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Optimal Control of a Three-State Diabetic Population Model with Interventions

Hanis Nasir[1]*

[1]Faculty of Ocean Engineering Technology and Informatics,
Universiti Malaysia Terengganu, 21030, Kuala Nerus, Terengganu, Malaysia

*Corresponding Author

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Abstract: This paper studies an optimal control problem to describe the population dynamics of diabetes in the presence of intervention effects. We propose two control variables representing the interventions to reduce the incidence of diabetes, and the interventions to reduce the incidence of complications. By applying the optimal control theory, we seek to minimize the relative cost associated with the intervention efforts and to reduce the total number of people with diabetes. The solution to the optimality system is approximated by using the Forward-Backward Sweep Method. The numerical simulations show that the number of diabetics who develop complications can be reduced by adopting optimal control strategies.

Keywords: Diabetes, optimal control, forward-backward sweep method

1. Introduction

Modeling the population dynamics is one of the approaches in mathematics to deal with the prevalence of diseased individuals. It is commonly used to simulate many complex systems and predict the number of diseased individuals at a time. A system can be transformed into a mathematical model by understanding the process of the system and proposing some assumptions. Studies using mathematical models are continuously expanding with the availability of computer software, new methodologies, and new hospitalized data. Generally, a mathematical model represents a complex phenomenon into mathematical equations with some parameters. In a mathematical model, the entire population is divided into compartments (or states) based on the individuals' status. Hence, the number of individuals in a compartment can be tracked. The individuals may jump into another compartment which is often described by an epidemiological parameter, and they can stay in one compartment only at one time [1]. Other than the human population, the compartmental model has also been applied to study the dynamics of a cell population in cancer phenomenon [2, 3, 4].

Glucose is the primary source of energy for the human body's cells. The glucose levels are regulated by insulin produced by the pancreatic beta-cells. Without insulin, the body's cells cannot absorb glucose and use it as energy—consequently, the glucose levels in the body increase. The common causes of high glucose levels are either the pancreatic beta-cells failing to produce enough insulin or the body's cells resisting the insulin or both [5].

Diabetes is a condition of having high blood glucose levels. The threshold value for an individual categorized as a person with diabetes is ≥ 7.0 mmol/L for a fasting-glucose level and ≥ 11.1 mmol/L for a 2-hour post-prandial. Type-2 diabetes is the primary type in the population, highly related to lifestyle choices. Diabetes can cause many complications. Some are fatal, such as heart attack and stroke. There are approximately 463 million diabetics worldwide [5, 6], and this number keeps growing every year. If the total number of people with diabetes keeps increasing every year, many resources will need to be allocated, particularly for the management of diabetes and the treatment of its complications.

*Corresponding author: hanisnasir20@gmail.com

Diabetes complex processes come together with atherosclerosis-related inflammation that may affect the cell lining of blood vessels. The immune system's reaction leads to atherosclerosis, where the immune cells mistakenly recognize that plaque as intruders. The immune cells attack, cause inflammation, cause the plaque to swell or rupture, and then block blood flow. In addition, diabetes increases the production of free radicals, high reactive molecules that damage the essential components of cells such as DNA. Even its exact related inflammation is not fully understood; past studies had shown that much CVDs mortality is from a condition of being diabetes, and CVDs are the major causes of diabetes-induced death.

Type 2 diabetes develops very gradually. Someone's sugar level will be in the condition of pre-diabetes, and after no preventive action is taken, persistent hyperglycemia occurs. Individuals with impaired glucose tolerance are already at increased risks of cardiovascular diseases. The excess blood sugar will reduce the blood vessel's elasticity and become narrow and impeding the blood flow. It increases the risk of high blood pressure and damages the small and prominent blood vessels (micro and macrovascular diseases). In others, diabetes causes the reduced ability for wound healing or infection, loss of sensation, vision loss, and metabolic problems, including diabetic ketoacidosis, hyperosmolar hyperglycemia, and mental health problems. Diabetes needs continuous medical treatment and self-management by diabetic individuals in order to prevent or delay diabetes complications. Unlike CVDs, modeling the diabetes progression at the population level has been studied many times [6].

