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Research article

On the fractional-order glucose-insulin interaction

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Abstract: We consider a fractional-order model of glucose and insulin interaction based on the intravenous glucose tolerance test (IVGTT). We show the existence of the model's solution, uniqueness, non-negativity, and boundadness. In addition, for the proposed fractional-order model, we establish sufficient conditions for stability or instability. Some conditions for bifurcation in the proposed model are presented using bifurcation theory. Further, in the case of first order the model is discretized by applying the forward Euler scheme. We investigate how small the time step size must be chosen to guarantee that the steady state solution is an attractive fixed point of the discretized model. Numerical simulations that we provided support the analytical results.

Keywords: diabetes disease; minimal model; mathematical modeling; stability analysis; computational simulation
Mathematics Subject Classification: 34C60, 92C42, 92D25, 92D30

1. Introduction and statement of main results

The complex glucose-insulin relationship has been studied; see [13, 14, 16, 37, 44, 48–50, 54]. These models consist of simply linear ordinary differential equations and were considered unacceptable for different reasons, such as parameters have poor fits to experimental data or are not identifiable [33]. Bolie [15], Ackerman et al. [4, 5], Gatewood et al. [27], Bergman et al. [14], Steil et al. [52], Caumo et al. [18], Gaetano and Arino [26], Gresl et al. [28] offered the glucose-insulin linear models homeostasis based on Intra-Venous Glucose Tolerance Test (IVGTT) method. The "Minimal Model" was proposed in 1980 by Bergman et al. [13, 14], and was updated in 1986. This model, which describes IVGTT experimental data well with the smallest collection of [13, 14, 44, 54] identifiable and meaningful parameters, can be considered to be the most famous model used in glucose metabolism physiological research.

Fractional calculus has shown to be a valuable tool for mathematical modeling of various open issues in mathematics, physics, biology, epidemiology and other scientific fields. Many scientists have

modeled them using fractional calculus; See [21–46]. There is significant potential for the principle of fractional calculus to transform the way we see the model and regulate the environment around us. It is naturally that the fractional order differential equations are used because they relate to memory systems Which exist in most biological systems [53]. Also they are, at least, as Stable as their integer-order counterpart [23, 36]. Discrete numerical calculus has attracted many scholars in recent years [10]. Scientists have been increasingly concerned about its applications in secure communication, neural networks, biology and other fields. Recently various complex dynamics reside in fractional-order iterated map, such as chaos, hyperchaos and coexisting attractors [11–14]. In epidemiology, fractional-order operators have been widely employed [47–50]. Meanwhile, the discrete mathematical model of COVID-19 has been analyzed in [3]. In this paper, analytical studies of a Caputo fractional-order glucose-insulin model (2.3) and its discretization are presented here. We show that the model (2.3) possesses an existence, uniqueness, nonnegative properties, and boundedness properties. We also prove that the proposed model possesses an existence, uniqueness, non-negativeness, as well as boundedness. We also carried out systematic studies on the stability of Caputo's fractional. Numerical solutions to the Caputo fractional model are obtained using the Euler-type method for fractional derivatives. Also, numerical simulations of the discretization fractional derivative order model are used to support analytical results.

2. The description of the model

In [26, 34], Gaetano, Arino and Li et al. had reinvestigated the dynamical behavior of the "Minimal Model" in both modeling and physiological aspect to understanding blood glucose regulatory system:

$$\begin{aligned} \frac{dG(t)}{dt} &= -p_1 G(t) - \frac{p_4 I(t) G(t)}{\beta G(t) + 1} + p_7, \quad G(0) = G_b + p_0, \\ \frac{dI(t)}{dt} &= p_6 G(t) - b_2 I(t), \quad I(0) = I_b + p_0 p_3. \end{aligned} \tag{2.1}$$

with $G_i = G_b$, for $t \in [-p_5, 0)$, where $G(t)$ [mg/dL], $I(t)$ [mU/L] are the concentration of blood glucose and insulin, G_b [mg/dL] is the concentration of basal blood glucose, I_b [mU/L] is the concentration of basal blood insulin, p_0 [mg/dl] is the theoretical glycemia after the instantaneous intake of glucose bolus at time 0, p_1 [1/min] is the insulin independent glucose clearance rate, p_2 [1/min] is the active insulin clearance rate (upt. decrease), p_3 [L/(min2mU)] is the increase caused by insulin in uptake ability, p_4 [1/min] is the destroy rate of blood insulin, p_5 [mg/dL] is the aim glucose level, p_6 [mUdL/Lmgmin] is the Pancreatic free rate after glucose bolus, and p_7 (mg/dl)[1/min] is the concentration at time 0 of the Plasma insulin, above basal insulinemia, immediately after the glucose bolus intake.

First, we consider the initial value problems for fractional differential equations in the form of

$$\begin{cases} D^q X(t) = f(X(t)), \\ X^{(k)}(t_0) = X_0^{(k)}. \end{cases} \tag{2.2}$$

where the fractional derivative D^q is in the sense of Caputo's definition, the function $f(X(t)) : \mathbb{R} \times \mathbb{R}^d \longrightarrow \mathbb{R}^d$ is called vector field, and the dimension $d \geq 1$. Particularly, $\mathbb{R}^d$ endowed a proper norm $\| \, . \, \|$ becomes a complete metric space. Denote by $\mathbb{R}^+$ the set of all non-negative real numbers.

Definition 1. *([45]) If $q \in \mathbb{R}^+$ is a non integer order, the fractional integral $J^q f(t)$ of the function $f(t)$ with $m \geq 0$ is defined as*

$$J_m^q f(t) = \frac{1}{\Gamma(q)} \int_m^t (t-\tau)^{q-1} f(\tau) d\tau, \quad t > m$$

where $\Gamma(z) = \int_0^\infty e^{-t} t^{z-1} dt$ is the Euler gamma function.

