Application of Inverse Methods to Problems from Systems Biology

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Inverse Problems: Computational Methods an Emerging Applications

UCLA Conference Center at Lake Arrowhead, 11.– 16.06.2006

Web-Page for further information:

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

1. What is systems biology ?
2. Forward and inverse problems in modeling
3. Three examples
4. Bifurcation analysis of gene regulation
5. Analysis of a synthetic oscillator

1. **What is systems biology ?**
2. Forward and inverse problems in modeling
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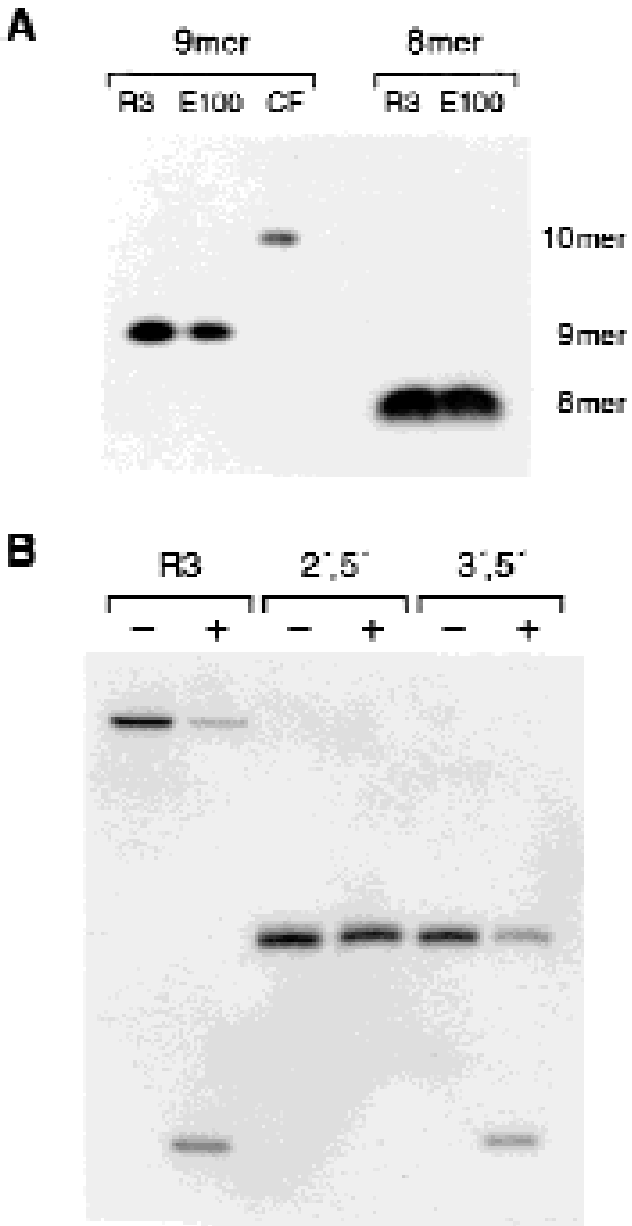
From qualitative data to quantitative modeling

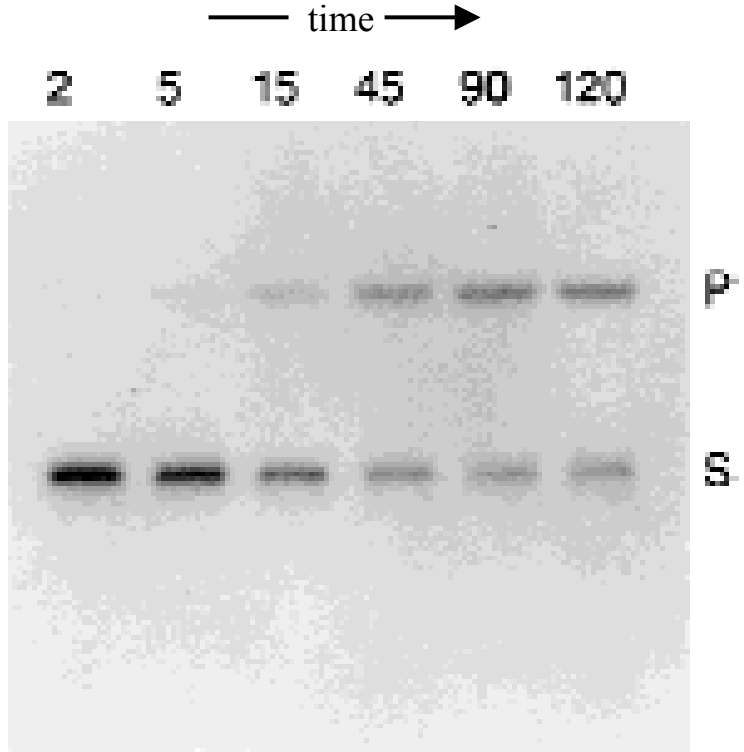
Genomics, proteomics, interactomics

Metabolomics, functional genomics

Systems biology

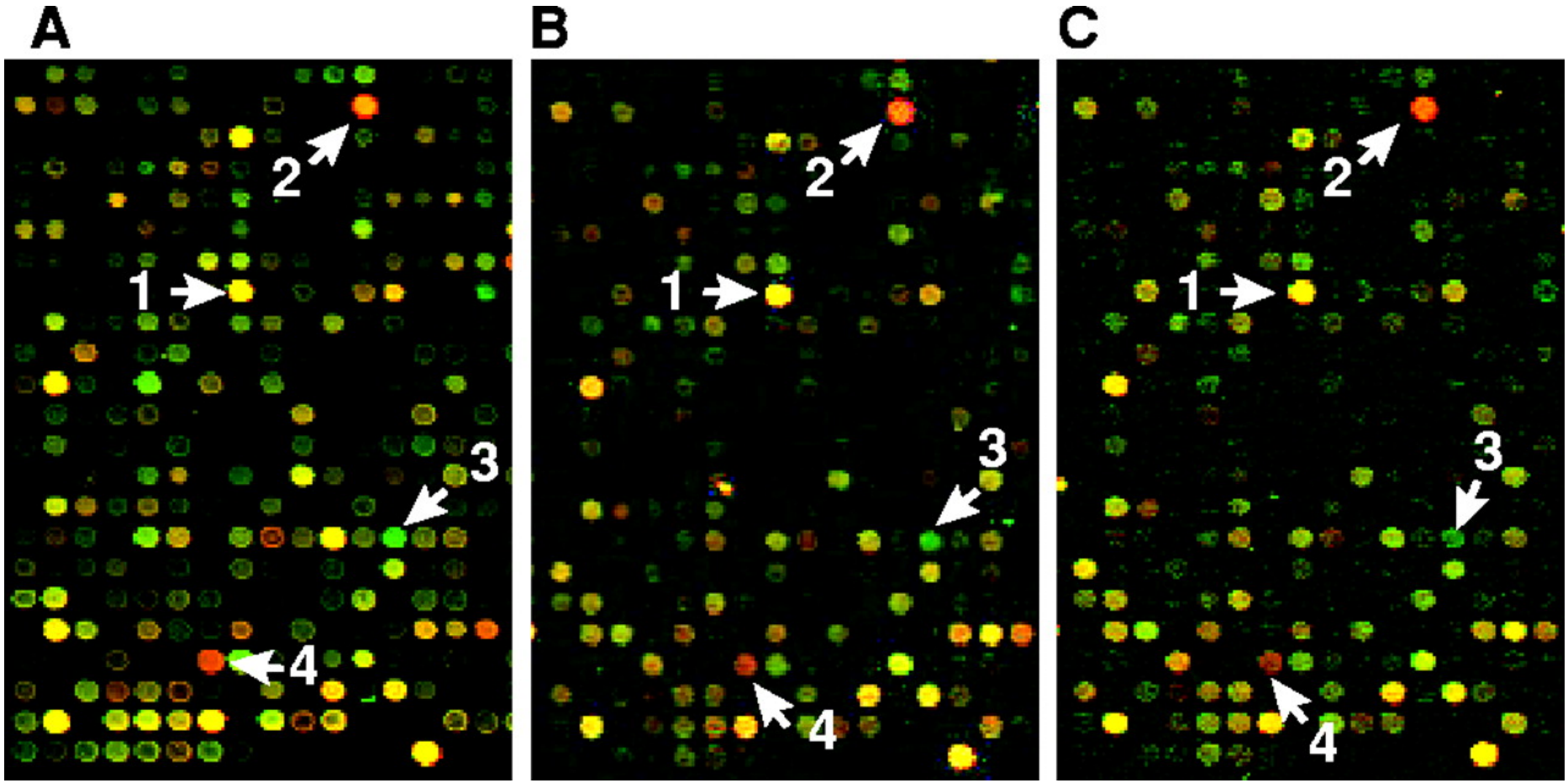
(quantitative biology)





Analysis by gel electrophoresis

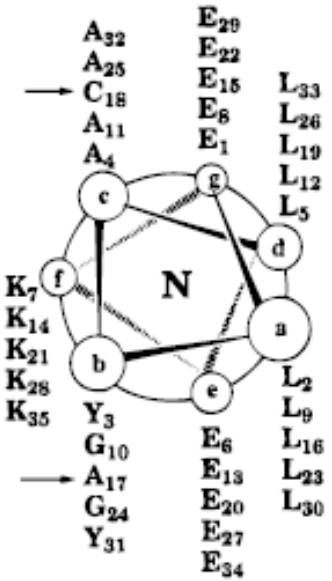
Jeff Rogers, Gerald F. Joyce.
RNA **7**:395-404, 2001



The same section of the microarray is shown in three independent hybridizations. Marked spots refer to: (1) protein disulfide isomerase related protein P5, (2) IL-8 precursor, (3) EST AA057170, and (4) vascular endothelial growth factor.

Gene expression DNA microarray representing **8613** human genes used to study transcription in the response of human fibroblasts to serum.

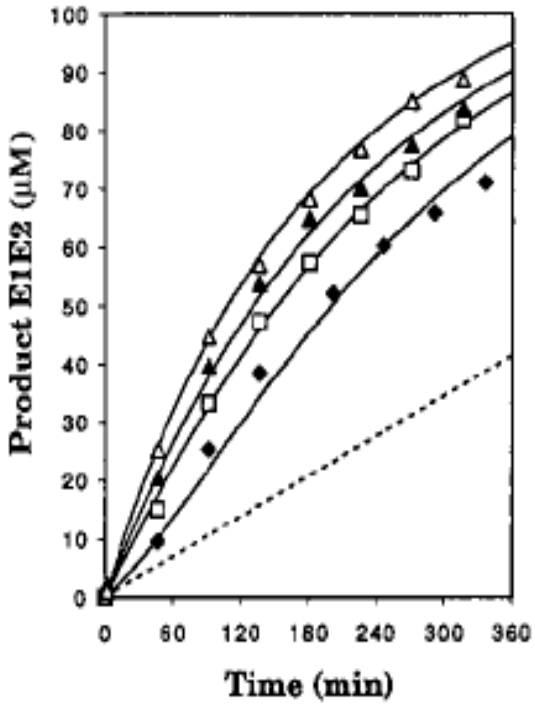
V.R.Iyer *et al*., *Science* **283**: 83-87, 1999

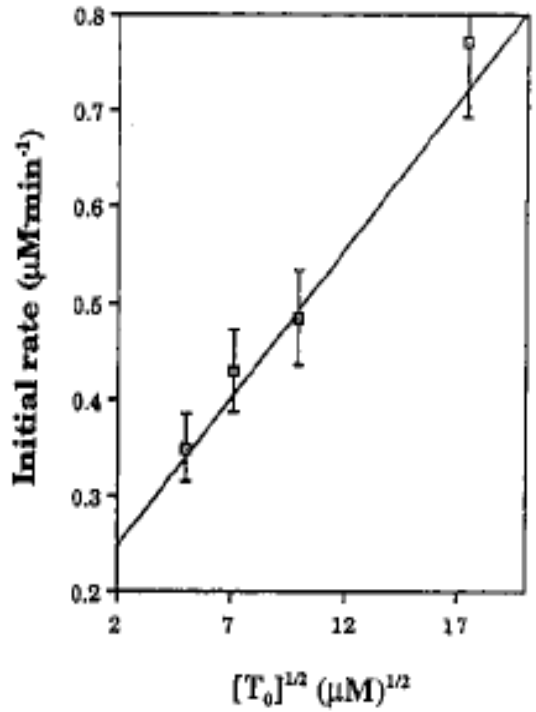


E1E2: Ac-ELYALEK-ELGALEK-ELACLEK-ELGALEK-ELYALEK-$CONH_2$

E1: Ac-ELYALEK-ELGALEK-ELA-COSR

E2: H_2N-CLEK-ELGALEK-ELYALEK-$CONH_2$





A pH-modulated, self-replicating peptide

Shao Yao, Indraneel Ghosh, Reena Zutshi, Jean Chmielewski.
J.Am Chem.Soc. **119**:10559-10560, 1997

$$A + B \rightarrow X$$
$$2\,X \rightarrow Y$$
$$Y + X \rightarrow D$$

$$\frac{da}{dt} = \frac{db}{dt} = -k_1 a b$$

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

$$\frac{dy}{dt} = k_2 x^2 - k_3 x y$$

$$\frac{dd}{dt} = k_3 x y$$

Stoichiometric equations

↓

SBML – systems biology markup language

↓

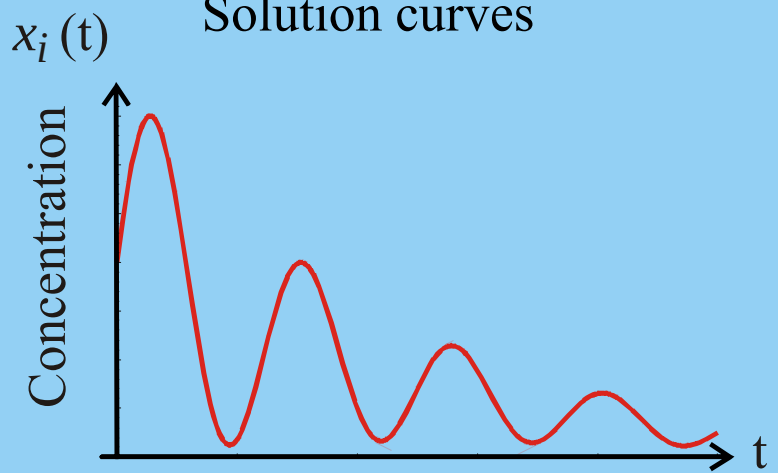
Kinetic differential equations

↓

ODE Integration

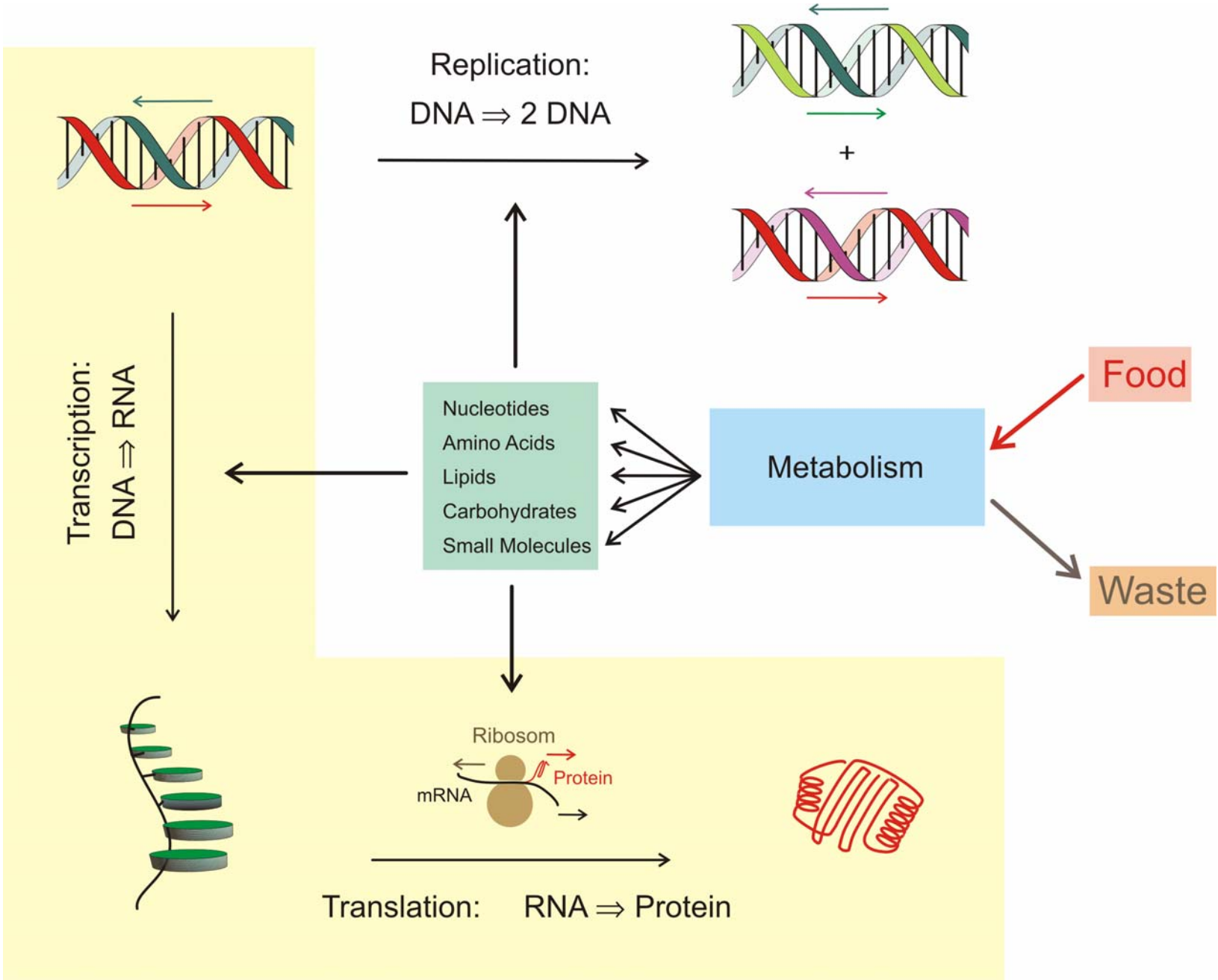
↓

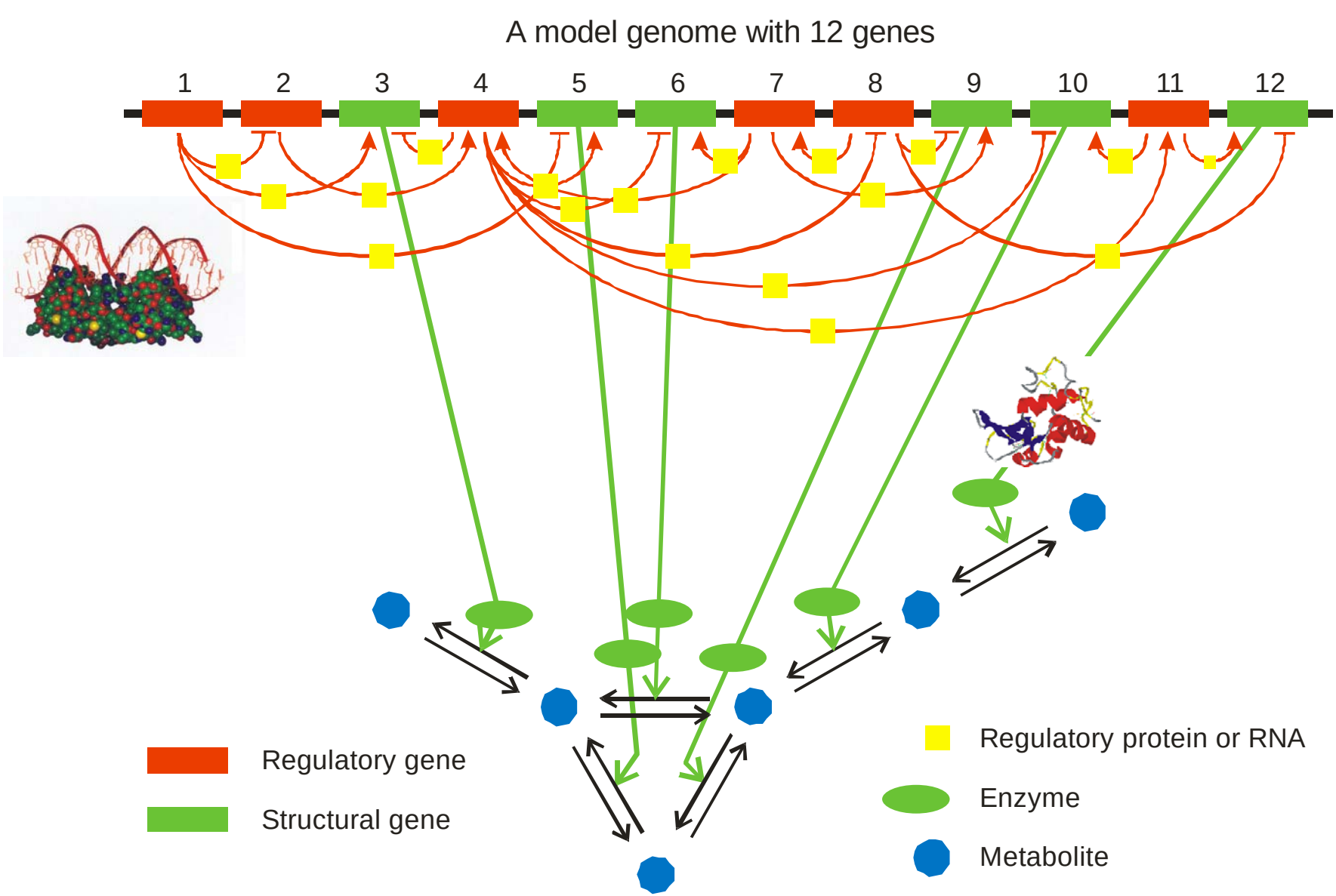
Solution curves



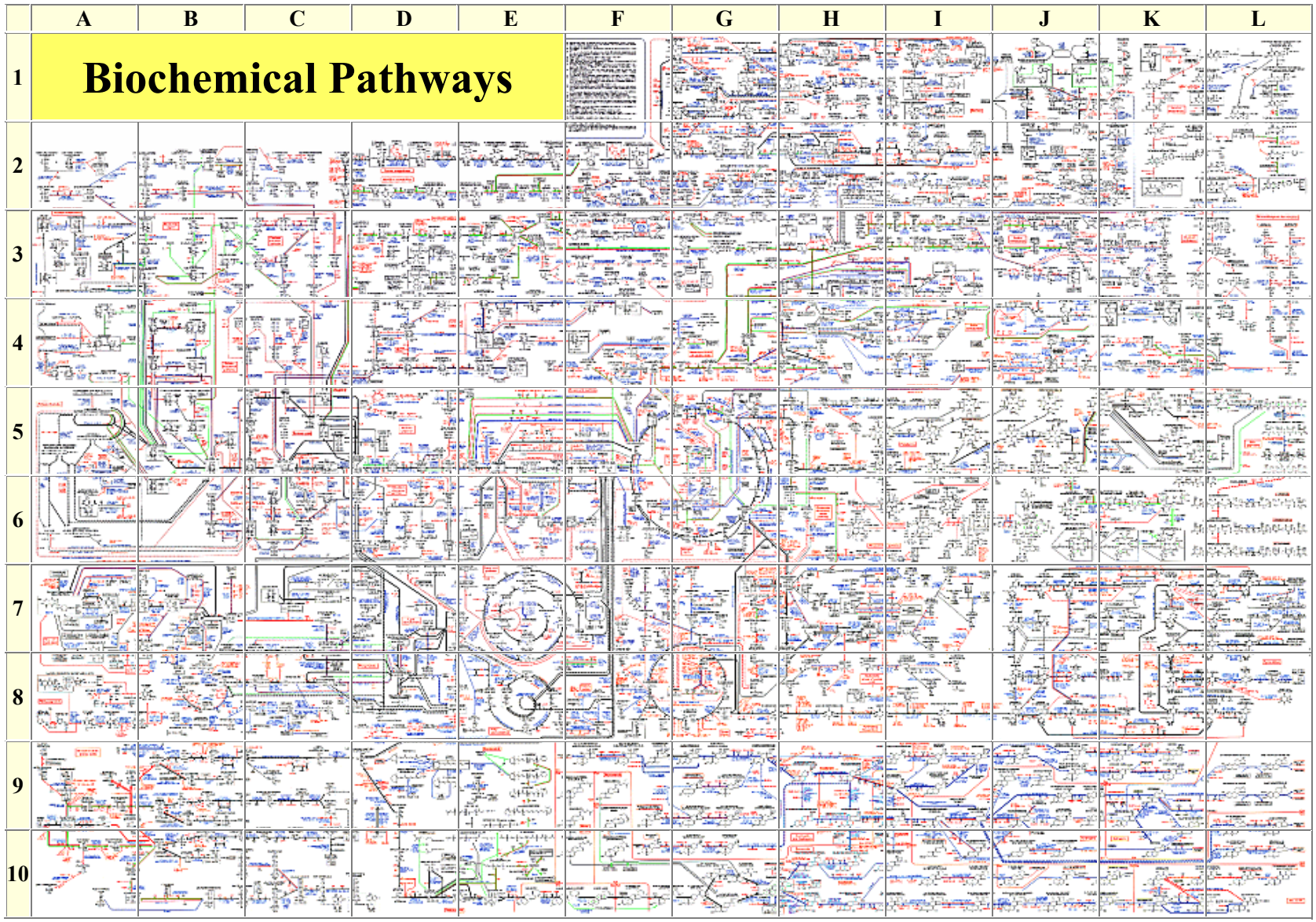
The elements of the simulation tool MiniCellSim

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


Replication:
DNA ⇒ 2 DNA
+
Transcription:
DNA ⇒ RNA
Nucleotides
Amino Acids
Lipids
Carbohydrates
Small Molecules
Metabolism
Food
Waste
Ribosom
Protein
mRNA
Translation: RNA ⇒ Protein

