

ANALYSIS OF IVGTT GLUCOSE-INSULIN INTERACTION MODELS WITH TIME DELAY

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ABSTRACT. In the last three decades, several models on the interaction of glucose and insulin following the intra venous glucose tolerance test (IVGTT) have appeared in the literature. One of the mostly used one is generally known as the “minimal model” which was first published in 1979 and modified in 1986. Recently, this minimal model has been challenged by De Gaetano and Arino [4] from both physiological and modeling aspects. Instead, they proposed a new and mathematically more reasonable model, called “dynamic model”. Their model makes use of certain simple and specific functions and introduces time delay in a particular way. The outcome is that the model always admits a globally asymptotically stable steady state. The objective of this paper is to find out if and how this outcome depends on the specific choice of functions and the way delay is incorporated. To this end, we generalize the dynamical model to allow more general functions and an alternative way of incorporating time delay. Our findings show that in theory, such models can possess unstable positive steady states. However, for all conceivable realistic data, such unstable steady states do not exist. Hence, our work indicates that the dynamic model does provide qualitatively robust dynamics for the purpose of clinic application. We also perform simulations based on data from a clinic study and point out some plausible but important implications.

1. Introduction. The dynamic relationship between glucose and its controlling hormone insulin has been mathematically modeled and studied by many researchers since the sixties ([2], [10], [12], [14], [17], [20], [7], and the references cited in [6]). Most of these models consist of several ordinary differential equations, the number of equations is often proportional to that of factors considered. Some of these equations are simply linear and were judged unacceptable for various reasons [1], such as parameters are not identifiable or have poor fits to experimental data.

Due to the increased occurrence of pathological conditions such as diabetes, obesity, and cardiovascular diseases, the quantification of insulin sensitivity from some relatively non-invasive tests has gained increased interest and importance in physiological research. This lead to some new studies on the existing models and

1991 *Mathematics Subject Classification.* 34K20, 92C50, 92D25.

Key words and phrases. Glucose, insulin, minimum model, delay differential equations, qualitative analysis.

the introduction of some alternative ones. Currently, the most widely used model in physiological research on the metabolism of glucose is the so-called “minimal model”, which describes intra venous glucose tolerance test (IVGTT) experimental data well with the smallest set of identifiable and meaningful parameters ([1], [13]). After incorporating the insulin dynamics, it takes the form of [4])

$$\begin{cases} \frac{dG(t)}{dt} = G' = -[b_1 + X(t)]G(t) + b_1G_b, \\ \frac{dX(t)}{dt} = X' = -b_2X(t) + b_3[I(t) - I_b], \\ \frac{dI(t)}{dt} = I' = b_4[G(t) - b_5]^+ - b_6[I(t) - I_b]. \end{cases} \quad (1.1)$$

The initial conditions are:

$$G(0) = b_0, \quad X(0) = 0, \quad I(0) = b_7 + I_b.$$

Here $G(t)$ [mg/dl], $I(t)$ [μ UI/ml] is the plasma glucose, insulin concentration at time t [min], respectively. $X(t)$ [min^{-1}] is an auxiliary function representing insulin-excitabile tissue glucose uptake activity, roughly proportional to insulin concentration in a “distant” compartment. G_b [mg/dl], I_b [μ UI/ml] is the subject’s baseline glycemia, insulinemia, respectively. b_0 [mg/dl] is the theoretical glycemia at time 0 after the instantaneous glucose bolus intake. b_1 [min^{-1}] is the insulin-independent constant of tissue glucose uptake rate. b_2 [min^{-1}] is the rate constant describing the spontaneous decrease of tissue glucose uptake ability. b_3 [$\text{min}^{-2}(\mu\text{UI/ml})^{-1}$] is the insulin-dependent increase in tissue glucose uptake ability, per unit of insulin concentration excess over the baseline. b_4 [$(\mu\text{UI/ml})(\text{mg/dl})^{-1}\text{min}^{-1}$] is the rate of pancreatic release of insulin after the intake of the glucose bolus, per minute per unit of glucose concentration above the “target” glycemia b_5 [mg/dl]. b_6 [$\mu\text{UI/ml}$] is the first order decay rate for insulin in plasma. b_7 [$\mu\text{UI/ml}$] is the plasma insulin concentration at time 0, above basal insulinemia, immediately after the glucose bolus intake.

While the above minimal model has minimal number of constant ($b_0 - b_7$), and has been very useful in physiological research works, [4] argues that it has the following three drawbacks associated with it. For this model, the parameter fitting is to be divided into two separate parts: first, using the recorded insulin concentration as given input data in order to derive the parameters in the first two equations in the model, then using the recorded glucose concentration as given input to derive the parameters in the third equation. However, the system is an integrated physiological dynamic system and one should treat it as a whole and be able to conduct a single-step parameter fitting process. Secondly, some of the mathematical results produced by this model are not realistic. Specifically, it can be shown that the minimal model does not admit an equilibrium and the solutions may not be bounded. Finally, the non-observable auxiliary variable $X(t)$ is artificially introduced to delay the action of insulin on glucose. An alternative and natural way is to explicitly introduce the time delay in the model. To address these issues, De Gaetano and Arino [4] introduced the following aggregated delay differential model which they named it as “dynamic model.” It takes the form of

$$\begin{cases} \frac{dG(t)}{dt} = G' = -b_1G(t) - b_4I(t)G(t) + b_7, \\ \frac{dI(t)}{dt} = I' = -b_2I(t) + \frac{b_6}{b_5} \int_{t-b_5}^t G(s)ds. \end{cases} \quad (1.2)$$

The initial condition now takes the form of

$$G(0) = G_b + b_0, I(0) = I_b + b_3b_0, \quad \text{and for } t \in [-b_5, 0), G(t) = G_b.$$

As in the minimal model, $G(t)$ [mg/dl], $I(t)$ [μ UI/ml] is the plasma glucose, insulin concentration at time t [min], respectively. The G_b, I_b, b_0, b_1, b_2 and b_3 are the same as or similar to that in the minimal model with same units. b_4 [$\text{min}^{-1}\text{pM}^{-1}$] is the constant measuring the insulin-dependent glucose disappearance rate per unit [pM] of plasma insulin concentration. b_5 [min] is the number of minutes of the past period whose plasma glucose concentrations influence the current pancreatic insulin secretion. b_6 [$\text{min}^{-1}\text{pM}/(\text{mg}/\text{dl})$] is the constant describing the second-phase pancreatic insulin secretion rate per unit of average plasma glucose concentration throughout the previous b_5 minutes. b_7 [$(\text{mg}/\text{dl})\text{min}^{-1}$] is the constant increase in plasma glucose concentration due to constant baseline liver glucose release.

While the dynamic model solves the problems of minimal model, it implicitly or explicitly made a few assumptions that may not be necessary or realistic. Specifically some of the interaction terms are too special and thus too restrictive. For example, the term $b_4I(t)G(t)$ assumes mass action law applies here. A more popular, general and realistic alternative is to replace this term by $b_4I(t)G(t)/(\alpha G(t)+1)$. Since in a unit of time, a unit of insulin can only process a limited amount of glucose. Also the way the delay is introduced is somewhat restrictive, the justification of which consists of only one subjective assumption “the delay term refers to the pancreatic secretion of insulin: effective pancreatic secretion at time t is *considered* to be proportional to the average value of glucose concentration in the b_5 minutes preceding time t ”. This naturally invites other plausible ways of incorporating the time delay. The most noteworthy outcome of the dynamical model is that it always admits a globally asymptotically stable steady state. The objective of this paper is to find out if and how this outcome depends on the specific choice of functions and the way delay is incorporated. To this end, we generalize the dynamical model to allow more general functions and an alternative way of incorporating time delay. Our findings show that in theory, such models can possess unstable positive steady states and produce oscillatory solutions. However, for all the clinic data reported in [4], such unstable steady states do not exist. Hence, our work indicates that the dynamic model does provide qualitatively robust dynamics for the purpose of clinic application. We also perform simulations based on data from a clinic study reported in [4] and point out some plausible but important implications.

We would like to point out that oscillation in human insulin secretion have been observed in two distinct period ranges, 10-15 min (i.e., rapid) and 80-150 min (i.e., ultradian) ([16], [15]). Often, the rapid oscillation is superimposed on the slow (ultradian) oscillation. To determine whether the ultradian oscillations could result from the interaction between insulin and glucose, a parsimonious nonlinear mathematical model consisting six ordinary differential equations including the major mechanisms involved in glucose regulation was developed by Sturis et al. [17] and

recently simplified by Tolic et al. [20] (which also contains more sophisticated receptor down-regulation model and receptor-modification model). More recently, this model was modified by incorporating delayed hepatic glucose production explicitly and systematically studied by Engelborghs et al. [7] via numerical bifurcation analysis. This model comprises two major negative feedback loops describing the effects of insulin on glucose utilization and glucose production, respectively, and both loops include the stimulatory effect of glucose on insulin secretion. The occurrence of sustained insulin and glucose oscillations was found numerically to be dependent on two essential features: 1) a time delay of 30-45 min for the effect of insulin on glucose production and 2) a sluggish effect of insulin on glucose utilization. Clearly, both “minimal model” and “dynamical model” do not account for the delayed (by about 30-45 minutes) influence of insulin on the hepatic glucose production ([17]) and are not constructed for the understanding of insulin oscillation. Their main purpose is to model the intra venous glucose tolerance test conducted for the study of metabolism of glucose.

