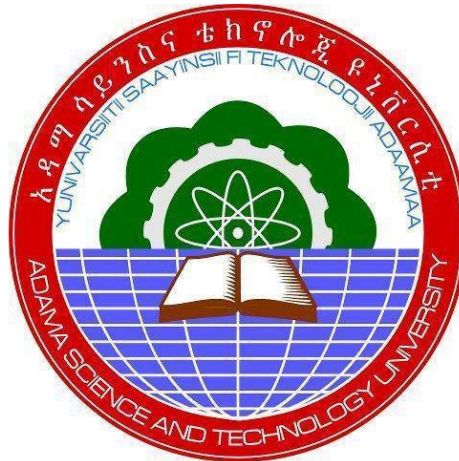


**A MATHEMATICAL MODELING AND ANALYSIS OF COVID-19
AND DIABETES CO-INFECTION WITH OPTIMAL CONTROL
AND COST-EFFECTIVENESS**



Chala Tena

A Thesis Submitted to Department of Applied Mathematics,
School of Applied Natural Sciences

Presented in Partial Fulfillment of the Requirement for the Degree of
Master's in Applied Mathematics(Mathematical Modeling)

Office of Graduate Studies
Adama Science and Technology University

October, 2022
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Declaration

I hereby declare that this Master Thesis entitled “*A mathematical modeling and analysis of COVID-19 and diabetic co-infection with optimal control and cost-effectiveness*” is my original work. That is, it has not been submitted for the award of any academic degree, diploma or certificate in any other university. All sources of materials that are used for this thesis have been duly acknowledged through citation.

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Recommendation of Advisor's

We, the advisors of this thesis, hereby certify that we have read the revised version of the thesis entitled “*A mathematical modeling and analysis of COVID-19 and diabetes co-infection with optimal control and cost-effectiveness*” prepared under our guidance by Chala Tena submitted in partial fulfillment of the requirements for the degree of Master's of Science in Applied Mathematics. Therefore, we recommend that the submission of revised version of the thesis to the department following the applicable procedures.

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Finally approval and acceptance of the thesis is contingent upon submission of its final copy to the Office of Postgraduate Studies (OPGS) through the Department Graduate committee (DGC) and School Graduate Committee (SGC)..

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ACRONYMS

COVID-19	Corona Virus Infectious Diseases-2019
EEP	Endemic Equilibrium Point
FEP	Free Equilibrium Point
IDF	International Diabetes Federation
ODE	Ordinary Differential Equation
MERS-COV	Middle East Respiratory Syndrome Coronavirus
PMP	Pontryagin Maximum Principle
SARS-COV	Severe Acute Respiratory Syndrome Coronavirus
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus-2
UNECA	United Nations Economic Commission for Africa
WHO	World Health Organization

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has emerged as one of the greatest challenges faced by humankind in the recent past. People with diabetes and related comorbidities are at increased risk of its complications and of COVID-19-related death. In this thesis, we studied the dynamics of COVID-19 and DIABETES co-infection. For this, we formulated a deterministic mathematical model to describe the transmission dynamics of COVID-19 and DIABETIC sub-models and analyzed each sub-models with analytical methods. The biological meaningfulness of each sub-models was proved and the stability analysis was performed by obtaining the basic reproduction number. In each sub-models the disease free equilibrium points are proved to be both locally and globally stable if the reproduction numbers are less than unity and the endemic equilibrium point is also both locally and globally stable if the reproduction numbers are greater than unity. The sensitivity analysis of each sub-models parameters has also been performed by using the normalized forward analysis. We have then proposed a deterministic mathematical model of the coinfection of COVID-19 and DIABETES. The coinfection model is qualitatively studied by proving the properties such as existence and uniqueness, boundedness, and positivity of the solutions. We computed the basic reproduction number of the coinfection and the disease free equilibrium point is locally stable and globally not stable and the system has no endemic equilibrium point. Furthermore, the coinfection model is extended in to an optimal control problem by adding three control measures as the prevention techniques against COVID-19, treatments for COVID-19 infections, and awareness program for DIABETIC without complications to optimally manage the disease. The optimal control was analyzed with Pontryagin's Minimum Principle. Different simulation cases were performed using MATLAB to supplement the analytical results and to identify the most appropriate control intervention strategies. The simulation results show that the prevalence of the coinfection was reduced when all three control measures were concurrently implemented. The most cost-effective control measure is determined through cost-effectiveness analysis

Keywords: *Mathematical Modeling; COVID-19; DIABETES; Sensitivity Analysis; Optimal Control; Pontryagin's Minimum Principle; Cost-effectiveness analysis.*

CHAPTER 1

INTRODUCTION

1.1 Back ground of the study

Coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus that attacks the respiratory system and it had been first discovered in humans in December 2019 in Wuhan city, Hubei province, China. The outbreak because of SARS-CoV-2 was declared a global health emergency or pandemic by the World Health Organization(WHO) on January 30, 2020. The Chinese government conducted quarantine within the city of Wuhan on January 23, 2020 as a step to regulate the pandemic (Waris et al., 2020). The effect of COVID-19 infection may vary from person to person. The illness from mild to moderate are often observed in most of the infected individuals and they may recover from the disease without getting hospitalized. COVID-19 infection is transmitted through the infected individuals via direct or indirect close contacts. Individuals with other comorbidities or with a compromised system are more prone to develop illness due to COVID-19 disease.

The novel coronavirus can cause mild, non-specific symptoms, including fever, cough, short-age of breath, muscle pain and tiredness just like those caused by SARS-CoV and MERS-CoV infections (Gralinski & Menachery, 2020). In additional serious cases, it can develop severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock which will lead to death. The virus is transmitted via respiratory droplets produced when an infected person coughing, sneezing and through talking in an exceedingly social distance but two meter. The estimated incubation period is 2-14 days, but may will be longer (Tang et al., 2020). The virus is most contagious when infected people are symptomatic, although can spread before symptoms appear (Rothe et al., 2020)

COVID-19 has drawn drastic attention and posses a healthcare threat globally. The devastating effects of the COVID-19 pandemic were highly associated with chronic medical con-



ditions, mainly diabetes mellitus. Diabetes could be a disease that happens when glucose, is too high and is one in every of underlying conditions related to a high risk of COVID-19 complications. World Health Organization reported that 18.3% of COVID-19 deaths in Africa are among people with diabetes (Organization et al., 2021). A recent WHO analysis evaluated data from 13 countries on underlying conditions or comorbidities in Africans who tested positive for COVID-19 revealed a 10.2% case fatality rate in patients with diabetes, compared with 2.5% for COVID-19 patients overall (Organization et al., 2022a). Having cardiopathy, arteria coronaria disease, and hypertension can cause more severely ill from COVID-19. However, the case death rate for people with diabetes is twice as high as the rate among patients littered with any comorbidity mentioned (Organization et al., 2022a)

Mathematical modeling plays a very important role in comprehending and providing useful techniques to predict and analysis the dynamics of communicable disease (Huppert & Katriel, 2013). The dynamical model study is used to investigate the vital parameters, predict future trends, and evaluate control measures to provide decisive information for decision making (Park et al., 2020). Recently, many mathematical models have been developed to study the transmission dynamics of COVID-19, see for example in (Ayana et al., 2020); (Deressa & Duressa, 2021); (Kifle & Obsu, 2022) and reference cited therein. Mathematical models for diabetes are also extensively studied in (Kompas et al., 2020); (Kouidere et al., 2020) and reference cited therein. The studies in (Ndii et al., 2020) described the effect of speeding the detection time of COVID-19 infected individuals and reducing the transmission rate using both deterministic and stochastic models. In (Hattaf et al., 2021), the authors developed a mathematical to describe the dynamics of COVID-19 by taking into account all modes of transmission and prosocial awareness. Moreover, an optimal control strategy was proposed in (Lemecha Obsu & Feyissa Balcha, 2020) that helps to reduce the number of exposed and infected population of COVID-19 considering the cost implementation. The coinfection of various diseases is widely studied, for instance, TB and HIV/AIDS coinfection (Awoke & Kassa, 2018), Hepatitis E and HIV (Alzahrani & Khan, 2020), and cholera-schistosomiasis coinfection in (Okosun et al., 2019). On the contrary, the study on COVID-19 and other coinfection are at its infant stage, and related mathematical literature is scant. For instance, COVID-19 and malaria coinfection are discussed in (Tchoumi et al., 2021) and TB and COVID-19 coinfection presented in (Mekonen et al., 2022), while diabetes and COVID-19 presented in (Anusha & Athithan, 2021) and (Kouidere et al., 2021). Anusha & Athithan (2021) studied a mathematical modeling of diabetes and COVID-19 co-existence. Their study showed that the transmission coefficient from the diabetes susceptible class to diabetes class and recovery rate plays a vital role in the reduction of reproduction number. Besides, the coinfection of the COVID-19 and diabetes model is analyzed in (Kouidere et



al., 2021). In their model, the authors studied to highlight the negative impact of the total quarantine on diabetics with optimal control to limit the impact of COVID-19 on diabetes. To the best of our knowledge, mathematical models considering the coinfection of diabetes and COVID-19 are rare and they prompt us for further investigation.

In the above reviewed literature the coinfection of COVID-19 and diabetes are scarce. In the current study we planned to bridge the gap by modeling coinfection of COVID-19 and diabetes with optimal control and cost-effectiveness by classify the population in to susceptible, exposed, asymptomatic, symptomatic, recovered, co-infected due to diabetic without complications and with complications, diabetes susceptible, pre-diabetes, diabetes without and with complications, then we formulate the governing mathematical modeling, Finally we present mathematical analysis of the formulated model, its numerical simulation and cost-effectiveness analysis.

1.2 Statement of the problem

Coronavirus disease 2019 (COVID-19) pandemic which began in Wuhan city is now the problem of the world. Globally, COVID-19 is affecting above 223 countries. According to WHO data, the total confirmed cases are 530,468,153 and the reported deaths due the disease is 6,308,131 deaths up to May 27, 2022. In Africa, COVID-19 case was first reported in Egypt on 14 February 2020. Then it addressed all the African countries. Initially, the disease was confined to capital cities, and gradually a significant number of countries in Africa are now reporting the cases in multiple provinces. Also, WHO report shows 8,972,475 total confirmed cases and 254,789 confirmed deaths are reported in Africa up to May 27, 2022. In Ethiopia the first confirmed case of COVID-19 was on 13 March 2020, in capital city of Ethiopia, Addis Ababa. Up to May 27, 2022, the total reported confirmed cases and death reported due to COVID-19 in Ethiopia respectively are 471,879, and 7,513 (Organization et al., 2022b). During the COVID-19 pandemic older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. However, diabetes is one of the major co-morbidity associated with severe illness and death from COVID-19 infection (Guo et al., 2020). The rate of fatality from COVID-19 is up to 50% higher in patients with diabetes than in the individual who does not have diabetes (Remuzzi & Remuzzi, 2020). In (Zhou et al., 2020), it was reported that 20 – 30% of patients who died from COVID-19 had diabetes. International Diabetes Federation and (Roglic et al., 2016) reported 463 million adults are having diabetes; nearly 760 billion USD was spent on healthcare; more than 310 million diabetes patients are living in urban areas and about 11.3% of deaths were due to diabetes.



Recently, epidemiological studies are focusing on the coinfection of COVID-19 and comorbidities, because comorbidities have been recognized as a risk factor for increased COVID-19 cases and higher fatality (Wang et al., 2020). Also, various studies have shown that diabetes is one of the major comorbidity associated with severe illness and death from COVID-19 infection (Maddaloni & Buzzetti, 2020). (Anusha & Athithan, 2021) proposed mathematical modeling co-existence of diabetes and COVID-19 with compartments consisting diabetes susceptible class $S_d(t)$, diabetes class $D(t)$, COVID-19 susceptible class $S_c(t)$, COVID-19 infected class $I_c(t)$ and COVID-19 recovered class $R_c(t)$. However, they did not consider optimal control and cost-effectiveness analysis. Thus, in this thesis we have developed new mathematical models with optimal control and cost-effectiveness analysis based on (Anusha & Athithan, 2021) by introducing exposed class, asymptomatic (infectious individuals who are not show symptoms of the disease), co-infected due to diabetic without complications and due to chronic cases, pre-diabetic class due to unhealthy life styles they followed and chronic class with optimal control strategies and studied both analytically and numerically with the help of Pontryagin's Minimum Principle.

1.3 Objectives of the study

1.3.1 General objective

The general objective of this study is to develop a mathematical modeling and investigation of COVID-19 and diabetic coinfection with optimal control and cost-effectiveness.

1.3.2 Specific objectives

- Formulate a deterministic mathematical model for coinfection of COVID-19 and diabetic patients.
- Perform analysis of the proposed mathematical model and extend to the optimal control.
- Investigate the efficacy of several strategies in controlling the disease and analysis the cost effectiveness.

1.4 Significant of the study

A well studied and organized thesis report on a mathematical model of COVID-19 and diabetes co-infection will provide strong information on how to design appropriate control and



preventive measures. Thus, the outcome of this study are helpful to:

- Determine the most profitable strategy.
- Encouraging diabetic patients to follow medical advice to prevent diabetes complications during COVID-19 pandemic.
- Propose a strategy for awareness campaigns to target diabetics through proper and balanced nutrition and physical exercise.
- Motivate other researchers for further study and mathematical analysis.

1.5 Operational Definition of Technical Terms

The following epidemiological terms are defined for later use.

Epidemic is the rapid spread of disease to a large number of people in a given population within a short period of time. In epidemiology, an infection is said to be **endemic** in a population when that infection is constantly maintained at a baseline level in a geographic area without external inputs. A **pandemic** is an epidemic of an infectious disease that has spread across a large region (Morens et al., 2009), for instance multiple continents or worldwide, affecting a substantial number of people.

1.6 Mathematical Preliminary

In this section, we state some theorems and give the definitions of important concepts for later use in this study. The aim is to clarify terminologies and results that are utilized in the subsequent chapters.

1.6.1 Linearization and the Jacobian

In most of the systems of real world problem, it becomes apparent that nearly all systems are non-linear, including the model we are examining. However, most of the theory that has been developed by mathematicians governing the behavior of systems of differential equations, especially stability, is centered upon linear systems. Thus, in order to further understand the behavior of a non-linear system it is first crucial to linearize the system. Essentially, this process approximates a non-linear system in a linear manner near the values around which a linear approximation occurs.

In a neighborhood of the equilibria we can make a linear approximation to determine the local character of the paths (Lukes, 1982). This technique allows the stability of the system

at the equilibria to be determined and provides a starting point for global investigations of solutions. The goal of this stability analysis is to perturb the system from equilibrium and study the behavior of the system. Thus, we will look to see if the solutions move towards or away from equilibrium. In order to linearize the system, we must compute the Jacobian matrix of the system. The Jacobian is the matrix of the partial derivatives of each function with respect to each variable. Essentially, the Jacobian provides a linear approximation of a system at any given value (Layek, 2015).

1.6.2 Routh-Hurwitz Criteria

The linear stability of a system of differential equations:

$$\frac{dX}{dt} = AX$$

where $X = (x_1, x_2, x_3, \dots, x_n)$ is determined by the roots of the characteristic polynomial, A is the Jacobian matrix of the linearized system. The solution of the system is obtained by setting $X = x_0 e^{\lambda t}$. Where x_0 is a constant vector to be determined, λ is the eigenvalue of A . The solution $X = x_0 e^{\lambda t}$ (the equilibrium point) is locally stable if all the roots of the characteristic polynomial:

$$P(\lambda) = \lambda^n + a_1 \lambda^{n-1} + a_2 \lambda^{n-2} + \dots + a_{n-1} \lambda + a_0$$

lie in the left hand complex plane that is $Re(\lambda) < 0$ for all roots λ of characteristic polynomial. Now consider the polynomial

$$\lambda^n + a_1 \lambda^{n-1} + a_2 \lambda^{n-2} + \dots + a_{n-1} \lambda + a_0 = 0$$

where all the coefficients $a_1, a_2, \dots, a_n$ are real and $a_n \neq 0$. The necessary and sufficient condition for all the roots of the characteristic polynomial equation to have $Re(\lambda) < 0$ is the Routh-Hurwitz condition (Merkin, 1997). These Routh-Hurwitz condition are with $a_n > 0$.

$$D_1 = a_1 > 0$$

$$\det(D_2) = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 - a_3 > 0$$

$$\det(D_3) = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{vmatrix} = a_1 a_2 a_3 - a_3^2 > 0$$

$$\det(D_n) = \begin{vmatrix} a_1 & a_3 & a_5 & \cdot & \cdot & \cdot \\ 1 & a_2 & a_4 & \cdot & \cdot & \cdot \\ 0 & a_1 & a_3 & \cdot & \cdot & \cdot \\ \cdot & & & & & \\ \cdot & & & & & \\ 0 & 0 & 0 & \cdot & \cdot & \cdot & a_k \end{vmatrix} > 0, \quad \text{for } k = 1, 2, 3, \dots, n.$$

1.6.3 Method of Computing Basic Reproduction Number

The basic reproduction number, which is denoted by R_0 the average number of new cases (infections), that one infected case will generate during its entire infectious life time. The basic reproduction number is an important non-dimensional quantity in epidemiology as it sets the threshold in the study of a disease both for predicting its outbreak and for evaluating its control strategies (Diekmann et al., 1990). Thus, whether a disease becomes persistent or dies out in a community depends on the value of the reproduction number R_0 . If $R_0 < 1$ it means that every infectious individual will cause less than one secondary infection which is impossible and hence the disease will die out and when $R_0 > 1$ every infectious individual will cause more than one secondary infection and hence the disease will invade the population. Therefore, the basic reproduction number is a threshold parameter for a disease and its biological significance is obvious. (Van den Driessche & Watmough, 2002) developed a technique for calculating the basic reproduction number of disease transmission models. This method is called the next generation operator method. Consider a disease transmission model that has non-negative initial conditions and can be expressed in terms of the following autonomous system:

$$\frac{dx_i}{dt} = \mathcal{F}_i(x) - \mathcal{V}_i(x) \quad (1.1)$$

where $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$. (Van den Driessche & Watmough, 2002)

- $\mathcal{F}_i(x)$ the rate of appearance of new infections in compartment i ,
- $\mathcal{V}_i^+(x)$ the rate of transfer of individuals into compartment i by all others means,
- $\mathcal{V}_i^-(x)$ be the rate of transfer of individuals out of compartment i ,

The functions $\mathcal{F}_i(x)$, $\mathcal{V}_i^+(x)$, $\mathcal{V}_i^-(x)$ are assumed to be at least twice continuous-differentiable in each variable (Van den Driessche & Watmough, 2002).

1.6.4 Determining the Direction of Bifurcation

Bifurcation is a qualitative changes in the behavior of systems, where one or more system parameters are varied. The study of bifurcation is concerned with how the structural and

behavioral change occurs when the parameter(s) are changing. The structural change and the transition behavior of a system are the central part of dynamical evolution. The point at which bifurcation occurs is known as the bifurcation point (Layek, 2015).

For the most part, in epidemic models, there are two distinct bifurcations at $R_0 = 1$ forward (supercritical) and backward (subcritical). A forward bifurcation happens when R_0 crosses unity from below; a small positive asymptotically stable equilibrium appears and the disease-free equilibrium loses its stability. On the other hand, a backward bifurcation happens when R_0 is less than unity; a small positive unstable equilibrium appears while the disease-free equilibrium and a larger positive equilibrium are locally asymptotically stable (Huang et al., 1992). Center manifold theory has been used to decide the local stability of a nonhyperbolic equilibrium (linearization matrix has at least one eigenvalue with zero real part) (Carr, 2012).

Theorem 1.6.1. (Castillo-Chavez & Song, 2004). Suppose, a general system of ODEs with a parameter ϕ is given by:

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \mapsto \mathbb{R}^n, f \in \mathcal{C}^2(\mathbb{R}^n \times \mathbb{R}) \quad (1.2)$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (1.2) for all values of the parameter ϕ , i.e. $f(0, \phi) = 0$ for all ϕ . Then the following assumption raised :

A_1 : $A = D_x f(0, 0) = \frac{\partial f_i}{\partial x_i}(0, 0)$ is the linearization matrix of system (1.2) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

A_2 : Matrix A has a non-negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue .

Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^n v_k w_i w_j \frac{\partial^2 f}{\partial x_i \partial x_j}(0, 0),$$

and

$$b = \sum_{k,i=1}^n v_k w_i \frac{\partial^2 f}{\partial x_i \partial \phi}(0, 0).$$

The local dynamics of (1.2) around 0 are totally determined by a and b .

- $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium
- $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium.



- $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears.
- $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable

1.6.5 Numerical Methods for System of ODEs

Numerical techniques that listed below are summarized from (Lenhart & Workman, 2007). When a system of ODEs involves equations that can not be solved analytically, numerical methods are used to compute its approximate solution. For example, fourth order Runge Kutta method (*RK4*) is widely used for solving initial value problems (IVP) for ordinary differential equation (ODE) which is given

$$\dot{x} = \frac{dx}{dt} = f(t, x), \quad x(t_0) = x_0$$

on the interval $t_0 \leq t \leq T$, we divide the interval into N small segments of constant length h , which is called the step size given by $h = \frac{T - t_0}{N}$. The numerical methods introduced for a single equation can be easily extended to systems of equations. For example, consider the system of ordinary differential equation with initial condition.

$$\begin{cases} \frac{dx}{dt} = f(t, x, y), & x(t_0) = x_0, \\ \frac{dy}{dt} = g(t, x, y), & y(t_0) = y_0. \end{cases} \quad (1.3)$$

We want to obtain a numerical solution on the interval $t_0 \leq t \leq T$. The first step is discretizing the interval by defining the time steps given by

$$t_n = t_0 + nh, \quad n = 0, 1, 2, \dots, N$$

where N is the number of steps. Again we use the notation x_n and y_n to denote the approximate values of $x(t, n)$ and $y(t, n)$, respectively. We can summarize the numerical techniques as:

Runge-Kutta Fourth Order

Given a well-posed initial-value problem (IVP) for the above condition (1.2), the Runge-Kutta method of order four (*RK4*) constructs a sequence of approximation points $(t, x) \approx (t, x(t))$ and $(t, y) \approx (t, y(t))$ to the exact solution of an ODE by to the exact solution of an

ODE by $t_{n+1} = t_n + h$ to get the following values of eight slope:

$$\left\{ \begin{array}{l} k_{11} = f(t_n, x_n, y_n), \\ k_{21} = f(t_n, x_n, y_n), \\ k_{12} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{11}, y_n + \frac{h}{2}k_{21}), \\ k_{22} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{11}, y_n + \frac{h}{2}k_{21}), \\ k_{13} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{12}, y_n + \frac{h}{2}k_{22}), \\ k_{23} = f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_{11}, y_n + \frac{h}{2}k_{21}), \\ k_{14} = f(t_n + h, x_n + hk_{13}, y_n + hk_{23}), \\ k_{24} = f(t_n + h, x_n + hk_{13}, y_n + hk_{23}). \end{array} \right. \quad (1.4)$$

Then we compute the next approximation using weighted averages of the above slopes,

$$\left\{ \begin{array}{l} x_{n+1} = x_n + \frac{h}{6}(k_{11} + 2(k_{12} + k_{13}) + k_{14}), \\ y_{n+1} = y_n + \frac{h}{6}(k_{21} + 2(k_{22} + k_{23}) + k_{24}). \end{array} \right. \quad (1.5)$$

In such process, the continuous time model is reduced to an approximate discrete time model that is amenable to computer simulation

1.6.6 Autonomous Linear System

Consider a system of ordinary differential equation which are autonomous.

$$\left\{ \begin{array}{l} \frac{dx}{dt} = f(t, x), \\ \frac{dy}{dt} = g(t, y). \end{array} \right. \quad (1.6)$$

The term autonomous refers to the fact that f and g are not trial function of t . Consider a general autonomous vector field

$$\frac{dx}{dt} = f(t, x), \quad x \in R^n \quad (1.7)$$

where $f : R^n \mapsto R^n$.

Definition 1.6.1. (Layek, 2015) A point $x_e \in R^n$ is an equilibrium point of the system (1.7) if $f(x_e) = 0$.

To determine the behavior near a critical point, we will linearize the non-linear system around the critical point and use our knowledge of linear systems. let (x_0, y_0) be the equilibrium

point of (1.6). If f and g are n -times continuously differentiable functions, then using the Taylor series expansion.

$$\begin{aligned} f(x, y) &= f(x_0, y_0) + f_x(x_0, y_0)(x - x_0) + f_y(x_0, y_0)(y - y_0) + \frac{1}{2!}f_{xx}(x_0, y_0)(x - x_0)^2 \\ &+ \frac{1}{2!}f_{yy}(x_0, y_0)(y - y_0)^2 + f_{xy}(x_0, y_0)(x - x_0)(y - y_0) + \dots \\ &\approx f(x_0, y_0) + f_x(x_0, y_0)(x - x_0) + f_y(x_0, y_0)(y - y_0) \\ &= f_x(x_0, y_0)(x - x_0) + f_y(x_0, y_0)(y - y_0). \end{aligned}$$

$$\begin{aligned} g(x, y) &= g(x_0, y_0) + g_x(x_0, y_0)(x - x_0) + g_y(x_0, y_0)(y - y_0) + \frac{1}{2!}g_{xx}(x_0, y_0)(x - x_0)^2 \\ &+ \frac{1}{2!}g_{yy}(x_0, y_0)(y - y_0)^2 + g_{xy}(x_0, y_0)(x - x_0)(y - y_0) + \dots \\ &\approx g(x_0, y_0) + g_x(x_0, y_0)(x - x_0) + g_y(x_0, y_0)(y - y_0) \\ &= g_x(x_0, y_0)(x - x_0) + g_y(x_0, y_0)(y - y_0). \end{aligned}$$

Then, the linearized form of Equation 1.6 can be expressed as:

$$\frac{dx}{dt} = Ax$$

where $A = \begin{bmatrix} f_x & f_y \\ g_x & g_y \end{bmatrix}$, $x = \begin{bmatrix} x \\ y \end{bmatrix}$ and A is called the Jacobian matrix.

Let $x = ue^{\lambda t}$ be solution of the system of differential equation

$$\frac{dx}{dt} = Ax$$

where u is a vector to determined. Then

$$\frac{dx}{dt} = ue^{\lambda t} = Ax \implies Ax - ue^{\lambda t} \implies x(A - \lambda I) = 0$$

The system will have a non-trivial solution if $\det((Ax - \lambda I)) = 0$.

Definition 1.6.2. (Layek, 2015) A point x_ϵ is said to be stable for a given $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any other solution, $y(t)$ of (1.7) satisfying $|x_\epsilon(t_0) - y(t_0)| < \delta$ implies $|x_\epsilon(t) - y(t)| < \epsilon$, for $t > t_0$, $t_0 \in \mathbb{R}$.

Definition 1.6.3. (Layek, 2015) A point x_ϵ is said to be locally asymptotically stable if it is stable and for any other solution, $y(t)$ of (1.7), there exists a constant $b > 0$ such that if $|x_\epsilon(t_0) - y(t_0)| < b$ then $\lim_{t \rightarrow \infty} (|x_\epsilon(t) - y(t)|) = 0$.

Theorem 1.6.2. (Perko, n.d.) Let x_0 be a hyperbolic equilibrium point of the nonlinear system (1.7) with $f \in C^1$ (continuously differentiable of order one). Then the stability of the



equilibrium point for the nonlinear system is structurally the same as that of the linear system $\dot{x} = Ax$. Where $A = Df(x_0)$.

Definition 1.6.4. (Layek, 2015) A function $V : \mathbb{R}^n \rightarrow \mathbb{R}$ is said to be positive definite if,

- $V(x) > 0$, for all $x \neq 0$,
- $V(x) = 0$, if and only if $x = 0$,
- $V(x) \rightarrow \infty$ as $x \rightarrow \infty$.

Any function V is called a Lyapunov function, if it satisfies the conditions of positive definite and $\frac{dV}{dt} \leq 0, \forall x \in D/x_0$.

Theorem 1.6.3. (Layek, 2015) Let x_0 be a hyperbolic equilibrium point of the nonlinear system (1.7) and consider $V : D \in \mathbb{R}^n \rightarrow \mathbb{R}$ be continuously differentiable function such that

- $V(x) > 0$,
- $V(x) = 0, \forall x \in D \subset \mathbb{R}$,
- $\frac{dV}{dt} < 0, \forall x \in D/x_0, ||x|| \rightarrow \infty \implies V(x) \rightarrow \infty$.

Then the point x_0 is globally asymptotically stable.

Definition 1.6.5. (Invariant Set) A set E is an invariant set with respect to (1.7) if $x(0) \in E$ implies $x(t) \in E, \forall t \in \mathbb{R}^+$ and a set E is positively invariant set with respect to (1.7) if $x(0) \in E$, implies $x(t) \in E, \forall t \geq 0$.

CHAPTER 2

LITERATURE REVIEW

In this section, we review some of mathematical models developed by different researchers to study the dynamics of coinfection COVID-19 pandemic and diabetic that are directly related to the objectives of this study. Currently, COVID-19 is of great concern to researches, governments, and all people because of the high rate of the infection spread and the significant number of deaths that occurred (Zeb et al., 2020).

Anusha & Athithan (2021) proposed a mathematical model for the coinfection of diabetes and COVID-19. Here, the population is divided into five compartments namely diabetes susceptible (S_d), diabetes (D), COVID-19 susceptible (S_c), COVID-19 infected (I_c) and COVID-19 recovered population(R_c). First, the basic properties and existence of equilibrium points of the model are discussed in detail. There exist two equilibria for the model: Disease Free Equilibrium and Endemic Equilibrium. Then they computed the basic reproduction number by using the next-generation matrix method. Moreover, sensitivity analysis of R_0 is performed to find the significant parameters for the disease prevalence. They observed that the transmission coefficient from the diabetes susceptible class to diabetes class and recovery rate plays a vital role in the reduction of reproduction number R_0 and they extend their deterministic model to stochastic model.

Kouidere et al. (2021) proposed optimal control of mathematical modeling of the spread of the COVID-19 pandemic with highlighting the negative impact of quarantine on diabetics people with cost-effectiveness. They have compiled two mathematical models, one for the transmission of the COVID-19 disease between people, and the second model for the dynamics of diabetes population. Their objective is to highlight the negative impact of the application of total quarantine on diabetics in particular. They have also proposed several strategies to limit the spread of the COVID-19 pandemic, which leads to the lifting of the quarantine and made recommendations to diabetics who must be followed during a health

emergency to avoid complications of diabetes. They introduced three controls which, respectively, represent Sensitization and prevention, quarantine, awareness program for diabetics people. They applied the results of the control theory and managed to obtain the characterizations of the optimal controls. The numerical simulation of the obtained results showed the effectiveness of the proposed control strategies.

Okyere & Prah (2022) studied a mathematical model of COVID-19 and Diabetes Mellitus comorbidity. The model was validated using demographical data of Ghana and current COVID-19 and Diabetic Mellitus parameter estimates in the literatures. The basic reproductive number of the model was determined. The basic properties of the model were examined. The model was locally stable at the endemic equilibrium point. Optimal controls were incorporated into the model to determine the effectiveness of two preventive control measures which are lockdown and vaccination. Both measures were very effective in controlling the spread of the disease.

