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OPTIMAL BLOOD GLUCOSE CONTROL IN TYPE 1 DIABETIC PATIENTS BY USING PONTRYAGIN'S MINIMUM PRINCIPLE AND EXTENDED KALMAN FILTER

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Abstract. *Artificial Pancreas (AP) is an advanced diabetes management technology. AP requires an automatic control algorithm to determine the level of insulin injection based on the glucose level calculated on the Continuous Glucose Monitoring (CGM) sensor. Bergman Minimal Model (BMM) is a basic model in describing the dynamics of glucose-insulin in the human body. This study aims to determine the optimal control using Pontryagin's Minimum Principle (PMP), which is subject to reducing glucose levels in type 1 diabetes patients to be within the normal glucose level interval of 80-120 mg/dL. The BMM parameter values will be estimated using EKF to support the acquisition of precise and personal numerical simulations. Based on the control design simulation that has been obtained, the optimal control of insulin injection is given maximally (25 mU/L) during the first two hours of observation; then, the level decreases slowly until it reaches 0 at 12 hours of observation. This scenario successfully reduces the patient's glucose levels at the end of the observation period from 170.4 mg/dL (without control) to 121.2 mg/dL. This result providing a confident basis for initial future research and development in diabetes management.*

Keywords: Bergman Minimal Model, Blood Glucose Control, Extended Kalman Filter, Optimal Control, Pontryagin's Minimum Principle

1. Introduction

Type 1 diabetes mellitus (T1DM) is one of the most frequent chronic illnesses in the world. The prevalence of T1DM is 5%–10% of all diabetes mellitus cases. Approximately 30 million people live with T1DM worldwide, with an estimated three-fold increase in prevalence by 2040 [1]. Individuals with T1D require life-long insulin replacement with multiple daily insulin injections, insulin pump therapy, or the use

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of an automated insulin delivery system. Without insulin, blood sugar cannot enter the cells and accumulates in the internal circulation. This results in high blood pressure (hyperglycemia), which can lead to critical conditions and complications ([2], [3]).

Diabetes patients often experience variations in glucose levels throughout the day due to carbohydrate consumption and insulin activity. Therefore, early warning is needed to anticipate spikes in glucose levels so as not to cause critical conditions such as hypoglycemia or hyperglycemia. Most people will inject insulin directly using an invasive method by injection. Although widely used, this method can cause post-injection pain. Nowadays, advanced diabetes management technologies, such as artificial devices like artificial pancreas, are used. An artificial pancreas is a system composed of three components that collaborate to replicate the way a healthy pancreas regulates blood glucose in the human body without even injecting insulin invasively and is often used in combination with real-time continuous glucose monitoring and control algorithms to provide real-time predictions of glucose levels ([4], [5]).

Numerous studies have been carried out in an attempt to both prevent and treat diabetes. Mathematical models must be created in order to comprehend the intricate relationships that exist between the body's use of glucose and insulin. The 1981-developed Bergman's Minimal Model is a mathematical model that is frequently utilized. The goal of this model is to simulate the variations in plasma, distant, and glucose insulin levels in people with Type 1 diabetes. Because it has few parameters and nevertheless offers acceptable accuracy, the Bergman Minimal Model (BMM) features a relatively simple nonlinear equation. Owing to this feature, the BMM is frequently selected for simple and rapid analytical needs [6]. Meal disturbances are considered in this model development since they are important variables in the regulation of glucose. As a result, the Extended Bergman Minimal Model (EBMM) is thought to be more in line with actual circumstances [7].

Numerous scholars have examined the Bergman Minimal Model, spanning from bifurcation studies [8], local and global equilibrium point stability analyses [7], sensitivity analyses [9], numerical simulations and sliding mode control [10]. To get results that are near to real conditions, numerical simulations based on precise data have not yet been added to the research. There are certain Bergman Minimal model parameters that are impossible to measure. Therefore, in order to generate a highly trustworthy system model, it is important to estimate the precise parameters based on the dynamics of the real reaction.

