The two faces of network dynamics

Evolving network models describe the dynamics/assembly/evolution of networks by the addition/removal of nodes and edges.
It is possible to have network dynamics even if there are no node/edge additions/removals, i.e. the network is fixed. This can be called dynamics on the network.

In many networks node attributes can change in time or depending on context. E.g.

- the abundance of chemicals in a chemical reaction network
- the health status of individuals in a disease contact network

For these networks it is not enough to specify the nodes and edges, we also need to define a node state (e.g. a continuous variable, or a discrete category).

Each node's state is determined by the states of the nodes adjacent to it (in directed networks the orientation of the edges should be toward the regulated node).

Understanding the dynamics and function of molecular/cellular networks

Cells are complex systems

- functionally diverse elements
- these elements' abundances and activities change in time or based on context
- diverse interactions that form networks
  - signal transduction-, gene regulatory-, metabolic-
- have a function that needs to be performed
  - sense and respond to the environment
  - maintain homeostasis
- need certain dynamical features
  - sensitive to some changes, insensitive/adaptable to others
  - robust to unwanted perturbations
- What is the relationship between the topological features of intracellular interaction networks and the dynamic behavior of cells?

Toward network dynamics

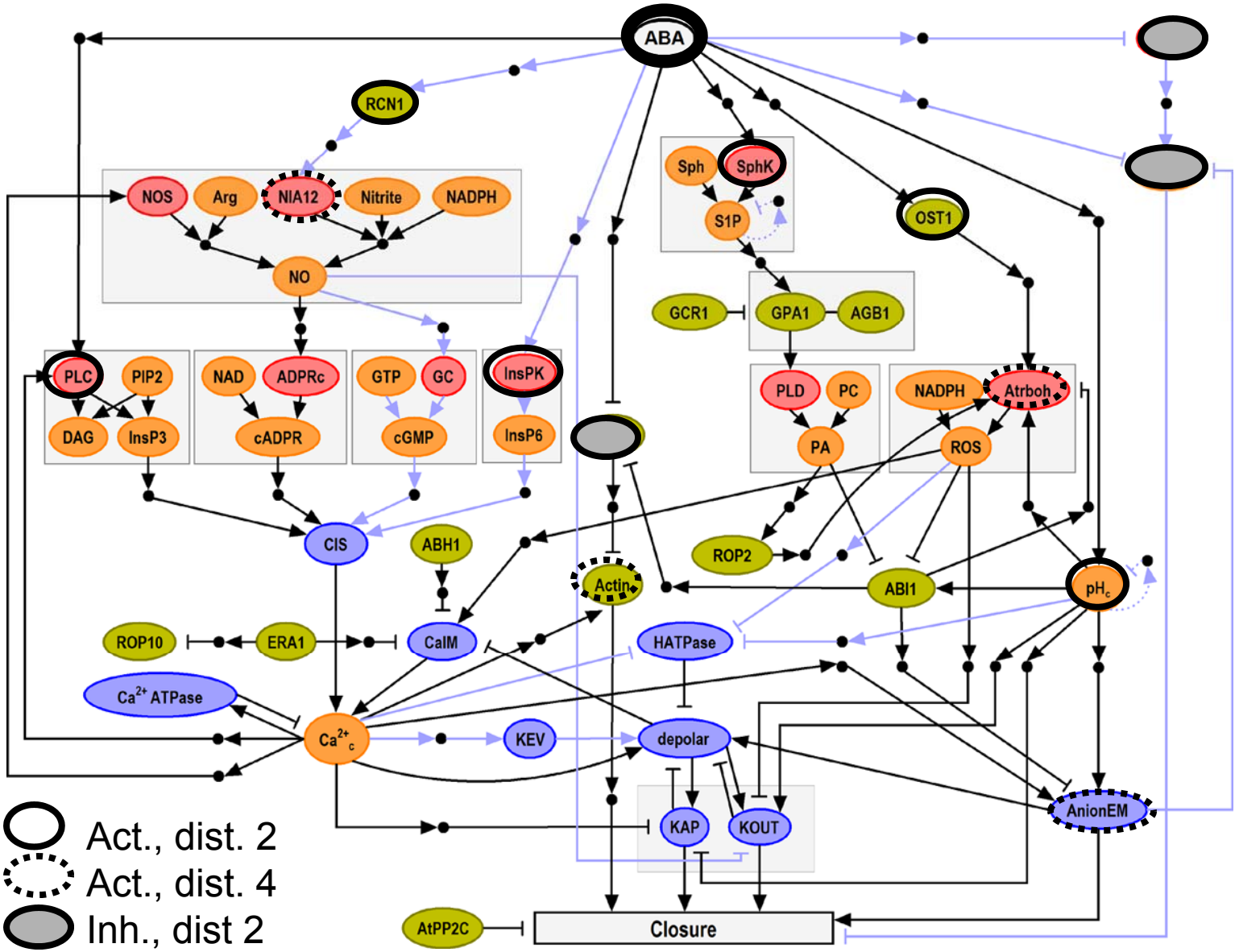
Network topology needs to be complemented by a description of network dynamics – states of the nodes and changes in the state

