Rate Equations & Reaction Networks

In reality, even at equilibrium, everything is constantly changing.

$$A + B \rightleftharpoons AB$$

How do we describe these dynamics from the statistical point of view?

↳ Turnover, assembly, production, disassembly, etc.

To get an idea of scale, let's estimate ATP turnover.

Daily Diet: Food ~ 2000 kcal per day

ATP ~ 12 kcal/mol

Assume 1/2 of the food ends up as ATP

↳ $\frac{1000 \text{ kcal/day}}{12 \text{ kcal/mol}} \approx 80 \frac{\text{mol}}{\text{day}}$

ATP MW ≈ 500 g/mol

mass of ATP = $80 \frac{\text{mol}}{\text{day}} \cdot \frac{500 \text{ g}}{\text{mol}} = 40 \text{ kg}$!!

$2 billion USD

⇒ clearly there must be turnover and recycling!

→ human body on avg contains only 250 g. of ATP at a time but turns over your body weight in ATP in one day

↳ AA battery

Turnover in the Cytoskeleton:

↳ Fig. 15.1, 15.2, 15.3

Estimate rate of actin assembly.

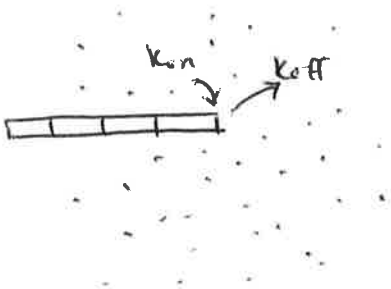
speed, v = 200 nm/s

monomer, m = 3 nm/monomer

→ $\frac{200}{3} \approx 70$ monomer/sec

Note: Not only average number, but location is important!

↳ Diffusion limited vs. Reaction limited



K. vs. D.

Chemical Picture of Biological Dynamics:

Rate Eqn: A mathematical tool that allows the description of the ✲ of molecules, their state, and location.

① Chemical concentrations vary in space & time:
↳ This was described by diffusion.
But remember! In a cell, the idea of local concentration may not be well-defined because:
↳ Too small number of molecules
↳ Molecules may be localized to membranes and/or organelles

② The rate eqn describes the time evolution.
Generally: $$\frac{dc_i}{dt} = f(c_i, K_i)$$

→ How c_i changes depends on the concentration of all molecules, c_i, and how it reacts, k_i.

Molecular Decay of Retinal

Retinal is a molecule that can undergo a conformational change due to photon absorption. It is the chemical basis of animal vision and allows some organisms to convert light to metabolic energy.
↳ show Fig. 15.5

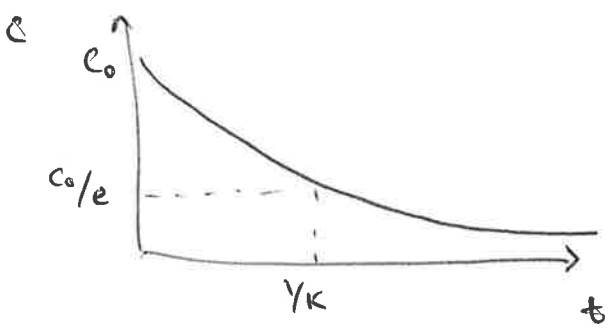
$A \xrightarrow{K} B$

This gives,

$$\frac{dc(t)}{dt} = -K \cdot c(t)$$

$$\frac{1}{c}dc = -k\,dt$$
$$\ln c = -kt + C$$
$$c(t) = c_0 \exp(-kt)$$
$$= c_0 \exp(-t/\tau) \quad \sqrt{\frac{1}{K} = \tau}$$

Soln: $c(t) = c_0 \exp(-kt)$ → see Fig 15.6



But the decay of one species can influence the concentration of another!

↳ see Fig. 15.8

For each A decaying, we have one more B.

