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Stability Analysis and Numerical Simulations of IVGTT Glucose-Insulin Interaction Models with Two Time Delays

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Abstract. This paper presents a systematic study of a mathematical model of glucose and insulin interaction with two time delays, with a focus on analytical studies, bifurcation analysis, and very well numerical simulations. This model based on the Intra-Venous Glucose Tolerance Test (IVGTT) and is presented with two time delays. One delay is the insulin response time to an increase in glucose concentration, and the hepatic glucose production time delay is the other. Then, we establish results on positivity, boundedness, and persistence. We also provide sufficient stability analysis conditions for both local and global asymptotic stability of the proposed models. For the latter, two different strategies are used: stability bifurcation analysis and Lyapunov-Krasovskii functionals. We investigate different regions of parameter space using two approaches, that yield different sets of sufficient conditions for global stability. The bifurcation graphs generated from our extensive and carefully designed simulations complement and confirm these analytical results. The insulin concentration level peaks after the glucose concentration level, according to the numerical simulations.

Keywords: glucose-insulin regulatory system, insulin secretion, ultradian oscillation, delay differential equation model.

AMS Subject Classification: 92C50; 34C60; 92D25.

1 Introduction and model description

Ultradian insulin secretory oscillations with a period of 50–150 minutes have been observed in the glucose-insulin regulatory system. The assessment of insulin sensitivity utilizing various relatively non-invasive techniques has received great interest and importance in physiological research as a result of the growing frequency of pathological diseases such as diabetes. This led some recent study into current models as well as the development of some new ones.

Several mathematicians have developed mathematical models on the interaction of glucose and insulin based on IVGTT in the last several decades, which have been presented in the literature (see [2,3,4,5,7,8,15]). To diagnose a diabetic individual, various glucose tolerance tests have been applied in the clinics and experimental researches. Bolie [5], Ackerman et al. [1,2], Gatewood et al. [8], Bergman et al. [4], Steil et al. [20], Caumo et al. [6], Gresl et al. [9] offered the glucose-insulin linear models homeostasis based on IVGTT method.

The so-called "Minimal Model," which describes intravenous glucose tolerance test experimental results well with the smallest set of identifiable and meaningful parameters, is the most widely used model in physiological research on glucose metabolism [18]. In 1980, Bergman et al. [3, 4] has been presented the "Minimal Model", and it was modified in 1986. This model can be considered the most famous model used in physiological research on glucose metabolism [3, 4, 7, 14, 15, 16, 17, 18]. According to of [7], once the insulin dynamics have been included in, it's in the form

$$\begin{aligned} x'(t) &= -(q_1 + w(t))x(t) + q_1 x_b, \quad x(0) = q_0, \\ w'(t) &= -q_2 w(t) + q_3(y(t) - y_b), \quad w(0) = 0, \\ y'(t) &= q_4[x(t) - q_5]^+ t - q_6(y(t) - y_b), \quad y(0) = q_7 + y_b, \end{aligned} \tag{1.1}$$

where $[x - q_5]^+$ is given by $\max\{0, x - p_5\}$, and $x(t)$ [mg/dL] to represent the concentration of plasma glucose at time $t \geq 0$; $w(t)$ [1/min] to represent insulin excitable tissue glucose uptake activity as an auxiliary function; $y(t)$ [mU/L] is the concentration of plasma insulin at time $t \geq 0$; x_b [mg/dL], (resp. y_b [mU/L]) represent the concentration of Basal blood glucose (resp. insulin); q_0 [mg/dL] represent the theoretical glycemia at time $t = 0$, immediately after the instantaneous glucose bolus intake; q_1 [1/min] represent the rate of glucose clearance in the absence of insulin; q_2 [1/min] represent the rate of the active insulin clearance (upt. decrease); q_3 [L/(min2mU)] represent the increase in uptake ability which caused by insulin; q_4 [1/min], represent the rate of decay of blood insulin; q_5 [mg/dL] represent the target level of glucose; q_6 [mUdL/Lmgmin] represent the rate of the Pancreatic release, immediately after glucose bolus; q_7 (mg/dl)[1/min] represent the concentration of Plasma insulin above basal insulinemia at time 0, quickly after the glucose bolus intake.

To overcome the drawback of the minimal model, a new model known as the "Dynamical model" was introduced by De Gaetano and Arino in [7]. The two parts of the minimum model are coupled in this model, the delay is specifically represented, and non-observable state variables are omitted. Furthermore, the hypothesis that the rate of insulin secretion by the pancreas is proportional to the time after the glucose stimulus is incorrect. The assumption that the rate of insulin secretion by the pancreas is proportional to the time elapsed because the glucose stimulus is not used again. The dynamical model (1.1) reads [7]:

$$\begin{aligned} x'(t) &= -p_1x(t) - p_4x(t)y(t) + p_7, \\ y'(t) &= -p_2y(t) + \frac{p_6}{p_5}\int_{t-p_5}^{t} x(\sigma)d\sigma, \end{aligned} \tag{1.2}$$

with $x(0) = x_b + p_0$, $y(0) = p_5 + p_0p_3$, $x(t) = x_b$, for $t \in [-p_5, 0)$, where p_0 [mg/dL] represent the theoretical glycemia at time $t = 0$, immediately after the instantaneous glucose bolus intake; p_1 [1/min] represent the rate of insulin-independent glucose clearance; p_2 [1/min] represent the rate of the active insulin clearance (upt. decrease); p_3 [L/(min2mU)] represent the increase in uptake ability which caused by insulin; p_4 [1/min], represent the rate of decay of blood insulin; p_5 [mg/dL] represent the target level of glucose; p_6 [mUdL/Lmgmin] represent the rate of the Pancreatic release, immediately after glucose bolus; p_7 (mg/dl)[1/min] represent the concentration of Plasma insulin above basal insulinemia at time 0, immediately after the glucose bolus intake.

Li et al. updated the dynamical model in [15] by replacing the term p_4xy with $\frac{p_4xy}{\beta x+1}$ in order to generalize the model and find a new way to incorporate the delay. For the distributed delay (p_5), the model (1.2) becomes

$$\begin{aligned} x'(t) &= -p_1x(t) - \frac{p_4x(t)y(t)}{\beta x(t)+1} + p_7, \qquad x(0) = x_b + p_0, \\ y'(t) &= -p_2y(t) + \frac{p_6}{p_5}\int_{-p_5}^{0} x(t+\sigma)d\sigma, \qquad y(0) = y_b + p_3p_0, \end{aligned} \tag{1.3}$$

with $x(0) = x_b + p_0$, $y(0) = y_b + p_0p_3$, $x(t) = x_b$, for $t \in [-p_5, 0)$.

For the discrete delay (p_5), the model (1.3) takes the following form:

$$\begin{aligned} x'(t) &= -p_1x(t) - \frac{p_4x(t)y(t)}{\beta x(t)+1} + p_7, \quad x(0) = x_b + p_0, \\ y'(t) &= p_6x(t-p_5) - p_2y(t), \qquad y(0) = y_b + p_0p_3. \end{aligned} \tag{1.4}$$

with $x(0) = x_b + p_0$, $y(0) = y_b + p_0p_3$, $x(t) = x_b$, for $t \in [-p_5, 0)$.

Glucose and insulin are two important factors which maintain the glucose-insulin regulatory system and also maintain the body homeostasis. In the whole mechanism, some delays are observed (i) a delay is observed when insulin is released from pancreas stimulated by raised glucose level ($p_5 = \tau_i$) and (ii) a delay is observed in the action of insulin to lower the raised glucose concentration (τ_g). Here, our aim is to generalise the mathematical model (1.4) given by Li et al. [15] by introducing the second delay (τ_g) together with the already existing delay τ_i.

The paper is organized in the following sections: A general mathematical model containing two delay terms for the glucose insulin interaction is presented in Section 2. Properties of the solutions of the model are given in Section 3. Global stability of the model is given in Section 4. Linearization and characteristic functions of the model are characterized in Section 5. In Section 6, local asymptotic stability is presented. Based on the results of “Global stability” Section 4, numerical simulation is performed in Matlab 2012b and periodic solutions are obtained for the various values of τ_i and τ_g as shown in the graphs for the discrete delay model.

2 Mathematical model description

The general mathematical model for the glucose-insulin dynamics [15] is given as:

$$\begin{aligned} x'(t) &= -\psi(x(t)) - \xi(x(t), y(t)) + p_7, \quad x(0) = x_b + p_0, \\ y'(t) &= -\sigma(y(t)) + \varphi(x(t-\tau_g)), \quad y(0) = y_b + p_0 p_3, \end{aligned} \tag{2.1}$$

$x(t) = x_b$, for $t \in [-\tau, 0)$, where $\psi(x(t))$, represents the glucose utilization independent of insulin; ξ represents the insulin mediated glucose utilization; $\sigma(y(t))$ represents the insulin disappearance; $\tau_i > 0$ is the time takes for a considerable effect on hepatic glucose production, such as recovery rate or half maximal suppression; $\tau_g > 0$ is the delay time between the insulin response to glucose stimulation and the time it takes for recently produced insulin to pass the endothelial barrier and become distant insulin; $\varphi(x(t-\tau_g))$, denotes the pancreatic insulin secretion simulated by raised glucose concentration.

Insulin facilitates glucose transport into cells in muscle and fat tissue. The cells subsequently use the glucose to fuel their metabolism. Glucose enters the bloodstream through two routes: infusion and hepatic glucose synthesis. Glucose infusion includes meal ingestion, oral glucose intake, continuous enteral nutrition absorption, and constant infusion. Endogenous glucose distribution by the liver results in hepatic glucose synthesis. The β–cells stop releasing insulin when the level of glucose in the blood drops too low. Instead, the α–cells, which are also found in Langerhans islets, begin to produce glucagon. Nonetheless, the time delay is anywhere from a few minutes to a half hour, if not longer. $\xi(x(t), y(t-\tau_i))$ represents hepatic glucose production.

