From Biochemical Kinetics to Systems Biology

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RICAM Special Semester on Quantitative Biology

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Web-Page for further information:

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

1. Biochemical kinetics and systems biology
2. Forward and inverse problems
3. Regulation kinetics and bifurcation analysis
4. Reverse engineering of dynamical systems
5. Future problems of quantitative biology

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Biochemical kinetics

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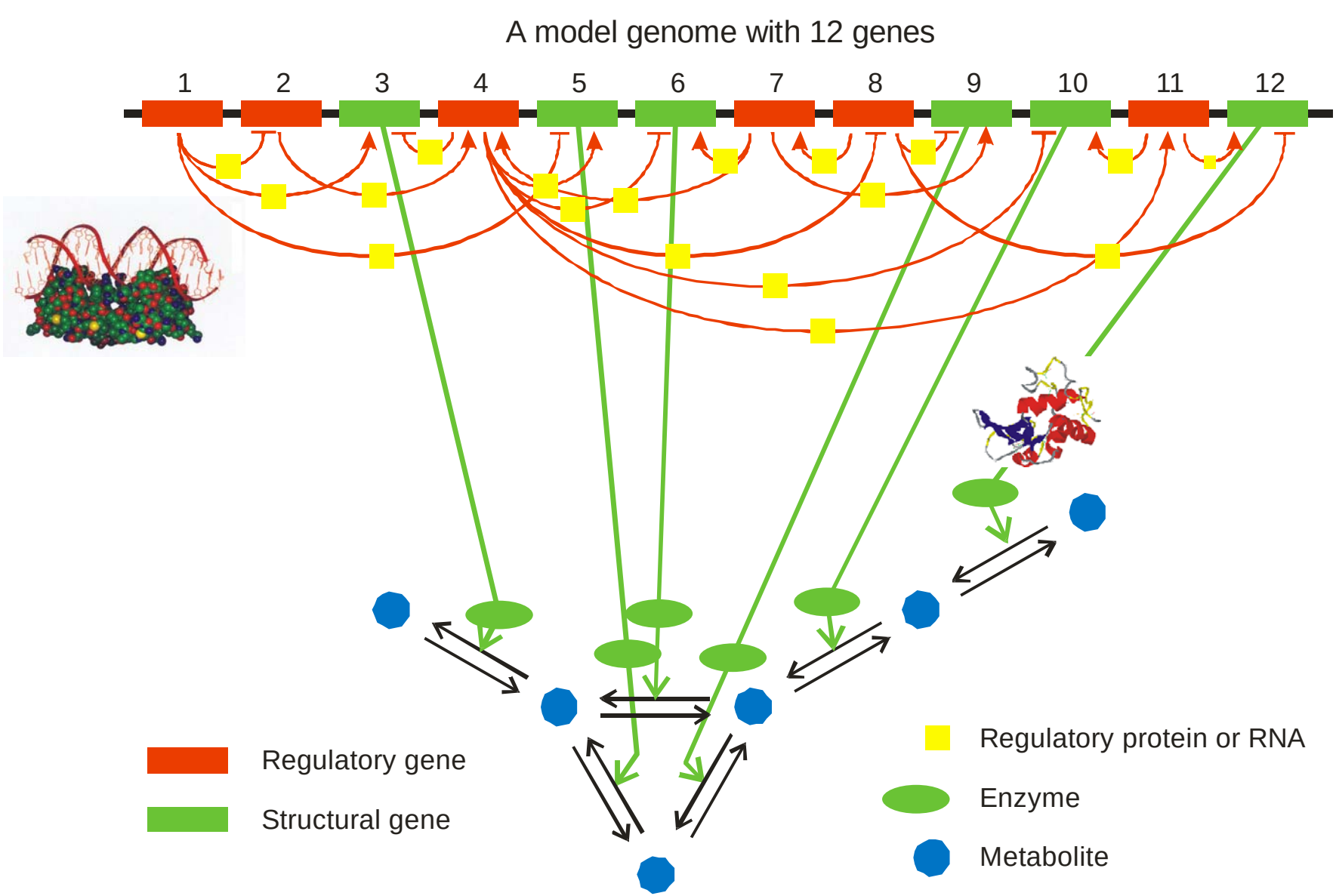
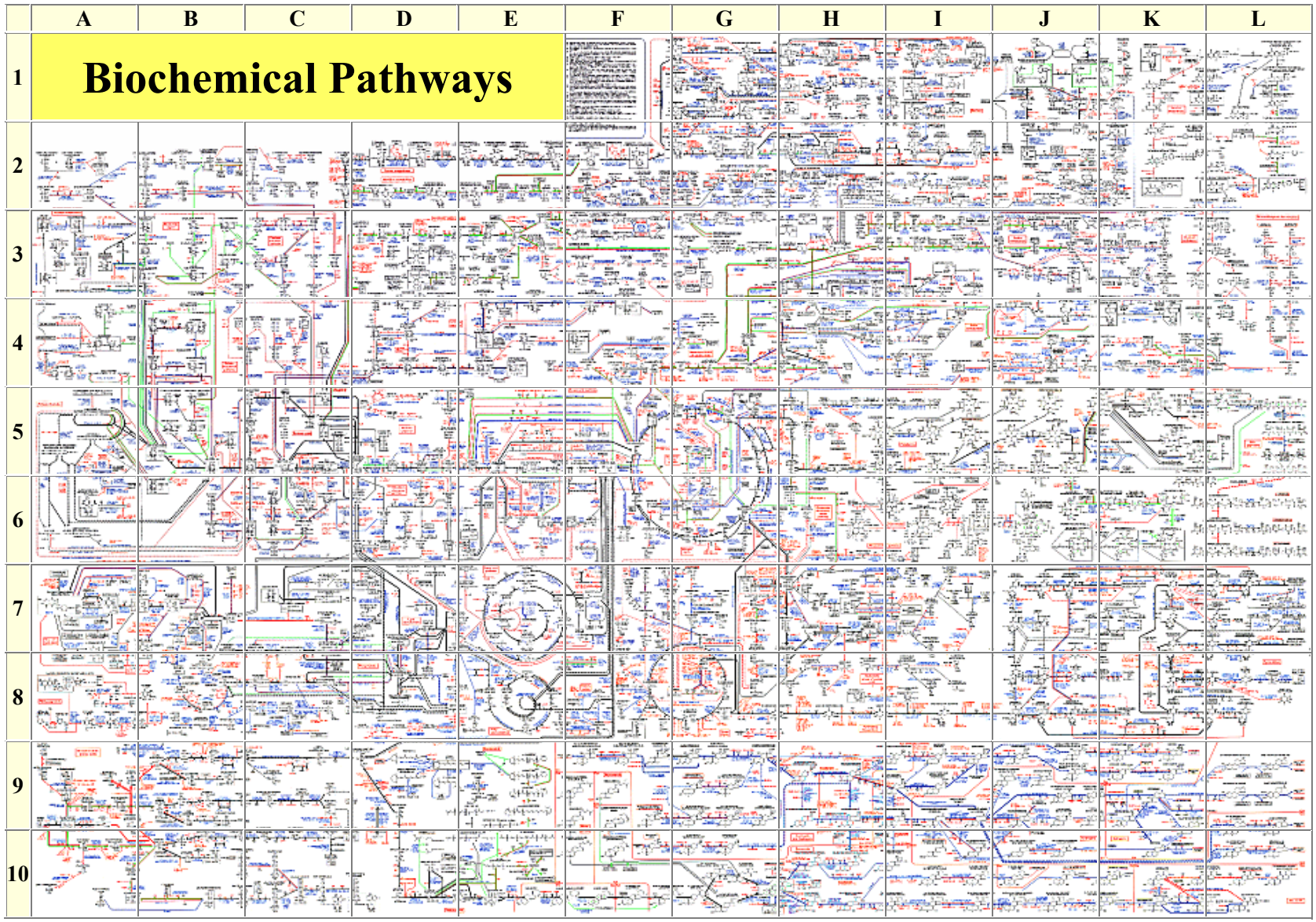
1990 -	Revival of biochemical kinetics in systems biology

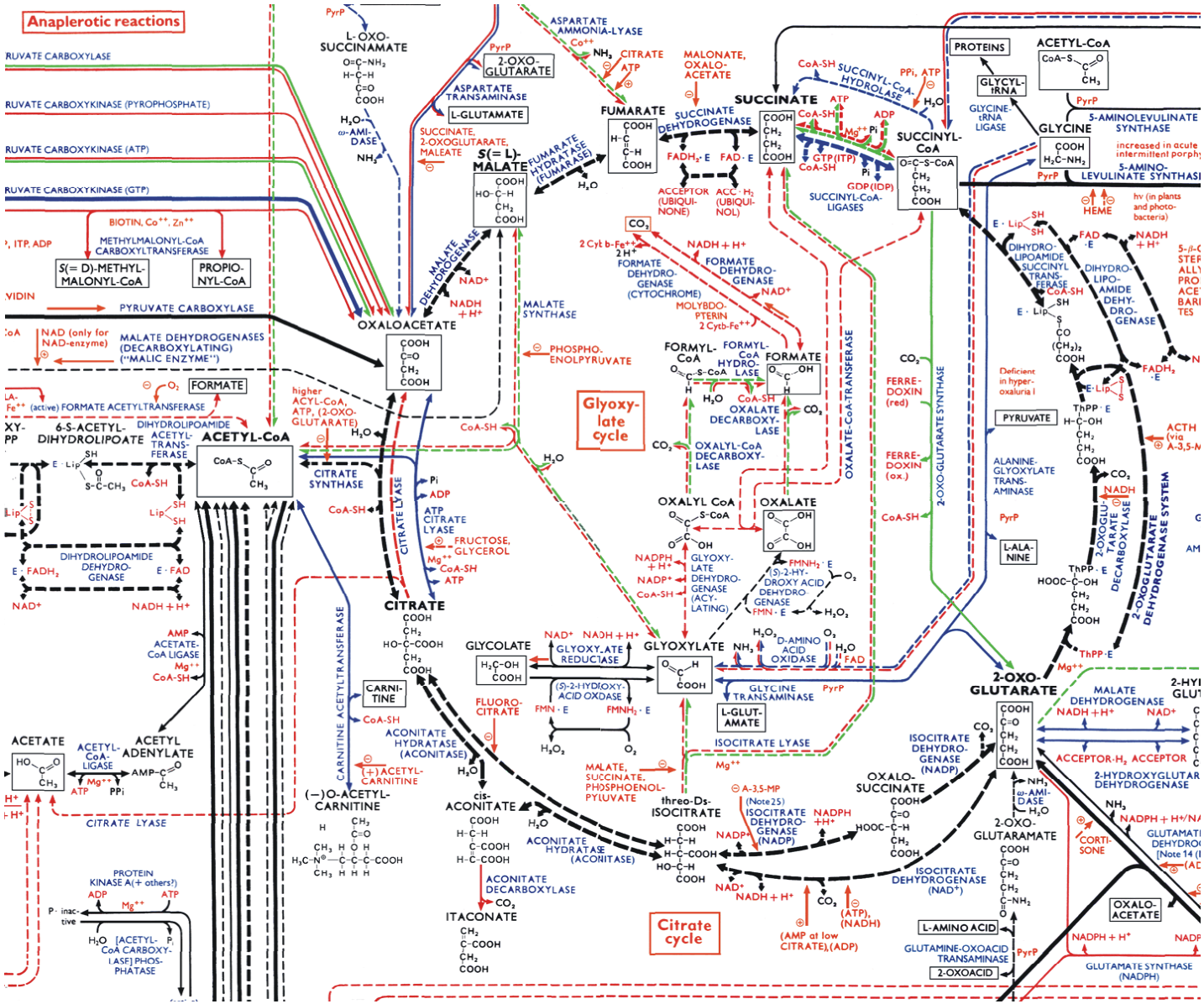


Sketch of a genetic and metabolic network



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

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



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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: $x(0)$

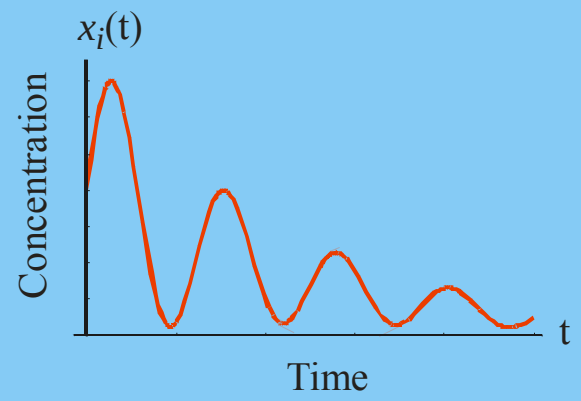
Boundary conditions:

