

Chemical reaction networks

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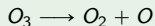
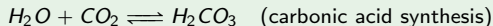
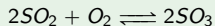
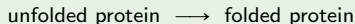
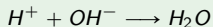
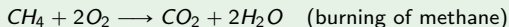
Overview

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



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.

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

If x is proportional to y , then this means that they differ by a constant k , i.e.,

$$x = ky.$$

If x is proportional to y and z , then for some constant k ,

$$x = kyz.$$

Mass-action kinetics

Law of mass-action kinetics

A *reaction rate* is proportional to the concentrations of the the reactants.

ODE model

$$\blacksquare A \xrightarrow{k} P: \quad \frac{d[P]}{dt} = k[A]$$

$$\blacksquare A \xrightarrow{k} P + Q: \quad \frac{d[P]}{dt} = k[A]$$

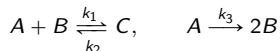
$$\blacksquare A + B \xrightarrow{k} P: \quad \frac{d[P]}{dt} = k[A][B]$$

$$\blacksquare 2A \xrightarrow{k} P: \quad \frac{d[P]}{dt} = k[A]^2$$

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

An example

Consider the following chemical reaction network:



Let $x_1(t)$, $x_2(t)$, and $x_3(t)$ denote the concentrations of A , B , and C . Then we get the system

$$\begin{aligned}\frac{dx_1}{dt} &= -k_1 x_1 x_2 + k_2 x_3 - k_3 x_1 \\ \frac{dx_2}{dt} &= -k_1 x_1 x_2 + k_2 x_3 + 2k_3 x_1 \\ \frac{dx_3}{dt} &= k_1 x_1 x_2 - k_2 x_3.\end{aligned}$$

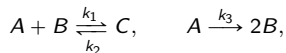
To find the steady-states, set each $x'_i = 0$ and solve the system.

This can be found by computing a Gröbner basis of the ideal

$$I = (-k_1 x_1 x_2 + k_2 x_3 - k_3 x_1, -k_1 x_1 x_2 + k_2 x_3 + 2k_3 x_1, k_1 x_1 x_2 - k_2 x_3).$$

An example

Consider the following chemical reaction network:



and the resulting system of nonlinear ODEs:

$$\begin{aligned}\frac{dx_1}{dt} &= -k_1 x_1 x_2 + k_2 x_3 - k_3 x_1 \\ \frac{dx_2}{dt} &= -k_1 x_1 x_2 + k_2 x_3 + 2k_3 x_1 \\ \frac{dx_3}{dt} &= k_1 x_1 x_2 - k_2 x_3.\end{aligned}$$

Questions

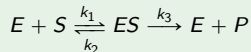
- Does the system have a positive or non-negative equilibrium?
- Does the system have *multiple* positive equilibria?
- Does the system have a *stable* positive equilibrium?
- Does the system have an *unstable* positive equilibrium?
- Do all positive species concentrations admit a positive cyclic composition trajectory?
- How do the answers to these questions depend on the rate constants?

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 $[ES]$:

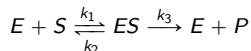
$$[ES] = \frac{E_0[S]}{\frac{k_2 + k_3}{k_1} + [S]}.$$

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.

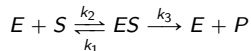
$$\frac{d[P]}{dt} = \frac{V_{\max}[S]}{\underbrace{K_m + [S]}_{f([S])}}, \quad \text{where } V_{\max} = k_3 E_0, \text{ and } K_m = \frac{k_2 + k_3}{k_1}$$

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 $[P]$.

