Dynamical Systems in Problems of Gene Regulation

Peter Schuster

Institut für Theoretische Chemie, Universität Wien, Austria
and
The Santa Fe Institute, Santa Fe, New Mexico, USA

CAS-MPG Partner Institute for Computational Biology

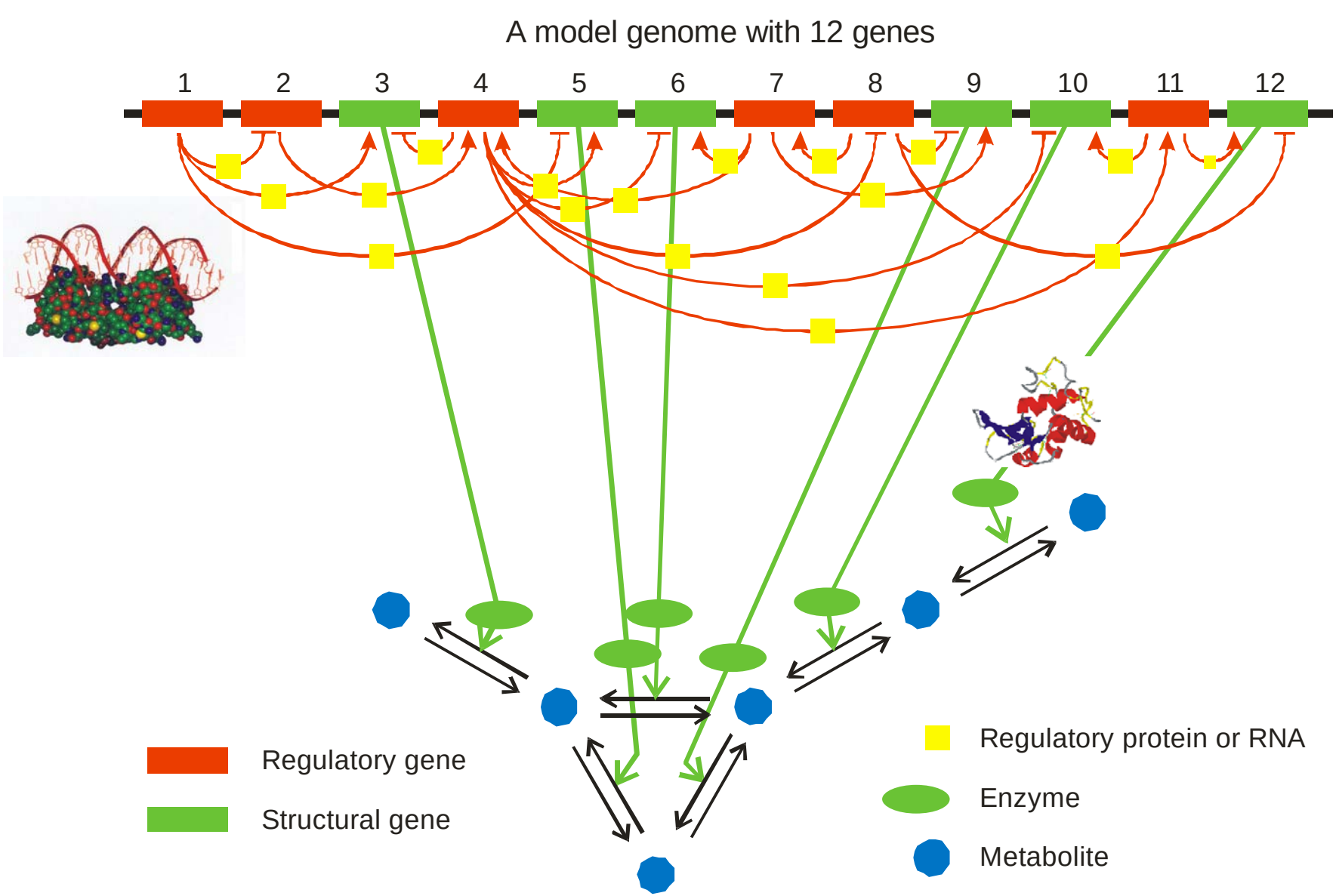
Shanghai, 26.10.2007

Web-Page for further information:

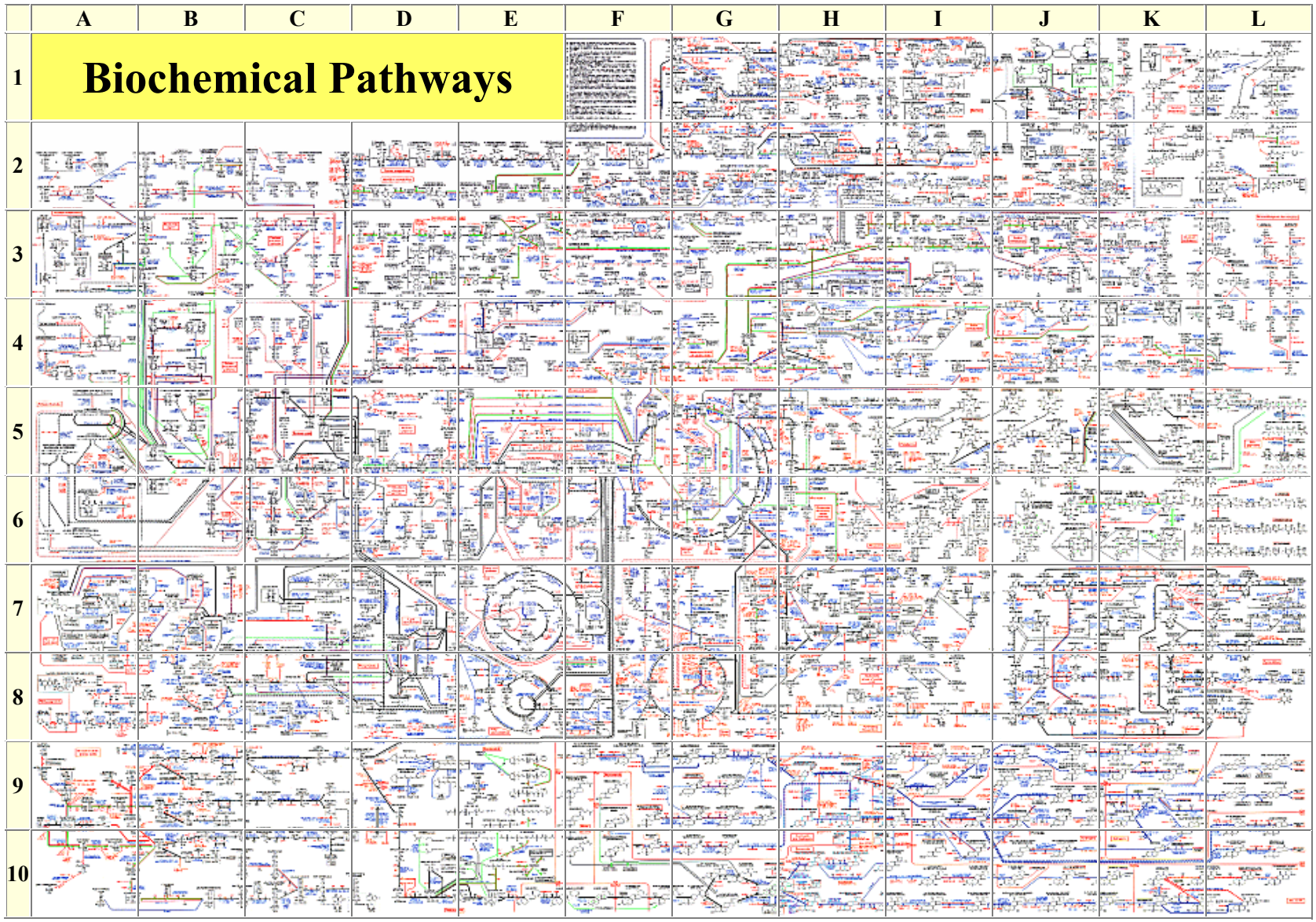
http://www.tbi.univie.ac.at/~pks

1. The problems of quantitative biology
2. Forward and inverse problems in reaction kinetics
3. Regulation kinetics and bifurcation analysis
4. Reverse engineering of dynamical systems
5. How to upscale from small models to cells?

1. **The problems of quantitative biology**
2. Forward and inverse problems in reaction kinetics
3. Regulation kinetics and bifurcation analysis
4. Reverse engineering of dynamical systems
5. How to upscale from small models to cells?

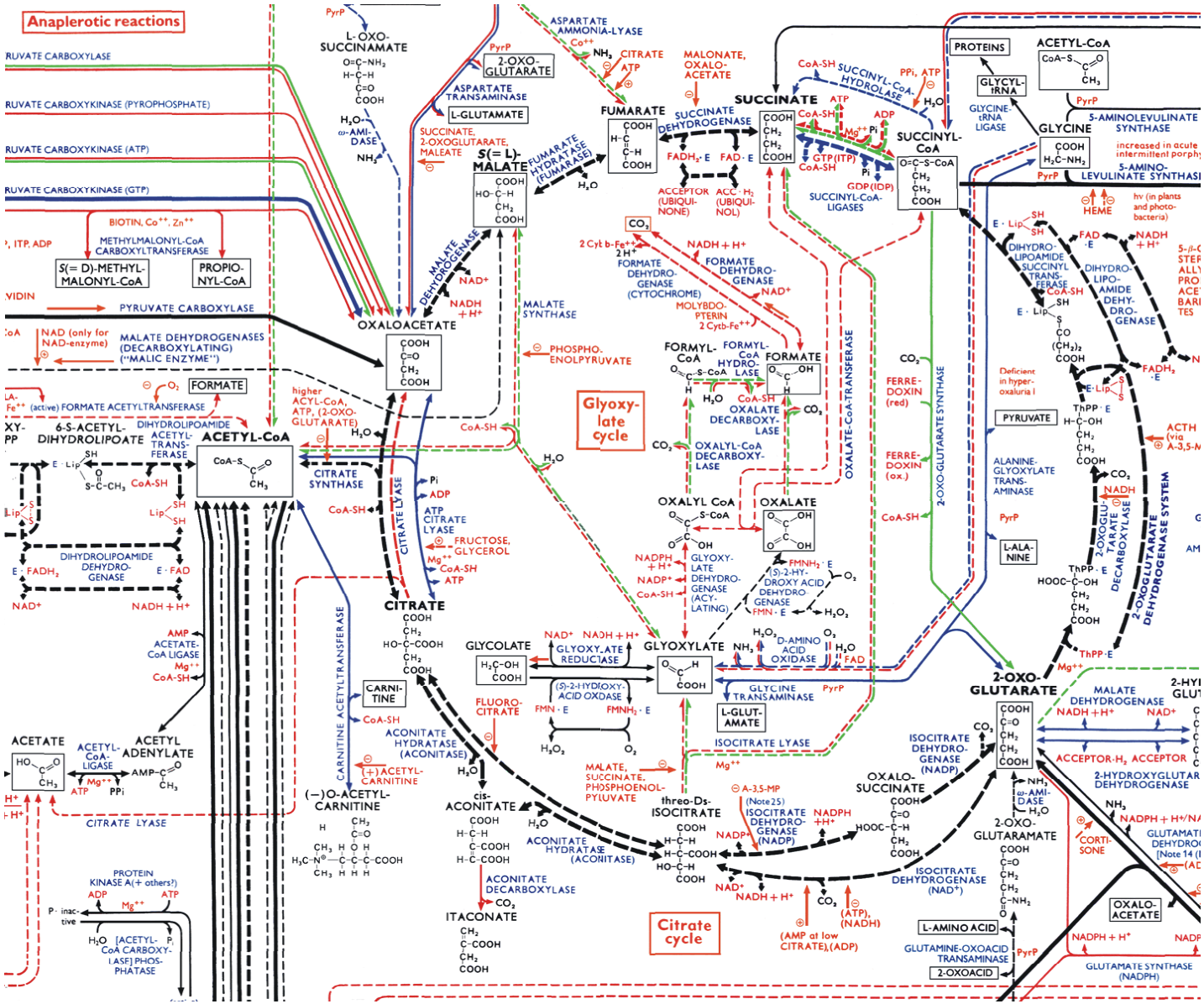


Sketch of a genetic and metabolic network



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

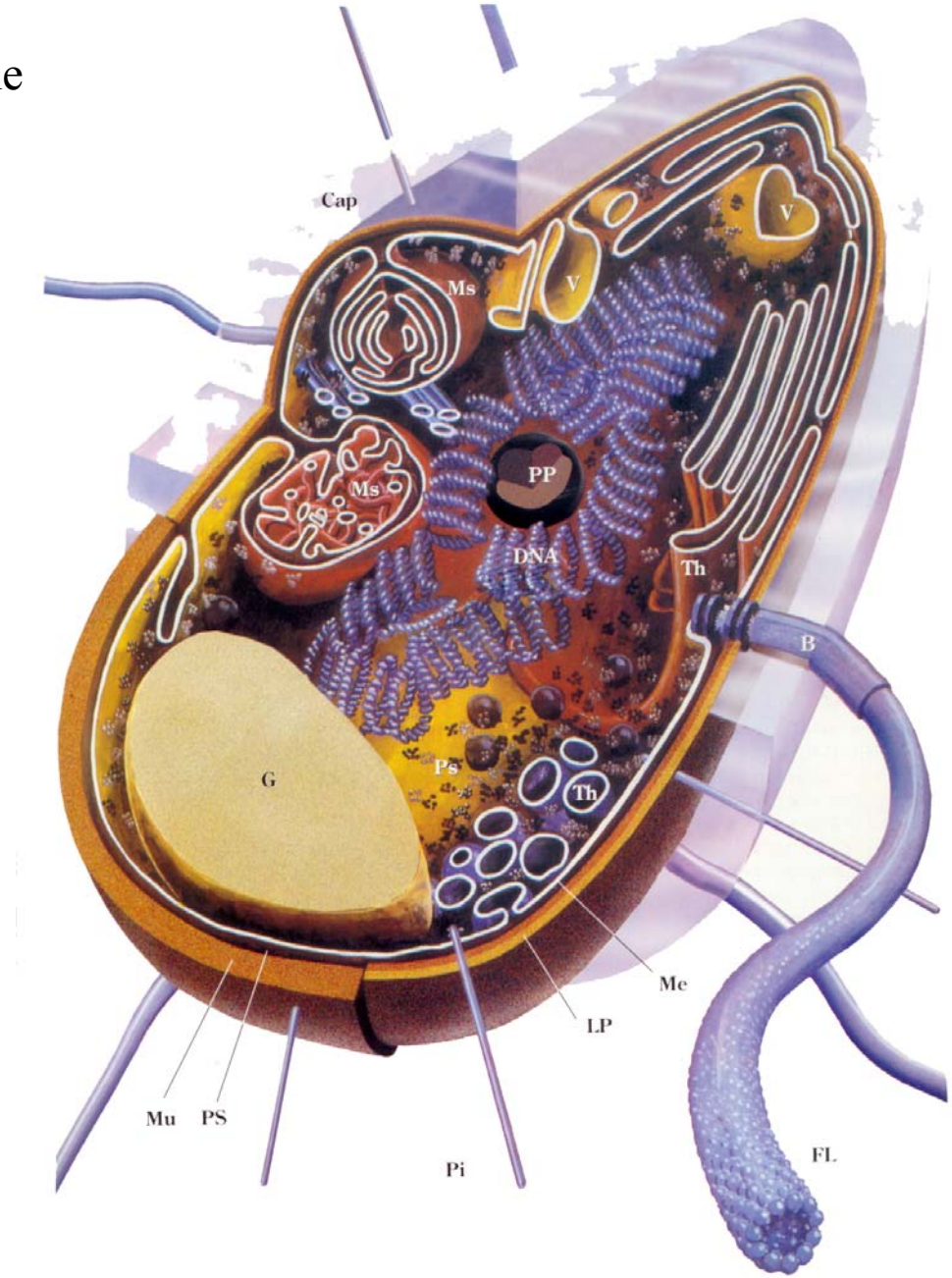
The citric acid or Krebs cycle (enlarged from previous slide).



The bacterial cell as an example for the simplest form of autonomous life

The human body:

10^{14} cells = 10^{13} eukaryotic cells +
$\approx 9 \times 10^{13}$ bacterial (prokaryotic) cells,
and $\approx$ 200 eukaryotic cell types



The spatial structure of the bacterium *Escherichia coli*

1. The problems of quantitative biology
2. **Forward and inverse problems in reaction kinetics**
3. Regulation kinetics and bifurcation analysis
4. Reverse engineering of dynamical systems
5. How to upscale from small models to cells?

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

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

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

Initial conditions: $x(0)$

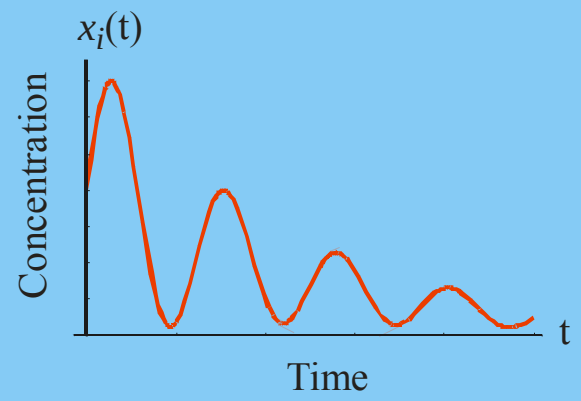
Boundary conditions:

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

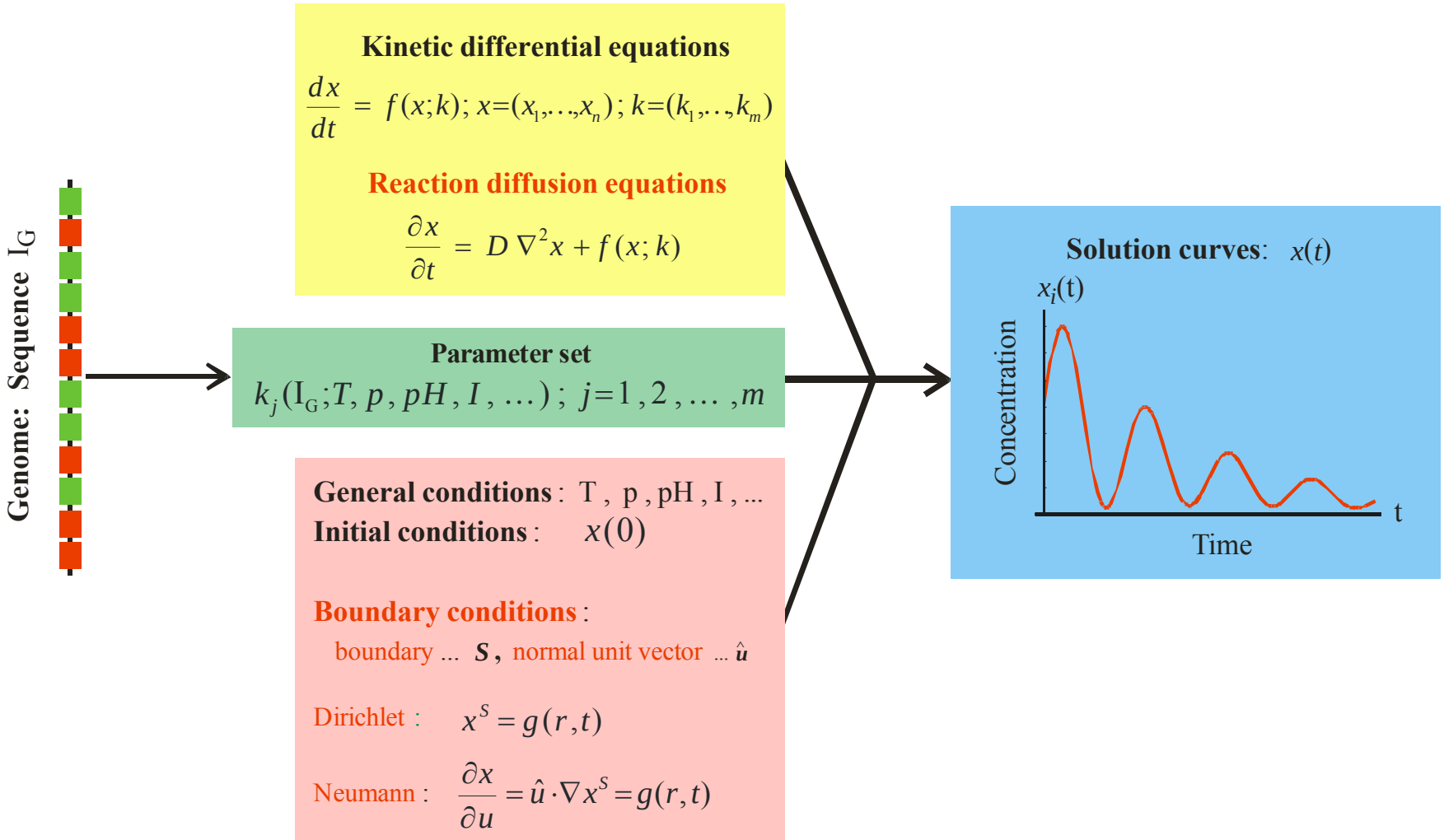
Dirichlet : $x^S = g(r,t)$

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

Solution curves: $x(t)$



The forward problem of chemical reaction kinetics (Level I)



