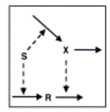
Modeling signal transduction networks by continuous and deterministic models

Receptor - ligand binding - assumed to be elementary reaction
Methylation, phosphorylation reactions – catalyzed by enzymes, Michaelis-Menten kinetics assumed
Dephosphorylation, protein degradation – spontaneous or catalyzed
Protein synthesis –catalyzed by mRNA

Steps: Designate one component as signal and one as response;
Write rates of change for the concentration of components based on the interactions they participate in;
Find steady state concentrations;
Determine the dependence of the steady state response on the signal strength.

Incoherent feed-forward loop

The signal acts on R both directly, and through an intermediary. S is assumed to work at saturation (plentiful substrate). The catalyzed decay is assumed to be elementary.

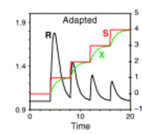


$$\frac{dR}{dt} = k_1 S - k_2 X\ R$$
$$\frac{dX}{dt} = k_3 S - k_4 X$$

Steady state:

$$X_{SS} = \frac{k_3 S}{k_4}$$
$$R_{SS} = \frac{k_1 k_4}{k_2 k_3}$$

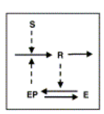
The steady state response does not depend on the signal.
Excitation- adaptation response to step changes in the signal.

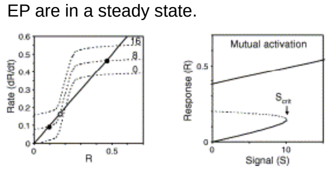


J. Tyson, K. Chen, B. Novak, Curr. Opin. Cell Biology 15, 221 (2003)

Positive feedback

R is catalyzing the phosphorylation of E, and E_P feeds back to R. Assume Michaelis-Menten kinetics for the phosphotransfer. Assume E and EP are in a steady state.

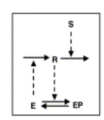


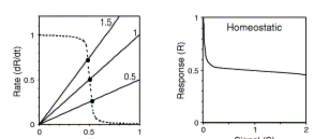


For $S < S_{crit}$ there are three possible steady-state R values.
Two of these solutions are stable - bistability
At $S = S_{crit}$ the response increases abruptly and irreversibly – one-way switch

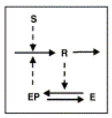
Negative feedback

R inhibits the enzyme catalyzing its synthesis. Assume Michaelis-Menten kinetics for the synthesis of R, and mass action kinetics for the decay of R. Assume E and EP are in a steady state.

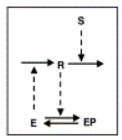




The response depends weakly on the signal – homeostasis.



Positive feedback



Negative feedback

1. What other difference is between these two processes besides the nature of the feedback? Is it important for the end result?

2. The negative regulation in all these examples was taken into account as a catalysis of the degradation process. How would you represent negative regulation of the synthesis?

Example: Modeling signal transduction in bacterial chemotaxis

System is biologically defined; known motility and excitation- adaptation behavior
Input: concentration of proteins in the signal transduction network
Hypotheses: receptor state determines the transmitter's efficiency
Validation: reproduces known output.
Explored: changes in reaction rates.

Insight: overall behavior is robust to changes in individual rates .

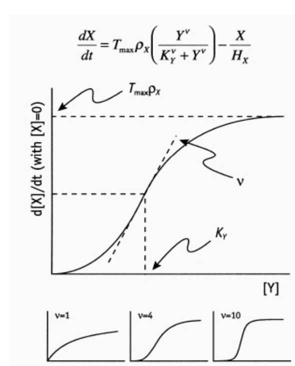
N. Barkai and S. Leibler, Nature 387, 913 (1997)
P. A. Spiro, J. S. Parkinson, H. G. Othmer, PNAS 94, 7263 (1997)

Continuous and deterministic modeling of gene regulatory networks

mRNA synthesis (transcription) – regulated by transcription factor(s)
Protein- level reactions described as in signal transduction networks

Steps: Choose an initial condition;
Write rates of change for the concentration of components;
Find steady state concentrations;
Determine the dependence of the steady state response on the initial condition or kinetic parameters.

Modeling transcriptional regulation

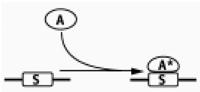


- X – mRNA
- Y – transcriptional activator

- Synthesis is a nonlinear function of activator
- Decay is uncatalyzed
- Parameters:
  - maximum rate $T_{max}\rho_X$
  - Half-maximal activity K_Y
  - Hill coefficient ν
  - Half- life H_X

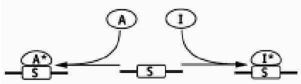
Assumption: combinatorial regulation of synthesis can be approximated with similar sigmoidal curves.

Transcriptional activation



$$\Phi([A], K_A, \nu_A) = \frac{\left(\frac{[A]}{K_A}\right)^{\nu_A}}{1 + \left(\frac{[A]}{K_A}\right)^{\nu_A}} = \left(\frac{[A]^{\nu_A}}{K_A{}^{\nu_A} + [A]^{\nu_A}}\right)$$

Competition between a transcriptional activator and a transcriptional repressor



$$[AS] = \frac{\Phi(A)(1 - \Phi(I))}{1 - \Phi(A)\Phi(I)} = \left(\frac{[A]^{\nu_A}\left(1 - \frac{[I]^{\nu_I}}{K_I{}^{\nu_I} + [I]^{\nu_I}}\right)}{K_A{}^{\nu_A} + [A]^{\nu_A}\left(1 - \frac{[I]^{\nu_I}}{K_I{}^{\nu_I} + [I]^{\nu_I}}\right)}\right)$$

Modeling the segment polarity gene network

First: System is biologically defined; known expression patterns
Input: segment polarity genes, interactions among gene products
Hypotheses: interaction network, transcription factors act as enzymes
Validation: reproduces known gene expression patterns.
Explored: changes in kinetic parameters

Insight: kinetic parameters less important than network topology.

G. von Dassow et al., Nature 406, 188 (2000)