Mathematical modeling and qualitative analysis of insulin therapies ☆

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Abstract

Several insulin therapies are widely in clinical use with the basic strategy that mimics insulin secretion in a normal glucose–insulin endocrine metabolic regulatory system. In this paper, we model the insulin therapies using a delay differential equation model. We study the dynamics of the model both qualitatively and quantitatively. The analytical results show the existence and uniqueness of a stable periodic solution that corresponds to ultradian insulin secretion oscillations. Numerically we simulate the insulin administration based on our model. The numerical simulation results are in agreement with findings of clinical studies.
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1. Introduction

Diabetes mellitus is a disease in which a patient's plasma glucose concentration level mostly remains above normal range [7,27]. In normal subjects, elevated glucose concentration caused by, for example, meal ingestion, stimulates the secretion of insulin from β-cells in pancreas. Insulin augments the glucose utilization by the cells that converts the glucose into energy [1,23,25]. If one does not have any β-cell in his or her pancreas or one's β-cells do not release insulin or enough insulin to trigger and augment glucose uptake, he or she is likely to develop diabetes mellitus.

Diabetes mellitus is typically classified as type 1 diabetes, type 2 diabetes, and gestational diabetes. Type 1 diabetes is mainly due to the fact that the pancreas does not have any β-cells and thus no insulin can be produced. Type 2 diabetes is mainly due to the disfunction of the glucose–insulin regulatory system [7]. Extensive research work has been carried out in studying how the glucose–insulin endocrine metabolic system works [3,4,8,19,23,25,32,36,37], how to detect the onset of diabetes and prediabetes [5,10,24,29], what causes the dysfunction of the metabolic system ([7,37] and references therein), and how to provide better treatments to diabetic patients ([11,28,35] and references therein).

Typical methods employed by the therapies include: (1) multiple daily insulin injection and (2) subcutaneous insulin infusion, for example, through an insulin pump. The basic idea of insulin therapy is to mimic the reaction of β-cells stimulated by elevated glucose concentration. According to the studies of the glucose–insulin metabolic regulatory system for normal people, self-sustained oscillatory insulin secretion occurs upon exogenous glucose infusion [23,25,31,32,36].

For a healthy person, glucose is absorbed exogenously in daily life. The typical exogenous infusion of glucose includes meal ingestion, oral glucose intake, constant enteral glucose absorption, and etc. Elevated glucose concentration can trigger the β-cells in pancreas to secrete insulin. Numerous in-vitro and in-vivo experiments have demonstrated that insulin is released from β-cells in two oscillatory modes: pulsatile oscillation [30] and ultradian oscillation [31]. While the rapid oscillation is believed to be caused by internal pacemakers, the ultradian oscillation is possibly triggered by the fluctuating glucose concentration levels, although the real cause remains unknown [23,25,30–32,36]. Insulin secreted from pancreas with pulsatile oscillation prevents the glucose concentration level from becoming high accumulatively. In insulin therapies, such insulin, or infused insulin for that purpose, is referred as basal insulin [28], while the insulin infused to mimic the insulin secretion from pancreas in an ultradian oscillation manner is referred as bolus insulin injection ([11,28] and references therein). Thus the task of insulin therapies is to mimic the insulin secretion at these two time scales. Fig. 1.1 shows an effective insulin replacement pattern.

Insulin therapies are mostly introduced based on clinical experiences, although mathematical models have been proposed for some specific situations [11]. In this paper, we propose a delay differential equation (DDE) model to simulate the pancreatic insulin secretion with exogenous insulin infusion upon the stimulation of elevated glucose concentration for type 1 diabetic patients. We study the model analytically and numerically. The existence and stability of the periodic solutions are established. We also investigate how the system behaves under periodic exogenous glucose infusion and insulin infusion. Further, we study the feasibility and possibility of an exogenous insulin infusion method that may restore the normal glucose–insulin metabolic system in type 1 diabetic patients.
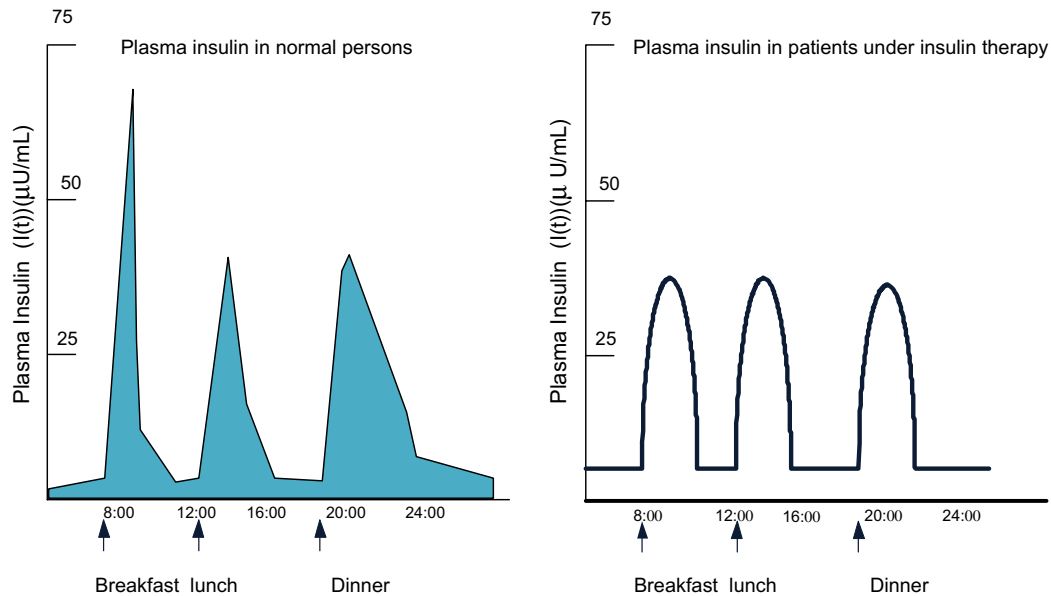
Fig. 1.1. An effective insulin replacement pattern (adapted from [28]).

2. Modeling insulin therapies

Type 1 diabetes occurs when the β-cells are exhausted and thus no insulin can be produced from pancreas. In this case, the glucose in plasma can not be utilized timely and efficiently. Hyperglycemia can cause serious damage to all the organ systems of the body. For this reason, type 1 diabetic patients must take insulin in order to help the cells to utilize glucose and keep the glucose concentration in its normal state.

