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.

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 resulting 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 0, 4, 6, 8, 10, 12, 14, 18, 21, 24, 30, 35, 40, 45, 50, 55, 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 physiologically 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,
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 $\tau$ so that the equilibrium point is globally stable when $\tau < \tau$. 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 $[1-t,0]$.

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 $\tau_0$ 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 glyce-mia 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 $\beta$-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 $\beta$-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 $\beta$-cells, insulin synthesis, movements of insulin in $\beta$-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 forming the first phase of secretion. This release is instantaneous or almost instantaneous since it takes almost no time for the glucose to diffuse in intravenous to transport to pancreas and the insulin in the ready releasable pool. This instantaneous insulin release is followed by the following actions: granules 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 secre-tion. 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 $\tau$ 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) [19]. 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]

\[
\begin{align*}
G'(t) &= b - aG(t)C(t), \\
I'(t) &= dG(t) - cI(t).
\end{align*}
\]

(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 \( \gamma \leq 1 \), 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 Fanunzi 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 \((G_0, I_0)\) and within two consecutive zeros \( t_0 < t < t_0 + 2\tau \). (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
\[
\bar{G} = \limsup_{t \to \infty} G(t), \quad \underline{G} = \liminf_{t \to \infty} G(t)
\]
and
\[
\bar{I} = \limsup_{t \to \infty} I(t), \quad \underline{I} = \liminf_{t \to \infty} I(t).
\]

(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]).
\[
d(G) \leq c I \leq \bar{G} \leq d(I G)
\]
\[
(\epsilon + a) \bar{G} \leq \bar{G} \leq (\epsilon + a) \underline{G}
\]

(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
\[
\frac{\gamma a_b}{1 + \frac{\gamma}{1 + \frac{\gamma}{1}}} \leq \epsilon + a b_b.
\]

(A4) If \( \gamma \leq 1 \), 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 \( (G_0, k_0) \) is locally stable; (ii) when \( \tau > \tau_0 \), the equilibrium is unstable. In other words, Model (1) and Model (3) undergo a Hopf bifurcation at \( \tau = \tau_0 \) when \( \tau \) increases from \( \tau = 0 \) (Theorem 6 in [18]).

(A6) In Model (1), the equilibrium is a global attractor if
\[
\frac{adG}{ce} \sup_{[0, G_0]} \frac{f(G)}{G_0} \sup_{[G_0, \infty)} \frac{f(G)}{G} < 1.
\]

(Theorem 2 in [9].)

(A7) Every fastly oscillated solution of Model (3) converges to the positive equilibrium if
\[
(1 - e^{-2\epsilon \tau}) \frac{adG_0}{ce} \sup_{[0, G_0]} \frac{f(G)}{G_0} \sup_{[G_0, \infty)} \frac{f(G)}{G} < 1,
\]
where \( M \) satisfies \( M f(M) = M f(M) = G f(G_0) \) for \( M < G_0 < M_0 \). (Theorem 3 in [9].)

Notice that the conditions for the globally asymptotically 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 NGTT 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 \( \tau \) 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 \( h(t) \leq p - qh(t) \), or \( h(t) \geq p - qh(t) \), where \( p, q > 0 \), then
\[
h(t) \leq \frac{p}{q} + \left( h(0) - \frac{p}{q} \right) e^{-qt}, \quad \text{or} \quad h(t) \geq \frac{p}{q} + \left( h(0) - \frac{p}{q} \right) e^{qt}
\]
for all \( t \geq 0 \).

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
\[
m_i = \min \left\{ I(0), \frac{k_2}{c} \right\} \leq I(t) \leq M_i = \max \left\{ I(0), \frac{d}{c} \right\}
\]
and
\[
m_c = \min \left\{ G(0), \frac{b}{k_1} \right\} \leq G(t) \leq M_c = \max \left\{ G(0), \frac{b}{k_3} \right\}
\]
where \( k_1 = e + a M, k_2 = d f(M_c) \) and \( k_3 = e + a m \).

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

Remark 1. The bounds given by the Lemma 2 are more accurate than the consequence in A2 by Palumbo et al. [18], which would result in
\[
\frac{bc}{ec + ad} \leq G \leq \frac{bc}{ec + ad} \left( \frac{\gamma}{\gamma^2 + 1} \right)^{\frac{1}{\gamma^2 + 1}}.
\]

by simple computation. However the upper bound \( M_c \) 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 \( M_c \) is dependent of the initial values \( G(0) \) and \( I(0) \) of the solution \( (G(t), I(t)) \).

