CHAOS
Theory and Applications
in Applied Sciences and Engineering

e-ISSN: 2687-4539
RESEARCH ARTICLE
Vol.4 / No.1 / 2022 / pp.10-18
https://doi.org/10.51537/chaos.988758

Analysis of a Fractional-order Glucose-Insulin Biological System with Time Delay

B. Fernández-Carreón [*,1], **J.M. Munoz-Pacheco** [*,2], **E. Zambrano-Serrano** [β,3] **and O.G. Félix-Beltrán** [*,4]

*Faculty of Electronics Sciences, Benemérita Universidad Autonóma de Puebla, Puebla 72570, Mexico, βFacultad de Ingeniería Mecánica y Eléctrica, Universidad Autonóma de Nuevo León, N.L. 66455, Mexico.

ABSTRACT In the human glucose-insulin regulatory system, diverse metabolic issues can arise, including diabetes type I and type II, hyperinsulinemia, hypoglycemia, etc. Therefore, the analysis and characterization of such a biological system is a must. It is well known that mathematical models are an excellent option to study and predict natural phenomena to some extent. In this way, fractional-order theory provides generalizations for derivatives and integrals to arbitrary orders giving us a framework to add memory properties and an additional dimension to the mathematical models to approximate real-world phenomena with higher accuracy. In this work, we study the glucose and insulin governing mechanisms using a fractional-order version of a mathematical model. Applying the fractional-order Caputo derivative, we can investigate different concentration rates among insulin, glucose, and healthy beta cells. Additionally, the model incorporates two time-lags to represent the elapsed time of two processes, i.e., the delay in secrete insulin for a blood glucose increment and the lag to get a glucose reduction caused by raised insulin level. Analytical results of the equilibrium points and their corresponding stability are given. Numerical results, including phase portraits and bifurcation diagrams, reveal that the fractional-order increases the chaotic regions, leading to potential metabolic problems. Vice versa, the system seems to work correctly when the behavior evolves to periodic windows.

KEYWORDS
Chaos
Chaotic systems
Fractional-orders
Glucose-insulin
Time-delay

INTRODUCTION

One of the most known metabolic issues is called diabetes mellitus, in which the blood sugar control mechanism is disrupted. As a result, insulin, the main control factor is not released at proper times, or the body cells are unaware of its presence (ADA 2020; Shabestari *et al.* 2018; Lozano 2006; Emerging Risk Factors Collaboration *et al.* 2010). Various pathological processes are involved in the development of diabetes mellitus, although the vast majority of cases can be included in two categories. In the first one, type 1 diabetes mellitus, where the cause is an absolute deficiency in insulin secretion, often with evidence of autoimmune destruction of pancreatic cells. The second and most typical case is type 2 diabetes mellitus, which is provoked by two factors: insulin resistance (generally associated with obesity), and an inadequate compensatory secretory response (Lozano 2006; R.Rosalba *et al.* 2018; Shabestari *et al.* 2018; ADA 2020; Bertram and Pernarowski 1998). Other disorders include hyperglycemia which is characterized by high blood sugar levels. In contrast, hypoglycemia, also known as low blood glucose or sugar, occurs when the level of glucose in the blood falls below normal. Hypoglycemia can be a side effect of insulin and other types of diabetes medicines that help the body produce more insulin.

Those metabolic disorders are a world problem according to World Health Organization (WHO). For instance, Mexico is the sixth country with diabetic patients and the seventh in obesity (Statista 2019) in the world, therefore, the prevalence of diabetes due to a previous diagnosis has increased with a positive annual trend of 2.7%. In 2016, the prevalence of diabetes was 9.4% higher than in 2012 and at least in Mexico until 2016 there were just over 6.4 million people diagnosed with diabetes, about 60,000 more than in 2012. 48.1% of people with diabetes also have a previous diagnosis of hypertension. This prevalence increases to 50.4%, if they live in urban areas, and to 60%, if they are 60 years

Manuscript received: 1 September 2021,
Revised: 2 December 2021,
Accepted: 14 December 2021.

[1] bere.fc.03@gmail.com
[2] jesusm.pacheco@correo.buap.mx (**Corresponding Author**)
[3] erneszambrano@gmail.com
[4] olga.felix@correo.buap.mx

old or older. 50.4% of people with diabetes also have a previous medical diagnosis of high cholesterol, which increases to 52.6% if they live in rural areas, and 55.5% if they are between 40 and 59 years old. 40.4% of people with diabetes also have obesity; this prevalence increases by 49.7% if they are between 40 and 59 years old (R.Rosalba *et al.* 2018; Statista 2019).

As can be noted, people with obesity and hypertension, who are prone to suffer metabolic disorders related to the proper regulation of insulin and glucose, are rapidly increasing each year (Shabestari *et al.* 2018; ADA 2020). Thus, many scientific areas are facing this problem from diverse points of view. It is well known that mathematical models are a proved option to understand the nonlinear dynamics of biological systems to some extent. *The goal is to get a more realistic model that covers all potential scenarios of the metabolic disorders in the glucose-insulin system*. In this manner, we may predict with a better approximation the health issues associated with insulin levels and how it affects glucose metabolism. Additionally, novel medical treatments could be carried on for better control of diabetes mellitus. Some pioneering works on this subject are those described by (Bajaj *et al.* 1987; Sarika *et al.* 2008; Lenbury *et al.* 2001; Chuedoung *et al.* 2009).

As first attempt to improve the precision of the models, many published works have included time-delays (Al-Hussein *et al.* 2020; Shabestari *et al.* 2018; Sarika *et al.* 2008; Palumbo *et al.* 2007; Chuedoung *et al.* 2009; Rajagopal *et al.* 2018). For instance, (Shabestari *et al.* 2018) analyzed the impact of different time lags in the behavior of insulin level that needs some time instants for having presence in plasma; and the lapsed time for an adequate glucose stimulation. In Ref. (Al-Hussein *et al.* 2020), they added an extra term to represent the insulin decline due to glucose interchange. The impact of the partial time lags in an electrically coupled Izhikevich neuron model was examined by (Shafiei *et al.* (2019)). There, it was shown that if the probability of partial time delays increases may imply the emergence of complex dynamical behaviors. A graphical representation of the time-delay effect for equations given by $\dot{X} = F(t, X(t), X(t-\tau))$ is shown in Fig. 1.

