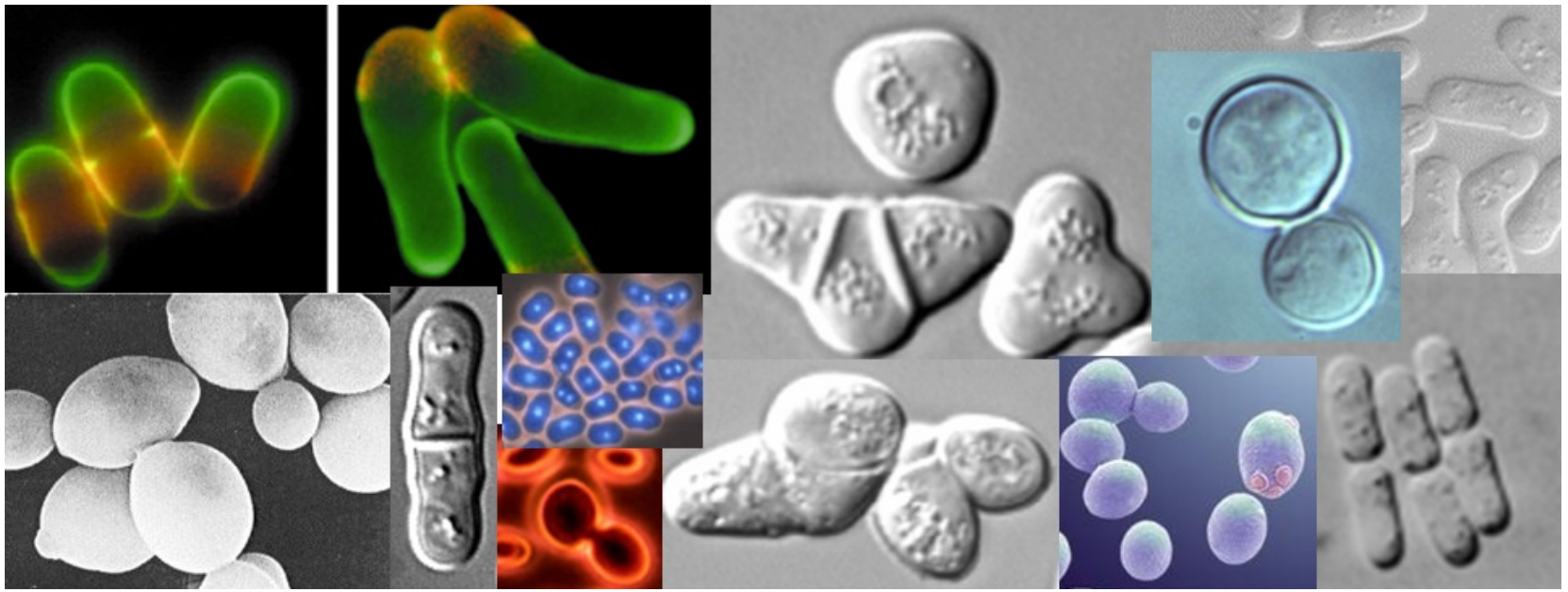
Molecular Network Dynamics



Attila Csikász-Nagy

The Microsoft Research - University of Trento
Centre for Computational and Systems Biology

Computational Systems Biology

DNA …TACCCGATGGCGAAATGC...

↓

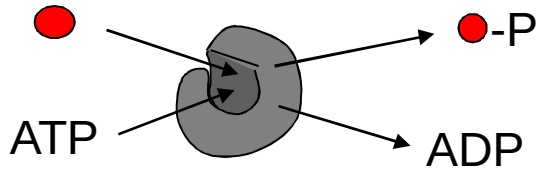
mRNA …AUGGGCUACCGCUUUACG...

↓

Protein …Met -Gly -Tyr -Arg -Phe -Thr...

↓

Enzyme



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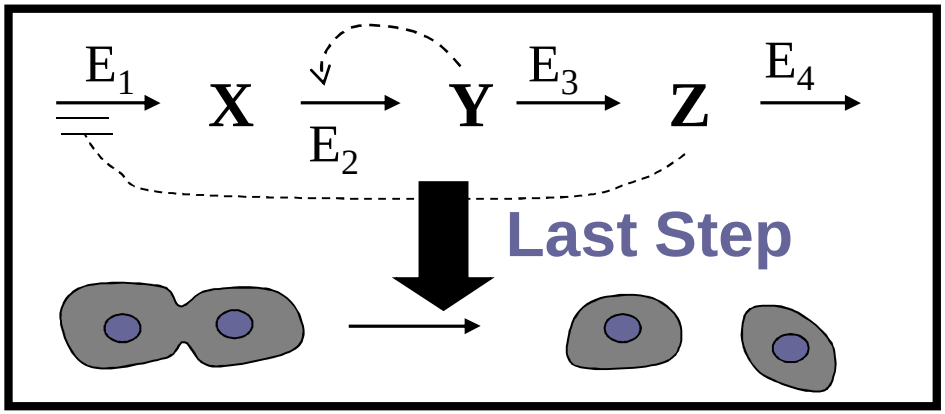
Reaction Network



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Cell Physiology

I.

Dynamical Systems Theory

Biophysical Journal Volume 90 June 2006 4361–4379

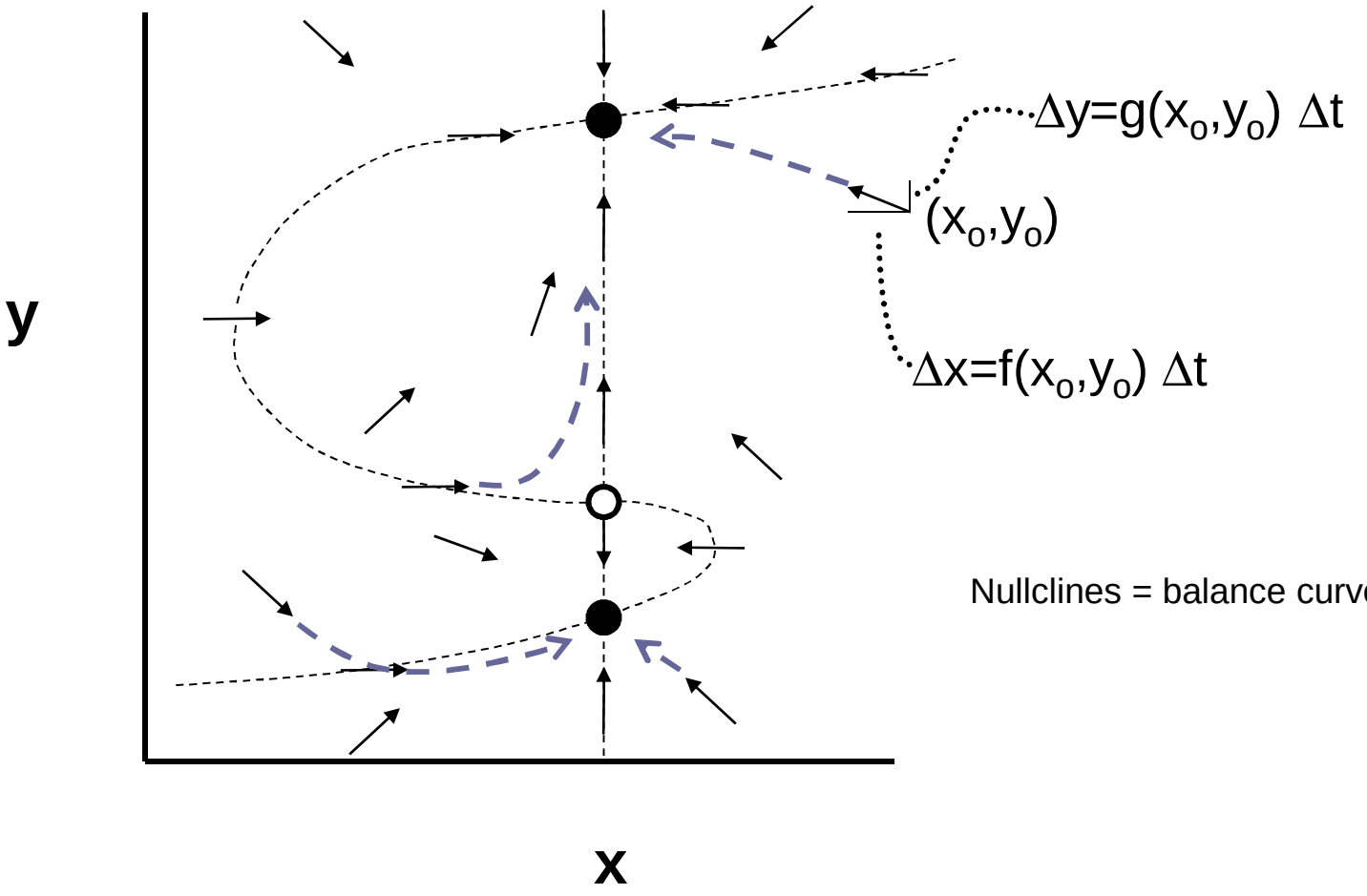
Analysis of a Generic Model of Eukaryotic Cell-Cycle Regulation

Attila Csikász-Nagy,*† Dorjsuren Battogtokh,* Katherine C. Chen,* Béla Novák,† and John J. Tyson*

Phase plane

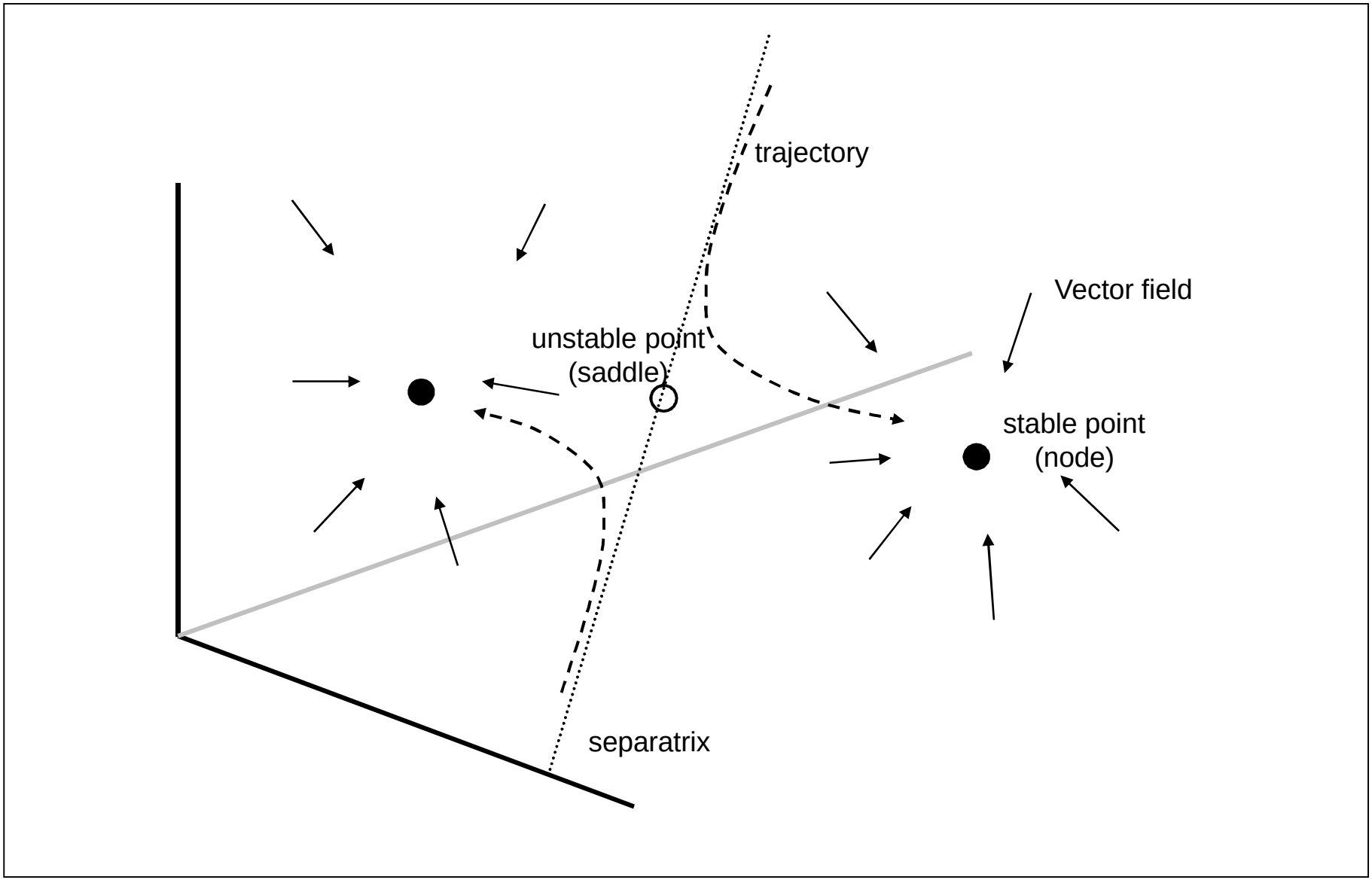
Two variable system:

