Advances in Difference Equations
a SpringerOpen Journal

RESEARCH Open Access

Optimal selection of injection doses and injection timings for insulin therapy in a limited time

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Abstract

In this paper, we study the injection strategies of insulin for the impulsive therapy of diabetes in a limited time. According to whether we consider the risk of hypoglycemia or not, we develop two different control objectives and investigate three different injection strategies for each control objective. We apply a time-rescaling method to overcome technical obstacles in optimal impulsive control and compute the gradient formulas of cost functions with respect to injection doses and injection timings. By means of numerical simulations we get the optimal injection doses and injection timings for each injection strategy. Our study indicates that for the control objective without considering the risk of hypoglycemia, the optimal injection timing control is more effective than the optimal injection dose control, whereas the mixed control achieves almost the same effect as the optimal injection timing control. For the other control objective considering the risk of hypoglycemia, the optimal injection timing control performs better than the optimal injection dose control in avoiding emergence of hypoglycemia, and the mixed control provides the best strategy in preventing hyperglycemia from occurrence.

Keywords: Insulin therapy; Optimal control; Injection dose; Injection timing

1 Introduction

Over the last few decades, diabetes mellitus has been a leading public health concern due to the overwhelming number of people living with this disease and large amounts of money (245 billion dollars in the US in 2012) spent in medical care [28]. Diabetes mellitus is a metabolic disorder, which is characterized by high plasma glucose level over a prolonged period, which may lead to frequent urination and increased thirst and hunger. If not treated, it can cause severe long-term complications such as diabetic ketoacidosis, cardiovascular disease, stroke, and chronic kidney disease. In general, diabetes is caused by either the pancreas producing insufficient insulin (type 1 diabetes) or the cells of the body not responding properly to the insulin produced (type 2 diabetes). Insulin therapy is an effective way for both types of diabetics to control high plasma glucose.

Insulin pump is a very common medical device, which can administrate insulin and its analogues. The use of it has highly improved the living quality of the patient compared

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with manual syringe [6, 9, 10, 13, 22, 25–27, 29]. Patients can determine the injection dose and injection timing when using an insulin pump. However, patients' lifestyle is affected since their carbohydrate intake is severely restricted and the dose of injected insulin is carefully computed to avoid occurrence of both hyperglycemia and hypoglycemia [13, 22]. That is why in recent years, more and more researchers are attracted to develop an artificial pancreas, which can provide the substitute endocrine functionality of a real and healthy pancreas [11–13, 30, 31].

Mathematical models are important tools to study insulin therapy for diabetes because they can deepen the understanding of the pharmacological mechanism and the changing regularity of the plasma glucose concentration. For example, some researchers studied the glucose–insulin regulatory system of healthy people [4, 7, 17, 32, 34], whereas others concentrated on the insulin sensitivity [5, 8, 16, 23]. Delay differential equation models were proposed in [15, 18, 35, 36] to reveal the reason of the sustained oscillations of the endocrine metabolic system. Doran et al. [3] investigated the insulin infusion process for critically ill patients in ICU. To mimic the relatively transient behavior of insulin injection, impulsive different equation models were formulated in [12, 13, 29] to study the glucose–insulin regulatory system with insulin therapy.

It is more important to keep the plasma glucose level under control with small fluctuations than to blindly lower it because of the risk of hypoglycemia, since hypoglycemia is much more dangerous than hyperglycemia. Optimal control is an invaluable mathematical tool to investigate injection strategies of insulin. By using optimal control theory it is entirely possible to achieve the goal of making the glucose level under control with small fluctuations while minimizing the treatment cost.

Since the state variables are affected by uncertain pulse jumps, there is technical difficulty in solving the optimal control problem governed by a switched impulsive dynamical system. To overcome such a difficulty, some work has been done, and several available methods have been applied to the optimal management in many fields [14, 19, 24, 33]. For example, the authors in [19] investigated and assessed various optimal strategies for a multipopulation model with epidemic and impulsive interventions, whereas in [24], different optimal release strategies of natural enemies for a pest management systems were studied.

In this paper, we formulate a mathematical model for the plasma glucose control in a limited time and investigate the optimal injection strategies of insulin based on specific control objectives. The rest of this paper is organized as follows. In Sect. 2, we formulate a model for the limited time control of plasma glucose with impulsive injection of insulin. In Sect. 3, we take into account both the fluctuations of plasma glucose level and the amount of insulin injected, and set two different control objectives according to whether we consider the risk of hypoglycemia or not. Then for each control objective, we investigate three different limited-time optimal injection strategies, and by using a time rescaling method we obtain the gradients of cost function with respect to all control parameters. In Sect. 4, we perform a series of numerical simulations to determine the optimal values of the injection timings and injection doses. Finally, we present a brief conclusion in Sect. 5.

2 Model formulation

Most theoretical studies on insulin therapy focused on the asymptotic behaviors of dynamical systems, which are applicable to long-term control of the the plasma glucose level.

However, if the plasma glucose concentration is much higher than the normal level, then to avoid permanent damage of patient's health, treatment should be taken to lower glucose concentration to a tolerable level in a short time. To the best of our knowledge, very few works on the limited time control of glucose concentration have been done. The work [20] studied a finite-time control of the plasma glucose level, which focuses on the glucose level at the terminate time of control but ignores the fluctuation during the control process. It is worth pointing out that the ignorance of extreme fluctuations of glucose concentration during control process may have undesirable consequences in the clinic.

Li, Kuang, and Mason [15, 17] proposed mathematical models obeying the mass conservation law to simulate the glucose–insulin regulation system. Then Song, Huang, and Li [29] developed these models by incorporating three physiological time delays and periodic impulsive deliveries of insulin and formulated the system as follows:

$$\begin{cases} \left.\begin{aligned} \frac{dG(t)}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t-\tau_m)) \\ &\quad + f_5(I(t-\tau_h)), \\ \frac{dI(t)}{dt} &= f_1(G(t-\tau_t)) - d_i I(t), \end{aligned}\right\} & t \neq kp, k = 1, 2, \ldots, \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \sigma, \end{aligned}\right\} & t = kp, \end{cases} \tag{1}$$

with $G(0) = G_0 > 0$ and $I(0) = I(0^+) = I_0 > 0$, where $G(t)$ and $I(t)$ represent the concentrations of the glucose and insulin at time t, respectively, G_{in} denotes the glucose input, $f_1(G)$ stands for the insulin secretion with elevated glucose concentration, $f_2(G)$ represents the glucose uptake, which is independent of insulin, $f_3(G)f_4(I)$ stands for the glucose utilization, which is dependent on insulin, $f_5(I)$ is the hepatic glucose production (HGP), τ_t, τ_m, τ_h are physiological time delays in the glucose–insulin regulation system, and $d_i > 0$ is the degradation rate of insulin. For the periodic impulsive deliveries of insulin, σ is the injection dose, whereas p is the delivery period.

Song et al. [29] focused on the study of the asymptotical behavior of the plasma glucose level after sufficiently long time of insulin treatment. However, it is of more clinical significance to consider the optimal limited-time control problem of glucose, that is, to determine the most efficient strategy of limited-time insulin injection at the minimal economic cost. For this purpose, we ignore the impact of the physiological time delays and formulate the following system incorporating limited-time control of glucose and impulsive deliveries of insulin:

$$\begin{cases} \left.\begin{aligned} \frac{dG(t)}{dt} &= G_{in} - f_2(G) - f_3(G)f_4(I) + f_5(I) = F_1(G, I), \\ \frac{dI(t)}{dt} &= f_1(G) - d_i I(t) = F_2(G, I), \end{aligned}\right\} & t \neq t_i, t \in [0, T], \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \sigma_i, \end{aligned}\right\} & t = t_i, i = 1, 2, \ldots, N-1, \\ G(0) = G(0^+) = G_0 > 0, \qquad I(0) = I(0^+) = I_0 > 0, \end{cases} \tag{2}$$

where T is a predefined adjustable constant, which represents the time length of control, t_i, $i = 1, 2, \ldots, N-1$, are the injection moments of insulin, which satisfy $0 \le t_1 \le t_2 \le \cdots \le t_{N-1} \le t_N = T$, whereas σ_i (μU/ml) > 0 is the injection dose at $t = t_i$. Assume that the upper

and lower bounds of the plasma glucose concentration that people can tolerate are A and B, respectively. If the plasma glucose concentration is kept within $[B, A]$, then both hypoglycemia and hyperglycemia can be avoided. We denote the ideal level of plasma glucose by $\alpha A + \beta B$, where $\beta \in [0, 1]$ and $\alpha + \beta = 1$.

Our aim in this paper is finding a method to determine the optimal injection moments and injection doses that can not only maintain the plasma glucose concentration at an idea level, but also minimize the treatment cost.

3 The optimal control problem

In this section, we present the optimal control problem about the plasma glucose by analyzing system (2). There are two key points we need to pay attention to. The first one is the medical cost. As is well known, there is no cure for diabetes mellitus, so if a person is diagnosed with diabetes, then a lifelong treatment is needed. Thus it is very important to reduce the medical cost as much as possible. The other thing that we are concerned about is the glucose fluctuation during therapy. This is directly related to the treatment effect. The ultimate goal of the treatment is to lower the plasma glucose concentration to normal level as soon as possible by injecting insulin or its analogues. We also need to ensure that the glucose level is not too high or too low, that is, the deviation from normal level should not be too large.