The paper is organized as follows. We present our general model and two other less general ones (still more general than the dynamic model), and their basic properties in the next section. Section 3 contains some general global stability results. Section 4 present a formal derivation of linearization and characteristic equations. Section 5 provides some delay independent local stability results and section 6 gives delay dependent stability conditions. Guided by the results of section 6, we performed extensive computer simulation (using clinic data) and succeeded in finding periodic solutions in our discrete delay model. Some of these simulation findings are reported in the last section, which also contains a brief discussion on the implications of our results.

2. Model and Preliminaries. We propose the following general and more realistic model for the interaction of glucose and insulin. This model includes the “dynamic model” (1.2) as a special case:

$$\begin{cases} \frac{dG(t)}{dt} = G'(t) = -f(G(t)) - g(G(t), I(t)) + b_7, \\ \frac{dI(t)}{dt} = I'(t) = -p(I(t)) + q(L(G_t)). \end{cases} \quad (2.1)$$

The initial condition is

$$G(0) = G_b + b_0, \quad I(0) = I_b + b_3 b_0, \quad \text{and} \quad G(t) \equiv G_b, \quad \text{for} \quad t \in [-b_5, 0),$$

where $G_t(\theta) = G(t + \theta)$, $t > 0$, $\theta \in [-b_5, 0]$. G_b [mg/dl], I_b [μ UI/ml] is the subject's baseline glycemia, insulinemia, respectively. Here $L(\phi) = \int_{-b_5}^0 \phi(s) d(\mu(s))$, and $\mu(s)$ is nondecreasing with $\int_{-b_5}^0 d(\mu(s)) = 1$. We will consider two cases for $L(G_t)$: the discrete and distributed cases. For discrete delay, $L(G_t) = G(t - b_5)$ and for distributed delay, $L(G_t) = \frac{1}{b_5} \int_{-b_5}^0 G(t + \theta) d\theta$. The parameters b_0, b_3, b_5 and b_7 are the same as in model (1.2). Functions f, g, p, q satisfy the following general conditions.

- (i) $f(0) = 0, f(\infty) = \infty, f'(x) > 0$
- (ii) $g(0, 0) = 0, g_x(x, y) > 0, g_y(x, y) > 0$
 $g(x, 0) = 0, g(0, y) = 0, g(\infty, y) < \infty$, and $g(x, \infty) = \infty$ when $x \neq 0$
- (iii) $p(0) = 0, p(\infty) = \infty, p'(x) > 0$

(iv) $q(x) = 0$, if and only if $x = 0$; $q(L(G_t + \varphi_t)) > q(L(G_t))$ for $\varphi_t \in C[-b_5, 0]$ with $\varphi_t(\theta) > 0$, $\theta \in [-b_5, 0]$. We always assume that the model (2.1) has a unique equilibrium point (G^*, I^*) in $\mathbf{R}_+^2 = \{(x, y) : x > 0, y > 0\}$.

For the convenience of analysis and applications, we propose the following specific model of glucose-insulin interaction.

$$\begin{cases} \frac{dG(t)}{dt} = G'(t) = -b_1G(t) - \frac{b_4I(t)G(t)}{\alpha G(t) + 1} + b_7 \\ \frac{dI(t)}{dt} = I'(t) = -b_2I(t) + b_6G(t - b_5) \end{cases} \quad (2.2)$$

with the same initial conditions of (2.1). The parameters have the same meaning as those in “dynamic model” (1.2).

Comparing with the “dynamic model” (1.2), model (2.2) has two notable and important differences: First, no mass action law is assumed for glucose concentration change due to the insulin-dependent net glucose tissue uptake. We assume instead that insulin-dependent net glucose tissue uptake takes the more general and realistic Michaelis-Menten form $G(t)/(\alpha G(t) + 1)$ which has a maximum capacity b_4/α . The parameter α in the response function $G(t)/(\alpha G(t) + 1)$ is non-negative. $1/\alpha$ is the half-saturation constant. The reason for this is simply due to the limit of time and the capacity of insulin’s ability of digesting glucose. Second, we assume that the effective pancreatic secretion (after the liver first-pass effect) at time t is affected by the value of glucose concentration in the b_5 minutes preceding time t instead of the average amount in that period.

When

$$L(G_t) = \frac{1}{b_5} \int_{-b_5}^0 G(t + \theta) d\theta,$$

and the Michaelis-Menten kinetics is assumed, the model (2.1) becomes

$$\begin{cases} G'(t) = -b_1G(t) - \frac{b_4I(t)G(t)}{\alpha G(t) + 1} + b_7 \\ I'(t) = -b_2I(t) + \frac{b_6}{b_5} \int_{-b_5}^0 G(t + \theta) d\theta \end{cases} \quad (2.3)$$

Clearly, both models (2.2) and (2.3) have a unique equilibrium point (G^*, I^*) in $\mathbf{R}_+^2 = \{(x, y) : x \geq 0, y \geq 0\}$, where

$$G^* = 2b_7 / \left((b_1 - \alpha b_7) + \sqrt{(b_1 - \alpha b_7)^2 + 4b_7 \left(\alpha b_1 + \frac{b_4 b_6}{b_2} \right)} \right) \quad \text{and} \quad I^* = \frac{b_6}{b_2} G^*.$$

Obviously, model (2.2)((2.3)) is a special case of model (2.1), where $f(x) = b_1x$, $g(x, y) = b_4xy/(\alpha x + 1)$, $p(x) = b_2x$ and $q(L(x_t)) = b_6x(t - b_5)$ ($q(L(x_t)) = (b_6/b_5) \int_{t-b_5}^{b_6} x(t - s) ds$). For $q(L(x_t)) = (b_6/b_5) \int_{t-b_5}^t x(s) ds$ and $\alpha = 0$, model (2.1) reduces to the dynamic model (1.2). For convenience, we define two new parameters a_1, γ for models (2.2) and (2.3):

$$a_1 = b_1/b_7, \quad \text{and} \quad \gamma = (b_4 b_6)/(b_1 b_2).$$

The following basic proposition is important for our study. Its proof is straightforward.

Proposition 2.1. *All solutions of model (2.1) exist for all $t > 0$, and are positive and bounded.*

Proof Let $(G(t), I(t))$ be a solution of (2.1). If $G(t_0) = 0$ for some $t_0 > 0$, then $G'(t_0) \leq 0$. However, at t_0 , due to the assumptions that $f(0) = g(0, y) = 0$, we have $G'(t_0) = -f(G(t_0)) - g(G(t_0), I(t_0)) + b_7 = b_7 > 0$. This contradiction shows that $G(t) > 0$ for all t in the interval of existence. If $I(\bar{t}_0) = 0$ for some $\bar{t}_0 > 0$, then $I'(\bar{t}_0) \leq 0$ and $0 \geq I'(\bar{t}_0) = -p(I(\bar{t}_0)) + q(L(G_{\bar{t}_0})) = q(L(G_{\bar{t}_0}))$. Since $G_{\bar{t}_0}(\theta) > 0$ for $\theta \in [-b_5, 0]$, $q(L(G_{\bar{t}_0})) > 0$ by (iv) and thus $I(t) > 0$ for all t in the interval of existence.

As for the boundedness of $G(t)$, by the first equation of (2.1),

$$G'(t) = -f(G(t)) - g(G(t), I(t)) + b_7 \leq -f(G(t)) + b_7.$$

Thus $G(t)$ is bounded by $M_G = \max\{G_b + b_0, f^{-1}(b_7)\}$. And hence $I(t)$ is bounded by $M_I = \max\{I_b + b_3b_0, p^{-1}(q(M_G))\}$ due to

$$I'(t) = -p(I(t)) + q(G_t) \leq -p(I(t)) + q(M_G).$$

The boundedness statement implies that solutions exist for all $t > 0$. This completes the proof. \square

Let $(G(t), I(t))$ be a solution of (2.1). Throughout this paper, we define

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

Due to the Proposition 2.1, we see that these limits are finite.

The following fluctuation lemma is elementary. We state it below without proof.

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

The following lemma is useful for establishing the fact that model (2.1) is always uniformly persistent, which implies that both components of solutions of the model are eventually bounded by positive constants from both above and below. Such bounds are independent of initial data.