Extended Kalman Filter (EKF), an extension of KF, known as the estimator for nonlinear systems (EKF). Compared to other estimators, EKF has a number of advantages, one of them being a faster computation time than EnKF [11]. EKFs have demonstrated efficacy in the estimation of nonlinear systems across several domains, encompassing mechanical engineering and health. The foreground region is tracked in order to detect object movement [12], the number of patients with HIV and AIDS is estimated [13], the time reproduction number of dengue transmissions is estimated [14], and parameters in heat transfer problems are estimated [15].

In terms of optimal control, Pontryagin's Minimum Principle (PMP) is a widely used optimal control algorithm. PMP is not just used in terms of optimal control but also terms of reinforcement learning [16]. Optimal control was applied to solve many optimization problems, such as minimizing the number of spreading COVID-19 [17], dengue [18], cancer [19], etc. In this research, we use PMP subjects to minimize the blood glucose level of type 1 diabetic patients and the cost of using insulin injection as the control variable. The BMM was used to describe the dynamic of glucose-insulin in the human body. The parameter of BMM was estimated first by using EKF to get the appropriate value that will be useful in terms of numerical simulation of optimal control.

2. Methodology

In this section, the methodology used in the research is explained, including related to the glucose-insulin mathematical model, extended Kalman filter (EKF), and Pontryagin's Minimum Principle (PMP) optimal dick method.

2.1. *Glucose-Insulin Mathematical Model*

The mathematical model that represents the dynamics of the interaction of glucose and insulin levels in the human body originated from a basic model developed by Bergman known as the Bergman Minimal Model (BMM). BMM consists of three compartments, namely, the blood glucose level (G), the impact of active insulin (I), and the insulin concentration in the bloodstream (I). A full description of the compartment, along with the model parameters, is given in Table 1.

The glucose-insulin model given in Equation (2.1) below.

$$\begin{aligned} \dot{G}(t) &= -p_1 G(t) - X(t)(G(t) + G_b) + U_g(t), \\ \dot{X}(t) &= -p_2 X(t) + p_3 I(t), \\ \dot{I}(t) &= -n(I(t) + I_b) + p_4 U_i(t). \end{aligned} \tag{2.1}$$

The glucose level in the blood will increase when the body receives food intake (meal disturbances) at a rate of $U_g(t)$ in the following equation (2.2):

$$U_g(t) = \frac{M_g A_g t \cdot \exp -t/t_{\max}}{t_{\max}^2}. \tag{2.2}$$

The quantity of carbohydrates in the meal is represented as M_g, with a constant value of 0.8, denoted as Ag in the model. The time when meal absorption reaches its maximum, referred to as $t_{\max}$, occurs at 50 minutes. Assuming a type 2 diabetes patient consumes three meals: breakfast at 7 AM, lunch at 12 AM, and dinner at 7 PM. Equation (2.2) can be expressed in the following step function form:

$$U_g(k) = \begin{cases} 0.025 D_{G_1}(k - k_1) \cdot \exp(-0.125(k - k_G)) & \text{if } k_1 \le k < k_2, \\ 0.025 D_{G_2}(k - k_2) \cdot \exp(-0.125(k - k_G)) & \text{if } k_2 \le k < k_3, \\ 0.025 D_{G_3}(k - k_3) \cdot \exp(-0.125(k - k_G)) & \text{if } k \ge k_3, \\ 0 & \text{else}, \end{cases} \tag{2.3}$$

where D_{G_1}, D_{G_2}, and D_{G_3} is the amount of carbohydrates consumed at each meal.

