

MODELING IMPULSIVE INSULIN DELIVERY IN INSULIN PUMP WITH TIME DELAYS*

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Abstract. We continue our attempt of modeling the open-loop control of glucose level by impulsive insulin injections. Several time delays exist in the system. The delays include the time needed for insulin from injection depot to transport to the interstitial compartment, the time for the slow inhibition of the hepatic glucose production (HGP), and the time for insulin secretion caused by the elevated glucose concentration level from remaining functional pancreatic β -cells. None of them are negligible. The model proposed in this paper incorporates these time delays. Our analytical studies show that all solutions are permanent, a periodic solution exists, and for the case of type 1 diabetes mellitus the periodic solution is unique and globally asymptotically stable. Numerically it has been shown that moderate time delays in the system are beneficial in lowering blood sugar level rather than harmful. In contrast, these time delays cause that the open-loop control takes a longer time to lower glucose concentration level. Our studies also elucidate the noticeable inhibitory effect on HGP by the remaining functional β -cells. Similarly to our previous work, we demonstrated that a smaller dose with higher delivery frequency has a better effect on continuous subcutaneous insulin injection administration. We expect that our findings are helpful for clinical therapies.

Key words. open-loop control, glucose level control, impulsive insulin delivery, time delays, insulin pump, artificial pancreas

AMS subject classifications. 92C50, 34K45, 34D20, 92D25

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1. Introduction. Diabetes mellitus is a metabolic disease characterized by high plasma glucose concentration level and caused by multiple pathogenic factors. In general, diabetes mellitus is classified into three main categories: type 1 diabetes (T1DM), usually juvenile onset, is mainly due to the dysfunction of the β -cells in the pancreas and no insulin can be synthesized and secreted; type 2 diabetes (T2DM), usually adult onset, is caused by insufficient utilization of insulin so that the glucose cannot be consumed timely; and gestational diabetes, which is defined as glucose intolerance of various degrees that is first detected during pregnancy. In the glucose-insulin regulatory system, elevated glucose concentration caused by meal ingestion, oral glucose intake, and hepatic and enteral glucose productions, incites the secretion of insulin from pancreatic β -cells, helping to return the glucose concentration to normal levels. When the glucose concentration level decreases, the secretion stops gradually [31].

Over the past decades, a number of models have been developed to describe the dynamic relationship between glucose and its controlling hormone insulin (see [2], [5],

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[22], [28], [31], [46], [48], [49], [51], [54], [55]). Ajmera et al. [2] reviewed the impact of mathematical models in diabetes and related complications in the past 50 years. The authors of [2] summarized almost all important mathematical models in this niche with a detailed classifications of these models. The most well-known model in clinic use is the minimal model by Bergman et al. [8], which is widely used to determine the insulin sensitivity index and the glucose effectiveness index through the intravenous glucose tolerance test (IVGTT). The models proposed by Sturis et al. [49] and Tolic, Mosekilde, and Sturis [51] elucidated that the ultradian oscillations of insulin secretion may be caused by the time delays rather than a pacemaker, while the models by Li and his colleagues [28], [31] mainly analyzed the effect of the time delays in the system, which are important factors for the sustained ultradian oscillations of insulin secretion. Bertram et al. [9] might possibly be the most representative work in modeling β -cell electrophysiology.

The ultimate goal of all the relevant research is of course to provide effective and efficient therapies for diabetic patients. Extensive research to this end has been carried out by researchers and medical doctors. Up to date, subcutaneous injection of insulin analogues is a commonly applied regimen in clinics. An insulin pump, a medical device for insulin administration, is popularly applied in continuous subcutaneous insulin injection (CSII) therapy for both T1DM and T2DM (see [10], [16], [19], [33], [38], [40], [42]). The pump administers insulin doses through a tiny implantable catheter and relieves the pain of the patient greatly. The therapies with insulin pump follow the so called *open-loop* approach, that is, insulin is injected without knowledge of plasma glucose level [22]. A large number of surveys and studies have shown that using an insulin pump can be an efficient and fast way to control the blood sugar and also reduce the number of hypoglycemic episode. The insulin pump has been in use for more than a decade in the fashion of open-loop control. It is expected that the loop can be *closed* by integrating a glucose monitoring system (GMS) with one or multiglucose sensors. Such a closed-loop control system is also called an *artificial pancreas*. A number of mathematical models and algorithms have been developed for the artificial pancreas ([17], [20], [25], [45], [47], [46], [48], and the references therein). Steil, Hipszer, and Reifman [46] summarized the progress of development of the artificial pancreas. The authors continue to advocate open collaborations between groups since individual investigators keep the details of the models and algorithms confidential. Nevertheless, as summarized by [2], using the glucose kinetic model in [21] with Bayesian parameter estimation, Hovorka et al. [20] developed a nonlinear predictive controller model for the case of fasting conditions in T1DM patients. Based on the minimal models by Bergman, Phillips, and Cobelli [7] and Cobelli, Toffolo, and Ferrannini [11], Fabietti et al. [17] proposed a model and developed an algorithm for an artificial pancreas, which was later validated using clinical data [18]. Dalla Man, Rizza, and Cobelli [14] proposed a whole-body insulin-glucose dynamical model for different physiological events following a meal by extending their previous model in [13]. This model was later developed into an *in silico* simulator, UVa simulator [12], and was accepted by the US Food and Drug Administration for preclinical trial and studying insulin treatments on animals in 2009 [25]. Wilinska et al. [56] presented a similar model for evaluating insulin delivery in T1DM patients in 2010. Interestingly it is a consensus that the 24-hour open-loop prediction is neither similar to nor dramatically different from the closed-loop control simulation results according to [46].

We proposed two ordinary differential equation (ODE) models in our previous work [22], which simulate periodic impulsive injection of insulin in open-loop control (insulin pump therapy), and state-feedback impulsive injection of insulin in closed-

loop control (artificial pancreas therapy), respectively. According to [15], [28], [30], [31], [49], [51], [54], and the references therein, there exist three physiological time delays in this system. The first one is due to the time needed for β -cells, stimulated by the elevated glucose concentration level, to release insulin; the second is the time needed for plasma insulin to cross the endothelial barriers and become interstitial insulin that can help cells, e.g., muscle and adipose cells, to consume glucose; and the third represents the delayed effect of increasing insulin concentration on inhibition of the HGP [49], [51]. However, we did not incorporate these time delays into the models, and some factors in the glucose-insulin system are also oversimplified. For example, the response functions are assumed to be in concrete simplified forms. In this paper, we incorporate aforesaid time delays and formulate a delay differential equation (DDE) model with impulsive inputs of insulin and general response functions. We expect that the analytical and numerical studies of this dynamic model can provide insightful guidance in the application of insulin pumps.

The paper is organized as follows. In section 2, we formulate an impulsive DDE model to simulate the impulsive insulin injection for diabetic patients in open-loop control. In section 3, we analyze the existence and stability of the periodic solution of the model. In section 4, the numerical simulations are carried out, which not only confirm the theoretical results, but also are complementary to those theoretical results with specific features. We finish this paper with a brief discussion in section 5.

2. Model formulation. Although the control is still in an open-loop fashion, the insulin pump is currently the most efficient and effective regime for T1DM. Closing the loop requires perceptive algorithms to predict accurate dose and precise timing with the ultimate goal to avoid hyperglycemia and reduce hypoglycemic episode. Perceptive algorithms must be robust to take account of all typical cases of physiological stress (e.g., overnight control, day-by-day variability, randomized food intake, and exercise), and able to address hypoglycemic episodes. Such algorithms shall be developed based on mathematical models that are truly realistically taking all clinical cases into account, and sufficiently robust on all model parameter values in physiological ranges (refer to section 1 for a brief summary). However in this paper we only formulate a DDE model for open-loop control with explicit time delays but leave the state-feedback case (close-loop control) for our future work.