$$\frac{dx}{dt} = f(x,y)$$
$$\frac{dy}{dt} = g(x,y)$$

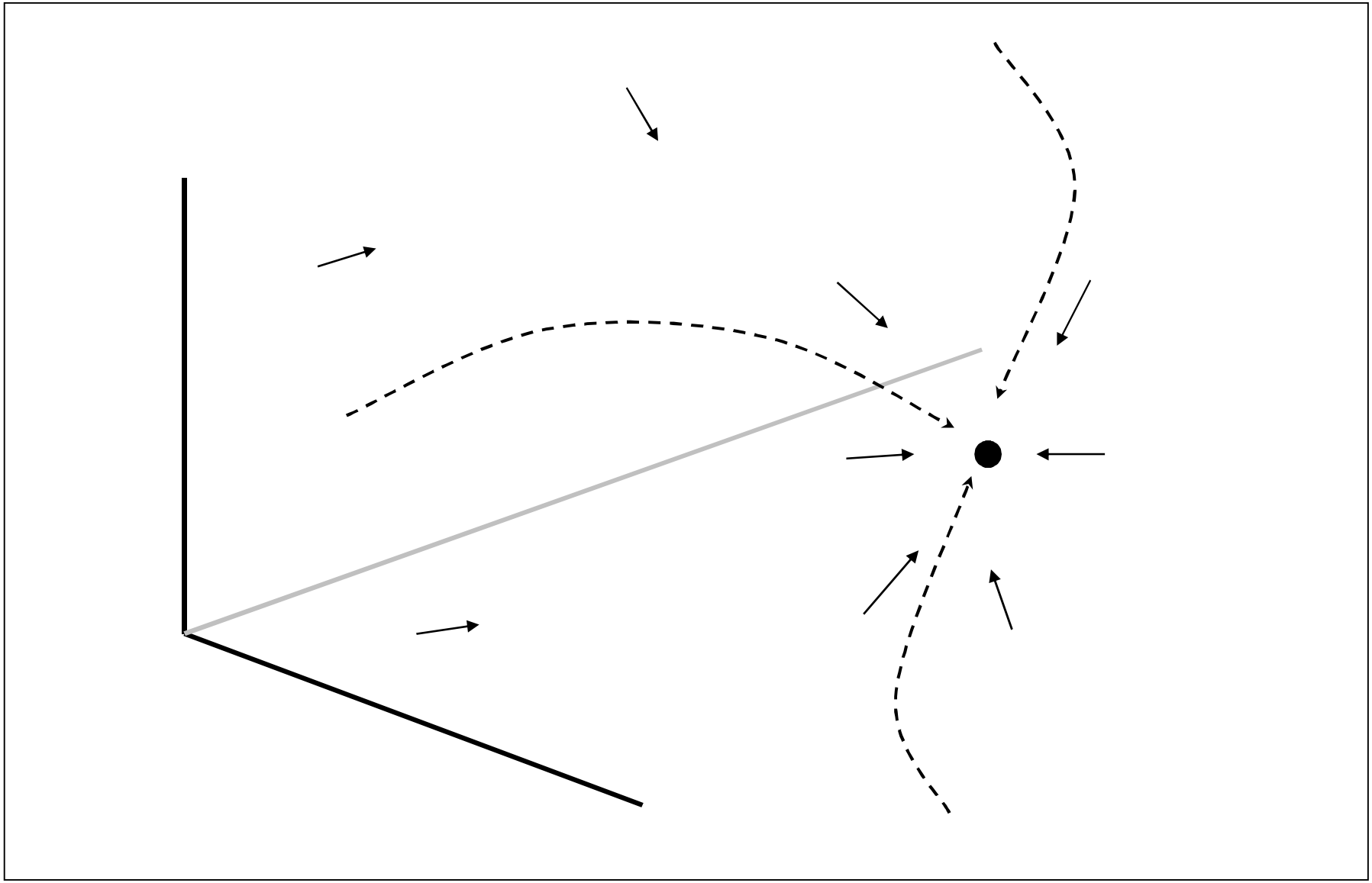


Nullclines = balance curves

Phase space

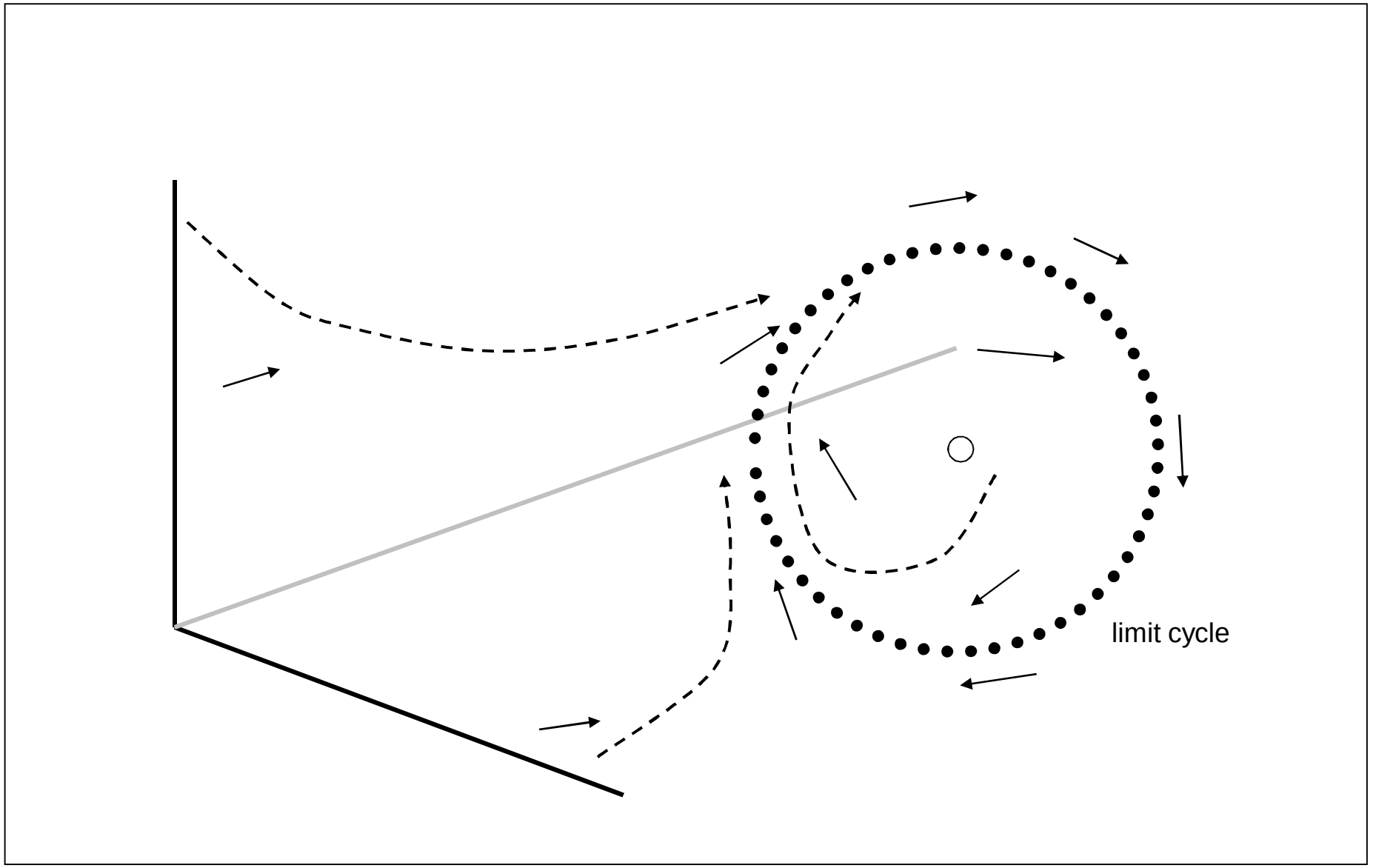

trajectory
Vector field
unstable point
(saddle)
stable point
(node)
separatrix

Bifurcation: change in number or stability of steady states



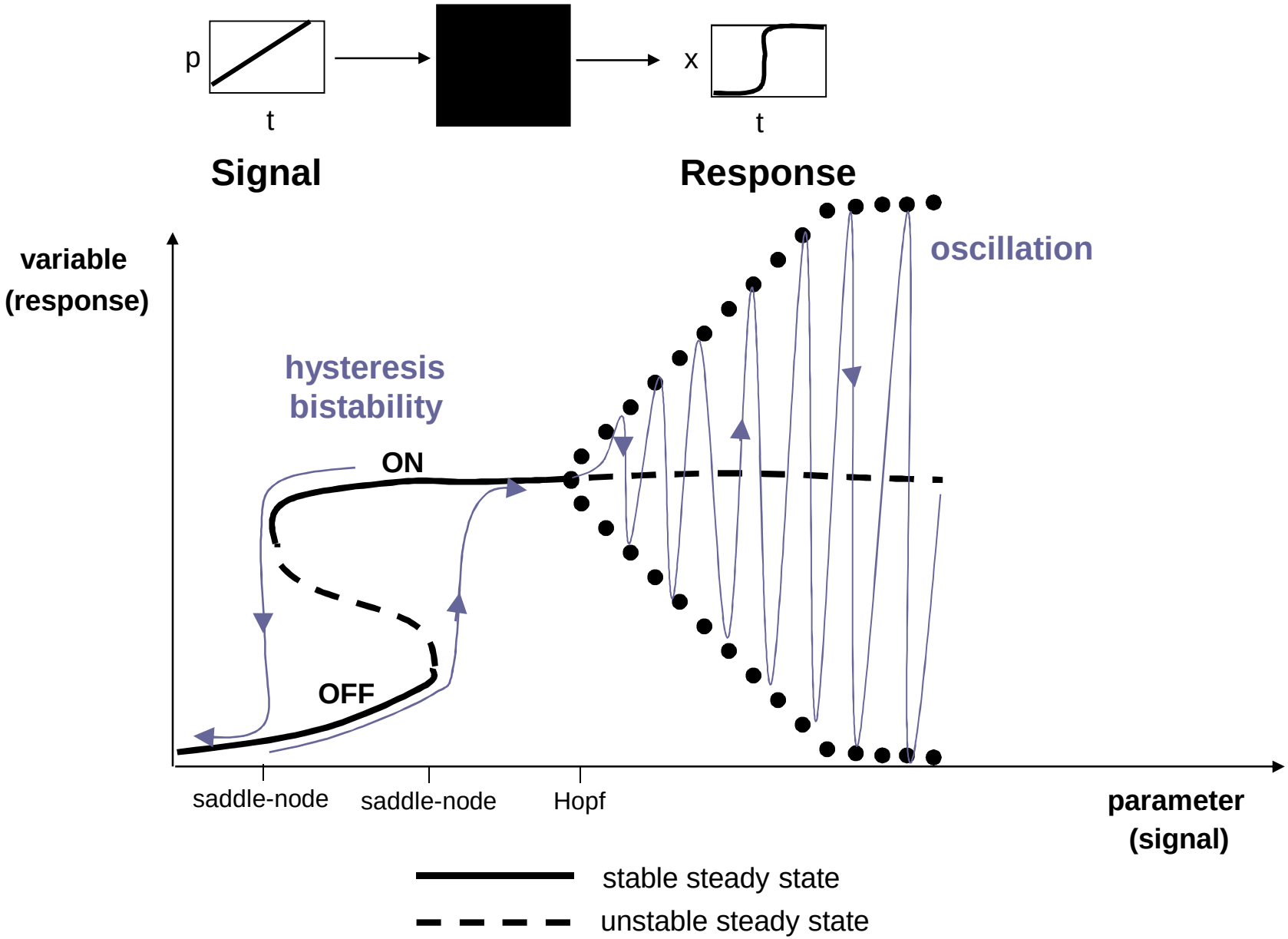
Saddle-Node bifurcation: one saddle and one node disappear

