Mathematical modeling of the population dynamics of tuberculosis

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Abstract

Tuberculosis (TB) is currently one of the major public health challenges in South Africa, and in many countries. *Mycobacterium tuberculosis* is among the leading causes of morbidity and mortality. It is known that tuberculosis is a curable infectious disease. In the case of incomplete treatment, however, the remains of *Mycobacterium tuberculosis* in the human system often results in the bacterium developing resistance to antibiotics. This leads to relapse and treatment against the resistant bacterium is extremely expensive and difficult. The aim of this work is to present and analyse mathematical models of the population dynamics of tuberculosis for the purpose of studying the effects of efficient treatment versus incomplete treatment. We analyse the spread, asymptotic behavior and possible eradication of the disease, versus persistence of tuberculosis. In particular, we consider inflow of infectives into the population, and we study the effects of screening. A sub-model will be studied to analyse the transmission dynamics of TB in an isolated population. The full model will take care of the inflow of susceptibles as well as inflow of TB infectives into the population. This dissertation enriches the existing literature with contributions in the form of optimal control and stochastic perturbation. We also show how stochastic perturbation can improve the stability of an equilibrium point. Our methods include Lyapunov functions, optimal control and stochastic differential equations. In the stability analysis of the DFE we show how backward bifurcation appears. Various phenomena are illustrated by way of simulations.

Declaration

I declare that *Mathematical modeling of the population dynamics of tuberculosis* is my own work, it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Ayodeji. O. Adebiyi March 15, 2016

Signed: .....

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Ayodeji .O. Adebiyi

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Chapter 1

Introduction

1.1 The impact of Tuberculosis

Tuberculosis (TB) is a bacterial infectious disease of humans and animals caused by the pathogen *Mycobacterium tuberculosis (MTB)*. The disease is characterized by the formation of tubercles on the lungs and other tissue of the body, often developing long after the initial infection. It is an airborne disease and one of the most common infectious diseases. TB is one of the oldest recorded human and animal diseases. It has been in animals before the existence of the human species. Evidence that supports human cases of TB as well as its role in human mortality goes back for centuries [18]. It is not noticeable when individuals are infected and that makes the transmission of the disease easier. TB is acquired through interactions with infectious individuals, interactions that include primarily the sharing of a common closed environment. Once infected, a person stays infected for many years, possibly latently-infected for life. The clinical observation of this disease reveals that the patient suffers from a latent fever that begins towards evening and vanishes again at the break of day. It is accompanied by violent coughing, which expels thin purulent sputum. The patient speaks with a hoarse voice, breathes with difficulty and has flushed cheeks. The entire body would turn ashen. The eyes have a weary expression, the patient is gaunt in appearance but often displays astonishingly

good physical or mental activity. In many cases, wheezes are to be heard in the chest, and when the disease spreads, sweating is seen on the upper parts of the chest. The patient loses appetite or suffers hunger pangs. They are often also very thirsty. The ends of the fingers swell and the fingernails curve abnormally. This infectious disease is so devastating that it has become a motivating force in the development of the fields of bacteriology and modern epidemiology [64]. Tuberculosis remains an expanding global crisis, killing about 2 million individuals and causing 8 million new cases of disease every year [11]. As a result of *Mycobacterium* replication together with tissue-damaging, the immune response converts the lung into a highly efficient aerosol-generating chamber that provides the source for continued transmission. It is estimated that one-third of the global population is currently infected with M. tuberculosis. TB is now the leading cause of death among HIV-positive persons worldwide and accounts for 40 percent of AIDS deaths in Africa and Asia (WHO, 1999). In the United States, active TB is included as an AIDS-defining opportunistic infection for HIV-infected persons (CDC, 1998). Adding further urgency to controlling TB, multidrug-resistant TB (MDRTB) has emerged as a serious problem in many parts of the world, including Russia, Latvia, Estonia, Argentina, the Dominican Republic, and the Ivory Coast (WHO, 1999). Up to 50 million people worldwide may be infected with MDRTB (WHO, 1999). In low-prevalence countries, drug resistance is generally more common in foreign-born populations, most likely reflecting inadequate treatment programs and inadequate drug availability in high-prevalence countries (Broekmans, 2000). Most of the individuals infected by TB stay in a latent stage, and only a small proportion of individuals develop active TB. Mathematical models have been used to study communicable diseases such as measles, influenza, chicken pox and rubeola [18]. TB is paradoxically different, despite its fundamental role in modern epidemiology and the development of bacteriology.

1.2 Immunobiology of Tuberculosis

This section presents a brief overview on the fundamental idea of the word immunology. This entails the study of the immune system, which is the body's defense system against disease. Viruses, bacteria, fungi and parasites are causative agents called pathogens. Immune response can be divided into two types which are the adaptive immune response and the innate immune response. An adaptive immune response is usually pathogen specific. It is developed as an adaptation to infection with that pathogen. An innate immune response is instant and not pathogen specific.

For immune response to be effective, the following tasks must be done by the immune system.

1. Immunological recognition: The immune system must be able to discover and recognize the pathogens.

2. Immune effector functions: Once infection by a pathogen has been detected, the Immune system must be able to contain or to clear the infection.

3. Immune regulation: The immune system can be harmful to the host's body if it is not kept in check. Therefore there must also be mechanisms for self-regulation.

4. Immunological memory: Adaptive immunity has a unique feature of generating immunological memory. Subsequent exposure to an already encountered pathogen will give way for a stronger and faster immune response.

For *Mycobacterium tuberculosis*, the causal agent of the disease is unclear whether an appropriate immune response at the time of inhalation can be effected. The predominant outcome appears to be the control of organism replication and spread through granuloma formation [27, 40]. This condition is referred to as latent tuberculosis infection and *Mycobacterium tuberculosis* has the ability to survive within these conditions and regenerate for extended periods of time. During the immunological effectiveness, the disease is absolutely prevented [55, 59]. Risk of reactivation begins once latent infection with *Mycobacterium tuberculosis* has been established [60].

1.3 Statement of the problem

Despite countless campaigns, and even with management and control strategies currently in place to achieve a TB free world [31], tuberculosis continues to cause a serious health problem world-wide. TB continues to claim lives in South Africa despite the interventions of government and private bodies. Hence there is an urgent need to assess the control strategies. A number of studies have been done on TB especially, over the past two decades. However, there is a need for more studies to be done to bring the effect of TB to the minimal. To the best of the author's knowledge, there has been no previous study tailored towards the effect of inflow of TB infectives into a population, at least not from the mathematical view point. Research has shown that migrant populations have had a critical role in the spread of infectious diseases since ancient times [8]. A good example of these is the recent outbreak of Ebola in the west Africa. Between 1989 and 1995, the population of Israel, a low tuberculosis (TB) prevalence country, rose from 4.5 to 5.6 million, mainly due to mass immigration from high and moderate TB prevalence countries [20]. Therefore, a mathematical model has been developed to establish the effect of direct inflow of TB infectives on the dynamics and treatment of TB. This study also intends to assess the impact of the rolling out of treatments as a control strategy.

1.4 Research objectives

1.4.1 General objectives

One of the objectives of this study is to show the effect of inflow of infectives on the dynamics and treatment of TB using deterministic and stochastic mathematical models. It will assist in understanding the impact of the immigrants on the transmission dynamics of tuberculosis in South Africa.

1.4.2 Specific objectives

The specific objectives of this study are:

- To formulate and analyse a mathematical model on transmission dynamics and treatment of TB disease in terms of the reproduction number, equilibrium points and stability.

- To model and analyse the effect of inflow of infectives on the dynamics and treatment of TB.

- Determine the behavior of each embedded parameter of the model.

- Comprehensive numerical simulations of the proposed model for understanding the disease dynamics.

- To present an optimal control problem in which the coefficient of the infection and latent production term in the control results from treatment.The representation of the optimal control is being utilized to solve numerically the optimality system.

- We also consider the corresponding stochastic model obtained from the deterministic model by introducing white noise. For this stochastic version, the global stability of the solution is shown. Comprehensive numerical simulations of the proposed model are carried out in order to understand the TB dynamics.

1.5 Significance of the study

The significances of the study will include the following:
(1) Our designed model will help health authorities to understand the effect of inflow of infectives of TB and set strategies on how to reduce the impact of immigration on TB transmission.
(2) The study can be used as a basis to create awareness and inform people of the effect of inflow of infectives of TB.

(3) The evaluation of the outcomes and impact will provide useful information that will help to minimize or eradicate the disease.
(4) This study can also act as a base for further research on the effect of inflow of infectives of TB and other related diseases.
(5) This dissertation generates information of the kind which is required by policy makers on health and / or immigration.

1.6 Dissertation structure

Chapter 1 describes the biological background of TB, and the role of mathematical models in epidemiology. The aims and objectives of the dissertation are laid out and the introductory chapter is concluded with a description of the structure of the dissertation.

Chapter 2 comprises a literature review on mathematical modeling of TB and incomplete treatment. The first part of the chapter is an overview of the mathematical models of TB. The overview includes the assumptions and results. The second part gives a review on inflow of infectives.

Chapter 3 provides some mathematical tools that are used throughout the rest of this dissertation. We present some definitions and notation on dynamical systems, stability analysis, and theories that are required to analyze such systems. Theorems and lemmas from optimal control theory and stochastic differential equations used in epidemiology modeling are presented.

Chapter 4 presents an analysis of a basic model of a TB epidemic with treatment. We calculate the basic reproduction number R_0. Also we develop analytical methods, and we study two steady states of the system: with and without inflow of infectives. These are the disease free equilibrium which biologically means the disease dies out, and on the other hand the endemic equilibrium which means persistence of the disease. We carry

out the global stability analysis of this model. Also we look into the bifurcation analysis, sensitivity analysis of R_0, and simulations.

Chapter 5 presents an optimal control problem relating to the model presented in Chapter 4, in which the level of treatment is the control variable. We solve the control problem analytically and run some numerical simulations to illustrate the behavior of the solution.

Chapter 6 develops a stochastic version of the TB model by adding random fluctuations onto the deterministic model. We establish the stochastic stability. Finally, qualitative results are illustrated by means of numerical simulations to verify stability.

We conclude, summarize and make recommendations on the main results in Chapter 7.

Chapter 2

Literature on modeling of tuberculosis

The increasing rate of tuberculosis (TB) cases in many countries of Sub-Saharan Africa over the past decade is largely attributed to the human immunodeficiency virus (HIV) and other emerging infections. Meanwhile, Mathematical models of disease transmission within human populations have been acknowledged in helping policy makers and epidemiologists interpret epidemiological trends and understand the dynamics of disease spread with efficiency of disease prevention and control [4].

Two decades have passed now with different people coming up with many mathematical models for TB. Susceptible-Infectious-Recovered (SIR) models and variants like Susceptible-Exposed-Infectious-Recovery (SEIR) models were introduced in the $1920s$ and helped to establish the foundations of much of the mathematical epidemiology.

In order to efficiently control and prevent infectious diseases like tuberculosis, one needs to be adequately informed about the mechanisms of the spread and the transmission dynamics of the disease. This will surely help our predictions as well as our strategies to eliminate the diseases. The study of epidemic dynamics is an important theoretic approach to investigate the transmission dynamics of infectious diseases because they describe change over time. Mathematical model formulation are literally based on

population dynamics, symptoms of infection, and the link with social and physiologic factors. By means of different analysis and numeric simulations, mathematical models can be used as a tool to understand the spread of infectious disease and how to manage or control it. Mathematical models developed for tuberculosis transmission are numerous.

Connell McCluskey (2004) [43] in his paper considered two models for tuberculosis, including treatment of latent and infective individuals. The first model in [43] assumes constant recruitment with a fixed fraction entering each class, with the consequence that TB never dies out and the stability analysis was done. Their second model concentrated on a general recruitment function whereby all recruitment is into the susceptible class. They concluded that the first model incorporates immigration of infectives at a constant rate, which makes it relevant and indicates that even with treatment in immigration of infectives, TB still remains endemic. Moreover, they said the differential equation system for the second model with general recruitment has a singularity at the origin when the total population size is zero. That concludes that in the absence of infective immigrants, then the second model of their paper predicts threshold conditions.

Carlos Castilo-Chavez and Zhilan Feng in (1997) [18] formulated a two group model for one-strain and two-strain TB in order to determine possible mechanisms that may be useful for the survival and spread of naturally resistant strains of TB as well as antibiotics-generated resistant strains of TB. They claimed that the analysis of their model will reveal that non-antibiotic co-existence is possible but rare for naturally resistant strains while co-existence is almost the rule for strains that result from the lack of compliance with antibiotic treatment by TB infected individuals. One of the possibilities is that such a person may develop active TB as a consequence of exogenous reinfection.

Zhilan Feng *et al* (2001) [29] modeled the qualitative behavior of a system of ordinary differential equations and a system of differential-integral equations for the dynamics of disease transmission for tuberculosis TB. They showed that the dynamics of the two models are directed by a reproduction number. They considered the scenario of $R_0 > 1$, then the disease-free equilibrium is unstable and there exists a unique positive (endemic) equilibrium. Moreover, the positive equilibrium is stable. Results showed that the qualitative

behaviors predicted by the model with arbitrarily distributed latent stage are similar to those given by the TB model with an exponentially distributed period of latency. They solidify the conclusions made above in [18] and also discusses the possibility of a person infected with TB may develop active TB as a result of endogenous infection.

Zhong-Wei Jia and other authors present two new theoretical frameworks in [32], investigating the impact of immigration on the transmission dynamics of tuberculosis. Analysis on the existence and stability of equilibra were presented with numerical simulations illustrating the behavior of their proposed model. They went further to apply the model in Canadian reported data on tuberculosis and a good match was observed between the model prediction and the reported data. Moreover, they made analysis on the extended model which involves the recruitment of the latent and infectious in immigrants to the main model. They found that the usual threshold condition does not apply and a unique equilibrium exists for all parameters values. They indicated that the disease does not disappear and becomes endemic in the host area, and also suggests that immigrants have a considerable influence on the overall transmission dynamics behavior of tuberculosis.

Yicang Zhou [66] presents a deterministic epidemiological model of TB transmission in two different demographical populations, in order to investigate the effects of this demographic distinction on the short-term incidence and long-term transmission dynamics, with special emphasis on the impact of immigration latent TB cases on the overall TB incidence rate in the whole population. They discussed the qualitative analysis using Canadian statistical data to estimate their model parameters in order to make short term predictions.

In the paper [9], a deterministic model is used to explore the potential impact of the combined effects of TB case detection in the presence of treatment. They analyzed the features of its equilibria and they made a note that the disease-free equilibrium may not be globally asymptotically stable when the reproduction number is less than one. The disease threshold number made it easier for them to assess the impact of active TB case with and without treatment. Also, they used the centre manifold theory to exhibit the phenomenon of backward bifurcation and deduced that when the reproduction number is

less than one, then there is possibility of backward bifurcation occurring decreases with increase of TB case detection. Their graphical representations suggest that increase in case finding accompanied by treatment of detected TB cases, result in a marked decrease of TB cases (both latent and active TB).

Cagri Ozacaglar and other authors in [53] observed and predicted epidemiological models which reviews earlier study on modeling different aspects of tuberculosis dynamics. They observed that there is an increase in the tuberculosis in 1990s and the emergence of drug- resistant in the first decade of the 21st century. They base their models on various mathematical systems such as systems of ordinary differential equations, simulation models Markov Chain and Monte Carlo method using a statistical analysis of TB patient data sets.

Carlos Castilo-Chavez and Zhilan Feng in [19] focus on the study of an age-structure model for the disease transmission dynamics of tuberculosis in populations that are subjected to a vaccination program. They first consider that the infection-free steady state is globally stable if the basic reproduction number R_0 is below one, and that an endemic steady state exists when the reproductive in the presence of vaccine is above one. They apply the theoretical results to vaccination policies to determine the optimal age or ages at which an individual should be vaccinated. It is shown that the optimal strategies can be either one- or two-age strategies. Their contribution consists of looking at a model where individuals are allowed to 'return' to previously visited classes, studying some global stability properties of this age-structure model, proving the existence of an endemic steady state when the commonly used method does not apply, and showing how to compute the optimal vaccination strategies in such situations.

Nishiura et al. in [50] predicted the future trend of drug-resistant TB in Thailand and also assessed the impact of the control strategies. They assumed that the present status of TB and the emergence of drug-resistant TB in Thailand are the consequence of past epidemics. The control strategies in the model were defined by specifying the value of the effective treatment rate (baseline value = 0.74) and the relative treatment efficacy (baseline value=0.84). It was predicted that the total number of new TB cases would

continue to decrease at the current level of intervention. Although a dramatic decline in the incidence rate of drug-sensitive cases is expected, drug-resistant cases are predicted to increase gradually, so that more than half of the TB strains would not be drug sensitive after 2020.