In the glucose and insulin regulations, three time delays exist (see [15], [28], [30], [31], [49], [51], [54], and the references therein). Sturis et al. [49] noticed the delayed inhibition of HGP when insulin concentration level increases. In 1979, Bergman et al. [8] observed that the effect of insulin on lowering glucose level is not immediate when they were developing the minimal model. It was later realized that the sluggish effect arises because insulin molecules need to be transported to the interstitial compartment and then exert their action on glucose disposal [6]. De Gaetano and Arino [15] and Li, Kuang, and Li [30] used an explicit time delay to model the IVGTT protocol. Li and his colleagues modeled the glucose-insulin regulatory system [28], [31] and insulin administrations [54], [55] with two explicit time delays. A more comprehensive review for modeling physiological systems by explicit time delays can be found in [3]. In summary, these time delays are (i) insulin secretion time delay $\tau_s > 0$: measured from the moment that the plasma glucose level is elevated to the moment that insulin is released from β -cells to the plasma compartment; (ii) insulin transport time delay $\tau_t > 0$: measured from the needed for plasma insulin is transported to the intercellular for insulin-dependent glucose utilization; and (iii) time delay of HGP $\tau_h > 0$: measured from the moment the elevated insulin level to the moment that HGP stops. When

modeling this system, these time delays are not negligible. We incorporate these delays explicitly to propose a DDE model for the open-loop control. It is worthwhile noting that the time delays can be modeled by using a rate constant with an additional auxiliary variable for the first order time delay. Even though, as pointed out by Li, Kuang, and Mason ([31, the third paragraph on p. 729]), such an approach is indeed a truncated Taylor expansion to first order of an explicit discrete time delay. However a higher order time delay should not be modeled by a single rate constant. Notice that the HGP delay τ_h is of a third order time delay according to Sturis et al. [49], that is, three auxiliary variables have to be added when modeling this delay by the rate constant approach [49]. The addition of the extra and unmeasurable auxiliary variables increases the dimension of the ODE system and could increase the difficulty in parameter estimation. The possible difficulty in parameter estimation caused by those unmeasurable variables and additional parameters could result in less accurate parameter values. To reduce such an unnecessary but possible issue, it is our modeling choice to model these time delays by explicit form. To this end, we extend model (2.2) in Huang et al. [22] by incorporating these delays and formulating a DDE model with periodic impulsive injection of exogenous insulin. The model is given by

$$(2.1) \quad \left\{ \begin{array}{l} \frac{dG(t)}{dt} = G_{in}(t) - f_2(G(t)) - f_3(G(t))f_4(I(t - \tau_t)) \\ \quad \quad \quad + f_5(I(t - \tau_h)), \\ \frac{dI(t)}{dt} = f_1(G(t - \tau_s)) - d_i I(t), \\ \left. \begin{array}{l} G(t^+) = G(t), \\ I(t^+) = I(t) + \sigma, \end{array} \right\} \quad t = kp,$$

with initial condition $G(t) = G_0 > 0, I(t) = I_0 > 0$ for $t \in [-\tau, 0]$, where $\tau = \max\{\tau_s, \tau_t, \tau_h\}$. The parameters $\tau_s > 0, \tau_t > 0$, and $\tau_h > 0$ represent the insulin secretion delay, insulin transport delay, and hepatic production delay discussed above, respectively. σ (mU) > 0 is the dose in each injection and p (min) > 0 is the period of the impulsive injection, that is, σ mU insulin is injected impulsively at the time mark $t = kp$ min, $k \in \mathbb{Z}^+ = \{1, 2, 3, \dots\}$. The moment immediately after the k th injection is denoted as $t = kp^+$ here.

According to [24], the shapes of the response functions f_1, f_2, f_3, f_4 , and f_5 are important instead of their forms. Throughout this paper we assume that for normal people, these functions are in generic forms as defined in [28] and [54] and satisfy the following conditions:

- (i) $G_{in}(t) \in C([0, \infty), (0, \infty))$ is a positive p -periodic function.
- (ii) $f_1(x)$ is assumed to be in sigmoidal shape, so we can suppose $f_1(x) \geq f_1(0) = m_1 \geq 0, M'_1 > f'_1(x) > 0$ for $x > 0$, and $\lim_{x \rightarrow \infty} f_1(x) = M_1$.
- (iii) $f_2(x) \geq f_2(0) = 0, M'_2 > f'_2(x) > 0$ for $x > 0$, and $\lim_{x \rightarrow \infty} f_2(x) = M_2$.
- (iv) $f_3(x) \geq f_3(0) = 0, f_4(x) \geq f_4(0) = m_4, M'_3 > f'_3(x) > m'_3 > 0$, and $M'_4 > f'_4(x) > 0$ for $x > 0$. Besides, $\lim_{x \rightarrow \infty} f_3(x) = M_3$ and $\lim_{x \rightarrow \infty} f_4(x) = M_4$.
- (v) $0 \leq f_5(x) \leq f_5(0) = M_5, -M'_5 < f'_5(x) < 0$ for $x > 0$, and $\lim_{x \rightarrow \infty} f_5(x) = 0$.

It is noteworthy that soluble insulin used in insulin pumps is in the form of oligomers. In such pumps, highly concentrated soluble insulin is present in hexameric form, which cannot be directly absorbed into the blood stream. The soluble insulin is injected into the subcutis in impulsive fashion. The insulin solution is diluted through mixing with the intercellular liquid, and the fraction of hexameric insulin is reduced

to about 60%. The dissolving process includes that hexamers dissolve into dimers and dimers dissolve into monomers. Because only (monomeric and) dimeric insulin molecules are small enough to penetrate the capillary wall and enter the blood stream, the rate of absorption is determined by the fraction of dimeric insulin. As reviewed in [27] and [35], quite a few models in both partial differential equation and ODE systems have been developed to describe such a dissolving process for long-acting and quick-acting insulin analogues, for example, Mosekilde et al. [34], Trajanoski et al. [52], Wach et al. [53], Tarín et al. [50], Wilinska et al. [57], and Li, Kuang, and Mason [29], in which the dynamics of a single dose injection in the injection depot is studied in detail. Particularly, Rasmussen et al. [39] reviewed the physical, chemical, and biological processes in the subcutaneous insulin depot after insulin aspart is injected. Such a process may greatly smooth out the impact of the impulseness of the injections. Thus the plasma insulin input may not be precisely in the impulsive fashion. Nevertheless, modeling the input of plasma insulin by impulse can still provide prudent illustration for impulsive dosing of rapid-acting insulin. We will study the impacts of the dissolving process on plasma insulin input from a variety of insulin analogues in detail in future work.

3. Qualitative analyses. In this section, we particularly investigate the existence and stability of the periodic solution of the model (2.1).

3.1. Preliminaries. Similarly to [22], we first show the positiveness and the boundedness of the solutions of the system (2.1).

PROPOSITION 3.1 (positiveness). *Suppose that $x(t) = (G(t), I(t))$ is a solution of the system (2.1) with $G(t) = G_0 > 0, I(t) = I_0 > 0$ for all $t \in [-\tau, 0]$, then $G(t) > 0, I(t) > 0$ for all $t > 0$.*

Proof. Let $(G(t), I(t))$ be a solution of the system (2.1) with $G(t) = G_0 > 0, I(t) = I_0 > 0$ for all $t \in [-\tau, 0]$. We first show that it is nonnegative. If $G(t)$ is not nonnegative, then there exists $t > 0$ such that $G(t) < 0$. Let $t^* = \inf\{t : G(t) < 0\}$, then $G(t^*) = 0$ and $G'(t^*) < 0$. By the first equation of the system (2.1), we have

$$G'(t^*) = G_{in}(t^*) + f_5(I(t^* - \tau_h)).$$

If $I(t) \geq 0$ for all $t > 0$, then we have $I(t^* - \tau_h) \geq 0$. It is obviously $f_5(I(t^* - \tau_h)) \geq 0$ and $G'(t^*) > 0$, which is a contradiction.

If there exists $t > 0$ such that $I(t) < 0$, let $t_* = \inf\{t : I(t) < 0\}$, then $I(t_*) = 0$ and $\lim_{t \rightarrow t_*^-} I'(t) < 0$. By the second equation of the system (2.1), we have

$$\lim_{t \rightarrow t_*^-} I'(t) = f_1(G(t_* - \tau_s)).$$

Then there are the following two cases.

When $t^* \leq t_*$, then $t^* - \tau_h < t_*$, $I(t^* - \tau_h) \geq 0$, we have $f_5(I(t^* - \tau_h)) \geq 0$ and $G'(t^*) > 0$, which is a contradiction.

When $t^* > t_*$, then $t_* - \tau_s < t^*$, $G(t_* - \tau_s) \geq 0$, we have $f_1(G(t_* - \tau_s)) \geq 0$ and $\lim_{t \rightarrow t_*^-} I'(t) \geq 0$, which is also a contradiction.