The forward problem of biochemical reaction kinetics (Level I)

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 :

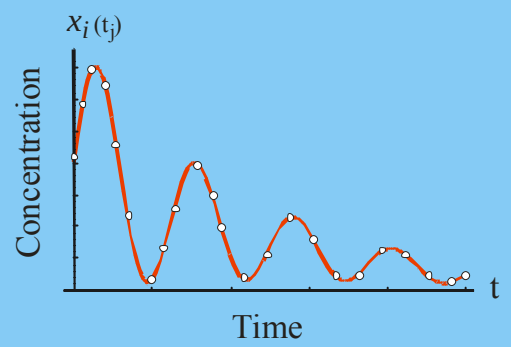
boundary ... S, normal unit vector... $\hat{u}$

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

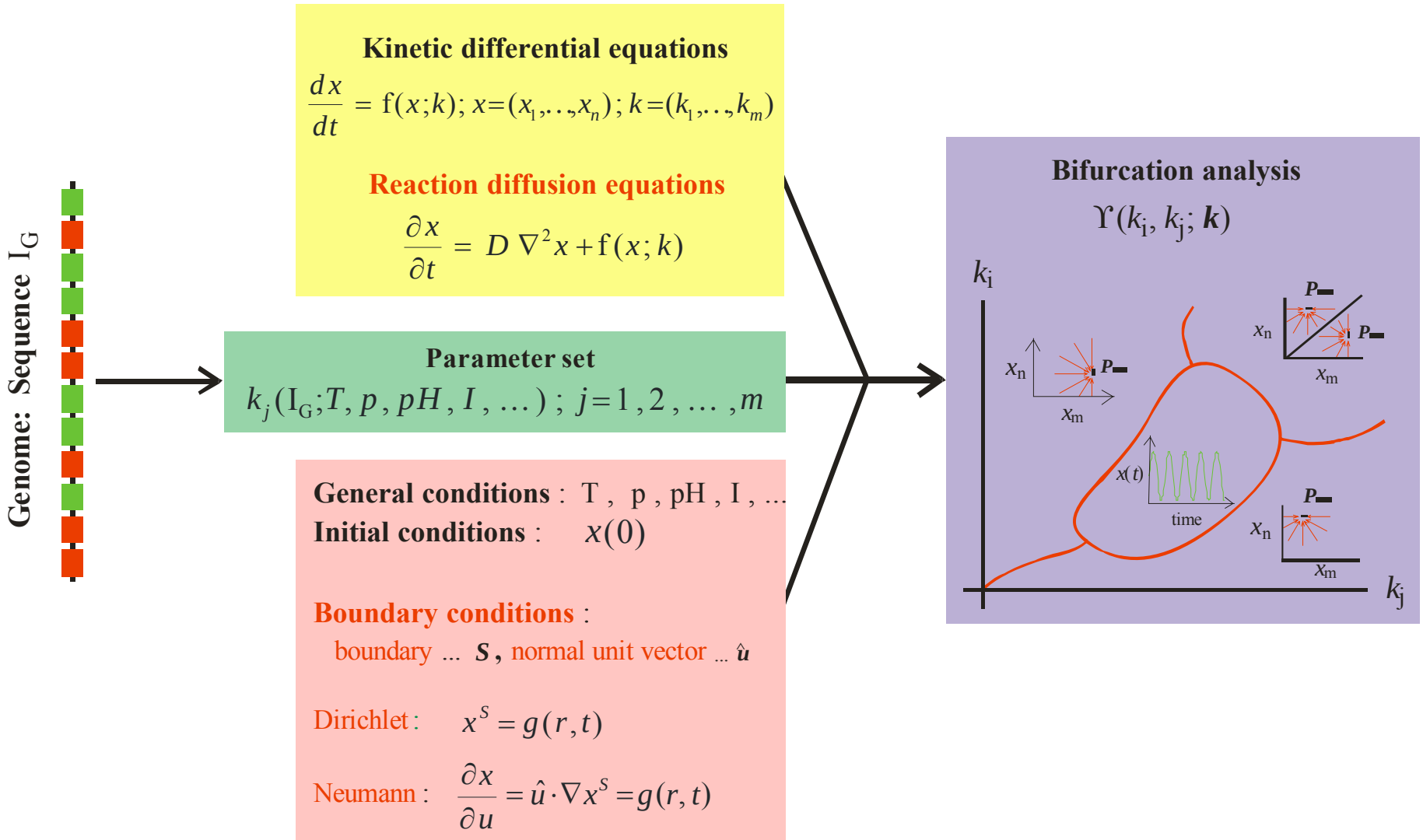
Neumann : $\frac{\partial x}{\partial u} = \hat{u} \cdot \nabla x^S = g(r,t)$

Data from measurements

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



The inverse problem of biochemical reaction kinetics (Level I)



The forward problem of bifurcation analysis (Level II)

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:

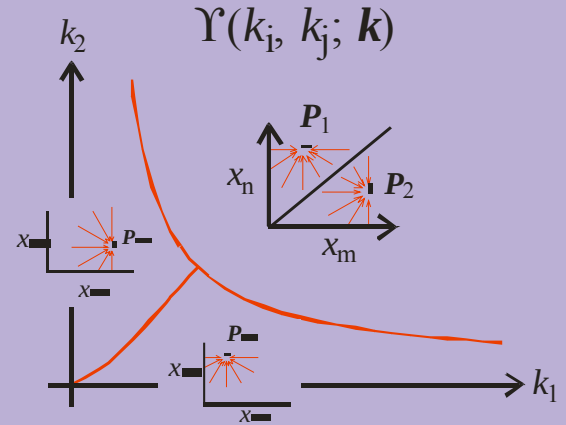
boundary ... $\boldsymbol{S}$, normal unit vector... $\hat{\boldsymbol{u}}$

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

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

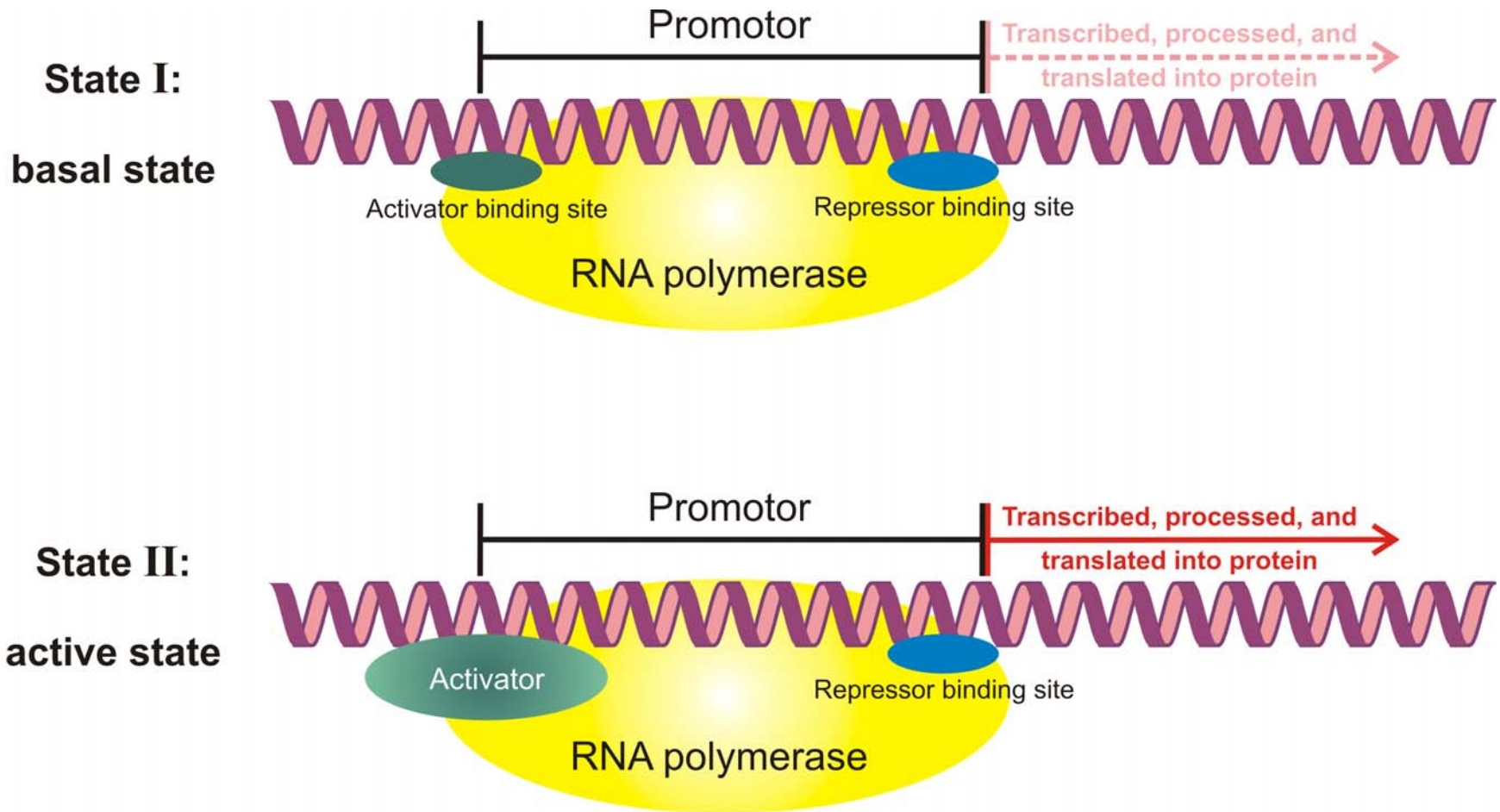
Bifurcation pattern

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



The inverse problem of bifurcation analysis (Level II)

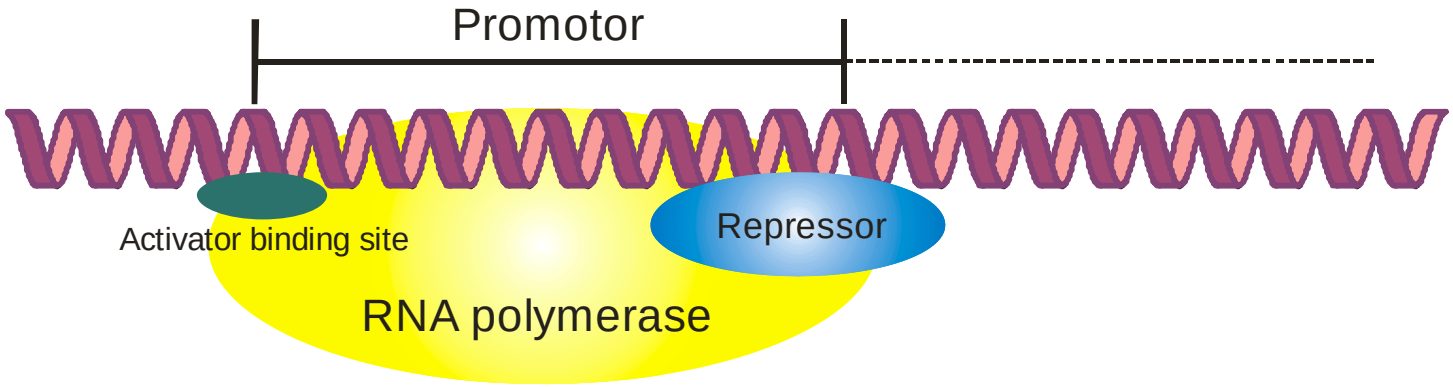
1. The problems of quantitative biology
2. Forward and inverse problems in reaction kinetics
3. **Regulation kinetics and bifurcation analysis**
4. Reverse engineering of dynamical systems
5. How to upscale from small models to cells?



Active states of gene regulation

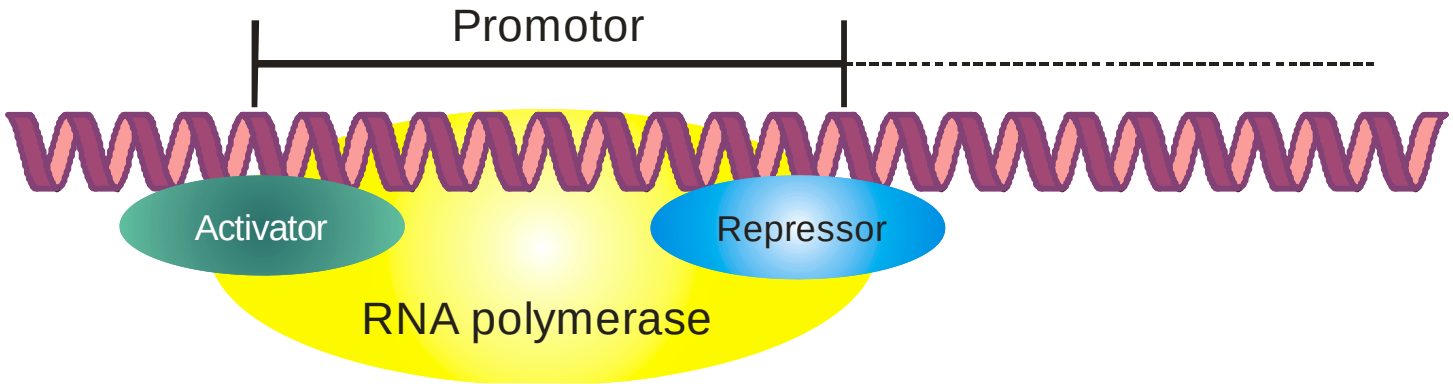
State III:

inactive state



State III:

inactive state



Inactive states of gene regulation

Available online at www.sciencedirect.com
ScienceDirect
Journal of Theoretical Biology 246 (2007) 395–419
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

Dynamic patterns of gene regulation I: Simple two-gene systems

Stefanie Widder[a], Josef Schicho[b], Peter Schuster[a,c,*]

[a]*Institut für Theoretische Chemie der Universität Wien, Währingerstraße 17, A-1090 Wien, Austria*
[b]*RICAM—Johann Radon Institute for Computational and Applied Mathematics of the Austrian Academy of Sciences, Altenbergerstraße 69, A-4040 Linz, Austria*
[c]*Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA*

Received 24 February 2006; received in revised form 7 January 2007; accepted 8 January 2007
Available online 16 January 2007

Abstract

Regulation of gene activities is studied by means of computer assisted mathematical analysis of ordinary differential equations (ODEs) derived from binding equilibria and chemical reaction kinetics. Here, we present results on cross-regulation of two genes through activator and/or repressor binding. Arbitrary (differentiable) binding function can be used but systematic investigations are presented for gene–regulator complexes with integer valued Hill coefficients up to $n = 4$. The dynamics of gene regulation is derived from bifurcation patterns of the underlying systems of kinetic ODEs. In particular, we present analytical expressions for the parameter values at which one-dimensional (transcritical, saddle-node or pitchfork) and/or two-dimensional (Hopf) bifurcations occur. A classification of regulatory states is introduced, which makes use of the sign of a 'regulatory determinant' D (being the determinant of the block in the Jacobian matrix that contains the derivatives of the regulator binding functions): (i) systems with $D<0$, observed, for example, if both proteins are activators or repressors, to give rise to one-dimensional bifurcations only and lead to bistability for $n \geqslant 2$ and (ii) systems with $D>0$, found for combinations of activation and repression, sustain a Hopf bifurcation and undamped oscillations for $n>2$. The influence of basal transcription activity on the bifurcation patterns is described. Binding of multiple subunits can lead to richer dynamics than pure activation or repression states if intermediates between the unbound state and the fully saturated DNA initiate transcription. Then, the regulatory determinant D can adopt both signs, plus and minus.

Keywords: Basal transcription; Bifurcation analysis; Cooperative binding; Gene regulation; Hill coefficient; Hopf bifurcation

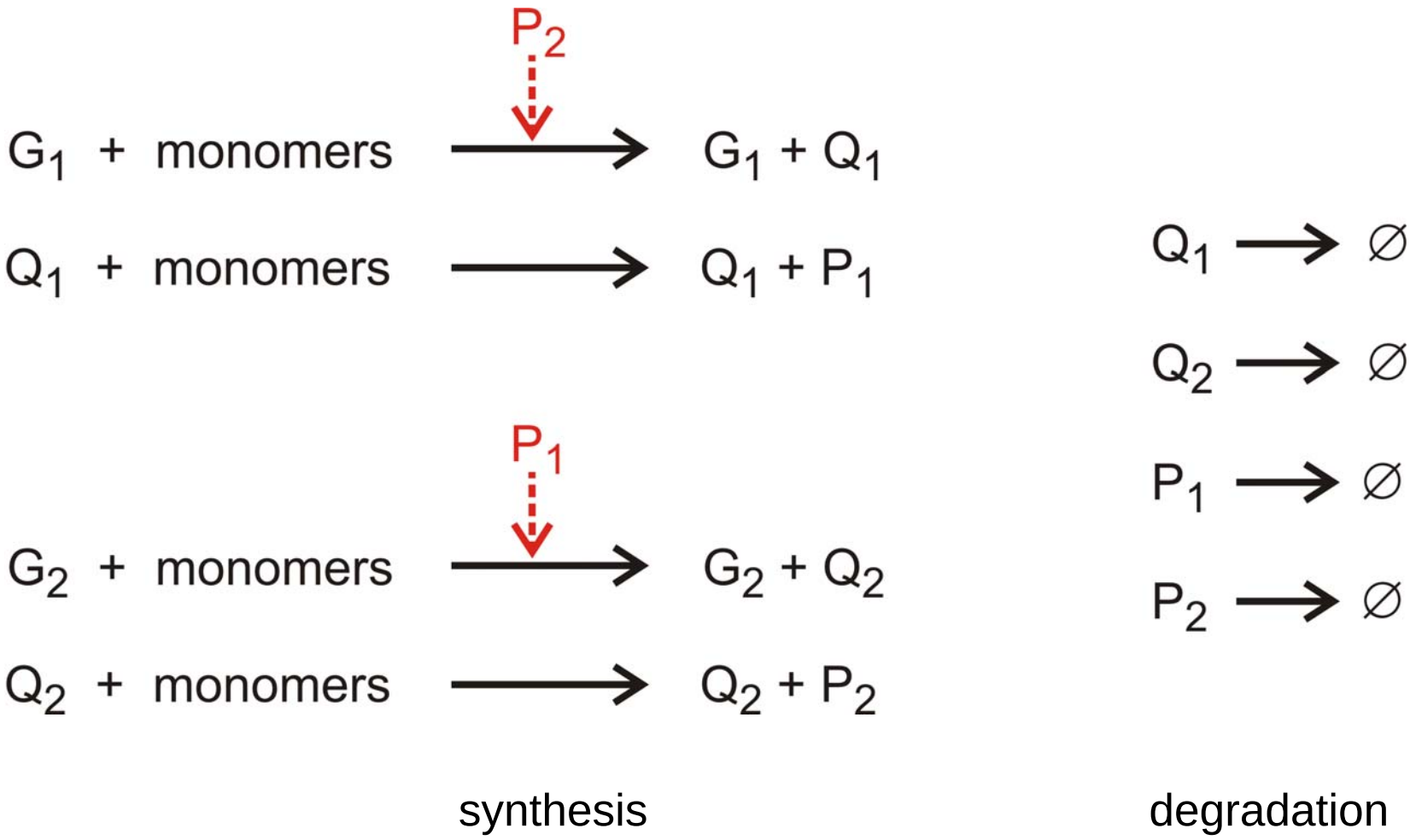
1. Introduction

Theoretical work on gene regulation goes back to the 1960s (Monod et al., 1963) soon after the first repressor protein had been discovered (Jacob and Monod, 1961). A little later the first paper on oscillatory states in gene regulation was published (Goodwin, 1965). The interest in gene regulation and its mathematical analysis never ceased (Tiwari et al., 1974; Tyson and Othmer, 1978; Smith, 1987) and saw a great variety of different attempts to design models of genetic regulatory networks that can be used in systems biology for computer simulation of *gen*(etic and met)*abolic* networks.[1] Most models in the literature aim at a minimalist dynamic description which, nevertheless, tries to account for the basic regulatory functions of large networks in the cell in order to provide a better understanding of cellular dynamics. A classic in general regulatory dynamics is the monograph by Thomas and D'Ari (1990). The currently used mathematical methods comprise application of Boolean logic (Thomas and Kaufman, 2001b; Savageau, 2001; Albert and Othmer, 2003), stochastic processes (Hume, 2000) and deterministic dynamic models, examples are Cherry and Adler (2000), Bindschadler and Sneyd (2001) and Kobayashi et al. (2003) and the recent elegant analysis of bistability (Craciun et al.,

*Corresponding author. Institut für Theoretische Chemie der Universität Wien, Währingerstraße 17, A-1090 Wien, Austria.
Tel.: +43 1 4277 52743; fax: +43 1 4277 52793.
E-mail address: pks@tbi.univie.ac.at (P. Schuster).

