

# Modeling biochemical reactions

Matthew Macauley

Department of Mathematical Sciences  
Clemson University

<http://www.math.clemson.edu/~macaule/>

Math 4500, Spring 2017

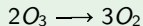
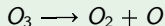
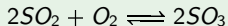
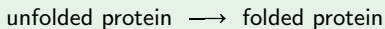
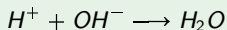
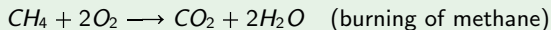
## Overview

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



## 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

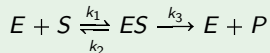
- $A \xrightarrow{k} P$ :  $\frac{d[P]}{dt} = k[A]$
- $A + B \xrightarrow{k} P$ :  $\frac{d[P]}{dt} = k[A][B]$
- $A + B \xrightleftharpoons[k_2]{k_1} P$ :  $\frac{d[P]}{dt} = k_1[A][B] - k_2[P]$

## Mass-action kinetics

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

### An example

Consider the following chemical reaction



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

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

### 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  $[ES]$ :

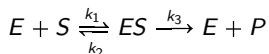
$$[ES] = \frac{E_0[S]}{\frac{k_2 + k_3}{k_1} + [S]}.$$

Alas, we can write

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

## Michaelis–Menten equation

Recall the following chemical reaction:



$E$  = 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.

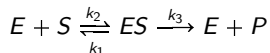
$$\frac{d[P]}{dt} = \frac{V_{\max}[S]}{\underbrace{K_m + [S]}_{f([S])}}, \quad \text{where } V_{\max} = k_3 E_0, \quad \text{and } K_m = \frac{k_2 + k_3}{k_1}$$

### Remarks

- The “reaction rate”,  $f([S])$ , is a strictly increasing function of  $[S]$ .
- $\lim_{[S] \rightarrow \infty} f([S]) = V_{\max}$ , (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:



$E$  = 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 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  $E$ :



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

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

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

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

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

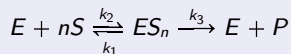
$$[ES_n] = \frac{E_0[S]^n}{\frac{k_2+k_3}{k_1} + [S]^n} \quad \implies \quad \boxed{\frac{d[P]}{dt} = \frac{V_{\max}[S]^n}{K_m + [S]^n}}.$$



## Multi-molecule binding

### Hill equation

Given the chemical reaction



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

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

This is called the **Hill equation** with **Hill coefficient**  $n$ .

### Remarks

- The “reaction rate”,  $f([S])$ , is a strictly increasing function of  $[S]$ .
- $\lim_{[S] \rightarrow \infty} f([S]) = V_{\max}$ , (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”  $y = \frac{t^n}{1+t^n}$ , for various values of  $n$ .