From the above, we know $G(t) \geq 0, I(t) \geq 0$ for $t > 0$.

Besides, it is clear that $dG(t)/dt > 0$ when $G(t) = 0$ and $dI(t)/dt \geq 0$ when $I(t) = 0$. Therefore we have $G(t) > 0, I(t) > 0$ for all $t > 0$ if $G(t) = G_0 > 0, I(t) = I_0 > 0$ for all $t \in [-\tau, 0]$. \square

PROPOSITION 3.2 (boundedness). *For a solution $(G(t), I(t))$ of the system (2.1) with positive initial values, there exists a positive constant H such that $G(t) \leq H$ and $I(t) \leq H$ for all $t \geq 0$.*

Proof. From the first equation of the system (2.1) we have

$$\frac{dG(t)}{dt} \leq \sup_{t \in [0, p]} G_{in}(t) - m'_3 m_4 G(t) + M_5,$$

then there exists a positive number $H_1 > 0$ such that $G(t) \leq H_1, t \geq 0$.

From the second and the fourth equations of the system (2.1), we have

$$\begin{cases} \frac{dI(t)}{dt} \leq M_1 - d_i I(t), & t \neq kp, \\ I(t^+) = I(t) + \sigma, & t = kp, \\ I(0) = I_0 > 0. \end{cases}$$

Now we consider the impulsive differential equation

$$(3.1) \quad \begin{cases} \frac{dI_1(t)}{dt} = M_1 - d_i I_1(t), & t \neq kp, \\ I_1(t^+) = I_1(t) + \sigma, & t = kp, \\ I_1(0^+) = I_0 > 0. \end{cases}$$

We know that the system (3.1) has a globally asymptotically stable positive periodic solution

$$\begin{cases} \tilde{I}_1(t) = \frac{M_1}{d_i} + \frac{\sigma \exp(-d_i(t - kp))}{1 - \exp(-d_i p)}, & t \in (kp, (k+1)p], k \in Z_+, \\ \tilde{I}_1(0^+) = \frac{M_1}{d_i} + \frac{\sigma}{1 - \exp(-d_i p)}, \end{cases}$$

and the solution of the system (3.1) takes the form

$$I_1(t) = (I_1(0^+) - \tilde{I}_1(0^+)) \exp(-d_i t) + \tilde{I}_1(t),$$

which satisfies $\lim_{t \rightarrow \infty} I_1(t) = \tilde{I}_1(t)$.

Then we can easily get

$$I(t) \leq I_1(t) \leq \frac{M_1}{d_i} + \frac{\sigma}{1 - \exp(-d_i p)} + |I_2(0^+) - \tilde{I}_2(0^+)| \quad \text{for } t \geq 0,$$

and therefore there exists a positive number $H \geq H_1$ such that $I(t) \leq H$ for $t \geq 0$. \square

3.2. Permanence. We shall show that the system (2.1) is permanent.

THEOREM 3.3. *The system (2.1) is permanent, that is, the solutions are bounded below and above by some constants.*

Proof. From the first equation of the system (2.1) we have

$$\frac{dG(t)}{dt} \geq \inf_{t \in [0, p]} G_{in}(t) - M'_2 G(t) - M'_3 M_4 G(t),$$

and

$$G(t) \geq \left(G_0 - \frac{\inf_{t \in [0, p]} G_{in}(t)}{M'_2 + M'_3 M_4} \right) \exp(-dt) + \frac{\inf_{t \in [0, p]} G_{in}(t)}{M'_2 + M'_3 M_4},$$

then there must exist $t_1 > 0$ such that $G(t) \geq \frac{\inf_{t \in [0, p]} G_{in}(t)}{2(M'_2 + M'_3 M_4)} > 0$ when $t > t_1$.

From the second and the fourth equations of system (2.1), we have

$$\begin{cases} \frac{dI(t)}{dt} \geq m_1 - d_i I(t), & t \neq kp, \\ I(t^+) = I(t) + \sigma, & t = kp, \\ I(0) = I_0 > 0. \end{cases}$$

Now we consider the impulsive differential equation

$$(3.2) \quad \begin{cases} \frac{dI_2(t)}{dt} = m_1 - d_i I_2(t), & t \neq kp, \\ I_2(t^+) = I_2(t) + \sigma, & t = kp, \\ I_2(0^+) = I_0 > 0. \end{cases}$$

We know that the system (3.2) has a globally asymptotically stable positive periodic solution

$$\begin{cases} \tilde{I}_2(t) = \frac{m_1}{d_i} + \frac{\sigma \exp(-d_i(t - kp))}{1 - \exp(-d_i p)}, & t \in (kp, (k + 1)p], k \in \mathbb{Z}_+, \\ \tilde{I}_2(0^+) = \frac{m_1}{d_i} + \frac{\sigma}{1 - \exp(-d_i p)}, \end{cases}$$

and the solution of the system (3.2) has the form

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

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

Then there must exist $t_2 > 0$ such that

$$I(t) \geq I_2(t) \geq \frac{\sigma \exp(-d_i p)}{2(1 - \exp(-d_i p))}$$

when $t > t_2$.

According to the above discussion and Proposition 3.2, we can conclude that the solutions of the system (2.1) are bounded below and above by some constants. \square

Remark. Physiologically, the permanence ensures that the glucose level will not blow out and the insulin level will not cumulatively become too high. If the insulin level is controlled carefully, the permanence implies that hypoglycemic episodes can be significantly reduced and hyperglycemia can be avoided.

3.3. Existence and stability of the periodic solution. We show that there exists a periodic solution for the model (2.1) and discuss the stability of the periodic solution in this section.

THEOREM 3.4. *If $\frac{M_1(1 - \exp(-d_i p)) + d_i \sigma}{(1 - \exp(-d_i p))^2} p \leq r_2$, then system (2.1) has a positive periodic solution $(G^*(t), I^*(t))$ with period p , where r_2 is a constant defined in (A.1) in Appendix A.*

The proof of Theorem 3.4 is based on the Krasnoselskii fixed point theorem (see Lemma A.1), and the details of the proof are listed in Appendix A.

For T1DM, almost all β -cells in the pancreas are dysfunctional and thus secrete almost no insulin. Diabetic patients need to rely on exogenous insulin through sub-

cutaneous injection. So we assume the term $f_1 = 0$ in model (2.1). In this case, we will show that the system (2.1) has a globally asymptotically stable positive periodic solution.

THEOREM 3.5. *Suppose $f_1 \equiv 0$, then the positive periodic solution $(G^*(t), I^*(t))$ of the system (2.1) is unique and globally asymptotically stable.*

The proof of Theorem 3.5 is based on a standard construction of a Lyapunov function and will be carried out in Appendix B.

For T2DM, the typical diagnostics are hyperglycemia and hyperinsulinemia which are most likely caused by insulin resistance. In this case, β -cells release more insulin to compensate for the insulin resistance [1], [41]. Therefore the term $f_1 \geq 0$ and satisfies the condition assumed in section 2. We will show the stability for this case by numerical analysis in the next section.

Remark. The unique stable periodic solution secures that the periodic injections of insulin, including CSII, produce controllable and reliable dynamics of plasma glucose and insulin in sustained oscillatory fashion.

Remark. Some T1DM patients still have certain functional β -cells that can still release insulin when the glucose level is elevated. In such case, the term $f_1 \geq 0$ and thus Theorem 3.4 applies.

4. Numerical analyses. In this section we continue to investigate important factors for the insulin pump in open-loop control by numerical simulations.

For simplicity, we will use the same functions $f_i, i = 1, 2, 3, 4$ in [22] for numerical analyses. In order to study the HGP delay, we choose the same function f_5 as used in [28], [31], [54], and [55]. These functions, $f_i, i = 1, 2, 3, 4, 5$, take the following forms:

$$f_1(x) = \frac{\sigma_1 x^2}{\alpha_1^2 + x^2}, \quad f_2(x) = \sigma_2 x, \quad f_3(x) = ax,$$

$$f_4(x) = c + \frac{mx}{n+x}, \quad f_5(x) = \frac{R}{1 + \exp(vx - \hat{c})},$$

where $\sigma_1, \sigma_2, \alpha_1, a, c, m, n, R, v$, and \hat{c} are positive constant parameters that are chosen and adjusted from [15], [28], [31], [32], [36], [37], [49], and [51] (refer to Table 1). Notice that the units of the parameters are for amounts according to [49] instead of concentrations. Unit conversion is made from amounts to concentrations for the purpose of display in the same way as in [28], [31] and [22].

