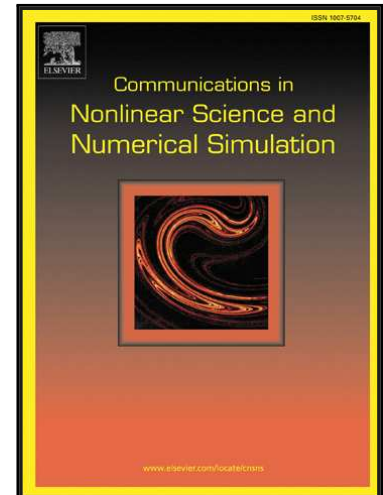# Accepted Manuscript

The regulatory system for diabetes mellitus: modeling rates of glucose infusions and insulin injections

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Highlights

- We develop novel glucose-insulin systems modeling rates of glucose infusions and insulin injections.

- The periodic solution for type 1 and permanence for type 2 diabetes of the system have been studied.

- The results showed that the period, the frequency and the dose of glucose infusions and insulin injections are crucial.

- The blood concentration can be controlled within a normal range using the proposed models.

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The regulatory system for diabetes mellitus: modeling rates of glucose infusions and insulin injections

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Abstract

Novel mathematical models with open and closed-loop control for type 1 or type 2 diabetes mellitus were developed to improve understanding of the glucose-insulin regulatory system. A hybrid impulsive glucose-insulin model with different frequencies of glucose infusions and insulin injections was analyzed, and the existence and uniqueness of the positive periodic solution for type 1 diabetes, which is globally asymptotically stable, was studied analytically. Moreover, permanence of the system for type 2 diabetes was demonstrated which showed that the glucose concentration level is uniformly bounded above and below. To investigate how to prevent hyperinsulinemia and hyperglycaemia being caused by this system, we developed a model involving periodic intakes of glucose with insulin injections applied only when the blood glucose level reached a given critical glucose threshold. In addition, our numerical analysis revealed that the period, the frequency and the dose of glucose infusions and insulin injections are crucial for insulin therapies, and the results provide clinical strategies for insulin-administration practices.

Keywords:
Diabetes, Glucose-insulin system, Glucose infusion, Insulin injection,
Critical glucose threshold

1. Introduction

Diabetes mellitus is an epidemic disease worldwide, characterized by plasma glucose concentrations mostly remaining above the normal range as a consequence of the absolute or relative lack of insulin. Depending on the pathogenic mechanisms involved, diabetes mellitus is divided into three types: type 1 diabetes, type 2 diabetes and gestational diabetes. Type 1 diabetes is generally due to the immune system of the patients destroying β cells in the islets of Langerhans of the pancreas and thus preventing production and secretion of insulin. In type 2 diabetes, either the β-cells do not produce enough insulin or the so-called insulin resistance occurs when the system becomes dysfunctional and prevents cells from taking up glucose efficiently [1]. Gestational diabetes refers to cases when pregnant women who have never had diabetes develop high plasma glucose levels during pregnancy. Since the discovery of diabetes, the main aims of researchers have been to find out how the endocrine metabolic system works [2, 3], the reasons for dysfunctions [4] and effective and efficient therapies improving the daily life of diabetic patients.

A typical therapy is subcutaneous injection of insulin or its analogues by using an insulin pump. This not only provides a basic treatment for type 1 diabetes [5], but also supplies a viable alternative for type 2 diabetes although the latter can be controlled, or even cured, by life-style changes such as dietary adjustment, physical exercise, stopping smoking and avoiding exposure to second-hand smoke [6-8]. A drawback of insulin therapy, however, is the difficulty in the monitoring of plasma glucose concentrations non-invasively. Thus, all current therapies are followed by the so-called open-loop approach in which glucose concentrations are not measured automatically. When an accurate non-invasive glucose monitoring technique is developed, the open-loop treatment can be replaced by closed-loop therapy, with an "artificial pancreas" delivering insulin automatically according to variations in blood glucose levels [9-11].

However, the need for reliable predictive models and the lack of effective and efficient control algorithms are two major impediments in the development of the artificial pancreas [12]. To conquer these issues, several reliable mathematical models which can determine the time and the dose of insulin injections for control algorithms have been proposed and investigated [13-15]. Such models reflect the interaction mechanisms between glucose and insulin in a kinetic system. Meanwhile, periodic insulin administration has been

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employed to mimic impulsive injections for type 1 or type 2 diabetes mellitus treatment regimes [14, 15]. Inspired by Wang et al. [14, 15], Huang et al. [12] formed a new model which takes impulsive insulin injection into account either periodically or by monitoring the plasma glucose concentration level. The model can be described by:

$$
\begin{cases}
\left.
\begin{aligned}
\frac{dG(t)}{dt} &= G_{in} - \sigma_2 G(t) - a\left(c + \frac{kI(t)}{l + I(t)}\right)G(t) + b, \\
\frac{dI(t)}{dt} &= \frac{\sigma_1 G^2(t)}{\alpha_1^2 + G^2(t)} - dI(t),
\end{aligned}
\right\} & t \neq h\tau, \\
\left.
\begin{aligned}
G(t^+) &= G(t), \\
I(t^+) &= I(t) + \sigma,
\end{aligned}
\right\} & t = h\tau,
\end{cases}
\tag{1.1}
$$

where $G(t)$ is the glucose concentration at time t, $I(t)$ is the insulin concentration at time t, G_{in} is the estimated average constant rate of glucose input, σ_2 indicates the insulin-independent glucose uptake rate, the term $aG(t)(c + mI(t)/(n + I(t)))$ stands for the insulin-dependent glucose utilization, b represents the hepatic glucose production, $\sigma_1 G^2(t)/(\alpha_1^2 + G^2(t))$ is insulin secretion stimulated by elevated glucose concentration caused by complex pathways including chemical-electrical processes, d indicates the insulin degradation rate. Furthermore, all parameters are positive [12] and the initial conditions are $G(0) = G_0 > 0, I(0) = I_0 > 0$. τ is the period of the impulsive injection, σ denotes the dose of insulin in each injection and is injected as an impulse at discrete times $t = h\tau, h \in Z^+ = \{1, 2, 3, ...\}$.

Although the authors obtained many meaningful results theoretically [12], for the sake of simplicity, they assumed that the constant glucose exogenous infusion rate G_{in} is described by a continuous process in a period. However, this can not reflect reality very well because constant glucose exogenous infusion is usually a discrete process with an impulse at discrete times [2], for example, uptake from food (i.e., from breakfast, lunch and dinner) or the rate of intravenous glucose infusion at intervals [3], although this might be provided continuously in a hospital context. Therefore, in order to better reflect reality and model the treatment currently available for clinical use, we consider that glucose infusion is applied only at each impulsive point τ_n, and at each impulsive point λ_m there is an impulsive injection of insulin. These modifications result in the following model based on the two impulsive point series [16, 17]:

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$$\begin{cases} \dfrac{dG(t)}{dt} = -\sigma_2 G(t) - a\left(c + \dfrac{kI(t)}{l+I(t)}\right)G(t) + b, \\[2mm] \dfrac{dI(t)}{dt} = \dfrac{\sigma_1 G^2(t)}{\alpha_1^2 + G^2(t)} - dI(t), \end{cases} \quad \left.\right\} t \neq \tau_n, t \neq \lambda_m,$$

$$\left.\begin{aligned} G(\tau_n^+) &= G(\tau_n) + G_{in}, \\ I(\tau_n^+) &= I(\tau_n), \end{aligned}\right\} \quad t = \tau_n,$$

$$\left.\begin{aligned} G(\lambda_m^+) &= G(\lambda_m), \\ I(\lambda_m^+) &= I(\lambda_m) + \sigma, \end{aligned}\right\} \quad t = \lambda_m,$$

$$(1.2)$$

where $\tau_n(n = 1, 2, ...)$ and $\lambda_m(m = 1, 2, ...)$ are impulsive point series at which glucose infusion and insulin injection are applied, respectively. It is thus possible to rank the different patterns of glucose infusion in terms of their dynamic effects in relation to the timing of insulin injection. Furthermore, it has been revealed that the oscillatory insulin delivery with a periodicity is more efficient in reducing plasma glucose concentration level [15, 18], and the main characteristic of system (1.2) is in agreement with how the insulin pump works in an open-loop fashion.

Although the insulin pumps with open-loop approach have made major contributions to clinical practice, open-loop therapy changes the life styles of the patients and increases their likelihoods of becoming hyperinsulinemic or hyperglycaemic. Therefore, from a theoretical point of view, the most effective insulin therapy for patients is to control their glucose levels within a desirable range, once the blood glucose reaches a critical glucose threshold (CGT) instead of periodic injections of insulin, as shown in Fig. 1. The critical glucose threshold can be defined as the glucose level in the blood when insulin injections must be taken to prevent the dangerous glucose level (DGL) from being reached and exceeded, where the DGL is the blood glucose level that will cause harm to patients. For example, insulin injections must be taken once the critical concentration of glucose is observed by a glucose monitoring system so that the DGL can not be exceeded, that is, sufficient lead time is needed between the time when the critical concentration of glucose is observed and the time when a treatment is applied (Obviously, CGT is less than DGL). Thus the most reasonable treatment is that insulin is injected automatically in a closed-loop technique integrated with the glucose monitoring system. Based on system (1.2), we propose a novel hybrid

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impulsive model with threshold:

$$
\begin{cases}
\dfrac{dG(t)}{dt} = -\sigma_2 G(t) - a\left(c + \dfrac{kI(t)}{l+I(t)}\right)G(t) + b, & t \neq \tau_n, \\[2mm]
\dfrac{dI(t)}{dt} = \dfrac{\sigma_1 G^2(t)}{\alpha_1^2 + G^2(t)} - dI(t), & G < G_C \quad \text{or} \quad I > I_C, \\[2mm]
\left.\begin{array}{l} G(\tau_n^+) = G(\tau_n) + G_{in}, \\ I(\tau_n^+) = I(\tau_n), \end{array}\right\} & t = \tau_n, \\[2mm]
\left.\begin{array}{l} G(\lambda_m^+) = G(\lambda_m), \\ I(\lambda_m^+) = I(\lambda_m) + \sigma, \end{array}\right\} & G \geq G_C \quad \text{and} \quad I \leq I_C,
\end{cases}
\tag{1.3}
$$

where $\tau_n(n = 1, 2, ...)$ is an impulsive point series at which glucose infusion works normally, and λ_m is the time series at which the glucose level reaches the CGT and the injection of insulin should be applied. The initial condition $G(0) = G_0 \leq G_C$, $I(0) = I_0$, G_C is an adjustable constant threshold value for the glucose level, I_C is another adjustable constant threshold value for the insulin level. When the blood glucose level reaches G_C (CGT), then the injection of insulin with dose of σ is performed and the glucose level must decrease when the insulin level surpasses I_C.

The paper is organized as follows: In section 2, we focus on system (1.2) and investigate its dynamic behaviors. The existence and stability of the positive periodic solution is studied under different cases. Furthermore, by using the comparison theorem, we have proved that the system (1.2) is permanent. In addition, numerical simulations have confirmed our theoretical work and insulin therapies for patients are also discussed. Moreover, in section (3), system (1.3) is investigated numerically and the simulation results revealed that the blood glucose level could be controlled very well within the normal range. Finally, we discuss our results combined with insulin therapies, but additional work is needed to provide reliable predictive models and efficient control algorithms for developing the artificial pancreas.

