# MODELING TRANSMISSION DYNAMICS OF TUBERCULOSIS INCLUDING VARIOUS LATENT PERIODS

by

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# ABSTRACT

The systems of equations created by Blower *et al*. (1995) and Jia *et al*. (2007) designed to model the dynamics of Tuberculosis are solved using the computer software SIMULINK. The results are first employed to examine the intrinsic transmission dynamics of the disease through two models developed by Blower *et al.* (1995). The "simple transmission model" was used primarily to give insight to the behavior of the susceptible, latent, and infectious groups of individuals. Then, we consider a more detailed transmission model which includes several additional factors. This model captures the dynamics of not only the susceptible, latent and infectious groups but also the non-infectious cases and the recovered cases. Using the SIMULINK results, it can be shown that the intrinsic dynamics of the disease contribute to the rise and decline of the disease seen in historical accounts. Next, the simulation results are used to study the equilibrium points of the disease which can be obtained by varying the parameters and therefore changing the value for the basic reproduction ratio ($\mathcal{R}_0$). Our model uses the system of equations developed by Jia *et al*. (2007). The SIMULINK results are used to visually confirm the hypothesis proposed by Jia *et al*. (2007) that the equilibrium behavior of the system when $\mathcal{R}_0 > 1$ is globally asymptotically stable.

This thesis is dedicated to Tom, Jake, JC and Robin, thank you for all of your patience and support.

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I would like to thank all of my professors. I have learned more these last two years than I thought there was to know. Specifically, I thank Dr. Mohapatra for teaching me how dedicated and caring a teacher can be.

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# CHAPTER 1: INTRODUCTION

## 1.1 Introduction

The outbreak and spread of disease has been questioned and studied for many years. The ability to make predictions about diseases could enable scientists to evaluate inoculation or isolation plans and may have a significant effect on the mortality rate of a particular epidemic. The modeling of infectious diseases is a tool which has been used to study the mechanisms by which diseases spread, to predict the future course of an outbreak and to evaluate strategies to control an epidemic [8].

## 1.2 History of Epidemic Models

From the beginning of recorded history communicable diseases have drastically affected the course of development of our planet. The Bible talks about the plagues, such as that mentioned in the book of Numbers 16:46-49. *"46Then Moses said to Aaron, "Take your censer and put incense in it, along with fire from the altar, and hurry to the assembly to make atonement for them. Wrath has come out from the LORD; the plague has started." 47So Aaron did as Moses said, and ran into the midst of the assembly. The plague had already started among the people, but Aaron offered the incense and made atonement for them. 48He stood between the living and the dead, and the plague stopped. 49But 14,700 people died from the plague, in addition to those who had died because of Korah*." From 1346 to 1350 the Black Death (bubonic plague) is blamed for reducing the population of Europe by one third. Between 1519 and 1530 the Indian population of Mexico declined from thirty million to three million due to outbreaks of various diseases brought from Europe, such as smallpox, measles and diphtheria. During the time span

of 1720 to 1722 the plague shrunk the population of some regions of France by as much as sixty percent [5]. These and other drastic reductions in population have perplexed scientists for many years.

The first scientist who systematically tried to quantify causes of death was John Graunt in his book *Natural and Political Observations made upon the Bills of Mortality*, in 1662. The bills he studied were listings of numbers and causes of deaths published weekly. Graunt's analysis of causes of death is considered the beginning of the "theory of competing risks" which according to Daley and Gani [8, p. 2] is "a theory that is now well established among modern epidemiologists".

The earliest account of mathematical modeling of spread of disease was carried out in 1766 by Daniel Bernoulli. Trained as a physician, Bernoulli created a mathematical model to defend the practice of inoculating against smallpox [14]. The calculations from this model showed that universal inoculation against smallpox would increase the life expectancy from 26 years 7 months to 29 years 9 months [2].

Following Bernoulli, other physicians contributed to modern mathematical epidemiology. Among the most acclaimed of these were A. G. McKendrick and W. O. Kermack, whose paper *A contribution to the Mathematical Theory of Epidemics* was published in 1927. A simple deterministic (compartmental) model was formulated in this paper and was successful in predicting the behavior of an epidemic very similar to that observed in many recorded epidemics [5].

## 1.3 Introduction to Tuberculosis

Tuberculosis, a common and potentially fatal disease is also known as TB or Consumption. TB is a bacterial infection by Mycobacterium tuberculosis which most commonly attacks the lungs. It can also affect the circulatory system, bones, joints, central nervous system (causing meningitis), even the skin. Seventy-five percent of TB cases are lung infections. Tuberculosis is a contagious disease spread through the air. Its communicability is similar to the common cold which spreads via sputum (phlegm) which is exhaled or sprayed in a sneeze or while speaking. Only persons with active lung infections can spread the disease. It is estimated that 1.6 million people died from TB in 2005, one third of the world's population is infected with TB and a new infection occurred globally every second [22].

Two items that make Tuberculosis particularly interesting for mathematical modeling are the facts that TB has been well documented in England and Wales since 1850 [21] and the fact that only ten percent of the people infected with TB ever become sick or infectious [22]. People with latent TB infections are not sick, have no symptoms of the disease, and cannot spread the disease to others [6]. The immune system of people infected with TB bacilli may "wall off" the bacteria, causing the disease to lie dormant for years [22]. Common factors associated with the disease to move from the latent state to the infectious state are mainly a suppressed immune system such as the one which occurs with HIV/AIDS, diabetes, and other diseases contributing to a weaker immune system. Some other causes are IV drug use, protein malnutrition, and inadequate treatment of a previous TB infection [7].

The first vaccine for TB was developed by Albert Clamette and Camille Guerin in 1906 but it was not until 1945 that the vaccine became widely distributed in the United States, Great Britain, and Germany. A reliable treatment for TB did not become available until 1946 when the antibiotic Streptomycin was developed. The decline in TB cases for over 100 years ended around 1980. Hopes of eradicating the disease were dashed with the rise of drug resistant strains of Tuberculosis. Treatment of TB can be a long process. Quality antibiotics have to be taken for periods lasting almost a year or more. When a patient does not complete the treatment, a particularly dangerous form of drug-resistant TB called Multi-Drug Resistant Tuberculosis (MDR-TB) occurs. Cases of MDR-TB are high in some countries, especially those in the former Soviet Union, and threaten TB control efforts [22]. However, MDR-TB is treatable. It can require up to two years of chemotherapy and more expensive second-line drugs which usually have many side effects. The emergence of a "super-bug TB" called XDR-TB; particularly in those patients suffering from HIV/AIDS poses the latest threat to TB control and confirms the need for better modeling of TB.

To give some reference, the number of TB deaths in the United States stands around 5.5 per 100,000. In Africa we find a 14 fold increase in the number of TB related deaths or 74 per 100,000. The next highest region is Southeast Asia at less than half of that viz. 31 per 100,000 [22].

On May 10, 2007, Andrew Speaker, an Atlanta lawyer, was told that he had MDR-TB. Because his TB was latent he was told that he was not contagious nor a threat to anyone. He was, however, strongly advised not to travel. On May 12, 2007 Speaker flew from the US to Paris and later to the Aegean Island of Santorini for his wedding, then on to Rome for his honeymoon. While he was in Rome, the CDC discovered that Mr. Speaker did not have the

MDR-TB but the more resistant strain XDR-TB. Mr. Speaker was then advised not to travel and to turn himself over to the Italian health authorities. Mr. Speaker evaded the Italians and the CDC, flew to Montreal, rented a car and drove back into the United States. During his trip, Mr. Speaker flew on seven airliners and could have potentially exposed 1280 fellow air travelers to the disease. Upon his return to the US, he became the first person to be forcibly subjected to a CDC isolation order since 1963. Judging by the international scare that Mr. Speaker's latent tuberculosis caused, we can see that the disease has not been eradicated and still strikes fear into the hearts of epidemiologists worldwide.