The model proposed in this manuscript is a general model of Jiaxu Li and Yang Kuang in [15]. The incorporation of time delay is well-analyzed in [15] by Jiaxu Li and Yang Kuang. In our model, as in [16] and [14], the delay is modeled by using a Michaelis-Menten form. Also, at time t, the effective insulin secretion is controlled by glucose concentrations in τ_i (in minutes) before time t, rather than the average amount in that period. More precisely, we consider the following system which representing the time evolution of the concentrations of glucose and insulin in the blood.

$$\begin{aligned} x'(t) &= -\psi(x(t)) - \xi(x(t), y(t-\tau_i)) + p_7, \\ y'(t) &= -\sigma(y(t)) + \varphi(x(t-\tau_g)). \end{aligned} \tag{2.2}$$

$x(0) = x_b + b_0$, $y(0) = y_b + b_0 b_3$, $x(t) = x_b$, for $t \in [-\max\{\tau_i, \tau_g\}, 0)$.

The functions ψ, ξ, σ, and φ all meet the following conditions:

(i) $\psi(0) = 0$, $\psi(\infty) = \infty$, $0 < \psi'(x) < \infty$,

(ii) $\xi(0,0) = 0$, $\xi_x(x,y) > 0$, $\xi_y(x,y) > 0$, $\xi(x,0) = 0$, $\xi(0,y) = 0$, $\xi(\infty, y) < \infty$, $\xi(x, \infty) = \infty$, if $x \neq 0$,

(iii) $\sigma(0) = 0$, $\sigma(\infty) = \infty$, $\sigma'(x) > 0$,

(iv) $\varphi(x) = 0$, if and only if $x = 0$, $\varphi(x(t-\tau_g)+\varphi_t)) > \varphi(x(t-\tau_g))$ for $\varphi_t \in C[-\max\{\tau_i, \tau_g\}, 0]$ with $\varphi_t(\theta) > 0$, $\theta \in C[-\max\{\tau_i, \tau_g\}, 0]$.

(v) $\varphi(x(t), y(t-\tau_i)+\varphi_t)) > \varphi(x(t), y(t-\tau_i))$ for $\varphi_t \in C[-\max\{\tau_i, \tau_g\}, 0]$ with $\varphi_t(\theta) > 0$, $\theta \in C[-b_5, 0]$, and $\xi(x, \infty) = \infty$, when $x \neq 0$.

Assume that (2.1) possesses a unique equilibrium point $E^* = (x^*, y^*)$ in $R_+^2 = \{(x, y) : x > 0, y > 0\}$. We propose the following specific model of glucose-insulin interaction for convenience of analysis and applications.

$$\begin{aligned} x'(t) &= -p_1 x(t) - \frac{p_4 y(t-\tau_i) x(t)}{\beta x(t) + 1} + p_7, \\ y'(t) &= p_6 x(t-\tau_g) - p_2 y(t), \end{aligned} \tag{2.3}$$

with $x(0) = x_b + p_0$, $y(0) = y_b + p_0 p_3$, $x_k = x_b$, for $t \in [-\max\{\tau_i, \tau_g\}, 0)$.

In this paper, based on the Intra-Venous Glucose Tolerance Test with two-time delays, we introduced a second delay and established a general mathematical model of glucose-insulin of modeling (2.1). Also, this studies focused on analytical studies, bifurcation analysis, and well-designed numerical simulations of the proposed model. Analytically, the system's linearisation is investigated, and conditions for global stability are determined using a linear matrix inequality (LMI) approach. We also explaining the impact using data from a clinical study. Detailed local and global stability studies are performed. The bifurcation diagrams produced from our extensive and carefully prepared simulations complement and confirm these analytical results. Also, one of our aim is to see if and how the model admits a globally asymptotically stable steady state, and to see if and how this depends on the functions used and how delay is incorporated. The findings show that both of these time delays are required for the maintenance of insulin secretion ultradian oscillations, with only a moderate glucose infusion rate and insulin breakdown rate able to maintain the oscillations continuing. The numerical diagrams are used to represent the analytic results.

3 Properties of the solutions

As in [15], one obtains the following preliminary results. We can show that system (2.2) has a unique steady state $E^* = (x^*, y^*)$. Note that $E^* = (x^*, y^*)$ are independent of τ_i, τ_g.

Proposition 1. *Let x^* be the unique solution of equation*

$$\begin{aligned} K(x) &= b - \psi(x) - \xi(x, \sigma^{-1}(\varphi(x))) = b > 0, \\ y^* &= \sigma^{-1}(\varphi(x^*)). \end{aligned} \tag{3.1}$$

Then, the model (2.2) has an unique positive steady state $E^* = (x^*, y^*)$.

Proof. We only need to show that Equation (2.2) has a single root in $(0, \infty)$. Take note of the fact that $\psi'(x) > 0$, $\xi_x(x, y) > 0$, $\xi_y(x, y) > 0$, then $K'(x) < 0$.

Also, we have

$$K(0) = b - \psi(0) - \xi(0, \sigma^{-1}(\varphi(0))) = 0,$$
$$\lim_{x \longrightarrow \infty} K(x) = b - \lim_{x \longrightarrow \infty} \psi(x) - \lim_{x \longrightarrow \infty} \xi(x, \sigma^{-1}(\varphi(x))) < 0,$$

so the proof is completed. □

Remark 1. Since $x^* > 0$ and $y^* > 0$ are always positive and all the parameters are positive, the interior-equilibrium point $E^* = (x^*, y^*)$

$$E^* = \left(\frac{(\beta p_2 p_7 - p_1 p_2) \pm \sqrt{(\beta p_2 p_7 - p_1 p_2)^2 + 4 p_2 p_7 (\beta p_1 p_2 + p_4 p_6)}}{2(\beta p_1 p_2 + p_4 p_6)}, \frac{p_6}{p_2} x^* \right)$$

of system (2.2) exists unconditionally.

Proposition 2. *[15] All of the model's (2.2) solutions exist and are bounded.*

Proof. Let $(x(t), y(t))$ be a solution of system (2.2). The boundedness of $x(t)$ can be obtained in the following sense. The first equation of (2.2) yields

$$x'(t) = b - \psi(x(t)) - \xi(x(t), y(t - \tau_i)) \leq b - \psi(x(t)).$$

Thus, by choosing $M_x = \max\,\{x_b + b_0, \psi^{-1}(b)\}$, $x(t)$ is bounded for all t. The second equation of the system (2.2) yields

$$y'(t) = -\sigma(y(t)) + \varphi(x(t - \tau_g)) \leq -\sigma(y(t)) + \varphi(M_x).$$

Thus, by choosing $M_y = \max\,\{y_b + b_3 b_0, \sigma^{-1}(\varphi(M_x))\}$, $y(t)$ is bounded for all t. The statement of boundedness implies that there are solutions for all $t > 0$. Thus the proof follows. □

Proposition 3. *[15] All of the model's (2.2) solutions are strictly positive for all $t > 0$.*

Proof. For all x, y, one obtains $|\psi'(x)|$, $|\xi_x(x, y)|$, $|\xi_y(x, y)|$, and $|\sigma'(x)|$ are bounded, Lipschitz, and completely continuous. Assume that $\varphi(x)$ is Lipschitz for $x \geqslant 0$, and $\varphi(x(\bar{t}_0 - \tau_g))$ is Lipschitz in $C[-\max\{\tau_i, \tau_g\}, 0]$. According to Proposition 1, for any $t \geqslant 0$, the solution of system (2.2) with the given initial condition exists and is unique. If $t_0 > 0$, then $x(t_0) = 0$ and $x(t_0) > 0$ are true for $t < t_0$. At t_0, since $\psi(0) = \xi(0, y) = 0$, the glucose equation becomes

$$x'(t) = -\psi(x(t_0)) - \xi(x(t_0), y(t_0 - \tau_i)) + b = b > 0.$$

Thus, for every $t > 0$, $x(t) \geqslant 0$. Similarly, if $\bar{t}_0 > 0$ exists, then $y(\bar{t}_0) = 0$ and $y(\bar{t}_0) > 0$ for $t < \bar{t}_0$. However, at $\bar{t}_0$, due to the assumptions that $\sigma(0) = 0$ and since $x(\bar{t}_0 + \theta - \tau_g) > 0$, for $\vartheta \in [-\max\{\tau_i, \tau_g\}, 0]$, $\varphi(x(\bar{t}_0 - \tau_g)) > 0$. However, the insulin equation at $\bar{t}_0$ becomes

$$y'(\bar{t}_0) = -\sigma(y(\bar{t}_0)) + \varphi(x(\bar{t}_0 - \tau_g)) = \varphi(x(\bar{t}_0 - \tau_g)) > 0.$$

Thus $y(t) \geqslant 0$, for all $t > 0$. □

These quantities are all finite according to Propositions 1–2.

Lemma 1. *[11] Consider the differentiable function $\psi : \mathbf{R} \longrightarrow \mathbf{R}$. If*

$$l = \lim_{t\longrightarrow\infty} \inf \psi(t) < \lim_{t\longrightarrow\infty} \sup \psi(t) = L,$$

then, for all k, there exist two sequences $\{t_k\} \uparrow \infty$ and $\{s_k\} \uparrow \infty$ satisfy

$$\psi'(t_k) = 0, \quad \psi'(s_k) = 0, \quad \lim_{k\longrightarrow\infty} \psi(t_k) \quad = L, \quad \lim_{k\longrightarrow\infty} \psi(s_k) = l.$$

Denote

$$\overline{x}= \lim_{t\longrightarrow\infty} \sup x(t), \;\; \underline{x}= \lim_{t\longrightarrow\infty} \inf x(t), \;\; \overline{y} = \lim_{t\longrightarrow\infty} \sup y(t), \;\; \underline{y} = \lim_{t\longrightarrow\infty} \inf y(t).$$

Proposition 4. *[15] All of the model's (2.2) solutions are uniformly bounded from above and below at some point.*

Proof. By Lemma 1, if $\underline{y} < \overline{y}$, then there are two sequences $\{t_k\} \uparrow \infty$, $\{s_k\} \uparrow \infty$ satisfies

$$y'(t_k) = 0, \qquad y'(s_k) = 0, \quad \lim_{k\longrightarrow\infty} y(t_k) \quad = \overline{y}, \quad \lim_{k\longrightarrow\infty} y(s_k) = \underline{y}.$$

As a result, the first equation (2.2) yields

$$0 = y'(t_k) = -\sigma(I(t_k)) + \varphi(x(t_k - \tau_g)), \text{ for all } k > k_0.$$

If $\nu > 0$ is an arbitrary constant, there exists $\delta_1 > 0$ satisfies

$$\begin{aligned} x(t - \tau_g) &\leq \overline{x} + \nu, \quad \text{for all } t \geq \delta_1, \\ y(t) &< \overline{y} + \nu, \quad \text{for all } t \geq \delta_1. \end{aligned}$$