Doran et al. [11] proposed a mathematical model for critically ill patients in intensive care units and suggested a simple automated insulin infusion for controlling the rise and duration of blood glucose excursion. The mathematical model is given as:

$$\begin{cases} \hat{G}' = -p_{\mathrm{G}}\hat{G} - S_{\mathrm{I}}I(\hat{G} + G_{\mathrm{B}}) + P(t), \\ \hat{I}' = -n(\hat{I} + I_{\mathrm{B}}) + u(t)/V_{\mathrm{I}}, \end{cases} \tag{2.1}$$

where, $\hat{G}$ (mmol/L) is the concentration of the plasma glucose above basal level, G_{B} (mmol/L). $\hat{I}$ (mU/L) is the concentration of the plasma insulin above basal level, I_{B} (mU/L). $u(t)$ (mU/min) is the exogenous insulin infusion rate. $P(t)$ (mmol/L/min) is the exogenous glucose input, V_{I} (L) is the volume of distribution, and n (min^{-1}) is the rate constant associated with the interstitial transfer of insulin to be utilized. p_{G} (min^{-1}) and S_{I} (L/mU/min) are patient-specific parameters, where p_{G} is the fractional clearance rate of plasma glucose at basal insulin, and S_{I} measures insulin sensitivity as defined in [6].

As the authors of [11] stated, additional model dynamics linking the two compartments in (2.1) may be needed. Actually, the missing part can be filled with a delay parameter that reflects the delayed insulin-dependent glucose utilization by cells, as this delay is a critical factor to ensure the self-sustained ultradian oscillations of insulin secretion [25]. Observing another delayed effect,

namely the hepatic glucose production, in the glucose–insulin regulatory system of normal people, based on the model proposed by Li and Kuang [23] and Li et al. [25] for normal glucose–insulin regulatory system, we propose the following generic model to simulate the dynamics of the insulin therapies for type 1 diabetic patients:

$$G' = G_{in}(t) - f_2(G(t)) - f_3(G(t))f_4(I(t - \tau_3)) + f_5(I(t - \tau_2)), \tag{2.2a}$$

$$I' = I_{in}(t) - d_i I(t), \tag{2.2b}$$

with initial condition $I(0) > 0$, $G(0) > 0$, and $I(t) \equiv I(0)$ for $t \in [-\max\{\tau_2, \tau_3\}, 0]$, $\tau_2, \tau_3 > 0$. The solution for Eqs. (2.2a) and (2.2b) with the described initial conditions exists and is unique (Kuang [21]).

The two major factors in the regulatory system model are glucose and insulin, denoting $G(t)$ and $I(t)$ as glucose and insulin concentration at time $t \geq 0$, respectively. $I_{in}(t)$ represents the exogenous insulin infusion rate. The term $G_{in}(t)$ is glucose intake rate. The other source of glucose production is the liver. When the plasma glucose concentration level drops, α-cells, also located in the Langerhan's islets in the pancreas, start to release another hormone, glucagon. Glucagon exerts control over pivotal metabolic pathways in the liver and leads the liver to dispense glucose. We denote by $f_5(I)$ the glucose production controlled by insulin concentration I. $\tau_2 > 0$ stands for the hepatic glucose production delay.

Glucose utilization also consists of two parts, namely, insulin-independent utilization and insulin-dependent utilization. The insulin-independent glucose consumers are mainly the brain and nerve cells. We denote this type of utilization by $f_2(G)$. The insulin-dependent glucose uptake is due to muscle, fat and other tissues. Insulin receptors activate the signaling cascade for GLUT4 translocation. GLUT4 transporters lead glucose molecules into cells, e.g., adipose and muscle. The cells then consume the glucose and convert it to energy. We denote $f_3(G)f_4(I)$ as the insulin-dependent glucose uptake. $\tau_3 > 0$ stands for the time delay for insulin-dependent glucose utilization by cells.

Engelborghs et al. [12] discussed a related model with the term $\alpha f_1(G)$, $0 \leq \alpha \leq 1$ to represent the degree of insulin delivered by the pancreas of a normal subject into the circulation to maintain blood glucose at its physiological level. $\alpha = 0$ means that the pancreas completely does not produce insulin. By incorporating appropriate terms, our insulin therapy model (2.2) could be adjusted to predicate the glucose level for the patients whose pancreas does not produce enough insulin to properly control blood sugar levels. Type 1 diabetes can occur at any age, but it usually starts in people younger than 30. Symptoms of Type 1 diabetes are usually severe and occur rapidly. Within 5–10 years, the insulin-producing β-cells of the pancreas are completely destroyed and the body can no longer produce insulin[2] [26]. Patients who rely on insulin therapies may be at an advanced stage of type 1 diabetes and their pancreas no longer produces insulin. Thus it is reasonable to assume that the pancreas on longer produces insulin for a patient undergoing intensive insulin therapy.

Experiments have shown that insulin degradation is proportional to insulin concentration [37]. Thus, as in [23,25,37], we assume the clearance rate is a constant and denote it by $d_i > 0$.

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[2] http://www.nlm.nih.gov/medlineplus/ency/article/000305.htm.

Throughout the paper, we assume the following conditions:

(H1) $G_{in}(t), I_{in}(t) \in C([0,\infty), (0,\infty))$ are positive ω-periodic functions.

(H2) $f_2(x), f_3(x), f_4(x) \in C^1[0,\infty)$ are positive for $x > 0$. $f_2(0) = f_3(0) = 0$.

(H3) $f_2'(x), f_3'(x), f_4'(x)$ are positive on $[0,\infty)$.

(H4) $f_5(x) \in C^1[0,\infty)$ is positive on $[0,\infty)$, $f_5'(x)$ is negative on $[0,\infty)$.

(H5) There exist positive numbers b_2, a_3, b_3 such that, for $0 \leqslant x \leqslant \infty$, $0 \leqslant f_2(x) \leqslant b_2 x$ and $a_3 x \leqslant f_3(x) \leqslant b_3 x$.

Assumptions (H1)–(H5) are quite natural. Note that if f_2 takes the form defined in (4.1) in Section 4, then $0 \leqslant f_2(G) \leqslant \frac{U_b}{C_2 V_g} G$. Thus conditions (H1)–(H5) cover the model functions in (4.1)–(4.4) used in [23,25,32], for numerical simulations. The shapes of the functions are important instead of their forms [20]. For the shapes of the functions, refer to Fig. 4.2 in Section 4 or [20,23,25] or [32]. Gottesman et al. [15] found that the insulin-independent glucose uptake f_2 follows Michaelis–Menten kinetics. In addition, Gottesman et al. [15] found that, in postabsorptive human subjects, 75–85% of glucose uptake is non-insulin-mediated.