Definition 2. *([45]) The Caputo fractional derivative $D^q f(t)$ of order $q > 0$, $n-1 < q < n$, $n \in \mathbb{N}$ is defined as*

$$D^q f(t) = \begin{cases} \frac{1}{\Gamma(n-q)} \int_0^t \frac{f^{(n)}(\tau)}{(t-\tau)^{q+1-n}} d\tau, & n-1 < q < n, \\ \frac{d^n}{dt^n} f(t), & q = n. \end{cases}$$

Hence, we suggest to establish a system of fractional glucose-insulin for modeling (2.1), based on the model presented in [34]:

$$\begin{aligned} D^q G(t) &= -p_1 G(t) - \frac{p_4 I(t) G(t)}{\beta G(t) + 1} + p_7, \\ D^q I(t) &= p_6 G(t) - p_2 I(t), \end{aligned} \tag{2.3}$$

with $G(0) = G_b + p_0$, $I(0) = I_b + p_0 p_3$, $G_i = G_b$, for $t \in [-p_5, 0)$.

Fractional derivatives describe dynamical systems better than classical calculus, where they reflect memory effects. This paper shows the effect of control on fractional models, representing epidemiological and biomedicine problems. Therefore, health organizations need a solution to such models.

We are also interested in applying the forward Euler scheme to discretize the system (2.1) in order to obtain the following system:

$$\begin{aligned} G_{n+1} &= G_n + h[-p_1 G_n - \frac{p_4 I_n G_n}{\beta G_n + 1} + p_7], \\ I_{n+1} &= I_n + h[p_6 G_n - p_2 I_n], \end{aligned} \tag{2.4}$$

where $0 < h < 1$ is the step size.

3. Preliminaries and known results

The supremumnorm is defined as

$$\| \phi \| = \sup_{t \in (0,T]} |\phi(t)|,$$

and norm of the matrix is

$$\| M \| = \sum_{i,j} \sup_{t \in (0,T]} |M_{i,j}|.$$

Denote by

$$\begin{aligned} \mathcal{J} = [t_0 - a, t_0 + a], \quad \mathcal{B} = \{X \in \mathbb{R}^d : \| X - X_0 \| \leq b\}, \\ \mathcal{D} = \{(t, X) \in \mathbb{R} \times \mathbb{R}^d : t \in \mathcal{J}, \quad X \in \mathcal{B}\}. \end{aligned}$$

Theorem 1. *([35], Theorem 2.1, see also [22]) Assume that the function $f : \mathcal{D} \longrightarrow \mathbb{R}^d$ satisfies the following conditions:*

(1) $f(X(t))$ is Lebesgue measurable with respect to t on $\mathcal{J}$;
(2) $f(X(t))$ is continuous with respect to X on $\mathcal{B}$;
(3) there exists a real-valued function $g(t) \in L^2(\mathcal{J})$ such that

$$\| f(X(t)) \| \leq g(t);$$

for almost every $t \in \mathcal{J}$, $X \in \mathcal{B}$. Then, for $q > \frac{1}{2}$, there at least exists a solution of the initial value problem (2.3) on the interval $[t_0 - \varepsilon, t_0 + \varepsilon]$ for some positive number ε.

Theorem 2. *([35], Theorem 2.2, see also [22]) Assume that all the assumptions of Theorem 2.3 hold and that there exists a real-valued function $\mu(t) \in L^4(\mathcal{J})$ such that*

$$\| f(X(t)) - f(Y(t)) \| \leq \mu(t) \| X(t) - Y(t) \|, \tag{3.1}$$

for almost every $t \in \mathcal{J}$ and all $X \in \mathcal{B}$. Then there exists a unique solution of the initial value problem (2.1) on $[t_0 - \varepsilon, t_0 + \varepsilon]$ for some positive number ε.

Theorem 3. *([35], Theorem 3.1) Assume that the vector field function $f(X(t))$ satisfies the first two condition of theorem 2.3 in the global space and*

$$\| f(X(t)) \| \leq \omega + \lambda \| X \|,$$

for almost every $t \in \mathbb{R}$, and all $X \in \mathbb{R}^d$. Here, ω, λ are two positive constants. Then, there exists a unique function $X(t)$ on $(-\infty, +\infty)$ solving the initial value problem (2.2).

Remark 1. *([35], Remark 3.2) Besides the hypotheses made in Theorem 2.5, if $\frac{\partial f(X(t))}{\partial X}$ is further assumed to be continuous with respect to X. Then, the solution $X(t)$ on $(-\infty, +\infty)$ solving the initial value problem* (2.2) *is not only existent but also unique.*

Lemma 1. *([55]) Let $u(t) \in \mathbb{R}^+$ be a continuous and derivable function. Thus, for any time instant $t \geq t_0$,*

$$D^q\Big(u(t) - u^* - u^* \ln \frac{u(t)}{u^*}\Big) \leq \left(1 - \frac{u^*}{u(t)}\right) D^q u(t), \quad u^* \in \mathbb{R}^+.$$

Lemma 2. *([30], Lemma 3) Let $u(t)$ be a continuous function on $[t_0, +\infty)$ and satisfying*

$$D^q u(t) + \lambda u(t) \leq \mu,$$

where $0 < q \leq 1$, $(\lambda, \xi) \in \mathbb{R}^2$ and $\lambda \neq 0$ and $t_0 \geq 0$ is the initial time. Then

$$u(t) \leq \Big(u(t_0) - \frac{\xi}{\lambda}\Big) E_q\Big[- \lambda (t - t_0)^q \Big] + \frac{\xi}{\lambda},$$

where E_q is the Mittag-Leffler function.

Lemma 3. *([41]) The equilibrium point* (x^*, y^*) *of the fractional differential system.*

$$D^\alpha x(t) = f_1(x, y), \quad x(0) = x_0$$
$$D^\alpha y(t) = f_2(x, y), \quad y(0) = y_0, \quad q \in (0, 1]$$

is locally asymptotically stable if and only if all eigenvalues η_i of the Jacobian matrix

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{bmatrix}. \tag{3.2}$$

evaluated at the equilibrium point (x^*, y^*), satisfy the condition that $|arg(\eta_i)| > \frac{q\pi}{2}$.