# CHAPTER 2: BACKGROUND STUDY

## 2.1 Deterministic Mathematical Models

When dealing with large populations, as in the case of tuberculosis, deterministic or compartmental mathematical models are used. In the deterministic model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of the epidemic. Letters such as *M*, *S*, *E*, *I*, and *R* are often used to represent different stages (as can be seen in Figure 1).

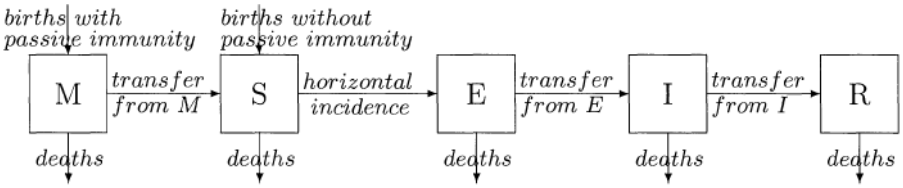



**Figure 1 General Transfer Diagram for the MSEIR Model**

**From "The Mathematics of Infectious Diseases," by Herbert W. Hethcote, 2000, Society for Industrial and Applied Mathematics, 42, 4, p. 601.**

The transition rates from one class to another are mathematically expressed as derivatives, hence the model is formulated using differential equations. While building such models, it must be assumed that the population size in a compartment is differentiable with respect to time and that the epidemic process is *deterministic*. In other words, the changes in population of a compartment can be calculated using only the history used to develop the model [5].

## 2.2 Basic SIR Model

In 1927, W. O. Kermack and A. G. McKendrick created a model in which they considered a fixed population with only three compartments, susceptible: *S(t)*, infected, *I(t)*, and

removed, *R(t)*. In this section, their basic model will be explored and applied to an outbreak of bubonic plague that occurred in Eyam, England, between 1665 and 1666. The concepts that were developed with the study of the model such as contact rate, infection rate and reproduction number will be defined.

As mentioned, the compartments used for this model consist of three classes: *S(t)* is used to represent the number of individuals not yet infected with the disease at time *t*, or those susceptible to the disease, *I(t)* denotes the number of individuals who have been infected with the disease and are capable of spreading the disease to those in the susceptible category, finally, *R(t)* is the compartment used for those individuals who have been infected and then recovered from the disease. Those in this category are not able to be infected again or to transmit the infection to others. The flow of this model may be considered as follows


Table 1 contains a summary of the notation used in this and the next sections.

**Table 1 Summary of Notation**

| | |
|---|---|
| M | Passively Immune Infants |
| S | Susceptibles |
| E | Exposed individuals in the latent period |
| I | Infectives |
| R | Removed with Immunity |
| $\beta$ | Contact Rate |
| $\mu$ | Average Death Rate |
| b | Average Birth Rate |
| $1/\varepsilon$ | Average Latent Period |
| $1/\gamma$ | Average Infectious Period |
| $\mathcal{R}_0$ | Basic Reproduction Number |

Using a fixed population, $N = S(t) + I(t) + R(t)$ (where $N$ is the total population) Kermack and McKendrick derived the following equations:

$$\frac{dS}{dt} = -\beta SI \tag{2.2.1}$$

$$\frac{dI}{dt} = \beta SI - \gamma I \tag{2.2.2}$$

$$\frac{dR}{dt} = \gamma I \tag{2.2.3}$$

Several assumptions were made in the formulation of these equations. First, an individual in the population must be considered as having an equal probability as every other individual of contracting the disease with a rate of $\beta$, which is considered the contact or infection rate of the disease. Therefore, an infected individual makes contact and is able to transmit the disease with $\beta N$ others per unit time and the fraction of contacts by an infected with a susceptible is $S/N$. The number of new infections in unit time per infective then is $(\beta N)(S/N)$, giving the rate of new infections (or those leaving the susceptible category) as $(\beta N)(S/N)I = \beta SI$ [5] as can be seen in (2.2.1). For the second and third equations, consider the population leaving the susceptible class as equal to the number entering the infected class. However, a number equal to the fraction ($\gamma$ which represents the mean recovery rate, or $1/\gamma$ the mean infective period) of infectives are leaving this class per unit time to enter the removed class. These processes which occur simultaneously are referred to as the *Law of Mass Action*, a widely accepted idea that the rate of contact between two groups in a population is proportional to the size of each of the groups concerned [8]. Finally, it is assumed that the rate of infection and removal is much faster

than the time scale of births and deaths; therefore, these factors are ignored in this model. Because $R$ is determined once $N$, $S$ and $I$ are known we now will use only the pair of equations:

$$\frac{dS}{dt} = -\beta SI \qquad (2.2.4)$$

$$\frac{dI}{dt} = (\beta S - \gamma)I \qquad (2.2.5)$$

Consider introducing a small number of infectives into a population of size $N$, where we assume $S(0) \approx N$ and $I(0) \approx 0$. If $S(0) \approx N < \gamma/\beta$, then the number of infectives decreases to zero and there is no epidemic. If $N > \gamma/\beta$, then the population in the infective category first increases to a maximum ($S = \gamma/\beta$) then decreases to zero and the epidemic occurs. We can now see that there is a threshold quantity which determines whether an epidemic occurs or the disease simply dies out. This quantity is called the basic reproduction number, denoted by $\mathcal{R}_0$, which can be defined as the number of secondary infections caused by a single infective introduced into a population made up entirely of susceptible individuals ($S(0) \approx N$) over the course of the infection of this single infective. This infective individual makes $\beta N$ contacts per unit time producing new infections with a mean infectious period of $1/\gamma$. Therefore, the basic reproduction number is

$$\mathcal{R}_0 = \frac{\beta N}{\gamma} \qquad (2.2.6)$$

This value quantifies the transmission potential of a disease. If the basic reproduction number falls below one ($\mathcal{R}_0 < 1$), i.e. the infective may not pass the infection on during the infectious period, the infection dies out. If $\mathcal{R}_0 > 1$ there is an epidemic in the population. In cases where

$\mathcal{R}_0 = 1$, the disease becomes endemic, meaning the disease remains in the population at a consistent rate, as one infected individual transmits the disease to one susceptible [20].

To glean additional information from these differential equations, we can divide equation (2.2.5) by equation (2.2.4) which yields

$$\frac{dI}{dS} = \frac{\frac{dI}{dt}}{\frac{dS}{dt}} = \frac{(\beta S - \gamma) I}{-\beta S I} = -1 + \frac{\gamma}{\beta S} \tag{2.2.7}$$

By using simple differential equation techniques we see that

$$I = -S + \frac{\gamma}{\beta} \log S + c \tag{2.2.8}$$

where $c$ is a constant. To calculate the constant we use the initial conditions given ($S(0) \approx N$ and $I(0) \approx 0$). With $S(0) + I(0) = N$ we substitute the value $t = 0$ into the solution and get

$$c = N - \frac{\gamma}{\beta} \ln S(0) \tag{2.2.9}$$

By substituting (2.2.9) into (2.2.8) we get

$$I = -S + \frac{\gamma}{\beta} \ln S + N - \frac{\gamma}{\beta} \ln S(0) \tag{2.2.10}$$

Finally, using the fact that $I(t) \to 0$ as $t \to \infty$ and let $S_\infty$ be the limiting value of $S(t)$ as $t \to \infty$, we obtain

$$N - \frac{\gamma}{\beta} \ln S(0) = S_\infty - \frac{\gamma}{\beta} \ln S_\infty \tag{2.2.11}$$

the *final size equation* [4]. This equation supports Kermack and McKendrick's conclusion in their paper of 1927, "An epidemic, in general, comes to an end, before the susceptible population has been exhausted" (p. 721).

The Great Plague in London was probably one of the first epidemics to be studied from a modeling standpoint. A substantial amount of information is known about the progression of the disease due to the fact that the weekly mortality bills from that time have been retained. The village of Eyam, England had two outbreaks of the plague in 1665 – 1666. With an initial population of only 350, the first phase of the epidemic killed 89, while the second phase saw the population decrease to only 83 persons. With the outbreak of the disease, the village rector was able to persuade the entire town to quarantine themselves to prevent the spread of the disease. Because of the quarantine the second phase of the Eyam epidemic has been used as a case study for modeling.

