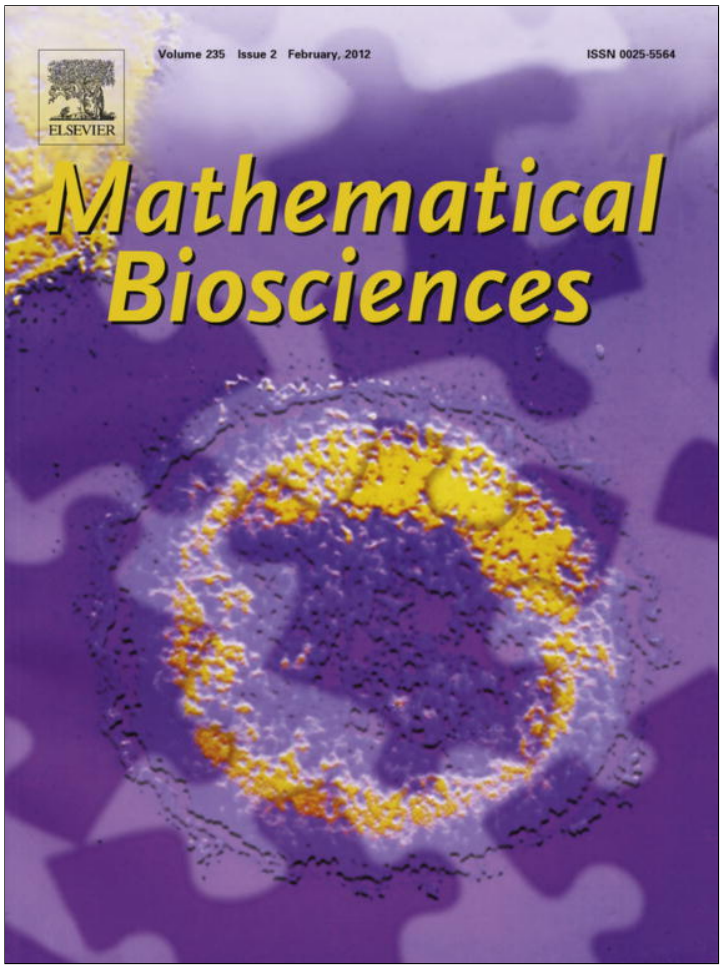

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The range of time delay and the global stability of the equilibrium for an IVGTT model ☆

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ABSTRACT

Diabetes mellitus has become a prevalent disease in the world. Diagnostic protocol for the onset of diabetes mellitus is the initial step in the treatments. The intravenous glucose tolerance test (IVGTT) has been considered as the most accurate method to determine the insulin sensitivity and glucose effectiveness. It is well known that there exists a time delay in insulin secretion stimulated by the elevated glucose concentration level. However, the range of the length of the delay in the existing IVGTT models are not fully discussed and thus in many cases the time delay may be assigned to a value out of its reasonable range. In addition, several attempts had been made to determine when the unique equilibrium point is globally asymptotically stable. However, all these conditions are delay-independent. In this paper, we discuss the range of the time delay and provide easy-to-check delay-dependent conditions for the global asymptotic stability of the equilibrium point for a recent IVGTT model through Liapunov function approach. Estimates of the upper bound of the delay for global stability are given in corollaries. In addition, the numerical simulation in this paper is fully incorporated with functional initial conditions, which is natural and more appropriate in delay differential equation systems.

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1. Introduction

Human bodies need to maintain a glucose concentration level in a narrow range (70–109 mg/dl or 3.9–6.04 mmol/l after overnight fast) [14]. If one's glucose concentration level is significantly out of the normal range, this person is considered to have a plasma glucose problem: hyperglycemia or hypoglycemia. Diabetes mellitus, or simply, diabetes, is characterized by high blood glucose levels resulted from defects in the glucose–insulin endocrine metabolic regulatory system, in which either the pancreas does not release insulin, or the cells do not properly use insulin to uptake glucose.

Diabetes mellitus has become an epidemic disease in the sense of life style. To diagnose whether or not an individual subject is already a diabetic or has the potential to develop such disease, the so-called metabolic portrait, including the insulin sensitivity index and glucose effectiveness, of the subject needs to be sketched. To this end, several glucose tolerance tests have been developed and applied in clinics and experiments [3–5,10,26]. The fundamental idea of such tests is to examine the response of insulin, called insulin sensitivity, after a large amount of glucose is infused into one's body. A commonly used protocol is the intravenous glucose tolerance test (IVGTT). In the procedure of IVGTT, overnight fast is required for the subject, and then the subject is given a bolus of glucose infusion intravenously, for example, 0.33 g/kg body weight [7] or 0.5 g/kg body weight of a 50% solution, and is administered into an antecubital vein in approximately 2 min. To observe the metabolic regulation between the glucose and insulin, within the next 180 min, the plasma glucose and serum insulin of the subject are sampled frequently at the time marks 2′, 4′, 6′, 8′, 10′, 12′, 14′, 18′, 21′, 24′, 30′, 35′, 40′, 45′, 50′, 60′, 70′, 80′, 90′, 100′, 120′, 140′, 160′ and 180′. According to the rich information constituted in the sampled data, appropriate analysis can reveal the metabolic portrait.

One popular approach of the analysis is as follows: (1) formulate or choose a well-formulated kinetic model based on physiology; (2) estimate the parameters of the IVGTT model with experimental data, and then (3) the parameter values are used to obtain physiological information, for example, the insulin sensitivity.

Several IVGTT models have been proposed and some are widely used [4,7,13,15,18,20,28]. All these models incorporate the insulin secretion delay implicitly in ordinary differential equation (ODE) model by using compartment-split technique or explicitly in delay differential equation (DDE) models. However, none of above work has discussed the reasonable range for the time delay and how to estimate the reasonable value of the delay according to the sampled data. Instead, the length of delay is often set to be larger than 20 min,

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which is in contrast to that the delay is between 5 and 15 min for normal subjects in normal environment [21,14,27]. Intuitively, the length of the delay in glucose tolerance test should not be longer than that in normal environment. In addition, several attempts have been made to obtain the conditions for the global stability of the equilibrium point of the models [9,13,18,20]. Unfortunately all the conditions are delay-independent. For the information about the delay $\tau > 0$, it is only known that there exists a $\tau_0 > 0$ such that the equilibrium point is locally stable if $\tau < \tau_0$; and unstable otherwise (thus a periodic solution is bifurcated out). To reveal the insight regarding the time delay, it would be very helpful to know an estimate of the upper bound $\bar{\tau}$ so that the equilibrium point is globally stable when $\tau < \bar{\tau}$. Applying the Liapunov function approach, we obtain delay dependent conditions for the global stability of the single delay IVGTT model proposed in [18]. Estimated upper bounds can be derived from these conditions explicitly or implicitly. We also improve the numerical simulations by using functional initial conditions in the delay differential equation model. To simulate the bolus glucose infusion and the abrupt insulin secretion, constant initial conditions with adjustments at time $t = 0$ are applied in [7,9,13,15,18,20]. This is neither natural to the design of the test, nor appropriate for a functional differential equation system. In this paper, we will shift the starting time of glucose infusion to $-2'$ and use a non-constant function as initial value in $[-\tau, 0]$.

We organize this paper as follows. We will first discuss the range of the length of the delay, then obtain some delay-dependent conditions for the global stability of the equilibrium point, from which estimated upper bounds of τ_0 are given in corollaries, and finally show numerical simulations for a DDE IVGTT model. We first in Section 3 introduce the IVGTT model proposed and studied in [9,18,20], followed by the analysis of the model, in which delay dependent conditions of the global stability of the unique equilibrium are given by utilizing Liapunov function in Section 4. In Section 5 we perform numerical simulations and we end this paper with discussions in Section 6.