Mugisha et al., in [44] formulated mathematical models for the dynamics of tuberculosis in a population which require to minimize and therefore eradicating tuberculosis. Both numerical and qualitative analysis were done and the effect of variation in the area size and recruitment rates was investigated. Analysis showed that there exists disease free-equilibrium point provided the characteristic area is greater than the probability of survival from latent stage to infectious stage and the number of latent infections produced by a typical infectious individual during his/her mean infectious period. The study recommends that the characteristic area per individual should be at least 0.25 square kilometers in order to minimize tuberculosis incidence. This work suggested that characteristic area can as well be looked at as an environmental stress that can lead to tuberculosis. The authors' model acted as a basis for the tuberculosis model of this study. However, this study intends to establish fast progression of the disease that was not looked at by the authors.

Murphy *et al* in [45] explicitly focus their TB model on the effects of heterogeneity in demographically distinct populations. In a deterministic model, the overall population is split into six sub-populations. They obviously interpret their model in terms of underlying genetic susceptibility, but the results are equally applicable to any environmental or behavior condition that creates variable susceptibility to TB. Their results indicate that in a population with a high level of genetic susceptibility, TB prevalence is only slightly affected by changes in transmission. Conversely, in a population with a small genetically susceptible sub-population, transmission rates are more important. They determine R_0 for an heterogeneous population using numerical simulations. They made several biological assumptions for simplicity in their model that differ from other model configurations, (1) Latently infected individuals cannot be reinfected by active TB individuals; (2) there exists an annual reactivation rate for latently infected individuals; and (3) the contact

rates are non-linear.

The above authors did not stop there, they expanded the same model in [45] to form a new model in [46] considering how the presence of a genetically susceptible sub-population alters the effects of TB treatment at both latent and active stages. It is assumed that treatment doesnt confer immunity, but instead it moves individuals from actively infected to latently infected. Treatment of latently infected individuals reduces their reactivation rate. Results indicate that exclusive treatment of latently infected individuals alone is not as effective as treatment of actively infected individuals alone. Treatment strategies of latently infected individuals show that low chemotherapy levels have almost no effect on reducing prevalence regardless of the genetic susceptibility level. Neither model considers MDR-TB, non-compliance with treatment or comorbidity.

Aparicio in [5] formulated a deterministic cluster model to specifically explore the impact of intense and long exposure to individuals with active TB on population level transmission dynamics. This was in contrast to Porco and Blower in [54], this model does not assume an average number of individuals infected per year from one infectious case. Specifically, this model gives a significant difference between epidemiologically active clusters and casual infections. Results generated from the model indicates that casual infections may be more important than cluster-generated secondary infections at a population level, they supported this result with molecular epidemiological data. The authors recommend the consideration of a lower bound on cluster size required for TB persistence as a new way to consider critical epidemic thresholds. Schinazi in [56] used a spatial stochastic model to also explore the role of social clusters in disease transmission. A similar result is shown in [5] which indicates that stress parameters influence the transmission of TB: the size of each individuals social cluster, and the infection rates within and outside of the cluster. When the infection rate is low outside the cluster, an epidemic is only possible when the average cluster size and within-cluster infection rate are large enough. They then compare this to the mean field model with corresponding parameters and discover that the qualitative model behavior is unchanged, indicating that the model results are robust to mixing heterogeneity.

Mushayabasa and Bhunu made their contributions in [48] towards an effective tuberculosis (TB) control by constructing a mathematical model to assess the impact of early therapy for latent TB and non-adherence on controlling TB transmission dynamics. They determined the equilibrium states of their model and examined the local stability. They also adopt the center manifold theory to establish that the model undergoes a backward bifurcation. Analysis of their model suggests that a high level of latent tuberculosis case findings, coupled with a decrease of defaulting rate, may be effective in controlling TB transmission dynamics in the community. Population-level effects of organized campaigns to improve early therapy and to guarantee successful completion of each treatment are evaluated through numerical simulations and presented in support of the analytical results.

Nyabadza and Winkler in [51] formulated a mathematical model that serves as predictive tool in Western Cape Province of South Africa, since tuberculosis is an insurmountable health burden in the region. They considered a TB compartmental model that is age dependent and whose parameters are set as functions of age. The model was fitted to the TB incidence data from the Cape Town metropole. The effective contact rate, a function of both age and time, was changed to fit the model to the notification rates of active TB disease cases. Their simulations illustrate that age structure plays an important role in the dynamics of TB. Projections on the future of the epidemic were made for each age group. The projected results show that TB incidence is likely to increase in the lower age groups of the population. It is clearly evident that even very simple models when applied to limited data can actually give valuable insights. Our results show that the age groups who have the highest incidence rates of active TB disease have the highest contribution in the transmission of TB. Furthermore, interventions should be targeted in the age group $25 - 34$ years.

An interesting job was done in [3] by considering an SEIR epidemic model with a limited resource for treatment. It is assumed that the treatment rate is proportional to the number of patients as long as this number is below a certain capacity and it becomes constant when that number of patients exceeds this capacity. Mathematical analysis is

used to study the dynamic behavior of this model. Existence and stability of disease-free and endemic equilibria are investigated. It is shown in their paper that this kind of treatment rate leads to the existence of multiple endemic equilibria where the basic reproduction number plays a big role in determining their stability.

Song, et al in [7] formulated models that incorporated local and individual interactions are introduced in the context of the trans-mission dynamics of tuberculosis (TB). The multi-level contact structure implicitly assumes that individuals are at risk of infection from close contacts in generalized household (clusters) as well as from casual (random) contacts in the general population. Epidemiological time scales are used to reduce the dimensionality of the model and singular perturbation methods are used to corroborate the results of time-scale approximations. The concept and impact of optimal average cluster or generalized household size on TB dynamics is discussed in their work. They also discuss the potential impact of their results on the spread of TB.

Generally, a number of gaps has been covered. Moreover, we are still left with un-answered questions as regards the extent to which modeling the effect of inflow of infectives on dynamics of TB is treated. This study will add to the existing knowledge by exploring the impact of optimal control strategies on the transmission and inflow of infectives of TB in South Africa.

Chapter 3

Mathematical preliminaries

3.1 Introduction

This chapter introduces and explain the various definitions and theorems that will be needed in this research project. In this chapter, we discuss the concepts related to stability and mathematical control. We will discuss the matrix and Hurwitz conditions in a simplified form, and present the Lyapunov function theorem. We discuss the reproduction number R_0 for a general compartmental disease transmission model based on a system of ordinary differential equations. For optimal control, existence and uniqueness of solutions will also be established. The basics of Brownian motions, SDE and stability of solutions of SDE systems are also presented.

3.2 Basics on ODE's in epidemic model

It is important to know whether or not we have a unique solution to a first order ordinary differential equation (ODE) initial value problem such as,

$$\frac{dx}{dt} = F(x,t),\ x(0) = x_0, \tag{3.1}$$

where $F(x)$ is bounded in a neighborhood of the point x_0.

Definition 3.2.1. [10] *(***Lipschitz condition)** A vector-valued function $X(x,t)$ satisfies the Lipschitz condition in a region $\mathbb{U}$ of (x,t)-space if and only if, for some constant L,

$$|X(x,t) - X(y,t)| \leq L\,|x-y| \;\; if \;\; (x,t) \; and \; (y,t) \in \mathbb{U} \tag{3.2}$$

Theorem 3.2.2. *(See Birkhoff and Rota [10]) Let E be an open subset containing x_0 and assume that $F \subseteq C^1(E)$. Then, there exist an $a > 0$ such that the initial value problem*

$$\dot{x} = f(x); \qquad x(0) = x_0 \tag{3.3}$$

has a unique solution $x(t)$ on the interval $[-a, a]$.

3.3 Equilibrium and stability analysis for ODE

Let us consider of an n dimensional initial value autonomous system of the form:

$$\frac{dX}{dt} = F(X), \qquad x(0) = x_0 \tag{3.4}$$

where $x \in \mathbb{R}^n$ and $F : \mathbb{R}^n \to \mathbb{R}^n$; with all the properties needed.

Definition 3.3.1. *[10]* An equilibrium solution, or fixed point, or steady-state solution of the system (3.4) is a constant solution x of the equation.

Theorem 3.3.2. *Suppose that x^* is an equilibrium solution of* (3.4)*, i.e., $F(x^*) = 0$.*

- *x^* is locally asymptotically stable (LAS) if all the eigenvalues of $DF(x^*)$ have negative real parts.*
- *If at least one eigenvalue has a positive real part then x^* is unstable. The eigenvalues are the roots of the characteristic equations of the Jacobian matrix.*

$$F(x) = 0 \tag{3.5}$$

We need to adopt the direct method of Lyapunov and the Routh-Hurwitz criteria in order to derive sufficient conditions for the global stability and asymptotic stability for such a point. The Routh-Hurwitz criteria has been used by many. Therefore it has become an important tool to establish sufficient conditions for all the roots of the characteristics polynomial. The Routh-Hurwitz Criteria is going to be used to establish the local stability of an equilibrium in this dissertation as we progress.

Theorem 3.3.3. [2] **Routh-Hurwitz Criteria**. *Consider the characteristic polynomial*

$$I(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_{n-1}\lambda + a_n, \tag{3.6}$$

where the coefficients a_i are real constants, such that $i = 1, ...n$, and λ is the identity matrix. The n eigenvalues from Hurwitz matrices considering the coefficients a_i of (3.6)

$$H_1 = (a_1),\ H = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix},\ H = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix},$$

and

$$H = \begin{pmatrix} a_1 & 1 & 0 & 0 & ... & 0 \\ a_3 & a_2 & a_1 & 1 & ... & 0 \\ a_5 & a_4 & a_3 & a_2 & ... & 0 \\ \vdots & \vdots & \vdots & \vdots & ... & \vdots \\ 0 & 0 & 0 & 0 & ... & a_n \end{pmatrix}$$

where $a_j = 0$ if $j > n$. All of the roots of the polynomial $I(\lambda)$ are negative or have negative real part iff the determinants of all Hurwitz matrices are positive,

$$\det(H_j) > 0\ j = 1, 2, .., n.$$

When $n = 2$ the Routh-Hurwitz Criteria simplify to $\det H_1 = a_1 > 0$ *and*

$$\det H_2 = \det \begin{pmatrix} a_1 & 1 \\ 0 & a_2 \end{pmatrix} = a_1 a_2 > 0$$

or $a_1 > 0$ and $a_2 > 0$. For a polynomial of degree $n = 2, 3, 4$ and 5, the Routh-Hurwitz Criteria are summarized as follows:

Routh-Hurwitz Criteria for $n = 2, 3, 4,$ and 5

$n = 2 : a_1 > 0$ and $a_2 > 0$.

$n = 3 : a_1 > 0, a_3 > 0$ and $a_1 a_2 > a_3$.

$n = 4 : a_1 > 0$ *and* $a_2 > 0, a_4 > 0$ and $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$.

$n = 5 : a_i > 0$ $i = 1, 2, 3, 4, 5, a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$ and

$(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_5^2$.

Definition 3.3.4. *[2]* Let U be an open subset of $\mathbb{R}^n$ containing the origin. A real-valued $C^1(U)$ function, $V : U \to \mathbb{R}$, $[(x, y) \in U, V(x, y) \in \mathbb{R}]$ is said to be positive definite on the set U if the following two conditions hold.
(i) $V(0, 0) = 0$
(ii) $V(x, y) > 0$ for all $(x, y) \in U$ with $(x, y) \neq 0$.
The function V is said to be negative definite if $-V$ is positive definite.

Definition 3.3.5. *[34]* $V(x)$ is said to be *positive (negative) definite* in a neighborhood U of the origin if $V(x) > 0$ $(V(x) < 0)$ for all $x \neq 0$ in U, and $V(0) = 0$. $V(x)$ is positive (negative) semi-definite in a neighborhood U of the origin if $V(x) \geq 0$ $(V(x) \leq 0)$ for all $x \neq 0$ in U, and $V(0) = 0$.

Theorem 3.3.6. *[34] Let $X^*(t) = 0$, $t \geq t_0$, be the zero solution of the regular system $\dot{X} = X(x)$, where $X(0) = 0$. Then $X(x(t))$ is uniformly stable for $t \geq t_0$ if there exists $V(x)$ with the following properties in some neighborhood of $X = 0$:*

(i) $V(x)$ and its partial derivatives are continuous;

(ii) $V(x)$ is positive definite;

(iii) $\dot{V}(x)$ is negative semi-definite.

Theorem 3.3.7. *[34] If we observe all the conditions of the Theorem* (3.3.6)*, except the last condition of (iii) and instead assume that*

(iii) $\dot{V}$ is negative definite.

Then the zero solution is asymptotically stable (and such a function V is called a strong Lyapunov function for the system).

3.4 The basic reproduction number R_0

The research work in [22], [23] and [47] explains reproduction number, denoted by R_0, as the expected number of secondary cases reproduced by one infected individual in his/her entire infectious period. R_0 is one of the most effective threshold parameters, which describes the features of mathematical problems concerning infectious diseases. When $R_0 < 1$, this simply implies that each infected individual can produce an average of less than one new infected individual during his/her entire period of infectiousness. In this situation the disease will not persist in the population and may be wiped out. But in a situation where $R_0 > 1$, then each infected individual produces on average more than one new infection, and the disease is spread in the population. The general method for calculating R_0 is adopted from [26]. Assume we have n disease compartments for the disease transmission model of the form:

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), i = 1, ..., n, \tag{3.7}$$

where

$$\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$$

and

$$f(x) = \begin{pmatrix} f_1(x) \\ 0 \\ 0 \\ 0 \\ f_n(x) \end{pmatrix}, \text{where } x = \begin{pmatrix} x_1 \\ 0 \\ 0 \\ 0 \\ x_n \end{pmatrix} \tag{3.8}$$

also

- $\mathcal{F}_i(x)$ is the rate of secondary infection increase of the i^{th} disease compartment
- $\mathcal{V}_i(x)$ is the rate of appearance of new infections in compartment i,
- $\mathcal{V}_i^-(x)$ is the rate of transfer out of the i^{th} compartment,

We consider these functions to be continuously differentiable at least twice. Furthermore,

$$\mathcal{X}_0 = \{x \geq 0 |\ x_i = 0;\ i = 1, ..., m\}.$$

where $\mathcal{X}_0$ denotes the set of all disease-free states. We assume that these functions satisfy the assumptions $\mathcal{H}_1$ ... $\mathcal{H}_5$ as described below:

$\mathcal{H}_1$: If $x_i \geq 0$, then $\mathcal{V}_i(x)$, $\mathcal{V}_i^-(x)$, $\mathcal{V}_i^+(x) \geq 0$ for i=1,...,n.
$\mathcal{H}_2$: If $x_i = 0$, then $\mathcal{V}_i^-(x) = 0$ and in particular, $\mathcal{V}_i^+(x) = 0$, if $X \in \mathcal{X}_s$ for i = 1,...,m this implies that there can be no transfer of individuals out of an empty compartment by any means. These two assumptions imply that if $x_i = 0$, then $f_i(x) \geq 0$. Therefore (3.8) is positively invariant [61]; that for each non-negative initial condition there is a unique, non-negative solution.

$\mathcal{H}_3$: $\mathcal{F}_i = 0$ if $i > m$ holding for the fact that the rate at which infection occurs (incidence of infection) in an uninfected compartment is zero.

$\mathcal{H}_4$: $\mathcal{F}_i = 0$ and $\mathcal{V}_i^+(x) = 0$ if $x \in \mathcal{X}_s$, $i = 1, ..., m$. Condition $\mathcal{H}_4$ is to guard against the disease-free subset being altered and this assumption ($\mathcal{H}_4$) implies that if a population is free of disease then it remains free with no room for immigration of infectives into the diseases free compartment.

$\mathcal{H}_5$: If $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts. The following lemma assures that, under conditions ($\mathcal{H}_1$) $\cdots$ ($\mathcal{H}_5$) the Jacobian, $Df(x_0)$ can be partitioned into a matrix of new infections and that of transfer of individuals in and out of a compartment.

