

OPTIMAL CONTROL FOR THE MODIFIED MINIMAL MODEL OF THE GLUCOSE-INSULIN DYNAMICS

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ABSTRACT. This article investigates an optimal control problem for the non-autonomous modified minimal model of the glucose-insulin kinetics. We attempt to control the blood glucose levels by providing a nutrient control for increasing the blood insulin concentration. The analysis for the model based on using Pontryagin's maximum principle is carried out. The numerical simulations for the optimal control system are graphically shown using the forward-backward sweep method to see effects of the control on the behavior of the modified minimal model.

1. INTRODUCTION

Diabetes mellitus is a metabolic disease that causes high blood sugar levels. The hormone insulin moves sugar from the blood into cells to be stored or used for energy. Insulin is a hormone produced by the pancreas, that regulates carbohydrate metabolism in the body. If the pancreas produces less insulin or cannot produce insulin then the residual glucose in the blood stream results in high blood sugar levels causing diabetes. In 2017 [1], diabetes resulted in approximately 4.2 million deaths. It is the 7th leading cause of death both globally and in the United States.

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For a number of years, scientists had attempted to build the relationship between amounts of glucose and insulin. The metabolism of glucose, involving the secretion of its controlling hormone insulin by the pancreas, has been modelled mathematically in many studies. Such models have been restricted to ordinary differential equations and delay differential equations. The most widely used model in physiological research on the metabolism of glucose and insulin is the so called a minimal model which is non-autonomous differential equations [2]. However, we will involve with the modified minimal model of the glucose-insulin dynamics [3], which was adapted from the minimal model. The modified model contains three first order differential equations which can be written as follows

$$(1.1) \quad \begin{aligned} \frac{dG(t)}{dt} &= -[b_1 + X(t)]G(t) + b_1G_b \\ \frac{dX(t)}{dt} &= -b_2X(t) + b_3[I(t) - I_b] \\ \frac{dI(t)}{dt} &= -b_6[I(t) - I_b] + b_4\max(0, G(t) - b_5)t, \end{aligned}$$

with the initial conditions $G(0) = G_0$, $X(0) = X_0$, $I(0) = I_0$. The state variables in the model are the blood glucose concentration at time t denoted by $G(t)$ [mg/dl], the blood insulin concentration at time t denoted by $I(t)$ [mU/l], and the auxiliary function representing insulin-excitabile tissue glucose uptake activity denoted by $X(t)$ [min^{-1}], which is proportional to the insulin concentration in a distant compartment. The meaning of the positive parameters $b_1, b_2, b_3, b_4, b_5, b_6, G_b, I_b$ are given in [3]. However, there are drawbacks for minimal model as mentioned in [4]. The disadvantages of the system are that it does not admit an equilibrium point and its solutions may not be bounded.

Recently, ideas of adding a controller into a system have been extensively applied in many fields. This is because the behaviors of many systems have some restrictions which can be better described using the controller [7]. In this paper, we attempt to control the blood glucose levels in diabetic patients using the optimal control in the modified model (1.1). Here our control $u(t)$ is some nutrients in order for increasing the blood insulin level. The rest of the paper is arranged as follows. Section 2 presents the methodology of the optimal control model. In Section 3, steps of numerical scheme for solving the optimal control problem are described. In Section 4, numerical simulations for

the optimal control model are given using the certain values of the parameters. Finally, the conclusions are given in the last section.

2. METHODOLOGY

In this section, we will provide fundamental concepts for solving an optimal control problem and then apply them to our problem.