2. Mathematical analysis of system (1.2) for open-loop technique

As mentioned before, for type 1 diabetes there is no insulin produced or secreted, this case corresponds to $\sigma_1 = 0$ in system (1.2) and (1.3). Now we investigate the dynamics of system (1.2) for type 1 diabetes.

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2.1. Existence and stability of the periodic solution of system (1.2) for type 1 diabetes

There are two impulsive point series when glucose infusion and insulin injection are applied. Therefore, it is possible to rank the different patterns of glucose infusion in terms of their dynamic effects in relation to the timing of insulin injection. We consider several different cases in terms of the timing of controlling the blood glucose level from a practical point of view.

Case 1 Glucose infusions are more frequent than insulin injections.

Assume $\lambda_{m+1} - \lambda_m \equiv T_N$ for all $m(m \in \mathcal{N})$, where T_N is the period of impulsive injections of insulin. For this case, the system (1.2) is said to be a T_N periodic system if there exists a positive integer k_p such that

$$\tau_{n+k_p} = \tau_n + T_N.$$

where k_p denotes the times of glucose infusions during the period T_N. This implies that in each period T_N, k_p times glucose infusions are applied.

When $\sigma_1 = 0$, the variable G does not appear in the second equation of system (1.2). Therefore, for the dynamics of insulin $I(t)$ we only need to consider the following subsystem:

$$\begin{cases} \dfrac{dI(t)}{dt} = -dI(t), & t \neq \tau_n, t \neq \lambda_m, \\ I(\tau_n^+) = I(\tau_n), & t = \tau_n, \\ I(\lambda_m^+) = I(\lambda_m) + \sigma, & t = \lambda_m, \end{cases} \quad (2.1)$$

Denote $\Delta_i = \tau_{i+1} - \tau_i$, $i = 0, 1, 2, ..., k_p$, where $\Delta_0 = \tau_1, \Delta_{k_p} = T_N - \tau_{k_p}$.

It is shown in Appendix A that there exists a globally stable T_N periodic solution $I^{T_N}(t)$ for system (2.1), substituting $I^{T_N}(t)$ into the first equation of (1.2) for $I(t)$, we get a positive T_N periodic solution with the complete expression $(I^{T_N}(t), G^{T_N}(t))$ over the h−th time interval $hT_N < t \leq (h+1)T_N$ of system (1.2) for type 1 diabetes. Now we prove that the positive periodic solution $(I^{T_N}(t), G^{T_N}(t))$ is globally stable under Case 1.

Theorem 2.1 If $\sigma_1 = 0$, then the positive T_N periodic solution $(I^{T_N}(t), G^{T_N}(t))$ of system (1.2) for type 1 diabetes is globally asymptotically stable.

Proof. The local stability of the periodic solution $(I^{T_N}(t), G^{T_N}(t))$ can be determined by considering the behavior of small amplitude perturbations $(u(t), v(t))$ of the solution. Define

$$G(t) = G^{T_N}(t) + u(t), \quad I(t) = I^{T_N}(t) + v(t),$$

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then it follows that

$$\left(\begin{array}{c} u(t) \\ v(t) \end{array} \right) = \Phi(t) \left(\begin{array}{c} u(0) \\ v(0) \end{array} \right),$$

where $\Phi(t)$ satisfies

$$\frac{d\Phi(t)}{dt} = \left(\begin{array}{cc} -\xi - \frac{akI^{T_N}(t)}{l+I^{T_N}(t)} & -\frac{akG^{T_N}(t)}{l+I^{T_N}(t)} \\ 0 & -d \end{array} \right) \Phi(t),$$

with $\Phi(0) = I$ the identity matrix. The linearization of the resetting impulsive condition of (1.2) becomes

$$\left(\begin{array}{c} u((h+1)T_N^+) \\ v((h+1)T_N^+) \end{array} \right) = \left(\begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array} \right) \left(\begin{array}{c} u((h+1)T_N) \\ v((h+1)T_N) \end{array} \right),$$

and

$$\left(\begin{array}{c} u((hT_N+\tau_i)^+) \\ v((hT_N+\tau_i)^+) \end{array} \right) = \left(\begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array} \right) \left(\begin{array}{c} u(hT_N+\tau_i) \\ v(hT_N+\tau_i) \end{array} \right).$$

Then the stability of the periodic solution $(I^{T_N}(t), G^{T_N}(t))$ is determined by the eigenvalues of

$$\theta = \left(\begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array} \right) \Phi(T_N).$$

Therefore, all eigenvalues of θ are given by

$$\eta_1 = exp\left(\int_{hT_N}^{(h+1)T_N} \left[-\xi - \frac{akI^{T_N}(t)}{l+I^{T_N}(t)} \right] dt \right) = \prod_{j=0}^{k_p} \eta^j, \eta_2 = e^{-dT_N},$$

where

$$\eta^j = exp\left(\int_{\tau_j+hT_N}^{\tau_{j+1}+hT_N} \left[-\xi - \frac{akI^* exp[-d(\sum\limits_{i=0}^{j-1}\Delta_i + t - \tau_j - hT_N)]}{l + I^* exp[-d(\sum\limits_{i=0}^{j-1}\Delta_i + t - \tau_j - hT_N)]} \right] dt \right),$$

from the expression of $I^{T_N}(t)$, when $t \in (\tau_j + hT_N, \tau_{j+1} + hT_N]$, we get

$$I^{T_N}(t) = I^* exp[-d\sum_{i=0}^{j-1}\Delta_i]exp[-d(t - \tau_j - hT_N)](j = 0 \cdots k_p),$$

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substitute it into η^j, by calculation,

$$\eta^j = exp(-\xi\Delta_j)\frac{\sigma exp[-d\sum\limits_{i=0}^{j}\Delta_i] + 1 - exp(-dT_N)}{\sigma exp[-d\sum\limits_{i=0}^{j-1}\Delta_i] + 1 - exp(-dT_N)},$$

it is obvious that $\eta^j < 1$. Besides, $\eta_2 < 1$ always hold. According to Floquet theory [19, 20], the positive T_N periodic solution $(I^{T_N}(t), G^{T_N}(t))$ is locally asymptotically stable.

In the following, we prove that the periodic solution $(I^{T_N}(t), G^{T_N}(t))$ is a global attractor. According to the proof of boundedness for the system (2.1), we can get $I(t) \to I^{T_N}(t)$ as $t \to \infty$. Choosing $\varepsilon_1 > 0$ and $\varepsilon_2 > 0$ small enough such that $(1 - \varepsilon_1)I^{T_N}(t) < I(t) < (1 + \varepsilon_2)I^{T_N}(t)$ for all $t > t_1 > 0$. From the first equation of system (1.2), we note that

$$\frac{dG(t)}{dt} \geq b - (\sigma_2 + ac)G(t) - \frac{akG(t)(1 + \varepsilon_2)I^{T_N}(t)}{l + (1 + \varepsilon_2)I^{T_N}(t)}$$

and

$$\frac{dG(t)}{dt} \leq b - (\sigma_2 + ac)G(t) - \frac{akG(t)(1 - \varepsilon_1)I^{T_N}(t)}{l + (1 - \varepsilon_1)I^{T_N}(t)}.$$

then we obtained the following two impulsive equations

$$\begin{cases} \dfrac{dG'(t)}{dt} = b - (\sigma_2 + ac)G'(t) - \dfrac{akG'(t)(1 + \varepsilon_2)I^{T_N}(t)}{l + (1 + \varepsilon_2)I^{T_N}(t)}, t \neq \tau_n, t \neq \lambda_m, \\ G'(\tau_n^+) = G'(\tau_n) + G_{in}, \qquad t = \tau_n, \\ G'(\lambda_m^+) = G'(\lambda_m), \qquad t = \lambda_m, \end{cases}$$

(2.2)

and

$$\begin{cases} \dfrac{dG''(t)}{dt} = b - (\sigma_2 + ac)G''(t) - \dfrac{akG''(t)(1 - \varepsilon_1)I^{T_N}(t)}{l + (1 - \varepsilon_1)I^{T_N}(t)}, t \neq \tau_n, t \neq \lambda_m, \\ G''(\tau_n^+) = G''(\tau_n) + G_{in}, \qquad t = \tau_n, \\ G''(\lambda_m^+) = G''(\lambda_m), \qquad t = \lambda_m. \end{cases}$$

(2.3)

According to the subsystem (A.2), we replace $I^{T_N}(t)$ by $(1 + \varepsilon_2)I^{T_N}(t)$ in equation (A.6), which yields a unique globally asymptotically stable positive

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periodic solution $G'^{T_N}(t)$ in interval $(hT_N, (h+1)T_N]$ for subsystem (2.2),

$$G'^{T_N}(t) = \begin{cases} G'_1(t), & t \in (hT_N, \tau_1 + hT_N], \\ G'_2(t), & t \in (\tau_1 + hT_N, \tau_2 + hT_N], \\ \vdots \\ G'_{k_p+1}(t), & t \in (\tau_{k_p} + hT_N, (h+1)T_N]. \end{cases}$$

Similarly, we get the expression of the periodic solution $G''^{T_N}(t)$ for subsystem (2.3),

$$G''^{T_N}(t) = \begin{cases} G''_1(t), & t \in (hT_N, \tau_1 + hT_N], \\ G''_2(t), & t \in (\tau_1 + hT_N, \tau_2 + hT_N], \\ \vdots \\ G''_{k_p+1}(t), & t \in (\tau_{k_p} + hT_N, (h+1)T_N]. \end{cases}$$

According to the Comparison theorem, for any $\varepsilon > 0$ small enough, there exists a $t_2 > t_1$ such that

$$G'^{T_N}(t) - \varepsilon < G'(t) \le G(t) \le G''(t) < G''^{T_N}(t) + \varepsilon$$

for all $t > t_2$. Let $\varepsilon, \varepsilon_1, \varepsilon_2 \to 0$, then $G'^{T_N}(t) \to G^{T_N}(t)$ and $G''^{T_N}(t) \to G^{T_N}(t)$, which leads to

$$G^{T_N}(t) - \varepsilon < G(t) < G^{T_N}(t) + \varepsilon$$

for all $t > t_2$, that is $G(t) \to G^{T_N}(t)$ as $t \to \infty$. It follows that the periodic solution $(I^{T_N}(t), G^{T_N}(t))$ is a global attractor, and consequently the global stability follows. This completes the proof.

Case 2 Insulin injections are more frequent than glucose infusions.

Assume $\tau_{n+1} - \tau_n \equiv T_p$ for all $n (n \in \mathcal{N})$, where T_p is the period of glucose infusions. For this case, system (1.2) is said to be a T_p periodic system if there exists a positive integer k_N such that

$$\lambda_{m+k_N} = \lambda_m + T_p.$$

This implies that in each period T_p, k_N times insulin injections are applied.

