Effect of Awareness Programs on Some Non Contagious Diseases: Model Based Study

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by

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Under the supervision of

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This thesis is dedicated to my Father
Hasib Molla
For his endless love, support and encouragement.

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CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled "**Effect of Awareness Programs on Some Non Contagious Diseases: Model Based Study**" submitted by Sri. **Saddam Mollah** who got his name registered on 5th September, 2018 (Reg. No. SMATH1415118) for the award of Ph.D. (Science) degree of Jadavpur University, is absolutely based upon his own work under the supervision of **Dr. Santosh Biswas**, Department of Mathematics, Jadavpur University, Kolkata-700032 and that neither this thesis nor any part of it has been submitted for either any degree/diploma or any other academic award anywhere before.

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Chapter 1

Introduction

1.1 Non contagious diseases

Non contagious disease (NCD) is a non-infectious health condition that do not transfer from human to human. The NCDs are the effects of a combination of genetic, physiological, behavioral, and environmental factors (WHO [2019]). NCDs are the major cause of mortality globally, accounting for 71% of all deaths each year, according to the World Health Organization (WHO [2019]). The four leading causes of mortality among NCDs are cardiovascular diseases (17.9 million), cancer (9.0 million), respiratory diseases (3.9 million), and diabetes (1.6 million). The general population is unaware of NCDs and their related risk factors. To minimize the burden of NCDs in the general population, we must prevent the risk factors by educating people about them. The Indian population is more likely to acquire NCDs as a specific genetic susceptibility, unplanned urbanization, and a quickly changing lifestyle. Previously, NCDs were thought to be a concern of the wealthy urban population, but as the trend has changed, the poor people have also been sensitive to NCDs with their complications at an earlier stage. There are several parallel advocacy activities to combat NCDs, with a special focus on important heart disease, cancer, diabetes, and stroke (Beaglehole et al. [2011]). Several strategies, including smoke management, improved nutrition, exercise, and reduced alcohol intake, have been proposed as immediate preventative measures to help delay the pandemic (Beaglehole et al. [2011]). This situation in India, particularly among rural populations, may be attributable to a lack of understanding of risk factors, inadequate health care facilities, unplanned urbanization, and limited government programs.

1.1.1 Key risk factors of non contagious diseases

Various characteristics can enhance the likelihood of developing NCDs and could be categorized in different ways. Risk factors are classified into modifiable or non-modifiable elements depending on whether they have changeable or unchangeable situations, respectively. The changeable risk factors are blood pressure, smoking, diabetes mellitus, physical inactivity, and high ancestry cholesterol, while the non-changeable risk factors draw in age, genetic determinant, race, and ethnicity. Except for age and gender, most of the risk factors for NCDs are modifiable (Hui [2017], Kontis et al. [2014]). Some modifiable risk factors can be adjusted at the individual level if the person adjusts his or her behavior such as poor diet, lack of physical exercise, and use of cigarettes and alcohol. However, some modifiable risk factors can be adjusted in legislation and government policy, such as poverty, poor living, and working circumstances, environmental factors such as pollution from factory smoke, automobiles, and even household cooking stoves all can raise the risk of various NCDs. These factors have a significant impact on the prevalence of NCDs (Campbell-Lendrum and Prüss-Ustün [2019]). The government can provide smokeless stoves to minimize interior pollution or impose fines on enterprises located in residential areas to reduce air pollution. There is also legislation prohibiting the sale of tobacco products near schools and universities so that youngsters do not begin smoking at a young age.

1.1.2 Impact on economic of non contagious diseases

NCDs are remarkable not just because of their prevalence, but also they impose a significant economic burden in the future decades. NCDs can have an impact on economic production in a variety of ways. When people of working-age die of a disease, the labor supply decreases immediately. Even if the disease is mild, it has an impact to reduce worker productivity and labor supply. Medical treatments for NCDs need significant resources. Investing in NCDs prevention, treatment, or delaying progression gives health and economic advantages to both (Chen et al. [2018], Hui [2017]).

Commonly NCDs are thought to be a sickness of the rich people. Although, NCDs can affect the poor and vulnerable as well. Poverty affects NCDs in a variety of ways, including maternal malnutrition. Additionally, poor individuals are unable to purchase and consume healthful foods such as nuts, fresh fruits, and so on. Poor people also live in areas where air pollution is more likely, such as near companies that emit dangerous chemicals. The risks of NCDs may be higher among the poor than among the rich, who are more aware of their health and have enough money to

engage in better lives. NCDs are linked to many health care expenses for their long and costly treatment. Individuals with NCDs cannot stop taking medications once they feel well - they must continue to take them to keep disease away, typically for the rest of their lives. However, many patients discontinue taking medications when they feel better or run out of money. Poor people may be unable to visit a health center regularly due to a lack of money. The burden of NCDs suppresses economic growth by limiting labor supply, lowering productivity and income, and reducing savings and investment (i.e lower incomes and increased medical costs). In addition, NCDs also threaten future economic and human development since poverty and disease are handed down frequently to the next generation. Health systems in low- and middle-income countries will have substantial challenges in adapting to rapidly expanding demand for services, which might constitute another effective barrier to reaching the development goals (Alwan et al. [2010]).

1.1.3 Role of environment on non contagious diseases

The impact of the environment on the risk of NCDs in the population has grown significantly in recent decades. Most of the worldwide environmental changes are the result of human actions that have harmed the natural system and its ability to produce food, clean water, fresh air, and increase global temperature. Researchers are interested in environmental risk factors and their impact on NCDs, which are the leading cause of death and disability worldwide (Prüss-Ustün et al. [2019], Frumkin and Haines [2019], Jamaluddine et al. [2016]). Up to 75 percent of worldwide NCDs are caused by damaging health outcomes as a result of exposure received in living and working environments combined with lifestyle factors . In 2016, air pollution was the second leading cause of NCDs over the world, after only tobacco smoking. NCDs cannot be managed effectively without the active participation of the global health community. The environment encloses not just global environmental changes such as urbanization and population aging, but also the social and physical surroundings in which people live (WHO [2014]). Interventions to decrease environmental health concerns may have several co-benefits, including increased social fairness, climate change mitigation, and energy efficiency. Researchers have been studying the link between human and social environment and their health since 1980 (Adler and Ostrove [1999]). Epidemiological research has shown the significance of social-environmental influences on population health (Berkman et al. [2014]). Their research emphasizes the importance of social-environmental factors with socioeconomic status at the population level.

1.1.4 Some keys of non contagious diseases

Diabetes (DM): All of the food we consume is broken down to a sugar known as glucose. The blood transports glucose throughout the body to provide energy. Insulin is the hormone that helps glucose flow from the blood into the cells. Due to dependency and independence of insulin, diabetes can be divided into Type-1 (T1) and Type-2 (T2) diabetes. In T1 diabetes, the body produces no insulin at all. The disease can affect persons of any age, although it most commonly affects children and young adults. In T2 diabetes, the body generates some insulin, but not enough. This type of diabetes was previously exclusively observed in adults, but it is currently becoming more common in children and adolescents.

Cancer: Cancer is a disease in which some cells develop uncontrolled and spread to other parts of the body. Cancer may begin practically anywhere in the human body, which is made up of billions of cells. Normally, human cells develop and proliferate to generate new cells as needed by the body. Cells die when they get too old or damaged to function, and new cells replace them. This organized process occasionally breaks down, allowing abnormal or damaged cells to grow and reproduce. These cells can combine to produce tumors, which are masses of tissue. Tumors may or may not be cancerous. Cancerous tumors can infect adjacent tissues and spread to other parts of the body to form new tumors. Non-cancerous tumors do not spread or infect neighboring tissues. When removed, non-cancerous tumors usually do not grow back, whereas cancerous tumors sometimes do.

Thalassemia: Thalassemia major develops when a child receives two defective globin genes from each parent. Thalassemia minor develops when a child gets one defective globin gene from only one parent. Individuals with thalassemia minor normally have no symptoms and can lead a normal life. Hence, if a child is diagnosed with thalassemia major, it means that both parents have defective globin genes. Thalassemia major is chronic, lifelong anemia that generally develops in childhood and necessitates regular blood transfusions due to red blood cell deformation. Thalassemia therapy needs a large volume of national blood supply due to the necessity of lifelong blood transfusion as a treatment procedure. Treatment for thalassemia frequently leads to serious problems such as iron excess, bone abnormalities, and cardiovascular disease.

1.1.5 Prevention and control of non contagious diseases

NCDs are a major health problem worldwide, harming health without showing symptoms until the disease has proceeded to an advanced stage. A comprehensive strategy is required, involving collaboration from many sectors, including health, education,

and promotion measures to prevent and control NCDs. Patients with NCDs, or those who are at risk of developing one, require long-term, individualized, and sustainable treatment. Primary care systems may develop and deliver health care programs to control NCDs in each community as well as diagnose diseases at an early stage (Jamaluddine et al. [2016], Boutayeb and Boutayeb [2005]). The lack of a well-designed plan to prevent disease development and transmission is the main reason for an increase in the number of patients with NCDs in poor and middle-income areas. A better lifestyle can help to the prevention, control, or reversal of the above modifiable risk factors (Budreviciute et al. [2020], Jamaluddine et al. [2016], Kontis et al. [2014]). Changes in lifestyle can help to mitigate the adverse effects. Healthy lifestyle efforts, such as healthy food availability and physical exercise, should be at the core concept of any NCDs-awareness plan. Various studies have shown that lifestyle variables have direct correlations to reduce NCDs risk and that modifying lifestyles in a favorable direction can significantly lower NCDs burden (Anand et al. [2008], Stein and Colditz [2004]). Dietary modifications, physical exercise, weight control, obesity management, tobacco avoidance, safe sex, and control of oncogenic viruses, as well as sun protection, pharmaceuticals, and no alcohol consumption, can all help to prevent NCDs (Stein and Colditz [2004]). The approach to preventing NCDs is based on risk component management, which includes resource allocation, multi-sectoral partnerships, knowledge and information management, and innovation at the individual, social, national, and global levels.

1.1.6 Awareness on non contagious diseases

Patients with NCDs require long-term treatment that is customized, proactive, and sustainable. Primary care may develop and deliver health care programs to control NCDs in each community and diagnose diseases at an early stage (Boutayeb and Boutayeb [2005]). The most important aspect of the prevention strategy is lifestyle management at the individual level, which can help society raise awareness of risk factor management. It is crucial to know how much global and local knowledge influences disease dynamics, and which type of awareness is more significant. Human behavior regarding the disease can be controlled by launching media campaigns. These efforts primarily aim to increase awareness levels in the community about diseases and to promote steps that can minimize the risk of disease (Misra et al. [2015, 2008]). As knowledge spreads, individuals react to it and gradually adjust their behavior to reduce their chance of developing the disease. Due to the complexities of behavioral changes in the population in the presence of awareness, it is critical to understand

how awareness impacts disease dynamics. The risk of the disease can be evaluated by surveying local people or the entire community. Global awareness is becoming increasingly important in human behavior as current communication technology improves, knowledge spreads, and travel patterns alter, which impacts positively the dynamics of disease (Apolloni et al. [2013]). Virtual communication tools like google, facebook, hotline are the prime source of information, which are free to access in the community. These new technologies have increased the active duties in the media, and the media is now alert everywhere, with the potential of capturing, monitoring, and reporting even tiny incidents of interest from one portion of the world to another nearly in real-time. In India, there are significant health differences between the wealthy and the poor, therefore a single health promotion program would not benefit everyone. Health promotion activities should be adjusted to the regional-wise needs of the community taking into consideration a variety of behaviors and lifestyles.

1.2 Mathematical models in epidemiology and their historical background

A mathematical model is an expression of a practical situation or real-world problem that employs mathematical principles and specific assumptions. Mathematical models are interdisciplinary methods, and are used in practically all scientific fields in various forms as statistical models, dynamic systems and game-theoretical models. One of the most common methodologies used in biomathematical research is mathematical modeling. It also has fascinating applications in the collection of non-communicable diseases. Mathematical modeling is a very intriguing academic subject with a variety of applications that contains sophisticated practical features. Researchers are developed models and describe the connected aspects of modeling through modeling activities. An epidemiological model is a mathematical representation of disease-based assumptions. Theoretical problems in epidemiology need a deep understanding of multi-layered, non-linear systems in which disease grow, and where important possibilities are influenced by pathogen biology or human behavior. It is reasonable to describe how the disease spreads in the community and explain who a portion of the population avoids the diseases during an epidemic. This description or model does not necessarily seek to contain all of the specific factors of the epidemic, but it focuses on the most critical factors of the disease. The typical procedure is to develop certain assumptions about how the epidemic will spread, express these assumptions in mathematical terms, and then transform them into a mathematical problem. The process

of developing a model includes stating key assumptions, establishing relationships between variables, and identifying the parameters with their relations that regulate their behavior. Of course, the selection of these characteristics is crucial to forming the model and depends largely on the particular disease. Mathematical models and simulations are effective experimental methods for developing and testing premises, evaluating quantitative hypotheses, addressing particular questions, measuring sensitivity to changes in parameter values, and predicting critical parameters from data. The parameters can be used to make accurate interpretations by fitting these models with epidemiological data. The solution of the model yields conclusions that can be compared to experimental data of the disease. This type of comparison generally needs to use numerical simulations to generate predictions and can be compared to observed facts. The effectiveness of the results deduced from the model depends on how the model was designed and the accuracy of the observed measures. The numerical solutions of the model are displayed using a graphical interface that allows us to reveal important properties of the models and diseases.

Daniel Bernoulli developed and solved the first epidemiological model for smallpox in 1760 to assess the efficiency of variolation of healthy persons with the smallpox virus. In 1906, Hamer developed and tested a discrete-time model to understand the reproduction of measles outbreaks (Hamer [1906]). His model may be the first attempt to assume that the incidence rate depends on the susceptible and infective. Kermack and McKendrick, set out to figure out why diseases span across a community without harming everyone (Kermack and McKendrick [1927]). The mathematical model used a mass-action incidence rate to represent the acquisition of infection and recovery with protection against reinfection. They found the solution of the model qualitatively and calculated the basic reproduction number from the parameters of the model. This finding not only corresponds to match observation but serves as a criterion for determining whether a disease outbreak will turn into an epidemic or die out. It would be essential to make more precise assumptions about the scenario to develop a more complex mathematical model to make more detailed forecasts about the incidence of the disease. A precise solution to such a model would very certainly be unachievable; numerical simulations will be required to get predictions that could be compared against observations. The mathematical problem in epidemiology helps to understand the underlying factors that impact disease propagation. At present, several mathematical models are available to study the dynamic nature of epidemics of both contagious and non-contagious diseases (Calabrese and Demers [2022], Anusha and Athithan [2021], Singh et al. [2018], Dhaheri and Kim [2018], Kim and Tridane [2017]).

1.3 Mathematical tools and their applications

The models developed in this thesis to examine the dynamics of NCDs are extremely nonlinear, hence analytic solutions to the model systems are not easy to achieve. The stability theory of differential equations can be used to predict the long-term behavior of such a system. The equilibrium point is a solution to a dynamical system. It is a solution where the state variables remain constant; it is a steady-state, or rest state of a system. Although an equilibrium point is a basic idea, it is a fundamental notion in dynamical systems and will serve as a foundation for studying more complex behavior. For the compartmental model, compartments can either flow amongst each other (population flows from one compartment to another) or interact (change in one compartment is dependent on the amount of another compartment) at some rate. These rates are referred to as the "parameters" in compartmental model. The parameters used in the model system are biologically relevant, and sensitive to influence the dynamics of the disease.

1.3.1 Equilibrium points

Consider a dynamical system of first-order differential equations

$$\dot{x} = f(x), \ \textit{where } x = (x_1, x_2, ..., x_n)^T, f = (f_1, f_2, ..., f_n)^T. \tag{1.3.1}$$

The state of the system is represented by the vector x, and the function f controls how the system evolves in time and $\dot{x}$ denotes differentiation of x w.r.t time. As the state variables of a dynamical system do not vary over time at equilibrium state E, the equilibrium points may be calculated from

$$f(x) = 0. \tag{1.3.2}$$

All the roots of the equation (1.3.2) are considered as equilibrium points. There can be one or multiple or no equilibrium points in a system. Readers can find more information on the classification of equilibrium points in two and three-dimensional systems in Lakshmanan & Rajasekar (2012) (Lakshmanan and Rajaseekar [2012]).

Theorem 1.3.1. *There is an optimum control* $(u_1^*, u_2^*) \in \mathfrak{U}$ *on a set interval [0,* t_f*] that is as follows:* $J(u_1^*, u_2^*) = \frac{min}{(u_1^*, u_2^*) \in \mathfrak{U}} \{J(u_1(t), u_2(t))\}$.

Theorem 1.3.2. Existence and Uniqueness Theorem
Let $f \in \mathbb{C}^1(E)$*, where* E *be an open subset of* $\mathbb{R}^n$*. Then for any* $x_0 \in E$*, there exist a*

positive real number δ such that the dynamical system (1.3.1) has a unique solution in [-δ, δ] (Perko [2001]).

1.3.2 Stability

An equilibrium point is stable if surrounding solutions either stay close to it in the future or tend to it. The following definitions can help to clarify these concepts of stability.

Theorem 1.3.3. *An equilibrium point $\overline{x}$ is called stable of the system (1.3.1), if for any $\epsilon > 0$, there exist a $\delta > 0$ depending on ϵ such that for arbitrary solution $y(t)$ of the system (1.3.1) satisfying $|y(t_0) - \overline{x}| < \delta$, then $|y(t) - \overline{x}| < \epsilon$ for $t > t_0$, $t_0 \in \mathbb{R}$ (Perko [2001]).*

Theorem 1.3.4. *An equilibrium point $\overline{x}$ is called asymptotically stable of the system (1.3.1), if it is stable and there exist a constant $p > 0$ satisfying $|y(t_0) - \overline{x}| < p$, then $\lim_{t\to\infty} |y(t) - \overline{x}| = 0$.*

Thus, to assess the stability of equilibrium $\overline{x}$, we must explore the nature of any solutions of the system (1.3.1) near to $\overline{x}$. The linearization of the nonlinear system (1.3.1) around $\overline{x}$ is a general technique for this aim. The linearization of the system (1.3.1) by the transformation $y = x - \overline{x}$ at the equilibrium point $\overline{x}$ is given by

$$\begin{aligned} \dot{y} &= Df(\overline{x})y, \quad y \in R^n \\ \therefore\ \dot{y} &= Ay, \quad where\ A\ = Df(\overline{x}) \end{aligned} \tag{1.3.3}$$

where " $\dot{}$ " denotes the differentiation w.r.t time and $Df(\overline{x})=\left(\frac{\partial f_i}{\partial x_j}\right)_{1\le i,j\le n}$ is the Jacobian of f at the equilibrium point $\overline{x}$. The system (1.3.3) is called the linearization of the system (1.3.1) at the equilibrium point $\overline{x}$.

Theorem 1.3.5. *An equilibrium point $\overline{x}$ is said to a hyperbolic equilibrium point of the system (1.3.3) if all the eigenvalues of the matrix A has non zero real part, otherwise the equilibrium point is said to be non hyperbolic equilibrium point.*

Theorem 1.3.6. *(Petras [2008]) Consider the following fractional-order system*

$$ {}_0^c D_t^q x(t) = f(x), x(0) = x_0 $$

with $0 < q \le 1$, $x \in \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$. The equilibrium point x^* of the above system is calculated by solving the equation $f(x^*) = 0$. Then x^* is said to be locally

asymptotically stable if all eigenvalues λ_i *of the Jacobian matrix* $J = \frac{\partial f}{\partial x}$ *evaluated at the equilibrium point satisfies*

$$| \, arg(\lambda_i) \, | > \frac{q\pi}{2}, i = 1, 2, ..., n.$$

The Hartman-Grobman theorem states that the corresponding linear system follows the same qualitative structure as the nonlinear system at a hyperbolic equilibrium point (Perko [2001]). The sign of the real part of eigenvalues of the Jacobian matrix are determined to estimate the local stability of the nonlinear system for hyperbolic equilibrium $\overline{x}$. The Routh-Hurwitz criterion is a technique formed by Edward John Routh and Hurwitz to establish the local stability of a dynamical system with the coefficients of a characteristic equation of the Jacobian matrix at an equilibrium (Iswanto [2012]). Hurwitz formulated a mechanism for arranging polynomial coefficients into a matrix in 1895, and this square matrix is known as the Hurwitz matrix. He concludes that the equilibrium point is stable if all the elements in the sequence of determinants of primary sub-matrices are positive. The Routh-Hurwitz criteria are frequently used to identify the sign of the roots of the characteristic equation of the Jacobian matrix at the equilibrium point.

The above theorem stated for arbitrary degrees of characteristic polynomial. In particular cases for n=2 and 3 are given bellow

- n=2, $r_1 > 0$, $r_2 > 0$.
- n=3, r_1, $r_3 > 0$, $r_3 < r_1 r_2$,

where r_i are the coefficients of λ^{i-1} in the characteristic equation of degree n and $1 \leq i \leq n$.

1.3.3 Optimal control theory

In 1950s, Lev Pontryagin and Richard Bellman produced optimal control theory based on Edward J. McShane's work on the theory of calculus of variation (Sargent [2000], Bryson [1996]). This control theory has a wide range of applications in physics and engineering. This is a well-known approach for optimizing a dynamical system. The optimal controls are concerned with developing control techniques or optimality criteria for the system to enhance its long-term stability. A cost function is constructed by the state and control variables to find the related cost by executing the controls.

Suppose we assume that the the function f in (1.3.1) depends on the control parameters u=(u_1, u_2,... u_m) which is belong to the set $\mathcal{U} \subset \mathbb{R}^m$ such that f : $R^n \times \mathcal{U} \rightarrow R^n$. Then the system in (1.3.1) can be written as an optimal control

problem in the following

$$\dot{x} = f(x(t), u(t)), \qquad x(0) = x_0, \tag{1.3.4}$$

where $x \in \mathbb{R}^n$ is the state space, $u \in \mathcal{U}$ is the control vector, and f is continuously differentiable function. Also the control vector is taken piecewise continuous function on $[t_0\ t_f]$ into $\mathbb{R}^m$. $x(t_0)$ is a known value of the vector state variables of the system at initial time. We define an objective function J as follows

$$J = \min_{(u_1,u_2)} \int_{t_0}^{t_f} (a_1x_1 + a_2x_2 + ... + a_nx_n + \frac{w_1}{2}u_1^2 + \frac{w_2}{2}u_2^2 + ... + \frac{w_m}{2}u_m^2)e^{-qt}dt, \tag{1.3.5}$$

where a_1, a_2,...,a_n are weights of the respective compartments and w_1, w_2,...,w_n are weights of the respective optimal controls.

The optimal controls (u_1, u_2,... u_m) are chosen in which the objective function J in (1.3.5) is minimized. This can be expressed in the following form

$$J(u_1^*, u_2^*, ..., u_m^*) = \min_{(u_1,u_2,...,u_m)\in\mathfrak{U}} J(u_1(t), u_2(t), ..., u_m(t)),$$

where the non empty control set is given by
$\mathcal{U}$=$\{(u_1, u_2, ..., u_m) : u_i(t)$ is Lebesgue measurable in $[t_0,\ t_f]$, $0 \leq u_i \leq 1, i = 1, 2, ...m\}$.

Since u_i is a smooth curve on $[t_0\ t_f]$. The integrand of the objective function in (1.3.5) is convex on $\mathcal{U}$ and bounded below by $q_1(|u_1^2 + u_2^2 + ... + u_m^2|)^{\frac{\alpha}{2}} - q_2$, where $\alpha > 1$ with $q_1, q_2 > 0$. By the definition of $\mathcal{U}$, it is closed and convex set. Thus, the optimal problem is bounded and linear in the control variables. Then from the existence of optimal control, there exist $(u_1^*, u_2^*, ..., u_m^*)$, which minimize the objective function (1.3.5). After that, we convert this optimal problem into a problem of maximizing a Hamiltonian function H at the control variables. The necessary conditions for effective controls are obtained by utilizing Pontryagins maximum principle under time-dependent controls to develop optimal strategies (Fleming et al. [1975]). Hamiltonian function with associate adjoint variables λ_1, λ_2,...,λ_n is given by

$$\begin{aligned} H =& a_1x_1 + a_2x_2 + ... + a_nx_n + \frac{w_1}{2}u_1^2 + \frac{w_2}{2}u_2^2 + ... + \frac{w_m}{2}u_m^2 + \\ & \lambda_1\frac{dx_1}{dt} + \lambda_2\frac{dx_2}{dt} + ... + \lambda_n\frac{dx_n}{dt}, \end{aligned} \tag{1.3.6}$$

where the adjoint variables or co-state variables are satisfy $\lambda_i(t_f)$=0, i=1, 2,...,n, and find out the following set of differential equations: $\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial x_1}$, $\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial x_2}$,...,$\frac{d\lambda_n}{dt} = -\frac{\partial H}{\partial x_n}$, with the optimality conditions $\frac{\partial H}{\partial u_j} = 0$, $j = 1, 2, ..., m$.
Finally, the required optimal controls are solved as
$u_1^* = \max\{0, \min\{1, u_1\}\}$, $u_2^* = \max\{0, \min\{1, u_2\}\}$,...,$u_m^* = \max\{0, \min\{1, u_m\}\}$.

1.3.4 Homotopy analysis method (HAM)

Most of the differential equations produced by physical or biological circumstances are nonlinear, making it difficult to solve the problems completely. There are a variety of analytic procedures available, including the asymptotic analysis and perturbation techniques, adomian decomposition method (ADM), and the variational iteration method (VIM). Liao developed Homotopy analysis method (HAM) in 1992, which is a very effective and simple method for solving any type of nonlinear problem without the need for linearization, perturbation, or discretization (Liao [1992]). Also many researchers has been involved in its theory and applications (Duarte et al. [2018], Arqub and El-Ajou [2013], Liao [2006, 2004, 2003], Liao and Cheung [2003], Shijun [1998]). Based on Homotopy and using a basic concept of topology and geometry, HAM generates consecutive approximations of the solution of the system that eventually converge to the actual solution. The method applies to arbitrary parameter values, and it gives a lot of flexibility in selecting an appropriate linear operator and base function to estimate the precise solution of nonlinear problems. An artificial parameter used in this method that allows for the simple adjustment and enlargement of the convergence region, as well as a rise in the rate of convergence of the series solutions. This method produced solutions based on our choice of auxiliary function, linear operator, initial guess, and auxiliary parameter value. We have a lot of flexibility with HAM in terms of how we build solutions to non-linear problems. This flexibility gives several advantages that are not accessible with traditional perturbation approaches. The HAM has been utilized in a wide range of mathematical and engineering applications. In recent years, HAM has been applied to a variety of models, including population models, prey-predator models, epidemic models, and so on.

1.3.5 Fractional order model

Fractional calculus is a centuries-old but still-relevant mathematical approach for unifying and generalizing the derivatives and integer-order integrals to any order. The idea of non-integer order derivatives (i.e the derivative of order $\frac{1}{3}$ or $\sqrt{2}$ of a function) began with a letter from L'Hospital to Leibniz debating the definition of the derivative in 1695. Following that, it noticed the curiosity of mathematicians in the 18th and 19th centuries to research this topic. Later, many important articles on various elements of fractional calculus were published (Acharya et al. [2005], Oldham and Spanier [1974]). Fractional-order systems have become an ideal tool for modeling epidemiological features and provide a fascinating modeling approach in the context

of biology since they allow for more degrees of freedom and add memory impact into the model. The fractional derivative is more difficult to solve than the classical model, although there are various numerical approaches for solving such problems. Fractional calculus has received widespread attention in previous decades for its extensive variety of applications in chemistry (Jiang and Qi [2012]), biology (Magin [2006]), physics (Qin et al. [2017]), engineering (Liu et al. [2004]) etc. Fractional order systems are more realistic and provide a proper interpretation in population biology than ordinary differential equations for describing a phenomenon. It is an important tool to describe the past behavior of individuals in the present and some hereditary properties of individuals in the community. Hence behaviors of the population have been explored using fractional-order derivatives based on the disease.

The ordinary differential equation is a local operator, where as a fractional-order equation is a non-local notion is that the future state is dependent not only on the current state but also on the past of its prior states. It should be remembered that the current states of any real-world dynamic system are dependent on the history of its previous states. Such situations encouraged researchers to investigate the fractional order model, which includes a lot of physical importance in terms of public health.

1.4 Literature review and motivation

Mathematical modeling is a powerful tool that has wide application in health sector and policy design. Theoretical researchers have used mathematical model-based analytical and numerical investigations, a suitable and effective technique for predicting the dynamics of diseases and concepts derived from the models. Hence, mathematical models are effective tools that can be used to investigate the impact of awareness on the prevalence of the disease. However, classical mathematical models consider homogeneous mixing, which means that all pairs of people have an equal possibility of contacting each other. Due to the difficulty of modeling the local population interaction pattern, such models can only explore global awareness. Funk et al. have explored how awareness affects the spread of disease (Funk et al. [2010]). They demonstrated that spreading awareness and lowering susceptibility in a social network not only reduces disease incidence but may also prevent epidemics in some situations. Thus awareness might be a good way to keep a disease under control. In addition, funk et al. looked at how awareness spreads and how it impacts the prevalence of the disease (Funk et al. [2009]). They demonstrated that increasing public awareness not only decreases the incidence rate of the disease but, in certain situations, prevents the disease from becoming an epidemic. Wu et al. employed the SIS model to explore

the role of awareness on disease transmission (Wu et al. [2012]). They identified three types of awareness in the model system: contact awareness, regional awareness, and global awareness. Their findings revealed that contact and local awareness have an impact on the transmission threshold, however, global awareness has no impact on the system. Rizzo et al. hypothesized that self-protection and quarantine behavior are effective strategies for controlling epidemic transmission in the SIS dynamic model, resulting in an increase in epidemic threshold and reduction in steady-state prevalence (Rizzo et al. [2014]). Misra et al. analyzed the impact of public awareness campaigns on the spread of infectious diseases and found that while awareness campaigns can help to reduce the spread of infectious diseases, the disease stays endemic for the immigration of individuals (Misra et al. [2011]).

Several mathematicians have studied the dynamics of various NCDs such as diabetes, cancer, thalassemia, and others during the last few decades. Boutayeb and Chetouani developed a population model to track the size of pre-diabetes and diabetic populations with and without complications (Boutayeb and Chetouani [2007]). Their model demonstrates how reducing the prevalence of pre-diabetes and regulating the progression of diabetes without and with complications can result in efficient and cost-effective measures. Anusha and Athithan developed and analyzed a mathematical model for T2 diabetes in a deterministic approach. Their findings indicate a reduction in diabetes-affected populations when compared to IDF statistics (Anusha and Athithan [2021], East and Africa [2017]). Singh et al. extended Butayeb's work by using the CaputoFabrizio fractional derivative to study the diabetes model and its implications in their model system (Singh et al. [2018]). They showed that the results of this fractional-order model are useful for medical professionals who deal with diabetes and related concerns. Srivastava et al. formulated a fractional-order model for diabetes mellitus with related complications. They demonstrated that the fractional-order model is more appropriate for describing the problem of diabetes and its consequences (Srivastava et al. [2019]). Daud et al. designed and analyzed a mathematical model to study the dynamics of diabetes during pregnancy (Daud et al. [2020]). Their findings suggest that disease outcomes may be influenced by some critical factors that are represented by model parameters. Kouidere et al. established a mathematical model with an optimal control method emphasizing the role of behavioral variables in complications of diabetes (Kouidere et al. [2020]). They tried to make the severity of diabetic complications and the adverse effects of an unbalanced lifestyle with the surrounding environment in the study.

Most of the cancer model published in the literature for tumor cell. Various mathematical models have been developed over the last few decades to account for

the complexity of immune responses to tumors (Liu et al. [2018], Khajanchi [2015]). In addition, Tang et al. formulated a fractional-order mathematical model of breast cancer with adverse effect of chemotherapi in the population level (Tang et al. [2022]). The dynamical behaviour of different stages of breast cancer is highlighted numerically with the role various input parameters in their study.

Also, thakur et al. employ pure-fraction to build a mathematical model for thalassemia illness diagnosis (Thakur et al. [2016]). According to their study, pure fractions can help regulate the transmission of the thalassemia gene and generate a new generation free of thalassemia major or other severe forms of the disease. Dhaheri et al. constructed a compartment model with three age groups and thalassemia control methods to assess the long-term efficiency of control strategies at a population level (Dhaheri and Kim [2018]). Kim and Tridane developed a mathematical model to evaluate the long-term impact and ability of community-based thalassemia prevention initiatives (Kim and Tridane [2017]). They found that preventative measures reduce the prevalence of thalassemia in a short time, but do not eradicate the disease in the long term. The result indicates that control strategies are only successful in reducing the prevalence of disease for a short time.

Thus many articles have been published about how mathematical models have aided decision-making, in the field of contagious and non-contagious diseases. However, as the preceding discussion shows, only a few mathematical models on NCDs have been developed till now. As far as I know, mathematical modeling in terms of the effect of awareness on NCDs has not yet been studied but may offer some new directions for further study of such disease control. From the preceding sections, it is clear that knowledge and awareness have a definite impact on NCDs to reduce their burden on the community. Thus there is a large scope to study the NCDs dynamics under the influence of awareness programs. To the best of our knowledge we first propose and analyze in NCD mathematical work on the effect of the awareness program on the diabetes mellitus model in a deterministic and stochastic environment. This thesis also focuses on how mathematical modeling may help with policy development and decision making of some NCDs. Furthermore, past behavioral and lifestyle characteristics of aware persons, such as food, physical activity, sedentary behavior, sleep, and stress, might sometimes impact their decision to repeat the behavior in the present. Thus the models of NCDs under awareness are dependent on the previous time, which can be obtained by using fractional calculus. Optimal control measures as a treatment and awareness of NCDs, and finding out the related cost-effective strategy for NCDs have not studied so far in the literature. Such unresolved concerns in past studies inspire us to explore new ideas and determination in the develop-

ment of theoretical and analytical research on some NCDs under awareness. In the present thesis, we are solely interested in a system of nonlinear differential equations of various noncontagious diseases (NCDs) such as diabetes, cancer, and thalassemia to investigate the dynamics of such diseases under the influence of education and awareness programs.

1.5 Structure of the thesis

In this thesis, I investigate the impact of awareness in the model systems on NCDs to prevent the disease prevalence in the community. The main aim of this thesis is to formulate and analyze the mathematical modeling arising from various population interactions for different NCDs. We analytically solve the systems and validate them numerically. Biological interpretation of the numerical results is discussed and gives some insights into the prevalence of NCDs. The thesis is divided into seven chapters, beginning with an "Introduction section" [1] and concluding with a "Future motivation" [7].

Chapter 2
Diabetes mellitus is a silent killer and a serious public health issue across the world, yet there is a lack of education and awareness about the disease. Understanding the causes of diabetes and how to avoid it requires a high level of awareness. As the world is not deterministic, biological fluctuations are always present in the population. With this inspiration, we propose a deterministic and stochastic mathematical models on the impact of awareness of diabetes. We look at the impact of awareness programs on diabetes mellitus on the prevalence of the disease in both deterministic and stochastic environments. The equilibrium point of the systems, their feasibility, and the local stability of both awareness-free and with-aware systems, are established. According to the numerical simulation, the solution of the stochastic system varies around the solution of the deterministic system and approaches the equilibrium point asymptotically. A biological interpretation of these findings is that when we add awareness to the model system, the number of diabetes mellitus cases is significantly decreased than without the awareness-model system. Furthermore, the observations from deterministic and stochastic systems suggest that an awareness campaign has a considerable impact on the community to reduce diabetes patients.

Chapter 3
T2 diabetes awareness and management among patients continue to be a concern for

stake holders. Awareness of T2 diabetes can help with early diagnosis and lower the risk of complications. In chapter 3, we conducted a detailed mathematical analysis of the influence of media-based public awareness campaigns and treatment on the complication of T2 diabetes. We first present a nonlinear mathematical model of T2 diabetes, after which we incorporate two control parameters into the model system. We solve the model deterministically and the effects of different parameters into the system are also identified by taking constant control parameters. The Pontryagin's maximal principle in time-dependent controls is used to develop optimal disease control strategies. Diabetes prevention and control strategies are emphasized as health care resources are always limited. We intended to assess the efficacy and costs of several strategies to determine which is the best cost-effective strategy. Again, if the treatment is not limited then not only disease prevalence, but also the economic burden can be minimized by using the control profiles. Numerical simulations suggest that both awareness control and recovery control have a significant impact on the optimal system and are economically feasible to reduce the prevalence of T2 diabetes.

Chapter 4

Diabetes mellitus is one of the leading causes of noncommunicable illness, although diabetes knowledge and awareness are lacking in mid-and low-income countries. In chapter 4, the mathematical model is derived by a nonlinear interaction between the number of diabetes patients and the cumulative density of diabetes awareness programs. Diabetes is a behavioral disease and not caused by pathogens, so increasing the number of diabetic people mostly depends on the unaware of susceptible people. We attempted to investigate the past behaviors of persons in the present about diabetes using fractional calculus. The fractional-order model is solved completely using an effective homotopy analysis approach. Analytical HAM solutions for the models are obtained by choosing a set of biologically feasible parameter values. Fractional-order derivative plays a significant role to incorporate past behavioral effects of the individuals within the model system. According to our findings, awareness campaigns can lower the number of diabetes patients in the community.

Chapter 5

Cancer is a serious public health issue globally, and public awareness of the disease plays a vital role in prevention, early detection, diagnosis, and treatment of cancer. The disease is influenced by several environmental cancer risk factors. In this chapter, we consider a mathematical model to explore the dynamics of cancer patients under awareness. The total population is subdivided into three different categories: un-

aware human, aware human, and cancer human. Cancer is not a contagious disease, so cancer patients mostly depend on the unaware human and aware human. Many environmental risk factors of cancer influence the incidence of the disease. To enclose the fluctuations in the system, we introduced stochastic perturbation factors in the form of white noise into the model system. Analyze the local stability analysis of both deterministic and stochastic model systems at the equilibrium point. Analytical findings are validated in numerical simulations by using a set of relevant parameter values of both deterministic and stochastic systems. The results suggest that a community-wide awareness campaign might help to prevent cancer in the community.

Chapter 6
Thalassemia is a prevalent genetic blood disorder that can be prevented with prenatal screening and education. In this chapter, we study the dynamics of a mathematical model of thalassemia patients with and without control profiles. The basic reproduction number is computed using constant control parameters, and the existence and stability of equilibria are also determined. A cost-effectiveness analysis is carried out using numerical simulations to determine the most cost-effective control approach out of all the possibilities. The combined impact of both controls is the most effective thalassemia prevention method. This chapter indicates that widespread public knowledge of the diseases, carrier screening, prenatal identification of carrier couples, and the avoidance of thalassemia carrier marriages to reduce the thalassemia patients in the community.
The thesis ends with future motivation in **Chapter** 7.

Chapter 2

Effect of Awareness Program on Diabetes Mellitus - Deterministic and Stochastic approach.[1]

2.1 Introduction

Diabetes mellitus (DM) is a complex group of non-communicable diseases caused by several reasons. Individuals suffering from diabetes have hyperglycemia, because either there is a lower production rate of insulin or the body cells do not produce enough insulin. The number of diabetic patients worldwide has increased fourfold since 1980. This rapidly increase contributed by population growth, aging and there are so many things, which are also responsible for it (Shashank et al. [2008], Lin et al. [2004], Singh et al. [1994]). World Health Organization (WHO) states that in 1980, there were only 108 million diabetic patients but surprisingly today it reached 422 million. If this trend is going on the number of diabetic patients will reach 628.6 million by the year 2045 (WHO [2016], Atlas et al. [2015]). In addition, according to the International Diabetes Federation (IDF) report 8.3% of the total world population has been suffering from diabetes, and this is expected to reach 9.9% by the year 2045 in the age of 20-79 years (East and Africa [2017]). Mainly the prevalence of diabetes is observed in low and middle-level socioeconomic countries all over the world. Diabetes mellitus (DM) is a group of metabolic disorders that are characterized by high blood sugar levels in the bloodstream for a long time. The left untreated diabetes can cause many complications. The classical symptoms of diabetes are polyuria, weight

[1] *The bulk of this chapter has been published in* ***Journal of Applied Mathematics and Computing****, 66 (2021) 61-86.*

loss, increase thirst, visual disturbance, and hunger (Jacobs [2016], Jung and Choi [2014], Lefebre and Pierson [2006]). As glucose is lost in the urine, it draws fluid and other small molecules with it, causing excessive urination, which in turn to prompt dehydration and thirst (Ramachandran [2014], Isley and Molitch [2005]). Weight loss occurs because of the rapid breakdown of body fat, and portion reserves to compensate for the loss of glucose and metabolic inefficiency due to the lack of insulin action.

Diabetes can be subdivided into different categories based on the characteristic of dependency and independence of insulin. Two such divisions are T1 diabetes and T2 diabetes. T1 diabetes includes insulin-dependence diabetes mellitus, affecting people under the age of 40 and accounts for about 10% to 15% of the total diagnosed cases of the diabetic population. T2 diabetes generally known as non-insulin-dependent diabetes, represents a major part (about 85%-90%) of the total diagnosed cases of the diabetic population. It depends on the risk factors: like a family history of diabetes, physical inactivity, older age, obesity, etc. T1 diabetes frequently grows all of a sudden and can create side effects e.g. polydipsia, polyuria, enuresis, absence of vitality, extraordinary tiredness, polyphagia, unexpected weight reduction, moderate mending wounds, repetitive infections and blurred vision with extreme drying out also, diabetic ketoacidosis in kids and youths (Kharroubi and Darwish [2015]). The signs in kids are more serious than in adolescents. The main reason for T2 DM is the lifestyle and genetic variables. It is recognized that a range of lifestyle variables are essential for T2 DM growth. These include physical inactivity, culture, smoking cigarettes, and moderate alcohol consumption (Wu et al. [2014], Olokoba et al. [2012]). The elements involved in the improvement of insulin resistance such as obesity is the most prevalent hazard factor prompting insulin lack of care and diabetes which includes a few systems that take an interest in the pathogenesis of the disease (Kharroubi and Darwish [2015], Otero et al. [2014]). Obesity incited insulin opposition is directly connected to expanded nutrient flux and energy gathering in tissues that straight forwardly influence cell responsiveness to insulin (Kharroubi and Darwish [2015], Ye [2013]).

Exercise is an incredible strategy to improve long-term glycemic control. Unmistakably controlling blood glucose through adjustment of eating routine and lifestyle ought to be a determination of diabetes treatment. Ordinary exercise has been appeared to improve blood-glucose control, decrease cardiovascular risk factors, add to weight reduction, and improve lifestyle. A careful assessment of an individual ought to be made by a doctor while incorporating an activity. Facts from the Diabetes Prevention Program (Group [2002]) also, the Finnish Diabetes Prevention Study (Lindstrom et al. [2003]) started in patients with prediabetes demonstrates that the proper way of

life change, including physical activity, can prompt a decreased occurrence of T2 DM by practically 58%. Some studies have demonstrated that resistance training and aerobic exercise are effective in improving the metabolic profile of grown-ups with T2DM (Cuff et al. [2003], Ishii et al. [1998]). It would be useful to maintain a healthy glycemic profile for T2 DM patients with additional physical exercise greater than 60 minutes per day (Misra et al. [2008]). Children and adolescents with T1 DM have been reported to finish a minimum of 30 to 60 minutes of daily physical activity of moderate intensity (Wu et al. [2014], Silverstein et al. [2005]).

Awareness plays a vital role in understanding about causes factors of diabetes and its prevention. Researchers have to focus on the need for a better systematical medical approach to diabetes in developing countries to increase education about diabetes among the patients to expand the awareness of diabetes at the community-level (Mohan et al. [2013]). Currently, the Internet is a prime source of health care information but TV, radio, SMS, hotline and newspaper also make significant roles for prevention of diabetes cruelly have to be highlighted (Bansode and Nagarajan [2017], Wee et al. [2002]). For preventing diabetic complications, we have to focus on awareness of health-risk factors such as mental stress, obesity, or weight loss, polyuria, and visual disturbance. A large collection of people are unaware of the risk factors and/or how much danger that disease. The public remains unaware of knowledge of causative factors like obesity, decreased physical activity, family history of diabetes, consuming more sweets, and other high calories or junk foods. Moreover, peoples are involved with an unhealthy diet, drinking alcohol, smoking/tobacco consumption, laziness, high blood pressure, and lack of physical activity (Shashank et al. [2008]). Lin *et al.* (Lin et al. [2004]) showed that immoderate rates of obesity and smoking can lead to depression among diabetic patients. They also explored that an unhealthy diet, lack of physical activity, and smoking can lead to acute complications like renal failure, heart failure, and blindness (Bansode and Nagarajan [2017], Singh et al. [1994]). Here we also noted that the higher rate of prevalence of diabetes occurred in Indian society as reported by WHO. The WHO has roughly calculated that diabetes mortality in India deemed for 2.8 lakh deaths in the year of 2008. For these above-mentioned reasons, the awareness programs on diabetes should incorporate the information on the manifestations of diabetes suggested by the British Diabetic Federation (Bansode and Nagarajan [2017], Singh et al. [1994]). On the other hand, the deterministic approach has some limitations in biology because randomness is not incorporated in the system. So, it is always difficult to predict the future states of the model system more accurately. Most of the natural phenomena do not behave in accordance with strictly deterministic laws as environmental fluctuation or uncertainty with respect to

time is present in such biological systems. Population fluctuation is one of the most important components in ecosystems. In addition, in the world many environmental factors that can affect the behavior of the disease in the biological system. Diabetes is a non-communicable behavioral disease, and it is crucial for diabetic patients to be aware of nature, risk factors, other complications, and treatment of diabetes. These are strongly related to environmental factors. In recent years, many authors studied the mathematical model of diabetes in terms of ordinary differential equations (ODEs) or partial differential equations (PDEs). They have mainly focused on the glucose-insulin regulation, epidemiology of diabetes and its complication (Srivastava et al. [2019], Pinto and Carvalho [2019], Mahata et al. [2017], Ajmera et al. [2013], Duun-Henriksen et al. [2013], Boutayeb et al. [2006]). Pinto et al. (Pinto and Carvalho [2019]) formulated a mathematical model to analyzed the clinical implications of DM in the dynamics of TB transmission. Srivastava et al. (Srivastava et al. [2019]) analyzed a model on DM and its related complications but they cited that their outcomes are not suitable as in the present scenario. Furthermore, awareness of diabetes is one of the key factors of the awareness program. It plays a vital role in ensuring better treatment and control of diabetes. There is an indication that increasing knowledge about diabetes and its complications have significant benefits including an increase in compliance to treatment so that decrease the complications associated with diabetes (Rani et al. [2008], Visser and Snoek [2004]). It is also important for diabetic people to be aware of nature, treatment, risk factors, and complications of disease by providing suitable modality to reduce complications (Deepa et al. [2014]). The above description clearly indicates that the awareness program in the context of diabetes mellitus with population fluctuation is therefore well accepted. Moreover, mathematical modeling in terms of ODEs and SDEs can play a vital role in helping to understand the potential efforts of the media coverage on diabetes.

