Senior Thesis in Mathematics

Mathematically Modelling the Dynamics of Tuberculosis

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Abstract

This thesis focuses on understanding the fundamentals of compartmental models in epidemiology and the role that differential equations play within this field of mathematics. Specifically, this thesis goes through the derivation and stability analyses of equilibrium points to systems following variants of the Basic SIR Model. Finally, the core part of this thesis focuses on studying the SLIT Model, a compartmental model developed by Castillo-Chavez and Feng, and the works of others, for modelling and understanding the dynamics of Tuberculosis (TB). It was found through rigorous proof that there exists a disease-free equilibrium point, and a unique TB-endemic equilibrium point within the SLIT Model. These results indicate that models based on a simple one-strain TB still provide useful insight in understanding how TB spreads within a population in reality.

Author's declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of Pomona College and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE: 04/12/2017

Dedication and acknowledgements

I would first like to thank my thesis advisor, Professor Adolfo J. Rumbos of the Mathematics Department of Pomona College. The door to Professor Rumbos's office was always open whenever I ran into a trouble spot or had a question about my research or writing. He allowed this paper to be my own work, but guided me when needed.

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I would also like to acknowledge Adam He and Beauttie Kuture of Pomona College. Not only were they helpful second readers of this thesis, but the amount of time spent working together through difficult courses was nothing but invaluable, and it's greatly because of them that this thesis is at the status it is. We'll be great in the food-truck industry.

Finally, I must express my most profound gratitude to my mother, Kim Phương Lê, and to my father, Trần Anh Tuân, for their unconditional love and support. It is because of your unconditional love and support that I have gone where I gone in the past; that I am where I am now; and that I will be where I will be in the future. My life is dedicated to paying the both of you back by a greater amount than what you have given me. I promise.

Con cảm ơn, Ba và Mẹ, rất nhiều. Con cảm ơn.

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Chapter 1

Introduction

Disease has been a large, shaping influence on much of human history. Before the success of modern medicine starting in the 1900s, disease often determined whether entire civilisations would prosper and advance or collapse. An example of a powerful disease is tuberculosis.

Similar to the Black Death, tuberculosis ravaged Europe enough to the point that it was labelled the principal agent of Europe's White Plague, which started around the 17^{th} century, lasted about two hundred years, and was the main cause of death in the 1650s. It's also believed that roughly one-third of the world population is infected with tuberculosis to this day, with roughly one per cent of the population becoming newly infected each year [World Health Organization, 2016].

To further the importance of understanding the dynamics of disease, both infectious and parasitic diseases like TB account for thirty-seven per cent of all years of potential life lost, *worldwide*. With such influential consequences about populations throughout the world, it is of much importance for humans to understand how diseases ravage and spread amongst people, so that we could effectively combat against the power of disease and understand critical points of time and conditions for a population to survive a disease.

This is where mathematics plays a crucial role in understanding diseases. Mathematical modelling has helped capture huge amounts of useful information when it comes to understanding the complexities and details of the

spread of a variety of diseases. Specifically, it is largely through the efforts of mathematical modelling that much of society today understands a great amount of the spread of TB, an illness that is still a major problem in many parts of the world today.

Though different models have been developed that focus upon studying the long-run dynamics of the spread of TB within a population, this thesis will primarily be investigating and reconstructing a popularly used simple compartmental epidemiological model, which will be prefaced briefly in a later section. To do this, a list of two basic compartmental models will be explained in order to provide the reader with proper knowledge about the field and the workings of the models.

1.1 Basic Tuberculosis Epidemiology

Tuberculosis is considered an infectious disease caused by the bacterium *Mycobacterium tuberculosis (MTB)*. Whilst it's possible for a person to be infected with TB through other body parts, MTB primarily infects victims through targeting the lungs, which implies that the disease is primarily an airborne disease. What makes TB a worrisome disease is that it occurs and affects societies all through the world. As stated by the World Health Organization (WHO) via their fact sheet on TB, the TB's biggest impacts on society are [World Health Organization, 2016]:

- Tuberculosis (TB) is one of the top 10 causes of death worldwide.
- In 2015, 10.4 million people fell ill with TB and 1.8 million died from the disease (including 0.4 million among people with HIV). Over 95% of TB deaths occur in low- and middle-income countries.
- Six countries account for 60% of the total, with India leading the count, followed by Indonesia, China, Nigeria, Pakistan and South Africa.
- One million children (0–14 years of age) fell ill with TB, and 170 thousand children (excluding children with HIV) died from the disease in 2015.
- Globally in 2015, an estimated 480 thousand people developed multidrug-resistant TB (MDR-TB).

- TB incidence has fallen by an average of 1.5% per year since 2000. This needs to accelerate to a 4–5% annual decline to reach the 2020 milestones of the "End TB Strategy".
- An estimated 49 million lives were saved through TB diagnosis and treatment between 2000 and 2015.
- Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals.

What makes the disease both unique and potent, however, is how victims aren't immediately infective. Instead, the vast majorities of victims to TB do not display symptoms whatsoever, meaning that most victims are considered to be *latent* TB victims. Furthermore, because TB is a disease with slow dynamics and a *long incubation period*, these two factors imply that the study of TB must be done in an extremely long interval of time.

Definition 1.1. The *latency/latent period* of a disease is defined to be the amount of time elapsed between the exposure to a pathogenic organism, a chemical, or radiation, and the point where symptoms and signs begin to appear because of that exposure.

Definition 1.2. The *infectious/incubation period* of a disease is defined to be the amount of time elapsed between the moment of exposure to a pathogen and the duration of symptoms and signs of disease.

However, it's important to note that TB is indeed treatable, and is difficult to defeat without proper treatment. As stated by the WHO,

> "TB is a treatable and curable disease. Active, drug-susceptible TB disease is treated with a standard 6 month course of 4 antimicrobial drugs that are provided with information, supervision and support to the patient by a health worker or trained volunteer. Without such support, treatment adherence can be difficult and the disease can spread. The vast majority of TB cases can be cured when medicines are provided and taken properly" [World Health Organization, 2016].

These facts about TB lead to the importance of mathematical modelling with respect to TB. Doing so correctly, the discipline can yield accurate

models that describe how TB spreads within a population, how much of the population becomes infective, and when a TB infection becomes an epidemic. With such knowledge, people can therefore figure out the adequate amount and timing of response to fight against TB.

Chapter 2

Compartmental Models in Epidemiology

2.1 Prerequisite Knowledge & Definitions

A popular method to model the spread and characteristics of a disease is constructing and using what are called compartmental models. This chapter is dedicated towards understanding the workings and ideas behind compartmental models in epidemiology, and will first cover the needed knowledge in both compartmental models and differential equations. The importance of this chapter is to ultimately understand the later compartmental model that is specifically tailored to mathematically model the spread of TB.

Definition 2.1. A *compartmental/deterministic model* is a model that abstracts the population it is modelling into separate and unique compartments under certain assumptions. The compartments are typically defined and separated by the different stages of the investigated disease. These different stages/compartments are often represented by letters such as $M, S, E, I,$ and R, as can be seen in Figure 2.1, where

- M is the sub-population of people born with maternal immunity;
- S is the sub-population of people born without maternal immunity;
- E is the sub-population of people exposed to the disease, but are not infectious;

- I is the sub-population of people infected by the disease, and that are displaying symptoms;
- R is the sub-population of people that have recovered from the disease.

Determining the interactions amongst these population compartments is often what determines the overall model and its results.

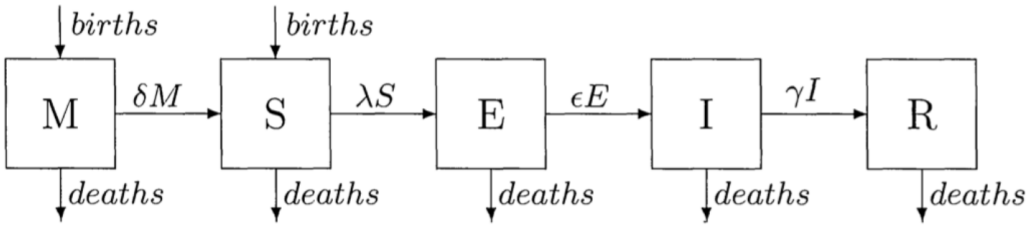

Figure 2.1: Flow diagram for the MSEIR Model. Figure reproduced from [Hethcote, 2000].

Once the population compartments and interactions have been established, compartmental models are often investigated and analysed through the usage of ordinary differential equations (ODEs).

Definition 2.2. In the simplest sense, a *differential equation* is a mathematical equation that relates an unknown function with its derivatives. An ordinary differential equation (ODE) is a differential equation of an function with only one independent variable. A partial differential equation (PDE) is a differential equation of multi-variable functions and their partial derivatives.

Remark 2.3. Though it isn't always the case, the vast majority (if not all) of the differential equations that will be focused upon on this thesis will be dependent on time t.

Most compartmental models in epidemiology are considered to be dynamic in the sense that the models are dependent upon time t. This dependence implies that the numbers in each compartment can fluctuate over time. Another aspect that makes compartmental diseases dynamic is how the interactions amongst compartments occur at every time t, which means that population members typically transfer and flow continuously between

compartments over time during the infectious period of a disease.

In order to properly understand and model a disease, one needs to understand the disease's infectious period and its basic reproductive number. This is necessary for not just TB, but for any disease in general. We therefore introduce the two following definitions.

Definition 2.4. For an arbitrary disease, we define the *basic reproductive number* as the expected number of people that become infected, when one infected individual is introduced into an entirely susceptible population, during this person's entire incubation/infectious period. We denote the basic reproductive number of a disease as R_o. This notation for the basic reproductive number will be used for the remainder of this thesis.

As demonstrated by James Holland Jones in his Stanford University notes, R_o can be mathematically viewed as the following [Jones, 2007]:

$$R_o \propto \left(\frac{infection}{contact}\right)\left(\frac{contact}{time}\right)\left(\frac{time}{infection}\right). \tag{2.1}$$

Remark 2.5. It should be noted that R_o is generally defined at the beginning and for the entire duration of an infectious disease's period. Furthermore, it must be mentioned that R_o is a parameter with no dimensions and is therefore not a rate, since being a rate would imply having units of $\frac{1}{time}$ [Jones, 2007].

