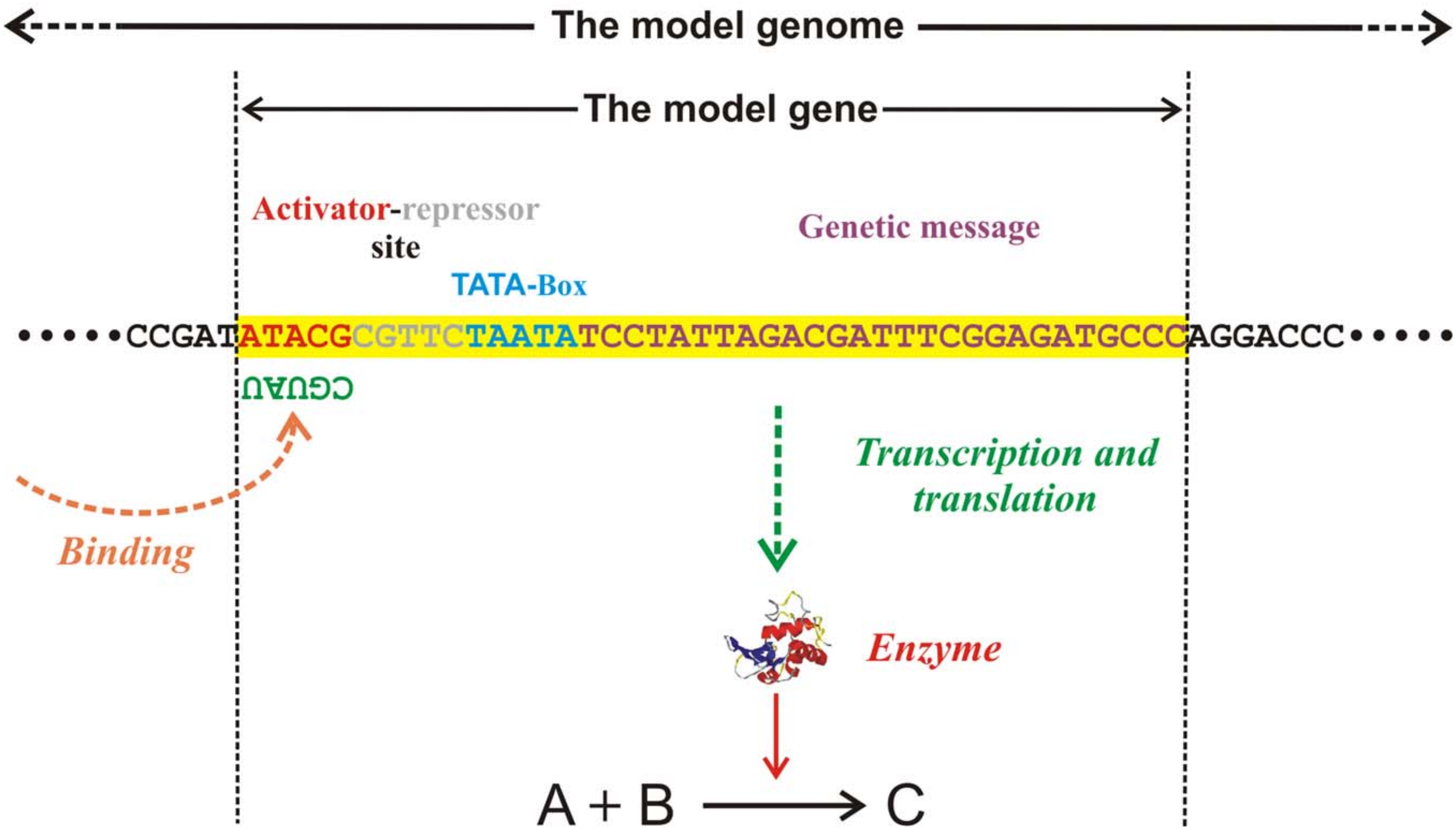
The regulatory logic of MiniCellSym



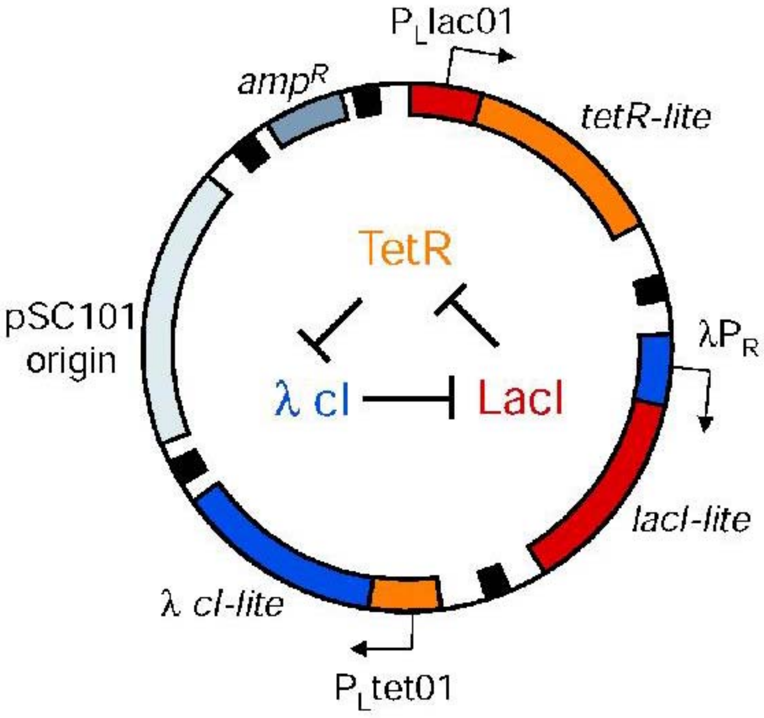
The chemical reaction dynamics of MiniCellSym