In this work, we study an optimal control problem of a diabetic population model. The primary purpose is to minimize the relative cost of implementing the intervention efforts and minimize the total number of people with diabetes, prioritizing people with diabetes with complications. In section 2, we discuss the population model of diabetes mellitus with optimal control. In section 3, we discuss the characterization of optimal control and its numerical simulations. Lastly, a brief conclusion is given in section 4.

2. Mathematical Model

Recently, Nasir and Mat Daud [6] suggested three compartments of the diabetes population consisting of the diabetics without and never experienced any complications, diabetics with complications, and post-treatment diabetics (see figure 1).

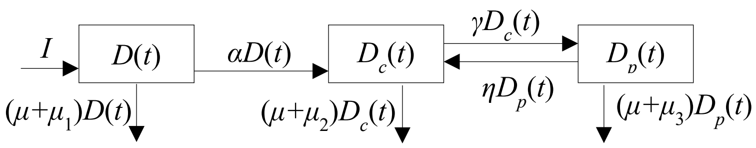

Fig. 1 - State variables introduced by Nasir and Mat Daud [6]

If we transform the dynamics presented in fig. 1 into mathematical equations, we obtain a system of ordinary differential equations, as follows:

$$\left.\begin{aligned}
\frac{dD(t)}{dt} &= I - \alpha D(t) - (\mu + \mu_1)D(t), \quad D(0) > 0, \\
\frac{dD_c(t)}{dt} &= \alpha D(t) + \eta D_p(t) - (\gamma + \mu + \mu_2)D_c(t), \quad D_c(0) > 0, \\
\frac{dD_p(t)}{dt} &= \gamma D_c(t) - \eta D_p(t) - (\mu + \mu_3)D_p(t), \quad D_p(0) > 0,
\end{aligned}\right\} \tag{1}$$

where $D(t)$ represents the number of diabetics without and never experienced any complications at time t, $D_c(t)$ represents the number of diabetics with complications at time t, and $D_p(t)$ represents the number post-treatment diabetics at time t. Moreover, the parameter I is the incidence of diabetes assuming without complication, α is the rate of incidence of the first complication, γ is the rate of completing treatment and recover, η is the incidence rate of a recurring complication event, μ is the non-diabetes-related death rate, and μ_i (i =1,2,3) is the death due to diabetes. The primary purpose is to investigate the control strategy using model (1).

Suppose $t \in [0, t_f]$ is the time interval of applying the optimal control strategies. Fig. 2 shows the compartmental diagram in the presence of optimal controls associated with system (1).

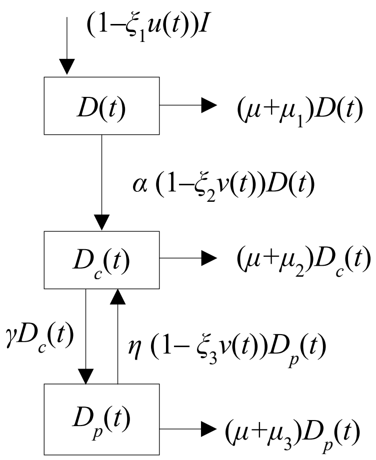

Fig. 2 - Population dynamics of diabetes mellitus with two control variables, *u*(*t*) and *v*(*t*)

Then, the associated diabetic population model with optimal control problem is given by:

$$\left.\begin{aligned} \frac{dD(t)}{dt} &= (1-\xi_1 u(t))I - \alpha(1-\xi_2 v(t))D(t) - (\mu+\mu_1)D(t), \quad D(0)>0, \\ \frac{dD_c(t)}{dt} &= \alpha(1-\xi_2 v(t))D(t) + \eta(1-\xi_3 v(t))D_p(t) - (\gamma+\mu+\mu_2)D_c(t), \quad D_c(0)>0, \\ \frac{dD_p(t)}{dt} &= \gamma D_c(t) - \eta(1-\xi_3 v(t))D_p(t) - (\mu+\mu_3)D_p(t), \quad D_p(0)>0. \end{aligned}\right\} \tag{2}$$

The control $u(t)$ represents the intervention efforts on non-diabetic individuals, while the control $v(t)$ represents the intervention efforts on diabetic individuals. The parameter $\xi_i \in [0,1]$, i =1,2,3, represents the adherence level or the effectiveness of the intervention efforts.