2.1. OPTIMAL CONTROL FOR ORDINARY DIFFERENTIAL EQUATIONS. The concepts for finding an optimal solution of the optimal control problem can be found in [5]. The description of the idea, which is called Pontryagin's maximum principle, is as follows. Consider the following optimal control problem when f and g are continuously differentiable functions in t, x, u :

$$(2.1) \quad \min_u J(x, u),$$

where

$$(2.2) \quad J(x, u) = \int_{t_0}^{t_1} f(t, x(t), u(t)) dt,$$

subject to

$$(2.3) \quad \begin{aligned} x'(t) &= g(t, x(t), u(t)), \\ x(t_0) &= x_0 \text{ and } x(t_1) \text{ free.} \end{aligned}$$

We want to find a piecewise continuous optimal control $u(t)$ and the associated state variable $x(t)$ to minimize the objective function $J(x, u)$ in Eq. (2.2) subject to the constraints in Eq. (2.3). The key technique for above optimal control problem is to solve a set of necessary conditions that an optimal control and corresponding state must satisfy. We define the Hamiltonian function H as

$$(2.4) \quad H(t, x, u, \lambda) = f(t, x(t), u(t)) + \lambda g(t, x(t), u(t)),$$

where f is the integrand of $J(x, u)$ and g is the right hand side function of the differential equation. We are minimizing H with respect to u at u^* so we have

$$(2.5) \quad \begin{aligned} \frac{\partial H}{\partial u} &= 0 \text{ at } u^* \Rightarrow f_u + \lambda g_u = 0 \quad (\text{optimality condition}), \\ -\frac{\partial H}{\partial x} &= \lambda' \Rightarrow \lambda' = -(f_x + \lambda g_x) \quad (\text{adjoint equation}), \end{aligned}$$

and the transversality condition

$$(2.6) \quad \lambda(t_1) = 0.$$

We are given the dynamics of the state equation:

$$(2.7) \quad \frac{\partial H}{\partial \lambda} = x' = g(t, x, u), \quad x(t_0) = x_0.$$

In addition, the minimization condition

$$(2.8) \quad H(t, x^*(t), u^*(t), \lambda^*(t)) = \min_{0 < u \leq u_{\max}} H(t, x^*(t), u(t), \lambda^*(t))$$

must hold for almost all $t \in [t_0, t_1]$.

2.2. OPTIMAL CONTROL FOR THE NON-AUTONOMOUS MODIFIED MINIMAL MODEL. In this section, we will establish the necessary conditions for our optimal control problem using the idea as described above. We begin with adding the control $u(t)$ into the third equation of the modified minimal model in Eq. (1.1). The control $u(t)$ is some nutrients activating the enlargement of insulin hormones so that the blood glucose level is reduced. The differential equations for our optimal control problem become

$$(2.9) \quad \begin{aligned} \frac{dG(t)}{dt} &= -[b_1 + X(t)]G(t) + b_1G_b, \\ \frac{dX(t)}{dt} &= -b_2X(t) + b_3[I(t) - I_b], \\ \frac{dI(t)}{dt} &= -b_6[I(t) - I_b] + b_4\max(0, G(t) - b_5)t + u(t). \end{aligned}$$

where $0 < u(t) \leq u_{\max} = 1$ and the initial conditions are

$$(2.10) \quad G(0) = G_0, \quad X(0) = X_0, \quad I(0) = I_0.$$

The goal of the optimal control strategies is to minimize the blood glucose level $G(t)$. This is done by minimizing the following objective functional J defined by

$$(2.11) \quad J(G(t), u(t)) = \int_0^T A(G(t) - l)^2 + u^2(t) dt,$$

where A is a weight parameter and l is a desired glucose level and by depending on the differential equation system (2.9). In conclusion, we want to obtain the control $u(t)$ that minimizes the functional J subject to the constraints (2.9),

(2.10) and free final conditions.

The Hamiltonian of our optimal control problem can be defined as

$$\begin{aligned}
 H = & A(G(t) - l)^2 + u^2(t) + \lambda_G(-(b_1 + X(t))G(t) + b_1G_b), \\
 & + \lambda_X(-b_2X(t) + b_3[I(t) - I_b]), \\
 (2.12) \quad & + \lambda_I(-b_6[I(t) - I_b] + b_4\max(0, G(t) - b_5)t + u(t)),
 \end{aligned}$$

where λ_G , λ_X and λ_I are the adjoint variables. Employing Eq. (2.7), we obtain the control system or the state equations as

$$\begin{aligned}
 G' &= \frac{\partial H}{\partial \lambda_G} = -[b_1 + X(t)]G(t) + b_1G_b, \\
 (2.13) \quad X' &= \frac{\partial H}{\partial \lambda_X} = -b_2X(t) + b_3[I(t) - I_b], \\
 I' &= \frac{\partial H}{\partial \lambda_I} = -b_6[I(t) - I_b] + b_4\max(0, G(t) - b_5)t + u(t).
 \end{aligned}$$