Definition 3. *([12, 24]) A fixed point* $E^* = (G^*, I^*)$ *of system* (2.2) *is called stable if* $|\eta_1| < 1$, $|\eta_2| < 1$ *and a source if* $|\eta_1| > 1$, $|\eta_2| > 1$. *It is called a saddle if* $|\eta_1| < 1$, $|\eta_2| > 1$ *or* $|\eta_1| > 1$, $|\eta_2| < 1$ *and a nonhyperbolic fixed point if either* $|\eta_1| = 1$, *or* $|\eta_2| = 1$. *It is called a spiral source if* $\eta_{1,2} = \sigma \pm i\mu$, $\mu \neq 0$, $\sigma, \mu \in \mathbb{R}$ *and* $|\eta_{1,2}| > 1$.

Lemma 4. *([24]) If* η_1 *and* η_2 *are the eigenvalues of Jacobian matrix* (3.2). *Then* $|\eta_1| < 1$ *and* $|\eta_2| < 1$ *if the following condition holds:*

(i) $1 - \det(J_2) > 0$,
(ii) $1 - \mathrm{tr}(J_2) + \det(J_2) > 0$, and
(ii) $1 + \mathrm{tr}(J_2) + \det(J_2) > 0$.

4. Properties of solutions of the fractional-order model

4.1. Local and global existence of the solution

The fractional-order system (2.3) can be written in the following form

$$\begin{cases} D^q X(t) = f(X(t)), \\ X^{(k)}(t_0) = X_0^{(k)}, \end{cases}$$

where

$$X = \begin{bmatrix} G \\ I \end{bmatrix}, \quad X_0 = \begin{bmatrix} G_0 \\ I_0 \end{bmatrix}, \quad f(X) = \begin{bmatrix} f_1(X) \\ f_2(X) \end{bmatrix} = \begin{bmatrix} -p_1 G(t) - \frac{p_4 I(t) G(t)}{\beta G(t) + 1} + p_7 \\ p_6 G(t) - b_2 I(t) \end{bmatrix}.$$

In this subsection, we study the existence and uniqueness of the solutions of the fractional system (2.3) in $\Omega \times (0, T]$ with

$$\Omega = \{(G, I) \in \mathbb{R}^2 : \max(|G|, |I|) \leq \Phi\}.$$

Theorem 4. *The sufficient condition for existence and uniqueness of the local solution of system* (2.3) *in the specified region* $\Omega \times (0, T]$ *with initial conditions* $X_0 = (G_0, I_0) \in \Omega$ *and* $t \in (0, T]$ *is*

$$\mu = \max\{p_1 + p_6 + p_4\Phi, p_2 + p_4\beta\Phi^2\}.$$

Proof. Since the vector function $f(X(t))$ satisfies all the assumption of Theorem 2.3, so we only need to prove the condition (3.1) of Theorem 2.4. For $X, \overline{X} \in \Omega$, one obtains

$$\begin{aligned}
&\|f(X) - f(\overline{X})\| \\
&= |f_1(X) - f_1(\overline{X})| + |f_2(X) - f_2(\overline{X})| \\
&= \Big| - p_1 G - \frac{p_4 IG}{\beta G + 1} + p_7 + p_1 \overline{G} + \frac{p_4 \overline{I}\,\overline{G}}{\beta \overline{G} + 1} - p_7 \Big| + |p_6 G - p_2 I - p_6 \overline{G} + p_2 \overline{I}| \\
&= \Big| - p_1 (G - \overline{G}) - p_4 \frac{\beta IG\overline{G} + IG - \beta G\overline{IG} - \overline{IG}}{(\beta G + 1)(\beta \overline{G} + 1)} \Big| + |p_6 (G - \overline{G}) + p_2 (I - \overline{I})| \\
&\leq (p_1 + p_6 + p_4 \Phi)\eta |G - \overline{G}| + (p_2 + p_4 \beta \Phi^2)|I - \overline{I}| \\
&\leq \mu \|X - \overline{X}\|,
\end{aligned}$$

where

$$\mu = \max\{p_1 + p_6 + p_4\Phi, p_2 + p_4\beta\Phi^2\}.$$

Thus, $f(X(t))$ satisfies the Lipschitz condition with respect to X and it follows from Theorem 2.4 that there exists a unique local solution $X(t)$ of system (2.3) with initial condition $X_0 = (G_0, I_0)$. □

In the next result, we prove the global existence of solutions for system (2.3).

Theorem 5. *For any given initial condition $X_0 = (G_0, I_0)$ satisfying* (2.3)*, there is a unique global solution $X(t)$, which remains in $\mathbb{R}^2$, of the model* (2.3).

Proof. Denote

$$B_0 = \begin{bmatrix} p_7 \\ 0 \end{bmatrix}, \quad B_1 = \begin{bmatrix} -p_1 & 0 \\ p_6 & -p_2 \end{bmatrix}, \quad B_2 = \begin{bmatrix} 0 & \frac{-p_4}{\beta} \\ 0 & 0 \end{bmatrix}.$$

Hence, system (2.3) reduces to where

$$F(X) = B_0 + B_1 X + \frac{\beta G}{\beta G + 1} B_2 X.$$

Thus

$$\begin{aligned}
\| F(X) \| &\leq \|B_0\| + \|B_1 X\| + \Big\| \frac{\beta G}{\beta G + 1} B_2 X \Big\| \\
&\leq \|B_0\| + \Big(\|B_1\| + \|B_2\| \Big) \|X\|.
\end{aligned}$$

It follows, from Theorem 2.5 that there exists a unique global solution $X(t)$ of system (2.3) with initial condition $X_0 = (G_0, I_0)$. □

4.2. Non-negativity and boundedness

We are only interested in solutions that are non-negative and bounded in terms of biological significance. The following result guarantees the non-negativity and boundedness solutions of system (2.3). Let $\Omega_+ = \{(G, I) \in \Omega : G \in \mathbb{R}_+ \text{ and } I \in \mathbb{R}_+\}$.