Oname et al. (2021) developed and analyzed a mathematical model for the dynamics of COVID-19 infection in order to assess the impacts of prior comorbidity on COVID-19 complications and COVID-19 re-infection. The model was simulated using data relevant to the dynamics of the diseases in Lagos, Nigeria, making predictions for the attainment of peak periods in the presence or absence of comorbidity. The model was shown to undergo the phenomenon of backward bifurcation which was caused by the parameter accounting for increased susceptibility to COVID-19 infection by comorbid susceptibles as well as the rate of re-infection by those who have recovered from a previous COVID-19 infection. The epidemiological interpretation of this phenomenon is that if recovery from COVID-19 does not confer lifelong immunity and efforts are not put in place to prevent COVID-19 infections by comorbid susceptible individuals, then the control of COVID-19 becomes difficult in the population, even when the associated reproduction number $R_{0c} < 1$. Hence, it is recommended that efforts should be made by those in authority and policy makers to recommend preventive measures to curb COVID-19 infection by comorbid susceptibles and re-infection with COVID-19 so as to bring the burden of COVID-19 infection very low at the community level.

Kompas et al. (2020) proposed a mathematical model of diabetes transmission through social contact which consider low and high risk susceptible population. From analytical results, they have a pair of equilibrium points, i.e. the disease-free equilibrium point and the endemic equilibrium point, which the existence and local stability depending on the related basic reproduction number R_0 . Based on analytic studies and numerical simulations, that having fewer susceptible individuals with healthy lifestyles and low risk due to the increas-



ing value of the proportion of susceptible individuals with healthy lifestyles and high risk, can increase the rate of spread of diabetes in the population, although not significantly. Furthermore, changes in the level of treatment interventions in diabetes infected individuals can suppress the number of infected individual even though it does not affect the size of R_0 .

All of the above authors were developed a mathematical model of COVID-19 and diabetes co-infection transmission dynamics by viewing in different aspects. They formulated their model by considering different compartments based on their assumptions and investigated the dynamical behavior, qualitative analysis of their model. However, they do not considered optimal control and cost-effectiveness analysis with compartments (susceptible, exposed, asymptomatic, symptomatic, recovered, co-infected due to diabetic without complications and with complications, diabetes susceptible, pre-diabetes, diabetes without and with complications) in their model. Thus, in order to fill the entire gap of the study in this research work we develop the mathematical model for COVID-19 and diabetes co-infection transmission dynamics based on proposed model by (Anusha & Athithan, 2021), we introduced exposed class, asymptomatic class, co-infected due to diabetic without and with complications cases, pre-diabetic class due to unhealthy life styles they followed and chronic class with optimal control strategies and cost-effectiveness analysis to study the co-infection of COVID-19 and diabetes.

CHAPTER 3

RESEARCH METHODOLOGY

In this section source of information, approach of the study and mathematical procedures are presented.

3.1 Source of Information

The applicable source of information for this research study are:

- WHO COVID-19 reports and International Diabetes Federation reports from internet, books and published journals.
- The model is compiled from two mathematical models, one from the transmission dynamics of COVID-19 and the second from the dynamics of diabetes population by adding the co-infected with both COVID-19 and diabetes.

3.2 Method of Data Analysis

The study involved both qualitative and quantitative analysis. We consulted a wide range of literature to find relevant model parameter values listed in Table (4.2). Whenever parameter values were not available in the literature, we assume realistic values for the purpose of simulation. Using the default parameter values in Table (4.2), numerical simulations are provided to support the analytical results. Numerical method used for simulation is forward and backward fourth order Runge-Kutta. Thus, the data is analyzed using MATLAB software and the results are displayed in the form of figures.

3.3 Descriptions of Mathematical Procedure

To achieve the objective of this research, we employ analytical and numerical method. First we developed the dynamic of spread of co-existence of diabetes and COVID-19 in a given



3.3. DESCRIPTIONS OF MATHEMATICAL PROCEDURE

population using a system of non-linear ordinary differential equations. In this research work, we implemented the Optimal control strategies using Pontryagin Minimum Principle (PMP) for identifying best control strategies with minimum cost and most profitable strategies by cost-effectiveness analysis. To supplement the analytical solution of the model, we performed a numerical simulation of the model by using Matlab software(ODE45).

CHAPTER 4

MODEL FORMULATION AND ANALYSIS

This chapter presents a deterministic mathematical model for COVID-19 pandemic and diabetic co-infection using a system of nonlinear ordinary differential equations. Model description and analysis are also detailed in order.

4.1 Description of the Model

In this section, we consider mathematical modeling for the dynamics of COVID-19 pandemic and diabetes. The total population $N(t)$ is divided into eleven compartments: Susceptible $S(t)$, Exposed $E(t)$, Asymptomatic $A(t)$, Infected with COVID-19 $I_c(t)$, Recovered $R(t)$, Individuals co-infected with COVID-19 and diabetes without complications I_{cd} , Individuals co-infected with COVID-19 and diabetes with complications I_{cc} , Diabetes susceptible class $S_d(t)$, Pre-diabetics $P(t)$, Diabetics without complication $D(t)$ and Diabetics with complications $C(t)$ population at time $t \geq 0$. Thus, total population is given by

$$N(t) = S(t) + E(t) + A(t) + I_c(t) + R(t) + I_{cd}(t) + I_{cc}(t) + S_d(t) + P(t) + D(t) + C(t)$$

The model assumed that susceptible individuals are recruited (by birth or immigration) into the population at a continuing rate Λ_1 . A proportion of the susceptible individuals become exposed to the COVID-19 infection at a rate $\lambda = \frac{\beta(bA + I_c)}{N_c}$ which is called force of infection (or rate of infection) as given in (Gurmu et al., 2020). Here, β denotes the effective contact rate with an infectious individuals and b represents the transmission coefficient of asymptomatic infectious individuals to susceptible individuals. In this context, $b > 1$, means the asymptomatic infected individuals infect the susceptible individuals more likely than the symptomatic infected individuals. In the contrary, $b < 1$, implies that the symptomatic infected individuals have more chance to infect the susceptible individuals than asymptomatic infected individuals. The case $b = 1$, tell us that both asymptomatic and symptomatic infected individuals have equal chance to infect the susceptible populations. Besides, we as-

sumed that an individuals in the compartment $E(t)$ may develop a symptoms of the COVID-19 infection and move to the symptomatic infected compartment $I(t)$ at a constant rate r . Individuals who do not show symptoms enter in to asymptomatic class $A(t)$ at a rate p . Further, individuals in the asymptomatic $A(t)$ compartment are assumed to be recovered due to natural immunity and move to recovered class $R(t)$ at a rate α_2 and infected individuals I_c recovered after receiving a treatment at a rate α_1 and move to the recovered class $R(t)$. Furthermore, infected individuals in compartment $I_c(t)$ are infected with diabetes without complications and diabetes with complications at a rate θ_1 and θ_2 respectively. Individuals in I_{CD} and I_{CC} are recovered from COVID-19 at a rate η_1 and η_2 join $R(t)$ respectively move to D and C at a rate ω_1 and ω_2 .

For diabetic model we assumed that healthy individuals are recruited (by birth with unhealthy lifestyles) in to the population at constant rate Λ_2 . A proportion of the diabetes susceptible individuals become pre-diabetics is at a rate $\frac{\beta_1 D}{N_d} S_d$ as given in (Hill et al., 2013) and in daily activities, diabetics without complications tend to have an unhealthy lifestyle. According to (Hill et al., 2013), the interaction between diabetics who have an unhealthy lifestyle and healthy individuals can result in lifestyle “transmission”. The impact of lifestyle “transmission” is incidence which increases the prevalence of diabetics. Pre-diabetics is decreased by the number μ (natural mortality) and also decreased by γ_1 (the probability of developing diabetes) and by γ_2 (the probability of developing diabetes at stage of complications). The amount of diabetics without complications $D(t)$ increased by the number $\gamma_1 P(t)$ and decreased by γ_3 (probability of a diabetic person developing a complication). The number of diabetics with serious complications ($C(t)$) increased by γ_2, γ_3 and decreased by δ_2 mortality rate because of complications) and also by μ (natural mortality).

4.1. DESCRIPTION OF THE MODEL

Table 4.1: Notations and Description of the model variables

Variable	Description
$S(t)$	Susceptible populations which are vulnerable to COVID-19 at time t
$E(t)$	The number of individuals who are exposed but are not yet infectious at time t
$A(t)$	Infectious individuals who are not show symptoms of the disease at time t
$I_C(t)$	Infected people with symptoms at time t .
$R(t)$	Individuals who have been recovered from the infection at time t
$I_{CD}(t)$	The people who are co-infected with COVID-19 and diabetes without complications at time t
$I_{CC}(t)$	The people who are co-infected with COVID-19 and diabetes with complications at time t
$S_d(t)$	Diabetes susceptible at time t
$P(t)$	Pre-diabetics people at time t
$D(t)$	Diabetics without complications at time t
$C(t)$	Diabetics with complications at time t

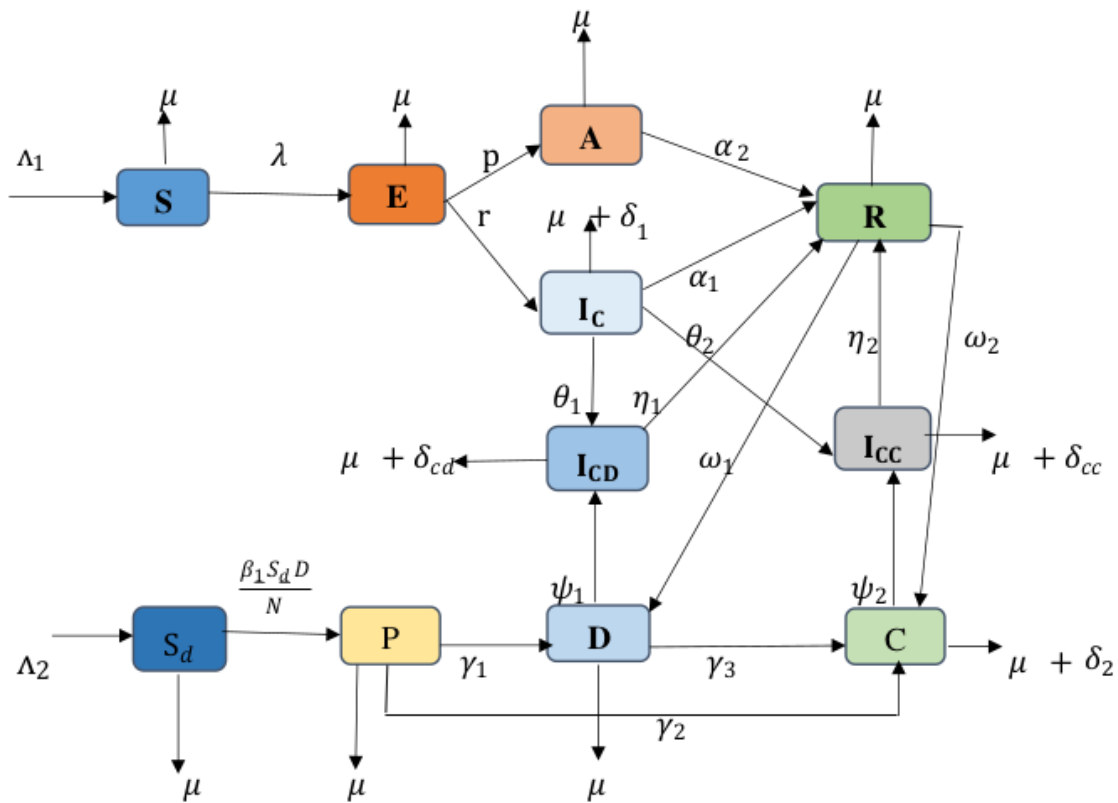


Figure 4.1: Compartmental flow diagram for COVID-19 and Diabetic co-infected people

4.1. DESCRIPTION OF THE MODEL

Based on the model description and flow diagram, the governing mathematical model can be systematically formulated as:

$$\begin{aligned}
 \frac{dS(t)}{dt} &= \Lambda_1 - (\mu + \lambda)S(t) \\
 \frac{dE(t)}{dt} &= \lambda S(t) - (\mu + p + r)E(t) \\
 \frac{dA(t)}{dt} &= pE(t) - (\mu + \alpha_2)A(t) \\
 \frac{dI_C(t)}{dt} &= rE(t) - (\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)I_C(t) \\
 \frac{dR(t)}{dt} &= \alpha_2 A(t) + \alpha_1 I_C(t) + \eta_1 I_{CD}(t) + \eta_2 I_{CC}(t) - (\mu + \omega_1 + \omega_2)R(t) \\
 \frac{dI_{CD}(t)}{dt} &= \theta_1 I_C(t) + \psi_1 D(t) - (\mu + \delta_{cd} + \eta_1)I_{CD}(t) \\
 \frac{dI_{CC}(t)}{dt} &= \theta_2 I_C(t) + \psi_2 C(t) - (\mu + \delta_{cc} + \eta_2)I_{CC}(t) \\
 \frac{dS_d(t)}{dt} &= \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D(t)}{N_d} S_d(t) \\
 \frac{dP(t)}{dt} &= \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu)P(t) \\
 \frac{dD(t)}{dt} &= \gamma_1 P(t) - (\gamma_3 + \mu + \psi_1)D(t) + \omega_1 R(t) \\
 \frac{dC(t)}{dt} &= \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2 + \psi_2)C(t) + \omega_2 R(t)
 \end{aligned} \tag{4.1}$$

where $\lambda = \frac{\beta(bA + I_C)}{N_c}$, $S(0) \geq 0$, $E(0) \geq 0$, $A(0) \geq 0$, $I_C(0) \geq 0$, $R(0) \geq 0$, $I_{CD}(0) \geq 0$, $I_{CC}(0) \geq 0$, $S_d(0) \geq 0$, $P(0) \geq 0$, $D(0) \geq 0$ and $C(0) \geq 0$ are the initial state.



4.1. DESCRIPTION OF THE MODEL

Table 4.2: Description of model parameters of COVID-19 and Diabetes co-infection and the values of parameters used in the numerical simulations

Parameter	Description	Value	Source
Λ_1	Recruitment rate of COVID-19 susceptible	146593	Calculated
Λ_2	Recruitment rate of diabetes susceptible	2470	Calculated
p	Rate of exposed individuals enter into asymptomatic infectious class	0.02557	(Kifle & Obsu, 2022)
r	Rate of exposed individuals enter into symptomatic infectious class	1/7	(Bugalia et al., 2020)
b	Transmission coefficient of asymptomatic individuals	0.77484	Assumed
μ	Natural mortality rate	0.001235	Calculated
β	Effective contact rate of infection	0.88	(Kifle & Obsu, 2022)
β_1	Intensive social contact rate	0.16263	(Widyaningsih et al., 2018)
α_1	Progression from compartment $I_C(t)$ to $R(t)$ due to effective treatment	0.00787	(Kifle & Obsu, 2022)
α_2	Rate at which asymptomatic individuals recovered	0.00827	(Kifle & Obsu, 2022)
θ_1	COVID-19 infection rate of individuals already infected with diabetes without complications	0.7421	Assumed
θ_2	COVID-19 infection rate of individuals already infected with diabetes with complications	0.4204	Assumed
ψ_1	Diabetes without complication infection rate of individuals already infected with COVID-19	0.00627	Assumed
ψ_2	Diabetes with complication infection rate of individuals already infected with COVID-19	0.04358	Assumed
η_1	Recovery rate of I_{CD} from COVID-19	0.04236	Assumed
η_2	Recovery rate of I_{CC} from COVID-19	0.067	Assumed
ω_1	Rate of movement of individuals from R to D due to recovery of I_{CD} from COVID-19	0.00642	Assumed
ω_2	Rate of movement of individuals from R to C due to recovery of I_{CC} from COVID-19	0.678	Assumed
δ_1	Mortality rate due to complications	0.023	(Mekonen et al., 2021)
γ_1	Probability of developing diabetes	0.2	(Kouidere et al., 2021)
γ_2	Probability of developing diabetes at stage of complications	0.3	(Kouidere et al., 2021)
γ_3	Probability of a diabetic person developing a complication	0.01	Kouidere et al. (2020)
δ_{cd}	Induced death rate for co-infected individuals in I_{CD} compartment	0.2157	Assumed
δ_{cc}	Induced death rate for co-infected individuals in I_{CC} compartment	0.1358	Assumed
δ_2	Mortality rate due to complications of diabetic	0.001	Kouidere et al. (2020)

4.2 Model Analysis

4.2.1 COVID-19 sub-model

Without considering the infections of people with diabetes, the COVID-19 sub-model is given by

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda_1 - (\mu + \lambda)S(t), \\
\frac{dE(t)}{dt} &= \lambda S(t) - (\mu + p + r)E(t), \\
\frac{dA(t)}{dt} &= pE(t) - (\mu + \alpha_2)A(t), \\
\frac{dI_C(t)}{dt} &= rE(t) - (\mu + \delta_1 + \alpha_1)I_C(t), \\
\frac{dR(t)}{dt} &= \alpha_2 A(t) + \alpha_1 I_C(t) - \mu R(t),
\end{aligned} \tag{4.2}$$

where

$$\lambda = \frac{\beta(bA + I_C)}{N_c}.$$

For this model the total population at time t is given by

$$N_c = S(t) + E(t) + A(t) + I_C(t) + R(t)$$

Then, differentiating N with respect to time we obtain:

$$\frac{dN_c}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dA}{dt} + \frac{dI_C}{dt} + \frac{dR}{dt} = \Lambda_1 - \mu N_c - \delta_1 I_C$$

Assume there is no death due to the disease ($\delta_1 I_C = 0$), we get

$$\begin{aligned}
\frac{dN_c}{dt} &\leq \Lambda_1 - \mu N_c, \\
\frac{dN_c}{dt} + \mu N_c &\leq \Lambda_1.
\end{aligned} \tag{4.3}$$

Applying the method of integrating factor one can obtain that

$$\frac{d}{dt}(N_c e^{\mu t}) \leq \Lambda_1 e^{\mu t} \tag{4.4}$$

Integrating both sides of the Equation (4.35) and simplifying it, then we have

$$N_c(t) \leq \frac{\Lambda_1}{\mu} + ce^{-\mu t} \quad (4.5)$$

as $t \rightarrow \infty$ in Equation (4.36) the population size, $N_c \leq \frac{\Lambda_1}{\mu}$, which implies that $0 \leq N_c \leq \frac{\Lambda_1}{\mu}$. Thus, the feasible region of the system (4.2) is given by the set

$$\Omega_c = \left\{ (S, E, A, I_C, R) \in \mathbb{R}_+^5 : 0 \leq N_c \leq \frac{\Lambda_1}{\mu} \right\} \quad (4.6)$$

is positively invariant. That is,

$$\begin{aligned} \frac{dS}{dt} \Big|_{S=0} &= \Lambda_1 \geq 0, & \frac{dE}{dt} \Big|_{E=0} &= \lambda S \geq 0, & \frac{dA}{dt} \Big|_{A=0} &= pE \geq 0, \\ \frac{dI_C}{dt} \Big|_{I_C=0} &= rE, & \frac{dR}{dt} \Big|_{R=0} &= \alpha_2 A + \alpha_1 I_C \geq 0 \end{aligned}$$

Consequently, this region attracts all solutions of the system and this restricted region will be enough to consider of the dynamics of the model (4.2).

Theorem 4.2.1. *(Existence and Uniqueness of the Solution) Let $t_0 > 0$ and the initial conditions satisfies $S(0) > 0$, $E(0) > 0$, $A(0) > 0$, $I_C(0) > 0$ and $R(0) > 0$ in the prescribed region Ω_c . Then the solutions of the model system (4.2) exists and unique in $\mathbb{R}_+^5$.*

Proof. The right hand side of (4.2) can be compactly written as

$$f(X) = \begin{pmatrix} \Lambda_1 - (\mu + \lambda)S(t) \\ \lambda S(t) - (\mu + p + r)E(t) \\ pE(t) - (\mu + \alpha_2)A(t) \\ rE(t) - (\mu + \delta_1 + \alpha_1)I_C(t) \\ \alpha_2 A(t) + \alpha_1 I_C(t) - R(t) \end{pmatrix} \quad (4.7)$$

where $X = [S, E, A, I_C, R]^T$. Here, f has a continuous partial derivative with respect to each state variables in $\mathbb{R}_+^5$ and all are bounded. Thus, f is locally Lipschitz in $\mathbb{R}_+^5$. Hence, the result is the direct consequence of the Fundamental Existence and Uniqueness Theorem (1.6.2). $\square$

Theorem 4.2.2. *(Non-negativity of Solutions) If $S(0) \geq 0$, $E(0) \geq 0$, $A(0) \geq 0$, $I_C \geq 0$ and $R(0) \geq 0$, the solutions $S(t)$, $E(t)$, $A(t)$, $I_C(t)$ and $R(t)$ of the system (4.2) are positive for all $t \geq 0$.*

Proof. From the system of differential Equation (4.2), let us take the first equation

$$\frac{dS(t)}{dt} = \Lambda_1 - (\mu + \lambda)S(t).$$

This equation can be expressed without loss of generality, after eliminating the positive term Λ_1 , as an inequality

$$\frac{dS(t)}{dt} \geq -(\mu_1 + \frac{\beta(bA + I_C)}{N_c})S(t).$$

Then using separable method of variables and applying integration from 0 to t , the solution of the differentially inequality can be obtained as

$$S(t) \geq S(0)e^{-\int_0^t \left(\mu + \frac{\beta(bA + I_C)}{N_c} \right) ds},$$

where $S(0)$ is obtain from initial condition. Since this exponential function is always non-negative, we can concluded that

$$S(t) \geq 0.$$

We can do similarly for $E(t)$ as follows,

$$\begin{aligned} \frac{dE(t)}{dt} &= \lambda S(t) - (\mu + p + r)E(t), \\ \frac{dE(t)}{dt} &\geq -(\mu + p + r)E(t), \\ \frac{dE(t)}{E(t)} &\geq -(\mu + p + r)dt. \end{aligned}$$

By the same approach one can easily obtain that

$$E(t) \geq E(0)e^{-(\mu+p+r)t}, \quad (4.8)$$

where $E(0)$ is obtain from initial condition. Clearly from (4.8) one can get that

$$E(t) \geq 0.$$

In a similar procedure,

$$\begin{aligned} A(t) &\geq A(0)e^{-(\mu+\alpha_2)t} \geq 0, \\ I_C(t) &\geq I_C(0)e^{-(\mu+\delta_1+\alpha_1)t} \geq 0, \\ R(t) &\geq R(0)e^{-\mu t} \geq 0, \end{aligned}$$

The proof is completed. □

4.2.2 COVID-19 Free Equilibrium Point

COVID-19 free equilibrium points are steady-state solutions where there is no COVID-19 infection. That is, all the infected classes are zero and the entire population comprise of

only susceptible individuals. To find the COVID-19 FEP, we equate the left hand side of the system (4.2) equal to zero at $E(t) = 0$, $I_C(t) = 0$ and $A(t) = 0$ to obtain COVID-19 FEP denoted by E_{0c} is given as

$$\begin{cases} \Lambda_1 - (\mu + \lambda)S(t) = 0, \\ \lambda S(t) - (\mu + p + r)E(t) = 0, \\ pE(t) - (\mu + \alpha_2)A(t) = 0, \\ rE(t) - (\mu + \delta_1 + \alpha_1)I_C(t) = 0, \\ \alpha_2 A(t) + \alpha_1 I_C(t) - \mu R(t) = 0, \end{cases}$$

solving for the non-infected state variable, we obtain the disease free equilibrium point

$$E_{0c} = \{S^0, E^0, A^0, I_C^0, R^0\} = \left\{ \frac{\Lambda_1}{\mu}, 0, 0, 0, 0 \right\}.$$

4.2.3 The Basic Reproduction Number for COVID-19 submodel

In this section, we determined the basic reproduction number for COVID-19 submodel, we use the next generation method given in (Van den Driessche & Watmough, 2002). It is the largest (dominant) eigenvalue (spectral radius) of the expression

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

In this method, first we rewrite the model equations, starting with newly infective classes

$$\begin{aligned} \frac{dE}{dt} &= \lambda S(t) - (\mu + p + r)E(t) \\ \frac{dA}{dt} &= pE(t) - (\mu + \alpha_2)A(t) \\ \frac{dI_C}{dt} &= rE(t) - (\mu + \delta_1 + \alpha_1)I_C(t) \end{aligned} \tag{4.9}$$

For this model, the associated matrices $\mathcal{F}$ and $\mathcal{V}$ the new infectious terms and the remaining transition terms are respectively given by

$$\mathcal{F}_i = \begin{bmatrix} \frac{\beta(bA + I_C)}{N_c} \\ 0 \\ 0 \end{bmatrix} \text{ and } \mathcal{V}_i = \begin{bmatrix} (\mu + p + r)E \\ (\mu + \alpha_2)A(t) - pE \\ (\mu + \delta_1 + \alpha_1)I_C - rE \end{bmatrix}.$$

The Jacobian matrices at the disease-free equilibrium point of $\mathcal{F}_i$ and $\mathcal{V}_i$ are obtained by derivating with respect to E, A and I_c . The result becomes

$$F(E_{0c}) = \begin{bmatrix} 0 & \beta b & \beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and } V(E_{0c}) = \begin{bmatrix} \mu + p + r & 0 & 0 \\ -p & \mu + \alpha_2 & 0 \\ -r & 0 & \mu + \delta_1 + \alpha_1 \end{bmatrix}$$

Let $k_1 = \mu + p + r$, $k_2 = \mu + \alpha_2$ and $k_3 = \mu + \delta_1 + \alpha_1$.

$$|V(E_{0c})| = \begin{vmatrix} k_1 & 0 & 0 \\ -p & k_2 & 0 \\ -r & 0 & k_3 \end{vmatrix} = k_1 k_2 k_3 \neq 0.$$

Hence, the matrix $\mathcal{V}(E_{0c})$ is invertible and thus

$$V(E_{0c})^{-1} = \begin{bmatrix} \frac{1}{k_1} & 0 & 0 \\ \frac{p}{k_1 k_2} & \frac{1}{k_2} & 0 \\ \frac{r}{k_1 k_3} & 0 & \frac{1}{k_3} \end{bmatrix}. \quad (4.10)$$

Moreover,

$$F(E_{0c})V(E_{0c})^{-1} = \begin{bmatrix} \frac{k_3 \beta p b + k_2 \beta r}{k_1 k_2 k_3} & \frac{\beta b}{k_2} & \frac{\beta}{k_3} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad (4.11)$$

Since F is non-negative and V is non-singular, then V^{-1} is non-negative and FV^{-1} is non-negative. The matrix FV^{-1} is called next generation matrix for the model (Van den Driessche & Watmough, 2002). The eigenvalues of the matrix FV^{-1} can be computed as

$\det(FV^{-1} - \lambda I) = |FV^{-1} - \lambda I| = 0$. Equivalently,

$$|FV^{-1} - \lambda I| = \begin{vmatrix} \frac{k_3\beta pb + k_2\beta r}{k_1k_2k_3} - \lambda & \frac{\beta b}{k_2} & \frac{\beta}{k_3} \\ 0 & 0 - \lambda & 0 \\ 0 & 0 & 0 - \lambda \end{vmatrix} \quad (4.12)$$

After simple manipulation, the eigenvalues are: $\lambda_1 = 0$, $\lambda_2 = 0$ and $\lambda_3 = \frac{k_3\beta pb + k_2\beta r}{k_1k_2k_3}$. Where $k_1 = \mu + p + r$, $k_2 = \mu + \alpha_2$ and $k_3 = \mu + \delta_1 + \alpha_1$. Finally, the basic reproductive number of COVID-19 submodel is given by:

$$R_{0c} = \frac{(\mu + \delta_1 + \alpha_1)\beta pb + (\mu + \alpha_2)\beta r}{(\mu + p + r)(\mu + \alpha_2)(\mu + \delta_1 + \alpha_1)}$$

4.2.4 Endemic Equilibrium Point for COVID-19 sub-model

The Endemic equilibrium point which denoted by E_c^1 is a steady state solution where the disease persists in the population. It can be obtained by setting the left hand side in (4.2) equal to zero. That means

$$\begin{cases} \Lambda_1 - (\mu + \lambda)S^*(t) = 0, \\ \lambda S^*(t) - (\mu + p + r)E^*(t) = 0, \\ pE^*(t) - (\mu + \alpha_2)A^*(t) = 0, \\ rE^*(t) - (\mu + \delta_1 + \alpha_1)I_C^*(t) = 0, \\ \alpha_2 A^*(t) + \alpha_1 I_C^*(t) - \mu R^*(t) = 0. \end{cases}$$

Solving the system of equation we obtain we can get the values of endemic equilibrium point.

$$S^* = \frac{k_1}{\lambda} E^* = \frac{k_1 N_c^*}{\beta(bA^* + I_C^*)} E^* \quad (4.13)$$

$$A^* = \frac{p}{k_2} E^* \quad (4.14)$$

$$I_C^* = \frac{r}{k_3} E^* \quad (4.15)$$

$$R^* = \frac{1}{\mu} \left(\frac{\alpha_2 p}{k_2} + \frac{\alpha_1 r}{k_3} \right) E^* \quad (4.16)$$

Next, S^* by inserting (4.14) and (4.15) into (4.13) one can get that,

$$S^* = \frac{k_1 k_2 k_3 N_c^*}{\beta(bpk_3 + rk_2)} \quad (4.17)$$

Since

$$R_{0c} = \frac{\beta(bpk_3 + rk_2)}{k_1 k_2 k_3},$$

$$S^* = \frac{N_c^*}{R_{0c}}. \quad (4.18)$$

By substitute one equation in to other we can obtain that,

$$E^* = \frac{\Lambda_1 k_2 k_3}{\beta(k_3 pb + k_2 r)} (R_{0c} - 1) \quad (4.19)$$

$$A^* = \frac{\Lambda_1 p k_3}{\beta(k_3 pb + k_2 r)} (R_{0c} - 1) \quad (4.20)$$

$$I_C^* = \frac{\Lambda_1 r k_2}{\beta(k_3 pb + k_2 r)} (R_{0c} - 1) \quad (4.21)$$

$$R^* = \frac{\Lambda_1 (\alpha_2 k_3 p + \alpha_1 k_2 r)}{\mu_1 \beta(k_3 pb + k_2 r)} (R_{0c} - 1) \quad (4.22)$$

4.2.5 Stability Analysis for COVID-19 submodel

Local stability of COVID-19 Free Equilibrium Point

Theorem 4.2.3. *The disease-free equilibrium E_{0c} of the system ((4.2)) is locally asymptotically stable if $R_{0c} < 1$.*

Proof. The Jacobian matrix at the disease-free equilibrium E_0 of the system (4.2) is

$$J(E_{0c}) = \begin{bmatrix} -(\mu + \frac{\beta(bA + I_C)}{N_C}) & 0 & -\frac{\beta bS}{N_c} & -\frac{\beta S}{N_C} & 0 \\ \frac{\beta(bA + I_C)}{N_C} & -k_1 & \frac{\beta bS}{N_c} & \frac{\beta S}{N_C} & 0 \\ 0 & p & -k_2 & 0 & 0 \\ 0 & r & 0 & -k_3 & 0 \\ 0 & 0 & \alpha_2 & \alpha_1 & -\mu \end{bmatrix} \quad (4.23)$$

Where $k_1 = \mu + p + r$, $k_2 = \mu + \alpha_2$ and $k_3 = \mu + \delta_1 + \alpha_1$. The eigenvalues of $J(E_{0c})$ are the

solutions of the characteristics equation $\det(J(E_{0c}) - \lambda I_5) = 0$ where I_5 is identity matrix of order 5. Then we have,

$$\left| J(E_{0c}) - \lambda I_5 \right| = \begin{vmatrix} -\mu - \lambda & 0 & -\beta b & -\beta & 0 \\ 0 & -k_1 - \lambda & \beta b & \beta & 0 \\ 0 & p & -k_2 - \lambda & 0 & 0 \\ 0 & r & 0 & -k_3 - \lambda & 0 \\ 0 & 0 & \alpha_2 & \alpha_1 & -\mu - \lambda \end{vmatrix} = 0$$

The corresponding characteristic equation has the following form:

$$(\mu + \lambda)^2 [\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3] = 0, \quad (4.24)$$

where

$$a_1 = k_1 + k_2 + k_3,$$

$$a_2 = k_1 k_3 + k_1 k_2 + k_2 k_3 - \beta p b - \beta r,$$

$$a_3 = k_1 k_2 k_3 - \beta p b k_3 - \beta r k_2 = k_1 k_2 k_3 (1 - R_{0c}).$$

Then solving Equation (4.24) we obtain

$$(\mu + \lambda)^2 = 0 \quad \text{or} \quad \lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0.$$

It can be observed that the first two eigenvalues $\lambda_1 = \lambda_2 = -\mu$ are negative. To determine the sign of the remaining three eigenvalues we use the Routh-Hurwitz criteria (Merkin, 1997) for the third order equation; $\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0$. According to the Routh-Hurwitz criteria the three roots of a polynomial of order three of the type $\rho(\lambda) = \lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3$ are real distinct and negative if the coefficients satisfy the conditions $a_1 > 0$, $a_2 > 0$, $a_3 > 0$ and $a_1 a_2 - a_3 > 0$. With this in mind,

let us check the conditions as follows:

- $a_1 > 0 \implies k_1 + k_2 + k_3 > 0$ because all parameters are positive and their sum is also positive.
- $a_2 > 0 \implies k_1 k_3 + k_1 k_2 + k_2 k_3 - \beta p b - \beta r > 0 \implies a_2 > 0$, **holds if** $k_1 k_3 + k_1 k_2 + k_2 k_3 > \beta p b + \beta r$
- $a_3 > 0 \implies k_1 k_2 k_3 - \beta p b k_3 - \beta r k_2 > 0 = k_1 k_2 k_3 (1 - \frac{\beta(k_3 p b + k_2 r)}{k_1 k_2 k_3}) > 0$. Hence $a_3 > 0$ if $R_{0c} < 1$ holds.
- Lastly $a_1 a_2 > a_3 \implies a_1 a_2 - a_3 > 0$

This implies those remained three eigenvalues are also real distinct and negative for $R_{0c} < 1$. Therefore, the disease free equilibrium point E_0 of the COVID-19 sub-model (4.2) is locally asymptotically stable if $R_{0c} < 1$. $\square$

Global Stability of the COVID-19 Free Equilibrium Point

Theorem 4.2.4. *The disease free equilibrium of the system (4.2) is globally asymptotically stable if $R_{0c} < 1$.*

Proof. To establish the global stability of the disease-free equilibrium point, we construct a Lyapunov function

$L(S, E, A, I_C, R) : \Omega_c \subset \mathbb{R}_+^5 \rightarrow \mathbb{R}^+$ defined as,

$$L = C_1 E + C_2 A + C_3 I_C \quad (4.25)$$

where C_1 , C_2 and C_3 are positive constants. Then the function $L(S, E, A, I_C, R)$ should satisfies the following three condition

- L is continuously differentiable
- $L > 0, \forall (S, E, A, I_C, R) \in \Omega_c - E_{0c}$ and $L(E_{0c}) = 0$.
- $\frac{dL}{dt} \leq 0$ in Ω_c . Then E_{0c} is stable.