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

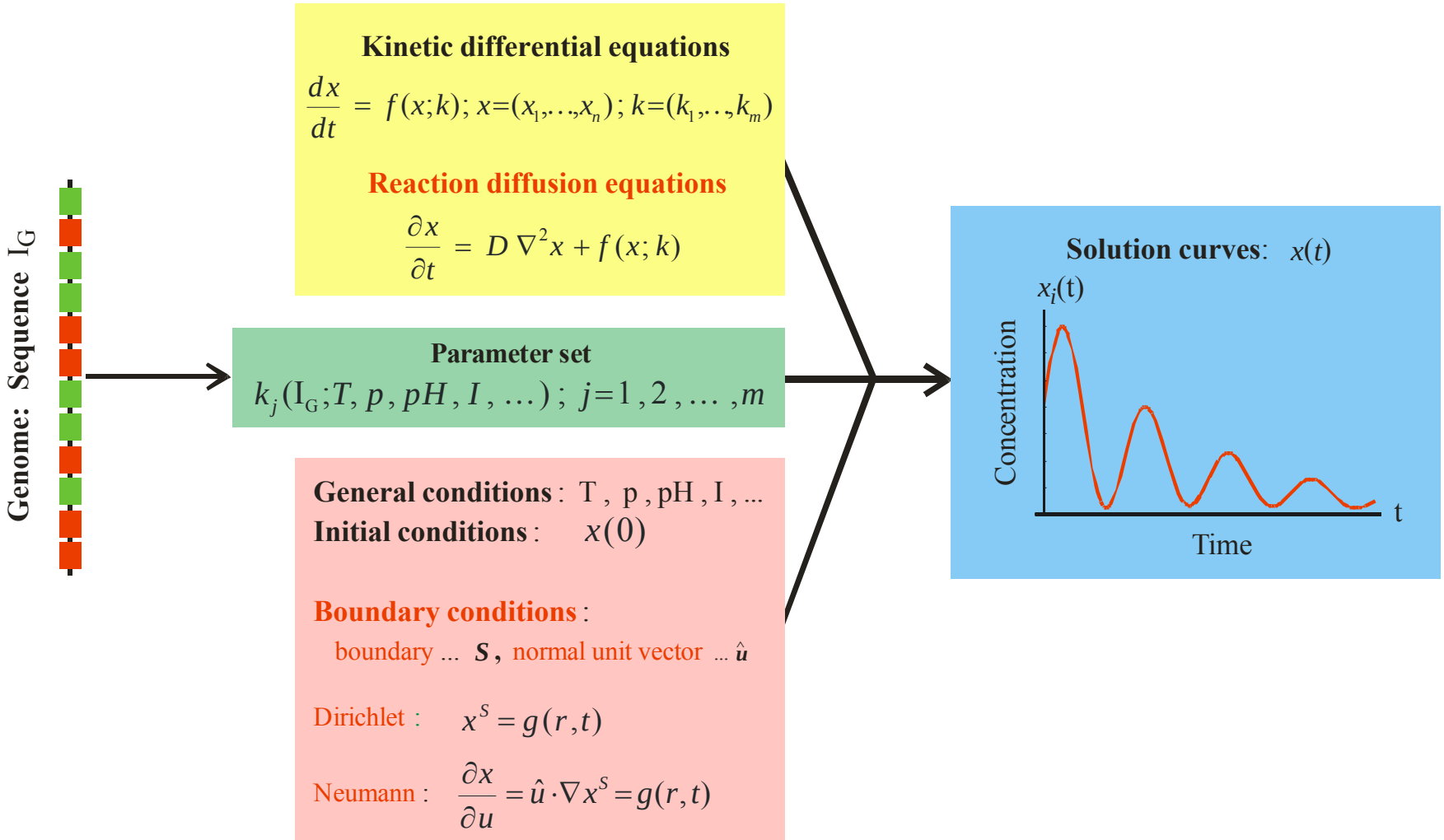
Dirichlet : $x^S = g(r,t)$

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

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

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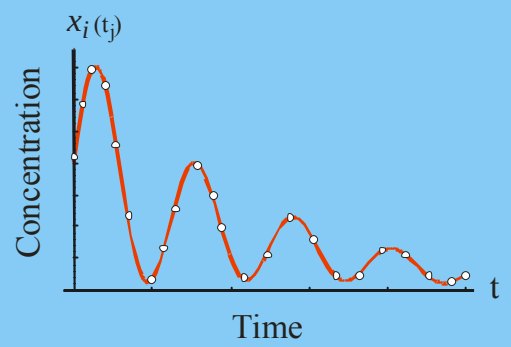
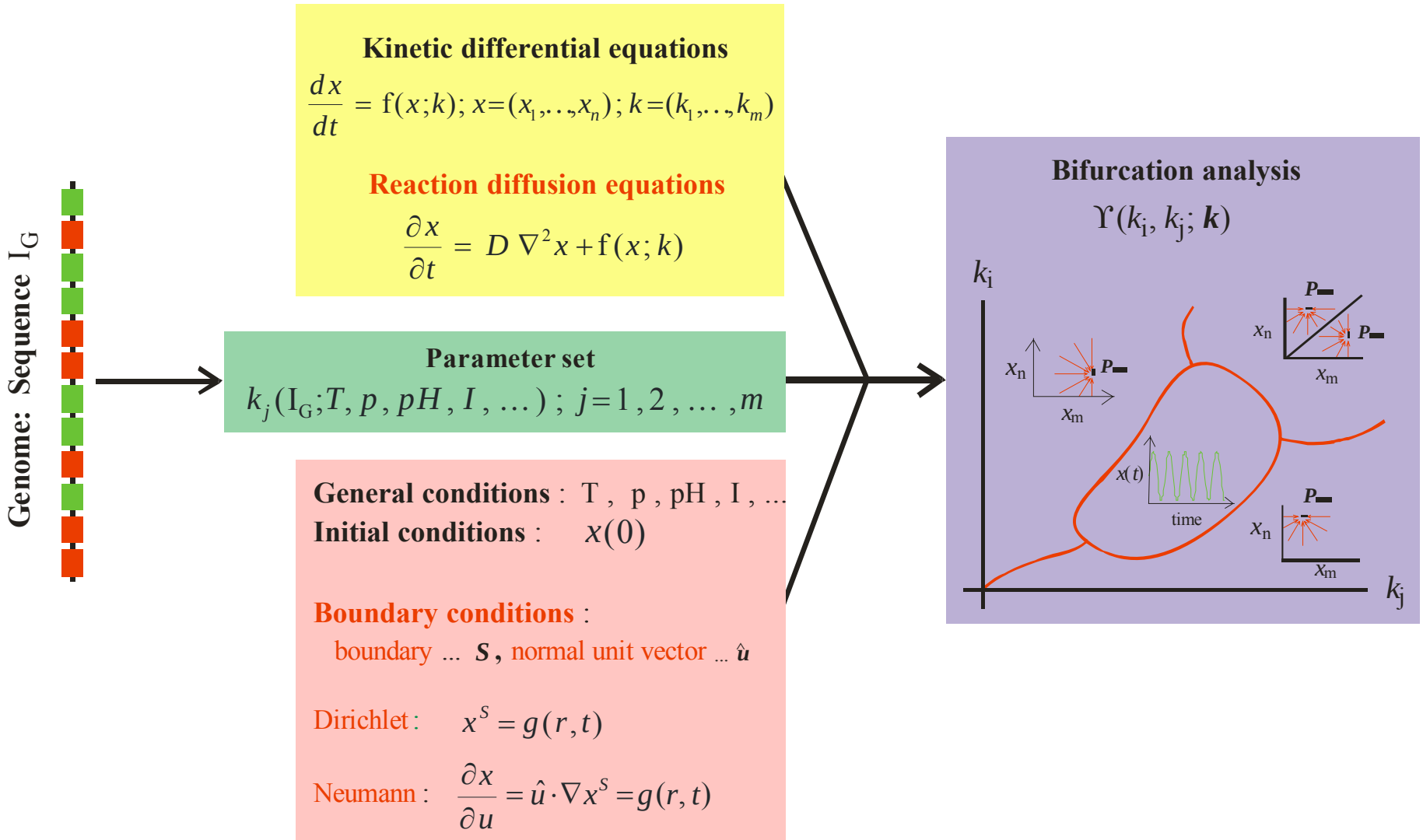
Neumann : $\frac{\partial x}{\partial u} = \hat{u} \cdot \nabla x^S = g(r,t)$

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:

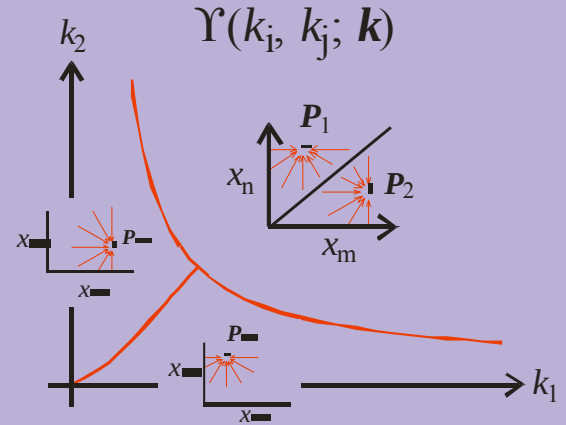
boundary ... $\boldsymbol{S}$, normal unit vector... $\hat{\boldsymbol{u}}$

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)

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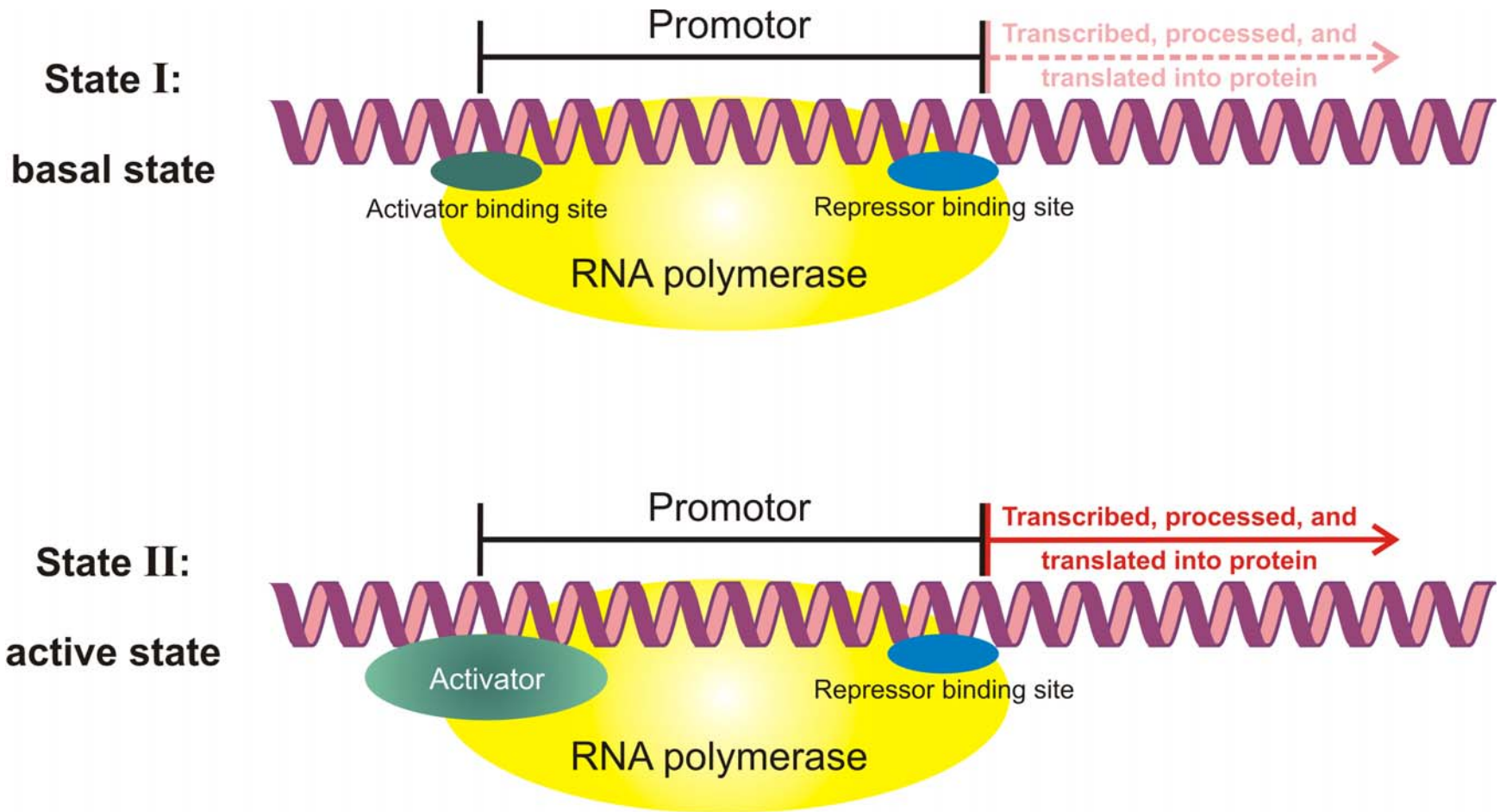
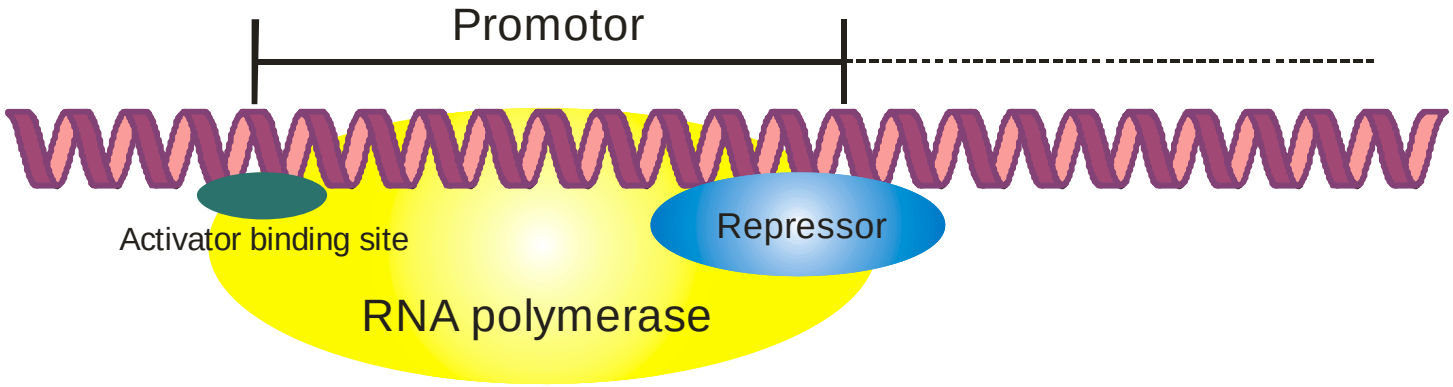


Active states of gene regulation

State III:

inactive state



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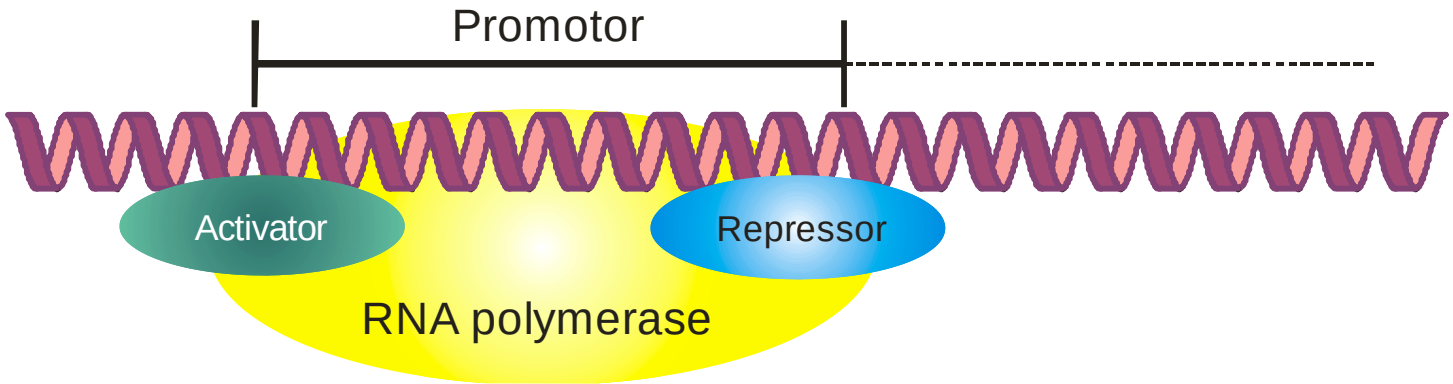

Inactive states of gene regulation

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

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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.,

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[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.

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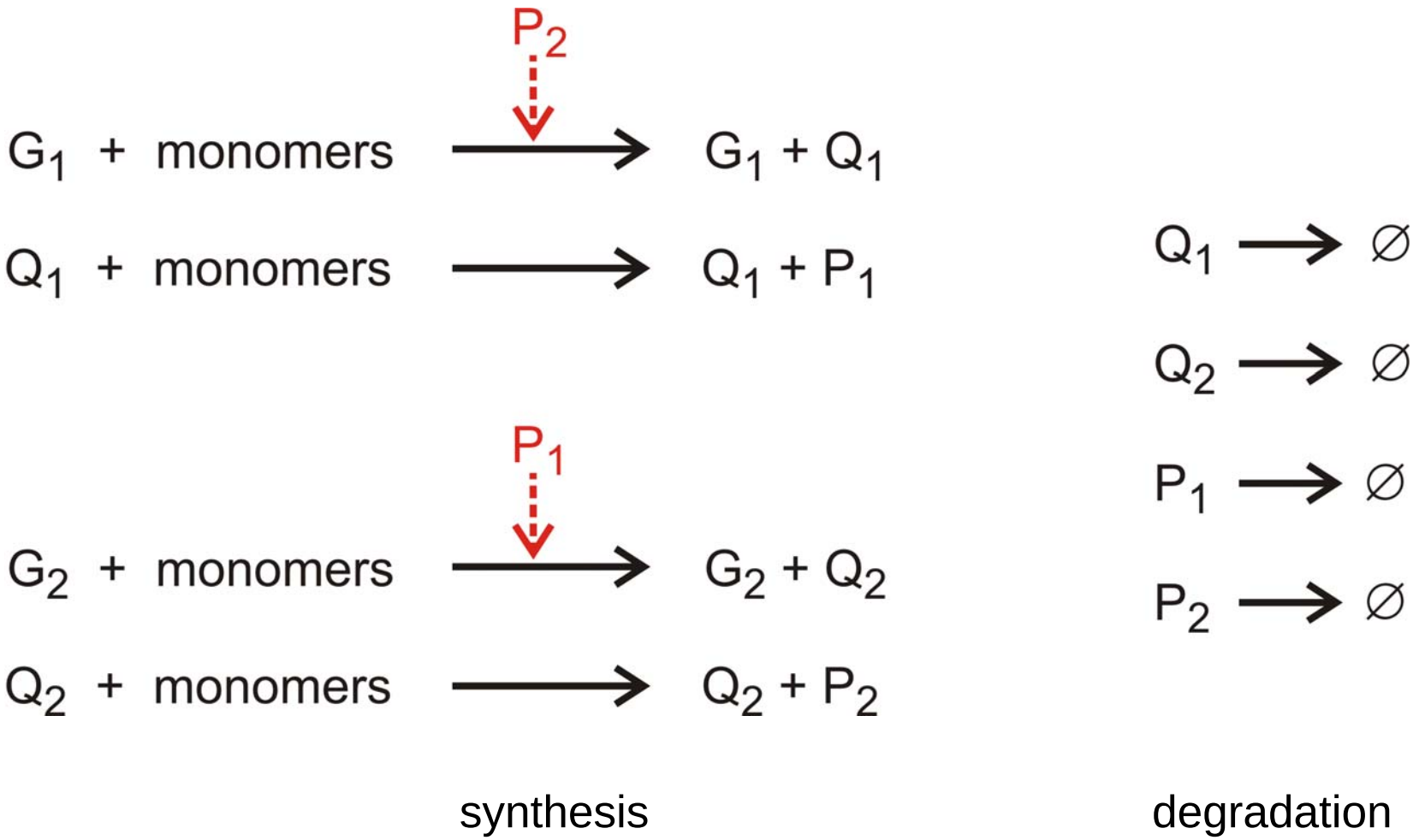
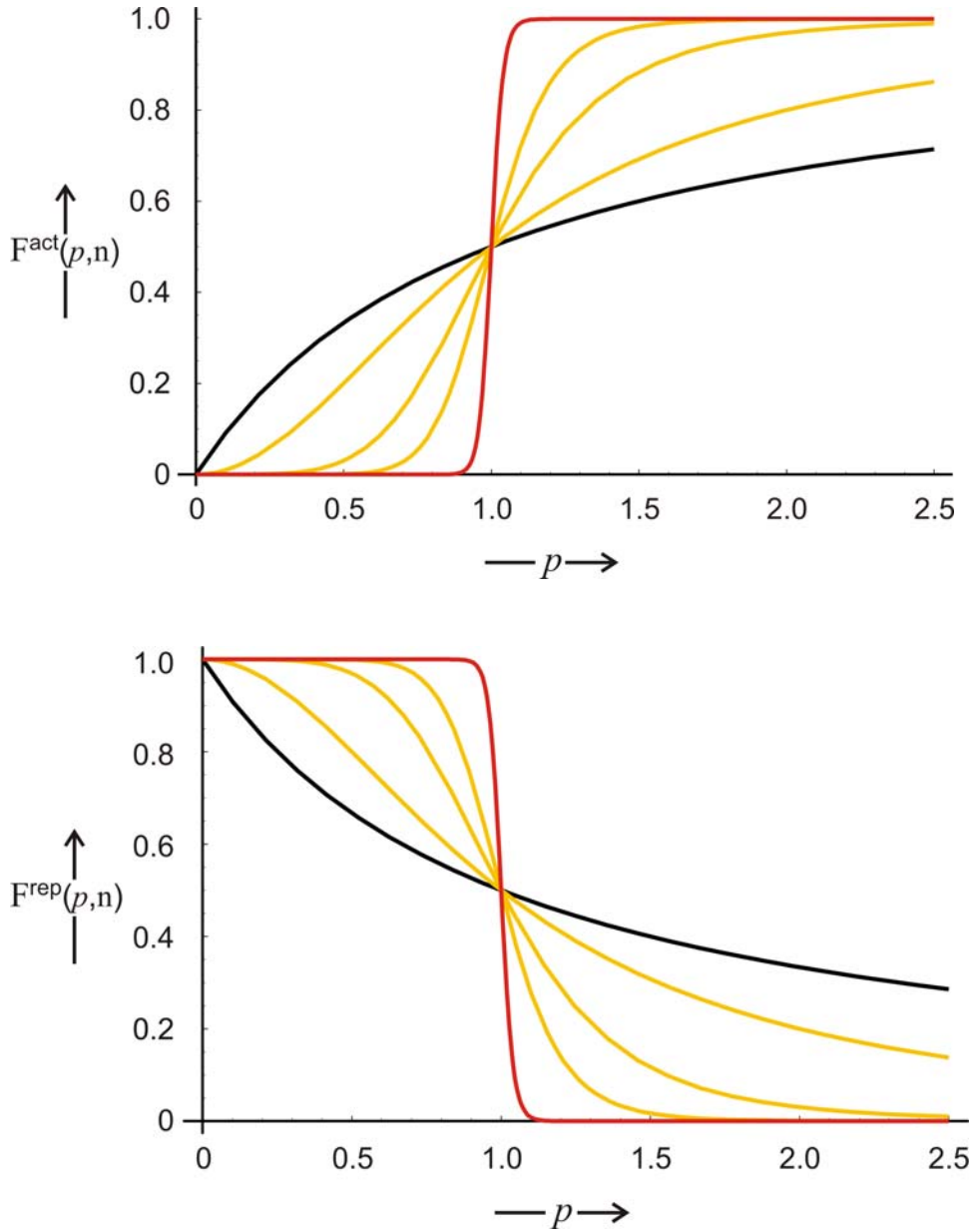


