Ideas on the Classification of Gene Regulatory Dynamics

Peter Schuster

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

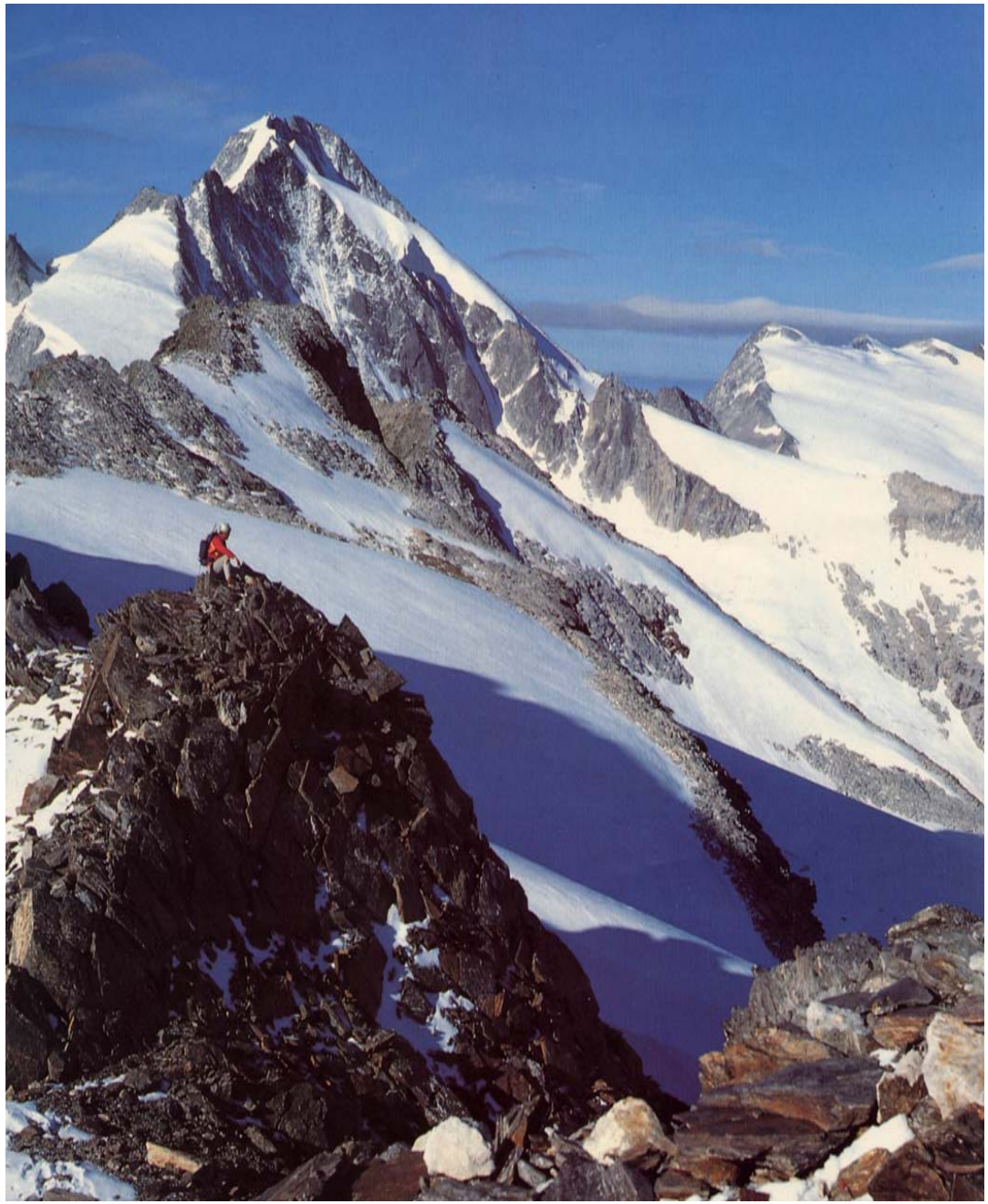
Symposium in Honor of René Thomas

Bruxelles, 30.– 31.05.2008

Happy Birthday René

Greetings from the Eastern Alps

Hochgall 3436 m



Web-Page for further information:

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

1. Forward and inverse problems in biology
2. Regulation kinetics and bifurcation analysis
3. Reverse engineering of dynamical systems

1. **Forward and inverse problems in biology**
2. Regulation kinetics and bifurcation analysis
3. Reverse engineering of dynamical systems

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: $x(0)$

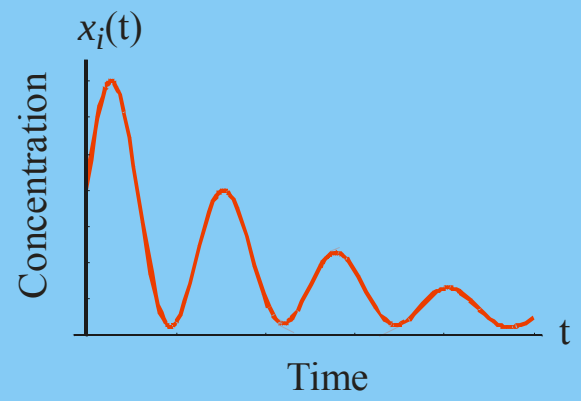
Boundary conditions:

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

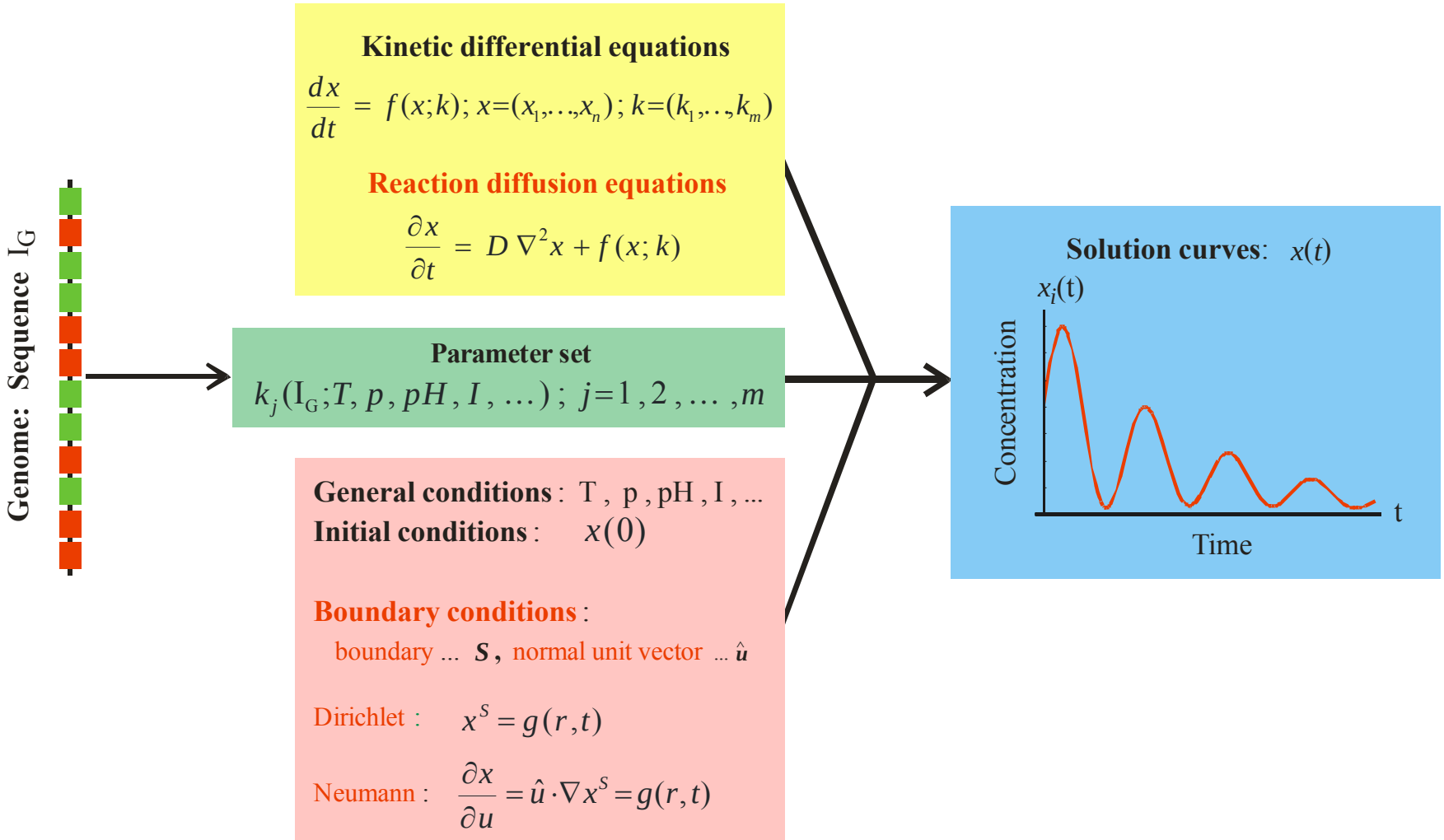
Dirichlet : $x^S = g(r,t)$

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 :

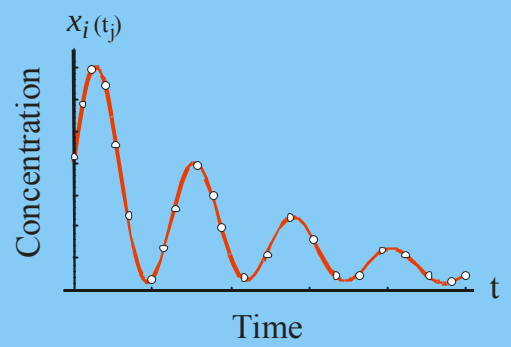
boundary ... S, normal unit vector... $\hat{u}$

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

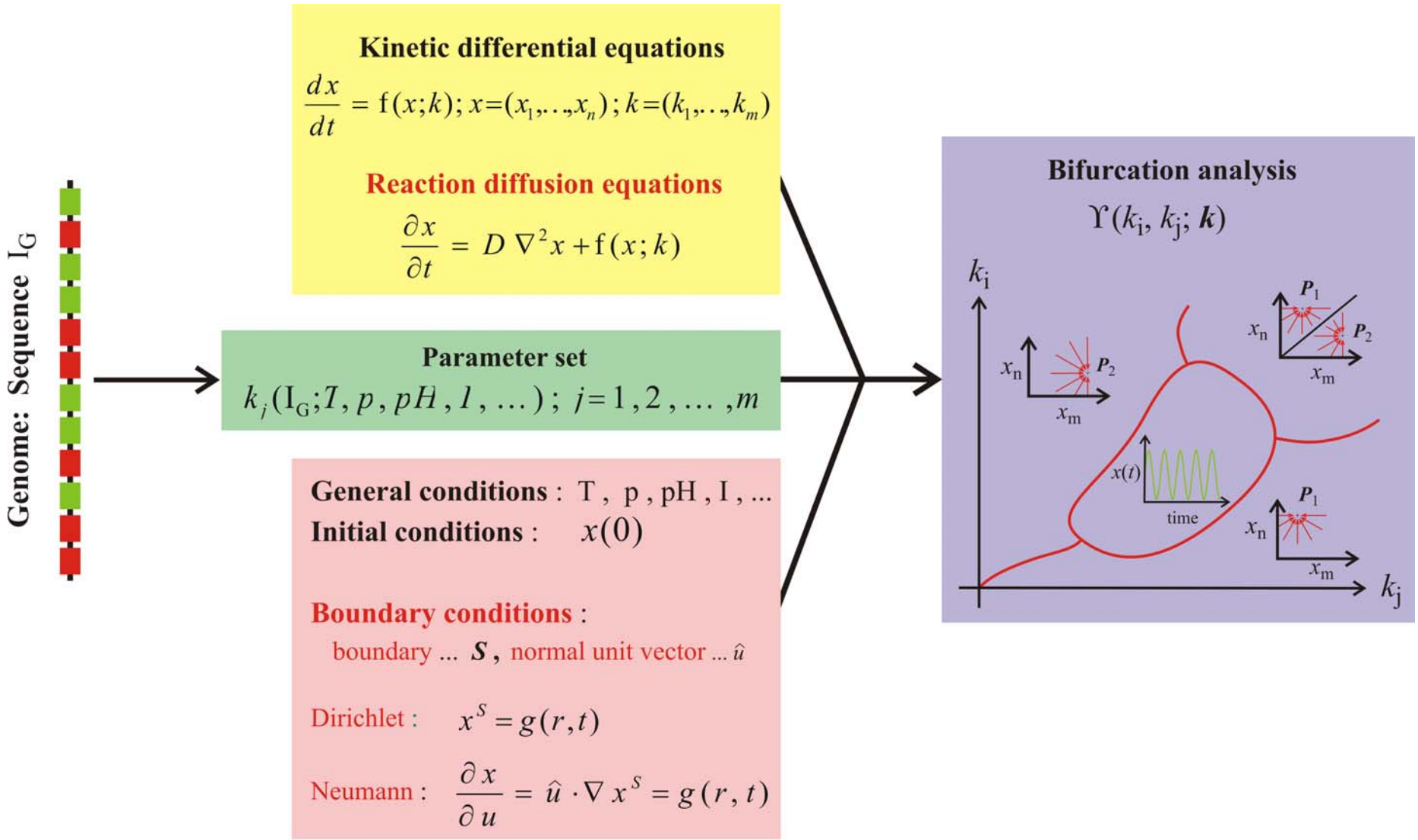
Neumann : $\frac{\partial x}{\partial u} = \hat{u} \cdot \nabla x^S = g(r,t)$

Data from measurements

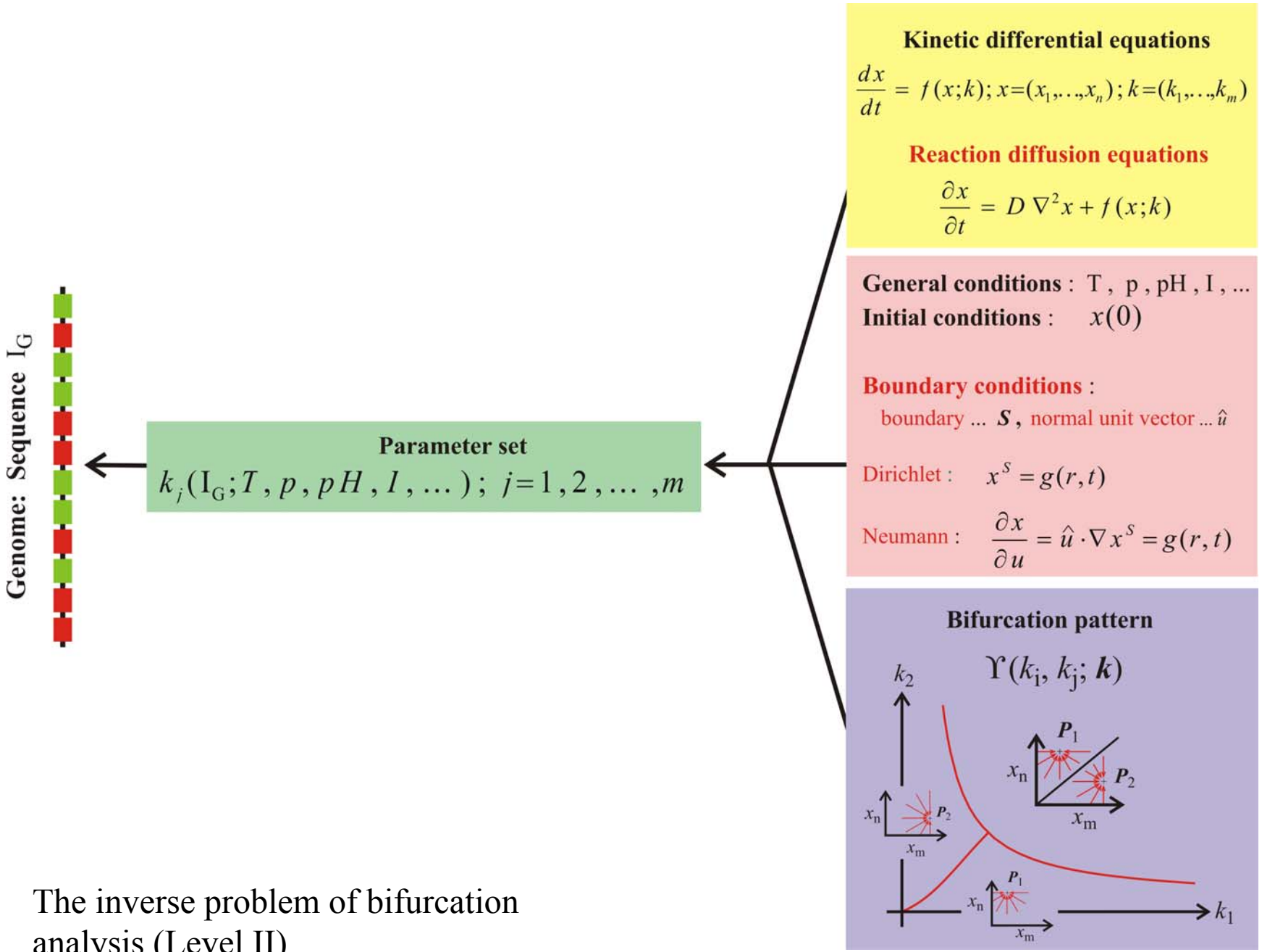
$x(t_j);\ j = 1, 2, \ldots, N$



The inverse problem of biochemical reaction kinetics (Level I)



The forward problem of bifurcation analysis (Level II)