2. Range of the time delay of insulin secretion

All discrete and distributed delay differential equation models for IVGTT explicitly involve a time delay between the rise in glycemia and the correspondingly stimulated insulin secretion. Thus, it is intuitive to ask following questions: What is the definition of the time delay? How long is the delay? De Gaetano and Arino [7] considered as indicative of the overall length of delay the average of delays of all studied subjects. All IVGTT models in [9,13,15,18,20] follow the same criterion, which yields a value of around 20 min.

The insulin secretion pathways consist of complex processes. The typical electric and chemical events can be summarized as follows according to [14] and the references therein. As the plasma glucose concentration is elevated, the insulin secretion from β-cells is determined by several cascading complex electric processes inside islet. These processes can be described in following steps: a glucose transporter GLUT2 transports glucose molecules into islet, the ratio of ATP (adenosine triphosphate) over ADP (adenosine diphosphate) is increased, the K^+ channels are closed and consequently the Ca^{2+} channels open, and then the influx of Ca^{2+} ions triggers insulin exocytosis from β-cell granules. Obviously such a chain of events causes a time delay for insulin release in responding to elevated glucose concentrations. Insulin release has effects on both hepatic glucose production and insulin-dependent glucose utilization [6]. It takes some time for the newly synthesized insulin to cross the endothelial barrier and eventually become the so-called 'remote insulin', then act on glucose uptake. This total delay time is approximately 5–15 min [6,27,29].

Bolus glucose infusion causes abrupt increase in plasma glucose concentration. Such an abrupt glucose increase stimulates biphasic insulin secretions, a rapid and approximately linear but short first phase release, followed by a slower and longer second phasic secretion. According to Overgaard et al. [17] and the references therein, such secretions relate to multiple aspects including the impact of glucose on β-cells, insulin synthesis, movements of insulin in β-cells, and eventually insulin release from granules. As glucose is infused intravenously, the metabolic system responds quickly. The rate of proinsulin synthesis is approximately linearly increased in translation of proinsulin mRNA. The proinsulin is split into insulin and C-peptide and stored in granules. A fraction of such granules is docked on the surface of the plasma membrane while others stay in the intracellular space with the ability of free movement. The group of granules docked on the surface of the plasma membrane is called readily-releasable pool (RRP), the insulin in which is released at the quick infusion of the glucose and forms the first phase of secretion. This release is instantaneous or almost instantaneous since it takes almost no time for the glucose infuse in intravenous to transport to pancreas and the insulin in the ready releasable pool. This instantaneous insulin release is followed by the following actions: grandules in intracellular space flow into the RRP and then their insulin is released. This release forms the second phase of secretion. This series of chemical and electrical events causes a time lag in the release after the observation of the increased glucose concentration. This time lag can be a few minutes [17].

Apparently, under normal conditions (meals), the first phase second in IVGTT is not significantly distinguishable from the secretion. Therefore time delay should exist and the range of the delay should not be longer than that in normal status. According to physiology cited in their work, Li et al. [14] defined the delay as the length of the delay τ as 'from the time that the glucose concentration level is elevated to the moment that the insulin has been transported to interstitial space and becomes remote insulin', and determined that the possible value of the delay falls in the biological range of 5–15 min [21]. Therefore we suspect that for most subjects, the length of the delay is shorter than 15 min in IVGTT. In most of the previous work, the time delay was chosen between 18 min and 24 min. The mean value, according to [18,20], is 19.271 min. It must be underscored that no direct relationship between the estimated parameter value and morphological features of the resulting state variable timecourse can be drawn. Therefore, empirically, in this paper we consider the delay as approximating the time between the primary insulin release and the trough in insulin concentration determined by its secondary release.

It is well known that a large delay can destabilize a system [11]. An accurate assessment of the delay can therefore play a critical role in elucidation of the metabolic portrait.

3. Single delay models for intravenous glucose tolerance test

3.1. The models

The Minimal Model, proposed by Bergman and his colleagues in 1979 [4] and 1980 [28], is believed to be one of the first widely employed models for the IVGTT [16]. The Minimal Model is in fact a combination of two separate ordinary differential equation (ODE) models, one for glucose kinetics and one for insulin kinetics. The time delay in the glucose–insulin regulatory system was simulated by the chain trick through an auxiliary variable [25]. However, certain mathematical problems arise in this unified Minimal Model, for example, the model fails to exhibit any equilibrium point and one of the state variables (insulin activity at the distant site) increases with time without any upper bound. In 2000, De Gaetano

and Arino [7] pointed out these issues and proposed the first delay differential equation (DDE) model, called *dynamic model*. This novel DDE model is not only well-posed in mathematics, but also more physiologically appealing as the time delay is contained in the model explicitly. The dynamic model was then generalized by Li et al. [13] in 2001. Another specific delay model proposed in 2004 by Mukhopadhyay et al. [15] also falls within the wide class of models contemplated by Li et al. [13]. The most recent model in IVGTT is a single delay differential equation model (SDM) (Model (1) below) proposed by De Gaetano and his colleagues [18] with specific function forms, which, even though it is a special case of the model proposed by Li et al. [13], motivates its ease in application, parameter choice physiologically and qualitative properties. A study of the obtained parameter estimates showed advantages in robustness and precision with the SDM compared with the Minimal Model [20]. In another piece of recent work, the same authors extended the class of subjects tested to cover a wide spectrum of insulin resistance and pointed to the drawbacks of 'decoupling' estimation methods as typically employed for the Minimal Model (advantages of the single delay model for the assessment of insulin sensitivity from the intravenous glucose tolerance test [19]).

Denote the plasma concentrations of glucose and insulin at time $t \geqslant -\tau$ by $G(t) > 0$ (mg/dl) and $I(t) > 0$ (μU/ml), respectively. The single delay model in [20] is given by

$$\begin{cases} G'(t) = b - eG(t) - aG(t)I(t), \\ I'(t) = df(G(t-\tau)) - cI(t) \end{cases} \tag{1}$$

with initial conditions $G(t) \equiv G_b$ for $t \in [-\tau, 0)$, $G(0) = G_b + G_\Delta$ and $I(0) = I_b + I_\Delta G_\Delta$, where $G_b > 0$ and $I_b > 0$ are basal levels of glycemia and insulinemia after overnight fast (also called baseline), and G_Δ and I_Δ are the theoretical increase over basal concentrations. The parameter $b > 0$ (mg/dl/min) is the rate of the constant glucose input; $e \geqslant 0$ (1/min) is the parameter for the insulin independent glucose utilization by, e.g., brain cells; $a > 0$ (ml/μU/min) is the parameter for the insulin dependent glucose utilization; $c > 0$ (1/min) is the rate of the insulin degradation; and the term $df(G(t-\tau))$ is the insulin secretion responded to the glucose stimulation with time delay $\tau \geqslant 0$

$$f(x) = \frac{x^\gamma}{\alpha^\gamma + x^\gamma}$$

with $d > 0$ (μU/mg/min) as the maximum secretionrate, $\alpha > 0$ as the half-saturation and $\gamma > 0$. If $\gamma \leqslant 1$, $f(x)$ is in the shape of Michaelis–Menten kinetics; if $\gamma > 1$, $f(x)$ is in sigmoidal shape. As discussed in [18], Model (1) has a unique equilibrium and the equilibrium point is at (G_b, I_b), so that after a perturbation the glucose and insulin blood levels will return back their basal value, which implies that

$$b = G_b(e + aI_b) \quad \text{and} \quad d = cI_b/(1 + (\alpha/G_b)^\gamma). \tag{2}$$

It must be noticed that the SDM also falls in the general class of models proposed and studied by Li et al. in [13]. Therefore all analytical results obtained in [13] automatically apply to the SDM. In the present work, in order to simplify mathematical notation at the possible expense of physiological clarity, we use a different notation for the parameters with respect to (1) from those in [9,18,20]. The relations are as follow: $a = K_{xgi}$, $b = T_{gh}/V_G$, $c = K_{xi}$, $d = T_{iG_{max}}/V_I$, and $e = K_{xg}$. According to both the Minimal Model [4,28] and the SDM (1) [20], the parameter a is called insulin sensitivity index, and the parameter e is called glucose effectiveness.