For this case, there are k_N times insulin injections during the period T_p. Similarly, denote $\Delta_i = \lambda_{i+1} - \lambda_i$, $i = 0, 1, 2, ..., k_N$, where $\Delta_0 = \lambda_1, \Delta_{k_N} = T_p - \lambda_{k_N}$. Because $\sigma_1 = 0$, then the variable G does not appear in the second

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equation of system (1.2). Therefore, for the dynamics of insulin $I(t)$ we only need to consider the following subsystem:

$$\begin{cases} \dfrac{dI(t)}{dt} = -dI(t), & t \neq \tau_n, t \neq \lambda_m, \\ I(\lambda_m^+) = I(\lambda_m) + \sigma, & t = \lambda_m, \\ I(\tau_n^+) = I(\tau_n), & t = \tau_n, \end{cases} \qquad (2.4)$$

It is shown in Appendix B that there exists a globally stable T_p periodic solution with the complete expression $(I^{T_p}(t), G^{T_p}(t))$ over the $h-$th time interval $hT_p < t \leq (h+1)T_p$ of system (1.2) for type 1 diabetes. Now we prove the stability of the positive periodic solution $(I^{T_p}(t), G^{T_p}(t))$ for Case 2.

Theorem 2.2 If $\sigma_1 = 0$, then the positive T_p periodic solution $(I^{T_p}(t), G^{T_p}(t))$ of system (1.2) for type 1 diabetes is global asymptotically stable.

The Proof is similar to that for Theorem 1, so we omit it here.

Case 3 Insulin injections and glucose infusions are employed with different periods.

Assume $\lambda_{m+1} - \lambda_m \equiv T_N$ for all m, and $\tau_{n+1} - \tau_n \equiv T_p$ for all n. In this case, T_N is the period of impulsive injections of insulin, T_p is the period of glucose infusions, $m, n (n \in \mathcal{N})$. Denote $\rho = T_p/T_N$, then ρ either is rational (i.e. T_p and T_N are rational dependent)or is irrational (i.e. T_p and T_N are rational independent). If ρ is rational, then $\rho = p/q$, $p, q \in \mathcal{N}$ and p, q are relatively prime. Let $T_0 = pT_N(= qT_p)$, then system (1.2) is a T_0 periodic system. This means that if ρ is rational, model (1.2) can be investigated by using similar methods as those in Cases 1 and 2; if ρ is irrational, then the dynamical behavior of model (1.2) becomes more complex and is quite difficult to investigate theoretically; see more details in reference ([21]).

From the analysis of Case 1 and Case 2 for type 1 diabetes, there is no insulin produced or secreted from the pancreas and the subcutaneous injections of insulin can stabilize the glucose-insulin concentration. It is shown that no matter whether glucose infusions are more frequent than insulin injections or insulin injections are more frequent than glucose infusions, there exists a positive globally stable periodic solution in system (1.2) for type 1 diabetes, and the periodic solution reflects the periodic oscillations of the glucose-insulin concentration when glucose infusions and insulin injections are applied.

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When $\sigma_1 > 0$, then the pancreas of the patients can produce and secrete a little but not enough insulin. However, it is quite difficult to show the existence of a periodic solution in this case, so we turn to investigate the permanence of the system (1.2).

2.2. Permanence of system (1.2) for type 2 diabetes: i.e. $\sigma_1 > 0$

The main feature of the diagnostics for type 2 diabetes are hyperglycemia and hyperinsulinemia which are most probably caused by insulin resistance. In order to compensate for the insulin resistance, pancreatic β-cells need to secrete more insulin. Therefore, the insulin secretion rate $\sigma_1 > 0$ in model (1.2). Now, we investigate the range of variation for glucose concentration $G(t)$ under impulsive infusions of glucose and insulin concentration $I(t)$ under impulsive injections of insulin with the open-loop technique for sufficiently large $t > 0$. This qualitative result could provide important advances for developing the artificial pancreas, precluding both hyperglycemia and hypoglycemia.

Theorem 2.3 If $\sigma_1 > 0$, then system (1.2) for type 2 diabetes is permanent.

Proof. From the second equation of system (1.2), we have

$$-dI(t) \leq \frac{dI(t)}{dt} \leq \sigma_1 - dI(t).$$

When $-dI(t) \leq dI(t)/dt$, considering the impulsive effects of Case 1 and Case 2. Then from section 2.1, both subsystems have unique global asymptotically stable positive periodic solutions, denoted as $I_1^{T_N}(t)$ with the period T_N and $I_2^{T_p}(t)$ with the period T_p, respectively. We get

$$I_1^{T_N}(t) = \begin{cases} I_1^* exp[-d(t - hT_N)], & t \in (hT_N, \tau_1 + hT_N], \\ I_1^* exp[-d\Delta_0]exp[-d(t - \tau_1 - hT_N)], \\ \quad t \in (\tau_1 + hT_N, \tau_2 + hT_N], \\ \vdots \\ I_1^* exp[-d\sum\limits_{i=0}^{k_p-1} \Delta_i]exp[-d(t - \tau_{k_p} - hT_N)], \\ \quad t \in (\tau_{k_p} + hT_N, (h+1)T_N], \end{cases}$$

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where $I_1^* = \sigma/(1 - exp[-dT_N])$.

$$I_2^{T_p}(t) = \begin{cases} I_2^* exp[-d(t - hT_p)], & t \in (hT_p, \lambda_1 + hT_p], \\ (I_2^* exp(-d\Delta_0) + \sigma)exp[-d(t - \lambda_1 - hT_p)], \\ t \in (\lambda_1 + hT_p, \lambda_2 + hT_p], \\ \vdots \\ \{I_2^* exp[-d(\sum\limits_{i=1}^{k_N-1} \Delta_i)] + C\}exp[-d(t - \lambda_{k_N} - hT_p)], \\ t \in (\lambda_{k_N} + hT_p, (h+1)T_p], \end{cases}$$

where $I_2^* = C_1/(1 - exp[-dT_p])$.

When $dI(t)/dt \leq \sigma_1 - dI(t)$, similarly, we can get two global asymptotically stable positive periodic solutions by considering the impulsive effects of Case 1 and Case 2, denoted as $I_3^{T_N}(t)$ and $I_4^{T_p}(t)$.

$$I_3^{T_N}(t) = \begin{cases} \frac{\sigma_1}{d} + (I_3^* - \frac{\sigma_1}{d})exp[-d(t - hT_N)], & t \in (hT_N, \tau_1 + hT_N], \\ \frac{\sigma_1}{d} + (I_3^* - \frac{\sigma_1}{d})exp(-d\Delta_0)exp[-d(t - \tau_1 - hT_N)], \\ t \in (\tau_1 + hT_N, \tau_2 + hT_N], \\ \vdots \\ \frac{\sigma_1}{d} + (I_3^* - \frac{\sigma_1}{d})exp[-d\sum\limits_{i=0}^{k_p-1} \Delta_i]exp[-d(t - \tau_{k_p} - hT_N)], \\ t \in (\tau_{k_p} + hT_N, (h+1)T_N], \end{cases}$$

where $I_3^* = \sigma_1/d + \sigma/(1 - exp[-dT_N])$,

$$I_4^{T_p}(t) = \begin{cases} \frac{\sigma_1}{d} + (I_4^* - \frac{\sigma_1}{d})exp[-d(t - hT_p)], & t \in (hT_p, \tau_1 + hT_p], \\ \frac{\sigma_1}{d} + (I_4^* - \frac{\sigma_1}{d})exp(-d\Delta_0)exp[-d(t - \tau_1 - hT_p)], \\ t \in (\tau_1 + hT_p, \tau_2 + hT_p], \\ \vdots \\ \frac{\sigma_1}{d} + \{(I_4^* - \frac{\sigma_1}{d})exp[-d(\sum\limits_{i=1}^{k_N-1} \Delta_i)] + C\}exp[-d(t - \lambda_{k_N} - hT_p)], \\ t \in (\tau_{k_N} + hT_p, (h+1)T_p], \end{cases}$$

where $I_4^* = \sigma_1/d + C_1/(1 - exp[-dT_p])$.

Denoted as $\tilde{I}_1(t) = \max\{I_1^{T_N}(t), I_2^{T_p}((t)\}$ and $\tilde{I}_2(t) = \min\{I_3^{T_N}(t), I_4^{T_p}(t)\}$, then according to the comparison theorem, for any sufficient small $\varepsilon > 0$, there exists a t_0 such that

$$\tilde{I}_1(t) - \varepsilon < \tilde{I}_1(t) \leq I(t) \leq \tilde{I}_2(t) < \tilde{I}_2(t) + \varepsilon, \quad t \geq t_0,$$

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and denoted as

$$\tilde{I}_1(T) = \max\{I_1^{T_N}((h+1)T_N), I_2^{T_p}((h+1)T_p)\}$$

and

$$\tilde{I}_2(T) = \min\{I_3^{T_N}(hT_N), I_4^{T_p}(hT_p)\},$$

then we have

$$\tilde{I}_1(T) = \liminf_{t\to\infty} \tilde{I}_1(t) \le \liminf_{t\to\infty} I(t) \le \limsup_{t\to\infty} I(t) \le \tilde{I}_2(T). \qquad (2.5)$$

From equation (2.5) and the second equation of system (1.2), it is easy to see that

$$
\begin{aligned}
b - (\sigma_2 + ac)G(t) - \frac{akG(t)\tilde{I}_2(T)}{l+\tilde{I}_2(T)} &\le \frac{dG(t)}{dt} \\
&\le b - (\sigma_2 + ac)G(t) - \frac{akG(t)\tilde{I}_1(T)}{l+\tilde{I}_1(T)},
\end{aligned}
\qquad (2.6)
$$

considering the impulsive effects of Case 1 and Case 2 for equation (2.6). By the same methods, we can get G_m and G_M such that

$$G_m \le \liminf_{t\to\infty} G(t) \le \limsup_{t\to\infty} G(t) \le G_M. \qquad (2.7)$$

According to (2.5) and (2.7), the system (1.2) for type 2 diabetes is permanent. This completes the proof.

2.3. Numerical investigations for open-loop control and its biological implications

In insulin therapies, the use of an insulin pump not only provides the basic treatment for type 1 diabetes but also provides a feasible alternative to insulin injections for type 2 diabetes [6-8]. System (1.2) is based on the open-loop technique with glucose infusions and insulin injections periodically at different impulsive point series. In this section, we will investigate the applications of model (1.2) numerically in clinical insulin therapies with the aim of mimicking the natural pattern of insulin injections by pumps so that the plasma glucose levels in blood can be controlled at normal levels.

The parameter values presented in Table 2.1 in our simulations are either determined by previous research [2, 3, 12, 22, 23], or from the models for the intravenous glucose tolerance test (IVGTT) [24-26]. Besides, the necessary

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Table 2.1: Parameter values for the model (1.2) and (1.3)

Parameters	Values	Units	Parameters	Values	Units
σ_1	1.27	μ U/min	σ_2	5×10^{-6}	min^{-1}
a	0.03	mg^{-1}	b	100	mg/min
c	40	mg/min	d	0.008	min^{-1}
k	900	mg/min	l	80	mg
α_1	350	mg			

conversions of units are made and the values are adjusted within reasonable ranges.