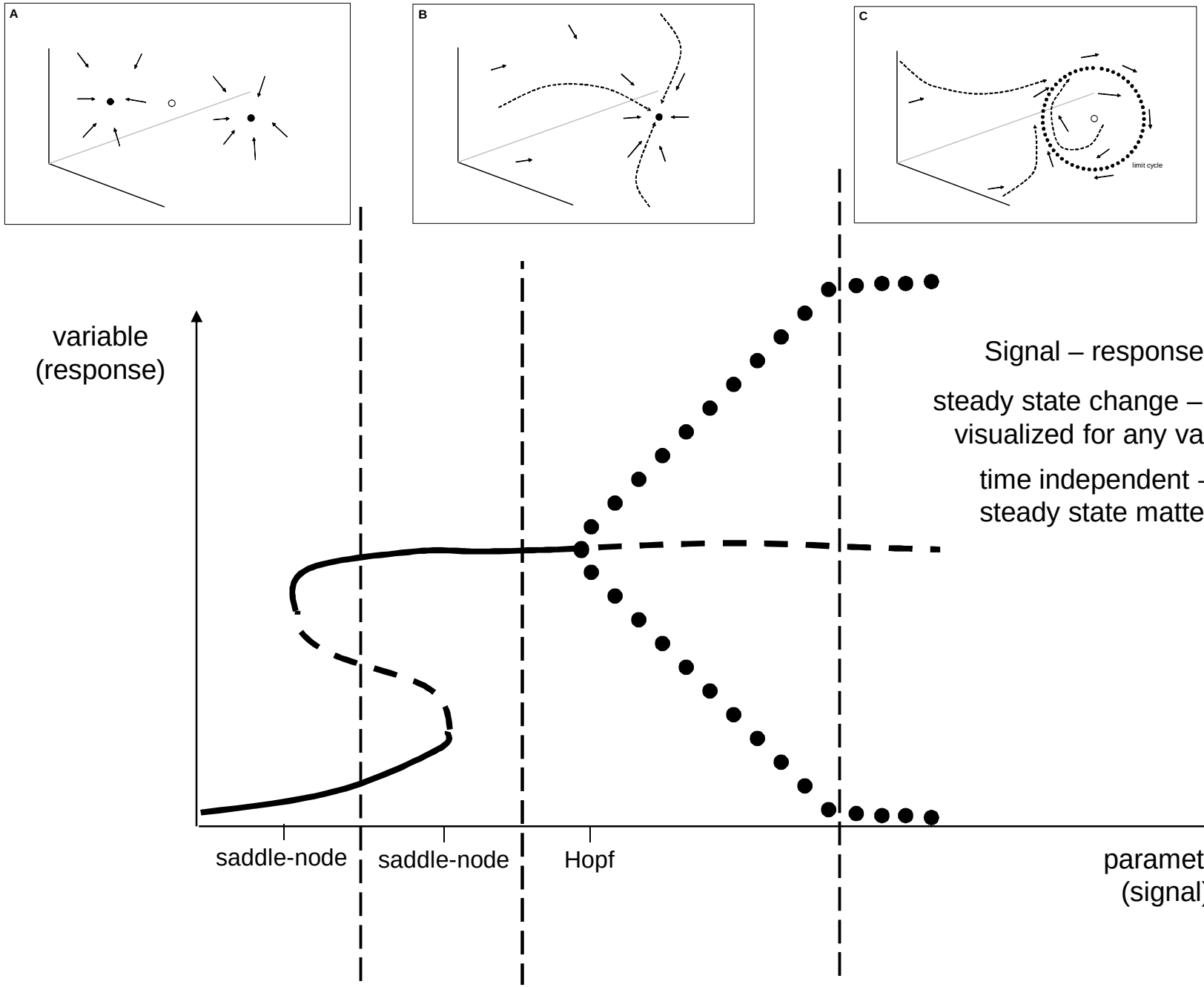
Bifurcation: change in number or stability of steady states

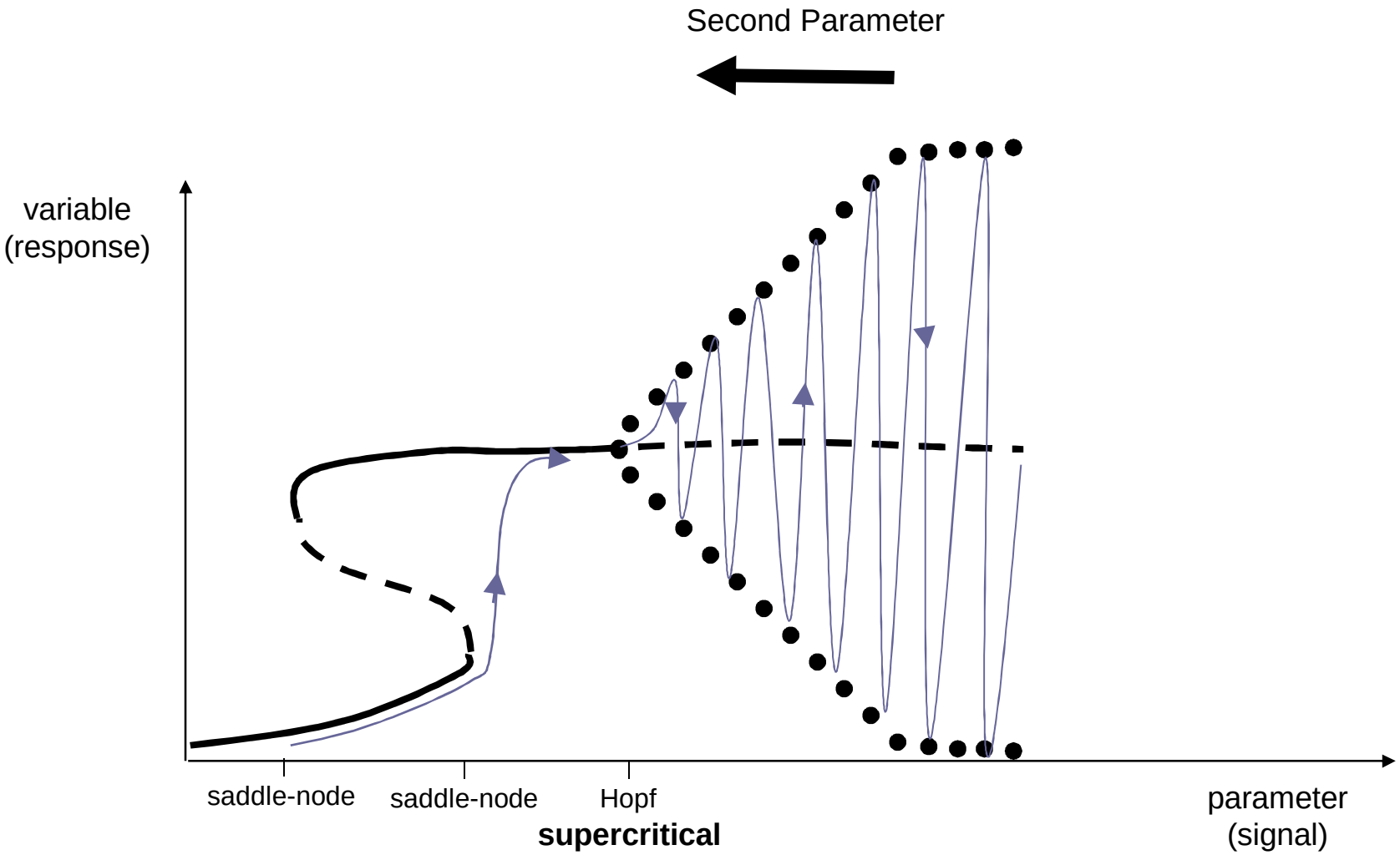


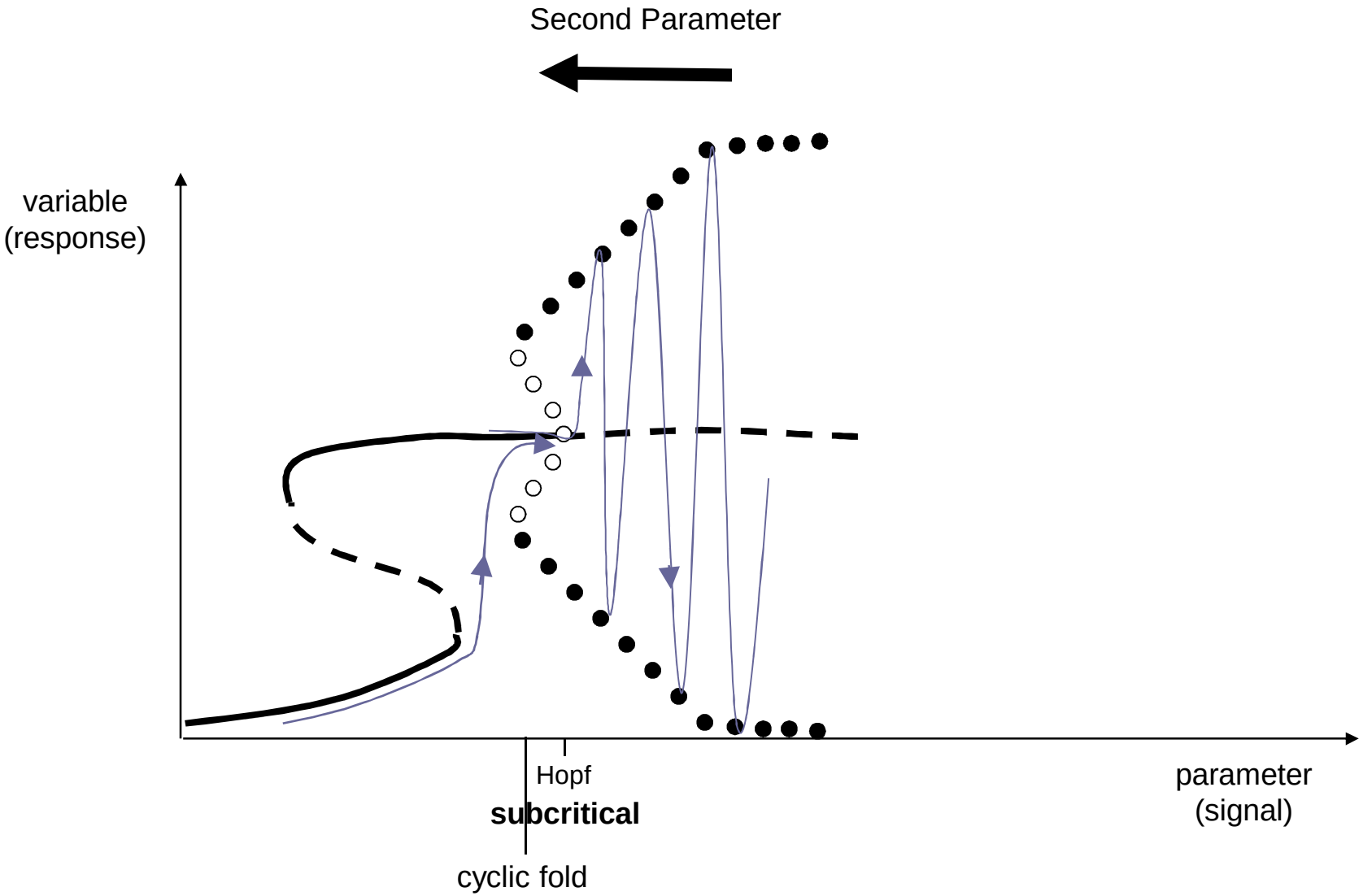
Hopf bifurcation: one node changes stability and a limit cycle is born

