Review

- Cell signaling network
- Several examples of cell signaling networks
- Dynamics of cell signaling networks：
  Oscillation， bistability and adaptation.
- Simulation-related softwares

2.2.1 Simulation tools

- Oscill8

Oscill8 is a suite of tools for analyzing dynamical systems which concentrates on understanding how the dynamical behavior depends on the parameters using bifurcation theory and reaction network theory.

http://sourceforge.jp/projects/sfnet_oscill8/

ODE file

```
# test
x'=a1*(1-x)-b1*x*(v*y)^r1/(k1+(v*y)^r1)
y'=a2*(1-y)-b2*y*x^r2/(k2+x^r2)
par v=0, a1=1, a2=1, b1=200
par b2=10, k1=30, k2=1, r1=4, r2=4
init x=0.1, y=0.1
done
```

Some skills in Oscill8

Example: let S=1 from t=500 to t=1000

- Global variable

global 1 t-500 {S=1}

global 1 t-1000 {S=0}

- Heaviside function

*S=s0*heav(t-500)*heav(1000-t)*

- Curve of S

aux S=S

Graphing software

Origin 8

1) One loop

$$\frac{dOUT}{dt} = k_{out\_on} * A * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

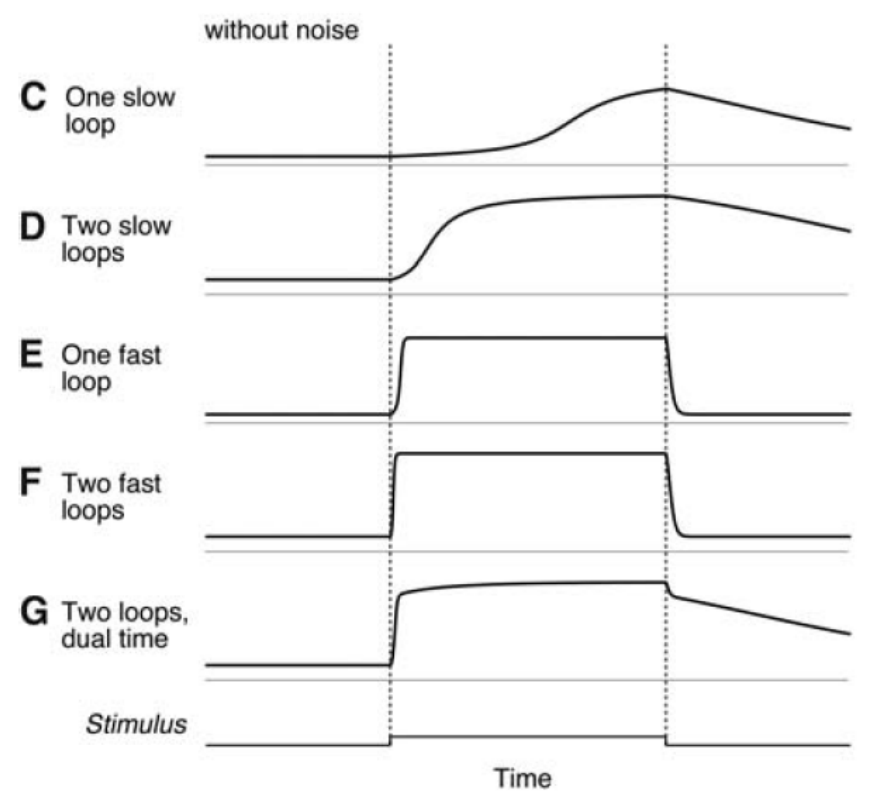
$$\frac{dA}{dt} = \left[stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}\right] * \tau_A$$

2) Two loops

$$\frac{dOUT}{dt} = k_{out\_on} * (A + B) * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

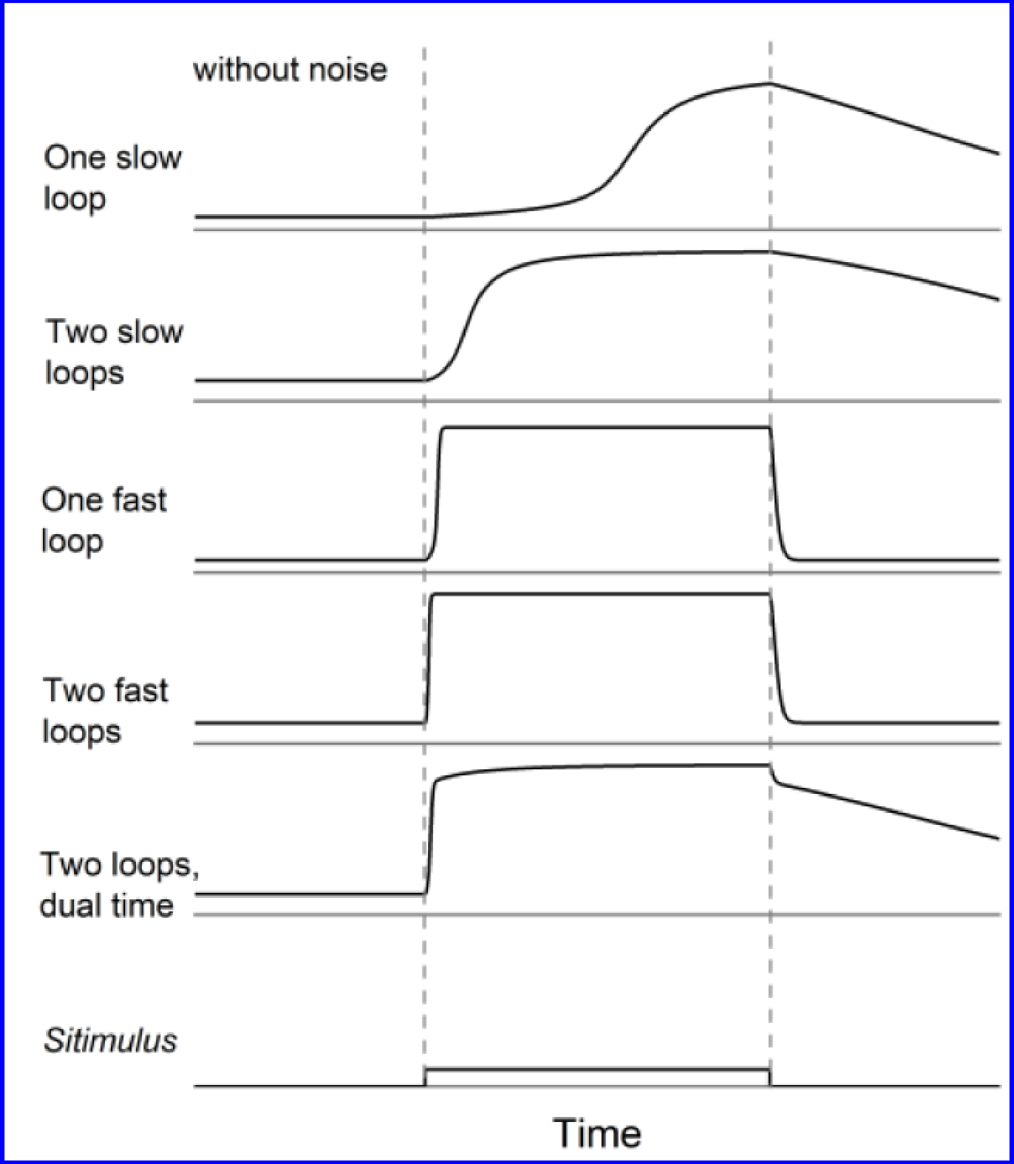
$$\frac{dA}{dt} = \left[stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}\right] * \tau_A$$

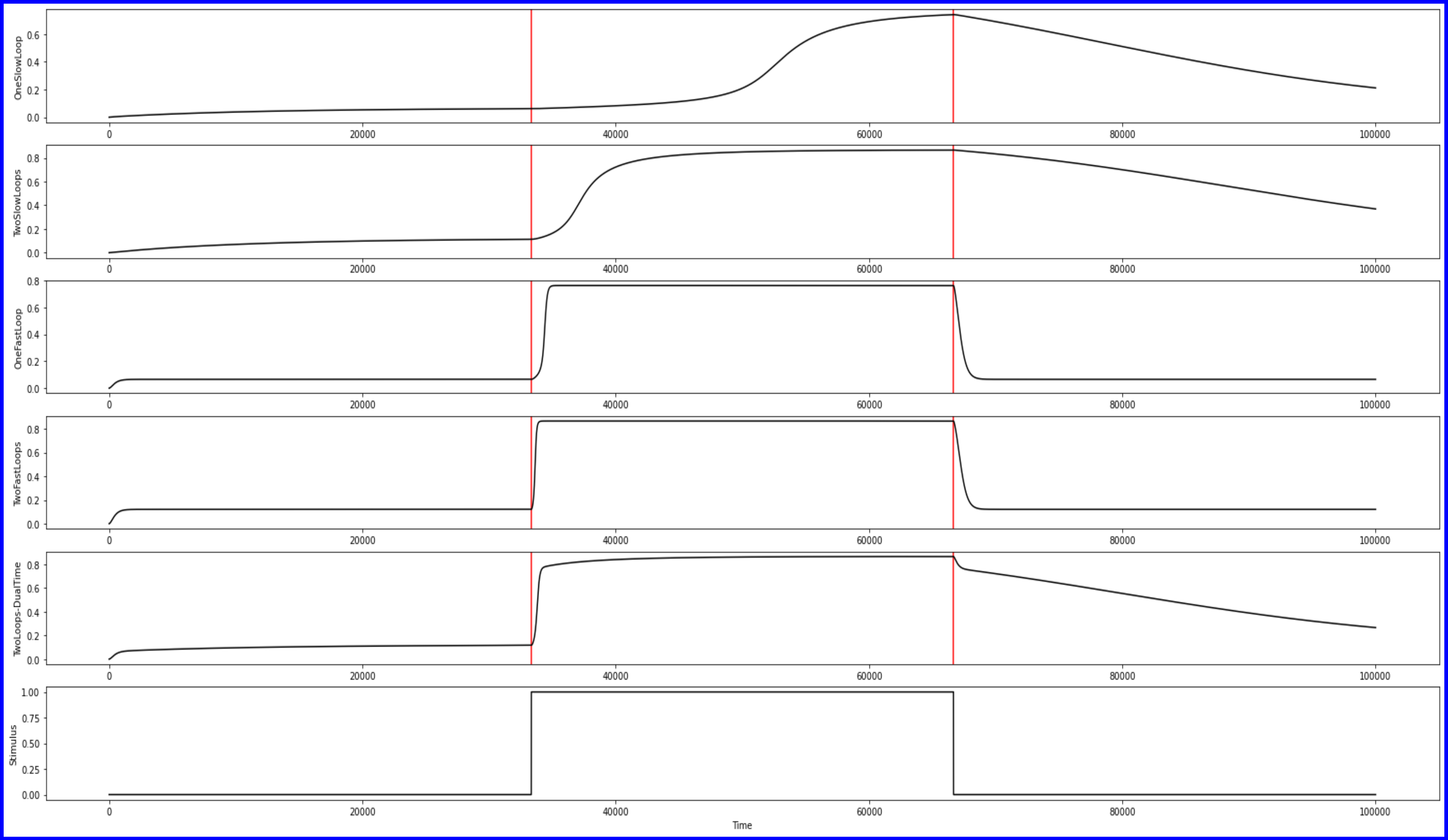
$$\frac{dB}{dt} = \left[stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - B) - B + k_{min}\right] * \tau_B$$