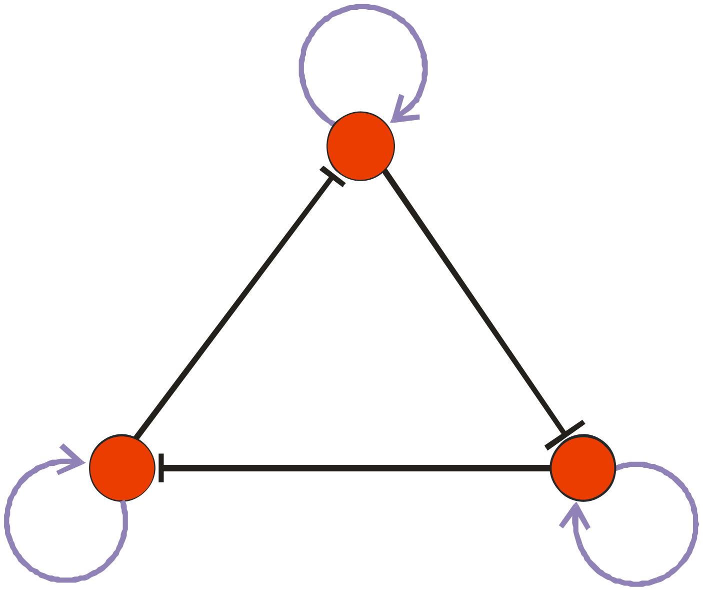


The model regulatory gene in MiniCellSim



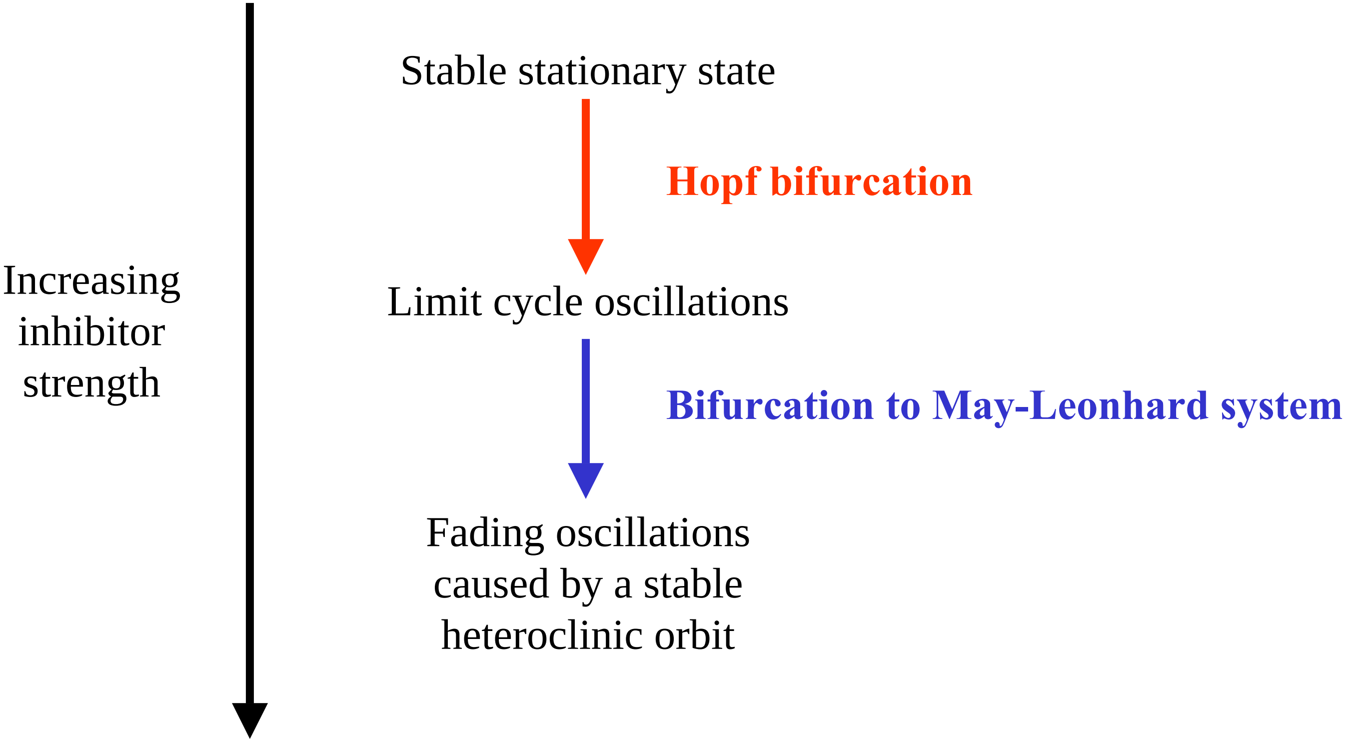
The model structural gene in MiniCellSim





An example simulated by MiniCellSim

The repressilator: M.B. Ellowitz, S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature* **403**:335-338, 2002