↳ This gives a coupling between A and B.

$$\frac{dC_A}{dt} = -\frac{dC_B}{dt} = -kC_A$$

If we start with all molecules in A and none in B

↳ $C_A(0) = C_0$; $C_B(0) = 0$

We know the total number is conserved,

$$C_A(t) + C_B(t) = C_0 \longrightarrow C_A = C_0 - C_B(t)$$

$$\Rightarrow \frac{dC_B}{dt} = kC_A = k(C_0 - C_B(t))$$

$$\Rightarrow C_B(t) = C_0(1 - \exp(-kt))$$

Overall we know,

$$\frac{dc}{dt} = 0 = -k_+ C_A + k_- C_B \longleftarrow \frac{dC_A}{dt} = -\frac{dC_B}{dt}$$

$$\Rightarrow \frac{C_A}{C_B} = \frac{k_-}{k_+}$$

k_+ and k_- are the two sources of concentration change.

⇒ At long time, the ratio between A and B is determined by these rates.

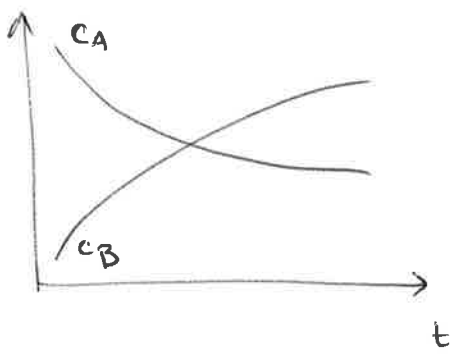
You can go back and solve the above system by k_+ and k_- to get,

$$C_A(t) = \alpha + \beta \exp[-t(k_+ + k_-)]$$

$$C_B(t) = \beta + \alpha \exp[-t(k_+ + k_-)]$$

where $\alpha = \frac{C_0 k_-}{k_+ + k_-}$

$$\beta = \frac{C_0 k_+}{k_+ + k_-}$$



Biomolecular Reactions

Conformational changes and decay are interesting, but only a small subset of interesting reactions.

Lets think of a Receptor - Ligand system → Fig 15.9

$$R + L \rightleftharpoons RL$$

The reaction will happen with rate k_{on} only if R and L are in the same box. → must be close!

Ω = total # of boxes

L = tot # of ligands in boxes ⟶ $P_L = \frac{L}{\Omega}$

R = tot # of receptors in boxes ⟶ $P_R = \frac{R}{\Omega}$

The change in the number RL during a time interval Δt can be described as,

$$\Delta N_{RL} = -(k_{off} \cdot N_{RL} \cdot \Delta t) + \Omega \cdot P_L \cdot P_R \cdot k_{on}' \cdot \Delta t$$

$-(k_{off} \cdot N_{RL} \cdot \Delta t)$: decay

Ω: # of boxes; $P_L \cdot P_R$: prob that boxes are occupied

Now turn this into a differential eqn by dividing by Δt and take the limit as $\Delta t \to dt$; $\Delta N \to dN$.

$$\frac{dN_{RL}}{dt} = -k_{off} N_{RL} + \Omega \frac{L}{\Omega} \frac{R}{\Omega} k_{on}'$$

Divide by $V = v\Omega$ to get concentrations

$$\frac{d}{dt}\left(\frac{N_{RL}}{v \cdot \Omega}\right) = -k_{off}\left(\frac{N_{RL}}{v \cdot \Omega}\right) + \frac{\Omega}{v \cdot \Omega} \cdot \frac{L}{v \cdot \Omega} \cdot \frac{R}{v \cdot \Omega} v^2 k_{on}'$$

$\frac{N_{RL}}{v \cdot \Omega}$ → [RL]; $\frac{N_{RL}}{v \cdot \Omega}$ → [RL]; $\frac{L}{v \cdot \Omega}$ → [L]; $\frac{R}{v \cdot \Omega}$ → [R]

$k_{on} = v \cdot k_{on}'$

$$\boxed{\frac{d[RL]}{dt} = -k_{off}[RL] + k_{on}[L][R]}$$

The important part is the coupling! If [L] or [R] changes over time it influences [RL] and this leads to biochemical reaction networks.

