

**A MATHEMATICAL MODEL OF TUBERCULOSIS
DIABETES CO-INFECTION WITH OPTIMAL CONTROL**

MUSYOKI EUNICE MUENI (MSc Applied Mathematics)

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**THESIS SUBMITTED IN FULFILLMENT OF THE AWARD OF THE
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DECLARATION

This thesis is my own work and has not been presented for a degree award in any other institution.

MUSYOKI EUNICE MUENI

I84/28140/2019

Department of Mathematics and Actuarial Science

Signature:..... Date:

This thesis has been submitted for examination with our approval as the university supervisors.

Prof. Winfred Nduku Mutuku

Department of Mathematics and Actuarial Science

Kenyatta University

Signature:..... Date:

Dr. Nancy Matendeche Imbusi

Department of Industrial & Engineering Mathematics,

Technical University of Kenya.

Signature:..... Date:

Dr. Paul Wanjau

Department of Industrial & Engineering Mathematics,

Technical University of Kenya.

Signature:  Date: 12/5/2025

DEDICATION

This thesis is dedicated to My husband Dominic and my children Celine and Adrian, whose unwavering support and encouragement have been my anchor throughout this academic journey.

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Table of Contents

DECLARATION	ii
DEDICATION	iii
ACKNOWLEDGEMENT	iv
List of Tables	ix
List of Figures	x
Acronyms and Abbreviations	xi
ABSTRACT	xiv
1 Introduction	1
1.1 Introduction	1
1.2 Background	1
1.3 Statement of the Problem	5
1.4 Objectives	7
1.4.1 General Objective	7
1.4.2 Specific Objectives	7
1.5 Significance of the Study	7
1.6 Justification of the Study	8
2 Literature Review	9
2.1 Introduction	9

2.2	Tuberculosis and Diabetes	9
2.2.1	Tuberculosis	9
2.2.2	Diabetes	12
2.3	Mathematical Models	14
2.3.1	Deterministic Models	15
2.3.2	Stochastic Models	17
2.3.3	Finite Difference Schemes	29
2.4	Empirical Review	32
2.4.1	Mathematical modelling of tuberculosis	32
2.4.2	Mathematical modelling of diabetes	40
2.4.3	Mathematical modeling of tuberculosis and diabetes co-infection	45
2.4.4	Summary of literature	47
3	Research Methodology	50
3.1	Introduction	50
3.2	Model formulation	50
3.3	Mathematical preliminary	54
3.3.1	Definitions	54
3.3.4	Laws, principles, and theorems/lemmas	55
3.4	Well-posed equation	57
3.5	Disease Free Equilibrium	58
3.6	Basic Reproduction Number	59
3.7	Stability analysis	61
3.8	Sensitivity analysis	62
3.9	Optimal control	65
3.9.1	Pontryagin's Maximum Principle	67
3.9.2	Hamiltonian function	68
3.10	Non-standard Finite Difference Scheme	69

3.10.1 Runge-Kutta Method	69
3.10.2 Forward Euler Method	70
4 Results: Model Formulation and Analysis	72
4.1 Introduction	72
4.2 Model formulation	72
4.2.1 Assumptions	76
4.2.2 Parameter estimation	76
4.2.3 Model analysis	78
4.2.4 Finite Difference Method	78
4.2.5 Nonstandard Finite Difference Method	84
4.3 Numerical solutions	88
4.3.1 Continuous-time Model	88
4.3.2 NSFD for TB-Diabetes Model	88
4.3.3 Phase planes	93
4.3.4 Well-posedness of the model	96
4.4 Disease Free Equilibrium	99
4.4.1 The DFE	99
4.4.2 Control Reproduction Number	100
4.5 Stability Analysis	102
4.5.1 Local Stability of DFE	102
4.5.2 Global Stability of DFE	103
4.5.3 Endemic Equilibrium	106
4.6 Sensitivity analysis of parameters	117
4.6.1 Elasticity Indices	117
4.6.2 Numerical solutions	118
4.7 Optimal Control to Tuberculosis and Diabetes Co-Infection	119
4.7.1 Introduction of controls	120

4.7.2	The extended mathematical model	122
4.7.3	Existence of optimal control	123
4.7.4	Characterization of controls	126
4.7.5	Numerical simulation for optimal control	129
5	Conclusion and Recommendations	132
5.1	Conclusion	132
5.2	Recommendations	134
	Bibliography	136
	Appendices	164
	Appendix A Publications	165
	Appendix B B	166
B.1	Stability of basic reproductive number	166
B.2	Snippet of the Codes	167

List of Tables

2.1	Game theory model	27
4.1	Parameter description and estimation	77
4.2	Comparison of numerical simulation results obtained based on continuous-time model and nsfd	90
4.3	Analytic solution of (4.59).	113
4.4	Elasticity indices of parameters in $\mathcal{R}_C$	117
4.5	Comparison of compartment equilibrium values in the presence and absence of optimal control	131

List of Figures

1.1	The percentage of TB-Diabetes cases	5
4.1	TB-Diabetes model	74
4.2	The graphical simulation of all compartment in the model diagram in Figure L_s, I_{DT}, D , and C	89
4.3	Graphical simulation of NSFD for $S, L_s, I_{DT}, I_{DT}, C_{DT}, D$ and C . . .	90
4.4	Comparison of the graphical simulation of population of compartment for the system in (4.1) and (4.10).	90
4.5	Graphical simulation of population of compartment C_{DT} . h (step size) increases from left to right.	91
4.6	Graphical simulation showing the role of h (step size) in determining the accuracy in the simulation. h increases from left to right.	92
4.7	Simulation of compartment population based on Table 4.1 with $S_0 = 1000; L_{f_0} = L_{s_0} = I_{T_0} = D_{T_0} = I_{DT_0} = C_{DT_0} = D_0 = C_0 = 0$ and $N = 1000$. $\beta = \frac{266}{10^5}$ resulting in approximated equilibrium values of $S^* = 1.704 \times 10^3$, $L_f^* = 1.87795 \times 10^5$, $L_s^* = 2.3127 \times 10^4$, $I_T^* = 2.115 \times 10^3$, $D_T^* = 2.702 \times 10^3$, $I_{DT}^* = 9.307 \times 10^3$, $C_{DT}^* = 3.813 \times 10^3$, $D^* = 3.513660 \times 10^6$, $C^* = 296$ and $\mathcal{R}_C = 1.0863$	118

4.8	Simulation of compartment population based on Table 4.1 with $S_0 = 1000; L_{f_0} = L_{s_0} = I_{T_0} = D_{T_0} = I_{DT_0} = C_{DT_0} = D_0 = C_0 = 0$ and $N = 1000$. $\beta = \frac{266}{10^5}$ resulting in approximated equilibrium values of $S^* = 192$, $L_f^* = 15342 \times 10^4$, $L_s^* = 1.888 \times 10^3$, $I_T^* = 172$, $D_T^* =$ 2.689×10^3 , $I_{DT}^* = 9.262 \times 10^3$, $C_{DT}^* = 3.794 \times 10^3$, $D^* = 3.95913 \times 10^6$, $C^* = 334$ and $\mathcal{R}_C = 0.1845$	119
4.9	Simulation of infectious population for different β values.	120
4.10	Simulation of the population of individuals in each compartment in the absence and presence of optimal control $S(t), S_o(t); L_f(t), L_{fo}(t);$ $I_T(t), I_{T_o}(t); D_T(t), D_{T_o}; I_{DT}(t), I_{DT_o}; C_{DT}(t), C_{DT_o}; D(t), D_o(t)$ and $C(t), C_o(t)$ based on parameter values in Table 4.1.	129
4.11	Simulation of the cost function for values of $[d, h] \in [0, 1] \forall t = 732$ days.	130

Acronyms and Abbreviations

The list describes several symbols that are used within the body of the document.

$ABMs$	Agent-based model
CGM	Continuous Glucose Monitoring
DFE	Disease Free Equilibrium
DM	Diabetes Mellitus
$MDR - TB$	Multidrug-Resistant
$NSFDS$	Non-Standard Finite Difference Schemes
ODE	Ordinary Differential Equation
$SEIR$	Susceptible Exposed Infectious Recovered
SIR	Susceptible Infectious Recovered
TB	Tuberculosis
WHO	World Health Organization

$XDR - TB$

Extensively Drug-Resistant

$\mathcal{R}_0$

Basic Reproduction Number

ABSTRACT

Tuberculosis and diabetes co-infection is a complex health issue that requires effective management. Understanding the dynamics and interactions between these two diseases is crucial for developing optimal control strategies. Diabetes' immune dysregulation can compromise the host's ability to control TB infection, leading to higher TB and DM-related complications and Kenya being a third world country, faces this challenge. Kenya ranks 13th in TB burden; diabetes triples TB risk. To understand the dynamics of this, a nine compartmental model for tuberculosis-diabetes co-infection is formulated. The Non-standard finite difference Scheme (NSFD) of the model is formulated from the first-order ordinary differential equations (ODE) to avoid full implicit schemes that are computationally expensive. The overly small step sizes in NSFD give the user autonomy in controlling the accuracy of the results, making it suitable for disease control applications. This paper expands existing model to incorporate the co-infection of diabetes and tuberculosis to understand disease complications better. Numerical simulations with different step sizes of the NSFD for the TB-Diabetes model are carried out to find the optimal step size, h . A comparison of the best resultant numerical simulation based on optimal h in NSFD indicates NSFD gives better results when compared with the corresponding first-order ode. The phase-plane analysis revealed that the NSFD formulated for tuberculosis and diabetes co-infection is generally asymptotically stable. Stability analysis of the ODE model based on $\mathcal{R}_C$ indicated that $\mathcal{R}_C \leq 1$ suggests potential epidemic eradication, while $\mathcal{R}_C \geq 1$ indicates a risk of epidemic spread. The sensitivity analysis highlighted the significant impact of TB transmission coefficient β and diabetes acquisition rate α_1 on $\mathcal{R}_C$, emphasizing the need for optimal control measures targeting these factors. A decrease in TB transmission coefficient led to a reduction in $\mathcal{R}_C$ from 1.0863 to 0.1845, suggesting the potential effectiveness of control strategies. Future studies should consider formulating the proposed model with varied control parameters such as medication to compare the results with those from first-order ode. The study also recommends exploring models considering different diabetes types in future research. The study's findings benefit various stakeholders, from the Ministry of Health and health institutions to planners and other researchers.

Chapter 1

Introduction

1.1 Introduction

In this chapter we present a brief overview of disease modeling using mathematical models, transmission dynamics of tuberculosis and diabetes, the problem statement, objectives of this research and the justification of the study.

1.2 Background

Infectious diseases such as HIV/AIDS, tuberculosis (TB), and malaria remain the leading causes of morbidity and mortality globally, accounting for approximately 10% of all deaths annually ([Ndung'u, 2012](#)). These diseases not only threaten public health but also significantly hinder social and economic development, particularly in low- and middle-income countries. To mitigate their spread, a thorough understanding of transmission dynamics is essential. One of the most effective methods for achieving this understanding is epidemic modeling.

Epidemiology, the scientific study of the distribution and determinants of health-related states in specific populations, relies heavily on data-driven methods ([Organization, 2009](#)). Epidemic modeling serves as a core analytical tool in epidemiology. It

facilitates understanding of disease transmission mechanisms, forecasts the progression of epidemics, and evaluates the effectiveness of intervention strategies such as isolation, vaccination, treatment, and quarantine ([Hethcote, 2000](#)). Given the economic implications of these interventions, identifying the most cost-effective strategy is crucial.

Mathematical modeling provides a robust alternative where experimental studies may be unethical, infeasible, or prohibitively expensive ([Elaydi and Lozi, 2024](#)). These models help conceptualize complex disease dynamics and allow researchers to simulate the impact of control measures. The realism of these models, however, depends on striking a balance between model simplicity and the accurate representation of core transmission mechanisms.

Tuberculosis, caused by the *Mycobacterium tuberculosis* complex (MTBC), affects both humans and animals ([Tientcheu et al., 2017](#)). Transmission occurs via airborne droplet nuclei (1–5 microns) expelled by infected individuals through coughing, sneezing, talking, or singing ([Wei and Li, 2016](#)). These particles can remain airborne for several hours, thereby increasing the risk of transmission in closed environments. In 2016 alone, approximately 10.4 million people contracted TB, and 1.7 million deaths were reported ([Barreira, 2018](#)); by 2019, the number of infections stood at 10 million, with 1.4 million deaths ([Fukunaga et al., 2021](#)).

Risk factors for TB infection include prolonged exposure to untreated individuals, HIV infection, malnutrition, tobacco use, alcohol abuse, and diabetes ([Dooley Jr et al., 1990](#); [MacNeil et al., 2020](#)). Latent TB infection (LTBI) occurs when the immune system suppresses bacterial activity. However, in immunocompromised individuals, LTBI may progress to active TB. Diagnosis often involves sputum culture testing, which confirms the presence of *M. tuberculosis* ([Society et al., 2000](#)).

TB presents in two primary forms: pulmonary and extra-pulmonary. While pul-

monary TB affects the lungs and is highly infectious, extra-pulmonary TB occurs in other organs and is less likely to be contagious ([Society et al., 2000](#)). Common symptoms include persistent cough (sometimes with blood), chest pain, weight loss, fever, and night sweats. TB treatment involves a combination of first-line drugs such as isoniazid, rifampin, ethambutol, and pyrazinamide, usually administered over six to nine months ([Falzon et al., 2017](#)). Poor adherence to treatment protocols may result in drug-resistant TB (MDR-TB) ([Aldila et al., 2018](#)).

Kenya ranks 13th among the 22 high TB burden countries, contributing significantly to the global case load ([Organization and Staff, 2013](#)).

Diabetes mellitus (DM), a metabolic disorder characterized by insulin insufficiency or resistance, impairs glucose regulation and can damage multiple organ systems ([Zadeng, 2014](#)). The disease is classified into Type 1 (autoimmune), Type 2 (insulin resistance), and gestational diabetes. Symptoms include fatigue, frequent urination, weight loss, and in severe cases, ketoacidosis and kidney failure. Globally, diabetes prevalence has surged, with 442 million cases reported in 2014. In 2016, 1.6 million deaths were attributed to diabetes ([Atlas et al., 2015](#)).

DM is a significant risk factor for TB, as it compromises immune function. It accelerates the reactivation of latent TB, worsens disease severity, and leads to treatment failure and increased mortality ([Tuli, 2014](#)). Research indicates that diabetes triples the risk of developing TB, contributing to approximately 10–15% of TB cases ([Momoh et al., 2019](#)). Furthermore, diabetic TB patients exhibit prolonged sputum conversion times and atypical radiological features, increasing the risk of misdiagnosis ([Lin et al., 2015](#)). WHO has issued guidelines for managing TB-DM co-infection ([Organization et al., 2006](#)), but implementation remains slow in sub-Saharan Africa ([Mburu, 2020](#)).

Several studies have analyzed TB-DM co-infection dynamics using compartmental

models. For instance, [Moualeu et al. \(2012\)](#) and [Malik et al. \(2018\)](#) employed SEIR frameworks and recommended treatment for latent TB and glucose control. [Pinto and Carvalho \(2019\)](#) explored co-existence implications using fractional-order models.

The mathematical analysis of infectious disease models often relies on differential equations ([Daun et al., 2008](#)), which are challenging to solve analytically. Consequently, numerical schemes such as Euler and Runge-Kutta are used ([Holst et al., 2000](#)). These classical methods, however, are often unstable ([Cresson and Pierret, 2016](#)). To overcome this, [Mickens \(1989\)](#) developed non-standard finite difference (NSFD) schemes that preserve the qualitative features of differential equations across all step sizes. These include positivity, boundedness, and dynamic consistency ([Patidar, 2005](#)).

NSFD schemes are particularly useful in solving non-linear and non-local epidemiological models ([Azizi, 2023](#)). Their application in TB modeling has demonstrated improved accuracy in capturing intervention effects such as treatment and quarantine ([Cruz and Castillo-Chavez, 1996](#); [Liao and Yang, 2017](#); [Malong et al., 2019](#)).

This study builds upon this body of work by developing a refined mathematical model for TB-DM co-infection and solving it using non-standard finite difference techniques. The goal is to better understand the dual disease dynamics and propose optimal, cost-effective intervention strategies.

Furthermore, the construction and analysis of NSFD methods to solve mathematical models was conducted by [Mickens \(2003\)](#), whose work has been applied by several researchers including [Jódar et al. \(2008\)](#), who constructed a non-standard finite scheme for influenza and showed that the differential equation model maintained the same properties as the continuous model. [Guerrero et al. \(2014\)](#) applied the NSFD scheme to a smoking prevalence model in Spain and compared their re-

sults with Euler, Runge-Kutta, and Trapezoidal methods, concluding that the NSFD scheme provided an effective alternative for solving mathematical models.

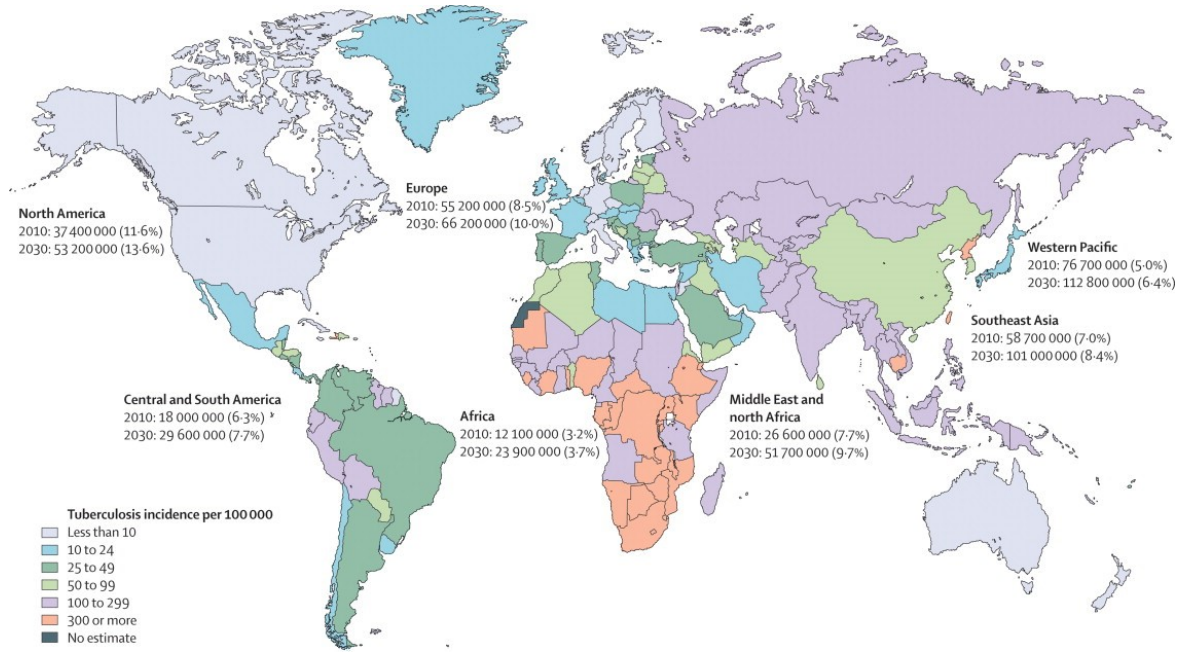


Figure 1.1: The percentage of TB-Diabetes cases

From the above information, it is evident that diabetes is a neglected risk factor for TB re-emergence. It is therefore very crucial to study TB-diabetes co-infection so as to align with the WHO's End TB Strategy, which aims to reduce TB incidences by 80% and TB-related deaths by 90% by 2030. Consequently, this research aims to develop a mathematical model to study the dynamics of TB-Diabetes co-infection using a non-standard finite difference scheme, thereby offering insight into its transmission and control.

1.3 Statement of the Problem

Kenya is a high TB burden country ranked 13th amongst the 22 countries globally, contributing to 80% of the global case load (Sudre et al., 1992). Diabetes Mellitus, on the other hand, is a syndrome of disordered metabolism which occurs when the pancreas does not produce enough insulin or when the body does not effectively

utilize the insulin produced. Insulin, which is made by the beta cells of the pancreas, regulates blood sugar. If not well regulated, hyperglycemia (high blood sugar levels) can occur, leading to severe damage to various body systems, especially the nerves, blood vessels, eyes, and kidneys ([Zadeng, 2014](#)). The global prevalence of diabetes has increased rapidly over the past few decades, raising significant public health concerns. According to the International Diabetes Federation (IDF), two individuals develop diabetes and two die from diabetes every 10 seconds ([Atlas et al., 2015](#)).

TB remains both a health and economic burden, particularly in Africa. Outbreaks lead to increased healthcare costs, including treatment and preventive drugs, emergency deployment of personnel, hospitalizations, and premature deaths. One of the global health objectives is to reduce TB incidence.

Although much research has been conducted on TB modeling, limited work has focused on TB-DM co-morbidity, despite the fact that diabetes increases the risk of TB infection by threefold. Some existing studies have approached TB-DM co-morbidity from a social science perspective. For instance, [Moualeu et al. \(2012\)](#) and [Malik et al. \(2018\)](#) analyzed TB-DM co-infection using SEIR models, concluding that diabetes influences TB spread. However, these studies did not propose an optimal control strategy, nor did they incorporate the complications that arise due to TB-DM co-infection. Moreover, their numerical simulations were conducted using the classical fourth-order Runge-Kutta method.

This study, therefore, proposes the development, analysis, and simulation of a nine-compartment TB-DM co-infection model using a non-standard finite difference (NSFD) scheme. NSFD will be employed to avoid the computational expense associated with fully implicit schemes and small step sizes. The model will be extended to incorporate optimal control strategies such as enhanced physical distancing and improved dietary practices.

1.4 Objectives

This study seeks to pursue the following objectives:

1.4.1 General Objective

To formulate a model of tuberculosis-diabetes co-infection with optimal control.

1.4.2 Specific Objectives

1. To formulate a mathematical model for tuberculosis and diabetes co-infection.
2. To analyze the model using non-standard finite difference schemes.
3. To perform a mathematical analysis of the transmission dynamics of TB-DM co-infection.
4. To investigate optimal control strategies for tuberculosis and diabetes co-infection.

1.5 Significance of the Study

This study analyzes the dynamics of tuberculosis and diabetes co-infection within human populations. Its outcomes will assist public health managers and other stakeholders in designing long-term intervention strategies for TB-DM co-infection. The findings can be used to educate the public, enhance disease detection, reduce TB incidence and prevalence, and support evidence-based allocation of healthcare resources.

In addition, the model provides a useful tool for guiding national TB-DM co-infection control programs. Insights from the study may also be valuable for future epidemiological modeling efforts. Furthermore, by analyzing parameter sensitivity indices, the research may help refine TB control strategies.

The proposed model extends [Malik et al. \(2018\)](#) by incorporating diabetes-related complications and their effects on TB. This comprehensive approach enhances un-

derstanding of the complex interaction between these diseases and supports real-world application. The model is simulated using non-standard finite difference methods to assess performance against traditional continuous-time models and determine the optimal step size h required to ensure convergence of the numerical solution.

1.6 Justification of the Study

Although considerable research has addressed tuberculosis dynamics, relatively little effort has been directed toward modeling TB-DM co-infection. Given that diabetes significantly increases TB risk, and considering the rising prevalence of diabetes worldwide, it is critical to address this gap.

To the best of our knowledge, no existing study has simulated TB-DM co-infection using non-standard finite difference schemes with optimal control strategies. Therefore, this study focuses on developing a nine-compartment TB-DM model with optimal control interventions including improved distancing and dietary habits. The NSFD approach will be used to solve the resulting system of differential equations efficiently and accurately.

Chapter 2

Literature Review

2.1 Introduction

The chapter presents two fold of the literature. The first fold entails the the general literature on mathematical modelling of diabetes and TB co-infection. The second presents the mathematical modelling using NSFD or related scheme and ODE-based models. The final sections presents the literature gap based on the literature.

2.2 Tuberculosis and Diabetes

2.2.1 Tuberculosis

Historical review of TB

Ancient Times ([Loddenkemper and Murray, 2021](#)): Tuberculosis has ancient roots, with evidence found in skeletal remains dating back thousands of years. Ancient civilizations, such as Egypt and India, likely had knowledge of the disease.

Middle Ages ([Pesanti, 1995](#)): Tuberculosis is thought to have been present in Europe during the Middle Ages. The term "consumption" was commonly used to describe symptoms associated with TB. **18th - 19th Centuries** ([Grigg, 1955](#)): The industrial

revolution and urbanization contributed to the spread of TB in crowded cities. The link between TB and crowded, unsanitary living conditions became more apparent. **Late 19th - Early 20th Centuries**([Sakula, 1982](#)): Robert Koch's discovery of the tubercle bacillus (*Mycobacterium tuberculosis*) in 1882 was a major breakthrough. The development of sanatoriums and the BCG vaccine (1921) marked significant efforts in TB control. **Mid-20th Century**([Bansal et al., 2018](#)): The introduction of antibiotics, particularly streptomycin, revolutionized TB treatment. Global efforts, such as the World Health Organization's (WHO) Directly Observed Treatment, Short-course (DOTS) strategy, aimed at TB control. **Late 20th - Early 21st Century**([Loddenkemper and Hauer, 2010](#)): The emergence of drug-resistant TB strains posed new challenges to treatment. The HIV/AIDS pandemic contributed to an increase in TB cases, especially in regions with high HIV prevalence. **Recent Advances (21st Century)** ([Zimmet et al., 2014](#)): Advancements in molecular diagnostics and whole-genome sequencing enhanced TB diagnosis and research. The development of new TB drugs, like bedaquiline and delamanid, provided additional treatment options. **Current Challenges and Future Outlook:** TB remains a major global health concern, with challenges such as drug resistance, co-infections, and healthcare disparities. Ongoing research focuses on novel treatments, vaccines, and improving healthcare infrastructure for TB control.

Historical review of TB modelling

Mathematical interventions in epidemics date back to 1760 when modelling of the spread of diseases which are infectious was carried out by Daniel Bernoulli. Bernoulli's work was extended by D'Alembert who came up with a method applicable to infectious and non- infectious diseases to deal with competing risks of death [Bernoulli \(1758\)](#). Pasteur in middle 1800's replicated the same by confirming the germ theory experimentally to create the first vaccine for rabies [Pasteur \(1881\)](#). Robert Koch discovered the anthrax bacillus in 1876, tuberculosis bacillus in 1882 and the cholera

vibrio in 1884, from which he became very famous (Koch, 1982). Modern epidemic modeling began with Hamer (1906) from then, a great number of special models have been developed by researchers for diseases like tuberculosis, measles, smallpox, herpes, malaria, AIDS, measles. Outlined is the chronology of mathematical modelling of TB.

Early Observations and Descriptive Models (Pre-20th Century) (Brauer et al., 2019): Early observations of TB symptoms were documented, but formal mathematical modeling had not yet begun. Physicians used descriptive models to categorize different patterns of TB progression.

Epidemiological Models (20th Century) (Mori, 1996): In the mid-20th century, epidemiological models started to emerge, emphasizing disease spread in populations. The development of compartmental models aimed to understand TB transmission dynamics.

Introduction of Mathematical Tools (Late 20th Century) (Davies et al., 2001): Mathematical tools, such as ODEs, became prevalent in TB modeling. Theoretical studies focused on understanding the impact of different factors on TB prevalence.

Computational Advances and Simulation Models (Late 20th - Early 21st Century) (Ozcaglar et al., 2012): Computational modeling allowed for more complex and realistic simulations of TB dynamics. Agent-based models and stochastic models gained popularity for capturing individual-level interactions and uncertainties.

Integration of Clinical Data (21st Century) (Herzog, 1998). Advances in data collection and integration of clinical data into models improved accuracy. The incorporation of molecular and genomic data enhanced the understanding of TB pathogenesis.

Global Collaborative Efforts (21st Century) (Gupta et al., 2004): Global initiatives, such as the World Health Organization's (WHO) Stop TB Partnership, emphasized the role of modeling in TB control. Mathematical models played a key role in informing policy decisions and strategic planning.

Current Challenges and Future Directions: Challenges include addressing drug-resistant TB, optimizing intervention strategies, and

considering co-infections like HIV/AIDS. Future research may focus on integrating multiple modeling approaches, including spatial and multiscale models, for a comprehensive understanding.

2.2.2 Diabetes

Historical review of diabetes

A historical review of diabetes reveals a fascinating journey spanning thousands of years, marked by observations, developments, and milestones as follows:

Ancient Observations (1500 BCE - 1000 CE): Ancient Egyptian papyruses describe a condition resembling diabetes, noting excessive urination and thirst ([Mohajan, 2023](#)). Indian physicians identified diabetes and classified it into two types ([Sharma et al., 2011](#)): sweet urine (Madhumeha) and non-sweet urine (Asrava). **Middle Ages (1000 CE - 1600 CE):** Diabetes gets its name from the Greek word "siphon," indicating the excessive urination characteristic of the disease ([GREGORY, 2023](#)). A Persian physician, Avicenna, describes diabetes symptoms and complications in his medical encyclopedia. **17th - 19th Centuries:** Thomas Willis coined the term "diabetes mellitus," emphasizing the sweet taste of urine ([Ahmed, 2002](#)). Claude Bernard discovers that the liver can produce glucose, laying the foundation for understanding glucose metabolism ([Tattersall, 1997](#)). Paul Langerhans identifies pancreatic islets, setting the stage for linking diabetes to the pancreas ([Yagihashi, 2015](#)). **Early 20th Century:** Banting and Best isolate insulin in 1921, revolutionizing diabetes treatment ([Owens et al., 2022](#)). Classification into Type 1 and Type 2 diabetes emerges. Blood glucose testing became possible with the invention of the Ames Reflectance Meter ([Clarke and Foster, 2012](#)). **Mid to Late 20th Century:** Oral hypoglycemic drugs are introduced, expanding treatment options ([Tattersall, 2017](#)). Hemoglobin A1c is identified as a marker for long-term glucose control. Diabetes complications and the importance of glycemic control gain recognition. **Late 20th to Early 21st Century:** Advancements in insulin delivery systems, including insulin

pumps. Diabetes technology evolves with the introduction of continuous glucose monitoring (CGM) systems ([Lasker et al., 2010](#)). Genetic factors influencing diabetes susceptibility are discovered. **Recent Advances (21st Century):** Precision medicine approaches for diabetes management gain attention. Artificial pancreas systems integrate insulin pumps and CGMs for automated glucose control ([Allen and Gupta, 2019](#)). Research explores stem cell therapy and gene editing for potential diabetes cures. **Current Challenges and Future Outlook:** The global rise in diabetes prevalence poses significant public health challenges ([Diabaté et al., 2023](#)). Ongoing research focuses on understanding diabetes at the molecular level and developing more personalized and effective treatments. Advances in digital health, telemedicine, and data analytics enhance diabetes care.

The historical journey of diabetes reflects the evolving understanding of the condition and the remarkable progress made in diagnosis, treatment, and management over the centuries. Despite challenges, ongoing research and technological innovations continue to shape the landscape of diabetes care.

Historical review of diabetes modelling

The history review of diabetes modelling is outlined as follows: **Early Observations (Pre-20th Century)** ([Swinburn, 1996](#)): Early observations of diabetes symptoms were documented, but formal mathematical modeling had not yet begun. Physicians classified diabetes into different types based on observable characteristics. **Insulin Discovery and Basic Modeling (Early to Mid-20th Century)** ([Kotchen, 2011](#)): The discovery of insulin by Banting and Best in 1921 revolutionized diabetes treatment. Initial mathematical models focused on insulin kinetics and glucose-insulin interactions. Simple compartmental models emerged to describe glucose metabolism and insulin action. **Glucose-Insulin Models (1960s - 1980s):** Researchers developed more sophisticated models incorporating feedback mechanisms between glucose and insulin ([Sorensen, 1985](#)). Pioneering work by Bergman and Cobelli led to the de-

velopment of compartmental models for glucose-insulin dynamics [Palumbo et al. \(2013\)](#). Minimal models, like the one by Bergman, were introduced to estimate insulin sensitivity. **Physiological-Based Models (1990s - 2000s)**: Physiological-based models became prominent, incorporating detailed representations of pancreatic function, insulin secretion, and peripheral glucose utilization ([Abuin et al., 2020](#)). The adoption of differential equations and system dynamics allowed for a more comprehensive understanding of diabetes dynamics. Models aimed at simulating glucose profiles and predicting responses to interventions. **Personalized and Systems Biology Models (2010s - Present)**([Chan and Ginsburg, 2011](#)): Advances in genetics and personalized medicine led to the incorporation of individualized patient data into models. Systems biology approaches integrate molecular-level data, allowing for a more holistic understanding of diabetes pathophysiology. Computational models are increasingly used to simulate and predict individual responses to various treatments. **Technological Advances and Digital Health (Recent Years)**: The integration of CGM data into models improved real-time simulations. Artificial intelligence and machine learning techniques applied to diabetes modeling for more accurate predictions ([Woldaregay et al., 2019](#)). Mobile apps and digital health platforms utilize modeling to assist in diabetes management. **Current Challenges and Future Directions**: Challenges include the need for more accurate and personalized models, considering diverse patient characteristics ([Melly et al., 2022a,b](#)). Ongoing research explores the integration of multiple data sources, such as genomics, metabolomics, and microbiomics, into comprehensive models. The quest for a fully closed-loop artificial pancreas system continues, aiming for precise glucose control in real-time.

2.3 Mathematical Models

Mathematical models for disease modelling are divided into two categories, namely deterministic and stochastic models.

2.3.1 Deterministic Models

These models are based on precise mathematical equations, do not involve randomness, and are, thus, commonly known as compartmental models ([Morrison, 2012](#)). Deterministic models assume that the initial conditions and the parameters of the model fully determine the system's behavior. They provide a clear, deterministic prediction of the system's evolution over time. Examples include compartmental models such as SIR and SEIR models. This model consists of differential equations and most classical mathematical models used in physics and engineering.