For type 1 diabetes, i.e., $\sigma_1 = 0$, there is no insulin secreted from the pancreas. Then an insulin pump is needed for patients to help their cells to take up glucose. From the analysis of Case 1 and Case 2 in section 2.1, we know that with different frequencies of glucose infusions and insulin injections, for the system (1.2) there always exists a globally stable periodic solution for type 1 diabetes. To substantiate our theoretical results and supply clinical insulin therapies in the practice, it is reasonable to take 12 hours (i.e., 720 minutes) as a period for insulin injections, and in this period, people always take up glucose every 4 hours. This is consistent with the character of Case 1, and with other parameters fixed, the numerical results are as shown in Fig. 2(a) and Fig. 2(b). It is shown that the blood glucose concentrations and insulin concentrations of the patients change periodically. After three glucose infusions, we see that the blood glucose level is beyond the reasonable range (for example, DGL is 125 mg/dl [15]), which can be dangerous for patients. Therefore, with the help of insulin, the blood glucose level is maintained within a normal range when glucose infusions are applied at most twice. That is the reason why doctors advise their patients not to take up glucose at dinner time. For Case 2, the patients take up glucose every 12 hours and insulin is injected three times in this period (see Fig. 2(c) and Fig. 2(d)). The stable periodic solution is shown in Fig. 2(c) and Fig. 2(d), and the results show that the blood glucose level will be always maintained at a low range, but excessive insulin infusions increase the risk of severe hypoglycemia [27]. Therefore, to be clinically acceptable, it is not only essential for a model based controller to prevent hyperglycaemia by reducing the frequencies of glucose infusions, but also to reduce the frequencies of insulin injections to prevent hypoglycemic and hyperinsulinemia episodes by

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making accurate predictions.

For type 2 diabetes, i.e., $\sigma_1 > 0$, and with all other parameters fixed, Fig. 3 shows the numerical results for cases when glucose infusions are more frequent than insulin injections and insulin injections are more frequent than glucose infusions, respectively. However, it is different from type 1 diabetes as patients can take up glucose three times without reaching the abnormal blood glucose level since the pancreases of these patients can secrete a small amount of insulin. So it presents a direct result of the differences in treatment between different types of diabetes mellitus.

When a patient injects insulin before he or she takes up glucose, how does this affects the dynamics of the glucose-insulin system ? To address this, we assume that a patient injects insulin $15min$ before he or she takes up glucose for type 1 diabetes, then we fix all other parameters as shown in Table 2.1 and the simulation result is shown in Fig. 4(a) and Fig. 4(b). Clearly, if the dose of injected insulin σ is $60\mu U$, then the blood glucose level is beyond the normal range. When $\sigma = 80\mu U$, then the blood glucose level is within the normal range. For type 2 diabetes, the blood glucose level is under control if $\sigma = 60\mu U$ (see Fig. 4(c) and Fig. 4(d)), the reason is that the pancreas can produce and secrete a little insulin. When $\sigma = 80\mu U$, this regime is more efficient. Thus this regime can control the blood glucose level easily within a normal range if the dose of injected insulin is chosen appropriately. In contrast, when a patient injects insulin after he takes up glucose, the blood glucose level increases immediately and is beyond the normal range (not shown here), thus insulin injections are not useful.

The numerical results show the periodic solutions which reflect the periodic oscillations of the glucose concentration and insulin concentration for the type 1 diabetes and type 2 diabetes, respectively. It is revealed that the glucose infusion period, the insulin injection period, the dose of impulsive injection of insulin and the dose of impulsive infusion of glucose play key roles in affecting the dynamics of the system (1.2).

3. Hybrid impulsive model (1.3) with critical glucose threshold

As mentioned before, insulin injections with the open-loop approach are widely used in clinical insulin therapies for patients. However, a drawback of the open-loop control is that this regime changes the life styles of patients and risks hypoglycemia or hyperinsulinemia. In recent years, with the aims of improving the life styles of patients, researchers have been making great

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efforts in developing an artificial pancreas [9-11], that is, insulin is injected once the blood glucose level reaches a threshold which is observed by a glucose monitoring system. Accordingly, the hybrid impulsive model (1.3) meets the requirements, and it can serve as a prototype to offer reliable predictive models and efficient control algorithms for designing an artificial pancreas.

In system (1.3), we assume that G_C is an adjustable constant threshold value for glucose level, and

$$I_C = \frac{l(b - G_C(\sigma_2 + ac))}{G_C(\sigma_2 + a(c + k)) - b}$$

which is determined by the intersection of the null-line

$$-\sigma_2 G(t) - a\left(c + \frac{kI(t)}{l + I(t)}\right) G(t) + b = 0$$

and the critical glucose threshold G_C. At impulsive point series τ_n (we assume that $\tau_n - \tau_{n-1} = T$), we do not change the life style of patients because they take up glucose normally. When the blood glucose level reaches CGT, observed by the glucose monitoring system, then insulin is injected to bring down the blood glucose level and the DGL can not be reached and exceeded. In the following, we will investigate the dynamic behaviors of system (1.3) numerically.

Now, we focus on type 1 diabetes, i.e., $\sigma_1 = 0$, when there is no insulin secreted from the pancreas. We fixed parameters as shown in Table 2.1. For a given CGT ($G_C = 100mg/dl$), when $T = 60min$, the simulation results indicate that system (1.3) is free from closed-loop control after two insulin injections, and the glucose is infused twice at the first small period of insulin injections and three times at the other (Fig. 5(a) and Fig. 5(b)). It is revealed that the blood glucose level may exceed $100mg/dl$ (CGT) at insulin injection time. However, the blood glucose level will never reach the DGL, that is, it takes a few minutes for the injected insulin analogues to be absorbed and start to help the patients to bring down their blood glucose, and that is why we select CGT as a control parameter rather than DGL. Once the period T increases to $120min$, system (1.3) is free from closed-loop control after insulin injection, and during the insulin injection period the patients take up glucose once too, as shown in Fig. 5(c) and Fig. 5(d). Looking back to Fig. 2(a) and Fig. 2(b), after three glucose infusions, the blood glucose level is beyond the reasonable range, which can be dangerous for patients,

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and the smaller the period between successive glucose infusions is, the more dangerous it is for the patient. Compared to Fig. 2(a) and Fig. 2(b), the results show that the blood glucose level never reaches DGL, which indicates that the patients will be relieved from hyperinsulinemia and hyperglycaemia. Meanwhile, if we fix T and other parameters, and change the dose of insulin within a reasonable range, then the blood glucose concentration is more easily controlled because the change of insulin leads to the change of the blood glucose level (Not shown here).

For type 2 diabetes, the parameters are shown in Table 2.1. Also, for a given CGT ($G_C = 100mg/dl$), we choose G_{in} as a control parameter because the change of T can only lead to a slight change in the amplitude compared with type 1 diabetes (the numerical results is similar to type 1 diabetes). When $G_{in} = 60mg/dl$, the simulation result indicates that the system (1.3) is free from closed-loop control after insulin injection once, and the glucose is infused twice during the period of insulin injection (see Fig. 6(a) and Fig. 6(b)). If we select $G_{in} = 80mg/dl$, during the insulin injection period, the patients take in glucose once (Fig. 5(c) and Fig. 5(d)). When $G_{in} = 100mg/dl$, then the insulin is injected once the glucose infusion is applied because the blood glucose level reaches CGT immediately (Fig. 6(c) and Fig. 6(d)). Accordingly, when we increase the dose of the glucose infusions, more frequent injections of insulin are efficient. If we fix other parameters and choose σ as a controlling parameter, then the results are similar to type 1 diabetes.

Furthermore, we denote the time points at which the blood glucose level reaches G_C as $t_n(n = 1, 2, \cdots)$. If $mod(t_n, T) \equiv 0$, then glucose and insulin are both injected at the same time t_n. If $mod(t_n, T) \neq 0$, then only insulin is injected. Besides, denote

$$\Delta_n = t_n - t_{n-1}, \tag{3.1}$$

with $t_0 = 0$, where n denotes the maximum number at which the $G(t)$ component increases and reaches G_C within the given time interval and Δ_n is its relatively duration (n may be finite or infinite, which depends on the solutions of the model (1.3)).

We fix parameters as shown in Table 2.1 and the baseline control parameter values are set as $G_{in} = 60mg/dl$, $\sigma = 60\mu U$ and $T = 60min$, then the effect of control parameters on the number n and consequently on the period Δ_n can be calculated from the model (1.3) and formula (3.1) numerically

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for a fixed time interval $t \in [0, 1000]$ (Fig. 7). The results indicate that the number n is 10 and the duration Δ_n stabilizes after $300min$. The effects of the injection dose of insulin σ on the number n and the period Δ_n are shown in Fig. 7(a). It can be seen that the larger the injection dose of insulin σ is, the smaller is the number n and consequently the larger is the period Δ_n. It suggests that increasing the dose σ will decrease the number n and postpone the CGT from being reached. Conversely, the number n is increasing and the period Δ_n is decreasing as the glucose infusion rate G_{in} increases (Fig. 7(b)). This implies that larger G_{in} will cause harms to patients. In addition, it is interesting to see that the duration Δ_n switches between $180min$ and $240min$ when the glucose infusion rate G_{in} is set as $80mg/dl$. Therefore, the glucose infusion rate G_{in} should be chosen carefully to bring down the blood glucose concentration for a fixed dose σ. Moreover, it is revealed that the number n and the period Δ_n are both increasing as the glucose infusion period T increases (details see Fig. 7(c)).

These results clarify that model (1.3) proposed here can help us to bring down the blood glucose level, to protect against hyperinsulinemia and hyperglycaemia, to offer reliable predictive models and efficient control algorithms and to help clinicians to design an artificial pancreas to cure diabetes.

4. Conclusion

Since the pioneering work on the dynamics of plasma insulin concentrations that led to the glucose-insulin regulatory system contributing to insulin therapies [28], numerous of research papers have appeared on the topic [1, 2, 9, 12, 14, 15, 29]. In recent years, many results have been obtained from the glucose-insulin regulatory system via a mathematical model of delay differential equations. Recently, Huang et al. proposed two novel mathematical models with impulsive injections of insulin or its analogues for type 1 and type 2 diabetes mellitus [12], and they assumed that the constant glucose infusion rate G_{in} is described by a continuous process in an impulsive injection period. However, such models cannot reflect the reality very well because the constant glucose exogenous infusion is usually a discrete process [3]. Therefore, we developed a novel glucose-insulin system (1.2) with open-loop control based on two impulsive point series in order to better reflect the reality and model the treatment currently available for clinical use. Moreover, in clinical insulin therapies, the most satisfactory treatment would be one in which glucose infusions could be administered periodically without

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changing the life styles of patients, combined with automatic insulin injections in a closed-loop technique integrated with a glucose monitoring system. So we proposed a novel hybrid impulsive model (1.3) with a critical glucose threshold.

The dynamics of our models were investigated by using the theory of impulsive differential equations [19, 20]. In particular, the existence and uniqueness of a positive globally asymptotically stable periodic solution of system (1.2) for type 1 diabetes was studied analytically, and the permanence of system (1.2) for type 2 diabetes was shown, which also means that the glucose concentration level is uniformly bounded above and below. By extensive numerical investigations, we found that when choosing different control parameters, an attractor from which the concentration of glucose and insulin oscillates with different amplitudes always exists. The results indicates that the dynamic behaviors of the glucose-insulin system may be affected dramatically by the period, the frequency and the dose of glucose infusions and insulin injections, and these elements are crucial for insulin therapies.