Next applying the formula (2.5) to the functional H , the adjoint equations are defined as

$$\begin{aligned}
 \lambda'_G &= -\frac{\partial H}{\partial G} = -\left[2A(G(t) - l) - \lambda_G(b_1 + X(t))\right. \\
 (2.14) \quad & \left.+ \lambda_I\max\left(0, \frac{(G(t) - b_5)}{|G(t) - b_5|}\right)b_4t\right], \\
 \lambda'_X &= -\frac{\partial H}{\partial X} = \lambda_GG(t) + \lambda_Xb_2, \\
 \lambda'_I &= -\frac{\partial H}{\partial I} = \lambda_Ib_6 - \lambda_Xb_3,
 \end{aligned}$$

with $\lambda_G(T) = 0$, $\lambda_X(T) = 0$, $\lambda_I(T) = 0$. Solving $\frac{\partial H}{\partial u} = 0$ for u , we obtain the optimal control u^* as follows

$$(2.15) \quad \frac{\partial H}{\partial u} = 2u^* + \lambda_I = 0 \Rightarrow u^* = -\frac{\lambda_I}{2}.$$

which given $u^* = -\frac{\lambda_I}{2}$.

3. FORWARD AND BACKWARD SWEEP METHOD FOR SOLVING OPTIMAL CONTROL MODIFIED MINIMAL MODEL

In this section, we apply the FBSM to solve our optimal control problem for an optimal solution. The method is developed using the Adams type predictor-corrector scheme (PECE) [6]. The rough outline of the forward and backward sweep algorithm for our optimal control problem is as follows:

Step 1: Divide the interval $[0, T]$ into N subintervals of uniform length and set

the stepsize $h = \frac{T}{N}$ so we have $t_n = nh$, $n = 0, 1, \dots, N$.

Step 2: Choose an initial guess of the control u .

Step 3: Using the initial conditions and the guess value for u , we solve the control system (2.13) forward in time using the PECE for the state solution (G_n, X_n, I_n) computed via the following predictor formulas

$$\begin{aligned}
 G_{n+1}^P &= G_0 + \sum_{j=0}^n (-[b_1 + X_j]G_j + b_1G_b), \\
 X_{n+1}^P &= X_0 + \sum_{j=0}^n (-b_2X_j + b_3[I_j - I_b]), \\
 I_{n+1}^P &= I_0 + \sum_{j=0}^n (-b_6[I_j - I_b] + b_4\max(0, G_j - b_5)t_j + u_j),
 \end{aligned}
 \tag{3.1}$$

and the corrector formulas for the state variables

$$\begin{aligned}
 G_{n+1} &= G_0 + \frac{h}{2} (-[b_1 + X_{n+1}^P]G_{n+1}^P + b_1G_b) + \frac{h}{2} (-(b_1 + X_0)G_0 + b_1G_b) \\
 &\quad + h[\sum_{j=1}^n (-(b_1 + X_j)G_j + b_1G_b)], \\
 X_{n+1} &= X_0 + \frac{h}{2} (-b_2X_{n+1}^P + b_3[I_{n+1}^P - I_b]) + \frac{h}{2} (-b_2X_0 + b_3[I_0 - I_b]), \\
 I_{n+1} &= I_0 + \frac{h}{2} (-b_6[I_{n+1}^P - I_b] + b_4\max(0, G_{n+1}^P - b_5)t_{n+1} + u_{n+1}) \\
 &\quad + \frac{h}{2} (-b_6[I_0 - I_b] + b_4\max(0, G_0 - b_5)t_0 + u_0) \\
 &\quad + h[\sum_{j=1}^n (-b_2X_j + b_3[I_j - I_b])]
 \end{aligned}
 \tag{3.2}$$

