MATH 537: Mathematical Methods in Biology
Winter 2022 Semester

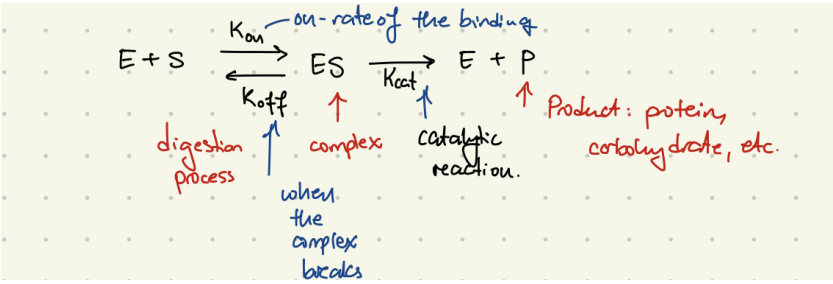
1 Introduction

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 $[ES]$:

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

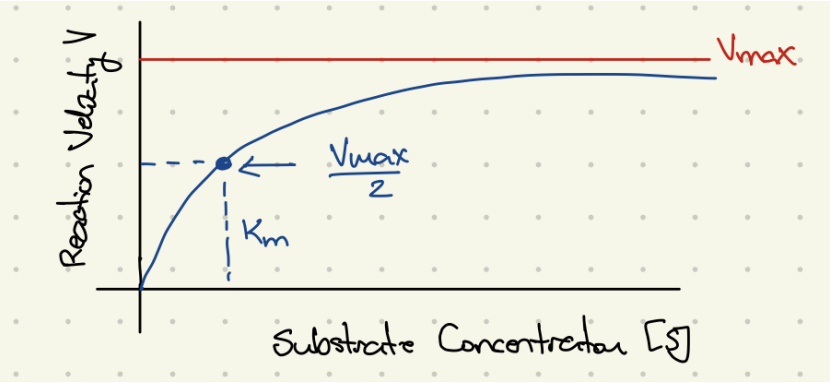
where $[E_T] = [E] + [ES]$ is the total concentration of the enzyme. It is conserved. Now, with this in hand, we want to shift our attention to the product P. It satisfies the following differential equation:

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

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 $x(t) = x_0 e^{at}$. Make the Ansatz that the solution is of the form $x = ve^{\lambda t}$, where λ could be in $\mathbb{C}$. Then,

$$\dot{x} = \lambda v e^{\lambda t} = Ax = Ave^{\lambda t}.$$

Hence, we need to solve

$$\lambda v = Av \iff (A - \lambda I)v = 0.$$

This is linear algebra now. If you start with a linear equation, great. This will apply globally. If the equation is non-linear, then use linearize, and we get local information near the steady state x_0. Now, we want to solve $\det(A - \lambda I)$ for λ to get the eigenvalues to determine the type of steady state we have.

1. If $\text{Re}(\lambda) < 0$ for all λ, then $x_0 = 0$ is stable (the long-term behaviour of the system goes to zero) $\rightarrow$ attracting.
2. If there exists a λ such that $\text{Re}(\lambda) > 0$, then $x_0 = 0$ is unstable (could be a saddle – a mixture of positive and negative).

So, we need to now find the eigenvalues of the Jacobian. We will be able to determine the stability based on the sign of $\text{Re}(\lambda)$. *Caution! Those eigenvalues determine the stability of the dynamics of the system very close to the steady state $x_0 = 0$. Indeed, the subspace spanned locally by the eigenvectors associated with the eigenvalues with negative (positive) real parts is called the* ***stable (unstable) manifolds****. These manifolds extend beyond this local region.* These manifolds extend beyond the local region.

If the eigenvalues have zero real parts (i.e., $\text{Re}(\lambda) = 0$), then we obtain the **central manifold**. Dynamics in that manifold are not straightforward. This will not be covered in this class, but be aware of it if it shows up in your work.