Using the modeling program SIMULINK, equations (2.2.4) and (2.2.5) of the SIR system have been modeled with the parameter values for the second phase of the Eyam epidemic, $\beta = 0.0178$, $\gamma = 2.73$, $S(0) = 254$, $I(0) = 7$, $N = 261$. The diagram of equations can be seen in Figure 2.

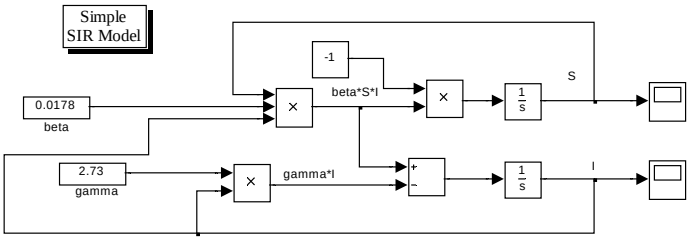



**Figure 2 SIMULINK Diagram for the Simple SIR Model**

Upon running the simulation, values for $S_\infty$ (the number of susceptible that did not contract the disease) and $I_{max}$ (the number of infected when $S = \gamma/\beta$) were calculated as can be seen in Figure 3, the graph of susceptible vs. infected from this simulation.

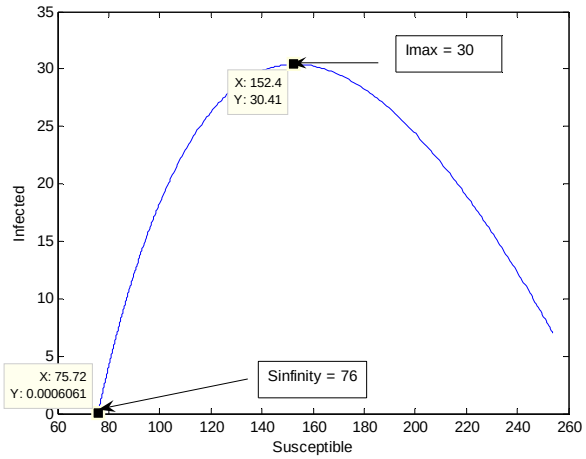
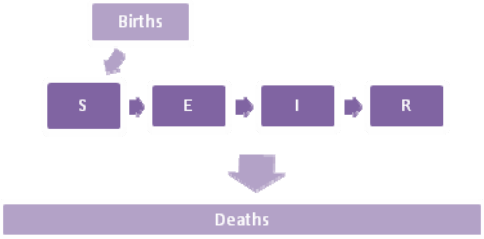



**Figure 3 Graph of Simple SIR Model Results**

The modeled data of $S_\infty = 76$ and $I_{max} = 30$ is very close to the observed data from the epidemic of $S_\infty = 83$ and $I_{max} = 29$. It should be noted however, that our model makes at least one assumption that is not true. The SIR model considers diseases transmitted from person to person, while this plague is transmitted by rat fleas. It is a speculation, however, that the second phase of the epidemic in Eyam may have been the pneumonic form of the plague. This is the form that spreads from person to person when they are in close contact with each other due to a quarantine situation [4]. Regardless of this possible difference, the basic SIR model, proposed initially by Kermack and McKendrick, is shown in this example to be a reasonable and accurate prediction of the behavior seen in the second phase of the Eyam epidemic.

## 2.3 SEIR Model

The SIR model discussed above takes into account only those diseases which cause an individual to be able to infect others immediately upon their infection. Many diseases have what is termed a *latent* or *exposed* phase, during which the individual is said to be *infected* but not *infectious*. Using the example of measles, there is a period of about seven to eight days that an individual is said to be exposed, while the virus multiplies. Following this period, the individual will develop a cough and a low grade fever. At this point the individual is said to be both *infected* and *infectious*. In such a case, a different model is required to describe the situation, one which considers this extra compartment for the population, the exposed or latent compartment. In this section the SEIR model including births and deaths will be explained along with an exploration of the differential equations describing the flow from one compartment to another. The flow of this model can be considered in the diagram below.




In this model the host population ($N$) is broken into four compartments: susceptible, exposed, infectious, and recovered, with the numbers of individuals in a compartment, or their densities denoted respectively by $S(t)$, $E(t)$, $I(t)$, $R(t)$, that is

$$N = S(t) + E(t) + I(t) + R(t)$$

Before directly exploring the equations let us consider the dynamics of the susceptible class ($S(t)$). In the beginning, $S(t)$ is considered to be the entire population being studied ($N$). In

such a case the population of *S(t)* increases with the birth rate (*b*), but decreases with the death of an individual. The rate at which individuals die is equal to the death rate (μ) times the number of susceptible individuals. Upon contact with an infectious individual, a fraction of *S(t)* moves from the susceptible class to the exposed class. (See equation 2.3.1 below).

$$\frac{dS}{dt} = b - \beta SI - \mu S \qquad (2.3.1)$$

The next three differential equations can be viewed in the same way, with individuals entering a compartment from the previous, and leaving a compartment to move on to the next compartment, or to death. (See Table 1 on page 7 for the definitions of the variables.)

$$\frac{dE}{dt} = \beta SI - (\varepsilon + \mu) E \qquad (2.3.2)$$

$$\frac{dI}{dt} = \varepsilon E - (\gamma + \mu) I \qquad (2.3.3)$$

$$\frac{dR}{dt} = \gamma I - \mu R \qquad (2.3.4)$$

Clearly, the first three equations are independent of *R*, thus we may reduce the system of equations and use only (2.3.1), (2.3.2), and (2.3.3).

The basic reproduction ratio for this model will be calculated using the *next generation method* as described by Hefferman *et al.* (2005). Consider the next generation matrix *G*, which is made up of two parts: $F$ and $V^1$, where

$$F = \left[ \frac{\partial F_i(x_0)}{\partial x_j} \right] \qquad (2.3.5)$$

and

$$V = \left[ \frac{\partial V_i(x_0)}{\partial x_j} \right] \tag{2.3.6}$$

The $F_i$ are the new infections, while the $V_i$ shows the transfers of infections from one compartment to another. Here, $x_0$ is the disease-free equilibrium state. To develop the basic reproduction ratio ($\mathcal{R}_0$) calculate the dominant eigenvalue of the matrix $G$. The next generation matrix for the above SEIR model needs to consider the number of ways that (1) new infections can arise and (2) individuals can move between compartments. In this model, there are two disease states, but only one way to create new infections

$$F = \begin{bmatrix} \frac{\beta b}{\mu} & 0 \\ 0 & 0 \end{bmatrix} \tag{2.3.7}$$

There are however, various ways to move between the compartments:

$$\mathrm{V} = \begin{bmatrix} 0 & \varepsilon + \mu \\ \gamma + \mu & -\varepsilon \end{bmatrix} \tag{2.3.8}$$

As mentioned earlier, $\mathcal{R}_0$ is the leading eigenvalue of the matrix $G = FV^{-1}$. This is fairly easy to calculate because $G$ is the $2 \times 2$ matrix:

$$G = \begin{bmatrix} \frac{\beta b \varepsilon}{\mu(\varepsilon + \mu)(\gamma + \mu)} & \frac{\beta b}{\mu(\gamma + \mu)} \\ 0 & 0 \end{bmatrix} \tag{2.3.9}$$

thus,

$$\mathcal{R}_0 = \frac{b\beta\varepsilon}{\mu(\varepsilon + \mu)(\gamma + \mu)} \tag{2.3.10}$$

We can see now that $\mathcal{R}_0$ is the product of the rate of production of new exposures and new infections.

It can be shown that there are two equilibrium points for this system of equations. The first is the disease free equilibrium, $S^* = b/\mu$, $I^* = 0$, $E^* = 0$ and $R^* = 0$, and the second is the endemic equilibrium where $S^* = \frac{b}{\mu R_0}$, $I^* = \frac{\mu}{\beta}(R_0 - 1)$, $E^* = \frac{\gamma + \mu}{\varepsilon} I^*$, $R^* = \frac{\gamma}{\mu} I^*$.