Increasing
inhibitor
strength

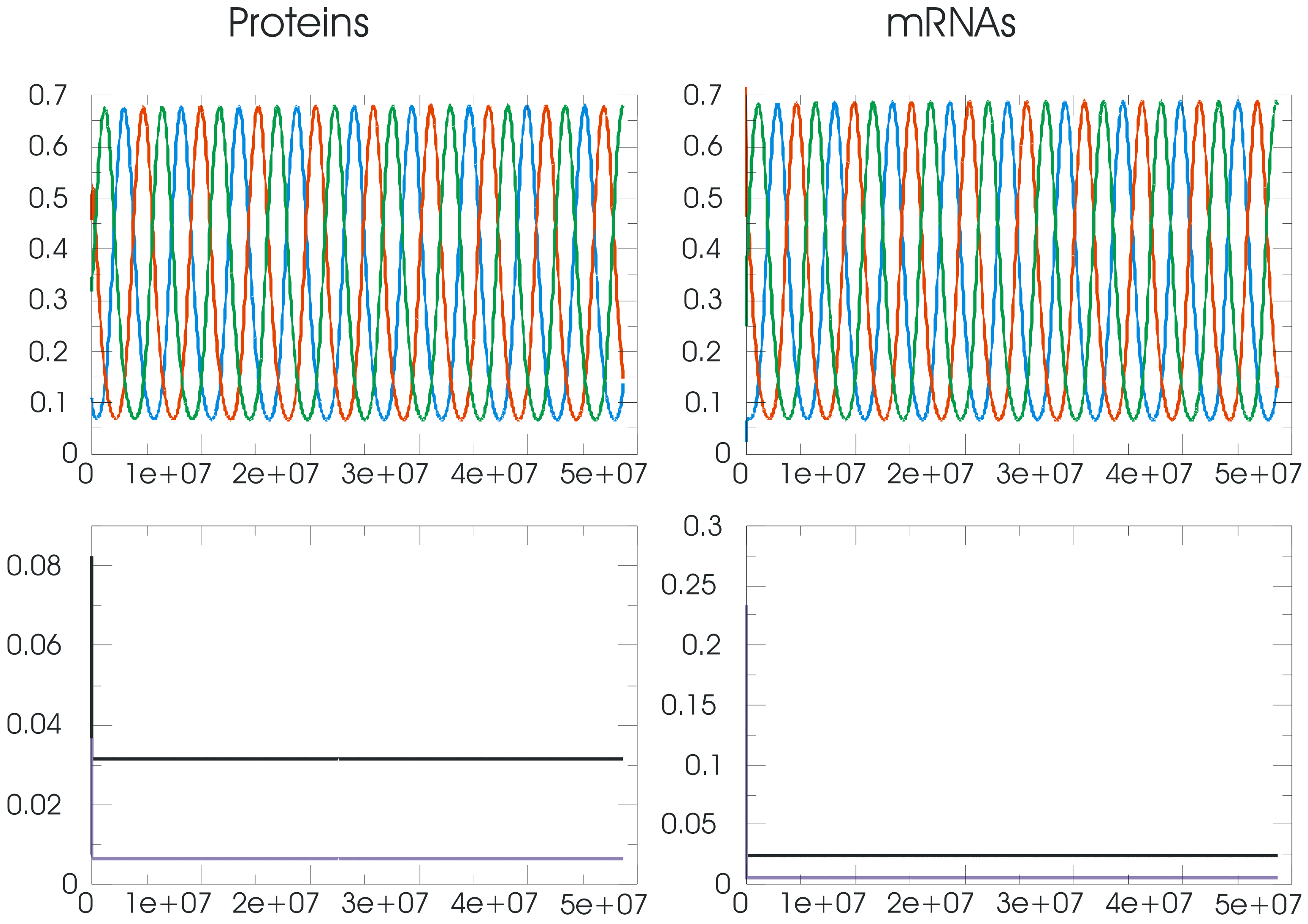
Stable stationary state

Hopf bifurcation

Limit cycle oscillations

Bifurcation to May-Leonhard system

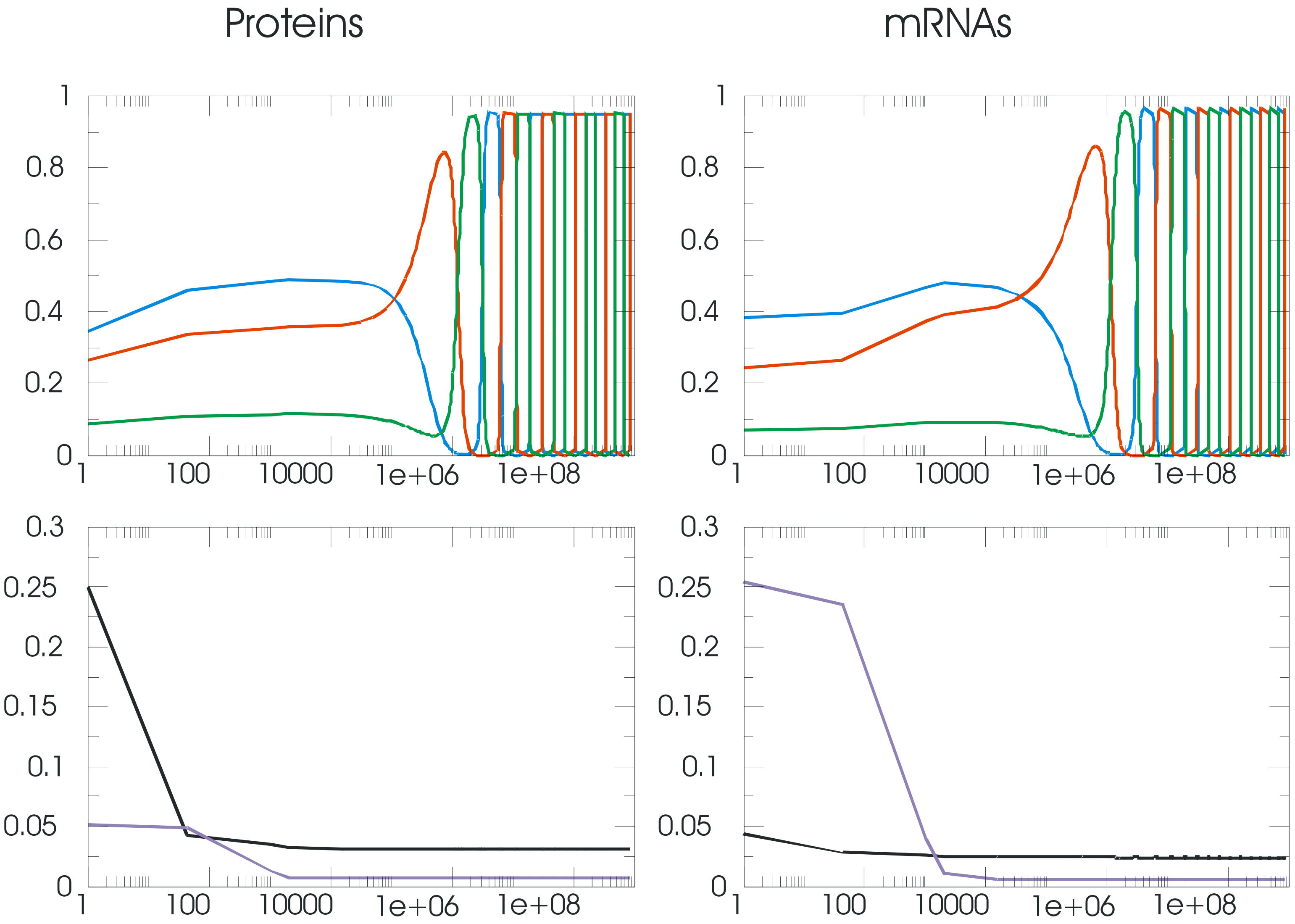
Fading oscillations
caused by a stable
heteroclinic orbit