Finally in this chapter, we have designed a diabetes awareness mathematical model with humans suffering from diabetes mellitus. To understand the impact of awareness programs conducted by media on the prevalence of the epidemiology of diabetes mellitus in humans, we modify the model considering a nonlinear interaction between susceptible and diabetic humans. The whole population is subdivided into three separate classes: unaware susceptible, aware susceptible, and diabetes. Individuals in both unaware and aware susceptible classes can be involved with diabetes mellitus but the probability of incidence of diabetes mellitus for individuals in aware class is less than those who are in unaware class (Nazar et al. [2016], Deeb [2008]). Diabetes is a metabolic disease and not caused by pathogens. So, the increase in the number of diabetes human depends mostly on the unaware susceptible. Next, we modify

the deterministic model by incorporating a white noise in the coefficient of growth rate equations, which is based on the standard technique in stochastic population modeling (Afanas'ev et al. [2013], Saha and Chakrabarti [2011], Bandyopadhyay and Chattopadhyay [2005], Cantrell and Cosner [2001], Cosner et al. [1999]). The main objective of this chapter is to study the dynamics of diabetes mellitus patients among human beings under awareness program driven by media. To the best of our knowledge, the present work is the first attempt in the mathematical study of the effect of the awareness program on diabetes mellitus in both deterministic and stochastic environment.

This chapter is organized as follows. In *Sect.* 2.2, we formulate a mathematical model, which is based on some basic assumptions and hypotheses. *Sect.* 2.3 contains an analysis of equilibrium and stability. In this section, we identify the equilibrium point, the conditions for their feasibility, and the local stability of both awareness free and aware systems. In *Sect.* 2.4, we describe a stochastic mathematical model. The stochastic stability of the equilibrium is presented in *Sect.* 2.5. In this section, we identify the existence and the conditions for stochastic asymptotical stability. We performed extensive numerical simulations to validate our analytical findings in both DDEs and SDEs and is presented in *Sect.* 2.6. Finally, the chapter ends with a conclusion in *Sect.* 2.7.

2.2 Model formulation

We consider that in the region under consideration, the density of total human population is $N(t)$ at time t. The total humans are divided into two classes; susceptible humans $S(t)$, diabetic humans $X(t)$. To construct the model, we make the following assumptions:

(A1) We assume that A is the constant rate of immigration in the susceptible humans. Diabetes is a noninfectious disease and it is well known that diabetes is not transmitted from human to human. Diabetes is a metabolic disease caused by inherited and/ or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. We consider some fraction β of susceptible human become diabetic per unit time. People suffering from diabetes have significantly much risk of death than the general population (Tripathy [2018]), e is the additional death rate of humans due to diabetes.

Then model with susceptible and diabetes human in the given region can be describe

as follows:

$$\begin{aligned} \frac{dS}{dt} &= A - \beta S - dS, \\ \frac{dX}{dt} &= \beta S - (d+e)X. \end{aligned} \tag{2.2.1}$$

In the above model (2.2.1) the parameter values are interpreted as follows: β is the incident rate of diabetes mellitus, the constant d is the natural death rate of humans. Using the fact that $N = S + X$, the system (2.2.1) is reduced to the following system:

$$\begin{aligned} \frac{dX}{dt} &= \beta(N - X) - (d+e)X, \\ \frac{dN}{dt} &= A - eX - dN. \end{aligned} \tag{2.2.2}$$

It is sufficient to study model system (2.2.2) in detail rather than model system (2.2.1). In the previous model, we have not considered awareness of diabetes among the population. Now if the awareness programs i.e. adequate information and education about diabetes, patients access treatment as soon as possible via media campaign are carried out in the high prevalence of diabetes region. Then people respond to it and eventually will change their behavior to alter their susceptibility (Bansode and Nagarajan [2017], Nazar et al. [2016], Deeb [2008]). Thus the total susceptible population $S(t)$ is sub-divided into two subclasses: the unaware susceptible humans $S_U(t)$ and the aware susceptible humans $S_A(t)$.

(A2) Most of the diabetic humans belong into some family and people who have a family history of diabetes. They are likely to be more aware as their likeness because they are accompanied their diabetic patients to the clinic, assisted in their care or stay with them in the hospital. Hence they have experienced about the symptoms, causes; management for this disease and also it creates a psychological fear (Perra et al. [2011]). Thus if the number of diabetic human increase then more unaware individuals become aware due to psychological fear. Therefore we assume that unaware susceptible human becomes aware at the rate $\lambda g(X)$, where λ is the maximum rate at which unaware susceptible individual becomes aware susceptible and $g(X)$ is the function of a number of diabetic human X, where g is an increasing function with $sup_{X\geq 0} g = 1$ and $inf_{X\geq 0} g = 0$. Furthermore, we consider an increasing functional form of $g(X)$, say $g(X) = \frac{X}{1+X}$ (Samanta and Chattopadhyay [2014], Samanta et al. [2013]). Additionally, educated people have a better knowledge of all aspects of diabetes mellitus. They might have learned from school or more likely from the Internet, magazines or books (Kurian et al. [2016], Baptiste-Roberts et al. [2007], Baranowski et al. [2003]). Thus unaware susceptible individuals become aware susceptible individuals depending on the number of diabetic human as well as the number of unaware

human. So we assume that $\lambda S_U \frac{X}{1+X}$ number of unaware susceptible human become aware in per unit time.

(A3) Better education and knowledge on diabetes to control and treat diabetes at right time can minimize the incidence of diabetes and consequently reduce morbidity and mortality in diabetics. Population-based awareness programs have focused on modifiable hazard elements that can decrease the incidence rate of diabetes. As the awareness disseminates, we consider unaware human become diabetic with a rate of β whereas the aware population has a lower chance of getting diabetes compared to unaware individuals (Nazar et al. [2016], Christie et al. [2009], Deeb [2008]). Hence we consider the fraction $\beta\beta_1$ of aware susceptible human become diabetic human in per unit time, where $\beta\beta_1$ represents the lowered incident rate of diabetes mellitus among the aware susceptible humans and the dimensionless number β_1 lies between 0 and 1.

Based on the aforementioned assumptions, we arrive at the following mathematical model:

$$\begin{aligned} \frac{dS_U}{dt} &= A - \lambda S_U \frac{X}{1+X} - \beta S_U - dS_U, \\ \frac{dS_A}{dt} &= \lambda S_U \frac{X}{1+X} - \beta\beta_1 S_A - dS_A, \\ \frac{dX}{dt} &= \beta S_U + \beta\beta_1 S_A - (d+e)X. \end{aligned} \tag{2.2.3}$$

In the above model (2.2.3) the parameter values are interpreted as follows: The constants d, e represent the natural death rate of humans and additional death rate of humans due to diabetes respectively.
Using the fact that $N = S_U + S_A + X$, the system (2.2.3) is transformed to the following system:

$$\begin{aligned} \frac{dX}{dt} &= \beta(N - S_A - X) + \beta\beta_1 S_A - (d+e)X, \\ \frac{dS_A}{dt} &= \lambda(N - S_A - X)\frac{X}{1+X} - \beta\beta_1 S_A - dS_A, \\ \frac{dN}{dt} &= A - dN - eX. \end{aligned} \tag{2.2.4}$$

It is sufficient to study model system (2.2.4) in detail rather than model system (2.2.3). For the analysis of model (2.2.4), we need the region of attraction, which is given by the set
$\Gamma = \left\{(X, S_A, N) \in R^3_+ : 0 \leq X, S_A \leq N \leq \frac{A}{d}\right\}$ and attracts all solutions initiating in the interior of the positive octant.

2.3 Equilibrium and stability analysis

The awareness free model system (2.2.2) has only one endemic equilibrium point $E_*(X_*, N_*)$, where $X_* = \frac{\beta A}{(d+e)(d+\beta)}$, $N_* = \frac{A(d+e+\beta)}{(d+e)(d+\beta)}$.

Again the model system (2.2.4) has only one endemic equilibrium $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$. In equilibrium $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$, the values of $\overline{X}_*, \overline{S}_{A*}, \overline{N}_*$ are obtained by solving the following algebraic equations:

$$\begin{aligned} &\beta(N - S_A - X) + \beta\beta_1 S_A - (d+e)X = 0, \\ &\lambda(N - S_A - X)\tfrac{X}{1+X} - \beta\beta_1 S_A - dS_A = 0, \\ &A - dN - eX = 0. \end{aligned} \tag{2.3.1}$$

Using $N = \frac{A-eX}{d}$ in the first two equations in (2.3.1) and then eliminating S_A from these two equations, we obtain

$$\overline{A}X^2 + \overline{B}X + \overline{C} = 0. \tag{2.3.2}$$

Where
$\overline{A} = \lambda d(1-\beta_1)(d+e) + (\beta+d)(d+e)(\lambda\beta_1 + \beta\beta_1 + d)$,
$\overline{B} = \beta A(\beta\beta_1 + d + \lambda A) - (\beta\beta_1 + d)(\beta + d)(d+e)$,
$\overline{C} = -\beta A(\beta\beta_1 + d)$.
Therefore from (2.3.2), we get $X = \frac{-\overline{B} \pm \sqrt{\overline{B}^2 - 4\overline{A}\overline{C}}}{2\overline{A}}$.
We find that $\overline{A} > 0$, $\overline{C} < 0$ and whatever be the value of $\overline{B}$, applying Descartes rule of sign, we can say that Eq. (2.3.2) has one positive as well as one negative root. The positive root is given by

$$X = \frac{-\overline{B} + \sqrt{\overline{B}^2 - 4\overline{A}\overline{C}}}{2\overline{A}}.$$

This positive value of X, say $\overline{X}_*$, from first two equations in (2.3.1), by eliminating $N - S_A - X$, we obtain

$$S_A\left(\beta\beta_1 + d + \beta_1\lambda\frac{\overline{X}_*}{1+\overline{X}_*}\right) = \left(\frac{d+e}{\beta}\right)\frac{\overline{X}_*^2}{1+\overline{X}_*}.$$

This determines a positive value of S_A say $\overline{S}_{A*}$.
Again from second equation in (2.3.1) by using $\overline{X}_*$ and $\overline{S}_{A*}$, we get a positive value of N namely $\overline{N}_* = \frac{1}{\lambda}[\overline{S}_{A*} + \overline{X}_* + \frac{1+\overline{X}_*}{\overline{X}_*}(\beta\beta_1 + d)\overline{S}_{A*}]$. Hence the positive nontrivial equilibrium point is $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$.

Remark 1. $\frac{d\overline{X}_*}{d\lambda} < 0$, *when* $\overline{X}_* > \frac{-\overline{B}}{2\overline{A}}$.
This indicates that number of diabetic patient decrease as the increase the rate at which unaware susceptible human becomes aware susceptible provided $\overline{X}_* > \frac{-\overline{B}}{2\overline{A}}$.

The stability of the system (2.2.2) around the equilibria is obtained by computing the variational matrix J corresponding the equilibrium point $E_*(X_*, N_*)$. The jacobian matrix J corresponding to the system (2.2.2) is $J \equiv \begin{bmatrix} -(\beta+d+e) & \beta \\ -e & -d \end{bmatrix}$.
Therefore the characteristic equation is given by

$$\rho^2 + (\beta + 2d + e)\rho + d(\beta + d + e) + e\beta = 0,$$

which gives $\rho_{1,2} = \frac{-(\beta+2d+e) \pm \sqrt{(\beta+2d+e)^2 - 4\{d(\beta+d+e)+e\beta\}}}{2}$.
Thus the eigenvalues ρ_1 and ρ_2 both are negative or have negative real part. Hence the equilibrium point is stable. The local stability of the system (2.2.4) around each of the equilibria is obtained by computing the variational matrix $\overline{J}$ corresponding the equilibrium point. The jacobian matrix corresponding to the system (2.2.4) is given below:

$$\overline{J} \equiv \begin{bmatrix} -(\beta+d+e) & -\beta(1-\beta_1) & \beta \\ \frac{(\beta\beta_1+d)S_A - \lambda X^2}{X(1+X)} & -\frac{\lambda X}{1+X} - \beta\beta_1 - d & \frac{\lambda X}{1+X} \\ -e & 0 & -d \end{bmatrix}.$$

Therefore at equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ the jacobian $\overline{J}$ reduces to

$$\overline{J}_{\overline{E}_*} \equiv \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix},$$

where

$$\begin{aligned} &a_{11} = -(\beta+d+e), a_{12} = -\beta(1-\beta_1), a_{13} = \beta, \\ &a_{21} = \frac{(\beta\beta_1+d)\overline{S}_{A*} - \lambda\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}, \\ &a_{22} = -\frac{\lambda\overline{X}_*}{1+\overline{X}_*} - \beta\beta_1 - d, a_{23} = \frac{\lambda\overline{X}_*}{1+\overline{X}_*}, a_{31} = -e, a_{32} = 0, a_{33} = -d. \end{aligned} \tag{2.3.3}$$

Therefore the characteristic equation is given by

$$|\overline{J}_{\overline{E}_*} - \rho I_3| = \rho^3 + \alpha_1\rho^2 + \alpha_2\rho + \alpha_3 = 0,$$

with $\alpha_1 = -(a_{11} + a_{22} + a_{33})$, $\alpha_2 = a_{11}a_{22} + a_{11}a_{33} + a_{22}a_{23} - a_{12}a_{21} - a_{13}a_{31}$,

$\alpha_3 = -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{12}a_{31}a_{23} + a_{13}a_{31}a_{22}$.

Theorem 2.3.1. *The equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ of the system (2.2.4) is asymptotically stable iff $\alpha_1 > 0$, $\alpha_3 > 0$ and $\alpha_1\alpha_2 - \alpha_3 > 0$. Moreover, the sufficient conditions for asymptotically stable of the equilibrium point $\overline{E}_*$ are $\beta\beta_1 + d > \lambda$ and $\overline{S}_{A*} > \overline{X}_*^2$.*

Proof. The characteristic equation of the system (2.2.4) at the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ is

$$\rho^3 + \alpha_1\rho^2 + \alpha_2\rho + \alpha_3 = 0.$$

By the Routh Hurwitz stability criterion, the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ is asymptotically stable iff $\alpha_1 > 0$, $\alpha_3 > 0$ and $\alpha_1\alpha_2 - \alpha_3 > 0$.
Now $\alpha_1 = -(a_{11} + a_{22} + a_{33}) > 0$, using the values of $\{a_{ii} : i = 1, 2, 3\}$ from (2.3.3);
$\alpha_3 = -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{12}a_{31}a_{23} + a_{13}a_{31}a_{22}$
$= -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{31}(a_{12}a_{23} - a_{13}a_{22})$
$= -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{31}(\beta\beta_1\frac{\lambda\overline{X}_*}{1+\overline{X}_*} + \beta\beta_1 + d\beta) > 0$, using the values of $\{a_{ij} : i, j = 1, 2, 3\}$ from (2.3.3).
Here $\alpha_1\alpha_2 - \alpha_3$
$= a_{11}a_{22}(-a_{11}-a_{23})+a_{22}a_{22}(-a_{11}+a_{23})+a_{22}a_{33}(-a_{11}-a_{23})+[-a_{11}a_{11}a_{33}+a_{11}a_{12}a_{21}+ a_{11}a_{13}a_{31} +a_{12}a_{21}a_{22} - a_{11}a_{33}a_{33} + a_{13}a_{31}a_{33} + a_{12}a_{31}a_{23}]$
Therefore $-a_{11} - a_{23} = (\beta + d + e - \frac{\lambda\overline{X}_*}{1+\overline{X}_*}) > \beta + d + e - \lambda$, as $0 < \frac{\lambda\overline{X}_*}{1+\overline{X}_*} < \lambda$,
From the condition $\beta\beta_1 + d > \lambda$ and $0 < \beta < 1$ imply that $\beta + d + e - \lambda > 0$
Hence $-a_{11} - a_{23} > 0$. Again $a_{11}a_{12}a_{21} = (\beta + d + e)\beta(1 - \beta_1)\frac{(\beta\beta_1+d)\overline{S}_{A*}-\lambda\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)} > 0$, using given conditions.
Similarly, Using these conditions and the values of $\{a_{ij} : i, j = 1, 2, 3\}$ from (2.3.3), the other terms within the square bracket are greater than zero.
Finally $\alpha_1\alpha_2 - \alpha_3 > 0$.
Hence the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ is asymptotically stable if $\beta\beta_1 + d > \lambda$ and $\overline{S}_{A*} > \overline{X}_*^2$. □

2.4 The stochastic model

The effect of the environment on the risk of diabetes mellitus in the population has been growing significantly throughout the last decades. Several studies have showed that environment and health outcomes have a synergistic relationship with diabetes mellitus such as obesity, metabolic syndrome, cardiovascular disease, hypertension, and physical activity (Dendup et al. [2018], Raman [2016], Rewers and Ludvigsson [2016], Murea et al. [2012]). Environmental factors are developed onset of diabetes by

increasing or decreasing behavioral, psychosocial and physical stressors (Dendup et al. [2018]). A wide variety of lifestyle components are also of noble significance to the development of DM, for example, physical inactivity, sedentary lifestyle, smoking and alcohol consumption (Wu et al. [2014]). These determine the factors of fluctuations in the population, extending from the inherent stochastic behavior of the individual of the population to the unavoidable external random perturbations (Vilar and Rubi [2018]).

The deterministic approach has some limitations in biology, it is always difficult to predict the future of the system accurately and randomness is not incorporated in the system. Due to the presence of fluctuations in the environment, the factors such as rate of immigration, the incident rate of diabetes mellitus of population, a death rate of individuals, awareness rate of individuals about diabetes, etc. involved in the model system fluctuates around some average value. To study the effect of population fluctuations in the environment, we introduce the stochastic perturbation terms into the growth equations of the model system (2.2.4). We consider stochastic differential equation involving the stochastic perturbation terms are of Gaussian white-noise type and performed mathematically as an Ito stochastic differential equation. The required stochastic models involve nonlinear SDEs, whose solutions create extreme complications. For solving the nonlinear SDEs, we can apply another standard technique of linearization of the nonlinear SDEs used by many authors (Afanas'ev et al. [2013], Saha and Chakrabarti [2011], Bandyopadhyay and Chattopadhyay [2005], Cantrell and Cosner [2001], Cosner et al. [1999]).

We assume that stochastic perturbations of the state variables in the model (2.2.4) around their values at equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ are of white noise type, which is proportional to the distances of X, S_A, N from equilibrium densities $\overline{X}_*, \overline{S}_{A*}, \overline{N}_*$. So the model system (2.2.4) becomes:

$$\begin{aligned} dX &= [\beta(N - S_A - X) + \beta\beta_1 S_A - (d+e)X]dt + \sigma_1(X - \overline{X}_*)d\xi_t^1, \\ dS_A &= [\lambda(N - S_A - X)\tfrac{X}{1+X} - \beta\beta_1 S_A - dS_A]dt + \sigma_2(S_A - \overline{S}_{A*})d\xi_t^2, \\ dN &= [A - dN - eX]dt + \sigma_3(N - \overline{N}_*)d\xi_t^3, \end{aligned} \tag{2.4.1}$$

where σ_i, i=1, 2, 3 are real constants and known as population fluctuations, $\xi_t^i = \xi_i(t)$, i=1, 2, 3 are independent from each other standard Wiener processes (Cantrell and Cosner [2001]) and the equilibrium point $(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ is asymptotically stable.
We investigate the asymptotic stability behavior of the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ for the system (2.4.1) and compare outcomes with those obtained for the model (2.2.4). Using the above class of stochasticity we determine the robustness of the

dynamical behavior of the model (2.2.4). We consider (2.4.1) as an Ito stochastic differential system of the following form

$$\begin{aligned} dX_t &= f(t, X_t)dt + g(t, X_t)d\xi_t, \\ X_{t0} &= X_0, \quad t \in [t_0,\ t_f], \end{aligned} \tag{2.4.2}$$

where the solutions $\{X_t, t \in [t_0, t_f]\}$ of the SDE is an Ito process. The terms $f(t, X_t)$, $g(t, X_t)$ are the functions of x and t, $f(t, X_t)$ is the slowly varying continuous component, known as *drift coefficient* and $g(t, X_t)$ is the rapidly varying continuous random component, known as *diffusion coefficient*. Also ξ_t is a 3-dimensional stochastic process having scalar wiener process components with increments $\triangle\xi_t^j = \xi_{t+\triangle t}^j - \xi_t^j = \xi^j(t + \triangle t) - \xi_j(t)$, j=1, 2, 3 are independent Gaussian random variables $N(0, \triangle t)$ (Cosner et al. [1999]).
Eq. (2.4.2) can be written as a stochastic integral equation

$$X_t = X_0 + \int_{t_0}^{t} f(s, X_s)ds + \int_{t_0}^{t} g(s, X_s)d\xi_s, \tag{2.4.3}$$

where the first integral, called a Riemann-Stieltjes integral and the second one, called an Ito integral.
In the case of system (2.4.1), $X_t = (X,\ S_A,\ N)^T$, $\xi_t = (\xi_t^1,\ \xi_t^2,\ \xi_t^3)^T$,

$$f = \begin{bmatrix} \beta(N - s_A - X) + \beta\beta_1 S_A - (d + e)X \\ \lambda(N - S_A - X)\frac{X}{1+X} - \beta\beta_1 S_A - dS_A \\ A - dN - eX \end{bmatrix},$$

$$g = \begin{bmatrix} \sigma_1(X - \overline{X}_*) & 0 & 0 \\ 0 & \sigma_2(S_A - \overline{S}_{A*}) & 0 \\ 0 & 0 & \sigma_3(N - \overline{N}_*) \end{bmatrix}.$$

Since the above diffusion matrix g depends on the solution X_t, system (2.4.1) is said to have multiplicative noise. Moreover, the diffusion matrix g is of diagonal form, so system (2.4.1) is said to have diagonal noise.

2.5 Stochastic stability of the equilibrium

The stochastic differential system (2.4.1) can be centered at its interior equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ by introducing the new variables $u_1 = X - \overline{X}_*$, $u_2 = S_A - \overline{S}_{A*}$ and $u_3 = N - \overline{N}_*$. Analytically it is quite impossible to derive asymptotic stability

in mean square sense by Lyapunov functions method by working on the complete nonlinear equations (2.4.1). For simplicity of mathematical calculation we deal with the SDEs obtained by the linearizing the drift coefficient f around the positive equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ (Afanas'ev et al. [2013], Saha and Chakrabarti [2011], Bandyopadhyay and Chattopadhyay [2005], Cantrell and Cosner [2001], Cosner et al. [1999]). Then the linearized system becomes

$$du(t) = f(u(t))dt + g(u(t))d\xi(t), \tag{2.5.1}$$

where $u(t) = (u_1, u_2, u_3)^T$ and

$$f(u(t)) \equiv \begin{bmatrix} a_{11}u_1 + a_{12}u_2 + a_{13}u_3 \\ a_{21}u_1 + a_{22}u_2 + a_{23}u_3 \\ a_{31}u_1 + a_{32}u_2 + a_{33}u_3 \end{bmatrix}, \; g(u(t)) \equiv \begin{bmatrix} \sigma_1 u_1 & 0 & 0 \\ 0 & \sigma_2 u_2 & 0 \\ 0 & 0 & \sigma_3 u_3 \end{bmatrix}$$

with

$a_{11} = -(\beta + d + e)$, $a_{12} = -\beta(1 - \beta_1)$, $a_{13} = \beta$, $a_{21} = \frac{(\beta\beta_1 + d)\overline{S}_{A*} - \lambda\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}$, $a_{22} = -\frac{\lambda\overline{X}_*}{1+\overline{X}_*} - \beta\beta_1 - d$, $a_{23} = \frac{\lambda\overline{X}_*}{1+\overline{X}_*}$, $a_{31} = -e$, $a_{32} = 0$, $a_{33} = -d$.

It is to be noted that in (2.5.1) the positive equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ corresponding to the trivial solution $(u_1, u_2, u_3) = (0, 0, 0)$. Let Ω be the set defined by $\Omega = \{(t \geq t_0) \times \mathbb{R}^3, \, t_0 \in \mathbb{R}^+\}$. Let $V(U, t) \in C_2(\Omega)$ be two times continuously differentiable function with respect to U and a continuous function with respect to time t, where U is a solution of the equation (2.5.1). According to Afanas'ev *et al.* (Afanas'ev et al. [2013]), with reference to equation (2.5.1) the expression for $LV(U, t)$ is defined by

$$LV(U,t) = \frac{\partial V(U,\, t)}{\partial t} + F^T(U)\frac{\partial V(U,\, t)}{\partial U} + \frac{1}{2}Tr\left[g^T(U)\frac{\partial^2 V(U,\, t)}{\partial U^2}g(U)\right], \tag{2.5.2}$$

with

$$\frac{\partial V(U,\, t)}{\partial t} = col(\frac{\partial V}{\partial u_1}, \frac{\partial V}{\partial u_2}, \frac{\partial V}{\partial u_3}), \;\; \frac{\partial^2 V(U,\, t)}{\partial U^2} = \left[(\frac{\partial^2 V(U,\, t)}{\partial u_i \partial u_j})_{i,j=1,2,3}\right]. \tag{2.5.3}$$

Where L is an operator and T stands for transposition of matrix.

The following theorem holds due to Afanas'ev *et al.* (Afanas'ev et al. [2013]).

Theorem 2.5.1. *Suppose there exist a function $V(U, t) \in C_2(\Omega)$ satisfying the following inequalities*

$$K_1|U|^\alpha \leq V(U,t) \leq K_2|U|^\alpha \tag{2.5.4}$$

$$LV(U,t) \leq -K_3|U|^{\alpha}, \quad K_i > 0, \quad i = 1,2,3, \quad \alpha > 0. \tag{2.5.5}$$

Then the trivial solution of (2.5.1) is exponentially α-stable for all time $t \geq 0$.

Note that if $\alpha = 2$ in equations (2.5.4) and (2.5.5), then the trivial solution of the equation (2.5.1) is exponential mean square stable. Thus we can prove the following:

Theorem 2.5.2. *If*
i) $(\beta + d + e) > \frac{\sigma_1^2}{2}$;
ii) $\frac{\lambda \overline{X}_*}{1+\lambda \overline{X}_*} + \beta\beta_1 + d > \frac{\sigma_2^2}{2}$;
iii) $\beta\beta_1 + d > \lambda$, $\overline{S}_{A*} > \overline{X}_*^2$, *and* $d > \frac{\sigma_3^2}{2}$;
and we choose ω_3 such that
$\omega_3 = Max\left\{\frac{\beta\omega_1^* - (\beta+d+e)\omega_4^*}{e}, \frac{\beta\omega_4^*}{d-\frac{\sigma_3^2}{2}}\right\}$. *Where ω_1^* and ω_4^* are given by* $\omega_1^* = \frac{(\beta\beta_1+d)\overline{S}_{A*} - \lambda\overline{X}_*^2}{\beta(1-\beta_1)\overline{X}_*(1+\overline{X}_*)}$, $\omega_4^* = \frac{1}{\beta(1-\beta_1)}\frac{\lambda\overline{X}_*}{1+\overline{X}_*}$, *then the zero solution of the system (2.4.1) is asymptotically mean square stable.*

Proof. Let us consider the following positive definite Lyapunov function

$$V(U(t),t) = \tfrac{1}{2}[\omega_1 u_1^2 + u_2^2 + \omega_3 u_3^2 + 2\omega_4 u_1 u_3], \tag{2.5.6}$$

where ω_i $(i = 1,2,3)$ are real positive constants to be chosen later. It is easy to check that inequalities (2.5.4) hold true for the Lyapunov function defined in (2.5.6) with $\alpha = 2$. Furthermore,
$LV(U,t) = (a_{11}u_1 + a_{12}u_2 + a_{13}u_3)\omega_1 u_1 + (a_{21}u_1 + a_{22}u_2 + a_{23}u_3)u_2 + (a_{31}u_1 + a_{32}u_2 + a_{33}u_3)\omega_3 u_3 + (a_{11}u_1 + a_{12}u_2 + a_{13}u_3)\omega_4 u_3 + (a_{31}u_1 + a_{32}u_2 + a_{33}u_3)\omega_4 u_1 + \frac{1}{2}Tr[g^T(U)\frac{\partial^2 V(U,t)}{\partial U^2}g(U)]$

$$\begin{aligned}
&= [-(\beta+d+e)u_1 - \beta(1-\beta_1)u_2 + \beta u_3]\omega_1 u_1 + \left[\left\{\frac{(\beta\beta_1+d)\overline{S}_{A*} - \lambda\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}\right\}u_1 \right.\\
&\left. - \left\{\frac{\lambda\overline{X}_*}{1+\overline{X}_*} + \beta\beta_1 + d\right\}u_2 + \frac{\lambda\overline{X}_*}{1+\overline{X}_*}u_3\right]u_2 + [-eu_1 - du_3]\omega_3 u_3 + [-(\beta+d\\
&+e)u_1 - \beta(1-\beta_1)u_2 + \beta u_3]\omega_4 u_3 + [-eu_1 - du_3]\omega_4 u_1 +\\
&\frac{1}{2}Tr\left[g^T(U)\frac{\partial^2 V(U,t)}{\partial U^2}g(U)\right].
\end{aligned} \tag{2.5.7}$$

Now, we find that $\frac{\partial^2 V}{\partial U^2} \equiv \begin{bmatrix} \omega_1 & 0 & \omega_4 \\ 0 & 1 & 0 \\ \omega_4 & 0 & \omega_3 \end{bmatrix}$.

Therefore, $g(U(t))^T \frac{\partial^2 V}{\partial U^2} g(U(t)) \equiv \begin{bmatrix} \omega_1\sigma_1^2u_1^2 & 0 & \omega_4\sigma_1\sigma_3u_1u_3 \\ 0 & \sigma_2^2u_2^2 & 0 \\ \omega_4\sigma_1\sigma_3u_1u_3 & 0 & \omega_3\sigma_3^2u_3^2 \end{bmatrix}$

and hence, $\frac{1}{2}Tr\left[g^T(U)\frac{\partial^2 V(U,t)}{\partial U^2}g(U)\right] = \frac{1}{2}[\omega_1\sigma_1^2u_1^2 + \sigma_2^2u_2^2 + \omega_3\sigma_3^2u_3^2]$.
Using this in (2.5.1) and simplifying, we get

$$\begin{aligned} LV(U,t) &= -[(\beta+d+e)\omega_1 + e\omega_4 - \frac{\sigma_1^2}{2}\omega_1]u_1^2 - \Big[\beta(1-\beta_1)\omega_1 \\ &- \frac{(\beta\beta_1+d)\overline{S}_{A*} - \lambda\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}\Big]u_1u_2 - [e\omega_3 - \beta\omega_1 + (\beta+d+e)\omega_4]u_1u_3 \\ &- \Big[\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*} + \beta\beta_1 + d - \frac{\sigma_2^2}{2}\Big]u_2^2 - \Big[\beta(1-\beta_1)\omega_4 - \frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*}\Big]u_2u_3 - \\ &\quad [(d-\frac{\sigma_3^2}{2})\omega_3 - \beta\omega_4]u_3^2. \end{aligned} \tag{2.5.8}$$

If we choose ω_1^*, ω_2^* in such away that

$$\beta(1-\beta_1)\omega_1 - \frac{(\beta\beta_1+d)\overline{S}_{A*} - \lambda\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)} = 0 \; and \; \beta(1-\beta_1)\omega_4 - \frac{\lambda\overline{X}_*}{1+\overline{X}_*} = 0.$$

i.e.,

$$\omega_1^* = \frac{(\beta\beta_1+d)\overline{S}_{A*} - \lambda\overline{X}_*^2}{\beta(1-\beta_1)\overline{X}_*(1+\overline{X}_*)} \;\; and \; \omega_4^* = \frac{\lambda\overline{X}_*}{\beta(1-\beta_1)(1+\overline{X}_*)}.$$

Then the equation (2.5.8) becomes

$$\begin{aligned} LV(U,t) < &-\left[(\beta+d+e)\omega_1^* - \frac{\sigma_1^2}{2}\omega_1^*\right]u_1^2 - [e\omega_3 - \beta\omega_1^* + (\beta+d+e)\omega_4^*]\,u_1u_3 \\ &-\left[\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*} + \beta\beta_1 + d - \frac{\sigma_2^2}{2}\right]u_2^2 - \left[(d-\frac{\sigma_3^2}{2})\omega_3 - \beta\omega_4^*\right]u_3^2. \end{aligned} \tag{2.5.9}$$

Thus, we can write

$$LV(U,t) < -u^TQu. \tag{2.5.10}$$

Where, $Q \equiv \begin{bmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{bmatrix}$

with $m_{11} = [(\beta+d+e)\omega_1^* - \frac{\sigma_1^2}{2}\omega_1^*]$; $m_{12} = m_{21} = 0$; $m_{13} = m_{31} = \frac{1}{2}[e\omega_3 - \beta\omega_1^* + (\beta + d + e)\omega_4^*]$; $m_{22} = [\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*} + \beta\beta_1 + d - \frac{\sigma_2^2}{2}]$; $m_{23} = m_{32} = 0$; $m_{33} = [(d - \frac{\sigma_3^2}{2})\omega_3 - \beta\omega_4^*]$.

Thus, we have $m_{ij} \geq 0$ for *i, j=1,2,3*; if the conditions *(i)* to *(iii)* of the Theorem 2.5.2 are hold. Therefore Q is a real symmetric positive definite matrix and hence all the three eigenvalues $\lambda_i(Q)$ (say) are real positive. Let $\lambda_m = min\{\lambda_i(Q), i = 1, 2, 3\}$, then $\lambda_m > 0$. Therefore, from inequality (2.5.10), we get $LV(u(t)) < -\lambda_m|u(t)|^2$. Hence the condition (2.5.5) of Theorem 2.5.1 is satisfied. This complete the proof of the theorem. □

2.6 Numerical simulation

2.6.1 For deterministic differential equations

To perform some numerical experiments to substantiate our analytical findings. For the numerical experiments, using 4th order Runge-Kutta method in MATLAB 7.6 software by choosing the following set of parameter values and the initial conditions in model systems:
$A = 370\ year^{-1}$, $\beta = 3.224 \times 10^{-3}\ year^{-1}$, $d = 0.00371\ year^{-1}$, $e = 7.8 \times 10^{-3}\ year^{-1}$, $\beta_1 = 0.01$, $\lambda = 0.55\ year^{-1}$, $S_U(0) = 9700$, $S_A(0) = 8640$, X(0)=1660, N(0)=20000.
Most of the above values of parameters are taken from different sources of research articles (Deo et al. [2017], Anjana et al. [2017], Deepa et al. [2014], Samanta et al. [2013], Sule and Barakade [2011], Misra et al. [2008]). We first investigate the awareness free system in the sense that there was no awareness program carried out in that region. Thus in this case we have taken people are either susceptible or diabetes patients (Anjana et al. [2017]). Using the ODE solver (ode45), we simulate both the systems: awareness free model (2.2.2) and awareness presence model (2.2.4). By using the above parameters, we have obtained the endemic equilibrium point $E_*(53360.25, 14946.43)$ for the model system (2.2.2). The characteristic values of the Jacobian matrix around endemic equilibrium point $E_*(53360.25, 14946.43)$ for the awareness free model (2.2.2) are $\rho_1 = -0.013868$ and $\rho_2 = -0.02302$. In this case, eigenvalues are negative and hence the equilibrium is locally asymptotically stable (LAS). So the system (2.2.2) is LAS around the endemic equilibrium point. Figure 2.1 it shows that number of diabetic patients increase as our current trends of diabetes mellitus patients with time evolves. To show the impact of incident rate of diabetes mellitus of human in the absence of awareness system (2.2.2). We choose the values of β are 3.224×10^{-3}, 4.224×10^{-3} and 5.224×10^{-3}. From Figure 2.2, it is clear that as the incident rate β increase, the number of diabetic patient X increase.

Now we introduce the awareness about diabetes driven by media or campaign in the model system (2.2.4). The parameter values in that model are taking same as in

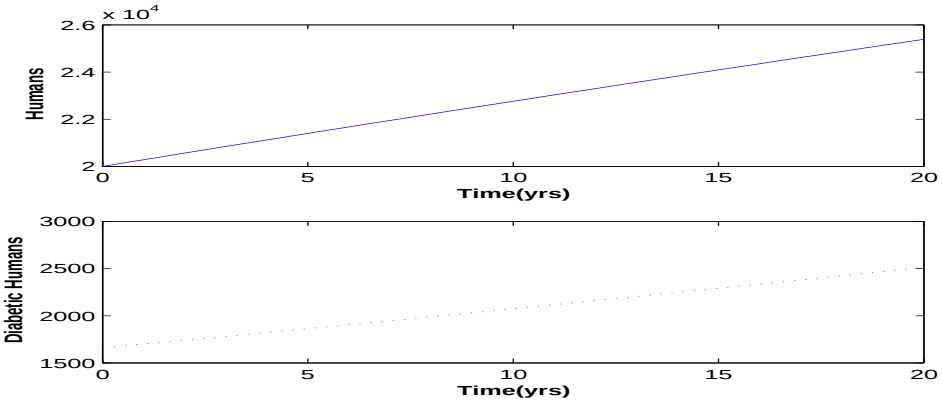


Figure 2.1: The figure depicts the solution of the system (2.2.2) in the absence of awareness for parameter values are $A = 370\ year^{-1}$, $\beta = 3.224 \times 10^{-3}\ year^{-1}$, $d = 0.00371\ year^{-1}$, $e = 7.8 \times 10^{-3}\ year^{-1}$.

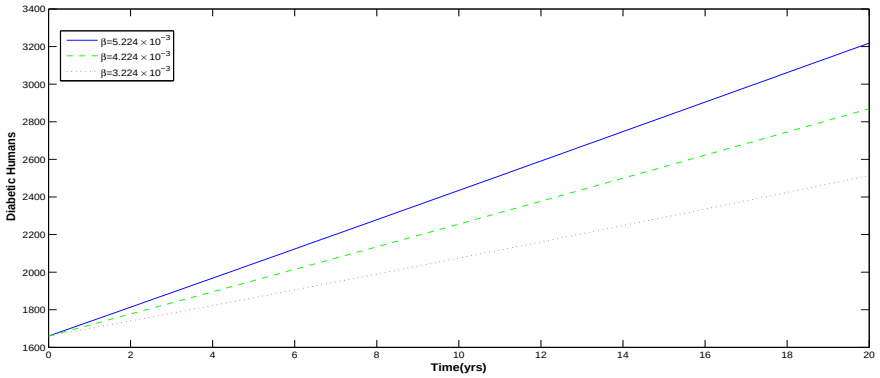


Figure 2.2: The figure depicts the role of incident rate of diabetes mellitus β of the system (2.2.2) in the absence of awareness. The diabetic humans increase over time as the value of β increase. The values of β are $3.224 \times 10^{-3}, 4.224 \times 10^{-3}, 5.224 \times 10^{-3}$ and the other parameters are same as Figure 2.1.

the previous Figure 2.1 and $\lambda = 0.55\ year^{-1}$, $\beta_1 = 0.01\ year^{-1}$. In this model aware susceptible become diabetic with lower rate than that of the unaware susceptible human (Nazar et al. [2016], Deeb [2008]). The equilibrium densities for this data are obtain as: $\overline{X}_* = 460.0, \overline{S}_{A*} = 97637.6, \overline{N}_* = 98763.4$. The eigenvalues of the variational matrix corresponding to the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ for the model system (2.2.4) in the presence of awareness are -0.555731, -0.0115201 and -0.0037422. We note that all three eigenvalues are negative. In addition, the necessary and sufficient conditions $\alpha_1 = 0.57097 > 0$, $\alpha_3 = 0.00002 > 0$ and $\alpha_1\alpha_2 - \alpha_3 = 0.16946 > 0$ of the Theorem 2.3.1 are satisfied. Thus, the endemic equilibrium point $\overline{E}_*(\overline{X}_*, \overline{S}_{A*}, \overline{N}_*)$ is locally asymptotically stable in the presence of the awareness for the given set of

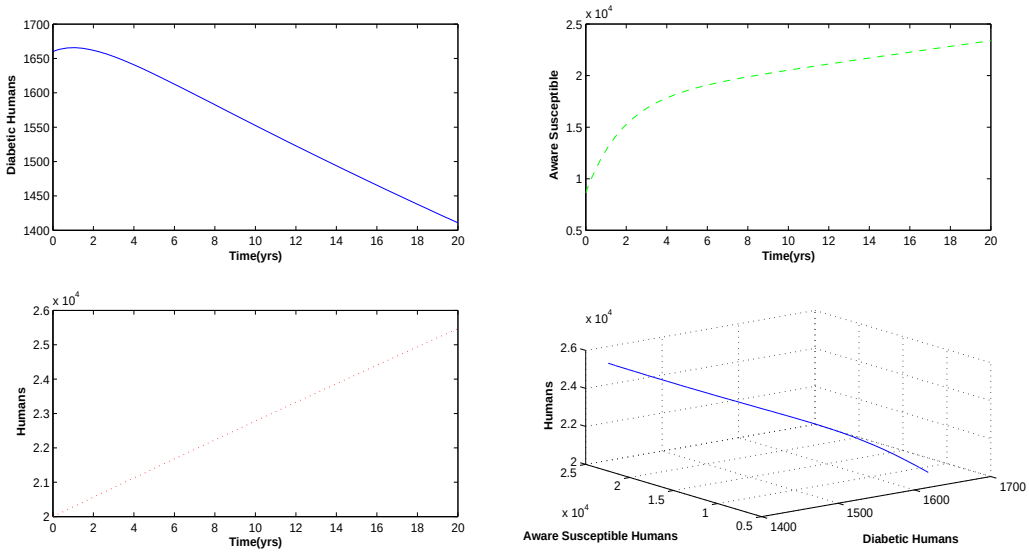


Figure 2.3: The figure depicts the solution of the system (2.2.4) in the presence of awareness for parameter values are $\lambda = 0.55$, $\beta_1 = 0.01$, and other parameter values as in Figure 2.1.

parameter values (see Figure 2.3). It is to be noted that as an experiment carried out for a long time to approach this endemic equilibrium point. From Figure 2.3, it is clear that aware susceptible individual increase with evaluation of time and number of diabetes patients decrease compared to without awareness model system (2.2.2) with evaluation of time. Hence awareness program driven by media helps to reduce the number of diabetes mellitus patients in the population because of more individuals are aware of diabetes mellitus by aware-induced isolation of susceptible people.

2.6.1.1 Role of diabetes mellitus for incidence rate β on aware system (2.2.4)

Most of the individuals spent a large proportion of their time at the office with a sedentary activity like sitting during work and reduce daily activity. It is a major factor for increasing the incidence of diabetes. From a biological point of view, the incident rate of diabetes mellitus in human plays an important role. We like to observe the dynamics of the system (2.2.4) for changing the values of β keeping the other parameters are fixed as in Figure 2.3. Figure 2.4 demonstrates the variation of diabetic human X, aware susceptible human S_A, unaware susceptible human S_U with respect to time for different values of β receptively. From this figure, it is clear that if the incident rate β increase, unaware susceptible human S_U and aware susceptible human S_A decrease but the diabetic human X increase with respect to

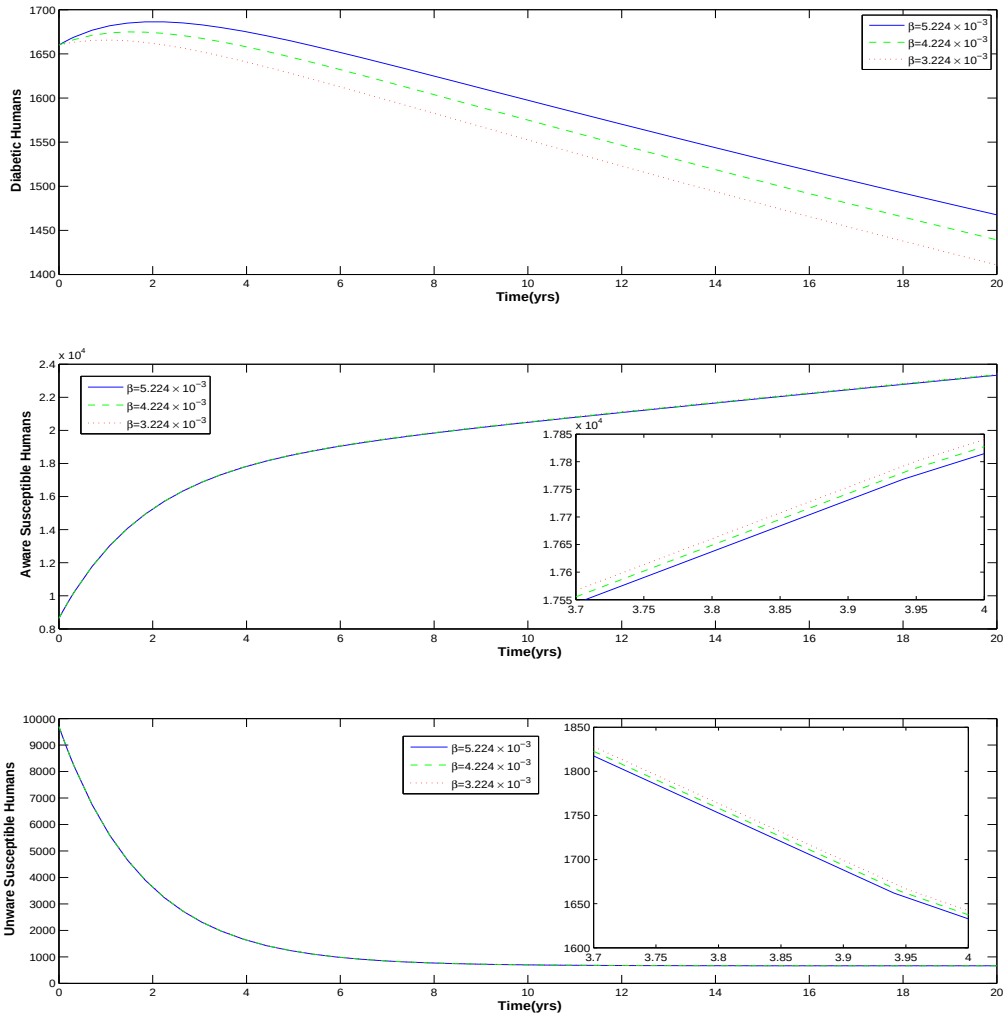


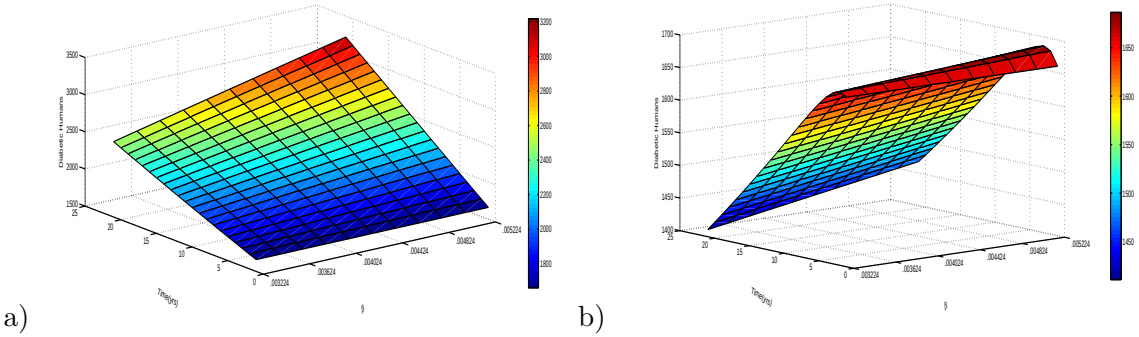
Figure 2.4: The figure depicts the role of diabetic human, unaware human and aware human with respect to time in the presence of awareness for different values of $\beta = 3.224\times10^{-3}, 4.224\times10^{-3}, 5.224\times10^{-3}$ and other values of parameters are same as Figure 2.3.

time t (yrs). From Table 2.1, we see that for increasing β diabetic human increase over time but the number of diabetic human in the presence of awareness system (2.2.4) become too much lower than that of the unaware system (2.2.2). We also plot 3D diagram of diabetic human for variation of β and time t (yrs), see Figure 2.5. Moreover, from the 3D phase diagram (Figure 2.6), we observe that both aware and unaware susceptible human decrease when β increase for a particular year. In this case, a biological importance is that the growth of incidence rate of diabetic mellitus pressure on population to decline the size of both unaware and aware human. Again, if we fixed the value of β in the aware system, the aware susceptible human increase

but the unaware susceptible decrease over time. Therefore incidence rate of diabetic mellitus increase the density of diabetic human as well decrease unaware human and aware human in the population.