The main determinants of glucose uptake from plasma in the body are brain glucose consumption (essentially constant, therefor represented as a zero-order kinetics) and muscle and adipose tissue consumption and storage (insulin and glucose-concentration dependent, hence second-order kinetics). Therefore, first-order, insulin-independent glucose utilization has often been considered negligible [9,18,20], i.e., $e = 0$. Therefore Model (1) can be further simplified as follows [20]

$$\begin{cases} G'(t) = b - aG(t)I(t), \\ I'(t) = df(G(t-\tau)) - cI(t). \end{cases} \tag{3}$$

The authors of [20] applied the Akaike Information Criterion (AIC) in model selection by comparing Model (3) with Model (1), and determined that Model (3) is more suitable for representing observed IVGTTs. Moreover, impaired insulin-dependent glucose disposal is one of the reasons of insulin resistance that is typical in type 2 diabetes. Decreased insulin-dependent glucose transport by GLUT4 also occurs, for example, in chronic alcohol users [22]. Low insulin sensitivity may also occur in type 1 diabetes and could be caused by impaired GLUT4 translocation [8]. This indicates that insulin-independent GLUT1 may be dominant in translocation of glucose molecules [8] at least in some disease states. These considerations, as well as potential concentration effects shifting (at least in the short term) glucose to the interstitial space, prompt a cautious re-evaluation of the role of insulin-independent tissue glucose uptake and therefore of the generally positive, even small, value of the parameter e.

3.2. Existing analytical results and numerical observations

While analysis of the original Minimal Model focused only on numerical simulations [4,28], a number of analytical studies for subsequent IVGTT models have been carried out [7,9,13,15,18]. Typically, these last authors studied the local stability of the unique steady state and then numerically demonstrated that larger delays would not destabilize the steady state, since numerically determined Hopf bifurcation points are far beyond the meaningful physiological range. Some analytical delay-independent conditions for global stability of the steady state were obtained for the models proposed by Giang et al. [9], Li et al. [13], and Palumbo et al. [18]. Particularly, when $\gamma \leqslant 1$, the unique equilibrium point is globally asymptotically stable by applying the Theorem 3.1 in [13] with simple computations, and a set of sufficient and necessary conditions is given for Model (1) [18]. However, physiology [12,14,16,21,23,27,29] and all the clinical data [9,18,20] show the existence of the time delay of the glucose stimulated insulin secretion. Existing delay dependent condition (Theorem 3 in [9]) on the global stability is not satisfied with clinical data (Remark 11 in [18]), although the conditions hold with some critical modification, for example, the time delay has to be smaller (Remark 9 in [9]). Nevertheless, the local stability of the equilibrium and numerically determined large Hopf bifurcation value of the time delay do not destabilize the equilibrium point for a wide reasonable set of parameter values [12,18]. Studies and applications of these models are extended by Panunzi et al. [20] in application, and Giang et al. [9] in analysis. For more details for the formulation and applications of Model (1) and Model (3), interested readers can refer to [9,18,20].

We summarize the analytical results obtained in above references in the following. The system (1) is called persistent if the solutions are eventually uniformly bounded by positive constants from both above and below. A fastly oscillated solution is defined as a solution $(G(t), I(t))$ that oscillates around the equilibrium (G_b, I_b) and within two consecutive zeros $t_0 < t_1$ of $I(t) - I_b, I(t)$ attains its maximum or minimum at $t_* < t_0 + 2\tau$. (Definition 6 and Theorem 3 in [9].)

Let $(G(t),I(t))$ be a solution of Model (1) or Model (3). Throughout this paper, we define

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

and

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

(A1) Model (1) and Model (3) are persistent (Proposition 2.2 in [13]; Theorem 2 in [18]). Thus, the limits defined above are finite.

(A2) Following inequalities hold (Lemma 2.1 in [13]; Remark 5 in [18]).

$$df(\underline{G}) \leqslant c\underline{I} \leqslant c\overline{I} \leqslant df(\overline{G}) \tag{4}$$

$$(e + a\underline{I})\overline{G} \leqslant b \leqslant (e + a\overline{I})\underline{G} \tag{5}$$

(A3) The necessary condition (Theorem 5.1 in [13]; Theorem 6 in [18]) and sufficient conditions (Theorem 4 in [18]) for global stability of Model (1) and Model (3) is

$$\frac{\gamma a I_b}{1 + \left(\frac{G_b}{\alpha}\right)^{\gamma}} \leqslant e + aI_b. \tag{6}$$

(A4) If $\gamma \leqslant 1$, the unique equilibrium Model (1) or the model (3) is globally asymptotically stable (apply Theorem 3.1 in [13] to this special case). Notice that this result does not need the assumption (2) or (6). So we only consider the case $\gamma > 1$ in this paper.

(A5) If the inequality in (6) does not hold, then there is a $\tau_0 > 0$ such that (*i*) when $\tau < \tau_0$, the equilibrium (G_b,I_b) is locally stable; (*ii*) when $\tau \geqslant \tau_0$, the equilibrium is unstable. In other words, Model (1) and Model (3) undergo a Hopf bifurcation at $\tau = \tau_0$ when τ increases from $\tau = 0$ (Theorem 6 in [18]).

(A6) In Model (1), the equilibrium is a global attractor if

$$\frac{adG_b}{ce}\sqrt{\sup_{[0,G_b]} f'(G) \sup_{[G_b,\infty)} f'(G)} < 1.$$

(Theorem 2 in [9].)

(A7) Every fastly oscillated solution of Model (3) converges to the positive equilibrium if

$$(1 - e^{-2c\tau})\frac{adG_b}{ceI_b}\sqrt{G_b M_* \sup_{[0,G_b]} f'(G) \sup_{[G_b,\infty)} f'(G)} < 1,$$

where M_* satisfies $m_* f(M_*) = M_* f(m_*) = G_b f(G_b)$ for $m_* < G_b < M_*$. (Theorem 3 in [9].)

Notice that the conditions for the globally asymptotical stability of the equilibrium in (A3), (A4) and (A6) are delay-independent. But (A3) is a necessary and sufficient condition, so the result in (A5) shall be either a weaker condition or equivalent to (A3). Nevertheless, according to [18], only 3% of clinical data satisfy the condition in (A3). So to ensure the global attractive behavior of the tolerance test, analysis on delay dependent global stability is necessary. Notice that the insulin dynamics in IVGTT may often reach its basal level without oscillation [18,20] as defined in [9], the application of the result in (A6) is limited. In addition, (A6) requires τ to be small enough so that the parameters fitted from the clinical data satisfy the condition ([9], Remark 9).

4. Global stability of the equilibrium

We will establish criteria to determine the global stability, which depend on the time delay, and thus provide the estimated upper bounds for time delay.

We state following well known fact without proof, which is useful in estimating the bounds of a solution $(G(t),I(t))$ of Model (1).

Lemma 1. *If $h'(t) \leqslant p - qh(t)$, or $h'(t) \geqslant p - qh(t)$, where p, $q > 0$, then*

$$h(t) \leqslant \frac{p}{q} + \left(h(0) - \frac{p}{q}\right)e^{-qt}, \quad \text{or} \quad h(t) \geqslant \frac{p}{q} + \left(h(0) - \frac{p}{q}\right)e^{-qt}$$

for all $t \geqslant 0$.