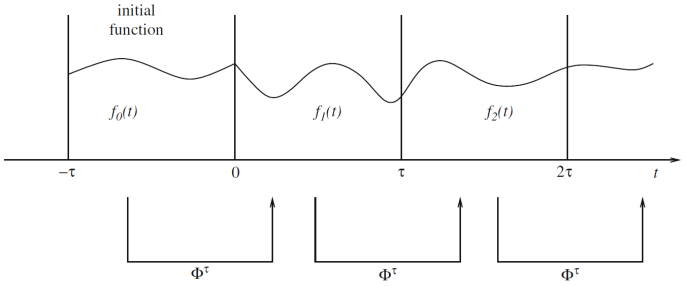


Figure 1 Implication of time-dependent delay in the solution of Delay Differential Equations (DDEs) (Lakshmanan and Senthilkumar 2010).

We observe that the solution is approximated mapping a initial function onto other subsequent functions in time intervals τ.

Moreover, the fractional calculus is recognized as one suitable option to increase the accuracy of the biological mathematical models because it permits the inclusion of arbitrary orders for the derivative operators in the differential equations of the underlying system (Ionescu *et al.* 2017; Rihan 2013; Teka *et al.* 2018; Assadi *et al.* 2017). Therefore, the biological system can have an extra degree of freedom, i.e., a real parameter given by the fractional order, to represent distinct behaviors. Additionally, the fractional-order provides a memory effect into the time evolution of the system, since its future solutions will depend on all past times and not only from recent events. A graphical representation of the memory could be given in a numerical fashion. Fig. 2 presents the fading memory in fractional-order systems as a function of binomial coefficients $c_j^{(q)}$. To compute the solution w_k, is necessary the whole vector of previous solutions, i.e., w_{k-1}, w_{k-2} , . . . , w_0. However, those previous solutions are weighted by the binomial coefficients. It means that the initial condition is always affected by a lower value than the former solutions. Because of that, we mention that past events contribute lesser than recent events to the current state.

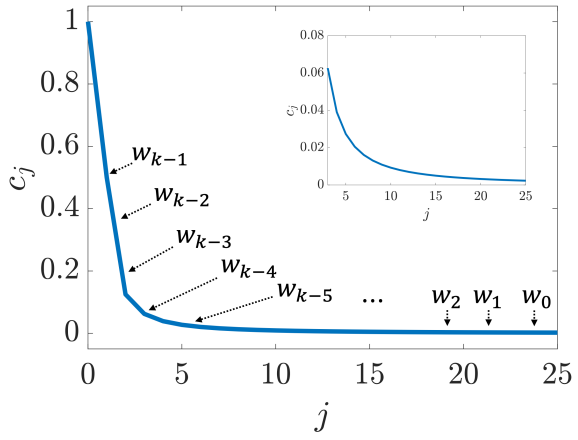


Figure 2 Numerical point of view of the fading memory of fractional-order systems according binomial coefficients $c_0^{(q)} = 1$, and $c_j^{(q)} = \left(1 - \frac{1+q}{j}\right) c_{j-1}^{(q)}$ with $q = 0.5$.

As a result, various works focusing on examining time lags for describing biological systems defined by fractional derivatives have been lately published. (Chinnathambi *et al.* 2021; Rihan *et al.* 2021; Singh and Pandey 2021; Yao and Tang 2021). Regarding fractional-order glucose-insulin models, (Zambrano-Serrano *et al.* 2018) analyzed the synchronized behavior between two β-cells-based fractional-order models under various cases of bursting signals. (Munoz-Pacheco *et al.* 2020) studied the estimation of metabolic disorders such as diabetes mellitus, hypoglycemia, and hyperinsulinemia using arbitrary order derivatives represented by a singular kernel.

In this framework, the fractional calculus-based models are essential to accurately capture the biological behaviors, including diabetes's related problems, and necessary to understanding this open topic. This work reports a time-delay chaotic glucose-insulin system with fractional differential equations. Our model incorporates Caputo derivatives to investigate the implications of the power-law memory kernel with the glucose-insulin interplay. Additionally, a pair of time delays define the lag between glucose detection and insulin secretion. Using the fractional calculus theory, we demonstrate the equilibrium points' stability and determine the fractional-order value where the system may present chaotic oscillations. We also derive numerical observations such as phase portraits and bifurcation diagrams to compare the integer and fractional-order models. The obtained results are consistent with the theoretical deductions and agree with previous findings in the area.

The paper outline is as follows. Section II introduces the proposed biological model along with its system parameters. Section III demonstrates the stability of the model for both equilibrium points and fractional-order. Section IV gives the results of the numerical simulations, and finally, Section V presents the conclusion.

FRACTIONAL-ORDER GLUCOSE-INSULIN METABOLIC SYSTEM WITH TIME LAGS

This section presents the proposed fractional-order glucose-insulin metabolic regulatory system with time delay inspired by the work reported in (Shabestari *et al.* 2018). They introduced an integer-order model with time lags to describe the primary control of insulin secretion, and glucose metabolism by the pancreatic beta cells in a feedback operation.

The model can represent the following phases. Typically, during meal consumption, the level of glucose increases considerably. Then, those levels are detected by the regulatory system, which promotes the generation and liberation of insulin by beta-cells. Next, the glucose concentration minimizes by the action of high levels of insulin, provoking that the human body burns and preserves nutrients. The second phase explains how insulin production reduces as a function of the average glucose level, for instance, when the organism does not receive any meal for a long time interval. As a result, the regulatory system changes from absorption to the post-absorption stage. One can see that this simple oscillatory process with negative feedback sustains a proper glucose level for the whole body, including organs and tissues. The reported integer-order model by (Shabestari *et al.* 2018) is:

$$\begin{aligned}
\frac{dx}{dt} &= r_1 y(t-\tau_g)z(t-\tau_g) - r_2 x + c_1 z(t-\tau_g),\\
\frac{dy}{dt} &= \frac{R_3 N}{z} - R_4 x(t-\tau_i) + C_2,\\
\frac{dz}{dt} &= R_5(y-\hat{y})(T-z) + R_6 z(T-z) - R_7 z,
\end{aligned} \tag{1}$$

where $x(t)$, $y(t)$, $z(t)$, and $\hat{y}$ represent the insulin level, glucose level, beta-cells number and the glucose metabolism considering its basal state, respectively. According to clinical experiments by (Palumbo *et al.* 2007), the delay for the insulin production, as a result of blood glucose level rising, could be set $\tau_g = 0.56$. The delay between augmented insulin level and glucose reduction is $\tau_i = 0.05$ as suggested (Prager *et al.* 1986).