[1]Discussion and analysis of combined genetic and metabolic networks has become so frequent and intense that we suggest to use a separate term, *genabolic networks*, for this class of complex dynamical systems.

0022-5193/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2007.01.004

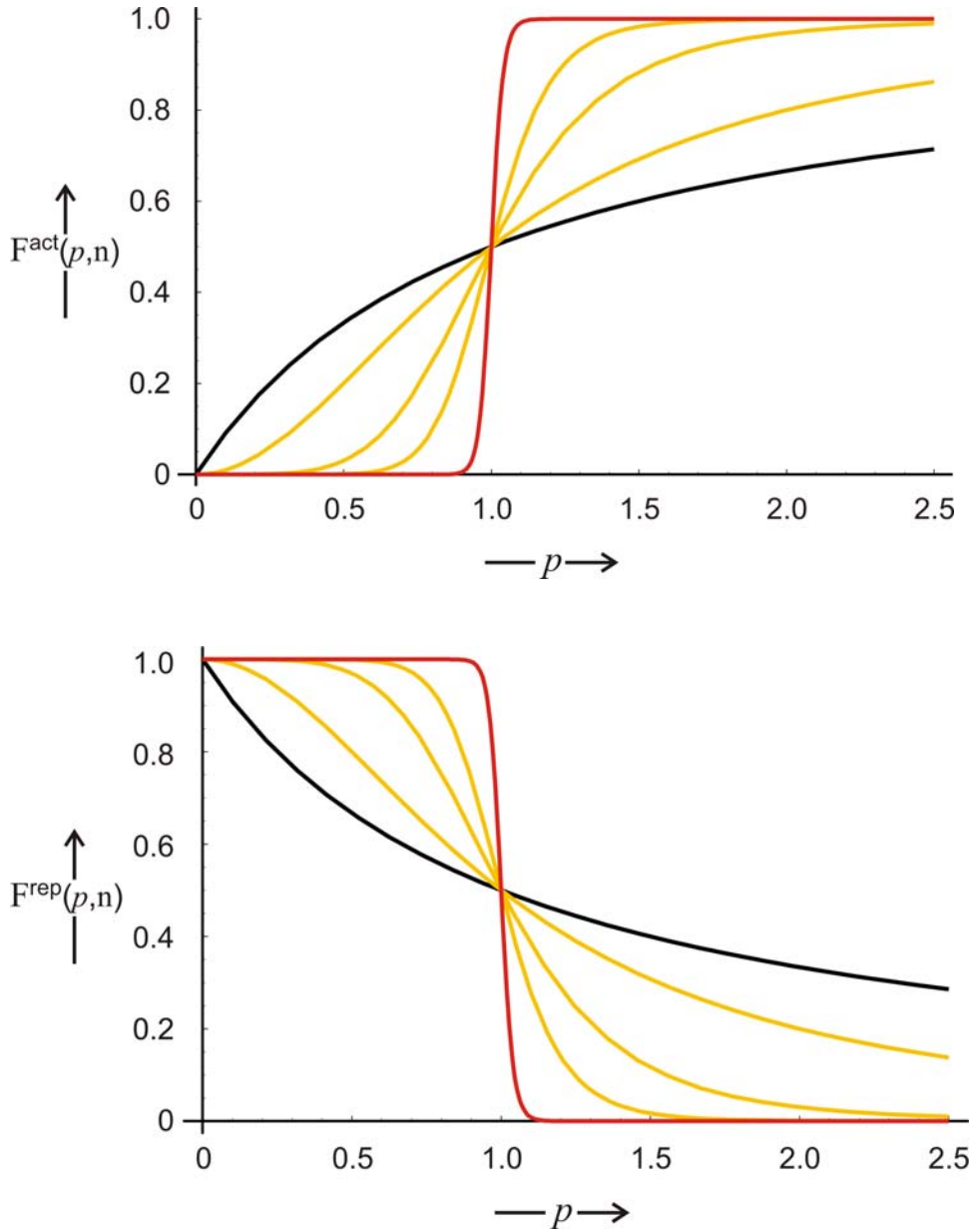


Cross-regulation of two genes

$$\text{Activation}: \quad F_i(p_j) = \frac{p_j^{\mathrm{n}}}{K + p_j^{\mathrm{n}}}$$

$$\text{Repression}: \quad F_i(p_j) = \frac{K}{K + p_j^{\mathrm{n}}}$$

$$i, j = 1,2$$



Gene regulatory binding functions

$[\mathrm{G}_1]=[\mathrm{G}_2]=g_0=\text{const.}$

$[\mathrm{Q}_1]=q_1,[\mathrm{Q}_2]=q_2,$

$[\mathrm{P}_1]=p_1,[\mathrm{P}_2]=p_2$

$$\text{Activation}: \quad F_i(p_j)=\frac{p_j^{\mathrm{n}}}{K+p_j^{\mathrm{n}}}$$

$$\text{Repression}: \quad F_i(p_j)=\frac{K}{K+p_j^{\mathrm{n}}}$$

$$i,j=1,2$$

$$\frac{dq_1}{dt}=k_1^{\mathrm{Q}}F_1(p_2)-d_1^{\mathrm{Q}}q_1$$

$$\frac{dq_2}{dt}=k_2^{\mathrm{Q}}F_2(p_1)-d_2^{\mathrm{Q}}q_2$$

$$\frac{dp_1}{dt}=k_1^{\mathrm{P}}q_1-d_2^{\mathrm{P}}p_1$$

$$\frac{dp_2}{dt}=k_2^{\mathrm{P}}q_2-d_2^{\mathrm{P}}p_2$$

Stationary points: $\bar{p}_1-\vartheta_1F_1(\vartheta_2F_2(\bar{p}_1))=0,\ \bar{p}_2=\vartheta_2F_2(\bar{p}_1)$

$$\vartheta_1=\frac{k_1^{\mathrm{Q}}k_1^{\mathrm{P}}}{d_1^{\mathrm{Q}}d_1^{\mathrm{P}}},\ \vartheta_2=\frac{k_2^{\mathrm{Q}}k_2^{\mathrm{P}}}{d_2^{\mathrm{Q}}d_2^{\mathrm{P}}}$$

Qualitative analysis of **cross-regulation** of two genes: Stationary points

$$\mathrm{A} = \left\{ a_{ij} = \frac{\partial \dot{x}_i}{\partial x_j} \right\} = \begin{pmatrix} -d_1^Q & 0 & k_1^Q \frac{\partial F_1}{\partial p_1} & k_1^Q \frac{\partial F_1}{\partial p_2} \\ 0 & -d_2^Q & k_2^Q \frac{\partial F_2}{\partial p_1} & k_2^Q \frac{\partial F_2}{\partial p_2} \\ k_1^P & 0 & -d_1^P & 0 \\ 0 & k_2^P & 0 & -d_2^P \end{pmatrix}$$

$$\text{Cross regulation}: \quad \frac{\partial F_1}{\partial p_1} = \frac{\partial F_2}{\partial p_2} = 0$$

$$\left|\mathrm{A} - \varepsilon \mathrm{I}\right| = \begin{vmatrix} -d_1^Q - \varepsilon & 0 & 0 & k_1^Q \frac{\partial F_1}{\partial p_2} \\ 0 & -d_2^Q - \varepsilon & k_2^Q \frac{\partial F_2}{\partial p_1} & 0 \\ k_1^P & 0 & -d_1^P - \varepsilon & 0 \\ 0 & k_2^P & 0 & -d_2^P - \varepsilon \end{vmatrix} = \begin{vmatrix} Q_D & Q_K \\ P_D & P_K \end{vmatrix}$$

Qualitative analysis of **cross-regulation** of two genes: Jacobian matrix

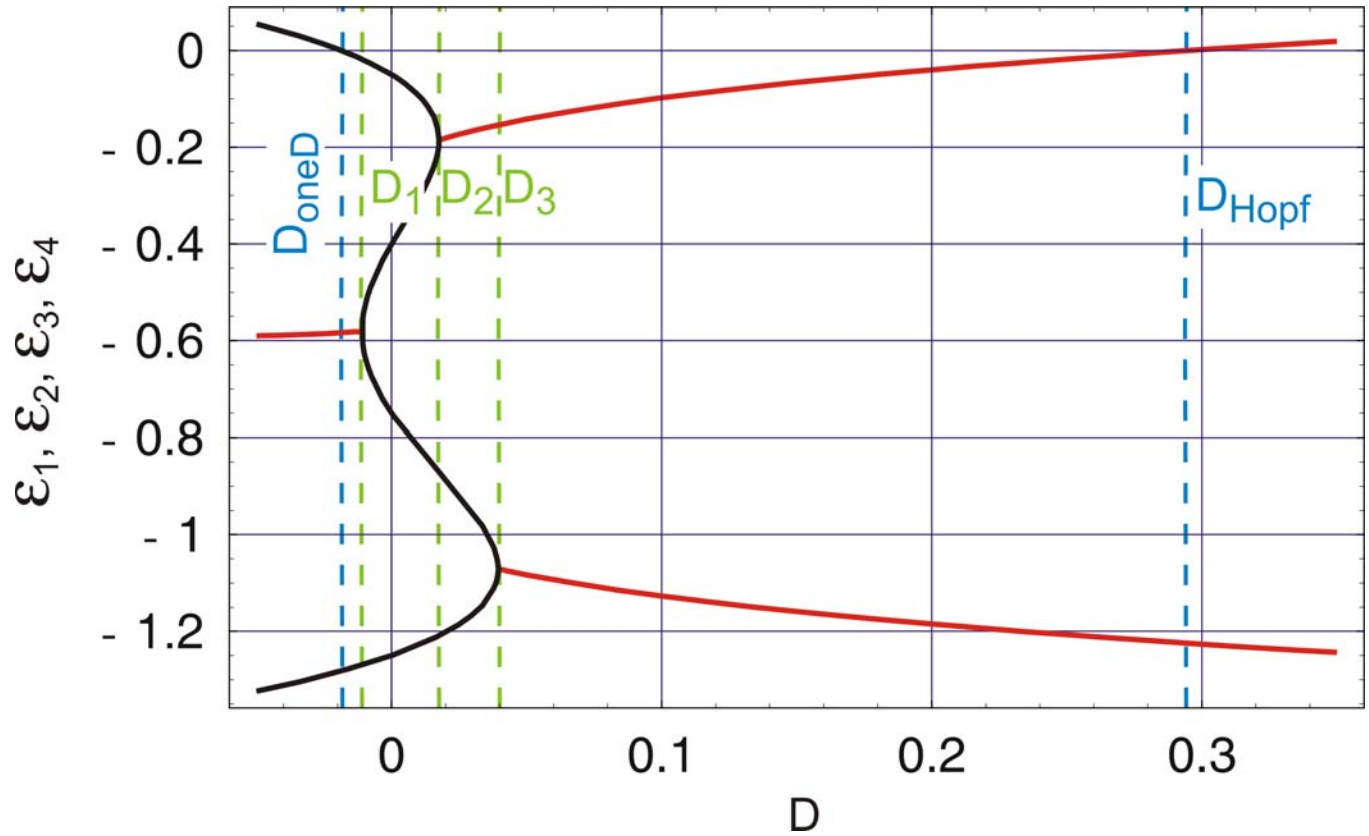
$$Q_D \cdot P_K = P_K \cdot Q_D \quad \text{and hence} \quad \begin{vmatrix} \mathrm{Q_D} & \mathrm{Q_K} \\ P_K & P_D \end{vmatrix} = \left| Q_D \cdot P_D - Q_K \cdot P_K \right|$$

$$\left| \mathrm{Q}_D \cdot \mathrm{P}_D - \mathrm{Q}_K \cdot \mathrm{P}_K \right| = \begin{vmatrix} \left(-d_1^Q - \varepsilon\right)\left(-d_1^P - \varepsilon\right) & -k_1^Q \dfrac{\partial F_1}{\partial p_2} k_1^P \\ -k_2^Q \dfrac{\partial F_2}{\partial p_1} k_2^P & \left(-d_2^Q - \varepsilon\right)\left(-d_2^P - \varepsilon\right) \end{vmatrix} =$$

$$= \left(-d_1^Q - \varepsilon\right)\left(-d_1^P - \varepsilon\right)\left(-d_2^Q - \varepsilon\right)\left(-d_2^P - \varepsilon\right) - k_1^Q k_2^Q k_1^P k_2^P \frac{\partial F_1}{\partial p_2}\frac{\partial F_2}{\partial p_1} = 0$$

$$(\varepsilon + d_1^{\mathrm{Q}})(\varepsilon + d_2^{\mathrm{Q}})(\varepsilon + d_1^{\mathrm{P}})(\varepsilon + d_2^{\mathrm{P}}) + D = 0$$

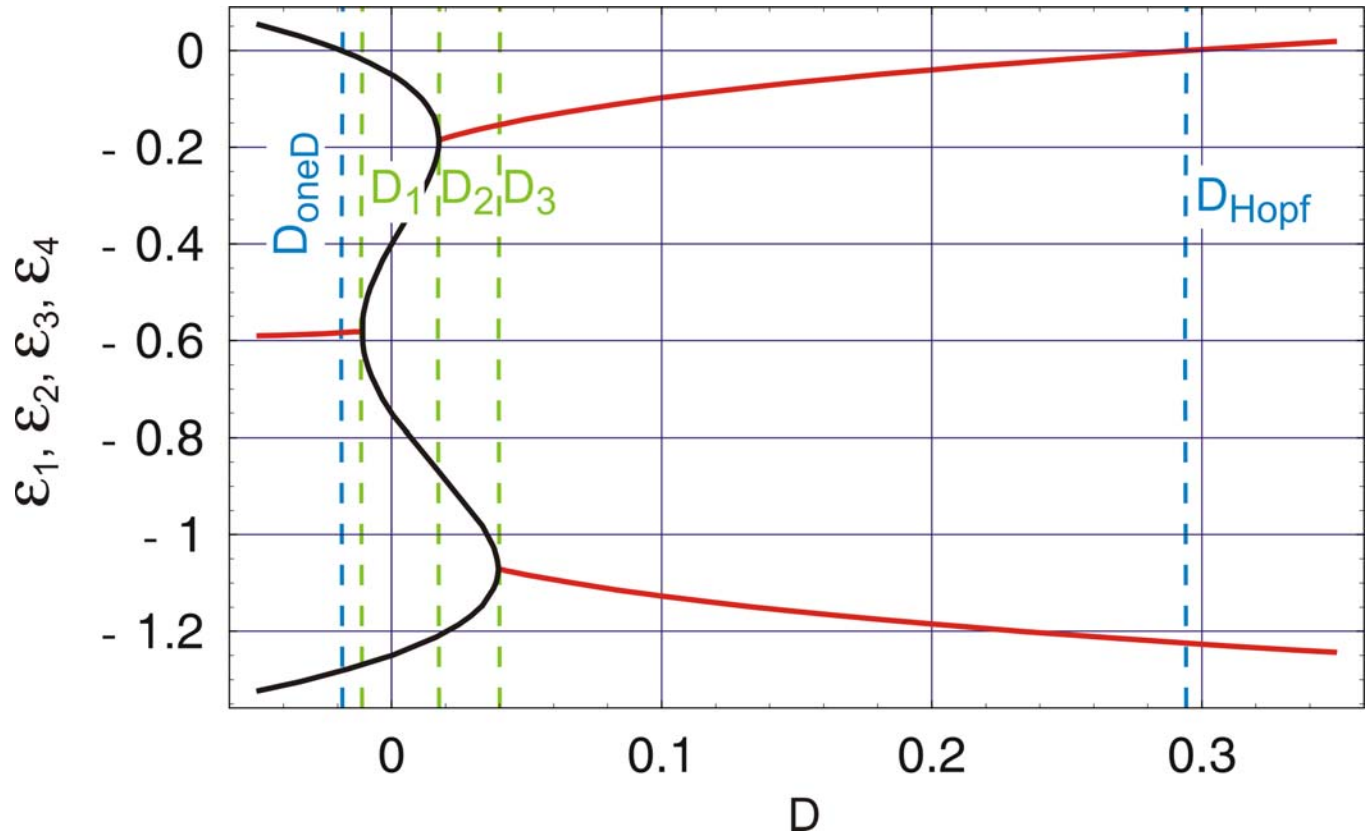
$$D = -k_1^{\mathrm{Q}} k_2^{\mathrm{Q}} k_1^{\mathrm{P}} k_2^{\mathrm{P}} \frac{\partial F_1}{\partial x_2}\frac{\partial F_2}{\partial x_1}$$



$$(\varepsilon + d_1^{\mathrm{Q}})(\varepsilon + d_2^{\mathrm{Q}})(\varepsilon + d_1^{\mathrm{P}})(\varepsilon + d_2^{\mathrm{P}}) + D = 0$$

