MATH 537: Mathematical Methods in Biology
Winter 2022 Semester

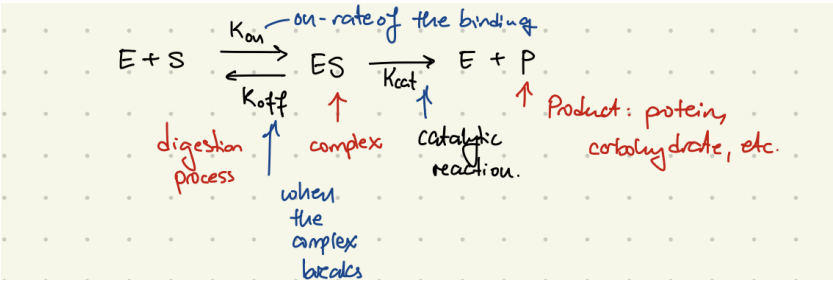
1 Introduction

There will be two parts of this course:

1. **Quantitative Immunology**. This will cover:
   (a) Epidemiological Models
   (b) Immunological Responses to Infectious Disease.
   (c) Immunological Responses to Autoimmune Disease.
   (d) T-cell receptor kinetics.
2. **Computational Neuro-Electrophysiology**. This part of the course will cover:
   (a) Membrane electrophysiology.
   (b) Excitable Systems (HH and ML models).
   (c) Multiscale Oscillations.
   (d) Dynamics of Neural Networks.

1.1 Basic Quantitative Concepts

We will first introduce some basic quantitative concepts, and provide a brief review of MATH 376, Non-Linear Dynamics. The first important concept is the idea of a **reaction model**. Consider an enzyme E interacting with a substrate S:



ES is the complex of the substrate bound to the enzyme, and P is the product of the reaction. In terms of units, we have that

$$[\ k_{\text{on}}\ ] = \frac{1}{(\text{concentration})(\text{time})}$$
$$[\ k_{\text{off}}\ ],\ [\ k_{\text{cat}}\ ] = \frac{1}{\text{time}}.$$

We want to study the concentrations of the molecules over time, which gives us ODEs. Let's see how this works by first focusing on the substrate S. The two things which affects the dynamics of S is k_{on} and k_{off}. We want to arrive at a differential equation for $\frac{d[S]}{dt}$, the rate of change of the concentration of S with respect to time. This is given by adding the loss term to the source term:

$$\frac{d[S]}{dt} = \underbrace{-k_{\text{on}}[E][S]}_{\text{loss term}} + \underbrace{k_{\text{off}}[ES]}_{\text{source term}} \tag{1}$$

The fact that we multiply the concentration of the components, S and E, is our first main principle: **mass-action kinematics**. One could do the same thing for all the molecules: in general, $\frac{d[X]}{dt}$ is the rate of change of the concentration of X:

$$\begin{aligned}\frac{d[S]}{dt} &= -k_{\text{on}}[E][S] + k_{\text{off}}[ES] \\ \frac{d[E]}{dt} &= -k_{\text{on}}[E][S] + (k_{\text{off}} + k_{\text{cat}})[ES] \\ \frac{d[P]}{dt} &= k_{\text{cat}}[ES] \\ \frac{d[ES]}{dt} &= k_{\text{on}}[E][S] - (k_{\text{off}} + k_{\text{cat}})[ES].\end{aligned}$$

Let's focus on the key equation: $\frac{d[ES]}{dt} = k_{\text{on}}[E][S] - (k_{\text{off}} + k_{\text{cat}})[ES]$. ES is not a stable molecule: it either goes to $E + S$ or $E + P$. Thus, it has fast dynamics, which will allow us to apply the second key principle: the **Quasi-Steady State Approximation (QSS)**: since the transient dynamics are very fast, or has a fast reaction velocity, it will reach a steady state very quickly. Thus, we may set $\frac{d[ES]}{dt}$ equal to zero and still have a reasonable approximation:

$$\frac{d[ES]}{dt} = k_{\text{on}}[E][S] - (k_{\text{off}} + k_{\text{cat}})[ES] = 0.$$

We can solve for $[ES]$:

$$[ES] = \frac{[E_T][S]}{\left(\frac{k_{\text{off}}+k_{\text{cat}}}{k_{\text{on}}}\right) + [S]},$$