Also, there exists an integer $k_0 > 0$ satisfies

$$\begin{aligned} x(t_k - \tau_g) &\leq \overline{x} + \nu, \quad \text{for all } k \geq k_0, \quad t_k \geq \delta_1, \\ y(t_k) &< \overline{y} + \nu, \quad \text{for all } k \geq k_0, \quad t_k \geq \delta_1. \end{aligned}$$

Hence, for sufficiently large k, and since p is increasing, one obtains

$$0 = -\sigma(y(t_k)) + \varphi(y(t_k - \tau_g)) \leq -\sigma(y(t_k)) + \varphi(\overline{x} + \nu).$$

Letting $k \longrightarrow \infty$ and then $\nu \longrightarrow 0$,

$$\sigma(\overline{y}) \leq \varphi(\overline{x}). \tag{3.2}$$

Also, by using the sequence s_k, one can show that

$$\sigma(\underline{y}) \geq \varphi(\underline{x}). \tag{3.3}$$

By combining (3.2) and (3.3), one obtains

$$\varphi(\underline{x}) \leq \sigma(\underline{y}) < \sigma(\overline{y}) \leq \varphi(\overline{x}), \;\; \sigma^{-1}(\varphi(\underline{x})) \leq \underline{y} < \overline{y} \leq \sigma^{-1}(\varphi(\overline{x})). \tag{3.4}$$

If $\underline{x} < \overline{x}$ then from Lemma 1, there are two sequences $\{\check{t}_\kappa\} \uparrow \infty$, $\{\check{s}_k\} \uparrow \infty$ satisfy

$$x'(\check{t}_k) = 0, \quad x'(\check{s}_k) = 0, \quad \lim_{k \longrightarrow \infty} x(\check{t}_k) \quad = \overline{x}, \quad \lim_{k \longrightarrow \infty} x(\check{s}_k) = \underline{x},$$

for all k. Then, the first equation of (2.2) yields

$$0 = x'(\check{t}_k) = -\psi(x(\check{t}_k)) - \xi(x(t_k), y(\check{t}_k - \tau_i)) + b,$$
$$0 = x'(\check{s}_k) = -\psi(x(\check{s}_k)) - \xi(x(s_k), y(\check{s}_k - \tau_i)) + b.$$

Let $\nu > 0$. Then there exists $\delta_2 > 0$ satisfies,

$$y(t) \leq \overline{y} + \nu, \qquad \text{for all } t \geq \delta_2.$$

For a sufficiently large k, $\check{s}_k - \tau_i \geq \delta_2$ and therefore

$$y(\check{s}_k - \tau_i) \geq \underline{y} + \nu.$$

Notice that ψ, ξ are continuous functions and for all $x > 0$, we have $\xi(x, y) > 0$. Without loss of generality, assume that $\lim_{k \longrightarrow \infty} y(\check{t}_k)$ and $\lim_{k \longrightarrow \infty} I(\check{s}_k - \tau_i)$ exist. Letting $k \longrightarrow \infty$ and then $\nu \longrightarrow 0$,

$$\begin{aligned} 0 = x'(\check{s}_k) &= \lim_{k \longrightarrow \infty} (-\psi(x(\check{s}_k)) - \xi(x(\check{s}_k), y(\check{s}_k - \tau_i))) + b \geq -\psi(\underline{x}) - \xi(\underline{x}, \overline{y}) + b, \\ 0 = x'(\check{t}_k) &= \lim_{k \longrightarrow \infty} (-\psi(x(\check{t}_k)) - \xi(x(\check{t}_k), I(\check{t}_k - \tau_i))) + b \leq -\psi(\overline{x}) - \xi(\overline{x}, \underline{y}) + b. \end{aligned} \tag{3.5}$$

Since $(x(t), y(t))$ is a solution of (2.2), then by using (3.5), one obtains

$$x'(t) = b - \psi(x(t)) - \xi(x(t_0), y(t - \tau_i)) \leq b - \psi(x(t)).$$

Using (3.5) and Lemma 1, one can obtain that $\overline{x} \leq \psi^{-1}(b)$, with $\overline{x} = \limsup_{t \longrightarrow \infty} x(t)$. Therefore,

$$\psi(\underline{x}) + \xi(\underline{x}, \sigma^{-1}(\varphi(\psi^{-1}(b)))) \geq \psi(\underline{x}) + \xi(\underline{x}, \sigma^{-1}(\varphi(\overline{x})),$$

which imply that $\underline{x} > 0$. Thus, the model (2.2) is uniformly persistent from Lemma 1. □

4 Global stability

We present some global stability results for the steady state $E^* = (x^*, y^*)$ in this section, as presented by [7] and [13].

Theorem 1. *[15] Let $E^* = (x^*, y^*)$ be the unique equilibrium point of system (2.2). For all $x \geq y > 0$, if the following condition*

$$\xi(x, \sigma^{-1}(\varphi(y))) - \xi(y, \sigma^{-1}(\varphi(x))) \geq 0$$

holds for a system (2.2), then $E^* = (x^*, y^*)$ is globally asymptotically stable.

Proof. If $\underline{y} < \overline{y}$, we have from (3.5) that

$$\varphi(\underline{x}) \le \sigma(\underline{y}) < \sigma(\overline{y}) \le \varphi(\overline{x}), \quad \sigma^{-1}(\varphi(\underline{x})) \le \underline{y} < \overline{y} \le \sigma^{-1}(\varphi(\overline{x})).$$

Then, if $\underline{x} < \overline{x}$, one obtains

$$-\psi(\underline{x}) - \xi(\underline{x}, \sigma^{-1}(\varphi(\overline{x}))) + b \leqslant -\psi(\underline{x}) - \xi(\underline{x}, \overline{y})) + b \leqslant 0,$$
$$-\psi(\overline{x}) - \xi(\overline{x}, \sigma^{-1}(\varphi(\underline{x}))) + b \geqslant -\psi(\overline{x}) - \xi(\overline{x}, \underline{y})) + b \geqslant 0.$$

Thus,

$$(\psi(\overline{x}) - \psi(\underline{x})) + \xi(\overline{x}, \sigma^{-1}(\varphi(\underline{x}))) - \xi(\underline{x}, \sigma^{-1}(\varphi(\overline{x}))) \leqslant 0.$$

From (3.1), one obtains

$$\xi(\overline{x}, \sigma^{-1}(\varphi(\underline{x}))) - \xi(\underline{x}, \sigma^{-1}(\varphi(\overline{x}))) \geqslant 0.$$

Thus, $\psi(\overline{x}) - \psi(\underline{x}) \leqslant 0$, that is $\underline{x} = \overline{x}$ which imply $\underline{y} = \overline{y}$. Since the only equilibrium point of system (2.2) is (x^*, y^*), then we have

$$x^* = \lim_{t \longrightarrow \infty} x(t), \qquad y^* = \lim_{t \longrightarrow \infty} y(t).$$

Therefore, the proof follows. □

Theorem 2. *[15] For all $x \ge y > 0$, If $E^* = (x^*, y^*)$ is the unique equilibrium point of system (2.2) and if the following condition*

$$\psi'(x) + \xi_x(x, \sigma^{-1}(\varphi(y))) - \xi_y(x, \sigma^{-1}(\varphi(y))) \frac{\varphi'(y)}{\sigma'(\sigma^{-1}(\varphi(y)))} \ge 0$$

holds for a system (2.2), then $E^* = (x^*, y^*)$ is globally asymptotically stable.

Proof. If $\underline{y} < \overline{y}$, then from (3.5), one obtains

$$\sigma^{-1}(\varphi(\underline{x})) \le \underline{y} < \overline{y} \le \sigma^{-1}(\varphi(\overline{x})).$$

Then, if $\underline{x} < \overline{x}$, one obtains

$$-\psi(\overline{x}) - \xi(\overline{x}, \sigma^{-1}(\varphi(\underline{x}))) + b \geqslant -\psi(\overline{x}) - \xi(\overline{x}, \underline{y})) + b \geqslant 0.$$

Thus,

$$(\psi(\overline{x}) - \psi(\underline{x})) + \xi(\overline{x}, \sigma^{-1}(\varphi(\underline{x}))) - \xi(\underline{x}, \sigma^{-1}(\varphi(\overline{x}))) \leqslant 0.$$

For all $(x, y) \in \mathbb{R}^2_+ = \{(x, y) : x > 0,\ y > 0\}$, one assume that

$$\Lambda(x, y) = \psi(x) + \xi(x, \sigma^{-1}(\varphi(y))).$$

Then (3.3) is equivalent to

$$\psi(\overline{x}, \underline{x}) - \psi(\underline{x}, \overline{x}) \leqslant 0.$$

By applying the mean value theorem, there exists a $\vartheta \in (0, 1)$ satisfies

$$\psi(\overline{x}, \underline{x}) - \psi(\underline{x}, \overline{x}) = (\overline{x} - \underline{x})(\Lambda_x(\xi, \xi) - \Lambda_y(\xi, \xi)),$$

where $\xi \cong \underline{x} + \vartheta(\overline{x} - \underline{x})$ and $\xi \cong \overline{x} - \vartheta(\overline{x} - \underline{x})$. Since

$$\Lambda_x(x,y)=\psi'(x)+\xi_x(x,\sigma^{-1}(\varphi(y))),\ \Lambda_y(x,y)=\xi_y(x,\sigma^{-1}(\varphi(y)))\frac{\varphi'(y)}{\sigma'(\sigma^{-1}(\varphi(y)))}.$$

Then, Equation (3.2) yields

$$\Lambda_x(x,y)-\Lambda_y(x,y)=\psi'(x)+\xi_x(x,\sigma^{-1}(\varphi(y))) - \frac{\xi_y(x,\sigma^{-1}(\varphi(y)))\varphi'(y)}{\sigma'(\sigma^{-1}(\varphi(y)))} \geq 0, \tag{4.1}$$

Also, Equations (3.4) and (3.5) imply that

$$(\overline{x} - \underline{x})(\Lambda_x(\xi,\xi) - \Lambda_y(\xi,\xi)) \leqslant 0.$$

Also, Equation (4.1) yields $\overline{x} - \underline{x} \leqslant 0$, which imply that $\overline{x} = \underline{x}$ and $\overline{y} = \underline{y}$. Since (x^*, y^*) is the only equilibrium point of system (2.2), one obtains

$$(x(t), y(t)) \longrightarrow (x^*, y^*) \quad \text{as } t \longrightarrow \infty.$$

This complete the proof. □

Theorem 3. *[15] Assume that $\xi(x,y) = \xi_1(x,y)/\xi_2(x)$ for model (2.3), where ξ_1, ξ_2 satisfy the following conditions:*
(i) $\xi_1(0,0) = 0$, $\xi_1(x,0) = \xi_1(0,y) = 0$,
(ii) for all $x > 0$ and $y > 0$, $\xi_2(x) \geqslant c > 0$, for some constant c, $\xi_2(\infty) = \infty$,
(iii) for all $x > 0$ and $y > 0$, $(\xi_1)_x(x,y) > 0$, $(\xi_1)_y(x,y) > 0$,
(iv) for all $x > 0$ and $y > 0$, $\xi_1(x,\infty) = \xi_1(\infty,y) = \infty$,
(v) for all $x > 0$, $\xi_2'(x) > 0$.
Then, (x^*, y^*) is globally asymptotically stable if
(a) $\xi_1(x,\sigma^{-1}(\varphi(y))) - \xi_1(y,\sigma^{-1}(\varphi(x))) \geq 0$, for all $x \geqslant y > 0$,
(b) $(\psi(x) - b)\xi_2(x)$ is increasing for all $x > 0$.