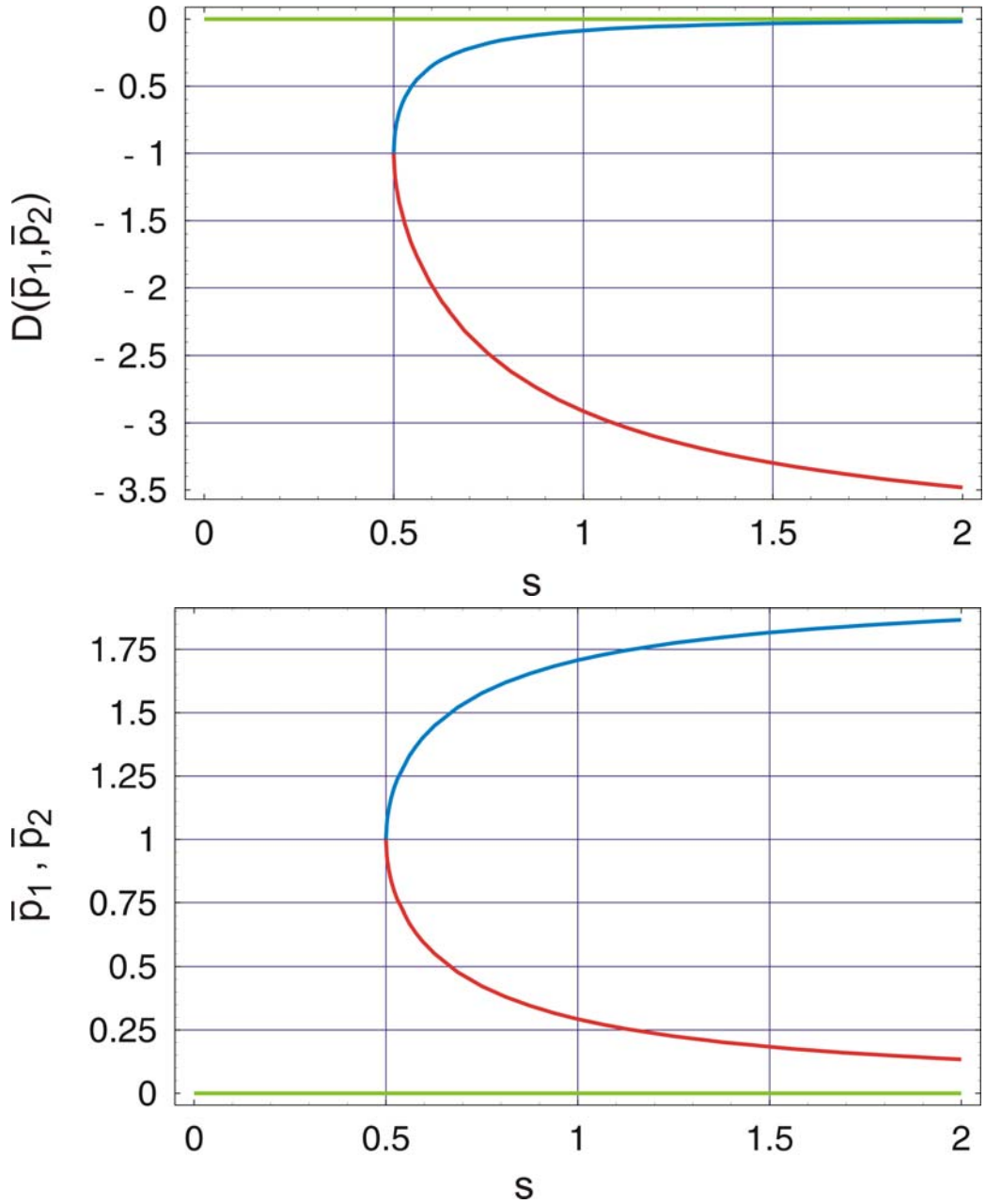
Eigenvalues of the Jacobian of the cross-regulatory two gene system

$$D = -k_1^{\mathrm{Q}} k_2^{\mathrm{Q}} k_1^{\mathrm{P}} k_2^{\mathrm{P}} \frac{\partial F_1}{\partial x_2} \frac{\partial F_2}{\partial x_1}$$

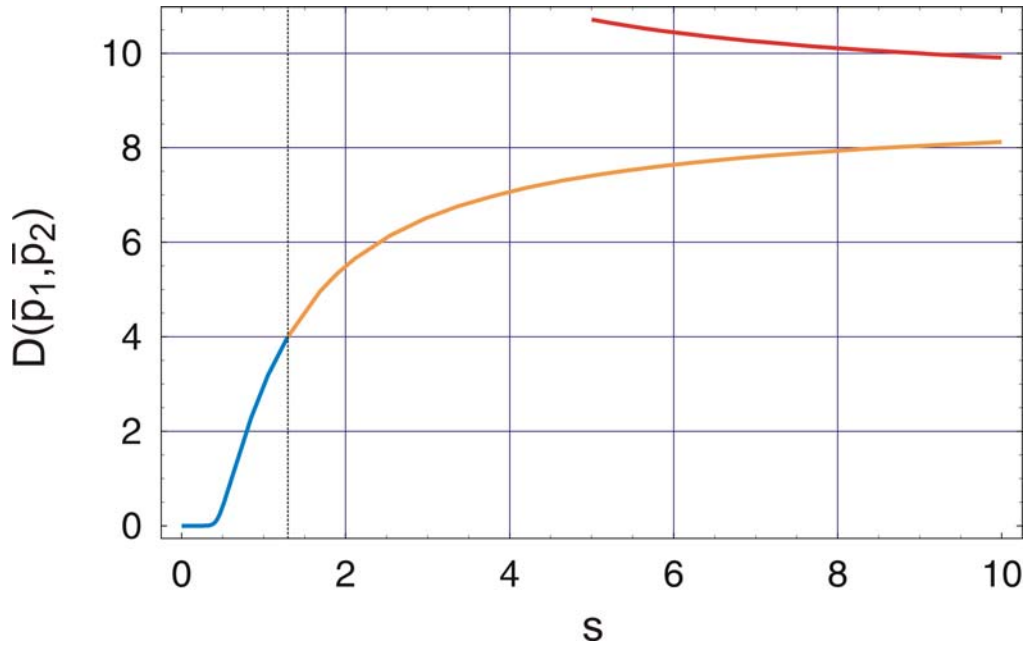


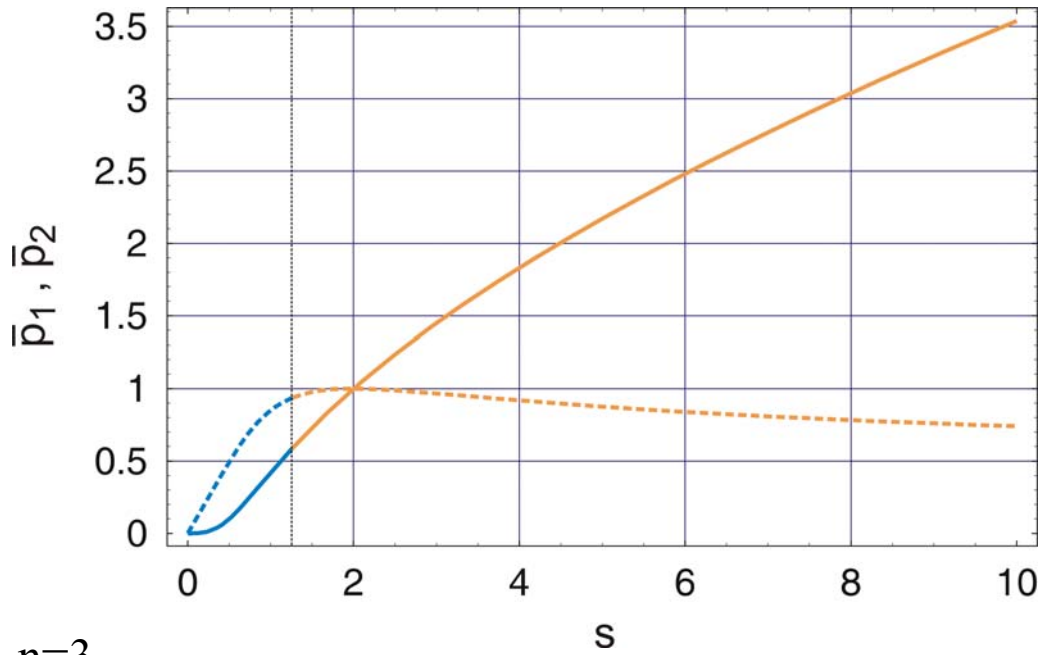
$$D_{\mathrm{OneD}} = -d_1^{\mathrm{Q}} d_2^{\mathrm{Q}} d_1^{\mathrm{P}} d_2^{\mathrm{P}}$$

$$D_{\mathrm{Hopf}} = \frac{(d_1^{\mathrm{Q}}+d_2^{\mathrm{Q}})(d_1^{\mathrm{Q}}+d_1^{\mathrm{P}})(d_1^{\mathrm{Q}}+d_2^{\mathrm{P}})(d_2^{\mathrm{Q}}+d_1^{\mathrm{P}})(d_2^{\mathrm{Q}}+d_2^{\mathrm{P}})(d_1^{\mathrm{P}}+d_2^{\mathrm{P}})}{(d_1^{\mathrm{Q}}+d_2^{\mathrm{Q}}+d_1^{\mathrm{P}}+d_2^{\mathrm{P}})^2}$$

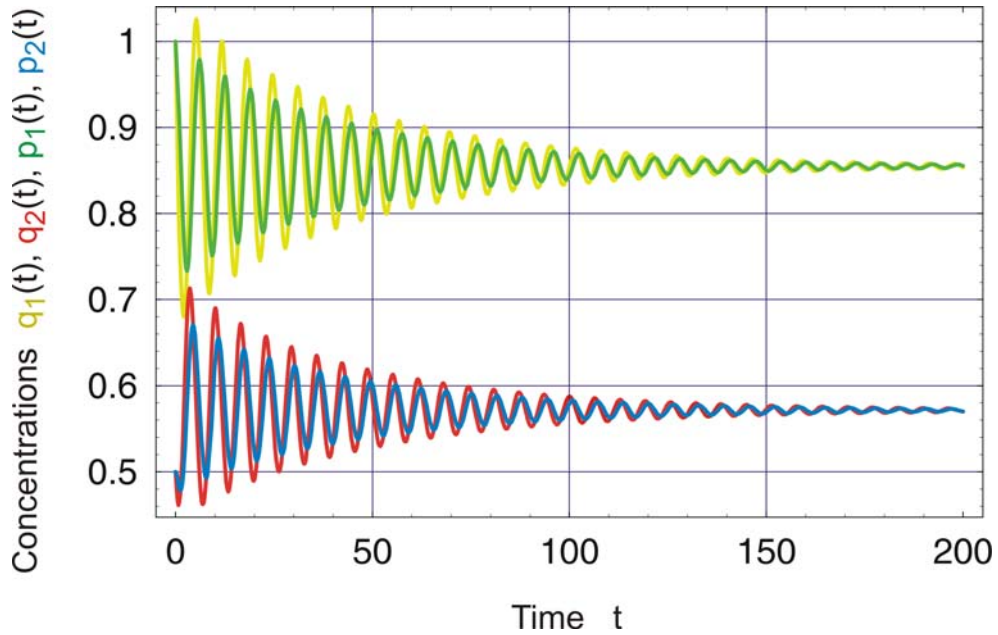


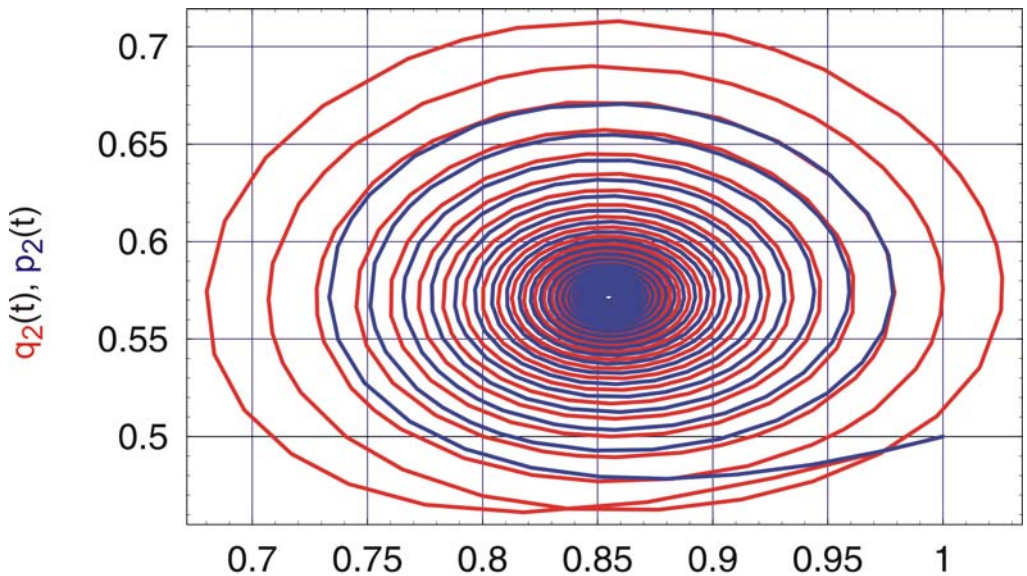
Regulatory dynamics at $D \leq 0$, act.-act., n=2



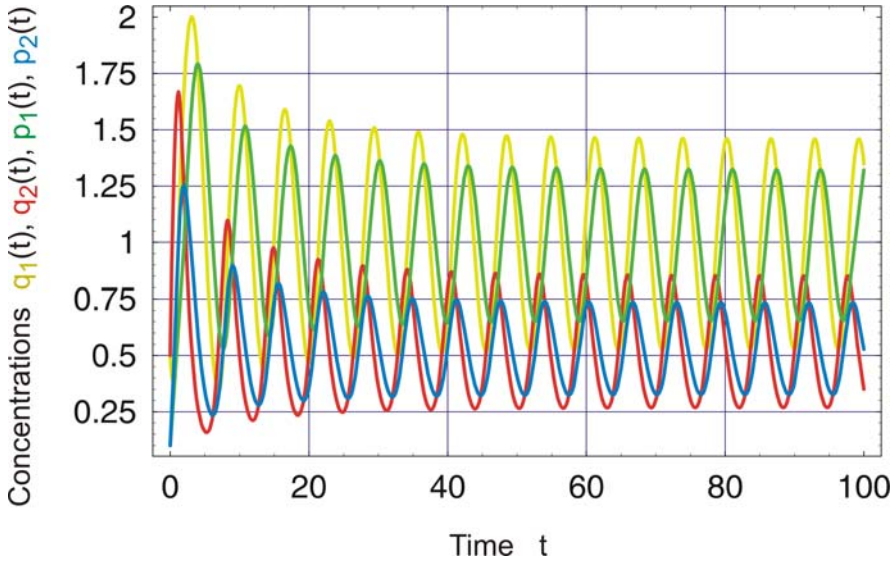


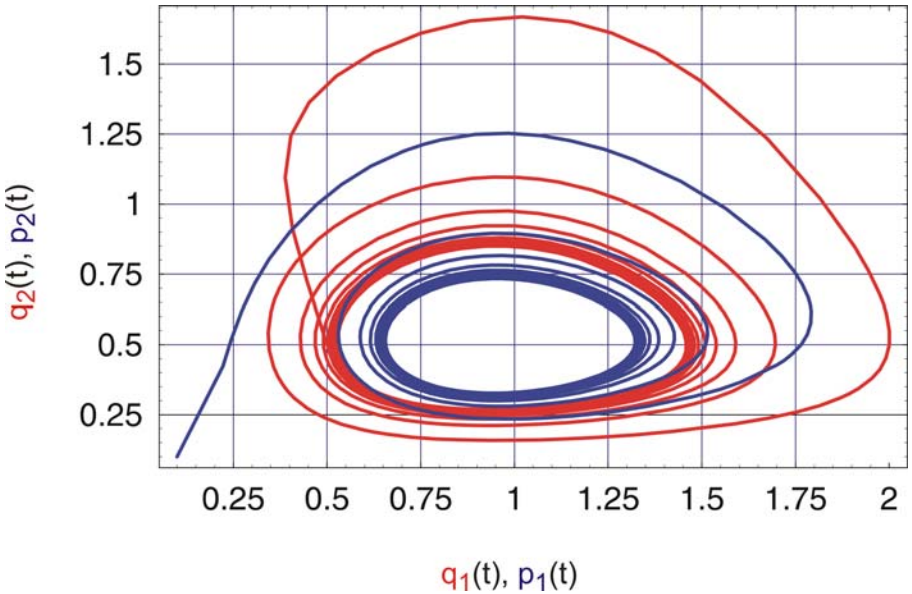
Regulatory dynamics at $D \geq 0$, act.-rep., n=3