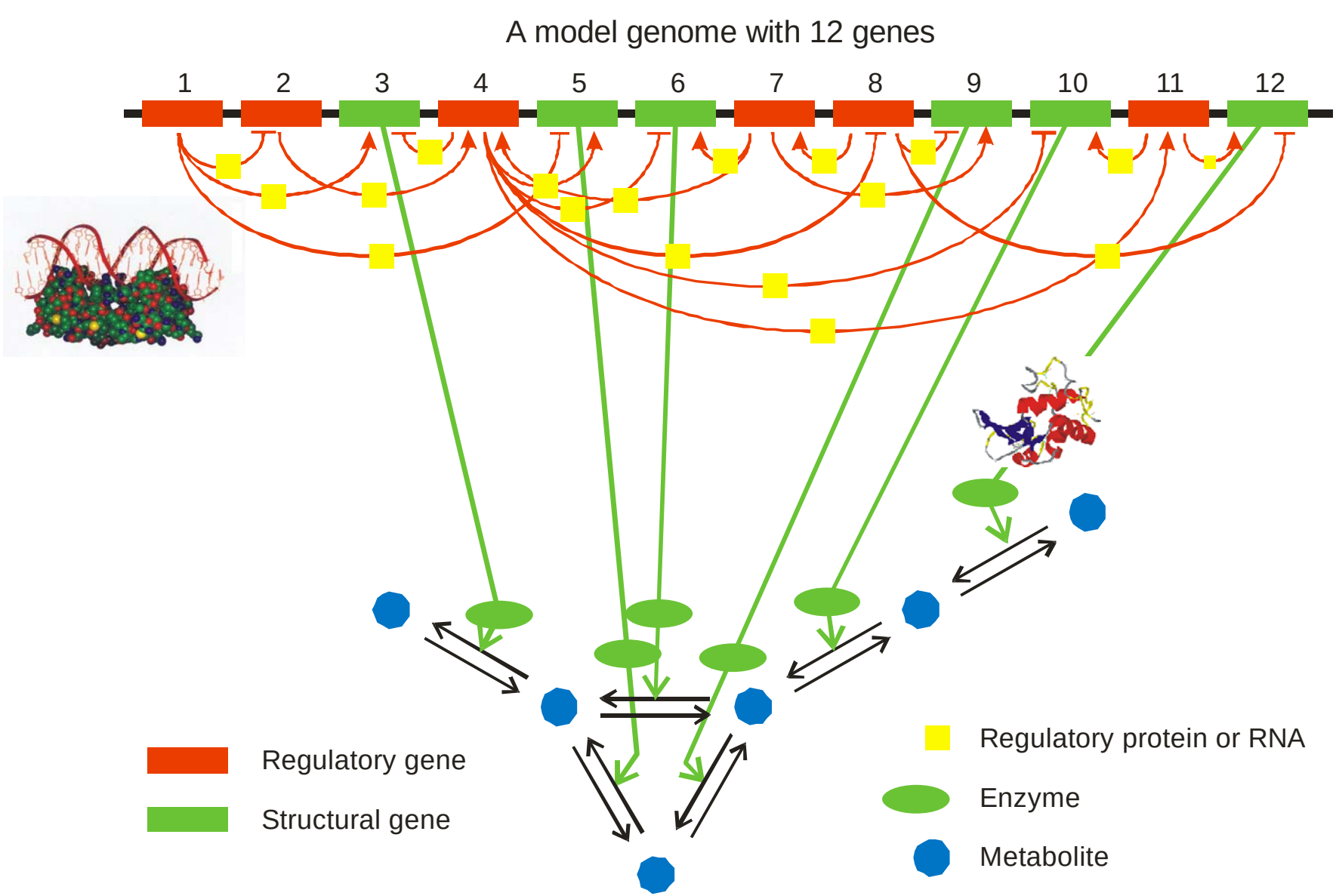


The inverse problem of bifurcation analysis (Level II)

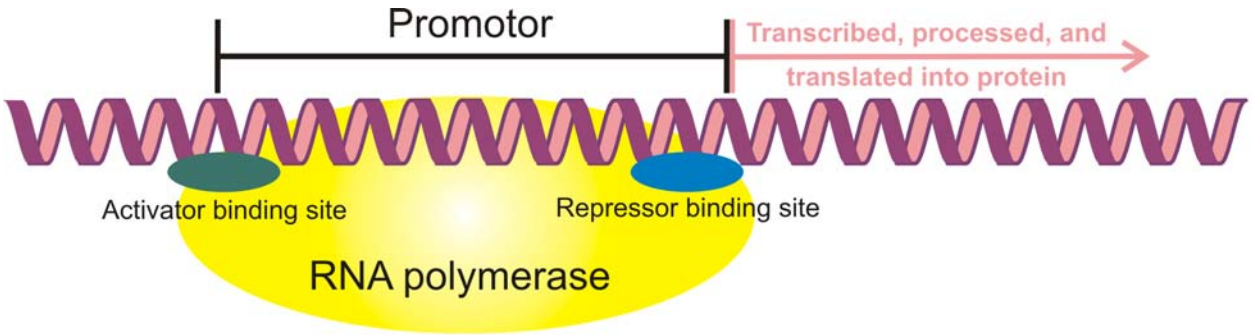
1. Forward and inverse problems in biology

2. **Regulation kinetics and bifurcation analysis**

3. Reverse engineering of dynamical systems



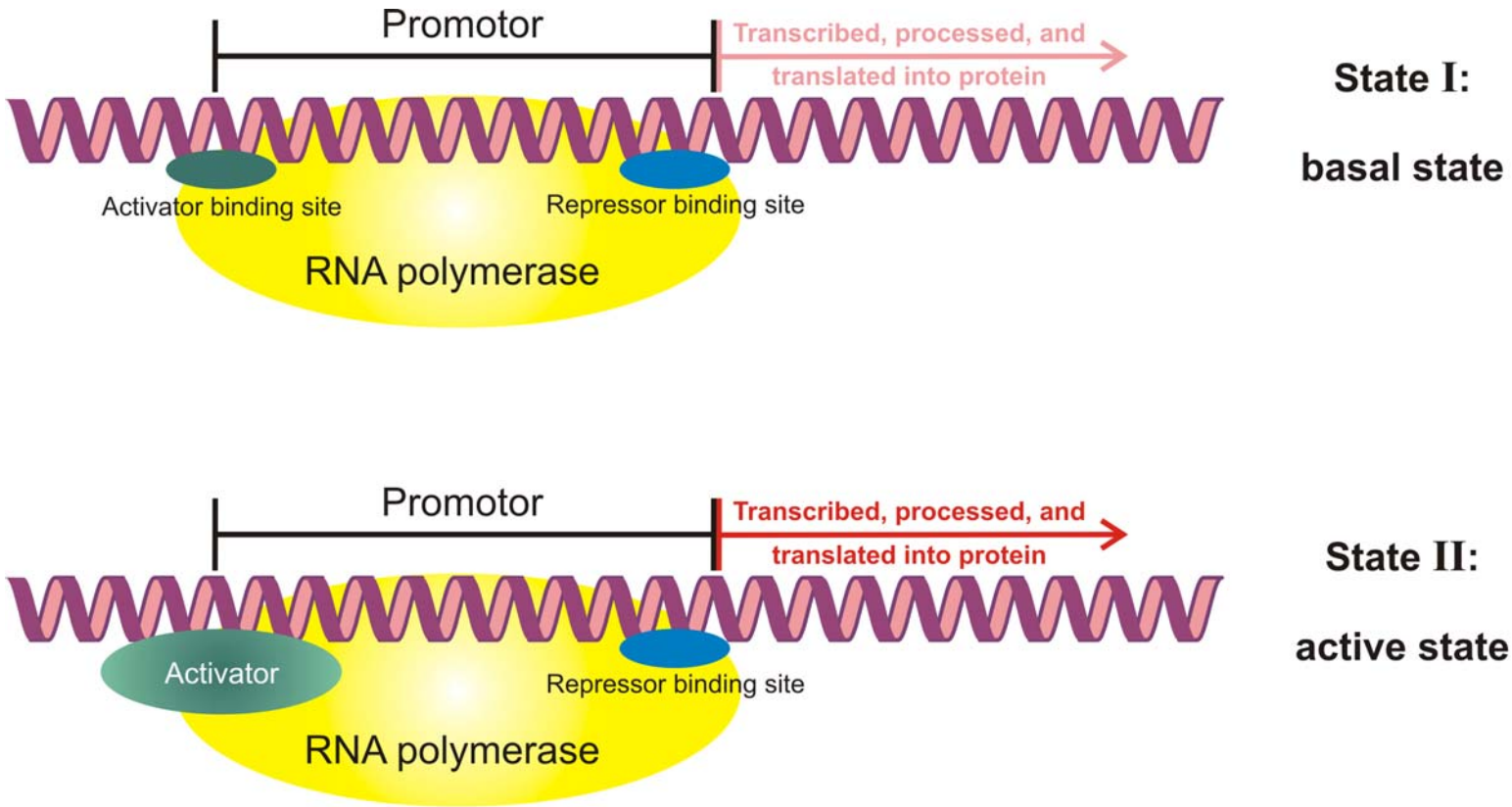
Sketch of a genetic and metabolic network



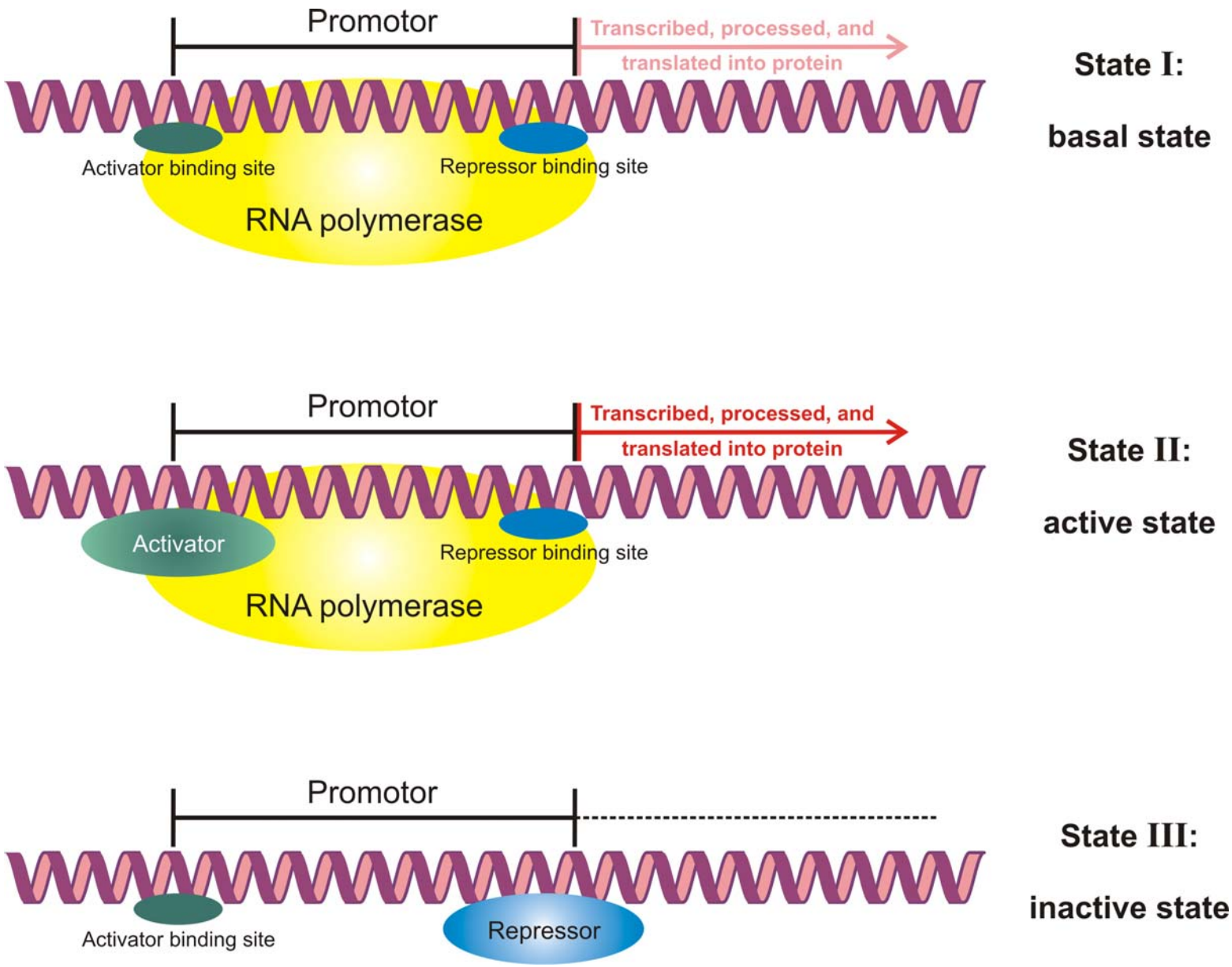
State I:

basal state

States of gene regulation in a bacterial expression control system – Jacob - Monod model



States of gene regulation in a bacterial expression control system – Jacob - Monod model



States of gene regulation in a bacterial expression control system – Jacob - Monod model