Table 1. The description of compartment and parameter of BMM

Notation	Description	Value	Unit
$G(t)$	The blood glucose level		mg/dL
$X(t)$	The impact of active insulin		1/min
$I(t)$	The insulin concentration in the bloodstream		mU/L
U_g (t)	Meal induced BGL disorder		mg/dL/min
$U_i(t)$	The rate of exogenous insulin		mU/L
p_1	The rate constant for glucose uptake in muscles and the liver, independent of insulin	Fitted	1/min
p_2	The rate at which tissue glucose uptake ability decreases	Fitted	1/min
p_3	The rate at which tissue glucose uptake capacity increases per unit of insulin concentration above the basal level	Fitted	$(mU/L)^{-1}$ min^{-2}
p_4	The rate at which tissue glucose uptake capacity increases	1/12	1/min
G_b	The baseline levels of BGL	120	mg/dL
I_b	The baseline level of insulin	10	mU/L
n	The insulin plasma time constant	0.25	1/min
t	The time		min

2.2. *Extended Kalman Filter*

The Extended Kalman Filter (EKF) is one of the suitable state observers for nonlinear models represented by first-order differential equations. The first step in implementing the EKF method is discretization, as the EKF is executed at discrete time intervals. The discretization process using the forward Euler method produces a discrete model of the system (2.1), as shown in system (2.4) below:

$$\begin{aligned}
G(k+1) &= G(k) + (-p_1(k)G(k) - X(k)(G(k)+G_b) + U_g(k))\Delta t,\\
X(k+1) &= X(k) + (-p_2(k)X(k) + p_3(k)I(k))\Delta t,\\
I(k+1) &= I(k) + (-n(I(k)+I_b) + p_4U_i(k))\Delta t,\\
p_1(k+1) &= p_1(k),\\
p_2(k+1) &= p_2(k),\\
p_3(k+1) &= p_3(k).
\end{aligned} \tag{2.4}$$

The Jacobian matrices of the model in system (2.1), where $\mathbf{x} = (G, X, I, p_1, p_2, p_3)^T$ as follows.

$$J = \begin{pmatrix} 1+(-p_1(k)-X(k))\Delta t & -(G(k)+G_b)\Delta t & 0 & -G(k)\Delta t & 0 & 0 \\ 0 & 1-p_2(k)\Delta t & p_3(k)\Delta t & 0 & -X(k)\Delta t & I(k)\Delta t \\ 0 & 0 & 1-n\Delta t & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \tag{2.5}$$

The real data used in this estimation is only the blood glucose level G Therefore, the output vector of the EKF method is defined as follows:

$$\mathbf{y} = C\mathbf{x}, \tag{2.6}$$

where $\mathbf{y} = G$, $C = \begin{pmatrix}1\ 0\ 0\ 0\ 0\ 0\end{pmatrix}$ and $\mathbf{x} = \begin{pmatrix}G\ X\ I\ p_1\ p_2\ p_3\end{pmatrix}^T$.

The EKF method consists of two main stages, namely the prediction stage and the update stage. In the prediction stage, the value of state at $k+1$ is calculated based on the value of state at k.

Predict:

$$\hat{x}(k+1|k) = f(\hat{x}(k|k)), \tag{2.7}$$

$$P(k+1|k) = J_f(\hat{x}(k|k))P(k|k)J_f(\hat{x}(k|k))^T + Q_F(k). \tag{2.8}$$

Update:

$$\tilde{y}(k+1) = y(k+1) - C\hat{x}(k+1|k), \tag{2.9}$$

$$K(k+1) = P(k+1|k)C^T(CP(k+1|k)C^T + R_F(k))^(-1), \tag{2.10}$$

$$\hat{x}(k+1|k+1) = \hat{x}(k+1|k) + K(k+1)\tilde{y}(k+1), \tag{2.11}$$

$$P(k+1|k+1) = (I - K(k+1)C)P(k+1|k). \tag{2.12}$$

Matrix K is the Kalman Gain, which is the key component in the update phase of the Extended Kalman Filter method Matrix Q_F represents the process covariance matrix, and matrix R_F represents the observation covariance matrix. Both of these matrices are obtained through tuning. The parameter values p_1, p_2, and p_3 have upper and lower bounds based on research conducted by medical researchers. Therefore, the parameter values need to be transformed to an appropriate scale. The transformation method is carried out using the following sigmoid function:

$$sig(x) = \frac{p_1\_\max}{p_1\_\max + e^{-x}}, \tag{2.13}$$

where x is the estimation value of p_1. The evaluation for model fitting was calculated using MAPE formula as follows.