Cross-regulation of two genes

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

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

$$i, j = 1,2$$



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

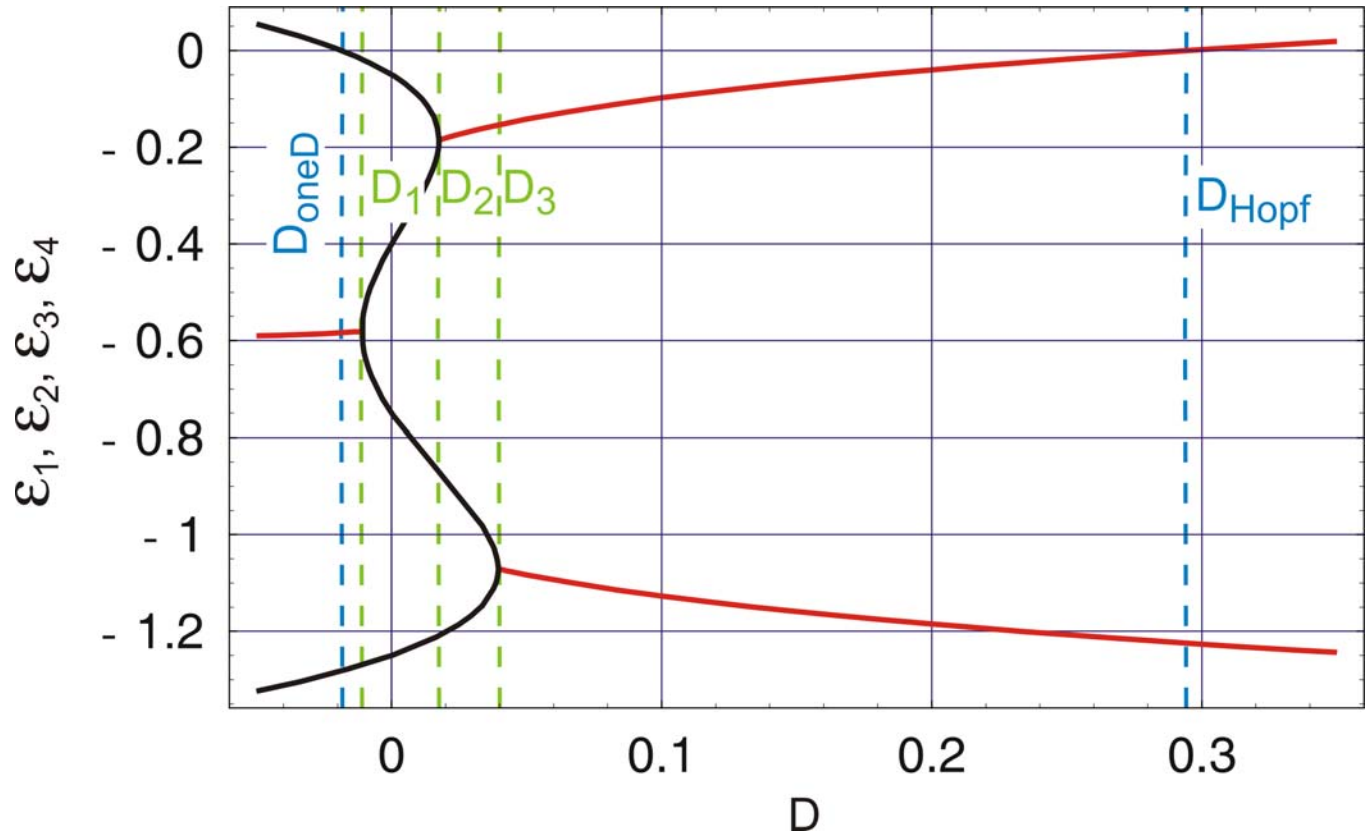
$$Q_D \cdot P_K = P_K \cdot Q_D \quad \text{and hence} \quad \begin{vmatrix} \mathrm{Q_D} & \mathrm{Q_K} \\ P_K & P_D \end{vmatrix} = \left| Q_D \cdot P_D - Q_K \cdot P_K \right|$$

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

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

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

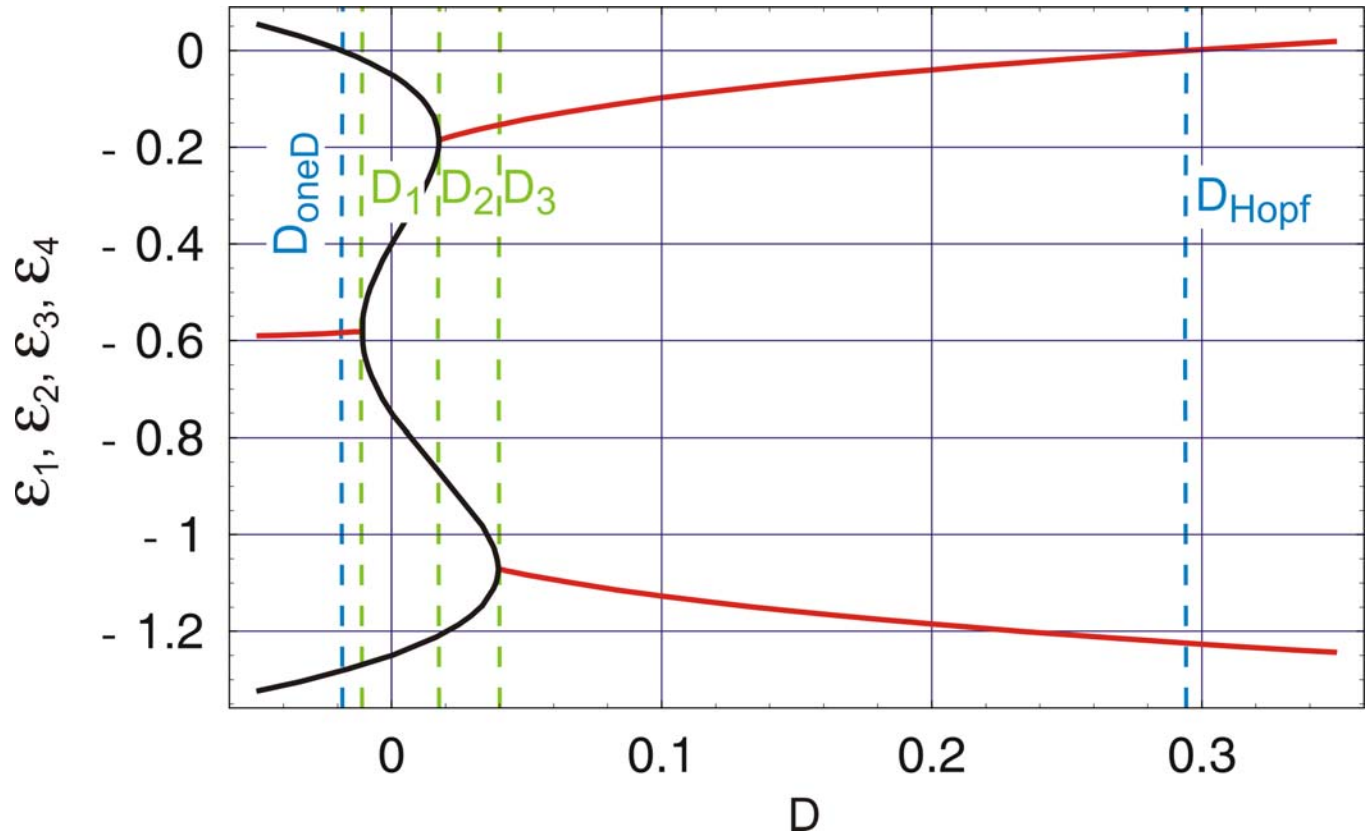
$$D = -k_1^{\mathrm{Q}} k_2^{\mathrm{Q}} k_1^{\mathrm{P}} k_2^{\mathrm{P}} \frac{\partial F_1}{\partial x_2}\frac{\partial F_2}{\partial x_1}$$