Clearly, the first two condition holds since L is nonnegative in Ω_c except at E_0 and $L(E_0) = 0$. Now let us check the third condition $\frac{dL}{dt} \leq 0$. Now differentiating L with respect to time we obtain

$$\begin{aligned} \frac{dL}{dt} &= C_1 \frac{dE}{dt} + C_2 \frac{dA}{dt} + C_3 \frac{dI_C}{dt} \\ \frac{dL}{dt} &= C_1 \left(\frac{\beta(bA + I_C)}{N_c} S - k_1 E(t) \right) + C_2 (pE(t) - k_2 A(t)) + C_3 (rE(t) - k_3 I_C(t)) \\ &\leq C_1 (\beta b A + \beta I_C - K_1 E) + C_2 (pE - k_2 A) + C_3 (rE - k_3 I_C), \quad \text{since } S \leq N_c \\ &= C_1 k_1 \left(\frac{C_2 p + C_3 r}{C_1 k_1} - 1 \right) E + (C_1 \beta b - C_2 k_2) A + (C_1 \beta - C_3 k_3) I_C \end{aligned} \quad (4.26)$$

Suppose $C_1 = \frac{C_2 k_2}{\beta b}$ and $C_3 = \frac{C_2 k_2 \beta}{\beta b k_3}$ and substitute in to (4.26) we can get

$$= \frac{C_2 k_1 k_2}{\beta b} \left(\frac{C_2 \beta p b k_3 + C_2 \beta k_2 r}{C_2 k_1 k_2 k_3} - 1 \right) E + 0$$

$$= \frac{C_2 k_1 k_2}{\beta b} \left(\frac{\beta p b k_3 + C_2 \beta k_2 r}{k_1 k_2 k_3} - 1 \right) E$$

$$\frac{dL}{dt} = \frac{C_2 k_1 k_2}{\beta b} (R_{0c} - 1) E$$

Hence $\frac{dL}{dt} \leq 0$ for $R_{0c} < 1$ and $\frac{dL}{dt} = 0$ if and only if $E = 0$. Therefore the largest compact invariant set in Ω_c is the singleton set $\left(\frac{\Lambda_1}{\mu}, 0, 0, 0, 0 \right)$, by La Salle (1976), every solution to equations of model (4.2) with initial conditions in Ω_c which approaches the disease-free equilibrium point as time t tends to infinity whenever $R_{0c} < 1$. This implies that the disease-free equilibrium is globally asymptotically stable in Ω_c . $\square$

Local stability of the Endemic Equilibrium

Theorem 4.2.5. *The Endemic Equilibrium point E_c^1 of the system (4.2) is locally asymptotically stable if $R_{0c} > 1$.*

Proof. To obtain the local stability of E_c^1 , the Jacobian matrix (4.27) of the model equations computed under local stability of DFE is used at E_c^1 . Thus, the jacobian matrix at E_c^1 becomes

$$J = \begin{bmatrix} -\left(\mu + \frac{\beta(bA^* + I_C^*)}{N_C}\right) & 0 & -\frac{\beta b S^*}{N_c} & -\frac{\beta S^*}{N_C} & 0 \\ \frac{\beta(bA^* + I_C^*)}{N_C} & -k_1 & \frac{\beta b S^*}{N_c} & \frac{\beta S^*}{N_C} & 0 \\ 0 & p & -k_2 & 0 & 0 \\ 0 & r & 0 & -k_3 & 0 \\ 0 & 0 & \alpha_2 & \alpha_1 & -\mu \end{bmatrix} \quad (4.27)$$

$$J(E_c^1) = \begin{bmatrix} -(\mu R_{0c}) & 0 & -\frac{\beta b}{R_{0c}} & -\frac{\beta}{R_{0c}} & 0 \\ (R_{0c} - 1)\mu_1 & -k_1 & \frac{\beta b}{R_{0c}} & \frac{\beta}{R_{0c}} & 0 \\ 0 & p & -k_2 & 0 & 0 \\ 0 & r & 0 & -k_3 & 0 \\ 0 & 0 & \alpha_2 & \alpha_1 & -\mu \end{bmatrix}$$

Where $k_1 = \mu + p + r$, $k_2 = \mu + \alpha_2$ and $k_3 = \mu + \delta_1 + \alpha_1$. The eigenvalues of $J(E_c^1)$ are the solutions of the characteristics equation $|J(E_c^1) - \lambda I_5| = 0$ where I_5 is identity matrix of order 5. Then we have

$$|J(E_c^1) - \lambda I_5| = \begin{vmatrix} (-\mu R_{0c} - \lambda) & 0 & -\frac{\beta b}{R_{0c}} & -\frac{\beta}{R_{0c}} & 0 \\ (R_{0c} - 1)\mu & -k_1 - \lambda & \frac{\beta b}{R_{0c}} & \frac{\beta}{R_{0c}} & 0 \\ 0 & p & -k_2 - \lambda & 0 & 0 \\ 0 & r & 0 & -k_3 - \lambda & 0 \\ 0 & 0 & \alpha_2 & \alpha_1 & -\mu - \lambda \end{vmatrix}$$

After computing determinant of the 5×5 matrix above, lastly we obtain the following characteristic equation

$$(\mu + \lambda) [\lambda^4 + A_1 \lambda^3 + A_2 \lambda^2 + A_3 \lambda + A_4] = 0 \quad (4.28)$$

where

$$A_1 = \mu R_{0c}$$

$$A_2 = \mu R_{0c}k_1 + \mu R_{0c}k_2 + \mu R_{0c}k_3 + k_1 + k_2 + k_3 - \frac{\beta(bp + r)}{R_{0c}}$$

$$A_3 = \mu R_{0c}k_1k_2 + \mu R_{0c}k_1k_2 + \mu R_{0c}k_2k_3 + k_1k_2 + k_1k_3 + k_2k_3 - \frac{\beta(bpk_3 + bp\mu + rk_2)}{R_{0c}}$$

$$A_4 = \mu R_{0c}k_1k_2k_3 - \left(\beta rk_2\mu + \frac{\beta bpk_3\mu}{R_{0c}} \right)$$

Clearly, from the Equation (4.28) we have $\lambda_1 = -\mu$ and $\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0$. Thus, the first eigenvalues λ_1 is negative since all the parameter are positive. To determine the sign of the remaining four eigenvalues we apply the Routh-Hurwitz criteria (Merkin, 1997) for the polynomial equation

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0.$$

The Routh-Hurwitz criteria implies that the roots of the eigen polynomial

$$\rho(\lambda) = \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4$$

are real distinct and negative if the coefficients satisfy the conditions $A_i > 0$ for $i = 1, 2, 3, 4, 5$ and the determinant of $\rho(\lambda) > 0$. It is straight forward to verify that this conditions are satisfied and hence the last four eigenvalues are real distinct and negative. That is

- $A_1 > 0 \implies \mu R_{0c} > 0$ if and only if $R_{0c} > 0$,
- $A_2 > 0 \implies \mu R_{0c}k_1 + \mu R_{0c}k_2 + \mu R_{0c}k_3 + k_1 + k_2 + k_3 - \frac{\beta(bp + r)}{R_{0c}} > 0$,
That is true if $\mu R_{0c}k_1 + \mu R_{0c}k_2 + \mu R_{0c}k_3 + k_1 + k_2 + k_3 > \frac{\beta(bp + r)}{R_{0c}}$,
- $A_3 > 0 \implies \mu R_{0c}k_1k_2 + \mu R_{0c}k_1k_2 + \mu R_{0c}k_2k_3 + k_1k_2 + k_1k_3 + k_2k_3 - \frac{\beta(bpk_3 + bp\mu + rk_2)}{R_{0c}} > 0$,
 $\implies \mu R_{0c}k_1k_2 + \mu R_{0c}k_1k_2 + \mu R_{0c}k_2k_3 + k_1k_2 + k_1k_3 + k_2k_3 > \frac{\beta(bpk_3 + bp\mu + rk_2)}{R_{0c}}$,
- $A_4 > 0 \implies \mu R_{0c}k_1k_2k_3 - \left(\beta rk_2\mu + \frac{\beta bpk_3\mu}{R_{0c}} \right) > 0$,
 $\implies \mu R_{0c}k_1k_2k_3 > \left(\beta rk_2\mu + \frac{\beta bpk_3\mu}{R_{0c}} \right)$.

and determinants

$$D_1 = A_1 > 0$$

$$D_2 = A_1 A_2 > 0$$

$$D_3 = A_1 A_2 - A_3 > 0$$

$$D_4 = A_1 A_2 A_3 - A_3^2 - A_1^2 A_4 > 0$$

Therefore the system 4.2 become local asymptotically stable at endemic equilibrium E_c^1 if $R_{0c} > 1$. With this we complete the proof. $\square$

Global stability of the Endemic Equilibrium Point

Theorem 4.2.6. *The endemic equilibrium point of the model Equation (4.2) is globally asymptotically stable if $R_{0c} > 1$.*

Proof. To establish this result define the Lyapunov function L by

$$L(S^*, E^*, A^*, I_C^*, R^*) = [S - S^* - S^* \ln(\frac{S}{S^*})] + [E - E^* - E^* \ln(\frac{E}{E^*})] + [A - A^* - A^* \ln(\frac{A}{A^*})] \\ + [I_C - I_C^* - I_C^* \ln(\frac{I_C}{I_C^*})] + [R - R^* - R^* \ln(\frac{R}{R^*})].$$

Differentiating L with respect to time t we obtain

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right) \frac{dS}{dt} + \left(1 - \frac{E^*}{E}\right) \frac{dE}{dt} + \left(1 - \frac{A^*}{A}\right) \frac{dA}{dt} + \left(1 - \frac{I_C^*}{I_C}\right) \frac{dI_C}{dt} + \left(1 - \frac{R^*}{R}\right) \frac{dR}{dt} \\ \frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right) (\Lambda_1 - (\mu + \lambda)) + \left(1 - \frac{E^*}{E}\right) (\lambda S - (\mu + p + r)E) + \left(1 - \frac{A^*}{A}\right) \\ (pE - (\mu + \alpha_2)A) + \left(1 - \frac{I_C^*}{I_C}\right) (rE - (\mu + \delta_1 + \alpha_1)I_C) + \left(1 - \frac{R^*}{R}\right) (\alpha_2 A + \alpha_1 I_C(t) - \mu R) \\ \frac{dL}{dt} = (\Lambda_1 - (\mu + \lambda)S) - S^* \Lambda_1 + S^* \mu S + S^* \lambda S + [(\lambda S - (\mu + p + r)E) - \frac{E^*}{E} \lambda S + E^* \mu + E^* p \\ + E^* r] + [(pE - (\mu + \alpha_2)A) - \frac{A^*}{A} pE - A^* \mu + A^* \alpha_2] + [(rE - (\mu + \delta_1 + \alpha_1)I_C) - \frac{I_C^*}{I_C} (rE + I_C^* \mu \\ + I_C^* \delta_2 + I_C^* \alpha_1)] + [(\alpha_2 A + \alpha_1 I_C(t) - \mu R) - \frac{R^*}{R} \alpha_2 A - \frac{R^*}{R} \alpha_1 I_C(t) + R^* \mu R]$$

After mathematical manipulation and collecting like terms it becomes

$$= [(\lambda + \mu)S^* + k_1 E^* + k_2 A^* + k_3 I_C^* + \mu_1 R^*] - [\Lambda_1 \frac{S^*}{S} + \lambda S \frac{E^*}{E} + pE \frac{A^*}{A} + rE \frac{I_C^*}{I_C} + \alpha_2 A \frac{R^*}{R} + \alpha_1 \frac{R^*}{R} \\ + \delta_1 I_C]$$

Setting

$$A = (\lambda + \mu)S^* + k_1E^* + k_2A^* + k_3I_C^* + \mu R^*$$

$$B = \Lambda_1 \frac{S^*}{S} + \lambda S \frac{E^*}{E} + pE \frac{A^*}{A} + rE \frac{I_C^*}{I_C} + \alpha_2 A \frac{R^*}{R} + \alpha_1 \frac{R^*}{R} + \delta_1 I_C$$

Compactly this becomes

$$\frac{dL}{dt} = A - B$$

Thus, we get $\frac{dL}{dt} \leq 0$ if $A < B$ and $\frac{dL}{dt} = 0$ if $A = B$, this holds if $S = S^*$, $E = E^*$, $A = A^*$, $I_C = I_C^*$ and $R = R^*$.

Therefore, the largest compact invariant set $\left\{ (S^*, E^*, A^*, I_C^*, R^*) \in \Omega_c; \frac{dL}{dt} = 0 \right\}$. Thus by La Salle (1976), E_c^1 is globally asymptotically stable in the set Ω_c for $A < B$ and $R_{0c} > 1$. $\square$

4.2.6 Sensitivity analysis for COVID-19 sub-model

Sensitivity analysis is a statistical technique that can be applied to mathematical or computational model to provide insight on how uncertainty in the input variables affect the model outputs and which input variables tends to drive variation in the outputs to achieve the desired goals (Powell et al., 2005). We compute the sensitivity indices of the basic reproductive number R_{0c} to the parameters in the model. These indices allow us how important each parameter is to disease transmission. Sensitivity analysis is mainly utilized to describe the robustness of model forecasting to the parameter values (since there are usually errors in the collection of data and presumed model parameter values) (Chitnis et al., 2008). Here, we perform a sensitivity analysis of the basic reproductive number R_{0c} to quantify the fluctuations in the $SEAI_C R$ model parameters. Now from this, we can identify the parameters that have a high impact on the basic reproduction number as well as on the disease transmission. Sensitivity indices permit us to quantify the relative change in a state variable when a parameter alters.

To perform sensitivity of R_{0c} we use the normalized forward sensitivity index of a variable to a parameter which is the ratio of the relative change in the variable to the relative change in the parameter. The explicit expression of R_{0c} is given by

$$R_{0c} = \frac{\beta[(\mu + \alpha_1)pb + (\mu + \delta_2 + \alpha_2)r]}{(\mu + p + r)(\mu + \alpha_2)(\mu + \delta_1 + \alpha_1)}.$$

The reproduction number above contains thirteen parameters and we compute the normalized forward sensitivity index for each parameters of R_{0c} .

Definition 4.2.1. (Rodrigues et al., 2013). The normalized forward sensitivity index of R_0 , which is differentiable with respect to a given parameter, w , is defined as:

$$\phi_w^{R_0} = \frac{\partial R_0}{\partial w} \times \frac{w}{R_0}. \quad (4.29)$$

By using Equation (4.29) we compute the normalized forward sensitivity indices of the model parameters as follows:

$$\begin{aligned} \phi_{\beta}^{R_{0c}} &= \frac{\partial R_{0c}}{\partial \beta} \times \frac{\beta}{R_{0c}} = 1, \\ \phi_p^{R_{0c}} &= \frac{\partial R_{0c}}{\partial p} \times \frac{p}{R_{0c}}. \\ &= \frac{p\beta[b(\mu + p + r)(\mu + \alpha_2)(\mu + \delta_1 + \alpha_1)^2 - [(\mu + \delta_1 + \alpha_1)pb + (\mu + \alpha_2)r](\mu + \alpha_2)(\mu + \delta_1 + \alpha_1)]}{(\mu + p + r)(\mu + \alpha_2)(\mu + \delta_1 + \alpha_1)\beta[(\mu + \delta_1 + \alpha_1)pb + (\mu + \alpha_2)r]} \end{aligned}$$

Similarly, we compute for the rest parameters and over all the sensitivity indices of the model parameters are summarized in Table 4.3.

Table 4.3: The normalized forward sensitivity indices of R_{0c} to model parameters evaluated at the baseline parameter values listed in Table.

Parameters	Description	Sensitivity indices
β	Effective contact rate of infection	1
r	Rate at which $E(t)$ moves to $I(t)$ class	+0.07575
b	Rate of transmission from $I(t)$ to $S(t)$	+0.1459
p	Rate of $E(t)$ enter into $A(t)$ class	-0.0313
μ	The natural death rate	-0.098266
α_1	Treatment rate for $I(t)$	-0.6560
α_2	Treatment rate $A(t)$ to $R(t)$	-0.1461
δ_1	Diseases induced mortality rate for $I(t)$	-0.1917

From the above Table (4.3) based on sign of the values of the parameters those with positive indices, β , b and r show that they have great impact on expanding the disease in the population. Due to if their values are increasing(decreasing) by some percentage then, the basic reproduction number R_{0c} increase(decrease) by the same percentage. For instance, if the parameter value of β increase for 10% then the value of R_{0c} will increase for 11.7%. In contrary, parameters p , μ , α_1 , α_2 and δ_1 those whose their sensitivity indices are negative have an influence of minimizing the spread of the disease in the community. Due to as their values increase by some percentage then, the basic reproduction number R_{0c} decreases. For instance the value of α_2 increase for 10% then the value of R_{0c} will decrease for 2.94%.

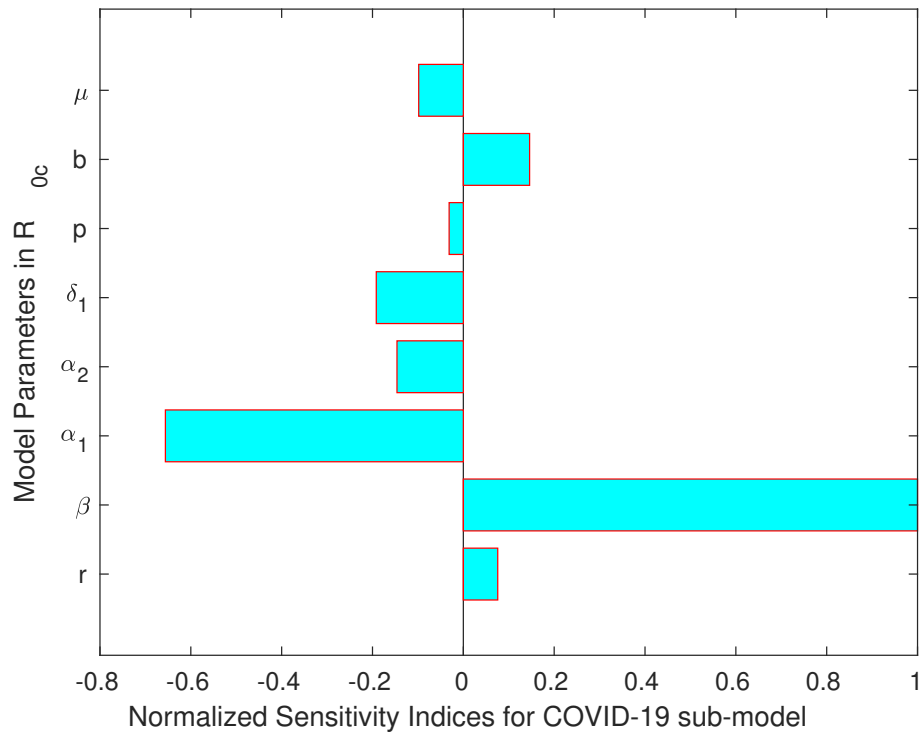


Figure 4.2: Normalized sensitivity indices of R_{0c} with respect to parameters of the model (4.2). Parameter values are taken from Table 4.3.

4.2.7 Bifurcation analysis of the COVID-19 sub-model

Using Castillo-Chavez & Song (2004) approach , we can identify the possibility of bifurcation occur for our system (4.2) at $R_{0c} = 1$ by choosing parameter from R_{0c} as $S = x_1$, $E = x_2$, $A = x_3$, $I_c = x_4$, $R = x_5$ and $N_c = x_1 + x_2 + x_3 + x_4 + x_5$. Moreover, by using vector notation $x = (x_1, x_2, x_3, x_4, x_5)^T$. Then the system (4.2) can be re-written in the form $\frac{dx}{dt} = (f_1, f_2, f_3, f_4, f_5)^T$.

$$\begin{aligned}
 \frac{dx_1}{dt} &= \Lambda_1 - (\mu + \lambda)x_1 = f_1, \\
 \frac{dx_2}{dt} &= \lambda x_1 - (\mu + p + r)x_2 = f_2, \\
 \frac{dx_3}{dt} &= p x_2 - (\mu + \alpha_2)x_3 = f_3, \\
 \frac{dx_4}{dt} &= r x_2 - (\mu + \delta_1 + \alpha_1)x_4(t) = f_4, \\
 \frac{dx_5}{dt} &= \alpha_2 x_3 + \alpha_1 x_4(t) - \mu x_5 = f_5.
 \end{aligned}
 \tag{4.30}$$

If we choose $\beta = \beta^*$ as bifurcation parameter, then at $R_{0c} = 1$ we get $\beta = \beta^* = \frac{k_1 k_2 k_3}{(\mu + \delta_1 + \alpha_1)pb + (\mu + \alpha_2)r}$. The disease free equilibrium is given by,

$$E_{0c} = (x_1^* = \frac{\Lambda_1}{\mu}, x_2^* = 0, x_3^* = 0, x_4^* = 0, x_5^* = 0).$$

Then the linearization matrix of system (4.30) at E_{0c} when $\beta = \beta^*$ is given by

$$|J(E_{0c}, \beta^*)| = \begin{vmatrix} -\mu & 0 & -\frac{k_1 k_2 k_3}{k_3 pb + k_2 r} b & -\frac{k_1 k_2 k_3}{k_3 pb + k_2 r} & 0 \\ 0 & -k_1 & \frac{k_1 k_2 k_3}{k_3 pb + k_2 r} b & \frac{k_1 k_2 k_3}{k_3 pb + k_2 r} & 0 \\ 0 & p & -k_2 & 0 & 0 \\ 0 & r & 0 & -k_3 & 0 \\ 0 & 0 & \alpha_2 & \alpha_1 & -\mu \end{vmatrix}$$

Clearly, 0 is eigenvalue of $J(E_{0c}, \beta^*)$ obtained at β^* after some computation or by substituting in characteristic equation. To compute the right eigenvector, $w = (w_1, w_2, w_3, w_4, w_5)^T$, we consider the system $J(E_{0c}, \beta^*)w = 0$. Then the system becomes

$$\begin{aligned} -\mu w_1 - \frac{k_1 k_2 k_3}{k_3 pb + k_2 r} b w_3 - \frac{k_1 k_2 k_3}{k_3 pb + k_2 r} w_4 &= 0, \\ -k_2 w_2 + \frac{k_1 k_2 k_3}{k_3 pb + k_2 r} b w_3 + \frac{k_1 k_2 k_3}{k_3 pb + k_2 r} w_4 &= 0, \\ p w_2 - k_2 w_3 &= 0, \\ r w_2 - k_3 w_4 &= 0, \\ \alpha_2 w_3 + \alpha_1 w_1 - \mu w_5 &= 0. \end{aligned} \tag{4.31}$$

From system (4.31) we obtain

$$w_1 = \frac{-k_1 w_2}{\mu}, w_3 = \frac{p w_2}{k_2}, w_2 = w_2 > 0, w_4 = \frac{r w_2}{k_3} \text{ and } w_5 = \frac{\alpha_2 \mu p - \alpha_1 k_1 k_2}{k_2 \mu^2}.$$

Next we compute the left eigenvector, $v = (v_1, v_2, v_3, v_4, v_5)$ from $v \cdot J(E_0, \beta^*) = 0$ and the sys-

tem becomes

$$\begin{aligned}
& -\mu v_1 = 0, \\
& -k_1 v_2 + p v_3 + r v_4 = 0, \\
& -\frac{k_1 k_2 k_3}{k_3 p b + k_2 r} b v_1 + \frac{k_1 k_2 k_3}{k_3 p b + k_2 r} b v_2 - k_2 v_3 + \alpha_2 v_5 = 0, \\
& -\frac{k_1 k_2 k_3}{k_3 p b + k_2 r} v_1 + \frac{k_1 k_2 k_3}{k_3 p b + k_2 r} v_2 - k_3 v_4 + \alpha_1 v_5 = 0, \\
& -\mu v_5 = 0.
\end{aligned} \tag{4.32}$$

From system (4.32) we obtain

$v_1 = v_5 = 0$, $v_3 = \frac{k_1 k_3 v_2}{k_3 p b + k_2 r}$, $v_4 = \frac{k_1 k_2 v_2}{k_3 p b + k_2 r}$. where v_2 is calculated to ensure that the eigenvectors satisfy the condition $v \cdot w = 1$. Since $v_1 = v_5 = 0$ from the component of v and all partial derivative of f_1 and f_5 are zero for $i, j = 1, 2, 3, 4, 5$ we don't need to compute derivatives of f_1 and f_5 . Thus, we evaluate a and b by substituting non zero partial derivative of f_2 , f_3 and f_4 only in to the formula.

From the partial derivatives of f_2 , f_3 and f_4 the only ones that are nonzero are the following:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \frac{\beta^* b \mu}{\Lambda_1}, \quad \frac{\partial^2 f_2}{\partial x_1 \partial x_4} = \frac{\partial^2 f_2}{\partial x_4 \partial x_1} = \frac{\beta^* \mu}{\Lambda_1},$$

with

$$\frac{\partial^2 f_2}{\partial x_1 \partial \beta^*} = \frac{\mu}{\Lambda_1} (b x_3^* + x_4^*), \quad \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = \frac{\mu}{\Lambda_1} (b x_3^*) \quad \frac{\partial^2 f_2}{\partial x_4 \partial \beta^*} = \frac{\mu x_1^*}{\Lambda_1}$$

and all the other partial derivatives of f_2 are zero. The direction of the bifurcation at $R_{0c} = 1$ is determined by the signs of the bifurcation coefficients a and b , obtained from the above partial derivatives as follows:

$$\begin{aligned}
a &= v_2 \sum_{i,j=1}^5 w_i w_j \frac{\partial^2 f}{\partial x_i \partial x_j} (E_0, \beta^*) \\
a &= 2v_2 w_1 w_4 \frac{\beta^* \mu}{\Lambda_1} + 2v_2 w_1 w_3 \frac{\beta^* b \mu}{\Lambda_1} \\
a &= 2v_2 \frac{-k_1 w_2}{\mu} \frac{r w_2}{k_3} \frac{\beta^* \mu}{\Lambda_1} + 2v_2 \frac{-k_1 w_2}{\mu} \frac{p w_2}{k_2} \frac{\beta^* b \mu}{\Lambda_1} \\
&= -2\beta^* k_1 \frac{k_2 r + b p k_3}{\Lambda_1 k_2 k_3} v_2 w_2^2 < 0
\end{aligned}$$

$$\begin{aligned}
 b &= \sum_{i=1}^5 v_2 w_i \frac{\partial^2 f_2}{\partial x_i \partial \beta^*}(E_0, \beta^*) \\
 &= v_2 w_1 \frac{\partial^2 f_2}{\partial x_1 \partial \beta^*} + v_2 w_3 \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} + v_2 w_4 \frac{\partial^2 f_2}{\partial x_4 \partial \beta^*} \\
 b &= \frac{k_1 p + k_2 r}{k_2 k_3} > 0
 \end{aligned}$$

Since $a < 0$ and $b > 0$, so the system (4.2) exhibits forward bifurcation at $R_{0c} = 1$.

