

Basics of Chemical Kinetics - 1



➤ 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

[A] = concentration of A = (# moles/volume) ; 1 mole = 6.023×10^{23} molecules

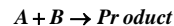
➤ Reaction rate law is an **algebraic equation** involving concentrations (not a differential equation)

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

➤ For a given reaction, the rate law is determined **experimentally**

➤ Measure [A] as a function of time and calculate slope (d[A]/dt) at various time points.

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

Other factors impacting rate constant

Temperature dependence

Concentration dependence

Rate Constant

- Catalyst
- Pressure
- Ionic strength (pH)
- Solvent

(Not really "constant", just independent of concentration)

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

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

➤ Reaction order can be fractional $r_A = -k \cdot [A]^1 \cdot [B]^{0.5}$

➤ Not every reaction has an order! $r_A = -k_1 \cdot [A]/(1+k_2 \cdot [B])$

(Temperature and concentration dependence not separable)

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



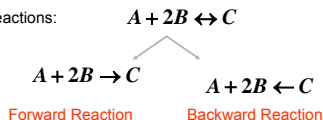
➤ Elementary reactions hypothesized to happen exactly how they are written!

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

➤ Elementary reactions are typically 1st or 2nd order

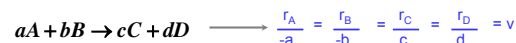
(Probability of three molecules colliding very low)

➤ Reversible reactions:



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➤ Reaction Stoichiometry + Law of Conservation of Mass



(Irrespective of whether reaction is elementary or not)

Reaction flux

$$d[A]/dt = -a \cdot v$$

$$d[B]/dt = -b \cdot v$$

$$d[C]/dt = c \cdot v$$

$$d[D]/dt = d \cdot v$$

Specify rate law

$$v = -k \cdot [A]^a \cdot [B]^b \quad \text{or} \\ v = -k \cdot [A] \cdot [B]$$

Specify initial conditions

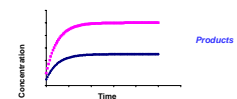
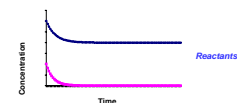
$$[A]_{(t=0)} = [A]_0$$

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

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

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

Concentration Time Course



Ex. 1 $A + B \rightarrow C$

Determine the relation between the reaction rates and the reaction flux.

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

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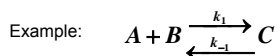
$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k[A][B] \quad \frac{d[C]}{dt} = k[A][B]$$

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



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

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

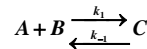
$$\frac{dC}{dt} = k_1 AB - k_{-1} C$$

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

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

Steady states

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



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

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

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.

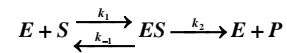
In this context, the reactants are called **substrates**.

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

Michaelis-Menten model of enzymatic reactions

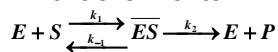
Leonor Michaelis, Maud Menten (1913)

1. A specific enzyme-substrate complex is a necessary intermediate in catalysis
2. The product does not revert to the original substrates



Ex. Draw two possible network representations of this process.

Michaelis-Menten kinetics



$$\frac{dS}{dt} = -k_1 E S + k_{-1} \overline{ES} \quad \frac{dE}{dt} = -k_1 E S + k_{-1} \overline{ES} + k_2 \overline{ES}$$

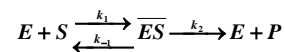
$$\frac{d\overline{ES}}{dt} = k_1 E S - k_{-1} \overline{ES} - k_2 \overline{ES} \quad \frac{dP}{dt} = k_2 \overline{ES}$$

Mass conservation: $E_T = E + \overline{ES}$

Assumption: the enzyme-substrate complex is in quasi-steady-state

$$\frac{d\overline{ES}}{dt} = 0, \quad \overline{ES} = ES \frac{k_1}{k_{-1} + k_2}$$

Michaelis-Menten kinetics (cont.)



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

$$\frac{dP}{dt} = k_2 \overline{ES}$$

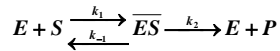
$$\overline{ES} = ES \frac{k_1}{k_{-1} + k_2}$$

$$E_T = E + \overline{ES}$$

$$K_M = \frac{k_{-1} + k_2}{k_1}$$

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

Michaelis-Menten kinetics (cont.)



$$\frac{dP}{dt} = k_2 E_T \frac{S}{K_M + S} \quad K_M = \frac{k_{-1} + k_2}{k_1}$$

Ex. 1

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

Ex. 2

What is the upper limit for k_2/K_M ?

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 $S \gg K_M \Rightarrow \frac{dP}{dt} \approx k_2 E_T$

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

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

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

The ultimate limit for enzyme efficiency is the diffusion-limited encounter of enzyme and substrate, or $10^9 s^{-1} mol^{-1}$

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)

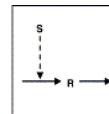
Protein synthesis and degradation

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

Protein degradation: protein \rightarrow

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:



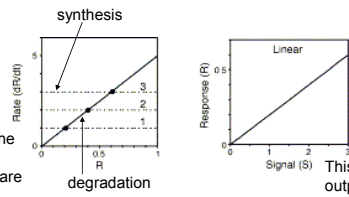
Solid edge: mass flow
Dashed edge: regulation

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 →

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



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

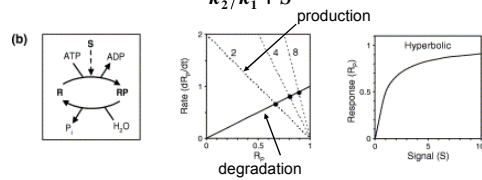
This is the input-output characteristic of the system.

Kinetics of phosphotransfer

Phosphorylation: protein → phospho-protein
 Dephosphorylation: phospho-protein → protein
 The first reaction is catalyzed by a kinase, assume first-order kinetics

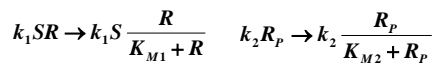
$$\frac{dR_p}{dt} = k_1 S R - k_2 R_p \quad R_T = R + R_p$$

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

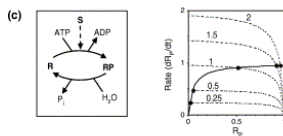


Phosphotransfer with Michaelis-Menten kinetics

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



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



Phosphotransfer with Michaelis-Menten kinetics

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

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

G - Goldbeter-Koshland function