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

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

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



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

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

$0 \leq s < 0.5$

one stable state

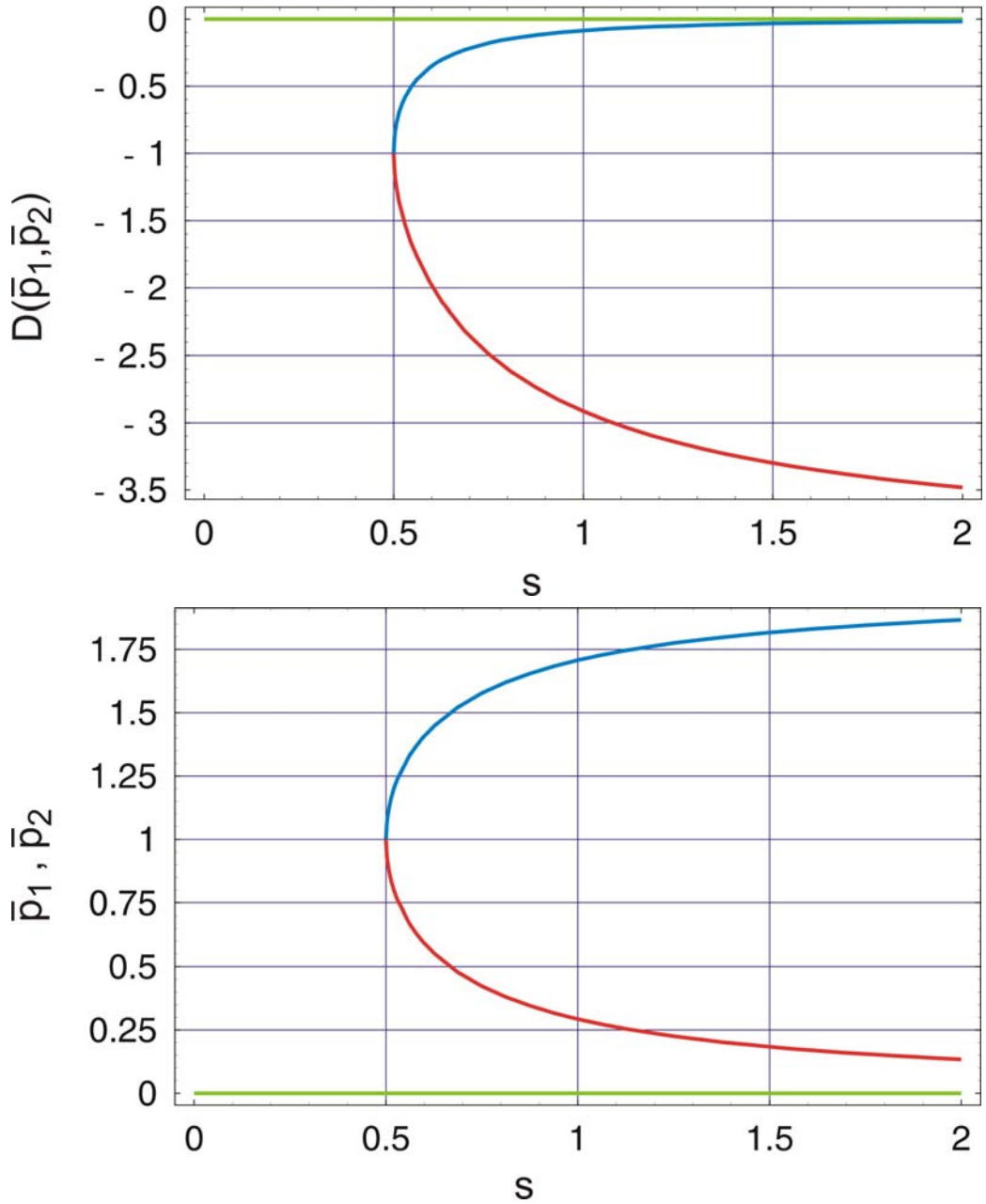
E: both genes off

$0.5 < s$

two stable states

E: both genes off

P: both genes on



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

$0 \leq s < 1.29$

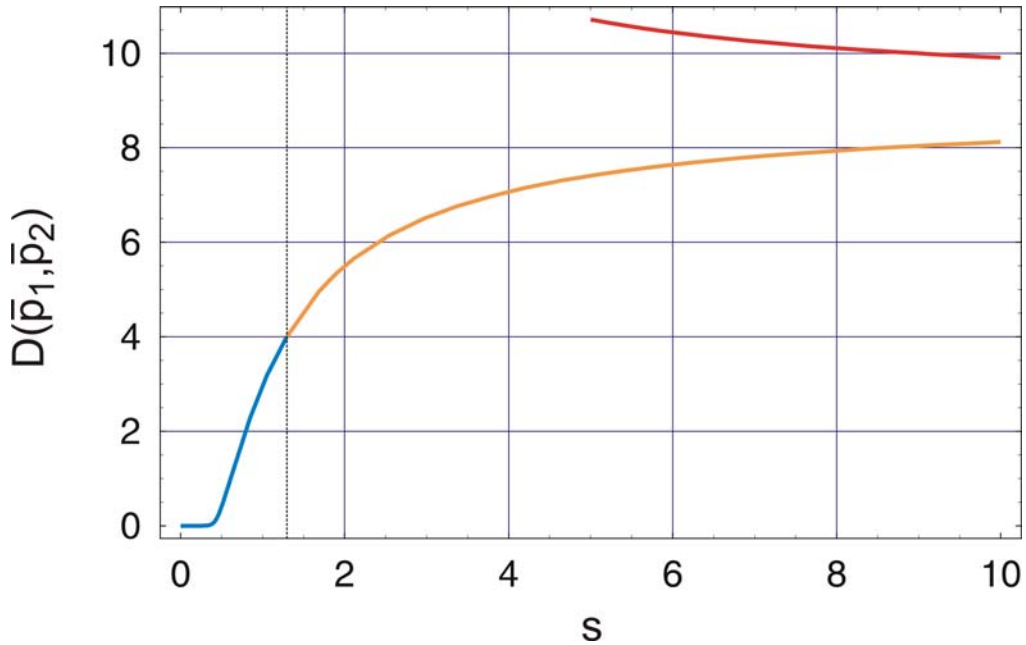
one stable state

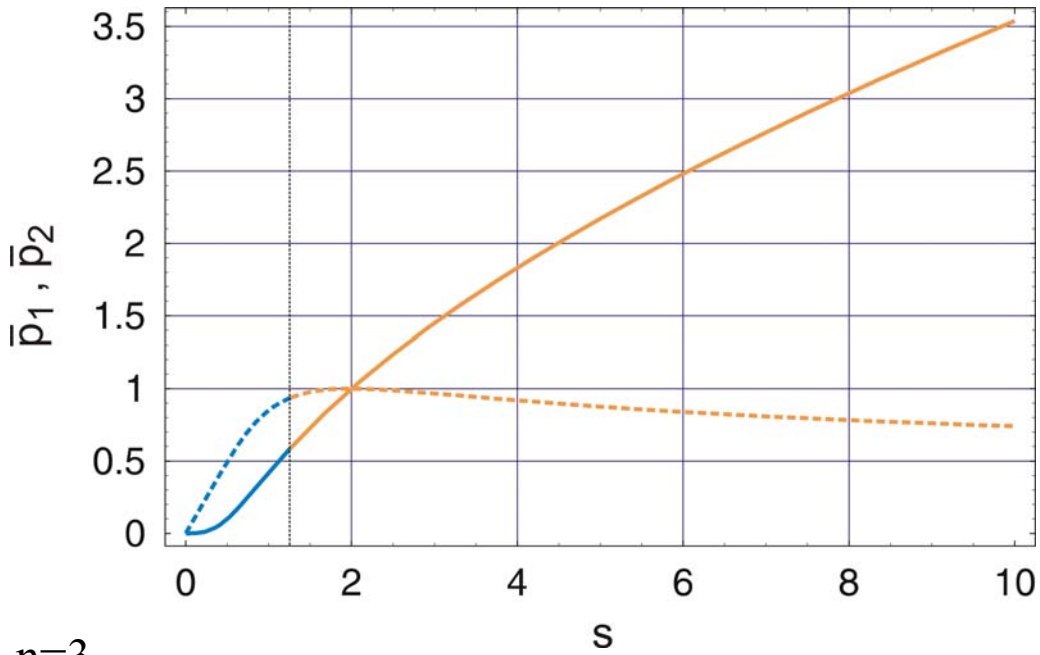
P: both genes on

$1.29 < s$

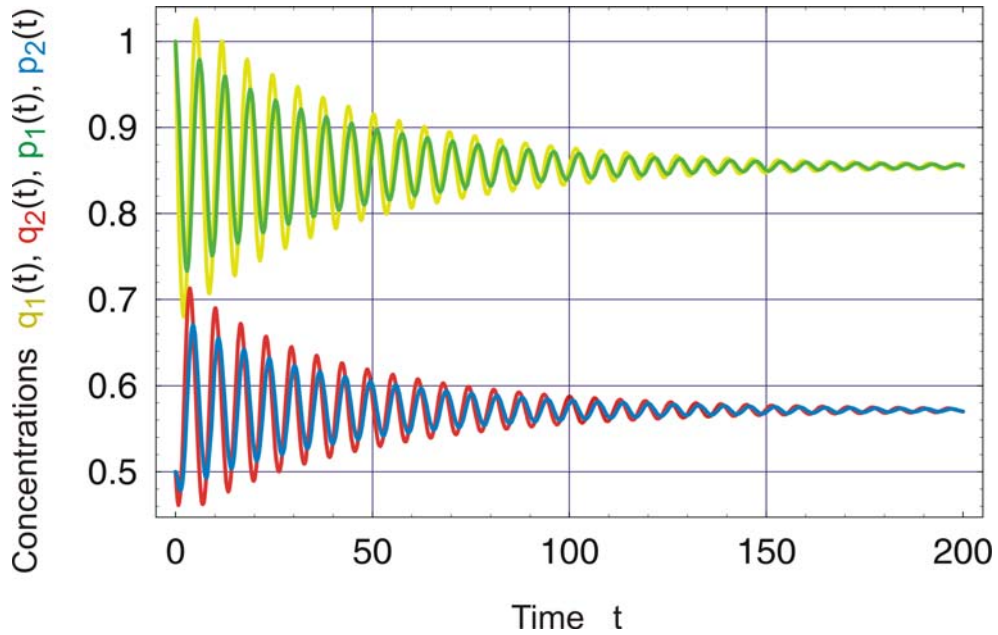
no stable state,

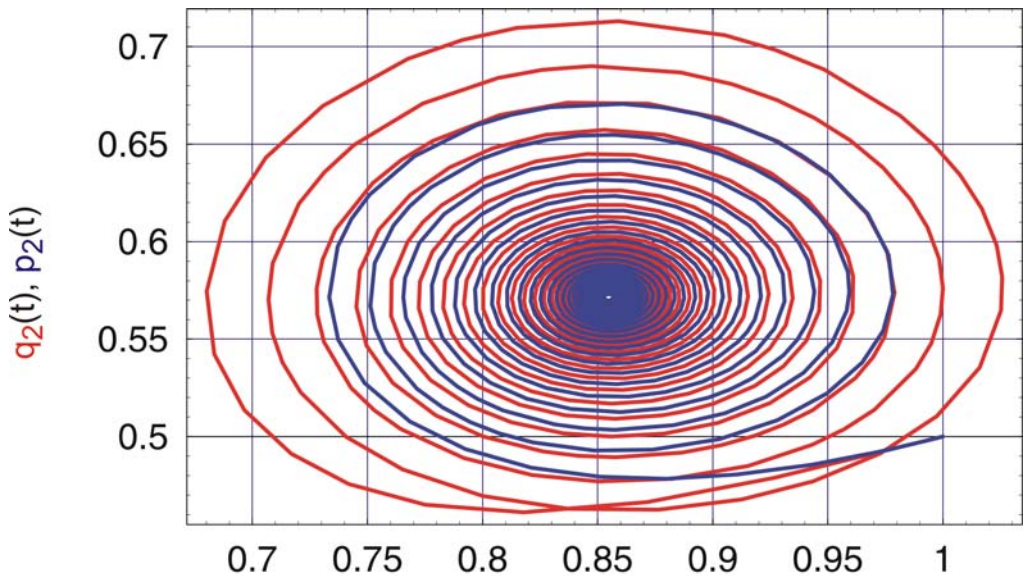
stable limit cycle



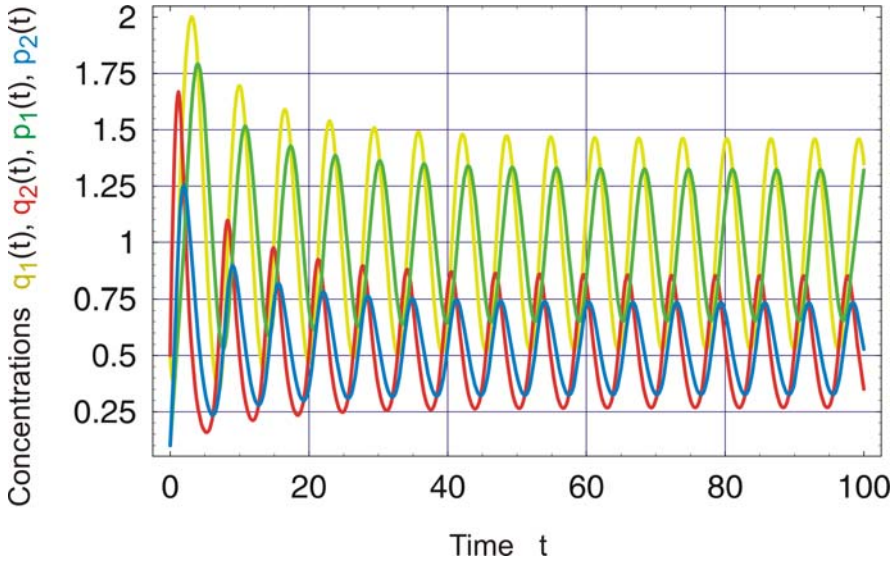


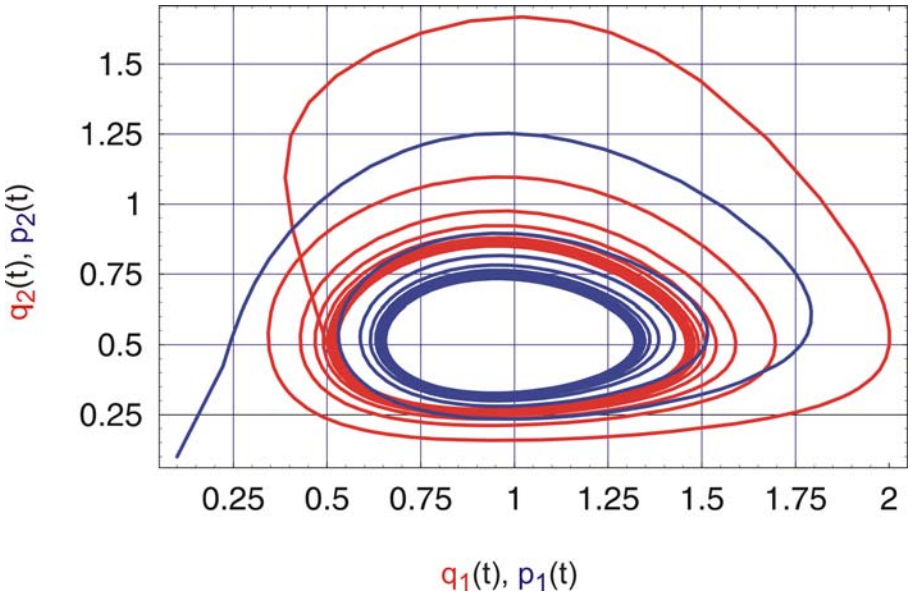
Regulatory dynamics at $D \geq 0$, act.-rep., n=3

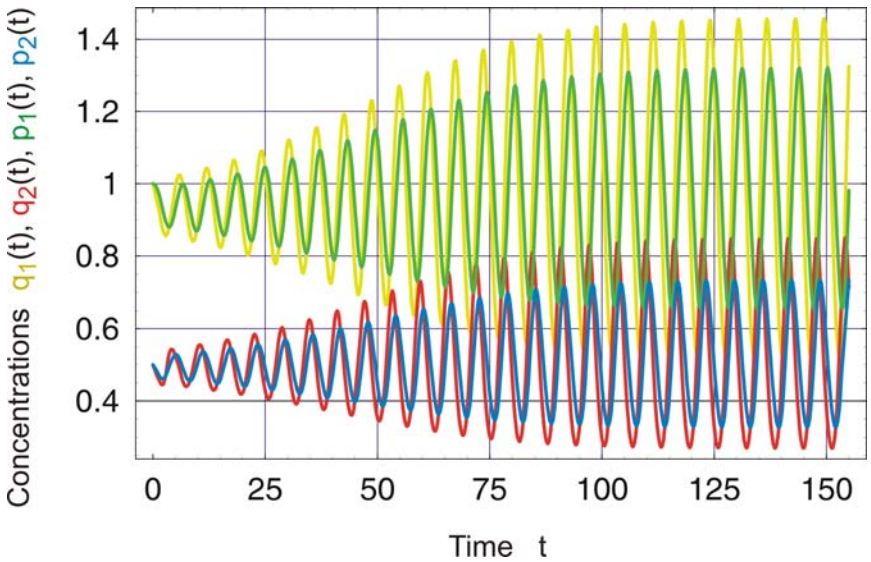


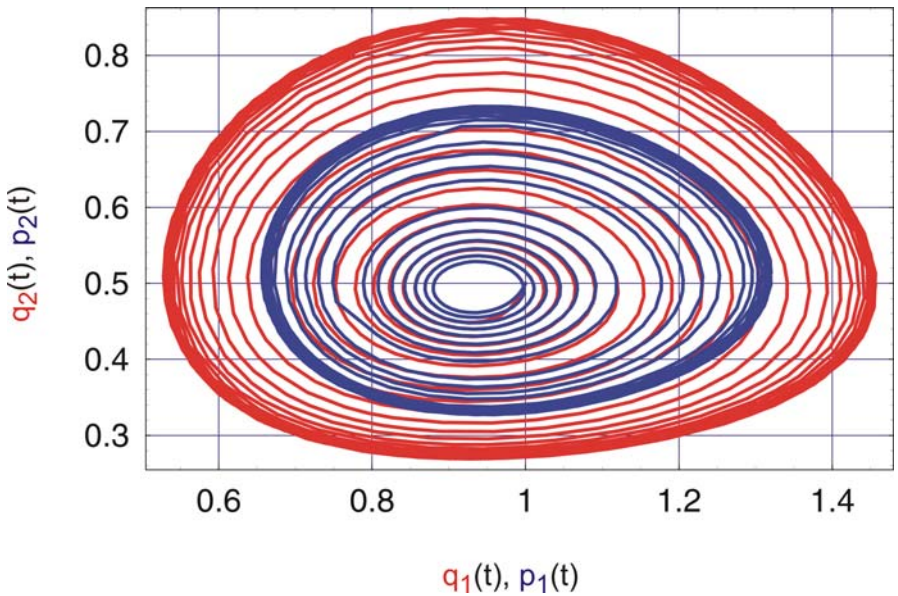


Regulatory dynamics at $D < D_{Hopf}$, act.-repr., n=3









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

$0 \leq s < 0.79$

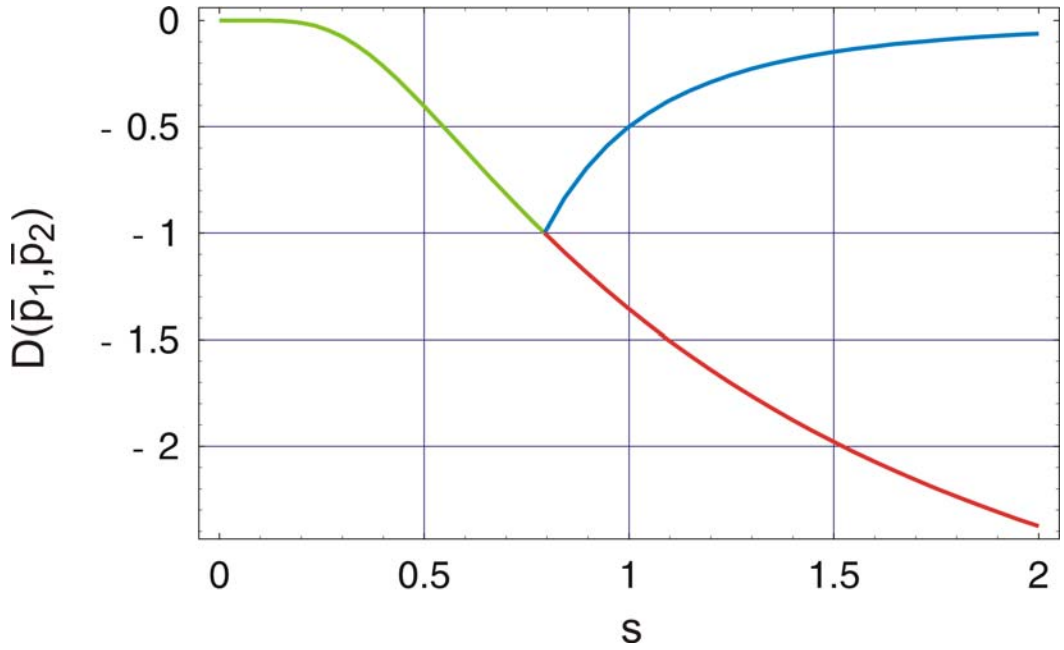
one stable state

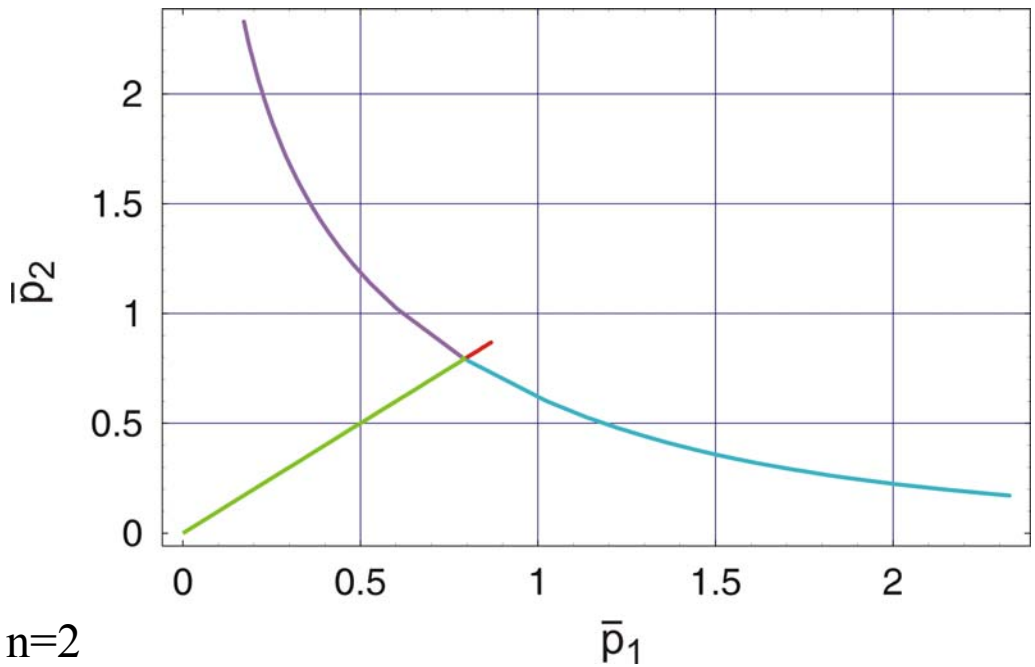
P: both genes on

$0.79 < s$

two stable states

P1: gene 1 on, gene 2 off
P2: gene 1 off, gene 2 on





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

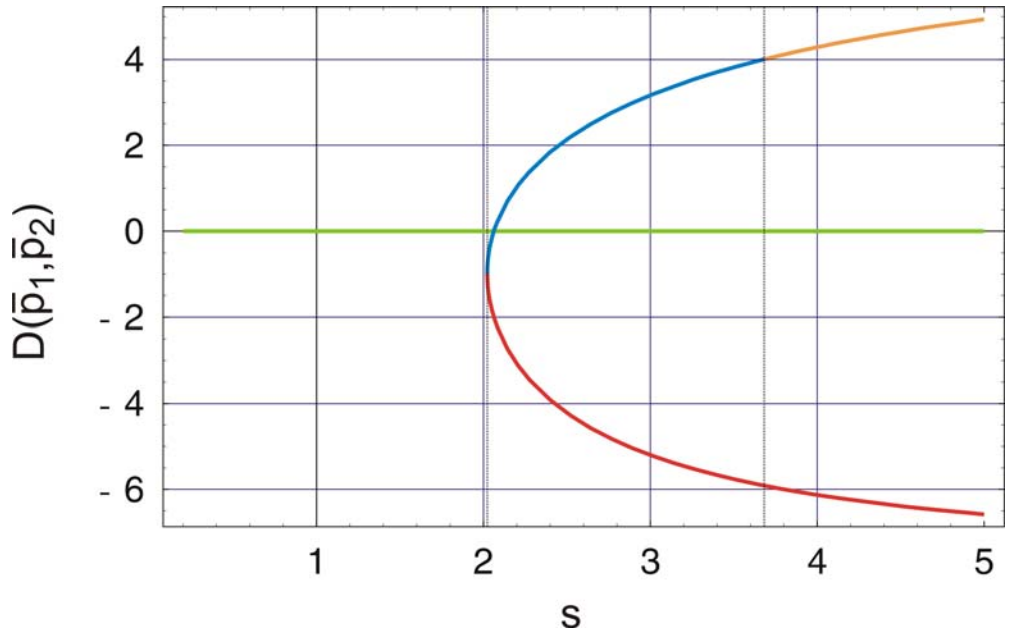
Hill coefficient: n	Act.-Act.	Act.-Rep.	Rep.-Rep.
1	S , E	S	S
2	E , B(E,P)	S	S , B(P_1,P_2)
3	E , B(E,P)	S , O	S , B(P_1,P_2)
4	E , B(E,P)	S , O	S , B(P_1,P_2)