Sturis et al. [33] reported that oscillatory insulin delivery with an ultradian periodicity is more efficient in reducing blood glucose levels than constant insulin administration. In their experiments administration of exogenous insulin followed a sinusoidal wave shape with a period of 120 min. In our model (2.2), $I_{in}(t)$ represents the exogenous insulin infusion rate profile and $G_{in}(t)$ is glucose intake rate function. Therefore we assume that $I_{in}(t)$ and $G_{in}(t)$ are positive periodic functions with period ω. Under natural assumptions, we establish the existence of a periodic solution of model (2.2) based on a fixed point theorem and its global stability by applying Liapunov function method.

3. Mathematical analysis

In this section, the positivity and boundedness of solutions of (2.2) will be examined. We will also state results for the existence of a positive solution of (2.2) and its global stability. Detailed proofs will be carried out in Appendices.

It is easy to check that the solution of (2.2b) is

$$I(t) = e^{-d_i t} I_0 + e^{-d_i t} \int_0^t I_{in}(s) e^{d_i s} \, ds.$$

In order to find an ω-periodic solution, $I(t + \omega) = I(t)$ for all t, consider the following

$$I(t + \omega) = e^{-d_i t} e^{-d_i \omega} \left(I_0 + \int_0^t I_{in}(s) e^{d_i s} \, ds + \int_t^{t+\omega} I_{in}(s) e^{d_i s} \, ds \right)$$

and we have

$$I(t + \omega) = e^{-d_i \omega} I(t) + e^{-d_i t} e^{-d_i \omega} \int_t^{t+\omega} I_{in}(s) e^{d_i s} \, ds.$$

By letting $I(t + \omega) = I(t)$, we can easily find that

$$I^*(t) = \frac{e^{-d_i t - d_i \omega}}{1 - e^{-d_i \omega}} \int_t^{t+\omega} I_{in}(s) e^{d_i s} \, ds \tag{3.1}$$

is a positive ω-periodic solution of (2.2b).

Lemma 3.1. *All solutions of model (2.2) exist for $t > 0$, and they are positive and bounded from above.*

Proof. It is clear that the insulin solution $I(t)$ is positive and bounded and exists for all $t > 0$. Now let $G(t)$ be a solution of (2.2a). Assume $G(t_0) = 0$ for some $t > 0$. Let $t_0 = \inf\{t: G(t) \leqslant 0\}$. Then $G(t_0) = 0$ and $G'(t_0) \leqslant 0$. However,

$$G'(t_0) = G_{in}(t_0) + f_5(I(t_0 - \tau_2)) > 0,$$

which is a contradiction. Therefore, $G(t) > 0$ for $t > 0$.

Now we show the boundedness of $G(t)$. From (2.2), we have

$$G'(t) \leqslant \max_{t \in [0, \omega]} G_{in}(t) - a_3 G(t) f_4(m_I) + f_5(0),$$

where $m_I > 0$ is the lower bound of $I(t)$ on $[0, \infty]$. Therefore,

$$G(t) \leqslant G(0) e^{-(a_3 f_4(m_I))t} + \frac{\max\limits_{t \in [0, \omega]} G_{in}(t) + f_5(0)}{a_3 f_4(m_I)}, \quad \text{for } t > 0.$$

The boundedness also implies that $G(t)$ exists for all $t > 0$. $\square$

Let $(I(t), G(t))$ be a solution of (2.2). We define

$$\overline{G} = \limsup_{t \to \infty} G(t), \quad \underline{G} = \liminf_{t \to \infty} G(t)$$

and

$$\overline{I} = \limsup_{t \to \infty} I(t), \quad \underline{I} = \liminf_{t \to \infty} I(t).$$

Lemma 3.1 implies that $\overline{G}, \underline{G}, \overline{I}, \underline{I}$ are all finite. The well known fluctuation lemma is stated below without proof. Its proof can be found in, e.g., Hirsch et al. [16].

Lemma 3.2. *Let $f: R \to R$ be a differentiable function. If $l = \liminf_{t \to \infty} f(t) \leqslant \limsup_{t \to \infty} f(t) = L$, then there are sequences $\{t_k\} \uparrow \infty$, $\{s_k\} \uparrow \infty$ such that for all k, $f'(t_k) = f'(s_k) = 0$, $\lim_{k \to \infty} f(t_k) = l$ and $\lim_{k \to \infty} f(s_k) = L$.*

Lemma 3.3. *Model (2.2) is uniformly persistent, i.e. solutions of model (2.2) are eventually uniformly bounded from above and below.*

Proof. It is clear that $0 < \underline{I} \leqslant \overline{I} < \infty$. We only need to show that $\underline{G} > 0$. If $\underline{G} < \overline{G}$, then there exist a sequence $\{t'_k\} \uparrow \infty$ such that

$$G'(t'_k) = 0, \quad \lim_{k \to \infty} G(t'_k) = \underline{G}.$$

Thus (2.2a) gives, for all k,

$$0 = G'(t'_k) = G_{in}(t'_k) - f_2(G(t'_k)) - f_3(G(t'_k))f_4(I(t'_k - \tau_3)) + f_5(I(t'_k - \tau_2)),$$

and since f_4 is increasing and f_5 is decreasing, we have

$$0 \geqslant G_{in}(t'_k) - f_2(G(t'_k)) - f_3(G(t'_k))f_4(M_I) + f_5(m_I),$$

where $M_I = \max_{t\in[0,\infty)}I(t) > 0$ and $m_I = \min_{t\in[0,\infty)}I(t) > 0$. Letting $k \to \infty$, we have

$$0 \geqslant \min_{t\in[0,\omega]} G_{in}(t) - f_2(\underline{G}) - f_3(\underline{G})f_4(M_I) + f_5(m_I).$$

If $\underline{G} = 0$, we have

$$0 \geqslant \min_{t\in[0,\omega]} G_{in}(t) + f_5(m_I) > 0,$$

which is a contradiction. If $\underline{G} = \overline{G}$, then $\lim_{t\to\infty}G(t)$ exists. If $\lim_{t\to\infty}G(t) = 0$, the glucose equation

$$G'(t) = G_{in}(t) - f_2(G(t)) - f_3(G(t))f_4(I(t - \tau_3)) + f_5(I(t - \tau_2)),$$

implies that $G'(t) > \epsilon > 0$ for sufficiently large $t > 0$. Thus $G(t) \to \infty$ as $t \to \infty$, which is also a contradiction. This completes the proof of the lemma. $\square$

Since (2.2b) has a periodic solution I^* defined in (3.1), we only need to show that there is a positive periodic solution for (2.2a) when $I(t) = I^*(t)$. We now state results for the existence of a periodic solution of (2.2) and its global stability.