Proof. We will show that $\overline{x} = \underline{x}$ and $\overline{y} = \underline{y}$. If $\underline{y} < \overline{y}$, then $\underline{x} < \overline{x}$ and

$$\sigma^{-1}(\varphi(\underline{x})) \leq \underline{y} < \overline{y} \leq \sigma^{-1}(\varphi(\overline{x})),\ -\psi(\underline{x}) - \xi_1(\underline{x},\sigma^{-1}(\varphi(\overline{x})))/\xi_2(\underline{x}) + b \leqslant 0,$$
$$-\psi(\overline{x}) - \xi_1(\overline{x},\sigma^{-1}(\varphi(\underline{x})))/\xi_2(\overline{x}) + b \geqslant 0.$$

Thus,

$$-(\psi(\underline{x}) - b)\xi_2(\underline{x}) - \xi_1(\underline{x},\sigma^{-1}(\varphi(\overline{x}))) \leqslant 0,$$
$$-(\psi(\overline{x}) - b)\xi_2(\overline{x}) - \xi_1(\overline{x},\sigma^{-1}(\varphi(\underline{x}))) \geqslant 0.$$

Hence,

$$((\psi(\overline{x})-b)\xi_2(\overline{x})-(\psi(\underline{x})-b)\xi_2(\underline{x}))+(\xi_1(\overline{x},\sigma^{-1}(\varphi(\underline{x})))-\xi_1(\underline{x},\sigma^{-1}(\varphi(\overline{x}))))\leqslant 0.$$

This, together with assumptions (a) and (b), yields

$$(\psi(\overline{x}) - b)\xi_2(\overline{x}) - (\psi(\underline{x}) - b)\xi_2(\underline{x}) = 0.$$

Which leads to $\overline{x} = \underline{x}$ and $\overline{y} = \underline{y}$. □

Corollary 1. [15] If $\xi(x,y) = \xi_1(x,y)/\xi_2(x)$ satisfies the assumption (i)–(v) of Theorem 3 and if (a) in Theorem 3 is replaced by

$$(a')\ \frac{\partial}{\partial x}\xi_1(x,\sigma^{-1}(\varphi(y))) - \frac{\partial}{\partial y}\xi_1(x,\sigma^{-1}(\varphi(y)))\frac{\varphi'(y)}{\sigma'(\sigma^{-1}(\varphi(y)))} \geq 0,$$

for all $x, y > 0$. Then, $E^* = (x^*, y^*)$ is globally asymptotically stable.

Proof. To prove this result, we need to show only that (a) in Theorem 3 is true when (a') holds. Let $u(x,y) = \xi_1(x,\sigma^{-1}(\varphi(y)))$. By applying the mean value theorem, there exists a $\vartheta \in (0,1)$ satisfies

$$u(x,y) - u(x,y) = (x-y)(u_x(\xi,\xi) - u_y(\xi,\xi)) = (x-y) \geqslant 0,$$

where $\xi \cong y + \vartheta(x-y)$ and $\xi \cong x - \vartheta(x-y)$. The proof follows. □

Corollary 2. [15] If $\beta \geqslant \gamma = \frac{p_4 p_6}{p_2}$ or $\beta \geqslant \sigma = \frac{p_1}{p_7}$ in (2.2), the only equilibrium point $E^* = (x^*, y^*)$ of (2.2) is globally asymptotically stable.

Proof. If $\beta \geqslant \gamma$, applying Theorem 2 to model (2.2) leads to

$$\psi'(x)+\xi_x(x,\sigma^{-1}(\varphi(y)))-\xi_y(x,\sigma^{-1}(\varphi(y)))\frac{\varphi'(y)}{\sigma'(\sigma^{-1}(\varphi(y)))} = p_1+\frac{p_4(p_6/p_2)y}{(\beta x+1)^2}$$
$$-\frac{p_4 x}{\beta x+1}\frac{p_6}{p_2} \geqslant p_1\Big(1-\frac{\gamma x}{\beta x+1}\Big) = p_1\frac{(\beta-\gamma)x+1}{\beta x+1} > 0, \text{ for } x > 0.$$

If $\beta \geqslant \sigma = p_1/p_7$, applying Theorem 3 to model (2.2) leads to

$$\frac{d}{dx}(\psi(x)-b)\xi_2(x) = \frac{d}{dx}(p_1 x - p_7)(\beta x+1) = 2p_1\beta x + (p_1 x - p_7) > 0,$$

for $x > 0$. □

Corollary 3. If $\sigma \geqslant \gamma$ in (2.2), then $E^* = (x^*, y^*)$ of (2.2) is globally asymptotically stable for $\beta \geqslant 0$.

5 Local stability and Hopf bifurcation

Lemma 2 [[12] (Theorem 3.1, page 77)]. *In the following delay differential equation, assume a_1, a_2, and $a_3 > 0$.*

$$y''(t) + a_1 y'(t) + a_2 y(t) + a_3 y(t-\tau) = 0, \quad \tau \geq 0, \tag{5.1}$$

then the characteristic equation's number of pairs of pure imaginary roots of

$$\lambda^2 + a_1\lambda + a_2 + a_3 e^{-\tau\lambda} = 0, \quad \tau \geq 0$$

can be zero, one, or two only.

Corollary 4. (i) If $2a_2 - a_1^2 < 2\sqrt{a_2^2 - a_3^2}$ with $a_2 > a_3$, then for $\tau > 0$ the number of such roots is zero. Also, for all $\tau > 0$, the trivial solution of (5.1) is stable.

(ii) If $a_2 < a_3$ or $a_3 = a_2$ and $2a_2 - a_1^2 > 0$, then for some $\tau > 0$ the number of such roots is one. Also, for $\tau < \tau_0$, the trivial solution of (5.1) is uniformly asymptotically stable, and for $\tau > \tau_0$ it becomes unstable, where τ_0 is a constant. Moreover, it undergoes a supercritical Hopf bifurcation at $\tau = \tau_0$.

(iii) If $2a_2 - a_1^2 > 2\sqrt{a_2^2 - a_3^2}$ with $a_2 > a_3$, then for $\tau > 0$ the number of such roots is two. Moreover, as τ increases, the stability of the trivial solution of (5.1) can change a finite number of times at most, and it eventually becomes unstable.

We'll now linearize the model (2.2). Let

$$x_1(t) = x(t) - x^*, \quad y_1(t) = x(t) - y^*,$$

then model (2.2) becomes

$$\begin{aligned} x_1'(t) &= -\psi(x_1(t) + x^*) - \xi(x(t) + x^*, y_1(t - \tau_i) + y^*) + b, \\ y_1'(t) &= -\sigma(y_1(t) + y^*) + \varphi(x_1(t - \tau_g) + x^*). \end{aligned}$$

Thus the linearized model of (2.2) about $E^* = (x^*, y^*)$ may be rewritten as:

$$x'(t) = -A_1 x(t) - A_2 y(t - \tau_i), \quad y'(t) \quad = A_3 x(t - \tau_g) - A_4 y(t),$$

where $A_1 = \psi'(x^*) + \xi_x(x^*, y^*)$, $A_2 = \xi_y(x^*, y^*)$, $A_3 = \varphi'(x^*)$, $A_4 = \sigma'(y^*)$. In matrix form, the linearization of (2.3) at $E^* = (x^*, y^*)$ is given by

$$\begin{bmatrix} x'(t) \\ y'(t) \end{bmatrix} = \begin{bmatrix} -A_1 & 0 \\ 0 & -A_4 \end{bmatrix} \begin{bmatrix} x(t) \\ y(t) \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ A_3 & 0 \end{bmatrix} \begin{bmatrix} x(t-\tau_g) \\ I(t-\tau_g) \end{bmatrix} + \begin{bmatrix} 0 & -A_2 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \xi(t-\tau_i) \\ y(t-\tau_i) \end{bmatrix}. \tag{5.2}$$

Its Jacobian matrix $J(E^*)$ at $E^* = (x^*, y^*)$ is given by

$$J(E^*) = \begin{bmatrix} -A_1 & -A_2 e^{-\tau_i \lambda} \\ A_3 e^{-\tau_g \lambda} & -A_4 \end{bmatrix}.$$

The eigenvalues are given by

$$\lambda^2 + p\lambda + r + q e^{-\lambda(\tau_g + \tau_i)} = 0, \tag{5.3}$$

where $p = A_1 + A_4$, $q = A_2 A_3$, $r = A_1 A_4$. For $\tau = \tau_g + \tau_i$, Equation (5.3) becomes

$$\lambda^2 + p\lambda + r + q e^{-\lambda\tau} = 0. \tag{5.4}$$

If the characteristic Equation (5.4) has a root $\lambda = i\omega (\omega > 0)$, then one obtains

$$q \sin \omega \tau = p \omega, \quad q \cos \omega \tau = \omega^2 - r,$$

which implies that

$$\omega^4 + (p^2 - 2r)\,\omega^2 + r^2 - q^2 = 0. \tag{5.5}$$

If the condition

$$p^2 - 2r > 0, \;\; r^2 - q^2 > 0 \tag{5.6}$$

holds, then Equation (5.6) has no positive roots. As a result, when $\tau \in [0, +\infty)$ meets the conditions, all roots of (5.5) have negative real parts (5.6). If

$$r^2 - q^2 < 0, \;\; p^2 - 2r > 0$$

hold, then Equation (5.5) has a unique positive root ω,

$$\omega^* = \frac{1}{\sqrt{2}}\sqrt{-(p^2 - 2r) \pm \sqrt{p^4 - 4rp^2 + 4q^2}}.$$

