RABIU ALIYU ABDULKADIR ANALYSIS OF TUBERCULOSIS MODEL WITH OPTIMAL AND ADAPTIVE CONTROLS NEU 2020

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A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES OF NEAR EAST UNIVERSITY

By
RABIU ALIYU ABDULKADIR

In Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy in Electrical and Electronic Engineering

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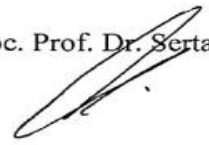
Assoc. Prof. Dr. Sertan Serte 	Committee Chairman, Department of Electrical and Electronic Engineering, NEU
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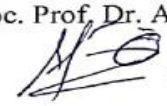
Assoc. Prof. Dr. Ali Özypici 	Department of Mathematics, CIU
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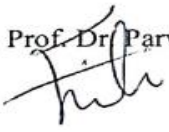
Assist. Prof. Dr. Parvaneh Esmaili 	Supervisor, Department of Electrical and Electronic Engineering, NEU

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To my parents…

ABSTRACT

Designing appropriate control intervention programs for handling of infectious disease such as tuberculosis (TB) involves elongated engagement with complex and challenging tasks. Several researches used mathematical model and control system theory as a valuable tool in studying the infectious disease dynamics and control. TB despite being a curable and preventable disease has become the world's leading infectious killer with an estimated total of 1.5 million deaths per annum. Although considerable progress has been made in developing a theoretical structure for studying TB's dynamics and control strategies, many challenging and critical open questions remain. Models that integrate the role of public awareness and isolation on controlling TB are rare. This thesis explores the conceptual use of optimal and adaptive control theory for the analysis of the TB dynamical model. The study looked at three different scenarios.

In the first scenario, a novel model of TB is analyzed using saturated incidence rate. Global asymptotic stability of the equilibria is established by a threshold quantity; the reproduction number (R_0) and proved using Lyapunov theory. Optimal control theory is applied to the model to demonstrate the use of control strategies in managing the disease. Two time-dependent control functions are employed to minimize infectious populations. The significance of the public awareness (measured by δ), and the optimal control functions, are illustrated numerically.

The second instance integrates three time-dependent control functions into a TB dynamical model, to find an optimal control strategy that minimizes the population of exposed and infected people and also the cost of executing the control actions. The necessary conditions for achieving the optimal controls are derived and solved numerically using Pontryagin's principle. Besides, an analysis of cost-effectiveness is carried out using an incremental cost-effectiveness ratio (ICER). The findings showed that a program of disease control incorporating vaccination, case holding, and case finding control measures would effectively curtail TB prevalence.

In the design of the optimal control approach, system parameters are assumed to be prior known and accurate. However, if the system contains uncertain parameters, the conventional control

techniques will not provide the desired results. Hence, in the third scenario, a robust nonlinear adaptive sliding mode control (ASMC) strategy is applied to the TB model considering parameter uncertainties. The control aims to decrease the population of individuals that are exposed and infected to zero by tracking a predefined reference trajectory. Adaption law is defined to update the parameter values to ensure the robustness of the control system against uncertainties. The stability of the closed-loop system is proved using the Lyapunov Function Theory, and the result is validated through numerical simulations.

The study identifies alternative solutions in finding practically useful optimal and adaptive control strategies and illustrates the essential applications of open-loop and closed-loop control systems. The work highlights a new methodology to inform realistic approaches towards realizing the United Nations (UN) 2030 plan for eradicating TB disease.

Keywords: Epidemiology; optimal control; adaptive control; sliding mode control; cost-effectiveness analysis; Lyapunov stability

ÖZET

Tüberküloz (TB) gibi bulaşıcı hastalıkların tedavisi için uygun kontrol müdahale programlarının tasarlanması, karmaşık ve zorlu görevlerle uzun süreli katılımı içerir. Birçok araştırma, bulaşıcı hastalık dinamikleri ve kontrolünü incelemek için matematiksel model ve kontrol sistemi analizini değerli bir araç olarak kullanmıştır. Tedavi edilebilir ve önlenebilir bir hastalık olmasına rağmen TB, yılda yaklaşık 1.5 milyon ölümle dünyanın önde gelen bulaşıcı katili haline gelmiştir. Her ne kadar TB'nin dinamiklerini ve kontrol stratejilerini incelemek için teorik bir yapı geliştirilmesinde kayda değer ilerleme kaydedilmiş olsa da, birçok zorlu ve eleştirel açık soru halen devam etmektedir. TB'nin kontrolünde kamuoyu bilinci ve izolasyonunun rolünü birleştiren modeller nadirdir. Bu tez, TB dinamik modelinin analizi için optimal ve uyarlanabilir kontrol teorisinin kavramsal kullanımını araştırmaktadır. Çalışma üç farklı senaryoya almiştir.

İlk senaryoda, yeni bir TB modeli doymuş olay oranı kullanılarak analiz edilir. Dengenin küresel asimptotik kararlılığı bir eşik miktarıyla belirlenir; üreme sayısı (R_0) ve Lyapunov teorisi kullanılarak kanıtlanmıştır. Hastalığın yönetiminde kontrol stratejilerinin kullanımını göstermek için modele optimal kontrol teorisi uygulanır. Enfeksiyöz popülasyonları en aza indirmek için iki zamana bağlı kontrol fonksiyonu kullanılır. Kamuoyu bilincinin önemi (δ le ölçülür) ve optimal kontrol fonksiyonları sayısal olarak gösterilmiştir.

İkinci örnek, maruz kalan ve enfekte kişilerin popülasyonunu en aza indiren ve aynı zamanda kontrol eylemlerini yürütmenin maliyetini en aza indiren optimal bir kontrol stratejisi bulmak için üç zamana bağlı kontrol fonksiyonlari bir TB dinamik modeline entegre eder. Optimal kontrollere ulaşmak için gerekli koşullar Pontryagin prensibi kullanılarak sayısal olarak elde edilir ve çözülür. Ayrıca, maliyet-etkinlik analizi, artımlı maliyet-etkinlik oranı (ICER) kullanılarak gerçekleştirilir. Bulgular, aşılama, vaka tutma ve vaka bulma kontrol önlemlerini içeren bir hastalık kontrol programının TB yayginlik etkili bir şekilde azaltacağını göstermiştir. Optimal kontrol yaklaşımının tasarımında, sistem parametrelerinin önceden bilindiği ve doğru olduğu varsayılmaktadır. Bununla birlikte, sistem belirsiz parametreler içeriyorsa, geleneksel kontrol teknikleri istenen sonuçları vermeyecektir. Bu nedenle, üçüncü senaryoda, parametre

belirsizlikleri göz önünde bulundurularak TB modeline güçlü bir doğrusal olmayan adaptif kayma modu kontrol (ASMC) stratejisi uygulanır. Kontrol, önceden tanımlanmış bir referans yörüngeyi takip ederek sıfıra maruz kalan ve sıfıra bulaşan bireylerin popülasyonunu azaltmayı amaçlamaktadır. Uyum yasası, kontrol sisteminin belirsizliklere karşı sağlamlığını sağlamak için parametre değerlerini güncellemek üzere tanımlanmıştır. Kapalı döngü sisteminin kararlılığı Lyapunov Fonksiyon Teorisi kullanılarak kanıtlanmıştır ve sonuç sayısal simülasyonlarla doğrulanmıştır.

Çalışma, pratik olarak kullanışlı optimal ve uyarlanabilir kontrol stratejileri bulmak için alternatif çözümler tanımlamakta ve açık-döngü ve kapalı-döngü kontrol sistemlerinin temel uygulamalarını göstermektedir. Çalışma, Birleşmiş Milletler TBC hastalığının ortadan kaldırılmasına yönelik 2030 planını gerçekleştirmeye yönelik gerçekçi yaklaşımları bilgilendirmek için yeni bir metodolojiyi vurgulamaktadır.

Anahtar kelimeler : Epidemiyoloji; optimal kontrol; uyarlanabilir kontrol; kayan mod kontrolü; maliyet-etkinlik analizi; Lyapunov kararlılığı

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LIST OF ABBREVIATIONS

UN:	United Nations
TB:	Tuberculosis
MTB:	Mycobacterium Tuberculosis
SEI:	Susceptible, Exposed, and Infectious
SEIR:	Susceptible, Exposed, Infectious, and Recovered
DFE:	Disease Free Equilibrium
EE:	Endemic Equilibrium
R_0:	Basic Reproduction Number
NGM:	Next Generation Matrix
ODE:	Ordinary Differential Equation
SSE:	Sum Squared Error
OCT:	Optimal Control Theory
PMP:	Pontryagin's Maximum Principle
ICER:	Incremental Cost-Effectiveness Ratio
SMC:	Sliding Mode Control
ASMC:	Adaptive Sliding Mode Control

CHAPTER 1
INTRODUCTION

1.1 Introduction

Epidemic diseases such as tuberculosis (TB) have been a contributing cause of billions of deaths in several decades. The entire world is committed to finding effective control and prevention strategies to contain the epidemic outbreak. Several researches used mathematical modelling and control system theory to study the infectious disease dynamics and facilitate the design of control intervention programs to curtail the spread of the diseases (Chalub & Souza, 2011; Giamberardino & Iacoviello, 2018; Heesterbeek et al., 2015; Li, 2015; Matthew & Keeling, 2008; Metcalf, Edmunds & Lessler, 2015; Zhang & Zhou, 2012). Recent reports from the world health organization (WHO) on the TB incidences have indicated that, despite the global pledge to eradicate the disease by 2030, the spread of TB persists (WHO, 2019). As a consequence, improved research is required so as to provide effective control strategies that will break the trajectories of TB and meet the global target. In this regard, this thesis explored the potential applications of optimal and adaptive control theory in the implementation of TB epidemic disease control strategies. The study can be used to suggest TB epidemic control programs and will serve as a support for the public health authorities.

1.2 Background of Study

Tuberculosis (TB) is a bacterial infection that usually starts in the body of a susceptible person (a healthy person that can contract the disease) as a result of infection by Mycobacterium tuberculosis (MTB). The disease is commonly transmitted through the air by the breath of healthy person and infected individuals, and the common symptoms of TB include coughing blood, fever and weight loss (Jumbo, Obaseki & Ikuabe, 2013). An infected person with MTB may develop active TB or remain latent. Latently infected people are asymptomatic and do not transmit the disease, but may progress to infectious (active TB) after a latency period (Rocha,

Silva & Torres, 2018). TB is treatable and can be cured. Nonetheless, inability to comply with the medication may lead to the emergence of drug-resistant TB (Bhunu, 2011). Various control interventions are available for TB prevention and treatment. Vaccination is the most preferred method of treating TB which is used to protect the susceptible individual from contracting the disease and subsequently prevent further dissemination of the infection. Reactivation of TB in an exposed person (latently infected individuals) can be controlled through a control effort known as "case finding", which involves the monitoring action by public health workers to find and treat the exposed individuals to stop them from becoming infectious. Furthermore, the development of drug-resistant TB can be prevented by employing intervention program referred to as "case holding". The case holding control effort represent the interventions made by health workers to ensure adherence to the proper treatment of the infected people (Chaulet, 1983; Gomes et al., 2007).

In order to predict the future characteristics of the infectious disease and plan reliable control intervention programs to minimize disease outbreak, a thorough understanding of dynamics of the disease transmission among populations is essential (Lin et al., 2020; Yang et al., 2020). Mathematical modelling and control theory has been one of the important tools for studying the dynamics and control of infectious disease (Lin et al., 2020; Sofia et al., 2015). Design and control analysis of epidemic models, however, involves a complex and quite challenging process; due to the inherent non-linearity, complexity, and parameter uncertainties associated with epidemic processes. This is in addition to the economic constraint of optimizing the demands of the control goals and minimization of the cost of implementing the control actions (Djouima et al., 2017; Gambhire et al., 2020).

Many studies on the mathematical modelling of the dynamics of TB transmission have been performed (Lopes et al., 2014; Okuonghae & Omosigho, 2011; Verver et al., 2005; Windarto & Anggriani, 2015). However, some of the previous TB predictive models included vaccination and control treatments and analyzed the disease management by evaluating the role of parameters of disease transmission in decreasing the value of the basic reproduction number, R_0, below the threshold limit (Lopes et al., 2014; Okuonghae & Omosigho, 2011; Windarto &

Anggriani, 2015). Generally, a reproduction number $R_0 < 1$ suggests that the disease is eradicated on its own, while $R_0 > 1$ shows that the disease will persist in the population (Li, Zhou & Hyman, 2004; Matthew & Keeling, 2008; Yi, Zhang, Mao, Yang & Li, 2009). These approaches have a major limitation of not taking into consideration the time-dependent control inputs.

Optimal control theory developed from the calculus of variation enables the incorporation of time-dependent control functions, and offers reliable tools to study the time-varying disease control strategies and determines the trade-offs between different control strategies and the cost of implementation (Zaman et al., 2017). The application of optimal control theory provides the public health authorities with useful suggestions on the impact of one control policy compared to others (Gani & Halawar, 2018). Optimal control has been applied in several biomedical problems, especially to cancer chemotherapy models (Chen et al., 2019; Saad & Hincal, 2018). These methods when implemented to infectious disease models, can offer tremendous insight into the best pathway to reduce disease burden. Many studies have considered the application of optimal control for specific diseases (El et al., 2019; Khamis et al., 2018; Lambura et al., 2020; Yaro et al., 2019).

Furthermore, the application of conventional optimal control methods requires that the epidemiological parameters are well known and accurate. This assumption is not always practical because the process of estimating such parameters from experimental data can result in inconsistent values. As a consequence, in the presence of modelling uncertainties and parametric variations, the conventional control techniques can yield unsatisfactory results. Meanwhile, robust and adaptive control techniques which employs feedback will provide more consistent results. The closed-loop control design can achieve the desired control goals irrespective of the model's parameter variations (Aghajanzadeh et al., 2017; Bera, Kumar & Biswas 2019; Rajaei, Vahidi-Moghaddam, Chizfahm & Mojtaba 2019).

1.3 Research Problem and Statement

The impact of tuberculosis (TB) on the economy and social life is quite devastating, including discrimination, anxiety, and poverty. TB, despite being a curable and preventable disease, has become the world's leading infectious killer with an estimated total of 1.5 million deaths per annum (WHO, 2019). The increase of new cases has been attributed to the collapse of public health programs, lack of funding in the developing countries, lack of awareness among the general public and exogenous re-infection, where a latently-infected individual acquires a new infection from another infectious (Bowong & Aziz Alaoui, 2013; Silva & Torres, 2013; Yang et al., 2016).

While considerable progress has been made in developing a theoretical framework for studying TB's dynamics and control methods, there are still many challenging and critical open questions. For instance, models integrating the role of public awareness on controlling TB are rare. Frost has recommended that TB incidences could be avoided by considering isolation and awareness in the control process (Frost, 1937). Moreover, there is a need for more studies on the optimal control applications which will provide detailed cost-effectiveness analysis and compare different control strategies to show the impact of a particular control strategy with respect to others. Another problem that needs to be addressed is the fact that conventional optimal control systems are affected by the variation in system parameters such as transmission rate, death rate and other epidemiological parameters. Subsequently, the performance of the system may be affected by uncertain parameters. When there are uncertain parameters in the system, the desired result cannot be obtained by conventional control techniques anymore.

This study will investigate the application of optimal and adaptive control theory for the analysis of TB transmission dynamics. The research would also consider the significance of incorporating public awareness into the TB control program. This method allows the most cost-effective intervention to be analyzed and the performance of the various combinations of the control measures to be compared. In the case of parameter uncertainty, the adaptive control design can ensure the robustness of the TB model.

1.4 Research Aim and Objectives

This research work aims to design and analyze optimal and adaptive control strategies for the control of TB epidemics, to study how these control measures can be implemented, over a given period of time, in order to reduce the population of exposed and infectious individuals, while minimizing the cost of implementation of the control interventions.

Following research objectives would facilitate the accomplishment of this aim:

1. Propose a novel mathematical model to study the dynamics of tuberculosis with saturated incidence rate.

2. Design and analysis of optimal TB control systems with different control strategies, and cost-effectiveness analysis to compare the implementation of the various control strategies.

3. Design and analysis of adaptive sliding mode control for the TB model considering parameter uncertainties.

1.5 Scope of the Study

The main emphasis of this research is on performing an analysis of the dynamics of TB epidemic with optimal and adaptive controls. The study would be based on SEI (susceptible-exposed-infectious) compartmental TB model with fast and slow progression. Within the SEI model, the entire population is divided into three groups, namely; susceptible (group of people that are healthy but can contract the disease), exposed (group of people that have been in contact with the disease agent but have not shown the symptoms of the disease) and infectious (individuals who have already developed the disease and now are infected). The research objectives will be addressed in three separate scenarios. Optimal control theory should be used in the first scenario to study the TB dynamics with saturated incidence rate. In this scenario, the control analysis will employ two time-dependent functions, namely the “case holding” and “case finding” as control inputs. The former represents the surveillance procedure concerning finding and treating people that are exposed to prevent them from being infectious. The later signifies the efforts rendered by health professionals to ensure adherence to the proper treatment of the infected

persons. The significance of public awareness (measured by δ) will be shown numerically. In the second scheme, the optimal control theory analysis would incorporate three time-dependent control functions, where the vaccination campaign program is used in addition to the two controls mentioned in the first scenario. To show how the parameter uncertainties will be handled, the study would consider the adaptive control system design based on sliding mode control scheme in the final scenario.

The optimal control strategies are implemented to reduce the exposed and infectious population while minimizing the cost of executing the control actions. The necessary conditions required to achieve the optimal controls will be derived using the Pontryagin's maximum principle. Incremental cost-effectiveness ratio (ICER) is used for the cost-effectiveness analysis. The asymptotic stability of the closed-loop system is shown analytically using the Lyapunov Function Theory. All the numerical simulations will be performed with the help of MATLAB/SIMULINK 2019b.

The study is limited to the deterministic compartmental model that considers the nature of the disease at the population level. The analysis of the TB dynamics is confined to three compartments, the susceptible, exposed, and infectious. Several estimates, selections, and assumptions were made as consideration of practical and feasible design.

1.6 Thesis Organization

The thesis report is organized in six chapters; and the research objectives are thoroughly elaborated in chapter 3, 4 and 5, which can be read independently from each other. The chapters are arranged as follows:

Chapter 1: In this chapter, the background of the study is presented. The chapter also discusses the problem statement, objective and scope of the study.

Chapter 2: Reviews the basic theories of epidemic modelling, optimal control and sliding mode control techniques. It also provides a thorough and concise literature review of the other related studies.

Chapter 3: This chapter illustrates the development of a new model of TB dynamics, considering the saturated incidence rate. The chapter further addresses the optimal control design and analysis of the proposed model.

Chapter 4: This chapter described another scenario of the optimal control strategy. In this scheme, besides the optimal control design, cost-effectiveness analysis of the different control interventions is also discussed.

Chapter 5: This chapter presents the step by step analysis of the TB dynamics with adaptive control scheme considering parameter uncertainties.

Chapter 6: In this chapter, the conclusion of the thesis work is presented along with recommendations for future work.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

In this chapter, the literature review on the relevant studies is presented. The chapter begins by reviewing the fundamental theories about mathematical modelling of epidemiology and basic mathematical epidemic models. The chapter also discusses the control strategies employed in epidemiology study including the constant control, optimal control and adaptive control strategies. Finally, a precise and concise review of the previous studies on the mathematical models and control strategies of TB are presented.

2.2 Mathematical Modelling of Epidemiology

Epidemiology is the topic which studies health and disease trends, and related factors in a particular population. The term “epidemiology” is derived from the Greek words “epi” meaning "over", “demos”, meaning "people" and “logos”, which means "study". It follows that the concept of epidemiology refers to the study of disease trends over human populations. The word "epidemiology" is believed to have been first used by a Spanish physician de Villalba's 1802 to explain the study of epidemics (Martcheva, 2013). However, Hippocrates (460-377 B.C.E.) is considered to be the father of epidemiology, because of his initial work of describing the disease to environment connection. Today, diseases like heart attack, cancer and stroke also received considerable attention in epidemiology (WHO, 2018). It is pertinent here, to define the following three epidemiology terms; endemic, epidemic and pandemic. The continuing outbreak of the disease is called endemic, while a sudden increase in the disease population is referred to as an epidemic, and a worldwide disease that impacts a high number of people is described as pandemic (Brauer, 2017).

Infectious disease refers to clinically proved illness occasioned by the incidence of a pathogenic microbial agent. These agents that trigger contagious diseases may be parasitic, fungal, bacterial

or toxic protein. For instance, the bacterial agents caused pneumonia and tuberculosis; whereas dermatomycoses are examples of fungal disease; macro parasites like helminth and protozoa are caused by parasitic infections; while virus infections cause diseases like influenza and HIV. The spread of the disease over a population is influenced by several factors, which include population increase, inadequate sanitation in developing countries, and modern infrastructure that allows foreign border crossings.

The disease is usually transmitted through person-person by either direct or indirect contact. Indirect contact means passing an infectious material, blood, or other substance in the body. Direct contact involves physical touch or sexual activity. Influenza can be contracted by indirect contact while human immunodeficiency virus (HIV) is spread through direct contact. Other forms of transmission occur when a healthy person inhales infected air. Infectious diseases under this category include tuberculosis, smallpox, chickenpox, pneumonia and measles. Moreover, four different types of transmission are considered for modelling purposes: direct, where the pathogen is transferred from human to human; vector-spread where the transfer is vector-to-human; vertical where the transfer is mother-to-child at birth; and environmental when human become infected by contact with pathogen through the environment (Hethcote, 2000; Sokat et al., 2019).

This thesis focused on the study of TB epidemic which is caused by bacteria (Mycobacterium tuberculosis) and transmitted from person to person through air.

2.2.1 Basic mathematical epidemic models

Epidemic models may be defined as mathematical models that deal with the spread of infectious diseases within a human population. The term mathematical model refers to system representation, using mathematical terminologies and techniques. Mathematical models can be extended to any process in engineering or natural sciences such as epidemiology, biology or some other well-defined systems. A mathematical model is built to characterize a system accurately, evaluate the effects of its various components, provide a rational understanding of

experimental data, interpret the response pattern of the system, predict the future behavior of the system and enhance system performance (Martcheva, 2013).

Figure 2.1 illustrates how the epidemic models are developed. The first step is to obtain an accurate scientific description of the system. Mathematical equations (usually differential equations) are then used to represent the system behavior. Subsequently, an extensive mathematical analysis is undertaken to show the existence, uniqueness and stability of the model's solution. Once the model is formulated, and the mathematical analysis is completed, the model is validated using accurate experimental data through a model fitting, and the model's parameters can be estimated. This is accompanied by a sensitivity analysis to assess the influence of the various system parameters on the system performance. Many useful information can be obtained via numerical simulations as well (Martcheva, 2013).

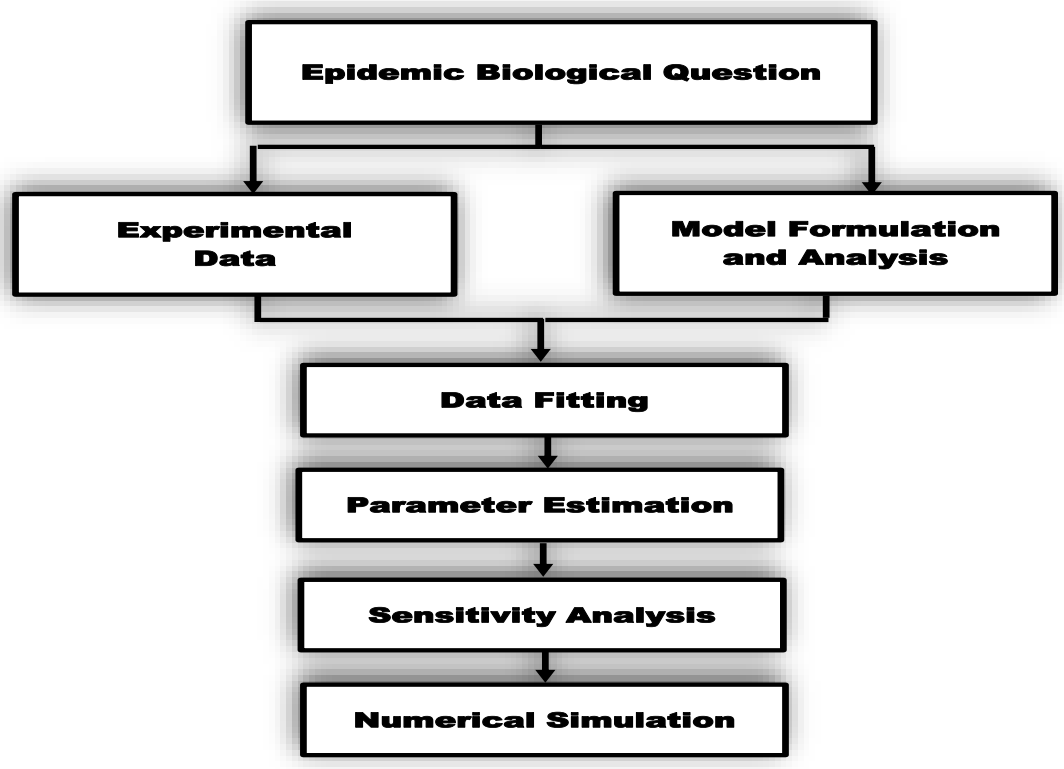


Figure 2.1: Epidemic model development (Martcheva, 2013)

This study focused on deterministic compartmental epidemic model. But stochastic models have been developed and used in the literature as well (Allen, 2017; Britton, 2010; Rao, 2014). In the stochastic models, probability distributions are used to represent the system state variables, while in deterministic models, the state variables are distinctively determined by model parameters and the initial states of the variables (Allen, 2017). The origin of compartmental epidemic models is dated back to the early twentieth century, with Kermack and McKendrick's work in 1927 (Wilkinson, Ball, & Sharkey, 2016). These models consider the nature of a disease outbreak at the population level. The whole population is grouped into separate compartments. Some mathematical parameters which serve as a link between the compartments defined the transfer of individuals from one group to another. Compartmental models are analyzed by using differential equations, and they are employed to forecast the behavior of the disease progression, such as prevalence, deaths, or the duration of the outbreak. It also provides an understanding of the most efficient technique for controlling the disease. The major types of compartmental models are discussed in the subsequent subsections; however, a comprehensive review of the subject can be found from (Keeling & Rohani, 2008).

i. SIR epidemic model

The SIR model is one of the most basic epidemic model developed by Kermack and McKendrick in 1927 (Wilkinson et al., 2016). Many variants of SIR model exist in the literature, usually modifying the principal model to include more information (Ameen, Baleanu, & Ali, 2020; Wang, 2015; Zhang, 2015). The SIR model describes the transmission of the disease by dividing the people into three groups. The first group known as susceptible (denoted by S), comprises of people that are healthy but can contract the disease. The second group called infectious (represented by I) contains individuals who have already developed the disease and now are infected. The recovered compartment (denoted by R) accommodates the individuals that have recovered from the disease.