$k_{out\_on} = 2$, $k_{out\_off} = 0.3$, $k_{out\_min} = 0.001$, $k_{min} = 0.01$, $n = 3$, $ec_{50} = 0.35$. For a fast loop, $\tau = 0.5$. For a slow loop, $\tau = 0.008$. The equations were solved numerically with Matlab 7.0.

Comments on Assignment 1




OneSlowLoop
TwoSlowLoops
OneFastLoop
TwoFastLoops
TwoLoops-DualTime
Stimulus
0
20000
40000
60000
80000
100000
Time

Some skills in Oscill8

Example: let S=1 from t=500 to t=1000

- Global variable

global 1 t-500 {S=1}

global 1 t-1000 {S=0}

- Heaviside function

*S=s0*heav(t-500)*heav(1000-t)*

Heaviside function

- Curve of S

aux S=S

2.2.2 Bifurcation theory（分岔）

1. What is bifurcation?

Most commonly applied to the mathematical study of dynamical systems, a **bifurcation** occurs when a small smooth change made to the parameter values (the bifurcation parameters) of a system causes a sudden 'qualitative' or topological change in its behavior. The name "bifurcation" was first introduced by Henri Poincaré in 1885 in the first paper in mathematics showing such a behavior.

2. Fixed points (定点或不动点)

x* is a fixed pont or equilibrium for

$$\frac{dx}{dt} = f(\mathrm{x})$$

satisfying $f(\mathrm{x}^*) = 0$

Linear stability analysis

Jacobian Matrix

$\dot{x}_i = f_i(x_j),\ i,j = 1,2,\dots\dots n \qquad x_i(t) = x_{i0} + \xi_i(t)$

$$\dot{\xi}_i = \sum_{j=1}^{n} a_{ij}\xi_j \quad \text{or} \quad \dot{\boldsymbol{\xi}} = \boldsymbol{A\xi} \qquad a_{ij} = \left(\frac{\partial f_i}{\partial x_j}\right)_0 \qquad A = \begin{vmatrix} a_{11} & a_{12}\dots & a_{1n} \\ a_{21} & a_{22}\dots & a_{2n} \\ \dots\dots & & \dots\dots \\ a_{n1} & a_{n2}\dots & a_{nn} \end{vmatrix}$$

Solutions of LSA and stability (n=2)

$$\dot{\xi}_1 = a_{11}\xi_1 + a_{12}\xi_2$$
$$\dot{\xi}_2 = a_{21}\xi_1 + a_{22}\xi_2$$

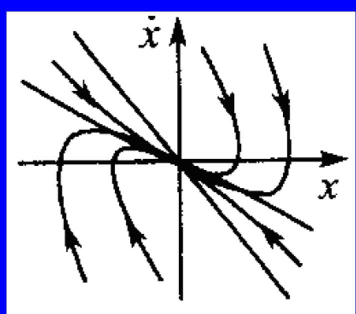
$$\begin{vmatrix} a_{11}-\lambda & a_{12} \\ a_{21} & a_{22}-\lambda \end{vmatrix} = 0 \qquad \lambda_1 = \frac{T+\sqrt{T^2-4\Delta}}{2},\ \lambda_2 = \frac{T-\sqrt{T^2-4\Delta}}{2}$$

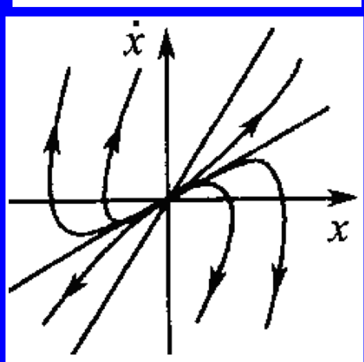
If the real parts of the eigenvalues are both negative, stable

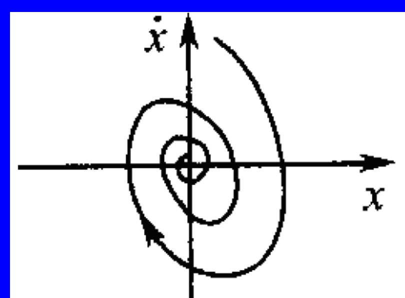
If one of them is positive, unstable; If one is zero, the other is negative. Critical case

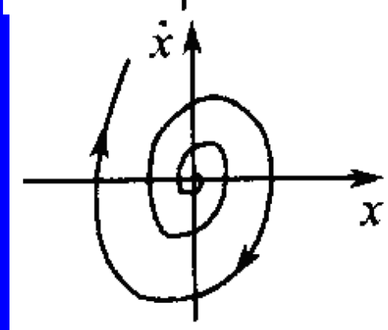
3. Types of fixed points

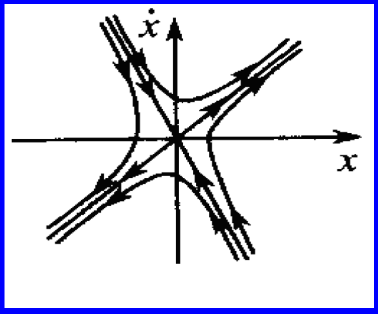
- Node $\Delta > 0,\ T^2 - 4\Delta \geq 0$ T<0, stable; T>0, unstable.
- Focus $\Delta > 0,\ T^2 - 4\Delta < 0$ T<0, stable; T>0, unstable.
- Saddle $\Delta < 0$ stable in only one direction
- Center T= 0, $\Delta > 0$ Critical case.

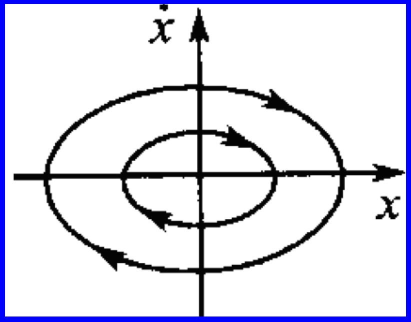


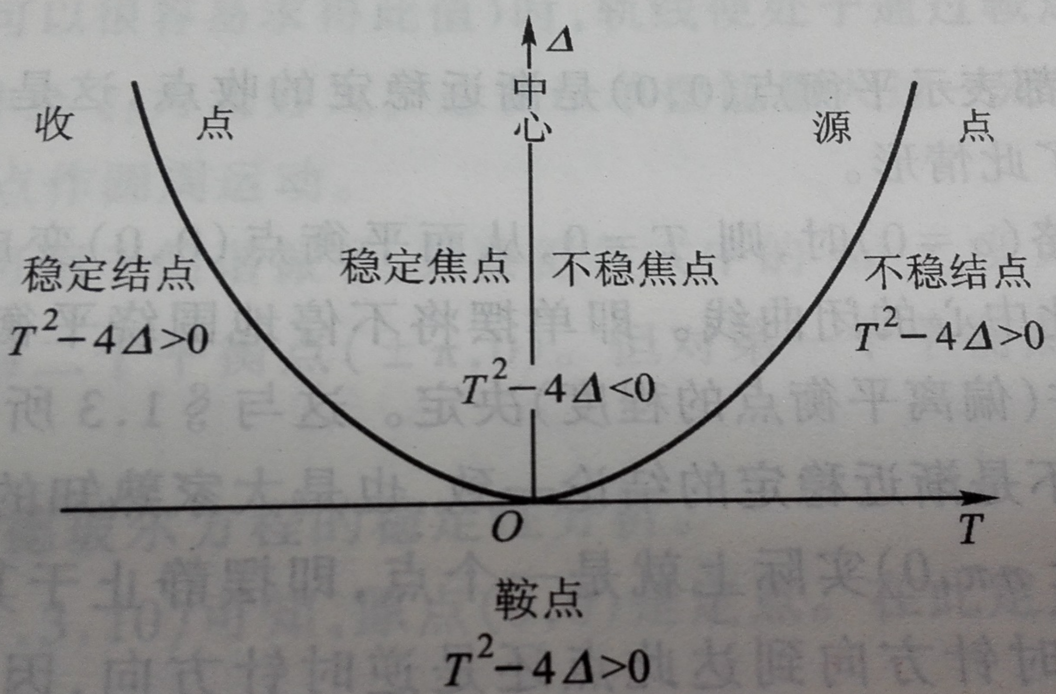












Δ
中心
收 点
源 点
稳定结点
$T^2-4\Delta>0$
稳定焦点
不稳焦点
不稳结点
$T^2-4\Delta>0$
$T^2-4\Delta<0$
O
T
鞍点
$T^2-4\Delta>0$