For the case of tuberculosis a model similar to the SEIR is needed. A person is neither sick nor infectious during the latency period of the disease. The rest of this paper is devoted to three different models of Tuberculosis, which is known to have several latent periods. The models to be studied consider the case of two latent periods. These models are related to the SEIR model, but are more accurately denoted $SE_1E_2IR$.

# CHAPTER 3: INTRINSIC TRANSMISSION DYNAMICS OF TB

## 3.1 Basic Reproduction Number of Tuberculosis

An interesting aspect to mathematical modelers about tuberculosis is the characteristic that only a fraction of those infected go on to get the disease. It is estimated that about 90% of infected individuals never develop TB [15]. For centuries, tuberculosis epidemics have been recorded. These epidemics rose and fell long before the disease became curable in the late 1940's. A proposed hypothesis formulated to explain the peaks and declines of the disease, attributes the trait of the *Mycobacterium tuberculosis* to survive in a latent state and then reactivate many years after the original infection [3]. This chapter will explore two models created by Blower *et al*. (1995). The purpose of their paper was to use the information about various latent periods to try to explain the pinnacles and depressions the disease has shown for many years, in other words to understand the historical epidemiology of TB.

As mentioned earlier, the basic reproduction number of a disease is a parameter that can be used to predict if a disease will spread. The development of a detailed expression for $\mathcal{R}_0$ allows for the evaluation of this transmission threshold. Recall that if $\mathcal{R}_0 < 1$ the disease will die out and if $\mathcal{R}_0 > 1$, an epidemic of the disease will occur. The expression for $\mathcal{R}_0$ for TB (which Blower *et al.* (1995) calculated from the simple model to be discussed in the section 3.2) is given in equation (3.1.1):

$$\mathcal{R}_0 = \mathcal{R}_0^{FAST} + \mathcal{R}_0^{SLOW} \qquad (3.1.1)$$

where

$$\mathcal{R}_0^{FAST} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{\mu+\mu_\tau}\right)p \qquad (3.1.2)$$

$$\mathcal{R}_0^{SLOW} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{\mu+\mu_\tau}\right)\left(\frac{(1-p)\nu}{\nu+\mu}\right) \qquad (3.1.3)$$

The expression for $\mathcal{R}_0$ for TB (which Blower *et al.* (1995) calculated from the detailed model to be discussed in the section 3.3) is given in equation (3.1.4):

$$\mathcal{R}_0 = \mathcal{R}_0^{FAST} + \mathcal{R}_0^{SLOW} + \mathcal{R}_0^{RELAPSE} \qquad (3.1.4)$$

where:

$$\mathcal{R}_0^{FAST} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{\mu+\mu_\tau+c}\right)pf \qquad (3.1.5)$$

$$\mathcal{R}_0^{SLOW} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{\mu+\mu_\tau+c}\right)\left(\frac{q(1-p)\nu}{\nu+\mu}\right) \qquad (3.1.6)$$

$$\mathcal{R}_0^{RELAPSE} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{(\mu+\mu_\tau+c)\left((\mu+\mu_\tau+c)-\left((2\omega c)/(2\omega+\mu)\right)\right)}\right)$$

$$\cdot\left(\left(p+\frac{(1-p)\nu}{\nu-\mu}\right)\left(\frac{\omega c}{2\omega+\mu}\right)\right) \qquad (3.1.7)$$

These equations show that a tuberculosis epidemic can be seen as a series of linked sub-epidemics [3]. The value of $\mathcal{R}_0$ in each of the sub-epidemics is determined by the product of three components: (1) the average number of infections that one infectious case causes per unit time; (2) the average time that an individual remains infectious (which is the same for FAST and

SLOW tuberculosis but is different for RELAPSE); and (3) the probability that a latent case will develop into an infectious case (which is different for FAST, SLOW or RELAPSE TB).

**Table 2 Parameter Notation and Values**

| Symbol | Meaning | Units | Min Value | Peak Value | Max Value | Notes |
|---|---|---|---|---|---|---|
| $(\beta b)/\mu$ | Average number of infections caused by one case | /year | 3 | 7 | 13 | |
| $1/\mu$ | Average life expectancy | years | 25 | | 75 | |
| $\beta$ | Transmission coefficient | /person/year | | | | Derived from estimate of $(\beta b)/\mu$ |
| b | Recruitment rate | people/year | | | | Derived from estimate of $(\beta b)/\mu$ |
| p | Proportion of new infections that develop TB within a year | | 0 | 0.05 | 0.30 | |
| $\nu$ | Progression rate to TB | /person/year | 0.00256 | | 0.00527 | This range of values corresponds to a range of 5 – 10% progression in 20 yrs. |
| f | Probability of developing FAST infectious TB | | 0.50 | 0.70 | 0.85 | |
| q | Probability of developing SLOW infectious TB | | | 0.50 | 0.85 | |
| $\mu_\tau$ | Mortality rate due to TB | /person/year | 0.058 | 0.139 | 0.461 | The peak value corresponds to a 50% death rate in 5 years |
| $2\omega$ | Rate of relapse to active TB | /person/year | 0 | 0.01 | 0.03 | |
| c | Natural cure rate | /person/year | 0.021 | 0.058 | 0.086 | The peak value corresponds to a 25% cure rate in 5 years |

Due to the uncertainty of many of the parameters when tuberculosis epidemics first began it is difficult to accurately calculate the value of $\mathcal{R}_0$. Blower *et al.* (1995) estimated $\mathcal{R}_0$ by using Latin Hypercube Sampling (LHS). The results from the uncertainty analysis of $\mathcal{R}_0$ can be seen in Figure 4.

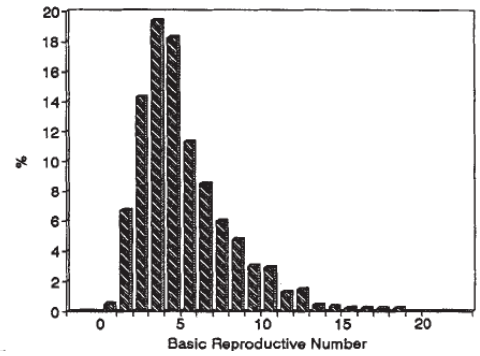



**Figure 4 Results from Latin Hypercube Sampling for $\mathcal{R}_0$**

**min. = 0.74, max. = 18.58, median = 4.47, mean = 5.16, std. dev. = 2.82 (From Blower *et al.* (1995)**

Results of the threshold analysis performed by Blower *et al.* (1995) can be used to answer some of the historical questions posed regarding the rise and fall of epidemics. Population growth, urbanization and industrialization have all been given as components that contributed to the increase of tuberculosis. Population growth clearly would have resulted in the population size increasing the threshold value causing the value of $\mathcal{R}_0$ to become greater than one, resulting in an epidemic. Industrialization (which caused an increase in poverty), malnutrition, pollution, and urbanization (a consequence of which would be the population living in much closer quarters) together would have resulted in the threshold population being exceeded and in turn $\mathcal{R}_0$ would have rapidly become greater than one, fostering major epidemics.

### 3.2 Simple Tuberculosis Transmission Model

The simple transmission model proposed by Blower *et al.* (1995) is built from three compartments: susceptible individuals (*S*), latently infected individuals (that is individuals who have been infected with *M. tuberculosis*, but do not have the clinical illness and therefore are noninfectious) (*L*) and active infectious tuberculosis cases (*I*). In this model, it is assumed that the infected individuals can develop active TB by either direct progression (the disease develops

immediately after infection) or endogenous reactivation (the disease develops years after the infection), because of these different ways of developing the disease, two types of TB must be modeled. These will be denoted as primary progressive tuberculosis (which will henceforth be referred to as FAST tuberculosis) and reactivation tuberculosis (which will be referred to as SLOW tuberculosis).

