Basics of Chemical Kinetics - 1

$$A \rightarrow \text{Product}$$

- Rate of reaction = rate of disappearance of A = $$r_A = \frac{d[A]}{dt}$$ = 
  
  # of moles of A reacting (“disappearing”) per unit time per unit volume

  $$[A] = \text{concentration of A} = \left( \frac{\text{# moles}}{\text{volume}} \right) ; 1 \text{ mole} = 6.023 \times 10^{23} \text{ molecules}$$

- 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.
Basics of Chemical Kinetics - 2

\[ A + B \rightarrow \text{Product} \]

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

**Temperature dependence**

**Concentration dependence**

**Rate Constant**

(Not really “constant”, just independent of concentration)

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

The reaction is of order \( \alpha \) with respect to A and of order \( \beta \) 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)

- Other factors impacting rate constant:
  - Catalyst
  - Pressure
  - Ionic strength (pH)
  - Solvent
Basics of Chemical Kinetics - 3

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

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

- 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 1\textsuperscript{st} or 2\textsuperscript{nd} order

  (Probability of three molecules colliding very low)

- Reversible reactions:

  \[ A + 2B \leftrightarrow C \]

  \[ A + 2B \rightarrow C \quad A + 2B \leftarrow C \]

  Forward Reaction  Backward Reaction
Basics of Chemical Kinetics - 4

➢ Reaction Stoichiometry + Law of Conservation of Mass

\[ aA + bB \rightarrow cC + dD \]

\[ \frac{r_A}{-a} = \frac{r_B}{-b} = \frac{r_C}{c} = \frac{r_D}{d} = v \]

(Irrespective of whether reaction is elementary or not)

Specify rate law

\[ v = -k \cdot [A]^a \cdot [B]^b \]

or

\[ v = -k \cdot [A] \cdot [B] \]

Specify initial conditions

• \[ A_{(t=0)} = [A]_0 \]
• \[ B_{(t=0)} = [B]_0 \]
• \[ C_{(t=0)} = [C]_0 \]
• \[ D_{(t=0)} = [D]_0 \]
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]
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 \([A], [B], [C]\)

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

Ex. 2

Write the condition(s) of mass conservation.

Hint: think of the reaction as a complex formation \[ A + B \rightarrow AB \]
Reversible reactions

Example: \[ A + B \xrightleftharpoons[k_1 \quad k_{-1}]{} C \]

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

\[
\begin{align*}
\frac{dA}{dt} &= \frac{dB}{dt} = -k_1 AB + k_{-1} C \\
\frac{dC}{dt} &= k_1 AB - k_{-1} C
\end{align*}
\]

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

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 where the concentrations do not change in time.

\[ A + B \xrightleftharpoons[k_-]{k_1} C \]

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

\[
C_{ss} = \frac{k_1}{k_-} \quad A_{ss} B_{ss} = \frac{k_1}{k_-} \left( A_0 - C_{ss} \right) \left( B_0 - C_{ss} \right)
\]

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 non-linearly 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

\[ E + S \xrightleftharpoons[{k_{-1}}]{{k_1}} ES \xrightarrow{k_2} E + P \]

Ex. Draw two possible network representations of this process.
Michaelis-Menten kinetics

\[ E + S \xrightarrow{k_1} ES \xrightarrow{k_2} E + P \]

\[
\frac{dS}{dt} = -k_1 E S + k_{-1} ES
\]

\[
\frac{dE}{dt} = -k_1 E S + k_{-1} ES + k_2 ES
\]

\[
\frac{dES}{dt} = k_1 E S - k_{-1} ES - k_2 ES
\]

\[
\frac{dP}{dt} = k_2 ES
\]

Mass conservation: \( E_T = E + ES \)

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

\[
\frac{dES}{dt} = 0, \quad ES = ES \frac{k_1}{k_{-1} + k_2}
\]
Michaelis-Menten kinetics (cont.)

\[ E + S \xrightleftharpoons[k_1]{k_{-1}} ES \xrightarrow{k_2} E + P \]

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

\[ \frac{dP}{dt} = k_2 ES \]

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

\[ ES = ES \frac{k_1}{k_{-1} + k_2} \]

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

\[ E_T = E + ES \]
Michaelis-Menten kinetics (cont.)

\[ E + S \xrightarrow{k_1} ES \xrightarrow{k_2} E + P \]

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

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**

\[S \gg K_M \quad \Rightarrow \quad \frac{dP}{dt} \approx k_2 E_T\]

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

**Limit 2**

\[S \ll K_M \quad \Rightarrow \quad \frac{dP}{dt} \approx \frac{k_2}{K_M} E_T S\]

The efficiency of an enzyme can be described by \(\frac{k_2}{K_M}\).

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

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:

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 $\rightarrow$ protein (sufficient supply of amino-acids)

Protein degradation: protein $\rightarrow$

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

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 $\rightarrow$ phospho-protein
Dephosphorylation: phospho-protein $\rightarrow$ protein

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

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

$$R_T = R + R_p$$

Steady state:

$$R_{P_{ss}} = R_T \frac{S}{k_2/k_1 + S}$$

![Diagram](image)
Phosphotransfer with Michaelis-Menten kinetics

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

\[ k_1 SR \rightarrow k_1 S \frac{R}{K_{M1} + R} \quad \text{and} \quad k_2 R_P \rightarrow k_2 \frac{R_P}{K_{M2} + R_P} \]

\[ \frac{dR_P}{dt} = k_1 S \frac{R_T - R_P}{K_{M1} + R_T - R_P} - \frac{k_2 R_P}{K_{M2} + R_P} \]
Phosphotransfer with Michaelis-Menten kinetics

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

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

G - Goldbeter-Koshland function