SIR model

The SIR model is a compartmental model used to understand the spread of infectious diseases in a population ([Tang et al., 2020](#)). It divides the population into three compartments: susceptible (S), infectious (I), and recovered (R). Example of SIR model is provided as follows ([Hens et al., 2012](#)):

$$\begin{aligned}\frac{dS}{dt} &= -\beta \cdot \frac{S \cdot I}{N} \\ \frac{dI}{dt} &= \beta \cdot \frac{S \cdot I}{N} - \gamma \cdot I \\ \frac{dR}{dt} &= \gamma \cdot I\end{aligned}$$

where

S : Number of susceptible individuals

I : Number of infectious individuals

R : Number of recovered individuals

N : Total population

β : Transmission rate

γ : Recovery rate

The total population N is given by $N = S + I + R$. The equations describe the rate of change of each compartment with respect to time. The first equation represents the rate at which susceptible individuals become infected, the second equation represents the rate at which infected individuals recover, and the third equation represents the rate at which individuals move from the infectious compartment to the recovered compartment.

SEIR model

The SEIR model is a compartmental model that includes an "Exposed" compartment in addition to the SIR model ([Chen et al., 2021](#); [Marques et al., 2021](#)). An example of a SEIR model can be described by the following set of ODEs:

$$\begin{aligned}\frac{dS}{dt} &= -\beta \cdot \frac{S \cdot I}{N} \\ \frac{dE}{dt} &= \beta \cdot \frac{S \cdot I}{N} - \sigma \cdot E \\ \frac{dI}{dt} &= \sigma \cdot E - \gamma \cdot I \\ \frac{dR}{dt} &= \gamma \cdot I\end{aligned}$$

Here, the variables represent the following:

S : Number of susceptible individuals

E : Number of exposed (but not yet infectious) individuals

I : Number of infectious individuals

R : Number of recovered individuals

N : Total population

β : Transmission rate

σ : Rate of exposed individuals becoming infectious

γ : Recovery rate

The total population N is given by $N = S + E + I + R$. The equations describe the rate of change of each compartment with respect to time. The first equation represents the rate at which susceptible individuals become exposed, the second equation represents the rate at which exposed individuals become infectious, the third equation represents the rate at which infectious individuals recover, and the fourth equation represents the rate at which individuals move from the infectious compartment to the recovered compartment.

2.3.2 Stochastic Models

Stochastic models incorporate randomness or uncertainty into the modeling process (Corlu et al., 2020; Ji and Jiang, 2014). They recognize that real-world systems often involve inherent variability, and outcomes are not entirely predictable. Stochastic models are particularly useful when dealing with small populations, early stages of an outbreak, or scenarios where random events play a significant role. Examples include stochastic differential equations, agent-based models, and simulations that involve random processes. In the stochastic SIR model, the deterministic dynamics of the original SIR model are replaced with random events, making the model more realistic and better suited for situations where the spread of the disease is influenced by chance events (Gourieroux and Lu, 2020; Li et al., 2017). An example of a stochastic SIR model is described by the following set of stochastic differential equations (SDEs) (Ball and Neal, 2002):

$$\begin{aligned}
dS &= -\beta \cdot \frac{S \cdot I}{N} \cdot dt - \sqrt{\beta \cdot \frac{S \cdot I}{N}} \cdot dW_1 \\
dI &= \beta \cdot \frac{S \cdot I}{N} \cdot dt - (\gamma \cdot I) \cdot dt - \sqrt{\gamma \cdot I} \cdot dW_2 \\
dR &= (\gamma \cdot I) \cdot dt + \sqrt{\gamma \cdot I} \cdot dW_3
\end{aligned}$$

where

S : Number of susceptible individuals

I : Number of infectious individuals

R : Number of recovered individuals

N : Total population

β : Transmission rate

γ : Recovery rate

dW_1, dW_2, dW_3 : Wiener processes (Brownian motions)

The total population N is given by $N = S + I + R$. The equations describe the stochastic changes in each compartment over time. The Wiener processes (dW_1, dW_2, dW_3) represent random fluctuations.

Agent-Based Models

Agent-based models (ABMs) are computational models that simulate the behavior of individual agents to study emergent phenomena at the level of the community ([Abar et al., 2017](#)). These models consist of dynamically interacting rule-based agents situated in space and time, residing in networks or lattice-like neighborhoods. The agents are programmed to behave and interact with other agents and the environment in certain ways, producing emergent effects that may differ from the effects of

individual agents.

ABMs have been used since the mid-1990s to solve a variety of business and technology problems ([Axtell and Farmer, 2022](#)). They have found applications in marketing, organizational behavior, supply chain optimization, consumer behavior modeling, social network effects, workforce management, and portfolio management. The flexibility of ABMs in capturing adaptation and heterogeneity makes them a potentially useful tool to inform decision-making in complex systems, and they have seen applications in various fields, including public health, policy informatics, and the philosophy of science.

Network Models

Network Models refer to the use of network theory to understand and simulate the spread of infectious diseases ([Keeling and Eames, 2005](#)). These models incorporate the structure of social, contact, or transportation networks to study how diseases propagate through populations. They provide insights into the dynamics of disease transmission, the impact of network structure on epidemic spread, and the effectiveness of control measures. Network models have been used to study various infectious diseases, including sexually transmitted diseases, influenza, and COVID-19.

The use of network models in disease modeling has led to new perspectives and insights, allowing for a more realistic representation of disease spread compared to traditional compartmental models ([Tang et al., 2020](#)). These models consider the interactions between individuals and the structure of the contact network, which can affect the speed and pattern of disease transmission. While network models can offer valuable insights, they also present challenges, such as the need for detailed data on contact networks and the complexity of working with such models. However, the insights gained from network models can contribute to a better understanding of epidemics and the development of more effective public health policies.

Spatial Models

The Spatial SIR model is described by the following set of partial differential equations (PDEs):

$$\begin{aligned}\frac{\partial S}{\partial t} &= D_S \nabla^2 S - \beta \cdot S \cdot I, \\ \frac{\partial I}{\partial t} &= D_I \nabla^2 I + \beta \cdot S \cdot I - \gamma \cdot I, \\ \frac{\partial R}{\partial t} &= D_R \nabla^2 R + \gamma \cdot I,\end{aligned}$$

where S is Density of susceptible individuals, I is the density of infectious individuals, R is Density of recovered individuals, D_S, D_I, D_R is the diffusion coefficients, β is the transmission rate, γ is the recovery rate, ∇^2 is the laplacian operator.

The equations describe the spatial spread of the disease over time. The diffusion terms (D_S, D_I, D_R) represent the movement of individuals, and the transmission and recovery terms are similar to those in the non-spatial SIR model.

Compartmental Age-Structured Models

The compartmental age-structured SIR model is a modification of the classic SIR model that takes into account the age distribution of the population ([Babajanyan and Cheong, 2021](#)). The model is particularly relevant for diseases such as COVID-19, where the impact on different age groups varies significantly. The age-structured SIR model divides the population into different age groups and computes the age distribution of individuals in each compartment. It considers the age-specific disease parameters, such as intensive care and mortality rates, and is used to understand the importance of age-targeted analysis in epidemic control.

The age-structured SIR model is a valuable tool for studying the dynamics of in-

fectious diseases, as it provides insights into how the disease spreads within and between different age groups (Ram and Schaposnik, 2021). It is a more realistic representation of disease transmission dynamics, especially for diseases that affect age groups differently. The model formulation involves age-dependent differential equations and can be used to analyze the impact of age-specific interventions and control strategies.

Recent research has focused on the development and application of age-structured compartmental models for various infectious diseases, including COVID-19 and tuberculosis (Andrade and Duggan, 2020; Parasnis et al., 2021). These models have been used to gain insights into the progression of active tuberculosis and to study the spread of infectious diseases through indirect contacts, taking into account the age structure of the population.

Age-Structured SIR model consists of equations for each age group, capturing interactions between different age groups through the contact matrix C_{ij} . The transmission and recovery processes are age-dependent, allowing for a more nuanced understanding of disease dynamics in different segments of the population. An example is presented as follows.

$$\begin{aligned}\frac{dS_i}{dt} &= -\beta \cdot S_i \cdot \sum_j C_{ij} \cdot I_j, \\ \frac{dI_i}{dt} &= \beta \cdot S_i \cdot \sum_j C_{ij} \cdot I_j - \gamma \cdot I_i, \\ \frac{dR_i}{dt} &= \gamma \cdot I_i,\end{aligned}$$

where S_i denotes the number of susceptible individuals in age group i , I_i is the number of infectious individuals in age group i , and R_i represents the number of

recovered individuals in age group i . The parameter β refers to the transmission rate, while γ denotes the recovery rate. The term C_{ij} represents the contact rate between individuals in age group i and those in age group j .

Genetic and Evolutionary models

Genetic and evolutionary models maps the disease spread within population of the different genes. Various researchers have used such models, for instance, [Fierst and Phillips \(2015\)](#) discusses Wagner’s model, which addresses the genetic and developmental evolution of a population of individuals. The model has been used to study macroevolutionary patterns, reproductive isolation, and modularity. It has also been applied to investigate the number of evolutionary steps separating phenotypic states and the relationship between network topology and the functional effects of genes.

[Arenas \(2015\)](#) discusses substitution models of evolution, which describe the process of genetic variation through fixed mutations. It highlights the need for the development of complex mixture models and robust methods to evaluate, compare, and apply these models, especially with the increasing amount of genomic data available.

[Delport et al. \(2009\)](#) study focuses on probabilistic models of sequence evolution, which are widely used in phylogenetics and molecular sequence evolution. It discusses the application of these models to alignments of coding sequences and the upsurge of interest in relating parameters of sequence evolution models, such as fitness and associated fixation probability.

The genetic and evolutionary model describes the interplay between the frequency of a genetic variant (P) and the frequency of a genotype (G) in a population. The equations incorporate factors such as growth rates, carrying capacities, selection coefficients, and interaction coefficients to simulate genetic and evolutionary dynamics. An example is described as follows:

$$\begin{aligned}\frac{dP}{dt} &= r \cdot P \cdot \left(1 - \frac{P}{K}\right) - s \cdot P \cdot G, \\ \frac{dG}{dt} &= m \cdot G \cdot \left(1 - \frac{G}{H}\right) - n \cdot P \cdot G,\end{aligned}$$

where P is the frequency of a particular genetic variant in the population, G is the frequency of a particular genotype in the population, r is intrinsic growth rate of the population, K is the carrying capacity of the environment, s is selection coefficient representing the fitness of the genetic variant, m is the intrinsic growth rate of the genotype, H is the genotypic carrying capacity, and n is the interaction coefficient between genetic variant and genotype.

Multiscale Models

Multiscale modeling is a method that uses multiple models at different scales to describe a system. It is particularly useful in fields like physics, chemistry, meteorology, and biology, where systems exhibit complex behavior across various spatial and temporal scales.

Multiscale modeling is used to simulate the behavior of systems with important features at multiple scales of time and/or space ([Steinhauser, 2017](#)). It is essential in integrated computational materials engineering, as it allows the prediction of material properties or system behavior based on knowledge of process-structure-property relationships. In multiscale modeling, different models are linked together either analytically or numerically, allowing for the study of a system using various approaches at different levels of resolution and complexity ([Brandt, 2002](#)). This approach helps to achieve a reasonable compromise between accuracy and efficiency. Multiscale analysis is an important component of multiscale modeling, aiming to derive effective macroscale models from complicated microscale models ([Jebahi et al., 2016](#)).

Techniques for multiscale analysis can be broadly divided into two classes: Local analysis techniques, such as matched asymptotics, which can be used to analyze localized singularities, boundary layers, and internal layers (Weinan and Lu, 2011).

The integration of machine learning and multiscale modeling has been proposed to analyze and interpret large datasets from different sources and levels of resolution in the biological, biomedical, and behavioral sciences (Peng et al., 2021). This combination can help manage ill-posed problems and explore massive design spaces. Multi-scale modeling has emerged as a concept to describe procedures that simulate continuum-scale behavior using information gleaned from computational models of finer scales in the system, rather than resorting to empirical constitutive models. This approach has led to the development of various methods that integrate new fields such as machine learning and material design (Fish et al., 2021). multiscale model captures interactions between macroscopic and microscopic scales. The macroscopic equations describe overall system behavior, while microscopic equations represent interactions at a finer scale. Diffusion coefficients, rate constants, and thresholds govern the multiscale dynamics. An example is presented as follows:

Macroscopic Scale:

$$\begin{aligned}\frac{\partial U}{\partial t} &= D_U \nabla^2 U - \alpha \cdot U \cdot V + \beta \cdot W \\ \frac{\partial V}{\partial t} &= D_V \nabla^2 V + \alpha \cdot U \cdot V - \beta \cdot W \\ \frac{\partial W}{\partial t} &= D_W \nabla^2 W + \gamma \cdot (U - \delta)\end{aligned}$$

Microscopic Scale:

$$\begin{aligned}\frac{du_i}{dt} &= D_{u_i} \nabla^2 u_i - \alpha \cdot u_i \cdot v_i + \beta \cdot w_i \\ \frac{dv_i}{dt} &= D_{v_i} \nabla^2 v_i + \alpha \cdot u_i \cdot v_i - \beta \cdot w_i\end{aligned}$$

$$\frac{dw_i}{dt} = D_{w_i} \nabla^2 w_i + \gamma \cdot (u_i - \delta)$$

where U , V , and W represent the concentrations at the macroscopic scale, while u_i , v_i , and w_i denote the concentrations at the microscopic scale for each subcomponent. The parameters D_U , D_V , and D_W are the diffusion coefficients at the macroscopic scale, and D_{u_i} , D_{v_i} , and D_{w_i} are the diffusion coefficients at the microscopic scale. The constants α , β , and γ denote the rate constants, and δ represents the threshold value.

Meta-Population models

Metapopulation models are used to study the dynamics of spatially separated populations of the same species ([Hanski, 1991](#)). They consist of a group of spatially separated populations of the same species. The term was coined by Richard Levins in 1969 to describe a model of population, and it is generally considered to consist of several distinct populations together with the interactions among them.

The metapopulation model describes organismal populations as existing in small subpopulations that together form a matrix of interconnected groups, inhabiting patches within a larger landscape ([esit Akçakaya, 2001](#)). The models have been explored in infectious disease epidemiology to study host-pathogen interactions and movements among different subpopulations. They serve as an ideal framework to characterize and quantify pathogen transfer and circulation between the environment and hosts.

The model is based on the dynamic aspect of population maintenance, embracing a regional perspective. It is a collection of relatively isolated, spatially distributed, local populations bound together by occasional dispersal between them ([Chesson, 2001](#)). An example of meta-population model is described as a modification of the SIR model. Birth and death rates, transmission, and recovery rates govern the inter-

actions within and between subpopulations. An example is presented as follows:

$$\begin{aligned}\frac{dS_i}{dt} &= \Lambda_i - \beta_i \cdot S_i \cdot I_i - \mu_i \cdot S_i, \\ \frac{dI_i}{dt} &= \beta_i \cdot S_i \cdot I_i - (\gamma_i + \mu_i) \cdot I_i, \\ \frac{dR_i}{dt} &= \gamma_i \cdot I_i - \mu_i \cdot R_i,\end{aligned}$$

where S_i denotes the number of susceptible individuals in subpopulation i , I_i is the number of infectious individuals in subpopulation i , and R_i represents the number of recovered individuals in subpopulation i . The parameter Λ_i denotes the birth rate, β_i is the transmission rate, γ_i is the recovery rate, and μ_i is the death rate, all specific to subpopulation i .

Game Theory models

Game theory is the study of mathematical models of strategic interactions among rational agents ([Laraki et al., 2019](#)). It has applications in various fields, including economics, social science, logic, systems science, and computer science. The theory models the interaction between multiple players in any scenario with specific rules and quantifiable consequences ([Ho et al., 2022](#)). It is used to analyze situations involving various decisions, limited resources, different outcomes resulting from different choices, and the possibility of competition or collaboration between players. Game theory is a theoretical framework for conceiving social situations among competing players and is used to lay out various scenarios and predict their most likely outcomes. The focus of game theory is the game, which serves as a model of an interactive situation among rational players. The key to game theory is that one player's payoff is contingent on the strategy implemented by the other player. The game identifies the players' identities, preferences, and available strategies and how

these strategies affect the outcome. Game theory is the study of how competitive strategies and participant actions can influence the outcome of a situation.

Game theory models have been increasingly used in infectious disease modeling to study the decision-making of individuals during an epidemic ([Chang et al., 2020](#); [Huang and Zhu, 2022](#); [Soltanolkottabi et al., 2020](#)). These models help understand the strategic interactions among rational agents, such as the choice between vaccination and social distancing. A review of research studies using game theory in infectious disease modeling identifies emerging trends in the field, such as the use of network-based models with imitation games. The choice of model depends on factors like the level of immunity in the population, the strength of immunity conferred by vaccines, and the size of the population.

[Huang and Zhu \(2022\)](#) demonstrates that game-theoretic frameworks are powerful in modeling the spreading processes of human-in-the-loop epidemics. It provides a multi-dimensional taxonomy of the existing literature that has proposed, studied, and analyzed game-theoretic models for human-in-the-loop epidemics. [Soltanolkottabi et al. \(2020\)](#) study investigates the social dynamics of vaccination and transmission in epidemic outbreaks with delayed emergence of symptoms, using a model of the public goods game. An example of game theory model in infectious disease modeling can be presented as:

Table 2.1: Game theory model

	Cooperate	Defect
Cooperate	$(R - c, R - c)$	(S, T)
Defect	(T, S)	(P, P)

where **Cooperate**: Individuals adhere to preventive measures (e.g., wearing masks, social distancing). **Defect**: Individuals do not adhere to preventive measures.

The entries in each cell represent the payoffs for individuals based on their combined

choices. In this example: If both individuals cooperate, they receive a payoff of $R - c$ (reward minus the cost of cooperation). If one cooperates and the other defects, the cooperator receives S (sucker's payoff), and the defector receives T (temptation to defect). If both defect, they receive a payoff of P (punishment).

The parameters R , S , T , P , and c depend on the specific infectious disease context and the effectiveness and costs associated with cooperation or defection.

Hybrid models

Hybrid models in infectious disease modeling refer to the integration of different modeling approaches, such as agent-based and equation-based models, to provide a more comprehensive understanding of disease dynamics. For instance, [Hunter et al. \(2020\)](#) study presented a hybrid model for the spread of infectious diseases, where the disease component of the model switches between agent-based and equation-based. The model is designed to capture the advantages of both approaches and provides insights into the impact of switching at different infection levels and spatial scales. [Benjamin \(2022\)](#) presented a Hybrid Incidence Susceptible-Transmissible-Removed (HI-STR) model, is proposed for pandemics. This model is designed to scale time to predict an epidemic's population density-dependent temporal propagation. The model validation demonstrates its potential for predicting an epidemic's population density-dependent temporal propagation.

[Zhao et al. \(2022\)](#) used the SIR and SEIR hybrid-based models to study and predict the spread of COVID-19. The hybrid model integrates different modeling approaches to provide insights into the spread of the disease and its potential impact on different populations.

[Arnst et al. \(2022\)](#) used hybrid stochastic model to represent the evolution of infectious diseases and their transmission. The model combined continuous-time and discrete-time parts to capture the variability of transmission dynamics, screening

efficacy, and other relevant factors. The model was designed to be applicable to various contexts, with a specific focus on infectious disease screening in a university campus. An example of hybrid-based model is presented as:

Compartmental Component:

$$\begin{aligned}\frac{dS}{dt} &= -\beta \cdot S \cdot I, \\ \frac{dI}{dt} &= \beta \cdot S \cdot I - \gamma \cdot I, \\ \frac{dR}{dt} &= \gamma \cdot I.\end{aligned}$$

where S denotes the number of susceptible individuals, I represents the infectious individuals, and R refers to the recovered individuals. The parameter β is the transmission rate, while γ is the recovery rate.

Individuals interact in a spatially explicit environment with movement rules, contact patterns, and infection dynamics. The compartmental component represents the overall dynamics of the population, while the agent-based component captures individual-level interactions, movement, and contact patterns. Hybrid model allows for a more detailed examination of localized transmission dynamics, heterogeneity in interactions, and the impact of individual behavior on disease spread.

2.3.3 Finite Difference Schemes

Finite difference schemes are numerical methods widely used for approximating solutions to differential equations by discretizing the spatial and temporal domains ([Jovanović and Süli, 2013](#); [Kajishima et al., 2017](#)). In infectious disease modeling, finite difference schemes are used to simulate the spread of infectious diseases and to analyze the effectiveness of control measures. Although standard finite difference schemes may be computationally more efficient, especially for well-behaved systems or when the focus is on obtaining results quickly rather than capturing extremely

detailed dynamics. In addition, the standard finite difference scheme involves approximating derivatives at discrete points using finite differences ([Langtangen and Linge, 2017](#)). The most commonly used finite difference scheme in mathematical modelling is non-standard finite difference (NSFD). This is because, as compared to standard finite difference scheme, NSFD has numerous advantages. [Ding et al. \(2013\)](#) study presents a non-standard finite difference (NSFD) scheme for an epidemic model with vaccination. The NSFD scheme was designed to calculate numerical solutions for the model and was shown to be more accurate than standard finite difference schemes. [Ding et al. \(2013\)](#) study proposes a nonstandard finite difference scheme for solving epidemic models for measles, dengue fever, smoking, and SVIR. The scheme was shown to be an efficient technique for solving epidemic models to control infectious diseases. [Li et al. \(2023\)](#) presented two nonstandard finite difference (NFSD) methods to solve SIR epidemic model. [Khan et al. \(2023\)](#) proposes a stochastic explicit finite difference scheme for solving stochastic partial differential equations. The scheme is used to model infectious disease dynamics and is shown to be a robust computational approach for simulating the spread of infectious diseases.

Standard methods may face limitations in certain situations, making NSFDS more preferable ([Conte et al., 2023](#)). NSFDS are employed when standard finite difference schemes encounter challenges such as stability issues, accuracy concerns, or difficulty handling specific boundary conditions. Unlike standard finite difference schemes, NSFDS may use non-uniform or adaptive grids for discretization, allowing for a more flexible representation of the problem's geometry or physics ([Bisheh-Niasar and Arab Ameri, 2018](#)).

NSFDS may use higher-order finite differences to achieve increased accuracy in approximating derivatives, which is crucial for applications requiring a higher level of precision ([Patidar, 2005](#)). NSFDS incorporate special techniques to handle singu-

larities or discontinuities effectively, which can be challenging for standard methods. NSFDS can be tailored to better handle irregularly shaped domains or complex boundary conditions by adapting the discretization strategy. NSFDS find applications in fluid dynamics, heat transfer, quantum mechanics, finance, and more, addressing unique challenges in each field. While NSFDS offer advantages in accuracy and flexibility, they may come with increased computational cost compared to standard methods, requiring a trade-off between accuracy and efficiency.

Differential equations are commonly used to analyze the dynamics of biological systems (Daun et al., 2008). These systems are usually so complex that their exact solutions are usually unattainable. As a result, numerical methods such as Euler and Runge-Kutta schemes are used to analyze them. Approximation theory is used in constructing these methods, and in ways, finite representation of the functions is produced (Holst et al., 2000). These methods are often prone to numerical instabilities (Cresson and Pierret, 2016). For that reason, an idea to construct numerical schemes that do not deal on the approximation problem but rather than look at dynamical information emerged and was developed by Mickens in 1989 and he named the new scheme non-standard schemes to distinguish them from the classical ones (Mickens, 1989). These sets of numerical analysis methods offered numerical solutions to differential equations by constructing discrete models whose solutions are of the same qualitative properties as the corresponding differential equations for all step sizes. The scheme thereby gave reliable numerical results by preserving the significant properties of their continuous analogs (Patidar, 2005). Non-standard finite difference schemes have performed better than those that are more prone to numerical instabilities. Also, the non-standard finite difference scheme performs better regarding positivity and boundedness of solutions compared to the standard finite difference schemes (Liao and Yang, 2017).

Non-standard difference schemes are popular numerical methods for solving dif-

ferential equations involving non-local, non-linear, or non-integer operators ([Azizi, 2023](#)). The schemes are used when traditional numerical methods fail to provide accurate solutions or become computationally expensive. In epidemiology, non-standard finite difference schemes have been used to model the spread of infectious diseases. These schemes are useful when traditional methods fail to capture the non-local and non-linear interactions between infected and susceptible individuals ([Cruz and Castillo-Chavez, 1996](#)). In modeling the spread of tuberculosis, non-standard finite difference schemes have been used to capture the non-local and non-linear interactions between infected and susceptible individuals ([Malong et al., 2019](#)). These schemes have been used to model the effect of treatment and quarantine on the spread of the disease.

Furthermore, the construction and analysis of NSFDM to solve mathematical models was conducted by [Mickens \(2003\)](#), which has been used by several researchers including [Jódar et al. \(2008\)](#) who constructed a nonstandard finite scheme of influenza and were able to show that the differential equation model shows the same properties as the continuous model. [Guerrero et al. \(2014\)](#) solved smoking prevalence in Spain using a Nonstandard finite difference scheme to which they compared their results with the Euler, Runge-Kutta, and Trapezoidal methods and concluded that the scheme was a good numerical method in solving mathematical models.

2.4 Empirical Review

2.4.1 Mathematical modelling of tuberculosis

[Tewa et al. \(2012\)](#) studied the spread of TB through a two patch epidemiological model. They made an assumption that susceptible individuals can migrate between two patches but not infective individuals. They formulated the model by considering a two patch SEI TB. They then analyzed the model by computing the disease free equilibrium (DFE) and basic reproductive number, R_0 . They went further and

determined the global stability of DFE by showing that DFE has global asymptotic stability when $\mathcal{R}_0 < 1$. The results gave an insight on how TB spreads and this is important especially when looking for mitigation policies.

[Mishra and Srivastava \(2014\)](#) formulated a model on pulmonary and MDR TB with vaccination. Here, they considered a quarantine class in their epidemic model for MDR TB patients. They observed that quarantine plays an important part in the control of the infection. They formulated Susceptible-Exposed-Infectious-Quarantine-Recovered-Susceptible having a Vaccinated class (SEI-QRS-V). The model was used in describing changing aspects of TB spread in relation to time in human being populace. In their work, they determined $\mathcal{R}_0$, DFE and their stability. They showed that if $\mathcal{R}_0 < 1$, DFE stability is global in the feasible zone and the disease is wiped out. If $\mathcal{R}_0 > 1$, an exceptional endemic balance occurs and has a nearby (local) asymptotic stability. Their model results were helpful in predicting tuberculosis trend and so planning the right control actions and strategies especially the quarantining of those individuals with MDR TB.

[Zhang et al. \(2015\)](#), did a mathematical model for Tuberculosis, where they included a recover or treatment (T) compartment, to form a S-L-I/J-T model. In their paper there was only one latent compartment, whereas the infectious compartment was divided into two, which is infectious and hospitalized (J) and infectious but not hospitalized (I). Through their work, they were able to show the dynamics of TB where we have a great number of individuals who were infectious but not hospitalized. These individuals play a big role in the spread of TB. This insight is very important when coming up with a control strategy.

[Athithan and Ghosh \(2015\)](#) studied a non-linear mathematical model of TB with a case detection and treatment. In the paper, the whole population under consideration was in four compartments; Susceptible, Exposed, Infectious and Recovered

(SEIR). They used this model to study transmission dynamics of TB. They computed R_0 and determined the equilibrium of the model. Their results showed that an increase in the rate of case detection lead to an increase in the threshold value of R_0 . Also, treatment reduced the equilibrium level of the infective class. The results were helpful in the sense that TB treatment was shown as an important control strategy.

[Taufik et al. \(2015\)](#), presented a paper titled ‘mathematical model for vaccinated tuberculosis disease with VEIT model’. In this model, there are four compartments; Vaccinated Exposed Infected and Treated (VEIT). The paper discussed about formation and analysis of the VEIT Model to TB virus infection by exogenous re-infection. They concluded that the model of vaccinated with exogenous re-infection has two equilibrium states; DFE and EEP. They showed that the eigenvalue of DFE is always negative so that the system stability is asymptotically stable at DFE. The results were very important in bringing about the TB transmission dynamic aspect of re-infection.

[Chacha \(2016\)](#), formulated a mathematical model that predicted the threat of TB as a contagious airborne infection under stable state and non-stable state situations. He did this by monitoring the amount of breath out air by contagious persons in a restricted environment. He demonstrated precisely and diagrammatically, the relationship between TB spread possibility and airborne level of infection, average amount of exhaled air taking into consideration TB occurrence and length of contact to contagious persons in a restricted environment. He chose an age structuring model since infection and illness frequency differ in diverse inhabitants on age dependent and host immune aspects. In his study, he found out that TB spread is prevalent in gatherings for instance; schools, public transportation and correctional facilities especially in developing countries. For any control strategy these aspects are very important and should be put in place. This study is very important in planning how to control the spread of TB.

Similarly, [Adebiyi \(2016\)](#) in his thesis titled mathematical modeling of population dynamics of TB presented and analyzed a SLIT (Susceptible Latent Infectious and Treated) model with the inflow of infective. He analyzed the spread, asymptotic behavior and possible eradication of the disease. He also carried out sensitivity analysis of R_0 to determine the parameter value that contributes more on the disease transmission. He utilized the sensitivity index analysis using partial derivatives when the variable is a differentiable function of the parameter. With the help of next generation matrix, it was found out that whenever $R_0 < 1$, DFE is locally asymptotically stable and unstable whenever $R_0 > 1$. The simulation results from the thesis indicated that despite presence of constant inflow of infective immigrants, a control strategy of complete treatment can help suppress the spread of TB.

[Ragonnet et al. \(2017\)](#), optimized the capturing of the latency dynamics in tuberculosis, by looking at six kind of models of transmission between susceptible, latent, and infected compartment. One of them explains the influence of fast propagation and slow propagation of the Mycobacterium Tuberculosis, from which the susceptible compartment will transfer into infected compartment if it includes fast propagation and will transfer into latent compartment if it is slow propagation.

[Enagi \(2017\)](#) modeled the effect of combining Immunization with Latent Tuberculosis treatment in controlling the spread of Tuberculosis. The administration of Bacillus Calmette Guerin (BCG) vaccines at birth protects children from early infection of the disease, but the effect of these vaccines expires with time. Their results showed that detection and treatment of latent tuberculosis infections using Isoniazid Preventive Therapy prevents the breakdown of latent infections into infectious cases, thus reducing greatly the rate of spread of the disease since only members of the infectious class can spread the disease to others. The DFE will be stable if effort is intensified in bringing down both the contraction rate and the rate of break down to infectious tuberculosis. A better understanding on how to break transmission from latent to

infectious is very helpful in controlling the spread of TB, however, some individuals can be infected with MDR-TB strain and therefore treatment with Isoniazid Preventive Therapy may not work. Therefore, there is need for another control strategy to reduce the transmission.

[Aldila et al. \(2018\)](#) developed a mathematical model of the spread of TB disease involving the age classes in a susceptible compartment under SEIR model. The model had two equilibrium points; DFE and EEP. The R_0 was constructed using the next generation matrix approach. They found out that TB transmission can be reduced through vaccination and increasing life expectancy. The results from simulation showed also that transmission can also be reduced through vaccine protection period and vaccine efficacy.

[Egonmwan and Okuonghae \(2019\)](#) study introduces a novel mathematical model examining the impact of diagnosing and treating latent and active tuberculosis (TB) on disease transmission dynamics. Mathematical analysis revealed backward bifurcation, indicating stable coexistence of disease-free and endemic equilibria when the reproduction number is below one. In the absence of reinfection, the disease-free solution was noted to be globally asymptotically stable. Uncertainty and sensitivity analyses identified key parameters influencing TB dynamics. Numerical simulations emphasized treatment rates for reducing the TB burden with increased diagnosis of latent cases. Limitations included a lack of demographic exploration, homogeneity assumptions, and a focus on treatment rates. The study recommended that future research should refine the model, validate predictions, explore interventions, and consider demographic complexities.

[Dhara et al. \(2019\)](#) used mathematical modeling to investigate the connection between diabetes and tuberculosis infection, utilizing data from six Indian territory hospitals. The study adopts standardized values for model parameters and formu-

lates the model with differential equations. Stability analysis of critical points is performed, and numerical experiments refine existing results using the fourth-order Adams–Bashforth–Moulton method. While providing valuable insights into the association, the study recommended that future research explore additional model accuracy factors, including demographic variables and comorbidities. Further investigation into preventive measures and interventions, guided by the identified stable points, is recommended for more effective control of this joint epidemic.

[Jajarmi et al. \(2019\)](#) investigated a novel fractional mathematical model examining the coexistence of diabetes and tuberculosis. The model differentiated between diabetic and non-diabetic populations, considering seven tuberculosis states for each. The study thoroughly examines model properties by employing a recently introduced Mittag–Leffler nonsingular kernel. A new numerical method facilitates efficient simulation, followed by discussions from mathematical and biological perspectives. The research formulated an optimal control problem, deriving conditions for reducing infected individuals. While the study is comprehensive, it recommends future research into validation of the model with clinical data, assessment of sensitivity to parameter variations, and discussion on real-world implications for clinical interventions, enhancing its practical applicability and robustness.

[Pinto and Carvalho \(2019\)](#) studied the impact of Diabetes Mellitus (DM) on Tuberculosis (TB) epidemiology investigated, with a focus on treatment failure and TB incidence. The study formulates a detailed mathematical fractional order model, categorizing the population into non-diabetics and diabetics. Seven TB statuses within each sub-population are considered, representing various infection and recovery stages. The research emphasizes the clinical implications of DM on the dynamics of TB transmission. Based on fractional order, the mathematical model enables a nuanced understanding of the complex interplay between DM and TB. The reproduction number is calculated to assess disease spread potential, and stability

analyses are conducted for disease-free and endemic equilibria. Numerical simulations provide biological insights. While the study contributes valuable information, further research is suggested, including the refinement of the model with considerations for varying DM severity and treatment adherence. Exploring interventions within the model's context could offer insights into strategies for managing the dual burden of DM and TB, informing more effective health policies.