Based on the above considerations, the problem in this paper can be stated as finding the optimal control parameter $\sigma_i > 0$ and injection timings $t_i \in [0, T]$ minimizing the cost function

$$J_1(\sigma_1, \sigma_2, \ldots, \sigma_{N-1}, t_1, t_2, \ldots, t_{N-1}) = l_0 \sum_{1}^{N-1} \sigma_i + l_1 \int_0^T \big(G(t) - (\alpha A + \beta B)\big)^2 \, dt \tag{3}$$

or

$$\begin{aligned} J_2(\sigma_1, \sigma_2, \ldots, \sigma_{N-1}, t_1, t_2, \ldots, t_{N-1}) = {} & l_0 \sum_{1}^{N-1} \sigma_i + l_1 \int_0^T \big(G(t) - (\alpha A + \beta B)\big)^2 \, dt \\ & + l_2 \int_0^T \big(G(t) - B\big)^2 \, dt, \end{aligned} \tag{4}$$

where l_0 is the unit price of insulin or its analogues, and l_1, l_2 are the balance factors between the glucose level and insulin cost in objective functions.

Remark 1 In insulin therapy, especially for the critically ill patients, besides hyperglycemia, hypoglycemia can also occur when a patient misses a meal or an overdose of insulin is injected. Compared to hyperglycemia, hypoglycemia is certifiably more dangerous to human health and can cause serious complications such as brain damage and quick unexpected death [12]. So in the second control objective, we particularly consider reducing the likelihood of hypoglycemia.

In the following, we study three different kinds of impulsive injection strategies.

3.1 Optimization by injection timing and injection dose

Let $\tau_i = t_i - t_{i-1}$ and

$$\tau_i^1 \le \tau_i \le \tau_i^2, \quad i = 1, 2, \dots, N, \tag{5}$$

where τ_i^1 and τ_i^2 are given constants that represent the lower and upper bounds of the time interval between the $(i-1)$th and ith injections. Assume that the injection dose σ_i satisfies

$$0 \le \sigma_i^1 \le \sigma_i \le \sigma_i^2, \quad i = 1, 2, \dots, N-1, \tag{6}$$

where σ_i^1 and σ_i^2 are also given constants that represent the lower and upper bounds of the ith injection dose.

Define the vectors $\mathfrak{P}_1 = (\tau_1, \tau_2, \dots, \tau_N)^T$ and $\mathfrak{P}_2 = (\sigma_1, \sigma_2, \dots, \sigma_{N-1})^T$, where τ_i and σ_i satisfy conditions (5) and (6), respectively. Let Ω_1 and Ω_2 be the sets of all $\mathfrak{P}_1 \in R^N$ and $\mathfrak{P}_2 \in R^{N-1}$ satisfying (5) and (6), respectively.

Since the mapping defined by the right-hand side of system (2) is smooth, this impulsive system has a unique solution $(G(t), I(t))^T$ corresponding to each pair $(\mathfrak{P}_1, \mathfrak{P}_2) \in (\Omega_1, \Omega_2)$ [1, 2].

Then the cost functions in (3) and (4) can be rewritten as

$$J_1(\mathfrak{P}_1, \mathfrak{P}_2) = l_0 \sum_1^{N-1} \sigma_i + l_1 \int_0^T \big(G(t) - (\alpha A + \beta B)\big)^2 \, dt \tag{7}$$

and

$$J_2(\mathfrak{P}_1, \mathfrak{P}_2) = l_0 \sum_1^{N-1} \sigma_i + l_1 \int_0^T \big(G(t) - (\alpha A + \beta B)\big)^2 \, dt + l_2 \int_0^T \big(G(t) - B\big)^2 \, dt. \tag{8}$$

For the control of plasma glucose, we raise the following optimal control problem:

($\mathbf{P_A}$): For the insulin treatment system (2), find a parameter vector pair $(\mathfrak{P}_1, \mathfrak{P}_2) \in (\Omega_1, \Omega_2)$ such that the cost function $J_1(\mathfrak{P}_1, \mathfrak{P}_2)$ or $J_2(\mathfrak{P}_1, \mathfrak{P}_2)$ is minimized.

Since the state variables $G(t)$ and $I(t)$ are affected by uncertain pulse effects (uncertain injection timing t_i and uncertain injection dose σ_i), this problem cannot be directly solved by currently available optimization techniques. To overcome such a difficulty, we introduce a time-scaling transform method (cf. Lee [14], Teo [33], Liang [19], and Pei [24]) and translate these uncertain pulse time points into fixed ones. Then the optimal control problem ($\mathbf{P_A}$) is transformed into an equivalent optimal parameter selection problem, which is regulated by an ordinary differential equation system with periodic boundary conditions.

According to system (2), let $t = t_{i-1} + (t_i - t_{i-1})s = \sum_{j=1}^{i-1} \tau_j + \tau_i s$ for $t \in (t_{i-1}, t_i] = (\sum_{j=1}^{i-1} \tau_j, \sum_{j=1}^{i} \tau_j]$ and define

$$G^i(s) = G\big(t_{i-1} + (t_i - t_{i-1})s\big), \qquad I^i(s) = I\big(t_{i-1} + (t_i - t_{i-1})s\big), \tag{9}$$

where $0 < s \le 1$, $i = 1, 2, \dots, N$, and $t_0 = 0$.

Then system (2) is transformed into the following N subsystems:

$$\begin{cases} \frac{dG^i(s)}{ds} = \tau_i[G_{in} - f_2(G^i) - f_3(G^i)f_4(I^i) + f_5(I^i)] \\ \qquad = \tau_i F_1^i(G^i, I^i), & s \in (0,1], i = 1,2,\dots,N, \\ \frac{dI^i(s)}{ds} = \tau_i[f_1(G^i) - d_i I^i] = \tau_i F_2^i(G^i, I^i), \end{cases} \tag{10}$$

with initial and boundary conditions

$$G^1(0) = G_0, \qquad I^1(0) = I_0, \tag{11}$$

and

$$\begin{cases} G^i(0) = G^{i-1}(1), \\ I^i(0) = I^{i-1}(1) + \sigma_i, \quad i = 2,3,\dots,N. \end{cases} \tag{12}$$

Subject to system (10)–(12), the cost functions (7) and (8) are transformed into equivalent new forms

$$\hat{J}_1(\mathfrak{P}_1, \mathfrak{P}_2) = l_0 \sum_1^{N-1} \sigma_i + l_1 \int_0^1 \sum_{i=1}^{N} \big(G^i(s) - (\alpha A + \beta B)\big)^2 \, ds \tag{13}$$

and

$$\begin{aligned} \hat{J}_2(\mathfrak{P}_1, \mathfrak{P}_2) = {} & l_0 \sum_1^{N-1} \sigma_i + l_1 \int_0^1 \sum_{i=1}^{N} \big(G^i(s) - (\alpha A + \beta B)\big)^2 \, ds \\ & + l_2 \int_0^1 \sum_{i=1}^{N} \big(G^i(s) - B\big)^2 \, ds. \end{aligned} \tag{14}$$

Then the optimal control problem ($\mathbf{P_A}$) is translated into

($\mathbf{P_B}$) For the insulin treatment system (10) with conditions (11) and (12), find a parameter vector pair $(\mathfrak{P}_1, \mathfrak{P}_2) \in (\Omega_1, \Omega_2)$ such that the cost function $\hat{J}_1(\mathfrak{P}_1, \mathfrak{P}_2)$ or $\hat{J}_2(\mathfrak{P}_1, \mathfrak{P}_2)$ is minimized.

It is easy to verify that this optimal parameter selection problem is equivalent to the previous optimal control problem. In the following, we only need to find parameters σ_i and τ_i that satisfy the requirements.

Note that for given parameters σ_i and τ_i, the initial conditions of the dynamical systems (10)–(12) are all determined. We easily see that the initial state value $(G^{i+1}(0), I^{i+1}(0))$ of $(G^{i+1}(s), I^{i+1}(s))$ depends on the state value $(G^i(1), I^i(1))$ of $(G^i(s), I^i(s))$ at $s = 1$. Thus for the optimization procedure, we first get $(G^1(s), I^1(s))$, $0 \le s \le 1$ by solving the dynamical systems (10)–(12) when $i = 1$. According to (12), $(G^1(1), I^1(1))$ is the initial value $(G^2(0), I^2(0))$ when $i = 2$. With this initial condition, we can further calculate $(G^2(s), I^2(s))$, $0 < s \le 1$. Repeat this procedure until $(G^N(s), I^N(s))$, $0 < s \le 1$, is obtained.

To solve the above optimization problem, we can apply the gradient-based optimization techniques as in [24]. In what follows, we discuss the gradient information of the objective function $\hat{J}_m$, $m = 1, 2$, with respect to the control parameters τ_i and σ_i.