For the case of T1DM, Theorem 3.5 shows the existence of a unique positive and globally stable periodic solution, which is demonstrated in Figure 1 with different initial glucose values. This figure also demonstrates that the plasma glucose needs about five insulin delivery cycles to be stabilized at an oscillatory homeostasis, even with different initial glucose levels.

TABLE 1
Model parameter values from [22] and [31].

Parameters	Values	Units	Parameters	Values	Units
$G_{in}(t) = G_{in}$	216	mg/min	m	900	mg/min
v	0.0967	mU ⁻¹	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
R	180	mg/min	\hat{c}	7.54	mU

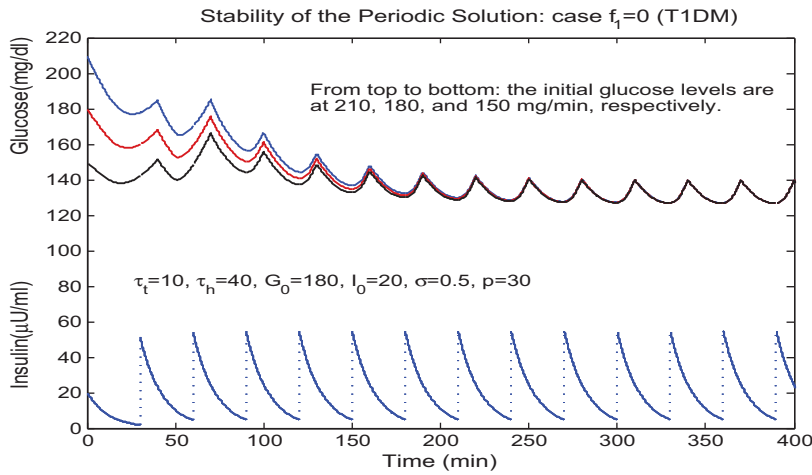


FIG. 1. Asymptotically stable periodic solutions of model (2.1) for T1DM.

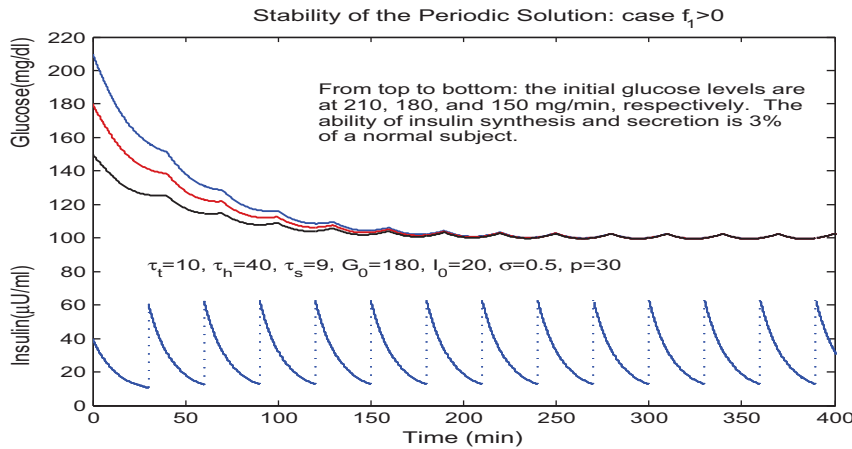


FIG. 2. Asymptotically stable periodic solutions of model (2.1) for T2DM or T1DM with some remaining β -cell functionality.

For T2DM or T1DM with certain functional β -cells, Theorem 3.3 ensures that all the solutions of the system (2.1) are bounded from below and above. Theorem 3.4 shows that a periodic solution exists. Furthermore our intensive numerical simulations reveal that the periodic solution is asymptotically stable (refer to Figure 2).

A major feature of model (2.1) is that time delays are integrated. Figure 3 shows the comparison of two profiles produced by the DDE model (2.1) and the ODE model (2.2) in [22] for the case of T1DM. The small subpanel is a zoomed in part of the time interval [300, 400]. The comparison reveals a significant observation that the DDE model is more effective than the ODE model in controlling the blood sugar. This observation points out that it is not necessary to reduce the reaction time of fast insulin analogues.

Now we investigate the effects of the glucose utilization delay τ_t and HGP delay τ_h . In view of the possible range of the delay τ_t and τ_h (see [28], [31], [43], [49], [51]), we select $\tau_t = 6, 12, 18$ and $\tau_h = 36, 40, 45$ min, respectively, while other parameters are

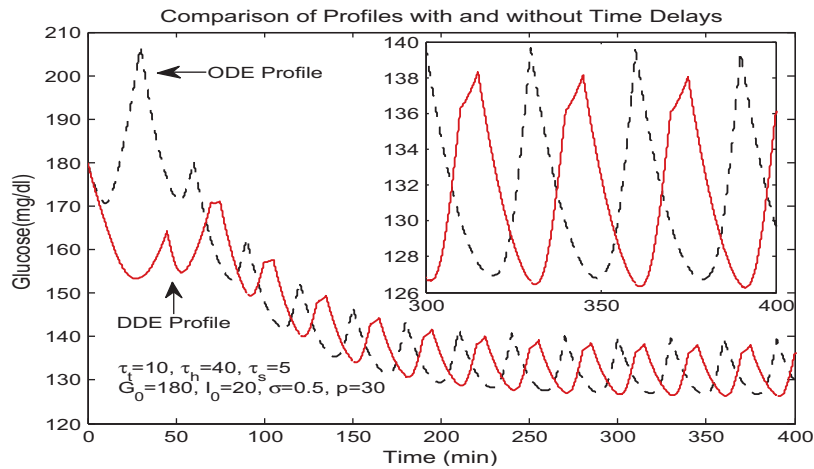


FIG. 3. Comparison of the profiles produced by the ODE and DDE models reveals that time delays might be beneficial for achieving better effects in lowering glucose level.

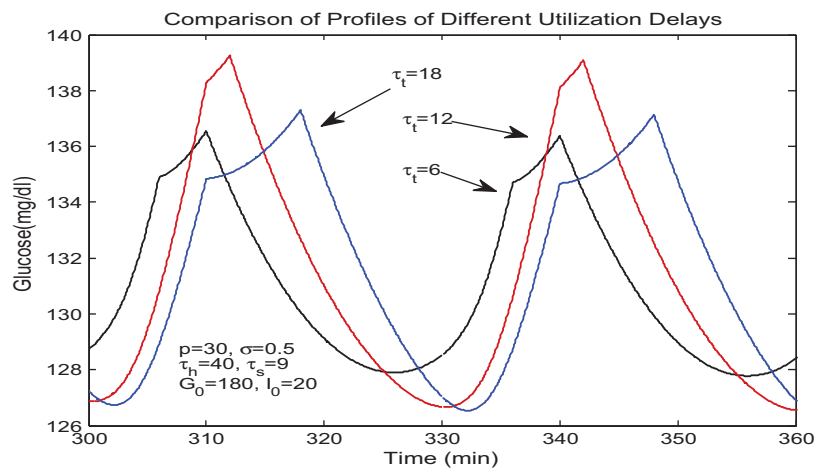


FIG. 4. Profiles produced by model (2.1) for various utilization time delays for the case of T1DM.

fixed at delivery period $p = 30$ min, injection dose $\sigma = 0.5$, secretion delay $\tau_s = 9$ min, initial glucose level $G_0 = 180$ mg/dl, and initial insulin level $I_0 = 20 \mu\text{U/l}$ (see [22], [28], [31], [43], [49], [51], [54]). Figures 4 and 5, respectively, show the comparisons of model profiles for various values of τ_t and τ_h in T1DM. Figure 4 demonstrates that larger delay ($\tau_t = 18$) can better lower the glucose level, but more importantly, the smaller delay ($\tau_t = 6$) makes a smaller fluctuation. Figure 5 clearly shows that the smaller HGP delay value, $\tau_h = 36$ min, has the best effect in the selected three values. Sturis et al. [49] have chosen $\tau_h = 36$ min as a typical HGP delay.