For the sake of convenience, we denote for \( \gamma > 1 \)
\[
L = \frac{(\gamma + 1)^2}{4\gamma^2} \left( \frac{\gamma - 1}{\gamma + 1} \right)^{\frac{1}{\gamma^2 + 1}},
\]
which is the maximum value of the derivative of \( df(G) \) for \( G > 0 \), and
\[
R = e + a b_b, \quad \text{and} \quad K = a M_c.
\]

By Lemma 2, \( L, R \) and \( K \) are independent of \( \gamma \). When consider Model (3), \( R = a b_b \).

When \( \tau = 0 \), Model (1) and Model (3) become a two-dimensionaldinary differential equation system. It is easy to show that the unique equilibrium \( (G_0, k_0) \) 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 \( (G_0, k_0) \). 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
\[
\tau < \min \left\{ \frac{2 u}{1 + \frac{2 c}{T - 1}}, \frac{2 c}{1 + \frac{2 c}{T - 1}} \right\}
\]
and
\[
\Delta = \frac{M_0^2 - 4 R (u - \frac{T}{2}) (c - \frac{T}{2}) (R + 2 K)}{2} < 0,
\]
where \( M_0 = \max(L, K, u) \), then the equilibrium \( (G_0, k_0) \) of Model (1) is globally and asymptotically stable.

Proof. Let
\[ W(G(t), I(t)) = \frac{1}{2}u(G(t) - G_0)^2 + \frac{1}{2}(I(t) - I_0)^2, \quad (11) \]
\[ U(G(t), I(t)) = C \int_{t-\tau}^{t} \int_{t-\tau}^{t} (G(s) - G_0)^2 \, ds \, dz + D \int_{t-\tau}^{t} (I(s) - I_0)^2 \, ds \, dz. \quad (12) \]

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
\[
df(G(t - \tau)) - f(G_0)) = df'(\xi)(G(t - \tau) - G_0)
\]
where \( \xi \) is between \( G(t - \tau) \) and \( G(t) \). Also, since \( u, v \geq \frac{1}{2}(2\alpha^2 + \tau^2) \) for all \( u, v \geq 0 \), we have
\[
||G(t) - I_0|| = \int_{t-\tau}^{t} G(s) \, ds \\
= \int_{t-\tau}^{t} (b - \alpha G(s) - \alpha G(s)) \, ds \\
\leq \int_{t-\tau}^{t} (\alpha b + \alpha(\alpha G(s) - G_0)) \, ds \\
= \frac{1}{2} \left( R \int_{t-\tau}^{t} (G(s) - G_0)^2 \, ds + K \int_{t-\tau}^{t} (I(s) - I_0)^2 \, ds + \tau(R + K)(I(t) - I_0)^2 \right). \]

Then
\[
\frac{d^2 W}{dt^2} = \frac{d}{dt} (\frac{dW}{dt}) = \frac{d}{dt} \left( \frac{1}{2}u(G(t) - G_0)^2 + \frac{1}{2}(I(t) - I_0)^2 \right) \\
+ (I(t) - I_0) \frac{d}{dt} \left( f(G(t) - \tau) - f(G_0) \right) - c(t) (I(t) - I_0) \\
\leq \frac{1}{2} \left( 2R \int_{t-\tau}^{t} (G(s) - G_0)^2 \, ds + K \int_{t-\tau}^{t} (I(s) - I_0)^2 \, ds + \tau(R + K)(I(t) - I_0)^2 \right). \]

Furthermore,
\[
\frac{dU}{dt} = -C \int_{t-\tau}^{t} (G(s) - G_0)^2 \, ds + C \tau(I(t) - I_0)^2 \\
+ D \int_{t-\tau}^{t} (I(s) - I_0)^2 \, ds + D \tau(I(t) - I_0)^2. \]

So, along the solution \((G(t), I(t))\) of Model (1), we have
\[
\frac{dV}{dt} \leq -uR(G - G_0)^2 + |df'(\xi)| - u\alpha G||G - G_0|| - I_0| \\
- \left( c - \frac{\tau}{2} \right) (I(t) - I_0)^2 + C \int_{t-\tau}^{t} (G(s) - G_0)^2 \, ds \\
+ D \int_{t-\tau}^{t} (I(s) - I_0)^2 \, ds - C \int_{t-\tau}^{t} (G(s) - G_0)^2 \, ds + C \tau(I(t) - I_0)^2 \\
- D \int_{t-\tau}^{t} (I(s) - I_0)^2 \, ds + D \tau(I(t) - I_0)^2. \]

Remark 2. Since \( M_0 \) 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 \( \tau \), which ensures the equilibrium is globally stable. Denote

\[ p_1 = \frac{cK + L(R + 2K)}{3LRL(K + 2)}, \quad q_1 = \frac{4Rc - KL}{3LRL(K + 2K)}, \]

and

\[ \hat{\tau} = \min \left\{ \frac{2}{K}, \frac{2c}{LRL(K + 2K)} \right\}. \]

Then we have

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

(i) \( \tau < \hat{\tau} \), if \( p_1^2 - q_1 < 0 \); \quad (13)