The process of transfer from one group to another is depicted in Figure 2.2. The susceptible individuals that become infected move from S compartment to I and the transmission rate is given by β. The recovery rate denoted by α signifies the rate at which individuals who have

recovered or died move from the infectious class to the recovered group. The number of people in the three compartments is a function of time, and can be written as S(t), I(t), and R(t). Therefore, the total size of the population at any instant of time N(t), is equal to the summation of the number of people in the three compartments, i.e. N = S(t)+I(t)+R(t).

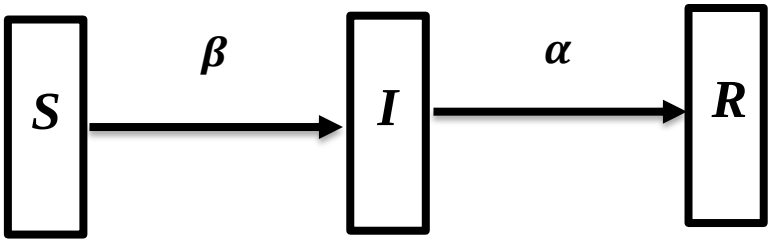


Figure 2.2: SIR epidemic model

The differential equations describing the system is given in Equation (2.1):

$$\begin{cases} \dot{S} = -\beta SI \\ \dot{I} = \beta SI - \propto \mathrm{I} \\ \dot{R} = \propto I \end{cases} \tag{2.1}$$

with initial conditions $S(0), I(0)$, and $R(0)$ (Wilkinson et al., 2016).

ii. SEIR epidemic model

Another essential type of epidemic model is the SEIR model, in which an additional compartment; exposed, denoted by E(t) is added between the susceptible and infectious classes. This is due to the fact that for several diseases when susceptible individuals become in contact with the disease agent (exposed), they do not proceed to the infected class instantly as in SIR model (Huang, 2008). The pathogen requires some time to reproduce in the host and to establish itself. The time the individual gets infected and is not yet infectious is deemed the latent stage. The Transfer Diagram for the SEIR model is shown in Figure 2.3.

The differential equations describing the system is given in Equation (2.2):

$$\begin{cases} \dot{S} = -\beta SI \\ \dot{E} = \beta SI - \gamma \mathrm{E} \\ \dot{I} = \gamma \mathrm{E} - \propto \mathrm{I} \\ \dot{R} = \propto I \end{cases} \tag{2.2}$$

where γ is the rate at which the exposed individuals proceed to the infectious class. Hence, the approximate time in the exposed class, also known as the latency period is given by $1/\gamma$ (Huang, 2008).

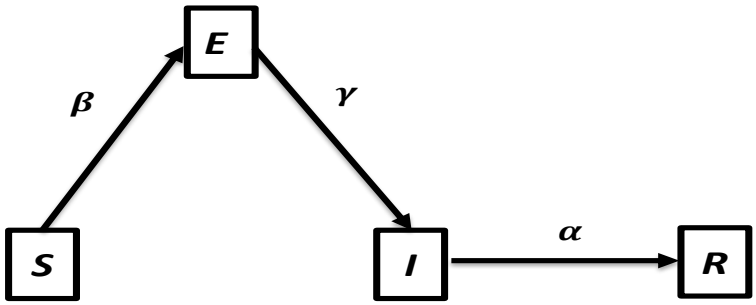


Figure 2.3: SEIR epidemic model

2.3 Control Strategies

Measures for infectious disease prevention and control include vaccination, treatment, and prophylaxis. In vaccination control strategy, inactivated micro-organisms will be introduced in to healthy person's body. The body's immune system detects and treats those vaccination agents as foreign ones. This leads to reactivation of the body immune response, and antibodies are produced to fight them. Consequently, when similar micro-organisms are detected in the body the antibodies will kill them much faster. Therefore, a person who is immunized is healthy from the disease. Thus, it is much harder for epidemic outbreak to occur where a sufficient number of individuals are vaccinated. Treatment involves use of specific procedure, agents, or regimen, like bed rest or a drugs in order to cure or lessen the disease. For certain infectious diseases, medications actually exist that can cure or decrease the influence of the disease. For instance, malaria and TB can be cured through medication. Prophylaxis is a set of steps employed to avoid

a particular infectious disease. There precautions may be wearing safety clothes, washing hands, physical distancing.

Researchers in the field of mathematical modelling and control systems analyzes the effects of these control measures by including them in to the epidemic models as a constant coefficient or as a time-dependent variable. The control strategy that incorporate the control measures as constant coefficient is regarded as constant control strategy. On the other hand, control strategies that consider the control measures as time-varying functions are classified as time-dependent control strategies. In the literature the time-dependent control strategies are often designed as either open-loop control system or closed-loop (feedback) control systems. The open-loop control system design is based on optimal control techniques while the closed loop s often based on feedback linear control methods or nonlinear adaptive control techniques (see Figure 2.5).

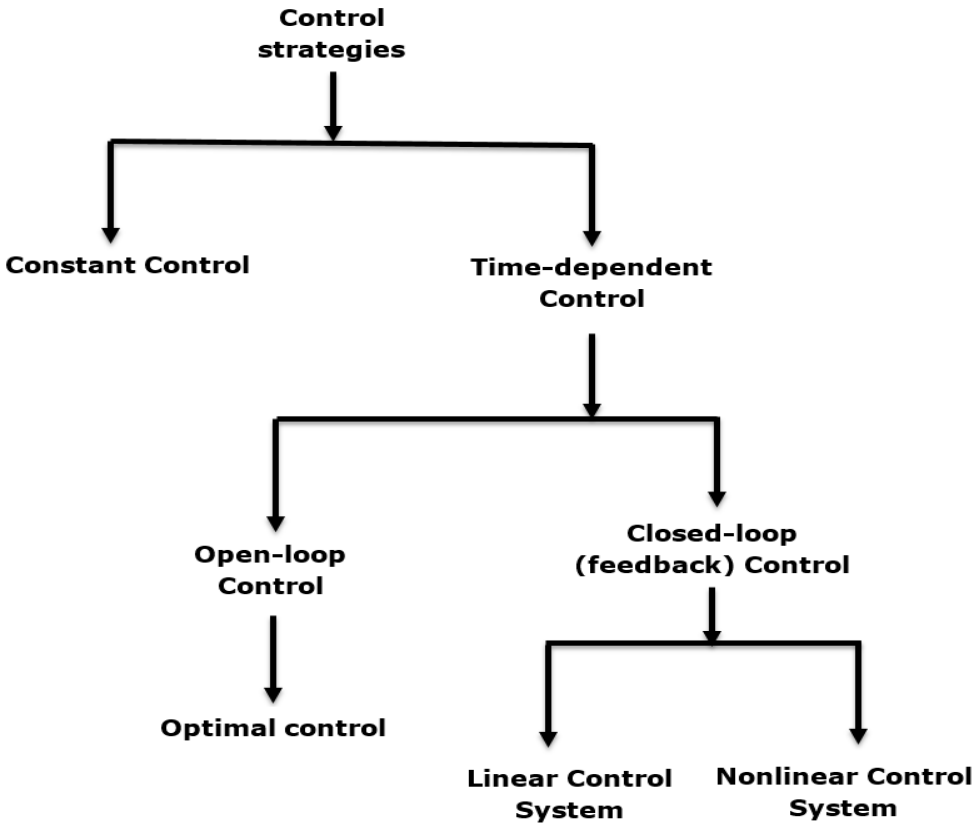


Figure 2.4: Control strategies

2.3.1 Constant control strategy

In the constant control strategy, the control measures such as vaccination, treatment, and prophylaxis are integrated in to the model as constant coefficients. Reproduction number is then computed for the mathematical models involving the control measures. The reproduction number depends on the control coefficient, and can be used to analyze the impact of the controls on the dynamics of the disease.

i. Basic reproduction number

The notion of basic reproduction number was first established by Sir Ronald Ross formed in the book titled "The Prevention of Malaria" published in 1911. The author discovered in this work that malaria is being transmitted between mosquitoes and humans. He then formulated a mathematical model to represent the dynamics of malaria and obtained a threshold quantity, now identified as the basic reproduction number (Hardy & Magnello, 2002).

The basic reproduction number, symbolized as R_0, is described as the estimated number of new infections which would be induced by only one infected person in a population of entirely susceptible, during the infectious cycle. For simple models, R_0, can be obtained by following the new cases in the population produced by single infective, by using the following expression:

$$R_0 = (rate\ of\ contact) \times (probability\ of\ infection\ in\ a\ contact) \times (period\ of\ infectiousness)$$

Nevertheless, for complex epidemic models with heterogeneity or seasonality with different susceptibility, following the new cases approach is not feasible. To handle these shortcomings, a more generalized method, based on a unique square matrix called the next-generation matrix (NGM), was introduced by (Diekmann, Heesterbeek, & Metz, 1990; Roddam, 2001). In the next-generation matrix approach, R_0 is calculated as the spectral radius of the 'next-generation

operator'. The operator formation involves the determination of two compartments from the model; namely the infected and non-infected compartments (Roddam, 2001).

To illustrate this concept, consider a compartmental epidemic model in which there are m compartments, among which n are infectious. Let x_i for $i = 1,2, \ldots\ldots, m$ denotes the number of people in i^{th} compartment, $F_i(x_i)$ refers to the rate at which new infections occur in compartment i, and $V_i(x_i) = V_i^-(x_i) - V_i^+(x_i)$, where V_i^- is the rate at which individuals are moved from the i^{th} compartment and V_i^+ is the rate at which individuals are moved to the i^{th} compartment by some other means.

According to Hefferman (Heffernan et al., 2005), the NGM operator G can be defined as a product of two partial derivatives matrices of $F_i$and V_i:

$$G = FV^{-1} \tag{2.3}$$

and

$$R_0 = \rho(FV^{-1}) \tag{2.4}$$

Where

$\rho(G)$ is the dominant eigenvalue (spectral radius) of matrix G,

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

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

$x_0 = disease\ free\ equilibrium$ and $i, j = 1, \ldots\ldots, n$

In mathematical epidemiology, R_0 is used as a threshold quantity to analyze the disease transmission dynamics.

2.3.2 Optimal control strategy

In the constant control strategies, the control coefficients are considered to be constant in time, but in reality, control strategies are variable in time. The control theory used to derive optimal control strategies that vary in time is called optimal control theory. In this section, we introduce the basic theory of optimal control.

i. Basic theory of optimal control

Optimal control is an essential area in modern control theory, which provides a systematic approach to design a controller that satisfies predefined performance criteria like time minimization, cost minimization and error minimization. Alternatively stated, optimal control theory is concerned with finding a set of control functions with corresponding system state trajectories that minimize (or maximize) a pre-defined cost function (performance index) while simultaneously satisfying some physical constraints (Bryson, 1996). The emergence of optimal control theory, as a recognized field, can be dated back to the mid-20th century. This is attributed to the advances made in the area of automatic control, along with several achievements made in mathematical theory, particularly regarding Bellman's dynamic programming, Wald's sequential analysis and Pontryagin's maximum principle (Grass et al., 2008). Being the intersection of control systems theory and mathematics, optimal control theory can be regarded as one of the most interdisciplinary research areas of today (Yaro et al., 2019).

The mathematics behind the optimal control theory is rooted from an essential aspect of mathematical analysis; the calculus of variation, developed in the 17^{th} century. The famous Johann Bernoulli's "brachistochrone" problem solved in the mid-1600, is often considered as the pioneering work in the calculus of variation. In 1662, Fermat used calculus of variation to find the solution to a minimum time problem, which lead to the derivation of the law of refraction. In the same period, Isaac Newton applied calculus of variation to decide the optimal shape of a ship's bow as a tradeoff between low water resistance and high ship cargo load. The evolution of calculus of variation theory was further advanced in 18^{th} and 19^{th} centuries by the works of Euler, Lagrange, Jacobi, Weistrass and Hamilton (Grass et al., 2008; Kamien & Schwart, 2000). In the 1950s, Soviet Union engineers sought the help of mathematicians in solving the problems that occur in steering aircraft. Pontryagin and his team got incolved in this area, and their work culminated in the prominent maximum principle; the method used in this study and several other optimal control solutions. The advent of the Pontryagin's Maximum Problem establishes a new age of optimal control theory as it offers optimum conditions for

optimization problems where constraints are defined by differential equations and paves the way for thorough work in the field (Pontryagin et al., 1962).

There are several methods to formulating problems involving optimal control, in which the system can be represented by the system of ordinary differential equations (ODEs), difference equations, partial differential equations (PDEs), stochastic differential equations (SDEs) etc. Optimal control theory is a well-developed for both nonlinear and linear systems. The progress in numerical and computational techniques, coupled with the emergence of faster computers, allows for the application of optimal control to solve more sophisticated science and engineering problems. It has been broadly applied in numerous fields of research, including electrical, mechanical, finance, economics and management, aerospace and aeronautic, biology, biomedical, health sciences, robotics, epidemiology, natural resources, demography, environment and so on.

ii. Optimal control solution using Pontryagin's maximum principle

The optimal control problem usually includes the description of the control system (process to be controlled) using ordinary differential equations (ODEs), control objectives, physical constraints and performance index.

Given the following ODEs-system

$$\begin{cases} \frac{dx}{dt} = \boldsymbol{y}(\boldsymbol{x}(t), t) \\ \boldsymbol{x}(0) = \boldsymbol{x_0} \end{cases}, \tag{2.5}$$

In which the unknown vector $\boldsymbol{x}: \mathbb{R}_+ \rightarrow \mathbb{R}^n$ is considered to be piecewise differentiable and continuous with given initial conditions $\boldsymbol{x_0} \in \mathbb{R}^n$ and $\boldsymbol{y}: \mathbb{R}^n \rightarrow \mathbb{R}^n$, Equation (2.5) is the system model which describes the dynamics of the process.

Accordingly, the above system becomes Let us generalize the system in Equation (2.5) by adding a new time-dependent function $\boldsymbol{u}(t)$ to the right-hand side, such that $\boldsymbol{u}: \mathbb{R}_+ \rightarrow D$, where $\boldsymbol{u}$ is from a set**,** $D \subset \mathbb{R}^m$.

$$\begin{cases} \frac{dx}{dt} = \boldsymbol{y}(\boldsymbol{x}(t), \boldsymbol{u}(t), t) \\ x(0) = x_0 \end{cases}, \tag{2.6}$$

The variable $\boldsymbol{u}(t)$ is known as the "control" and the new system described in Equation (2.6) is referred to as the "controlled system". Now, due to the existence of the control variable, the corresponding solution $\boldsymbol{x}(t)$ (system response) depends on the system initial conditions x_0 and the control variable. The vectors $\boldsymbol{x}$, $\boldsymbol{u}$ and function $\boldsymbol{y}$ can be generalized as:

$$\boldsymbol{x}(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ . \\ . \\ . \\ x_n(t) \end{bmatrix},$$

$$\boldsymbol{u}(t) = \begin{bmatrix} u_1(t) \\ u_2(t) \\ . \\ . \\ . \\ u_m(t) \end{bmatrix},$$

and

$$\boldsymbol{y}(\boldsymbol{x}(t), \boldsymbol{u}(t), t) = \begin{bmatrix} y_1(x_1(t),\ x_2(t), \dots x_n(t), u_1(t), u_2(t), \dots, u_m(t)) \\ y_2(x_1(t),\ x_2(t), \dots x_n(t), u_1(t), u_2(t), \dots, u_m(t)) \\ . \\ . \\ . \\ y_n(x_1(t),\ x_2(t), \dots x_n(t), u_1(t), u_2(t), \dots, u_m(t)) \end{bmatrix}.$$

After the development of the controlled system, next, the control objective is defined using a suitable performance index. In respect of epidemic control models, the aim is to obtain a cost of control inputs that will minimize the prevalence and/or minimize the cost of controlling the disease. More explicitly, the objective functional is given by:

$$J[\boldsymbol{u}] = \int_0^T L\big(\boldsymbol{x}(t), \boldsymbol{u}(t)\big)dt, \tag{2.7}$$

Where $\boldsymbol{x}(t)$ solves (2.6) for specified control $\boldsymbol{u}(t)$. The *Lagrangian* function L is continuous and differentiable representing the running payoff, such that L: $\mathbb{R}^n \times D \to \mathbb{R}$. Both the final time T and the function L are given. Thus the optimal control problem is to determine the control u^* that minimizes the objective functional (2.7) subject to the system state (2.6) over the closed interval $[0, T]$, that is,

$$J[\boldsymbol{u}^*] = \min_{\boldsymbol{u}\in\mathfrak{V}} J[\boldsymbol{u}]. \tag{2.8}$$

Where $\mathfrak{V}$ is the set of admissible controls defined by

$$\mathfrak{V} = \big\{\boldsymbol{u}(t) \in L^1\big(0, t_f\big) | \boldsymbol{u}(t) \in D\big\}.$$

The control $u^*(t)$, if exist, is referred to as the optimal control. The next step is to check the existence of the optimal control pair (u^*, x^*), this can be achieved by using theorem 4.1 from (Bather et al., 1976a):

Theorem 2.1: Suppose that,

I. $\boldsymbol{y}$ is of class C^1 and there exist a constant ε exists such that

$|y(t, 0, 0)| \leq \varepsilon$,

$|y_x(\, t, \boldsymbol{x}, \boldsymbol{u})| \leq \varepsilon(1 + |\, \boldsymbol{u}|)$, and

$|y_u(\, t, \boldsymbol{x}, \boldsymbol{u})| \leq \varepsilon$;

II. The admissible set φ of solutions to system (2.7) along with initial conditions and associated control in $\mathfrak{V}$ is nonempty;

III. $y(\, t, \boldsymbol{x}, \boldsymbol{u}) = a(\, t, \boldsymbol{x}) + b(\, t, \boldsymbol{x})\boldsymbol{u}$;

IV. The optimal control set U is closed, compact and convex;

V. The objective functional integrand $L\big(\boldsymbol{x}(t), \boldsymbol{u}(t)\big)$ is convex in U.

Then there exists an optimal control u^* and the corresponding optimal solution x^* to the problem (2.8). Now that the existence of the optimal control has been proved, the solution of the optimal control is provided by the Pontryagin's maximum principle (Pontryagin et al., 1962). Let introduce a time-varying Lagrange multiplier vector $\lambda(t)$ and define a new function H (called Hamiltonian function) for all time $t \in \big[0, t_f\big]$ as

$$H(\boldsymbol{x}(t), \boldsymbol{u}(t), \lambda(t), t) = L\big(\boldsymbol{x}(t), \boldsymbol{u}(t)\big) + \sum_{j=1}^{n} \lambda_j(t) y_j(\boldsymbol{x}(t), \boldsymbol{u}(t), t) \quad (2.9)$$

Theorem 2.2: (Pontryagin's Maximum Principle). For the optimality of control $u^*(t)$ and associated optimal trajectory, $x^*(t)$, it is necessary that there exists a nonzero co-state vector $\lambda^*(t)$ that is a solution to the co-state system

$$\frac{d\lambda}{dt} = -\frac{\partial H(\boldsymbol{x}(t), \boldsymbol{u}(t), \lambda(t), t)}{\partial t} \quad (2.10)$$

Such that

$$H(\boldsymbol{x}(t), \boldsymbol{u}(t), \lambda(t), t) = \min_{\boldsymbol{u} \in \mathcal{U}} H\big(x^*(t), \boldsymbol{u}(t), \lambda^*(t)\big)$$

Consequently, the necessary conditions for optimizing the Hamiltonian are (Neilan & Lenhart, 2010):

1. Optimality condition

$$\frac{dH}{dt} = 0$$

2. The co-state system

$$\frac{d\lambda_j(t)}{dt} = -\frac{\partial H(\boldsymbol{x}(t), \boldsymbol{u}(t), \lambda(t), t)}{\partial x_i}$$

3. Transversality condition

$$\lambda_j\big(t_f\big) = 0.$$

For minimization, we must also have

$$\frac{\partial^2 H}{\partial u^2} \geq 0 \text{ at } u^*.$$

2.3.3 Feedback control strategy

The optimal control strategy used in the existing studies are mostly designed as an open-loop control system. Open loop control scheme is often affected by changes in the control system parameters. Therefore, the optimal control strategies are applied with the assumption that the system parameters are well known and accurate. This is a critical unrealistic situation as the estimation from experimental data of such parameters can lead to inaccurate values. This scheme, though used quite frequently, cannot always assure the desired result.

Closed loop control, also known as feedback control, eliminates the shortcomings of open loop control. Feedback control has been recently employed in the design of control strategies for epidemic models (M. De la Sen et al., 2012; N. Yi et al., 2009). For instance, various vaccination laws based on feedback control theory have appeared in the literature during the last years such as state-feedback control (M. De la Sen et al., 2012), feedback linearization (Manuel de la Sen et al., 2011; Giamberardino & Iacoviello, 2019), observer-based control (Alonso-Quesada et al., 2012), and pulse vaccination (S. Gao, Chen, et al., 2008; S. Gao, Teng, et al., 2008).

However, many of the above controllers are linear, while the epidemic models are nonlinear. Also, epidemic models contain uncertain parameters which are attributed to errors in recording the infection incidences, unreported cases and errors resulting from the process of estimating the model parameters (Huynh et al., 2015; Jung, 2002). Design of control systems for systems with considerable parameter uncertainty can be approached by adaptive control. Adaptive design methods extract knowledge of the plant parameters online and update the control law. There are several strategies to design adaptive controllers such as $H\infty$, fuzzy, or neural network based techniques (C. Y. Chen & Chiu, 2008; Gaya et al., 2014; Khodaei-mehr et al., 2018; Tong et al., 2007). Among them, sliding-mode control is one of the most well-known technique due

to its simple design process, accuracy and reliability. The historical background and basic theory of the adaptive sliding mode control will be discussed in the forthcoming section.

i. Adaptive sliding mode control

Sliding mode control (SMC) technique is among the most successful robust control approaches applied to complex nonlinear systems operating in the presence of both structured and unstructured uncertainties. The study of sliding mode operation is dated back to 1950s in the Soviet Union and was first used in variable structure systems (VSS). Over the last decades, several researchers from control engineering community have been giving so much attention to SMC strategy which leads to numerous improvements in the area (Sra-Ramirez, 1989; V. I. Utkin, 1977; Young et al., 1999). The design of SMC basically begins with the development of the switching function that will keep the system state on the sliding surface, followed by the formulation of the control law that maintains the system trajectory on the sliding manifold under the influence of uncertainties.

There are many different robust controller design strategies such as back-stepping control (Krstic et al., 1995), neural network control (M. Wang et al., 2011), fuzzy control (Tong et al., 2007) and H∞ control (B. M. Chen, 2000). The critical advantage of SMC over other robust control strategies include high performance in controlling nonlinear systems, design simplicity, suitability for discrete-time and multi-input multi-output (MIMO) systems. It doesn't also require exact modelling of the plant since its less sensitive to parameter variation and un-modelled system dynamics and guarantees stability and robustness in many uncertain systems where linear controllers fail (Gambhire et al., 2020). In SMC design the control action is a discontinuous function which implies that the controller can be implemented with traditional power converters using "on/off" as the admissible operation mode (Iordanou & Surgenor, 1996).

The practical application of the conventional SMC faced so many challenges due to its chattering feature. The reason behind chattering is attributed to the fast dynamics of SMC, in the sense that the controller switching frequency is assumed to be infinite in the ideal SMC. Nevertheless, in practical applications, although the frequency is high, it is finite because of the

nonlinearity of the system. As a result, the sliding mode takes place around the neighborhood of the sliding surface with very high frequency that is inversely proportional to the controller's switching frequency. The chattering issue associated with conventional SMC was addressed by the introduction of second-order sliding in the middle of 1980s (Levant, 1993).

After the successful implementation of the "second-order sliding" many improved versions of the SMC were developed. The recent development in SMC design methods is central to addressing the salient issues associated to the conventional SMC such as removal of chattering, improvement of closed-loop performance, reducing the computational complexity, the implementation for higher-order systems, compensating the effects of un-modelled dynamics and adaptability in uncertain systems. In the early 2000s, higher-order SMC concepts were developed to address the restriction on the sliding order. Higher-order SMC provide an n^{th} order of sliding precision in terms of sampling interval as against the first order of the conventional SMC (Levant, 2003).

In the traditional SMC system, states may take infinite time before reaching the equilibrium. The issue of the convergence to equilibrium was solved with the emergence of terminal sliding mode control (TSMC) (Y. Feng et al., 2014; Venkataraman & Gulati, 1993). Though TSMC ensures the convergence of the system states to equilibrium in a finite time, however, the sliding surface is nonlinear and the convergence takes longer time when the initial conditions are very far from the origin. This leads to the introduction of improved TSMC known as "fast terminal sliding mode control" which is often written as (FTSMC). FSTMC further manages to achieve faster convergence of the system states due to the introduction of linear counterpart in the terminal sliding manifold (Abolvafaei & Ganjefar, 2019; Hernández et al., 2020). TSMC also encounters a problem of singularity, in which control law is infinite in some portion of the state space; thus another variant of TSMC, called "non-singular terminal sliding mode control (NTSMC)" was developed (Y. Feng et al., 2013; J. Yang et al., 2013). Furthermore, a new concept referred to as "Integral Sliding Mode Control (ISMC)" was also proposed in the literature. In ISMC, the order of the motion equation in this new type of Sliding Mode is equal to the dimension of the state space. Therefore, the robustness of the system can be guaranteed

throughout an entire response of the system, starting from the initial time instance (V. Utkin & Shi, 1996).

The recent development in SMC approaches includes the adaptive SMC, event-triggered SMC and intelligent SMC approaches. In case of event-triggered SMC, the control action is only applied when the event takes place, and the system response remains in the bounded region of the desired sliding surface (Behera et al., 2018; Wu et al., 2017; Yu & Hao, 2016). The adaptive SMC method includes adaptive control gain with regards to internal parameter uncertainties and external disturbances, to ensure the robustness of the controlled system in the presence of prior unknown uncertainties (Inverter, 2018; Taylor et al., 2010; V. I. Utkin & Poznyak, 2013). Lately, many researchers combine the robustness of SMC and different capacities of the intelligent control techniques (neural network and fuzzy logic) to improve the performance of the standard SMC (Ajoudani & Erfanian, 2009; Esmaili & Haron, 2017, 2015).

ii. Basic theory of adaptive sliding mode control

From the theory perspective, SMC is a control method that regulates the given closed-loop dynamics so as to match a sliding surface. Since feedback-controlled systems behavior depends on the dynamics of the closed-loop system, the system is controlled by designing the closed-loop behavior by selecting a desirable sliding surface.

To demonstrate the design of SMC, consider a sliding surface s, defined as

$$s = \dot{e} + \lambda e = 0 \tag{2.11}$$

Where λ is a positive constant, e and $\dot{e}$ are the trajectory error and derivative of the error, respectively. It is clear from Equation (2.11) that the error converges exponentially.

