Modeling biochemical reactions

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Overview

In biochemistry, 2+ species, or “reactants” can react if they come together and collide.

Alternatively, one species can degrade.

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

Examples

\[ CH_4 + 2O_2 \rightarrow CO_2 + 2H_2O \] (burning of methane)

\[ H^+ + OH^- \rightarrow H_2O \]

folded protein \(\rightarrow\) unfolded protein

\[ 2SO_2 + O_2 \leftrightarrow 2SO_3 \]

\[ O_3 \rightarrow O_2 + O \]

\[ 2O_3 \rightarrow 3O_2 \]
Mass-action kinetics

Classification of reactions:

- $A \rightarrow P$: “uni-molecular”
- $A + B \rightarrow P$: “bi-molecular”
- $A + B + C \rightarrow P$: “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

- $A \xrightarrow{k} P$: $\frac{d[P]}{dt} = k[A]
- A + B \xrightarrow{k} P$: $\frac{d[P]}{dt} = k[A][B]
- A + B \xrightarrow{k_1}{k_2} P$: $\frac{d[P]}{dt} = k_1[A][B] - k_2[P]$
Mass-action kinetics

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

### An example

Consider the following chemical reaction

$$E + S \xrightleftharpoons[k_2]{k_1} ES \xrightarrow{k_3} E + P$$

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

\[
\begin{align*}
\frac{d[ES]}{dt} &= k_1[E][S] - (k_2 + k_3)[ES] \\
\frac{d[P]}{dt} &= k_3[ES] \\
E_0 &= [E] + [ES], \quad E_0 = \text{initial enzyme concentration}
\end{align*}
\]

### Assumptions

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

\[
\frac{d[P]}{dt} = k_3[ES] = \frac{k_3E_0[S]}{\frac{k_2 + k_3}{k_1} + [S]} = \frac{V_{\text{max}}[S]}{K_m + [S]}.
\]
Michaelis–Menten equation

Recall the following chemical reaction:

\[ E + S \xrightleftharpoons[k_2]{k_1} ES \xrightarrow{k_3} E + P \]

\( E = \) 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.

\[
\frac{d[P]}{dt} = \frac{V_{\text{max}} [S]}{K_m + [S]}, \quad \text{where } V_{\text{max}} = k_3 E_0, \quad \text{and } K_m = \frac{k_2 + k_3}{k_1}
\]

**Remarks**

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

Recall the following chemical reaction:

\[ E + S \underset{k_1}{\overset{k_2}{\rightleftharpoons}} ES \overset{k_3}{\rightarrow} E + P \]

\( E = \) 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

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

Usually, \( V_{\text{max}} \), \( K_m \), and \( S_0 \) are known quantities. 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 \( E \):

\[
E + nS \overset{k_1}{\underset{k_2}{\rightleftharpoons}} ES_n \overset{k_3}{\rightarrow} E + P
\]

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

\[
\begin{align*}
\frac{d[ES_n]}{dt} &= k_1[E][S]^n - (k_2 + k_3)[ES_n] \\
\frac{d[P]}{dt} &= k_3[ES_n] \\
E_0 &= [E] + [ES_n], \quad E_0 = \text{initial enzyme concentration}
\end{align*}
\]

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

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

Plugging this into \(E_0 = [E] + [ES_n]\) and solving for \([ES_n]\) yields

\[
[ES_n] = \frac{E_0[S]^n}{\frac{k_2 + k_3}{k_1} + [S]^n} \quad \Rightarrow \quad \frac{d[P]}{dt} = \frac{V_{\text{max}}[S]^n}{K_m + [S]^n}.
\]
Multi-molecule binding

Hill equation

Given the chemical reaction

\[
E + nS \xrightarrow{k_2/k_1} ES_n \xrightarrow{k_3} E + P
\]

we derived the following ODE involving \([P]\) and \([S]\):

\[
\frac{d[P]}{dt} = \frac{V_{\text{max}}[S]^n}{K_m + [S]^n}, \quad \text{where } V_{\text{max}} = k_3E_0, \quad \text{and } K_m = \frac{k_2 + k_3}{k_1}
\]

This is called the **Hill equation** with **Hill coefficient** \(n\).

Remarks

- The “reaction rate”, \(f([S])\), is a strictly increasing function of \([S]\).
- \(\lim_{[S] \to \infty} f([S]) = V_{\text{max}}, \) (biologically, the maximum reaction rate)
- \(f(K_m^{1/n}) = \frac{1}{2}V_{\text{max}}.\)
- 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” \( y = \frac{t^n}{1 + t^n} \), for various values of \( n \).