Table 1 System parameters for fractional-order glucose-insulin metabolic regulatory system.

Parameter	Value	Parameter	Value	Parameter	Value
r_1	0.472	r_2	0.25	R_3	0.82
R_4	0.6	R_5	0.3	R_6	0.3
R_7	0.2	$\hat{y}$	1.42	N	1.27
T	1.5	c_1	0.1	C_2	0.8

Indeed, certain metabolic disorders, such as hyperglycemia (extremely high glucose) and hypoglycemia (low glucose), are associated with inaccurate time delay values. $r_1 y(t-\tau_g)z(t-\tau_g)$ explains the increments both insulin and glucose as a function of the time delay τ_g; $r_2 x$ means the speed of insulin reduction unassociated with glucose; $c_1 z(t-\tau_g)$ s the insulin raising rate as a function of the beta-cells, which does not depend on any other element. Additionally, the average number of beta-cells is represented as N; while the glucose decreasing cadence when the insulin is secreted with τ_i is given by $R_4 x(t-\tau_i)$. T is the entire population of beta-cells; $R_5(y-\hat{y})(T-z)$ denotes the increment of dividing beta-cells against the non-dividing ones that are induced by the interaction between glucose and the starving stage. $R_6 z(T-z)$ means raise of z because of synergy relating to dividing and nondividing beta-cells, whereas $R_7 z$ is its diminution. (Prager *et al.* 1986; Chuedoung *et al.* 2009; Shabestari *et al.* 2018).

The behavior of the *integer-order* glucose-insulin system (1), with delays $\tau_g = 0.56$ $\tau_i = 0.05$, initial conditions $[x(0), y(0), z(0)] = [6.03, 1.79, 0.82]$, and parameters in Table 1 is shown in Fig. 3. We observe that the system behaves periodically, presumably having a healthy behavior, i.e., the interaction between glucose and insulin is correct.

Fractional-order model derivation

Motivated by the memory characteristics of the arbitrary-order derivatives, we derive herein a fractional-order version of the glucose-insulin system (1). By using the Caputo derivative, we obtain

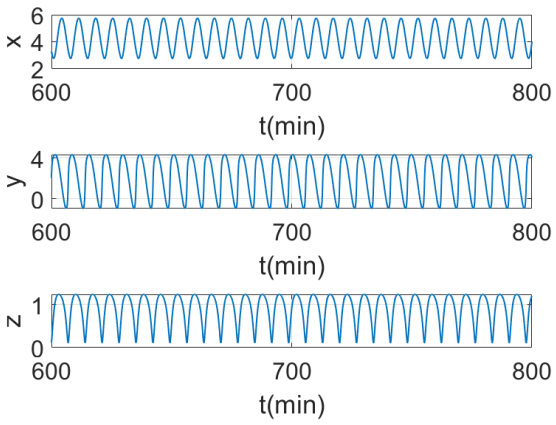
$$\begin{aligned}
{}_{t_0}^{C}D_t^q x(t) &= r_1 y(t-\tau_g)z(t-\tau_g) - r_2 x + c_1 z(t-\tau_g),\\
{}_{t_0}^{C}D_t^q y(t) &= \frac{R_3 N}{z} - R_4 x(t-\tau_i) + C_2,\\
{}_{t_0}^{C}D_t^q z(t) &= R_5(y-\hat{y})(T-z) + R_6 z(T-z) - R_7 z.
\end{aligned} \tag{2}$$

where q represents the fractional-order and ${}_{t_0}^{C}D_t^q(\cdot)$ is defined by

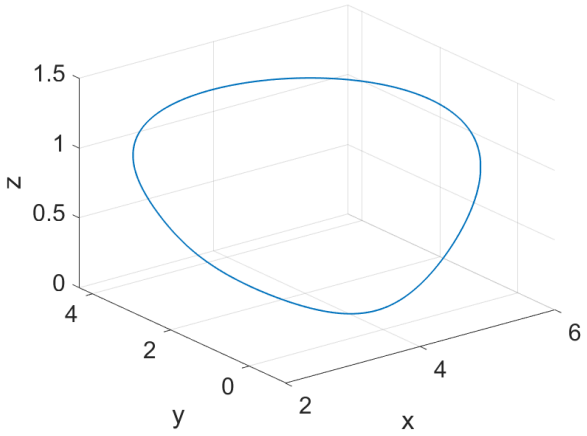
Definition 1 *Consider $f : [0, +\infty] \to \mathbb{R}$ as a function with order $n-1 \leq q < n$, thus, it can be denoted by the fractional-order derivative in the Caputo sense as*

$${}_{t_0}^{C}D_t^q g(t) = \Delta \int_{t_0}^{t} \frac{g^{(n)}(\tau)}{(t-\tau)^{q+1-n}} d\tau, \quad t > 0, \tag{3}$$

where Δ is the Gamma function of $\frac{1}{\Gamma(n-q)}$ and $n-1 \leq q < n$.



(a)



(b)

Figure 3 (a) Time evolution and (b) phase portrait of the integer-order glucose-insulin system (1) under $\tau_i = 0.05$ and $\tau_g = 0.56$. $[x, y, z]$ represent the glucose, insulin, and beta-cells, respectively.

According to (Diethelm 2010), the Caputo and Riemann-Liouville (RL) derivatives are equivalent for initial value problems (IVP) with similar initial conditions. Moreover, the Caputo derivative interpretation (3) generalizes formally the integer-order derivative using Laplace transformation. Finally, it is well known that Caputo derivative can be the left inverse of the fractional integral given by RL.