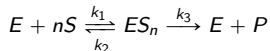
Together, this means $S_0 \approx [S] + [P]$. Taking $\frac{d}{dt}$ of both sides yields

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

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 $[S]$:

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

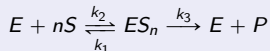
Plugging this into $E_0 = [E] + [ES_n]$ and solving for $[ES_n]$ yields

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

Multi-molecule binding

Hill equation

Given the chemical reaction



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

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

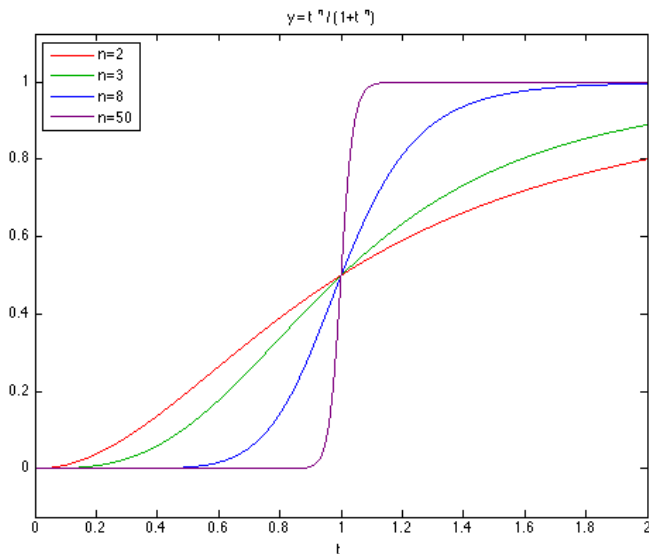
This is called the **Hill equation** with **Hill coefficient** n .

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.

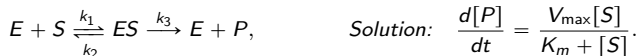
Hill equations

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



Michaelis–Menten variants

We just saw an equation for where 1 molecule of a substrate reacts with an enzyme:



Suppose two substrates compete for the same enzyme:



$$E_0 = [E] + [ES] + [ET].$$

Exercise (HW): Solve for $\frac{d[P]}{dt}$ and $\frac{d[Q]}{dt}$.

Question

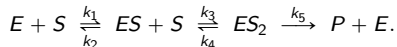
How does the effects of the competition affect the dynamics of the system?

Michaelis–Menten variants

We just saw an equation for where 2 molecules of a substrate reacts with an enzyme:



But what if the binding is sequential?



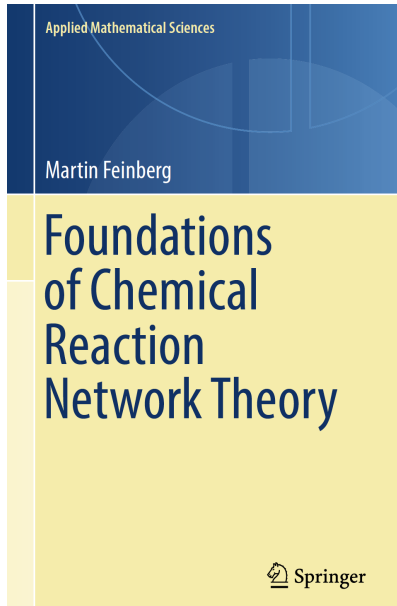
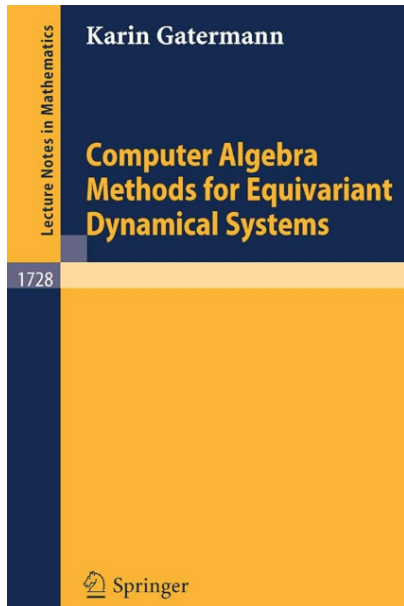
This is really two separate reactions:



Question

When does this system become roughly the same as the Hill equation with coefficient $n = 2$?

For more information



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