The corresponding critical value τ_n^* of the delay is

$$\tau_n^* = \frac{1}{\omega^*}\arccos\left(\frac{(\omega^*)^2 - r}{q}\right) + \frac{2n\pi}{\omega^*}, \;\; n = 0, \pm 1, \pm 2, ...$$

If $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$ is a root of (5.4) close to $\tau = \tau^*$ sa that $\alpha(\tau^*) = 0$ and $\omega(\tau^*) = \omega^*$. When $\lambda(\tau)$ is substituted into (5.4) and by differentiate with respect to τ, the result is

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{(2\lambda + p)e^{-\lambda\tau}}{2d\lambda} - \frac{\tau}{\lambda},$$

which leads to

$$\left[\frac{d(Re\lambda(\tau))}{d\tau}\right]^{-1}_{\tau_g = \tau_{1n}} = \left[\frac{(2\lambda + p)e^{\lambda\tau}}{2d\lambda}\right]_{\tau = \tau_n} = \frac{p^2 - 2r + 2\omega^2}{2d^2} > 0.$$

Noting that

$$\text{sign}\left[\frac{d(Re\lambda)}{d\tau_g}\right]_{\tau = \tau_n} = \text{sign}\left[Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\right]_{\tau = \tau_n} = 1,$$

one obtains

$$\frac{d(Re\lambda)}{d\tau}|_{\tau = \tau_n} > 0.$$

As a result of the transversability condition, Hopf bifurcation occurs at $\tau = \tau_n$. As a result, we can obtain the following theorem via Kuang [12]:

Theorem 4. *If $\tau = \tau_g + \tau_i$ with $r < q$. Then, for $\tau < \tau_n^*$, E^* is asymptotically stable and unstable for $\tau > \tau_n^*$. Furthermore, when $\tau = \tau_n^*$, (2.2) undergoes a Hopf bifurcation at E^*.*

Corollary 5. If $\tau_i = 0, \tau_g > 0$ with $r < q$ and $E^* = (x^*, y^*)$ is the positive unique equilibrium point of the system (2.2). Then, for $\tau_g < \tau_g^*$, E^* is asymptotically stable and unstable for $\tau_g > \tau_g^*$. Furthermore, when $\tau_g = \tau_g^*$, (2.2) undergoes a Hopf bifurcation at $E^* = (x^*, y^*)$, where

$$\tau_g^* = \frac{1}{\omega^*}\arccos\left(\frac{(\omega^*)^2 - r}{q}\right).$$

Corollary 6. If $\tau_g = 0, \tau_i > 0$ with $r < q$ and E^* is the positive unique equilibrium point of the system (2.2). Then, for $\tau_i < \tau_i^*$, E^* is asymptotically stable and unstable for $\tau_i > \tau_i^*$. Furthermore, when $\tau_i = \tau_i^*$, (2.2) undergoes a Hopf bifurcation at E^*, where

$$\tau_i^* = \frac{1}{\omega^*} \arccos\left(\frac{(\omega^*)^2 - r}{q}\right).$$

Corollary 7. For $\tau_g = \tau_i = \tau \neq 0$ with $r < q$, E^* is asymptotically stable if $\tau < \tau^\bullet$ and unstable if $\tau > \tau^\bullet$. Moreover, when $\tau = \tau^\bullet$, (2.2) undergoes a Hopf bifurcation at E^*, where

$$\tau^\bullet = \frac{1}{2\omega^*} \arccos\left(\frac{(\omega^*)^2 - r}{q}\right).$$

Theorem 5. *If $\tau_g > 0$, $\tau_i \in [0, \tau_{i_0})$ with $r < q$, E^* is asymptotically stable for $\tau_g \in [0, \tau_g^\bullet)$. If $\tau_g = \tau_g^\bullet$ and a set of periodic solutions bifurcate from $E*$, system (2.2) undergoes a Hopf bifurcation at $E*$, where*

$$\tau_g^\bullet = \frac{1}{\omega_0} \arcsin\left(\frac{E_1 k_3 + E_2(k_2 - k_1)}{E_1^2 + E_2^2}\right) + \frac{2n\pi}{\omega_0}, \quad n = 0, \pm 1, \pm 2, ...,$$

$E_1 = q \cos \omega \tau_i$, $E_2 = q \sin \omega \tau_i$, $k_1 = \omega^2$, $k_2 = r$, $k_3 = p\omega$.

Proof. We consider Equation (5.3) with $\tau_i \in [0, \tau_{i_0})$ and τ_g is considered as the bifurcation parameter. If the characteristic Equation (5.3) has a root of $\lambda = i\omega(\omega > 0)$, one gets

$$E_1 \cos \omega \tau_g - E_2 \sin \omega \tau_g = k_1 - k_2, \quad E_1 \sin \omega \tau_g + E_2 \cos \omega \tau_g = k_3. \tag{5.7}$$

Equation (5.7) is simplified to give

$$\tau_g^\bullet = \frac{1}{\omega_0} \arcsin\left(\frac{E_1 k_3 + E_2(k_2 - k_1)}{E_1^2 + E_2^2}\right) + \frac{2n\pi}{\omega_0}, \quad n = 0, \pm 1, \pm 2, ...,$$

Differentiating Equation (5.3) with respect to τ_g, we obtain

$$[2\lambda + p - \varphi(\tau_g + \tau_i)e^{-\lambda(\tau_g + \tau_i)}]\frac{d\lambda}{d\tau_g} = \lambda q e^{-\lambda(\tau_g + \tau_i)}.$$

Thus,

$$\left(\frac{d\lambda}{d\tau_g}\right)^{-1} = \frac{2\lambda + p - \varphi(\tau_g + \tau_i)e^{-\lambda(\tau_g + \tau_i)}}{\lambda q e^{-\lambda(\tau_g + \tau_i)}} = \frac{2\lambda + p}{\lambda q e^{-\lambda(\tau_g + \tau_i)}} - \frac{\tau_g + \tau_i}{\lambda}.$$

Thus,

$$Re\,[d\lambda/d(\tau_g)]^{-1} \neq 0.$$

Therefore, Hopf bifurcation occurs at $\tau_g = \tau_g^\bullet$. $\square$

Theorem 6. *If $\tau_i > 0$, $\tau_g \in [0, \tau_{g_0})$, with $r < q$ and if E^* is the positive unique equilibrium point of the system (2.2), then for $\tau_i \in [0, \tau_i^\bullet)$, E^* is asymptotically stable. System (2.2) undergoes a Hopf bifurcation at E^* when $\tau_i = \tau_i^\bullet$, and a family of periodic solutions bifurcates from E^*, where*

$$\tau_i^\bullet = \frac{1}{\omega^*} \arccos\left(\frac{F_2 k_3 + F_2(k_1 - k_2)}{F_1^2 + F_2^2}\right) + \frac{2n\pi}{\omega_0}, \quad n = 0, \pm 1, \pm 2, ..., \tag{5.8}$$

where $F_1 = q \cos \omega \tau_g$, $F_2 = q \sin \omega \tau_g$.

Proof. We consider Equation (5.3) with $\tau_g \in [0, \tau_{\xi_0})$ and τ_i is considered as the bifurcation parameter. If the characteristic Equation (5.3) has a root of $\lambda = i\omega(\omega > 0)$, one gets

$$F_1 \cos \omega \tau_i - F_2 \sin \omega \tau_i = k_1 - k_2, \quad F_1 \sin \omega \tau_i + F_2 \cos \omega \tau_i = k_3. \tag{5.9}$$

Equation (5.9) is simplified to give (5.8). Differentiating Equation (5.3) with respect to τ_i, we obtain

$$[2\lambda + p - \varphi(\tau_g + \tau_i)e^{-\lambda(\tau_g+\tau_i)}]\frac{d\lambda}{d\tau_i} = \lambda q e^{-\lambda(\tau_g+\tau_i)},$$

thus

$$\left(\frac{d\lambda}{d\tau_i}\right)^{-1} = \frac{2\lambda + p - \varphi(\tau_g + \tau_i)e^{-\lambda(\tau_g+\tau_i)}}{\lambda q e^{-\lambda(\tau_g+\tau_i)}} = \frac{2\lambda + p}{\lambda q e^{-\lambda(\tau_g+\tau_i)}} - \frac{\tau_g + \tau_i}{\lambda}.$$

Thus,

$$Re\,[d\lambda/d\tau_i]^{-1} \neq 0.$$

Therefore, the transversability condition holds at $\tau_i = \tau_i^\bullet$. □

6 Local asymptotic stability

Using Linear Matrix Inequalities and the construction of an appropriate Lyapunov functional (LMIs), the boundary of the asymptotic stability region for the linear system (5.2) is investigated numerically. He et al. [10] established a method for systems of delayed differential equations with two delays, which is used here. The method relies through using free weighting matrices to represent Leibniz-Newton form relationships. If the free weighting matrices sufficient to satisfy the criteria for the set of LMIs exist, the linear system (5.2) with delays is asymptotically stable.