[Fatmawati et al. \(2020\)](#) introduced a novel fractional model to explore tuberculosis (TB) dynamics in two age groups—children and adults. The model formulation and basic results were presented, employing fractional operators, Caputo and Atangana-Baleanu, to obtain a generalized model. A unique numerical approach was developed for approximate solutions, and graphical analyses with varied fractional orders showcase the flexibility of the Atangana-Baleanu operator compared to Caputo. Graphical representations illustrated a rapid decrease in TB infection with decreasing fractional order. Limitations included a primary focus on fractional orders and lack of clinical validation, urging future research to explore additional factors and enhance real-world applicability.

[Ayinla et al. \(2021\)](#) addressed the urgency of combating TB, the leading cause of death from a single infectious agent, through a comprehensive mathematical model involving seven classes. The model highlights the importance of vaccination, diagnosis, and treatment in controlling TB dynamics, revealing conditions for backward bifurcation and the need for a high vaccination rate to eliminate TB from the community. Prioritizing diagnosis over treatment is recommended. While providing crucial insights, the study lacks clinical validation and comparisons with real-world data, suggesting future research directions to enhance practical applicability, explore additional factors, and refine the model with demographic details.

[Moya et al. \(2021\)](#) study addresses the global Tuberculosis (TB) challenge through

a deterministic mathematical model. It evaluated TB therapy efficacy, considering HIV/AIDS and diabetes influences on disease spread and drug resistance. The model captured the intricate interplay of TB, HIV/AIDS, and diabetes, exploring multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) dynamics. Key features included determining the basic reproduction number $\mathcal{R}_0$ in different sub-populations. The study delved into mathematical and epidemiological properties, focusing on $\mathcal{R}_0$ in various sub-populations. Conditions identified when parameters associated with TB treatment resistance impact transmission negatively. Computational simulations compare TB cases across compartments. The study recommended that future research should explore other factors such as improving interventions for the diabetic population, and emphasize comprehensive TB management among the vulnerable group.

[Moya et al. \(2021\)](#) presents a mathematical model using Caputo fractional derivatives to investigate tuberculosis treatment resistance, considering interactions with HIV/AIDS and diabetes. It classified resistance into MDR-TB and XDR-TB, analyzing disease-free equilibrium points in different sub-populations. Computational simulations for various fractional orders were conducted. The research should clinically validate model predictions, consider additional factors influencing resistance dynamics, and conduct sensitivity analyses for enhanced robustness. Discussions on translating findings into practical control strategies and addressing potential limitations would augment the study's real-world applicability.

[Agwu et al. \(2023\)](#) develops and analyzes a mathematical model to understand the co-dynamics of diabetes and tuberculosis co-infection. The study emphasized positivity and boundedness of solutions; the research conducts local and global stability assessments and bifurcation analysis, revealing dynamic behaviors. Pontryagin's Maximum Principle is employed to derive optimal control conditions, leading to a cost-effectiveness analysis of various strategies. The study recommends a combined

approach, preventing diabetes through a healthy lifestyle and TB through personal hygiene. While offering valuable insights and optimal control strategies, future research is urged to implement identified strategies, consider disease evolution, and refine the model for more effective controls.

[Elaydi and Lozi \(2024\)](#) study develops discrete-time models of TB, including SEI frameworks without treatment and an extended SEIT model incorporating treatment. It introduces two reproduction numbers: the traditional R_0 based on the disease-free equilibrium and a novel $R_0(E^*)$ based on the endemic equilibrium. The disease-free equilibrium is globally stable when $R_0 \leq 1$, while the endemic equilibrium is locally stable if $R_0(E^*) < 1 < R_0$. These findings enhance understanding of TB transmission thresholds and offer a basis for evaluating intervention strategies.

2.4.2 Mathematical modelling of diabetes

[Boutayeb et al. \(2004, 2014\)](#) addressed the global rise in diabetes incidence and complications, emphasizing the associated burden on individuals and society. Utilizing ordinary differential equations and numerical approximations, the research monitored populations of diabetes with and without complications. Diverse scenarios were explored based on specific parameters, illustrating the dynamic evolution from diabetes to complications. The model highlighted the potential for efficient and cost-effective strategies by intervening in diabetes incidence and controlling progression to the complications stage. The study recommended that future research should focused on empirical validation and consider additional factors influencing diabetes dynamics for a more comprehensive understanding.

[De Gaetano et al. \(2008\)](#) tackled the complex task of mathematically modeling the progression of type 2 diabetes, emphasizing the need for a realistic representation of long-term physiological adaptation to insulin resistance. Despite experimental verification challenges due to the disease's extended period, the research ensured

model assumptions aligned with established physiology. The study formulated a model for pancreatic islet compensation, established qualitative characteristics, discussed parameter values, and simulated the model's performance over a lifetime. The proposed model offers a realistic depiction of glucose-insulin system evolution, with notable differences from prior models. While valuable, future research should prioritize empirical validation, consider additional factors, and explore practical implications for clinical applications. Continuous model updates could enhance its utility.

[Rosado \(2009\)](#) In this study, the metabolic disorder of diabetes was explored through a mathematical model, considering hereditary and environmental influences. Various hormones, such as insulin and glucagon, regulating blood glucose levels, were examined. The model, an extension of [Ackerman et al. \(1969\)](#) work, included three hormone concentrations and is based on a 3x3 system of non-homogeneous ordinary differential equations. A nonlinear least squares method achieved calibration with glucose intolerance test data. Simulations yielded a diagnostic indicator for diabetes, complemented by a user-friendly graphical interface for data input and result visualization. While insightful, further discussions on model limitations and potential refinements were warranted for practical application.

[Magombedze et al. \(2010\)](#) study explored Type 1 diabetes, focusing on the dynamic interplay between harmful auto-reactive T cells and regulatory T cells, leading to a quantitative imbalance and insufficient regulation. The study noted that a mathematical model reveals a collective, dynamical instability, rather than a single etiological factor, triggers diabetes onset. The study underscores the need for model validation against empirical data, encourages exploration of specific etiological factors, and suggests potential clinical implications for managing Type 1 diabetes. Future research might refine the model with demographic considerations and investigate strategies to augment regulatory T cells, offering insights into therapeutic avenues.

[Karpel'ev et al. \(2015\)](#) addressed the growing interest in mathematical modeling of carbohydrate metabolism regulation, driven by developing "closed-loop" insulin pumps. The pumps controlled insulin infusion based on blood glucose levels, requiring accurate glycemia predictions for automated insulin control algorithms. The primary goal is to predict blood glucose changes from diverse external factors. The review discusses two major model classes—empirical and theoretical—focused on the insulin-glucose system. Despite the absence of an ideal model, success in blood glucose level control modeling is crucial for advancing diabetes prevention, treatment technologies, and the development of artificial pancreas systems. However, the review could benefit from exploring the practical implications and limitations of existing models for clinical applications.

[Akinsola and Oluyo \(2019\)](#) study explored the significance of mathematical models in understanding and predicting the behavior of systems. The methodology involved investigating the stability of critical points in the model at different parameter values, utilizing eigenvalue sensitivity and eigenvalue elasticity analyses to identify critical parameters influencing the population growth of diabetics with complications. MATLAB and Maple were employed for coding mathematical algorithms and numerical solutions. Results indicated asymptotic stability, with complications control rate identified as crucial. The conclusion emphasizes the potential for comprehensive treatment and interventions to reduce the population of diabetics with complications, providing valuable insights for effective diabetes management. The study recommended a need for practical interventions.

[Mahata et al. \(2019\)](#) study proposed a diabetes model in a fuzzy environment, representing real-world imprecision with fuzzy parameters. Using a system of linear differential equations with fuzzy initial conditions, the model employed the generalized Hukuhara derivative for solution. Stability analysis demonstrated biological significance, while numerical simulations offered visual insights. The study needed

a detailed discussion on fuzzy number selection and biological implications, prompting future research. The study recommended a need for validation against real-world data and a more extensive discussion on numerical results and external factors could enhance the model's utility.

[Srivastava et al. \(2019\)](#) noted that diabetes affects one in 11 individuals globally and is projected to rise to 629 million by 2045, prompting an investigation into a fractional-order model capturing diabetes and its complications. The study proposes a model that defines parameters characterizing the diabetic population and associated complications over time. Employing the homotopy decomposition method (HDM) for problem resolution, the research delves into the model's theoretical aspects, exploring its existence, uniqueness, and stability. The study recommended that future research should validate the model empirically, consider alternative resolution methods, and explore practical implications and interventions for a more comprehensive approach.

[Baleanu et al. \(2020\)](#) study introduces a novel fractional model for the human liver, utilizing the Caputo–Fabrizio derivative with an exponential kernel. The research investigated the existence of a unique solution through the Picard–Lindelöf approach and fixed-point theory. Implementing the homotopy analysis transform method, the mathematical model is analyzed for convergence. Numerical experiments illustrated the model's superiority over the existing integer-order model, validated through comparisons with real clinical data. The study recommended that future research could enhance practical applicability by validating the model with extensive clinical data and exploring alternative numerical methods. Additional investigations into the model's implications and real-world applications are also warranted.

[Mari et al. \(2020\)](#) explored the historical use and evolving role of mathematical modeling in glucose metabolism, citing motivations such as calculating physiological

parameters and providing quantitative representations of pathophysiological mechanisms. With the increasing impact of type 2 diabetes, the study noted that models have progressed from whole-body processes to cellular representations, bridging in vivo and in vitro research. Models' variable success is noted, with attention on clinically applied and iconic models. The study recommended a balance between adherence to reality and practical usefulness. It underscores the need for ongoing research to address unresolved issues, explore in vitro potential, and adapt to the evolving landscape of diabetes research.

[Melly et al. \(2022b\)](#) study investigated glucose-insulin dynamics crucial for diabetes management, presenting a well-posed mathematical model. Utilizing the basic reproductive number and sensitivity analysis, the research emphasizes the insufficiency of assumed insulin quantity. It proposed an optimal control strategy involving increased insulin-dependent glucose disappearance, mainly after five weeks. The study recommended that future research could explore alternative insulin strategies, assess practical implications of optimal control, incorporate additional parameters like exercise-induced glucose loss, validate predictions against clinical data, and extend study durations for comprehensive insights into long-term effects.

[Melly et al. \(2022a\)](#) addresses glucose concentration regulation in type-I diabetes through stimulant measures, lacking prior mathematical modeling. A proposed mathematical model considers extra glucose intake stimulating insulin production, demonstrating real-life applicability. Numerical simulations reveal continuous glucose and insulin concentration increases, highlighting the need for optimal control in type-I diabetes management. Sensitivity analysis identifies the pivotal role of the constant rate of insulin-independent glucose disappearance. Optimal control investigation suggests increasing this rate after the 15th hour. Future studies should explore additional parameters, such as exercise-induced glucose loss, to enhance the model's comprehensiveness and practical applicability.

[Andima et al. \(2022\)](#) study addresses diabetes, a growing concern in Kenyan communities, focusing on complicated diabetic cases within constrained hospitalization settings. A mathematical model was formulated, considering carrying capacity and per capita hospitalization rate. Numerical solutions using depicted results graphically suggest that enhancing the quality of life in the susceptible class reduces diabetes cases while increasing the proportion of treated diabetics raises hospital admissions. Moreover, an increase in carrying capacity reduces the number of hospitalized individuals. The study recommended a need for comprehensive insights.

[Okyere and Ackora-Prah \(2022\)](#) addressed the heightened vulnerability of individuals with diabetes to severe complications from COVID-19 in the African region, constituting a substantial proportion of related deaths. It formulated and analyzed a deterministic comorbidity model of diabetes-COVID-19, exploring fundamental properties such as the basic reproductive number, equilibrium points, and stability. Sensitivity analysis assesses parameter impacts, and time-dependent optimal controls were introduced for effective disease containment strategies. Validation of Ghana's COVID-19 cases confirmed the model's relevance, revealing increased mortality in individuals with diabetes. The optimal control model underscored the efficacy of lockdown and vaccination measures in reducing infections. The study emphasized the need for heightened attention to COVID-19 patients with diabetes.

2.4.3 Mathematical modeling of tuberculosis and diabetes co-infection

From the social sciences and medical sciences researches, a number of researches has been done on TB-Diabetes co-infection. The findings obtained are of great importance in helping get a proper insight on how the two infections co-incur and how to control them. [Mburu et al. \(2018\)](#), looked at the prognostic factors among TB and TB-DM comorbidity. In their findings, they concluded that some factors like

employment status, smoking, alcohol intake and patient regime are associated with Diabetes among TB patients.

[Baghaei et al. \(2013\)](#) did a research on diabetes mellitus and tuberculosis facts and controversies. In their research they acknowledged that the comorbidity of diabetes and tuberculosis is the next challenge for global tuberculosis control. They however suggested active screening of TB patients for diabetes as well as treatment for both diseases together.

[Kumar and Meena \(2020\)](#) did a research on the bidirectional association of tuberculosis and diabetes. They found out that both diseases affect each other negatively. They suggested that to reduce TB incidences, there is need to reduce diabetes in a given population.

The analysis of tuberculosis and diabetes co-infection through mathematical modeling has been done by many authors. For instance [Malik et al. \(2018\)](#); [Moualeu et al. \(2012\)](#) similarly analyzed the dynamics for the transmission of TB in people with diabetes using a SEIR model, and they found a need to look at intervention strategies. In their study, they proposed chemoprophylaxis treatment for latent TB individuals. They also stressed the need to treat active TB individuals and control glucose levels for diabetic individuals. Malik developed Moualeu's work by looking at the possibility of diabetes being transmitted vertically from newborns and included this aspect in their model. [Pinto and Carvalho \(2019\)](#) studied Diabetes Mellitus and TB Co-existence and their Clinical implications from a fractional-order perspective.

[Agwu et al. \(2023\)](#) The study explored a mathematical model for the co-dynamics of diabetes and tuberculosis co-infection, analyzing its positivity, boundedness, and stability. Local and global stability are verified, and bifurcation analysis is conducted. The Pontryagin's Maximum Principle establishes conditions for optimal control, and cost-effectiveness analysis compares various strategies. The findings highlight that

a combined prevention approach, promoting healthy lifestyles to prevent diabetes and personal hygiene for tuberculosis, is the least expensive and most cost-effective strategy for reducing the disease burden.

[Verma et al. \(2023\)](#) introduces an epidemiological model to analyze the dynamics of simultaneous occurrences of tuberculosis and COVID-19. The proposed deterministic compartmental model extended the classical SIS model. The study derives the basic reproduction number $\mathcal{R}_0$ and conducted stability analysis, establishing the stability conditions for disease-free and endemic equilibria. Numerical simulations were performed to visually represent the theoretical findings and explore the transmission dynamics of both diseases during the initial and subsequent waves of COVID-19 in India. The study recommended future studies into the topic with varied compartmental models.

2.4.4 Summary of literature

The literature comprehensively explores mathematical models in understanding the dynamics of tuberculosis (TB) dynamics and its co-infections, particularly with diabetes and COVID-19. [Tewa et al. \(2012\)](#) focused on a two-patch epidemiological model for TB spread, emphasizing migration of susceptible individuals between patches. [Mishra and Srivastava \(2014\)](#) incorporated vaccination and quarantine into an SEI-QRS-V model for pulmonary and MDR TB, revealing the importance of quarantine in infection control. [Zhang et al. \(2015\)](#) introduced a model with separate infectious and hospitalized compartments, shedding light on the role of non-hospitalized infectious individuals in TB spread. [Athithan and Ghosh \(2015\)](#) studied a non-linear TB model, highlighting the impact of case detection and treatment on transmission dynamics. [Taufik et al. \(2015\)](#) presented a VEIT model for vaccinated TB, exploring equilibrium states and stability, particularly the asymptotic stability of the disease-free equilibrium. [Chacha \(2016\)](#) developed a model predicting TB spread in various environments, emphasizing the prevalence in specific settings like

schools and correctional facilities.

Additionally, [Adebiyi \(2016\)](#) analyzed a SLIT model with infective inflow, demonstrating the importance of complete treatment in suppressing TB spread. [Ragonnet et al. \(2017\)](#) optimized latency dynamics capture in TB, considering different transmission models. [Enagi \(2017\)](#) investigated the combined effect of immunization and latent TB treatment, emphasizing the role of Bacillus Calmette Guerin (BCG) vaccines and Isoniazid Preventive Therapy. [Aldila et al. \(2018\)](#) developed an age-structured SEIR model for TB, highlighting the effectiveness of vaccination and increased life expectancy in reducing transmission. [Egonmwan and Okuonghae \(2019\)](#) explored a SLIT model with infective inflow, emphasizing the impact of treatment on TB spread and stability conditions based on R_0 . [Dhara et al. \(2019\)](#) focused on the connection between diabetes and TB, revealing the significance of diagnosis and treatment in controlling TB dynamics. [Jajarmi et al. \(2019\)](#) presented a fractional model for diabetes-TB coexistence, differentiating between diabetic and non-diabetic populations.

Furthermore, [Pinto and Carvalho \(2019\)](#) formulated a detailed fractional order model for TB and diabetes, categorizing the population into non-diabetics and diabetics with various TB statuses. [Fatmawati et al. \(2020\)](#) explored TB dynamics in two age groups through a fractional model, comparing Caputo and Atangana-Baleanu operators. [Ayinla et al. \(2021\)](#) addressed the urgency of combating TB through a comprehensive mathematical model, emphasizing the importance of vaccination, diagnosis, and treatment. [Moya et al. \(2021\)](#) studied TB therapy efficacy, considering HIV/AIDS and diabetes influences on disease spread and drug resistance. The model explored multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) dynamics. [Moya et al. \(2021\)](#) focused on TB treatment resistance, considering interactions with HIV/AIDS and diabetes, and classified resistance into MDR-TB and XDR-TB.

Moreover, [Agwu et al. \(2023\)](#) developed a mathematical model for diabetes and TB co-infection, assessing stability, bifurcation, and optimal control strategies. The study recommended a combined approach, preventing diabetes through a healthy lifestyle and TB through personal hygiene, as a cost-effective strategy. The literature also delved into the bidirectional association between TB and diabetes, exploring prognostic factors [Mburu et al. \(2018\)](#), controversies [Baghaei et al. \(2013\)](#), and the impact on disease dynamics [Kumar and Meena \(2020\)](#). The analysis emphasized the need for active screening, simultaneous treatment, and interventions to reduce diabetes incidences.

The literature demonstrates a robust exploration of mathematical models in understanding and managing TB and its co-infections, particularly with diabetes and COVID-19. The models highlight the intricate dynamics of these diseases, providing valuable insights into effective control strategies and emphasizing the interconnectedness of various factors influencing disease spread. The studies underscore the importance of comprehensive approaches, including vaccination, diagnosis, and treatment, to curb the prevalence of TB and its co-infections.

Chapter 3

Research Methodology

3.1 Introduction

This chapter outlines the methodology used to develop and analyze the tuberculosis-diabetes (TB-DM) co-infection model. The study begins with the formulation of a nine-compartmental deterministic model capturing the interactions between TB and DM. Mathematical preliminaries, including basic definitions, principles, and theorems, are then presented to guide model analysis. The disease-free equilibrium (DFE) and the basic reproduction number $\mathcal{R}_0$ are derived, followed by stability and sensitivity analyses. The model is extended to incorporate optimal control strategies using Pontryagin's Maximum Principle and Hamiltonian function formulation. To solve the system of ordinary differential equations, a Non-Standard Finite Difference (NSFD) scheme is employed due to its stability and ability to preserve qualitative properties of the continuous model across varying step sizes.

3.2 Model formulation

Consider a diverse population with individuals characterized by age, behavior, spatial position, or disease stage. Despite these variations, the population can be catego-

rized into n homogeneous compartments. This section develops a general epidemic model for such a population. Let $x = (x_1, \dots, x_n)^t$, where each $x_i \geq 0$ represents the number of individuals in each compartment. The compartments are arranged so that the first m compartments pertain to infected individuals to enhance clarity. The epidemiological interpretation of the model determines the classification between infected and uninfected compartments and cannot be solely inferred from the structure of the equations, as discussed below. Some models may have multiple plausible interpretations. The basic reproduction number is not solely determined by the mathematical model's structure but relies on how infected and uninfected compartments are defined. We denote $\mathbf{X}_s$ as the set of all disease-free states.

$$\mathbf{X}_s = \{x \geq 0 \mid x_i = 0, i = 1, \dots, m\} \quad (3.1)$$

In order to calculate $\mathcal{R}_0$, it is crucial to distinguish the occurrence of new infections from all other population changes. Define $\mathcal{F}_i(x)$ as the rate at which new infections appear in compartment i , $\mathcal{V}_i^+(x)$ as the rate at which individuals are transferred into compartment i through various means, and $\mathcal{V}_i^-(x)$ as the rate at which individuals are transferred out of compartment i . We assume that each function is continuously differentiable at least twice in each variable. The disease transmission model comprises non-negative initial conditions along with the following system of equations:

$$\dot{x}_i = f_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x), \quad i = 1, \dots, n, \quad (3.2)$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$, and the functions satisfy assumptions (A1)-(A5) outlined below. Since each function represents a directed transfer of individuals, they are all non-negative. Hence,

(A1) If $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$ for $i = 1, \dots, n$.

If a compartment is empty, there can be no transfer of individuals out of the compartment by death, infection, or any other means. Therefore,

(A2) If $x_i = 0$, then $\mathcal{V}_i^- = 0$. Specifically, if $x \in \mathcal{X}_5$, then $\mathcal{V}_i^- = 0$ for $i = 1, \dots, m$.

Consider the disease transmission model given by (3.2) with $f_i(x), i = 1, \dots, n$, satisfying conditions (A1) and (A2). If $x_i = 0$, then $f_i(x) \geq 0$, and thus, the non-negative cone $(x_i \geq 0, i = 1, \dots, n)$ is forward invariant. According to Theorems 1.1.8 and 1.1.9 in Huang et al. (1992, p. 37), for each non-negative initial condition, there is a unique, non-negative solution. The next condition arises from the simple fact that the incidence of infection for uninfected compartments is zero.

(A3) $\mathcal{F}_i = 0$ if $i > m$.

To ensure that the disease-free subspace is invariant, we assume that if the population is free of disease, then the population will remain free of disease. In other words, there is no (density-independent) immigration of infectives. This condition is stated as follows:

(A4) If $x \in \mathcal{X}_s$, then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \dots, m$.

The remaining condition is based on the derivatives of f near a DFE. For our purposes, we define a DFE of (3.2) to be a (locally asymptotically) stable equilibrium solution of the disease-free model. Note that we need not assume that the model has a unique DFE. Consider a population near the DFE x_0 . If the population remains near the DFE (i.e., if the introduction of a few infective individuals does not result in an epidemic), then the population will return to the DFE according to the linearized system

$$\dot{x} = Df(x_0)(x - x_0), \quad (3.3)$$

where $Df(x_0)$ is the derivative $[\partial f_i / \partial x_j]$ evaluated at the DFE, x_0 (i.e., the Jacobian matrix). Here, and in what follows, some derivatives are one-sided since x_0 is on the domain boundary. We restrict our attention to systems in which the DFE is stable in the absence of new infection. Consequently,

(A5) If $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

The conditions listed above allow us to partition the matrix $Df(x_0)$ as shown by the following lemma.

Lemma 1. If x_0 is a DFE of (1) and $f_i(x)$ satisfies (A1)-(A5), then the derivatives DFF (x_0) and $D\mathcal{V}(x_0)$ are partitioned as

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}, \quad (3.4)$$

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

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0) \right] \text{ and } V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0) \right] \text{ with } 1 \leq i, j \leq m. \quad (3.5)$$

Further, F is non-negative, V is a non-singular M -matrix and all eigenvalues of J_4 have positive real part.

Proof. Let $x_0 \in \mathcal{X}_s$ represent a Disease-Free Equilibrium (DFE). According to (A3) and (A4), $(\partial \mathcal{F}_i / \partial x_j)(x_0) = 0$ holds if either $i > m$ or $j > m$. Similarly, based on (A2) and (A4), for $x \in \mathcal{X}_s$, $\mathcal{V}_i(x) = 0$ for $i \leq m$. Consequently, $(\partial \mathcal{V}_i / \partial x_j)(x_0) = 0$ for $i \leq m$

and $j > m$. This verifies the stated partition and zero blocks. The non-negativity of F is a consequence of (A1) and (A4).

Consider $\{e_j\}$ as the Euclidean basis vectors, where e_j is the j -th column of the $n \times n$ identity matrix. For $j = 1, \dots, m$,

$$\left(\frac{\partial \mathcal{V}_i}{\partial x_j}\right)(x_0) = \lim_{h \rightarrow 0^+} \left(\frac{\mathcal{V}_i(x_0 + he_j) - \mathcal{V}_i(x_0)}{h}\right). \quad (3.6)$$

To demonstrate that V is a non-singular M-matrix, observe that if x_0 is a DFE, then, by (A2) and (A4), $\mathcal{V}_i(x_0) = 0$ for $i = 1, \dots, m$. Moreover, if $i \neq j$, then the i^{th} component of $x_0 + he_j = 0$ and $\mathcal{V}_i(x_0 + he_j) \leq 0$ due to (A1) and (A2). Consequently, $\partial \mathcal{V}_i / \partial x_j \leq 0$ for $i \leq m$ and $j \neq i$, and V exhibits the Z sign pattern (refer to Appendix A). Additionally, as per (A5), all eigenvalues of V have positive real parts. These two conditions establish that V is a non-singular M-matrix (Busenberg and Van den Driessche, 1992, p. 135). Condition (A5) also implies that the eigenvalues have positive real parts.

□

3.3 Mathematical preliminary

3.3.1 Definitions

Definition 3.3.2. *Lyapunov function is a non-negative function that decreases in time along the orbits of a dynamical system. It helps study the stability of the equilibrium points Mabotsa et al. (2022).*

Definition 3.3.3. *We say that a non-singular $n \times n$ matrix A is Volterra-Lyapunov stable if there exist a positive diagonal $n \times n$ matrix M such that $MA + A^T M^T < 0$.*

3.3.4 Laws, principles, and theorems/lemmas

Definition 3.3.5. *Mass action law states that when substances A and B react with each other, the reaction rate is proportional to the concentration of A , denoted by $[A]$, and the concentration of B .*

Theorem 3.3.1. *[LaSalle's Invariance Principle] Suppose there is a neighbourhood D of O and continuously differentiable (time-independent) positive definite function $V : D \rightarrow \mathbb{R}$ whose orbital derivative $\dot{V}$ is negative semi-definite. Let I be the union of all complete orbits contained in $\{x \in D \mid \dot{V}(x) = 0\}$. Then there is a neighbourhood U of O such that for every $x_0 \in U$, $\omega(x_0) \subseteq I$ [Mabotsa et al. \(2022\)](#).*

Theorem 3.3.2. *[Pontryagin's Principle] Necessary conditions that (x^*, u^*) be an optimal solution for the optimal control problem are the existence of a non-zero k dimensional vector λ and an n -dimensional vector function $P(t)$ such that for $t \in [t_0, t_1]$:*

$$\dot{P}(t) = -P(t)f(t, x^*, u^*)$$

and

$$P(t)f(t, x, u) = H(t, x, u) = \max_{u \in U} \{H(t, x, u)\}.$$

Theorem 3.3.3. *[Next generation matrix method] In compartmental models for infectious disease transmission, individuals are categorized into several compartments: some are called disease compartments if the individuals therein are infected, while others are called non-disease compartments. Suppose that there are $n > 0$ disease compartments and $m > 0$ non-disease compartments. Then a general compartmental disease transmission model can be written as*

$$X' = \mathcal{F}(x, y) - \mathcal{V}(x, y), \quad y' = g(x, y),$$

with $g = (g_1, \dots, g_m)^T$. Here 1 denotes differentiation with respect to time ; $x = (x_1, \dots, x_n)^T \in \mathbb{R}^n$ and $y = (y_1, \dots, y_m)^T \in \mathbb{R}^m$ represent the populations in disease compartments and non-disease compartments, respectively; $F = (F_1, \dots, F_n)^T$ and $V = (V_1, \dots, V_n)^T$, where F_i represents the rate of new infections in the i^{th} disease compartment; and V_i represents the transition terms, for example, death and recovery in the i^{th} disease compartment. Assume that $F_i(0, y) = 0$, $V_i(0, y) = 0$, $F_i(x, y) \geq 0$, $V_i(x, y) \leq 0$ whenever $x_i = 0$, and $\sum_{i=1}^n \mathcal{V}_i(x, y) \geq 0$ for all $x, y \geq 0$, $i = 1, \dots, n$. Also assume that the disease-free system $y' = g(0, y)$ has a unique equilibrium $y = y_0 > 0$ that is locally asymptotically stable within the disease-free space. Define two $n \times n$ matrices

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j} (0, y_0) \right], \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j} (0, y_0) \right].$$

Assume that $F \geq 0$ and $V^{-1} \geq 0$, which are biologically reasonable. Then the next generation matrix is $K = FV^{-1}$, and the basic reproduction number $\mathcal{R}_0$ can be defined as the spectral radius of K that is,

$$\mathcal{R}_0 = \rho(FV^{-1}).$$

Lemma 3.3.4. Let $D = \begin{bmatrix} d_{11} & d_{22} \\ d_{33} & d_{44} \end{bmatrix}$ be a 2×2 matrix. Then D is Volterra-Lyapunov stable if and only if $d_{11} < 0$, $d_{22} < 0$ and $\det(D) > 0$. This indicates that all the equations are feasible in endemic equilibrium.

3.4 Well-posed equation

The well-posedness of a mathematical model, refers to the model's ability to have a unique, meaningful solution for a given set of initial conditions (Mabotsa et al., 2022; Melly et al., 2022b; Van den Driessche and Watmough, 2002). A well-posed model is stable and produces solutions that behave consistently with the underlying physical or biological system. The well-posedness of the basic SIR model can be discussed based on the following criteria:

1. **Existence of Solutions:** The SIR model equations have smooth and continuous solutions for any set of initial conditions. The solutions exist for a specified time interval, allowing the model to describe the evolution of the disease over time.
2. **Uniqueness of Solutions:** The SIR model equations have unique solutions for a given set of initial conditions. This uniqueness ensures that there is only one possible trajectory for the spread of the disease under specific starting conditions.
3. **Stability of Solutions:** The SIR model exhibits stability properties, indicating that small changes in initial conditions or parameters lead to small changes in the solutions. This stability is crucial for predicting the long-term behavior of the system.
4. **Physical Interpretability:** The model's parameters and variables have clear and meaningful interpretations in the context of infectious disease dynamics. The infection rate (β) and recovery rate (γ) are physically meaningful parameters that govern the dynamics of the system.

The basic SIR model is well-posed, meeting the criteria of existence, uniqueness, stability, and physical interpretability. It provides a solid mathematical foundation

for studying the dynamics of infectious diseases in populations.

3.5 Disease Free Equilibrium

Using the basic SIR model is described by the following system of differential equations:

$$\begin{aligned}\frac{dS}{dt} &= -\beta \frac{SI}{N}, \\ \frac{dI}{dt} &= \beta \frac{SI}{N} - \gamma I, \\ \frac{dR}{dt} &= \gamma I,\end{aligned}\tag{3.7}$$

where S is the number of susceptible individuals, I is the number of infectious individuals, and R is the number of recovered individuals. The variable N denotes the total population. The parameter β represents the infection rate, while γ denotes the recovery rate.

The Disease-Free Equilibrium (DFE) occurs when there are no infectious individuals ($I = 0$). To find the DFE, set $I = 0$ in the system of equations:

$$\begin{aligned}\frac{dS}{dt} &= -\beta \frac{S_0^* \cdot 0}{N} = 0, \\ \frac{dI}{dt} &= \beta \frac{S_0^* \cdot 0}{N} - \gamma \cdot 0 = 0, \\ \frac{dR}{dt} &= \gamma \cdot 0 = 0,\end{aligned}$$

where i_0^* denotes the DFE. Therefore, the Disease-Free Equilibrium is obtained when S is any constant value, and I and R are both zero.

3.6 Basic Reproduction Number

Defining the matrix of partial derivatives of the right-hand side of the SIR equations concerning the state variables at the disease-free equilibrium ($S = N, I = 0, R = 0$):

The Next Generation Matrix (NGM) method is a robust tool for assessing the stability of compartmental models, particularly in the field of epidemiology. It is frequently employed in models such as the SIR model to ascertain the basic reproductive number $\mathcal{R}_0$, a pivotal parameter indicating the potential for disease spread.

The basic reproduction number, denoted $\mathcal{R}_0$, is defined as 'the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual' (Diekmann et al., 1990) and (Feng and Velasco-Hernández, 1997, p. 17). If $\mathcal{R}_0 < 1$, an infected individual, on average, produces fewer than one new infected individual over its infectious period, preventing the infection from growing. Conversely, if $\mathcal{R}_0 > 1$, each infected individual, on average, generates more than one new infection, allowing the disease to invade the population. For a single infected compartment, $\mathcal{R}_0$ is simply the product of the infection rate and the mean duration of the infection. However, for more complex models with multiple infected compartments, this simple heuristic definition of $\mathcal{R}_0$ falls short. A more general basic reproduction number can be defined as the number of new infections produced by a typical infective individual in a population at a Disease-Free Equilibrium (DFE).

To ascertain the fate of a 'typical' infective individual introduced into the population, the dynamics of the linearized system (3.3) with reinfection turned off are considered. In other words, the system

$$\dot{x} = -D\mathcal{V}(x_0)(x - x_0) \tag{3.8}$$

By (A5), the DFE is locally asymptotically stable in this system. Thus, (3.8) can be utilized to determine the fate of a small number of infected individuals introduced to a disease-free population. Let $\psi_i(0)$ be the number of infected individuals initially in compartment i , and let $\psi(t) = (\psi_1(t), \dots, \psi_m(t))^t$ be the number of these initially infected individuals remaining in the infected compartments after t time units, where the vector ψ corresponds to the first m components of x . The partitioning of $DV(x_0)$ implies that $\psi(t)$ satisfies $\psi'(t) = -V\psi(t)$, which has the unique solution $\psi(t) = e^{-tV}\psi(0)$. According to Lemma 1, V is a non-singular M-matrix, making it invertible with all of its eigenvalues having positive real parts. Consequently, integrating $F\psi(t)$ from zero to infinity yields the expected number of new infections produced by the initially infected individuals as the vector $FV^{-1}\psi(0)$. Given that F is non-negative and V is a non-singular M-matrix, V^{-1} is also non-negative (Berman and Plemmons, 1994, p. 137), as is FV^{-1} .