Remark 2.6. One of the earliest cornerstone successes that led to the popularity of compartmental models in epidemiology was the work done by Kermack and McKendrick in their 1927 paper, *A Contribution to the Mathematical Theory of Epidemics*. Kermack and McKendrick were the first to successfully develop a complete mathematical model for the spread of disease through the abstraction of a population into compartments. They divided a homogeneous population into the three compartments of susceptible S, infective I, and recovered R, and described the flow and transfer of individuals between these departments through the usage of differential equations [McKendrick and Kermack, 1927]. The system of equations is now often regarded as the baseline SIR Model for most complex compartmental models. Although the model derived has no explicit solutions, the duo were the first to discover that

> "in general, a threshold density of population is found to exist, which depends on the infectivity, recovery, and death rates peculiar to the epidemic. No epidemic can occur if the population density is below this threshold value. Small increases in the infectivity rate may lead to large epidemics; also, if the population density slightly exceeds its threshold value the effect of an epidemic will be to reduce the density as far below the threshold as initially it was above it" [McKendrick and Kermack, 1927].

In other words, Kermack and McKendrick were the first to derive and describe what is known today as the basic reproductive number of a disease, R_o. Perhaps the most important result found by Kermack and McKendrick was that "similar results are indicated for the case in which transmission [of a disease] is through an intermediate host" [McKendrick and Kermack, 1927]. This essentially states that the idea of compartmental epidemiological models can be applied to diseases that have a latency period, such as TB.

With the prerequisite knowledge covered, detailed coverage of the basic compartmental model in epidemiology will now be understandable to the reader: The Basic SIR Model. The overall plan of this chapter is to first study the Basic SIR Model. We then account for both birth and death rates in a population, resulting in the study of the SIR Model with Vital Dynamics. Understanding all of the components of the SIR Models will therefore equip us when tackling the compartmental model for TB.

2.2 The Basic SIR Model

2.2.1 The Basic SIR Model: General Understanding & Assumptions

Though Kermack and McKendrick's paper is a cornerstone in the field, analysis of the SIR Model and SIR Model with Vital Dynamics will be based off upon Herbert G. Hethcote's "The Mathematics of Infectious Diseases", since Hethcote's formulation and descriptions of both models are updated in terms of differential equation techniques, and the terminology used to describe certain values in compartmental models. Hethcote begins by describing the assumptions and set-up for what he calls the "Classic Endemic Model" [Hethcote, 2000], which we call the Basic

SIR Model. Hethcote serves not only as a useful reference for understanding the fundamentals of compartmental models, but often goes into depth behind the meaning of any equilibrium points found in the SIR Model, and further explains the interpretations behind parameters and thresholds like R_o. However, it must be pointed out that many important steps in the derivation of the final results laid out in his paper are not explicitly shown, making the paper often difficult to comprehend without independent work and previous knowledge of the models beforehand. It is for this reason that this thesis explicitly analyses the two SIR Model versions by hand, as this thesis does not assume prior knowledge of the field of compartmental models, let alone prior knowledge of the application of compartmental models to TB.

The general SIR Model of a disease first assumes that a total population $N(t)$ can be divided into three sub-populations called compartments. Let $S(t)$, $I(t)$, and $R(t)$ denote the respective population sizes of the susceptible, infected, and recovered categories of the total population, $N(t)$. It's assumed that any individual can only be a member of exactly one compartment, meaning the three are mutually exclusive. The Basic SIR Model additionally assumes that

- Total population demography is closed; meaning that there's neither births nor deaths.
- Total population N is constant or fixed.
- The spread of disease is a short-term event.
- The disease spreads through interaction between the susceptible and infection compartments.
- The rate at which susceptible individuals can get infected by contact with infectious individuals is proportional to the product of the number of susceptible individuals and the fraction of infected individuals with constant of proportionality $\beta > 0$. Thus, the infection rate is $\beta S\frac{I}{N}$. Observe that β has units of $\frac{1}{time}$.
- β can also be thought of as the average number of adequate contacts (i.e. contacts sufficient for transmission of the disease) of a person per unit time.

- The rate at which an infected individual recovers is proportional to the number of infected individuals, with constant of proportionality $\gamma > 0$. Observe that γ has units of $\frac{1}{time}$.
- The only way for a person to leave the susceptible compartment is to become infected.
- The only way for a person to leave the infected compartment is to recover.
- Age, sex, and socio-economic status do not affect a person's chances of becoming infected.
- Inherited immunity does not exist in the basic model.
- There is no latency period.
- The population is homogeneous.

The assumptions of the Basic SIR Model can be better understood and visualised through the following flow diagram:

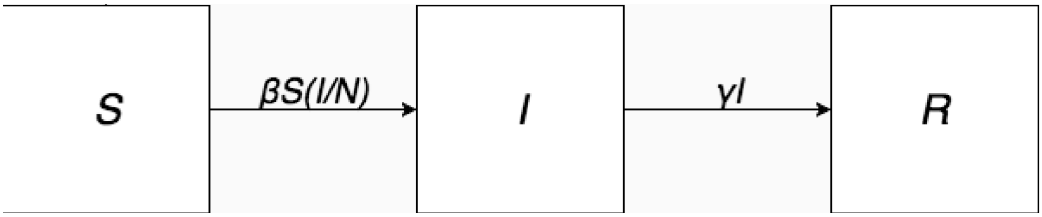

Figure 2.2: Basic SIR Model flow diagram.

2.2.2 The Basic SIR Model: Derivation

Because we assumed that $N(t)$ is fixed, we can state that

$$S + I + R = N, \tag{2.2}$$

where N is a constant. Note that the quantity of each sub-population is unknown at any time t, since individuals are able to move from one class to another (or die off) at any time.

To determine the differential equations for each of these sub-populations, we use the following general conservation principle:

$$\frac{dQ}{dt} = \text{Rate of } Q \text{ in} - \text{Rate of } Q \text{ out}, \tag{2.3}$$

for a differentiable quantity Q. We will be applying this principle to each sub-population to derive their respective differential equations.

Rate of Change of the Susceptible Population S

We apply the conservation principle (Equation (1.3)) upon the susceptible class to determine its rate of change with respect to time. Because N is fixed, we know that the rate of change of S flowing in is zero, as no new individuals are born.

Recall that $\beta S\frac{I}{N}$ represents the rate of infection, and how it's assumed that infection occurs with interaction between the susceptible sub-population and the fraction of infective individuals. We can understand this from how it's assumed that β is the average number of adequate contacts of a person per unit time. This implies that $\beta\frac{I}{N}$ represents the number of contacts with infectives of one susceptible per unit time. Thus, $\beta S\frac{I}{N}$ represents the number of new infectious cases per unit time (i.e. the infection rate) (Hethcote 2000, pg. 602). Therefore, we can say that the rate of S out is

$$\text{Rate of S Out} = \beta S\left(\frac{I}{N}\right),$$

(see also the flow diagram).

Thus, the difference of these two rates represent the rate of change of S with respect to time t:

$$\frac{dS}{dt} = -\beta S\left(\frac{I}{N}\right). \tag{2.4}$$

Rate of Change of the Infected Population I

We apply the conservation principle (Equation (1.3)) upon the infective class to determine its rate of change with respect to time. From above and the Basic SIR Model diagram, we see that

$$\text{Rate of I In} = \beta S\left(\frac{I}{N}\right).$$

To determine the Rate of I Out, observe that an infected individual can only recover at rate γ. Therefore, we know

$$\text{Rate of I Out} = \gamma I,$$

(see also the flow diagram).

Therefore, we obtain

$$\frac{dI}{dt} = \beta S\left(\frac{I}{N}\right) - \gamma I. \tag{2.5}$$

Rate of Change of the Recovered Population R

We apply the conservation principle (Equation (1.3)) upon the recovered class to determine its rate of change with respect to time. Recall that the Basic SIR Model does not assume inherited immunity. Furthermore, the model assumes that there's a linear progression for an individual in the SIR Model: $S \to I \to R$. By not assuming any death, this means that the rate of R out is zero, whilst the rate of R in is simply the rate of I out. Therefore, we obtain

$$\frac{dR}{dt} = \gamma I. \tag{2.6}$$

Remark 2.7. Because it's assumed that total population N is constant, this means that (1.5) can be determined from (1.3) and (1.2), as seen above in the logic used for derivation of the differential equations. This allows one to simply focus on studying only the system of ODEs

$$\begin{cases} \frac{dS}{dt} &= -\beta S\left(\frac{I}{N}\right); \\ \frac{dI}{dt} &= \beta S\left(\frac{I}{N}\right) - \gamma I. \end{cases} \tag{2.7}$$

2.2.3 The Basic SIR Model: R_o

The disease spread becomes epidemic when $\frac{dI}{dt} > 0$. Therefore, in view of the second equation on (2.7), we can state an epidemic occurs when

$$\frac{\beta S}{N} > \gamma, \text{ or } \frac{N}{S} < \frac{\beta}{\gamma}.$$

Recall that γ is the recovery rate. This means that $\frac{1}{\gamma}$ is the average duration of infection. Observe that β represents the contact and infection rate between the S and I sub-populations. Therefore, we can state that $\frac{\beta}{\gamma}$ represents the expected number of people that become infected, as a result of one infected individual in an entirely susceptible population, during the entire period of infection. Therefore, we can state that this value is the basic reproduction number, R_o:

$$R_o = \frac{\beta}{\gamma}. \tag{2.8}$$

Because R_o comes from an entirely susceptible population, this means that when $S = N$, then an epidemic occurs when

$$R_o > 1.$$

Remark 2.8. From quick inspection, one can see that the components of R_o are:

- β: The average number of adequate contacts of a person per unit time; meaning that its units are $\frac{1}{time}$.
- γ: The recovery rate; meaning that its units are $\frac{1}{time}$.

This allows one to see that R_o is indeed dimensionless, and therefore not a rate as mentioned by James Holland Jones [Jones, 2007].