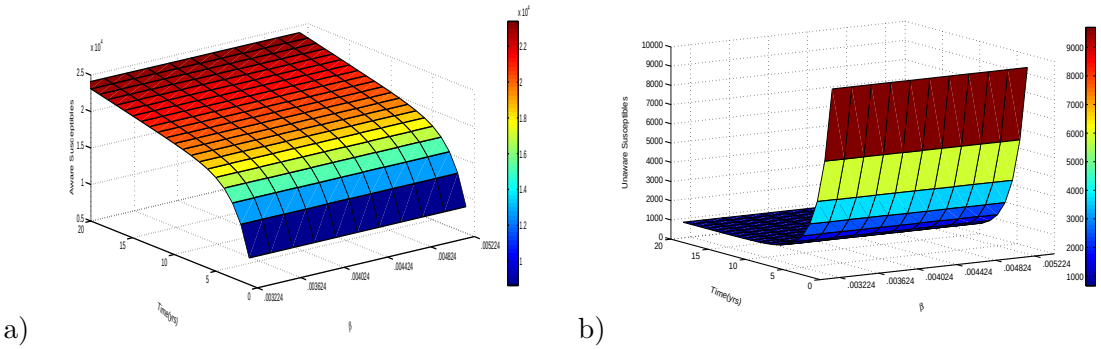
Table 2.1: Number of diabetic humans in unaware system (2.2.2)[US] and aware system (2.2.4)[AS] for different values of incident rate of diabetes mellitus β:

$\beta(1/year)$	1st Year		2nd Year		3rd Year		4th Year		5th Year	
	US	AS	US	AS	US	AS	US	AS	US	AS
3.244×10^{-3}	1700.18	1665.68	1740.68	1661.93	1781.47	1652.85	1822.57	1660.80	1863.95	1627.13
4.244×10^{-3}	1718.50	1673.32	1777.26	1674.20	1836.28	1668.04	1895.54	1657.95	1645.65	1955.05
5.244×10^{-3}	1763.80	1680.96	1813.78	1686.46	1890.93	1683.20	1968.23	1657.00	2045.69	1664.07



a) b)

Figure 2.5: The figure depicts the role of diabetic human with respect to time in the unaware system (2.2.2) (left side) and aware system (right side) (2.2.4) for the different values of β and other values of parameters are same as Figure 2.3.



a) b)

Figure 2.6: The figure depicts the role of aware susceptible human (left side) and unaware susceptible human (right side) with respect to time in the presence of awareness for different values of β and other values of parameters are same as Figure 2.3.

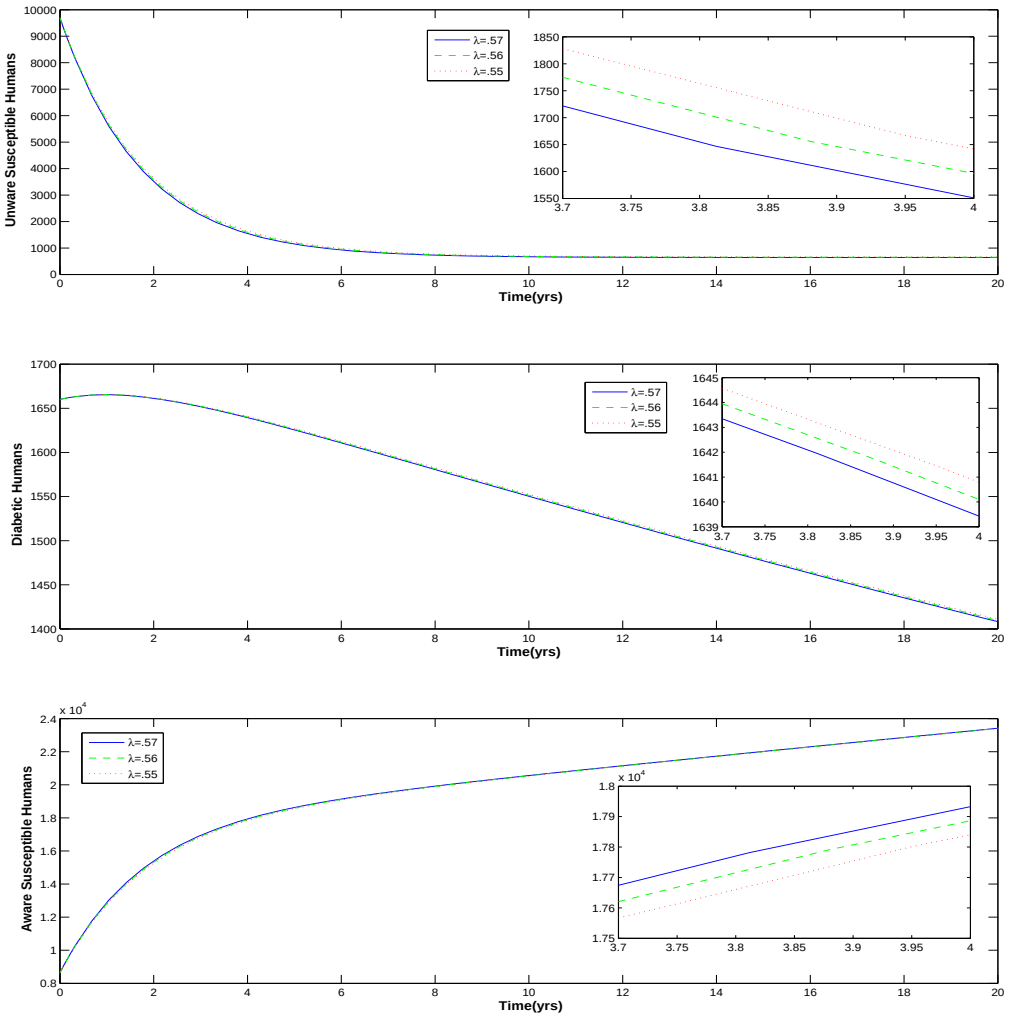


Figure 2.7: The figure depicts the role of diabetic human, unaware human and aware human with respect to time in the presence of awareness for different values of λ =0.55, 0.56, 0.57 and other values of parameters are same as Figure 2.3.

2.6.1.2 Effect of aware coefficient λ in the system (2.2.4)

On the biological background, awareness about the diabetic among human beings is also taken an important role in population dynamics. We have studied the population dynamics of the model for a wide range of parameter values of the aware coefficient λ and keeping the other parameters fixed as in Figure 2.3. Figure 2.7 demonstrates the variation of diabetic human X, aware susceptible human S_A, unaware susceptible human S_U with respect to time t for different values of aware coefficient λ receptively. From this figure, it is clear that as λ increase the aware susceptible human S_A in-

crease but the diabetic human X and unaware susceptible human S_U are decreasing with respect to time (yrs). A biological realization of this result is that an increase of awareness coefficient pressure on human being to reduce the density of unaware susceptible human and increase the density of aware susceptible human. This leads to decrease of diabetic human density. We also observe that for a fixed time, the number diabetic human and unaware susceptible human decrease if the value of λ increases. Whereas the aware susceptible human increase as increases λ. Furthermore, for a particular value of λ, as time increases the number of aware susceptible human increase but diabetic human and unaware susceptible human decrease. For clear visualization, we draw a 3D diagram (Figure 2.8) of diabetic human, aware susceptible human and unaware susceptible human for different value of λ and time t (yrs). So an awareness program plays a crucial role to reduce the number of diabetic mellitus among the human beings.

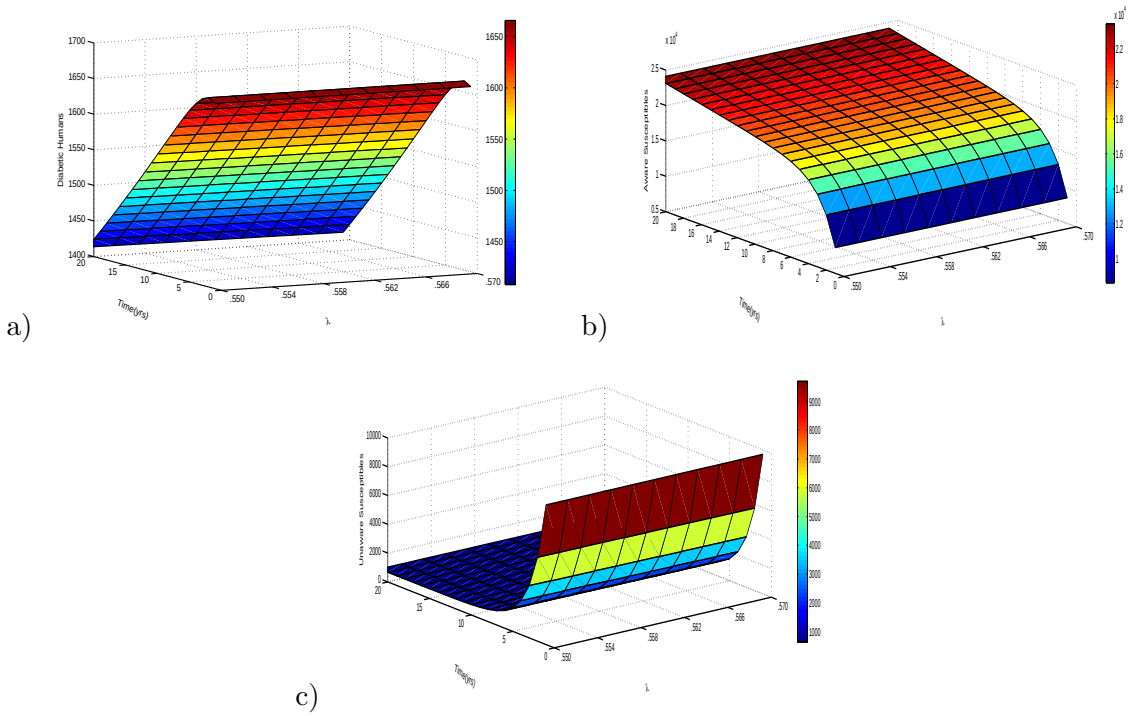


Figure 2.8: The figure depicts the role of diabetic human, aware human and unaware human with respect to time in the presence of awareness for different values of λ and other values of parameters are same as Figure 2.3.

2.6.2 For stochastic differential equations:

In order to achieve good stability results of the sample paths or trajectories of the SDEs (2.4.1), we stochastically simulate the solution of that SDEs. For this case, we have to remember that approximate trajectories or sample paths of direct simulations of Ito process would be closed to that of the original Ito process, and it follows that an idea of a strong solution of the SDEs (2.4.1). We use the Milstein scheme to obtain the strong solution of the system of SDEs (2.4.1), which has a strong convergence of order one (Upadhyay et al. [2019]).
We now discretized the time interval $[t_0, t_f]$ as:
$t_0 = 0 < t_1 < ... < t_n < ... < t_N < t_{N+1} = t_f$ and the Milsteine numerical scheme for the system of SDEs (2.4.1) is
$X(k+1) = X(k)+[\beta(N(k)-S_A(k)-X(k))+\beta\beta_1 S_A(k)-(d+e)X(k)]\Delta t+\sigma_1(X(k)-\overline{X}_*)I_{1,k}\sqrt{\Delta t}+0.5\sigma_1^2(X(k)-\overline{X}_*)(I_{1,k}^2\Delta t-\Delta t)$,
$S_A(k+1) = S_A(k)+[\lambda(N(k)-S_A(k)-X(k))\frac{X(k)}{1+X(k)}-\beta\beta_1 S_A(k)-dS_A(k)]\Delta t+\sigma_2(S_A(k)-\overline{S}_{A*})I_{2,k}\sqrt{\Delta t}+0.5\sigma_2^2(S_A(k)-\overline{S}_{A^*})(I_{2,k}^2\Delta t-\Delta t)$,
$N(k+1) = N(k)+[A-dN(k)-eX(k)]\Delta t+\sigma_3(N(k)-\overline{N}_*)I_{3,k}\sqrt{\Delta t}+0.5\sigma_3^2(N(k)-\overline{N}_*)(I_{3,k}^2\Delta t-\Delta t)$.
Where $I_{d,k}$ is the k-th realization of I_d and I_d is the Gaussian random variable N(0,1). Here the parameters values are taken same as the Figure 2.3 of the deterministic system (2.2.4) for comparing the solutions of the stochastic system (2.4.1).

Using the above numerical simulation method, we have drawn Figure 2.9 with the help of MATLAB 7.6 software. We construct a Lyapunov function, to show the equilibrium point is asymptotically stable in a mean square sense. Stability of the equilibrium point depends on the system parameters and the population fluctuations σ_1, σ_2, σ_3. We consider the small population fluctuations $\sigma_1 = 0.01$, $\sigma_2 = 0.01$, $\sigma_3 = 0.01$ with a fixed set of parameter values as prescribed in Figure 2.3. We observe that the conditions $(\beta+d+e) = 0.014734 > \frac{\sigma_1^2}{2}$=0.00005, $\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*}+\beta\beta_1+d = 0.552549 > \frac{\sigma_2^2}{2} = 0.00005$, $d = .00371 > \frac{\sigma_3^2}{2} = 0.00005$, including Theorem 2.3.1 are satisfied. Therefore, all conditions of the Theorem 2.5.2 are numerically verified. From the conditions of Theorem 2.5.2, we also observe that σ_1, σ_2, σ_3 are very small relative to the equilibrium densities. We have also studied the population dynamics of a stochastic model (2.4.1) for a wide range of parameter values of the aware coefficient λ and keeping the other parameters fixed as in Figure 2.3. We make some comparison of the results of the deterministic and stochastic models. The trajectories of the stochastic model given by the Figure 2.9 with same initial conditions as deterministic model. It is observed that trajectories are oscillatory around the endemic equilibrium

point which is absent in deterministic model. This oscillation comes due to the random noise that does not incorporated in deterministic model. From Figure 2.10, we observe that as λ increase the aware susceptible human increase whereas the diabetic human and unaware susceptible human are decreasing w.r.t time (yrs) but the trajectories of population are oscillatory behavior around population densities of the endemic equilibrium point. So, we get the almost same behavior of the variables as deterministic together with oscillatory nature if we increase λ.

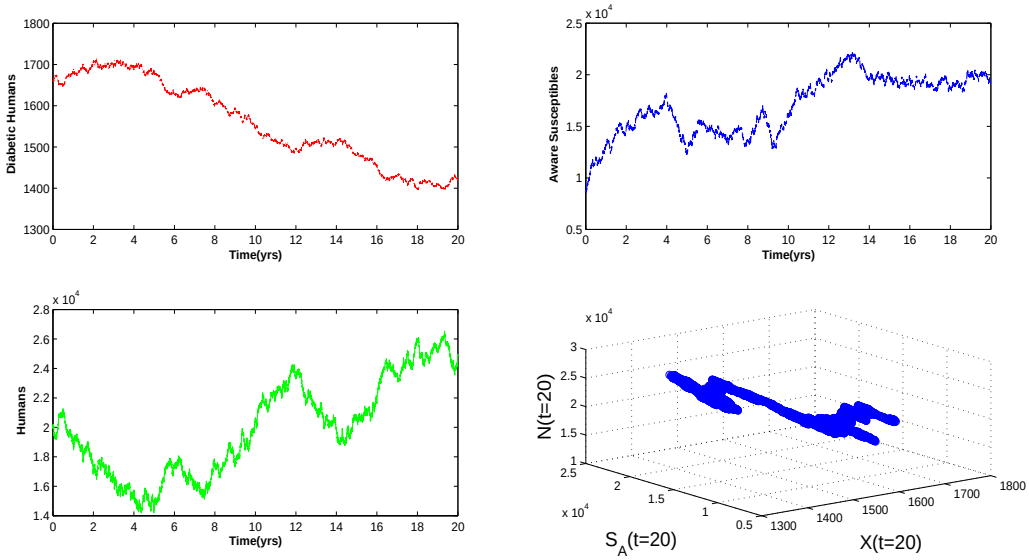


Figure 2.9: The solution of the stochastic differential equation (2.4.1) for $\sigma_1 = \sigma_2 = \sigma_3 = 0.01$ and the remaining parameters are same as Figure 2.3.

2.7 Conclusion

We have studied the dynamics of diabetes mellitus patients in the population by introducing awareness driven by media. To understand the impact of awareness, we have compared the dynamics of both with awareness (2.2.4) and without awareness system (2.2.2) to different aspects. Since diabetes is a non-infectious disease, the incident rate of diabetes mellitus depends only on the susceptible human but not on the diabetic human. So, we obtain only one endemic equilibrium point for both the model systems (2.2.2) and (2.2.4). We deduced the necessary and sufficient conditions (Theorem 2.3.1) for the stability of the equilibrium point. Stability of the endemic equilibrium point guarantee that the existence and survival of all the variables in the model system. Biologically it is very important because it provides actual interaction

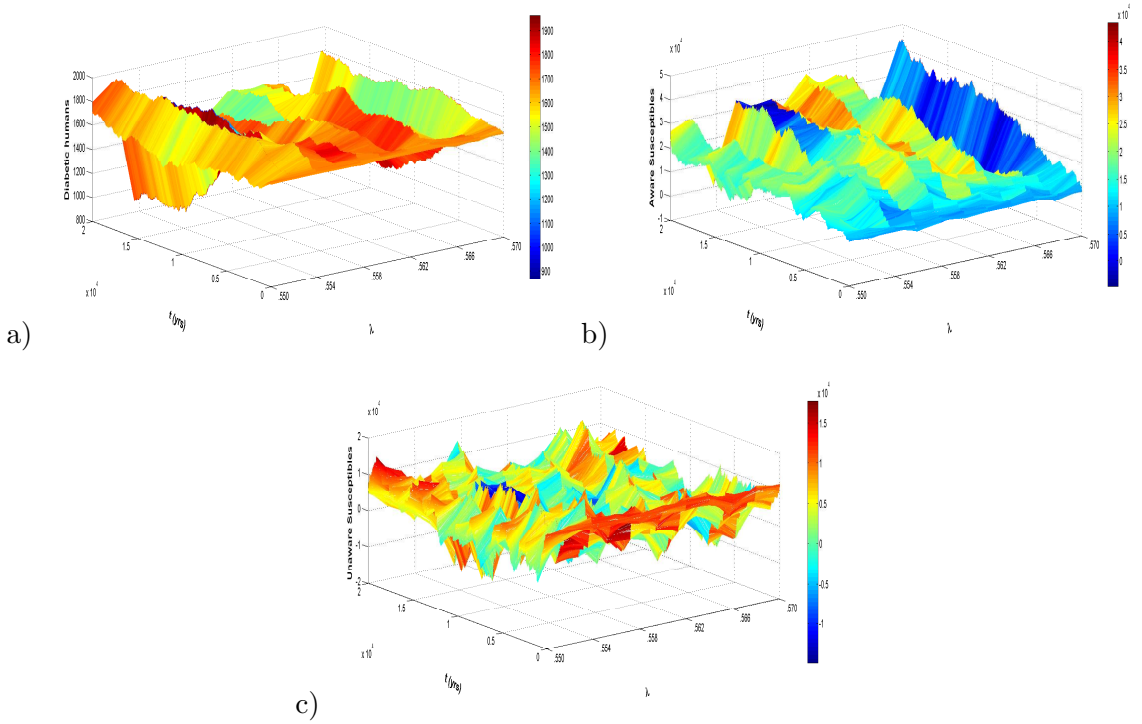


Figure 2.10: The figure depicts the role of diabetic human, aware human and unaware human with respect to time in stochastic differential equation (2.4.1) for different values of λ from 0.550 to 0.570 and other values of parameters are same as Figure 2.3 with $\sigma_1 = \sigma_2 = \sigma_3 = 0.01$.

among all the variables in the model system. In this state actual balance is possible in the population. By using the suitable parameter values of the model systems numerical simulation was performed to investigate the behavior of the populations. We have drawn the phase portraits of the model systems and compare their results in different aspects. In the model (2.2.2), it shows that for increasing β in the absence of awareness model then the size of diabetic humans increase with time. Furthermore, in the presence of awareness model (2.2.4) if we increase the awareness rate λ then the number of aware individuals increase but diabetic human decrease over time. A biological realization of these results is that when we apply awareness on the model system the number of diabetes mellitus is too much lower than the without awareness model system. Also, the above observations indicate that an awareness program driven by media has a significant effect to control diabetes mellitus patients.

Again real-world system does not obey strictly deterministic laws there is always fluctuation is present in the population. Natural disasters, climate change, the behavior of individuals, pollution are also regulated by the stability of the ecosystem. Thus we introduced the stochastic perturbation terms into the growth equations of aware susceptible, diabetes, and total population to incorporate the intensity of en-

vironmental fluctuation in the model system (2.2.4). We derived a set of sufficient conditions (Theorem 2.5.2) for the zero solution of the system (2.4.1) to be asymptotically mean-square stable. The numerical simulation suggests that the solution of the stochastic system fluctuates around the solution of the deterministic system (2.2.4) and goes asymptotically to the equilibrium point under the population fluctuations (see Figure 2.9).

Diabetes mellitus is a silent killer with growing public health hazard all over the world. However, its complications can be controlled through proper awareness program and treatment. This chapter represents a snapshot of the study of DM in a region under awareness. There are several directions in which the present chapter can be extended. First of all, we constructed the model for DM under awareness program but we did not consider awareness programs in the model system as a component. Although this will increase the dimension of the model but would give the much qualitative dynamics of the variables as in (Al Basir et al. [2018]). Another promising direction for future study is to consider fractional derivative in our model system as in (Pinto and Carvalho [2019]). Fractional derivatives incorporate previous time in the model system and DM is a behavioral disease is related to previous behavior of individuals. Thus fractional derivative will be played an important role in the study of DM under awareness.

Chapter 3

Optimal control for the complication of Type 2 diabetes: The role of awareness programs by media and treatment[2]

3.1 Introduction

According to global diabetes prevalence figures from 2014, 422 million people were living with T2 diabetes, with the same tendency diabetic patients expected to rise approximately to 642 million by 2035 (WHO [2016]). The prevalence of T2 diabetes is rising in low- and middle-income countries, although more than 75 percent of adults with the disease live in developed countries (Sattar [2019], WHO [2016]). South Asia is now dealing with an increase in the prevalence of T2 diabetes and its related complications (Ramachandran and Snehalatha [2010]). Diabetes complications are the fourth leading cause of death worldwide. Diabetes and its related complications kill over three million people per year. Diabetic patients suffer from complications such as stroke, coronary heart disease, and myocardial infarction (Sami et al. [2017]). Complications like nephropathy, retinopathy, and neuropathy have a depressing impact on the patient and a significant burden on the health sector. Diabetes and its complications cause substantial financial damage to people with diabetes and their families. It also includes the health system and the burden on the national economy. T2 diabetes is primarily associated with many lifestyle factors in humans, includ-

[2] *The bulk of this chapter has been accepted for publication in* ***International Journal of Dynamics and Control***

ing regular smoking, excessive alcohol use, obesity, and insufficient physical exercise. Risk factors related to the behavior of individuals are also responsible for a significant percentage of premature deaths due to coronary disease, which is co-related to diabetes mellitus (Danaei et al. [2014]). T2 diabetes occurs due to insulin insensitivity caused by insulin tolerance. It decreases insulin supply and glucose transfer through to the muscle cells, liver, and fat cells. This causes a rise breakdown in the fat with hyperglycemia. Recently, impaired alpha-cell activity has been identified as a factor in the pathophysiology of T2 diabetes (Olokoba et al. [2012]). Improving and maintaining glycemic regulation over time is an effective recommendation for T2 diabetes patients. But, this is not an easy action due to the irreversible disposition of the disease, which necessitates prompt medication optimization. T2 diabetes occurs when insulin release is not enough to compensate for the underlying metabolic disorder. As secretory ability decreases over time, the majority of patients with T2 diabetes are expected will ultimately undergo insulin therapy (Prospective [1995]). Diabetes is becoming a growing burden that is possibly placing a threat on the present healthcare system. Diabetes is related to various health issues that it makes more difficult to manage. Effective measures are needed to address the health condition to postpone the consequences of T2 diabetes.

Diabetes can not be cured permanently. Although, knowledge and awareness of the individuals can delay the prevalence of diabetes (Asif [2014]). People are informed about diabetes prevention through media campaigns that emphasize good nutrition and physical activity to minimize their risk of acquiring the disease (Misra et al. [2015], Bassuk and Manson [2005]). Knowledge of awareness on diabetes and management among the patients remains a challenge for stake holders around the world (Sami et al. [2017]). Awareness is needed to improve adherence to medical therapy. Awareness on diabetes mellitus can aid in the early diagnosis of the condition and reduce the risk of complications. Diabetes is connected with decreased levels of physical activity and an increase in the incidence of obesity. Physical exercise should be promoted in the population as a top priority to reduce complication of T2 diabetes (Kennerly and Kirk [2018]). Physical activity can help with diabetes control as well as reduce the complications of diabetes (Hayes and Kriska [2008]). Having metabolic/bariatric surgery is a crucial step in reducing the complications of diabetes, which can also be achieved through lifestyle management. Blood sugar, blood pressure, and cholesterol levels in a reasonable range can reduce the complications such as eye, foot, or heart issues. Recent articles (Hallberg et al. [2019], Steven et al. [2015]) state that diabetes reversal is proposed as a standard T2 diabetes treatment and control. There are currently several classes of oral and injectable medications accessible for the treatment

of T2 diabetes (Hallberg et al. [2019], Marín-Peñalver et al. [2016]). Complications of diabetes are issues that develop immediately (acute) or gradually (chronic) that affect multiple organ systems in the body. Diabetes complications can have a substantial influence on the quality of life and could lead to long-term impairment. Complications of diabetes can be exacerbated by smoking, obesity, high blood pressure, high cholesterol, and a lack of regular exercise. Thus from the above references, awareness and treatment of diabetes can reduce the complication of diabetes. But without complication of T2 diabetes human are more prone to develop complications by altering the lifestyle factors than the general people.

Due to limitations of resources, the most effective use of available control measures should be prioritized to achieve the most possible benefit. Many research articles have been published recently using control strategies of disease dynamics in optimal control theory (Das and Samanta [2022], Odionyenma et al. [2022], Ukanwoke et al. [2022], Gani and Halawar [2018]). Pontryagin et al. first introduced maximum principle on the theory of optimal control, popularly known as *Pontryagin's maximum principle* (A Pontryagin et al. [1962]). Later Fleming and Rishel effectively applied it to the various mathematical models to explore the optimal control theory including HIV disease, pandemic influenza, and malaria disease (Heimann [1979]). Okosun et al. studied the effect of treatment and surveillance of unaware infections on the HIV/AIDS epidemic outbreak by using the fundamental function of optimal control theory (Okosun et al. [2013]).

Some research articles have been published so far to explore the dynamics of diabetes of mathematical models by utilizing various factors (Mollah and Biswas [2021], Anusha and Athithan [2021], Kouidere et al. [2020], Makanda [2019]). Makanda provided a mathematical model for the impact of drug non-adherence on diabetes management (Makanda [2019]). He showed that nonclinical actions such as anti-smoking initiatives, awareness about unhealthy lifestyles could aid in diabetes management. Kompas et al. developed a mathematical model of diabetes transmission through social interaction. They obtained the behavior of diabetes by taking into account the various risks among susceptible individuals (Kompas et al. [2020]). Boutayeb et al. formulated a mathematical model to study the dynamics of pre-diabetes and diabetes with and without complications (Boutayeb and Chetouani [2007]). They tried to show how to reduce the prevalence of without and with complications of diabetes. Recently, Kouidere et al. formulated a mathematical modeling with optimal control on the prevalence of diabetes mellitus (Kouidere et al. [2020]). They applied four controls in the model system such as awareness program through education and media, treatment, and psychological support. Diabetes patients are known

to be more vulnerable to infections including severe covid-19 (Shauly-Aharonov et al. [2021]). Anusha et al. formulated a mathematical model for the co-existence of diabetes and covid-19. They showed that T2 diabetes patients are more likely to get covid-19 if they have come into touch with covid-19 infected individuals (Anusha and Athithan [2021]). Mollah et al. developed mathematical models by considering the effect of awareness of diabetes mellitus in the general population in both deterministic and stochastic environments (Mollah and Biswas [2021]). Their finding showed that awareness program on the population may reduced the diabetes mellitus. Mollah et al. also developed a model based on a nonlinear interactions between the number of diabetic patients and the density of diabetes awareness programs (Mollah et al. [2022]). They indicated that diabetes education and awareness campaigns help to reduce the prevalence of diabetes (Mollah et al. [2022]). Kouidere et al. also designed a model to characterize the dynamics of diabetes by emphasizing the negative influence of socio-environmental factors on diabetic patients (Kouidere et al. [2021]). They suggest a control strategy for implementing the public awareness programs for diabetes patients from the harmful effects of a lifestyle. It is clear that researchers are interested in modeling of diabetes and its related complications. Though, only limited mathematical models are developed to characterize the influence of media coverage and treatment function on T2 diabetes transmission dynamics. Diabetes prevention and control strategies are emphasized as health care resources are always limited. However, mathematical methods for studying T2 diabetes transmission patterns that include the media impact and treatment are mostly unexplored in the limited resources of treatment. To address the study gap, further study is needed to determine the optimal methods for reducing the complications T2 diabetes with a cost-effective strategy in the limited treatment environment.

In this chapter, we develop a deterministic model to investigate the impact of awareness and saturated treatment in the dynamics of diabetes. According to the literatures, this type of work has not been carried out by considering the saturated treatment rate for T2 diabetes. The model system was thoroughly examined, including positivity of solutions, boundedness, equilibrium, and stability analysis. Again, we consider the deterministic model system as an optimal control problem by taking awareness M and treatment u as time depended control parameters. The sufficient conditions for optimal control for T2 diabetes are obtained utilizing the *Pontryagin's maximum principle* in time-dependent controls to find optimal strategies for disease control. We intended to assess the efficacy and costs of several therapies to determine which is the best cost-effective strategy. Thus for this goal, cost-effective analysis is a beneficial tool. Even though numerous cost-effectiveness assessments of diabetes

have been published as a systematic review of the literatures. We implement a complete set of control actions into a comprehensive mathematical model to improve the severity of the T2 diabetes burden and lower the cost of these efforts. The main goal of this chapter is to evaluate the role of awareness and treatment of complications of T2 diabetes in struggling against the disease and find out the related cost-effective strategies.

This chapter is organized as follows. In *Sect.* 3.2, we develop a T2 diabetes mathematical model under some basic assumptions and hypotheses. *Sect.* 3.3 contains positivity and boundedness of the solutions, and an analysis of equilibrium and stability of the system. In *Sect.* 3.4, we use Pontryagains principle to solve the optimal control problem and deduce the derivation of the existence of the optimal problem. Numerical simulation of the model with constant controls is carried out *Sect.* 3.5. In section *Sect.* 3.6, discuss the numerical simulation of the optimal control strategies with time dependent controls. Cost-effectiveness analysis of various optimal control strategies is discussed in *Sect.* 3.7. Finally, the chapter ends with a discussion and conclusion in *Sect.* 3.8.

3.2 Model formulation

We consider a population where human suffering from T2 diabetes. We divide the total population by unaware susceptible S_U, aware susceptible S_A, and T2 diabetes mellitus patients, where T2 diabetes mellitus patients subdivided into with complication X_C, and without complication X_W according to their complications. We make the following assumptions regarding T2 diabetes.

(A) We assume that A is the constant rate of immigration at any time and all newly recruited individuals go to the unaware susceptible class. Diabetes mellitus is not an infectious disease and not transmitted from human to human. So, we have taken β is the incident rate of unaware susceptible to diabetes complication and $\beta\beta_1$ $(0 < \beta_1 < 1)$ is the lower incident rate of aware susceptible to T2 diabetes complication (Mollah and Biswas [2021]).

(B) The development of T2 diabetes is a progressive procedure in which the body is not able to produce enough insulin for its and additionally the body cells become resistant to insulin effects. Thus the direct recovery from T2 diabetes to susceptible does not possible only remission is possible. We consider the treatment function $f_u(X_C) = \frac{buX_C}{1+\gamma uX_C}$ of complication of T2 diabetes to without complication in saturated form, where treatment effect is denoted by u (Cao et al. [2022], Kar et al. [2019]). Here $\frac{b}{\gamma}$ denotes the supply of medical resources per unit time and γ denotes

the saturation constant related to treatment control. Initially, treatment function f_u increases when complications of diabetes X_C increases and reaches its maximum values, and then it becomes constant for further increasing of X_C. This type of dynamics is seen when resource for treatment is limited in the health care systems. Hence the limited supply of treatment is also involved in the model system by the saturated type treatment function. This is applied to any small or large population and reverse the effect of complication due to delay the treatment.

(C) The media effect is determined by the parameter M that the population being aware and alter their susceptibility. We consider a portion pS_UM of unaware class directly joins the aware class, where p is the awareness rate at which it is implemented (Kar et al. [2019]).

(D) Recovery of T2 diabetes is not permanent. Through diet changes, weight loss, and medication patients may be able to reach and hold normal blood sugar levels. We consider a portion θX_W of without complication of diabetes become complication and join in X_W, where θ is the coefficient of X_W at which without complications of diabetes human joins to the class of complications of diabetes human. We consider d is the natural death rate and e is the additional death rate due to complication of diabetes of all individuals in the different classes respectively.
Based on the aforementioned assumptions, we derive the following model

$$\begin{aligned}
\frac{dS_U}{dt} &= A - pS_UM - \beta S_U - dS_U, \\
\frac{dS_A}{dt} &= pS_UM - \beta\beta_1 S_A - dS_A, \\
\frac{dX_C}{dt} &= \beta S_U + \beta\beta_1 S_A - \frac{buX_C}{1+\gamma\ uX_C} - (d+e)X_C + \theta X_W, \\
\frac{dX_W}{dt} &= \frac{buX_C}{1+\gamma\ uX_C} - \theta X_W - dX_W,
\end{aligned} \tag{3.2.1}$$

with the initial conditions are $S_U(0) > 0$, $S_A(0) >$, $X_C(0) > 0$, $X_W(0) > 0$.

3.3 Basic properties of the system for fixed controls

In this section, we have treated media control M and treatment control u are as constants. The model system then becomes relatively simple, but this will give the additional potential to draw more biological insights. First we showed the positivity of solutions and boundedness of the system and subsequently we found the steady state and showed the local stability conditions of the steady state.

3.3.1 Positivity of solutions

Theorem 3.3.1. *Let the initial conditions $S_U(0) > 0$, $S_A(0) > 0$, $X_C(0) > 0$, and $X_W(0) > 0$. Then the solution (S_U, S_A, X_C, X_W) of the system (3.2.1) remains positive for all $t > 0$.*

Proof. From the first equation of the system (3.2.1), we have
$\frac{dS_U}{dt} = A - pS_UM - \beta S_U - dS_U \geq -(pM + \beta + d)S_U$.
This can be written as:
$\frac{dS_U}{S_U} \geq -(pM + \beta + d)dt$.
Integrating both sides of the above inequality, we obtain
$S_U(t) \geq S_U(0)e^{-\int_0^t (pM+\beta+d)ds} > 0$, for all $t > 0$.

Again, from the second equation of the system (3.2.1), we have
$\frac{dS_A}{dt} = pS_UM - \beta\beta_1 S_A - dS_A \geq -(\beta\beta_1 + d)S_A$.
This can be written as:
$\frac{dS_A}{S_A} \geq -(\beta\beta_1 + d)dt$.
Integrating both sides of the above inequality, we obtain
$S_A(t) \geq S_A(0)e^{-\int_0^t (\beta\beta_1+d)ds} > 0$, for all $t > 0$.
Similarly employing the same approach, it can be shown that
$X_C(t) > 0$ and $X_W(t) > 0$, for all $t > 0$. □

3.3.2 Boundedness

Proposition 1. *All feasible solutions of the system (3.2.1) with positive initial conditions are uniformly bounded in the region*
$\Gamma_\varepsilon = \left\{(S_U, S_A, X_C, X_W) \in R_+^4 : S_U + S_A + X_C + X_W \leq \frac{A}{d} + \varepsilon\right\}$.

Proof. Let $W(t)$=$S_U(t)$+$S_A(t)$+$X_C(t)$ + $X_W(t)$, then we have
$\frac{dW}{dt}$=$A - dW - eX_C$ [by using (3.2.1)]
or, $\frac{dW}{dt}$+dW$\leq A$.
Now applying the theory of differential inequality we get
$0 < W(t) \leq \frac{A}{d} + e^{-dt}W(0)$.
Which implies $limsup_{t\to\infty}W(t) \leq \frac{A}{d}$.
Thus all the solutions of (3.2.1) with positive initial values are ultimately bounded in the region $\Gamma_\varepsilon = \left\{(S_U, S_A, X_C, X_W) \in R_+^4 : S_U + S_A + X_C + X_W \leq \frac{A}{d} + \varepsilon\right\}$ for any $\varepsilon > 0$. Hence the result. □

3.3.3 Equilibrium and stability analysis

The model system (3.2.1) has only one endemic steady state $L^*(S_U^*, S_A^*, X_C^*, X_W^*)$. In steady state $L^*(S_U^*, S_A^*, X_C^*, X_W^*)$, the values of $S_U^*, S_A^*, X_C^*, X_W^*$ are obtained by solving the following algebraic equations:

$$\begin{aligned} &A - pS_UM - \beta S_U - dS_U = 0,\\ &pS_UM - \beta\beta_1 S_A - dS_A = 0,\\ &\beta S_U + \beta\beta_1 S_A - \tfrac{buX_C}{1+\gamma uX_C} - (d+e)X_C + \theta X_W = 0,\\ &\tfrac{buX_C}{1+\gamma uX_C} - \theta X_W - dX_W = 0. \end{aligned} \tag{3.3.1}$$

From the first two equations in (3.3.1), we obtain
$S_U^*=\frac{A}{pM+\beta+d}$, $S_A^*=\frac{pM}{\beta\beta_1+d}\frac{A}{pM+\beta+d}$.
Again, eliminating X_W from the last two equations in (3.3.1), we obtain a quadratic equation in X_c as:

$$R_1X_C^2 + R_2X_C + R_3 = 0, \tag{3.3.2}$$

where
$R_1 = d(d+e)\gamma u + \theta\gamma u(d+e) > 0,$
$R_2 = \beta ud + \theta(d+e) - \theta\gamma u\beta S_U - \theta\gamma u\beta\beta_1 S_A + d(d+e) - d\gamma u\beta S_U - d\gamma u\beta\beta_1 S_A,$
$R_3 = -(\beta\theta S_U + \beta\beta_1\theta S_A + \beta dS_U + \beta\beta_1 dS_A) < 0.$
Therefore from (3.3.2), we get $X_C = \frac{-R_2\pm\sqrt{R_2^2-4R_1R_3}}{2R_1}$.
We find that $R_1 > 0$, $R_3 < 0$, and any values of R_2, it must have $-4R_1R_3 > 0$.
Hence, $(R_2^2 - 4R_1R_3) > R_2^2 > 0$. Thus the positive root is given by

$$X_C^* = \frac{-R_2 + \sqrt{R_2^2 - 4R_1R_3}}{2R_1}.$$

From the last equation in (3.3.1), by substituting X_C^*, we obtain $X_W^* = \frac{1}{\theta+d}\frac{\beta uX_C}{1+\gamma uX_C}$.
Finally, we obtained the positive endemic steady state $L^*(S_U^*, S_A^*, X_C^*, X_W^*)$.

The jacobian matrix to the system (3.2.1) at the steady state $L^*(S_U^*, S_A^*, X_C^*, X_W^*)$ is given below:

$$J_{L^*} \equiv \begin{bmatrix} -(pM+\beta+d) & 0 & 0 & 0 \\ pM & -\beta\beta_1 - d & 0 & 0 \\ \beta & \beta\beta_1 & -\frac{bu}{(1+\gamma u X_C^*)^2} - (d+e) & \theta \\ 0 & 0 & \frac{bu}{(1+\gamma u X_C^*)^2} & -(\theta+d) \end{bmatrix}.$$

Therefore the characteristic equation is given by

$$|J_{L^*} - \rho I_4| = (pM+\beta+d+\rho)(\beta\beta_1+d+\rho)(\rho^2 + B_1\rho + C_1) = 0,$$

with $B_1 = \frac{bu}{(1+\gamma u X_C^*)^2} + 2d + e + \theta$, $C_1 = \frac{bdu}{(1+\gamma u X_C^*)^2} + (d+e)(d+\theta)$.

Now, $\rho^2 + B_1\rho + C_1 = 0$,

Since, $B_1^2 - 4C_1 = \{\frac{bu}{(1+\gamma u X_C^*)^2} + 2d + e + \theta\}^2 - 4\{\frac{bdu}{(1+\gamma u X_C^*)^2} + (d+e)(d+\theta)\}$ $= \{\frac{bu}{(1+\gamma u X_C^*)^2}\}^2 + \frac{2bu(e+\theta)}{(1+\gamma u X_C^*)^2} + (e-\theta)^2 > 0$. Also, $B_1^2 > B_1^2 - 4C_1$ as $C_1 > 0$. Then, we get two negative roots $\frac{-B_1 \pm \sqrt{B_1^2 - 4C_1}}{2}$. Hence four eigenvalues of the jacobian matrix J_{L^*} are given by:
ρ_1=-$(pM+\beta+d)$, ρ_2=-$(\beta\beta_1+d)$, $\rho_3 = \frac{-B_1 + \sqrt{B_1^2 - 4C_1}}{2}$, and $\rho_4 = \frac{-B_1 - \sqrt{B_1^2 - 4C_1}}{2}$.
Since all the eigenvalues are negative, the system (3.2.1) is locally asymptotically stable at the steady state $L^*(S_U^*, S_A^*, X_C^*, X_W^*)$.

3.4 Application of optimal control to the T2 diabetes model

The main objective of the present chapter is to assess both complications of T2 diabetes mellitus patients and financial outcomes by considering time-dependent controls like media control parameter M, and treatment control parameter u into the model system (3.2.1). Due to the cost of treatment and media awareness, it is always important to find out a strategy in which minimize the prevalence of diabetes patients also associated cost on it and maximize aware susceptible human. Optimal control theory is important and effective to find out such strategies. Hence we consider an objective function as follows:

$$J = \underset{u,M}{min} \int_0^{t_f} (A_1 X_C - A_2 S_A + A_3 u^2 + A_4 M^2) e^{-qt} dt, \tag{3.4.1}$$

subject to the system of differential equation (3.2.1). Here A_1, A_2 are the measure of the cost of interventions on [0 t_f] of diabetes patients, aware susceptible respectively. Also A_3, A_4 are respectively taken as weight of the cost of interventions of the square of treatment and media awareness control and q is the relatively discount rate. We choose a quadratic cost on the controls to determine nonlinear interaction arising in the cost at high implementation level. The cost can be defined the funds need for treatment including implementation of awareness campaign. Our main aim to find out an optimal control $(u^*, M^*) = min\{J(u, M) : (u, M) \in \mathfrak{U},\}$
where $\mathfrak{U}$=$\{(u, M)$:$0 \leq u(t), M(t) \leq 1$ for t $\in [0, t_f]$ $\}$ is the control set.
Here we applying *Pontryagain's* principle to solve the optimal control problem and the derivation of the existence of the optimal problem is given below.

$$H = A_1X_C - A_2S_A + A_3u^2 + A_4M^2 + \lambda_1\frac{dS_U}{dt} + \lambda_2\frac{dS_A}{dt} + \lambda_3\frac{dX_C}{dt} + \lambda_4\frac{dX_W}{dt} \quad (3.4.2)$$

where the adjoint variables or co-state variables λ_i, i=1, 2, 3, 4 are the solutions of the following set of differential equations:

$$\begin{array}{rcl} \frac{d\lambda_1}{dt} & = & (pM + \beta + d)\lambda_1 - pM\lambda_2 - \beta\lambda_3, \\ \frac{d\lambda_2}{dt} & = & A_2 + (\beta\beta_1 + d)\lambda_2 - \beta\beta_1\lambda_3, \\ \frac{d\lambda_3}{dt} & = & -A_1 + (d + e + \frac{bu}{(1+\gamma uX_C)^2})\lambda_3 - \frac{bu}{(1+\gamma uX_C)^2}\lambda_4, \\ \frac{d\lambda_4}{dt} & = & -\theta\lambda_3 + (\theta + d)\lambda_4, \end{array} \quad (3.4.3)$$

and satisfying the transversality conditions at t_f i.e. $\lambda_i(t_f)$=0, i=1, 2, 3, 4.

Theorem 3.4.1. *There exist an optimal control $(u^*, M^*) \in \mathfrak{U}$ on a fixed interval [0, t_f] such that $J(u^*, M^*)$=$\frac{min}{u,M}\{J(u(t), M(t))\}$.*

Proof. Since the solutions of the system are bounded then there always exist a solution to the optimal control system (Heimann [1979]). Thus the set of all controls and corresponding state variables are nonempty. From definition, the control set is closed and convex. The integrand of the cost functional is $A_1X_C - A_2S_A + A_3u^2 + A_4M^2$, which is convex on the control set $\mathfrak{U}$. Also there exist p_i, q_i, i=1, 2, and $b > 1$ such that $A_1X_C - A_2S_A + A_3u^2 + A_4M^2 \geq p_1 + q_1|u(t)|^b$, and $A_1X_C - A_2S_A + A_3u^2 + A_4M^2 \geq p_2 + q_2|M(t)|^b$, where p_1, p_2 depend on the upper bound of X_C, S_A respectively and $q_i = A_i$, i=1, 2. Hence there exist an optimal control to the optimal system. □

Theorem 3.4.2. *If $\lambda_3 > \lambda_4$, then there is an optimal control (u^*, M^*) that minimizes the objective function J over $\mathfrak{U}$ is given by u^*=$max\{0, min(\overline{u}, 1)\}$ and M^*=$max\{0, min(\overline{M}, 1)\}$, where $\overline{u}$=$\frac{1}{3}\frac{2^{\frac{4}{3}}A_3}{(B+\sqrt{B^2-C})^{\frac{1}{3}}} + \frac{(B+\sqrt{B^2-C})^{\frac{1}{3}}}{2^{\frac{4}{3}}A_3\gamma^2X_C^2} - \frac{2}{\gamma X_C}$, $\overline{M}$=$\frac{(\lambda_2-\lambda_1)pS_U}{2A_4}$ with B=$16A_3^3\gamma^3X_C^3$ +*

$108A_3^2b\gamma^4X_C^5\lambda_3$-$108A_3^2b\gamma^4X_C^5\lambda_4$ *and* C=$256A_3^6\gamma^6X_C^6$.