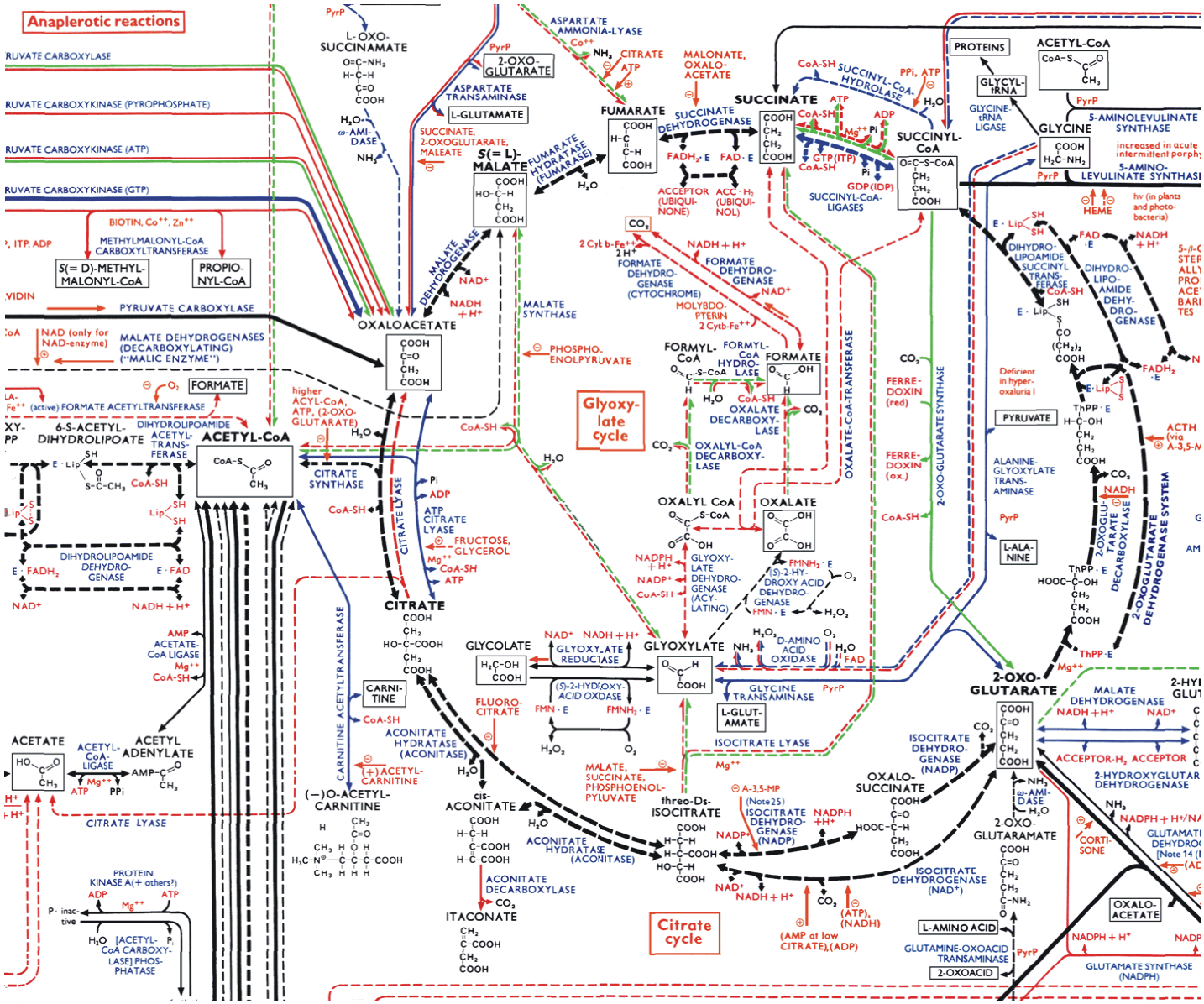


Sketch of a genetic and metabolic network

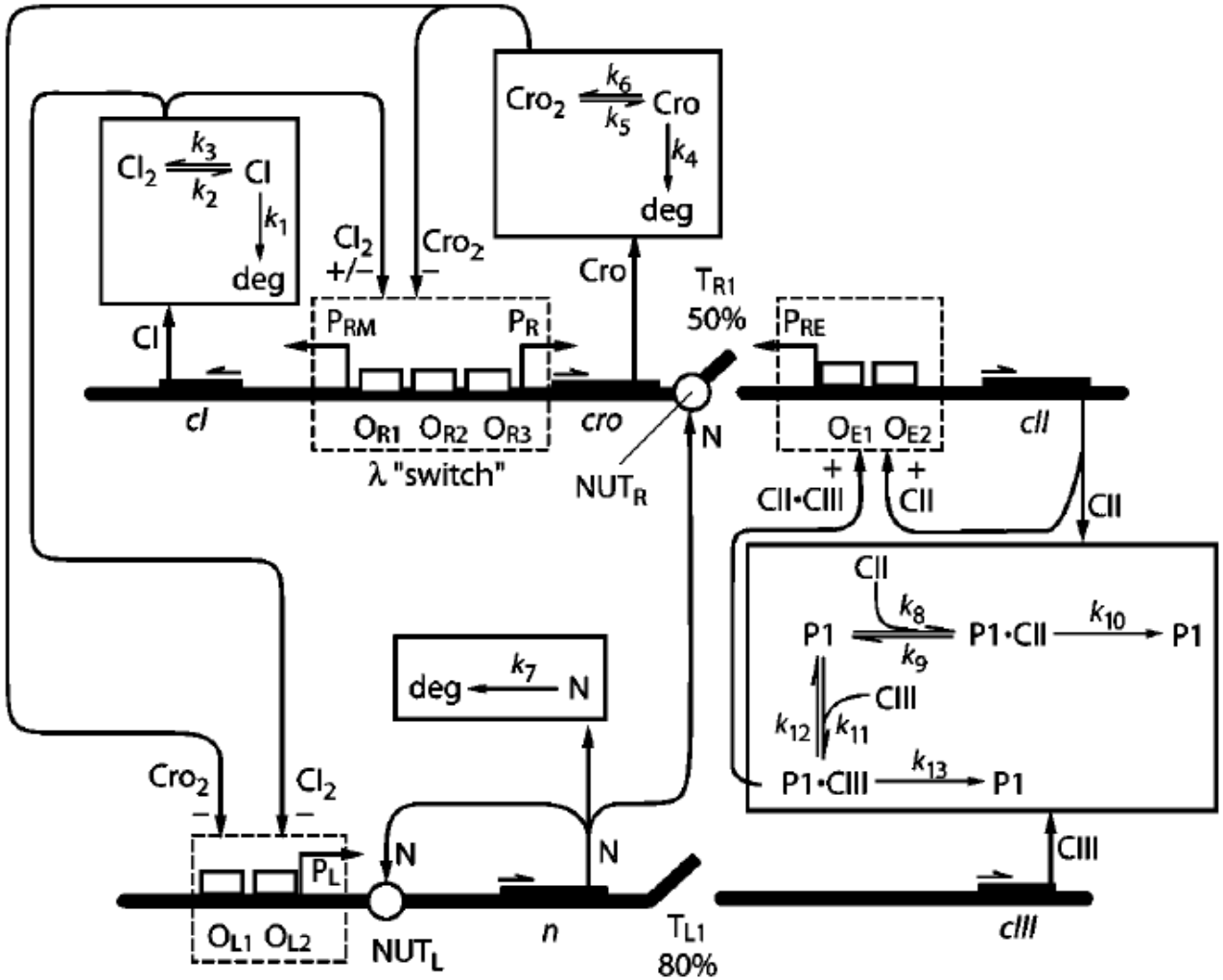


The reaction network of cellular metabolism published by Boehringer-Ingelheim.

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



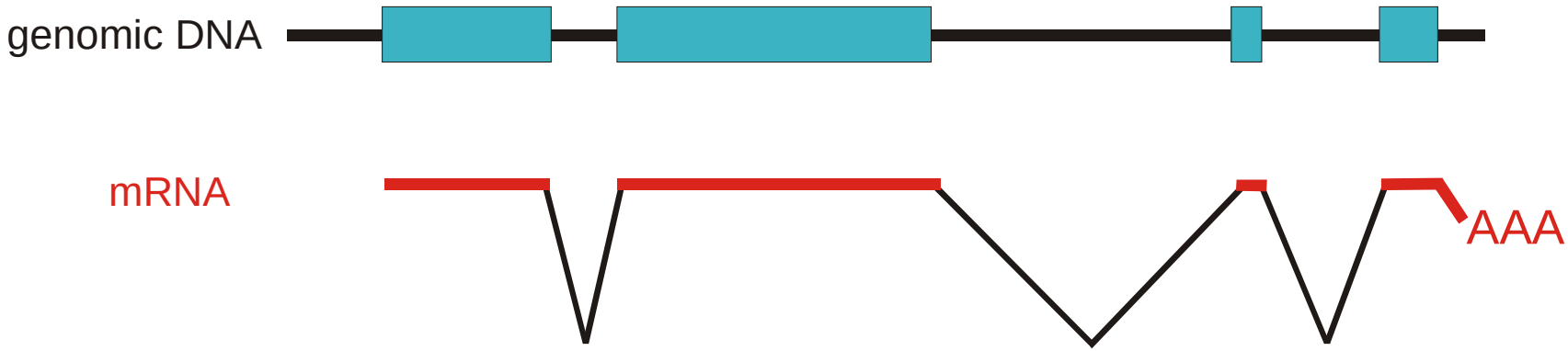
E. coli:	Length of the Genome	4×10^6 Nucleotides
	Number of Cell Types	1
	Number of Genes	4 290
Man:	Length of the Genome	3×10^9 Nucleotides
	Number of Cell Types	200
	Number of Genes	30 000 - 60 000



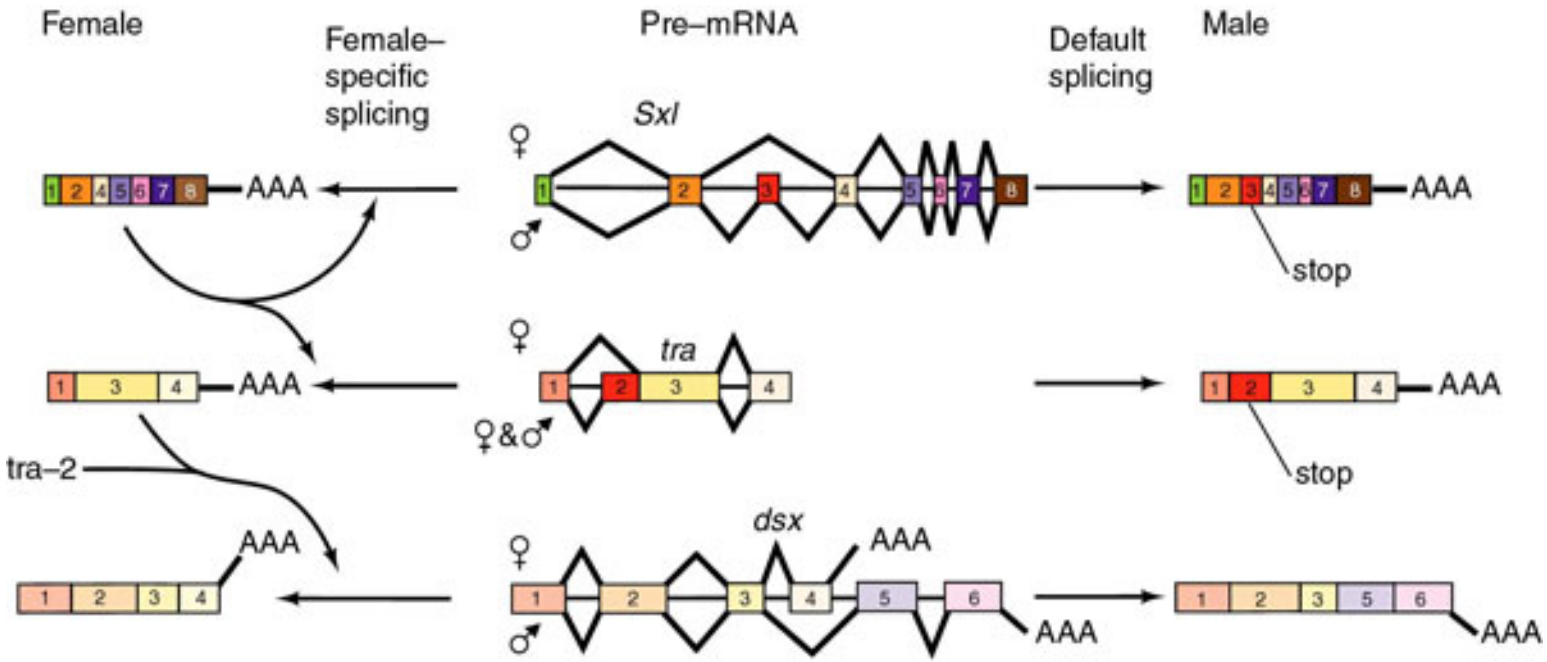
The bacteriophage λ lysis/lysogeny decision circuit.

A. Arkin, J. Ross, H.H. McAdams. *Genetics* **149**:1633-1648, 1998.

Elimination of introns through splicing



The gene is a stretch of DNA which after transcription and processing gives rise to a mRNA



Sex determination in ***Drosophila*** through alternative splicing

The process of protein synthesis and its regulation is now understood but the notion of the gene as a stretch of DNA has become obscure. The gene is essentially associated with the sequence of unmodified amino acids in a protein, and it is determined by the nucleotide sequence as well as the dynamics of the the process eventually leading to the m-RNA that is translated.

The difficulty defining the gene

Helen Pearson,
Nature **441**: 399-401, 2006

WHAT IS A GENE?

The idea of genes as beads on a DNA string is fast fading. Protein-coding sequences have no clear beginning or end and RNA is a key part of the information package, reports **Helen Pearson**.

'Gene' is not a typical four-letter word. It is not offensive. It is never bleeped out of TV shows. And where the meaning of most four-letter words is all too clear, that of gene is not. The more expert scientists become in molecular genetics, the less easy it is to be sure about what, if anything, a gene actually is.

Rick Young, a geneticist at the Whitehead Institute in Cambridge, Massachusetts, says that when he first started teaching as a young professor two decades ago, it took him about two hours to teach fresh-faced undergraduates what a gene was and the nuts and bolts of how it worked. Today, he and his colleagues need three months of lectures to convey the concept of the gene, and that's not because the students are any less bright. "It takes a whole semester to teach this stuff to talented graduates," Young says. "It used to be we could give a one-off definition and now it's much more complicated."

In classical genetics, a gene was an abstract concept — a unit of inheritance that ferried a characteristic from parent to child. As biochemistry came into its own, those characteristics were associated with enzymes or proteins, one for each gene. And with the advent of molecular biology, genes became real, physical things — sequences of DNA which when converted into strands of so-called messenger RNA could be used as the basis for building their associated protein piece by piece. The great coiled DNA molecules of the chromosomes were seen as long strings on which gene sequences sat like discrete beads.

This picture is still the working model for many scientists. But those at the forefront of genetic research see it as increasingly old-fashioned — a crude approximation that, at best, hides fascinating new complexities and, at worst, blinds its users to useful new paths of enquiry.

Information, it seems, is parceled out along chromosomes in a much more complex way than was originally supposed. RNA molecules are not just passive conduits through which the gene's message flows into the world but active regulators of cellular processes. In some cases, RNA may even pass information across generations — normally the sole preserve of DNA.

An eye-opening study last year raised the possibility that plants sometimes rewrite their DNA on the basis of RNA messages inherited from generations past[1]. A study on page 469 of this issue suggests that a comparable phenomenon might occur in mice, and by implication in other mammals[2]. If this type of phenomenon is indeed widespread, it "would have huge implications," says evolutionary geneticist Laurence Hurst at the University of Bath, UK.

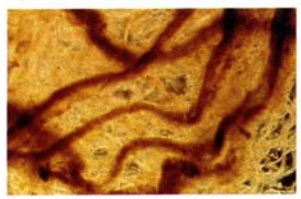
"All of that information seriously challenges our conventional definition of a gene," says molecular biologist Bing Ren at the University of California, San Diego. And the information challenge is about to get even tougher. Later this year, a glut of data will be released from the international Encyclopedia of DNA Elements (ENCODE) project. The pilot phase of ENCODE involves scrutinizing roughly 1% of the human genome in unprecedented detail; the aim is to find all the sequences that serve a useful purpose and explain what that purpose is. "When we started the ENCODE project I had a different view of what a gene was," says contributing researcher Roderic Guigo at the Center for Genomic Regulation in Barcelona. "The degree of complexity we've seen was not anticipated."

"We've come to the realization that the genome is full of overlapping transcripts."
— Phillip Kapranov

Under fire

The first of the complexities to challenge molecular biology's paradigm of a single DNA sequence encoding a single protein was alternative splicing, discovered in viruses in 1977 (see 'Hard to track', overleaf). Most of the DNA sequences describing proteins in humans have a modular arrangement in which exons, which carry the instructions for making proteins, are interspersed with non-coding introns. In alternative splicing, the cell snips out introns and sews together the exons in various different orders, creating messages that can code for different proteins. Over the years geneticists have also documented overlapping genes, genes within genes and countless other weird arrangements (see 'Muddling over genes', overleaf).

Alternative splicing, however, did not in itself require a drastic reappraisal of the notion of a gene; it just showed that some DNA sequences could describe more than one protein. Today's assault on the gene concept is more far reaching, fuelled largely by studies that show the previously unimagined scope of RNA.



Spools of DNA (above) still harbour surprises, with one protein-coding gene often overlapping the next.

P. PLAILLY/SPL

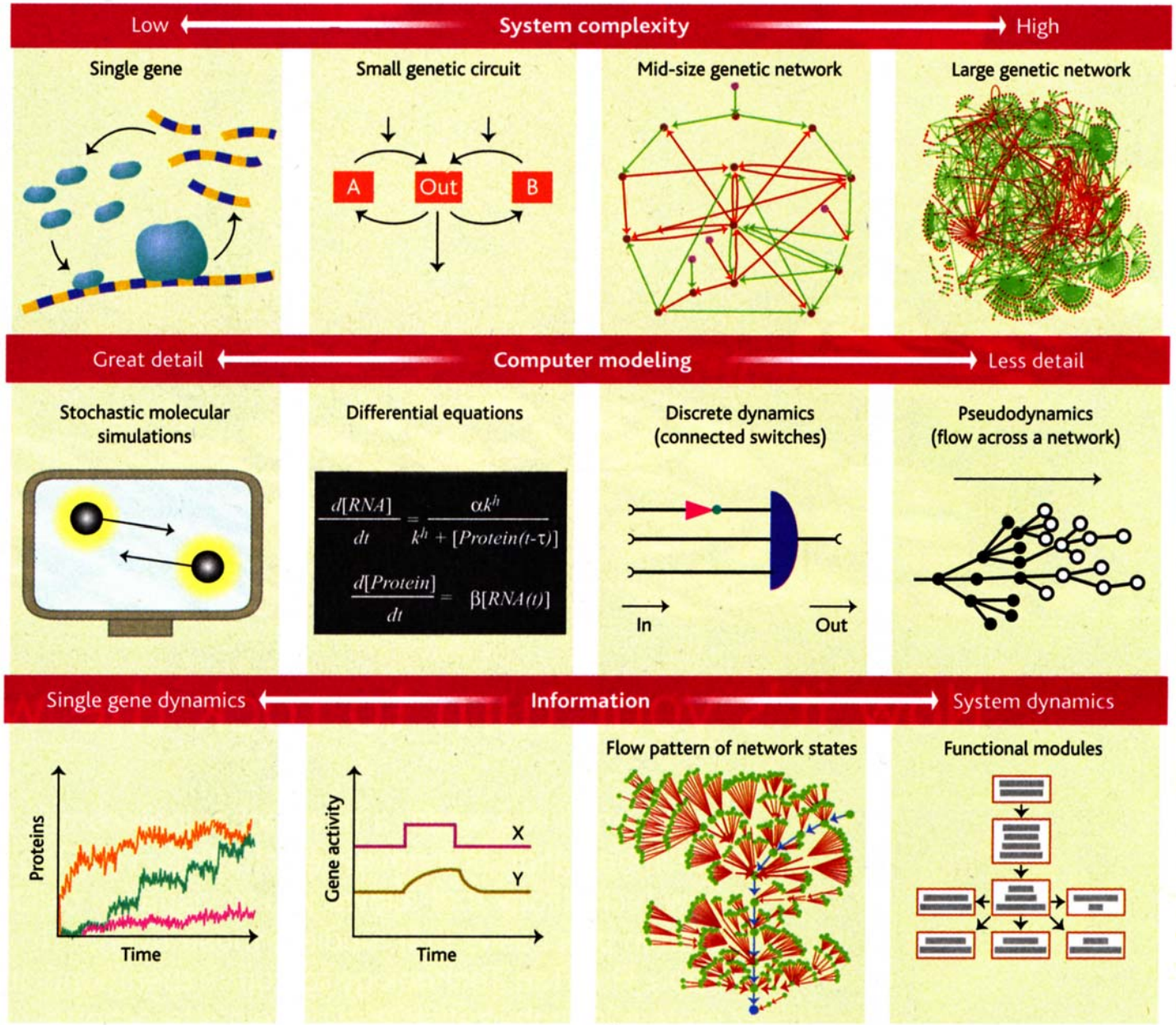
The one gene, one protein idea is coming under particular assault from researchers who are comprehensively extracting and analysing the RNA messages, or transcripts, manufactured by genomes, including the human and mouse genome. Researchers led by Thomas Gingeras at the company Affymetrix in Santa Clara, California, for example, recently studied all the transcripts from ten chromosomes across eight human cell lines and worked out precisely where on the chromosomes each of the transcripts came from[3].

The picture these studies paint is one of mind-boggling complexity. Instead of discrete genes dutifully mass-producing identical RNA transcripts, a teeming mass of transcription converts many segments of the genome into multiple RNA ribbons of differing lengths. These ribbons can be generated from both strands of DNA, rather than from just one as was conventionally thought. Some of these transcripts come from regions of DNA previously identified as holding protein-coding genes. But many do not. "It's somewhat revolutionary," says Gingeras's colleague Phillip Kapranov. "We've come to the realization that the genome is full of overlapping transcripts."

Other studies, one by Guigo's team[4], and one by geneticist Rotem Sorek[5], now at Tel Aviv University, Israel, and his colleagues, have hinted at the reasons behind the mass of transcription. The two teams investigated occasional reports that transcription can start at a DNA sequence associated with one protein and run straight through into the gene for a completely different protein, producing a fused transcript. By delving into databases of human RNA transcripts, Guigo's team estimate that 4–5% of the DNA in regions conventionally recognized as genes is transcribed in this way. Producing fused transcripts could be one way for a cell to generate a greater variety of proteins from a limited number of exons, the researchers say.

Many scientists are now starting to think that the descriptions of proteins encoded in DNA know no borders — that each sequence reaches into the next and beyond. This idea will be one of the central points to emerge from the ENCODE project when its results are published later this year.