A direct application of Lemma 1 is to estimate the bounds of a solution $(G(t),I(t))$. We have

Lemma 2. *If $(G(t),I(t))$ is a solution with positive initial conditions of Model (1), then*

$$m_I \doteq \min\left\{I(0), \frac{k_2}{c}\right\} \leqslant I(t) \leqslant M_I \doteq \max\left\{I(0), \frac{d}{c}\right\}$$

and

$$m_G \doteq \min\left\{G(0), \frac{b}{k_1}\right\} \leqslant G(t) \leqslant M_G \doteq \max\left\{G(0), \frac{b}{k_3}\right\}.$$

where $k_1 = e + aM_I$, $k_2 = df(m_G)$ and $k_3 = e + am_I$.

The proof is straight forward in observing the positiveness of such solutions (Theorem 1 in [18]).

Remark 1. The bounds given by the Lemma 2 is more accurate than the consequence in A2 by Palumbo et al. [18], which would result in

$$\frac{bc}{ec + ad} \leqslant \underline{G} \leqslant \overline{G} \leqslant \frac{bc}{ec + adf\left(\frac{bc}{ec+ad}\right)}.$$

by simple computation. However the upper bound M_G of $G(t)$ for $t > 0$ rather than the bound at limiting status of $G(t)$ plays an important role when applying the Theorem 3 to determine the global stability of the equilibrium. Notice that M_G is dependent of the initial values $G(0)$ and $I(0)$ of the solution $(G(t),I(t))$ only.

For the sake of convenience, we denote for $\gamma > 1$

$$L = d\frac{(\gamma+1)^2}{4\gamma\alpha}\left(\frac{\gamma-1}{\gamma+1}\right)^{\frac{\gamma-1}{\gamma}}, \tag{7}$$

which is the maximum value of the derivative of $df(G)$ for $G > 0$, and

$$R = e + aI_b, \quad \text{and} \quad K = aM_G. \tag{8}$$

By Lemma 2, L, R and K are independent of τ. When consider Model (3), $R = aI_b$.

When $\tau = 0$, Model (1) and Model (3) become a two-dimensional ordinary differential equation system. It is easy to show that the unique equilibrium (G_b,I_b) is globally asymptotically stable by Poincaré–Bendixson theorem. When $\tau > 0$, the models are functional differential equations. Poincaré–Bendixson Theorem does not apply. To establish a criterion of delay dependent global stability, we construct a Liapunov function and prove that the solutions of Model (1) or Model (3) are attracted to the equilibrium (G_b,I_b). Similar approach in this area can be found in [1,2,30,31].

Theorem 3. *If there exists a positive constant $u > 0$ such that*

$$\tau < \min\left\{\frac{2u}{L}, \frac{2c}{L(R+2K)}\right\} \tag{9}$$

and

$$\Delta \doteq M_u^2 - 4R\left(u - \frac{\tau}{2}L\right)\left(c - \frac{\tau}{2}L(R+2K)\right) < 0, \tag{10}$$

where $M_u = \max\{L, Ku\}$, then the equilibrium (G_b,I_b) of Model (1) is globally and asymptotically stable.

Proof. Let

$$W(G(t),I(t)) = \frac{1}{2}u(G(t)-G_b)^2 + \frac{1}{2}(I(t)-I_b)^2, \tag{11}$$

$$U(G(t),I(t)) = C\int_{t-\tau}^{t}\int_{z}^{t}(G(s)-G_b)^2\,ds\,dz + D\int_{t-\tau}^{t}\int_{z}^{t}(I(s)-I_b)^2\,ds\,dz. \tag{12}$$

where $C = \frac{1}{2}RL$ and $D = \frac{1}{2}KL$.

Let

$$V(G(t),I(t)) = W(G(t),I(t)) + U(G(t),I(t)),$$

then, clearly, V is a Liapunov function.

By Mean Value Theorem, we have

$$\begin{aligned} d(f(G(t-\tau)) - f(G_b)) &= df'(\xi)(G(t-\tau)-G_b) \\ &= df'(\xi)((G(t-\tau)-G(t)) + (G(t)-G_b)) \end{aligned}$$

where ξ is between $G(t-\tau)$ and $G(t)$. Also, since $uv \leqslant \frac{1}{2}(u^2+v^2)$ for all $u,\ v \geqslant 0$, we have

$$\begin{aligned} &|(I(t)-I_b)(G(t)-G(t-\tau))| \\ &= \left|(I(t)-I_b)\int_{t-\tau}^{t}G'(s)\,ds\right| \\ &= \left|\int_{t-\tau}^{t}(b-eG(s)-aG(s)I(s))(I(t)-I_b)\,ds\right| \\ &= \left|\int_{t-\tau}^{t}(e(G(s)-G_b)(I(t)-I_b) + aG(s)(I(s)-I_b)(I(t)-I_b) \right. \\ &\quad \left. + aI_b(G(s)-G_b)(I(t)-I_b))\,ds\right| \\ &= \left|\int_{t-\tau}^{t}((e+aI_b)(G(s)-G_b)(I(t)-I_b) + aG(s)(I(s)-I_b)(I(t)-I_b))\,ds\right| \\ &\leqslant \frac{1}{2}\left[(e+aI_b)\left(\int_{t-\tau}^{t}(G(s)-G_b)^2\,ds + \tau(I(t)-I_b)^2\right)\right. \\ &\quad \left. + aG_M\left(\int_{t-\tau}^{t}(I(s)-I_b)^2\,ds + \tau(I(t)-I_b)^2\right)\right] \\ &\leqslant \frac{1}{2}\left[R\int_{t-\tau}^{t}(G(s)-G_b)^2\,ds + K\int_{t-\tau}^{t}(I(s)-I_b)^2\,ds + \tau(R+K)(I(t)-I_b)^2\right]. \end{aligned}$$

Then

$$\begin{aligned} \frac{d}{dt}W &= u(G(t)-G_b)[-e(G(t)-G_b) - a(G(t)(I(t)-I_b) + I_b(G(t)-G_b))] \\ &\quad + (I(t)-I_b)[d(f(G(t-\tau)) - f(G_b)) - c(I(t)-I_b)] \\ &= -ue(G-G_b)^2 - uaG(G-G_b)(I-I_b) - uaI_b(G-G_b)^2 \\ &\quad + d(I-I_b)[f(G(t-\tau)) - f(G_b)] - c(I-I_b)^2 \\ &= -(ue+uaI_b)(G-G_b)^2 - uaG(G-G_b)(I-I_b) \\ &\quad - c(I-I_b)^2 + d(I-I_b)[f(G(t-\tau)) - f(G_b)] \\ &= -u(e+aI_b)(G-G_b)^2 - uaG(G-G_b)(I-I_b) \\ &\quad - c(I-I_b)^2 + df'(\xi)(I-I_b)[(G(t-\tau)-G(t)) + (G(t)-G_b)] \\ &= -u(e+aI_b)(G-G_b)^2 + (df'(\xi) - uaG)(G-G_b)(I-I_b) \\ &\quad - c(I-I_b)^2 + df'(\xi)(I-I_b)(G(t-\tau)-G(t)) \\ &\leqslant -u(e+aI_b)(G-G_b)^2 + |df'(\xi) - uaG\|G-G_b\|I-I_b| \\ &\quad - c(I-I_b)^2 + L|(I-I_b)(G(t-\tau)-G(t))| \\ &\leqslant -uR(G-G_b)^2 + |df'(\xi) - uaG\|G-G_b\|I-I_b| - c(I-I_b)^2 \\ &\quad + \frac{1}{2}L\left[R\int_{t-\tau}^{t}(G(s)-G_b)^2\,ds + K\int_{t-\tau}^{t}(I(s)-I_b)^2\,ds + \tau(R+K)(I(t)-I_b)^2\right] \\ &= -uR(G-G_b)^2 + |df'(\xi) - uaG\|G-G_b\|I-I_b| \\ &\quad - \left(c - \frac{\tau}{2}L(R+K)\right)(I-I_b)^2 + C\int_{t-\tau}^{t}(G(s)-G_b)^2 ds + D\int_{t-\tau}^{t}(I(s)-I_b)^2\,ds. \end{aligned}$$