Proof. Equating to zero to the derivatives of the Hamiltonian function with the controls, we get $\frac{\partial H}{\partial u}$=0 and $\frac{\partial H}{\partial M}$=0. Now $\frac{\partial H}{\partial u}$=0, gives $u(1+\gamma uX_C)^2 = \frac{(\lambda_3-\lambda_4)bX_C}{2A_3}$. Then one real root of the equation is given by $\overline{u}$=$\frac{1}{3}\frac{2^{\frac{4}{3}}A_3}{(B+\sqrt{B^2-C})^{\frac{1}{3}}} + \frac{(B+\sqrt{B^2-C})^{\frac{1}{3}}}{2^{\frac{4}{3}}A_3\gamma^2X_C^2}$ -$\frac{2}{\gamma X_C}$, where B, C have given in statement of the theorem (Kar et al. [2019]).

Now, B^2-C= $(16A_3^3\gamma^3X_C^3 + 108A_3^2b\gamma^4X_C^5\lambda_3 - 108A_3^2b\gamma^4X_C^5\lambda_4)^2 - 256A_3^6\gamma^6X_C^6$,
=$\{108A_3^2b\gamma^4X_C^5(\lambda_3-\lambda_4) + 32A_3^3\gamma^3X_C^3\}\{108A_3^2b\gamma^4X_C^5(\lambda_3-\lambda_4)\}$,
=$\{108A_3^2b\gamma^4X_C^5(\lambda_3-\lambda_4)\}^2 + 32\times 108A_3^5\gamma^7bX_C^8(\lambda_3-\lambda_4)$.
Thus, $B^2-C>0$ if $\lambda_3>\lambda_4$.

Again $\frac{\partial H}{\partial M}$=0, gives $\overline{M}$=$\frac{(\lambda_2-\lambda_1)pS_U}{2A_4}$.
Since the controls are bounded by 0 and 1. We set u^*=0 when $\overline{u}\le 0$, $u^*=1$ when $\overline{u}\ge 1$, and $u^*=\overline{u}$ when $0<\overline{u}<1$. Similar conditions are also hold for M^*. □

3.5 Numerical simulation with constant control

To find out a better understanding of the complication of T2 diabetes in the population and corresponding health care cost, we first investigated the dynamics of the model system with different vital parameter values and then analyzed the system with various control strategies. We have taken the biologically relevant parameter values in the following:

$A=12000$; $p=0.5$; $\beta=0.001$; $d=0.00001$; $\beta_1=0.000007$; $\gamma=0.000004$; $e=0.0007$; $\theta=0.0000002$; $b=0.003$; $M=0.2$; $u=0.8$; $A_1=1$; $A_2=10$; $A_3=1$; $A_4=10000000$;
and the initial population size $S_U(0)=500000$; $S_A(0)=476858$; $X_C(0)=118283$; $X_W(0)=35485$; to corroborate our analytical finding by using MATLAB software.
Figure 3.1 represents the behavior of the variables unaware susceptibles S_U, aware susceptibles S_A, complications of diabetes X_C, and without complications of diabetes X_W of the model (3.2.1) with constant control values and they eventually approach to the endemic steady state $L^*(118800, 1.18717\times10^9, 176542, 1.34491\times10^9)$. From Figure 3.1, it also demonstrates that both media and treatment control have the ability to reduce the prevalence of complications of T2 diabetes. Moreover, the eigenvalues of the model (3.2.1) at L^* are ρ_1=-0.10101, ρ_2=-0.00099, ρ_3=-0.00001, and ρ_4 =-0.00001. Thus the model (3.2.1) is locally asymptotically stable at the steady state L^*.

Now we discuss the dynamics for wide range of different significant parameters M, u, β, and p of the model system (3.2.1) to explore the relationship of T2 diabetes

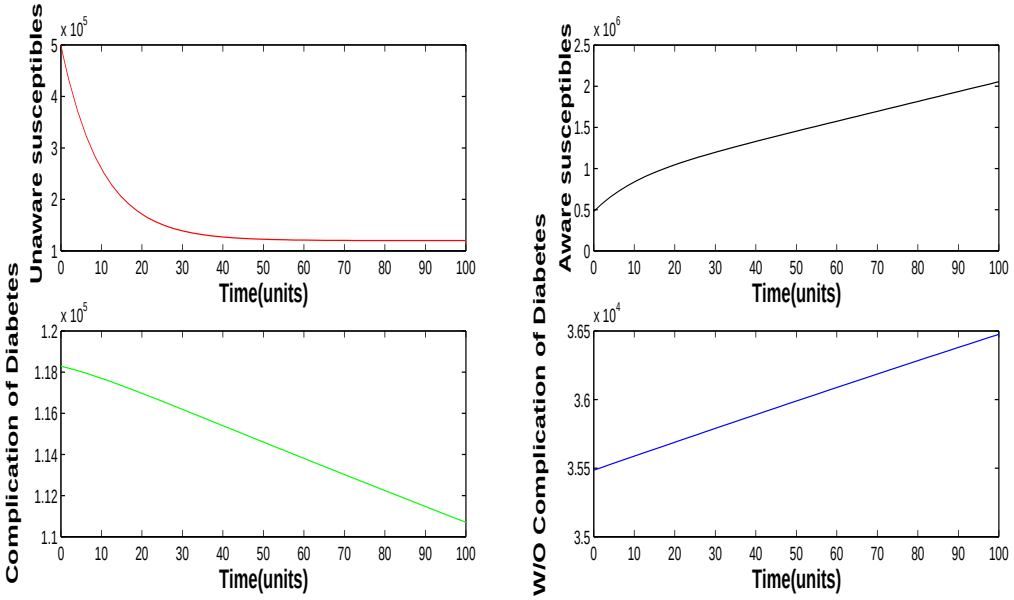


Figure 3.1: The figure depicts the solution of the model system (3.2.1) of the variables S_U, S_A, X_C, and X_W for parameter values $A = 12000$, $p = 0.5$, $\beta = 0.001$, $d = 0.00001$, $\beta_1 = 0.000007$, $\gamma = 0.000004$, $e = 0.0007$, $\theta = 0.0000002$, $b = 0.003$, $M = 0.2$, $u = 0.8$.

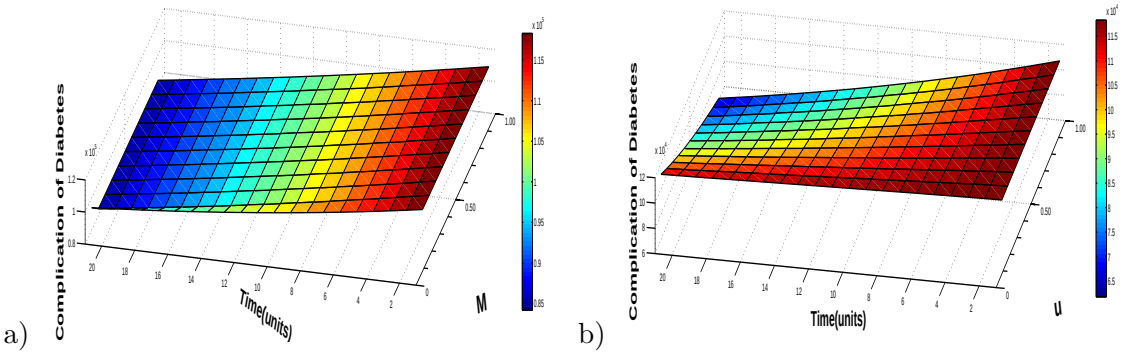
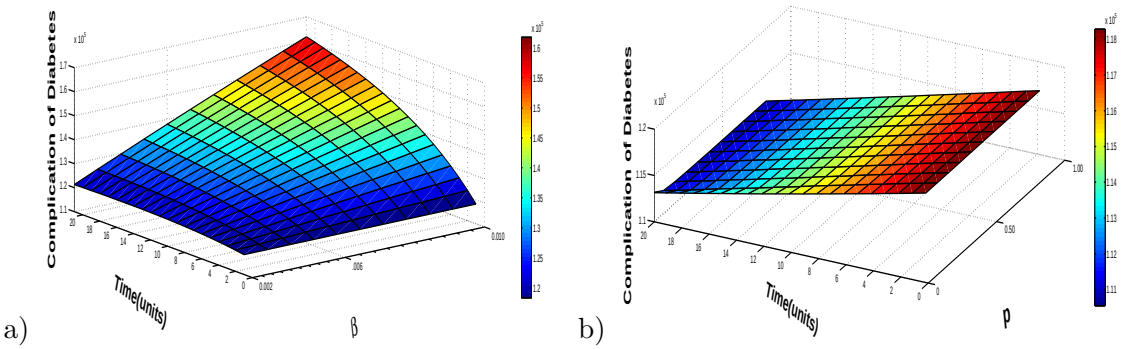


Figure 3.2: The figures depict the role of the complications of diabetes X_C with respect to time for different values of u and M respectively and other values of parameters are kept same as Figure 3.1.

with different parameter values.

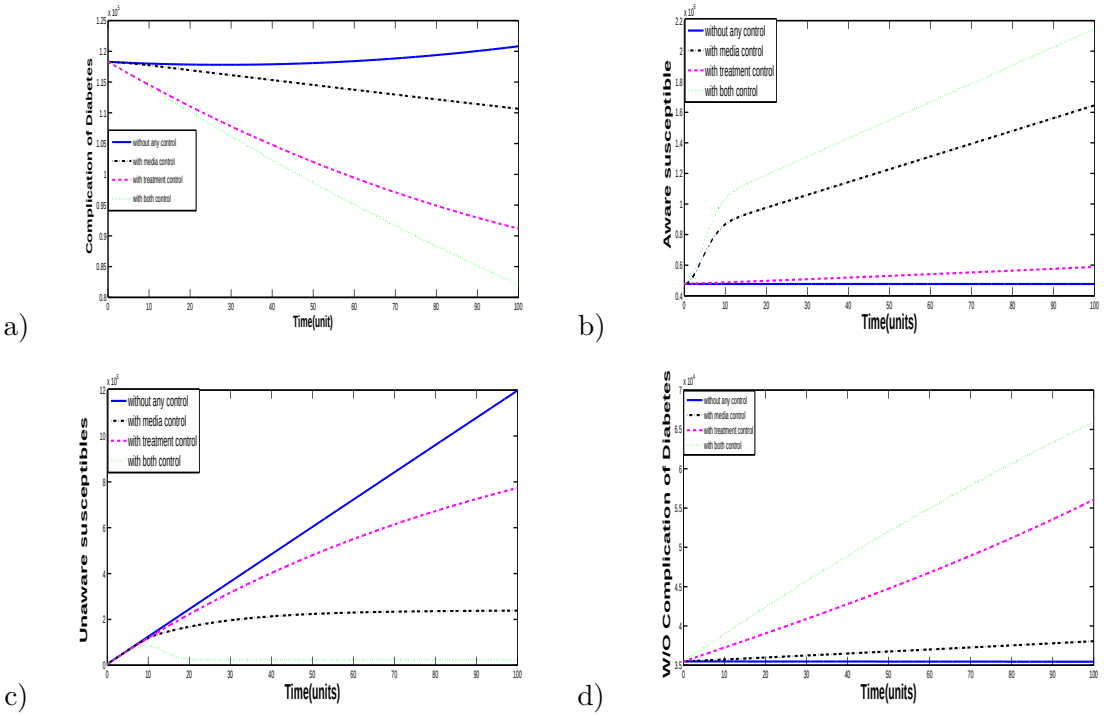
3.5.1 Impact of the media control parameter M of T2 diabetes on the model system

The dissemination of awareness not only reduces diabetes prevalence but in some cases can even prevent the onset of diabetes, meaning that awareness can be an effective disease prevention measure (Funk et al. [2009]). Knowledge and awareness



a) b)

Figure 3.3: The figures depict the role of the complications of diabetes X_C with respect to time for different values of β and p respectively and other values of parameters are kept same as Figure 3.1.

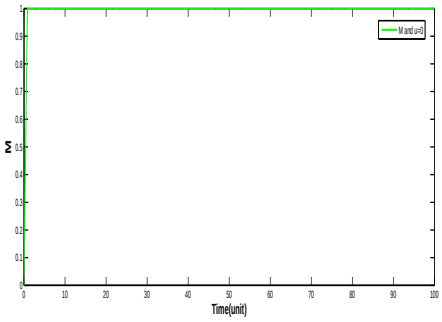


a) b) c) d)

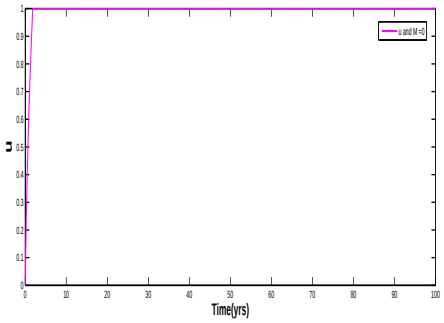
Figure 3.4: The figure depicts the role of a) complications of diabetic human, b) aware susceptibles, c) unaware susceptibles, and d) without complications of diabetes with different types of optimal control for any time t.

about diabetes of how to monitor and treat diabetes at the right time will reduce complications of diabetes and thus decrease death in diabetes (Nazar et al. [2016]). From Figure 3.2a), we see that if we increase the media control parameter M, the number of complications of diabetes X_C decrease for any particular time t. Thus awareness via media control plays an effective role in fighting against complications

a)



b)



c)

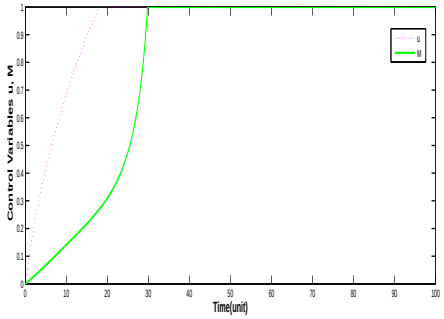


Figure 3.5: The figures depict the role of a) only media control parameter M, b) only recovery control parameter u, c) both media control parameter M and recovery control parameter u at any time.

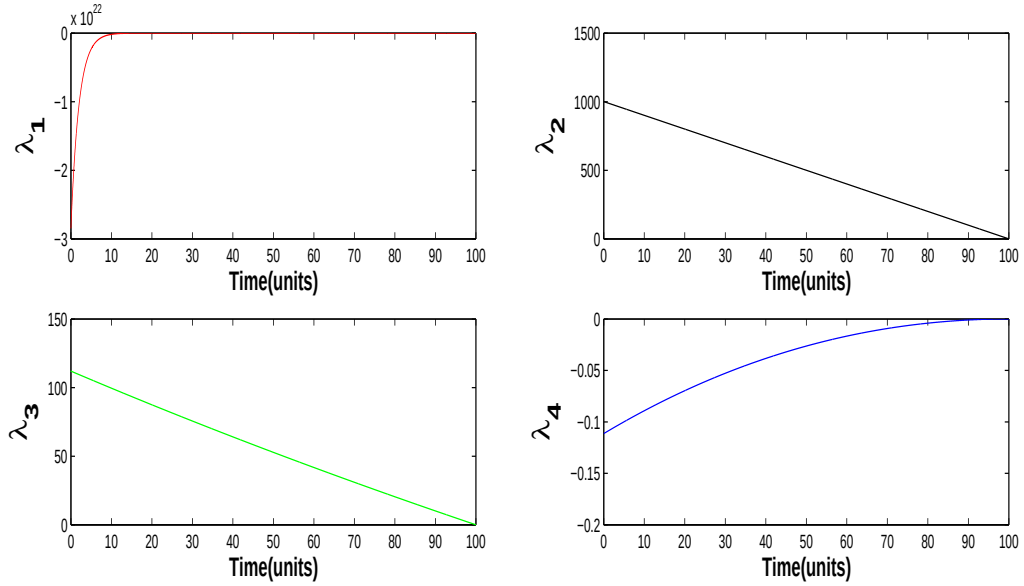


Figure 3.6: The figure depicts the role of the adjoint variables when both optimal controls are applied.

of T2 diabetes and effectively decreasing diabetes patients.

3.5.2 Impact of the treatment control parameter u of T2 diabetes on the model system

The prevalence of T2 diabetes is increasing, so finding an effective treatment is becoming a top priority for fighting against the disease (Wu et al. [2014]). Different types of treatment are available for the remission of the complications of T2 diabetes such as bariatric surgery, low-calorie diets, and carbohydrate-restricted diets (Hallberg et al. [2019], Steven et al. [2015]). From Figure 3.2b), it shows that if we increase the treatment control parameter u, the number of complications of diabetes X_C decrease for any specified time t. Thus treatment is an important priority to tackle the prevalence of T2 diabetes.

3.5.3 Effect of the incidence rate β of T2 diabetes on the model system

Sedentary behavior, lack of exercise, smoking, and alcohol consumption are all lead to the rapid increases in the incidence of T2 diabetes (Wu et al. [2014]). It is critical to improve prevention measures for recognizing high-risk individuals and identifying possibly modifiable risk factors to decrease the incidence of T2 diabetes. From Figure 3.3a), its demonstrated that if we increase incident rate β then number of diabetes complication X_C also increase for any specified time t. Sedentary behavior, lack of exercise, smoking, and alcohol consumption are risk factors to the rising incidence of T2 diabetes in individuals.

3.5.4 Role of awareness coefficient p of T2 diabetes on the model system

Awareness about the complications of diabetes and sequential rise in dietary knowledge, attitude, and practices can manage better control diabetes. Some research articles have shown that awareness of diabetes will significantly increase the quality of life of patients and reduce the burden of the disease on their family (Sami et al. [2017], Magurová et al. [2012]). From Figure 3.3b), it shows that if we increase awareness coefficient p, the number of complications of T2 diabetes X_C is also slightly decreased with any particular time t.

3.6 Numerical simulation with optimal control

In this section, we carried out numerical simulations to show the effect of the control strategies on the T2 diabetes mathematical model. Solving the optimality system

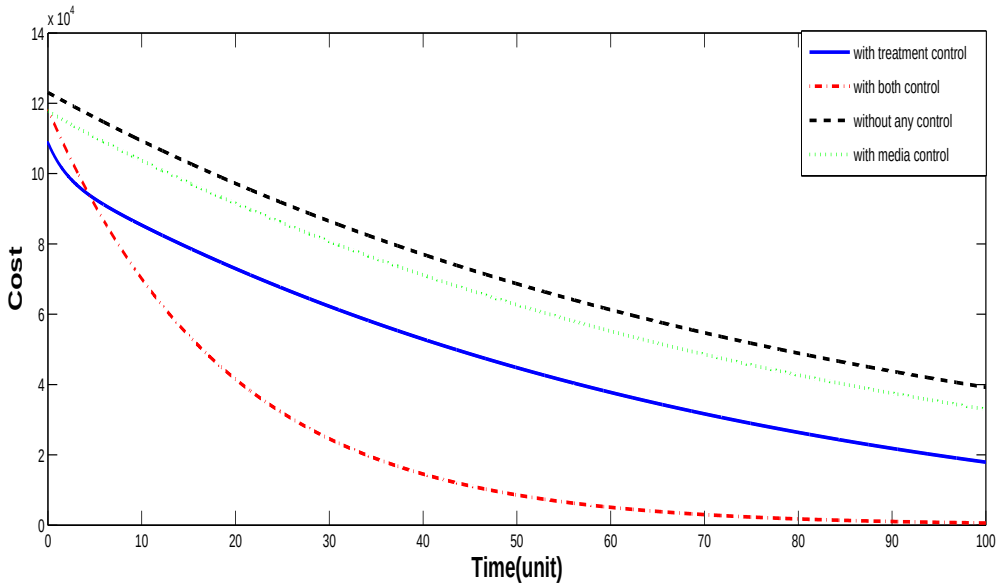
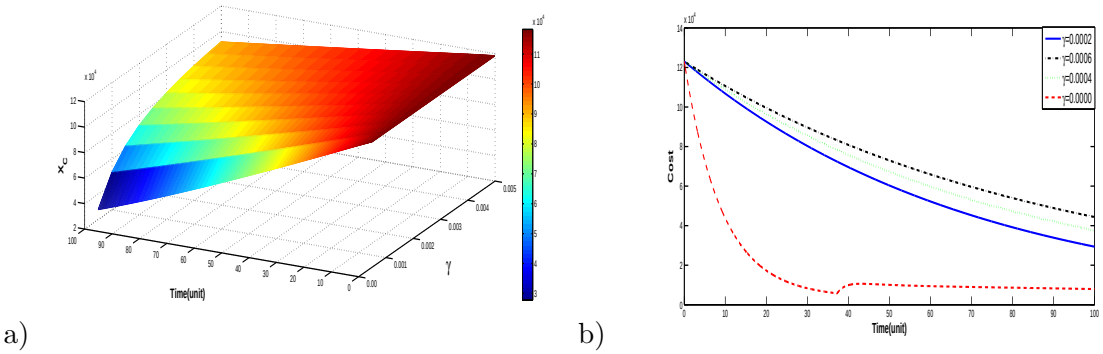


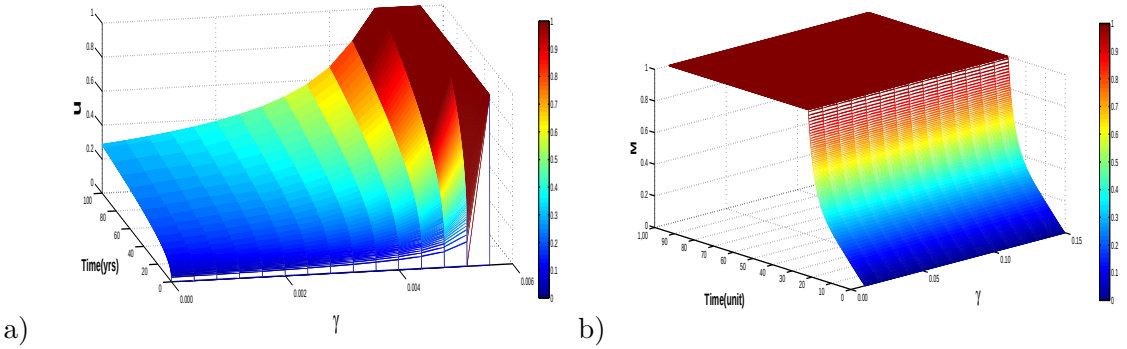
Figure 3.7: The figure depicts the related costs under the various control strategies.



a) b)

Figure 3.8: The figures depict the role of the a) complications of diabetes X_C with respect to time for different values of γ and b) related costs with respect to for different values of γ.

(3.2.1) and (3.4.3) and corresponding their initial conditions, we obtained solutions of the optimal system. At first, we take an initial guess of the control variables, then state variables of the model system (3.2.1) are solved using the RK4 method forward in time. Next, using initial control guess and state variables corresponding adjoint system (3.4.3) is solved by using RK4 method backward in time. This iterative method ends when the current state, adjoint, and control values are converged sufficiently (Kumar et al. [2020a], Agusto and ELmojtaba [2017], Agusto [2013]). In addition, different types of strategies are taken with the combination of control profiles as strategy 1 (only media control), strategy 2 (only treatment control), and strategy 3 (together with the media and treatment controls) to figure out the effects



a) b)

Figure 3.9: The figures depict the role of the a) optimal control profiles u with respect to time for different values of γ and b) optimal control profiles M with respect to time for different values of γ and other values of parameters are kept same as Figure 3.1.

of media and treatment controls in the system.

First of all, we solve the control system (3.4.1) in different types of control strategies with the same initial population size and parameters values are used in the previous section. The corresponding outcomes of the control system have been displayed in Figure 3.4. It is clear that in the absence of control, the complication of T2 diabetes increases gradually and resulting in a massive disease prevalence in the population. In addition, aware susceptible and without complication of T2 diabetes remain low due to the rapid increase of complication of T2 diabetes.

Again from strategy 1, it is clear that the slope of the line of complications of T2 diabetes decreases and delays the prevalence of T2 diabetes compared to the absence of control. Consequently, strategy 1 plays a prominent role in reducing the prevalence of T2 diabetes over time. The optimal path of M for strategy 1 is displayed in Figure 3.5a) and found that awareness program M executing over the entire period with full potential. Next, in strategy 2, it is clear that the slope of the line of complications of T2 diabetes decreases, and the graph lies below from strategy 1. Thus strategy 2 has a significant impact on the prevalence of T2 diabetes to minimize the disease. The optimal path of u in this strategy is displayed in Figure 3.5b) and found that recovery u has been executing over time with full potential.

Finally, in strategy 3, it is clear that the graph of complications of T2 diabetes is at a minimal level over time compared to earlier cases. Thus, in this case, there is no rapid prevalence of T2 diabetes. Consequently, it significantly minimizes the complication of T2 diabetes. Also, rapid growth is observed in aware susceptible humans and without the complication of diabetes under strategy 3. In addition, the curve of unaware susceptible human rapid growth is happening initially after that, it gradually decays and stays at a lower level than any other earlier cases. The optimal

Table 3.1: DAR and ACER of all strategies

Strategies	Total infection averted	Total recovered	DAR	ACER
Strategy 1	3.5012×10^7	8.8679×10^4	394.82	0.022042
Strategy 2	9.5097×10^7	4.8757×10^7	1.9504	0.010210
Strategy 3	1.3008×10^8	4.8743×10^7	2.6687	0.024642

Table 3.2: ICER of all strategies

Strategies	Total infection averted	Total costs	ICER
Strategy 1	3.5012×10^7	8.8679×10^4	4.427×10^{-4}
Strategy 2	9.5097×10^7	4.8757×10^7	6.66×10^{-5}
Strategy 3	1.3008×10^8	4.8743×10^7	-5.72×10^{-5}

path of the controls M and u for strategy 3 is displayed in Figure 3.5c) and found that awareness program M and recovery control u executing over the entire period but relatively lower than the previous strategies. Whereas Figure 3.6 represents the role of the corresponding adjoint variables when both optimal controls are applied. Here it is noted that λ_1 and λ_3 are increasing over time, but λ_2 and λ_4 are decreasing over time. These findings are consistent with the results of the earlier research studies (Odionyenma et al. [2022], Kumar et al. [2020a], Kar et al. [2019]).

3.7 Cost-effectiveness analysis

Controlling and reducing T2 diabetes in a population can be time-consuming and costly. As a result, cost-effectiveness analysis is needed to decide the most cost-effective approach to use for strategy 1 (only media control), strategy 2 (only treatment control), and strategy 3 (together with the media and treatment controls). In this segment, we use cost-effectiveness analysis to look at the cost-effectiveness of treatment and personal safety management measures (e.g physical activity and dietary choices), as well as the benefits that come with them. We have used three different methods like Disease averted ratio (DAR), Average cost-effectiveness ratio (ACER) and Incremental cost-effectiveness ratio (ICER) given in one by one in the

Table 3.3: ICER of all strategies

Strategies	Total infection averted	Total costs	ICER
Strategy 2	9.5097×10^7	4.8757×10^7	2.06×10^{-4}
Strategy 3	1.3008×10^8	4.8743×10^7	0.23×10^{-4}

following subsections to evaluate the most cost effective strategy.

3.7.1 Disease averted ratio (DAR)

The disease averted ratio (DAR) is calculated as follows:

$$DAR = \frac{Number\ of\ disease\ averted}{Number\ of\ recovered}$$

The *number of disease averted* is termed by the difference between the total diabetic individuals without control and the total disease individuals with control over the same period of time. The strategy with the highest DAR values is the least cost effective. From Table 3.1, we see that strategy 2 is the least cost effective strategy.

3.7.2 Average cost-effectiveness ratio (ACER)

A single intervention's average cost effectiveness ratio (ACER) is compared to the no-intervention baseline alternative. ACER is determined as

$$ACER = \frac{Total\ cost\ produced\ by\ the\ intervention}{Total\ number\ of\ disease\ averted},$$

where the total cost is evaluated from the objective function given in equation (3.4.1). From this cost effectiveness approach strategy 2 is the least cost effective strategy (see Table 3.1).

3.7.3 Incremental cost-effectiveness ratio (ICER)

The incremental cost-effectiveness ratio (ICER) measures the extra cost per added health result and the costs of different control measures are assumed to be proportional to the number of controls deployed. One intervention is compared to the next-less-effective alternative in order to equate two or more opposing intervention methods incrementally. Then the ICER can be calculated as follows:

$$ICER = \frac{Difference\ in\ disease\ averted\ costs\ in\ strategies\ i\ and\ j}{Difference\ in\ total\ number\ of\ disease\ averted\ in\ strategies\ i\ and\ j}.$$

The variations in the costs of disease averted or cases avoided, the costs of intervention(s), and the costs of averting production losses, among other things, are included in the ICER numerator (where applicable). On the other hand, the ICER numerator is the difference in health effects, which may include the total number of disease avertedor the number of susceptibility cases avoided. Therefore,

ICER(Strategy 1)$=\frac{1.5501\times10^4}{3.5012\times10^7}=0.000443$,
ICER(Strategy 2)$=\frac{1.9501\times10^4-1.5501\times10^4}{9.5097\times10^7-3.5012\times10^7}=0.0000066$,
ICER(Strategy 3)$=\frac{1.7551\times10^4-1.9501\times10^4}{1.3008\times10^7-9.5097\times10^7}=0.000024$.

From the Table 3.2, comparing ICER(strategy 1), and ICER(strategy 2), shows a cost saving of 0.4427 for strategy 2 over strategy 1. The minimum ICER from strategy 2 is indicated that strategy 1 is strongly dominated. This means that strategy 1 is comparatively much costly and less effective to implement than the strategy 2. Thus we can exclude strategy 1 from the other set of two strategies as it will not be effective on the limited resource.
Again similarly strategy 2 is compared with strategy 3 to obtain alternative intervention. Computation of ICER as follows:
ICER(Strategy 2)$=\frac{1.9501\times10^4-1.5501\times10^4}{9.5097\times10^7}=0.0004206$,
ICER(Strategy 3)$=\frac{1.7551\times10^4-1.9501\times10^4}{1.3008\times10^7-9.5097\times10^7}=0.000024$.
From Table 3.3 it is clear that strategy 3 is strongly dominated by strategy 2. This means that strategy 2 is much costly compared to strategy 3. Thus strategy 3 is more cost effective compared to strategy 2.

Remark 2. *The results of DAR, ACER, and ICER are not same although they demand that strategy 1 is not cost effective. Health policy maker should decide which control will be least cost effective to tackle the disease.*

3.7.4 Cost design analysis

We undertake a cost design analysis and comparison research to determine the appropriateness and cost-effectiveness of these strategies (1, 2, and 3). Figure 3.7 represents the temporal profile of the cost under different types of control profile. In the absence of controls, the produced cost is solely attributable to complications of diabetes (productivity loss), which is extremely high (as indicated in the black color dashed curve in Figure 3.7) since the count of T2 diabetes patients is maximum in this case. Thus disease outbreak not only produces a large epidemic but also imposes a significant financial burden on communities. From Figure 3.7, it also demonstrates that when both the controls are applied, the total corresponding cost is minimal. Also further noticed that cost induced by only treatment control is less than in either case of media control. Thus from this cost design analysis, strategy 2 is economically effective than strategy 1, whereas strategy 3 is highly economically better than all other strategies during the epidemic.

3.7.5 Effect of saturation on the optimal controls and cost function

We vary the saturation constant γ to see how limitations in medical resources affect the optimal control and the cost function. When γ=0 in Figure 3.8a) (i.e recovery of T2 diabetes is sufficiently large), then the number of complications of T2 diabetes is relatively lower than all other values of X_C for positive values of γ. Also Figure 3.8b) demonstrates that by increasing the higher values of γ the corresponding cost is found to be higher under the strategy. To avoid an excessive number of figures we just left the figures under strategy 3 for different values of γ. Consequently, if the treatment is not limited (i.e if γ=0), then not only disease but also economic burden can be minimized using both the control profiles. Next, Figure 3.9 represents optimal controls for different values of γ. It is clear that when saturation constant γ increases then a higher potential of the optimal control u is needed to minimize the disease. In addition, there is no significant impact of the control M by changing the value of γ.

3.8 Discussion and conclusion

Mathematical modeling has become an important theoretical tool for understanding fundamental features of a wide range of medical-biological processes. Dynamics of mathematical modeling of T2 diabetes under appropriate diagnosis, prevention, awareness and recovery of individuals allowing understanding to control the disease. Now researchers have been formulating mathematical models on diabetes mellitus to simulate, analyze, and understand the dynamics of diabetes. Earlier Mollah et al. (Mollah and Biswas [2021]) formulated mathematical models under deterministic as well as the stochastic environment and tried to investigate the dynamics of diabetes mellitus under the effect of awareness. Their results reflect that awareness can prevent diabetes mellitus in the community. A related work Kouidere et al. proposed a mathematical model with optimal control strategy highlighting the impact of behavioral factors on the complication of diabetes (Kouidere et al. [2020]). They showed only the effectiveness of the control techniques but did not evaluate the best possible strategy for controlling the disease. In this regard, the novelty of our proposed model is that effect of media and saturated treatment function are taken as control measures to find out the most cost-effective strategy with the limited resources.

In the present chapter, we propose a mathematical model of T2 diabetes by considering awareness M and treatment u are constant parameters. The complete analysis of the model system (3.2.1) including the positivity of solutions, boundedness, stability is carried out, and Figure 3.2 is plotted for varying values of M and u to

verify their effectiveness in the system (3.2.1). It is observed that both awareness and treatment have a significant impact on the prevalence of complication of T2 diabetes mellitus. Again, we have considered the model system (3.2.1) as an optimal control problem by taking awareness M and saturated treatment u as time depended control parameters to assess the complication of T2 diabetes and financial cost over a finite time. Existence conditions for the optimal solution of the control problem (3.2.1) is discussed and some effective strategies for controlling the disease are identified. We used numerical simulation to verify the control problem (3.2.1) and encountered optimal control solution for the problem, which can minimize the objective functional outcome (3.4.1). From numerical simulations, optimal control strategies have a significant impact on reducing the complication of diabetes in the population has displayed in Figure 3.4. When different types of control strategies are applied in the system (3.2.1) then the complication of diabetes decrease and without complications of diabetes increase. In strategy 3, the graph of complications of diabetes is the least, and the graph of without complications of diabetes is the highest at any time when compared to the other strategies. Thus the result emphasizes that awareness and treatment reduce the complication of diabetes and turn them into without complication of diabetes. Overall in strategy 3, significantly minimizes the prevalence of T2 diabetes than strategy 1 or strategy 2. Also, awareness control M and treatment control u in strategy 3 execute over the entire period but their values are relatively lower than strategy 1 and strategy 2 (See Figure 3.5). Thus in strategy 3, optimal control functions are needed relatively lower potential than strategy 1 and strategy 2 to obtain the least prevalence of the disease. In addition, the results of DAR, ACER, and ICER agreed that strategy 1 is not a cost-effective strategy other than strategy 2 and strategy 3. Also, cost design analysis is performed and the related cost is displayed in Figure 3.9 to establish the most cost effective disease-control strategy with the limited resource. Results showed that if the treatment is not limited, then not only disease prevalence but also economic burden can be minimized using both the control profiles (i.e in strategy 3). Thus, it is very effective for the policymakers to follow the strategy 3. Again, findings of the numerical simulation shows that if the treatment is not limited (i.e if γ=0), then complication of diabetes is remain least for all time in Figure 3.8,a). Also, from Figure 3.9 when saturation constant γ increases then a higher potential of the optimal control u is needed to minimize the disease. Thus from the above substantial outcomes, it is evident that the model is biologically well motivated.

Chapter 4

Impact of awareness program on *Diabetes Mellitus* described by fractional-order model solving by homotopy analysis method.[3]

4.1 Introduction

Diabetes mellitus (DM) is one of the most common diseases, and its prevalence is increasing globally. Diabetes affects 415 million individuals aged 20 to 79 in 2015, 552 million by 2030, and 642 million by 2040, according to current projections (IDF [2011]). Diabetes education can help diabetes patients avoid developing chronic co-morbidities, which have a major influence on their quality of life. Information may assist people in assessing their diabetes risk, encouraging them to seek appropriate medication and care, and inspiring them to take responsibility for their illness for the rest of their lives (Moodley and Rambiritch [2007]). A few components have been related to poor diabetes learning, including lower instructive dimension, more seasoned age, lower pay, shorter diabetes length (Hu et al. [2013], Fenwick et al. [2013], Al-Adsani et al. [2009], Gunay et al. [2006], Firestone et al. [2004], Bruce et al. [2003]). Of course, lower training level has reliably developed as a free hazard factor for constrained diabetes information. Better diabetes education of individuals has been meant that attending to a diabetes instruction course, having medical coverage and home glucose checking (Hu et al. [2013], Fenwick et al. [2013], Gunay et al. [2006], Firestone et al. [2004]). These diabetes educational interventions have consistently

[3] *The bulk of this chapter has been published in Journal of* ***Ricerche di Matematica****, 66 (2021) 61-86.*

been showing to improve diabetes knowledge, fasting glucose, personal satisfaction, self-care activities, HbA1c level, and circulatory strain (Fenwick et al. [2013]). This is not unexpected in some respects because the conductors of non-communicable disease epidemics such as diet, smoking, alcohol consumption, and physical inactivity are self-evidently behavior (Kelly and Barker [2016]). It prevents facing the complexities of cultural, political and financial variables that affect health of people and, consequently strong private desires that may not want individuals to modify their behavior in healthier respect. The behaviors identified with DM are likewise interrelated. For example, poor sleep changes the circulation of leptin and ghrelin levels, which leads to an increase in calorie consumption (Taheri et al. [2004]). There is evidence that energy-dense and sweet meals reduce the stress-induced effects of glucocorticoids in the brain (Dallman et al. [2003]). Instead, growing physical exercise can relieve pressure, partly by encouraging neurohormone manufacturing like norepinephrine connected with enhanced cognitive function and elevated mood (Spring et al. [2012]). However, past the need to alter behaviors, good, lifelong practices need to be developed. Short-term behavioral modifications are often accompanied by relapse, and continuous behavioral change, i.e. maintaining healthy behaviors throughout life, should be a significant objective of future measures. A few components related to constrained diabetes information in this study are modifiable and could be tended to in focused meditations.

For instance, instructive projects to improve diabetes information in the zones of eating routine, work out, blood-sugar levels and testing, and exercises could be created and assessed in clinical and network settings. The roles of diabetes educators and the settings in which they work are changing and increasing because of the diabetes epidemic and its huge fitness and financial burden, powerful diabetes care and prevention is developing precedence among clinicians and policymakers alike. Education is the main key additives in making sure higher treatment and control of diabetes. To assist diabetes patients accomplish this objective, patients, families, medical attendants and medicinal services doctors need large amounts of information and mindfulness about DM pathology, chance components, the board, and entanglements. Finally, it is necessary that increasing education on diabetes and related complexities can improve the patient's consistency to treatment and health-related plans (Deepa et al. [2014]). In this manner, social insurance establishments must encourage diabetes training and receive educational interventions to help and improve diabetes anticipation and management.

Fractional calculus has been applying to the mathematical model over the decades because of its theory of applications in several real problems in a vast area in the field

of science and engineering (Podlubny [1999], Luchko and Gorenflo [1998], Miller and Ross [1993]). Many researchers have been attracted to fractional derivatives due to the importance of their applications in fluid dynamics, biology, physics, epidemiology, engineering, and many others. The fact that in most cases the real problem of the physical behavior does not depend only at the instant time but also on the previous time of interval, which may be obtained by using a fractional derivative. Integer order derivative system is a sub case of fractional derivative we can easily get the solution of the ordinary differential equation from FODE's by putting the derivative order equal to unity. Also, FDE's can be able to minimize the error occurring in the model system due to neglecting some parameters. Most of the FDE's generated by physical or biological situations are highly nonlinear and hence to find the solutions to these problems is very difficult. There are several analytic techniques are available likewise Adomian decomposition method (ADM), Variational iteration method (VIM). In 1992 Liao proposed HAM which is very effective and easily use to solve any kind of nonlinear models without linearization, perturbation or discretization. Homotopy is a fundamental topic of topology and geometry, based on it HAM generates a successive approximation of the solution that converges to the exact solution of the considered problem. The method is applicable for arbitrary parameter values and it has great freedom to chose a suitable linear operator and base function to approximate the exact solution of the nonlinear problems and also by using proper value of an auxiliary parameter that gives a way to regulate and enlarge the convergence region and increase the rate of convergence of the series solutions. The HAM has been used in a variety of fields of mathematics and engineering. In recent years HAM also applied to the population model, prey-predator model, chaos, etc. Many mathematicians and researchers have been studying the fractional-order model as well as deterministic model on diabetes mellitus and its related complications but they have not talked about the awareness of diabetes among individuals which can minimize the disease (Dubey and Goswami [2021], Zhang et al. [2019], Srivastava et al. [2019], Singh et al. [2018], Ding et al. [2011]). The primary goal of this chapter is to study the number of diabetic patients in the population by providing awareness among the population by a fractional-order model.

This chapter is arranged in this way: In *Sect.* 4.2, we develop a mathematical model based on certain fundamental assumptions and hypotheses. We provide some essential concepts and outcomes that will be used in our work in *Sect.* 4.3. In *Sect.* 4.4, the systematic approach of HAM introduced. An analytical procedure of the homotopy analysis method is carried out by using residual approach and ratio approach to find out the optimal value of the convergence control parameter in *Sect.* 4.5. In

Sect. 4.6 numerical simulations were performed with a specific set of parameter values. We also performed local sensitivity analysis and parameter estimation of the model. Finally, this chapter ends with a conclusion in *Sect.* 4.7.

4.2 Model formulation

In this section, we have formed a mathematical model to study the dynamics Diabetes Mellitus, where the total human population is $N^1(t_1)$ at instant t_1. The whole population of human is subdivided into two sub-classes, namely susceptible humans $S^1(t_1)$, diabetic humans $X^1(t_1)$ and the constant rate of immigration in form of unaware susceptible is A^1. Patients will have access to treatment as quickly as feasible if awareness measures, such as proper diabetes information and education, are implemented through a media campaign in diabetes-prone areas. The whole susceptible population $S^1(t_1)$ is partitioned into two subclasses: the unaware susceptible humans $S_U^1(t_1)$ and the aware humans $S_A^1(t_1)$. As education and awareness spreads, people react to it and eventually alter their behavior to change their sensitivity (Mollah and Biswas [2021], Bansode and Nagarajan [2017], Nazar et al. [2016], Deeb [2008]). Let $M^1(t_1)$ denote the cumulative density of media-driven diabetes awareness and education programs in that region at instant t_1. The awareness campaign will be effective only if persons at the hazard of diabetes become aware of the need to take action to avoid diabetes and those who currently have diabetes receive the quality of treatment they deserve (Lefèbvre and Pierson [2004]). People with a family history of diabetes would also wish to know about diabetes since they have encountered symptoms, causes, and diabetes treatment (Foma et al. [2013]). So, we assumed that the rate of change of cumulative density of awareness programs $M^1(t_1)$ is proportional to the number of diabetic individuals (Misra et al. [2011]). The fact that diabetes does not pass from humans to humans is well known. Diabetes is some kind of metabolic disorder triggered by pancreas hereditary and/or obtained insulin manufacturing defect or insulin ineffectiveness. We assume that the unaware susceptible becomes diabetic at a rate of β^1. Incidence of diabetes is less likely of an aware population (Mollah and Biswas [2021], Nazar et al. [2016], Deeb [2008]).

All the diabetic patients are a member of families and those who have a diabetes ancestry will most likely become more aware as their likeness because they are going with their patients to the center aided their consideration or remain with them at the medical clinic. Henceforth they have encountered about the manifestations, causes, the executives for this disease. Educated individuals have enough knowledge among all parts of diabetes mellitus. They may have gained from college or more

probable from the web, magazines, books or various type of diabetes awareness program (Kurian et al. [2016], Baptiste-Roberts et al. [2007], Baranowski et al. [2003]). So, we have taken unaware susceptible humans become aware at a rate λ^1, where λ^1 is the implementation rate at which unaware susceptible individuals become aware susceptible and it is proportional to number of diabetes population X^1.

Most of the above key assumptions are taken from (Mollah and Biswas [2021], Das et al. [2020], Samanta and Chattopadhyay [2014], Samanta et al. [2013]). Taking the foregoing facts into account, we have developed a nonlinear mathematical model of diabetes mellitus under education and awareness:

$$\begin{aligned}
\frac{dS_U^1}{dt_1} &= A^1 - \lambda^1 S_U^1 M^1 - \beta^1 S_U^1 - dS_U^1, \\
\frac{dS_A^1}{dt_1} &= \lambda^1 S_U^1 M^1 - \beta^1 \beta_1 S_A^1 - dS_A^1, \\
\frac{dX^1}{dt_1} &= \beta^1 S_U^1 + \beta^1 \beta_1 S_A^1 - (d + e^1) X^1, \\
\frac{dM^1}{dt_1} &= \mu^1 X^1 - e_0^1 M^1,
\end{aligned} \tag{4.2.1}$$

with initial sizes $S_U^1(0) = S_{U_0}^1 > 0$, $S_A^1(0) = S_{A_0}^1 > 0$, $X^1(0) = X_0^1 > 0$, $M^1(0) = M_0^1 > 0$.

The parameters used in the model (4.2.1) are described as follows: incident rate of diabetes mellitus is denoted by β^1. $\beta^1\beta_1$ is a lower incident rate of diabetes mellitus of the aware susceptible humans (Nazar et al. [2016], Deeb [2008]). The unit less number β_1 is the reduced probability of diabetes mellitus and $0< \beta_1 <1$. The constants d^1, e^1 are the natural death rate and additional death rate of human due to diabetes respectively. The proportionality constant μ^1 regulates the deployment of awareness campaigns. There are several barriers for introducing awareness among people (Bansode and Nagarajan [2017], Shashank et al. [2008]). The parameter e_0 denotes the depletion rate due to ineffectiveness, social, economic, lack of accessibility to health, and psychological obstacles in the population, among other factors (Bansode and Nagarajan [2017], Shashank et al. [2008]).