First step - pseudo-dynamics: propagation of activation in interaction space, starting from a source (signal)

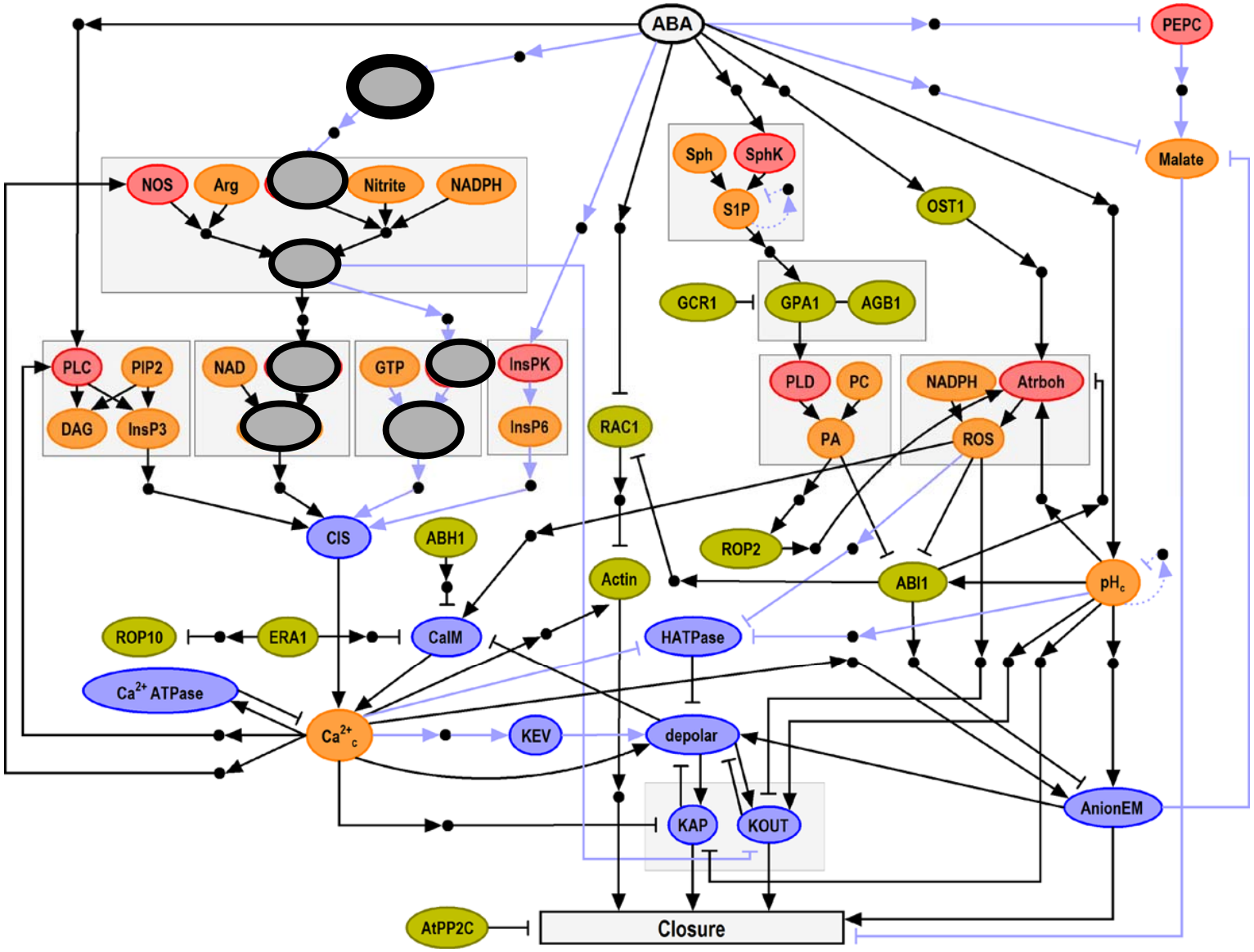
This can only be done in directed networks. In effect we use topological analysis as a proxy for dynamic information on signal propagation.