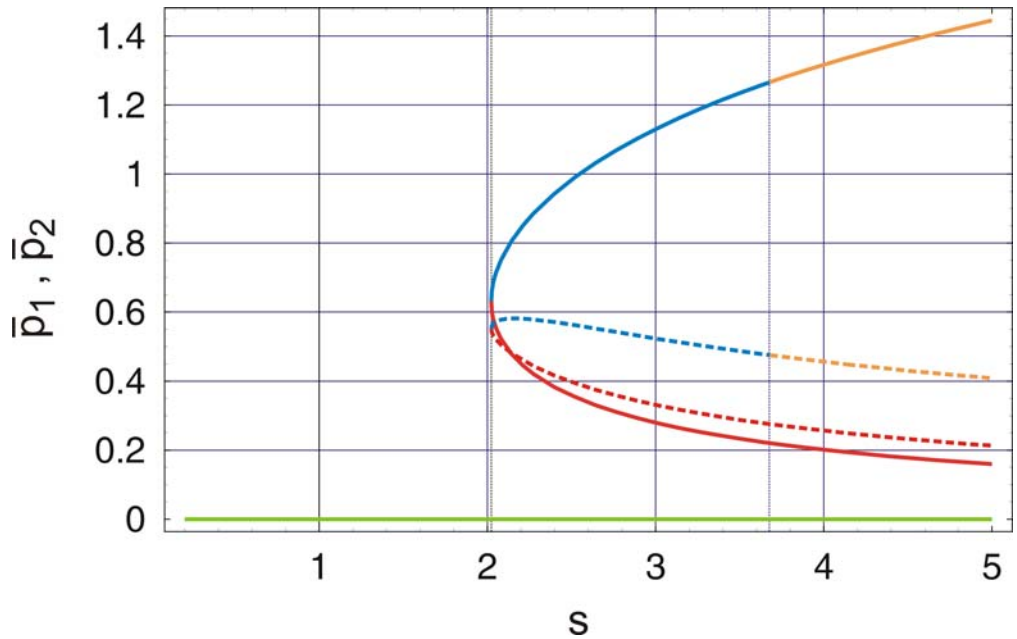
$$\text{Activation}: \quad F_i(p_j) = \frac{p_j^{\mathrm{n}}}{K + p_j^{\mathrm{n}}}$$

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

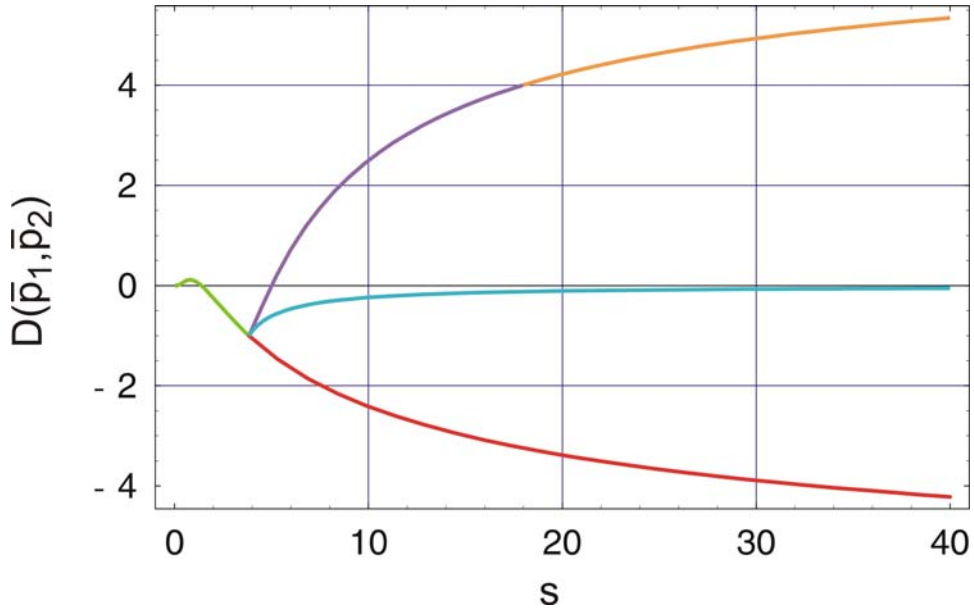
$$\text{Intermediate}: \quad F_i(p_j) = \frac{p_j^{\mathrm{m}}}{\kappa_1 + \kappa_2\, p_j + \kappa_3\, p_j^2 + \ldots + p_j^{\mathrm{n}}}$$

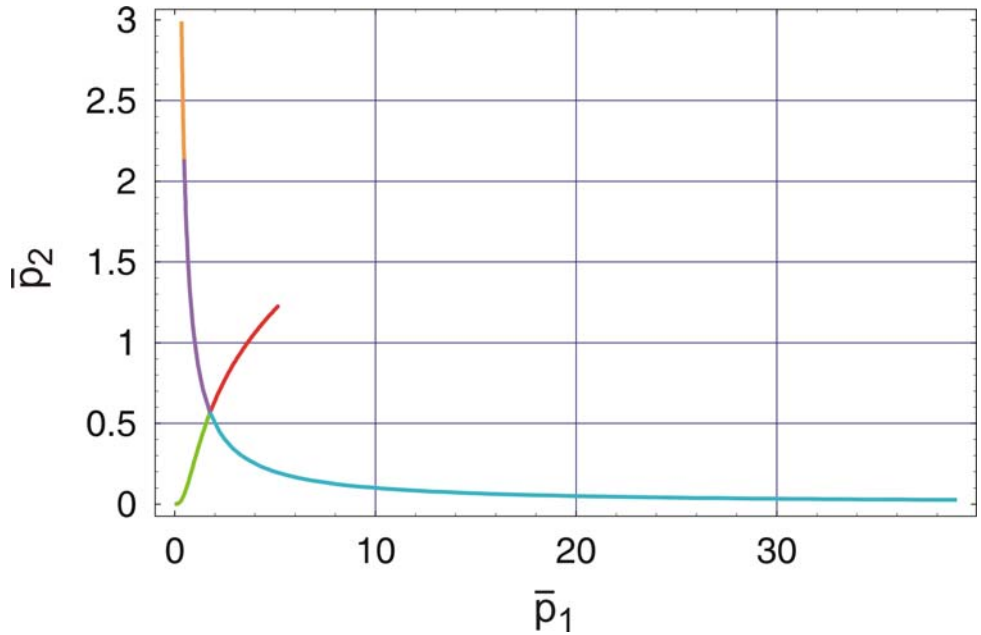
$$i, j = 1,2; \quad 1 \le m \le n-1$$





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



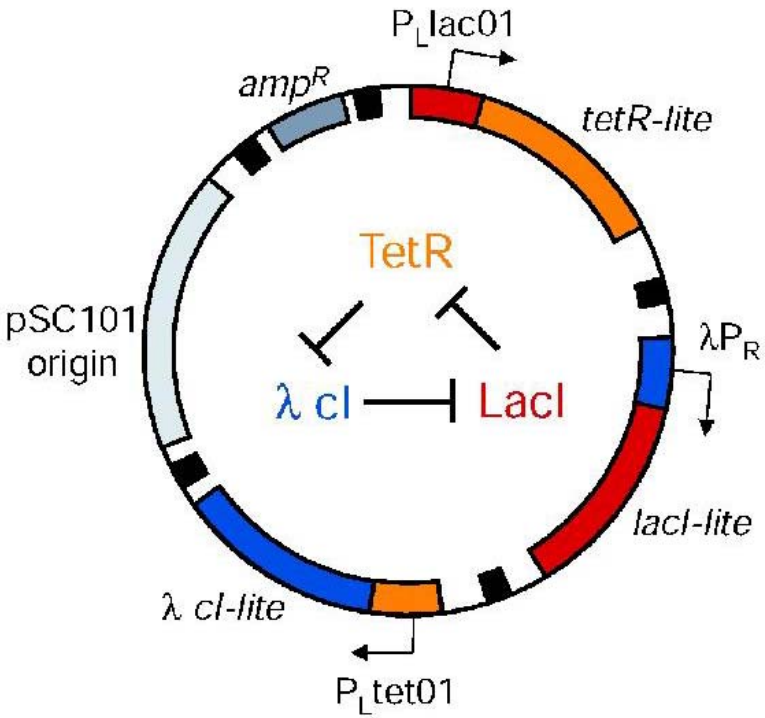


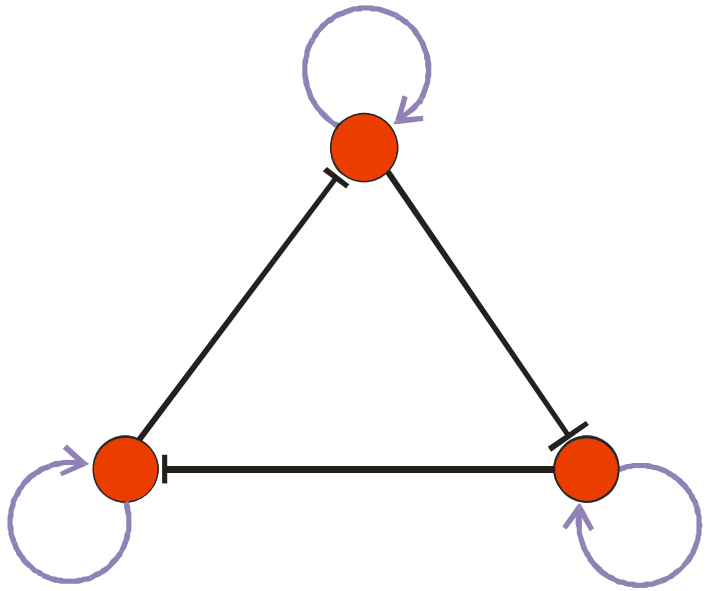
Regulatory dynamics, rep.-int., m=2, n=4

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

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

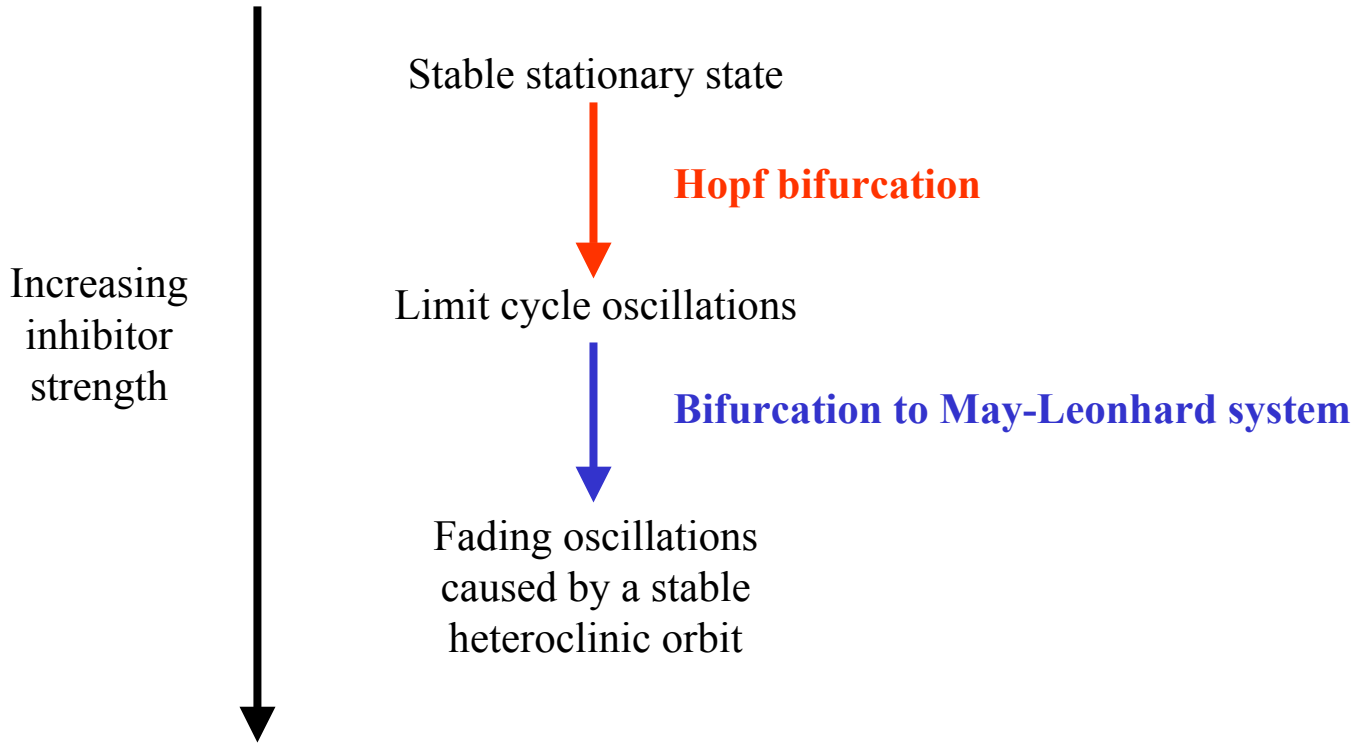
Upscaling to more genes: $n = 3$

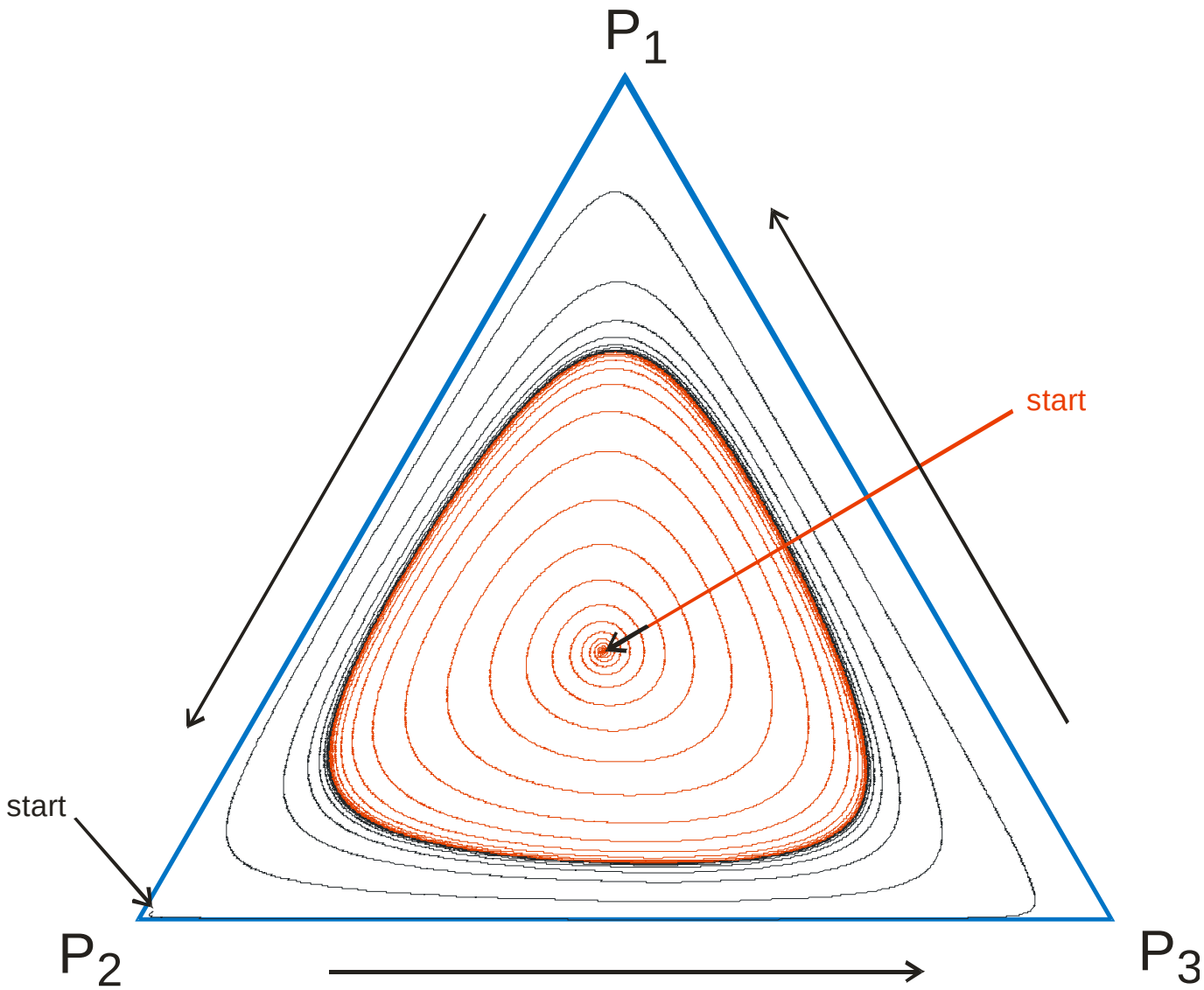




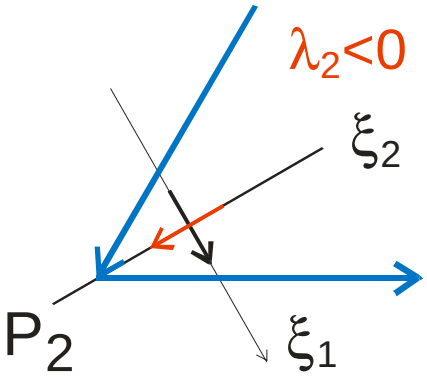
An example analyzed and simulated by MiniCellSim