Furthermore,

$$\begin{aligned} \frac{dU}{dt} &= -C\int_{t-\tau}^{t}(G(s)-G_b)^2\,ds + C\tau(G(t)-G_b)^2 \\ &\quad - D\int_{t-\tau}^{t}(I(s)-I_b)^2\,ds + D\tau(I(t)-I_b)^2 \end{aligned}$$

So, along the solution $(G(t),I(t))$ of Model (1), we have

$$\begin{aligned} \frac{dV}{dt} &\leqslant -uR(G-G_b)^2 + |df'(\xi) - uaG\|G-G_b\|I-I_b| \\ &\quad - \left(c - \frac{\tau}{2}L(R+K)\right)(I-I_b)^2 + C\int_{t-\tau}^{t}(G(s)-G_b)^2 ds \\ &\quad + D\int_{t-\tau}^{t}(I(s)-I_b)^2\,ds - C\int_{t-\tau}^{t}(G(s)-G_b)^2\,ds + C\tau(G(t)-G_b)^2 \\ &\quad - D\int_{t-\tau}^{t}(I(s)-I_b)^2\,ds + D\tau(I(t)-I_b)^2 \\ &= -(uR - C\tau)(G-G_b)^2 + |df'(\xi) \\ &\quad - uaG\|G-G_b\|I-I_b| - \left(c - \tau\left(\frac{1}{2}L(R+K) + D\right)\right)(I-I_b)^2 \\ &= -\left(uR - \frac{\tau}{2}LR\right)(G-G_b)^2 + |df'(\xi) - uaG\|G-G_b\|I-I_b| \\ &\quad - \left(c - \tau\left(\frac{1}{2}L(R+K) + \frac{1}{2}LK\right)\right)(I-I_b)^2 \\ &= -R\left(u - \frac{\tau}{2}L\right)(G-G_b)^2 + |df'(\xi) - uaG\|G-G_b\|I-I_b| \\ &\quad - \left(c - \frac{\tau}{2}L(R+2K)\right)(I-I_b)^2 \leqslant -R\left(u - \frac{\tau}{2}L\right)(G-G_b)^2 \\ &\quad + M_u|G-G_b\|I-I_b| - \left(c - \frac{\tau}{2}L(R+2K)\right)(I-I_b)^2 < 0, \end{aligned}$$

in observing that the conditions (9) and (10) hold. □

Remark 2. Since M_u can be dependent of $G(0)$ or $I(0)$ in some cases, the global stability is not uniform.

We derive two corollaries from the above theorem, which give the estimates of the bounds for the delay τ, which ensures the equilibrium is globally stable. Denote

$$p_1 = \frac{cK + L(R+2K)}{KL(R+2K)}, \quad q_1 = \frac{4Rc - KL}{KRL(R+2K)}$$

and

$$\tilde{\tau} = \min\left\{\frac{2}{K}, \frac{2c}{L(R+2K)}\right\}.$$

Then we have

Corollary 1. *The unique equilibrium of Model (1) is globally asymptomatically stable, if the delay τ satisfies either of the following conditions:*

$$\text{(i)}\quad \tau < \tilde{\tau}, \quad \text{if } p_1^2 - q_1 < 0; \tag{13}$$

$$\text{(ii)}\quad \tau < \min\left\{\tilde{\tau}, p_1 - \sqrt{p_1^2 - q_1}\right\}, \quad \text{if } p_1^2 - q_1 > 0, \quad q_1 > 0; \tag{14}$$

$$\text{(iii)}\quad \tau \in \left(p_1 + \sqrt{p_1^2 - q_1}, \tilde{\tau}\right), \quad \text{if } p_1^2 - q_1 > 0, \quad p_1 + \sqrt{p_1^2 - q_1} < \tilde{\tau}; \tag{15}$$

$$\text{(iv)}\quad \tau < \tilde{\tau} \quad \text{and } \tau \neq p_1, \text{if } p_1^2 - q_1 = 0; \tag{16}$$

Proof. Notice that $M_u = \max\{L, Ku\}$ in Theorem 3. Let $u = L/K$, then $M_u = L$. Therefore (9) becomes $\tau < \tilde{\tau}$, and (10) holds if and only if

$$
\begin{aligned}
&M_u^2 - 4R\Big(u-\frac{\tau}{2}L\Big)\Big(c-\frac{\tau}{2}L(R+2K)\Big)\\
&= L^2 - 4R\Big(\frac{L}{K}-\frac{\tau}{2}L\Big)\Big(c-\frac{\tau}{2}L(R+2K)\Big)\\
&= L\Big[L - 4R\Big(\frac{1}{K}-\frac{\tau}{2}\Big)\Big(c-\frac{\tau}{2}L(R+2K)\Big)\Big]\\
&= L\Big[L - 4R\Big(\frac{c}{K}-\frac{\tau}{2}c-\frac{\tau}{2}\frac{L(R+2K)}{K}+\frac{\tau^2}{4}L(R+2K)\Big)\Big]\\
&= L\Big[L - \frac{4Rc}{K}+2\tau R\Big(c+\frac{L(R+2K)}{K}\Big)-\tau^2RL(R+2K)\Big]\\
&= -L^2R(R+2K)\Big[\frac{-L+\frac{4Rc}{K}}{RL(R+2L)}-\frac{2R(c+\frac{L(R+2K)}{K})}{RL(R+2K)}\tau+\tau^2\Big]\\
&= -L^2R(R+2K)\Big[\frac{4Rc-KL}{KRL(R+2K)}-\frac{2(cK+L(R+2K))}{KL(R+2K)}\tau+\tau^2\Big]\\
&= -L^2R(R+2K)(q_1-2p_1\tau+\tau^2) < 0.
\end{aligned}
$$

Then it is straight forward to obtain the conclusion. □

Denote

$$H = c-\frac{\tau}{2}L(R+2K) \quad \text{and} \quad \bar{\tau} = \frac{2Rc}{L(R+K)^2}.$$

If $\tau < \bar{\tau}$, then

$$
\begin{aligned}
2RH - K^2L\tau &= 2RH - K^2L\tau = 2R\Big(c-\frac{\tau}{2}L(R+2K)\Big) - K^2L\tau\\
&= 2Rc - (RL(R+2K)+K^2L)\tau\\
&= 2Rc - L(R(R+2K)+K^2)\tau\\
&= 2Rc - L(R^2+2RK+K^2)\tau = 2Rc - L(R+K)^2\tau > 0.
\end{aligned}
$$

Hence, we can define

$$u_0 = \frac{4RH+\sqrt{8RH(2RH-K^2L\tau)}}{2K^2} > 0.$$

Therefore, we have

Corollary 2. *The unique equilibrium of Model (1) is globally asymptomatically stable if*

$$\tau < \min\Big\{\frac{2u_0}{L}, \bar{\tau}\Big\}, \quad \text{and} \quad u_0 > \frac{L}{K}. \tag{17}$$

Proof. We choose an appropriate $u > 0$ so that the inequality (10) holds. Let $u > L/K$. Then $M_u = Ku$ in Theorem 3 and thus (10) holds if and only if

$$K^2u^2 - 4R\Big(u-\frac{\tau}{2}L\Big)H = K^2u^2 - 4RHu + 2RLH\tau < 0.$$

So the existence of such $u > 0$ is equivalent to

$$(4RH)^2 - 4K^2\cdot 2RLH\tau = 8RH(2RH-K^2L\tau) > 0$$

and the larger root u_0 of $P(u) = K^2u^2 - 4RHu + 2RKH\tau = 0$ is greater than L/K. Notice (17). We choose any $u \in (L/K, u_0)$ so that both conditions in the Theorem 3 are satisfied. □

Remark 3. The inequalities of (i), (ii) and (iv) in Corollary 1 provide estimated upper bounds of the time delay of insulin secretion stimulated by glucose. Since H in (17) is dependent of τ, one can estimate an upper bound of τ implicitly.