图 1.4.6 定点的分区

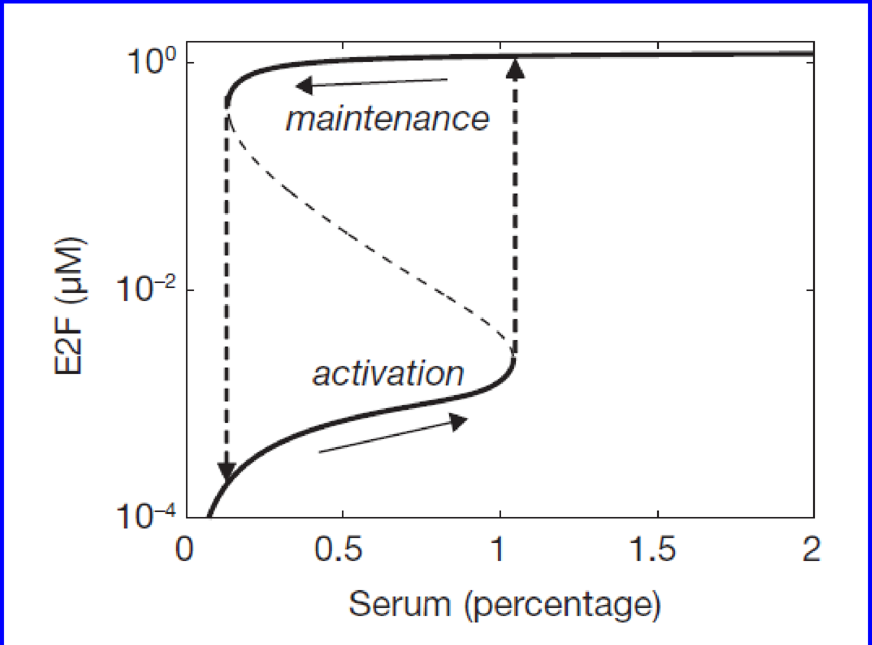
4. Types of bifurcations

- Saddle-node bifurcation
- Hopf bifurcation
- Transcritical bifurcation
- Pitchfork bifurcation
- Period doubling bifurcation

Saddle-node bifurcation(鞍结分岔)

- A **saddle-node bifurcation** is a local bifurcation in which two fixed points of a dynamical system collide and annihilate each other.

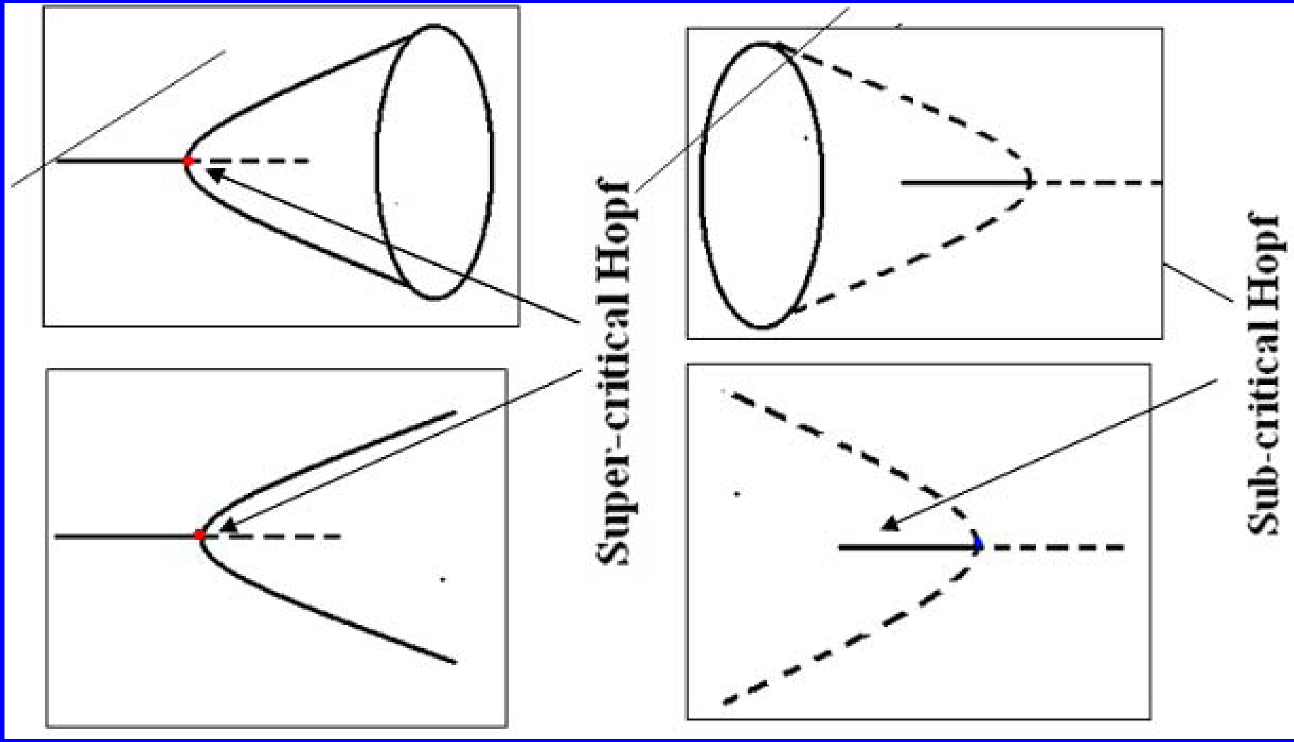
Stable node point and unstable saddle point



Hopf bifurcation

- In the mathematical theory of bifurcations, a Hopf or Poincaré–Andronov–Hopf bifurcation, named after Henri Poincaré, Eberhard Hopf, and Aleksandr Andronov, is a local bifurcation in which a fixed point of a dynamical system loses stability as a pair of complex conjugate eigenvalues of the linearization around the fixed point cross the imaginary axis of the complex plane. Under reasonably generic assumptions about the dynamical system, we can expect to see a small-amplitude limit cycle branching from the fixed point.

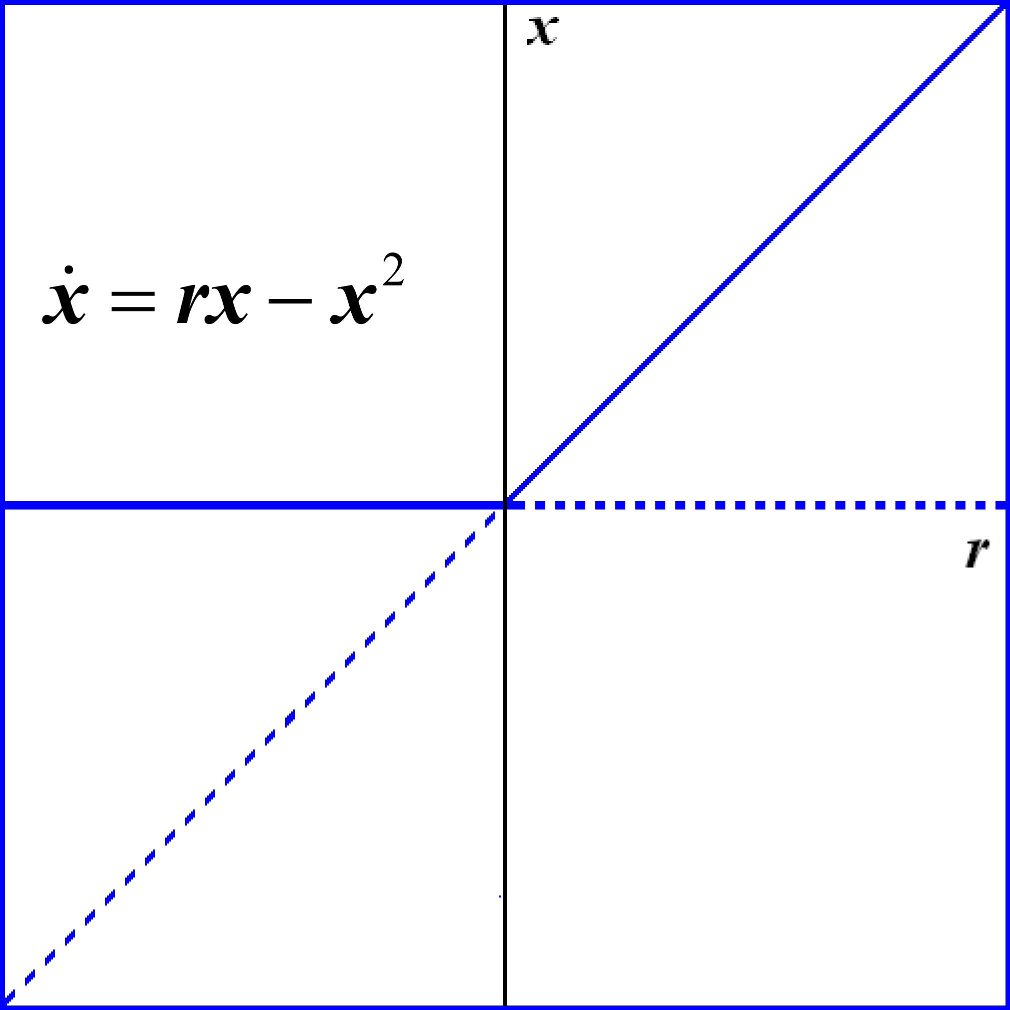
Supercritical and subcritical Hopf Bifurcation