Kapranov and others say that they have documented many examples of transcripts in which protein-coding exons from one part of the genome combine with exons from another



Stefan Bornholdt. Less is more in modeling large genetic networks. ***Science* 310**, 449-450 (2005)

1. What is systems biology ?
2. **Forward and inverse problems in modeling**
3. Three examples
4. Bifurcation analysis of gene regulation
5. Analysis of a synthetic oscillator

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: $x(0)$

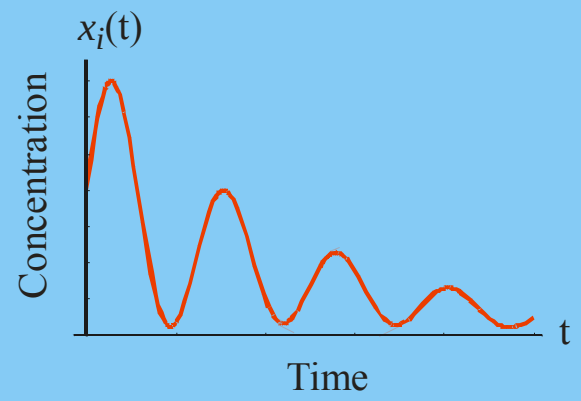
Boundary conditions:

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

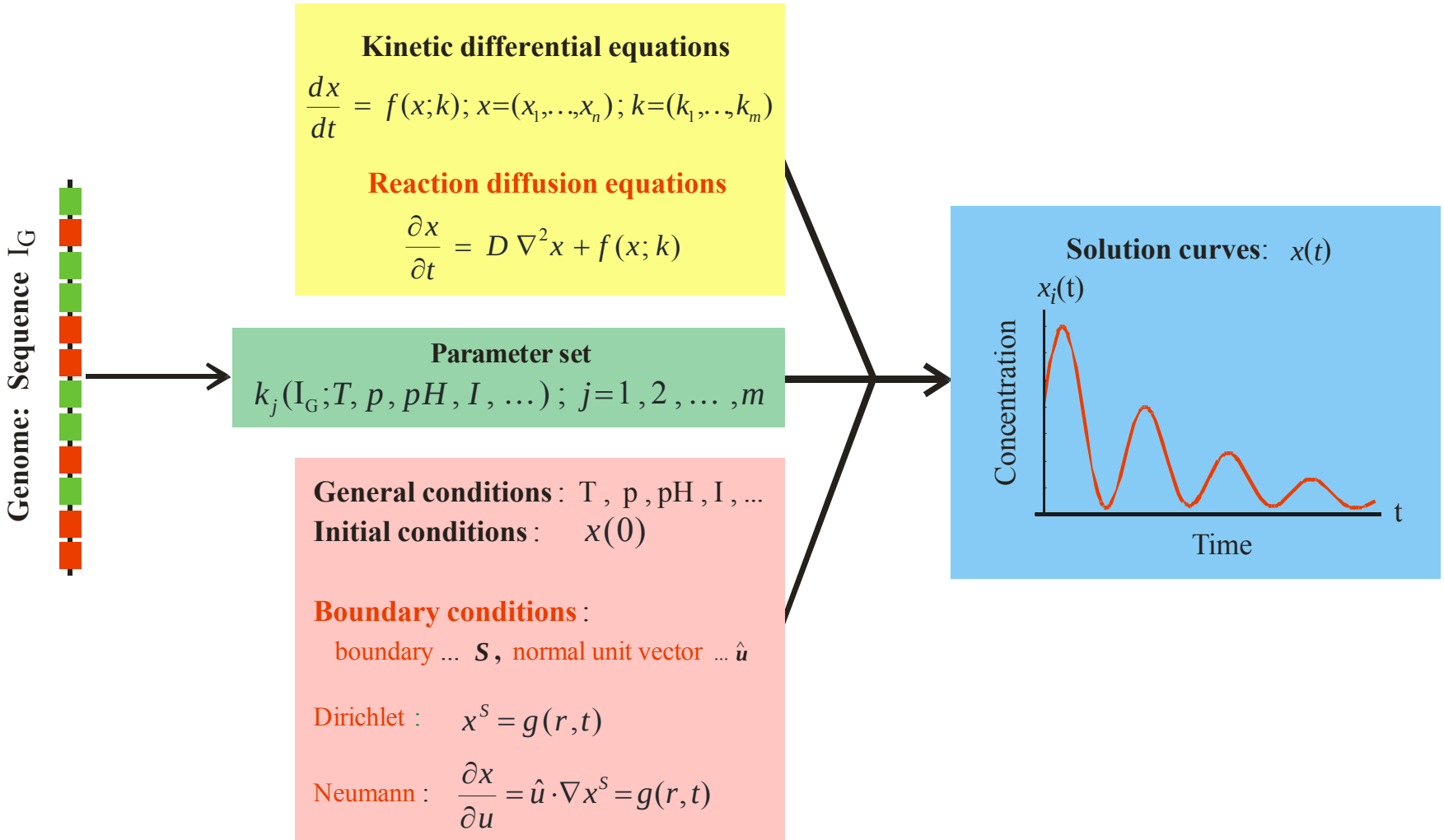
Dirichlet : $x^S = g(r,t)$

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 :

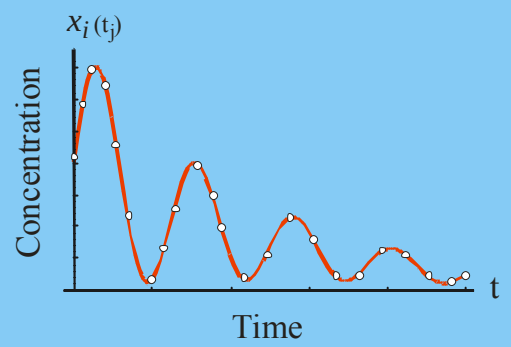
boundary ... S, normal unit vector... $\hat{u}$

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

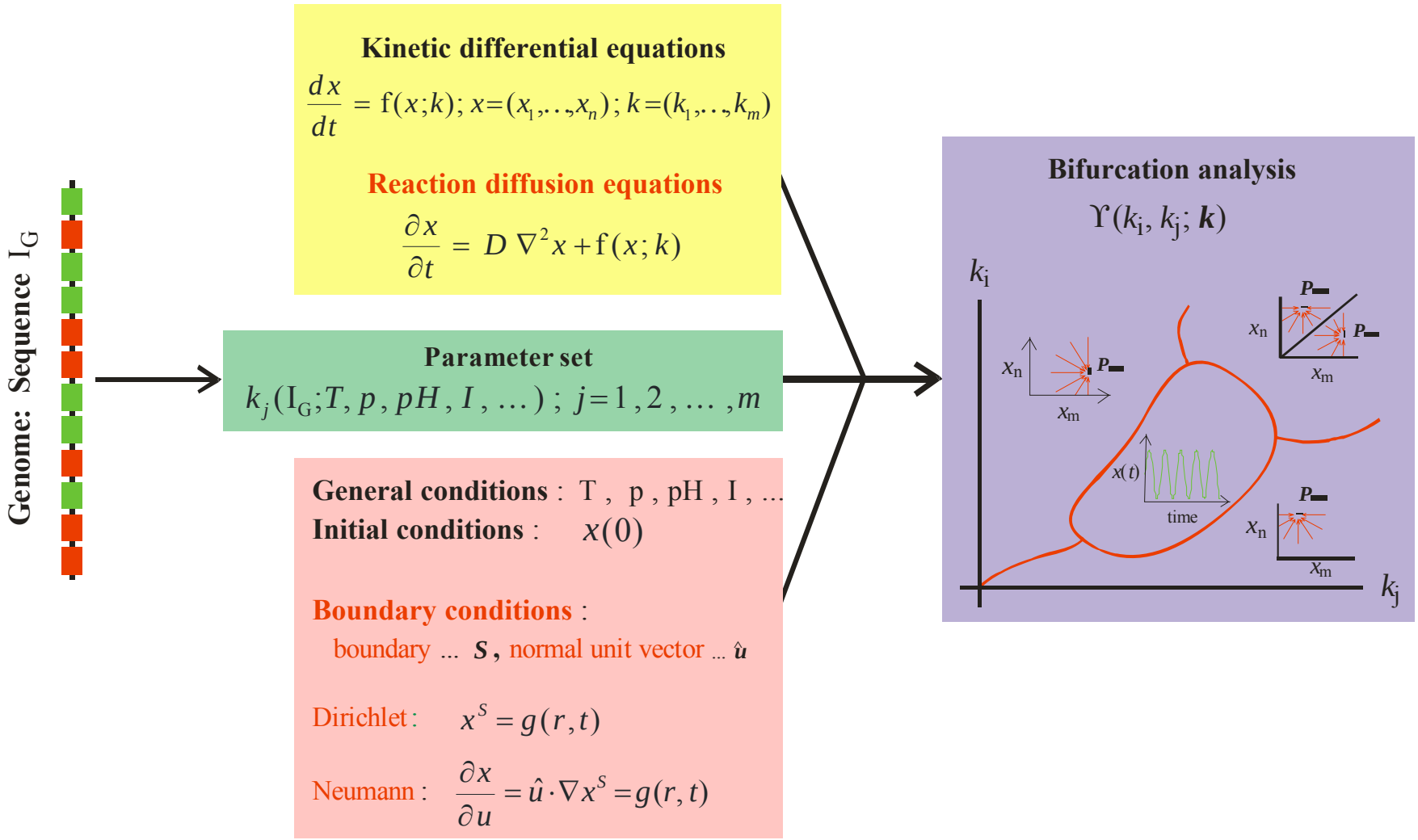
Neumann : $\frac{\partial x}{\partial u} = \hat{u} \cdot \nabla x^S = g(r,t)$

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)

Genome: Sequence I_G

Parameter set

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

Kinetic differential equations

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

Reaction diffusion equations

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

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

Initial conditions: $x(0)$

Boundary conditions:

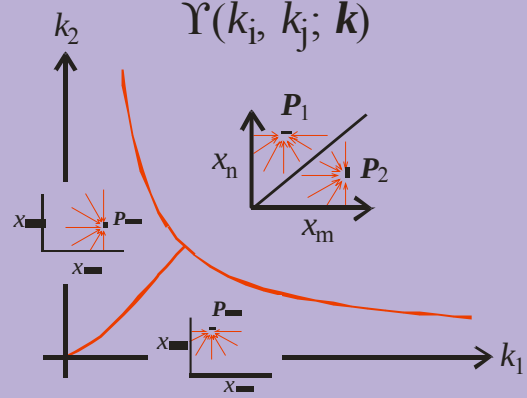
boundary ... S , normal unit vector... $\hat{u}$

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

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

Bifurcation pattern

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



The inverse problem of bifurcation analysis (Level II)

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

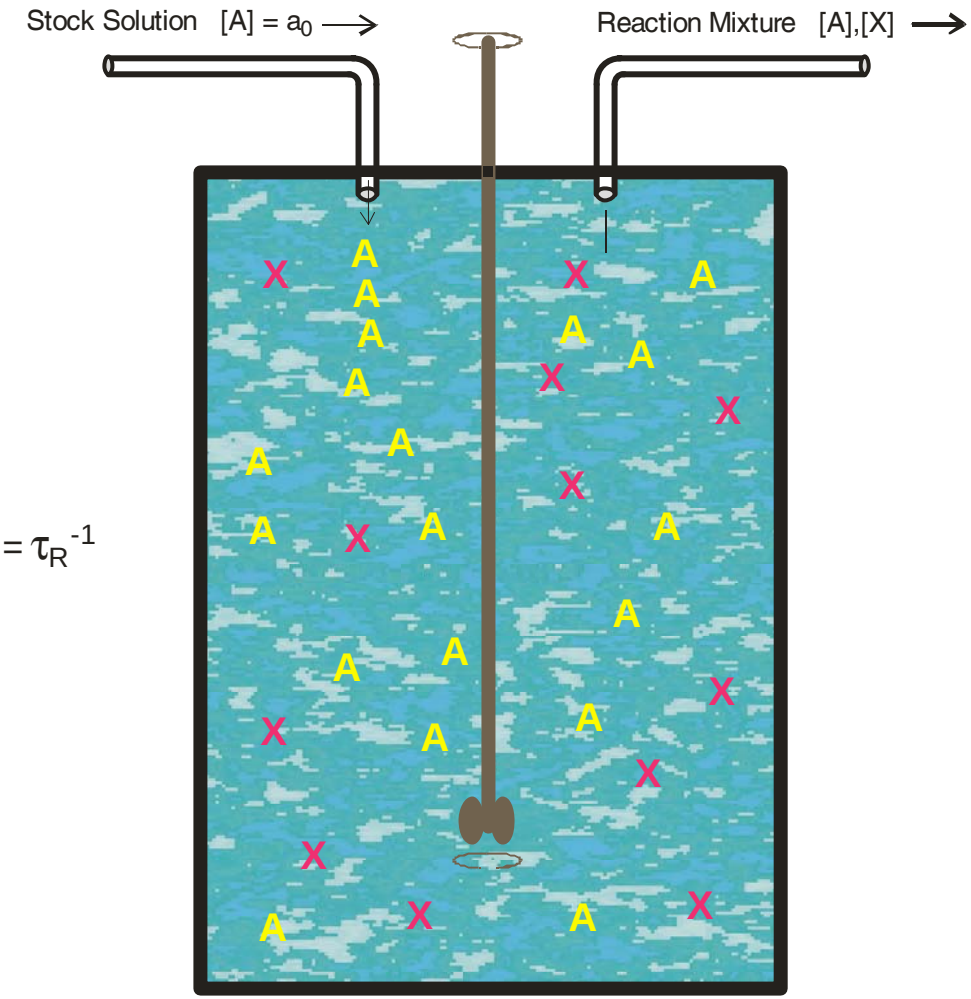
$$\mathbf{A} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathbf{X}$$

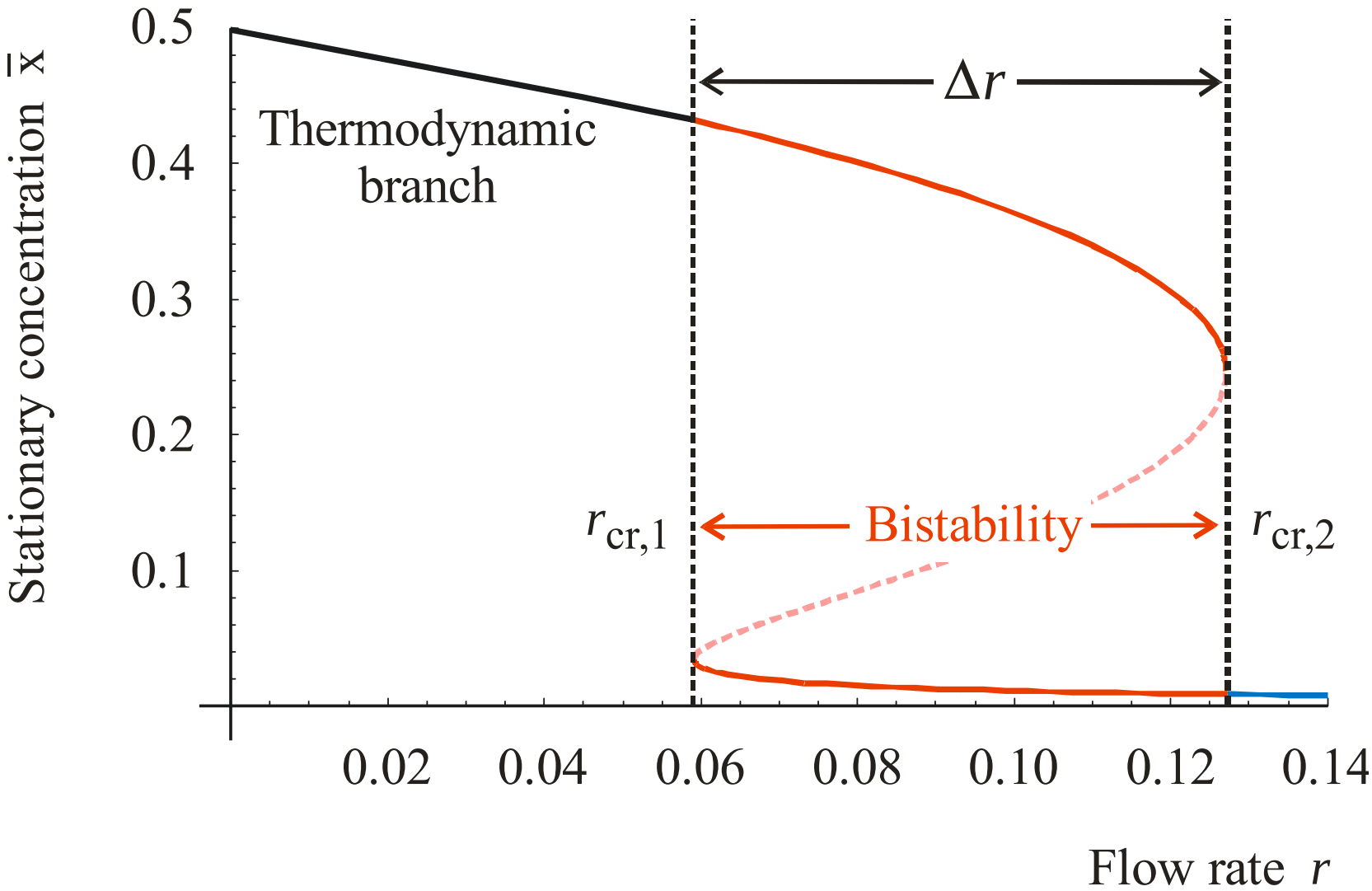
$$\mathbf{A} + 2\,\mathbf{X} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} 3\mathbf{X}$$

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

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

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




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

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

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

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

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

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

Kinetic differential equations:

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

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

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

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

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

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

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

Kinetic differential equations:

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

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

Steady states:

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

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

Kinetic differential equations:

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

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

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

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

Steady states:

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

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

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

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

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

Kinetic differential equations:

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

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

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

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

Steady states:

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

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

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

Polynomial discriminant of the cubic equation:

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

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

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

Kinetic differential equations:

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

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

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

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

Steady states:

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

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

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

Polynomial discriminant of the cubic equation:

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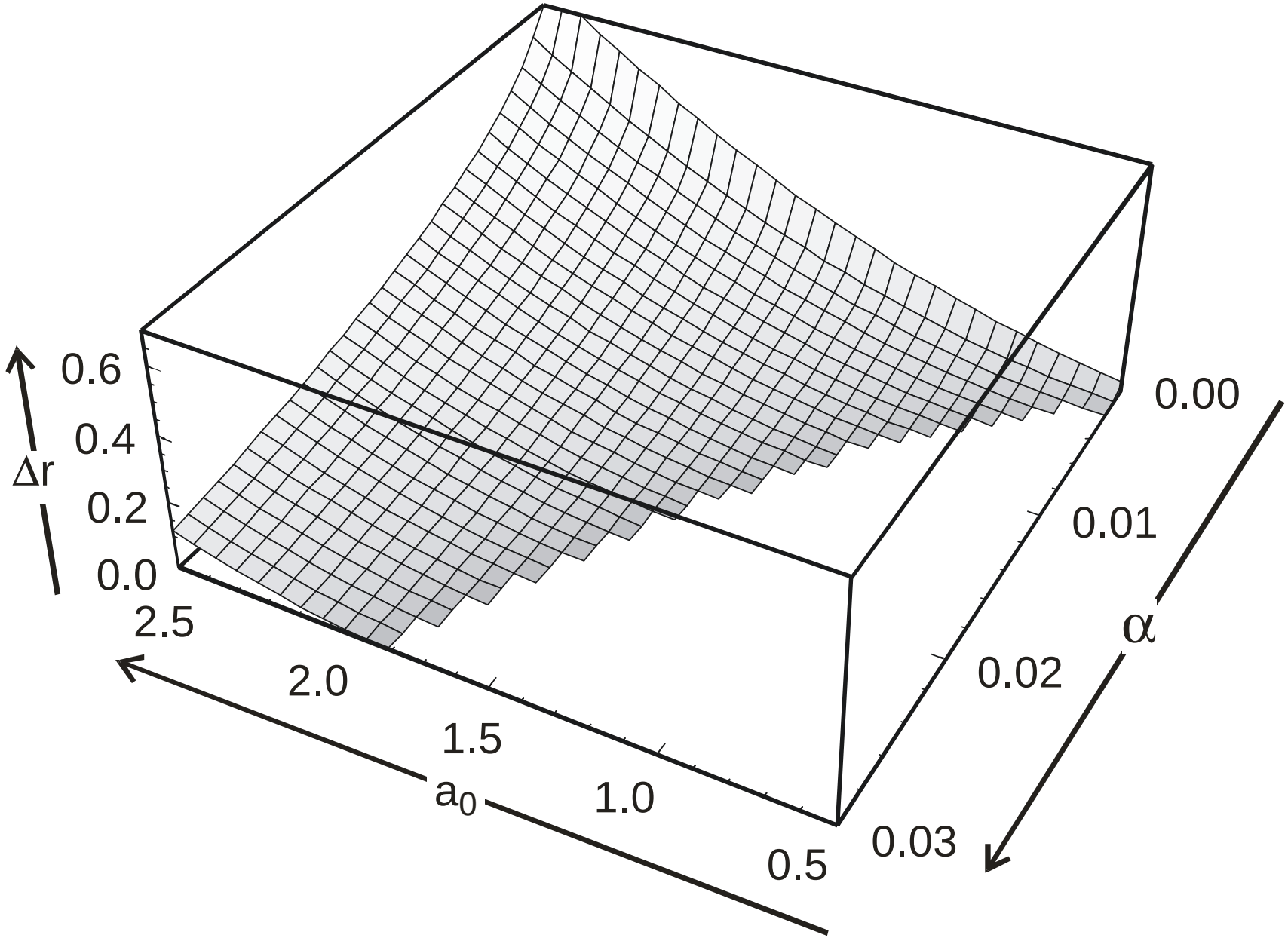
$$216\,\mathrm{D} = r^3 + r^2 (6\alpha - \frac{{a_0}^2}{8}) + r\,(12\alpha^2 - 5\alpha\,{a_0}^2) + 8\alpha^3 + 4\alpha^2 {a_0}^2 + \frac{\alpha\,{a_0}^4}{2} = 0$$

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

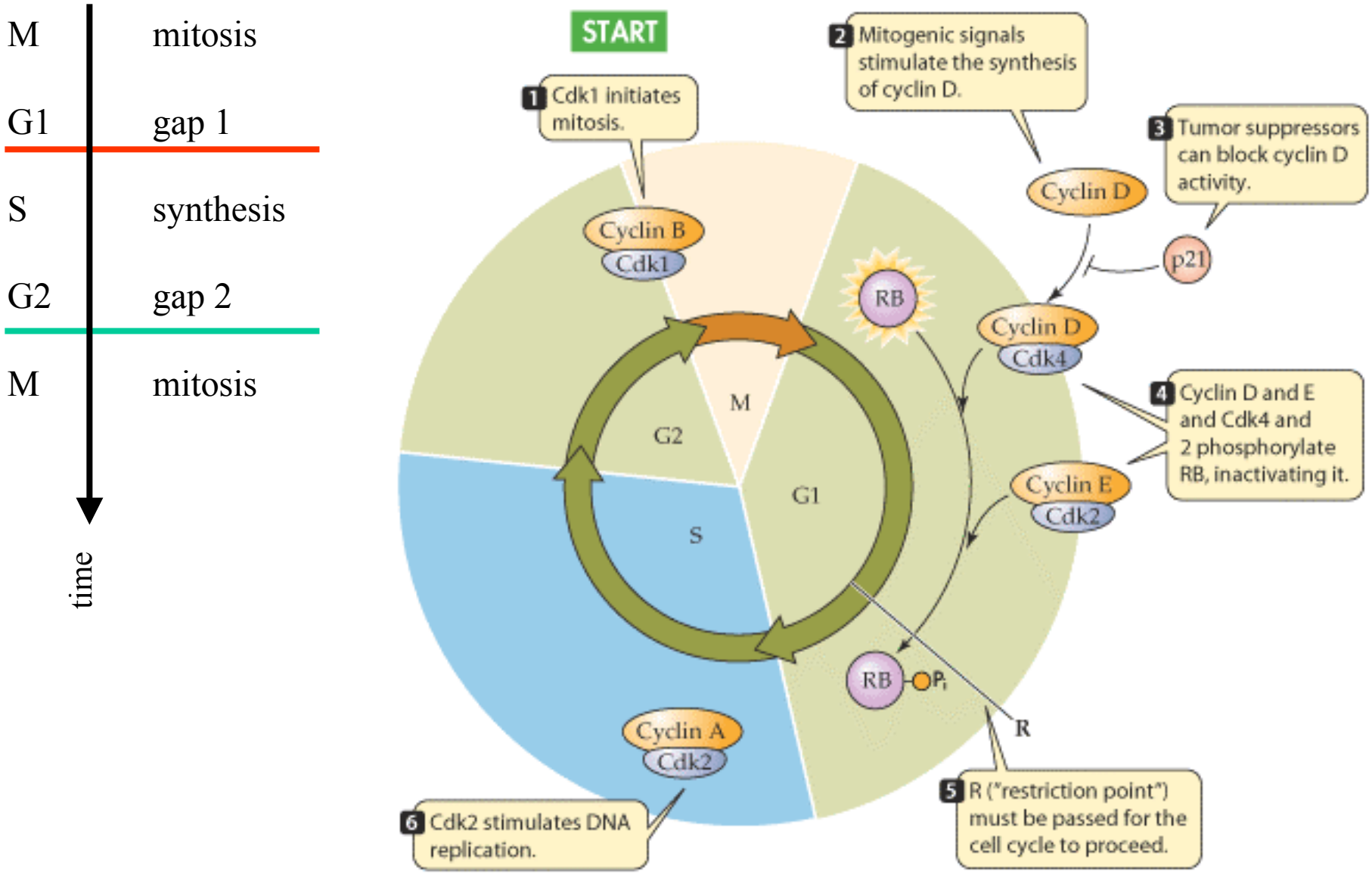


Range of hysteresis as a function of the parameters a_0 and α

1. What is systems biology ?
2. Forward and inverse problems in modeling
3. **Three examples**
4. Bifurcation analysis of gene regulation
5. Analysis of a synthetic oscillator