Now, consider a second-order system in Equation (2.12)

$$\ddot{x} = y(x) + u \tag{2.12}$$

Where x is the state of the system, and u is the equivalent control law. using Equation (2.11) and defining the trajectory error as $e = x - x_d$, we have

$$\ddot{x} = \ddot{x}_d - \lambda\dot{e},$$

Thus the control law u may be expressed as

$$u = \ddot{x}_d - \lambda\dot{e} - y \tag{2.13}$$

A discontinuous term says $\Gamma Sgn(s)$ is added in the control law, for $\Gamma > 0$, so as to make the dynamics of the system converged to the sliding surface in finite time, despite the existence of parameter uncertainties. Thus, control law becomes

$$u = \ddot{x}_d - \lambda\dot{e} - y - \Gamma Sgn(s) \tag{2.14}$$

and

$$\dot{s} = y - \hat{y} - \Gamma Sgn(s) \tag{2.15}$$

Young et al. (Young et al., 1999) have shown that the convergence and stability of the controlled system can be achieved by selecting $\Gamma > \|y - \hat{y}\|$. The asymptotic stability of the system can be achieved using the conventional SMC in the presence of uncertainties.

2.4 Mathematical Modelling and Control Study of TB

TB is caused by bacterial infection and spread from one person to another indirectly through the air. When a person with TB sneezes, cough or spit, he releases the TB germs into air, and healthy individual becomes infected by inhaling only a few of these germs (WHO, 2019). Mathematical models, which are generally based on differential equations, have been very useful in modelling the dynamics of epidemic diseases such as TB. They help in understanding the nature of the diseases transmission within a population and assist public health authorities in planning control interventions (Hethcote, 2000). In this section, some key previous studies on the mathematical modelling and control of TB are presented.

2.4.1 Mathematical modelling of TB

The study of TB has received so much attention from researchers due to the increase in the burden and losses caused by TB in many societies, especially in the developing countries. As a

result, numerous mathematical models of TB have been investigated in the literature. These models have attempted to addressed many of the characteristics of the TB dynamics, ranging from latency among the exposed individuals, fast and slow progression, reinfection coinfection and multi-strain among others (see Figure 2.5).

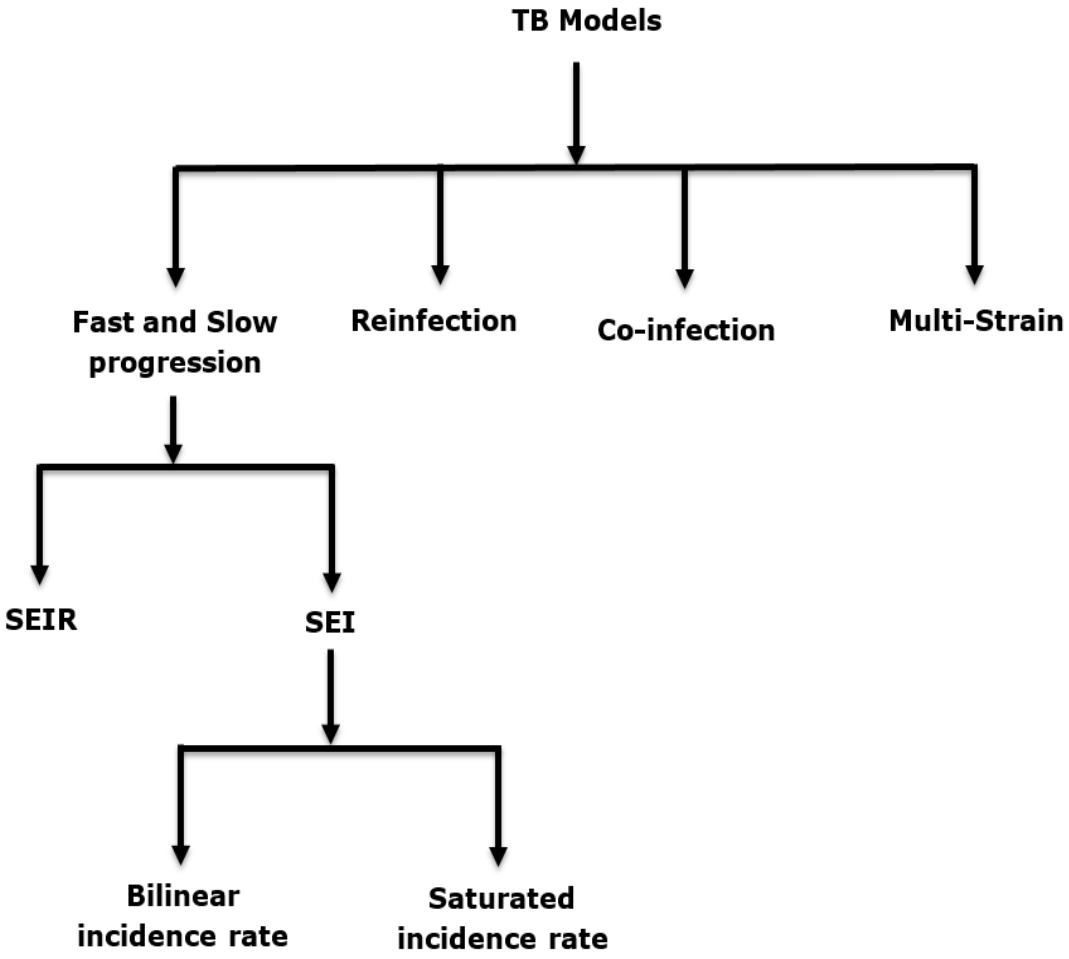


Figure 2.5: TB Epidemic models

Fast and slow progression are two distinct ways used by many models to show how susceptible people transfer to the active TB class after infection. This is attributed to the fact that when susceptible individuals come in contact with the infectious group, not all individuals exposed automatically developed the active TB, hence, they consider fast and slow infection

development. The exposed population initially have an elevated chance of progressing to active TB; over time, the pace of growth slows down (Bowong, 2010; Mccluskey, 2006). Zhang et al. studied the dynamics of tuberculosis with fast and slow progression and media coverage (Zhang et al., 2019).

Meanwhile some models (Liu & Zhang, 2011) have also consider the probability of reinfection among the latent and recovered individuals. Such models indicated that TB dynamics might be influenced by reinfection, but only occurs while infectious and latent population come in (Cohen et al., 2007; Disease et al., 1997; Rodrigues et al., 2007; Verver et al., 2005; Vynnycky & Fine, 1997). Because the recovery from TB does not grant maximum protection as stated by (Verver et al., 2005), Many models also discussed the effect of exogenous reinfection on the dynamics of TB (Bowong, 2010; Z. Feng et al., 2000; Mccluskey, 2006; D. Okuonghae et al., 2010; Silva & Torres, 2013b). Rocha et al. (Rocha et al., 2018) used the dynamic model provided by Lopez et al (Lopes et al., 2014), to checked the impact of immigration from areas with an outbreak of tuberculosis to another country. Also, a study by (Khajanchi et al., 2018) analysis the dynamics of TB transmission with exogenous reinfections and endogenous reactivation. Recent work by Das et al. investigated the transmission dynamics of tuberculosis with multiple re-infections (Das et al., 2020)

Moreover, other studies considered the dynamics of TB co-infection with other epidemics. This include, HIV-TB co-infection (Mallela et al., 2016; Pinto & Carvalho, 2017; Tanvi & Aggarwal, 2020b). Helminth-TB co-infection (Babu & Nutman, 2016). Influenza and TB co-infection (Walaza et al., 2020). The co-infection model is also developed and evaluated for the propagation mechanisms of human papillomavirus (HPV) and TB to gain insight into the effect of the dissemination of both of the two pathogens (Omame et al., 2020).

Drug-resistant strain (McBryde et al., 2017). Chavez and Feng (Castillo-chavez & Feng, 1997) and Bhunu (Bhunu, 2011) have developed some models that take into account various strains of TB, drug-sensitivity, drug-resistance, and multiple-drug-resistance. Two-strain TB model is described in (Castillo-chavez & Feng, 1997) with drug-resistant and drug-sensitive strains. Meskaf et al. studied the global stability of a two-strain epidemic model with non-monotone

incidence rates (Meskaf et al., 2020). A Multi-strain mathematical model is developed in (Fofana et al., 2017) to investigate the role of pyrazinamide in the emergence of extensively drug- resistant TB. In (Houska et al., 2016) a nonlinear multi-strain TB model is analyzed with three strains drug-sensitive, emerging multi-drug resistant and extensively drug-resistant.

The literature survey shows that substantial number of the current TB dynamic models are of the SEIR types and also used bilinear incidence rates. Meanwhile, many other nonlinear incidence rates are still available in the literature; such as non-monotone, saturated and fractional incidence rates (Windarto & Anggriani, 2015) which were used in modelling of several other diseases offering useful and more practical information (Chong et al., 2013; Ojo et al., 2018; P. Wang & Jia, 2019).

2.4.2 Control strategies of TB

Many studies on the mathematical modelling of the dynamics of TB transmission, especially compartmental TB predictive models included vaccination and control treatments and analysed the disease management by evaluating the role of parameters of the control measures in decreasing the value of the basic reproduction number, R_0, below the threshold limit (Lopes et al., 2014; Okuonghae & Omosigho, 2011; Windarto & Anggriani, 2015). Generally, It is considered that the disease becomes endemic and remain in the population if $R_0 > 1$, and the disease is deemed to vanish from the society gradually if $R_0 < 1$ (Baba & Hincal, 2017; Das et al., 2020; Khajanchi et al., 2018; Y. D. Zhang et al., 2019). These approaches have a major limitation of not taking into consideration the time-dependent control variables.

In 2002 Jung et al. (Jung, 2002) published what many believe to have been the first application of time-dependent optimal control strategies on the TB dynamic model, with two types of latent and infectious persons (infected with normal and resistant strain TB) with the aim of reducing the number of resistant TB infected and latent populations. To accomplish the goal, two control measures were proposed: a case finding intervention, used to identify individuals latently afflicted with normal TB that have more chances of developing the active TB disease and hence may benefit from preventive treatment; and a case holding control, describing the attempt to

deter medication relapse in normal contagious individuals with TB and relating to activities and strategies used to guarantee the regularity of drug consumption over a sufficient period of time to acheive a cure. Afterwards, many researchers employed the optimal control strategy on various TB models, suggesting different objective criteria according to specific control goals. In (Hattaf et al., 2009) the problem of reducing the population of infectious is addressed by incorporating a control input, which represent the effort to prevent exogenous reinfection. The application of case finding intervention is proposed by (D. Okuonghae et al., 2010), reflecting the fraction of active people infected detected and isolated in a building, for successful care and avoidance of interaction with vulnerable and exposed people, and a control plan focused on the medical screening of immigrants before they are given permission to stay. Denysiuk et al. (Denysiuk et al., 2018) found a model for TB-HIV and suggested effective control strategies using optimal control theory. The control objectives were to reduce the number of people diagnosed with HIV and the cost associated with disease prevention and treatment.

Similarly, Gao and Huang in (D. peng Gao & Huang, 2018) incorporated three control concepts and extended the optimal control principle to the Liu and Zhang (Liu & Zhang, 2011) SILT type model with vaccination compartment. Athithan and Ghosh (Athithan & Ghosh, 2015) employed an SEIR TB model and used detection as a control strategy to reduce the spread of the disease. Their proposed approach minimizes the objective function, taking into account the number of persons exposed and infected and the cost of detection. Mallela et al. (Mallela et al., 2016) proposed optimal control analysis and investigated the effect of simultaneous treatment of HIV and TB in the case of people with HIV–TB co-infection. Their analysis revealed that co-infection prevention strategies alone are insufficient to cure the diseases; for optimal disease eradication, multiple therapies and medications treating individuals infected with a particular disease are required. Optimal control of a nonlinear fractional multi-strain TB model is studied by (Houska et al., 2016). The model incorporates three strains drug-sensitive, emerging multi-drug resistant and extensively drug-resistant. Four control variables were considered and the study compared the performance of the optimal control method and the generalized Euler method. Recently, Tanvi & Aggarwal (Tanvi & Aggarwal, 2020), studied the dynamics of HIV-

TB co-infection with detection as optimal intervention strategy, With the aim of minimizing infective and the cost of applying effort towards the detection and the treatment.

Besides, there is a high degree of studies using SMC techniques, due to its essential properties. Currently, SMC is commonly used as an automatic controller in various applications such as power electronics (Chang et al., 2008; Chiu & Shen, 2012; Ding et al., 2018), robotic manipulators (Abadi et al., 2020; Ma & Sun, 2018; Y. Wang et al., 2019; S. Yi & Zhai, 2019), multiple robot synchronization (Esmaili & Haron, 2017, 2015), biomedical engineering applications (Asadi & Nekoukar, 2018; Djouima et al., 2017; Riani et al., 2018), chemical processes (Aksu & Coban, 2019; Herrera et al., 2020; Musmade et al., 2020; Zhu et al., 2020), and many more. Despite the many successes achieved by SMC in various applications, there is less attention to this control strategy in epidemic models. However, (Ibeas et al., 2013) present a superficial application of SMC for the design of a vaccination law in the context of epidemic models. Hence, this study will develop an adaptive sliding mode controller for TB epidemic model.

In chapter 3, mathematical modelling and optimal control of a novel TB model is proposed with saturated incidence rate. The saturated incidence rate will be used to analyze the impact of public awareness on the control of the disease transmission (Ojo et al., 2018). Moreover, in chapter 4, optimal control and cost-effectiveness analysis of a TB model with three different control interventions will be discussed. The study incorporated three time-dependant control interventions, representing the vaccination, case finding and case holding, with aim finding the most suitable and cost-effective control strategy for the elimination of TB. We further, show the effect of the parameter uncertainties on the open-loop optimal control system numerically. Also in chapter 5, we develop an adaptive sliding mode control for the TB model in the present of parameter uncertainties.

The analysis in chapter 4 and chapter 5 are based on modified nonlinear TB model proposed by (Mccluskey, 2006). The model is described by a system of ODEs:

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta SI - \mu S \\ \frac{\mathrm{dE}}{dt} = (1-p)\beta SI - \kappa E - \mu \mathrm{E} \\ \frac{dI}{dt} = p\beta SI + aE - \mathrm{dI} - \mu \mathrm{I} \end{cases} \tag{2.16}$$

The system parameters, along with their meanings, are summarised in Table 2.1.

Table 2.1: Parameter description as presented in (Mccluskey, 2006)

Parameter Symbol	Parameter description
Λ	Overall recruitment into susceptible compartment
μ	Natural death rate
D	Disease induced death rate
β	Disease transmission coefficient
p	The proportion of newly infected individuals that undergo fast progression to the infectious class
a	The rate at which exposed individuals move to the infectious compartment

The population is separated into three compartments depending on the epidemiological status: individuals that are healthy but can contract the disease are categorised as susceptible class $S(t)$; the exposed class $E(t)$ contains individuals that have been in contact with the infected class but are not yet showing any symptoms; and the infectious class $I(t)$ represents individuals with active TB. It is assumed that the rate of disease transmission to susceptible individuals is bilinear βSI, with a fraction p undergoing fast progression to the infectious compartment, and the remaining $(1-p)$ exhibiting slow progress into the exposed class. It is considered that the time taken by the exposed individuals to move to the infectious class follows an exponential

distribution, with a mean waiting time of $1/a$. The exposed class are assumed to have latent TB which can be cured and removed upon receiving adequate treatment; otherwise, they will progress to the infectious class.

CHAPTER 3
DYNAMICS AND OPTIMAL CONTROL OF TB EPIDEMIC WITH SATURATED INCIDENCE RATE

3.1 Introduction

This chapter presents mathematical modelling and optimal control analysis of TB dynamics using saturated incidence rate. A detailed mathematical analysis of the proposed model is given in the chapter, this include the derivation of the basic reproduction number, R_0, proving the existence and uniqueness of model's solution as well as global stability of the equilibria. The mathematical analysis is then followed by model fitting to real data and sensitivity analysis to identify the influence of the model parameters on the output quantity. The optimal control problem that integrates time-dependent control functions is then formulated. The necessary conditions for optimal disease control are obtained by using Pontryagin's maximum principle. In order to complement the analytical analysis, the chapter is concluded with some numerical simulations.

3.2 Model Formulation

The study presents an SEI compartmental TB model using saturated incidence rate. The SEI model is a variant of SEIR compartmental model mentioned in Equation (2.2). The model transfer diagram is illustrated in Figure 3.1. In the transfer diagram S, E, and I, respectively, represent the group of the susceptible, exposed and infectious people. The exposed group comprises of individuals that were in contact with contagious persons but did not reveal any symptoms of infection. A fraction of the exposed group is eliminated through successful chemoprophylaxis or by natural death, while others are transferred into the infectious compartment. In the infectious compartment, there are people who got infected with active TB and can infect others. The population is assumed to be homogeneous with equal natural death rate (μ).

The recruitment is performed through the susceptible compartment at a constant rate Λ, and the disease is transmitted as the result of interaction between infectious and susceptible persons with a saturated incidence rate $\frac{\beta SI}{1+\delta I}$. In each group, the rate of natural death μ is assumed to be the same, and the disease-induced death occurs only in the infectious class at the rate $d \geq \mu$. The fraction p of the newly infected persons proceed to the infectious group immediately, while the rest $(1-p)$ undergoes gradual progression via the exposed group. The rate of transfer from the exposed group to the infectious class is $(1-r_1)E$, and $r_2 I$ is the rate at which individuals, because of ineffective therapy, move back from the infectious group to the exposed group.

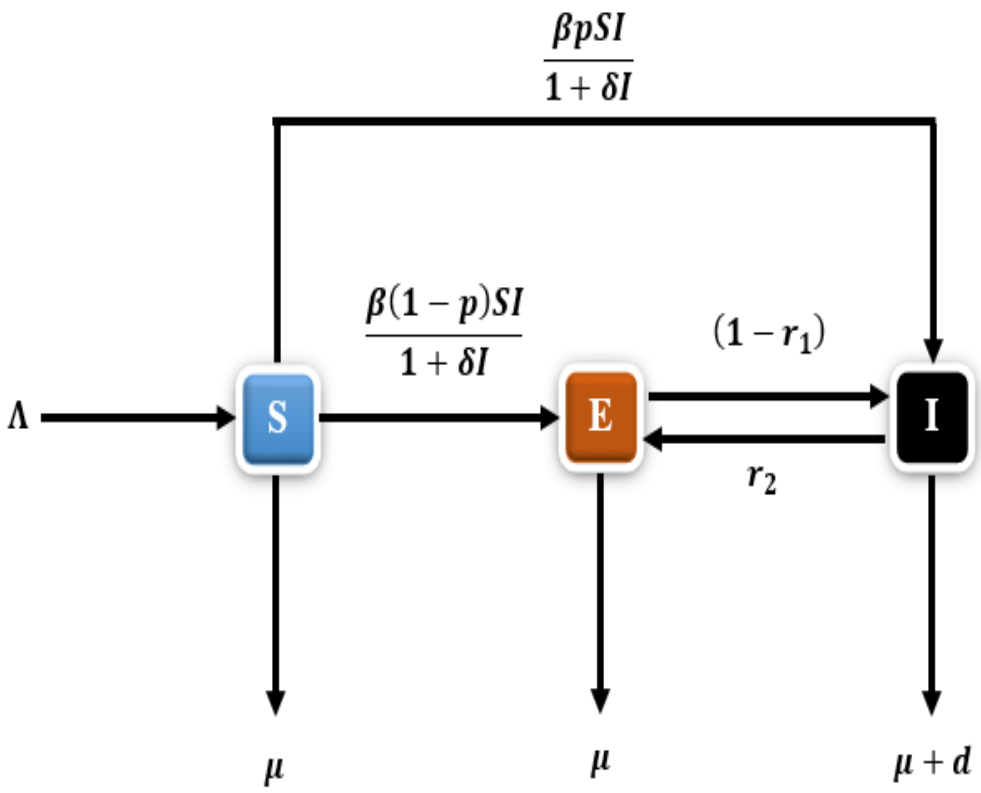


Figure 3.1: Model (3.1) transfer diagram

The dynamical model is given by the following system of ordinary differential equations (ODEs).

$$\begin{aligned}\dot{S} &= \Lambda - \mu S - \frac{\beta SI}{1+\delta I} \\ \dot{E} &= \frac{\beta(1-p)SI}{1+\delta I} + r_2 \mathrm{I} - \left(\mu + (1 - r_1)\right)\mathrm{E} \\ \dot{I} &= (1 - r_1)E + \frac{\beta pSI}{1+\delta I} - (r_2 + \mu + d)I\end{aligned} \tag{3.1}$$

For simplicity, let $a = (1 - r_1)$ and $\mathrm{b} = r_2 + \mu + \mathrm{d}$, and the system (3.1) becomes;

$$\begin{aligned}\dot{S} &= \Lambda - \mu S - \frac{\beta SI}{1+\delta I} \\ \dot{E} &= \frac{\beta(1-p)SI}{1+\delta I} + r_2 \mathrm{I} - (\mu + a)\mathrm{E} \\ \dot{I} &= aE + \frac{\beta pSI}{1+\delta I} - bI\end{aligned} \tag{3.2}$$

3.2.1 Existence of equilibria

Following the model formulation, two equilibrium points are obtained by setting equations in (3.2) to zero, and solving simultaneously. The equilibrium points are the disease-free equilibrium (G_0) and the endemic equilibrium (G_1). The disease-free equilibrium is the state where the disease vanishes. Whereas the endemic equilibrium is the state under which the disease cannot be eradicated entirely but persist within the population. The two equilibrium points will be described in sections i and ii.

i. Disease-free equilibrium (DFE)

The system Disease-Free Equilibrium (DFE) model $G_0 = (S_0, E_0, I_0) = (\frac{\Lambda}{\mu}, 0, 0)$ always exists, since $S_0, E_0, I_0 \geq 0$.

ii. Endemic equilibrium (EE)

The system Endemic Equilibrium (EE) model $G_1 = (S_1, E_1, I_1)$ exists if $S_1, E_1, I_1 \geq 0$.

That is

$$S_1 = \frac{ab - ar_2 + a\delta\Lambda + \mu b + \delta p\Lambda\mu}{(a + p\mu)(\delta\mu + \beta)}$$

$$= \frac{1}{\mu\delta + \beta}\left[\frac{\beta S_0[\mu b + a(b - r_2)}{\beta S_0(a + \mu p)} + \frac{\delta\Lambda(a + \mu p)}{(a + \mu p)}\right]$$

$$S_1 = \frac{1}{\mu\delta + \beta}\left[\frac{\beta S_0}{R_0} + \delta\Lambda\right] \tag{3.3}$$

S_1 always exists.

$$E_1 = \frac{(-b + bp - pr_2)(a\mu b - a\mu r_2 - \Lambda\beta a - \Lambda\beta p\mu + \mu^2 b)}{(a\delta\mu b - a\delta\mu r_2 + b\beta a - \beta a r_2 + \mu^2\delta b + \beta b\mu)(a + p\mu)}$$

$$= \frac{-[b(1 - p) + pr_2][-\Lambda\beta(a + \mu p) + \mu(\mu b + a(b - r_2)]}{[\mu\delta(\mu b + a(b - r_2)] + \beta(\mu b + a(b - r_2)(a + \mu p)}$$

$$= \frac{-\mu(b(1 - p) + pr_2)}{(\mu\delta + \beta)(a + \mu p)}[1 - R_0]$$

$$E_1 = \frac{\mu(b(1 - p) + pr_2)}{(\mu\delta + \beta)(a + \mu p)}[R_0 - 1] \tag{3.4}$$

E_1 exists if $R_0 \geq 1$.

$$I_1 = -\frac{a\mu b - a\mu r_2 - \Lambda\beta a - \Lambda\beta p\mu + \mu^2 b}{a\delta\mu b - a\delta\mu r_2 + b\beta a - \beta a r_2 + \mu^2\delta b + \beta b\mu}$$

$$= \frac{-[-\beta\Lambda(a + \mu p)] + \mu[\mu b + ab - ar_2]}{\mu\delta[a(b - r_2) + \mu b] + \beta[a(b - r_2) + \mu b]}$$

$$I_1 = \frac{\mu}{\mu\delta + \beta}[R_0 - 1] \tag{3.5}$$

I_1 exists if $R_0 \geq 1$.

3.2.2 Basic reproduction number (R_0)

This is described as the number of new infections an infectious person will cause in a population of fully susceptible people. In epidemiology, it is supposed that the epidemic will vanish when $R_0 \leq 1$, and endures when $R_0 > 1$.

In this study, the basic reproduction number R_0 is derived through next-generation matrix (NGM) technique (Roddam, 2001). Let define; $\mathcal{F}_i(x)$ as the amount of emergence of new infections in i^{th} group per unit time, $v_i^+(x)$ rate at which individuals are moving in to i, and $v_i^-(x)$ rate at which individuals are moving out of i.

$$F(x_i) = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right] \; and \; V(x_i) = \left[\frac{\partial v_i(x_0)}{\partial x_j}\right], \quad i \leq j \leq m$$

$where \; v_i(x) = v_i^-(x) - v_i^+(x)$

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

$where \; \rho(\mathrm{X})$ is the spectral radius of X

Now, for the model described in (3.2),

$$\mathcal{F}_i = \begin{bmatrix} 0 \\ \dfrac{\beta(1-p)SI}{1+\delta I} \\ \dfrac{\beta pSI}{1+\delta I} \end{bmatrix}$$

$$v_i = \begin{bmatrix} -\Lambda + \mu S + \dfrac{\beta SI}{1+\delta I} \\ -r_2 I + (\mu + a)E \\ -\mathrm{aE} + b\mathrm{I} \end{bmatrix}$$

$$F = \begin{bmatrix} 0 & \dfrac{\beta(1-p)S}{1+\delta I} - \dfrac{\beta(1-p)SI\delta}{(1+\delta I)^2} \\ 0 & \dfrac{\beta pS}{1+\delta I} - \dfrac{\beta pSI\delta}{(1+\delta I)^2} \end{bmatrix} \qquad (3.6)$$

At Disease-free equilibria

$$F(G_0) = \begin{pmatrix} 0 & \beta(1-p)S_0 \\ 0 & \beta p S_0 \end{pmatrix}$$

$$V(G_0) = \begin{pmatrix} \mu + a & -r_2 \\ -a & b \end{pmatrix}$$

$$V^{-1} = \frac{1}{\mu b + ab - ar_2}\begin{pmatrix} b & r_2 \\ a & \mu + a \end{pmatrix} \tag{3.7}$$

It follows that,

$$FV^{-1} = \frac{1}{\mu b + ab - ar_2}\begin{pmatrix} a\beta(1-p)S_0 & (\mu + a)\beta(1-p)S_0 \\ a\beta p S_0 & (\mu + a)\beta p S_0 \end{pmatrix} \tag{3.8}$$

The eigenvalues are;

$$\lambda_1 = 0, \lambda_2 = \frac{(\mu p + a)\beta S_0}{\mu b + ab - ar_2} \tag{3.9}$$

And the spectral radius of FV^{-1} is given by

$$\rho(FV^{-1}) = R_0 = \frac{(\mu p + a)\beta S_0}{\mu b + ab - ar_2} \tag{3.10}$$

3.3 Mathematical Analysis

In this section, the proposed model is analyzed mathematically to show the existence, uniqueness and stability of the model's solution. We start by determining the invariant region and showing that all solutions of the model (3.2) are positive for all $t \geq 0$.