Stable limit cycles at the opposite side of the stable fixed points

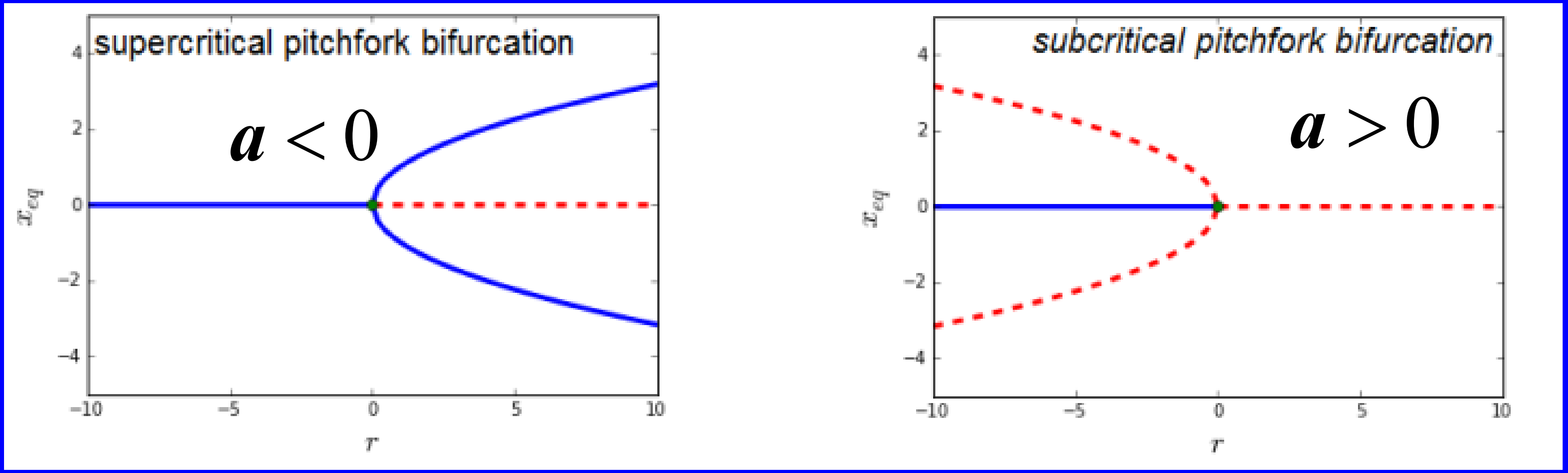
Unstable limit cycles at the same side of the stable fixed points