Theorem 3.4. *Model (2.2) has a positive periodic solution (G^*, I^*), where I^* is defined in (3.1).*

Theorem 3.5. *The periodic solution $(G^*(t), I^*(t))$ in Theorem 3.4 is globally asymptotically stable and unique, i.e., any solution $(G(t), I(t))$ with initial conditions $G(0) > 0$ and $I(0) > 0$ satisfies $|G(t) - G^*(t)| \to 0$, $|I(t) - I^*(t)| \to 0$ as $t \to \infty$.*

The proof of Theorem 3.4 is based on the Krasnoselskii fixed point theorem (Lemma A.1), and see Appendix A for details. The proof of Theorem 3.5 is based on a standard construction of a Lyapunov functional and will be carried out in Appendix B.

4. Applications in clinical insulin therapies

The management of type 1 diabetes mellitus has changed dramatically over the past 30 years. In particular, new insulin strategies have improved the ability to maintain near-normal glycemia. Factors such as onset, peak and duration of action can influence the ability of a particular insulin regimen in controlling glucose levels. The key to effective insulin therapy is an understanding of insulin pharmacokinetics that, when implemented, can results in improved diabetes control.

In this section we demonstrate how model (2.2) can be used in clinical insulin therapy strategies by selecting appropriate insulin infusion function I_{in} according to different types of insulin products. Currently, various insulin are available for subcutaneous injection, for example, rapid-acting insulin (Lispro and Aspart), short-acting insulin (Buffered regular insulin), intermediate-acting insulin (Lente, NHP), and long-acting insulin (Glargine and Ultralente). Fig. 4.1 (adapted from [28]) and Table 4.1 (adapted from [9]) list the onset, peak and duration of some types of insulin products. With different types of insulin products, therapies and algorithms can be developed for treatments of different diabetes.

We will use the same functions in [4,23,25,32,36] for numerical analysis. These functions, f_i, $i = 2,3,4,5$, take the following forms with experimentally determined parameters given in Table 4.2 [4,23,25,32].
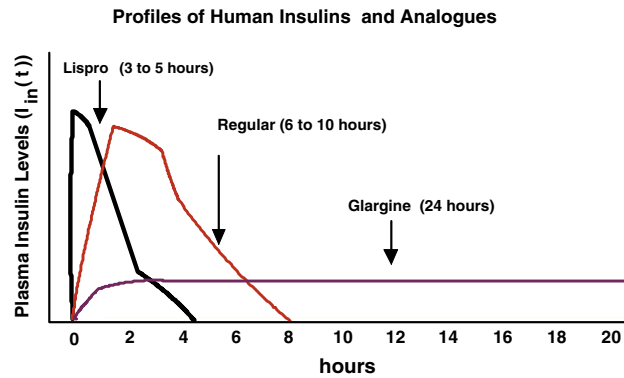
Profiles of Human Insulins and Analogues

Fig. 4.1. Onset of action, peak, and duration of action of exogenous insulin preparations (Lispro, Regular and Glargine) (adapted from [28]).

Table 4.1
Pharmacokinetics of available insulin products [9]

Insulin	Onset	Peak	Duration
Lispro	5–15 min	30–90 min	3–5 h
Aspart	10–20 min	1–3 h	3–5 h
Regular insulin	30–60 min	1–5 h	6–10 h
Buffered regular insulin	30–60 min	1–3 h	8 h
Lente	1–3 h	6–14 h	16–24 h
NPH	1–2 h	6–14 h	16–24+ h
Glargine	1.1 h	None	24 h
Ultralente	4–6 h	8–20 h	>24 h

Table 4.2
Parameters of the functions in (4.1, 4.2, 4.2, 4.4)

Parameters	Units	Values	Parameters	Units	Values
V_g	l	10	U_0	mg min^{-1}	40
U_b	mg min^{-1}	72	U_m	mg min^{-1}	940
C_2	mg l^{-1}	144	β		1.77
C_3	mg l^{-1}	1000	C_4	mU l^{-1}	80
V_p	l	3	R_g	mg min^{-1}	180
V_i	l	11	$\hat{\alpha}$	l mU^{-1}	0.29
t_i	min	100	C_5	mU l^{-1}	26

$$f_2(G) = U_b(1 - \exp(-G/(C_2 V_g))), \tag{4.1}$$

$$f_3(G) = G/(C_3 V_g), \tag{4.2}$$

$$f_4(I) = U_0 + (U_m - U_0)/(1 + \exp(-\beta \ln(I/C_4(1/V_i + 1/(0.2t_i))))), \tag{4.3}$$

$$f_5(I) = R_g/(1 + \exp(\hat{\alpha}(I/V_p - C_5))). \tag{4.4}$$

The units of G and I in the functions (4.1)–(4.4) are in mg and mU, respectively. They are converted to mg/dl and μU/ml when plotting the figures.

As an application of model (2.2) we discuss the effects of regular insulin and insulin lispro for type 1 diabetes. Regular (rapid onset of action, short duration of action) insulin and insulin lispro are the commonly-used insulins. As shown in Table 4.1 and Fig. 4.1, regular insulin has an onset of action (begins to reduce blood sugar) about 30 min after injection, reaches a peak effect at 1–5 h, and has lasting effects for 6–10 h. Insulin lispro, an ultra rapid-acting insulin, is a chemically-modified, natural insulin. Comparing to regular insulin, insulin lispro has a more rapid onset of action, an earlier peak effect, and a shorter duration of action. It could reaches peak activity in 5 min after injection. The piecewise functions in (4.6) and (4.7) and Fig. 4.4 (left) and Fig. 4.5 (left) mimic the infusion rates of lispro and regular insulin, respectively(refer to Table 4.1 and Fig. 4.1).
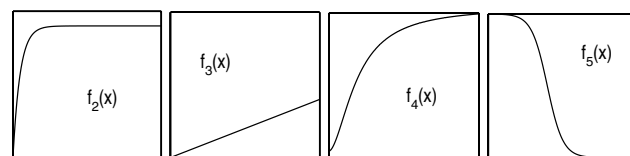

Fig. 4.2. Shapes of functions f_2 (upper left), f_3 (upper right), f_4 (lower left) and f_5 (lower right). These figures are adapted from [25].
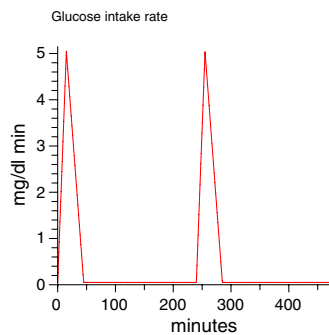