2.2.4 The Basic SIR Model: Nondimensionalisation

To make analysis easier on (2.7), we will nondimensionalise the system, which means we will attempt to make all of the variables no longer have units (dimensions). Consider the following scaled variables:

$$\hat{s} = \frac{S}{N}, \ \hat{i} = \frac{I}{N}, \ \tau = \frac{t}{\lambda},$$

where λ has units of time. By the Chain Rule, we know that

$$\frac{d\hat{s}}{d\tau} = \frac{d\hat{s}}{dt} \times \frac{dt}{d\tau} = \lambda \frac{d\hat{s}}{dt} = \frac{\lambda}{N} \frac{dS}{dt},$$

and

$$\frac{d\hat{i}}{d\tau} = \frac{d\hat{i}}{dt} \times \frac{dt}{d\tau} = \lambda \frac{d\hat{i}}{dt} = \frac{\lambda}{N} \frac{dI}{dt}.$$

Therefore,

$$\begin{cases} \frac{d\hat{s}}{d\tau} & = -\beta\lambda\hat{s}\hat{i}; \\ \frac{d\hat{i}}{d\tau} & = \beta\lambda\hat{s}\hat{i} - \gamma\lambda\hat{i}. \end{cases} \tag{2.9}$$

Observe that $\gamma\lambda$ is dimensionless, since γ has units of $\frac{1}{time}$ and λ has units of time. We can set

$$\gamma\lambda = 1,$$

so that

$$\lambda = \frac{1}{\gamma}.$$

Observe now that $\beta\lambda = \frac{\beta}{\gamma} = R_o$. We can therefore simplify the system of ODEs to

$$\begin{cases} \frac{d\hat{s}}{d\tau} & = -R_o\hat{s}\hat{i}; \\ \frac{d\hat{i}}{d\tau} & = R_o\hat{s}\hat{i} - \hat{i}. \end{cases} \tag{2.10}$$

Measuring time in units of $\frac{1}{\gamma}$, and considering $\hat{s}$ and $\hat{i}$ as fractions of N, we obtain the nondimensionalised system of

$$\begin{cases} \frac{ds}{d\tau} & = -R_o si; \\ \frac{di}{d\tau} & = R_o si - i. \end{cases} \tag{2.11}$$

2.2.5 The Basic SIR Model: Equilibrium Points & Stability Analysis

With the system of ODEs in (2.7) now nondimensionalised in (2.11), we will attempt to find the equilibrium points (s, i), where $\frac{ds}{d\tau} = \frac{di}{d\tau} = 0$. One can have a better understanding of equilibrium points for more general systems under the following definition:

Definition 2.9. Consider the system of differential equations $\dot{x} = f(x)$, where $f : \mathbb{R}^n \to \mathbb{R}^n$. An point $x_e \in \mathbb{R}^n$ is an *equilibrium point* if $f(x_e) = 0$. Another way to view equilibrium points is that x_e is an *equilibrium point* if and only if $x(t) = x_e$ is a *trajectory*, for all t.

Under inspection, we see that (1.7) has infinitely many equilibrium points (s^*, i^*) where

$$s^* = \xi, \text{ for } \xi \in [0, 1]; \tag{2.12}$$

$$i^* = 0. \tag{2.13}$$

Having the set of equilibrium points now, consider the following definitions of two important stability types that an equilibrium point can take:

Definition 2.10. Consider the system of differential equations $\dot{x} = f(x)$, where $f : \mathbb{R}^n \to \mathbb{R}^n$, and point $x_e \in \mathbb{R}^n$ is an equilibrium point.

- x_e is a *globally asymptotically stable* (*g.a.s.*) equilibrium point if for every trajectory $x(t)$, we have $x(t) \to x_e,\ t \to \infty$.
- x_e is a *locally asymptotically stable* (*l.a.s.*) equilibrium point if $\exists \epsilon > 0$ such that $|x(0) - x_e| \leq \epsilon \implies x(t) \to x_e,\ t \to \infty$.
- It should be noted that an equilibrium point can also be either *unstable* or *(not asymptotically) stable*.

Though the SIR Model does not have an analytical solution, it's still possible to figure out the stability of these infinite equilibrium points by observing the trajectories in the phase plane. To do this, consider the phase portrait of system (2.7) when $R_o = 3$, as computed by Hethcote [Hethcote, 2000]:

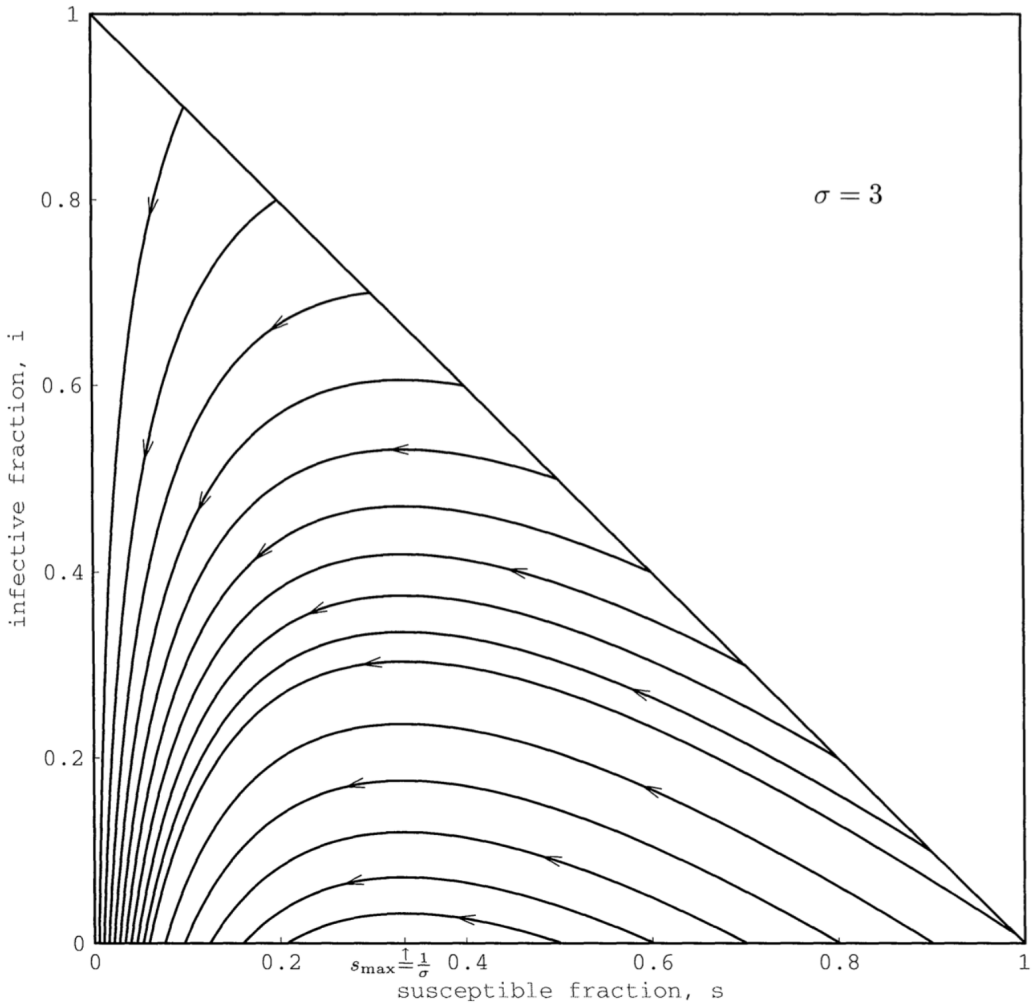

Figure 2.3: Phase plane portrait for the Basic SIR Epidemic Model with a basic reproductive number $R_o = 3$. Figure reproduced from [Hethcote, 2000].

Therefore, we know that all equilibrium points where $\xi > \frac{1}{3}$ are unstable. We can see from the phase portrait that the equilibrium points $(\xi, 0)$, where $\xi < \frac{1}{3}$, are stable.

2.3 The Basic SIR Model with Vital Dynamics

2.3.1 The Basic SIR Model with Vital Dynamics: General Understanding & Assumptions

Though the Basic SIR Model gives important insight on how diseases become epidemic, and the importance of the basic reproductive number R_o, it isn't quite versatile and applicable to modelling many diseases in reality, since the model ignores important aspects of real life like vital dynamics (i.e. birth and death). In order to have an understanding at how TB can be modelled in reality, we review compartmental models with vital dynamics in epidemiology, and analyse the stability of said models. The model has the following assumptions:

- The birth and death rates are equal to a constant μ.
- Total population N is constant or fixed, because the birth and death rates are equal. Thus, $S + I + R = N$ remains constant.
- The disease spreads through interaction between the susceptible and infection compartments.
- The rate at which susceptible individuals can get infected by contact with infectious individuals is proportional to the product of the number of susceptible individuals and the fraction of infected individuals with constant of proportionality $\beta > 0$. Thus, the infection rate is $\beta S \frac{I}{N}$.
- β is assumed to be fraction of contacts between a susceptible person and the fraction of the infective population that results in successful transmission, in a unit of time. This implies that the transmission rate is in units of $\frac{1}{time}$.
- $\beta \frac{I}{N}$ is used instead of βI because, for large populations, it's more realistic for the transmission rate of infection to depends on the fraction of infected individuals to the population instead of absolute numbers.
- The rate at which an infected individual recovers is proportional to the number of infected individuals with constant of proportionality $\gamma > 0$. Observe γ has units of $\frac{1}{time}$.

- The only ways for a person to leave the susceptible compartment are to become infected or to die.
- The only ways for a person to leave the infected compartment are to recover or to die.
- The only way for a person to leave the recovered compartment is to die. That is, once a person recovers, it is no longer susceptible.
- Age, sex, and socio-economic status do not affect a person's chances of becoming infected.
- All persons are born into the susceptible compartment.
- Inherited immunity does not exist in the basic model.
- There is no latency period.
- The population is homogeneous.

The assumptions of the Basic SIR Model with Vital Dynamics can be better understood and visualised through the following flow diagram:

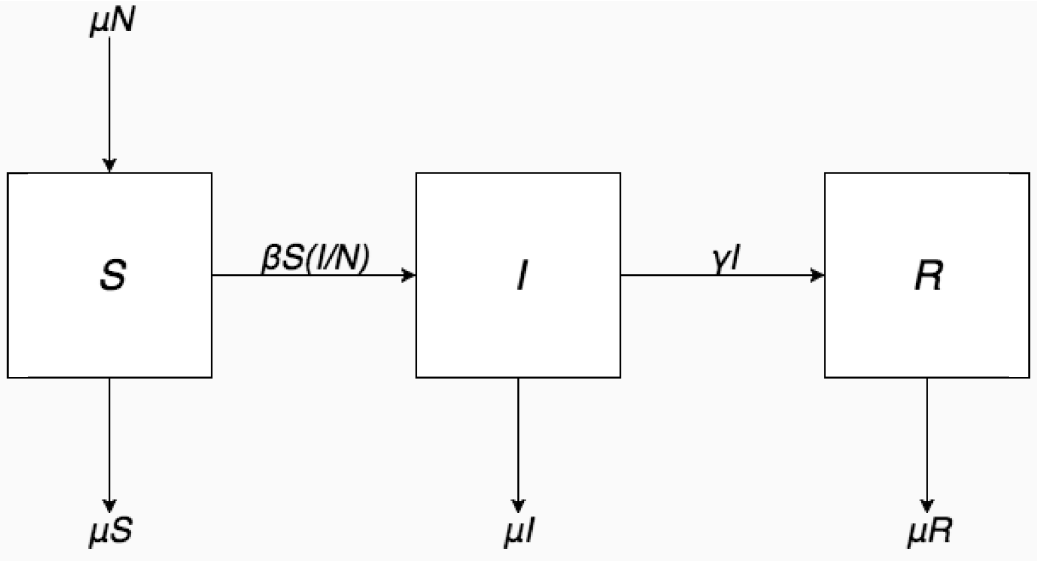

Figure 2.4: Basic SIR Model with vital Dynamics flow diagram.