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

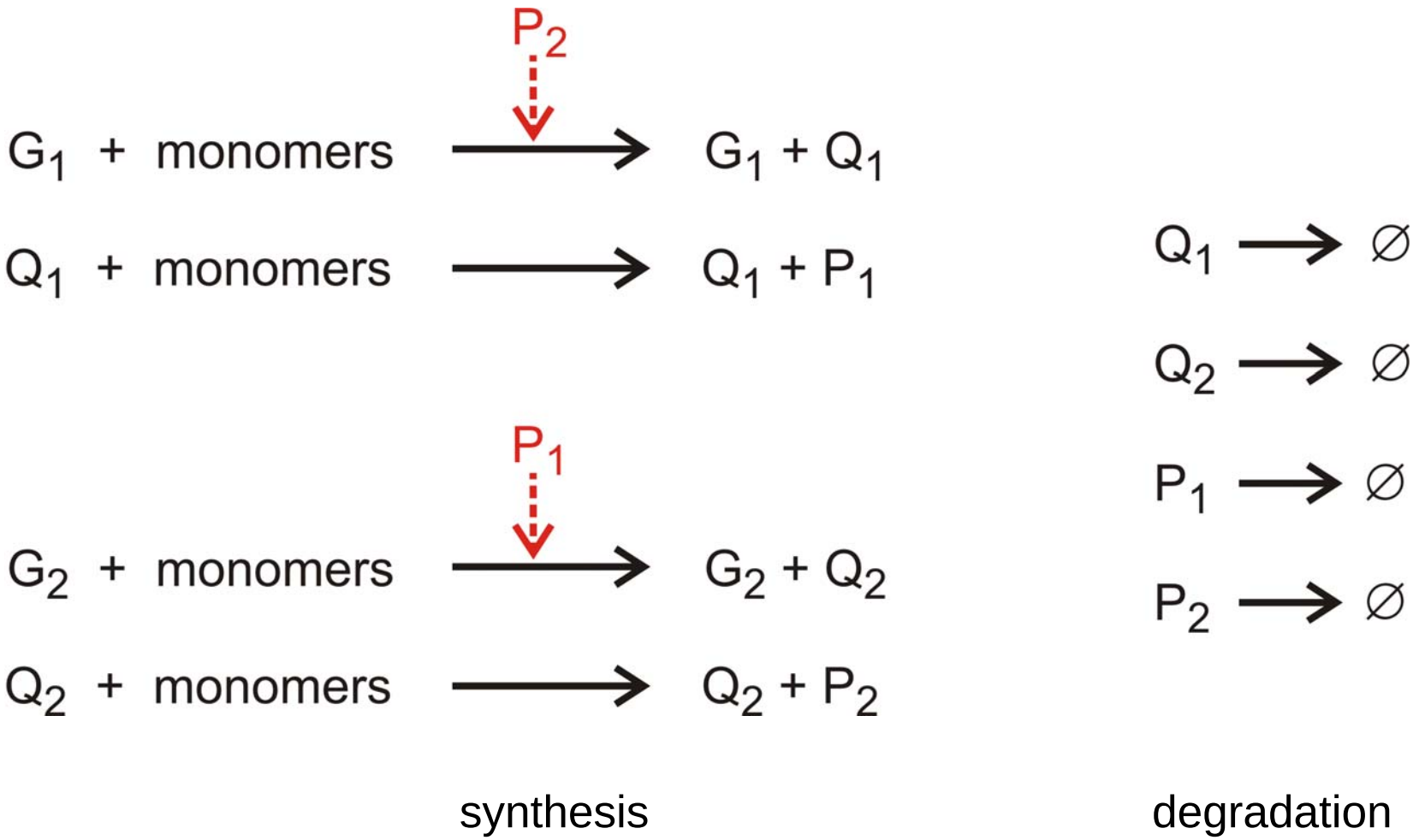
1. Introduction

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

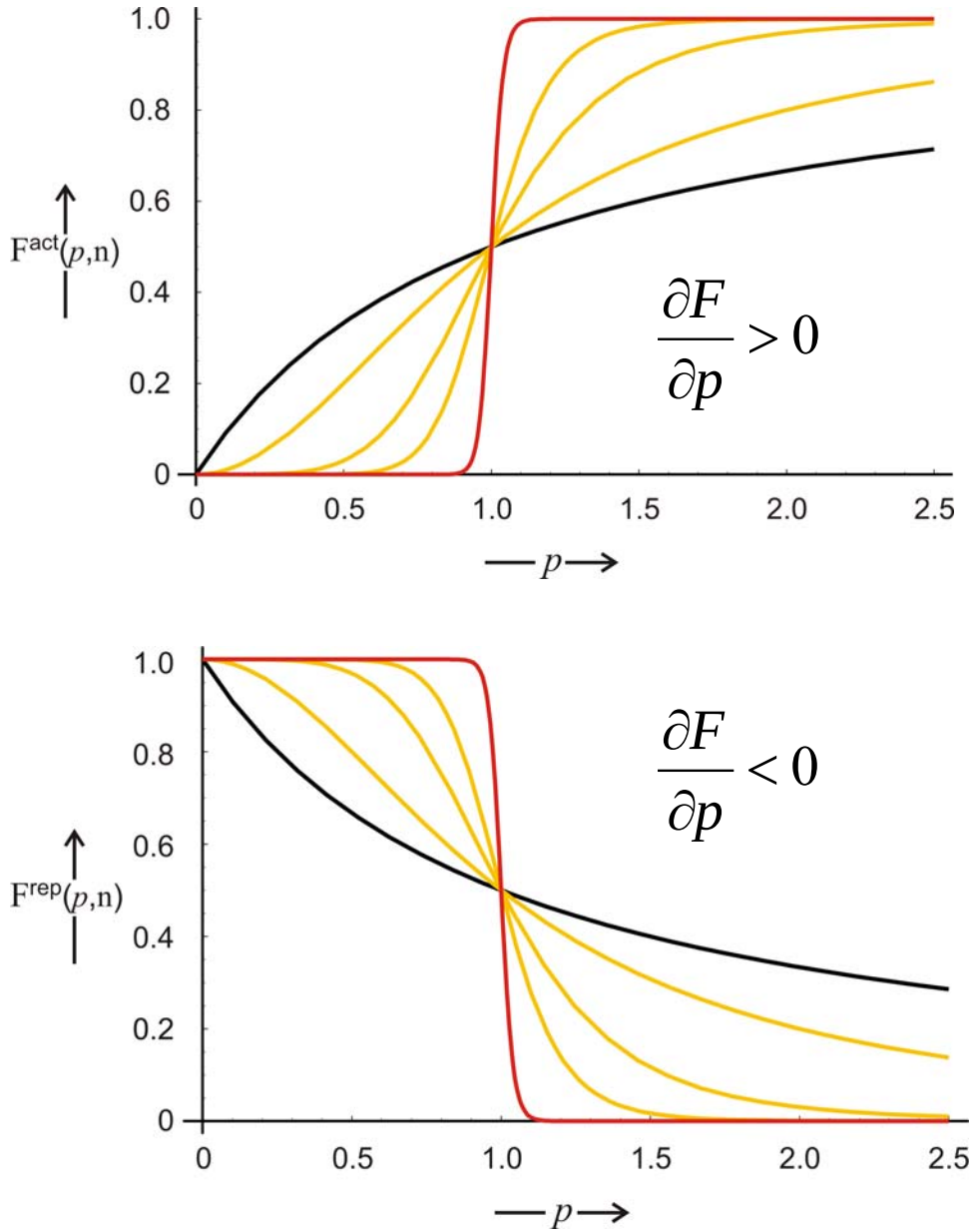


Cross-regulation of two genes

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

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

$$i, j = 1,2$$



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

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

M. Marcus. Two determinant condensation formulas. *Linear Multilinear Algebra*. **22**:95-102, 1987.

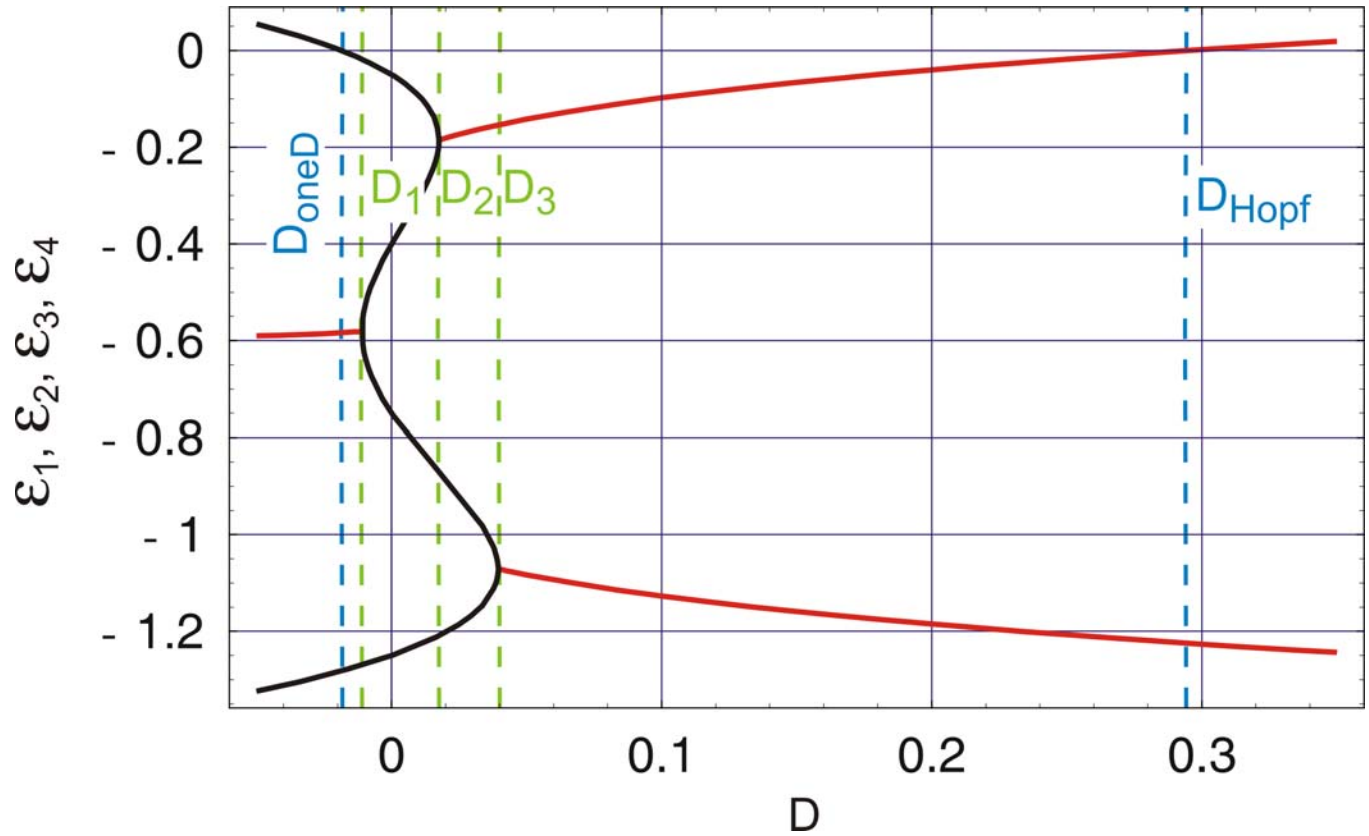
I. Kovacs, D.S. Silver, S.G. Williams. Determinants of commuting-block matices. *Am.Math.Mon*. **106**:950-952, 1999.

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

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

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

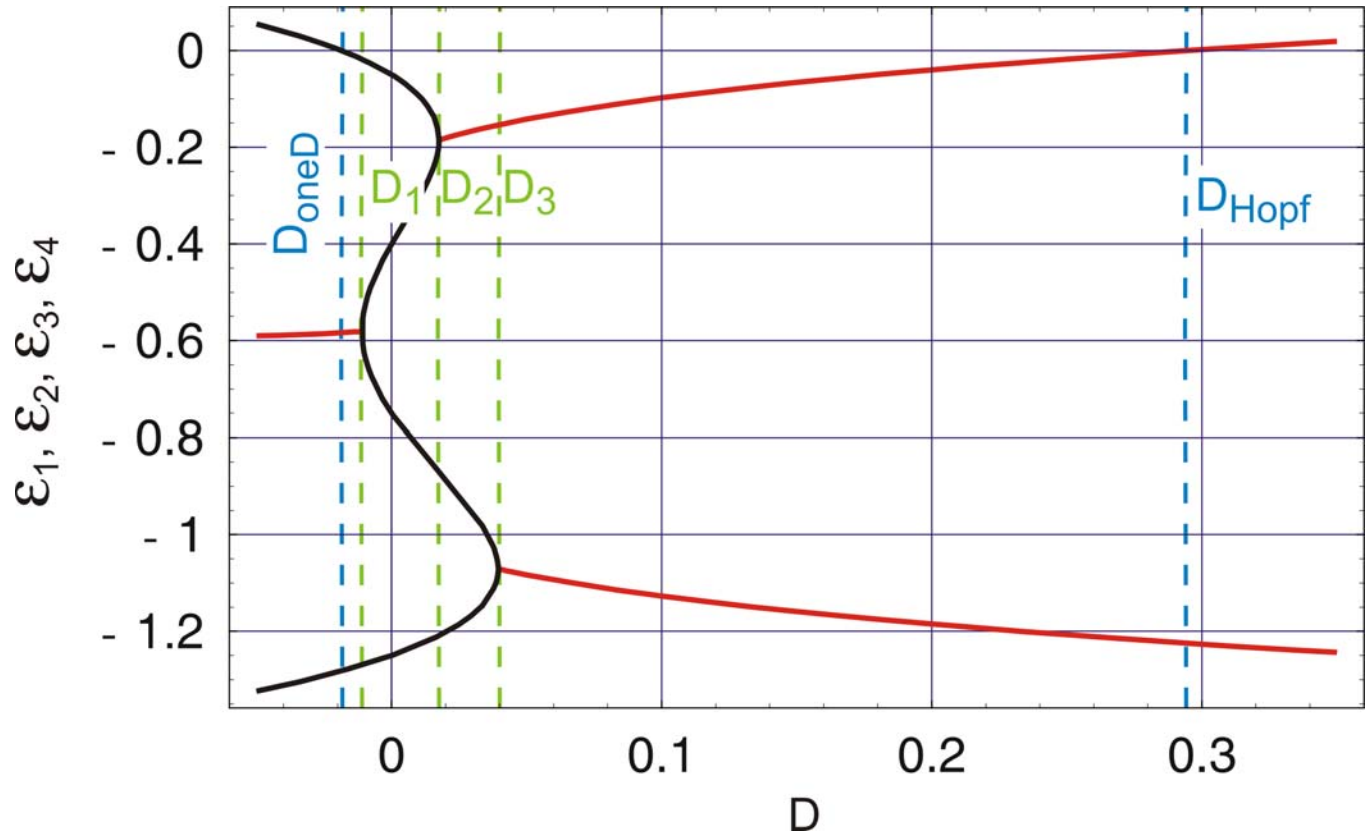
$$D = -k_1^{\mathrm{Q}} k_2^{\mathrm{Q}} k_1^{\mathrm{P}} k_2^{\mathrm{P}} \frac{\partial F_1}{\partial p_2}\frac{\partial F_2}{\partial p_1}$$



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

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

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

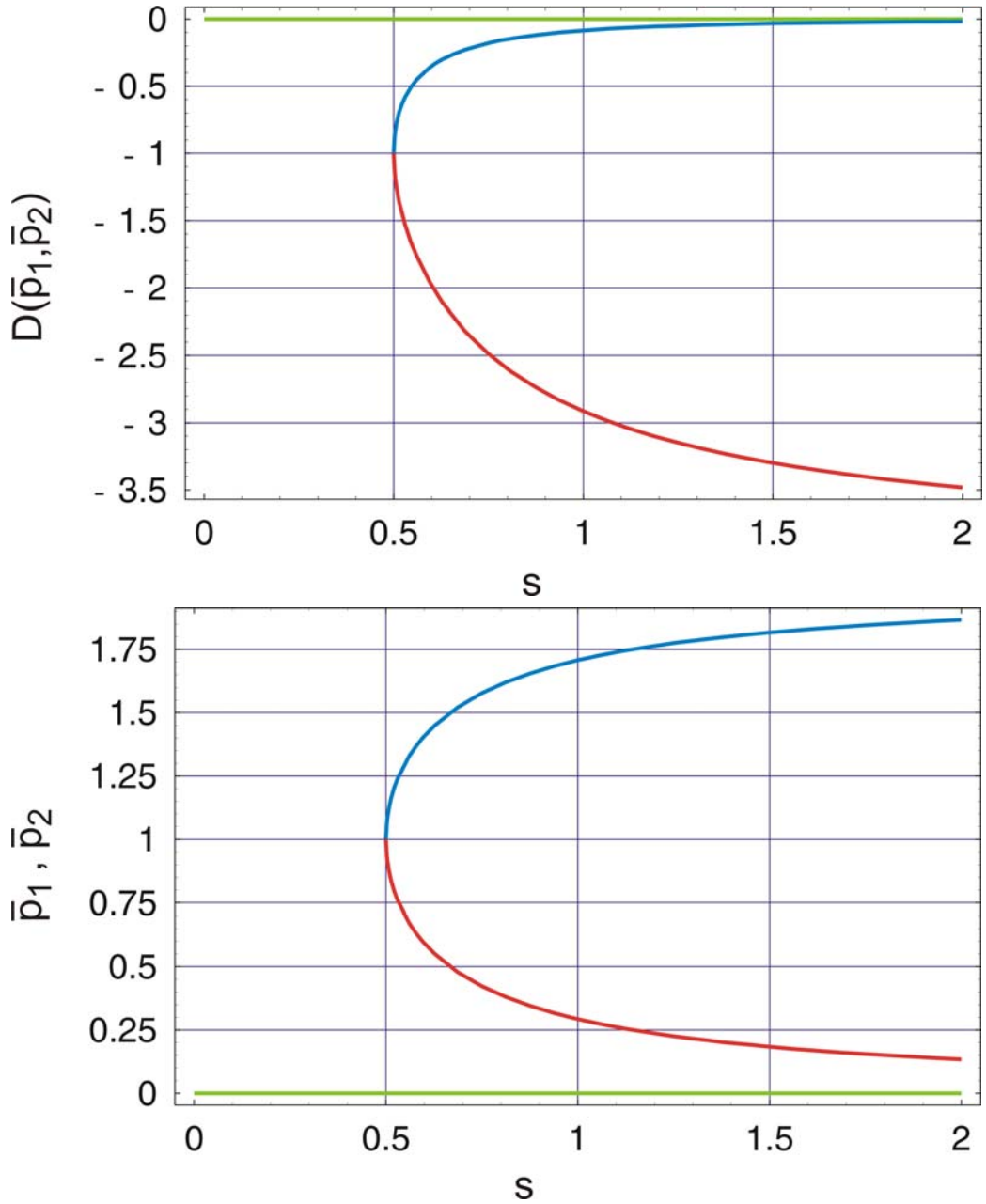


$$D_{\mathrm{OneD}} = -d_1^{\mathrm{Q}} d_2^{\mathrm{Q}} d_1^{\mathrm{P}} d_2^{\mathrm{P}}$$

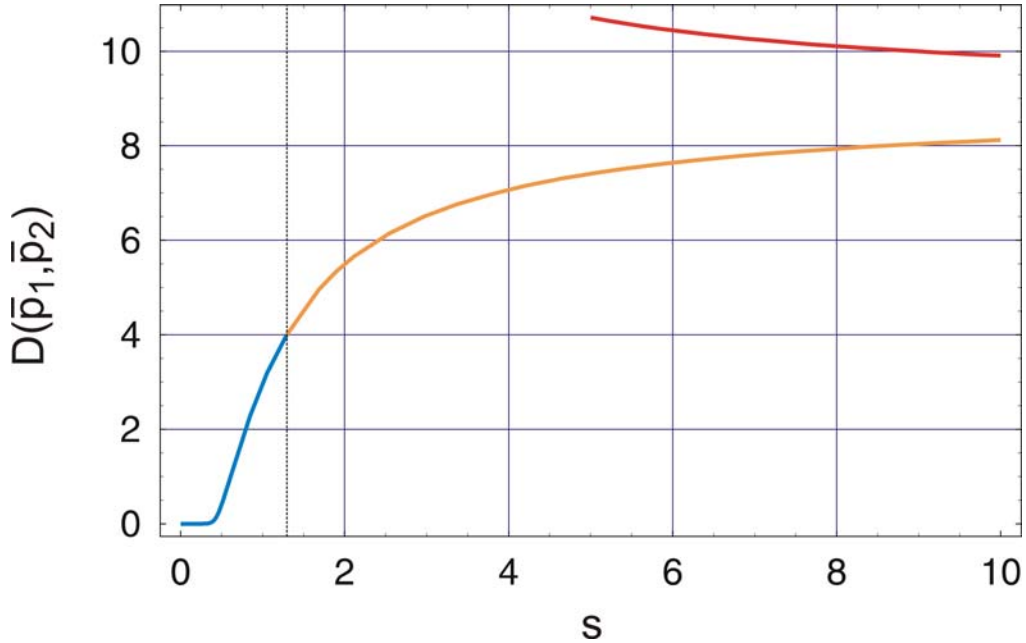
$$D_{\mathrm{Hopf}} = \frac{(d_1^{\mathrm{Q}}+d_2^{\mathrm{Q}})(d_1^{\mathrm{Q}}+d_1^{\mathrm{P}})(d_1^{\mathrm{Q}}+d_2^{\mathrm{P}})(d_2^{\mathrm{Q}}+d_1^{\mathrm{P}})(d_2^{\mathrm{Q}}+d_2^{\mathrm{P}})(d_1^{\mathrm{P}}+d_2^{\mathrm{P}})}{(d_1^{\mathrm{Q}}+d_2^{\mathrm{Q}}+d_1^{\mathrm{P}}+d_2^{\mathrm{P}})^2}$$