Lemma 3.4.1. *[26]. If x_0 is a DFE of (3.7) and $\mathcal{F}_i(x)$ satisfies the assumptions ($\mathcal{H}_1$) through ($\mathcal{H}_5$), then the derivatives $DF(x_0)$ and $DV(x_0)$ are partitioned as*

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \text{and } D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices defined by

$$F = [\ \tfrac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\ ], \text{and}\ \ V = [\ \tfrac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\ ],\ \text{where } 1 \leq i, j \leq m$$

Furthermore, F is non-negative, V is a non-singular M -matrix and all the eigenvalues of J_4 have positive real parts. Thus the matrix V^{-1} is non-negative, and so is FV^{-1}.

If an infected individual is introduced into a compartment k of a disease free population, then the (j, k) entry of V^{-1} can be interpreted as the average length of time an individual spends in compartment j during its lifetime. The (i, j) entry of F can be interpreted as the rate at which infected individuals in compartment j produce new infections in compartment i.

The matrix FV^{-1} is called the next generation matrix for the model [26]. The (i,k) entry of the next generation matrix is the expected number of new infections in compartment i produced by the infected individual originally placed into compartment k. The basic reproduction number, R_0 , is obtained as

$$R_0 = \rho(FV^{-1})$$

where $\rho(FV^{-1})$ denotes the spectral radius of FV^{-1}. R_0 is a threshold parameter for the stability of the DFE [22].

3.5 General optimal control method

Optimal control theory is now a mature mathematical discipline with numerous applications, essentially in decision making regarding complex situations. In dealing with an optimal control problem for ODEs, we have an ultimate goal to adjust control u such that it minimizes or maximizes a given objective functional, $J(u(t), x(t), t)$. Here $x(t)$ is the state variable and $u(t)$ is the control. Our major considerations are the control and the state variables, because the functional solely depends on them. There are a number of different methods for calculating the optimal control for specific model. We take for example, Hamilton-Jacobi-Bellman equations which allows the calculation of the optimal control for stochastic differential equations model system with given constraints, Pontryagin's maximum principle which allows the calculation of the optimal control for an ordinary differential equations model system with given constraints, etc.

We consider a first order ordinary differential equation with the state variable that satisfies a differential equation which depends on the control variable:

$$\dot{x(t)} = h(t, x(t), u(t));\ x_0 = x(0),\ 0 \leq t \leq t_h, \tag{3.8}$$

where $\dot{x(t)}$ denotes the derivative with respect to time t. We are interested in a problem of the following form:

$$\max \int_0^T f(t, x(t), u(t))dt$$

subject to the conditions

$$\dot{x(t)} = h(t, x(t), u(t)),$$

where

$x(0) = x_0$ and $x(T)$ is free.

Optimal control theory is based on two fundamental ideas. (1) The dynamic programming and the associated optimality principle. (2) The maximum principle applied only to deterministic problems which was introduced by Pontryagin in the Soviet Union [57].

Theorem 3.5.1. *(***Pontryagins Maximum Principle***) If u^* and x^* are optimal for problem* (3.8)*, then there exists a piecewise differential adjoint variable $\lambda(t)$ such that*

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))$$

for each control u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda h(t, x(t), u(t)) \tag{3.9}$$

and

$$\lambda^{'}(t) = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},$$
$$\lambda(t_f) = 0.$$

Here f is the integrand of the objective functional and h, the right hand side of the given dynamical system.

If the Hamiltonian attains its maximal in the variable u, it has critical points at u^*.

$$i.e., \frac{\partial H}{\partial u} = 0.$$

The function $\lambda(t)$ is the shadow price or co-state variable. This denotes the increase of the objective function due to marginal increase of the state variable. At any time the decision maker can use the control variable to generate direct contributions to the objective function (represented by the term $f(t, x(t), u(t))$) in the Hamiltonian (3.9)), or it can use the control variable to change the value of the state variable in order to generate contributions to the objective function in the future. These indirect contributions are measured by the term $\lambda(t)g(t, x(t), u(t))$ in the Hamiltonian.

3.6 Stochastic Differential Equations

Brownian motion, also known as the Wiener process, is a formal stochastic process modelled on the irregular random motion of small particles immersed in a liquid or gas. The concept of stochastic process has application in a wide range of fields, such as finance, engineering, biology, etc. This is now a useful tool in epidemiology and other areas of Mathematics, [41].

Definition: Let $(\Omega, \mathcal{F}, P)$ be a probability space with filtration $\{\mathcal{F}_t\}_{t \geq t_0}$. A one-dimensional Brownian motion is a real-valued continuous $\{\mathcal{F}_t\}$-adapted process $\{B_t\}_{t \geq t_0}$ with the following properties:

(i) $B_0 = 0$ a.s.;

(ii) for $0 \leq s < t < \infty$, the increment $B_t - B_s$ is independent of $\{\mathcal{F}_s\}$,

(iii) B_t is continuous in $t \geq 0$.

We consider the possible solutions $X_t(\omega)$ of the stochastic differential equation

$$dX_t = b(t, X_t)dt + \sigma(t, X_t)dW_t, \quad b(t,x) \in \mathbb{R},\ \sigma(t, X_t) \in \mathbb{R} \tag{3.10}$$

where W_t is a 1-dimensional Wiener process. Interpretation of (3.10) above is that X_t satisfies the stochastic integral equation,

$$X_t = X_0 + \int_0^t b(s, X_s)ds + \int_0^t \sigma(s, X_s)dW_s \tag{3.11}$$

Taking into consideration the d-dimensional stochastic differential equation

$$dX(t) = f(x(t), t)dt + g(x(t), t)dW(t), \tag{3.12}$$

where $f : U \to \mathbb{R}^n$; $g : U \to \mathbb{R}^n \times p$; $U \subset \mathbb{R}^n$, in a given range,

$$X = (x_1, x_2, ..., x_n) \in U;$$

$$W = (W_1, W_2, ..., W_p)$$

is the d-dimensional Wiener process.

On $t_0 \leq t \leq T$, with initial value of $x(t_0) = x_0$. The first term represents the continuity of f in the deterministic component or drift coefficient while the second term represents the continuity of the random component or diffusion coefficient [14]. Also f is chosen as an m-vector-valued function, g is regarded as an $m \times d$ matrix-valued function.

Definition 3.6.1. We define any given initial value $x_0 \in U$. Then equation (3.11) has a unique global solution such that $X(t_0) = X_0$, and is denoted by $X(t; t-0, X_0)$. If $f(0,t) = 0$ and $g(0,t) = 0$ for all $t > t_0$, then the equation (3.12) has the solution $X(t) = 0$ corresponding to the initial value X_0, the solution is called the trivial solution or equilibrium position.

3.7 Stability

Consider the general n-dimensional stochastic system

$$dx(t) = f(t, x(t))dt + g(t, x(t))dB(t) \tag{3.13}$$

on $t \geq 0$ with initial value $x(0) = x_0$. The solution is denoted by $x(t, x_0)$. Assume that $f(t, 0) = g(t, 0) = 0$ for all $t \geq 0$, so the origin point is an equilibrium of (3.20) The equilibrium $x = 0$ of the system (3.20) is said to be:

(i) Stable in probability if for all $\epsilon > 0$,

$$\lim_{x_0 \to 0} P\left(\sup_{t \geq 0} |x(t, x_0)| \geq \epsilon\right) = 0;$$

(ii) Almost surely exponentially stable if for all $x_0 \in \mathbb{R}^n$,

$$\limsup_{x_0 \to \infty} \frac{1}{t} \ln |x(t, x_0)| < 0 \qquad a.s$$

We refer the reader to the papers of Lahrouz et al., [36] and Witbooi, [62].

Chapter 4

A basic model of Tuberculosis

4.1 Introduction

We here introduce a compartmental model of TB in a population. The size of the population, at a given time t, is denoted by $N(t)$. The model divides the entire population into four groups or classes according to their epidemiological status. We explicitly incorporate the inflow of infectives. The first of these groups consists of individuals in the population who have not come into effective contact with the *Mycobacterium* and is known as the class S of susceptibles. When healthy individuals come into contact with an unhealthy infected person, they get infected but are not infectious instantly, so they are known as the latent class L. Over time the latent individuals becomes contagious, capable of transmitting the disease to healthy individuals in a population. This is called the infectious class I. From the class I an individual may go into a treatment program, and such individuals form a class T. These four classes capture the entire population. At any point t in time, the sizes of these classes are $S(t), L(t), I(t)$ and $T(t)$. We are of the opinion that it is highly expedient for public health policy makers to understand the significant impact of inflow of infective immigrants in the transmission dynamics of tuberculosis.

Another objective of this dissertation as earlier indicated is to assess the impact of

optimal control strategies of TB in South Africa and other developing countries in Sub-Saharan Africa. Also, we consider treatment as an intervention to reduce the rate at which TB infected immigrants that migrates into our countries and environments. Ordinarily an indi-vidual can develop TB in different ways but human-to-human transmission is still the increasing means of transmission of TB. This work differs from [18] essentially in that we are considering inflow of infectives, and we study an optimal control problem on the disease.

4.2 Model formulation

Our model is based on the SLIT transmission model [18], but additionally, we allow for inflow of infected individuals into the population.

The total population size at time t is denoted by $N(t)$ and therefore we have:

$$N(t) = S(t) + L(t) + I(t) + T(t). \tag{4.1}$$

The model we study here is a deterministic model of population dynamics of the Tuberculosis epidemic. The Stochastic version of this model will be looked into in the later chapter. A flow diagram of the Tuberculosis model is sketched in Figure 4.1 below.

The following system of equations describes the population dynamics with a unique allowance of direct inflow of infectives into the population.

4.3 Assumptions

1. Here we assume a homogeneous mixing of individuals in the population which means that every uninfected individual has an equal likelihood of being infected

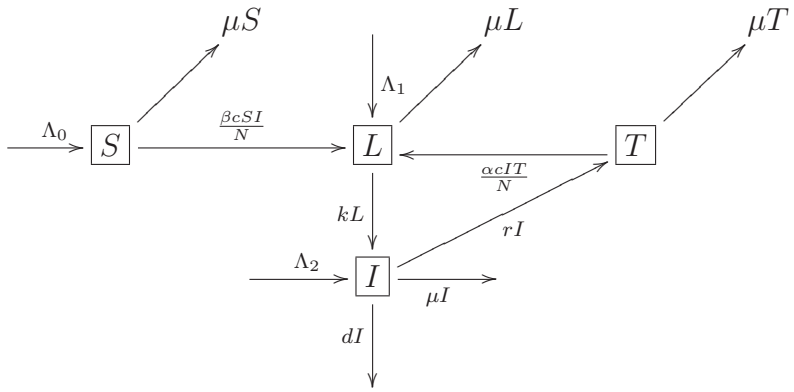


Figure 4.1: Compartmentalised diagram showing the TB model with inflow of infectives.

when coming into adequate contact with infectious individuals and that transmission of the infection occurs with a standard incidence rate.

2. We also assume that some recruits, that is, newborns and immigrants, may possibly be latently infected at the time they are born or migrate into the population. Thus they will emerge in the susceptible class, S at a rate, Λ_0, the latent class at a rate Λ_1 or the infective class at a rate Λ_2 .

3. Infected individuals recover from the symptoms of TB after treatment.

4. Inflow of infectives into the group varies as explained above.

5. We further assume that all parameters to be used in this model are positive.

A full definition of the parameters used in our model are stated in Table 4.1.

Table 4.1: Symbols and Definitions of Model parameters.

Symbols	Description
Λ_0	The recruitment rate in the susceptible class
Λ_1	The rate of inflow of Latently infected in the Latent class
Λ_2	The rate of inflow of infectives in the infective class
μ	The natural death rate coefficient
d	The disease-induced death rate coefficient
β	the probability that susceptible (S) individuals become infected by one infectious individual per contact per unit of time
α	the probability that Treated individuals (T) become infected by one infectious individual per contact per unit of time
c	The per-capita contact rate
k	The rate at which an individual leaves the Latent(L) class by becoming infectious
r	The treatment rates for infectious individuals

Considering the definitions, assumptions and inter-relations between the variables and the parameters, the basic dynamics of TB with direct inflow of infectives is described by the following system of ordinary differential equations:

$$\begin{aligned} \frac{dS}{dt} &= \Lambda_0 - \beta c\frac{SI}{N} - \mu S, \\ \frac{dL}{dt} &= \Lambda_1 + \beta c\frac{SI}{N} - (\mu + k)L + \alpha cT\frac{I}{N}, \\ \frac{dI}{dt} &= \Lambda_2 + kL - (\mu + d + r)I, \\ \frac{dT}{dt} &= rI - \alpha cT\frac{I}{N} - \mu T. \end{aligned} \tag{4.2}$$

For convenience we introduce extra variables:

$$\mu_1 = \mu + k \text{ and } \quad \mu_2 = \mu + d + r.$$

Therefore our model becomes:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda_0 - \beta c\frac{SI}{N} - \mu S, \\
\frac{dL}{dt} &= \Lambda_1 + \beta c\frac{SI}{N} - \mu_1 L + \alpha c T\frac{I}{N}, \\
\frac{dI}{dt} &= \Lambda_2 + kL - \mu_2 I, \\
\frac{dT}{dt} &= rI - \alpha c T\frac{I}{N} - \mu T.
\end{aligned} \tag{4.3}$$

with initial conditions;

$$S(0) = S_0 > 0,\ L(0) = L_0 \geq 0,\ I(0) = I_0 \geq 0,\ T = T_0 \geq 0.$$

The force of infection is $\beta c\frac{I}{N}$ and c is the per-capita contact rate. The total population size of system (4.3) is given by:

$$\begin{aligned}
\frac{dN}{dt} &= \Lambda_0 - \beta c\frac{SI}{N} - \mu S + \Lambda_1 + \beta c\frac{SI}{N} - \mu_1 L \\
&+ \alpha c T\frac{I}{N} + \Lambda_2 + kL - \mu_2 I + rI - \alpha c T\frac{I}{N} - \mu T.
\end{aligned} \tag{4.4}$$

We recall that $\mu_1 = \mu + k$ and $\mu_2 = \mu + d + r$. By substitution then:

$$\frac{dN}{dt} = \Lambda_0 + \Lambda_1 + \Lambda_2 - \mu(S + L + I + T) - dI, \tag{4.5}$$

and the system (4.3) can now be written as:

$$\begin{aligned}
\frac{dN}{dt} &= \Lambda_0 + \Lambda_1 + \Lambda_2 - \mu N - dI, \\
\frac{dL}{dt} &= \Lambda_1 + \beta c\frac{N - L - I - T}{N} I - \mu_1 L + \alpha c T\frac{I}{N}, \\
\frac{dI}{dt} &= \Lambda_2 + kL - \mu_2 I, \\
\frac{dT}{dt} &= rI - \alpha c T\frac{I}{N} - \mu T.
\end{aligned} \tag{4.6}$$

with initial conditions;

$N(0) = N_0 > 0,\ L(0) = L_0 \geq 0,\ I(0) = I_0 \geq 0,\ T = T_0 \geq 0.$

A good look at the continuity of the right-hand side of the above system of equations in (4.6) and its derivative reveals that the model is well posed for $N > 0$.

4.4 Basic properties of the model

In this section, the basic properties of model system (4.3) which are useful in the proofs of stability are studied. These are the invariant region and positivity of solutions. The former describes the region in which the solutions of system (4.3) makes biological sense while the latter describes non-negativity of solutions of system (4.3). The model under consideration monitors a human population and as such, we need to have that all the parameters and the variables of the model are positive for all $t \geq 0$.

4.4.1 Invariant region

Note that

$$\frac{dN}{dt} \leq \Lambda - \mu N, \tag{4.7}$$

where $\Lambda = \Lambda_0 + \Lambda_1 + \Lambda_2$. We now apply Birkhoff and Rota's theorem on differential inequality (4.7). By separation of variables of differential inequality (4.7), we get

$$\frac{dN}{\Lambda - \mu N} \leq dt. \tag{4.8}$$

Integrating (4.8) on both sides gives, $\int \frac{dN}{\Lambda - \mu N} \leq \int dt = \frac{-1}{\mu} \ln(\Lambda - \mu N) + c$,

$$\ln(\Lambda - \mu N) \geq -\mu(t + c).$$

Therefore,

$$\Lambda - \mu N \geq Ae^{-\mu t}, \tag{4.9}$$

where A is a constant. Now, applying the initial condition $N(0) = N_0$ in (4.9), we get

$$A = \Lambda - \mu N_0. \tag{4.10}$$

Substituting (4.10) into (4.9) gives

$$\Lambda - \mu N \geq \Lambda - \mu N_0 e^{-\mu t} \tag{4.11}$$

Making N the subject in (4.11) we have,

$$N \leq \frac{\Lambda}{\mu} - \left[\frac{\Lambda - \mu N_0}{\mu}\right] e^{-\mu t} \tag{4.12}$$

As $t \to \infty$ in (4.12) above, the population size N, approaches

$$0 \leq N \leq \frac{\Lambda}{\mu} \Rightarrow N \to \frac{\Lambda}{\mu} \tag{4.13}$$

Therefore, the feasible solutions set of system (4.3) enters the region

$$\Omega = \left\{(S, L, I, T) \in \mathbb{R}^4_+ : N \leq \frac{\Lambda}{\mu}\right\}.$$

In this case, whenever $N > \frac{\Lambda_0}{\mu}$, then $\frac{dN}{dt} < 0$ which means that $N \to \frac{\Lambda}{\mu}$. On the other hand, whenever $N \leq \frac{\Lambda_0}{\mu}$, every solution with initial condition in $\mathbb{R}^4_+$ remains in that region for $t > 0$. Thus, the region Ω is positively-invariant.