4.3 Diabetes sub-model

Without considering the infectious of people with COVID-19, the diabetes sub-model is given by

$$\begin{aligned}
 \frac{dS_d(t)}{dt} &= \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D(t)}{N_d} S_d(t), \\
 \frac{dP(t)}{dt} &= \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu) P(t), \\
 \frac{dD(t)}{dt} &= \gamma_1 P(t) - (\gamma_3 + \mu) D(t), \\
 \frac{dC(t)}{dt} &= \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2) C(t).
 \end{aligned} \tag{4.33}$$

For this submodel, the total population at time t is given by

$$N_d = S_d(t) + P(t) + D(t) + C(t)$$

Then, differentiating N with respect to time we obtain:

$$\frac{dN_c}{dt} = \frac{dS_d}{dt} + \frac{dP}{dt} + \frac{dD}{dt} + \frac{dC}{dt} = \Lambda_2 - \mu N_d - \delta_2 C$$

Assume there is no death due to the disease ($\delta_2 C = 0$), we get

$$\begin{aligned}
 \frac{dN_d}{dt} &\leq \Lambda_2 - \mu N_d \\
 \frac{dN_d}{dt} + \mu N_d &\leq \Lambda_2
 \end{aligned} \tag{4.34}$$

Multiplying both side by integrating factor yields,

$$\frac{d}{dt}(N_d e^{\mu t}) \leq \Lambda_2 e^{\mu t} \tag{4.35}$$

Integrating both sides of the Equation (4.35) from $[0, t]$ and simplifying it, then we have

$$N_d(t) \leq \frac{\Lambda_2}{\mu} + ce^{-\mu t} \quad (4.36)$$

as $t \rightarrow \infty$ in Equation (4.36) the population size, $N_d \leq \frac{\Lambda_2}{\mu}$, which implies that $0 \leq N_d \leq \frac{\Lambda_2}{\mu}$. Thus, the feasible region of the system (4.33) is given by the set

$$\Omega_d = \left\{ (S_d, P, D, C) \in \mathbb{R}_+^4 : 0 \leq N_d \leq \frac{\Lambda_2}{\mu} \right\}. \quad (4.37)$$

Which is positively invariant. That is,

$$\begin{aligned} \frac{dS_d}{dt} \Big|_{S_d=0} &= \Lambda_2 \geq 0, & \frac{dP}{dt} \Big|_{P=0} &= \frac{\beta_1 S_d D}{N_d} \geq 0, \\ \frac{dD}{dt} \Big|_{D=0} &= \gamma_1 P \geq 0, & \frac{dC}{dt} \Big|_{C=0} &= \gamma_2 P + \gamma_3 D \geq 0. \end{aligned}$$

Therefore, the region Ω_d attracts all solutions of the system (4.33).

Theorem 4.3.1. *(Existence and Uniqueness of the Solution) Let $t_0 > 0$ and the initial conditions satisfies $S_d(0) > 0$, $P(0) > 0$, $D(0) > 0$ and $C(0) > 0$ in the prescribed region Ω_d . Then the solutions of the model system (4.33) exists and unique in $\mathbb{R}_+^4$.*

Proof. The right hand side of (4.33) can be compactly written as

$$f(X) = \begin{pmatrix} \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D(t)}{N_d} S_d(t) \\ \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu) P(t) \\ \gamma_1 P(t) - (\gamma_3 + \mu) D(t) \\ \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2) C(t) \end{pmatrix} \quad (4.38)$$

where $X = [S_d, P, D, C]^T$. Here, f has a continuous partial derivative with respect to each state variables in $\mathbb{R}_+^4$ and all are bounded. Thus, f is locally Lipschitz in $\mathbb{R}_+^4$. Hence, the result is the direct consequence of the Fundamental Existence and Uniqueness Theorem (1.6.2). $\square$

Theorem 4.3.2. *(Non-negativity of Solutions) If $S_d(0) \geq 0$, $P(0) \geq 0$, $D(0) \geq 0$, and $C(0) \geq 0$, the solutions $S_d(t)$, $P(t)$, $D(t)$, and $C(t)$ of the system (4.33) are positive for all $t \geq 0$.*

Proof. We shall prove this theorem by the method of contradiction. For this, assume that the total population $N_d(t) \neq 0$ for all $t \geq 0$. For the first equation in the submodel (4.33), there

exists time t_1 such that the susceptible population becomes $S_d(t_1) = 0$, and $\frac{dS_d(t_1)}{dt} \leq 0$ provided that

$$P(0) \geq 0, D(0) \geq 0, C(0) \geq 0, 0 \leq t \leq t_1.$$

This implies that

$$\left. \frac{dS_d}{dt} \right|_{t=t_1} = \Lambda_2 - \mu S_d(t_1) - \frac{\beta_1 D(t)}{N_d} S_d(t_1) = \Lambda_2 < 0,$$

which is a contradiction. Thus, we conclude that $S_d(t) > 0, \forall t \geq 0$.

Next, corresponding to the second Equation in (4.33), assume that there exists time t_2 such that the pre-diabetes population satisfies $P(t_2) = 0$ and $\frac{dP(t_2)}{dt} < 0$ whenever $S_d(0) \geq 0, D(0) \geq 0, C(0) \geq 0, 0 \leq t \leq t_2$.

Again, from this we obtain that

$$\left. \frac{dP}{dt} \right|_{t=t_2} = \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu) P(t_2) = \frac{\beta_1 D(t)}{N_d} S_d(t) < 0,$$

which is a contradiction. Thus, we conclude that $P(t) > 0, \forall t \geq 0$. By similar approach it can be shown that $D(0) \geq 0, C(0) \geq 0, \forall t \geq 0$. Hence, we conclude that all the state variables $S_d(0) \geq 0, P(0) \geq 0, D(0) \geq 0, C(0) \geq 0$. This complete the proof. $\square$

Diabetic Free Equilibrium Point

Diabetic free equilibrium points are steady-state solutions where there is no diabetic infection. That is, all the infected classes are zero and the entire population comprise of only susceptible individuals. To find the disease free equilibrium (DFE), we equate the left hand side of the system (4.33) equal to zero at $P(t) = 0, D(t) = 0$ and $C(t) = 0$. We denote diabetic-free equilibrium point by E_{0d} . Equating system (4.33) equal to zero, we have that;

$$\begin{cases} \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D(t)}{N_d} S_d(t) = 0, \\ \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu) P(t) = 0, \\ \gamma_1 P(t) - (\gamma_3 + \mu) D(t) = 0, \\ \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2) C(t) = 0. \end{cases}$$

Solving for the non-infected state variable, we obtain the disease free equilibrium point

$$E_{0d} = \{S_d^0, P^0, D^0, C^0\} = \left\{ \frac{\Lambda_2}{\mu}, 0, 0, 0 \right\}$$

4.3.1 The Basic Reproduction Number for Diabetic sub-model

In this section, we determined the basic reproduction number for diabetic sub-model. For this, we use the next generation method given in (Van den Driessche & Watmough, 2002), as in section [4.2.3] first we rewrite the submodel equations, starting with newly infective classes

$$\begin{aligned}\frac{dP}{dt} &= \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu)P(t), \\ \frac{dD}{dt} &= \gamma_1 P(t) - (\gamma_3 + \mu)D(t), \\ \frac{dC}{dt} &= \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2)C(t).\end{aligned}\tag{4.39}$$

For this model, the associated matrices $\mathcal{F}$ and $\mathcal{V}$ the new infectious terms and the remaining transition terms are respectively given as

$$\mathcal{F}_i = \begin{bmatrix} \frac{\beta_1 D}{N_d} S_d \\ 0 \\ 0 \end{bmatrix} \text{ and } \mathcal{V}_i = \begin{bmatrix} (\mu + \gamma_1 + \gamma_2)P \\ (\mu + \gamma_3)D(t) - \gamma_1 P \\ (\mu + \delta_3)C - \gamma_2 P - \gamma_3 D \end{bmatrix}$$

The Jacobian matrices at the disease-free equilibrium point of $\mathcal{F}_i$ and $\mathcal{V}_i$ are obtained by derivating with respect to P, D and C . As following:

$$F(E_{0d}) = \begin{bmatrix} 0 & \beta_1 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and } V(E_{0d}) = \begin{bmatrix} \mu + \gamma_1 + \gamma_2 & 0 & 0 \\ -\gamma_1 & \mu + \gamma_3 & 0 \\ -\gamma_2 & -\gamma_3 & \mu + \delta_3 \end{bmatrix}$$

Let $k_1 = \mu + \gamma_1 + \gamma_2$, $k_2 = \mu + \gamma_3$ and $k_3 = \mu + \delta_3$

$$|V(E_{0d})| = \begin{vmatrix} k_1 & 0 & 0 \\ -\gamma_1 & k_2 & 0 \\ -\gamma_2 & -\gamma_3 & k_3 \end{vmatrix} = k_1 k_2 k_3 \neq 0.$$

Hence, the matrix $\mathcal{V}(E_{0d})$ is invertible and thus

$$V(E_{0d})^{-1} = \begin{bmatrix} \frac{1}{k_1} & 0 & 0 \\ \frac{\gamma_1}{k_1 k_2} & \frac{1}{k_2} & 0 \\ \frac{\gamma_1 \gamma_3 + \gamma_2 k_2}{k_1 k_2 k_3} & \frac{\gamma_3}{k_2 k_3} & \frac{1}{k_3} \end{bmatrix} \quad (4.40)$$

Moreover,

$$F(E_{0d})V(E_{0d})^{-1} = \begin{bmatrix} \frac{\beta_1 \gamma_1}{k_1 k_2} & \frac{\beta_1}{k_2} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad (4.41)$$

The eigenvalues of the matrix FV^{-1} can be computed as $\det(FV^{-1} - \lambda I) = |FV^{-1} - \lambda I| = 0$. Equivalently,

$$|FV^{-1} - \lambda I_3| = \begin{vmatrix} \frac{\beta_1 \gamma_1}{k_1 k_2} - \lambda & \frac{\beta_1}{k_2} & 0 \\ 0 & 0 - \lambda & 0 \\ 0 & 0 & 0 - \lambda \end{vmatrix}. \quad (4.42)$$

Clearly the eigenvalues are: $\lambda_1 = 0$, $\lambda_2 = 0$ and $\lambda_3 = \frac{\beta_1 \gamma_1}{k_1 k_2}$, where $k_1 = \mu + \gamma_1 + \gamma_2$, $k_2 = \mu + \gamma_3$ and $k_3 = \mu + \delta_2$. Finally, the basic reproductive number is given by $R_{0d} = \rho(FV^{-1})$. That is,

$$R_{0d} = \frac{\beta_1 \gamma_1}{(\mu + \gamma_1 + \gamma_2)(\mu + \gamma_3)}$$

4.3.2 Endemic Equilibrium Point of Diabetic sub-model

The Endemic equilibrium point which denoted by E_d^1 is a steady state solution where the disease persists in the population. The endemic equilibrium $E_d^1 = (S_d^*, P^*, D^*, C^*)$ can be

obtained by setting the left hand side in (4.33) equal to zero. That means

$$\begin{cases} \Lambda_2 - \mu S_d^*(t) - \frac{\beta_1 D(t)^*}{N_d} S_d^*(t) = 0, \\ \frac{\beta_1 D(t)^*}{N_d} S_d^*(t) - (\gamma_1 + \gamma_2 + \mu) P^*(t) = 0, \\ \gamma_1 P^*(t) - (\gamma_3 + \mu) D^*(t) = 0, \\ \gamma_2 P^*(t) + \gamma_3 D^*(t) - (\mu + \delta_2) C^*(t) = 0. \end{cases}$$

From the above system we can get the values of endemic equilibrium point.

$$\begin{cases} S_d^* = \frac{N_d^*}{R_{0d}}, \\ P^* = \frac{k_2 \Lambda_2}{\gamma_1 \beta_1} (R_{0d} - 1), \\ D^* = \frac{\Lambda_2}{\beta_1} (R_{0d} - 1), \\ C^* = \frac{\Lambda_2 (\gamma_2 k_2 + \gamma_1 \gamma_3)}{k_3 \gamma_1 \beta_1} (R_{0d} - 1). \end{cases} \quad (4.43)$$

4.3.3 Stability Analysis For Diabetic Free Equilibrium Point

Local Stability of Diabetic Free Equilibrium Point

Theorem 4.3.3. *The disease-free equilibrium E_{0d} of the system (4.33) is locally asymptotically stable if $R_{0d} < 1$.*

Proof. The Jacobian matrix at the disease-free equilibrium E_0 of the system (4.33) is

$$J = \begin{bmatrix} -(\mu + \frac{\beta_1 D}{N_d}) & 0 & -\frac{\beta_1 S_d}{N_d} & 0 \\ \frac{\beta_1 D}{N_d} & -k_1 & \frac{\beta_1 S_d}{N_d} & 0 \\ 0 & \gamma_1 & -k_2 & 0 \\ 0 & \gamma_2 & \gamma_3 & -k_3 \end{bmatrix} \quad (4.44)$$

Where $k_1 = \mu + \gamma_1 + \gamma_2$, $k_2 = \mu + \gamma_3$ and $k_3 = \mu + \delta_2$. The eigenvalues of $J(E_0)$ are the solutions of the characteristics equation $\det(J(E_0) - \lambda I_4) = 0$ where I_4 is identity matrix of order 4. Then we have

$$\left| J(E_{0d}) - \lambda I_4 \right| = \begin{vmatrix} -\mu - \lambda & 0 & -\beta_1 & 0 \\ 0 & -k_1 - \lambda & \beta_1 & 0 \\ 0 & \gamma_1 & -k_2 - \lambda & 0 \\ 0 & \gamma_2 & \gamma_3 & -k_3 - \lambda \end{vmatrix} = 0$$

The corresponding characteristic equation has the following form

$$(\mu_2 + \lambda) \left[\lambda^3 + b_1 \lambda^2 + b_2 \lambda + b_3 \right] = 0 \quad (4.45)$$

where

$$\begin{aligned} b_1 &= k_1 + k_2 + k_3 = (\mu + \gamma_1 + \gamma_2) + (\mu + \gamma_3) + (\mu + \delta_3), \\ b_2 &= k_1 k_3 + k_1 k_2 + k_2 k_3 - \beta_1 \gamma_1 - \beta_2 \gamma_2 = (\mu + \gamma_1 + \gamma_2)(\mu + \gamma_3) + (\mu + \gamma_1 + \gamma_2), \\ &\quad (\mu + \delta_2) + (\mu + \gamma_3)(\mu + \delta_2) - \beta_1 \gamma_1, \\ b_3 &= k_1 k_2 k_3 - \beta_1 \gamma_1 k_3 = k_1 k_2 k_3 (1 - R_{0d}). \end{aligned}$$

Then solving Equation (4.45) we obtain

$$(\mu + \lambda) = 0 \quad \text{or} \quad \lambda^3 + b_1 \lambda^2 + b_2 \lambda + b_3 = 0.$$

It can be observed that the first eigenvalues $\lambda_1 = -\mu$ is negative. To determine the sign of the remaining three eigenvalues we use the Routh-Hurwitz criteria (Merkin, 1997) for the third order equation; $\lambda^3 + b_1 \lambda^2 + b_2 \lambda + b_3 = 0$. According to the Routh-Hurwitz criteria the three roots of a polynomial of order three of the type $\rho(\lambda) = \lambda^3 + b_1 \lambda^2 + b_2 \lambda + b_3$ are real distinct and negative if the coefficients satisfy the conditions $b_1 > 0$, $b_2 > 0$, $b_3 > 0$ and $b_1 b_2 - b_3 > 0$.

Let us check the conditions as follows:

- $b_1 > 0 \implies k_1 + k_2 + k_3 > 0$, because all parameters are positive and their sum is also positive,
- $b_2 > 0 \implies k_1 k_3 + k_1 k_2 + k_2 k_3 - \beta_1 \gamma_1 > 0 \implies b_2 > 0$ **holds if** $k_1 k_3 + k_1 k_2 + k_2 k_3 > \beta_1 \gamma_1$.
- $b_3 > 0 \implies k_1 k_2 k_3 - \beta_1 \gamma_1 k_3 > 0 = k_1 k_2 k_3 \left(1 - \frac{\beta_1 \gamma_1 k_3}{k_1 k_2 k_3}\right) > 0 \implies 1 > \frac{\beta_1 \gamma_1 k_3}{k_1 k_2 k_3} = R_{0d} \implies 1 > R_{0d}$, hence $b_3 > 0$ if $R_{0d} < 1$ holds.
- Lastly $b_1 b_2 > b_3 \implies b_1 b_2 - b_3 > 0$.

This implies those remained three eigenvalues are also real distinct and negative for $R_{0d} < 1$. Therefore, the disease free equilibrium point E_{0d} of the system (4.33) is locally asymptotically stable if $R_{0d} < 1$. In the next, we investigate global stability of the diabetes free equilibrium point. $\square$

Global Stability of the Diabetic Free Equilibrium Point

Theorem 4.3.4. *The disease free equilibrium of the system (4.33) is globally asymptotically stable if $R_{0d} < 1$.*

Proof. To prove the global stability of the disease-free equilibrium point, we construct a Lyapunov function

$L(S_d, P, D, C) : \Omega_d \subset \mathbb{R}_+^4 \mapsto \mathbb{R}^+$ defined as

$$L = C_1 P + C_2 D \quad (4.46)$$

where C_1, C_2 and C_3 are positive constants. Then the function $L(S_d, P, D, C)$ should satisfies the following three condition to be

- L is continuously differentiable.
- $L > 0, \forall (S_d, P, D, C) \in \Omega_d - E_{0d}$ and $L(E_{0d}) = 0$.
- $\frac{dL}{dt} \leq 0$ in Ω_d . Then E_{0d} is stable.

Clearly, the first two condition holds since L is nonnegative in Ω_d except at E_{0d} and $L(E_0) = 0$. Now let us check the third condition $\frac{dL}{dt} \leq 0$. Now differentiating L with respect to time we obtain

$$\begin{aligned} \frac{dL}{dt} &= C_1 \frac{dP}{dt} + C_2 \frac{dD}{dt} \\ \frac{dL}{dt} &= C_1 \left(\frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu) P \right) + C_2 (\gamma_1 P(t) - (\gamma_3 + \mu) D) \\ &\leq C_1 (\beta_1 D - K_1 P) + C_2 (\gamma_1 P - k_2 D) \quad \text{Since } S_d \leq N_d \\ &= C_1 k_1 \left(\frac{C_2 \gamma_1}{C_1 k_1} - 1 \right) P + (C_1 \beta_1 - C_2 k_2) D \end{aligned} \quad (4.47)$$

Suppose $C_2 = \frac{C_1 \beta_1}{k_2}$ and substitute in to (4.47) we can get

$$\begin{aligned} &= C_1 k_1 \left(\frac{C_1 \beta_1 \gamma_1}{C_1 k_1 k_2} - 1 \right) P + 0 \\ &= C_1 k_1 \left(\frac{\beta_1 \gamma_1}{k_1 k_2} - 1 \right) P \end{aligned}$$

$$\frac{dL}{dt} \leq C_1 k_1 (R_{0d} - 1) P$$

Hence $\frac{dL}{dt} \leq 0$ for $R_{0d} < 1$ and $\frac{dL}{dt} = 0$ if and only if $P = 0$. Therefore the largest compact invariant set in Ω_d is the singleton set $\left(\frac{\Lambda_2}{\mu}, 0, 0, 0\right)$, by La Salle (1976), every solution to equations of model (4.33) with initial conditions in Ω_d which approaches the disease-free equilibrium point as time t tends to infinity whenever $R_{0d} < 1$. This implies that the diabetes-free equilibrium is globally asymptotically stable in Ω_d . $\square$

4.3.4 Stability Analysis of Endemic Equilibrium for Diabetic sub-model

Local stability of the Endemic Equilibrium Point

Theorem 4.3.5. *The Endemic Equilibrium point E_d^1 of the system (4.33) is locally asymptotically stable if $R_{0d} > 1$.*

Proof. To obtain the local stability of E_d^1 , the Jacobian matrix (4.33) of the model equations computed under local stability of DFE is used at E_d^1 . Thus, the jacobian matrix at E_d^1 becomes

$$J = \begin{bmatrix} -(\mu + \frac{\beta_1 D^*}{N_d}) & 0 & -\frac{\beta_1 S_d^*}{N_d} & 0 \\ \frac{\beta_1 D^*}{N_d} & -k_1 & \frac{\beta_1 S_d^*}{N_d} & 0 \\ 0 & \gamma_1 & -k_2 & 0 \\ 0 & \gamma_2 & \gamma_3 & -k_3 \end{bmatrix} \quad (4.48)$$

Where $k_1 = \mu + \gamma_1 + \gamma_2$, $k_2 = \mu + \gamma_3$ and $k_3 = \mu + \delta_2$. The eigenvalues of $J(E_d^1)$ are the solutions of the characteristics equation $|J(E_d^1) - \lambda I_4| = 0$ where I_4 is identity matrix of order 4. Then we have

$$|J(E_d^1) - \lambda I_4| = \begin{bmatrix} (-\mu R_{0d} - \lambda) & 0 & -\frac{\beta_1}{R_{0d}} & 0 \\ \mu(R_{0d} - 1) & -k_1 - \lambda & \frac{\beta_1}{R_{0d}} & 0 \\ 0 & \gamma_1 & -k_2 - \lambda & 0 \\ 0 & \gamma_2 & \gamma_3 & -k_3 - \lambda \end{bmatrix} \quad (4.49)$$

After computing determinant of the 4×4 matrix above, lastly we get the following characteristic equation

$$(k_3 + \lambda) [\lambda^3 + B_1 \lambda^2 + B_2 \lambda + B_3] = 0 \quad (4.50)$$

where

$$\begin{aligned} B_1 &= \mu R_{0d} + k_1 + k_2, \\ B_2 &= \mu R_{0d}k_1 + \mu R_{0d}k_2 + k_1k_2 - \frac{\beta_1\gamma_1}{R_{0d}}, \\ B_3 &= \mu R_{0d}k_1k_2 - \left(\frac{\beta_1\mu\gamma_1}{R_{0d}} \right). \end{aligned}$$

Clearly, from the Equation (4.50) we have $\lambda_1 = -k_3$ since the all parameters are positive and $\lambda^3 + B_1\lambda^2 + B_2\lambda + B_3 = 0$. Thus, the first eigenvalues λ_1 is negative due to all the parameter are positive. To determine the sign of the remaining four eigenvalues we apply the Routh-Hurwitz criteria (Merkin, 1997) for the polynomial equation

$$\lambda^3 + B_1\lambda^2 + B_2\lambda + B_3 = 0,$$

The Routh-Hurwitz criteria implies that the roots of the eigen polynomial

$$\rho(\lambda) = \lambda^3 + B_1\lambda^2 + B_2\lambda + B_3,$$

are real distinct and negative if the coefficients satisfy the conditions $B_i > 0$ for $i = 1, 2, 3, 4$ and the determinant of $\rho(\lambda) > 0$. It is straight forward to verify that this conditions are satisfied and hence the last four eigenvalues are real distinct and negative. That is

- $B_1 > 0 \implies \mu R_{0d} + k_1 + k_2 > 0$ because all parameters are positive and their sum is also positive.
- $B_2 > 0 \implies \mu R_{0d}k_1 + \mu R_{0d}k_2 + k_1k_2 - \frac{\beta_1\gamma_1}{R_{0d}} > 0 \implies \mu R_{0d}k_1 + \mu R_{0d}k_2 + k_1k_2 > \frac{\beta_1\gamma_1}{R_{0d}}$
- $B_3 > 0 \implies \mu R_{0d}k_1k_2 - \left(\frac{\beta_1\mu\gamma_1}{R_{0d}} \right) > 0 \implies \mu R_{0d}k_1k_2 > \left(\frac{\beta_1\mu\gamma_1}{R_{0d}} \right) \implies 1 > \frac{1}{R_{0d}} \implies R_{0d} > 1$

and determinants

$$\begin{aligned} D_1 &= B_1 > 0, \\ D_2 &= B_1B_2 > 0, \\ D_3 &= B_1B_2 - B_3 > 0. \end{aligned}$$

Therefore the system (4.33) become local asymptotically stable at endemic equilibrium E_d^1 if $R_{0d} > 1$. □

Global stability of Endemic Equilibrium Point

Theorem 4.3.6. *The endemic equilibrium point of the model Equation (4.33) is globally asymptotically stable if $R_{0d} > 1$.*

Proof. To show this result define the Lyapunov function L by

$$L(S_d^*, P^*, D^*, C^*) = [S_d - S_d^* - S_d^* \ln(\frac{S_d}{S_d^*})] + [P - P^* - P^* \ln(\frac{P}{P^*})] + [D - D^* - D^* \ln(\frac{D}{D^*})] + [C - C^* - C^* \ln(\frac{C}{C^*})].$$

Differentiating L with respect to time t we obtain

$$\begin{aligned} \frac{dL}{dt} &= \left(1 - \frac{S_d^*}{S_d}\right) \frac{dS_d}{dt} + \left(1 - \frac{P^*}{P}\right) \frac{dP}{dt} + \left(1 - \frac{D^*}{D}\right) \frac{dD}{dt} + \left(1 - \frac{C^*}{C}\right) \frac{dC}{dt} \\ \frac{dL}{dt} &= \left(1 - \frac{S_d^*}{S_d}\right) (\Lambda_2 - \mu S_d - \frac{\beta_1 D S_d}{N_d}) + \left(1 - \frac{P^*}{P}\right) (\frac{\beta_1 S_d D}{N_d} - (\mu + \gamma_1 + \gamma_2) P) + \left(1 - \frac{D^*}{D}\right) \\ &\quad (\gamma_1 P - (\mu + \gamma_3) D) + \left(1 - \frac{C^*}{C}\right) (\gamma_2 P + \gamma_1 D - (\mu + \delta_2) C) \\ \frac{dL}{dt} &= [\Lambda_2 - (\mu + \frac{\beta_1 D}{N}) S_d - \frac{S_d^*}{S_d} \Lambda_2 + \mu S_d^* + S^* \frac{\beta_1 D}{N}] + [(\frac{\beta_1 D}{N}) S_d - (\mu + \gamma_1 + \gamma_2) P - \frac{P^*}{P} (\frac{\beta_1 D}{N}) S_d + P^* \mu + P^* \gamma_1 \\ &\quad + P^* \gamma_2] + [\gamma_1 P - (\mu + \gamma_3) P - \gamma_1 P \frac{D^*}{D} + \mu D^* + \gamma_3 D^*] + \gamma_2 P + \gamma_1 D - (\mu + \delta_2) C - \gamma_2 P \frac{C^*}{C} - \gamma_3 D \frac{C^*}{C} + \mu C^* + \delta_2 C^* \end{aligned}$$

After mathematical manipulation and collecting like terms it becomes

$$[(\frac{\beta_1 D}{N} + \mu) S_d^* + k_1 P^* + k_2 D^* + \mu C^*] - [\Lambda_2 \frac{S_d^*}{S_d} + \frac{P^*}{P} (\frac{\beta_1 D}{N}) S_d + \gamma_1 P \frac{D^*}{D} + \gamma_2 P \frac{C^*}{C} + \gamma_3 D \frac{C^*}{C} + \delta_2 C],$$

setting

$$\begin{aligned} M_1 &= (\frac{\beta_1 D}{N} + \mu_1) S_d^* + k_1 P^* + k_2 D^* + \mu_2 C^*, \\ M_2 &= \Lambda_2 \frac{S_d^*}{S_d} + \frac{P^*}{P} (\frac{\beta_1 D}{N}) S_d + \gamma_1 P \frac{D^*}{D} + \gamma_2 P \frac{C^*}{C} + \gamma_3 D \frac{C^*}{C} + \delta_3 C. \end{aligned}$$

Compactly this becomes

$$\frac{dL}{dt} = M_1 - M_2$$

Thus, we get $\frac{dL}{dt} \leq 0$ if $M_1 < M_2$ and $\frac{dL}{dt} = 0$ if $M_1 = M_2$, this holds if $S_d = S_d^*, P = P^*, D = D^*$ and $C = C^*$. Therefore, the largest compact invariant set is $\{(S_d^*, P^*, D^*, C^*) \in \Omega_d; \frac{dL}{dt} = 0\}$, by the La Salle (1976). Hence E_d^1 is globally asymptotically stable in the set Ω_d for $M_1 < M_2$ and $R_{0d} > 1$. $\square$

4.3.5 Sensitivity analysis of Diabetic sub-model

To perform sensitivity of R_{0d} we use the normalized forward sensitivity index of a variable to a parameter which is the ratio of the relative change in the variable to the relative change in the parameter. The explicit expression of R_{0d} is given by

$$R_{0d} = \frac{\beta_1 \gamma_1}{(\mu + \gamma_1 + \gamma_2)(\mu + \gamma_3)}$$

The reproduction number above contains thirteen parameters and we compute the normalized forward sensitivity index for each parameters of R_{0d} .

Definition 4.3.1. (Rodrigues et al., 2013). The normalized forward sensitivity index of R_0 , which is differentiable with respect to a given parameter, w , is defined as:

$$\phi_w^{R_0} = \frac{\partial R_0}{\partial w} \times \frac{w}{R_0} \quad (4.51)$$

By using Equation (4.51) we compute the normalized forward sensitivity indices of the model parameters as follows:

$$\begin{aligned} \phi_{\beta_1}^{R_{0d}} &= \frac{\partial R_{0d}}{\partial \beta_1} \times \frac{\beta_1}{R_{0d}} = 1 \\ \phi_{\gamma_1}^{R_{0d}} &= \frac{\partial R_{0d}}{\partial \gamma_1} \times \frac{\gamma_1}{R_{0d}} = \frac{\beta_1[(\mu + \gamma_1 + \gamma_2)(\mu + \gamma_3) - \gamma_1(\mu + \gamma_3)]}{(\mu + \gamma_1 + \gamma_2)(\mu + \gamma_3)\beta_1\gamma_1} \end{aligned}$$

Similarly, we compute for the rest parameters and over all the sensitivity indices of the model parameters are summarized in Table 4.4 below.

Table 4.4: Sensitivity indices for Diabetic sub-model parameters

Parameters	Description	Sensitivity indices
β_1	Intensive social contact rate	1
γ_1	Rate of $P(t)$ enter into $D(t)$ class	+0.611
γ_2	Rate of $P(t)$ enter into $C(t)$	-0.611
γ_3	Rate at which $D(t)$ moves to $C(t)$ class	-0.9055
μ	Natural death rate	-0.1166

From the above Table (4.4) based on sign of the values of the parameters those with positive indices, β_1 and γ_1 show that they have great impact on expanding the disease in the population. Pretend that, if the parameter value of γ_1 increase for 20% then the value of R_{0d} increase by 10.3%. In contrary, parameters γ_2 , μ and γ_3 those whose their sensitivity indices are negative have an influence of minimizing the spread of the disease in the community. Suppose that, the value of parameter γ_3 increase for 10% then the value of R_{0d} decrease by 8.62%.