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

(iii) \( \tau \in \left[ p_1 + \sqrt{p_1^2 - q_1}, \hat{\tau} \right] \), if \( p_1^2 - q_1 > 0 \), \( p_1 + \sqrt{p_1^2 - q_1} < \hat{\tau} \); \quad (15)

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

**Proof.** Notice that \( M_0 = \max[L, R] \) in Theorem 3. Let \( u = \frac{R}{L} \), then \( M_0 = L \). Therefore (9) becomes \( \tau < \hat{\tau} \), and (10) holds if and only if
$$M_u^2 - 4R \left( u - \frac{\tau}{2} L \right) \left( c - \frac{\tau}{2} L(R + 2K) \right) = L^2 - 4R \left( L \frac{1}{R} - \frac{\tau}{2} L \right) \left( c - \frac{\tau}{2} L(R + 2K) \right) = L \left[ L - 4R \left( \frac{c}{R} \frac{1}{2} - \frac{\tau}{2} \right) \left( L(R + 2K) \right) + \frac{\tau^2}{4} L(R + 2K) \right] = L \left[ L - 4R \left( \frac{c}{R} \frac{1}{2} + 2\tau R \left( \frac{c}{R} + L(R + 2K) \right) - \frac{\tau^2}{2} \frac{L(R + 2K)}{R} \right) \right] = -L^2 R(2K) \left[ \frac{-L + \frac{4R}{8} \frac{L}{R} R(L + 2K)}{2} R(L + 2K) \right] \frac{2Rc - RL}{L(R + 2K)} \right] \frac{4Rc - RL}{KL(R + 2K)} - \frac{2(cK + L(R + 2K))}{KL(R + 2K)} \tau + \frac{\tau^2}{2} \right] = -L^2 R(2K) \left( q_i - 2p, \tau + \frac{\tau^2}{2} < 0. \right.$$ Then it is straightforward to obtain the conclusion. □

Denote

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

If $\tau < 0$, then

$$2RH - K^2 \tau = 2RH - K^2 L \tau = 2RK \left( c - \frac{\tau}{2} L(R + 2K) \right) - K^2 L \tau = 2RK - \left( RL(R + 2K) + K^2 \right) \tau \quad \text{and} \quad 2RH - L(R + 2K) - K^2 \tau = 2RK - L(R + 2K) + K^2 \tau = 2RK - L(R + 2K) + K^2 \tau = 2RK - L(R + 2K) + K^2 \tau > 0.$$ Hence, we can define

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

Therefore, we have

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

$$\tau < \min \left\{ \frac{2u_0}{L}, \tau \right\} \quad \text{and} \quad u_0 > \frac{L}{R}.$$

**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

$$K^2 u^2 - 4R \left( u - \frac{\tau}{2} L \right) H = K^2 u^2 - 4RHu + 2RH \tau < 0.$$ So the existence of such $u > 0$ is equivalent to

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

and the larger root $u_0$ of $P(u) = K^2 u^2 - 4RHu + 2RH \tau = 0$ is greater than $L/K$. Notice (17). We choose any $u \in (u_0, K/u_0)$ 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 $\tau$, one can estimate an upper bound of $\tau$ 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 the 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 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.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Blood Glucose (mg/dl)</th>
<th>Insulin (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>87.7358</td>
<td>67.9245</td>
</tr>
<tr>
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<td>124.4519</td>
<td>103.8312</td>
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<td>2</td>
<td>161.0006</td>
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</tr>
<tr>
<td>3</td>
<td>198.0000</td>
<td>157.5000</td>
</tr>
<tr>
<td>4</td>
<td>235.0000</td>
<td>184.0000</td>
</tr>
</tbody>
</table>

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 27. 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.

<table>
<thead>
<tr>
<th>Time (min)</th>
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<th>Insulin (mU/L)</th>
</tr>
</thead>
<tbody>
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<tr>
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<tr>
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</tr>
<tr>
<td>7</td>
<td>255.00</td>
<td>265.0000</td>
</tr>
</tbody>
</table>

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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 [−τ, 0]. Therefore we use a piece-wise linear function

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

while \(\ell(0) = l_0\), where \(\delta\) (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 \(G_0\) and \(l_0\) are taken from the first row at time mark −δ minute in the data tables and \(G_0\) and \(l_0\) are taken from the second row at time mark 0 from the data tables. Assume that \(\phi(t)\) is linearly increasing from \(G_0\) to \(G_b\) in \([-\tau, -\delta]\) 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 \(G_0\) to \(G_b\) 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,
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 $M_c$ in Lemma 2. We suspect that a better estimate of $M_c$ 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 physiological 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.
Since a minor 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 $M_2$ of $G$ in Lemma 2 could be smaller, which would help in checking the conditions of the corollaries.

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**References**