To interpret the entries of FV^{-1} and develop a meaningful definition of $\mathcal{R}_0$, consider the fate of an infected individual introduced into compartment k of a disease-free population. The (j, k) entry of V^{-1} represents the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection. The (i, j) entry of F indicates the rate at which infected individuals in compartment j produce new infections in compartment i . Thus, the (i, k) entry of the product FV^{-1} signifies the expected number of new infections in compartment i produced by the infected individual initially introduced into compartment k . Following Diekmann et al. (1990), F^{-1} is termed the next generation matrix for the model, and $\mathcal{R}_0$ is defined as

$$\mathcal{R}_0 = \rho(FV^{-1}), \quad (3.9)$$

where $\rho(A)$ denotes the spectral radius of a matrix A . $\mathcal{R}_0$ represents the average

number of secondary infections generated by one infectious individual in a completely susceptible population.

3.7 Stability analysis

In epidemiology, the stability analysis of infectious disease models involves investigating the long-term behavior of the system to determine whether equilibrium points are stable or unstable (Van den Driessche and Watmough, 2002). The stability of these equilibrium points provides insights into the potential outcomes of disease dynamics. Considering the basic SIR model described in (3.7),

Theorem 3.7.1. *The Disease-Free Equilibrium (DFE) occurs when there are no infectious individuals in the population, i.e., $I^* = 0$. At the DFE, the system of equations simplifies to:*

$$\frac{dS}{dt} = 0, \quad (3.10)$$

$$\frac{dI}{dt} = 0, \quad (3.11)$$

$$\frac{dR}{dt} = 0. \quad (3.12)$$

Proof. The DFE is achieved when $I^* = 0$, and the equations become:

$$\frac{dS}{dt} = -\beta \frac{S \cdot 0}{N} = 0, \quad (3.13)$$

$$\frac{dI}{dt} = \beta \frac{S \cdot 0}{N} - \gamma \cdot 0 = 0, \quad (3.14)$$

$$\frac{dR}{dt} = \gamma \cdot 0 = 0. \quad (3.15)$$

Thus, the system remains at the Disease-Free Equilibrium when $I^* = 0$. □

Theorem 3.7.2 (Stability of the Disease-Free Equilibrium). *The Disease-Free Equilibrium is locally asymptotically stable if the basic reproduction number $\mathcal{R}_0 < 1$.*

Proof. The basic reproduction number $\mathcal{R}_0$ is given by:

$$\mathcal{R}_0 = \frac{\beta}{\gamma}. \quad (3.16)$$

If $\mathcal{R}_0 < 1$, then the Disease-Free Equilibrium is locally asymptotically stable. $\square$

Lyapunov Stability Analysis:

Define the Lyapunov function $V(S, I, R) = I + \frac{S}{N}$. The time derivative of V along the trajectories of the system is given by:

$$\begin{aligned} \frac{dV}{dt} &= \frac{dI}{dt} + \frac{1}{N} \frac{dS}{dt} \\ &= \beta \frac{SI}{N} - \gamma I + \frac{1}{N} \cdot 0 \\ &= -\gamma I + \beta \frac{SI}{N} \\ &= I(\beta - \gamma - \beta \frac{I}{N}). \end{aligned} \quad (3.17)$$

Since $\mathcal{R}_0 = \frac{\beta}{\gamma} < 1$, $\beta - \gamma < 0$. Thus, $\frac{dV}{dt} < 0$, and by the LaSalle Invariance Principle, the Disease-Free Equilibrium is locally asymptotically stable. This concludes the stability analysis for the basic SIR model.

3.8 Sensitivity analysis

Sensitivity analysis is a crucial aspect of mathematical modeling that helps understand the impact of changes in model parameters on the model's outcomes (Gumel et al., 2021). It provides insights into the robustness and reliability of the model by assessing how variations in input parameters influence the output. Here, we discuss the importance of sensitivity analysis in mathematical modeling.

Sensitivity analysis involves studying how uncertainty or variations in the input parameters of a mathematical model affect the model's predictions, outputs, and overall behavior. Its importance in mathematical modelling is outlined as follows

1. **Identifying Critical Parameters:** Sensitivity analysis helps identify which parameters have the most significant influence on the model's outcomes. This information is crucial for prioritizing efforts in data collection and refining parameter estimates.
2. **Quantifying Model Robustness:** By varying input parameters within plausible ranges, sensitivity analysis provides a measure of the model's robustness. Models that are less sensitive to variations in parameters are generally considered more reliable.
3. **Model Calibration and Validation:** Sensitivity analysis is an integral part of the model calibration and validation process. It helps assess how well the model captures the essential dynamics by comparing model predictions with observed data under different parameter scenarios.
4. **Decision-Making Under Uncertainty:** In decision-making processes where outcomes are uncertain, sensitivity analysis provides decision-makers with insights into the potential impact of different scenarios. This aids in making informed decisions and managing risks.
5. **Optimizing Resource Allocation:** Sensitivity analysis helps identify parameters that, if better known, would significantly reduce uncertainties in model predictions. This information guides the allocation of resources for data collection and research.
6. **Improving Model Structure:** If a model is highly sensitive to certain parameters, it may indicate a need for model refinement or the inclusion of additional

factors. Sensitivity analysis guides model improvement efforts by highlighting areas of uncertainty.

7. **Communicating Model Limitations:** Sensitivity analysis provides a transparent way to communicate the limitations of a model. It helps stakeholders understand the degree of confidence in model predictions and the factors that contribute to uncertainties.
8. **Avoiding Overfitting:** Sensitivity analysis helps avoid overfitting, where a model is too closely tailored to specific data, by highlighting the parameters that have the most impact on the model's generality.

In summary, sensitivity analysis plays a vital role in enhancing the reliability, interpretability, and utility of mathematical models. It assists in making informed decisions, managing uncertainties, and improving the overall quality of the modeling process.

Given that $\mathcal{R}_0 = \frac{\beta}{\gamma}$, the sensitivity equations are as follows:

1. **Sensitivity with respect to β :**

$$\frac{d\mathcal{R}_0}{d\beta} = \frac{1}{\gamma} \quad (3.18)$$

2. **Sensitivity with respect to γ :**

$$\frac{d\mathcal{R}_0}{d\gamma} = -\frac{\beta}{\gamma^2} \quad (3.19)$$

1. **Sensitivity with respect to β :**

- **Interpretation:** A small increase in the transmission rate β will result in an increase in $\mathcal{R}_0$. The larger the value of γ , the smaller the impact of

changes in β on $\mathcal{R}_0$.

2. Sensitivity with respect to γ :

- **Interpretation:** A small increase in the recovery rate γ will result in a decrease in $\mathcal{R}_0$. The smaller the value of γ , the larger the impact of changes in γ on $\mathcal{R}_0$.

1. **Choose Parameter Values:** Assign values for β and γ .
2. **Calculate $\mathcal{R}_0$:** Use the formula $\mathcal{R}_0 = \frac{\beta}{\gamma}$ to calculate $\mathcal{R}_0$.
3. **Compute Sensitivity Indices:** Substitute the parameter values into the sensitivity equations to calculate the sensitivity indices.
4. **Normalize Sensitivity Indices:** If desired, normalize the sensitivity indices by dividing each index by the corresponding parameter value.
5. **Interpret Results:** Analyze the sensitivity indices to understand how changes in β and γ influence $\mathcal{R}_0$.
6. **Visualize Results:** Create visualizations, such as sensitivity plots, to represent the sensitivity indices.

3.9 Optimal control

Optimal control is a powerful mathematical framework employed to find the best possible inputs or decisions that optimize the performance of a system (Rachah et al., 2015). This technique is widely used in mathematical modeling for various applications, ranging from engineering and economics to biology and ecology. In mathematics, optimal control deals with determining the inputs or controls over time that lead to the optimal performance of a system (Bonyah et al., 2016; Kirk, 2004). It involves the minimization or maximization of an objective function, sub-

ject to a set of constraints and the dynamic evolution of the system. Importance of optimal control is highlighted as follows

Optimal control is essential across various disciplines for improving decision-making and performance. In terms of resource optimization, it enables efficient allocation in systems such as manufacturing and traffic flow, minimizing costs and maximizing efficiency. For system performance enhancement, particularly in engineering and robotics, optimal control ensures that control inputs are dynamically adjusted to achieve goals like increased energy efficiency or reduced response time. In economics, it plays a vital role in modeling decisions that maximize profits and minimize long-term costs through optimal resource distribution. Within biological and ecological systems, optimal control helps model population dynamics, predator-prey interactions, and disease spread, informing strategies for resource utilization and ecosystem management. In aerospace and space exploration, it is critical for trajectory planning, spacecraft control, and mission efficiency—ensuring accurate positioning and minimal fuel use. Environmental conservation also benefits from optimal control by facilitating the design of sustainable resource policies and pollution management strategies. Lastly, in medicine, optimal control is applied to determine effective drug dosage regimens, developing treatment plans that enhance therapeutic effects while reducing adverse side effects.

Various optimization methods, such as Pontryagin's Maximum Principle and dynamic programming, are commonly employed for solving optimal control problems. These methods provide insights into the optimal trajectories and controls for the given system. Optimal control is a versatile and indispensable tool in mathematical modeling. Its applications span across diverse fields, contributing to the efficient management of systems and the improvement of overall performance. By finding optimal solutions, optimal control enhances decision-making processes and aids in addressing complex challenges in science, engineering, economics, and beyond.

3.9.1 Pontryagin's Maximum Principle

Pontryagin's Maximum Principle is a fundamental concept in optimal control theory (Lewis, 2006). Developed by the Soviet mathematician Lev Pontryagin (Das et al., 2024), it provides necessary conditions for an optimal control of a dynamical system.

Considering a controlled system described by the differential equations:

$$\dot{x}(t) = f(x(t), u(t)), \quad (3.20)$$

where $x(t)$ is the state vector, $u(t)$ is the control vector, and f represents the system dynamics.

Let J be the cost functional defined as:

$$J[u(\cdot)] = \int_{t_0}^{t_f} L(x(t), u(t), t) dt + \Phi(x(t_f)), \quad (3.21)$$

where L is the instantaneous cost, and Φ is the terminal cost.

Pontryagin's Maximum Principle states that if $u^*(t)$ is an optimal control for the system, then there exists a nontrivial absolutely continuous vector-valued function $\lambda(t)$ (called the adjoint vector or costate) such that the following conditions are satisfied:

1. Hamiltonian Maximization:

$$\mathcal{H}(x^*(t), u^*(t), \lambda^*(t), t) = \max_u \mathcal{H}(x^*(t), u, \lambda^*(t), t), \quad (3.22)$$

where the Hamiltonian function is given by $\mathcal{H}(x, u, \lambda, t) = L(x, u, t) + \lambda^T f(x, u, t)$.

2. State Equations:

$$\dot{x}^*(t) = \frac{\partial \mathcal{H}}{\partial \lambda}(x^*(t), u^*(t), \lambda^*(t), t). \quad (3.23)$$

3. Adjoint Equations:

$$\dot{\lambda}^*(t) = -\frac{\partial \mathcal{H}}{\partial x}(x^*(t), u^*(t), \lambda^*(t), t). \quad (3.24)$$

4. Transversality Conditions:

$$\lambda^*(t_f) = -\frac{\partial \Phi}{\partial x}(x^*(t_f)), \quad (3.25)$$

$$\Phi(x^*(t_f)) = 0. \quad (3.26)$$

Pontryagin's Maximum Principle provides insights into the optimal control strategy. The optimal control should maximize the Hamiltonian, which combines the instantaneous cost and the influence of the adjoint vector. The adjoint vector, in turn, satisfies differential equations that are related to the sensitivity of the cost functional with respect to variations in the state.

3.9.2 Hamiltonian function

The Hamiltonian function plays a crucial role in Pontryagin's Maximum Principle and provides a convenient way to formulate and analyze optimal control problems (Aseev and Kryazhimskii, 2007). Its structure allows for a systematic application of Pontryagin's Maximum Principle, leading to valuable insights into optimal control strategies.

Consider a controlled system described by the differential equations (3.20)

The Hamiltonian function $\mathcal{H}$ associated with this system is defined as:

$$\mathcal{H}(x, u, \lambda, t) = L(x, u, t) + \lambda^T f(x, u, t), \quad (3.27)$$

where $L(x, u, t)$ is the instantaneous cost function, λ is the adjoint vector (also known

as the costate), $f(x, u, t)$ represents the system dynamics, and t is time. The Hamiltonian function consists of two main components:

1. **Instantaneous Cost:** $L(x, u, t)$ represents the immediate cost associated with the state x , the control u , and the time t . It quantifies the expense or benefit incurred at each moment.
2. **Adjoint and System Dynamics:** $\lambda^T f(x, u, t)$ combines the adjoint vector λ with the system dynamics $f(x, u, t)$. The adjoint vector represents the sensitivity of the cost with respect to variations in the state.

The Hamiltonian function is central to the formulation of the Pontryagin's Maximum Principle, which provides necessary conditions for an optimal control. The maximum condition in the principle involves maximizing the Hamiltonian with respect to the control.

$$\max_u \mathcal{H}(x, u, \lambda, t) = \mathcal{H}_{\max}(x, \lambda, t) \quad (3.28)$$

This maximization condition guides the selection of the optimal control strategy that minimizes the overall cost.

3.10 Non-standard Finite Difference Scheme

Using (3.7) NSFD with both the Runge-Kutta method and the forward Euler method the process of analyzing the model can be shown as follows

3.10.1 Runge-Kutta Method

The Runge-Kutta method is a numerical method used to solve ordinary differential equations. For the SIR model in (3.7), the equations can be solved iteratively as follows:

$$\begin{aligned}
k_1 &= h \cdot \left(-\beta \cdot \frac{S \cdot I}{N} \right) \\
l_1 &= h \cdot \left(\beta \cdot \frac{S \cdot I}{N} - \gamma \cdot I \right) \\
m_1 &= h \cdot (\gamma \cdot I) \\
k_2 &= h \cdot \left(-\beta \cdot \frac{(S + k_1/2) \cdot (I + l_1/2)}{N} \right) \\
l_2 &= h \cdot \left(\beta \cdot \frac{(S + k_1/2) \cdot (I + l_1/2)}{N} - \gamma \cdot (I + l_1/2) \right) \\
m_2 &= h \cdot (\gamma \cdot (I + l_1/2)) \\
k_3 &= h \cdot \left(-\beta \cdot \frac{(S + k_2/2) \cdot (I + l_2/2)}{N} \right) \\
l_3 &= h \cdot \left(\beta \cdot \frac{(S + k_2/2) \cdot (I + l_2/2)}{N} - \gamma \cdot (I + l_2/2) \right) \\
m_3 &= h \cdot (\gamma \cdot (I + l_2/2)) \\
k_4 &= h \cdot \left(-\beta \cdot \frac{(S + k_3) \cdot (I + l_3)}{N} \right) \\
l_4 &= h \cdot \left(\beta \cdot \frac{(S + k_3) \cdot (I + l_3)}{N} - \gamma \cdot (I + l_3) \right) \\
m_4 &= h \cdot (\gamma \cdot (I + l_3)) \\
S_{n+1} &= S_n + \frac{k_1 + 2k_2 + 2k_3 + k_4}{6} \\
I_{n+1} &= I_n + \frac{l_1 + 2l_2 + 2l_3 + l_4}{6} \\
R_{n+1} &= R_n + \frac{m_1 + 2m_2 + 2m_3 + m_4}{6}
\end{aligned}$$

3.10.2 Forward Euler Method

The forward Euler method is a simple numerical method for solving ordinary differential equations. The SIR model equations using the forward Euler method can be expressed as:

$$\begin{aligned}
S_{n+1} &= S_n - h \cdot \beta \cdot \frac{S_n \cdot I_n}{N} \\
I_{n+1} &= I_n + h \cdot \left(\beta \cdot \frac{S_n \cdot I_n}{N} - \gamma \cdot I_n \right) \\
R_{n+1} &= R_n + h \cdot \gamma \cdot I_n
\end{aligned}$$

where S_n , I_n , and R_n represent the values of S , I , and R at time t_n , and h is the time step.

The above procedure shows a detailed application of NSFD to the basic SIR model using the Runge-Kutta method and the forward Euler method. These provide valuable steps that are used in analysing the research.

Chapter 4

Results: Model Formulation and Analysis

4.1 Introduction

The chapter presents the results of the study based on the model formulated. Later sections of the paper outlines the optimal control measures that were investigated based on the sensitivity analysis.

4.2 Model formulation

S The model description that represents the dynamics of tuberculosis and diabetes co-infection is divided into compartments where the compartment S are healthy individuals, and is increased by Λ , the recruitment of individuals by birth. It is decreased by λS (individuals getting TB), $\alpha_1 S$ (Individuals acquiring Diabetes) and by μS (natural deaths).

L_f The compartment L_f (individuals with fast propagating TB) is increased by $p\lambda S$ (proportion of susceptible individuals developing a fast propagating TB) and πL_s (individuals with slow propagating TB developing fast propagating

TB), and is decreased by μ (natural death), $\sigma_1 L_f$ (individuals with fast propagating TB becoming infectious).

L_s The compartment L_s (individuals with slow propagating TB) is increased by $(1 - p)\lambda S$ (susceptible individuals developing slow propagating TB) and $\rho_1 I_T$ (those infectious and treated individual getting a slow propagation TB) and is decreased by μL_s (natural deaths), λL_f (individuals with slow propagating TB developing fast propagating TB), $\sigma_2 L_s$ (individuals with slow propagating TB becoming infectious), $\alpha_2 L_s$ (individuals with slow propagating TB acquiring diabetes) and $\delta_1 L_s$ (TB induced deaths).

I_T The compartment I_T (TB infectious individuals) is increased by $\sigma_2 L_s$ (individuals with slow propagating TB becoming infectious) and $\sigma_1 L_f$ (individuals with fast propagating TB becoming infectious) and is decreases by $\rho_1 I_T$ (those infectious and treated gets a slow propagation TB), μI_T (natural deaths) and $\delta_2 I_T$ (TB induced deaths).

D_T The compartment D_T (individuals with TB and diabetes) and is increased by $\alpha_2 L_s$ (individuals with slow propagating TB acquiring diabetes), ηD (individuals with diabetes getting TB) and $\rho_2 I_{DT}$ individuals with diabetes but treated of TB becomes exposed to TB. The class is decreased by μD_T (natural death) and $\sigma_3 D_T$ (individuals becomes infectious of TB).

I_{DT} The compartment I_{DT} (individuals with diabetes and infectious of TB) is increased by $\sigma_3 D_T$ (individuals become infectious of TB) and $\omega_2 C_{DT}$ (proportion of individuals with diabetes complications due to TB). The class is decreased by $\rho_2 I_{DT}$ (individuals with diabetes but treated of TB becomes exposed to TB), μ (natural death rate), $\delta_2 I_{DT}$ (disease induced deaths) and $\theta_2 I_{DT}$ (proportion of individuals progressing to individual with diabetes complications due to TB).

C_{DT} The compartment C_{DT} (individuals with diabetes complications due to TB) and is increased by $\theta_2 I_{DT}$ (individuals infectious with TB and has Diabetes developing complications) and decreases by $\omega_2 C_{DT}$ (individuals receiving treatment of the complications), μC_{DT} (natural death) and $\delta_3 C_{DT}$ (TB induced deaths due to complications).

D The compartment D (individuals with diabetes) is increased by $\alpha_1 S$ (susceptible individuals acquiring diabetes) and $\omega_1 C$ (individuals with diabetes complications getting treatment of the complications) and is decreased by μD (natural deaths), $\theta_1 D$ (diabetic individuals getting diabetes complications) and λD (individuals with diabetes getting TB).

C The compartment C (diabetic individuals with complications) is increased by $\theta_1 D$ (diabetic individuals getting diabetes complications) and is decreased by μC (natural deaths), $\delta_3 C$ (induced deaths due to diabetes complications) and $\omega_1 C$ (individuals with diabetes complications getting treatment of the complications).

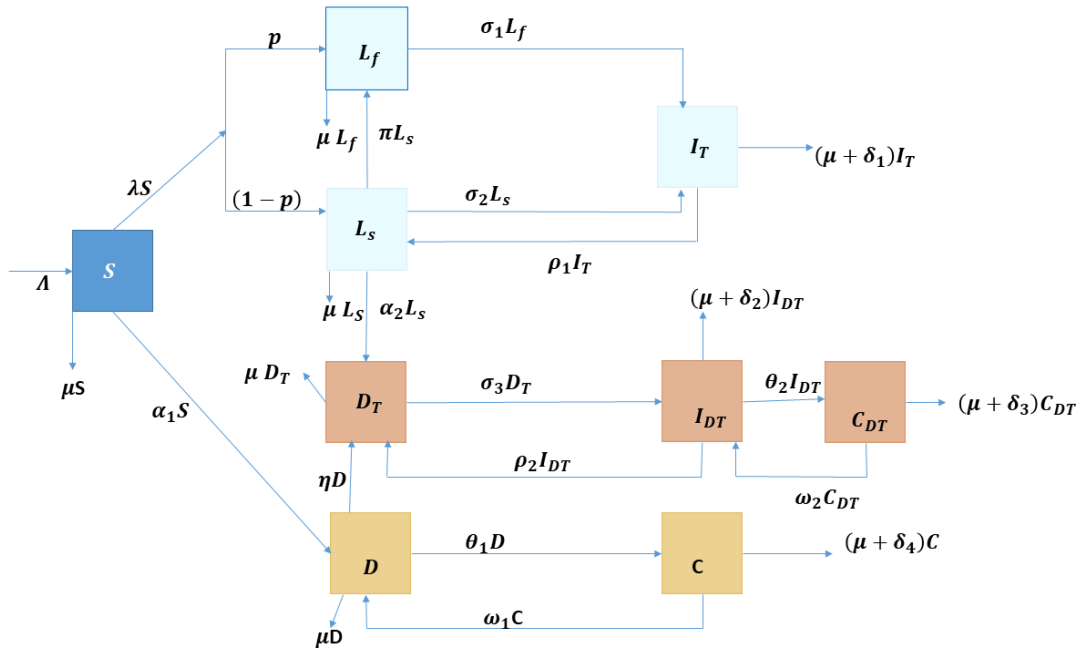


Figure 4.1: TB-Diabetes model

Following the description given in the flow diagram, the model system is described by the first order differential equations given in (4.1).

$$\begin{aligned}
\frac{dS}{dt} &= \overbrace{\Lambda}^{\text{recruitment}} - \overbrace{\beta I S}^{L_f L_s \text{ transmission}} - \overbrace{\alpha_1 S}^{D \text{ transmission}} - \overbrace{\mu S}^{\text{natural deaths}}, \\
\frac{dL_f}{dt} &= \overbrace{p\beta I S}^{S \text{ becomes } L_f} + \overbrace{\pi L_s}^{L_s \text{ becoming } L_f} - \overbrace{\sigma_1 L_f}^{L_f \text{ becoming } I_T} - \overbrace{\mu L_f}^{\text{natural deaths}}, \\
\frac{dL_s}{dt} &= \overbrace{(1-p)\beta I S}^{S \text{ becoming } L_s} + \overbrace{\rho_1 I_T}^{I_T \text{ transforming to } L_s} - \overbrace{\pi L_s}^{L_s \text{ becoming } L_f} - \overbrace{\sigma_2 L_s}^{I_T \text{ becoming } L_s} - \overbrace{\alpha_2 L_s}^{L_s \text{ becoming } D_T} - \overbrace{\mu L_s}^{\text{natural deaths}}, \\
\frac{dI_T}{dt} &= \overbrace{\sigma_2 L_s}^{L_s \text{ becomes infectious}} + \overbrace{\sigma_1 L_f}^{L_f \text{ becomes infectious}} - \overbrace{\rho_1 I_T}^{I_T \text{ becomes } L_s} - \overbrace{\delta_1 I_T}^{\text{disease induced death}} - \overbrace{\mu I_T}^{\text{natural deaths}}, \\
\frac{dD_T}{dt} &= \overbrace{\alpha_2 L_s}^{L_s \text{ become diabetic}} + \overbrace{\eta D}^{D \text{ acquires TB}} + \overbrace{\rho_2 I_{DT}}^{I_{DT} \text{ exposed to TB}} - \overbrace{\sigma_3 D_T}^{D_T \text{ become infectious}} - \overbrace{\mu D_T}^{\text{natural deaths}}, \\
\frac{dI_{DT}}{dt} &= \overbrace{\sigma_3 D_T}^{D_T \text{ become infectious}} + \overbrace{\omega_2 C_{DT}}^{C_{DT} \text{ becomes } I_{DT} \text{ due to TB}} - \overbrace{\rho_2 I_{DT}}^{I_{DT} \text{ is exposed to TB}} - \\
&\quad \overbrace{\theta_2 I_{DT}}^{I_{DT} \text{ gets complication due to TB}} - \overbrace{\delta_2 I_{DT}}^{\text{disease induced death}} - \overbrace{\mu I_{DT}}^{\text{natural deaths}}, \\
\frac{dC_{DT}}{dt} &= \overbrace{\theta_2 I_{DT}}^{I_{DT} \text{ gets complication due to TB}} - \overbrace{\omega_2 C_{DT}}^{C_{DT} \text{ becomes } I_{DT} \text{ due to TB}} - \overbrace{\delta_3 C_{DT}}^{\text{disease induced death}} - \overbrace{\mu C_{DT}}^{\text{natural deaths}}, \\
\frac{dD}{dt} &= \overbrace{\alpha_1 S}^{S \text{ acquires diabetes}} + \overbrace{\omega_1 C}^{\text{treated } C} - \overbrace{\eta D}^{D \text{ gets TB}} - \overbrace{\theta_1 D}^{D \text{ getting complications}} - \overbrace{\mu D}^{\text{natural deaths}}, \\
\frac{dC}{dt} &= \overbrace{\theta_1 D}^{D \text{ getting complications}} - \overbrace{\omega_1 C}^{C \text{ getting treatment}} - \overbrace{\delta_4 C}^{\text{disease induced deaths}} - \overbrace{\mu C}^{\text{natural deaths}},
\end{aligned} \tag{4.1}$$

where $\lambda = \beta I$ and $I = I_T + I_{DT}$, subject to the initial conditions in (4.2).

$$\left. \begin{aligned} S(0) &= S_0, \quad L_s(0) = L_{s0}, \quad I_T(0) = I_{T0}, \quad L_f(0) = L_{f0}, \quad I_{DT} = I_{0DT}, \\ C_{DT} &= C_{0DT}, \quad D_T(0) = D_{T0}, \quad D(0) = D_0, \quad C(0) = C_0. \end{aligned} \right\} \tag{4.2}$$

The model (4.1) is an extension of some earlier mentioned modelling studies such as:

1. [Malik et al. \(2018\)](#) by including diabetes complications and tuberculosis complications due to diabetes.
2. [Malik et al. \(2018\)](#); [Moualeu et al. \(2012\)](#); [Pinto and Carvalho \(2019\)](#) by incorporating the non-standard finite difference method to carry out the numerical simulation of the model.

4.2.1 Assumptions

The following assumptions were made when developing the model:

1. Recruitment is by birth only.
2. Individuals in the infectious class are treated and develop latent slow TB to which they can also become infectious.
3. No permanent immunity upon treatment.
4. Individuals with TB complications due to diabetes even when treated are still infectious of TB.

4.2.2 Parameter estimation

The estimated birth rate in Kenya was reported at 27.67 births per year for 1000 births in 2022 according to the World Bank collection of development indicators ([WBD, 2022](#)). Thus, $\Lambda = 100$ per year. The mortality rate in Kenya was estimated to 5.09 deaths per 1000 people. Thus, $\mu = 0.00746$ per year. While the mortality rate due to TB estimated at 3.875 deaths per 1000 people per year according to World Health Organization ([Sudre et al., 1992](#)). $\delta_1 = 0.173$ Diabetes death rate is estimated at 30.43 per 100000 per year people by the World health organization ([Sudre et al., 1992](#)). Table 4.1 shows the description of the parameters used in the model.

Table 4.1: Parameter description and estimation

Description	Symbol	Value/yr	Range	Source
TB transmission coefficient	β	$\frac{233}{100,000}$	$\frac{188 \text{ to } 266}{100,000}$	Enos et al. (2018)
Recruitment rate	Λ	$\frac{8.06}{1000} \times 53 \times 10^6$	—	Assumed
TB induced mortality	δ_1	$\frac{50}{100,000}$	$\frac{9 \text{ to } 97}{100,000}$	Gichuki and Mategula (2021)
Diabetic-TB induced mortality	δ_2	$\frac{426}{100,000}$	$\frac{89 \text{ to } 616}{100,000}$	Kunjok et al. (2020)
Diabetic complication mortality	δ_3	$\frac{10.9}{100,000}$	$\frac{7.2 \text{ to } 82.6}{100,000}$	(PAHO); Purdy et al. (2020)
Diabetes induced mortality	δ_4	$\frac{20.9}{100,000}$	$\frac{7.2-82.6}{100,000}$	Sudre et al. (1992)
Latent fast TB to infectious rate	σ_1	$\frac{558}{100,000}$	$\frac{455 \text{ to } 662}{100,000}$	Enos et al. (2018)
Latent slow TB to infectious rate	σ_2	3.33%	2% – 5%	for Disease Control et al. (2012)
Diabetic to TB infection rate	σ_3	14.8%	7.1% – 23.8%	Stevenson et al. (2007)
Diabetes acquisition rate	α_1	2.2%	1.4% – 3.1%	Mohamed et al. (2018)
Diabetes acquisition with TB exposure	α_2	2.16	1.19 – 3.93	Dobler et al. (2012)
Reinfection rate for treated TB	ρ_1	80.1%	78% – 85%	Park et al. (2020)

Table 4.1 – continued from previous page

Description	Symbol	Value/yr	Range	Source
Reinfection rate for TB-DM	ρ_2	31%	12% – 44%	Mburu et al. (2018)
Treatment rate for diabetic complications	ω_1	38%	25% – 45%	Otieno et al. (2021)
Treatment rate for TB-DM complications	ω_2	0.5%	0.1% – 45%	Buasroung et al. (2022)
Latent fast TB development rate	p	6%	5% – 10%	for Disease Control (CDC)
Natural mortality rate	μ	$\frac{8.06}{1000}$	$\frac{7.9-8.1}{1000}$	ATLAS (2023)
Complicated diabetes acquisition rate	θ_1	3.2%	2.8% – 4.4%	Najafipour et al. (2021)
Complicated diabetes due to TB	θ_2	$\frac{1}{20}$	$\frac{1 \text{ to } 6}{20}$	Owiti et al. (2017)
Latent slow to fast progression rate	π	$\frac{1220}{10^6} \times 0.08$	$\frac{48 \text{ to } 1299}{10^6}$	Esmail et al. (2014)
TB acquisition in diabetics	η	$\frac{112}{1134}$	$\frac{90 \text{ to } 130}{1134}$	Owiti et al. (2017)

4.2.3 Model analysis

In this section, a brief overview of the finite difference scheme as well as the non-finite difference scheme of the TB-Diabetes model is developed and analyzed.

4.2.4 Finite Difference Method

Finite difference methods are well known numerical methods that offer an alternative way of solving differential equations by approximating them with difference

equations (Thomas, 2013). These methods work by discretizing the continuous domain into a finite number of grid points and approximating the derivatives at each grid point using finite differences. The basic idea behind finite difference methods is to replace the continuous derivative in a differential equation with a finite difference approximation that involves only function values at nearby points. The resulting differential equations can then be solved using standard numerical techniques.

Different types of finite difference methods depend on the order of the difference approximation used to approximate the derivatives (Zuazua, 2005). For example, forward, backward, and central differences can approximate the first derivative, and second-order central differences can approximate the second derivative. Finite difference methods are widely used in many areas of science and engineering to solve partial differential equations (PDEs) that describe the behaviour of physical systems (Farlow, 1993). They are relatively simple to implement and can be used to solve problems that are too complex to solve analytically. However, they can be computationally expensive, especially for problems with large domains or high-dimensional spaces.

Finite difference formulas can be used at equally spaced grid points which are used to approximate the differential equations by transforming them into a system of algebraic equations to solve. Therefore in this method finite differences are used to approximate derivatives. In the transformation of a continuous time model to a discrete time model, discrete variable $k \in N$ replaces the continuous variable $t \in (0, \infty)$, while the continuous variable y is replaced by discrete value y_k and the resulting equation is a difference equation.

For instance, we are going to use the Taylor's theorem to introduce the standard finite difference method, we let h be the step size between the terms of the independent variable x and we also increase x by h to get the Taylor series expansion:

$$f(x + h) = f(x) + hf'(x) + \frac{h^2}{2!}f''(x) + \dots\dots$$

The Taylor series expansion solves to:

$$f'(x) = \frac{f(x + h) - f(x)}{h} \quad (4.3)$$

$$f'(x) = \frac{f(x) - f(x - h)}{h} \quad (4.4)$$

$$f'(x) = \frac{f(x + h) - f(x - h)}{2h} \quad (4.5)$$

equation (4.3), (4.4) and (4.5) above are referred to as the forward difference, backward difference and central difference approximation respectively. The central difference approximation is taken as the most accurate of the three because its truncation error is given by $O(h^2)$. When using the finite difference Methods, the discretization error between the numerical solution and the exact solution is determined by the errors that arise when changing from a differential operator to a difference operator.