3.3.1 Existence and uniqueness of solution

Theorem 3.1: $D_\varepsilon = \left\{(S, E, I) \in R_+^3 : 0 \leq S + E + I \leq \frac{\Lambda}{\mu} + \varepsilon\right\}$ is positively invariant and absorbing set which attracts all the solutions of (3.2).

Proof 3.1: Consider a function

$$Z(t) = S(t) + E(t) + I(t)$$

$$\begin{aligned} \dot{Z} &= \dot{S} + \dot{E} + \dot{I} \\ &= \Lambda - \mu S - \frac{\beta SI}{1+\delta I} + \frac{\beta(1-p)SI}{1+\delta I} + r_2 \mathrm{I} - (\mu + \mathrm{a})\mathrm{E} + \mathrm{aE} + \frac{\beta pSI}{1+\delta I} - b\mathrm{I} \\ &= \Lambda - \mu Z - dI \leq \Lambda - \mu Z \end{aligned} \tag{3.11}$$

Which means,

$$\dot{Z} \leq 0, \ for\ Z > \frac{\Lambda}{\mu} \tag{3.12}$$

Which implies D_ε is positively invariant set.

Now, solving (3.11),

$$\dot{Z} + \mu Z \leq \Lambda$$

Using the integrating factor as $e^{\int \mu dt} = e^{\mu t}$

$$\dot{Z}e^{\mu t} + \mu Z e^{\mu t} \leq \Lambda e^{\mu t}$$

$$\frac{d}{dt}(Ze^{\mu t}) \leq \Lambda e^{\mu t} \tag{3.13}$$

Integrating both sides,

$$Ze^{\mu t} \leq \frac{\Lambda}{\mu} e^{\mu t} + c$$

Where c is a constant of integration, which implies that

$$Z \leq \frac{\Lambda}{\mu} + ce^{-\mu t} \tag{3.14}$$

Using the initial conditions, when $t = 0$, as $Z(0)$

$$Z \leq \frac{\Lambda}{\mu} + Z(0)e^{-\mu t} \tag{3.15}$$

$$as\ t \to \infty, \ \ 0 \leq Z(t) \leq \frac{\Lambda}{\mu} + \varepsilon$$

Which implies that D is an attractive set, hence, every solution remains in the region D. Therefore, the region D is positively-invariant (i.e solutions remain positive for all times) and the model is well posed.

3.3.2 Global stability analysis

Theorem 3.2: If $R_0 \leq 1$, then the DFE model G_0 is globally asymptotically stable on

$$D = \left\{(S, E, I) \in R_+^3 : 0 \leq S + E + I \leq \frac{\Lambda}{\mu}\right\}.$$

Proof 3.2: Consider the following Lyapunov function;

$$V = aE + (\mu + a)I \tag{3.16}$$

The time derivative of Equation (3.16), is obtained as

$$\begin{aligned}
\dot{V}(S, E, I) &= a\dot{E} + (\mu + a)\dot{I} \\
&= a\left[\frac{\beta(1-p)SI}{1+\delta I} + r_2 \mathrm{I} - (\mu + \mathrm{a})\mathrm{E}\right] + (\mu + a)\left[\mathrm{aE} + \frac{\beta pSI}{1+\delta I} - b\mathrm{I}\right] \\
&= a\frac{\beta(1-p)SI}{1+\delta I} + ar_2 \mathrm{I} - \mathrm{a}(\mu + \mathrm{a})\mathrm{E} + \mathrm{a}(\mu + \mathrm{a})\mathrm{E} + (\mu + \mathrm{a})\frac{\beta pSI}{1+\delta I} - \\
&\quad (\mu + a)bI \\
&= \frac{\beta SI}{1+\delta I}(a - ap + \mu p + ap) + (ar_2 - b\mu - ab)I \\
&= \left[\frac{\beta S(a+\mu p)}{1+\delta I} - (b\mu + a(b - r_2))\right] I \\
&\leq \left[\beta S(a + \mu p) - \left(b\mu + a(b - r_2)\right)\right] I \\
&\leq \left[\beta S_0(a + \mu p) - \left(b\mu + a(b - r_2)\right)\right] I \\
&= \left(b\mu + a(b - r_2)\right)\left[\frac{\beta S_0(a+\mu p)}{b\mu + a(b-r_2)} - \frac{b\mu + a(b-r_2)}{b\mu + a(b-r_2)}\right] I \\
&= -\left(b\mu + a(b - r_2)\right)[1 - R_0]
\end{aligned} \tag{3.17}$$

This implies $\dot{V}(S,E,I) \leq 0 \;\; if \;\; R_0 \leq 1$.

By Lasalle invariant principle (Bhatia & Szegö, 1970), the DFE is, therefore globally asymptotically stable.

Theorem 3.3: The EE G_1 is globally asymptotically stable if $R_0 > 1$.

Proof 3.3: Consider the following Lyapunov function

$$V = (S - S_1 lnS) + \frac{a}{\mu p + a}(E - E_1 lnE) + \frac{\mu + a}{\mu p + a}(I - I_1 lnI) \tag{3.18}$$

The time derivative of Equation (3.18), is given by

$$\begin{aligned}
\dot{V} &= \left(1 - \frac{S_1}{S}\right)\dot{S} + \frac{a}{\mu p + a}\left(1 - \frac{E_1}{E}\right)\dot{E} + \frac{\mu + a}{\mu p + a}\left(1 - \frac{I_1}{I}\right)\dot{I} \\
&= \left(1 - \frac{S_1}{S}\right)\left[\Lambda - \mu S - \frac{\beta SI}{1 + \delta I}\right] + \frac{a}{\mu p + a}\left(1 - \frac{E_1}{E}\right)\left[\frac{\beta(1-p)SI}{1 + \delta I} + r_2 I - (\mu + a)E\right] \\
&+ \frac{\mu + a}{\mu p + a}\left(1 - \frac{I_1}{I}\right)\left[aE + \frac{\beta pSI}{1 + \delta I} - bI\right] \\
&= \left(1 - \frac{S_1}{S}\right)\left[\mu S_1 + \frac{\beta S_1 I_1}{1 + \delta I_1} - \mu S - \frac{\beta SI}{1 + \delta I}\right] \\
&+ \frac{a}{\mu p + a}\left(1 - \frac{E_1}{E}\right)\left[\frac{\beta(1-p)SI}{1 + \delta I} + r_2 I - \frac{\beta(1-p)S_1 I_1}{1 + \delta I_1}\frac{E}{E_1} - r_2 I_1 \frac{E}{E_1}\right] \\
&+ \frac{\mu + a}{\mu p + a}\left(1 - \frac{I_1}{I}\right)\left[aE + \frac{\beta pSI}{1 + \delta I} - bI\right]
\end{aligned}$$

$$\begin{aligned}
&\leq \frac{-\mu(S - S_1)^2}{S} \\
&+ \beta S_1 I_1 \left[\left(1 - \frac{S_1}{S}\right)\left(\frac{-SI}{S_1 I_1} + 1\right) + \frac{a}{\mu p + a}(1-p)\left(1 - \frac{E_1}{E}\right)\left(\frac{SI}{S_1 I_1} - \frac{E}{E_1}\right)\right. \\
&\quad \left. + \frac{\mu + a}{\mu p + a} p\left(1 - \frac{I_1}{I}\right)\left(\frac{SI}{S_1 I_1} - \frac{I}{I_1}\right) + \frac{\mu + a}{\mu p + a}\left(\frac{a(1-p)}{\mu + a}\right)\left(1 - \frac{I_1}{I}\right)\left(\frac{E}{E_1} - \frac{I}{I_1}\right)\right] \\
&\quad + r_2 I_1 \left[\frac{a}{\mu p + a}\left(1 - \frac{E_1}{E}\right)\left(\frac{I}{I_1} - \frac{E}{E_1}\right) + \frac{\mu + a}{\mu p + a}\left(\frac{a}{\mu + a}\right)\left(1 - \frac{I_1}{I}\right)\left(\frac{E}{E_1} - \frac{I}{I_1}\right)\right]
\end{aligned} \tag{3.19}$$

Let

$$x_1 = \frac{S}{S_1}, x_2 = \frac{E}{E_1}, x_3 = \frac{I}{I_1} \tag{3.20}$$

Then

$$\begin{aligned}
\dot{V} &\leq \frac{-\mu(S-S_1)^2}{S} \\
&+\beta S_1 I_1 \left[\left(1-\frac{1}{x_1}\right)(-x_1x_3+1) + \frac{a}{\mu p+a}(1-p)\left(1-\frac{1}{x_2}\right)(x_1x_3-x_2)\right. \\
&\left.+\frac{\mu+a}{\mu p+a}p\left(1-\frac{1}{x_3}\right)(x_1x_3-x_3) + \frac{\mu+a}{\mu p+a}\left(\frac{a(1-p)}{\mu+a}\right)\left(1-\frac{1}{x_3}\right)(x_2-x_3)\right] \\
&+r_2 I_1 \left[\frac{a}{\mu p+a}\left(1-\frac{1}{x_2}\right)(x_3-x_2) + \frac{\mu+a}{\mu p+a}\left(\frac{a}{\mu+a}\right)\left(1-\frac{1}{x_3}\right)(x_2-x_3)\right] \\
&= \frac{-\mu(S-S_1)^2}{S} + \beta S_1 I_1 \left[1+x_3-\frac{1}{x_1}+\frac{a}{\mu p+a}(1-p)\left(1-\frac{x_1x_3}{x_2}-x_3-\frac{x_2}{x_3}\right)\right. \\
&\left.+\frac{\mu+a}{\mu p+a}p(1-x_1-x_3)\right] - r_2 I_1 \left[\frac{a}{\mu p+a}\frac{(x_2-x_3)^2}{x_2x_3}\right]
\end{aligned} \tag{3.21}$$

Hence, $\dot{V} \leq 0$, if

$$n = 1+x_3-\frac{1}{x_1}+\frac{a}{\mu p+a}(1-p)\left(1-\frac{x_1x_3}{x_2}-x_3-\frac{x_2}{x_3}\right)+\frac{\mu+a}{\mu p+a}p(1-x_1-x_3) \leq 0$$

Since

$$\frac{\partial n(x_1,x_2,x_3,p)}{\partial p} = \frac{-a(\mu+a)}{(\mu p+a)^2}\left[1+x_1-\frac{x_1x_3}{x_2}-\frac{x_2}{x_3}\right] \tag{3.22}$$

Fixing $x_1, x_2,$ and x_3 implies that $\frac{\partial n}{\partial p}$ has a constant sign for p. Hence, n attains its maximum at $p = 0 \; or \; p = 1$.

If $p = 0$, n variable will be rewritten as:

$$n = 3 - \frac{x_1 x_3}{x_2} - \frac{x_2}{x_3} - \frac{1}{x_1}$$

If $p = 1$, n variable will be rewritten as:

$$n = 2 - x_1 - \frac{1}{x_1}$$

In both cases, $n \leq 0$ using the relation between geometric and arithmetic means.

3.4 Model Fitting

Model fitting is used to validate a mathematical model. It is a process by which the conformity of a mathematical model to real-world data is established (Halder & Bhattacharya, 2011). After developing a model, model fitting is often used to get estimates of the parameters, and it also provides high reliability in the model. In order to fit an epidemic compartmental model, it is expected that data for at least one class in the model is available in time-series format. In epidemiology, the most widely used method for model fitting is the least-square technique. In the least-squares approach, the model response curve is fitted through the data points in such a way that the sum of the squares of the residual between the data points and the points on the fitted curve is minimal. For instance, if we are to fit the prevalence of a disease $I(t)$, and we have the real data set in the form of time series as $\{(t_1, Y_1), \ldots\ldots\ldots\ldots, (t_N, Y_N)\}$, then following expression of sum-squared error (SSE) should be minimized:

$$SSE = \sum_{i=1}^{N} [Y_i - I(t_i)]^2 \qquad (3.23)$$

For the fitting of the proposed model, TB prevalence data is collected from (Centers for Disease Control and Prevention, 2018). The data includes the yearly tuberculosis cases in the United States from 1988 to 2018. However, minimization of (3.23) is a nonlinear optimization problem because the epidemic model is described by nonlinear differential equations and cannot be solved explicitly. Meanwhile, for our work, the solution is obtained numerically using Matlab2019b software.

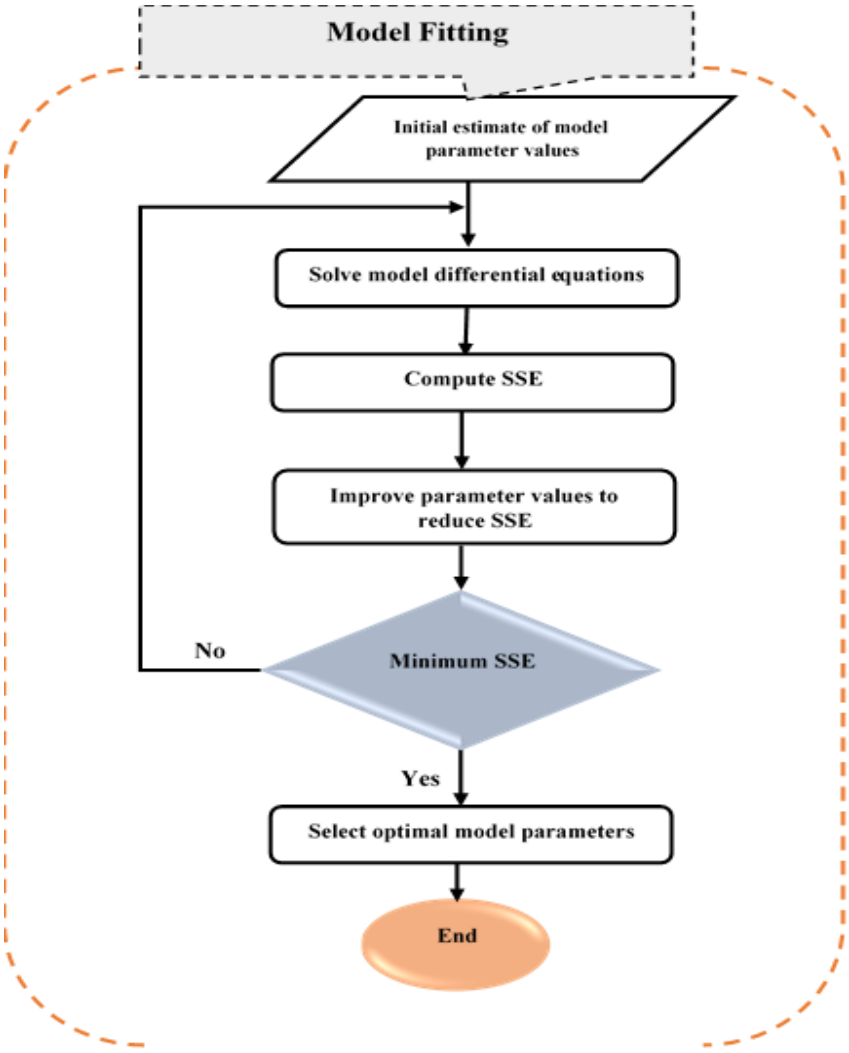


Figure 3.2: Model fitting flowchart (Martcheva, 2013)

The computation involves two stages: first, the differential equation is solved, followed by iterative minimization of the error function. An initial estimate of the parameter values is given, and the differential equations are solved with the initial values. The SSE is then evaluated, and accordingly parameters are adjusted to reduce the SSE. The differential equation is solved again, with the improved parameter values, and the procedure is repeated until the SSE converges (Martcheva, 2013).

The process can be concisely explained in the following steps (see Flowchart 3.2):

Step 1: Initial estimate of the model parameters

Step 2: Solve the model differential equations with the initially estimated parameters

Step 3: Compute SSE

Step 4: Adjust the values of the parameters so as to reduce the SSE

Step 5: Repeat step 2 to 4 with the new values until the minimum value of SSE is obtained.

3.5 Sensitivity Analysis

While studying the infectious diseases mathematically, after the estimation of the model parameters, it is essential to determine the significant model parameters that influence disease transmission. Therefore, sensitivity analysis is performed in mathematical studies. This is critical in enabling us to identify the key input parameters that should be the center of focus for the disease to be contained. In this study, the sensitivity analysis is performed to ascertain the uncertainty of the parameters to the proposed TB model through the threshold quantity; the basic reproduction number R_0. The sensitivity analysis is carried out using the normalized sensitivity index. The normalized sensitivity index of an output quantity y, to an input parameter x is represented as Π_x^y and defined by (Woldegerima et al., 2018):

$$\tilde{s}_x = \Pi_x^y = \frac{x}{y}\frac{\partial y}{\partial x} \tag{3.24}$$

Now, consider the basic reproduction number of the proposed TB model given by

$$R_0 = \frac{(\mu p - r_1 + 1)\beta\Lambda}{\mu\big((1-r_1)(r_2+\mu+\mathrm{d})-(1-r_1)r_2+(r_2+\mu+\mathrm{d})\mu\big)} \tag{3.25}$$

and the set of the input parameters for R_0

$$\Upsilon = \{\Lambda, \beta, p, d, \mu, r_1, r_2\} \tag{3.26}$$

The normalized sensitivity index of R_0, to a parameter $x \in \Upsilon$ is given by:

$$\tilde{s}_x = \Pi_x^{R_0} = \frac{x}{R_0}\frac{\partial R_0}{\partial x} \tag{3.27}$$

Using the sensitivity index definition (3.27), following indices are obtained for R_0 (3.25) relative to each of the parameters in (3.26):

$$\begin{aligned}\Pi_{\Lambda}^{R_0} &= \frac{\Lambda}{R_0}\frac{\partial R_0}{\partial \Lambda} \\ &= \left(\frac{(\mu p - r_1 + 1)\beta}{\mu\big((1-r_1)(r_2+\mu+\mathrm{d})-(1-r_1)r_2+(r_2+\mu+\mathrm{d})\mu\big)}\right) \\ &\times \left(\frac{\mu\big((1-r_1)(r_2+\mu+\mathrm{d})-(1-r_1)r_2+(r_2+\mu+\mathrm{d})\mu\big)}{(\mu p - r_1 + 1)\beta}\right) \\ &= 1\end{aligned} \tag{3.28}$$

$$\Pi_{\beta}^{R_0} = \frac{\beta}{R_0}\frac{\partial R_0}{\partial \beta} = 1 \tag{3.29}$$

$$\Pi_{p}^{R_0} = \frac{p}{R_0}\frac{\partial R_0}{\partial p} = \frac{p\mu}{\mu p - r_1 + 1} \tag{3.30}$$

$$\begin{aligned}\Pi_{d}^{R_0} &= \frac{d}{R_0}\frac{\partial R_0}{\partial d} \\ &= -\frac{d(1-r_1+\mu)}{(1-r_1)(r_2+\mu+\mathrm{d})-(1-r_1)r_2+(r_2+\mu+\mathrm{d})\mu}\end{aligned} \tag{3.31}$$

$$\begin{aligned}\Pi_{\mu}^{R_0} &= \frac{\mu}{R_0}\frac{\partial R_0}{\partial \mu} \\ &= \frac{-2p\mu^3+\big((p+3)r_1-dp-3+(-r_2-1)p\big)\mu^2+2(r_1-1)(d-r_1+r_2+1)\mu-d(r_1-1)^2}{\big(\mu^2+(d-r_1+r_2+1)\mu-d(r_1-1)\big)(\mu p-r_1+1)}\end{aligned} \tag{3.32}$$

$$\begin{aligned}\Pi_{r_1}^{R_0} &= \frac{r_1}{R_0}\frac{\partial R_0}{\partial r_1} \\ &= \frac{r_1\mu\big((1-r_1)(r_2+\mu+\mathrm{d})-(1-r_1)r_2+(r_2+\mu+\mathrm{d})\mu\big)\big((p-1)\mu+(p-1)d-r_2\big)}{(\mu p-r_1+1)\big(\mu^2+(d-r_1+r_2+1)\mu-d(r_1-1)\big)^2}\end{aligned} \tag{3.33}$$

$$\begin{aligned}\Pi_{r_2}^{R_0} &= \frac{r_2}{R_0}\frac{\partial R_0}{\partial r_2} \\ &= -\frac{r_2\mu}{(1-r_1)(r_2+\mu+\mathrm{d})-(1-r_1)r_2+(r_2+\mu+\mathrm{d})\mu}\end{aligned} \tag{3.34}$$

3.6 Optimal Control System

In this section, the optimal TB control system is formulated by modifying the TB model defined in (3.1). The purpose of the optimal control analysis is to obtain the optimal trajectories of the system states; S, E and I in response to the control scheme. The constants rate of chemoprophylaxis r_1 and treatment rate r_2 are substituted with control functions $u_1(t)$ and $u_2(t)$ respectively. The control input $u_1(t)$ characterized the monitoring action that involves finding and treating people that are exposed in order to stop them from becoming infectious (known as "case finding"), while $u_2(t)$ symbolizes the interventions made by health workers to ensure adherence to the proper treatment of the infected people (known as "case holding"). The control inputs $u_1(t)$ and $u_2(t)$ are regarded as Lebesgue integrable and bounded functions having values within the closed range $[0,1]$ (Gao & Huang, 2018). The parameters are the same as those in (3.1), and the optimal TB controlled system is described as:

$$\begin{aligned} \dot{S} &= \Lambda - \mu S - \frac{\beta SI}{1+\delta I} \\ \dot{E} &= \frac{\beta(1-p)SI}{1+\delta I} + u_2(\mathrm{t})\mathrm{I} - \mu\mathrm{E} - \big(1-u_1(\mathrm{t})\big)E \\ \dot{I} &= \big(1-u_1(\mathrm{t})\big)E + \frac{\beta pSI}{1+\delta I} - u_2(\mathrm{t})\mathrm{I} - (\mu+d)\mathrm{I} \end{aligned} \tag{3.35}$$

and state variables set

$$X(t) = \big(S(t), E(t), I(t)\big) \tag{3.36}$$

The cost of implementation of the control is taken as quadratic, similar to (Jung, 2002b), and the aim is to reduce disease prevalence and cost of control actions. Consequently, the objective functional is defined as

$$J(u_1, u_2) = \int_0^{t_f} \left(a_1 E(t) + a_2 I(t) + \frac{w_1}{2}u_1^2(t) + \frac{w_2}{2}u_2^2(t)\right) dt \tag{3.37}$$

The constant factors a_1, a_2, w_1 and w_2 are positive weights associated with the exposed class, infectious class and the control measures.

3.6.1 Optimal control analysis

The problem can then be stated as to identify optimal control inputs u_1^* and u_2^* and optimal system states $X^* = (S^*, E^*, I^*)$, which minimizes the performance index (3.37) over a fixed-time interval $[0, t_f]$, subjects to the system constrain (3.35). States mathematically as

$$J(X^*, u_1^*, u_2^*) = \min_{\Gamma} J(X, u_1, u_2) \tag{3.38}$$

Where

$$\Gamma = \{X \in W^{1.1}([0, t_f]; \mathbb{R}^3), (u_1, u_2) \in L^1([0, t_f]; \mathbb{R}) | X(0) \geq 0, \text{and (3.35) are satisfied}\}$$

The criteria required for optimal disease control can be derived from the maximum principle introduced by Pontraygin (Bather et al., 1976b). Consider the Hamiltonian function *H* described as:

$$\begin{aligned} H(X, u_1, u_2, \lambda) = {} & a_1 E(t) + a_2 I(t) + \frac{w_1}{2} u_1^2(t) + \frac{w_2}{2} u_2^2(t) \\ & + \lambda_1 \left(\Lambda - \mu S - \frac{\beta SI}{1 + \delta I} \right) \\ & + \lambda_2 \left(\frac{\beta(1-p)SI}{1 + \delta I} + u_2(\mathrm{t})\mathrm{I} - \mu \mathrm{E} - \big(1 - u_1(\mathrm{t})\big)E \right) \\ & + \lambda_3 \left(\big(1 - u_1(\mathrm{t})\big)E + \frac{\beta pSI}{1 + \delta I} - u_2(\mathrm{t})\mathrm{I} - (\mu + d)\mathrm{I} \right) \end{aligned} \tag{3.39}$$

For the minimization of the performance index (3.37) over a fixed final time t_f, the optimal control pair u_1^* and u_2^* and corresponding states $X^* = (S^*, E^*, I^*)$ should satisfy the following necessary conditions:

1. The conditions of optimality

$$\begin{aligned} \frac{\partial H(X, u_1, u_2, \lambda)}{\partial u_1} &= 0 \\ \frac{\partial H(X, u_1, u_2, \lambda)}{\partial u_2} &= 0 \end{aligned} \tag{3.40}$$

2. The conditions for the optimal control system

$$\dot{S} = \frac{\partial H(X, u_1, u_2, \lambda)}{\partial \lambda_1}$$

$$\dot{E} = \frac{\partial H(X, u_1, u_2, \lambda)}{\partial \lambda_2}$$

$$\dot{I} = \frac{\partial H(X, u_1, u_2, \lambda)}{\partial \lambda_3}$$

3. The conditions for the co-state system

$$\begin{aligned} \dot{\lambda}_1 &= -\frac{\partial H(X,u_1,u_2,\lambda)}{\partial S}, \\ \dot{\lambda}_2 &= -\frac{\partial H(X,u_1,u_2,\lambda)}{\partial E}, \\ \dot{\lambda}_3 &= -\frac{\partial H(X,u_1,u_2,\lambda)}{\partial I}. \end{aligned} \tag{3.41}$$

where λ_1, λ_2, and λ_3 are the co-state variables.

4. The condition for the minimization

$$H(X^*, u_1^* t, u_2^*, \lambda^*) = \min_{0 \le u_1, u_2 \le 1} H(X^*, u_1, u_2, \lambda^*), \text{ is valid for } t \in [0, t_f].$$

5. The conditions for the transversality

$$\lambda_i(t_f) = 0, \ i = 1,2,3 \tag{3.42}$$

are also true.