Lemma 2.1. *Consider model (2.1). If $\underline{I} < \overline{I}$, then*

$$p^{-1}(q(\underline{G})) \leq \underline{I} < \overline{I} \leq p^{-1}(q(\overline{G})).$$

If $\underline{G} < \overline{G}$, then

$$-f(\underline{G}) - g(\underline{G}, \overline{I}) + b_7 \leq 0, \quad \text{and} \quad -f(\overline{G}) - g(\overline{G}, \underline{I}) + b_7 \geq 0. \quad (2.4)$$

Proof Since $\underline{I} < \overline{I}$, by Lemma A, there exists $\{t_k\} \uparrow \infty$, $\{s_k\} \uparrow \infty$, such that $I'(t_k) = I'(s_k) = 0$, $\lim_{k \rightarrow \infty} I(t_k) = \overline{I}$ and $\lim_{k \rightarrow \infty} I(s_k) = \underline{I}$. Notice that p, q are continuous, $q'(\cdot) > 0$ and $(G(t), I(t))$ is a solution of (2.1). Hence, we have

$$0 = I'(t_k) = -p(I(t_k)) + q(L(G_{t_k})) \quad \text{for all } k.$$

For any $\varepsilon > 0$, there exists $k_0 > 0$, such that

$$\overline{G} + \varepsilon > G_{t_k}(\theta), \quad \theta \in [-\tau, 0] \quad \text{for all } k > k_0.$$

Hence condition (iv) implies that $q(L(G_{t_k})) \leq q(\overline{G} + \varepsilon)$ for $k > k_0$. Therefore,

$$0 = -p(I(t_k)) + q(L(G_{t_k})) \leq -p(I(t_k)) + q(\overline{G} + \varepsilon).$$

By letting $k \rightarrow \infty$ and $\varepsilon \rightarrow 0$, we have

$$p(\overline{I}) \leq q(\overline{G}). \quad (2.5)$$

Similarly, we have Therefore

$$p(\underline{I}) \geq q(\underline{G}). \quad (2.6)$$

(2.5) and (2.6) lead to

$$q(\underline{G}) \leq p(\underline{I}) < p(\bar{I}) \leq q(\bar{G})$$

and then

$$p^{-1}(q(\underline{G})) \leq \underline{I} < \bar{I} \leq p^{-1}(q(\bar{G})).$$

If $\underline{G} < \bar{G}$, by Lemma A there exists $\{t'_k\} \uparrow \infty$, $\{s'_k\} \uparrow \infty$, such that $G'(t'_k) = G'(s'_k) = 0$, $\lim_{k \rightarrow \infty} G(t'_k) = \bar{G}$ and $\lim_{k \rightarrow \infty} G(s'_k) = \underline{G}$. Thus we have

$$0 = G'(t'_k) = -f(G(t'_k)) - g(G(t'_k), I(t'_k)) + b_7$$

and

$$0 = G'(s'_k) = -f(G(s'_k)) - g(G(s'_k), I(s'_k)) + b_7$$

for all k .

Since f, g are continuous and $g_2(x, y) > 0$ for all $x > 0$, without loss of generality, assuming $\lim_{k \rightarrow \infty} I(t'_k)$ and $\lim_{k \rightarrow \infty} I(s'_k)$ exist, we have

$$\begin{aligned} 0 &= \lim_{k \rightarrow \infty} (-f(G(t'_k)) - g(G(t'_k), I(t'_k))) + b_7 \\ &= -f(\bar{G}) - g(\bar{G}, \lim_{k \rightarrow \infty} I(t'_k)) + b_7 \\ &\leq -f(\bar{G}) - g(\bar{G}, \underline{I}) + b_7 \end{aligned}$$

and

$$\begin{aligned} 0 &= \lim_{t \rightarrow \infty} (-f(G(s'_k)) - g(G(s'_k), I(s'_k))) + b_7 \\ &= -f(\underline{G}) - g(\underline{G}, \lim_{k \rightarrow \infty} I(s'_k)) + b_7 \\ &\geq -f(\underline{G}) - g(\underline{G}, \bar{I}) + b_7. \end{aligned}$$

This completes the proof. \square

Proposition 2.2. *The model (2.1) is uniformly persistent. That is, solutions are eventually uniformly bounded by positive constants from both above and below.*

Proof For a solution $(G(t), I(t))$ of (2.1), by Proposition 2.1,

$$\begin{aligned} G'(t) &= -f(G(t)) - g(G(t), I(t)) + b_7 \\ &\leq -f(G(t)) + b_7. \end{aligned}$$

Using Lemma A, we can obtain that $\bar{G} \leq f^{-1}(b_7)$, where $\bar{G} \triangleq \limsup_{t \rightarrow \infty} G(t)$.

Notice that (2.4) implies

$$f(\underline{G}) + g(\underline{G}, p^{-1}(q(f^{-1}(b_7)))) \geq f(\underline{G}) + g(\underline{G}, p^{-1}(q(\bar{G}))) \geq b_7,$$

which shows that $\underline{G} > 0$. This together with Lemma (2.1) shows that the model (2.1) is uniformly persistent. \square

3. Some Global Stability Results. In this section, we provide several global stability results for the steady state (G^*, I^*) . Most of them are derived by applying fluctuation lemma type arguments and the mean value theorem. The same method was used by [4] to establish the global stability of the positive steady state. As we shall see, for the general model (2.1), global asymptotically stability of (G^*, I^*) is conditional.

Using mainly fluctuation type argument and Lemma 2.1, we can obtain

Theorem 3.1. *For model (2.1), if*

$$g(x, p^{-1}(q(y))) - g(y, p^{-1}(q(x))) \geq 0, \quad (3.1)$$

for all $x \geq y > 0$, then the unique equilibrium point (G^*, I^*) of (2.1) is globally asymptotically stable.

Proof If $\underline{I} < \bar{I}$, then from Lemma 2.1,

$$p^{-1}(q(\underline{G})) \leq \underline{I} < \bar{I} \leq p^{-1}(q(\bar{G})).$$

Thus $\underline{G} < \bar{G}$ and

$$\begin{aligned} -f(\underline{G}) - g(\underline{G}, p^{-1}(q(\bar{G}))) + b_7 &\leq -f(\underline{G}) - g(\underline{G}, \bar{I}) + b_7 \leq 0, \\ -f(\bar{G}) - g(\bar{G}, p^{-1}(q(\underline{G}))) + b_7 &\geq -f(\bar{G}) - g(\bar{G}, \underline{I}) + b_7 \geq 0. \end{aligned}$$

Therefore

$$(f(\bar{G}) - f(\underline{G})) + (g(\bar{G}, p^{-1}(q(\underline{G}))) - g(\underline{G}, p^{-1}(q(\bar{G})))) \leq 0.$$

Due to (3.1), we have

$$g(\bar{G}, p^{-1}(q(\underline{G}))) - g(\underline{G}, p^{-1}(q(\bar{G}))) \geq 0.$$

Hence

$$f(\bar{G}) - f(\underline{G}) \leq 0,$$

which indicates $\bar{G} = \underline{G}$ and thus $\bar{I} = \underline{I}$. Since (G^*, I^*) is the only equilibrium point of (2.1), we have

$$\lim_{t \rightarrow \infty} G(t) = G^* \quad \text{and} \quad \lim_{t \rightarrow \infty} I(t) = I^*.$$

The proof is completed. \square

Theorem 3.2. *For model (2.1), if*

$$f'(x) + g_x(x, p^{-1}(q(y))) - g_y(x, p^{-1}(q(y))) \frac{q'(y)}{p'(p^{-1}(q(y)))} > 0 \quad (3.2)$$

for all $x, y > 0$, then the unique equilibrium point (G^*, I^*) of (2.1) is globally asymptotically stable.

Proof If $\underline{I} < \bar{I}$, then from Lemma 2.1,

$$p^{-1}(q(\underline{G})) \leq \underline{I} < \bar{I} \leq p^{-1}(q(\bar{G}))$$

we see that $\underline{G} < \bar{G}$, and

$$(f(\bar{G}) - f(\underline{G})) + (g(\bar{G}, p^{-1}(q(\underline{G}))) - g(\underline{G}, p^{-1}(q(\bar{G})))) \leq 0. \quad (3.3)$$

Let

$$F(x, y) = f(x) + g(x, p^{-1}(q(y))), \quad (x, y) \in \mathbf{R}_+^2 = \{(x, y) : x > 0, y > 0\}.$$

Then (3.3) is equivalent to

$$F(\overline{G}, \underline{G}) - F(\underline{G}, \overline{G}) \leq 0. \quad (3.4)$$