Theorem 1 *Diethelm (2010) For $n \geq 0$ and g being a continuous function, then*

$$ {}_{t_0}^{C}D_t^{qRL}J^q g(x) = g(x), \tag{4} $$

but not its right inverse:

Theorem 2 *Diethelm (2010) Being $n \geq 0$, $m = \lceil n \rceil$ with $g \in \Theta^m[a_1, a_2]$. Thus*

$$ {}^{RL}J_{t_0}^{qC}D_t^q g(x) = g(x) - \sum_{k=0}^{m-1} \frac{D^k g(a_1)}{k!}(x-a_1)^k, \tag{5} $$

where ${}^{RL}J^q$ means the RL integral. We choose the Caputo derivative because the IVP in the fractional-order domain can be stated analogously to the integer-order case, which gives us a physical interpretation of the fractional derivative (Petráš 2011). Additionally, we can represent the memory characteristics of the power-law kernel in the dynamical evolution of biological systems (Munoz-Pacheco *et al.* 2020).

STABILITY ANALYSIS

Equilibrium points

As the first step, we should analyze the stability of the equilibrium points under the related theory of delay-time systems (Lakshmanan and Senthilkumar 2010; Lazarević 2011; Naifar *et al.* 2019). By selecting $f(x, y, z) = 0$ and system parameters of Table 1 for the fractional-order glucose-insulin system (2), we obtain the following equilibrium points, $E_1 = (-1.97, 1.77, -0.53)$ and $E_2 = (3.19, 1.59, 0.94)$. By computing the Jacobian matrix, we can study the local asymptotic stability at each one of the equilibrium points. Thus, we have

$$ J_E = \begin{pmatrix} J_{11} & J_{12} & J_{13} \\ J_{21} & 0 & J_{23} \\ 0 & J_{32} & J_{33} \end{pmatrix}. \tag{6} $$

$$ |J_E - \lambda I| = 0, \tag{7} $$

where $J_E = J_0 + e^{-\lambda\tau}J_{\tau_g,\tau_i}$. J_0 is the Jacobian matrix of system (2) without delay ($\tau = 0$), whereas J_{τ_g,τ_i} is the Jacobian matrix under the delays τ_g and τ_i, respectively. I indicates an identity matrix whereas λ the corresponding eigenvalues.

Using the parameters in Table 1, we obtain

$$ J_{11} = -\tfrac{1}{4}, \quad J_{12} = \tfrac{59z^*e^{-\lambda\tau_g}}{125}, \quad J_{13} = e^{-\lambda\tau_g}\left(\tfrac{59y^*}{125} + \tfrac{1}{10}\right), $$
$$ J_{21} = -\tfrac{3e^{-\lambda\tau_i}}{5}, \quad J_{23} = -\tfrac{5207}{5000z^{*2}}, $$
$$ J_{32} = \tfrac{9}{20} - \tfrac{3z^*}{10}, \quad J_{33} = \tfrac{169}{250} - \tfrac{3z^*}{5} - \tfrac{3y^*}{10}. $$

Evaluating $E^* = (x^*, y^*, z^*)$ in Jacobian matrix (6), the pseudo-characteristic equations for E_1 and E_2 are, respectively.

$$ \begin{aligned} \lambda^3 - 0.2096\lambda^2 - 0.4099e^{-\lambda\tau} + 2.176\lambda \\ +0.1488\lambda e^{-\lambda\tau} + 0.5728 \quad = 0. \end{aligned} \tag{8} $$

$$ \begin{aligned} \lambda^3 + 0.6131\lambda^2 - 0.1826e^{-\lambda\tau} + 0.2917\lambda \\ -0.2652\lambda e^{-\lambda\tau} + 0.05022 \quad = 0. \end{aligned} \tag{9} $$

with $\tau = \tau_g + \tau_i$. We observe that both equilibrium points are saddle points as shown in Table 2. E_1 is index-2 since has one real negative eigenvalue and a complex conjugate pair with a positive real part. On the other hand, E_2 is index-1 because has three real eigenvalues with two negative and one positive (Sprott 2015). It is worthy to note that the stability of equilibrium points depends on the time lags.

Table 2 Stability type of the equilibrium points for the proposed fractional-order time-delay glucose-insulin system with $\tau_g = 0.56$ and $\tau_i = 2.55$.

Equilibrium points	Eigenvalues	Stability
$E_1 = (-1.97, 1.77, -0.53)$	$\lambda_1 = -0.044,$ $\lambda_{2,3} = 0.230 \pm 1.449i,$	index-2 saddle point
$E_2 = (3.19, 1.59, 0.94)$	$\lambda_1 = 1.697,$ $\lambda_2 = -0.782$ $\lambda_3 = -1.528$	index-1 saddle point

Now, the next step is focusing on the positive equilibrium point E_2 to examine its repercussions in the system dynamics since it is associated profoundly with the discrete-time lags. For time delay τ, we may denote the characteristic equation as

$$\eta_1(\lambda) + \eta_2(\lambda)e^{-\lambda\tau} = 0, \tag{10}$$

that is the linearized case, i.e. evaluated at $E^* = (x^*, y^*, z^*)$, with

$$\begin{aligned} \eta_1(\lambda) &= \lambda^3 + \eta_{1,1}\lambda^2 + \eta_{1,2}\lambda + \eta_{1,3}, \\ \eta_2(\lambda) &= \eta_{2,1}\lambda^2 + \eta_{2,2}\lambda + \eta_{2,3}, \end{aligned} \tag{11}$$

Without any loss of generality, the characteristic eq. (10) when the positive equilibrium point E_2 is not affected by the time delays ($\tau_g = 0$ and $\tau_i = 0$), becomes

$$\lambda^3 + (\eta_{1,1} + \eta_{2,1})\lambda^2 + (\eta_{1,2} + \eta_{2,2})\lambda + (\eta_{1,3} + \eta_{2,3}) = 0, \tag{12}$$

Using Routh-Hurwitz criterion, the roots of (6) have non-positive real parts, that is, E^* is asymptotically stable for $P_1 = \eta_{1,1} + \eta_{2,1} > 0$, $P_2 = \eta_{1,3} + \eta_{2,3} > 0$, and $P_3 = (\eta_{1,1} + \eta_{2,1})(\eta_{1,2} + \eta_{2,2}) - (\eta_{1,3} + \eta_{2,3}) > 0$. Due to $P1 = 0.6131$, $P_2 = -0.132$, and $P_3 = 0.148$, E_2 is unstable when $\tau = 0$.