4.4.2 Positivity of solutions

Lemma 4.4.1. *Let the initial data be* $\{(S_0, L_0, I_0, T_0) \geq 0\} \in \Omega$. *Then, the solution set* $\{S(t), L(t), I(t), T(t)\}$ *of system* (4.3) *is positive for all* $t > 0$

Proof. Let $\lambda = \frac{\beta c I}{N}$. From the first equation of model system (4.3),

$$\frac{dS}{dt} = \Lambda_0 - \lambda S - \mu S \geq -(\lambda + \mu)S.$$

That is,

$$\frac{dS}{dt} \geq -(\lambda + \mu)S. \tag{4.14}$$

Integrating (4.14) by separation of variables gives

$$\int \frac{dS}{S} \geq -\int (\lambda + \mu)dt.$$

Therefore,

$$S(t) \geq S(0)e^{-\int (\lambda+\mu)dt} > 0.$$

□

This proves that $S(t) > 0$ for all $t \geq 0$. Similarly, it can be shown that the remaining variables of system (4.3) are also positive $\forall t > 0$.

Remark 4.4.2. *$e^k > 0$ for all $k \in \mathbb{R}$.*

4.5 Equilibrium and stability analysis

This section focuses on the existence and stability of the equilibrium points of the model system (4.3).

4.5.1 Equilibrium of the model

Our model system in equation (4.3) obviously does not have a disease-free equilibrium due to the inflow of infecteds at a constant rate. However, we study the model (4.3) without the inflow of infectives in the next subsection. There exists a non-negative equilibrium point of the model in equation (4.6). This endemic equilibrium $E_1 = (N^*, L^*, I^*, T^*)$ exists when tuberculosis infection persists in the population, i.e., $I^* \neq 0$, where N^*, L^*, I^* and T^* are positive solutions of the following system of algebraic equations.

$$0 = \Lambda_0 + \Lambda_1 + \Lambda_2 - \mu N - dI,$$

$$\begin{aligned} 0 &= \Lambda_1 + \beta c \frac{N-L-I-T}{N} I - \mu_1 L + \alpha c T \frac{I}{N}, \\ 0 &= \Lambda_2 + kL - \mu_2 I, \\ 0 &= rI - \alpha c T \frac{I}{N} - \mu T. \end{aligned} \tag{4.15}$$

4.5.2 The Existence of the disease-free equilibrium, E_0

In this subsection, we have a special case whereby all the immigrants are susceptible in the absence of direct inflow of tuberculosis infectives into the population. Also, we consider the rate of interaction between the individuals in the latent class to be low i.e $c << \beta$. This scenario is basically found in underdeveloped or poor countries where people do not migrate much and may not even be aware of their status. This is different in the case of developed countries where there are high levels of awareness and facilities to detect and control the spread.

In view of this scenario where $\Lambda_1 = 0$ and $\Lambda_2 = 0$ for system in (4.3), then R_0 is a threshold parameter for local stability of the disease free equilibrium of the model and there can be a trace of bifurcation which we shall also investigate in this chapter.

Considering the state where there is no infection i.e $(L = I = T = 0)$, our model has a steady state E_0, given by

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right). \tag{4.16}$$

4.5.3 Basic reproduction number, R_0.

The basic reproduction number R_0 is defined as the effective number of secondary infections caused by a typical infected individual during his entire period of infectiousness [22]. This definition is basically for the models that represent the spreading of infection in a population. It can be obtained by taking the largest eigenvalue of:

$$\left[\frac{\partial F_i(E_0)}{\partial x_j}\right] \cdot \left[\frac{\partial V_i(E_0)}{\partial x_j}\right]^{-1}, \tag{4.17}$$

where:

F_i is the rate of appearance of new infection in compartment i,
V_i^+ is the transfer of individuals into compartment i,
V_i^- is the transfer of individuals out of the compartment i by all other means,
and E_0 is the disease-free equilibrium.

The basic reproductive number R_0 is often considered as the threshold quantity that determines whether an infection can invade and persist in a new host population. In this model, if $R_0 \leq 1$ then the infection in the community dies out; while if $R_0 > 1$, then there is a unique positive epidemic equilibrium.

Consequently, from system 4.3, we obtain F_i and V_i as

$$F_i = \begin{pmatrix} 0 \\ \frac{\beta cSI}{N} + \frac{\alpha cTI}{N} \\ 0 \\ 0 \end{pmatrix}, \tag{4.18}$$

and

$$V_i = \begin{pmatrix} \frac{\beta cSI}{N} + \mu S - \Lambda_0 \\ (\mu + k)L \\ (\mu + d + r)I - kL \\ \frac{\alpha cTI}{N} + \mu T - rI \end{pmatrix}.$$

The infected compartments are L and I, we know an equilibrium solution with L=I=0 has the form $x_0 = (S_0, L_0, I_0, T_0)^t$, where S_0 is any positive solution of $S = \frac{\Lambda_0}{\mu}$. This will be a DFE if and only if $\Lambda'(S_0) < \mu$. Without loss of generality,

assume $S_0 = 1$ is a DFE. Then $x_0 = (S_0, L_0, I_0, T_0)^t = (1, 0, 0, 0)$ [26]. Evaluating at the DFE, we have,

$$F = \begin{pmatrix} 0 & \beta c \\ 0 & 0 \end{pmatrix}. \tag{4.19}$$

$$V = \begin{pmatrix} (\mu + k) & 0 \\ -k & \mu + d + r \end{pmatrix}. \tag{4.20}$$

Now, taking the inverse of matrix (4.20) leads to

$$V^{-1} = \begin{pmatrix} \frac{1}{k+\mu} & 0 \\ \frac{k}{(k+\mu)(d+r+\mu)} & \frac{1}{d+r+\mu} \end{pmatrix}. \tag{4.21}$$

Now, we compute FV^{-1} by,

$$FV^{-1} = \begin{pmatrix} 0 & \beta c \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{k+\mu} & 0 \\ \frac{k}{(k+\mu)(d+r+\mu)} & \frac{1}{d+r+\mu} \end{pmatrix} \tag{4.22}$$

$$= \begin{pmatrix} \frac{k\beta c}{(k+\mu)(d+r+\mu)} & \frac{\beta c}{d+r+\mu} \\ 0 & 0 \end{pmatrix} \tag{4.23}$$

Now, we calculate the eigenvalues of matrix (4.23) to determine the basic reproduction number, R_0 defined as the spectral radius (dominant eigenvalue) of the matrix. This is computed by $|A - I\lambda| = 0$ where A is matrix (4.23) and I is a 2×2 identity matrix. Hence, matrix (4.23) becomes

$$\begin{vmatrix} \frac{k\beta c}{(k+\mu)(d+r+\mu)} & \frac{\beta c}{d+r+\mu} \\ 0 & 0 \end{vmatrix} = 0 \tag{4.24}$$

From matrix (4.24) we obtain two eigenvalues, λ_1 and λ_2 which are given by

$$\lambda_1 = \frac{k\beta c}{(k + \mu)(d + r + \mu)}$$

and

$$\lambda_2 = 0$$

The eigenvalues of FV^{-1} are $\left\{0, \frac{k\beta c}{(k+\mu)(d+r+\mu)}\right\}$. Clearly, λ_1 is the dominant eigenvalue and becomes the basic reproductive number R_0 of the model

$$R_0 = \frac{k\beta c}{(k+\mu)(d+r+\mu)} = \frac{\beta c}{\mu_2}\frac{k}{\mu_1}. \tag{4.25}$$

The average number of susceptibles infected by a typical infectious individual during his or her contagious period, is $\frac{\beta c}{\mu_2}$ and the fraction of population which survives the latent period, is given by $\frac{k}{\mu_1}$. R_0 can be explained as the average number of secondary infections that are produced when one infected individual is introduced into a group of susceptible individuals. For many deterministic TB (Tuberculosis bacteria) models, an endemic can get started in a fully susceptible population if and only if $R_0 > 1$.

Theorem 4.5.1. *[26] The disease-free equilibrium of system* (4.3)*, is locally asymptotically stable if* $R_0 < 1$.

4.5.4 Existence and stability of endemic equilibrium

In the presence of infection, that is $I \neq 0$, model system (4.3) has a non-trivial equilibrium point, E_1 is called the endemic equilibrium point, i.e, the disease persists in the population. This is given by $E_1 = (S^*, L^*, I^*, T^*) \neq 0$. Under the assumption $\beta = \alpha$ in [17, 18], the use of the variables, N, L, I is enough. Hence, model (4.6) reduces to;

$$\begin{aligned} \frac{dN}{dt} &= \Lambda_0 + \Lambda_1 + \Lambda_2 - \mu N - dI, \\ \frac{dL}{dt} &= \Lambda_1 + \beta c\frac{N-L-I}{N}I - \mu_1 L, \\ \frac{dI}{dt} &= \Lambda_2 + kL - \mu_2 I. \end{aligned} \tag{4.26}$$

The unique endemic equilibrium of (4.26) is given by $E_1 = (S^*, L^*, I^*)$, where

$$\begin{aligned} N^* &= \frac{\tau R_0 \Lambda}{dk(R_0 - 1) + \mu\tau R_0} \\ L^* &= \frac{\mu_2 I^* - \Lambda_2}{k} \\ I^* &= \frac{(\Lambda_2 + k(R_0 - 1))N^*}{\tau R_0}, \end{aligned} \tag{4.27}$$

where

$$\tau = \mu + d + r + k \text{ and } \Lambda = \Lambda_0 + \Lambda_1 + \Lambda_2.$$

Noticing that

$$\frac{N^* - L^* - I^*}{N^*} = \frac{1}{R_0}$$

4.5.5 Local stability of the endemic equilibrium point

An endemic equilibrium means that the disease persists and is endemic in the system or given population. We investigate the local stability of the endemic equilibrium point by calculating the variational matrix for E_1.

$$M(E_1) = \begin{bmatrix} -\mu & 0 & -d \\ m_{21} & -m_{22} & m_{23} \\ 0 & k & -\mu_2 \end{bmatrix},$$

where

$m_{21} = a(R_0 - 1), \quad m_{22} = (aR_0 + \mu_1), \quad m_{23} = \frac{\beta c}{R_0} - aR_0, \quad m_{24} = aR_0,$

and

$$a = \frac{\beta c}{R_0}\frac{I^*}{N^*}.$$

The characteristic equation corresponding to $M(E_1)$ is given by

$$f(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{4.28}$$

with

$$\begin{aligned} a_1 &= aR_0 + 3\mu + k + r + d, \\ a_2 &= aR_0(2\mu + k + r + d) + \mu(2\mu + k + r + d), \\ a_3 &= \mu aR_0(\mu + k + r + d) + kad(R_0 - 1). \end{aligned}$$

We can easily determine that $a_i > 0$ $(i = 1, 2, 3)$ and $a_1, a_3 > 0$. Since it is obvious that $a_1a_2 > a_3$, then the Routh Hurwitz criterion is satisfied. It follows that E_1 is locally asymptotically stable [18].

4.6 Sensitivity of Basic Reproduction Number R_0

Sensitivity analysis for the basic reproduction number R_0 is being investigated to help determine the parameter value that contributes more on the disease transmission. In order to find out, then we utilize the sensitivity index analysis by using partial derivatives when the variable is a differentiable function of the parameter.

Definition 4.6.1. *The normalised forward sensitivity index of a variable to a parameter is a ratio of the relative change in the variable to the relative change in the parameter. When a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives:*

$$\Upsilon_m^{R_0} = \frac{\partial R_0}{\partial m} \times \frac{m}{R_0}$$

The derivation of the sensitivity of R_0 to each of the parameters is described in Table (4.2) below. The sensitivity index for the parameters in our model is shown as follows:

$$\begin{aligned}
\frac{\partial R_0}{\partial \mu} \times \frac{\mu}{R_0} &= -\frac{(\mu\,(d+r+2\,\mu+k)}{(k+\mu)\,(d+r+\mu)}, \\
\frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} &= 1, \\
\frac{\partial R_0}{\partial k} \times \frac{k}{R_0} &= \frac{\mu}{k+\mu}, \\
\frac{\partial R_0}{\partial c} \times \frac{c}{R_0} &= 1, \\
\frac{\partial R_0}{\partial d} \times \frac{d}{R_0} &= -\frac{d}{d+r+\mu}, \\
\frac{\partial R_0}{\partial r} \times \frac{r}{R_0} &= -\frac{r}{d+r+\mu}.
\end{aligned} \tag{4.29}$$

Table 4.2: Parameters values and sensitivity indices of R_0

Parameters	Parameter description	Values	Sources	Sensitivity
μ	Per capita death rate	0.1430	[18]	-0.1498
k	Rate of Indiv. from L class to I class	0.5	[18]	+0.8108
β	Prob.that S class and T class become I class.	0.1	Estimated	+1.0000
c	contact rate	4	Estimated	+1.0000
d	disease induced rate	0.3500	Estimated	-0.2771
r	per capita treatment rate for I class	1	[18]	-0.66979

Table 4.2 consist of parameter values deduced from [18] and the estimated values were also deduced relatively to WHO report on Tuberculosis in South African [31]. The most sensitive parameters towards the spread of tuberculosis infection are the probabilities that susceptible and treated individuals become infected by one infectious individual per contact per unit of time (β) and the per-capita contact rate

c. Moreover, it is noteworthy that per capita death rate μ, disease induced rate d, and per capita treatment rate for I class r contribute to a decline in the spread of TB infection. For all the parameters, the sign of the sensitivity indices of R_0 agrees with the intuitive expectation as to whether R_0 increases or decreases when the parameters increases.

4.7 Global stability

In the paper [18] it is assumed that if $\alpha = \beta$, then the DFE is globally stable whenever $R_0 < 1$. We now present a global stability theorem which is slightly more general and we use the Lyapunov function approach for the formulation of our stability theorem. We introduce the following invariant R_* similar to R_0.