By the mean value theorem, there exists a $\theta \in (0, 1)$ such that

$$F(\overline{G}, \underline{G}) - F(\underline{G}, \overline{G}) = (\overline{G} - \underline{G})(F_x(\xi, \eta) - F_y(\xi, \eta)) \quad (3.5)$$

where $\xi \triangleq \underline{G} + \theta(\overline{G} - \underline{G})$ and $\eta \triangleq \overline{G} - \theta(\overline{G} - \underline{G})$. Notice that

$$F_x(x, y) = f'(x) + g_x(x, p^{-1}(q(y)))$$

and

$$F_y(x, y) = g_y(x, p^{-1}(q(y))) \frac{q'(y)}{p'(p^{-1}(q(y)))}.$$

From (3.2)

$$\begin{aligned} F_x(\xi, \eta) - F_y(\xi, \eta) &= f'(\xi) + g_x(\xi, p^{-1}(q(\eta))) \\ &\quad - g_y(\xi, p^{-1}(q(\eta))) \frac{q'(\eta)}{p'(p^{-1}(q(\eta)))} > 0. \end{aligned} \quad (3.6)$$

On the other hand, (3.4) and (3.5) lead to

$$(\overline{G} - \underline{G})(F_x(\xi, \eta) - F_y(\xi, \eta)) \leq 0.$$

Clearly, (3.6) leads to $\overline{G} - \underline{G} \leq 0$ and thus $\overline{G} = \underline{G}$ and $\overline{I} = \underline{I}$. Since (G^*, I^*) is the only equilibrium point of (2.1), we have

$$(G(t), I(t)) \rightarrow (G^*, I^*) \quad \text{as } t \rightarrow \infty.$$

This completes the proof. \square

In model (2.1), if $g(x, y)$ takes the special form

$$g(x, y) = g_1(x, y)/g_2(x)$$

where

- (v) $g_1(0, 0) = 0$, $g_1(x, 0) = g_1(0, y) = 0$ for all $(x, y) > 0$,
- (vi) $g_2(x) \geq c > 0$ for some constant c . $g_2(\infty) = \infty$.
- (vii) $(g_1)_x(x, y) > 0$, $(g_1)_y(x, y) > 0$, for all $x, y > 0$.
- (viii) $g_1(x, \infty) = g_1(\infty, y) = \infty$ for $x, y > 0$, $xy \neq 0$.
- (ix) $g'_2(x) > 0$ for all $x > 0$,

then we have

Theorem 3.3. *For model (2.1), $g(x, y) = g_1(x, y)/g_2(x)$, where g_1, g_2 satisfy (v)–(ix). Then (G^*, I^*) is globally asymptotically stable if*

- (a) $(f(x) - b_7)g_2(x)$ is increasing for all $x > 0$
- (b) $g_1(x, p^{-1}(q(y))) - g_1(y, p^{-1}(q(x))) \geq 0$ for all $x \geq y > 0$.

Proof We shall show that $\overline{G} = \underline{G}$ and $\underline{I} = \overline{I}$. By Lemma 2.1, if $\underline{I} < \overline{I}$, then $\underline{G} < \overline{G}$ and

$$p^{-1}(q(\underline{G})) \leq \underline{I} < \overline{I} \leq p^{-1}(q(\overline{G})),$$

$$-f(\underline{G}) - g_1(\underline{G}, p^{-1}(q(\overline{G}))) / g_2(\underline{G}) + b_7 \leq 0$$

and

$$-f(\overline{G}) - g_1(\overline{G}, p^{-1}(q(\underline{G}))) / g_2(\overline{G}) + b_7 \geq 0.$$

Thus

$$-(f(\underline{G}) - b_7)g_2(\underline{G}) - g_1(\underline{G}, p^{-1}(q(\overline{G}))) \leq 0 \quad (3.7)$$

and

$$-(f(\overline{G}) - b_7)g_2(\overline{G}) - g_1(\overline{G}, p^{-1}(q(\underline{G}))) \geq 0. \quad (3.8)$$

Hence, (3.7) and (3.8) imply

$$((f(\overline{G}) - b_7)g_2(\overline{G}) - (f(\underline{G}) - b_7)g_2(\underline{G})) + (g_1(\overline{G}, p^{-1}(q(\underline{G}))) - g_1(\underline{G}, p^{-1}(q(\overline{G})))) \leq 0. \quad (3.9)$$

This together with the assumptions (a) and (b), we obtain

$$(f(\overline{G}) - b_7)g_2(\overline{G}) - (f(\underline{G}) - b_7)g_2(\underline{G}) = 0.$$

This implies that $\overline{G} = \underline{G}$, and therefore $\overline{I} = \underline{I}$. This completes the proof. \square

Corollary 3.1. *For model (2.1), assume $g(x, y) = g_1(x, y)/g_2(x)$, where g_1, g_2 satisfy (v)–(ix). If (b) in Theorem 3.3 is replaced by*

(b') $\frac{\partial}{\partial x}g_1(x, p^{-1}(q(y))) - \frac{\partial}{\partial y}g_1(x, p^{-1}(q(y)))\frac{q'(y)}{p'(p^{-1}(q(y)))} \geq 0$ for all $x, y > 0$, then (G^, I^*) is globally asymptotically stable.*

Proof We shall show that (b) in Theorem 3.3 is true when (b') holds. Let

$$u(x, y) = g_1(x, p^{-1}(q(y))), \quad x, y > 0.$$

By the mean value theorem, for $x \geq y > 0$, there exists $\theta \in (0, 1)$ such that

$$\begin{aligned} u(x, y) - u(y, x) &= u_x(\xi, \eta)(x - y) + u_y(\xi, \eta)(x - y) \\ &= (x - y)(u_x(\xi, \eta) - u_y(\xi, \eta)) \\ &= (x - y) \geq 0, \end{aligned}$$

where $\xi = y + \theta(x - y)$, $\eta = x - \theta(x - y)$. This completes the proof. \square

The following are direct results of the applications of the above theorems to the specific models (2.2) and (2.3).

Corollary 3.2. *For model (2.2) ((2.3)), if $\alpha \geq \gamma$, then the only equilibrium point (G^*, I^*) of (2.2) ((2.3)) is globally asymptotically stable.*

Proof We shall apply Theorem 3.2 to model (2.2) ((2.3)). For model (2.2), we have

$$\begin{aligned} &f'(x) + g_x(x, p^{-1}(q(y))) - g_y(x, p^{-1}(q(y)))\frac{q'(y)}{p'(p^{-1}(q(y)))} \\ &= b_1 + \frac{b_4(b_6/b_2)y}{(\alpha x + 1)^2} - \frac{b_4x}{\alpha x + 1} \frac{b_6}{b_2} \\ &\geq b_1 \left(1 - \frac{\gamma x}{\alpha x + 1}\right) \\ &= b_1((\alpha - \gamma)x + 1)/(\alpha x + 1) > 0 \end{aligned}$$

for all $x > 0$, if $\alpha \geq \gamma$. \square

Corollary 3.3. *For model (2.2) ((2.3)), if $\alpha \leq a_1 = b_1/b_7$, then the only equilibrium point (G^*, I^*) of (2.2)((2.3)) is globally asymptotically stable.*

Proof We shall apply Theorem 3.3 to model (2.2). For (a) to hold, we need

$$\begin{aligned} \frac{d}{dx}((f(x) - b_7)g_2(x)) &= \frac{d}{dx}((b_1x - b_7)(\alpha x + 1)) \\ &= 2b_1\alpha x + (b_1 - \alpha b_7) > 0 \end{aligned}$$

for all $x > 0$. This is true if $b_1 - \alpha b_7 \geq 0$, i.e., $\alpha \leq b_1/b_7$. \square

For (b) to hold, we need only to observe that

$$g_1(x, p^{-1}(q(y))) - g_1(y, p^{-1}(q(x))) \equiv 0 \quad \text{for all } x, y > 0.$$

Combining the above two corollaries, we immediately arrive at the following conclusion

Corollary 3.4. *For model (2.2) ((2.3)), if $a_1 \geq \gamma$, i.e.,*

$$b_1/b_7 \geq b_4b_6/b_1b_2,$$

then (G^, I^*) is globally asymptotically stable for all $\alpha \geq 0$ and $b_5 > 0$.*

4. Linearization and Characteristic Equations. Although we have obtained several global stability results, we have yet to study the local stability systematically. One of our motivation to study the general model (2.1) is to see if oscillatory solution can exist for certain parameter values. Recall that both the minimal and dynamic models permit only globally asymptotically stable positive steady states. We would like to know if and how this may change for more realistic models. To this end, we need to obtain the characteristic equations associated to our models.

Consider first model (2.1). Let

$$G_1(t) = G(t) - G^*, \quad I_1(t) = I(t) - I^*. \quad (4.1)$$

then model (2.1) is translated to

$$\begin{cases} G_1'(t) = -f(G_1(t) + G^*) - g(G_1(t) + G^*, I_1(t) + I^*) + b_7 \\ I_1'(t) = -p(I_1(t) + I^*) + q(L((G_1)_t + G^*)) \end{cases} \quad (4.2)$$

and has a unique equilibrium point at $(0, 0)$.