To apply Pontryagin's maximum principle, we set

$$\lambda^T = \left[\left(\lambda^1\right)^T, \left(\lambda^2\right)^T, \ldots, \left(\lambda^N\right)^T\right]^T, \qquad F^i = \left(F_1^i, F_2^i\right)^T, \qquad \lambda^i(s) = \left(\lambda_1^i(s), \lambda_2^i(s)\right)^T,$$
$$y_i(s) = \left(G^i(s), I^i(s)\right)^T, \qquad y = \left(y_1^T, y_1^T, \ldots, y_N^T\right)^T, \qquad \mathfrak{P}_1 = (\tau_1, \tau_2, \ldots, \tau_N)^T,$$

and then from (12) easily get

$$y_i(0) = \phi^{i-1}\left(y_{i-1}(1), \sigma_{i-1}\right) = \left(G^{i-1}(1), I^{i-1}(1) + \sigma_{i-1}\right)^T, \quad i = 2, 3, \ldots, N-1.$$

Now we consider the first kind of cost function, that is, when $\hat{J} = \hat{J}_1$. Define the Hamiltonian function for this optimization problem as follows:

$$H(y, \mathfrak{P}_1, \lambda) = \sum_{i=1}^{N} H_i\left(y_i, \tau_i, \lambda^i\right) = \sum_{i=1}^{N} H_i\left(G^i, I^i, \tau_i, \lambda_1^i, \lambda_2^i\right), \tag{15}$$

where

$$\begin{aligned} H_i\left(y_i, \tau_i, \lambda^i\right) &= l_1\left(G^i - (\alpha A + \beta B)\right)^2 + \tau_i \lambda_1^i F_1^i + \tau_i \lambda_2^i F_2^i \\ &= l_1\left(G^i - (\alpha A + \beta B)\right)^2 + \tau_i \left(\lambda^i\right)^T F^i, \quad i = 1, 2, \ldots, N, \end{aligned} \tag{16}$$

and $\lambda^i = (\lambda_1^i(s), \lambda_2^i(s))^T$ is the corresponding costate governed by the following backward initial-boundary-value problem:

$$\begin{cases} \dot{\lambda}_1^i(s) = -\frac{\partial H_i}{\partial G^i} = -2l_1(G^i - (\alpha A + \beta B)) - \tau_i\{\lambda_1^i \frac{\partial F_1^i}{\partial G^i} + \lambda_2^i \frac{\partial F_2^i}{\partial G^i}\}, \\ \dot{\lambda}_2^i(s) = -\frac{\partial H_i}{\partial I^i} = -\tau_i\{\lambda_1^i \frac{\partial F_1^i}{\partial I^i} + \lambda_2^i \frac{\partial F_2^i}{\partial I^i}\} \end{cases} \tag{17}$$

with

$$\begin{cases} \lambda_1^N(1) = 0, \qquad \lambda_2^N(1) = 0, \\ \lambda_1^i(1) = \lambda_1^{i+1}(0), \qquad \lambda_2^i(1) = \lambda_2^{i+1}(0), \quad i = 2, 3, \ldots, N-1. \end{cases} \tag{18}$$

For the second kind of control, that is, when $\hat{J} = \hat{J}_2$, the expression of the Hamiltonian function (15) remains unchanged, but due to the difference between $\hat{J}_1$ and $\hat{J}_2$, the expression of H_i becomes

$$\begin{aligned} H_i\left(y_i, \tau_i, \lambda^i\right) &= l_1\left(G^i - (\alpha A + \beta B)\right)^2 + l_2\left(G^i - B\right)^2 + \tau_i \lambda_1^i F_1^i + \tau_i \lambda_2^i F_2^i \\ &= l_1\left(\left(G^i - (\alpha A + \beta B)\right)^2 + l_2\left(G^i - B\right)^2 + \tau_i \left(\lambda^i\right)^T F^i, \quad i = 1, 2, \ldots, N, \end{aligned} \tag{19}$$

and the corresponding costate $\lambda^i = (\lambda_1^i(s), \lambda_2^i(s))^T$ takes the form

$$\begin{cases} \dot{\lambda}_1^i(s) = -\frac{\partial H_i}{\partial G^i} = -2l_1(G^i - (\alpha A + \beta B)) - 2l_2(G^i - B) - \tau_i\{\lambda_1^i \frac{\partial F_1^i}{\partial G^i} + \lambda_2^i \frac{\partial F_2^i}{\partial G^i}\}, \\ \dot{\lambda}_2^i(s) = -\frac{\partial H_i}{\partial I^i} = -\tau_i\{\lambda_1^i \frac{\partial F_1^i}{\partial I^i} + \lambda_2^i \frac{\partial F_2^i}{\partial I^i}\} \end{cases} \tag{20}$$

with initial-boundary-value condition (18).

Then by the results in [21] we can obtain the following expressions for gradients of the cost function $\hat{J}_m(\mathfrak{P}_1, \mathfrak{P}_2)$, $m = 1, 2$, with respect to the injection timing τ_i and injection dose σ_l.

Theorem 3.1 *For the cost functions*

$$\hat{J}_m(\mathfrak{P}_1, \mathfrak{P}_2) = \hat{J}_m(\sigma_1, \sigma_2, \ldots, \sigma_{N-1}, \tau_1, \tau_2, \ldots, \tau_N), \quad m = 1, 2,$$

defined in (13) *and* (14), *the gradients with respect to* σ_i, $i = 1, 2, \ldots, N-1$, *are given by*

$$\nabla_{\sigma_i} \hat{J}_m = l_0 + \lambda_2^{i+1}(0), \tag{21}$$

whereas the gradients with respect to τ_k, $k = 1, 2, \ldots, N$, *are given by*

$$\nabla_{\tau_k} \hat{J}_m = \int_0^1 \left(\lambda^k(s)\right)^T F^k(s)\, ds = \int_0^1 \left(\lambda_1^k F_1^k(s) + \lambda_2^i F_2^k(s)\right) ds, \tag{22}$$

where $\lambda_l^n(s)$, $i = 1, 2$, $n = 1, 2, \ldots, N$, *can be obtained from equations* (17) *and* (20) *for* $\hat{J}_1$ *and* $\hat{J}_2$, *respectively.*

3.2 Optimization by injection dose for periodic injection

In this subsection, we consider a simple scenario in clinic. Suppose that the same dose (denoted by σ_d) of insulin or its analogues is periodically injected during the limited time $[0, T]$ and $N-1$ injections are totally planed. Then the injection period is $\tau = \frac{T}{N}$, that is, a fixed amount σ_d of insulin or its analogues is periodically injected into the plasma at the moments $i\tau$, $i = 1, 2, \ldots, N-1$. Hence system (2) has the following form:

$$\begin{cases} \left.\begin{aligned} &\frac{dG(t)}{dt} = G_{in} - f_2(G) - f_3(G) f_4(I) + f_5(I) = F_1(G, I), \\ &\frac{dI(t)}{dt} = f_1(G) - d_i I(t) = F_2(G, I), \end{aligned}\right\} \quad t \neq i\tau, t \in [0, T], \\ \left.\begin{aligned} &G(t^+) = G(t), \\ &I(t^+) = I(t) + \sigma_d, \end{aligned}\right\} \quad t = i\tau, i = 1, 2, \ldots, N-1, \\ G(0) = G(0^+) = G_0 > 0, \qquad I(0) = I(0^+) = I_0 > 0. \end{cases} \tag{23}$$

We also assume that the injection dose σ_d satisfies

$$0 \leq \sigma_d^1 \leq \sigma_d \leq \sigma_d^2, \tag{24}$$

where σ_d^1 and σ_d^2 are given constants that represent the lower and upper bounds of the fixed injection dose.

Then for this scenario, the cost function of control problem $(\mathbf{P_A})$ becomes

$$\tilde{J}_1(\sigma_d) = l_0(N-1)\sigma_d + l_1 \int_0^T \left(G(t) - (\alpha A + \beta B)\right)^2 dt \tag{25}$$

or

$$\tilde{J}_2(\sigma_d) = l_0(N-1)\sigma_d + l_1 \int_0^T \left(G(t) - (\alpha A + \beta B)\right)^2 dt + l_2 \int_0^T \left(G(t) - B\right)^2 dt. \tag{26}$$

Here σ_d is the unique control parameter. We need to find an injection dose $\sigma_d \in [\sigma_d^1, \sigma_d^2]$ such that $\tilde{J}_1(\sigma_d)$ or $\tilde{J}_2(\sigma_d)$ is minimized.

Just as in Sect. 3.1, for $i = 1, 2, \ldots, N$, let $t = (i-1)\tau + s\tau$. Then system (23) is converted into the following N subsystems:

$$\begin{cases} \frac{dG^i(s)}{ds} = \tau[G_{in} - f_2(G^i) - f_3(G^i)f_4(I^i) + f_5(I^i)] \\ \qquad\quad = \tau F_1^i(G^i, I^i), & s \in (0,1], i = 1, 2, \ldots, N, \\ \frac{dI^i(s)}{ds} = \tau[f_1(G^i) - d_i I^i] = \tau F_2^i(G^i, I^i), \end{cases} \tag{27}$$

with initial condition (11) and

$$\begin{cases} G^i(0) = G^{i-1}(1), \\ I^i(0) = I^{i-1}(1) + \sigma_d, \quad i = 2, 3, \ldots, N. \end{cases} \tag{28}$$

The cost functions (25) and (26) are then equivalently transformed into

$$\hat{\tilde{J}}_1(\sigma_d) = l_0(N-1)\sigma_d + l_1 \int_0^1 \sum_{i=1}^{N} \big(G^i(s) - (\alpha A + \beta B)\big)^2 \, ds \tag{29}$$

and

$$\hat{\tilde{J}}_2(\sigma_d) = l_0(N-1)\sigma_d + l_1 \int_0^1 \sum_{i=1}^{N} \big(G^i(s) - (\alpha A + \beta B)\big)^2 \, ds + l_2 \int_0^1 \sum_{i=1}^{N} \big(G^i(s) - B\big)^2 \, ds. \tag{30}$$

Therefore the optimal problem can be described as follows: find $\sigma_d \in [\sigma_d^1, \sigma_d^2]$ such that $\hat{\tilde{J}}_1(\sigma_d)$ or $\hat{\tilde{J}}_2(\sigma_d)$ is minimized.