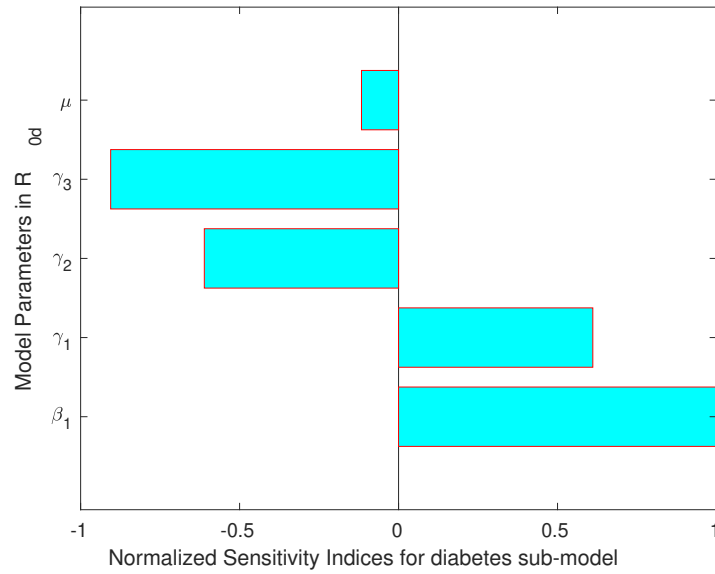


Figure 4.3: Normalized sensitivity indices of R_{0d} with respect to parameters of the model (4.33). Parameter values are taken from Table 4.4

4.4 Analysis of the Co-infection Model

In this case, the total population at time t is given by

$$N = S(t) + E(t) + A(t) + I_C(t) + R(t) + I_{CC}(t) + I_{CD}(t) + S_d(t) + P(t) + D(t) + C(t)$$

Then, differentiating N with respect to time we obtain:

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dE}{dt} + \frac{dA}{dt} + \frac{dI_C}{dt} + \frac{dR}{dt} + \frac{dI_{CC}}{dt} + \frac{dI_{CD}}{dt} + \frac{dS_d}{dt} + \frac{dP}{dt} + \frac{dD}{dt} + \frac{dC}{dt} = \\ &\Lambda_1 + \Lambda_2 - \mu N - \delta_1 I_C - \delta_{cc} I_{CC} - \delta_{cc} I_{CD} - \delta_2 C \end{aligned}$$

Assume there is no death due to the disease ($\delta_1 I_C = \delta_{cc} I_{CC} = \delta_{cc} I_{CD} = \delta_2 C = 0$), we get where $\Lambda = \Lambda_1 + \Lambda_2$.

$$\begin{aligned} \frac{dN}{dt} &\leq \Lambda - \mu N, \\ \frac{dN}{dt} + \mu N &\leq \Lambda. \end{aligned} \tag{4.52}$$

Multiplying both side by integrating factor yields,

$$\frac{d}{dt}(Ne^{\mu t}) \leq \Lambda e^{\mu t} \tag{4.53}$$

Integrating both sides of the equation (4.53) from $[0, t]$ and simplifying it, then we have

$$N(t) \leq \frac{\Lambda}{\mu} + ce^{-\mu t} \quad (4.54)$$

as $t \rightarrow \infty$ in equation (4.54) the population size, $N \leq \frac{\Lambda}{\mu}$, which implies that $0 \leq N_c \leq \frac{\Lambda}{\mu}$. Thus, the feasible region of the system (4.1) is given by the set

$$\Omega = \left\{ (S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C) \in \mathbb{R}_+^{11} : 0 \leq N \leq \frac{\Lambda}{\mu} \right\}, \quad (4.55)$$

which is positively invariant. That is,

$$\left. \frac{dI_{CD}}{dt} \right|_{I_{CD}=0} = \theta_1 I_C + \psi_1 D \geq 0, \quad \left. \frac{dI_{CC}}{dt} \right|_{I_{CC}=0} = \theta_2 I_C + \psi_2 D \geq 0$$

Consequently, this region attracts all solutions of the system and this restricted region will be enough to consider of the dynamics of the model (4.1).

Theorem 4.4.1. *(Existence and Uniqueness of the Solution) Let $t_0 > 0$ and the initial conditions satisfies $S(0) > 0$, $E(0) \geq 0$, $A(0) > 0$, $I_C(0) > 0$, $R(0) > 0$, $I_{CD}(0) > 0$, $I_{CC}(0) > 0$, $P(0) > 0$, $D(0) > 0$ and $C(0) > 0$ in the prescribed region Ω . Then the solutions of the model system (4.2) exists and unique in $\mathbb{R}_+^{11}$.*

Proof. The right hand side of (4.1) can be compactly written as

$$f(X) = \begin{pmatrix} \Lambda_1 - (\mu + \lambda)S(t) \\ \lambda S(t) - (\mu + p + r)E(t) \\ pE(t) - (\mu + \alpha_2)A(t) \\ rE(t) - (\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)I_C(t) \\ \alpha_2 A(t) + \alpha_1 I_C(t) + \eta_1 I_{CD}(t) + \eta_2 I_{CC}(t) - (\mu + \omega_1 + \omega_2)R(t) \\ \theta_1 I_C(t) + \psi_1 D(t) - (\mu + \delta_{cd} + \eta_1)I_{CD}(t) \\ \theta_2 I_C(t) + \psi_2 D(t) - (\mu + \delta_{cc} + \eta_2)I_{CC}(t) \\ \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D(t)}{N_d} S_d(t) \\ \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu)P(t) \\ \gamma_1 P(t) - (\gamma_3 + \mu + \psi_1)D(t) \\ \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2 + \psi_2)C(t) \end{pmatrix} \quad (4.56)$$

where $X = [S, E, A, I_C, R, I_{CD}, I_{CC}, P, D, C]^T$. Here, f has a continuous partial derivative with respect to each state variables in $\mathbb{R}_+^{11}$ and all are bounded. Thus, f is locally Lipschitz in $\mathbb{R}_+^{11}$. Hence, the result is the direct consequence of the Fundamental Existence and Uniqueness Theorem (1.6.2). $\square$

Theorem 4.4.2. *(Non-negativity of Solutions) If $S(0) \geq 0$, $E(0) \geq 0$, $A(0) \geq 0$, $I_C \geq 0$*



4.4. ANALYSIS OF THE CO-INFECTION MODEL

$0, R(0) \geq 0, I_{CD} \geq 0, I_{CC} \geq 0, S_d(0) \geq 0, P(0) \geq 0, D(0) \geq 0$ and $R(0) \geq 0$, the solutions $S(t), E(t), A(t), I_C(t), R(t), I_{CD}(t), I_{CC}(t), S_d(t), P(t), D(t)$ and $C(t)$ of the system (4.1) are positive for all $t \geq 0$.

Proof. From the system of differential equation (4.1), let us take the equation

$$\frac{dI_{CD}(t)}{dt} = \theta_1 I_C(t) + \psi_1 D(t) - (\mu + \delta_{cd} + \eta_1) I_{CD}(t),$$

This equation can be expressed without loss of generality, after eliminating the positive term $\theta_1 I_C$ and $\psi_1 D$, as an inequality

$$\frac{dI_{CD}(t)}{dt} \geq -(\mu + \delta_{cd} + \eta_1) I_{CD}(t).$$

Then using separable method of variables and applying integration from 0 to t , the solution of the differentially inequality can be obtained as

$$I_{CD}(t) \geq I_{CD}(0) e^{-\int_0^t (\mu + \delta_{cd} + \eta_1) ds},$$

where $I_{CD}(0)$ is obtain from initial condition. Since this exponential function is always non-negative, we can concluded that

$$I_{CD}(t) \geq 0.$$

We can do similarly for $I_{CC}(t)$ as follows,

$$\frac{dI_{CC}(t)}{dt} = \theta_2 I_C(t) + \psi_2 D(t) - (\mu + \delta_{cc} + \eta_1) I_{CD}(t),$$

$$\frac{dI_{CC}(t)}{dt} \geq -(\mu + \delta_{cc} + \eta_2) I_{CC}(t).$$

By the same approach one can easily obtain that

$$I_{CC}(t) \geq I_{CC}(0) e^{-\int_0^t (\mu + \delta_{cc} + \eta_2) ds}, \quad (4.57)$$

clearly from (4.57) one can obtain that

$$I_{CC}(t) \geq 0.$$

□

4.4.1 Disease Free Equilibrium Point for Co-infection Model

Disease free equilibrium points are steady-state solutions where there is no COVID-19 and diabetic infection. That is, all the infected classes are zero and the entire population comprise

of only susceptible individuals. To find the disease free equilibrium, we equate the left hand side of the system (4.33) equal to zero at $P(t) = 0$, $E(t) = 0$, $A(t) = 0$, $I_C(t) = 0$, $I_{CD}(t) = 0$, $I_{CC}(t) = 0$, $P(t) = 0$, $D(t) = 0$ and $C(t) = 0$. We denote disease-free equilibrium point by E_0 . Equating system (4.58) equal to zero, we have that;

$$\left\{ \begin{array}{l} \frac{dS(t)}{dt} = \Lambda_1 - (\mu + \lambda)S(t) = 0, \\ \frac{dE(t)}{dt} = \lambda S(t) - (\mu + p + r)E(t) = 0, \\ \frac{dA(t)}{dt} = pE(t) - (\mu + \alpha_2)A(t) = 0, \\ \frac{dI_C(t)}{dt} = rE(t) - (\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)I_C(t) = 0, \\ \frac{dR(t)}{dt} = \alpha_2 A(t) + \alpha_1 I_C(t) + \eta_1 I_{CD}(t) + \eta_2 I_{CC}(t) - (\mu + \omega_1 + \omega_2)R(t) = 0, \\ \frac{dI_{CD}(t)}{dt} = \theta_1 I_C(t) + \psi_1 D(t) - (\mu + \delta_{cd} + \eta_1)I_{CD}(t) = 0, \\ \frac{dI_{CC}(t)}{dt} = \theta_2 I_C(t) + \psi_2 C(t) - (\mu + \delta_{cc} + \eta_2)I_{CC}(t) = 0, \\ \frac{dS_d(t)}{dt} = \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D(t)}{N_d} S_d(t) = 0, \\ \frac{dP(t)}{dt} = \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu)P(t) = 0, \\ \frac{dD(t)}{dt} = \gamma_1 P(t) - (\gamma_3 + \mu + \psi_1)D(t) + \omega_1 R(t) = 0, \\ \frac{dC(t)}{dt} = \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2 + \psi_2)C(t) + \omega_2 R(t) = 0. \end{array} \right. \quad (4.58)$$

Solving for the non-infected state variable, we obtain the disease free equilibrium point

$$E_0 = \{S^0, E^0, A^0, I_C^0, R^0, I_{CD}^0, I_{CC}^0, S_d^0, P^0, D^0, C^0\} = \left\{ \frac{\Lambda_1}{\mu}, 0, 0, 0, 0, 0, 0, \frac{\Lambda_2}{\mu}, 0, 0, 0 \right\}$$

4.4.2 The Basic Reproduction Number for Co-infection Model

In this section, we determined the basic reproduction number for coinfection model. By the same approach in previous section, rewriting the system with newly infected class as follows,

$$\begin{aligned}
 \frac{dE}{dt} &= \lambda S(t) - (\mu + p + r)E(t) \\
 \frac{dA}{dt} &= pE(t) - (\mu + \alpha_2)A(t) \\
 \frac{dI_C}{dt} &= rE(t) - (\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)I_C(t) \\
 \frac{dI_{CD}(t)}{dt} &= \theta_1 I_C(t) + \psi_1 D(t) - (\mu + \delta_{cd} + \eta_1)I_{CD}(t) \\
 \frac{dI_{CC}(t)}{dt} &= \theta_2 I_C(t) + \psi_1 C(t) - (\mu + \delta_{cc} + \eta_2)I_{CC}(t) \\
 \frac{dP(t)}{dt} &= \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu)P(t) \\
 \frac{dD(t)}{dt} &= \gamma_1 P(t) - (\gamma_3 + \mu + \psi_1)D(t) + \omega_1 R(t) \\
 \frac{dC(t)}{dt} &= \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2 + \psi_2)C(t) + \omega_2 R(t)
 \end{aligned} \tag{4.59}$$

For this model, the associated matrices $\mathcal{F}$ and $\mathcal{V}$ the new infectious terms and the remaining transition terms are respectively given as

$$\mathcal{F}_i = \begin{bmatrix} \frac{\beta(bA + I_C)}{N_c} \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{\beta_1 D}{N_d} S_d \\ 0 \\ 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V}_i = \begin{bmatrix} k_1 E \\ k_2 A(t) - pE \\ k_3 I_C - rE \\ K_4 I_{CD} - \theta_1 I_C - \psi_1 D \\ K_5 I_{CC} - \theta_2 I_C - \psi_2 C \\ k_6 P \\ k_7 D - \gamma_1 P - \omega_1 R \\ k_8 C - \gamma_2 P - \gamma_3 D - \omega_2 R \end{bmatrix}$$

The Jacobian matrices at the disease-free equilibrium point of $\mathcal{F}_i$ and $\mathcal{V}_i$ are obtained by derivating with respect to $E, A, I_C, I_{CD}, I_{CC}, P, D$ and C as following



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$$F(E_0) = \begin{bmatrix} 0 & \beta b & \beta & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \text{ and } V(E_0) = \begin{bmatrix} k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -p & k_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ -r & 0 & k_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\theta_1 & k_4 & 0 & 0 & -\psi_1 & 0 \\ 0 & 0 & -\theta_2 & 0 & k_5 & 0 & 0 & -\psi_2 \\ 0 & 0 & 0 & 0 & 0 & k_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_1 & k_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_2 & -\gamma_3 & k_8 \end{bmatrix}$$

$$|V(E_0)| = \begin{vmatrix} k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -p & k_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ -r & 0 & k_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\theta_1 & k_4 & 0 & 0 & -\psi_1 & 0 \\ 0 & 0 & -\theta_2 & 0 & k_5 & 0 & 0 & -\psi_2 \\ 0 & 0 & 0 & 0 & 0 & k_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_1 & k_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_2 & -\gamma_3 & k_8 \end{vmatrix} = k_1 k_2 k_3 k_4 k_5 k_6 k_7 k_8 \neq 0$$

Hence, the matrix $\mathcal{V}(E_0)$ is invertible and thus

$$V(E_0)^{-1} = \begin{bmatrix} \frac{1}{k_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{p}{k_1 k_2} & \frac{1}{k_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{r}{k_1 k_3} & 0 & \frac{1}{k_3} & 0 & 0 & 0 & 0 & 0 \\ \frac{\theta_1 r}{k_1 k_3 k_4} & 0 & \frac{\theta_1}{k_3 k_4} & \frac{1}{k_4} & 0 & 0 & \frac{\psi_1}{k_7} & 0 \\ \frac{\theta_2 r}{k_1 k_3 k_4} & 0 & \frac{\theta_2}{k_3 k_5} & 0 & \frac{1}{k_5} & 0 & 0 & \frac{\psi_2}{k_8} \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{k_6} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\gamma_1}{k_6 k_7} & \frac{1}{k_7} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\gamma_1 \gamma_3 + k_7 \gamma_2}{k_6 k_7 k_8} & \frac{\gamma_3}{k_7 k_8} & \frac{1}{k_8} \end{bmatrix} \quad (4.60)$$

$$F(E_0)V(E_0)^{-1} = \begin{bmatrix} \frac{k_3\beta bp + k_2\beta r}{k_1k_2k_3} & \frac{\beta b}{k_2} & \frac{\beta}{k_3} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_1\gamma_1}{k_6k_7} & \frac{\beta_1}{k_7} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Computing the eigenvalues are: $\lambda_1 = 0, \lambda_2 = 0, \lambda_3 = 0, \lambda_4 = 0, \lambda_5 = 0, \lambda_6 = 0, \lambda_7 = \frac{k_3\beta bp + k_2\beta r}{k_1k_2k_3}$ and $\lambda_8 = \frac{\beta_1\gamma_1}{k_6k_7}$, where $k_1 = \mu + p + r, k_2 = \alpha_2 + \mu, k_3 = \mu + \delta_2 + \alpha_1 + \theta_1 + \theta_2, k_4 = \mu + \delta_{cd} + \eta_1, k_5 = \mu + \delta_{cc} + \eta_2, k_6 = \mu + \gamma_1 + \gamma_2, k_7 = \mu + \gamma_3 + \psi_1$, and $k_8 = \mu + \delta_3 + \psi_2$. Therefore, the reproduction number for coinfection model is

$$R_0 = \max \{ \lambda_7, \lambda_8 \} \quad (4.61)$$

$$R_0 = \max \left\{ \frac{\beta[(\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)pb + (\alpha_2 + \mu)r]}{(\mu + p + r)(\mu + \alpha_2)(\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)}, \frac{\beta_1\gamma_1}{(\mu + \gamma_1 + \gamma_2)(\mu + \gamma_3 + \psi_1)} \right\}$$

4.4.3 Stability Analysis of Disease Free Equilibrium Point of Co-infection

Local Stability of Disease Free Equilibrium Point of Co-infection

Theorem 4.4.3. *The disease-free equilibrium E_0 of the system ((4.1)) is locally asymptotically stable if $R_0 < 1$.*

Proof. The Jacobian matrix at the disease-free equilibrium E_0 of the system (4.1) is

$$J(E_0) = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_1 & \beta b & \beta & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & p & -k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & r & 0 & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha_2 & \alpha_1 & -k_4 & \eta_1 & \eta_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \theta_1 & 0 & 0 & -k_5 & 0 & 0 & \psi_1 & 0 & 0 \\ 0 & 0 & \theta_2 & 0 & 0 & 0 & -k_6 & 0 & 0 & \psi_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu & 0 & -\beta_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_7 & \beta_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_1 & -k_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_2 & \gamma_3 & -k_9 \end{bmatrix} \quad (4.62)$$



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Where $k_1 = \mu + p + r$, $k_2 = \alpha_2 + \mu_1 + \delta_1$, $k_3 = \mu_1 + \delta_2 + \alpha_1 + \theta_1 + \theta_2$, $k_4 = \mu + \omega_1 + \omega_2$, $k_5 = \mu + \delta_{cd} + \eta_1$, $k_6 = \mu + \delta_{cc} + \eta_2$, $k_7 = \mu + \gamma_1 + \gamma_2$, $k_8 = \mu + \gamma_3 + \psi_1$ and $k_9 = \mu + \delta_3 + \psi_2$. The eigenvalues of block chain matrix $J(E_0)$ are the solutions of the characteristics equation $\det(J(E_0) - \lambda I_{11}) = 0$, where I_{11} is identity matrix of order 11. Then the block matrices are

$$J_1(E_0) = \begin{bmatrix} -k_1 & \beta b & \beta \\ p & -k_2 & 0 \\ r & 0 & -k_3 \end{bmatrix}, \quad J_2(E_0) = \begin{bmatrix} -k_4 & \eta_1 & \eta_2 \\ 0 & -k_5 & 0 \\ 0 & 0 & -k_6 \end{bmatrix} \text{ and } J_3(E_0) = \begin{bmatrix} -k_7 & \beta_1 \\ \gamma_1 & -k_8 \end{bmatrix}.$$

After computing the determinant of the block chain matrices, then corresponding characteristics equation of $\det(J(E_0) - \lambda I_{11})$ is,

$$(\mu + \lambda)^2(k_9 + \lambda)(k_4 + \lambda)(k_5 + \lambda)(k_6 + \lambda)[\lambda^5 + A_1\lambda^4 + A_2\lambda^3 + A_3\lambda^2 + A_4\lambda + A_5] = 0. \quad (4.63)$$

Where

$$A_1 = k_1 + k_2 + k_3 + k_7 + k_8,$$

$$A_2 = k_1k_2 + k_1k_3 + k_2k_3 + \beta bp + \beta r + k_7k_8 - \beta_1\gamma_1 + (k_1 + k_2 + k_3)(k_7 + k_8),$$

$$A_3 = (k_1 + k_2 + k_3)(k_7k_8 - \beta_1\gamma_1) + (k_1k_2 + k_1k_3 + k_2k_3 + \beta bp + \beta r)(k_7 + k_8)(-k_1k_2k_3 + \beta bpk_3 + \beta rk_2),$$

$$A_4 = (k_1k_2 + k_1k_3 + k_2k_3 + \beta bp + \beta r)(k_7k_8 - \beta_1\gamma_1) + (k_7 + k_8)(-k_1k_2k_3 + \beta bpk_3 + \beta rk_2),$$

$$A_5 = (-k_1k_2k_3 + \beta bpk_3 + \beta rk_2)(k_7k_8 - \beta_1\gamma_1).$$

Clearly, from Equation (4.63) we have $\lambda_1 = \lambda_2 = -\mu$, $\lambda_3 = -k_9$, $\lambda_4 = -k_4$, $\lambda_5 = -k_5$, $\lambda_6 = -k_6$, since the all parameters are positive and $\lambda^5 + A_1\lambda^4 + A_2\lambda^3 + A_3\lambda^2 + A_4\lambda + A_5 = 0$. Thus, $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 are negative due to all the parameters are positive. Consequently, using the Routh-Hurwitz stability criterion, the roots of the equation $\lambda^5 + A_1\lambda^4 + A_2\lambda^3 + A_3\lambda^2 + A_4\lambda + A_5$ have negative real parts if the following condition holds.

$$\begin{cases} A_i > 0, \text{ for all } i=1, \dots, 5, A_1A_2A_3 > A_3^2 + A_1^2A_4, \\ (A_1A_4 - A_5)(A_1A_2A_3 - A_3^2 + A_1^2A_4) > A_5(A_1A_2 - A_3)^2 + A_1A_5^2. \end{cases}$$

Hence, the proof is completed. □

Global Stability of Disease Free Equilibrium Point of Co-infection

To investigate the global stability of disease free equilibrium, we use the method used by (Castillo-Chavez et al., 2002), and rewrite model system (4.1) as follows

$$\begin{cases} \frac{dX}{dt} = F(X, Z), \\ \frac{dZ}{dt} = G(X, Z), \quad G(X, 0) = 0, \end{cases} \quad (4.64)$$

where $X = (S, R, S_d)$ and $Z = (E, A, I_C, I_{CD}, I_{CC}, P, D, C)$ with $X \in \mathbb{R}_+^3$ denotes the number of uninfected individuals while $Z \in \mathbb{R}_+^8$ represents the number of infected and co-infected individuals. The disease-free equilibrium is denoting $E_0 = (X_0, 0, X_{0d}) = (\frac{\Lambda_1}{\mu}, 0, 0, 0, 0, 0, 0, \frac{\Lambda_2}{\mu}, 0, 0, 0)$. The conditions (H_1) and (H_2) below must be met to guarantee global asymptotically stability:

(H_1) For $\frac{dX}{dt} = F(X, 0)$, the equilibrium point E_0 is globally stable,

(H_2) $G(X, Z) = AZ - \hat{G}(X, Z)$, $\hat{G}(X, Z) \geq 0$ for $(X, Z) \in \mathbb{R}_+^8$,

where $A = D_Z G(X_0, 0, X_{0d})$ is a Metzler matrix (the non-diagonal entities of A are non-negative), and $\mathbb{R}_+^8$ is the biological feasible region of the model.

Theorem 4.4.4. *The disease free equilibrium point $E_0 = (X_0, 0, X_{0d})$ of the system ((4.1)) is globally asymptotically stable if $R_0 < 1$ and the conditions (H_1) and (H_2) holds.*

Proof. From the co-infection model (4.1), we have

$$\frac{dX}{dt} = F(X, Z) = \begin{bmatrix} \Lambda_1 - (\mu + \lambda)S(t) \\ \alpha_2 A(t) + \alpha_1 I_C(t) + \eta_1 I_{CD}(t) + \eta_2 I_{CC}(t) - (\mu + \omega_1 + \omega_2)R(t) \\ \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D}{N_d} S_d \end{bmatrix}$$

Hence

$$F(X, 0) = \begin{bmatrix} \Lambda_1 - \mu S(t) \\ 0 \\ \Lambda_2 - \mu S_d(t) \end{bmatrix}$$

$$\frac{dZ}{dt} = G(X, Z) = \begin{bmatrix} \lambda S(t) - (\mu + p + r)E(t) \\ pE(t) - (\mu + \alpha_2)A(t) \\ rE(t) - (\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)I_C(t) \\ \theta_1 I_C(t) + \psi_1 D(t) - (\mu + \delta_{cd} + \eta_1)I_{CD}(t) \\ \theta_2 I_C(t) + \psi_1 C(t) - (\mu + \delta_{cc} + \eta_2)I_{CC}(t) \\ \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu)P(t) \\ \gamma_1 P(t) - (\gamma_3 + \mu + \psi_1)D(t) + \omega_1 R(t) \\ \gamma_2 P(t) + \gamma_3 D(t) - (\mu + \delta_2 + \psi_2)C(t) + \omega_2 R(t) \end{bmatrix}$$

Therefore,

$$A = D_Z G(E_0, 0) = \begin{bmatrix} -c_1 & \beta b & \beta & 0 & 0 & 0 & 0 & 0 \\ p & -c_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ r & 0 & -c_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \theta_1 & -c_4 & 0 & 0 & \psi_1 & 0 \\ 0 & 0 & \theta_2 & 0 & -c_5 & 0 & 0 & \psi_2 \\ 0 & 0 & 0 & 0 & 0 & -c_6 & \beta_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_1 & -c_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_2 & \gamma_3 & -c_8 \end{bmatrix}$$

which is a Metzler Matrix. where, $c_1 = \mu + p + r$, $c_2 = \mu + r$, $c_3 = \mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2$, $c_4 = \mu + \delta_{cd} + \eta_1$, $c_5 = \mu + \delta_{cc} + \eta_2$, $c_6 = \gamma_1 + \gamma_2 + \mu$, $c_7 = \gamma_3 + \mu + \psi_1$, $c_8 = \mu + \delta_2 + \psi_2$. Here, $\hat{G}(X, Z) = AZ - G(X, Z)$, and hence

$$\hat{G}(X, Z) = \begin{bmatrix} \hat{G}_1(X, Z) \\ \hat{G}_2(X, Z) \\ \hat{G}_3(X, Z) \\ \hat{G}_4(X, Z) \\ \hat{G}_5(X, Z) \\ \hat{G}_6(X, Z) \\ \hat{G}_7(X, Z) \\ \hat{G}_8(X, Z) \end{bmatrix} = \begin{bmatrix} \beta b A + \beta I_C - \lambda S \\ 0 \\ 0 \\ 0 \\ \beta_1 D - \frac{\beta_1 D}{N_d} S_d \\ -\omega_1 R \\ -\omega_2 R \end{bmatrix}$$

Thus $\hat{G}_7(X, Z) = -\omega_1 R < 0$ and $\hat{G}_8(X, Z) = -\omega_2 R < 0$. This shows that condition (H_2) is not satisfied for $\hat{G}(X, Z) \not\geq 0$. As a result, E_0 and then the disease-free equilibrium point E_0 may not be globally asymptotically stable. $\square$

CHAPTER 5

OPTIMAL CONTROL ANALYSIS

In chapter four, we discussed model formulation and its detailed analysis without considering the intervention measures. In this chapter, the intervention mechanism is addressed using the theory of optimal control and Pontryagin's minimum principle which govern the necessary conditions for the optimal control of the spread of COVID-19 and diabetes co-infection.

5.1 Extension into optimal control

In this section, we extended a model presented in chapter 4 to study the transmission dynamics of co-infection of COVID-19 and diabetic. In this model, we introduce three control functions, the control function u_1 represents personal protective measures (wearing face mask, keeping personal sanitation (hand washing, using sanitizer) and social distancing) that help to reduce contact rate, the second control u_2 which represents intensive medical care for all the confirmed cases with COVID-19 to increase recover rate of the individuals and u_3 represents awareness program for diabetics without complications. We assume that the controls are bounded between 0 and 1. In the context of this assumption, when the controls take the minimum value 0, it means no extra measures are implemented for the reduction of the co-infected with COVID-19 and diabetics. While the maximum value 1 corresponds to 100% successfully implementation of the prevention program. Thus, we assumed $0 \leq u_i < 1$, $i = 1, 2, 3$. After incorporating the three controls in (4.1) we obtain the following optimal

control problem

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda_1 - (\mu + \lambda(1 - u_1(t)))S(t), \\
\frac{dE(t)}{dt} &= (1 - u_1(t))\lambda S(t) - (\mu + p + r)E(t), \\
\frac{dA(t)}{dt} &= pE(t) - (\mu + \alpha_2)A(t), \\
\frac{dI_C(t)}{dt} &= rE(t) - (\mu + \delta_1 + \alpha_1)I_C(t) - (\theta_1 + u_2(t))I_C(t) - (\theta_2 + u_2(t))I_C(t), \\
\frac{dR(t)}{dt} &= \alpha_2 A(t) + \alpha_1 I_C(t) + \eta_1 I_{CD}(t) + \eta_2 I_{CC}(t) - (\mu + \omega_1 + \omega_2)R(t), \\
\frac{dI_{CD}(t)}{dt} &= (\theta_1 + u_2(t))I_C(t) + \psi_1(1 - u_3(t))D(t) - (\mu + \delta_{cd} + \eta_1)I_{CD}(t), \\
\frac{dI_{CC}(t)}{dt} &= (\theta_2 + u_2(t))I_C(t) + \psi_2 C(t) - (\mu + \delta_{cc} + \eta_2)I_{CC}(t), \\
\frac{dS_d(t)}{dt} &= \Lambda_2 - \mu S_d(t) - \frac{\beta_1 D(t)}{N_d} S_d(t), \\
\frac{dP(t)}{dt} &= \frac{\beta_1 D(t)}{N_d} S_d(t) - (\gamma_1 + \gamma_2 + \mu)P(t), \\
\frac{dD(t)}{dt} &= \gamma_1 P(t) - \gamma_3(1 - u_3(t))D(t) - \mu D(t) - \psi_1(1 - u_3(t))D(t) + \omega_1 R(t), \\
\frac{dC(t)}{dt} &= \gamma_2 P(t) + \gamma_3(1 - u_3(t))D(t) - (\mu + \delta_2)C(t) - \psi_2 C(t) + \omega_2 R(t).
\end{aligned} \tag{5.1}$$

Where $\lambda = \frac{\beta(bA + I_C)}{N_c}$, $S(0) \geq 0$, $E(0) \geq 0$, $A(0) \geq 0$, $I_C(0) \geq 0$, $R(0) \geq 0$, $I_{CD}(0) \geq 0$, $I_{CC}(0) \geq 0$, $S_d(0) \geq 0$, $P(0) \geq 0$, $D(0) \geq 0$ and $C(0) \geq 0$ are the initial state.

The objective of this extension is to find the optimal values $\bar{u} = (\bar{u}_1, \bar{u}_2, \bar{u}_3)$ of the controls $u = (u_1, u_2, u_3)$ such that the associated state trajectories, are solution of the system (5.1) in the intervention time interval $[0, T]$ with initial conditions to minimize the objective functional.

The optimal control problem is to minimize the objective (cost) functional (J) considering the costs of preventive measure of susceptible individuals, cost of intensive medical care of symptomatic infected individuals and cost of awareness program for diabetics without complications. The goal of the implemented strategy is to reduce exposed, symptomatic, coinfectd individuals with optimal cost.