Let

$$\beta_* = \max\{\beta, \alpha\},$$

and

$$R_* = \frac{k\beta_* c}{(\mu_1)(\mu_2)}. \tag{4.30}$$

Theorem 4.7.1. *If $R_* < 1$, then E_0 is globally asymptotically stable.*

Proof. Let us assume that $R_* < 1$. Then $R_* - 1 < 0$, and therefore

$$\frac{\mu_1\mu_2}{k}(R_* - 1) < 0. \tag{4.31}$$

We can choose $\epsilon_1 > 0$, sufficiently small such that

$$\frac{\mu_1\mu_2}{k}(R_* - 1) + \epsilon_1\mu_2 < 0. \tag{4.32}$$

We can also choose $\epsilon_2 > 0$, sufficiently small such that the following two conditions hold:

$$\frac{\mu_1\mu_2}{k}(R_* - 1) + \epsilon_1\mu_2 + \epsilon_2 r < 0, \tag{4.33}$$

and

$$-\epsilon_1 k < 0. \tag{4.34}$$

Let A be the constant:

$$A = \frac{\mu_1}{k} - \epsilon_1.$$

Now we define a function $V(L, I, T)$ as follows:

$$V = L + AI + \epsilon_2 T. \tag{4.35}$$

Then V is a positive definite function. We shall prove that $\frac{dV}{dt}$ is negative.

$$\begin{aligned}
\frac{dV}{dt} &= \frac{\beta\, cSI}{N} - \mu_1 L + \frac{\alpha\, cIT}{N} + A\left(kL - \mu_2 I\right) + \epsilon_2\left(rI\right) - \frac{\alpha\, cIT}{N} - \mu T \\
&\leq \frac{\beta\, cSI}{N} - \mu_1 L + \frac{\alpha\, cIT}{N} + A\left(kL - \mu_2 I\right) + \epsilon_2\left(rI\right) - \mu T \\
&\leq \frac{\beta_*\, cSI}{N} + \frac{\alpha_*\, cIT}{N} - A\mu_2 I + \epsilon_2 rI + AkL - \mu_1 L - \mu T.
\end{aligned}$$

Now we note that

$$\frac{\beta_*\, cSI}{N} + \frac{\alpha_*\, cIT}{N} = \beta_*\, cI\frac{S+T}{N} \leq \beta_* cI.$$

Then we have an inequality

$$\frac{dV}{dt} \leq Q_I I + Q_L L - \mu T, \tag{4.36}$$

with

$$Q_I = \beta_* c - A\mu_2 + \epsilon_2 r, \tag{4.37}$$

$$Q_L = -Ak - \mu_1. \tag{4.38}$$

Now we analyse the latter two coefficients

$$\begin{aligned}
Q_I &= \beta_* c - \left(\frac{\mu_1}{k} - \epsilon_1\right)\mu_2 + \epsilon_2 r \\
&= \beta_* c - \frac{\mu_1\mu_2}{k} + \epsilon_1\mu_2 + \epsilon_2 r \\
&= \frac{\mu_1\mu_2}{k}(R_* - 1) + \epsilon_1\mu_2 + \epsilon_2 r \\
&< 0.
\end{aligned}$$

$$\begin{aligned} Q_L &= \left(\frac{\mu_1}{k} - \epsilon_1\right) k - \mu_1 \\ &= -\epsilon_1 k \\ &< 0. \end{aligned}$$

This proves that $\frac{dV}{dt}$ is negative definite in the variables L, I, T. Therefore E_0 is globally asymptotically stable. □

4.8 Bifurcation analysis

The disease-free equilibrium of the model is locally asymptotically stable when $R_0 < 1$ and unstable if $R_0 > 1$. Generally, when $R_0 = 1$, another equilibrium point bifurcates from the disease-free equilibrium. One way of determining the direction of bifurcation (forward or backward) in an epidemiological model is the use of the centre manifold method. This method reduces the system under consideration to a "smaller" system which has the same qualitative properties and which can be studied in a relatively easier way. For more details on the centre manifold, see [15, 61].

In this section we consider the nature of the equilibrium solutions of the disease transmission model near the bifurcation point $x = x_0, R_0 = 1$ in a neighbourhood of the DFE, x_0. For notation convenience, we let $\tau = R_0 - 1$ and rewrite the system 3.7 in chapter 3 to be:

$$\dot{x} = f(x, \tau) \tag{4.39}$$

with the assumption that f is continuously differentiable at least twice in both x and τ [26]. We have the following results.

Theorem 4.8.1. *Consider the disease transmission model defined by* (3.7) *with the function* $f(x, \tau)$ *satisfying the conditions* $(A1) - (A5)$ *in [26] and the parameter* τ

as described above. Assume that the zero eigenvalue of $D_x f(x_0, 0)$ *is simple. Let*

$$a = \frac{v}{2} D_{xx} f(x_0, 0)\omega^2 = \frac{1}{2} \sum_{i,j,k=1}^{n} v_i \omega_j \omega_k \left(\frac{\partial^2 f_i}{\partial x_j \partial x_k}(x_0, 0) \right), \tag{4.40}$$

and

$$b = v D_{x\tau} f(x_0, 0)\omega = \sum_{i,j=1}^{n} v_i \omega_j \frac{\partial^2 f_i}{\partial x_j \partial x_\tau}(x_0, 0). \tag{4.41}$$

and assume that $b \neq 0$. *Then* $\exists\ \delta > 0$ *such that*

(i) if $a < 0$, *then there are locally asymptotically stable endemic equilibria near* x_0 *for* $0 < \tau < \delta$ *and*

(ii) if $a > 0$, *then there are unstable endemic equilibria near* x_0 *for* $-\delta < \tau < 0$.

The sign of a determines the nature of the endemic equilibria near the bifurcation point [26].

Proof. We apply Theorem 4.8.1 to analyse the existence and stability of endemic in 4.3, we have

$$D_x f(x_0, 0) = \begin{pmatrix} -\mu_1 & \beta c & 0 & 0 \\ k & -\mu_2 & 0 & 0 \\ 0 & -\beta c & -\mu & 0 \\ 0 & r & 0 & -\mu \end{pmatrix} \begin{matrix} L \\ I \\ S \\ T \end{matrix},$$

by re-arranging our matrix with respect to L, I, S, T on the right hand side.

Remark 4.8.2. *At the disease-free equilibrium point,* $x_0 = (S_0, L_0, I_0, T_0)^t = (1, 0, 0, 0)$.

The eigenvalues of the matrix are given by the solution of

$$(\lambda + \mu)^2 \left[(\lambda + \mu_2)(\lambda + \mu_1) - k(\beta c) \right]$$

When $R_0 = 1$, we obtain the following roots

$$\lambda_1 = 0, \lambda_2 = -(2\mu + k + r + d), \lambda_3 = -\mu, \lambda_4 = -\mu$$

We shall now analyse the existence and stability of endemic equilibria near the bifurcation point $x = x_0$ and $R_0 = 1$ using the centre manifold.
We let $x_1 = L, x_2 = I, x_3 = S, x_4 = T$. Then the second partial derivatives of f are given by

$$\frac{\partial^2 f_i}{\partial x_1 \partial x_2} = \frac{\partial^2 f_i}{\partial x_2 \partial x_1} = -\beta c,$$

$$\frac{\partial^2 f_i}{\partial x_4 \partial x_2} = \frac{\partial^2 f_i}{\partial x_2 \partial x_4} = \alpha c - \beta c,$$

$$\frac{\partial^2 f_i}{\partial x_2^2} = -2\beta c,$$

We get

$$a = -\beta c v_1 \omega_2 \left(\omega_1 + \omega_2 + \left(1 - \frac{\alpha c}{\beta c} \right) \omega_4 \right).$$

Biologically, $\alpha c < \beta c$ and so we shall now calculate the values of v_1, $\omega_1, \omega_2, \omega_4$ to determine the sign of a. Solving for the left nullvector v corresponding to the zero eigenvalue,
$vD_x f(x_0, 0) = 0$, when $R_0 = 1$, we obtain

$$v_3 = v_4 = 0,$$

and

$$v_2 = \frac{\mu_1}{k} v_1. \tag{4.42}$$

Therefore, the left nullvector is given by

$$v = (v_1, v_2, v_3, v_4) = \left(1, \frac{\mu_1}{k}, 0, 0 \right).$$

For the right nullvector, $Dxf(x_0, 0)\omega = 0$, we obtain

$$\omega = \begin{pmatrix} \omega_1 \\ \omega_2 \\ \omega_3 \\ \omega_4 \end{pmatrix} = \begin{pmatrix} \left(\frac{\mu_1}{\beta c}\right) \\ 1 \\ -\frac{\beta c}{\mu}\left(\frac{\mu}{\beta c}\right) \\ \frac{\mu r(\mu_1)}{\mu \beta c} \end{pmatrix}.$$

This shows that v_1, ω_1, ω_2 and ω_4 are positive. Since $\alpha c < \beta c$, then $a < 0$. By theorem 4.8.2, we conclude that there is a branch of endemic equilibrium points that exist for values of $R_0 > 1$. Moreover, these equilibrium points are stable. That is, a forward bifurcation occurs at $R_0 = 1$. As considered by [26], we shall now include exogenous reinfection for the tuberculosis treatment model see [16], by adding the reinfection rate $\frac{\chi cI}{N}L$ to the infective compartment and -$\frac{\chi cI}{N}L$ to the latent compartment. The second partial derivatives of f are given by the following:

$$\frac{\partial^2 f_1}{\partial x_2^2} = -2\beta c,$$

$$\frac{\partial^2 f_1}{\partial x_1 \partial x_2} = \frac{\partial^2 f_1}{\partial x_2 \partial x_1} = -\beta c - \chi c,$$

$$\frac{\partial^2 f_1}{\partial x_4 \partial x_2} = \frac{\partial^2 f_1}{\partial x_2 \partial x_4} = \alpha c - \beta c,$$

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \chi c.$$

Thus

$$a = -\beta c v_1 \omega_2 \left(\omega_1 + \omega_2 + \left(1 - \frac{\alpha c}{\beta c}\right)\omega_4 + \omega_1 \omega_2 \chi c (v_2 - v_1)\right).$$

We can notice here that the changes that we made in the system by adding another force of infection to the infective class and minus it from the latent class do not affect $Df(x_0)$ and therefore, the expression we have for v and ω remain the same. This implies $v_2 - v_1 > 0$ and therefore $a > 0$ if and only if

$$\chi c > \chi^c c := \frac{\beta c v_1 \omega_2 \left(\omega_1 + \omega_2 + (1 + \frac{\alpha}{\beta})\omega_4\right)}{\omega_2 \omega_1 (v_2 - v_1)}$$

Thus,
if $\chi c > \chi^c c$ or $\chi c < \chi^c c$ then there is a branch of endemic equilibrium points (EEP) that exists for values of $R_0 < 1$ or $R_0 > 1$ respectively. These EEPs are stable if $\chi c > \chi^c c$ and unstable if $\chi c < \chi^c c$. □

Remark 4.8.3. We demonstrate by this example that accounting for exogenous reinfection may lead to backward bifurcation. This happens when $\chi c > \chi^c c$. This phenomena of backward bifurcation makes it more difficult to eradicate a disease when introduced into a purely susceptible population. Infact, to achieve this, any control measure will have to bring R_0 below a critical value and the critical value is beow 1 for the disease to die out of the population.

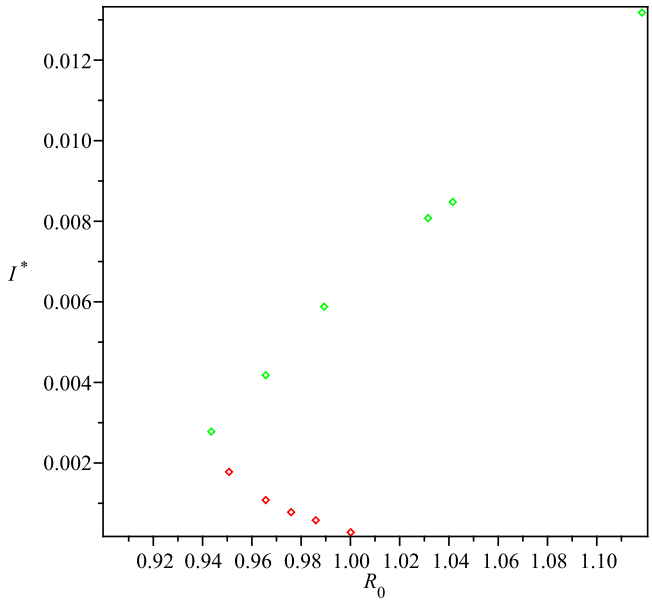


Figure 4.2: Plot I^* vs R_0

4.9 Numerical simulations

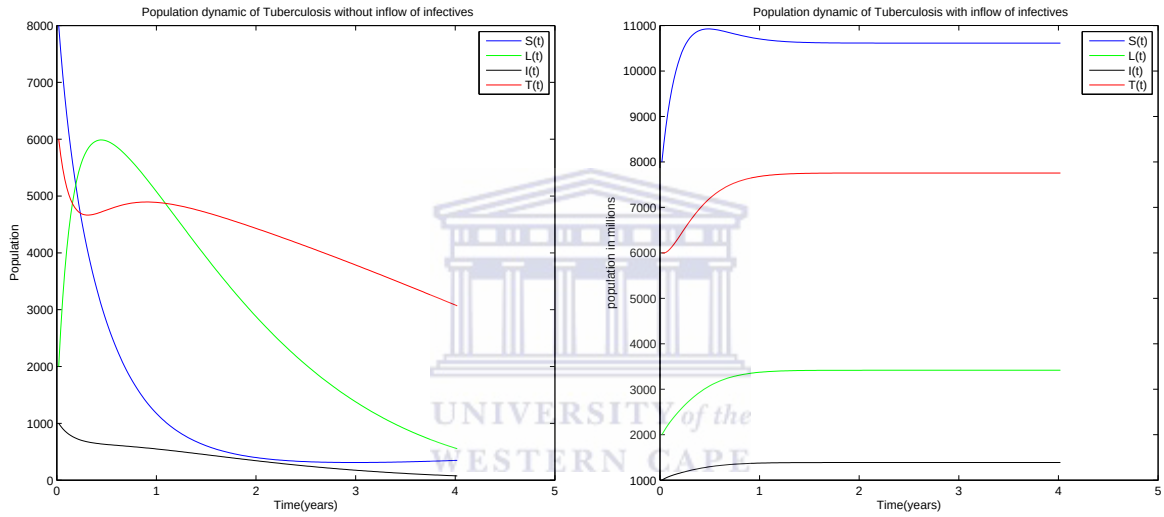
In this section, we illustrate the analytical results in this work by carrying out numerical simulations of the model using a set of parameter values given in Table 4.2 Those which are not in the table are Λ_0, Λ_1 and Λ_0, related to parameter values that are in line with literature on TB and relatively in accordance to the report of WHO as stated above. We choose:

$$\Lambda_0 = 2000, \Lambda_1 = 500, \Lambda_0 = 500.$$

The model system 4.2 is simulated using ODE solvers coded in Matlab programming language. We simulate both with inflow of infectives and without inflow of infectives of TB dynamics, as well as the effect of varying each intervention parameter on the number of latent and infected populations. All figures are plotted using the parameter values presented in Table 4.2 and the following initial conditions;
$S(0) = 8000, L(0) = 2000, I(0) = 1000, T(0) = 600.$

The results of numerical simulation are displayed graphically. In Fig.4.3(a) the variation of population with time is shown for different classes without inflow of infectives. It is seen that in the absence of infective inflow into the population, the susceptible population decreases continuously which results in an increase in latent population first and then it decreases as all latent will either go to infective or be treated and the infective population decreases. Fig.4.3(b) shows the variation of population in all classes with inflow of infectives. It is found that susceptible population first increases with time. It is expected that due to inflow of immigrants into the population, susceptible population will balance the mortality in all classes, therefore, infection becomes more endemic and persist. In Figs.(4.13) (a) and (b), the variation of latent population and that of infective population is shown for different rates of inflow of infectives and the probabilities of infection per contacts with susceptible and treated. It is clear that when the latent patients do not have contact with infectives and the inflow of infectives is restricted, then the number of infectives decreases. Also, Fig. (4.13)(b) shows the variation of infective population with rate of inflow of infectives Λ_2, it is clear that if inflow of infected immigrants increases, the number of infectives increases which ultimately increases the prevalence of the disease. The effect of increasing the number of contacts with the infective population is shown in Fig.(4.14) and it is seen that if the number of contacts with infectives is higher the risk of infection increases. Thus, to reduce the spread of TB infection it is desired to keep the number of contact with the infectives at minimum by reducing the inflow of infectives and getting tested for TB. The rate at which patients in latent class proceed to infective class is plotted in Fig.(4.15)(a) and (b). It is found that with increase in k, the population in latent class decreases whereas that of infective class increases.

In the next chapter, we shall deal with the optimal control of the model 4.2



(a) (b)

Figure 4.3: Deterministic variation of population in different classes with and without the inflow of infectives.

Figure 4.4: Simulations of TB model showing various classes with and without inflow of infectives .