Minimum fractional-order

As well known, the stability region for fractional-order systems extends beyond the left-half plane in the complex plane to the positive one also (Petráš 2011), as shown in Fig. 4.

Let us consider the standard form of a nonlinear dynamical system in the fractional-order domain as

$${}_{t_0}^{C}D_t^q x = Ax + Bu, \tag{13}$$

where $x \in \mathbb{R}^n$, $u \in \mathbb{R}^m$,, $A \in \mathbb{R}^{n\times n}$, and $B \in \mathbb{R}^{n\times m}$; and ${}_{t_0}^{C}D_t^q x = [{}_{t_0}^{C}D_t^q x_1, \ldots, {}_{t_0}^{C}D_t^q x_n]^T$ denotes Caputo derivative while q is the fractional-order. For the autonomous scenario, system (13) can be expressed by ${}_{t_0}^{C}D_t^q x = Ax$, being $x(0) = x_0 and\ 0 < q < 1$. In this manner, its stability conditions are analyzed by the next postulates (Petráš 2011; Munoz-Pacheco *et al.* 2020):

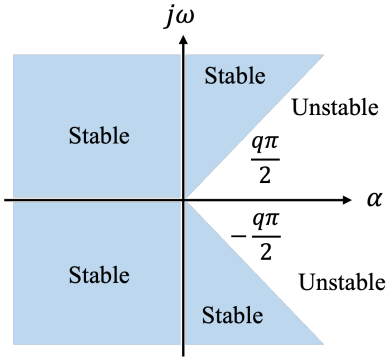


Figure 4 Stability region of fractional order linear time invariant systems with order $0 < q < 1$.

- A system in the form of ${}_{t_0}^{C}D_t^q x = Ax$ is considered *asymptotically stable* as long as the whole set of eigenvalues, λ, satisfies $|\arg(\lambda)| > \frac{q\pi}{2}$, which indicates the evolution $x(t)$ converges to 0 as t^{-q}.
- A system in the form of ${}_{t_0}^{C}D_t^q x = Ax$ is considered *stable* as long as the whole set of eigenvalues, λ, satisfies $|\arg(\lambda)| > \frac{q\pi}{2}$ whereas the critical eigenvalues fulfills with $|\arg(\lambda)| = \frac{q\pi}{2}$ having a geometric multiplicity of one.

Therefore, for a certain fractional-order q, system ${}_{t_0}^{C}D_t^q x = Ax + Bu$, is unstable when at least one of their eigenvalues at equilibrium point E^*, yields (Petráš 2011)

$$q > \frac{2}{\pi}\arctan\frac{|Im(\lambda)|}{|Re(\lambda)|}. \tag{14}$$

For the fractional-order delay-time glucose-insulin system (2), the small value of the fractional-order where the system becomes unstable is $q \geq 0.9$ under the eigenvalues from equilibrium point E_2. This result suggest that chaos behavior, which may be related to an metabolic disorder of the glucose-insulin biological system, can be observed at interval $0.9 \leq q \leq 1$.

Lemma 1 *An index-2 saddle point is an equilibrium point that preserves the next conditions for their eigenvalues. It must have a negative real eigenvalue $\lambda_1 < 0$, and a pair of complex eigenvalues that satisfies $|arg(\lambda_2)| = |arg(\lambda_3)| < q\pi/2$. Viceversa, when $\lambda_1 > 0$ and $|arg(\lambda_2)| = |arg(\lambda_3)| > q\pi/2$, we have an index-1 saddle point.*

From Lemma 1, we confirm that equilibrium points E_1 and E_2 are index-2 and index-1 saddle points respectively. In next section, we explore the effect of the fractional-order in the dynamical behavior of time-delay glucose-insulin system (2).

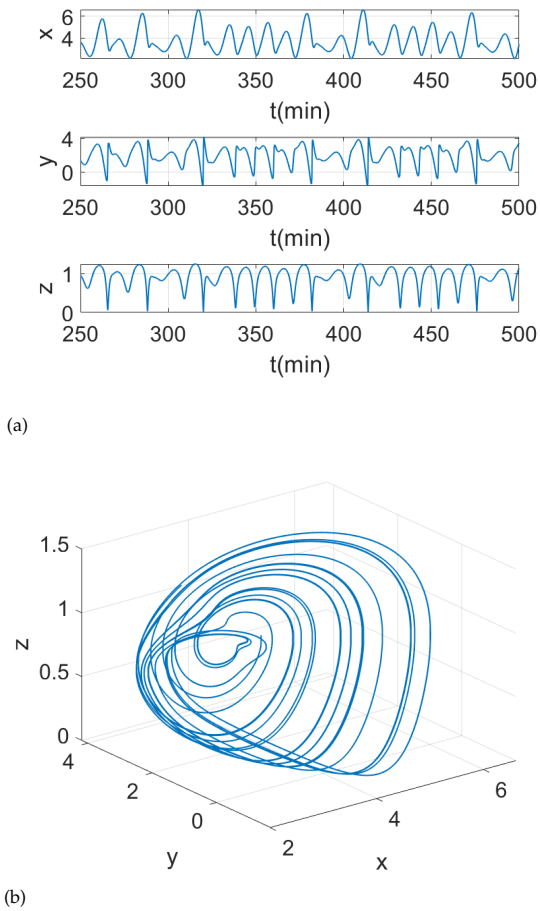


Figure 5 (a) Time evolution and (b) phase portrait of the fractional order time-delay glucose-insulin system (2) with $q = 0.95$, $\tau_i = 2.55$, and $\tau_g = 0.56$. $[x, y, z]$ represent the glucose, insulin, and beta-cells, respectively. 50% of iterations were discard to avoid transient effects.