Q: What topological properties should be studied and what dynamic properties do they reflect?

Pseudodynamic signal propagation



Pseudodynamic effects of knockouts



Forward and reverse dynamic modeling

Dynamic modeling of interaction network:

Input: components; interactions; states of components

Hypotheses: interaction network; transfer functions; parameters

Output: behavior of components in time

Validation: capture known behavior

Explore: study cases that are not accessible experimentally

change parameters, change assumptions

Reverse problem: Network inference from dynamic information:

Input: components; states of components (in time)

Hypotheses: regulatory framework

Output: proposed regulatory network

Validation: capture known interactions

We will study network inference later in the course.

Types of dynamic models

1. Continuous - similar to chemical kinetics
   - differential equations
2. Discrete - assume a small set of qualitative states
   - the changes in state are given by discrete (logical) rules

1. Deterministic - no randomness is involved in the development of future states of the system
2. Stochastic - non-deterministic in that the next state of is not fully determined by the previous state.
   - can take into account the fluctuations in mRNA/protein numbers and external noise

Continuous and deterministic models: < medium-size networks,
> medium node abundances.
Stochastic models: small networks, low node abundances
Discrete models: > medium networks, bimodal node abundances

Basics of Chemical Kinetics - 1

$$A \rightarrow Product$$

- Rate of reaction = rate of disappearance of A = $r_A = d[A]/dt$ =

# of moles of A reacting ("disappearing") per unit time per unit volume

- Reaction rate law is an <u>algebraic equation</u> involving concentrations

$r_A = -k\,[A]$ $\qquad$ $r_A = -k\,[A]^2$ $\qquad$ $r_A = -k_1\,[A]/(1+k_2[A])$

- For a given reaction, the rate law is determined experimentally

$$A + B \rightarrow Product$$

- In general : $r_A = -k \cdot f([A],[B],\ldots)$

Rate Constant $\qquad$ ***Concentration dependence***

- Reaction Order (power): $\qquad r_A = -k \cdot [A]^{\alpha} \cdot [B]^{\beta}$

The reaction is of order α with respect to A and of order β with respect to B

Basics of Chemical Kinetics - 2

➢Elementary Reaction: Reaction order of each species is identical with the stoichiometric coefficient of that species

$$A + 2B \rightarrow C \qquad r_A = -k \cdot [A] \cdot [B]^2$$

Interpretation: One molecule of A colliding with 2 molecules of B to produce C)

➢Elementary reactions are typically 1st or 2nd order

(Probability of three molecules colliding very low)

➢Reversible reactions: $A + 2B \leftrightarrow C$

$A + 2B \rightarrow C$ Forward Reaction

$A + 2B \leftarrow C$ Backward Reaction

Basics of Chemical Kinetics - 3

Law of Conservation of Mass + elementary reaction

$$aA + bB \rightarrow cC + dD$$

$$\frac{r_A}{-a} = \frac{r_B}{-b} = \frac{r_C}{c} = \frac{r_D}{d} = k \cdot [A]^a \cdot [B]^b$$