$$\begin{aligned}
I_{n+1} = & I_0 + \frac{h}{2}[-b_6[I_{n+1}^P - I_b] + b_4\max(0, G_{n+1}^P - b_5)t_{n+1} \\
& + u_{n+1}] + \frac{h}{2}(-b_6[I_0 - I_b] + b_4\max(0, G_0 - b_5)t_0 + u_0) \\
& + h \sum_{j=1}^n (-b_6[I_j - I_b] + b_4\max(0, G_j - b_5)t_j + u_j).
\end{aligned}$$

Step 4: Using the transversality conditions $\lambda_G(T) = \lambda_X(T) = \lambda_I(T) = 0$ and the

values for u and (G_n, X_n, I_n) , we solve the adjoint system (2.14) backward in time using the PECE for the adjoint variable $(\lambda_{G,n}, \lambda_{X,n}, \lambda_{I,n})$ calculated through the following predictor formulas

$$\begin{aligned}
\lambda_{G,N-n-1}^P &= h \sum_{j=0}^n [2A(G_{N-j} - l) - \lambda_{G,N-j}(b_1 + X_{N-j}) \\
&\quad + \lambda_{I,N-j}\max(0, \frac{G_{N-j} - b_5}{|G_{N-j} - b_5|})b_4t_{N-j}], \\
\lambda_{X,N-n-1}^P &= h \sum_{j=0}^n (-\lambda_{G,N-j}G_{N-j} - \lambda_{X,N-j}b_2), \\
\lambda_{I,N-n-1}^P &= h \sum_{j=0}^n (-\lambda_{X,N-j}b_3 - \lambda_{I,N-j}b_6),
\end{aligned}
\tag{3.3}$$

and the corrector formulas

$$\begin{aligned}
\lambda_{G,N-n-1} &= \frac{h}{2}(2A(G_N - l) - \lambda_{G,N}(b_1 + X_N) + \lambda_{I,N}\max(0, \frac{G_N - b_5}{|G_N - b_5|})b_4t_N) \\
&\quad + h[\sum_{j=1}^n (2A(G_{N-j} - l) - \lambda_{G,N-j}(b_1 + X_{N-j}) \\
&\quad + \lambda_{I,N-j}\max(0, \frac{G_{N-j} - b_5}{|G_{N-j} - b_5|})b_4t_{N-j}) \\
&\quad + \frac{h}{2}[2A(G_{N-n-1} - l) - \lambda_{G,N-n-1}^P(b_1 + X_{N-j}) \\
&\quad + \lambda_{I,N-n-1}^P\max(0, \frac{G_{N-n-1} - b_5}{|G_{N-n-1} - b_5|})b_4t_{N-n-1})],
\end{aligned}$$

$$\begin{aligned}
(3.4) \quad \lambda_{X,N-n-1} &= \frac{h}{2}(-\lambda_{G,N}G_N - \lambda_{X,N}b_2) + h\left[\sum_{j=1}^n(-\lambda_{G,N-j}G_N - \lambda_{X,N-j}b_2)\right. \\
&\quad \left. + \frac{h}{2}[-\lambda_{G,N-n-1}^p G_{N-n-1} - \lambda_{X,N-n-1}^p b_2]\right], \\
\lambda_{I,N-n-1} &= \frac{h}{2}(\lambda_{X,N}b_3 - \lambda_{I,N}b_6) + h\left[\sum_{j=1}^n(\lambda_{X,N-j}b_3 - \lambda_{I,N-j}b_6)\right. \\
&\quad \left. + \frac{h}{2}(\lambda_{X,N-n-1}^p b_3 - \lambda_{I,N-n-1}^p b_6)\right],
\end{aligned}$$

where $n = 0, 1, 2, \dots, N-1$.

Step 5: Update the control u by inserting the new solution (G_n, X_n, I_n) and the new adjoint variable $(\lambda_{G,n}, \lambda_{X,n}, \lambda_{I,n})$ into Eq. (2.15) and then set $u^* = \min(1, \frac{-\lambda_I}{2})$.