Thus the linearized system of (4.2) is given by

$$\begin{cases} G_1'(t) = -(f'(G^*) + g_x(G^*, I^*))G_1(t) - g_y(G^*, I^*)I_1(t), \\ I_1'(t) = -p'(I^*)I_1(t) + q'(G^*)L((G_1)_t). \end{cases}$$

For convenience, we still use $G(t)$ and $I(t)$ to represent $G_1(t)$ and $I_1(t)$, respectively, and define

$$A = f'(G^*) + g_x(G^*, I^*), \quad B = g_y(G^*, I^*), \quad C = q'(G^*), \quad D = p'(I^*).$$

Then A, B, C and D are positive. The linearized system of (4.2) can be rewritten as

$$\begin{cases} G'(t) = -AG(t) - BI(t) \\ I'(t) = -DI(t) + CL(G_t). \end{cases} \quad (4.3)$$

It's easy to see that

$$G''(t) = -(A + D)G'(t) - ADG(t) - BCL(G_t). \quad (4.4)$$

Denote that

$$a = A + D, \quad c = AD, \quad d = BC \quad \text{and} \quad \tau = b_5.$$

Then (4.4) can be rewritten as

$$G''(t) + aG'(t) + cG(t) + dL(G_t) = 0. \quad (4.5)$$

If $L(G_t)$ takes the discrete delay form, i.e., $L(G_t) = G(t - \tau)$, $t > 0$, then the characteristic equation of (4.5) is given by

$$D(\lambda) = \lambda^2 + a\lambda + c + de^{-\tau\lambda} = 0. \quad (4.6)$$

If $L(G_t)$ takes the form of distributed delay, i.e., $L(G_t) = (1/\tau) \int_{t-\tau}^t G(\theta)d\theta$, $t > 0$, then the characteristic equation of (4.5) is given by

$$\tilde{D}(\lambda) = \lambda^2 + a\lambda + c + \frac{d}{\tau} \int_{-\tau}^0 e^{\lambda\theta} d\theta = 0. \quad (4.7)$$

5. Delay Independent Stability Results for Discrete Delay Model. In this section we consider only the case of *discrete delay* in model (2.1) and therefore the results are applicable to model (2.2). We need the following theorem from [11](Theorem 3.1, page 77).

Theorem B In the following second order real scalar linear neutral delay equation

$$x''(t) + \sigma x''(t - \tau) + ax'(t) + bx'(t - \tau) + cx(t) + dx(t - \tau) = 0, \quad (5.1)$$

where $\tau \geq 0$. Assume $|\sigma| < 1$, $c + d \neq 0$ and $a^2 + b^2 + (d - \sigma c)^2 \neq 0$. Consider the roots of characteristic equation of (4.6)

$$\lambda^2 + \sigma\lambda^2 e^{-\lambda\tau} + a\lambda + b\lambda e^{-\lambda\tau} + c + de^{-\lambda\tau} = 0. \quad (5.2)$$

(I) If there are no such roots, then the stability of the zero solution does not change for any $\tau > 0$.

(II) If there are any imaginary roots with positive imaginary part, an unstable zero solution never becomes stable for any $\tau \geq 0$. If the zero solution is asymptotically stable for $\tau = 0$, then it is uniformly asymptotically stable for $\tau < \tau_0$, and it becomes unstable for $\tau > \tau_0$ where $\tau_0 > 0$ is a constant. It undergoes a supercritical Hopf bifurcation at $\tau = \tau_0$.

(III) If there are two imaginary roots with positive imaginary part, $i\omega_+$ and $i\omega_-$, such that $\omega_+ > \omega_- > 0$, then the stability of the zero solution can change (when changes from stable to unstable, the zero solution undergoes a supercritical Hopf bifurcation) a finite number of times at most as τ is increased, and eventually it becomes unstable.

The number of such roots are determined by the following conditions.

If $c^2 \leq d^2$, then there is only one such root.

If $c^2 > d^2$, then there are two such roots provided that

- (A) $b^2 + 2c - a^2 - 2d\sigma > 0$, and
- (B) $(b^2 + 2c - a^2 - 2d\sigma)^2 > 4(1 - \sigma^2)(c^2 - d^2)$.

Otherwise, there is no such solution.

Lemma 5.1. *In (4.6), the stability of (0,0) is determined as follows.*

Case (1). If $AD > BC$, then the stability of (0,0) does not change as $\tau \geq 0$ is increasing;

Case (2). If $AD \leq BC$, then the stability of (0,0) can at most change once from stable to unstable, i.e., if (0,0) is stable, when $\tau = 0$, then (0,0) becomes unstable

when $\tau \geq \tau_0 > 0$ for some $\tau_0 > 0$; if $(0, 0)$ is unstable when $\tau = 0$, $(0, 0)$ remains unstable for all $\tau > 0$.

Proof Compare (4.6) with (5.1). We have

$$\sigma = 0, \quad a = A + D, \quad b = 0, \quad c = AD, \quad d = BC.$$

Thus,

$$\begin{aligned} b^2 + 2c - a^2 - 2d\sigma &= 2c - a^2 = 2AD - (A + D)^2 \\ &= -(A^2 + D^2) \leq 0. \end{aligned}$$

Hence, (A) is violated, and hence the case (III) in (Theorem B). That is, $(0, 0)$ cannot have multiple stability switches.

Since $A, B, C, D > 0$, we see that $c^2 > d^2$ ($c^2 \leq d^2$) is equivalent to $c > d$ ($c \leq d$). Thus we proved Case (1) and Case (2). \square

From Lemma 5.1, we have

Theorem 5.1. For (2.1), we have the following results on the local stability of $(0, 0)$.

Case (i). If

$$(f'(G^*) + g_x(G^*, I^*))p'(I^*) \leq g_y(G^*, I^*)q'(G^*),$$

then (G^*, I^*) has at most one stability switch as $\tau \geq 0$ increases.

Case (ii). If

$$(f'(G^*) + g_x(G^*, I^*))p'(I^*) > g_y(G^*, I^*)q'(G^*),$$

then stability of (G^*, I^*) does not change for any $\tau \geq 0$.

Proof Notice that (4.3) is the linearized system of (2.1) at (G^*, I^*) , and $A = f'(G^*) + g_x(G^*, I^*)$, $D = p'(I^*)$, $B = g_y(G^*, I^*)$, $C = q'(G^*)$. \square

Corollary 5.1. For model (2.2), the local stability of (G^*, I^*) can be determined as follows.

Case (i). If $\gamma > \frac{1}{2}(11 + 5\sqrt{5})a_1$, then there is at most one stability switch of (G^*, I^*) . Specifically, if (G^*, I^*) is stable when $b_5 = 0$, then there exists $\tau_0 > 0$ such that (G^*, I^*) is stable for $b_5 \in [0, \tau_0)$ and unstable for $b_5 \geq \tau_0$; if (G^*, I^*) is unstable when $b_5 = 0$, then (G^*, I^*) is unstable for all $b_5 > 0$.

Case (ii). If $\gamma \leq \frac{1}{2}(11 + 5\sqrt{5})a_1$, then the stability of (G^*, I^*) does not change for all $b_5 \geq 0$.

Proof By Theorem 5.1, we need only to check the sign of

$$(f'(G^*) + g_x(G^*, I^*))p'(I^*) - g_y(G^*, I^*)q'(G^*). \quad (5.3)$$

Notice that

$$G^* = 2b_7 / ((b_1 - \alpha b_7) + \sqrt{(b_1 - \alpha b_7)^2 + 4b_7(\alpha b_1 + b_4 b_6 / b_2)}), \quad \text{and } I^* = \frac{b_6}{b_2} G^*, \quad (5.4)$$

and

$$\begin{aligned} f'(x) &= b_1, & p'(x) &= b_2, & q'(x) &= b_6, \\ g_x(x, y) &= \frac{b_4 y}{(\alpha x + 1)^2}, & g_y(x, y) &= \frac{b_4 x}{\alpha x + 1}. \end{aligned}$$

Let

$$\beta = b_4 b_6 / b_2 (= b_1 \gamma).$$

Then (5.3) becomes

$$\begin{aligned}
& b_2 \left(b_1 + \frac{\beta G^*}{(\alpha G^* + 1)^2} \right) - \frac{b_4 b_6 G^*}{\alpha G^* + 1} \\
&= \frac{b_2}{(\alpha G^* + 1)^2} (b_1(\alpha G^* + 1)^2 - \beta \alpha G^{*2}) \\
&= \frac{b_2}{(\alpha G^* + 1)^2} (\sqrt{b_1}(\alpha G^* + 1) + \sqrt{\beta} \sqrt{\alpha} G^*) (\sqrt{b_1}(\alpha G^* + 1) - \sqrt{\beta} \sqrt{\alpha} G^*).
\end{aligned}$$

Let

$$\begin{aligned}
w(\alpha) &= \sqrt{b_1}(\alpha G^* + 1) - \sqrt{\beta} \sqrt{\alpha} G^* \\
&= \sqrt{b_1} (1 + (\sqrt{\alpha} - \sqrt{\gamma}) \sqrt{\alpha} G^*) \\
&= \sqrt{b_1} w_1(\alpha).
\end{aligned}$$

