International Journal of Biomathematics
Vol. 7, No. 4 (2014) 1450035 (21 pages)

DOI: 10.1142/S1793524514500351

World Scientific
www.worldscientific.com

Modeling and qualitative analysis of diabetes therapies with state feedback control

Mingzhan Huang*,† and Xinyu Song*,‡

*College of Mathematics and Information Science
Xinyang Normal University, Xinyang 464000, P. R. China

†Research Institute of Forest Resource Information Techniques
Chinese Academy of Forestry, Beijing 100091, P. R. China
‡xysong88@163.com

Received 6 September 2013
Accepted 24 March 2014
Published 7 May 2014

For the therapies of diabetes mellitus, a novel mathematical model with two state impulses: impulsive injection of insulin and impulsive injection of glucagon, is proposed. To avoid hypoglycemia and hyperglycemia, the injections of insulin and glucagon are determined by closely monitoring the plasma glucose level of the patients. By using differential equation geometry theory, the existence of periodic solution and the attraction region of the system have been obtained, which ensures that injections in such an automated way can keep the blood glucose concentration under control. The simulation results verify that the better insulin injection strategy in closed-loop control is a larger dose but longer interval rather than a smaller dose but shorter interval. Besides, our numerical analysis reveals that medicine studies and practice that slow down the insulin degradation are helpful for the plasma glucose control. Our findings can provide significant guidance in both design of artificial pancreas and clinical treatment.

Keywords: Glucose–insulin system; state impulse; periodic solution; successor function.

Mathematics Subject Classification 2010: 92C50, 34C60, 92D25

1. Introduction

With the economic development and the improvement of people's life, diabetes is becoming more common almost everywhere in the world. Diabetes is a metabolism disorder of the glucose–insulin regulatory system. It is mainly caused by the fact that either the pancreas do not release or release little insulin (the case is classified as type 1 diabetes), or the glucose cannot be transported out of the blood because of body cells' inefficient use of insulin (the case is classified as type 2 diabetes).

‡Corresponding author.

If one's body does not have enough insulin in the plasma or the body cells cannot utilize insulin sufficiently to uptake glucose, his or her plasma glucose level will remain dangerously high, that is to say, he or she will develop diabetes mellitus. Over the past decades, extensive research work has been done in studying how to provide better treatments to diabetic patients [8, 24, 26].

The most typical diagnostic in diabetes is hyperglycemia, and the common treatment regimen is injecting insulin subcutaneously either daily or continuously. Nowadays, insulin pump, a medical device for administration of insulin, is popularly used in continuous subcutaneous insulin infusion (CSII) therapy for both types 1 and 2 diabetes [3, 9, 16, 19, 20]. All insulin pumps used by diabetics treatment follow the so-called *open loop* approach, that is, insulin is injected without knowledge of plasma glucose level [12]. A patient using insulin pump has to inject insulin manually before or after meal ingestion to avoid hyperglycemia, and the dose has to be carefully computed based on the carbohydrate to be ingested [12]. But there are a lot of difficulties for common people to do that. On the one hand, not all the food people buy mark the carbohydrate content in their instruction, so a diabetic does not know exactly how much carbohydrate he or she intakes; on the other hand, because of low educational level, many diabetics cannot complete the transformation between the amount of carbohydrate and the dose of insulin injection correctly. So two risks in the open-loop control are hypoglycemia and hyperglycemia, which are caused by insulin over-dosing and under-dosing, respectively.

Besides, critically ill patients in Intensive Care Unit (ICU) are extremely diverse in the causes and dynamics of their hyperglycemia [8]. As a result, their response to an insulin injection or a glucose input can vary significantly and hyperglycemia and hypoglycemia often occur at the same time. Hypoglycemia also occurs when a senior patient or other elderly person with diabetes misses a meal or snack. Compared with hyperglycemia, hypoglycemia is even more dangerous for the patients. Severe hypoglycemia can cause fainting and brain damage, in some cases, may lead to quick and unexpected deaths. A treatment option to this emergency is to inject an amount glucagon subcutaneously or intramuscularly. This medication acts by mobilizing glucose from glycogen stores in the liver. It works quickly, raising blood glucose within several minutes [11].

To avoid the episodes of hyperglycemia and hypoglycemia simultaneously, also to improve the life styles of the patients whose daily routine is severely disrupted by the above therapy regimen, researchers have made great efforts to close the *open loop*, that is, to develop an artificial pancreas [12, 21, 22]. Artificial pancreas or closed-loop control of glucose level in diabetes is an integrated system consisting of a reliable real time glucose monitor, a control algorithm and an injection device, e.g. insulin pump. As a controller, artificial pancreas can substitute the endocrine functionality of a real and healthy pancreas for diabetic patients and automatically keep their plasma glucose level under control. The control algorithm can be either empirical- or model-based. Although artificial pancreas is still in development, the

research about it has attracted lots of attentions and considerable work has been done [1, 2, 4, 10, 12].

In this paper, we will try to propose a new model to simulate the impulsive insulin injection and glucagon injection in closed-loop control in view of the feedback from glucose monitoring system, then study the model analytically and numerically.

In [12], Huang *et al.* extended the model proposed by Li *et al.* [14] and Li and Kuang [13], incorporated impulsive injection of exogenous insulin in view of the feedback from the glucose monitoring system, and proposed the following system:

$$\begin{cases} \left.\begin{aligned} \frac{dG(t)}{dt} &= G_{\text{in}} - \sigma_2 G - a\left(c + \frac{mI}{n+I}\right)G + b, \\ \frac{dI(t)}{dt} &= \frac{\sigma_1 G^2}{\alpha_1^2 + G^2} - d_i I(t), \end{aligned}\right\} & G < L_G \quad \text{or} \quad I > I_C, \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \sigma, \end{aligned}\right\} & G = L_G \quad \text{and} \quad I \le I_C, \end{cases} \tag{1}$$

with initial condition $G(0) = G_0 \le L_G$, $I(0) = I_0$, where $G(t)$ and $I(t)$ represent the plasma glucose concentration and insulin concentration at time $t \ge 0$, respectively. G_{in} represents the constant glucose exogenous infusion, $\sigma_2 G(t)$ and $aG\left(c + \frac{mI(t)}{k+I(t)}\right)$ stand for the insulin-independent and insulin-dependent glucose consumption respectively, and $b > 0$ is the hepatic glucose production rate. The term $\frac{\sigma_1 G^2(t)}{\alpha_1^2 + G^2(t)}$ is the insulin secretion stimulated by elevated glucose concentration, and $d_i I$ indicates the insulin degradation with $d_i > 0$ as a constant degradation rate. Here, $\sigma_1, \sigma_2, \alpha_1, a, c, m$ and k are positive constants. Parameter $\sigma(\mu\text{U/ml}) > 0$ is the dose in each injection. The constant $I_C = nk_1/(m - k_1), k_1 = a^{-1}L_G^{-1}(G_{\text{in}} + b - \sigma_2 L_G) - c$, which is determined by the intersection of the null-cline $G_{\text{in}} - \sigma_2 G - a\left(c + \frac{mI}{n+I}\right)G + b = 0$ and the horizontal line $G = L_G$. L_G is an adjustable constant threshold value: when the glucose level reaches the threshold value, which implies hyperglycemia occurs, the impulsive inject of insulin with dose σ (μU/ml) shall be performed.

As mentioned in [12], two critical and harmful episodes in therapies of insulin administration are hypoglycemia and hyperglycemia. Clearly, in system (1), the threshold value L_G can keep the glucose level not too high, that is, avoid the episode of hyperglycemia. But the system did not pay as much attention to the possible occurrence of hypoglycemia. In order to avoid hyperglycemia in diabetes therapies, we must carefully determine correct dose and right timing of insulin injection. Also, when the glucose level from the feedback of the glucose monitoring system is too low, that is to say, hypoglycemia occurs, we must carefully determine correct dose and right timing of glucagon injection. For the sake of simplicity, we suppose the transformation between the glucagon injection dose and the change of

plasma glucose concentration is a function expression

$$y = f(x),$$

that is, when a diabetic with symptoms of hypoglycemia is injected glucagon with dose $x(\mu\text{U/ml})$, the glucose concentration will increase by $y(\text{mg/dl})$.

Motivated by the work of [6, 12], we propose the glucose–insulin system with two state impulses: impulsive injection of insulin and impulsive injection of glucagon, as follows:

$$\begin{cases} \left.\begin{aligned} \frac{dG(t)}{dt} &= G_{\text{in}} - \sigma_2 G - a\left(c + \frac{mI}{n+I}\right)G + b, \\ \frac{dI(t)}{dt} &= \frac{\sigma_1 G^2}{\alpha_1^2 + G^2} - d_i I(t), \end{aligned}\right\} & \{L_A < G < L_G\} \quad \text{or} \\ & \{G = L_G \text{ and } I > I_C\}, \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \sigma, \end{aligned}\right\} & G = L_G \quad \text{and} \quad I \le I_C, \\ \left.\begin{aligned} G(t^+) &= G(t) + g_{in}, \\ I(t^+) &= I(t), \end{aligned}\right\} & G = L_A, \end{cases} \tag{2}$$

with initial condition $L_A < G(0) = G_0 \le L_G, 0 < I(0) = I_0$, where L_G and L_A are adjustable constant threshold value for glucose level: when the glucose level reaches or passes the threshold value L_G, which means the occurrence of hyperglycemia, the impulsive injection of insulin with dose $\sigma(\mu\text{U/ml})$ shall be performed, and it is easy to see that the glucose level must decrease when the insulin level surpass the point I_C; when the glucose level reduces to the threshold value L_A, which means the occurrence of hypoglycemia, the impulsive injection of glucagon with dose σ_0 $(\mu\text{U/ml})$ can be performed, for simplicity, we directly denote the glucose level impulsively increase by $g_{\text{in}}(\text{mg/dl})$, where $g_{\text{in}} = f(\sigma_0)$.

In this paper, we mainly discuss the dynamics properties of the system (2). The paper is organized as follows. In Sec. 2, some notation and definitions of the geometric theory of semi-continuous dynamical systems are provided. In Sec. 3, we mainly discuss the existence of the periodic solutions and the attraction region of the system by differential equation geometry theory. The paper ends with some discussions and numerical simulations in Sec. 4, which not only confirm the theoretical results, but also are complementary to those theoretical results with specific features.

2. Preliminaries

In this section, we give some notation and definitions of the geometric theory of semi-continuous dynamical systems which will be useful for the following discussions.

Definition 1 ([5]). Consider the state-dependent impulsive differential equations

$$\begin{cases} \left.\begin{aligned} \frac{dx}{dt} &= \bar{P}(x,y), \\ \frac{dy}{dt} &= \bar{Q}(x,y), \end{aligned}\right\} & (x,y) \notin M\{x,y\}, \\ \left.\begin{aligned} \triangle x &= \alpha(x,y), \\ \triangle y &= \beta(x,y), \end{aligned}\right\} & (x,y) \in M\{x,y\}. \end{cases} \tag{3}$$

We define the dynamic system consisting of the solution mappings of the system (3) a semi-continuous dynamical system, denoted as (Ω, f, φ, M). We require that the initial point P of the system (3) should not be in the set $M\{x,y\}$, that is $P \in \Omega = R_+^2 \backslash M\{x,y\}$, and the function φ is a continuous mapping that satisfies $\varphi(M) = N$. Here φ is called the impulse mapping, where $M\{x,y\}$ and $N\{x,y\}$ represent the straight lines or curves in the plane R_+^2, $M\{x,y\}$ is called the impulse set, and $N\{x,y\}$ is called the phase set.

Remark 1. For the system (2), there are two state impulses. The first impulse set can be written as $M_1 = \{(I,G) : G = L_G \text{ and } 0 < I \leq I_C\}$ and for any $(I,G) \in M_1$, we have $\varphi_1(I,G) = (I + k\sigma, G)$, where k is an integer such that $I + k\sigma > I_C$, $I + (k-1)\sigma \leq I_C$, that is to say, the phase set corresponding to the first impulse can be written as $N_1 = \{(I,G) : G = L_G \text{ and } I_C < I \leq I_C + \sigma\}$. The second impulse set can be written as $M_2 = \{(I,G) : I > 0, G = L_A\}$, and for any $(I,G) \in M_2$, we have $\varphi_2(I,G) = (I, G + g_{\text{in}})$, that is to say, the phase set corresponding to the second impulse can be written as $N_2 = \{(I,G) : I > 0, G = L_A + g_{in}\}$.

Definition 2 ([5]). For the semi-continuous dynamical system defined by the state-dependent impulsive differential equations (3), the solution mapping $f(P,t) : \Omega \to \Omega$ consists of two parts:

(1) Let $\pi(P,t)$ denote the Poincaré mapping with the initial point P of the following system

$$\begin{cases} \frac{dx}{dt} = \bar{P}(x,y), \\ \frac{dy}{dt} = \bar{Q}(x,y). \end{cases}$$

If $f(P,t) \cap M\{x,y\} = \emptyset$, then $f(P,t) = \pi(P,t)$.

(2) If there exists a time point T_1 such that $f(P,T_1) = H \in M\{x,y\}$, $\varphi(H) = \varphi(f(P,T_1)) = P_1 \in N\{x,y\}$ and $f(P_1,t) \cap M\{x,y\} = \emptyset$, then $f(P,t) = \pi(P,T_1) + f(P_1,t)$.

Remark 2. For (2) in Definition 2, if $f(P_1,t) \cap M\{x,y\} \neq \emptyset$, and there exists a time point T_2 such that $f(P_1,T_2) = H_1 \in M\{x,y\}$, $\varphi(H_1) = \varphi(f(P_1,T_2)) =$

$P_2 \in N\{x, y\}$ and $f(P_2, t) \cap M\{x, y\} = \emptyset$, then $f(P, t) = \pi(P, T_1) + f(P_1, t) = \pi(P, T_1) + \pi(P_1, T_2) + f(P_2, t)$.

If $f(P_2, t) \cap M\{x, y\} \neq \emptyset, \ldots, f(P_{k-1}, t) \cap M\{x, y\} \neq \emptyset$ and $f(P_k, t) \cap M\{x, y\} = \emptyset$, then we can repeat the above steps and have the following form:

$$f(P, t) = \sum_{i=1}^{k} \pi(P_{i-1}, T_i) + f(P_k, t), \quad P_0 = P.$$

Definition 3 ([5]). If there exists a point $P \in N\{x, y\}$ and a time point T_1 such that $f(P, T_1) = H \in M\{x, y\}$ and $\varphi(H) = \varphi(f(P, T_1)) = P \in N\{x, y\}$, then $f(P, t)$ is called an order one periodic solution of the system (3) whose period is T_1.

Definition 4. Suppose $\Gamma = f(P, t)$ is an order one periodic solution of the system (3). If for any $\varepsilon > 0$, there must exist $\delta > 0$ and $t_0 \geq 0$, such that for any point $P_1 \in U(P, \delta) \cap N\{x, y\}$, we have $\rho(f(P_1, t), \Gamma) < \varepsilon$ for $t > t_0$, then we call the order one periodic solution Γ is orbitally asymptotically stable.

Definition 5 ([5]). Suppose the impulse set M and phase set N of the system (3) are straight lines and a coordinate system can be defined in the phase set N. Let point $A \in N$ and its coordinate is a. Assume that the trajectory from the point A intersects the impulse set M at a point A', and, after impulsive effect, the point A' is mapped to the point $A_1 \in N$ with the coordinate a_1, then we call point A_1 is the successor point of point A, and the successor function of point A is $F(A) = a_1 - a$.

Remark 3. For system (2), we define the coordinate of point $H \in N_1 = \{(G, I) \,|\, G = L_G, I \geq I_C\}$ as its coordinate in I-axis which we denote as I_H.

Lemma 1 ([5]). *Successor function $F(A)$ is continuous.*

Lemma 2. *For the systems* (2)*, if there exist two points $A \in N_1, B \in N_1$ such that $F(A)F(B) < 0$, then there must exist a point $C \in N_1$ which is between the points A and B such that $F(C) = 0$, thus the system must have an order one periodic solution which passes through the point C.*

Proof. By Lemma 1, we can easily get that there must exist a point $C \in N_1$ which is between the points A and B such that $F(C) = 0$. According to Definition 5, we know $\Gamma = f(C, t)$ is an order one periodic solution. That completes the proof. □

Lemma 3 ([27] Bendixson theorem of impulsive differential equations). *Assume Ω is a Bendixson region of* (3)*, if Ω does not contain any critical points of* (3)*, then* (3) *has a closed orbit in Ω.*

3. Dynamic Analysis of the System (2)

For type 1 diabetes, almost all of the β-cells in pancreas are dysfunctional and no insulin can be secreted, so the parameter $\sigma_1 = 0$ in both Models (1) and (2). For

type 2 diabetes, a typical diagnostics is both hyperglycemia and hyperinsulinmia, that is, the pancreas can still release some insulin, and hyperinsulinmia is possibly caused by insulin resistance. Therefore, $\sigma_1 > 0$ for type 2 diabetes.

In this section, we mainly discuss the existence of the periodic solution and the attraction region of system (2) by the geometric theory of differential equation. Before that, we consider the qualitative characteristics of the system (2) without impulsive effect. In such case, the system (2) can be written as

$$\begin{cases} \dfrac{dG(t)}{dt} = (G_{\text{in}} + b) - (\sigma_2 + ac)G - \dfrac{amGI}{n+I} = P_1(G, I), \\ \dfrac{dI(t)}{dt} = \dfrac{\sigma_1 G^2}{\alpha_1^2 + G^2} - d_i I(t) = Q_1(G, I). \end{cases} \tag{4}$$

Similar to the discussions in [12], we can get when $\sigma_1 = 0$, the system (4) has a unique equilibrium $E^0(G^0, 0)$, where $G^0 = (G_{\text{in}} + b)/(\sigma_2 + ac)$, and E^0 is a global asymptotically stable node with two separatrices $I = 0$ and $G = kI$, where $k = amG^0/(n(d_i - \sigma_2 - ac))$. When $\sigma_1 > 0$, the system (4) has a unique positive equilibrium $E^*(G^*, I^*)$ which is a global asymptotically stable node or focus.

The isocline $\frac{dG}{dt} = P_1(G, I) = 0$ has an asymptotic line $G = \frac{G_{\text{in}}+b}{\sigma_2+ac+am} = G_s$. Thus, in the system (2), if $L_A \leq G_s$, the horizontal lines $G = L_A$ would not intersect with the isocline $\frac{dG}{dt} = P_1(G, I) = 0$, which implies that the trajectory from the initial point between the lines $G = L_G$ and $G = L_A$ will never undergo the second kind of impulsive effect and remain above the line $G = L_A$. So we assume that $G_s < L_A < L_A + g_{\text{in}} < L_G < G^0$ for the case $\sigma_1 = 0$ and $G_s < L_A < L_A + g_{\text{in}} < L_G < G^*$ for the case $\sigma_1 > 0$ throughout this section. Clinically, if $L_A < G_s$, or L_G is above G^0 or G^*, some other medical treatment is required to bring the glucose level up or down in practice.

Therefore, in this paper, we mainly study the system (2) in the region

$$W = \{(G, I) \,|\, L_A \leq G \leq L_G, 0 < I < \infty\}.$$

3.1. *Existence of periodic solutions*

Now we study the existence of periodic solutions of Model (2) for the case of type 1 diabetes ($\sigma_1 = 0$) and the case of type 2 diabetes ($\sigma_1 > 0$), respectively.

Theorem 1. *For the case $\sigma_1 = 0$, if $G_s < L_A < L_A + g_{\text{in}} < L_G < G^0$ and $I_C < \sigma$, then the system (2) must have a periodic solution in the region W.*

Proof. Suppose that the G-isoline $\frac{dG}{dt} = 0$ intersects the horizontal line $G = L_G$ and $G = L_A$ at point $C(L_G, I_C)$ and point $M(L_A, I_M)$, respectively. For system (4), the trajectory passing through point M must intersect the line $G = L_G$ at two points, then we denote them by $Q(L_G, I_Q)$ and $S(L_G, I_S)$, where $I_Q < I_S$. Besides, we consider the point $D(L_G, I_D)$, where $I_D = I_C + \sigma$.

Based on the position relations between points D and S, the existence of periodic solution to (2) is discussed.

Case 1. $I_D < I_S$, that is, the point D lies on the left of point S.

In the following, we prove that the system (2) has a unique order one periodic solution, which only undergoes the first kind impulsive effect.

Obviously, the trajectory of the system (2) from point D must intersect the line $G = L_G$ again at a point $H(L_G, I_H)$, where $0 < I_H < I_C$, then the point H is mapped to a point $H'(L_G, I_{H'})$ after an impulsive effect of the first kind, where $I_D > I_{H'} = I_H + \sigma > I_C$ (because $I_C < \sigma, I_D = I_C + \sigma$). Again, the trajectory of the system (2) passing through point H' must intersect the line $G = L_G$ at a point $H_1(L_G, I_{H_1})$, and the point H_1 is mapped to a point $H_1'(L_G, I_{H_1'})$ after an impulsive effect of the first kind, where $I_{H_1'} = I_{H_1} + \sigma$. Since distinct trajectories do not intersect, we can easily get $0 < I_H < I_{H_1} < I_C < I_{H'} < I_{H_1'} < I_D < I_S$. Because point D is in the phase set, point H is the impulse point of point D and point H' is the successor point of point D, we can get the successor function of point D is $F(D) = I_{H'} - I_D < 0$. Besides, for point H' in the phase set, point H_1 is the impulse point of point H' and point H_1' is the successor point of point H', so we can get the successor function of point H' is $F(H') = I_{H_1'} - I_{H'} > 0$. By Lemmas 1 and 2, there must exist a point R in the first phase set which is between the points H' and D such that $F(R) = 0$, thus the system (2) has an order one periodic solution which makes point R as its phase point and only undergoes the first kind impulsive effect (refer to the left panel of Fig. 1).

Now, we prove the uniqueness of the order one periodic solution. Choose an arbitrary point P in region W, the trajectory of system (2) from point P must intersect the horizontal line $G = L_G$ or $G = L_A$ without undergoing any impulsive effect. Because the horizontal line $G = L_A$ is the second impulse set of system (2), the trajectory of system (2) which intersects the horizontal line $G = L_A$ must be mapped to the inner of the region W and then intersects the horizontal line $G = L_G$ after undergoing several impulsive effects of the second kind. Besides, the segment $\{(G, I) \,|\, G = L_G, 0 \le I \le I_C\}$ is the first impulse set of the system (2),

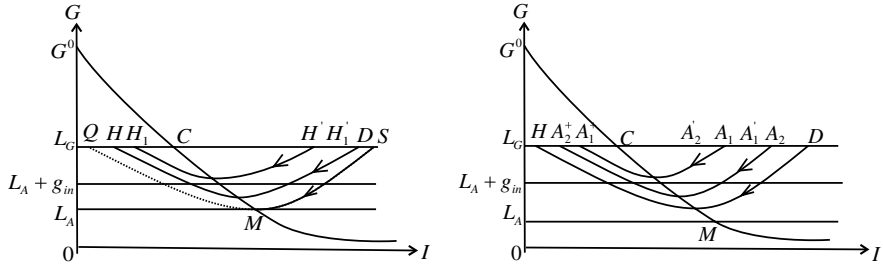

Fig. 1. Existence and uniqueness of order one periodic solution of (2) for Case 1.

and the trajectory of system (2) which intersects this segment must be mapped to the corresponding phase set $\{(G, I) \,|\, G = L_G, I_C < I \leq I_C + \sigma\}$ which is also in the horizontal line $G = L_G$. So the trajectory of system (2) in region W must intersect the horizontal line $G = L_G$ at a point $A(L_G, I_A), I_A > I_C$.

Arbitrarily choose two points A_1 and A_2 in the first phase set, where $I_C < I_{A_1} < I_{A_2} \leq I_D$. Then the trajectories of the system (2) through points A_1 and A_2 must intersect the line $G = L_G$ at some points A_1^+ and A_2^+ respectively, which are in the impulse set and satisfy $I_H < I_{A_2^+} < I_{A_1^+} < I_C$. The points A_1^+ and A_2^+ must be mapped to two points in the phase set after impulsive effect which we denote by A_1' and A_2' respectively, where $I_{A_1'} = I_{A_1^+} + \sigma$ and $I_{A_2'} = I_{A_2^+} + \sigma$. Obviously, the point A_i^+ is the impulse point of A_i and the point A_i' is the successor point of A_i, $i = 1, 2$. Then the successor functions of A_1 and A_2 satisfy $F(A_2) - F(A_1) = (I_{A_2'} - I_{A_2}) - (I_{A_1'} - I_{A_1}) = (I_{A_2'} - I_{A_1'}) + (I_{A_1} - I_{A_2}) < 0$, which means the successor function $F(A)$ is monotone decreasing in the segment $\overline{CD}$, thus there exists only one point R such that $F(R) = 0$ (refer to the right panel of Fig. 1).

Besides, for any point $A \in \overline{DS}$, that is, $I_D < I_A < I_S$, the trajectory of the system (2) from point A must intersect the line $G = L_G$ without any impulsive effect at some point A_1, where $I_Q < I_{A_1} < I_C$. Then the point A_1 is mapped to the point $A_1'(L_G, I_{A_1'})$ after an impulsive effect of the first kind, where $I_A > I_D > I_{A_1'} = I_{A_1} + \sigma > I_C$. Obviously, the point A_1' is the successor point of A, and the trajectory from point A_1' will ultimately remain in the region encircled by the closed curve $\widehat{DH} \cup \overline{HCD}$, then we know the system (2) has no periodic solution passing through the point A where $A \in \overline{DS}$ (refer to the left panel of Fig. 2).

For any point $P(L_G, I_P), I_P \geq I_S$, the trajectory of the system (2) from point P must intersect the line $G = L_A$ without any impulsive effect at some point A_1, then the trajectory from point A_1 will enter into and remain in the region encircled by the closed curve $\widehat{SMQ} \cup \overline{QCS}$ after undergoing at least one impulsive effect of the second kind, then we get that the system (2) has no periodic solution passing through the point P (refer to the right panel of Fig. 2).

To sum up, the system (2) has a unique order one periodic solution in the region W when $I_D < I_S$.

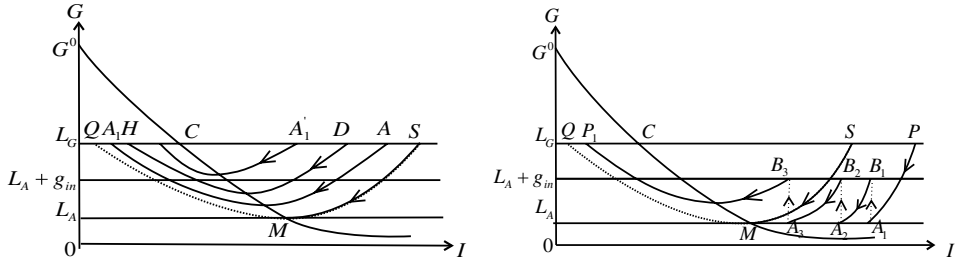

Fig. 2. Uniqueness of order one periodic solution of system (2) for Case 1.

Case 2. $I_D = I_S$, that is, the point D is exactly the point S.

Select the point $\tilde{D}(L_G, I_{\tilde{D}})$ which is close to the point S, where $I_{\tilde{D}} < I_S$. Then the trajectory of the system (2) through point $\tilde{D}$ must intersect the line $G = L_G$ again at a point $\tilde{H}(L_G, I_{\tilde{H}})$ which is close to the point Q, where $0 < I_Q < I_{\tilde{H}} < I_C$. The point $\tilde{H}$ is mapped to a point $\tilde{H}'(L_G, I_{\tilde{H}'})$ after impulsive effect, where $I_{\tilde{D}} > I_{\tilde{H}'} = I_{\tilde{H}} + \sigma > I_C$. Again, the trajectory of the system (2) passing through point $\tilde{H}'$ must intersect the line $G = L_G$ at a point $\tilde{H}_1(L_G, I_{\tilde{H}_1})$, and the point $\tilde{H}_1$ is mapped to a point $\tilde{H}_1'(L_G, I_{\tilde{H}_1'})$ after an impulsive effect of the first kind, where $I_{\tilde{H}_1'} = I_{\tilde{H}_1} + \sigma$. Since distinct trajectories do not intersect, we can easily have $0 < I_{\tilde{H}} < I_{\tilde{H}_1} < I_C < I_{\tilde{H}'} < I_{\tilde{H}_1'} < I_{\tilde{D}} < I_S$. Because point $\tilde{D}$ is in the phase set, point $\tilde{H}$ is the impulse point of point $\tilde{D}$ and point $\tilde{H}'$ is the successor point of point $\tilde{D}$, we can get the successor function of point $\tilde{D}$ is $F(\tilde{D}) = I_{\tilde{H}'} - I_{\tilde{D}} < 0$. Besides, for point $\tilde{H}'$ in the phase set, point $\tilde{H}_1$ is the impulse point of point $\tilde{H}'$ and point H_1' is the successor point of point H', so we can get the successor function of point $\tilde{H}'$ is $F(\tilde{H}') = I_{\tilde{H}_1'} - I_{\tilde{H}'} > 0$. By Lemmas 1 and 2, there must exist a point R in the first phase set which is between the points $\tilde{H}'$ and $\tilde{D}$ such that $F(R) = 0$, thus the system (2) has an order one periodic solution which makes point R as its phase point and only undergoes the first kind impulsive effect (refer to the left panel of Fig. 3).

By similar arguments as Case 1, we can get that the order one periodic solution is the unique periodic solution of (2) in the region W.

Case 3. $I_D > I_S$, that is, the point D lies on the right of point S.

Suppose the trajectory of the system (4) from point S intersects the horizontal line $G = L_A + g_{\text{in}}$ at point K and the trajectory from point D intersects the horizontal line $G = L_A$ at point N. Select the point $J(L_A + g_{\text{in}}, I_M)$ which is the phase point of point M after the second kind impulsive effect, and the trajectory of the system (4) passing through point J must intersect the horizontal line $G = L_G$ at two points, then we denote them by F and E, where $I_F < I_C < I_E$ (refer to the right panel of Fig. 3). Because the point Q is in the first impulse set, so it must

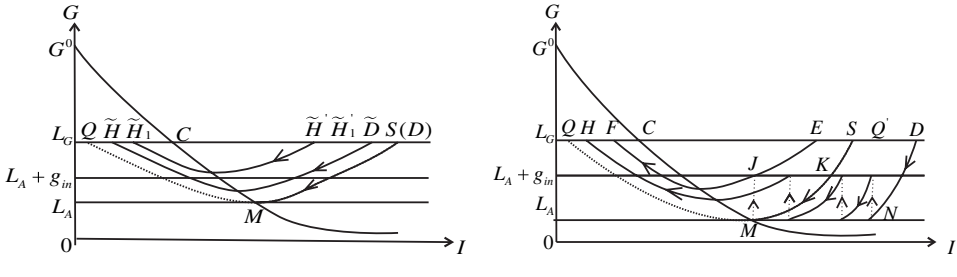

Fig. 3. Existence of periodic solution of (2) for Cases 2 and 3.

be mapped to a point $Q'(L_G, I_{Q'})$ after an impulsive effect of the first kind, where $I_{Q'} = I_Q + \sigma$. Based on the position of point Q', there are the following cases:

(i) $I_{Q'} \geq I_S$, that is, the point Q' lies on the right of or is exactly point S.

Because $0 < I_Q < I_C$, $I_{Q'} = I_Q + \sigma < I_D = I_C + \sigma$, that is to say, the point Q' is between the points S and D (refer to the right panel of Fig. 3). Consider the region Ω_1 encircled by the closed curve $\widehat{DN} \cup \overline{NM} \cup \widehat{MQ} \cup \overline{QF} \cup \widehat{FJ} \cup \overline{JK} \cup \widehat{KS} \cup \overline{SD}$. We can easily know that the region Ω_1 is an invariant set of system (2), and we also call it a Bendixson region. Because Ω_1 does not contain any critical points of system (2), by Lemma 3, there exists a periodic orbit of the system (2) in Ω_1.

Obviously, the periodic orbit of the system (2) in Ω_1 must undergo two kinds of impulsive effects.

(ii) $I_{Q'} < I_S$, that is, the point Q' lies on the left of point S.

By similar arguments as Case 2, we can get that there must exist a point R in the first phase set which is between the points Q' and S such that $F(R) = 0$, thus the system (2) has an order one periodic solution which makes the point R as its phase point and only undergoes the first kind impulsive effect.

To sum up, the system (2) always has periodic solutions in the region W under the conditions of Theorem 1. That completes the proof. □

By similar arguments, although slightly more complicated, we have the following results for type 2 diabetes. We omit the proof.

Theorem 2. *For the case* $\sigma_1 > 0$, *if* $G_s < L_A < L_A + g_{in} < L_G < G^*$ *and* $I_C < \sigma$, *then the system* (2) *must have a periodic solution in the region* W.

3.2. *The attraction region of the system* (2)

In this section, we study the attraction region of the system (2). Obviously, we only need to consider the attraction region of the system with the initial point $P(L_G, I_P)$ on the horizontal lines $G = L_G$, where $I_P > I_C$.

From the discussion of Cases 1 and 2 in Theorem 1, we know that, when $I_D \leq I_S$, system (2) has a unique order one periodic solution in the region W which only undergoes impulsive effect of the first kind. In the following, we can prove that there is an attraction region of the system (2) in W for these two cases.

Theorem 3. *For the case* $\sigma_1 = 0$ $(\sigma_1 > 0)$, *if* $G_s < L_A < L_A + g_{\text{in}} < L_G < G^0$ $(G_s < L_A < L_A + g_{\text{in}} < L_G < G^*)$ *and* $I_C < \sigma < I_C + \sigma = I_D \leq I_S$, *then the system* (2) *has an attraction region in* W.

Proof. In the following discussion, for any point A in the first impulse set, we denote its phase point by A' and we have $I_{A'} = I_A + \sigma$.

According to Theorem 1, the system (2) has a unique order one periodic solution that makes the point $R(L_G, I_R)$ as its phase point, where $I_{H'} < I_R < I_D$.

Consider the successor point H' of point D (which is defined in Theorem 1 and refer to Fig. 4), we can easily get $I_C < I_{H'} < I_R$. The trajectory passing through point H' intersects the impulse set again at point H_1 which is the impulse point of H', and after undergoing an impulsive effect, point H_1 is mapped to point H_1' which is the successor point of H'. We denote the impulse point of the order one periodic solution by R'. Because distinct trajectories do not intersect, we have $I_H < I_{R'} < I_{H_1} < I_C$ and $I_R < I_{H_1'} < I_D$.

Similarly, the trajectory passing through point H_1' must intersect the impulse set again at point H_2 which is the impulse point of H_1', and after an impulsive effect, the point H_2 must be mapped to point H_2' which is the successor point of H_1'. Then we have $I_H < I_{H_2} < I_{R'}$ and $I_{H'} < I_{H_2'} < I_R$.

Repeat the above steps, the trajectory from point D will come across impulsive effect infinite times. Denote the phase point corresponding to the ith impulsive effect by H_{i-1}', $i = 1, 2, \ldots$, where $H_0' = H'$. Then we have

$$I_C < I_{H_0'} < I_{H_2'} < I_{H_4'} < \cdots < I_{H_{2k}'} < I_{H_{2(k+1)}'} < \cdots < I_R$$

and

$$I_D > I_{H_1'} > I_{H_3'} > I_{H_5'} > \cdots < I_{H_{2k+1}'} > I_{H_{2(k+1)+1}'} > \cdots > I_R.$$

Thus $\{I_{H_{2k}'}\}$, $k = 0, 1, 2, \ldots$, is a monotonically increasing sequence, and $\{I_{H_{2k+1}'}\}$, $k = 0, 1, 2, \ldots$, is a monotonically decreasing sequence (see Fig. 4), and furthermore we suppose,

$$I_{H_{2k}'} \to I_{R^*} \le I_R, \quad \text{as } k \to \infty; \quad \text{and} \quad I_{H_{2k+1}'} \to I_{R_1^*} \ge I_R, \quad \text{as } k \to \infty,$$

where the interval $[R^*, R_1^*]$ can be the single point R.

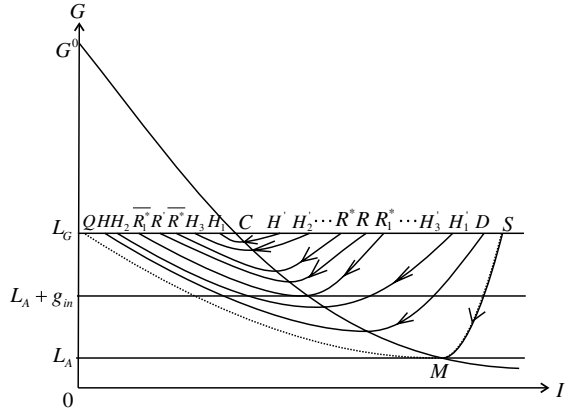

Fig. 4. Illustration of the attraction region of the system (2).

For convenience, the impulse points of points R^* and R_1^* are denoted by points $\bar{R}^*$ and $\bar{R}_1^*$ respectively, and obviously, the region Ω_0 encircled by the closed curve $\overline{R^*R_1^*} \cup \widehat{R_1^*\bar{R}_1^*} \cup \overline{\bar{R}_1^*\bar{R}^*} \cup \widehat{R^*\bar{R}^*}$ is an invariant set. If point R^* is exactly point R_1^*, we know the invariant set Ω_0 is exactly the unique order one cycle $\widehat{R\bar{R}'} \cup \overline{R'R}$.

Choose an arbitrary point $P_0 \in \overline{H'R^*}$, which is different from the point R^*, and there must exist an integer k such that $I_{H'_{2k}} < I_{P_0} < I_{H'_{2(k+1)}}$. The trajectory from point P_0 will also undergo impulsive effect infinite times. We denote the phase point corresponding to the lth-impulsive effect by P_l, $l = 0, 1, 2, \ldots$, then for any l, $I_{H'_{2(k+l)}} < I_{P_{2l}} < I_{H'_{2(k+l+1)}}$ and $I_{H'_{(2k+l+1)+1}} < I_{P_{2l+1}} < I_{H'_{2(k+l)+1}}$, so $\{I_{P_{2l}}\}$, $l = 0, 1, 2, \ldots$, is also monotonic increasing, and $\{I_{P_{2l+1}}\}$, $l = 0, 1, 2, \ldots$, is also monotonic decreasing, and

$$I_{P_{2l}} \to I_{R^*}, \quad \text{as } l \to \infty; \quad \text{and} \quad I_{P_{2l+1}} \to I_{R_1^*}, \quad \text{as } l \to \infty.$$

Therefore, the successor points of the phase points corresponding to the successive impulsive effect are attracted to the region Ω_0.

By similar discussions, we can get that the trajectory from point $P_0 \in \overline{R_1^*D}$ is also attracted to the region Ω_0. Thus the system (2) has an attraction region Ω_0 in the region encircled by the closed curve $\widehat{D\bar{H}} \cup \overline{H\bar{H}_1} \cup \overline{\bar{H}_1\bar{H}'} \cup \overline{H'D}$ (see Fig. 4).

Besides, for any point $A \in \overline{CH'}$, that is, $I_C < I_A < I_{H'}$, after undergoing one impulsive effect of the first kind, the trajectory of the system (2) from point A must enter the region encircled by the closed curve $\widehat{D\bar{H}} \cup \overline{H\bar{H}_1} \cup \widehat{\bar{H}_1H'} \cup \overline{H'D}$, then it will ultimately tend to the region Ω_0, so the region Ω_0 is an attraction region of the system (2) in the region encircled by the closed curve $\widehat{D\bar{H}} \cup \overline{HCD}$.

According to the discussion in Case 1 of Theorem 1, for any point $A(L_G, I_A)$, $I_A > I_D$, the trajectory of the system (2) from point A must enter the region encircled by the closed curve $\widehat{D\bar{H}} \cup \overline{HCD}$ after undergoing some impulsive effects of the two kinds, so it will also ultimately tend to the region Ω_0, then the region Ω_0 is an attraction region of the system (2) in the region W. The proof is completed. □

Theorem 4. *For the case* $\sigma_1 = 0\,(\sigma_1 > 0)$, *if* $G_s < L_A < L_A + g_{\text{in}} < L_G < G^0\,(G_s < L_A < L_A + g_{\text{in}} < L_G < G^*)$, $I_C < \sigma$ *and* $I_C + \sigma = I_D > I_S$, *then there is an attraction region of the system* (2) *in* W.

Proof. According to the discussion of Case 3 in Theorem 1 and based on the position of point Q' which is the phase point of point Q, there are three cases:

Case 1. $I_{Q'} \geq I_S$, that is, the point Q' lies on the right of or is exactly point S.

In Theorem 1, we have proved that the region Ω_1 encircled by the closed curve $\widehat{D\bar{N}} \cup \overline{N\bar{M}} \cup \widehat{\bar{M}Q} \cup \overline{QF} \cup \widehat{FJ} \cup \overline{JK} \cup \widehat{K\bar{S}} \cup \overline{SD}$ is a Bendixson region and contain a periodic orbit of the system (2) (refer to the right panel of Fig. 3). We can also prove that the region Ω_1 is the attraction region of the system (2) in W.

Choose an arbitrarily point $A \in \overline{CS}$. The trajectory of the system (2) through point A must intersect the line $G = L_G$ at a point $A_1(L_G, I_{A_1})$, where

$I_Q < I_{A_1} < I_C$. The point A_1 is mapped to the point $A'(L_G, I_{A'})$ after impulsive effect, where $I_Q + \sigma = I_{Q'} < I_{A'} < I_D = I_C + \sigma$. So the trajectory of the system (2) through point A will ultimately enter into and remain in the region Ω_1.

For any point $P(L_G, I_P), I_P \geq I_S$, the trajectory of the system (2) from point P must intersect the line $G = L_A$ without any impulsive effect at some point A_1, then the trajectory from point A_1 will enter into and remain in the region encircled by the closed curve $\widehat{SMQ} \cup \overline{QCS}$ after undergoing at least one impulsive effect of the second kind, that is to say, the trajectory from point A_1 will intersect the $\overline{CS}$ after undergoing several impulsive effects. So the trajectory of the system (2) through point P will ultimately enter into and remain in the region Ω_1.

To sum up, when $I_{Q'} \geq I_S$, the region Ω_1 is an attraction region of the system (2) in W.

By similar arguments as Case 1, we can get the results of the other two cases. We omit the discussion.

Case 2. $I_E \leq I_{Q'} < I_S$, that is, the point Q' is between the points E and S (refer to the left panel of Fig. 5).

We can get an attraction region of the system (2) in W which is encircled by the closed curve $\widehat{DN} \cup \overline{NM} \cup \widehat{MQ} \cup \overline{QF} \cup \widehat{FE} \cup \overline{ED}$.

Case 3. $I_C < I_{Q'} < I_E$, that is, the point Q' is between the points C and E (refer to the right panel of Fig. 5).

The trajectory of the system (2) from point Q' must intersect the line $G = L_G$ without any impulsive effect at some point L. We can get an attraction region of the system (2) in W which is encircled by the closed curve $\widehat{DN} \cup \overline{NM} \cup \widehat{MQ} \cup \overline{QL} \cup \widehat{LQ'} \cup \overline{Q'D}$.

To sum up, there is always an attraction region of the system (2) in W. That completes the proof. □

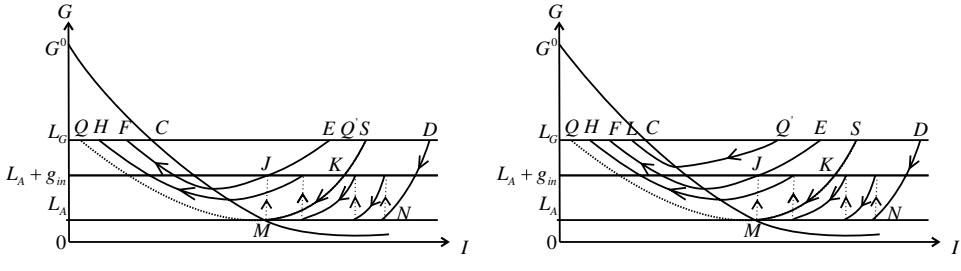

Fig. 5. Attraction region of the system (2) for Cases 2 and 3.

4. Numerical Simulation and Discussion

In this paper, we build a novel semicontinuous dynamics system model to simulate the therapy for diabetics with artificial pancreas. Compared with system (2.3) proposed in [12], our new model not only considers the control of hyperglycemia but also avoids the occurrence of hypoglycemia. By a semicontinuous dynamics system, the insulin delivery and glucagon injection can be modeled by two state-dependent impulse. This will be potential contributions to the development of the artificial pancreas.

Because of the complicated pathology of diabetes mellitus, in a lot of elderly diabetes and critically ill patients, hyperglycemia and hypoglycemia usually show up at the same time. Equipped with a reliable real-time glucose monitoring system, artificial pancreas knows the plasma glucose level clearly, and it can give a timely injection of insulin or glucagon automatically when hyperglycemia or hypoglycemia occurs. Therefore, artificial pancreas will be the best instrument for the diabetes therapy in the future. Model (2) provides a robust model with the most important and critical feature, that is, the timing of injection and what to be injected are determined by the plasma glucose level read from an accurate glucose monitor. Researchers for artificial pancreas are widely agreed that for each model, we should get a better understanding of strength and weakness in validating different control algorithms [22] and develop clinical applicable controls. In this section, we apply Model (2) under a few typical clinical situations and study the simulation results.

The parameter values in our simulations are chosen and adjusted from [7, 13–15, 17, 18, 23, 25] (refer to Table 1). Just like [12–14], unit conversion is also made in our simulation.

For the artificial pancreas with closed-loop approach, our theoretical results (Theorems 1 and 2) ensure that the system must exist a positive periodic solution, whether for type 1 or type 2 diabetes (see Figs. 6 and 7). Compare Fig. 6 with Fig. 7, we find that under the same treatment conditions, type 1 diabetes need much more exogenous insulin injection than type 2 diabetes to keep the plasma glucose level under control. Within 500 minutes, the glucose concentration reaches to 190 mg/dl (the predefined threshold level to avoid hyperglycemia) twice for type 2 diabetes while eight times for type 1 diabetes. This is mainly because the pancreas of type 2 diabetes can still release some insulin to uptake glucose, but type 1 diabetes are completely dependent on exogenous insulin.

Table 1. Model parameter values from [12].

Parameters	Values	Units	Parameters	Values	Units
G_{in}	216	mg/min	m	900	mg/min
b	100	mg/min	n	80	mg
σ_2	5×10^{-6}	min^{-1}	σ_1	6.27	mU/min
a	3×10^{-5}	mg^{-1}	α_1	105	mg
c	40	mg/min	d_i	0.08	min^{-1}

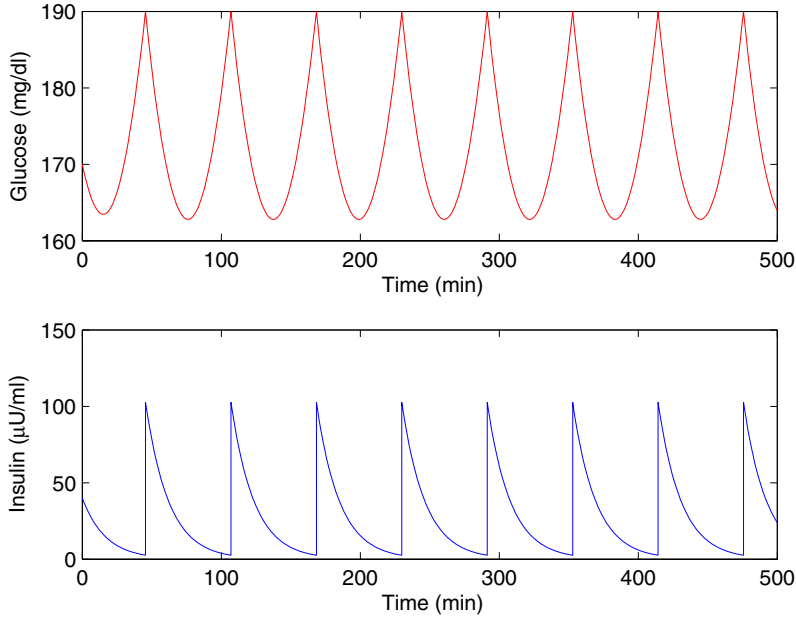

Fig. 6. Positive periodic solutions of Model (2) for type 1 diabetes ($\sigma_1 = 0$) with $\sigma = 1\,\mathrm{U}$, $g_{\mathrm{in}} = 10\,\mathrm{mg/ml}$, $L_G = 190\,\mathrm{mg/dl}$ and $L_A = 60\,\mathrm{mg/dl}$.

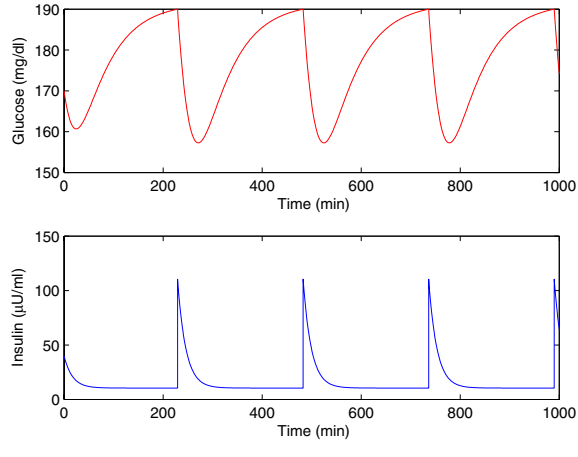

Fig. 7. Positive periodic solutions of Model (2) for type 2 diabetes ($\sigma_1 = 6.27$) with $\sigma = 1\,\mathrm{U}$, $g_{\mathrm{in}} = 10\,\mathrm{mg/ml}$, $L_G = 190\,\mathrm{mg/dl}$, and $L_A = 60\,\mathrm{mg/dl}$.

According to Fig. 8, when we set the insulin injection dose suitable enough, the periodic solution may be orbitally asymptotically stable. Even though the orbitally asymptotic stability cannot be obtained, the plasma glucose concentration can be always remained in an ideal range by Theorems 3 and 4.

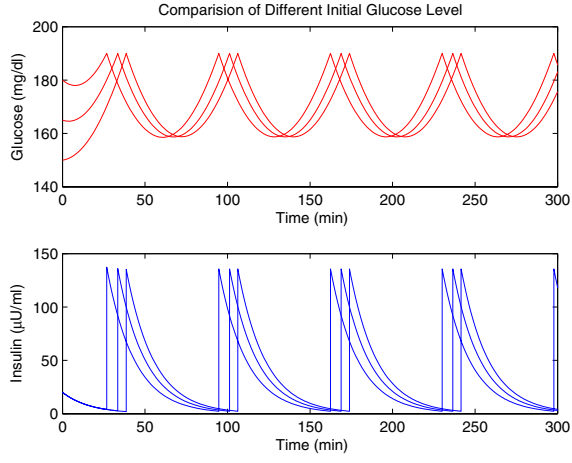

Fig. 8. Comparison of the profiles produced by Model (2) with different initial glucose levels.

Just like we had done in [12], we study the insulin injection strategies for a patient equipped with artificial pancreas. We set the delivery impulse at different intervals but at the same total daily dose, compare the profiles and then can get a similar conclusion: for the same daily total dose, the impulsive injection with larger dose but longer period is more effective to control hyperglycemia than the injection with smaller dose but shorter period (refer to Fig. 9). This can provide significant guidance in the algorithm design of the artificial pancreas.

The parameter values in Table 1 are initially adjusted from [23, 25] which mainly study the glucose–insulin regulatory system of healthy people, and they obtained their data from experiments. But for severe diabetics, especially the critically ill patients in ICU, who are often sedated and in a highly monitored state, they are extremely diverse in the causes and dynamics of their hyperglycemia and very small amounts of glucose input can cause significant response to their plasma glucose and insulin levels [8]. So the glucose exogenous infusion rate for critically ill patients should also be sharply reduced. Besides, the insulin degradation rate may also change greatly. We perform a group of numerical simulations to research the therapy for severe diabetics with an artificial pancreas.

According to Fig. 10, we find that for type 1 diabetics, if his insulin degradation rate becomes far below normal while he still must reduce the glucose intake to a very low level because of the risk of hyperglycemia, he may suffer from hyperglycemia and hypoglycemia at the same time. When an artificial pancreas is equipped, the timely injections of insulin and glucagon help the patient to adjust his glucose level to a safe range.

However, for severe diabetics of type 2, if the insulin degradation rate becomes low enough, the glucose–insulin regulatory system itself can restore his plasma glucose concentration to safe level, both insulin and glucagon injections are not

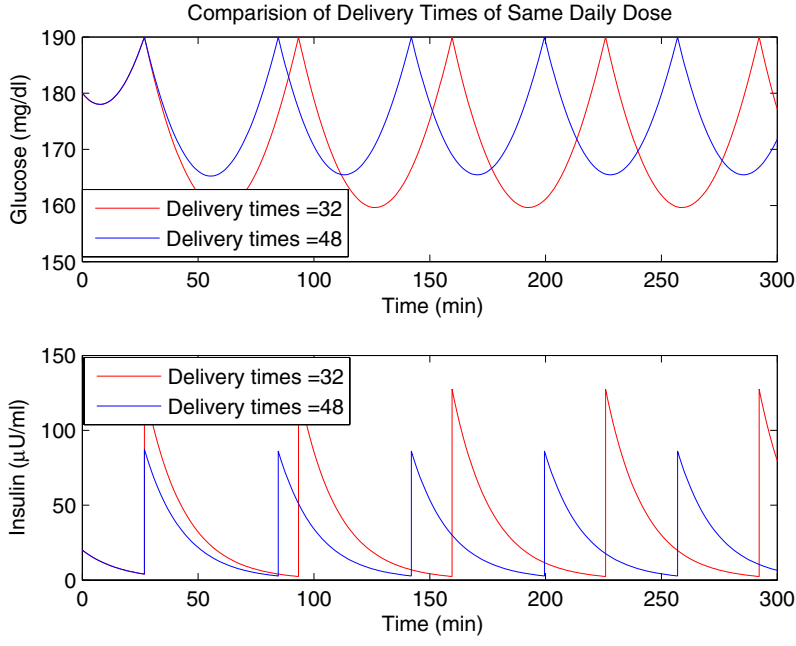

Fig. 9. Comparison of the profiles produced by Model (2) with different doses controlled by a pre-set threshold level of glucose concentration.

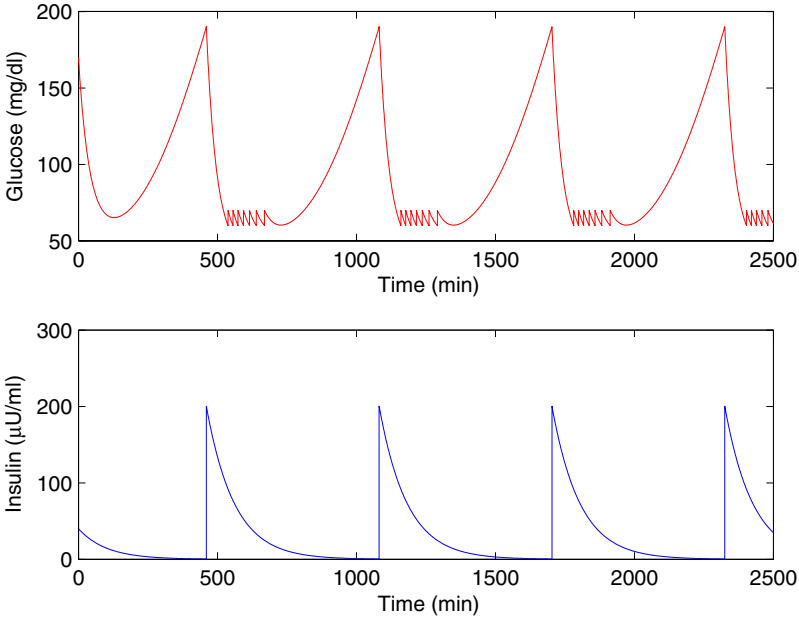

Fig. 10. Positive periodic solutions of Model (2) for type 1 diabetes ($\sigma_1 = 0$) with $G_{\text{in}} = 10\,\text{mg/min}$, $d_i = 0.01\ \text{min}^{-1}$, $\sigma = 1\,\text{U}$, $g_{\text{in}} = 10\,\text{mg/ml}$, $L_G = 190\,\text{mg/dl}$ and $L_A = 60\,\text{mg/dl}$.

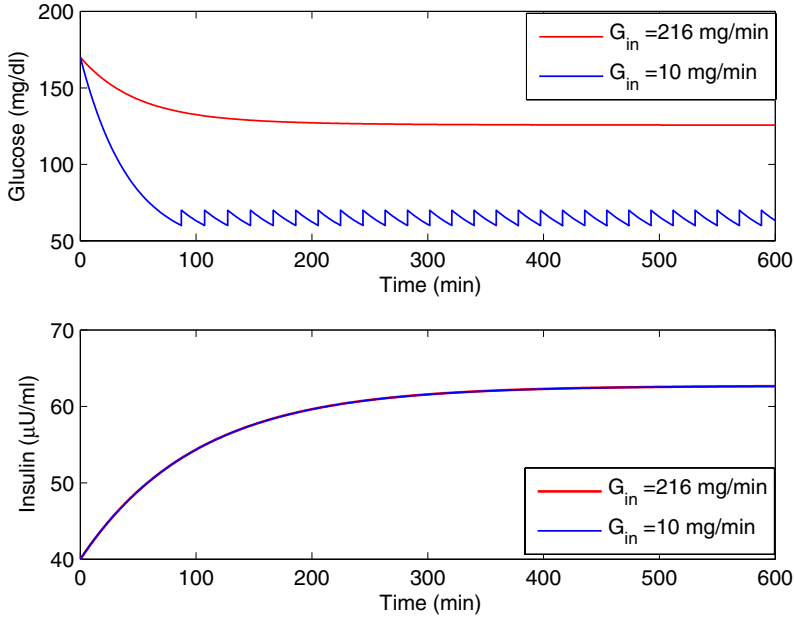

Fig. 11. Positive periodic solutions of Model (2) for type 2 diabetes ($\sigma_1 = 6.27$) with $d_i = 0.01\ \text{min}^{-1}$, $\sigma = 1\,\text{U}$, $g_{\text{in}} = 10\,\text{mg/ml}$, $L_G = 190\,\text{mg/dl}$ and $L_A = 60\,\text{mg/dl}$.

needed (see Fig. 11 when $G_{\text{in}} = 216\,\text{mg/min}$). In this case, if the patient reduces the glucose infusion blindly, hypoglycemia may occur (see Fig. 11 when $G_{\text{in}} = 10\,\text{mg/min}$). This also suggests that, for type 2 diabetics, medicine studies and practice that slow down the insulin degradation are helpful for the plasma glucose control.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (11171284), the Innovation Scientists and Technicians Troop Construction Projects of Henan Province (104200510011), program for Innovative Research Team (in Science and Technology) in University of Henan Province (2010IRTSTHN006) and Sci-tech program project of Henan Province (122300410034).

References

[1] A. M. Albisser, B. S. Leibel, T. G. Ewart, Z. Davidovac, C. K. Botz and W. Zingg, An artificial endocrine pancreas, *Diabetes* **23** (1974) 389–396.
[2] S. Bennett, *A History of Control Engineering 1930–1955*, IEE Control Engineering Series, No. 47 (Institution of Electrical Engineers, 1993).
[3] B. W. Bode, Insulin pump use in type 2 diabetes, *Diabetes Technol. Ther.* **12** (2010) S17–S21.
[4] D. Bruttomesso, A. Farret, S. Costa, M. C. Marescotti, M. Vettore, A. Avogaro, A. Tiengo, C. D. Man, J. Place, A. Facchinetti, S. Guerra, L. Magni, G. De Nicolao,

C. Cobelli, E. Renard and A. Maran, Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: Preliminary studies in Padova and Montpellier, *J. Diabetes Sci. Technol.* **3** (2009) 1014–1021.

[5] L. S. Chen, Pest control and geometric theory of semi-continuous dynamical system, *J. Beihua Univ.* **12** (2011) 1–9.

[6] C. J. Dai, M. Zhao and L. S. Chen, Homoclinic bifurcation in semi-continuous dynamic systems, *Int. J. Biomath.* **5**(6) (2012) 1250059, 19 pp.

[7] A. De Gaetano and O. Arino, Mathematical modeling of the intravenous glucose tolerance test, *J. Math. Biol.* **40** (2000) 136–168.

[8] C. V. Doran, J. G. Chase, G. M. Shaw and K. T. Moorhead, Derivative weighted active insulin control algorithms and intensive care unit trials, *Control Engrg. Pract.* **13** (2005) 1129–1137.

[9] http://docnews.diabetesjournals.org/content/2/8/5.full.

[10] http://en.wikipedia.org/wiki/PID_controller.

[11] http://www.diabeticcareservices.com/diabetes-education/hypoglycemia-and-hyperglycemia-and-the-elderly.

[12] M. Z. Huang, J. X. Li, X. Y. Song and H. J. Guo, Modeling impulsive injections of insulin: Towards artificial pancreas, *SIAM J. Appl. Math.* **72** (2012) 1524–1548.

[13] J. X. Li and Y. Kuang, Analysis of a glucose–insulin regulatory models with time delays, *SIAM J. Appl. Math.* **67** (2007) 757–776.

[14] J. X. Li, Y. Kuang and C. Mason, Modeling the glucose–insulin regulatory system and ultradian insulin secretory oscillations with two time delays, *J. Theor. Biol.* **242** (2006) 722–735.

[15] J. X. Li, H. Y. Wang, P. Palumbo, S. Panunzi and A. De Gaetano, The range of time delay and the global stability of the equilibrium for an IVGTT model, *Math. Biosci.* **235** (2012) 128–137, doi:10.1016/j.mbs.2011.11.005.

[16] D. M. Maahs, L. A. Horton and H. P. Chase, The use of insulin pumps in youth with type 1 diabetes, *Diabetes Technol. Ther.* **12** (2010) S59–S65.

[17] P. Palumbo, S. Panunzi and A. De Gaetano, Qualitative behavior of a family of delay-differential models of the glucose–insulin system, *Discrete Contin. Dynam. Syst. B* **7** (2007) 399–424.

[18] S. Panunzi, P. Palumbo and A. De Gaetano, A discrete single delay model for the intravenous glucose tolerance test, *Theor. Biol. Med. Model.* **4** (2007) 35, doi:10.1186/1742-4682-4-35.

[19] P. Raskin *et al.*, Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes, *Diabetes Care* **26** (2003) 2598–2603.

[20] J. Roszler, Senior pumpers: Some seniors may benefit from pump therapy even more than young people do, *Diabetes Forecast* **55** (2002) 37–40.

[21] G. M. Steil, B. Hipszer and J. Reifman, Mathematical modeling research to support the development of automated insulin-delivery systems, *J. Diabetes Sci. Technol.* **3** (2009) 388–395.

[22] G. M. Steil, B. Hipszer and J. Reifman, Update on mathematical modeling research to support the development of automated insulin-delivery systems, *J. Diabetes Sci. Technol.* **4** (2010) 759–769.

[23] J. Sturis, K. S. Polonsky, E. Mosekilde and E. Van Cauter, Computer model for mechanisms underlying ultradian oscillations of insulin and glucose, *Amer. J. Physiol.* **260** (1991) E801–E809.

[24] C. L. Thompson, K. C. Dunn, M. C. Menon, L. E. Kearns and S. S. Braithwaite, Hyperglycemia in the hospital, *Diabetes Spectrum* **18** (2005) 20–27.

[25] I. M. Tolic, E. Mosekilde and J. Sturis, Modeling the insulin-glucose feedback system: The significance of pulsatile insulin secretion, *J. Theor. Biol.* **207** (2000) 361–375.
[26] H. Y. Wang, J. X. Li and Y. Kuang, Mathematical modeling and qualitative analysis of insulin therapies, *Math. Biosci.* **210** (2007) 17–33.
[27] L. C. Zhao, L. S. Chen and Q. L. Zhang, The geometrical analysis of a predator–prey model with two state impulses, *Math. Biosci.* **238** (2012) 55–64.