Let's consider a special case: two-dimensional systems $n = 2$. Suppose we have a system of equations of the form:

$$\frac{dx}{dt} = f(x, y; \mu)$$
$$\frac{dy}{dt} = g(x, y; \mu),$$

where μ is a parameter.

1. Calculate the Jacobian (linearize). The Jacobian matrix is:

$$J := A = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix} := \begin{bmatrix} a & b \\ c & d \end{bmatrix}.$$

   At the steady state, denoted by (x_0, y_0), $\frac{dx}{dt} = 0$ and $\frac{dy}{dt} = 0$.
2. Solve $\det(A - \lambda I) = 0$, i.e.,

$$\det \begin{bmatrix} a - \lambda & b \\ c & d - \lambda \end{bmatrix} = 0.$$

   Applying the previous analysis, we obtain:

$$\begin{aligned} \det(A - \lambda I) &= (a - \lambda)(d - \lambda) - bc \\ &= \lambda^2 - \underbrace{(a + d)}_{\text{trace}} \lambda + \underbrace{(ad - bc)}_{\det}. \end{aligned}$$

   This equation is called the **characteristic equation**. This means that $\det(A - \lambda I) = \lambda^2 - \text{tr}(A)\lambda + \det(A) = 0$. The eigenvalues are:

$$\lambda_{1,2} = \frac{\text{tr}(A) \pm \sqrt{\text{tr}(A)^2 - 4\det(A)}}{2}.$$

   Hence, we can re-write the characteristic equation as:

$$\begin{aligned} \det(A - \lambda I) &= (\lambda - \lambda_1)(\lambda - \lambda_2) \\ &= \lambda^2 - (\lambda_1 + \lambda_2)\lambda + \lambda_1 \lambda_2. \end{aligned}$$

Question. If the eigenvalues are real and the determinant is negative, what can we say about the eigenvalues?

Answer: assuming that they are non-zero, λ_1 and λ_2 have opposite signs. If they are of opposite signs, the steady state is unstable. It's a saddle since it's a mixture of signs. Let's explore the whole parameter space based on the trace and the determinant.