(a)

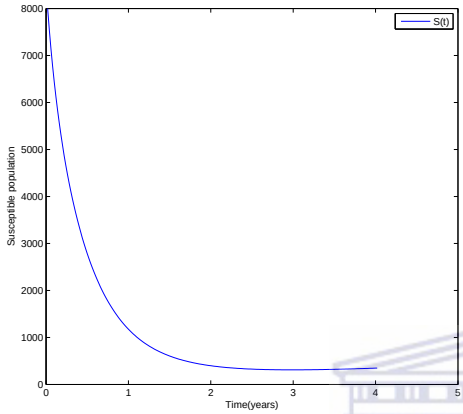


Figure 4.5: susceptibles class without infectives

(b)

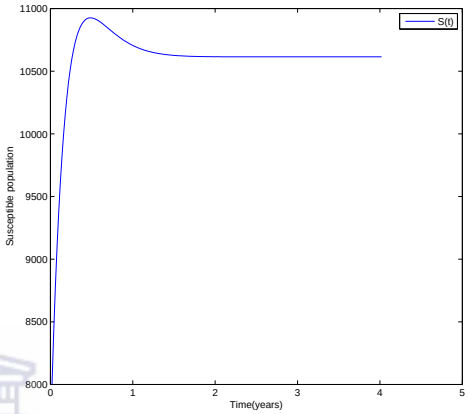


Figure 4.6: Susceptible class with infectives

(c)

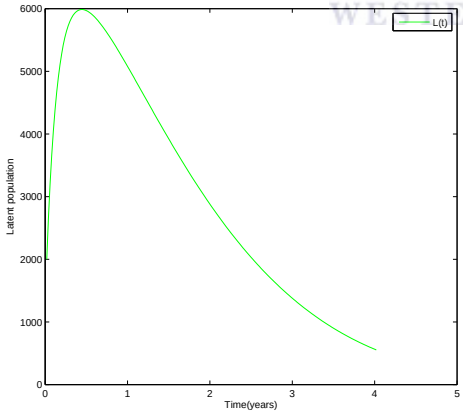


Figure 4.7: Latent class without infectives

(d)

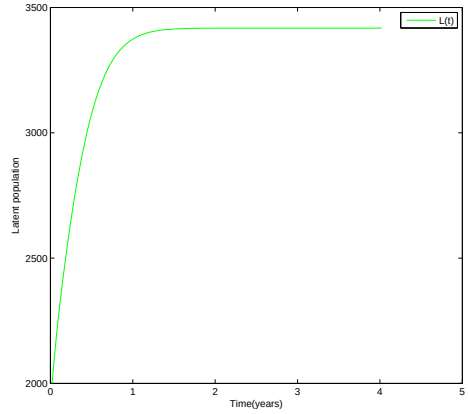


Figure 4.8: Latent class with infectives

(e)

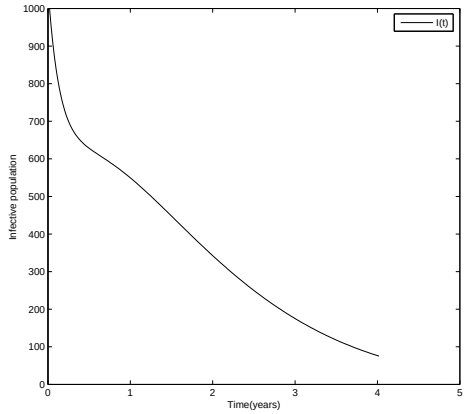


Figure 4.9: Infective class without a direct inflow of infectives

(f)

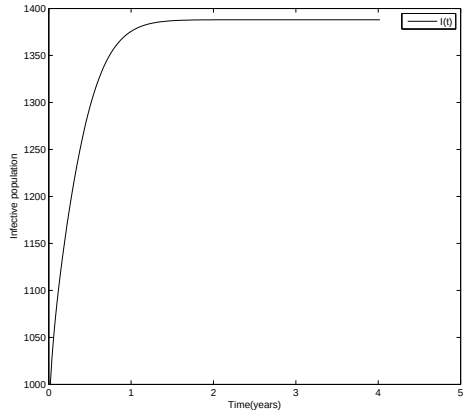


Figure 4.10: Infective class with a direct inflow of infectives

(g)

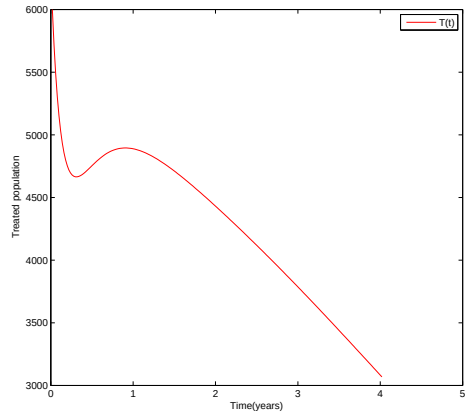


Figure 4.11: Treatment class without infectives

(h)

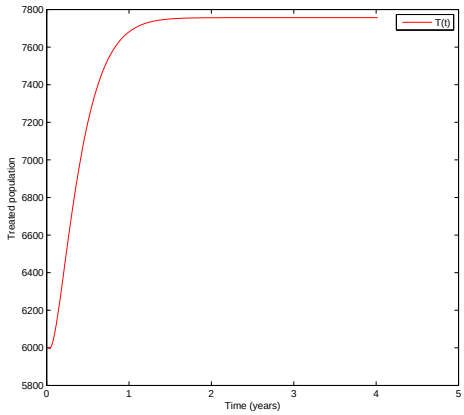
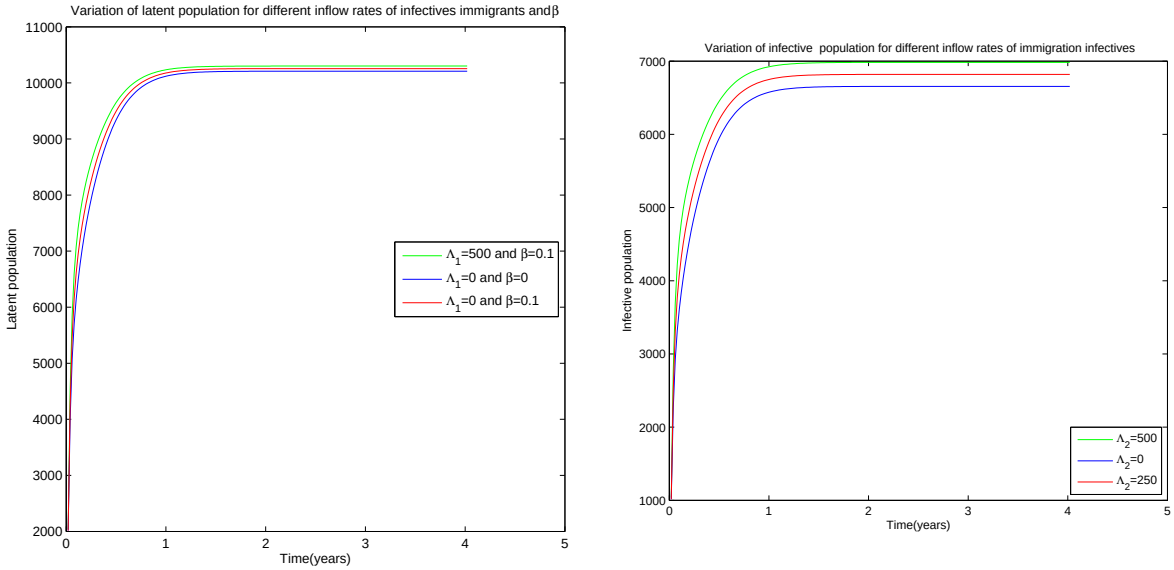


Figure 4.12: Treatment class with infectives



(a) (b)

Figure 4.13: Deterministic variation of latent population
(a) with diff. inflow rate of infectives and the prob. of infection per contacts in Latent class. (b) diff. inflow rate of infectives in infective class.

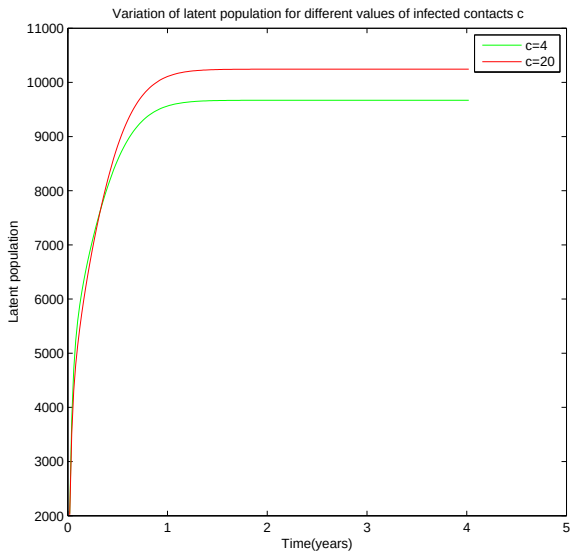
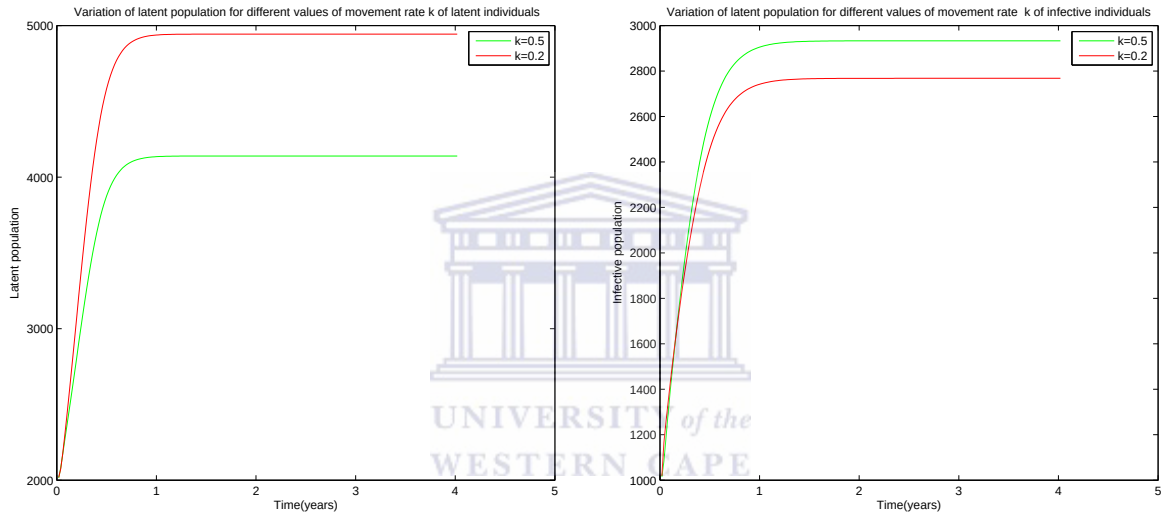


Figure 4.14: Deterministic variation of latent population for diff. values of c



(a) (b)

Figure 4.15: Deterministic variation of latent and infective population (a) diff. values of k in Latent class (b) diff. values of k in Infective class

Chapter 5

Optimal control problem

5.1 Introduction

Optimal control is a systematic mathematical framework for decision making in complex scenarios. The modelling of tuberculosis in this dissertation is a rational basis for policies designed to curb or control the spread of TB in South Africa. There are two major types of control strategies available to curtail the spread of tuberculosis. There are pharmaceutical interventions (drugs, vaccines) and non-pharmaceutical interventions such as quarantine or information and education campaigns. In this chapter we apply optimal control theory to determine an effective roll-out of treatment to control the spread of tuberculosis, using a model in which there is immigration with direct inflow of infectives.

We assume that rI individuals per time are removed from the infected class and added to the treated class. The mathematical system with controls is given by the nonlinear differential equations

$$\begin{aligned} \frac{dS}{dt} &= \Lambda_0 - \beta c\frac{SI}{N} - \mu S, \\ \frac{dL}{dt} &= \Lambda_1 + \beta c\frac{SI}{N} - (\mu + k)L + \alpha cT\frac{I}{N}, \end{aligned} \tag{5.1}$$

$$\begin{aligned}\frac{dI}{dt} &= \Lambda_2 + kL - (\mu + d + r(t))I, \\ \frac{dT}{dt} &= r(t)I - \alpha cT\frac{I}{N} - \mu T.\end{aligned}$$

5.2 Control problem and solution

Our optimal control problem amounts to minimizing the objective function below

$$J(r(.)) = \int_0^\tau \left[c_2 r^2(t) - S(t)\right] \, \mathrm{d}t. \tag{5.2}$$

The control $r(t)$ is the proportion of the infectives that is treated per unit time.

By $r^*(t)$ we denote our optimal treatment rate subject to the system of equations in model (5.1). We have four state variables $S(t), L(t), I(t)$ and $T(t)$ with appropriate initial conditions. In other words, we seek the optimal control $(r^*(t))$ such that

$$J(r^*(t)) = \min\left\{J(r(t)) : (r(t)) \in U\right\}, \tag{5.3}$$

where U is the set of admissible controls defined by

$$U = \{(r(t)) : 0 \leq r(t) \leq 1, t \in [0, \tau],$$

$$r \text{ is a Lebesque measurable function.}\}$$

Let $r_{\max}$ be the maximum attainable value for $r(t)$. The parameter c_2 is the relative weighting constant. The maximum $r_{\max}$ will depend on the amount of resources available to implement the control measure.

Our goal is to minimize $J(r(.))$ subject to the system in (5.1) of differential equations, together with the initial conditions [1]

$$S(0) = S_0 \geq 0, \qquad L(0) = L_0 \geq 0, \qquad I(0) = I_0 \geq 0, \qquad T(0) = T_0 \geq 0. \tag{5.4}$$

The Hamiltonian for this problem is as follows:

$$\begin{aligned} & H(t,S,L,I,T,\lambda_1,\lambda_2,\lambda_3,\lambda_4) \\ = \;& c_2 r^2(t) - S(t) \\ + \;& \lambda_1(t)\left[\Lambda_0 - \frac{\beta c S I}{N}(t) - \mu(t)S(t)\right] \\ + \;& \lambda_2(t)\left[\Lambda_1 + \frac{\beta c S I}{N}(t) - \mu(t) + k(t) + \frac{\alpha c T I}{N}(t)\right] \\ + \;& \lambda_3(t)\left[\Lambda_2 + k(t)L(t) - (\mu(t) + d(t) + r(t))I(t)\right] \\ + \;& \lambda_4(t)\left[r(t)I(t) - \frac{\alpha c T I}{N}(t) - \mu(t)T(t)\right]. \end{aligned} \tag{5.5}$$

Theorem 5.1 *There exists a solution to problem* (5.2)*. It satisfies the following system of differential equations*:

$$\begin{aligned} \dot{\lambda_1} &= 1 + \lambda_1\left(\frac{\beta c I}{N} + \mu\right) - \lambda_2\left(\frac{\beta c I}{N}\right), \\ \dot{\lambda_2} &= \lambda_2(\mu + k) - \lambda_3 k, \\ \dot{\lambda_3} &= \lambda_1\left(\frac{\beta c S}{N}\right) - \lambda_2\left(\frac{\beta c S}{N} + \frac{\alpha c T}{N}\right) + \lambda_3(\mu + d + r) - \lambda_4\left(r - \frac{\alpha c T}{N}\right), \\ \dot{\lambda_4} &= -\lambda_2\left(\frac{\alpha c I}{N}\right) + \lambda_4\left(\frac{\alpha c I}{N} + \mu\right), \end{aligned} \tag{5.6}$$

with transversality conditions:

$$\lambda_1(\tau) = \lambda_2(\tau) = \lambda_3(\tau) = \lambda_4(\tau) = 0.$$

The optimal treatment strategy is given by

$$r^*(t) = \min\left(1, \max\left(0, I^*(t)(\frac{\lambda_3^*(t) - \lambda_4^*(t)}{2c_2})\right)\right). \tag{5.7}$$

Proof. The existence of an optimal control can be proved since the Hamiltonian is convex with respect to $r(t)$. Partial derivatives of the Hamiltonian with respect to

different state variables were calculated in order to obtain the time derivatives $\dot{\lambda}_i$ of the costate variables. Due to $S(\tau)$, $L(\tau)$, $I(\tau)$ and $T(\tau)$ being free, the following transversality conditions hold [1]:

$$\lambda_1(\tau) = 0, \qquad \lambda_2(\tau) = 0, \qquad \lambda_3 = 0, \qquad \lambda_4 = 0. \tag{5.8}$$

The system of equations (5.5) in the theorem is derived from

$$\dot{\lambda_1}(t) = -\frac{\partial H^*}{\partial S}, \qquad \dot{\lambda_2}(t) = -\frac{\partial H^*}{\partial L}, \qquad \dot{\lambda_3}(t) = -\frac{\partial H^*}{\partial I}, \qquad \dot{\lambda_4}(t) = -\frac{\partial H^*}{\partial T}. \tag{5.9}$$

The final section of the proof, is to show how the control is formed, i.e., $r^*(t)$. The functions $r_i^*(t)$ must optimize H. By differentiating H with respect to r we obtain the optimality conditions that follows:

$$\frac{\partial H}{\partial r} = 2c_2 r - \lambda_3 I + \lambda_4 I = 0. \tag{5.10}$$

Therefore, we substitute $r(t) = r^*$. Then, we solve the optimal control pair (r^*) to obtain

$$r^* = I\left(\frac{\lambda_3 - \lambda_4}{2c_2}\right), \tag{5.11}$$

The introduction of bounds $0 \leq r(t) \leq r_{\max}$ on the control gives equ. (5.7). See [1] and [28]. □

5.3 Numerical results and discussion

In this section we study the system (5.1) in order to identify the dynamic behavior of the model numerically. The system in equation (5.1) is integrated by fourth order Runge-kutta method using the parameter values provided in Table 4.2, our estimated values were done relatively to suit the World Health Organisation report on Tuberculosis in South Africa in 2012, [31].