We will apply Corollaries 1 and 2 in next section with experimental data obtained from [7,20].

5. Numerical simulations

In order to exemplify the computation of the proposed stability criteria, we considered sets of parameter values consistent with adaptation to data from actual IVGTT experiments. Simulations are performed by using Matlab delay differential equation solver dde23 [24]. We considered three sets of experimental data from [7] listed in Table 1, and two sets from [20] listed in Table 2. In

Table 1
Experimental data published in [7]. We obtained these data by manually measuring the data in related figures in [7]. The first column is the time in minute to sample the blood with a two-minute shift. The second and third columns are the data for subject 6. The first trough is at about 8′ mark. The fourth and fifth columns are the data from for the subject 7 and its first trough is at about 12′ mark. The sixth and seventh columns are the data for subject 8 and there is no clear trough.

min	G (mg/dl)	I (μU/l)	G (mg/dl)	I (μU/l)	G (mg/dl)	I (μU/l)
−2	87.7358	67.9245	87.2117	38.5744	77.9874	57.9000
0	225.4717	413.2075	299.3711	179.4549	226.4151	1031.4000
2	214.1509	410.3774	259.9581	103.9832	228.9308	915.7000
4	203.7736	305.6604	253.2495	99.7904	203.7736	759.7000
6	200.0000	286.7925	244.0252	93.9203	201.2579	772.3000
8	195.2830	234.9057	225.5765	104.8218	196.2264	646.5000
10	192.4528	317.9245	223.8994	77.1488	183.6478	669.2000
13	174.5283	278.3019	203.7736	88.8889	173.5849	513.2000
18	158.4906	238.6792	188.6792	95.5975	148.4277	508.2000
23	150.0000	250.0000	170.2306	79.6646	123.2704	440.3000
28	131.1321	233.9623	150.9434	97.2746	115.7233	327.0000
33	118.8679	203.7736	134.1719	86.3732	100.6289	286.8000
38	115.0943	153.7736	119.9161	108.1761	95.5975	226.4000
48	106.6038	169.8113	101.4675	44.4444	85.5346	166.0000
58	93.3962	115.0943	89.7275	24.3187	75.4717	148.4000
78	82.0755	111.3208	85.5346	33.5430	72.9560	118.2000
98	77.3585	53.7736	85.5346	29.3501		
118	83.0189	46.2264	88.0503	37.7358	77.9874	67.9000
138	83.0189	58.4906	87.2117	31.0273	80.5031	42.8000
158	82.0755	64.1509	86.3732	33.5430	77.9874	60.4000
178	85.8491	55.6604	87.2117	46.9602	80.5031	57.9000

Table 2
Experimental data published in [20]. We obtained these data by manually measuring the data in related figures in [20]. The first column is the time in minute to sample the blood with a two-minute shift. The second and third columns are the data for subject 13. The first trough is at 18′ mark. The fifth and sixth columns are the data for subject 27. The first trough is at about 12′ mark.

min	G (mg/dl)	I (μU/l)	min	G (mg/dl)	I (μU/l)
−2	74.20	24.0	−2	86.47	44.00
0	183.40	231.0	0	345.90	1036.00
2	171.90	127.5	2	275.64	1067.00
4	164.80	124.5	4	263.03	914.00
6	164.10	146.0	6	241.41	415.00
8	150.10	102.5	8	228.80	455.00
10	140.00	129.0	10	227.90	404.00
13	135.10	92.0	12	218.89	216.00
			16	208.98	344.00
18	136.20	88.5	19	199.97	282.00
23	127.00	113.5	22	192.77	232.00
28	118.90	179.5	28	175.65	294.00
			33	163.94	193.00
38	100.90	126.5	38	157.64	227.00
			43	149.53	210.00
48	90.10	91.5	48	147.73	188.00
58	83.40	64.0	58	132.41	116.00
68	79.10	34.0	68	108.99	194.00
78	76.40	30.0	78	97.28	154.00
			88	93.68	95.00
			98	89.18	72.00
118	73.30	28.0	118	84.67	50.00
138	77.30	27.0	138	79.27	38.00
158	76.40	33.5	158	72.06	36.00
178	73.00	23.5	178	72.06	33.00

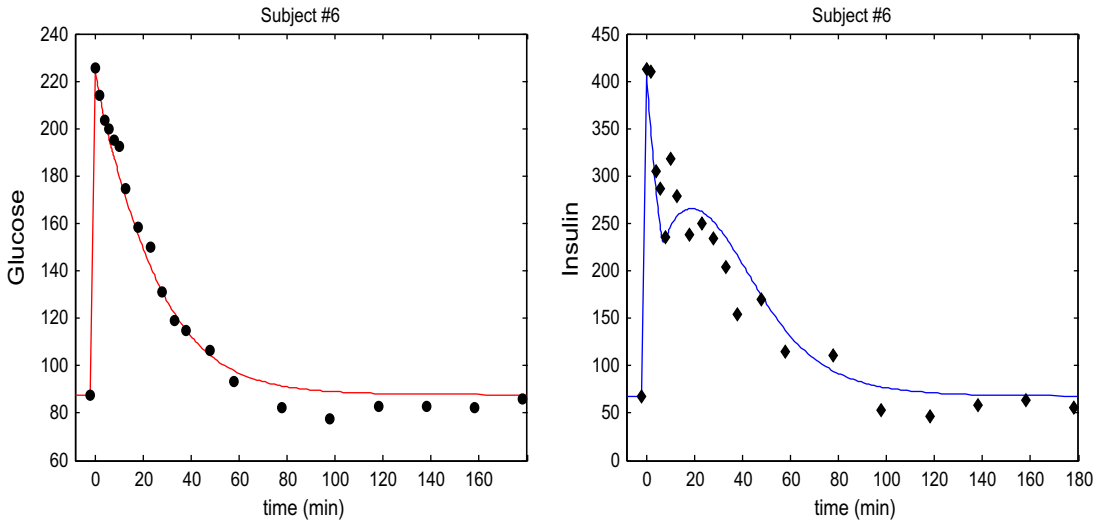

Fig. 1. Profiles of subject 6 in [7] produced by Model (1) with parameters $a = 3.77371 \times 10^{-5}$, $b = 2.16826$, $c = 0.1125$, $d = 35.8389$, $e = 0.0221502$, $\alpha = 120.506$, $r = 4.11393$ and $\tau = 8.25$. The proposed parameters satisfy the condition (14) in Corollary 1, and both condition (17) in Corollary 2. The upper bound computed from Corollary 1 is 12.2539; while the bound computed from Corollary 2 is 15.5167. The second peak is clearly shown.