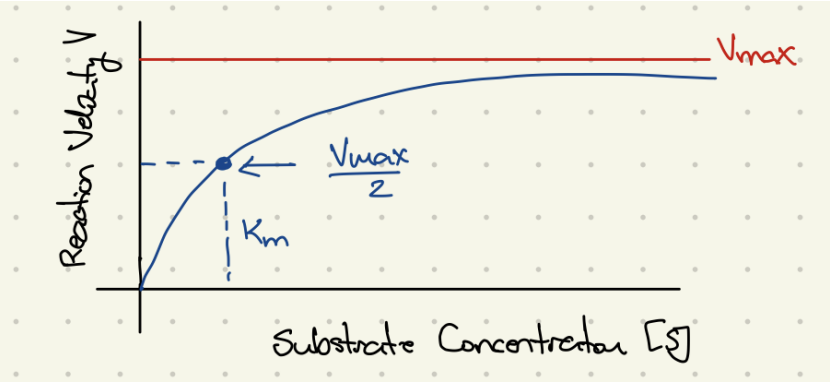
where $[E_T] = [E] + [ES]$ is the total concentration of the enzyme. It is conserved. Now, with this in hand, we want to shift our attention to the product P. It satisfies the following differential equation:

$$\frac{d[P]}{dt} = k_{\text{cat}}[ES].$$

Using the QSS approximation done above, we can substitute in an approximation for $[ES]$. It yields the following reaction velocity for the product P given by:

$$v = k_{\text{cat}}[ES] = \frac{k_{\text{cat}}[E_T][S]}{\left(\frac{k_{\text{off}}+k_{\text{cat}}}{k_{\text{on}}}\right) + [S]} = V_{\max}\frac{[S]}{k_M + [S]}, \tag{2}$$

where $V_{\max} = k_{\text{cat}}[E_T]$ and $k_M = \frac{k_{\text{off}}+k_{\text{cat}}}{k_{\text{on}}}$. This is a hyperbolic function of just $[S]$. This leads us to our next key concept: **Michaelis-Menter Kinetics**, which is represented by the $V_{\max}\frac{[S]}{k_M+[S]}$ term. We can plot this function:



The value k_M is the **half-maximum activation**. Why? Because at $[S] = k_M$, we have that $v = \frac{V_{\max}}{2}$.

What if we have multiple enzymes that could interact with the substrate? In this case, we observe a phenomenon called **cooperativity in the binding**. This means that we will have a sigmoidal curve to describe the kinetics rather than a hyperbolic curve. This leads us to our next key concept: the sigmoid kinetics are described by a **Hill Function**:

$$v = V_{\max} \frac{[S]^n}{k_M^n + [S]^n}, \tag{3}$$

where n is the **Hill Coefficient**. $\rightarrow$ **Homework 1 Q1**.

Now, to summarize.

1. Mass-Action Kinetics: we can take the product of the two terms: $X + Y \rightarrow [X][Y]$.
2. Quasi-Steady State (QSS) Approximation: the dynamics are very fast, so we can set the differential equation to zero.
3. Michaelis-Menten Kinetics:

$$v = V_{\max} \frac{[S]}{k_M + [S]}. \tag{4}$$

4. Sigmoidal Kinetics (Hill Function) (in the case of $n = 1$, we recover (3)).

$$v = V_{\max} \frac{[S]^n}{k_M^n + [S]^n}. \tag{5}$$

1.2 Stability Analysis

Suppose we have a system of ODEs. There are two types:

1. **Autonomous**: $\dot{x} = F(x)$.
2. **Non-Autonomous**: $\dot{x} = F(x, t)$.

In this course, we will only consider autonomous systems of ODEs. If the ODE is simple enough, we can analytically solve it. Then, there will be no need for stability analysis. However, in many scenarios, the system cannot be solved analytically. So a very powerful tool at our disposal is non-linear dynamics, which allows us to explore the long-term behaviour of the solution, rater than the transient dynamics of the system. To see what mathematical tools this will use, we will work through an example.