Let's consider the equilibrium case,

$$\frac{d[RL]}{dt} = 0$$

$$\Rightarrow k_{off}[RL]_{eq} = k_{on}[L]_{eq}[R]_{eq}$$

$$\Rightarrow \frac{[L]_{eq}[R]_{eq}}{[RL]_{eq}} = \frac{k_{off}}{k_{on}} = k_d$$

We have recovered the Law of Mass Action directly from the rate equation!

But the previous dynamical equation tells us more since it gives quantitative insight into the time evolution of the reactions.

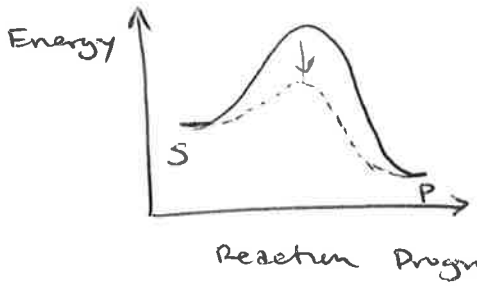
For more examples and review a good resource is the UC Davis Biowiki:

biowiki.ucdavis.edu/Biochemistry/Transport_and_Kinetics/Rapid_Equilibrium_and_Steady-State_Enzyme_Kinetics

Enzyme Kinetics

What do enzymes do? Anyone have a guess?

Enzymes lower the activation barrier for a reaction to occur.



↓ ΔG

$$E + S \rightleftharpoons ES \rightleftharpoons E + P$$

- The enzyme will bind to the substrate S before being turned into the product P.
- Enzymes aren't used up! They are still there at the end!

So let's simplify this process,

Recall,

$$A \rightarrow B \qquad \text{Rate} = K[A] \rightarrow \text{speed of the reaction} \uparrow V$$

Now,

$$E + S \overset{①}{\rightleftharpoons} ES \overset{②}{\rightleftharpoons} E + P$$

① $\text{Rate}_1 = K_1[E][S]$

② $\text{Rate}_2 = k_2[ES]$

So for the overall rate of our system we have,

$$\text{Rate} = V = \frac{d[P]}{dt}$$

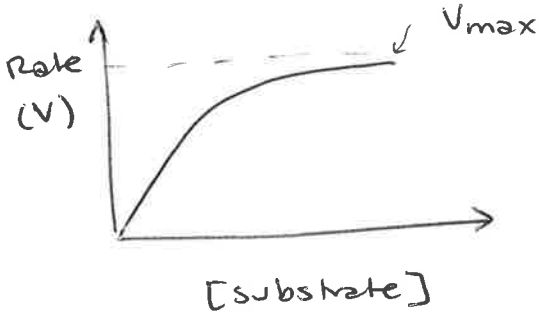
If we want to ↑ Rate then ↑ [S], ↑ [E], since K = const.

As in many situations, let's assume the enzyme concentration is constant, [E] = constant.

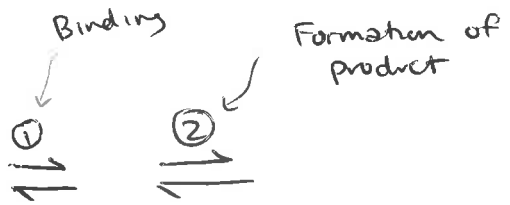
- Each enzyme can catalyze 10 rxns/sec

  Max Rate = 40 rxns/sec → V_{max}

- At high [S], the enzymes will be saturated and thus no matter if you ↑↑ [S], there is still a V_{max} determined by [E].



Assumptions:



① Solutions behave ideally...

② [E] → constant .... leads to V_{max}

K → constant

③ S → P w/o enzyme is negligible.