Transcritical bifurcation

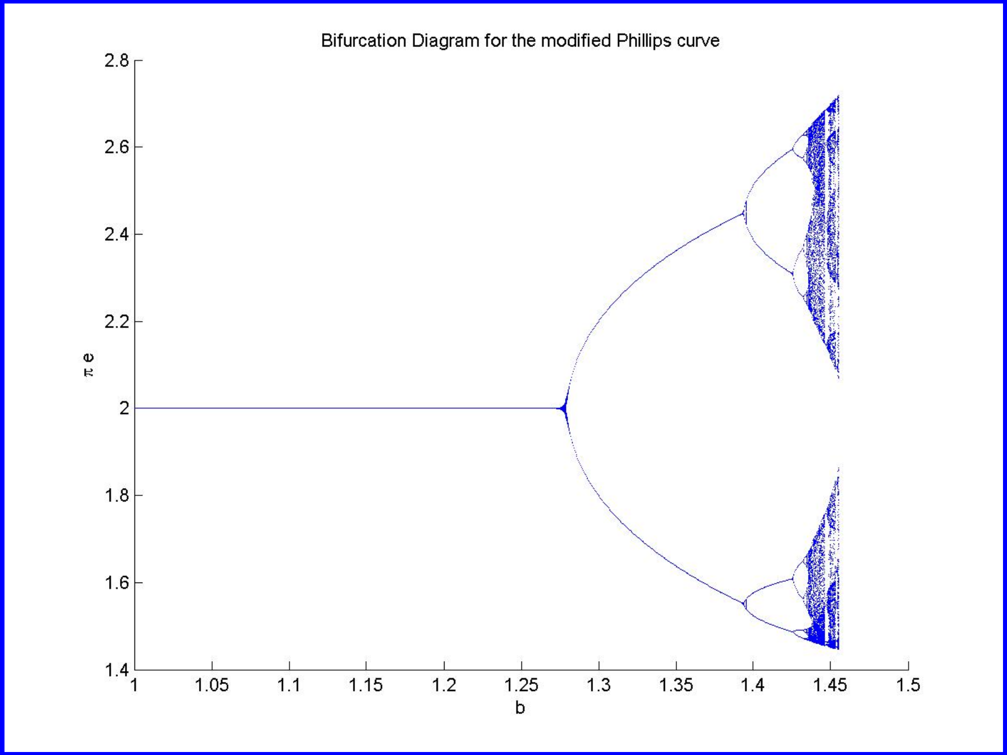


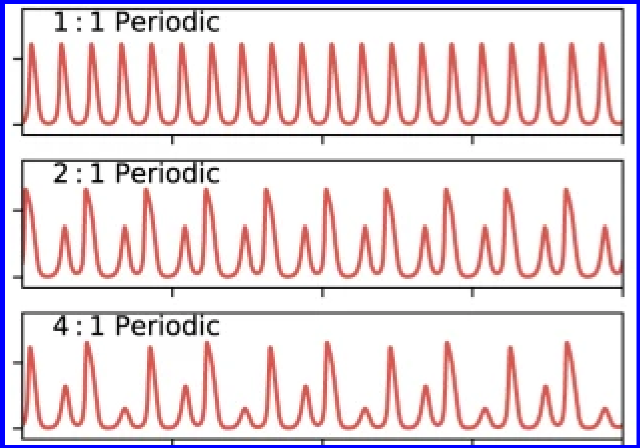
Pitchfork bifurcation

$$\boxed{\dot{x} = rx + ax^3}$$



Period doubling bifurcation

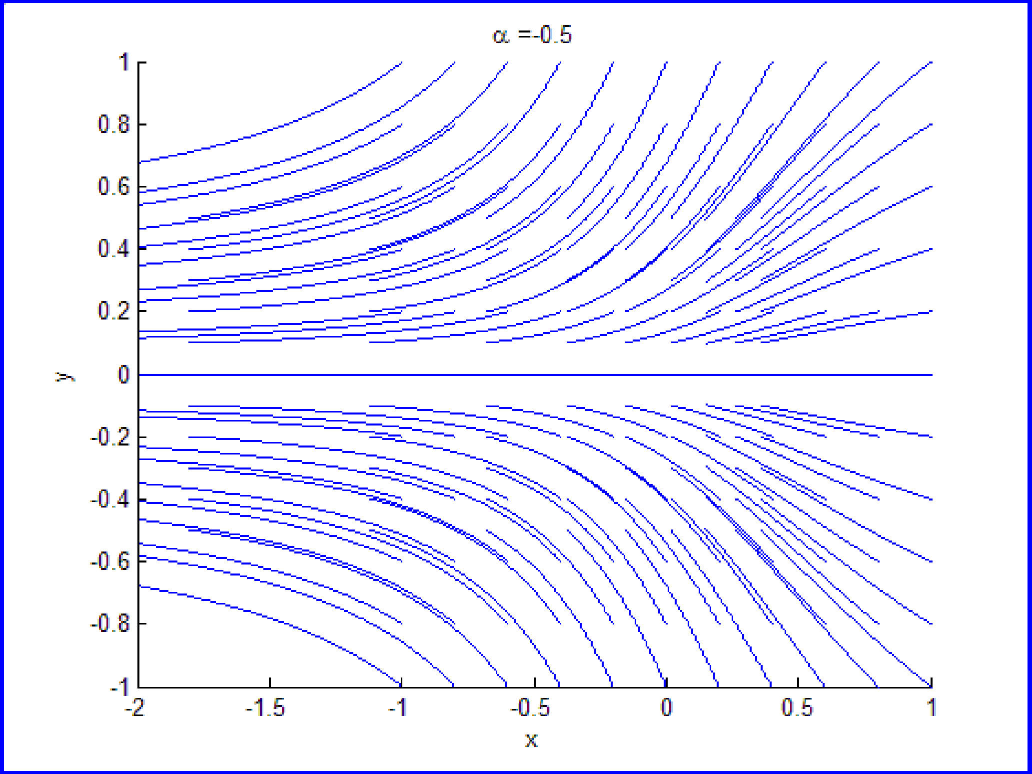




Phase portrait

phase portrait of SN bifurcation

$$\frac{dx}{dt} = \alpha - x^2$$
$$\frac{dy}{dt} = -y.$$

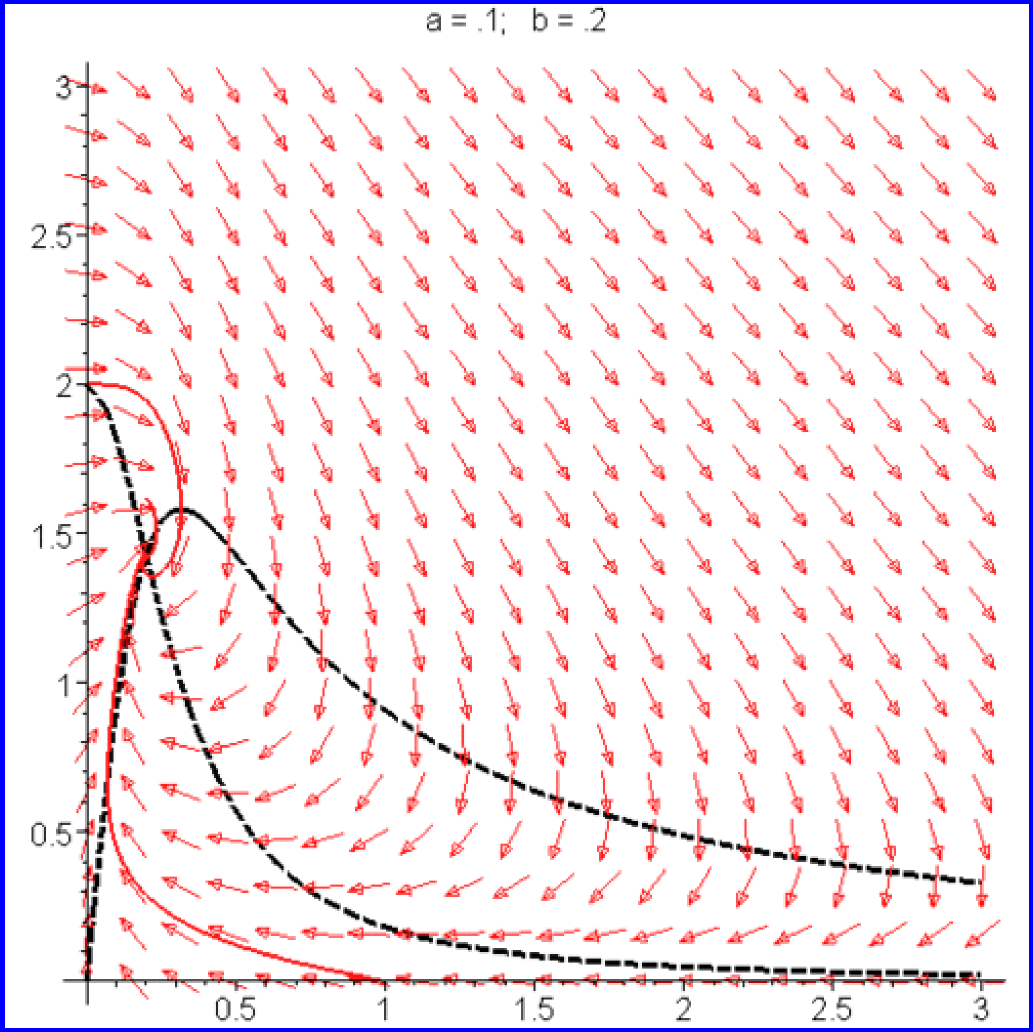


Examples

phase portrait of an oscillator

$$\frac{dx}{dt} = -x + ay + x^2 y$$

$$\frac{dy}{dt} = b - ay - x^2 y$$



2.3 Ultrasensitivity and dynamics of biological network

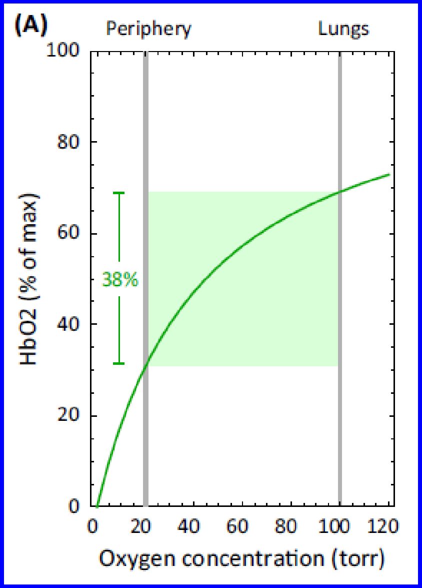
2.3.1 Michaelian responses and zero-order ultrasensitivity

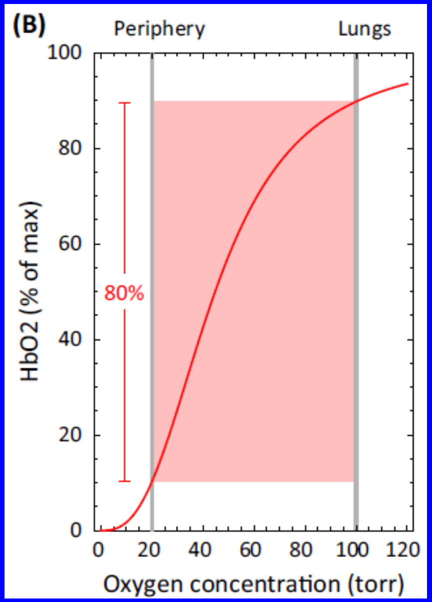
- a. Hyperbolic or Michaelian signal-response

$$\frac{dXP}{dt} = k_1 kinase(X_{tot} - XP) - k_{-1}\, p'ase \cdot XP$$

$$Output = \frac{Input}{K + Input}$$

The binding of oxygen to hemoglobin

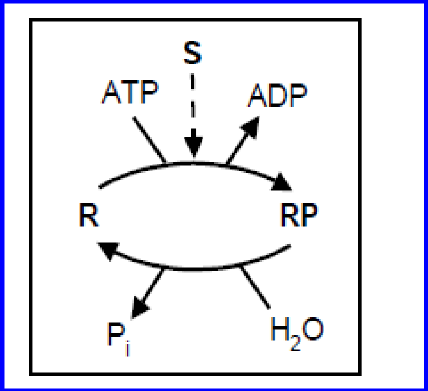




Ferrell Jr, J. E. and S. H. Ha (2014). Trends in Biochemical Sciences **39**(10): 496-503.

Derivation

Reaction:



Mass action:

$$\frac{dR_P}{dt} = k_1 S(R_T - R_P) - k_2 R_P$$

where $R_T = R_P + R$

Steady states:

$$R_{P,ss} = \frac{R_T S}{(k_2/k_1) + S}.$$

b. Ultrasensitivity

- An ultrasensitive response is often (though not always) sigmoidal – flat at high and low inputs and steep in between – and often the curve is well-approximated by the Hill equation.

Some examples of ultrasensitivity

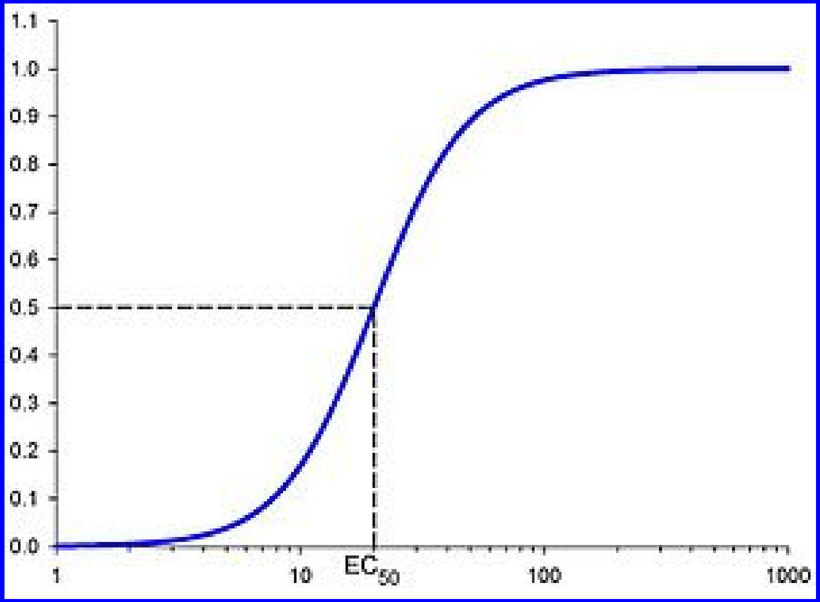
Stimulus	Response	Effective Hill exponent	Experimental system	Refs
Acetylcholine	Nicotinic cholinergic receptor conductance	1.3	Chicken neuronal homomeric $\alpha 7$ receptors	[23]
Delta (in trans only)	Notch production	1.7	CHO cells	[24]
Mos	MEK1	1.7	*Xenopus laevis* oocyte extracts	[25]
Phosphorylase kinase/phosphatase	Glycogen phosphorylase	2	Reconstituted mammalian muscle enzymes	[21]
RsbQP	σ^B	2.1	*Bacillus subtilis*	[26]
AICAR	AMPK	2.5	Rat INS-1 cells	[27]
Ca^{2+}	Calmodulin-dependent cAMP phosphodiesterase	2.7[a]	Purified beef heart proteins	[28]
IP_3	Calcium release	3	Permeabilized rat basophilic leukemia cells	[29]
Cdk1	Wee1A	3.5	*Xenopus laevis* egg extracts	[30]
Anisomycin	Jnk	3–10	HeLa, HEK293, and Jurkat cells	[31]
Sorbitol	Jnk	4–9	HeLa, HEK293, and Jurkat cells	[31]
Mos	Erk2	5	*Xenopus laevis* oocytes	[25]
Cln2	Cln2 synthesis	5	*S. cerevisiae*	[32]
KinA	σ^E and σ^F	10	*Bacillus subtilis*	[33]
CheY-P	Flagellar motor output	$\sim$10–20	*Escherichia coli*	[34–36]
Cdk1	Cdc25C	11	*Xenopus laevis* egg extracts	[37]
Delta (cis and trans)	Notch production	12	CHO cells	[24]
Cdk1	APC/C^{Cdc20}	$\geq$17	*Xenopus laevis* egg extracts and embryos	[38,39]
Yan	ERK	Not determined	*Drosophila embryos*	[22]

Ferrell Jr, J. E. and S. H. Ha (2014). Trends in Biochemical Sciences **39**(10): 496-503.