For convenience, the admissible control set is $W = U \times V$, where U and V are defined as

$$\begin{aligned} U &= \left\{u \quad \text{measurable} \quad : \quad u \in [u_0, 1], \forall t \in [0, t_f]\right\}, \\ V &= \left\{v \quad \text{measurable} \quad : \quad v \in [v_0, 1], \forall t \in [0, t_f]\right\}. \end{aligned} \tag{3}$$

We also assumed $(u, v) = (u_0, v_0)$ is the minimal intervention efforts, while $(u, v) = (1, 1)$ is the maximal intervention efforts. The objective functional is

$$J(u,v) = \min_{u,v\in W} \int_0^{t_f} \left[A_1 D(t) + A_2 D_c(t) + A_3 D_p(t) + B_1 u^2(t) + B_2 v^2(t) \right] \, dt, \tag{4}$$

where $A_i \geq 0$, i = 1, 2, 3, and $B_j > 0$, j = 1, 2, are the weight factors. The goal, therefore, is to characterize an optimal control pair (u^*, v^*) such that:

(i) the total number of diabetics over the interval $[0, t_f]$ is minimized, and
(ii) the relative cost of applying the control strategies in the same interval is also minimized.

3. Results and Discussion

The existence of (u^*, v^*) follows directly from [7]. Then, by using the Pontryagin Maximum principle [8], we obtain the following theorem.

Theorem 1 *Let* ($\tilde{D}$, $\tilde{D}_c$, $\tilde{D}_p$) *be the optimal solution of state system* (2) *with an optimal control pair* (u^*, v^*), *there exist adjoint variables* $(\lambda_1, \lambda_2, \lambda_3)$ *satisfying*

$$\left.\begin{aligned}
\frac{d\lambda_1(t)}{dt} &= \alpha\left(1-\xi_2 v^*\right)\left(\lambda_1(t)-\lambda_2(t)\right)+(\mu+\mu_1)\lambda_1(t)-A_1,\\
\frac{d\lambda_2(t)}{dt} &= \gamma\left(\lambda_2(t)-\lambda_3(t)\right)-A_2+\left(\mu+\mu_2\right)\lambda_2(t),\\
\frac{d\lambda_3(t)}{dt} &= \left(\eta+\mu+\mu_3\right)\lambda_3(t)+\eta\left(1-\xi_3 v^*\right)\left(\lambda_3(t)-\lambda_2(t)\right)-A_3,
\end{aligned}\right\} \tag{5}$$

with the transversality condition $\lambda_i(t_f) = 0$, i=1,2,3. *Moreover,* $u^*=\min\{\max\{u_0, u\}, 1\}$ *and* $v^*= \min\{\max\{v_0, v\}, 1\}$, *where* $u=\frac{\xi_1 I\lambda_1(t)}{2B_1}$, *and* $v=\frac{1}{2B_2}\left[\alpha\xi_2\tilde{D}(t)\left(\lambda_2(t)-\lambda_1(t)\right)+\eta\xi_3\tilde{D}_p(t)\left(\lambda_2(t)-\lambda_3(t)\right)\right]$.

Proof. The Hamiltonian equation is given by

$$\begin{aligned}
H = {} & A_1D(t)+A_2D_c(t)+A_3D_p(t)+B_1u^2(t)+B_2v^2(t)\\
& +\lambda_1(t)\left[(1-\xi_1u(t))I-\alpha(1-\xi_2v(t))D(t)-(\mu+\mu_1)D(t)\right]\\
& +\lambda_2(t)\left[\alpha(1-\xi_2v(t))D(t)+\eta(1-\xi_3v(t))D_p(t)-(\gamma+\mu+\mu_2)D_c(t)\right]\\
& +\lambda_3(t)\left[\gamma D_c(t)-\eta(1-\xi_3v(t))D_p(t)-(\mu+\mu_3)D_p(t)\right].
\end{aligned}$$