We make the above system non-dimensionalized under the the following transformations:

$$S_U = \frac{S_U^1}{S_{U_0}^1}, \quad S_A = \frac{S_A^1}{S_{U_0}^1}, \quad X = \frac{X^1}{S_{U_0}^1}, \quad M = \frac{M^1}{S_{U_0}^1}, \quad t_1 = \frac{t}{\lambda^1 S_{U_0}^1}.$$

Then the system (4.2.1) transformed in the following form:

$$\begin{aligned} \frac{dS_U}{dt} &= A - S_U M - \beta S_U - dS_U, \\ \frac{dS_A}{dt} &= S_U M - \beta\beta_1 S_A - dS_A, \\ \frac{dX}{dt} &= \beta S_U + \beta\beta_1 S_A - (d+e)X, \\ \frac{dM}{dt} &= \mu X - e_0 M, \end{aligned} \tag{4.2.2}$$

and the corresponding parameters are transformed in the form

$$A = \frac{A^1}{\lambda^1 (S^1_{U_0})^2}, \quad \beta = \frac{\beta^1}{\lambda^1 S^1_{U_0}}, \quad d = \frac{d^1}{\lambda^1 S^1_{U_0}}, \quad e = \frac{e^1}{\lambda^1 S^1_{U_0}},$$
$$\mu = \frac{\mu^1}{\lambda^1 S^1_{U_0}}, e_0 = \frac{e^1_0}{\lambda^1 S^1_{U_0}}.$$

Diabetes is a behavioral disease and many behavioral factors play important roles in making diabetes more complicated in human body. People past behavior may seem rather obvious to influence future behavioral decisions. It may seem appropriate to assume that individuals are more likely to use their previous behavior as a foundation for their future behavioral decisions, if they do not have the motivation or capacity to think carefully about the implications of making those choices at the moment (Albarracin and Wyer Jr [2000]). Thus, modeling phenomena is dependent on prior time, which may be accomplished by using fractional calculus. Recently, a large amount of research has been conducted on the application of fractional differential equations in a variety of applications such as liquid dynamics, visco-elasticity, biology, physics, and chemistry (Dubey and Goswami [2021], Srivastava et al. [2019], Singh et al. [2018], Arqub and El-Ajou [2013], Lakshmikantham et al. [2009], Kilbas et al. [2006]).

In this chapter, we would like to analyze the behavior of the fractional diabetes awareness model by replacing the fractional differential operator to the linear differential operator in model system (4.2.2). Then, we get the following fractional diabetes awareness model as follows

$$\begin{aligned} D^{\mu_1}_* S_U &= A - S_U M - \beta S_U - dS_U, \\ D^{\mu_2}_* S_A &= S_U M - \beta\beta_1 S_A - dS_A, \\ D^{\mu_3}_* X &= \beta S_U + \beta\beta_1 S_A - (d+e)X, \\ D^{\mu_4}_* M &= \mu X - e_0 M, \end{aligned} \tag{4.2.3}$$

where $D^{\mu_i}_*$ represents the fractional order derivative operator with the sense of Caputo with $0 < \mu_i \leq 1$, i=1, 2, 3, 4.

4.3 Some preliminaries

In order to do the analysis of the model, we first give some very useful definitions and properties of the fractional derivative which we will use in the current chapter. We adopt *Caputo's* definition of fractional order derivative and *Riemann Lioville* integral definition (Calcagni [2012], Podlubny [1999], Luchko and Gorenflo [1998], Miller and Ross [1993], Oldham and Spanier [1974]).

Definition 1. A function $f : (0, \infty) \to \mathbf{R}$ is said to belong to the space C_μ, $\mu \in \mathbf{R}$, if we find a number $p > \mu$ $(p \in \mathbf{R})$ such that: $f(t) = t^p f_1(t)$, where $f_1 : (0, \infty) \to \mathbf{R}$, and it is said to belong to the space C_μ^n if and only if $h(n) \in C_\mu$, $n \in \mathbf{N}$, where $h : (0, \infty) \to \mathbf{R}$ is a function.
Clearly, $C_\mu \subset C_k$ if $k \leq \mu$.

Definition 2. Let $f : (0, \infty) \to \mathbf{R}$ be a function and $f \in C_\mu$, $\mu \geq -1$. Then the *Riemann-Liouville* fractional integral operator (J^α), $\alpha > 0$ is defined as:
$J^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} f(s) ds$, $J^0 f(t) = f(t)$, where $\Gamma(\alpha)$ denotes the *Gamma* function.

Basic properties of the operator J^α are mentioned below:
For $f \in C_\mu$, $\mu \geq -1$, $\alpha, \beta \geq 0$ and $\gamma \leq -1$, then we have
i) $J^\alpha J^\beta f(t) = J^{\alpha+\beta} f(t) = J^\beta J^\alpha f(t)$,
ii) $J^\alpha t^\gamma = \frac{\Gamma(\gamma+1)}{\Gamma(\alpha+\gamma+1)} t^{\alpha+\gamma}$.

Definition 3. *Caputo* fractional derivative of $f \in C_{-1}^n$ is defined by
$D_*^\alpha f(x) = J^{n-\alpha}(D^n f(x))$, $n - 1 < \alpha \leq n$, where $n \in \mathbf{N}$ and α is the order of the derivative. In addition, two use full properties are stated about them.
(1) $D_*^\alpha J^\alpha f(t) = f(t)$,
(2) $J^\alpha D_*^\alpha f(t) = f(t) - \sum_{k=0}^{n-1} f^{(k)}(0^+) \frac{t}{k!}$, $\quad t > 0$.

4.4 Systematic approach of HAM

The HAM was developed by Chinese mathematician Shijun Liao in between 1991s to 2010s also many researchers has been involved in its theory and applications (Correia Ramos [2018], Duarte et al. [2018], Arqub and El-Ajou [2013], Shijun [1998], Liao [1992, 2003, 2004, 2006], Liao and Cheung [2003]). Now we summarize the systematic way of this method to understand properly and then we will find an approximate

solution of the fractional order model by implementing this scheme. We consider differential equation with parameter derivative.

$$N[D_*^\alpha] = 0, \quad \alpha > 0, \tag{4.4.1}$$

where N denotes the non-linear operator, D_*^α is the fractional derivative defined in *Sect.* 4.3 and $f(t)$ is any function of the variable t. For simplicity, a continuous mapping from f(t)$\rightarrow$ $\phi(t,q)$, the homotopy embedding parameter q changes from 0 to 1. This means that $\phi(t,q)$ changes from the initial approximation $f_0(t)$ to the exact solution $f(t)$. Liao (Liao [1992]) constructs $zero^{th}$-order deformation equation as follows

$$(1-q)L[\phi(t;q) - f_0(t)] = qhH(t)N[D_*^\alpha \phi(t,q)], \tag{4.4.2}$$

where L denotes the auxiliary linear operator such that $L(0) = 0$, $h(\neq 0)$ is an auxiliary parameter, $H(h,t)(\neq 0)$ denotes auxiliary function, and $\phi(t,q)$ is a function of two variables t and q. HAM must have adequate flexibility in selecting the auxiliary parameter h.
When we expand $\phi(t,q)$ in the *Taylor* series about q, we get

$$\phi(t,q) = f_0(t) + \sum_{m=1}^{\infty} f_m(t) q^m, \tag{4.4.3}$$

with

$$f_m(t) = \frac{1}{m!} \frac{\partial^m \phi(t,q)}{\partial q^m} \mid_{q=0} . \tag{4.4.4}$$

Taking the convergence of the homotopic series into account and applying the relation $\phi(t,1) = f(t)$, and substituting $q = 1$ in (4.4.3), we have the series solution:

$$f(t) = f_0(t) + \sum_{m=1}^{\infty} f_m(t), \tag{4.4.5}$$

which is the required series solution of the differential equation (4.4.1).
Differentiating (4.4.2) m-times w.r.t embedding parameter q then putting $q = 0$ and dividing them by $m!$ and then applying (4.4.4), we get the so-called m-th order deformation equation as follows

$$L[f_m(t) - \chi_m f_{m-1}(t)] = hH(t)R_m[f_1(t), f_2(t), ..., f_{m-1}(t)], \tag{4.4.6}$$

where

$$R_m[f_1(t), f_2(t), ..., f_{m-1}(t)] = \frac{1}{(m-1)!}\frac{\partial^{m-1} N_*[\phi_1(t,q),\phi_2(t,q)...\phi_n(t,q)]}{\partial q^{m-1}}|_{q=0} \tag{4.4.7}$$

and $\chi_m = \begin{cases} 0 \quad , \quad n \leq 1 \ , \\ 1 \quad , \quad n > 1. \end{cases}$

Now the higher order deformation equation is controlled by the same linear operator L and the term $R_m[f_1(t), f_2(t), ..., f_{m-1}(t)]$ can be expressed simply by $f_1(t), f_2(t), ..., f_{m-1}(t)$ and also partial differential is a linear operator. So, we get a one-parameter family of power series solution which is obtained by solving the higher-order deformation equation one after the other, which can be easily symbolically solved by MATLAB or MATHEMATICA.
Operating both sides by L^{-1}, we get

$$f_m(t) = \chi_m f_{m-1}(t) + hL^{-1}H(t)R_m[f_1(t), f_2(t), ..., f_{m-1}(t)]. \tag{4.4.8}$$

4.5 Solution of the fractional-order diabetic model

From the previous discussion, we will find the solution of the fractional-order model by using HAM. At first we take the initial approximations $S_{U_0}(t)$, $S_{A_0}(t)$, $X_0(t)$, $M_0(t)$ of $S_U(t)$, $S_A(t)$, $X(t)$, $M(t)$ and the auxiliary linear operators are
$L[\phi_i(t,q)] = D_*^{\alpha}[\phi_i(t,q)]$, where $0 < \alpha_i \leq 1$, i=1,2,3,4,
with the properties that $L[C_i] = 0$ and $C_i (i = 1, 2, 3, 4)$ are integral constants.
Thus we define the following non-linear operators from the fractional diabetes awareness model (4.2.3):

$$\begin{aligned} N_1[\phi_1(t,q)] &= D_*^{\mu_1}[\phi_1(t,q)] - A + \phi_1(t,q)\phi_4(t,q) + (\beta + d)\phi_1(t,q), \\ N_2[\phi_2(t,q)] &= D_*^{\mu_2}[\phi_2(t,q)] - \phi_1(t,q)\phi_4(t,q) + (\beta\beta_1 + d)\phi_2(t,q), \\ N_3[\phi_3(t,q)] &= D_*^{\mu_3}[\phi_3(t,q)] - \beta\phi_1(t,q) - \beta\beta_1\phi_2(t,q) + (d+e)\phi_3(t,q), \\ N_4[\phi_4(t,q)] &= D_*^{\mu_4}[\phi_4(t,q)] - \mu\phi_3(t,q) + e_0\phi_4(t,q). \end{aligned} \tag{4.5.1}$$

Let $h(\neq 0)$ and $H_i(\neq 0)$ represent the so-called *auxiliary parameter* and *auxiliary function* respectively.
Considering the embedding parameter q in [0,1], the $zero^{th}$ order deformation equa-

tions are:

$$\begin{aligned}(1-q)L[\phi_1(t,q)-S_{U_0}(t)] &= qhH_1(t)N_1[\phi_1(t,q)],\\ (1-q)L[\phi_2(t,q)-S_{A_0}(t)] &= qhH_2(t)N_2[\phi_2(t,q)],\\ (1-q)L[\phi_3(t,q)-X_0(t)] &= qhH_3(t)N_3[\phi_3(t,q)],\\ (1-q)L[\phi_4(t,q)-M_0(t)] &= qhH_4(t)N_4[\phi_4(t,q)],\end{aligned} \tag{4.5.2}$$

and subject to the initial conditions:
$\phi_1(0,q)=S_{U_0}(t)$, $\phi_2(0,q)=S_{A_0}(t)$, $\phi_3(0,q)=X_0(t)$, $\phi_4(0,q)=M_0(t)$.
Therefore, for $q=0$ and $q=1$, $zero^{th}$ order deformation equations (4.5.2) becomes:
$\phi_1(t,0)=S_{U_0}(t), \phi_2(t,0)=S_{A_0}(t), \phi_3(t,0)=X_0(t), \phi_4(t,0)=M_0(t)$;
and $\phi_1(t,1)=S_U(t), \phi_2(t,1)=S_A(t), \phi_3(t,1)=X(t), \phi_4(t,1)=M(t)$, respectively.
When the parameter q changes from 0 to 1 the functions $\phi_1(t,q), \phi_2(t,q)$, $\phi_3(t,q)$, and $\phi_4(t,q)$ varies from S_{U_0}, S_{A_0}, X_0 and M_0 to the exact solutions $S_U(t)$, $S_A(t)$, $X(t)$ and $M(t)$, respectively. Next, expanding $\phi_1(t,q)$, $\phi_2(t,q)$, $\phi_3(t,q)$, and $\phi_4(t,q)$ in *Maclaurin's* series w.r.t q, we obtain the following power series:

$$\begin{aligned}\phi_1(t,q) &= S_{U_0}(t)+\textstyle\sum_{m=1}^{\infty} S_{U_m}(t)q^m,\\ \phi_2(t,q) &= S_{A_0}(t)+\textstyle\sum_{m=1}^{\infty} S_{A_m}(t)q^m,\\ \phi_3(t,q) &= X_0(t)+\textstyle\sum_{m=1}^{\infty} X_m(t)q^m,\\ \phi_4(t,q) &= M_0(t)+\textstyle\sum_{m=1}^{\infty} M_m(t)q^m,\end{aligned} \tag{4.5.3}$$

where

$$\begin{aligned}S_{U_m}(t) &= \tfrac{1}{m!}\tfrac{\partial^m\phi_1(t,q)}{\partial q^m}|_{q=0},\\ S_{A_m}(t) &= \tfrac{1}{m!}\tfrac{\partial^m\phi_2(t,q)}{\partial q^m}|_{q=0},\\ X_m(t) &= \tfrac{1}{m!}\tfrac{\partial^m\phi_3(t,q)}{\partial q^m}|_{q=0},\\ M_m(t) &= \tfrac{1}{m!}\tfrac{\partial^m\phi_4(t,q)}{\partial q^m}|_{q=0}.\end{aligned} \tag{4.5.4}$$

Now, we have to choose h so that the series (4.5.3) is convergent at $q=1$.
From the equation (4.5.3), we get the homotopy series solutions

$$\begin{aligned}S_{U_m}(t) &= S_{U_0}(t)+\textstyle\sum_{m=1}^{\infty} S_{U_m}(t),\\ S_{A_m}(t) &= S_{A_0}(t)+\textstyle\sum_{m=1}^{\infty} S_{A_m}(t),\\ X_m(t) &= X_0(t)+\textstyle\sum_{m=1}^{\infty} X_m(t),\\ M_m(t) &= M_0(t)+\textstyle\sum_{m=1}^{\infty} M_m(t).\end{aligned} \tag{4.5.5}$$

Again, from the so-called m^{th} order deformation equations (4.4.6) and (4.4.7), we have

$$\begin{aligned} L_1[S_{U_m}(t) - \chi_m S_{U_{m-1}}(t)] = &\quad hH_1(t)R_* S_{U_m}(\overrightarrow{S}_{U_{m-1}}(t)), m = 1, 2, 3, ..., \\ L_2[S_{A_m}(t) - \chi_m S_{A_{m-1}}(t)] = &\quad hH_2(t)R_* S_{A_m}(\overrightarrow{S}_{A_{m-1}}(t)), m = 1, 2, 3, ..., \\ L_3[X_m(t) - \chi_m X_{m-1}(t)] = &\quad hH_3(t)R_* X_m(\overrightarrow{X}_{m-1}(t)), m = 1, 2, 3, ..., \\ L_4[M_m(t) - \chi_m M_{m-1}(t)] = &\quad hH_4(t)R_* M_m(\overrightarrow{M}_{m-1}(t)), m = 1, 2, 3, ..., \end{aligned} \tag{4.5.6}$$

with the initial sizes,

$$S_{U_m}(0) = 0, S_{A_m}(0) = 0, X_m(0) = 0, M_m(0) = 0, \tag{4.5.7}$$

where

$$R_* S_{U_m}(\overrightarrow{S}_{U_{m-1}}(t)) = D_*^{\mu_1} S_{U_{m-1}}(t) + \sum_{i=0}^{m-1} S_{U_i}(t) M_{m-1-i}(t) + (\beta + d) S_{U_{m-1}}(t)$$

$$-A(1 - \chi_m),$$

$$R_* S_{A_m}(\overrightarrow{S}_{A_{m-1}}(t)) = D_*^{\mu_2} S_{A_{m-1}}(t) + \sum_{i=0}^{m-1} S_{U_i}(t) M_{m-1-i}(t) + (\beta\beta_1 + d) S_{A_{m-1}}(t),$$

$$R_* X_m(\overrightarrow{X}_{m-1}(t)) = D_*^{\mu_3} X_{m-1}(t) - \mu S_{U_{m-1}}(t) - \beta\beta_1 S_{A_{m-1}}(t) + (d + e) X_{m-1}(t),$$

$$R_* M_m(\overrightarrow{M}_{m-1}(t)) = D_*^{\mu_4} M_{m-1}(t) - \mu X_{m-1} + e_0 M_{m-1}(t).$$

Setting H_i(t)=1, and $L_i = D_*^{\mu_i}$ for $i = 1, 2, 3, 4$. Then right inverse of $D_*^{\mu_j}$ is J^{μ_j}, the $Riemann - Liouville$ fractional integral operator defined in *Sect.* 4.3. The solution of the m^{th} order deformation equation (4.5.6) at initial conditions (4.5.7) is given by

$$\begin{aligned} S_{U_m}(t) = &\quad \chi_m S_{U_{m-1}}(t) + hJ^{\mu_1}[R_* S_{U_m}(\overrightarrow{S}_{U_{m-1}}(t)], \\ S_{A_m}(t) = &\quad \chi_m S_{A_{m-1}}(t) + hJ^{\mu_2}[R_* S_{A_m}(\overrightarrow{S}_{A_{m-1}}(t)], \\ X_m(t) = &\quad \chi_m X_{m-1}(t) + hJ^{\mu_3}[R_* X_m(\overrightarrow{X}_{m-1}(t))], \\ M_m(t) = &\quad \chi_m M_{m-1}(t) + hJ^{\mu_4}[R_* M_m(\overrightarrow{M}_{m-1}(t))]. \end{aligned} \tag{4.5.8}$$

Then, from this recursion relation we can calculate up to M^{th} order homotopy terms, which is an approximation of the homotopy series (4.5.5).
Finally, taking few number of terms from the beginning in series (4.5.5), approximate solutions of $S_U(t)$, $S_A(t)$, $X(t)$, $M(t)$ of the M^{th} order approximation solutions

(corresponding to $M+1$ term) is given by:

$$\begin{aligned}\psi_{S_{U_m}}(t) &= S_{U_0}(t) + \sum_{m=1}^{M} S_{U_m}(t),\\ \psi_{S_{A_m}(t)} &= S_{A_0}(t) + \sum_{m=1}^{M} S_{A_m}(t),\\ \psi_{Xm(t)} &= X_0(t) + \sum_{m=1}^{M} X_m(t),\\ \psi_{Mm(t)} &= M_0(t) + \sum_{m=1}^{M} M_m(t).\end{aligned} \tag{4.5.9}$$

4.5.1 Optimal convergence control parameter

The homotopy series solution is dependent on the physical variable t and the convergence control parameter h. The parameter h can be selected so that it ensure the interval of convergence and increase the rate of convergence, that reach the solution at a quickest rate. This is the beauty of HAM that differs from any other analytical techniques. So, how to find such h that gives a proper interval of convergence together with convergence will be faster? Therefore, we will discuss in this section the two best approaches to find h.

4.5.1.1 Squared residual approach for finding optimal value of h

This is the well known approach to find the value of h in HAM. In this method we substitute the Homotopy approximate series solution and the initial conditions into the original governing system of equations (4.2.3) and then we compute the related residual error functions as follows:

$$\begin{aligned}R_{S_U}(h_{S_U},t) &= D_*^{\mu_1}[\psi_1(t,h_{S_U})] - A + \psi_1(t,h_{S_U})\psi_4(t,h_M) + (\beta+d)\psi_1(t,h_{S_U}),\\ R_{S_A}(h_{S_A},t) &= D_*^{\mu_2}[\psi_2(t,h_{S_A})] - \psi_1(t,h_{S_U})\psi_4(t,h_M) + (\beta\beta_1+d)\psi_2(t,h_{S_A}),\\ R_X(h_X,t) &= D_*^{\mu_3}[\psi_3(t,h_X)] - \beta\psi_1(t,h_{S_U}) - \beta\beta_1\psi_2(t,h_{S_A}) + (d+e)\psi_3(t,h_X),\\ R_M(h_M,t) &= D_*^{\mu_4}[\psi_4(t,h_M)] - \mu\psi_3(t,h_X) + e_0\psi_4(t,h_M).\end{aligned} \tag{4.5.10}$$

When these residual error functions tend to zero, then HAM solution is also approach to the original solution. Yabushita et al. (Yabushita et al. [2007]) gave an optimization method to find convergence control parameter by using squared residual error technique. After that inspired by his work many researchers have been using this technique to obtain convergence control parameter (Duarte et al. [2018], Arqub and El-Ajou [2013], Liao [2010]). Thus we consider squared residual error to find convergence control parameter for respective component functions.
$SRE_{S_U}(h) = \int_0^1 [R_{S_U}(h_{S_U},t)]^2 dt$, $SRE_{S_A}(h) = \int_0^1 [R_{S_A}(h_{S_A},t)]^2$,
$SRE_X(h) = \int_0^1 [R_X(h_X,t)]^2$, $SRE_M(h) = \int_0^1 [R_M(h_M,t)]^2$.
We have to find the respective value of h for which $SRE_{S_U}(h)$, $SRE_{S_A}(h)$, $SRE_X(h)$, $SRE_M(h)$ are minimum, which can be obtained by solving the equations

$\frac{d}{dh}[SRE_{S_U}(h)] = 0$, $\frac{d}{dh}[SRE_{S_A}(h)] = 0$, $\frac{d}{dh}[SRE_X(h)] = 0$, $\frac{d}{dh}[SRE_M(h)] = 0$.
Then the respective values of h are optimal value for which the functions $SRE_{S_U}(h)$, $SRE_{S_A}(h)$, $SRE_X(h)$, $SRE_M(h)$ are minimum, we denoted $h^*_{S_U}, h^*_{S_A}, h^*_X, h^*_M$ are their respective optimal values of h.

4.5.1.2 Ratio approach for finding interval and optimal value of h

The aforesaid squared residual approach for finding optimal value of h is theoretically rigorous and not always be efficient. Consequently a better and more efficient technique always be targeted. For this purpose here we describe another useful convergence criterion addressed in (Liao [2013]) for identifying value of h.
First we consider $f_0, f_1, f_2, ..., f_k$ are the k+1 homotopy terms from the series (4.5.9)

$$f(t) \quad = \quad f_0(t) + \sum_{m=1}^{k+1} f_m(t),$$

and also magnitude of the ratio defined by

$$\left| \frac{f_{k+1}(t)}{f_k(t)} \right|. \tag{4.5.11}$$

Now, for preassigned value of h, if this ratio is less then unity then convergence of the solution series is guaranteed. But for the faster rate of convergence of the homotopy solution towards the exact solution, we should keep this ratio so close to zero as possible. This is a sufficient criterion for the HAM solution to be converged. In addition, we need to find an optimal value of h that gives this ratio so close to zero. We consider L^2 in the ratio (4.5.11), this would be very easier than squared residual approach. Taking time interval Ω, (4.5.11) becomes

$$\beta \quad = \quad \frac{\int_\Omega [f_k(t)]^2 dt}{\int_\Omega [f_{k-1}(t)]^2 dt}.$$

This is the proper way for computing the convergence control parameter h. For suitable approximation, we draw the figure β versus h, then it not only shows the effective region of the convergence but also gives the optimal value of h for which β is minimum.
This can be done simultaneously by practically plotting β versus h in such a way that

$$\beta = \frac{\int_\Omega [f_k(t)]^2 dt}{\int_\Omega [f_{k-1}(t)]^2 dt} < 1 \qquad and \qquad \frac{d\beta}{dh} = 0. \tag{4.5.12}$$

Table 4.1: Parameter description and their corresponding values used for this chapter

Dimensional Parameters	Biological Meaning	Dimensional Values	Dimensionless Parameters	Dimensionless Values
A^1	Constat rate of immigration	2.0×10^4	A	4.1×10^{-4} Puram [2019]
λ^1	Implementation rate from US to AS	2.0×10^{-4}	–	– Samanta et al. [2013]
β^1	Incidence rate of DM	8.8×10^{-3}	β	8.8×10^{-5} Rowley et al. [2017]
e^1	Additional death rate due to DM	3.0×10^{-2}	e	3.0×10^{-4} Tripathy [2018]
d^1	Natural death rate	1.0×10^{-2}	d	1.0×10^{-4} Misra et al. [2011]
μ^1	Implementation rate of awareness program	5.0×10^{-4}	μ	5.0×10^{-6} Misra et al. [2011]
e_0^1	Depletion rate of awareness program	6.0×10^{-2}	e_0	6.0×10^{-4} Misra et al. [2011]
β_1	Reduce factor of incidence rate of DM		β_1	5.0×10^{-3}

4.6 Numerical simulations

We used the parameter values given in the Table 4.1 to perform numerical simulations for validate our analytical findings. The model parameters are derived from a variety of studies and existing literatures. Thus, we perform a sensitivity analysis to understand the most sensitive parameters with respect to the diabetic human X.

4.6.1 Local sensitivity analysis and parameter estimation

The local sensitivity analysis governs the impact of changes in parameter values of the model output. Due to the worked by Martin Fink et al. (Fink et al. [2008]), we get a sensitivity graph using the code developed by Martin Fink (Fink [2006]) by using automatic differentiation (myAD code) (see the sensitivity Figure 4.1(a)). From the sensitivity Figure 4.1(a) it is quite to difficult to recognize the most sensitive parameters with respect to the diabetic human X. To identity the sensitive parameters from the figure, we compute the sensitivity coefficient by non-dimensionalizing the sensitivity functions and by calculating L2-norm of the resulting functions, stated as

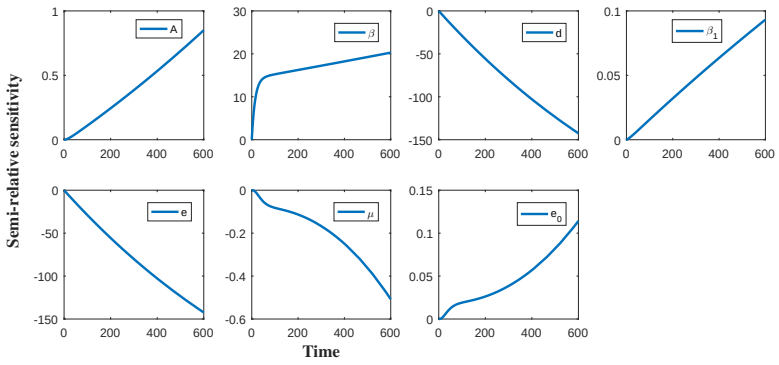
$$\xi_{ij} = \left\| \frac{\partial x_i}{\partial q_j} \frac{q_j}{\max x_i} \right\|_2^2 = \int_{t_0}^{t_f} \left| \frac{\partial x_i}{\partial q_j} \frac{q_j}{\max x_i} \right|^2 dt.$$

By using the above defined L2-norm, we compare and rank the sensitivity function, then identify the most influential parameters (in descending order) (Banerjee et al. [2015]) to the least ones (see the Figure 4.1(b)), which designates that the parameters d, e and β are the most sensitive parameters, together along with A, μ, β_1, and e_0.

A parameter is called practically identifiable if a unique estimation can be acquired

from various initial values using the existing data. After calculating the normalized sensitivity function matrix S by applying automatic differentiation (AD) (Fink [2006]), we define the *Fisher's* information matrix $K = S^T S$. It can be observed that the m parameters are locally identifiable iff the column rank of the matrix S is equal to m, or equivalently $\det(S^T S) \neq 0$. Then, we apply the QR factorization policy with the column pivoting that is implemented in the MATLAB routine qr, $[Q,\ R,\ P] = qr(K)$. This procedure indicates a permutation matrix P in such a way that $KP = QR$ (i.e QR being the factorization of KP). The indices in the first k-columns of P recognize the k-parameters that are most estimable. Here, d, e, and β are the system parameters that are most sensitive from the sensitivity analysis.

a)



b)

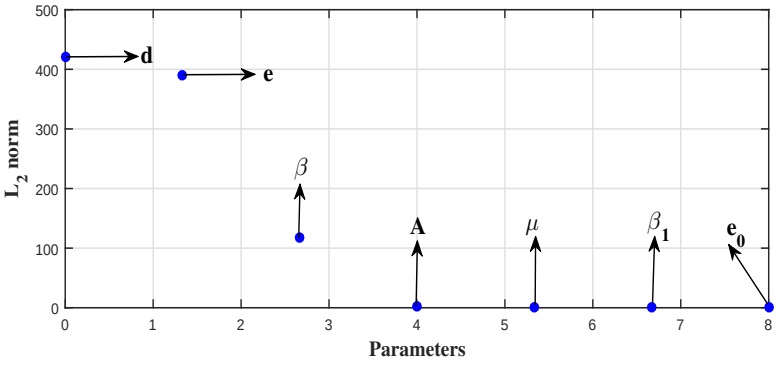


Figure 4.1: Semi-relative sensitivities of the parameters using automatic differentiation and the associated L_2-norm. (a) Sensitivity of the model parameters is identified by the maximum deviation with respect to the state variable X (along y-axis). It can also be identified the time intervals when the system is most sensitive to such changes. (b) Quantification of the sensitivity coefficient by computing the L_2-norm.

The HAM gives an approximate analytical solution of the non-linear fractional differential equation in the form of an infinite power series. We need to practical task to evaluate and analyze this solution.

For numerical simulation we used the parameter values which are given in Table 4.1. To analyze explicitly of the model system, we consider the behavior of the solutions of the model system for distinct values of the parameters μ_i, $i = 1, 2, 3, 4$. For this we consider the following two cases:

4.6.2 Case 1

In this case, we analyze the fractional-order diabetes awareness model when $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1$. We determined the partial sums up to eight order approximations for $S_U(t)$, $S_A(t)$, $X(t)$, $M(t)$ respectively, which are given below:

$\phi_{S_U,k}(t) = \sum_{m=0}^{8} S_{U_m}(t)$=$468+13.3664ht+46.7824h^2t+93.5648h^3t+116.956h^4t+93.5648h^5t+46.7824h^6t+13.3664h^7t+1.6708h^8t-61.76h^2t^2+...-0.000123995h^8t^6-2.294910^{-6}h^7t^7-2.0080410^{-6}h^8t^7+4.2546710^{-9}h^8t^8$,

$\phi_{S_A,k}(t) = \sum_{m=0}^{8} S_{A_m}(t)$=$432-153.55ht$-$537.425h^2t-1074.85h^3t-1343.56h^4t-1074.85h^5t-537.425h^6t-153.55h^7t-19.1938h^8t+61.4982h^2t^2+...+0.000165348h^6t^6+0.000283454h^7t^6+0.000124011h^8t^6+2.294710^{-6}h^7t^7+2.0078610^{-6}h^8t^7-4.2557510^{-9}h^8t^8$,

$\phi_{X,k}(t) = \sum_{m=0}^{8} X_m(t)$=$100+1.78368ht+6.24288h^2t+12.4858h^3t+15.6072h^4t+12.4858h^5t+6.24288h^6t+1.78368h^7t+0.22296h^8t+0.0258351h^2t^2+...-1.6604310^{-8}h^8t^6+1.9966710^{-10}h^7t^7+1.7470810^{-10}h^8t^7+1.0853110^{-12}h^8t^8$,

$\phi_{M,k}(t) = \sum_{m=0}^{8} M_m(t)$=$42-76.64ht-268.24h^2t-536.48h^3t-670.6h^4t-536.48h^5t-268.24h^6t-76.64h^7t-9.58h^8t-1.65334h^2t^2-...+1.270110^{-8}h^6t^6+2.1773210^{-8}h^7t^6+9.5257810^{-9}h^8t^6+9.5547810^{-11}h^7t^7+8.3604310^{-11}h^8t^7-2.970510^{-13}h^8t^8$.

Table 4.2: Optimal values of $h_{S_U}, h_{S_A}, h_X, h_M$ and their respective squared residual error functions.

Component functions	Optimal value of h	Minimum value of SRE
S_U	-0.956645	4.5×10^{-3}
S_A	-0.956646	4.6×10^{-3}
X	-0.983807	1.4×10^{-9}
M	-0.996344	1.6×10^{-9}

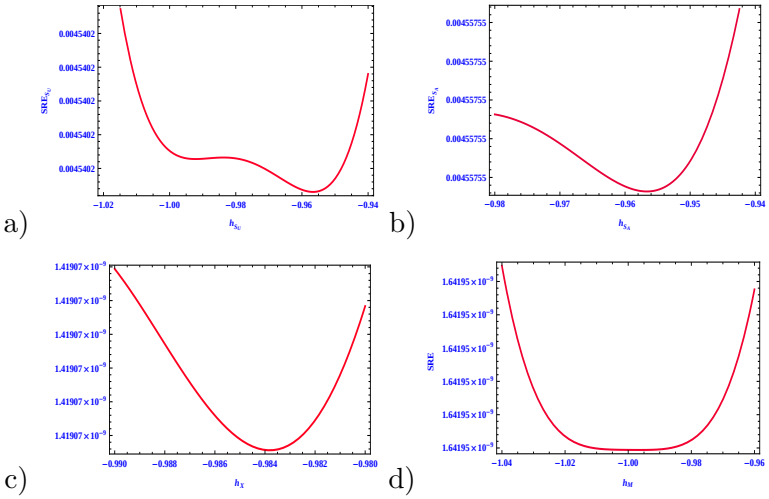


Figure 4.2: The figures represent (from left to right) exact squared residual error functions: $SRE_{S_U}, SRE_{S_A}, SRE_X, SRE_M$ versus $h_{S_U}, h_{S_A}, h_X, h_M$ respectively for Case 1 ($\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1$) and rest of system parameters are taken from Table 4.1.

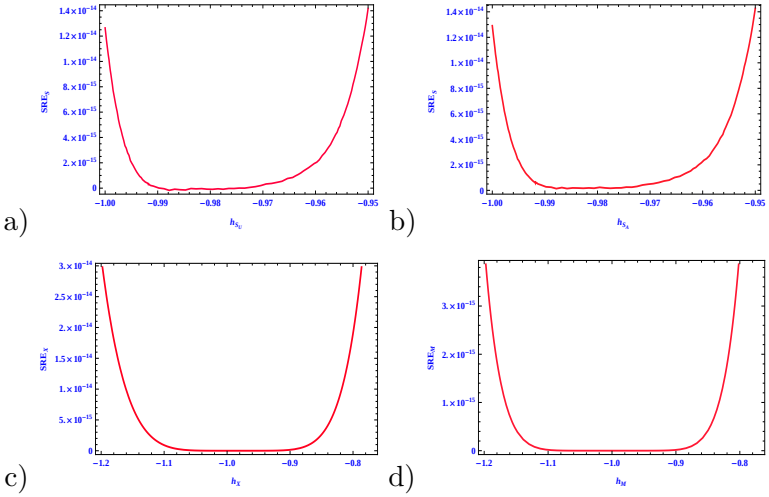


Figure 4.3: The figures depict (from left to right) exact squared residual error functions: $SRE_{S_U}, SRE_{S_A}, SRE_X, SRE_M$ versus h_{S_U}, h_{S_A}, h_X, h_M respectively for Case 2 ($\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$) and rest of system parameters are taken from Table 4.1.

Table 4.3: Optimal values of $h_{S_U}, h_{S_A}, h_X, h_M$ and their respective squared residual error functions.

Component functions	Optimal value of h	Minimum value of SRE
S_U	-0.980120	-6.6×10^{-17}
S_A	-0.982152	9.9×10^{-17}
X	-0.987425	1.3×10^{-23}
M	-0.999628	-2.6×10^{-23}

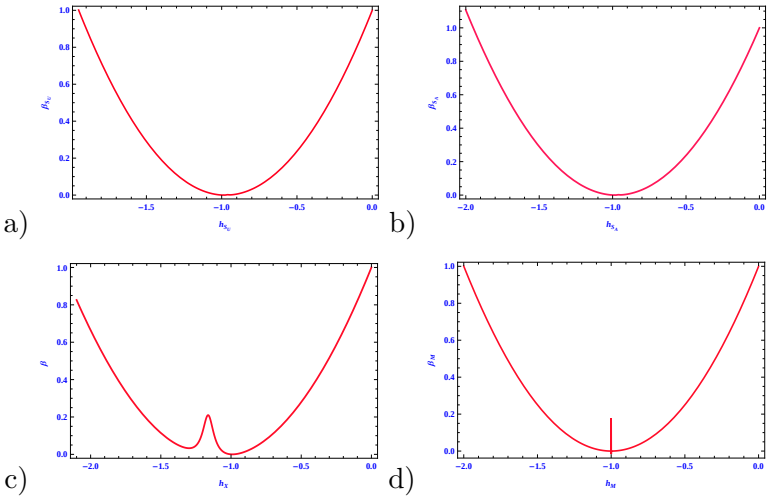


Figure 4.4: The figures depict (from left to right) $\beta_{S_U}, \beta_{S_A}, \beta_X, \beta_M$ versus $h_{S_U}, h_{S_A}, h_X, h_M$ respectively for Case 1 ($\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1$) and rest of system parameters are taken from Table 4.1.

4.6.3 Case 2

In this case we analyze the fractional-order diabetes awareness system when $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$. We determined the partial sums up to eighth order approximations for $S_U(t)$, $S_A(t)$, $X(t)$, $M(t)$ respectively, which are given below:

$$
\begin{aligned}
\phi_{S_U,k}(t) &= \sum_{m=0}^{8} S_{U_m}(t) = 468 + 14.5435ht^{0.75} + 50.9023h^2t^{0.75} \\
&+ 101.805h^3t^{0.75} + 127.256h^4t^{0.75} + 101.805h^5t^{0.75} + 50.9023h^6t^{0.75} \\
&+ 14.5435h^7t^{0.75} + 1.81794h^8t^{0.75} - 92.9183h^2t^{1.5} - ... \\
&- 0.0000217106h^7t^{5.25} - 0.0000189968h^8t^{5.25} + 2.8502910^{-8}h^8t^6, \\
\phi_{S_A,k}(t) &= \sum_{m=0}^{8} S_{A_m}(t) = 432 - 167.073ht^{0.75} - 584.754h^2t^{0.75} - \\
&\quad 1169.51h^3t^{0.75} - 1461.88h^4t^{0.75} - 1169.51h^5t^{0.75} \\
&- 584.754h^6t^{0.75} - 167.073h^7t^0.75 - 20.8841h^8t^{0.75} + 92.5244h^2t^{1.5} \\
&+ ... + 0.0000217087h^7t^{5.25} + 0.0000189951h^8t^{5.25} - 2.8523910^{-8}h^8t^6, \\
\phi_{X,k}(t) &= \sum_{m=0}^{8} X_m(t) = 100 + 1.94076ht^{0.75} + 6.79266h^2t^{0.75} + 13.5853h^3t^{0.75} \\
&+ 16.9817h^4t^{0.75} + 13.5853h^5t^{0.75} + 6.79266h^6t^{0.75} + 1.94076h^7t^{0.75} \\
&+ 0.242595h^8t^{0.75} + 0.038869h^2t^{1.5} + 0.155476h^3t^{1.5} \\
&+ ...1.8840710^{-9}h^7t^{5.25} + 1.6485610^{-9}h^8t^{5.25} + 2.108910^{-11}h^8t^6,
\end{aligned}
$$

$$\begin{aligned}\phi_{M,k}(t) &= \sum_{m=0}^{8} M_m(t) = 42 - 83.3893ht^{0.75} - 291.863h^2t^{0.75} - 583.725h^3t^{0.75} \\ &- 729.657h^4t^{0.75} - 583.725h^5t^{0.75} - 291.863h^6t^{0.75} - 83.3893h^7t^{0.75} \\ &- 10.4237h^8t^{0.75} - 2.48747h^2t^{1.5} - 9.94986h^3t^{1.5} - ... \\ &+ 1.6330510^{-9}h^7t^{5.25} + 1.4289210^{-9}h^8t^{5.25}5.522610^{-12}h^8t^6.\end{aligned}$$

The auxiliary parameter h is present in the series solution. We have already discussed two efficient methods in *Sect.* 4.5.1 for computing the auxiliary parameter h in such a way that approximate solution converge to the exact solution quickly.
From the squared residual error technique as cited in *Sect.* (4.5.1.1), for the above mentioned two cases (i.e, Case 1 and Case 2) the squared residual error functions SRE_{S_U}, SRE_{S_A}, SRE_X, SRE_M versus h_{S_U}, h_{S_A}, h_X , h_M for the solutions S_U, S_A, X, M has been displayed in Figure 4.2 and Figure 4.3 respectively. From Figure 4.3 a), it is observed that the squared residual error SRE_{S_U} is minimum at $h = -0.980120$ and in the deleted neighborhood of $h = -0.980120$, squared residual error SRE_{S_U} is slightly higher compared to the SRE_{S_U} at h_{S_U}= -0.980120. Thus squared residual error approach yield $h = -0.980120$ is an optimal value for the variable S_U. Similarly, all others optimal values have computed for the variables of the model system for $\mu_i =$ 1.00 and 0.75, $i = 1, 2, 3, 4$ under the squared residual approach have summarized in Table 4.2 and Table 4.3 respectively.

Again from the scheme as stated in the *Sect.* (4.5.1.2), for the above two cases (i.e, Case 1 and Case 2) we have plot β versus h curve in Figure 4.4 and Figure 4.5 by solving the equation (4.5.12). From Figure 4.4 a), it shows that (-2.0, 0) is an interval of convergence of h for the variable S_U. In this interval, β_{S_U} is minimum at h_{S_U}=-0.959964 for the variable S_U. Thus ratio approach yields h_{S_U}= -0.959964 is an optimal value for the variable S_U. Similarly, all others interval of convergence and optimal values have computed for the variables S_A, X, M of the model system for $\mu_i = 1.00$ and 0.75, $i = 1, 2, 3, 4$ under the ratio approach have summarized in Table 4.4 and Table 4.5 respectively. Optimal values of h indicated by the squared residual approach and ratio approach are slightly different for the variables of the model system for $\mu_i = 0.75, 1.00$; $i = 1, 2, 3, 4$ (see Table 4.4 and Table 4.5). Thus from those two sets of optimal values of h, we have drawn the solution curves (Figure 4.6 to Figure 4.9) of the model system for $\mu_i = 0.75, 1.00$; $i = 1, 2, 3, 4$. Therefore from those figures, we have got almost the same solution behavior of the model system for $\mu_i =$ 0.75, 1.00; $i = 1, 2, 3, 4$. The dynamics of the related variables in Figure 4.6 to Figure 4.9, we observe that aware susceptible human S_A increase but unaware susceptible

human S_U and diabetic human decrease X with respect to time t under cumulative density of awareness program M. Similar pattern of figures can be represent for all values of the fractional derivatives μ_i, i=1, 2, 3, 4. To avoid excess number of figures in the chapter here we just leave only two values of μ_i, $i = 1, 2, 3, 4$.

Table 4.4: Optimal values of $h_{S_U}, h_{S_A}, h_X, h_M$ and their respective intervals of convergence for Case 1 ($\mu_i = 1.00$, $i = 1, 2, 3, 4$).

β curves	optimal values of h	Interval of convergence
β_{S_U}	-0.959964	(-2.0 0.0)
β_{S_A}	-0.960096	(-2.0 0.0)
β_X	-0.991690	(-2.1 0.0)
β_M	-0.996353	(-2.0 0.0)

Table 4.5: Optimal values of $h_{S_U}, h_{S_A}, h_X, h_M$ and their respective intervals of convergence for Case 2 (μ_i =0.75, $i = 1, 2, 3, 4$).

β curves	optimal values of h	Interval of convergence
β_{S_U}	-0.984792	(-2.0 0.0)
β_{S_A}	-0.984807	(-1.9 0.0)
β_X	-0.990104	(-2.3 0.0)
β_M	-0.999658	(-2.0 0.0)

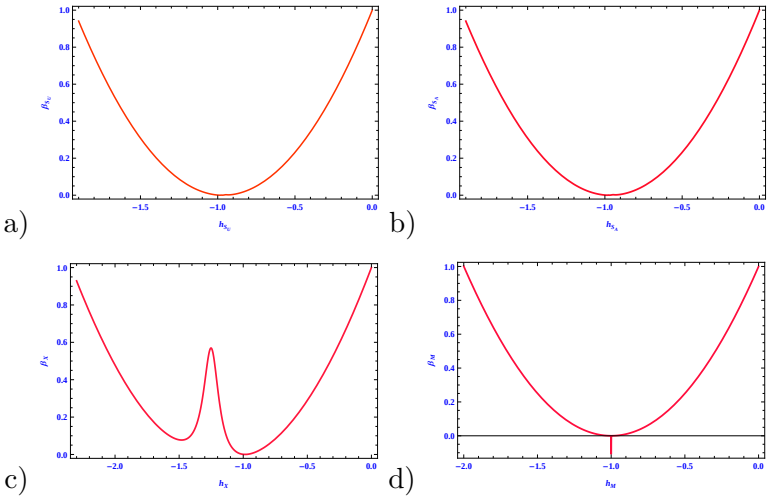
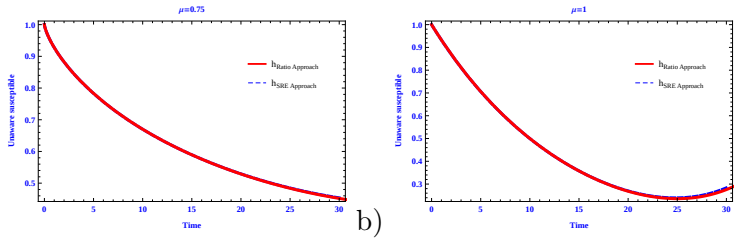
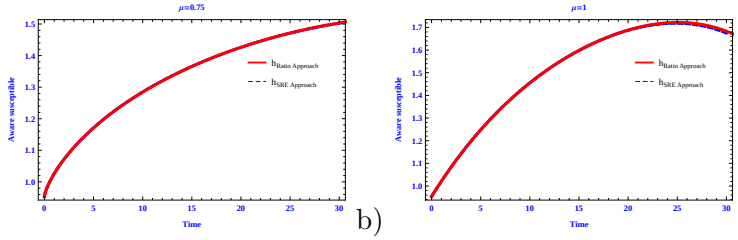


Figure 4.5: The figures represent (from left to right) $\beta_{S_U}, \beta_{S_A}, \beta_X, \beta_M$ versus $h_{S_U}, h_{S_A}, h_X, h_M$ respectively for Case 2 ($\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$) and rest of system parameters are taken from Table 4.1



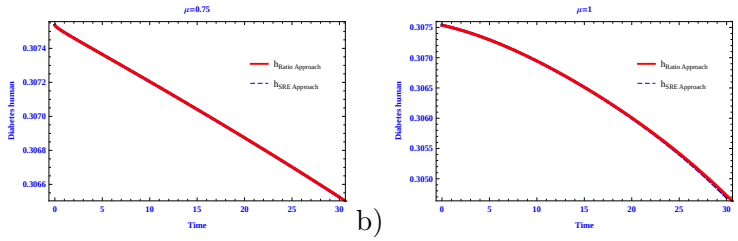
a) b)

Figure 4.6: The figures depict the role of unaware susceptible S_U with respect to time when (a) $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$; red solid line for h=-0.984792, blue dashed line for h=-0.980120 and (b) $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1$; red solid line for h=-0.959964, blue dashed line for h=-0.956645.



a) b)

Figure 4.7: The figures depict the role of aware susceptible S_A with respect to time when (a) $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$; red solid line for h=-0.984807, blue dashed line for h=-0.982152 and (b) $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1$; red solid line for h=-0.960096, blue dashed line for h=-0.956646.