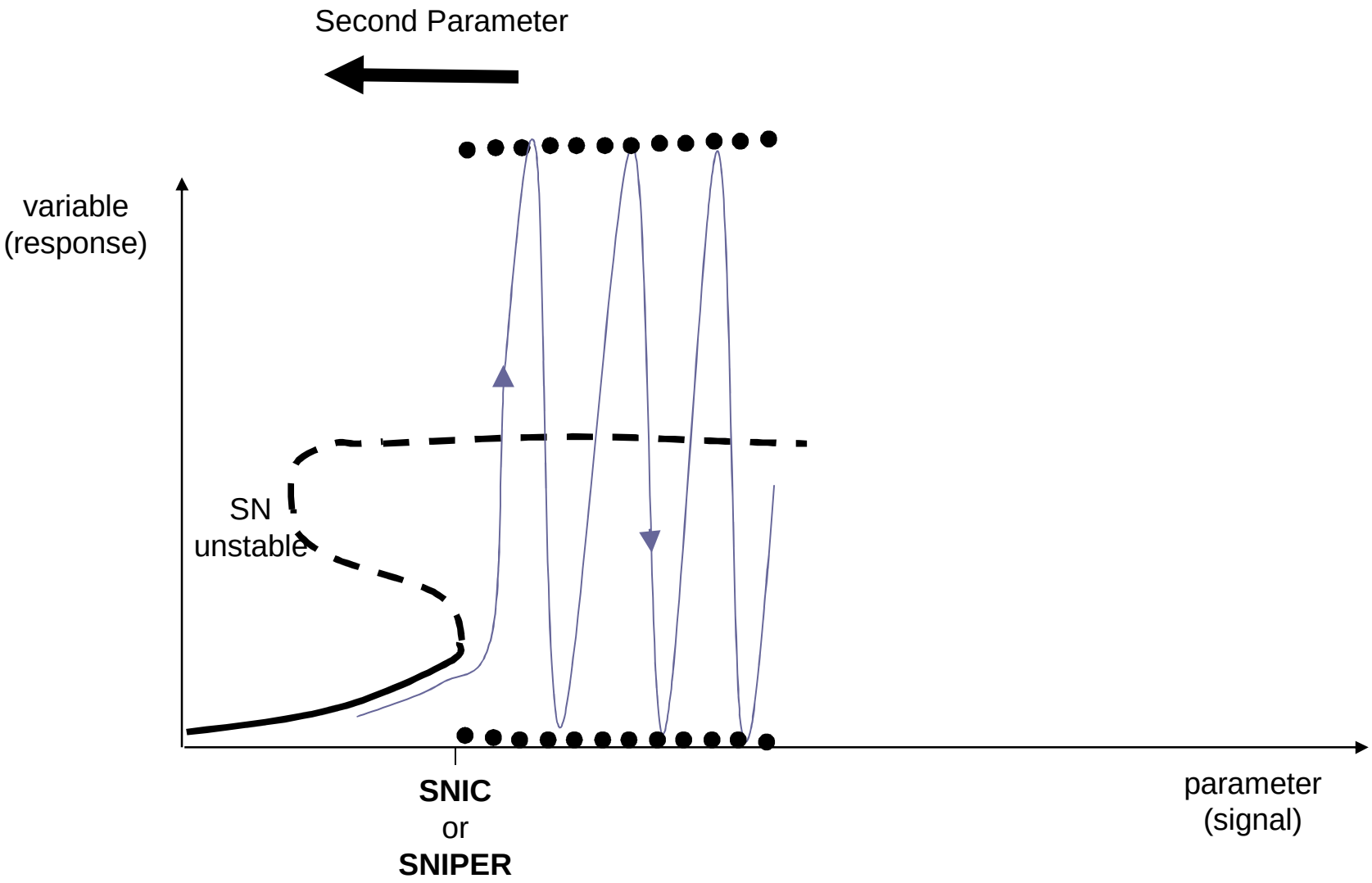
One-parameter bifurcation diagram



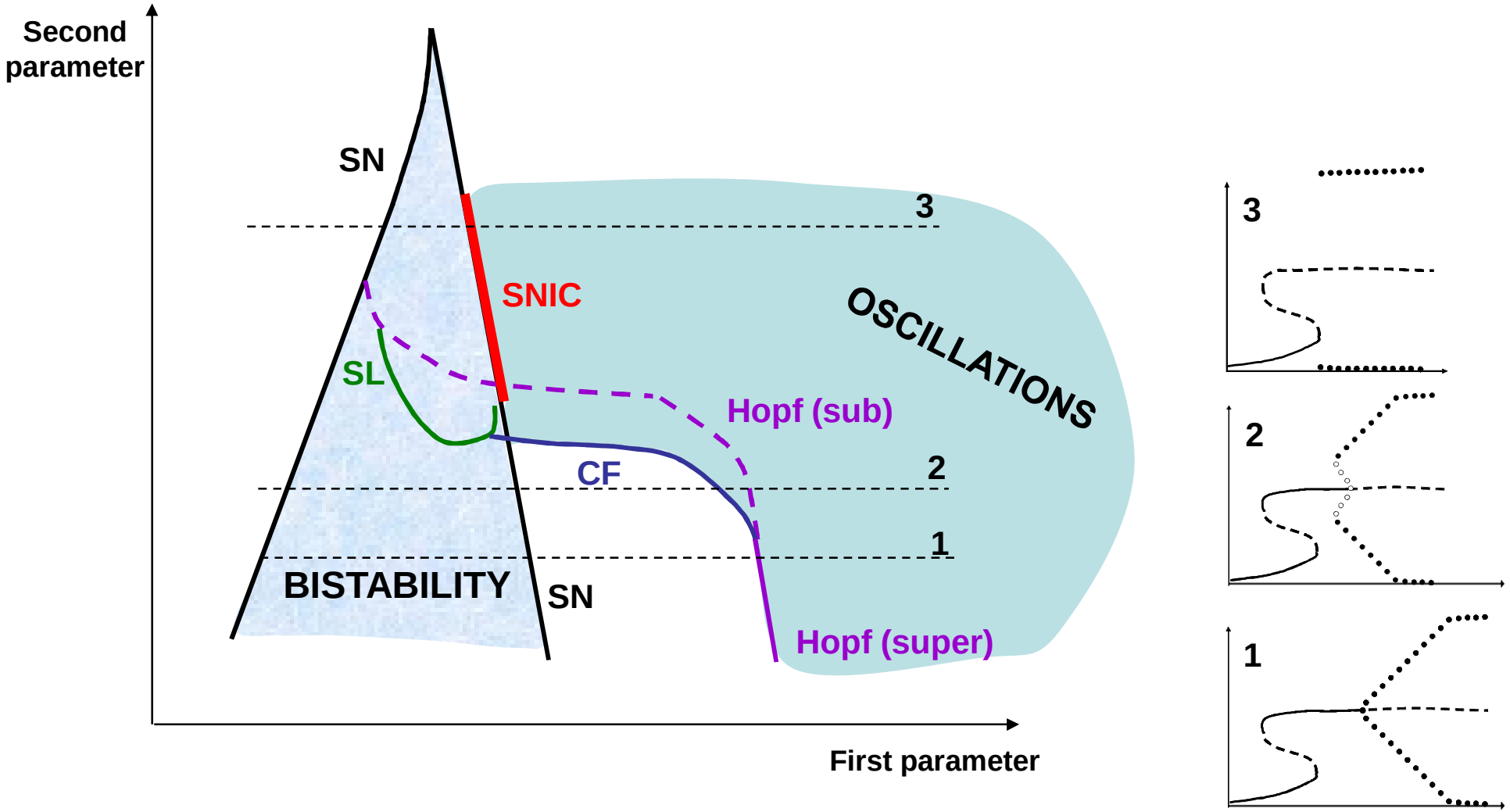

A
B
C
limit cycle
variable
(response)
Signal – response curve
steady state change – can be visualized for any variable
time independent – only steady state matters
saddle-node
saddle-node
Hopf
parameter
(signal)


Second Parameter
variable
(response)
saddle-node
saddle-node
Hopf
supercritical
parameter
(signal)


Second Parameter
variable
(response)
Hopf
subcritical
cyclic fold
parameter
(signal)


Second Parameter
variable
(response)
SN
unstable
SNIC
or
SNIPER
parameter
(signal)

Two-parameter bifurcation diagram



II.

Molecular Network Dynamics

Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell

John J Tyson[*†], Katherine C Chen[*‡] and Bela Novak[§]

Design principles of biochemical oscillators

Béla Novák and John J. Tyson‡*

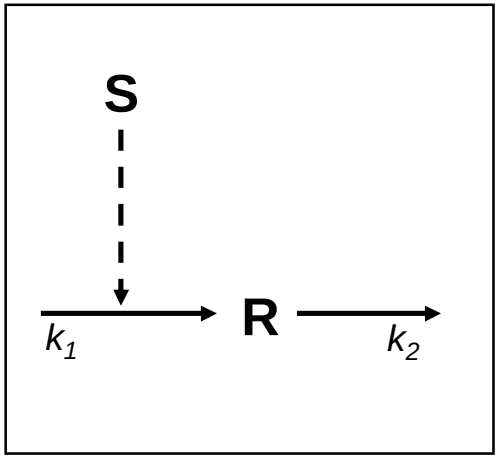
NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 9 | DECEMBER 2008 | 981

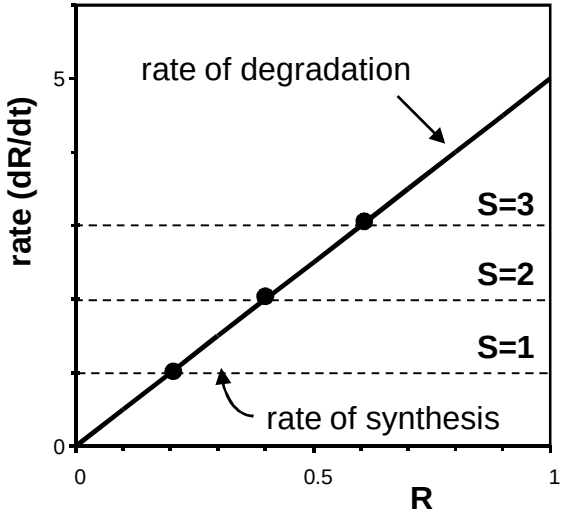
Functional Motifs in Biochemical Reaction Networks

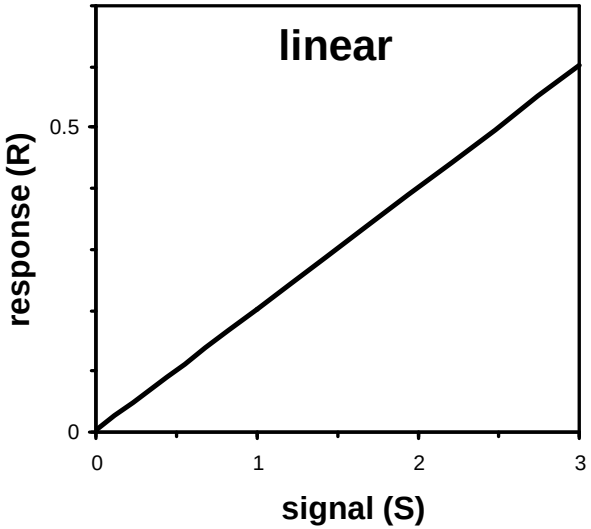
John J. Tyson[1] and Béla Novák[2]

Annu. Rev. Phys. Chem. 2010. 61:219–40

Gene Expression



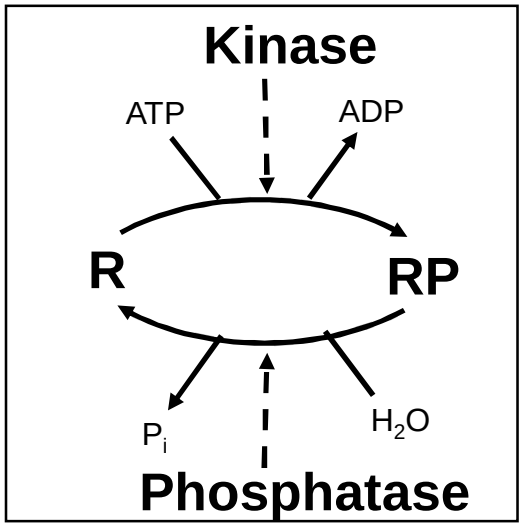


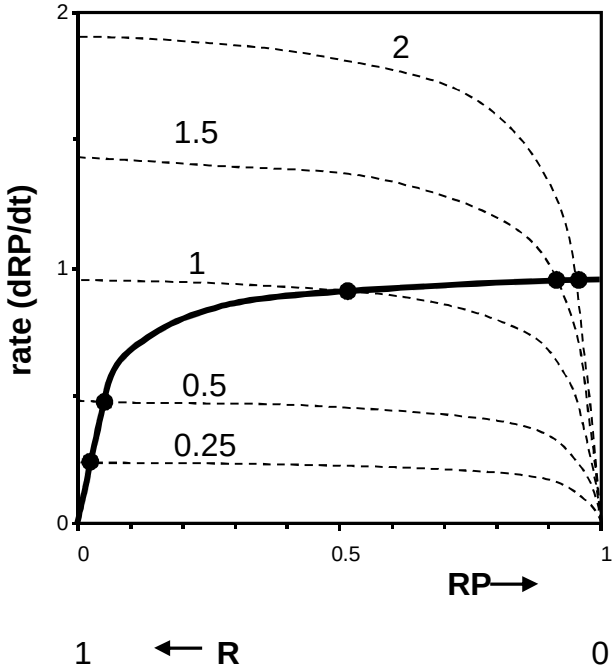


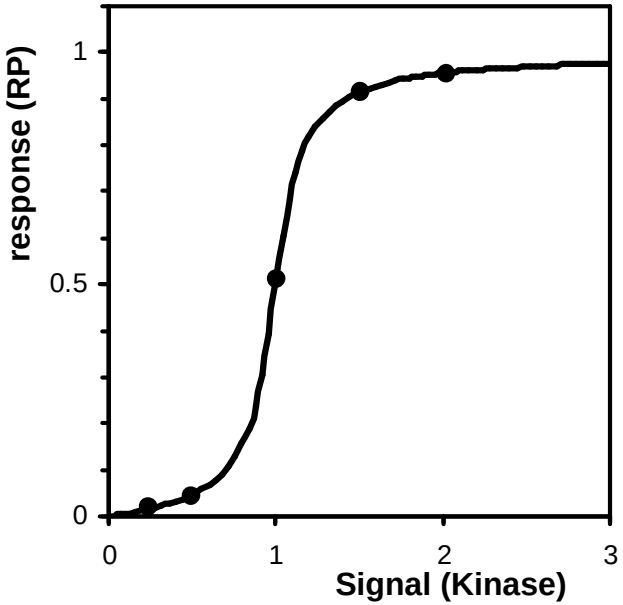
$$\frac{\mathrm{d}R}{\mathrm{d}t} = k_1 S - k_2 R, \quad R_{\mathrm{ss}} = \frac{k_1 S}{k_2}$$