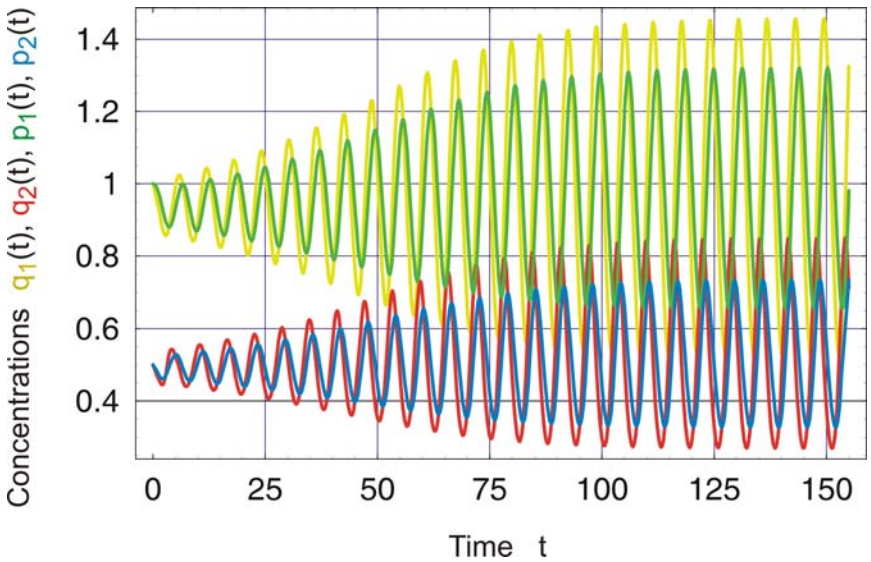


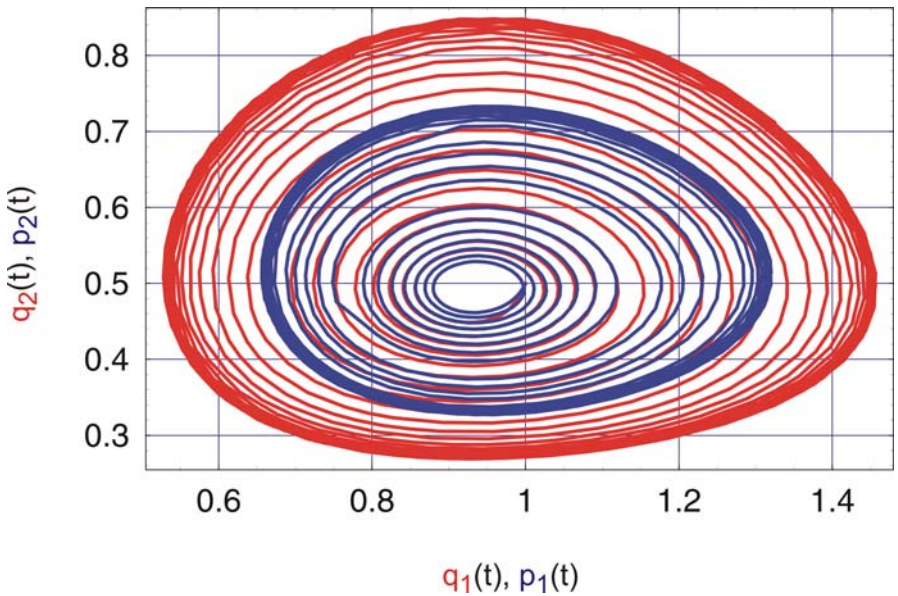


Regulatory dynamics at $D < D_{Hopf}$, act.-repr., n=3

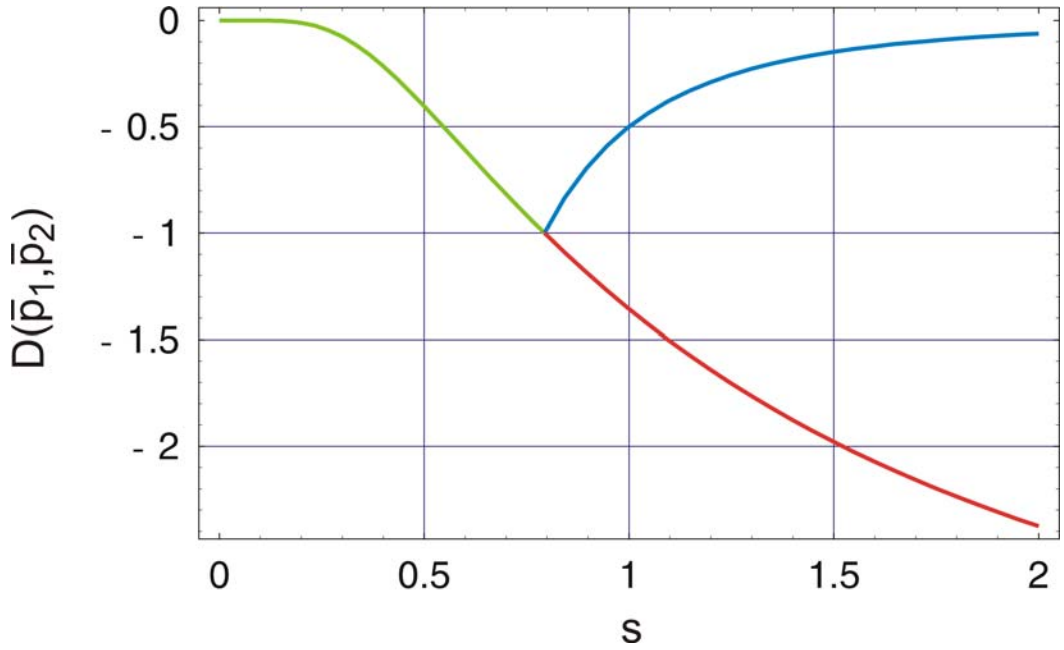


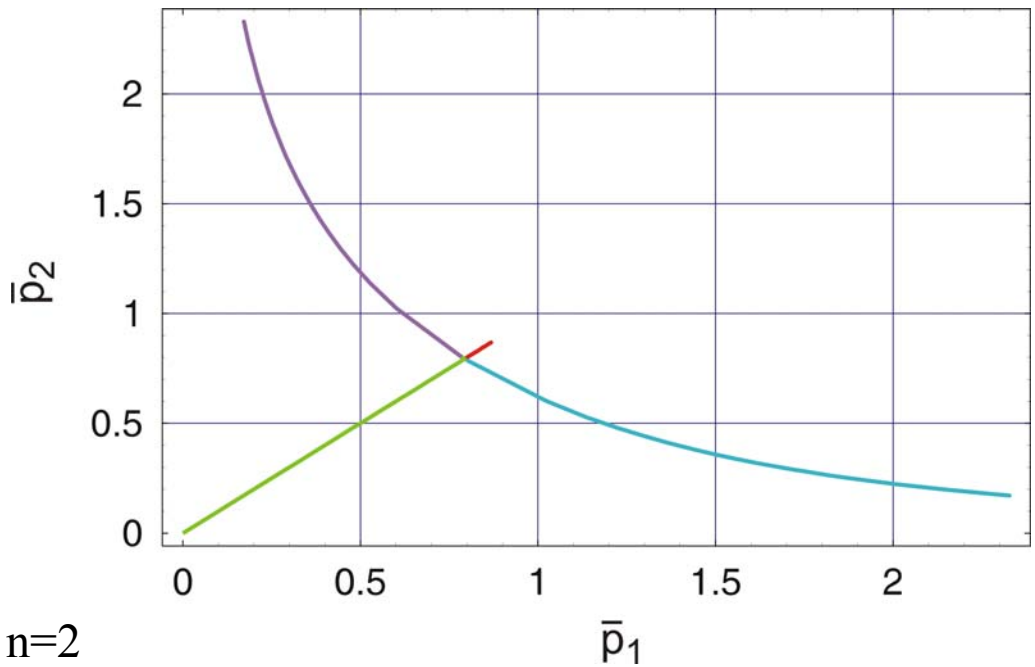






Regulatory dynamics at $D > D_{Hopf}$, act.-repr., n=3





Regulatory dynamics at $D \leq 0$, rep.-rep., n=2

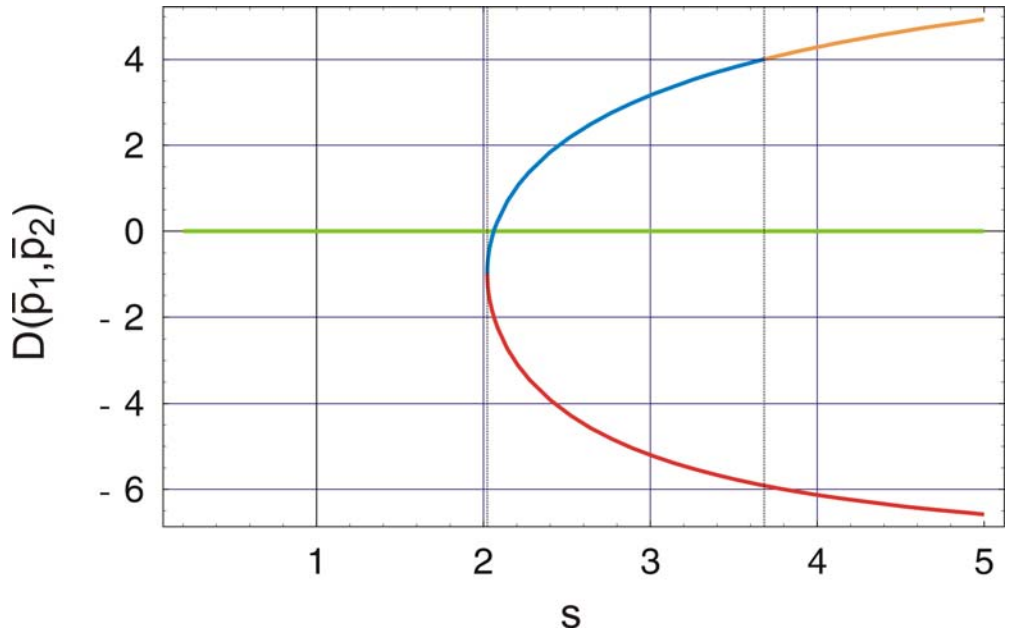
Hill coefficient: n	Act.-Act.	Act.-Rep.	Rep.-Rep.
1	S , E	S	S
2	E , B(E,P)	S	S , B(P_1,P_2)
3	E , B(E,P)	S , O	S , B(P_1,P_2)
4	E , B(E,P)	S , O	S , B(P_1,P_2)

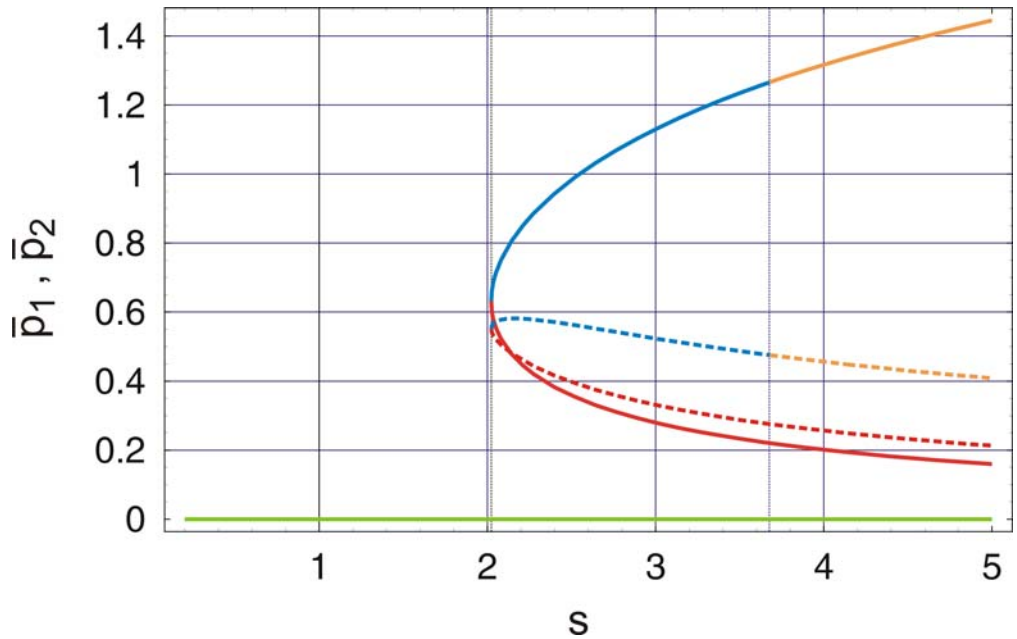
$$\text{Activation}: \quad F_i(p_j) = \frac{p_j^{\mathrm{n}}}{K + p_j^{\mathrm{n}}}$$

$$\text{Repression}: \quad F_i(p_j) = \frac{K}{K + p_j^{\mathrm{n}}}$$

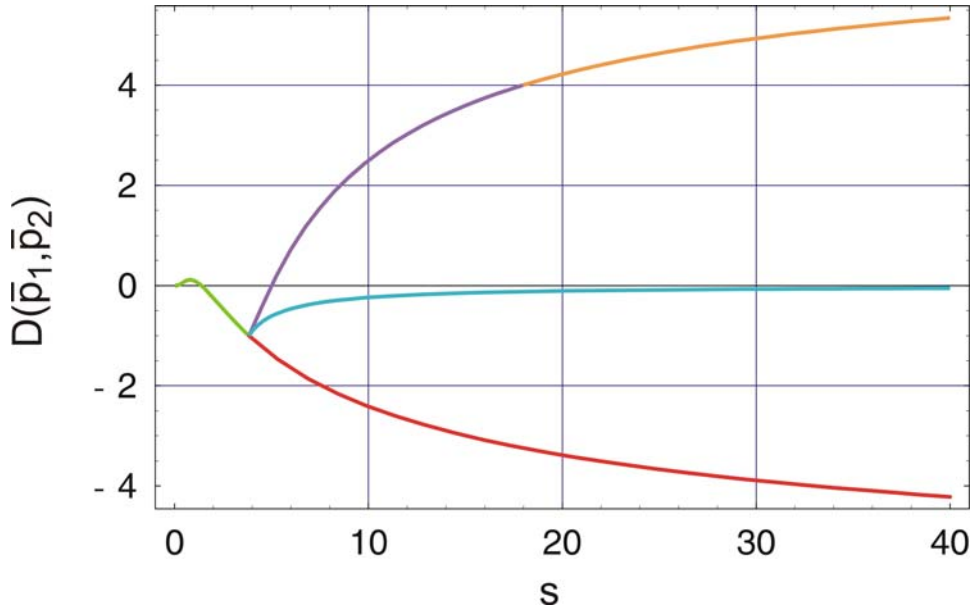
$$\text{Intermediate}: \quad F_i(p_j) = \frac{p_j^{\mathrm{m}}}{\kappa_1 + \kappa_2\, p_j + \kappa_3\, p_j^2 + \ldots + p_j^{\mathrm{n}}}$$

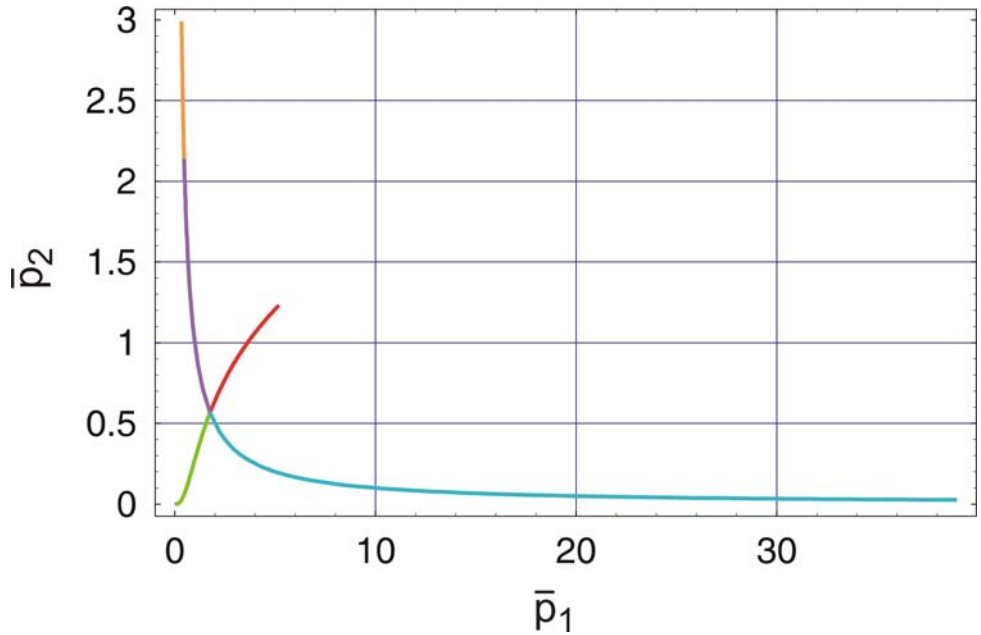
$$i, j = 1,2; \quad 1 \le m \le n-1$$





Regulatory dynamics, int.-act., m=2, n=4



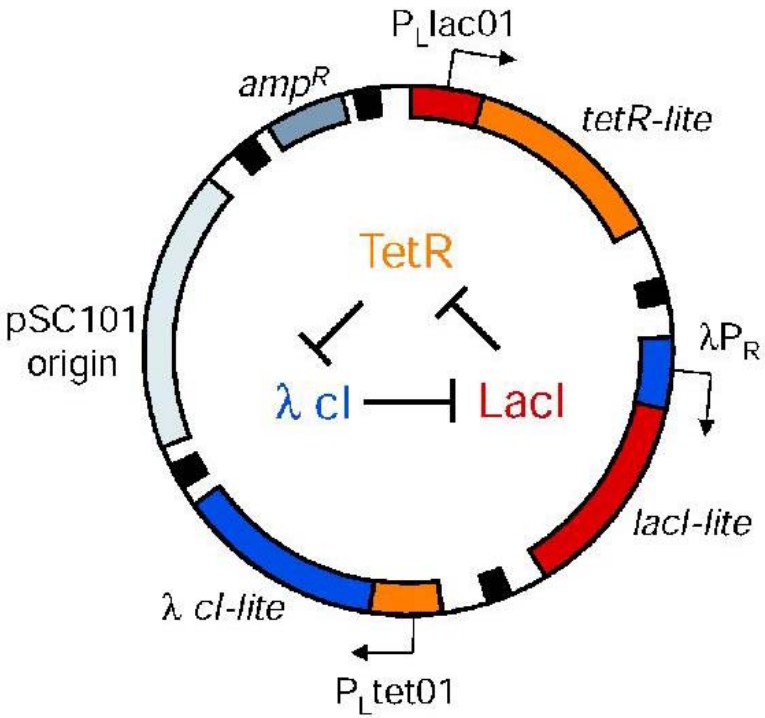


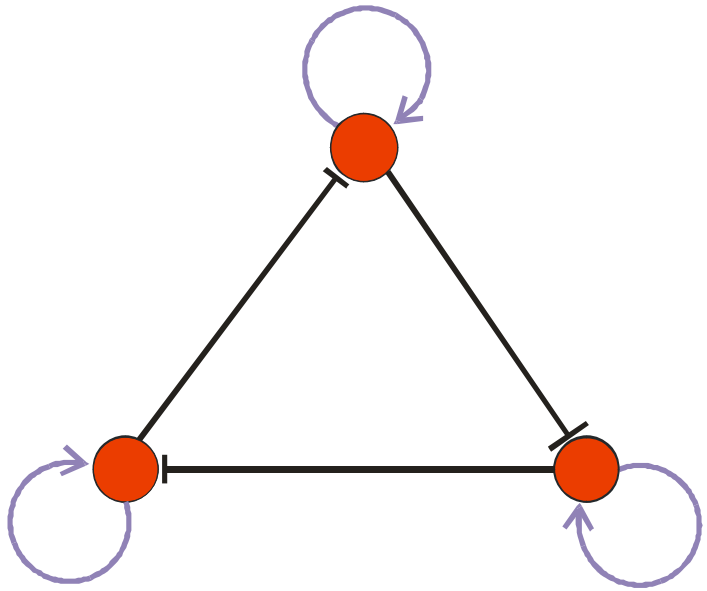
Regulatory dynamics, rep.-int., m=2, n=4

$$\left|\mathrm{Q}_d \cdot \mathrm{P}_d - \mathrm{Q}_k \cdot \mathrm{P}_k\right| = \begin{vmatrix} \left(-d_1^Q - \varepsilon\right)\left(-d_1^P - \varepsilon\right) & 0 & -k_1^P k_1^Q \dfrac{\partial F_1}{\partial p_3} \\ -k_2^P k_2^Q \dfrac{\partial F_2}{\partial p_1} & \left(-d_2^Q - \varepsilon\right)\left(-d_2^P - \varepsilon\right) & 0 \\ 0 & -k_3^P k_3^Q \dfrac{\partial F_3}{\partial p_2} & \left(-d_3^Q - \varepsilon\right)\left(-d_3^P - \varepsilon\right) \end{vmatrix}$$

$$D = -k_1^Q k_2^Q k_3^Q k_1^P k_2^P k_3^P \frac{\partial F_1}{\partial p_3}\frac{\partial F_2}{\partial p_1}\frac{\partial F_3}{\partial p_2}$$