Theorem 3.4: The optimal solutions, S^*, E^*, I^* and relevant optimal control inputs u_1^* *and* u_2^*, that minimizes $J(X, u_1, u_2)$ over Γ, exist. The co-state functions $\lambda_1^*(t)$, $\lambda_2^*(t)$, $\lambda_3^*(t)$ also exist, so that

$$
\begin{aligned}
\dot{\lambda}_1(t) &= \lambda_1^*(t)\left(\mu + \frac{\beta I^*(t)}{1+\delta I^*(t)}\right) - \lambda_2^*(t)\frac{\beta(1-p)I^*(t)}{1+\delta I^*(t)} - \lambda_3^*(t)\frac{\beta p I^*(t)}{1+\delta I^*(t)} \\
\dot{\lambda}_2(t) &= \lambda_2^*(t)\left(\mu + \left(1-u_1^*(t)\right)\right) - \lambda_3^*(t)\left(1-u_1^*(t)\right) - a_1 \\
\dot{\lambda}_3(t) &= \lambda_1^*(t)\frac{\beta S^*(t)}{\left(1+\delta I^*(t)\right)^2} - \lambda_2^*(t)\left(\frac{\beta(1-p)S^*(t)}{\left(1+\delta I^*(t)\right)^2} + u_2^*(t)\right) \\
&\quad -\lambda_3^*(t)\left(\frac{\beta p S^*(t)}{\left(1+\delta I^*(t)\right)^2} - u_2^*(t) - (\mu+d)\right) - a_2
\end{aligned}
\tag{3.43}
$$

Conditions for the transversality,

$$
\lambda_i^*(t_f) = 0, \quad i = 1,2,3 \tag{3.44}
$$

Correspondingly, the continuous piecewise characterization of the two control inputs hold as follows:

$$
\begin{aligned}
u_1^*(t) &= min\left\{max\left\{0, \frac{\left(\lambda_3^*(t)-\lambda_2^*(t)\right)E^*(t)}{w_1}\right\}, 1\right\} \\
u_2^*(t) &= min\left\{max\left\{0, \frac{\left(\lambda_3^*(t)-\lambda_2^*(t)\right)I^*(t)}{w_2}\right\}, 1\right\}
\end{aligned}
\tag{3.45}
$$

Proof 3.4: The existence of the optimal solutions and the equivalent control inputs are obtained from the boundedness of the system states solution and its Lipschitz property with regard to state variables as well as the convexity of J with regards to the control inputs u_1 and u_2. The optimal control functions given by (3.45) are unique because of boundedness of the state and co-state systems and the Lipschitz property of (3.35) and (3.43) (Bather et al., 1976). Also, the system (3.43) is derived from the conditions of the co-state system (3.40). At the same time, the characterization of the optimal control inputs (3.45) is extracted from the optimal system condition (3.40) defined in the Pontryagin's principles.

Eventually, the optimality system consists of the optimal control inputs (3.45), the condition of transversality (3.44), the optimal TB control system (3.35) and the initial conditions $S_0, E_0, I_0 \geq 0$.

3.7 Simulation Results and Discussions

This section presents the simulation results and discussions. Numerical simulations are usually performed using professional software to support the theoretical facts and provides a graphical representation of the results. In this section the result of the model fitting sensitivity analysis and the proposed TB model is presented.

3.7.1 Model fitting results

The proposed model has seven parameters from which four are estimated, while the remaining three are to be fitted. The values of the disease transmission rate (β) and recruitment rate (Λ) are obtained from (Yang et al., 2016). The constant treatment rates r_1 and r_2 which takes values in the range [0,1], are estimated to be 0.95 and 0.2 respectively (McBryde et al., 2017). The fitted and estimated parameter values are presented in Table 3.1 in which the disease-induced death rate (d), fraction of the susceptible that under goes fast progression to infected (p) and the rate of natural death (μ) are found through the fitting method explained in section 3.4. Figure 3.3 shows the fitting of the model through the data instances.

Table 3.1: Parameter Estimation

Parameter	Value	Unit
Λ	1000	person year^{-1}
β	0.003	person^{-1} year^{-1}
r_1	0.95	constant
r_2	0.2	constant
μ	0.3	year^{-1}
p	0.5	constant
d	0.55	year^{-1}

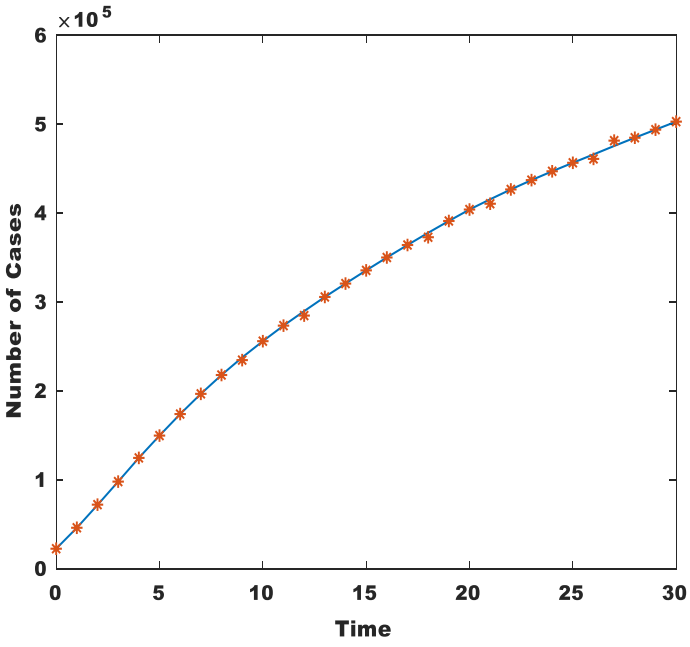


Figure 3.3: Model fitting for TB cases

3.7.2 Sensitivity analysis result

The sensitivity index values of the model parameters with respect to R_0 are computed using the normalized sensitivity coefficients obtained in equations (3.28)-(3.34) and the parameters defined in Table 3.1. The result is shown in Table 3.2. Parameters with positive index are directly proportional to the value of $\mathcal{R}_0$, which means the prevalence of the disease increases as the parameter values increase. Whereas the negative index values indicate inverse proportionality; and hence, parameters with a negative index will decrease the prevalence of the disease when they are increased. The results in Table 3.2 show that β (disease transmission rate) has the potential to worsen the TB outbreak. This suggests that reducing contact between healthy humans and infected individuals will help in controlling the spread of the disease. Moreover, the prevalence of the disease can be decreased by increasing the constant treatment rates r_1 and r_2. Figure 3.4 shows the graphical representation of the index values

Table 3.2: Sensitivity index of parameter values with respect to R_0

Parameter (x)	Index Value
Λ	1.00
β	1.00
p	0.75
d	-0.54
μ	-1.42
r_1	-2.49
r_2	-0.17

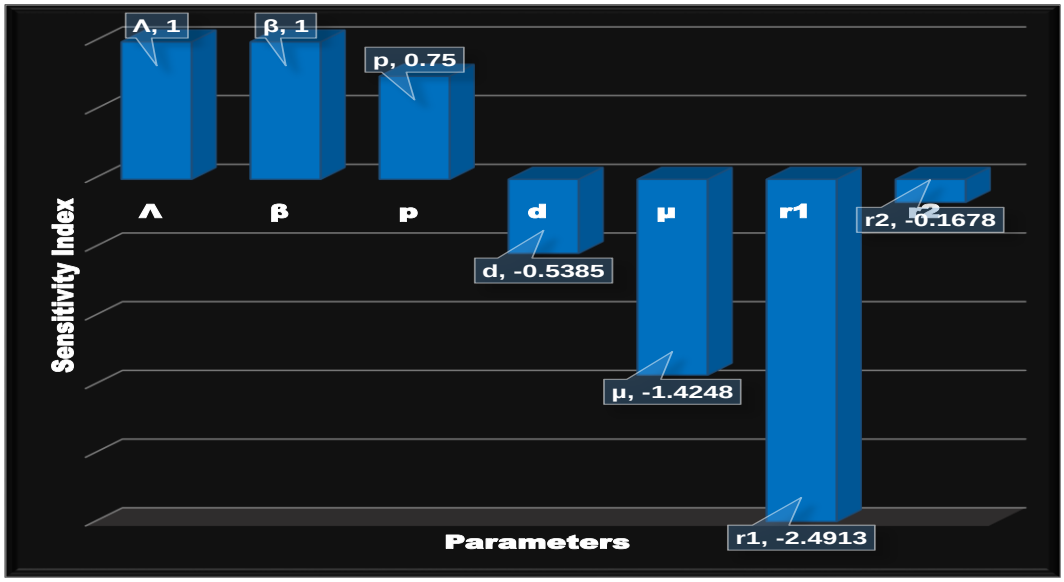


Figure 3.4: Bar charts of the sensitivity index values

3.7.3 Model simulation results

In this section the proposed TB model is simulated in the case without optimal controls and optimal controls. The initial values are defined as $S_0 = 3800, E_0 = 1800$ and $I_0 = 200$ respectively, for the susceptible, exposed and infectious classes. The epidemiological parameters obtained in Table 3.1, along with the initial values of the state variables, are used in the simulations.

Using Matlab2019b platform with ode45 solver, the TB model given by the system (3.2) is solved numerically. The optimal control system which comprises of the system states and co-states (6 ODEs) is solved by utilizing the forward-backwards sweeping technique. In this approach, the system of the state equations (3.35) is solved forward in time, by substituting the initial estimate of the control values and the values of the states' initial conditions. Using the current state iteration value, control variables and the conditions of transversality (3.44), the co-state equations are computed backwards in time. Subsequently, the system states and co-state values are substituted into the control characterization (3.45) to obtain the update of the control values. The procedure is repeated until the values converged.

Figure 3.5 depicts the dynamic of TB when the reproduction ratio is less than one. It can be observed that both the number of the exposed (E) and infectious (I) individuals vanish; due to the fact that $R_0 < 1$. In Figure 3.6, the dynamics of the tuberculosis is shown when the basic reproduction number is greater than one. It is clear from the figure that both population of the exposed (E) and infected (I) groups persist, and there is endemic because $R_0 > 1$.

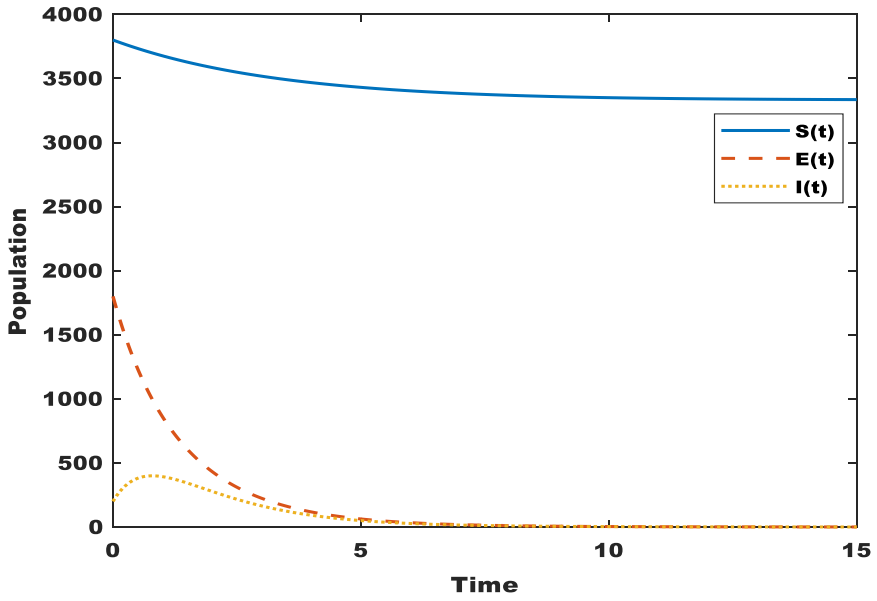


Figure 3.5: Both exposed and infected individuals vanished with $R_0 < 1$

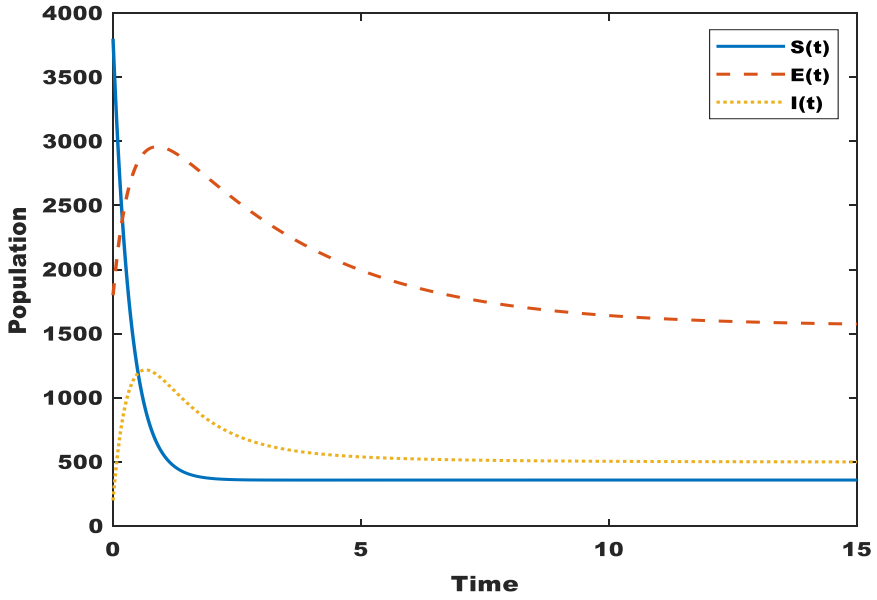


Figure 3.6: Persistence of exposed and infectious population with $R_0 > 1$

In order to express the influence of the public awareness parameter δ, three different values are considered $\delta = 0.4, 0.6$ and 0.8, and the result is illustrated in Figure 3.7. Thus it could be readily observed that there is a further decrease in the infectious population with an increase in the value of δ. Which means the spread of the disease can be significantly reduced by increasing public awareness.

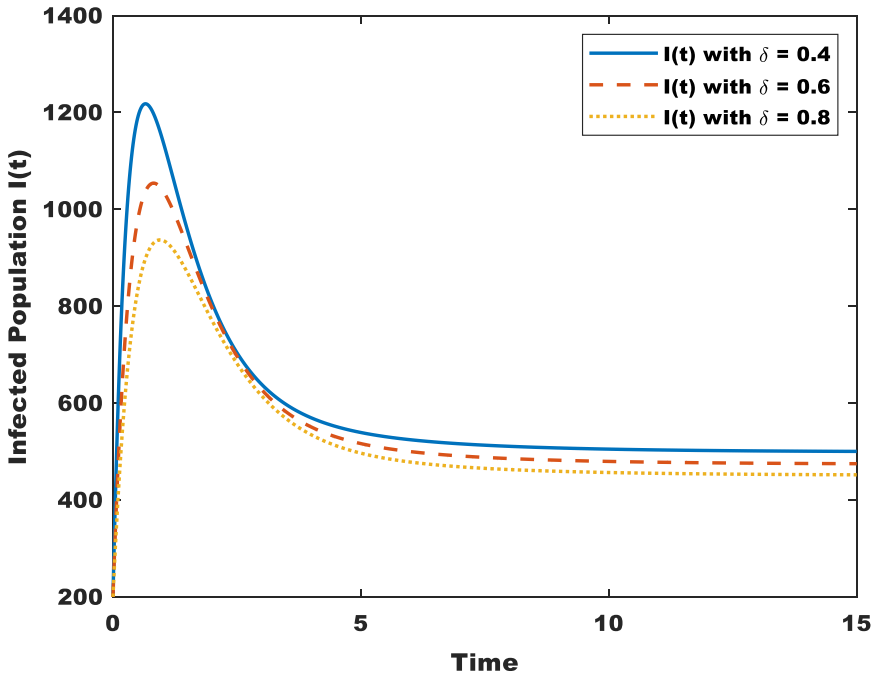


Figure 3.7: Effect of awareness on the infectious population

Figure 3.8 demonstrates the trajectories of the optimal control strategies. The control input $u_1(t)$ (solid line) and the control input $u_2(t)$, are plotted as function of time. From this figure it is suggested that the case finding intervention (u_1) should be maintained at the highest level during the entire period of the control program, to successfully mitigate the disease.

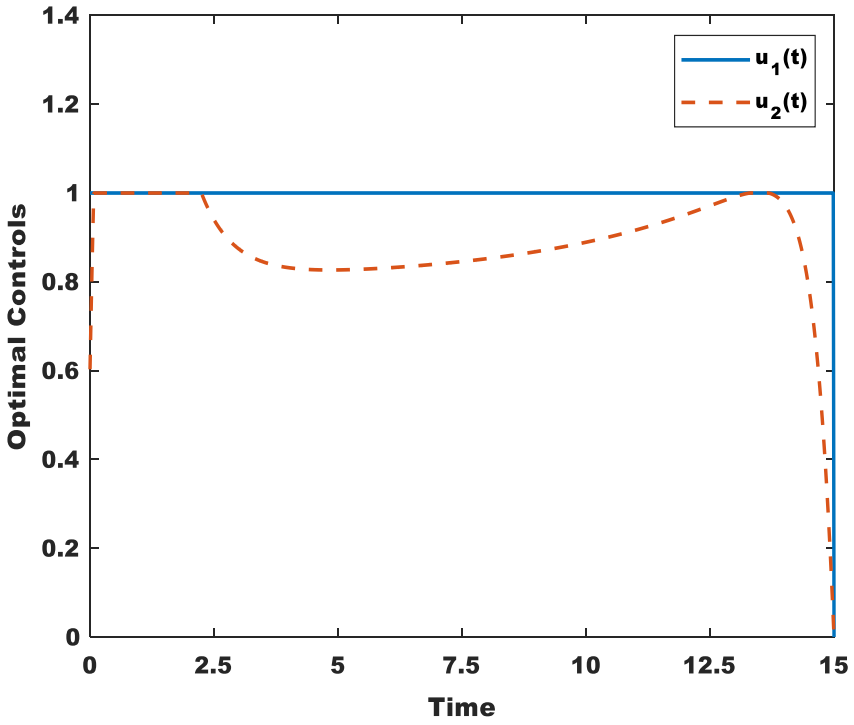


Figure 3.8: Optimal controls profile: with weight constant $a_1 = 20, a_2 = 100,$ $w_1 = 100\ and\ w_2 = 8000.$

Figure 3.9 illustrates the effect of application of optimal control strategies on the infectious group. The influence of using the individual control strategy separately ($u_1(t)$ or $u_2(t)$) and employing the two control strategies ($u_1(t)$ and $u_2(t)$) simultaneously are shown in this figure. From the figure, it can be seen that the effect of combining the two control strategies in minimizing the infectious population (dash-dotted curve) is greater than the individual strategies. Using case finding (u_1) strategy alone also has more impact in reducing the population of the infectious (dotted curve) than using the case holding (u_2) strategy alone. In Figure 3.10, the effect of integrating public awareness (measured by δ) in the control intervention program is illustrated (dash-dotted curve). It shows that by using the $\delta = 0.8$ (high public awareness) the influence of the optimal control strategies in minimizing the disease prevalence is further increased.

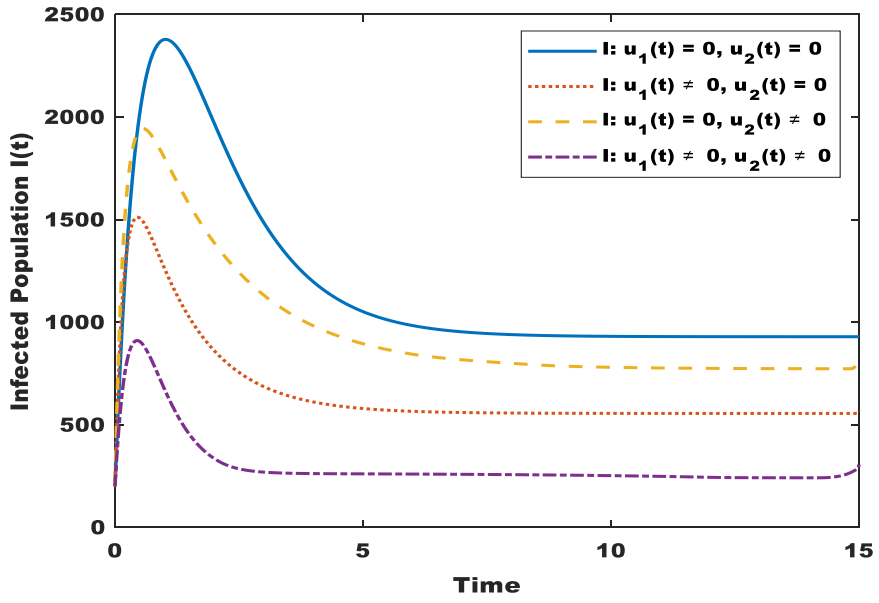


Figure 3.9: Effect of different optimal controls combination on the infected population

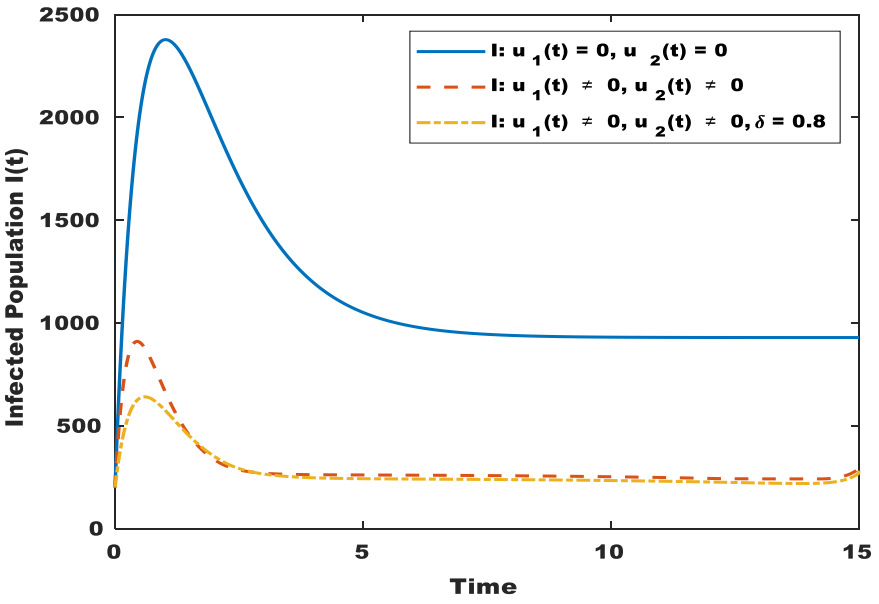


Figure 3.10: Effects of combining optimal control with awareness

The results demonstrate how the inclusion of optimal control management method help in reducing the population of the infectious and hence minimized the prevalence of the disease.

It is observed from the result (see Figure 3.10) that, at the end of the program, the total number of the infected individuals is 929 when there is no optimal control intervention, is 308 when the optimal control intervention is employed, and 282 when public awareness is included in the control implementation. It follows that by the completion of the control period, about 623 infections will be avoided, and 647 if high public awareness campaign is integrated into the program. Therefore, the best method for minimizing the disease is to continuously conduct the control program and awareness to the general public. The analysis presented in this chapter differs from others (Bowong & Aziz Alaoui, 2013; Mushayabasa & Bhunu, 2013), since it incorporated saturated incidence rate and considered the impact of public awareness on the control of the disease transmission.

CHAPTER 4
OPTIMAL CONTROL AND COST-EFFECTIVENESS ANALYSIS OF TB WITH THREE DIFFERENT CONTROL INTERVENTIONS

4.1 Introduction

This chapter presents optimal control and cost-effectiveness analysis of a TB model with three different control interventions. The study incorporated three time-dependant control interventions and their various combinations, to find the most suitable and cost-effective control strategy for the minimization of the TB disease. Also, the effect of the parameter uncertainties on the open-loop optimal control system is shown through numerical simulations. The analysis in this chapter is based on the nonlinear TB model proposed by (Mccluskey, 2006), described in Equation (2.16).

4.2 Optimal Control System

In this scenario, the optimal control system with the three time-dependent control inputs $u_1(t)$, $u_2(t)$ and $u_3(t)$ is given by the following system of ODEs:

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta SI - \big(\mu + u_1(t)\big)S \\ \frac{dE}{dt} = (1-p)\beta SI - aE - \big(\mu + u_2(t)\big)E \\ \frac{dI}{dt} = p\beta SI + aE - dI - \big(\mu + u_3(t)\big)I \end{cases} \tag{4.1}$$

where the control input $u_1(t)$ denotes the vaccination given to a fraction of the susceptible individuals to provide them with immunity from the disease, while $u_2(t)$ and $u_3(t)$ represents the control interventions through the case finding and case holding respectively. The optimal control inputs are assumed to be bounded, integrable, Lebesgue functions with values in the closed set $[0,1]$. The state variables and the objective functional (performance index) are defined in (4.2) and (4.3) respectively.

$$X(t) = \big(S(t), E(t), I(t)\big) \tag{4.2}$$

$$J(u_1, u_2, u_3) = \int_0^{t_f} \left(b_1 E(t) + b_2 I(t) + \frac{w_1}{2} u_1^2(t) + \frac{w_2}{2} u_2^2(t) + \frac{w_3}{2} u_3^2(t) \right) dt \qquad (4.3)$$

The control objective is to deter the outbreak of the disease by reducing/minimizing the population of both the exposed and infectious persons, and also, reduce the cost of implementing the control program. The total cost of the control includes the disease-induced cost and the cost of vaccination and control interventions. Moreover, the cost associated with the control actions is taken to be nonlinear and quadratic, as in (Gao & Huang, 2018). Subsequently, the optimal control problem is to find the optimal controls u_1^*, u_2^* and u_3^* along with an equivalent set of state variables $X^* = (S^*, E^*, I^*)$ over the fixed time interval $[0, t_f]$ that minimises the objective functional (4.4) subject to the control system's dynamic constraints (4.1) as:

$$J(X^*, u_1^*, u_2^*) = \min_{\Psi} J(X, u_1, u_2, u_2) \qquad (4.4)$$

with

$$\Psi = \left\{ X \in W^{1.1}\left([0, t_f]; \mathbb{R}^3\right), (u_1, u_2, u_3) \in L^1\left([0, t_f];\ \mathbb{R}\right) \middle| X(0) \geq 0,\ (4.1) \text{ are satisfied} \right\}$$

4.3 Optimal Control Analysis

4.3.1 Existence of the optimal control

Theorem 4.1: There exist optimal controls $u_1^*, u_2^* \, and \, u_3^*$ and an associated optimal solution S^*, E^*, I^* to the problem defined in (4.4).

Proof 4.1: This theorem can be proved by adopting the conditions stated in Theorem 4.1 and Corollary 4.1 from (Bather et al., 1976a) and verifying the nontrivial conditions. Let $\varphi\left(\vec{X}, \vec{u}, t\right)$ represent the right-hand side of (4.1), the following conditions should be satisfied to prove the existence of the optimal control solutions.

Condition I: φ is of class C^1 and a constant ζ exists such that

$$|\varphi(0, 0, t)| \leq \eta,$$

$\left|\varphi_{\vec{X}}\left(\vec{X},,\vec{u},t\right)\right| \leq \eta(1+|\vec{u}|)$, and

$\left|\varphi_{\vec{u}}\left(\vec{X},,\vec{u},t\right)\right| \leq \eta$;

Condition II: The admissible set $\mathcal{F}$ of all solutions to system (4.1) along with associated control in Ψ is nonempty;

Condition III: $\varphi\left(\vec{X},\vec{u},t\right) = a\left(\vec{X},t\right) + b\left(\vec{X},t\right)\vec{u}$;

Condition IV: The optimal control set $U = \left[0,u_{1_{max}}\right] \times \left[0,u_{2_{max}}\right] \times \left[0,u_{3_{max}}\right]$ is closed, compact and convex;

Condition V: The objective functional integrand is convex in U.