We define the cost functional for the minimization problem as

$$J[u_1, u_2, u_3] = \int_0^T \left(C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} \sum_{i=1}^3 B_i u_i^2 \right) \mapsto \min \tag{5.2}$$

subject to (5.1) with its initial condition and where C_1 , C_2 , C_3 , C_4 and C_5 are relative con-

stant that measures the relative importance of reducing the associated classes on the spread of the disease and the relative weight constants B_i is a measure of the relative cost of the interventions associated with the control u_i for $i = 1, 2, 3$ and balances the units of integrand to reduce the dominance of any of the term in the integral. In the cost functional, the term $C_1 E(t)$ describe the cost related to exposed class, $C_2 I(t)$ denotes the cost related to symptomatic compartment, $C_3 I_{CD}(t)$ denotes the cost related to co-infected with diabetic without complications, $C_4 I_{CC}(t)$ denotes the cost related to co-infected with diabetic with complications while $-C_5 D(t)$ denotes the cost related to diabetic without complications that improve awareness program. Additionally, the functional J corresponds the total cost due to co-infected and its control strategies. Lastly, the fixed constant T denotes the terminal intervention time. The set of admissible control functions is defined by

$$\Omega = \left\{ (u_1(\cdot), u_2(\cdot), u_3(\cdot)) \in (L^\infty(0, T))^3 : 0 \leq u_1(t), u_2(t), u_3(t) < 1, t \in [0, T] \right\} \quad (5.3)$$

Then we consider the optimal control problem of obtaining $\bar{S}, \bar{E}, \bar{A}, \bar{I}_C, \bar{R}, \bar{I}_{CD}, \bar{I}_{CC}, \bar{S}_d, \bar{P}, \bar{D}$ and $\bar{C}$ associated with an admissible control $(u_1(t), u_2(t), u_3(t)) \in \Omega$, on the intervention time interval $[0, T]$, subjected to the state control system (5.1) in $\mathbb{R}_+^{11}$ with its initial condition and minimizing the cost functional (5.2). More precisely, the optimal control problem can be defined as

$$J[\bar{u}_1, \bar{u}_2, \bar{u}_3] = \min_{\Omega} J[u_1(\cdot), u_2(\cdot), u_3(\cdot)] \quad (5.4)$$

satisfying (5.1) and its initial conditions.

5.2 Existence of the optimal control problem

In this section, we prove the existence of an optimal control for model (5.1).

Theorem 5.2.1. *There exist an optimal control $u = (u_1, u_2, u_3)$ and the corresponding solution vector $(\bar{S}, \bar{E}, \bar{A}, \bar{I}_C, \bar{R}, \bar{I}_{CD}, \bar{I}_{CC}, \bar{S}_d, \bar{P}, \bar{D})$ to the state initial value problem (5.1) that minimizes the cost functional $J(u)$ of (5.2) over the set of admissible control Ω .*

Proof. The non trivial requirement on the set of admissible controls and the set of end conditions are followed by (Fleming & Rishel, 2012).

(i). The set of all solution to system (5.2) with corresponding control functions in Ω is non empty.

(ii). The control set is convex and closed.

(iii). The integral of the objective function is convex.

(iv). The integrand $F(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u)$ in equation (5.2) is convex with respect to control variables and additionally fulfills that

$F(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u) \geq g(u)$, where g is continuous and $\|u\|^{-1}g(u) \rightarrow$

$+\infty$ as $\|u\| \rightarrow \infty$. If the solutions of the state equations are a priori bounded and if the state equations are continuous and Lipschitz continuous in the state variables, then there is a unique solution corresponding to every admissible control in the given domain. With the result that, if $g(t, x, u)$ is bounded, continuous, and Lipschitz in the state variable, then there exist a unique solution corresponding to every admissible control Ω . Hence, for any $u \in \Omega$ and the state variables, we have

$$0 \leq N \leq \frac{\Lambda}{\mu} \quad (5.5)$$

and non empty by model assumption. Furthermore, with the bounded established (5.5) it implies that the state system is continuous and bounded. It is possible to show the boundedness of the partial derivative with respect to the state variable i.e $\frac{\partial g}{\partial x}$ exist and finite, which established the system is Lipschitz with respect to the state variables. This established the proof of condition (i) is complete.

To prove (ii), consider $\Omega = \{u \in \mathbb{R}^3 : \|u\| \leq 1\}$, let $u_1, u_2 \in \Omega$ such that $u_1 \leq 1$ and $u_2 \leq 1$. Then for any $k \in [0, T]$, $\|ku_1 + (1 - k)u_2\| \leq k\|u_1\| + (1 - k)\|u_2\| \leq 1$. This implies that Ω is convex and closed.

Next we verify condition (iii) as follows; the integral of the cost function is given by

$$F(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u) = C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} \sum_{i=1}^3 B_i u_i^2 \quad (5.6)$$

Recall that any affine function is a convex and the sum of a convex function is a convex (Chong & Zak, 2004). Thus, F is convex on Ω and (iii) is satisfied.

Finally, to verify condition (iv), The integrand of the cost functional

$F(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u) = C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} \sum_{i=1}^3 B_i u_i^2$, is the sum of convex function and hence convex with respect to control variables. Furthermore,

$$F(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u) = \left(C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} \sum_{i=1}^3 B_i u_i^2 \right) \geq \frac{1}{2} \sum_{i=1}^3 B_i u_i^2 \quad (5.7)$$

Let $\delta = \min(\frac{B_1}{2}, \frac{B_2}{2}, \frac{B_3}{2}) > 0$ and define a continuous function $g(u) = \delta \|u\|^2$. Then from equation (5.6) we have

$F(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u) \geq g(u)$. Clearly $\|u\|^{-1} g(u) \rightarrow +\infty$ as $\|u\| \rightarrow \infty$. Thus, condition (iv) is achieved. With this we conclude that the existence of an optimal

control $(\bar{S}, \bar{E}, \bar{A}, \bar{I}_C, \bar{R}, \bar{I}_{CD}, \bar{I}_{CC}, \bar{S}_d, \bar{P}, \bar{D}, \bar{u})$ that minimizes the cost functional of (5.2) over the set of admissible control Ω . The proof is completed. $\square$

5.3 Characterization of Optimal Control Solutions

In order to derive the necessary conditions for the optimal control pair the Pontryagin's Minimum Principle (Pontryagin et al., 2018) is used. According to the Pontryagin's Minimum Principle, if $\bar{u} \in \Omega$ (5.4) with fixed final time T , then there exists a non-trivial absolutely continuous mapping

$$\lambda : [0, T] \rightarrow \mathbb{R}^{11} = (\lambda_i(t), i = 1 \dots 11)$$

called the adjoint vector, such that

$$J[u_1, u_2, u_3] = \int_0^T \left(C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} \sum_{i=1}^3 B_i u_i^2 \right) \mapsto \min \quad (5.8)$$

subject to $\sum_{i=1}^{11} \lambda_i(t) g_i(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u_1, u_2, u_3)$

where $g_i(t, S, E, A, I_C, R, I_{CD}, I_{CC}, S_d, P, D, C, u_1, u_2, u_3)$ stands for the right hand side of the constraints (5.1) for $i = 1, 2, 3 \dots 11$. Then

1. The Hamiltonian of the given system is defined as follows:

$$H = C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} \sum_{i=1}^3 B_i u_i^2 + \sum_{i=1}^{11} \lambda_i(t) g_i(t) \quad (5.9)$$

2. The control system,

$$\begin{aligned} S' &= \frac{\partial H}{\partial \lambda_1}, E' = \frac{\partial H}{\partial \lambda_2}, A' = \frac{\partial H}{\partial \lambda_3}, I_C' = \frac{\partial H}{\partial \lambda_4}, R' = \frac{\partial H}{\partial \lambda_5}, I_{CD}' = \frac{\partial H}{\partial \lambda_6}, I_{CC}' = \frac{\partial H}{\partial \lambda_7}, S_d' = \frac{\partial H}{\partial \lambda_8}, \\ P' &= \frac{\partial H}{\partial \lambda_9}, D' = \frac{\partial H}{\partial \lambda_{10}}, C' = \frac{\partial H}{\partial \lambda_{11}}. \end{aligned}$$

3. The adjoint system

$$\begin{aligned} \lambda_1 &= -\frac{\partial H}{\partial S}, \lambda_2 = -\frac{\partial H}{\partial E}, \lambda_3 = -\frac{\partial H}{\partial A}, \lambda_4 = -\frac{\partial H}{\partial I_C}, \lambda_5 = -\frac{\partial H}{\partial R}, \lambda_6 = -\frac{\partial H}{\partial I_{CD}}, \lambda_7 = -\frac{\partial H}{\partial I_{CC}}, \\ \lambda_8 &= -\frac{\partial H}{\partial S_d}, \lambda_9 = -\frac{\partial H}{\partial P}, \lambda_{10} = -\frac{\partial H}{\partial D}, \lambda_{11} = -\frac{\partial H}{\partial C}. \end{aligned}$$

4. The optimality condition

$$H(\bar{S}, \bar{E}, \bar{A}, \bar{I}_C, \bar{R}, \bar{I}_{CD}, \bar{I}_{CC}, \bar{S}_d, \bar{P}, \bar{D}, \bar{u}, \bar{\lambda}) = \min_{\Omega_\epsilon} H(\bar{S}, \bar{E}, \bar{A}, \bar{I}_C, \bar{R}, \bar{I}_{CD}, \bar{I}_{CC}, \bar{S}_d, \bar{P}, \bar{D}, \bar{u}, \bar{\lambda})$$

holds for almost all $t \in [0, T]$.

5. Moreover, the transversality condition

$\lambda_i(T)$, for all $i = 1, 2, \dots, 11$ also holds true. In the following result, we give the characterization of optimal control.

Theorem 5.3.1. *The optimal control problem (5.4) with fixed final time T admits a unique optimal solution $(\bar{S}, \bar{E}, \bar{A}, \bar{I}_C, \bar{R}, \bar{I}_{CD}, \bar{I}_{CC}, \bar{S}_d, \bar{P}, \bar{D})$ associated with an optimal control $u = (u_1, u_2, u_3)$ for all $t \in [0, T]$. Moreover, there exist adjoint function λ_i , for $i = 1, 2, 3, \dots, 11$ such that*

$$\left\{ \begin{array}{l} \frac{d\lambda_1}{dt} = (\lambda_1 - \lambda_2)(1 - u_1)\lambda + \mu\lambda_1, \\ \frac{d\lambda_2}{dt} = -C_1 + \lambda_1(\mu + p + r) - \lambda_2p - \lambda_3r, \\ \frac{d\lambda_3}{dt} = \frac{\beta bS}{N_c}(1 - u_1)(\lambda_1 - \lambda_2) + \mu\lambda_3 + \alpha_2(\lambda_3 - \lambda_5), \\ \frac{d\lambda_4}{dt} = -C_2 + \frac{\beta S}{N_c}(1 - u_1)(\lambda_1 - \lambda_2) + (\mu + \delta_1)\lambda_4 + \alpha_1(\lambda_4 - \lambda_5) + (\theta_1 + u_2)(\lambda_4 - \lambda_6) \\ + (\theta_2 + u_2)(\lambda_4 - \lambda_7), \\ \frac{d\lambda_5}{dt} = \mu\lambda_5 + \omega_1(\lambda_5 - \lambda_{10}) + \omega_2(\lambda_5 - \lambda_{11}), \\ \frac{d\lambda_6}{dt} = -C_3 + \eta_1(\lambda_6 - \lambda_5) + (\mu + \delta_{cd})\lambda_6, \\ \frac{d\lambda_7}{dt} = -C_4 + \eta_2(\lambda_7 - \lambda_5) + (\mu + \delta_{cc})\lambda_7, \\ \frac{d\lambda_8}{dt} = \mu\lambda_8 + \frac{\beta_1 D}{N_d}(\lambda_8 - \lambda_9), \\ \frac{d\lambda_9}{dt} = \mu\lambda_9 + \gamma_1(\lambda_9 - \lambda_{10}) + \gamma_2(\lambda_9 - \lambda_{11}), \\ \frac{d\lambda_{10}}{dt} = C_5 - \psi_1(1 - u_3)(\lambda_{10} + \lambda_6) + \frac{\beta S_d}{N_d}(\lambda_8 - \lambda_9) + \gamma_3(1 - u_3)(\lambda_{10} - \lambda_{11}) + \mu\lambda_{10}, \\ \frac{d\lambda_{11}}{dt} = \psi_2(\lambda_{11} - \lambda_7) + (\mu + \delta_2)\lambda_{11}. \end{array} \right. \quad (5.10)$$

With transversality conditions $\lambda_i(T) = 0$ for all $i = 1, 2, 3, \dots, 11$. Moreover, the corresponding optimal controls $(\bar{u}_1(t), \bar{u}_2(t), \bar{u}_3(t))$ are given by

$$\begin{aligned} \bar{u}_1 &= \min \left\{ \max \left\{ 0, \frac{\bar{\lambda}\bar{S}(\lambda_2 - \lambda_1)}{B_1} \right\}, 1 \right\}, \\ \bar{u}_2 &= \min \left\{ \max \left\{ 0, \frac{[(\lambda_6 - \lambda_4) + (\lambda_7 - \lambda_4)]I_C}{B_2} \right\}, 1 \right\}, \\ \bar{u}_3 &= \min \left\{ \max \left\{ 0, \frac{[\psi_1(\lambda_6 + \lambda_{10}) + \gamma_3(\lambda_{11} + \lambda_{10})]D}{B_3} \right\}, 1 \right\}. \end{aligned}$$

Proof. The Hamiltonian function associated with the system is defined as follows:

$$\begin{aligned}
 H(\bar{S}, \bar{E}, \bar{A}, \bar{I}_C, \bar{R}, \bar{I}_{CD}, \bar{I}_{CC}, \bar{S}_d, \bar{P}, \bar{D}, \bar{C}, \bar{u}_1, \bar{u}_2, \bar{u}_3) = & C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} \\
 \sum_{i=1}^3 B_i u_i^2 + \sum_{i=1}^{11} \lambda_i(t) g_i(t) = & C_1 E + C_2 I_C + C_3 I_{CD} + C_4 I_{CC} - C_5 D + \frac{1}{2} (B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2) + \lambda_1 \\
 [\Lambda_1 - (\mu + \lambda(1 - u_1(t)))S(t)] + & \lambda_2 [(1 - u_1(t))\lambda S(t) - (\mu + p + r)E(t)] + \lambda_3 [pE(t) - (\mu + \alpha_2)A(t)] \\
 + \lambda_4 [rE(t) - (\mu + \delta_1 + \alpha_1)I_C(t) - & (\theta_1 + u_2(t))I_C(t) - (\theta_2 + u_2(t))I_C(t)] + \lambda_5 [\alpha_2 A(t) + \alpha_1 I_C(t) + \\
 \eta_1 I_{CD}(t) + \eta_2 I_{CC}(t) - (\mu + \omega_1 + \omega_2)R] + & \lambda_6 [(\theta_1 + u_2(t))I_C(t) + \psi_1(1 - u_3(t))D(t) - (\mu + \delta_{cd} + \eta_1) \\
 I_{CD}] + \lambda_7 [(\theta_2 + u_2(t))I_C(t) + \psi_2 C(t) - & (\mu + \delta_{cc} + \eta_2)I_{CC}] + \lambda_8 [\Lambda_2 - (\mu + \frac{\beta_1 D(t)}{N_d})S_d(t)] \\
 + \lambda_9 [\frac{\beta_1 S_d(t)D(t)}{N_d} - (\gamma_1 + \gamma_2 + \mu)P(t)] + & \lambda_{10} [\gamma_1 P(t) - \gamma_3(1 - u_3(t))D(t) - \mu D(t) + \psi_1(1 - u_3(t))D \\
 + \omega_1 R(t)] + \lambda_{11} [\gamma_2 P(t) + \gamma_3(1 - u_3(t))D(t) - & (\mu + \delta_2)C(t) - \psi_2 C(t) + \omega_2 R(t)]
 \end{aligned}$$

where $\lambda_i(t)$, for $i = 1, 2, 3, \dots, 11$ are the adjoint functions. The adjoint system can be obtained as follows,

$$\left\{ \begin{aligned}
 \frac{d\lambda_1}{dt} &= (\lambda_1 - \lambda_2)(1 - u_1)\lambda + \mu\lambda_1, \\
 \frac{d\lambda_2}{dt} &= -C_1 + \lambda_1(\mu + p + r) - \lambda_2 p - \lambda_3 r, \\
 \frac{d\lambda_3}{dt} &= \frac{\beta b S}{N_c} (1 - u_1)(\lambda_1 - \lambda_2) + \mu\lambda_3 + \alpha_2(\lambda_3 - \lambda_5), \\
 \frac{d\lambda_4}{dt} &= -C_2 + \frac{\beta S}{N_c} (1 - u_1)(\lambda_1 - \lambda_2) + (\mu + \delta_1)\lambda_4 + \alpha_1(\lambda_4 - \lambda_5) + (\theta_1 + u_2)(\lambda_4 - \lambda_6) \\
 &+ (\theta_2 + u_2)(\lambda_4 - \lambda_7), \\
 \frac{d\lambda_5}{dt} &= \mu\lambda_5 + \omega_1(\lambda_5 - \lambda_{10}) + \omega_2(\lambda_5 - \lambda_{11}), \\
 \frac{d\lambda_6}{dt} &= -C_3 + \eta_1(\lambda_6 - \lambda_5) + (\mu + \delta_{cd})\lambda_6, \\
 \frac{d\lambda_7}{dt} &= -C_4 + \eta_2(\lambda_7 - \lambda_5) + (\mu + \delta_{cc})\lambda_7, \\
 \frac{d\lambda_8}{dt} &= \mu\lambda_8 + \frac{\beta_1 D}{N_d}(\lambda_8 - \lambda_9), \\
 \frac{d\lambda_9}{dt} &= \mu\lambda_9 + \gamma_1(\lambda_9 - \lambda_{10}) + \gamma_2(\lambda_9 - \lambda_{11}), \\
 \frac{d\lambda_{10}}{dt} &= C_5 + \psi_1(1 - u_3)(\lambda_{10} - \lambda_6) + \frac{\beta S_d D}{N_d}(\lambda_8 - \lambda_9) + \gamma_3(1 - u_3)(\lambda_{10} - \lambda_{11}) + \mu\lambda_{10}, \\
 \frac{d\lambda_{11}}{dt} &= \psi_2(\lambda_{11} - \lambda_7) + (\mu + \delta_2)\lambda_{11}.
 \end{aligned} \right.$$

The state variables are not assigned at the final time T . Hence, following (Lenhart & Workman, 2007) the transversality conditions (or boundary conditions) becomes $\lambda_i(t)$, for $i = 1, 2, 3, \dots, 11$.

By the optimality condition, we obtain $\bar{u}_i$ from $\frac{\partial H}{\partial u_i} = 0$ for $i = 1, 2, 3$. This implies

$$\begin{aligned}
 (i). \quad \frac{\partial H}{\partial u_1} &= B_1 u_1 + \bar{\lambda} \bar{S}(\lambda_1 - \lambda_2) \implies \bar{u}_1 = \frac{\bar{\lambda} \bar{S}(\lambda_2 - \lambda_1)}{B_1} \text{ where } \bar{\lambda} = \frac{\beta(b\bar{A} + \bar{I}_C)}{N_c} \\
 (ii). \quad \frac{\partial H}{\partial u_2} &= B_2 u_2 + [(\lambda_4 - \lambda_6) + (\lambda_4 - \lambda_7)] I_C \implies \bar{u}_2 = \frac{[(\lambda_6 - \lambda_4) + (\lambda_7 - \lambda_4)] I_C}{B_2} \\
 (iii). \quad \frac{\partial H}{\partial u_3} &= B_3 u_3 - [\psi_1(\lambda_{10} + \lambda_6) + \gamma_3(\lambda_{10} + \lambda_{11})] D \implies \bar{u}_3 = \frac{[\psi_1(\lambda_6 + \lambda_{10}) + \gamma_3(\lambda_{11} + \lambda_{10})] D}{B_3}
 \end{aligned}$$

From boundedness on $\bar{u} = (\bar{u}_1, \bar{u}_2, \bar{u}_3)$ and minimality condition we obtain;

$$\begin{aligned}
 \bar{u}_1 &= \begin{cases} 0, & \text{if } \frac{\partial H}{\partial u_1} > 0, \\ \frac{\bar{\lambda} \bar{S}(\lambda_2 - \lambda_1)}{B_1}, & \text{if } \frac{\partial H}{\partial u_1} = 0, \\ 1, & \text{if } \frac{\partial H}{\partial u_1} < 0. \end{cases} \\
 \bar{u}_2 &= \begin{cases} 0, & \text{if } \frac{\partial H}{\partial u_2} > 0, \\ \frac{[(\lambda_6 - \lambda_4) + (\lambda_7 - \lambda_4)] I_C}{B_2}, & \text{if } \frac{\partial H}{\partial u_2} = 0, \\ 1, & \text{if } \frac{\partial H}{\partial u_2} < 0. \end{cases} \\
 \bar{u}_3 &= \begin{cases} 0, & \text{if } \frac{\partial H}{\partial u_3} > 0, \\ \frac{[\psi_1(\lambda_6 + \lambda_{10}) + \gamma_3(\lambda_{11} + \lambda_{10})] D}{B_3} = 0, & \text{if } \frac{\partial H}{\partial u_3} = 0, \\ 1, & \text{if } \frac{\partial H}{\partial u_3} < 0. \end{cases}
 \end{aligned}$$

In compact form, the optimal control $\bar{u} = (\bar{u}_1, \bar{u}_2, \bar{u}_3)$ can be summarized as

$$\begin{aligned}
 \bar{u}_1 &= \min \left\{ \max \left\{ 0, \frac{\bar{\lambda} \bar{S}(\lambda_2 - \lambda_1)}{B_1} \right\}, 1 \right\}, \\
 \bar{u}_2 &= \min \left\{ \max \left\{ 0, \frac{[(\lambda_6 - \lambda_4) + (\lambda_7 - \lambda_4)] I_C}{B_2} \right\}, 1 \right\}, \\
 \bar{u}_3 &= \min \left\{ \max \left\{ 0, \frac{[\psi_1(\lambda_6 + \lambda_{10}) + \gamma_3(\lambda_{11} + \lambda_{10})] D}{B_3} \right\}, 1 \right\}.
 \end{aligned}$$

This completes the proof. □

CHAPTER 6

NUMERICAL SIMULATION

In this chapter, we present and discuss numerically the behaviour of the solutions of the system (4.2) and (5.1) for different values of parameters given in the model. The simulation process is carried out using MATLAB software. We start by estimating the values of parameter used in the model. Then we illustrate the simulation results graphically.

6.1 Simulation procedure and graphical results discussion

In this section, we illustrate numerically the solution of the optimal control problem proposed in system (5.1) and explain the impact of control strategy on the spread of the diseases. For this purpose, we use the forward-backward sweep method presented in the book of (Lenhart & Workman, 2007).

To briefly summarize the numerical simulation procedure, first we perform forward fourth order Runge-Kutta scheme to solve system (5.1) over the interval $[0, T]$ with its initial condition and the transversality conditions $\lambda_i(T) = 0$; $i = 1, 2, 3, \dots, 11$, where $T = 30$ is simulation time. In contrary we use backward fourth order Runge-Kutta scheme to solve system (5.10) using the current iteration solution of (5.1). The control is updated by using a convex combination of the previous control and the values computed in the characterizations process. The iteration continuous until the values of the unknowns at the previous iteration are very close to the values of present iteration.

To perform the numerical simulation, we assumed the initial population of $E(0) = 75000$, $A(0) = 25000$, $R(0) = 20000$, $S_d(0) = 1000000$, $P(0) = 500000$, $D(0) = 300000$, $C(0) = 200000$, $I_{CD}(0) = 5$, $I_{CC}(0) = 2$ and the remaining $I_C(0) = 26$ from the collected real data (Habtamu, 2021). Also the initial susceptible population is obtained $S(0) = N - (E(0) + A(0) + I_C(0) + R(0) + S_d(0) + P(0) + D(0) + C(0) + I_{CD} + I_{CC}) = 118870848$ and the total population of Ethiopia is $N(0) = 120990881$ populations. The natural death rate is computed as $\mu = \frac{1}{(67.44 \times 12)}$ per year, where 67.44 years is the av-



average life expectancy in Ethiopia (WHO, 2022a). The recruitment rate, is then calculated as $\Lambda_1 = \mu \times N_c(0) = 146593$ per month, where $N_c = 118990874$ and $\Lambda_2 = \mu \times N_d = 2470$ per month, where $N_d = 2000000$. The cost coefficients corresponding to our controls u_i ; $i = 1, 2, 3$ variables are estimated to be $B_1 = 20$, $B_2 = 20$, $B_3 = 15$ and the relative importance of reducing the associated classes on the spread of the disease are $C_1 = 1$, $C_2 = 10000$, $C_3 = 200$, $C_4 = 1$ and $C_5 = 1$, using all necessary information above as input, we analysis and compare the numerical results of the effect of controls on the spread of COVID-19 and diabetes co-infection in populations.

Implementing one intervention only is not enough to reduce the disease totally from the community. Thus we considered the following listed strategies which incorporate pairwise control and all control intervention at a time.

- **Strategy A:** Applying preventive measures (u_1) and intensive medical care for all the confirmed cases with COVID-19 of the individuals (u_2) without considering awareness program for diabetics without complications for low levels of physical activity and irregular eating patterns (u_3).
- **Strategy B:** Applying preventive measures (u_1) and awareness program for diabetics without complications for low levels of physical activity and irregular eating patterns (u_3) without considering intensive medical care for all the confirmed cases with COVID-19 of the individuals (u_2).
- **Strategy C:** Applying intensive medical care for all the confirmed cases with COVID-19 of the individuals (u_2) and awareness program for diabetics without complications for low levels of physical activity and irregular eating patterns (u_3) without considering preventive measures (u_1).
- **Strategy D:** Using all the three control preventive measures (u_1), intensive medical care for all the confirmed cases with COVID-19 of the individuals (u_2) and awareness program for diabetics without complications for low levels of physical activity and irregular eating patterns (u_3).

6.1.1 Strategy A: Control with preventive measures and intensive medical care

Under this strategies, we simulated the model using preventive measures (u_1) and intensive medical care for all the confirmed cases of the individuals (u_2) to optimize the objective functional $J(u)$ without considering awareness program for diabetics without complications for low levels of physical activity and irregular eating patterns (u_3) were set to zero.

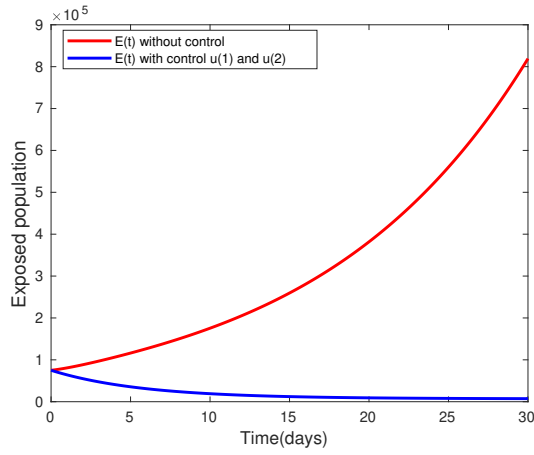


Figure 6.1: Exposed population without and with control u_1 and u_2

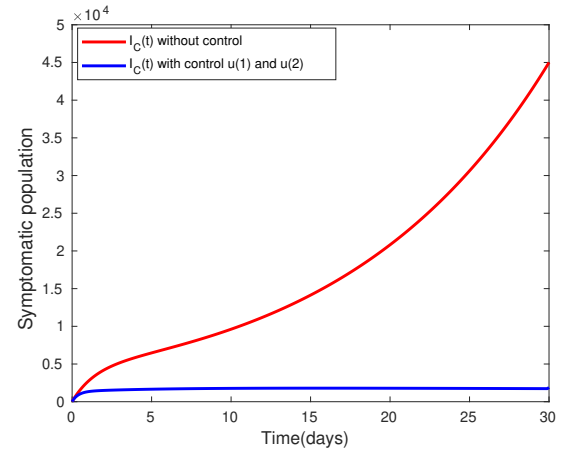


Figure 6.2: Symptomatic population without and with control u_1 and u_2

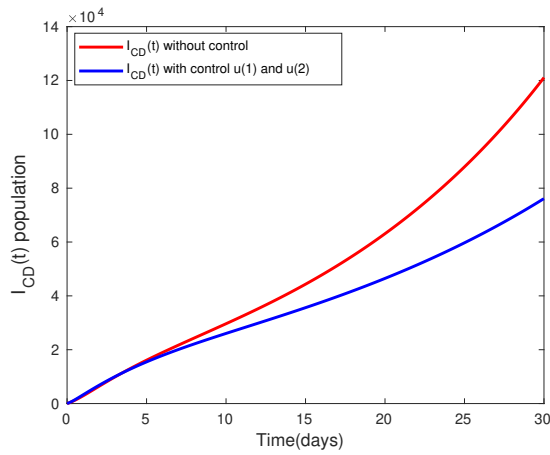


Figure 6.3: $I_{CD}(t)$ population without and with control u_1 and u_2

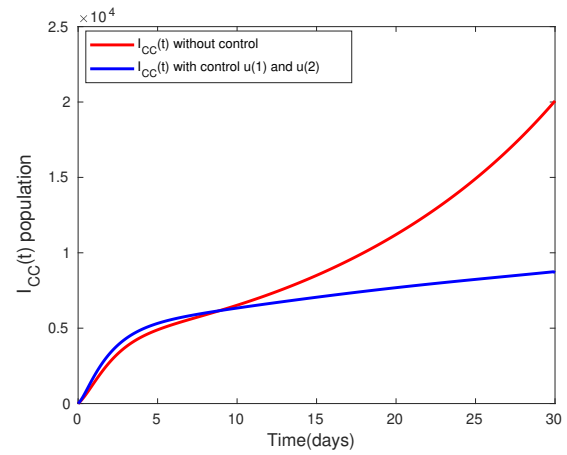


Figure 6.4: $I_{CC}(t)$ population without and with control u_1 and u_2

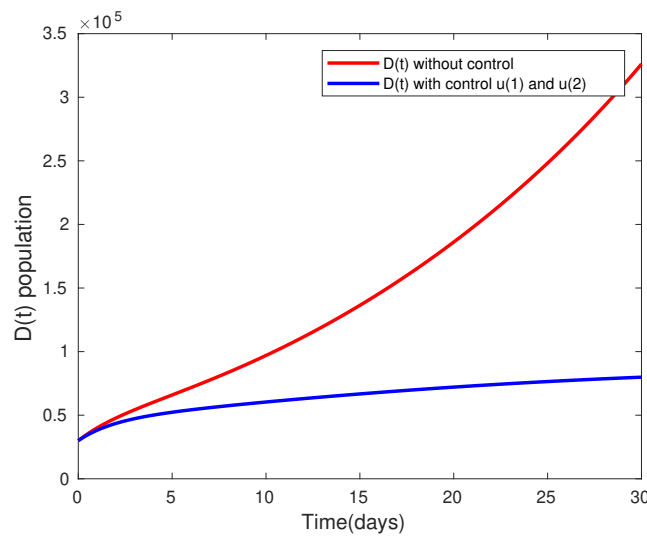


Figure 6.5: Diabetic without complications population without and with control u_1 and u_2

From the numerical result depicted in Figure 6.1 above, we observed that in the absence of control strategies the number of exposed populations of COVID-19 are increasing rapidly to 8.19×10^5 and in the presence of u_1 and u_2 controls the number of exposed populations of COVID-19 are decreasing and about 8365.52 at final time. From the second numerical result depicted in Figure 6.2 above experimented, we observed that the number of symptomatic individuals of COVID-19 are increasing rapidly in the absence of control strategies and it will be 4.5×10^4 and in the presence of u_1 and u_2 controls the number of symptomatic populations are decreasing and 1891.105 at final time. From the third numerical result depicted in Figure 6.3 above, we observed that the number of COVID-19 and diabetic without complications are increasing rapidly in the absence of control strategies and it will be 12×10^4 and in the presence of u_1 and u_2 controls decreased to 7.607×10^4 at final time. From Figure 6.4 the number of COVID-19 and diabetic with complications are increasing to 2.01×10^4 and in the presence of u_1 and u_2 controls decreased to 8687.537 at final time. From the Figure 6.5 in the absence of control strategies diabetic without complications are increasing to 3.2×10^5 and in the presence of u_1 and u_2 controls decreased to 7.98×10^4 at final time. Hence, this strategy is effective to reduce the number of exposed and symptomatic individuals and less effective to reduce the number of both co-infected individuals and diabetic without complications individuals.