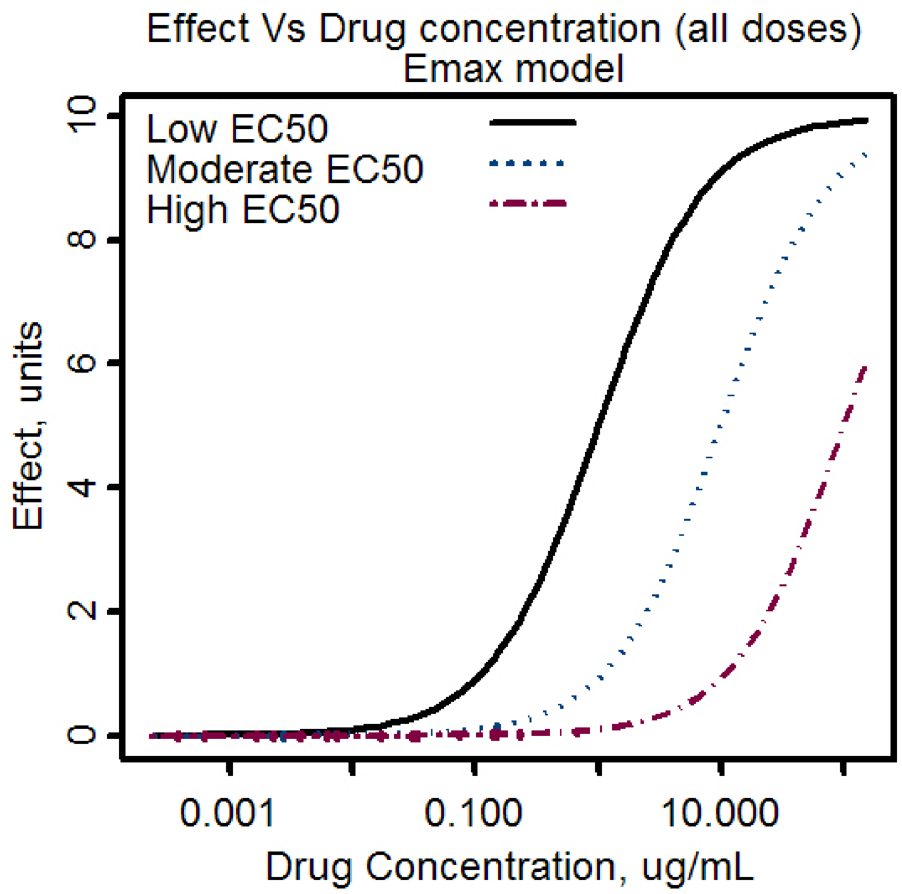
Some index

- EC50

The term **half maximal effective concentration (EC_{50})** refers to the concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum after a specified exposure time. It is commonly used as a measure of drug's potency.



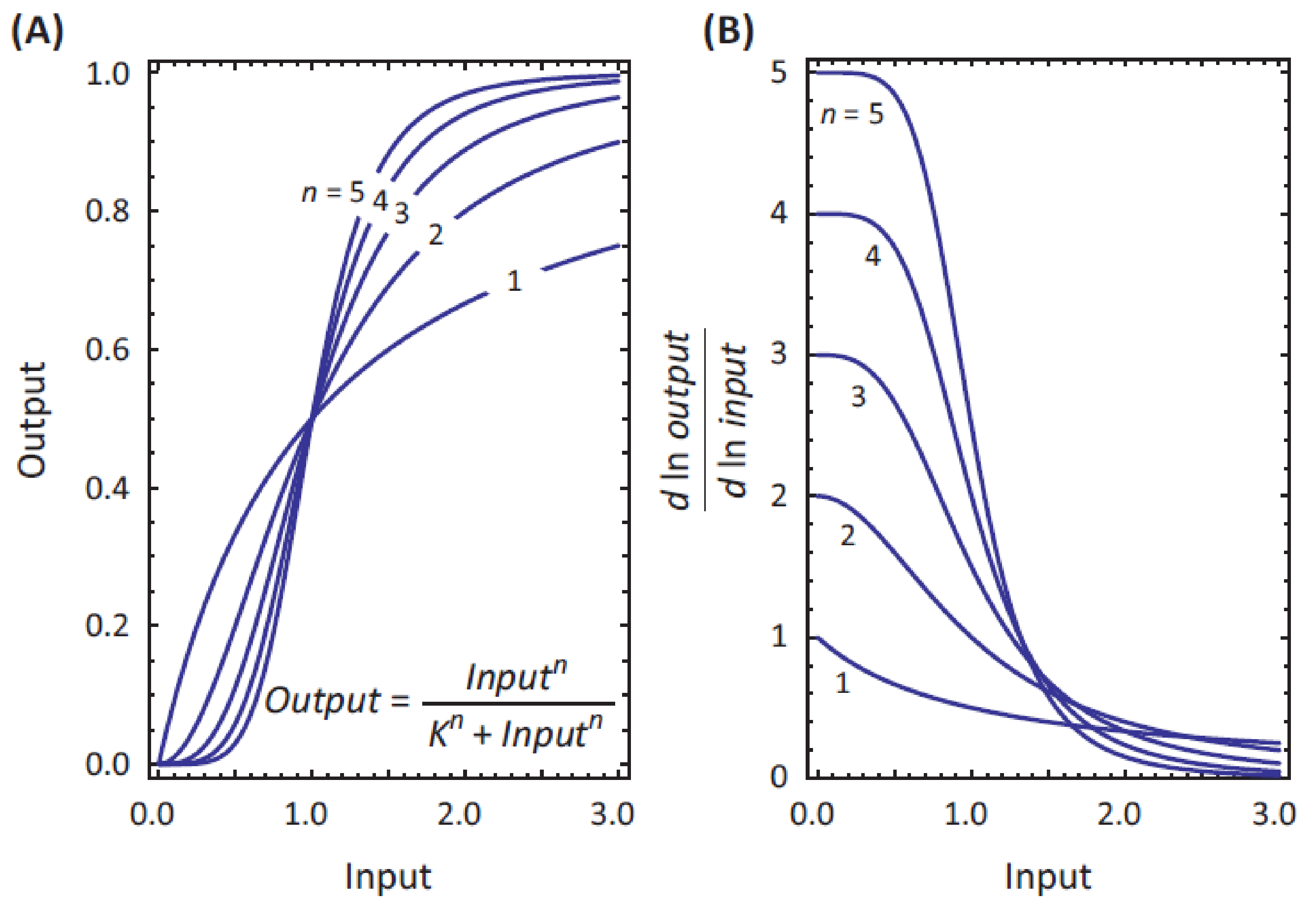
Implications of EC50



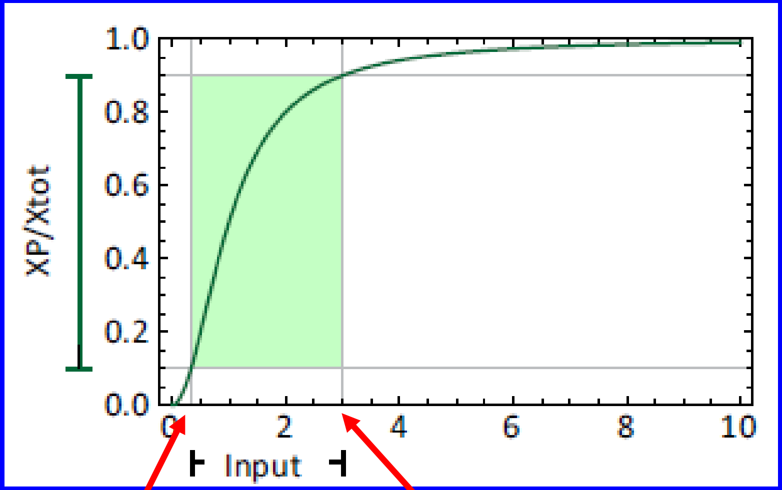
Local sensitivity

$$S_{local} = \lim_{\Delta Input \to 0} \frac{\Delta Output}{Output} \bigg/ \frac{\Delta Input}{Input} = \frac{dOutput}{dInput} \cdot \frac{Input}{Output}$$
$$= \frac{d \ln Output}{d \ln Input}$$

Goldbeter and Koshland



Global sensitivity: EC90 / EC10



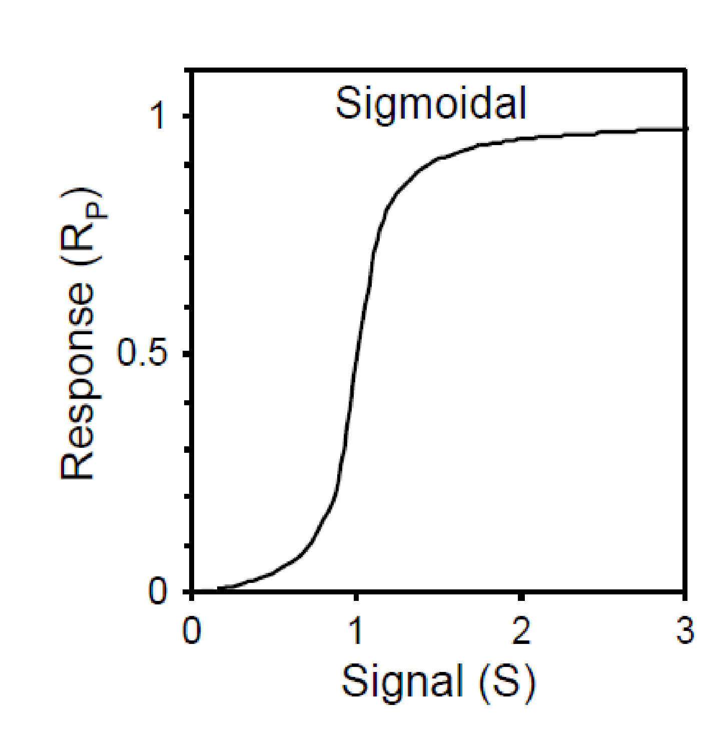
EC10

EC90

Michaelian system
EC90 / EC10= ?

Ultrasensitive response
EC90/EC10 =?