Forward and Backward Euler method

The Euler method is a basic algorithm for numerically solving first-order differential equations. Leonhard Euler Beethoven of mathematics introduced it in 1768 [Euler \(1768\)](#). Forward and backward Euler methods are two common types of finite difference methods used to numerically approximate solutions to ordinary differential equations (ODEs). The forward Euler method is a first-order method that uses a forward difference approximation to the first derivative of the solution at a given time point ([Biswas et al., 2013](#)). The main difference between these methods is that

the forward Euler method uses the derivative at the current time point to update the solution. In contrast, the backward Euler method uses the derivative at the next time point (Peskin and Schlick, 1989). This makes the backward Euler method more stable, especially for stiff ODEs, but also more computationally expensive because it requires solving a nonlinear equation at each time step. Both methods have advantages and disadvantages, and the choice of method depends on the specific problem being solved and the desired level of accuracy and computational efficiency.

Euler idea changes a differential equation to an algebraic one and is used to solve initial valued problem of the form:

$$y'(t) = f(t, y(t)), y(t_0) = y_0$$

Truncating the Taylor series expansion forms the basis of the Euler method.i.e

$$\begin{aligned} y(t_n + h) = y_{n+1} &= y_n + h \left. \frac{dy}{dt} \right|_{t_n, y_n} + \frac{1}{2} h^2 \left. \frac{d^2 y}{dt^2} \right|_{t_n, y_n} + \frac{1}{3!} h^3 \left. \frac{d^3 y}{dt^3} \right|_{t_n, y_n} + \dots \\ &= y_n + h f(t_n, y_n) + O(h^2). \end{aligned} \quad (4.6)$$

Equation (4.6) is the Euler forward equation which is explicit. A method can be explicit if one finds the y_{n+j} , $j = 0, 1, 2, 3, \dots, k$ by recursively determining y_{n+j} iterate from the previous iterate. otherwise, it is implicit. The Euler backward method is an example of an implicit method. It is obtained by truncating the Taylor series expansion of the form:

$$\begin{aligned} y_n &= y(t_{n+1} - h) = y(t_{n+1}) - h \left. \frac{dy}{dt} \right|_{t_{n+1}} + \frac{1}{2} h^2 \left. \frac{d^2 y}{dt^2} \right|_{t_{n+1}} - \dots \\ y_{n+1} &= y_n + h f(t_{n+1}, y_{n+1}) + O(h^2). \end{aligned}$$

For the finite difference method to be useful, the convergence property is required as the minimum property. A numerical method is said to be convergent if the numerical

solutions obtained approaches the exact solution as the step lengths approaches zero. For convergence property, the Euler forward method requires overly small step sizes. On the other hand, the Euler backward method is computational expensive since it gives an implicit equation for computation of y_{n+1} which is time consuming.

Runge-Kutta method

For the numerical solution of a differential equation, the Runge Kutta method of various orders could be adopted. The Runge Kutta first order are often referred to as the Euler forward method, where the derivatives of y at the given time step are used to do the extrapolations of the solution at the next time step ([Koroche, 2021](#)). On the other hand, the Runge-Kutta methods extrapolates the solution to the future time step using the information on the 'slope' at more than one point. To obtain the Runge-Kutta second order method, we truncate the Taylor series expansion by including one more term. such as

$$y_{n+1} = y_n + hf(t_n, y_n) + \frac{1}{2}h^2 f'(t_n, y_n) + O(h^3)$$

Runge-Kutta simplified the second order method by writing it as:

$$y_{n+1} = y_n + h(a_1 k_1 + a_2 K_2)$$

where, $k_1 = f(t_n, y_n)$ and $k_2 = f(t_n + p_I h, y_n + q_{II} k_1 h)$. The simplified form is easier to use since one is not needed to calculate $f'(t_n, y_n)$. The constants a_1 , a_2 , p and q have to be calculated so as the outcome is a method with local truncation error of $O(h^3)$ Runge-Kutta method of higher order can also be developed in the same way. Commonly used is the Runge Kutta fourth order method. Runge-Kutta fourth order

method is given by (4.7).

$$\left. \begin{aligned} k_1 &= hf(y_n, t_n) \\ k_2 &= hf(y_n + k_1/2, t_n + h/2) \\ k_3 &= hf(y_n + k_2/2, t_n + h/2) \\ k_4 &= hf(y_n + k_3, t_n + h) \\ y_{n+1} &= y_n + (k_1 + 2k_2 + 2k_3 + k_4)/6 \end{aligned} \right\} \quad (4.7)$$

The Runge- Kutta methods are explicit techniques therefore, they are conditionally stable.

Euler method applied to the TB-Diabetes Model

A forward Euler method can be constructed for our equation model (4.1) by replacing the derivative part with the forward difference approximation (4.6) and the non-derivative part approximated at base time level. This yields:

$$\left. \begin{aligned} \frac{S_1^{n+1} - S^n}{l} &= \Lambda - (\alpha_1 + \beta I^n + \mu) S_1^n, \\ \frac{L_f^{n+1} - L_f^n}{l} &= p\beta I^n S^n + \pi L_s^n - (\sigma_1 + \mu) L_f^n, \\ \frac{L_s^{n+1} - L_s^n}{l} &= (1 - p_1)\beta I^n S_1^n + \rho_1 I_T^n - \pi L_s^n - (\alpha_2 + \sigma_2 + \mu) L_s^n, \\ \frac{I_T^{n+1} - I_T^n}{l} &= \sigma_2 L_s^n + \sigma_1 L_f^n - (\rho_1 + \delta_1 + \mu) I_T^n, \\ \frac{D_T^{n+1} - D_T^n}{l} &= \alpha_2 L_s^n + \eta D^n + \rho_2 I_{DT}^n - (\sigma_3 + \mu) D_T^n, \\ \frac{I_{DT}^{n+1} - I_{DT}^n}{l} &= \sigma_3 D_T^n + \omega_2 C_{DT}^n - (\rho_2 + \delta_2 + \mu) I_{DT}^n, \\ \frac{C_{DT}^{n+1} - C_{DT}^n}{l} &= \theta_2 I_{DT}^n - (\omega_2 + \mu + \delta_3) C_{DT}^n, \\ \frac{D^{n+1} - D^n}{l} &= \alpha_1 S^n + \omega_1 C^n - \eta D^n - (\theta_1 + \mu) D^n, \\ \frac{C^{n+1} - C^n}{l} &= \theta_1 D^n - (\delta_4 + \omega_1 + \mu) C^n. \end{aligned} \right\} \quad (4.8)$$

where $l > 0$ is an increment in time and $t \geq 0$ at the points $t_n = nl (n = 0, 1, 2, 3, \dots)$

is discretized in the standard way. Expression in (4.8) can be rewritten as given in (4.9).

$$\left. \begin{aligned} S_1^{n+1} &= S^n + (\Lambda - (\alpha_1 + \beta I^n + \mu)S_1^n)l, \\ L_f^{n+1} &= L_f^n + (p\beta I^n S^n + \pi L_s^n - (\sigma_1 + \mu)L_f^n)l, \\ L_s^{n+1} &= L_s^n + ((1 - p_1)\beta I^n S_1^n + \rho_1 I_T^n - \pi L_s^n - (\alpha_2 + \sigma_2 + \mu)L_s^n)l, \\ I_T^{n+1} &= I_T^n + (\sigma_2 L_s^n + \sigma_1 L_f^n - (\rho_1 + \delta_1 + \mu)I_T^n)l, \\ D_T^{n+1} &= D_T^n + (\alpha_2 L_s^n + \eta D^n + \rho_2 I_{DT}^n - (\sigma_3 + \mu)D_T^n)l, \\ I_{DT}^{n+1} &= I_{DT}^n + (\sigma_3 D_T^n + \omega_2 C_{DT}^n - (\rho_2 + \delta_2 + \mu)I_{DT}^n)l, \\ C_{DT}^{n+1} &= C_{DT}^n + (\theta_2 I_{DT}^n - (\omega_2 + \mu + \delta_3)C_{DT}^n)l, \\ D^{n+1} &= D^n + (\alpha_1 S^n + \omega_1 C^n - \eta D^n - (\theta_1 + \mu)D^n)l, \\ C^{n+1} &= C^n + (\theta_1 D^n - (\delta_4 + \omega_1 + \mu)C^n)l. \end{aligned} \right\} \quad (4.9)$$

4.2.5 Nonstandard Finite Difference Method

This scheme is a set of numerical analysis method developed by [Mickens \(1989\)](#) to offer numerical solutions to differential equations by constructing discrete model. However in 2003, he Constructed and analyzed a NSFDM to solve mathematical models using a set of rules [Mickens \(2003\)](#). These rules are mentioned below:

1. Rule 1: The discrete and the corresponding derivative should be of the same order, if it occurs otherwise then there will be instabilities in the solution.
2. Rule 2: For the discrete derivatives, the denominator functions should be expressed as a function of the step-sizes compared with those conventionally used. Considering the equation $\frac{du}{dt} = f(t, u, \lambda)$, the convection denominator is given by

$$\frac{du}{dt} \rightarrow \frac{u_{k+1} - u_k}{\Delta t}$$

which is replaced by a non-negative function

$$\phi(h) = h + O(h^2), \text{ where } h = \Delta t, \quad t \rightarrow t_k = hk, \quad u(t) \rightarrow u_k,$$

and k is an integer. The exact discrete first derivative is of the form

$$\frac{du}{dt} \rightarrow \frac{u_{k+1} - u_k}{\phi(h)}, \text{ where } \phi(h) = 1 + O(h^2)$$

3. Rule 3: Non-linear terms should be replaced by nonlocal discrete representations. For example u^2 is replaced by $u_{k+1}u_k$.

4. Rule 4: If there is any special condition holding for the solutions of the differential equation, then the same condition should hold for the finite difference scheme. Otherwise, numerical instabilities may arise. A good example is the condition of positivity that must be satisfied in modeling infectious diseases. If the discrete equations allows any negative solutions, then there will be numerical instabilities.

Non-standard finite Difference Scheme for TB-Diabetes Model

We consider a non-standard finite difference scheme for the first order system of differential equations in (4.1) for the TB-diabetes model.

$$\left. \begin{aligned} \frac{S^{n+1} - S^n}{\phi_1(h)} &= \Lambda - (\alpha_1 + \beta I^n + \mu) S^{n+1}, \\ \frac{L_f^{n+1} - L_f^n}{\phi_2(h)} &= p\beta I^n S^{n+1} + \pi L_s^{n+1} - (\sigma_1 + \mu) L_f^{n+1}, \\ \frac{L_s^{n+1} - L_s^n}{\phi_3(h)} &= (1-p)\beta I^n S^{n+1} + \rho_1 I_T^{n+1} - (\alpha_2 + \sigma_2 + \pi + \mu) L_s^{n+1}, \\ \frac{I_T^{n+1} - I_T^n}{\phi_4(h)} &= \sigma_2 L_s^{n+1} + \sigma_1 L_f^{n+1} - (\rho_1 + \delta_1 + \mu) I_T^{n+1}, \\ \frac{D_T^{n+1} - D_T^n}{\phi_5(h)} &= \alpha_2 L_s^{n+1} + \eta D^{n+1} + \rho_2 I_{DT}^{n+1} - (\sigma_3 + \mu) D_T^{n+1}, \\ \frac{I_{DT}^{n+1} - I_{DT}^n}{\phi_6(h)} &= \sigma_3 D_T^{n+1} + \omega_2 C_{DT}^{n+1} - (\rho_2 + \delta_2 + \mu) I_{DT}^{n+1}, \\ \frac{C_{DT}^{n+1} - C_{DT}^n}{\phi_7(h)} &= \theta_2 I_{DT}^{n+1} - (\omega_2 + \mu + \delta_3) C_{DT}^{n+1}, \\ \frac{D^{n+1} - D^n}{\phi_8(h)} &= \alpha_1 S^{n+1} + \omega_1 C^{n+1} - \eta D^{n+1} - (\theta_1 + \mu) D^{n+1}, \\ \frac{C^{n+1} - C^n}{\phi_9(h)} &= \theta_1 D^{n+1} - (\delta_4 + \omega_1 + \mu) C^{n+1}. \end{aligned} \right\}$$

where the denominator function is given by:

$$\phi_j(h, k_j^*) = \frac{1 - e^{-k_j^* h}}{k_j^*}, \text{ and } k_j^* = \max \{|\gamma_i|\}, \quad \gamma_i = \left. \frac{\partial f}{\partial x} \right|_{x=x_i}$$

with $f(\bar{x}) = 0$, $i = 1, 2, 3, 4, \dots$, $j = 1, 2, 3, 4, \dots$. Therefore, we have

$$\left. \begin{aligned} \phi_1(h) &= \frac{1 - e^{-(\alpha_1 + \mu)h}}{\alpha_1 + \mu}, & \phi_2(h) &= \frac{1 - e^{-(\sigma_1 + \mu)h}}{\sigma_1 + \mu}, & \phi_3(h) &= \frac{1 - e^{-(\alpha_2 + \sigma_2 + \pi + \mu)h}}{(\alpha_2 + \sigma_2 + \pi + \mu)}, \\ \phi_4(h) &= \frac{1 - e^{-(\rho_1 + \delta_1 + \mu)h}}{\rho_1 + \delta_1 + \mu}, & \phi_5(h) &= \frac{1 - e^{-(\sigma_3 + \mu)h}}{\sigma_3 + \mu}, & \phi_6(h) &= \frac{1 - e^{-(\rho_2 + \delta_2 + \mu)h}}{\rho_2 + \delta_2 + \mu}, \\ \phi_7(h) &= \frac{1 - e^{-(\omega_2 + \delta_3 + \mu)h}}{(\omega_2 + \delta_3 + \mu)}, & \phi_8(h) &= \frac{1 - e^{-(\theta_1 + \mu)h}}{(\theta_1 + \mu)}, & \phi_9(h) &= \frac{1 - e^{-(\delta_4 + \omega_1 + \mu)h}}{\delta_4 + \omega_1 + \mu}. \end{aligned} \right\}$$

In its explicit form, the system becomes

$$\begin{aligned}
S^{n+1} &= \frac{\Lambda\phi_1(h)+S^n}{1+(\lambda+\mu+\alpha_1)\phi_1(h)}, \\
L_f^{n+1} &= \frac{p\beta I^n S^{n+1}\phi_2(h)+\pi L_s^{n+1}\phi_2(h)+L_f^n}{1+[(\sigma_1+\mu)]\phi_2(h)}, \\
L_s^{n+1} &= \frac{[(1-p)\beta I^n S^{n+1}+\rho_1 I_T^{n+1}]\phi_3(h)}{1+(\sigma_2+\mu+\alpha_2+\pi)\phi_3(h)}, \\
I_T^{n+1} &= \frac{[\sigma_1 L_f^{n+1}+\sigma_2 L_s^{n+1}]\phi_4(h)+I_T^n}{1+(\rho_1+\delta_1+\mu)\phi_4(h)}, \\
D_T^{n+1} &= \frac{[\alpha_2 L_s^{n+1}+\eta D^{n+1}+\rho_2 I_{DT}^{n+1}]\phi_5(h)+D^n}{1+(\mu+\sigma_3)\phi_5(h)}, \\
I_{DT}^{n+1} &= \frac{[\sigma_3 D_T^{n+1}+\omega_2 C_{DT}^{n+1}]\phi_6(h)+I_{DT}^n}{1+(\theta_2+\mu+\rho_2+\delta_2)\phi_6(h)}, \\
C_{DT}^{n+1} &= \frac{[\theta_2 I_{DT}^{n+1}]\phi_7+C_{DT}^n}{1+(\omega_2+\mu+\delta_3)\phi_7(h)}, \\
D^{n+1} &= \frac{[\alpha_1 S^{n+1}+\omega_1 C^{n+1}]\phi_8(h)+D^n}{1+(\eta+\theta_1+\mu)\phi_8(h)}, \\
C^{n+1} &= \frac{\theta_1 D^{n+1}\phi_9(h)+C^n}{1+(\omega_1+\delta_4+\mu)\phi_9(h)}.
\end{aligned} \tag{4.10}$$

The following theorems shows positivity and boundedness of the system.

Theorem 4.2.1. If all the initial value as well as parameter values of the discrete system are positive, then the numerical solution of the system will also be positive for all $n \geq 0$.

Proof. Since the terms in the right-hand side of (4.10) are all positive, it follows that this method preserves the positivity property of our model. $\square$

Theorem 4.2.2. The NSFD scheme defines the discrete dynamical system on the biologically feasible region

$$D =$$

$$\left\{ (S^n, L_s^n, L_f^n, I_{DT}^n, D_T^n, I_T^n, D^n, C^n) \in R_+^8 : 0 \leq S^n + L_s^n + L_f^n + I_{DT}^n + D_T^n + I_T^n + D^n + C^n < \frac{\Lambda}{\mu} \right\}.$$

Proof. The denominator of the terms in the right-hand side of (4.10) are greater than one, and $S^n + L_s^n + L_f^n + I_{DT}^n + D_T^n + I_T^n + D^n + C^n < \frac{\Lambda}{\mu}$ in D , it follows that the numerical solutions given out by positivity-preserving method (4.10) are bounded for all t . $\square$

4.3 Numerical solutions

Numerical solutions are often implemented for approximating mathematical problems using numerical methods, such as finite difference methods (Smith et al., 1985). They are used when an analytical solution is either unavailable or not feasible to compute. The approach involves discretizing the problem into a finite number of points or elements and then approximating the values of the unknowns at these points or elements. The approximations are typically obtained by solving a system of linear or nonlinear equations, which can be constructed using various numerical techniques, such as matrix algebra, interpolation, or optimization. The accuracy of a numerical solution in this paper depends on the size of the discretization, the properties of the problem, and the precision of the numerical algorithms used to solve the problem.

4.3.1 Continuous-time Model

To simulate a first-order ordinary differential equation (ODE), we use parameter values in Table 4.1 to compute and simulate the state variable in (4.1) via MATLAB's built-in *ode45* solver. This is achieved via the fourth-order Runge-Kutta method. The results presented in Figure 4.2 are based on the initial condition of $S = L_F = L_s = I_T = D_T = I_{DT} = C_{DT} = D = C = 0$.

Figure 4.2 indicated that S (healthy individuals) increases rapidly until an equilibrium is reached around 2000. The graphical simulation of $L_f, L_s, I_T, D_T, I_{DT}, C_{DT}, D$ and C increases gradually to around 15000, 1900, 170, 2700, 9261, 3800, 4×10^6 and 330, respectively.

4.3.2 NSFD for TB-Diabetes Model

To simulate NSFD, we use parameter values in Table 4.1 to compute and simulate the state variable in (4.10) via MATLAB's built-in *ode45* solver. This is achieved via the fourth-order Runge-Kutta method. The results presented in Figure 4.3 are based

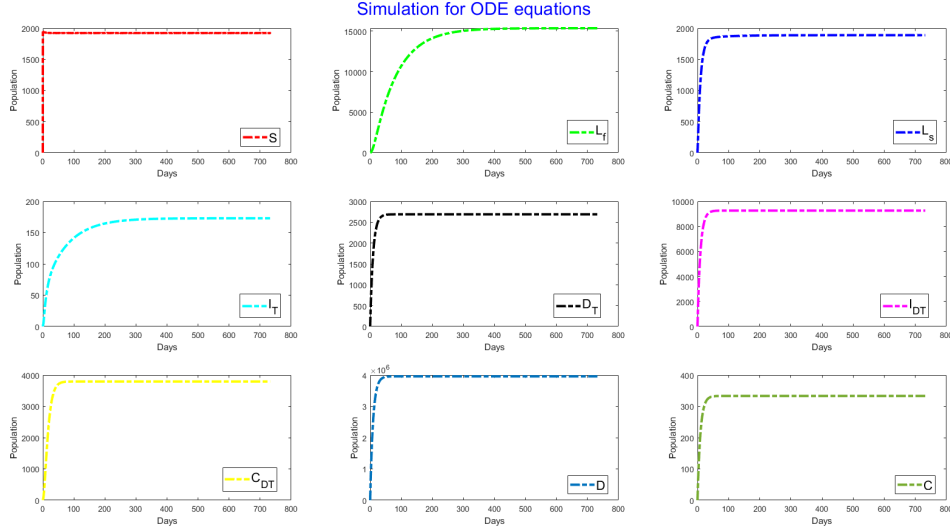


Figure 4.2: The graphical simulation of all compartment in the model diagram in Figure L_s , I_{DT} , D , and C

on the initial conditions being zero, that is $S = L_F = L_s = I_T = D_T = I_{DT} = C_{DT} = D = C = 0$ and $h = [0 : 50]$ and $N = 99$.

Figure 4.3 show that the simulation of the compartments reaches equilibrium points. Therefore, comparing case-by-case simulations for NSFD and order is inevitable to understand why NSFD was applied in this work. A comparison of the simulation results of NSFD and continuous-time model is presented in Figure 4.4.

Figure 4.4 suggests that for S under the continuous-time model and nsfd exhibit almost similar simulation results. However, the NSFD results tend to have a similar growth pattern to the continuous-time model, which is inconsistent in cases such as S . The equilibrium points in NSFD are also attained at higher values when compared to their corresponding continuous-time model, except for those of S , L_f and I_T . In both methods, L_s and D have almost similar equilibrium points. A summary of the ablation comparison of equilibrium points attained in both cases is presented in Table 4.2.

Table 4.2 indicates that in many simulations, the continuous-time model simulation

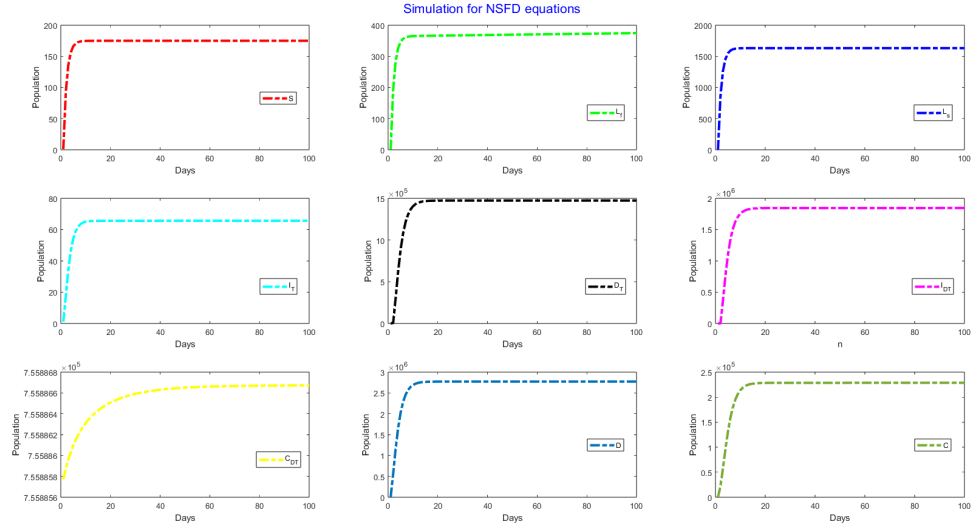


Figure 4.3: Graphical simulation of NSFD for $S, L_s, I_{DT}, I_{DT}, C_{DT}, D$ and C

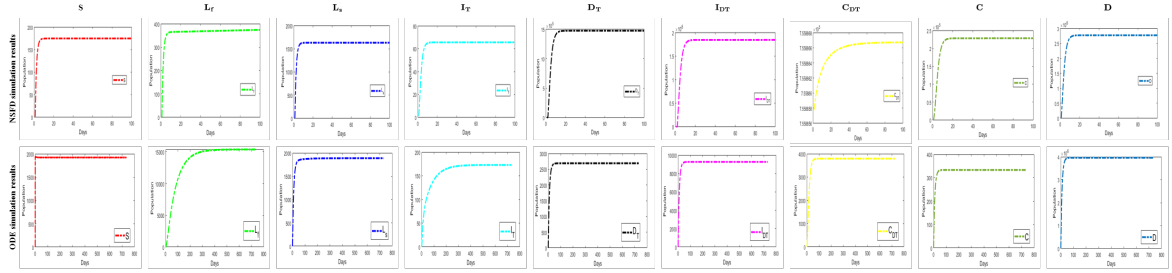


Figure 4.4: Comparison of the graphical simulation of population of compartment for the system in (4.1) and (4.10).

Table 4.2: Comparison of numerical simulation results obtained based on continuous-time model and nsfd

Compartment	Higher Equilibrium	
	continuous-time	nsfd
S	✓	
L_f	✓	
L_s	✓	
I_T	✓	
D_T		✓
I_{DT}		✓
C_{DT}		✓
C	✓	
D		✓

gave a higher approximated equilibrium when compared to nsfd results. The observations suggest that NSFD could be more accurate compared to continuous-time model. The accuracy could be due to overly small step sizes. For instance, an increase h , give results better results compared to lower have of h as illustrated in Figure 4.5.

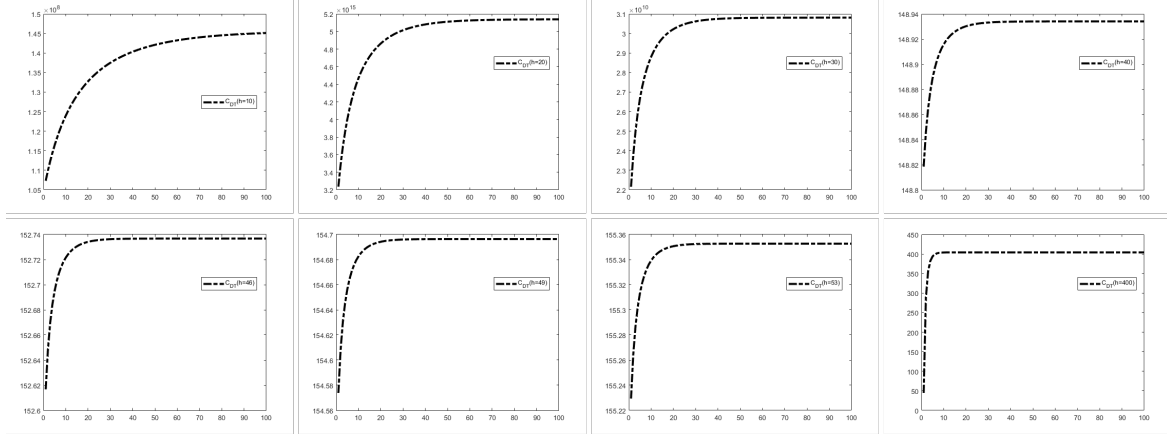
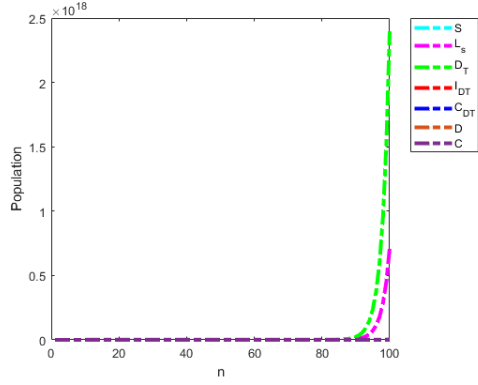


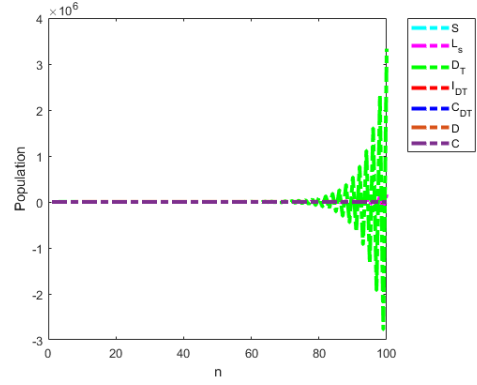
Figure 4.5: Graphical simulation of population of compartment C_{DT} . h (step size) increases from left to right.

Figure 4.5 shows comparison of simulated result for compartment C_{DT} with varied step size h . Lower h indicate unstable results compared to higher h . However, the increase is limited to optimal results posted by other compartments. Figure 4.6 illustrates that optimal value of h is feasible since very higher values yields results that are uninterpreted.

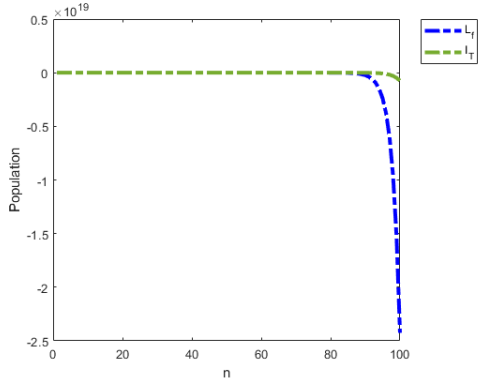
Figure 4.6(a) and Figure 4.6(c) shows that at $h = 20$, the simulation is not presentable; hence no results are attained. At higher $h = 400$ (see Figures 4.6(b) and 4.6(f)), the simulation, like that of L_f , becomes distorted. Thus, determining h that gives optimal values for all the compartments was the first stage during the simulation. Unlike the traditional first-order continuous-time model, NSFD offers an alternative to establishing accurate results by determining optimal h . Thus, scholars could rely on it to provide insightful recommendations for problems such as controlling tuberculosis and diabetes co-infection.



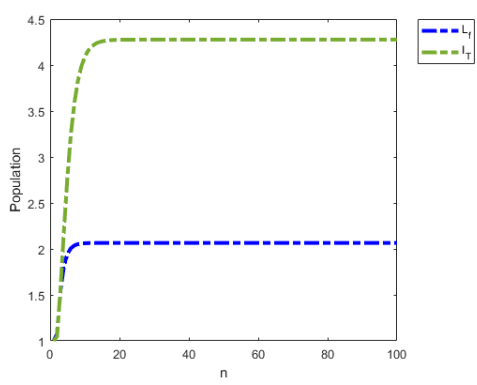
(a) $h = 20$



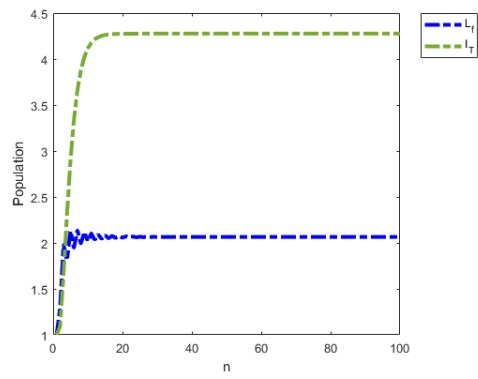
(b) $h = 400$



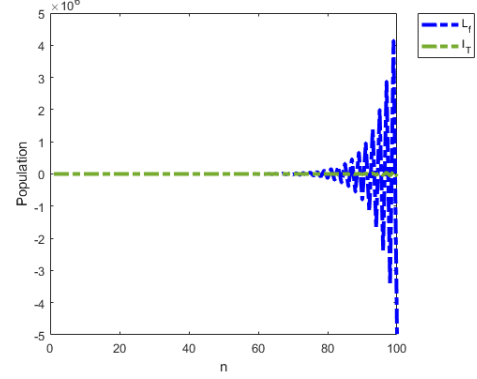
(c) $h = 20$



(d) $h = 50$ optimal



(e) $h = 80$



(f) $h = 400$

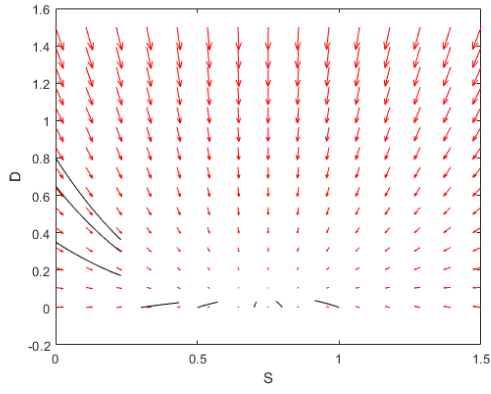
Figure 4.6: Graphical simulation showing the role of h (step size) in determining the accuracy in the simulation. h increases from left to right.

4.3.3 Phase planes

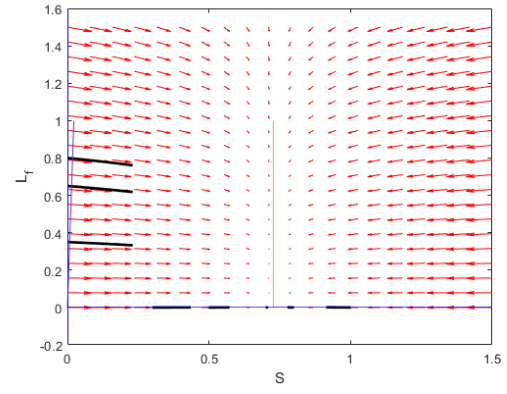
The phase plane is a graphical representation of the behavior of a dynamic system over time (Tchernichovski and Golani, 1995). It is a two-dimensional plot that shows the relationship between the system's state variables and their rates of change. In a phase plane plot, the horizontal axis represents the value of one state variable, while the vertical axis represents the value of another state variable. The state of the system at any given time can be represented as a point in the phase plane. The trajectories in the phase plane represent the behavior of the system over time. The direction and shape of the trajectories can provide important information about the system's stability (Beuter and Garfinkel, 1985). The slope of the trajectory at any given point represents the rate of change of the state variables at that point. Different types of behavior can be observed in the phase plane, such as stable and unstable equilibria. The phase plane is a powerful tool for understanding the behavior of complex dynamic systems, such as the relationship between tuberculosis and diabetes co-infection.

The model presented in Figure 4.1 suggests that there is a possible 11 phase plane plots ($S - D$, $S - L_f$, $S - L_s$, $L_f - L_s$, $L_f - I_T$, $L_s - I_T$, $L_s - D_T$, $D_T - D$, $D_T - I_{DT}$, $D - C$, $I_{DT} - C_{DT}$). Figures 4.7(a) - 4.7(j) present a summary of the phase plane plots.