Then $\text{sign (5.3)} = \text{sign } w_1(\alpha)$. We have

$$\begin{aligned}
w_1(\alpha) &= 1 + (\sqrt{\alpha} - \sqrt{\gamma}) \sqrt{\alpha} G^* \\
&= 1 + \frac{2b_7 \sqrt{\alpha} (\sqrt{\alpha} - \sqrt{\gamma})}{b_1 - \alpha b_7 + \sqrt{(b_1 - \alpha b_7)^2 + 4b_1 b_7 (\alpha + \gamma)}} \\
&= \frac{\sqrt{(b_1 - \alpha b_7)^2 + 4b_1 b_7 (\alpha + \gamma)} + (b_1 + b_7 \alpha - 2b_7 \sqrt{\gamma \alpha})}{b_1 - \alpha b_7 + \sqrt{(b_1 - \alpha b_7)^2 + 4b_1 b_7 (\alpha + \gamma)}}.
\end{aligned}$$

Let

$$v(\alpha) = \sqrt{(b_1 - 2b_7)^2 + 4b_1 b_7 (\alpha + \gamma)} + (b_1 + b_7 \alpha - 2b_7 \sqrt{\gamma \alpha})$$

then $\text{sign (5.3)} = \text{sign } v(\alpha)$.

$$\begin{aligned}
v(\alpha) &= \sqrt{(b_1 + \alpha b_7)^2 + 4b_1 b_7 \gamma} + (b_1 + b_7 \alpha - 2b_7 \sqrt{\gamma \alpha}) \\
&= \frac{4b_1 b_7 \gamma + 4b_1 b_7 \sqrt{\gamma \alpha} + 4b_7^2 \sqrt{\gamma} \alpha^{3/2} - 4b_7^2 \gamma \alpha}{\sqrt{(b_1 + 2b_7)^2 + 4b_1 b_7 \gamma} - (b_1 + b_7 \alpha - 2b_7 \sqrt{\gamma \alpha})} \\
&= \frac{4b_7^2 \sqrt{\gamma} (\alpha^{3/2} - \sqrt{\gamma} \alpha + a_1 \sqrt{\alpha} + a_1 \sqrt{\gamma})}{\sqrt{(b_1 + \alpha b_7)^2 + 4b_1 b_7 \gamma} - (b_1 + b_7 \alpha - 2b_7 \sqrt{\gamma \alpha})}.
\end{aligned}$$

Let $\mu = \sqrt{\alpha}$ and

$$J(\mu) = \mu^3 - \sqrt{\gamma} \mu^2 + a_1 \mu + a_1 \sqrt{\gamma}, \quad \mu \geq 0.$$

Then

$$\text{sign (5.3)} = \text{sign } v(\alpha) = \text{sign } J(\mu).$$

Notice that

$$J'(\mu) = 3\mu^2 - 2\sqrt{\gamma} \mu + a_1$$

$$\Delta_J = 4\gamma - 12a_1 = 4(\gamma - 3a_1)$$

$J'(\mu) = 0$ gives two extreme points if and only if $\Delta_J > 0$. So if $\Delta_J \leq 0$, $J(\mu) > 0$. If $\Delta_J > 0$, $J(\mu)$ has the possibility to assume negative value.

Assume now that $\Delta_J > 0$, i.e., $\gamma - 3a_1 > 0$. We shall find the minimum value of $J(\mu)$, $\mu \geq 0$. Solving $J'(\mu) = 0$, we obtain

$$\mu_{1,2} = \frac{1}{6} (2\sqrt{\gamma} \pm 2\sqrt{\gamma - 3a_1}) = \frac{1}{3} (\sqrt{\gamma} \pm \sqrt{\gamma - 3a_1}).$$

Clearly $\mu_0 = \frac{1}{3}(\sqrt{\gamma} + \sqrt{\gamma - 3a_1})$ is the minimum point of $J(\mu)$, $\mu \geq 0$.

$$\begin{aligned}
J(\mu_0) &= a_1\sqrt{\gamma} + \mu_0(\mu_0^2 - \sqrt{\gamma}\mu_0 + a_1) \\
&= a_1\sqrt{\gamma} + \frac{1}{27}(\sqrt{\gamma} + \sqrt{\gamma - 3a_1})(\gamma + 2\sqrt{\gamma(\gamma - 3a_1)} + \gamma - 3a_1 \\
&\quad - 3\gamma - 3\sqrt{\gamma(\gamma - 3a_1)} + 9a_1) \\
&= a_1\sqrt{\gamma} + \frac{1}{27}(\sqrt{\gamma} + \sqrt{\gamma - 3a_1})(-\gamma - \sqrt{\gamma(\gamma - 3a_1)} + 6a_1) \\
&= a_1\sqrt{\gamma} + \frac{1}{27}(-2\gamma\sqrt{\gamma} + 9a_1\sqrt{\gamma} - 2(\gamma - 3a_1)\sqrt{\gamma - 3a_1}) \\
&= \frac{1}{27}(36a_1\sqrt{\gamma} - 2\gamma\sqrt{\gamma} - 2(\gamma - 3a_1)\sqrt{\gamma - 3a_1}) \\
&= \frac{2}{27}((18a_1 - \gamma)\sqrt{\gamma} - (\gamma - 3a_1)\sqrt{\gamma - 3a_1}) \\
&\leq 0 \text{ if } \gamma \geq 18a_1.
\end{aligned}$$

Assume $3a_1 < \gamma < 18a_1$, then

$$J(\mu_0) = \frac{2}{27} \frac{(18a_1 - \gamma)^2\gamma - (\gamma - 3a_1)^2(\gamma - 3a_1)}{(18a_1 - \gamma)\sqrt{\gamma} + (\gamma - 3a_1)\sqrt{\gamma - 3a_1}}.$$

Let $h(a_1, \gamma) = \gamma(18a_1 - \gamma)^2 - (\gamma - 3a_1)(\gamma - 3a_1)^2$, then $\text{sign } J(\mu_0) = \text{sign } h(a_1, \gamma)$. We have

$$\begin{aligned}
h(a_1, \gamma) &= \gamma(15a_1 - (\gamma - 3a_1))^2 - (\gamma - 3a_1)(\gamma - 3a_1)^2 \\
&= -27a_1(\gamma^2 - 11a_1\gamma - a_1^2) \\
&= -27a_1\left(\gamma + \frac{-11 + 5\sqrt{5}}{2}a_1\right)\left(\gamma - \frac{11 + 5\sqrt{5}}{2}a_1\right) \\
&< 0 \text{ iff } \gamma > \frac{11 + 5\sqrt{5}}{2}a_1.
\end{aligned}$$

This completes the proof. \square

6. Delay Dependent Stability Conditions. The stability results in the previous section do not depend on the values of the delay (b_5). However, they do suggest that for some parameter values (delay is included), the positive steady state may become unstable. It is thus interesting to locate such parameter values. Such task turns out to be very complex. Instead, we shall single out parameter region where no stability switch can take place. Specifically, we would like to obtain some upper bound on the delay length (while holding other parameters steady) for the positive steady state to remain stable. Specifically, we shall seek the relationship of such upper bound with the value of α . We shall consider both model (2.2) and (2.3). Recall that the following notations in Section 4,

$$A = f'(G^*) + g_x(G^*, I^*), \quad B = g_y(G^*, I^*), \quad C = q'(G^*), \quad D = p'(I^*).$$

and

$$a = A + D, \quad c = AD, \quad d = BC, \quad \tau = b_5.$$

Define

$$H(\alpha) = \frac{f'(G^*) + g_x(G^*, I^*) + p'(I^*)}{g_y(G^*, I^*)q'(G^*)}.$$

6.1. The case of discrete delay. We shall consider here the characteristic equation (4.6) below. Recall that

$$D(\lambda) = \lambda^2 + a\lambda + c + de^{-\tau\lambda} = 0.$$

If there exists a $\tau_0 > 0$ such that the trivial solution of (4.3) is unstable for all $\tau \geq \tau_0$, then there must be an $\omega > 0$ such that $D(\omega i) = 0$. Thus

$$-\omega^2 + a\omega i + c + d(\cos \tau\omega - i \sin \omega\tau) = 0,$$

and hence

$$\begin{cases} \omega^2 = c + d \cos \omega\tau, \\ a\omega = d \sin \omega\tau. \end{cases} \quad (6.1)$$

Since $a > 0$ and $\omega > 0$, (6.1) implies that $\tau \geq a/d$. This leads to the following

Theorem 6.1. *In linear equation (4.5), if $L(G_t) = G(t - \tau)$, $t > 0$, $\tau > 0$, and $\tau < a/d$, then the trivial solution of (4.5) is globally asymptotically stable.*

Applying theorem 6.1 to model (2.2), we have

Corollary 6.1. *In model (2.2), if $L(G_t) = G(t - \tau)$, $t > 0$, $\tau > 0$, and $\tau < H(\alpha)$, then the equilibrium point (G^*, I^*) is locally asymptotically stable.*