If certain functionality of β -cells in insulin secretion remains, even small, it helps to control the blood sugar level significantly. In Figure 6, the lower profile shows that the blood sugar level is significantly lowered even if only 3% of secreting functionality of β -cells remains. Possibly, this is because not only can the small percentage of insulin production directly uptake blood sugar, but also its inhibitory effect on HGP via insulin secretion.

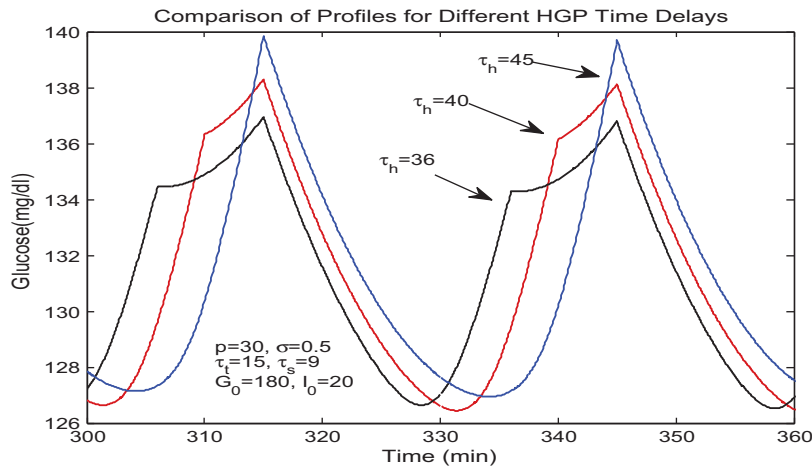


FIG. 5. Profiles produced by model (2.1) for various HGP time delays for the case of T1DM.

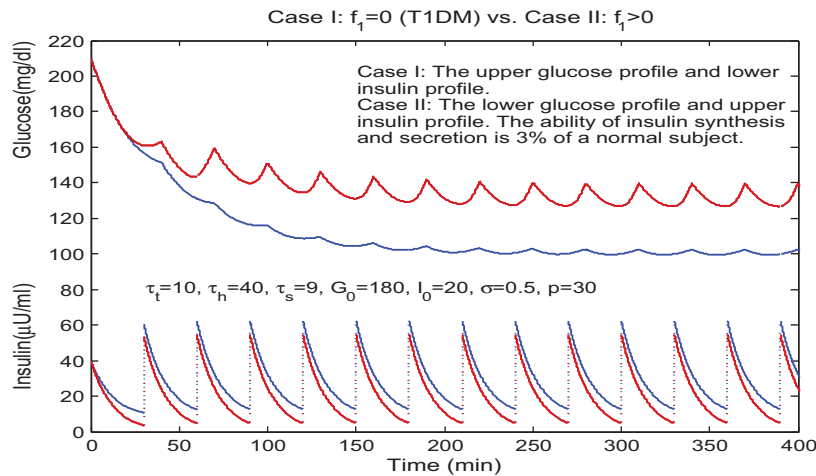


FIG. 6. In open-loop control, certain remaining β -cell functionality helps to control blood sugar significantly.

We also numerically investigated the secretion delay τ_s for T1DM with certain functional β -cells (for example, 3% of a normal subject) but we did not observe a significant effect as expected although the tiny remaining β -cell functionality is somewhat significant as shown in Figure 6.

Similarly to that in [22], we investigate the widely used administration strategy, CSII. We set total daily insulin dose fixed and set four different delivery frequencies and doses. In Figure 7, we set the delivery frequency $p = 7.5, 15, 22.5, 30$ min and the corresponding dose $\sigma = 0.125, 0.25, 0.375, 0.5$ U/min for T1DM. In Figure 8 we set $p = 7.5, 15, 30, 45$ min with the corresponding dose $\sigma = 0.1, 0.2, 0.4, 0.6$ U/min for T2DM (or T1DM with 3% functional β -cells). These result in the same total daily dose $\sigma = 24$ U and 19.2 U, respectively. We compare the profiles and obtain a similar conclusion to that in [22]: for the same daily total dose, the impulsive injection with a smaller dose but shorter period is more effective for controlling plasma glucose level than the injection with a larger dose but longer period.

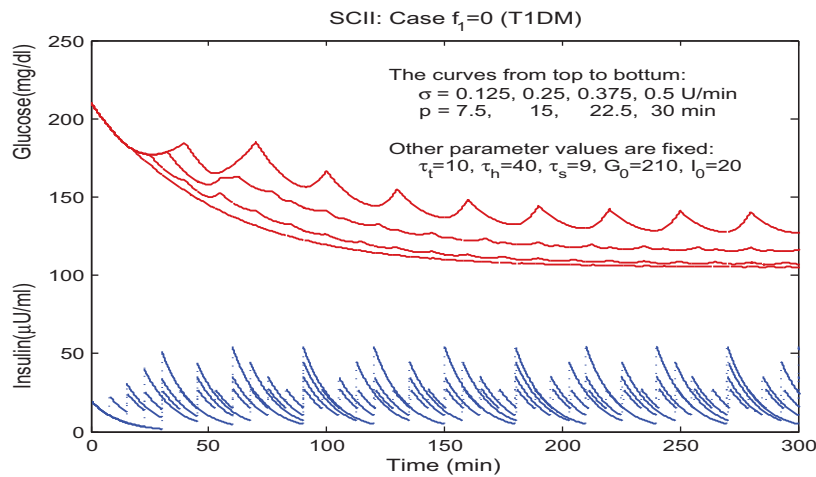


FIG. 7. Comparisons of profiles generated by model (2.1) for various delivery doses and injection time periods for T1DM.

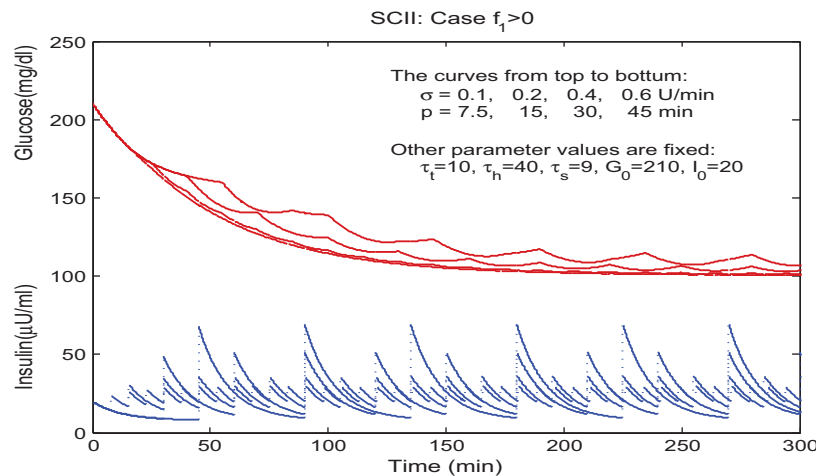


FIG. 8. Comparisons of profiles generated by model (2.1) for various delivery doses and injection time periods for a subject who has a certain insulin secreting functionality of β -cells (3%).

For a particular individual, the insulin degradation rate is also intrinsic. Our numerical simulations show that a small change of the insulin degradation rate has a big effect on the glucose level. While physiological delays and insulin degradation rate are intrinsic for a specific individual, exogenous food intake is controllable by diet. Small change of the glucose infusion rate G_{in} can cause large fluctuation of glucose level. This elucidates that it is beneficial for diabetic patients to eat less.

5. Discussions. In this paper, we extended our work in [22] and proposed a novel DDE model to simulate the dynamic regulations between glucose and insulin for the case of open-loop control in an insulin pump system. We expect that the theoretical and simulation results can provide guidance for clinical therapy for T1DM and T2DM. The analytical studies of the model (2.1) ensure that all solutions are permanent, that is, bounded from both below and above (Theorem 3.3). The homeostasis appears to be a periodic solution (Theorem 3.4), and the periodic solution

is unique and globally asymptotically stable for the case of T1DM (Theorem 3.5). This suggests that a small physiological perturbation would not disturb the system severely. It is not difficult to deduce two expressions in terms of the model parameters, which can be applied to determine the dose and frequency and control the blood sugar level within a predefined range (refer to [22] for the method). Figure 3 clearly shows that moderate time delays in the system help to lower the blood sugar level. In other words, moderate time delays could reduce glucose fluctuations (Figures 4 and 5). They are beneficial instead of harmful. Our numerical simulations demonstrate that a therapy that inject a smaller dose with higher frequency has a better effect than a therapy by a larger dose with a lower frequency. These observations not only have significant implications in the design of algorithms for the insulin pump but also give reasonable suggestions for clinical insulin administration.