Signal-Response Curve
Bifurcation diagram

Protein Phosphorylation



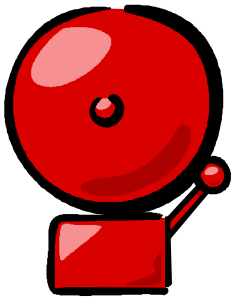




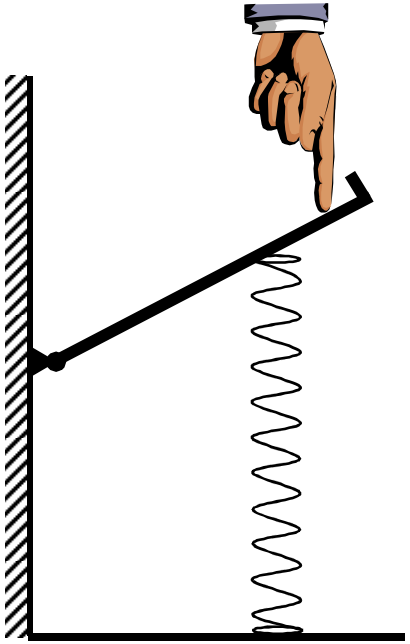
"Buzzer"

Goldbeter & Koshland, 1981

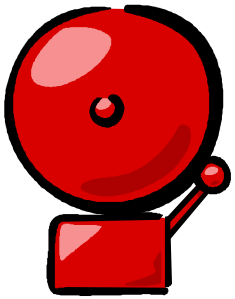
Switches



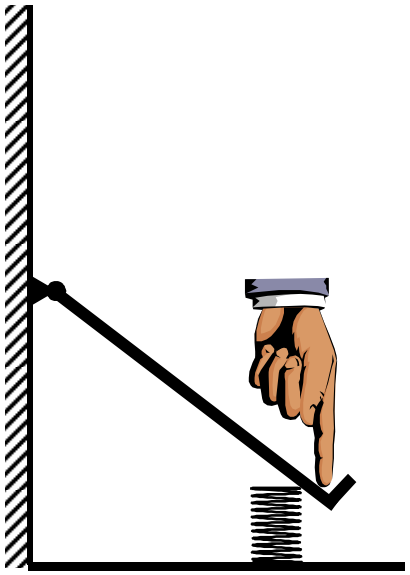
Buzzer



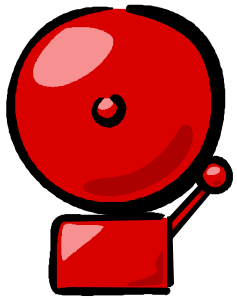
Switches



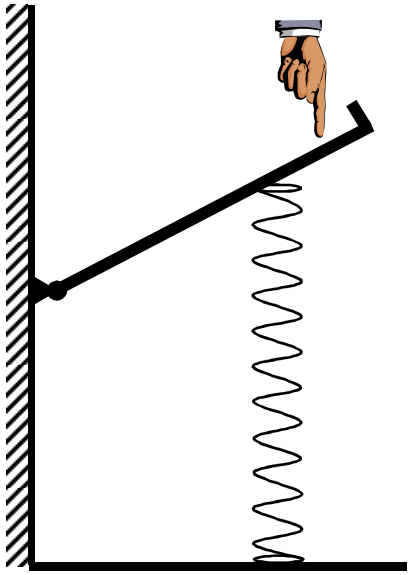
Buzzer

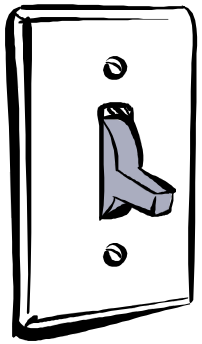


Switches

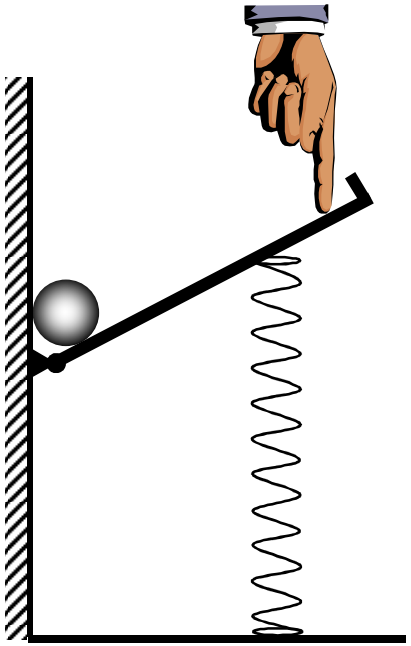


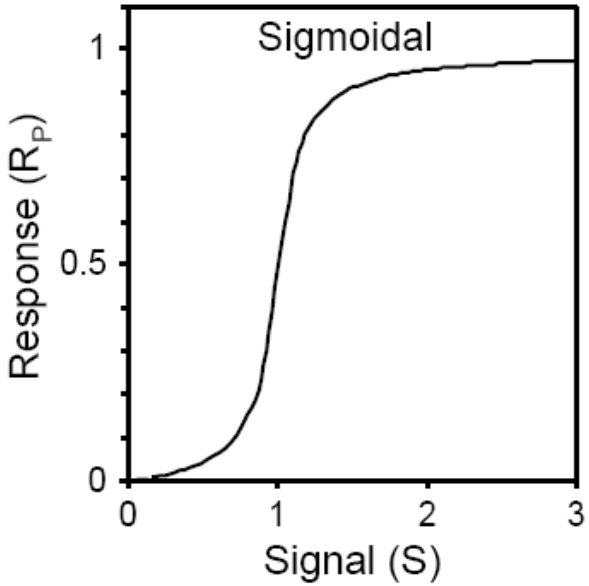
Buzzer



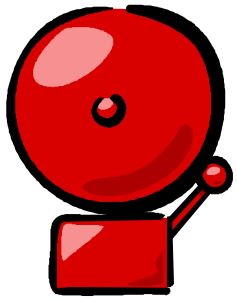


Toggle switch
One way switch

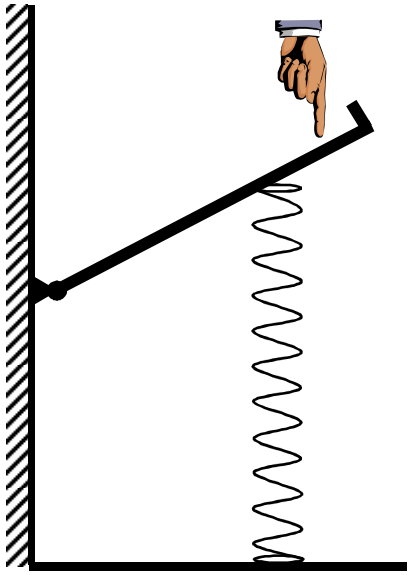


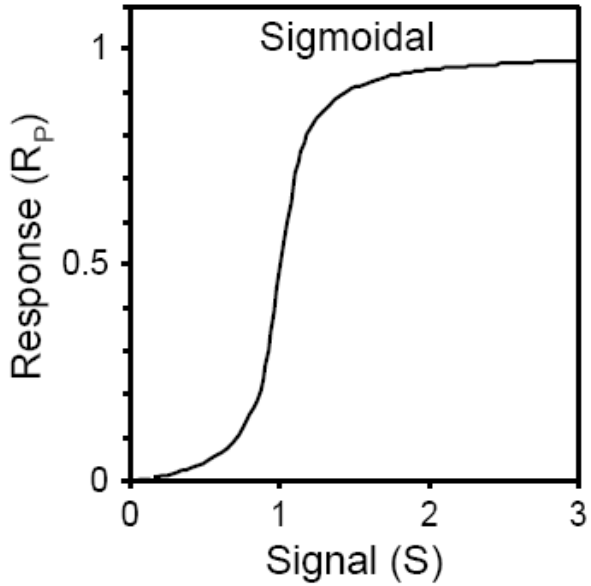