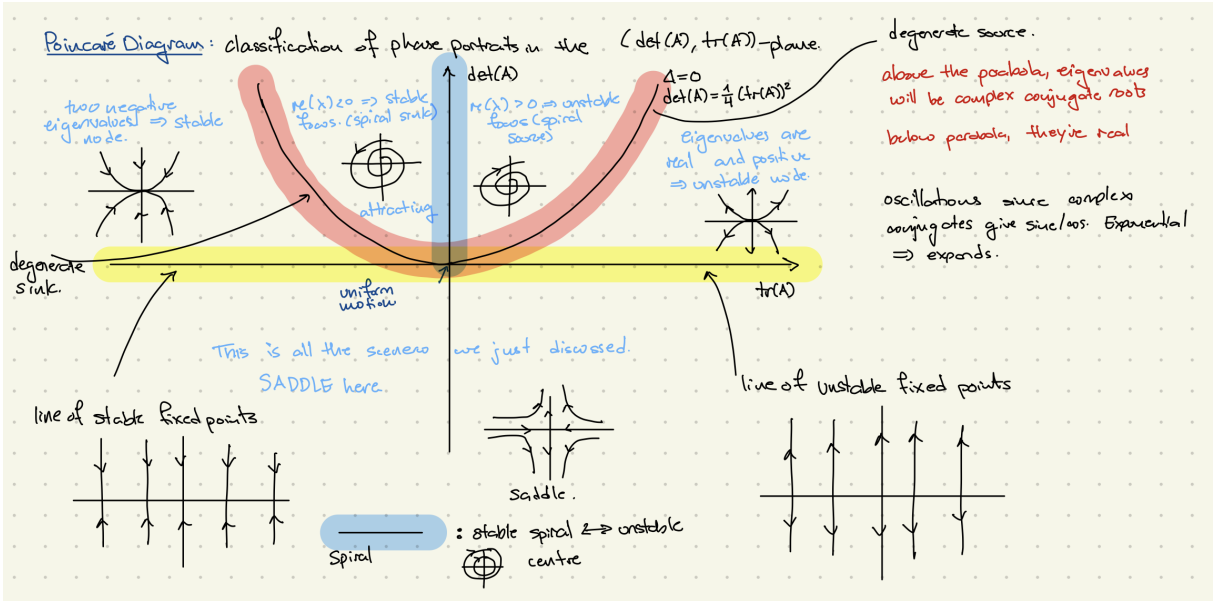


Figure 1: Poincare Diagram

Now imagine we have a parameter which acts as a bifurcation parameter. While changing the parameter, suppose we go from a stable focus to an unstable focus. Then, the dynamics are changing. If you cross the vertical axis, for example, this generates a **Hopf Bifurcation**. There are two types: **supercritical** and **subcritical** bifurcations. [to add: diagram]

1.3 Applying this to a real biological system

Let's consider epidemiological models. They are the simplest type of model which describe the spread of diseases in a population with an attempt to predict the situation down the road. This can guide decision-making at a governmental level. These are compartmental models which divide a population of individuals that could get infected with an infectious disease (e.g. SARS-CoV-2) into sub-populations. The simplest of such models is the **SIR Model**, which divides the population into three sub-populations: susceptible (S), infected (I), and recovered (R). This is an extremely powerful model in predicting several diseases.

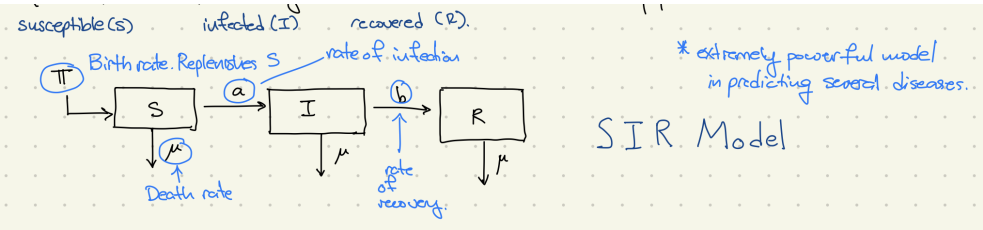


Figure 2: SIR Model

One can then use first principles to formulate a mathematical model of the system to study how this disease progresses over time (does it persist (become **endemic** or does it die out?).

1.3.1 Definitions

1. **Basic Reproductive Number (R_0)**: one way we can determine if a disease persists or dies out. It's the number of secondary infections by a primary infection that can die or recover in a population that's totally susceptible. This shows you how much the disease is spreading in a population.
   (a) $R_0 > 0$: the disease persists $\rightarrow$ becomes endemic.
   (b) $R_0 < 1$: the disease dies out.
2. **How do experimentalists quantify R_0?** They can experimentally calculuate it using the following equation:

$$R_0 = \beta c D, \tag{9}$$

   where β is the transmission probability, c is the number of contacts, and D is the average time spent infectious. $D = \frac{1}{b}$ if the infection rate is b.
   (a) Issue: we cannot quantify β, c, and D. So, the way to quantify them is to use the model we introduced.

Steps to quantify R_0:

1. Calculate the **disease-free equilibrium** (I and $R = 0$: there are no infected individuals, and consequently there are no recovered individuals).
2. Create the Jacobian matrix.
3. Evaluate the Jacobian at the disease-free equilibrium.
4. Find all the eigenvalues.

5. If all the eigenvalues are $< 0 \Rightarrow$ stable. Then, the disease goes away. If even one eigenvalue is $> 0 \Rightarrow$ unstable. Then, the disease persists, and the system will evolve since there is a non-zero amount of infected individuals.
6. The largest eigenvalue will be the R_0-like threshold.