Using the Hamiltonian function defined in (15) and (16), we obtain the following costate equations associated with $\hat{\tilde{J}}_1(\sigma_d)$:

$$\begin{cases} \dot{\lambda}_1^i(s) = -\frac{\partial H_i}{\partial G^i} = -2l_1(G^i - (\alpha A + \beta B)) - \tau\{\lambda_1^i \frac{\partial F_1^i}{\partial G^i} + \lambda_2^i \frac{\partial F_2^i}{\partial G^i}\}, \\ \dot{\lambda}_2^i(s) = -\frac{\partial H_i}{\partial I^i} = -\tau\{\lambda_1^i \frac{\partial F_1^i}{\partial I^i} + \lambda_2^i \frac{\partial F_2^i}{\partial I^i}\} \end{cases} \tag{31}$$

with initial-boundary-value condition (18).

According to the Hamiltonian function defined in (15) and (19), we get the following costate equations corresponding to $\hat{\tilde{J}}_2(\sigma_d)$:

$$\begin{cases} \dot{\lambda}_1^i(s) = -\frac{\partial H_i}{\partial G^i} = -2l_1(G^i - (\alpha A + \beta B)) - 2l_2(G^i - B) - \tau\{\lambda_1^i \frac{\partial F_1^i}{\partial G^i} + \lambda_2^i \frac{\partial F_2^i}{\partial G^i}\}, \\ \dot{\lambda}_2^i(s) = -\frac{\partial H_i}{\partial I^i} = -\tau\{\lambda_1^i \frac{\partial F_1^i}{\partial I^i} + \lambda_2^i \frac{\partial F_2^i}{\partial I^i}\} \end{cases} \tag{32}$$

with initial-boundary-value condition (18).

Denote

$$y_i(s) = \big(G^i(s), I^i(s)\big)^T, \qquad y_i(0) = \phi^{i-1}\big(y_{i-1}(1), \sigma_d\big).$$

From (23) it follows that

$$\phi^{i-1}\big(y_{i-1}(1),\sigma_d\big) = \big(G^{i-1}(1), I^{i-1}(1) + \sigma_d\big)^T, \quad i = 2,3,\ldots,N-1.$$

Applying the results in [21] again, we get the following result.

Theorem 3.2 *For the cost functions* $\hat{\tilde{J}}_m(\sigma_d)$, $m = 1,2$, *defined in* (29) *and* (30), *the gradient with respect to the injection dose* σ_d *is given by*

$$\nabla\hat{\tilde{J}}_m(\sigma_d) = l_0(N-1) + \sum_{i=1}^{N-1}\lambda_2^{i+1}(0). \tag{33}$$

3.3 Optimization by injection timings for a given injection dose

In this subsection, we consider another simple scenario in clinic. Assume that insulin or its analogues is injected at irregular moments $0 \le t_1 \le t_2 \le \cdots \le t_{N-1} \le T$ with the same injection dose σ_d. The injection dose σ_d and injection timings $t_1, t_2, \ldots, t_{N-1}$ are all decision variables. Then system (2) is converted into the following form:

$$\begin{cases} \left.\begin{aligned} &\tfrac{dG(t)}{dt} = G_{in} - f_2(G) - f_3(G)f_4(I) + f_5(I) = F_1(G,I),\\ &\tfrac{dI(t)}{dt} = f_1(G) - d_iI(t) = F_2(G,I), \end{aligned}\right\} \quad t \ne t_i, t \in [0,T],\\ \left.\begin{aligned} &G(t_i^+) = G(t_i),\\ &I(t_i^+) = I(t_i) + \sigma_d, \end{aligned}\right\} \quad i = 1,2,\ldots,N-1,\\ G(0) = G(0^+) = G_0 > 0, \qquad I(0) = I(0^+) = I_0 > 0. \end{cases} \tag{34}$$

Here the injection timings t_i, $i = 1,2,\ldots,N$, and injection dose σ_d satisfy conditions (5) and (24), respectively.

Then the cost function in control problem $(\mathbf{P_A})$ is translated into

$$\bar{J}_1(\mathfrak{P}_1,\sigma_d) = l_0(N-1)\sigma_d + l_1\int_0^T \big(G(t) - (\alpha A + \beta B)\big)^2\,dt \tag{35}$$

or

$$\bar{J}_2(\mathfrak{P}_1,\sigma_d) = l_0(N-1)\sigma_d + l_1\int_0^T \big(G(t) - (\alpha A + \beta B)\big)^2\,dt + l_2\int_0^T \big(G(t) - B\big)^2\,dt, \tag{36}$$

where $\mathfrak{P}_1 = (\tau_1,\tau_2,\ldots,\tau_N)^T$, $\tau_i = t_i - t_{i-1}$.

Let $t = \sum_{j=1}^{i-1}\tau_j + \tau_i s$ for $i = 1,2,\ldots,N$, and transform system (34) into

$$\begin{cases} \tfrac{dG^i(s)}{ds} = \tau_i[G_{in} - f_2(G^i) - f_3(G^i)f_4(I^i) + f_5(I^i)]\\ \qquad\quad = \tau_i F_1^i(G^i,I^i), & s \in (0,1], i = 1,2,\ldots,N,\\ \tfrac{dI^i(s)}{ds} = \tau_i[f_1(G^i) - d_iI^i] = \tau_i F_2^i(G^i,I^i), \end{cases} \tag{37}$$

with initial and boundary conditions (11) and (28).

Cost functions (35) and (36) are converted to

$$\hat{\tilde{J}}_1(\mathfrak{P}_1,\sigma_d) = l_0(N-1)\sigma_d + l_1\int_0^1 \sum_{i=1}^{N}\big(G^i(s) - (\alpha A + \beta B)\big)^2\,ds \tag{38}$$

and

$$\begin{aligned}\hat{\tilde{J}}_2(\mathfrak{P}_1,\sigma_d) = {} & l_0(N-1)\sigma_d + l_1\int_0^1 \sum_{i=1}^{N}\big(G^i(s) - (\alpha A + \beta B)\big)^2\,ds \\ & + l_2\int_0^1 \sum_{i=1}^{N}\big(G^i(s) - B\big)^2\,ds.\end{aligned} \tag{39}$$

The optimal problem can be restated as follows: find $\mathfrak{P}_1 \in \Omega_1$ and $\sigma_d \in [\sigma_d^1, \sigma_d^2]$ such that $\hat{\tilde{J}}_1(\mathfrak{P}_1,\sigma_d)$ or $\hat{\tilde{J}}_2(\mathfrak{P}_1,\sigma_d)$ is minimized.

Similarly to Sects. 3.1 and 3.2, we apply the Hamiltonian function defined in (15) and (16) and obtain the same costate equations (17) with initial-boundary-value condition (18) corresponding to $\hat{\tilde{J}}_1(\mathfrak{P}_1,\sigma_d)$.

Using the Hamiltonian function defined in (15) and (19), we get the costate equations (20) with initial-boundary-value condition (18) corresponding to $\hat{\tilde{J}}_2(\mathfrak{P}_1,\sigma_d)$.

The following conclusion can be drawn by the same method as in the preceding two subsections.

Theorem 3.3 *For the cost functions $\hat{\tilde{J}}_m(\mathfrak{P}_1,\sigma_d)$, $m = 1,2$, defined in (38) and (39), the gradient with respect to the injection dose σ_d is given by*

$$\nabla_{\sigma_d}\hat{\tilde{J}}_m(\mathfrak{P}_1,\sigma_d) = l_0(N-1) + \sum_{i=1}^{N-1}\lambda_2^{i+1}(0), \tag{40}$$

whereas the gradients with respect to the injection doses τ_k, $k = 1,2,\ldots,N$, are given by

$$\nabla_{\tau_k}\hat{\tilde{J}}_m(\mathfrak{P}_1,\sigma_d) = \int_0^1 \big(\lambda^k(s)\big)^T F^k(s)\,ds = \int_0^1 \big(\lambda_1^k F_1^k(s) + \lambda_2^i F_2^k(s)\big)\,ds. \tag{41}$$

4 Optimal injection strategies and numerical simulations

In this section, we perform a series of numerical simulations for systems (2), (23), and (34), which not only confirm the results obtained in Sect. 3, but complement those results with some specific features. We will determine the optimal values of the injection doses and injection timings that can keep the plasma glucose under control with smaller oscillations and less treatment cost.

To begin with, we will present a step-by-step algorithm for the computation of the cost function and its gradient at a given feasible pair $(\mathfrak{P}_1,\mathfrak{P}_2) \in (\Omega_1,\Omega_2)$ [21, 24]. We take the case in Sect. 3.1 as an example.

(i) We first solve directly the dynamical system (10) with initial and boundary conditions (11) and (12) for $i = 1,2,\ldots,N$ to obtain $G_i(s)$, $I_i(s)$, $s \in [0,1]$.