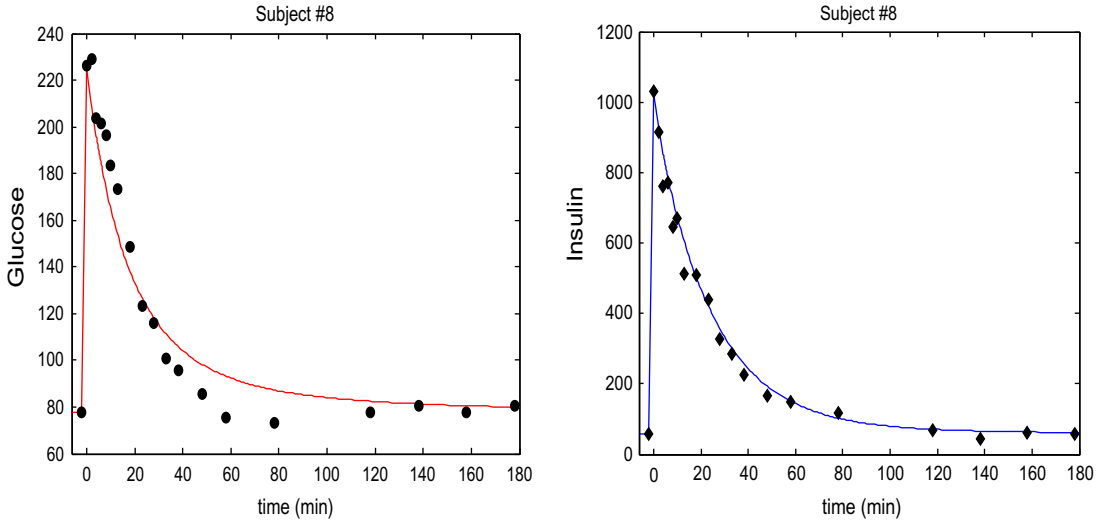

Fig. 2. Profiles of subject 8 in [7] produced by Model (1) with parameters $a = 3.55846 \times 10^{-5}$, $b = 0.550617$, $c = 0.05$, $d = 11.4347$, $e = 0.00499998$, $\alpha = 126.001$, $r = 2.25483$ and $\tau = 6.24999$. The proposed parameters satisfy the condition (14) in Corollary 1, and both condition (17) in Corollary 2. The upper bound computed from Corollary 1 is 39.5225; while the bound computed from Corollary 2 is 49.2619. No second peak is observed.

the original datasets, the time mark $0'$ is the starting time of the bolus glucose infusion, and the time mark $2'$ is the first blood sampling time. We further depart from published work in hypothesizing that glycemia increase between the start of infusion to the first observed glycemia point follows an ascending linear ramp. Moreover, in observing that indeed the bolus glucose infusion belongs to the initial condition of the delay differential equation model (1), we introduce a $-2'$ shift of the time marks in experimental data points.

The initial condition for a delay differential equation with maximum delay τ is a function defined in the interval $[-\tau, 0]$. Therefore we use a piece-wise linear function

$$\phi(t) = \begin{cases} G_b, & \text{for} \quad t \in [-\tau, -\delta], \\ G_0 + \delta^{-1}(G_0 - G_b)t, & \text{for} \quad t \in (-\delta, 0]; \end{cases} \tag{18}$$

while $I(0) = I_0$, where δ (minute), $0 < \delta < \tau$, is the total time needed for the bolus glucose infusion, which is assumed that $\delta = 2$ min in this paper. Here G_b and I_b are taken from the first row at time mark $-\delta$ minute in the data tables and G_0 and I_0 are taken from the second row at time mark $0'$ from the data tables. Assume that $\phi(G) = G_b$ on $[-\tau, -\delta]$ to reflect that the subject has been in fasting state and has maintained the glucose level at baseline. Assuming that $\phi(t)$ is linearly increasing from G_b to G_0 in $(-\delta, 0]$ is in observation that the glucose infusion finishes in δ minutes and the measurement starts. It is of interest to note the actual connection between steepness of secondary increase and length of delay with the ramp glucose infusion that when a rapid increase of secondary insulin secretion is desired, the ramp initial condition produce shorter, impulsive starting values longer time delays; conversely, when a slower increase of secondary insulin secretion must be produced, the ramp starting condition implies longer and impulsive starting values shorter time delays.

The ranges determined by Corollaries 1 and 2 for the delay parameter τ are the values for τ so that the globally asymptotic stability of the equilibrium (the basal state) is secured, that is,

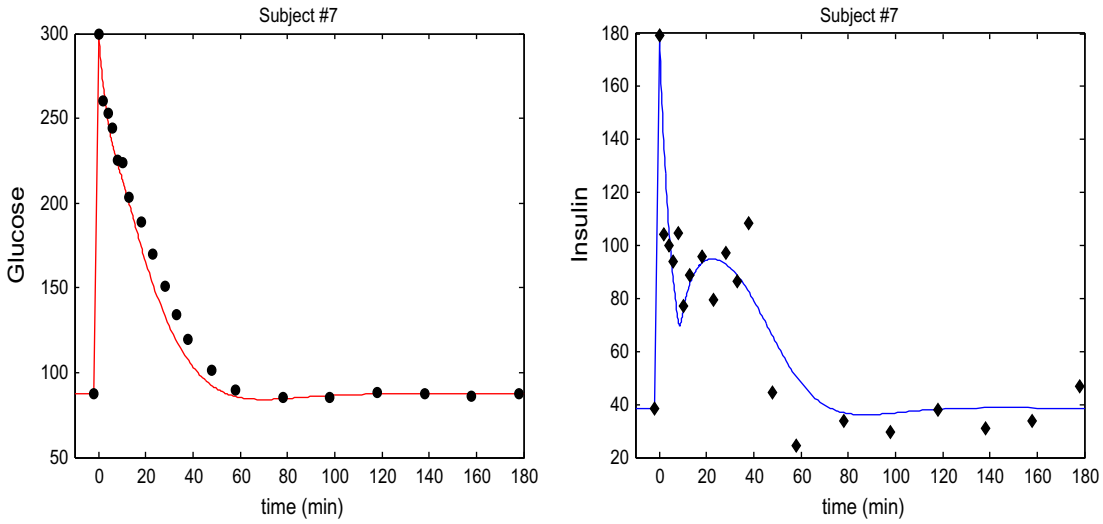

Fig. 3. Profiles of subject 7 in [7] produced by Model (1) with parameters $a = 0.000369212$, $b = 1.24217$, $c = 0.18146$, $d = 18.9992$, $e = 1.0081 \times 10^{-6}$, $\alpha = 102.628$, $r = 3.31137$ and $\tau = 10.1688$. The delay parameter τ is out of the upper bounds computed from Corollaries 1 and 2. The second peak is clearly shown.

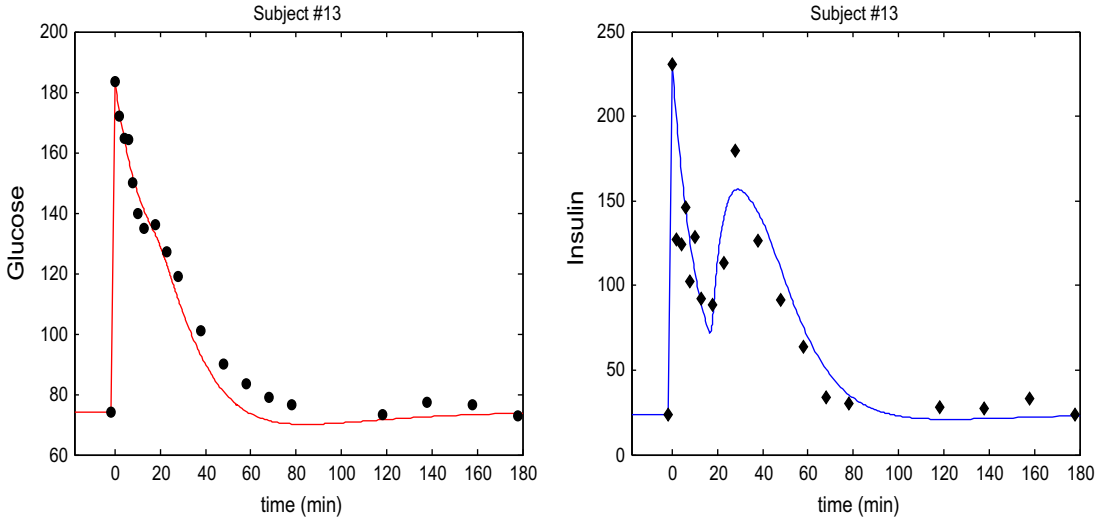

Fig. 4. Profiles of subject 13 in [20] produced by Model (1) with parameters $a = 0.000117609$, $b = 0.862168$, $c = 0.09$, $d = 225.199$, $e = 0.0087969$, $\alpha = 367.165$, $r = 2.9$ and $\tau = 18$. The delay parameter τ is out of the upper bounds computed from Corollaries 1 and 2. The second peak is clearly shown.