Reaction flux

$$d[A]/dt = -a\,k\,[A]^a\,[B]^b$$

$$d[B]/dt = -b\,k\,[A]^a\,[B]^b$$

$$d[C]/dt = c\,k\,[A]^a\,[B]^b$$

$$d[D]/dt = d\,k\,[A]^a\,[B]^b$$

Initial conditions

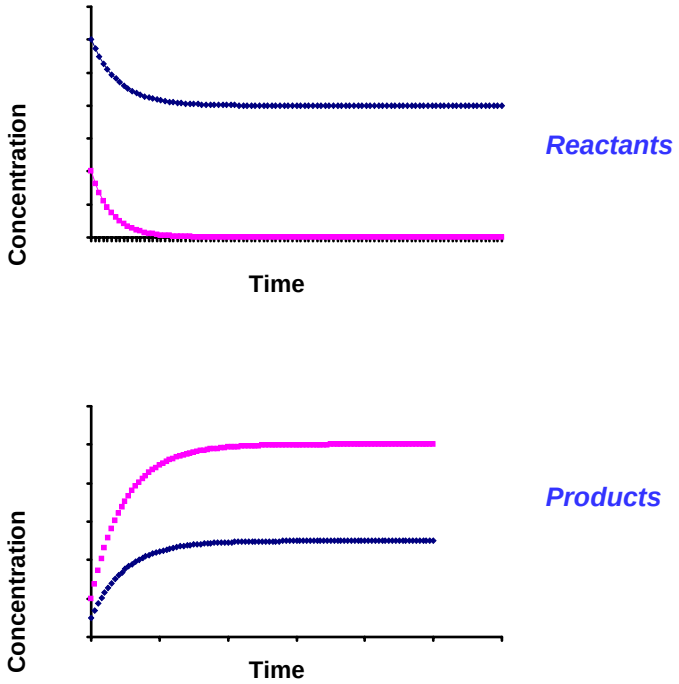
$$[A]_{(t=0)} = [A]_0$$

$$[B]_{(t=0)} = [B]_0$$

$$[C]_{(t=0)} = [C]_0$$

$$[D]_{(t=0)} = [D]_0$$

Concentration Time Course



Ex. 1 $\boldsymbol{A + B \rightarrow C}$

Assume the reaction is elementary. Determine the rate of change of [A], [B], [C]

Ex. 1 $A + B \rightarrow C$

Assume the reaction is elementary. Determine the rate of change of [A], [B], [C]

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k[A][B] \qquad \frac{d[C]}{dt} = k[A][B]$$

Ex. 2

Write the condition(s) of mass conservation.

Hint: think of the reaction as a complex formation $A + B \rightarrow \overline{AB}$

Reversible reactions

Example: $A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$

For simplicity, we'll leave off the brackets from [A], ..

$$\frac{dA}{dt} = \frac{dB}{dt} = -k_1 AB + k_{-1} C$$

$$\frac{dC}{dt} = k_1 AB - k_{-1} C$$

Mass conservation: $A + C = A_0$ $B + C = B_0$

Units: k_1 – (mol/volume/time)$^{-1}$, k_{-1} – (time)$^{-1}$

Steady states

If the rates of the forward and backward reactions are equal, the system is able to reach a steady state in which the concentrations do not change in time

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

$$\frac{dA}{dt} = \frac{dB}{dt} = \frac{dC}{dt} = 0 \qquad \text{if} \qquad k_1 AB - k_{-1} C = 0$$

$$C_{ss} = \frac{k_1}{k_{-1}} A_{ss} B_{ss} = \frac{k_1}{k_{-1}} (A_0 - C_{ss})(B_0 - C_{ss})$$

Solve for C_{ss}

Enzyme-catalyzed reactions

Most reactions in biological systems would not take place at perceptible rates in the absence of enzymes.

Enzymes are specialized proteins that bind specific reactants, get them close together, and by this, accelerate the reaction up to a million times.

In this context, the reactants are called substrates.

In enzyme-catalyzed reactions the rate of product synthesis depends nonlinearly on the concentration of the substrate.

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Michaelis-Menten model of enzymatic reactions

Leonor Michaelis, Maud Menten (1913)

1. A specific enzyme-substrate complex is a necessary intermediate in catalysis
2. This complex is in a quasi-steady state
3. The step that yields the product is irreversible

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \overline{ES} \xrightarrow{k_2} E + P$$

Ex. Draw two possible network representations of this process.

Michaelis-Menten kinetics (cont.)

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \overline{ES} \xrightarrow{k_2} E + P$$

Goal: express the rate of product synthesis as a function of substrate concentration

$$\left.\begin{aligned} \overline{ES} &= ES\,\frac{k_1}{k_{-1}+k_2} \\ E_T &= E + \overline{ES} \\ K_M &= \frac{k_{-1}+k_2}{k_1} \end{aligned}\right\} \quad \frac{dP}{dt} = k_2 E_T\,\frac{S}{K_M + S}$$

Ex. Draw the dependence of the rate of product synthesis on the substrate concentration. Characterize three limits/points on the curve.