(ii) Applying $G_i(s)$ and $I_i(s)$ obtained in the last step, we solve backwards the costate system (17) with boundary conditions (18) and the costate system (20) with boundary conditions (18), and get $\lambda_1^i(s)$ and $\lambda_2^i(s)$ for $i = 1,2,\ldots,N$.

(iii) According to (13) and (14), we evaluate the cost functions $\hat{J}_m(\mathfrak{P}_1, \mathfrak{P}_2)$, $m = 1, 2$, by using $G_i(s)$ and $I_i(s)$.

(iv) Applying $G_i(s)$, $I_i(s)$, $\lambda_1^i(s)$, and $\lambda_2^i(s)$, we compute $\nabla_{\tau_i}\hat{J}_m(\mathfrak{P}_1, \mathfrak{P}_2)$ for $i = 1, 2, \ldots, N$ and $\nabla_{\sigma_l}\hat{J}_m(\mathfrak{P}_1, \mathfrak{P}_2)$ for $l = 1, 2, \ldots, N-1$.

As mentioned in [13] and [29], it is more important to choose the geometrical shapes of the five response functions f_i, $i = 1, \ldots, 5$, in systems (1) and (2) than their specific expressions. To satisfy geometric properties of these functions introduced in [13] and [29], we select the following forms of f_i, $i = 1, \ldots, 5$, as Song et al. [29] did:

$$f_1(x) = \frac{\sigma_1 x^2}{\alpha_1^2 + x^2}, \qquad f_2(x) = \sigma_2 x, \qquad f_3(x) = ax,$$
$$f_4(x) = c + \frac{mx}{n + x}, \qquad f_5(x) = \frac{R}{1 + \exp(\nu x - \hat{c})}.$$

Here σ_1, σ_2, α_1, a, c, m, n, R, ν, and $\hat{c}$ are positive constants, and their values are chosen from [15, 17, 18] (see Table 1), whereas we assume that the maximum secretory rate of the diabetics is about 3% of normal subjects. Besides, we select the upper and lower limits of the plasma glucose concentration that people can tolerate as $A = 200$ mg/dl and $B = 50$ mg/dl, respectively, and the weight parameters are selected as $\alpha = \frac{1}{3}$ and $\beta = \frac{2}{3}$. The unit price of insulin and the balance factors are chosen as $l_0 = 0.005$ and $l_1 = l_2 = 0.01$. For convenience, unit conversion has been made from amounts to concentrations in the same way as in [15, 17], and [13].

By simple calculation we get

$$f_1'(x) = \frac{2\sigma_1\alpha_1^2 x}{(\alpha_1^2 + x^2)^2}, \qquad f_2'(x) = \sigma_2, \qquad f_3'(x) = a,$$
$$f_4'(x) = \frac{mn}{(n + x)^2}, \qquad f_5'(x) = -\frac{R\nu \exp(\nu x - \hat{c})}{(1 + \exp(\nu x - \hat{c}))^2},$$

and according to equation (10), we have

$$\lambda_1^i \frac{\partial F_1^i}{\partial G^i} + \lambda_2^i \frac{\partial F_2^i}{\partial G^i} = -\lambda_1^i \left[f_2'(G^i) + f_3'(G^i) f_4(I^i)\right] + \lambda_2^i f_1'(G^i),$$
$$\lambda_1^i \frac{\partial F_1^i}{\partial I^i} + \lambda_2^i \frac{\partial F_2^i}{\partial I^i} = -\lambda_1^i \left[f_3(G^i) f_4'(I^i) - f_5'(I^i)\right] - d_i \lambda_2^i.$$

Table 1 Model parameter values

Parameters	Values	units	Parameters	Values	units
G_{in}	216	mg/min	m	900	mg/min
ν	0.0967	$\mathbf{mU}^{-1}$	n	80	mg
σ_2	5×10^{-6}	$\mathbf{min}^{-1}$	σ_1	6.27	mU/min
a	3×10^{-5}	$\mathbf{mg}^{-1}$	α_1	105	mg
c	40	mg/min	d_i	0.08	$\mathbf{min}^{-1}$
R	180	mg/min	$\hat{c}$	7.54	mU

Then equations (17) and (20) can be transformed respectively into

$$\begin{cases} \dot{\lambda}_1^i = -\frac{\partial H_i}{\partial G^i} = -2(G^i - (\alpha A + \beta B)) + \tau_i\{\lambda_1^i[\sigma_2 + a(c + \frac{mI^i}{n+I^i})] - \lambda_2^i \frac{2\sigma_1\alpha_1^2 G^i}{(\alpha_1^2+(G^i)^2)^2}\}, \\ \dot{\lambda}_2^i = -\frac{\partial H_i}{\partial I^i} = \tau_i[\lambda_1^i(\frac{amnG^i}{(n+I^i)^2} + \frac{Rv\exp(vI^i-\hat{c})}{(1+\exp(vI^i-\hat{c}))^2}) + \lambda_2^i d_i], \\ \lambda_1^i(1) = 0, \\ \lambda_2^i(1) = 0, \quad i = 2,3,\ldots,N, \end{cases} \tag{42}$$

and

$$\begin{cases} \dot{\lambda}_1^i = -\frac{\partial H_i}{\partial G^i} \\ \quad = -2(G^i - (\alpha A + \beta B)) - 2(G^i - B) + \tau_i\{\lambda_1^i[\sigma_2 + a(c + \frac{mI^i}{n+I^i})] - \lambda_2^i \frac{2\sigma_1\alpha_1^2 G^i}{(\alpha_1^2+(G^i)^2)^2}\}, \\ \dot{\lambda}_2^i = -\frac{\partial H_i}{\partial I^i} = \tau_i[\lambda_1^i(\frac{amnG^i}{(n+I^i)^2} + \frac{Rv\exp(vI^i-\hat{c})}{(1+\exp(vI^i-\hat{c}))^2}) + \lambda_2^i d_i], \\ \lambda_1^i(1) = 0, \\ \lambda_2^i(1) = 0, \quad i = 2,3,\ldots,N. \end{cases} \tag{43}$$

We will look for the optimal values of the control parameters in different injection modes by using Matlab programs. We use minutes as time units and take 240 min as the total control time, that is, $T = 240$ min. Four injections of insulin are planed and these 240 min will be divided into five segments ($N = 5$).

In the following, we will study three different optimal strategies in impulsive control for each cost function by numerical simulations. Surely, there is no guarantee that the optimal solution we find numerically is unique, so we just present some optimal ones with special initial injection periods and doses by the above steps.

Due to the difference between two types of cost function, the costate equations are different, and so are the corresponding gradient formulas of the cost function with respect to control parameters. We will discuss the optimal injection strategies in two cases.

4.1 Optimal injection strategies for the first cost function

4.1.1 Optimal injection dose for periodic injection

We first consider the optimization of injection dose for periodic injection, that is,

$$\tau_1 = \tau_2 = \tau_3 = \tau_4 = \tau_5 = \frac{T}{N} = 48.$$

Starting with an initial injection dose $\sigma_d = 130$, if only simple impulsive releases are used without any optimal control, then we obtain that after five periods the cost value is $\tilde{\mathcal{J}}_1 = 145.3126$ and the plasma glucose level at the terminal time is $G(T) = 106.83$ mg/dl.

Under the constraint $80 \le \sigma_d \le 200$, we solve the corresponding optimal problem by the algorithm listed above in Matlab. We get the optimal injection dose $\sigma_d^* = 133.564$, the corresponding cost value $\tilde{\mathcal{J}}_1^* = 145.1660$, and the plasma glucose level at the terminal time is $G^*(T) = 105.74$ mg/dl. After comparing the time series diagrams of plasma glucose level for this kind of optimal control, noncontrol and simple impulsive control in Fig. 1(a), we find that this optimal control strategy has a very small advantage in lowering plasma glucose concentration. It is worth pointing out that it costs a little more insulin to achieve such an effect (see Table 2).

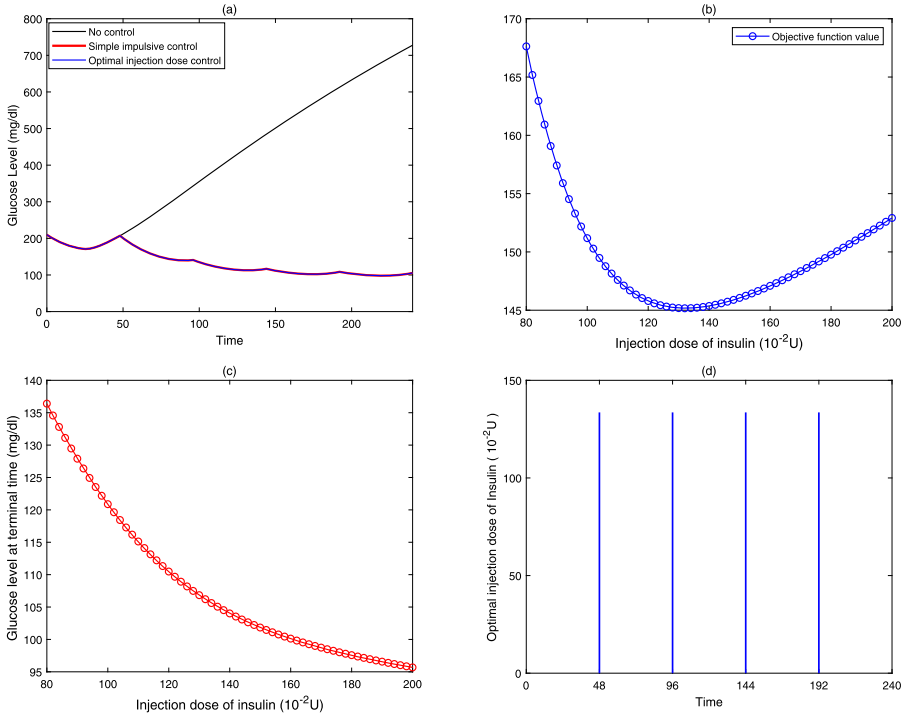

Figure 1 Dose control for the first cost function: (**a**) Comparisons of plasma glucose level under different control modes; **(b)** Impact of the intensity of each injection on the optimal cost value; (**c**) Impact of the intensity of each injection on the glucose level at time T; (**d**) Injection strategy of the optimal dose control