The susceptible population is modeled beginning with the constant influx into the category at a rate of *b*. The individuals leaving the susceptible class and entering the latent class are then removed. This is done by using the occurrence of infection rate, calculated as the product of the number of susceptibles present at time *t* (*S(t)*) and the per capita force of infection at time *t* ($\lambda(t)$); where $\lambda(t) = \beta I$. Here, $\lambda(t)$ is defined as the per-susceptible risk of becoming infected with the virus and is calculated as the product of the number of infected individuals at time *t* and β, the transmission coefficient, which indicates the likelihood that an infectious case will transmit the infection to a susceptible individual. Finally, the fraction of those who die from natural causes are also removed. Equation (3.2.1) shows this.

$$\frac{dS}{dt} = b - \lambda S - \mu S \qquad (3.2.1)$$

Those individuals who have become infected with *M. tuberculosis* are calculated to enter the infected class (at a probability of *p*) or the latent class (with a probability of $(1 - p)$). Those entering the latent class will either go on to develop tuberculosis at an average rate of $\nu$ or die of other causes, because the rate of progression of the disease is slow. Therefore, equation (3.2.2) specifies the instantaneous rate of change in the number of latent individuals.

$$\frac{dL}{dt} = (1-p)\lambda S - \nu L - \mu L \qquad (3.2.2)$$

Individuals with active infectious tuberculosis die, either due to natural causes at a rate of $\mu$, or because of the disease itself, at a rate of $\mu_\tau$. Therefore, the number of active TB cases, *I*, obeys the equation

$$\frac{dI}{dt} = \nu L + p\lambda S - (\mu + \mu_\tau)I \qquad (3.2.3)$$

The model of these equations using SIMULINK can be seen in figure 5. The results of the simulation using the following parameter values can be seen in figure 6; $b$ = 4,400, $\mu$ = 0.0222, $p$ = 0.05, $\nu$ = 0.00256, $\mu_I$ = 0.139 and $\beta$ = 0.00005.

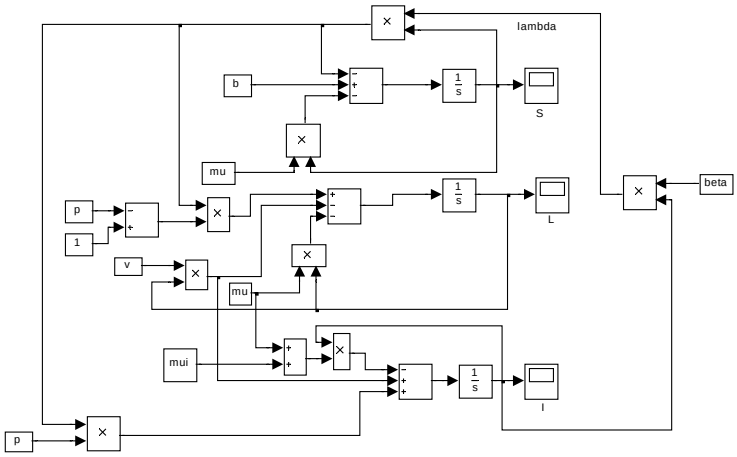



**Figure 5 SIMULINK Diagram of Simple Transmission Model**

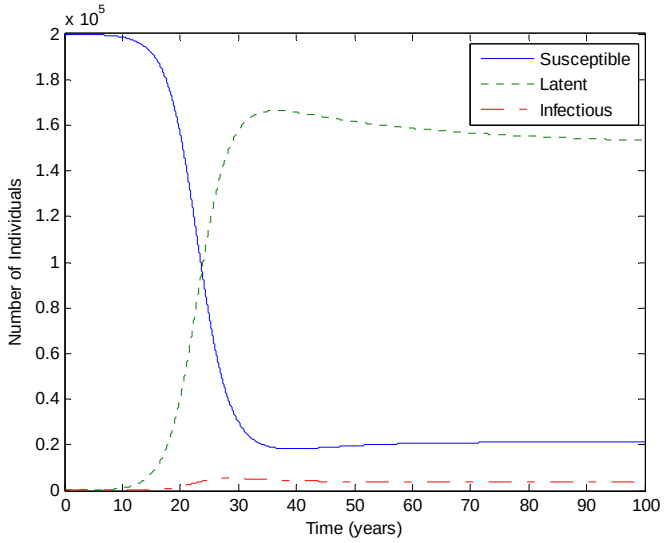



**Figure 6 Graph of Results from Simple Transmission Model**

**Susceptible, latent, infectious levels of Simple Transmission Model using one infectious introduced into a susceptible population of 200,000**

## 3.3 Detailed Tuberculosis Transmission Model

The detailed transmission model proposed by Blower *et al.* (1995) differs from the simple model in that the detailed model considers three additional factors that serve to reproduce some of the intricacies of the natural history of tuberculosis: (1) only a certain portion of cases are assumed to be infectious (a fraction $f$ of cases develop FAST tuberculosis due to primary progression, and a fraction $q$ develop SLOW tuberculosis because of endogenous reactivation); (2) a case may be cured without treatment at a rate of $c$, and hence move into the non-infectious removed category; (3) an individual in the state of recovered may either relapse (and with equal probability, develop either infectious ($I_i$) or non-infectious ($I_n$) tuberculosis) at a rate of $\omega$ (hence the rate of relapse is $2\omega$) or may die of other causes. The equations defining each of the five population states are as follows

$$\frac{dS}{dt} = b - \lambda S - \mu S \qquad (3.3.1)$$

$$\frac{dL}{dt} = (1-p)\lambda S - (\nu + \mu)L \qquad (3.3.2)$$

$$\frac{dI_i}{dt} = pf\lambda S + q\nu L + \omega R - (\mu + \mu_\tau + c)I_i \qquad (3.3.3)$$

$$\frac{dI_n}{dt} = p(1-f)\lambda S + (1-q)\nu L + \omega R - (\mu + \mu_\tau + c)I_n \qquad (3.3.4)$$

$$\frac{dR}{dt} = c(I_i + I_n) - (2\omega + \mu)R \qquad (3.3.5)$$

Again, using the computer package SIMULINK, these equations were solved. Figure 7 shows the diagram of this model. The simulation was run using parameter values as follows: $b$ = 4,400, $\mu$ = 0.0222, $p$ = 0.05, $\nu$ = 0.00256, $f$ = 0.70, $q$ = 0.85, $\omega$ = 0.005, $\mu_\tau$ = 0.139, $c$ = 0.058, $\beta$ = 0.00005. Initial conditions used were one infected introduced to a susceptible population of 200,000 individuals.

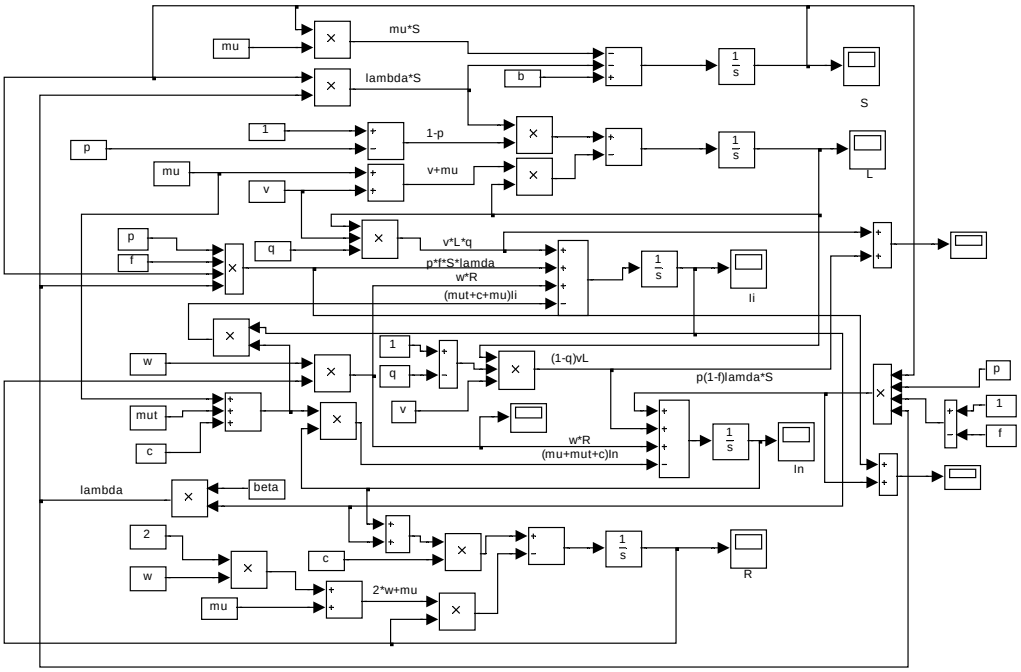



**Figure 7 SIMULINK Diagram of Detailed Transmission Model**

A graphic representation of the simulated results is given in Figure 8. From this graph it can be seen that the disease initially increases but then decreases without any change in the parameter values. This change is due to the intrinsic transmission dynamics of tuberculosis.