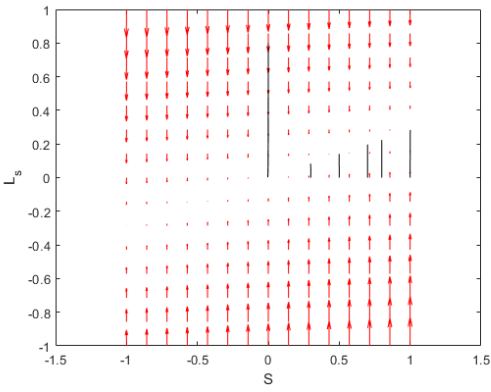
Figure 4.7(a) plots a phase plane of S against D representing the state of the system. The system shows the equilibrium is at $\simeq 0.1$. All the arrows point to equilibrium, suggesting a stable system. The arrows slope towards the positive direction, suggesting S and D are increasing. The arrows converge to a stable equilibrium, suggesting asymptotically stable $S - D$. A similar observation is noted in the phase plane plot between $S - L_f$ in Figure 4.7(b), $S - L_s$ phase plane in Figure 4.7(c), $L_f - I_T$ phase plane in Figure 4.7(e), $L_s - I_T$ phase plane in Figure 4.7(f), $L_s - D_T$ phase plane in Figure



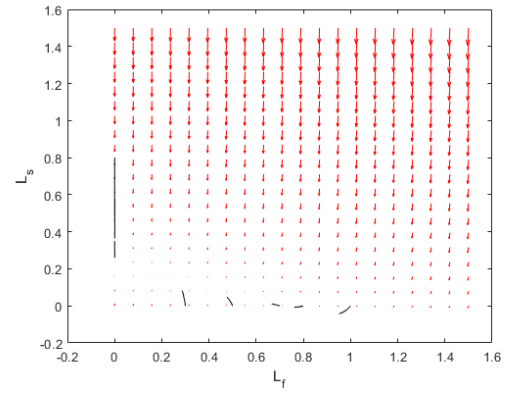
(a) S - D phase plane



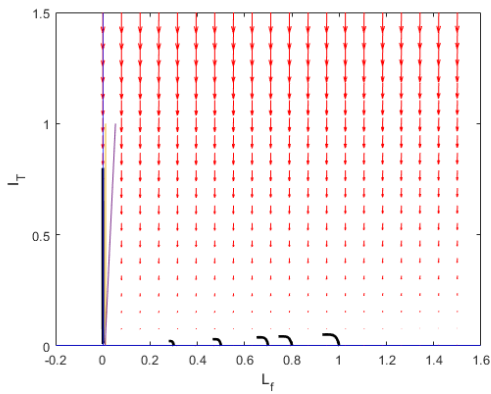
(b) S - L_f phase plane



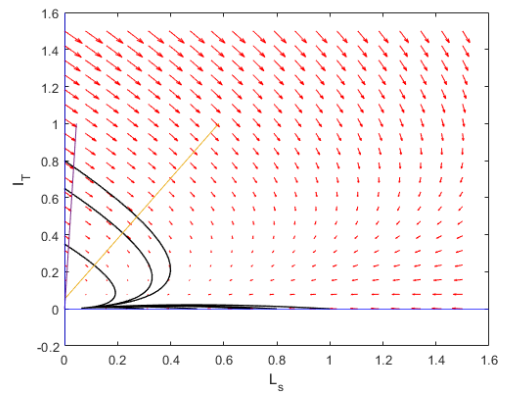
(c) S - L_s phase plane



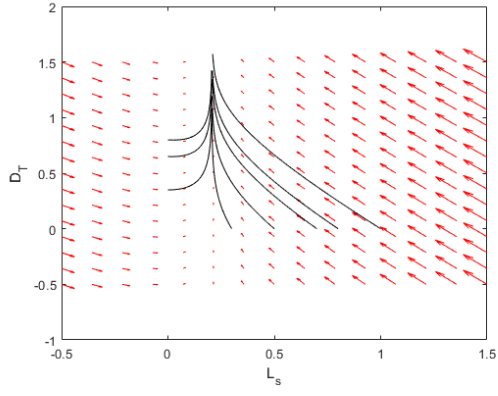
(d) L_f - L_s phase plane



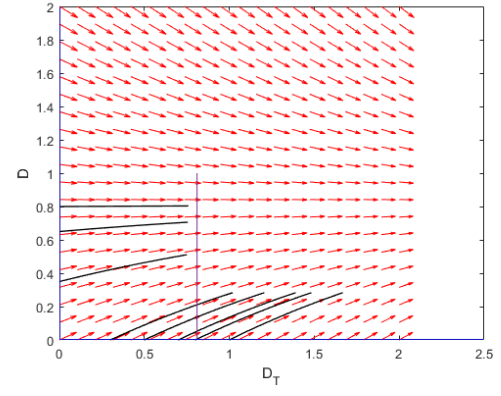
(e) L_f - I_T phase plane



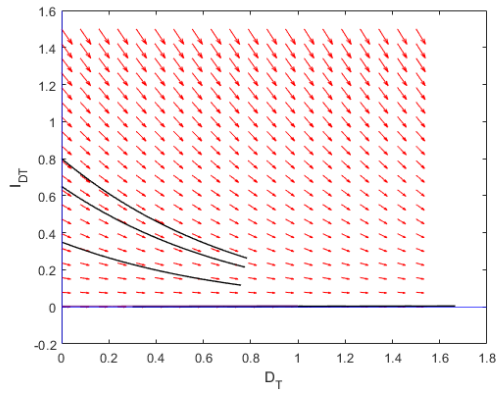
(f) L_s - I_T phase plane



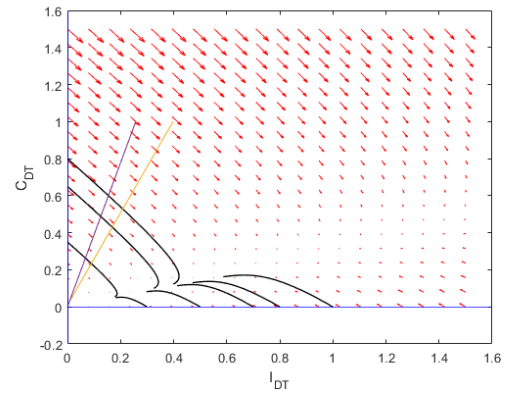
(g) L_S - D_T phase plane



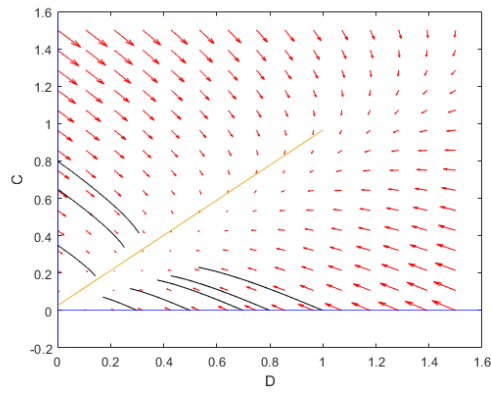
(h) D_T - D phase plane



(i) D_T - I_{DT} phase plane



(j) C_{DT} - I_{DT} phase plane



(k) D - C phase plane

4.7(g), D_T - D phase plane in Figure 4.7(h), D_T - I_{DT} phase plane in Figure 4.7(i), C_{DT} - I_{DT} phase plane in Figure 4.7(j) and D - C phase plane in Figure 4.7(k). However, in D - C phase plane in Figure 4.7(k), the direction of arrows at the equilibrium is points to the negative, hence D and C is decreasing. The phase plane between L_f - L_s in Figure 4.7(d) is invisible, a sign that the system is unpredictable.

4.3.4 Well-posedness of the model

For the TB-Diabetes model in (4.1) to be epidemiologically meaningfully, it must be proven that all solutions with non-negative initial data will remain non-negative for all time.

Theorem 4.3.1. *If initial values $S(0), L_f(0), L_s(0), I_T(0), D_T(0), I_{DT}(0), C_{DT}(0), D(0), C(0)$ are non-negative, then the solution $(S(t), L_f(t), L_s(t), I_T(t), D_T(t), I_{DT}(t), C_{DT}(t), D(t), C(t))$ of system (4.1) is non-negative for all $t \geq 0$.*

Proof. We use the Theorem by Birkhoff and Rota on differential inequality Birkhoff and Rota (1983), we have

$$\lim_{x \rightarrow \infty} \sup N \leq \frac{\Lambda}{\mu} \quad (4.11)$$

Suppose, $N(0) \leq \frac{\Lambda}{\mu}$, then $N(t) \leq \frac{\Lambda}{\mu}$, then the system represented by (4.1) is biologically feasible in the region given by

$$\Omega = \left\{ (S, L_f, L_s, I_T, D_T, I_{DT}, C_{DT}, D, C) \in \mathbb{R}_+^9 : N \leq \frac{\Lambda}{\mu} \right\}$$

Thus, the set Ω is positively invariant, i.e. all the solutions in Ω remain in $\Omega \forall t \geq 0$.

The system (4.1) is supplemented by the initial conditions (4.2) with initial condi-

tions can be expressed as: $\frac{dX}{dt} = f(X)$, $X(0) = X_0$, where

$X = (S, L_f, L_s, I_T, D_T, I_{DT}, C_{DT}, D, C)$ is a vector in $\mathbb{R}^9$, and

$f(X) = \left(f_1(X), f_2(X), f_3(X), f_4(X), f_5(X), f_6(X), f_7(X), f_8(X), f_9(X) \right)^T$ is a vector field in $\mathbb{R}^9$ such that $f_1(X) - f_9(X)$ are defined by

$$\begin{aligned}
f_1(X) &= \frac{dS}{dt} = \Lambda - \beta IS - \alpha_1 S - \mu S, \\
f_2(X) &= \frac{dL_f}{dt} = p\beta IS + \pi L_s - \sigma_1 L_f - \mu L_f, \\
f_3(X) &= \frac{dL_s}{dt} = (1-p)\beta IS + \rho_1 I_T - \pi L_s - \sigma_2 L_s - \alpha_2 L_s - \mu L_s, \\
f_4(X) &= \frac{dI_T}{dt} = \sigma_2 L_s + \sigma_1 L_f - \rho_1 I_T - \delta_1 I_T - \mu I_T, \\
f_5(X) &= \frac{dD_T}{dt} = \alpha_2 L_s + \eta D + \rho_2 I_{DT} - \sigma_3 D_T - \mu D_T, \\
f_6(X) &= \frac{dI_{DT}}{dt} = \sigma_3 D_T + \omega_2 C_{DT} - \rho_2 I_{DT} - \theta_2 I_{DT} - \delta_2 I_{DT} - \mu I_{DT}, \\
f_7(X) &= \frac{dC_{DT}}{dt} = \theta_2 I_{DT} - \omega_2 C_{DT} - \delta_3 C_{DT} - \mu C_{DT}, \\
f_8(X) &= \frac{dD}{dt} = \alpha_1 S + \omega_1 C - \eta D - \theta_1 D - \mu D, \\
f_9(X) &= \frac{dC}{dt} = \theta_1 D - \omega_1 C - \delta_4 C - \mu C,
\end{aligned} \tag{4.12}$$

It is easy, using the standard dynamical system in Theorem 2.1.3 ([Stuart and Humphries, 1998](#), p. 102) to see that f is differentiable, hence, locally Lipschitz, thus there exists a unique local solution of (4.1) based on some open ball containing $X(0)$. Thus, there exist unique solution in some open ball containing $X(0)$. Suppose we have $X(0) = (S_0, L_{f0}, L_{s0}, I_{T0}, D_{T0}, I_{DT0}, C_{DT0}, D_0, C_0) \geq 0$. From (4.1), $S'(t) = \Lambda \geq 0$, whenever $S = 0$, $L'_f = p\beta IS + \pi L_s \geq 0$, whenever $L_f = 0$, $L'_s = (1-p)\beta IS + \rho_1 I_T \geq 0$, whenever $L_s = 0$, $I'_T = \sigma_2 L_s + \sigma_1 L_f \geq 0$, whenever $I_T = 0$, $D'_T = \alpha_2 L_s + \eta D + \rho_2 I_{DT} \geq 0$, whenever $D_T = 0$, $I'_{DT} = \sigma_3 D_T + \omega_2 C_{DT} \geq 0$, whenever $I_{DT} = 0$, $C'_{DT} = \theta_2 I_{DT} \geq 0$, whenever $C_{DT} = 0$, $D' = \alpha_1 S + \omega_1 C \geq 0$, whenever $D = 0$ and $C' = \theta_1 D \geq 0$ whenever $C = 0$.

Using Proposition B.7 of [Smith and Waltman \(1995\)](#), the solution of the system (4.1)

is non-negative. We can now proceed to verify the dissipation condition as follows:

$$\begin{aligned}
F(X).X &= (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9).(S, L_f, L_s, I_T, D_T, I_{DT}, C_{DT}, D, C) \\
&= f_1 S + f_2 L_f + f_3 L_s + f_4 I_T + f_5 D_T + f_6 I_{DT} + f_7 C_{DT} + f_8 D + f_9 C \\
&= D(C\omega_1 - Dm_8 + S\alpha_1) - C_D T(C_D T m_7 - I_D T \theta_2) \\
&\quad - L_s(L_s m_3 - I_T \rho_1 + L_s \pi + S\beta(p-1)(I_D T + I_T)) - C(Cm_9 - D\theta_1) \\
&\quad + D_T(D\eta + L_s \alpha_2 - D_T m_5 + I_D T \rho_2) + I_D T(C_D T \omega_2 - I_D T m_6 + D_T \sigma_3) \\
&\quad + I_T(L_f \sigma_1 - I_T m_4 + L_s \sigma_2) + L_f(L_s \pi - L_f m_2 + S\beta p(I_D T + I_T)) \\
&\quad - S(Sm_1 - \Lambda + S\beta(I_D T + I_T)) \\
&= \left[(m_1 + m_2 + m_3 + m_4 + m_5 + m_6 + m_7 + m_8 + m_9) \right. \\
&\quad \left. (S^2 + L_f^2 + L_s^2 + I_T^2 + D_T^2 + I_{DT}^2 + C_{DT}^2 + D^2 + C^2) \right] \\
&= \left[+ D(C\omega_1 + S\alpha_1) - C_D T(-I_D T \theta_2) \right. \\
&\quad \left. - L_s(-I_T \rho_1 + L_s \pi + S\beta(p-1)(I_D T + I_T)) - C - D\theta_1 \right] \\
&\quad + D_T(D\eta + L_s \alpha_2 + I_D T \rho_2) + I_D T(C_D T \omega_2 + D_T \sigma_3) \\
&\quad + I_T(L_f \sigma_1 + L_s \sigma_2) + L_f(L_s \pi + S\beta p(I_D T + I_T)) \\
&\leq a|X|^2 + q
\end{aligned} \tag{4.13}$$

where, a and q represent constants whose magnitudes are positive, and $m_1 = (\alpha_1 + \mu)m_2 = (\mu + \sigma_1), m_3 = (\sigma_2 + \mu + \alpha_2), m_4 = (\rho_1 + \mu + \delta_1), m_5 = (\mu + \sigma_3), m_6 = (\rho_2 + \theta_2 + \mu + \delta_2), m_7 = (\omega_2 + \mu + \delta_3), m_8 = (\eta + \mu + \theta_1), m_9 = (\omega_1 + \delta_4 + \mu)$. Therefore, $X(t)$ of the system (4.1) is well defined in time. Hence, $S(t) \leq N, L_f(t) \leq N, L_s(t) \leq N, I_T(t) \leq N, D_T(t) \leq N, I_{DT}(t) \leq N, C_{DT}(t) \leq N, D(t) \leq N, C(t) \leq N; \forall t \geq 0$. Thus, X is bounded. $\square$

4.4 Disease Free Equilibrium

4.4.1 The DFE

The disease-free equilibrium (DFE) is the state where there is no infection in the population, that is, $I_T = I_{DT} = 0$. Using the S equation, we obtain,

$$S_0^* = \frac{\Lambda}{m_1}. \quad (4.14)$$

We use (4.14) with L_s to obtain

$$L_{s_0}^* = 0. \quad (4.15)$$

Similarly, we use (4.14) and (4.15) with L_f to obtain

$$L_{f_0}^* = 0. \quad (4.16)$$

We use (4.16) and (4.15) to obtain

$$D_{T_0}^* = \frac{\eta}{m_5}. \quad (4.17)$$

Factorizing the values of $I_{T_0}^* = I_{DT_0}^* = 0$ in C_{DT} we obtain $C_{DT_0}^* = 0$, from where we obtain

$$D_0^* = \frac{\alpha_1 S_0^* + \omega_1 C_0^*}{m_7}. \quad (4.18)$$

We use C to get

$$C_0^* = \frac{\theta_1 D_0^*}{m_9}. \quad (4.19)$$

We use (4.19) in (4.18) and manipulate algebraically to obtain

$$\begin{aligned} D_0^* &= \frac{m_9 \alpha_1 S_0^*}{\Pi_1} \\ C_0^* &= \frac{\theta_1 \alpha_1 S_0^*}{\Pi_1}, \end{aligned} \quad (4.20)$$

where $\Pi_1 = m_9 m_7 - \omega_1 \theta_1$. Therefore, the dfe of the system (4.1) is given by

$$\left(S_0^*, L_{f_0}^*, L_{s_0}^*, I_{T_0}^*, D_{T_0}^*, I_{DT_0}^*, C_{DT_0}^*, D_0^*, C_0^* \right) = \left(S_0^*, 0, 0, 0, \frac{\eta}{m_5}, 0, 0, \frac{m_9 \alpha_1 S_0^*}{\Pi_1}, \frac{\theta_1 \alpha_1 S_0^*}{\Pi_1} \right), \quad (4.21)$$

where S_0^* is given by (4.14).

4.4.2 Control Reproduction Number

We use the method described in [Aligaz and Munganga \(2019\)](#); [Van den Driessche and Watmough \(2002\)](#) to rewrite our main system in the following form:

$$\begin{aligned} \dot{x}_i &= \mathcal{F}(x, y) - \mathcal{V}_{\Gamma_i}(x, y) \\ \dot{y}_j &= g(x, y) \end{aligned} \quad (4.22)$$

with

$$\begin{aligned} x &= (L_s, I_T, D_T, I_{DT}, C_{DT})^\top \\ y &= (S, L_f, D, C)^\top. \end{aligned}$$

Let $F = \nabla \mathcal{F}|_{(S^*, V^*, 0)}$, and $V = \nabla \mathcal{V}|_{(S^*, V^*, 0)}$, be the Jacobian matrices of maps $\mathcal{F}$ and

$\mathcal{V}$ evaluated at the *DfE*.

$$\mathcal{F} = \begin{pmatrix} (1-p)\beta IS \\ \sigma_1 L_f \\ \eta D \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V} = \mathcal{V}^- - \mathcal{V}^+ = \begin{pmatrix} m_3 L_s - \rho_1 I_T \\ m_4 I_T - \sigma_2 L_s \\ m_5 D_T - \alpha_2 L_s \\ m_6 I_{DT} - \omega_2 C_{DT} - \alpha_3 D_T \\ m_7 C_{DT} - \theta_2 I_{DT} \end{pmatrix}. \quad (4.23)$$

Vector $\mathcal{F}$ represents the rate of new infections in compartment i , vector $\mathcal{V}^+$ represents the rate of new infections in compartment i by other means and vector $\mathcal{V}^-$ is the rate of transfer of individuals out of compartment i . Jacobian matrices for $\mathcal{F}$ and $\mathcal{V}$ at dfe are given by matrices F and $\mathcal{V}$ respectively and are defined as follows:

$$F = \frac{\partial \mathcal{F}}{\partial X}$$

and

$$\mathcal{V} = \frac{\partial \mathcal{V}}{\partial X}.$$

F and its corresponding value at dfe,

$$F = \begin{pmatrix} 0 & \frac{\Lambda}{m_1}\beta(1-p) & 0 & \frac{\Lambda}{m_1}\beta(1-p) & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}; V = \begin{pmatrix} m_3 & -\rho_1 & 0 & 0 & 0 \\ -\sigma_2 & m_4 & 0 & 0 & 0 \\ -\alpha_2 & 0 & m_5 & 0 & 0 \\ 0 & 0 & -\sigma_3 & m_6 & -\omega_2 \\ 0 & 0 & 0 & -\theta_2 & m_7 \end{pmatrix}.$$

The next-generation matrix of the system of the model is given by FV^{-1} . The control reproduction number is given by the spectral radius of FV^{-1} , meaning $FV^{-1} = \mathcal{R}_C$ or the largest eigenvalues of FV^{-1} . Thus,

$$\mathcal{R}_C = \left(\frac{\Lambda}{m_1}\right) \left(\frac{\beta(1-p)}{m_5}\right) \left(\frac{\alpha_2 m_4 m_7 \sigma_3 + m_5 m_6 m_7 \sigma_2 - m_5 \omega_2 \sigma_2 \theta_2}{(m_6 m_7 - \omega_2 \theta_2)(m_3 m_4 - \rho_1 \sigma_2)}\right). \quad (4.24)$$

Equation (4.24) indicates that one case of secondary infection of tuberculosis and diabetes co-infections in a susceptible population can cause spread in the entire population.

4.5 Stability Analysis

4.5.1 Local Stability of DFE

Theorem 4.5.1. *The DFE, $X_0 = \left(S_0^*, 0, 0, 0, \frac{\eta}{m_5}, 0, 0, \frac{m_9 \alpha_1 S_0^*}{\Pi_1}, \frac{\theta_1 \alpha_1 S_0^*}{\Pi_1}\right)$ for the system (4.1), X_0 is locally asymptotically stable if $\mathcal{R}_C < 1$ and unstable if $\mathcal{R}_C > 1$ where $\mathcal{R}_C$ is defined by (4.24).*

Proof. See proof of Theorem 4.5.1 in [Van den Driessche and Watmough \(2002\)](#) $\square$

4.5.2 Global Stability of DFE

Theorem 4.5.2. *If $\mathcal{R}_0 \leq 1$, then the DFE of system (4.1) is globally asymptotically stable in*

$\Omega = \{X = (S, L_f, L_s, I_T, D_T, I_{DT}, C_{DT}, D, C) \in \mathbb{R}^9 : S + L_f + L_s + I_T + D_T + I_{DT} + C_{DT} + D + C \leq N \text{ and it is unstable if } \mathcal{R}_C > 1.$

Proof. We use matrix-theoretic method as suggested by [Aligaz and Munganga \(2019\)](#); [Shuai and van den Driessche \(2013\)](#); [Van den Driessche and Watmough \(2002\)](#). Let $x = (L_s, I_T, D_T, I_{DT}, C_{DT})^T$ and $y = (S, L_f, D, C)$. We consider F , V , $\mathcal{F}$ and $\mathcal{V}$ as defined in Section 4.4.2. If the disease compartments for the system are given by,

$$\frac{dx}{dt} = \mathcal{F}(x, y) - \mathcal{V}(x, y)$$

and dynamics of infected compartments is given by

$$\frac{dx}{dt} = (F - V)x - f(x, y).$$

Thus, we can obtain $f(x, y)$ as follows;

$$\begin{aligned} f(x, y) &= (F - \mathcal{V})x - \mathcal{F}(x, y) + \mathcal{V}(x, y) \\ &= \begin{pmatrix} \frac{\beta(Sm_1 - \Lambda)(p-1)(D_T\sigma_3 + I_T m_6 m_7 - I_T \omega_2 \theta_2)}{m_1(m_6 m_7 - \omega_2 \theta_2)} \\ -L_f \sigma_1 \\ -D\eta \\ 0 \\ 0 \end{pmatrix} \end{aligned} \quad (4.25)$$

while

$$V^{-1}F = \begin{pmatrix} 0 & \frac{\Lambda\beta m_4(1-p)}{m_1(m_3m_4-\rho_1\sigma_2)} & 0 & -\frac{\Lambda\beta m_4(p-1)}{m_1(m_3m_4-\rho_1\sigma_2)} & 0 \\ 0 & \frac{\Lambda\beta\sigma_2(1-p)}{m_1(m_3m_4-\rho_1\sigma_2)} & 0 & \frac{\Lambda\beta\sigma_2(1-p)}{m_1(m_3m_4-\rho_1\sigma_2)} & 0 \\ 0 & \frac{\Lambda\alpha_2\beta m_4(1-p)}{\Gamma_1} & 0 & \frac{\Lambda\alpha_2\beta m_4(1-p)}{\Gamma_1} & 0 \\ 0 & \frac{\Lambda\alpha_2\beta m_4 m_7 \sigma_3(1-p)}{\Gamma_1} & 0 & \frac{\Lambda\alpha_2\beta m_4 m_7 \sigma_3(1-p)}{\Gamma_1} & 0 \\ 0 & \frac{\Lambda\alpha_2\beta m_4 \sigma_3 \theta_2(1-p)}{\Gamma_1} & 0 & \frac{\Lambda\alpha_2\beta m_4 \sigma_3 \theta_2(1-p)}{\Gamma_1} & 0 \end{pmatrix}.$$

where

$$\Gamma_1 = m_1(m_3m_4m_5m_6m_7 - m_3m_4m_5\omega_2\theta_2 - m_5m_6m_7\rho_1\sigma_2 + m_5\omega_2\rho_1\sigma_2\theta_2)$$

We see that $F \geq 0$, $V^{-1} \geq 0$, $f(x, y) \geq 0$ in $\Omega \subset \mathbb{R}_+^9$; thus $V^{-1}F$ is reducible. We can therefore construct Lyapunov function based on Theorem 2.1 and 2.2 as stated by [Shuai and van den Driessche \(2013\)](#). We denote the left eigenvectors of $V^{-1}F$ corresponding to the eigenvalue of $\mathcal{R}_C$ by $\{v_1, v_2, v_3v_4, v_5\}$.

Then

$$(v_1, v_2, v_3v_4, v_5) V^{-1}F = \mathcal{R}_C(v_1, v_2, v_3, v_4, v_5)$$

or

$$(v_1, v_2, v_3, v_4, v_5) V^{-1}F = \begin{pmatrix} 0 & \frac{\Lambda\beta(1-p)}{m_1} \left(\frac{\Gamma_4 v_4}{\Gamma_1} + \frac{m_4 v_1}{\Gamma_2} + \frac{\sigma_2 v_2}{\Gamma_2} + \frac{\alpha_2 m_4 v_3}{\Gamma_3} \right) & 0 & \frac{\Lambda\beta(1-p)}{m_1} \left(\frac{\Gamma_4 v_4}{\Gamma_1} + \frac{m_4 v_1}{\Gamma_2} + \frac{\sigma_2 v_2}{\Gamma_2} + \frac{\alpha_2 m_4 v_3}{\Gamma_3} \right) & 0 \end{pmatrix}, \quad (4.26)$$

where $\Gamma_2 = m_3m_4 - \rho_1\sigma_2$, $\Gamma_3 = m_5\Gamma_2$, $\Gamma_4 = \alpha_2m_4m_7\sigma_3$

and

$$\mathcal{R}_C(v_1, v_2, v_3, v_4, v_5) = \overbrace{\left\{ \left(\frac{\Lambda}{m_1} \right) \left(\frac{\beta(1-p)}{m_5} \right) \left(\frac{\alpha_2m_4m_7\sigma_3 + m_5m_6m_7\sigma_2 - m_5\omega_2\sigma_2\theta_2}{\Gamma_6\Gamma_2} \right) \right\}}^{\mathcal{R}_C} (v_1, v_2, v_3, v_4, v_5), \quad (4.27)$$

where $\Gamma_6 = m_6m_7 - \omega_2\theta_2$. We use equations (4.26) and (4.27) to derive a possible solution as $v_1 = 0$, $v_3 = 0$, $v_5 = 0$ and to allow workability, let $v_4 = \psi_t$, where ψ_t is a random parameter and v_2 is given by

$$v_2 = \left(\frac{m_1\mathcal{R}_C}{\Lambda\beta(1-p)} - \frac{\Gamma_4\psi_t}{\Gamma_1} \right) \left(\frac{\Gamma_1}{\sigma_2} \right). \quad (4.28)$$

Suppose we let $\psi_t = 1$, then

$$v_2 = \left(\frac{m_1\mathcal{R}_C}{\Lambda\beta(1-p)} - \frac{\Gamma_4}{\Gamma_1} \right) \left(\frac{\Gamma_1}{\sigma_2} \right). \quad (4.29)$$

Therefore, $\Pi^T = (0, v_2, 0, 1, 0)$. Thus, by Theorem 2.1 of [Shuai and van den Driessche \(2013\)](#), we have $\mathcal{Q} = \Pi^T V^{-1}x$ as the Lyapunov function of the model given by;

$$\begin{aligned} \mathcal{Q} &= \Pi^T V^{-1}x \\ &= I_T \left(\frac{m_3v_2}{\Gamma_2} + \frac{\alpha_2m_7\rho_1\sigma_3}{\Gamma_1} \right) + L_s \left(\frac{\sigma_2v_2}{\Gamma_2} + \frac{\Gamma_4}{\Gamma_1} \right) + \frac{C_D T \omega_2}{\Gamma_6} + \frac{I_D T m_7}{\Gamma_6} + \frac{D_T m_7 \sigma_3}{m_5 m_6 m_7 - m_5 \omega_2 \theta_2} \end{aligned} \quad (4.30)$$

We differentiate $\mathcal{Q}$ at DFE to get

$$\begin{aligned}\mathcal{Q}'|_{DFE} &= (\mathcal{R}_C - 1) \Pi^T x - \Pi^T V^{-1} f(x, y) \\ &= 0.\end{aligned}\tag{4.31}$$

This implies that $x = 0$ and $f(x, y) = 0$ or $y = (S, L_f, D, C)^\top = \left(S_0^*, 0, \frac{m_9 \alpha_1 S_0^*}{\Pi_1}, \frac{\theta_1 \alpha_1 S_0^*}{\Pi_1}\right)^\top$. Therefore, $\left(S_0^*, 0, 0, 0, \frac{\eta}{m_5}, 0, 0, \frac{m_9 \alpha_1 S_0^*}{\Pi_1}, \frac{\theta_1 \alpha_1 S_0^*}{\Pi_1}\right)$ is the only invariant set in Ω where $\mathcal{Q}' = 0$. Thus, by LaSalle's invariance principle [Arsie and Ebenbauer \(2009\)](#), the DFE, and is globally asymptotically stable in Ω and $\mathcal{R}_C \leq 1$. $\square$

We use LaSalle's invariance principle [Bebernes \(1979\)](#) to prove global stability of DFE as follows; if $\mathcal{Q} = 0$,

$$(\mathcal{R}_C - 1) \Pi^T x = I_T (\mathcal{R}_C + 1) + \frac{D_T \sigma_3 (\mathcal{R}_C + 1)}{\Gamma_6},\tag{4.32}$$

Equation (4.32) is only feasible when $\mathcal{R}_C < 1$ or $\mathcal{R}_C > 1$.

Thus, $\left(S_0^*, 0, 0, 0, \frac{\eta}{m_5}, 0, 0, \frac{m_9 \alpha_1 S_0^*}{\Pi_1}, \frac{\theta_1 \alpha_1 S_0^*}{\Pi_1}\right)$ is the only invariant set in Ω which satisfies $\mathcal{Q}' = 0$ when $\mathcal{R}_C < 1$. Therefore, by LaSalle's invariance principle, the DFE is globally asymptotically in Ω when $\mathcal{R}_C < 1$. Therefore, by continuity $\mathcal{Q}'$ remains positive in a small neighbourhood of X_0 .