Step 6: Check convergence for the control u^* , the solution (G_n, X_n, I_n) and the adjoint variable $(\lambda_{G,n}, \lambda_{X,n}, \lambda_{I,n})$. If values of the variables in this iteration and the last iteration are negligibly close, then the current values are as solutions. If values are not close enough, return to Step 2.

4. NUMERICAL SIMULATIONS

In this section, we employ the schemes derived in Section 3 to compute numerical solutions of the optimal control problem (2.9)-(2.11). The parameter values [3] and the initial conditions are $b_1 = 0.1, b_2 = 0.0142, b_3 = 9.94 \times 10^{-5}, b_4 = 0.046, b_5 = 82.9370, b_6 = 0.2814, I_b = 7, G_b = 70, G_0 = 180, X_0 = 0, I_0 = 60$.

Figure 1 shows the numerical optimal solutions $G(t), X(t), I(t)$ for the optimal control problem in Eqs. (2.9)-(2.11), the transversality conditions $\lambda_G(10) = \lambda_X(10) = \lambda_I(10) = 0$, the weight parameter $A = 1$ and the desired glucose level $l = 135$ (diabetic patient).

Figure 2 demonstrates the numerical optimal solutions $G(t), X(t), I(t)$ for the optimal control problem in Eqs. (2.9)-(2.11) based on using the parameter values and initial conditions described in Table 2, the transversality conditions $\lambda_G(10) = \lambda_X(10) = \lambda_I(10) = 0$, the weight parameter $A = 1$ and the desired glucose level $l = 70$ (normal person).