2.3.2 The Basic SIR Model with Vital Dynamics: Derivation

Note that the quantity of each sub-population can vary at any time t because of the fact that individuals are able to move from one class to another (or die off) at any time.

To determine the differential equations for each of these sub-populations, we first recall the general conservation principle: For some quantity $Q(t)$, we have that

$$\frac{dQ}{dt} = \text{Rate of } Q \text{ in} - \text{Rate of } Q \text{ out.} \tag{2.14}$$

We will be applying this principle to each sub-population to derive their respective differential equations.

Rate of Change of the Susceptible Population, S

Because we assumed that both birth and death rates are equal to μ, we can state that the number of newborns that appear (and are therefore susceptible) is the quantity μN. Therefore, we can state that

$$\text{Rate of S In} = \mu N,$$

(see also the flow diagram).

Since birth and death rates are equal, we know that the susceptible population die at rate μS. Besides dying, the only way someone can exit the S compartment is to be infected. By the model assumptions and the Basic SIR Model with Vital Dynamics diagram, the infection rate is $\beta S\frac{I}{N}$; so we have

$$\text{Rate of S Out} = \mu S + \beta S\frac{I}{N}.$$

Thus, by the conservation principle,

$$\frac{dS}{dt} = \mu N - \mu S - \beta S\frac{I}{N}. \tag{2.15}$$

Rate of Change of the Infected Population, I

The only way for someone to enter the infected population class is by getting infected. And again, by the model assumptions and the Basic SIR Model with Vital Dynamics diagram, the infection rate is $\beta S\frac{I}{N}$; so,

$$\text{Rate of I In} = \beta S\frac{I}{N}.$$

To determine the rate of I out, first recall that the two ways for someone to move out of the infected population is by dying or getting healed. The number of infective persons who die per unit time is μI, and by a rate of γ, the infected population recover and move onto the next compartment. Therefore, we have:

$$\text{Rate of I Out} = \gamma I + \mu I,$$

(see also the flow diagram).

Thus, the difference of these two rates represent the rate of change of I with respect to time t:

$$\frac{dI}{dt} = \beta S\frac{I}{N} - \gamma I - \mu I. \tag{2.16}$$

Rate of Change of the Recovered Population, R

The only way for someone to enter the recovered population is by recovering as an infected person. Since we assumed that the infected population recovers at rate γ (refer back to the Basic SIR Model with Vital Dynamics diagram),

$$\text{Rate of R In} = \gamma I.$$

Furthermore, we know that μR people per unit time die at every time t. Since dying is the only way to exit the recovered population, we can state that

$$\frac{dR}{dt} = \gamma I - \mu R. \tag{2.17}$$

Remark 2.11. Because it's assumed that total population N is constant, this means that (2.17) can be determined from (2.15) and (2.16), as seen

above in the logic used for derivation of the differential equations. This allows one to simply focus on studying only the system of ODEs

$$\begin{cases} \frac{dS}{dt} &= \mu N - \mu S - \beta S \left(\frac{I}{N}\right); \\ \frac{dI}{dt} &= \beta S \left(\frac{I}{N}\right) - \gamma I - \mu I. \end{cases} \tag{2.18}$$

2.3.3 The Basic SIR Model with Vital Dynamics: R_o

Observe from above that the disease dies out if $\frac{dI}{dt} < 0$, and that an epidemic occurs if $\frac{dI}{dt} > 0$. Thus, in view of the second equation in (2.18), an epidemic occurs if

$$\frac{\beta S}{N} > \gamma + \mu, \text{ or } \frac{S}{N} > \frac{\gamma + \mu}{\beta}, \text{ or } \frac{N}{S} < \frac{\beta}{\gamma + \mu}.$$

We can therefore state that the basic reproductive number of a disease in the Basic SIR Model with Vital Dynamics is equal to the average number of adequate contacts of an infectious person, β, multiplied with the death-adjusted infectious period, $\frac{1}{\gamma+\mu}$. In other words,

$$R_o = \frac{\beta}{\gamma + \mu}. \tag{2.19}$$

Remark 2.12. From quick inspection, one can see that the components of R_o are:

- β: The average number of adequate contacts of a person per unit time; meaning that its units are $\frac{1}{time}$.
- γ: The recovery rate; meaning that its units are $\frac{1}{time}$.
- μ: The death and birth rates; meaning that their units are both $\frac{1}{time}$.

This allows one to see that R_o is indeed dimensionless, and therefore not a rate, as pointed out by by Jones [Jones, 2007].

2.3.4 The Basic SIR Model with Vital Dynamics: Nondimensionalisation

To make the analysis on this system of ODEs easier, we will nondimensionalise the system. Consider the following scaled variables:

$$\hat{s} = \frac{S}{N},\ \hat{i} = \frac{I}{N},\ \tau = \frac{t}{\lambda},$$

where λ has units of time. By the Chain Rule, we know that

$$\frac{d\hat{s}}{d\tau} = \frac{d\hat{s}}{dt} \times \frac{dt}{d\tau} = \lambda \frac{d\hat{s}}{dt} = \frac{\lambda}{N}\frac{dS}{dt},$$

and

$$\frac{d\hat{i}}{d\tau} = \frac{d\hat{i}}{dt} \times \frac{dt}{d\tau} = \lambda \frac{d\hat{i}}{dt} = \frac{\lambda}{N}\frac{dI}{dt}.$$

Thus, we have

$$\begin{cases} \frac{d\hat{s}}{d\tau} & = \lambda\mu - \lambda\mu\hat{s} - \beta\lambda\hat{s}\hat{i}; \\ \frac{d\hat{i}}{d\tau} & = \beta\lambda\hat{s}\hat{i} - \lambda\hat{i}\left(\gamma + \mu\right). \end{cases} \tag{2.20}$$

Observe now that $\beta\lambda$ is dimensionless, since β has units of $\frac{1}{time}$ and λ has units of time. Therefore, we can state that

$$\beta\lambda = 1, \text{or } \lambda = \frac{1}{\beta}.$$

Observe now that $\lambda\left(\gamma + \mu\right) = \frac{1}{\beta}\left(\gamma + \mu\right) = \frac{1}{R_o}$. We can therefore simplify our system of ODEs to

$$\begin{cases} \frac{d\hat{s}}{d\tau} & = \frac{\mu}{\beta}\left(1 - \hat{s}\right) - \hat{s}\hat{i}; \\ \frac{d\hat{i}}{d\tau} & = \hat{s}\hat{i} - \frac{1}{R_o}\hat{i}. \end{cases} \tag{2.21}$$

Let $\alpha = \frac{\mu}{\beta}$. We therefore obtain the system

$$\begin{cases} \frac{d\hat{s}}{d\tau} & = \alpha\left(1 - \hat{s}\right) - \hat{s}\hat{i}; \\ \frac{d\hat{i}}{d\tau} & = \hat{s}\hat{i} - \frac{1}{R_o}\hat{i}. \end{cases} \tag{2.22}$$

Measuring time in units of $\frac{1}{\gamma}$, and considering $\hat{s}$ and $\hat{i}$ as fractions of N, we obtain the nondimensionalised system

$$\begin{cases} \frac{ds}{d\tau} & = \alpha\left(1 - s\right) - si; \\ \frac{di}{d\tau} & = si - \frac{1}{R_o}i. \end{cases} \tag{2.23}$$

2.3.5 The Basic SIR Model with Vital Dynamics: Equilibrium Points

With the system of ODEs now nondimensionalised in (2.23), we find the equilibrium points (s^*, i^*) by solving the system

$$\begin{cases} \frac{ds}{d\tau} &= \alpha\,(1-s) - si; \\ \frac{di}{d\tau} &= si - \frac{1}{R_o} i. \end{cases} \tag{2.24}$$

Under quick inspection, we see that (2.24) has a solution $(1, 0)$. In order to find any other equilibrium points, we solve the system by setting both equations equal to zero, and explicitly solving for (s^*, i^*).

Solving (2.23) for the case on which $i \neq 0$, we obtain

$$s^* = \frac{1}{R_o},$$

and

$$i^* = \alpha(R_o - 1).$$

Therefore, the two equilibrium points of the SIR Model with Vital Dynamics are:

$$(s^*, i^*) = (1, 0); \tag{2.25}$$

$$(s^*, i^*) = \left(\frac{1}{R_o}, \alpha\,(R_o - 1)\right). \tag{2.26}$$

We will now study the stability of equilibrium points (2.25) and (2.26).

2.3.6 The Basic SIR Model with Vital Dynamics: Equilibrium Points & Nullclines

We can also find the equilibrium points, (s^*, i^*), by performing analysis in the phase plane.

Nullcline Analysis

Definition 2.13. For a two-dimensional, autonomous system

$$\begin{cases} \frac{dx}{dt} &= f(x,y); \\ \frac{dy}{dt} &= g(x,y); \end{cases}$$

the *nullclines* are curves given by

$$f(x,y) = 0, \tag{2.27}$$

and

$$g(x,y) = 0. \tag{2.28}$$

We shall refer to (2.26) as the $\dot{x} = 0$ *nullcline*. On this curve, the vector field $\begin{pmatrix} f(x,y) \\ g(x,y) \end{pmatrix}$ is vertical.

We refer to (2.27) as the $\dot{y} = 0$ *nullcline*. On this nullcline, the vector field $\begin{pmatrix} f(x,y) \\ g(x,y) \end{pmatrix}$ is horizontal. The points where an $\dot{x} = 0$ nullcline and a $\dot{y} = 0$ nullcline meet are the equilibrium points.

The $\dot{s} = 0$ nullcline is the curve given by

$$i = \alpha \left(\frac{1}{s} - 1 \right).$$

The $\dot{i} = 0$ nullcline are solutions of

$$i \left(s - \frac{1}{R_o} \right) = 0.$$

We get two curves:

$$i = 0 \text{ (the } s\text{-axis)},$$

and the vertical line

$$s = \frac{1}{R_o}.$$

Consider two possibilities: $R_o > 1$ and $R_o < 1$. When $R_o < 1$, $(1,0)$ is the only equilibrium point in the first quadrant (which is the only quadrant we

care about, as one cannot have a negative sub-population fraction). When $R_o > 1$, both $(1, 0)$ and $\left(\frac{1}{R_o}, \bar{i}\right)$ are equilibrium points. The findings from these nullclines are displayed in Figure 2.5 below.