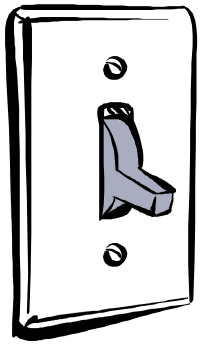
Switches



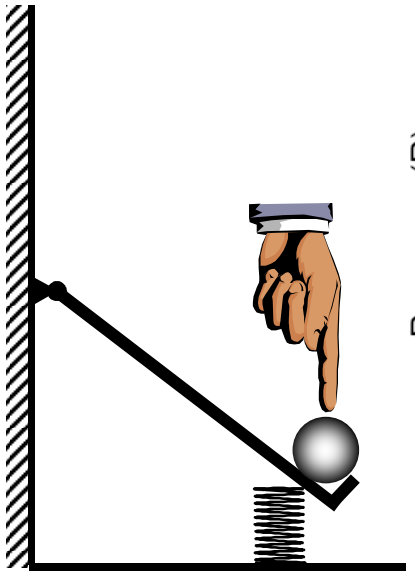
Buzzer



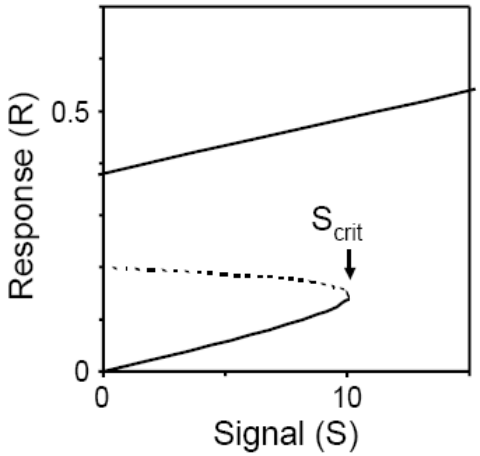




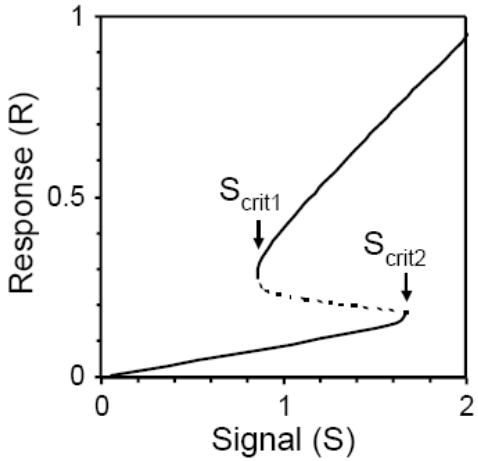
Toggle switch
One way switch



Irreversible switch

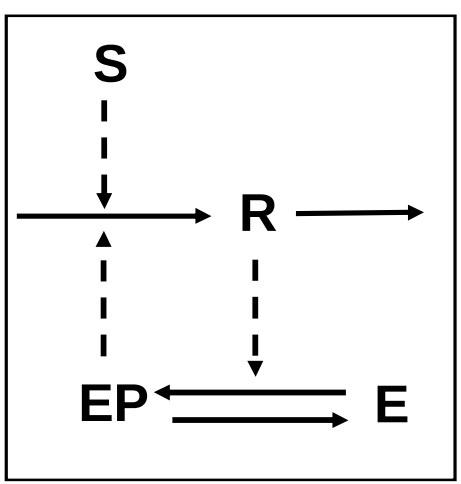


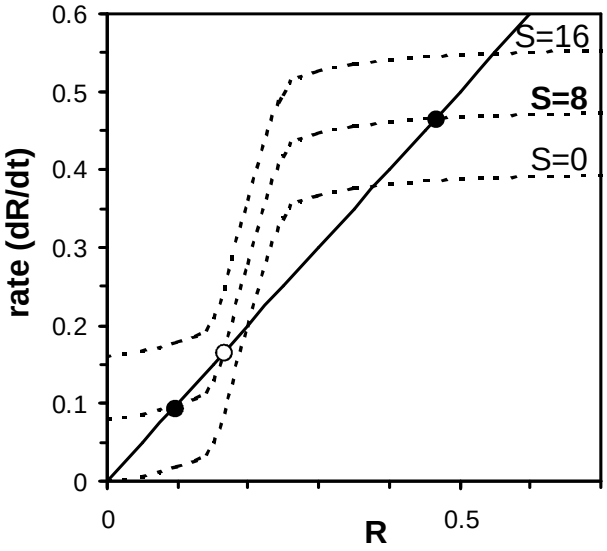
Reversible switch

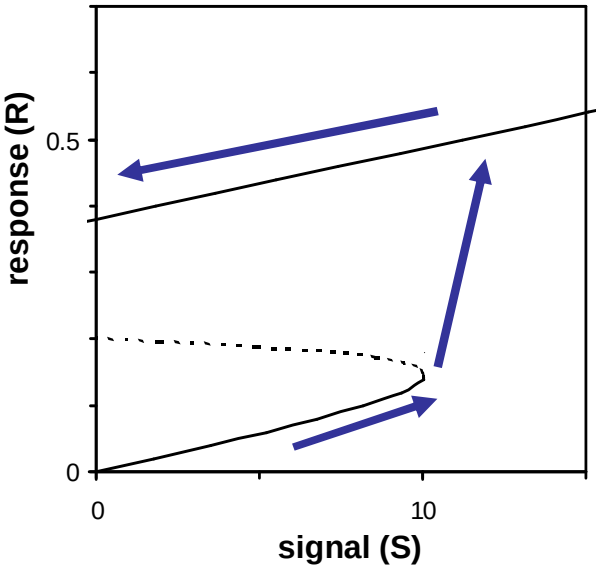


Positive Feedback

on synthesis



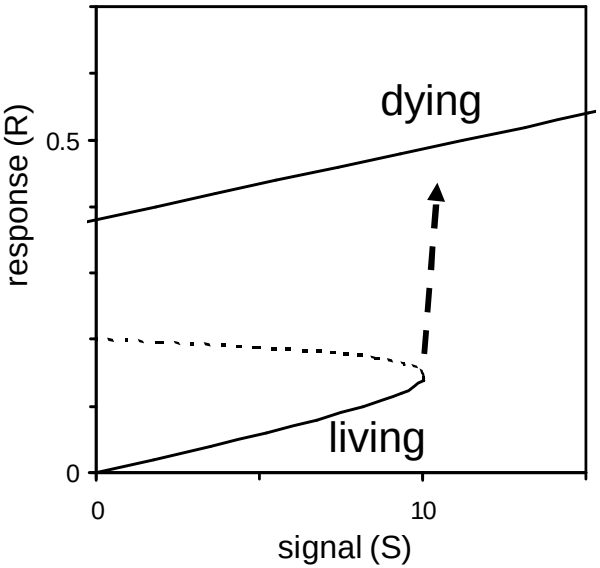


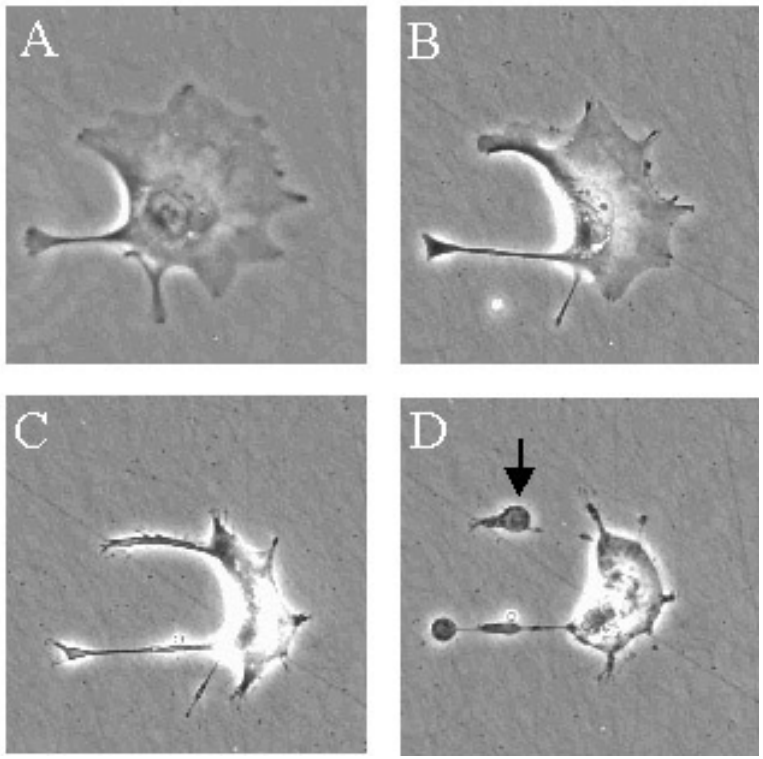


Bistability

Griffith, 1968

Example:

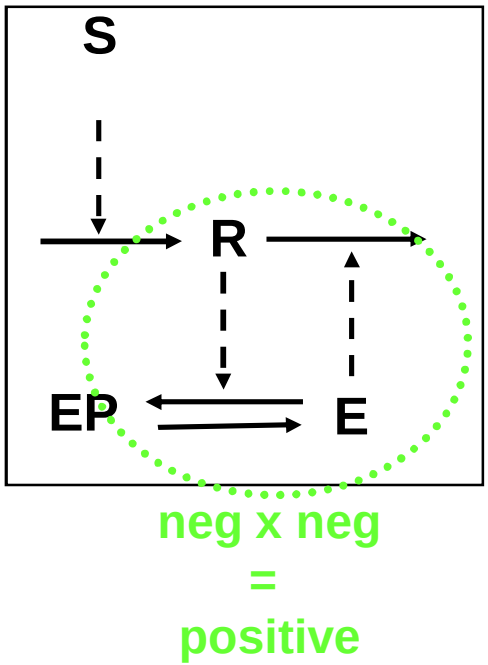


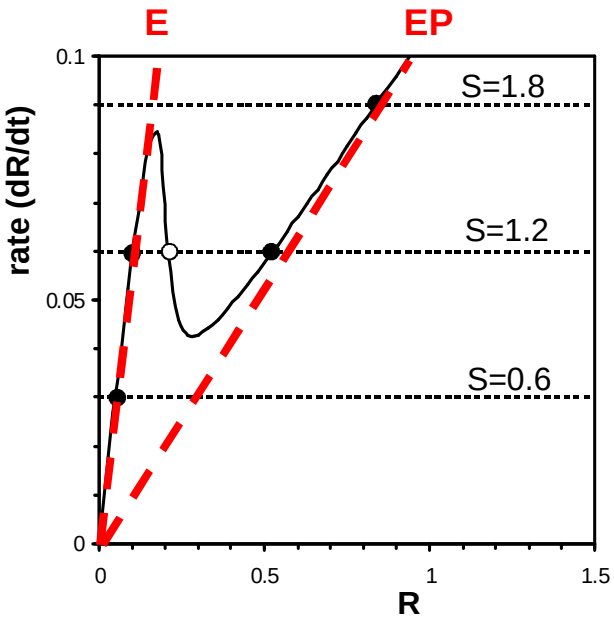


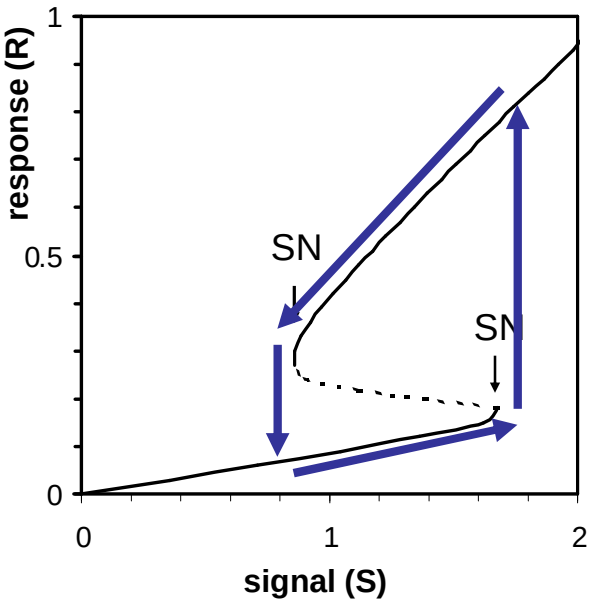
Apoptosis
(Programmed Cell Death)