NUMERICAL RESULTS AND DISCUSSION

To compute the solutions of system (2), we apply the numerical algorithm proposed by (Petráš 2011) which claims that the general numerical solution of the fractional differential equation

$$ {}_aD_t^q w(t) = f(w(t), t), $$

can be expressed as

$$ w(t_k) = f\left(w(t_{k-1}), t_{k-1}\right) h^q - \sum_{j=1}^{k} c_j^{(q)} w(t_{k-j}), \qquad (15) $$

with $k = 1, 2, \ldots, n$, $n = \frac{T_f}{h}$, h the time step, and $c_j^{(q)}$ are binomial coefficients given by $c_0^{(q)} = 1$, and $c_j^{(q)} = \left(1 - \frac{1+q}{j}\right) c_{j-1}^{(q)}$.

This approach is based on the fact that for a wide class of functions, the three definitions, Caputo, Riemann-Liouville and Grünwald-Letnikov, are equivalent. In this manner, the numerical solution of fraction-order time-delay glucose-insulin system (2) applying algorithm (15) can be obtained with

$$ \begin{aligned} x_k &= \left(r_1 y_{k-1-m_1} z_{k-1-m_1} - r_2 x_{k-1} + c_1 z_{k-1-m_1}\right) h^q - \sum_{j=1}^{k} c_j^{(q)} x_{k-j}, \\ y_k &= \left(\frac{R_3 N}{z_{k-1}} - R_4 x_{k-1-m_2} + C_2\right) h^q - \sum_{j=1}^{k} c_j^{(q)} y_{k-j}, \\ z_k &= \left(R_5 (y_{k-1} - \hat{y})(T - z_{k-1}) + R_6 z_{k-1}(T - z_{k-1}) - R_7 z_{k-1}\right) h^q \\ &\quad - \sum_{j=1}^{k} c_j^{(q)} z_{k-j}, \end{aligned} \qquad (16) $$

where $m_1 = \frac{\tau_g}{h}$ and $m_2 = \frac{\tau_i}{h} \in \mathbb{Z}^+$. With $h = 0.01$, $q = 0.95$, initial conditions $[x(t), y(t), z(t)] = [6.03, 1.79, 0.82]$ for $-\tau_g \leq t \leq 0$, and parameters in Table 1, the fractional-order time-delay glucose-insulin system (2) leads to a chaos behavior as given in Fig. 5. The revealed results agree well with the literature in the area (Baghdadi *et al.* 2015; Al-Hussein *et al.* 2020; Kroll 1999; Aram *et al.* 2017), where a chaotic behavior in the biological system is stated as indication of a probable health issue (metabolic dysfunction).

Due to the importance of analyzing the glucose-insulin system under several conditions (Chuedoung *et al.* 2009), we compute the bifurcation diagrams for two cases. First, we discover the relation between the fractional-order and dynamical behaviors of the glucose-insulin regulatory system.

To do that, we have chosen $\tau_g = 0.56$, and $\tau_i = 2.55$ because they coincide with those lags seen in tests carried out on healthy human beings, where there is usually 1 or 2 minutes delay for insulin to be secreted. Additionally, the delay increases up to 10 minutes in children with malnutrition (Bertram and Pernarowski 1998; Forrest and Payne Robinson 1925).

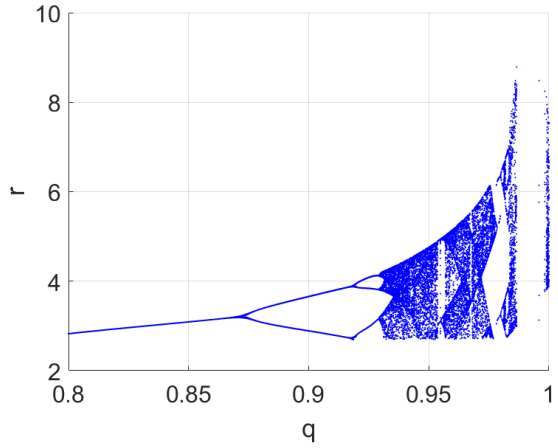


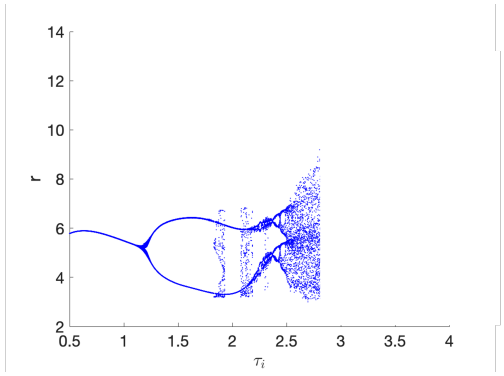
Figure 6 Bifurcation diagram for q with $\tau_g = 0.56$ y $\tau_i = 2.55$.

The bifurcation diagram for the fractional-order $q = 0.95$ is illustrated in Fig. 6. Herein, r defines glucose-insulin behavior as $r = \sqrt{x(t_k)^2 + y(t_k)^2}$ (Muñoz-Pacheco 2019; Munoz-Pacheco *et al.* 2020). We also follow the suggestions given in (Jafari *et al.* 2021) for getting a correct bifurcation diagram.

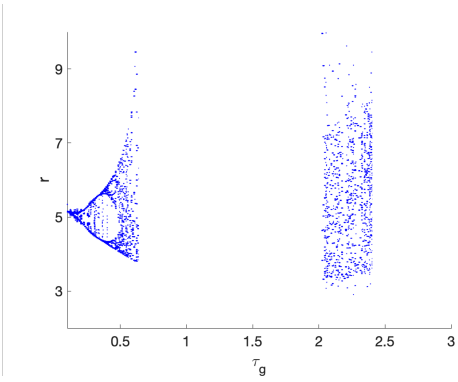
The extra parameter q permits us to gain insights into the glucose-insulin regulatory system because the memory effects can be taken into account in the process of secreted insulin in response to glucose concentrations. Figure 6 shows the bifurcation diagram for the case $0.93 \leq q \leq 1$. One can observe a chaotic behavior as was predicted by Eq. 14 and Lemma 1. It is worthy to note that not only the chaotic behavior is observed for integer-order $q = 1$ but also for fractional-orders. This result suggest that the regulation of

the glucose trough insulin is highly complex when a power-law kernel is considered to describe the long memory effects. For a fractional-order $q < 0.93$, the glucose-insulin system evolves to regular oscillations, which could be associated to a healthy state. A similar periodic behavior has been observed for typical results in the human metabolic system (Tasaka *et al.* 1994; Li *et al.* 2006).