Soluble insulin as used in insulin pumps tends to form oligomers, i.e., two insulin molecules bind together to form a dimer, and three dimers bind together to form a hexamer [23], [44]. The fraction of insulin in each of these forms is determined by the overall insulin concentration in accordance with the law of mass action. In the pump, the insulin concentration is high (100 IU/ml), and practically all insulin is in hexameric form. When injected into the subcutis impulsively, the insulin solution is diluted through mixing with the intercellular liquid, and the fraction of hexameric insulin is reduced to about 60%. In practice, only (monomeric and) dimeric insulin molecules are small enough to penetrate the capillary wall and enter the blood stream. Hence, the rate of absorption is determined by the fraction of dimeric insulin. As dimeric insulin is absorbed, the overall insulin concentration near the injection site decreases, an increasing fraction of the insulin will be in dimeric form, and the absorption rate will increase and then deliver a major dose of insulin to the blood stream. The impulsive and periodic pumping process will build up a depot with high-molecular insulin at the injection site, and the presence of this depot may smooth out the impulsive and periodic variations in the absorption rate but could also accumulate the residual of insulin. The accumulation could cause fluctuation of glucose level including hypoglycemic episode. Because of the delayed absorption process, an optimal regulation of the blood glucose level requires that the system can anticipate the insulin requirements of the patients. In order to more accurately estimate the insulin in the whole body, the absorption process shall be considered in the model in more detail. However we simplified this process in the model (2.1) by simple impulsive injections. We shall investigate the impacts of the built-up high-molecular depot and accumulation of residual insulin on the absorption rate of insulin and the fluctuation of glucose level in our future work. As discussed in section 2, the dissolving process of injected insulin in the depot may greatly smooth out the impact of the impulsiveness of the injections and the plasma insulin input may not be precisely in the impulsive fashion. We shall compare the modeling effects on controlling blood sugar in the wave form in the model (2.1) with those resulting from insulin pump models that include a subcutaneous depot as well.

Insulin administration in open-loop control normally provides the basal insulin requirement at a given repetition frequency. Bolus injections are needed for the major insulin requirement before meals. Close-loop control through the feedback from GMS for the insulin pump will improve the lifestyles of the patients, which is the ultimate goal of this research area.

Appendix A. Proof of Theorem 3.4. In this section, we will prove Theorem 3.4 by Krasnoselskii's fixed point theorem. We first introduce some notation and definitions from [26] which will be useful for the following discussion.

Suppose X is a Banach space and K is a closed, nonempty subset of X . K is said to be a cone if

- (1) $\alpha u + \beta v \in K$ for all $u, v \in K$ and all $\alpha, \beta > 0$,
- (2) $u, -u \in K$, imply $u = 0$.

LEMMA A.1 (Krasnoselskii’s fixed point theorem). *Let X be a Banach space and let $K \subset X$ be a cone in X . Assume that Ω_1, Ω_2 are open subsets of X with $0 \in \Omega_1, \overline{\Omega_1} \in \Omega_2$ and let*

$$T : K \cap (\overline{\Omega_2} \setminus \Omega_1) \rightarrow K$$

be a completely continuous operator, such that either

- (1) $\|Tx\| \leq \|x\|, x \in K \cap \partial\Omega_1$ and $\|Tx\| \geq \|x\|, x \in K \cap \partial\Omega_2$
or
- (2) $\|Tx\| \geq \|x\|, x \in K \cap \partial\Omega_1$ and $\|Tx\| \leq \|x\|, x \in K \cap \partial\Omega_2$
is true. Then T has a fixed point in $K \cap (\overline{\Omega_2} \setminus \Omega_1)$.

To prove Theorem 3.4, we consider the Banach space

$$X = \{(u(t), v(t)) | u(t) \in C[R, R], v(t) \in (PC[J, R] \cap C^1[J', R]), u(t+p) = u(t), v(t+p) = v(t)\}$$

with $\|(u, v)\| = \max\{\sup_{t \in [0, p]} |u(t)|, \sup_{t \in [0, p]} |v(t)|\}$, where $J = [0, \infty)$, $J_0 = [0, p]$, $J_1 = (p, 2p], \dots, J_k = (kp, (k+1)p], \dots, J' = J \setminus \{p, 2p, \dots, kp, \dots\}$, and $PC[J, R] = \{v(t) : J \rightarrow R | v(t) \text{ is continuous when } t \neq kp, v(kp^-) \text{ and } v(kp^+) \text{ exist and } v(kp) = v(kp^-), k = 1, 2, \dots\}$.

In order to apply Lemma A.1, we define a cone K in X by

$$K = \left\{ (u, v) \in X : u(t) \geq \frac{A}{B} \sup_{t \in [0, p]} |u(t)|, \quad v(t) \geq \frac{C}{D} \sup_{t \in [0, p]} |v(t)| \right\},$$

where A, B, C, D are defined by the following expressions:

$$A = \frac{1}{\exp(M'_2 p + M'_3 M_4 p) - 1} > 0, \quad B = \frac{\exp(M'_2 p + M'_3 M_4 p)}{\exp(m'_3 m_4 p) - 1} > 0,$$

$$C = \frac{1}{\exp(d_i p) - 1} > 0, \quad D = \frac{\exp(d_i p)}{\exp(d_i p) - 1} > 0.$$

Notice that $M'_2 > 0$ and $M'_3 > m'_3 > 0$, we have $A < B$ and $C < D$. Let

$$(A.1) \quad r_1 = Ap \left(\inf_{t \in [0, p]} G_{in}(t) \right) \quad \text{and} \quad r_2 = Bp \left(\sup_{t \in [0, p]} G_{in}(t) + M_5 \right);$$

we then define two open sets Ω_{r_1} and Ω_{r_2} as

$$\Omega_{r_1} = \{(u, v) \in X : \|(u, v)\| < r_1\}$$

and

$$\Omega_{r_2} = \{(u, v) \in X : \|(u, v)\| < r_2\},$$

thus $\partial\Omega_{r_i} = \{(u, v) \in X : \|(u, v)\| = r_i\}, i = 1, 2$, and $K \cap (\overline{\Omega_2} \setminus \Omega_1) = \{(u, v) \in X : r_1 \leq \|(u, v)\| \leq r_2\}$.

Define the map $T(u, v) = (T_1(u, v), T_2(u, v)) : K \cap (\overline{\Omega_2} \setminus \Omega_1) \rightarrow X$ by

$$T_1(u(t), v(t)) = \int_t^{t+p} U_u(t, s)[G_{in}(s) + f_5(v(s - \tau_h))]ds$$

and

$$T_2(u(t), v(t)) = \int_t^{t+p} U_v(t, s) \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds$$

for $t < kp \leq t + p, k \in N$, where

$$U_u(t, s) = \frac{\exp\{\int_t^s [\frac{f_2(u(\theta))}{u(\theta)} + \frac{f_3(u(\theta))}{u(\theta)} f_4(v(\theta - \tau_t))]d\theta\}}{\exp\{\int_0^p [\frac{f_2(u(\theta))}{u(\theta)} + \frac{f_3(u(\theta))}{u(\theta)} f_4(v(\theta - \tau_t))]d\theta\} - 1},$$

and

$$U_v(t, s) = \frac{\exp(d_i(s - t))}{\exp(d_i p) - 1}.$$

Notice that

$$m'_3 m_4 \leq \frac{f_2(u(\theta))}{u(\theta)} + \frac{f_3(u(\theta))}{u(\theta)} f_4(v(\theta - \tau_t)) \leq M'_2 + M'_3 M_4,$$

thus we have $A \leq U_u(t, s) \leq B, t \leq s \leq t + p$. Obviously, we also have $C \leq U_v(t, s) \leq D, t \leq s \leq t + p$. In order to use the above fixed point theorem we need the following lemmas.

LEMMA A.2. $S \subset PC[J, R]$ is a relatively compact set if and only if all functions in S are uniform bounded and they are equicontinuous in every $J_k (k = 1, 2, \dots)$.

LEMMA A.3. $T : K \cap (\overline{\Omega_2} \setminus \Omega_1) \rightarrow K$ is compact and continuous.