the conditions given in these corollaries are sufficient. In applying the corollaries to these sets of parameter values, we found that the parameters for subject 6 and 8 satisfy both Corollaries 1 and 2. From the proposed parameter values, we determined numerically that an upper bound for the delay for subject 6 is 8.35226 min (Fig. 1), and 49.2619 min for subject 8 (Fig. 2). However, parameters of subject 7, 13 and 27 do not satisfy either corollary, although the asymptotic stability of the equilibrium appears obvious by numerical simulation (Figs. 3–5). We noticed in simulations that conditions of the corollaries are not satisfied due to the rough estimate of the upper bound M_G in Lemma 2. We suspect that a better estimate of M_G would improve the scope of applications of Corollaries 1 and 2.

It is worthwhile to stress the role of the parameter value e. In [18,20], the insulin-independent glucose elimination rate parameter e is set to zero. However, from a physiological point of view, insulin-independent glucose elimination rate could be greater than zero [8,22], so that this term should not simply be ignored. More discussions can be found in [19].

6. Discussion

The length of delay in a delay differential equation model often plays a critical role in that large delays can destabilize the system. Appropriately determining the range of the delay based on physiology and clinical data is important in theoretical study. In this paper, we suggest that the value of the delay parameter should be set at approximately the time mark of the first clear trough in insulin data. This would help the clinician to assess immediately, even though roughly, this value in applications. Clearly, a full statistical estimation of model parameters based on an appropriate loss functional and an efficient optimization algorithm would provide asymptotic properties for the values attributed to the delay. Our simulations reveal that the delay may be slightly greater than the time to the first clear trough in the insulin concentration time course (refer to Table 3 for comparisons of the observed troughs and computed delays). However, even accurate statistical identification of the time delay value from experimental data would not always allow to draw definite conclusions on the stability of the system in a given subject.

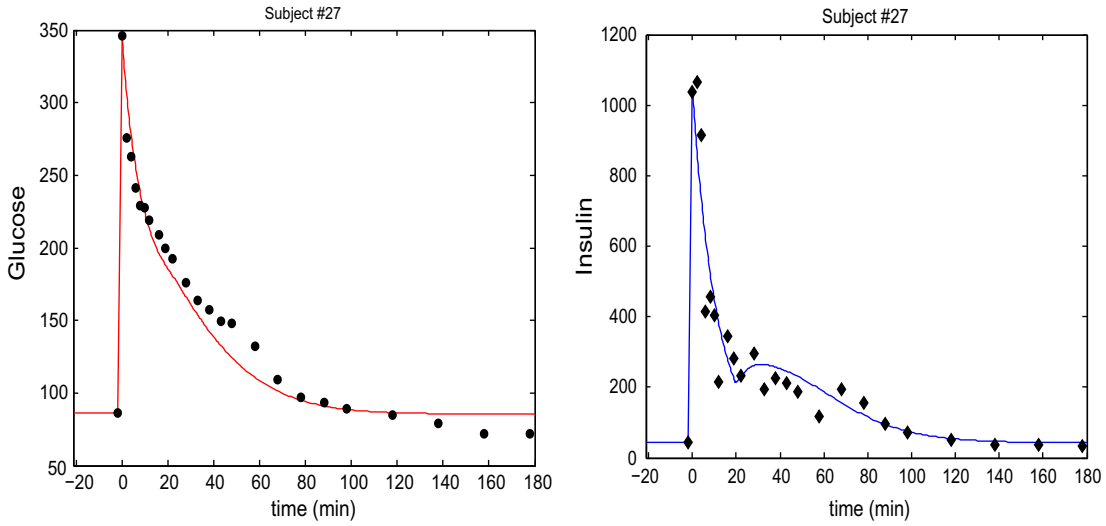

Fig. 5. Profiles of subject 27 in [20] produced by Model (1) with parameters $a = 6.37576 \times 10^{-5}$, $b = 0.246901$, $c = 0.09$, $d = 32.3333$, $e = 5 \times 10^{-5}$, $\alpha = 160$, $r = 3.2$ and setting $\tau = 21.25$. The delay parameter τ is out of the upper bounds computed from Corollaries 1 and 2. The second peak is shown.

Table 3
Comparison of the observed delay lengths according to the first clear troughs and the computed delay lengths. For subjects 6, 7 and 13, the time delays simulated are close to the time marks of the observed first clear troughs. There is no clear trough for the subject 8, while there are two clear troughs for the subject 27. The time delay fitted in simulation for subject 27 is between these two time marksbut near to the second. The upper bounds of delays determined by Corollaries 1 and 2 for subject 6 and 8 are also listed. 'N.A.' for subject 7, 13 and 27 indicates that the conditions of both corollaries are not satisfied.

Subjects	#6	#7	#8	#13	#27
Troughs	8	10	None	18	22
Delays	8.25	10.1688	6.24999	18	21.25
Upper bounds	15.5167	N.A.	49.2619	N.A.	N.A.

Sometimes experimental observations do not allow the investigator to detect a clear first trough in insulinemia for some subjects. For example, there seems no secondary peak or trough for subject 8, but there are seemingly multiple peaks of insulin secretion for subject 27, one at 12′ and one at 22′ according to Table 2. (Also, refer to Table 3.) In addition, the actual secondary insulin secretion peak may not be perceptible for some subjects: for example, the simulation for the subject 8 is near-ideal (Fig. 2) without the second peak of insulin secretion. For subject 27, the data at time mark 12′ seems an outlier. So we obtained a profile with clear second peak for $\tau = 21.25$ (Fig. 5).

In performing numerical studies for delay differential equation systems, in many cases, particularly for short time dynamics like the IVGTT models, using reasonable functional initial conditions is essential. In this paper, we made use of ramp initial conditions on glycemia, which are more plausible than impulsive jumps to the highest concentration value adopted until now. This approach should produce more convincing numerical results in clinical applications.

It is important to find out delay dependent condition of the global stability for Model (1), under which the clinical data satisfy the conditions. According to Theorem 4.3 and its corollaries, adding a term of insulin-independent glucose uptake, although small, helps considerably in ensuring global stability of the equilibrium, even though AIC does not support this addition from a mere statistical viewpoint, and even though the physiological significance of this term is debatable. Indeed, setting $e = 0$ or $e > 0$ small might not affect the remaining parameter point estimates to any substantial degree. Since a small value of insulin-independent glucose tissue uptake cannot be excluded physiologically according to [8,22], we add it to the model in order to exploit the mathematical advantage, which it offers, in satisfying the conditions of both corollaries. It can be seen that for larger e, the estimation of the upper bound M_G of G in Lemma 2 could be smaller, which would help in checking the conditions of the corollaries.

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