6.1.2 Strategy B: Control with preventive measures and awareness program

Under this strategies, we simulated the model using preventive measures (u_1) and awareness program for diabetics without complications for low levels of physical activity and irregular eating patterns (u_3) to optimize the objective functional $J(u)$ without considering intensive medical care for all the confirmed cases of the individuals (u_2) were set to zero.

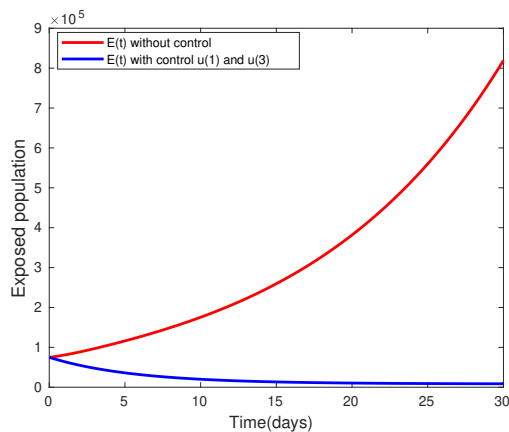


Figure 6.6: Exposed population without and with control u_1 and u_3

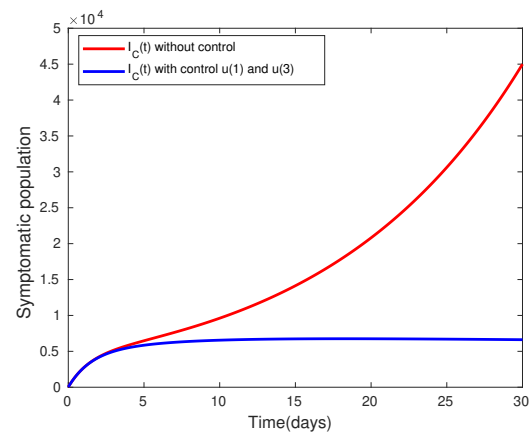


Figure 6.7: Symptomatic population without and with control u_1 and u_3

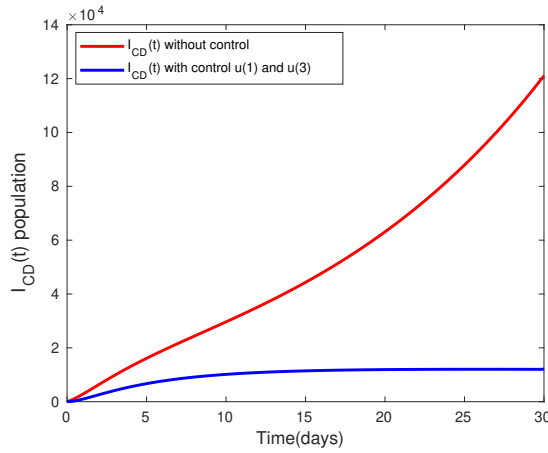


Figure 6.8: $I_{CD}(t)$ population without and with control u_1 and u_3

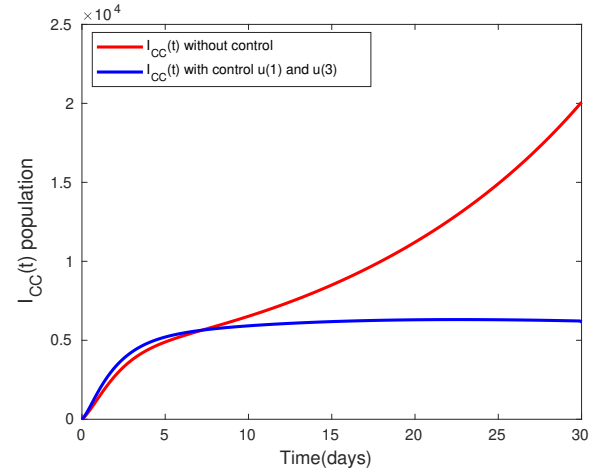


Figure 6.9: $I_{CC}(t)$ population without and with control u_1 and u_3

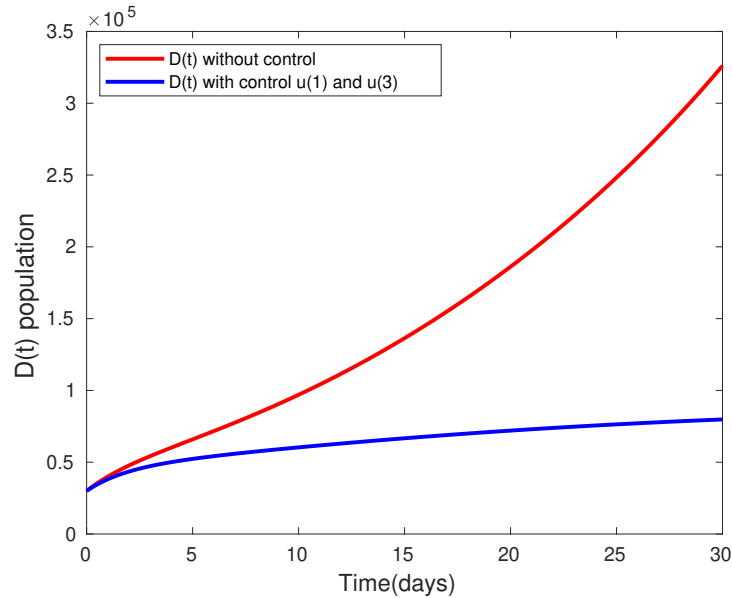


Figure 6.10: Diabetic without complications population without and with control u_1 and u_3

From the numerical result depicted in Figure 6.6 above, we observed that in the absence of control strategies the number of exposed populations of COVID-19 are increasing to 8.19×10^5 and in the presence of u_1 and u_3 controls the number of exposed populations of COVID-19 are decreasing and about 9946.7 at final time. From the second numerical result depicted in Figure 6.7 above experimented, we observed that the number of symptomatic individuals of COVID-19 are increasing rapidly in the absence of control strategies and it will be 4.5×10^4 and in the presence of u_1 and u_3 controls the number of symptomatic populations are decreasing and 6621.97 at final time. From the third numerical result depicted in Figure 6.8 above, we observed that the number of COVID-19 and diabetic without complications are increasing rapidly in the absence of control strategies and it will be 12×10^4 and in the



presence of u_1 and u_3 controls decreased to 12.28×10^3 at final time. From Figure 6.9 the number of COVID-19 and diabetic with complications are 2.01×10^4 and in the presence of u_1 and u_3 controls 6156.028 at final time. From the Figure 6.10 in the absence of control strategies diabetes without complications are 3.2×10^5 and in the presence of u_1 and u_3 controls 7.9772×10^4 at final time. Hence, this strategy is effective to reduce the number of exposed, symptomatic and co-infected class $I_{CC}(t)$ individuals and less effective to reduce the number of diabetic without complications and co-infected $I_{CD}(t)$ individuals.

6.1.3 Strategy C: Intensive medical care and awareness program

Under this strategies, we simulated the model using intensive medical care for all the confirmed cases of the individuals (u_2) and awareness program for diabetics without complications for low levels of physical activity and irregular eating patterns (u_3) to optimize the objective functional $J(u)$ without considering preventive measures (u_1) were set to zero.

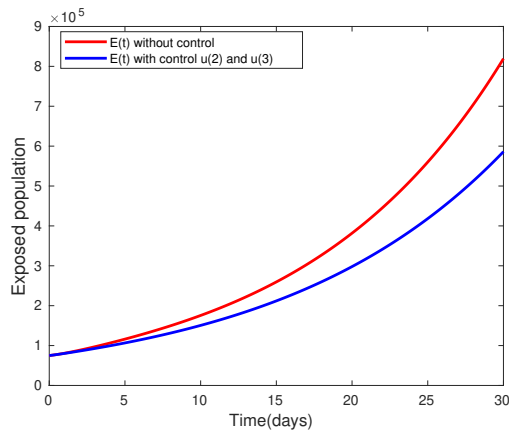


Figure 6.11: Exposed population without and with control u_2 and u_3

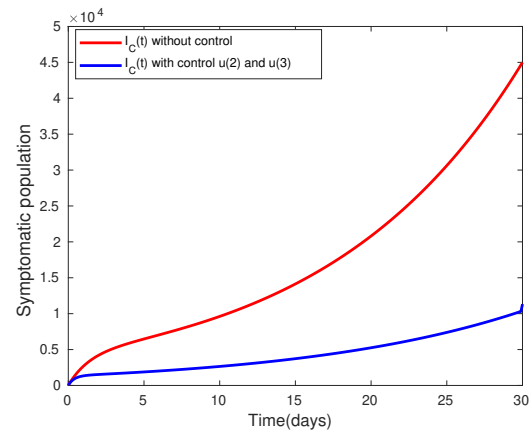


Figure 6.12: Symptomatic population without and with control u_2 and u_3

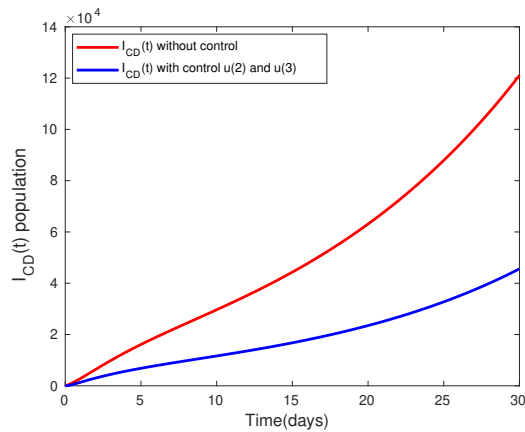


Figure 6.13: $I_{CD}(t)$ population without and with control u_2 and u_3

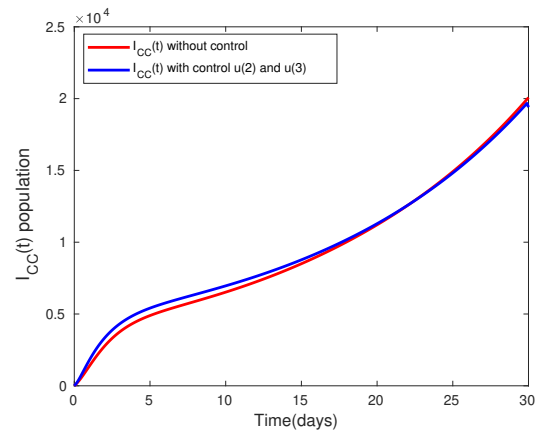


Figure 6.14: $I_{CC}(t)$ population without and with control u_2 and u_3

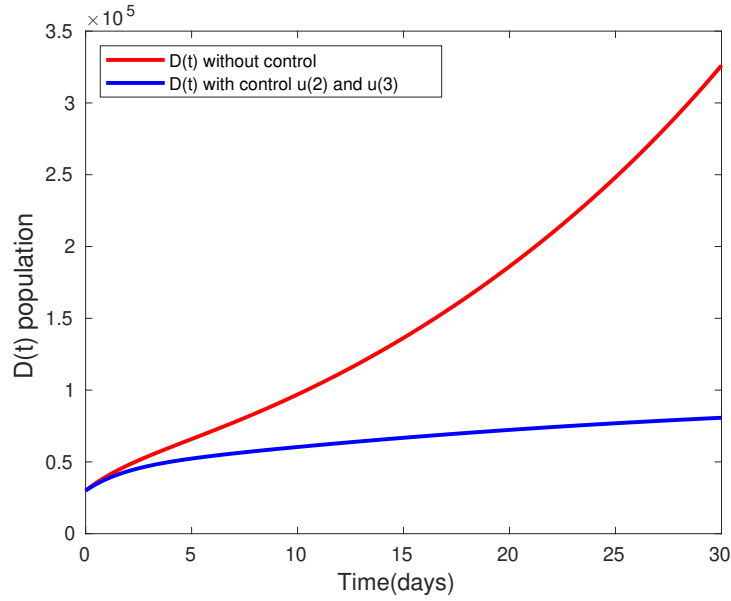


Figure 6.15: Diabetic without complications population without and with control u_2 and u_3

From the numerical result depicted in Figure 6.11 above, we observed that in the absence of control strategies the number of exposed populations of COVID-19 are 8.19×10^5 and in the presence of u_2 and u_3 controls the number of exposed populations of COVID-19 are decreasing and about 5.8×10^5 at final time. From the second numerical result depicted in Figure 6.12 above experimented, we observed that the number of symptomatic individuals of COVID-19 are increasing rapidly in the absence of control strategies and it will be 4.5×10^4 and in the presence of u_2 and u_3 controls the number of symptomatic populations are decreasing and 1.133×10^4 at final time. From the third numerical result depicted in Figure 6.13 above, we observed that the number of COVID-19 and diabetic without complications are increasing rapidly in the absence of control strategies and it will be 12×10^4 and in the presence of u_2 and u_3 controls decreased to 4.55×10^4 at final time. From Figure 6.14 the number of COVID-19 and diabetic with complications are 2.01×10^4 and in the presence of u_2 and u_3 controls 1.94×10^4 at final time. From the Figure 6.15 in the absence of control strategies diabetes without complications are 3.2×10^5 and in the presence of u_2 and u_3 controls 8.074×10^4 at final time. Hence, this strategy is less effective to reduce the number of exposed, symptomatic, diabetic without complications and both co-infected ($I_{CD}(t)$, $I_{CC}(t)$) individuals.

6.1.4 Applying all control strategies

Here we have applied all the three control intervention on each compartment and from the numerical result depicted in each Figure below when all the three controls implemented the number of all populations are decreasing.

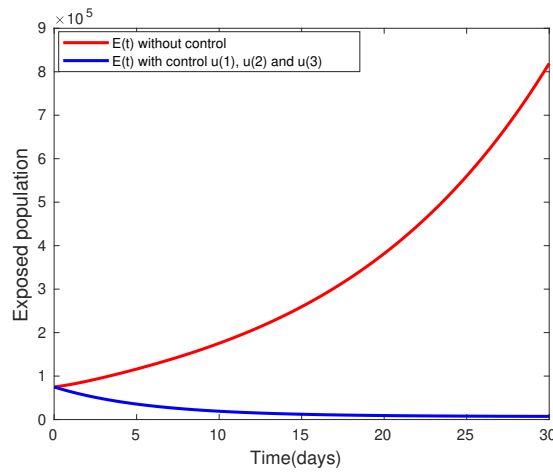


Figure 6.16: Exposed population without and with control u_1 , u_2 and u_3

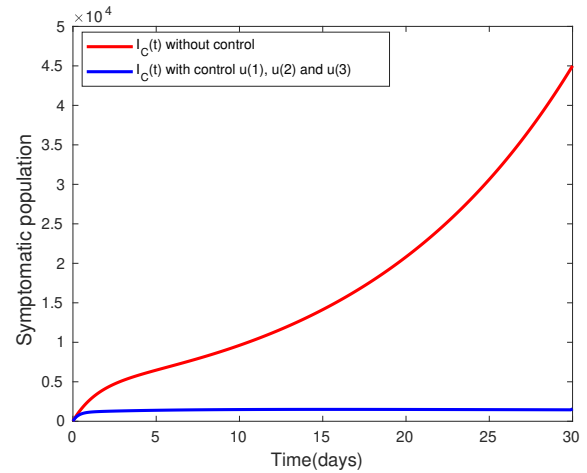


Figure 6.17: Symptomatic population without and with control u_1 , u_2 and u_3

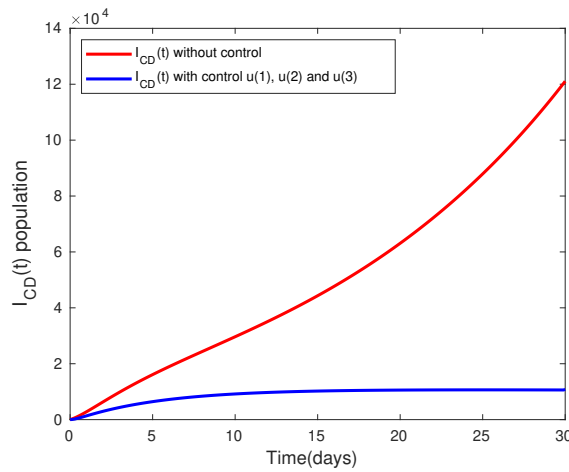


Figure 6.18: $I_{CD}(t)$ population without and with control u_1 , u_2 and u_3

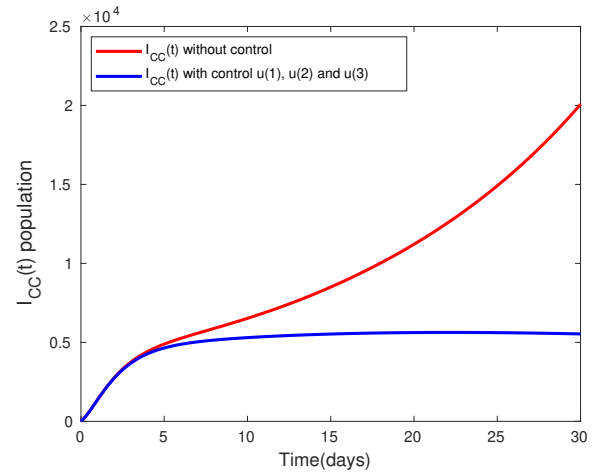


Figure 6.19: $I_{CC}(t)$ population without and with control u_1 , u_2 and u_3

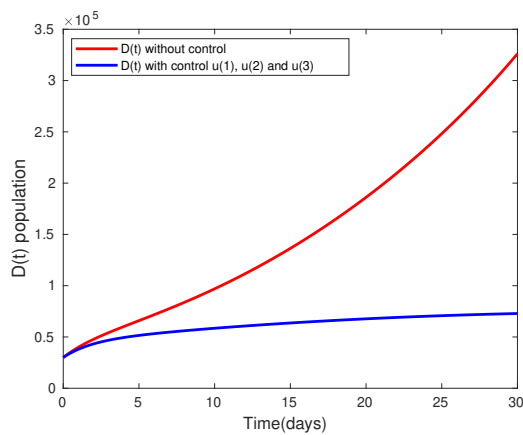


Figure 6.20: Diabetic without complications population without and with control u_1 , u_2 and u_3

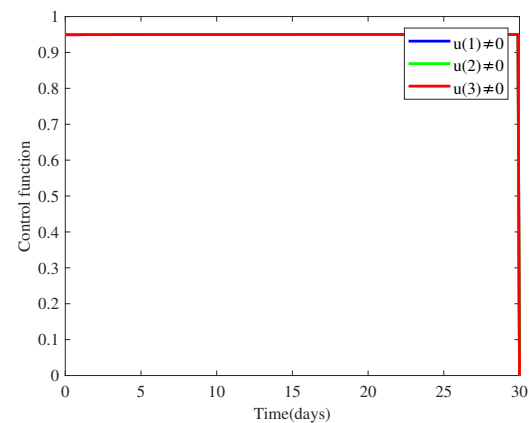


Figure 6.21: Profiles of optimal control function u_1, u_2 and u_3

From the numerical result depicted in Figure 6.16 above, we observed that in the absence of control strategies the number of exposed populations of COVID-19 are 8.19×10^5 and in the presence of u_1 , u_2 and u_3 controls the number of exposed populations of COVID-19 are decreasing and about 8365 at final time. From the second numerical result depicted in Figure 6.17 above experimented, we observed that the number of symptomatic individuals of COVID-19 are increasing rapidly in the absence of control strategies and it will be 4.5×10^4 and in the presence of u_1 , u_2 and u_3 controls the number of symptomatic populations are rapidly decreasing to 1581 at final time. From the third numerical result depicted in Figure 6.18 above, we observed that the number of COVID-19 and diabetic without complications are increasing rapidly in the absence of control strategies and it will be 12×10^4 and in the presence of u_1 , u_2 and u_3 controls decreased to 10811 at final time. From Figure 6.19 the number of COVID-19 and diabetic with complications are 2.01×10^4 and in the presence of u_1 , u_2 and u_3 controls 5533 at final time. From the Figure 6.20 in the absence of control strategies diabetes without complications are 3.2×10^5 and in the presence of u_1 , u_2 and u_3 controls 7.288×10^4 at final time. Hence, this strategy is effective to reduce the number of exposed, symptomatic, diabetic without complications and both co-infected ($I_{CD}(t)$, $I_{CC}(t)$) individuals as compared to the strategy A , B and C .

6.2 Cost-effectiveness analysis

Cost-effectiveness analysis is used to determine the most cost-effective optimal control measure among the combined and all implementation of the three given control measures in order to optimally mitigate the spread of COVID-19 and diabetes co-infection at the lowest cost possible. Hence, cost-effectiveness analysis is explored using the incremental cost effectiveness ratio ($ICER$) (Asamoah et al., 2020), which is used compare the differences between costs and health outcomes of two competing intervention strategies. The $ICER$ formula is given by

$$ICER = \frac{\text{Change in total costs between control measures}}{\text{Change in total number of infection averted by control measures}}$$

Table 6.1: Total costs and total averted infections for strategies A–D

Strategy	Total averted infections (TA)	Total cost (TC)
A	2.73×10^7	28.5
B	2.91×10^7	33.25
C	1.03×10^7	23.75
D	2.9334×10^7	42.75

Strategy A is compared with strategy B with respect to increased effectiveness, in reference

to Table 6.1. So:

$$ICER(A) = \frac{TC(A)}{TA(A)} = \frac{28.5}{2.73 \times 10^7} = 1.044 \times 10^{-6}$$

$$ICER(B) = \frac{TC(B) - TC(A)}{TA(B) - TA(A)} = \frac{33.25 - 28.5}{2.91 \times 10^7 - 2.73 \times 10^7} = 2.638 \times 10^{-6}$$

Since $ICER(A) < ICER(B)$, then strategy B is less effective than strategy A. Therefore, strategy B is excluded from the set of alternatives.

Next, strategy A is compared to strategy C. The ICER values for strategy C and strategy A are calculated below:

$$ICER(A) = \frac{TC(A)}{TA(A)} = \frac{28.5}{2.73 \times 10^7} = 1.044 \times 10^{-6}$$

$$ICER(C) = \frac{TC(C) - TC(A)}{TA(C) - TA(A)} = \frac{23.75 - 28.5}{1.03 \times 10^7 - 2.73 \times 10^7} = 2.794 \times 10^{-7}$$

Since $ICER(C) < ICER(A)$, then strategy A is less effective than strategy C. Therefore, strategy A is excluded from the set of alternatives.

Next, strategy C is compared to strategy D. The ICER values for strategy C and strategy D are calculated below:

$$ICER(C) = \frac{TC(C) - TC(A)}{TA(C) - TA(A)} = \frac{23.75 - 28.5}{1.03 \times 10^7 - 2.73 \times 10^7} = 2.794 \times 10^{-7}$$

$$ICER(D) = \frac{TC(D) - TC(C)}{TA(D) - TA(C)} = \frac{42.75 - 23.75}{2.9334 \times 10^7 - 1.03 \times 10^7} = 9.982 \times 10^{-7}$$

$ICER(C) < ICER(D)$, then strategy D is less effective than strategy C. Therefore, the conclusion is that strategy C (medical treatment for all the confirmed cases of the individuals with COVID-19 and awarress campaigns to protect potential individuals infected with the virus, prevent contact with people infected with COVID-19) is the most effective and profitable strategy.

CHAPTER 7

RESULT AND DISCUSSION

In this thesis work, we have considered a mathematical model of transmission dynamics of COVID-19 and diabetes co-infection. We have developed a eleven compartmental deterministic mathematical model, namely susceptible, exposed, asymptomatic, symptomatic, diabetes susceptible, pre-diabetes, diabetes with and with out complications, coinfectd with COVID-19 and diabetes without complications, coinfectd with COVID-19 and diabetes with complications and recovered populations and investigated the dynamical behavior of each sub-model. The sub-model analysis show that there exists a domain where the model is epidemiologically and mathematically well-posed. We have stated about the invariant region in which each sub-model solution is bounded. The existence and uniqueness of the solution of the sub-model equation is show by the direct consequence of the Fundamental Existence and Uniqueness Theorem and positivity of the solution of the sub-model is shown. Using the next generation matrix method, we have found a basic reproduction number of the sub-model system of (4.2) and (4.33). We have then proposed a deterministic mathematical model of the coinfection of COVID-19 and diabetes. The coinfection model is qualitatively studied by proving the properties such as existence and uniqueness, boundedness, and positivity of the solutions. We computed the basic reproduction number of the coinfection of the system (4.1) and it is given by

$$R_0 = \max \left\{ \frac{\beta[(\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)pb + (\alpha_2 + \mu)r]}{(\mu + p + r)(\mu + \alpha_2)(\mu + \delta_1 + \alpha_1 + \theta_1 + \theta_2)}, \frac{\beta_1\gamma_1}{(\mu_2 + \gamma_1 + \gamma_2)(\mu_2 + \gamma_3 + \psi_1)} \right\}$$

which helps us to determine the dynamical behavior of the system. Based on the values of R_0 we have only one disease free equilibrium point for the model systems (4.1) with locally stable and globally unstable. Also sensitivity indices of each sub-models with respect to the model parameters and bifurcation analysis are performed to reveal the transmission dynamics of COVID-19.

We have addressed the main target of this thesis work which is an optimal control problem

relative to the coinfection model so as to minimize the exposed, symptomatic, COVID-19 coinfecting with diabetes without and with complications and diabetes without complications populations as well as to minimize the cost of control using Pontryagin's minimum principle which govern the necessary conditions for the optimal control of the spread of coinfection. We have considered three kinds of controls to reduce/mitigate the transmission dynamic of COVID-19 and diabetes coinfection. Those control functions are u_1 (preventive measures), u_2 (intensive medical care for all the confirmed cases) and u_3 (awareness program for diabetics without complications). We applied those control intervention in order to fit our goal to minimize the objective function.

The numerical simulation of the model system (4.1) and (5.1) have been performed and the simulation process is carried out using MATLAB software. we present the results obtained by numerically solving the optimality system. In our control problem, we have initial conditions for the state variables and terminal conditions for the adjoints. We solve the optimality system by an iterative method with forward fourth order Runge-Kutta scheme solving of the state system followed by backward fourth order Runge-Kutta scheme solving of the adjoint system. We start with an initial guess for the controls at the first iteration and then before the next iteration. The control function is updated by using a convex combination of the previous control and the values computed in the characterizations process. Further more, to reduce the COVID-19 and diabetes co-infection disease we have experimented by combining pair wise and all the three controls. We focused on the exposed $E(t)$, symptomatic $I(t)$, both COVID-19 and diabetes coinfecting ($I_{CD}(t)$ and $I_{CC}(t)$) and diabetes without complications $D(t)$ in order to minimize the objective function. As the numerical result show as, it is more efficient when all the three controls (u_1, u_2, u_3) are considered in simulation at a time to reduce the spread of the co-infectious diseases. The cost-effectiveness analysis is also performed to determine the most profitable strategy for diabetic patients during COVID-19 pandemic according to our developed model, thus medical treatment for COVID-19 and awareness program for diabetic with out complications are most profitable strategy.

Conclusion and Recommendation

Conclusion

In this thesis work, we develop a deterministic mathematical model which describes the transmission dynamics of COVID-19 and diabetes coinfection with optimal control using a system of nonlinear ordinary differential equations. In chapter four, we have developed a eleven-compartmental deterministic mathematical model, namely susceptible, exposed, asymptomatic, symptomatic, diabetes susceptible, pre-diabetes, diabetes with and with out complications, co-infected with COVID-19 and diabetes without complications, co-infected with COVID-19 and diabetes with complications and recovered populations. The biological meaningfulness of the model is proved by showing the existence, uniqueness, positivity, and boundedness of solutions in a given region. Then, the equilibria are computed for the co-infection model and each sub-models independently. The stability analysis of these equilibria is also presented with the help of the calculated respective basic reproduction numbers. The analytical results in both sub-models reveal that the disease-free equilibrium points are locally and globally stable if the basic reproduction numbers are less than one which is computed by using Jacobian matrix and Lyapunov functions respectively. Furthermore, there exists locally and globally stable endemic equilibrium point for the basic reproduction numbers greater than one. Besides, the co-infection model the systems has only disease free equilibrium point which is locally stable investigated via corresponding basic reproduction number and globally unstable done by using metzler matrix. Sensitivity analysis of the sub-models have been studied and determined a parameter which plays greater role in the transmission dynamics of COVID-19 and diabetes coinfection.

In chapter five, an optimal control problem relative to the coinfection model so as to minimize the exposed and symptomatic and maximize the awareness program for diabetic without complications populations as well as to minimize the cost of control using Pontryagin's minimum principle have been addressed. We have used three controls those are u_1 (preventive measures), u_2 (intensive medical care for all the confirmed cases) and u_3 (awareness program for diabetics without complications).

In chapter six, the numerical simulation of the model system have been carried out using MATLAB software. For the numerical simulation the parameters of the model system have been taken from different source that cited been there. In order to reduce the co-infection of COVID-19 and diabetic we have used by combining pair wise and all the three controls at a time t in order to minimize the objective function. The numerical result show as, it is more efficient when control all the three controls are considered in simulation to reduce the co-infectious disease. The cost-effectiveness analysis show as, medical treatment for COVID-19 patients and awareness program are the most effective strategy.

Recommendation

The mathematical models on pandemic diseases are rather simple, but nevertheless they give insight into some of the consequences of public health policies. Controlling the spread of epidemic disease is now a world wide challenging problem and important issue to study. So, to predict and identify the cost-effective strategies to control the spread of COVID-19 and diabetes co-infection diseases and minimize the cost of the control interventions are the primary goals of all concerned stake holders such as health sector, policy-makers, researchers and others. Since eradication of COVID-19 and diabetes co-infection is challenge especially in developing countries. Based on the findings of this study, we recommend to government and concerned stake holders to reduce the coinfection of COVID-19 and diabetes implement a combination of all prevention target program's such as education campaign to increase awareness program on how to protect themselves from getting both COVID-19 and diabetes disease, providing treatment for those who are infected with COVID-19 to reduce the contact rate with diabetes patients and people with diabetes must exercise regularly. Also, the diabetic patients should visit hospital immediately in emergency conditions, such as chest pain, altered senses, shortness of breath, drowsiness, weakness in the limbs, and vomiting during COVID-19 pandemic.

Future Work

In the future work, we will plan to extend the study of this model by using fractal-fractional Caputo-Fabrizio operator.