Table 2 Comparison of the optimal dose control and the simple impulsive control

	$G(T)$	Total release	Cost value
Optimal control	105.74	534.256	145.1660
Impulsive control	106.83	520	145.3126

In addition, we investigate the influence of injection dose on the cost function and the glucose concentration at time T (see Figs. 1(b) and (c)), and find that when the injection dose varies within the interval $80 \leq \delta_d \leq 200$, the cost function $\tilde{\mathcal{J}}_1(\delta_d)$ admits a minimum point, which verifies the optimum results we obtained. Furthermore, note that the plasma glucose level at the terminal time T continues decreasing with the increase of the injection dose. We depict the optimal control laws in Fig. 1(d).

4.1.2 Optimal injection timings with fixed injection dose

To be consistent with Sect. 4.1.1, we choose the same initial injection dose $\sigma_d = 130$ and select $\tau_1 = 24$, $\tau_2 = \tau_3 = \tau_4 = 48$, and $\tau_5 = 72$ as the initial injection intervals. Besides, to determine the optimal time intervals τ_i and optimal injection dose σ_d minimizing the cost function $\bar{\mathcal{J}}_1$, we consider the constraint conditions

$$0 \leq \tau_i \leq 120, i = 1, 2, \ldots, 5, \quad \sum_{1}^{5} \tau_i = 240, \tag{44}$$

and $80 \leq \sigma_d \leq 200$.

Then solving this optimal problem in Matlab, we obtain the following optimal injection intervals:

$$\begin{aligned} &\tau_1^* = 31.6154, \qquad \tau_2^* = 44.1648, \qquad \tau_3^* = 44.1600, \\ &\tau_4^* = 44.4768, \qquad \tau_5^* = 75.5832 \end{aligned} \tag{45}$$

and the optimal injection dose

$$\sigma_d^* = 131.888. \tag{46}$$

In addition, we get the minimum cost value $\bar{\mathcal{J}}_1^* = 123.8571$ and the plasma glucose level at the terminal time $G^*(T) = 171.67$ mg/dl.

We also plot the time series diagrams of the plasma glucose level for the optimal injection timing control, optimal injection dose control, and noncontrol in Fig. 2(a). We can see from the comparison of these curves that the optimal injection timing control has obvious advantage since it achieves a better glucose control effect with relatively low cost function value. Besides, for every $\sigma_d \in [80, 200]$, we determine the corresponding optimal time intervals under restriction (44) and then calculate the value of the cost function and the plasma glucose concentration at time $T = 240$. From Fig. 2(b) we see that when the injection dose varies within the interval $80 \le \sigma_d \le 200$, the cost function $\bar{\mathcal{J}}_1(\mathfrak{P}_1, \sigma_d)$ also admits a minimum point. This further confirms the optimum values we have obtained. Similarly, the plasma glucose level at the terminal time T also keeps decreasing with the

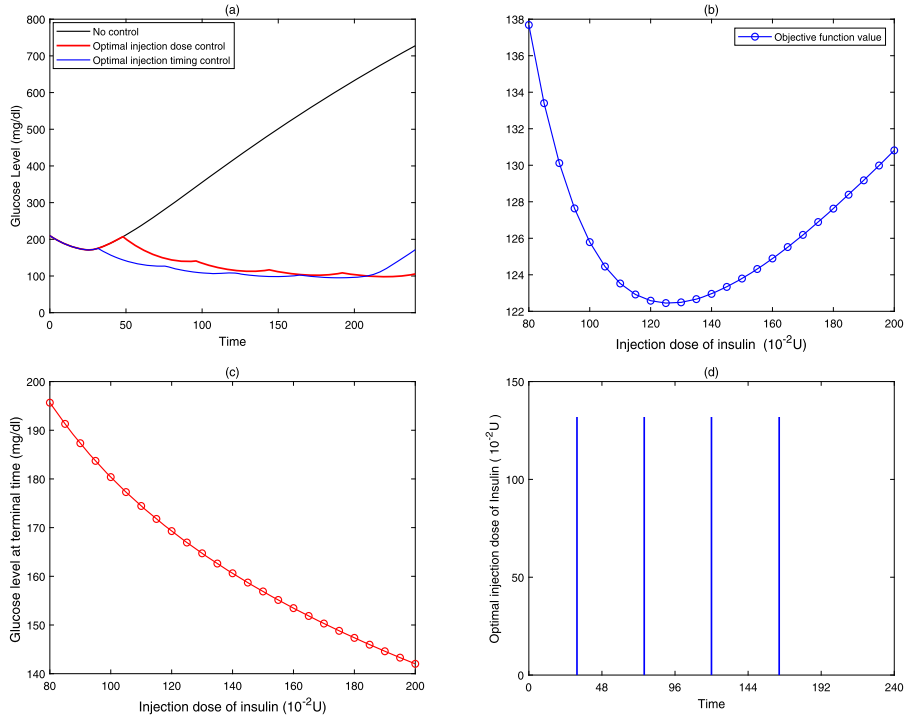

Figure 2 Timing control for the first cost function: (**a**) Comparisons of plasma glucose level under different control modes; (**b**) Impact of the intensity of each injection on the optimal cost value; (**c**) Impact of the intensity of each injection on the glucose level at time T; (**d**) Injection strategy of the optimal timing control

increase of the injection dose (see Fig. 2(c)). Graphical output in Fig. 2(d) directly displays our optimal injection timing control strategy expressed by (45) and (46).

4.1.3 Optimal injection timings and injection doses

Keeping the same initial injection intervals $\tau_1 = 24$, $\tau_2 = \tau_3 = \tau_4 = 48$, and $\tau_5 = 72$ and choosing the initial injection dose $\sigma_1 = \sigma_2 = \sigma_3 = \sigma_4 = 130$, we deal with the optimal problem with constraints (44) and $80 \leq \delta_i \leq 200$, $i = 1, 2, 3, 4$. Then after solving this optimal problem, we obtain the set of optimal injection doses

$$\sigma_1^* = 130.936, \qquad \sigma_2^* = 130.908, \qquad \sigma_3^* = 130.804, \qquad \sigma_4^* = 130.48 \tag{47}$$

and the set of optimal injection intervals

$$\begin{aligned} &\tau_1^* = 30.4848, \qquad \tau_2^* = 44.028, \qquad \tau_3^* = 44.0256, \\ &\tau_4^* = 45.2928, \qquad \tau_5^* = 76.1712. \end{aligned} \tag{48}$$

This injection strategy is shown by Fig. 3(b). Besides, we obtain that the minimum cost value $\mathcal{J}_1^* = 123.9197$ and the plasma glucose level at the terminal time is $G^*(T) = 174.24$ mg/dl. The time series diagrams of the plasma glucose level under four types of control modes are plotted in Fig. 3(a), and we can see that the mixed optimal control produces almost the same effect as the optimal injection timing control in this view.

Finally, we compare these three optimal injection strategies to evaluate their effectiveness (refer to Table 3 and Fig. 4). We find that the optimal injection timing control is superior to the optimal injection dose control because of the lower glucose level in most of the time with less cost value. The mixed control produces almost the same control effect as the optimal injection timing control does; however, it entails the smallest insulin cost. Figure 4(b) shows that the optimal injection dose control provides the least effective result at the cost of injecting the most insulin in the whole control process. Combining the optimal selection of injection timing with it results in much better performance in both the control effect of the plasma glucose and the cost value.