4.5.3 Endemic Equilibrium

Endemic Equilibrium Points

Using (4.24) and simplifying the constants yields

$$\begin{aligned}
\mathcal{R}_C &= \left(\frac{\Lambda}{m_1} \right) \left(\frac{\beta(1-p)}{m_5} \right) K_B, \\
\rightarrow \Lambda &= \frac{\mathcal{R}_C m_1 m_5}{\beta(1-p)K_R},
\end{aligned} \tag{4.33}$$

where $K_R = \left(\frac{\alpha_2 m_4 m_7 \sigma_3 + m_5 m_6 m_7 \sigma_2 - m_5 \omega_2 \sigma_2 \theta_2}{(m_6 m_7 - \omega_2 \theta_2)(m_3 m_4 - \rho_1 \sigma_2)} \right)$. Using S and simplifying yields,

$$\begin{aligned}
S^* &= \frac{\Lambda}{\beta I^* + m_1}, \\
\text{Substituting } \Lambda \text{ from (4.33),} \\
\rightarrow S^* &= \frac{\mathcal{R}_C m_1 m_5}{(\beta I^* + m_1)(\beta(1-p)K_R)}, \\
&= \frac{\mathcal{R}_C K_B}{\beta I^* + m_1},
\end{aligned} \tag{4.34}$$

where $K_B = \frac{m_1 m_5}{\beta(1-p)K_R}$. Re-writing (4.34) to find explicit value of I^* yields

$$I^* = \frac{\mathcal{R}_C K_B}{S^* \beta} - \frac{m_1}{\beta}. \tag{4.35}$$

Using L_f yields

$$L_f^* = \frac{p\beta I^* S^* + \pi L_s^*}{m_2}. \tag{4.36}$$

Using L_s yields

$$L_s^* = \frac{(1-p)\beta I^* S^* + \rho_1 I_T^*}{m_3}. \tag{4.37}$$

Using I_T yields

$$I_T^* = \frac{\sigma_2 L_s^* + \sigma_1 L_f^*}{m_4}. \tag{4.38}$$

Using D_T yields

$$D_T^* = \frac{\alpha_2 L_s^* + \eta D^* + \rho_2 I_{DT}^*}{m_5}. \quad (4.39)$$

Using I_{DT} yields

$$I_{DT}^* = \frac{\sigma_3 D_T^* + \omega C_{DT}^*}{m_6}. \quad (4.40)$$

Using C_{DT} yields

$$C_{DT}^* = \frac{\theta_2 I_{DT}^*}{m_7}. \quad (4.41)$$

Using D yields

$$D^* = \frac{\alpha_1 S^* + \omega_1 C^*}{m_8}. \quad (4.42)$$

Using C yields

$$C^* = \frac{\theta_1 D^*}{m_9} \quad (4.43)$$

Substituting (4.43) into (4.42) and simplifying yields

$$D^* = \frac{\alpha_1 S^* m_1}{K_M}, \quad (4.44)$$

where $K_M = m_1 m_8 - \omega_1 \theta_1$. Using (4.41) with (4.40) yields

$$I_{DT}^* = \frac{\sigma_3 m_7 D_T^*}{\Gamma_6}. \quad (4.45)$$

Substituting (4.45) and (4.44) into (4.39) yields

$$D_T^* = \frac{L_S^* \Phi_1 + \Phi_2 S^*}{K_D}, \quad (4.46)$$

where $\Phi_1 = \alpha_2 K_M \Gamma_2$, $\Phi_2 = \eta \alpha_1 m_1 \Gamma_6$ and $K_D = m_5 \Gamma_6 - \rho_2 \sigma_3 m_7 K_M$. Substituting (4.38) into (4.37) yields,

$$L_s^* = \frac{\Phi_3 I^* S^* + \rho_1 \sigma_1 L_f^*}{\Gamma_2}, \quad (4.47)$$

where $\Phi_3 = (1 - p)\beta m_4$. Substituting (4.47) into (4.36) yields

$$L_f^* = \frac{I^* S^* \Phi_5}{\Phi_4}, \quad (4.48)$$

where $\Phi_4 = m_2 \Gamma_2 - \rho_1 \sigma_2 \pi$ and $\Phi_5 = \Gamma_2 p \beta + \pi \Phi_3$. Substituting (4.35) into (4.48) yields

$$L_f^* = \frac{\mathcal{R}_C K_B - S^* m_1 \Phi_5}{\beta \Phi_4}. \quad (4.49)$$

Substituting (4.49) and (4.35) into (4.47) yields

$$L_s^* = \frac{\mathcal{R}_C K_B \Phi_6 - S^* m_1 \Phi_7}{\beta \Phi_4 \Gamma_2} \quad (4.50)$$

where $\Phi_6 = \Phi_4\Phi_3 + \rho_1\sigma_1$ and $\Phi_7 = \Phi_3\Phi_4 + \rho_1\sigma_1\Phi_5$. Using (4.50) into (4.46) results to

$$D_T^* = \frac{\mathcal{R}_C\Phi_8 + (\Phi_9 - m_1\Phi_7)S^*}{K_D\beta\Phi_4\Gamma_2}, \quad (4.51)$$

where $\Phi_8 = \Phi_1K_B\Phi_6$ and $\Phi_9 = \beta\Phi_4\Gamma_2\Phi_2$. Substituting (4.51) into (4.45) yields

$$I_{DT}^* = \frac{\mathcal{R}_C\Phi_{11} + \sigma_3m_7\Phi_{12}S^*}{\Phi_{10}}, \quad (4.52)$$

where $\Phi_{10} = \Gamma_6K_D\beta\Phi_4\Gamma_2$, $\Phi_{11} = \sigma_3m_7\Phi_8$ and $\Phi_{12} = \Phi_9 - m_1\Phi_7$. Using (4.52) into (4.41) yields

$$C_{DT}^* = \frac{\Phi_{12}\Phi_{11}\mathcal{R}_C + \Phi_{13}S^*}{m_7\Phi_{10}}, \quad (4.53)$$

where $\Phi_{13} = \sigma_3m_7\Phi_{12}\Phi_2$. Substituting (4.44) into (4.43) yields

$$C^* = \frac{\theta_1\alpha_1m_1S^*}{m_9K_M}. \quad (4.54)$$

Using (4.49) and (4.50) in (4.38) yields

$$I_T^* = \frac{\mathcal{R}_CK_B\Phi_{14} - \Phi_{15}S^*m_1}{\beta\Phi_4\Gamma_2}, \quad (4.55)$$

where $\Phi_{14} = \sigma_2\Phi_6 + \sigma_1\Gamma_2$ and $\Phi_{15} = \sigma_2\Phi_2 + \sigma_2\Phi_5\Gamma_2$. Using (4.54) and (4.52), I^* can be written explicitly as

$$I^* = \frac{\Phi_{21}\mathcal{R}_C + \Phi_{22}S^*}{\Phi_{20}} \quad (4.56)$$

where $\Phi_{16} = \Phi_{10}K_B\Phi_{14}$, $\Phi_{17} = \beta\Phi_4\Gamma_2\Phi_{11}$, $\Phi_{18} = \beta\Phi_4\Gamma_2\sigma_3m_7\Phi_{12}$, $\Phi_{19} = \Phi_{10}\Phi_{15}m_1$, $\Phi_{20} = \beta\Phi_4\Gamma_2\Phi_{10}$, $\Phi_{21} = \Phi_{16} + \Phi_{17}$ and $\Phi_{22} = \Phi_{18} - \Phi_{19}$. Substitute (4.56) into (4.34) and simplifying yields

$$\Phi_{22}S^* + (\beta\Phi_{21}\mathcal{R}_C + m_1\Phi_{20})S^* - \mathcal{R}_CK_B\Phi_{20} = 0. \quad (4.57)$$

The endemic equilibrium point of the system (4.1) is given by (4.58)

$$\begin{aligned} S^* &= \\ L_f^* &= \left(\frac{\mathcal{R}_CK_B - S^*m_1\Phi_5}{\beta\Phi_4} \right) \\ L_s^* &= \left(\frac{\mathcal{R}_CK_B\Phi_6 - S^*m_1\Phi_7}{\beta\Phi_4\Gamma_2} \right) \\ I_T^* &= \left(\frac{\mathcal{R}_CK_B\Phi_{14} - \Phi_{15}S^*m_1}{\beta\Phi_4\Gamma_2} \right) \\ D_T^* &= \left(\frac{\mathcal{R}_C\Phi_8 + (\Phi_9 - m_1\Phi_7)S^*}{K_D\beta\Phi_4\Gamma_2} \right) \\ I_{DT}^* &= \left(\frac{\mathcal{R}_C\Phi_{11} + \sigma_3m_7\Phi_{12}S^*}{\Phi_{10}} \right) \\ C_{DT}^* &= \left(\frac{\Phi_{12}\Phi_{11}\mathcal{R}_C + \Phi_{13}S^*}{m_7\Phi_{10}} \right) \\ D^* &= \left(\frac{\alpha_1S^*m_1}{K_M} \right) \\ C^* &= \left(\frac{\theta_1\alpha_1m_1S^*}{m_9K_M} \right) \end{aligned} \quad (4.58)$$

Global Stability of endemic equilibrium

Lemma 4.5.3. When $\mathcal{R}_C > 1$, there exists a unique endemic equilibrium X^* given by

$S^* = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$, where $a = \Phi_{22}$, $b = (\beta\Phi_{21}\mathcal{R}_C + m_1\Phi_{20})$ and $c = -\mathcal{R}_CK_B\Phi_{20}$. When

$\mathcal{R}_0 \leq 1$, there is no endemic equilibrium.

Proof. From (4.58), S^* can be simplified as

$$0 = aS^{*2} + bS^* + c, \quad (4.59)$$

where

$$a = \Phi_{22} \quad (4.60a)$$

$$b = (\beta\Phi_{21}\mathcal{R}_C + m_1\Phi_{20}) \quad (4.60b)$$

$$c = -\mathcal{R}_C K_B \Phi_{20} \quad (4.60c)$$

Equation (4.59) suggests that there are two endemic equilibria as

$$S_1^* = \frac{-b + \sqrt{b^2 - 4ac}}{2a} \quad S_2^* = \frac{-b - \sqrt{b^2 - 4ac}}{2a}. \quad (4.61)$$

Equation (4.61) indicates that the following cases are feasible;

1. When $\mathcal{R}_C > 1$, then

S_1^* exists iff $(\sqrt{b^2 + 4ac}) > b$.

S_2^* will not exist. Thus a possibility of the existence of only one real root.

2. When $\mathcal{R}_C = 1$, then

S_1^* exists iff $(\sqrt{b^2 + 4ac}) > b$.

S_2^* will not exist. Thus a possibility of the existence of only one real root.

3. When $\mathcal{R}_C < 1$:

S_1^* exist iff $b^2 > 4ac$ and $(\sqrt{b^2 + 4ac}) > b$.

S_2^* will not exist. Thus a possibility of the existence of only one real root

Table 4.3 summarizes the analytical solution of (4.59) based on $\mathcal{R}_C$.

Table 4.3: Analytic solution of (4.59).

$\mathcal{R}_C$	c	$4ac$	b	$b^2 - 4ac$	$-b + \sqrt{b^2 - 4ac}$	$-b - \sqrt{b^2 - 4ac}$	Comment
> 1	< 0	< 0	> 0	> 0	> 0	< 0	1 EE
$= 1$	< 0	< 0	> 0	> 0	> 0	< 0	1 EE
< 1	> 0	> 0	> 0	> 0 iff $b^2 > 4ac$	> 0 iff $b^2 > 4ac$	< 0	No EE

Table 4.3 shows that when $\mathcal{R}_C < 1$, there is no endemic equilibrium, but if $\mathcal{R}_C > 1$, a unique endemic equilibrium is obtained when

$$S^* = S_1^* = \frac{-b + \sqrt{b^2 - 4ac}}{2a}$$

□

Theorem 4.5.4. *If $\mathcal{R}_C > 1$, the unique equilibrium is globally asymptotically stable in Ω .*

Proof. The proof is based on Volterra-Lyapunov stable matrices according to Liao and Wang (2012). The Lyapunov function is defined as follows;

$$\begin{aligned}
L = & \varpi_1(S - S^*)^2 + \varpi_2(L_f - L_f^*)^2 + \varpi_3(L_s - L_s^*)^2 + \varpi_4(I_T - I_T^*)^2 \\
& + \varpi_5(D_T - D_T^*)^2 + \varpi_6(I_{DT} - I_{DT}^*)^2 \\
& + \varpi_7(C_{DT} - C_{DT}^*)^2 + \varpi_8(D - D^*)^2 + \varpi_9(C - C^*)^2
\end{aligned} \tag{4.62}$$

where ϖ_i are positive constants. $\frac{\partial L}{\partial x_i}$ yields

$$\begin{aligned}
L' &= -2\varpi_1 (S - S^*)^2 (\beta + m_1) - 2\varpi_1 (S - S^*) (I_T - I_T^*) (\beta S^*) - 2\varpi_1 (S - S^*) (I_{DT} - I_{DT}^*) (\beta S^*) \\
&\quad - 2\varpi_2 (L_f - L_f^*)^2 (m_2) + 2\varpi_2 (L_f - L_f^*) (S - S^*) (p\beta (I_T^* + I_{DT}^*)) \\
&\quad + 2\varpi_2 (L_f - L_f^*) (L_s - L_s^*) (\pi) \\
&\quad + 2\varpi_2 (L_f - L_f^*) (I_T - I_T^*) (p\beta S^*) + 2\varpi_2 (L_f - L_f^*) (I_{DT} - I_{DT}^*) (p\beta S^*) \\
&\quad + 2\varpi_3 (L_s - L_s^*)^2 (-m_3) + 2\varpi_3 (L_s - L_s^*) (S - S^*) ((1-p)\beta I_T^*) \\
&\quad + 2\varpi_3 (L_s - L_s^*) (I_T - I_T^*) ((1-p)\beta I_{DT}^*) + 2\varpi_3 (L_s - L_s^*) (I_{DT} - I_{DT}^*) ((1-p)\beta I_T^*) \\
&\quad - 2\varpi_4 (I_T - I_T^*)^2 (m_4) + 2\varpi_4 (I_T - I_T^*) (L_f - L_f^*) (\sigma_1) + 2\varpi_4 (I_T - I_T^*) (L_s - L_s^*) (\sigma_2) \\
&\quad - 2\varpi_5 (D_T - D_T^*)^2 (m_5) + 2\varpi_5 (D_T - D_T^*) (L_s - L_s^*) (\alpha_2) + 2\varpi_5 (D_T - D_T^*) (D - D^*) (\eta) \\
&\quad - 2\varpi_6 (I_{DT} - I_{DT}^*)^2 (m_6) + 2\varpi_6 (I_{DT} - I_{DT}^*) (D_T - D_T^*) (\sigma_3) \\
&\quad + 2\varpi_6 (I_{DT} - I_{DT}^*) (C_{DT} - C_{DT}^*) (\omega_2) \\
&\quad - 2\varpi_7 (C_{DT} - C_{DT}^*)^2 (m_7) + 2\varpi_7 (C_{DT} - C_{DT}^*) (I_{DT} - I_{DT}^*) (\theta_2) \\
&\quad - 2\varpi_8 (D - D^*)^2 (m_8) + 2\varpi_8 (D - D^*) (S - S^*) (\alpha_1) + 2\varpi_8 (D - D^*) (C - C^*) (\omega_1) \\
&\quad - 2\varpi_9 (C - C^*)^2 (m_9) + 2\varpi_9 (C - C^*) (D - D^*) (\theta_1) \\
&= Y(MA + A^T M^T)Y^T
\end{aligned} \tag{4.63}$$

where $Y = \begin{pmatrix} S - S^*, L_f - L_f^*, L_s - L_s^*, I_T - I_T^*, \\ D_T - D_T^*, I_{DT} - I_{DT}^*, C_{DT} - C_{DT}^*, D - D^*, C - C^* \end{pmatrix}$,
 $M = \text{diag}(m_1, m_2, m_3, m_4, m_5, m_6, m_7, m_8, m_9)$ and

$$A = \begin{pmatrix} -(\beta I^* + m_1) & 0 & 0 & -\beta S^* & 0 & -\beta S^* & 0 & 0 & 0 \\ p\beta I^* & -m_2 & \pi & p\beta S^* & 0 & p\beta S^* & 0 & 0 & 0 \\ (1-p)\beta I^* & 0 & -m_3 & (1-p)\beta I_{DT}^* & 0 & (1-p)\beta I_T^* & 0 & 0 & 0 \\ 0 & \sigma_1 & \sigma_2 & -m_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha_2 & 0 & -m_5 & 0 & 0 & \eta & 0 \\ 0 & 0 & 0 & 0 & \sigma_3 & -m_6 & \omega_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \theta_2 & -m_7 & 0 & 0 \\ \alpha_1 & 0 & 0 & 0 & 0 & 0 & 0 & -m_8 & \omega_1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \theta_1 & -m_9 \end{pmatrix} \quad (4.64)$$

Evaluating the $\det(A)$ at X_{x_t} gives

$$\begin{aligned} \det(A) &= (m_7\omega_1\theta_1 - m_7m_8m_9) m_1m_2m_3m_4m_5m_6 \\ &+ (m_8m_9\omega_2\theta_2 - \omega_1\omega_2\theta_1\theta_2) m_1m_2m_3m_4m_5 \\ &+ (\Lambda\beta m_7m_8m_9p\sigma_1 - \Lambda\beta m_7\omega_1p\sigma_1\theta_1) m_3m_5m_6 \\ &+ (\Lambda\beta\omega_1\omega_2p\sigma_1\theta_1\theta_2 - \Lambda\beta m_8m_9\omega_2p\sigma_1\theta_2) m_3m_5 \\ &- \frac{1}{m_1} (\Lambda\alpha_1\beta\eta m_7m_9\sigma_3) m_2m_3m_4 \end{aligned} \quad (4.65)$$

$$\frac{dS}{dt} = \Lambda - \beta I^* S - m_1 S^* = 0, \quad (4.66)$$

$$\frac{dL_f}{dt} = p\beta I^* S^* + \pi L_s^* - m_2 L_f^* = 0, \quad (4.67)$$

$$\frac{dL_s}{dt} = (1-p)\beta I^* S^* + \rho_1 I_T^* - m_3 L_s^* = 0, \quad (4.68)$$

$$\frac{dI_T}{dt} = \sigma_2 L_s^* + \sigma_1 L_f^* - m_4 I_T^* = 0, \quad (4.69)$$

$$\frac{dI_{DT}}{dt} = \sigma_3 D_T^* + \omega_2 C_{DT}^* - m_6 I_{DT}^* = 0, \quad (4.70)$$

$$\frac{dC_{DT}}{dt} = \theta_2 I_{DT}^* - m_7 C_{DT}^* = 0 \quad (4.71)$$

In order to prove that $\det(A) > 0$, then all then $S^* > 0, L_f^* > 0, L_s^* > 0, I_T^* > 0, I_{DT}^* > 0, C_{DT}^* > 0, D_T^* > 0$. Suppose $S^* \geq 0$ and $S^* = 0$, then (4.66) reduces to

$$\Lambda = 0. \quad (4.72)$$

Equation (4.72) is not feasible, since $\Lambda \neq 0$, hence, $S^* > 0$. Suppose $L_s^* \geq 0$ and $L_s = 0$, then (4.67) and (4.68) reduces to

$$\begin{aligned} p\beta I^* S^* - m_2 L_f^* &= 0, \\ &\rightarrow L_f^* = \frac{p\beta I^* S^*}{m_2}, \\ (1-p)\beta I^* S^* + \rho_1 I_T^* &= 0, \\ &\rightarrow I_T^* = \frac{(p-1)\beta I^* S^*}{\rho_1}. \end{aligned} \quad (4.73)$$

Equation (4.69) yields

$$\begin{aligned} \sigma_2 L_s^* + \sigma_1 L_f^* - m_4 I_T^* &= 0 \\ &\rightarrow I_T^* = \frac{\sigma_1 p \beta I^* S^*}{m_2 m_4} \end{aligned} \quad (4.74)$$

Equating (4.73) and (4.74) yields

$$\begin{aligned} \frac{(p-1)\beta I^* S^*}{\rho_1} &= \frac{\sigma_1 p \beta I^* S^*}{m_2 m_4} \\ \rightarrow \frac{(p-1)}{\rho_1} &= \frac{\sigma_1 p}{m_2 m_4} \end{aligned} \quad (4.75)$$

Equation (4.75) is not feasible since $\frac{(p-1)}{\rho_1} \neq \frac{\sigma_1 p}{m_2 m_4}$. Hence, $L_s^* > 0, \implies \det(A) > 0$. Therefore, $M(-A) + [M(-A)]^T > 0$ which implies that the matrix A is Volterra-

Lyapunov stable and M is a constant matrix. Thus, when $\mathcal{R}_C > 1$, the endemic equilibrium of the system is globally asymptotically stable in Ω .

□

4.6 Sensitivity analysis of parameters

The parameter values listed in Table 4.1 to perform a sensitivity analysis of parameters in control reproduction number $\mathcal{R}_C$ in (4.24). The results will inform the strength of the disease control.

4.6.1 Elasticity Indices

The elasticity index ζ of parameter ν_i is given by $\frac{\nu_i \partial \mathcal{R}_C}{\mathcal{R}_C \partial \nu_i}$. ζ is a measure of the relative change in $\mathcal{R}_C$ to relative change in ν_i . ν_i with the largest absolute magnitude has a higher influence on $\mathcal{R}_C$ and affects the transmission dynamics of diabetes and TB co-infection. Table 4.4 shows elasticity indices of parameters computed based on the baseline given in Table 4.1 with an assumed $N=1000$. The table shows the indices arranged in descending order based on magnitude.

Table 4.4: Elasticity indices of parameters in $\mathcal{R}_C$

Parameter	Elasticity Index
β	1.0000
α_1	-1.0000
δ_2	-0.5598
σ_2	0.4343
α_2	-0.4306
ρ_1	-0.4050
δ_1	-0.0262
μ	-0.0081
p	-0.0060
ρ_2	-0.0041
θ_2	-6.3014×10^{-4}
σ_3	3.0747×10^{-5}
ω_1	2.5813×10^{-5}
δ_3	-2.4035×10^{-5}

Table 4.4 indicates β (TB transmission coefficient) and α_1 (rate of acquiring diabetes) are the most elastic parameters. The least elastic parameter is δ_3 (Diabetic complication-induced mortality for diabetic individuals). The results align with the expectation that transmission and acquisition of the disease are often the most perceived elastic parameters Janmey and Miller (2011).

4.6.2 Numerical solutions

The analysis of the model is presented using numerical simulations. The numerical simulations of (4.1) are presented in two cases based on the baseline values in Table 4.1: when $\mathcal{R}_C > 1$ (Figure 4.7) and when $\mathcal{R}_C < 1$ (Figure 4.8).

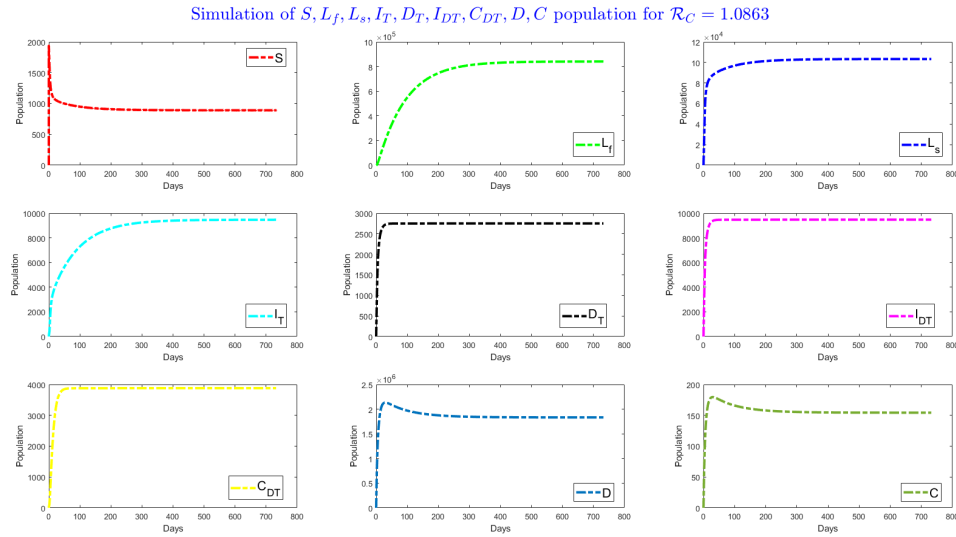


Figure 4.7: Simulation of compartment population based on Table 4.1 with $S_0 = 1000$; $L_{f0} = L_{s0} = I_{T0} = D_{T0} = I_{DT0} = C_{DT0} = D_0 = C_0 = 0$ and $N = 1000$. $\beta = \frac{266}{10^5}$ resulting in approximated equilibrium values of $S^* = 1.704 \times 10^3$, $L_f^* = 1.87795 \times 10^5$, $L_s^* = 2.3127 \times 10^4$, $I_T^* = 2.115 \times 10^3$, $D_T^* = 2.702 \times 10^3$, $I_{DT}^* = 9.307 \times 10^3$, $C_{DT}^* = 3.813 \times 10^3$, $D^* = 3.513660 \times 10^6$, $C^* = 296$ and $\mathcal{R}_C = 1.0863$.

Figure 4.7 considers higher TB transmission coefficient $\beta = \frac{266}{10^5}$ which yields $\mathcal{R}_C = 1.0863$ with trajectories reaching unique equilibrium $S^* = 1.704 \times 10^3$, $L_f^* = 1.87795 \times 10^5$, $L_s^* = 2.3127 \times 10^4$, $I_T^* = 2.115 \times 10^3$, $D_T^* = 2.702 \times 10^3$, $I_{DT}^* = 9.307 \times 10^3$, $C_{DT}^* = 3.813 \times 10^3$, $D^* = 3.513660 \times 10^6$, and $C^* = 296$.

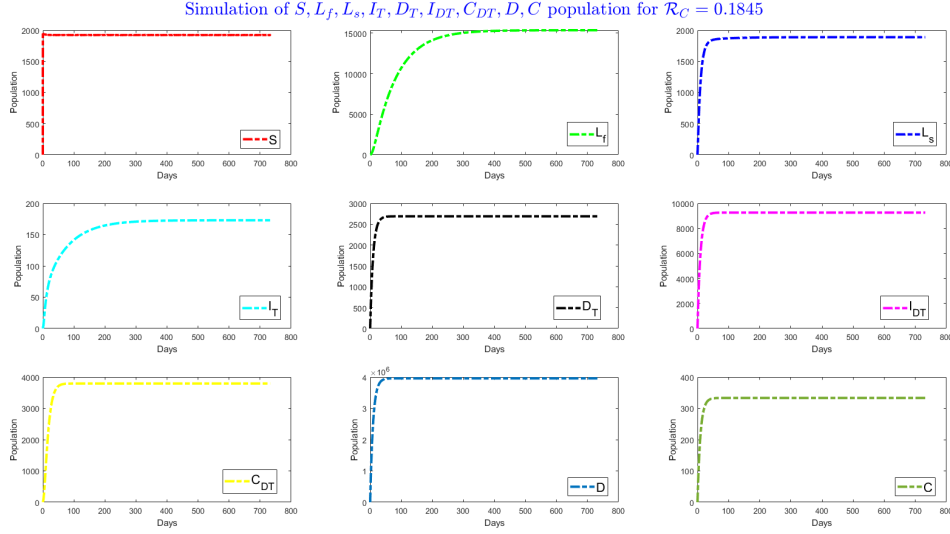


Figure 4.8: Simulation of compartment population based on Table 4.1 with $S_0 = 1000; L_{f0} = L_{s0} = I_{T0} = D_{T0} = I_{DT0} = C_{DT0} = D_0 = C_0 = 0$ and $N = 1000$. $\beta = \frac{266}{10^5}$ resulting in approximated equilibrium values of $S^* = 192$, $L_f^* = 15342 \times 10^4$, $L_s^* = 1.888 \times 10^3$, $I_T^* = 172$, $D_T^* = 2.689 \times 10^3$, $I_{DT}^* = 9.262 \times 10^3$, $C_{DT}^* = 3.794 \times 10^3$, $D^* = 3.95913 \times 10^6$, $C^* = 334$ and $\mathcal{R}_C = 0.1845$.

Figure 4.8 considers higher TB transmission coefficient $\beta = \frac{233}{10^5}$ which yields $\mathcal{R}_C = 0.1845$ with trajectories reaching unique equilibrium $S^* = 192$, $L_f^* = 15342 \times 10^4$, $L_s^* = 1.888 \times 10^3$, $I_T^* = 172$, $D_T^* = 2.689 \times 10^3$, $I_{DT}^* = 9.262 \times 10^3$, $C_{DT}^* = 3.794 \times 10^3$, $D^* = 3.95913 \times 10^6$, and $C^* = 334$. In both cases (Figure 4.7 and Figure 4.8), trajectories approach equilibrium, an indication of the stability of DFE in most cases of the state variables. A plot of different β values shows increasing the β values increases the population of infectious population (See Figure 4.9).

4.7 Optimal Control to Tuberculosis and Diabetes Co-Infection

Research has focused on incorporating optimal control strategies to manage the co-infection of tuberculosis and diabetes. Numerous studies have introduced optimal control models to investigate the influence of diabetes on tuberculosis (TB) infection and its treatment. These investigations have delved into the application of optimal

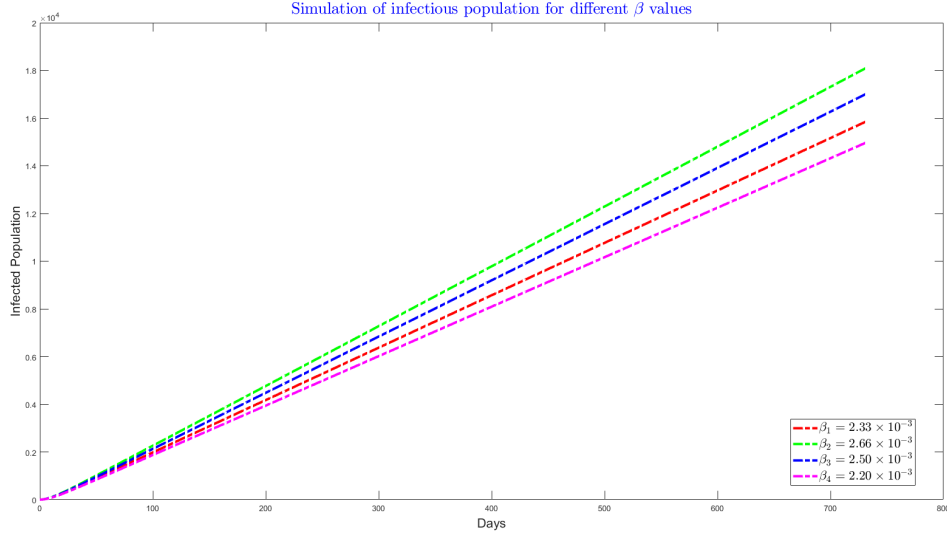


Figure 4.9: Simulation of infectious population for different β values.

control strategies for mitigating multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) [Moya et al. \(2022\)](#); [Sweilam et al. \(2019\)](#). Furthermore, analyses employing optimal control have been suggested for co-infection models, incorporating measures such as TB sensitization, dietary sensitization, and TB vaccination [Diabaté et al. \(2023\)](#). The studies underscore the significance of concurrently addressing TB and diabetes for effective outcomes, emphasizing the necessity for comprehensive strategies in managing co-infection scenarios [Awoke and Kassa \(2018\)](#); [Diabaté et al. \(2023\)](#).

4.7.1 Introduction of controls

Table 4.4 shows the TB transmission coefficient β has the highest elasticity index followed by the rate of acquiring diabetes α_1 . Thus, the control considers these two parameters: distancing (it will reduce TB transmission coefficient) and improvement in diet (since it will reduce the rate of diabetes among individuals).

Distancing measures are crucial in reducing the transmission of TB, an infectious disease that spreads through the air when infected individuals cough, sneeze, or talk [Hossain et al. \(2022\)](#). Social distancing, respiratory hygiene practices, proper

ventilation, isolation of individuals with active TB infections, and public awareness campaigns can help reduce the transmission coefficient of TB. These measures limit close contact, especially in crowded or enclosed spaces, and promote good respiratory hygiene practices.

Diabetes is a chronic condition characterized by elevated blood glucose levels due to insufficient insulin production or ineffective insulin use. Lifestyle factors, including diet, play a crucial role in developing and managing diabetes [Hu \(2011\)](#). A balanced diet focusing on whole grains, fruits, vegetables, lean proteins, and healthy fats helps regulate blood sugar levels. Maintaining a healthy weight and consuming fibre-rich foods can help stabilize blood sugar levels. Avoiding processed sugars and refined carbohydrates can prevent diabetes. Including healthy fats like avocados, nuts, and olive oil can improve insulin sensitivity and cardiovascular health. Regular monitoring and consulting with healthcare professionals can provide personalized guidance on dietary choices and lifestyle modifications.

Distancing

Let $d \in [0, 1]$ (where d is an arbitrary letter used to indicate the control due to distancing) be a time-dependent and Lebesgue measurable control representing an improvement in distancing efforts that reduce TB transmission coefficient. Distancing includes respiratory hygiene practices, proper ventilation, isolation of individuals with active TB infections, and public awareness campaigns. The set of admissible distancing controls is

$$D = d(t) : [0, T] \longrightarrow [0, 1] \text{ and is Lebesgue measurable.}$$

Healthy Diet

Let $h \in [0, 1]$ (where h is an arbitrary letter used to indicate the control due to a healthy diet) be a time-dependent and Lebesgue measurable control representing an improvement in healthy diet efforts that reduces the rate of acquiring diabetes. The set of admissible healthy diet controls is

$$H = h(t) : [0, T] \longrightarrow [0, 1] \text{ and is Lebesgue measurable.}$$

For simplicity, let denote the control $u = (d, h)$ and the set of admissible controls $U = D \times H$.

4.7.2 The extended mathematical model

Distancing reduces the TB transmission coefficient and is given by $d\beta$. Thus, $d\beta IS$ gives the portion practising distancing. The improved diet reduces the rate of acquiring diabetes and is given by $h\alpha_1$. Thus, $h\alpha_1 S$ gives the portion practising an improved diet. Therefore, the extended mathematical model of (4.1) is given as:

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \left([1 - h]\alpha_1 + [1 - d]\beta I + \mu \right) S, \\ \frac{dL_f}{dt} &= pd\beta IS + \pi L_s - m_2 L_f, \\ \frac{dL_s}{dt} &= (1 - p)(d\beta)IS + \rho_1 I_T - \pi L_s - m_3 L_s, \\ \frac{dI_T}{dt} &= \sigma_2 L_s + \sigma_1 L_f - m_4 I_T, \\ \frac{dD_T}{dt} &= \alpha_2 L_s + \eta D + \rho_2 I_{DT} - m_5 D_T, \\ \frac{dI_{DT}}{dt} &= \sigma_3 D_T + \omega_2 C_{DT} - m_6 I_{DT}, \\ \frac{dC_{DT}}{dt} &= \theta_2 I_{DT} - m_7 C_{DT}, \\ \frac{dD}{dt} &= h\alpha_1 S + \omega_1 C - m_8 D, \\ \frac{dC}{dt} &= \theta_1 D - m_9 C, \end{aligned} \tag{4.76}$$

with the initial conditions given in (4.2).

Intervention needs to minimize the number of new cases and the cost of implementing controls. The cost may include improving distancing and diet. Thus, the control $u = (d, h)$ is considered optimal if it minimizes the objective function

$$J = \int_0^T \left(A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] + A_2 d^2 + A_3 h^2 \right) dt \quad (4.77)$$

where A_1 is the unit cost of new infection per individual, $A_2 = A_3$ is the unit cost of implementing the controls per time unit. A_1, A_2 and A_3 balance coefficients that transform the integrand into cost per time unit, and $(1 - h)\alpha_1 S$ represents the cost of new cases. Thus, we state the optimal control problem as follows:

$$\min_{u \in U} J(u) \quad (4.78)$$

subject to (4.76) and (4.2).

4.7.3 Existence of optimal control

Theorem 4.7.1. *There exists an optimal control u^* and the corresponding solution $(S^*, L_f^*, L_s^*, I_T^*, D_T^*, I_{DT}^*, C_{DT}^*, D^*, C^*)$ to the initial value problem given by (4.76) that minimizes the objective function given by (4.77) on U .*

Proof. The initial value problem (4.76) can be written as

$$X' = f(t, X, u),$$

with $X(0) = X_0$.