Theorem 6. *The solutions of system* (2.3)*, which start in* Ω_+ *are uniformly bounded within a region*

$$V_1 = \{(G, I) \in \Omega_+ : H(t) \leq \frac{p_7}{\lambda} + \varepsilon, \text{ for all } \varepsilon > 0\}. \tag{4.1}$$

Proof. Let $(G(t), I(t))$ be a solution of system (2.3). By taking $H(t) = G(t) + I(t)$, one obtains

$$D^q H(t) = (p_6 - p_1)G(t) - p_2 I - \frac{p_4 I(t)G(t)}{\beta G(t) + 1} + p_7 .$$

Hence, for all $\lambda > 0$,

$$D^q H(t) + \lambda H(t) \leq (\lambda + p_6 - p_1)G(t) + (\lambda - p_2)I + p_7.$$

One can choose $\lambda < \min\{p_1 - p_6, p_2\}$. Thus

$$D^q H(t) + \lambda H(t) \leq p_7. \tag{4.2}$$

Following Lemma 2.8, one obtains

$$0 \leq H(t) \leq \Big(H(t_0) - \frac{p_7}{\lambda}\Big)E_q[-\lambda(t - t_0)^q] + \frac{p_7}{\lambda} \longrightarrow \frac{p_7}{\lambda}, \quad t \longrightarrow \infty.$$

Hence, the solutions of (2.3) starting from Ω_+ are uniformly bounded in the open region V_1. □

Theorem 7. *The solutions of system* (2.3)*, which start in* Ω_+ *are nonnegative.*

Proof. From the first equation of system (2.4), one obtains

$$D^q G(t) = -p_1 G(t) - \frac{p_4 I(t)G(t)}{\beta G(t) + 1} + p_7. \tag{4.3}$$

Again from Eq (4.3), one obtains

$$G(t) + I(t) \leq \frac{p_7}{\lambda}. \tag{4.4}$$

So from Eqs (4.3) and (4.4), one obtains

$$\begin{aligned} D^q G(t) &\geq -p_1 G(t) - \Big(\frac{p_4}{\beta}\Big) + p_7 \\ &= (\lambda - p_1)G(t) + \Big(\lambda - \frac{p_4}{\beta}\Big)I(t) \\ &= k_1 G(t) + k_2 I(t) \end{aligned}$$

where $k_1 = (\lambda - p_1)$, and $k_2 = \Big(\lambda - \frac{p_4}{\beta}\Big)$.

Now according to the positivity of Mittag-Leffer function $E_{q,1} > 0$ for any $q \in (0, 1)$, it follows that

$$G(t) \geq G_0 E_{q,1}(-\lambda t^q) \Rightarrow G \geq 0.$$

From second equation of system (1.2), one obtains

$$D^q I(t) = p_6 G(t) - p_2 I(t) \geq -p_2 I(t).$$

Thus

$$I(t) \geq I_0 E_{q,1}(-\lambda t^q) \Rightarrow I \geq 0.$$

Hence all solution of system (2.3) are non-negative. □

5. Dynamical behaviour of the fractional-order model

5.1. Local and global stability of equilibria

In this subsection, some explicit conditions for the occurrence of a Hopf bifurcation for Eq (2.3) will be established. To find the fixed points, let

$$D^q G(t) = 0,$$
$$D^q I(t) = 0.$$

Thus, the equilibrium point $E^* = (G^*, I^*)$ of (2.3) is given by

$$G^* = \frac{(\beta p_7 - p_1) \pm \sqrt{(\beta p_7 - p_1)^2 + 4p_7(\beta p_1 + \frac{p_4 p_6}{p_2})}}{2(\beta p_1 + \frac{p_4 p_6}{p_2})},$$
$$I^* = \frac{p_6}{p_2} G^*.$$

To linearize the fractional model (2.3), about $E^* = (G^*, I^*)$, we use the transformation $x(t) = G(t) - G^*$, $y(t) = I(t) - I^*$. Eq (2.3) can be converted to

$$\begin{aligned} D^q x(t) &= -p_1(x(t) + G^*) - \frac{p_4(y(t) + I^*)(x(t) + G^*)}{\beta(x(t) + G^*) + 1} + p_7, \\ D^q y(t) &= p_6(x(t) + G^*) - p_2(y(t) + I^*). \end{aligned} \tag{5.1}$$

Then the linearization of Eq (4.2) at the origin leads to

$$\begin{aligned} D^q x(t) &= -A_1 x(t) - A_2 y(t), \\ D^q y(t) &= A_3 x(t) - A_4 y(t). \end{aligned} \tag{5.2}$$

where

$$A_1 = \Big(p_1 + \frac{p_4 I^*}{\beta G^* + 1} - \frac{\beta p_4 I^* G^*}{(\beta G^* + 1)^2}\Big), \quad A_2 = \frac{p_4 G^*}{\beta G^* + 1}, \quad A_3 = p_6, \quad A_4 = p_2.$$

Then, the Jacobian matrix $J_1(E^*)$ at E^* for the fractional model (5.2) is given by

$$J_1(E^*) = \begin{bmatrix} -A_1 & -A_2 \\ A_3 & -A_4 \end{bmatrix}.$$

Its characteristic equation is

$$P_1(\sigma) = \sigma^2 + (A_1 + A_4)\sigma + A_1 A_4 + A_3 A_2 = 0, \tag{5.3}$$

and its eigenvalues are

$$\sigma_{1,2} = \frac{1}{2}\Big(\operatorname{tr}(J_1) \pm \sqrt{\operatorname{tr}^2(J_1) - 4\det(J_1)}\Big),$$

with $\operatorname{tr}(J_1) = -(A_1 + A_4)$, and $\det(J_1) = A_1 A_4 + A_2 A_3$. That is, the roots of the characteristic Eq (4.3) are

$$\sigma_1 = \frac{-(A_1 + A_4) + \sqrt{(A_1 + A_4)^2 - 4(A_1 A_4 + A_3 A_2)}}{2},$$

$$\sigma_2 = \frac{-(A_1 + A_4) - \sqrt{(A_1 + A_4)^2 - 4(A_1A_4 + A_3A_2)}}{2}.$$

Then, sum of the roots $= -(A_1 + A_4)$ and product of the roots $= A_1A_4 + A_2A_3$. Thus, one can say that both the roots of (6.1) are real and negative or complex conjugate with negative real parts if and only if

$$A_1 + A_4 > 0 \text{ and } A_1A_4 + A_2A_3 > 0.$$

Hence, one obtains the following result.