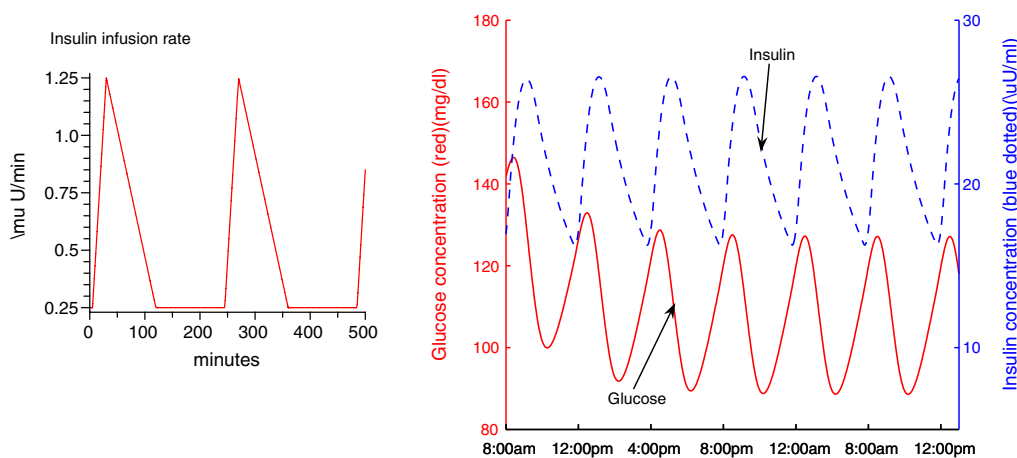Fig. 4.3. Glucose intake rate G_{in} in 4.5.

Fig. 4.4. (Left) Graph of insulin infusion function $I_{in_{lispro}}$ in (4.6). (Right) Profile of model (2.2) for insulin lispro from 08:00 am to 12:00 pm when $\tau_2 = 15$ min, $\tau_3 = 5$ min, $d_i = 0.0076$ min^{-1}.
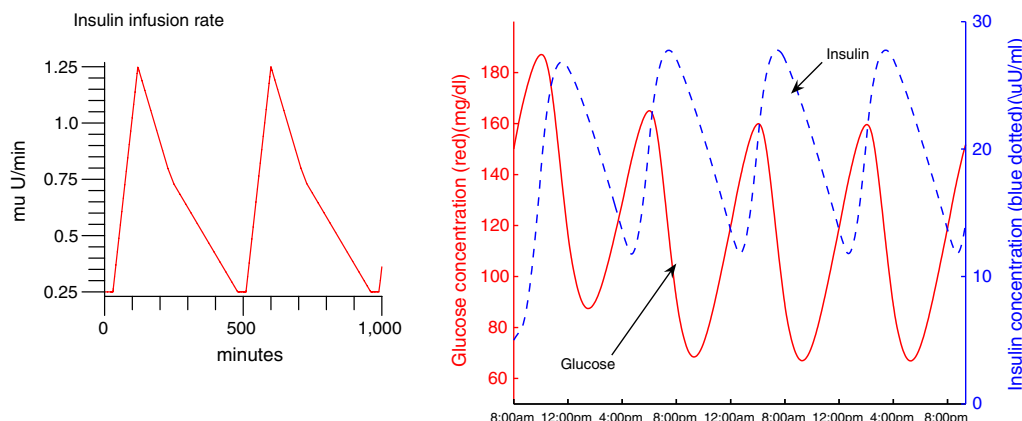
Fig. 4.5. (Left) Graph of regular insulin infusion function $I_{in_{regular}}$ in (4.7). (Right) Profile of model (2.2) for $\tau_2 = 15$ min, $\tau_3 = 5$ min, $d_i = 0.0107$ (min^{-1}) and $\omega = 480$ min, glucose intake function G_{in} in Fig. 4.3 and insulin infusion function I_{in} in (4.7).

We further assume that a subject takes a meal every 4 h ($\omega = 240$ min). The maximum glucose intake is 5 mg/min that is attained at 15 min. The whole duration of the glucose intake is 45 min. The function (4.5) and (4.3) represent the glucose intake functions.

$$
G_{in}(t) = \begin{cases} 0.05 + \frac{5}{15}t, & 0 \leqslant t < 15 \ (\text{min}), \\ 0.05 + 5\frac{45-t}{45-15}, & 15 \leqslant t < 45 \ (\text{min}), \\ 0.05, & 45 \leqslant t \leqslant 240 \ (\text{min}). \end{cases} \tag{4.5}
$$

$$
I_{in_{lispro}}(t) = \begin{cases} 0.25, & 0 \leqslant t \leqslant 5 \ (\text{min}), \\ 0.25 + 1 \cdot (1 + \frac{t-30}{30-5}), & 5 \leqslant t < 30 \ (\text{min}), \\ 0.25 + 1 \cdot (1 - \frac{t-30}{120-30}), & 30 \leqslant t < 120 \ (\text{min}), \\ 0.25, & 120 \leqslant t \leqslant 240 \ min. \end{cases} \tag{4.6}
$$

$$
I_{in_{regular}}(t) = \begin{cases} 0.25, & 0 \leqslant t \leqslant 30 \ (\text{min}), \\ 0.25 + 1 \cdot (1 + \frac{t-120}{90}), & 30 \leqslant t < 120 \ (\text{min}), \\ 0.25 + 1 \cdot (1 - 0.5\frac{t-120}{120}), & 120 \leqslant t < 240 \ (\text{min}), \\ 0.25 + 0.5 \cdot (1 - \frac{t-240}{240}), & 240 \leqslant t \leqslant 480 \ (\text{min}). \end{cases} \tag{4.7}
$$

For simplicity, it is assumed that the glucose intake $G_{in}(t)$ and insulin infusion $I_{in}(t)$ are periodic piecewise linear functions defined by the two expressions over a period of ω. They can be extended to any periodic continuous function on $[0, \infty)$.

Fig. 4.4 (left) and Fig. 4.5 (left) are the rates of injections of insulin lispro and regular insulin, respectively. Fig. 4.4 (right) and Fig. 4.5 (right) show the glucose and insulin profiles after the subcutaneous injections of insulin lispro and regular insulin, respectively. They demonstrate the glucose and insulin concentration profiles under the exogenous infusion of glucose and insulin. It is demonstrated that the profiles are close to those of a normal subject shown in Fig. 1.1.