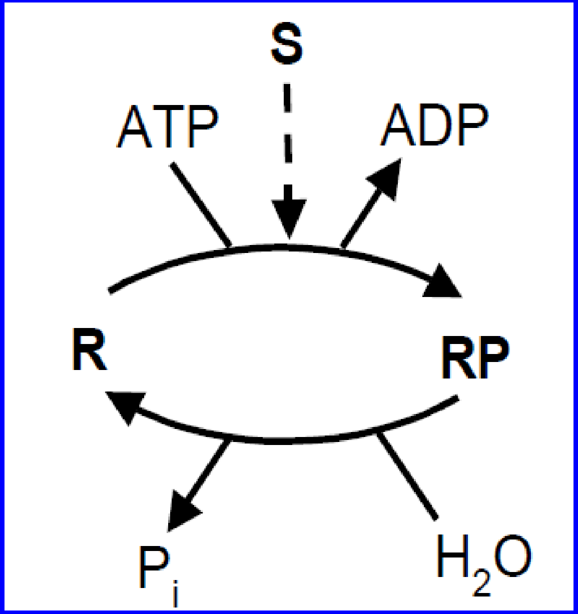
Efficient Hill exponent



$$n = \frac{\mathrm{Log}[81]}{\mathrm{Log}[EC90/EC10]}$$

Zero-order ultrasensitivity

Both the phosphorylation and dephosphorylation reactions are saturable and governed by Michaelis-Menten kinetics:



$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

Steady states:

$$k_1 S(R_T - R_P)(K_{m2} + R_P) = k_2 R_P (K_{m1} + R_T - R_P).$$

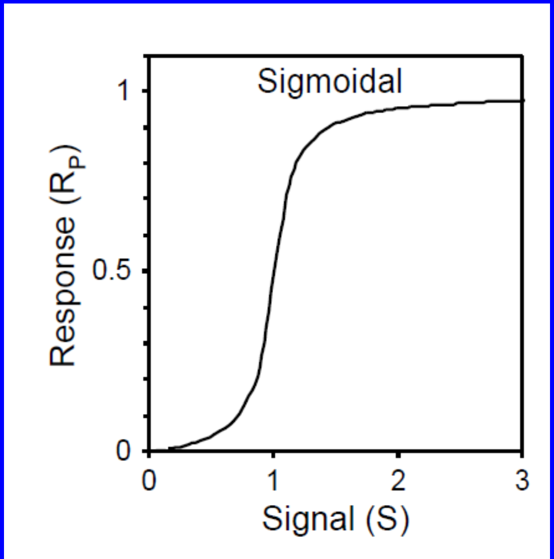
The biophysically acceptable solution (0 < RP < RT) of this equation is

$$\frac{R_{P,ss}}{R_T} = G(k_1, S, k_2, \frac{K_{m1}}{R_T}, \frac{K_{m2}}{R_T}),$$

$$\frac{R_{P,ss}}{R_T} = G(k_1, S, k_2, \frac{K_{m1}}{R_T}, \frac{K_{m2}}{R_T})$$

$$G(u, v, J, K) = \frac{2uK}{v - u + vJ + uK + \sqrt{(v - u + vJ + uK)^2 - 4(v - u)uK}}$$

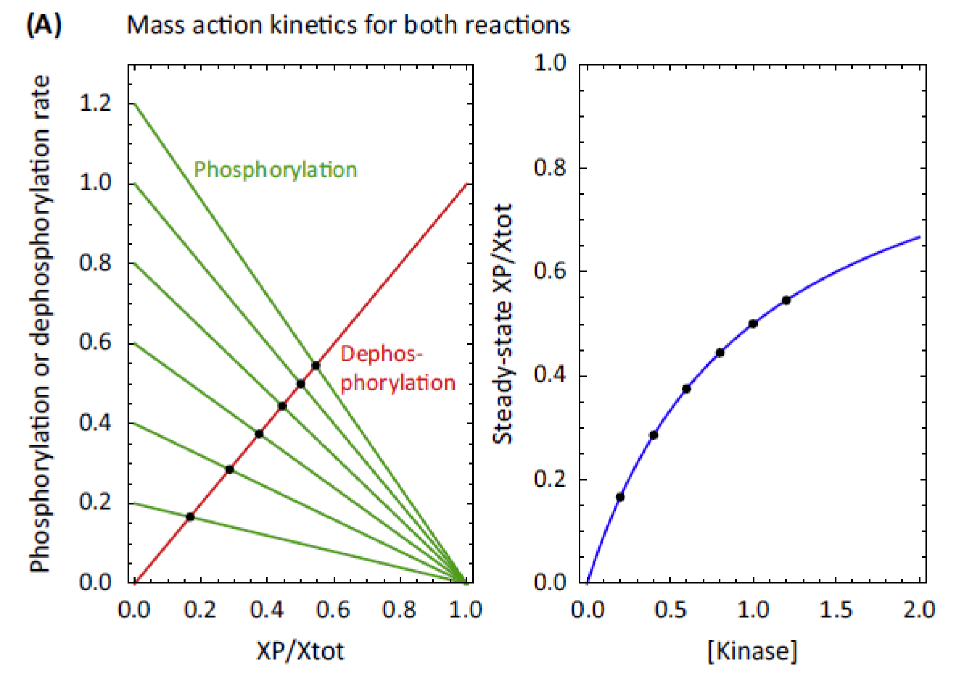
it is a sigmoidal curve if J and K are both <<1



Tyson, J. J., K. C. Chen, et al. (2003). " Curr Opin Cell Biol **15**: 221-231.

Michaelian responses and zero-order ultrasensitivity: rate-balance analysis

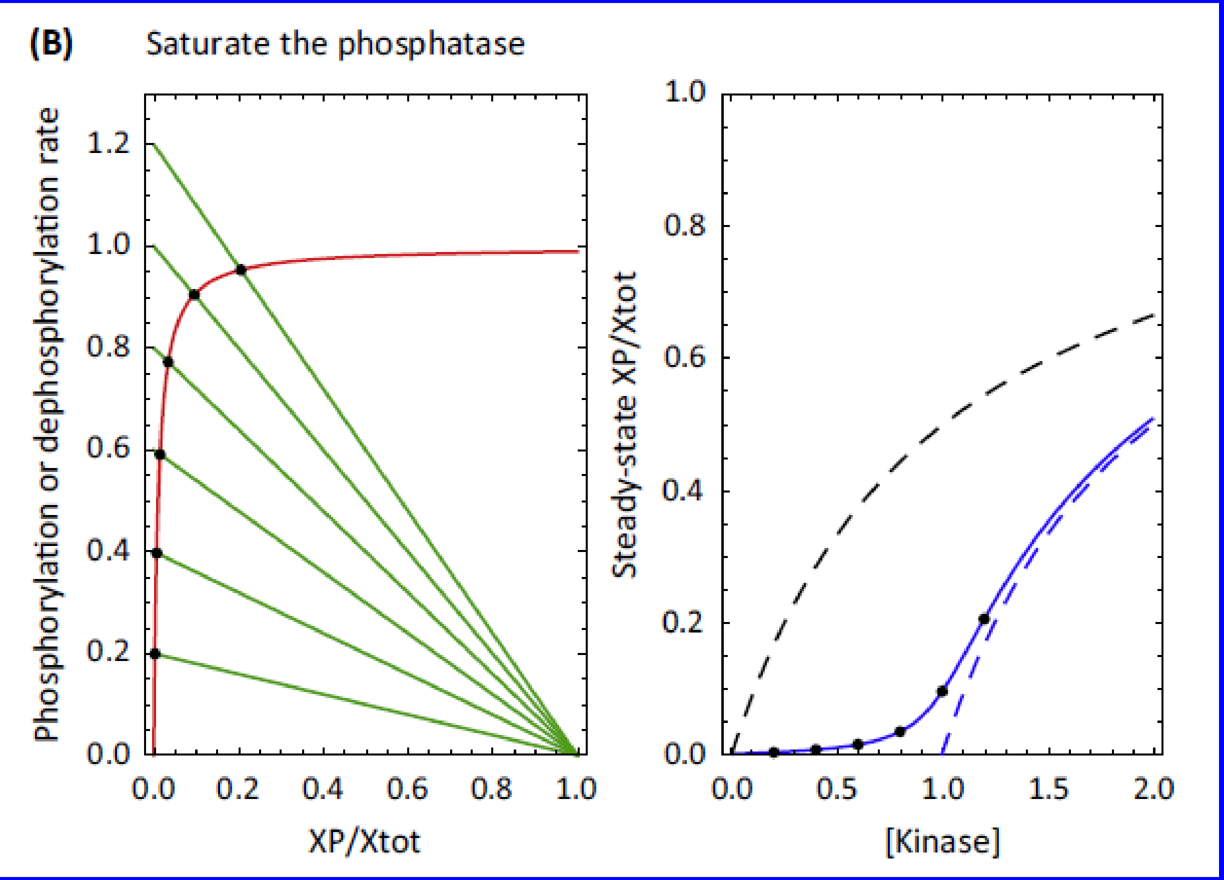
$$\frac{dXP}{dt} = k_1 kinase(X_{tot} - XP) - k_{-1}\, p'ase \cdot XP$$



Ferrell Jr, J. E. and S. H. Ha (2014). Trends in Biochemical Sciences **39**(10): 496-503.