$$\text{MAPE} = \sum_{i=1}^{N} \frac{y_i - \hat{y}_i}{y_i}, \tag{2.14}$$

where y_i being the actual glucose level of the patient at time i, $\hat{y}_i$ being the predicted glucose level of the patient at time i, and N being the number of data points. Finally, a filtering step is added to minimize the MAPE error value using the following formula:

$$\hat{y}(k) = \frac{1}{y_n}(\hat{x}(k) + \hat{x}(k-1) + \cdots + \hat{x}(k-y_n+1)). \tag{2.15}$$

2.3. *Pontryagin Minimum Principle (PMP)*

The steps to solve the optimal control problem using the Pontryagin Minimum Principle (PMP) are as follows.

(1) Define the performance index (to maximize or minimize) according to the control objective. In this study, the control objective is to minimize the blood glucose level G and the cost of insulin injection U_i.

$$J = min \int_0^T G + \frac{1}{2}CU_i^2 \; dt. \tag{2.16}$$

(2) Define the Hamiltonian function based on the following formula:

$$H = J + \lambda \dot{X}$$

where $\mathbf{x} = (G, X, I)$ and λ is Lagrange multiplier.

(3) Determine the optimal control U_i^* by solving the equation $\frac{\partial H}{\partial U_i} = 0$ (stationer condition).

(4) Determine the state equation by formula: $\dot{Y} = \frac{\partial H}{\partial \lambda}$.

(5) Determine the costate equation by formula $\dot{\lambda} = -\frac{\partial H}{\partial \mathbf{x}}$.

(6) The values of the state and costate are then substituted into the control U_i^*. Next, the control U_i^* is substituted into the state equation to obtain the optimal solution. All of these equations are solved numerically using the forward-backward sweep algorithm.

3. Result and Discussion

3.1. *Parameter Estimation*

The estimation of parameters using the EKF method is a meticulous process that involves tuning for the Q_F and R_F matrices. In this study, we have rigorously determined the most optimal Q_F and R_F matrices (with minimum error) for each model, specifically $Q_F = diag\big(20, 20, 10, 0.01, 0.002, 0.002\big)$ and $R_F = 10$. The parameter limits for each parameters are $p_1 \in [0, 0001], p_2 \in [0, 0014],$ and $p_3 \in [0, 994 \times 10^{-6}]$. The initial values for other parameters are taken from 1, with $X(0) = 0$ and $I(0) = 10$. The dataset containing blood glucose levels from four patients observed over one week can be accessed at. This dataset originates from the KDH 2020 activity commonly referred to as The OhioT1DM Dataset.

The estimated results of the three parameters, in consecutive order, are provided in Table 2, Table 3, and Table 4. The validation results of real data and estimated data, a crucial aspect of this study, are displayed in Figure 1. The estimated data closely follows the trend of the real data, as shown in the Figure 1. This is further supported by the MAPE values, which range around 10^{-3} for all four fitted patient data. This demonstrates the superiority of the EKF method in fitting fluctuating data trends, such as in this blood glucose level data. The EKF calculates the estimation values for p_1, p_2, and p_3 in each iteration, which can lead to fluctuations in the obtained estimates and potential non-convergence. Therefore, a transformation is necessary to constrain the values appropriately and facilitate parameter convergence. The converged values for parameters p_1 and p_2 from patient_id 563 are shown in Figure 2.

Table 2. Parameter estimation result of p_1

Patient	Min	Max	Mean	MAPE
Patient_id 540	1.8043e-05	5.3529e-05	5.0104e-05	10^{-3}
Patient_id 544	1.7439e-05	5.2408e-05	5.0128e-05	1.1×10^{-3}
Patient_id 559	1.6808e-05	5.3025e-05	5.0100e-05	0.9×10^{-3}
Patient_id 563	1.6926e-05	5.3480e-05	5.0123e-05	10^{-3}