It appears that the ranges of the glucose profiles with insulin lispro are smaller than those for regular insulin. This is in agreement with the findings by Recasens et al. [34], which investigated the effects of intensive insulin therapy using lispro in comparison with intensive insulin therapy using regular insulin for type 1 diabetes. Forty-five newly diagnosed type 1 diabetic subjects participated in the 12-month follow-up study. They found that glucose profiles for insulin lispro are lower than those for regular insulin although insulin lispro is as effective as regular insulin in optimizing metabolic control. It is also reported in [34] that the number of mild hypoglycemic episodes (glucose level below 60 mg/dl) tended to be lower with lispro, but not significantly. That could explain the reason that the bottom of the glucose oscillations in Fig. 4.5 is close to 60 mg/dl.

5. Dicussion

Model (2.2) utilizes the functions f_2–f_5 in ((4.1)–(4.4)) and the parameter values in Table 4.2 from [32,36], which are based on experimental data. These experimental data was taken from normal subjects. Type 1 diabetes is usually due to autoimmune destruction of the pancreatic beta cells which produce insulin [26]. With proper insulin treatments, patients can maintain plasma glucose within a normal range although hypoglycemia and hyperglycemia could happen. Therefore, these functions and parameters can be used in the insulin therapy model (2.2) for type 1 diabetic patients.

As discussed in Section 2, by incorporating α $f_1(G), 0 \leqslant \alpha \leqslant 1$ into model (2.2), model (2.2) could be adapted to model insulin therapies for the patients whose pancreas does not produce enough insulin to properly control plasma glucose concentration levels. Mathematically, periodicity and persistence of the model with $\alpha f_1(G)$ can be obtained in a similar way. Local stability may be proved via a properly constructed Lyapunov function with delays.

Insulin is absorbed and enters plasma after subcutaneous injection and then regulates glucose level. Patient factors, including individual variations in insulin absorption, levels of exercise, local massage, and, especially, local subcutaneous blood flow can influence the effectiveness of an insulin regimen [13]. The time it takes to absorb one half of an injected dose of insulin may vary by 25–50 percent among individual patients [17]. For example, NPH insulin may have a duration of action of 18 h in one patient but only 9 or 10 h in another patient [17]. It is also reported in Fernqvist et al. [14] that short intense physical exercise can accelerate the absorption of subcutaneously injected insulin. Hildebrandt [18] investigated the influence of skinfold thickness on the absorption rate of subcutaneously injected insulin. Model (2.2) can be adjusted to reflect the patient factors by incorporating a time delay in I_{in}. We may further investigate these factors in future work.

It is interesting to note that the delays do affect the amplitude of the glucose concentration. From Fig. 4.4, it appears that the peaks of the stable glucose concentration are over 130 mg/dl when $\tau_2 = 15$ min and $\tau_3 = 5$ min. Now we set $\tau_2 = 50$ min and $\tau_3 = 5$ min. Fig. 5.1 shows that the peaks of glucose concentration are below 130 mg/dl. Recall that $f_5(I(t - \tau_2))$ represents the glucose production of the liver and τ_2 stands for delayed effects. This indicates that the amplitude of the stable glucose concentration depends on the delays.
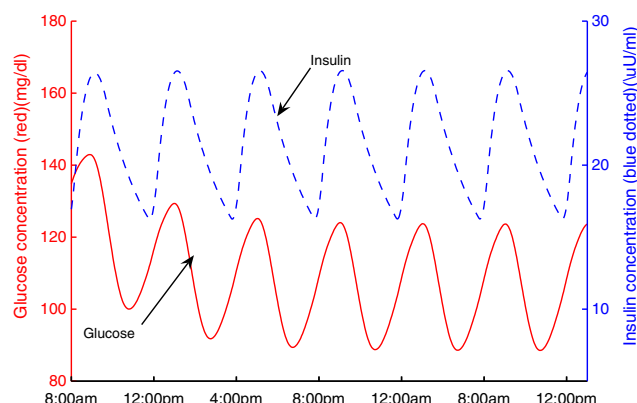
Fig. 5.1. Profile of model (2.2) for insulin lispro from 08:00am to 12:00pm when $\tau_2 = 50$ min, $\tau_3 = 5$ min, $d_i = 0.0076$ min^{-1}.

6. Acknowledgements

Appendix A

Proof of Theorem 3.4. In this section, we will give a proof of Theorem 3.4. A related result can be found in [38]. Before we state the Krasnoselskii fixed point theorem let us recall some concepts and conclusions on an operator in a cone in [22]. Let X be a Banach space and K be a closed, non-empty subset of X. K is said to be a cone if (i) $\alpha u + \beta v \in K$ for all u, $v \in K$ and all $\alpha, \beta > 0$ and (ii) $u, -u \in K$ imply $u = 0$. Assume Ω is a bounded open subset in X with the boundary $\partial\Omega$, and let $T : K \cap \overline{\Omega} \to K$ be completely continuous such that $Tx \neq x$ for $x \in \partial\Omega \cap K$.

Lemma A.1.

Krasnoselskii's Fixed Point Theorem [22]. *Let X be a Banach space and let $K \in X$ be a cone in X. Assume that Ω_1, Ω_2 are open subsets of X with $0 \in \Omega_1, \overline{\Omega_1} \subset \Omega_2$ and let*

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

be a completely continuous operator such that either (i) $\|Tx\| \leqslant \|x\|$, $x \in K \cap \partial\Omega_1$ and $\|Tx\| \geqslant \|x\|$, $x \in K \cap \partial\Omega_2$ or (ii) $\|Tx\| \geqslant \|x\|$, $x \in K \cap \partial\Omega_1$ and $\|Tx\| \leqslant \|x\|$, $x \in K \cap \partial\Omega_2$ is true. Then T has a fixed point in $K \cap (\overline{\Omega_2} \setminus \Omega_1)$.

In order to apply Lemma A.1 to prove Theorem 3.4, consider the Banach space

$$X = \{u(t) : u(t) \in C(\mathbb{R}, \mathbb{R}), u(t + \omega) = u(t)\}$$

with $\|u\| = \sup_{t \in [0,\omega]} |u(t)|$, $u \in X$. Define a cone K in X by

$$K = \{u \in X : u(t) \geqslant \frac{A}{B} \|u\| \ t \in [0, \omega]\}.$$

where A, B are defined by the following expressions: $A = \dfrac{1}{e^{b_2\omega+b_3\int_0^\omega f_4(I^*(\theta-\tau_3))\,d\theta}-1} > 0$ and

$B = \dfrac{e^{b_2\omega+b_3\int_0^\omega f_4(I^*(\theta-\tau_3))\,d\theta}}{e^{a_3\int_0^\omega f_4(I^*(\theta-\tau_3))\,d\theta}-1} > 0$. Let $r_1 = A\int_0^\omega [G_{\text{in}}(s)+f_5(I^*(s-\tau_2))]\,ds$ and $r_2 = B\int_0^\omega[G_{\text{in}}(s)+f_5(I^*$