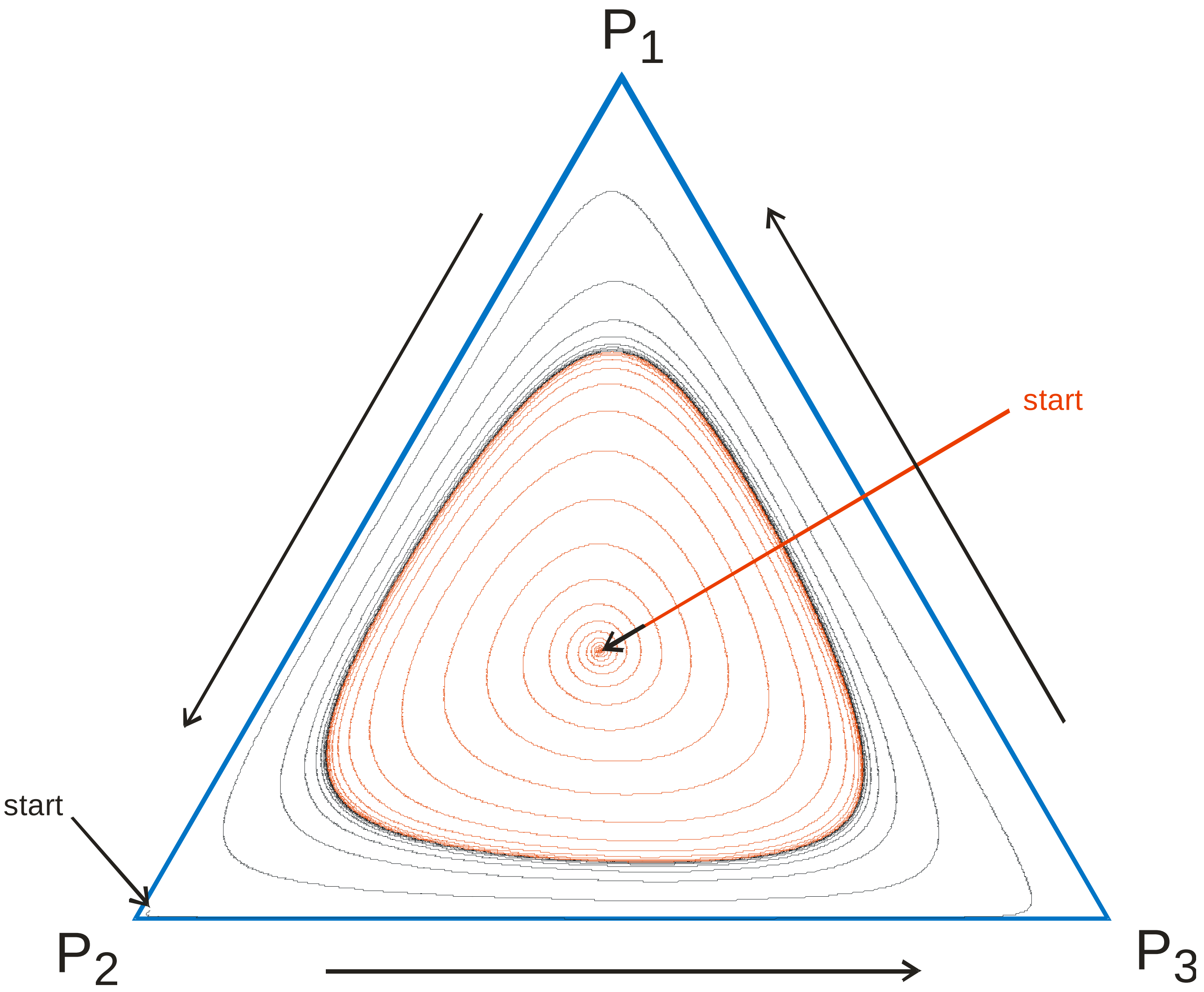
Proteins

mRNAs

The repressilator limit cycle



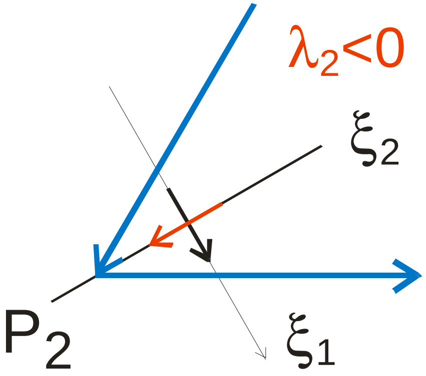
The repressilator limit cycle (logarithmic time scale)