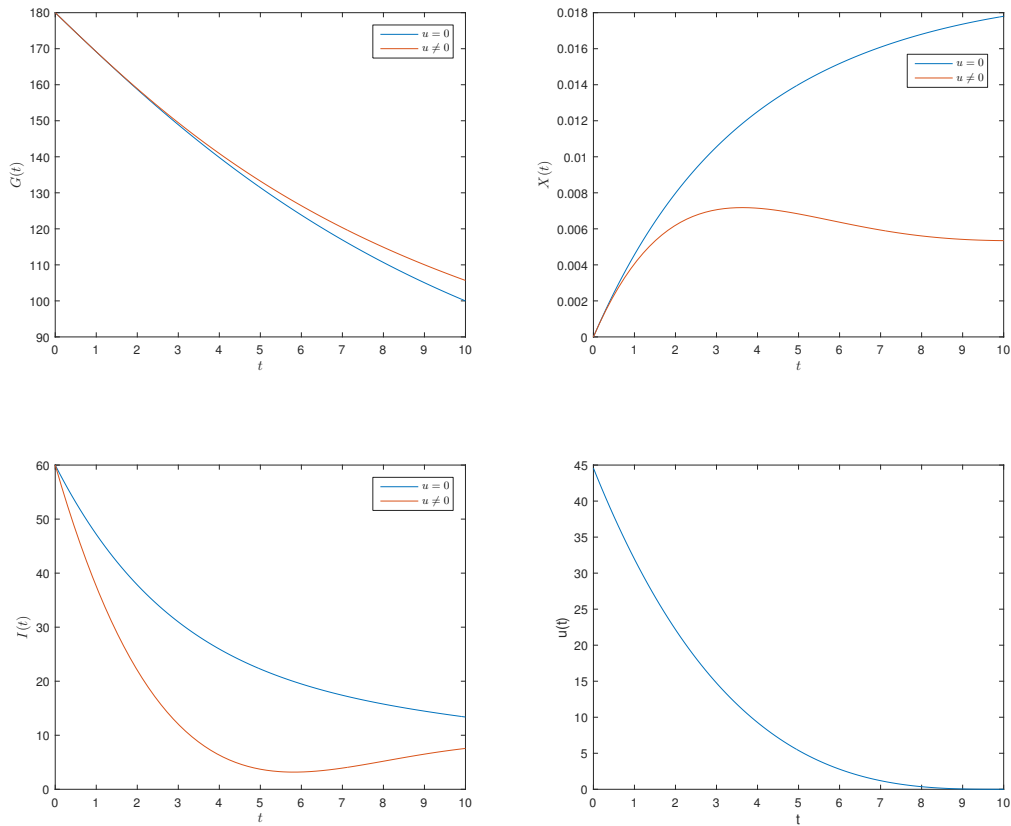


FIGURE 1. The numerical solutions $G(t)$, $X(t)$, $I(t)$ and the control $u(t)$ of the optimal control problem (2.9)-(2.11) with the terminal time $T = 10$ for a diabetic patient.

5. CONCLUSIONS

In this article, we have presented the optimal control problem for non-autonomous modified minimal model. The providing nutrients in order for increasing the insulin level, which is interpreted as our control $u(t)$, is used to control the blood glucose level $G(t)$. The analytical optimal solutions of the problem have been obtained using the Pontryagin's maximum principle. The numerical results of the optimality system have been numerically simulated using the FBSM to investigate the effect of the control $u(t)$ and the desired glucose level l on the behaviors of the optimal state solutions. Finally, the numerical results have been obtained by following the obtained necessary conditions for the problem.

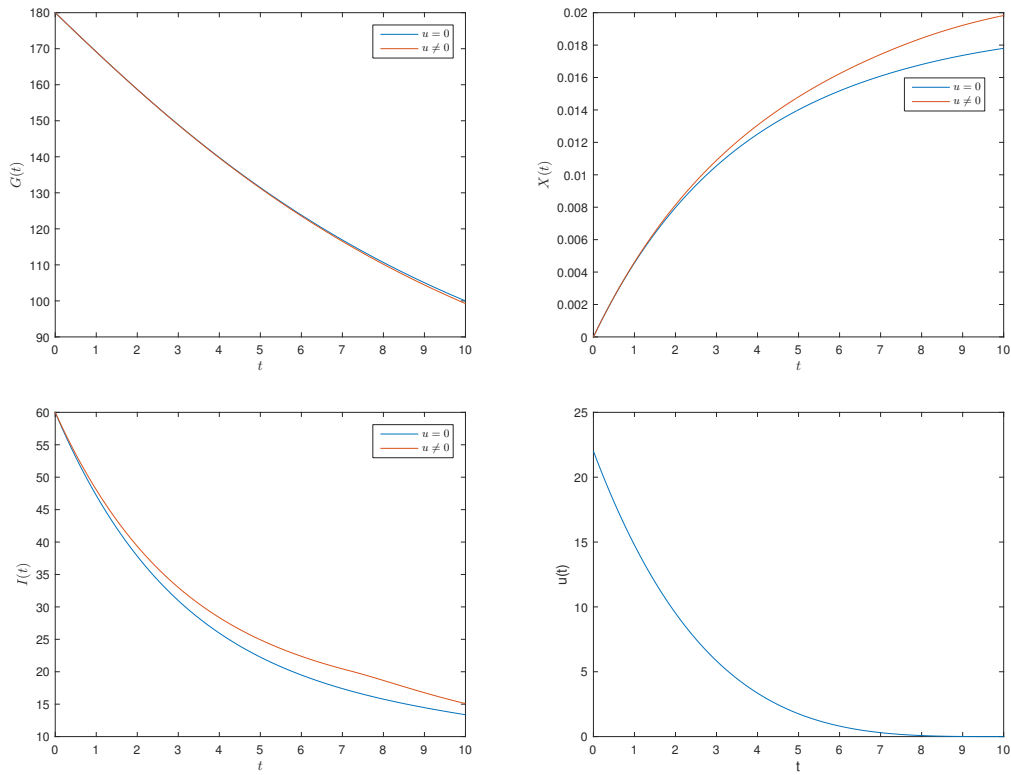


FIGURE 2. The numerical solutions $G(t)$, $X(t)$, $I(t)$ and the control $u(t)$ of the optimal control problem (2.9)-(2.11) with the terminal time $T = 10$ for a normal person.

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