Our deterministic model were examined critically and we study the effects of the control (r) on the Infectious classes for the following values of Λ_1 and Λ_2.

$$(\Lambda_1 = 500, \Lambda_2 = 500)\,(\Lambda_1 = 1000, \Lambda_2 = 1000)\,.$$

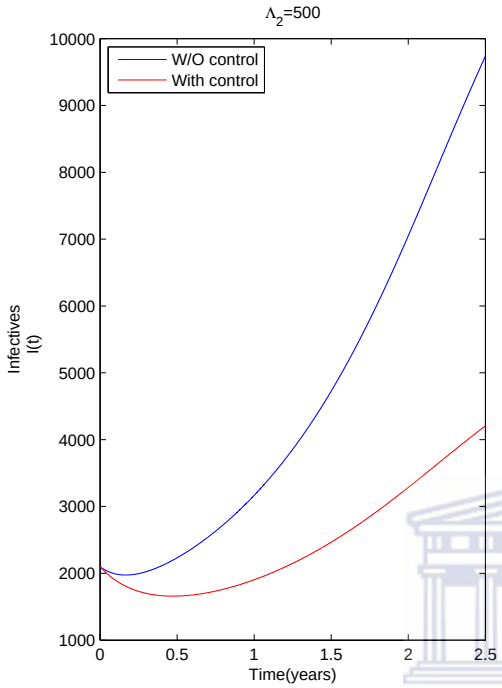
For the construction of Fig. 5.1, the initial conditions are:

$$S(0) = 5000, L(0) = 400, I(0) = 2010, T(0) = 1000.$$

Figures (c) and (d) represent the number of infected individuals (I) with and without controls for different value of Λ_2. When r is kept fixed, at the value $r = 1$, (blue and yellow curves), a sharp increase in the number of infected individuals has been noticed. In presence of the optimal controls, the number I (red curve) decreases. Figure (f) gives the optimal control pair (r^*). It is worth mentioning that if r is fixed, then there is no control. Finally, the table 5.2 below gives a comparison of the number of infected individuals at the final time $2\frac{1}{2}$(years) in both cases with or without controls.

Figure 5.1: Simulations of TB model showing the effect of Optimal control and various classes.

(c)



(d)

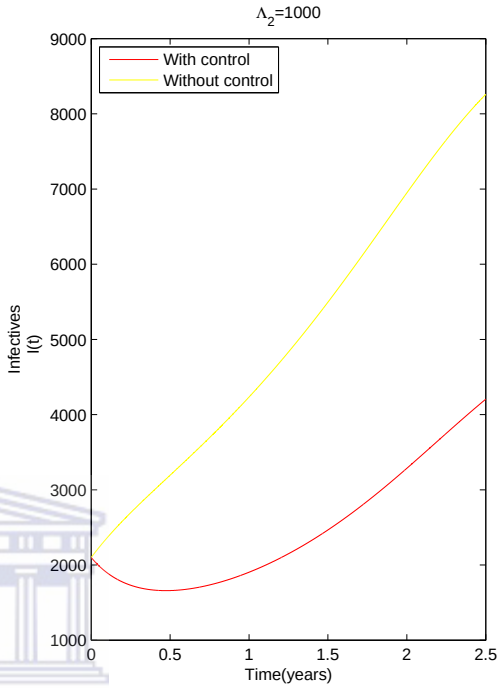
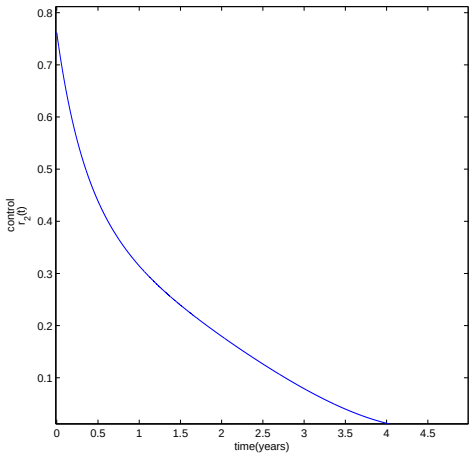


Figure 5.2: The function I with and without controls when $\Lambda_2 = 500$

Figure 5.3: The function I with and without controls when $\Lambda_2 = 1000$

(f)



Λ_2	Infectious individuals	
	W/o controls	**With controls**
500	9800	**4100**
1000	8200	**4200**

The number of infected individuals at the final time

Chapter 6

A Stochastic Tuberculosis Model

6.1 Introduction

Stochastic differential equations (SDE) arise from the need to model chance variations. They are used when known heterogeneities are important as in small or isolated populations. Stochastic models have several advantages and can provide an additional degree of realism compared to their deterministic counterparts [52]. They, however, can be laborious to set up and need many simulations to yield useful predictions. In general, stochastic epidemic models can literally be formulated in three different ways: Discrete time Markov chain (DTMC) models, Continuous time Markov chain (CTMC) models and Stochastic differential equation (SDE) model. Construction of these stochastic methods differ due to the underlying assumptions [2]. SDE models are based on a diffusion process, where both the time and the state variables are continuous. In our model we will use the SDE approach. It has been applied in various papers, such as [36] by Lahrouz et al., [21] by Dalal et al., [25] by Ding et al. and [63] by Yang et al. The paper [35] of Jovanovic and Krstic presents a stochastic model of vector-borne diseases. There are models in which a stochastic perturbation has been inserted into each of the differential equations. Examples of these models are found in [39] by Lu, [65], [33] and [35]. We also have found that there are instances where stochastic perturbation are introduced in such a way that the

total population size is still a deterministic function of time and this is what we do in our model. Such models are found in [30] by Gray et al., [36] by Lahrouz et al. and [58] by Tornatore et al. We note that for systems of stochastic differential equations, different versions of stability are defined and studied in the literature. We refer to the book [41] of Mao and several papers, for instance, [65], [33], [30], [36] and [58]. One of the most important differences between the stochastic and deterministic epidemic models is their asymptotic dynamics.

6.2 Stochastic model

We assume $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq t_0}, \mathbb{P})$ to be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\geq t_0}$. Let $W(t)$ be a 3-dimensional Wiener process defined on this probability space. We assume that the three coordinates $W_1(t), W_2(t)$, and $W_3(t)$ are mutually independent.
We introduce stochastic perturbation into the model (4.2) and we obtain the following system of stochastic differential equations:

$$\begin{aligned} dS &= \left[\Lambda_0 - \beta c\frac{SI}{N} - \mu S\right] dt, \\ dL &= \left[\Lambda_1 + \beta c\frac{SI}{N} - \mu_1 L + \alpha c\frac{IT}{N}\right] dt + \sigma_1 L dW_1, \\ dI &= [\Lambda_2 + kL - \mu_2 I]\, dt + \sigma_2 I dW_2, \\ dT &= \left[rI - \alpha c\frac{IT}{N} - \mu T\right] dt + \sigma_3 T dW_3. \end{aligned} \tag{6.1}$$

We note that if $\Lambda_1 = 0$ and $\Lambda_2 = 0$, then the disease free state $E^* = (S^*, L^*, I^*, T^*) = (\frac{\Lambda_0}{\mu}, 0, 0, 0)$ is an equilibrium point.
We note that the coefficients are locally Lipschitz in the sense of [41]. Consequently the system has a unique local solution for any feasible initial state. In order to study stability of E^*, we assume that there are global solutions which are almost surely non-negative.

6.3 Stability of the SDE model for Tuberculosis

In this section, we proceed to study the stability. The theorem below can be interpreted as saying that, at least, the stochastic perturbations do not destabilize the system. Let us define the invariant β_* and R_* as follows:

$$\beta_* = \max\{\beta, \alpha\},$$

and

$$R_* = \frac{k\beta_* c}{\mu_1\mu_2},$$

we recall that

$$\mu_1 = \mu + k, \mu_2 = \mu + d + r.$$

Theorem 6.3.1. *If $R_* < 1$, $\Lambda_1 = 0$ and $\Lambda_2 = 0$, then disease free equilibrium is a.s exponentially stable.*

Proof. We can choose $\epsilon_1 > 0$ and $\epsilon_2 > 0$ sufficiently small such that the following conditions hold.

$$\frac{\mu_1\mu_2}{k}(R_* - 1) + \epsilon_1\mu_2 < 0, \tag{6.2}$$

and

$$\frac{\mu_1\mu_2}{k}(R_* - 1) + \epsilon_1\mu_2 + \epsilon_2 r < 0. \tag{6.3}$$

Now let

$$A = \frac{\mu_1}{k} - \epsilon_1.$$

We define a function $V = L + AI + \epsilon_2 T$ and we note that $V(L(t), I(t), T(t))$ is positive. Thus we can define

$$Z(t) = \ln V(t).$$

We now calculate the differential, dZ:

$$\begin{aligned} dZ &= \frac{1}{V}dL + \frac{A}{V}dI + \frac{\epsilon_2}{V}dT - \frac{1}{2}\left[\frac{1}{V^2}dL^2 + \frac{A^2}{V^2}dI^2 + \frac{{\epsilon_2}^2}{V^2}dT^2\right] \\ &= \left(\frac{\beta\, cSI}{N} - \mu_1 L + \frac{\alpha\, cIT}{N}\right)V^{-1}dt \\ &+ \frac{A\,(kL - \mu_2 I)}{V}dt + \epsilon_2\left(rI - \frac{\alpha\, cIT}{N} - \mu\, T\right)V^{-1}dt \\ &+ \left[\sigma_1 L dW_1 + \sigma_2 I dW_2 + \sigma_3 T dW_3\right]V^{-1} \\ &- \frac{1}{2}\left[\left({v_1}^2 + {v_2}^2 + {v_3}^2\right)\right]dt, \end{aligned}$$

where ${v_1}^2 = \frac{{\sigma_1}^2 L^2}{V^2}$, ${v_2}^2 = \frac{{\sigma_2}^2 I^2}{V^2}$, and ${v_3}^2 = \frac{{\sigma_3}^2 T^2}{V^2}$.

Then,

$$dZ = \mathcal{L}V\ dt + \left[\sigma_1 L dW_1 + \sigma_2 I dW_2 + \sigma_3 T dW_3\right]V^{-1},$$

where

$$\begin{aligned} \mathcal{L}V &= \left(\frac{\beta\, cSI}{N} - \mu_1 L + \frac{\alpha\, cIT}{N}\right)V^{-1} \\ &+ \frac{A\,(kL - \mu_2 I)}{V} + \epsilon_2\left(rI - \frac{\alpha\, cIT}{N} - \mu\, T\right)V^{-1} \\ &- \frac{1}{2}\left[\left({v_1}^2 + {v_2}^2 + {v_3}^2\right)\right]. \end{aligned}$$

Therefore:

$$Z = Z_0 + \int_0^t \mathcal{L}V\ dt + \sum_{i=1}^{3} G_i(t) \tag{6.4}$$

where each $G_i(t)$ is a martingale defined as

$$G_1(t) = \int_0^t \frac{(\sigma_1 L)\ dW_1}{V}, \qquad G_2(t) = \int_0^t \frac{(\sigma_2 I)\ dW_2}{V}, \qquad G_3(t) = \int_0^t \frac{(\sigma_3 T)\ dW_3}{V}.$$

Then

$$\lim_{t\to\infty}\frac{Z}{t} = \lim_{t\to\infty}\frac{Z_0}{t} + \lim_{t\to\infty}\frac{1}{t}\int_0^t \mathcal{L}V\ dt + \lim_{t\to\infty}\frac{1}{t}\sum_{i=1}^{3} G_i(t).$$

Regarding the quadratic variations of the stochastic integral $G_i(t)$ we have

$$\int_0^t \frac{(\sigma_1 L)^2}{V^2}\, ds \leq \sigma_1^2 t, \qquad \int_0^t \frac{(\sigma_2 I)^2}{V^2}\, ds \leq \sigma_2^2 t, \qquad \int_0^t \frac{(\sigma_3 T)^2}{V^2}\, ds \leq \sigma_3^2 t.$$

By the strong law of large numbers for martingales [41], we therefore have

$$\limsup_{t\to\infty} \frac{1}{t} \sum_{i=1}^{3} G_i(t) = 0 \quad (a.s).$$

It finally follows from (6.4) by dividing t on both sides and then letting $t \to \infty$ that

$$\limsup_{t\to\infty} \frac{\ln Z(t)}{t} \leq \limsup_{t\to\infty} \frac{1}{t} \int_0^t \mathcal{L}V\, dt \quad (a.s).$$

We note that

$$\begin{aligned} \mathcal{L}V &\leq \left(\frac{\beta\, cSI}{N} - \mu_1 L + \frac{\alpha\, cIT}{N}\right) V^{-1} \\ &+ \frac{A\,(kL - \mu_2 I)}{V} + \epsilon_2 \left(rI - \frac{\alpha\, cIT}{N} - \mu\, T\right) V^{-1} \\ &- \frac{1}{2}\left[\left({v_1}^2 + {v_2}^2 + {v_3}^2\right)\right]. \end{aligned} \tag{6.5}$$

Now, it follows as in (6.5) that

$$\begin{aligned} \mathcal{L}V &< \left(\frac{\beta\, cSI}{N} - \mu_1 L + \frac{\alpha\, cIT}{N}\right) V^{-1} \\ &+ \frac{A\,(kL - \mu_2 I)}{V} + \epsilon_2 \left(rI - \frac{\alpha\, cIT}{N} - \mu\, T\right) V^{-1} \\ &- \frac{1}{2}\left[\left({v_1}^2 + {v_2}^2 + {v_3}^2\right)\right], \end{aligned}$$

and in fact

$$\limsup_{t\to\infty} \frac{1}{t} \int_0^t \mathcal{L}\mathcal{V} < 0.$$

Therefore,

$$\limsup_{t\to\infty} \frac{\ln Z(t)}{t} < 0.$$

This finally proves the $(a.s.)$ exponential stability. □

Remark 6.3.2. Theorem (6.3.1) implies that $Z(t)$ goes extinct exponentially $(a.s.)$ whenever $R_* < 1$ with the consequence that T-class also goes to extinction $(a.s.)$

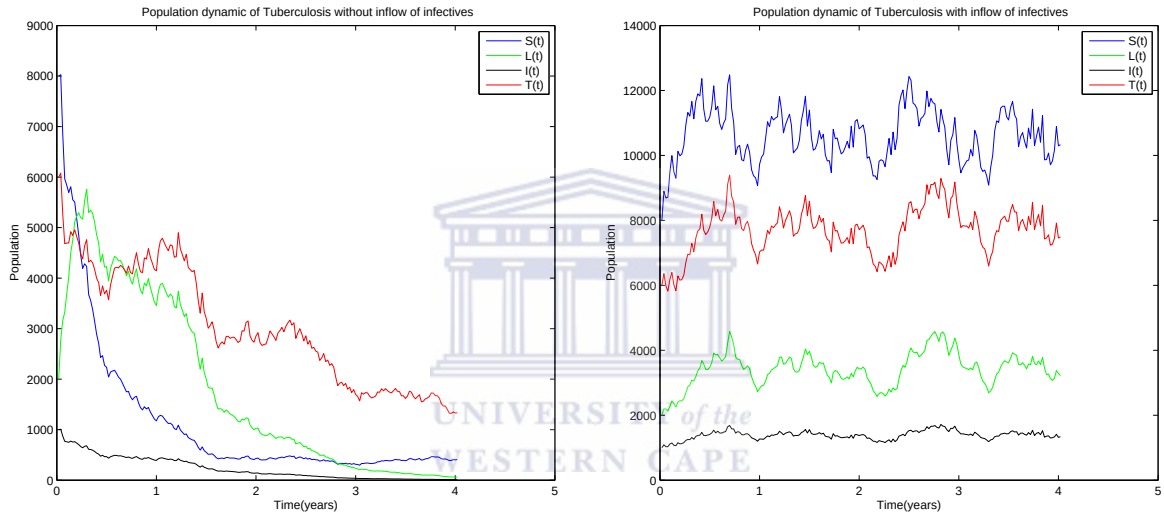
6.4 Simulations

In this section we simulate the SDE model in (6.1) numerically for the same parameters in Table 4.2 except σ. In all simulations we use a single value for all the σ_i, i.e., $\sigma_1 = \sigma_2 = \sigma_3 = \sigma$, with initial conditions:

$$S(0) = 5000, L(0) = 400, I(0) = 2010, T(0) = 1000.$$

Figs.(6.1)(a) and (b) show the variation of $S(t), L(t), I(t), T(t)$ within time, that is the inflow of infectives and without the inflow of infectives. As we know that the population dynamics is inevitably subjected to environmental noise. So, it is important to examine the inclusion of stochastic effects into deterministic models as explained in the introduction. We observe that there is excellent agreement with the solutions to the corresponding deterministic case in Fig. 6.2(a,c,d,e,f). In contrast to the deterministic solutions, the stochastic solutions do not converge to the equilibria in Fig.6.2(b,g,h) of the deterministic System (4.2). However, Theorems (4.6.1) and (6.3.1) relate the behavior of the stochastic system to the asymptotic deterministic behavior. Indeed, if the intensities of noise are sufficiently small, the stochastic solution can be expected to remain close to the inflow of infectives or without the inflow of infectives. However, in the case when $R_0 \leq 1$ and there is no inflow of infected individuals, that is $\Lambda_1 = \Lambda_2 = 0$, it seems likely that the number of infectives will tend to 0 almost surely as t goes to infinity. We hope to study this statement for future investigation.