Theorem 7. *The system (5.2) is asymptotically stable, for given scalars $\tau_i \geq 0$ $(k = 1, 2)$, if there exist semi-positive definite symmetric matrices $\mathbb{W}_k = \mathbb{W}_k^T \geq 0$, $\mathbb{X}_k = \mathbb{X}_k^T \geq 0$, $\mathbb{Y}_k = \mathbb{Y}_k^T \geq 0$ and $\mathbb{Z}_k = \mathbb{Z}_k^T \geq 0$ $(k = 1, 2, 3)$, two positive definite symmetric matrices $P = P^T > 0$ and $Q_k = Q_k^T > 0$ $(k = 1, 2)$, and any matrices N_k, S_k, T_k $(k = 1, 2, 3)$ and $\mathbb{X}_{kj}$, $\mathbb{Y}_{kj}$, $\mathbb{Z}_{kj}$ $(1 \leq k < j \leq 3)$ satisfy the* *following LMIs*

$$\Upsilon = \begin{bmatrix} \Upsilon_{11} & \Upsilon_{12} & \Upsilon_{13} \\ \Upsilon_{12}^T & \Upsilon_{22} & \Upsilon_{23} \\ \Upsilon_{13}^T & \Upsilon_{23}^T & \Upsilon_{33} \end{bmatrix} < 0, \qquad \Psi_1 = \begin{bmatrix} \mathbb{X}_{11} & \mathbb{X}_{12} & \mathbb{X}_{13} & N_g \\ \mathbb{X}_{12}^T & \mathbb{X}_{22} & \mathbb{X}_{23} & N_i \\ \mathbb{X}_{13}^T & X_{23}^T & \mathbb{X}_{33} & N_3 \\ N_g^T & N_i^T & N_3^T & \mathbb{W}_g \end{bmatrix} \geq 0 \tag{6.1}$$

$$\Psi_2 = \begin{bmatrix} \mathbb{Y}_{11} & \mathbb{Y}_{12} & \mathbb{Y}_{13} & S_g \\ \mathbb{Y}_{12}^T & \mathbb{Y}_{22} & \mathbb{Y}_{23} & S_i \\ \mathbb{Y}_{13}^T & Y_{23}^T & \mathbb{Y}_{33} & S_3 \\ S_g^T & S_i^T & S_3^T & \mathbb{W}_i \end{bmatrix} \geq 0, \;\; \Psi_3 = \begin{bmatrix} \mathbb{Z}_{11} & \mathbb{Z}_{12} & \mathbb{Z}_{13} & kT_g \\ \mathbb{Z}_{12}^T & \mathbb{Z}_{22} & \mathbb{Z}_{23} & kT_i \\ \mathbb{Z}_{13}^T & \mathbb{Z}_{23}^T & \mathbb{Z}_{33} & kT_3 \\ \Gamma T_g^T & \Gamma T_i^T & \Gamma T_3^T & \mathbb{W}_3 \end{bmatrix} \geq 0,$$

$$\Gamma = \begin{cases} 1, & if \quad \tau_g \geq \tau_i, \\ -1, & if \quad \tau_g < \tau_i, \end{cases}$$

$$\begin{aligned}
\Upsilon_{11} &= PA_0 + A_0^T P + Q_1 + Q_2 + N_1 + N_1^T + S_1 + S_1^T + A_0^T H A_0 + \hbar_1 \mathbb{X}_{11} \\
&\quad + \hbar_2 \mathbb{Y}_{11} + |\hbar_1 - \hbar_2| \mathbb{Z}_{11}, \\
\Upsilon_{12} &= PA_1 - N_1 + N_2^T + S_2^T - T_1 + A_0^T H A_1 + \hbar_1 \mathbb{X}_{12} + \hbar_2 \mathbb{Y}_{12} + |\hbar_1 - \hbar_2| \mathbb{Z}_{12}, \\
\Upsilon_{13} &= PA_2 + N_3^T + S_3^T - S_1 + T_1 + A_0^T H A_2 + \hbar_1 \mathbb{X}_{13} + \hbar_2 \mathbb{Y}_{13} + |\hbar_1 - \hbar_2| \mathbb{Z}_{13}, \\
\Upsilon_{22} &= -Q_1 - N_2 - N_2^T - T_2 - T_2^T + \mathbb{A}_1^T H A_1 + \hbar_1 \mathbb{X}_{22} + \hbar_2 \mathbb{Y}_{22} + |\hbar_1 - \hbar_2| \mathbb{Z}_{22}, \\
\Upsilon_{23} &= -N_3^T - S_2 + T_2 - T_3^T + A_1^T H A_2 + \hbar_1 \mathbb{X}_{23} + \hbar_2 \mathbb{Y}_{23} + |\hbar_1 - \hbar_2| \mathbb{Z}_{23}, \\
\Upsilon_{33} &= -Q_2 - S_3 - S_3^T + T_3 + T_3^T + A_2^T H A_2 + \hbar_1 \mathbb{X}_{33} + \hbar_2 \mathbb{Y}_{33} + |\hbar_1 - \hbar_2| \mathbb{Z}_{33}, \\
H &= \hbar_1 \mathbb{W}_1 + \hbar_2 \mathbb{W}_2 + |\hbar_1 - \hbar_2| \mathbb{W}_3.
\end{aligned}$$

Proof. First, for the case $\tau_g \geq \tau_i$, denote by $x = [u, v]^T$ and consider the following Lyapunov functional. The Lyapunov-Krasovskii functional candidate $\mho(x(t))$ is chosen in the following form:

$$\begin{aligned}
\mho(x(t)) = & x^T(t)\, P\, x(t) + \int_{t-\tau_g}^{t} x^T(s)\, q_1\, x(s)\, ds + \int_{t-\tau_i}^{t} x^T(s)\, q_2\, x(s)\, ds \\
& + \int_{-\tau_g}^{0} \int_{t+z}^{t} x'^T(s)\, \mathbb{W}_1\, x'(s)\, ds\, dz + \int_{-\tau_i}^{0} \int_{t+z}^{t} x'^T(s)\, \mathbb{W}_2\, x'(s)\, ds\, dz \\
& + \int_{-\tau_g}^{-\tau_i} \int_{t+z}^{t} x'^T(s)\, \mathbb{W}_3\, x'(s)\, ds\, dz,
\end{aligned}$$

where $P = P^T > 0$ and $Q_k = Q_k^T > 0$ $(i = 1, 2)$, and $\mathbb{W}_k = \mathbb{W}_k^T > 0$, are to be determined. By calculating $\dot{\mho}(t)$ along the solutions of system (5.2) yields

$$\begin{aligned}
\dot{\mho}(x(t)) &= 2x^T(t)\, P\, [A_0 x(t) + A_1 x(t - \tau_g) + A_2 x(t - \tau_i)] + x^T(t)\, Q_1\, x(t) \\
&- x^T(t - \tau_g)\, Q_1\, x(t - \tau_g) + x^T(t)\, Q_2\, x(t) - x^T(t - \tau_g)\, Q_2\, x(t - \tau_i) \\
&+ \hbar_1 x'^T(t)\, \mathbb{W}_1\, x'(t) - \int_{t-\tau_g}^{t} x'^T(s)\, \mathbb{W}_1\, x'(s)\, ds + \hbar_2 x'^T(t)\, \mathbb{W}_2\, x'(t) \\
&- \int_{t-\tau_i}^{t} x'^T(s)\, \mathbb{W}_2\, x'(s)\, ds + (\hbar_1 - \hbar_2) x'^T(t)\, \mathbb{W}_3\, x'(t) - \int_{t-\tau_g}^{t-\tau_i} x'^T(s)\, \mathbb{W}_3\, x'(s)\, ds.
\end{aligned} \tag{6.2}$$

Using the Newton-Leibnitz formula, the following equations are true for any matrices N_k, S_k, and T_k $(k = 1, 2, 3)$, with appropriate dimensions,

$$\begin{aligned}
&2\left[x^T(t)\,N_1 + x^T(t-\tau_g)\,N_2 + x^T(t-\tau_i)\,N_3\right]\\
&\qquad\times\left[x(t) - x(t-\tau_g) - \int_{t-\tau_g}^{t} x'(s)\,ds\right] = 0,\\
&2\left[x^T(t)\,S_1 + x^T(t-\tau_g)\,S_2 + x^T(t-\tau_i)\,S_3\right]\\
&\qquad\times\left[x(t) - x(t-\tau_i) - \int_{t-\tau_i}^{t} x'(s)\,ds\right] = 0,\\
&2\left[x^T(t)\,T_1 + x^T(t-\tau_g)\,T_2 + x^T(t-\tau_i)\,T_3\right]\\
&\qquad\times\left[x(t-\tau_i) - x(t-\tau_g) - \int_{t-\tau_g}^{t-\tau_i} x'(s)\,ds\right] = 0.
\end{aligned} \tag{6.3}$$

While on the contrary, for any appropriately dimensioned matrices $\mathbb{X}_{jj} = \mathbb{X}_{jj}^T \geq 0$, $\mathbb{Y}_{jj} = \mathbb{Y}_{jj}^T \geq 0$ and $\mathbb{Z}_{jj} = \mathbb{Z}_{jj}^T \geq 0$ $(j = 1, 2, 3)$ and any matrices $\mathbb{X}_{kj}$, $\mathbb{Y}_{kj}$, $\mathbb{Z}_{kj}$ $(1 \leq k < j \leq 3)$, the following equation holds holds

$$\begin{bmatrix} x(t) \\ x(t-\tau_g) \\ x(t-\tau_i) \end{bmatrix}^T \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{12}^T & A_{22} & A_{23} \\ A_{13}^T & A_{23}^T & A_{33} \end{bmatrix} \begin{bmatrix} x(t) \\ x(t-\tau_g) \\ x(t-\tau_i) \end{bmatrix} = 0, \tag{6.4}$$

where $A_{kj} = \tau_\xi(\mathbb{X}_{kj} - \mathbb{X}_{kj}) + \tau_i(\mathbb{Y}_{kj} - \mathbb{Y}_{kj}) + (\tau_g - \tau_i)(\mathbb{Z}_{kj} - \mathbb{Z}_{kj})$, $1 \leq k \leq j \leq 3$. Adding the left sides of (6.3) to $\dot{\mho}(x(t))$ yields

$$\begin{aligned}
\dot{\mho}(x(t)) =&\xi_1^T(t)\,\Upsilon\,\xi_1(t) - \int_{t-\tau_g}^{t} \xi_2^T(t,s)\,\mathbb{W}_1\,\xi_2(t,s)\,ds\\
&- \int_{t-\tau_i}^{t} \xi_2^T(t,s)\,\mathbb{W}_2\,\xi_2(t,s)\,ds - \int_{t-\tau_g}^{t-\tau_i} \xi_2^T(t,s)\,\mathbb{W}_3\,\xi_2(t,s)\,ds,
\end{aligned}$$

where Υ,Ψ_k, k=1, 2, 3 (where $k = 1$ in Ψ_3) are defined in (6.1), respectively and

$$\xi_1(t) = [x^T(t) \;\; x^T(t-\tau_g) \;\; x^T(t-\tau_i)]^T, \quad \xi_2(t,s) \;\; = [\xi_1^T(t) \;\; x'^T(s)]^T.$$

If $\Upsilon < 0$ and $\Psi_k \geq 0$, $k = 1, 2, 3$, then

$$\dot{\mho}(x(t)) < -\nu\|x(t)\|^2, \quad \text{for a sufficiently small } \nu > 0.$$

Then, system (5.2) is asymptotically stable if LMIs (6.2)–(6.4) hold.