Then, we find the adjoint function for every variable ($D(t)$, $D_c(t)$, $D_p(t)$) with zero transversality. We obtain

$$\begin{aligned}
\frac{d\lambda_1(t)}{dt} &= -\frac{\partial H}{\partial D(t)} = \alpha\left(1-\xi_2 v^*\right)\left(\lambda_1(t)-\lambda_2(t)\right)+(\mu+\mu_1)\lambda_1(t)-A_1,\ \ \lambda_1(t_f)=0,\\
\frac{d\lambda_2(t)}{dt} &= -\frac{\partial H}{\partial D_c(t)} = \gamma\left(\lambda_2(t)-\lambda_3(t)\right)-A_2+\left(\mu+\mu_2\right)\lambda_2(t),\ \ \lambda_2(t_f)=0,\\
\frac{d\lambda_3(t)}{dt} &= -\frac{\partial H}{\partial D_p(t)} = \left(\eta+\mu+\mu_3\right)\lambda_3(t)+\eta\left(1-\xi_3 v^*\right)\left(\lambda_3(t)-\lambda_2(t)\right)-A_3,\ \ \lambda_3(t_f)=0.
\end{aligned}$$

Next, we find the characterization of the optimal control variables u^* and v^*. We obtain

$$\begin{aligned}
\frac{\partial H}{\partial u} &= 0 \ \Rightarrow\ u=\frac{\xi_1 I\lambda_1(t)}{2B_1},\\
\frac{\partial H}{\partial v} &= 0 \ \Rightarrow\ v=\frac{1}{2B_2}\left[\alpha\xi_2\tilde{D}(t)\left(\lambda_2(t)-\lambda_1(t)\right)+\eta\xi_3\tilde{D}_p(t)\left(\lambda_2(t)-\lambda_3(t)\right)\right].
\end{aligned}$$

Using bounds on the controls (the sets given in (3)), we obtain the following characterization equations:

$$\begin{aligned}
u^* &= \min\left\{\max\left\{u_0, u(t)\right\}, 1\right\},\\
v^* &= \min\left\{\max\left\{v_0, v(t)\right\}, 1\right\}.
\end{aligned}$$

The proof is complete. □

The optimality system for the optimal control problem consists of the state system (2) and the adjoint system (5). Then, the uniqueness of this optimality system can be shown by the standard approach (see [8, 9]).

To illustrate the reliability of the controlled system, the optimality system is solved numerically using the Forward-Backward Sweep Method [8, 10], with the Runge-Kutta-fourth order iterative scheme. The algorithm is roughly based on the following steps:

Step 1: Set initial guesses for u^* and v^* over the interval $t\in[0,t_f]$ and the tolerance value.

Step 2: Compute the variables $D(t)$, $D_c(t)$, and $D_p(t)$ of system (2) forward in time with the Runge-Kutta-fourth order iterative scheme.

Step 3: Compute the adjoint variables $\lambda_1(t)$, $\lambda_2(t)$, and $\lambda_3(t)$ of system (5) backward in time with the Runge-Kutta-fourth order iterative scheme.

Step 4: Compute the optimal control characterizations, u^* and v^*.

Step 5: Calculate the errors of variables $D(t)$, $D_c(t)$, $D_p(t)$, $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$, u^*, and v^* between the current and previous values. If at least one of the errors is greater than the tolerance value, return to Step 2. Otherwise, the current values are the outputs.