In practice, a good insulin therapy is one in which the blood glucose level can be brought down to a normal range (here CGT) without changing the life style of patients. System (1.3) is proposed based on this ideal. To avoid hyperinsulinemia and hyperglycaemia, we assumed that insulin is injected only when the blood glucose level reaches CGT and periodic repeated intakes of glucose are applied. The simulation results indicate that the blood glucose level never reaches or exceeds DGL, the times of insulin injections would be reduced under certain conditions, and increasing the dose of the glucose infusions, more frequent injections of insulin are efficient. More importantly, the factors which affect the number n (i.e. the number at which the blood glucose reaches G_C) and its relatively duration Δ_n are discussed. The simulation results indicate that the number n and duration Δ_n largely depends on the injection dose of insulin, glucose infusion rate G_{in} and glucose infusion period T. Therefore, hybrid system (1.3) with closed-loop control is suitable for providing reliable predictive models and efficient control algorithms for the development of an artificial pancreas.

Note that two time delays always exist in the normal glucose-insulin regulatory system: one is the hepatic glucose production delay and the other is the time delay for insulin-dependent glucose utilization by cells [14]. So it would be more reasonable for system (1.2) and system (1.3) to take two delays into account. Furthermore, in this paper, for the sake of simplicity, the insulin degradation rate is assumed to be proportional to insulin concen-

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tration. However, it is more realistic to assume that the insulin degradation rate obeys Michaelis-Menten kinetics [15]. Moreover, the effect of physical exercise on the dynamics of glucose and insulin has been investigated [30], thus it is interesting to show how does this affects the dynamics if we put this into our proposed models. Recently, non-smooth dynamic systems or Filippov systems have been applied widely in many fields of science [31-33], as a result, the dynamical behaviors of the glucose-insulin system could be investigated more clearly once we consider such models. Consequently, to address these with the aim of improving strategies for the treatment of diabetes, such research is planned for the near future and will be reported elsewhere.

Appendix A. Analyzing system (1.2) for Case 1

Now, we investigate the periodic solution of system (2.1). Since the insulin dynamics is linear and not affected by the more frequent glucose infusions, hence the solution of (2.1) is not piecewise-continuous but it is strictly continuous even at $\tau_1, \tau_2, \cdots, \tau_{k_p}$. Therefore, we consider any given time interval $(hT_N, (h+1)T_N]$, where h is a positive integer. Integrating the first equation of system (2.1) from hT_N to $(h+1)T_N$ yields

$$I(t) = I(hT_N^+)exp[-d(t - hT_N)], \quad t \in (hT_N, (h+1)T_N].$$

At time $(h+1)T_N$, then insulin is injected once and

$$I((h+1)T_N^+) = I(hT_N^+)exp[-dT_N] + \sigma.$$

Denote $I_h = I(hT_N^+)$, then we have the following difference equation:

$$I_{h+1} = exp[-dT_N]I_h + \sigma,$$

solving the equation yields a unique steady state:

$$I^* = \frac{\sigma}{1 - exp[-dT_N]}.$$

Clearly, $exp[-dT_N] < 1$, therefore, the system (2.1) has a globally stable T_N periodic solution (denoted by $I^{T_N}(t)$), which can be calculated as follows:

$$I^{T_N}(t) = I^* exp[-d(t - hT_N)], \qquad t \in (hT_N, (h+1)T_N]. \tag{A.1}$$

Substituting $I^{T_N}(t)$ into the first equation of (1.2) for $I(t)$, we have

$$\begin{cases} \dfrac{dG(t)}{dt} = b - (\sigma_2 + ac)G(t) - \dfrac{akG(t)I^{T_N}(t)}{l + I^{T_N}(t)}, & t \neq \tau_n, t \neq \lambda_m, \\ G(\tau_n^+) = G(\tau_n) + G_{in}, & t = \tau_n, \\ G(\lambda_m^+) = G(\lambda_m), & t = \lambda_m, \end{cases} \tag{A.2}$$

Denote $\xi = \sigma_2 + ac$, and then integrating the first equation of system (A.2) from hT_N to $\tau_1 + hT_N$ yields

$$\begin{aligned} G(t) &= G(hT_N^+)exp[-\int_{hT_N^+}^t(\xi + \tfrac{akI^{T_N}(s)}{l+I^{T_N}(s)})ds] \\ &\quad + b\int_{hT_N^+}^t[exp(-\int_u^t(\xi + \tfrac{akI^{T_N}(s)}{l+I^{T_N}(s)})ds)]du \\ &= G(hT_N^+)exp[-\xi(t - hT_N)]exp[-ak\int_{hT_N^+}^t \tfrac{I^{T_N}(s)}{l+I^{T_N}(s)}ds] \\ &\quad + b\int_{hT_N^+}^t\{exp[-\xi(t-u)]exp[-ak\int_u^t \tfrac{I^{T_N}(s)}{l+I^{T_N}(s)}ds]\}du. \end{aligned} \tag{A.3}$$

From system (2.1), when $hT_N^+ \leq b_1 \leq b_2 \leq (\tau_1 + hT_N)$, we have

$$\begin{aligned} exp[-ak\int_{b_1}^{b_2} \tfrac{I^{T_N}(t)}{l+I^{T_N}(t)}dt] &= exp[\tfrac{ak}{d}\int_{b_1}^{b_2} \tfrac{-dI^{T_N}(t)}{l+I^{T_N}(t)}dt] \\ &= exp[\tfrac{ak}{d}\int_{b_1}^{b_2}(\tfrac{d\ln(l+I^{T_N}(t))}{dt})dt] \\ &= exp[\tfrac{ak}{d}\ln(\tfrac{l+I^{T_N}(b_2)}{l+I^{T_N}(b_1)})] \\ &= (\tfrac{l+I^{T_N}(b_2)}{l+I^{T_N}(b_1)})^{\frac{ak}{d}}. \end{aligned} \tag{A.4}$$

From equation (A.3) and (A.4), when $hT_N < t \leq (\tau_1 + hT_N)$, it follows

$$\begin{aligned} G(t) &= G(hT_N^+)exp[-\xi(t - hT_N)](\tfrac{l+I^{T_N}(t)}{l+I^{T_N}(hT_N^+)})^{\frac{ak}{d}} \\ &\quad + b\int_{hT_N^+}^t\{exp[-\xi(t-u)](\tfrac{l+I^{T_N}(t)}{l+I^{T_N}(u)})^{\frac{ak}{d}}\}du \\ &= G(hT_N^+)exp[-\xi(t - hT_N)](\tfrac{l+I^{T_N}(t)}{l+I^{T_N}(hT_N^+)})^{\frac{ak}{d}} \\ &\quad + b(l + I^{T_N}(t))^{\frac{ak}{d}}\int_{hT_N^+}^t \tfrac{exp[-\xi(t-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}}du. \end{aligned}$$

At time $\tau_1 + hT_N$, glucose infusion is applied once and

$$\begin{aligned} G((\tau_1 + hT_N)^+) &= G(hT_N^+)exp(-\xi\Delta_0)(\tfrac{l+I^{T_N}(\tau_1+hT_N)}{l+I^{T_N}(hT_N^+)})^{\frac{ak}{d}} \\ &\quad + b(l + I^{T_N}((\tau_1 + hT_N)^+))^{\frac{ak}{d}}\int_{hT_N^+}^{(\tau_1+hT_N)^+} \tfrac{exp[-\xi(\tau_1+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}}du + G_{in}. \end{aligned}$$

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Again, integrating the first equation of system (A.2) from $\tau_1 + hT_N$ to $\tau_2 + hT_N$ yields

$$
\begin{aligned}
G(t) &= G((\tau_1 + hT_N)^+) exp[-\xi(t - \tau_1 - hT_N)] \left(\frac{l+I^{T_N}(t)}{l+I^{T_N}((\tau_1+hT_N)^+)}\right)^{\frac{ak}{d}} \\
&+ b(l + I^{T_N}(t))^{\frac{ak}{d}} \int_{(\tau_1+hT_N)^+}^t \frac{exp[-\xi(t-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du \\
&= G(hT_N^+) exp[-\xi(\Delta_0 + t - \tau_1 - hT_N)] \left(\frac{l+I^{T_N}(t)}{l+I^{T_N}(hT_N^+)}\right)^{\frac{ak}{d}} \\
&+ b(l + I^{T_N}(t))^{\frac{ak}{d}} \{ exp[-\xi(t - \tau_1 - hT_N)] \int_{hT_N^+}^{(\tau_1+hT_N)^+} \frac{exp[-\xi(\tau_1+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du \\
&+ \int_{(\tau_1+hT_N)^+}^t \frac{exp[-\xi(t-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du \} \\
&+ G_{in} exp[-\xi(t - \tau_1 - hT_N)] \left(\frac{l+I^{T_N}(t)}{l+I^{T_N}((\tau_1+hT_N)^+)}\right)^{\frac{ak}{d}},
\end{aligned}
$$

At time $\tau_2 + hT_N$, glucose is taken up again and it is easy to get $G((\tau_2 + hT_N)^+)$,

$$
\begin{aligned}
G((\tau_2 + hT_N)^+) &= G(hT_N^+) exp[-\xi(\Delta_0 + \Delta_1)] \left(\frac{l+I^{T_N}((\tau_2+hT_N)^+)}{l+I^{T_N}(hT_N^+)}\right)^{\frac{ak}{d}} \\
&+ b(l + I^{T_N}((\tau_2 + hT_N)^+))^{\frac{ak}{d}} \{ exp(-\xi\Delta_1) \int_{hT_N^+}^{(\tau_1+hT_N)^+} \frac{exp[-\xi(\tau_1+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du \\
&+ \int_{(\tau_1+hT_N)^+}^{(\tau_2+hT_N)^+} \frac{exp[-\xi(\tau_2+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du \} + G_{in}[1 + exp(-\xi\Delta_1) \left(\frac{l+I^{T_N}((\tau_2+hT_N)^+)}{l+I^{T_N}((\tau_1+hT_N)^+)}\right)^{\frac{ak}{d}}],
\end{aligned}
$$

by induction, we can see that

$$
\begin{aligned}
G(t) &= G(hT_N^+) exp[-\xi(\sum_{i=0}^{k_p-1} \Delta_i)] exp(t - \tau_{k_p} - hT_N) \left(\frac{l+I^{T_N}(t)}{l+I^{T_N}(hT_N^+)}\right)^{\frac{ak}{d}} \\
&+ b(l + I^{T_N}(t))^{\frac{ak}{d}} A + G_{in} B,
\end{aligned}
$$

for all $t \in (\tau_{k_p} + hT_N, (h+1)T_N]$, where

$$
\begin{aligned}
A &= exp(-\xi \sum_{i=1}^{k_p-1} \Delta_i) exp(-\xi(t - \tau_{k_p} - hT_N)) \int_{hT_N^+}^{(\tau_1+hT_N)^+} \frac{exp[-\xi(\tau_1+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du \\
&+ exp(-\xi \sum_{i=2}^{k_p-1} \Delta_i) exp(-\xi(t - \tau_{k_p} - hT_N)) \int_{(\tau_1+hT_N)^+}^{(\tau_2+hT_N)^+} \frac{exp[-\xi(\tau_2+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du \\
&+ \cdots + \int_{(\tau_{k_p}+hT_N)^+}^t \frac{exp[-\xi(t-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}} du,
\end{aligned}
$$

and

$$B = exp(-\xi \sum_{i=1}^{k_p-1} \Delta_i) exp(-\xi(t-\tau_{k_p}-hT_N))(\frac{l+I^{T_N}(t)}{l+I^{T_N}((\tau_1+hT_N)^+)})^{\frac{ak}{d}}$$
$$+ exp(-\xi \sum_{i=2}^{k_p-1} \Delta_i) exp(-\xi(t-\tau_{k_p}-hT_N))(\frac{l+I^{T_N}(t)}{l+I^{T_N}((\tau_2+hT_N)^+)})^{\frac{ak}{d}}$$
$$+ \cdots + (\frac{l+I^{T_N}(t)}{l+I^{T_N}((\tau_{k_p}+hT_N)^+)})^{\frac{ak}{d}}.$$

At time $(h+1)T_N$, glucose is not taken up, and we get $G((h+1)T_N^+)$,

$$G((h+1)T_N^+) = G(hT_N^+)exp(-\xi T_N)(\frac{l+I^{T_N}((h+1)T_N^+)}{l+I^{T_N}(hT_N^+)})^{\frac{ak}{d}}$$
$$+ b(l+I^{T_N}((h+1)T_N^+))^{\frac{ak}{d}}A_1 + G_{in}B_1,$$

where

$$A_1 = exp(-\xi(T_N-\tau_1)) \int_{hT_N^+}^{(\tau_1+hT_N)^+} \frac{exp[-\xi(\tau_1+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}}du$$
$$+ exp(-\xi(T_N-\tau_2)) \int_{(\tau_1+hT_N)^+}^{(\tau_2+hT_N)^+} \frac{exp[-\xi(\tau_2+hT_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}}du$$
$$+ \cdots + \int_{(\tau_{k_p}+hT_N)^+}^{(h+1)T_N^+} \frac{exp[-\xi((h+1)T_N-u)]}{(l+I^{T_N}(u))^{\frac{ak}{d}}}du,$$

and

$$B_1 = exp(-\xi(T_N-\tau_1))(\frac{l+I^{T_N}((h+1)T_N^+)}{l+I^{T_N}((\tau_1+hT_N)^+)})^{\frac{ak}{d}}$$
$$+ exp(-\xi(T_N-\tau_2))(\frac{l+I^{T_N}((h+1)T_N^+)}{l+I^{T_N}((\tau_2+hT_N)^+)})^{\frac{ak}{d}}$$
$$+ \cdots + (\frac{l+I^{T_N}((h+1)T_N^+)}{l+I^{T_N}((\tau_{k_p}+hT_N)^+)})^{\frac{ak}{d}}.$$

Besides it is easy to see $I^{T_N}(h+1)T_N^+ = I^{T_N}(hT_N^+) = exp[-dT_N]I^* + \sigma$, Denote $G_h = G(hT_N^+)$, then we get the following difference equation:

$$G_{h+1} = G_h exp(-\xi T_N) + b(l+I^{T_N}((h+1)T_N^+))^{\frac{ak}{d}}A_1 + G_{in}B_1, \quad (A.5)$$

where

$$0 < b(l+I^{T_N}((h+1)T_N^+))^{\frac{ak}{d}}A_1 + G_{in}B_1,$$

$$0 < exp(-\xi T_N)\left(\frac{l+I^{T_N}((h+1)T_N^+)}{l+I^{T_N}(hT_N^+)}\right)^{\frac{ak}{d}} = exp(-\xi T_N) < 1,$$

then for equation (A.5) there exists a unique positive steady state

$$G^* = \frac{b(l+exp[-dT_N]I^*+\sigma)^{\frac{ak}{d}}A_1 + G_{in}B_1}{1-exp(-\xi T_N)},$$

24

consequently, the subsystem (A.2) has a globally stable T_N periodic solution (denote by G^{T_N}), which can be calculated as follows:

$$G^{T_N}(t) = \begin{cases} G_1(t), & t \in (hT_N, \tau_1 + hT_N], \\ G_2(t), t \in (\tau_1 + hT_N, \tau_2 + hT_N], \\ \vdots \\ G_{k_p+1}(t), t \in (\tau_{k_p} + hT_N, (h+1)T_N], \end{cases} \tag{A.6}$$

where

$$\begin{aligned} G_1(t) &= G^* exp[-\xi(t - hT_N)] \left(\frac{l + I^{T_N}(t)}{l + I^{T_N}(hT_N^+)} \right)^{\frac{ak}{d}} \\ &+ b(l + I^{T_N}(t))^{\frac{ak}{d}} \int_{hT_N^+}^t \frac{exp[-\xi(t-u)]}{(l + I^{T_N}(u))^{\frac{ak}{d}}} du, \end{aligned}$$

$$\begin{aligned} G_2(t) &= G^* exp[-\xi(\Delta_0 + t - \tau_1 - hT_N)] \left(\frac{l + I^{T_N}(t)}{l + I^{T_N}(hT_N^+)} \right)^{\frac{ak}{d}} \\ &+ b(l + I^{T_N}(t))^{\frac{ak}{d}} \left\{ exp[-\xi(t - \tau_1 - hT_N)] \int_{hT_N^+}^{(\tau_1 + hT_N)^+} \frac{exp[-\xi(\tau_1 + hT_N - u)]}{(l + I^{T_N}(u))^{\frac{ak}{d}}} du \right. \\ &\left. + \int_{(\tau_1 + hT_N)^+}^t \frac{exp[-\xi(t-u)]}{(l + I^{T_N}(u))^{\frac{ak}{d}}} du \right\} \\ &+ G_{in} exp[-\xi(t - \tau_1 - hT_N)] \left(\frac{l + I^{T_N}(t)}{l + I^{T_N}((\tau_1 + hT_N)^+)} \right)^{\frac{ak}{d}}, \end{aligned}$$

and

$$\begin{aligned} G_{k_p+1}(t) &= G^* exp[-\xi(\sum_{i=0}^{k_p - 1} \Delta_i)] exp(t - \tau_{k_p} - hT_N) \left(\frac{l + I^{T_N}(t)}{l + I^{T_N}(hT_N^+)} \right)^{\frac{ak}{d}} \\ &+ b(l + I^{T_N}(t))^{\frac{ak}{d}} A + G_{in} B. \end{aligned}$$

Appendix B. Analyzing system (1.2) for Case 2

Here, we investigate the periodic solution of subsystem (2.4). We consider any given time interval $(hT_p, (h+1)T_p]$, where h is a positive integer. Integrating the first equation of system (2.4) from hT_p to $\lambda_1 + hT_p$ yields

$$I(t) = I(hT_p^+) exp[-d(t - hT_p)], \quad t \in (hT_p, \lambda_1 + hT_p].$$

At time $\lambda_1 + hT_p$, insulin injection occurs and

$$I((\lambda_1 + hT_p)^+) = I(hT_p^+) exp(-d\lambda_1) + \sigma = I(hT_p^+) exp(-d\Delta_0) + \sigma.$$

Similarly, integrating the first equation of model (2.4) from $\lambda_1 + hT_p$ to $\lambda_2 + hT_p$ yields

$$\begin{aligned} I(t) &= I((\lambda_1 + hT_p)^+) exp[-d(t - \lambda_1 - hT_p)] \\ &= (I(hT_p^+) exp(-d\Delta_0) + \sigma) exp[-d(t - \lambda_1 - hT_p)], \end{aligned}$$

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where $t \in (\lambda_1 + hT_p, \lambda_2 + hT_p]$. And at time $\lambda_2 + hT_p$, insulin injection occurs again and

$$
\begin{aligned}
I((\lambda_2 + hT_p)^+) &= I((\lambda_1 + hT_p)^+)exp[-d\Delta_1] + \sigma \\
&= I(hT_p^+)exp[-d(\Delta_0 + \Delta_1)] + \sigma exp(-d\Delta_1) + \sigma,
\end{aligned}
$$

By induction, we can see that

$$
I(t) = \{I(hT_p^+)exp[-d(\sum_{i=1}^{k_N-1}\Delta_i)] + C\}exp[-d(t - \lambda_{k_N} - hT_p)],
$$

for all $t \in (\lambda_{k_N} + hT_p, (h+1)T_p]$, and denote $C = \sigma[exp(-d(\sum_{i=1}^{k_N-2}\Delta_i) + exp(-d\sum_{j=2}^{k_N-2}\Delta_j) + \cdots + exp(-d\Delta_{k_N-2})]$. At time $(h+1)T_p$, there is no insulin injected and

$$
\begin{aligned}
I((h+1)T_p^+) &= I(hT_p^+)exp[-dT_p] + \sigma[exp(-d(\sum_{i=1}^{k_N-1}\Delta_i) \\
&\quad + exp(-d\sum_{j=2}^{k_N-1}\Delta_j) + \cdots + exp(-d\Delta_{k_N-1})] \\
&= I(hT_p^+)exp[-dT_p] + C_1.
\end{aligned}
$$

Denote $I_h = I(hT_p^+)$, then we have the following differential equation:

$$
I_{h+1} = exp[-dT_p]I_h + C_1,
$$

solving the equation yields a unique positive steady state:

$$
I^* = \frac{C_1}{1 - exp[-dT_p]}.
$$

Clearly, $C_1 > 0$ and $exp[-dT_p] < 1$ always holds, therefore, system (2.4) has a globally stable T_p periodic solution (denoted by $I^{T_p}(t)$), which can be calculated as follows:

$$
I^{T_p}(t) = \begin{cases}
I^*exp[-d(t - hT_p)], & t \in (hT_p, \lambda_1 + hT_p], \\
(I^*exp(-d\Delta_0) + \sigma)exp[-d(t - \lambda_1 - hT_p)], \\
t \in (\lambda_1 + hT_p, \lambda_2 + hT_p], \\
\vdots \\
\{I^*exp[-d(\sum_{i=1}^{k_N-1}\Delta_i)] + C\}exp[-d(t - \lambda_{k_N} - hT_p)], \\
t \in (\lambda_{k_N} + hT_p, (h+1)T_p],
\end{cases} \tag{B.1}
$$

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Substituting $I^{T_p}(t)$ into the first equation of (1.2) for $I(t)$, we have

$$\begin{cases} \dfrac{dG(t)}{dt} = b - (\sigma_2 + ac)G(t) - \dfrac{akG(t)I^{T_p}(t)}{l + I^{T_p}(t)}, & t \neq \tau_n, t \neq \lambda_m, \\ G(\lambda_m^+) = G(\lambda_m), & t = \lambda_m, \\ G(\tau_n^+) = G(\tau_n) + G_{in}, & t = \tau_n, \end{cases} \quad (B.2)$$

then integrating the first equation of (B.2) from hT_p to $\lambda_1 + hT_p$ yields

$$\begin{aligned} G(t) = {}& G(hT_p^+)exp[-\xi(t - hT_p)](\tfrac{l+I^{T_p}(t)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}} \\ & + b(l + I^{T_p}(t))^{\frac{ak}{d}} \int_{hT_p^+}^{t} \tfrac{exp[-\xi(t-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du. \end{aligned}$$

obviously,

$$\begin{aligned} G((\lambda_1 + hT_p)^+) = {}& G(hT_p^+)exp(-\xi\Delta_0)(\tfrac{l+I^{T_p}(\lambda_1+hT_p)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}} \\ & + b(l + I^{T_p}((\lambda_1 + hT_p)^+))^{\frac{ak}{d}} \int_{hT_p^+}^{(\lambda_1+hT_p)^+} \tfrac{exp[-\xi(\lambda_1+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du. \end{aligned}$$