We use the results of Theorem 4.1 in [Berkovitz \(1976\)](#) to establish the existence of optimal control based on the following conditions:

1. There exist $\mathcal{C}_1$ and $\mathcal{C}_2$ such that

(a) [a] $|f(t, X, u)| \leq \mathcal{C}_1(1 + X)$ and

(b) [b] $|f(t, X_1, u) - f(t, X_2, u)| \leq \mathcal{C}_1|X_1 - X_2|$,
for all $t \geq 0$,

$$X_1, X_2 \in \left\{ \left(S, L_f, L_s, I_T, D_T, I_{DT}, C_{DT}, D, C \in \mathbb{R}_+^9 \right) \left| \begin{array}{l} S + L_f + L_s + I_T + D_T + I_{DT} + C_{DT} + D + C = N, \end{array} \right. \right\}$$

and $u \in U$, where $U = \left\{ u = (d, h) : 0 \leq d, h \leq 1 \right\}$

2. The set of controls and corresponding state variables is non-empty.

3. The control set U is convex and closed, $f(t, X, u) = \varphi_1(t, X) + \varphi_2(t, X)u$ and L is convex on U , where $L = A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] + A_2 d(t)^2 + A_3 h(t)^2$ is the integrand in (4.77).

4. There exist $\mathcal{C}_3 > 0$, $\mathcal{C}_4 > 1$ and $\mathcal{C}_5 \geq 0$ such that

$$L(t, X, u) \geq \mathcal{C}_3|u|^{\mathcal{C}_4} - \mathcal{C}_5. \quad (4.79)$$

Since f is $\mathcal{C}^1$, conditions 1a and 1b are implied by suitable bounds on partial derivatives of f and on $f(t, 0, 0)$. Since f is continuous and bounded on a finite time interval Theorem 9.2.1 of [Lukes \(1982\)](#) guarantees the existence of at least one local solution. The set $U = \{(d, h) : d \in [0, 1] \text{ and } h \in [0, 1]\}$ is closed. By definition, the set $Q = \{d : d \in [0, 1] \text{ is Lebesgue measurable}\}$ is convex if $d_1, d_2 \in Q$ and

$\gamma_1 \in [0, 1] \implies \left[(1 - \gamma_1)d_1 + \gamma_1 d_2 \in D \right]$
 $(1 - \gamma_1)d_1 + \gamma_1 d_2 - 2 \geq 0$ since $\gamma_1, d_1, d_2 \in [0, 1]$, and $(1 - \gamma_1)d_1 + \gamma_1 d_2 \leq (1 - \gamma_1) + \gamma_1$
since $d_1, d_2 \leq 1$.

Therefore, $(1 - \gamma_1)d_1 + \gamma_1 d_2$ lies in D implies that Q is convex. Similarly, D is convex since, according to [Loffe and Tihomirov \(1979\)](#), the Cartesian of convex sets is convex; thus, $U = D \times H$ is a convex set. The function f is linear in each control variable d and h , hence can be written as $f(t, X, u) = \varphi_1(t, X) + \varphi_1(t, X)u$. L is convex on U since it is quadratic in u and the constants A_3 and A_5 are positive. Therefore,

$$\begin{aligned} L &= A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] + A_2 d^2 + A_3 h^2 \\ &\leq A_2 d^2 + A_3 h^2 + A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] \text{ since } d \geq 0, h \geq 0. \end{aligned} \quad (4.80)$$

Taking into consideration that

$$\begin{aligned} A_1 \left[\beta I S \right] &\leq A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] \text{ since } d \leq 1 \text{ and } h \leq 1 \\ &\leq A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] \text{ since } d\beta I S \leq I S. \\ &\leq A_1 \left[N^2 \right] \text{ since } S \leq N \text{ and } I = (I_T + T_{DT}) \leq N. \end{aligned} \quad (4.81)$$

Both sides of inequality are non-negative, thus,

$$A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] \geq -A_1 \left[\alpha_1 S + \beta I S \right]. \quad (4.82)$$

We substitute (4.82) and (4.81) into (4.80) to have

$$\begin{aligned}
L &\leq A_2 q(t)^2 + A_3 h(t)^2 - A_1 \left[\alpha_1 N + \beta N^2 \right] \\
&\geq \mathcal{C}_3 |u|^{\mathcal{C}_4} - \mathcal{C}_5
\end{aligned} \tag{4.83}$$

where $\mathcal{C}_3 = \min A_2, A_3$, $\mathcal{C}_4 = 2$ and $\mathcal{C}_5 = A_1 \left[\alpha_1 N + \beta N^2 \right]$.

□

4.7.4 Characterization of controls

We use Pontryagin's Maximum principle stated in Theorem 5.1 of [Berkovitz \(1976\)](#) to find the best possible control for the system. Lets define the Hamiltonian H as follows;

$$\begin{aligned}
H(X, u, p) &= f(t, X, u) + L(t, X, u) \\
&= p_1 f_1 + p_2 f_2 + p_3 f_3 + p_4 f_4 + p_5 f_5 + p_6 f_6 + p_7 f_7 + p_8 f_8 + p_9 f_9 + L \\
&= p_1 \left[\Lambda - [1 - d]\beta IS - ([1 - h]\alpha_1 + \mu) S \right] \\
&\quad + p_2 \left[p[1 - d]\beta IS + \pi L_s - m_2 L_f \right] \\
&\quad + p_3 \left[(1 - p)[1 - d]\beta IS + \rho_1 I_T - m_3 L_s \right] \\
&\quad + p_4 \left[\sigma_2 L_s + \sigma_1 L_f - m_4 I_T \right] \\
&\quad + p_5 \left[\alpha_2 L_s + \eta D + \rho_2 I_{DT} - m_5 D_T \right] \\
&\quad + p_6 \left[\sigma_3 D_T + \omega_2 C_{DT} - m_6 I_{DT} \right] \\
&\quad + p_7 \left[\theta_2 I_{DT} - m_7 C_{DT} \right] \\
&\quad + p_8 \left[[1 - h]\alpha_1 S + \omega_1 C - m_8 D \right] \\
&\quad + p_9 \left[\theta_1 D - m_9 C \right] \\
&\quad + \left(A_1 \left[\left([1 - h]\alpha_1 + [1 - d]\beta I \right) S \right] + A_2 d^2 + A_3 h^2 \right)
\end{aligned} \tag{4.84}$$

where $p = (p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9)$ and $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9$ are adjoint variables for the state variable $S, L_s, L_s, I_T, D_T, I_{DT}, C_{DT}, D, C$.

Theorem 4.7.2. *Given an optimal solution (X^*, u^*) of the control problem (4.78), there exists $p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9$, a solution set to the adjoint system*

$$\begin{aligned}
\dot{p}_1 &= -\frac{\partial H}{\partial S} = p_1[1-d]\beta I + p_1 m_1 - p_2 p[1-d]\beta I + p_3(1-p)[1-d]\beta I \\
&\quad - p_8[1-h]\alpha_1 - A_1 \left([1-h]\alpha_1 + [1-d]\beta I \right) \\
\dot{p}_2 &= -\frac{\partial H}{\partial L_f} = p_2 m_2 - p_4 \sigma_1 \\
\dot{p}_3 &= -\frac{\partial H}{\partial L_s} = -p_2 \pi + p_3 m_3 - p_4 \alpha_2 - p_5 \alpha_2 \\
\dot{p}_4 &= -\frac{\partial H}{\partial I_T} = p_1[1-d]\beta S - p_2 p[1-d]\beta S - p_3(1-p)[1-d]\beta S \\
&\quad - p_3 \rho_1 + p_4 m_4 - A_1[1-d]\beta S \\
\dot{p}_5 &= -\frac{\partial H}{\partial D_T} = p_5 m_5 - p_6 \sigma_3 \\
\dot{p}_6 &= -\frac{\partial H}{\partial I_{DT}} = p_1[1-d]\beta S - p_2 p[1-d]\beta S - p_3(1-p)[1-d]\beta S \\
&\quad - p_5 \rho_2 + p_6 m_6 - A_1[1-d]\beta S \\
\dot{p}_7 &= -\frac{\partial H}{\partial C_{DT}} = -p_6 \omega_2 + p_7 m_7 \\
\dot{p}_8 &= -\frac{\partial H}{\partial D} = -p_5 \eta + p_8 m_8 - p_9 \theta_1 \\
\dot{p}_9 &= -\frac{\partial H}{\partial C} = -p_8 \omega_1 + p_9 m_9
\end{aligned} \tag{4.85}$$

with transversality condition

$$\begin{aligned}
p_1(T) = 0, \quad p_2(T) = 0, \quad p_2(T) = 0, \quad p_4(T) = 0, \quad p_5(T) = 0, \quad p_6(T) = 0, \\
p_7(T) = 0, \quad p_8(T) = 0, \quad p_9(T) = 0,
\end{aligned}$$

such that $u^* = \min_{u \in U} H(X, p, u)$, $t \in [0, T]$. Furthermore, controls can be character-

ized as

$$d^* = \min \left(1, \max \left(0, \frac{1}{2A_2} \left[\beta IS \left(p_1 + p_2 p + p_3(1-p) + A_1 \right) \right] \right) \right) \text{ and}$$

$$h^* = \min \left(1, \max \left(0, \frac{1}{2A_3} \left[\alpha_1 S \left(p_8 - p_1 + A_1 \right) \right] \right) \right).$$

Proof. The optimal control is derived from the optimality condition $\left. \frac{\partial H}{\partial u} \right|_{u^*} = 0$.

$$\begin{aligned} \left. \frac{\partial H}{\partial d} \right|_{d^*} &= -\beta IS(p_1 + p_2 p + p_3(1-p) + A_1) + 2A_2 d^* \\ \implies d^* &= \frac{1}{2A_2} \left[\beta IS(p_1 + p_2 p + p_3(1-p) + A_1) \right] \end{aligned} \quad (4.86)$$

and

$$\begin{aligned} \left. \frac{\partial H}{\partial h} \right|_{h^*} &= p_1 \alpha_1 S - p_8 \alpha_1 S - A_1 \alpha_1 S + 2A_3 h^* \\ \implies h^* &= \frac{1}{2A_3} \left[\alpha_1 S(p_8 - p_1 + A_1) \right]. \end{aligned} \quad (4.87)$$

We consider the properties of the control space as

$$d^* = \begin{cases} 0, & \text{if } \frac{1}{2A_2} \left[\beta IS(p_1 + p_2 p + p_3(1-p) + A_1) \right] \geq 0, \\ \frac{1}{2A_2} \left[\beta IS(p_1 + p_2 p + p_3(1-p) + A_1) \right] & \text{if } 0 < \frac{1}{2A_2} \left[\beta IS(p_1 + p_2 p + p_3(1-p) + A_1) \right] < 1, \\ 1 & \text{if } \frac{1}{2A_2} \left[\beta IS(p_1 + p_2 p + p_3(1-p) + A_1) \right] \geq 1. \end{cases} \quad (4.88)$$

Thus, d^* can be characterized as

$$d^* = \min \left(1, \max \left(0, \frac{1}{2A_2} \left[\beta IS(p_1 + p_2 p + p_3(1-p) + A_1) \right] \right) \right).$$

Similarly, h^* can be characterized as

$$h^* = \min \left(1, \max \left(0, \frac{1}{2A_3} \left[\alpha_1 S (p_8 - p_1 + A_1) \right] \right) \right).$$

We also noted from (4.86) and (4.87) respectively that

$\left. \frac{\partial^2 H}{\partial d^2} \right|_{d^*} = 2A_2 > 0$ and $\left. \frac{\partial^2 H}{\partial h^2} \right|_{h^*} = 2A_3 > 0$. Since A_2 and A_3 are positive constants introduced in (4.77), this indicates that $u^* = (d^*, h^*)$ minimizes the Hamiltonian function $H(X, p, u)$. $\square$

4.7.5 Numerical simulation for optimal control

The optimal problem (4.78) was solved numerically based on parameter values in Table 4.1. We compared numerical solutions with optimal control and without any intervention. The compartments are plotted side by side in the presence and absence of control measures $d \in [0, 1]$ and $h \in [0, 1]$ with $S_0 = L_{f0} = L_{s0} = I_{T0} = D_{T0} = I_{DT0} = C_{DT0} = D_0 = C_0 = 0$

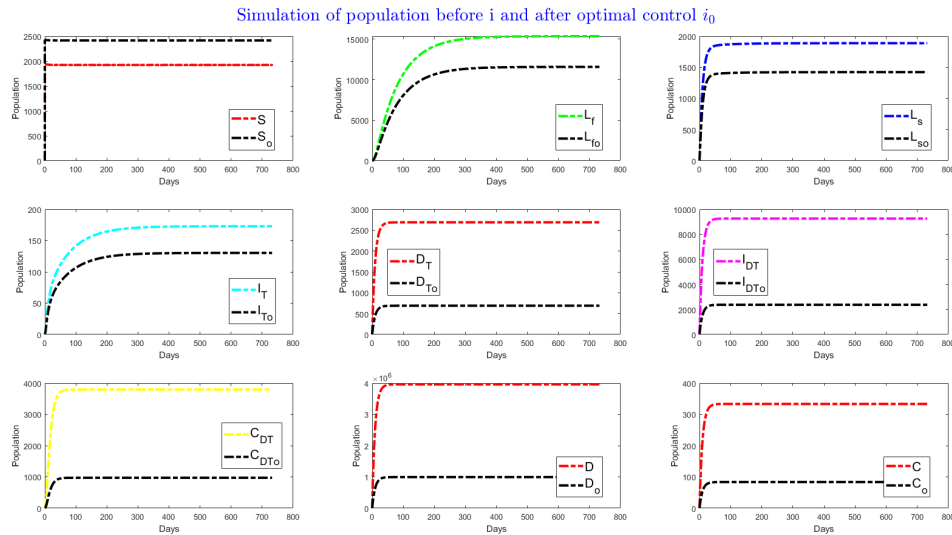


Figure 4.10: Simulation of the population of individuals in each compartment in the absence and presence of optimal control $S(t), S_o(t); L_f(t), L_{fo}(t); I_T(t), I_{To}(t); D_T(t), D_{To}; I_{DT}(t), I_{DT_o}; C_{DT}(t), C_{DT_o}; D(t), D_o(t)$ and $C(t), C_o(t)$ based on parameter values in Table 4.1.

A comparison of trajectories in the presence and absence of optimal control reveals that, as depicted in Figure 4.10, susceptible individuals increase in the presence of optimal control. This is because the improvement in the distancing and healthy diet reduced the population who could be in the components of diabetic-tuberculosis co-infection. The population of all other compartments reduces in the presence of optimal control. A plot of cost function is presented in Figure 4.11.

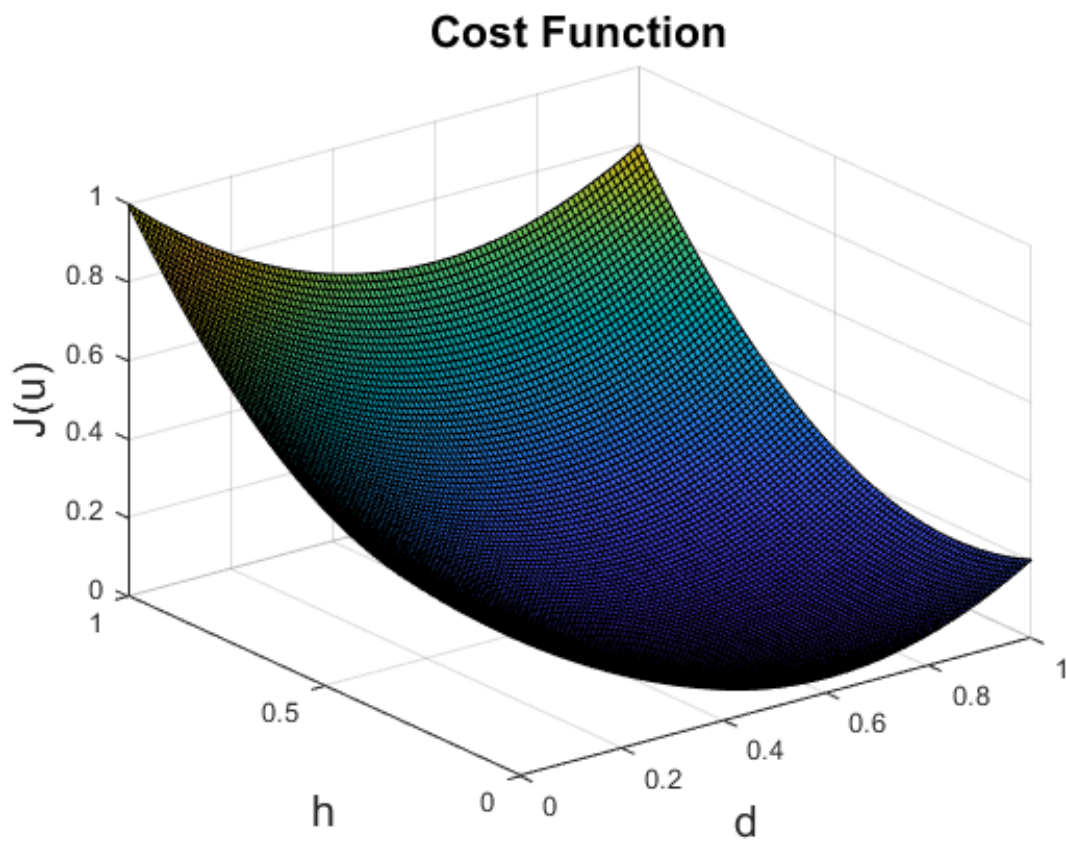


Figure 4.11: Simulation of the cost function for values of $[d, h] \in [0, 1] \forall t = 732$ days.

Figure 4.11 suggests that the minimum cost function is attained when $h \simeq .2$ and $d \simeq .6$. This indicate that optimal results are attained when the $h = .2$ and $d = .6$. These approximated values are used to generate the simulation results in Figure 4.10 and the estimated equilibrium results presented in Table 4.5.

Table 4.5: Comparison of compartment equilibrium values in the presence and absence of optimal control

Compartment	Without optimal (i)	With optimal (i_o)
S^*	1920	2424
L_f^*	15341	2896
L_s^*	1888	358
I_T^*	172	32
D_T^*	2689	677
I_{DT}^*	9263	2330
C_{DT}^*	3795	955
D^*	3.9591×10^6	9.9841×10^5
C^*	334	85

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

Existing studies have formulated numerous mathematical models for TB-diabetes co-infection. However, discrete TB-diabetes models still hold significant research value. In this study, a non-standard finite difference (NSFD) scheme for TB-diabetes co-infection is developed. Numerical simulations are presented and compared with the corresponding first-order ordinary differential equations (ODEs). The results indicate that the first-order ODE yields a higher approximated equilibrium than the NSFD results. These observations suggest that the NSFD scheme may offer greater accuracy than the first-order ODE, likely due to the use of very small step sizes that help achieve stable equilibrium points.

For instance, increasing the step size h improves the results in the NSFD scheme (see Figure 4.5). Although larger step sizes reduce computational time and memory usage, they may fail to produce meaningful insights for disease control recommendations. Therefore, the NSFD method offers a robust alternative for obtaining accurate results by enabling the identification of an optimal step size h . This makes the method useful for generating reliable recommendations in contexts such as control-

ling tuberculosis and diabetes co-infection.

The phase plane analysis (see Figures 4.7(a)–4.7(k)) presents the stability conditions across different compartments. The stability is assessed by observing the convergence or divergence of trajectories around the equilibrium points. The results show that, except for the L_f – L_s compartment—which exhibits oscillatory behavior—and the D – C compartment—where trajectories indicate a decreasing equilibrium—all other compartments are asymptotically stable with increasing equilibrium values.

Future studies should consider reformulating the proposed model with varied control parameters, such as the inclusion of medication, and compare the outcomes with those derived from first-order ODE approaches.

In this research, previous models, such as the one presented by Malik et al. (2018), have been extended to incorporate the co-infection dynamics of diabetes and tuberculosis. This extension enhances our understanding of the complex interactions and complications associated with both diseases. A stability analysis of the model using the control reproduction number $\mathcal{R}_C$ revealed that $\mathcal{R}_C \leq 1$ implies the potential for epidemic eradication, while $\mathcal{R}_C \geq 1$ suggests the disease may persist in the population.

Sensitivity analysis of the parameters in $\mathcal{R}_C$ identified the TB transmission coefficient β and the diabetes acquisition rate α_1 as key contributors. Consequently, optimal control measures should prioritize reducing these two parameters. For example, decreasing β reduced $\mathcal{R}_C$ from 1.0863 to 0.1845, supporting the efficacy of control strategies that target these transmission pathways.

An expanded model was also developed to incorporate potential optimal control strategies, such as promoting increased social distancing and improved dietary habits. Graphical simulations demonstrated a reduction in the number of infected individu-

als when such controls were applied to lower the TB transmission coefficient and the diabetes acquisition rate. These findings confirm the effectiveness of the proposed optimal control measures.

5.2 Recommendations

Tuberculosis and diabetes co-infection presents a complex public health challenge that requires effective and integrated management strategies. Understanding the dynamics and interactions between these two diseases is crucial for developing optimal control measures. The co-infection is bidirectional, with each disease influencing the severity and progression of the other. The immune dysregulation caused by diabetes compromises the host's ability to control TB infection, leading to higher TB- and DM-related complications. Conversely, TB infection can exacerbate glucose dysregulation in patients with diabetes, thereby worsening metabolic outcomes.

Comprehending these intricate relationships allows for the formulation of targeted interventions—ranging from pharmacological strategies and lifestyle modifications to integrated treatment protocols—that can more effectively manage TB-diabetes co-infection. These strategies not only mitigate disease progression and improve patient outcomes but also inform future research and clinical practice. By implementing optimal control strategies, healthcare professionals can better address the complexity of TB-DM co-infection.

The research suggests the following recommendations:

1. **Exploration of Discrete TB-Diabetes Models:** While many mathematical models for TB-diabetes co-infection exist, discrete models still hold research value. Future studies should explore and develop various types of discrete models to assess their accuracy and performance compared to continuous models.
2. **Comparison with First-Order ODEs:** The study suggests that the numerical

solution obtained through the Non-Standard Finite Difference (NSFD) scheme could be more accurate than that from first-order ordinary differential equations (ODEs). Future studies should systematically compare results from NSFD and first-order ODEs under varying parameters and step sizes to evaluate their respective strengths and limitations.

3. **Optimal Step Size Determination:** The importance of selecting an optimal step size (h) in NSFD for achieving accurate results is highlighted. Future research should aim to develop methodologies or algorithms for the automated determination of the optimal step size, balancing computational cost, memory usage, and result reliability for disease control decisions.
4. **Extension of the Proposed Model:** The proposed model can be further extended by incorporating a variety of control parameters, including medication. Future studies should investigate the effects of these controls on TB-DM dynamics and compare outcomes with those obtained from classical ODE-based models.
5. **Incorporation of Medication as a Control Parameter:** The formulation of the proposed model should consider medication as a key control parameter. Future research could examine the influence of pharmacological intervention on disease progression and compare the results with existing models to evaluate the efficacy of medication as a control strategy.
6. **Sensitivity Analysis of Control Parameters:** Conducting sensitivity analysis on control parameters—such as medication, distancing, and lifestyle adjustments—can provide critical insights into their impact on TB-diabetes dynamics. This will help identify the most influential parameters for developing effective intervention strategies.

7. **Optimal Control Approaches:** The study underscores the potential of optimal control approaches—such as enhanced physical distancing and improved dietary habits—in reducing infection levels. Future research should further explore, refine, and validate these strategies with an emphasis on their real-world feasibility and implementation challenges.
8. **Real-World Validation and Clinical Implications:** Future studies should focus on validating mathematical models using real-world epidemiological and clinical data to enhance reliability and relevance. Moreover, exploring the clinical implications of model predictions—especially regarding public health recommendations—can support practical solutions for managing TB-diabetes co-infection.

Future studies should focus on validating mathematical models with real-world data to enhance their reliability and applicability. Additionally, exploring the clinical implications of the model findings, especially regarding disease control recommendations and public health strategies, can contribute to practical solutions for managing TB-diabetes co-infection.

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Appendices

Appendix A

Publications

Appendix B

B

B.1 Stability of basic reproductive number

Consider $s(A)$ as the maximum real part of the eigenvalues of A (referred to as the spectral abscissa), and let $\rho(A)$ denote the maximum modulus of the eigenvalues of A (referred to as the spectral radius). Using M-matrix theory, let $B = [b_{ij}]$ have the Z sign pattern, where $b_{ij} \leq 0$ for all $i \neq j$. If $B = sI - P$, where I is the identity matrix, P is non-negative ($P \geq 0$ entrywise), and $s > \rho(P)$, then B qualifies as a non-singular M-matrix. In the case where $s = \rho(P)$, B becomes a singular M-matrix. Several equivalent definitions of M-matrices exist, one of which asserts that if a matrix B has the Z sign pattern and $s(B) > 0$, then B is a non-singular M-matrix ([33](#), p. 135).

Lemma B.1.1. *Let H be a non-singular M-matrix, and assume that B and BH^{-1} exhibit the Z sign pattern. Then, B is a non-singular M-matrix if and only if BH^{-1} is a non-singular M-matrix.*

The forward implication is presented in a slightly different form as Exercise 6 b of Horn and Johnson ([97](#), p. 127), and the reverse implication is outlined in Berman

and Plemmons (33, p. 159).

In general, Lemma B.1.1 does not hold when B is a singular M-matrix. It can be demonstrated to hold when B is singular and irreducible; however, this condition is insufficient for our purposes. Specifically, our proof of Theorem 4 relies on the subsequent lemma.

Lemma B.1.2. *Let H be a non-singular M-matrix, and suppose $K \geq 0$. Then, (i) $(H - K)$ is a non-singular M-matrix if and only if $(H - K)H^{-1}$ is a non-singular M-matrix. (ii) $(H - K)$ is a singular M-matrix if and only if $(H - K)H^{-1}$ is a singular M-matrix.*

Proof. Let $B = H - K$. Then both B and $BH^{-1} = I - KH^{-1}$ exhibit the Z sign pattern. (Recall that $H^{-1} \geq 0$ since H is a non-singular M-matrix.) Consequently, Lemma B.1.1 implies statement (i). A separate continuity argument can be constructed for each implication in the singular case. $\square$

B.2 Snippet of the Codes

```
function dydt = NSDSeunice(t,y)
dydt = zeros(size(y));
% parameter values; Lambda=0.0277;lambda=0.03
%%
%revised
% lambda=0.03;beta=259/1000;Lambda=100;delta_1=39/100000;
% delta_2=319/100000;delta_3=7/100;delta_4=2.15/100;sigma_1
    =0.03;
% sigma_2=0.03;sigma_3=0.0026;alpha_1=460/10000;alpha_2
    =37.2/100;
```

```

% rho_1=66.8/100;rho_2=9.88/100;omega_1=4.25/100;omega_2
    =28/100;
% p=3.875/1000;p_1=7.5/100;p_s=3.875/1000;mu=7.46/1000;
% theta_1=3.3/100;theta_2=9.2/100;rho_3=0.7372;
%%
%**** use death rate per day, then convert to per year,
    1371*366
%https://countrymeters.info
% n=366;
% beta=(233/10^7)/n;%consider 0.0003 if the graphs fails to
    rise and flatten gradually
% %beta=259/100000;
% Lambda=((8.06/10^3)*53*10^6)/n;
% delta_1=(50/10^5)/n;delta_2=(426/10^5)/n;delta_3
    =(10.9/10^5)/n;delta_4=(20.9/10^5)/n;
% sigma_1=(558/10^5)/n;sigma_2=(3.33/100)/n;sigma_3=(0.148)/
    n;
% alpha_1=(2.2*10^(-1))/n;alpha_2=(2.16)/n;
% rho_1=(80.1/100)/n;rho_2=(31/100)/n;%not yet
% omega_1=(38/100)/n;omega_2=(.5/100)/n;p=(6/100)/n;mu
    =8.06/1000;
% theta_1=(3.2/100)/n;theta_2=(1/20)/n;
% pi=((1220/10^6)*0.08)/n;eta=(112/1134)/n;
%%
%====little better
%=====+++++++gave the best results

```

```

% beta=233/10^6;%consider 0.0003 if the graphs fails to rise
    and flatten gradually
% %beta=259/100000;
% Lambda=(8.06/10^3)*53*10^6;
% delta_1=50/10^3;delta_2=426/10^(1);delta_3=10.9/10^2;
    delta_4=20.9/10^5;
% sigma_1=558/10^5;sigma_2=3.33/100;sigma_3=0.148;
% alpha_1=2.2*10^(2);alpha_2=2.16;%alpha_1=2.2*10^(3) gave
    the best results
% rho_1=80.1/100;rho_2=31/100;%not yet
% omega_1=38/100;omega_2=.5/100;p=6/100;mu=8.06/1000;
% theta_1=3.2/100;theta_2=1/20;
% pi=(1220/10^3)*0.08;eta=112/1134;
%%

beta=233/10^6;%consider 0.0003 if the graphs fails to rise
    and flatten gradually 233/10^6 gives gradual figures
%beta=259/100000;
%beta_1=233/10^5; beta_2=266/10^5;beta_3=250/10^5;beta_4
    =220/10^5;
Lambda=(8.06/10^3)*53*10^6;
delta_1=50/10^3;delta_2=426/10^(1);delta_3=10.9/10^2;delta_4
    =20.9/10^5;
sigma_1=558/10^5;sigma_2=3.33/100;sigma_3=0.148*1000;
alpha_1=2.2*10^(2);alpha_2=2.16;%alpha_1=2.2*10^(3) gave the
    best results
rho_1=80.1/100;rho_2=31/100;%not yet

```

```

omega_1=38/1;omega_2=.5/100; p=6/1000;mu=8.06/1000;
theta_1=3.2/1000;theta_2=1/20;
pi=(1220/10^3)*0.08;eta=112/(1134);
%% introduce optimal control parameter
h=.8;
d=.8;
%%
%working well without considering the year to days
    conversion
% n=1;
% beta=(233/10^7)/n;%consider 0.0003 if the graphs fails to
    rise and flatten gradually
% %beta=259/100000;
% Lambda=((8.06/10^3)*53*10^6)/n;
% delta_1=(50/10^5)/n;delta_2=(426/10^5)/n;delta_3
    =(10.9/10^5)/n;delta_4=(20.9/10^5)/n;
% sigma_1=(558/10^5)/n;sigma_2=(3.33/100)/n;sigma_3=(0.148)/
    n;
% alpha_1=(2.2*10^(1))/n;alpha_2=(2.16)/n;
% rho_1=(80.1/100)/n;rho_2=(31/100)/n;%not yet
% omega_1=(38/100)/n;omega_2=(.5/100)/n;p=(6/100)/n;mu
    =(8.06/1000)/n;
% theta_1=(3.2/100)/n;theta_2=(1/20)/n;
% pi=((1220/10^6)*0.08)/n;eta=(112/1134)/n;
%%
% Lambda=0.0277;lambda=0.03;delta_1=0.0039;delta_2=0.275;
    delta_3=0.05;delta_4=0.0003;sigma_1=0.03;

```

```

% sigma_2=0.0003;sigma_3=0.00026;alpha_1=3/1000;alpha_2=0.1;
    rho_1=0.0986;rho_2=0.7372;
% omega_1=0.08;omega_2=0.002;p_1=3.875/1000;p=3.875/1000;mu
    =0.0051;theta_1=0.05;theta_2=0.1;rho_3=0.7372;
%%
S= y(1);
L_f=y(2);
L_s=y(3);
I_T=y(4);
D_T=y(5);
I_DT=y(6);
C_DT=y(7);
D=y(8);
C=y(9);
%I=y(10);
%%
So= y(10);
L_fo=y(11);
L_so=y(12);
I_To=y(13);
D_To=y(14);
I_DTo=y(15);
C_DTo=y(16);
Do=y(17);
Co=y(18);
%%
I=I_T+I_DT;

```

```

lambda=beta*I;

%%

%N=S+L_F+L_s+I_T+D_T+I_DT+C_DT+D+C=1000

%%

dydt(1)=Lambda-(alpha_1+lambda+mu)*S;
dydt(2)=p*lambda*S+pi*L_s-(mu+sigma_1)*L_f;
dydt(3)=(1-p)*lambda*S+rho_1*I_T-pi*L_s-(sigma_2+mu+alpha_2)
    *L_s;
dydt(4)=sigma_2*L_s+sigma_1*L_f-(rho_1+mu+delta_1)*I_T;
dydt(5)=alpha_2*L_s+eta*D+rho_2*I_DT-(mu+sigma_3)*D_T;
dydt(6)=sigma_3*D_T+omega_2*C_DT-(rho_2+theta_2+mu+delta_2)*
    I_DT;
dydt(7)=theta_2*I_DT-(omega_2+mu+delta_3)*C_DT;
dydt(8)=alpha_1*S+omega_1*C-(eta+mu+theta_1)*D;
dydt(9)=theta_1*D-(omega_1+delta_4+mu)*C;

%% effect of beta on the population of I
% dydt(10)=beta_1*I;
% dydt(11)=beta_2*I;
% dydt(12)=beta_3*I;
% dydt(13)=beta_4*I;

%%

dydt(10)=Lambda-((1-h)*alpha_1+(1-d)*lambda+mu)*So;
dydt(11)=p*(1-d)*lambda*So+pi*L_so-(mu+sigma_1)*L_fo;
dydt(12)=(1-p)*(1-d)*lambda*So+rho_1*I_To-pi*L_so-(sigma_2+
    mu+alpha_2)*L_so;
dydt(13)=d*sigma_2*L_so+sigma_1*L_fo-(rho_1+mu+delta_1)*I_To
    ;

```

```

dydt(14)=d*alpha_2*L_so+eta*Do+rho_2*I_DTo-(mu+sigma_3)*D_To
;
dydt(15)=d*sigma_3*D_To+omega_2*C_DTo-(rho_2+theta_2+mu+
delta_2)*I_DTo;
dydt(16)=d*theta_2*I_DTo-(omega_2+mu+delta_3)*C_DTo;
dydt(17)=(1-h)*alpha_1*So+omega_1*Co-(eta+mu+theta_1)*Do;
dydt(18)=d*theta_1*Do-(omega_1+delta_4+mu)*Co;
end

```