s > 0.5: bistability

both genes on
or
both genes off

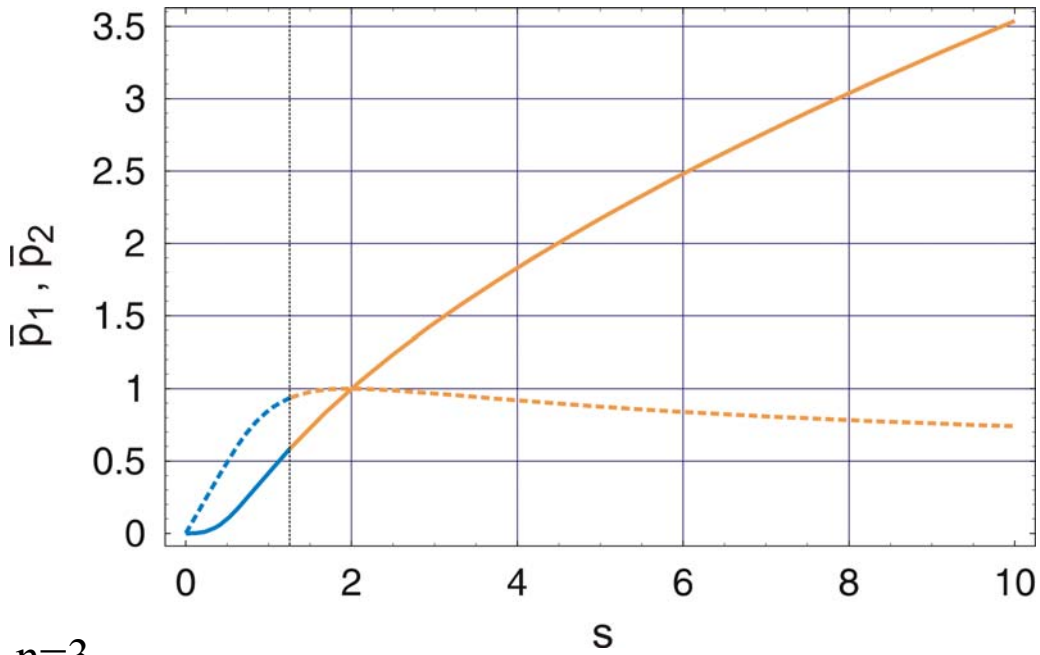


Regulatory dynamics at $D \leq 0$, act.-act., n=2

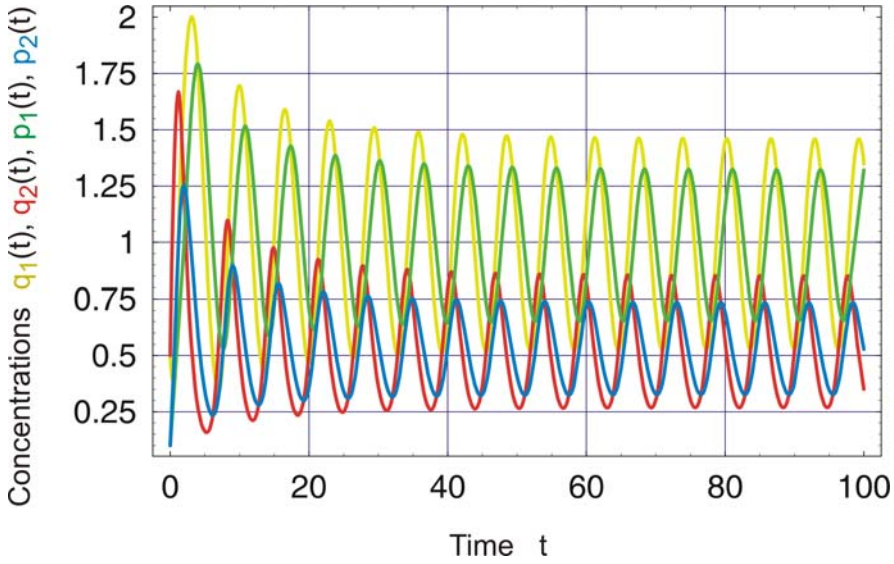


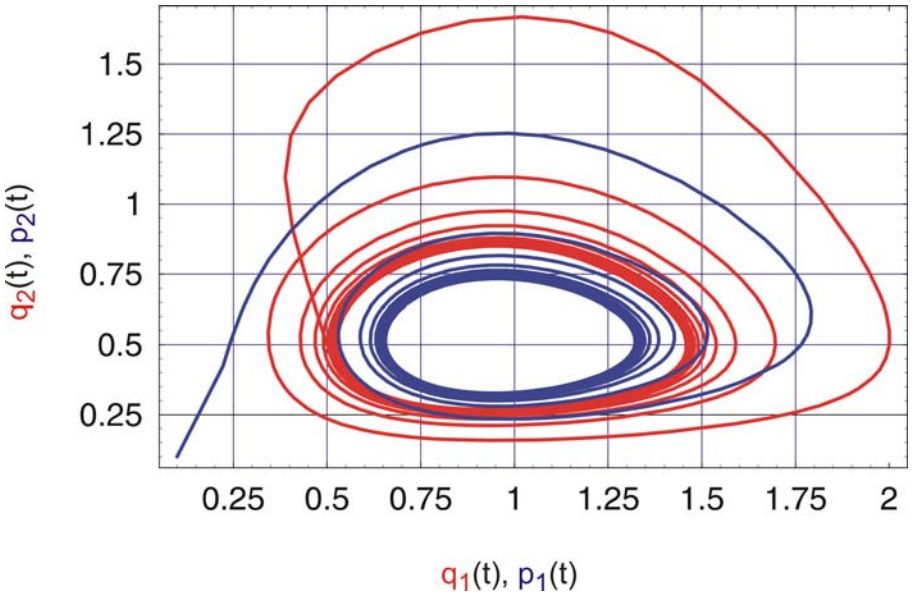
s > 1.29: stable limit cycle

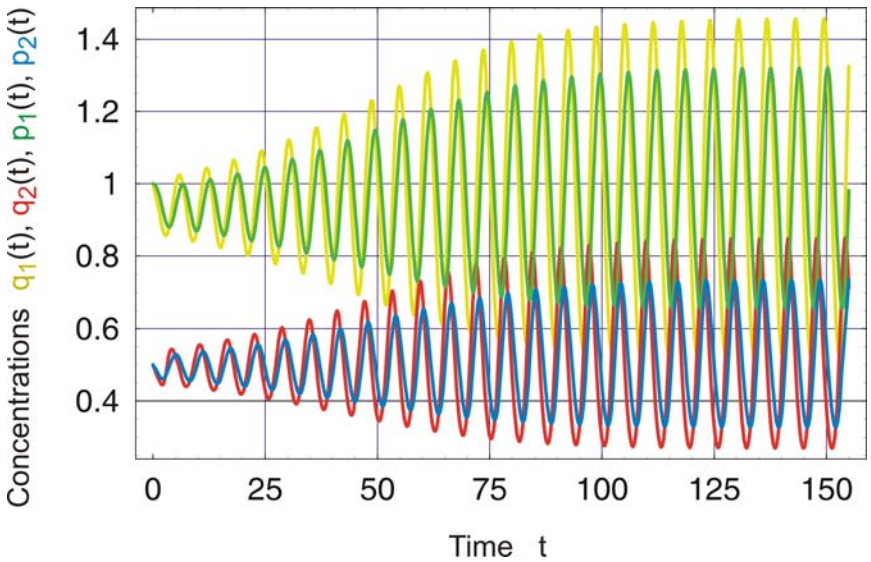
gene activity oscillating

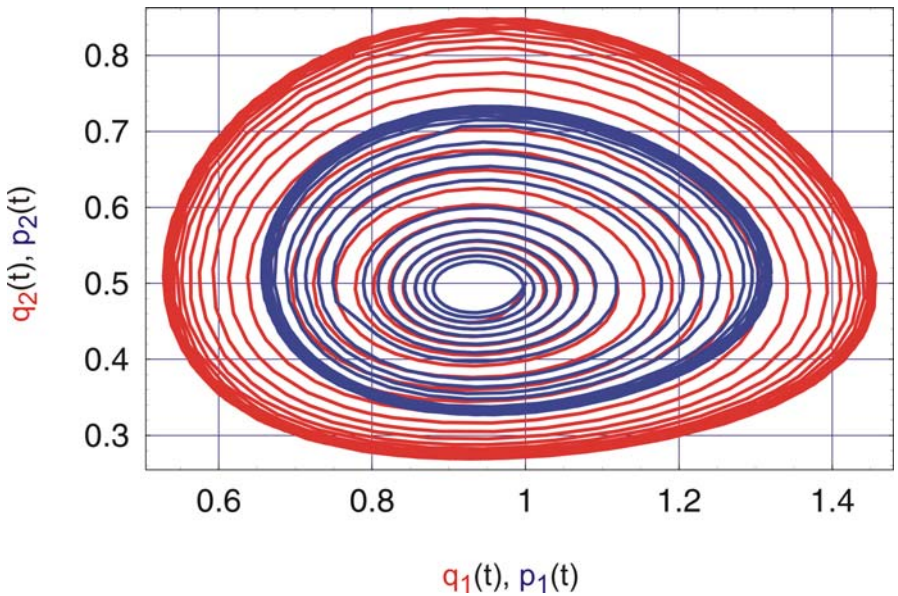


Regulatory dynamics at $D \geq 0$, act.-rep., n=3

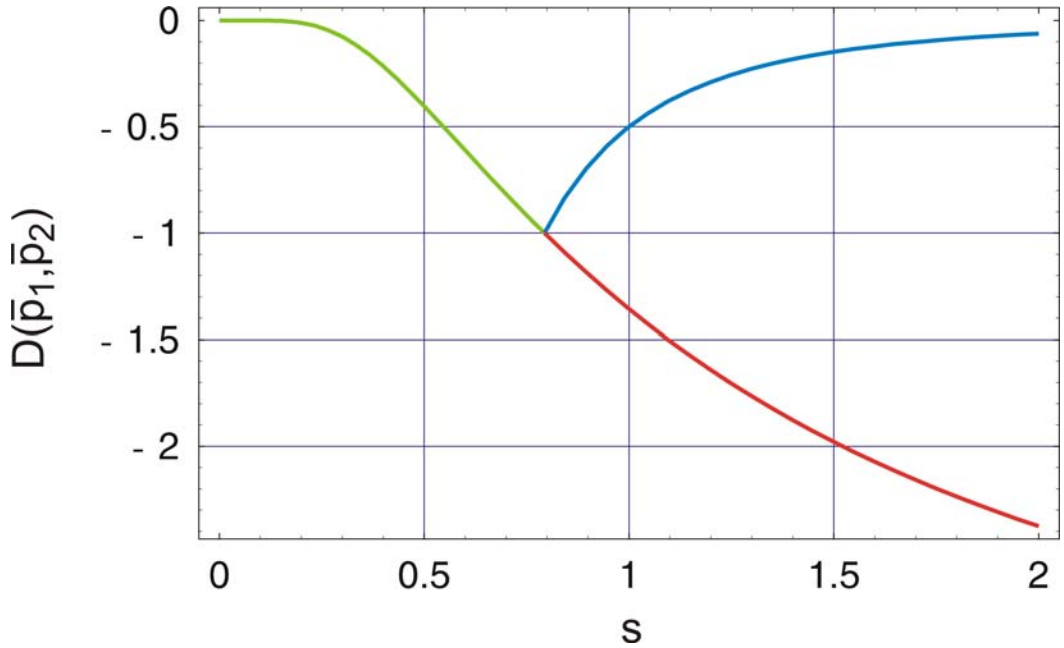






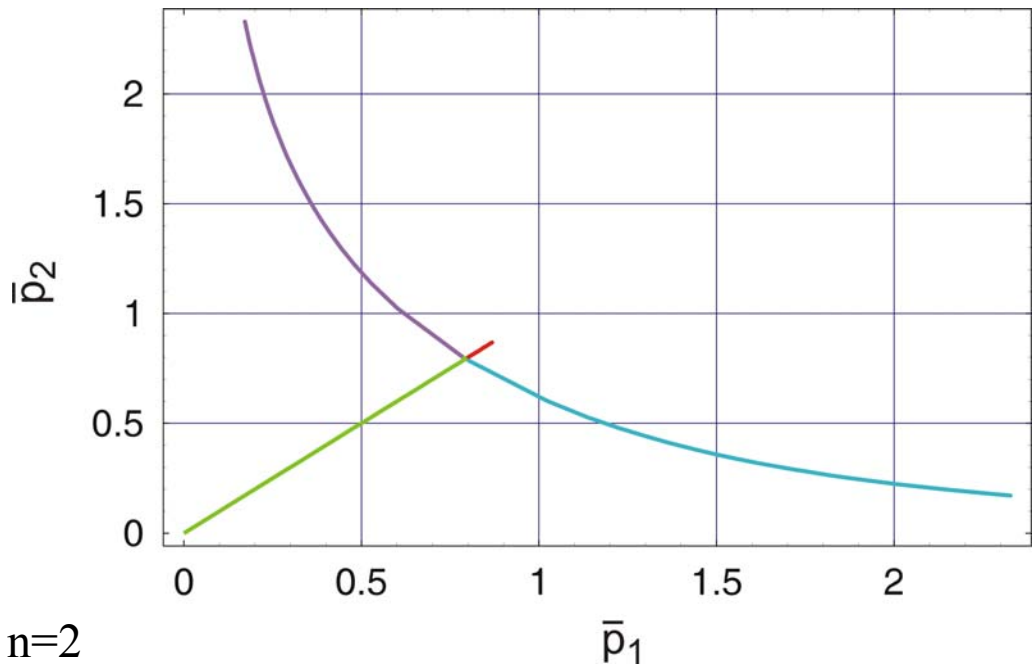


Regulatory dynamics at $D > D_{Hopf}$, act.-repr., n=3



s > 0.794: bistability

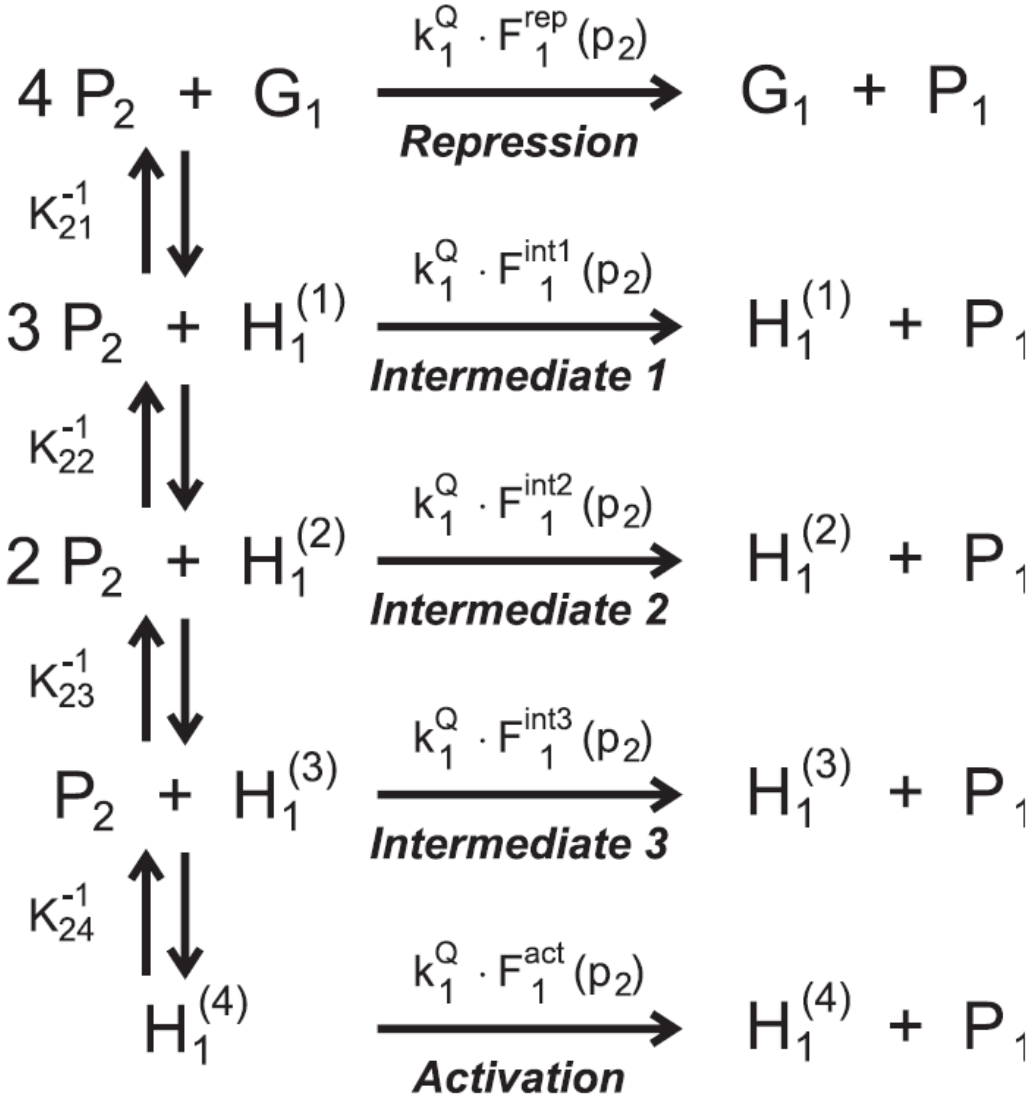
gene 1 on and gene 2 off
or
gene 1 off and gene 2 on



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)

E ..... „extinction“, both genes off
S ..... „stable fixed point“ with both genes (partially) active
O ..... „oscillations“, stable limit cycle
B ..... „bistability“
P_1 ..... gene 1 on and gene 2 off
P_2 ..... gene 1 off and gene 2 on
P ..... both genes active


$4\,P_2 + G_1$
$k_1^Q \cdot F_1^{rep}(p_2)$
Repression
$G_1 + P_1$
K_{21}^{-1}
$3\,P_2 + H_1^{(1)}$
$k_1^Q \cdot F_1^{int1}(p_2)$
Intermediate 1
$H_1^{(1)} + P_1$
K_{22}^{-1}
$2\,P_2 + H_1^{(2)}$
$k_1^Q \cdot F_1^{int2}(p_2)$
Intermediate 2
$H_1^{(2)} + P_1$
K_{23}^{-1}
$P_2 + H_1^{(3)}$
$k_1^Q \cdot F_1^{int3}(p_2)$
Intermediate 3
$H_1^{(3)} + P_1$
K_{24}^{-1}
$H_1^{(4)}$
$k_1^Q \cdot F_1^{act}(p_2)$
Activation
$H_1^{(4)} + P_1$

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

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

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

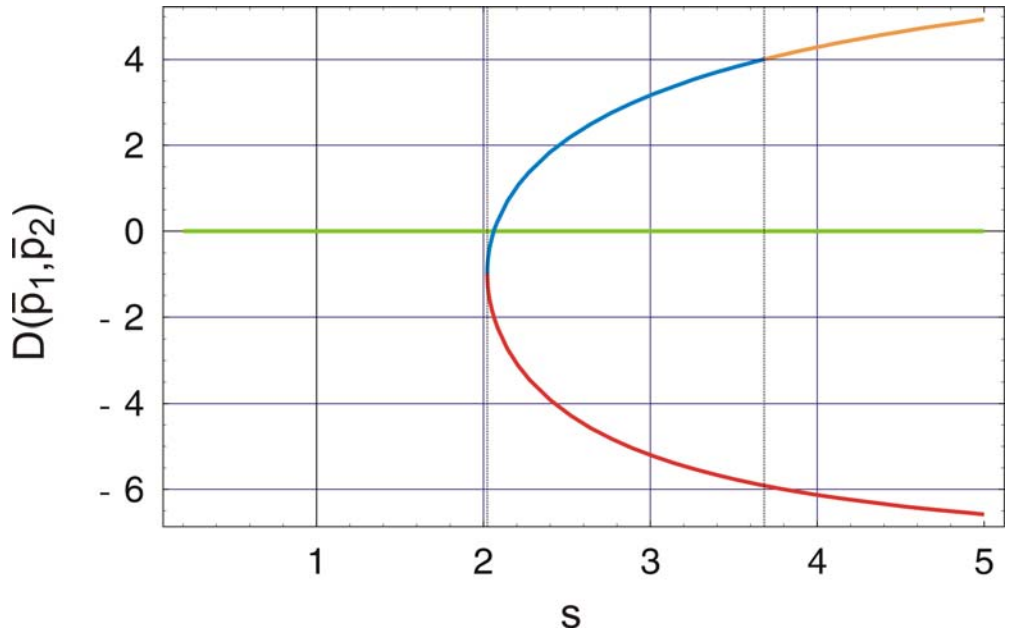
$$i, j = 1,2; \quad 1 \le m \le n-1$$

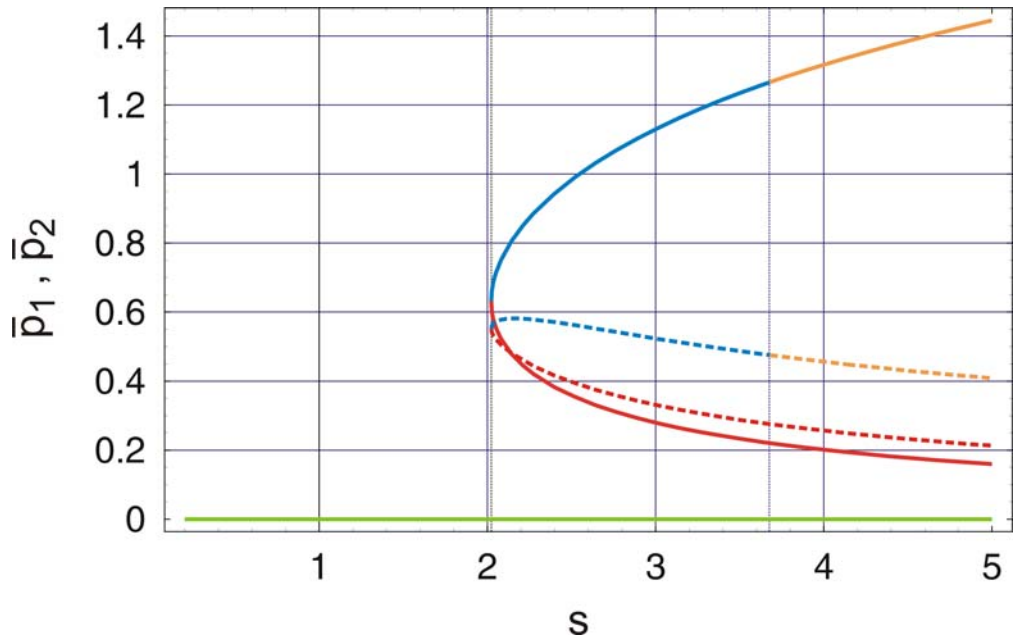
3.67 > s > 2.02: bistability

both genes on or both genes off

s > 3.67: bistability and stable limit cycle

both genes off or gene activity oscillating





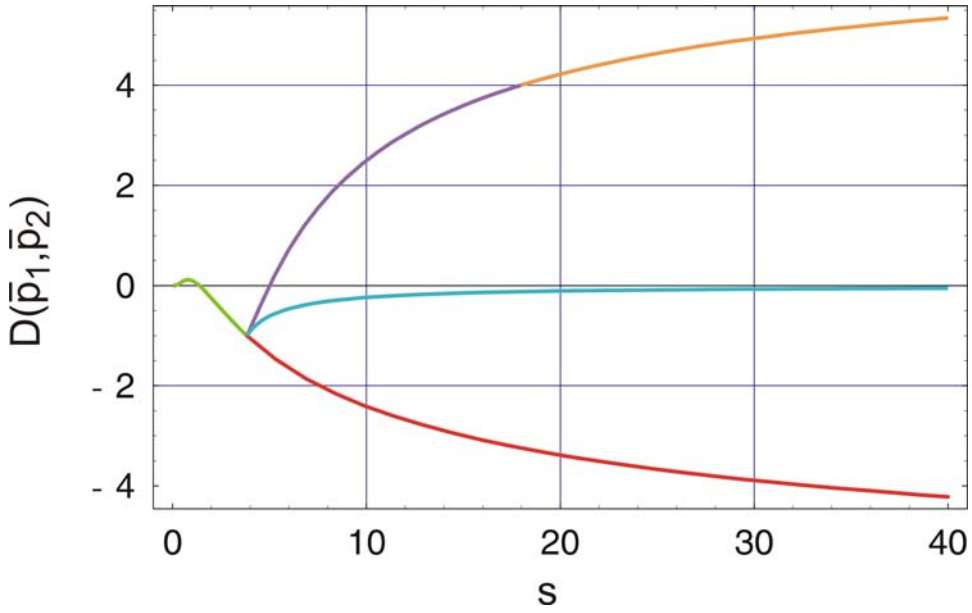
Regulatory dynamics, int.-act., m=2, n=4