As second scenario, we study the implications of the time-delay on the fractional-order system (2). As first step, we compute the bifurcation diagram of the lags related to insulin (τ_i) and glucose (τ_g) but using an integer-order, i.e. *no memory*. The chaotic regions are confined to an small sections about $\tau_i = 2.5$, and $\tau_g = 0.5$ and $\tau_g = 2.5$ as given in Fig. (7). When memory is not considered, the influence of delays may not be so decisive for the proper operation of the glucose-insulin feedback mechanism.



(a)



(b)

Figure 7 Bifurcation diagram for the integer-order time-delay glucose-insulin system (2). (a) τ_i with $\tau_g = 0.56$ y $q = 1$; and (b) τ_g with $\tau_i = 2.55$ y $q = 1$.

In our last case, we now compute the bifurcation diagram of the glucose-insulin regulatory system (2) with a fractional-order $q = 0.95$, i.e., with a *power-law-type memory*, as displayed in Fig. 8. We found that the chaotic regions are broader than the integer-order case.

For both delays a period-doubling cascade leads to chaotic states about $\tau_i \approx 2.1$ and $\tau_g \approx 0.2$. Next, the chaotic behavior is disrupted by a crisis scenario ($\tau_i \approx 3.5$ and $\tau_g \approx 1.5$), and the system shifts to one- or two-period oscillations but only to converge to chaos again under the same mechanism at $\tau_i \approx 3.9$ and $\tau_g \approx 1.8$.

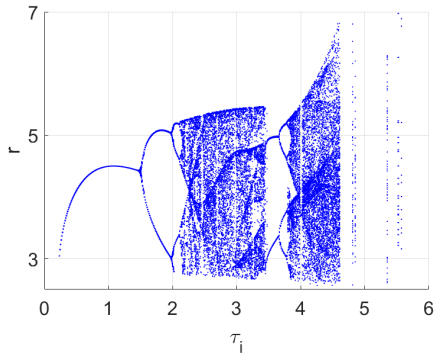
For both delays a period-doubling cascade leads to chaotic states about $\tau_i \approx 2.1$ and $\tau_g \approx 0.2$. Next, the chaotic behavior is disrupted by a crisis scenario ($\tau_i \approx 3.5$ and $\tau_g \approx 1.5$), and the system shifts to one- or two-period oscillations but only to converge to chaos again under the same mechanism at $\tau_i \approx 3.9$ and $\tau_g \approx 1.8$.

Besides, the spectrum of Lyapunov exponents for two different values of q are computed and showed in Table 3. They were calculated employing the approach proposed in (Sano and Sawada 1985). These results display a positive Lyapunov exponent implying that chaotic behavior is observed due to sensitivity to initial conditions.

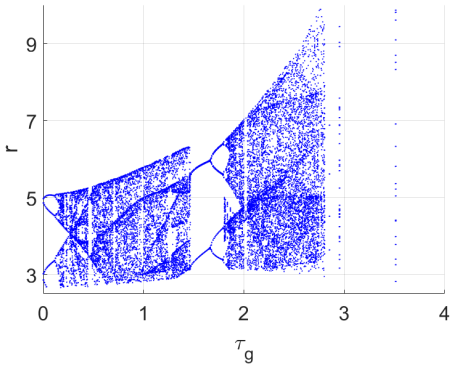
Table 3 Lyapunov exponents for different values of q.

Fractional-order	Spectrum of Lyapunov exponents		
$q = 0.97$	$LE_1 = 0.434$	$LE_2 = 0$	$LE_3 = -3.25$
$q = 0.95$	$LE_1 = 0.368$	$LE_2 = 0$	$LE_3 = -2.758$

From these observations, the memory of fractional-order derivatives described by Caputo in eq. (2) elucidates new insights about the glucose-insulin regulatory system since the memory and time-delay are vital for the onset of chaos where the pancreas might not supply an adequate quantity of insulin to regulate the glucose level. Finally, the system exhibits a stable periodic state (i.e., without any reasonable condition of metabolic disruptions) when the insulin lag is lower than two minutes and fractional-order $q < 0.9$.



(a)



(b)

Figure 8 Bifurcation diagram for the fractional-order time-delay glucose-insulin system (2). (a) τ_i with $\tau_g = 0.56$ y $q = 0.95$; and (b) τ_g with $\tau_i = 2.55$ y $q = 0.95$.

CONCLUSION

The dynamical analysis of a fractional-order time-delay glucose-insulin system was performed applying the Caputo derivative. In particular, we studied the implications between the common disorders represented as chaotic states and a power-law memory kernel. It was observed that the fractional-order biological system alternates between a chaotic behavior (a health disorder) and a disorder-free state, as a function of not only time-delay but also fractional-order. We computed phase portraits and bifurcations diagrams to understand that regulatory mechanism, which confirmed that the fractional-order operator, i.e., a memory profile, provides improved accuracy of the underlying glucose-insulin disorders. Numerical simulations were in good agreement with the theoretical findings. Researchers from many scientific areas can also extend this work to other biological systems, which require considering the memory of past events in a non-Markovian approach. In future work, we will investigate a control scheme to drive the glucose-insulin system to stable behavior.

Acknowledgments

This work was supported by 2021 VIEP-BUAP project.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Availability of data and material

Not applicable.

LITERATURE CITED

ADA, A. D. A., 2020 Classification and diagnosis of diabetes: Standards of medical care in diabetes. Diabetes Care **43**: S14–S31.

Al-Hussein, A.-B. A., F. Rahma, L. Fortuna, M. Bucolo, M. Frasca, *et al.*, 2020 A new time-delay model for chaotic glucose-insulin regulatory system. International Journal of Bifurcation and Chaos **30**: 2050178.

Aram, Z., S. Jafari, J. Ma, J. C. Sprott, S. Zendehrouh, *et al.*, 2017 Using chaotic artificial neural networks to model memory in the brain. Communications in Nonlinear Science and Numerical Simulation **44**: 449–459.