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

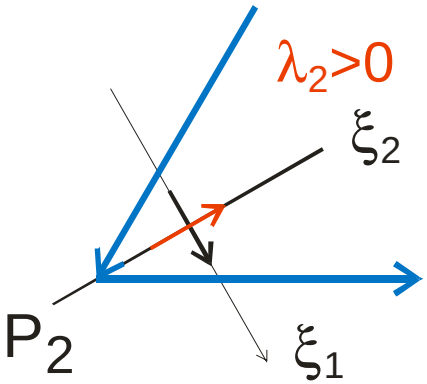

Increasing inhibitor strength
Stable stationary state
Hopf bifurcation
Limit cycle oscillations
Bifurcation to May-Leonhard system
Fading oscillations caused by a stable heteroclinic orbit



The repressilator limit cycle

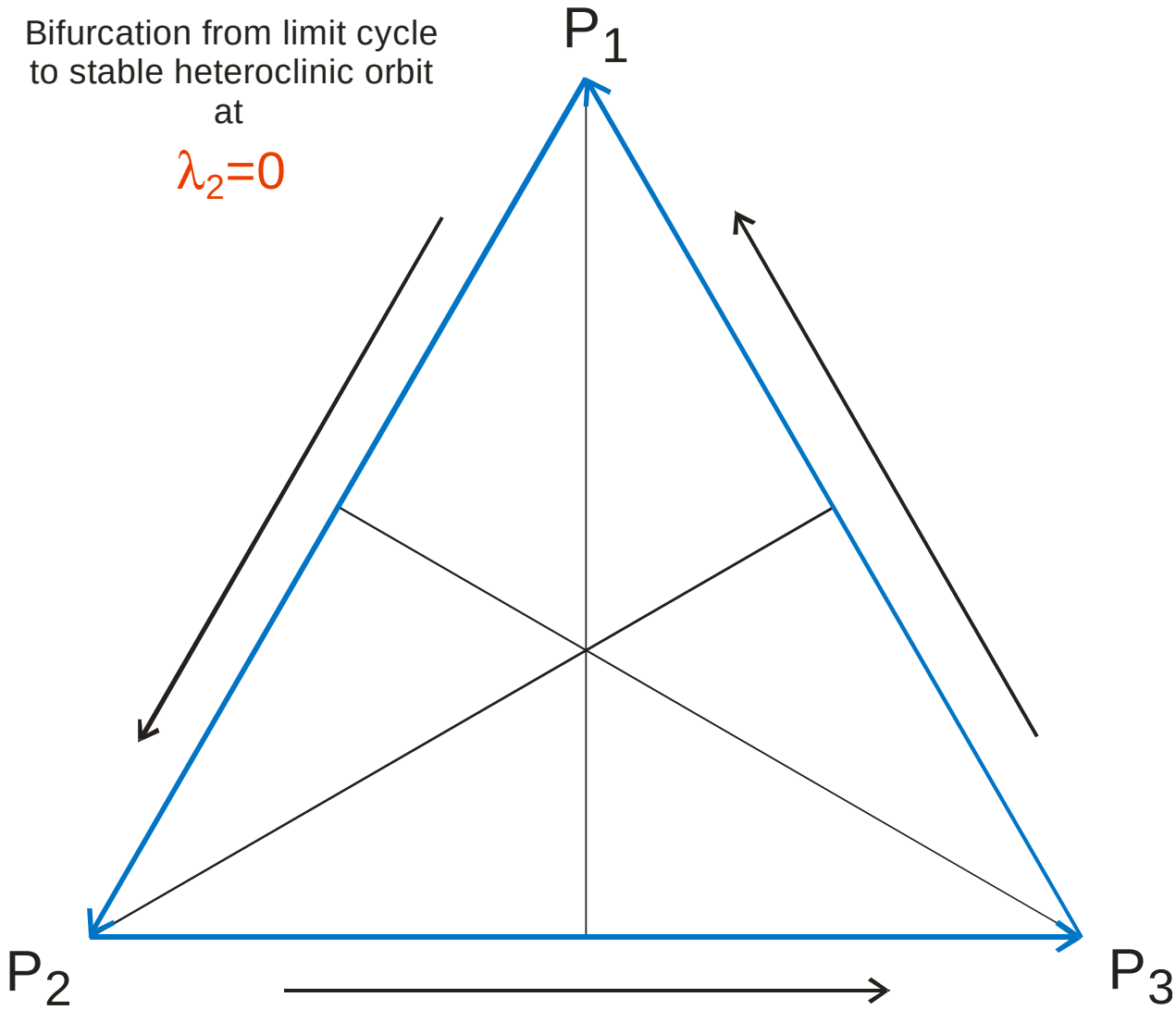


Stable heteroclinic orbit

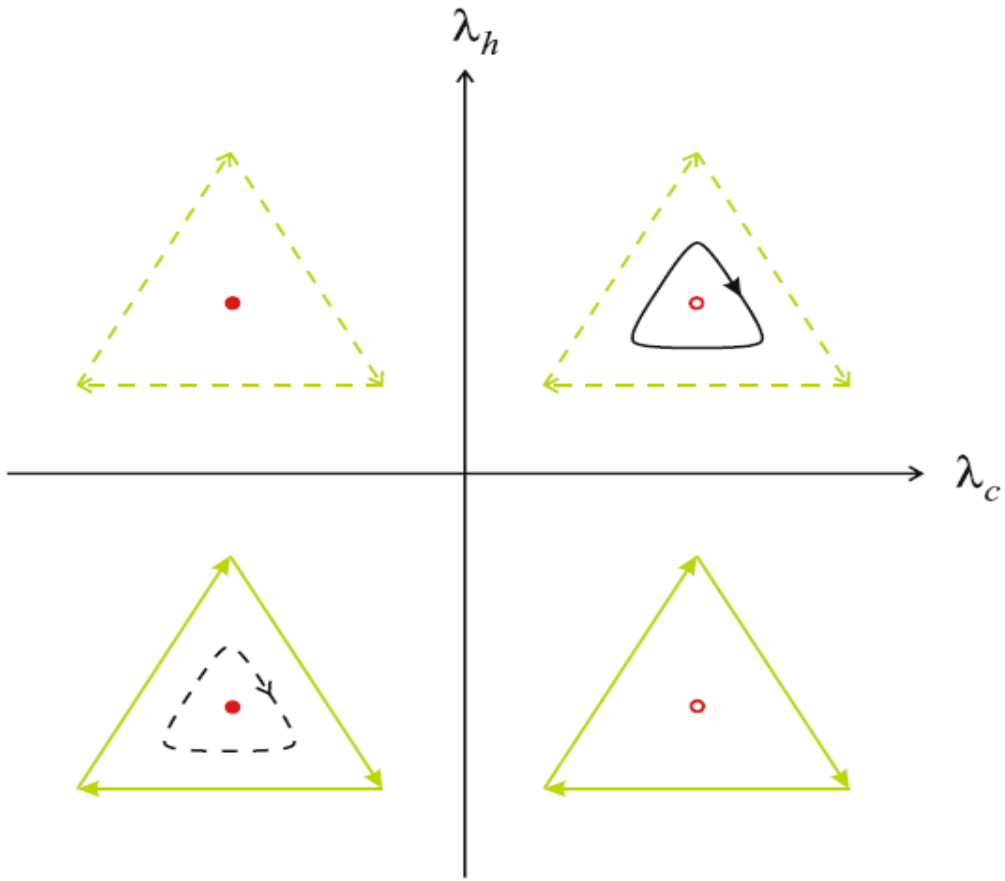


Unstable heteroclinic orbit

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

Stationarity approximation

$$\frac{dp_1}{dt} = k_1^P q_1 - d_1^P p_1 \quad \text{and} \quad \frac{dp_2}{dt} = k_2^P q_2 - d_2^P p_2$$

$$\bar{p}_1 = \frac{k_1^P}{d_1^P}\bar{q}_1 = \kappa_1 \bar{q}_1 \quad \text{and} \quad \bar{p}_2 = \frac{k_1^P}{d_2^P}\bar{q}_2 = \kappa_2 \bar{q}_2$$

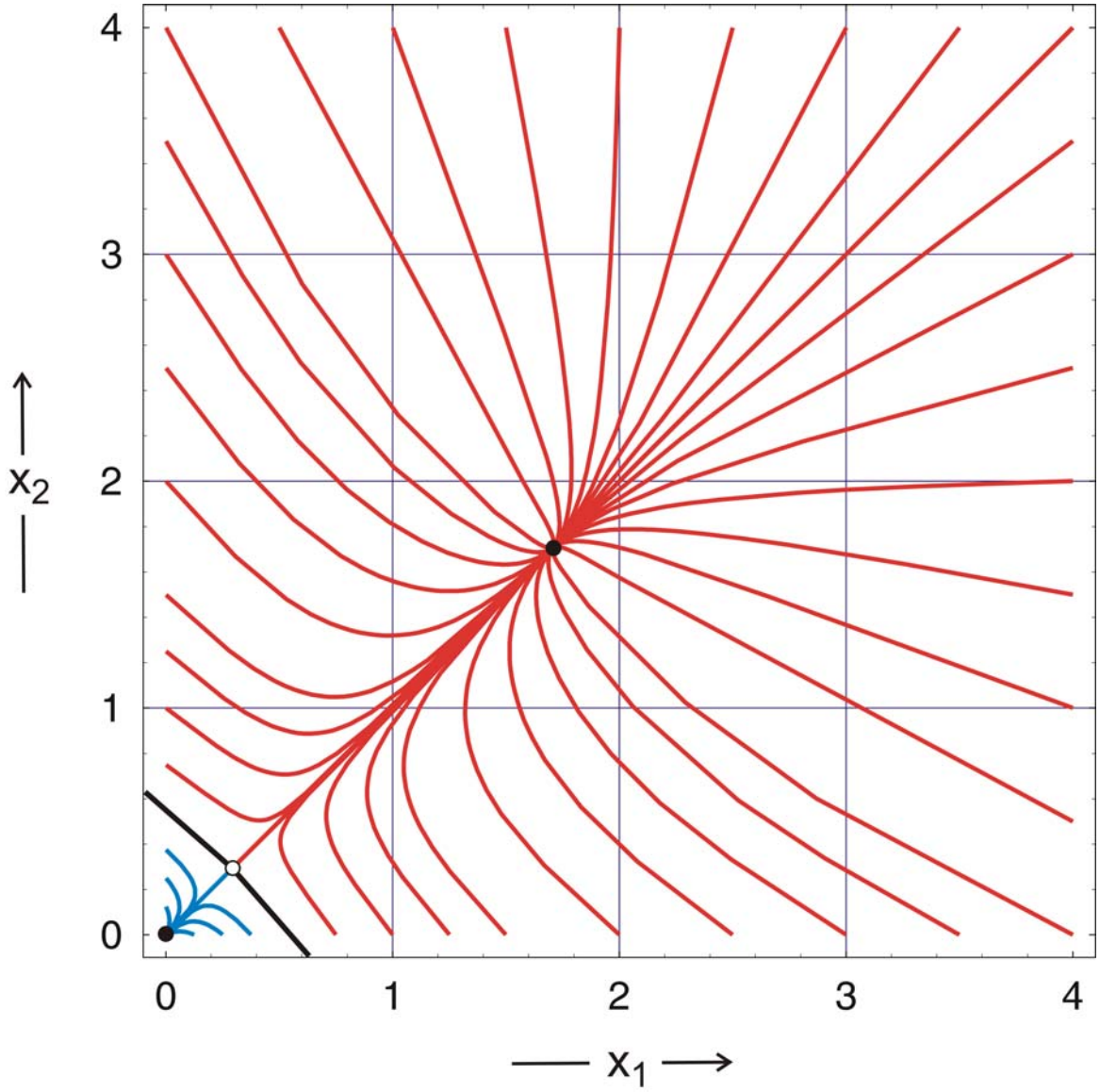
$$\frac{dx_1}{dt} = k_1 F_1(\kappa_2 x_2) - d_1 x_1 \quad \text{and} \quad \frac{dx_2}{dt} = k_2 F_2(\kappa_1 x_1) - d_2 x_2$$

$$K_1 \Rightarrow K_1 \Big/ \kappa_1^n \quad \text{and} \quad K_2 \Rightarrow K_2 \Big/ \kappa_2^n$$