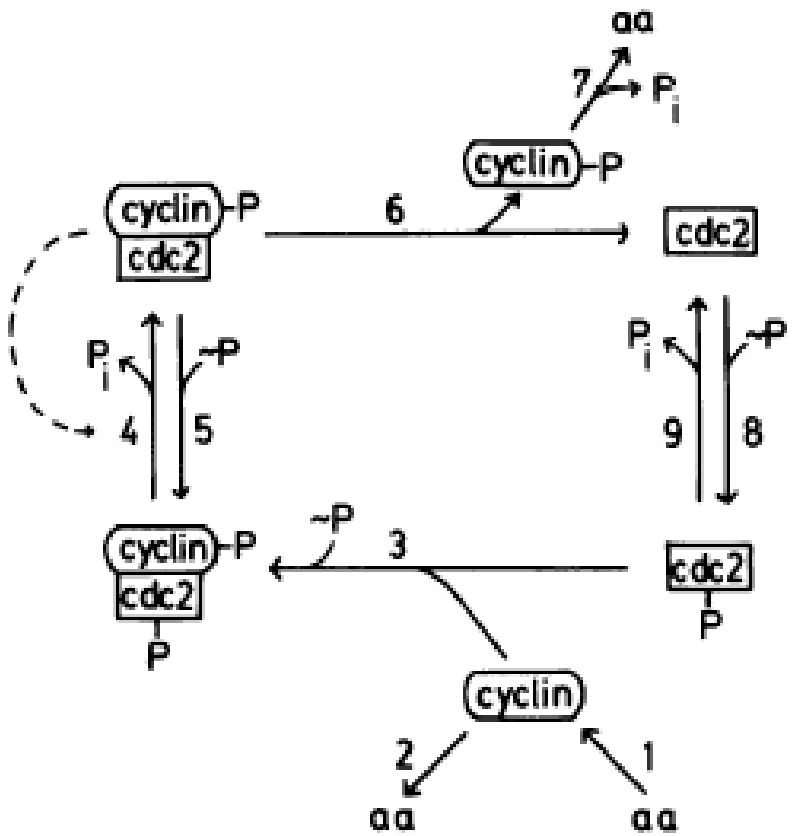
The cell division cycle

Talk by Philipp Kügler



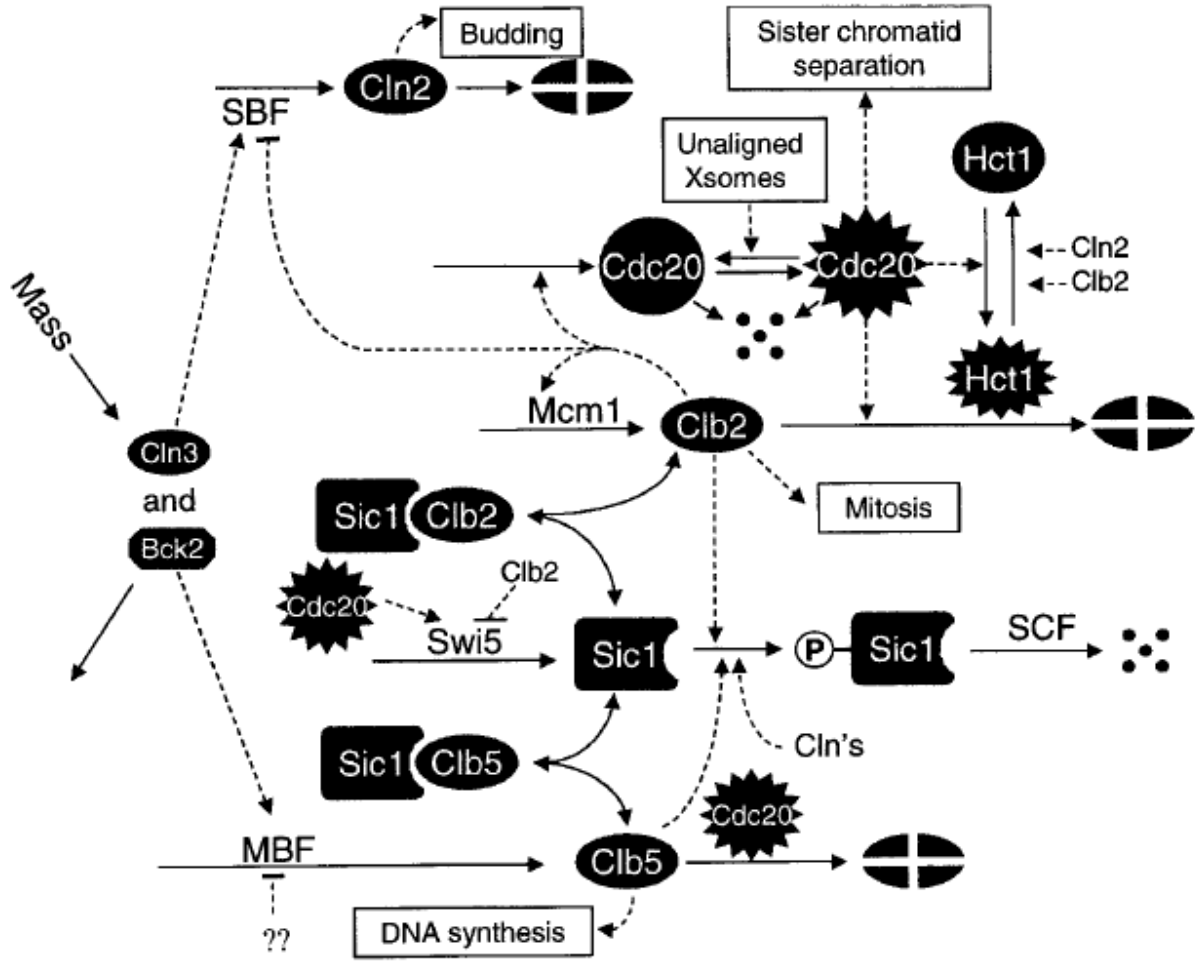
The division cycle of eukaryotic cells

$$
\begin{aligned}
d[\mathrm{C2}]/dt &= k_6[\mathrm{M}] - k_8[\sim P][\mathrm{C2}] + k_9[\mathrm{CP}] \\
d[\mathrm{CP}]/dt &= -k_3[\mathrm{CP}][\mathrm{Y}] + k_8[\sim P][\mathrm{C2}] - k_9[\mathrm{CP}] \\
d[\mathrm{pM}]/dt &= k_3[\mathrm{CP}][\mathrm{Y}] - [\mathrm{pM}]F([\mathrm{M}]) + k_5[\sim P][\mathrm{M}] \\
d[\mathrm{M}]/dt &= [\mathrm{pM}]F([\mathrm{M}]) - k_5[\sim P][\mathrm{M}] - k_6[\mathrm{M}] \\
d[\mathrm{Y}]/dt &= k_1[\mathrm{aa}] - k_2[\mathrm{Y}] - k_3[\mathrm{CP}][\mathrm{Y}] \\
d[\mathrm{YP}]/dt &= k_6[\mathrm{M}] - k_7[\mathrm{YP}]
\end{aligned}
$$



John J. Tyson. Modeling the cell division cycle: cdc2 and cyclin insteractions.

Proc.Natl.Acad.Sci. **88**:7328-7332, 1991.



The budding yeast cell cycle.

Katherine C. Chen, Attila Csikasz-Nagy, Bela Gyorffy, John Val, Bela Novak, John J. Tyson. *Molecular Biology of the Cell* **11**:369-391, 2000.

Budding yeast cell cycle model

Equations governing cyclin-dependent kinases

$$\frac{d}{dt}[Cln2] = (k'_{s,n2} + k''_{s,n2}[SBF]) \cdot mass - k_{d,n2}[Cln2]$$

$$\frac{d}{dt}[Clb2]_T = (k'_{s,b2} + k''_{s,b2}[Mcm1]) \cdot mass - V_{d,b2}[Clb2]_T,\ V_{d,b2} = k'_{d,b2}([Hct1]_T - [Hct1]) + k''_{d,b2}[Hct1] + k'''_{d,b2}[Cdc20]$$

$$\frac{d}{dt}[Clb5]_T = (k'_{s,b5} + k''_{s,b5}[MBF]) \cdot mass - V_{d,b5} \cdot [Clb5]_T,\ V_{d,b5} = k'_{d,b5} + k''_{d,b5}[Cdc20]$$

$$[Bck2] = [Bck2]^0 \cdot mass, \qquad [Cln3]^* = [Cln3]_{max} \frac{D_{e3} \cdot mass}{J_{n3} + D_{e3} \cdot mass}$$

$$[Clb2]_T = [Clb2] + [Clb2/Sic1], \quad [Clb5]_T = [Clb5] + [Clb5/Sic1]$$

$$[Sic1]_T = [Sic1] + [Clb2/Sic1] + [Clb5/Sic1]$$

Equations governing the inhibitor of Clb-dependent kinases

$$\frac{d}{dt}[Sic1]_T = k'_{s,c1} + k''_{s,c1}[Swi5] - \left(k_{d1,c1} + \frac{V_{d2,c1}}{J_{d2,c1} + [Sic1]_T}\right) \cdot [Sic1]_T$$

$$\frac{d}{dt}[Clb2/Sic1] = k_{a,b2}[Clb2] \cdot [Sic1] - \left(k_{d,b2} + V_{d,b2} + k_{d1,c1} + \frac{V_{d2,c1}}{J_{d2,c1} + [Sic1]_T}\right) \cdot [Clb2/Sic1]$$

$$\frac{d}{dt}[Clb5/Sic1] = k_{a,b5}[Clb5] \cdot [Sic1] - \left(k_{d,b5} + V_{d,b5} + k_{d1,c1} + \frac{V_{d2,c1}}{J_{d2,c1} + [Sic1]_T}\right) \cdot [Clb5/Sic1]$$

$$V_{d2,c1} = k_{d2,c1}(\varepsilon_{c1,n3}[Cln3]^* + \varepsilon_{c1,b2}[Bck2] + [Cln2] + \varepsilon_{c1,b5}[Clb5] + \varepsilon_{c1,b2}[Clb2])$$

Equations governing the Clb degradation machinery

$$\frac{d}{dt}[Cdc20]_T = (k'_{s,20} + k''_{s,20}[Clb2]) - k_{d,20}[Cdc20]_T$$

$$\frac{d}{dt}[Cdc20] = k_{a,20}([Cdc20]_T - [Cdc20]) - (V_{i,20} + k_{d,20}) \cdot [Cdc20]$$

$$V_{i,20} = \begin{cases} k'_{i,20}, & \text{for END\_M + 12 min} < t < \text{START\_S} \\ k''_{i,20}, & \text{for START\_S} < t < \text{END\_M} \end{cases}$$

$$\frac{d}{dt}[Hct1] = \frac{(k'_{a,t1} + k''_{a,t1}[Cdc20]) \cdot ([Hct1]_T - [Hct1])}{J_{a,t1} + [Hct1]_T - [Hct1]} - \frac{V_{i,t1}[Hct1]}{J_{i,t1} + [Hct1]}$$

$$V_{i,t1} = k'_{i,t1} + k''_{i,t1}([Cln3]^* + \varepsilon_{i,t1,n2}[Cln2] + \varepsilon_{i,t1,b5}[Clb5] + \varepsilon_{i,t1,b2}[Clb2])$$

Equations for growth, DNA synthesis, budding and spindle formation

$$\frac{d}{dt}mass = \mu \cdot mass, \quad \frac{d}{dt}[ORI] = k_{s,on}([Clb5] + \varepsilon_{on,b2}[Clb2]) - k_{d,on}[ORI]$$

$$\frac{d}{dt}[BUD] = k_{s,bud}([Cln2] + [Cln3]^* + \varepsilon_{bud,b5}[Clb5]) - k_{d,bud}[BUD], \quad \frac{d}{dt}[SPN] = k_{s,spn}\frac{[Clb2]}{J_{spn} + [Clb2]} - k_{d,spn}[SPN]$$

Equations governing transcription factors

$$[SBF] = [MBF] = G(V_{a,sbf}, k'_{i,sbf} + k''_{i,sbf}[Clb2], J_{a,sbf}, J_{i,sbf}),\ V_{a,sbf} = k_{a,sbf}([Cln2] + \varepsilon_{sbf,n3}([Cln3]^* + [Bck2]) + \varepsilon_{sbf,b5}[Clb5]),$$

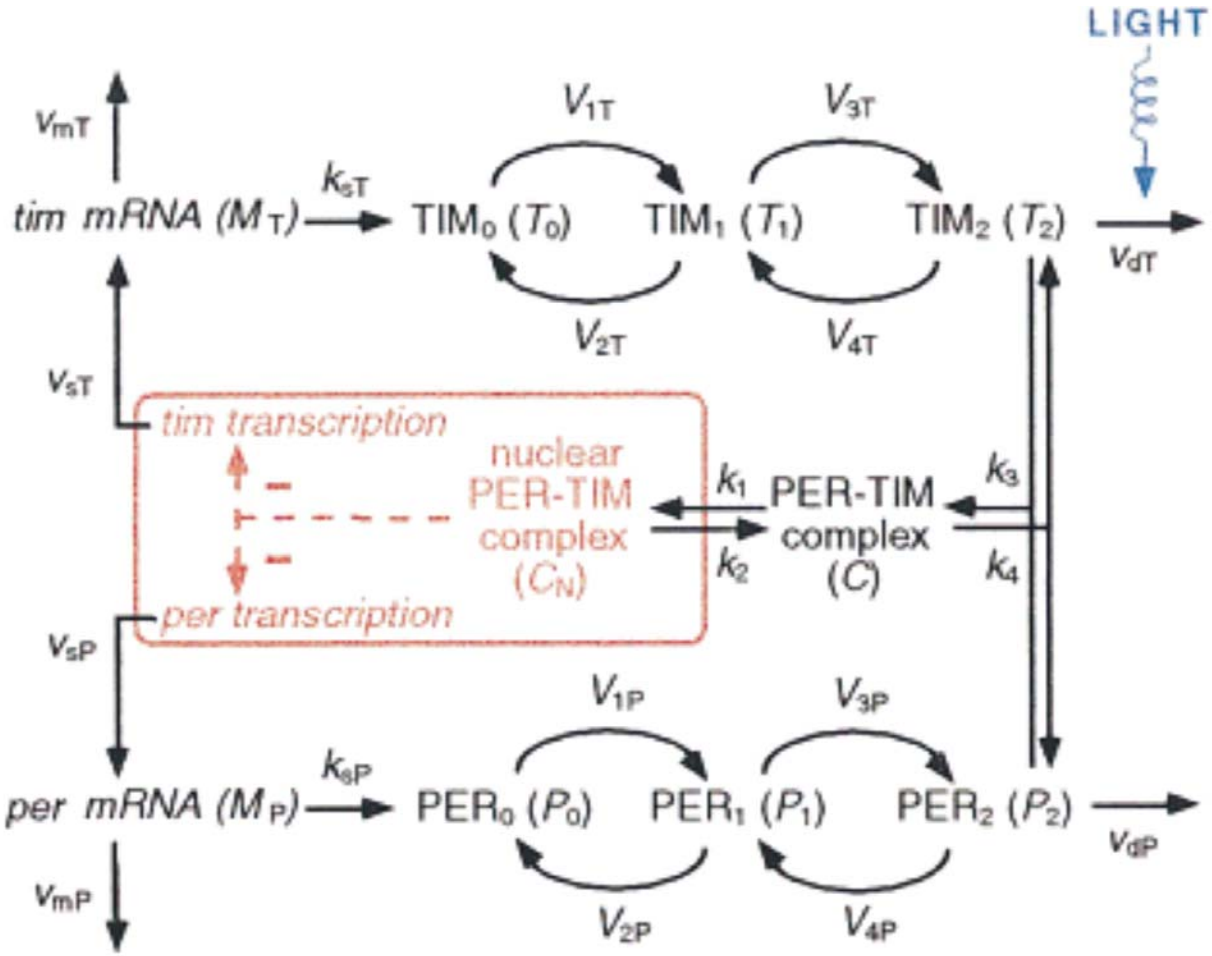
$$[Mcm1] = G(k_{a,mcm}[Clb2], k_{i,mcm}, J_{a,mcm}, J_{i,mcm}),\ [Swi5] = G(k_{a,swi}[Cdc20], k'_{i,swi} + k''_{i,swi}[Clb2], J_{a,swi}, J_{i,swi})$$

Circadian rhythms

Talk by James Lu

PER ... period protein

TIM ... timeless protein



Jean-Christophe Leloup, Albert Goldbeter. Modeling the molecular regulatory mechanism of circadian rhythms in *Drosophila*. *BioEssays* **22**:84-93, 2000.

$$\frac{dM_P}{dt} = v_{sP}\frac{K_{IP}^n}{K_{IP}^n + C_N^n} - v_{mP}\frac{M_P}{K_{mP} + M_P} - k_d M_P \quad (1a)$$

$$\frac{dP_0}{dt} = k_{sP}M_P - V_{1P}\frac{P_0}{K_{1P} + P_0} + V_{2P}\frac{P_1}{K_{2P} + P_1} - k_d P_0 \quad (1b)$$

$$\frac{dP_1}{dt} = V_{1P}\frac{P_0}{K_{1P} + P_0} - V_{2P}\frac{P_1}{K_{2P} + P_1} - V_{3P}\frac{P_1}{K_{3P} + P_1} + V_{4P}\frac{P_2}{K_{4P} + P_2} - k_d P_1 \quad (1c)$$

$$\frac{dP_2}{dt} = V_{3P}\frac{P_1}{K_{3P} + P_1} - V_{4P}\frac{P_2}{K_{4P} + P_2} - k_3 P_2 T_2 + k_4 C - v_{dP}\frac{P_2}{K_{dP} + P_2} - k_d P_2 \quad (1d)$$

$$\frac{dM_T}{dt} = v_{sT}\frac{K_{IT}^n}{K_{IT}^n + C_N^n} - v_{mT}\frac{M_T}{K_{MT} + M_T} - k_d M_T \quad (1e)$$

$$\frac{dT_0}{dt} = k_{sT}M_T - V_{1T}\frac{T_0}{K_{1T} + T_0} + V_{2T}\frac{T_1}{K_{2T} + T_1} - k_d T_0 \quad (1f)$$

$$\frac{dT_1}{dt} = V_{1T}\frac{T_0}{K_{1T} + T_0} - V_{2T}\frac{T_1}{K_{2T} + T_1} - V_{3T}\frac{T_1}{K_{3T} + T_1} + V_{4T}\frac{T_2}{K_{4T} + T_2} - k_d T_1 \quad (1g)$$

$$\frac{dT_2}{dt} = V_{3T}\frac{T_1}{K_{3T} + T_1} - V_{4T}\frac{T_2}{K_{4T} + T_2} - k_3 P_2 T_2 + k_4 C - v_{dT}\frac{T_2}{K_{dT} + T_2} - k_d T_2 \quad (1h)$$

$$\frac{dC}{dt} = k_3 P_2 T_2 - k_4 C - k_1 C + k_2 C_N - k_{dC} C \quad (1i)$$

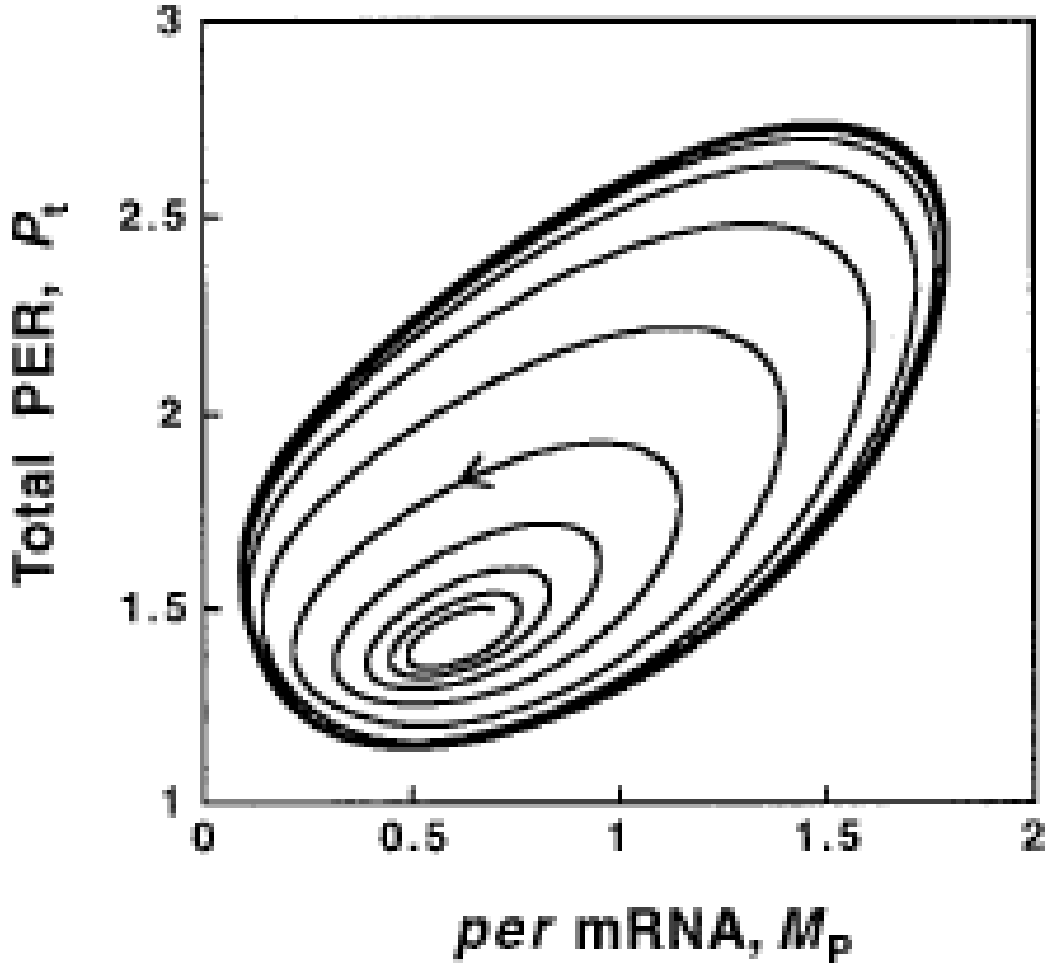
$$\frac{dC_N}{dt} = k_1 C - k_2 C_N - k_{dN} C_N. \quad (1j)$$

$$P_t = P_0 + P_1 + P_2 + C + C_N \quad (2)$$

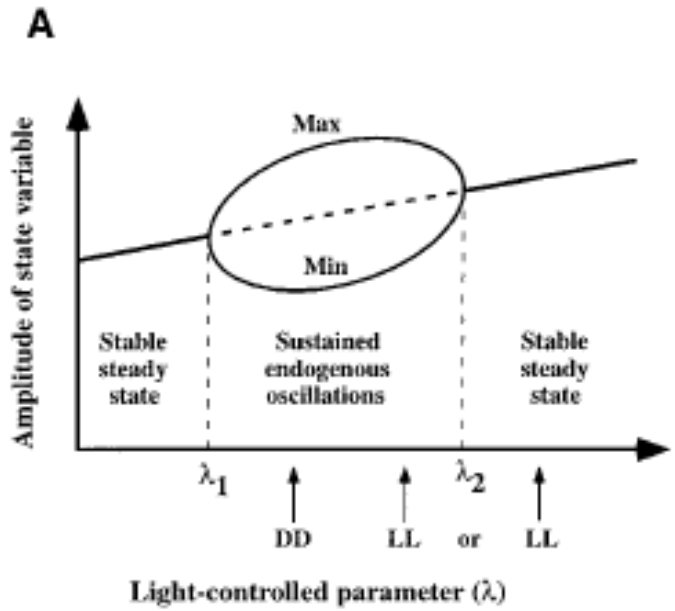
$$T_t = T_0 + T_1 + T_2 + C + C_N. \quad (3)$$

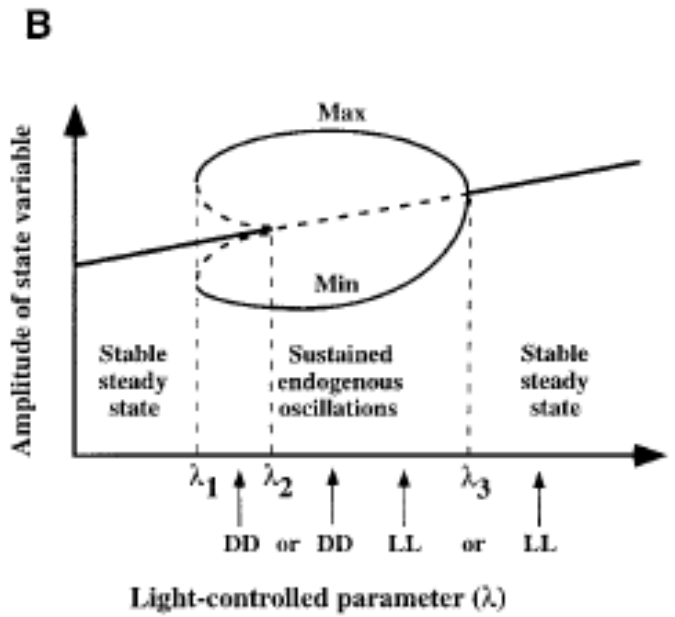
Jean-Christophe Leloup, Albert Goldbeter.
Modeling the molecular regulatory mechanism of circadian rhythms in *Drosophila*.

BioEssays **22**:84-93, 2000.



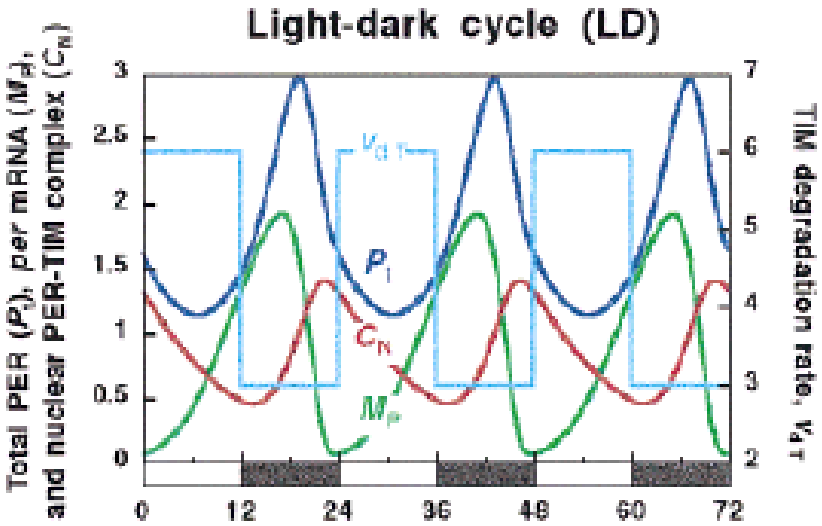
Jean-Christophe Leloup, Albert Goldbeter. Modeling the molecular regulatory mechanism of circadian rhythms in *Drosophila*. *BioEssays* **22**:84-93, 2000.

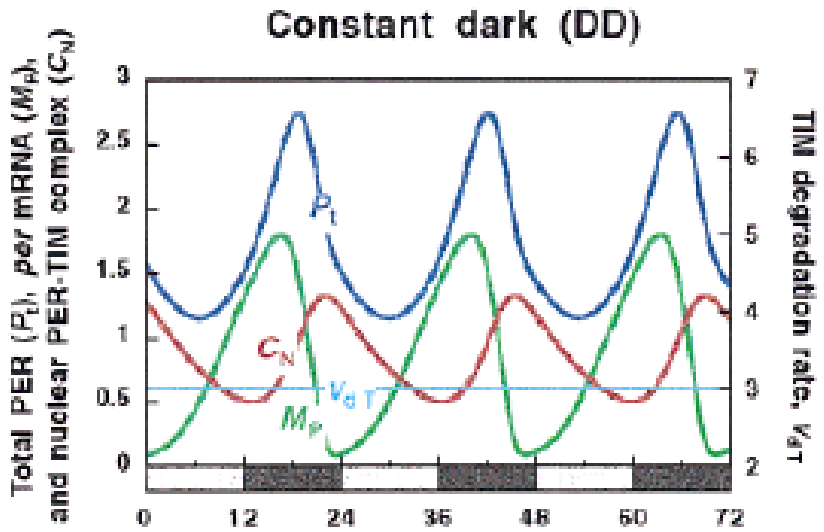


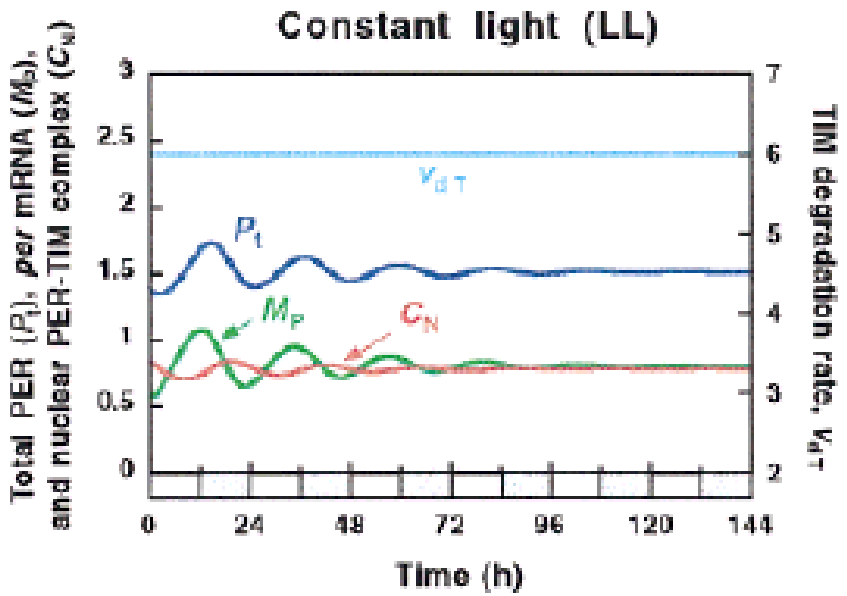


Jean-Christophe Leloup, Albert Goldbeter.
Modeling the molecular regulatory mechanism of circadian rhythms in *Drosophila*.