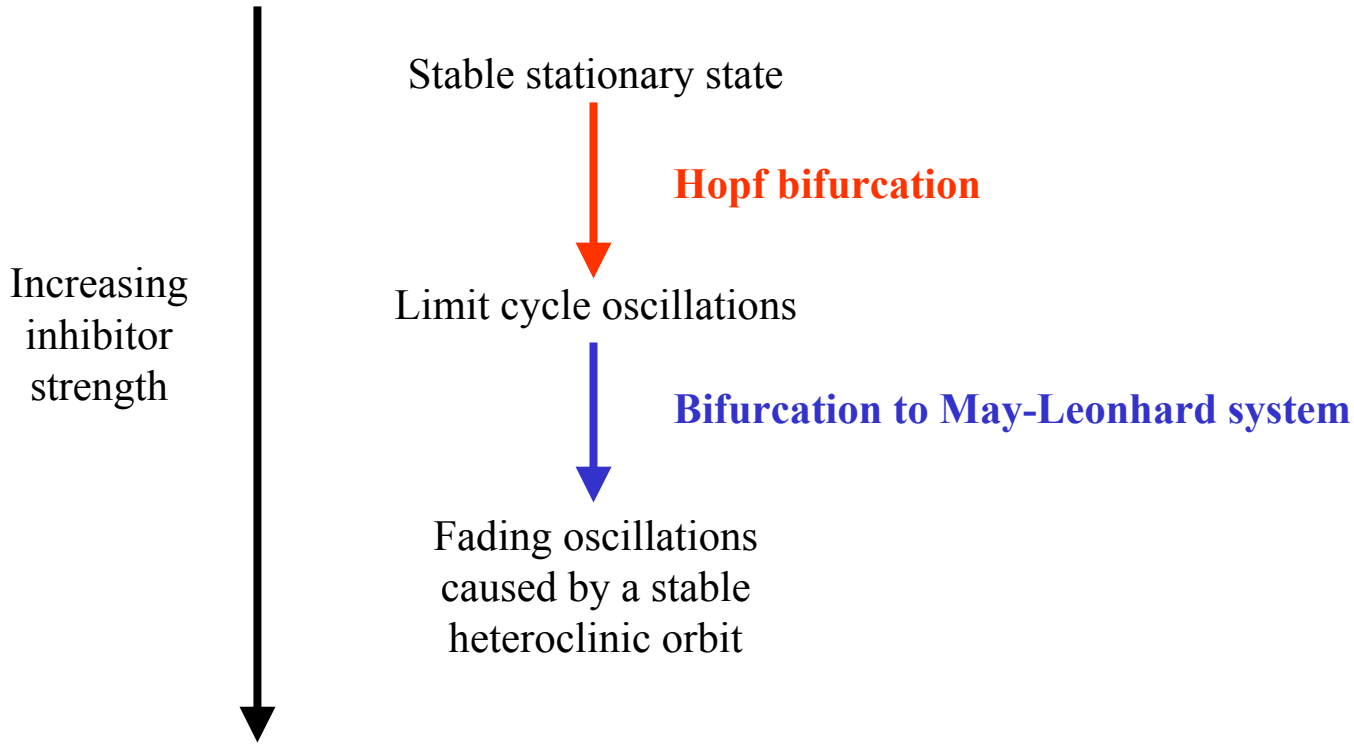
Upscaling to more genes: $n = 3$

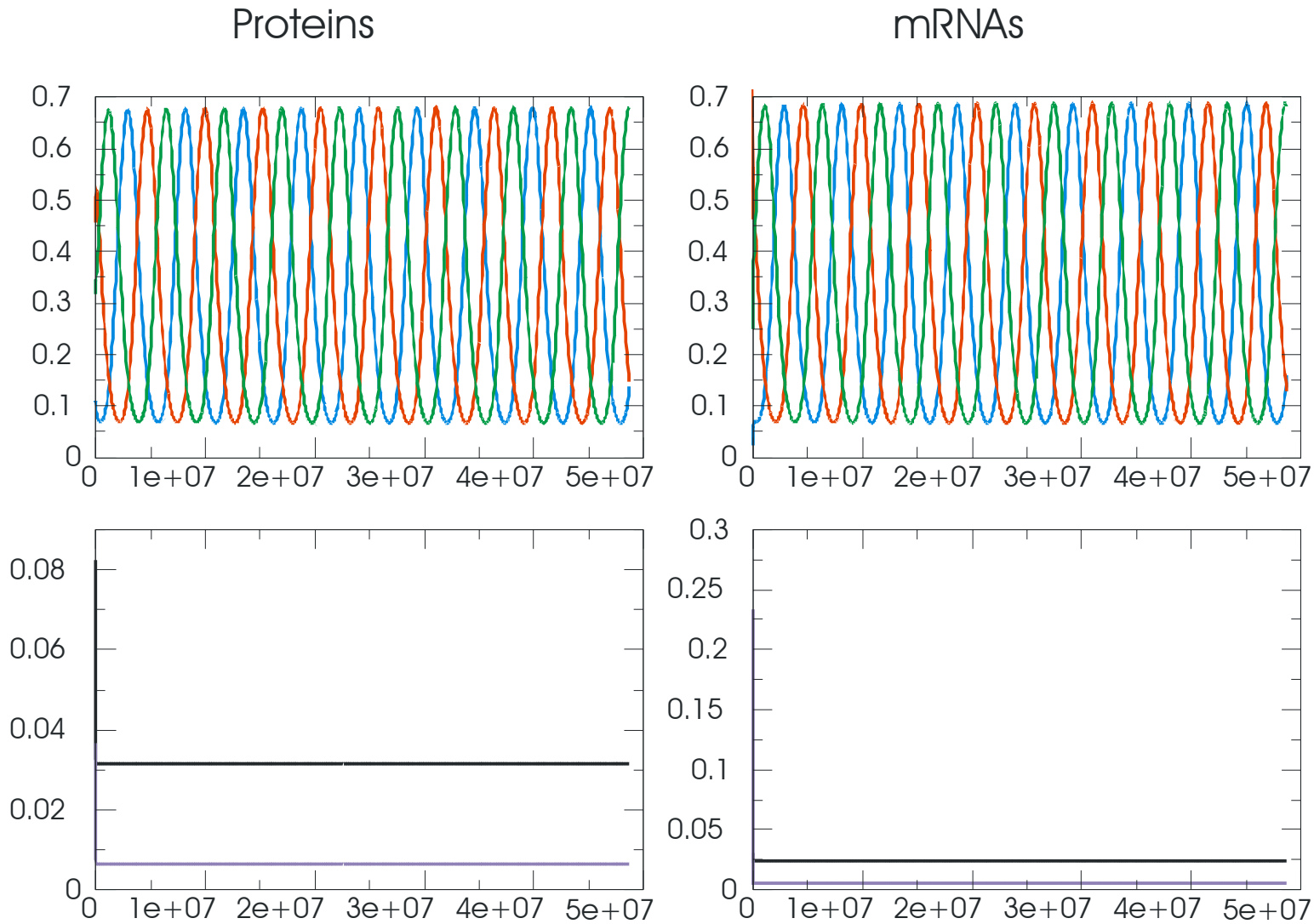




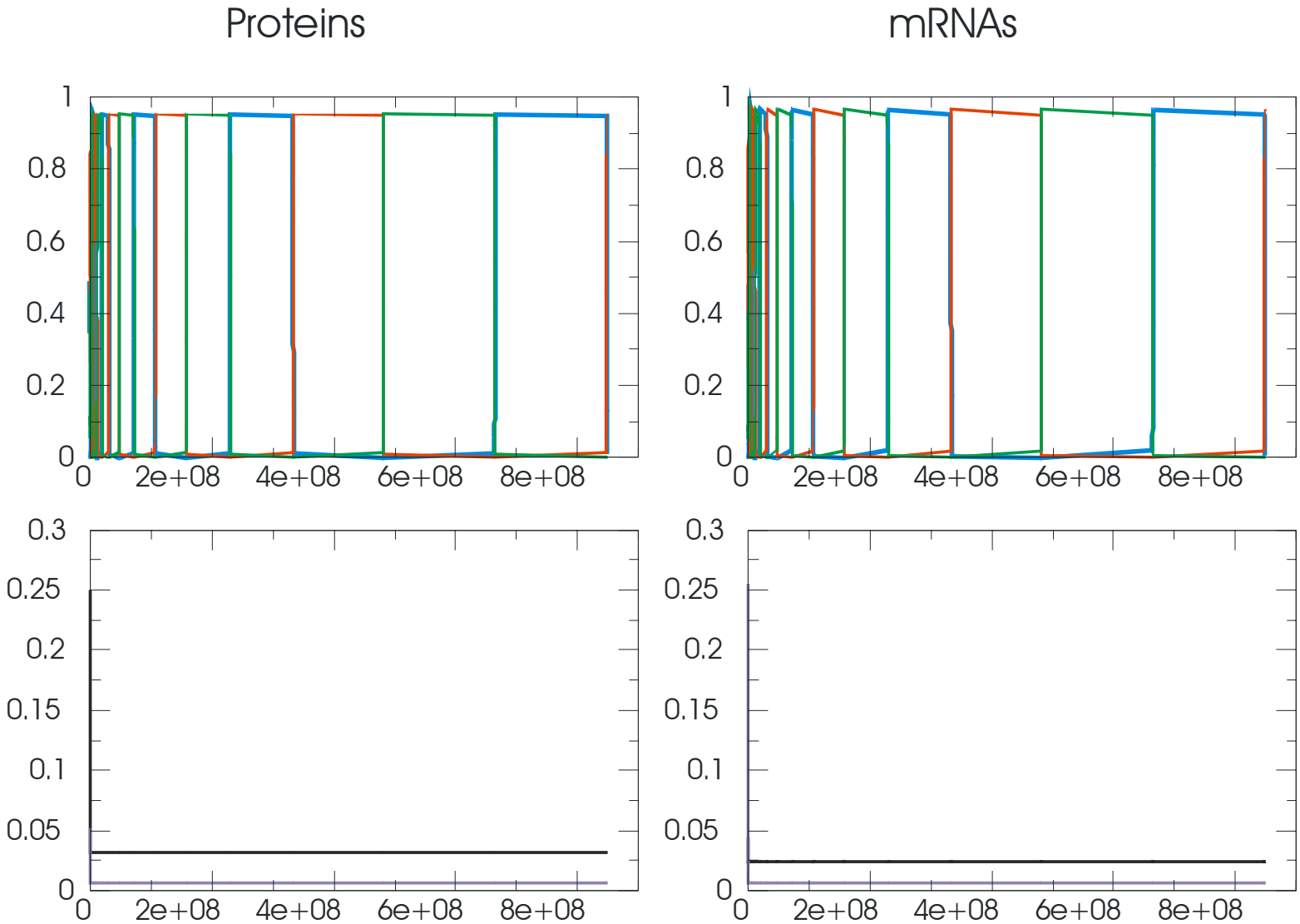
An example analyzed and simulated by MiniCellSim

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

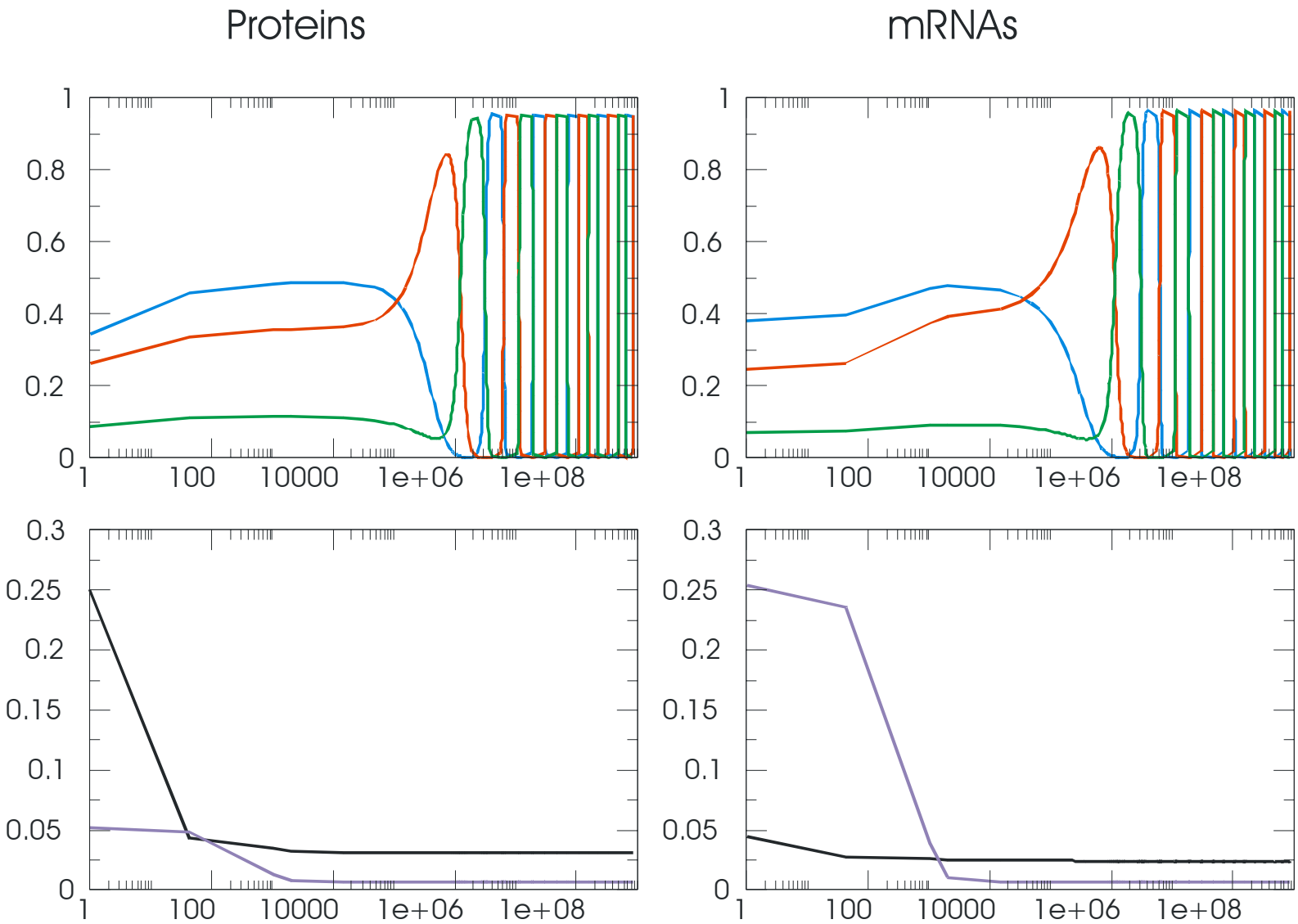

Increasing inhibitor strength
Stable stationary state
Hopf bifurcation
Limit cycle oscillations
Bifurcation to May-Leonhard system
Fading oscillations caused by a stable heteroclinic orbit



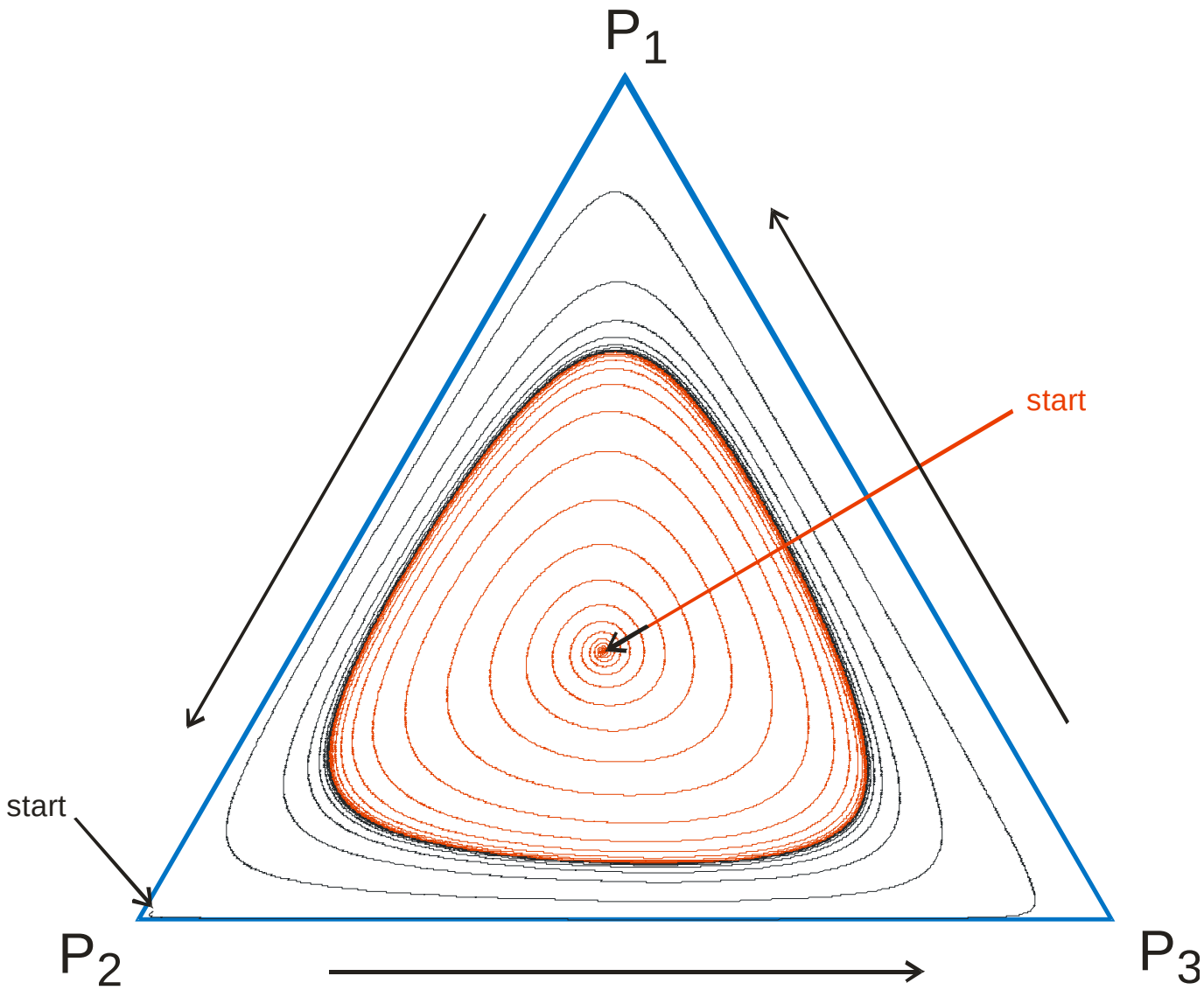
The repressilator limit cycle



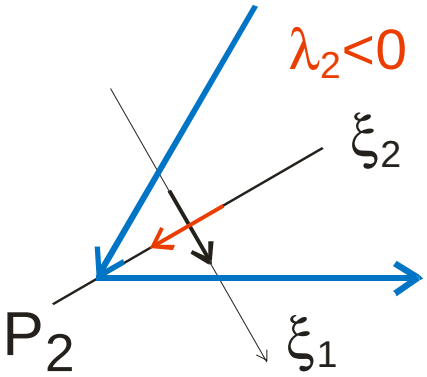
The repressilator heteroclinic orbit



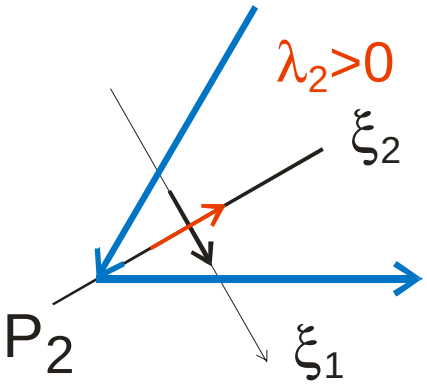
The repressilator heteroclinic orbit (logarithmic time scale)



The repressilator limit cycle

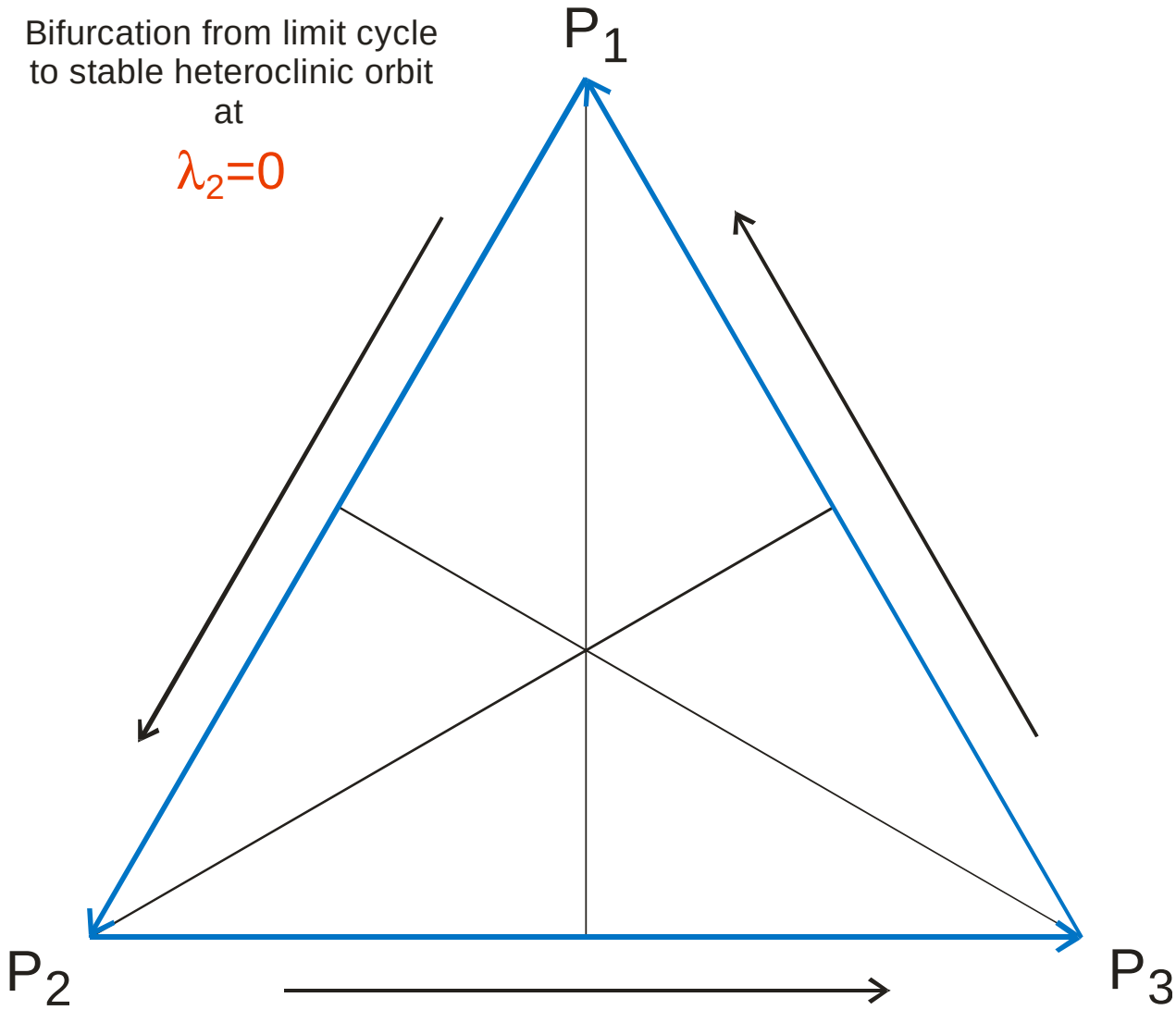


Stable heteroclinic orbit

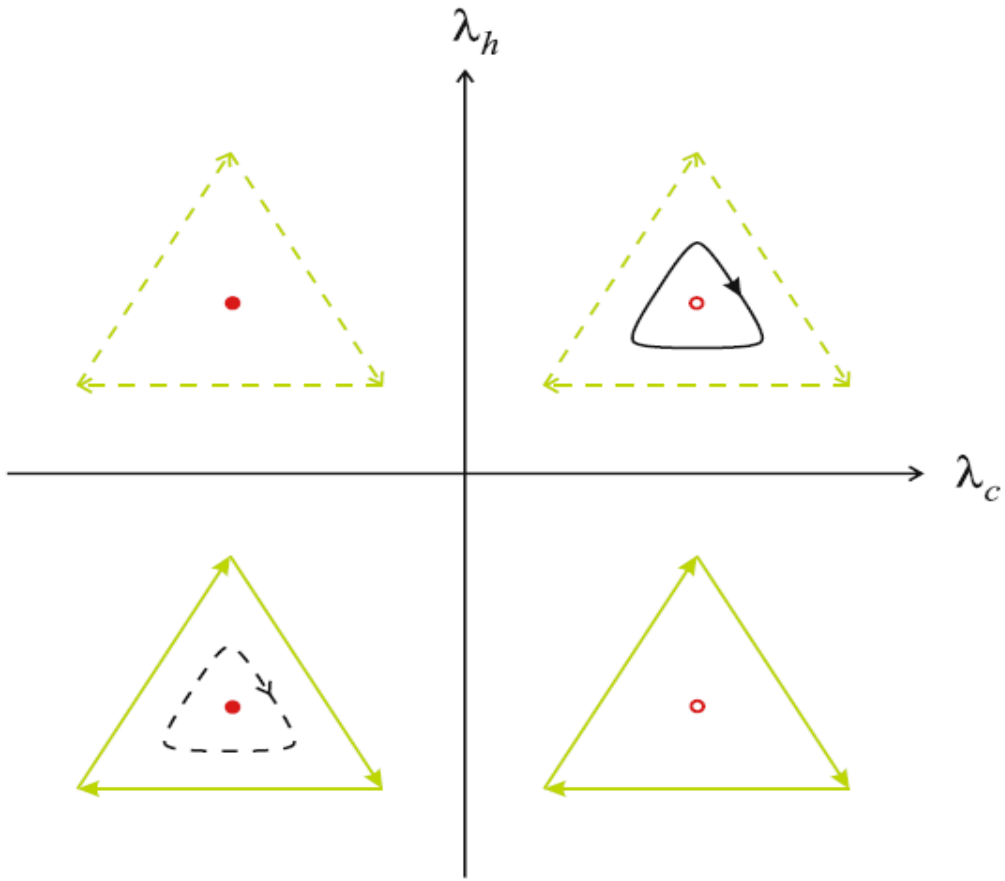


Unstable heteroclinic orbit

Bifurcation from limit cycle to stable heteroclinic orbit at $\lambda_2=0$



The repressilator heteroclinic orbit


λ_h
λ_c

$$(\varepsilon + d_1^{\mathrm{Q}}) \ldots (\varepsilon + d_n^{\mathrm{Q}})(\varepsilon + d_1^{\mathrm{P}}) \ldots (\varepsilon + d_n^{\mathrm{P}}) + D = 0$$