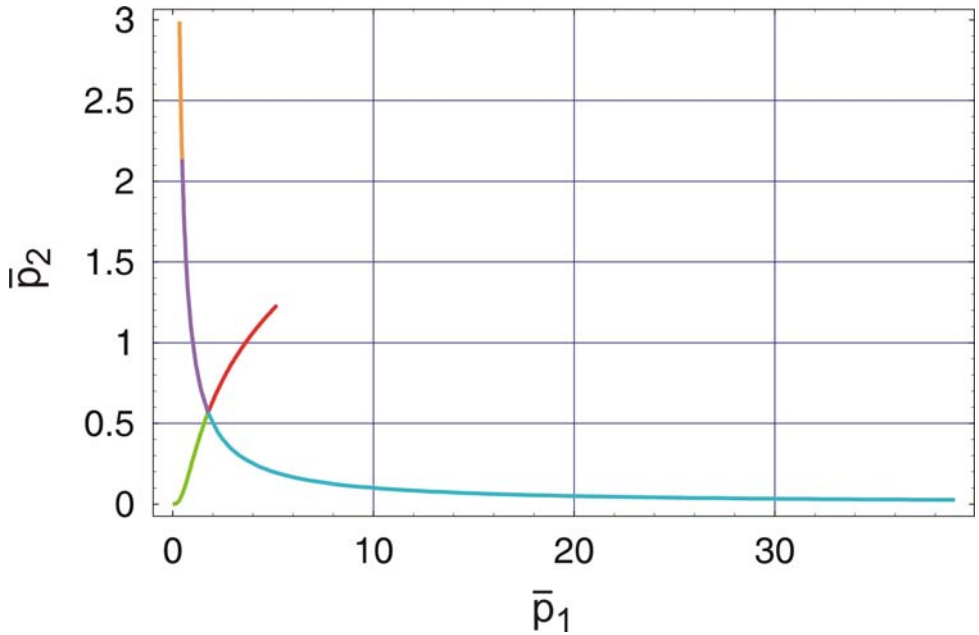
17.96 > s > 3.883: bistability

gene 1 on and gene 2 off
or
gene 1 off and gene 2 on

s > 17.96: bistability and stable limit cycle

gene 1 on and gene 2 off
or
gene activity oscillating





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: $n = 3$

J. Math. Biol. (2006) 53:905–937
DOI 10.1007/s00285-006-0035-9

Mathematical Biology

A generalized model of the repressilator

Stefan Müller · Josef Hofbauer · Lukas Endler · Christoph Flamm · Stefanie Widder · Peter Schuster

Received: 8 June 2006 / Revised: 11 July 2006 /
Published online: 2 September 2006

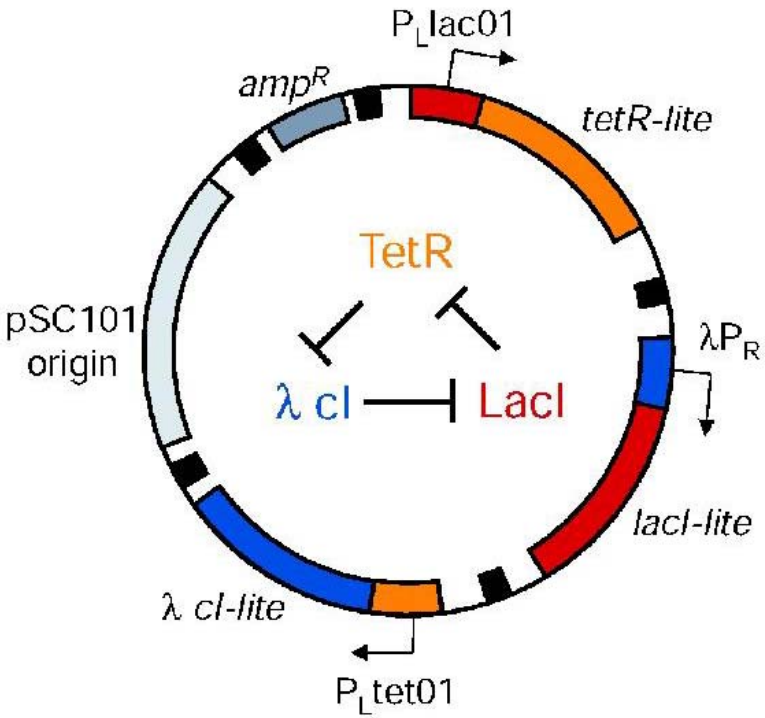
Abstract The repressilator is a regulatory cycle of n genes where each gene represses its successor in the cycle: $1 \dashv 2 \dashv \cdots \dashv n \dashv 1$. The system is modelled by ODEs for an arbitrary number of identical genes and arbitrarily strong repressor binding. A detailed mathematical analysis of the dynamical behavior is provided for two model systems: (i) a repressilator with leaky transcription and single-step cooperative repressor binding, and (ii) a repressilator with auto-activation and cooperative regulator binding. Genes are assumed to be present in constant amounts, transcription and translation are modelled by single-step kinetics, and mRNAs as well as proteins are assumed to be degraded by first order reactions. Several dynamical patterns are observed: multiple steady states, periodic and aperiodic oscillations corresponding to limit cycles and heteroclinic cycles, respectively. The results of computer simulations are complemented by a detailed and complete stability analysis of all equilibria and of the heteroclinic cycle.

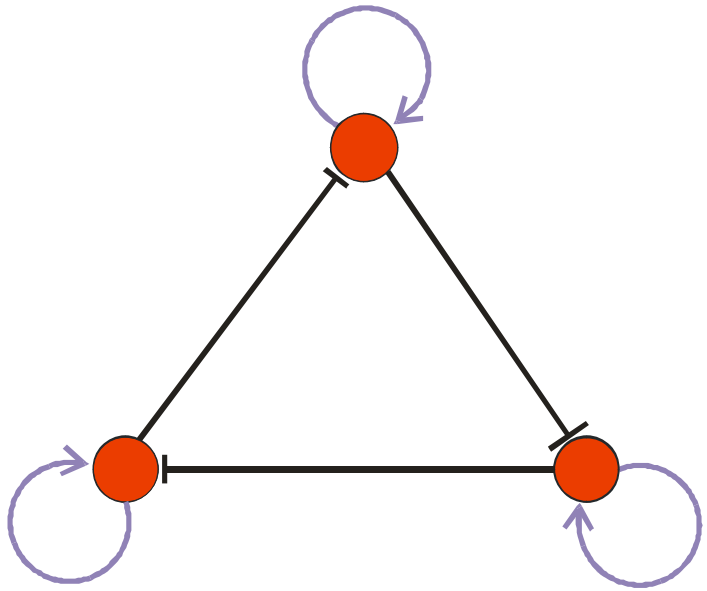
Keywords Gene regulatory network · Negative feedback loop · Repressilator · Stability analysis · Hopf bifurcation · Heteroclinic cycle

S. Müller (✉)
Johann Radon Institute for Computational and Applied Mathematics,
Austrian Academy of Sciences, Altenbergerstraße 69, 4040 Linz, Austria
e-mail: stefan.mueller@oeaw.ac.at

J. Hofbauer
Department of Mathematics, University College London, London WC1E 6BT, UK

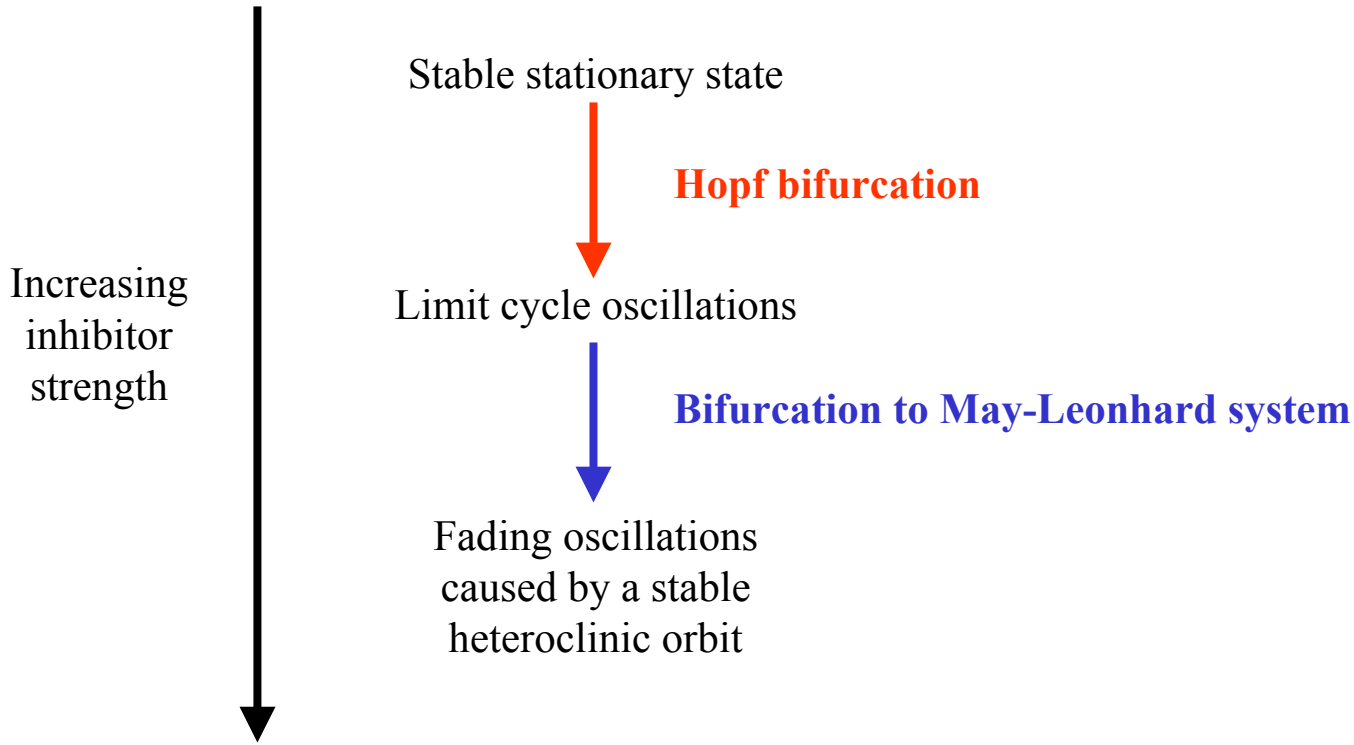
L. Endler · C. Flamm · S. Widder · P. Schuster
Institute for Theoretical Chemistry, University of Vienna,
Währingerstraße 17, 1090 Wien, Austria

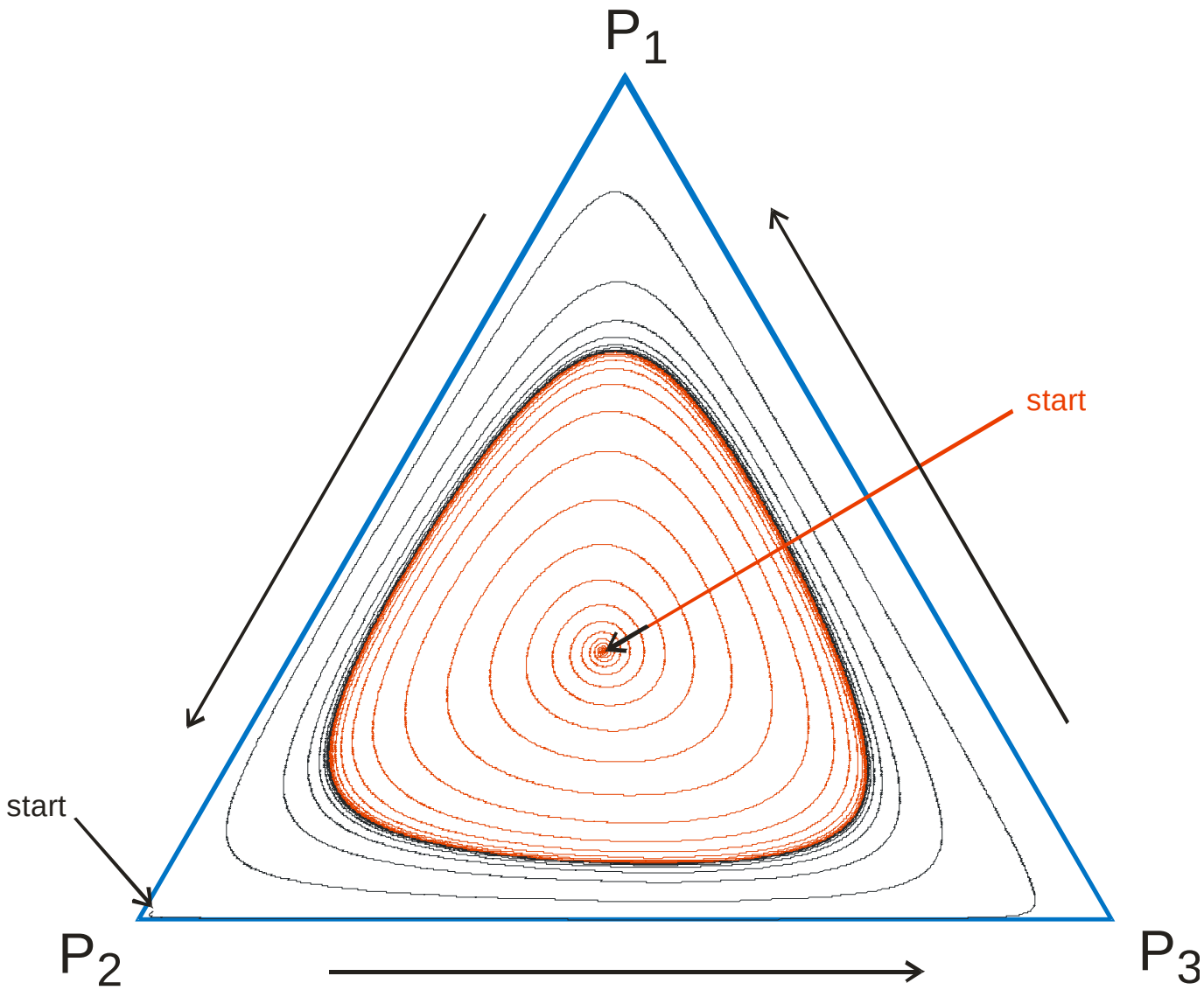




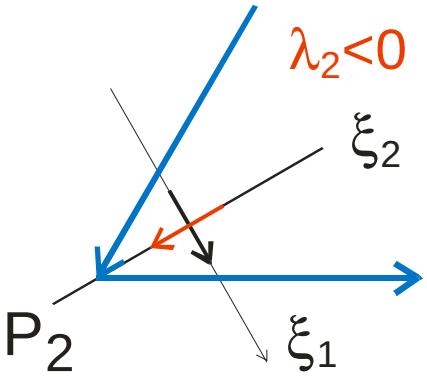
An example analyzed and simulated by MiniCellSim

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

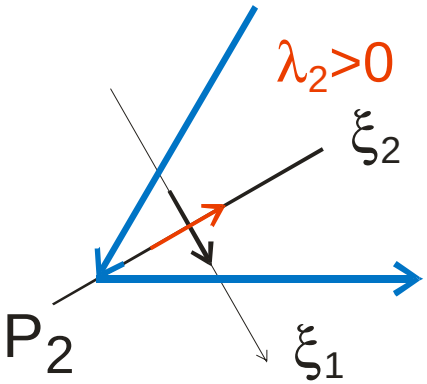

Increasing inhibitor strength
Stable stationary state
Hopf bifurcation
Limit cycle oscillations
Bifurcation to May-Leonhard system
Fading oscillations caused by a stable heteroclinic orbit