BioEssays **22**:84-93, 2000.





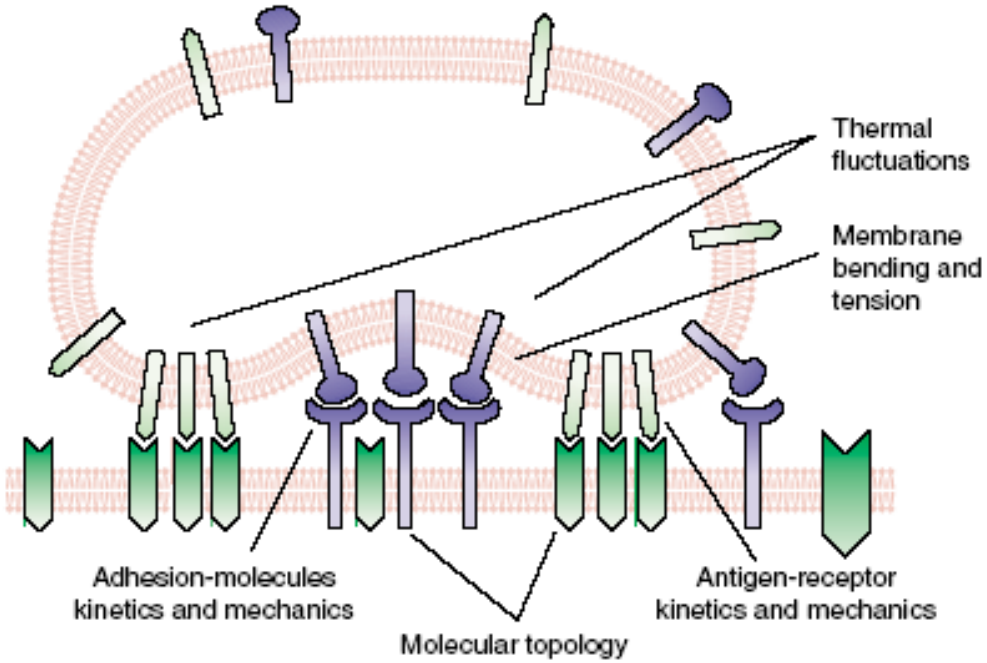


Jean-Christophe Leloup, Albert Goldbeter. Modeling the molecular regulatory mechanism of circadian rhythms in *Drosophila*.

BioEssays **22**:84-93, 2000.

The immune synapse

Joined work with Gerhard Schütz (Linz), Alois Sonnleitner (Linz) and Hannes Stockinger (Wien) and the RICAM Group of Heinz Engl.



$$\frac{\partial C_T}{\partial t} = D_T \nabla^2 C_T - k_{on}(z) C_T C_M + k_{off}(1-P) C_{TM} + \vec{V}.\vec{\nabla} C_T \quad \text{[Eqn 1]}$$

$$\frac{\partial C_M}{\partial t} = D_M \nabla^2 C_M - k_{on}(z) C_T C_M + k_{off} C_{TM} \quad \text{[Eqn 2]}$$

$$\frac{\partial C_{TM}}{\partial t} = D_{TM}\left[\nabla^2 C_{TM} + \frac{1}{k_B T}\vec{\nabla} C_{TM}.\vec{\nabla}\frac{\delta F}{\delta C_{TM}}\right] + k_{on}(z)\, C_T C_M - k_{off} C_{TM} \quad \text{[Eqn 3]}$$

$$\frac{\partial C_{Al}}{\partial t} = D_{Al} \nabla^2 C_{Al} - k_l(z)\, C_{Al} C_{Bl} + k_{-l} C_l \quad \text{[Eqn 4]}$$

$$\frac{\partial C_{Bl}}{\partial t} = D_{Bl} \nabla^2 C_{Bl} - k_l(z)\, C_{Al} C_{Bl} + k_{-l} C_l \quad \text{[Eqn 5]}$$

$$\frac{\partial C_l}{\partial t} = D_l\left[\nabla^2 C_l + \frac{1}{k_B T}\vec{\nabla} C_l.\vec{\nabla}\frac{\delta F}{\delta C_l}\right] + k_l(z) C_{Al} C_{Bl} - k_{-l} C_l \quad \text{[Eqn 6]}$$

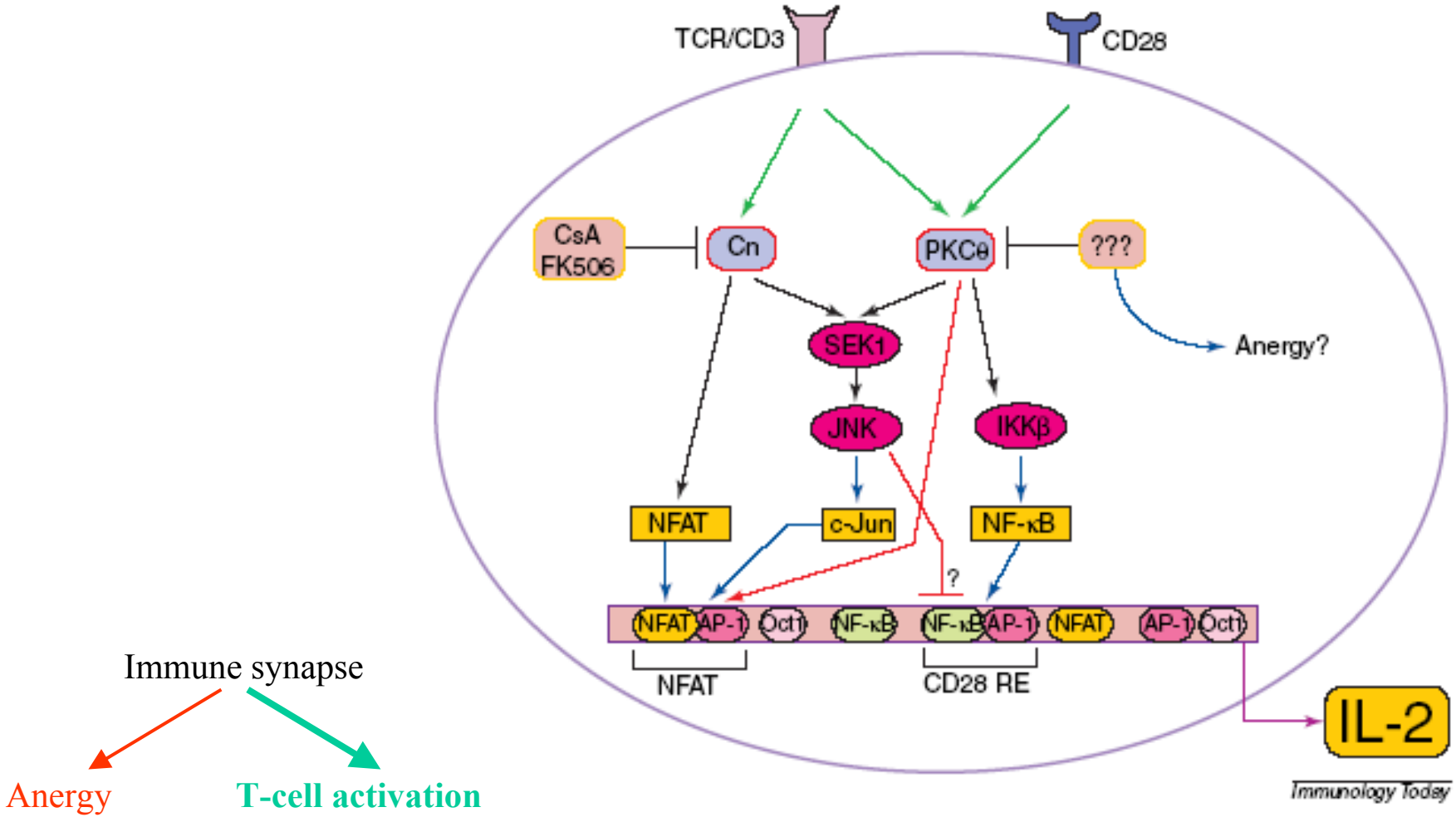
$$\frac{\partial z}{\partial t} = -M\frac{\delta F}{\delta z} + \xi \quad \text{[Eqn 7]}$$

$$F = \frac{\lambda_T}{2}\iint dxdy C_{TM}(x,y,t)[z(x,y,t) - z_{TM}]^2 + \sum_l \frac{\lambda_l}{2}\iint dxdy C_l(x,y,t)[z(x,y,t) - z_l]^2 + \frac{1}{2}\iint dxdy\left[\gamma(\nabla z)^2 + \kappa(\nabla^2 z)^2\right] \quad \text{[Eqn 8]}$$

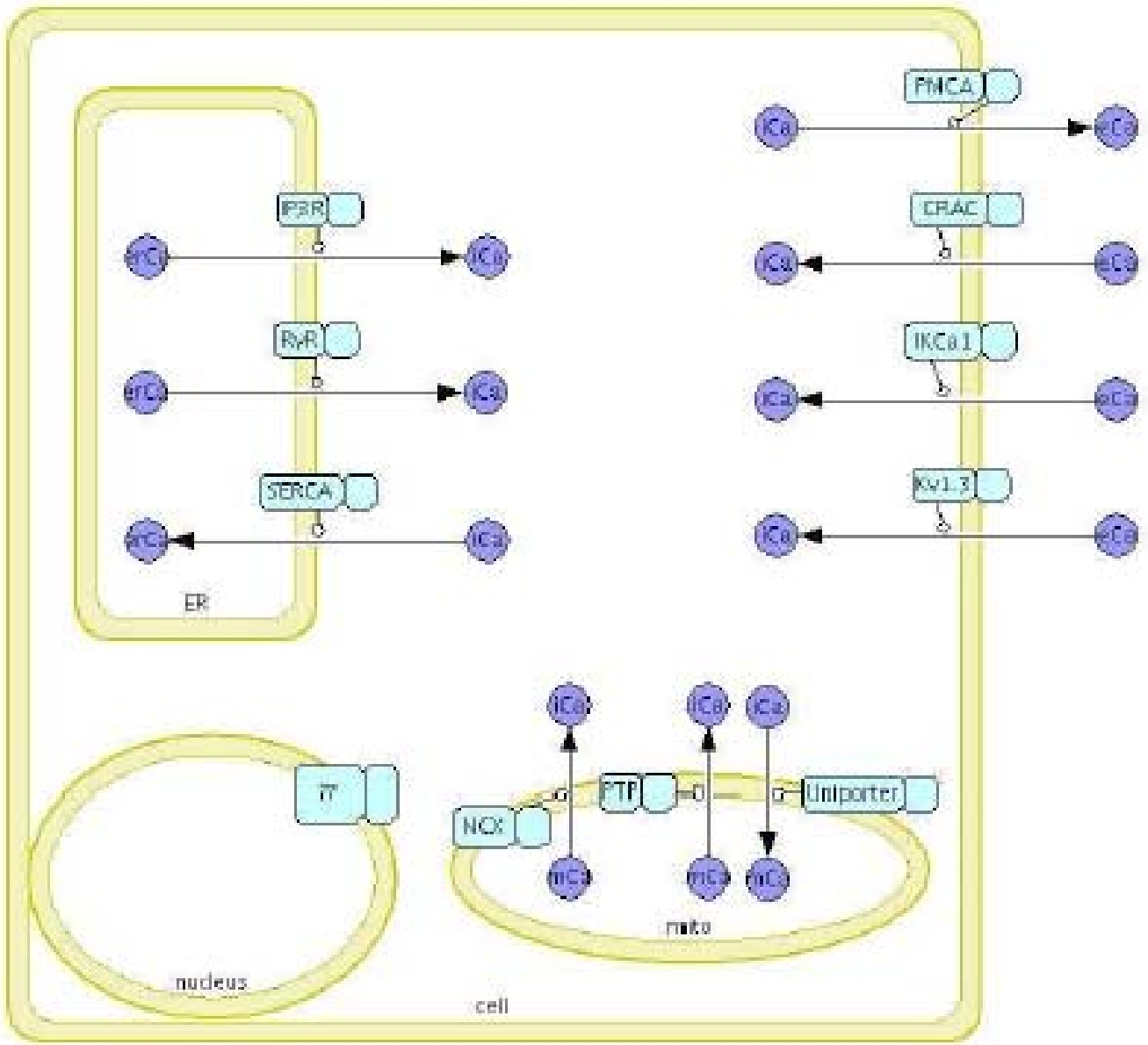
The immune synapse assembly model

Sung-Joo E. Lee, Yuko Hori, Jay T. Groves, Michael L.Dustin, Arup K. Chakraborty.

Trends in Immunology **23**:492-499, 2002

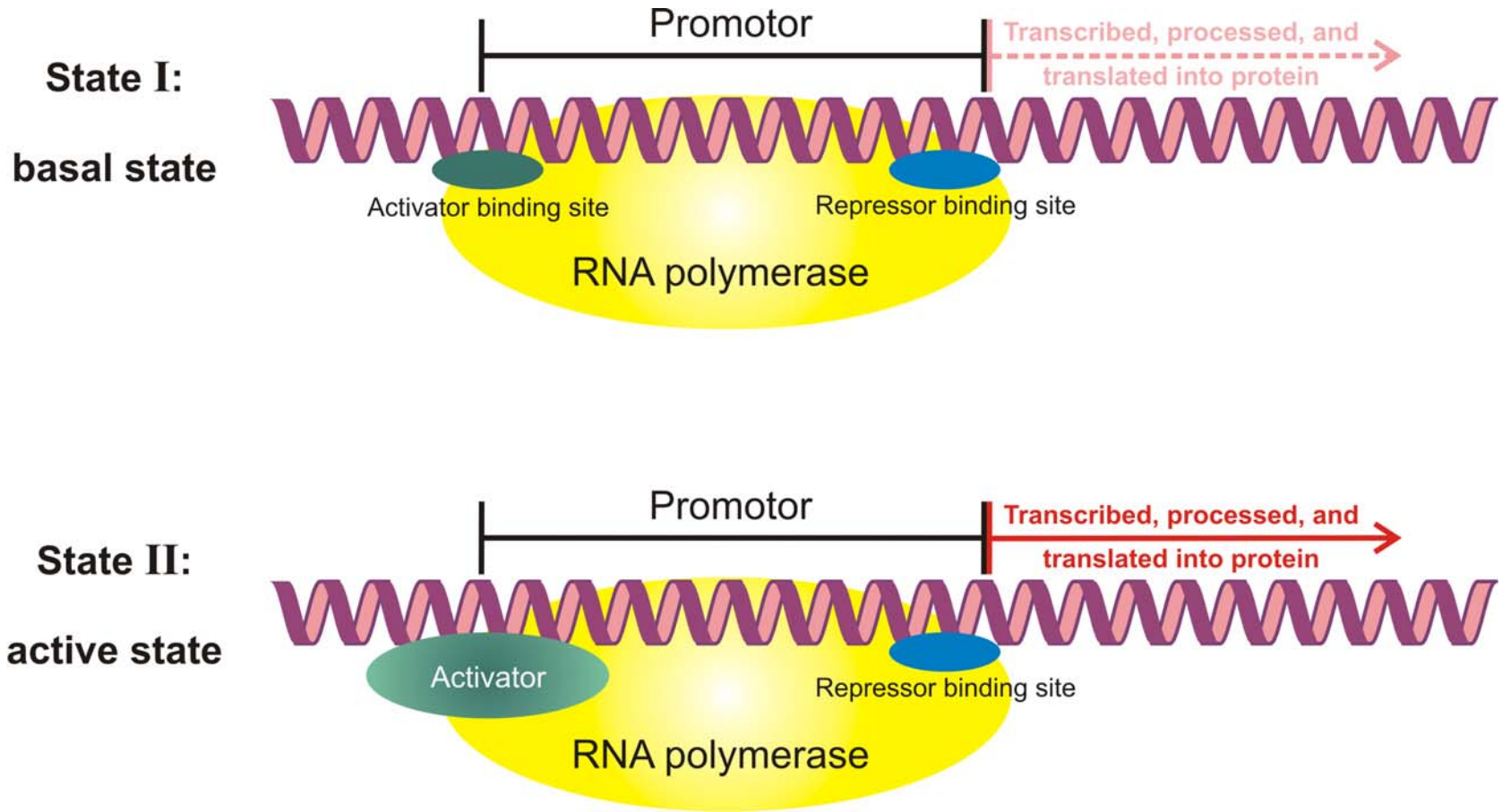


Amnon Altman, Noah Isakow, Gottfried Baier. *Immunology Today* **21**:567-573, 2000

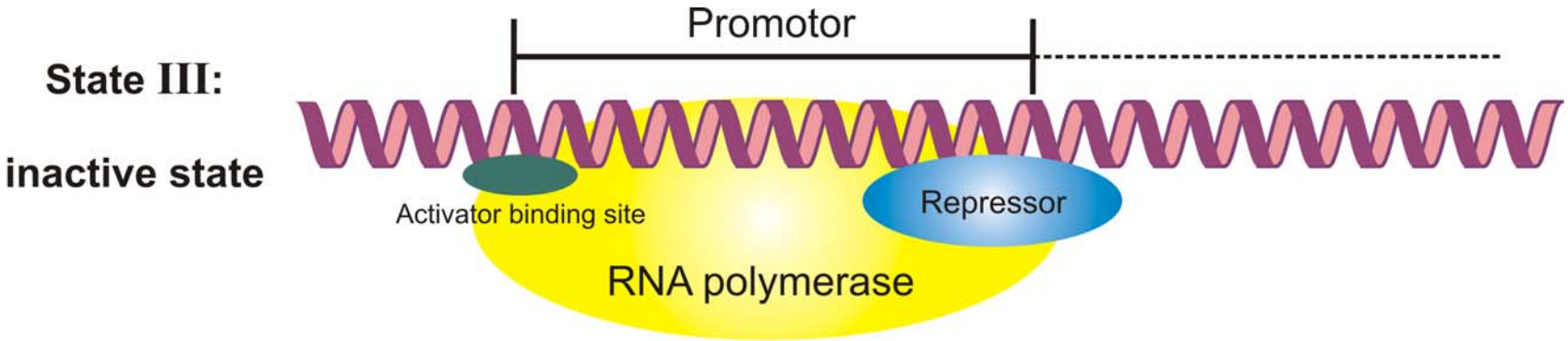


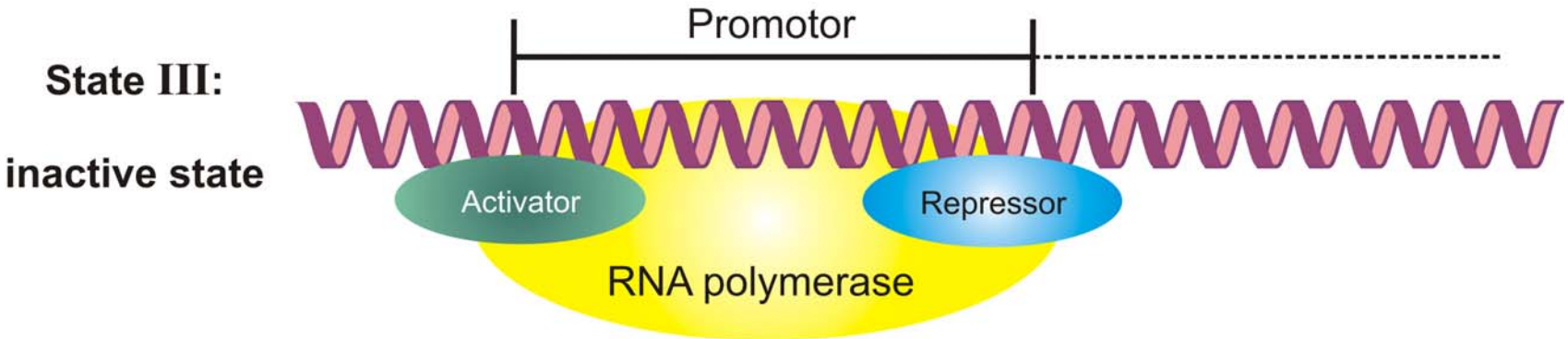
Ca^{2+} transport
in the T-cell

1. What is systems biology ?
2. Forward and inverse problems in modeling
3. Three examples
4. **Bifurcation analysis of gene regulation**
5. Analysis of a synthetic oscillator

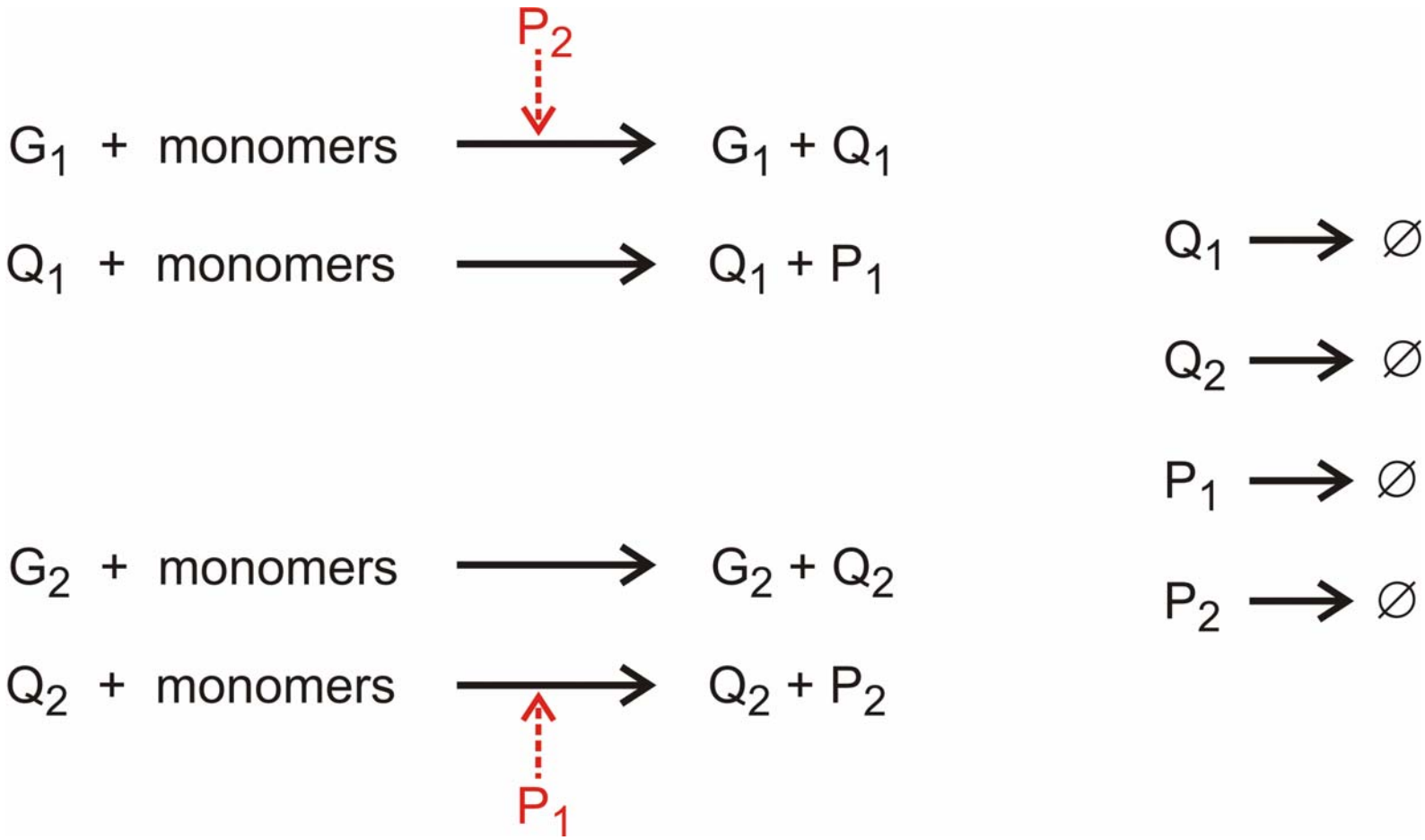


Basal transcription and active state of a gene





Inactive or silent state of a gene

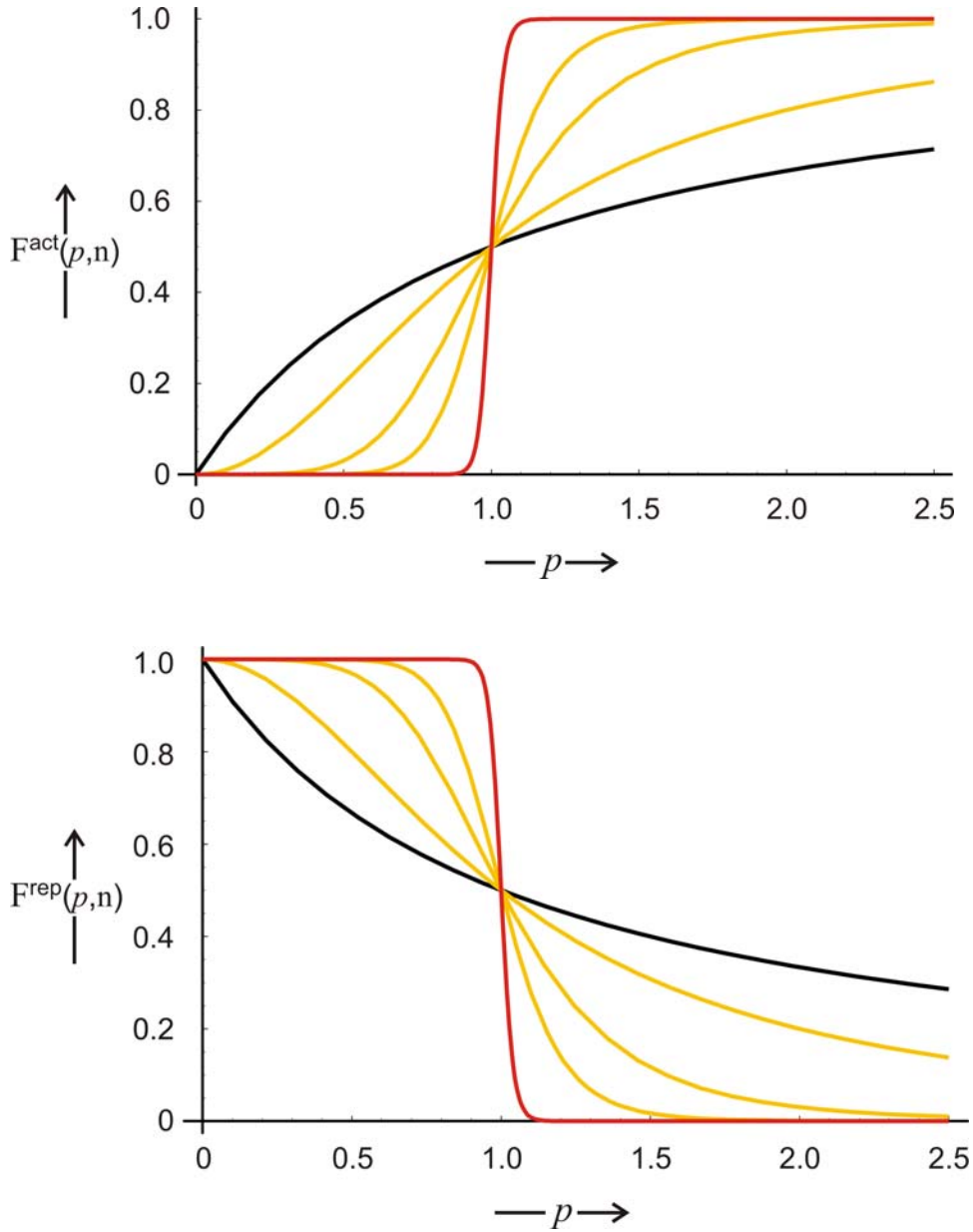


Cross-regulation of two genes

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

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

$$i, j = 1,2$$



Gene regulatory binding functions

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

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

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

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

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

$$i, j = 1,2$$

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

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

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

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

Stationary points: $\bar{p}_1-\vartheta_1 F_1(\vartheta_2 F_2(\bar{p}_1))=0,\ \bar{p}_2=\vartheta_2 F_2(\bar{p}_1)$