Lemma 5. *The equilibrium point $E^* = (G^*, I^*)$ of the fractional model* (2.3) *is locally asymptotically stable if and only if both conditions $A_1 + A_4 > 0$ and $A_1A_4 + A_2A_3 > 0$ hold simultaneously.*

On other direction, following Lemma 2.9, the sufficient condition for the local asymptotic stability of E^* is given by

$$|\arg \sigma_1| > \frac{q\pi}{2}, \quad |\arg \sigma_2| > \frac{q\pi}{2},$$

i.e.,

$$\left|\frac{\sqrt{4\Delta - \mathrm{tr}^2(J)}}{\mathrm{tr}(J)}\right| > \tan\frac{q\pi}{2},$$

i.e.,

$$\left|\frac{\sqrt{4[A_1A_4 + A_2A_3] - (A_1 + A_4)^2}}{A_1 + A_4}\right| > \tan\frac{q\pi}{2}.$$

Now, we study the global stability of E^*.

Theorem 8. *The positive equilibrium point $E^* = (G^*, I^*)$ of the fractional-order model* (2.3) *is globally asymptotically stable in $V_2 = \{(G, I) \in \Omega_+ : \frac{G}{G^*} > \frac{I^*}{I} > 1, \quad \beta \leq \frac{p_6}{\nu p_4 G^*}, \nu = min\{I\}\}$.*

Proof. Consider the following positive definite Lyapunov function:

$$L(G, I) = \left(G - G^* - G^* \ln\frac{G}{G^*}\right) + \left(I - I^* - I^* \ln\frac{I}{I^*}\right).$$

From Lemma 2.7, one obtains the fractional derivative of L with respect to t as

$$\begin{aligned}
D^q L(G,I) &\leq \Big(\frac{G-G^*}{G}\Big)D^q G + \Big(\frac{I-I^*}{I}\Big)D^q I \\
&= \Big(\frac{G-G^*}{G}\Big)\Big(-p_1 G(t) - \frac{p_4 IG}{\beta G+1} + p_7\Big) + \Big(\frac{I-I^*}{I}\Big)(p_6 G(t) - p_2 I(t)) \\
&= \Big(\frac{G-G^*}{G}\Big)\Big(-p_1(G-G^*) - \frac{p_4 IG}{\beta G+1} + \frac{p_4 I^* G^*}{\beta G^*+1}\Big) \\
&+ \Big(\frac{I-I^*}{I}\Big)(p_6(G-G^*) - p_2(I-I^*)) \\
&= -\frac{p_1}{G}(G-G^*)^2 - \frac{p_2}{I}(I-I^*)^2 + \frac{p_6}{I}(I-I^*)(G-G^*) \\
&+ \Big(\frac{G-G^*}{G}\Big)\Big(\frac{-\beta G^* p_4 IG + \beta G p_4 I^* G^* + p_4(I^* G^* - IG)}{(\beta G+1)(\beta G^*+1)}\Big) \\
&= -\frac{p_1}{G}(G-G^*)^2 - \frac{p_2}{I}(I-I^*)^2 + \frac{p_4}{G}\frac{(G-G^*)(I^* G^* - IG)}{(\beta G+1)(\beta G^*+1)} \\
&+ \frac{p_6}{I}(I-I^*)(G-G^*) + \beta G^* p_4 \frac{(G-G^*)(I^*-I)}{(\beta G+1)(\beta G^*+1)} \\
&\leq -\frac{p_1}{G}(G-G^*)^2 - \frac{p_2}{I}(I-I^*)^2 + \frac{p_4}{G}\frac{(G-G^*)(I^* G^* - IG)}{(\beta G+1)(\beta G^*+1)} \\
&+ \frac{p_6}{I}(I-I^*)(G-G^*) + \beta G^* p_4 (G-G^*)(I^*-I) \\
&= -\frac{p_1}{G}(G-G^*)^2 - \frac{p_2}{I}(I-I^*)^2 + \frac{p_4}{G}\frac{(G-G^*)(I^* G^* - IG)}{(\beta G+1)(\beta G^*+1)} \\
&+ (\beta G^* p_4 - \frac{p_6}{I})(G-G^*)(I^*-I).
\end{aligned}$$

Thus, $D^v L(G,I) < 0$ in V_2. Furthermore $D^q L(G,I) = 0$ implies that $G = G^*$, and $I = I^*$. Therefore, the singleton $\{E^*\}$ is the only invariant set such that $D^q L(G,I) = 0$. The Lasalle invariance principle (see [31, 51]) gives conclusion that E^* is globally asymptotically stable on Ω^+. □

5.2. Hopf bifurcation in the fractional-order system

The Hopf bifurcation of system (2.3) occurs when

$$|\arg \sigma_1| = \frac{q\pi}{2}, \quad |\arg \sigma_2| = \frac{q\pi}{2},$$

i.e.,

$$\Big|\frac{\sqrt{4\Delta - \mathrm{tr}^2(J)}}{\mathrm{tr}(J)}\Big| = \tan\frac{q\pi}{2},$$

Then

$$\Big|\frac{\sqrt{4[A_1A_4 + A_2A_3] - (A_1+A_4)^2}}{A_1+A_4}\Big| = \tan\frac{q\pi}{2}$$

is a sufficient conditions of occurring the Hopf bifurcation of the system (2.3).

6. Discretized of the first-order model of glucose-insulin interaction

In this subsection, we discretize the system (2.1) by using the forward Euler discretization method in integer order. Replacing $\frac{dG(t)}{dt}$ and $\frac{dI(t)}{dt}$ by the difference quotients

$$\frac{G(t+h)-G(t)}{h}, \text{ and } \frac{I(t+h)-I(t)}{h}, \text{respectively.}$$

In this way, one obtains the following system of difference equations:

$$G_{n+1} = G_n + h[-p_1 G_n - \frac{p_4 I_n G_n}{\beta G_n + 1} + p_7],$$
$$I_{n+1} = I_n + h[p_6 G_n - p_2 I_n],$$

where $0 < h < 1$ is the step size. We have $G_{n+1} = G_n = G$ and $I_{n+1} = I_n = I$ at a fixed point. It can be easily determined that (2.4) has the same fixed point as that given by $E^* = (G^*, I^*)$ in the fractional order model (2.3), where

$$G^* = \frac{(\beta p_7 - p_1) \pm \sqrt{(\beta p_7 - p_1)^2 + 4p_7(\beta p_1 + \frac{p_4 p_6}{p_2})}}{2(\beta p_1 + \frac{p_4 p_6}{p_2})},$$
$$I^* = \frac{p_6}{p_2} G^*.$$