Again, integrating the first equation of (B.2) from $\lambda_1 + hT_p$ to $\lambda_2 + hT_p$ yields

$$\begin{aligned} G(t) = {}& G((\lambda_1 + hT_p)^+)exp[-\xi(t - \lambda_1 - hT_p)](\tfrac{l+I^{T_p}(t)}{l+I^{T_p}((\lambda_1+hT_p)^+)})^{\frac{ak}{d}} \\ & + b(l + I^{T_p}(t))^{\frac{ak}{d}} \int_{(\lambda_1+hT_p)^+}^{t} \tfrac{exp[-\xi(t-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du \\ = {}& G(hT_p^+)exp[-\xi(\Delta_0 + t - \lambda_1 - hT_p)](\tfrac{l+I^{T_p}(t)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}} \\ & + b(l + I^{T_p}(t))^{\frac{ak}{d}} \{ exp[-\xi(t - \lambda_1 - hT_p)] \int_{hT_p^+}^{(\lambda_1+hT_p)^+} \tfrac{exp[-\xi(\lambda_1+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du \\ & + \int_{(\lambda_1+hT_p)^+}^{t} \tfrac{exp[-\xi(t-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du \}, \end{aligned}$$

at time $\lambda_2 + hT_p$, it is easy to get $G((\lambda_2 + hT_p)^+)$,

$$\begin{aligned} G((\lambda_2 + hT_p)^+) = {}& G(hT_p^+)exp[-\xi(\Delta_0 + \Delta_1)](\tfrac{l+I^{T_p}((\lambda_2+hT_p)^+)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}} \\ & + b(l + I^{T_p}((\lambda_2 + hT_p)^+))^{\frac{ak}{d}} \{ exp(-\xi\Delta_1) \int_{hT_p^+}^{(\lambda_1+hT_p)^+} \tfrac{exp[-\xi(\lambda_1+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du \\ & + \int_{(\lambda_1+hT_p)^+}^{(\lambda_2+hT_p)^+} \tfrac{exp[-\xi(\lambda_2+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du \}. \end{aligned}$$

By induction, we can see that

$$\begin{aligned} G(t) = {}& G(hT_p^+)exp[-\xi(\sum_{i=0}^{k_N-1} \Delta_i)]exp(t - \lambda_{k_N} - hT_p)(\tfrac{l+I^{T_p}(t)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}} \\ & + b(l + I^{T_p}(t))^{\frac{ak}{d}} D, \end{aligned}$$

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for all $t \in (\lambda_{k_N} + hT_p, (h+1)T_p]$, where

$$D = exp(-\xi \sum_{i=1}^{k_N-1} \Delta_i) exp(-\xi(t - \lambda_{k_N} - hT_p)) \int_{hT_p^+}^{(\lambda_1+hT_p)^+} \frac{exp[-\xi(\lambda_1+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du$$
$$+ exp(-\xi \sum_{i=2}^{k_N-1} \Delta_i) exp(-\xi(t - \lambda_{k_N} - hT_p)) \int_{(\lambda_1+hT_p)^+}^{(\lambda_2+hT_p)^+} \frac{exp[-\xi(\lambda_2+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du$$
$$+ \cdots + \int_{(\lambda_{k_N}+hT_p)^+}^{t} \frac{exp[-\xi(t-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du,$$

At time $(h+1)T_p$, glucose is taken up once, and we get

$$G((h+1)T_p^+) = G(hT_p^+)exp(-\xi T_p)(\frac{l+I^{T_p}((h+1)T_p^+)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}}$$
$$+ b(l + I^{T_p}((h+1)T_p^+))^{\frac{ak}{d}} D_1 + G_{in},$$

where

$$D_1 = exp(-\xi(T_p - \lambda_1)) \int_{hT_p^+}^{(\lambda_1+hT_p)^+} \frac{exp[-\xi(\lambda_1+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du$$
$$+ exp(-\xi(T_p - \lambda_2)) \int_{(\lambda_1+hT_p)^+}^{(\lambda_2+hT_p)^+} \frac{exp[-\xi(\lambda_2+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du$$
$$+ \cdots + \int_{(\lambda_{k_N}+hT_p)^+}^{(h+1)T_p^+} \frac{exp[-\xi((h+1)T_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du.$$

Denote $G_h = G(hT_p^+)$, then we get the following difference equation:

$$G_{h+1} = G_h exp(-\xi T_p)(\frac{l+I^{T_p}((h+1)T_p^+)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}}$$
$$+ b(l + I^{T_p}((h+1)T_p^+))^{\frac{ak}{d}} D_1 + G_{in}, \tag{B.3}$$

where

$$0 < b(l + I^{T_p}((h+1)T_p^+))^{\frac{ak}{d}} D_1 + G_{in},$$

$$0 < exp(-\xi T_p) \left(\frac{l + I^{T_p}((h+1)T_p^+)}{l + I^{T_p}(hT_p^+)} \right)^{\frac{ak}{d}} < 1.$$

Then for equation (B.3) there exists a unique steady state

$$G^* = \frac{b(l + I^{T_p}((h+1)T_p^+))^{\frac{ak}{d}} D_1 + G_{in}}{1 - exp(-\xi T_p)(\frac{l+I^{T_p}((h+1)T_p^+)}{l+I^{T_p}(hT_p^+)})^{\frac{ak}{d}}},$$

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consequently, the subsystem (B.2) has a globally stable T_p periodic solution (denote by G^{T_p}), which can be calculated as follows:

$$G^{T_p}(t) = \begin{cases} G_1^1(t), & t \in (hT_p, \lambda_1 + hT_p], \\ G_2^1(t), t \in (\lambda_1 + hT_p, \lambda_2 + hT_p], \\ \vdots \\ G_{k_N+1}^1(t), t \in (\lambda_{k_N} + hT_p, (h+1)T_p], \end{cases} \tag{B.4}$$

where

$$\begin{aligned} G_1^1(t) &= G^* exp[-\xi(t - hT_p)] \left(\frac{l+I^{T_p}(t)}{l+I^{T_p}(hT_p^+)}\right)^{\frac{ak}{d}} \\ &\quad + b(l + I^{T_p}(t))^{\frac{ak}{d}} \int_{hT_p^+}^t \frac{exp[-\xi(t-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du, \end{aligned}$$

$$\begin{aligned} G_2^1(t) &= G^* exp[-\xi(\Delta_0 + t - \lambda_1 - hT_p)] \left(\frac{l+I^{T_p}(t)}{l+I^{T_p}(hT_p^+)}\right)^{\frac{ak}{d}} \\ &+ b(l + I^{T_p}(t))^{\frac{ak}{d}} \{exp[-\xi(t - \lambda_1 - hT_p)] \int_{hT_p^+}^{(\lambda_1+hT_p)^+} \frac{exp[-\xi(\lambda_1+hT_p-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du \\ &+ \int_{(\lambda_1+hT_p)^+}^t \frac{exp[-\xi(t-u)]}{(l+I^{T_p}(u))^{\frac{ak}{d}}} du\} \end{aligned}$$

and

$$\begin{aligned} G_{k_N+1}^1(t) &= G^* exp[-\xi(\sum_{i=0}^{k_N-1} \Delta_i)] exp(t - \lambda_{k_N} - hT_p) \left(\frac{l+I^{T_p}(t)}{l+I^{T_p}(hT_p^+)}\right)^{\frac{ak}{d}} \\ &\quad + b(l + I^{T_p}(t))^{\frac{ak}{d}} D. \end{aligned}$$

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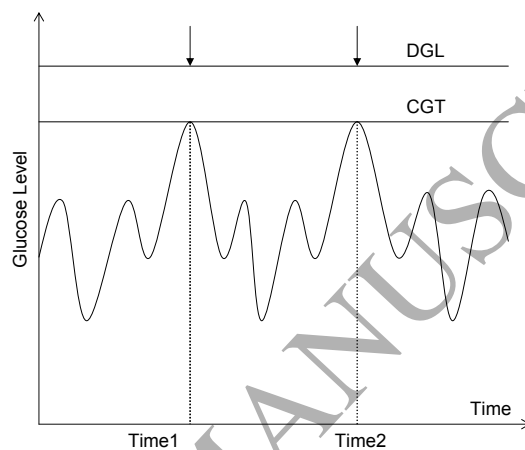
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Figure Legends

Figure 1: Dangerous glucose level (DGL)=lowest blood level that will cause harm to patients. Critical glucose threshold (CGT)= blood glucose level at which insulin should be injected to prevent an increasing blood glucose concentration from reaching the dangerous glucose level for patients. The arrows indicate points when the blood glucose levels exceed the critical glucose threshold and an insulin therapy method would be applied.
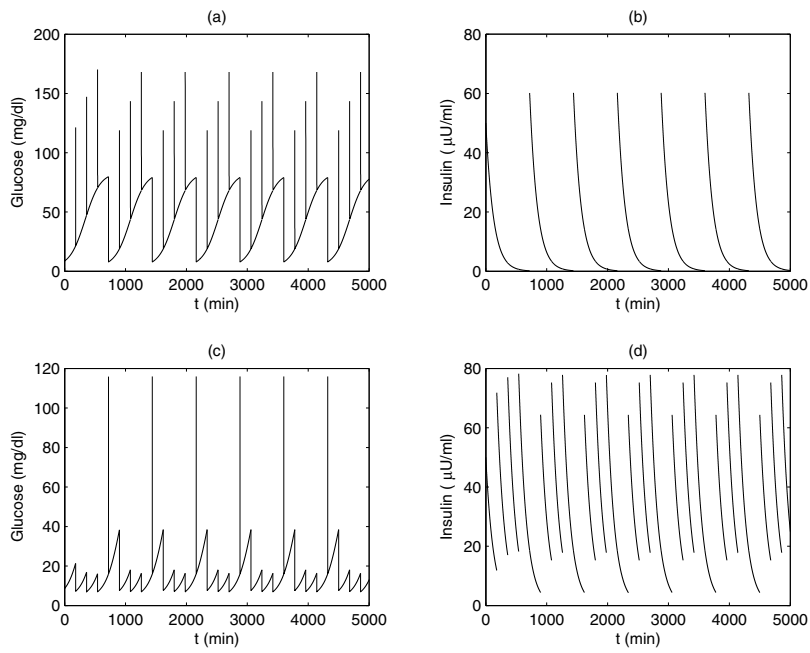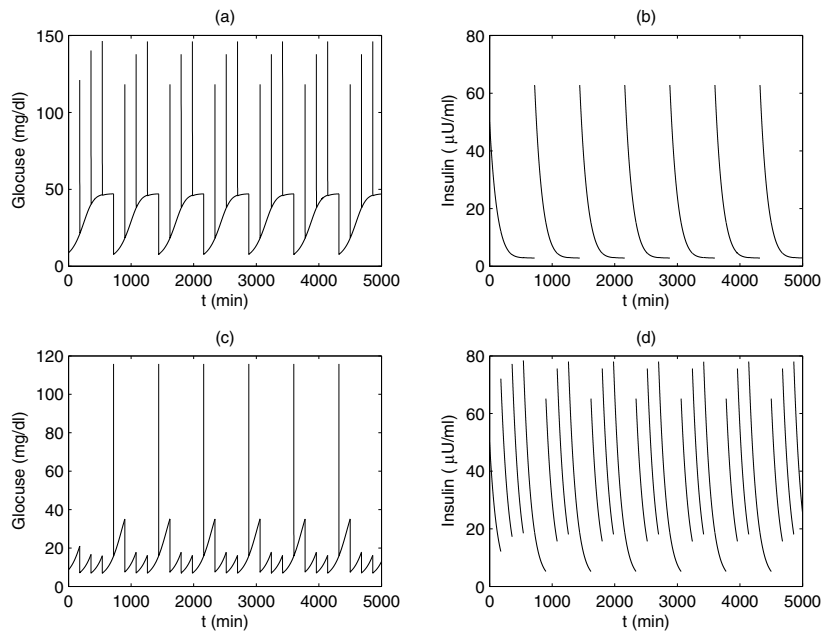
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Figure 2: Numerical results for type 1 diabetes of system (1.2). (a) and (b) for Case 1 with $\sigma = 60\mu U$, $G_{in} = 100mg$, $k_p = 3$, $T_N = 720min$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$ and $\Delta_i = \Delta$. (a) Glucose profile with three glucose infusions within an insulin injection period, (b) Insulin profile with three glucose infusions within an insulin injection period. (c) and (d) for Case 2 with $\sigma = 60\mu U$, $G_{in} = 100mg$, $k_N = 3$, $T_p = 720min$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$ and $\Delta_i = \Delta$. (c) Glucose profile with three insulin injections within an glucose infusion period, (d) Insulin profile with three insulin injections within a glucose infusion period.