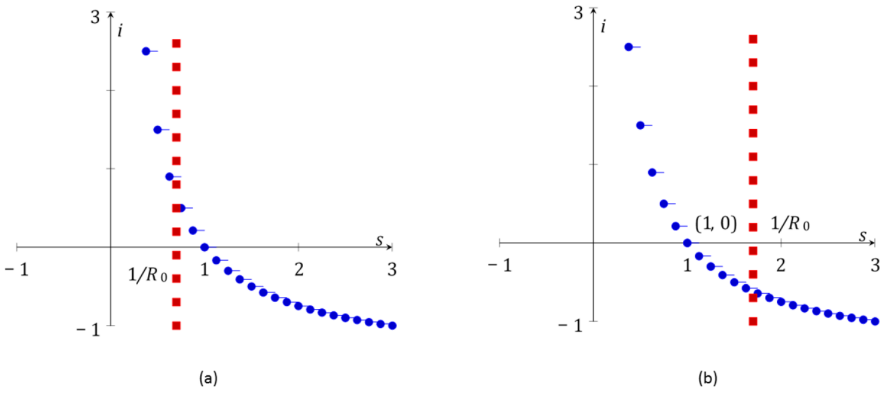

Figure 2.5: (a) si-nullclines on the phase-plane portrait of the Basic SIR Model with Vital Dynamics when $R_o > 1$. (b) si-nullclines on the phase-plane portrait of the Basic SIR Model with Vital Dynamics when $R_o < 1$.

2.3.7 The Basic SIR Model with Vital Dynamics: Stability Analysis

Stability Analysis of (1,0)

For the vector field

$$F(s,i) = \begin{pmatrix} \alpha(1-s) & -si \\ si & -\frac{1}{R_o}i \end{pmatrix},$$

the derivative map, or Jacobian matrix, is given by

$$J(s,i) = DF(s,i); \tag{2.29}$$

$$J(s,i) = \begin{pmatrix} -\alpha - i & -s \\ i & s - \frac{1}{R_o} \end{pmatrix}. \tag{2.30}$$

Evaluating the Jacobian matrix at $(1,0)$, we get

$$J(1,0) = \begin{pmatrix} -\alpha & -1 \\ 0 & 1 - \frac{1}{R_o} \end{pmatrix}. \tag{2.31}$$

Since this is an upper triangular matrix, $J(1,0)$ has two eigenvalues

$$\lambda_1 = -\alpha; \tag{2.32}$$

$$\lambda_2 = 1 - \frac{1}{R_o}. \tag{2.33}$$

From this, we see that the disease-free equilibrium $(1,0)$ is a sink-type and an equilibrium point when $R_o < 1$, since this will result in both λ_1 and λ_2 are negative. On the other hand, $(1,0)$ is an unstable saddle point when $R_o > 1$. Intuitively, if a disease is only able to produce fewer than one secondary case, we can expect a disease-free equilibrium. However, without outside intervention, if a disease can produce more than one secondary cases based off one initial infected person, it is unlikely that the result is disease-free.

Stability Analysis of $\left(\frac{1}{R_o}, \alpha\left(R_o - 1\right)\right)$

Consider again the Jacobian matrix $J(s,i)$ of the original system of ODEs:

$$J(s,i) = \begin{pmatrix} -\alpha - i & -s \\ i & s - \frac{1}{R_o} \end{pmatrix}. \tag{2.34}$$

Evaluating the Jacobian matrix at $\left(\frac{1}{R_o}, \alpha\left(R_o - 1\right)\right)$, we get

$$J\left(\frac{1}{R_o}, \alpha\left(R_o - 1\right)\right) = \begin{pmatrix} -\alpha R_o & -\frac{1}{R_o} \\ \alpha(R_o - 1) & 0 \end{pmatrix}. \tag{2.35}$$

We will solve for the roots of the characteristic polynomial

$$P(\lambda) = \lambda^2 + \alpha R_o \lambda + \frac{\bar{i}}{R_o},$$

where $\bar{i} = \alpha(R_o - 1)$, of the Jacobian matrix in (2.35). Through the quadratic formula, we obtain the following two eigenvalues

$$\lambda = \frac{-\alpha R_o}{2} \pm \sqrt{\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o}}. \tag{2.36}$$

Assume that $R_o > 1$. It then follows that $\bar{i} = \alpha(R_o - 1) > 0$. We consider two cases.

(i) If $\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o} < 0$, then the eigenvalues given by (2.36) are complex with negative real parts. Hence, $(\frac{1}{R_o}, \bar{i})$ is a stable spiral equilibrium point. Thus, $(\frac{1}{R_o}, \bar{i})$ is asymptotically stable.

(ii) If $\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o} \leq 0$, then, since $\bar{i} > 0$, we see that

$$\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o} < \left(\frac{\alpha R_o}{2}\right)^2;$$

so that

$$\sqrt{\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o}} < \frac{\alpha R_o}{2};$$

$$-\frac{\alpha R_o}{2} + \sqrt{\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o}} < 0.$$

Therefore, we get

$$(\alpha R_o)^2 - \frac{4\bar{i}}{R_o} \geq (\alpha R_o)^2.$$

This shows that the two roots of the characteristic polynomial are negative, or have negative real parts. This implies that the equilibrium point $\left(\frac{1}{R_o}, \bar{i}\right)$ is a sink-type, asymptotically stable equilibrium point when $R_o > 1$.

If $\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o} = 0$, then $J(s^*, i^*)$ has only one real eigenvalue that is negative. Hence, in this case, (s^*, i^*) is also both a sink and asymptotically stable.

Finally, if $\left(\frac{\alpha R_o}{2}\right)^2 - \frac{\bar{i}}{R_o} < 0$, then both eigenvalues are complex with real part $-\frac{\alpha R_o}{2}$, which is negative. Thus, in this case, (s^*, i^*) is both a spiral sink and asymptotically stable.

Interpretation of both real and complex scenarios is as follows:

- Real case: Since the reproductive number is greater than 1, the infection will be able to spread in a population. Each compartment will eventually reach the stable equilibrium point at $s = \frac{1}{R_o}$ and $i = \alpha(R_o - 1)$.
- Complex case (spiralling sink equilibrium): Similarly, since the reproductive number is greater than 1, the infection will be able to spread in a population. Each compartment will increase or decrease as it goes towards the stable equilibrium point at $s^* = \frac{1}{R_o}$ and $i^* = \alpha(R_o - 1)$.

Chapter 3

The Castillo-Chavez and Feng (1997) Simple Tuberculosis (SLIT) Model

Understanding the analyses done and results gained from both variants of the SIR Model, we now move on to understand one of the basic epidemiological models for TB, which was developed and analysed by [Castillo-Chavez and Feng, 1997].

3.1 The SLIT Model: General Understanding & Assumptions

The Castillo-Chavez and Feng Simple TB Model first assumes that a total population $N(t)$ can be divided into four sub-populations called compartments. Specifically, let $S(t)$, $L(t)$, $I(t)$, and $T(t)$ respectively represent Susceptible, Latent (infected, but not showing and experiencing symptoms). Infectious, and (effectively) Treated (analogous to Recovered) individuals of the total population, $N(t)$. It should be noted that it is for these categories that the model will be referred to as the SLIT Model for the remaining contents of the paper. Similar to both variants of the Basic SIR Model, it's additionally assumed that any individual can be only a member of exactly one compartment; therefore, the four compartments are mutually exclusive. The SLIT Model for TB can be visualised through the following flow diagram:

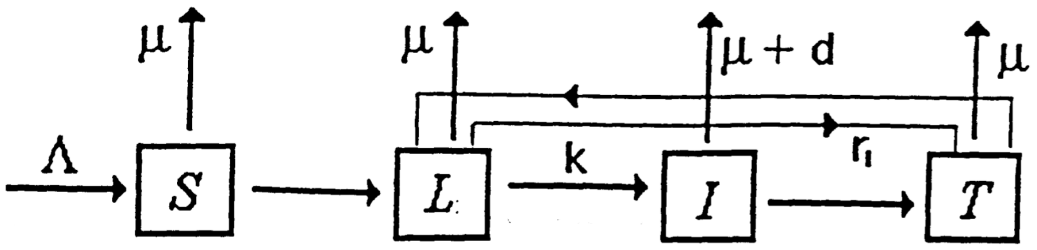

Figure 3.1: SLIT Model flow diagram. Figure reproduced from [Castillo-Chavez and Feng, 1997].

Having a brief understanding of the SLIT Model, consider its assumptions:

- Λ is the overall birth rate. We assume that Λ is constant. It has units of $\frac{population}{time}$.
- μ is the per-capita natural death rate. We assume that μ is constant. It has units of $\frac{1}{time}$.
- d is the per-capita TB-induced death rate. We assume that d is constant. It has units of $\frac{1}{time}$.
- c is the per-capita contact rate of an infectious person. It is constant and has units of number of *contacts*. c can also be viewed as the average number of contacts that an infectious individual has.
- r_1 is the per-capita treatment rate for latent individuals. We assume that r_1 is constant. It has units of $\frac{1}{time}$.
- r_2 is the per-capita treatment rate for infectious individuals. We assume that r_2 is constant. It has units of $\frac{1}{time}$.
- k is the rate at which an individual leaves the latent class by becoming infectious; it has units of $\frac{1}{time}$.
- $\beta \in [0, 1]$ is the probability that susceptible individuals become infected by one infectious individual; it has units of $\left(\frac{1}{contact}\right)\left(\frac{1}{time}\right)$.

- $\beta' \in [0, 1]$ is the probability that latent individuals become infected by one infectious individual; it has units of $\left(\frac{1}{contact}\right)\left(\frac{1}{time}\right)$.
- Susceptible and treated individuals can become latent again if infected via contact with an infectious individual.
- $N = S + L + I + T$. Total population N is variable because of the extra mortality in the infectious class I.
- TB spreads through interaction (i.e., contact) between the susceptible and infection compartments.
- When infected, susceptible individuals enter the latent compartment; this means that people don't immediately show TB symptoms when infected.
- Only latent individuals can enter the infectious compartment.
- βc is the average number of susceptible individuals that are infected, and therefore enter the latent compartment, because of contact with an infectious individual.
- $\beta' c$ is the average number of treated individuals that become infected, and therefore enter the latent compartment, because of contact with an infectious individual.
- The rate at which susceptible individuals become latent by contact with infectious individuals is proportional to the product of the number of susceptible individuals, the fraction of infected individuals, and βc. Therefore, the rate of transfer from susceptible to latent compartments is $\beta c S \frac{I}{N}$.
- The rate at which treated individuals become latent by contact with infectious individuals is proportional to the product of the number of treated individuals, the fraction of infected individuals, and $\beta' c$. Therefore, the rate of transfer from the treated to latent compartments is $\beta' c T \frac{I}{N}$.
- $\beta c \frac{I}{N}$ is used instead of $\beta c I$ because for large populations, it's more realistic for the transmission rate of infection to depend on the fraction of infected individuals to the population instead of the absolute number.