On the other hand, when $\tau_g < \tau_i$, one candidate Lyapunov-Krasovskii functional as

$$\begin{aligned}
\mho(x(t)) =&x^T(t)\,P\,x(t) + \int_{t-\tau_g}^{t} x^T(s)\,q_1\,x(s)\,ds + \int_{t-\tau_i}^{t} x^T(s)\,q_2\,x(s)\,ds\\
&+ \int_{-\tau_g}^{0}\int_{t+z}^{t} x'^T(s)\,\mathbb{W}_1\,x'(s)\,ds\,dz + \int_{-\tau_i}^{0}\int_{t+z}^{t} x'^T(s)\,\mathbb{W}_2\,x'(s)\,ds\,dz\\
&+ \int_{-\tau_g}^{-\tau_i}\int_{t+z}^{t} x'^T(s)\,\mathbb{W}_3\,x'(s)\,ds\,dz.
\end{aligned}$$

Equation (6.3) becomes

$$2\left[x^T(t)\,T_1 + x^T(t-\tau_g)\,T_2 + x^T(t-\tau_i)\,T_3\right] \times \Big[x(t-\tau_i) - x(t-\tau_g) \\ - \int_{t-\tau_i}^{t-\tau_g} x'(s)\,ds\Big] = 0.$$

Thus, a similar result follows as in the procedure for the case $\tau_g \geq \tau_i$. Thus the proof follows. □

Remark 2. We would like to mention that we used the Liapunov function approach as in [17] because our theorem is a special case of a corresponding result that was concluded in [17].

7 Numerical solutions

The numerical solutions presented in this section for system (2.3) are simulated. Using the numerical method described in the works [10,12,19]. Comparing the two systems (2.2) and (2.3), we deduce that:

$$\psi(x(t)) = p_1 x(t), \quad \xi(x(t), y(t-\tau_i)) = \frac{p_4 x(t) y(t-\tau_i)}{\beta x(t) + 1},$$
$$\sigma(y(t)) = p_2 y(t), \quad \varphi(x(t-\tau_g)) = p_6 x(t-\tau_g).$$

For a system (2.3), the characteristic equation is given by

$$\lambda^2 + p\lambda + r + qe^{-\lambda(\tau_g+\tau_i)} = 0,$$

where

$$p = \left(p_1 + p_2 + \frac{p_4 y^*}{\beta x^* + 1} - \frac{\beta p_4 y^* x^*}{(\beta x^* + 1)^2}\right),$$
$$r = \left(p_1 p_2 + \frac{p_2 p_4 y^*}{\beta x^* + 1} - \frac{\beta p_2 p_4 y^* x^*}{(\beta x^* + 1)^2}\right), \quad q = \frac{p_4 p_6 x^*}{\beta x^* + 1}.$$

Table 1. De Gaetano and Arino's parameter values for subjects 6 and 7 [7].

Parameter	ξ_b	I_b	p_0	p_1	p_2	p_3	p_4	p_6	p_7
Value	$\frac{mg}{dl}$	pM	$\frac{mg}{dl}$	min^{-1}	min^{-1}	$\frac{dlpM}{mg}$	$\text{min}^{-1}\ \text{pM}^{-1}$	$\frac{dlpM}{mg}$	$\frac{mg}{dlmin}$
6	88	68.6	209	0.0002	0.0422	1.64	0.000109	0.033	0.68
7	87	37.9	311	0.0001	0.2196	0.64	0.000373	0.096	1.24

In the following cases, we use the values of parameters in Table 1 for subject 7.

Case 1. $\tau_g = \tau > 0$, $\tau_i = 0$. For a subject 6, $E^* = (133.8791, 104.6922)$, $w = 0.0043$ and

$$\tau^* = \frac{1}{\omega}\arccos\left(\frac{(\omega^*)^2 - r}{q}\right) = 457.7211.$$

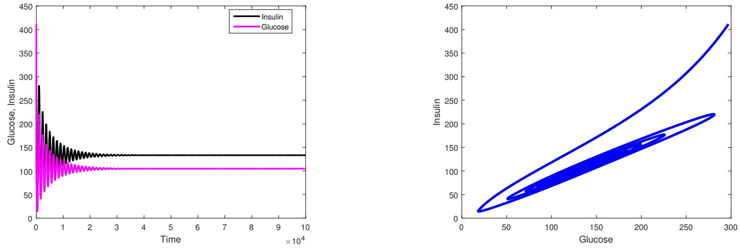

Figure 1. Glucose-insulin dynamics: dynamics and phase plain for $\tau = 400 < \tau^* = 457$ min.

For $t \in [0, 100000]$, from Corollary 5, as shown in Figure 1, there exist a critical value $\tau^* = 457.7211$ so that E^* is asymptotically stable when $\tau = 400 < \tau^*$.

When τ reaches the critical value τ^*, E^* loses its stability and a Hopf bifurcation occurs, as shown in Figure 2.

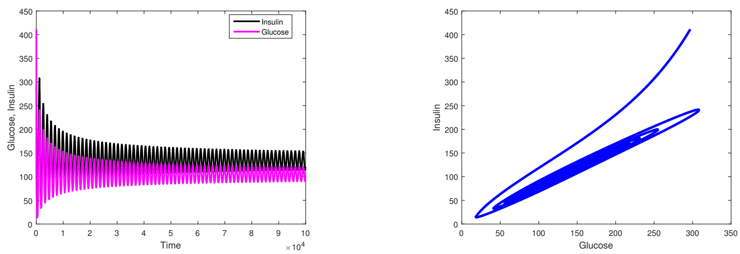

Figure 2. Glucose-insulin dynamics: dynamics and phase plain for $\tau^* = 457$ min.

Yet, it is unstable, and when it does, a Hopf bifurcation occurs if $\tau = 500 > \tau^*$, as shown in Figure 3.

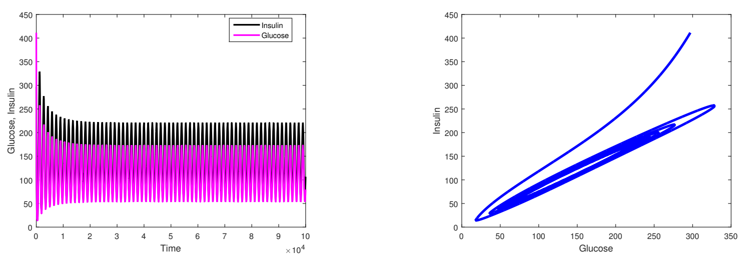

Figure 3. Glucose-insulin dynamics: dynamics and phase plain for $\tau = 500 > \tau^* = 457$ min.

Case 2. $\tau_i = \tau > 0$, $\tau_g = 0$. For a subject 6, $E^* = (133.8791, 104.6922)$, $w = 0.0043$ and

$$\tau^* = \frac{1}{\omega}\arccos\left(\frac{(\omega^*)^2 - r}{q}\right) = 457.7211.$$

For $t \in [0, 100000]$, from Corollary 6, there exist a critical value $\tau^* = 457.7211$ and E^* is asymptotically stable if $\tau = 400 < \tau^*$, as shown in Figure 4.

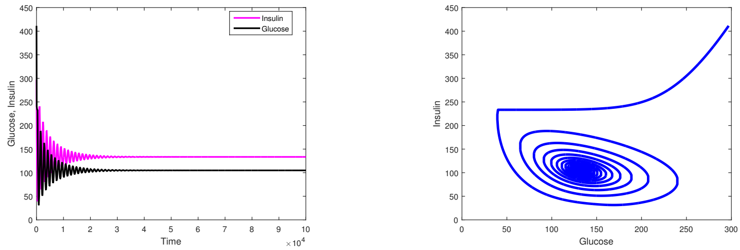

Figure 4. Glucose-insulin dynamics: dynamics and phase plain for $\tau = 400 < \tau^* = 457$ min.

E^* loses its stability and a Hopf bifurcation occurs, if τ passes through the critical value τ^*, as shown in Figure 5.

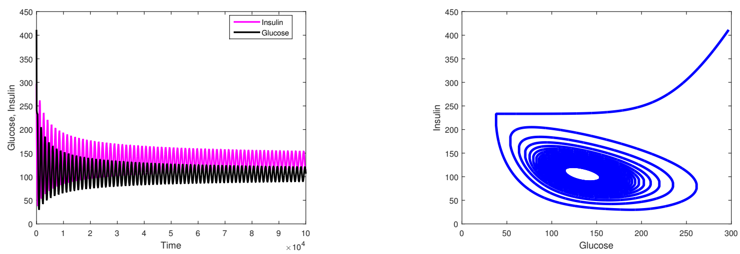

Figure 5. Glucose-insulin dynamics: dynamics and phase plain for $\tau^* = 457$ min.

Yet, it is unstable, and when it does, a Hopf bifurcation occurs if $\tau = 500 > \tau^*$, as shown in Figure 6.

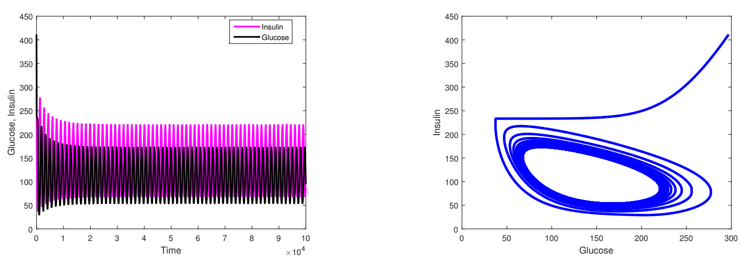

Figure 6. Glucose-insulin dynamics: dynamics and phase plain for $\tau = 500 > \tau^* = 457$ min.