$$D = -\, k_1^Q\, k_2^Q \ldots k_n^Q\, k_1^P\, k_2^P \ldots k_n^P\, \frac{\partial F_1}{\partial p_n} \frac{\partial F_2}{\partial p_1} \ldots \frac{\partial F_n}{\partial p_{n-1}}$$

Upscaling to *n* genes with cyclic symmetry

1. The problems of quantitative biology
2. Forward and inverse problems in reaction kinetics
3. Regulation kinetics and bifurcation analysis
4. **Reverse engineering of dynamical systems**
5. How to upscale from small models to cells?

$$\dot{x} = f(x\,;\,p);\quad x=(x_1,\ldots,x_n);\quad p=(p_1,\ldots,p_m);\; p\in \mathrm{P}\subset \mathbf{R}^m$$

Σ … bifurcation manifold

$$p=(p_i\,,\,p_s)\in \mathrm{P}_i\times \mathrm{P}_s\,;\quad \mathrm{P}=\mathrm{P}_i\oplus \mathrm{P}_s\,;\,\Sigma(p_s)\equiv\ \Sigma\cap\{p_s\}$$

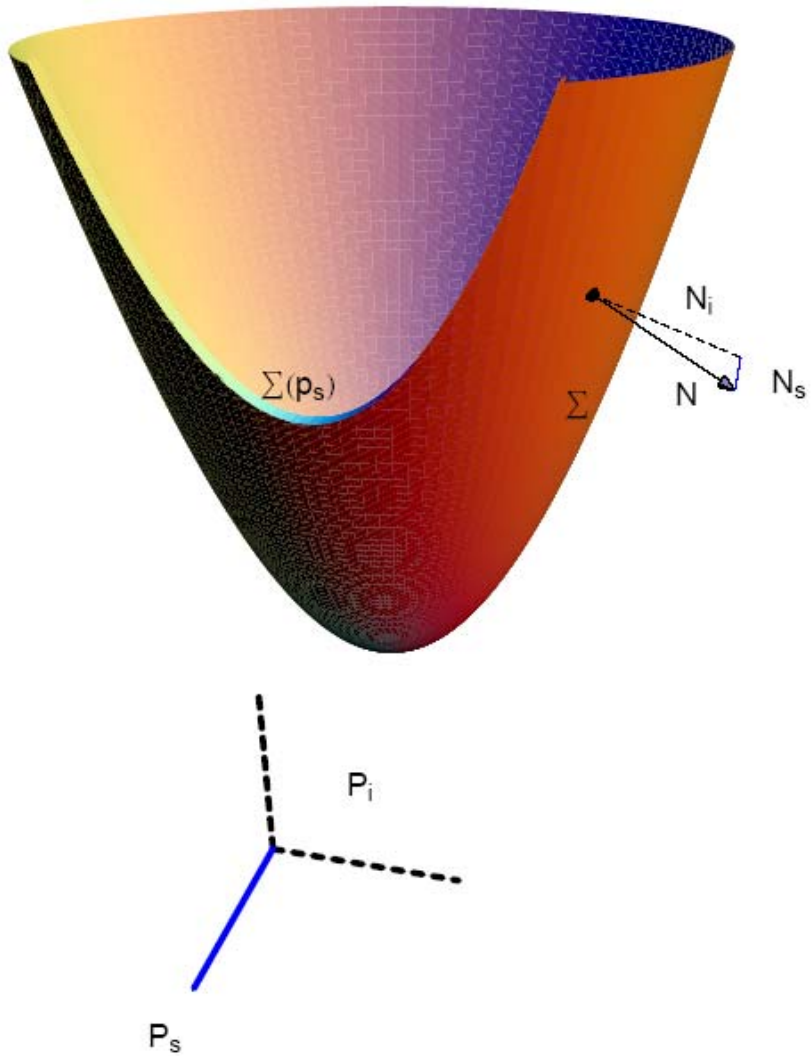
$$F(p)\equiv(F(p)_i\,,F(p_s))=\left(\pi_{\perp\Sigma(p_s)}\,p_i\ ,\ p_s\right)\ \ldots\ \text{forward operator}$$

$$\min_{p_s}\ J(p)=\min_{p_s}\ \left\|F(p)_i-p_i\right\|\quad \ldots\ \text{formulation of the inverse problem}$$

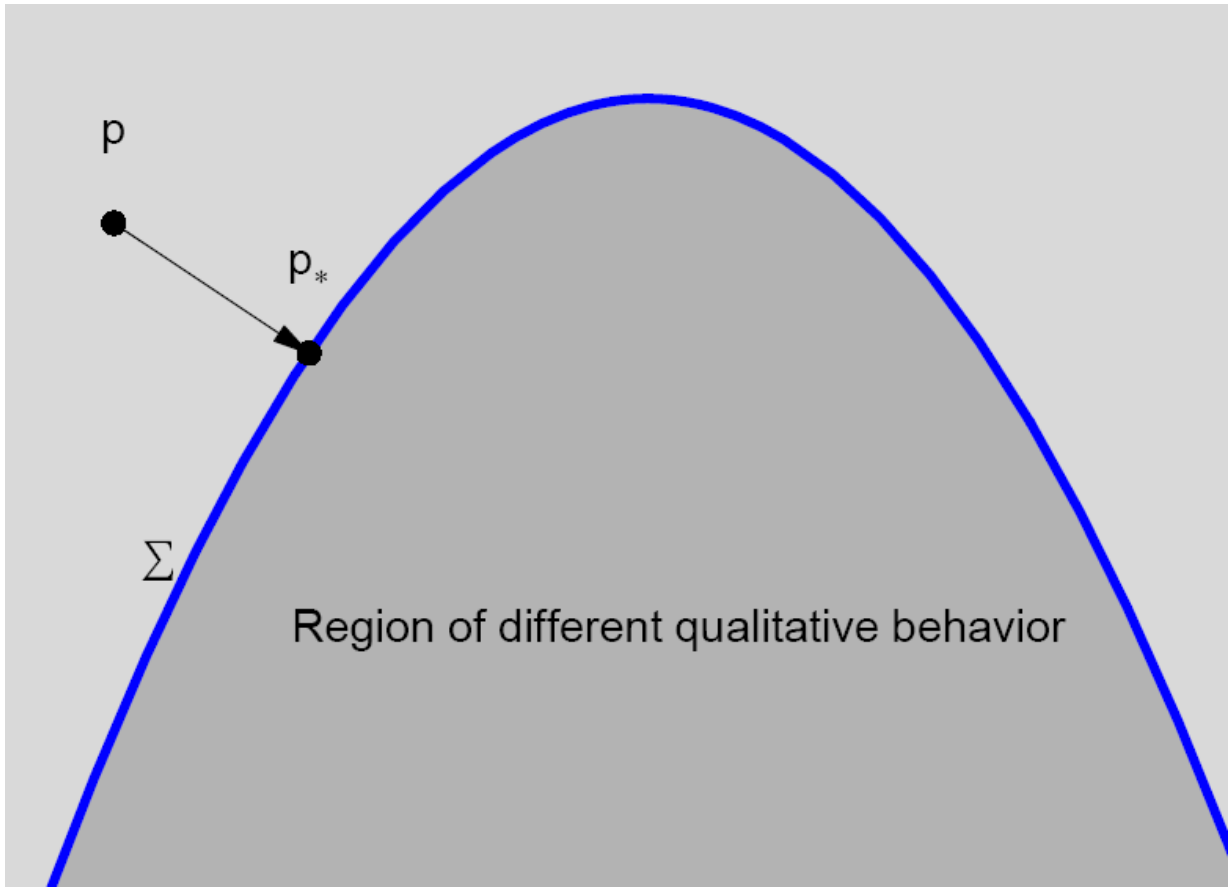
$$\text{subject to}\quad p_{\text{low}}\le p\le p_{\text{upp}}$$

$$\text{and}\quad 0\le c(F(p)_i)$$

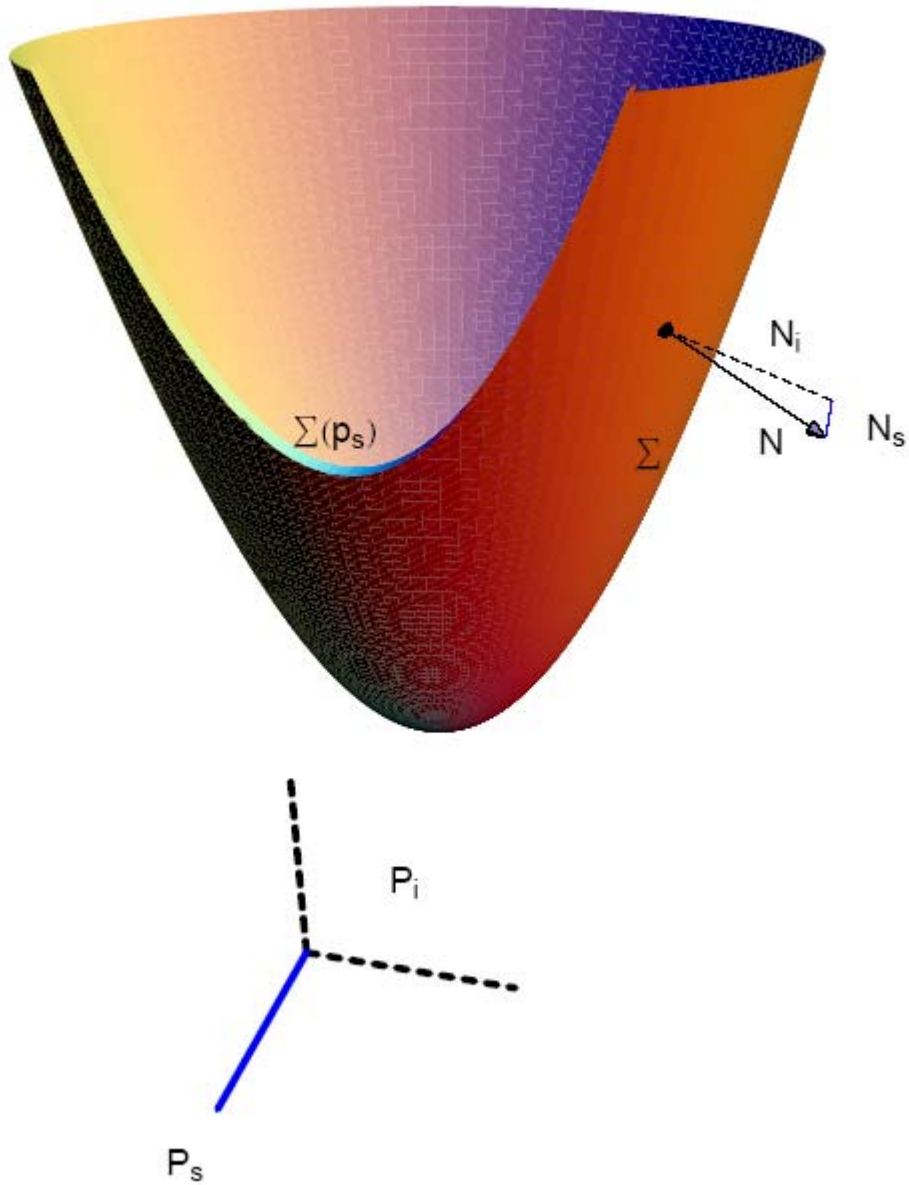
J. Lu, H.W. Engl, P. Schuster. Inverse bifurcation analysis: Application to simple gene systems. *AMB Algorithms for Molecular Biology* **1**, no.11, 2006.

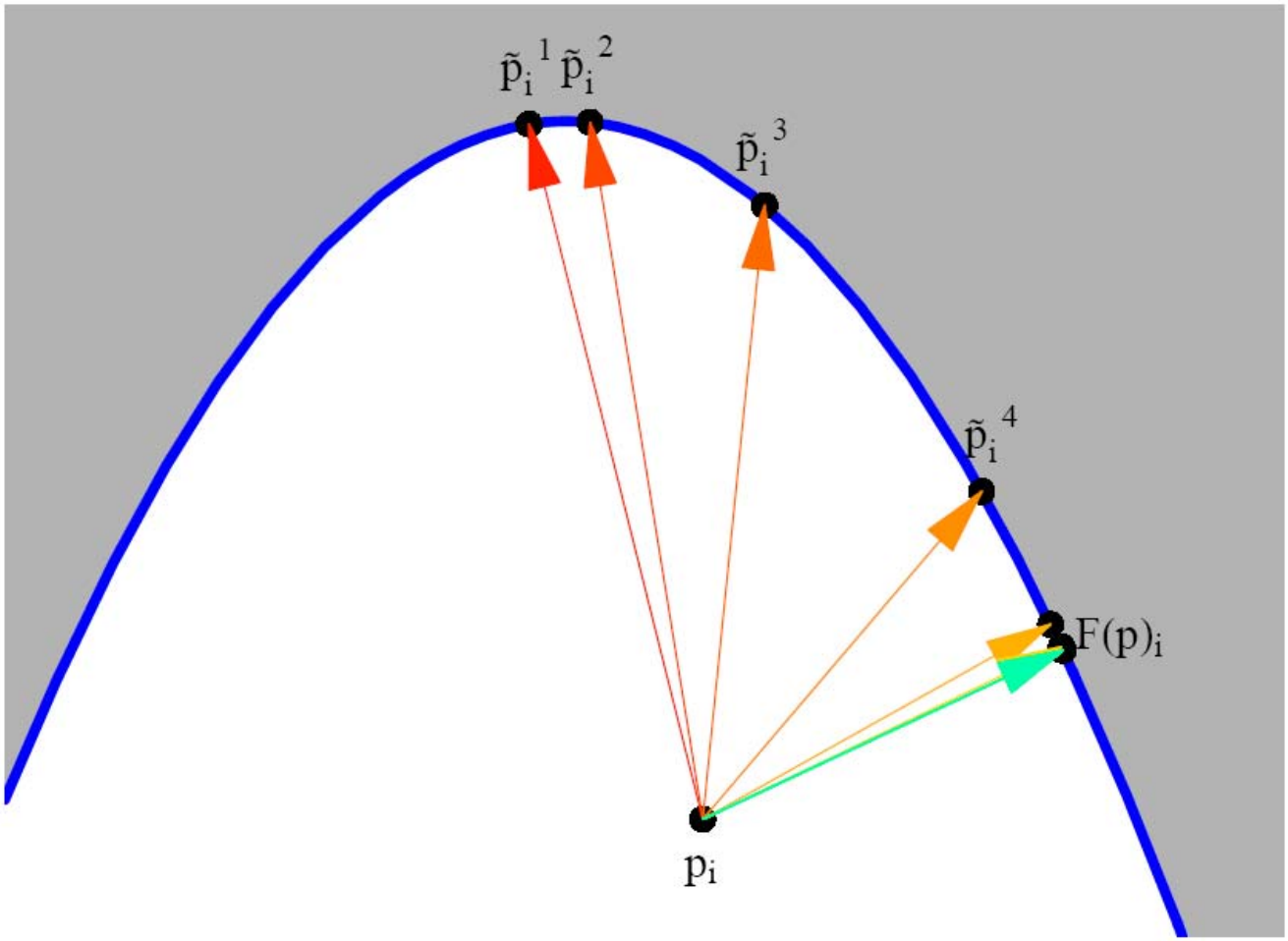


The bifurcation manifold



Defininition of the forward operator $F(p)$


N_i
$\Sigma(p_s)$
Σ
N
N_s
P_i
P_s



Iterative solution for min J(p)

ALGORITHM: LOCMINDIST$\big(x, (p_i, p_s), v, \epsilon,\big)$

- Set initial parameter: $p^0 \leftarrow p$, $x^0 \leftarrow x$
- FOR $j = 1, \cdots, j_{max}$
  1. From p and x, continue along parameter ray $\{(p_i + rv, p_s)\colon\ r \in \mathbb{R}_+\}$, until bifurcation point p^b detected
  2. Compute normal vector at bifurcation point p^b: $v \leftarrow N_i(p^b)$
  3. Update: parameter iterate $p^j \leftarrow p^b$
     ODE solution at bifurcation point $x^j \leftarrow x(p^b)$
  4. Terminate if $\|p^j - p^{j-1}\|/\|p^0\| < \epsilon$

  END
- Return $[(p_i^j, p_s), x^j]$

ALGORITHM: APPLYF$\big(x_{\text{init}}, (p_i, p_s), \epsilon\big)$

- $x_{\text{init}} \leftarrow$ INITODESOLN(x_{init}, p)
- Generate initial search vectors $V \leftarrow \{v_1, v_2, \cdots, v_{\max}\}$
- FOR $j = 1, \cdots, \dim(V)$

$$\begin{aligned} [F^j, x^j] &\leftarrow \text{LOCMINDIST}(x_{\text{init}}, p, v_j, \epsilon) \\ d_j &\leftarrow \|F^j - p\| \end{aligned}$$

  END
- $j_m \leftarrow \arg\min_{j=1,\cdots,\dim(V)} d_j$
- Return $[F^{j_m}, x^{j_m}, x_{\text{init}}]$

ALGORITHM: INVERSE BIFURCATION

- Inputs:
  - SBML document
  - Initial parameter $p_i \in P_i$, $p_s \in P_s$, ODE solution x_{init}
  - Parameter bounds $p_{\text{low}}, p_{\text{upp}} \in \mathbb{R}^m$
  - Tolerances $\epsilon_{\text{proj}}, \epsilon_{\text{optim}} > 0$
  - Step-size constraint $\Delta p_{\max} \in \mathbb{R}^m$
  - Nonlinear constraints $c : P_i \to \mathbb{R}^k$
- Constrained optimization step:

  FOR $j = 1, \cdots, j_{\max}$
  - $[F, x, x_{\text{init}}] \leftarrow$ APPLYF$(x_{\text{init}}, (p_i, p_s), \epsilon)$
  - $F'^* \leftarrow$ APPLYFDERIVADJ(F, x)
  - $c \leftarrow$ APPLYC(F, x)
  - $c'^* \leftarrow$ APPLYCDERIVADJ(F, F'^*, x)
  - $[p_s, \tilde{H}] \leftarrow$ SQPSTEP$(F, F'^*, p_{\text{low}}, p_{\text{upp}}, c, c'^*, \tilde{H}, \Delta p_{\max})$
  - $J_{j+1} \leftarrow \|F(p) - p\|$
  - Terminate if $|(J_{j+1} - J_j)/J_0| \leq \epsilon_{\text{optim}}$

  END

$$\frac{dx_{2k-1}}{dt} = \beta_{2k-1}(f_{2k-1} - x_{2k-1})$$
$$\frac{dx_{2k}}{dt} = \beta_{2k}(x_{2k-1} - x_{2k}),$$

$k = 1, 2, 3$

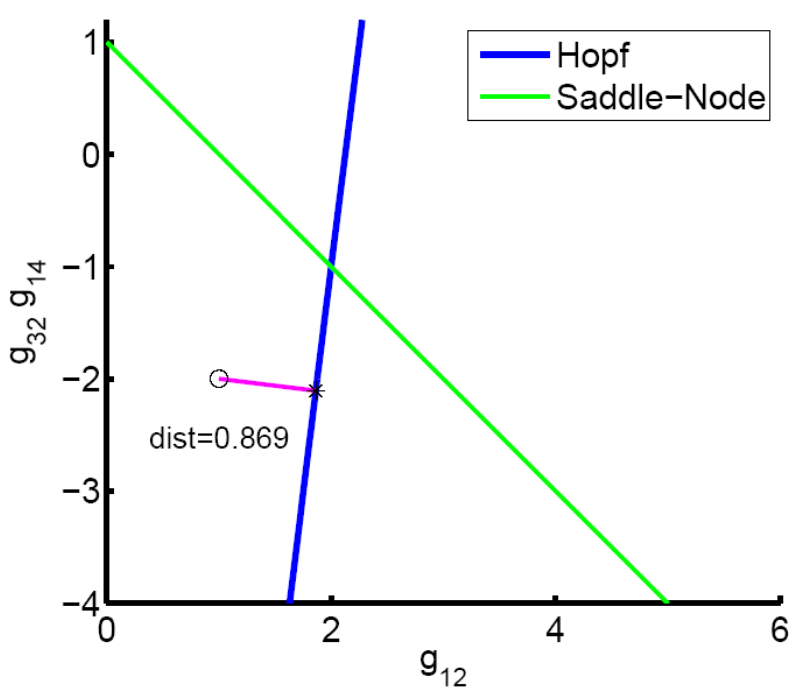
$$f_1 = \begin{cases} B & \text{for } x_2^{g12} x_4^{g14} \le B \\ x_2^{g12} x_4^{g14} & \text{for } B < x_2^{g12} x_4^{g14} < M \\ M & \text{for } x_2^{g12} x_4^{g14} \ge M \end{cases}$$

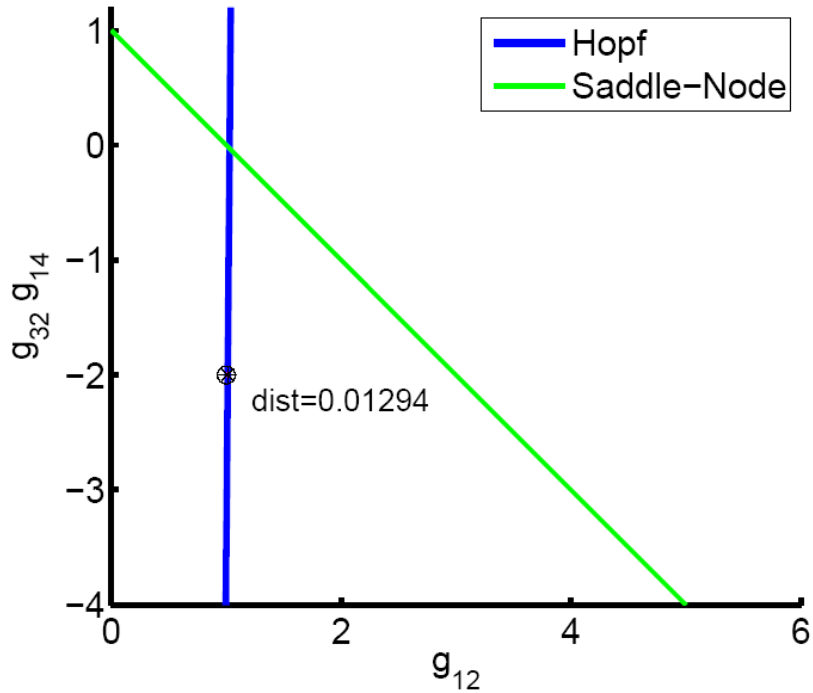
$$f_3 = \begin{cases} B & \text{for } x_2^{g32} \le B \\ x_2^{g32} & \text{for } B < x_2^{g32} < M \\ M & \text{for } x_2^{g32} \ge M \end{cases}$$

$$f_5 = \begin{cases} 1/M & \text{for } x_4^{g54} \le 1/M \\ x_4^{g54} & \text{for } 1/M < x_4^{g54} < 1/B \\ 1/B & \text{for } x_4^{g54} \ge 1/B \end{cases},$$

Switch or oscillatory behavior in Escherichia coli

T.S. Gardner, C.R. Cantor, J.J. Collins. Construction of a genetic toggle switch in Escherichia coli. *Nature* **403**:339-342, 2000.
M.R. Atkinson, M.A. Savageau, T.J. Myers, A.J. Ninfa. Development of genetic circuitry exhibiting toggle switch or oscillatory behavior in Escherichia coli. *Cell* **113**:597-607, 2003.





Inverse bifurcation analysis of switch or oscillatory behavior in Escherichia coli

J. Lu, H.W. Engl, P. Schuster. Inverse bifurcation analysis: Application to simple gene systems. *AMB Algorithms for Molecular Biology* **1**:11, 2006.

$$\begin{aligned}\dot{x}_i &= \beta_i(y_i - x_i) \\ \dot{y}_i &= \alpha_i \left(\frac{1-\delta_i}{1 + x_{i-1 \mod n}^{h_i}} + \delta_i \right) - y_i, \; i = 0, \cdots, n-1\end{aligned}$$

$$\alpha_i = \alpha, \beta_i = \beta, h_i = h, \delta_i = \delta$$

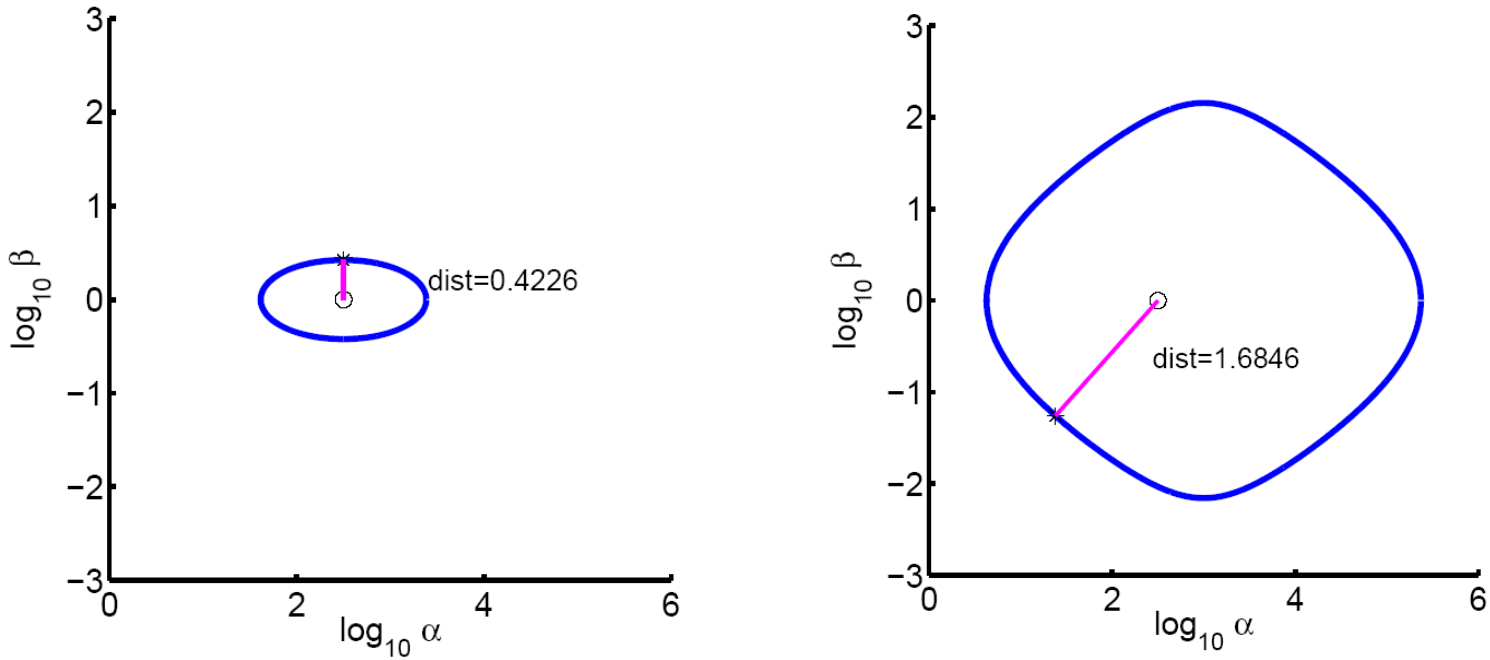
$$p_i = (\alpha, \beta)$$

$$p_s = (\delta, h)$$

$$(10^{-4}, 0) \leq (\delta, h) \leq (10^{-1}, 2)$$

Inverse bifurcation analysis of the repressilator model

S. Müller, J. Hofbauer, L. Endler, C. Flamm, S. Widder, P. Schuster. A generalized model of the repressilator. *J. Math. Biol.* **53**:905-937, 2006.



Inverse bifurcation analysis of the repressilator model

J. Lu, H.W. Engl, P. Schuster. Inverse bifurcation analysis: Application to simple gene systems. *AMB Algorithms for Molecular Biology* **1**:11, 2006.

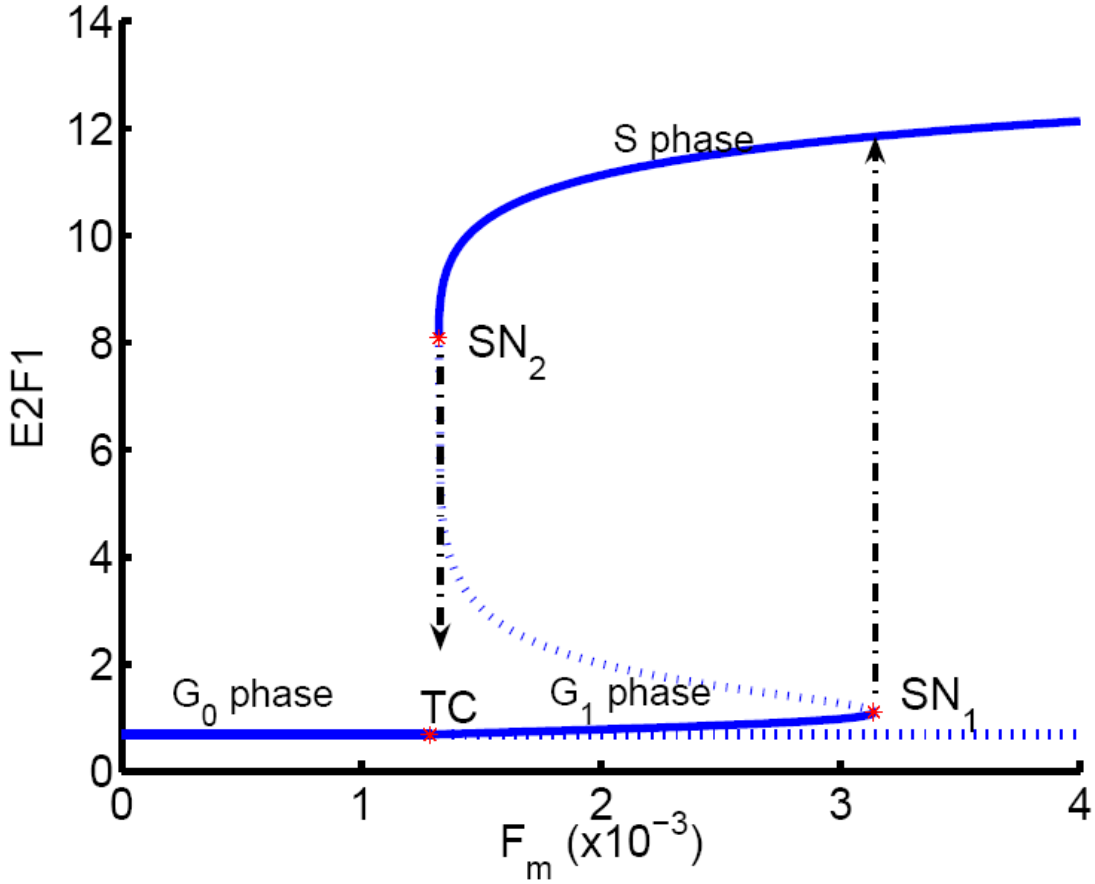
$$\frac{d}{dt}[\mathrm{pRB}] = k_1 \frac{[\mathrm{E2F1}]}{K_{m1} + [\mathrm{E2F1}]} \frac{J_{11}}{J_{11} + [\mathrm{pRB}]} - \phi_{\mathrm{pRB}}[\mathrm{pRB}]$$

$$\frac{d}{dt}[\mathrm{E2F1}] = k_P + k_1 \frac{a^2 + [\mathrm{E2F1}]^2}{K_{m2}^2 + [\mathrm{E2F1}]^2} \frac{J_{12}}{J_{12} + [\mathrm{pRB}]} - \phi_{\mathrm{E2F1}}[\mathrm{E2F1}]$$

$$\frac{d}{dt}[\mathrm{AP1}] = F_m + k_{25}[\mathrm{E2F1}] \frac{J_{15}}{J_{15} + [\mathrm{p}RB]} \frac{J_{65}}{J_{11} + [\mathrm{pRB'}]} - \phi_{\mathrm{AP1}}[\mathrm{AP1}]$$

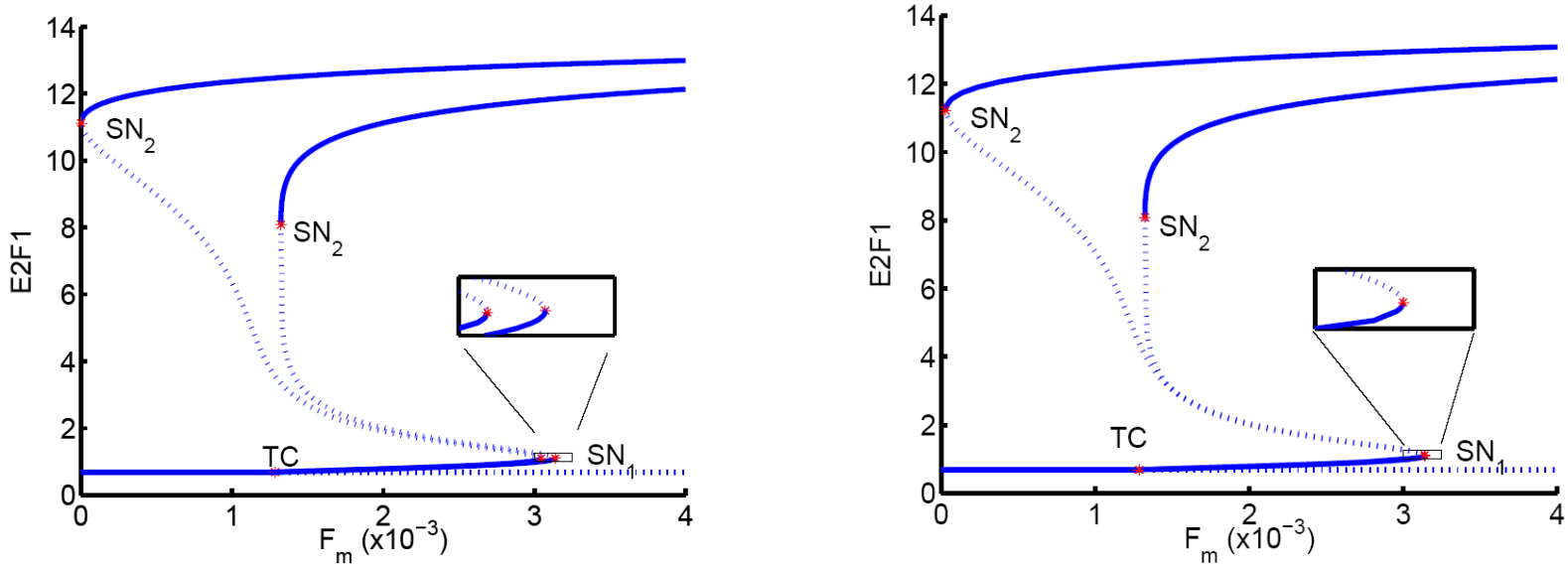
A simple dynamical cell cycle model

J.J. Tyson, A. Csikasz-Nagy, B. Novak. The dynamics of cell cycle regulation. *Bioessays* **24**:1095-1109, 2002



A simple dynamical cell cycle model

J.J. Tyson, A. Csikasz-Nagy, B. Novak. The dynamics of cell cycle regulation. *Bioessays* **24**:1095-1109, 2002



Inverse bifurcation analysis of a dynamical cell cycle model

J. Lu, H.W. Engl, P. Schuster. Inverse bifurcation analysis: Application to simple gene systems. *AMB Algorithms for Molecular Biology* **1**:11, 2006.

1. The problems of quantitative biology
2. Forward and inverse problems in reaction kinetics
3. Regulation kinetics and bifurcation analysis
4. Reverse engineering of dynamical systems
5. **How to upscale from small models to cells?**

Suitable systems for upscaling:

1. Linear systems via large eigenvalue problems
2. Cascades
3. Cyclic systems in case of high symmetry
4. Sufficiently simple networks ???

Acknowledgement of support

Universität Wien

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

Wiener Wissenschafts-, Forschungs- und Technologiefonds (WWTF)
Project No. Mat05

Jubiläumsfonds der Österreichischen Nationalbank
Project No. Nat-7813

European Commission: Contracts No. 98-0189, 12835 (NEST)

Austrian Genome Research Program – GEN-AU: Bioinformatics Network (BIN)

Österreichische Akademie der Wissenschaften

Siemens AG, Austria

Universität Wien and the Santa Fe Institute

Coworkers

Universität Wien

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

Paul E. Phillipson, University of Colorado at Boulder, CO

Heinz Engl, Philipp Kügler, **James Lu**, **Stefan Müller**, RICAM Linz, AT

Jord Nagel, **Kees Pleij**, Universiteit Leiden, NL

Walter Fontana, Harvard Medical School, MA

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

Ulrike Göbel, Walter Grüner, **Stefan Kopp**, **Jaqueline Weber,** Institut für Molekulare Biotechnologie, Jena, GE

Ivo L.Hofacker, **Christoph Flamm**, **Andreas Svrček-Seiler**, Universität Wien, AT

Kurt Grünberger, Michael Kospach , **Andreas Wernitznig**, **Stefanie Widder**, **Stefan Wuchty**, Universität Wien, AT

Jan Cupal, **Stefan Bernhart**, **Lukas Endler**, **Ulrike Langhammer**, **Rainer Machne**, **Ulrike Mückstein**, **Hakim Tafer, Thomas Taylor**, Universität Wien, AT

Web-Page for further information:

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