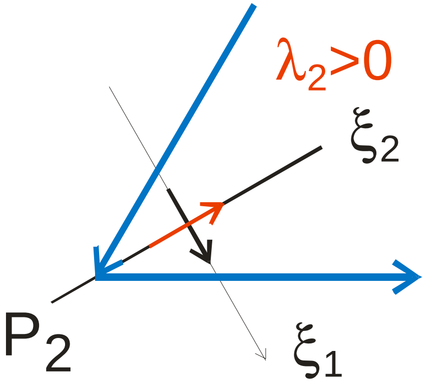
The repressilator limit cycle

Bifurcation from limit cycle
to stable heteroclinic orbit
at

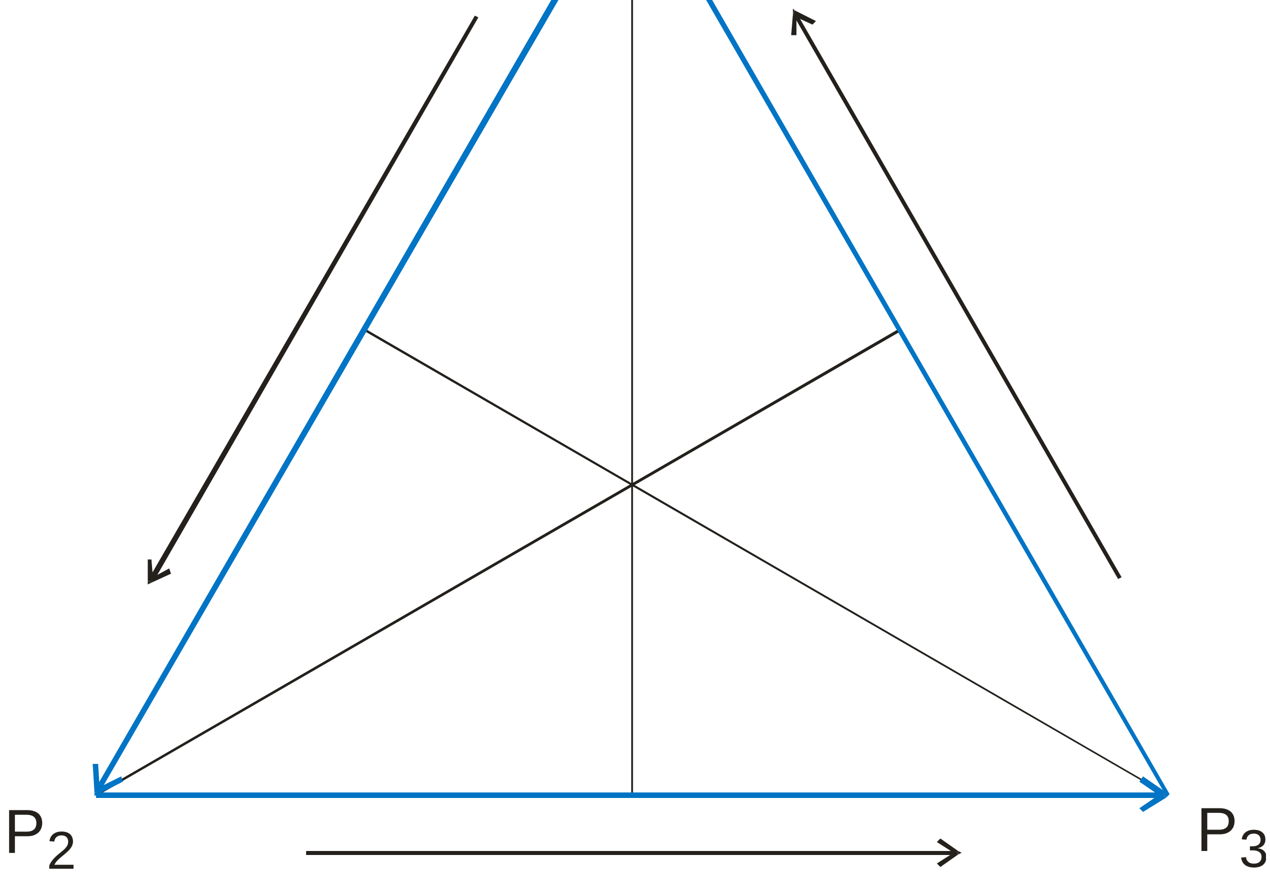
$\lambda_2=0$



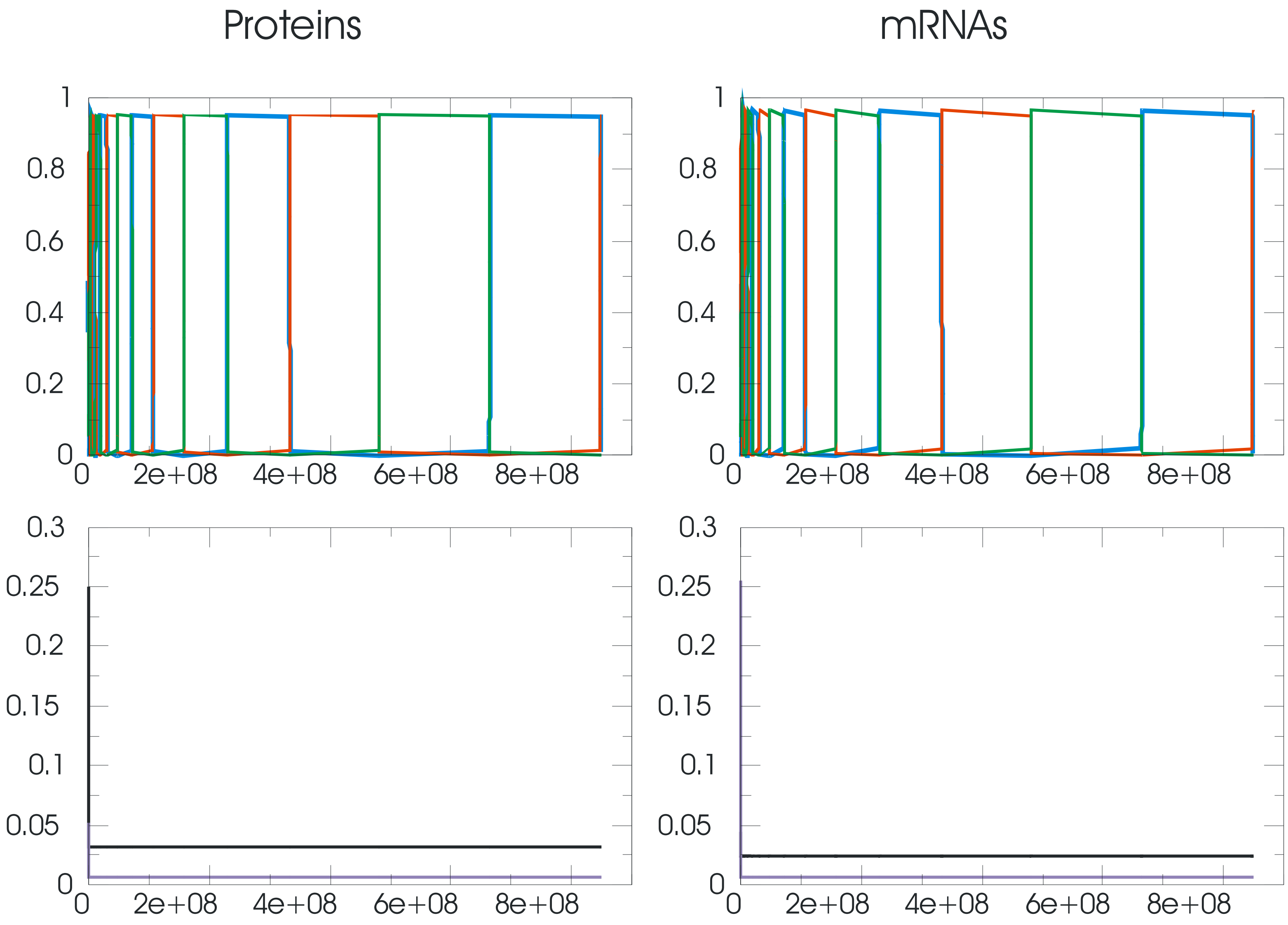
Stable heteroclinic orbit



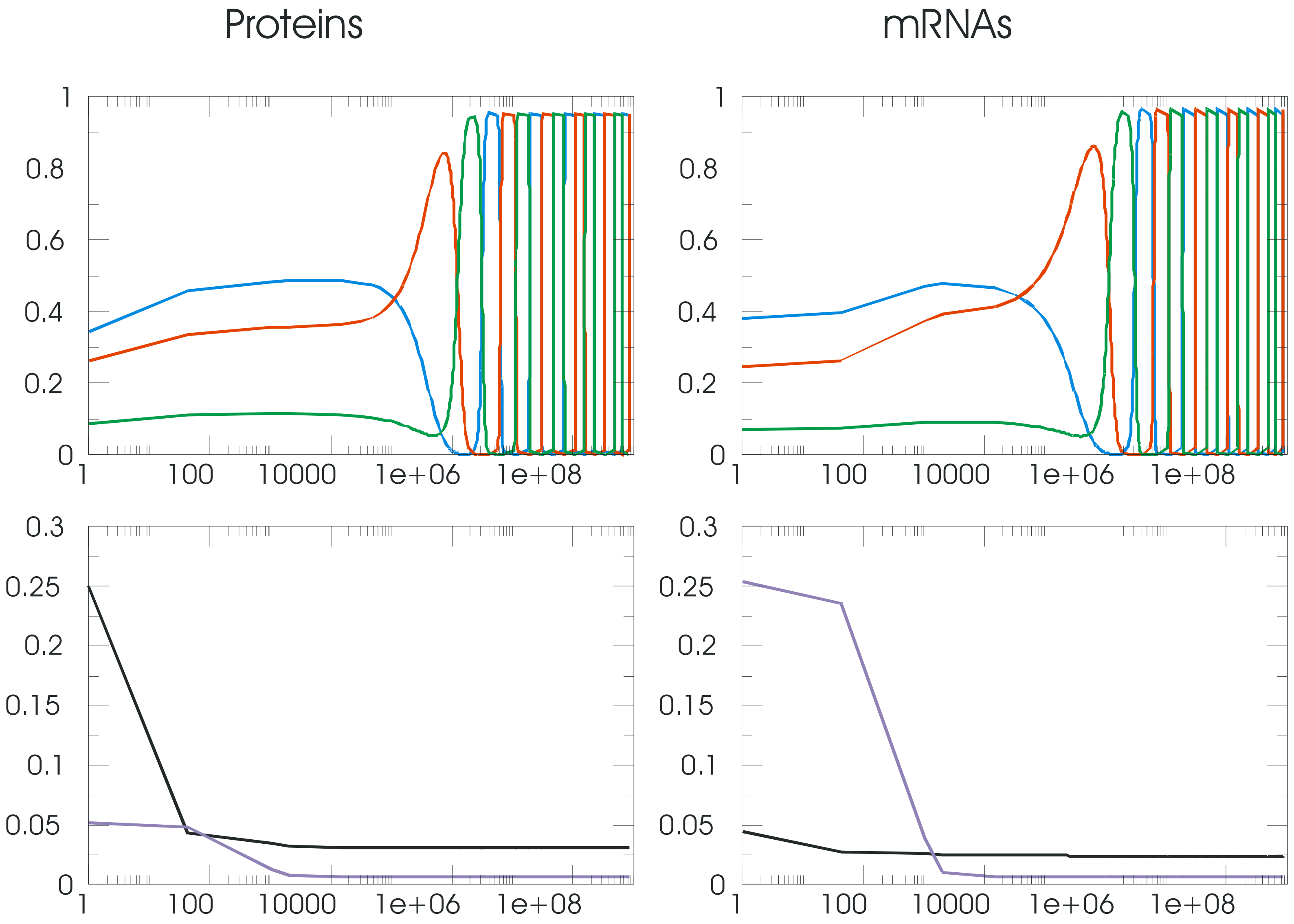
Unstable heteroclinic orbit



The repressilator heteroclinic orbit



The repressilator heteroclinic orbit



The repressilator heteroclinic orbit (logarithmic time scale)

1. What is computational systems biology?
2. Genabolic networks
3. Genomes and cellular networks
4. Forward and inverse problems
5. Reverse engineering – A simple example
6. Activation and silencing of genes
7. MiniCellSim – A simulation tool
8. **Evolution of genabolic networks**