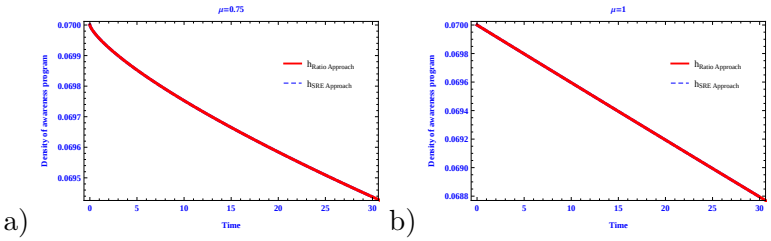


a) b)

Figure 4.8: The figures depict the role of diabetes individuals X with respect to time when (a) when $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$; red solid line for h=-0.990104, blue dashed line for h=-0.987425 and (b) $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1$; red solid line for h=-0.991690, blue dashed line for h=-0.983807.

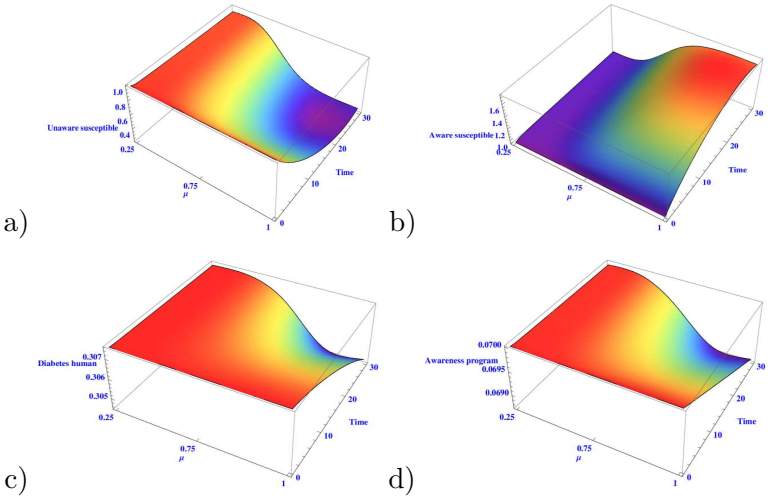
In Figure 4.10, it is shown the dynamics of relevant variables of the system for different values of μ_i, $i = 1, 2, 3, 4$. This 3D figure shows that aware susceptible human S_A increase but unaware susceptible S_U and diabetic human X decrease for increasing the values of the order of the fractional derivative μ_i, i=1, 2, 3, 4. This chapter gives an outline of how to behave the dynamics of diabetes mellitus patients under awareness among individuals in the fractional order derivative model.

Figure 4.11 shows the variation of S_U, S_A, X, and M with time t for different values of the implementation rate of awareness program μ when $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$.



a) b)

Figure 4.9: The figures depict the role of cumulative density of awareness program M with respect to time when (a) $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$; red solid line for h=-0.999659, blue dashed line for h=-0.999629 and (b) $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1$; red solid line for h=-0.996353, blue dashed line for h=-0.996344.



a) b) c) d)

Figure 4.10: The 3D figures depict the role of unaware human, aware human, diabetic human and awareness program with respect to time for different values of μ_i.

It is clear that if μ increase, then S_A increase but X, and S_U decrease with respect to time t (yrs). Again Figure 4.12 shows the variation of S_U, S_A,X, and M with time t for different values of the implementation rate of awareness program μ, when $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1.00$. It is clear that if μ increase, then S_A increase but X, and S_U decrease with time t (yrs). Hence prevalence of diabetes decrease if implementation rate of awareness program μ increases. Here it is noted that diabetic human X more decrease for $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 0.75$ compared to $\mu_1 = \mu_2 = \mu_3 = \mu_4 = 1.00$ [see Figure 4.11 c) and Figure 4.12 c)] in the model system (4.2.3) for different values of μ. This is seen for all values of μ_i $(i = 1, 2, 3, 4)$.

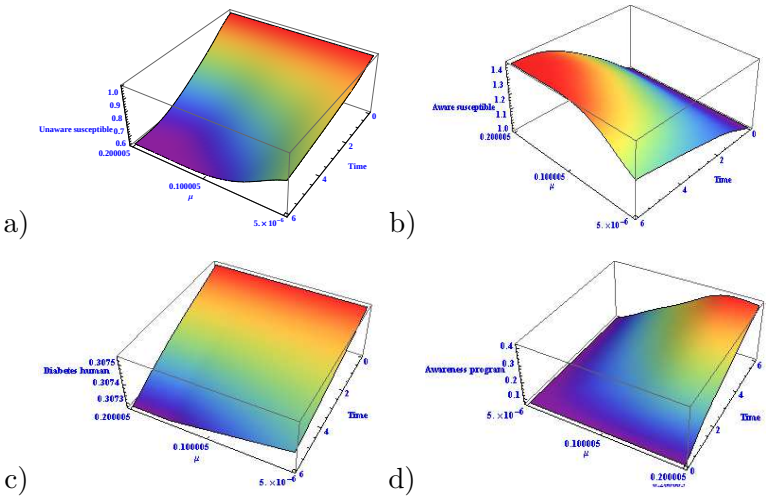


Figure 4.11: The 3D figures depict the role of unaware human, aware human, diabetic human and awareness program with respect to time for different values of μ when μ_i=0.75, i=1,2,3,4.

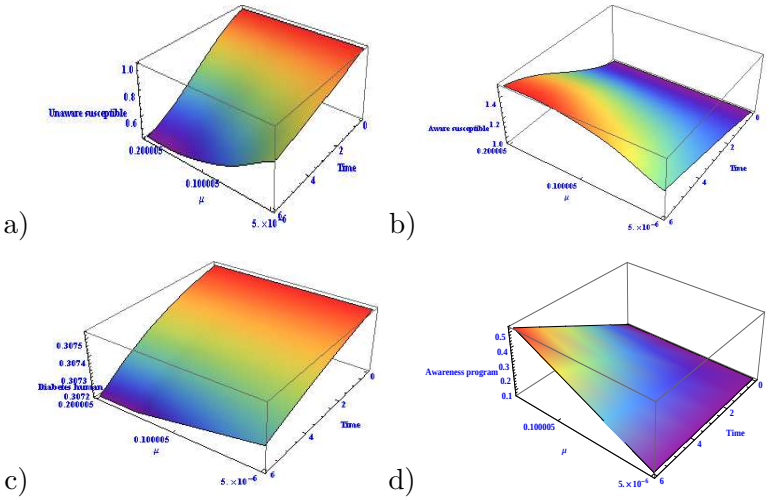


Figure 4.12: The 3D figures depict the role of unaware human, aware human, diabetic human and awareness program with respect to time for different values of μ when μ_i=1, i=1,2,3,4.

4.7 Conclusion

In this chapter, we suggested a fractional order model for DM in the presence of awareness among individuals which is obtained by a nonlinear interaction between number of diabetes patients and cumulative density of awareness program. This chapter represents the dynamics of diabetes patients with respect to time under awareness among individuals. We use the HAM to solve the nonlinear model completely as this is a very efficient method to solve any nonlinear differential equations with any parameter values. We analyzed the model for distinct order of the fractional derivative μ_i,

$i = 1, 2, 3, 4$, and biologically relevant parameter implementation rate of awareness μ. We observed that by increasing the implementation rate of awareness μ, the aware individual increases whereas the prevalence of diabetes decreases over time. Consequently the burden of DM decrease under awareness among individual. We observed that the burden of DM decrease under awareness among individual. Although prevalence of DM in the population constitutes a major challenge with respect to treatment in the health care system.

An ordinary differential equation describes a physical situation at any instant manner whereas fractional derivative has the property of blurring memory and depend on value of the memory parameter μ_i $(i = 1, 2, 3, 4)$ at any instant time. This memory represents present behavior after following past behavior of the individuals. In this chapter, we have introduced FDE to incorporate the behavior of an individual in an awareness of diabetes mellitus framework. Various types of past behavioral and lifestyle factors are known to be important to the development of diabetes.

It is observed that the FDE model system for μ_i=0.75 $(i = 1, 2, 3, 4)$ the number of diabetic patients decrease slower than the corresponding ODE model system for μ_i=1 $(i = 1, 2, 3, 4)$. People who are aware of diabetes under the cumulative density of awareness program but their perceptions from past behavior sometimes influences their decision to repeat the behavior in present time such as diet, physical activity, sedentary behavior, sleep, stress, etc. So in this case number of diabetic patients decrease slowly due to the past behavior of individuals. Here μ_i $(i = 1, 2, 3, 4)$ plays a significant role to incorporate past behavioral effects of the individuals within model system. The fractional order may ensure more freedom to fit the real data for a particular patients.

Chapter 5

Effect of Awareness Program on Cancer - Deterministic and Stochastic approach[4]

5.1 Introduction

Cancer is a significant public health issue throughout the world due to its burden of disease, fatality, and an inclination to increase incidence. In India, the day-by-day burden of cancers growths is around one million, with a death rate of 67.2 for every 100,000, which is primarily the result of late diagnosis (WHO [2012]). Boyle et al. (Boyle et al. [2008]) states that there is a large prevalence of cancer worldwide and it may reach 20 million by 2030, with almost 70% of cancer deaths will occur in low- and middle-income nations. The risk of cancer is growing in emerging nations with enhanced life expectancy and exposure to smoking cigarettes, greater intake of fatty sugar, calorie-dense sustenance, frequent and excessive sun exposure, and decreased physical activity (Puri et al. [2010]).

Some articles state that major parts of cancer are only detected in advanced stages when they can not be treatable, this case arises particularly in developing countries (WHO [2012], Nandakumar et al. [2004]). The reality is that there are established testing techniques in the event of head and neck cancers, cervical cancer, and breast cancer, i.e., the most prevalent cancers in India, to capture the disease soon when it is curable (Veerakumar and Kar [2017]). In nations like India, facilities for adequate cancer screening and governance are grossly restricted. Knowledge of

[4] *The bulk of this chapter has been published in* ***Bulletin of Calcutta Mathematical Society****, 13 (5) (2021), 421-446.*

signs and symptoms of cancer and their testing together with therapy technique has also been small here. That is why most cancer patients were diagnosed in India at an advanced and not treatable stage (Veerakumar and Kar [2017], San Turgay et al. [2005]). The principal way to decrease the worldwide burden of cancer is prevention through lifestyle and environmental measures (Danaei et al. [2005]). Good nutrition, physical activity, and maintenances of body weight are projected to prevent at least one-third of cancers (Lazcano-Ponce [2009]). Smoking tobacco leads to an estimated 20 percent of all cancer fatalities, with roughly 80 percent of all instances of lung cancer occurring in males and 50 percent of all instances of tobacco smoking in females worldwide (Lazcano-Ponce [2009]). It is commonly recognized that awareness plays a significant role in enhancing human behavior. Cancer can be reduced through behavioral modifications of modifiable cancer risk factors (Lagerlund et al. [2015]). Assessing the general public understanding of cancer risk factors is thus a key step toward identifying possible areas for awareness. The deterministic approach does not incorporate the fluctuations in the model system which is always present in the biological system. So it is very difficult for prediction in future. Most environmental factors do not strictly follow deterministic law as there are some uncertainties is present with respect to time in the biological system. Many environmental factors are stimulated the risk factors of cancer in the population. Cancer is a behavioral disease and it is important for cancer patients aware of nature, risk factors, treatment, and other related complications of cancer (Lagerlund et al. [2015], Lazcano-Ponce [2009], Nandakumar et al. [2004]).

The main purpose of this chapter is to study the dynamics of cancer patients in the population under awareness driven by media. As far as we know the present work is the first attempt in the mathematical study under an awareness program on cancer in both deterministic and stochastic environments. Although researchers have been investigating the dynamics on the assumptions that how cancer cells can be eliminated in the human body (Khajanchi et al. [2018], Khajanchi [2015]). We proposed and analyzed a mathematical model in this chapter with humans suffering from cancer. For the impact of awareness programs driven by mass media on the prevalence of cancer, we considered a nonlinear interaction between unaware susceptible and cancer humans. The total population is subdivided into three different classes: unaware susceptible, aware susceptible, and cancer human. Both unaware and aware individuals can be infected with cancer but the probability of incidence of cancer for an aware individual is less than an unaware individual. Cancer is not a contagious disease, it is not transferred by contact. So, cancer human depends mostly on the unaware class and aware class. In addition, some proportion of cancer humans will

recover from cancer and a fraction of these recovered individuals will join the aware class and the remaining fraction will join the unaware class. After that, we have given the stochastic perturbation to the deterministic model directly in sense of white noise to incorporate the fluctuation in the system (Mollah and Biswas [2021], Afanas'ev et al. [2013], Bandyopadhyay and Chattopadhyay [2005], Berezovskaya et al. [2001], Cantrell and Cosner [2001], Cosner et al. [1999]).

This chapter is written as follows. In *Sect.* 5.2, we present a mathematical construction under awareness, which has given under basic assumptions. *Sect.* 5.3 contains model analysis in terms of local stability of equilibrium point. In this section, we find the equilibrium point and the conditions of their feasibility and local stability. In *Sect.* 5.4, we formulated a stochastic version of the model. The stochastic mean square stability at the equilibrium is presented in *Sect.* 5.5. In this section, we find the existence and the sufficient conditions for stochastic asymptotical mean square stability. We have given numerical simulations to validate our analytical findings in both DDEs and SDEs, and is presented in *Sect.* 5.6. Finally, the chapter ends with a discussion and conclusion in *Sect.* 5.7.

5.2 Model construction

The total human is divided into two classes: susceptible human $S(t)$, cancer human $X(t)$. If the awareness programs i.e. adequate information and education about cancer are carried out in the region, the total susceptible population $S(t)$ is subdivided into two subclasses: the unaware susceptible human $U(t)$ and the aware susceptible human $A(t)$. We have considered a region where people suffering from cancer. We make some necessary assumptions to construct the model system in the following.

(I) We assume Π is the constant rate of immigration in the form of unawareness susceptible to that region and d is the natural death rate of human beings. Cancer is a fatal disease and it is the second leading cause of death worldwide (Rajpal et al. [2018]). We take e as the additional death rate due to cancer.

(II) Family members, educated people, and personally experienced with cancer (caregiver or patients) are more aware compared to the general population (Mollah and Biswas [2021], Elangovan et al. [2017], Hvidberg et al. [2014]). We assume that unaware susceptible human becomes aware susceptible at a rate $\lambda g(X)$, where λ is the maximum rate at which unaware susceptible individual becomes aware susceptible and $g(X)$ is the function of infected population density X. g is an increasing function with $sup_{X\geq 0} g = 1$ and $inf_{X\geq 0} g = 0$. Furthermore, we consider the specific functional form of $g(X)$, say $g(X) = \frac{X}{1+X}$. So, we assume that the unaware susceptible individual

becomes aware of the susceptible individual depending on the number of diabetic humans i.e. if the number of diabetic patients increases, more unaware individuals become aware.

(III) Cancer is not a contagious disease, it is not transferred from human to human. The incidence of cancer is increased due to the risk factors such as smoking, unhealthy diet, physical inactivity, and obesity (Al-Azri et al. [2014], Luqman et al. [2014]). We consider unaware susceptible humans become cancer at a rate of β. Some research articles indicated that public awareness of cancer risk factors plays an important role to reduce the incidence of cancer (Al-Azri et al. [2014], Luqman et al. [2014]). Hence aware susceptible human has less chance to involve in cancer than unaware susceptible. We consider $\beta\beta_1$ as the incidence rate of aware susceptible humans to cancer, where $0 < \beta_1 < 1$.

(IV) Some types of cancer can be cured whenever they are detected and the remaining of them can be cured only if detected at an early stage (Rajpal et al. [2018], Coyte et al. [2014]). For example, acute leukemia and some types of lymphoma can be curable under chemotherapy but some of the common cancers such as colon cancer, breast cancer, prostate cancer, and pancreatic cancer are curable only if detected at an early stage. We assume that a proportion of cancer individuals recover through treatment. Recovered individuals can be at risk to develop second primary cancer due to genetic, behavioral risk factors, and treatment particularly radiotherapy and chemotherapy (Coyte et al. [2014]). So, we assume that a fraction p of recovered people will join the aware susceptible class whereas reaming fraction $(1-p)$ will join the unaware susceptible class.

Based on the above key assumptions, we formulated the following mathematical model:

$$\begin{aligned} \frac{dU}{dt} &= \Pi - \lambda U \frac{X}{1+X} - \beta U - dU + (1-p)\gamma X, \\ \frac{dA}{dt} &= \lambda U \frac{X}{1+X} - \beta\beta_1 A - dA + p\gamma X, \\ \frac{dX}{dt} &= \beta U + \beta\beta_1 A - \gamma X - (d+e)X. \end{aligned} \tag{5.2.1}$$

The parameters used in the model (5.2.1) are interpreted as: γ is a recovery rate i.e. after surgery cancer patients become susceptible human per unit time. $\beta\beta_1$ is the lowered incident rate of cancer from aware susceptible human. The dimensionless number β_1 is a constant, its value lies between 0 and 1. Using the transformation

$M = U + A + X$, the system (5.2.1) becomes to the following system:

$$\begin{aligned} \frac{dX}{dt} &= \beta(M - A - X) + \beta\beta_1 A - \gamma X - (d + e)X, \\ \frac{dA}{dt} &= \lambda(M - A - X)\frac{X}{1+X} - \beta\beta_1 A - dA + p\gamma X, \\ \frac{dM}{dt} &= \Pi - dM - eX. \end{aligned} \tag{5.2.2}$$

The region of attraction for the model (5.2.2) is given by:
$\Gamma = \left\{(X, A, M) \in R_+^3 : 0 \leq X, A \leq M \leq \frac{\Pi}{d}\right\}$ and all solutions are initiating in the interior of the positive octant.

5.3 Model analysis: local stability of equilibrium point

The system (5.2.2) has only one positive endemic equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$. For the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$, the components $\overline{X}_*, \overline{A}_*, \overline{M}_*$ are satisfied the following set of equations:

$$\begin{aligned} &\beta(M - A - X) + \beta\beta_1 A - \gamma X - (d + e)X = 0, \\ &\lambda(M - A - X)\frac{X}{1+X} - \beta\beta_1 A - dA + p\gamma X = 0, \\ &\Pi - dM - eX = 0. \end{aligned} \tag{5.3.1}$$

From third equation, using $M = \frac{\Pi - eX}{d}$ in the first two equations in (5.3.1) and then eliminating A from these two equations, we obtain

$$A_1 X^2 + A_2 X - A_3 = 0. \tag{5.3.2}$$

Where
$A_1 = (\beta e + d\gamma + d^2 + de + \lambda\beta)(\beta\beta_1 + d + \gamma) + (dp\gamma - de - \lambda d)\beta(1 - \beta_1)$,
$= e\beta^2\beta_1 + \beta e\gamma + d\gamma\beta\beta_1(1 - p) + d^2\gamma + d\gamma^2 + d^2\beta\beta_1 + d^3 + d^2\gamma + de\beta\beta_1 + d^2 e + de\gamma + \lambda\beta^2\beta_1 + \lambda\gamma\beta + dp\gamma\beta + de\beta\beta_1 + \lambda d\beta\beta_1$,
$A_2 = (\beta\beta_1 + d)(\beta e + d\gamma + d^2 + de + d\beta) - \beta\Pi(\beta\beta_1 + d + \lambda) + (p\gamma d + \lambda\Pi)\beta(1 - \beta_1)$,
$A_3 = -\beta\Pi(\beta\beta_1 + d)$.
Therefore from (5.3.2), we get $X = \frac{-A_2 \pm \sqrt{A_2^2 - 4A_1A_3}}{2A_1}$. We find that $A_1 > 0$, $A_3 > 0$ and whatever be the value of A_2, applying Descartes rule of sign, we can say that Eq. (5.3.2) has one positive as well as one negative root. The positive root is given by

$$X = \frac{-A_2 + \sqrt{A_2^2 - 4A_1A_3}}{2A_1}.$$

From this positive value of X, say $\overline{X}_*$, we get nontrivial positive equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$.
The jacobian matrix for the system (5.2.2) at the point $(X,\ A,\ M)$ is given by

$$\overline{J} \equiv \begin{bmatrix} -(\beta+\gamma+d+e) & -\beta(1-\beta_1) & \beta \\ \frac{(\beta\beta_1+d)A+(p\gamma-\lambda)X^2}{X(1+X)} & -\frac{\lambda X}{1+X} - \beta\beta_1 - d & \frac{\lambda X}{1+X} \\ -e & 0 & -d \end{bmatrix}.$$

For the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ the matrix $\overline{J}$ reduces to $\overline{J}_{\overline{E}_*} \equiv \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$,
where

$$\begin{aligned} &a_{11} = -(\beta+\gamma+d+e), a_{12} = -\beta(1-\beta_1), a_{13} = \beta, \\ &a_{21} = \frac{(\beta\beta_1+d)\overline{A}_*+(p\gamma-\lambda)\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}, a_{22} = -\frac{\lambda\overline{X}_*}{1+\overline{X}_*} - \beta\beta_1 - d, \\ &a_{23} = \frac{\lambda\overline{X}_*}{1+\overline{X}_*}, a_{31} = -e, a_{32} = 0, a_{33} = -d. \end{aligned} \tag{5.3.3}$$

Then the characteristic equation for the matrix is given by

$$|\overline{J}_{\overline{E}_*} - \rho I_3| = \rho^3 + \alpha_1\rho^2 + \alpha_2\rho + \alpha_3 = 0,$$

where
$\alpha_1 = -(a_{11}+a_{22}+a_{33}),\ \alpha_2 = a_{11}a_{22} + a_{11}a_{33} + a_{22}a_{23} - a_{12}a_{21} - a_{13}a_{31},$
$\alpha_3 = -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{12}a_{31}a_{23} + a_{13}a_{31}a_{22}.$

Theorem 5.3.1. *The sufficient condition for the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ of the system (5.2.2) is asymptotically stable if $p\gamma > \lambda$.*

Proof. The characteristic equation of the system (5.2.2) at the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ is

$$\rho^3 + \alpha_1\rho^2 + \alpha_2\rho + \alpha_3 = 0.$$

By the Routh-Hurwitz stability criterion, the equilibrium point
$\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{N}_*)$ is asymptotically stable if
$\alpha_1 > 0,\ \alpha_3 > 0$ and $\alpha_1\alpha_2 - \alpha_3 > 0$.
Now $\alpha_1 = -(a_{11}+a_{22}+a_{33}) > 0$, using the values of $\{a_{ii} : i = 1,2,3\}$ from (5.3.3);
$\alpha_3 = -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{12}a_{31}a_{23} + a_{13}a_{31}a_{22}$
$= -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{31}(a_{12}a_{23} - a_{13}a_{22})$
$= -a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33} - a_{31}(\beta\beta_1\frac{\lambda\overline{X}_*}{1+\overline{X}_*} + \beta\beta_1 + d\beta) > 0$, using the values of $\{a_{ij} : i,j = 1,2,3\}$ from (5.3.3).

Here $\alpha_1\alpha_2 - \alpha_3$
$= -a_{22}(a_{11}a_{11} + a_{22}a_{23}) + a_{11}a_{22}(a_{23} + a_{22}) - a_{22}a_{33}(a_{11} + a_{23}) - a_{11}a_{11}a_{33} + a_{11}a_{12}a_{21} + a_{11}a_{13}a_{31} + a_{12}a_{21}a_{22} - a_{11}a_{33}a_{33} + a_{13}a_{31}a_{33} + a_{12}a_{31}a_{23}$
$= -a_{22}\{(\beta+\gamma+d+e)^2 - (\frac{\lambda\overline{X}_*}{1+\overline{X}_*} + \beta\beta_1 + d)(\frac{\lambda\overline{X}_*}{1+\overline{X}_*})\} + a_{22}a_{11}(\beta\beta_1+d) + a_{22}a_{33}(\beta+\gamma+d+e - \frac{\lambda\overline{X}_*}{1+\overline{X}_*}) - a_{11}a_{11}a_{33} + a_{11}a_{12}a_{21} + a_{11}a_{13}a_{31} + a_{12}a_{21}a_{22} - a_{11}a_{33}a_{33} + a_{13}a_{31}a_{33} + a_{12}a_{31}a_{23}$.
Therefore $\gamma > \lambda$ as $0 < p < 1$ and $0 < \frac{\overline{X}_*}{1+\overline{X}_*} < 1$, This imply that $\beta+\gamma+d+e > \lambda\frac{\overline{X}_*}{1+\overline{X}_*}$.
Again $\gamma > \lambda$ and $0 < \beta_1 < 1$, This imply that $\beta + \gamma + d + e > \lambda\frac{\overline{X}_*}{1+\overline{X}_*} + \beta\beta_1 + d$.
We also note that $a_{21} = \frac{(\beta\beta_1+d)\overline{A}_* + (p\gamma-\lambda)\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)} > 0$ as $p\gamma > \lambda$.
Using these conditions and the values of $\{a_{ij} : i, j = 1, 2, 3\}$ from (5.3.3), we see that $\alpha_1\alpha_2 - \alpha_3 > 0$ and hence the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ is asymptotically stable if $p\gamma > \lambda$. □

5.4 The stochastic model

Recent biological mechanisms for cancer indicate that environment and genetics play an important role to develop cancer in human beings, which suggests that numerous external factors coupled with internal genetic changes may lead to human cancer. Internal factors (such as inherited mutations, hormones, and immune conditions) and environmental/acquired factors (such as tobacco, diet, radiation, and infectious organisms) are the main reasons to develop cancer. Some research articles indicate that cancers are not hereditary from the origin but dietary propensities, smoking, liquor utilization, and diseases have a significant impact on the development of cancer (Anand et al. [2008], Irigaray et al. [2007]). The facts that the genetic components cannot be adjusted but the behavioral and ecological variables are conceivably modifiable (Anand et al. [2008], Irigaray et al. [2007]). Many behavioral factors that influence the incident and mortality rate of cancer likewise tobacco, liquor, diet, obesity, infectious agents, natural contaminations, and radiation (Anand et al. [2008]). The most harmful cause of cancer is cigarette consumption. Smoking is triggering more than 85% of all lung cancer and 30% of all mortality (Anand et al. [2008]). A variety of studies have found that excessive alcohol use is a contributing factor for oral cavity, pharynx, hypopharynx, larynx, and esophagus, as well as stomach, pancreatic, mouth, and breast cancers (Anand et al. [2008], Irigaray et al. [2007], Tuyns [1979]). In addition, environmental pollution has a great impact on some types of cancers. It involves outdoor air emissions from carbon particles related to polycyclic aromatic hydrocarbons; indoor air emissions from cigarette smoke, some organic compounds such as benzene and 1,3-butadiene; food contamination from food additives and car-

cinogens (Anand et al. [2008], Guan et al. [2008]). All these factors of external forces that act on the population that create the stochastic behavior of the individuals in the population.

Thus to incorporate the fluctuations in the model system, we have given the stochastic perturbation directly to the model system (5.2.1) in the sense of white noise (Mollah and Biswas [2021], Afanas'ev et al. [2013], Bandyopadhyay and Chattopadhyay [2005]). The required stochastic model is given by:

$$\begin{aligned} dX &= [\beta(M-A-X)+\beta\beta_1 A-\gamma X-(d+e)X]dt+\sigma_1(X-\overline{X}_*)d\xi_t^1,\\ dA &= [\lambda(M-A-X)\tfrac{X}{1+X}-\beta\beta_1 A-dA+p\gamma X]dt+\sigma_2(A-\overline{A}_*)d\xi_t^2,\\ dM &= [\Pi-dM-eX]dt+\sigma_3(M-\overline{M}_*)d\xi_t^3, \end{aligned} \tag{5.4.1}$$

where σ_i, i=1, 2, 3 are the population fluctuations, $\xi_t^i = \xi_i$(t), i=1, 2, 3 are pairwise independent standard Wiener processes Cantrell and Cosner [2001] and the equilibrium point $(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ is asymptotically stable.

The Ito-stochastic differential form for the system (5.4.1) is given by

$$\begin{aligned} dX_t &= f(t,X_t)dt+g(t,X_t)d\xi_t,\\ X_{t0} &= X_0, \quad t\in[t_0,\ t_f], \end{aligned} \tag{5.4.2}$$

The set of solutions $\{X_t, t\in[t_0,t_f]\}$ of the SDE (5.4.2) is an Ito process. The terms $f(t,X_t)$ and $g(t,X_t)$ are slowly varying continuous component called *drift coefficient* and $g(t,X_t)$ is the rapidly varying continuous random component called *diffusion coefficient* respectively. Also ξ_t is a 3-D stochastic process having wiener process components with increments $\triangle\xi_t^i = \xi_{t+\triangle t}^i - \xi_t^i = \xi^i(t+\triangle t)-\xi_i(t)$, i=1, 2, 3 are independent Gaussian random variate $N(0,\triangle t)$ (Cosner et al. [1999]).

Stochastic integral equation form of the Eq. (5.4.2) is

$$X_t = X_0 + \int_{t_0}^t f(s,X_s)ds + \int_{t_0}^t g(s,X_s)d\xi_s, \tag{5.4.3}$$

First integral is *Riemann-Stieltjes* integral and the second integtal is called an *Ito-integral*. For the system (5.4.1), we get

$X_t = (X,\ A,\ M)^T$, $\xi_t = (\xi_t^1,\ \xi_t^2,\ \xi_t^3)^T$,

$$f = \begin{bmatrix} \beta(M-A-X)+\beta\beta_1 A-\gamma X-(d+e)X \\ \lambda(M-A-X)\frac{X}{1+X}-\beta\beta_1 A-dA+p\gamma X \\ \Pi-dM-eX \end{bmatrix},$$

$$g = \begin{bmatrix} \sigma_1(X - \overline{X}_*) & 0 & 0 \\ 0 & \sigma_2(A - \overline{A}_*) & 0 \\ 0 & 0 & \sigma_3(M - \overline{M}_*) \end{bmatrix}.$$

The diffusion matrix g of the system (5.4.1) is called multiplicative noise. Also, diagonal matrix g of the system (5.4.1) is called diagonal noise.

5.5 Stochastic stability analysis

We transformed the system (5.4.1) around the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ by introducing the transformations $u_1 = X - \overline{X}_*$, $u_2 = A - \overline{A}_*$ and $u_3 = M - \overline{M}_*$. Analytically it is quite difficult to investigate the asymptotic stability of the nonlinear model system (5.4.1) in a mean-square sense. For simplicity, we linearized the transformed system (Mollah and Biswas [2021], Bandyopadhyay and Chattopadhyay [2005], Berezovskaya et al. [2001]) and we obtained the as follows

$$du(t) = f(u(t))dt + g(u(t))d\xi(t), \tag{5.5.1}$$

where $u(t) = (u_1, u_2, u_3)^T$, $f(u(t)) \equiv \begin{bmatrix} a_{11}u_1 + a_{12}u_2 + a_{13}u_3 \\ a_{21}u_1 + a_{22}u_2 + a_{23}u_3 \\ a_{31}u_1 + a_{32}u_2 + a_{33}u_3 \end{bmatrix}$,

$g(u(t)) \equiv \begin{bmatrix} \sigma_1 u_1 & 0 & 0 \\ 0 & \sigma_2 u_2 & 0 \\ 0 & 0 & \sigma_3 u_3 \end{bmatrix}$ with $a_{11} = -(\beta + \gamma + d + e)$, $a_{12} = -\beta(1 - \beta_1)$, $a_{13} = \beta$, $a_{21} = \frac{(\beta\beta_1 + d)\overline{A}_* + (p\gamma - \lambda)\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}$, $a_{22} = -\frac{\lambda\overline{X}_*}{1+\overline{X}_*} - \beta\beta_1 - d$, $a_{23} = \frac{\lambda\overline{X}_*}{1+\overline{X}_*}$, $a_{31} = -e$, $a_{32} = 0$, $a_{33} = -d$.

Then the equilibrium point $\overline{E}_*$ $(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ corresponds to the trivial solution $(u_1, u_2, u_3) = (0, 0, 0)$. Let $\Omega = \{(t \geq t_0) \times \mathbb{R}^3, t_0 \in \mathbb{R}^+\}$ and $V(\xi, t) \in C_2(\Omega)$ be twice continuously differentiable function with respect to ξ and t, where ξ satisfies the equation (5.5.1). Due to Afanas'ev *et al.* (Afanas'ev et al. [2013]), $LV(\xi, t)$ is defined associated to the system (5.5.1) by

$$LV(\xi, t) = \frac{\partial V(\xi,\ t)}{\partial t} + F^T(\xi)\frac{\partial V(\xi,\ t)}{\partial \xi} + \frac{1}{2}Tr\left[g^T(\xi)\frac{\partial^2 V(\xi,\ t)}{\partial \xi^2}g(\xi)\right], \tag{5.5.2}$$

with

$$\frac{\partial V(\xi,\ t)}{\partial t} = col(\frac{\partial V}{\partial u_1}, \frac{\partial V}{\partial u_2}, \frac{\partial V}{\partial u_3}),\ \frac{\partial^2 V(\xi,\ t)}{\partial \xi^2} = \left[(\frac{\partial^2 V(\xi,\ t)}{\partial u_i \partial u_j})_{i,j=1,2,3}\right]. \tag{5.5.3}$$

Where L and T represent an operator and transposition of a matrix respectively. The following theorem is given due to Afanas'ev *et al.* (Afanas'ev et al. [2013]) by

Theorem 5.5.1. *Let $V(\xi,t) \in C_2(\Omega)$ satisfies the following inequalities*

$$K_1|\xi|^\alpha \leq V(\xi,t) \leq K_2|\xi|^\alpha \tag{5.5.4}$$

$$LV(\xi,t) \leq -K_3|\xi|^\alpha, \quad K_i > 0, \quad i = 1,2,3, \quad \alpha > 0. \tag{5.5.5}$$

The sufficient conditions for zero solution to be asymptotically mean square stable of the system (5.5.1) is given by

Theorem 5.5.2. *If the following conditions hold*
i) $(\beta+\gamma+d+e) > \frac{\sigma_1^2}{2}$;
ii) $\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*} + \beta\beta_1 + d > \frac{\sigma_2^2}{2}$;
iii) $\gamma > \lambda$, $d > \frac{\sigma_3^2}{2}$;
and we choose ω_3 such that
$\omega_3 = Max\left\{\frac{\beta\omega_1^* - (\beta+\gamma+d+e)\omega_4^*}{e}, \frac{\beta\omega_4^*}{d-\frac{\sigma_3^2}{2}}\right\}$. *Where ω_1^* and ω_4^* are given by*
$\omega_1^* = \frac{(\beta\beta_1+d)\overline{A}_* + (p\gamma-\lambda)\overline{X}_*^2}{\beta(1-\beta_1)\overline{X}_*(1+\overline{X}_*)}$,
$\omega_4^* = \frac{1}{\beta(1-\beta_1)}\frac{\lambda\overline{X}_*}{1+\overline{X}_*}$, *then zero solution of the system (5.5.1) is asymptotically mean square stable.*

Proof. We consider a following positive definite Lyapunov function

$$V(\xi(t),t) = \tfrac{1}{2}[\omega_1 u_1^2 + u_2^2 + \omega_3 u_3^2 + 2\omega_4 u_1 u_3], \tag{5.5.6}$$

where ω_i $(i = 1,2,3)$ are real positive constants to be chosen later. It is easy to check that inequalities (5.5.4) hold true for the Lyapunov function defined in (5.5.6) with $\alpha = 2$. Furthermore, $LV(\xi,t) = (a_{11}u_1 + a_{12}u_2 + a_{13}u_3)\omega_1 u_1 + (a_{21}u_1 + a_{22}u_2 + a_{23}u_3)u_2 + (a_{31}u_1 + a_{32}u_2 + a_{33}u_3)\omega_3 u_3 + (a_{11}u_1 + a_{12}u_2 + a_{13}u_3)\omega_4 u_3 + (a_{31}u_1 + a_{32}u_2 + a_{33}u_3)\omega_4 u_1 + \frac{1}{2}Tr[g^T(\xi)\frac{\partial^2 V(\xi,t)}{\partial\xi^2}g(\xi)]$,

$$
\begin{aligned}
&= [-(\beta+\gamma+d+e)u_1 - \beta(1-\beta_1)u_2 + \beta u_3]\omega_1 u_1 \\
&+[\{\frac{(\beta\beta_1+d)\overline{A}_* + (p\gamma-\lambda)\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}\}u_1 - \{\frac{\lambda\overline{X}_*}{1+\overline{X}_*} + \beta\beta_1 + d\}u_2 \\
&+\frac{\lambda\overline{X}_*}{1+\overline{X}_*}u_3]u_2 + [-eu_1 - du_3]\omega_3 u_3 + [-(\beta+\gamma+d+e)u_1 \\
&-\beta(1-\beta_1)u_2 + \beta u_3]\omega_4 u_3 + [-eu_1 - du_3]\omega_4 u_1 + \frac{1}{2}Tr[g^T(\xi)\frac{\partial^2 V(\xi,t)}{\partial\xi^2}g(\xi)].
\end{aligned} \tag{5.5.7}
$$

Now, we find that $\frac{\partial^2 V}{\partial \xi^2} \equiv \begin{bmatrix} \omega_1 & 0 & \omega_4 \\ 0 & 1 & 0 \\ \omega_4 & 0 & \omega_3 \end{bmatrix}$.

Therefore, $g(\xi(t))^T \frac{\partial^2 V}{\partial \xi^2} g(\xi(t)) \equiv \begin{bmatrix} \omega_1\sigma_1^2u_1^2 & 0 & \omega_4\sigma_1\sigma_3u_1u_3 \\ 0 & \sigma_2^2u_2^2 & 0 \\ \omega_4\sigma_1\sigma_3u_1u_3 & 0 & \omega_3\sigma_3^2u_3^2 \end{bmatrix}$ and hence,

$\frac{1}{2}Tr[g^T(\xi)\frac{\partial^2 V(\xi,t)}{\partial\xi^2}g(\xi)] = \frac{1}{2}[\omega_1\sigma_1^2u_1^2 + \sigma_2^2u_2^2 + \omega_3\sigma_3^2u_3^2]$.
Using this in (5.5.1) and simplifying, we get

$$
\begin{aligned}
LV(\xi,t) = &-[(\beta+\gamma+d+e)\omega_1 + e\omega_4 - \frac{\sigma_1^2}{2}\omega_1]u_1^2 - [\beta(1-\beta_1)\omega_1 \\
&-\frac{(\beta\beta_1+d)\overline{A}_* + (p\gamma-\lambda)\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)}]u_1u_2 - [e\omega_3 - \beta\omega_1 \\
&+(\beta+\gamma+d+e)\omega_4]u_1u_3 - [\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*} + \beta\beta_1 + d - \frac{\sigma_2^2}{2}]u_2^2 \\
&-[\beta(1-\beta_1)\omega_4 - \frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*}]u_2u_3 - [(d-\frac{\sigma_3^2}{2})\omega_3 - \beta\omega_4]u_3^2.
\end{aligned} \tag{5.5.8}
$$

If we choose ω_1^*, ω_2^* in such way that

$$
\beta(1-\beta_1)\omega_1 - \frac{(\beta\beta_1+d)\overline{A}_* + (p\gamma-\lambda)\overline{X}_*^2}{\overline{X}_*(1+\overline{X}_*)} = 0 \text{ and } \beta(1-\beta_1)\omega_4 - \frac{\lambda\overline{X}_*}{1+\overline{X}_*} = 0.
$$

i.e.,

$$
\omega_1^* = \frac{(\beta\beta_1+d)\overline{A}_* + (p\gamma-\lambda)\overline{X}_*^2}{\beta(1-\beta_1)\overline{X}_*(1+\overline{X}_*)} \text{ and } \omega_4^* = \frac{\lambda\overline{X}_*}{\beta(1-\beta_1)(1+\overline{X}_*)}.
$$

Then the equation (5.5.8) becomes

$$
\begin{aligned}
LV(\xi,t) < & -\left[(\beta+\gamma+d+e)\omega_1^* - \frac{\sigma_1^2}{2}\omega_1^*\right]u_1^2 \\
& -\left[e\omega_3 - \beta\omega_1^* + (\beta+\gamma+d+e)\omega_4^*\right]u_1u_3 \\
& -\left[\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*} + \beta\beta_1 + d - \frac{\sigma_2^2}{2}\right]u_2^2 - \left[(d-\frac{\sigma_3^2}{2})\omega_3 - \beta\omega_4^*\right]u_3^2.
\end{aligned} \tag{5.5.9}
$$

Thus, we can write

$$
LV(\xi,t) < -u^TQu. \tag{5.5.10}
$$

Where, $Q \equiv \begin{bmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{bmatrix}$ with $m_{11} = [(\beta+\gamma+d+e)\omega_1^* - \frac{\sigma_1^2}{2}\omega_1^*]$; $m_{12} = m_{21} = 0$; $m_{13} = m_{31} = \frac{1}{2}[e\omega_3 - \beta\omega_1^* + (\beta+\gamma+d+e)\omega_4^*]$; $m_{22} = [\frac{\lambda\overline{X}_*}{1+\lambda\overline{X}_*} + \beta\beta_1 + d - \frac{\sigma_2^2}{2}]$; $m_{23} = m_{32} = 0$; $m_{33} = [(d-\frac{\sigma_3^2}{2})\omega_3 - \beta\omega_4^*]$.

Thus, we have $m_{ij} \geq 0$ for *i, j=1,2,3*; if the conditions *(i)* to *(iii)* of the Theorem 5.5.2 are hold. Therefore Q is a real symmetric positive definite matrix and hence all the three eigenvalues $\lambda_i(Q)$ (say) are real positive. Let $\lambda_m = min\{\lambda_i(Q), i = 1,2,3\}$, then $\lambda_m > 0$. Therefore, from inequality (5.5.10), we get $LV(u(t)) < -\lambda_m|u(t)|^2$. Hence the condition (5.5.5) of Theorem 5.5.1 is satisfied. This complete the proof of the theorem. □

Table 5.1: The set of fixed parameter values taken from various literature sources:

Parameter	Ecological meaning	Parameter values	Reference
Π	rate of immigration of human	20430 $year^{-1}$	Samanta et al. [2013], Misra et al. [2011]
β	incident rate of cancer	0.00063 $year^{-1}$	Rajpal et al. [2018]
p	probability of recovered human become aware	0.90	Samanta et al. [2013]
d	natural death rate	0.00044 $year^{-1}$	Samanta and Chattopadhyay [2014]
e	death rate due to cancer	0.00079 $year^{-1}$	Rajpal et al. [2018]
β_1	dimensionless quantity ($0 < \beta_1 < 1$)	0.10	[*estimated*]
λ	awareness coefficient	0.20 $year^{-1}$	Huo and Wang [2014]
γ	recovery rate	0.30 $year^{-1}$	Rajpal et al. [2018]

5.6 Numerical results

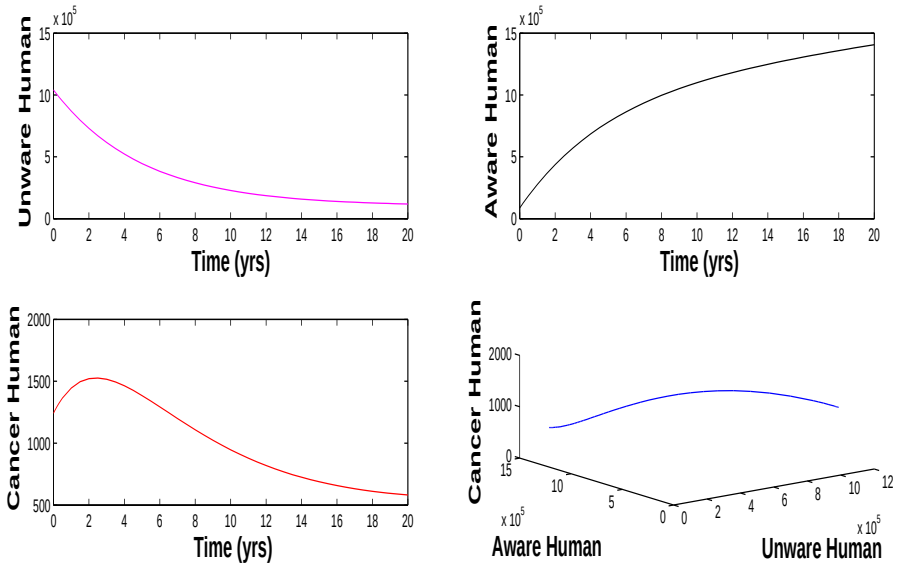


Figure 5.1: The figure depicts the solution of the system (5.2.2) and the parameter values taken from Table 5.1.

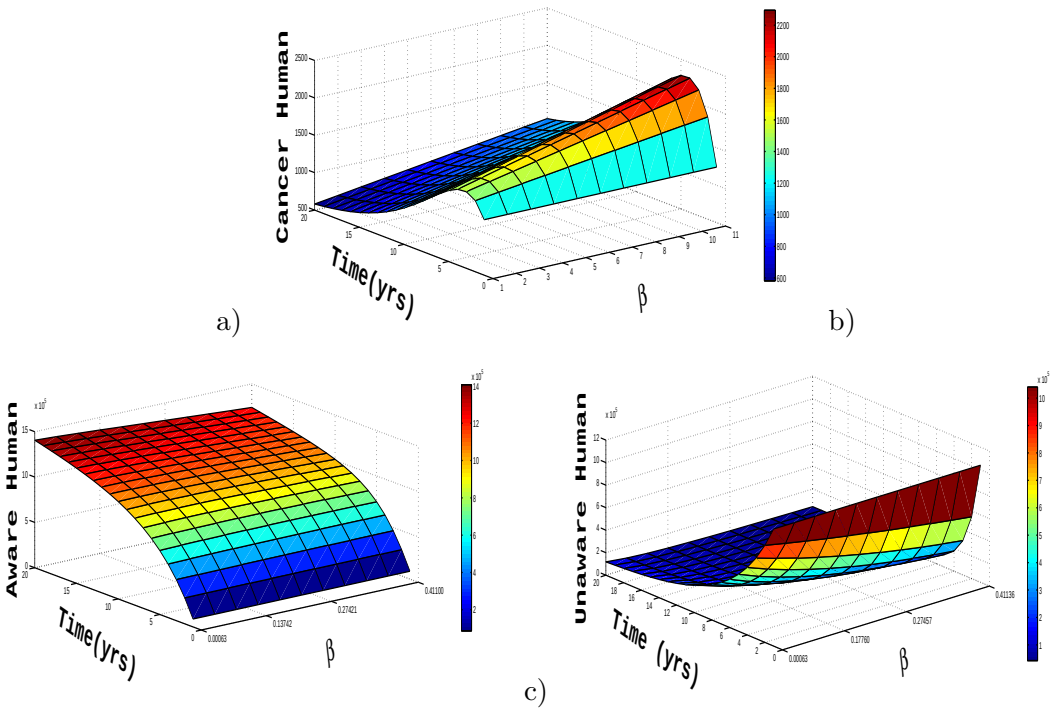


Figure 5.2: The figure depicts the role of a) cancer human, b) aware susceptible human, and c) unaware susceptible human with respect to time of the system (5.2.2) for different values of β and other values of parameters taken from Table 5.1.