Mutual Inhibition

on degradation

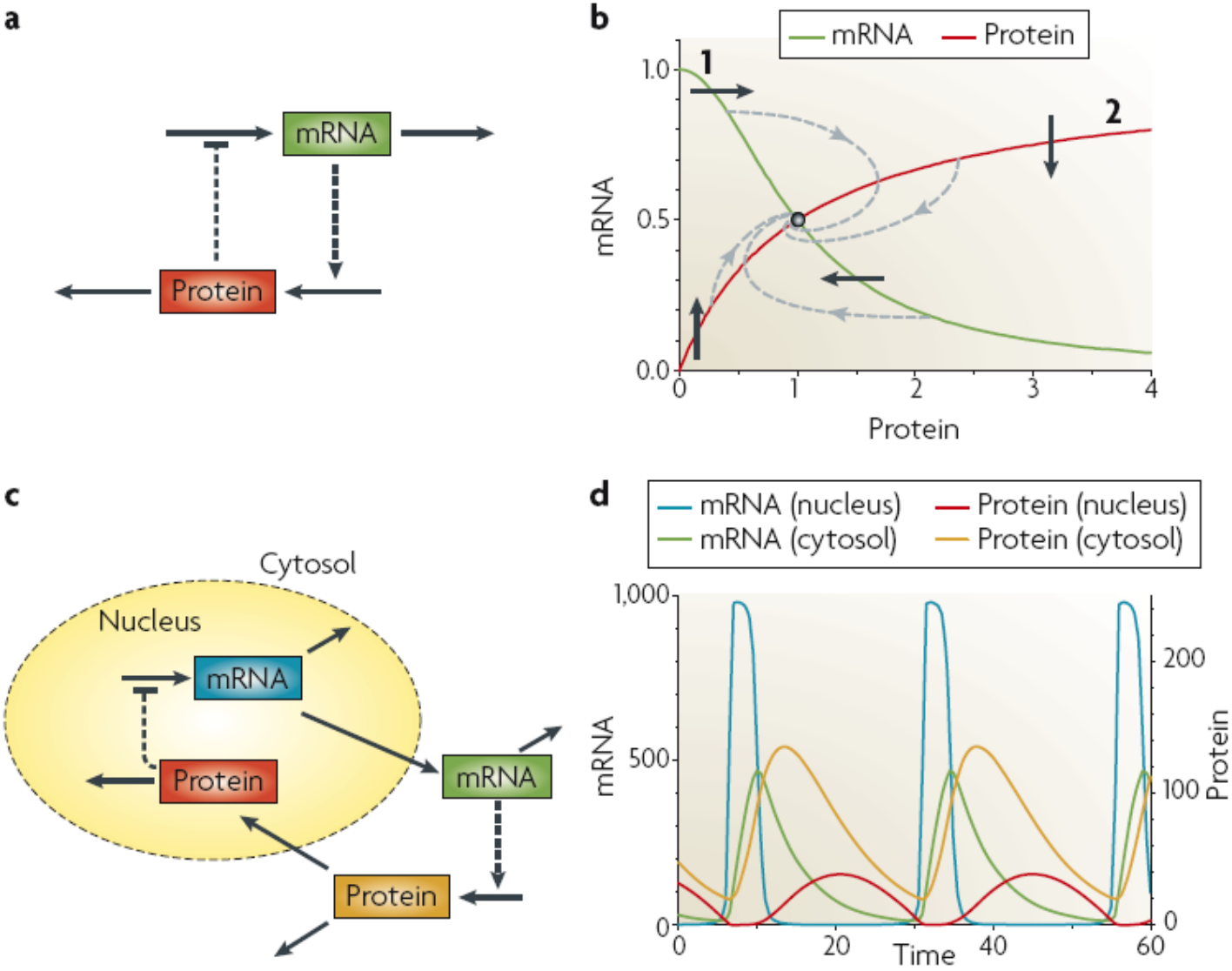




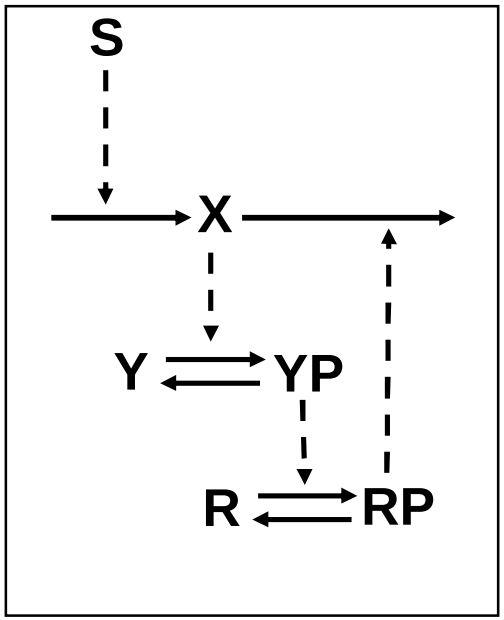


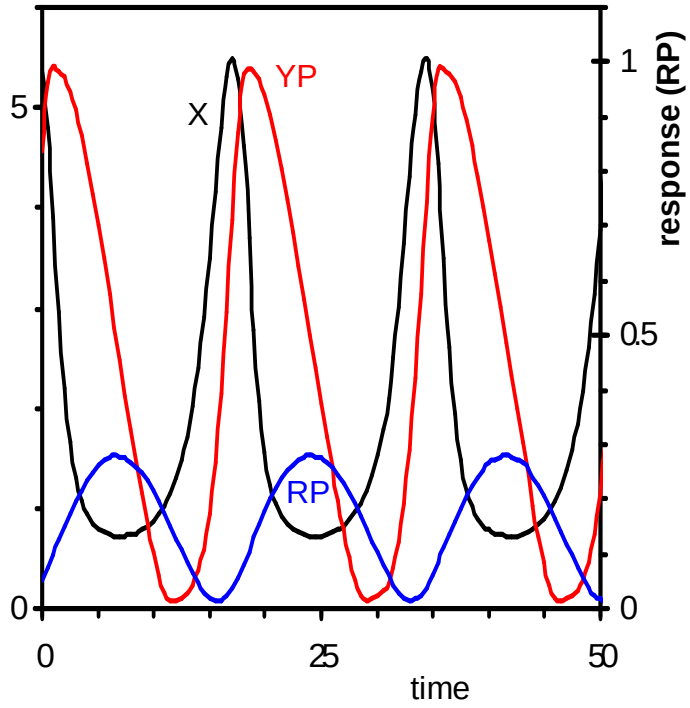
Bistability

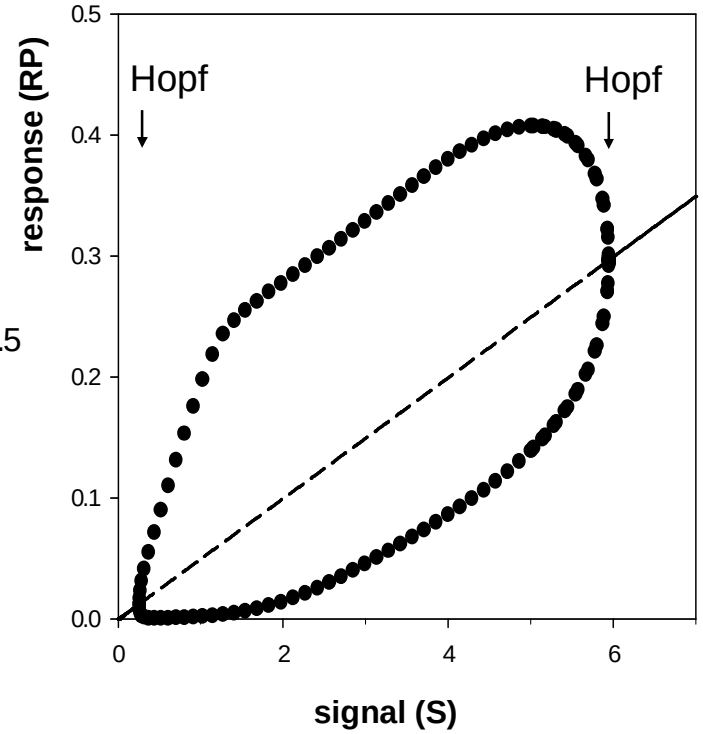
Negative Feedback Loop



Negative Feedback Loop

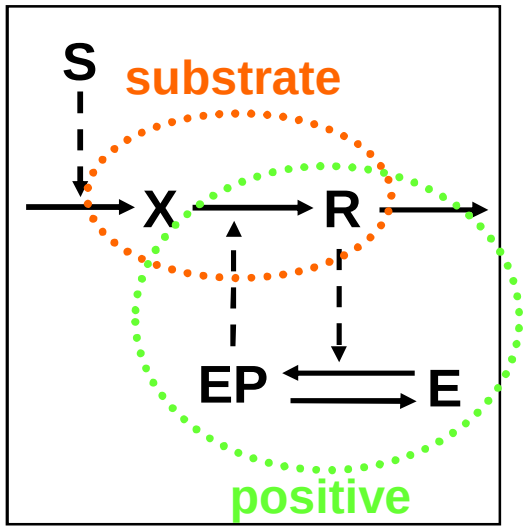


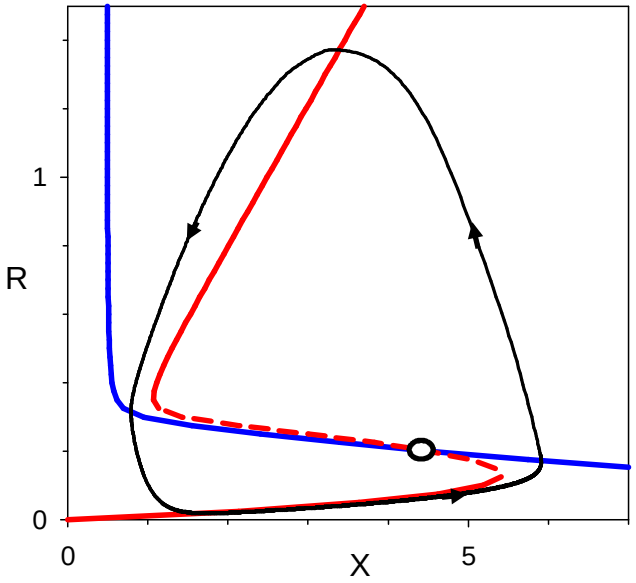


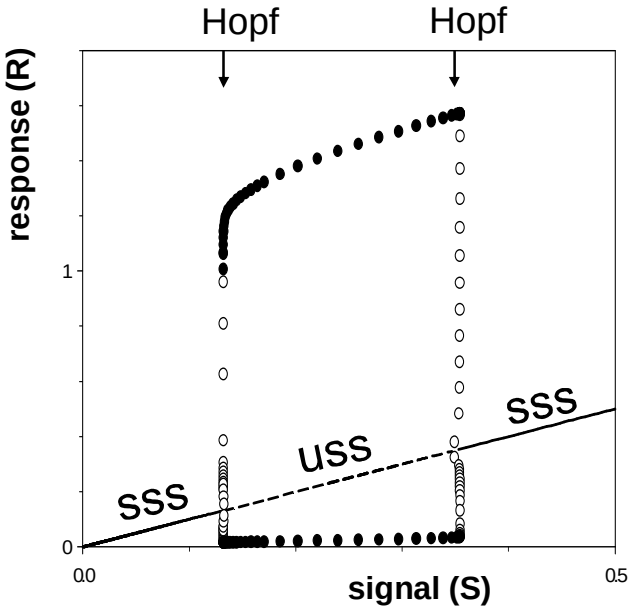


Goodwin, 1965

Positive Feedback & Substrate Depletion







Oscillation

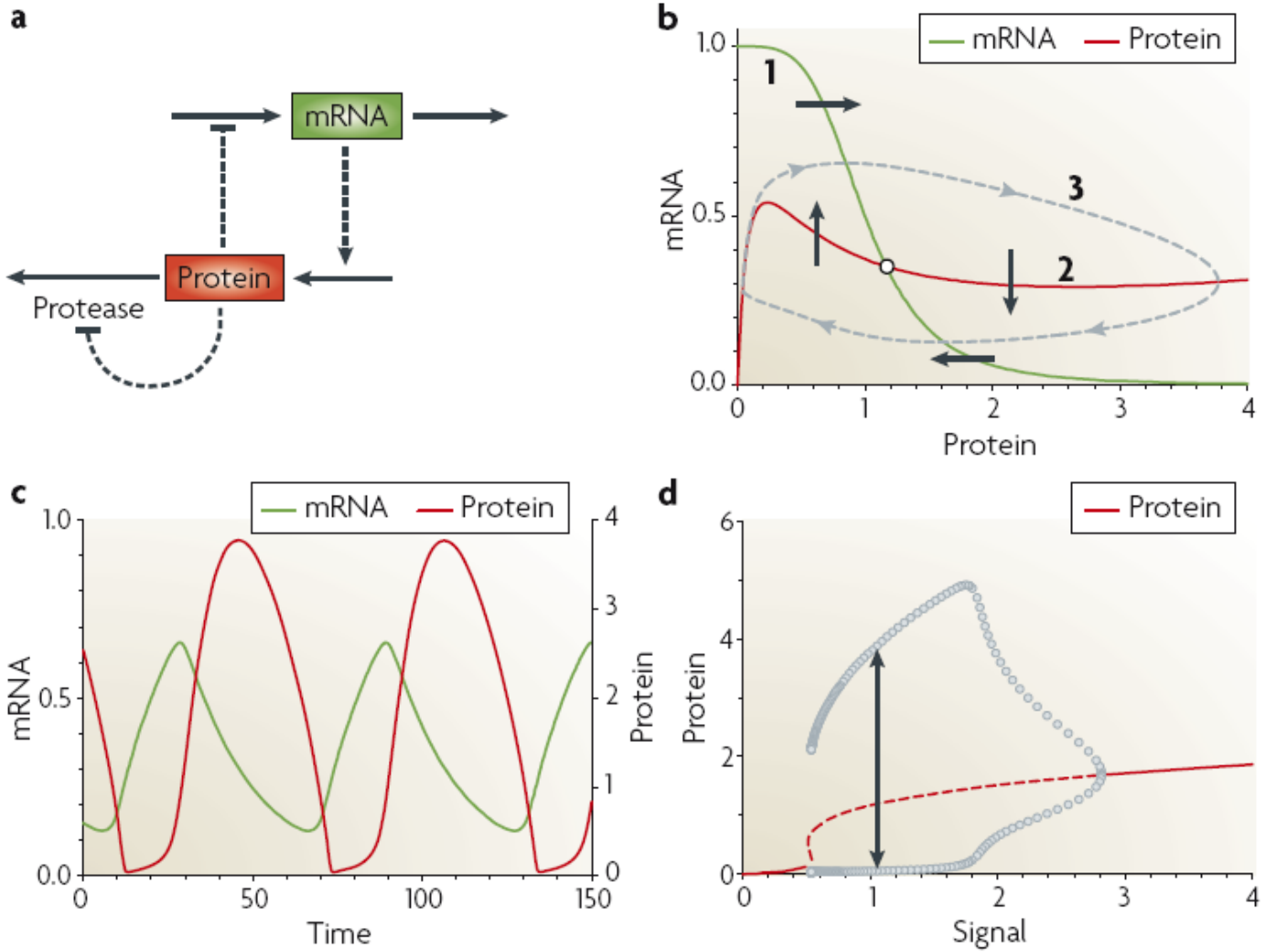
relaxation oscillation

Higgins, 1965; Selkov, 1968

"Blinker"

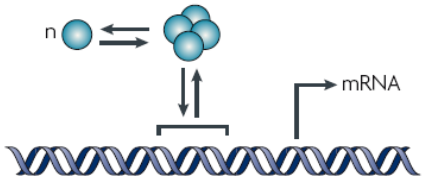
Glycolytic Oscillations

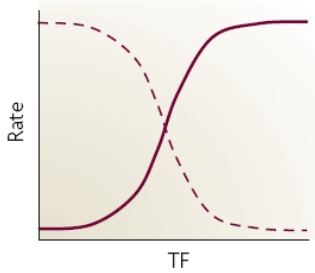
Combining positive and negative feedback loops