Example 1. Consider the following ODE:

$$ay'' + by' + cy = 0.$$

This is a second-order linear differential equation. We solve this using the characteristic polynomial: we need to find the roots of the characteristic equation,

$$am^2 + bm + c,$$

which are

$$m_{1,2} = -\frac{b}{2a} \pm \frac{\sqrt{b^2 - 4ac}}{2a}.$$

Suppose $b^2 - 4ac < 0$. Then,

$$m_{1,2} = -\alpha \pm i\beta.$$

Hence, the solution of the DE is given by:

$$y = e^{-\alpha t}[C_1 \cos(\beta t) + C_2 \sin(\beta t)].$$

Notice that:

$$y' = -\alpha e^{-\alpha t}[C_1 \cos(\beta t) + C_2 \sin(\beta t)] + e^{-\alpha t}\beta[-C_1 \sin(\beta t) + C_2 \cos(\beta t)].$$

As $t \to \infty$ for $\alpha > 0$, we get that both y and y' go to zero. Hence, $(y, y') = (0, 0)$ is asymptotically stable. That's one approach. Another is to make the following substitution to obtain a system of first-order differential equations:

$$\begin{aligned} x_1 &= y \\ x_2 &= y'. \end{aligned}$$

Then,

$$\begin{cases} x_1' &= x_2 \\ x_2' &= \frac{(-bx_2 - cx_1)}{a} \end{cases}$$

In matrix notation, this gives us:

$$\begin{bmatrix} x_1' \\ x_2' \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\frac{c}{a} & -\frac{b}{a} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}.$$

Since we can directly find a matrix that represents F, F is linear. We find the steady state by setting the derivative equal to zero:

$$\begin{bmatrix} x_1' \\ x_2' \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

Hence, the equilibrium is $(x_1, x_2) = (0, 0)$. We only know that this is stable by our prior analysis. If we did not want to solve the ODE, or could not solve the ODE, we can study the matrix $\begin{bmatrix} 0 & 1 \\ -\frac{c}{a} & -\frac{b}{a} \end{bmatrix}$ to investigate stability.

1.2.1 Stability Properties of the Steady States

If the system is linear, $\dot{x} = A(x - x_0)$, then $x = x_0$ is the steady state. If the system is non-linear, $\dot{x} = F(x)$, then we can linearize the system around its steady state $x = x_0$ (where $F(x_0) = 0$). Recall that the Taylor expansion approximates the function near x_0:

$$f(x) \approx f(x_0) + f'(x_0)(x - x_0). \tag{6}$$

Writing the equation out in matrix notation,

$$\begin{aligned} \dot{x} &= F(x) \\ \begin{bmatrix} \dot{x}_1 \\ \vdots \\ \dot{x}_n \end{bmatrix} &= \begin{bmatrix} f_1(x_1, ..., x_n) \\ \vdots \\ f_n(x_1, ..., x_n) \end{bmatrix}, \end{aligned}$$

we apply the Taylor expansion to linearize around $x_0 = (x_{10}, ..., x_{n0})$:

$$\begin{bmatrix} \dot{x}_1 \\ \vdots \\ \dot{x}_n \end{bmatrix} = \underbrace{\begin{bmatrix} f_1(x_{10}, ..., x_{n0}) \\ \vdots \\ f_n(x_{10}, ..., x_{n0}) \end{bmatrix}}_{=0} + \underbrace{\begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & & \vdots \\ \frac{\partial f_n}{\partial x_1} & \cdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix}}_{\text{jacobian}} \begin{bmatrix} x_1 - x_{10} \\ \vdots \\ x_n - x_{n0} \end{bmatrix} + \text{ h.o.t} \tag{7}$$

$$\Rightarrow x \approx \underbrace{[\text{Jac}(F)]_{x_0}}_{:=A}(x - x_0) = A(x - x_0). \tag{8}$$

Hence, the linearization of F at x_0 can tell us some information about the <u>local</u> behaviour near the steady state (it's only global if F is linear). Now substitute $y := x - x_0$ (shift the steady state to the origin). Then, $\dot{y} = \dot{x}$, and so $\dot{y} = Ay$ and so the steady state again $y = 0$. This shows us that WLOG, we can always shift the steady state to the origin. So, let's study the stability properties of the steady state $x_0 = 0$ for the linear equation,

$$\dot{x} = Ax.$$

The solution of $x' = ax$ is $x(t) = x_0 e^{at}$.