By writing $\varphi\left(\vec{X},\vec{u},t\right)$ as in (4.5), it is evident that $\varphi\left(\vec{X},\vec{u},t\right)$ is of class $C^1$and $|\varphi(0,0,t)| = \Lambda$.

$$\varphi\left(\vec{X},\vec{u},t\right) = \begin{pmatrix} \Lambda - \beta SI - \left(\mu + u_1(t)\right)S \\ (1-p)\beta SI - aE - \left(\mu + u_2(t)\right)E \\ p\beta SI + \kappa E - dI - \left(\mu + u_3(t)\right)I \end{pmatrix} \tag{4.5}$$

also,

$$\left|\varphi_{\vec{X}}\left(\vec{X},\vec{u},t\right)\right| = \left|\begin{pmatrix} -\beta I - \mu - u_1 & 0 & -\beta S \\ (1-p)\beta I & -a-\mu-u_2 & (1-p)\beta S \\ p\beta I & \kappa & p\beta S - d - \mu - u_3 \end{pmatrix}\right| \tag{4.6}$$

and

$$\left|\varphi_{\vec{u}}\left(\vec{X},\vec{u},t\right)\right| = \left|\begin{pmatrix} -S & 0 & 0 \\ 0 & -E & 0 \\ 0 & 0 & -I \end{pmatrix}\right| \tag{4.7}$$

Owing to the boundedness of the state variables S, E and I, a constant η exists such that

$$|\varphi(0,0,t)| \leq \eta, \left|\varphi_{\vec{X}}\left(\vec{X},,\vec{u},t\right)\right| \leq \eta(1+|\vec{u}|), \text{and } \left|\varphi_{\vec{u}}\left(\vec{X},,\vec{u},t\right)\right| \leq \eta, \tag{4.8}$$

hence, the condition I is satisfied.

It can be deduced from condition I, for constant control, that a unique solution exists for the system (4.1), and it follows that condition II holds.

Furthermore, $\varphi\left(\vec{X},\vec{u},t\right)$ can be expanded as

$$\varphi\left(\vec{X},\vec{u},t\right)=\begin{pmatrix}\Lambda-\beta SI-\left(\mu+u_1(t)\right)S\\(1-p)\beta SI-aE-\left(\mu+u_2(t)\right)E\\p\beta SI+aE-dI-\left(\mu+u_3(t)\right)I\end{pmatrix}$$
$$=\begin{pmatrix}\Lambda-\beta SI-\mu S\\(1-p)\beta SI-aE-\mu E\\p\beta SI+aE-dI-\mu I\end{pmatrix}_{3\times1}+\left(\begin{pmatrix}-S&0&0\\0&-E&0\\0&0&-I\end{pmatrix}_{3\times3}\times\begin{pmatrix}u_1\\u_2\\u_3\end{pmatrix}_{3\times1}\right)$$

therefore, condition III is also satisfied.

Condition IV and condition V can be investigated by verifying the convexity of the integrand over the objective functional $r\left(\vec{X},\vec{u},t\right)$. The convexity is satisfied if for any two control vectors $\vec{u}$ and $\vec{v}$ and a constant $\rho\in[0,\ 1]$

$$(1-\rho)r\left(\vec{X},\vec{u},t\right)+\rho r\left(\vec{X},\vec{v},t\right)\geq r\left(\vec{X},(1-\rho)\vec{u}+\rho\vec{v},t\right)\qquad(4.9)$$

Where

$$r\left(\vec{X},\vec{u},t\right)=b_1E(t)+b_2I(t)+\frac{w_1}{2}u_1^2(t)+\frac{w_2}{2}u_2^2(t)+\frac{w_3}{2}u_3^2(t)$$

Considering the left-hand side of (4.9), we have

$$(1-\rho)r\left(\vec{X},\vec{u},t\right)+\rho r\left(\vec{X},\vec{v},t\right)=b_1E(t)+b_2I(t)+(1-\rho)\left[\frac{w_1}{2}u_1^2(t)+\right.$$
$$\left.\frac{w_2}{2}u_2^2(t)+\frac{w_3}{2}u_3^2(t)\right]+\rho\left[\frac{w_1}{2}v_1^2(t)+\frac{w_2}{2}v_2^2(t)+\frac{w_3}{2}v_3^2(t)\right]$$

and the right-hand side of (4.10) gives

$$r\left(\vec{X},(1-\rho)\vec{u}+\rho\vec{v},t\right)=b_1E(t)+b_2I(t)+\frac{w_1}{2}[(1-\rho)u_1+\rho v_1]^2+$$
$$\frac{w_2}{2}[(1-\rho)u_2+\rho v_2]^2+\frac{w_3}{2}[(1-\rho)u_3+\rho v_3]^2$$

it follows that,

$$
\begin{aligned}
&(1-\rho)r\left(\vec{X},\vec{u},t\right)+\rho r\left(\vec{X},\vec{v},t\right)-r\left(\vec{X},(1-\rho)\vec{u}+\rho\vec{v},t\right)\\
&=\frac{w_1}{2}[(1-\rho)u_1^2+\rho v_1^2]+\frac{w_2}{2}[(1-\rho)u_2^2+\rho v_2^2]+\frac{w_3}{2}[(1-\rho)u_3^2+\rho v_3^2]\\
&\quad-\frac{w_1}{2}[(1-\rho)u_1+\rho v_1]^2-\frac{w_2}{2}[(1-\rho)u_2+\rho v_2]^2-\frac{w_3}{2}[(1-\rho)u_3+\rho v_3]^2\\
&=\frac{w_1}{2}\{(1-\rho)u_1^2+\rho v_1^2-[(1-\rho)u_1+\rho v_1]^2\}+\frac{w_2}{2}\{(1-\rho)u_1^2+\rho v_1^2-[(1-\rho)u_1+\rho v_1]^2\}\\
&\quad+\frac{w_3}{2}\{(1-\rho)u_2^2+\rho v_2^2-[(1-\rho)u_3+\rho v_3]^2\}\\
&=\frac{w_1}{2}\{\rho(1-\rho)(u_1-v_1)^2\}+\frac{w_2}{2}\{\rho(1-\rho)(u_2-v_2)^2\}+\frac{w_3}{2}\{\rho(1-\rho)(u_3-v_3)^2\}\\
&\geq 0,
\end{aligned}
$$

consequently, both conditions IV and V are true, and the proof is completed.

4.3.2 Optimal control system characterisation

It has been proved in the previous section that the optimal controls that minimise the functional (4.3) subject to the system dynamic (4.1) exist. The necessary conditions for this control can be derived from the Pontryagin's principle (Pontryagin et al., 1962). Following the Pontryagin's principle, the control u_1^*, u_2^* and u_3^* with equivalent states variables X^* are optimal and minimises the objective functional (4.3) for a fixed final time t_f, if the following conditions holds:

1. The conditions for optimality

$$
\begin{cases}
\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial u_1}=0\\
\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial u_2}=0\\
\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial u_3}=0
\end{cases}
\tag{4.10}
$$

2. The conditions for the optimal control system

$$\begin{cases} \frac{dS}{dt} = \frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial \lambda_1} \\ \frac{dE}{dt} = \frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial \lambda_2} \\ \frac{dI}{dt} = \frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial \lambda_3} \end{cases}$$

3. The conditions for the co-state system

$$\begin{cases} \frac{d\lambda_1}{dt} = -\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial S} \\ \frac{d\lambda_2}{dt} = -\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial E} \\ \frac{d\lambda_3}{dt} = -\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial I} \end{cases} \tag{4.11}$$

4. The condition for minimisation

$$H(X^*, u_1^*, u_2^*, u_3^*, \lambda^*) = \min_{0 \le u \le 1} H(X^*, u_1, u_2, u_3, \lambda^*), \text{ holds for } t \in [0, t_f].$$

5. The conditions for the transversality

$$\lambda_i(t_f) = 0, \ i = 1,2,3 \tag{4.12}$$

are also true.

The Hamiltonian function (H) is described as:

$$\begin{aligned} H(X,u_1,u_2,u_3,\lambda) = b_1E(t) + b_2I(t) + \frac{w_1}{2}u_1^2(t) + \frac{w_2}{2}u_2^2(t) + \frac{w_3}{2}u_3^2(t) \\ +\lambda_1\left[\Lambda - \beta SI - \left(\mu + u_1(t)\right)S\right] \\ + \lambda_2\left[(1-p)\beta SI - kE - \left(\mu + u_2(t)\right)E\right] \\ + \lambda_3\left[p\beta SI + kE - dI - \left(\mu + u_3(t)\right)I\right] \end{aligned}$$

Theorem 4.2: There exist co-state variables $\lambda_1^*(t), \ \lambda_2^*(t), \ \lambda_3^*(t),$ given the optimal solution, S^*, E^*, I^* and associated control $u_1^*, u_2^* \ and \ u_3^*$ that minimises $J(X, u_1, u_2, u_3)$ over Ψ, such that

$$\begin{cases} \frac{d\lambda_1}{dt} = \lambda_1^*(t)[\beta I^*(t) + \mu + u_1^*(t)] - \lambda_2^*(t)(1-p)\beta I^*(t) - \lambda_3^*(t)p\beta I^*(t) \\ \frac{d\lambda_2}{dt} = \lambda_2^*(t)[\mu + k + u_2^*(t)] - b_1 \\ \frac{d\lambda_3}{dt} = \lambda_1^*(t)\beta S^*(t) - \lambda_2^*(t)(1-p)\beta S^*(t) - \lambda_3^*(t)[p\beta S^*(t) - d - \mu - u_3^*(t)] - b_2 \end{cases} \quad (4.13)$$

Together with the transversality conditions

$$\lambda_i^*(t_f) = 0, \ i = 1,2,3 \quad (4.14)$$

Equally, the piecewise characterization of the continuous optimal control function is given as:

$$\begin{aligned} u_1^*(t) &= min\left\{max\left\{0, \frac{\lambda_1^*(t)S^*(t)}{w_1}\right\}, 1\right\} \\ u_2^*(t) &= min\left\{max\left\{0, \frac{\lambda_2^*(t)E^*(t)}{w_2}\right\}, 1\right\} \\ u_3^*(t) &= min\left\{max\left\{0, \frac{\lambda_3^*(t)I^*(t)}{w_3}\right\}, 1\right\} \end{aligned} \quad (4.15)$$

Proof 4.2: The co-state system (4.13) and the optimal control characterisation (4.15) are obtained from the specific application of conditions (4.11) and (4.10) of Pontryagin's principle, respectively. The optimal control (4.15) is unique over an adequately short final time t_f, because of the Lipschitz property and boundedness of the state (4.1) and co-state (4.13) systems (Bather et al., 1976).

The overall optimality system encompasses the system (4.1) and its initial conditions, the co-state system (4.13) along with transversality conditions (4.14), and the optimal control characterisation (4.15);

$$
\begin{cases}
\frac{dS}{dt} = \Lambda - \beta SI - \left(\mu + u_1(t)\right)S \\
\frac{dE}{dt} = (1-p)\beta SI - kE - \left(\mu + u_2(t)\right)E \\
\frac{dI}{dt} = p\beta SI + kE - dI - \left(\mu + u_3(t)\right)I \\
\frac{d\lambda_1}{dt} = \lambda_1^*(t)[\beta I^*(t) + \mu + u_1^*(t)] - \lambda_2^*(t)(1-p)\beta I^*(t) - \lambda_3^*(t)p\beta I^*(t) \\
\frac{d\lambda_2}{dt} = \lambda_2^*(t)[\mu + k + u_2^*(t)] - b_1 \\
\frac{d\lambda_3}{dt} = \lambda_1^*(t)\beta S^*(t) - \lambda_2^*(t)(1-p)\beta S^*(t) - \lambda_3^*(t)[p\beta S^*(t) - d - \mu - u_3^*(t)] - b_2 \\
S(0), E(0), I(0) \geq 0, \\
\lambda_i^*(t_f) = 0, \ i = 1,2,3 \\
u_1^*(t) = min\left\{max\left\{0, \frac{\lambda_1^*(t)S^*(t)}{B_1}\right\}, 1\right\} \\
u_2^*(t) = min\left\{max\left\{0, \frac{\lambda_2^*(t)E^*(t)}{B_2}\right\}, 1\right\} \\
u_3^*(t) = min\left\{max\left\{0, \frac{\lambda_3^*(t)I^*(t)}{B_3}\right\}, 1\right\}
\end{cases}
\tag{4.16}
$$

4.4 Simulation Results and Discussion

In this section, numerical simulations are implemented to validate the analytical results. The epidemiological parameters used for the simulation are obtained from Table 3.1. The optimality system (4.16) is solved by employing the forward-backwards sweep technique described in (Lenhart & Workman, 2007). In this technique, the state equations are first solved forward in time using a 4th-order Runge Kutta algorithm, using the initial guess of the control variables and state variables initial conditions. The co-state equations are solved backwards in time using 4th-order Runge Kutta algorism, using the current iteration values of the states and control variables and transversality conditions. The control variables are then updated by using the values of the states and co-states obtained from the current iteration. The process is repeated until the results converge.

The dynamics of the three state variables (S, E and I) when there is no control intervention, are shown in Figure 4.1. From the simulation result, the number of exposed and infectious individuals at the final time is 1228 and 573, respectively. The result indicates that there is

endemic since no control measures have been taken. In figure 4.2, the dynamics of the populations is illustrated in the case when optimal controls are incorporated to avert the disease. It can be observed that at the end of the control program, both the number of exposed and infectious groups have been reduced to zero. This suggests that with a proper application of the three controls, the disease can be eliminated from the population.

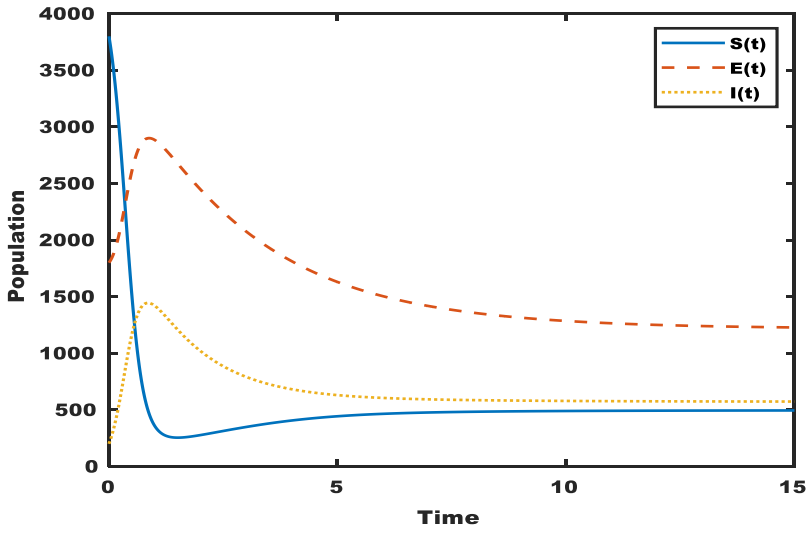


Figure 4.1: Dynamics of TB without control intervention

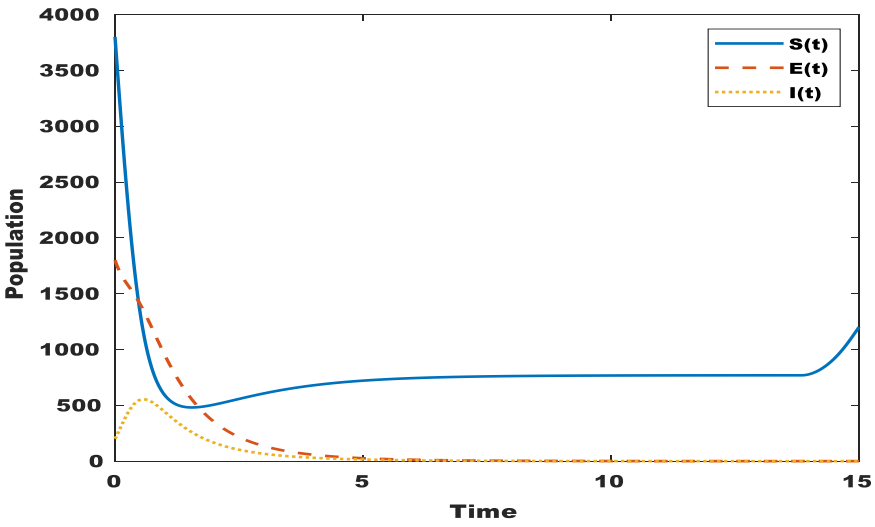


Figure 4.2: Dynamics of TB with optimal control intervention

The profiles of the control functions are portrayed in Figure 4.3. The figure demonstrates the combination of the three control actions over time. For the successful containment of the disease, the tree controls should be maintained at the maximum level for the most of the period. However, at time $t = 12.5$ the case finding applied to the exposed grouped and the case holding used to the infectious start to decrease smoothly to zero.

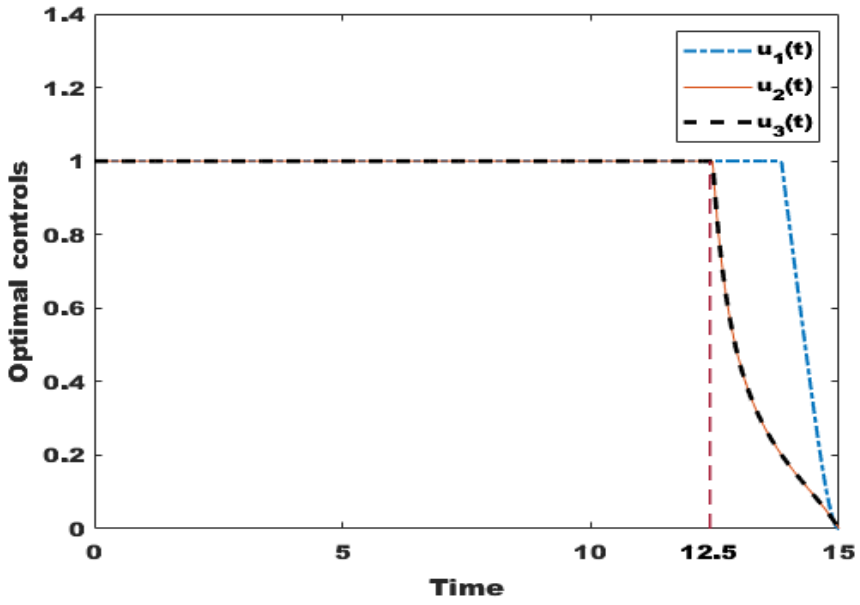


Figure 4.3: Profiles of the optimal control functions: with weight constants

$b_1 = 20, b_2 = 500, w_1 = 50, w_2 = 500$ and $w_3 = 500$.

For comparison, the trajectories of the exposed and the infectious people under different control strategies (with at least two control inputs) are shown in Figure 4.4 and 4.5 accordingly. It can be observed from Figure 4.4 and 4.5, incorporating different combinations of the control inputs have different effects on minimizing the population of the exposed and infectious individuals. It is noted that the population of the exposed can only be totally eliminated when all the three control inputs are used simultaneously. The combination of u_1, u_2, and u_3 has the highest influence on the minimization of the exposed population, followed by u_1 and u_2, u_1 and u_3, u_2 and u_3 consecutively. Similarly, observing the dynamics of the infectious under different strategies revealed that the infectious population could be extinct by employing u_1, u_2, and u_3

simultaneously or by effective use of u_1, and u_3. The influence of u_1, u_2 and u_2, u_3 on the infectious group is approximately the same. It is also observed that the combination of the three controls (vaccination, case finding and case holding) is more effective than the other combinations whereas, u_2, and u_3 has the least effect on curtailing the disease. This could be associated to the fact that the vaccination campaign (u_1) would prevent a portion of the susceptible that might potentially contract the disease by providing them with immunity.

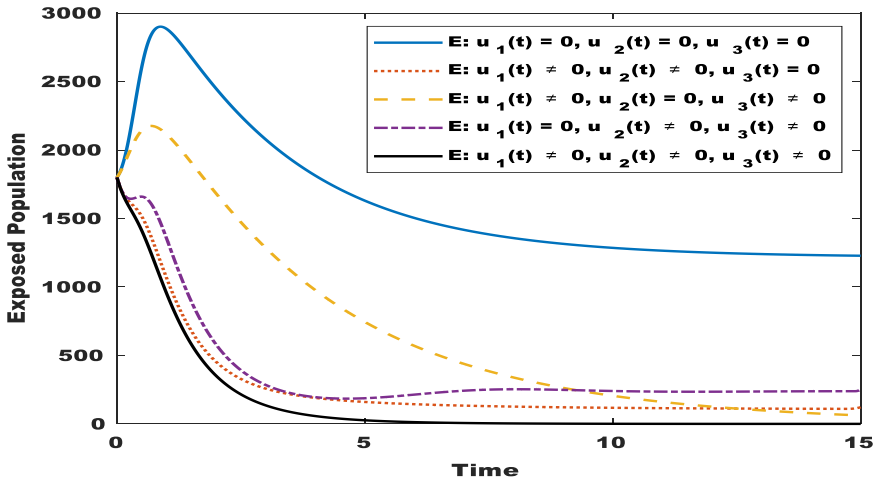


Figure 4.4: Exposed population trajectories under different control strategies

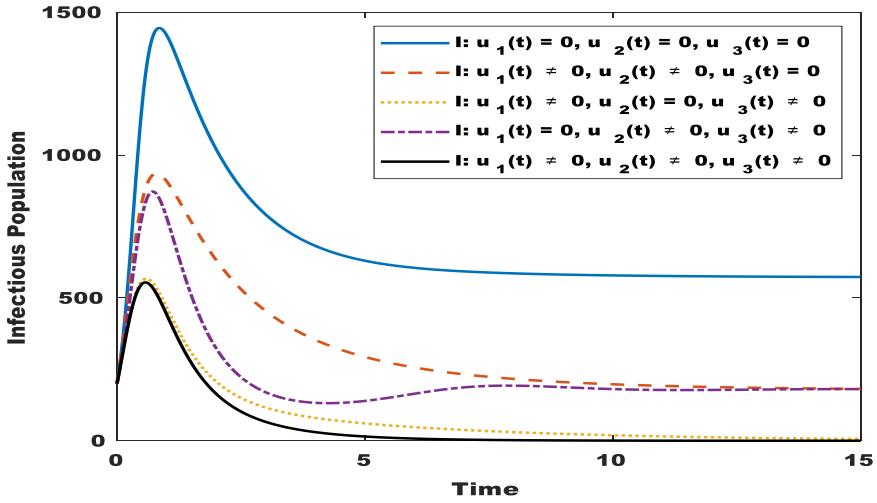


Figure 4.5: Infectious population trajectories under different control strategies

Figure 4.6 and 4.7 described the effects of the parameter uncertainties on the system dynamics. In this regard, two levels of uncertainties (20% and 40%) are considered. Uncertainties in the epidemiological parameters are attributed to errors in recording the incidences, unreported incidences and errors associated with the process of estimating the model parameters (Huynh et al., 2015; Jung, 2002). The simulations show that in the presence of the parameter uncertainties will have some effect on the system response. This can be linked to the fact that the optimal control system is an open-loop and design is carried out with the assumption that the system parameters are accurately estimated.

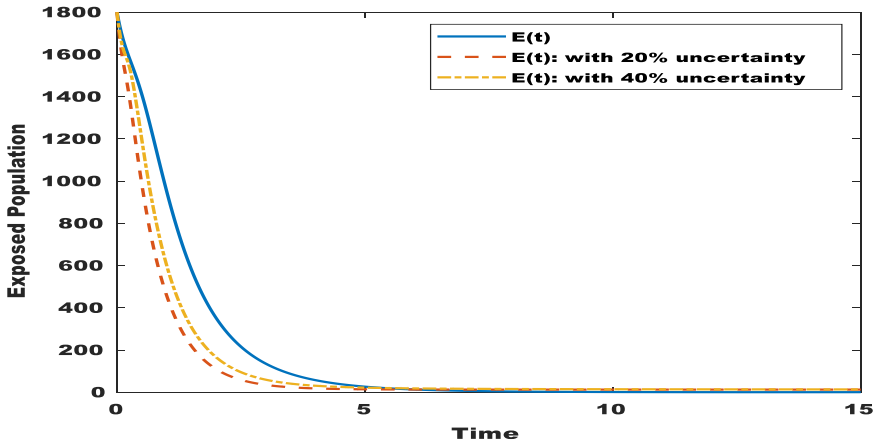


Figure 4.6: Effects of parameter uncertainties on the trajectory of the exposed

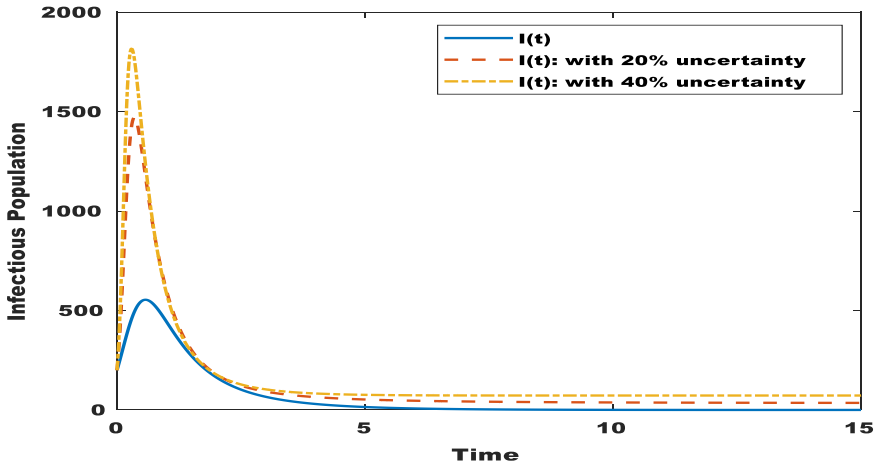


Figure 4.7: Effects of parameter uncertainties on the trajectory of the infectious

4.5 Cost-Effectiveness Analysis

In this section, the cost-effectiveness of the various control strategies is investigated based on the incremental cost-effectiveness ratio (ICER), explained in (Tilahun et al., 2017). The analysis is conducted to establish the most effective strategy that creates a balance between the controls requirements and the cost of implementation. ICER reveals the level of the economic value of one policy to other alternative methods. The ICER is given by the ratio of the cost difference between two approaches (incremental cost) and the difference between the number of averted cases (incremental effect) (York, 2016). The analysis considered only methods that combined two or more control inputs (see Table 4.2), in view of the fact that a single control input may not be enough in handling the disease. The cumulative number of incidences prevented by each method is calculated by subtracting the number of infectious at the end of the program from the number of infectious when there is no control. Additionally, the cost is considered to be equal to the corresponding objective cost value.