The Jacobian matrix of system (2.4) is given by

$$J_2(E^*) = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}, \tag{6.1}$$

where $a_{11} = 1 - Kh$, $a_{12} = -\frac{p_4 G^* h}{(\beta G^* + 1)}$, $a_{21} = h p_6$, and $a_{22} = 1 - p_2 h$, with $K = p_1 + \frac{p_4 I^*}{(\beta G^* + 1)^2}$, and $B = \frac{p_4 p_6 G^*}{(\beta G^* + 1)}$. Note that $K > 0$ and $B > 0$. Its characteristic equation is

$$P_2(\eta) = \eta^2 - (a_{11} + a_{22})\eta + a_{11}a_{22} - a_{12}a_{21} = 0.$$

Following Lemma 4.2, on can obtain the following theorem:

Theorem 9. *The positive equilibrium point $E^* = (G^*, I^*)$ of the discrtized fractional-order model* (2.4) *is stable if $m < \min\{m_1, m_2\}$, $m_1 = \sqrt[q]{\frac{(p_2+K)\Gamma(q+1)}{p_2 K + B}}$, $m_2 = \sqrt[q]{\frac{2\Gamma(q+1)}{p_2 + K}}$, for $q \in (0, 1]$ and unstable otherwise.*

Proof. At $E^* = (G^*, I^*)$, the eigenvalues η_1 and η_2 of the Jacobian matrix (6.1) is given by

$$\eta_{1,2} = \frac{1}{2}\Big(\operatorname{tr}(J_2) \pm \sqrt{\operatorname{tr}^2(J) - 4\det(J_2)}\Big),$$

where

$$\operatorname{tr}(J_2) = a_{11} + a_{22} = 2 - (p_2 + K)h,$$
$$\det(J_2) = a_{11}a_{22} - a_{12}a_{21} = 1 - (p_2 + K)h + (p_2 K + B)h^2.$$

By simple calculation, one obtains

(i) $1 - \det(J_2) = h[(p_2 + K) - (p_2K + B)h] > 0$, if $m < m_1$, $m_1 = \sqrt[q]{\frac{(p_2+K)\Gamma(q+1)}{p_2K+B}}$,

(ii) $1 - \mathrm{tr}(J_2) + \det(J_2) = (p_2 + K)h^2 > 0$, and

(iii) $1 + \mathrm{tr}(J_2) + \det(J_2) = 2(2 - (p_2 + K))h + (p_2 + K)h^2 > 0$, if $m < m_2$, $m_2 = \sqrt[q]{\frac{2\Gamma(q+1)}{p_2+K}}$.

Then, following Lemma 4.2, the positive equilibrium point $E^* = (G^*, I^*)$ of the discrtized fractional-order model (2.4) is stable if $m < \min\{m_1, m_2\}$, for $q \in (0, 1]$ and unstable otherwise. □

6.1. Bifurcation in the discrtization fractional-order system

Neimark-Sacker bifurcation (NSB) is the equivalent of the continuous systems' Hopf bifurcation and is also the main tool for proof of the existence of quasi-periodic orbits for the map [11].

Flip bifurcation happens when a new limit cycle occurs from an existing limit cycle, also called as period-doubling bifurcation, and the period of the new limit cycle is twice that of the old one.

Fold bifurcation, also called saddle-node bifurcation, is the collision or disappearance of two equilibria in the system.

Lemma 6. *The interior equilibrium point E^* loses its stability*

(i) via NSB when $(p_2 + K)h = 1$.
(ii) via flip bifurcation (period doubling) when $2(p_2 + K)h = 4 + (p_2K + B)h^2$.

Proof. (i) NSB is occurred when associated Jacobian matrix J_2 has two complex conjugate eigenvalues with modulus 1 [24]. It means

$$\det(J_2) = 1, \quad \text{and } -2 < \mathrm{tr}(J_2) < 2.$$

Then

$$(p_2 + K)h = 1.$$

(ii) When a single eigenvalue becomes equal to -1, flip bifurcation occurs. Flip bifurcation is expressed as a characteristic equation of the related Jacobian matrix in the form of

$$1 + \mathrm{tr}(J_2) + \det(J_2) = 0.$$

It follows

$$2(p_2 + K)h = 4 + (p_2K + B)h^2. \tag{6.2}$$

Thus, by flip bifurcation, the equilibrium point E^* loses its stability when Eq (6.2) follows.

When a real eigenvalue passes through 1, a fold bifurcation or transcritical bifurcation occurs, or it is defined as

$$1 - \mathrm{tr}(J_2) + \det(J_2) = 0.$$

It follows

$$(p_2K + B)h^2 = 0.$$

which is not possible. Since all involved parameters are taken as positive. □

7. Numerical simulations

Numerical simulations that we provided support the analytical results. First, by using the Matlab program and using a set of parameter values in Table 1, one simulate numerical system (2.3) for different values of fractional order q to support analytical results (Figure 1). The nonlinear system (2.3) is solved by using Adams-Bashforth-Moulton method. Consider the following:

$$D^q G(t) = -0.0565 \times G - \frac{5.72 \times 10^{-6} \times I \times G}{0.01 \times G} + 4.43,$$
$$D^q I(t) == 0.031 \times G - 0.0438 \times I,$$

with $G(0) = 295$, $I(0) = 1008.43$, $q = 0.5$, $m = 0.001$.

Table 1. Parameters and their values taken from [26].

