Modeling biochemical reactions

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Overview

In biochemistry, 2+ species, or "reactants" can react if they come toegether and collide.

Alternatively, one species can degrade.

More is needed, though: correct orientation, enough energy, etc.

Examples

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O \quad \text{(burning of methane)}$$

$$H^+ + OH^- \longrightarrow H_2O$$

$$\text{unfolded protein} \longrightarrow \text{folded protein}$$

$$2SO_2 + O_2 \rightleftharpoons 2SO_3$$

$$O_3 \longrightarrow O_2 + O$$

$$2O_3 \longrightarrow 3O_2$$

Mass-action kinetics

Classification of reactions:

- $A \longrightarrow P$: "uni-molecular"
- $A + B \longrightarrow P$: "bi-molecular"
- $A + B + C \longrightarrow P$: "tri-molecular"

Law of mass-action kinetics

A *reaction rate* is proportional to the probability of collision of reactants involved.

Assume this probability is proportional to the concentration of each reactant R, denoted $[R]$.

ODE model

- $A \xrightarrow{k} P$: $\dfrac{d[P]}{dt} = k[A]$
- $A + B \xrightarrow{k} P$: $\dfrac{d[P]}{dt} = k[A][B]$
- $A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} P$: $\dfrac{d[P]}{dt} = k_1[A][B] - k_2[P]$

Mass-action kinetics

Enzymes are proteins that catalyze reactions (up to 10^{12}-fold!)

An example

Consider the following chemical reaction

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

E = enzyme, S = substrate, ES = enzyme-substrate complex, and P = product.

$$\begin{cases} \dfrac{d[ES]}{dt} = k_1[E][S] - (k_2 + k_3)[ES] \\ \dfrac{d[P]}{dt} = k_3[ES] \\ E_0 = [E] + [ES], \qquad E_0 = \text{ initial enzyme concentration} \end{cases}$$

Assumptions

- E_0 is constant.
- Enzyme-substrate complex reaches equilibrium much earlier than the product does, so $\dfrac{d[ES]}{dt} \approx 0$.

Mass-action kinetics

Goal

Write the differential equation $\frac{d[P]}{dt} = k_3[ES]$ in terms of $[S]$, not $[ES]$.

Since $\frac{d[ES]}{dt} \approx 0$, we can simplify the ODE for $[ES]$:

$$\frac{d[ES]}{dt} = k_1[E][S] - (k_2 + k_3)[ES] = 0\,.$$

Upon solving for $[E]$, we get

$$[E] = \frac{(k_2 + k_3)[ES]}{k_1[S]}\,.$$

Plugging this into $E_0 = [E] + [ES]$ and solving for $[ES]$:

$$[ES] = \frac{E_0[S]}{\frac{k_2+k_3}{k_1} + [S]}\,.$$

Alas, we can write

$$\frac{d[P]}{dt} = k_3[ES] = \frac{k_3 E_0[S]}{\frac{k_2+k_3}{k_1} + [S]} = \frac{V_{\max}[S]}{K_m + [S]}\,.$$

Michaelis–Menten equation

Recall the following chemical reaction:

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

E = enzyme, S = substrate, ES = enzyme-substrate complex, and P = product.

Definition

The Michaelis–Menten equation is one of the best-known models of enzyme kinetics.

$$\frac{d[P]}{dt} = \underbrace{\frac{V_{\max}[S]}{K_m + [S]}}_{f([S])}, \qquad \text{where } V_{\max} = k_3 E_0, \quad \text{and } K_m = \frac{k_2 + k_3}{k_1}$$

Remarks

- The "reaction rate", $f([S])$, is a strictly increasing function of $[S]$.
- $\lim_{[S]\to\infty} f([S]) = V_{\max}$, (biologically, the maximum reaction rate)
- $f(K_m) = \frac{1}{2} V_{\max}$.
- The reaction rate $f([S])$ is proportional to E_0.

Michaelis–Menten equation

Recall the following chemical reaction:

$$E + S \underset{k_1}{\overset{k_2}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

E = enzyme, S = substrate, ES = enzyme-substrate complex, and P = product.

Further assumptions

- Substrate concentration is conserved: $S_0 = [S] + [ES] + [P]$.
- $E_0 \ll S_0$, so $[ES] \ll [S]$ and $[P]$.

Together, this means $S_0 \approx [S] + [P]$. Taking $\frac{d}{dt}$ of both sides yields

$$\frac{d[S]}{dt} = -\frac{d[P]}{dt} = -\frac{V_{\max}[S]}{k_m + [S]}\,.$$

Usually, $V_{\max}$, K_m, and S_0 are known quanities. This is now something we can easily solve, graph, analyze, etc.

Multi-molecule binding

Consider a reaction where n molecules of a substrate S react with an enzyme E:

$$E + nS \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES_n \xrightarrow{k_3} E + P$$

The enzyme-substrate complex here is ES_n. By mass-action kinetics,

$$\begin{cases} \dfrac{d[ES_n]}{dt} = k_1[E][S]^n - (k_2 + k_3)[ES_n] \\ \dfrac{d[P]}{dt} = k_3[ES_n] \\ E_0 = [E] + [ES_n], \qquad E_0 = \text{ initial enzyme concentration} \end{cases}$$

As before, assume $[ES_n]$ reaches equilibrium much quicker than $[P]$ and $[S]$:

$$\frac{d[ES_n]}{dt} = 0 \qquad \Longrightarrow \qquad [E] = \frac{(k_2 + k_3)[ES_n]}{k_1[S]^n}.$$

Plugging this into $E_0 = [E] + [ES_n]$ and solving for $[ES_n]$ yields

$$[ES_n] = \frac{E_0[S]^n}{\frac{k_2+k_3}{k_1} + [S]^n} \qquad \Longrightarrow \qquad \boxed{\frac{d[P]}{dt} = \frac{V_{\max}[S]^n}{K_m + [S]^n}}.$$

Multi-molecule binding

Hill equation

Given the chemical reaction

$$E + nS \underset{k_1}{\overset{k_2}{\rightleftharpoons}} ES_n \xrightarrow{k_3} E + P$$

we derived the following ODE involving $[P]$ and $[S]$:

$$\frac{d[P]}{dt} = \underbrace{\frac{V_{\max}[S]^n}{K_m + [S]^n}}_{f([S])}, \qquad \text{where } V_{\max} = k_3 E_0, \quad \text{and } K_m = \frac{k_2 + k_3}{k_1}$$

This is called the Hill equation with Hill coefficient n.

Remarks

- The "reaction rate", $f([S])$, is a strictly increasing function of $[S]$.
- $\lim_{[S]\to\infty} f([S]) = V_{\max}$, (biologically, the maximum reaction rate)
- $f(K_m^{1/n}) = \frac{1}{2} V_{\max}$.
- The reaction rate $f([S])$ is proportional to E_0.
- $n = 1$ is just the Michaelis–Menden equation.

Hill equations

The following shows several "Hill functions" $y = \dfrac{t^n}{1+t^n}$, for various values of n.