Michaelis-Menton Kinetics

- Enzymes make reactions "go" faster!

$$E + S \underset{-1}{\overset{1}{\rightleftharpoons}} ES \underset{-2}{\overset{2}{\rightleftharpoons}} E + P$$

- Steady state assumption → [ES] = constant
  - ↳ Formation = Loss of ES

Formation of ES = Loss of ES

$Rate_1 + Rate_{-2} = Rate_{-1} + Rate_2$ b/c arrow direction

↳ since products are typically stable, $Rate_{-2} \approx 0$

$$E + S \underset{-1}{\overset{1}{\rightleftharpoons}} ES \xrightarrow{2} E + P$$

Rate eqn: $k_1[E][S] = k_{-1}[ES] + k_2[ES]$ ← eqm eqn

Total amount of [E],

$[E]_{TOT} = [E] + [ES]$ solve for [E] and plug in eqm eqn

$$k_1([E]_{TOT} - [ES])[S] = [ES](k_{-1} + k_2)$$

$$k_1[E]_{TOT}[S] - k_1[ES][S] = [ES](k_{-1} + k_2)$$

divide by k_1

$$[E]_{TOT}[S] - [ES][S] = [ES]\left(\underbrace{\frac{k_{-1} + k_2}{k_1}}_{K_M}\right)$$

$$[E]_{TOT}[S] = [ES]K_M + [ES][S]$$

↳ $$[ES] = \frac{[E]_{TOT}[S]}{K_M + [S]}$$

Remember the overall speed of our reaction is,

$$V_0 = \frac{dP}{dt} = k_2 [ES]$$

To get this form above multiply previous by k_2,

$$k_2 [ES] = \frac{k_2 [E]_{TOT} [S]}{K_M + [S]} \qquad (*)$$

If $V_0 = V_{max}$ i.e. substrate concentration really high

Then $[E]_{TOT} = [ES]$ b/c all enzyme is saturated by substrate

$\therefore$ $k_2 [E]_{TOT} = V_{max}$

From (*),

$$\boxed{V_0 = \frac{V_{max} [S]}{K_M + [S]}}$$

Michaelis-Menton Equation

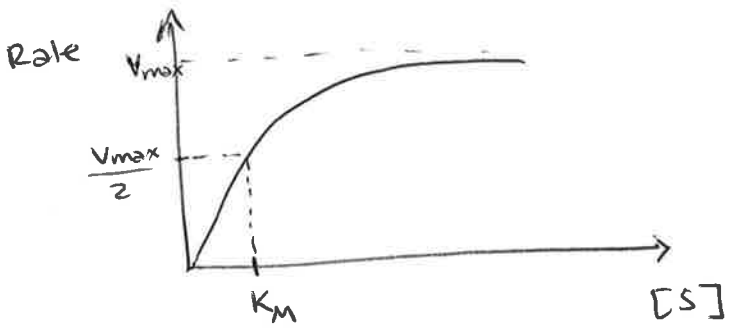
So what is K_M?

Now lets say $K_M = [S]$,

Then

$$V_0 = \frac{V_{max} [S]}{2 [S]} = \frac{V_{max}}{2}$$

$\therefore$ K_M is the $[S]$ where $V_0 = \frac{1}{2} V_{max}$



lower K_M the more effective the enzyme at low $[S]$.

catalytic Efficiency:

$K_M = [S]$ where $V_0 = \frac{1}{2} V_{max}$ units of $K_M \Rightarrow M$

$K_{CAT} = \frac{V_{max}}{[E]_{TOT}}$ Turnover number units of $K_{CAT} \rightarrow sec^{-1}$

catalytic efficiency $= \frac{K_{CAT}}{K_M}$ $\uparrow K_{CAT}$ $\downarrow K_M$

Michaelis - Menten Summary

① Steady - State Assumption

$$E + S \rightleftharpoons ES \rightarrow P$$

Formation of ES = Loss of ES

② $$V_0 = \frac{V_{max}[S]}{K_M + [S]}$$ Michaelis - Menten Equation

③ Catalytic Efficiency = $$\frac{K_{CAT}}{K_M}$$

Note: Give students the paper and matlab code for the Chemical Oscillations lecture.