Proof. In view of the definition of K , for $(u, v) \in K$ and $t < kp \leq t + p$, we have

$$\begin{aligned} T_1(u, v)(t + p) &= \int_{t+p}^{t+2p} U_u(t + p, s)[G_{in}(s) + f_5(v(s - \tau_h))]ds \\ &= \int_t^{t+p} U_u(t + p, \theta + p)[G_{in}(\theta + p) + f_5(v(\theta + p - \tau_h))]d\theta \\ &= \int_t^{t+p} U_u(t, s)[G_{in}(s) + f_5(v(s - \tau_h))]ds = T_1(u, v)(t), \\ T_2(u, v)(t + p) &= \int_{t+p}^{t+2p} U_v(t + p, s) \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp[d_i((k + 1)p - (t + p))]}{\exp(d_i p) - 1} \right] ds \\ &= \int_t^{t+p} U_v(t + p, \theta + p) \left[f_1(u(\theta + p - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] d\theta \\ &= \int_t^{t+p} U_v(t, s) \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds = T_2(u, v)(t). \end{aligned}$$

Besides, for every $(u, v) \in K \cap (\overline{\Omega_2} \setminus \Omega_1)$ and $t < kp \leq t + p$,

$$\begin{aligned} T_1(u, v)(t) &\geq A \int_t^{t+p} [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &= \frac{A}{B} B \int_0^p [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &\geq \frac{A}{B} \sup_{t \in [0, p]} |T_1(u, v)(t)|, \\ T_2(u, v)(t) &\geq C \int_t^{t+p} \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds \\ &= \frac{C}{D} D \int_0^p \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds \\ &\geq \frac{C}{D} \sup_{t \in [0, p]} |T_2(u, v)(t)|. \end{aligned}$$

Thus $T(K \cap (\overline{\Omega_2} \setminus \Omega_1)) \subset K$.

It is easy to know that T is continuous, we can also show it is compact.

Indeed, let $S \subseteq (K \cap (\overline{\Omega_2} \setminus \Omega_1))$ be a bounded set; now we prove all functions in $T(S)$ are uniform bounded and they are equicontinuous in every $J_k (k = 1, 2, \dots)$.

For every $(u(t), v(t)) \in S$ and $t < kp \leq t + p$, we know

$$\|T(u(t), v(t))\| = \max \left\{ \sup_{t \in [0, p]} |T_1(u(t), v(t))|, \sup_{t \in [0, p]} |T_2(u(t), v(t))| \right\}.$$

Besides, by

$$\begin{aligned} T_1(u, v)(t) &\leq B \int_t^{t+p} [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &= B \int_0^p [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &\leq Bp \left(\sup_{t \in [0, p]} G_{in}(t) + M_5 \right) \end{aligned}$$

and

$$\begin{aligned} T_2(u, v)(t) &\leq D \int_t^{t+p} \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds \\ &\leq Dp \left(M_1 + \frac{d_i \sigma \exp(d_i p)}{\exp(d_i p) - 1} \right), \end{aligned}$$

we get

$$\|T(u(t), v(t))\| \leq \max \left\{ Bp \left(\sup_{t \in [0, p]} G_{in}(t) + M_5 \right), Dp \left(\beta M_1 + \frac{d_i \sigma \exp(d_i p)}{\exp(d_i p) - 1} \right) \right\},$$

and all functions in $T(S)$ are uniform bounded.

Besides, for every $(u(t), v(t)) \in S$ and $t \in J_k (k = 1, 2, \dots)$, it is easy to know the derivative functions of $T_i(u, v)(t), i = 1, 2$, are uniform bounded, so all functions in $T(S)$ are equicontinuous in J_k .

From the above, we know T is compact by Lemma A.2. That completes the proof. \square

LEMMA A.4. *If (u, v) is a fixed point of T in $K \cap (\overline{\Omega_2} \setminus \Omega_1)$, then (u, v) is a positive periodic solution of the systems (2.1).*

Proof. If $(u, v) \in K \cap (\overline{\Omega}_2 \setminus \Omega_1)$ and $T_1(u, v) = u, T_2(u, v) = v$, then for $t < kp \leq t + p, k = 1, 2, \dots$, we have

$$\begin{aligned} u'(t) &= \frac{d}{dt} \int_t^{t+p} U_u(t, s) [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &= U_u(t, t + p) [G_{in}(t + p) + f_5(v(t + p - \tau_h))] - U_u(t, t) [G_{in}(t) + f_5(v(t - \tau_h))] \\ &\quad + \int_t^{t+p} \frac{dU_u(t, s)}{dt} [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &= (U_u(t, t + p) - U_u(t, t)) [G_{in}(t) + f_5(v(t - \tau_h))] \\ &\quad - \left(\frac{f_2(u(t))}{u(t)} + \frac{f_3(u(t))}{u(t)} f_4(v(t - \tau_t)) \right) T_1(u, v)(t) \\ &= G_{in}(t) + f_5(v(t - \tau_h)) - f_2(u(t)) - f_3(u(t)) f_4(v(t - \tau_t)) \end{aligned}$$

and

$$\begin{aligned} v'(t) &= \frac{d}{dt} \int_t^{t+p} U_v(t, s) \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds \\ &= (U_v(t, t + p) - U_v(t, t)) \left[f_1(u(t - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] \\ &\quad + \int_t^{t+p} \frac{dU_v(t, s)}{dt} \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds \\ &\quad + \int_t^{t+p} U_v(t, s) \left(\frac{d_i \sigma (-d_i) \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right) ds \\ &= f_1(u(t - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} + (-d_i) T_2(u, v)(t) \\ &\quad + \int_t^{t+p} \frac{\exp(d_i(s - t))}{\exp(d_i p) - 1} \cdot \frac{d_i \sigma (-d_i) \exp(d_i(kp - t))}{\exp(d_i p) - 1} ds \\ &= f_1(u(t - \tau_s)) - d_i v(t) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \\ &\quad + \frac{1}{\exp(d_i p) - 1} \cdot \frac{d_i \sigma (-d_i) \exp(d_i(kp - t))}{\exp(d_i p) - 1} \int_t^{t+p} \exp(d_i(s - t)) ds \\ &= f_1(u(t - \tau_s)) - d_i v(t). \end{aligned}$$

Besides, for $t < kp$ and $t \rightarrow kp^-$, we get

$$\begin{aligned} \lim_{t \rightarrow kp^-} T_2(u, v)(t) &= \int_{kp}^{(k+1)p} U_v(kp, s) \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - kp))}{\exp(d_i p) - 1} \right] ds \\ &= \int_{kp}^{(k+1)p} \frac{\exp(d_i(s - kp))}{\exp(d_i p) - 1} f_1(u(s - \tau_s)) ds + \frac{\sigma}{\exp(d_i p) - 1}, \end{aligned} \tag{A.2}$$

and for $kp < t < (k + 1)p$ and $t \rightarrow kp^+$, we get

$$\begin{aligned} \lim_{t \rightarrow kp^+} T_2(u, v)(t) &= \int_{kp}^{(k+1)p} U_v(kp, s) \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp[d_i((k + 1)p - kp)]}{\exp(d_i p) - 1} \right] ds \\ &= \int_{kp}^{(k+1)p} \frac{\exp(d_i(s - kp))}{\exp(d_i p) - 1} f_1(u(s - \tau_s)) ds + \frac{\sigma \exp(d_i p)}{\exp(d_i p) - 1}. \end{aligned} \tag{A.3}$$

By (A.2) and (A.3), we get

$$T_2(u, v)(kp^+) = T_2(u, v)(kp) + \sigma.$$

Thus, (u, v) is a positive periodic solution of the system (2.1). That completes the proof. \square

We now prove the existence of a periodic solution of the system (2.1).