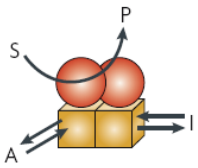
Sources of nonlinearity

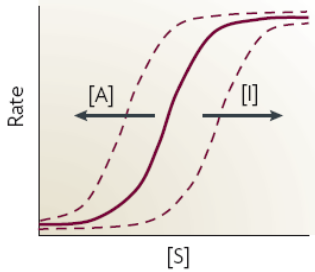
Oligomer binding



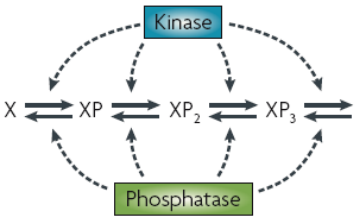


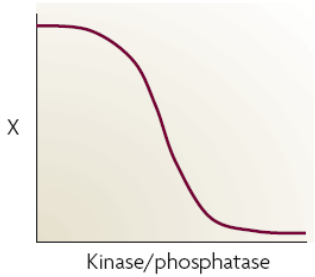
Cooperativity and allostery



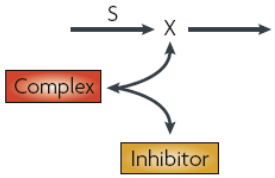


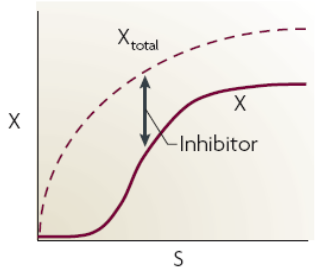
Multisite regulation



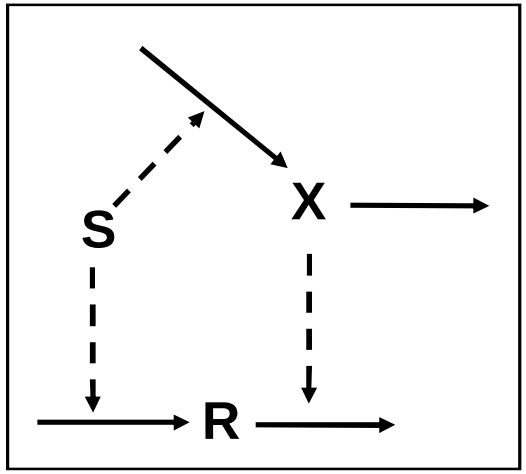


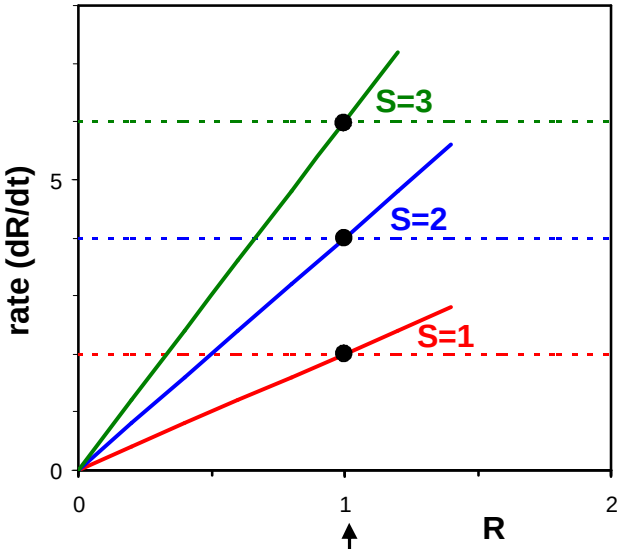
Stochiometric inhibition

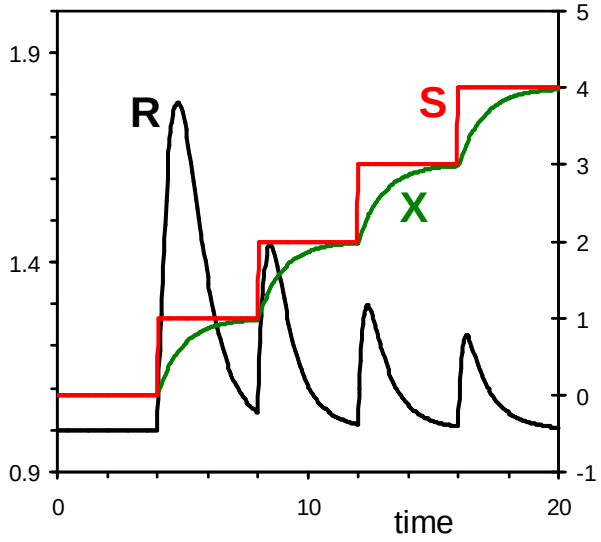




Sniffer







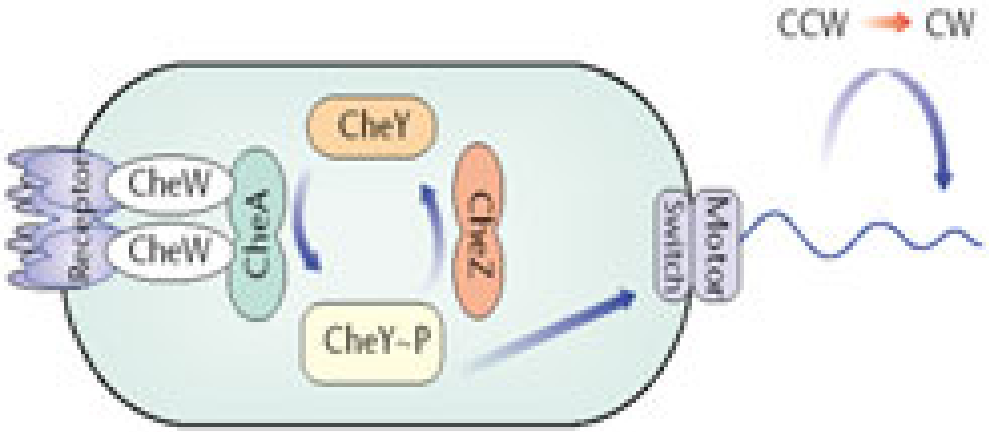
$$\frac{dR}{dt} = k_1 S - k_2 X R$$

$$\frac{dX}{dt} = k_3 S - k_4 X$$

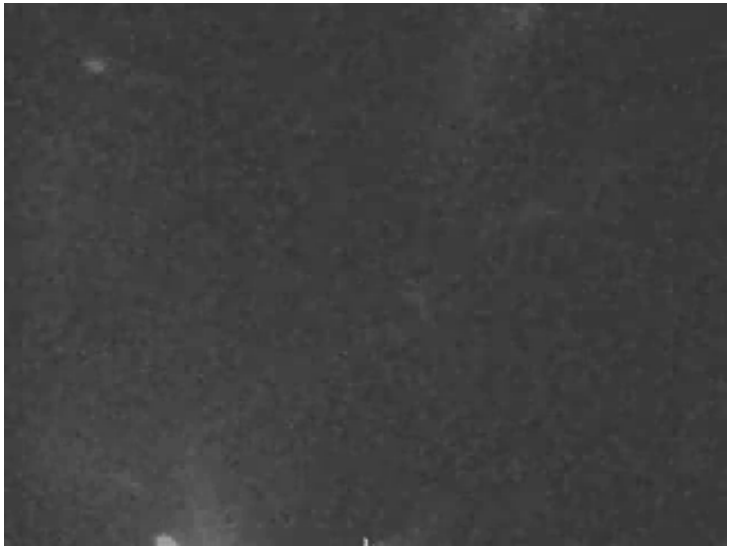
Response is independent of Signal

(Levchenko & Iglesias, 2002)

Example: Bacterial Chemotaxis



Barkai & Leibler, 1997
Goldbeter & Segel, 1986
Bray, Bourret & Simon, 1993



Two component motifs

total: $3^4 = 81$

With inhibitory self interactions:

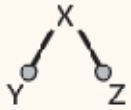
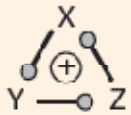
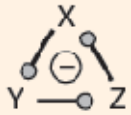
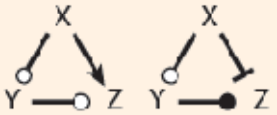
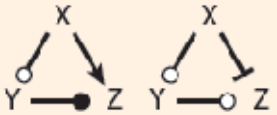
$3^2 = 9$ (6)

Motif	Sign pattern	Description
X Y	$\begin{pmatrix} - & 0 \\ 0 & - \end{pmatrix}$	Null
X → Y	$\begin{pmatrix} - & 0 \\ + & - \end{pmatrix}$	Transducer
X ⊣ Y	$\begin{pmatrix} - & 0 \\ - & - \end{pmatrix}$	Inverter
X ⇄ Y	$\begin{pmatrix} - & - \\ + & - \end{pmatrix}$	Negative feedback
X ⇄ Y	$\begin{pmatrix} - & + \\ + & - \end{pmatrix}$	Positive feedback
X ⊣⊣ Y	$\begin{pmatrix} - & - \\ - & - \end{pmatrix}$	Double-negative feedback

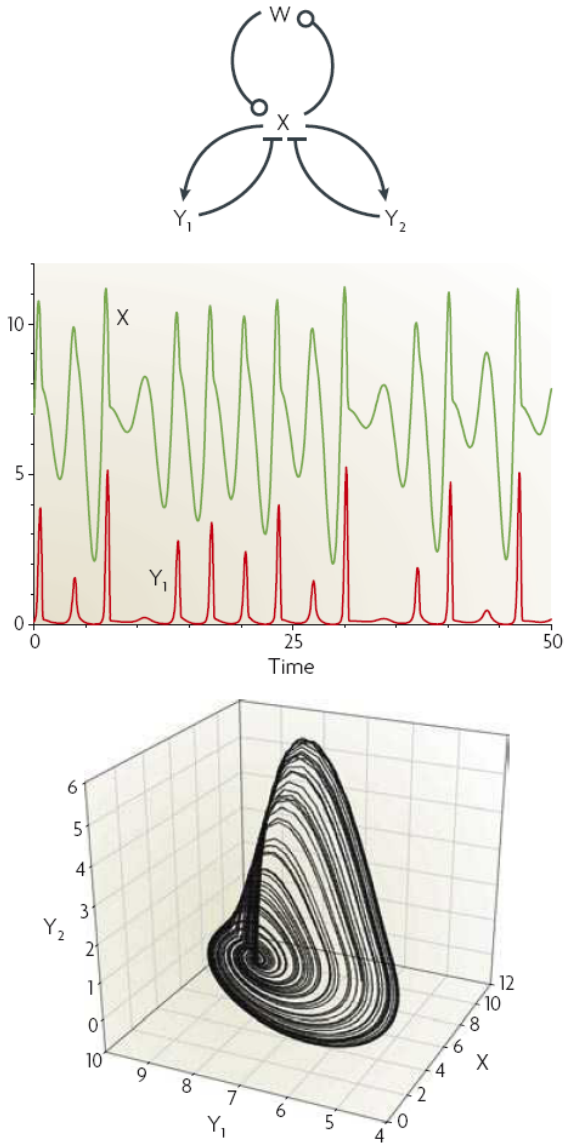
Three component motifs

total : $3^9 = 19683$

$3^6 = 729$ (138)

Motif	Description	Functions
X — Y — Z	Signal transduction	Threshold, inversion, ...
	Branch	
	Logic gate	AND, OR, ...
	Positive FBL	MSS
	Negative FBL	OSC
	Coherent FFL	Noise suppression
	Incoherent FFL	Adaptation, cock & fire

Chaotic behavior in a three component network



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John J. Tyson[1] and Béla Novák[2]

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Béla Novak

John J. Tyson

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Béla Novák and John J. Tyson†*

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Analysis of a Generic Model of Eukaryotic Cell-Cycle Regulation

Attila Csikász-Nagy,[*†] Dorjsuren Battogtokh,[*] Katherine C. Chen,[*] Béla Novák,[†] and John J. Tyson[*]

Recommended readings

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Vol. 93, pp. 10078–10083, September 1996
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the FEBS Journal

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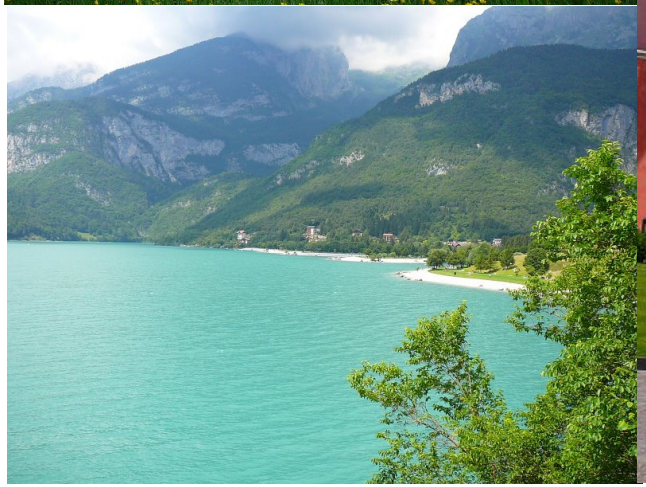
Centre for Computational and Systems Biology



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