Parameter	G(0)	I(0)	p_1	p_2	p_4	p_6	p_7	β
Value	295	1008.43	0.0565	0.0438	5.72×10^{-6}	0.031	4.43	0.01

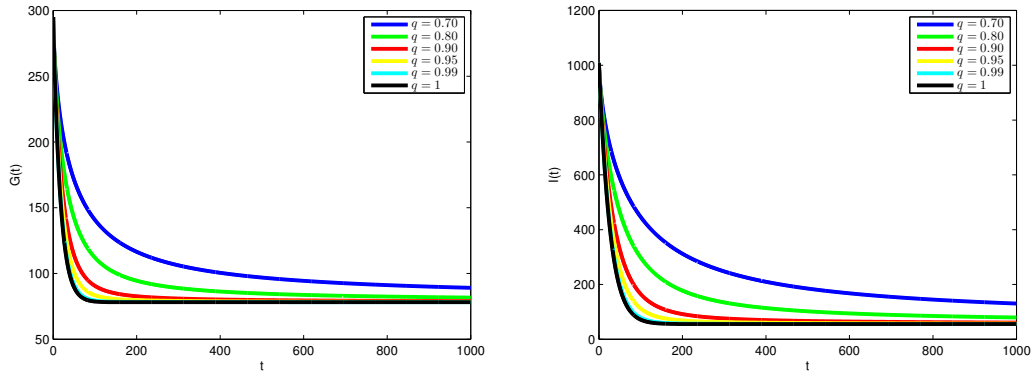

Figure 1. Dynamical behaviour of the Glucose and Insulin interaction for different values of q.

For these parameter, $E^* = (78.4404, 55.5172)$ is asymptomatically stable. According to Theorem 4.2, E^* is globally asymptotically stable of system (2.3). In the collection of Figure 2, we analyse the relationship between the glucose and insulin for different fractional order q.

Second, numerical simulations of the discretized first order system (2.4) are given by taking the parameter values as shown in Table 1 by using the mathematica program. Consider the following system:

$$G_{n+1} = G_n + \frac{m^q}{\Gamma(q+1)}[-0.0565 \times G_n - \frac{5.72 \times 10^{-6} \times I_n \times G_n}{0.01 \times G_n + 1} + 4.43],$$
$$I_{n+1} = I_n + \frac{m^q}{\Gamma(q+1)}[0.031 \times G_n - 0.0438 \times I_n],$$

with $G(0) = 295$, $I(0) = 1008.43$.

By simple calculation, system (2.4) has an equilibrium point E^*. Also, one obtains
(i) $1 - \det(J_2) = h\Big[(p_2 + K) - (p_2K + B)h\Big] = 0.0930 > 0$, where $h = 0.95 < h_1 = \frac{(p_2+K)}{p_2K+B} = 40.3720$,
(ii) $1 - \mathrm{tr}(J_2) + \det(J_2) = \Big(p_2 + K\Big)h^2 = 0.0906 > 0$, and
(iii) $1 + \mathrm{tr}(J_2) + \det(J_2) = 2(2 - (p_2 + K))h + \Big(p_2 + K\Big)h^2 = 3.6999 > 0$, where $h = 0.95 < h_2 = \frac{2}{p_2+K} = 19.9204$.

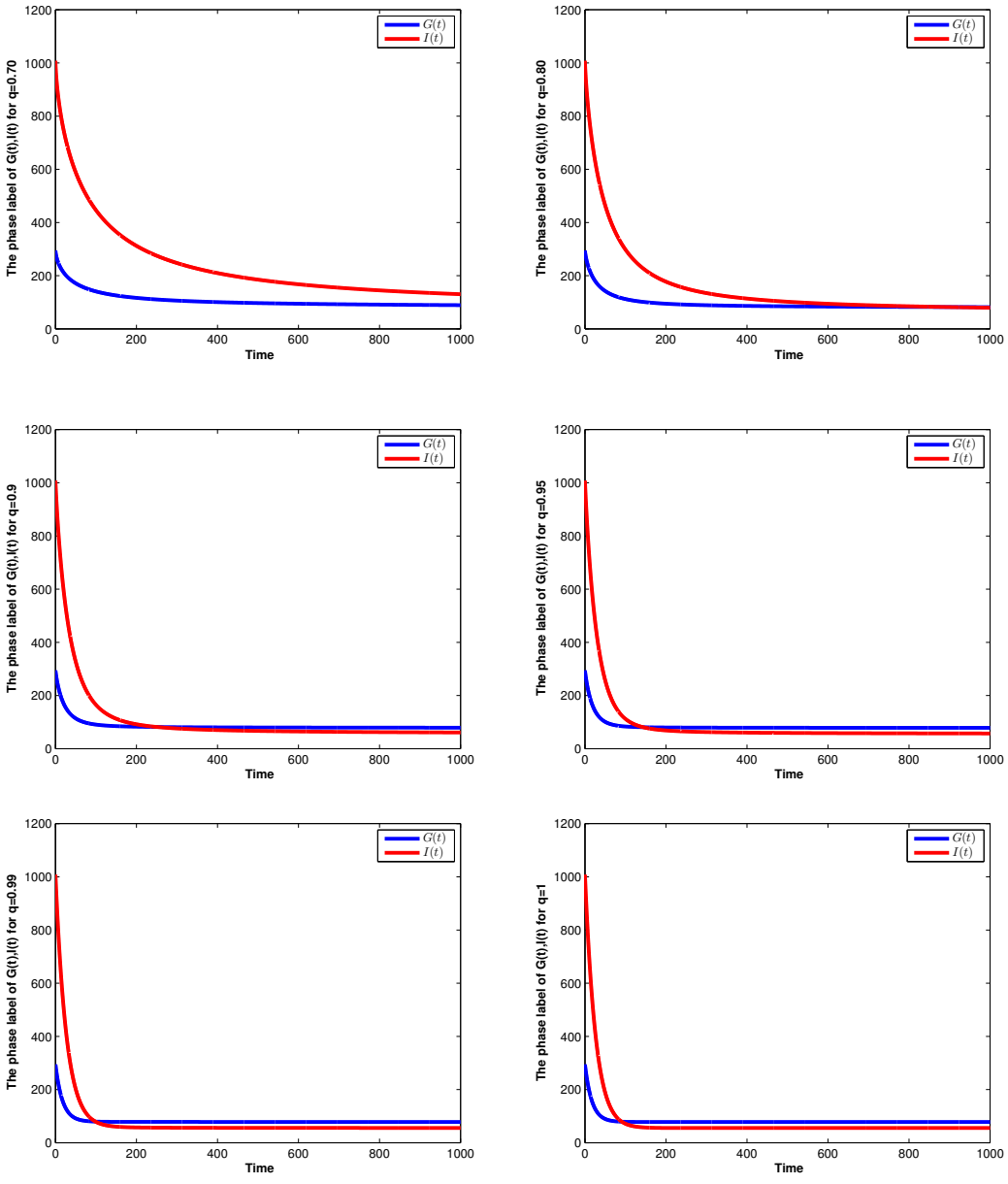

Figure 2. Phase plot $(G - I)$ for different values of q.