In summary, the numerical simulations in this study show that adding noise to deterministic model affects the stability and able to change the dynamics of the model system from stable situation to unstable one, which is in line with what was done in [37]. Moreover, as illustrated in Figs. (6.1)(6.3), (6.4) and (6.5), the strong noise may give a divergence between stochastic and deterministic behaviors.

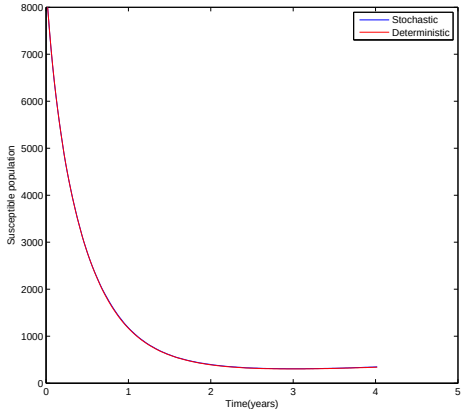


(a) (b)

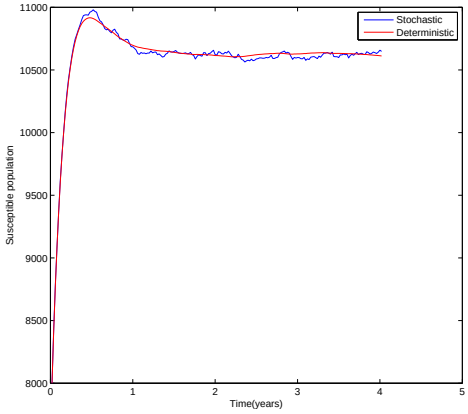
Figure 6.1: Stochastic variation of population in different classes with and without the inflow of infectives with $\sigma = 0.78$

Figure 6.2: Simulations of TB model showing the various classes with $\sigma = 0.023$.

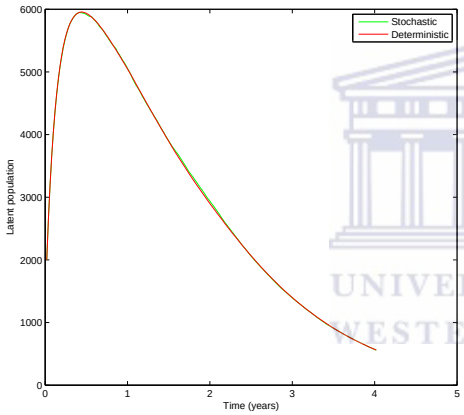
(a)



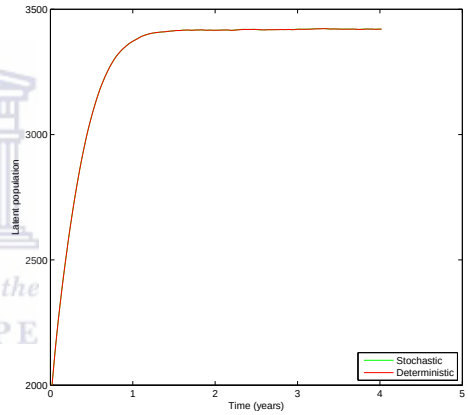
(b)



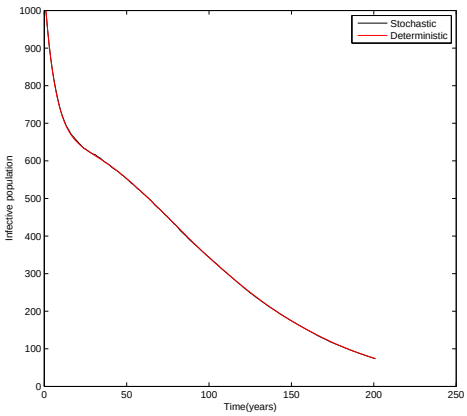
(c)



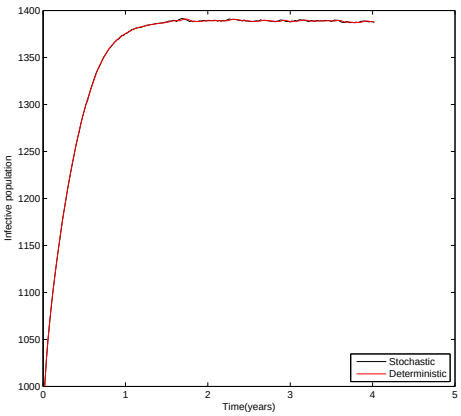
(d)



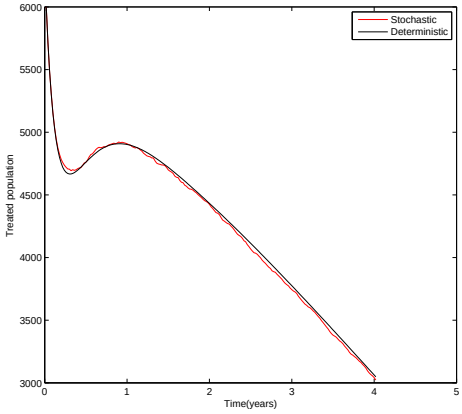
(e)



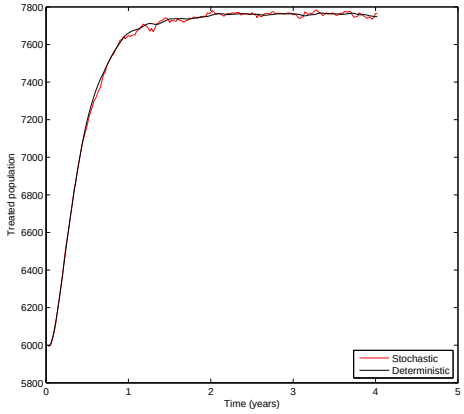
(f)

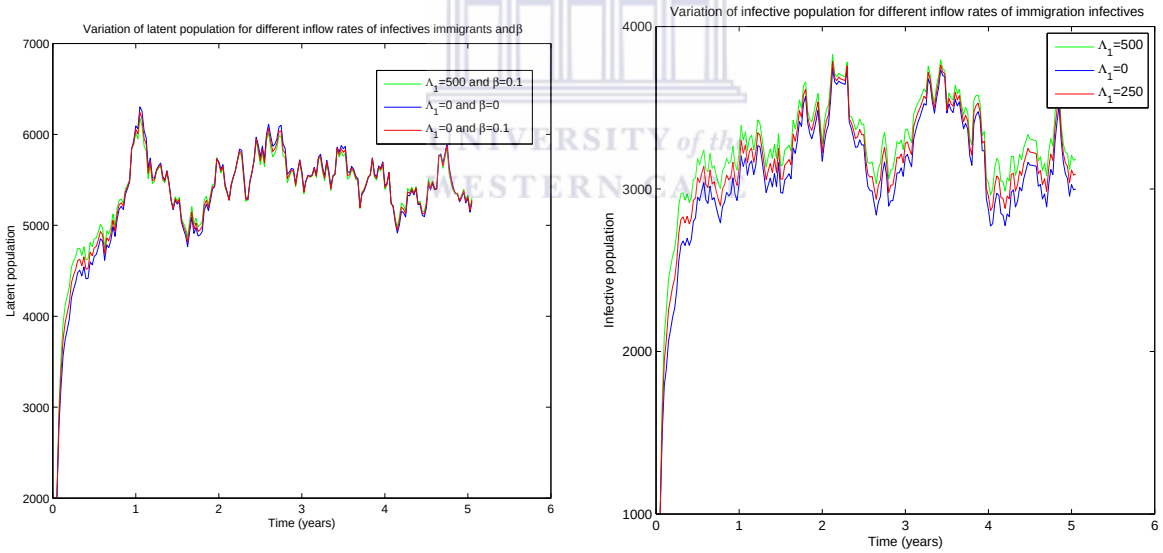


(g)



(h)





(a)

(b)

Figure 6.3: Stochastic variation of latent and Infective population with $\sigma = 0.78$ (a) inflow rates of infectives and β in latent class (b) inflow rates of infectives in infective class.

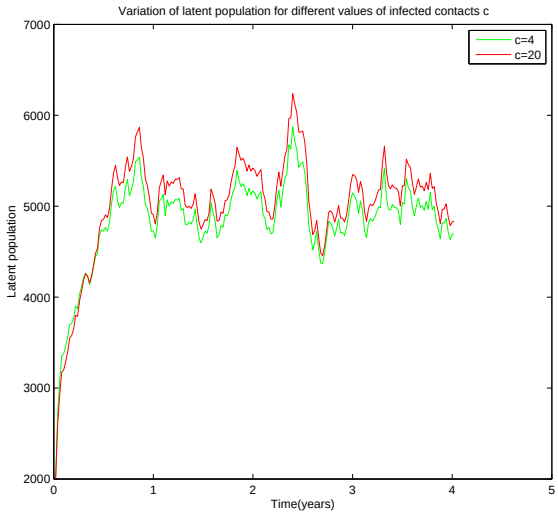
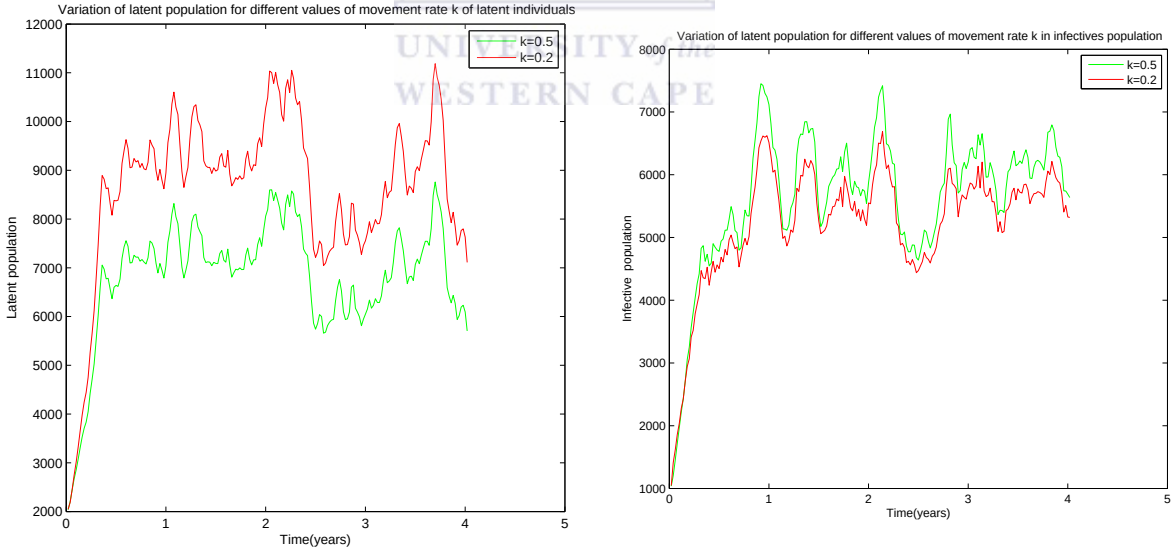


Figure 6.4: Diff. values for contact c latent infected with $\sigma = 0.78$



(a) (b)

Figure 6.5: Stochastic variation of different values of k in latent and infective class with $\sigma = 0.78$

Chapter 7

Conclusion

7.1 Introduction

In this study, we have presented and analysed a tuberculosis model with inflow of infectives in a population. It is assumed that susceptibles become infected via contacts with infectives and all infectives ultimately develop TB.

Qualitative analysis of the model was carried out for when $\Lambda_1 = \Lambda_2 = 0$ and some inferences have been drawn regarding the spread of TB by way of establishing local and global stability results. With the help of the next generation method and theorem by Van den Driessche and Wat, it was found that whenever the basic reproduction number is less than one, that is, $R_0 < 1$, the disease free equilibrium point is locally asymptotically stable and unstable whenever the basic reproduction number is greater than one, that is, $R_0 > 1$. The existence and stability of the endemic point was determined by using Routh-Hurwitz criteria. It was found that the TB model with inflow of infectives exhibits a backward bifurcation at $R_0 = 1$: In this case, the disease-free equilibrium co-exists with the endemic equilibrium that is locally asymptotically stable when $R_0 < 1$: The stability nature of solutions will determine whether or not the disease will disappear from the population. Numerical simulations of the model are carried out in order to look into the

TB dynamics in usage of treatment.

We propose an effective strategy to reduce and control the number of infected individuals when there is a constant inflow of infective immigrants. The optimal control theory has been applied in the context of a TB model with inflow of infectives; and that includes a control representing the effort that reduces the contact rate between individuals, and a therapeutic treatment. By using the Pontryagin's maximum principle, the explicit expression of the optimal control was obtained. Simulation results indicate that despite the presence of a constant inflow of infective immigrants, the proposed control strategy of a complete treatment can help suppress the spread of TB and is effective in reducing the number of patients.

We looked also at a stochastic model describing the population dynamics of a TB epidemic. Our focus is on a stochastic differential equation TB model without inflow of infectives. In our model, we assume that the stochastic perturbation is a white noise type that is directly proportional to $L(t), I(t), T(t)$ and is influenced on the derivatives $\frac{dL(t)}{dt}$, $\frac{dI(t)}{dt}$, and $\frac{dT(t)}{dt}$, respectively. This is a well-established way of introducing stochastic environmental noise into biologically realistic population dynamic models that have been used in various journals. Our study have provided analytic proof of almost sure exponential stability of the solution to the SDE model (6.1) in the case $R_0 < 1$, while there is no inflow other than into the S-class.

7.2 Conclusion

Based on the results of this work, we conclude that unchecked inflow of infectives to a country like South Africa is a silent killer if it is not dealt with. We conclude that treatment of sensitive TB results in a reduction of TB in South Africa as most TB cases come from failure to properly administer TB treatments and the rate at which infective immigrants migrate into the country. On the other hand, diagnosis, health education of infectives with sensitive TB and proper policy on infective immigrants are more important

in the reduction of new TB cases because they lead to appropriate treatment. However, there is need to treat, diagnose and educate more people if we are to ever dream of completely eliminating TB in South Africa. Also, the treatment rate of infected individuals should be correlated to the number of diagnosed individuals to ensure that all TB cases are not left unattended.

Despite the successful completion of this study, there were challenges met along the way. For instance, estimating the enhancement of infective immigrant parameters was a big challenge on how to determine and locate the degree of normal rate of infectives inflow into South Africa. However, the results are reasonably applicable to the South African context.

7.3 Future Work

As tuberculosis continues to claim more lives, it is imperative to have comprehensive researches done in order to explore possible new control strategies of the infection as well as assessing the impact of the existing control strategies. Based on the model of this study, it is proposed that future work should consider;

- Carrying out a cost-effectiveness analysis of the control strategies of TB in the model.
- Expanding the model to incorporate vaccination of susceptible population, immigrants and newborns, thus assess its role on the dynamics of TB.
- An investigation on the efficacy of TB treatments and up-take in educational programs.
- Usage of real data for the inflow of infectives into the country can be considered.
- It will also be good to Mathematically show the extent to which the global dynamics of the stochastic version of our model is governed by its reproduction number R_0.
- Extinction, persistence [6, 13], ergodic property, herd immunity [24] and the effects of different types of noise can also be considered in future.

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