$(s-\tau_2))]\,ds$. We then define two open sets Ω_{r_1} and Ω_{r_2} as $\Omega_{r_1} = \{u \in X : \|u\| < r_1\}$ and $\Omega_{r_2} = \{u \in X : \|u\| < r_2\}$. Note that $\partial\Omega_{r_i} = \{u \in X : \|u\| = r_i\}, i = 1,2$ and $K \cap (\overline{\Omega_2} \setminus \Omega_1) = \{X : u \in K, r_1 \leqslant \|u\| \leqslant r_2\}$. Now if $u \in K \cap (\overline{\Omega_2}\setminus\Omega_1)$, then $\min_{t\in[0,\omega]}u(t) \geqslant \frac{A}{B}\|u\| \geqslant \frac{A}{B}r_1 > 0$. Define the map $T : K \cap (\overline{\Omega_2}\setminus\Omega_1) \to X$ by

$$Tu(t) = \int_t^{t+\omega} U_u(t,s)[G_{\text{in}}(s)+f_5(I^*(s-\tau_2))]\,ds, \tag{6.1}$$

where

$$U_u(t,s) = \frac{e^{\int_t^s \left[\frac{f_2(u(\theta))}{u(\theta)}+\frac{f_3(u(\theta))}{u(\theta)}f_4(I^*(\theta-\tau_3))\right]d\theta}}{e^{\int_0^\omega \left[\frac{f_2(u(\theta))}{u(\theta)}+\frac{f_3(u(\theta))}{u(\theta)}f_4(I^*(\theta-\tau_3))\right]d\theta}-1}.$$

Note that

$$a_3 f_4(I^*(\theta-\tau_3)) \leqslant \frac{f_2(u(\theta))}{u(\theta)}+\frac{f_3(u(\theta))}{u(\theta)}f_4(I^*(\theta-\tau_3)) \leqslant b_2 + b_3 f_4(I^*(\theta-\tau_3))$$

Thus $A \leqslant U_u(t,s) \leqslant B$, $t \leqslant s \leqslant t+\omega$. We now able to show the following properties of the operator T.

Lemma A.2. $T : K \cap (\overline{\Omega_2}\setminus\Omega_1) \to K$ *is compact and continuous.*

Proof. In view of the definition of K, for $u \in K$, we have

$$(Tu)(t+\omega) = \int_{t+\omega}^{t+2\omega} U_u(t+\omega,s)[G_{\text{in}}(s)+f_5(I^*(s-\tau_2))]\,ds$$

$$= \int_t^{t+\omega} U_u(t+\omega,\theta+\omega)[G_{\text{in}}(\theta+\omega)+f_5(I^*(\theta+\omega-\tau_2))]\,d\theta$$

$$= \int_t^{t+\omega} U_u(t,s)[G_{\text{in}}(s)+f_5(I^*(s-\tau_2))]\,ds = (Tu)(t)$$

It is easy to see that $\int_t^{t+\omega}[G_{\text{in}}(s)+f_5(I^*(s-\tau_2))]\,ds$ is a constant because of the periodicity of $[G_{\text{in}}(t)+f_5(I^*(t-\tau_2))]$. One can show that, for $u \in K \cap (\overline{\Omega_2}\setminus\Omega_1)$,

$$Tu(t) \geqslant A\int_t^{t+\omega}[G_{\text{in}}(s)+f_5(I^*(s-\tau_2))]\,ds$$

$$= \frac{A}{B}B\int_0^\omega[G_{\text{in}}(s)+f_5(I^*(s-\tau_2))]\,ds \geqslant \frac{A}{B}\|Tu\|.$$

Thus $T(K \cap (\overline{\Omega_2}\setminus\Omega_1)) \subset K$ and it is easy to show that T is compact and continuous. □

Now if we can find a fixed point problem of T in $K \cap (\overline{\Omega_2}\setminus\Omega_1)$, then it will be a positive periodic solution of (2.2a) when $I(t) = I^*(t)$.

Lemma A.3.

If u is a fixed point problem of T in $K \cap (\overline{\Omega_2} \setminus \Omega_1)$, then u is a positive periodic solution of (2.2a) when $I(t) = I^*(t)$.

Proof. If $u \in K \cap (\overline{\Omega_2} \setminus \Omega_1)$ and $Tu = u$, then

$$
\begin{aligned}
u'(t) &= \frac{\mathrm{d}}{\mathrm{d}t}\left(\int_t^{t+\omega} U_u(t,s)[G_{\mathrm{in}}(s) + f_5(I^*(s - \tau_2))]\,\mathrm{d}s \right) \\
&= U_u(t, t+\omega)(G_{\mathrm{in}}(t+\omega) + f_5(I^*(t+\omega - \tau_2))) \\
&\quad - U_u(t,t)(G_{in}(t) + f_5(I^*(t - \tau_2])) \\
&\quad - \left(\frac{f_2(u(t))}{u(t)} + \frac{f_3(u(t))}{u(t)} f_4(I^*(t - \tau_3)) \right) Tu(t) \\
&= -\left(\frac{f_2(u(t))}{u(t)} + \frac{f_3(u(t))}{u(t)} f_4(I^*(t - \tau_3)) \right) u(t) + [G_{\mathrm{in}}(t) + f_5(I^*(t - \tau_2))] \\
&= G_{\mathrm{in}}(t) + f_5(I^*(t - \tau_2)) - f_2(u(t)) - f_3(u(t))f_4(I^*(t - \tau_3)).
\end{aligned}
$$

Thus u is a positive ω-periodic solution of (2.2a). □

We are now in a position to prove Theorem 3.4. Indeed, for $u \in \partial\Omega_{r_1}$, we have

$$
\begin{aligned}
Tu(t) &\geqslant A \int_t^{t+\omega} [G_{\mathrm{in}}(s) + f_5(I^*(s - \tau_2))]\,\mathrm{d}s \\
&= A \int_0^\omega [G_{\mathrm{in}}(s) + f_5(I^*(s - \tau_2))]\,\mathrm{d}s = r_1.
\end{aligned}
$$

Thus, for $u \in \partial\Omega_{r_1}$, $\|Tu\| \geqslant \|u\|$. On the other hand, for $u \in \partial\Omega_{r_2}$, we have

$$
\begin{aligned}
Tu(t) &\leqslant B \int_t^{t+\omega} [G_{\mathrm{in}}(s) + f_5(I^*(s - \tau_2))]\,\mathrm{d}s \\
&= B \int_0^\omega [G_{\mathrm{in}}(s) + f_5(I^*(s - \tau_2))]\,\mathrm{d}s = r_2.
\end{aligned}
$$

Thus, $u \in \partial\Omega_{r_2}$, $\|Tu\| \leqslant \|u\|$. It follows from Lemma A.1 that T has a fixed point in $\Omega_{r_2} \setminus \overline{\Omega}_{r_1}$, and hence (2.2) has a positive ω-periodic solution. This completes the proof. □

Appendix B

Proof of Theorem 3.5. In this section we provide a proof of Theorem 3.5. First we state a lemma from [2] without proof, which will be employed to establish the stability.