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

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

act-act $$\bar{p}_1 \cdot \left(\bar{p}_1^{n \cdot n} \vartheta_2^n - \bar{p}_1^{n \cdot n-1} \vartheta_1 \vartheta_2^n + K_2 \cdot \sum_{k=0}^{n} \bar{p}_1^{n \cdot (n-k)} \binom{n}{k} K_1^k \right) = 0$$

act-rep $$K_2 \cdot \left(\sum_{k=0}^{n} \bar{p}_1^{n \cdot (n-k)+1} \binom{n}{k} K_1^k \right) + (\bar{p}_1 - \vartheta_1) \cdot (\vartheta_2 K_1)^n = 0$$

rep-rep $$(\bar{p}_1 - \vartheta_1) \cdot K_2 \cdot \left(\sum_{k=0}^{n} \bar{p}_1^{n \cdot (n-k)} \binom{n}{k} K_1^k \right) + \bar{p}_1 \cdot (\vartheta_2 K_1)^n = 0$$

$$\bar{p}_2 = \frac{\vartheta_2 \, \bar{p}_1^n}{K_1 + \bar{p}_1^n} \quad \text{or} \quad \bar{p}_2 = \frac{\vartheta_2 \, K_1}{K_1 + \bar{p}_1^n}$$

Stationary protein concentrations for Hill coefficient *n*

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

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

Special case: $F_1 = F_1(p_2)$ and $F_2 = F_2(p_1)$

$$\Gamma(\bar{p}_1, \bar{p}_2) = -\begin{vmatrix} 0 & \frac{\partial F_1}{\partial p_2} \\ \frac{\partial F_2}{\partial p_1} & 0 \end{vmatrix} = \frac{\partial F_1}{\partial p_2} \cdot \frac{\partial F_2}{\partial p_1}$$

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

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

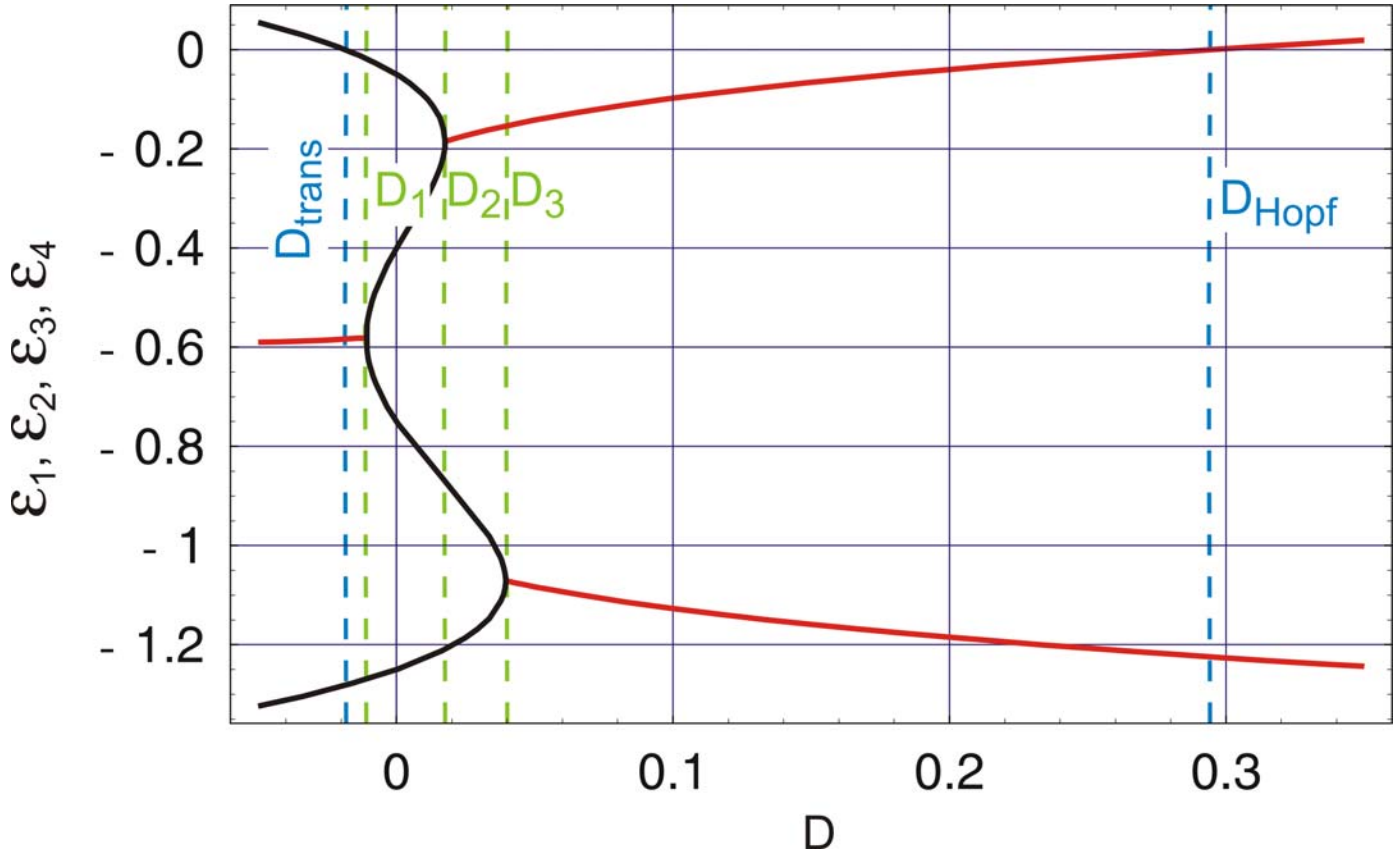
$$D = -k_1^{\mathrm{Q}} k_2^{\mathrm{Q}} k_1^{\mathrm{P}} k_2^{\mathrm{P}} \Gamma(\overline{p}_1, \overline{p}_2)$$

$$\Gamma(\overline{p}_1, \overline{p}_2) = -\begin{vmatrix} 0 & \dfrac{\partial F_1}{\partial p_2} \\ \dfrac{\partial F_2}{\partial p_1} & 0 \end{vmatrix} = \frac{\partial F_1}{\partial p_2} \cdot \frac{\partial F_2}{\partial p_1}$$

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

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

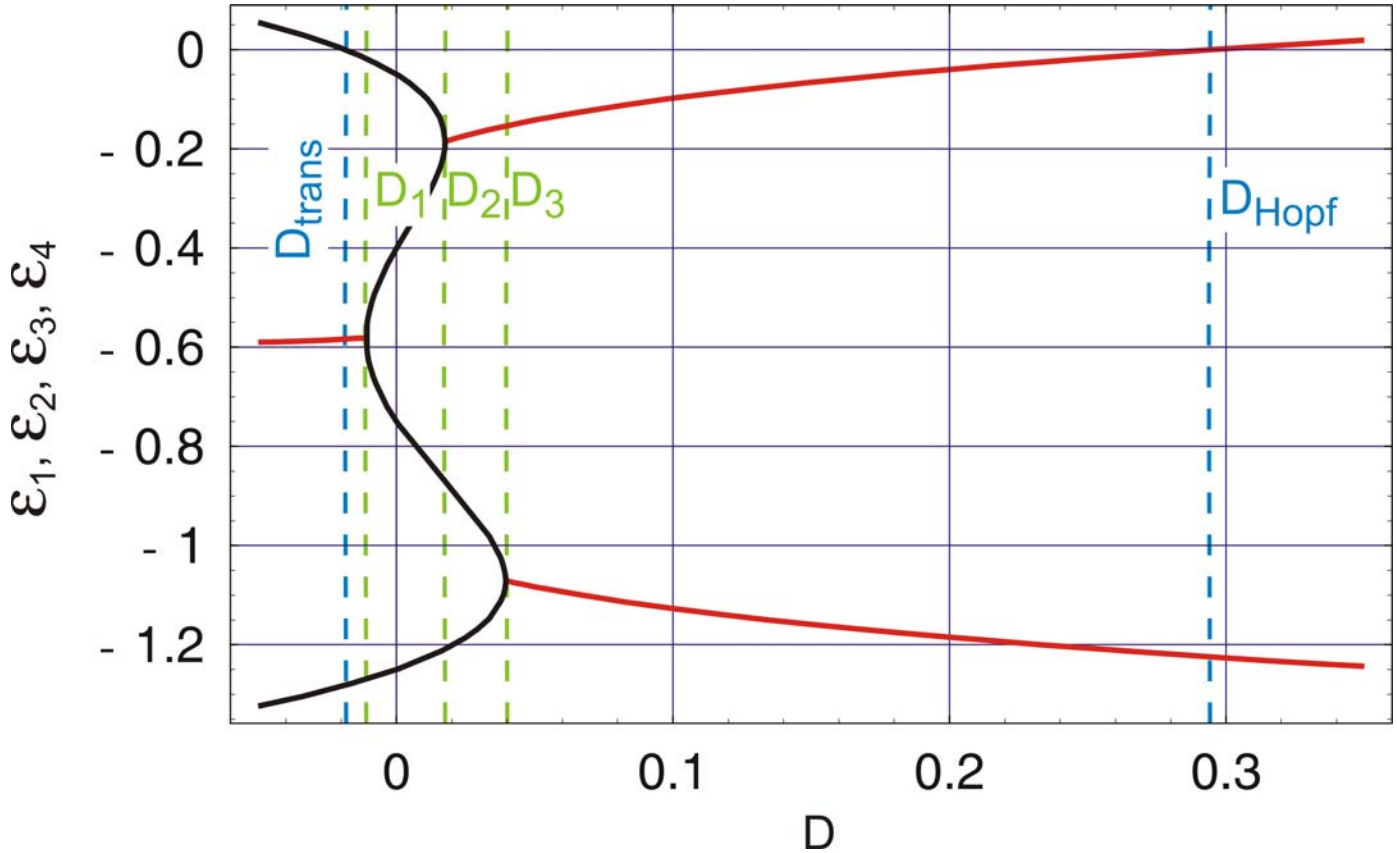
$$D = -k_1^{\mathrm{Q}} k_2^{\mathrm{Q}} k_1^{\mathrm{P}} k_2^{\mathrm{P}} \Gamma(\overline{p}_1, \overline{p}_2)$$



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

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

$$D = -k_1^{\mathrm{Q}} k_2^{\mathrm{Q}} k_1^{\mathrm{P}} k_2^{\mathrm{P}} \Gamma(\bar{p}_1, \bar{p}_2)$$



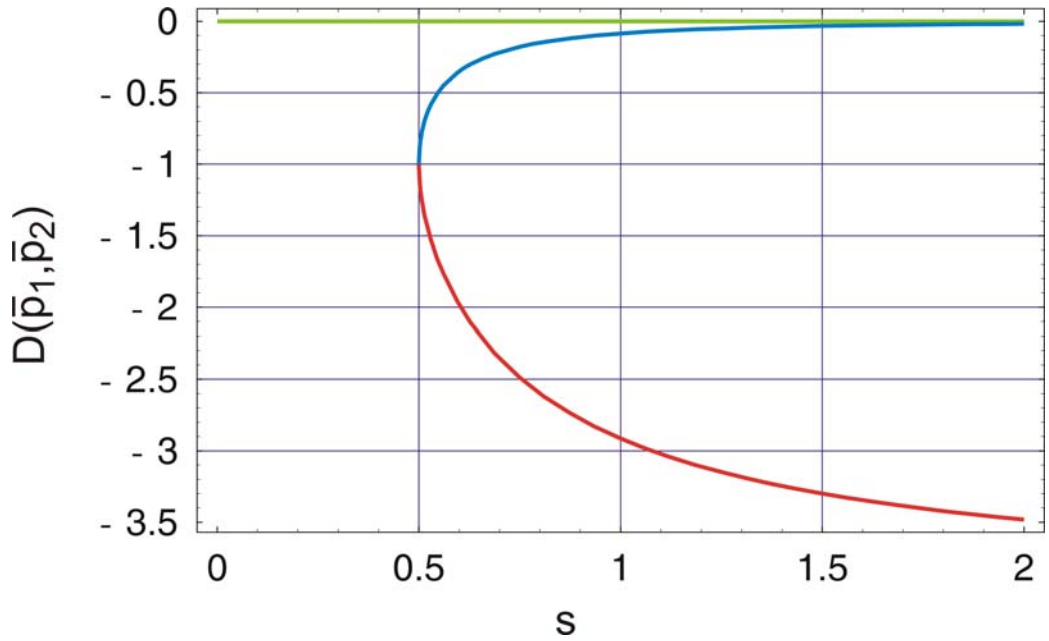
$$D_{\text{trans}} = -d_1^{\text{Q}} d_2^{\text{Q}} d_1^{\text{P}} d_2^{\text{P}}$$

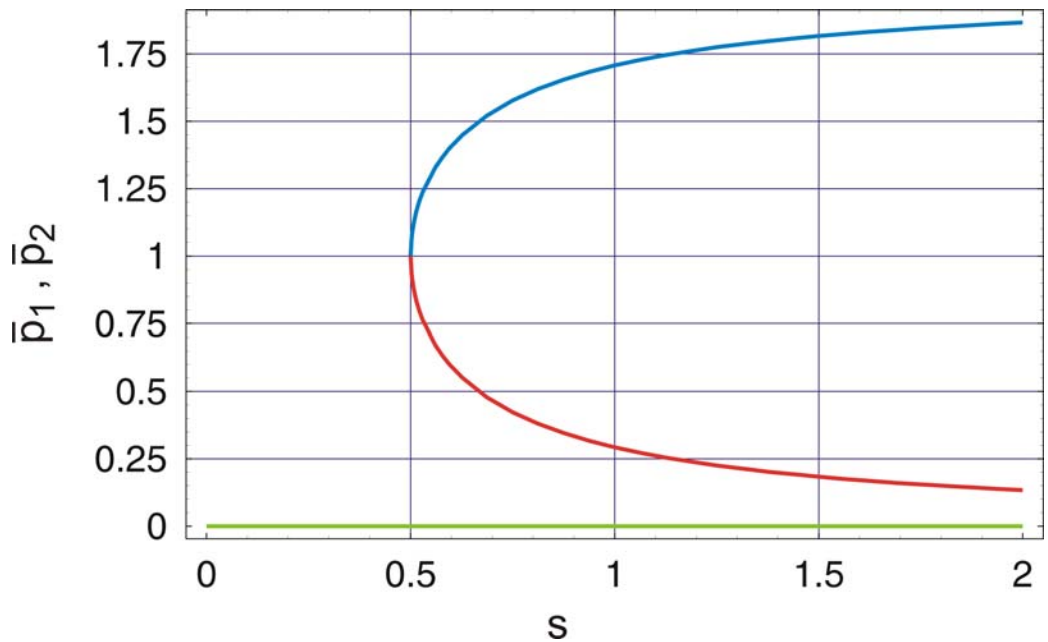
$$D_{\text{Hopf}} = \frac{(d_1^{\text{Q}}+d_2^{\text{Q}})(d_1^{\text{Q}}+d_1^{\text{P}})(d_1^{\text{Q}}+d_2^{\text{P}})(d_2^{\text{Q}}+d_1^{\text{P}})(d_2^{\text{Q}}+d_2^{\text{P}})(d_1^{\text{P}}+d_2^{\text{P}})}{(d_1^{\text{Q}}+d_2^{\text{Q}}+d_1^{\text{P}}+d_2^{\text{P}})^2}$$

Auxiliary parameter s

$K_{1,2} = \xi_{1,2} / s$

$k^{Q}_{1,2} = \zeta_{1,2} (\alpha + \beta s)$



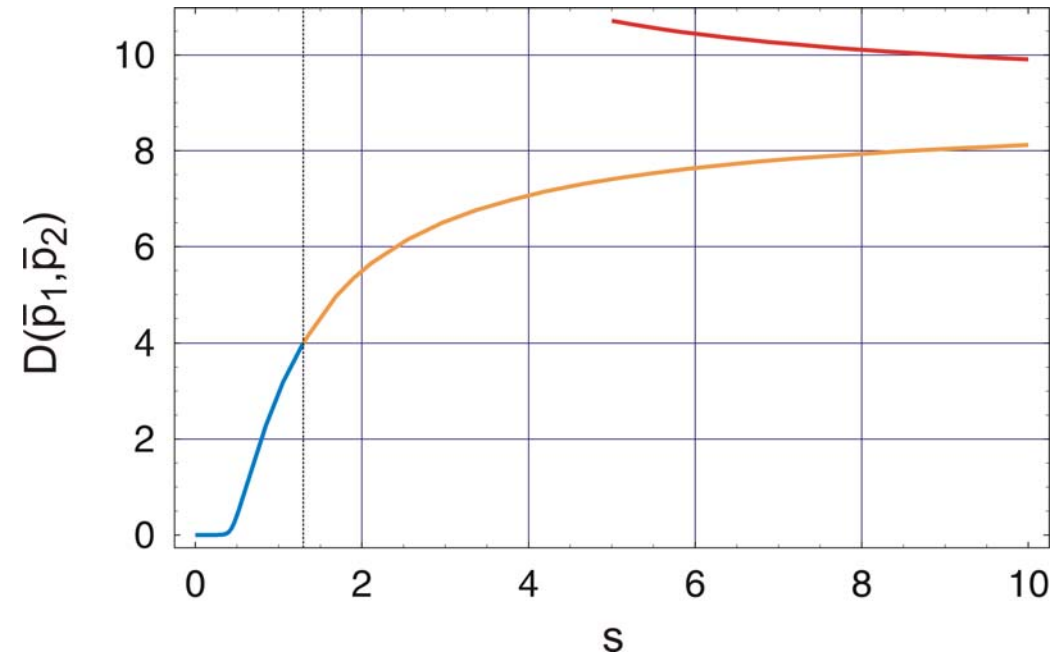


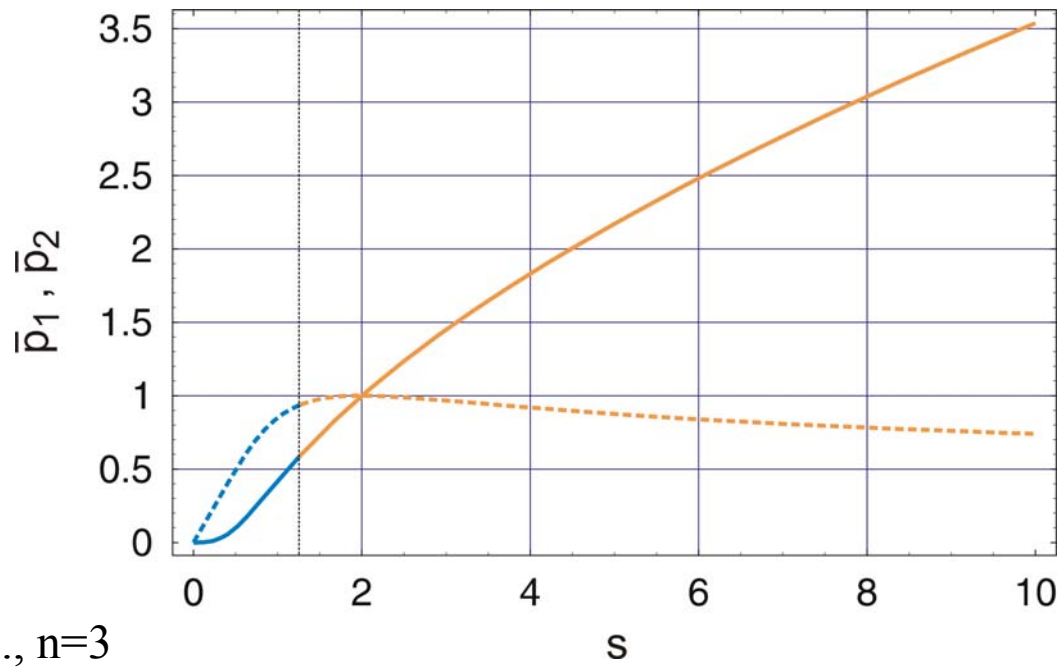
Regulatory dynamics at $D \leq 0$, act.-act., n=2

Auxiliary parameter s

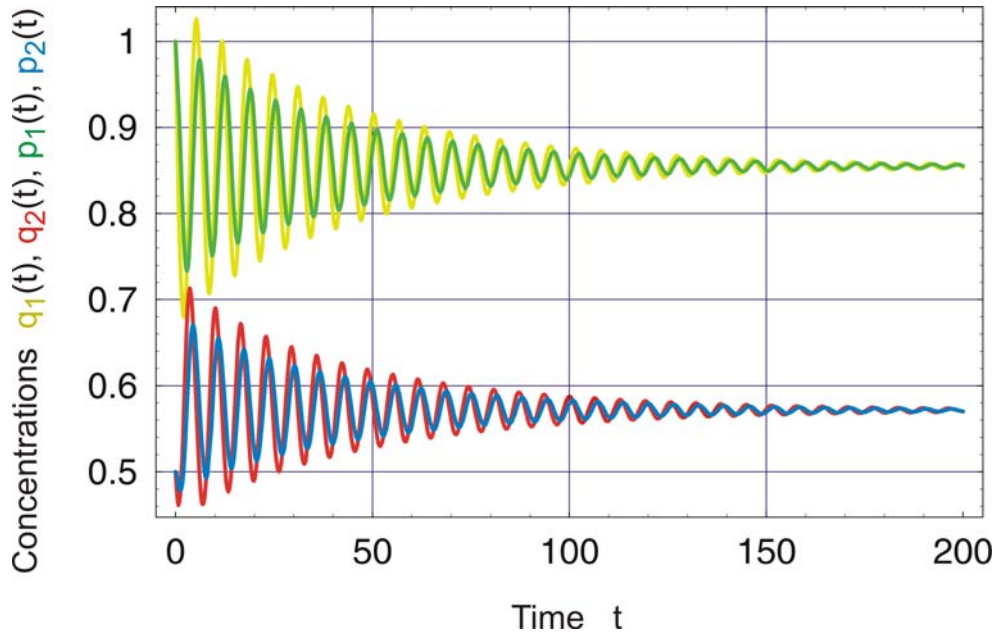
$K_{1,2} = \xi_{1,2} / s$

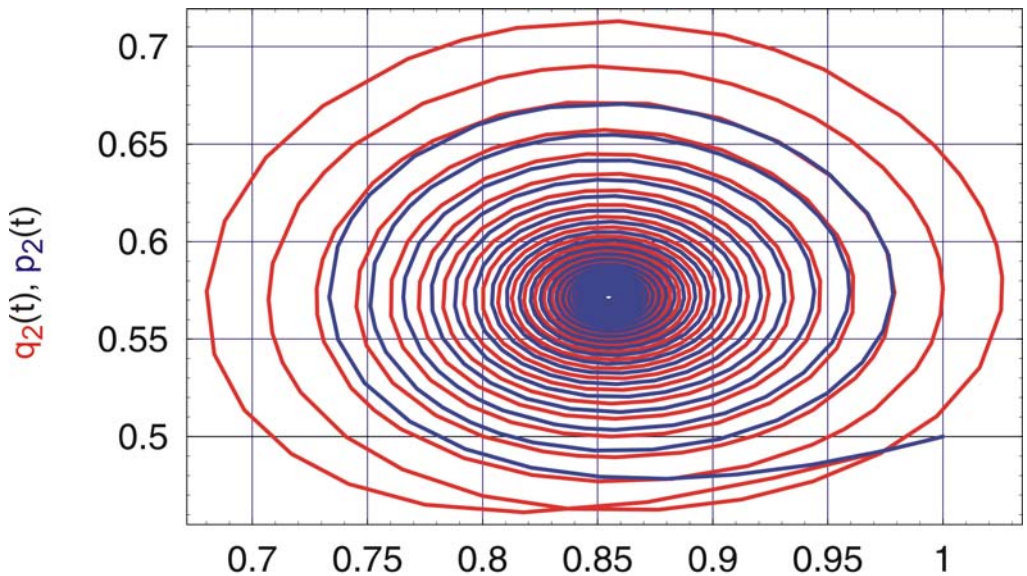
$k^{Q}_{1,2} = \zeta_{1,2} (\alpha + \beta s)$