The repressilator limit cycle

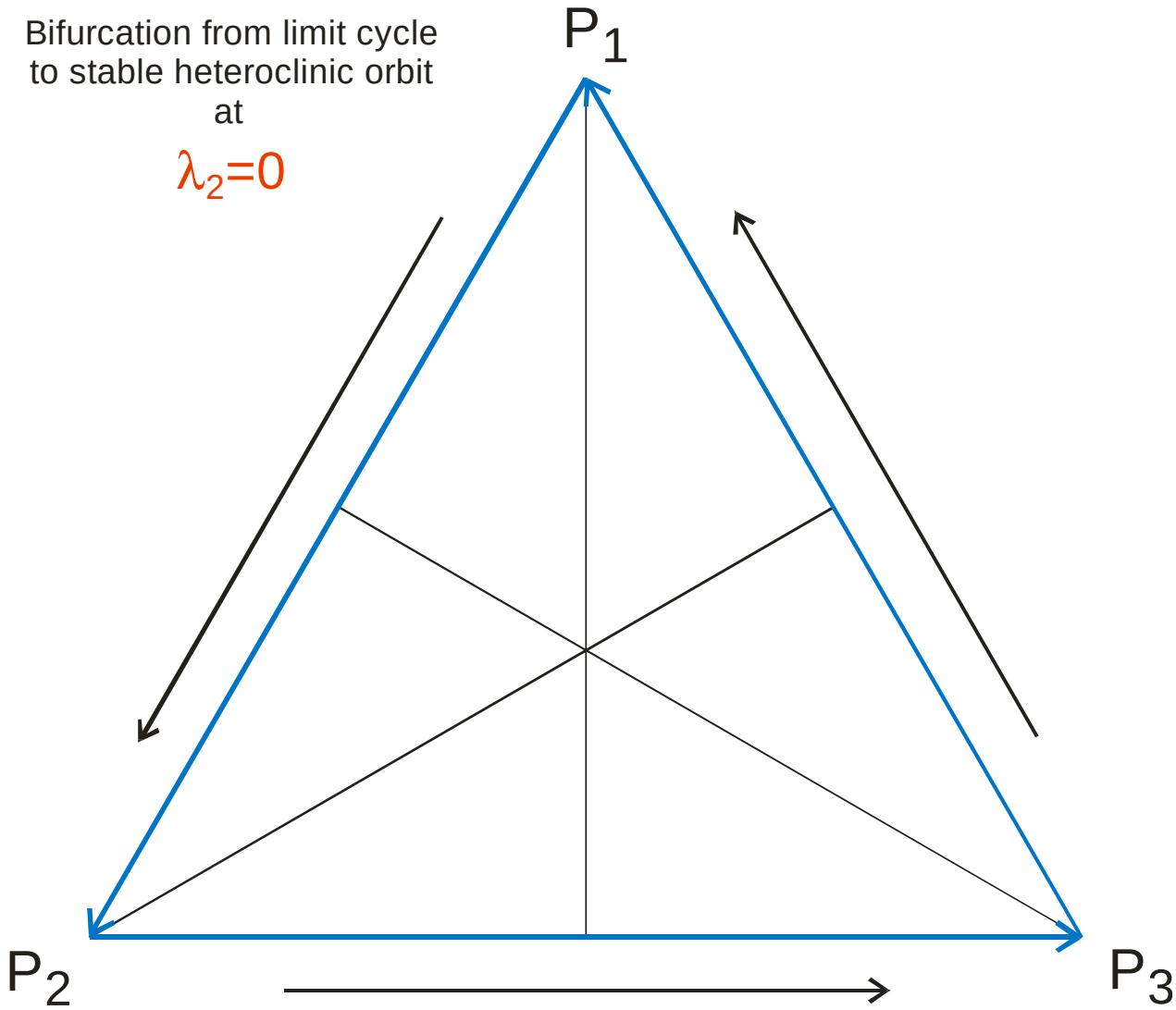


Stable heteroclinic orbit

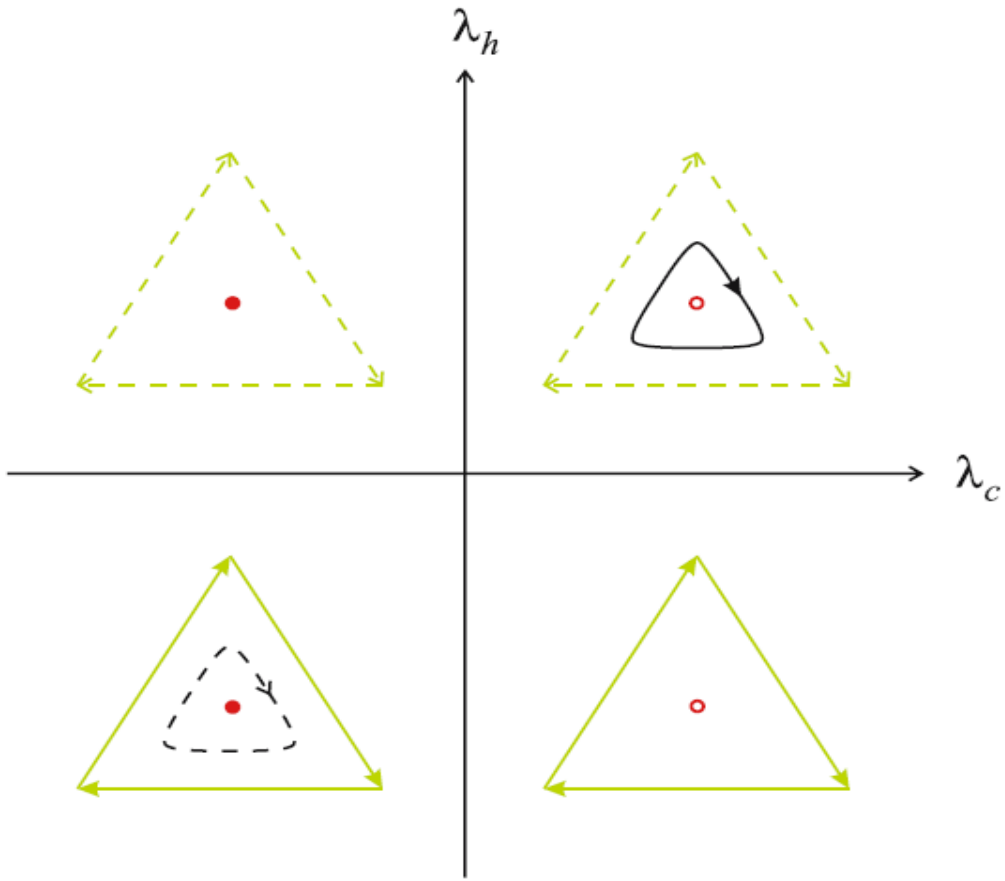


Unstable heteroclinic orbit

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

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

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

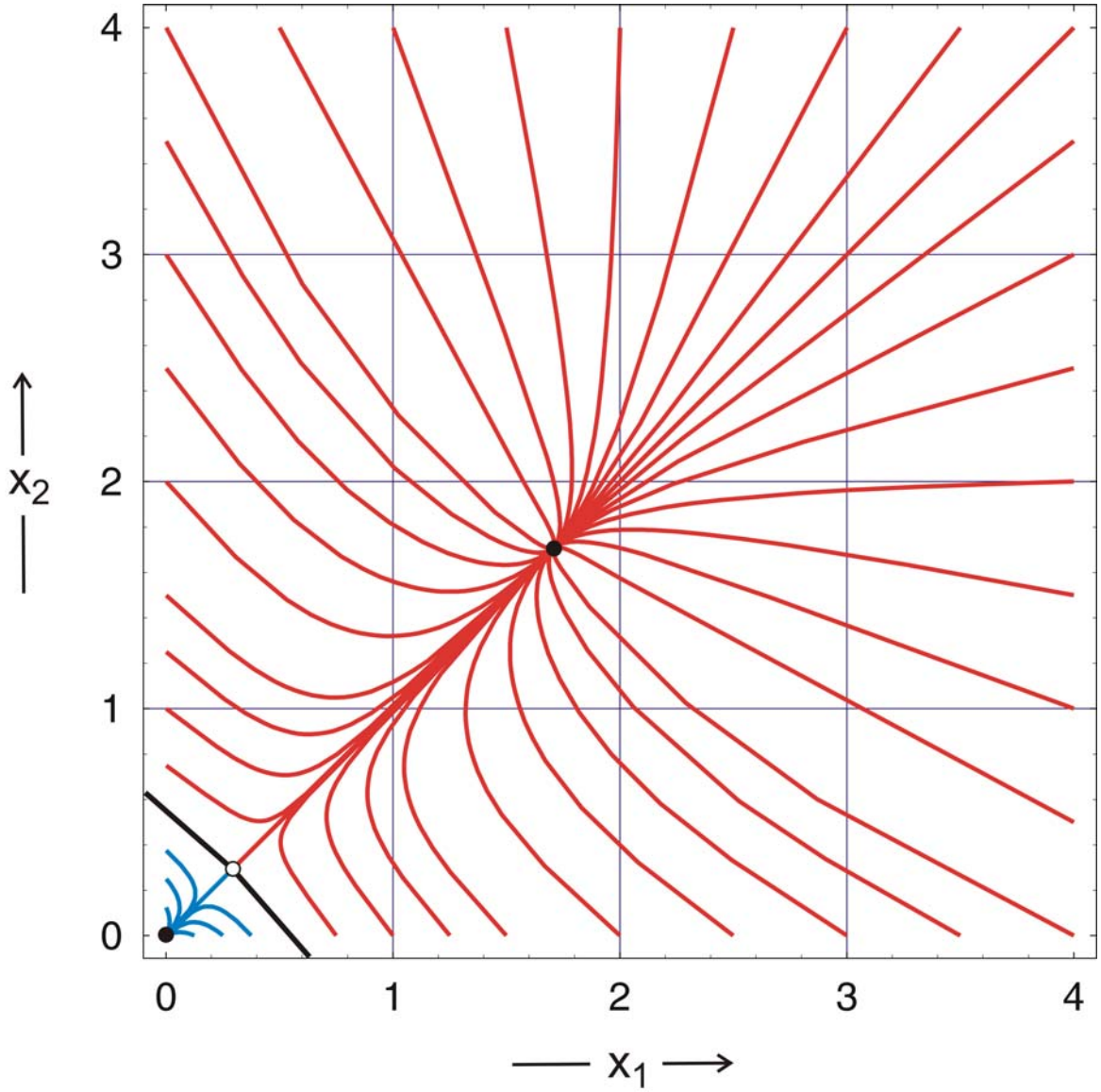
$$\frac{dx_1}{dt} = k_1 F_1(\kappa_2 x_2) - d_1 x_1 \quad \text{and} \quad \frac{dx_2}{dt} = k_2 F_2(\kappa_1 x_1) - d_2 x_2$$

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

two stable states

E: both genes off

P: both genes on

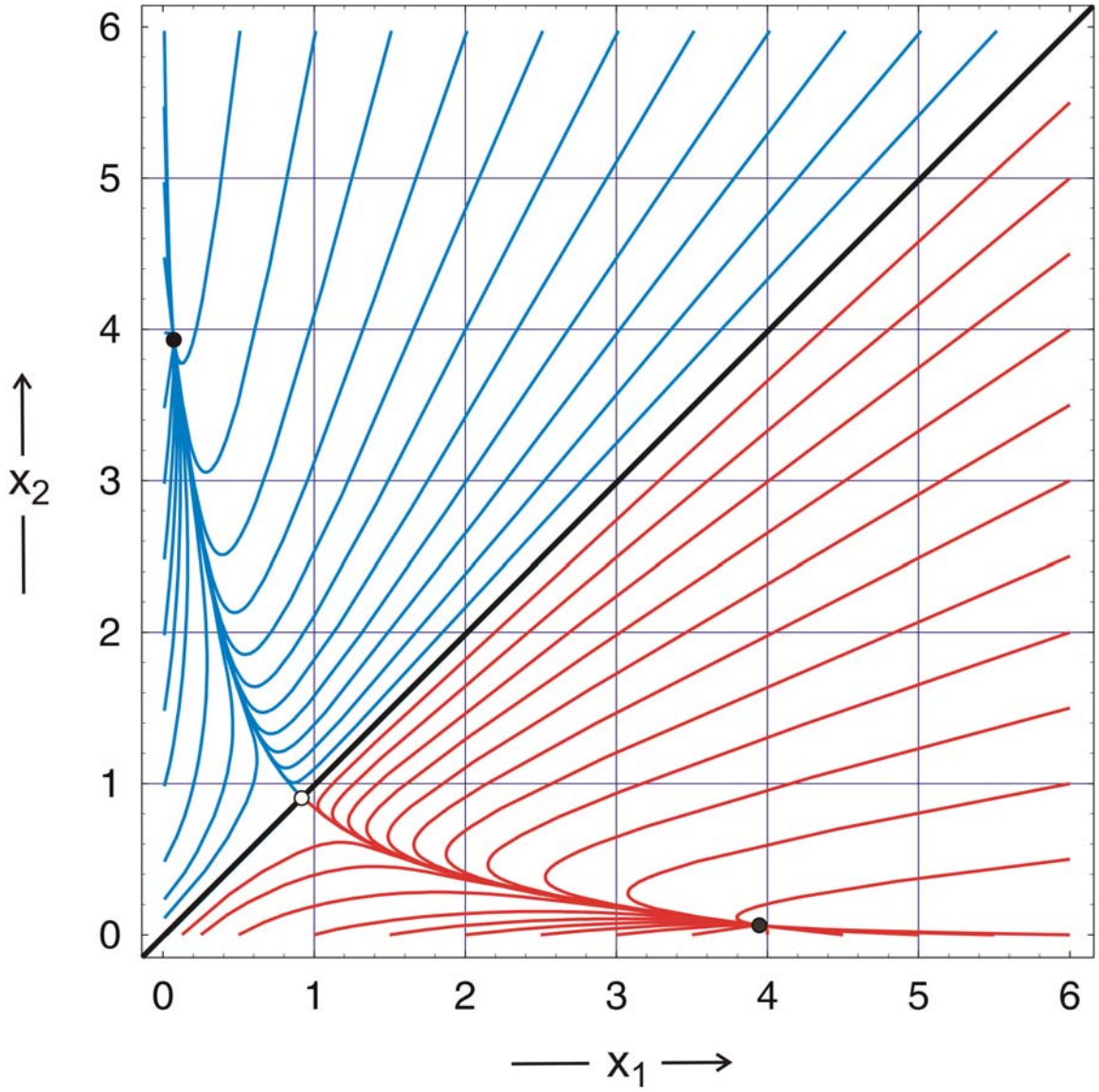


Simplified two gene system (x_1,x_2): act2-act2

two stable states

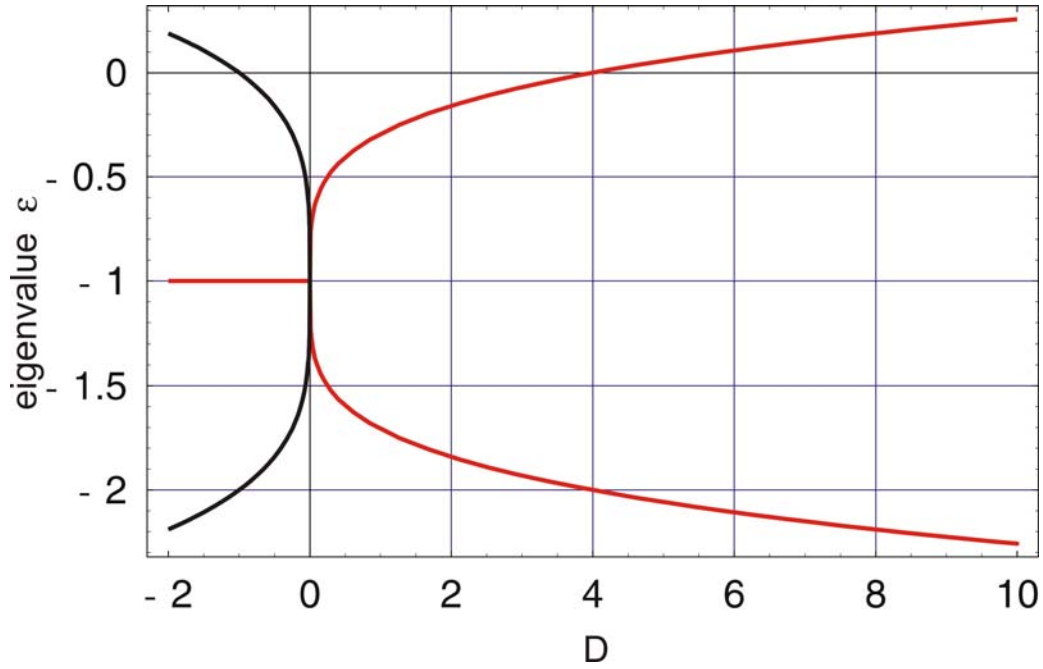
P_1: gene 1 on, gene 2 off

P_2: gene 1 off, gene 2 on

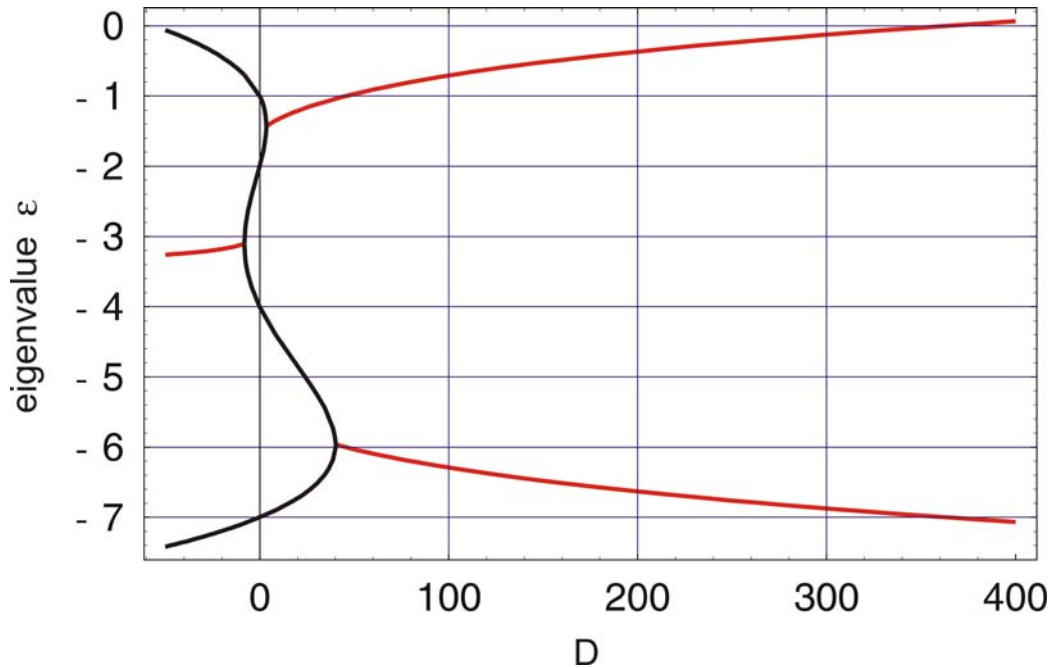


Simplified two gene system (x_1,x_2): rep2-rep2

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

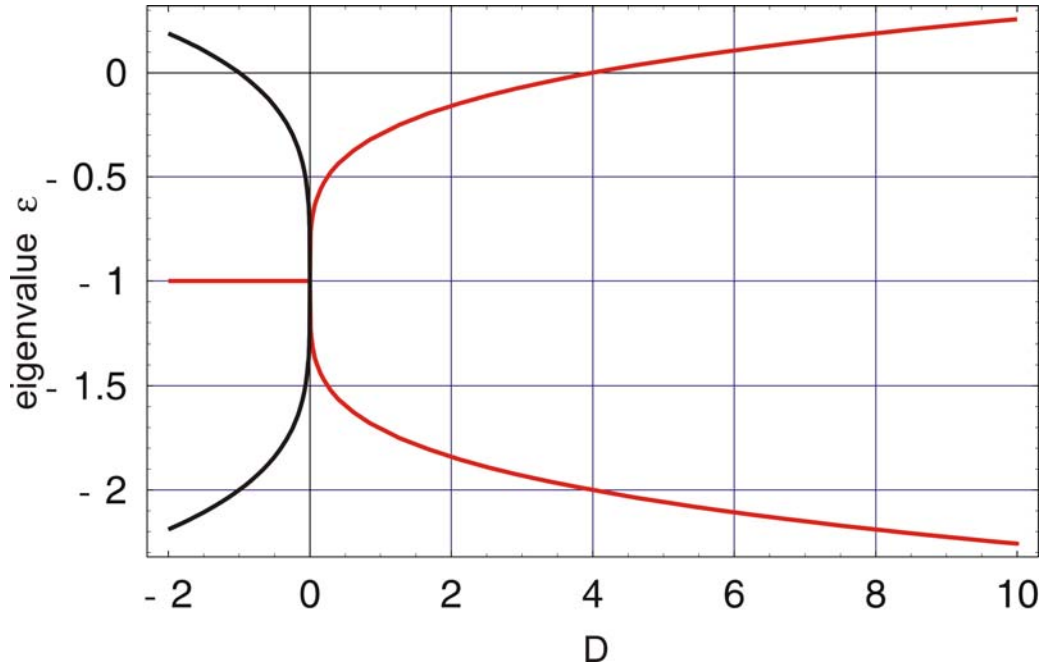


full two gene system:
„asymmetric“
(q_1,q_2,p_1,p_2)