By Theorem 5.1, the equilibrium point E^* is stable of system (2.4). Behavior of $G(t)$, and $I(t)$, for different values of h, showing glucose and insulin dynamics are shown in Figures 3 and 4. Also, the behavior of Glucose, and Insulin concentration versus time for different cases $h = 0.75$, $h = 0.85$, and

$h = 0.95$ see Figure 5.

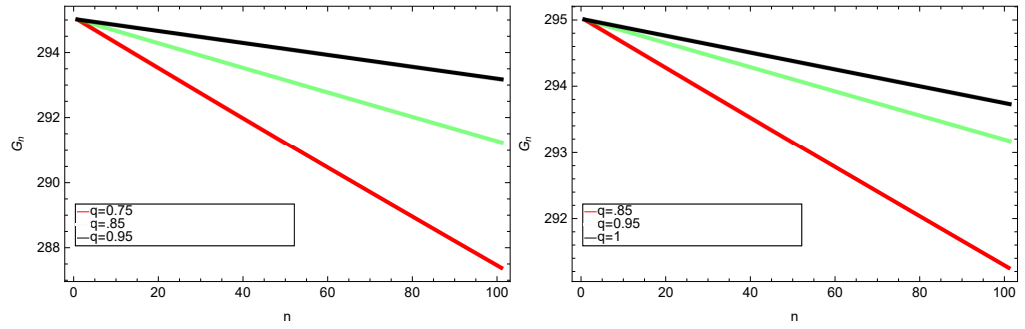

Figure 3. Behaviour of $G(t)$ for different values of q, showing Glucose dynamics.

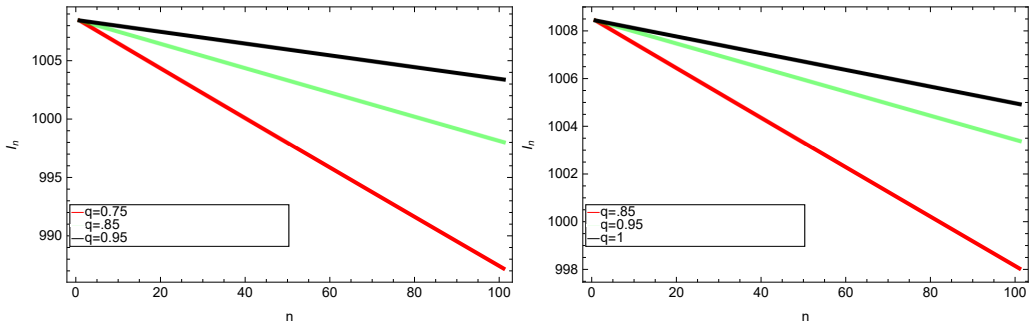

Figure 4. Behaviour of $I(t)$ for different values of q, showing insulin dynamics.

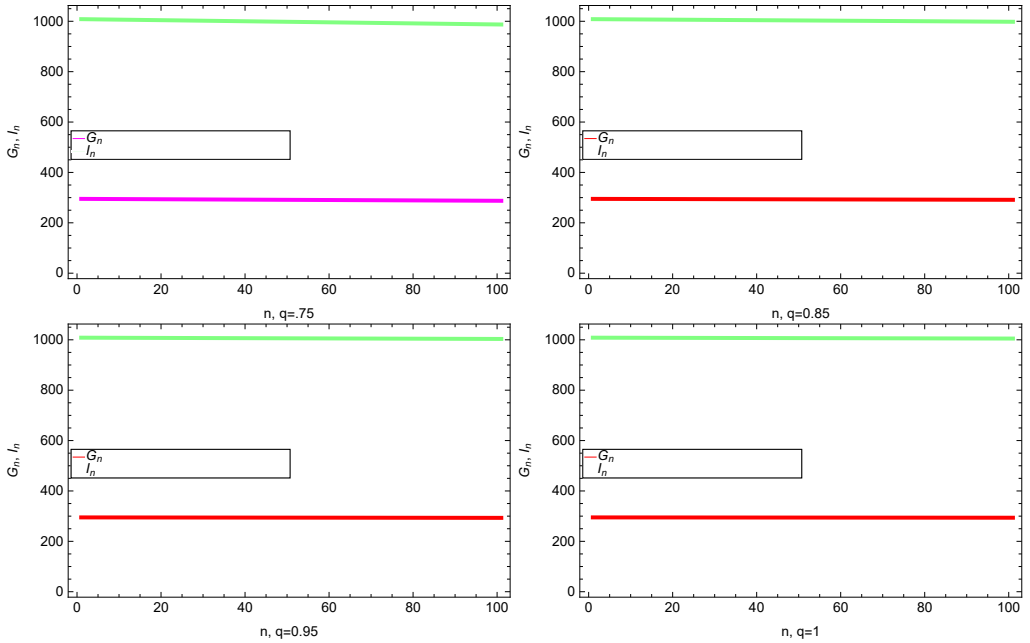

Figure 5. Glucose and insulin concentration versus time for different cases of $q = 0.75$, $q = 0.85$, $q = 0.95$, and $q = 1$.

8. Conclusions

In this work, the fractional-order model (2.3) based on the IVGTT was analyzed to learn the dynamics of interaction the glucose and insulin in the human body. Euler discretization scheme was applied to discretize fractional-order system model (2.3). Our results suggested the conditions on parameters, such the existence of periodic solution surrounding the equilibrium point. A Hopf bifurcation arises in this analysis. From the above discussions, one can deduce that the model is physiologically consistent and the suggested model may be a useful tool for further research on Diabetes Mellitus.

Availability of data and materials

The data in this work taken from the reference [26].

Conflict of interest

The author declare no conflict of interest.

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