two stable states

E: both genes off

P: both genes on

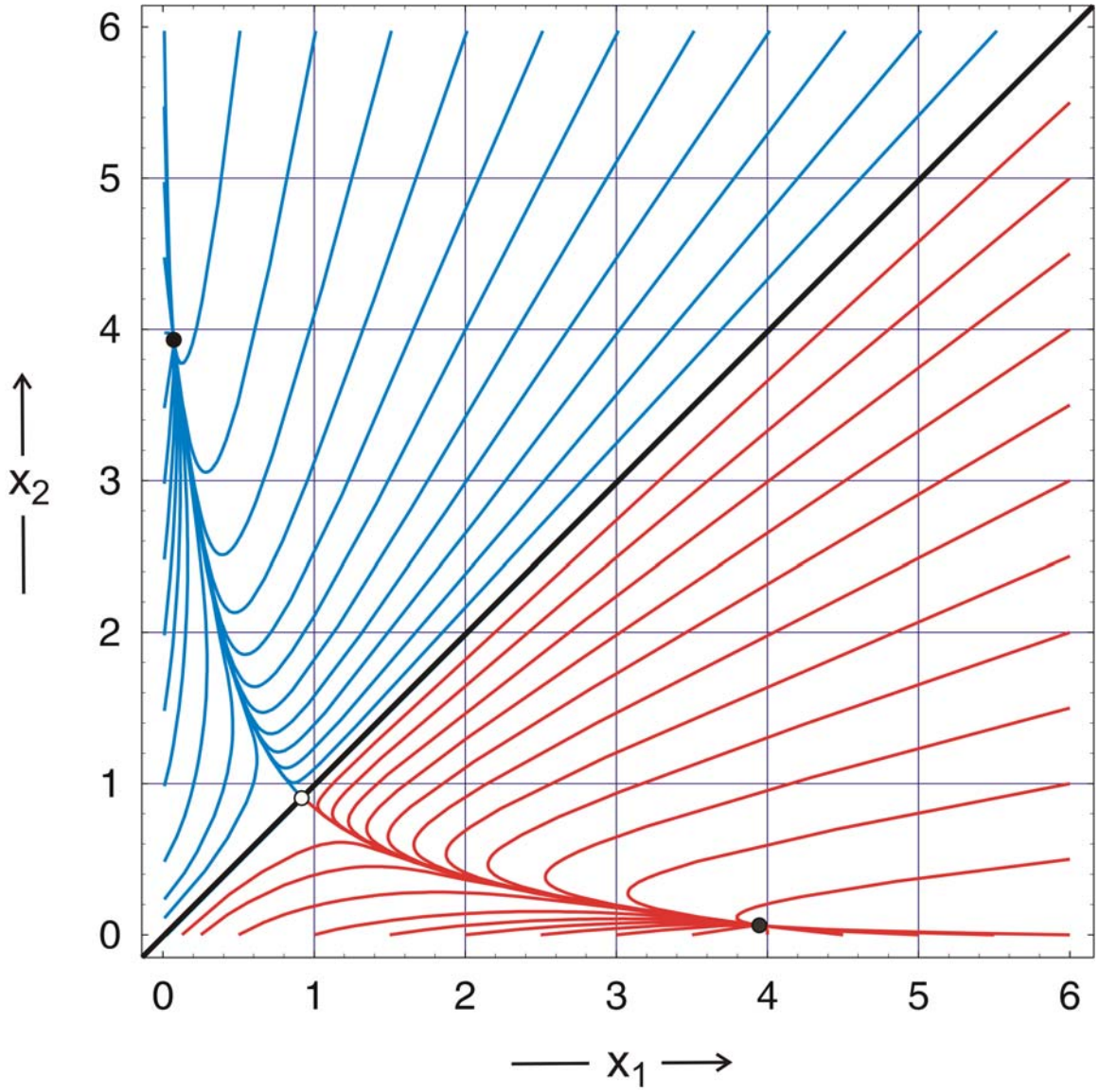


Simplified two gene system (x_1,x_2): act2-act2

two stable states

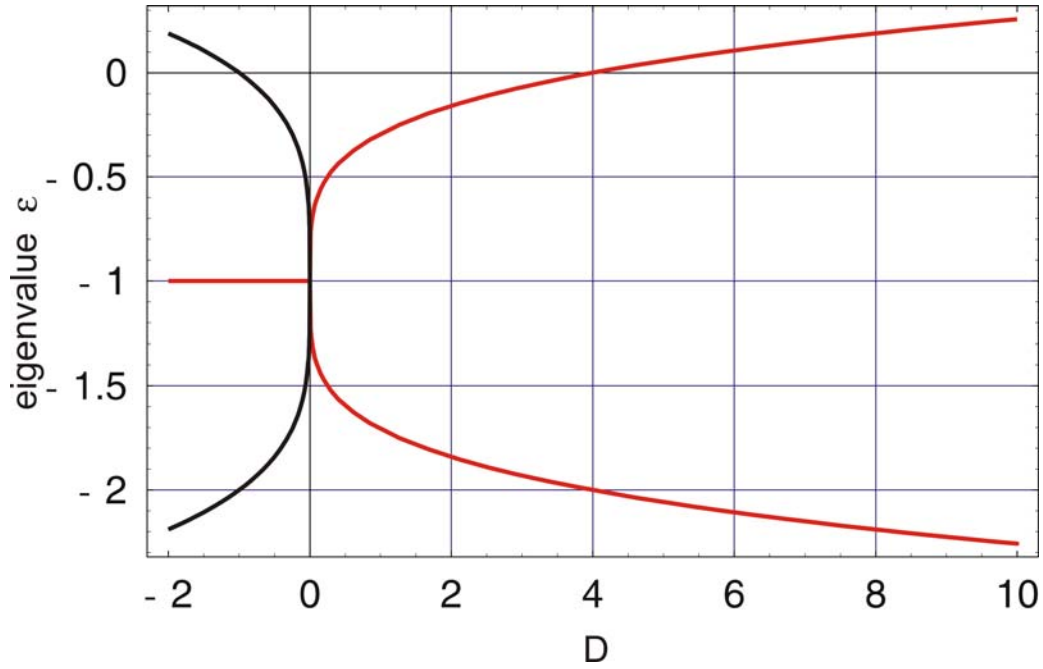
P_1: gene 1 on, gene 2 off

P_2: gene 1 off, gene 2 on

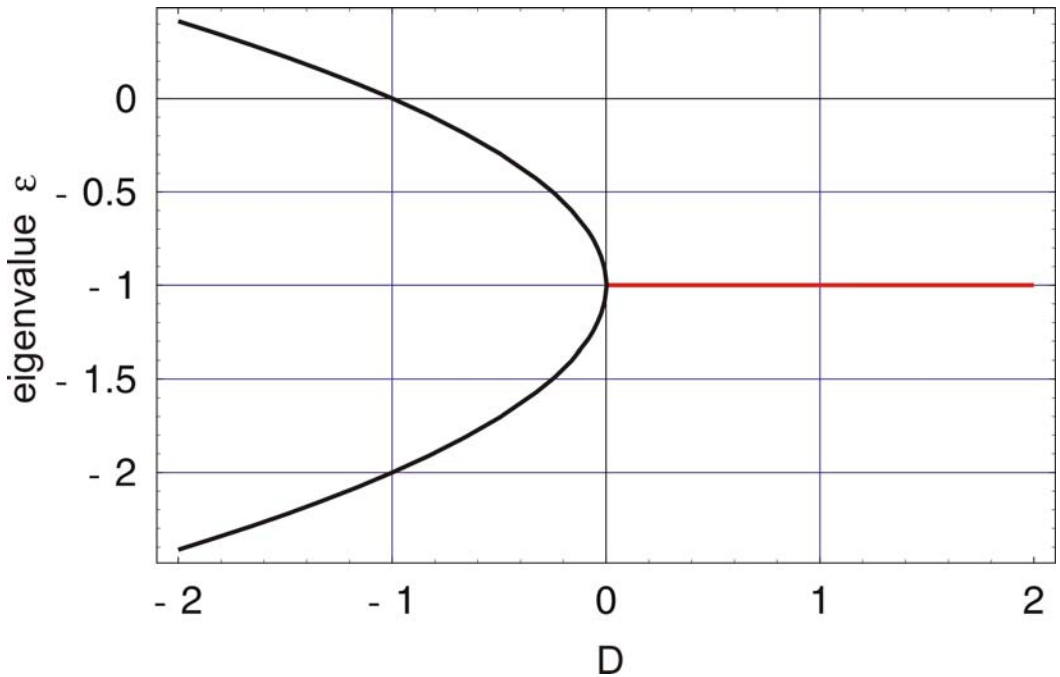


Simplified two gene system (x_1,x_2): rep2-rep2

full two gene system:
(q_1,q_2,p_1,p_2)

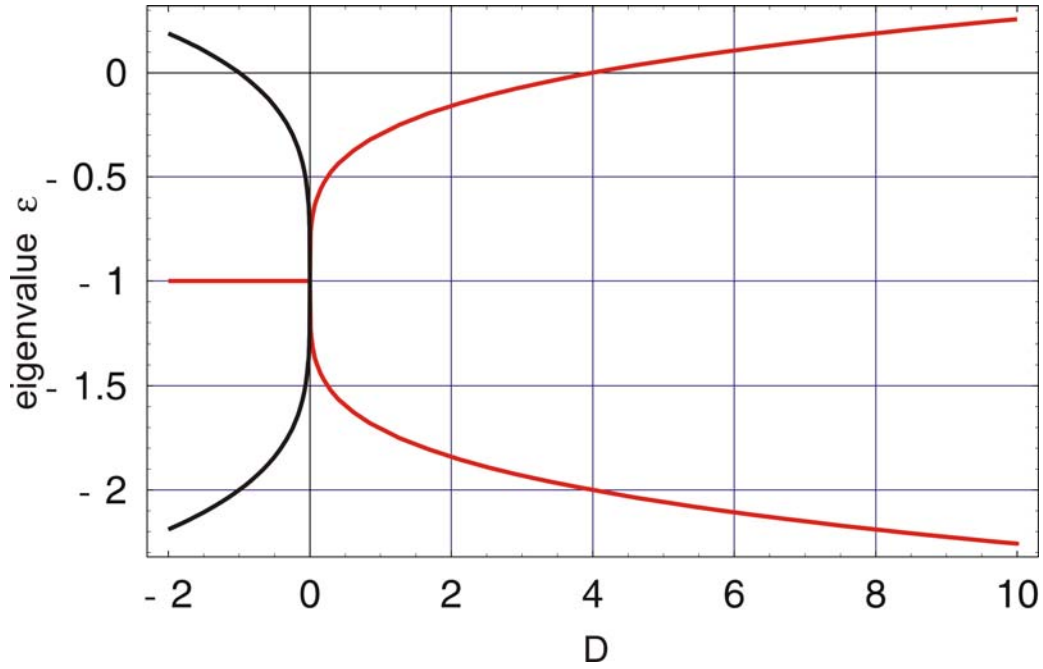


simplified two gene system:
(x_1,x_2)

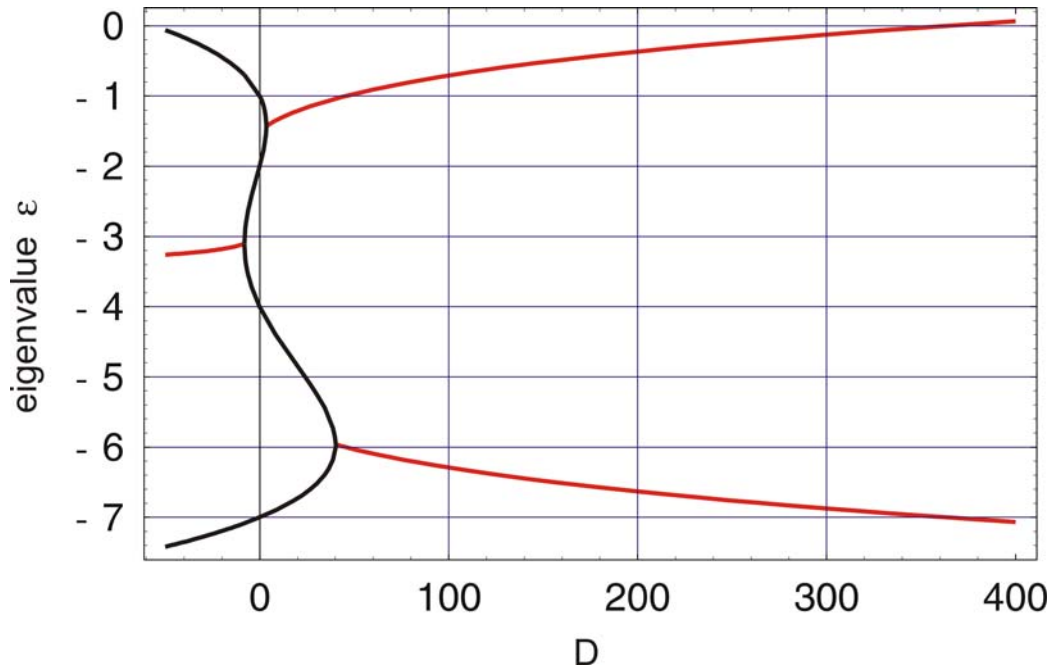


Bifurcation analysis

full two gene system:
„symmetric“
(q_1,q_2,p_1,p_2)

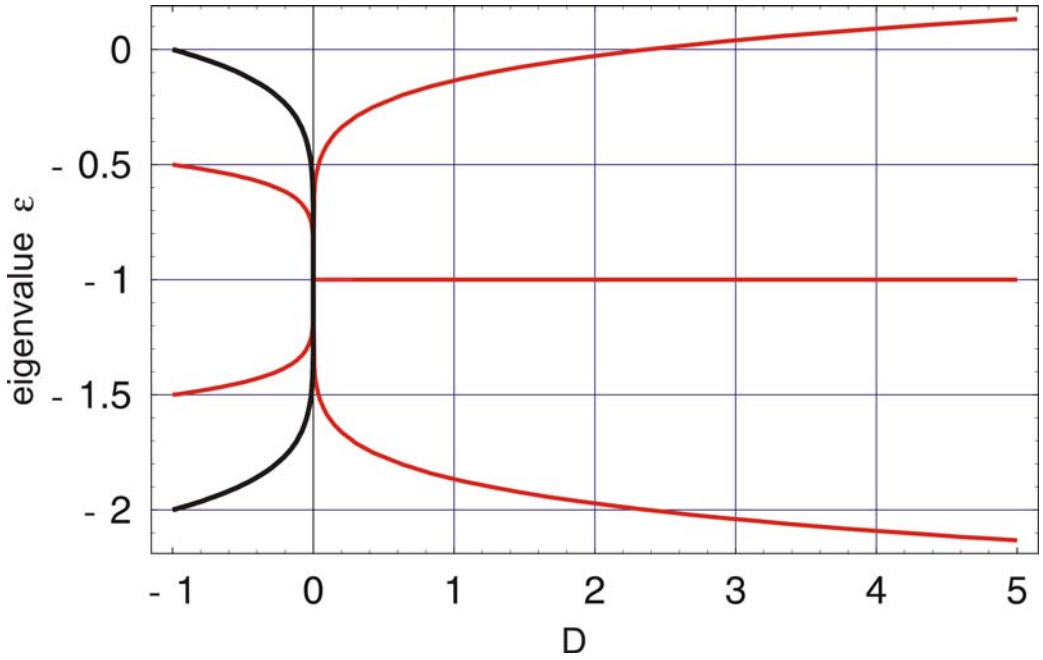


full two gene system:
„asymmetric“
(q_1,q_2,p_1,p_2)

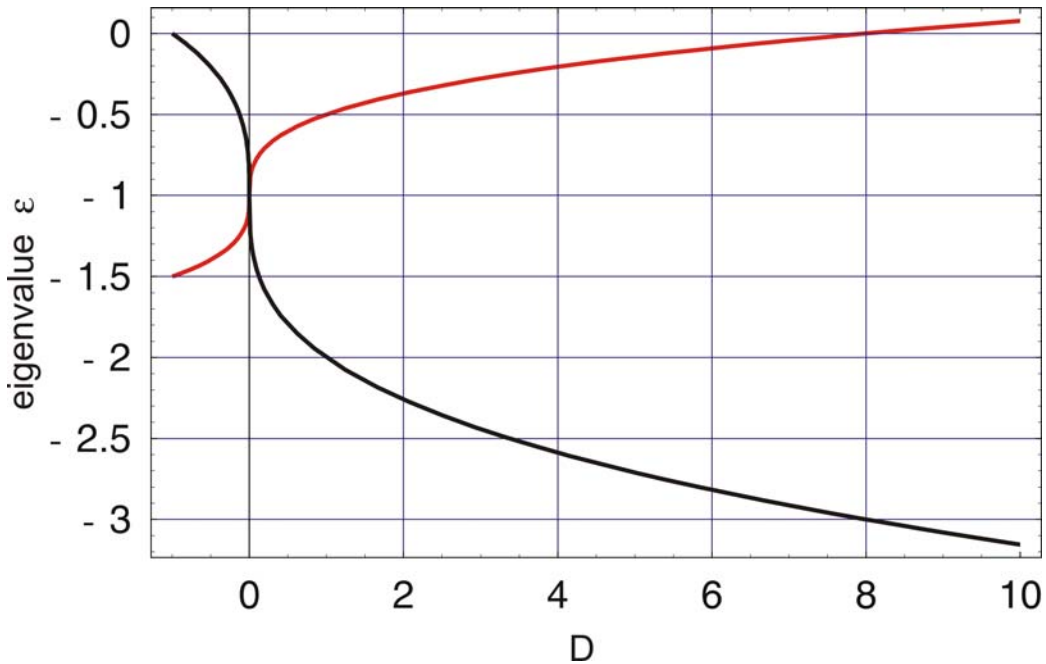


Bifurcation analysis

full three gene system:
(q_1,q_2,q_3,p_1,p_2,p_3)



simplified three gene system:
(x_1,x_2,x_3)



Bifurcation analysis

1. Biochemical kinetics and systems biology
2. Forward and inverse problems
3. Regulation kinetics and bifurcation analysis
4. **Reverse engineering of dynamical systems**
5. Future problems of quantitative biology

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

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.