For the simulation result presented in Fig. 3, we compare the dynamics of system (2), with and without optimal control using the following parameters set:

$$\left.\begin{aligned} &I = 15, \quad \alpha = 0.075, \quad \eta = 0.25, \quad \gamma = 0.15, \quad \mu = 0.015, \mu_1 = 0.01, \quad \mu_2 = 0.075, \quad \mu_3 = 0.05, \\ &A_1 = 2, \quad A_2 = 4, \quad A_3 = 1, \quad B_1 = 40, \quad B_2 = 40, \quad \xi_1 = 0.75, \quad \xi_2 = 0.75, \quad \xi_3 = 0.75, \\ &D(0) = 125, \quad C(0) = 10, \quad C_P(0) = 15, \quad t_f = 25, \quad u_0 = 0.15, \quad v_0 = 0.2. \end{aligned}\right\} \tag{6}$$

The selection of parameter values is challenging when dealing with model simulations. The parameter values in (6) were chosen randomly as an example of system (2). From fig. 3(a, b, c), the total numbers of all subpopulations of diabetes reduced after implementing the control strategies. From fig. 3(d), we can also observe that the control u^* is given at a maximal level compared to v^*. It suggests that prioritize should be given to controlling the non-diabetics from developing diabetes, while the intervention efforts to reduce the incidence of complications can be kept at a minimum level for about the first ten years.

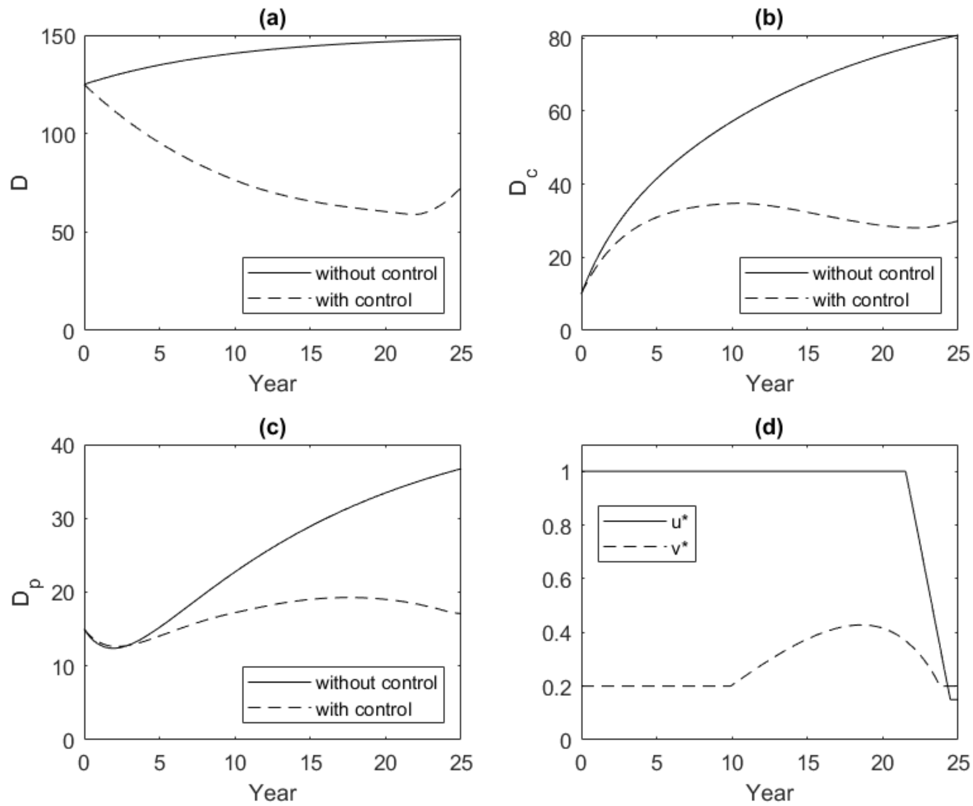

Fig. 3 - (a-c) The change of the number of diabetic individuals under the optimal control strategies; (d) The variation of optimal control strategies (u^*, v^*)

4. Conclusion

Several modeling studies of the diabetes population have been done with different explanations [6]. With such modelings, essential factors were interpreted, significance parameters were obtained, and predictions were made. By definition, mathematical models are greatly simplified representations of any complex system. This present work aims to reduce the total number of people with diabetes, especially the diabetics with complications utilizing the optimal control method. First, we introduced a controlled diabetics model. An objective function is proposed to minimize the total diabetics with the least relative cost. Then, some numerical simulations are illustrated, showing that complications can be reduced effectively by implementing optimal control strategies. Furthermore, we obtained that a priority should be given to preventing the incidence of diabetes.

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