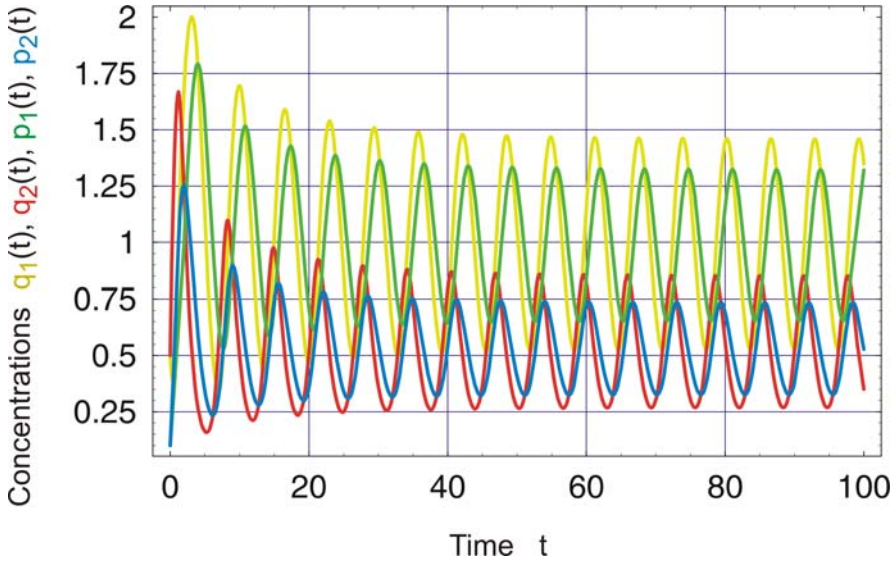


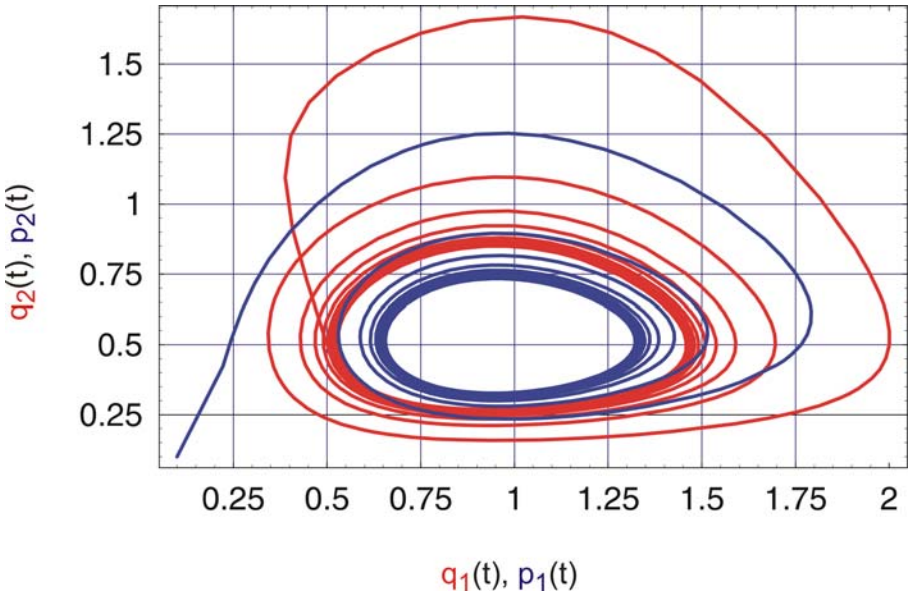
Regulatory dynamics at $D \geq 0$, act.-rep., n=3

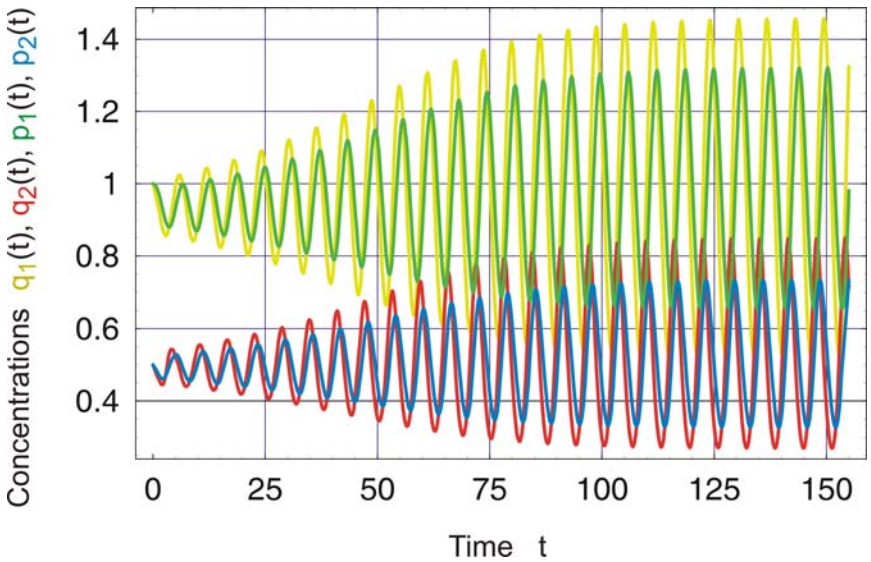


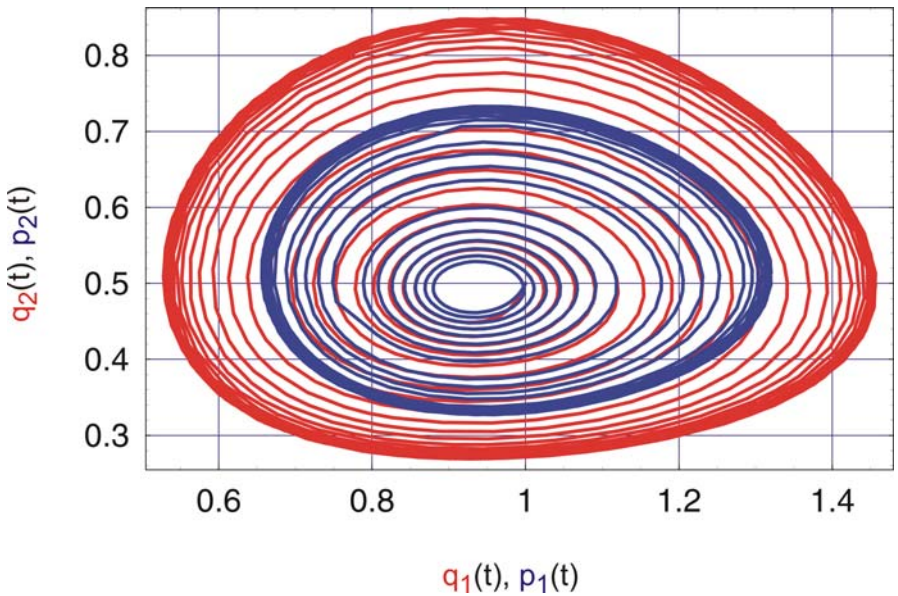


Regulatory dynamics at $D < D_{Hopf}$, act.-repr., n=3







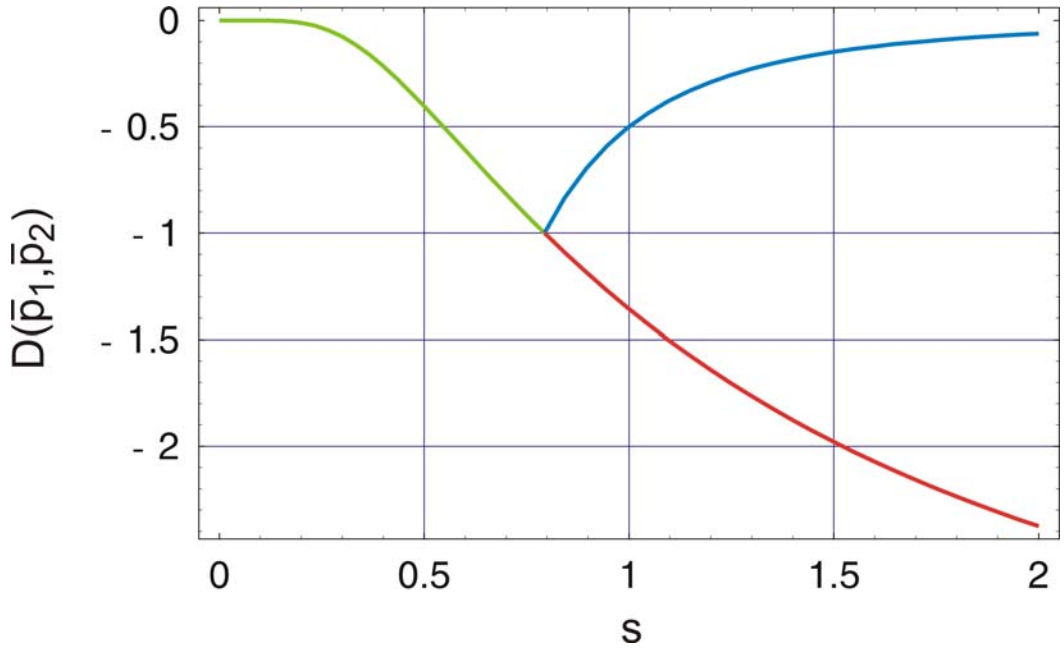


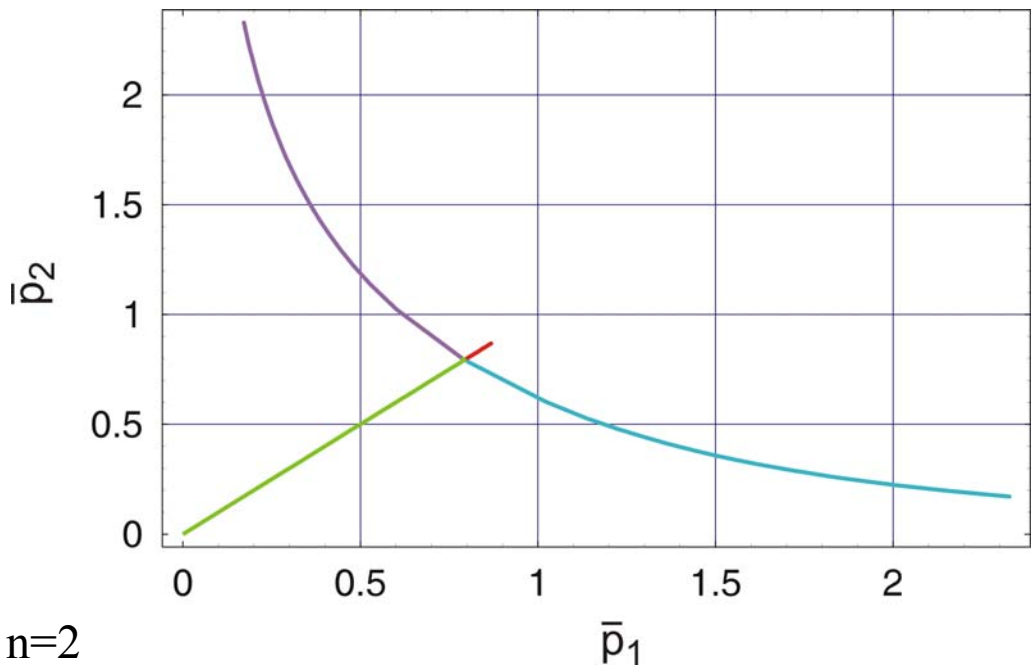
Regulatory dynamics at $D > D_{Hopf}$, act.-repr., n=3

Auxiliary parameter s

$K_{1,2} = \xi_{1,2} / s$

$k^{Q}_{1,2} = \zeta_{1,2} (\alpha + \beta s)$





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)

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

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

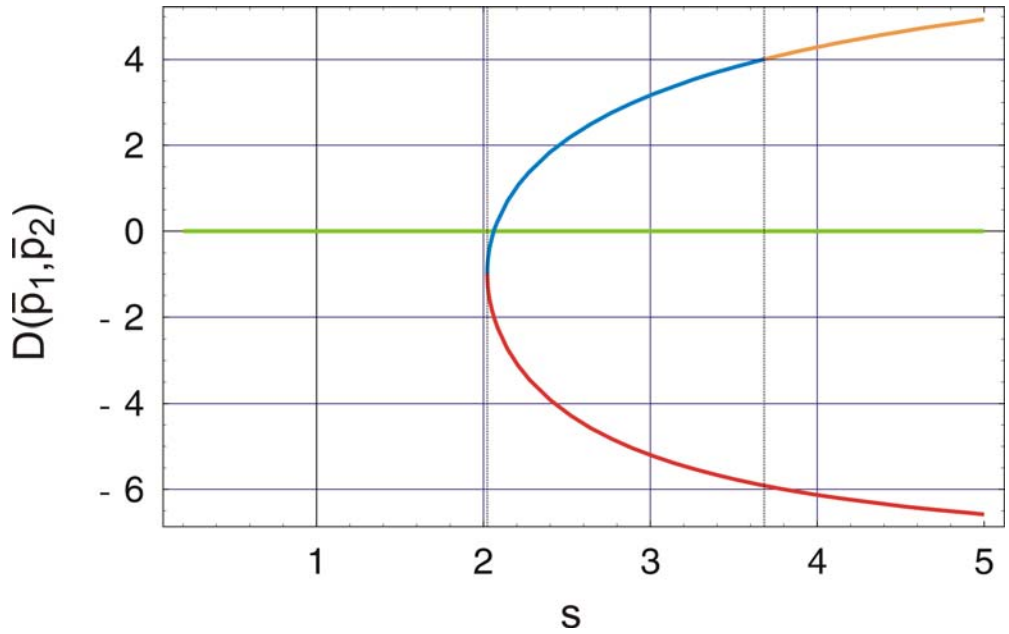
$$\text{Intermediate}: \quad F_i(p_j) = \frac{p_j^{\mathrm{m}}}{\kappa_1 + \kappa_2\, p_j + \kappa_3\, p_j^2 + \ldots + p_j^{\mathrm{n}}}$$

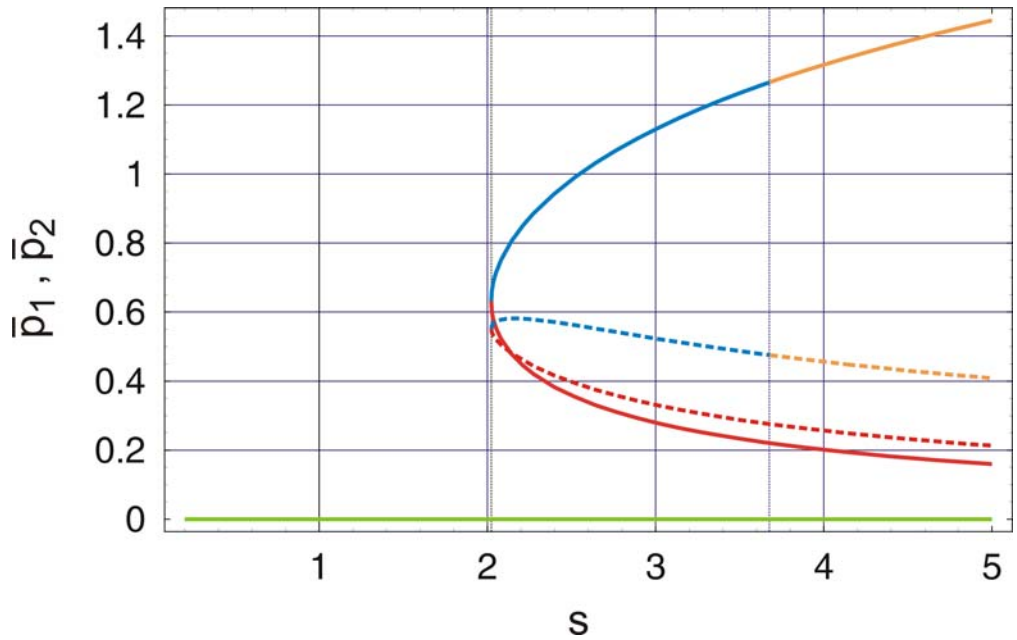
$$i, j = 1,2; \quad 1 \le m \le n-1$$

Auxiliary parameter s

$K_{1,2} = \xi_{1,2} / s$

$k^{Q}_{1,2} = \zeta_{1,2} (\alpha + \beta s)$



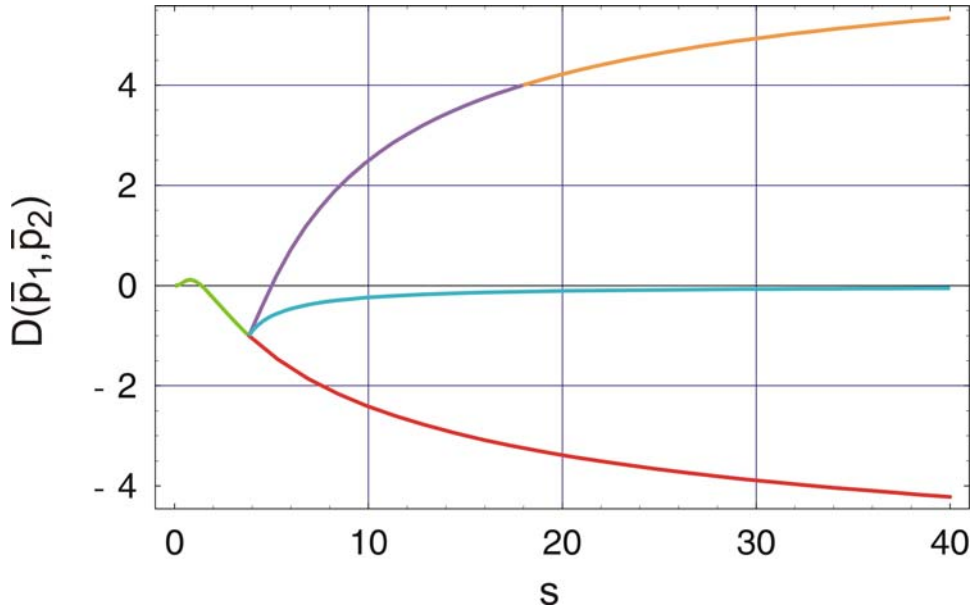


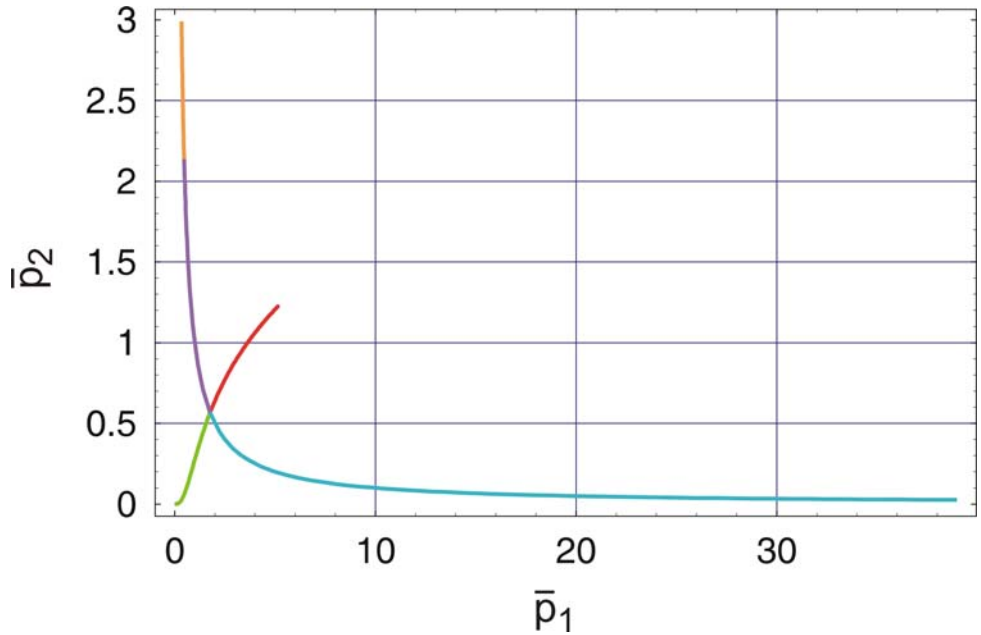
Regulatory dynamics, int.-act., m=2, n=4

Auxiliary parameter s

$K_{1,2} = \xi_{1,2} / s$

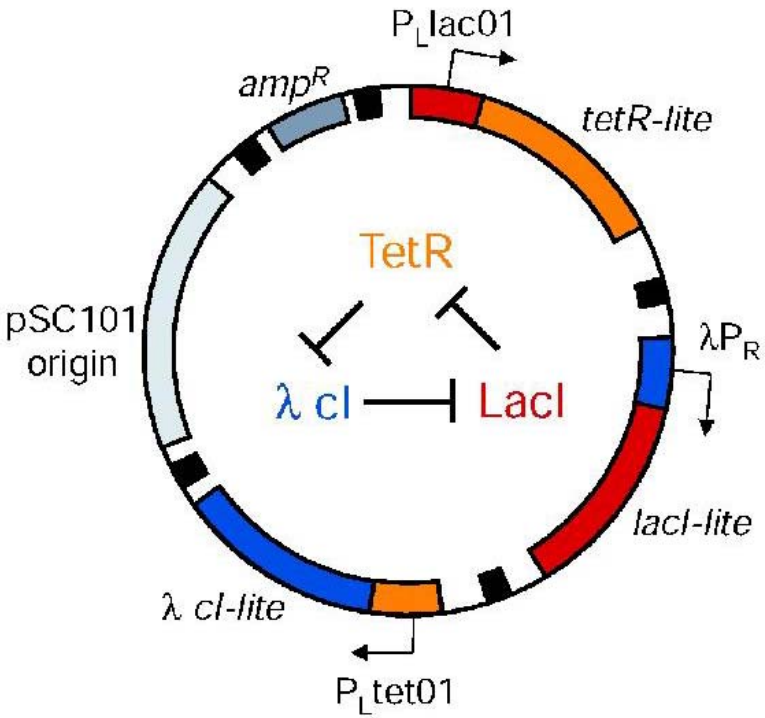
$k^{Q}_{1,2} = \zeta_{1,2} (\alpha + \beta s)$

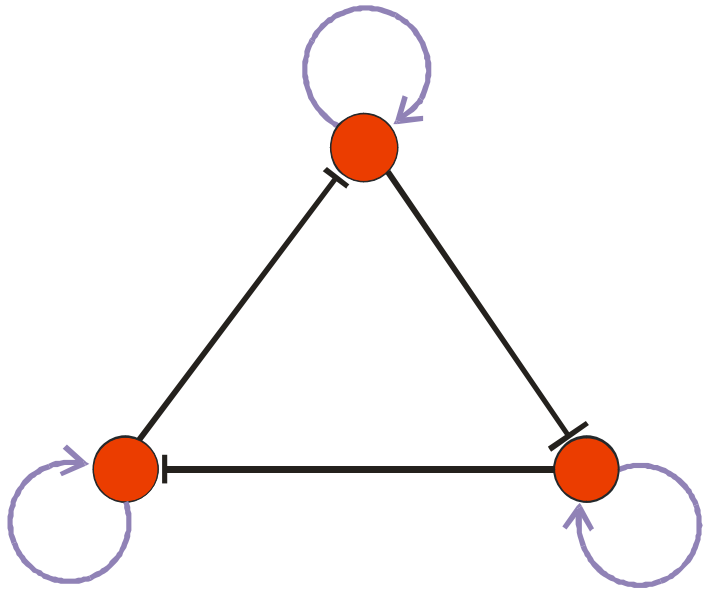




Regulatory dynamics, rep.-int., m=2, n=4

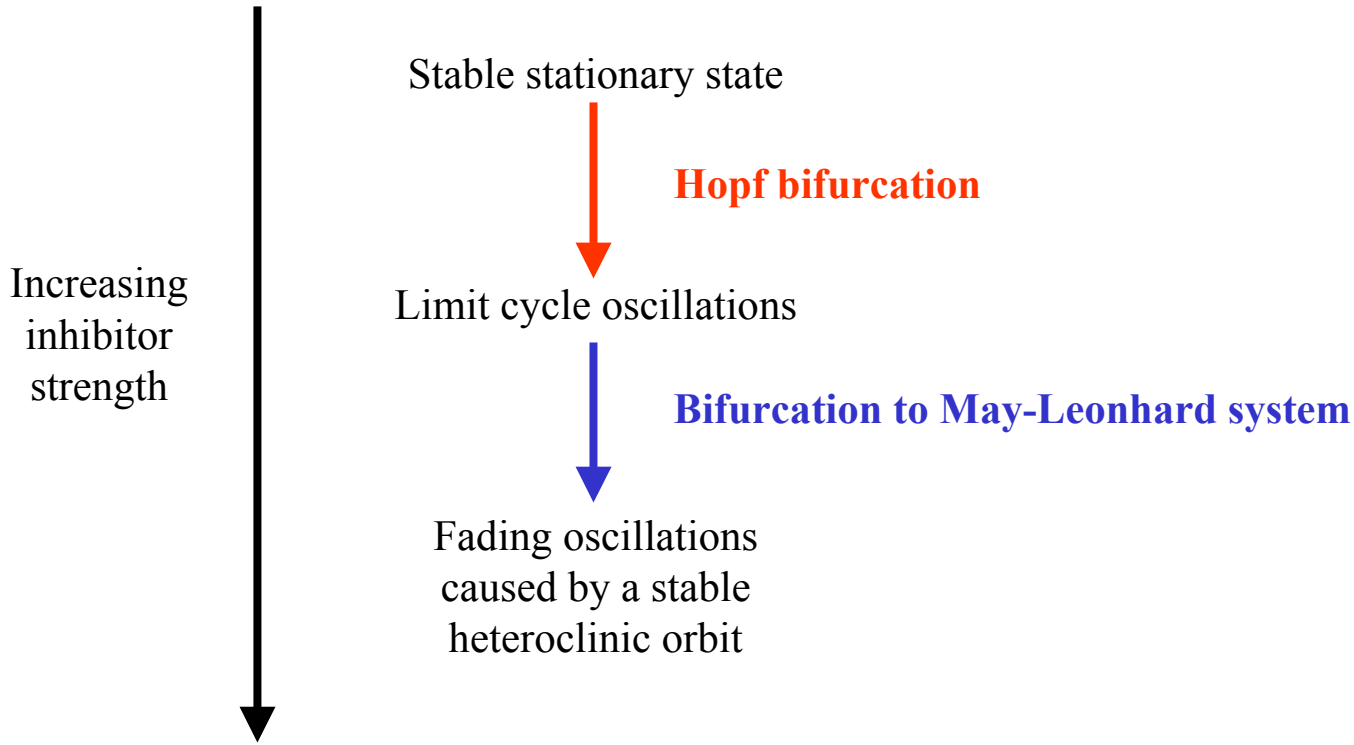
1. What is systems biology ?
2. Forward and inverse problems in modeling
3. Three examples
4. Bifurcation analysis of gene regulation
5. **Analysis of a synthetic oscillator**