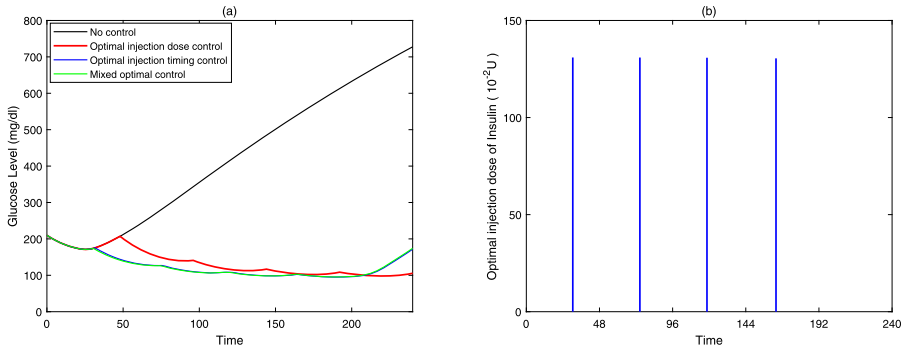

Figure 3 Mixed control for the first cost function: (**a**) Comparisons of plasma glucose level under different control modes; (**b**) Injection strategy of the mixed optimal control

Table 3 Comparison of different injection strategies

	Optimal control parameters	$\mathcal{J}_1^*$	$G^*(T)$
Dose control	$\sigma_d^* = 133.564$	145.1660	105.74
Timing control	$\tau_1^* = 31.6152$, $\tau_2^* = 44.1648$, $\tau_3^* = 44.16$, $\tau_4^* = 44.4768$, $\tau_5^* = 75.5832$, $\sigma_d^* = 131.888$	123.8571	171.67
Mixed control	$\tau_1^* = 30.4848$, $\tau_2^* = 44.028$, $\tau_3^* = 44.0256$, $\tau_4^* = 45.2928$, $\tau_5^* = 76.1712$, $\sigma_1^* = 130.936$ $\sigma_2^* = 130.908$, $\sigma_3^* = 130.804$ $\sigma_4^* = 130.48$	128.34	174.24

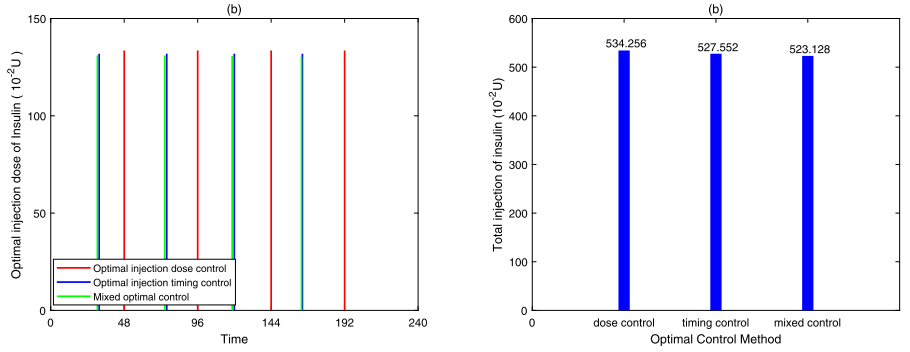

Figure 4 Comparison of three optimal strategies for the first cost function: (**a**) Comparison of three injection strategies: the red, blue, and green segments are for dose control, timing control, and mixed control, respectively; (**b**) Comparison of total injection of insulin for three optimal control methods

4.2 Optimal injection strategies for the second cost function

It is very complicated to consider the treatment for critically ill patients in Intensive Care Unit. Since their response to an insulin injection or a glucose input can vary significantly, both hyperglycemia and hypoglycemia may occur in a injection period. In this subsection, we study a different type of control objective function to prevent the occurrence of hypoglycemia. Assume that the glucose input rate G_{in} is slightly lower, that is, $G_{in} = 120$.

4.2.1 Optimal injection dose for periodic injection

First, we consider the optimization of injection dose for periodic injection, that is,

$$\tau_1 = \tau_2 = \tau_3 = \tau_4 = \tau_5 = \frac{T}{N} = 48.$$

Starting with an initial injection dose $\sigma_d = 132$, if only simple impulsive releases are used but no optimal control is taken, then we obtain that after five periods, the cost value is $\tilde{\mathcal{J}}_2 = 327.8569$ and the plasma glucose level at the terminal time is $G(T) = 51.581$ mg/dl.

Solving the corresponding optimal problem numerically in Matlab, we get that under the constraint $0 \le \sigma_d \le 200$, the optimal injection dose is $\sigma_d^* = 99.164$ and the corresponding cost value is $\tilde{\mathcal{J}}_2^* = 323.9829$, whereas the plasma glucose level at the terminal time is

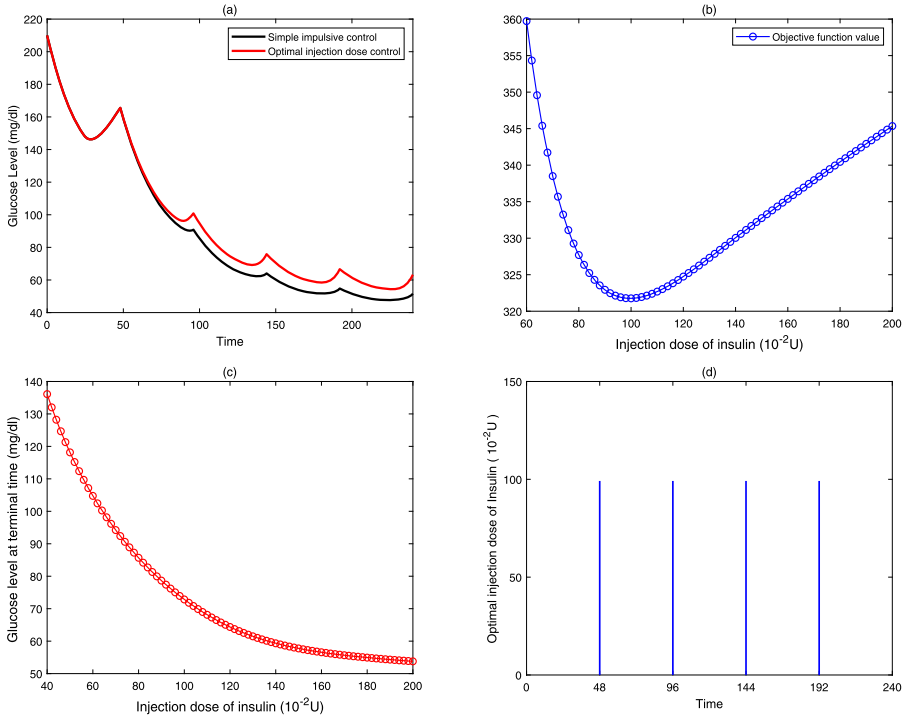

Figure 5 Dose control for the second cost function: (**a**) Comparisons of plasma glucose level under different control modes; (**b**) Impact of the intensity of each injection on the optimal cost value; (**c**) Impact of the intensity of each injection on the glucose level at time T; (**d**) Injection strategy of the optimal dose control

Table 4 Comparison of the optimal dose control and the simple impulsive control

	$G(T)$	Total release	Cost value
Optimal control	63.264	396.656	323.9829
Impulsive control	51.581	528	327.8569

$G^*(T) = 63.264$ mg/dl. We plot the time series diagrams of plasma glucose level for both this optimal control and simple impulsive control in Fig. 5(a). We find that the optimal injection dose control has obvious advantages in avoiding occurrence of hypoglycemia, as well as saving injection dose of insulin (see Fig. 5(a) and Table 4).

We also investigate the influence of injection dose on the cost function and the glucose concentration at time T. Figure 5(b) shows that when the injection dose varies within the interval $0 \leq \delta_d \leq 200$, the cost function $\tilde{\mathcal{J}}_2(\delta_d)$ admits a minimum point, which verifies the optimal results we obtained. Figure 5(c) indicates that the plasma glucose level at the terminal time T decreases with an increase of the injection dose. The optimal control laws are depicted in Fig. 5(d).

4.2.2 Optimal injection timings with a fixed injection dose

We choose the same initial injection dose $\sigma_d = 132$ and select $\tau_1 = \tau_2 = \tau_3 = 36$, $\tau_4 = 48$, and $\tau_5 = 84$ as the initial injection intervals. To determine the optimal time intervals τ_i and optimal injection dose σ_d that minimize the cost function $\bar{\mathcal{J}}_2$, we consider the following

constraint conditions:

$$0 \le \tau_i \le 120, i = 1, 2, \ldots, 5, \quad \sum_{1}^{5} \tau_i = 240, \tag{49}$$

and $0 \le \sigma_d \le 200$.

Then solving this optimal problem in Matlab gives the following optimal injection intervals:

$$\begin{aligned} &\tau_1^* = 33.3408, \quad \tau_2^* = 47.4336, \quad \tau_3^* = 55.824, \\ &\tau_4^* = 48.8568, \quad \tau_5^* = 54.5448 \end{aligned} \tag{50}$$

and optimal injection dose

$$\sigma_d^* = 97.692. \tag{51}$$

Besides, we get the cost value $\bar{J}_2^* = 308.0294$ and the plasma glucose level at the terminal time $G^*(T) = 78.219$ mg/dl.