Enzyme-catalyzed reactions

$$\frac{dP}{dt} = k_2 E_T \frac{S}{K_M + S}$$

K_M is equal to the substrate concentration at which the reaction rate is half its maximal value.

Limit 1 $S >> K_M \quad \Rightarrow \quad \frac{dP}{dt} \approx k_2 E_T$

$k_2 E_T$ is the number of substrate molecules converted in a unit time when the enzyme is fully saturated with substrate.

Limit 2 $S << K_M \quad \Rightarrow \quad \frac{dP}{dt} \approx \frac{k_2}{K_M} E_T S$

The efficiency of an enzyme can be described by k_2 / K_M

Chemical kinetics-like models of cellular processes

Assumption: cellular synthesis and degradation processes can be described as simple or enzyme-catalyzed reactions

Ex.: receptor - ligand binding

methylation reactions – catalyzed by methylating enzymes,

phosphorylation - catalyzed by kinases

dephosphorylation – spontaneous or catalyzed by phosphatases

protein synthesis –catalyzed by mRNA,

protein degradation – spontaneous or catalyzed

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

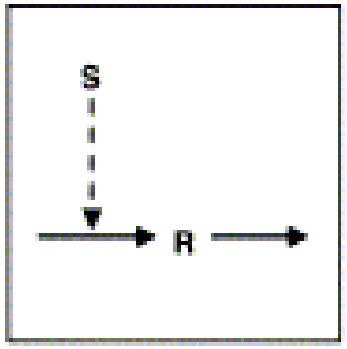
Protein synthesis and degradation

Protein synthesis: mRNA → protein (sufficient supply of amino-acids)

Protein degradation: protein →

Notations in Tyson et al 2003: The source element (here the mRNA) is denoted S (for signal). One component (here the protein) is designated as the response.

Network diagram:



Solid edge: mass flow
Dashed edge: regulation

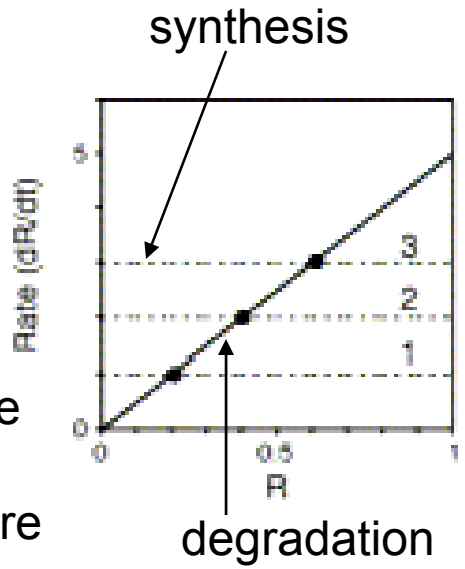
Q: Draw an alternative network, more in line with what we have seen before, where edges connect two nodes and signify regulation.

Kinetics of protein synthesis and degradation

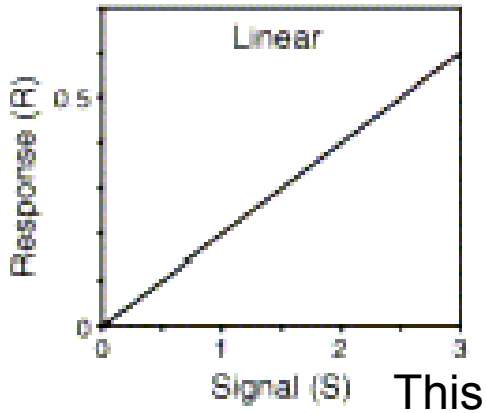
Protein synthesis: mRNA → protein (sufficient supply of amino-acids)

Protein degradation: protein →

$$\frac{dR}{dt} = k_1 S - k_2 R \qquad \text{Steady state:} \qquad R_{ss} = \frac{k_1 S}{k_2}$$



The points where the synthesis and degradation terms are equal indicate the steady states.



This is the input-output characteristic of the system.