6.2. The case of distributed delay. We now consider the characteristic equation (4.7) of linear equation (4.5) for the case of $L(G_t) = \frac{1}{\tau} \int_{t-\tau}^t G(\theta) d\theta$, $t > 0$, $\tau > 0$,

$$\tilde{D}(\lambda) = \lambda^2 a\lambda + c + \frac{d}{\tau} \int_{-\tau}^0 e^{\lambda\theta} d\theta = 0. \quad (6.2)$$

If the trivial solution of (4.5) is unstable for some $\tau > 0$, then there exist $u \geq 0$ and $v > 0$ such that $\lambda = u + iv$ is a solution of (6.2), i.e.,

$$(u + iv)^2 + a(u + iv) + c + \frac{d}{\tau} \int_{-\tau}^0 e^{\theta u} (\cos v\theta + i \sin v\theta) d\theta = 0.$$

Thus

$$u^2 - v^2 + au + c + \frac{d}{\tau} \int_{-\tau}^0 e^{\theta u} \cos v\theta d\theta = 0, \quad (6.3)$$

and

$$2uv + av + \frac{d}{\tau} \int_{-\tau}^0 e^{\theta u} \sin v\theta d\theta = 0. \quad (6.4)$$

Since $v > 0$, we see that (6.4) implies

$$2u + a = -\frac{d}{\tau} \int_{-\tau}^0 e^{u\theta} \frac{\sin v\theta}{v} d\theta.$$

Therefore

$$\begin{aligned} 2u + a &\leq \frac{d}{\tau} \left| \int_{-\tau}^0 e^{u\theta} \cdot \frac{\sin v\theta}{v} d\theta \right| \\ &\leq \frac{d}{\tau} \int_{-\tau}^0 |\theta| d\theta = \frac{1}{2} d\tau. \end{aligned}$$

Hence we have $u \leq \frac{1}{2} \left(\frac{1}{2} \tau d - a \right)$. This leads to the following

Theorem 6.2. *In linear equation (4.5), if $L(G_t) = (1/\tau) \int_{-\tau}^0 G(t + \theta)d\theta$, $t > 0$, $\tau > 0$ and $\tau < 2a/d$, then the trivial solution of (4.5) is globally asymptotically stable.*

From theorem 6.2, we have

Corollary 6.2. *In model (2.2), if $L(G_t) = (1/\tau) \int_{-\tau}^0 G(t + \theta)d\theta$, $t > 0$, $\tau > 0$, and $\tau < 2H(\alpha)$, then the equilibrium point (G^*, I^*) is locally asymptotically stable.*

6.3. Expression of $H(\alpha)$ for model (2.2) and (2.3). In the following, we shall give the explicit expression of $H(\alpha)$ for model (2.2) and (2.3). This is useful in applications and in planning computer simulations. Recall that model (2.1) reduces to model (2.2) ((2.3)) if

$$f(x) = b_1x, \quad g(x, y) = \frac{b_4xy}{\alpha x + 1}, \quad p(x) = b_2x, \quad \text{and} \quad q(L(u_t)) = b_6L(u_t), \quad u_t \in C.$$

In this case, we have

$$f'(x) = b_1, \quad g_x(x, y) = \frac{b_4y}{(\alpha x + 1)^2}, \quad g_y(x, y) = \frac{b_4x}{\alpha x + 1}, \quad p'(x) = b_2, \quad x \geq 0$$

and $q'(L(u_t)) = b_6$ for $u_t \in C$.

Recall that model (2.2) ((2.3)) assumes the existence of a unique steady state (G^*, I^*) in \mathbf{R}_+^2 , where G^* and I^* are given by (5.4). Let $S(\alpha) = \alpha + \frac{1}{G^*}$, then

$$\begin{aligned} S(\alpha) &= \alpha + \frac{1}{2b_7} \left[(b_1 - \alpha b_7) + \sqrt{(b_1 - \alpha b_7)^2 + 4b_7(\alpha b_1 + b_4b_6/b_2)} \right] \\ &= \frac{1}{2b_7} \left[(b_1 + b_7\alpha) + \sqrt{(b_1 + b_7\alpha)^2 + 4b_4b_6b_7/b_2} \right]. \end{aligned}$$

Therefore

$$\begin{aligned} H(\alpha) &= \frac{f'(G^*) + g_x(G^*, I^*) + p'(I^*)}{g_y(G^*, I^*)q'(G^*)} \\ &= \frac{b_1 + b_2 + (b_4I^*/(\alpha G^* + 1)^2)}{(b_6b_4G^*/\alpha G^* + 1)} \\ &= \frac{b_1 + b_2}{b_4b_6} \frac{\alpha G^* + 1}{G^*} + \frac{1}{b_2(\alpha G^* + 1)} \\ &= \frac{b_1 + b_2}{b_4b_6} S(\alpha) + \frac{(G^*)^{-1}}{b_2S(\alpha)}. \end{aligned}$$

Let $\Delta = (b_1 + b_7\alpha)^2 + 4b_4b_6b_7/b_2$. Notice that

$$\begin{aligned} \frac{(G^*)^{-1}}{S(\alpha)} &= \frac{(b_1 - \alpha b_7) + \sqrt{(b_1 - \alpha b_7)^2 + 4b_7(\alpha b_1 + (b_4b_6/b_2))}}{(b_1 + b_7\alpha) + \sqrt{\Delta}} \\ &= \frac{[(b_1 - \alpha b_7) + \sqrt{\Delta}][(b_1 + b_7\alpha) - \sqrt{\Delta}]}{4b_4b_6b_7/b_2} \\ &= \frac{b_2}{4b_4b_6b_7} [\Delta + (b_1 - b_7\alpha)\sqrt{\Delta} - (b_1 + b_7\alpha)\sqrt{\Delta} - (b_1^2 - b_7^2\alpha^2)] \\ &= \frac{b_2}{2b_4b_6b_7} [b_7^2\alpha^2 - b_7\alpha\sqrt{\Delta} + b_1b_7\alpha + 2b_4b_6b_7/b_2]. \end{aligned}$$

P	G_b	I_b	b_0	b_1	b_2	b_3	b_4	b_5	b_6	b_7
U	$\frac{\text{mg}}{\text{dl}}$	pM	$\frac{\text{mg}}{\text{dl}}$	min^{-1}	min^{-1}	$\frac{\text{dlpM}}{\text{mg}}$	$\text{min}^{-1}\text{pM}^{-1}$	min	$\frac{\text{dlpM}}{\text{mgmin}}$	$\frac{\text{mg}}{\text{dlmin}}$
6	88	68.6	209	0.0002	0.0422	1.64	1.09E-04	23	0.033	0.68
7	87	37.9	311	0.0001	0.2196	0.64	3.73E-04	23	0.096	1.24

TABLE 1. Parameter values for subjects 6 and 7, from De Gaetano and Arino [4]. P stands for parameters, U stands for units and 6, 7 stand for subject 6, 7, respectively.

Thus,

$$\begin{aligned}
H(\alpha) &= \frac{b_1 + b_2}{2b_4b_6b_7} [(b_1 + b_7\alpha) + \sqrt{\Delta}] \\
&\quad + \frac{1}{2b_4b_6b_7} [b_7^2\alpha^2 - b_7\alpha\sqrt{\Delta} + b_1b_7\alpha + 2b_4b_6b_7/b_2] \\
&= \frac{1}{2b_4b_6b_7} [b_7^2\alpha^2 + (b_1 + b_2 - b_7\alpha)\sqrt{\Delta} \\
&\quad + (2b_1 + b_2)b_7\alpha + 2b_4b_6b_7/b_2].
\end{aligned}$$

7. Simulation and discussion. In a clinic study reported in [4], ten healthy volunteers participated (5 males and 5 females). All of them had negative family and personal histories for diabetes mellitus and other endocrine diseases, were on no medications and had maintained a constant weight for the six months preceding that study. For detailed experiment description, see [4]. They were able to show that the dynamic model does produce solutions that fit well with the data collected from that experiment. The parameter values for these individuals are listed in their Table 1. Using these parameters and Corollary 3.4, we found that for all these persons except the sixth person (female) and the seventh person (male), and all values of α and delay lengths, solutions always tend to the positive steady state for both models (2.2) and (2.3). Since one of our main objectives is to see if unstable positive steady state is possible for our models and some of these ten persons, and our theoretical results failed to exclude such possibility, we thus focused our simulations on the subjects 6 and 7 (sixth and seventh persons). The relevant parameter values (obtained through the above mentioned clinic study) for these two persons are summarized in table 1.