As shown in Table 4.2, strategy A combined vaccination and case finding controls, strategy B combined vaccination with a case holding controls; strategy C applied case finding and case holding controls. In contrast, strategy D considered the vaccination, case finding and case holding controls simultaneously. The strategies are then compared in pairs as follows. We begin by comparing the cost-effectiveness of strategy (A) and strategy (B):

$$ICER(\text{strategy A}) = \frac{13068}{391} = 33$$

$$ICER(\text{strategy B with respect to strategy A}) = \frac{(13068-15559)}{(391-566)} = 14$$

which shows that strategy B is less costly in relation to strategy A. Strategy A is then ignored, and the analysis continues by comparing strategy B with C as:

$$ICER(\text{strategy B}) = \frac{15559}{566} = 27$$

$$ICER(\text{strategy C wth respect to strategy B}) = \frac{(15559-16705)}{(566-391)} = -7$$

It follows that strategy C is cheaper compared to strategy B and hence, strategy B is ignored, and the analysis continues by comparing strategy C and strategy D as follows:

$$ICER(\text{strategy C}) = \frac{16705}{391} = 42$$

$$ICER(\text{strategy D wth respect to strategy C}) = \frac{(16705-10105)}{(391-0)} = 17$$

Eventually, strategy D with ICER equal to 17 is more cost-effective compared to strategy C. Therefore, the control program that considers the application of strategy D (combined three controls simultaneously) will achieve a more efficient result.

Table 4.1: Cost-effectiveness of the control methods

Methods	**Infectious at the final time $I(t_f)$**	**Prevented cases**	**Cost value (J)**
No control	573	NA	NA
Strategy A (u_1 and u_2)	182	391	13068
Strategy B (u_1 and u_3)	7	566	15559
Strategy C (u_2 and u_3)	182	391	16705
Strategy D (u_1, u_2 and u_3)	0	573	10105

Comparable to this research (Jung, 2002b; Mushayabasa & Bhunu, 2013; Y. Yang et al., 2016) have presented optimal control analysis on TB with various time-dependent control inputs. Unlike this study, which analysed the implementation of three optimal controls (vaccination,

case finding and treatment of infectious via case holding) and their various combinations, Yang et al. (2016) included vaccination and treatment only while Jung (2002) and Mushayabasa & Bhunu (2013) both limited their analysis to the use of case holding and case finding. Moreover, these studies have a general shortcoming of not performing a comprehensive numerical sensitivity analysis to evaluate the impact of parameter uncertainty on the dynamics of the system, as provided herein. In addition, the current study has expanded the optimal control analysis by conducting cost-effectiveness analysis to ascertain the cost and effectiveness of the proposed control measures.

CHAPTER 5
ADAPTIVE SLIDING MODE CONTROL ANALYSIS OF TB EPIDEMIC MODEL

5.1 Introduction

In optimal control design approach, system parameters are assumed to be priori known and accurate. However, if the system contains uncertain parameters, the conventional control techniques such as the linear feedback and optimal control will not provide the desired results. Since their design demand that the system parameters are predetermined. Nevertheless, robust adaptive control methods can guarantee the stability of the system and also provide adaptation law through which the estimation of the parameters can be updated. In this chapter, development of adaptive sliding mode control for nonlinear uncertain tuberculosis epidemic model is presented. The design considered a compartmental nonlinear TB model proposed by (Mccluskey, 2006) of the SEI type (where S, E, and I represent the population of susceptible, exposed and infected, respectively) and two control variables $u_1$and u_2 (representing "case finding" and "case holding" programs). The control's aim is decreasing the population of individuals that are exposed and infected to zero by tracking a predefined reference trajectory. To ensure the robustness of the control system against uncertainty an adaptation law is established in order to update the parameter value estimation. Moreover, Lyapunov stability of the closed-loop system is proved.

5.2 Model Description

The nonlinear tuberculosis control system is described by Equations (5.1) - (5.3).

$$\dot{\mathrm{S}} = \Lambda - \beta SI - \mu S \tag{5.1}$$

$$\dot{\mathrm{E}} = (1-p)\beta SI - aE - \mu E - u_1(\mathrm{t})\mathrm{E} \tag{5.2}$$

$$\dot{I} = p\beta SI + aE - (d+\mu)\mathrm{I} - u_2(\mathrm{t})\mathrm{I} \tag{5.3}$$

The description of the epidemiological parameters is the same as in chapter two. The system contains three state variables S, E and I representing the number of susceptible, exposed and

infected individuals, respectively, along with their initial conditions $S_0 = S(0), E_0 = E(0)$ and $I_0 = I(0)$. The control signal u_1 is the rate of case finding control scheme that detects and treats a fraction of individual exposed, while u_2 is the control initiative that guarantees successful treatment of individuals infected. The control inputs seek to reduce the population of individuals that are exposed and infected with the TB (hence appeared in Equations (5.2) and (5.3)).

5.3 Adaptive Sliding Mode Control (ASMC) Structure

The structure of ASMC for uncertain tuberculosis model is illustrated in Figure 5.1. The closed-loop control system consists of the ASMC controller block, the uncertain tuberculosis model and adaptation laws. By setting appropriate control signals u_1 and u_2, the ASMC controller regulates the values of the state variables. The tuberculosis model contains uncertain parameters due to the discrepancies that occur in different communities. The adaptation laws are included for updating the controller gains in order to maintain the system stability and keep the system response close to the desired conditions despite the presence of the uncertainties.

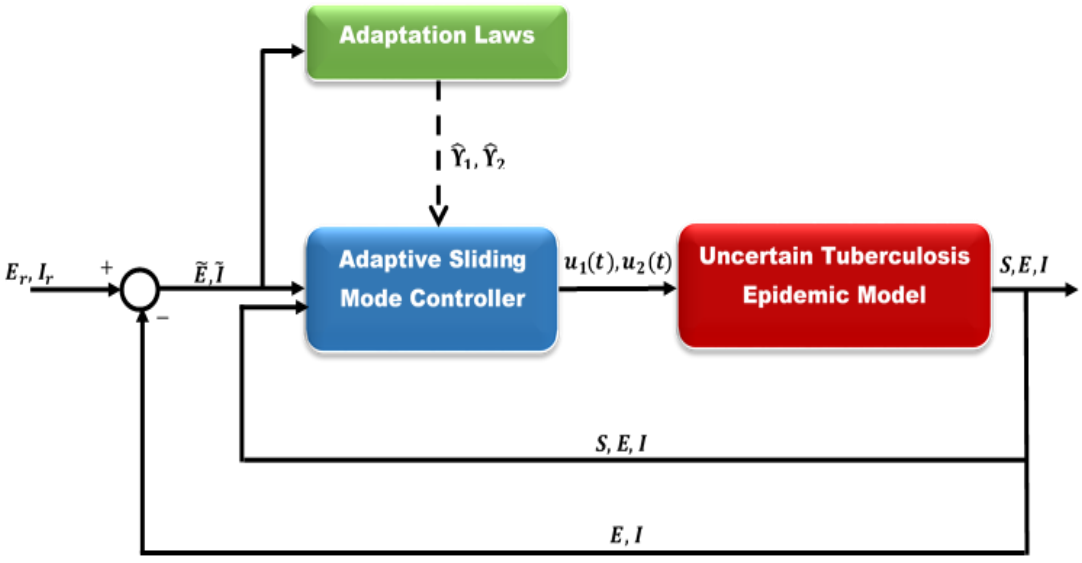


Figure 5.1: The structure of ASMC for uncertain TB model

The control objectives are said to be achieved when the actual population of the exposed and infected groups $(E \text{ and } I)$ accurately track a predefined desired reference trajectories

($E_r \to 0\ and\ I_r \to 0$). In order to realize the control objectives, this implies that the tracking error should be zero for all the time during the process. That is,

$$e(t) = 0, \quad \forall\ t \geq 0,$$

$$\tilde{E} = E - E_r = 0,$$

$$\tilde{I} = I - I_r = 0.$$

In which $\tilde{E}$ and $\tilde{I}$ denotes the tracking error of exposed and infected individuals, accordingly. Also, E_r and E, and I_r and I represent the desired and actual number of exposed and infected populations, respectively.

5.3.1 Adaptive sliding mode control design

The step by step design procedure of the ASMC is presented here. Consider a sliding variable $\Theta(t)$ with integral term (Ibeas et al., 2014):

$$\Theta(t) = e(t) + \phi \int_0^t e(\tau)d\tau \tag{5.4}$$

The sliding surface that guarantee the controller objectives is given as

$$\Theta(t) = e(t) + \phi \int_0^t e(\tau)d\tau = 0 \tag{5.5}$$

Where ϕ is a positive sliding surface constant gain, and the time derivative of the sliding surface is given by

$$\dot{\Theta}(t) = \dot{e}(t) + \phi e(t) \tag{5.6}$$

Now, the characterization of $u_1(\mathrm{t})$, that guarantee the control of the exposed individuals can be obtained by re-written Equation (5.6) as

$$\dot{\Theta}(t) = \dot{\tilde{E}} + \phi_1 \tilde{E} = 0$$

$$\dot{\Theta}(t) = \dot{\mathrm{E}} - \dot{E}_r + \phi_1(E - E_r) = 0 \tag{5.7}$$

By replacing the dynamics of exposed E class from Equation (5.2) in to Equation (5.7),

$$\dot{\Theta}(t) = (1-p)\beta SI - aE - \mu E - u_1(\mathrm{t})\mathrm{E} - \dot{E}_r + \phi_1(E - E_r)$$

hence, the case finding $u_1(\mathrm{t})$ control input is obtained as:

$$u_1(t) = -\frac{\left(\dot{E}_r - \phi_1(E - E_r)\right)}{E} - \frac{(1-p)\beta SI}{E} - a - \mu \tag{5.8}$$

Similarly, the characterization of $u_2(\mathrm{t})$, that guarantee the control of the infected individuals can be achieved from

$$\dot{\Theta}(t) = \dot{\tilde{I}} + \phi_2\tilde{I} = \dot{\mathrm{I}} - \dot{I}_r + \phi_2(I - I_r) = 0 \tag{5.9}$$

Also, substituting the dynamics of the exposed I from Equation (5.3) into Equation (5.9), the case holding $u_2(\mathrm{t})$ control input is found to be

$$u_2(\mathrm{t}) = -\frac{\left(\dot{I}_r - \phi_2(I - I_r)\right)}{I} + p\beta S + a\frac{E}{I} - d - \mu \tag{5.10}$$

In pursuance of designing the adaptive control law, control inputs (5.8) and (5.10) will be express in terms of a matrix $\boldsymbol{X}$ and a vector $\boldsymbol{\theta}$ containing the state variables and the parameters of the system, respectively.

$$u_1(t) = -\frac{\left(\dot{E}_r - \phi_1(E - E_r)\right)}{E} + \boldsymbol{X_1}(S,\ E,\ I)\boldsymbol{\theta_1} \tag{5.11}$$

$$u_2(\mathrm{t}) = -\frac{\left(\dot{I}_r - \phi_2(I - I_r)\right)}{I} + \boldsymbol{X_2}(S,\ E,\ I)\boldsymbol{\theta_2} \tag{5.12}$$

Where, $\boldsymbol{X_1}$ and $\boldsymbol{X_2}$ are functions of system states variable $S,\ E\ and\ I$. While, $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ contain the uncertain parameters of the system.

Accordingly, $\boldsymbol{X_1}$, $\boldsymbol{X_2}$, $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are defined as

$$\boldsymbol{X_1} = \left[\frac{SI}{E} \ -1 \ -1\right] \tag{5.13}$$

$$\boldsymbol{X_2} = \left[S \ \frac{E}{I} \ -1 \ -1 \ \right] \tag{5.14}$$

$$\boldsymbol{\theta_1} = [(1-p)\beta \ \ a \ \ \mu]^T \tag{5.15}$$

$$\boldsymbol{\theta_2} = [p\beta \ \kappa \ a \ \mu]^T \tag{5.16}$$

Furthermore, since the actual system parameters $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ contain uncertainties, and the ASMC control laws are therefore designed using estimated model parameters $\widehat{\boldsymbol{\theta}}_{\boldsymbol{1}}$ and $\widehat{\boldsymbol{\theta}}_{\boldsymbol{2}}$, and adaptive laws that handle the mismatch between the actual and estimated parameters (Taylor et al., 2010):

$$u_1(\mathrm{t}) = -\frac{(\dot{E}_r - \phi_1 \tilde{E})}{E} + \boldsymbol{X_1}(S, \ E, \ I)\hat{\theta}_1 + \widehat{\Upsilon}_1 \frac{sgn(\tilde{E})}{E} \tag{5.17}$$

$$u_2(\mathrm{t}) = -\frac{(\dot{I}_r - \phi_2 \tilde{I})}{I} + \boldsymbol{X_2}(S, \ E, \ I)\hat{\theta}_2 + \widehat{\Upsilon}_2 \frac{sgn(\tilde{I})}{I} \tag{5.18}$$

Where the vectors $\widehat{\boldsymbol{\theta}}_{\boldsymbol{1}}$ and $\widehat{\boldsymbol{\theta}}_{\boldsymbol{2}}$ denotes the estimated parameters, given by

$$\widehat{\boldsymbol{\theta}}_{\boldsymbol{1}} = \left[(1-\hat{p})\hat{\beta} \ \ \hat{a} \ \ \hat{\mu}\right]^T \tag{5.19}$$

$$\widehat{\boldsymbol{\theta}}_{\boldsymbol{2}} = \left[\hat{\mathrm{p}}\hat{\beta} \ \ \hat{\mathrm{a}} \ \ \hat{d} \ \ \hat{\mu}\right]^T \tag{5.20}$$

The adaptation gains $\widehat{\Upsilon}_1$ and $\widehat{\Upsilon}_2$ are included to compensate the discrepancies between estimated and actual parameters so as to attain the control objectives. The adaptation gains are updated through the adaptation laws, defined as (Sharifi & Moradi, 2017):

$$\dot{\widehat{\Upsilon}}_1 = \kappa_1 \left|\tilde{E}\right|, \qquad \widehat{\Upsilon}_1(0) = \Upsilon_{10} > 0 \tag{5.21}$$

$$\dot{\widehat{\Upsilon}}_2 = \kappa_2 \left|\tilde{I}\right|, \qquad \widehat{\Upsilon}_2(0) = \Upsilon_{20} > 0 \tag{5.22}$$

The positive constants κ_1 and κ_2 signifies the rate at which the adaptation gains are updated in reference to the tracking errors $\left(\tilde{E} \ and \ \tilde{I}\right)$. While $\widehat{\Upsilon}_{10}$ and $\widehat{\Upsilon}_{20}$ represent the initial values of the adaptation gain.

5.3.2 Closed-loop TB control system

In this section, the closed-loop control system of the tuberculosis is established by employing the ASMC designed in sub-section 5.3.1. In this regard, the control laws (5.17) and (5.18) are substituted into dynamics of E and I in Equations (5.2) and (5.3), respectively.

$$-\frac{(\dot{E}-\dot{E}_r+\phi_1\tilde{E})}{E} = \big(1-(\hat{p}-p)\big)\big(\hat{\beta}-\beta\big)\frac{SI}{E} - (\hat{a}-a) - (\hat{\mu}-\mu) + \hat{\Upsilon}_1\frac{sgn(\tilde{E})}{E} \quad (5.23)$$

$$-\frac{(\dot{I}-\dot{I}_r+\phi_2\tilde{I})}{I} = (\hat{p}-p)\big(\hat{\beta}-\beta\big)S + (\hat{a}-a)\frac{E}{I} - \big(\hat{d}-d\big) - (\hat{\mu}-\mu) + \hat{\Upsilon}_2\frac{sgn(\tilde{I})}{I} \quad (5.24)$$

Subsequently, the closed-loop dynamics are obtained as

$$\dot{\tilde{E}} = -\phi_1\tilde{E} - E\boldsymbol{X_1}(S,\ E,\ I)\tilde{\theta}_1 - \hat{\Upsilon}_1 sgn\big(\tilde{E}\big) \quad (5.25)$$

$$\dot{\tilde{I}} = -\phi_2\tilde{I} - I\boldsymbol{X_2}(S,\ E,\ I)\tilde{\theta}_2 - \hat{\Upsilon}_2 sgn(\tilde{I}) \quad (5.26)$$

Where $\dot{\tilde{E}}$ and $\dot{\tilde{I}}$ are the derivatives of the tracking errors, while $\widetilde{\boldsymbol{\theta}}_{\boldsymbol{1}}$ and $\widetilde{\boldsymbol{\theta}}_{\boldsymbol{2}}$ represent the bounded model parameter estimation errors defined as

$$\dot{\tilde{E}} = \dot{E} - \dot{E}_r \quad (5.27)$$

$$\dot{\tilde{I}} = \dot{I} - \dot{I}_r \quad (5.28)$$

$$\widetilde{\boldsymbol{\theta}}_{\boldsymbol{1}} = \widehat{\boldsymbol{\theta}}_{\boldsymbol{1}} - \boldsymbol{\theta}_{\boldsymbol{1}} \quad (5.29)$$

$$\widetilde{\boldsymbol{\theta}}_{\boldsymbol{2}} = \widehat{\boldsymbol{\theta}}_{\boldsymbol{2}} - \boldsymbol{\theta}_{\boldsymbol{2}} \quad (5.30)$$

Now, owing to the fact that the system state variables $(S,\ E,\ I)$ and model parameter estimation errors ($\widetilde{\boldsymbol{\theta}}_{\boldsymbol{1}}$ and $\widetilde{\boldsymbol{\theta}}_{\boldsymbol{2}}$) are bounded, one can establish that the terms $E\boldsymbol{X_1}(S,\ E,\ I)\widetilde{\boldsymbol{\theta}}_{\boldsymbol{1}}$ and $I\boldsymbol{X_2}(S,\ E,\ I)\widetilde{\boldsymbol{\theta}}_{\boldsymbol{2}}$ are bounded (see (Taylor et al., 2010)), and therefore there exist some positive constants ε_1 and ε_2 such that:

$$\big|E\boldsymbol{X_1}(S,\ E,\ I)\widetilde{\boldsymbol{\theta}}_{\boldsymbol{1}}\big| \leq\ \varepsilon_1 \quad (5.31)$$

$$\left|I\boldsymbol{X_2}(S,\ E,\ I)\widetilde{\boldsymbol{\theta}}_{\boldsymbol{2}}\right| \leq\ \varepsilon_2 \tag{5.32}$$

5.3.3 Lyapunov stability of closed-loop TB control system

Consider a quadratic Lyapunov function (Moradi et al., 2015) defined as:

$$V = \frac{1}{2}\left[\tilde{E}^2 + \tilde{I}^2 + \frac{1}{\kappa_1}\left(\widehat{\Upsilon}_1 - \varepsilon_1\right)^2 + \frac{1}{\kappa_2}\left(\widehat{\Upsilon}_2 - \varepsilon_2\right)^2\right] \tag{5.33}$$

Based on Equation (5.33), V is positive definite ($V \geq 0$). Now, taking the derivative of (5.33),

$$\dot{V} = \tilde{E}\dot{\tilde{E}} + \tilde{I}\dot{\tilde{I}} + \frac{1}{\kappa_1}\left(\widehat{\Upsilon}_1 - \varepsilon_1\right)\dot{\widehat{\Upsilon}}_1 + \frac{1}{\kappa_2}\left(\widehat{\Upsilon}_2 - \varepsilon_2\right)\dot{\widehat{\Upsilon}}_2 \tag{5.34}$$

By substituting (5.25) and (5.26) in to (5.34) following expression is obtained as

$$\begin{aligned}\dot{V} &= \tilde{E}\left[-\phi_1\tilde{E} - EX_1(S,\ E,\ I)\tilde{\theta}_1 - \widehat{\Upsilon}_1 sgn\left(\tilde{E}\right)\right] + \frac{1}{\kappa_1}\left(\widehat{\Upsilon}_1 - \varepsilon_1\right)\dot{\widehat{\Upsilon}}_1 \\ &+ \tilde{I}\left[-\phi_2\tilde{I} - IX_2(S,\ E,\ I)\tilde{\theta}_2 - \widehat{\Upsilon}_2 sgn(\tilde{I})\right] + \frac{1}{\kappa_2}\left(\widehat{\Upsilon}_2 - \varepsilon_2\right)\dot{\widehat{\Upsilon}}_2 \\ &= -\phi_1\tilde{E}^2 - \tilde{E}\left(EX_1(S,\ E,\ I)\tilde{\theta}_1\right) - \widehat{\Upsilon}_1\tilde{E}sgn\left(\tilde{E}\right) + \frac{1}{\kappa_1}\left(\widehat{\Upsilon}_1 - \varepsilon_1\right)\dot{\widehat{\Upsilon}}_1 \\ &- \phi_2\tilde{I}^2 - \tilde{I}\left(IX_2(S,\ E,\ I)\tilde{\theta}_2\right) - \widehat{\Upsilon}_2\tilde{I}sgn(\tilde{I}) + \frac{1}{\kappa_2}\left(\widehat{\Upsilon}_2 - \varepsilon_2\right)\dot{\widehat{\Upsilon}}_2\end{aligned} \tag{5.35}$$

Considering the fact that $\tilde{E}sgn\left(\tilde{E}\right) = \left|\tilde{E}\right|$ and $\tilde{I}sgn(\tilde{I}) = \left|\tilde{I}\right|$, and by substituting the adaptation laws (5.21) and (5.22), $\dot{V}$ is achieved as

$$\begin{aligned}\dot{V}(t) = &-\phi_1\tilde{E}^2 - \tilde{E}\left(EX_1(S,\ E,\ I)\tilde{\theta}_1\right) - \hat{\Upsilon}_1\left|\tilde{E}\right| + \frac{1}{\kappa_1}\left(\hat{\Upsilon}_1 - \varepsilon_1\right)\kappa_1\left|\tilde{E}\right| \\ &-\phi_2\tilde{I}^2 - \tilde{I}\left(IX_2(S,\ E,\ I)\tilde{\theta}_2\right) - \hat{\Upsilon}_2\left|\tilde{I}\right| + \frac{1}{\kappa_2}\left(\hat{\Upsilon}_2 - \varepsilon_2\right)\kappa_2\left|\tilde{I}\right|\end{aligned} \tag{5.36}$$

Given (5.31) and (5.32) and further simplification it is reduced to

$$\dot{V} = -\phi_1\tilde{E}^2 + \varepsilon_1\left|\tilde{E}\right| - \hat{\Upsilon}_1\left|\tilde{E}\right| + \frac{1}{\kappa_1}\left(\hat{\Upsilon}_1 - \varepsilon_1\right)\kappa_1\left|\tilde{E}\right| - \phi_2\tilde{I}^2 + \varepsilon_2\left|\tilde{I}\right| - \hat{\Upsilon}_2\left|\tilde{I}\right| + \frac{1}{\kappa_2}\left(\hat{\Upsilon}_2 - \varepsilon_2\right)\kappa_2\left|\tilde{I}\right|$$

$$\dot{V} = -\phi_1\tilde{E}^2 - \phi_2\tilde{I}^2 \leq 0 \tag{5.37}$$

Since λ_1 and λ_2 are positive constants, $\dot{V}$ is negative semi-definite ($\dot{V} \leq 0$). Hence, the designed adaptive control strategy given by (5.17) and (5.18) ensures the stability of the closed-loop tuberculosis control system. Moreover, employing the Barbalat's lemma (Slotine & Li, 1991) the asymptotic stability of the system may be proved by taking the derivative of (5.37)

$$\ddot{V} = -2\phi_1 \tilde{E}\dot{\tilde{E}} - 2\phi_2 \tilde{I}\dot{\tilde{I}} \tag{5.38}$$

Because of the boundedness of the exposed and infected dynamics (5.2) and (5.3), the derivatives Ė and İ equally bounded. Given (5.27) and (5.28) and the boundedness of $\dot{E}_r$, Ė, $\dot{I}_r$ and İ, it can be established that $\dot{\tilde{E}}$ and $\dot{\tilde{I}}$ are bounded too. It emerges that $\ddot{V}$ is bounded based on the Barbalat's lemma $\left(\dot{V} \to 0 \; as \; t \to \infty\right)$. Subsequently, the tracking errors converge ($\tilde{E} \to 0$ and $\tilde{I} \to 0$), which means the population of the exposed and infected converges to their reference trajectories ($E - E_r$ and $I \to I_r$), and hence the closed-loop tuberculosis control system is asymptotically stable regardless of parameter uncertainties.

5.4 Simulation Results and Discussion

Numerical simulation is conducted on the developed closed-loop tuberculosis control system, and the result is reported here. The purpose of the simulation is demonstrating the effectiveness of the developed control system and hence supports the established theoretical facts. In this regard, various simulation scenarios are considered. In the first instance, the nonlinear tuberculosis model is simulated without control; afterwards, the closed-loop tuberculosis is simulated along with the control inputs and predefined reference trajectories. In the second scenario, the capabilities of the control system to handle parameter uncertainties are shown. Finally, a performance comparison between the adaptive controller and the optimal controller (discussed in chapter 4) is shown.

The actual and estimated epidemiological parameters are given in Table 5.1. The actual parameters are assumed to be the same as the simulation parameters in the previous chapters. For brevity, the estimated parameters are considered to contained 20% and 40% uncertainties as given in Equation (5.39) and (5.40), respectively.

That is,

$$\widehat{\boldsymbol{\theta}}_{\mathbf{20}} = 1.2\boldsymbol{\theta}_i \tag{5.39}$$

$$\widehat{\boldsymbol{\theta}}_{\mathbf{40}} = 1.4\boldsymbol{\theta}_i \tag{5.40}$$

for $i = 1, 2$

Where $\boldsymbol{\theta}$, $\widehat{\boldsymbol{\theta}}_{\mathbf{20}}$ and $\widehat{\boldsymbol{\theta}}_{\mathbf{40}}$ represents the actual model parameters, estimated parameters with 20% uncertainty and estimated parameters with 40% uncertainty, respectively.

Table 5.1: Simulation Parameters

Nominal parameter	**Value**	
$\boldsymbol{\theta}_{\mathbf{1}} = [(1-\mathrm{p})\beta\ \mathrm{a}\ \mu]^{\mathrm{T}}$	$[0.0015\ \ 0.05\ \ 0.3]^{\mathrm{T}}$	
$\boldsymbol{\theta}_{\mathbf{2}} = [\mathrm{p}\beta\ \mathrm{a}\ \mathrm{d}\ \mu]^{\mathrm{T}}$	$[0.0015\ \ 0.05\ \ 0.55\ \ 0.3]^{\mathrm{T}}$	
Uncertain parameter	$\hat{\theta}_{20}$	$\hat{\theta}_{40}$
$\widehat{\boldsymbol{\theta}}_{\mathbf{1}} = \left[(1-\hat{\mathrm{p}})\hat{\beta}\ \hat{\mathrm{a}}\ \hat{\mu}\right]^{\mathrm{T}}$	$[0.0018\ \ 0.06\ \ 0.36]^{\mathrm{T}}$	$[0.0021\ \ 0.07\ \ 0.42]^{\mathrm{T}}$
$\widehat{\boldsymbol{\theta}}_{\mathbf{2}} = \left[\hat{\mathrm{p}}\hat{\beta}\ \hat{\mathrm{a}}\ \ \hat{\mathrm{d}}\ \hat{\mu}\right]^{\mathrm{T}}$	$[0.0018\ \ 0.06\ \ 0.66\ \ 0.36]^{\mathrm{T}}$	$[0.0021\ \ 0.07\ \ 0.77\ \ 0.42]^{\mathrm{T}}$

The reference trajectories for the reduction of the exposed and infected individuals (E_r, I_r) are designed as descending exponential functions to mimic a planned tuberculosis control intervention program that aimed at eliminating the tuberculosis epidemic by reducing the number of the exposed and infected population to zero. The reference trajectories over control program period t are defined as:

$$E_r = \left(E_0 - E_f\right)e^{-\epsilon_1 t} + E_f \tag{5.41}$$

$$I_r = \left(I_0 - I_f\right)e^{-\epsilon_2 t} + I_f \tag{5.42}$$

Where E_0, E_f, I_0, and I_f represents the initial and final values of the exposed and infected population. The desired steady-state (final) number of the exposed and infected individuals are considered to be zero i.e. $E_f = I_f = 0$, $\epsilon_1 = 0.5$, $\epsilon_1 = 0.5$, $\epsilon_2 = 0.4$, and the control program period $t = 15$. Figure 5.2 shows the desired trajectories for the specified parameters. As shown in the figure, the decrease in the number of exposed is more gradual compared to the infected, since the spread of the disease can be better handle if the number of infected are eliminated faster then followed by the exposed.