Kinetics of phosphotransfer

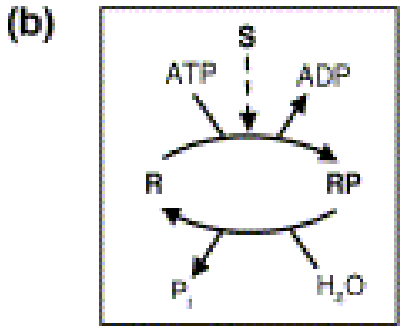
Phosphorylation: protein → phospho-protein

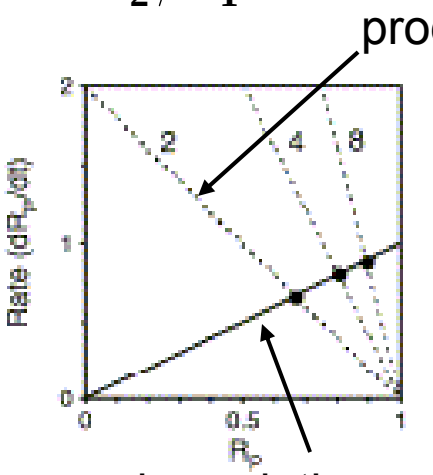
Dephosphorylation: phospho-protein → protein

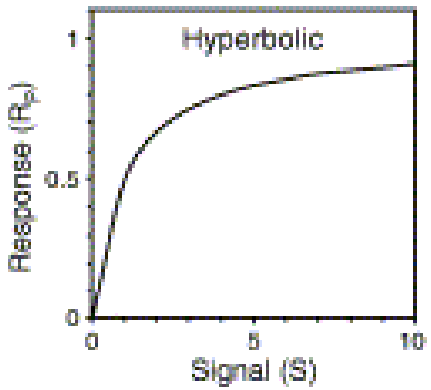
The first reaction is catalyzed by a kinase, assume first –order kinetics

$$\frac{dR_P}{dt} = k_1 SR - k_2 R_P \qquad R_T = R + R_P$$

Steady state: $$R_{P\,ss} = R_T \frac{S}{k_2/k_1 + S}$$





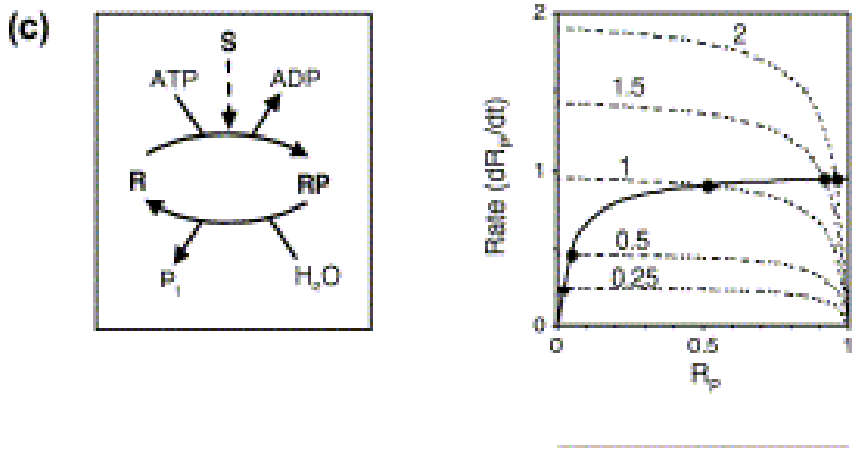


Phosphotransfer with Michaelis-Menten kinetics

Assume that the phosphorylation and dephosphorylation reactions follow Michaelis-Menten kinetics

$$k_1 SR \rightarrow k_1 S \frac{R}{K_{M1} + R} \qquad k_2 R_P \rightarrow k_2 \frac{R_P}{K_{M2} + R_P}$$

$$\frac{dR_P}{dt} = k_1 S \frac{R_T - R_P}{K_{M1} + R_T - R_P} - \frac{k_2 R_P}{K_{M2} + R_P}$$



Phosphotransfer with Michaelis-Menten kinetics

$$\frac{dR_P}{dt} = k_1 S \frac{R_T - R_P}{K_{M1} + R_T - R_P} - \frac{k_2 R_P}{K_{M2} + R_P}$$

Steady state: $$R_{P\,ss} = R_T G\left(k_1 S, k_2, \frac{K_{M1}}{R_T}, \frac{K_{M2}}{R_T} \right)$$

G - Goldbeter-Koshland function