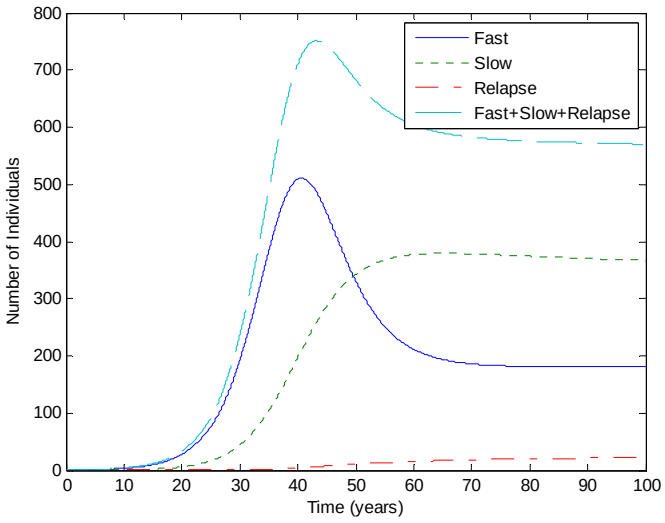



**Figure 8 Results of Detailed Transmission Model**

Figure 9 shows the asymptotic behavior of the solutions of this model. The leveling of the infected plots show at what point the disease maintains an endemic level in the population.

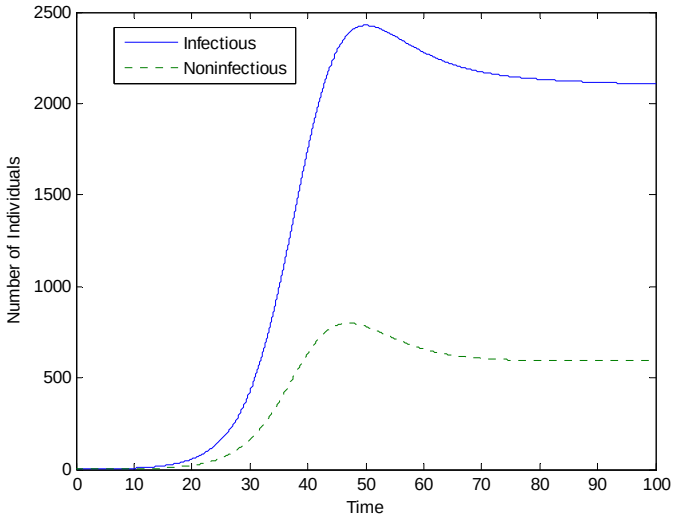



**Figure 9 Number of Infected Individuals vs. Time**

The asymptotic stability was proved analytically by Feng *et al*. (2001) and not only confirmed the simulations for the "slow/fast" model but also for models where individuals develop infectious TB at any possible rate.

# CHAPTER 4: STUDY OF $\mathcal{R}_0$ AND EQUILIBRIUM POINTS

## 4.1 Model Formulation

As we saw in the previous chapter, the intrinsic transmission dynamics are at least partly responsible for the decline of the disease in the absence of treatment. One of the key aspects of these dynamics is the basic reproduction number ($\mathcal{R}_0$). In this chapter we will study a model that explores the equilibrium points when $\mathcal{R}_0 \leq 1$ and when $\mathcal{R}_0 > 1$.

The model to be discussed was proposed by Jia *et al*. (2007). This model uses five compartments: the susceptible group ($S$), the short latent period group ($E_1$), those at high risk of reactivation to active TB, the long latent period group ($E_2$), those whose disease progresses slowly, the infectious group ($I$), and the recovered group ($R$), where $N = S + E_1 + E_2 + I + R$. Therefore, the model consists of five differential equations, but can be simplified to the first four due to the fact that these are independent of R:

$$\frac{dS}{dt} = b - \beta IS - \mu S \qquad (4.1.1)$$

$$\frac{dE_1}{dt} = p_1\beta IS - (k_1 + \mu)E_1 \qquad (4.1.2)$$

$$\frac{dE_2}{dt} = p_2\beta SI - (k_2 + \mu)E_2 \qquad (4.1.3)$$

$$\frac{dI}{dt} = (k_1E_1 + k_2E_2) - (r + \mu + \mu_I)I \qquad (4.1.4)$$

$$\frac{dR}{dt} = rI - \mu R \qquad (4.1.5)$$

where $b$ is the constant recruitment into the susceptible population; β is the transmission coefficient; $p_1$, $p_2$, ($p_1 + p_2 = 1$) are the rates from susceptible to the short latent period ($E_1$) and the long latent period ($E_2$) groups, respectively; $k_1$, $k_2$, ($k_1 >> k_2$) are the rates from $E_1$ and $E_2$ to infectious, respectively; $r$ is the natural cure rate; μ is the natural death rate; $\mu_I$ is the disease-induced death rate. This system is studied in the domain

$$\Omega = \left\{ \begin{array}{l} \left(S, E_1, E_2, I, R\right) \in R_+^5 \\ 0 \le S + E_1 + E_2 + I + R \le \dfrac{b}{\mu} \end{array} \right\}$$

Jia *et al*. (2007) formulated the following threshold parameter:

$$\mathcal{R}_0 = \frac{b\beta}{\mu\left(r + \mu + \mu_I\right)} \sum_{i=1}^{2} \frac{p_i k_i}{k_i + \mu}$$

It is clear that the basic reproduction ratio is the anticipated number of secondary active cases caused by one case during that individual's infectious period. Here, however, the infectious period is calculated as the mean of $E_1$ and $E_2$.

## 4.2 Discussion of Equilibrium Points

Similar to the equilibrium discussion in chapter two, it can be shown that for this model there is a disease-free equilibrium at

$$S^* = b/\mu \qquad E_1^* = 0 \qquad E_2^* = 0 \qquad I^* = 0$$

Jia *et al*. (2007) give the following expressions which can be calculated as the endemic equilibrium for their model:

$$S^* = \frac{b}{\mu R_0}$$

$$I^* = \frac{\mu}{\beta}(R_0 - 1)$$

$$E_i^* = \frac{p_i b}{k_i + \mu}\left(1 - \frac{1}{R_0}\right),\ i = 1, 2.$$

The following theorem is the main result of Jia *et al*. (2007, p. 424)

**Theorem 1**. *If $\mathcal{R}_0 \le 1$, the disease-free equilibrium $P_0$ is the only equilibrium of the system and it is globally asymptotically stable.*

**Proof**. To prove Theorem 1, the Lyapunov function is defined for the disease free equilibrium $P_0$, as follows:

$$V = k_1(k_2 + \mu)E_1 + k_2(k_1 + \mu)E_2 + (k_1 + \mu)(k_2 + \mu)I$$

If $\mathcal{R}_0 \le 1$, a simple calculation shows that

$$V' = k_1(k_2 + \mu)E_1' + k_2(k_1 + \mu)E_2' + (k_1 + \mu)(k_2 + \mu)I'$$

$$= (k_1 + \mu)(k_2 + \mu)(r + \mu + \mu_I)(R_0 - 1)I$$

$$\le 0.$$

Moreover, $V' = 0$ holds if and only if $I = 0$. Therefore the maximum compact invariant set in $\Omega$ is $\{P_0\}$. LaSalle's Invariance Principle implies that $P_0$ is global asymptotically stable in $\Omega$ [16].