We plot the time series diagrams of the plasma glucose level for the optimal injection timing control, optimal injection dose control, and simple impulsive control in Fig. 6(a). These three curves show that with a relatively low cost function value, the optimal injec-

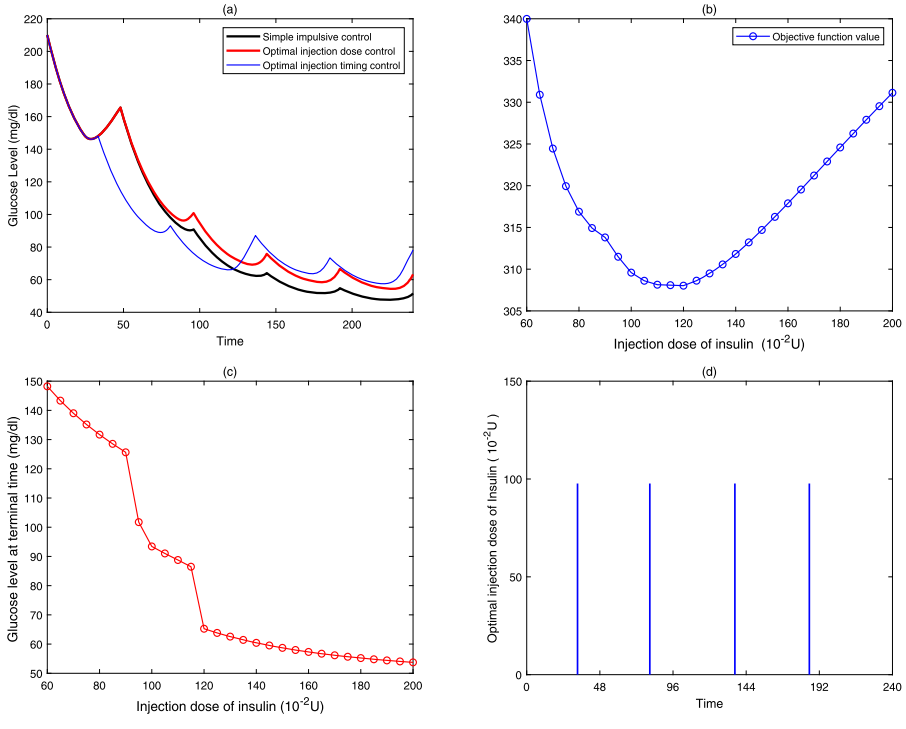

Figure 6 Timing control for the second cost function: (**a**) Comparisons of plasma glucose level under different control modes; (**b**) Impact of the intensity of each injection on the optimal cost value; (**c**) Impact of the intensity of each injection on the glucose level at time T; (**d**) Injection strategy of the optimal timing control

tion timing control is the most robust in preventing hypoglycemia from occurring. For every $\sigma_d \in [0, 200]$, we determine the corresponding optimal time intervals under constraint (49) and then calculate the value of the cost function and the plasma glucose concentration at time $T = 240$. From Fig. 6(b) we find that when the injection dose varies within the interval $0 \leq \sigma_d \leq 200$ and the cost function $\bar{\mathcal{J}}_2(\mathfrak{P}_1, \sigma_d)$ admits a minimum point, which is consistent with the optimal result we have obtained. Figure 6(c) shows a decrease of the plasma glucose level at the terminal time T with an increase of the injection dose. Our optimal timing control strategy expressed by (50) and (51) is shown in Fig. 6(d).

4.2.3 Optimal injection timing and injection dose

To deal with the optimal problem with constraints (44) and $0 \leq \delta_i \leq 200$, $i = 1, 2, 3, 4$, we keep the same initial injection intervals $\tau_1 = \tau_2 = \tau_3 = 36$, $\tau_4 = 48$, $\tau_5 = 84$ and choose the initial injection doses as $\sigma_1 = \sigma_2 = \sigma_3 = \sigma_4 = 132$. Solving this optimal problem numerically, we obtain the set of optimal injection doses

$$\sigma_1^* = 119.148, \qquad \sigma_2^* = 114.984, \qquad \sigma_3^* = 118.68, \qquad \sigma_4^* = 131.02 \tag{52}$$

and the set of optimal injection intervals

$$\begin{aligned} &\tau_1^* = 32.28, \qquad \tau_2^* = 51.267, \qquad \tau_3^* = 53.3976, \\ &\tau_4^* = 47.868, \qquad \tau_5^* = 55.1784. \end{aligned} \tag{53}$$

This injection strategy is shown in Fig. 7(b). We obtain the minimum cost value $\mathcal{J}_2^* = 310.9245$ and the plasma glucose level at the terminal time $G^*(T) = 65.105$ mg/dl. The time series diagrams of the plasma glucose level under four types of control modes are plotted in Fig. 7(a). We find that compared with optimal dose control and optimal timing control, mixed optimal control provides better performance in avoiding occurrence of hyperglycemia.

Table 5 and Fig. 8(a) give a comparison of these three optimal injection strategies. We find that the optimal injection timing control is superior to the optimal injection dose control in avoiding problems with hypoglycemia. Although the mixed control is the most effective in preventing hyperglycemia from occurring, it takes the largest consumption of insulin (see Fig. 8(b)).

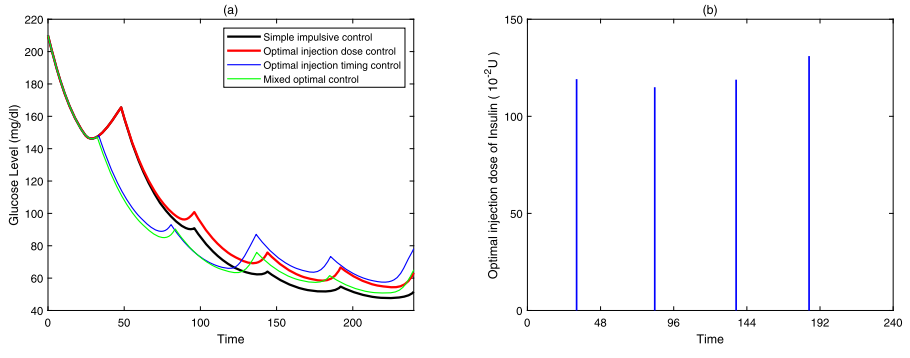

Figure 7 Mixed control for the second cost function: (**a**) Comparisons of plasma glucose level under different control modes; (**b**) Injection strategy of the mixed optimal control

Table 5 Comparison of different injection strategies

	Optimal control parameters	$\mathcal{J}_2^*$	$G^*(T)$
Dose control	$\sigma_d^* = 99.164$	323.9829	63.264
Timing control	$\tau_1^* = 33.3408$, $\tau_2^* = 47.4336$, $\tau_3^* = 55.824$, $\tau_4^* = 48.8568$, $\tau_5^* = 54.5448$, $\sigma_d^* = 97.692$	308.0294	78.219
Mixed control	$\tau_1^* = 32.28$, $\tau_2^* = 51.276$, $\tau_3^* = 53.3976$, $\tau_4^* = 47.868$, $\tau_5^* = 55.1784$, $\sigma_1^* = 119.148$ $\sigma_2^* = 114.984$, $\sigma_3^* = 118.868$, $\sigma_4^* = 131.02$	310.9245	65.105

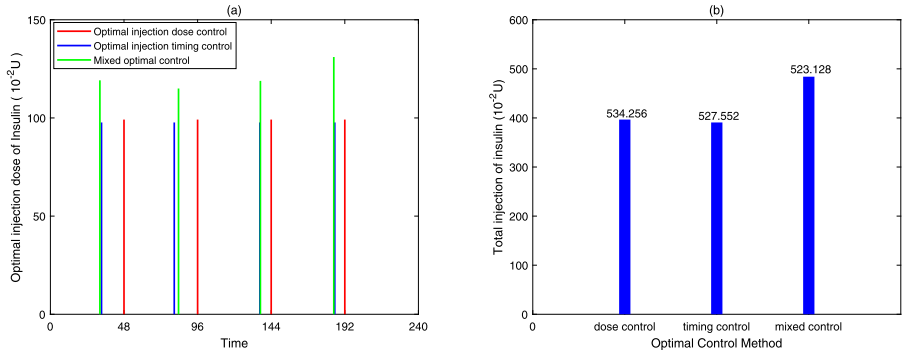

Figure 8 Comparison of three optimal strategies for the second cost function: (**a**) Comparison of three injection strategies: the red, blue, and green segments are for dose control, timing control, and mixed control, respectively; (**b**) Comparison of total injection of insulin for three optimal control methods

5 Conclusion

In this paper, we formulated a novel switched impulsive dynamical system and used optimal control theory to study therapy protocols for diabetics with insulin pump in a limited time. Compared with model proposed in [20], our new model considers not only the endpoint control of plasma glucose level but also the fluctuations during the control process, which is in more accordance with the actual situation.

Taking into account both the fluctuations of plasma glucose level and the amount of insulin injected, we investigated three therapy strategies for two different objective functions. To solve technical problems in optimal impulsive control, we applied a time rescaling method and obtained gradient formulas of cost functions with respect to injection doses and injection timings. We numerically obtained optimal values of injection doses and timings for each therapy strategy. Numerical results indicate that for the objective function without considering the risk of hypoglycemia, the optimal injection timing control is superior to the optimal injection dose control, whereas the mixed control gets almost the same effect as the optimal injection timing control at a cost of less insulin injected. Numerical simulations also suggest that for the objective function considering the risk of hypoglycemia, the optimal injection timing control is superior to the optimal injection dose control in preventing hypoglycemia problems, and the mixed control is the best performing strategy in avoiding problems with hyperglycemia.

Acknowledgements
The authors are very grateful to the editor and the anonymous referees for their valuable comments and constructive suggestions, which helped us to significantly improve the paper.

Funding
This work is supported by the National Natural Science Foundation of China (11901502, 11701495, and 11871415), Training program for Young Core Instructors in Henan Province (2019GGJS157), Foundation of Henan Educational Committee under Contract (21A110022), Program for Science & Technology Innovation Talents in Universities of Henan Province (21HASTIT026), Nanhu Scholars Program for Young Scholars of XYNU.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Authors' contributions
All authors read and approved the final manuscript.

Publisher's Note

Received: 4 March 2020 Accepted: 9 November 2020 Published online: 23 November 2020

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