Table 3. Parameter estimation result of p_2

Patient	Min	Max	Mean	MAPE
Patient_id 540	0.0025	0.0075	0.070	10^{-3}
Patient_id 544	0.0025	0.0075	0.070	1.1×10^{-3}
Patient_id 559	0.0025	0.0075	0.070	0.9×10^{-3}
Patient_id 563	0.0025	0.0075	0.070	10^{-3}

Table 4. Parameter estimation result of p_2

Patient	Min	Max	Mean	MAPE
Patient_id 540	1.6443e-06	4.9871e-06	4.9725e-06	10^{-3}
Patient_id 544	1.6433e-06	4.9828e-06	4.9723e-06	1.1×10^{-3}
Patient_id 559	1.6416e-06	4.9853e-06	4.9723e-06	0.9×10^{-3}
Patient_id 563	1.6421e-06	4.9824e-06	4.9722e-06	10^{-3}

3.2. *Pontryagin's Minimum Principle*

The main issue of optimal control in this research is to lower the blood glucose levels of type 2 diabetes patients to a normal range, which is 80-120 mg/dL. Therefore,

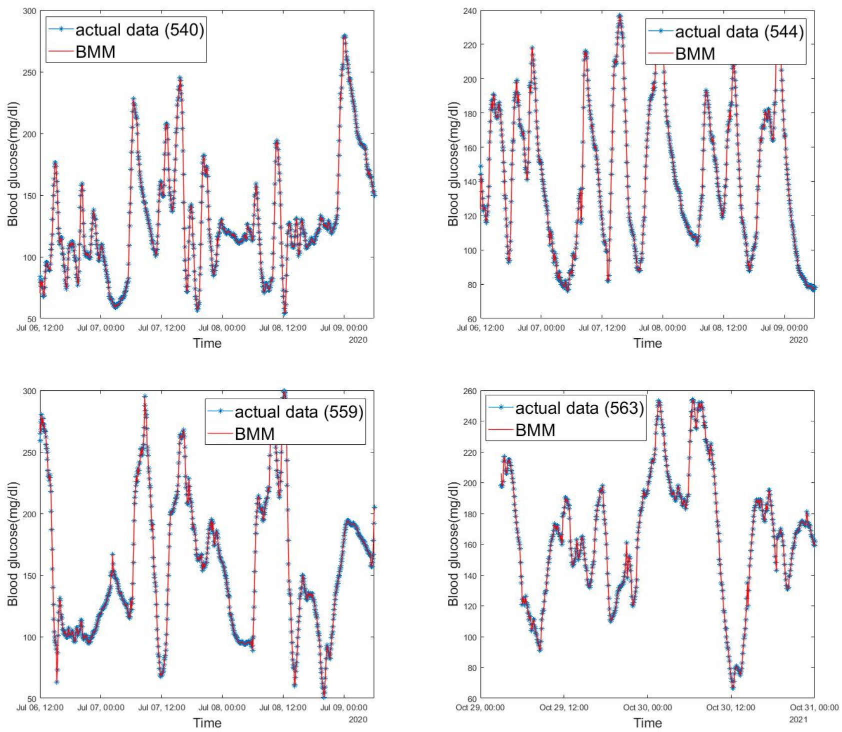

Figure. 1. Validation results of blood glucose level of (a) Patient_ id 540, (b) Patient_ id 544 (c) Patient_ id 559 dan (d) Patient_ id 563.

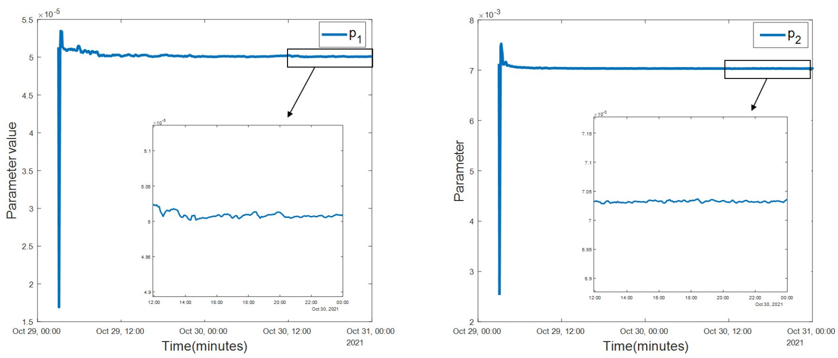

Figure. 2. Convergence estimation result of p_1 and p_2

the performance index for control is formulated as follows:

$$J = \min \int_0^T G + \frac{1}{2} C U_i^2 \, dt. \tag{3.1}$$

Based on the performance index and system (2.1), the Hamiltonian function is obtained in the following equation:

$$H = G + \frac{1}{2}CU_i^2 + \lambda_1(-p_1G(t) - X(t)(G(t) + G_b) + U_g(t)) \\ + \lambda_2(-p_2X(t) + p_3I(t)) + \lambda_3(-n(I(t) + I_b) + p_4U_i(t)).$$

Optimal control is obtained when stationary conditions are met, $\frac{\partial H}{\partial U_i} = 0$. Therefore, it is obtained that:

$$CU_i + \lambda_3 p_4 = 0 \iff U_i = -\frac{\lambda_3 p_4}{C}.$$

Taking into account the maximum limit of insulin injected into the body ($U_{i\_\max}$), then the optimal control U_i is:

$$U_i^* = \min\{U_{i\_\max}, \max\{0, -\frac{\lambda_3 p_4}{C}\}\}, \tag{3.2}$$

with the transversality condition $\lambda_i^*(t_f) = 0$, $i = 1, 2, 3$ and t_f is the final time.

The state equation obtained from the formula $x = \frac{\partial H}{\partial \lambda}$ is none other than system (2.1). The control equation (3.2) contains the costate variable or adjoint variable λ, so it is necessary to solve the costate equation through $\lambda = -\frac{\partial H}{\partial \mathbf{x}}$. We obtained:

$$\dot{\lambda}_1 = \frac{-\partial H}{\partial G} = -[1 + \lambda_1(-p_1 - X)] = -1 + \lambda_1(p_1 + X), \tag{3.3}$$

$$\dot{\lambda}_2 = \frac{-\partial H}{\partial X} = -[\lambda_1(-G - G_b) + \lambda_2(-p_2)] = \lambda_1(G + G_b) + p_2\lambda_2, \tag{3.4}$$

$$\dot{\lambda}_3 = \frac{-\partial H}{\partial I} = -[\lambda_2 p_3 - n\lambda_3] = -\lambda_2 p_3 + n\lambda_3. \tag{3.5}$$

Next, the optimal control simulation is conducted using the forward-backward sweep algorithm. The parameter values used in the simulation are $p_1 = 5.0123e-05$, $p_2 = 0.007$, $p_3 = 4.9722e-06$, while other parameters use the values from Table 2. The initial values used are $(G_0, X_0, I_0) = (200, 0, 55)$, and the observation time is $0 \leq t \leq 24$ hours. In this study, 4 control scenarios are examined by varying the weight values C and the maximum insulin injection value $U_{i\_\max}$.

Table 5. Simulation result of PMP control

Scenario	C	$U_{i\_\max}$	**Performance index** J	**Without control**	**With control**	**Percentage decrease**
Scenario 1	80	22	7.3338e+06	170.4	170	0.23%
Scenario 2	80	25	8.4812e+06	170.4	155.9	8.51%
Scenario 3	60	22	7.3607e+06	170.4	155.1	8.98%
Scenario 4	60	25	8.1323e+06	170.4	121.2	28.87%