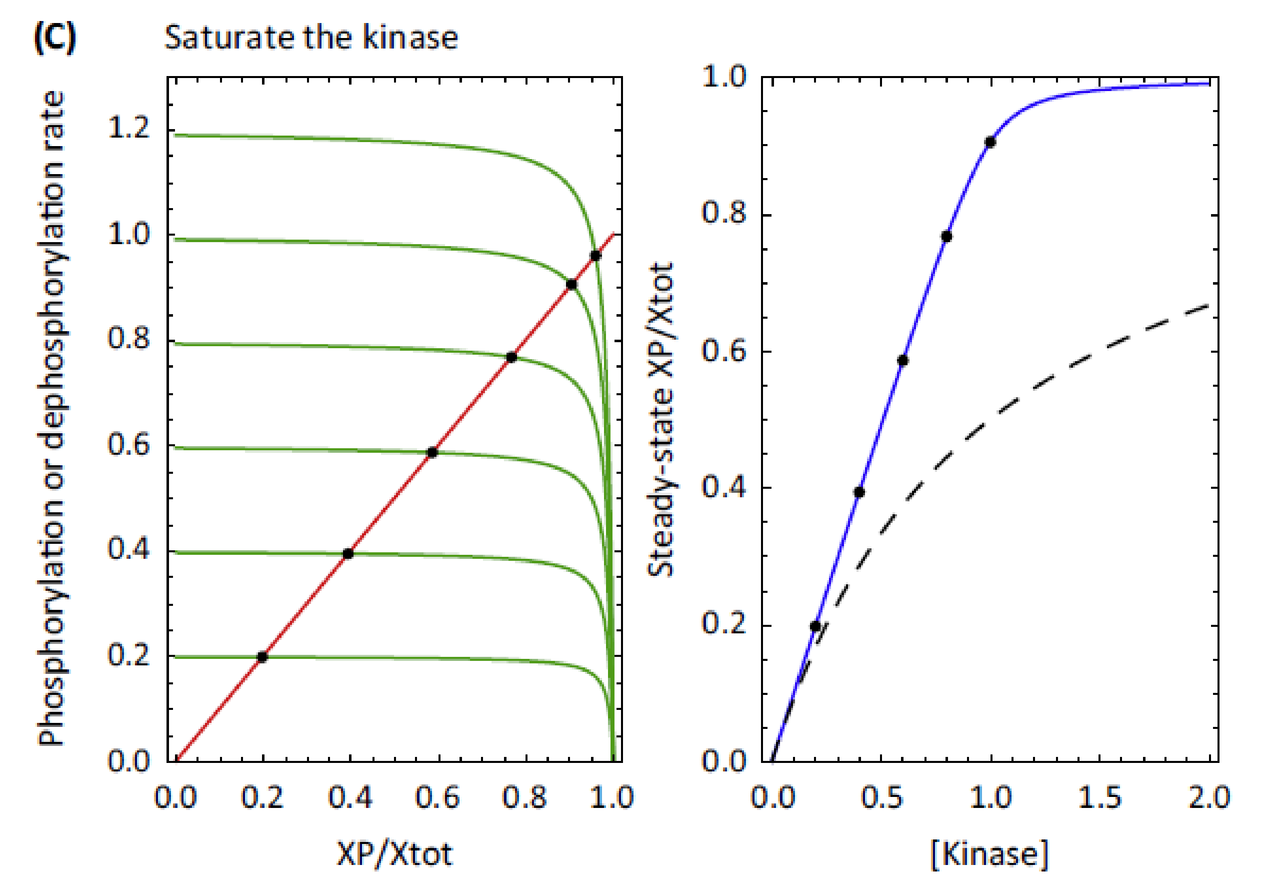
Michaelian responses and zero-order ultrasensitivity: rate-balance analysis

$$\frac{dXP}{dt} = k_1\, kinase\,(X_{tot} - XP) - k_{-1}\, p'ase \frac{XP}{K_{m2} + XP}$$



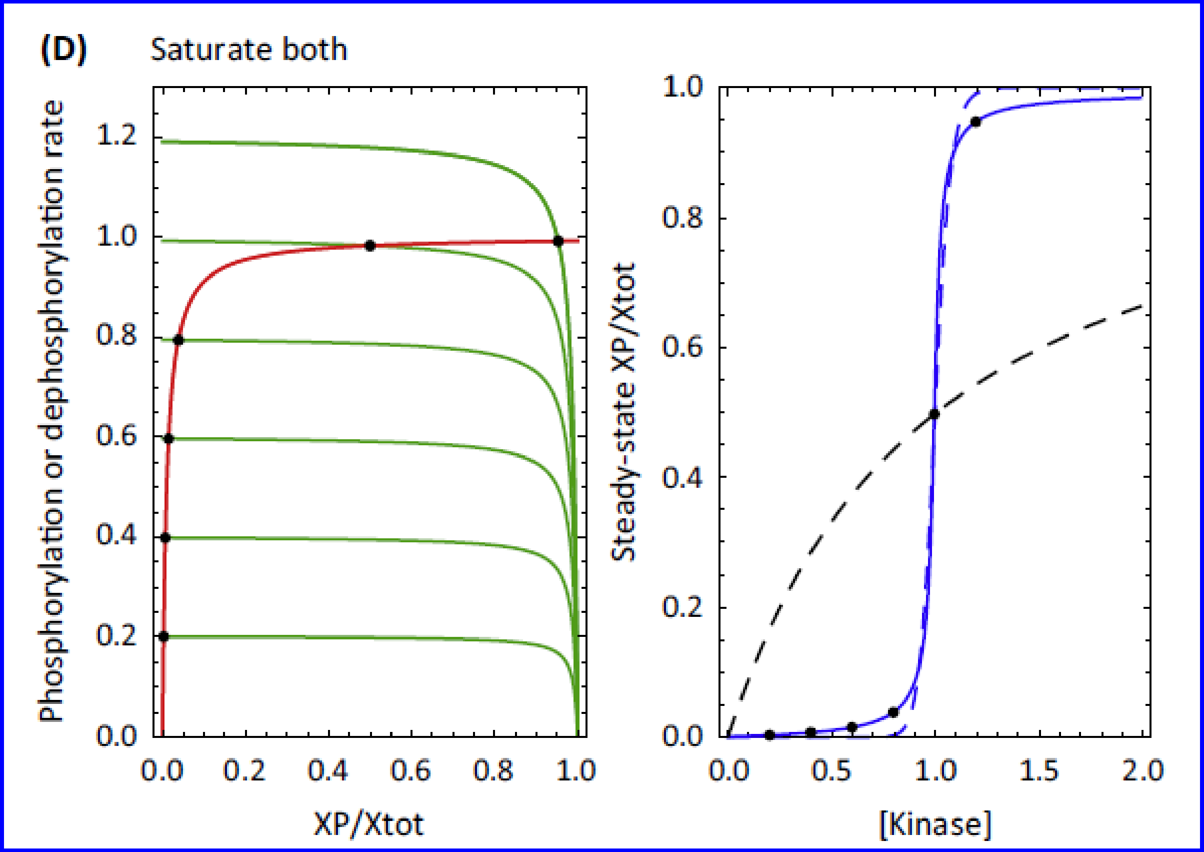
Michaelian responses and zero-order ultrasensitivity: rate-balance analysis

$$\frac{dXP}{dt} = k_1\, kinase \frac{X_{tot} - XP}{K_{m1} + X_{tot} - XP} - k_{-1}\, p'ase \cdot XP$$



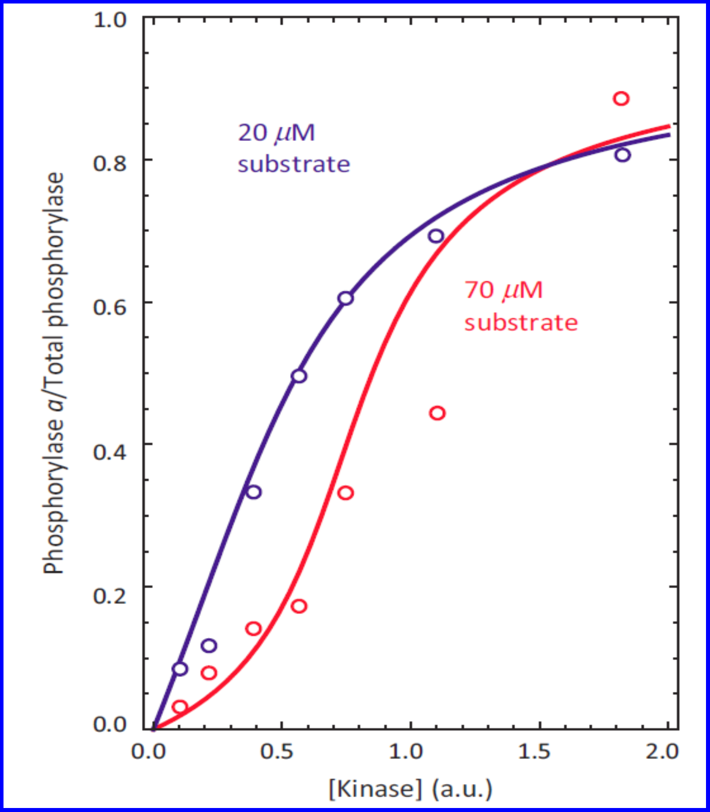
Michaelian responses and zero-order ultrasensitivity: rate-balance analysis

$$\frac{dXP}{dt} = k_1 kinase \frac{X_{tot} - XP}{K_{m1} + X_{tot} - XP} - k_{-1} p' ase \frac{XP}{K_{m2} + XP}$$



Zero-order ultrasensitivity in a reconstituted phosphorylation system

The fitted curves are from the Goldbeter–Koshland equation based on the measured Km values, and the effective Hill coefficients were 1.35 (blue curve) and 2.35 (red curve).



Meinke, M. H., J. S. Bishop, et al. (1986). PNAS **83(9): 2865-2868.**

Assignment 2

1) One loop

$$\frac{dOUT}{dt} = k_{out\_on} * A * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

$$\frac{dA}{dt} = [stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}] * \tau_A$$

2) Two loops

$$\frac{dOUT}{dt} = k_{out\_on} * (A + B) * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

$$\frac{dA}{dt} = [stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}] * \tau_A$$

$$\frac{dB}{dt} = [stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - B) - B + k_{min}] * \tau_B$$

Plotting the bifurcation diagram of the one-loop and two-loop systems ([Out] versus S) in the following paper: Brandman, O., J. E. Ferrell, Jr., et al. (2005). Science **310**(5747): 496-498. Illustrating the history-(in)dependent properties of the system by plotting the dynamic curves of the system for “S” values at the bistable area with different initial values.