Lemma B.1.

Let h be a real number and f be a non-negative function defined on $[h, \infty)$ such that f is integrable on $[h, \infty)$ and is uniformly continuous on $[h, \infty)$. Then $\lim_{t\to\infty} f(t) = 0$.

Proof. of Theorem 3.5. In Theorem 3.4, we prove there is a positive periodic solution $(G^*(t), I^*(t))$ of (2.2). We will show that it is globally asymptotically stable. Assume $(G(t), I(t))$ is a solution of (2.2). First define a Lyapunov function $V_I(t) = \frac{1}{2}[I(t) - I^*(t)]^2$. Thus $\dot{V}_I = [I(t) - I^*(t)][\dot{I}(t) - \dot{I}^*(t)] = [I(t) - I^*(t)][-d_i I(t) + d_i I^*(t)] = -d_i[I(t) - I^*(t)]^2$. Then we have $\dot{V}_I = -2d_i V_I$ for $t > 0$, and then $V_I(t) = V_I(0)e^{-2d_i t}$. Therefore, $\lim_{t \to \infty}[I(t) - I^*(t)] = 0$. Now we investigate the stability of $G^*(t)$. Consider

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

where $m > 0$ is to be chosen later. The derivative of $V(t)$ along the solution of (2.2) takes the form of

$$
\begin{aligned}
\dot{V}(t) = & -2md_i V_I(0)e^{-2d_i t} \\
& + (G(t) - G^*(t))(G_{\text{in}}(t) - f_2(G(t)) - f_3(G(t))f_4(I(t - \tau_3)) + f_5(I(t - \tau_2)) \\
& - G_{\text{in}}(t) + f_2(G^*(t)) + f_3(G^*(t))f_4(I^*(t - \tau_3)) - f_5(I^*(t - \tau_2))) \\
= & -2md_i V_I(0)e^{-2d_i t} - (G(t) - G^*(t))^2 f_2'(\xi_2) \\
& - (G(t) - G^*(t))(I(t - \tau_3) - I^*(t - \tau_3))f_3(G(t))f_4'(\xi_4) \\
& - (G(t) - G^*(t))^2 f_3'(\xi_3)f_4(I^*(t - \tau_3)) \\
& - (G(t) - G^*(t))(I^*(t - \tau_2) - I(t - \tau_2))f_5'(\xi_5)
\end{aligned}
$$

where ξ_2, ξ_3 are between $G(t)$ and $G^*(t)$. ξ_4 is between $I(t - \tau_3)$ and $I^*(t - \tau_3)$. ξ_5 is between $I(t - \tau_2)$ and $I^*(t - \tau_2)$. Note that $f_5'(\xi_5)$ is negative because of (H4). We will make use of the inequality $2ab \leqslant \epsilon a^2 + b^2/\epsilon, \epsilon > 0$.

$$
\begin{aligned}
\dot{V}(t) \leqslant & -2md_i V_I(0)e^{-2d_i t} - (G(t) - G^*(t))^2 f_2'(\xi_2) \\
& + \frac{1}{2}\epsilon(G(t) - G^*(t))^2 f_3(G(t))f_4'(\xi_4) + \frac{1}{2\epsilon}(I(t - \tau_3) - I^*(t - \tau_3))^2 f_3(G(t))f_4'(\xi_4) \\
& - (G(t) - G^*(t))^2 f_3'(\xi_3)f_4(I^*(t - \tau_3)) \\
& + \frac{1}{2}\epsilon(G(t) - G^*(t))^2 |f_5'(\xi_5)| + \frac{1}{2\epsilon}(I^*(t - \tau_2) - I(t - \tau_2))^2 |f_5'(\xi_5)| \\
& (-2md_i + \frac{1}{\epsilon}e^{2d_i \tau_3}f_3(G(t))f_4'(\xi_4) + \frac{1}{\epsilon}|f_5'(\xi_5)|e^{2d_i \tau_2})V_I(0)e^{-2d_i t} \\
& - (G(t) - G^*(t))^2 (f_2'(\xi_2) + f_3'(\xi_3)f_4(I^*(t - \tau_3)) - \frac{\epsilon}{2}f_3(G(t))f_4'(\xi_4) - \frac{\epsilon}{2}|f_5'(\xi_5)|)
\end{aligned}
$$

Note that, by Lemma 3.3, ξ_2, ξ_3, ξ_4 and ξ_5 are bounded from below and above. Now if we choose $\epsilon > 0$ small enough that

$$f_2'(\xi_2) + f_3'(\xi_3)f_4(I^*(t - \tau_3)) - \epsilon\tfrac{1}{2}f_3(G(t))f_4'(\xi_4) - \epsilon\tfrac{1}{2}|f_5'(\xi_5)| > \alpha > 0$$

where, $\alpha > 0$ is a constant. For this $\epsilon > 0$ we further choose $m > 0$ large enough that

$$-2md_i + \frac{1}{\epsilon}e^{2d_i \tau_3}f_3(G(t))f_4'(\xi_4) + \frac{1}{\epsilon}|f_5'(\xi_5)|e^{2d_i \tau_2} < -\alpha < 0.$$

Hence,

$$\dot{V}(t) \leqslant -\alpha V_I(0)e^{-2d_i t} - \alpha(G(t) - G^*(t))^2 \tag{4.2}$$

Thus $V(t)$ is decreasing. Integrating on both sides of (4.2) from 0 to t and rearranging the terms produce

$$V(t) + \alpha V_I(0) \int_0^t e^{-2d_i s} \, ds + \alpha \int_0^t (G(s) - G^*(s))^2 \, ds \leqslant V(0).$$

Hence, $(G(t) - G^*(t))^2 \in L^1[0, \infty)$. It is also easy to see that $(G(t) - G^*(t))^2$ and the derivative of $(G(t) - G^*(t))^2$ are 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

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

Therefore, the periodic solution is globally asymptotically stable, which also implies the uniqueness of the periodic solution of (2.2). This completes the proof. $\square$

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