Assadi, I., A. Charef, D. Copot, R. D. Keyser, T. Bensouici, *et al.*, 2017 Evaluation of respiratory properties by means of fractional order models. Biomedical Signal Processing and Control **34**: 206 – 213.

Baghdadi, G., S. Jafari, J. C. Sprott, F. Towhidkhah, and M. H. Golpayegani, 2015 A chaotic model of sustaining attention problem in attention deficit disorder. Communications in Nonlinear Science and Numerical Simulation **20**: 174–185.

Bajaj, J., G. S. Rao, J. S. Rao, and R. Khardori, 1987 A mathematical model for insulin kinetics and its application to protein-deficient (malnutrition-related) diabetes mellitus (PDDM). Journal of Theoretical Biology **126**: 491 – 503.

Bertram, R. and M. Pernarowski, 1998 Glucose diffusion in pancreatic islets of langerhans. Biophysical Journal **74**: 1722 – 1731.

Chinnathambi, R., F. A. Rihan, and H. J. Alsakaji, 2021 A fractional-order model with time delay for tuberculosis with endogenous reactivation and exogenous reinfections. Mathematical Methods in the Applied Sciences **44**: 8011–8025.

Chuedoung, M., W. Sarika, and Y. Lenbury, 2009 Dynamical analysis of a nonlinear model for glucose–insulin system incorporating delays and β -cells compartment. Nonlinear Analysis: Theory, Methods & Applications **71**: e1048 – e1058.

Diethelm, K., 2010 *The analysis of fractional differential equations: An application-oriented exposition using differential operators of Caputo type*. Springer Science & Business Media.

Emerging Risk Factors Collaboration *et al.*, 2010 Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet **375**: 2215–22.

Forrest, E. and H. M. Payne Robinson, 1925 Insulin, growth hormone and carbohydrate tolerance in jamaican children rehabilitated from severe malnutrition .

Ionescu, C., A. Lopes, D. Copot, J. Machado, and J. Bates, 2017 The role of fractional calculus in modeling biological phenomena: A review. Communications in Nonlinear Science and Numerical Simulation **51**: 141 – 159.

Jafari, A., I. Hussain, F. Nazarimehr, S. M. R. H. Golpayegani, and S. Jafari, 2021 A simple guide for plotting a proper bifurcation diagram. International Journal of Bifurcation and Chaos **31**: 2150011.

Kroll, M. H., 1999 Biological variation of glucose and insulin includes a deterministic chaotic component. Biosystems **50**: 189–201.

Lakshmanan, M. and D. Senthilkumar, 2010 *Dynamics of Nonlinear Time-Delay Systems*. Springer-Verlag Berlin Heidelberg.

Lazarević, M., 2011 Stability and stabilization of fractional order time delay systems. Scientific Technical Review **61**: 31–45.

Lenbury, Y., S. Ruktamatakul, and S. Amornsamarnkul, 2001 Modeling insulin kinetics: responses to a single oral glucose administration or ambulatory-fed conditions. Biosystems **59**: 15 – 25.

Li, J., Y. Kuang, and C. C. Mason, 2006 Modeling the glucose–insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays. Journal of theoretical biology **242**: 722–735.

Lozano, J. A., 2006 Diabetes mellitus. Offarm **25 (10)**: 66–78.

Muñoz-Pacheco, J. M., 2019 Infinitely many hidden attractors in a new fractional-order chaotic system based on a fracmemristor. The European Physical Journal Special Topics **228**: 2185–2196.

Munoz-Pacheco, J. M., C. Posadas-Castillo, and E. Zambrano-Serrano, 2020 The effect of a non-local fractional operator in an asymmetrical glucose-insulin regulatory system: Analysis, synchronization and electronic implementation. Symmetry **12**: 1395.

Naifar, O., A. M. Nagy, A. B. Makhlouf, M. Kharrat, and M. A. Hammami, 2019 Finite-time stability of linear fractional-order time-delay systems. International Journal of Robust and Nonlinear Control **29**: 180–187.

Palumbo, P., S. Panunzi, and A. De Gaetano, 2007 Qualitative behavior of a family of delay-differential models of the glucose-insulin system. Discrete and Continuous Dynamical Systems. Series B **2**.

Petráš, I., 2011 *Fractional-Order Nonlinear Systems*. Springer.

Prager, R., P. Wallace, and J. M. Olefsky, 1986 In vivo kinetics of insulin action on peripheral glucose disposal and hepatic glucose output in normal and obese subjects. The Journal of Clinical Investigation **78**: 472–481.

Rajagopal, K., V.-T. Pham, F. R. Tahir, A. Akgul, H. R. Abdolmohammadi, *et al.*, 2018 A chaotic jerk system with non-hyperbolic equilibrium: Dynamics, effect of time delay and circuit realisation. Pramana **90**: 1–8.

Rihan, F., A. Arafa, R. Rakkiyappan, C. Rajivganthi, and Y. Xu, 2021 Fractional-order delay differential equations for the dynamics of hepatitis c virus infection with ifn-α treatment. Alexandria Engineering Journal **60**: 4761–4774.

Rihan, F. A., 2013 Numerical modeling of fractional-order biological systems. Abstract and Applied Analysis **2013**: 11.

R.Rosalba, B.Ana, A.Carlos, Z.Emiliano, V.Salvador, *et al.*, 2018 Prevalencia de diabetes por diagnóstico médico previo en méxico. Salud Pública de México **60**: 1–9.

Sano, M. and Y. Sawada, 1985 Measurement of the lyapunov spectrum from a chaotic time series. Physical review letters **55**: 1082.

Sarika, W., Y. Lenburya, K. Kumnungkit, and W. Kunphasuruang, 2008 Modelling glucose-insulin feedback signal interchanges involving β-cells with delays. ScienceAsia **34**: 77–86.

Shabestari, P. S., K. Rajagopal, B. Safarbali, S. Jafari, and P. Duraisamy, 2018 A novel approach to numerical modeling of metabolic system: Investigation of chaotic behavior in diabetes mellitus. Complexity **2018**.

Shafiei, M., F. Parastesh, M. Jalili, S. