MODELING IMPULSIVE INJECTIONS OF INSULIN ANALOGUES: TOWARDS ARTIFICIAL PANCREAS *

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Abstract. We propose two novel mathematical models with impulsive injection of insulin or its analogues for type 1 and type 2 diabetes mellitus. One model incorporates with periodic impulsive injection of insulin. We analytically showed the existence and uniqueness of a positive globally asymptotically stable periodic solution for type 1 diabetes, which implies that the perturbation due to insulin injection will not disturb the homeostasis of plasma glucose concentration. We also showed that the system is uniformly permanent for type 2 diabetes, that is, the glucose concentration level is uniformly bounded above and below. The other model has the feature that determines the insulin injection by closely monitoring the glucose level when the glucose level reaches or passes a predefined but adjustable threshold value. We analytically proved the existence and stability of the order one periodic solution, which ensures that the perturbation by the injection in such an automated way can make the blood glucose concentration under control. Our numerical analyses confirm and further enhance the usefulness and robustness of our models. The first model has implications in clinic that the glucose level of a diabetic can be controlled within desired level by adjusting the values of two model parameters, injection period and injection dose. The second model is probably the first attempt to conquer some critical issues in the design of artificial pancreas with closed-loop approach. For both cases, our numerical analysis reveal that smaller but shorter insulin delivery therapy is more efficient and effective. This can be significant in design and development of insulin pump and artificial pancreas.

1. Introduction. Diabetes mellitus is a disease, in which plasma glucose concentration level mostly remains above normal range. Diabetes mellitus is typically classified as type 1 diabetes, type 2 diabetes, and gestational diabetes. Type 1 diabetes is mainly due to that almost all β-cells in pancreas are lost or dysfunctional and thus no insulin can be synthesized and secreted from pancreas. Type 2 diabetes is probably due to the disfunction of the glucose-insulin regulatory system, for example, insulin resistance, so that insulin cannot be utilized sufficiently by cells to uptake glucose. To compensate the insulin resistance, β-cells need to synthesize more insulin for the ineffective glucose utilization. Typical diagnostic in type 2 diabetes is both hyperglycemia and hyperinsulinmia. It has been a long history for researchers and medical doctors to find the mechanisms how the system becomes dysfunctional and how to provide effective and efficient therapies for diabetic patients. The most common regimens are inject insulin analogues subcutaneously either daily or continuously. The continuous subcutaneous insulin infusion (CSII) therapy is achieved by using insulin pump, a medical device for administration of insulin or its analogues. The use of insulin pump not only has greatly increased for type 1 diabetes ([18]), also provides a feasible alternative for type 2 diabetes ([6], [22], [24], [35]) in exogenous injection of insulin or its analogues. All insulin pumps used by diabetics in daily life

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nowadays follow the so called *open loop* approach, that is, insulin is injected without knowledge of plasma glucose level. While these therapies provide important and improved treatments for diabetic patients, however, such regimes change the life styles of the patients, for example, a patient has to inject insulin manually before or after meal ingestions to avoid hyperglycemia, and the dose has to be carefully computed by the carbohydrate to be ingested. A risk in the open loop control is hypoglycemia episode. In recent years, to improve the life styles or make the life style of the patients to return back or close to as a normal person, researchers have been making great efforts in study to develop technology and close the loop, which is called artificial pancreas ([26], [27]).

The artificial pancreas, which is still in development, is a controller that would substitute the endocrine functionality of a real and healthy pancreas for diabetic patients and automatically keep their plasma glucose level under control ([32]). Equipped with the endocrine functionality of a healthy pancreas, the patient would have been relieved from the inconvenience in food intake and manual activities for insulin injection. The major impediments for the development of artificial pancreas include following issues: a) need of reliable predictive models; b) effective and efficient control algorithms; and c)unreliable real time glucose monitoring system ([27]). However, the issues a) and b) are not fully solved in open-loop control devices either.

In this paper we propose two models that simulate impulsive injection of insulin in open-loop control in the fashion of periodic impulses, and in closed-loop control in view of the feedback from glucose monitoring system. This paper is probably the first attempt to conquer the issues a) and b) in a mathematical model with impulsive administration of insulin for the development of artificial pancreas. We shall show the existence of periodic solutions and its global stability, or permanence of the system, which ensure the possibility and feasibility of such insulin administrations. The analytical results and numerical observations have great implications to the development of artificial pancreas. The paper is organized as follows. In Section 2, we formulate two impulsive differential equation models to simulate the impulsive insulin injection for diabetic patients. In Section 3, the qualitative analysis of the model with periodic impulsive injection of insulin analogues is given and the theoretical and practical regime in controlling glucose level within ideal range is also discussed. In Section 4, we mainly discuss the existence and stability of the order one periodic solution of the models with state dependent impulsive injection of insulin analogues for diabetes mellitus by differential equation geometry theory and the method of successor functions. While the numerical simulations are carried out in Section 5, which not only confirm the theoretical results, but also are complementary to those theoretical results with specific features. We finish this paper by discussing the implications of these models to the development of artificial pancreas and pointing out future needed work in improving these models in Section 6.

2. Model formulation. The terminology "artificial pancreas" can be traced to 1974 in [2]. Although the PID (proportional-integrative-derivative) controller is considered as the best controller when the underlying mechanisms are not completely known in applications ([5]), model-based control is preferred due to limitations existed in PID controllers ([7]) and optional control of the system or its stability is not guaranteed by PID algorithms ([33]). Model-based algorithms require reliable models that determine the time and the dose for insulin injections. Several such models have been proposed (e.g., [11], [30], [31]). Such models reflect the physiology of the insulin

secretion stimulated by glucose and also glucose metabolism with helps of insulin or exogenously delivered insulin analogues.

The metabolic model proposed by the authors of [11] used data from conducted closed-loop insulin delivery trials to describe intraday variation of model parameters and concluded that the model systems do not have to comprise large number of compartments and variables, that is, the differential equation system does not need to be high dimensional. Another type of models closely relevant is to compute glucose fluxes after meal ingestion, for example, Hovorka et al ([10]), which makes a computational frame work by combining the maximum likelihood theory and the ordinary differential equation system.

Two critical and harmful episodes in therapies of insulin administration are hypoglycemia caused by over-dosing and hyperglycemia caused by under-dosing. The model-based algorithms used by insulin pumps and future artificial pancreas should be designed to avoid such episodes. To carefully determine correct dose of insulin and right timing of injection, it is necessary to understand the dynamics of the regulations between glucose and insulin in physiology. Therefore a model based on physiology is much needed and it is extremely important to study the model analytically so that the episodes of hyperglycemia and hypoglycemia can be evaded.

To this end, we extend the model proposed by Li et al ([16]) and Li and Kuang ([14]), which models the physiological oscillatory insulin secretion stimulated by elevated glucose, and form a new model taking account of impulsive insulin injection either periodically or by monitoring the plasma glucose concentration level. A similar effort has been attempted by Wang et al. ([30], [31]), in which periodic insulin administration was employed to mimic impulsive injection for the regime of type 1 or type 2 diabetes mellitus. The model in [16] and [14] is given by

$$\begin{cases} \dfrac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t-\tau_2)), \\ \dfrac{dI}{dt} = f_1(G(t-\tau_1)) - d_i I, \end{cases} \tag{2.1}$$

where G_{in} is the estimated average constant rate of glucose input, $f_1(G(t-\tau_1))$ is insulin secretion stimulated by elevated glucose concentration with a time delay τ_1 caused by complex pathways including chemical-electrical processes, $f_2(G)$ is the the insulin independent glucose uptake, while $f_3(G)f_4(I)$ stands for the insulin-dependent glucose utilization, $f_5(I(t-\tau_2))$ is the hepatic glucose production (HGP) with a time delay τ_2, and, lastly, $d_i I$ indicates the insulin degradation with $d_i > 0$ as the constant degradation rate. Refer to Fig. 3 in [16] for the shapes and forms of the response functions f_1, f_2, f_3, f_4 and f_5, which are originally determined by Sturis et al in [28].

We modify the model diagram given in Fig. 2 in [16] and obtain following model diagram in Fig. 2 including exogenous insulin injection and the feedback of monitored glucose concentration level.

In normal subjects, liver is the first organ that the newly secreted insulin arrives, and the HGP is controlled by insulin. For type 1 and type 2 diabetics using artificial pancreas, no or little insulin is secreted from β-cells and the exogenous insulin is injected in subcutance. Therefore the control power of HGP by insulin level is not significant (refer to Fig. 2). Thus, we assume that the HGP $f_5(I(t-\tau_2))$ is assumed to be at a constant rate $b > 0$. Furthermore, according to [12], the shapes of the response functions are important instead of the forms. So for simplicity, we assume

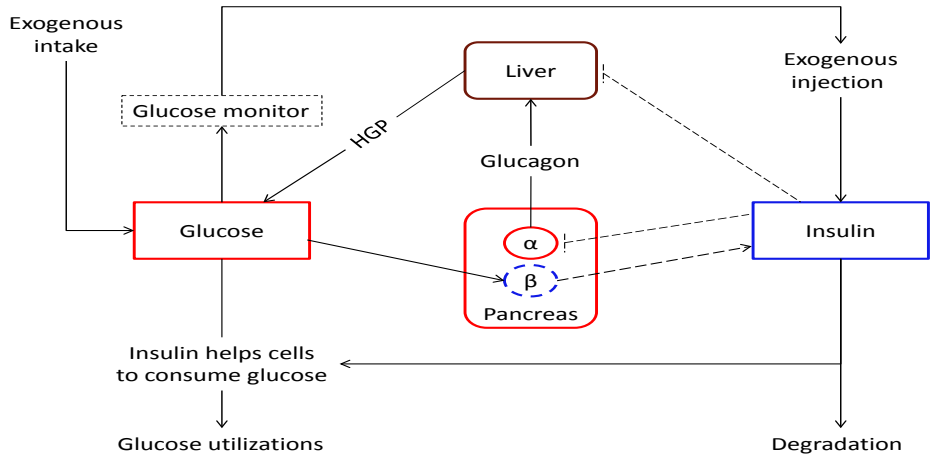

FIG. 2.1. *Model Diagram. For type 1 and type 2 diabetes, β-cells do not secrete or secrete insufficient insulin. Insulin is injected exogenously. Therefore the repression of insulin on hepatic glucose production and α-cells secreting glucagon is in significant. Insulin injection can be in viewing the input from glucose monitoring device.*

that

$$f_1(x) = \frac{\sigma_1 x^2}{\alpha_1^2 + x^2}, \qquad f_2(x) = \sigma_2 x, \qquad f_3(x) = ax, \qquad f_4(x) = c + \frac{mx}{n+x},$$

where $\sigma_1, \sigma_2, \alpha_1, a, c, m$ and n are positive constant parameters that are chosen and adjusted from [9], [14], [16], [17], [20], [21], [28] and [29] (refer to Table 5.1). Thus we first formulate following two-compartment model with periodic impulsive injection of exogenous insulin

$$\begin{cases} \left.\begin{aligned} \frac{dG(t)}{dt} &= G_{in} - \sigma_2 G - a\Big(c + \frac{mI}{n+I}\Big)G + b, \\ \frac{dI(t)}{dt} &= \frac{\sigma_1 G^2}{\alpha_1^2 + G^2} - d_i I(t), \end{aligned}\right\} & t \neq k\tau, \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \sigma, \end{aligned}\right\} & t = k\tau, \end{cases} \tag{2.2}$$

with initial condition $G(0) = G_0 > 0, I(0) = I_0 > 0$, where σ (μU/ml) > 0 is the dose in each injection and τ (min) > 0 is the period of the impulsive injection. That is, σ (μU/ml) insulin is injected as an impulse at discrete times $t = k\tau$, $k \in Z^+ = \{1, 2, 3, \ldots\}$. The moment immediately after the k^{th} injection is denoted as $t = k\tau^+$ here.

The feature of Model (2.2) is that insulin is injected subcutaneously periodically, which is in agreement with how the insulin pump works in an open-loop fashion. We shall perform analytical analysis in Section 3 for the existence, uniqueness and stability for the periodic solution with two adjustable parameters σ and τ in a reasonable region. The periodic solution reflects the dynamics of the glucose and insulin for

the patients and the clinical doctors can adjust these two parameters to determine the dose and periodic timing of injection so that the range of plasma glucose can be controlled within a desirable range.

Although the insulin pumps with open-loop technique have been in the market for clinical use, the ideal treatment is that the insulin administration can be automatically determined by the so called closed-loop technique integrated with glucose monitoring system. This would build an artificial pancreas. In the design of an artificial pancreas, it is critical to inject insulin or its analogues in observing the glucose level from a monitoring system, and the injections are prompt. Based on the model (2.1), we here propose a novel model simulating the injection of insulin as impulse in observing the glucose level, and investigate the dynamical behaviors. The model is given by

$$\begin{cases} \left.\begin{aligned} \frac{dG(t)}{dt} &= G_{in} - \sigma_2 G - a\Big(c + \frac{mI}{n+I}\Big)G + b, \\ \frac{dI(t)}{dt} &= \frac{\sigma_1 G^2}{\alpha_1^2 + G^2} - d_i I(t), \end{aligned}\right\} & G < L_G \text{ or } I > I_C, \\ \left.\begin{aligned} G(t^+) &= G(t), \\ I(t^+) &= I(t) + \sigma, \end{aligned}\right\} & G = L_G \text{ and } I \le I_C, \end{cases} \tag{2.3}$$

with initial condition $G(0) = G_0 \le L_G, I(0) = I_0$, where the constant $I_C = nk_0/(m - k_0), k_0 = a^{-1}L_G^{-1}(G_{in} + b - \sigma_2 L_G) - c$, which is determined by the intersection of the null-cline $G_{in} - \sigma_2 G - a\Big(c + \frac{mI}{n+I}\Big)G + b = 0$ and the horizonal line $G = L_G$ in the (I, G)-plane. L_G is an adjustable constant threshold value for glucose level – when the glucose level reaches the threshold value, the impulsive inject of insulin with dose σ (μU/ml) shall be performed. It is easy to see that the glucose level must decrease when the insulin level surpass the point I_C. We shall show that periodic solution exists with orbital stability in Section 4.

Remark. For type 1 diabetes, all or most β-cells are dysfunctional and thus secrete no insulin. So the parameter $\sigma_1 = 0$ in Model (2.2) and Model (2.3). For type 2 diabetes, a typical diagnostics of type 2 diabetes is both hyperglycemia and hyperinsulinmia. Hyperinsulinmia is possibly caused by insulin resistance. Therefore, $\sigma_1 > 0$ and $a > 0$ is small for type 2 diabetes in Model (2.2) and Model (2.3).

3. Analysis of Model (2.2) for open loop control. In this section, we consider the system (2.2) in two cases. We first consider the case $\sigma_1 = 0$, which means that pancreas does not release insulin and patients can only rely on exogenous insulin through subcutaneous injection. We show that the system has a globally asymptotically stable positive periodic solution. Secondly, we consider the case $\sigma_1 > 0$, which means that the pancreas may release some insulin, we show that the system (2.2) is *permanent*, that is, the glucose concentration level is bounded above by a constant and below by another constant.

3.1. Preliminaries. For the sake of convenience, following notations and definitions are assumed throughout the paper.

Let $R_+ = [0, \infty)$, $R_+^2 = \{(x, y) \in R_+^2 : x \ge 0, y \ge 0\}$, $\Omega = \text{int}R_+^2$. Denote $f = (g, h)^T$ as the mapping defined by the right-hand side of the system (2.2).

Let $V : R_+ \times R_+^2 \to R_+$. Then V is said to belong to class V_0 if

(i) V is continuous on $(k\tau,(k+1)\tau]\times R_+^2$, and $\lim_{(t,y)\to(k\tau^+,x)} V(t,y)=V(k\tau^+,x)$ exists and is finite.

(ii) V is locally Lipschitzian in x.

DEFINITION 3.1. *Let $V\in V_0$, then for $V(t,x)\in(k\tau,(k+1)\tau]\times R_+^2$, the upper right derivative of $V(t,x)$ with respect to the impulsive differential system (2.2) is defined as*

$$D^+V(t,x)=\limsup_{h\to 0}\frac{1}{h}[V(t+h,x+hf(t,x))-V(t,x)].$$

DEFINITION 3.2. *(Bainov and Simeonov [3]) Let $r(t)=r(t,t_0,x_0)$ be a solution of the system (2.2) on $[t_0,t_0+l)$. $r(t)$ is called the maximal solution of the system (2.2) if for any solution $x(t,t_0,x_0)$ of the system (2.2) existing on $[t_0,t_0+l)$, then*

$$x(t)\le r(t),\quad t\in[t_0,t_0+l).$$

The minimal solution $\rho(t)$ can be defined similarly.

DEFINITION 3.3. *The system (2.2) is said to be uniformly persistent if there is a $q>0$ (independent of the initial conditions) such that every solution $(G(t),I(t))$ of the system (2.2) satisfies*

$$\liminf_{t\to\infty} G(t)\ge q,\quad \liminf_{t\to\infty} I(t)\ge q.$$

DEFINITION 3.4. *The system (2.2) is said to be permanent if every solution $(G(t),I(t))$ is bounded below by a positive constant and above by another positive constant, respectively.*

LEMMA 3.5. *Let $m\in V_0$, and assume that*

$$\begin{cases} D^+m(t)\le g(t,m(t)), & t\ne t_k,\quad k=1,2,\cdots,\\ m(t_k^+)\le\psi_k(m(t_k)), & t=t_k,\quad k=1,2,\cdots, \end{cases}$$

where $g\in C(R_+\times R_+,R)$, $\psi_k\in C(R,R)$ and $\psi_k(u)$ is nondecreasing in u for each $k=1,2,\cdots$. Let $r(t)$ be the maximal solution of the scalar impulsive differential equation

$$\begin{cases} \dot u=g(t,u), & t\ne t_k, & k=1,2,\cdots,\\ u(t_k^+)=\psi_k(u(t_k)), & t=t_k, t_k>t_0\ge 0, & k=1,2,\cdots,\\ u(t_0)=u_0, \end{cases}\tag{3.1}$$

which exists on $[t_0,\infty)$. Then, $m(t_0^+)\le u_0$ implies that $m(t)\le r(t)$ for $t\ge t_0$. Similar result can be obtained when all the directions of the inequalities in the lemma are reversed and $\psi_k(u)$ is nonincreasing.

Remark. In Lemma 3.5, if g is smooth enough to guarantee the existence and uniqueness of solution for the initial value problem of the system (3.1), then $r(t)$ is indeed the unique solution of (3.1).

Next we show the positivity and the boundedness of the solutions of the system (2.2).

Let $x(t)=(G(t),I(t))^T$ be a solution of the system (2.2). Notice that it is continuous on $(k\tau,(k+1)\tau]$, $k\in Z_+$, and $x(k\tau^+)=\lim_{t\to k\tau^+} x(t)$ exists. Thus the global existence and uniqueness of solutions of system (2.2) is ensured by the smoothness of $f=(g,h)^T$ ([3], [4]).

Clearly, $dG(t)/dt > 0$ when $G(t) = 0$, and $dI(t)/dt \geq 0$ when $I(t) = 0$. Therefore we have

PROPOSITION 3.6. *(Positivity) Suppose that $x(t)$ is a solution of the system (2.2) with $x(0^+) \geq 0$, then $x(t) \geq 0$ for all $t \geq 0$, and further if $x(0^+) > 0$, then $x(t) > 0$ for all $t > 0$.*

Following lemma summarizes some basic properties of the linear system (3.2). We state it below without proof. Interested readers can refer to [25].

LEMMA 3.7. *The linear system*

$$\begin{cases} \dot{u}(t) = a_1 - b_1 u(t), & t \neq k\tau, \\ u(t^+) = u(t) + p, & t = k\tau, \\ u(0^+) = u_0 \geq 0, \end{cases} \tag{3.2}$$

has a unique positive periodic solution $\tilde{u}(t)$ with period τ and for every solution $u(t)$ of (3.2) such that $|u(t) - \tilde{u}(t)| \to 0$ as $t \to \infty$, where

$$\tilde{u}(t) = \frac{a_1}{b_1} + \frac{p \exp(-b_1(t - k\tau))}{1 - \exp(-b_1\tau)}, \quad t \in (k\tau, (k+1)\tau], k \in Z_+,$$

$$\tilde{u}(0^+) = \frac{a_1}{b_1} + \frac{p}{1 - \exp(-b_1\tau)},$$

and $\tilde{u}(t)$ is globally asymptotically stable. Besides, we have $u(t) = (u(0^+) - \tilde{u}(0^+)) \exp(-b_1 t) + \tilde{u}(t)$, and $\lim_{t\to\infty} u(t) = \tilde{u}(t)$. Especially, if $a_1 = 0$, the system (3.2) has a unique positive periodic solution $\tilde{u}(t) = p \exp(-b_1(t - k\tau))/(1 - \exp(-b_1\tau))$ with initial value $\tilde{u}(0^+) = p/(1 - \exp(-b_1\tau))$ and $\tilde{u}(t)$ is globally asymptotically stable.

Now we can show the boundedness of the solutions of the system (2.2).

PROPOSITION 3.8. *(Boundedness) For a solution $(G(t), I(t))$ of the system (2.2) with positive initial values, there exists a positive constant M such that $G(t) \leq M$ and $I(t) \leq M$ for all $t \geq 0$.*

Proof. From the first equation of the system (2.2) we have

$$\frac{dG(t)}{dt} \leq (G_{in} + b) - (\sigma_2 + ac)G,$$

then there exits a positive number $M_1 > 0$ such that $G(t) \leq M_1, t \geq 0$.

From the second and the forth equation of system (2.2), we have

$$\begin{cases} \dfrac{dI(t)}{dt} \leq \sigma_1 - d_i I(t), & t \neq k\tau, \\ I(t^+) = I(t) + \sigma, & t = k\tau, \\ I(0) = I_0 > 0. \end{cases}$$

Now we consider the impulsive differential equation

$$\begin{cases} \dfrac{dI_2(t)}{dt} = \sigma_1 - d_i I_2(t), & t \neq k\tau, \\ I_2(t^+) = I_2(t) + \sigma, & t = k\tau, \\ I_2(0^+) = I_0 > 0. \end{cases} \tag{3.3}$$

By Lemma 3.7, we know that the system (3.3) has a globally asymptotically stable positive periodic solution

$$\begin{cases} \tilde{I}_2(t) = \dfrac{\sigma_1}{d_i} + \dfrac{\sigma \exp(-d_i(t-k\tau))}{1-\exp(-d_i\tau)}, & t \in (k\tau,(k+1)\tau], k \in Z_+, \\ \tilde{I}_2(0^+) = \frac{\sigma_1}{d_i} + \frac{\sigma}{1-\exp(-d_i\tau)}, \end{cases}$$

and the solution of the system (3.3) has the form

$$I_2(t) = (I_2(0^+) - \tilde{I}_2(0^+))\exp(-d_i t) + \tilde{I}_2(t),$$

which satisfies $\lim_{t\to\infty} I_2(t) = \tilde{I}_2(t)$.

By Lemma 3.5, we have

$$I(t) \le I_2(t) \le \frac{\sigma_1}{d_i} + \frac{\sigma}{1-\exp(-d_i\tau)} + |I_2(0^+) - \tilde{I}_2(0^+)|, \quad \text{for } t \ge 0,$$

then there exits a positive number $M \ge M_1$ such that $I(t) \le M$, $t \ge 0$. □

3.2. Existence and stability of the periodic solution for type 1 diabetes: the case $\sigma_1 = 0$. No or very few insulin is released from pancreas for type 1 diabetes. This can be modeled in Model (2.2) by assuming that the maximum insulin secretion rate $\sigma_1 = 0$. In this subsection we prove that a globally asymptotically stable periodic solution exists if exogenous insulin is injected in the fashion of periodic impulse.

THEOREM 3.9. *If $\sigma_1 = 0$, then system (2.2) has a unique positive periodic solution $(\tilde{G}(t), \tilde{I}(t))$ with period τ.*

Proof. Note that the variable G does not appear in the second equation of the system (2.2), hence for the dynamics of insulin $I(t)$ we only need to consider the subsystem

$$\begin{cases} \dfrac{dI(t)}{dt} = -d_i I(t), & t \ne k\tau, \\ \\ I(t^+) = I(t) + \sigma, & t = k\tau, \\ I(0) = I_0 > 0. \end{cases} \tag{3.4}$$

According to Lemma 3.7, the system (3.4) has a unique periodic solution

$$\tilde{I}(t) = \frac{\sigma \exp(-d_i(t-k\tau))}{1-\exp(-d_i\tau)}, \qquad t \in (k\tau,(k+1)\tau], k \in Z_+,$$

with period τ and $\tilde{I}(t)$ is globally asymptotically stable.

Substituting $\tilde{I}(t)$ into the first equation of (2.2) for $I(t)$, we have

$$\begin{cases} \dfrac{dG(t)}{dt} = (G_{in}+b) - (\sigma_2+ac)G - \dfrac{amG\tilde{I}(t)}{n+\tilde{I}(t)}, & t \ne k\tau, \\ G(t^+) = G(t), & t = k\tau. \end{cases} \tag{3.5}$$

Integrating and solving the equations (3.5) between pulses, we can get, for $k\tau < t \le$

$(k+1)\tau$,

$$\begin{aligned} G(t) &= G(k\tau)\exp\Big[-\int_{k\tau^+}^{t}\Big(\sigma_2+ac+\frac{am\tilde{I}(s)}{n+\tilde{I}(s)}\Big)ds\Big] \\ &\quad+(G_{in}+b)\int_{k\tau^+}^{t}\Big[\exp\Big(-\int_{u}^{t}\Big(\sigma_2+ac+\frac{am\tilde{I}(s)}{n+\tilde{I}(s)}\Big)ds\Big)\Big]du \\ &= G(k\tau)\exp[-(\sigma_2+ac)(t-k\tau)]\exp[-am\int_{k\tau^+}^{t}\frac{\tilde{I}(s)}{n+\tilde{I}(s)}ds] \\ &\quad+(G_{in}+b)\int_{k\tau^+}^{t}\Big\{\exp[-(\sigma_2+ac)(t-u)]\exp[-am\int_{u}^{t}\frac{\tilde{I}(s)}{n+\tilde{I}(s)}ds]\Big\}du. \end{aligned} \tag{3.6}$$

From system (3.4) we get, for $k\tau^+ \le b_1 \le b_2 \le (k+1)\tau$,

$$\begin{aligned} \exp\Big[-am\int_{b_1}^{b_2}\frac{\tilde{I}(t)}{n+\tilde{I}(t)}dt\Big] &= \exp\Big[\frac{am}{d_i}\int_{b_1}^{b_2}\frac{-d_i\tilde{I}(t)}{n+\tilde{I}(t)}dt\Big] \\ &= \exp\Big[\frac{am}{d_i}\int_{b_1}^{b_2}\Big(\frac{d\ln(n+\tilde{I}(t))}{dt}\Big)dt\Big] \\ &= \exp\Big[\frac{am}{d_i}\ln\Big(\frac{n+\tilde{I}(b_2)}{n+\tilde{I}(b_1)}\Big)\Big] \\ &= \Big(\frac{n+\tilde{I}(b_2)}{n+\tilde{I}(b_1)}\Big)^{\frac{am}{d_i}}. \end{aligned} \tag{3.7}$$

By (3.6) and (3.7), for $k\tau < t \le (k+1)\tau$, we get

$$\begin{aligned} G(t) &= G(k\tau)\exp[-(\sigma_2+ac)(t-k\tau)]\Big(\frac{n+\tilde{I}(t)}{n+\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} \\ &\quad+(G_{in}+b)\int_{k\tau^+}^{t}\Big\{\exp[-(\sigma_2+ac)(t-u)]\Big(\frac{n+\tilde{I}(t)}{n+\tilde{I}(u)}\Big)^{\frac{am}{d_i}}\Big\}du \\ &= G(k\tau)\exp[-(\sigma_2+ac)(t-k\tau)]\Big(\frac{n+\tilde{I}(t)}{n+\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} \\ &\quad+(G_{in}+b)(n+\tilde{I}(t))^{\frac{am}{d_i}}\int_{k\tau^+}^{t}\frac{\exp[-(\sigma_2+ac)(t-u)]}{(n+\tilde{I}(u))^{\frac{am}{d_i}}}du, \end{aligned}$$

and

$$\begin{aligned} G((k+1)\tau) &= G(k\tau)\exp[-(\sigma_2+ac)\tau]\Big(\frac{n+\tilde{I}(\tau)}{n+\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} \\ &\quad+(G_{in}+b)(n+\tilde{I}(\tau))^{\frac{am}{d_i}}\int_{0^+}^{\tau}\frac{\exp[-(\sigma_2+ac)(\tau-u)]}{(n+\tilde{I}(u))^{\frac{am}{d_i}}}du \\ &\triangleq f\big(G(k\tau)\big), \end{aligned} \tag{3.8}$$

where $f(G) = A\times G + B$ and

$$0 < A = \exp[-(\sigma_2+ac)\tau]\Big(\frac{n+\tilde{I}(\tau)}{n+\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} < 1,$$

and

$$B = (G_{in} + b)(n + \tilde{I}(\tau))^{\frac{am}{d_i}} \int_{0^+}^{\tau} \frac{\exp[-(\sigma_2 + ac)(\tau - u)]}{(n + \tilde{I}(u))^{\frac{am}{d_i}}} du > 0.$$

Equation (3.8) has a unique fixed point $\bar{G} = \frac{B}{1-A} > 0$. If $0 < G < \bar{G}$, then $G < f(G) < \bar{G}$, and if $G > \bar{G}$, then $\bar{G} < f(G) < G$, so we can know $\bar{G}$ is globally asymptotically stable, and the corresponding period solution $\tilde{G}(t)$ of system (3.5) is also globally asymptotically stable, where

$$\begin{aligned}\tilde{G}(t) = {} & \frac{B}{1-A} \exp[-(\sigma_2 + ac)(t - k\tau)] \Big(\frac{n + \tilde{I}(t)}{n + \tilde{I}(0^+)} \Big)^{\frac{am}{d_i}} \\ & + (G_{in} + b)(n + \tilde{I}(t))^{\frac{am}{d_i}} \int_{k\tau^+}^{t} \frac{\exp[-(\sigma_2 + ac)(t - u)]}{(n + \tilde{I}(u))^{\frac{am}{d_i}}} du,\end{aligned}$$

for $k\tau < t \leq (k+1)\tau$ and $k \in Z_+$, with initial value $\tilde{G}(0^+) = \frac{B}{1-A}$.

According to the above discussion, we get that system (2.2) has a unique positive periodic solution $(\tilde{G}(t), \tilde{I}(t))$. This completes the proof. □

THEOREM 3.10. *If $\sigma_1 = 0$, then the positive periodic solution $(\tilde{G}(t), \tilde{I}(t))$ of the system (2.2) is globally asymptotically stable.*

Proof. we first prove the local stability of the $\tau-$period solution and then prove that the stability is a global behavior.

The local stability of the $\tau-$period solution $(\tilde{G}(t), \tilde{I}(t))$ may be determined by considering the behavior of small-amplitude perturbations $(v_1(t), v_2(t))^T$ of the solution. Define

$$G(t) = \tilde{G}(t) + v_1(t), \quad I(t) = \tilde{I}(t) + v_2(t),$$

where $v_1(t)$, $v_2(t)$ are small perturbations, which can be written as

$$\begin{pmatrix} v_1(t) \\ v_2(t) \end{pmatrix} = \Phi(t) \begin{pmatrix} v_1(0) \\ v_2(0) \end{pmatrix},$$

where $\Phi(t)$ satisfies

$$\frac{d\Phi(t)}{dt} = \begin{pmatrix} -(\sigma_2 + ac) - \frac{am\tilde{I}(t)}{n+\tilde{I}(t)} & -\frac{am\tilde{G}(t)}{n+\tilde{I}(t)} \\ 0 & -d_i \end{pmatrix} \Phi(t),$$

with $\Phi(0) = I$, the identity matrix. The resetting conditions of system (2.2) become

$$\begin{pmatrix} v_1(k\tau^+) \\ v_2(k\tau^+) \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} v_1(k\tau) \\ v_2(k\tau) \end{pmatrix}.$$

Hence, according to the Floquet theory ([3]), if the absolute values of both eigenvalues of

$$M = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \Phi(\tau) = \Phi(\tau)$$

are less than one, then the τ-period solution is locally stable.

$$\Phi(\tau) = \begin{pmatrix} \exp(\int_0^\tau [-(\sigma_2 + ac) - \frac{am\tilde{I}(t)}{n+\tilde{I}(t)}]dt) & * \\ 0 & e^{-d_i\tau} \end{pmatrix},$$

there is no need to calculate the exact form of $(*)$ as it is not required in the following analysis. Then the eigenvalues of M denoted by λ_1, λ_2 are

$$\lambda_1 = \exp\Big\{\int_0^\tau \Big[-(\sigma_2+ac) - \frac{am\tilde{I}(t)}{n+\tilde{I}(t)}\Big]dt\Big\} < 1 \quad \text{and} \quad \lambda_2 = \exp(-d_i\tau) < 1.$$

So the periodic solution $(\tilde{G}(t), \tilde{I}(t))$ is locally asymptotically stable.

In the following, we show that the periodic solution is a global attractor. According to Proposition 3.8 we have $\lim_{t\to\infty} I(t) = \tilde{I}(t)$. If ε_1 and $\varepsilon_2 > 0$ are small enough, then there exists a $t_1 > 0$ such that $(1-\varepsilon_1)\tilde{I}(t) < I(t) < (1+\varepsilon_2)\tilde{I}(t)$ for all $t > t_1$. From the first equation of the system (2.2), we have

$$\frac{dG}{dt} \geq (G_{in}+b) - (\sigma_2+ac)G - \frac{am(1+\varepsilon_2)G\tilde{I}(t)}{n+(1+\varepsilon_2)\tilde{I}(t)},$$

and

$$\frac{dG}{dt} \leq (G_{in}+b) - (\sigma_2+ac)G - \frac{am(1-\varepsilon_1)G\tilde{I}(t)}{n+(1-\varepsilon_1)\tilde{I}(t)}.$$

Consider the following impulsive equations

$$\begin{cases} \dfrac{dG_1}{dt} = (G_{in}+b) - (\sigma_2+ac)G_1 - \dfrac{am(1+\varepsilon_2)G_1\tilde{I}(t)}{n+(1+\varepsilon_2)\tilde{I}(t)}, & t \neq k\tau, \\ G_1(t^+) = G_1(t), & t = k\tau, \end{cases} \tag{3.9}$$

and

$$\begin{cases} \dfrac{dG_2}{dt} = (G_{in}+b) - (\sigma_2+ac)G_2 - \dfrac{am(1-\varepsilon_1)G_2\tilde{I}(t)}{n+(1-\varepsilon_1)\tilde{I}(t)}, & t \neq k\tau, \\ G_2(t^+) = G_2(t), & t = k\tau. \end{cases} \tag{3.10}$$

According to the proof of Theorem 3.9, both system (3.9) and system (3.10) have unique globally asymptotically stable positive periodic solution

$$\begin{aligned} \tilde{G}_1(t) = {} & \frac{B_1}{1-A_1}\exp[-(\sigma_2+ac)(t-k\tau)]\Big(\frac{n+(1+\varepsilon_2)\tilde{I}(t)}{n+(1+\varepsilon_2)\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} \\ & + (G_{in}+b)(n+(1+\varepsilon_2)\tilde{I}(t))^{\frac{am}{d_i}}\int_{k\tau^+}^t \frac{\exp[-(\sigma_2+ac)(t-u)]}{(n+(1+\varepsilon_2)\tilde{I}(u))^{\frac{am}{d_i}}}du, \end{aligned}$$

for $k\tau < t \leq (k+1)\tau$, where

$$0 < A_1 = \exp[-(\sigma_2+ac)\tau]\Big(\frac{n+(1+\varepsilon_2)\tilde{I}(\tau)}{n+(1+\varepsilon_2)\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} < 1,$$

$$B_1 = (G_{in}+b)(n+(1+\varepsilon_2)\tilde{I}(\tau))^{\frac{am}{d_i}}\int_{0^+}^\tau \frac{\exp[-(\sigma_2+ac)(\tau-u)]}{(n+(1+\varepsilon_2)\tilde{I}(u))^{\frac{am}{d_i}}}du > 0,$$

and

$$\begin{aligned} \tilde{G}_2(t) = {} & \frac{B_2}{1-A_2}\exp[-(\sigma_2+ac)(t-k\tau)]\Big(\frac{n+(1-\varepsilon_1)\tilde{I}(t)}{n+(1-\varepsilon_1)\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} \\ & + (G_{in}+b)(n+(1-\varepsilon_1)\tilde{I}(t))^{\frac{am}{d_i}}\int_{k\tau^+}^t \frac{\exp[-(\sigma_2+ac)(t-u)]}{(n+(1-\varepsilon_1)\tilde{I}(u))^{\frac{am}{d_i}}}du, \end{aligned}$$

for $k\tau < t \le (k+1)\tau$, where

$$0 < A_2 = \exp[-(\sigma_2 + ac)\tau]\Big(\frac{n + (1-\varepsilon_1)\tilde{I}(\tau)}{n + (1-\varepsilon_1)\tilde{I}(0^+)}\Big)^{\frac{am}{d_i}} < 1,$$

and

$$B_2 = (G_{in} + b)(n + (1-\varepsilon_1)\tilde{I}(\tau))^{\frac{am}{d_i}} \int_{0^+}^{\tau} \frac{\exp[-(\sigma_2 + ac)(\tau - u)]}{(n + (1-\varepsilon_1)\tilde{I}(u))^{\frac{am}{d_i}}} du > 0.$$

By Lemma 3.5, we get, for $\varepsilon > 0$ small enough, there exits a $t_2 > t_1$ such that

$$\tilde{G}_1(t) - \varepsilon < G_1(t) \le G(t) \le G_2(t) < \tilde{G}_2(t) + \varepsilon, \quad t > t_2,$$

let $\varepsilon, \varepsilon_1, \varepsilon_2 \to 0$, we get $\tilde{G}_1(t) \to \tilde{G}(t)$ and $\tilde{G}_2(t) \to \tilde{G}(t)$, then $G(t) \to \tilde{G}(t)$ as $t \to \infty$. That completes the proof. □

3.3. Permanence for type 2 diabetes: the case $\sigma_1 > 0$. One diagnostics of type 2 diabetes and prediabetes is hyperglycemia and hyperinsulinmia, which is most likely caused by insulin resistance. In this case, pancreatic β-cells still secrete insulin and might possibly secrete extra insulin to compensate the insulin resistance ([1], [23]), although the compensation is not enough for type 2 diabetes to uptake glucose. Therefore the maximum insulin secreting rate $\sigma_1 > 0$ in Model (2.2). We study the range of variation for plasma glucose concentration $G(t)$ and insulin concentration $I(t)$ under impulsive injection of insulin for sufficiently large $t > 0$. Such qualitative result has implications in design regimes of exogenous insulin injection, in which both episodes of hyperglycemia and hypoglycemia can be avoided. We show the following

THEOREM 3.11. *If $\sigma_1 > 0$, the system (2.2) is permanent, that is, the solutions are bounded below and above by some constants.*

Proof. From the second and the forth equation of the system (2.2) we have

$$\begin{cases} -d_i I(t) \le \dfrac{dI(t)}{dt} \le \sigma_1 - d_i I(t), & t \ne k\tau, \\ I(t^+) = I(t) + \sigma, & t = k\tau, \\ I(0) = I_0 > 0. \end{cases}$$

Now we consider the impulsive differential equation

$$\begin{cases} \dfrac{dI_1(t)}{dt} = -d_i I_1(t), & t \ne k\tau, \\ I_1(t^+) = I_1(t) + \sigma, & t = k\tau. \end{cases} \tag{3.11}$$

By Lemma 3.7 and Proposition 3.8, both system (3.3) and (3.11) have unique globally asymptotically stable positive periodic solutions

$$\tilde{I}_1(t) = \frac{\sigma \exp(-d_i(t - k\tau))}{1 - \exp(-d_i\tau)}, \quad t \in (k\tau, (k+1)\tau], \quad k \in Z_+,$$

$$\tilde{I}_2(t) = \frac{\sigma_1}{d_i} + \frac{\sigma \exp(-d_i(t - k\tau))}{1 - \exp(-d_i\tau)}, \quad t \in (k\tau, (k+1)\tau], \quad k \in Z_+.$$

According to Lemma 3.5 and Lemma 3.7, for sufficiently small $\varepsilon > 0$, there exists a $t_0 > 0$, such that

$$\tilde{I}_1(t) - \varepsilon < I_1(t) \le I(t) \le I_2(t) < \tilde{I}_2(t) + \varepsilon, \quad t \ge t_0,$$

then we have

$$\begin{aligned} \tilde{I}_1(\tau) = \frac{\sigma \exp(-d_i\tau)}{1-\exp(-d_i\tau)} &= \lim_{t\to\infty} \inf \tilde{I}_1(t) \le \lim_{t\to\infty} \inf I(t) \le \lim_{t\to\infty} \sup I(t) \\ &\le \lim_{t\to\infty} \sup \tilde{I}_2(t) = \frac{\sigma_1}{d_i} + \frac{\sigma}{1-\exp(-d_i\tau)} = \tilde{I}_2(0^+). \end{aligned} \tag{3.12}$$

By (3.12) and the first equation of the system (2.2), we know for t large enough that

$$\begin{aligned} (G_{in}+b) - (\sigma_2+ac)G - \frac{amG\tilde{I}_2(0^+)}{n+\tilde{I}_2(0^+)} &\le \frac{dG(t)}{dt} \\ &\le (G_{in}+b) - (\sigma_2+ac)G - \frac{amG\tilde{I}_1(\tau)}{n+\tilde{I}_1(\tau)}. \end{aligned} \tag{3.13}$$

Let

$$\begin{aligned} G^1(\sigma,\tau) &\triangleq \frac{G_{in}+b}{\sigma_2+ac+\frac{am\tilde{I}_2(0^+)}{n+\tilde{I}_2(0^+)}} \\ &= \frac{(G_{in}+b)\Big(n+\frac{\sigma_1}{d_i}+\frac{\sigma}{1-\exp(-d_i\tau)}\Big)}{(\sigma_2+ac)\Big(n+\frac{\sigma_1}{d_i}+\frac{\sigma}{1-\exp(-d_i\tau)}\Big)+am\Big(\frac{\sigma_1}{d_i}+\frac{\sigma}{1-\exp(-d_i\tau)}\Big)}, \\ G^2(\sigma,\tau) &\triangleq \frac{G_{in}+b}{\sigma_2+ac+\frac{am\tilde{I}_1(\tau)}{n+\tilde{I}_1(\tau)}} \\ &= \frac{(G_{in}+b)\Big(n+\frac{\sigma\exp(-d_i\tau)}{1-\exp(-d_i\tau)}\Big)}{(\sigma_2+ac)\Big(n+\frac{\sigma\exp(-d_i\tau)}{1-\exp(-d_i\tau)}\Big)+am\Big(\frac{\sigma\exp(-d_i\tau)}{1-\exp(-d_i\tau)}\Big)}. \end{aligned} \tag{3.14}$$

By (3.13) we get

$$G^1(\sigma,\tau) \le \lim_{t\to\infty} \inf G(t) \le \lim_{t\to\infty} \sup G(t) \le G^2(\sigma,\tau). \tag{3.15}$$

According to (3.12) and (3.15), we know that the system (2.2) is permanent. That completes the proof. □

Remark. The permanence of Model (2.2) qualitatively guarantees that the glucose level is controlled within the designated range so that no hyperglycemia or hypoglycemia would occur. With carefully selected parameters, we demonstrate the dynamical behavior in Section 5 quantitatively by carefully selected parameters in simulations.

3.4. Keep glucose level under control for type 1 diabetics. In this subsection, we propose a theoretical and practical regime for type 1 diabetes to control glucose level within ideal range by adjusting insulin dose σ and injection period τ.

Almost all β-cells are dysfunctional for type 1 diabetics, which is modeled by setting $\sigma_1 = 0$ in Model (2.2). In this case, the system (2.2) has a unique boundary equilibrium $E(G^0, 0)$ when exogenous insulin dose $\sigma = 0$, where $G^0 = (G_{in}+b)/(\sigma_2+ac)$.

In fact, it is easy to see that $E(G^0, 0)$ is a globally asymptotically stable node in this case, which indicates that the glucose level would stay at high level G^0.

When the impulsive injection of insulin is set up in Model (2.2), that is, $\sigma > 0$, by (3.14) and (3.15), we have $\lim_{t\to\infty} \sup G(t) \leq G^2(\sigma, \tau) < G^0$, which implies that the infused insulin makes the concentration of glucose to drop below $G^2(\sigma, \tau)$ after certain time.

Suppose that an ideal range of glucose concentration level is between G_{min} and G_{max}, for example, 70mg/dl-160mg/dl after meal ingestion. Without loss of generality, assume that $G_{min} \geq G^1(\sigma, \tau)$ and $G_{max} \leq G^2(\sigma, \tau)$. By (3.15), illustrated below, we are able to control the glucose concentration level within the ideal range by adjusting the values of injection dose σ and injection period τ.

First suppose that we fix the value of the period of injection τ. Then we can select σ so that

$$\begin{cases} G_{min} \leq G^1(\sigma, \tau), \\ G_{max} \geq G^2(\sigma, \tau). \end{cases}$$

Obviously, both $G^1(\sigma, \tau)$ and $G^2(\sigma, \tau)$ are decreasing in σ and $G^1(\sigma, \tau) \leq G^2(\sigma, \tau)$ for all $\sigma > 0$.

If there exist two points $\sigma_c \leq \sigma^c$ such that

$$\begin{cases} G^1(\sigma^c, \tau) = G_{min}, \\ G^2(\sigma_c, \tau) = G_{max}, \end{cases}$$

then for this fixed value of the period of injection τ, we can select any dose $\sigma \in [\sigma_c, \sigma^c]$ so that $G_{min} \leq G(\sigma, \tau) \leq G_{max}$. In other words, we can regulate the glucose concentration in the ideal range by manipulating the value of σ in the range of $[\sigma_c, \sigma^c]$.

Similarly, if the value of the insulin dose σ is fixed, by (3.14), it is easy to see that both $G^1(\sigma, \tau)$ and $G^2(\sigma, \tau)$ are increasing in τ. Suppose that there exist two points $\tau_c \leq \tau^c$ such that

$$\begin{cases} G^1(\sigma, \tau_c) = G_{min}, \\ G^2(\sigma, \tau^c) = G_{max}, \end{cases}$$

then with the fixed insulin dose σ, we can choose any injection period $\tau \in [\tau_c, \tau^c]$ such that $G_{min} \leq G(\sigma, \tau) \leq G_{max}$. That is, we can regulate the glucose concentration in the ideal range by adjusting the value of τ in the range of $[\tau_c, \tau^c]$.

Thus the two parameters, τ and σ, define a region when they vary in the ranges aforementioned. We can select the dose of insulin σ and the period of injection τ in this region and therefore the plasma glucose is controlled in the range. We draft the strategy in follows.

Consider (3.14), let

$$x_1(\sigma, \tau) = n + \frac{\sigma_1}{d_i} + \frac{\sigma}{1 - \exp(-d_i\tau)}. \tag{3.16}$$

We have

$$\begin{aligned} G^1(\sigma,\tau) &= G^1(x_1(\sigma,\tau)) \\ &= \frac{x_1(\sigma,\tau)}{\frac{\sigma_2+ac}{G_{in}+b}x_1(\sigma,\tau)+\frac{am}{G_{in}+b}(x_1(\sigma,\tau)-n)} \\ &= \frac{x_1(\sigma,\tau)}{\frac{\sigma_2+ac+am}{G_{in}+b}x_1(\sigma,\tau)-\frac{amn}{G_{in}+b}} \\ &\triangleq \frac{x_1(\sigma,\tau)}{Cx_1(\sigma,\tau)-D}, \end{aligned} \tag{3.17}$$

where

$$C=\frac{\sigma_2+ac+am}{G_{in}+b}>0 \quad \text{and} \quad D=\frac{amn}{G_{in}+b}>0.$$

Similarly, let

$$x_2(\sigma,\tau)=n+\frac{\sigma\exp(-d_i\tau)}{1-\exp(-d_i\tau)}. \tag{3.18}$$

By (3.14), we have

$$G^2(\sigma,\tau)=G^2(x_2(\sigma,\tau)) \triangleq \frac{x_2(\sigma,\tau)}{Cx_2(\sigma,\tau)-D}. \tag{3.19}$$

Therefore, (3.16) and (3.18) together imply, for any $\sigma \geq 0$ and $\tau > 0$,

$$x_1(\sigma,\tau) > x_2(\sigma,\tau).$$

According to (3.17) and (3.19), we consider the following function

$$h(x)=\frac{x}{Cx-D}, \quad \text{for } x>\frac{D}{C}.$$

Clearly, $h(x)$ is decreasing in x. Let

$$\begin{cases} G_{min} \leq G^1(x_1(\sigma,\tau)), \\ G_{max} \geq G^2(x_2(\sigma,\tau)), \end{cases} \tag{3.20}$$

according to (3.15). Thus we obtain the solution of (3.20)

$$\begin{cases} x_1(\sigma,\tau) \leq \dfrac{DG_{min}}{CG_{min}-1} = h^{-1}(G_{min}) \triangleq x_1^0, \\ x_2(\sigma,\tau) \geq \dfrac{DG_{max}}{CG_{max}-1} = h^{-1}(G_{max}) \triangleq x_2^0. \end{cases}$$

Notice that both $x_i(\sigma,\tau)$, $i=1,2$, are increasing in σ for fixed τ, and are decreasing in τ for fixed σ. Thus in the (σ,τ)-plane, a region can be enclosed by the curves $x_1(\sigma,\tau)=x_1^0$, and $x_2(\sigma,\tau)=x_2^0$, denoted by W. From (3.17) and (3.18), if insulin dose σ and injection period τ fall in the region W, i.e., $(\sigma,\tau)\in W$, then glucose concentration can be controlled in the range $[G_{min}, G_{max}]$.

4. Analysis of Model (2.3) for closed-loop control. In this section, we mainly discuss the existence and stability of the order one periodic solution of Model (2.3) by the geometric theory of differential equation and the method of successor functions. Before that, we consider the qualitative characteristics of the system (2.3) without impulsive effect. In such case, the system (2.3) can be written as

$$\begin{cases} \dfrac{dG(t)}{dt} = (G_{in} + b) - (\sigma_2 + ac)G - \dfrac{amGI}{n+I} = P_1(G, I), \\ \dfrac{dI(t)}{dt} = \dfrac{\sigma_1 G^2}{\alpha_1^2 + G^2} - d_i I(t) = Q_1(G, I). \end{cases} \tag{4.1}$$

Clearly, for $\sigma_1 = 0$, the system (4.1) has a unique equilibrium $E^0(G^0, 0)$, where $G^0 = (G_{in} + b)/(\sigma_2 + ac)$ and E^0 is a global asymptotically stable node with two separatrixes $I = 0$ and $G = kI$, where $k = amG^0/(n(d_i - \sigma_2 - ac))$.

For $\sigma_1 > 0$, the system (4.1) has a unique equilibrium $E^*(G^*, I^*)$ with $G^* > 0$ and $I^* > 0$. The linearized system of (4.1) at the equilibrium $E^*(G^*, I^*)$ is given by

$$\begin{cases} \dfrac{dG(t)}{dt} = a_{11}G + a_{12}I, \\ \dfrac{dI(t)}{dt} = a_{21}G + a_{22}I, \end{cases}$$

where $a_{11} = -(\sigma_2 + ac) - \frac{amI^*}{n+I^*}$, $a_{12} = -\frac{amnG^*}{(n+I^*)^2}$, $a_{21} = \frac{2\alpha_1^2\sigma_1 G^*}{(\alpha_1^2+(G^*)^2)^2}$, $a_{22} = -d_i$.

Let $\triangle = (a_{11} - a_{22})^2 + 4a_{12}a_{21}$. When $\triangle \geq 0$, E^* is a stable node, and when $\triangle < 0$, E^* is a stable focus. In other words, E^* is locally stable. Notice that

$$\frac{\partial P_1}{\partial G} + \frac{\partial Q_1}{\partial I} = -(\sigma_2 + ac) - \frac{amI}{n+I} - d_i < 0.$$

Thus there exists no closed orbit for the system (4.1) according to Bendixson Theorem ([19]), and therefore E^* is global asymptotically stable.

The isocline $\frac{dG}{dt} = P_1(G, I) = 0$ has an asymptotic line $G = \frac{G_{in}+b}{\sigma_2+ac+am} \triangleq G_s$. Thus, in the system (2.3), if $L_G \leq G_s$, the horizontal lines $G = L_G$ would not intersect with the isocline $\frac{dG}{dt} = P_1(G, I) = 0$, and $I_C = +\infty$, which implies that the trajectory from the initial point below the line $G = L_G$ will undergo infinite impulsive effect and remain in the line $G = L_G$. So we assume that $G_s < L_G < G^0$ for the case $\sigma_1 = 0$, and $G_s < L_G < G^*$ for the case $\sigma_1 > 0$ throughout this section. Clinically, if $L_G < G_s$, the glucose level is probably not in hyperglycemic state; if L_G is above G^0 or G^*, some other medical treatment is required to bring the glucose level down in practice.

4.1. Definitions and notations of the geometric theory of the semi-continuous dynamical systems . We first introduce some notations and definitions of the geometric theory of semi-continuous dynamical systems, which will be useful for the discussion of system (2.3). Definitions 4.1-4.5 and Lemma 4.6 are from Chen ([8]).

DEFINITION 4.1. *Consider the state-dependent impulsive differential equations*

$$\begin{cases} \left.\begin{array}{l} \dfrac{dx}{dt} = \bar{P}(x,y), \\ \\ \dfrac{dy}{dt} = \bar{Q}(x,y), \end{array}\right\} & (x,y) \notin M\{x,y\}, \\ \\ \left.\begin{array}{l} \triangle x = \alpha(x,y), \\ \triangle y = \beta(x,y), \end{array}\right\} & (x,y) \in M\{x,y\}. \end{cases} \tag{4.2}$$

We define the dynamical system consisting of the solution mapping of the system (4.2) a semi-continuous dynamical system, denoted as (Ω, f, φ, M). We require that the initial point P of the system (4.2) should not be in the set $M\{x,y\}$, that is $P \in \Omega = R_+^2 \setminus M\{x,y\}$, 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. For the system (2.3), $\Omega = \{(I,G) : G \le L_G \text{ and } 0 \le I < \infty\}$, $M = \{(I,G) : G = L_G \text{ and } I \le I_C\}$, and for any $(I,G) \in M$, we have $\varphi(I,G) = (I + k\sigma, G)$, where k is an integer such that $I + k\sigma > I_C$, $I + (k-1)\sigma \le I_C$.

DEFINITION 4.2. *For the semi-continuous dynamical system defined by the state-dependent impulsive differential equations (4.2), the solution mapping $f(P,t) : \Omega \to \Omega$ consists of two parts:*

(i) Let $\pi(P,t)$ denote the poincaré map with the initial point P of the following system

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

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

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

Remark. For (ii) in Definition 4.2, if $f(P_1,t) \cap M\{x,y\} \neq \emptyset$, and there exists a time point T_2 such that $f(P_1,T_2) = H_1 \in M\{x,y\}$ and $\varphi(H_1) = \varphi(f(P_1,T_2)) = P_2 \in N\{x,y\}$, then $f(P,t) = \pi(P,T_1) + f(P_1,t) = \pi(P,T_1) + \pi(P_1,T_2) + f(P_2,t)$. Iteratively, if $f(P_{i-1},t) \cap M\{x,y\} \neq \emptyset$ for $i = 2,3,4,\ldots,k$ for some $k > 1$, then

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

DEFINITION 4.3. *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 (4.2) whose period is T_1.*

DEFINITION 4.4. *Suppose $\Gamma = f(P,t)$ is an order one periodic solution of the system (4.2). If for any $\varepsilon > 0$, there must exist $\delta > 0$ and $t_0 \ge 0$, 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.*

Remark. Orbitally asymptotic stability is different from Lyapunov asymptotic stability. An order one periodic solution $\Gamma = f(P,t)$ of the system (4.2) is Lyapunov asymptotically stable if for any $\varepsilon > 0$, then there must exist $\delta > 0$ and $t_0 \geq 0$ such that, for the solution $g(P_1,t)$ starting from any point $P_1 \in U(P,\delta)$, $|g(P_1,t) - f(P,t)| < \varepsilon$ for all $t > t_0$.

Notice that when the impulse set M and the phase set N of the system (4.2) are straight lines, a coordinate system can be well defined in the phase set N. Let $A \in N$ be a point and its coordinate is a. Assume that the trajectory from the point A intersects the impulse set M at a point $A' \in M$, and, after impulsive effect, the point A' is mapped to the point $A_1 \in N$ with the coordinate a_1. Then we define the successor point and the successor function as follows.

DEFINITION 4.5. *The point A_1 is called the successor point of A, and the function $F_1(A) = a_1 - a$ is called the successor function of point A.*

Throughout this paper, in the system (2.3), we define the coordinate of any point $A \in N$ as the distance between A and the G-axis, denoted by I_A. Therefore we have

LEMMA 4.6. *The successor function $F(A)$ is continuous.*

A direction application of Lemma 4.6 leads to following result that plays an important role to study Model (2.3) in next subsection.

LEMMA 4.7. *For the systems (2.3), if there exist two points $A, B \in N$ such that $F(A)F(B) < 0$, then there must exist a point $C \in N$ between the points A and B such that $F(C) = 0$, thus the system must have an order one periodic solution.*

Proof. The continuousness of the successor function by Lemma 4.6 implies the existence of a point $C \in N$ between the points A and B and $F(C) = 0$. Denote C' as the impulse point of C. Since $F(C) = 0$, that is, $\varphi(C') = C$. According to Definition 4.3, $\Gamma = f(C,t)$ is an order one periodic solution. □

4.2. Existence, uniqueness and stability of order one periodic solution. We study Model (2.3) in this section for the case of type 1 diabetes ($\sigma_1 = 0$) and the case of type 2 diabetes ($\sigma_1 > 0$), respectively.

THEOREM 4.8. *For the case $\sigma_1 = 0$, if $G_s < L_G < G^0$ and $I_C < \sigma$, then the system (2.3) has a unique order one periodic solution.*

Proof. Suppose that the horizontal line $G = L_G$ intersects $\frac{dG}{dt} = 0$ at point $C(L_G, I_C)$. Select the point $D(L_G, I_D)$, where $I_D = I_C + \sigma$. Then the trajectory of the system (2.3) through point D must intersect the line $G = L_G$ again at a point $Q(L_G, I_Q)$, where $0 < I_Q < I_C$. The point Q is mapped to the point $Q^{'}(L_G, I_{Q'})$ after impulsive effect, where $I_D > I_{Q'} = I_Q + \sigma > I_C$ (because$I_C < \sigma, I_D = I_C + \sigma$). Again, the trajectory of the system (2.3) passing through point $Q^{'}$ must intersect the line $G = L_G$ at a point $Q_1(L_G, I_{Q_1})$, and the point Q_1 is mapped to the point $Q_1^{'}(L_G, I_{Q_1'})$ after impulsive effect, where $I_{Q_1'} = I_{Q_1} + \sigma$. Since distinct trajectories do not intersect, we can easily have $0 < I_Q < I_{Q_1} < I_C < I_{Q'} < I_{Q_1'} < I_D$. Since the point D is in the phase set, point Q is the impulse point of point D and point $Q^{'}$ is the successor point of point D, we can get the successor function of point D is $F(D) = I_{Q'} - I_D < 0$. Besides, for the point $Q^{'}$ in the phase set, point Q_1 is the impulse point of point $Q^{'}$ and point $Q_1^{'}$ is the successor point of point $Q^{'}$, so we can get the successor function of point $Q^{'}$ is $F(Q^{'}) = I_{Q_1'} - I_{Q'} > 0$. By Lemma 4.6 and Lemma 4.7, there must exist a point M between the points Q' and D such that $F(M) = 0$, and thus the system (2.3) has an order one periodic solution that has the point M as its phase point (refer to the left panel of Fig. 4.1.).

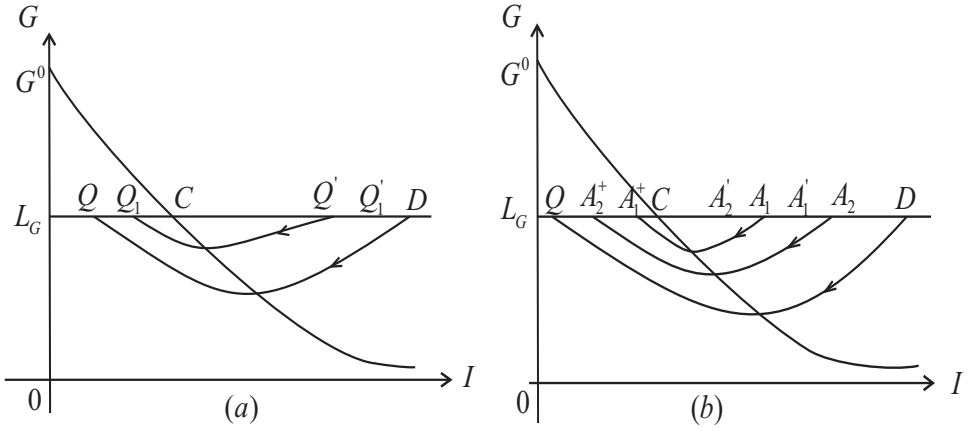

FIG. 4.1. *Existence and uniqueness of order one periodic solution of (2.3).*

In the following, we prove the uniqueness of the order one periodic solution. Arbitrarily choose two points A_1 and A_2 in the phase set, where $I_C < I_{A_1} < I_{A_2} < I_D$. Then the trajectories of the system (2.3) 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 $I_Q < I_{A_2^+} < I_{A_1^+} < I_C$. The points A_1^+ and A_2^+ must be mapped to two points in the phase set after impulsive effect which we denote as $A_1^{'}$ 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 M such that $F(M) = 0$ (refer to the right panel in Fig. 4.1). That completes the proof. □

We shall show the order one periodic solution is orbitally asymptotically stable. That implicates in clinic that some perturbation would not affect the effect of treatment drastically.

THEOREM 4.9. *For the case $\sigma_1 = 0$, if $G_s < L_G < G^0$ and $I_C < \sigma$, then the order one periodic solution of the system (2.3) is orbitally asymptotically stable.*

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

According to Theorem 4.8, the system (2.3) has a unique order one periodic solution that has the point $M(L_G, I_M)$ as its phase point, where $I_{Q'} < I_M < I_D$.

Consider the successor point $Q^{'}$ of point D (which is defined in Theorem 4.8 and refer to the left panel of Fig. 4.2), we know $I_C < I_{Q'} < I_M$. The trajectory passing through the point $Q^{'}$ must intersect the impulse set again at point Q_1 which is the impulse point of $Q^{'}$, and the point Q_1 must be mapped to point $Q_1^{'}$ after impulsive effect which is the successor point of $Q^{'}$. Besides, we denote the impulse point of the order one periodic solution as M'. Because distinct trajectories do not intersect, we can easily get $I_Q < I_{M'} < I_{Q_1} < I_C$ and $I_M < I_{Q_1'} < I_D$.

Similarly, the trajectory passing through the point $Q_1^{'}$ must intersect the impulse set again at point Q_2 which is the impulse point of $Q_1^{'}$, and the point Q_2 must be

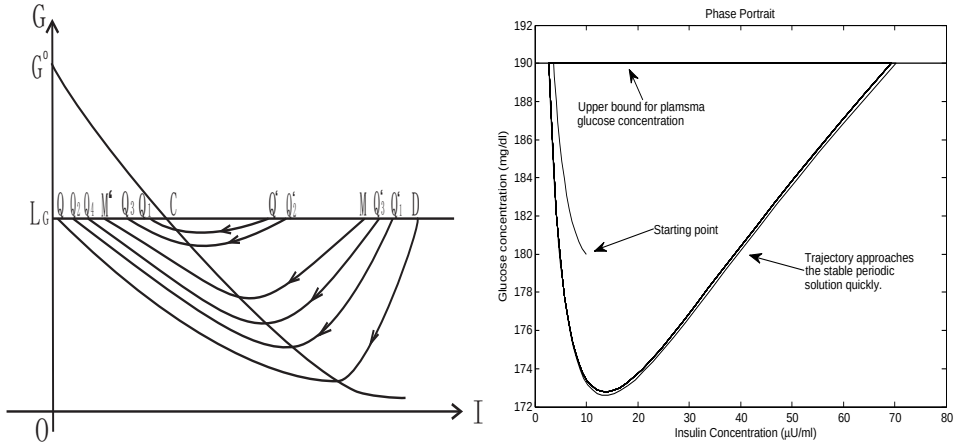

FIG. 4.2. *Left Panel: Illustration of the orbitally asymptotically stability of the order one periodic solution of the system (2.3) when* $G_s < L_G < G^0$ *and* $I_C < \sigma$. *Right Panel: Orbit in phase plane by Model (2.3). It is shown that the solution is asymptotically orbital stable. It is also clearly seen that the glucose concentration is controlled by a preset threshold value with* $L_G = 160, \sigma = 100, G(0) = 155$, *and* $I(0) = 55$.

mapped to point $Q_2^{'}$ after impulsive effect which is the successor point of $Q_1^{'}$. We have $I_Q < I_{Q_2} < I_{M'}$ and $I_{Q'} < I_{Q_2'} < I_M$.

Repeat the above steps, the trajectory from point D will come across impulsive effect infinitely times. Denote the phase point corresponding to the i^{th} impulsive effect as $Q_{i-1}^{'}$, $i = 1, 2, \cdots$, where $Q_0^{'} = Q'$. We have

$$I_C < I_{Q_0'} < I_{Q_2'} < I_{Q_4'} < \cdots < I_{Q_{2k}'} < I_{Q_{2(k+1)}'} < \cdots < I_M,$$

and

$$I_D > I_{Q_1'} > I_{Q_3'} > I_{Q_5'} > \cdots < I_{Q_{2k+1}'} > I_{Q_{2(k+1)+1}'} > \cdots > I_M.$$

Thus $\{I_{Q_{2k}'}\}, k = 0, 1, 2, \cdots$, is a monotonically increasing sequence, and $\{I_{Q_{2k+1}'}\}, k = 0, 1, 2, \cdots$, is a monotonically decreasing sequence (see the left panel of Fig. 4.2), and furthermore,

$$I_{Q_{2k}'} \to I_M, \text{ as } k \to \infty; \quad \text{and} \quad I_{Q_{2k+1}'} \to I_M, \text{ as } k \to \infty.$$

Choose an arbitrary point $P_0 \in \overline{Q'D}$, which is different from the point M. Without loss of generality, we assume that $I_{Q'} < I_{P_0} < I_M$ (otherwise, $I_M < I_{P_0} < I_D$, the discussion is similar). There must exist an integer k such that $I_{Q_{2k}'} < I_{P_0} < I_{Q_{2(k+1)}'}$. The trajectory from point P_0 will also undergo impulsive effect infinitely times. We denote the phase point corresponding to the l^{th} impulsive effect as P_l, $l = 0, 1, 2, \ldots$, then for any l, $I_{Q_{2(k+l)}'} < I_{P_{2l}} < I_{Q_{2(k+l+1)}'}$ and $I_{Q_{(2k+l+1)+1}'} < I_{P_{2l+1}} < I_{Q_{2(k+l)+1}'}$, so $\{I_{P_{2l}}\}, l = 0, 1, 2, \cdots$, is also monotonically increasing, and $\{I_{P_{2l+1}}\}, l = 0, 1, 2, \cdots$, is also monotonically decreasing, and

$$I_{P_{2l}} \to I_M, \text{ as } l \to \infty; \quad \text{and} \quad I_{P_{2l+1}} \to I_M, \text{ as } l \to \infty.$$

Therefore, in either case, the successor points of the phase points corresponding to the successive impulsive effect are attracted to the point M, which implies that the order one periodic solution of the system (2.3) is orbitally asymptotically stable. □

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

THEOREM 4.10. *When $\sigma_1 > 0$, if $G_s < L_G < G^*$ and $I_C < \sigma$, then the system (2.3) has a unique order one periodic solution, and it is orbitally asymptotically stable.*

The right panel in Fig. 4.2 displays one orbit with initial condition below the threshold value and its stability. Fig. 5.3 shows that the plasma glucose level is controlled under the predefined threshold value 190 mg/dl with various initial values.

5. Numerical simulations. The use of insulin pump, also called continuous subcutaneous insulin infusion (CSII) therapy, has greatly increased for type 1 diabetes ([18]). It can also provide a feasible alternative to insulin injections for type 2 diabetes ([6], [22], [24], [35]). Model (2.2) proposed in this paper is based on physiology for the regulation of glucose and insulin with the mimicking of subcutaneous injection of analogue with periodic impulse. Thus Model (2.2) is close to the practical situation in clinic for the so called open-loop administration. The loop can be closed in clinical therapies by incorporating the feedback for blood suger from accurate glucose monitoring system. In such case, Model (2.3) provides a robust model with the most important and critical feature, that is, the timing of insulin injection is determined by the blood suger level read from an accurate glucose monitor. A wide accepted agreement by researchers for artificial pancreas is for each model to get a better understanding of strength and weakness in validating different control algorithms ([27]) and develop clinical applicable controls. In this section, we apply Model (2.2) and Model (2.3) under a few typical clinical situations and study the simulation results.

Insulin analogues sold in market off-shelf are usually stored at temperatures between 36°F - 46°F (2°C - 8°C) in different concentration, e.g., 40U or 100U in a 10ml vial. The units of insulin and glucose in our model are μU/ml and mg/dl, respectively. So we need to make necessary conversion to obtain the dose as the model input of insulin injection. Two common methods, the weight method and an individual plan, are often employed to determine dose through insuli-to-carb ratios. Weight method assumes that insulin resistance increases along with weight so the dose should be larger if apatient has gained weight. Individual plan method is an empirical process by deploying a series of daily doses and then adjusting accordingly to find the best plan. (Refer to [36].) In our simulation, we assume that the volume of the plasma compartment in human is 10 liter (l). According to the dose calculator suggested by [34], we calculate that for dose as follows. If inject xU for a $y$kg subject every z minute, then, in each time, the injected insulin $T = x\text{U}\times y \times 10^6\mu\text{U}$. For every 30 minutes, the total injected mass for 48 times in 24 hours is at $m = T/48\mu$U, so the concentration $I = m(10 * 10^3)\mu$U/ml. For example, if inject 0.5U for a 85kg subject every 30 minute, then total injected insulin $T = 0.5\text{U}\times 85 = 42.5$U, that is $T = 42.5\text{U}\times 10^6\mu$U. For every 30 minutes, the injected mass is at $m = T/48 = 885420\mu\text{U} \approx 0.89$U, so the concentration $I = m/(10 \times 10^3) = 88.5420\mu$U/ml.

The parameter values in our simulations are determined either by comparing the response functions f_1, f_2, f_3, f_4 and f_5 in [28] and [29], or from the models for intravenous glucose tolerance test (IVGTT) in [9], [17], [20] and [21] (see Table 5.1), which were estimated by experiments. Since the units of glucose and insulin of the model in [28] are mass, unit conversion is made, as in [14] and [16], for display.

TABLE 5.1

Approximated model parameter values from existing references. Necessary conversions of units are made and the values are adjusted within reasonable ranges.