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

$k = 1, 2, 3$

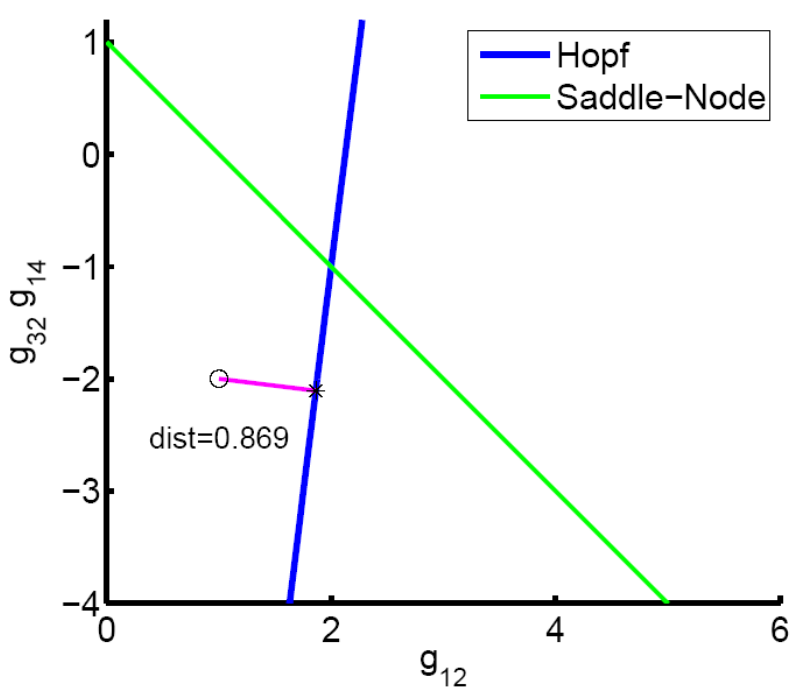
$$f_1 = \begin{cases} B & \text{for } x_2^{g12} x_4^{g14} \le B \\ x_2^{g12} x_4^{g14} & \text{for } B < x_2^{g12} x_4^{g14} < M \\ M & \text{for } x_2^{g12} x_4^{g14} \ge M \end{cases}$$

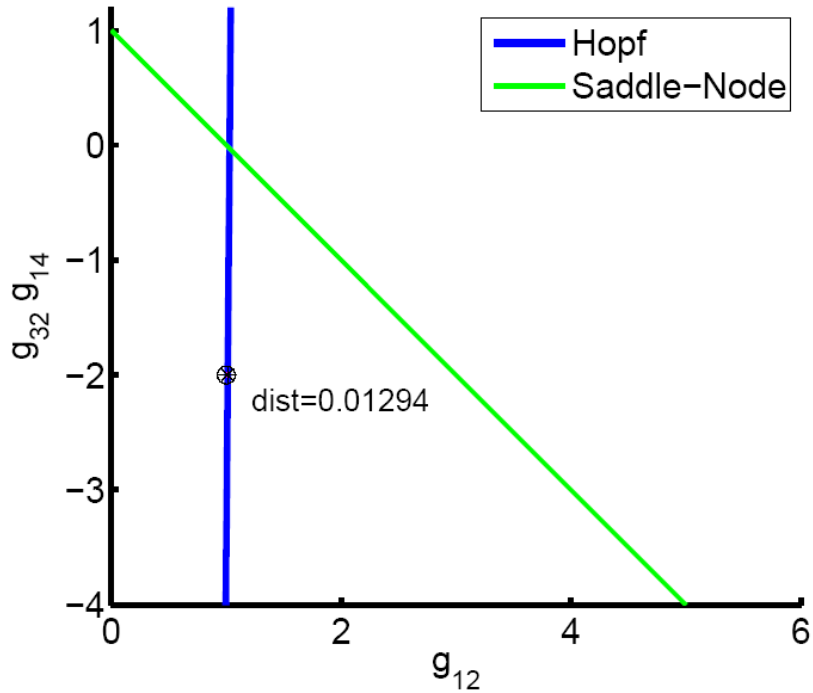
$$f_3 = \begin{cases} B & \text{for } x_2^{g32} \le B \\ x_2^{g32} & \text{for } B < x_2^{g32} < M \\ M & \text{for } x_2^{g32} \ge M \end{cases}$$

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

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.

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

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

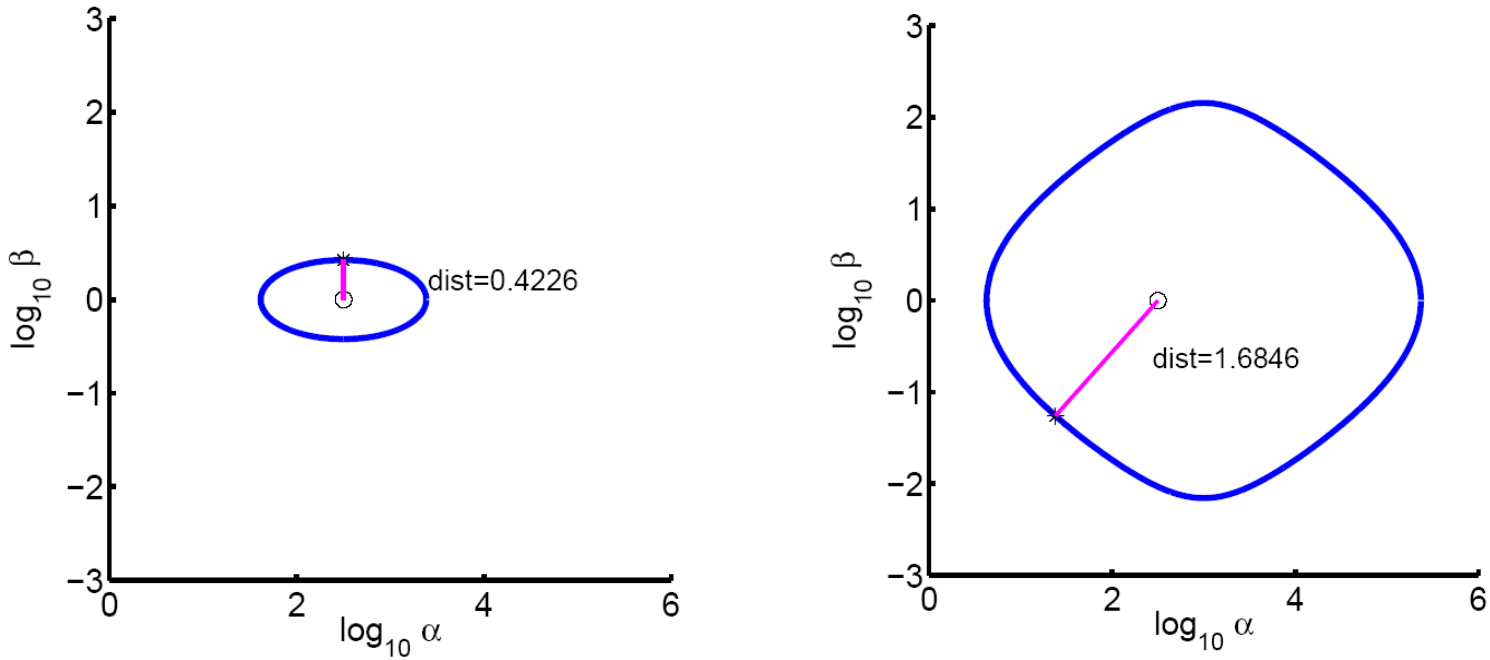
$$p_i = (\alpha, \beta)$$

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

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

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.

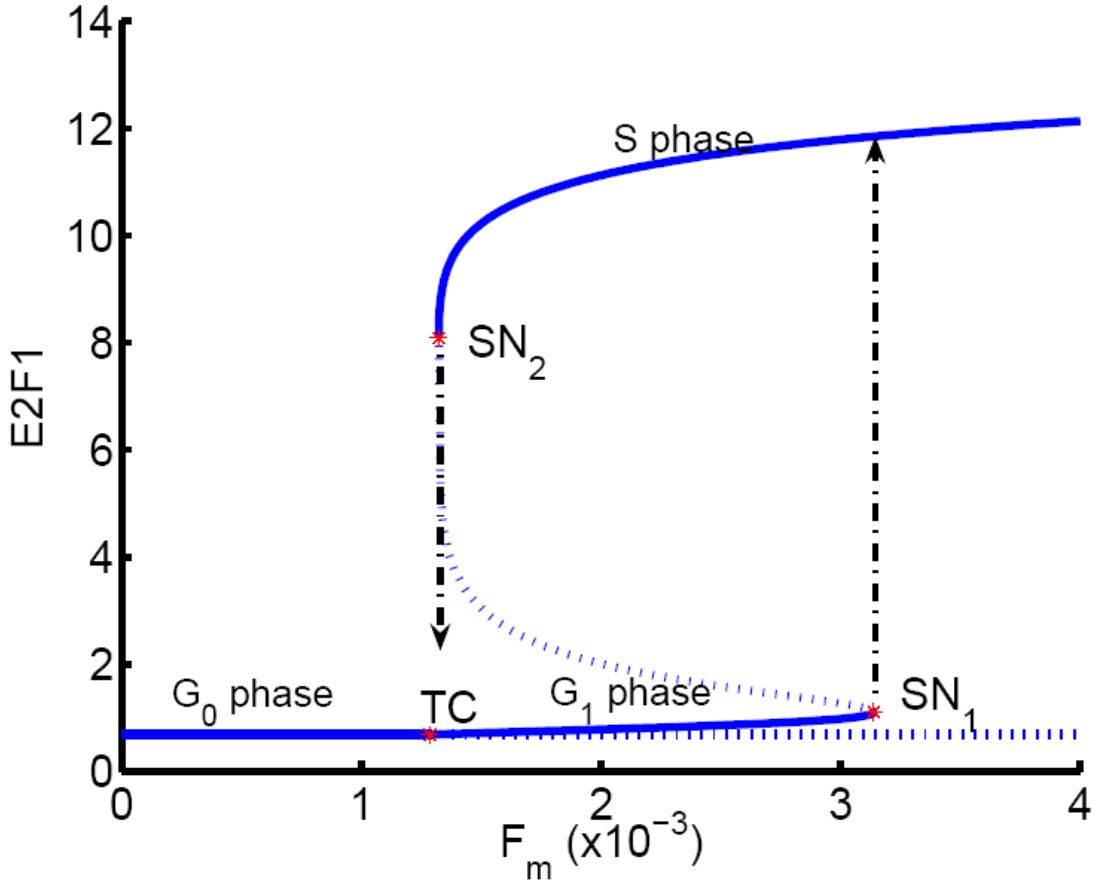
$$\frac{d}{dt}[\mathrm{pRB}] = k_1 \frac{[\mathrm{E2F1}]}{K_{m1} + [\mathrm{E2F1}]} \frac{J_{11}}{J_{11} + [\mathrm{pRB}]} - \phi_{\mathrm{pRB}}[\mathrm{pRB}]$$

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

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

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



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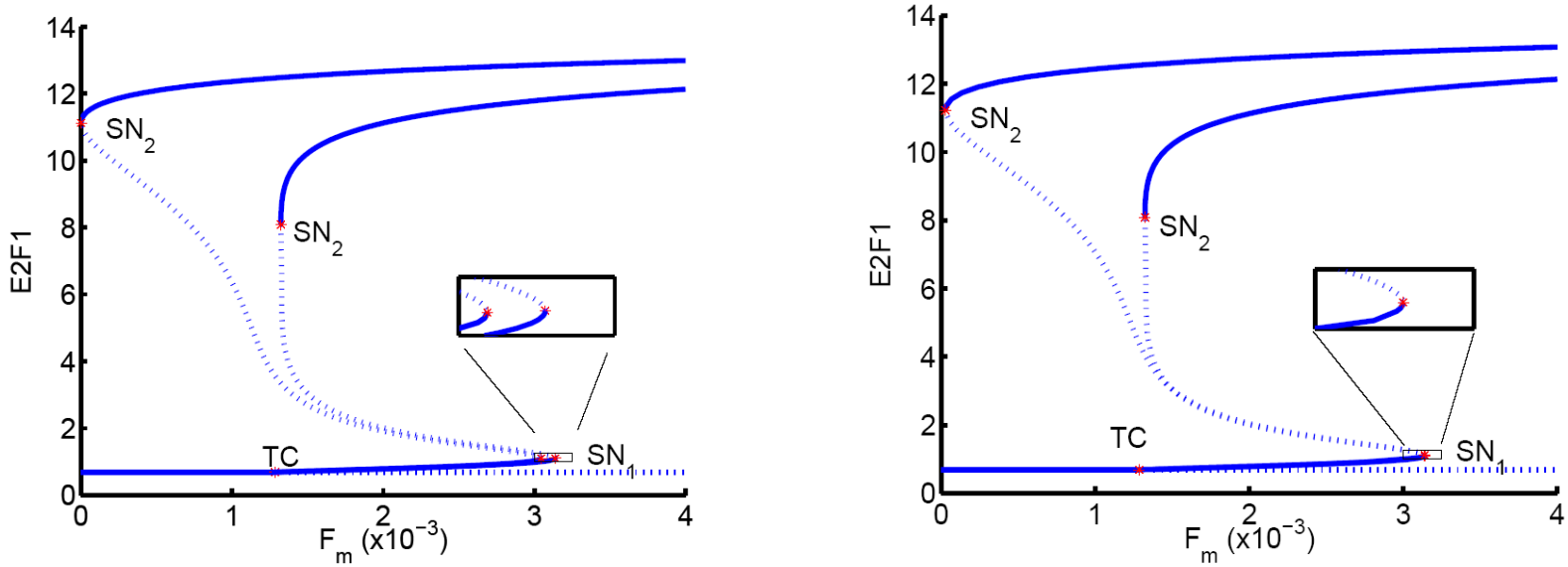
J.J. Tyson, A. Csikasz-Nagy, B. Novak. The dynamics of cell cycle regulation. *Bioessays* **24**:1095-1109, 2002



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. Biochemical kinetics and systems biology
2. Forward and inverse problems
3. Regulation kinetics and bifurcation analysis
4. Reverse engineering of dynamical systems
5. **Future problems of quantitative biology**

Challenges of quantitative biology

1. Validation of data from different sources
2. Low particle numbers and stochasticity
3. Conformational heterogeneity of biomolecules
4. High dimensionality of molecular dynamical systems
5. Spatial heterogeneity of cells and cell organelles

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Suitable systems for upscaling

1. Linear systems via large eigenvalue problems
2. Cascades
3. Cyclic systems
4. Sufficiently simple networks and flux analysis

Challenges of quantitative biology

1. **Validation of data from different sources**
2. **Low particle numbers and stochasticity**
3. **Conformational heterogeneity of biomolecules**
4. **High dimensionality of molecular dynamical systems**
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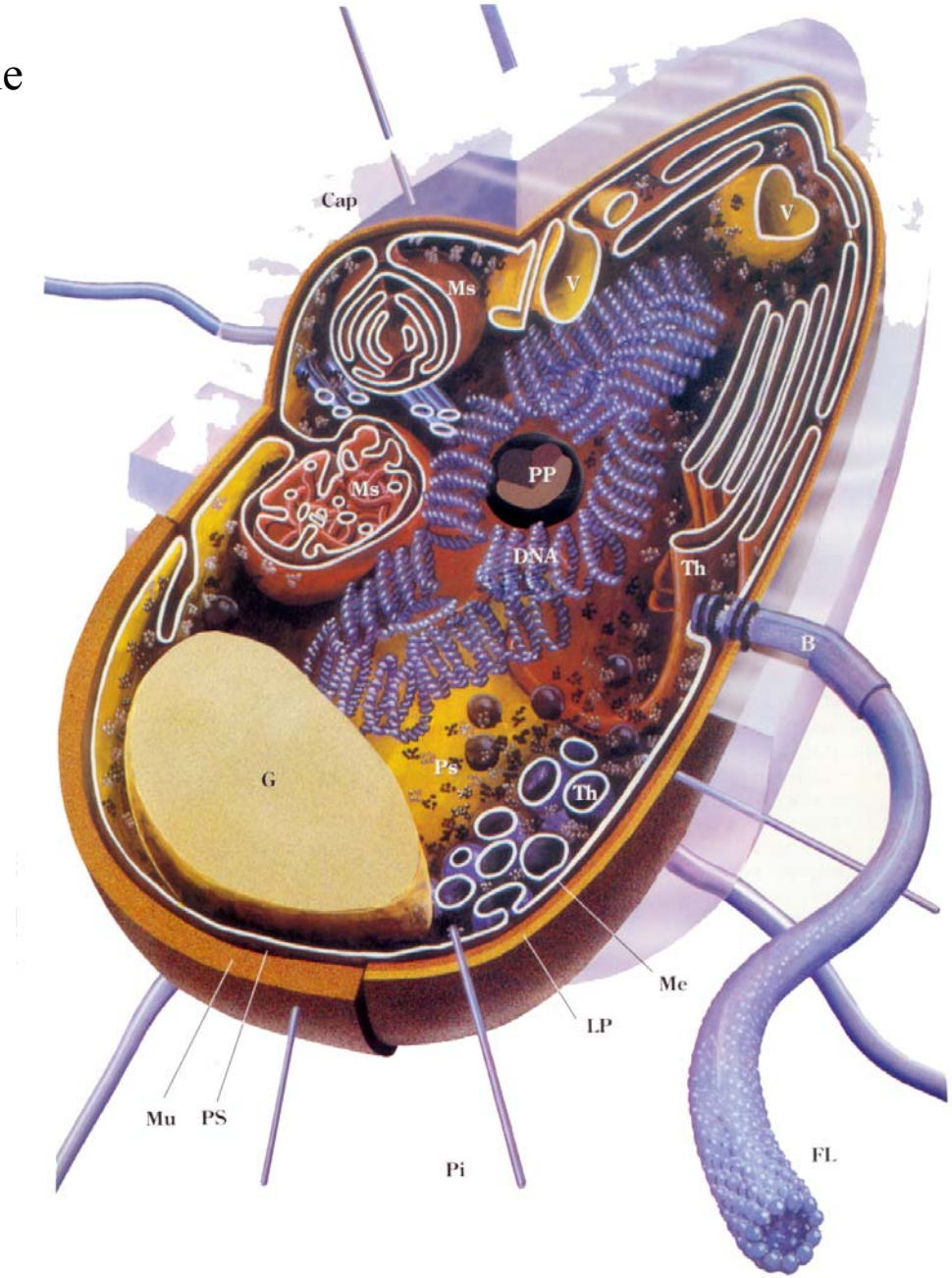
The bacterial cell as an example for the simplest form of autonomous life

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*

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Project No. Nat-7813

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