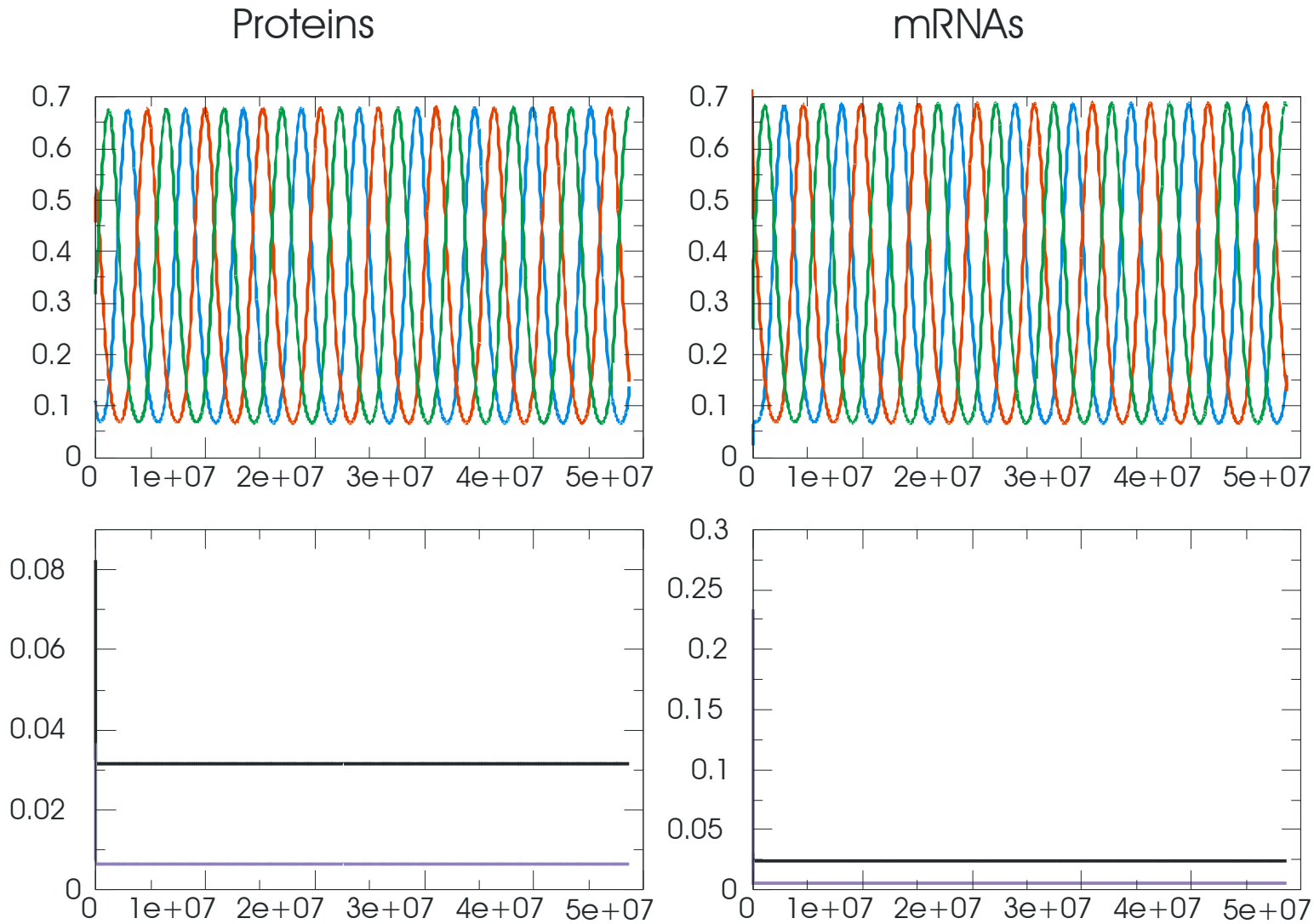




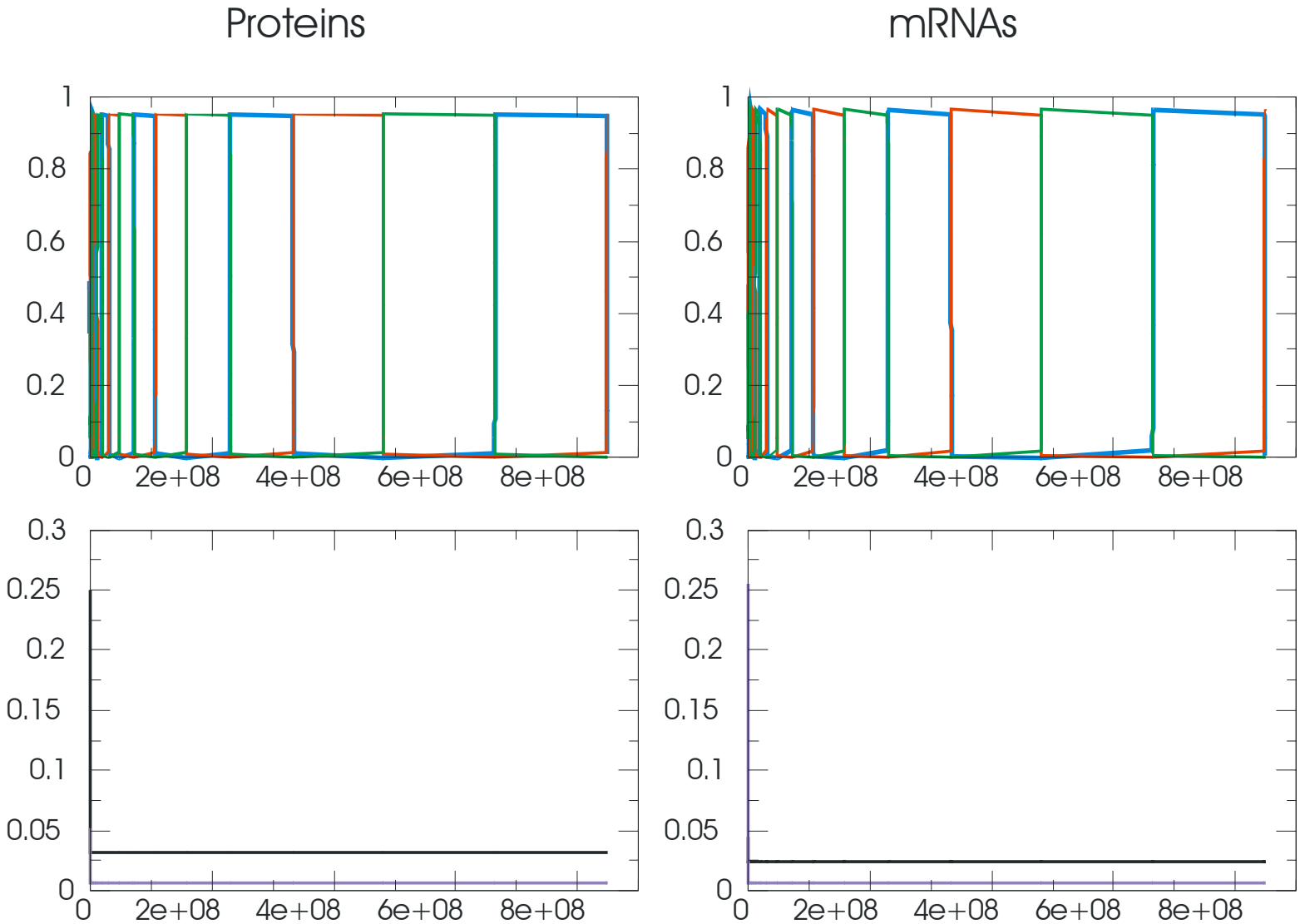
An example analyzed and simulated by MiniCellSim

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

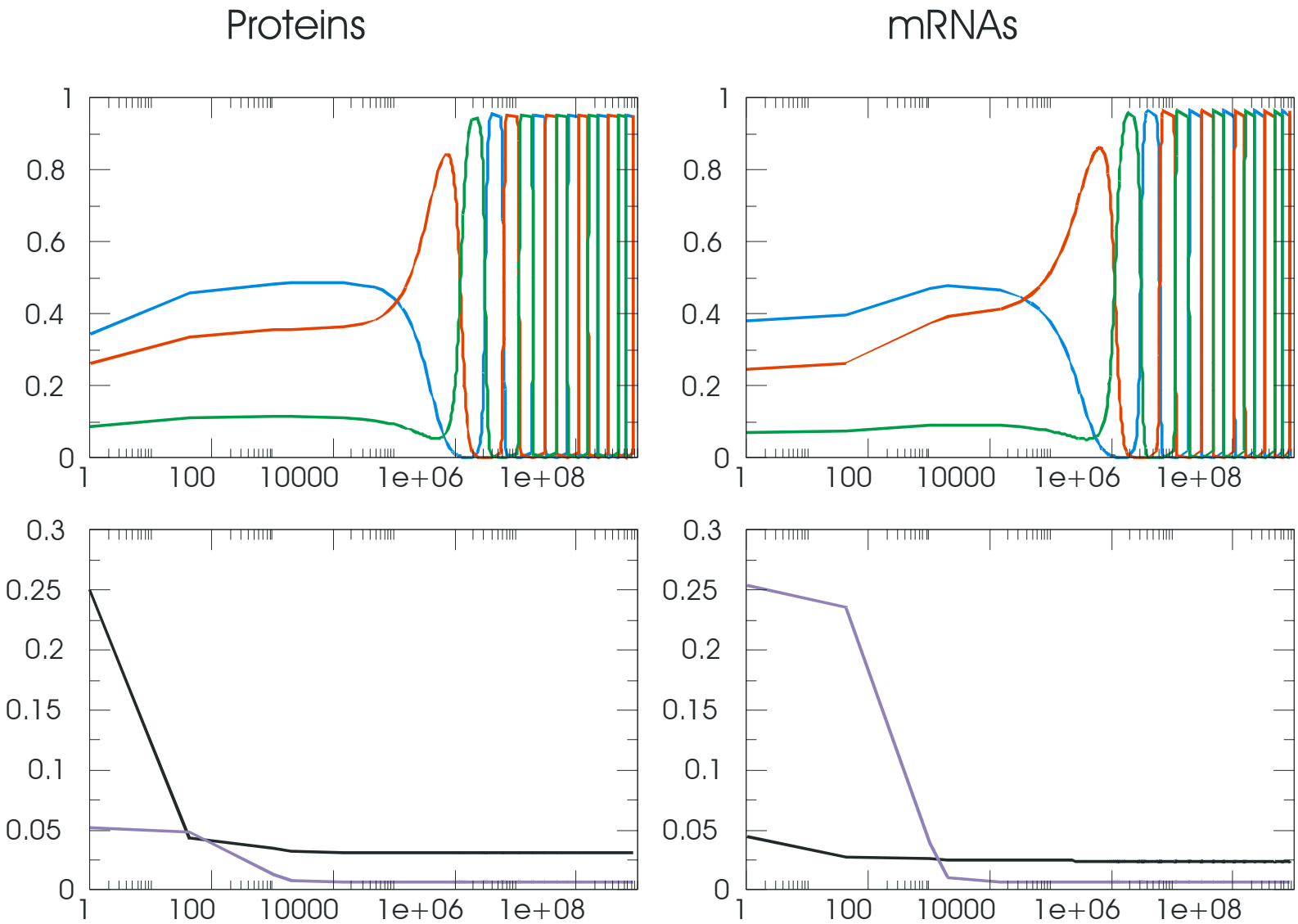

Increasing inhibitor strength
Stable stationary state
Hopf bifurcation
Limit cycle oscillations
Bifurcation to May-Leonhard system
Fading oscillations caused by a stable heteroclinic orbit



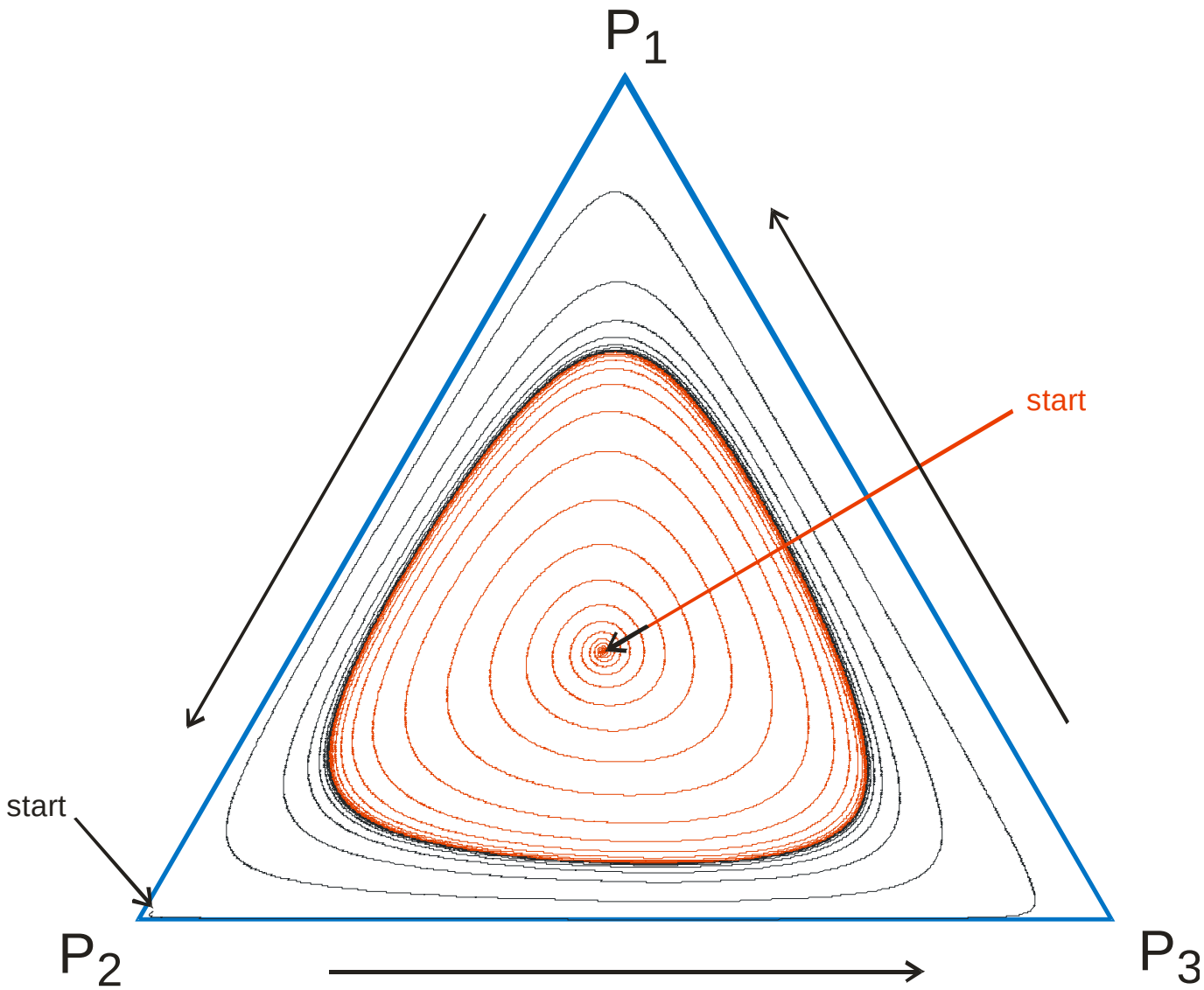
The repressilator limit cycle



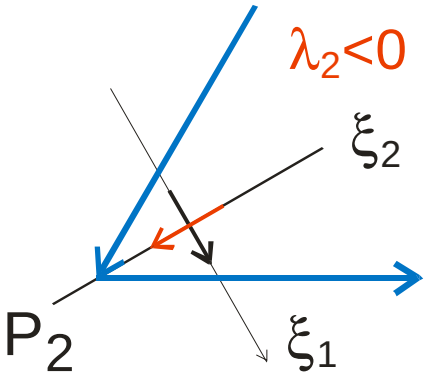
The repressilator heteroclinic orbit



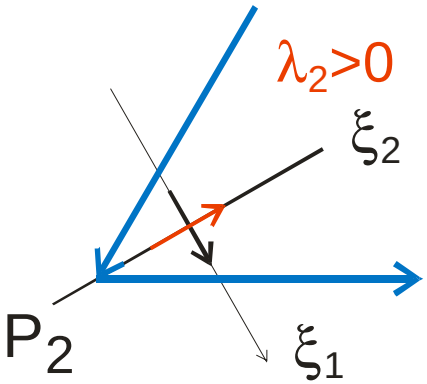
The repressilator heteroclinic orbit (logarithmic time scale)



The repressilator limit cycle

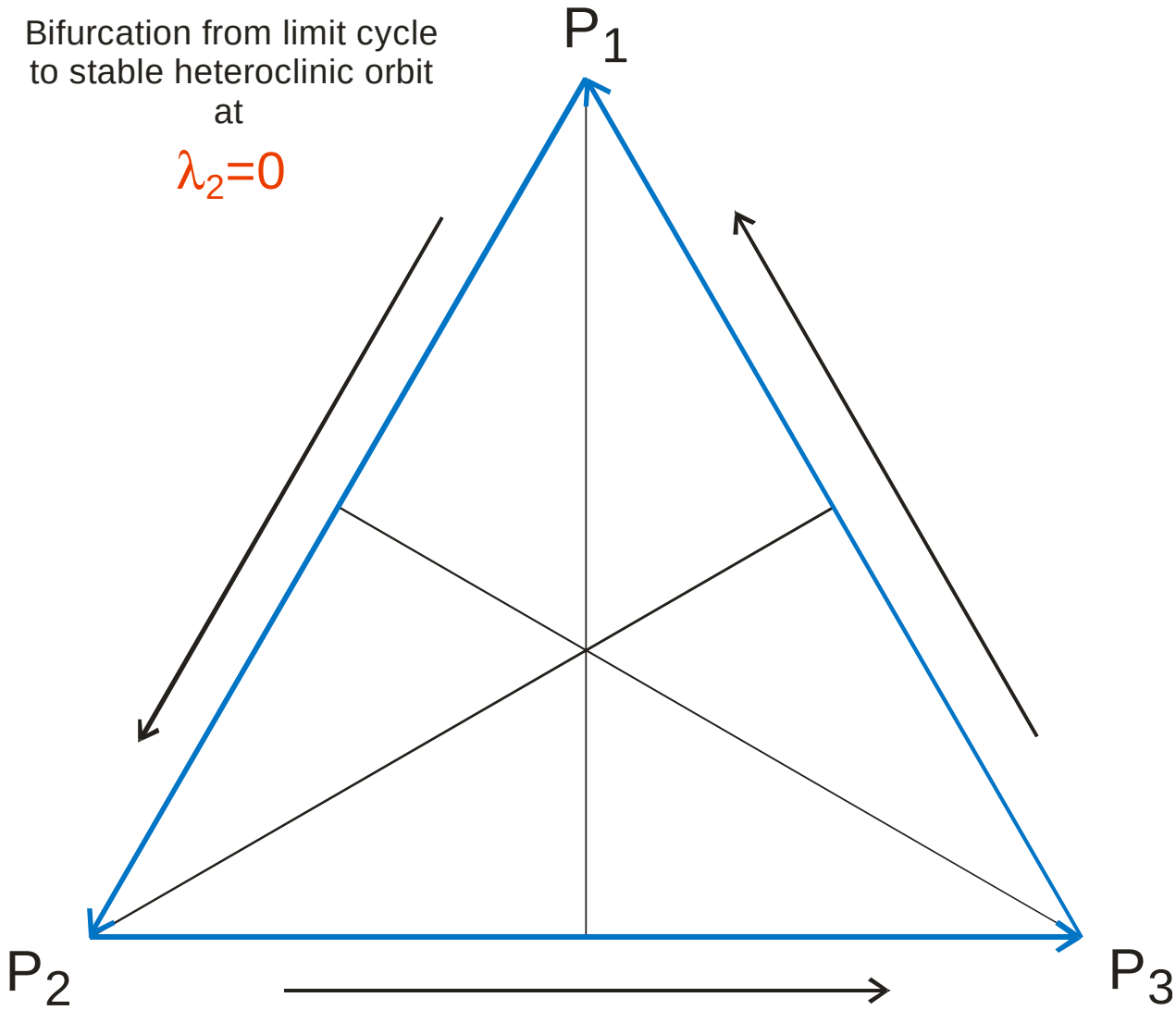


Stable heteroclinic orbit



Unstable heteroclinic orbit

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

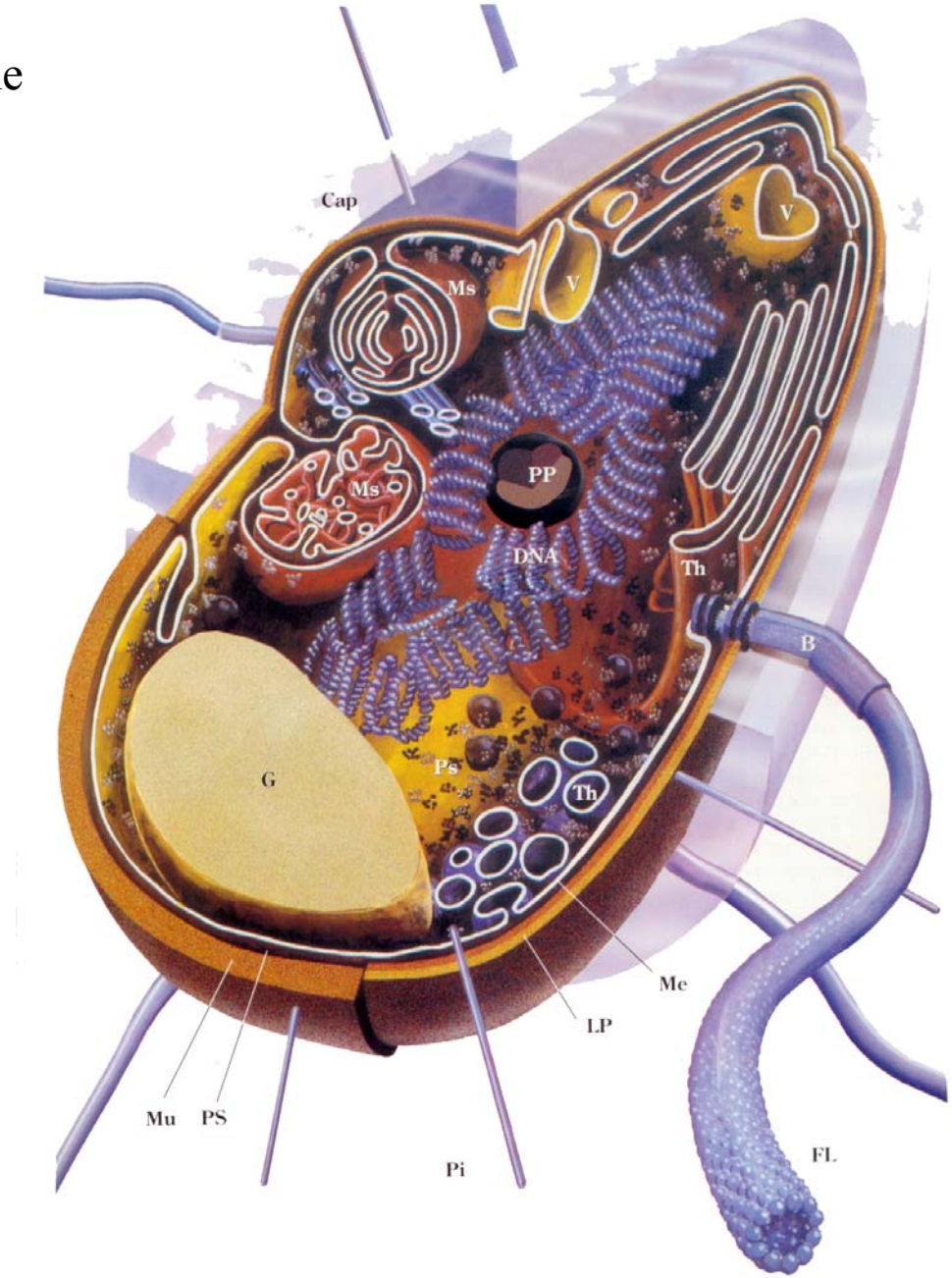


The repressilator heteroclinic orbit

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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