Case 3. For $\tau_g = \tau_i = \tau \neq 0$. For a subject 6, $E^* = (133.8791, 104.6922)$, $w = 0.0043$ and

$$\tau^{\bullet} = \frac{1}{2\omega^*} \arccos\left(\frac{(\omega^*)^2 - r}{q}\right) = 228.8606.$$

For $t \in [0, 100000]$, from Corollary 7, there exist a critical value $\tau^* = 228.8606$. When $\tau = 200 < \tau^\bullet$, E^* is asymptotically stable as shown in Figure 7.

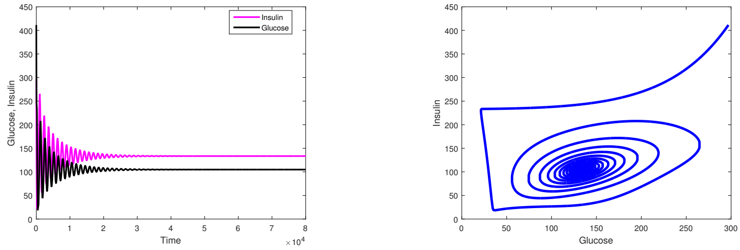

Figure 7. Glucose-insulin dynamics: dynamics and phase plain for $\tau = 200 < \tau^\bullet = 228$ min.

If τ passes through the critical value $\tau^\bullet$, E^* loses its stability and a Hopf bifurcation occurs, as shown in Figure 8.

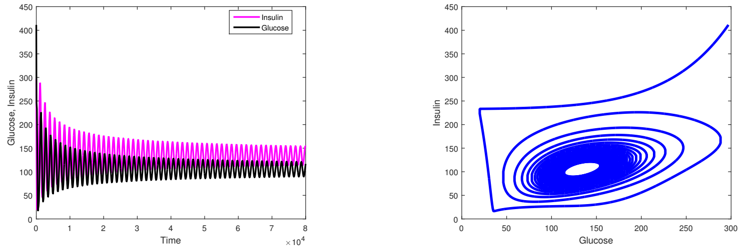

Figure 8. Glucose-insulin dynamics: dynamics and phase plain for $\tau^\bullet = 228$ min.

Yet, it is unstable, and when it does, a Hopf bifurcation occurs if $\tau = 300 > \tau^\bullet$, as shown in Figure 9.

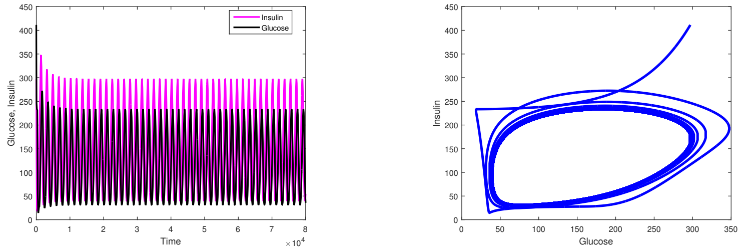

Figure 9. Glucose-insulin dynamics: dynamics and phase plain for $\tau = 300 > \tau^\bullet = 228$ min.

Case 4. For $\tau_g > 0$, $\tau_i = 31$. For a subject 7, $E^* = (189.3229, 82.7641)$, $w = 0.0063$ and

$$\tau_g^* = \frac{1}{\omega_0} \arcsin\left(\frac{E_1 k_3 + E_2(k_2 - k_1)}{E_1^2 + E_2^2}\right) = 249.5378.$$

For $t \in [0, 100000]$, from Theorem 5, there exist a critical value $\tau_g^* = 249.5378$ and E^* is asymptotically stable when $\tau_g = 200 < \tau_g^*$, which is shown in Figure 10.

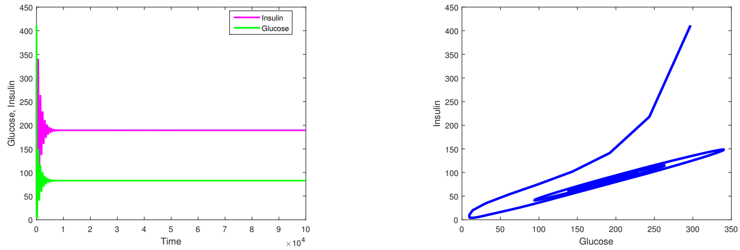

Figure 10. Glucose-insulin dynamics: dynamics and phase plain for $\tau_g = 200 < \tau_g^* = 249$ min.

E^* loses its stability and a Hopf bifurcation occurs, if τ_g passes through the critical value τ^*, as shown in Figure 11.

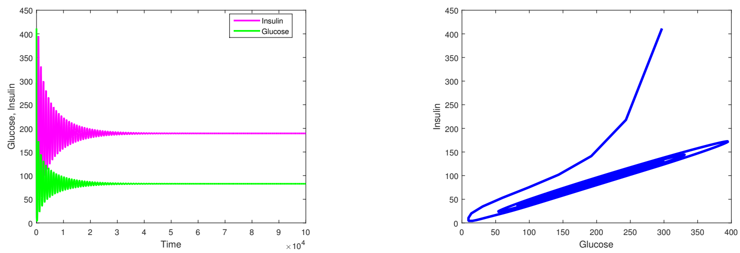

Figure 11. Glucose-insulin dynamics: dynamics and phase plain for $\tau_g^* = 249$ min.

Yet, it is unstable, and when it does, a Hopf bifurcation occurs if $\tau_g = 300 > \tau_g^*$, as shown in Figure 12.

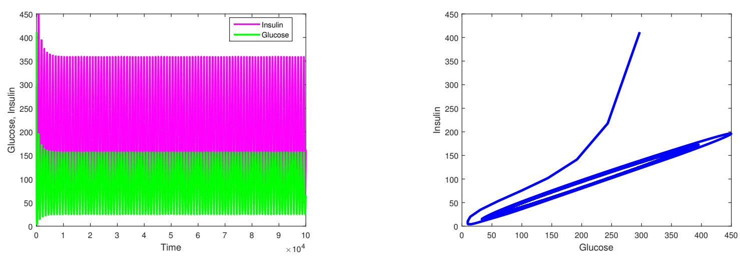

Figure 12. Glucose-insulin dynamics: dynamics and phase plain for $\tau_g = 300 > \tau_g^* = 249$ min.

Case 5. For $\tau_i > 0$, $\tau_g = 31$. For a subject 7, $E^* = (455.5880, 199.1642)$, $w = 0.0026$ and

$$\tau_i = \frac{1}{\omega_0} \arcsin\left(\frac{F_1 k_3 + F_2(k_1 - k_2)}{F_1^2 + F_2^2}\right) = 497.2424.$$

For $t \in [0, 100000]$, from Theorem 6, there exist a critical value $\tau_k^* = 497.2424$ and E^* is asymptotically stable when $\tau_i = 450 < \tau_k^*$, as shown in Figure 13.

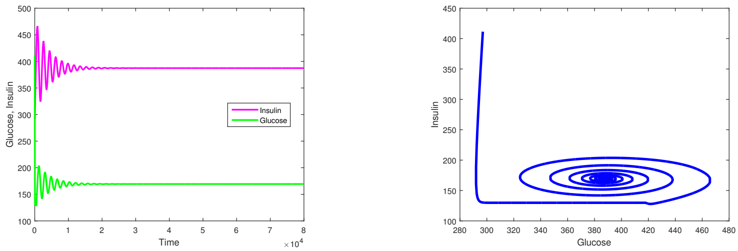

Figure 13. Glucose-insulin dynamics: dynamics and phase plain for $\tau_i = 450 < \tau_i^* = 500$ min.

E^* loses its stability and a Hopf bifurcation occurs, if τ_i passes through the critical value τ_i^*, as shown in Figure 14.

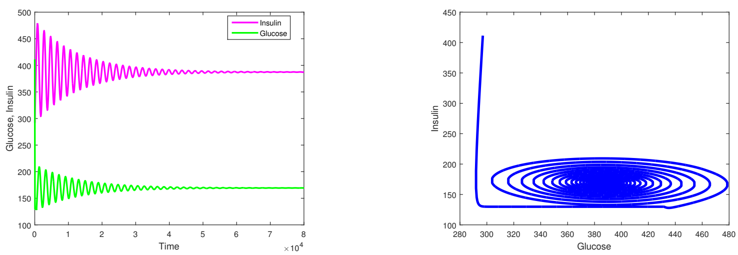

Figure 14. Glucose-insulin dynamics: dynamics and phase plain for $\tau_i^* = 500$ min.

Yet, it is unstable, and when it does, a Hopf bifurcation occurs if $\tau_i = 550 > \tau_i^*$, as shown in Figure 15.

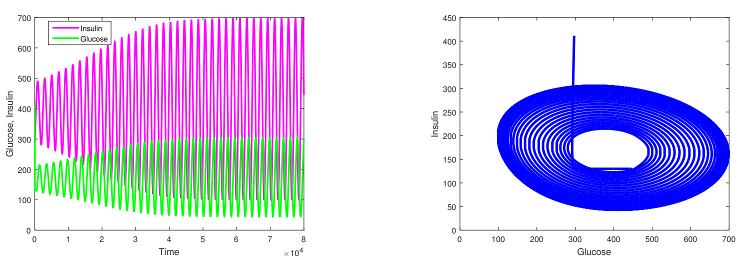

Figure 15. Glucose-insulin dynamics: dynamics and phase plain for $\tau_i = 550 > \tau_i^* = 500$ min.

8 Conclusions

In the present work, we proposed a general IVGTT glucose-insulin model with two discrete delays which focuses on the metabolism of glucose and insulin. More precisely, we have investigated a delay-differential models (2.2) and (2.3) of the glucose insulin system in terms of the stability analysis of its positive solution. It's been determined that the unique positive equilibrium is globally stable around an unique equilibrium point, and that it has solutions which is positive and bounded for all times. The first main results referred to the characterization of the global stability properties of the model. In particular, a new condition on the model structural parameters is offered, such that if it is satisfied, the model is guaranteed to be globally asymptotically stable. Two main contributions are made by the present work towards a better understanding of the glucose-insulin control system. Our findings highlight the requirements that must be met for a periodic solution to exist around the interior equilibrium. All of the numerical results and graphs in the paper were consistent with those in the relevant corresponding papers. Numerical results of the model provides the range of time delays which produce periodic solutions and more number of oscillations can be obtained in the same range as compared with the model of Li et al. [17].

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