- The only ways for a person to leave the susceptible compartment are to become latent or die naturally.
- The only ways for a person to leave the latent compartment are to become infected, become treated, die naturally, or die by TB.
- The only ways for a person to leave the infected compartment are to become treated, die naturally, or die by TB.
- The only way for a person to leave the treated compartment is to become latent again or die naturally.
- Age, sex, and socio-economic status do not affect a person's chances of becoming infected.
- All persons are born into the susceptible compartment.
- Inherited immunity does not exist in the SLIT model.
- The population is homogeneous.

3.2 The SLIT Model: Derivation

Note that the quantity of each sub-population varies with t because individuals are able to move from one class to another (or die off) at any time.

To determine the differential equations for each of these sub-populations, we first recall the following general conservation principle: For some quantity $Q(t)$, we have that

$$\frac{dQ}{dt} = \text{Rate of } Q \text{ in} - \text{Rate of } Q \text{ out.} \tag{3.1}$$

We will be applying this principle to each sub-population to derive their respective differential equations.

Rate of Change of the Susceptible Population, S

Given our assumptions that the birth rate Λ is constant and is the overall birth rate, we can state that

$$\text{Rate of S In} = \Lambda,$$

(see also the flow diagram).

With the per-capita death rate being μ, we know that the number of susceptible individuals that die naturally per unit time is μS. Besides dying, the only way someone can exit the susceptible compartment is to become latent via infection. By the model assumptions (see also the flow diagram), the rate from the susceptible to the latent compartments is $\beta c S \frac{I}{N}$. Therefore, we have

$$\text{Rate of S Out} = \mu S + \beta c S \frac{I}{N}.$$

Thus, by the conservation principle,

$$\frac{dS}{dt} = \Lambda - \mu S - \beta c S \frac{I}{N}. \tag{3.2}$$

Rate of Change of the Latent Population, L

Recall from the above model assumptions that $\beta c S \frac{I}{N}$ represents the rate at which individuals move from the susceptible to latent compartments, and that $\beta' c T \frac{I}{N}$ represents the rate at which individuals move from the treated to the latent compartments. Therefore, we can state that

$$\text{Rate of L In} = \beta c S \frac{I}{N} + \beta' c T \frac{I}{N},$$

(see also the flow diagram).

We know from the above assumptions that μL represents the total number of latent individuals that die naturally per unit time. Furthermore, we know that kL represents the number of latent individuals per unit time that become infected and move into the infected compartment, and that $r_1 L$ represents the number of latent individuals per unit time that are treated and therefore move into the treated compartment. Therefore, we have

$$\text{Rate of L Out} = (\mu + k + r_1)L,$$

(see also the flow diagram).

Thus, by the conservation principle,

$$\frac{dL}{dt} = \beta cS\frac{I}{N} + \beta' cT\frac{I}{N} - (\mu + k + r_1)L. \tag{3.3}$$

Rate of Change of the Infected Population, I

Recall from above that kL is the number of latent individuals per unit time that become infected and move into the infected compartment. Since no one is born infected, we know that

$$\text{Rate of I In} = kL,$$

(see also the flow diagram).

Unlike all other compartments, because people in this compartment are infected, this means that dI represents the number of infected individuals that die because of TB. Combined with μI, being the number of infected individuals per unit time that die naturally, and $r_2 I$, the number of infected individuals per unit time that are treated from TB, and thus move into the treated compartment, we have that

$$\text{Rate of I Out} = (\mu + d + r_2)I,$$

(see also the flow diagram).

Thus, by the conservation principle,

$$\frac{dI}{dt} = kL - (\mu + d + r_2)I. \tag{3.4}$$

Rate of Change of the Treated Population T

We know that $r_1 L$ and $r_2 I$ represent the number of latent and infected individuals per unit time that are treated from TB, respectively. Combined with the assumption that no one is born with immunity, we get that

$$\text{Rate of T In} = r_1 L + r_2 I,$$

(see also the flow diagram).

Since this model does not assume permanent recovery, we know that $\beta' cT\frac{I}{N}$ represents the number of treated individuals per unit time that become infected with TB again, and thus move into the latent compartment. When combined with the number of treated individuals per unit time that die naturally, μT, we have

$$\text{Rate of T Out} = \beta' cT\frac{I}{N} + \mu T,$$

(see also the flow diagram).

Thus, by the conservation principle,

$$\frac{dT}{dt} = r_1 L + r_2 I - \left(\beta' c\frac{I}{N} + \mu\right) T. \tag{3.5}$$

Remark 3.1. Because it's assumed that total population N is divided only into these four compartments, (3.5) can be determined if (3.2), (3.3), and (3.4) are known, as seen above in the logic used for derivation of the differential equations. This allows one to simply focus on studying only the following system of ODEs

$$\begin{cases} \frac{dS}{dt} &= \Lambda - \mu S - \beta cS\frac{I}{N}; \\ \frac{dL}{dt} &= \beta cS\frac{I}{N} + \beta' cT\frac{I}{N} - (\mu + k + r_1)L; \\ \frac{dI}{dt} &= kL - (\mu + d + r_2)I. \end{cases}$$

3.3 The SLIT Model: R_o

Recall from above that a disease's reproductive number, R_o, is a dimensionless quantity that states the number of secondary infectious cases produced by an infectious individual during his or her effective incubation period when introduced in an entirely susceptible population.

R_o for the SLIT Model is essentially comprised of infected and latent components. Specifically, we can view R_o as

$$R_o = (\text{infected component}) \times (\text{latent component})$$

To find the infected component of R_o for the SLIT Model for TB, observe that this quantity is dependent upon both the latent and infected populations. Observe how $\mu + d + r_2$ represents the total rate at which individuals leave the infected compartment. Therefore, we know that

$$\frac{1}{\mu + d + r_2}$$

represents the effective incubation period of a TB-infected individual. Recall that βc represents the average number of susceptible people that get TB because of contact with an infected individual. Therefore, we can state that

$$\frac{\beta c}{\mu + d + r_2} \tag{3.6}$$

represents the average number of susceptibles that get TB because of contact with an infected individual during his or her incubation period, and is the first component of R_o.

To find the latent component of R_o for the SLIT Model for TB, observe how $\mu + k + r_1$ represents the total rate at which individuals leave the latent compartment. Therefore, we know that

$$\frac{1}{\mu + k + r_1}$$

represents the effective latency period of an individual with TB (but not showing symptoms). Recall that k is the rate at which a person leaves the latent compartment and enters the infected compartment. Therefore, we can state that

$$\frac{k}{\mu + k + r_1} \tag{3.7}$$

is the fraction of all latent individuals that become infectious, and therefore show TB symptoms, during TB's effective latency period, and is the second compartment of R_o.

We can therefore state that the product of these two components yields the overall R_o for TB in the SLIT Model, which is

$$R_o = \left(\frac{\beta c}{\mu + d + r_2}\right)\left(\frac{k}{\mu + k + r_1}\right). \tag{3.8}$$

Remark 3.2. One way of thinking of R_o in (3.8) is seeing how the two components represents the journey of an individual in the model, starting in the susceptible (or treated) compartments and ending at the infected compartment. Specifically, we can see that (3.6) represents an individual moving from the susceptible/treated compartments to the latent compartment. Similarly, (3.7) represents an individual moving from the latent compartment to the infected compartment.

Therefore, we can view (3.8), the product of these two quantities, as the movement from the susceptible/treated compartments to the infected compartment in the SLIT Model for TB.

Understanding the components making up R_o of the SLIT Model, we now turn towards the stability analysis of the model, by specifically proving the following theorem:

Theorem 3.3. *[Castillo-Chavez and Feng, 1997] Let $\beta = \beta'$. Let R_o be as defined in Equation (3.8). If $R_o < 1$, then the disease-free equilibrium, E_o, is globally asymptotically stable. If $R_o > 1$, then the unique TB-endemic equilibrium, E_1, is locally asymptotically stable.*

The method used to prove the stabilities of both equilibrium points in Theorem 3.3 are special in that it relies on real analysis rather than the typical methods of algebraic manipulation. However, before attempting to prove the above stability properties, we first must consider and prove the Fluctuations Lemma [Hirsch et al., 1985] in the following section.

3.4 The Fluctuations Lemma

To understand the Fluctuations Lemma and its following proof, considering the following definitions of the limit superior and limit inferior.

Definition 3.4. Consider some sequence (x_n). The *limit superior*, or $\limsup_{n\to\infty} x_n = x^\infty$ is then the supremum of all sequential limits of (x_n). In similar fashion, the *limit inferior*, or $\liminf_{n\to\infty} x_n = x_\infty$ is the infimum of all sequential limits of x_n.

Lemma 3.5. *[Hirsch et al., 1985] Suppose that a function $f : \mathbb{R}^+ \to \mathbb{R}$ is twice differentiable and that*

$$f_\infty < f^\infty. \tag{3.9}$$

Then, there are sequences $(\tau_n) \uparrow \infty$ and $(\sigma_n) \uparrow \infty$ such that

$$f(\tau_n) \to f^\infty, \text{ as } n \to \infty; \tag{3.10}$$

$$f'(\tau_n) = 0, \text{ for all } n; \tag{3.11}$$

$$f''(\tau_n) \leq 0, \text{ for all } n; \tag{3.12}$$

and

$$f(\sigma_n) \to f_\infty, \text{ as } n \to \infty; \tag{3.13}$$

$$f'(\sigma_n) = 0, \text{ for all } n; \tag{3.14}$$

$$f''(\sigma_n) \geq 0, \text{ for all } n. \tag{3.15}$$

In other words, f fluctuates infinitely often between relative maximum and minimum values, which, respectively, approach f_∞ and f^∞.

Proof. [Hirsch et al., 1985]

Let $T \geq 0$ and $\lambda \in (f_\infty, f^\infty)$ be arbitrary. By assuming the estimate in (3.9) and using continuity and the Intermediate Value Theorem, there exists points t_1, t_2, and t_3 such that $T < t_1 < t_2 < t_3$, and

$$f(t_1) = \lambda;$$

$$f(t_2) > \lambda;$$

$$f(t_3) = \lambda.$$

By Rolle's Theorem, we have that there exists a point $\tau \in (t_1, t_3)$ such that $f'(\tau) = 0$ and $f''(\tau) \leq 0$.