Jia *et al*. (2007) go on to make a supposition that if $\mathcal{R}_0 > 1$, the unique endemic equilibrium $P^*$ is globally asymptotically stable in $\Omega$.

This supposition is supported with the results of several simulations performed using SIMULINK. The model used can be viewed in figure 10.

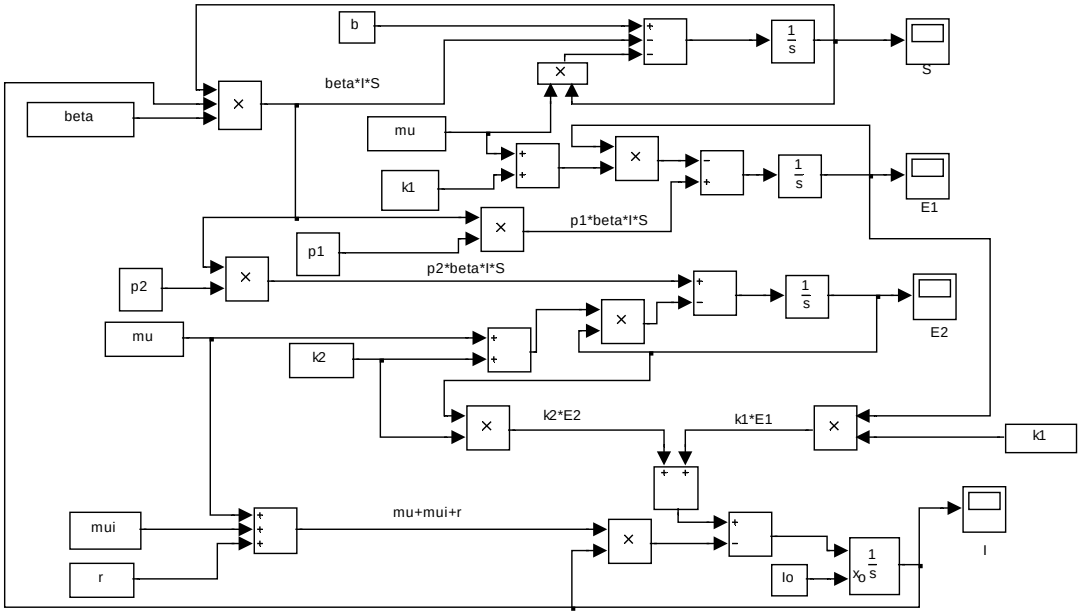



**Figure 10 SIMULINK Model of Jia *et al*. (2007) System**

The parameter values for these simulations are similar to those used by Blower *et al.* (1995) and are as follows: $b = 500$, $k_1 = 0.475$ (95% of the latent move on to infectious within two years), $k_2 = 0.0025$ (5% do not move on until after twenty years), $\mu = 0.0222$, $p_1 = 0.30$, $p_2 = 0.70$, $\mu_I = 0.139$, $\beta = 0.00005$, $r = 0.058$. Using these parameter values the researcher calculated the value for $\mathcal{R}_0 = 1.836$ and the infectious endemic equilibrium point $I^* = 371$. The results from this model can be seen in the following graph (Figure 11) which confirms the calculated value

for $I^*$ and shows that the asymptotical behavior of this equilibrium point is independent of the initial conditions for $I_0$. This visually confirms the conclusion proposed by Jia *et al*. (2007) that the endemic equilibrium is globally asymptotically stable in $\Omega$ if $\mathcal{R}_0 > 1$.

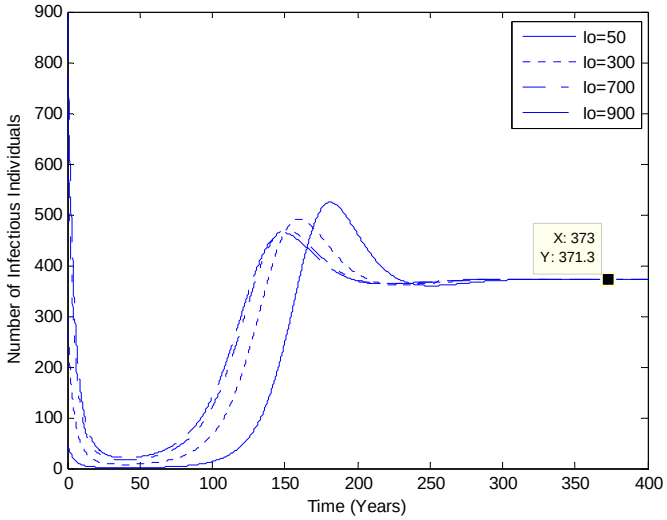



**Figure 11 Graph of Infectious vs. Time (Changing *Io* Values)**

The following graphs, which feature changing parameter values, indicate a trend to an equilibrium point. Each of these simulations was done introducing an initial 50 infected individuals into a population of susceptible individuals. Figure 12 changes the progressive rate from $E_1$ to $E_2$. It can be seen that this graph confirms the equilibrium results of Figure 11 regardless of the rate of progression of the disease. Figure 13, however, indicates that a change of the rate from $S$ to $E_1$ and $E_2$ results in a different progression of the disease as well as different equilibrium values.

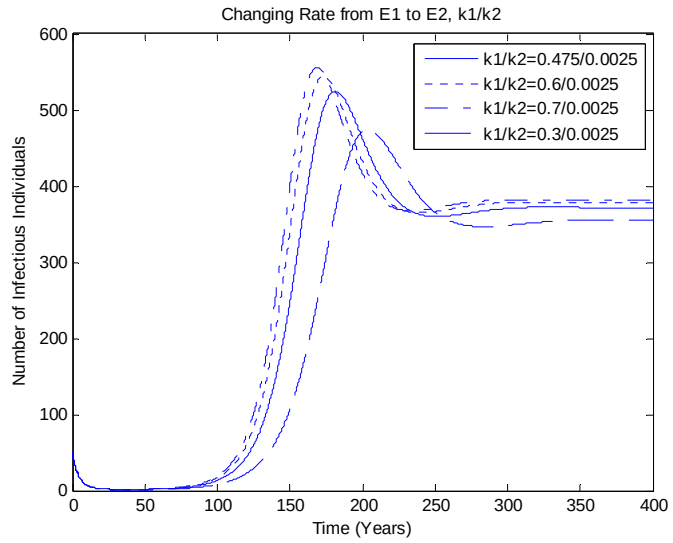



**Figure 12 Graph of Infectious vs. Time (Changing *k* Values)**

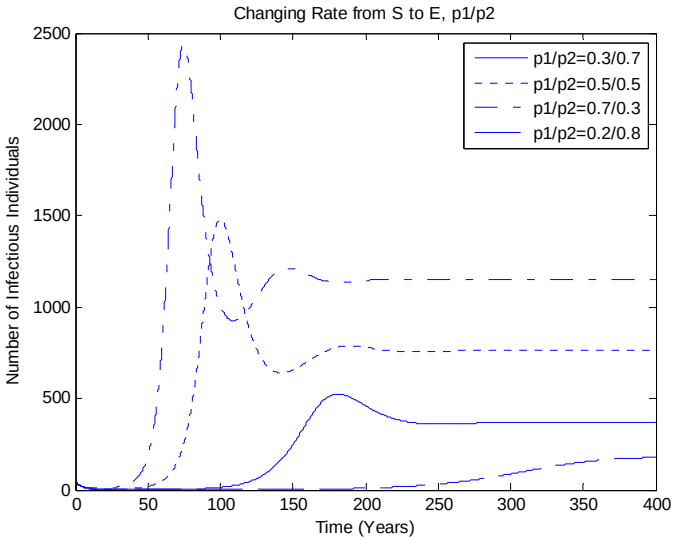



**Figure 13 Graph of Infectious vs. Time (Changing *p* Values)**

# CHAPTER 5: CONCLUSION

Many communicable diseases have been modeled using differential equations. The purpose of this thesis was to examine in detail several mathematical models for tuberculosis and then to solve them using SIMULINK. The simulations done using SIMULINK provided data that generally supported the conclusions attained by Blower *et al*. (1995) and Jia *et al*. (2007).