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Figure 3: Numerical results for type 2 diabetes of system (1.2). (a) and (b) for Case 1 with $\sigma = 60\mu U$, $G_{in} = 100mg$, $k_p = 3$, $T_p = 720min$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$ and $\Delta_i = \Delta$. (a) Glucose profile with three glucose infusions within an insulin injection period, (b) Insulin profile with three insulin injections within a glucose infusion period. (c) and (d) for Case 2 with $\sigma = 60\mu U$, $G_{in} = 100mg$, $k_N = 3$, $T_p = 720min$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$ and $\Delta_i = \Delta$. (c) Glucose profile with three insulin injections within a glucose infusion period, (d) Insulin profile with three insulin injections within a glucose infusion period.
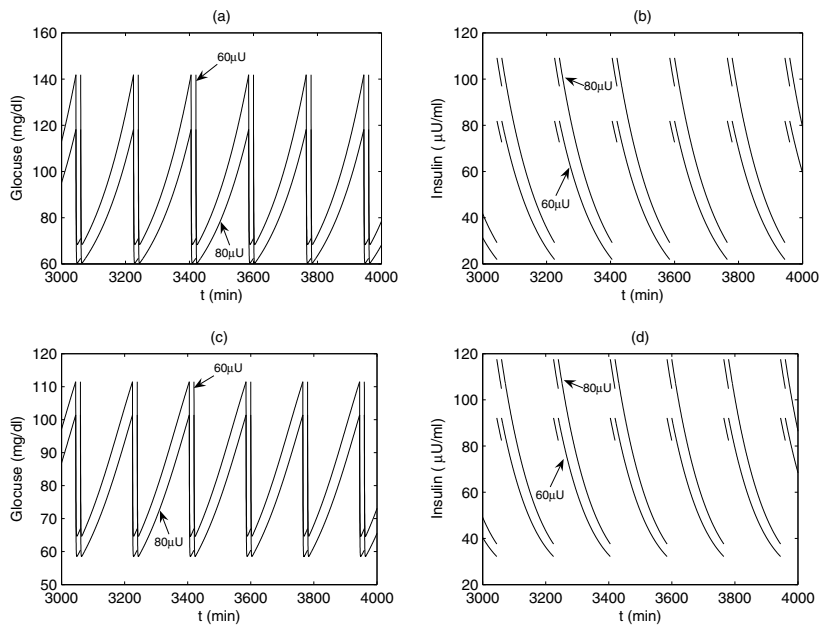
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Figure 4: Numerical results of system (1.2). (a) and (b) for type 1 diabetes with $G_{in} = 100mg$, $T_N = 165min$, $T_p = 180min$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$, and $\Delta_i = \Delta$. (a) Glucose profile with insulin injections $15min$ before uptakes of glucose, (b) Insulin profile with insulin injections $15min$ before uptakes of glucose. (c) and (d) for type 2 diabetes with $G_{in} = 100mg$, $T_N = 165min$, $T_p = 180min$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$ and $\Delta_i = \Delta$. (a) Glucose profile with insulin injections $15min$ before uptakes of glucose, (b) Insulin profile with insulin injections $15min$ before uptakes of glucose.
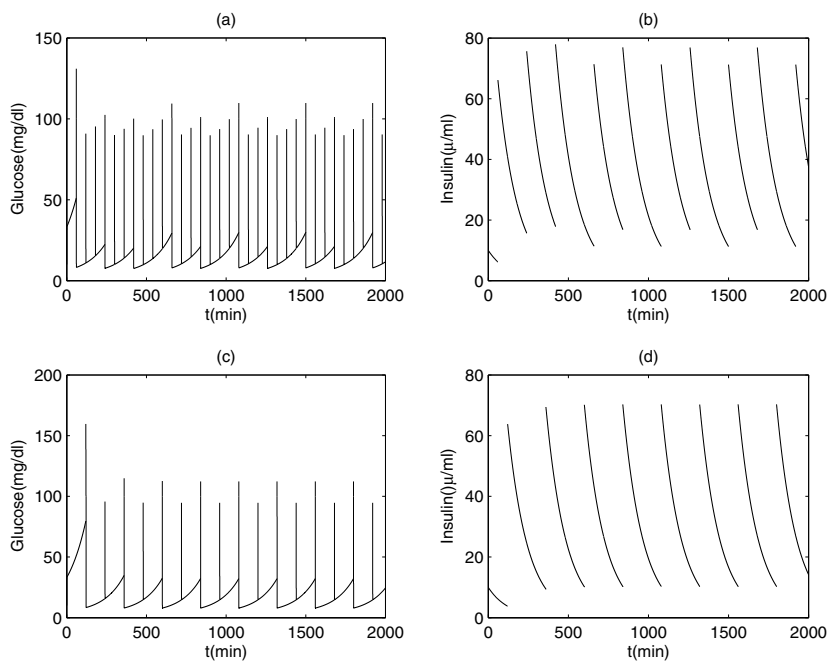
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Figure 5: Numerical results for type 1 diabetes of system (1.3) with $\sigma = 60\mu U$, $G_{in} = 80mg$, $G_C = 100mg/dl$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$, $T = 60min$ for (a) and (b), $T = 120min$ for (c) and (d). (a) and (c) Glucose profile with insulin therapy, (b) and (d) Insulin profile with insulin therapy.
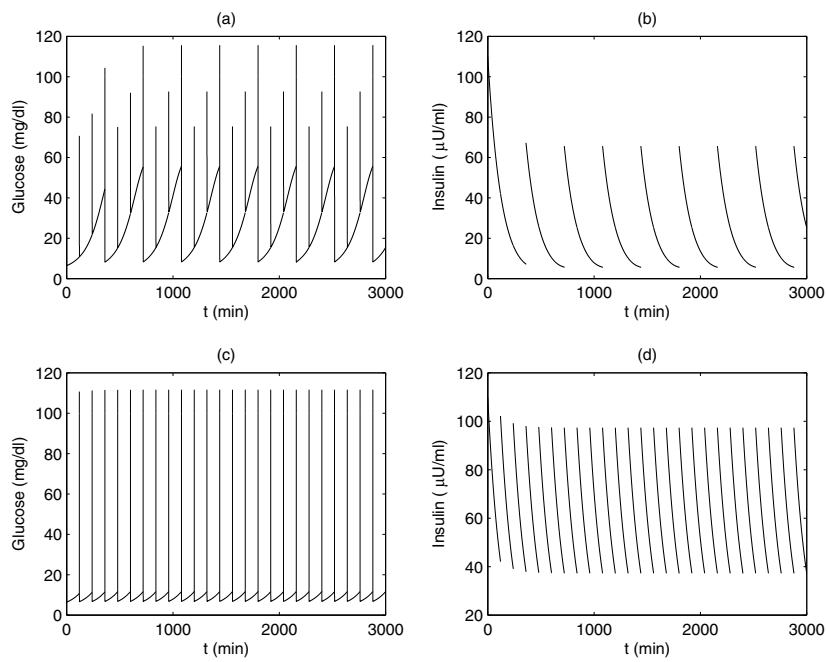
Figure 6: Numerical results for type 2 diabetes of system (1.3) with $\sigma = 60\mu U$, $T = 120min$, $G_C = 100mg/dl$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$, $G_{in} = 60mg$ for (a) and (b), $G_{in} = 100mg$ for (c) and (d). (a) and (c) Glucose profile with insulin therapy, (b) and (d) Insulin profile with insulin therapy.
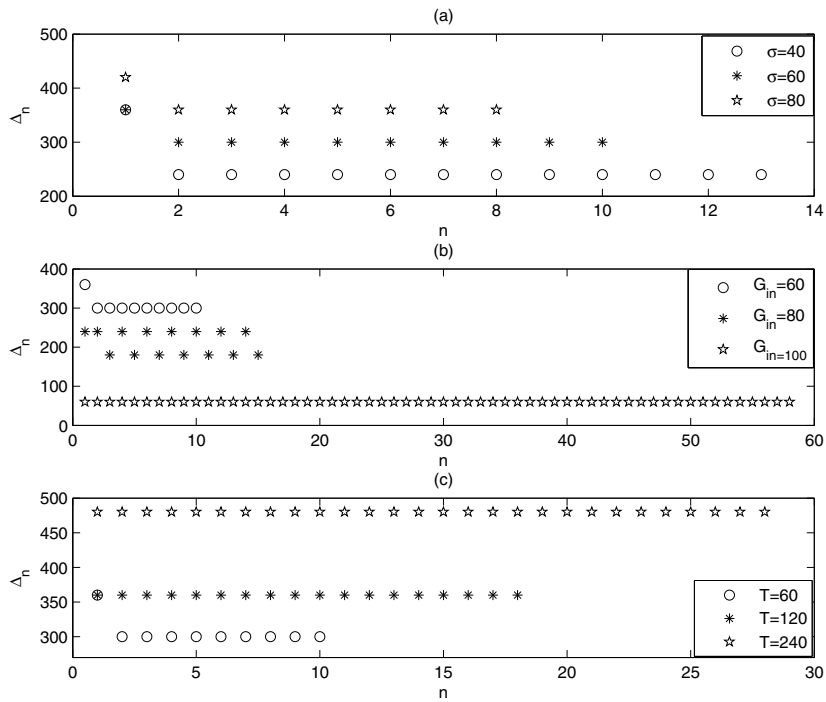
Figure 7: The effects of control parameters σ, G_{in} and T on the number of n and period Δ_n for type 2 diabetes of system (1.3). The baseline parameter values are as follows: $\sigma = 60\mu U$, $T = 60min$, $G_C = 60mg/dl$, $G_0 = 100mg/dl$, $I_0 = 50\mu U/ml$, other parameters are fixed in Table 2.1. Here we run the model (1.3) from 0 to 1000 and plot the effects of the injection dose of insulin σ on the number of n and period Δ_n in (a), glucose infusion rate G_{in} in (b) and glucose infusion period T in (c).