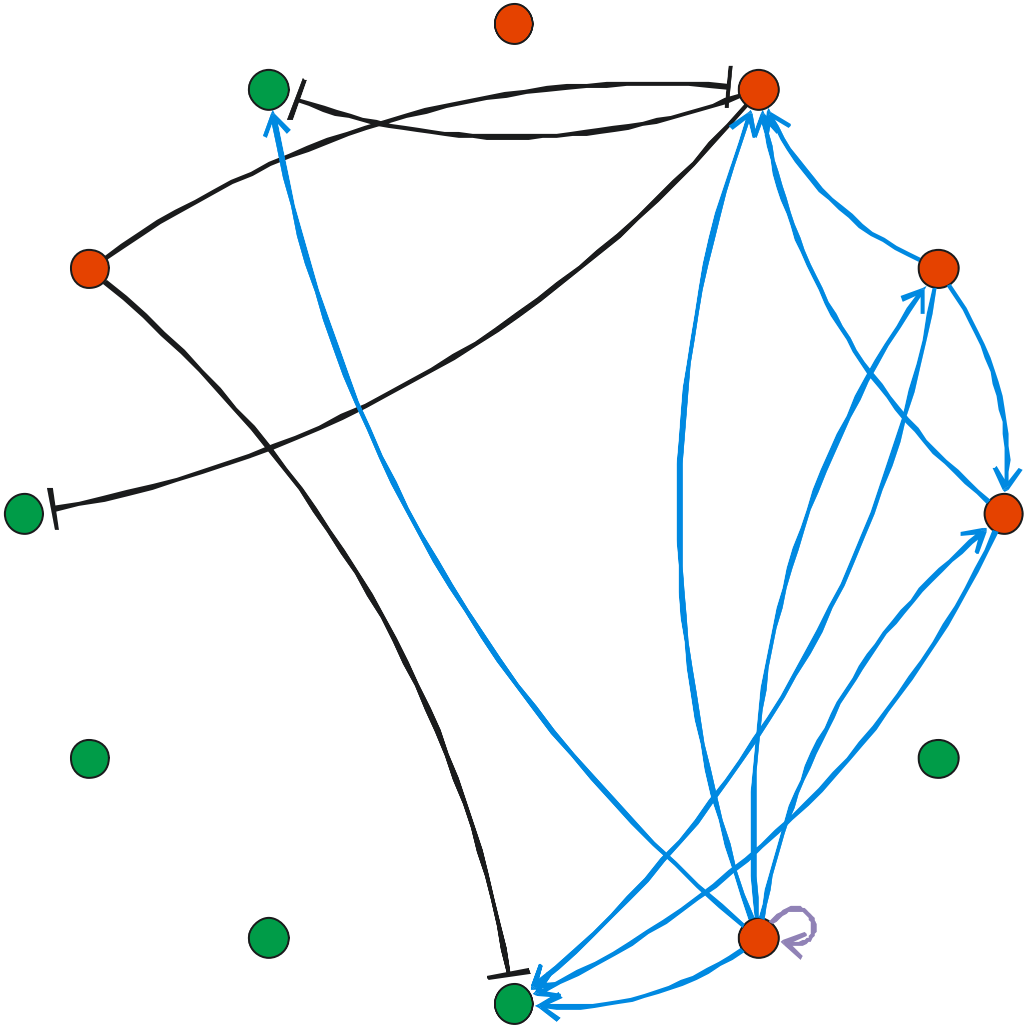
Evolutionary time: 0000

Number of genes: 12

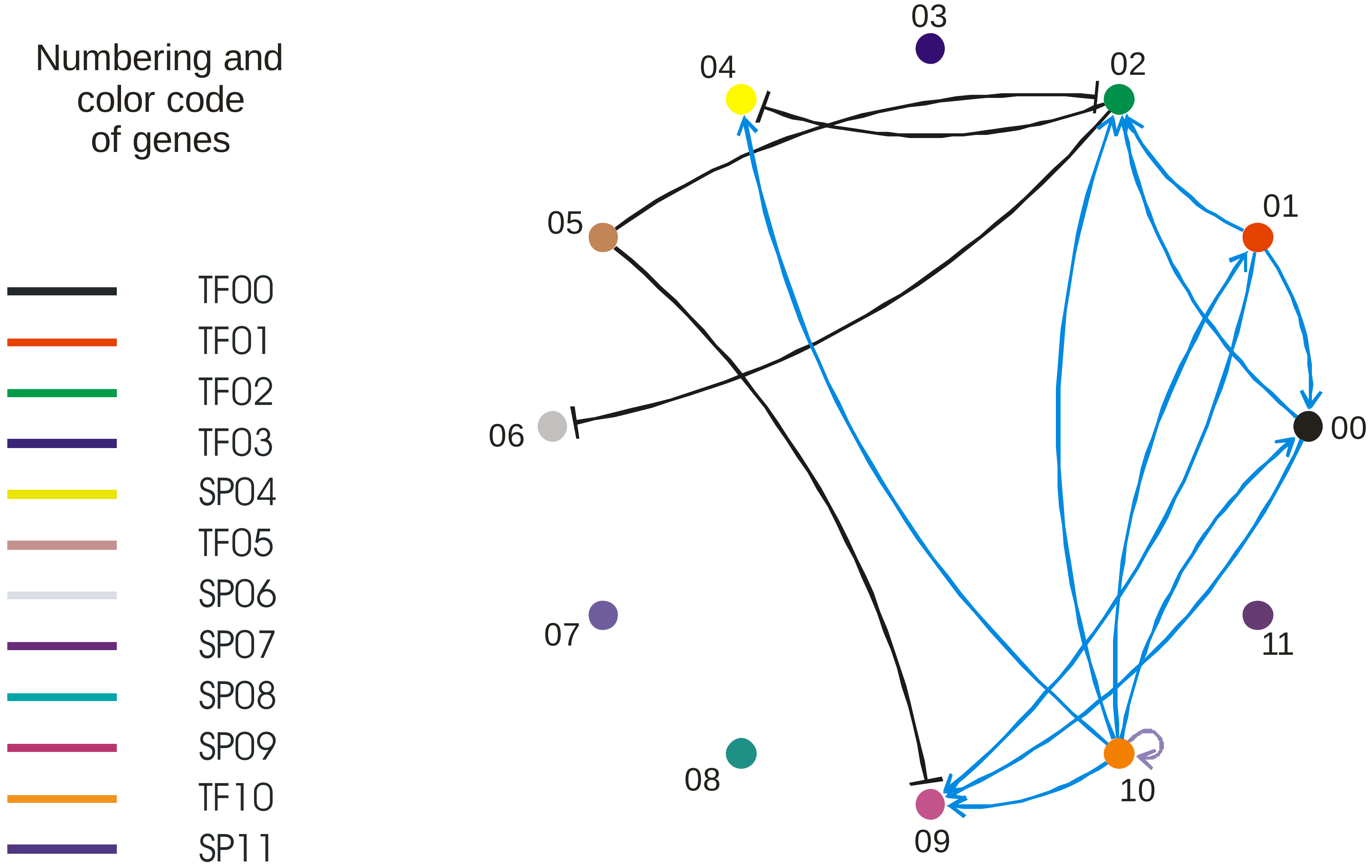
06 structural + 06 regulatory

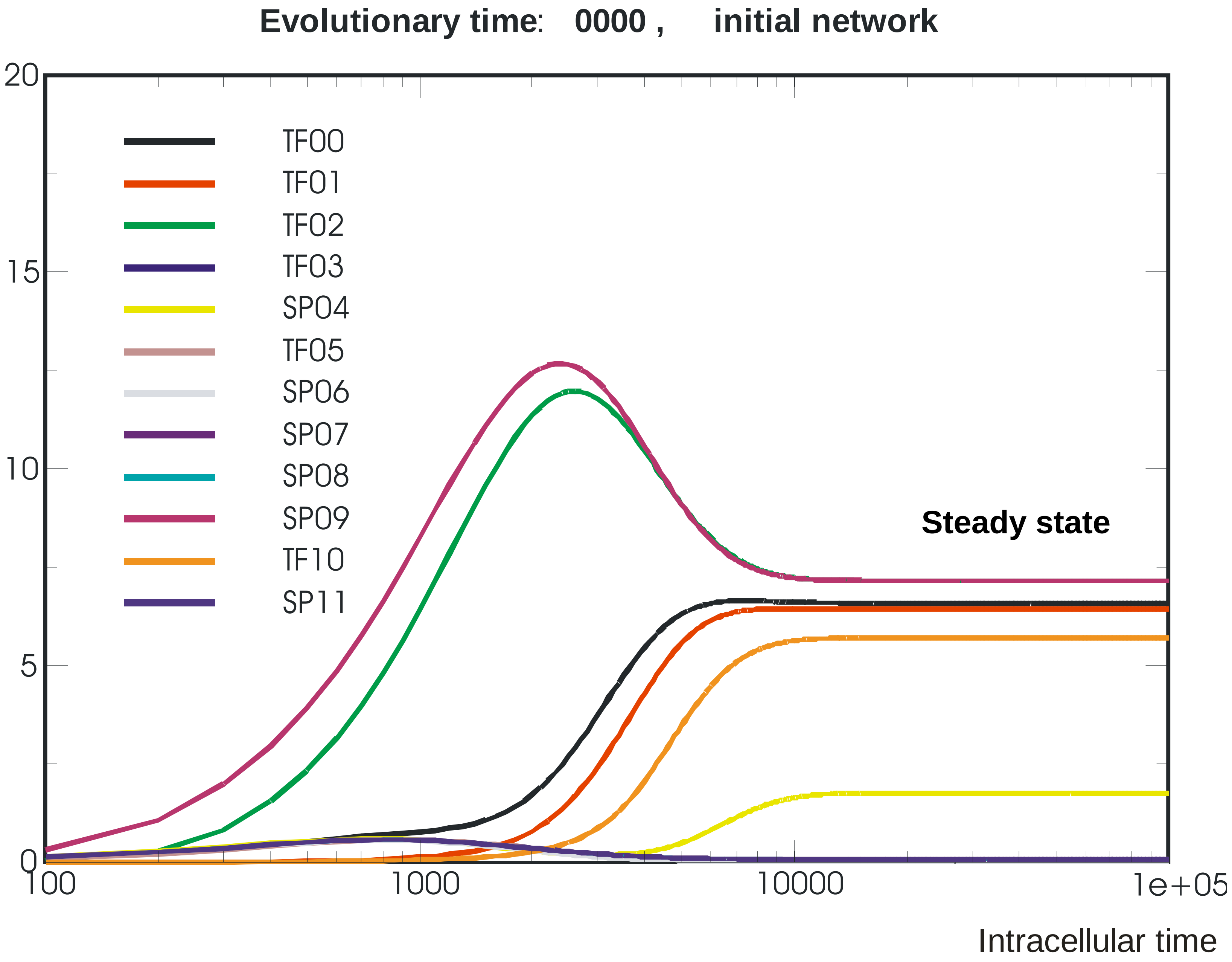
Number of interactions: 15

04 inhibitory + 10 activating +
+ 1 self-activating



Network formed by a random sequence of 200 nucleotides


Numbering and color code of genes
TF00
TF01
TF02
TF03
SP04
TF05
SP06
SP07
SP08
SP09
TF10
SP11
03
04
02
05
01
06
00
07
11
08
10
09

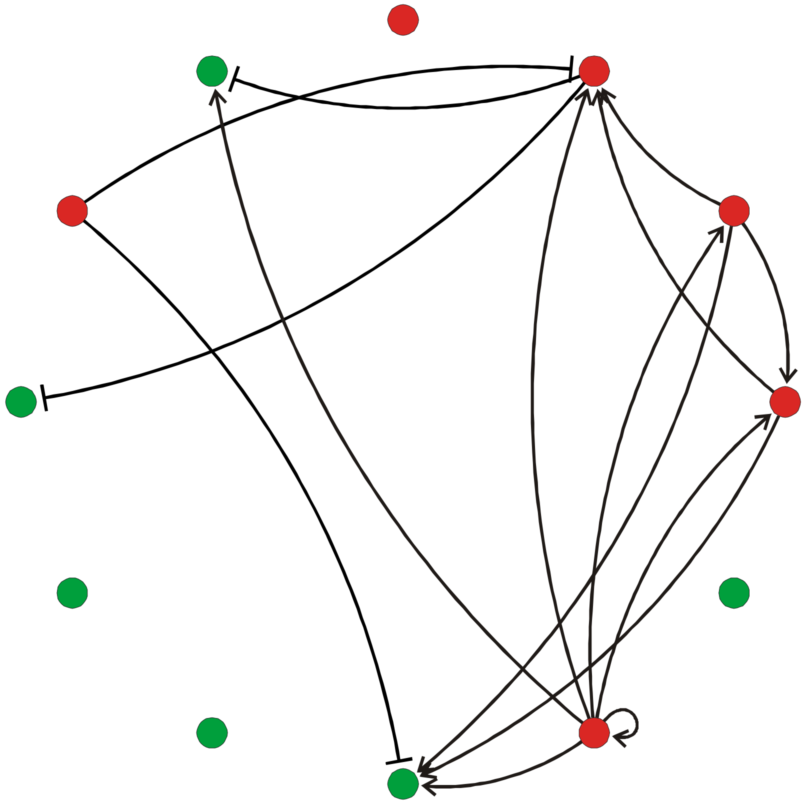

Evolutionary time: 0000 , initial network
20
15
10
5
0
100
1000
10000
1e+05
Intracellular time
TF00
TF01
TF02
TF03
SP04
TF05
SP06
SP07
SP08
SP09
TF10
SP11
Steady state

Evolution of a genabolic network:

Initial genome: Random sequence of chain length **n = 200**,
AUGC alphabet

Simulation with a mutation rate: **p = 0.01**

Evolutionary time unit >> time unit of regulatory kinetics



Observed events:

(i) Loss of a gene through corruption of the initiation signal “**TA**” (analogue of the **TATA** box)

(ii) Creation of a gene

(iii) Change in the connections through mutation driven changes in the binding affinities of translation factors to the regulatory sites

(iv) Genes may change their class (tf ⇔sp)

Windows Media Player.lnk

Conclusion and outlook on inverse problems

☑	1.	RNA minimum free energy folding and inverse folding for the design of secondary structures.
✓ in progress	2.	Kinetic folding of RNA and design of molecules with multiple states and predefined folding kinetics.
✓ in progress	**3.**	**Computation of the dynamics of cellular genetic and metabolic networks for known rate constants and its inverse problem** (Level I).