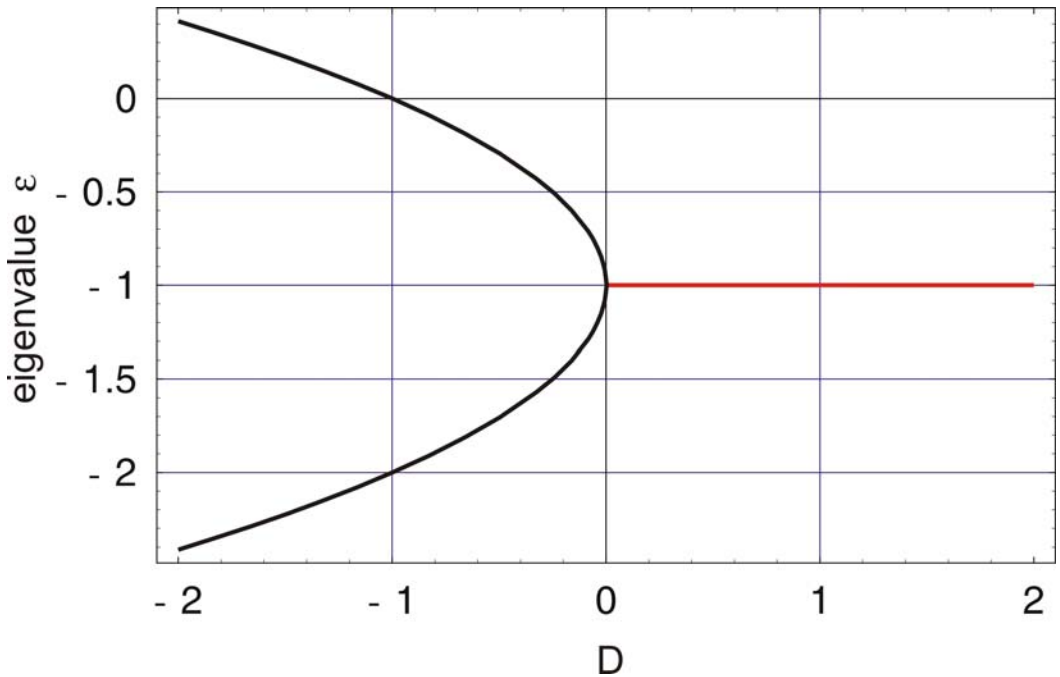


Bifurcation analysis

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

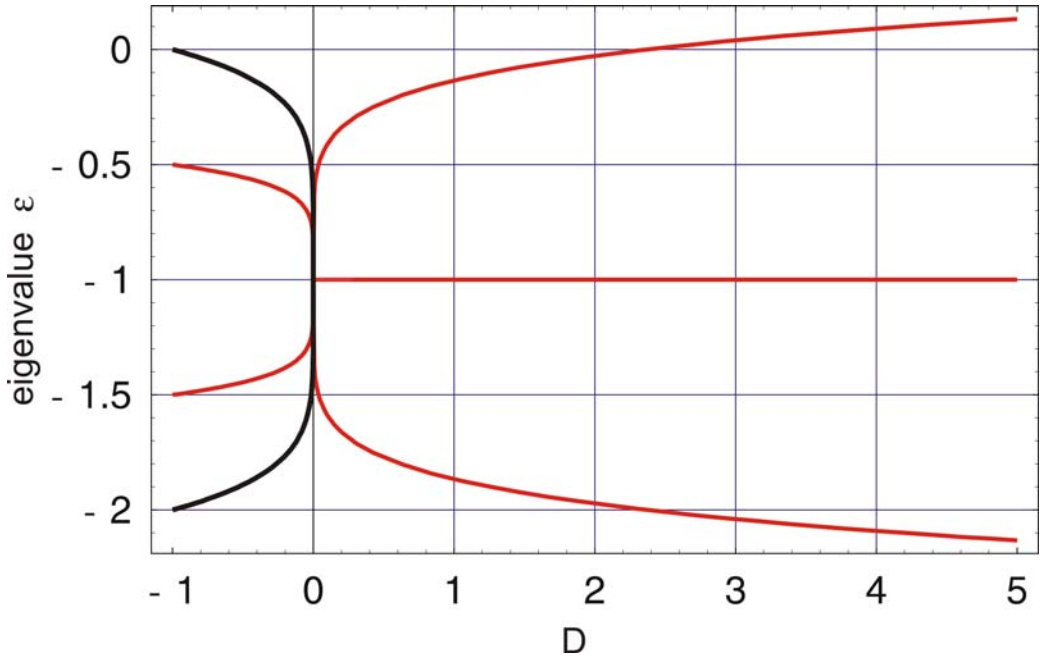


simplified two gene system:
(x_1,x_2)

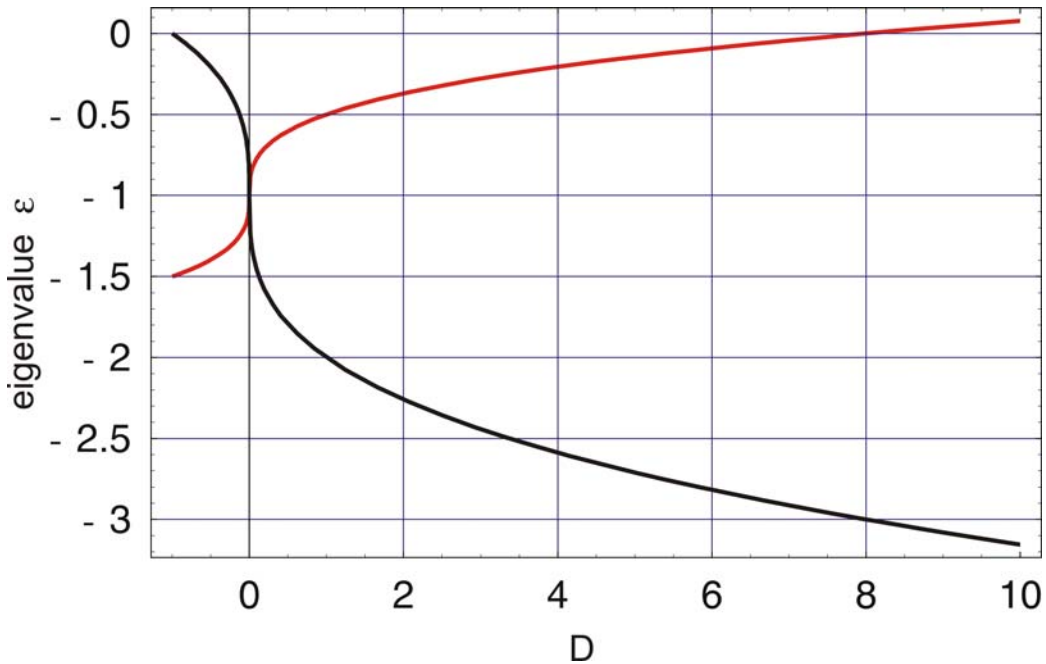


Bifurcation analysis

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. Forward and inverse problems in biology
2. Regulation kinetics and bifurcation analysis
3. **Reverse engineering of dynamical systems**

Algorithms for Molecular Biology BioMed Central

Research

Open Access

Inverse bifurcation analysis: application to simple gene systems

James Lu*[1], Heinz W Engl[1] and Peter Schuster[2]

Address: [1]Johann Radon Institute for Computational and Applied Mathematics, Austrian Academy of Sciences, Altenbergerstrasse 69, A-4040 Linz, Austria and [2]Theoretical Biochemistry Group, Institute for Theoretical Chemistry, University of Vienna, Währingerstrasse 17, A-1090 Vienna, Austria

Email: James Lu* - james.lu@oeaw.ac.at; Heinz W Engl - heinz.engl@oeaw.ac.at; Peter Schuster - pks@tbi.univie.ac.at

* Corresponding author

Published: 21 July 2006

Algorithms for Molecular Biology 2006, 1:11 doi:10.1186/1748-7188-1-11

Received: 21 June 2006
Accepted: 21 July 2006

This article is available from: http://www.almob.org/content/1/1/11

Abstract

Background: Bifurcation analysis has proven to be a powerful method for understanding the qualitative behavior of gene regulatory networks. In addition to the more traditional *forward problem* of determining the mapping from parameter space to the space of model behavior, the *inverse problem* of determining model parameters to result in certain desired properties of the bifurcation diagram provides an attractive methodology for addressing important biological problems. These include understanding how the robustness of qualitative behavior arises from system design as well as providing a way to engineer biological networks with qualitative properties.

Results: We demonstrate that certain inverse bifurcation problems of biological interest may be cast as optimization problems involving minimal distances of reference parameter sets to bifurcation manifolds. This formulation allows for an iterative solution procedure based on performing a sequence of eigen-system computations and one-parameter continuations of solutions, the latter being a standard capability in existing numerical bifurcation software. As applications of the proposed method, we show that the problem of maximizing regions of a given qualitative behavior as well as the reverse engineering of bistable gene switches can be modelled and efficiently solved.

1 Background

The use of mathematical models provides tools for the analysis of complex molecular interactions aiming at an understanding of processes occurring in living cells. For many problems in cellular control, stochastic effects and time-delays can be ignored and systems of first-order ordinary differential equations (ODEs) can adequately model the underlying processes. Denoting by x and p the biochemical concentrations and parameters, respectively, the instantaneous change in x is described by the vector field f:

$$\dot{x} = f(x, p). \quad (1)$$

In the study of such systems, an important goal is to understand how the observed physiological behavior arises out of gene network topology and parameters p. Some of these questions may be studied via examining the *bifurcation manifolds* Σ of the ODE system, which partition the parameter space into regions of different qualitative behavior (see e.g., [1] for a general overview to bifurcation theory). From ODE models and measured parameters, the *forward problem* of computing the bifurcation diagram has contributed significantly towards elucidating the complex mechanisms underlying cellular processes. For instance, mathematical and symbolic bifurcation analysis has led to an understanding of the possible dynamical behaviors

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

Σ … bifurcation manifold

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

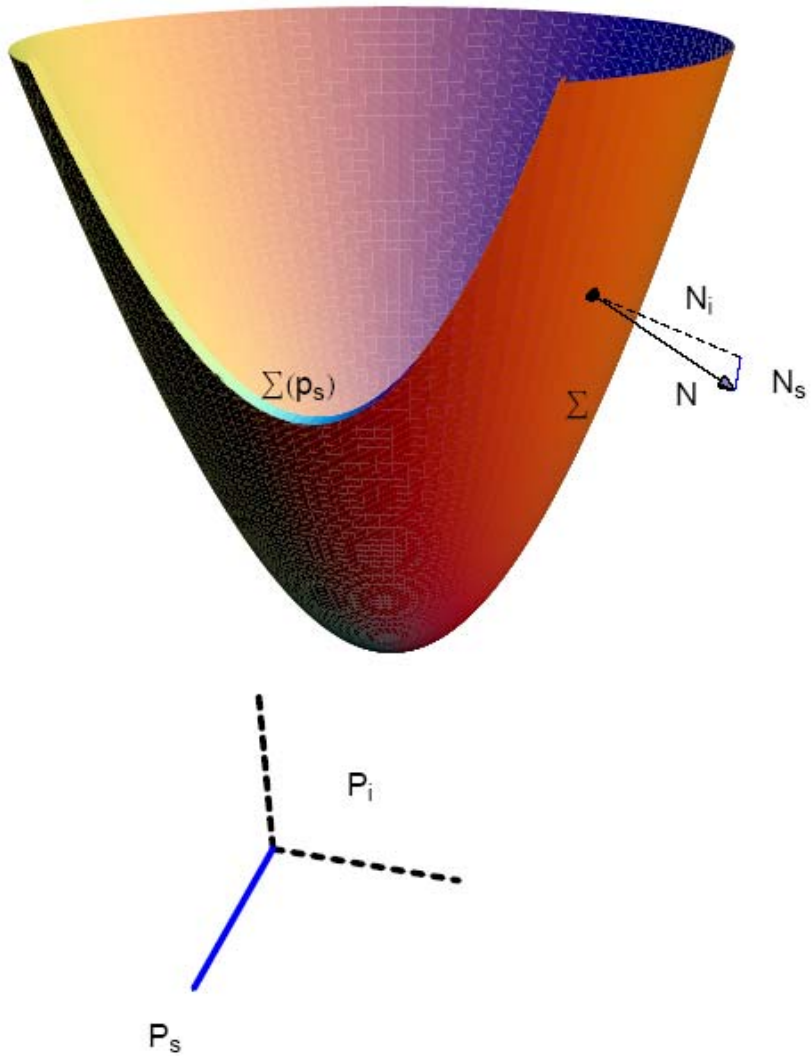
$$F(p)\equiv(F(p)_i\,,F(p_s))=\left(\pi_{\perp\Sigma(p_s)}\,p_i\ ,\ p_s\right)\ \ldots\ \text{forward operator}$$

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

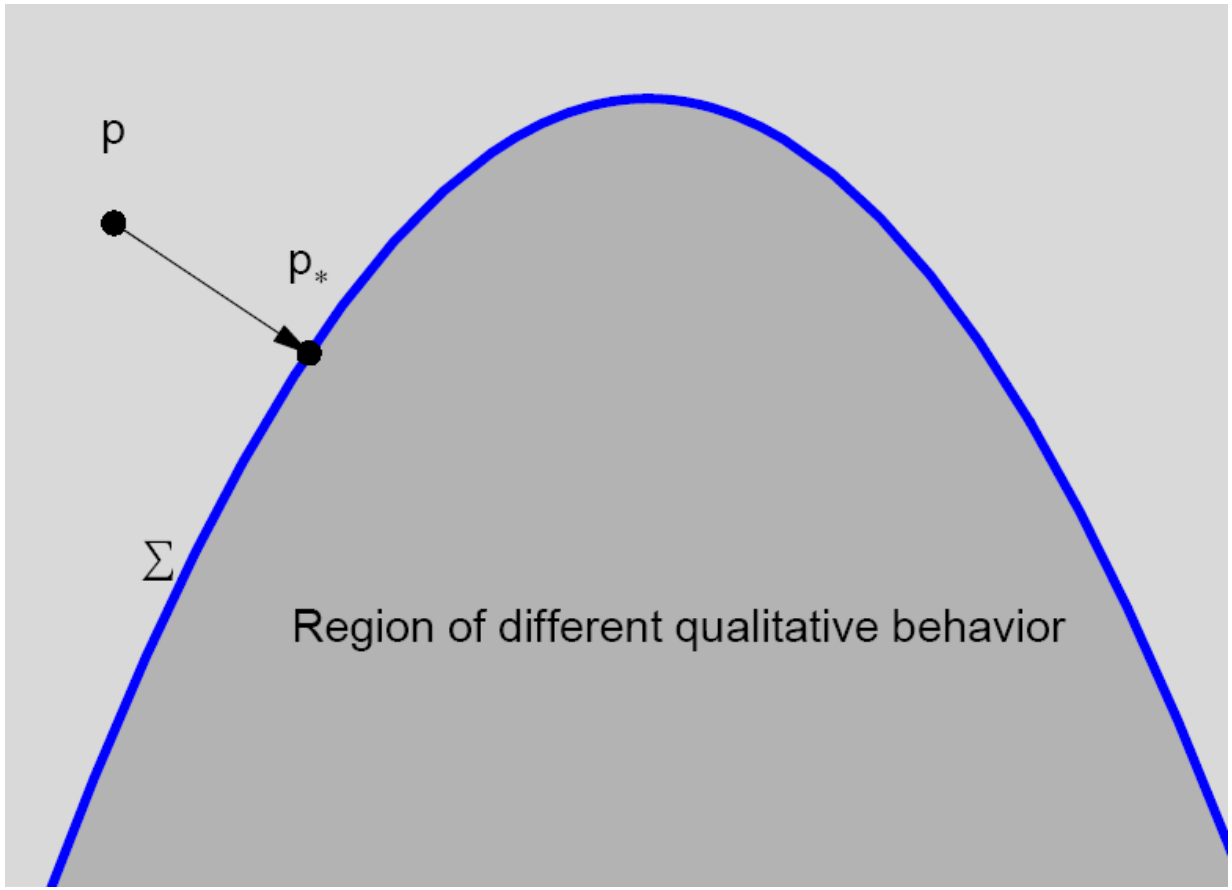
$$\text{subject to}\quad p_{\text{low}}\le p\le p_{\text{upp}}$$

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

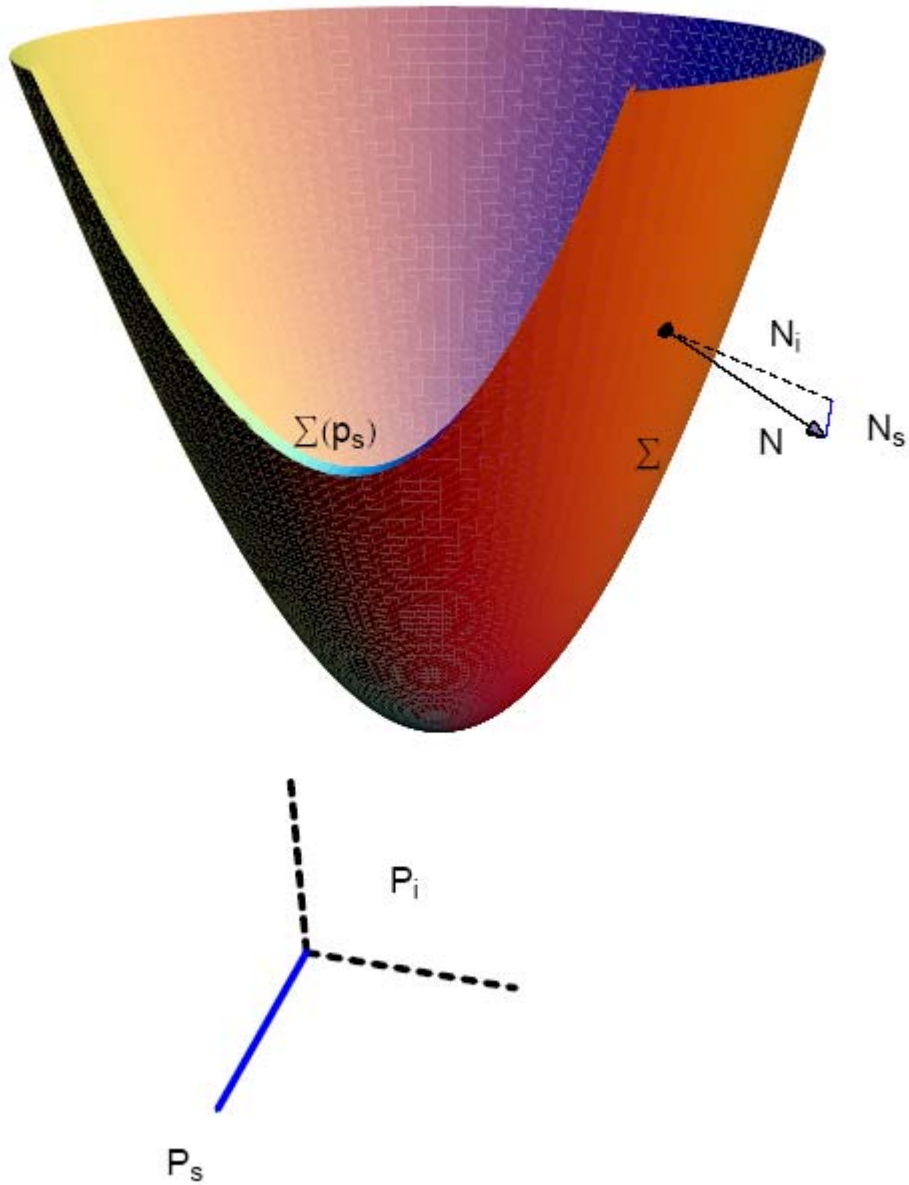
J. Lu, H.W. Engl, P. Schuster. Inverse bifurcation analysis: Application to simple gene systems. *AMB Algorithms for Molecular Biology* **1**, no.11, 2006.