Knowing this, choose an increasing sequence (λ_n) such that $f_\infty < \lambda_n < f^\infty$, for all n, and $\lim_{n\to\infty} \lambda_n = f^\infty$. From what we have shown above, there

exists increasing sequences (t_n) and (τ_n) such that $\tau_n > t_n \uparrow \infty$, for all n, $f(\tau_n) > f(t_n) = \lambda_n$, for all n, $f'(\tau_n) = 0$, for all n, and $f''(\tau_n) \leq 0$, for all n. Letting $n \to \infty$, we obtain

$$f^\infty \leq \liminf_{n\to\infty} f(\tau_n) \leq \limsup_{n\to\infty} f(\tau_n) \leq f^\infty.$$

Thus, we have $\lim_{n\to\infty} f(\tau_n) = f^\infty$, which establishes the assertions in (3.10), (3.11), (3.12).

To show the assertions in (3.13), (3.14), and (3.15), consider the function $F(t) = -f(t)$, for all $t \in \mathbb{R}^+$. Applying the steps above with $F(t)$ will show the existence of an increasing sequence (σ_n) that satisfies the assertions in (3.13), (3.14), and (3.15). This concludes the proof of the Fluctuations Lemma.

□

The Fluctuations Lemma is vital for the stability analysis proof of the SLIT Model's equilibrium points, as it is used to prove the following required lemma for Theorem 3.3.

Lemma 3.6. *[Thieme, 1993] Let $f : [0, \infty] \to \mathbb{R}$ be bounded and twice differentiable with bounded second derivative. Let $t_n \to \infty$ and $f(t_n)$ converge to $\liminf_{t\to\infty} f(t) = f_\infty$ or $\limsup_{t\to\infty} f(t) = f^\infty$. Then*

$$f'(t_n) \to 0, \text{ as } n \to \infty.$$

3.5 The SLIT Model: Equilibrium Points & Stability Analysis

Knowing the explicit formula for R_o and Thieme's Lemma (Lemma 3.6) now, we turn to finding and analysing the explicit equilibrium points for the SLIT Model. We assume that $\beta = \beta'$ for simplicity.

Recall the SLIT Model system:

$$\begin{cases} \frac{dS}{dt} &= \Lambda - \mu S - \beta c S \frac{I}{N} = 0; \\ \frac{dL}{dt} &= \beta c S \frac{I}{N} + \beta c T \frac{I}{N} - (\mu + k + r_1)L = 0; \\ \frac{dI}{dt} &= kL - (\mu + d + r_2)I = 0; \\ \frac{dT}{dt} &= r_1 L + r_2 I - \frac{\beta c T I}{N} - \mu T = 0. \end{cases} \tag{3.16}$$

The equilibrium points of the SLIT system in (3.16) are solutions of the system

$$\begin{cases} \Lambda - \mu S - \beta c S \frac{I}{N} &= 0; \\ \beta c S \frac{I}{N} + \beta c T \frac{I}{N} - (\mu + k + r_1)L &= 0; \\ kL - (\mu + d + r_2)I &= 0; \\ r_1 L + r_2 I - \frac{\beta c T I}{N} - \mu T &= 0. \end{cases} \tag{3.17}$$

Solving for L in the third equation in (3.17) yields

$$L = \frac{(\mu + d + r_2)I}{k}. \tag{3.18}$$

Substituting for L onto the second equation in (3.17), we obtain

$$\frac{\beta C S}{N} I + \frac{\beta c T}{N} I - \frac{(\mu + k + r_1)(\mu + d + r_2)}{k} I = 0,$$

which can be factored into

$$I \left[\frac{\beta c S}{N} + \frac{\beta c T}{N} - \frac{(\mu + k + r_1)(\mu + d + r_2)}{k} \right] = 0.$$

We therefore have that, either

$$I = 0, \tag{3.19}$$

or

$$\frac{\beta c S}{N} + \frac{\beta c T}{N} = \frac{(\mu + k + r_1)(\mu + d + r_2)}{k},$$

or

$$\frac{S}{N} + \frac{T}{N} = \left(\frac{\mu + k + r_1}{k} \right) \left(\frac{\mu + d + r_2}{\beta c} \right),$$

or

$$\frac{S}{N} + \frac{T}{N} = \frac{1}{R_o}. \tag{3.20}$$

3.5.1 $R_o < 1$

Consider the case when $R_o < 1$ and $I = 0$. We then get from (3.18) that $L = 0$. It then follows from the fourth equation in (3.17) that $T = 0$. Consequently, it follows from the first equation in (3.17) that

$$\Lambda - \mu S = 0,$$

which yields

$$S = \frac{\Lambda}{\mu}.$$

We therefore get the disease-free equilibrium point

$$E_o = (S^*, L^*, I^*, T^*) = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right). \tag{3.21}$$

As stated in Theorem 3.3, we want to show that E_o is *g.a.s.* when $R_o < 1$.

Proof. [Castillo-Chavez and Feng, 1997]

To do this, we first will show that the number of infected people, I, is bounded. Recall that $N = S + L + I + T$. By definition and because there cannot be negative amounts of people of any kind, we know that $0 \leq I \leq N$. Therefore, to show that I is bounded, we need to show that N is bounded.

Because $N = S + L + I + T$, we know that $\frac{dN}{dt} = \frac{dS}{dt} + \frac{dL}{dt} + \frac{dI}{dt} + \frac{dT}{dt}$, adding equations (3.2), (3.3), (3.4), and (3.5) together yields the following differential equation:

$$\frac{dN}{dt} = \Lambda - \mu N - dI.$$

Thus,

$$\frac{dN}{dt} \leq \Lambda - \mu N,$$

or

$$\frac{dN}{dt} + \mu N \leq \Lambda. \tag{3.22}$$

By multiplying both sides of (3.22) with integrating factor $e^{\mu t}$, we obtain

$$e^{\mu t}\left(\frac{dN}{dt} + \mu N\right) \leq \Lambda e^{\mu t};$$

which implies that

$$\frac{d}{dt}\left[Ne^{\mu t}\right] \leq \Lambda e^{\mu t}. \tag{3.23}$$

Integrating on both sides of (3.23) from 0 to t, we obtain

$$\int_0^t \frac{d}{d\tau}\left[Ne^{\mu\tau}\right] d\tau \leq \int_0^t \Lambda e^{\mu\tau} d\tau,$$

or

$$e^{\mu t}N(t) - N_o \leq \frac{\Lambda}{\mu}e^{\mu t} - \frac{\Lambda}{\mu};$$

from which we get that

$$e^{\mu t}N(t) \leq \frac{\Lambda}{\mu}e^{\mu t} + N_o - \frac{\Lambda}{\mu} \leq \frac{\Lambda}{\mu}e^{\mu t} + N_o;$$

so that, dividing by $e^{\mu t}$, for all t,

$$N(t) \leq \frac{\Lambda}{\mu} + \frac{N_o}{e^{\mu t}}, \text{ for all } t.$$

Consider the scenarios of when $N(t) \leq \frac{\Lambda}{\mu}$ and when $N(t) > \frac{\Lambda}{\mu}$. The first case would result in $N(t) < \frac{\Lambda}{\mu}$. The second scenario would result in $\frac{\Lambda}{\mu} < N(t) \leq \frac{\Lambda}{\mu} + N_o$. Therefore, we can state that N is bounded in general. This means that by definition of compartments, we know that S, L, I, T are bounded as well.

Since the functions S, L, I, and T are differentiable functions of t, it follows from the equations in (3.16) that S, L, I, and T are twice differentiable with continuous second derivatives.

Knowing that I is bounded and is twice differentiable, we can therefore apply Lemma 3.6.

Choose a sequence $t_n \to \infty$ such that

$$I(t_n) \to I^\infty,\ I'(t_n) \to 0,\ \text{as } n \to \infty.$$

Observe now that the above limit can be expressed as

$$\lim_{n\to\infty}[kL(t_n) - (\mu + d + r_2)T(t_n)] = 0,$$

on view of the third equation in (3.16).

Thus,

$$\begin{aligned} I(t_n) &= \frac{\mu + d + r_2}{\mu + d + r_2} I(t_n); \\ &= \frac{1}{\mu + d + r_2}[(\mu + d + r_2)I(t_n) - kL(t_n) + kL(t_n)]; \\ &= \frac{1}{\mu + d + r_2}[(\mu + d + r_2)I(t_n) - kL(t_n)] + \frac{k}{\mu + d + r_2} L(t_n); \\ &= \frac{-1}{\mu + d + r_2} I'(t_n) + \frac{k}{\mu + d + r_2} L(t_n), \end{aligned}$$

from which we get that

$$\lim_{n\to\infty} I(t_n) = I^\infty = \lim_{n\to\infty} \frac{k}{\mu + d + r_2} L(t_n).$$

Recall that L is continuous, bounded, and twice differentiable. This means that Lemma 3.6 is applicable. Recall further that, by Definition 3.6, L^∞ is the supremum of all sequential limits of L. Therefore,

$$\lim_{n\to\infty} L(t_n) = \frac{\mu + d + r_2}{k} I^\infty \leq L^\infty; \tag{3.24}$$

so that

$$I^\infty \leq \frac{k}{\mu + d + r_2} L^\infty. \tag{3.25}$$

By Lemma 3.6, choose a sequence $s_n \to \infty$ such that

$$L(s_n) \to L^\infty,\ L'(s_n) \to 0,\ \text{as } n \to \infty.$$

With our assumption that $\beta = \beta'$, the expression for $L'(s_n)$ can be re-written as

$$L'(s_n) = \beta c I \left(\frac{S+T}{N} \right) - (\mu + k + r_1) L(s_n).$$

Because $\frac{S+T}{N} \leq 1$, we can state that

$$L'(s_n) \leq \beta c I(s_n) - (\mu + k + r_1) L(s_n),\ \text{for all } n.$$

Assume that there exists a sequence $(s_n) \subseteq [0, \infty)$ such that $s_n \to \infty$ as $n \to \infty$ and

$$L(s_n) \to L^\infty,\ L'(s_n) \to 0,\ \text{as } n \to \infty.$$

Consider

$$L'(s_n) + (\mu + k + r_1) L(s_n) \leq \beta c I(s_n).$$

Because $\lim_{n\to\infty} L'(s_n) = 0$, we then obtain that

$$(\mu + k + r_1) L^\infty \leq \beta c \limsup_{n\to\infty} I(s_n).$$

Consequently,

$$(\mu + k + r_1) L^\infty \leq \beta c I^\infty.$$

Recall that

$$R_o = \left(\frac{\beta c}{\mu + d + r_2} \right) \left(\frac{k}{\mu + k + r_1} \right).$$

We also know that

$$I^\infty \leq \frac{k}{\mu + d + r_2} L^\infty;$$

therefore,

$$(\mu + k + r_1)L^\infty \leq \beta c \left(\frac{k}{\mu + d + r_2}\right) L^\infty.$$