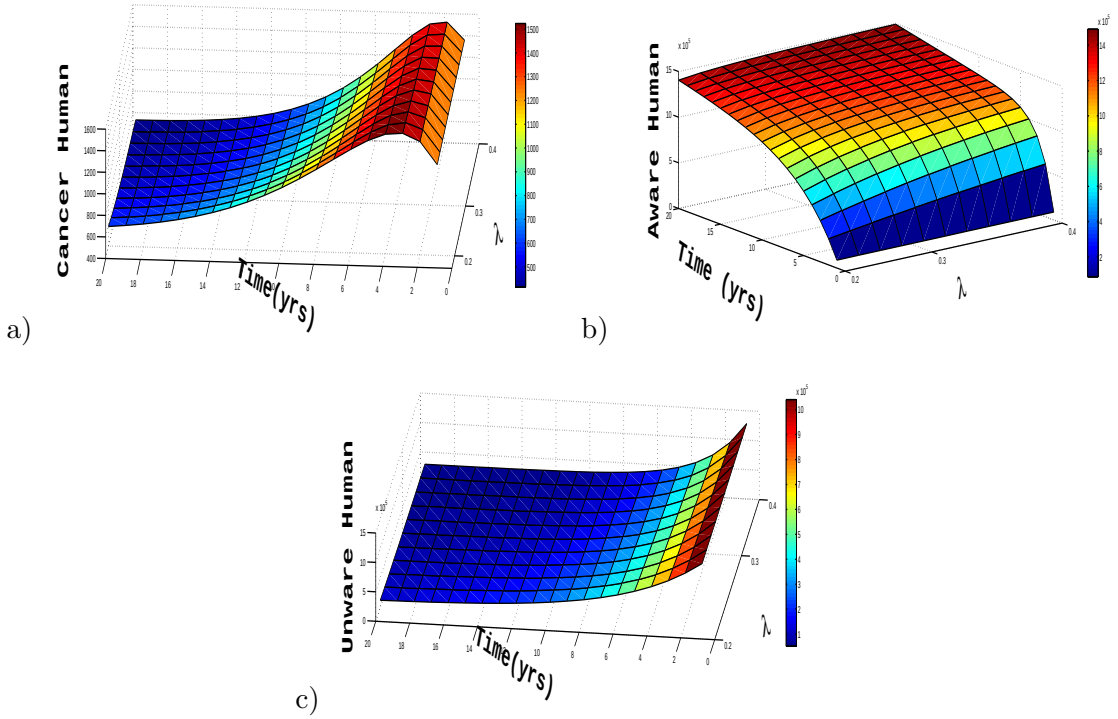


Figure 5.3: The figure depicts the role of a) cancer human, b) aware susceptible human, and c) unaware susceptible human with respect to time of the system (5.2.2) for different values of λ and other values of parameters taken from Table 5.1.

5.6.1 For deterministic differential equations

In this section, we support some numerical experiments to corroborate our analytical findings. Here we use the set of relevant parameters given in Table 5.1 and MATLAB is used for the simulations.

For the considered set of parameters values, the sufficient condition for the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ of the model system (5.2.2) is satisfied. The equilibrium point for this data are obtained as: $\overline{X}_* = 4742.80, \overline{A}_* = 343304.42, \overline{M}_* = 352572.04$. and in addition, eigenvalues of the variational matrix corresponding to the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ of the model system (5.2.2) are given by $\rho_1 = -0.206563$, $\rho_2 = -0.204206$, and $\rho_3 = -0.00440222$. All the eigenvalues are negative. Thus the equilibrium point $\overline{E}_*(\overline{X}_*, \overline{A}_*, \overline{M}_*)$ is locally asymptotically stable. Hence experiment takes a long time to approach the equilibrium point. The behavioral pattern of unaware humans, aware humans, cancer humans have presented in Figure 5.1. It is clear from the figure that cancer human increase initially but after some times it becomes decrease for time. Also, aware humans increase, and unaware humans decrease after time.

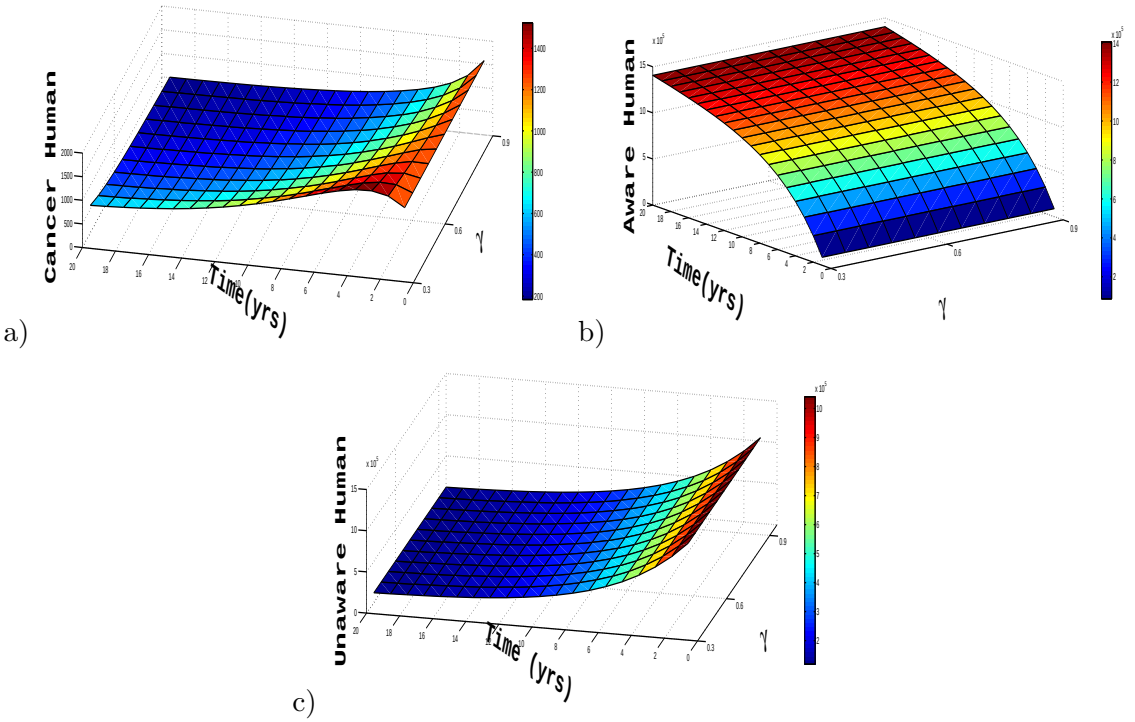


Figure 5.4: The figure depicts the role of a) cancer human, b) aware susceptible human, and c) unaware susceptible human with respect to time of the system (5.2.2) for different values of γ and other values of parameters taken from Table 5.1.

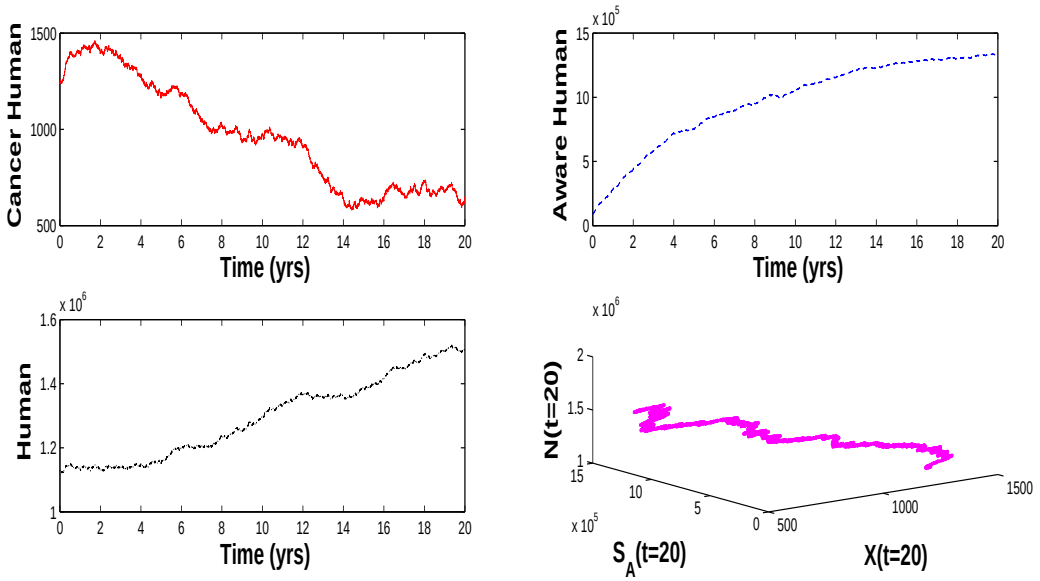


Figure 5.5: The figure depicts the solution of the system (5.2.2) and the parameter values taken from Table 5.1 with $\sigma_1 = \sigma_2 = \sigma_3 = 0.001$.

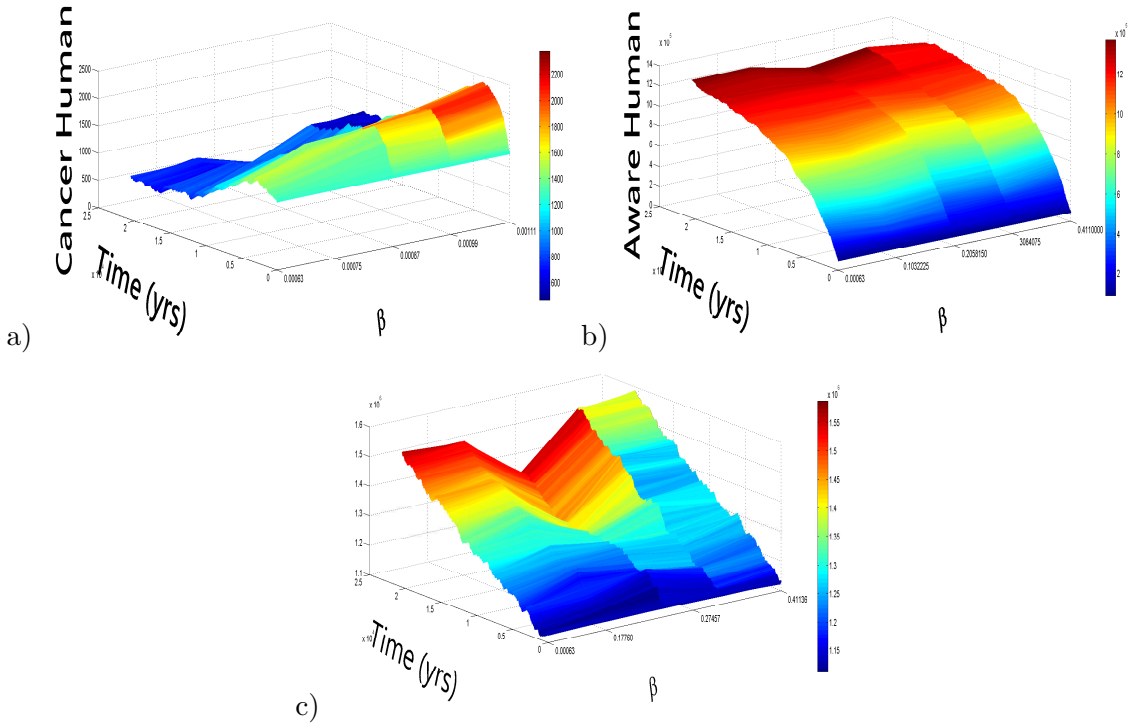


Figure 5.6: The figure depicts the role of a) cancer human, b) aware susceptible human, and c) human with respect to time of the system (5.4.1) for different values of β and other values of parameters taken from Table 5.1 with $\sigma_1 = \sigma_2 = \sigma_3 = 0.001$.

5.6.1.1 Effects of the varying incidence rate β on the system (5.2.1)

The increasing incidence of cancer is due to several factors, including population growth, behavior change, and aging as well as the changing the prevalence of certain causes of cancer linked to social and economic development. From a biological point of view, the incident rate of cancer plays a prominent role in human beings. We observed the dynamics of the model system for different values of β and other parameters are kept the same as the Table 5.1. For increasing values of β=0.00063 to 0.41100, from Figure 5.2 number of cancer humans X and a number of unaware human U increase but the number of aware susceptible human A decrease with respect to any time t relative to the Figure 5.1.

5.6.1.2 Effects of the varying awareness rate λ on the system (5.2.1)

Biologically awareness on cancer efforts to reduce cancer in population. We studied the model system for various values of the parameter λ=0.2 to 0.4 and keeping the other parameters are fixed as in Table 5.1. From Figure 5.3 it shows that number of aware susceptible human A increase but the number of cancer human X and unaware

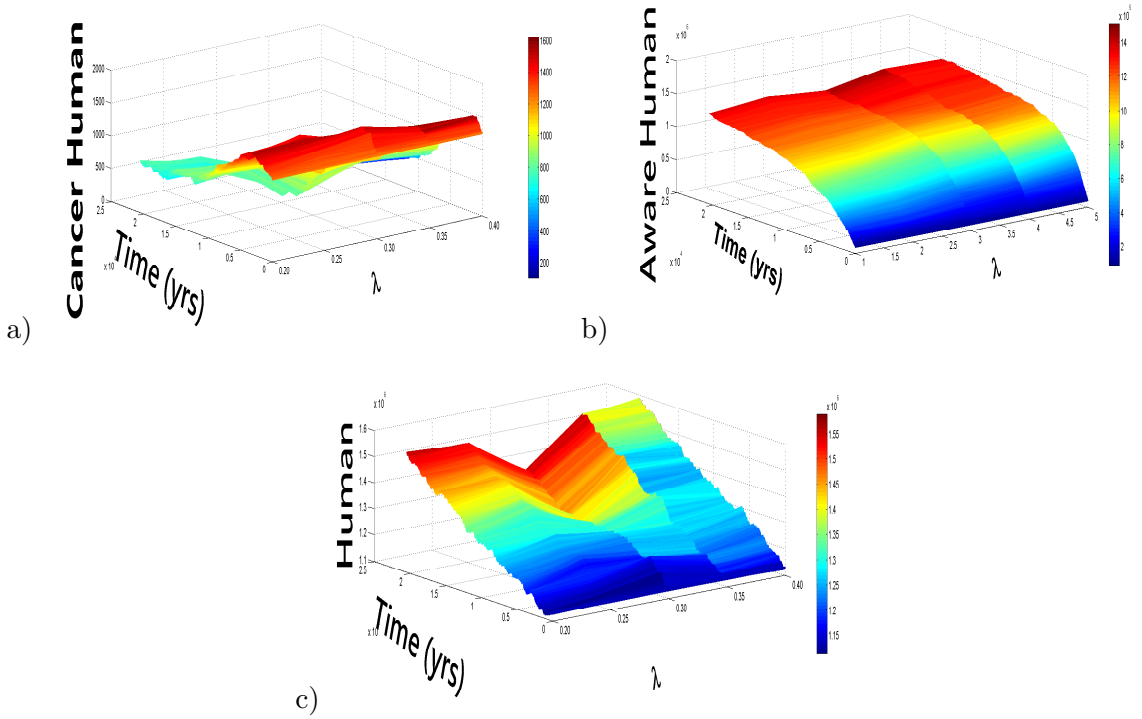


Figure 5.7: The figure depicts the role of a) cancer human, b) aware susceptible human, and c) human with respect to time of the system (5.4.1) for different values of λ and other values of parameters taken from Table 5.1 with $\sigma_1 = \sigma_2 = \sigma_3 = 0.001$.

human U decrease with respect to time t.

5.6.1.3 Effects of the varying recovery rate γ on the system (5.2.1)

Some studies suggest that cancer can be successfully recovered if it is detected at right time. Thus awareness of cancer plays a significant role in early detection, diagnosis, and treatment. We observed the dynamics of the model system for various values of γ=0.3 to 0.9 with remaining parameters are kept the same as in Table 5.1. Then Figure 5.4 illustrates that aware susceptible human A and unaware susceptible human U increase but cancer human X decreases for increasing γ with respect to a fixed time t.

5.6.2 For stochastic differential equations

The *Milsteine* scheme is used to obtain the stochastic solution of SDEs (5.4.1), which is a one order strong convergence.
We partitioned the time interval $[t_0, t_f]$ as:
$t_0 = 0 < t_1 < ... < t_n < ... < t_N < t_{N+1} = t_f$ and the *Milsteine* numerical scheme for

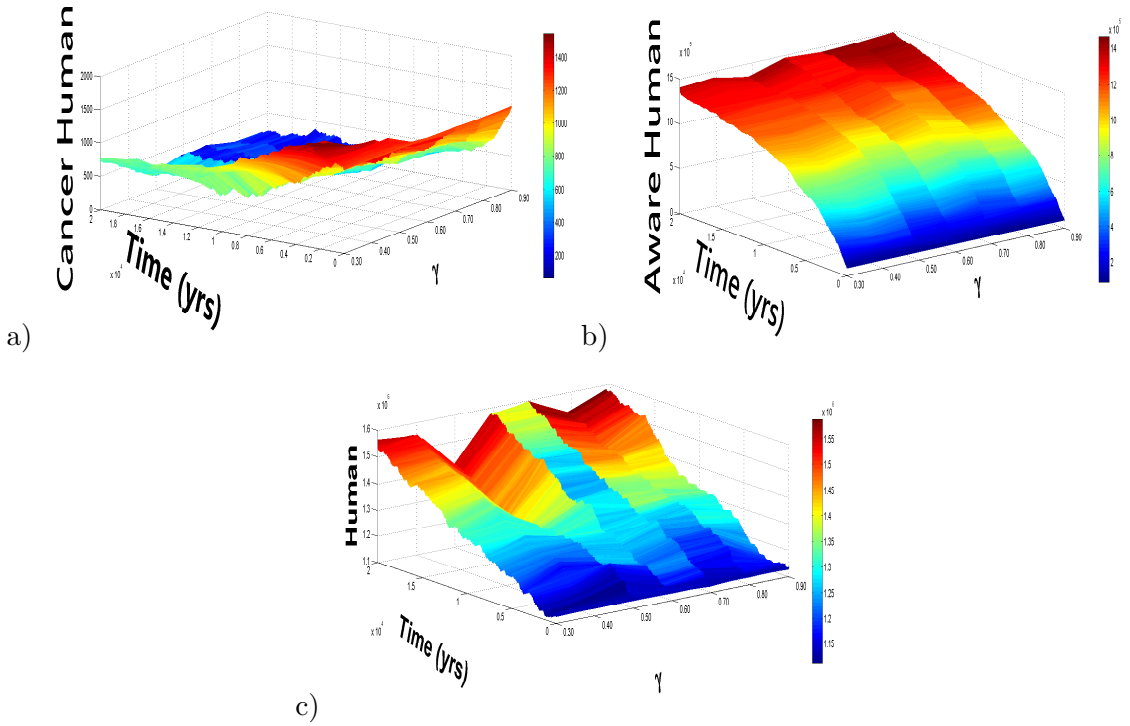


Figure 5.8: The figure depicts the role of a) cancer human, b) aware susceptible human, and c) human with respect to time of the system (5.4.1) for different values of γ and other values of parameters taken from Table 5.1 with $\sigma_1 = \sigma_2 = \sigma_3 = 0.001$.

the SDEs (5.4.1) is

$X(k+1) = X(k) + [\beta(M(k) - A(k) - X(k)) + \beta\beta_1 A(k) - \gamma X(k) - (d+e)X(k)]\Delta t + \sigma_1(X(k) - \overline{X}_*)I_{1,k}\sqrt{\Delta t} + 0.5\sigma_1^2(X(k) - \overline{X}_*)(I_{1,k}^2\Delta t - \Delta t),$

$A(k+1) = A(k) + [\lambda(M(k) - A(k) - X(k))\frac{X(k)}{1+X(k)} - \beta\beta_1 A(k) - dA(k) + p\gamma X(k)]\Delta t + \sigma_2(A(k) - \overline{A}_*)I_{2,k}\sqrt{\Delta t} + 0.5\sigma_2^2(A(k) - \overline{A}_*)(I_{2,k}^2\Delta t - \Delta t),$

$M(k+1) = M(k) + [\Pi - dM(k) - eX(k)]\Delta t + \sigma_3(M(k) - \overline{M}_*)I_{3,k}\sqrt{\Delta t} + 0.5\sigma_3^2(M(k) - \overline{M}_*)(I_{3,k}^2\Delta t - \Delta t),$

with $I_{d,k}$ is a *k-th* realization of I_d and I_d is a Gaussian random variate $N(0,1)$. Here we use *Euler-Maruyama* method to simulate the stochastic model (5.4.1). For the parameter values given in Table 5.1 with $\sigma_1 = \sigma_2 = \sigma_3 = 0.001$, all the conditions of Theorem 5.5.2 are satisfied. Thus the zero solution of the SDE model (5.4.1) is asymptotically mean square stable. We have drawn the phase portrait of the SDE model (5.4.1) in Figure 5.5 by using the above numerical scheme with the help of MATLAB 7.6 software. It is observed that trajectories are oscillatory in a small neighborhood of the equilibrium point, which is absent in the deterministic model. This oscillation comes due to the random noise that does not incorporate in the

deterministic model. From Figure 5.6, we get the same behavior of the variables as the Figure 5.2 obtained by deterministic model together with oscillation if we increase β. Again from Figure 5.7 and Figure 5.8 same behavior is observed of the variables as the Figure 5.3 and Figure 5.4 respectively obtained by deterministic together with oscillation for increasing λ and γ.

5.7 Discussion and conclusion

This chapter has discussed the prime impact of public awareness on cancer disease in a population. The main feature of this model is that unaware individuals become aware by the public awareness campaign in the form of nonlinear interaction of unaware susceptible and cancer humans. We have obtained analytical expression for biologically feasible equilibrium point and find the stability conditions for stability for deterministic as well as stochastic. Stability conditions of the endemic equilibrium point ensure that the existence of all the variables in the model system. Biologically it is very important that as it provides actual interaction in the model system. Using the parameter values given in Table 5.1 numerical simulation of the model systems has been carried out. Graphical results of both the model systems are compared in different aspects. A biological realization from the results of both the model systems is that awareness of cancer has the ability to reduce the disease. Knowledge and awareness among different underlying components of cancer are required on the individuals. These include smoking, red meat, obesity, lack of exercise, chronic inflammation, and hormones. Again to incorporate the intensity of population fluctuations in the model we introduced stochastic perturbation terms directly in the model system. From the dynamics of the deterministic and SDEs models, we see that all the trajectories are oscillatory for the stochastic model which is absent in the deterministic case. The oscillations come due to the rapid fluctuation of the environment in the population.

Cancer is growing all over the world although its incidence can be controlled through awareness and treatment. The incidence rate of cancer is influenced by various types of factors such as age, gender, race, local environmental factors, diet, and genetics. But awareness of the individuals has the ability to reduce the incidence of cancer. We observed the dynamics of the variables for both the model system for different values of β, λ, and γ. From 3D Figure 5.2 and Figure 5.6, it is clear that for the increasing incidence of cancer, the number of cancer patients increases for a particular time t with oscillations arise in the Figure 5.6. Again from the biological point of view, awareness plays an important role in population dynamics. Thus if we increase λ then from Figure 5.3 and Figure 5.7, cancer humans decrease for a

particular time t with oscillations arise in Figure 5.7. Thus it is important to increase awareness of cancer in the community via cancer education campaigns, preventive risk factors, early detection of cancer, and screening facility. Hence they are helping to boost the recovery of cancer humans. From Figure 5.4 and Figure 5.8, cancer human decrease with respect to time with oscillation arise in Figure 5.8 for increasing γ. Thus public awareness campaign provides a viable complement to the health authorities. The present chapter can be generalized in several directions. The time delay may be present in the cancer model due to the non-instantaneous response of people to the awareness campaigns same as (Al Basir et al. [2018]). Another useful direction to explore complicated dynamics would be considering cancer recovery individuals to the modeling which could be defined as a non-linear interaction of awareness program. This would be increased the dimension of the model but potentially give better insights into the complication of cancer dynamics same as (Agaba et al. [2017]). The results of the aforesaid model could be useful for design and implementation strategies for targeted awareness programs and study the dynamics of cancer disease.

Chapter 6

Modeling with cost-effective analysis to control thalassemia disease in the population

6.1 Introduction

Thalassemia is a category of anemia caused by hereditary abnormalities in hemoglobin production. The component of red blood cells that transports oxygen in hemoglobin. It is made up of two proteins, one alpha, and the other beta. If the body does not produce one of these two proteins enough, red blood cells do not develop properly and are not able to transport adequate oxygen. This leads to anemia that develops in childhood and goes throughout adulthood. Thalassemia major develops when a child receives two defective globin genes, one from each parent. Thalassemia minor develops when a child gets one defective globin gene from only one parent. Thalassemia minor individuals often have no symptoms and can live a normal life without therapy (Kim and Tridane [2017]). Thalassemia major is chronic, lifelong anemia that often develops in childhood with commonly requires regular blood transfusions. Thalassemia therapy needs lifelong blood transfusions as part of the treatment protocol, and it requires a large volume of national bloodstock, which may place a challenge on the usage of blood for other treatments (Borgna-Pignatti and Gamberini [2011]). Furthermore, frequent blood transfusion in the body can occur certain complications such as iron overload in various organs, alloimmunization, and transmitted infection through injection (Abolghasemi et al. [2007], Bhatti et al. [2004]). Thalassemia therapy frequently leads to serious problems such as iron excess, bone abnormalities, and cardiovascular disease. Thalassemia is a severe illness with a variety of life-threatening

consequences as well as psychosocial and economical issues. Increased incidence, inefficient management, and failure of preventative efforts are attributable to a lack of information and awareness among the general population (Mazzone et al. [2009]).

There are different strategies to prevent thalassemia, which include parental awareness, population screening, genetic counseling, and prenatal diagnosis. Public education campaigns about thalassemia for patients and their families, as well as communication between health care providers and physicians, are very successful in reducing the disease prevalence. In various nations where the thalassemia occurrence rate is very high, methodologies like knowledge improvement and informative courses, screening, and early determination lead to a remarkable decrease in thalassemia occurrences (Cao et al. [2002]). Premarital screening can distinguish at-risk couples and give them the necessary knowledge to reconsider their marriage decisions and understand their reproductive options. Although, in traditional Asian societies, marriage is a complicated process. If previously decided, at-risk couples may opt to continue with their marriage. The couple and their family may face severe social shame or stigma if their marriage is called off. Hence, raising awareness is a significant part of a thalassemia prevention initiative. Awareness among affected families has a crucial role in changing the mindsets of the families regarding lowering the possibilities of thalassemia running in families (Uddin et al. [2017]). Patients and their families should be educated about thalassemia, and there should be effective communication between health care professionals and patients. Thalassemia is more prevalent in rural regions, indicating a lack of education and knowledge about the disease and how to prevent it (Iqbal et al. [2015]).

Many descriptive studies pointed out that preventing disease transmission through screening programs and prenatal diagnosis is essential to the global reduction of thalassemia. Kumar et al. carried out a study on the evaluation of factors affecting awareness of thalassemia (Kumar et al. [2020b]). They claimed that various factors influence public awareness of thalassemia, which impacts the outcome of screening programs . They also demand that successful implementation of a thalassemia screening program is required to decrease the financial stress on health care systems and the emotional impact on families suffering from the disease. Badagabettu et al. prepared a descriptive cross-sectional survey design to examine thalassemia knowledge among young women aged 18–24 years from a selected undergraduate institution (Badagabettu et al. [2022]). They found that participants were not informed of thalassemia and the importance of carrier screening, lack of knowledge, and were unaware of the disease. Hossain et al. found in their research that significant knowledge gaps and widespread misconceptions concerning thalassemia in Bangladesh (Hossain et al. [2020]). Pre-

mawardhana et al. conducted a cross-sectional island-wide survey in Sri lanka. They mentioned that to achieve the primary goal of reducing affected births, the Ministry of Health must lead screening and awareness campaigns (Premawardhana et al. [2019]). Wahidiyat et al. conducted observational research on thalassemia knowledge, attitude, and practice among Indonesian teenagers (Wahidiyat et al. [2021]). They concluded that thalassemia screening for youth is critically needed, and future treatments must consider sociodemographic characteristics that may influence how they perceive the condition.

Mathematical modeling is a powerful tool for resolving problems and making efficient determinations for policies in epidemiology, public health, and biological sciences. Recently many researchers have been focusing their study on mathematical models of thalassemia to evaluate the dynamics in different aspects. A few analytical studies have been undertaken to examine the efficiency of thalassemia preventive methods and the cost-effectiveness of thalassemia preventive programs at the community level. Thakur et al. formulated a mathematical model on the transmission of thalassemia using the concept of pure fractions (Thakur et al. [2016]). They deduced results to reduce the transmission of the thalassemia gene and create a new generation without the thalassemia major gene. Some studies have also been carried out theoretically to assess the cost-effectiveness of thalassemia preventive programs, which include population education, screening of populations, genetic counseling, and prenatal diagnosis (Mallik et al. [2010], Sangani et al. [1990]). Reed-Embleton et al. conducted a study on prevalence-based cost-of-disease in thalassemia children in Sri Lanka (Reed-Embleton et al. [2020]). They showed that thalassaemia has a huge economic impact on Sri Lankan health systems and the families of thalassemia children. Esmaeilzadeh et al. examined that screening is a very cost-effective, long-term value-for-money technique that has therapeutic and economical advantages over-controlling thalassemia patients (Esmaeilzadeh et al. [2021]). Kim and Tridane formulated a mathematical model to assess the long-term impact and ability of thalassemia preventive interventions at the community level (Kim and Tridane [2017]). They found that preventative measures reduce the prevalence of thalassemia in a short time, but do not eradicate the disease in the long term. Thus there is still a need for further research to find out the best approaches for regulating thalassemia patients with a cost-effective strategy in the community.

To address this study gap, we extended the work (Kim and Tridane [2017]) to examine the advantages of using awareness-induced premarital screening rates and awareness-induced marriage reconsider rate of adults as control measures to lower the burden of thalassemia in the population and its related costs. The optimal con-

trol technique is used in the present chapter to create compromises between thalassemia prevalence levels and the cost effects of non-pharmaceutical interventions to aid decision-making. The economic impact of thalassemia is determined by the disease prevalence at birth, treatment availability, efficacy, and treatment cost. Next, we examined the impact of these control efforts as the intensity of the thalassemia varies (i.e R_0 varies). Now, researchers are interested in this particular feature of R_0's influence on controls (Kumar et al. [2020a], Lee et al. [2010]). Lee et al. designed an influenza model in 2010 to examine the effect of antiviral therapy and isolation for various values of the basic reproduction number (Lee et al. [2010]). They realized that the combined impact of both controls considerably reduces the disease burden for all values of R_0. Again, Kumar et al. formulated an optimal control model with the effect of information-induced vaccination and recovery of infected via limited treatment (Kumar et al. [2020a]). They demonstrated the impact of the basic reproduction number on proposed control strategies as well as the dynamics of infectious diseases.

The rest of the chapter is organized as follows: *Sect.* 6.2 describes a mathematical model to study the dynamics of thalassemia including different control functions. A mathematical analysis of the thalassemia model is carried out in *Sect.* 6.3. In *Sect.* 6.4, the optimal control problem is formulated by considering different control functions in the thalassemia system and defining the objective function used in the optimal control framework. In *Sect.* 6.5, numerical simulation is performed by utilizing different types of control strategies. Finally, the chapter ends with a conclusion summarized in *Sect.* 6.6.

6.2 Model formulation

In this section we would formulate an ODE model under public awareness of thalassemia. As the hereditary pattern of thalassemia, marriages between thalassemia carriers would considerably increase the incidence of thalassemia major in the population (Hasanshahi and Khanjani [2021]). Thalassemia is an inherited blood disease that is passed to the next generations through marriage. We divide the total adult population into seven subgroups described in Table 6.1. Then we formulate a mathematical model by considering the interactions among those subgroups and necessary assumptions are given below.

(A1) We assume that A_M, and A_F are the rates of immigration of the adults in the form of unaware of thalassemia to S_M and S_F respectively.

(A2) People with a positive family history of thalassemia have higher knowledge and they are more likely to undergo a thalassemia premarital screening (Patel et al.

[2016]). Thus if the thalassemia patients increase, then the number of thalassemia-aware individuals also tend to increase due to psychological fear. People with a higher level of education are also aware of the risk of thalassemia compared to uneducated individuals. Thus we consider $\sigma_M \frac{T}{1+T} S_M$ and $\sigma_F \frac{T}{1+T} S_M$ are the rates of unaware male and female adults to non-carrier male and female adults respectively. As the screening test is going in the community, some fraction of the above rates can be determined as thalassemia carriers. We consider the terms $\sigma_M \beta_1 \frac{T}{1+T} S_M$ and $\sigma_F \beta_1 \frac{T}{1+T} S_M$ that identify thalassemia carrier in unaware males and females adult respectively, where $0 < \beta_1 < 1$.

(A3) People who are aware of thalassemia can reconsider their marriage decision. The possibility of a marriage that thalassemia major child will not occur are given by (Kim and Tridane [2017])

- non-carrier male × non-carrier female or non-carrier male × carrier female
- carrier male × non-carrier female

i.e non-carrier male adult can marry either non-carrier female adult or carrier female adult, as in these cases thalassemia major baby will not occur. Thus we consider the term $\beta_M S_M^A (S_F^A + C_F)$ of the marriage of non-carrier adult with non-carrier female adult or carrier female adult, where β_M is the marriage rate of a non-carrier male adult. Similarly, we take $\beta_F S_F^A (S_M^A + C_M)$ as a marriage rate of a non-carrier female adult with non-carrier male adult or carrier male adult, where β_F is the marriage rate of non-carrier female adult.

(A4) Identified carriers are aware of their marriage decision. We assume that they always marry non-carrier individuals so that thalassemia patients will not occur. Hence, carrier male adult can marry non-carrier female adult only. Thus we consider the term $\delta_M C_M S_F^A$ of the marriage of carrier male adult with a non-carrier female adult, where δ_M is the marriage rate of a non-carrier male adult. Similarly, we take $\delta_F C_F S_M^A$ as a marriage rate of carrier female adult with a non-carrier male adult.

(A5) People who are unaware of thalassemia have the possibility of marriage with unaware adults only. In this case thalassemia major child can occur. We consider the term $\gamma S_M S_F$ as a marriage between unaware adults, where γ is the marriage rate of an unaware adult.

Considering the above assumptions in mind, we extended the model in (Kim and Tridane [2017]) in the following simplified form

Table 6.1: All the variable names and their characteristics

Variables Name	Characteristics
S_M, S_F	Unaware adults: male and female
S_M^A, S_F^A	Non-carrier of thalassemia: male and female
C_M, C_F	Carrier of thalassemia: male and female
T	Thalassemia patients

$$\begin{aligned}
\frac{dS_M}{dt} &= A_M - \sigma_M \tfrac{T}{1+T} S_M - \sigma_M \beta_1 \tfrac{T}{1+T} S_M - \gamma S_M S_F - d_M S_M, \\
\frac{dS_F}{dt} &= A_F - \sigma_F \tfrac{T}{1+T} S_F - \sigma_F \beta_1 \tfrac{T}{1+T} S_F - \gamma S_M S_F - d_F S_F, \\
\frac{dS_M^A}{dt} &= \sigma_M \tfrac{T}{1+T} S_M - \beta_M S_M^A (S_F^A + C_F) - d_M S_M^A, \\
\frac{dS_F^A}{dt} &= \sigma_F \tfrac{T}{1+T} S_F - \beta_F S_F^A (S_M^A + C_M) - d_F S_F^A, \\
\frac{dC_M}{dt} &= \sigma_M \beta_1 \tfrac{T}{1+T} S_M - \delta_M C_M S_F^A - d_M C_M, \\
\frac{dC_F}{dt} &= \sigma_F \beta_1 \tfrac{T}{1+T} S_F - \delta_F C_F S_M^A - d_F C_F, \\
\frac{dT}{dt} &= \gamma \nu \tfrac{T}{1+T} S_M S_F - eT - \tfrac{1}{2}(d_M + d_F) T,
\end{aligned} \tag{6.2.1}$$

where

$$\begin{aligned}
S_M(0) > 0, S_F(0) > 0, S_M^A(0) > 0, S_F^A(0) > 0, \\
C_M(0) > 0, C_F(0) > 0, T(0) > 0.
\end{aligned} \tag{6.2.2}$$

Table 6.2: List of parameters and their description

Parameters	Descriptions
A_M, A_F	Immigration rate of adult to unaware male and female adult
β_M, β_F	Marriage rate of non-carrier male (female) adult with non-carrier or carrier female (male) adult
σ_M, σ_F	Premarital screening rates of unaware male (female) to non-carrier male (female) of thalassemia
$\sigma_M\beta_1$, $\sigma_F\beta_1$	Premarital screening rates of unaware male (female) to carrier male (female) of thalassemia
δ_M, δ_F	Marriage rate of carrier male (female) adult with non carrier female (male) adult
γ	Marriage rate between unaware male and female adult.
d_M, d_F	Death rate of male and female
e	Death rate due to thalassemia
ν	Proportionality constant

6.2.1 Positivity of solutions

Theorem 6.2.1. *Let all the initial conditions $S_M(0) > 0$, $S_F(0) > 0$, $S_M^A(0) > 0$, $S_F^A(0) > 0$, $C_M(0) > 0$, $C_F(0) > 0$, and $T(0) > 0$. Then the solution (S_M, S_F, S_M^A, S_F^A, C_M, C_F, T) of the system (6.2.1) remains positive for all $t > 0$.*

Proof. From the first equation of the system (6.2.1), we have
$\frac{dS_M}{dt} = A_M - \sigma_M \frac{T}{1+T} S_M - \sigma_M \beta_1 \frac{T}{1+T} S_M - \gamma S_M S_F - d_M S_M$,
This can be written as:
$\frac{dS_M}{S_M} \geq -(\sigma_M \frac{T}{1+T} + \sigma_M \beta_1 \frac{T}{1+T} + \gamma S_F + d_M)dt$,
Integrating both sides of the above inequality, we obtain
$S_M(t) \geq S_M(0) e^{-\int_0^t (\sigma_M \frac{T}{1+T} + \sigma_M \beta_1 \frac{T}{1+T} + \gamma S_F + d_M)ds} > 0$, for all $t > 0$.

Similarly employing the same approach for all the variables, it can be easily shown that
$S_F(t) > 0$, $S_M^A(t) > 0$, $S_F^A(t) > 0$, $C_M(t) > 0$, $C_F(t) > 0$, $T(t) > 0$ for all $t > 0$. □

6.2.2 Boundedness

Proposition 2. *Let $S_M(0) > 0$, $S_F(0) > 0$, $S_M^A(0) > 0$, $S_F^A(0) > 0$, $C_M(0) > 0$, $C_F(0) > 0$, $T(0) > 0$ be the initial conditions of the system (6.2.1). Then the system (6.2.1) has non negative solution (S_M, S_F, S_M^A, S_F^A, C_M, C_F, T) for all $t > 0$. In addition, $limSup_{t\to\infty}$ $W(t) < \frac{A_M + A_F}{d}$. Moreover, if $W(0) < \frac{A_M + A_F}{d}$, then $W(t) < \frac{A_M + A_F}{d}$ is the feasible solution of the system (6.2.1).*
Thus the region of attraction is given by
$\Gamma = \left\{(S_M, S_F, S_M^A, S_F^A, C_M, C_F, T) \in R_+^7 : W(t) \leq \frac{A_M + A_F}{d}\right\}$ *and attracts all solutions initiation in the positive interior of septagon, where* $W = S_M + S_F + S_M^A + S_F^A + C_M + C_F + T$.

Proof. From, the first equation of the system (6.2.1)
$\frac{dS_M}{dt} + (\sigma_M \frac{T}{1+T} + \sigma_M \beta_1 \frac{T}{1+T} + \gamma S_F) S_M + d_M S_M > 0$.
Integrating this from 0 to t, we get
$\frac{d}{dt}[S_M(t) exp\{\int_0^t (\sigma_M \frac{T}{1+T} + \sigma_M \beta_1 \frac{T}{1+T} + \gamma S_F)(\bar{w})d\bar{w} + dt\}] > 0$.
This imply that
$S_M(t) > S_M(0) exp\{-(\int_0^t (\sigma_M \frac{T}{1+T} + \sigma_M \beta_1 \frac{T}{1+T} + \gamma S_F)(\bar{w})d\bar{w} + dt)\} > 0$, $t > 0$.
This means that S_M is non negative for all $t > 0$.
Similarly, it can be shown that S_F, S_M^A, S_F^A, C_M, C_F, T are all non negative for all $t > 0$.
Again, since $W = S_M + S_F + S_M^A + S_F^A + C_M + C_F + T$.

$\therefore \frac{dW}{dt} = \frac{dS_M}{dt} + \frac{dS_F}{dt} + \frac{dS_M^A}{dt} + \frac{dS_F^A}{dt} + \frac{dC_M}{dt} + \frac{dC_F}{dt} + \frac{dT}{dt}$,
$\frac{dW}{dt} = A_M + A_F - \beta_M S_M^A(S_F^A + C_F) - \beta_F S_F^A(S_M^A + C_M) - \delta_M C_M S_F^A - \delta_F C_F S_M^A - \gamma(2 - \nu\frac{T}{1+T})S_M S_F - eT - d_M S_M - d_F S_F - d_M S_M^A - d_F S_F^A - d_M C_M - d_F C_F - \frac{1}{2}(d_M + d_F)T$
$\frac{dW}{dt} < A_M + A_F - dW$, as $0 < \nu < 1$ and $d{=}min\{d_M, \quad d_F\}$,
solving this, we get
$W(t) < W(0)e^{-dt} + \frac{A_M+A_F}{d}(1 - e^{-dt})$.
Hence, $W(t) < \frac{A_M+A_F}{d}$ as $t \to \infty$.
Also, if $W(0) < \frac{A_M+A_F}{d}$, then $W(t) < \frac{A_M+A_F}{d}$. □

6.3 Model equilibria and stability analysis

This section deduce thalassemia free equilibrium point, thalassemia present equilibrium point, calculate the basic reproduction number and carry out stability analysis.

6.3.1 Disease-free equilibrium

In the absence of thalassemia (i.e for $T{=}0$), the model (6.2.1) has a disease free equilibrium point $E_0\,(S_M^*, S_F^*, 0, 0, 0, 0, 0)$, where $S_M^* = \frac{A_M}{\gamma S_F^* + d}$,
and $S_F^* = \frac{\gamma(A_F - A_M) + d^2 + \sqrt{(\gamma(A_M - A_F) + d^2)^2 + 4\gamma d A_F}}{2\gamma}$.

6.3.2 Basic reproduction number

The estimated number of secondary cases created by a typical disease individual in a susceptible community defines as a basic reproduction number and denoted by R_0 (Diekmann et al. [1990]). Here, we define basic reproduction number $R_0{=}\frac{(\gamma S_M S_F)^2}{A_M A_F}$. Then the thalassemia can not passes to offspring when $R_0 < 1$ because thalassemia individual creates less than one new thalassemia major child during the period. Again, if $R_0 > 1$, the thalassemia major child can occur as thalassemia carrier community creates more than one new thalassemia offspring during the period.

The jacobian $\overline{J}$ of the system (6.2.1) at $E_0\,(S_M^*, S_F^*, 0, 0, 0, 0, 0)$ is given by

$$\overline{J} \equiv \begin{bmatrix} -\frac{A_M}{S_M} & -\gamma S_M & 0 & 0 & 0 & 0 & -\sigma_M S_M - \sigma_M \beta_1 S_M \\ -\gamma S_F & -\frac{A_F}{S_F} & 0 & 0 & 0 & 0 & -\sigma_F S_F - \sigma_F \beta_1 S_F \\ 0 & 0 & -d & 0 & 0 & 0 & \sigma_M S_M \\ 0 & 0 & 0 & -d & 0 & 0 & \sigma_F S_F \\ 0 & 0 & 0 & 0 & -d & 0 & \sigma_M \beta_1 S_M \\ 0 & 0 & 0 & 0 & 0 & -d & \sigma_F \beta_1 S_F \\ 0 & 0 & 0 & 0 & 0 & 0 & -(\gamma + d) \end{bmatrix}.$$

Then the five eigenvalues of the above matrix are given by
$-(\gamma + d)$, $-d$, $-d$, $-d$, $-d$,
and the remaining two eigenvalues are determined by $2\times$ 2 matrix

$$\overline{M} \equiv \begin{bmatrix} -\frac{A_M}{S_M} & -\gamma S_M \\ -\gamma S_F & -\frac{A_F}{S_F} \end{bmatrix}.$$

So, Trace $\overline{M}=-\frac{A_M}{S_M} - \frac{A_F}{S_F}$ and Det$\overline{M}=\frac{A_M}{S_M}\frac{A_F}{S_F} - \gamma^2 S_M S_F$. Thus the eigenvalues of matrix $\overline{M}$ have negative real parts iff Trace$\overline{M} < 0$ and Det$\overline{M} > 0$.

Theorem 6.3.1. *The disease-free equilibrium E_0 of the model (6.2.1) is locally asymptotically stable in Γ_ε if $R_0 < 1$, and unstable if $R_0 > 1$.*

6.3.3 Thalassemia present equilibrium point

We find the existence conditions of the thalassemia present equilibrium point. From the system equations in (6.2.1), we obtain

$$AT^3 + BT^2 + CT + D = 0, \tag{6.3.1}$$

where $A = \gamma(\frac{1}{2}(d_M + d_F) + e)^2$,
$B = (\frac{1}{2}(d_M + d_F) + e)\{\gamma(\frac{1}{2}(d_M + d_F) + e) - \gamma(\nu A_M - \frac{1}{2}(d_M + d_F) - e) - \gamma(\nu A_F - \frac{1}{2}(d_M + d_F) - e) - \nu(\sigma_M + \sigma_M\beta_1 + d_M)(\sigma_F + \sigma_F\beta_1 + d_F)\}$,
$C = \gamma(\nu A_M - \frac{1}{2}(d_M + d_F) - e)(\nu A_F - \frac{1}{2}(d_M + d_F) - e) - (\frac{1}{2}(d_M + d_F) + e)\{\gamma(\nu A_M - \frac{1}{2}(d_M + d_F) - e) + \gamma(\nu A_F - \frac{1}{2}(d_M + d_F) - e) + \nu d_F(\sigma_M + \sigma_M\beta_1 + d_M) + \nu d_M(\sigma_F + \sigma_F\beta_1 + d_F)\}$,
and

$D = \gamma(\nu A_M - \frac{1}{2}(d_M + d_F) - e)(\nu A_F - \frac{1}{2}(d_M + d_F) - e) - \nu(\frac{1}{2}(d_M + d_F) + e)d_M d_F.$

The equation (6.3.1) has exactly two positive roots T_1^* and T_2^* (say) if the discriminants Δ of the equation is zero, where

$\Delta = 18ABCD - 4B^3D + B^2C^2 - 4AC^3 - 27A^2D^2.$

From these two positive vales of T_1^* and T_2^*, we obtain two distinct thalassemia present equilibrium points of the model system (6.2.1) as $(S_{M_1}^*, S_{F_1}^*, S_{M_1}^{A^*}, S_{F_1}^{A^*}, C_{M_1}^*, C_{F_1}^*, T_1^*)$ and $(S_{M_2}^*, S_{F_2}^*, S_{M_2}^{A^*}, S_{F_2}^{A^*}, C_{M_2}^*, C_{F_2}^*, T_2^*)$.