Before looking at these TB models, the classical SIR model developed by Kermack and McKendrick was applied to an outbreak of bubonic plague in Eyam, England. The results of the SIMULINK simulation of this model showed results very similar to the data from the actual outbreak. To understand and trust this model is crucial, due to the fact that many more complex models were developed from the SIR model.

The first tuberculosis model examined using SIMULINK was proposed by Blower *et al*. (1995). In their article they looked at two models of TB. The first one, which they termed their "simple transmission model," was created to show the dynamics of only the susceptible, the latent, and the active or infectious groups of individuals. The graph of these results give us an indication of the existence of an endemic equilibrium with the case of parameter values yielding a basic reproduction ratio greater than one ($\mathcal{R}_0 > 1$).

Next, the "detailed transmission model" by Blower *et al*. (1995) was solved using SIMULINK. The graph of these results illustrates the individual concentrations of the three types of TB modeled (fast, slow and relapse). These results also show that the historical rise and subsequent decline of TB is due, at least partly, to the intrinsic dynamics of the disease itself.

Finally, a system of equations by Jia *et al*. (2007) was modeled with SIMULINK. The main purpose of this model was to examine the equilibrium points of a TB model with various latent periods. Jia *et al*. (2007) provided analytical results proving that if $\mathcal{R}_0 \leq 1$, the disease-free equilibrium is globally asymptotically stable in the domain. If $\mathcal{R}_0 > 1$, Jia *et al*. (2007) made the conjecture that the endemic equilibrium is also globally asymptotically stable in the domain. Solving this model using SIMULINK provided numerical simulations that show all solutions go toward the equilibrium as time goes to infinity, which generally supports the conjecture made.

As proposed, SIMULINK solved several disease models composed of differential equations. In addition, SIMULINK provided a tool with easy access to changing parameter values and analyzing additional variations of the disease progression.

# APPENDIX: MATLAB CODE USED TO PRODUCE GRAPHS

```
clc; close; clear all;

% tuberculosis parameters for TBBlower
b = 4400;  %recruitment to susceptible population
mu = 0.0222;  %per capita average non-TB mortality rate (natural death rate)
p = 0.05;  %5% of infected individuals develop TB w/in 1 year
v = 0.00256;  %5% of infected individuals develop TB w/in 20 years (rate of
developing TB slowly)
%f = 0.70;  %develop TB because of primary progression
%q = 0.85;  %develop TB because of endogenous reactivation
%w = 0.005;  %recovered state & either relapse into infectious or non-
infectious TB (per capita)
mui = 0.139;  %50% of untreated cases died in 5 years
%c = 0.058;  %cured w/o treatment
beta = 0.00005;  %transmission coefficient (likelihood I transmits to S)


sim('blowersimp')


x = S_t(:,1);
y = S_t(:,2);
z = L_t(:,2);
q = I_t(:,2);
plot(x,y,'-',x,z,':',x,q,'-.')
legend ('Susceptible','Latent','Infectious')
xlabel ('Time (years)')
ylabel ('Number of Individuals')
```

```
clc; close; clear all;
% tuberculosis parameters for TBBlower
b = 4400;  %recruitment to susceptible population
mu = 0.0222;  %per capita average non-TB mortality rate (natural death rate)
p = 0.05;  %5% of infected individuals develop TB w/in 1 year
v = 0.00256;  %5% of infected individuals develop TB w/in 20 years (rate of
developing TB slowly)
f = 0.70;  %develop TB because of primary progression
q = 0.85;  %develop TB because of endogenous reactivation
w = 0.005;  %recovered state & either relapse into infectious or non-
infectious TB (per capita)
mut = 0.139;  %50% of untreated cases died in 5 years
c = 0.058;  %cured w/o treatment
beta = 0.00005;  %transmission coefficient (likelihood I transmits to S)


sim('TBBlower');


x = Ti_t(:,1);


y = F_t(:,2);
z = Sl_t(:,2);
q = A_t(:,2);
r = (y+z+q);
plot(x,y,'-',x,z,':',x,q,'-.',x,r,'--')
legend ('Fast','Slow','Relapse','Fast+Slow+Relapse')
xlabel ('Time (years)')
ylabel ('Number of Individuals')
```

```
clc; close; clear all;
% tuberculosis parameters for TBBlower
b = 4400;  %recruitment to susceptible population
mu = 0.0222;  %per capita average non-TB mortality rate (natural death rate)
p = 0.05;  %5% of infected individuals develop TB w/in 1 year
v = 0.00256;  %5% of infected individuals develop TB w/in 20 years (rate of
developing TB slowly)
f = 0.70;  %develop TB because of primary progression
q = 0.85;  %develop TB because of endogenous reactivation
w = 0.005;  %recovered state & either relapse into infectious or non-
infectious TB (per capita)
mut = 0.139;  %50% of untreated cases died in 5 years
c = 0.058;  %cured w/o treatment
beta = 0.00005;  %transmission coefficient (likelihood I transmits to S)


sim('TBBlower');


x = Ti_t(:,1);
y = Ti_t(:,2);
z = L_t(:,2);
q = S_t(:,2);
r = R_t(:,2);
w = Tn_t(:,2);
plot(x,y,'-',x,w,':')
legend('Infectious','Noninfectious')
xlabel('Time')
ylabel('Number of Individuals')
```

```
clc; close; clear all;
% tuberculosis parameters
b = 500;  %constant return to S
beta = 0.00005;  %transmission coefficient
mu = 0.0222;  %natural death rate
mui = 0.139;  %disease induced death rate
k1 = 0.475;  %rate from E1 to I
k2 = 0.0025;  %rate from E2 to I
r = 0.058;  %natural cure rate
p1 = 0.3;  %rate from S to E1
p2 = 0.7;  %rate from S to E2
Io = 50; %infected initial condition

sim('tuberculosis');

x = S_t(:,1);
y = I_t(:,2);
plot(x,y,'-')
hold on

b = 500;  %constant return to S
beta = 0.00005;  %transmission coefficient
mu = 0.0222;  %natural death rate
mui = 0.139;  %disease induced death rate
k1 = 0.475;  %rate from E1 to I
k2 = 0.0025;  %rate from E2 to I
r = 0.058;  %natural cure rate
p1 = 0.30;  %rate from S to E1
p2 = 0.70;  %rate from S to E2
Io = 300; %infected initial condition

sim('tuberculosis');

x = S_t(:,1);
w = I_t(:,2);
```

```
plot(x,w,':')
% legend('Io=50', 'Io=300')
hold on

b = 500;  %constant return to S
beta = 0.00005;  %transmission coefficient
mu = 0.0222;  %natural death rate
mui = 0.139;  %disease induced death rate
k1 = 0.475;  %rate from E1 to I
k2 = 0.0025;  %rate from E2 to I
r = 0.058;  %natural cure rate
p1 = 0.30;  %rate from S to E1
p2 = 0.70;  %rate from S to E2
Io = 700; %infected initial condition

sim('tuberculosis');

x = S_t(:,1);
f = I_t(:,2);
plot(x,f,'-.')
hold on

b = 500;  %constant return to S
beta = 0.00005;  %transmission coefficient
mu = 0.0222;  %natural death rate
mui = 0.139;  %disease induced death rate
k1 = 0.475;  %rate from E1 to I
k2 = 0.0025;  %rate from E2 to I
r = 0.058;  %natural cure rate
p1 = 0.30;  %rate from S to E1
p2 = 0.70;  %rate from S to E2
Io = 900; %infected initial condition

sim('tuberculosis');

x = S_t(:,1);
```

```
k = I_t(:,2);
plot(x,k,'--')
xlabel ('Time (Years)')
ylabel ('Number of Infectious Individuals')
legend('Io=50', 'Io=300', 'Io=700', 'Io=900')
hold off
```

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