Example 2 (SIR Model)**.** We will derive the following set of differential equations which come from the SIR model:

$$\begin{cases} \frac{dS}{dt} = \pi - aSI - \mu S \\ \frac{dI}{dt} = aSI - bI - \mu I \\ \frac{dR}{dt} = bI - \mu R. \end{cases} \tag{10}$$

Note that the aSI comes from mass-action kinetics. Let's explain where the differential equation for S comes from; the ones for I and R are an exercise. Look at the S box: the source term is π, and there are two sink terms: a and μ. S needs to be exposed to I in order to be infected, so by mass-action kinetics we get $-aSI$. Since μ is the death rate, μS is a sink term as well. Before moving on to analyze this, note that R never feeds back into I or S: the differential equation for R is independent of the previous two, so we can ignor eit and consider a two-dimensional model. This is an example of a **feedforward system**. Let's apply the steps.

1. Find the disease-free state. To find a steady state, recall that

$$\left(\frac{dS}{dt}, \frac{dI}{dt}, \frac{dR}{dt}\right) = (0, 0, 0).$$

   Since it's disease-free, we further impose that $I = 0$ and $R = 0$. It is an exercise to check that this yields

$$\left(\frac{\pi}{\mu}, 0, 0\right), \tag{11}$$

   as the disease-free steady state.
2. Find the Jacobian matrix:

$$\begin{bmatrix} \frac{\partial S'}{\partial S} & \frac{\partial S'}{\partial I} & \frac{\partial S'}{\partial R} \\ \frac{\partial I'}{\partial S} & \frac{\partial I'}{\partial I} & \frac{\partial I'}{\partial R} \\ \frac{\partial R'}{\partial S} & \frac{\partial R'}{\partial I} & \frac{\partial R'}{\partial R} \end{bmatrix} = \begin{bmatrix} -aI - \mu & -aS & 0 \\ aI & aS - b - \mu & 0 \\ 0 & b & -\mu \end{bmatrix}. \tag{12}$$

3. Substitute the disease-free steady-state in:

$$[\text{Jac}]_{(\pi/\mu, 0, 0)} = \begin{bmatrix} -\mu & -\frac{a\pi}{\mu} & 0 \\ 0 & \frac{a\pi}{\mu} - b - \mu & 0 \\ 0 & b & -\mu \end{bmatrix}. \tag{13}$$

4. Find the eigenvalues:

$$\det(J - \lambda I) = (\mu + \lambda)^2 \left(\frac{a\pi}{\mu} - b - \mu - \lambda\right) = 0.$$

   This yields

$$\lambda = -\mu, -\mu, \frac{a\pi}{\mu} - b - \mu,$$

are the eigenvalues. The only eigenvalue that could be positive is the last one. Since we want something mathematically interesting to happen, we do not want the disease to vanish: we want the disease to be endemic and persist. So, we re-arrange the largest eigenvalue to find that

$$R_0^{\text{SIR}} = \frac{a\pi}{\mu(b+\mu)}. \tag{14}$$

We find that $R_0 > 1 \iff \frac{a\pi}{\mu} - b - \mu > 0$.

We can reach the same exact conclusion using a different route. We can use the **endemic equilibrium** for the SIR model:

$$(\overline{S}, \overline{I}, \overline{R}) = \left(\frac{b+\mu}{a}, \frac{\pi}{b+\mu} - \frac{\mu}{a}, \frac{b\pi}{\mu(b+\mu)} - \frac{b}{a} \right). \tag{15}$$

Exercise: check it.
We now ask ourselves how we can determine the stability. We will use a trick which we will use a lot throughout the course. We want $I > 0$, since $I \leq 0$ would be not physiological. The disease persists when $\overline{I} > 0$. So,

$$\frac{\pi}{b+\mu} - \frac{\mu}{a} > 0 \iff \frac{\pi}{b+\mu} > \frac{\mu}{a} \iff \frac{a\pi}{\mu(b+\mu)} > 1.$$

But that's R_0^{SIR}. As $R_0 = 1$ is passed, we move from a disease-free equilibrium (which is stable) to the endemic equilibrium (unstable). So, we call $R_0 = 1$ a **trans-critical bifurcation**.