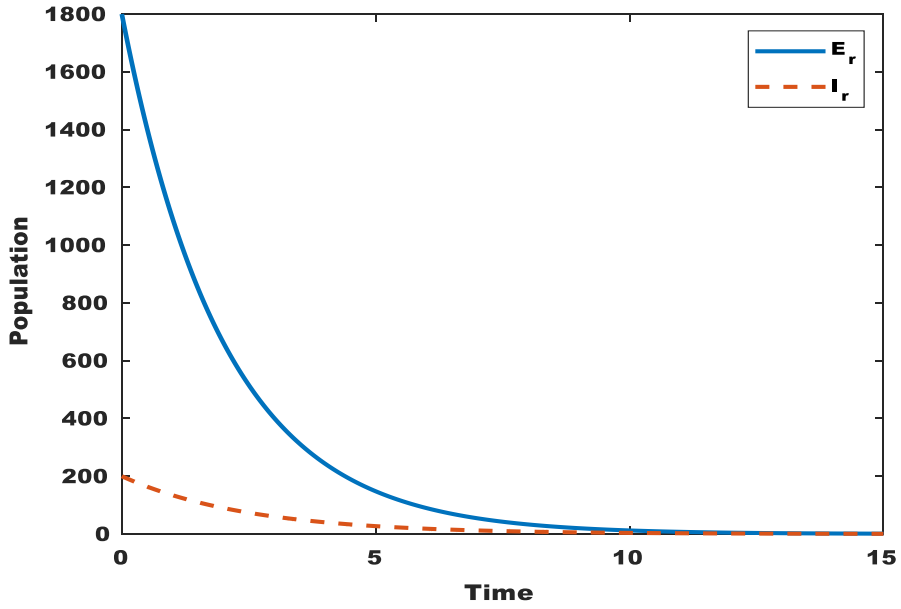


Figure 5.2: Control reference signals

Figure 5.3 shows the trajectories of the susceptible, exposed and infected populations when there is no control intervention (control inputs $u_1 = u_2 = 0$). It can be vividly observed that the number of healthy susceptible people decreases while the population of the exposed and infected are increasing. This means there is an epidemic and the disease remain in the community. This undesirable situation can be averted by employing appropriate control inputs.

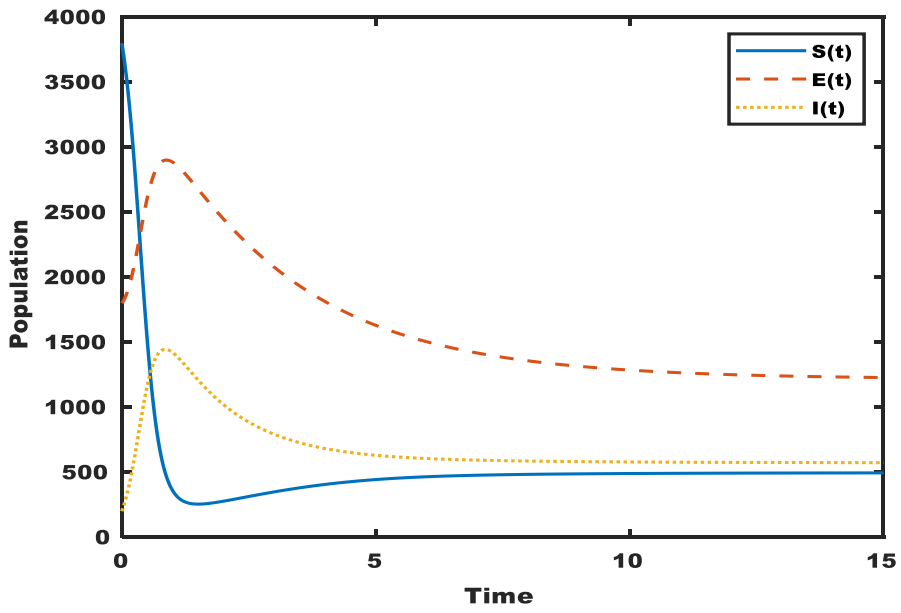


Figure 5.3: Dynamics of TB without control

Afterwards, the closed-loop tuberculosis control system along with the adaptive control inputs $u_1(t)$ and $u_2(t)$ is simulated using the actual system parameters, and desired reference values of the exposed and infected individuals (see Figure 5.4). The controller parameters are adjusted to $\phi_1 = \phi_2 = 48, \quad \Upsilon_{10} = \Upsilon_{20} = 2, \quad \kappa_1 = 0.2$ and $\kappa_2 = 1$ to accomplish a high rate of convergence of the tracking errors with a settling time $t_{SE} = 0.6522$ and $t_{SI} = 0.5435$ for the exposed and infectious, respectively. Furthermore, it can be seen from figure 5.4, that there is high accuracy in the tracking of the descending reference trajectories of the exposed and infected population. The mean absolute tracking error (MAE) for the exposed and infectious trajectories is found to be equal to 0.080954 and 0.00002 respectively.

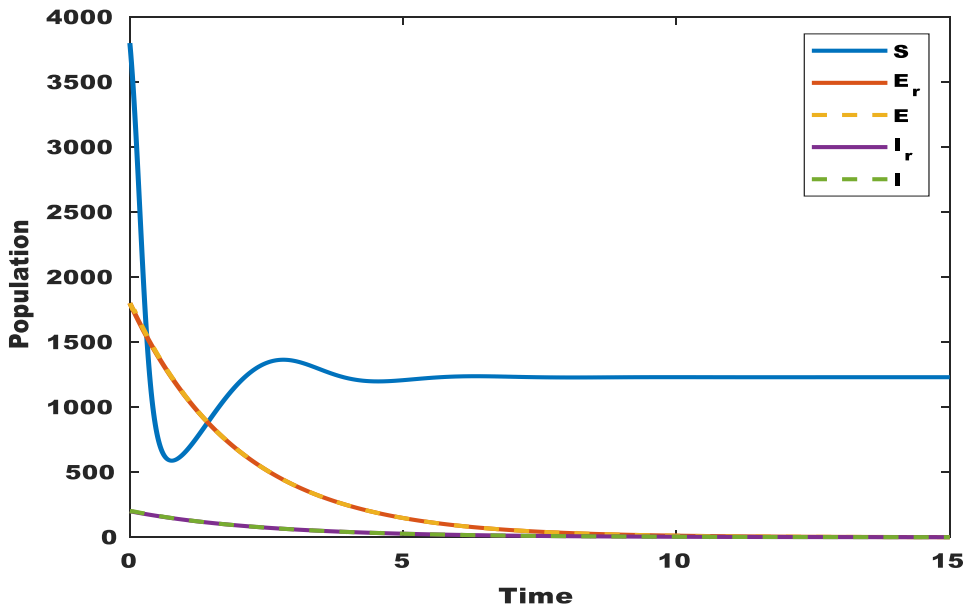
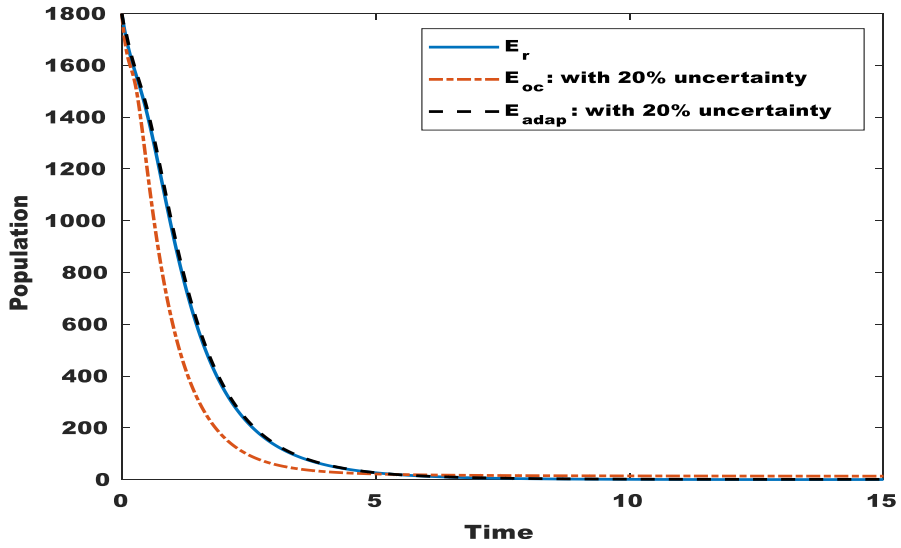


Figure 5.4: Closed-loop TB control system with adaptive control inputs

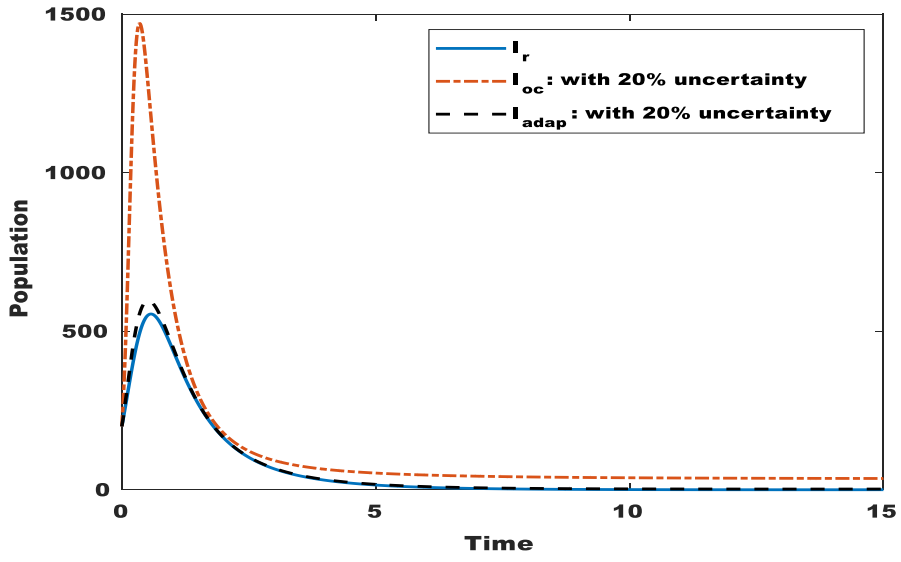
For the purpose of comparison, the performance of the adaptive controller in handling the effect of the parameter uncertainties is compared with the optimal controller designed in chapter four. In this scenario, the optimal trajectories of the exposed and infected individuals obtained from the optimal controller in chapter 4, are used as reference inputs (E_r, I_r). Figures 5.5 and 5.6 show the resulting dynamics of the exposed and infected individuals in case of the tuberculosis control system with adaptive control and the tuberculosis model with conventional optimal control in the presence of 20% and 40% uncertainties.

As shown in Figure 5.5and 5.6, in the presence of parameter uncertainties, the performance of the conventional optimal controller is affected and the trajectories of both the exposed and infectious population deviated from the reference trajectories. The mean absolute tracking error (MAE), for the optimal controller in the presence of 20% uncertainty is 51.2283 and 69.1930 for the exposed and infectious trajectories, and is found to be equal to 71.0222, 102.8563 in the presence of 40% uncertainty. Besides, the result of the adaptive controller demonstrated the robustness of the controller in handling the parametric uncertainties, with MAE of 0.8494, and 0.7357 for the exposed and infectious under 20% uncertainty, and 0.9332 and 1.0780 in the

presence of 40% uncertainty. Hence, the adaptive controller successfully tracks the reference trajectories of the exposed and infectious population.

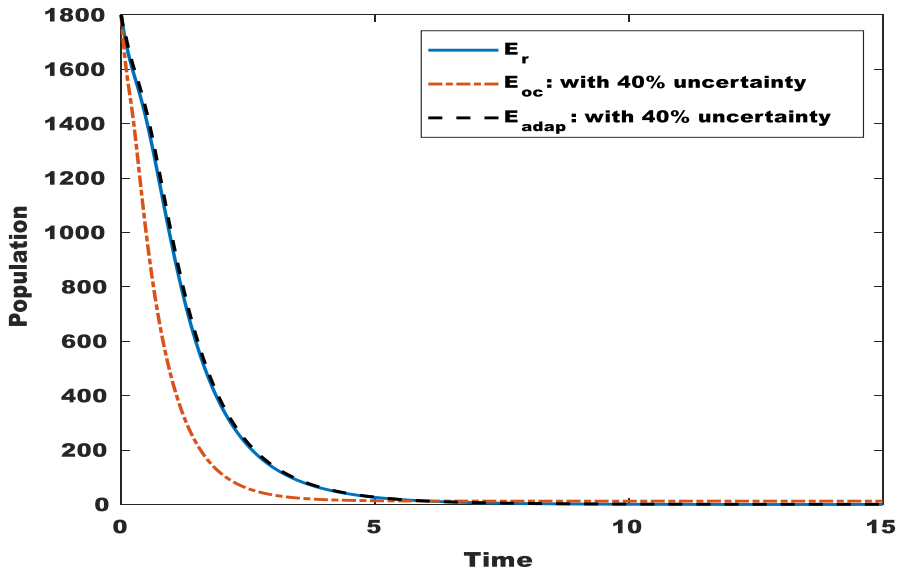


(a)

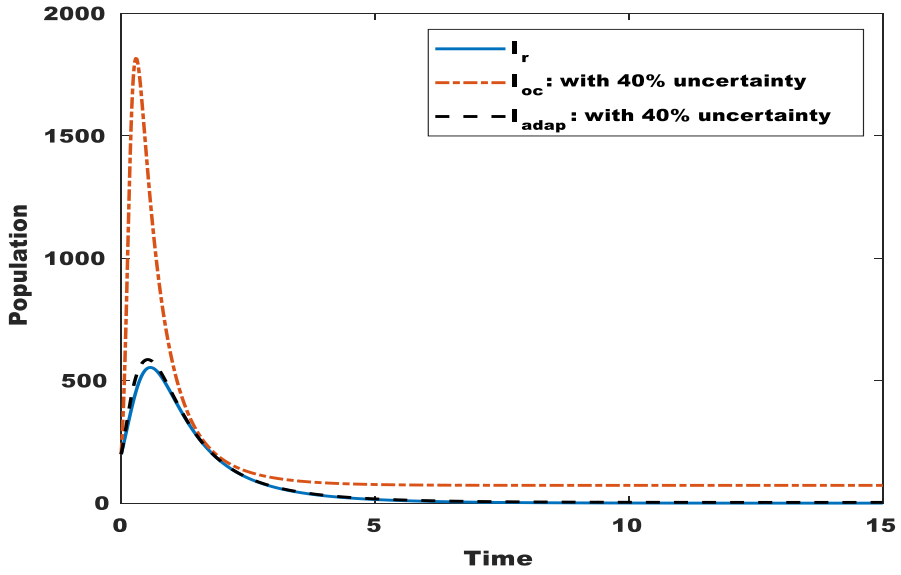


(b)

Figure 5.5: Effect of 20% uncertainty in the estimated model parameters: (a) Exposed population (b) Infectious population



(a)



(b)

Figure 5.6: Effect of 40% uncertainty in the estimated model parameters: (a) Exposed population (b) Infectious population

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

In this thesis, optimal and adaptive control analysis of TB model has been presented. The study is carried out in three configurations. In the first case, optimal control of TB dynamic model is presented with saturated incidence rate. The analysis considered two time-dependent control functions; which describe TB case findings among the individuals that are exposed and case holding treatment on the infectious, and a constant control coefficient δ, describing the public awareness. The model's global stability was established using Lyapunov function theory, and the optimal controls were characterized using the concept of Pontryagin's principle. Through numerical simulations, the impact of the public awareness, as well as the optimal control inputs in managing the spread of the disease, has been demonstrated. The result indicated that incorporating public awareness in the TB control program will have a significant influence on the eradication of the disease.

Similarly, in the second instance, the analysis combined three time-dependent control inputs with the third control function representing the vaccination campaign. The necessary conditions for the eradication of the disease were obtained by the application of the Pontrayagin's principle. In this analysis, the effect of the various control strategies on the reduction of the exposed and infectious population was shown numerically. It was observed from the result that the combination of the three controls (vaccination, case finding and case holding) is more effective than the other combinations whereas, the combination of case finding and case holding without vaccination has the least effect on curtailing the disease. This suggested that vaccination campaign is essential in any epidemic control program as it prevents a fraction of the healthy individuals that might potentially contract the disease by providing them with immunity. It has also been observed that parameter uncertainties may affect the system response. This can be attributed to the fact that the optimal control system is an open-loop and the design is done under

the basis that accurate parameters of the system are available. The economic feasibility of the proposed control approaches was investigated, and the result suggests that the cost-effective way to curb the disease outbreak is to jointly incorporate the three control measures.

Furthermore, as observed from the second scenario, if the system contains uncertain parameters, the traditional optimal control method may not give the desired results. This lead to the third scenario where adaptive sliding mode control (ASMC) was implemented considering the parameter uncertainties. The goal of the control was to reduce the population of individuals that are exposed and infected to zero by tracking a predefined reference trajectory. Adaption law is established to update the parameter values to ensure the robustness of the control system against uncertainties. The stability of the closed-loop system is demonstrated using the Lyapunov Function Principle, and numerical simulations showed the result.

The conclusion suggests that the proposed optimal and adaptive control systems are very useful and provide efficient tools for understanding TB transmission and control. The use of saturated incidence rate establishes another perspective in comprehending the spread of TB. The incorporation of public awareness in the analysis also revealed the fact that controlling social activities has a significant role in handling epidemic diseases. The optimal control analysis offers a solution to the problem of balancing the desired control goals and the cost of executing the control action them. In addition, the adaptive control system is robust against the various level of uncertainties and ensures the convergence of the number of exposed and infectious individuals to the desired values. The analysis explores possible approaches and highlights the important implementations of open-loop and closed-loop control systems in epidemiology. The research will serve as a reliable framework to inform practical methods for curtailing TB diseases in any society.

6.2 Recommendations

The procedure of development and analysis of mathematical epidemic models is complex and quite challenging, due to the inherent nonlinearity in epidemiological systems. Meanwhile, recent studies revealed that the application of data-driven methods such as machine learning

algorithms could alternatively produce accurate epidemic predictive models. Because there is increased in computational power, the use of machine learning algorithms in epidemiology is promising and should be thoroughly investigated.

The conventional optimal control systems are generally designed through the indirect implementation of Pontryagin's principle, which is an open-loop control system framework. The future work should consider closed-loop optimal control approaches such as the linear-quadratic regulators (LQR) and model predictive controls (MPC). Moreover, some other promising control techniques such as observers, neural network (NN), inverse neural network, neuro-fuzzy and H∞ controllers can be applied.

The future work will also consider the concurrent application of the optimal control and adaptive control systems to achieve an optimal adaptive control system. This is possible by first applying the optimal control strategy to obtain the optimal and cost-effective trajectories of the system state variables and utilize the result in as reference inputs (desired outputs) in the adaptive control design.

The risk of developing active TB is higher in the developing countries. Although therapy is possible, precise diagnosis is needed first. In many cases X-ray machines are available in these countries, but often the radiological expertise is insufficient to correctly analyze the images. Machine learning algorithms that could easily and efficiently execute this task will greatly enhance the ability to diagnose and properly handle the disease.

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APPENDIX 1

ETHICAL APPROVAL LETTER

TO GRADUATE SCHOOL OF APPLIED SCİENCES

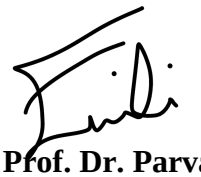
REFERENCE: RABIU ALIYU ABDULKADIR (20166800)

I would like to inform you that the above candidate is one of our postgraduate students in Electrical and Electronics Engineering department he is taking thesis under my supervision and the thesis entailed: **ANALYSIS OF TUBERCULOSIS MODEL WITH OPTIMAL AND ADAPTIVE CONTROLS.** The data used in his thesis does not require any ethical report.

Please do not hesitate to contact me if you have any further queries or questions.

Thank you very much indeed.

Best Regards,



Assist. Prof. Dr. Parvaneh Esmaili

Electrical and Electronics Engineering Department,
Faculty of Engineering,
Near East Boulevard, ZIP: 99138
Nicosia / TRNC, North Cyprus,
Mersin 10 – Turkey.
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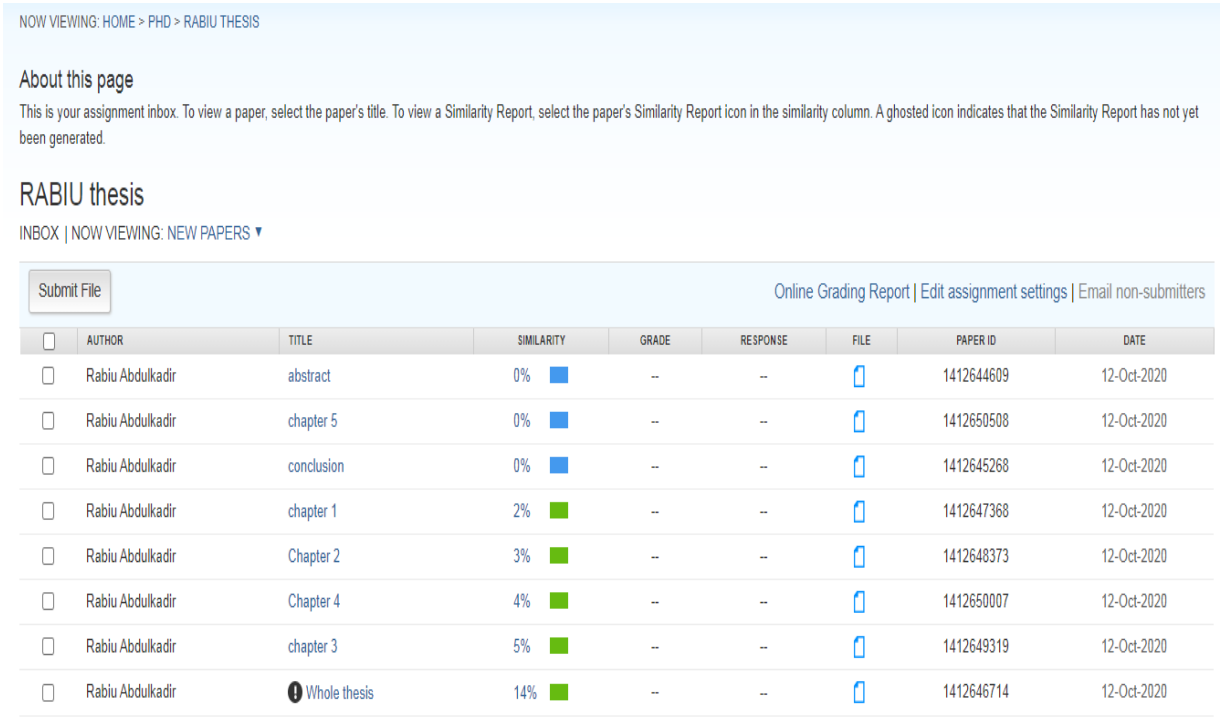
APPENDIX 2

SIMILARITY REPORT

Assist. Prof. Dr. Parvaneh Esmaili



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APPENDIX 3

CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name	: Abdulkadir, Rabiu Aliyu
Nationality	: Nigeria
Date and Place of Birth	: 12 October 1989, Kano
Marital Status	: Married

EDUCATION

Degree	Institution	Year of Graduation
M. Tech.	Sharda University, Department of Electrical and Electronics Engineering	2015
B. Eng.	KUST, Department of Electrical Engineering	2011

WORK EXPERIENCE

Year	Place	Enrollment
2020-present	Department of Mechatronics Engineering, NEU	Research Assistant
2012-present	Department of Electrical Engineering, KUST	Lecturer
2011-2012	Department of Computer Engineering, MAPOLY	Assistant Lecturer

FOREIGN LANGUAGES

- *English, fluently spoken and written*
- *Arabic, understood*

HONORS AND AWARDS

- *Kano State Scholarship Award, 2016.*
- *Merit Award, Sharda University, 2015.*
- *Kano State Scholarship Award, 2014.*
- *Best Graduating Student Award, KUST, 2011.*

MEMBERSHIP OF PROFESSIONAL ORGANIZATIONS

- *Member, Institute of Electrical and Electronics Engineers (IEEE).*
- *Member International Association of Engineers (IAENG).*
- *Registered Engineer with Council for the Regulation of Engineering in Nigeria*.

PUBLICATIONS IN INTERNATIONAL REFERRED JOURNALS (IN COVERAGE OF SSCI/SCI-EXPANDED):

- Baba, I., Abdulkadir, R. A., & Esmaili, P. (2019). Analysis of Tuberculosis Model with Saturated Incidence Rate and Optimal Control. *Physica A*, 540(2020) 123237.
- Abdulkadir, R. A., Ali, S. I, Abba, S. I., & Esmaili, P. (2020). Forecasting of Daily Rainfall at Ercan Airport Northern Cyprus: A Comparison of linear and non-linear Models. *DWT*, 177(2020) 297-305.

PUBLICATIONS IN INTERNATIONAL REFERRED JOURNALS (IN COVERAGE OF WEB OF SCIENCE AND SCOPUS):

- Abdulkadir, R. A. & Esmaili, P. (2020). Optimal Control and Cost-effectiveness Analysis of Tuberculosis Model with Fast and Slow Progression. *ITJEMAST*, 11(07) 1-13.

THESES

Master

- Abdulkadir, R. A. (2015). *Development of Intelligent Tracking Device for Dementia Affected Persons*. Master Thesis, Sharda University, Department of Electrical and Electronics Engineering, Faculty of Engineering, Greater Noida, India.

Lisans

- Abdulkadir, R. A. (2011). *Development Microprocessor Based Intelligent Door Lock.* Undergraduate Project (B. Eng.), Kano University of Science and Technology, Department of Electrical Engineering, Faculty of Engineering, Kano, Nigeria.

COURSES GIVEN

- Introduction to Capstone Design
- Capstone Design Project
- Digital Electronics
- Control Systems Engineering
- Principles of Electrical Engineering I
- Principles of Electrical Engineering II

HOBBIES

- Reading, Travel and Football.