This can be rearranged such that

$$L^\infty \leq \left(\frac{\beta c}{\mu + d + r_2}\right)\left(\frac{k}{\mu + k + r_1}\right) L^\infty;$$

so that

$$L^\infty \leq R_o L^\infty,$$

or

$$(1 - R_o)L^\infty \leq 0.$$

Hence, because we are assuming that $R_o < 1$, it follows that $L^\infty \leq 0$. But because $L_\infty \geq 0$, we have that $L^\infty = 0$. Consequently, because

$$0 \leq L_\infty \leq L^\infty \leq 0,$$

we get that

$$\lim_{t\to\infty} L(t) = 0. \tag{3.26}$$

Combining (3.19) and (3.20) together, we also obtain

$$\lim_{t\to\infty} I(t) = 0. \tag{3.27}$$

Recall that $\frac{dN}{dt} = \Lambda - \mu N - dI$. Knowing that N is bounded, we can apply Lemma 3.6 similarly such that

$$\frac{dN}{dt} \to 0,$$

which implies that

$$\Lambda - \mu N - dI \to 0;$$

so

$$\frac{\Lambda - dI}{\mu} \to N, \text{ as } t \to \infty.$$

We then have that

$$N_\infty \geq \frac{\Lambda - dI^\infty}{\mu} = \frac{\Lambda}{\mu}.$$

Observe that $\frac{dN}{dt} < 0$, for all $N > \frac{\Lambda}{\mu}$. Therefore, we can just consider $N \leq \frac{\Lambda}{\mu}$. Therefore, we have $N^\infty \leq \frac{\Lambda}{\mu}$. This implies that $N_\infty = N^\infty = \frac{\Lambda}{\mu}$. Therefore, we can state that

$$N(t) \to \frac{\Lambda}{\mu}, \text{ as } t \to \infty. \tag{3.28}$$

By definition of the treated compartment T, we know that

$$I(t), L(t) \to 0, \text{ as } t \to \infty \tag{3.29}$$

imply that

$$T(t) \to 0, \text{ as } t \to \infty. \tag{3.30}$$

Thus, we have proven that the disease-free equilibrium point, E_o, is globally asymptotically stable when $R_o < 1$.

□

3.5.2 $R_o > 1$

Consider the case when $R_o > 1$ and (3.20) is true. To make the algebra easier, under these conditions, we rewrite system (3.16) as follows:

$$\begin{cases} \frac{dN}{dt} &= \Lambda - \mu N - dI; \\ \frac{dL}{dt} &= \frac{\beta c I(N-L-I)}{N} - (\mu + k + r_1)L; \\ \frac{dI}{dt} &= kL - (\mu + d + r_2)L. \end{cases} \tag{3.31}$$

The equilibrium points of the SLIT system in (3.31) are solutions of the system

$$\begin{cases} \Lambda - \mu N - dI &= 0; \\ \frac{\beta c I(N-L-I)}{N} - (\mu + k + r_1)L &= 0; \\ kL - (\mu + d + r_2)L &= 0. \end{cases} \tag{3.32}$$

Solving for the L from the third equation of (3.32) yields

$$L^{**} = \frac{(\mu + d + r_2)I^{**}}{k}. \tag{3.33}$$

Substituting for L into the second equation of (3.32), we obtain

$$\frac{\beta cI}{N}\left[N - \frac{(\mu + d + r_2)I}{k} - I\right] - \frac{(\mu + k + r_1)(\mu + d + r_2)I}{k} = 0,$$

or

$$\frac{\beta cI}{N}\left[N + \frac{-kI - (\mu + d + r_2)I}{k}\right] - \frac{\beta c(\mu + k + r_1)}{\beta c}\left[\frac{(\mu + d + r_2)I}{k}\right] = 0,$$

or

$$\frac{\beta cI}{N}\left[N + \frac{-kI - (\mu + d + r_2)I}{k}\right] - \frac{\beta cI}{R_o} = 0,$$

or

$$\beta cI + \frac{\beta cI[-kI - (\mu + d + r_2)I]}{kN} - \frac{\beta cI}{R_o} = 0,$$

or

$$\beta cI - \frac{\beta cI^2[\mu + d + r_2 + k]}{kN} - \frac{\beta cI}{R_o} = 0,$$

or

$$\beta cI\left\{1 - \frac{I(\mu + d + r_2 + k)}{kN} - \frac{1}{R_o}\right\} = 0.$$

Let $\alpha = \mu + d + r_2 + k$. Thus, we obtain

$$\beta cI\left\{1 - \frac{\alpha I}{kN} - \frac{1}{R_o}\right\} = 0. \tag{3.34}$$

We therefore have that, either

$$I = 0, \tag{3.35}$$

or

$$1 - \frac{\alpha I}{kN} - \frac{1}{R_o} = 0. \tag{3.36}$$

Observe how when $I = 0$, we have that $L = 0$ and that $N = \frac{\Lambda}{\mu}$. This means $I = 0$ will result in the equilibrium point $(N^{**}, L^{**,I^{**}}) = \left(\frac{\Lambda}{\mu}, 0, 0\right)$, which is the disease-free equilibrium point E_o.

On the other hand, if $1 - \frac{\alpha I}{kN} - \frac{1}{R_o} = 0$ in the expression in (3.34), we obtain

$$I^{**} = \frac{N^{**}k(R_o - 1)}{\alpha R_o}. \tag{3.37}$$

Substituting I into the first equation of (3.32), we obtain

$$\Lambda - \mu N - \frac{dkN(R_o - 1)}{\alpha R_o} = 0,$$

or

$$\mu N + \frac{dkN(R_o - 1)}{\alpha R_o} = \Lambda,$$

or

$$N\left[\mu + \frac{dkN(R_o - 1)}{\alpha R_o}\right] = \Lambda,$$

or

$$N\left[\frac{\alpha\mu R_o + dk(R_o - 1)}{\alpha R_o}\right] = \Lambda,$$

or

$$N^{**} = \frac{\alpha\Lambda R_o}{\alpha\mu R_o + dk(R_o - 1)}. \tag{3.38}$$

Combining (3.30), (3.34), and (3.35) together, we therefore obtain the unique TB-endemic equilibrium point of the SLIT Model when $R_o > 1$, $E_1 = (N^{**}, L^{**}, I^{**})$:

$$E_1 = \left[\frac{\alpha\Lambda R_o}{\alpha\mu R_o + dk(R_o - 1)}, \frac{(\mu + d + r_2)I^{**}}{k}, \frac{N^{**}k(R_o - 1)}{\alpha R_o}\right]. \tag{3.39}$$

As stated in Theorem 3.3, we want to show that E_1 is *l.a.s.* when $R_o > 1$.

Proof. [Castillo-Chavez and Feng, 1997]

To do this, first observe that

$$\frac{N^{**} - L^{**} - I^{**}}{N^{**}} = \frac{1}{R_o}.$$

With this in mind, consider the derivative map of system (3.28), or Jacobian matrix evaluated at E_1:

$$J(N^{**}, L^{**}, I^{**}) = \begin{pmatrix} -\mu & 0 & -d \\ a(R_o - 1) & -(aR_o + \mu + k + r_1) & \frac{\beta c}{R_o} - \alpha R_o \\ 0 & k & -(\mu + d + r_2) \end{pmatrix},$$

where $a = \frac{\beta c}{R_o} \cdot \frac{I^{**}}{N^{**}}$. We obtain the following characteristic polynomial for local stability analysis,

$$P(\lambda) = \lambda^3 - \tau\lambda^2 + \sigma\lambda - \delta = 0, \tag{3.40}$$

where

$$\begin{aligned} \tau &= -(aR_o + 3\mu + d + k + r_1 + r_2); \\ \sigma &= aR_o(2\mu + d + k + r_2) + \mu(2\mu + d + k + r_1 + r_2); \\ \delta &= -[\alpha\mu aR_o + adk(R_o - 1)]. \end{aligned}$$

To consider E_1 as a locally asymptotically stable equilibrium point, the eigenvalues of (3.37) must all have a negative real part. We consider the following stability criterion to determine the signs of $Re(\lambda)$.

Definition 3.7. [Meiss, 2007] The *Routh-Hurwitz stability criterion* determines whether all the roots of a polynomial have negative real parts. Consider the following cubic characteristic polynomial.

$$P(\lambda) = \lambda^3 - \tau\lambda^2 + \sigma\lambda - \delta.$$

The Routh-Hurwitiz stability criterion states if λ is a root of the polynomial, that $Re(\lambda) < 0$ if and only if $\tau < 0$ and $\sigma\tau < \delta < 0$.

Using Definition 3.7, we can see from polynomial (3.37) that $\tau, \delta < 0$. Through algebra, we can also see that $\sigma\tau < \delta$. Therefore, we see that the Routh-Hurwitz stability criterion is satisfied. It therefore follows that E_1 is *l.a.s.* when $R_o > 1$.

□

Chapter 4

Discussion

In this paper, the basics of compartmental models in epidemiology were introduced and studied through examining two variants of the Basic SIR Model. It was through analyses of these models that we could establish an understanding of important characteristics that determine whether a disease dies out or becomes an epidemic within a population; most importantly, we learnt about the reproductive number of the disease, R_o. With such knowledge of definitions and stability analysis, a compartmental model for one-strain TB and no bacterial resistance, developed by Castillo-Chavez and Feng, became the paper's primary focus in order to understand how such a strain would spread under such conditions. It was found that two unique solutions exist for such a one-strain TB infection upon a homogeneously mixed population: a disease-free solution and a unique TB-endemic solution. Furthermore, it was found that, whether the population tends towards having an epidemic or not, depends mainly on the reproductive number of this one-strain TB: R_o.

However, it should be noted that this model does have some flaws. Perhaps the biggest natural limitation of this model is that it doesn't account for the effects of long and variable latency periods — A key characteristic of TB. However, it should be noted that Castillo-Chavez and Feng accounted for these characteristics, and the modified model showed no difference in the qualitative dynamics and analysis of TB [Castillo-Chavez and Feng (1996)]. However, other limitations still exists, such as the model's limited applicability of modelling the dynamics of TB because of the assumption of a homogeneously mixed population. Furthermore, the SLIT Model ignores

drug-resistant strains of TB, which still remains to be a major threat to all societies.

Despite these limitations, however, the results from the SLIT Model definitely have some importance in that it gives some insight into what determines the effectiveness of TB. By understanding the factors and parameters that determine the reproductive number of one of the deadliest modern diseases, society can therefore have some idea of where TB stands within their population, and begin to have an idea of how to reduce the effectiveness of TB transmission.

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