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Appendix

Matlab Program for model (5.1) both without and with optimal control

```
1 function y =EI(t ,y1 ,y2 ,y3 ,y4 ,y5 ,y6 ,y7 ,y8 ,y9 ,y10 ,y11 )
2 %Parameters of the model
3 Lambdal=146593;
4 Nc = 118990874;
5 Nd = 2000000;
6 Lambda2=2470;
7 beta=0.88;
8 beta1=0.16263;
9 mu = 0.001235;
10 p= 0.02557;
11 r = 1/7;
12 b = 0.77484;
13 alpha1 = 0.00787;
14 alpha2 = 0.00827;
15 delta1 =0.023;
16 delta2 = 0.001;
17 gamma1 = 0.2;
18 gamma2 = 0.3;
19 gamma3 = 0.01;
20 theta1 = 0.7421;
21 theta2 = 0.4204;
22 psi1 = 0.00627;
23 psi2 = 0.04358;
24 omegal = 0.00642;
25 omega2 = 0.678;
26 eta1 = 0.04236;
27 eta2 = 0.678;
28 deltacd = 0.2157;
```



```
29  deltacc = 0.1358;
30  C1 =1;C2=10000;C3=200;C4=1;C5=1;
31  B1 =20;B2 =20;B3 =15;
32  %Parameters of the Runge–Kutta (4th order) method
33  test = -1;
34  delta = 0.001;
35  tf=30;
36  M = 300;
37  t = linspace(0,tf,M+1);
38  h = tf/M;
39  h2 = h/2;
40
41  x1=zeros(1,M+1);
42  x2=zeros(1,M+1);
43  x3=zeros(1,M+1);
44  x4=zeros(1,M+1);
45  x5=zeros(1,M+1);
46  x6=zeros(1,M+1);
47  x7=zeros(1,M+1);
48  x8=zeros(1,M+1);
49  x9=zeros(1,M+1);
50  x10=zeros(1,M+1);
51  x11=zeros(1,M+1);
52
53  %Vectors for system restrictions and control
54  lambda1 = zeros(1,M+1);
55  lambda2 = zeros(1,M+1);
56  lambda3 = zeros(1,M+1);
57  lambda4 = zeros(1,M+1);
58  lambda5 = zeros(1,M+1);
59  lambda6 = zeros(1,M+1);
60  lambda7 = zeros(1,M+1);
61  lambda8 = zeros(1,M+1);
62  lambda9 = zeros(1,M+1);
63  lambda10 = zeros(1,M+1);
64  lambda11 = zeros(1,M+1);
65
```



```
66 u1 = zeros(1,M+1);
67 u2 = zeros(1,M+1);
68 u3 = zeros(1,M+1);
69 %Initial conditions of the model
70 x1(1) = 118870848;
71 x2(1) = 75000;
72 x3(1) = 25000;
73 x4(1) = 26;
74 x5(1) = 20000;
75 x6(1) = 5;
76 x7(1) = 2;
77 x8(1) = 1000000;
78 x9(1) = 500000;
79 x10(1) = 300000;
80 x11(1) = 200000;
81
82 %Iterations of the method
83 while(test < 0)
84     oldx1 = x1;
85     oldx2 = x2;
86     oldx3 = x3;
87     oldx4 = x4;
88     oldx5 = x5;
89     oldx6 = x6;
90     oldx7 = x7;
91     oldx8 = x8;
92     oldx9 = x9;
93     oldx10 = x10;
94     oldx11 = x11;
95
96     oldlambda1 = lambda1;
97     oldlambda2 = lambda2;
98     oldlambda3 = lambda3;
99     oldlambda4 = lambda4;
100    oldlambda5 = lambda5;
101    oldlambda6 = lambda6;
102    oldlambda7 = lambda7;
```



```

103     oldlambda8 = lambda8;
104     oldlambda9 = lambda9;
105     oldlambda10 = lambda10;
106     oldlambda11 = lambda11;
107
108     oldu1 = u1;
109     oldu2 = u2;
110     oldu3 = u3;
111
112     for i = 1:M % forward in state
113         auxu1 = 1-u1(i);
114         auxu2 = u2(i);
115         auxu3 = 1-u3(i);
116
117         m11 = Lambda1 - (((beta*(b*x3(i)+x4(i)))/Nc)*auxu1+
            mu)*x1(i);
118         m12 = auxu1*((beta*(b*x3(i)+x4(i)))/Nc)*x1(i)-(mu+p+r
            )*x2(i);
119         m13 = p*x2(i)-(mu+alpha2)*x3(i);
120         m14 = r*x3(i)-(mu+delta1+alpha1)*x4(i)-(theta1+auxu2)
            *x4(i)-(theta2+auxu2)*x4(i);
121         m15 = alpha2*x3(i)+alpha1*x4(i)+eta1*x6(i)+eta2*x7(i)
            -(mu+omega1+omega2)*x5(i);
122         m16 = (auxu2+theta1)*x4(i)+psi1*auxu3*x10(i)-(mu+
            deltacd+eta1)*x6(i);
123         m17 = (auxu2+theta2)*x4(i)+psi2*x11(i)-(mu+deltacc+
            eta2)*x7(i);
124         m18 = Lambda2-((beta1*x10(i))/Nd+mu)*x8(i);
125         m19 = ((beta1*x10(i))/Nd)*x8(i)-(gamma1+gamma2+mu)*x9
            (i);
126         m110 = gamma1*x9(i)-gamma3*auxu3*x10(i)-mu*x10(i)+
            psi1*auxu3*x10(i)+omega1*x5(i);
127         m111 = gamma2*x9(i)+gamma3*auxu3*x10(i)-(mu+delta2)*
            x11(i)-psi2*x11(i)+omega2*x5(i);
128
129
130     %

```



```

131      % Second Runge–Kutta parameter in state
132      %-----
133
134      aux1 = x1(i)+h2*m11; aux2 = x2(i)+h2*m12; aux3 = x3(i)
          +h2*m13; aux4 = x4(i)+h2*m14; aux5 = x5(i)+h2*m15;
          aux6 = x6(i)+h2*m16; aux7 = x7(i)+h2*m17; aux8 =
          x8(i)+h2*m18; aux9 = x9(i)+h2*m19; aux10 = x10(i)+
          h2*m110; aux11 = x11(i)+h2*m111;
135      auxu1 = 1-0.5 * (u1(i) + u1(i+1));
136      auxu2 = 0.5 * (u2(i) + u2(i+1));
137      auxu3 = 1-0.5 * (u3(i) + u3(i+1));
138
139      m21 = Lambda1 - (((beta*(b*aux3+aux4))/Nc)*auxu1+mu)
          *aux1;
140      m22 = auxu1*((beta*(b*aux3+aux4))/Nc)*aux1-(mu+p+r)*
          aux2;
141      m23 = p*aux2-(mu+alpha2)*aux3;
142      m24 = r*aux3-(mu+delta1+alpha1)*aux4-(theta1+auxu2)*
          aux4-(theta2+auxu2)*aux4;
143      m25 = alpha2*aux3+alpha1*aux4+eta1*aux6+eta2*aux7-(mu
          +omega1+omega2)*aux5;
144      m26 = (auxu2+theta1)*aux4+psi1*auxu3*aux10-(mu+
          deltacd+eta1)*aux6;
145      m27 = (auxu2+theta2)*aux4+psi2*aux11-(mu+deltacc+eta2
          )*aux7;
146      m28 = Lambda2-((beta1*aux10)/Nd)*aux8-mu*aux8;
147      m29 = ((beta1*aux10)/Nd)*aux8-(gamma1+gamma2+mu)*aux9
          ;
148      m210 = gamma1*aux9-gamma3*auxu3*aux10-mu*aux10+psi1*
          auxu3*aux10+omega1*aux5;
149      m211 = gamma2*aux9+gamma3*auxu3*aux10-(mu+delta2)*
          aux11-psi2*aux11+omega2*aux5;
150
151
152      %-----
153      % Third Runge–Kutta parameter in state
154      %-----

```



```

155      aux1 = x1(i)+h2*m21; aux2 = x2(i)+h2*m22; aux3 = x3(i)
      +h2*m23; aux4 = x4(i)+h2*m24; aux5 = x5(i)+h2*m25;
      aux6 = x6(i)+h2*m26; aux7 = x7(i)+h2*m27; aux8 =
      x8(i)+h2*m28; aux9 = x9(i)+h2*m29; aux10 = x10(i)+
      h2*m210; aux11 = x11(i)+h2*m211;
156      auxu1 = 1-0.5 * (u1(i) + u1(i+1));
157      auxu2 = 0.5 * (u2(i) + u2(i+1));
158      auxu3 = 1-0.5 * (u3(i) + u3(i+1));
159
160      m31 = Lambda1 - ((beta*(b*aux3+aux4)/Nc)*auxu1+mu)*
      aux1;
161      m32 = auxu1*(beta*(b*aux3+aux4)/Nc)*aux1-(mu+p+r)*
      aux2;
162      m33 = p*aux2-(mu+alpha2)*aux3;
163      m34 = r*aux3-(mu+delta1+alpha1)*aux4-(theta1+auxu2)*
      aux4-(theta2+auxu2)*aux4;
164      m35 = alpha2*aux3+alpha1*aux4+eta1*aux6+eta2*aux7-(mu
      +omega1+omega2)*aux5;
165      m36 = (auxu2+theta1)*aux4+psi1*auxu3*aux10-(mu+
      deltacd+eta1)*aux6;
166      m37 = (auxu2+theta2)*aux4+psi2*aux11-(mu+deltacc+eta2
      )*aux7;
167      m38 = Lambda2-((beta1*aux10)/Nd)*aux8-mu*aux8;
168      m39 = ((beta1*aux10)/Nd)*aux8-(gamma1+gamma2+mu)*aux9
      ;
169      m310 = gamma1*aux9-gamma3*auxu3*aux10-mu*aux10+psi1*
      auxu3*aux10+omega1*aux5;
170      m311 = gamma2*aux9+gamma3*auxu3*aux10-(mu+delta2)*
      aux11-psi2*aux11+omega2*aux5;
171
172      %-----
173      % Fourth Runge-Kutta parameter in state
174      %-----
175
176      aux1 = x1(i)+h*m31; aux2 = x2(i)+h*m32; aux3 = x3(i)+h
      *m33; aux4 = x4(i)+h*m34; aux5 = x5(i)+h*m35; aux6
      = x6(i)+h*m36; aux7 = x7(i)+h*m37; aux8 = x8(i)+h

```



```

    *m38; aux9 = x9(i)+h*m39; aux10 = x10(i)+h*m310;
    aux11 = x11(i)+h*m311;
177     auxu1 = 1-u1(i+1);
178     auxu2 = u2(i+1);
179     auxu3 = 1-u3(i+1);
180
181     m41 = Lambda1 - (((beta*(b*aux3+aux4))/Nc)*auxu1)*
        aux1-mu*aux1;
182     m42 = auxu1*((beta*(b*aux3+aux4))/Nc)*aux1-(mu+p+r)*
        aux2;
183     m43 = p*aux2-(mu+alpha2)*aux3;
184     m44 = r*aux3-(mu+delta1+alpha1)*aux4-(theta1+auxu2)*
        aux4-(theta2+auxu2)*aux4;
185     m45 = alpha2*aux3+alpha1*aux4+eta1*aux6+eta2*aux7-(mu+
        omegal+omega2)*aux5;
186     m46 = (auxu2+theta1)*aux4+psi1*auxu3*aux10-(mu+deltacd
        +eta1)*aux6;
187     m47 = (auxu2+theta2)*aux4+psi2*aux11-(mu+deltacc+eta2)
        *aux7;
188     m48 = Lambda2-((beta1*aux10)/Nd)*aux8-mu*aux8;
189     m49 = ((beta1*aux10)/Nd)*aux8-(gamma1+gamma2+mu)*aux9;
190     m410 = gamma1*aux9-gamma3*auxu3*aux10-mu*aux10+psi1*
        auxu3*aux10+omegal*aux5;
191     m411 = gamma2*aux9+gamma3*auxu3*aux10-(mu+delta2)*
        aux11-psi2*aux11+omega2*aux5;
192
193     %Runge-Kutta new approximation
194     x1(i+1) = x1(i) + (h/6)*(m11 + 2*m21 + 2*m31 + m41);
195     x2(i+1) = x2(i) + (h/6)*(m12 + 2*m22 + 2*m32 + m42);
196     x3(i+1) = x3(i) + (h/6)*(m13 + 2*m23 + 2*m33 + m43);
197     x4(i+1) = x4(i) + (h/6)*(m14 + 2*m24 + 2*m34 + m44);
198     x5(i+1) = x5(i) + (h/6)*(m15 + 2*m25 + 2*m35 + m45);
199     x6(i+1) = x6(i) + (h/6)*(m16 + 2*m26 + 2*m36 + m46);
200     x7(i+1) = x7(i) + (h/6)*(m17 + 2*m27 + 2*m37 + m47);
201     x8(i+1) = x8(i) + (h/6)*(m18 + 2*m28 + 2*m38 + m48);
202     x9(i+1) = x9(i) + (h/6)*(m19 + 2*m29 + 2*m39 + m49);
203     x10(i+1) = x10(i) + (h/6)*(m110 + 2*m210 + 2*m310 +

```



```

    m410);
204    x11(i+1) = x11(i) + (h/6)*(m111 + 2*m211 + 2*m311 +
    m411);
205
206 end
207
208
209 %-----
210 % Backward Runge–Kutta iterations in co–state variables
211 %-----
212
213
214 for i = 1:M
215     j = M + 2 - i;
216
217     %-----
218     % First Runge–Kutta parameter in co–state
219     %-----
220
221     auxu1 = 1-u1(j);
222     auxu2 = u2(j);
223     auxu3 = 1-u3(j);
224
225     h1=lambda1(j)-lambda2(j);
226     h22= mu+p+r;
227     h3 = lambda3(j)-lambda5(j);
228     h4 = lambda4(j)-lambda5(j);
229     h5 = lambda4(j)-lambda6(j);
230     h6 = lambda4(j)-lambda7(j);
231     h7 = lambda5(j)-lambda10(j);
232     h8 = lambda5(j)-lambda11(j);
233     h9 = lambda6(j)-lambda5(j);
234     h10 = lambda7(j)-lambda5(j);
235     h11 = lambda8(j)-lambda9(j);
236     h12 = lambda9(j)-lambda10(j);
237     h13 = lambda9(j)-lambda11(j);
238     h14 = lambda10(j)+lambda6(j);
```



```

239     h15 = lambda10(j)-lambda11(j);
240     h16 = lambda11(j)-lambda7(j);
241
242     n11 = h1*auxu1*(beta*(b*x3(j)+x4(j))/Nc)+lambda1(j);
243     n12 = -C1+lambda1(j)*h22-lambda2(j)*p-lambda3(j)*r;
244     n13 = ((beta*b*x1(j))/Nc)*auxu1*h1+mu*lambda3(j)+
           alpha2*h3;
245     n14 = -C2+((beta*b*x1(j))/Nc)*auxu1*h1+(mu+delta1)*
           lambda4(j)+alpha1*h4+      (theta1+auxu2)*h5+(
           theta2+auxu2)*h6;
246     n15 = mu*lambda5(j)+omegal*h7+omega2*h8;
247     n16 = -C3+eta1*h9+(mu+deltacd)*lambda6(j);
248     n17 = -C4+eta2*h10+(mu+deltacc)*lambda7(j);
249     n18 = mu*lambda8(j)+((beta1*x10(j))/Nd)*h11;
250     n19 = mu*lambda9(j)+gamma1*h12+gamma2*h13;
251     n110 = C5-psi1*auxu3*h14+((beta1*x8(j))/Nd)*h11+
           gamma3*auxu3*h15+mu*lambda10(j);
252     n111 = psi2*h16+(mu+delta2)*lambda11(j);
253
254
255     %-----
256     % Second Runge-Kutta parameter in co-state
257     %-----
258
259     aux1 = 0.5*(x1(j)+x1(j-1));    aux3 = 0.5*(x3(j)+x3(j
           -1));    aux8 = 0.5*(x8(j)+x8(j-1));
260     auxL1 = lambda1(j)-h2*n11;    auxL2 = lambda2(j)-h2*n12
           ;    auxL3 = lambda3(j)-h2*n13;
261     auxL4 = lambda4(j)-h2*n14;    auxL5 = lambda5(j)-h2*n15
           ;    auxL6 = lambda6(j)-h2*n16;    auxL7 = lambda7(j)-h2
           *n17;    auxL8 = lambda8(j)-h2*n18;    auxL9 = lambda9(j
           )-h2*n19;    auxL10 = lambda10(j)-h2*n110;    auxL11 =
           lambda11(j)-h2*n111;
262
263
264     auxu1 = 1-u1(j);
265     auxu2 = u2(j);

```



```

266      auxu3 = 1-u3(j);
267
268      h1=lambda1(j)-lambda2(j);
269      h22 = mu+p+r;
270      h3 = lambda3(j)-lambda5(j);
271      h4 = lambda4(j)-lambda5(j);
272      h5 = lambda4(j)-lambda6(j);
273      h6 = lambda4(j)-lambda7(j);
274      h7 = lambda5(j)-lambda10(j);
275      h8 = lambda5(j)-lambda11(j);
276      h9 = lambda6(j)-lambda5(j);
277      h10 = lambda7(j)-lambda5(j);
278      h11 = lambda8(j)-lambda9(j);
279      h12 = lambda9(j)-lambda10(j);
280      h13 = lambda9(j)-lambda11(j);
281      h14 = lambda10(j)+lambda6(j);
282      h15 = lambda10(j)-lambda11(j);
283      h16 = lambda11(j)-lambda7(j);
284
285
286      n21 = h1*auxu1*(beta*(b*aux3+aux4)/Nc)+auxL1;
287      n22 = -C1+auxL1*h22-auxL2*p-auxL3*r;
288      n23 = ((beta*b*aux1)/Nc)*auxu1*h1+mu*auxL3+alpha2*h3;
289      n24 = -C2+((beta*b*aux1)/Nc)*auxu1*h1+(mu+delta1)*
          auxL4+alpha1*h4+(theta1+auxu2)*h5+(theta2+auxu2)*
          h6;
290      n25 = mu*auxL5+omega1*h7+omega2*h8;
291      n26 = -C3+eta1*h9+(mu+deltacd)*auxL6;
292      n27 = -C4+eta2*h10+(mu+deltacc)*auxL7;
293      n28 = mu*auxL8+((beta1*aux10)/Nd)*h11;
294      n29 = mu*auxL9+gamma1*h12+gamma2*h13;
295      n210 = C5-psi1*auxu3*h14+((beta1*aux8)/Nd)*h11+gamma3
          *auxu3*h15+mu*auxL10;
296      n211 = psi2*h16+(mu+delta2)*auxL11;
297
298
299

```



```

300      %-----
301      % Third Runge–Kutta parameter in co–state
302      %-----
303
304      aux1 = 0.5*(x1(j)+x1(j-1));    aux3 = 0.5*(x3(j)+x3(j-1));
          aux8 = 0.5*(x8(j)+x8(j-1));
305      auxL1 = lambda1(j)-h2*n11;    auxL2 = lambda2(j)-h2*n12
          ;    auxL3 = lambda3(j)-h2*n13; auxL4 = lambda4(j)-
          h2*n14;    auxL5 = lambda5(j)-h2*n15; auxL6 =
          lambda6(j)-h2*n16; auxL7 = lambda7(j)-h2*n17;
          auxL8 = lambda8(j)-h2*n18; auxL9 = lambda9(j)-h2*
          n19; auxL10 = lambda10(j)-h2*n110; auxL11 =
          lambda11(j)-h2*n111;
306
307
308      auxu1 = 1-u1(j);
309      auxu2 = u2(j);
310      auxu3 = 1-u3(j);
311
312      h1=lambda1(j)-lambda2(j);
313      h22 = mu+p+r;
314      h3 = lambda3(j)-lambda5(j);
315      h4 = lambda4(j)-lambda5(j);
316      h5 = lambda4(j)-lambda6(j);
317      h6 = lambda4(j)-lambda7(j);
318      h7 = lambda5(j)-lambda10(j);
319      h8 = lambda5(j)-lambda11(j);
320      h9 = lambda6(j)-lambda5(j);
321      h10 = lambda7(j)-lambda5(j);
322      h11 = lambda8(j)-lambda9(j);
323      h12 = lambda9(j)-lambda10(j);
324      h13 = lambda9(j)-lambda11(j);
325      h14 = lambda10(j)-lambda6(j);
326      h15 = lambda10(j)-lambda11(j);
327      h16 = lambda11(j)-lambda7(j);
328
329      n31 = h1*auxu1*(beta*(b*aux3+aux4)/Nc)+auxL1;

```



```

330     n32 = -C1+auxL1*h22-auxL2*p-auxL3*r ;
331     n33 = (( beta*b*aux1 )/Nc)*auxu1*h1+mu*auxL3+alpha2*h3 ;
332     n34 = -C2+(( beta*b*aux1 )/Nc)*auxu1*h1+(mu+delta1)*
        auxL4+alpha1*h4+( theta1+auxu2)*h5+( theta2+auxu2)*
        h6 ;
333     n35 = mu*auxL5+omega1*h7+omega2*h8 ;
334     n36 = -C3+eta1*h9+(mu+deltacd)*auxL6 ;
335     n37 = -C4+eta2*h10+(mu+deltacc)*auxL7 ;
336     n38 = mu*auxL8+(( beta1*aux10 )/Nd)*h11 ;
337     n39 = mu*auxL9+gamma1*h12+gamma2*h13 ;
338     n310 = C5-psi1*auxu3*h14+(( beta1*aux8 )/Nd)*h11+gamma3
        *auxu3*h15+mu*auxL10 ;
339     n311 = psi2*h16+(mu+delta2)*auxL11 ;
340
341
342     %-----
343     % Fourth Runge-Kutta parameter in co-state
344     %-----
345
346     aux1 = x1(j-1);    aux8 = x8(j-1);
347     auxL1 = lambda1(j)-h2*n11;    auxL2 = lambda2(j)-h2*
        n12;    auxL3 = lambda3(j)-h2*n13;    auxL4 = lambda4(
        j)-h2*n14;    auxL5 = lambda5(j)-h2*n15;    auxL6 =
        lambda6(j)-h2*n16;    auxL7 = lambda7(j)-h2*n17;
        auxL8 = lambda8(j)-h2*n18;    auxL9 = lambda9(j)-h2*
        n19;    auxL10 = lambda10(j)-h2*n110;    auxL11 =
        lambda11(j)-h2*n111 ;
348
349     auxu1 = 1-u1(j) ;
350     auxu2 = u2(j) ;
351     auxu3 = 1-u3(j) ;
352
353     h1=lambda1(j)-lambda2(j) ;
354     h22 = mu+p+r ;
355     h3 = lambda3(j)-lambda5(j) ;
356     h4 = lambda4(j)-lambda5(j) ;
357     h5 = lambda4(j)-lambda6(j) ;

```



```

358      h6 = lambda4(j)-lambda7(j);
359      h7 = lambda5(j)-lambda10(j);
360      h8 = lambda5(j)-lambda11(j);
361      h9 = lambda6(j)-lambda5(j);
362      h10 = lambda7(j)-lambda5(j);
363      h11 = lambda8(j)-lambda9(j);
364      h12 = lambda9(j)-lambda10(j);
365      h13 = lambda9(j)-lambda11(j);
366      h14 = lambda10(j)-lambda6(j);
367      h15 = lambda10(j)-lambda11(j);
368      h16 = lambda11(j)-lambda7(j);
369
370      n41 = h1*auxL1*(beta*(b*aux3+aux4)/Nc)+auxL1;
371      n42 = -C1+auxL1*h22-auxL2*p-auxL3*r;
372      n43 = ((beta*b*aux1)/Nc)*auxL1*h1+mu*auxL3+alpha2*h3;
373      n44 = -C2+((beta*b*aux1)/Nc)*auxL1*h1+(mu+delta1)*
          auxL4+alpha1*h4+(theta1+auxu2)*h5+(theta2+auxu2)*
          h6;
374      n45 = mu*auxL5+omega1*h7+omega2*h8;
375      n46 = -C3+eta1*h9+(mu+deltacd)*auxL6;
376      n47 = -C4+eta2*h10+(mu+deltacc)*auxL7;
377      n48 = mu*auxL8+((beta1*aux10)/Nd)*h11;
378      n49 = mu*auxL9+gamma1*h12+gamma2*h13;
379      n410 = C5-psi1*auxu3*h14+((beta1*aux8)/Nd)*h11+gamma3
          *auxu3*h15+mu*auxL10;
380      n411 = psi2*h16+(mu+delta2)*auxL11;
381
382
383
384      %-----
385      % Runge-Kutta new approximation in co-state
386      %-----
387
388
389      lambda1(j-1) = lambda1(j) - h/6*(n11 + 2*n21 + 2*n31
          + n41);
390      lambda2(j-1) = lambda2(j) - h/6*(n12 + 2*n22 + 2*n32

```



```

+ n42);
391 lambda3(j-1) = lambda3(j) - h/6*(n13 + 2*n23 + 2*n33
+ n43);
392 lambda4(j-1) = lambda4(j) - h/6*(n14 + 2*n24 + 2*n34
+ n44);
393 lambda5(j-1) = lambda5(j) - h/6*(n15 + 2*n25 + 2*n35
+ n45);
394 lambda6(j-1) = lambda6(j) - h/6*(n16 + 2*n26 + 2*n36
+ n46);
395 lambda7(j-1) = lambda7(j) - h/6*(n17 + 2*n27 + 2*n37
+ n47);
396 lambda8(j-1) = lambda8(j) - h/6*(n18 + 2*n28 + 2*n38
+ n48);
397 lambda9(j-1) = lambda9(j) - h/6*(n19 + 2*n29 + 2*n39
+ n49);
398 lambda10(j-1) = lambda10(j) - h/6*(n110 + 2*n210 + 2*
n310 + n410);
399 lambda11(j-1) = lambda11(j) - h/6*(n111 + 2*n211 + 2*
n311 + n411);
400
401
402 end
403
404 D =( beta.*(b.*x3+x4).*(lambda2-lambda1)).*x1;
405 F= ((lambda4-lambda6)+(lambda4-lambda7)).*x4;
406 G=(psi1.*(lambda6+lambda10)+gamma3.*(lambda11+lambda10)).*
x10;
407
408 u1 = min( max(0,D./B1), 0.95);
409 u2 = min( max(0,F./B2), 0.95);
410 u3 = min( max(0,G./B3), 0.95);
411
412 u1 = 0.5*(u1 + oldu1);
413 u2 = 0.5*(u2 + oldu2);
414 u3 = 0.5*(u3 + oldu3);
415 dt = t(i+1)-t(i);
416 J = sum(( C1*x2+C2*x4+C3*x6+C4*x7-C5*x10+1/2*B1*u1.^2+1/2*

```



```

    B2*u2.^2+1/2*B3*u3.^2 )*dt);
417 P=B1*u1+B2*u2+B3*u3;
418
419
420 %-----
421 % Absolute error for convergence
422 %-----
423
424
425
426
427 temp1 = delta*sum(abs(x1)) - sum(abs(olddx1 - x1));
428 temp2 = delta*sum(abs(x2)) - sum(abs(olddx2 - x2));
429 temp3 = delta*sum(abs(x3)) - sum(abs(olddx3 - x3));
430 temp4 = delta*sum(abs(x4)) - sum(abs(olddx4 - x4));
431 temp5 = delta*sum(abs(x5)) - sum(abs(olddx5 - x5));
432 temp6 = delta*sum(abs(x6)) - sum(abs(olddx6 - x6));
433 temp7 = delta*sum(abs(x7)) - sum(abs(olddx7 - x7));
434 temp8 = delta*sum(abs(x8)) - sum(abs(olddx8 - x8));
435 temp9 = delta*sum(abs(x9)) - sum(abs(olddx9 - x9));
436 temp10 = delta*sum(abs(x10)) - sum(abs(olddx10 - x10));
437 temp11 = delta*sum(abs(x11)) - sum(abs(olddx11 - x11));
438
439 temp12 = delta*sum(abs(u1)) - sum(abs(oldu1 - u1));
440 temp13 = delta*sum(abs(u2)) - sum(abs(oldu2 - u2));
441 temp14 = delta*sum(abs(u3)) - sum(abs(oldu3 - u3));
442
443 temp15 = delta*sum(abs(lambda1)) - sum(abs(olddlambda1 -
    lambda1));
444 temp16 = delta*sum(abs(lambda2)) - sum(abs(olddlambda2 -
    lambda2));
445 temp17 = delta*sum(abs(lambda3)) - sum(abs(olddlambda3 -
    lambda3));
446 temp18 = delta*sum(abs(lambda4)) - sum(abs(olddlambda4 -
    lambda4));
447 temp19 = delta*sum(abs(lambda5)) - sum(abs(olddlambda5 -
    lambda5));

```



```
448     temp20 = delta*sum(abs(lambda6)) - sum(abs(olddambda6 -
        lambda6));
449     temp21 = delta*sum(abs(lambda7)) - sum(abs(olddambda7 -
        lambda7));
450     temp22 = delta*sum(abs(lambda8)) - sum(abs(olddambda8 -
        lambda8));
451     temp23 = delta*sum(abs(lambda9)) - sum(abs(olddambda9 -
        lambda9));
452     temp24 = delta*sum(abs(lambda10)) - sum(abs(olddambda10 -
        lambda10));
453     temp25 = delta*sum(abs(lambda11)) - sum(abs(olddambda11 -
        lambda11));
454
455     test = min(temp1, min(temp2, min(temp3, min(temp4, min(
        temp5, min(temp6, min(temp7, min(temp8, min(temp9, min(
        temp10, min(temp11, min(temp12, min(temp13, min(temp14, min(
        temp15, min(temp16, min(temp17, min(temp18, min(temp19, min(
        temp20, ...
456     min(temp21, min(temp22, min(temp23, min(temp24, temp25))))))
        )))))))
457 end
458
459 y(1,:) = t;
460 y(2,:) = x1;
461 y(3,:) = x2;
462 y(4,:) = x3;
463 y(5,:) = x4;
464 y(6,:) = x5;
465 y(7,:) = x6;
466 y(8,:) = x7;
467 y(9,:) = x8;
468 y(10,:) = x9;
469 y(11,:) = x10;
470 y(12,:) = x11;
471 y(13,:) = lambda1;
472 y(14,:) = lambda2;
473 y(15,:) = lambda3;
```



REFERENCES

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474 y(16,:) = lambda4;  
475 y(17,:) = lambda5;  
476 y(18,:) = lambda6;  
477 y(19,:) = lambda7;  
478 y(20,:) = lambda8;  
479 y(21,:) = lambda9;  
480 y(22,:) = lambda10;  
481 y(23,:) = lambda11;  
482 y(24,:) = u1;  
483 y(25,:) = u2;  
484 y(26,:) = u3;  
485 y(27,:) = J;  
486 y(28,:) = P;  
487 box on  
488 hold on;  
489 plot(y(1,:),y(5:28,:), 'r', 'LineWidth',2)  
490 xlabel('Time(days)', 'fontsize',12)  
491 ylabel('cases', 'fontsize',13)  
492 legend('E(t) without control', 'I(t) without control')  
493 end
```