in progress ✓	**4.**	**Genetic and metabolic dynamics in parameter space and reverse engineering of model systems with predefined full dynamical behavior (Level II) seems doable. Mathematical tools can be applied successfully also to multidimensional dynamical systems.**
☑	**5.**	**Random sequences give rise to functional networks in the model.**
✓ in progress	**6.**	**Evolution of small genetic and metabolic networks can be simulated properly and with reasonable efforts.**
	7.	Upscaling remains a hard but promising problem.

Acknowledgement of Support

Universität Wien

Fonds zur Förderung der wissenschaftlichen Forschung (FWF)
Projects No. 09942, 10578, 11065, 13093
13887, and 14898

Jubiläumsfonds der Österreichischen Nationalbank
Project No. Nat-7813

European Commission: Project No. EU-980189

Austrian Genome Research Program – GEN-AU

Wiener Wissenschafts- und Technologie Fonds (WWTF)
Project No. Mat-05

Siemens AG, Austria

Universität Wien and the Santa Fe Institute

Universität Wien

Coworkers

Walter Fontana, Harvard Medical School, MA

Christian Forst, **Christian Reidys**, Los Alamos National Laboratory, NM

Peter Stadler, **Bärbel Stadler**, Universität Leipzig, GE

Josef Hofbauer, University College, London, UK

Robert Giegerich, Universität Bielefeld, GE

Heinz Engl, **Stefan Müller**, Johann Radon-Institut für
Angewandte und Computergestützte Mathematik der
Österreichischen Akademie der Wissenschaften, Linz, AT

Christoph Flamm, **Ivo L.Hofacker**, **Gottfried Köhler**
Andreas Svrček-Seiler, **Stefanie Widder**, Universität Wien, AT

Lukas Endler, **Ulrike Langhammer**, **Ulrike Mückstein**
Stefan Bernhart, Universität Wien, AT

Web-Page for further information:

http://www.tbi.univie.ac.at/~pks

Technical report:

Binding of activators and inhibitors to DNA.
Part I. Equilibria