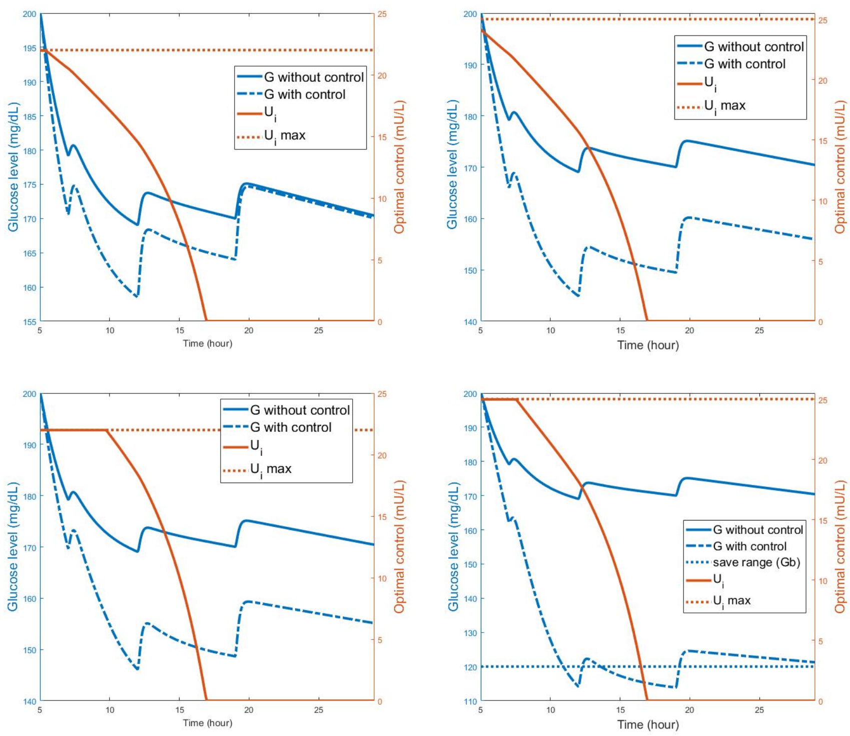

Figure. 3. Optimal control simulation of (a)1st scenario (b)2nd scenario (c)3rd scenario (d)4th scenario.

Figure 3 displays the results of the fourth control scenario simulation. Figure 3(a) shows the glucose levels graph of the patient and optimal control resulting from the implementation of Scenario 1 with $C = 80$ and $U_{i\_\max} = 22$ mU/L Scenario 1 provides the smallest decrease among the four scenarios, with only a 0.23% reduction at the end of the observation period Figure 3(b) presents the glucose levels of the patient and optimal control from the implementation of Scenario 2 with $C = 80$ and $U_{i\_\max} = 25$ mU/L In Figure 3(b), a significant decrease in blood glucose levels is observed after applying the control The second control scenario results in an 8.51% reduction at the end of the observation period.

The 3(c) graph represents the glucose levels of patients and optimal controls resulting from the implementation of Scenario 3 with $C = 60$ and $U_{i\_\max} = 22$ mU/L. The results from the third scenario are similar to those of the second scenario. The application of the third scenario resulted in a decrease of 8.98% at the end of the observation period. Overall, the implementation of the second and third scenarios has been able to reduce glucose levels in diabetic patients. However, it has yet to bring them within the normal range of 80-120 mg/dL.

Figure 3(d) shows the patient's glucose level and optimal control from Scenario 4 with $C = 60$ and $U_{i\_\max} = 25$ mU/L. In Scenario 4, the patient's glucose level was able to be lowered to the normal limit of 120 mg/dL. The fourth scenario provides a decrease of 28.87% among the other four scenarios. The patient's glucose level at the end of the observation time at the time of no control of 170.4 mg/dL can be lowered to 121.2 mg/dL by applying scenario 4. In summary, a comparison of the results of the four scenarios at the end of the simulation time is shown in Table 5.

4. Conclusion

In this study, the optimal control for glucose and insulin regulation in the human body has been studied through the Bergman Minimal Model and Pontryagin's Minimum Principle (PMP). The model parameter values have been estimated first using the EKF method and obtained very good results with an error of around 10^{-3}. Optimal control with the aim of minimizing glucose levels in type 1 diabetes patients has been compiled using PMP, with the control variable being insulin injection. Based on the numerical simulation of the control design and the estimated model parameter values, it was obtained that the application of control can provide a decrease in patient glucose levels of up to 28.87%. In subsequent studies, a more robust optimal control method can be considered and can cover constraints related to the control variables.

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