The jacobian matrix J of the system (6.2.1) at $E(S_M, S_F, S_M^A, S_F^A, C_M, C_F, T)$ is given by

$$J = \begin{bmatrix} a_{11} & a_{12} & 0 & 0 & 0 & 0 & a_{17} \\ a_{21} & a_{22} & 0 & 0 & 0 & 0 & a_{27} \\ a_{31} & 0 & a_{33} & a_{34} & 0 & a_{36} & a_{37} \\ 0 & a_{42} & a_{43} & a_{44} & a_{45} & 0 & a_{47} \\ a_{51} & 0 & 0 & a_{54} & a_{55} & 0 & a_{57} \\ 0 & a_{62} & a_{63} & 0 & 0 & a_{66} & a_{67} \\ a_{71} & a_{72} & 0 & 0 & 0 & 0 & a_{77} \end{bmatrix},$$

where

$a_{11} = \frac{A_M}{S_M}; a_{12} = -\gamma S_M;\ a_{17} = -\sigma_M \frac{S_M}{(1+T)^2} - \sigma_M \beta_1 \frac{S_M}{(1+T)^2};\ a_{21} = -\gamma S_F; a_{22} = \frac{A_F}{S_F};$
$a_{27} = -\sigma_F \frac{S_F}{(1+T)^2} - \sigma_F \beta_1 \frac{S_F}{(1+T)^2}); a_{31} = \sigma_M \frac{T}{1+T}; a_{33} = -\beta_M(S_F^A + C_F) - d;\ a_{34} = -\beta_M *$
$S_M^A; a_{36} = -\beta_M S_M^A; a_{37} = \sigma_M \frac{S_M}{(1+T)^2};\ a_{42} = \sigma_F \frac{T}{1+T};\ a_{44} = -\beta_F(S_M^A + C_M) - d; a_{45} =$
$-\beta_F S_F^A; a_{47} = \sigma_F \frac{S_F}{(1+T)^2};\ a_{51} = \sigma_M \beta_1 \frac{T}{1+T}; a_{54} = -\delta_M C_M; a_{55} = -\delta_M S_F^A - d; a_{57} =$
$\sigma_M \beta_1 \frac{S_F}{(1+T)^2};\ a_{62} = \sigma_F \beta_1 \frac{T}{1+T}; a_{63} = -\delta_F C_F; a_{66} = -\delta_F S_M^A - d; a_{67} = \sigma_F \beta_1 \frac{S_F}{(1+T)^2};$
$a_{71} = \mu T \frac{S_F}{1+T}; a_{72} = \mu T \frac{S_M}{1+T};\ a_{77} = -(r+d).$

The characteristic equation is given by

$$\begin{aligned} \psi(x) \;=\; & -[\{x(x-a_{55}) + a_{44}(a_{55}-x) - a_{45}a_{54}\}\{x(x-a_{66}) - a_{36}a_{63}\} \\ & + a_{34}a_{43}(x-a_{55})(x-a_{66}) - a_{33}\{a_{44}(x-a_{55}) + x(a_{55}-x) \\ & + a_{45}a_{54}\}(x-a_{66})][-a_{22}x^2 - a_{77}x^2 - a_{17}a_{71}x - a_{27}a_{72}x \\ & + a_{22}a_{77}x - a_{12}\{a_{21}(x-a_{77}) + a_{27}a_{71}\} + a_{11}\{a_{22}(x-a_{77}) \\ & + x(a_{77}-x) + a_{27}a_{72}\} + a_{17}a_{22}a_{71} - a_{17}a_{21}a_{72} + x^3]. \end{aligned}$$

Analytically it is quite difficult to find an explicit form of the characteristic equation and conditions for stability of the system at thalassemia present equilibrium point. Let ρ_i be the coefficient of x^i in the above characteristic equation, where i=0, 1,...,6. By Routh-Hurwitz criterion, it can be found the sufficient conditions for the

stability of thalassemia present equilibrium point.

6.4 Application of optimal control to the thalassemia model

Here we define and analyze an optimal control problem by introducing awareness induced premarital screening rate and marriage reconsider rate. Awareness is the most effective as well as applicable preventive and control policy during the prevalence of thalassemia. Constant controls may be costly because it requires treatment at better ranges for all periods. Effective manipulation can be achievable in a finite time when time-based controls are taken to consideration (Okosun et al. [2013]). An effective intervention plan minimizes the number of thalassemia cases at the lowest possible cost (Kar and Jana [2013]). The following controls are used in the optimal system:
• Control $u_1(t) \in [0,1]$ introducing awareness induced premarital screening rate.
• Control $u_2(t) \in [0,1]$ awareness induced marriage reconsider rate between unaware male and female adults.

Considering the above control functions, the model can be reformulated as optimal control problem in the following form by applying similar techniques (Mandal et al. [2021], Bandekar and Ghosh [2021], Verma [2020], Srivastav and Ghosh [2016])

$$\begin{aligned}
\tfrac{dS_M}{dt} &= A_M - \sigma_M(1+u_1)\tfrac{T}{1+T}S_M - \sigma_M\beta_1(1+u_1)\tfrac{T}{1+T}S_M \\
&\quad -\gamma(1-u_2)S_MS_F - d_MS_M, \\
\tfrac{dS_F}{dt} &= A_F - \sigma_F(1+u_1)\tfrac{T}{1+T}S_F - \sigma_F\beta_1(1+u_1)\tfrac{T}{1+T}S_F \\
&\quad -\gamma(1-u_2)S_MS_F - d_FS_F, \\
\tfrac{dS_M^A}{dt} &= \sigma_M(1+u_1)\tfrac{T}{1+T}S_M - \beta_MS_M^A(S_F^A + C_F) - d_MS_M^A, \\
\tfrac{dS_F^A}{dt} &= \sigma_F(1+u_1)\tfrac{T}{1+T}S_F - \beta_FS_F^A(S_M^A + C_M) - d_FS_F^A, \\
\tfrac{dC_M}{dt} &= \sigma_M\beta_1(1+u_1)\tfrac{T}{1+T}S_M - \delta_MC_MS_F^A - d_MC_M, \\
\tfrac{dC_F}{dt} &= \sigma_F\beta_1(1+u_1)\tfrac{T}{1+T}S_F - \delta_FC_FS_M^A - d_FC_F, \\
\tfrac{dT}{dt} &= \gamma\nu(1-u_2)\tfrac{T}{1+T}S_MS_F - eT - \tfrac{1}{2}(d_M+d_F)T,
\end{aligned} \tag{6.4.1}$$

with

$$S_M(0) > 0, S_F(0) > 0, S_M^A(0) > 0, S_F^A(0) > 0, C_M(0) > 0, C_F(0) > 0, T(0) > 0. \tag{6.4.2}$$

Control variables $(1+u_1)$ and $(1-u_2)$ are employed in the system (6.2.1) to describe

the dynamics of rising efforts made for effective awareness-induced premarital screening rate and awareness-induced marriage reconsider rate between unaware male and female adults as in (Tchuenche et al. [2011]).

The main goal of this work is to reduce the thalassemia cases by introducing two effective awareness-induced time-dependent controls u_1 and u_2 into the model system (6.2.1). Because of the high expense of treatment and the lack of public awareness, it is important to devise a plan that reduces the number of thalassemia cases and the related costs with increasing the number of people who are aware of the disease. Optimal control theory is a very useful and efficient tool for identifying such techniques (Verma [2020], Srivastav and Ghosh [2016], Kar and Jana [2013]). As a result, an objective function is defined as follows:

$$J = \min_{(u_1,u_2)} \int_0^{t_f} (A_1 T - A_2 S_M^A - A_3 S_F^A + \frac{A_4}{2} u_1^2 + \frac{A_5}{2} u_2^2) e^{-qt} dt, \tag{6.4.3}$$

subject to the optimal system (6.4.1). Here A_1, A_2, and A_3 represent the cost of interventions on $[0,\ t_f]$ of thalassemia patients, aware male adult, and aware female adult respectively. Also A_3 and A_4 are used as weights for the cost of square of the controls u_1 and u_2 respectively with discount rate is denoted by q. We employed quadratic cost on the controls to find nonlinear interactions in the cost at a high implementation level. The associated cost is related to blood transfusion, iron chelation drugs, treatment of side effects, premarital tests in the laboratory. The best possible control is attempted, such that

$$(u_1^*, u_2^*) = \min_{(u_1,u_2)\in \mathfrak{U}} J(u_1, u_2) \tag{6.4.4}$$

where $\mathfrak{U}$=$\{(u_1, u_2)$:$0 \leq u_1(t), u_2(t) \leq 1$ for $t \in [0,\ t_f]\ \}$ is the control set.

The optimal control problem is solved using Pontryagain's approach, and it is described below:

$$\begin{aligned} H = A_1 T - A_2 S_M^A - A_3 S_F^A + \frac{A_4}{2} u_1^2 + \frac{A_5}{2} u_2^2 + \lambda_1 \frac{dS_M}{dt} + \lambda_2 \frac{dS_F}{dt} \\ + \lambda_3 \frac{dS_M^A}{dt} + \lambda_4 \frac{dS_M^A}{dt} + \lambda_5 \frac{dC_M}{dt} + \lambda_6 \frac{dC_F}{dt} + \lambda_7 \frac{dT}{dt}, \end{aligned} \tag{6.4.5}$$

where the adjoint variables or co-state variables $\lambda_i(t_f)$=0, i=1, 2...7, are find out the following set of differential equations:

$$
\begin{aligned}
\tfrac{d\lambda_1}{dt} &= \sigma_M(1+u_1)\tfrac{T}{1+T}\lambda_1 + \sigma_M\beta_1(1+u_1)\tfrac{T}{1+T}\lambda_1 + \gamma(1-u_2)S_F\lambda_1 + d_M\lambda_1 + \\
&\quad \gamma(1-u_2)S_F\lambda_2 - \sigma_M(1+u_1)\tfrac{T}{1+T}\lambda_3 - \sigma_M\beta 1(1+u_1)\tfrac{T}{1+T}\lambda_5 \\
&\quad +\gamma(1-u_2)\eta\tfrac{T}{1+T}S_F\lambda_7, \\
\tfrac{d\lambda_2}{dt} &= \sigma_F(1+u_1)\tfrac{T}{1+T}\lambda_2 + \sigma_F\beta - 1(1+u_1)\tfrac{T}{1+T}\lambda_2 + \gamma(1-u_2)S_M\lambda_2 \\
&\quad +d_F\lambda_2 + \gamma(1-u_2)S_M\lambda_1 - \sigma_F(1+u_1)\tfrac{T}{1+T}\lambda_4 - \sigma_F\beta 1(1+u_1)\tfrac{T}{1+T}\lambda_6 \\
&\quad +\gamma(1-u_2)\eta\tfrac{T}{1+T}S_M\lambda_7, \\
\tfrac{d\lambda_3}{dt} &= A_2 + \beta_M(S_F^A + C_F)\lambda_3 + \lambda_3 d_M + \beta_F S_F^A\lambda_4 + \delta_F C_F\lambda_6, \\
\tfrac{d\lambda_4}{dt} &= A_3 + \beta_F(S_M^A + C_M)\lambda_4 + d_F\lambda_4 + \beta_M S_M^A\lambda_3 + \delta_M C_M\lambda_5, \\
\tfrac{d\lambda_5}{dt} &= \beta_F S_F^A\lambda_4 + \delta_M S_F^A\lambda_5 + d_M\lambda_5, \\
\tfrac{d\lambda_6}{dt} &= \beta_M S_M^A\lambda_3 + \delta_F S_M^A\lambda_6 + d_F\lambda_6, \\
\tfrac{d\lambda_7}{dt} &= -A_1 + \sigma_M(1+u_1)(1+\beta_1)S_M\lambda(T)\lambda_1 \\
&\quad +\sigma_F(1+u_1)(1+\beta_1)S_F\lambda(T)\lambda_2 - \sigma_M(1+u_1)S_M\lambda(T)\lambda_3 \\
&\quad -\sigma_F(1+u_1)S_F\lambda(T)\lambda_4 - \sigma_M(1+u_1)\beta_1 S_M\lambda(T)\lambda_5 - \\
&\quad \sigma_F(1+u_1)\beta_1 S_M\lambda(T)\lambda_6 - \gamma\eta(1-u_2)S_M S_F\lambda(T)\lambda_7 - e\lambda_7 \\
&\quad -\tfrac{1}{2}(d_M + d_F)\lambda_7,
\end{aligned}
$$

where $\lambda(T) = \frac{T}{(1+T)^2}$ and satisfying the transversality conditions at t_f. i.e.

$$\lambda_i(t_f) = 0, i = 1, 2, ..., 7. \tag{6.4.6}$$

Theorem 6.4.1. *There is an optimum control $(u_1^*, u_2^*) \in \mathfrak{U}$ on a set interval [0, t_f] that is as follows:*

$$J(u_1^*, u_2^*) = \min_{(u_1,u_2)\in\mathfrak{U}} J(u_1(t), u_2(t)).$$

Proof. Boundedness of the solution of the system (6.2.1) yields that there is a optimal solution to the control system (6.4.1) (Fleming et al. [1975]). Hence the collection of optimal solutions of the control system (6.4.1) and respective state variables are nonempty. The control set is closed and convex by the definition. The integrand of the cost functional in (6.4.3) is

$$(A_1T - A_2S_M^A - A_3S_F^A + \frac{A_4}{2}u_1^2 + \frac{A_5}{2}u_2^2)e^{-qt}.$$

Clearly, it is convex on set $\mathfrak{U}$. Also there is p_i, q_i, i=1, 2, and $b > 1$ such that $(A_1T - A_2S_M^A - A_3S_F^A + \frac{A_4}{2}u_1^2 + \frac{A_5}{2}u_2^2)e^{-qt} \geq p_i + q_i|u_i(t)|^b$, where p_i depend on the maximum value of T, S_M^A, S_F^A and $q_i = A_i$, i=1, 2. Hence, the system has an optimal control. □

Theorem 6.4.2. *The optimum control* (u_1^*, u_2^*) *of the optimal system (6.4.1) that minimizes the objective function* J *in (6.4.3) over* $\mathfrak{U}$ *is given by* $u_1^*=max\{0,min(\overline{u_1},1)\}$ *and* $u_2^*=max\{0,min(\overline{u_2},1)\}$,
where $\overline{u_1}=\frac{1}{A_4}\{\lambda_1(1+\beta_1)\sigma_M\frac{T}{1+T}S_M+\lambda_2(1+\beta_1)\sigma_F\frac{T}{1+T}S_F-\lambda_3\sigma_M\frac{T}{1+T}S_M-\lambda_4\sigma_F\frac{T}{1+T}S_F-\lambda_5\sigma_M\beta_1\frac{T}{1+T}S_M-\lambda_6\sigma_F\beta_1\frac{T}{1+T}S_F\}$, *and* $\overline{u_2}=\frac{1}{A_5}\{-\lambda_7\gamma\eta\frac{T}{1+T}S_MS_F-\lambda_1\gamma S_MS_F-\lambda_2\gamma S_MS_F\}$.

Proof. Differentiating the Hamiltonian function H w. r. t the optimal controls u_1 and u_2, and equating them to equal to zero, we get $\frac{\partial H}{\partial u_1}=0$ and $\frac{\partial H}{\partial u_2}=0$. Now $\frac{\partial H}{\partial u_1}=0$ gives $\overline{u_1}=\frac{1}{A_4}\{\lambda_1(1+\beta_1)\sigma_M\frac{T}{1+T}S_M+\lambda_2(1+\beta_1)\sigma_F\frac{T}{1+T}S_F-\lambda_3\sigma_M\frac{T}{1+T}S_M-\lambda_4\sigma_F\frac{T}{1+T}S_F-\lambda_5\sigma_M\beta_1\frac{T}{1+T}S_M-\lambda_6\sigma_F\beta_1\frac{T}{1+T}S_F\}$.
Again, $\frac{\partial H}{\partial u_2}=0$ gives $\overline{u_2}=\frac{1}{A_5}\{-\lambda_7\gamma\eta\frac{T}{1+T}S_MS_F-\lambda_1\gamma S_MS_F-\lambda_2\gamma S_MS_F\}$.
Since the controls are bounded by 0 and 1. We set $u_1^*=0$ when $\overline{u_1}\leq 0$, $u_1^*=1$ when $\overline{u_1}\geq 1$, and $u_1^*=\overline{u_1}$ when $0<\overline{u_1}<1$. Similar conditions are also hold for u_2^*. □

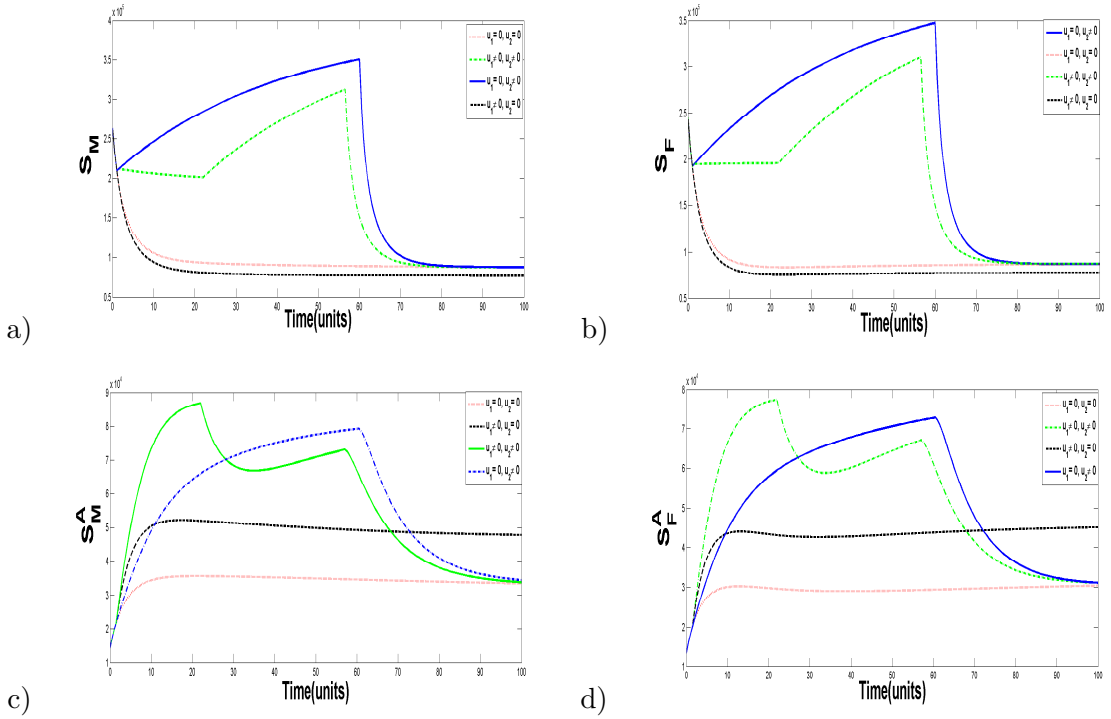


Figure 6.1: The figure represents the role of a) S_M, b) S_F, c) S_M^A, and d) S_F^A respect to time in different types of control strategies.

6.5 Numerical simulation

In this section, we conduct numerical simulations for both dynamical system (6.2.1) and control system (6.4.1) to investigate the obtained analytical insights. The forward-

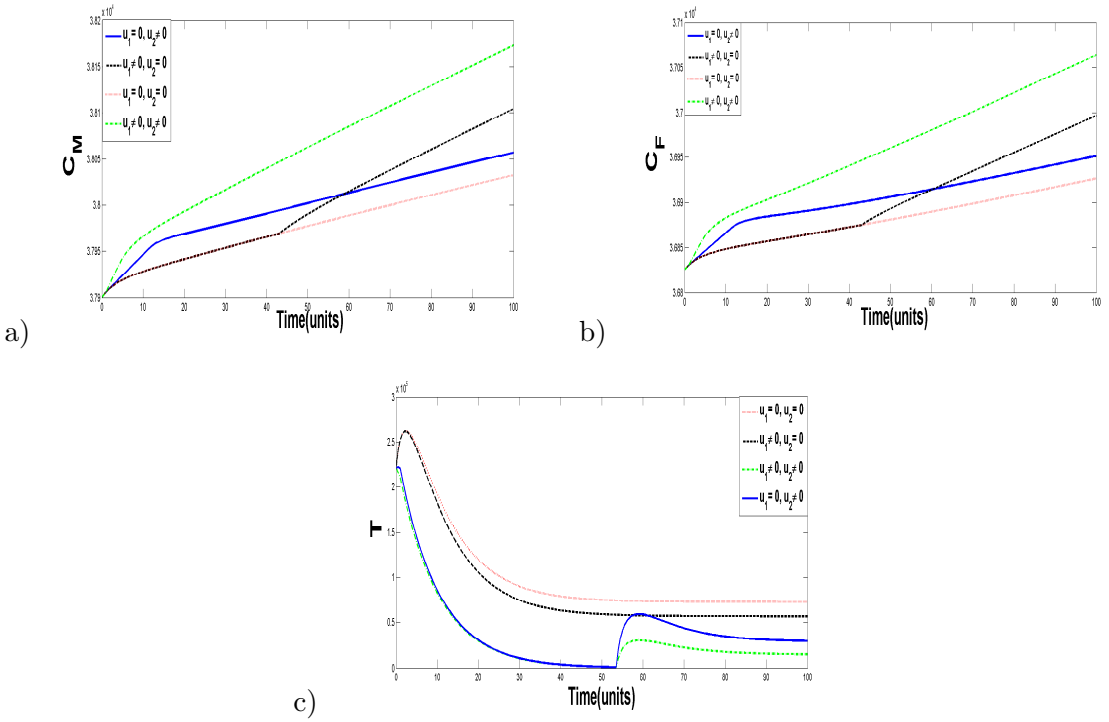


Figure 6.2: The figure represents the role of a) C_M, b) C_F, and c) T respect to time in different types of control strategies.

Figure 6.3: The figure depicts the profiles of cost under various types of control strategies in time t.

backward sweep procedure is used for the simulations to solve the control system (6.4.1). We use the following set of parameter values to corroborate our analytical findings in MATLAB:

A_M=9850.77; A_F=9850.76; $\sigma_M = 0.0252$; $\sigma_F = 0.0251$; $\beta_1 = 0.0001$, $\delta_M = 0.000000001$, $\delta_F = 0.000000001$; $\gamma = 0.000001$; $d_M = 0.0000001$; $d_F = 0.0000001$; $e = 0.10$; $\nu = 0.95$. The period for the controls are taken on 100 units of time with the initial size of the populations taken as $S_M^A(0) = 14290$, $S_F^A(0) = 13331$,

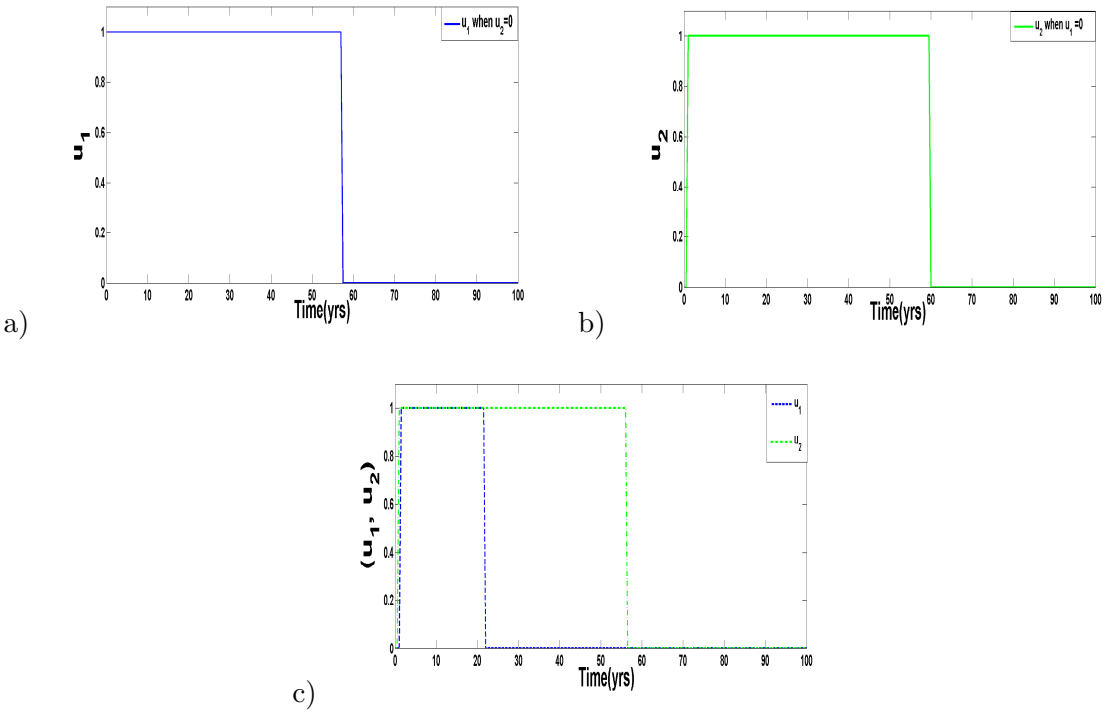


Figure 6.4: The figure depicts the role of a) optimal control function u_1 when $u_2 = 0$, b) optimal control function u_2 when $u_1 = 0$, and c) both optimal control function u_1 and u_2.

$C_M(0) = 37900$, $C_F(0) = 36825$, $T(0) = 220762$. and weight parameters are $A_1 = 100$, $A_2 = 160$, $A_3 = 140$ $A_4 = 170$, $A_5 = 180$.

First of all, we solve the optimal system (6.4.1) and adjoint system (6.4.6) with the control variables using numerical iterative method. Optimal system (6.4.1) is solved forward in time by taking initial sizes of the variables while adjoint system is solved by backward in time using MATLAB software. Optimal controls are updated as in state variables, adjoint variables, and Hamiltonian of the system. This iterative process is continued till get the desired accuracy of the variables in time interval [0, 100].

The numerical findings were carried out in four strategies to assess the efficacy of the proposed control techniques independently. Without control means no control applied in the system (i.e when $u_1 = 0$, $u_2 = 0$), strategy A means only u_1 control is applied in the system (i.e when $u_1 \neq 0$, $u_2 = 0$), strategy B means only u_2 control is applied in the system (i.e when $u_1 = 0$, $u_2 \neq 0$), strategy C means when both controls u_1 and u_2 are applied in the system (i.e when $u_1 \neq 0$, $u_2 \neq 0$).

Kim and Tridane developed a population-level mathematical model to examine the long-term effect and efficacy of thalassemia prevention (Kim and Tridane [2017]).

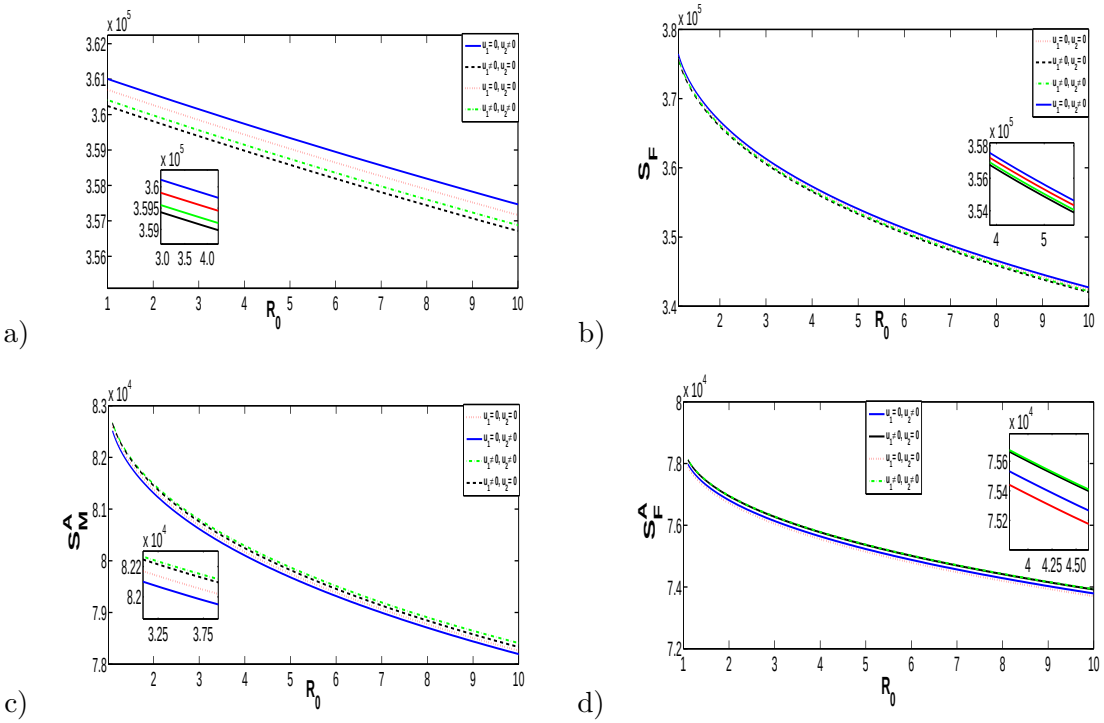


Figure 6.5: The figure represents the role of a) S_M, b) S_F, c) S_M^A, and d) S_F^A under various types of control strategies with respect to different values of R_0.

They only showed that premarital screening and education appear to help reduce the thalassemia cases. It is crucial to figure out how long these measures can keep sustaining in the population and whether they can genuinely control the thalassemia with cost effective strategies. We also undertake a cost design analysis and comparison study to determine the appropriateness and cost-effectiveness of strategies A, B, and C.

6.5.1 Without control

The system (6.4.1) is solved numerically with the above stated parameters initial sizes. The corresponding outcomes of the variables are displayed in Figures 6.1, 6.2. Figure 6.2c) shows that thalassemia patients grow rapidly and reaches its maximum peak within 5 units of time. Thus high prevalence is observed initially after that a gradual decay observed due to psychological awareness of thalassemia in the community. The corresponding cost diagram for without control have displayed in Figure 6.3. In without controls strategies, the produced cost is solely attributable to thalassemia patients only (blood transfusion, iron chelation drugs, treatment of side effects) and is shown to be quite high because the thalassemia cases are highest in this situation.

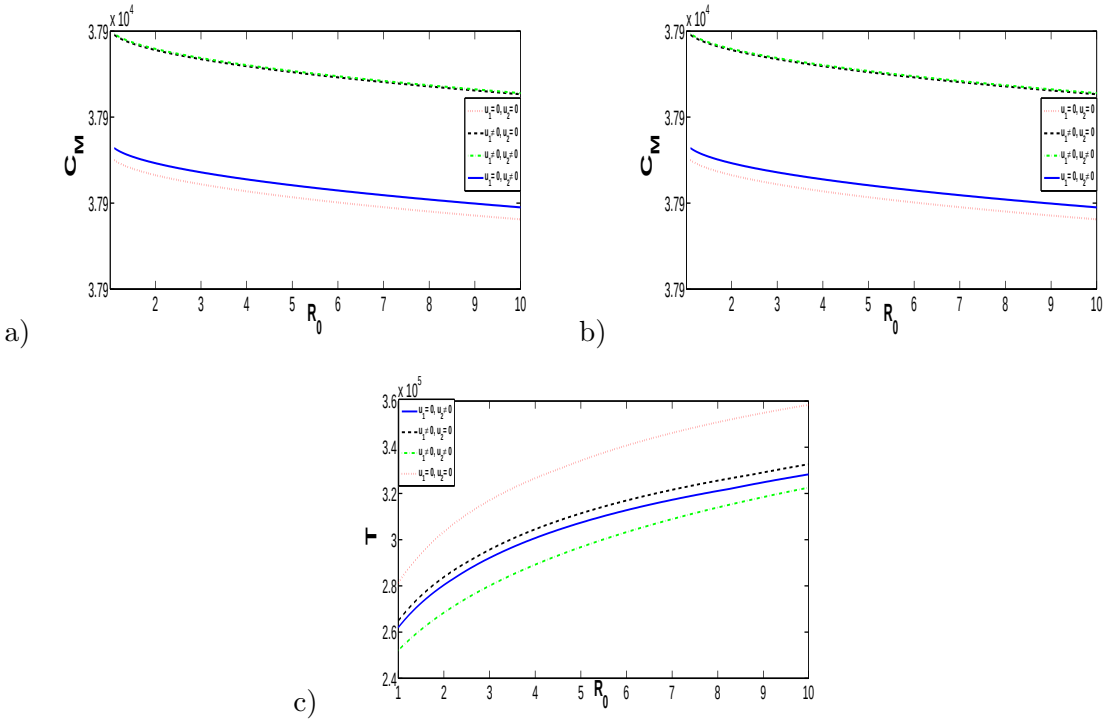


Figure 6.6: The figure represents the role of a) C_M, b) C_F, and c) T under various types of control strategies with respect to different values of R_0.

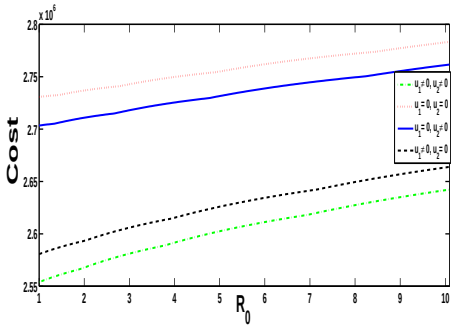


Figure 6.7: The figure depicts the profiles of cost in different values of R_0 under various types of control strategies.

As a result, not only does the prevalence of thalassemia produce a large pandemic, but it also places a significant economic strain on communities. This approach is consistent with the findings of the previous research articles (Teytsa et al. [2021], Kumar et al. [2020a], Kar et al. [2019]).

6.5.2 Strategy A

Awareness induced premarital screening rate is applied in the control system (6.4.1) to minimize the thalassemia patients in the community. The objective function J in (6.4.3) is minimize for u_1 in [0,1]. The control profile for the strategy A is also displayed in Figure 6.3a). It is observed that when strategy A is applied to the control system, then u_1 needs to execute almost 60 units of time with full potential. The optimal solution for the strategy A of the system (6.4.1) is displayed in Figures 6.1, 6.2. Figure 6.2c) shows that strategy A does not alter the peak of the disease compared to without control but reduces the period of the disease prevalence. The solution of control system in Figure 6.2c) under strategy A (i.e $u_1 \neq 0, u_2 = 0$), it shows that thalassemia patients grow and reaches maximum peak in 5 units of time in strategy A, whereas maximum peak in this case is lower than the case of without control. Thus strategy A reduces the occurrence of thalassemia than without control strategy. Figures 6.1c), d) show that S_M^A, S_F^A increase than the previous case of without control. Figures 6.2a), b) show that thalassemia carrier in both gender increase in the strategy A compared to without control strategy. The corresponding cost diagram for strategy A have also displayed in Figure 6.3. It shows that cost for the strategy A is relatively lower than the without control. Thus the strategy A not only reduce thalassemia patients but also minimize the related cost on it. This strategy agrees with the findings of other investigations (Momoh et al. [2021], Kar et al. [2019], Gani and Halawar [2018], Lee et al. [2010]).

6.5.3 Strategy B

Awareness induced marriage reconsider rate between unaware male and female adults u_2 is applied to the system (6.4.1). The objective function J is minimize for u_2 in [0,1]. The control profile for the strategy B is also displayed in Figure 6.3b). It shows that when strategy B is considered in the system, then u_2 also needs to execute almost 60 units of time with full potential. The optimal solution for the strategy B of the system (6.4.1) is displayed in 6.1, 6.2. Figure 6.2c) shows that there is no epidemic peak in strategy B, and also strategy B reduces the period of the thalassemia prevalence compared to previous strategies. The cost diagram for the strategy B is displayed in Figure 6.3. This shows that cost for the strategy B is relatively lower than the without control. Thus strategy B reduces thalassemia patients and minimizes the associated cost. This outcome is consistent with earlier research (Momoh et al. [2021], Kumar et al. [2020a], Kar et al. [2019]).

6.5.4 Strategy C

Awareness induced premarital screening rate and marriage reconsider rate between unaware male and female adults u_1 and u_2 both are applied to the system (6.4.1). The objective function J is minimize for u_1 and u_2 in [0,1]. The control profile for the strategy C is also displayed in Figure 6.3c). The role of the optimal controls under strategy C have shown in Figure 6.4. It is observed that when considering each control (i.e in strategy A or strategy B) one at a time, then they need to execute almost 60 units of time with full potential. When strategy C (i.e both controls) are applied, they execute in less time with full potential than strategy A and strategy B to obtain optimal solution. The optimal solution for the strategy C of the system (6.4.1) is displayed in Figures 6.1, 6.2. Finally, from Figure 6.2c) under strategy C (i.e $u_1 \neq 0, u_2 \neq 0$), it shows that thalassemia decreases with respect to time and graph of thalassemia in this case is lower than all previous strategies. Figures 6.1c),d) show that initially S_M^A, S_F^A increase than the case of strategy A and after 30 units of time it gradually decreases compared to strategy A. Figure 6.2a),b) show that thalassemia carrier in both gender increase in the strategy C compared to strategy B. Thus we realize that each of the strategies introduced into the system has positively demonstrated that thalassemia can be controlled by providing awareness in the community. Strategy C yields the best result to minimize thalassemia compared to strategy A and strategy B. The corresponding cost diagram for strategy C have also displayed in Figure 6.3. It demonstrates that the total cost is the least when strategy C (i.e both controls) is used compared to strategy A and strategy B. It is also noted that the cost of strategy A is also lower than the strategy B. Thus strategy A is more economically feasible than strategy B, but strategy C is very economically viable throughout the pandemic.

This demonstrates that spreading knowledge and awareness among the population at a higher rate, can help to reduce the magnitude of thalassemia. However, the combined effect (i.e strategy C) of both the strategies u_1 and u_2 need to execute comparatively lower than the value of u_1 and u_2 in strategy A and strategy B respectively. Again, we find that strategy A reduces the epidemic peak than without control. Whereas strategy B reduces the occurrence of thalassemia and, there is no epidemic peak in this case. Furthermore, the overall impact of strategy C has been proven to be very successful and economically feasible throughout the pandemic. This strategy is comparatively consistent along with more the findings of the earlier study (Teytsa et al. [2021], Kumar et al. [2020a], Kar et al. [2019], Gani and Halawar [2018]).

6.5.5 Impact of R_0 on the optimal control

We examine the effects of optimal awareness and marriage reconsider controls on thalassemia dynamics under various degrees of transmissibility as determined by the basic reproduction number R_0. In general, diseases with large reproduction numbers have high epidemic peaks. Figures 6.5, 6.6 depict the effect of optimal strategies on the variables of the optimal system as a function of R_0. Taking each variable highest value on the time period for different values of the basic reproduction number is plotted in figure under different control strategies. The Figure 6.6c) shows that, regardless of the control technique, the high epidemic peaks of the thalassemia rise as R_0 increases. From Figure 6.6c) it is also observed that strategy B decreases the epidemic peak than the strategy A for different values of R_0. Although in strategy C graph of epidemic peak potentially increase for different values of R_0 but relatively decrease compared to other strategies. The combined effect of both controls (i.e strategy C) is crucial in reducing epidemic peaks and consequently, the thalassemia prevalence.

Since optimal controls are implicit functions of R_0. Thus higher R_0 values lead to the immediate execution of all resources but are not effective much. In the case of Strategies A, B, and C, efforts must be sustained for a short amount of time since high R_0 rapidly decreases the aware population (see in Figure 6.6). The effect of a single optimum control is comparatively not efficient than the effect of the together use of multi-strategies. From Figure 6.5c), it shows that low values of R_0 can be managed optimally by implementing an initial full effort during the remaining epidemic period. The efficacy of controls over a long time stems from the fact that at low levels of R_0, there are still enough aware individuals are present for the controls to reduce the thalassemia cases. We further plot the profile of cost as a function of R_0 for different types of control strategies in Figure 6.7. It shows that cost is too much higher in without control but relatively lower in strategy C. Thus strategy C not only reduces thalassemia patients but also lowers the related cost on it. It is also worth mentioning that when the disease is severe (i.e $R_0 > 1$), both controls are required to reduce disease burden. A similar pattern of dynamics of the information impact has been observed by (Kumar et al. [2020a], Lee et al. [2010]). In their research, the authors examined the impact of information on healthy people of behavioral reactions to prevent diseases by adopting protective measures.

6.6 Conclusion

This chapter presents a mathematical analysis on the reliability of education and awareness of the population to control the thalassemia disease. The mathematical analysis has been performed using various types of control measures and different types of techniques as stability analysis, optimal control, and cost-effective analysis. It is crucial to figure out how long these measures can keep sustaining in the population and whether they can genuinely control the thalassemia.

The positivity, boundedness, and equilibrium analysis of the deterministic model are all fully treated. The stability of the thalassemia free and thalassemia present equilibrium points are investigated. We used analysis to verify the control system (6.4.1) and found the solution of the control variables for the optimal problem that can optimize the objective functional in (6.4.3). We demonstrated the existence of optimal controls analytically and distinguished them using pontryagins maximum principle. Three control strategies were used to get the results, and a comparison was done to investigate the efficacy of adapt control systems in order to determine the optimal scenario. Strategy 1 to 3 demonstrate that both control techniques can reduce thalassemia patients and associated expenditures. Overall, the findings show that the control measures have significant potential for managing thalassemia disorders.

We also examined at how the basic reproduction number R_0 affects the control strategies and the prevalence of thalassemia. The thalassemia free equilibrium point is stable till the basic reproduction number R_0 is less than unity according to stability analysis. Regardless of the control technique, it is observed that the high epidemic peaks of the thalassemia rise as R_0 increases. Finally, numerical observation demonstrates combined effect of both the controls yielded the best effective strategy to prevent the thalassemia outbreak and also minimizes the related cost on it. This chapter strongly advocates comprehensive public awareness of thalassemia, carrier screening, prenatal identification of carrier couples, and avoiding marriages between carriers.

Chapter 7

Future motivation

The thesis investigates the modern application of mathematical modeling in analyzing the impact of awareness of various NCDs in the community. The developed models are very precious for evaluating the role of awareness of NCDs in the community and minimizing the burden of the disease. The aim of the mathematical models are to improve knowledge of real-world issues by framing model strategies that are user-friendly and more predictive of future difficulties. This thesis highlights the application of mathematical modeling on NCDs to solve various difficulties and challenges in medicine and biology. This leads us to be aware of the complexity of NCDs and their impact on human populations, and the level of intervention strategies that provide the most needed and effective coverage to populations. The mathematical modeling of NCDs provides insight into how to lower the death rates caused by non-communicable diseases. Hence it raises its goals and objectives to promote human health and manage demographic challenges in epidemiology. This thesis also represents the importance of mathematical modeling in epidemiology by revealing the many stages of different NCDs and their impact on the human body. Recently mathematical models have become significant tools for studying and interpreting the patterns of noncontagious diseases. It is evident from the "Literature review and motivation" [1.4] section that little effort has been focused on investigating the biological regulation of noncontagious diseases using mathematical models. I attempted to examine and describe how awareness affects the non-contagious disease by incorporating stochasticity, optimal control, and fractional-order derivatives into the model system. However, the solutions of these models are not easy to achieve because human interventions and response to awareness program, and limited resources, make the models more critical and challenging to public health. One of the major difficulties in non-contagious diseases management is developing a plan in such a way not only prevention of disease

but also the associated costs upon it. The numerical simulation tools MATLAB and MATHEMATICA give a graphical representation of the result of the model system for non-contagious diseases. The graphical representation is simple to grasp, and it provides additional information about the transformation, dissemination, and recovery of non-contagious diseases.

One of the most crucial aspects of the thesis is future motivation. I have already addressed how this thesis can contribute to the study of non-contagious diseases. Also, there are several directions in which the present work can be extended for further study. In the previous chapters, we have considered the constant rate of immigration and the uniform incidence rate for the individuals in the model systems. Thus the model for NCDs can be improved by taking the varying rate of immigration and age dependency incidence in the system. As the incidence rate of NCDs tends to increase with age (Hui [2017]). Again, inducing genetic information is an important step toward developing effective modeling of NCDs. Indeed, genetic variations improve screening, diagnosis, and early effective intervention of awareness focusing on NCDs (Jamaluddine et al. [2016]). Including the genetic component of NCDs in the model system might provide further insight into disease management options. After that, certain infectious diseases like influenza A H1N1 and covid-19 raise the chance of developing NCDs. As the global monitoring framework of WHO exclusively addresses two infectious pathogens: hepatitis B virus (HBV) and human papillomavirus (HPV) are developed the complications of NCDs (Coates et al. [2020]). Considering the co-infection of HBV and HPV on the assumptions, a highly nonlinear mathematical model on NCDs can be generated. Finally, mathematical models that include a delay are more realistic since time-delays occur in practically every biological circumstances. The problem of NCDs is the long lag time between disease causes and outcomes (Budreviciute et al. [2020]). In addition, we anticipate that a delay-induced mathematical model will be more effective in examining time-lag aspects throughout the awareness period due to non-instantaneous response to awareness programs of individuals. In mathematical perspective, a time delay inclusion is needed for accurate modeling of NCDs models. These ideas and mathematical techniques employed in this thesis are intend to inspire future scholars. Before concluding my thesis, I want to emphasize the importance of mathematical models and tools in understanding the complicated biological circumstances of a system. NCDs models are developed in the thesis based on theoretical methods. I hope experimental biologists can use those findings to discover meaningful answers to the problem. Thus, collaborating with experimental biologists might improve the current work on NCDs. I shall attempt to collaborate with an experimental biologist in the future.

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List of Publications

- **Saddam Mollah** and Santosh Biswas. "Effect of awareness program on diabetes mellitus: deterministic and stochastic approach". *Journal of Applied Mathematics and Computing*, Volume 66, No. 1 (2021), 61-86.

- **Saddam Mollah** and Santosh Biswas. "Optimal control for the complication of Type 2 diabetes: The role of awareness programs by media and treatment". *International Journal of Dynamics and Control*, (accepted for publication).

- **Saddam Mollah**, Santosh Biswas, and Subhash Khajanchi. "Impact of awareness program on diabetes mellitus described by fractional-order model solving by homotopy analysis method". *Ricerche di Matematica*, (2022), https://doi.org/10.1007/s11587-022-00707-3.

- **Saddam Mollah** and Santosh Biswas. "Effect of awareness program on cancer-Deterministic and stochastic approach". *Bulletin of Calcutta Mathematical Society*, Volume 113, No. 5 (2021), 421-446.

- **Saddam Mollah** and Santosh Biswas. "Modeling with cost-effective analysis to control thalassemia disease in the population". (Communicated).

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