Even for subjects 6 and 7, according to our extensive computer simulation work by XPP for window 98/NT ([8]), the steady state is globally asymptotically stable in all practically meaningful values of time delay $\tau = b_5$ and α . Nevertheless, we did find that the positive steady state can be unstable (if $a_1 < \gamma$ and $\alpha \in (a_1, \gamma)$ provided the delay is large enough). Figures 1–2 illustrate such instability with nontrivial periodic solutions for the discrete delay model (2.2), using the data (except b_5 and α) given in the table 1 for subjects 6 and 7. For discrete delay model (2.2), we need the time delay to be as long as close to 550 minutes in order to observe sustainable oscillatory solutions for both subjects 6 (550) and 7 (600). The values of α are 0.01 and 0.05 for subject 6 and subject 7, respectively. Since for both subjects, the actual delay length is only 23 minutes, we believe that it is very unlikely to observe any sustainable oscillatory solutions in real life experiments for these subjects. In other word, the global asymptotical results reported in [4] is confirmed at least practically by the more general model (2.1).

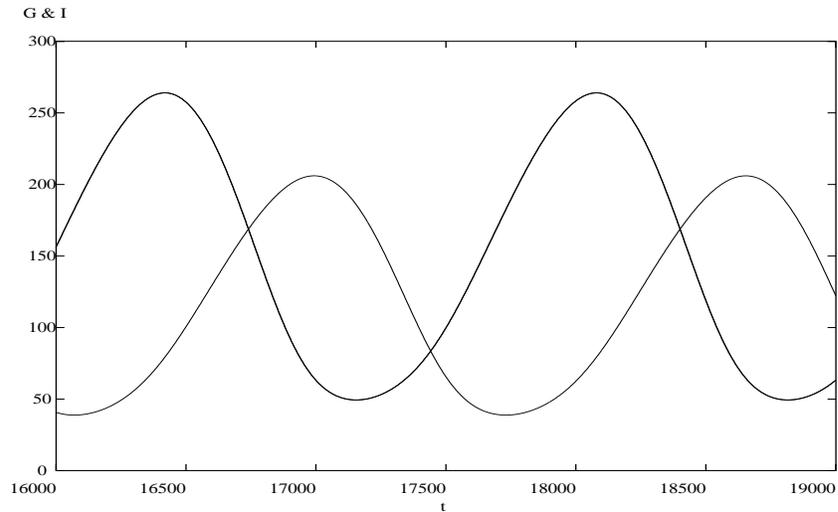


FIGURE 1. A periodic solution for the discrete delay model (2.2) for subject 6. The large amplitude curve depicts the glucose concentration, while the other one depicts insulin concentration. Here $\alpha = 0.01$, and $b_5 = 550$.

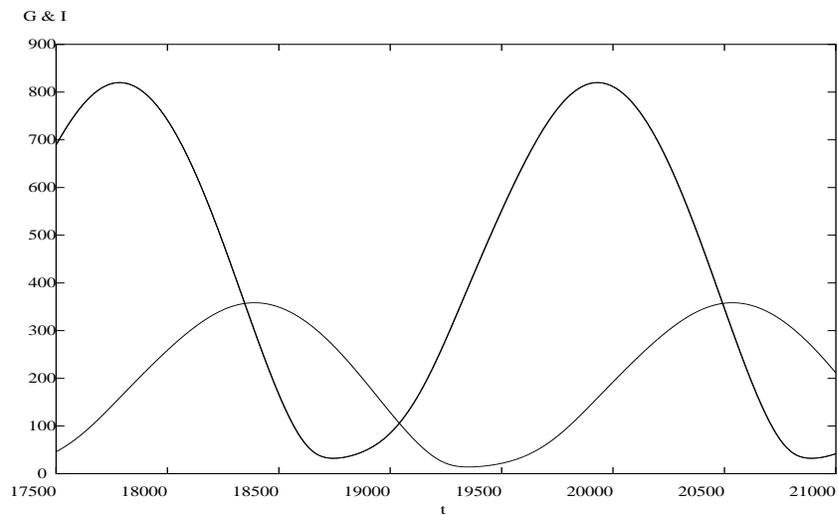


FIGURE 2. A periodic solution for the discrete delay model (2.2) for subject 7. The large amplitude curve depicts the glucose concentration, while the other one depicts insulin concentration. Here $\alpha = 0.05$, and $b_5 = 600$.

From purely theoretical point of view, we can still make a few insightful statements. For both very large or small values of α , the positive steady state is believed to be globally asymptotically stable for any conceivable persons. For relatively small α and large delay, oscillatory solutions become possible. This indicates that it is important to have α in the model, since the value of α is most likely small, but not

too small. Indeed, from the simulation results (figures 1-2), we see α is in the range of 0.01 to 0.05, which translates into a range of 20 to 100 for half saturation value of G . This range is very close or comparable to the experiment values of G depicted in figures 2 and 3 in [4], where G start at values around 250 and drop down quickly (in about 40 minutes) to values close to 100. The added work for measuring α should not be overwhelming, since more than enough measurements are recorded. The additional work is mathematical. We would like to point out here that including α in the model may very well change the values of other parameters, in particular that of b_4 .

From corollary 5.1, we know that the positive steady state may be unstable if $\gamma > \frac{1}{2}(11 + 5\sqrt{5})a_1$, which is equivalent to $b_4b_6b_7 > \frac{1}{2}(11 + 5\sqrt{5})b_1^2b_2$. In view of the fact that the values of b_1 (from 0.0001 to 0.0565) and b_4 (from 3.51E-08 to 3.73E-04) change significantly from one person to another, we see that the likely candidates for having sustainable oscillatory glucose and insulin levels are subjects that have high values of b_4 (insulin-dependent glucose disappearance rate) and low values of b_1 (the spontaneous or insulin-independent glucose first order disappearance rate). That is, those subjects who can not process their glucose quick enough when insulin level is low but respond very well with added insulin.

Roughly speaking, when the delay is short (less than 60 minutes), we probably will not see any sustainable oscillatory solutions. However, for large enough delays, this may be possible. In such cases, the larger the half-saturation constant (i.e., $1/\alpha$), the more likely that the steady state is to be unstable. Even when the delay is small and the steady state is stable, the solutions may converge to the steady state in an oscillatory way. This can give rise to subsequent peaks of glucose and insulin, as observed in the experiment of De Gaetano and Arino [4].

If $\alpha = 0$, then we know the positive steady state is always locally stable. If $\alpha > 0$, the positive steady state remains stable for small and medium delays. Only for large values of delay and appropriate values of α , the positive steady state may lose its stability. Therefore, delay or the saturating glucose uptake functional response ($G/(\alpha G + 1)$) alone will not destabilize the steady state. In other words, for model (2.1), oscillatory solutions resulted from delayed suitable nonlinear glucose uptake mechanism. More complex nonlinear glucose uptake mechanism can be found in [17]. This is in striking contrast to the well known predator-prey dynamics (see [11]), where either alone will be enough to produce periodic solutions.

A potential application of our study here is to find better ways of delivering insulin and timing of the intake of glucose. Previous studies are largely done on linear compartment models ([18], [19]) or on the minimal type models [9]. Our theoretical and simulation work shows that in clinic applications, we can safely assume that after about 40 minutes, solutions are close and stay close to steady state levels. Another possible usage of our work is to design effective ways to estimate the involved parameters for clinic applications. For minimal model, such effort is documented in [5]. The recent development of PET technology provides a possibility of effectively monitor subjects' glucose and insulin levels through noninvasive method [3]. This should be very helpful in estimating parameters for individuals in order to design proper controls for their glucose and insulin levels.

Model (2.1) is constructed for the study of IVGTT which focuses on the metabolism of glucose. More in-depth study of insulin-glucose interaction may need to take into account of the insulin influence on the hepatic glucose production. This may, however, increase the number of equations in a plausible mathematical model.

Indeed, this is evidenced in the work of Sturis et al. [17] and Tolic et al. [20]. Their models consist of six nonlinear ordinary differential equations. Three of which tract the plasma insulin, intercellular insulin and glucose respectively. The other three are auxiliary linear chain equations used to mimic delay action between insulin in plasma and its effect on the hepatic glucose production. An alternative approach is to introduce such delay explicitly in the glucose equation which will reduce the number of equations from six to three. This is basically the approach of [7], except that they made a further simplification assumption that plasma insulin concentration is the same as the intercellular insulin concentration. However, in [7], they have also considered the possible continuous and theoretical external assistance to the patients (this artificial delivering of insulin results in the so-called technology delay). This yields a system of two nonlinear delay differential equations with two discrete delays, one in each equation. With or without such assistance, diabetic patients can exhibit intrinsic glucose oscillation. This reinforces the results reported in [17]. Our results show that in theory, even without hepatic glucose production, generalized dynamic model can produce oscillatory solutions.

Acknowledgments. We would like to thank Professor Edoardo Beretta for providing us the manuscript of De Gaetano and Arino [4] prior to its publication. We also would like to thank referees for their many valuable suggestions that improved the presentation of this paper. Research for Yang Kuang is partially supported by NSF Grant DMS-0077790.

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Received October 2000; revised January 2001.

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