Parameters	Values	units	References
G_{in}	2.16	mg/dl	[14], [16], [28], [29]
b	1	mg/dl/min	[9], [14], [16], [28], [29]
σ_2	5×10^{-6}	min^{-1}	[9], [17]
a	3×10^{-5}	mg^{-1}	[9], [14], [16], [17], [28], [29]
c	0.4	mg/dl/min	[14], [16], [28], [29]
m	9.0	mg/dl/min	[14], [16], [28], [29]
n	80	mg/dl	[28]
σ_1	20.9	μU/ml/min	[28]
α_1	105	mg/dl	[14], [16], [17], [20], [21], [28], [29]
d_i	0.06	min^{-1}	[14], [16], [17]

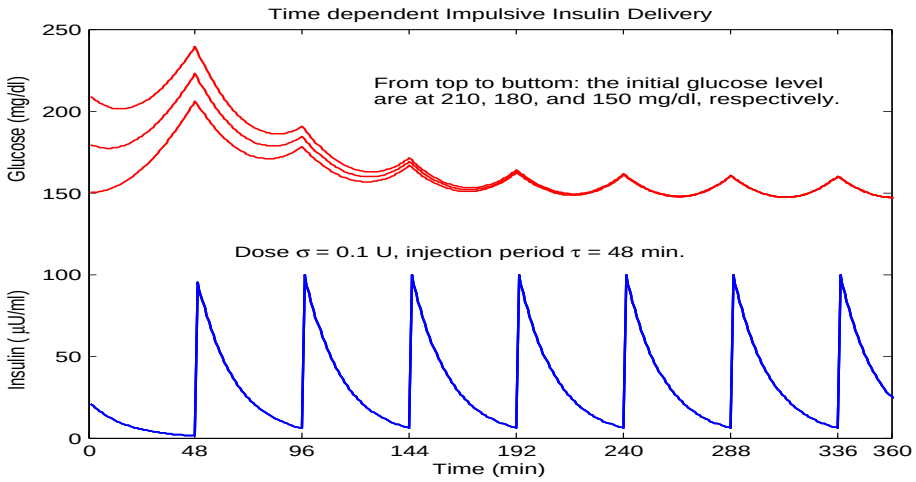

FIG. 5.1. *Positive periodic solutions of (2.2) for type 1 diabetes ($\sigma_1 = 0$) with different initial values with $\sigma = 1000$ (mU).*

For insulin pump in open-loop approach for type 1 diabetes, according to Theorem 3.9 and 3.10, a unique positive and globally stable periodic solution exists (refer to Fig. 5.1). Fig. 5.1 also reveals that, with different initial glucose levels, about three delivery cycles are needed to make plasma glucose in an oscillatory homeostasis.

For type 2 diabetes ($\sigma_1 > 0$), Theorem 3.11 ensures that the solutions are bounded above and below (refer to Fig. 5.2). We compare the profiles by setting the delivery impulses in different periods but at the same total daily dose. We noticed that under the open-loop environment, for the same daily total dose, the impulsive injection with smaller dose but shorter period has more efficient effect on controlling plasma glucose level than the injection with larger dose but longer period, which is demonstrated by Fig. 5.2. The numerical observation is similar for the case of type 1 diabetes ($\sigma_1 = 0$) (which is not shown in this paper).

For the case of artificial pancreas with closed-loop approach, our theoretical results (Theorem 4.8, 4.9 and 4.10 qualitatively ensure that the state-dependent impulsive

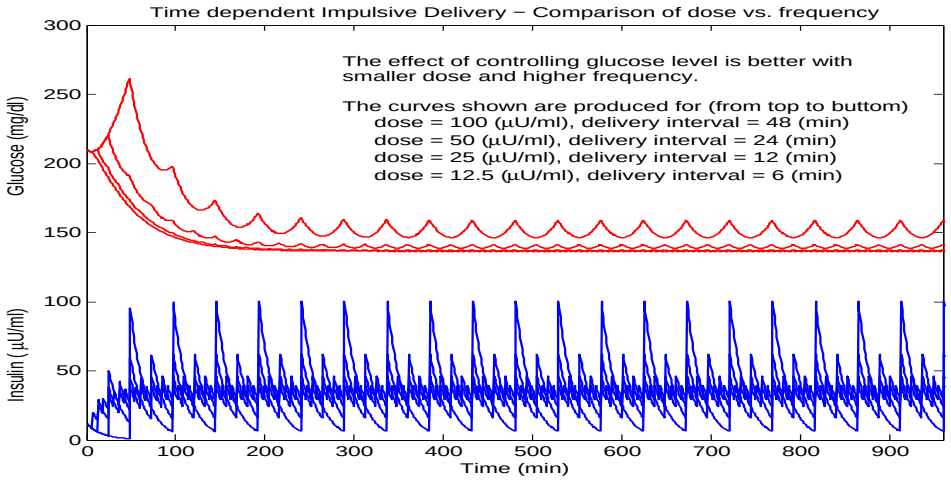

FIG. 5.2. *Comparison of the profiles produced by Model (2.2) for type 2 diabetes ($\sigma_1 > 0$) with the same total daily dose vs different delivery periods.*

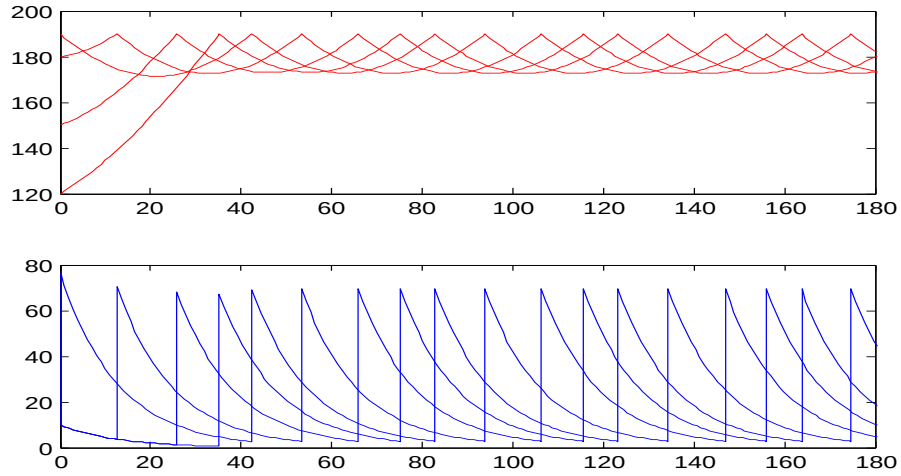

FIG. 5.3. *Comparison of the profiles produced by Model (2.3) with different initial glucose levels. Glucose concentration is controlled under the threshold level $L_G = 190$ while $\sigma = 1000(mU)$.*

insulin delivery will maintain the system at a sustained oscillatory homeostasis controlled by a predefined threshold value (L_G). Given the model parameters in Table 5.1, $L_C = 106.6345$. Fig. 5.4 exhibits not only orbital stable periodic solutions, but also that smaller dose creates smaller amplitude and shorter period or faster frequency. It is clear shown that the glucose concentration is successfully controlled under the threshold value 190mg/dl. In this case, we would suggest to apply larger dose so that the glucose concentration stays in lower level for longer time. However, dose has to be carefully calculated to avoid hypoglycemic episodes.

6. Discussions. In this paper we proposed two models that have potential contributions to the designs of algorithms for insulin pump, and the development of artificial pancreas. This is probably the first attempt to formulate a physiological

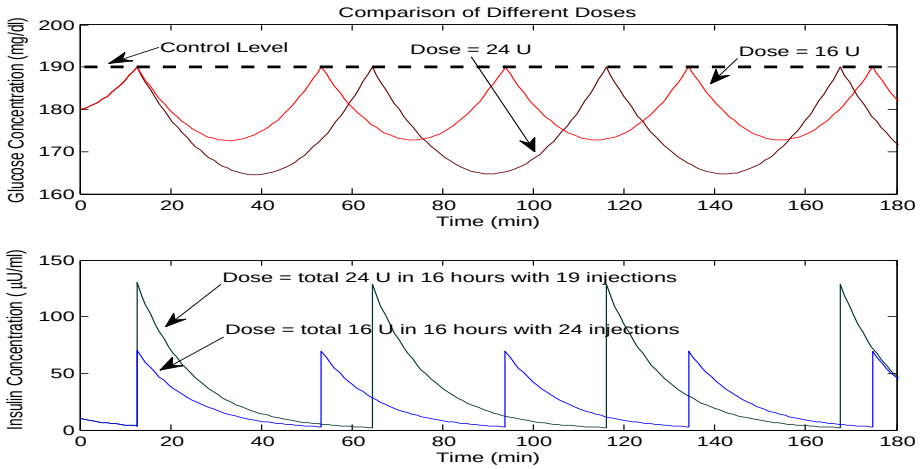

FIG. 5.4. *Comparison of the profiles produced by Model (2.3) with different doses controlled by a pre-set threshold level of glucose concentration with* $L_G = 160, \sigma = 100, G(0) = 155$ *and* $I(0) = 55$.

and metabolic model by a semi-continuous dynamical system. This novel approach enables that insulin delivery can be modeled by periodic impulse and state-dependent impulse.

The analytical studies of Model (2.2) with periodic impulsive insulin delivery and the semi-continuous system model (2.3) with state-dependent impulse ensures that blood suger level is under control provided that some undemanding conditions are satisfied (refer to (Theorem 3.9, Theorem 3.10, Theorem 3.11, Theorem 4.8, Theorem 4.9 and Theorem 4.10). Numerical simulations reveal that smaller dose with shorter period of impulsive injection produces more efficient and effective outcome in controlling glucose level than a therapy using larger dose with longer period of impulse for open-loop oriented insulin pumps. In contrast, for artificial pancreas with closed-loop design, larger dose will keep glucose level remaining at lower level for longer time. This is ideal if hypoglycemic episodes can be prevented. These observations could have significant implications in the endeavors of designing efficient and effective algorithms based on open loop models for insulin pump, and development of control algorithms for artificial pancreas based on models in the fashion of closed-loop regulations.

It is well known that a time delay exists for insulin secretion upon the stimulation of elevated glucose concentration level ([16], [28]). Another time delay comes from control system sensing the blood suger level and feedback to the model. It would be more realistic if these two time delays are incorporated in Model (2.2) and Model (2.3). We will consider such delays in next study.

Mostly likely, insulin injected subcutaneously by insulin pump is insulin analogues, for example, fast-acting aspart and long-acting glargine ([15]). The dissolution of such analogues in injection depot follows certain dynamics. Certain impact is inevitably imposed on to the dynamics of plasma glucose level. Several pharmacokinectical models are proposed for the dissolution of insulin analogues in injection depot, which is used to estimate plasma insulin concentration. The most recent model in this area is a systemic model proposed by Li and Kuang ([15]), in which plasma insulin is integrated as a variable thus the computation for plasma insulin level is more accurate. Li and Johnson summerize above in [13]. Information obtained from

such models may be useful in design and development of artificial pancreas.

The exogenous glucose input in the models proposed in this paper is estimated at an average constant rate G_{in}. In reality, the glucose input rate can never be a constant. Instead, it varies with time, for example, meal ingections affect the input rate. The authors of [11] simulate meal ingestion by

$$R_A(t) = \frac{C_H(t)}{V_G \tau_m^2} t e^{-\frac{1}{\tau_m}},$$

where C_H is the amount of carbohydrate consumed at time t, τ_m is the peak time of absorption, and V_G is the glucose distribution volume. We also speculate that a combination of the model proposed by Hovorka et al ([10]) as the input of the endogenous glucose with the models proposed in this paper could form a more comprehensive and reliable simulation model.

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