For $(u, v) \in \partial\Omega_{r_1}$, we have $\|(u, v)\| = r_1$, and

$$\begin{aligned} T_1(u, v) &\geq A \int_t^{t+p} [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &\geq Ap \left(\inf_{t \in [0, p]} G_{in}(t) \right) = r_1; \end{aligned}$$

then we get

$$\|T(u, v)\| \geq \|(u, v)\|.$$

For $(u, v) \in \partial\Omega_{r_2}$, we have $\|(u, v)\| = r_2$, and

$$\begin{aligned} T_1(u, v) &\leq B \int_t^{t+p} [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &= B \int_0^p [G_{in}(s) + f_5(v(s - \tau_h))] ds \\ &\leq Bp \left(\sup_{t \in [0, p]} G_{in}(t) + M_5 \right) = r_2, \\ T_2(u, v) &\leq D \int_t^{t+p} \left[f_1(u(s - \tau_s)) + \frac{d_i \sigma \exp(d_i(kp - t))}{\exp(d_i p) - 1} \right] ds \\ &\leq D \int_t^{t+p} f_1(u(s - \tau_s)) ds + D \frac{d_i \sigma \exp(d_i p)}{\exp(d_i p) - 1} p \\ &= D \int_t^{t+p} f_1(u(s - \tau_s)) ds + \frac{d_i \sigma p (\exp(d_i p))^2}{(\exp(d_i p) - 1)^2}. \end{aligned}$$

By $m_1 < f_1(x) < M_1$, we get

$$T_2(u, v) \leq DM_1 p + \frac{d_i \sigma p (\exp(d_i p))^2}{(\exp(d_i p) - 1)^2} = \frac{M_1(1 - \exp(-d_i p)) + d_i \sigma}{(1 - \exp(-d_i p))^2} p.$$

If $\frac{M_1(1 - \exp(-d_i p)) + d_i \sigma}{(1 - \exp(-d_i p))^2} p \leq r_2$, we get $\|T(u, v)\| \leq \|(u, v)\|$ for $(u, v) \in \partial\Omega_{r_2}$. Then T has a fixed point in $K \cap (\overline{\Omega_2} \setminus \Omega_1)$ by Krasnoselskii's fixed point theorem, which also means the system (2.1) has a positive periodic solution $(G^*(t), I^*(t))$ with period p . This completes the proof of Theorem (3.4).

Appendix B. Proof of Theorem 3.5. In this section we provide a proof of Theorem 3.5. First we state a lemma without proof; interested readers can refer to [4].

LEMMA B.1. *Let h be a real number and f be a nonnegative function defined on $[h, \infty)$ such that f is integrable on $[h, \infty)$ and is uniformly continuous on $[h, \infty)$. Then $\lim_{t \rightarrow \infty} f(t) = 0$.*

Proof of Theorem 3.5. If $f_1 \equiv 0$, from the second and the fourth equation of system (2.1), we have

$$I(t) = I_0 \exp(-d_i t) + \sum_{0 < kp < t} \sigma \exp(-d_i(t - kp)), \quad k \in N.$$

Let $V_I(t) = \frac{1}{2}(I(t) - I^*(t))^2$, then

$$\begin{aligned} V_I(t) &= \frac{1}{2}(I_0 \exp(-d_i t) - I^*(0^+) \exp(-d_i t))^2 \\ &= \frac{1}{2}(I_0 - I_0^*)^2 \exp(-2d_i t) \\ &= V_I(0) \exp(-2d_i t) \end{aligned}$$

and

$$\dot{V}_I(t) = -2d_i V_I(0) \exp(-2d_i t) = -2d_i V_I(t), \quad t > 0.$$

Consider

$$V(t) = mV_I(t) + \frac{1}{2}[G(t) - G^*(t)]^2,$$

where $m > 0$ is a constant to be chosen later. The derivative of $V(t)$ along the solution of the system (2.1) has the following form:

$$\begin{aligned} \dot{V}(t) &= -2md_i V_I(0) \exp(-2d_i t) \\ &\quad + (G(t) - G^*(t)) \left[- (f_2(G(t)) - f_2(G^*(t))) \right. \\ &\quad \quad - (f_3(G(t))f_4(I(t - \tau_t)) - f_3(G^*(t))f_4(I^*(t - \tau_t))) \\ &\quad \quad \left. + (f_5(I(t - \tau_h)) - f_5(I^*(t - \tau_h))) \right] \\ &= -2md_i V_I(0) \exp(-2d_i t) - (G(t) - G^*(t))^2 (f_2'(\xi_2) + f_3'(\xi_3)f_4(I(t - \tau_t))) \\ &\quad - (G(t) - G^*(t))(I(t - \tau_t) - I^*(t - \tau_t))f_3(G^*(t))f_4'(\xi_4) \\ &\quad + (G(t) - G^*(t))(I(t - \tau_h) - I^*(t - \tau_h))f_5'(\xi_5) \\ &\leq -2md_i V_I(0) \exp(-2d_i t) - (G(t) - G^*(t))^2 (f_2'(\xi_2) + f_3'(\xi_3)f_4(I(t - \tau_t))) \\ &\quad + \frac{1}{2}\varepsilon_1 (G(t) - G^*(t))^2 f_3(G^*(t))f_4'(\xi_4) \\ &\quad + \frac{1}{2\varepsilon_1} (I(t - \tau_t) - I^*(t - \tau_t))^2 f_3(G^*(t))f_4'(\xi_4) \\ &\quad + \frac{1}{2}\varepsilon_2 (G(t) - G^*(t))^2 |f_5'(\xi_5)| + \frac{1}{2\varepsilon_2} (I(t - \tau_h) - I^*(t - \tau_h))^2 |f_5'(\xi_5)| \\ &= -(G(t) - G^*(t))^2 \left[f_2'(\xi_2) + f_3'(\xi_3)f_4(I(t - \tau_t)) \right. \\ &\quad \quad \left. - \frac{\varepsilon_1}{2} f_3(G^*(t))f_4'(\xi_4) - \frac{\varepsilon_2}{2} |f_5'(\xi_5)| \right] + V_I(0) \exp(-2d_i t) \\ &\quad \left(-2md_i + \frac{\exp(2d_i \tau_t)}{\varepsilon_1} f_3(G^*)f_4'(\xi_4) + \frac{\exp(2d_i \tau_h)}{\varepsilon_2} |f_5'(\xi_5)| \right), \end{aligned}$$

where ξ_2, ξ_3 are between $G(t)$ and $G^*(t)$, ξ_4 is between $I(t - \tau_t)$ and $I^*(t - \tau_t)$, ξ_5 is between $I(t - \tau_h)$ and $I^*(t - \tau_h)$, $\varepsilon_1 > 0, \varepsilon_2 > 0$ are arbitrary constants. We made use of the inequality $2ab \leq \varepsilon a^2 + \frac{b^2}{\varepsilon}$ in the above derivation.

Choose $\varepsilon_1 > 0, \varepsilon_2 > 0$ small enough such that

$$f'_2(\xi_2) + f'_3(\xi_3)f_4(I(t - \tau_t)) - \frac{\varepsilon_1}{2}f_3(G^*(t))f'_4(\xi_4) - \frac{\varepsilon_2}{2}|f'_5(\xi_5)| > \alpha > 0,$$

where α is a positive constant small enough. For the $\varepsilon_1, \varepsilon_2$ we had chosen, we further choose $m > 0$ large enough such that

$$-2md_i + \frac{\exp(2d_i\tau_t)}{\varepsilon_1}f_3(G^*)f'_4(\xi_4) + \frac{\exp(2d_i\tau_h)}{\varepsilon_2}|f'_5(\xi_5)| < -\alpha < 0;$$

then we have

$$(B.1) \quad \dot{V}(t) < -\alpha V_I(0) \exp(-2d_it) - \alpha(G(t) - G^*(t))^2,$$

thus $V(t)$ is decreasing. Integrating on both sides of B.1 from 0 to t and rearranging the terms produce

$$V(t) + \alpha V_I(0) \int_0^t \exp(-2d_is) ds + \alpha \int_0^t (G(s) - G^*(s))^2 ds \leq V(0).$$

Then we get, $(G(t) - G^*(t))^2 \in L^1(0, \infty)$, It is also easy to see that $(G(t) - G^*(t))^2$ and its derivative are both bounded on $[0, \infty)$. Then it follows that $(G(t) - G^*(t))^2$ is uniformly continuous on $[0, \infty)$. By Lemma B.1, we have

$$\lim_{t \rightarrow \infty} (G(t) - G^*(t))^2 = 0.$$

Besides, we have

$$\lim_{t \rightarrow \infty} (I(t) - I^*(t))^2 = \lim_{t \rightarrow \infty} 2V_I(t) = \lim_{t \rightarrow \infty} 2V_I(0) \exp(-2d_it) = 0.$$

Therefore, the periodic solution is globally asymptotically stable, which also implies the uniqueness of the periodic solution of (2.1). This completes the proof.

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