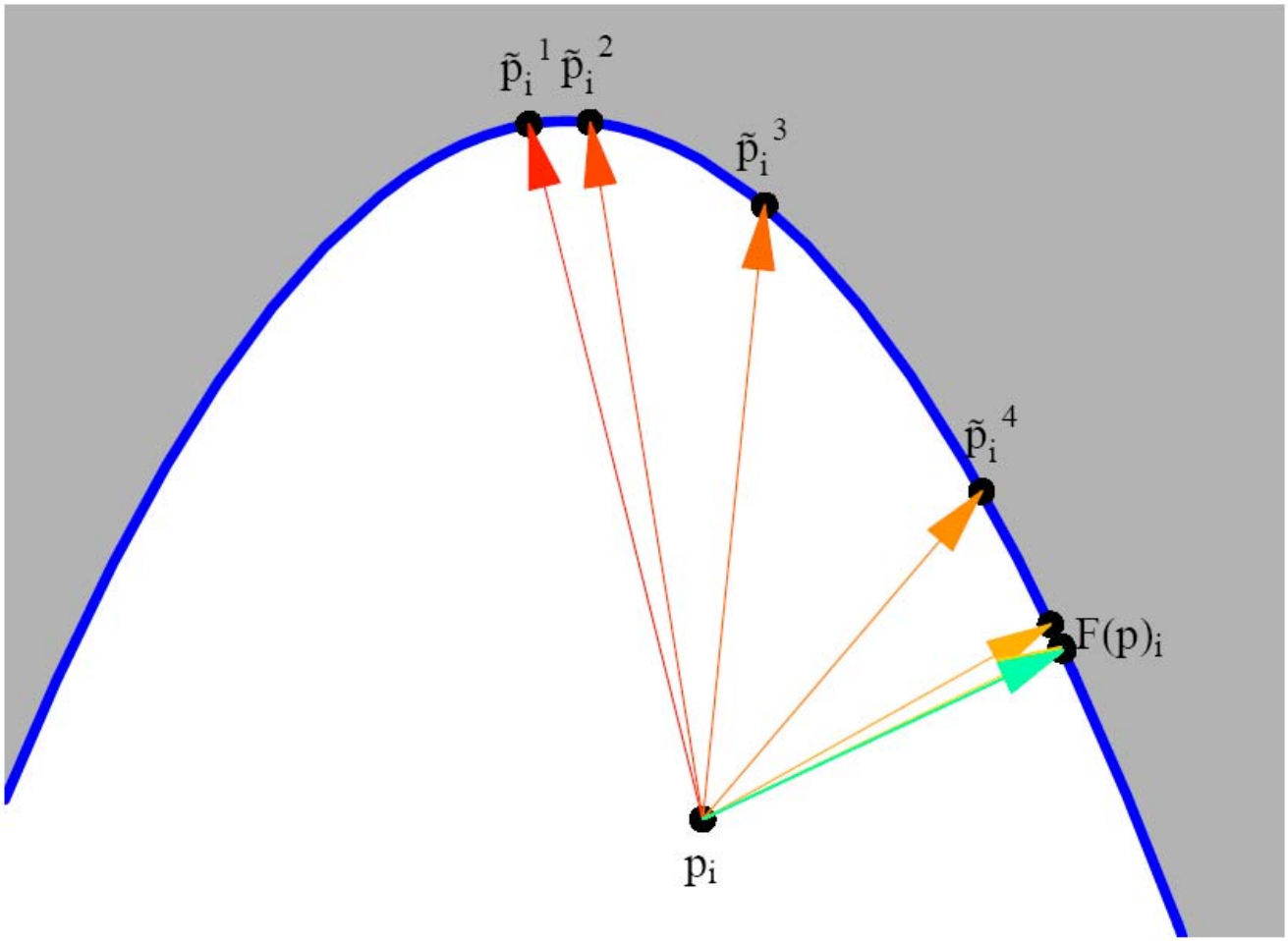


The bifurcation manifold



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

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

$k = 1, 2, 3$

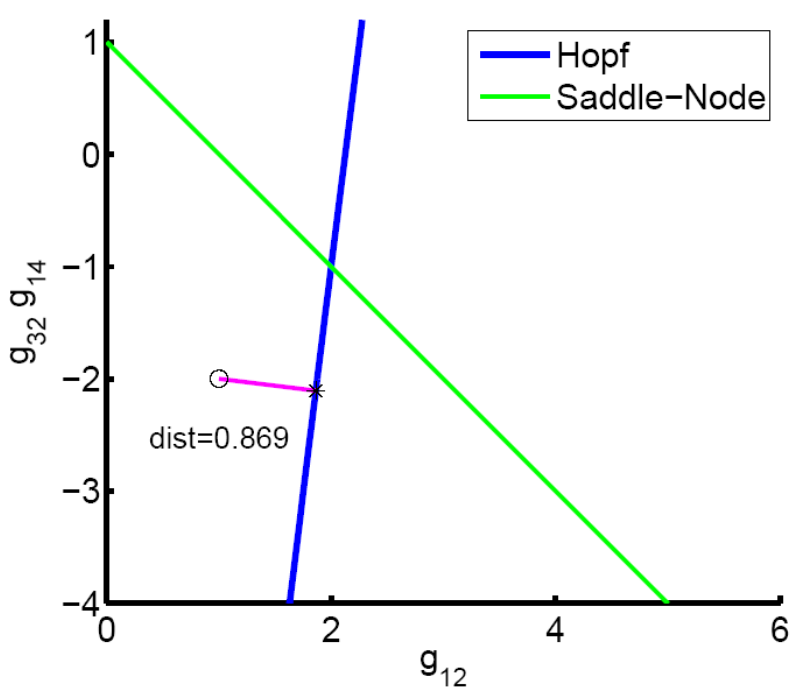
$$f_1 = \begin{cases} B & \text{for } x_2^{g12} x_4^{g14} \le B \\ x_2^{g12} x_4^{g14} & \text{for } B < x_2^{g12} x_4^{g14} < M \\ M & \text{for } x_2^{g12} x_4^{g14} \ge M \end{cases}$$

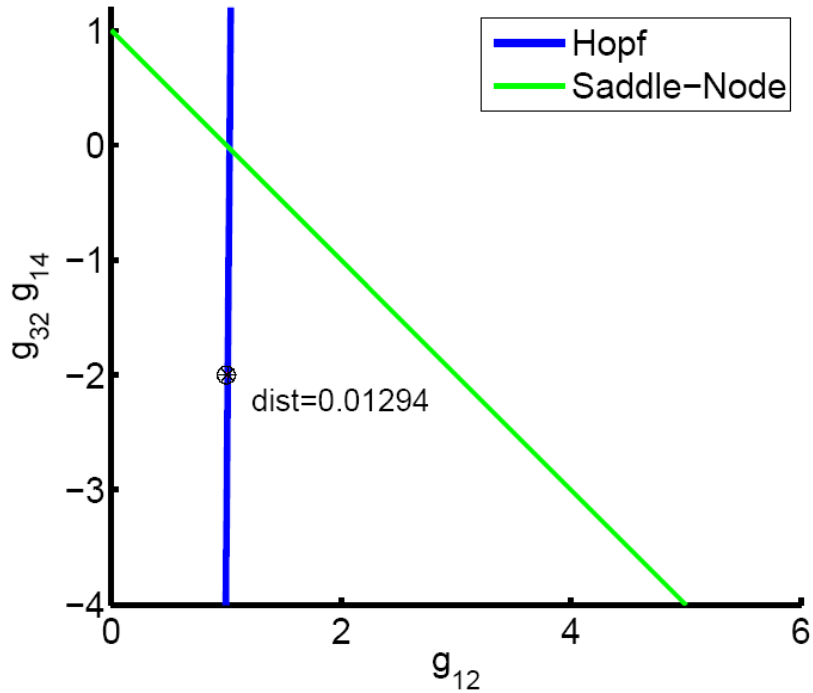
$$f_3 = \begin{cases} B & \text{for } x_2^{g32} \le B \\ x_2^{g32} & \text{for } B < x_2^{g32} < M \\ M & \text{for } x_2^{g32} \ge M \end{cases}$$

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

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.

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

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

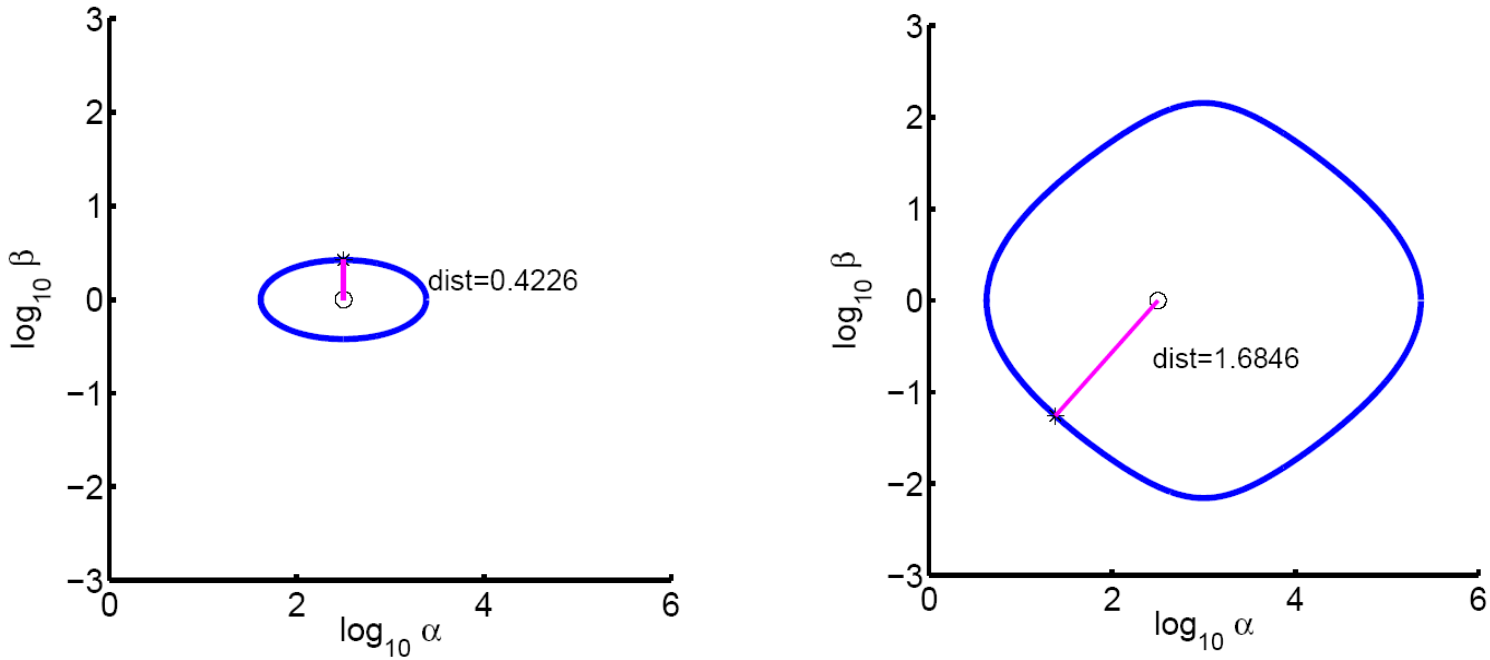
$$p_i = (\alpha, \beta)$$

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

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

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.

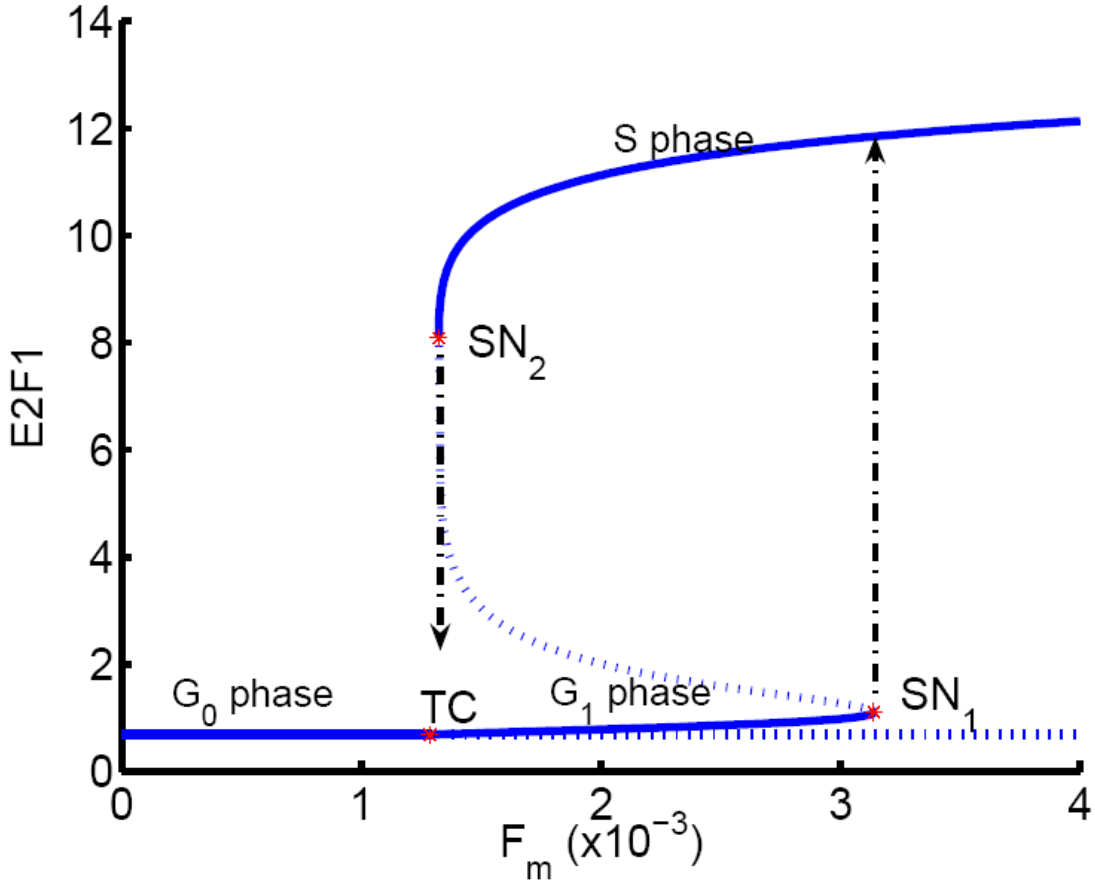
$$\frac{d}{dt}[\mathrm{pRB}] = k_1 \frac{[\mathrm{E2F1}]}{K_{m1} + [\mathrm{E2F1}]} \frac{J_{11}}{J_{11} + [\mathrm{pRB}]} - \phi_{\mathrm{pRB}}[\mathrm{pRB}]$$

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

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

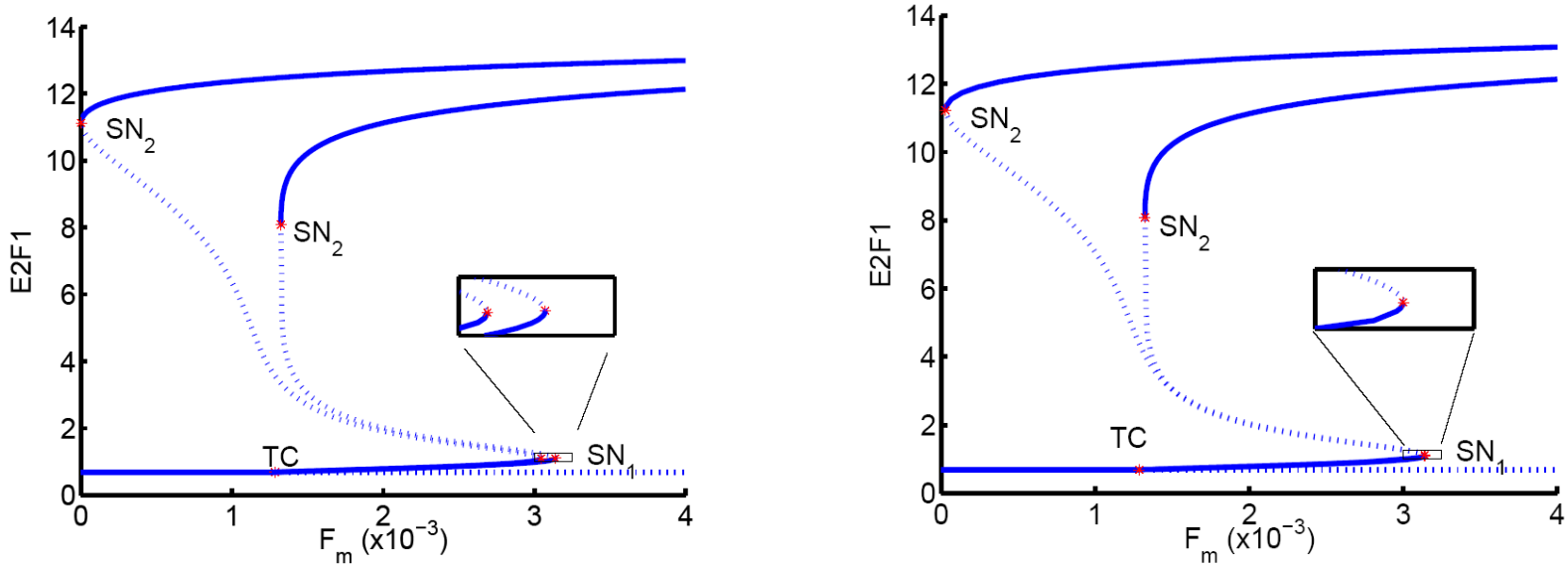
A simple dynamical cell cycle model

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.

Monatsh Chem 139, 427–446 (2008)
DOI 10.1007/s00706-008-0892-6
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Review

Modeling in biological chemistry. From biochemical kinetics to systems biology

Peter Schuster[1,2]

[1] Institute of Theoretical Chemistry, University of Vienna, Wien, Austria
[2] Santa Fe Institute, Santa Fe, NM, USA

Received 20 November 2007; Accepted 10 January 2008; Published online 14 March 2008

Abstract A brief review on biochemical kinetics in the twentieth century mainly concerned with enzyme kinetics and cooperative processes is presented. Molecular biology and, in particular, structural biology provided the basis for modeling biological phenomena at the molecular level. Structure was recognized as the ultimate and only level at which biological processes find an explanation that is satisfactory for chemists and physicists. A new epoch in biology was initiated by successful extensions of the molecular approach from individual molecules and reactions to the cellular and organismic level. Starting with sequencing of whole genomes in the 1980s more and more techniques became available that are suitable for upscaling from molecules to cells. A series of research programs was initiated: *genomics* dealing with sequencing the *DNA* of whole organisms, *proteomics* considering all proteins of a cell and their interactions, *metabolomics* studying all metabolic reactions of a cell or an organism, and *functional genomics* or *systems biology* aiming at an exploration of the dynamics of complete biological entities. At the same time computational facilities have experienced an unexpected development in speed of calculations and storing devices. At present computer simulations of whole cells at molecular resolution are within reach. The challenge for the theorist in biology is to develop methods for handling the enormously complex networks of gene regulation and metabolism in such a way that biological questions can be addressed. This goal cannot be achieved by dynamical systems theory alone. What is needed is a joint effort from different mathematical disciplines supported by empirical knowledge and tools from discrete mathematics to informatics. Two sections with selected examples from our own laboratory dealing with structural bioinformatics of *RNA* and with a dynamical systems approach to gene regulation are added.

Keywords Biochemical kinetics; Dynamical systems; *RNA* bioinformatics; *RNA* secondary structures; Systems biology.

Correspondence: Peter Schuster, Institute of Theoretical Chemistry, University of Vienna, Währinger Straße 17, A-1090 Wien, Austria. E-mail: pks@tbi.univie.ac.at

Chemical reactions, molecular structures, and cellular biology

In this section a historically motivated review of different mathematical techniques applied to problems in biochemistry and molecular biology is presented in three parts: (i) dynamical systems derived from chemical reaction kinetics, (ii) free energy optimization problems in predictions and design of biopolymer structures, and (iii) methods from discrete mathematics applied in the comparison and analysis of sequence data.

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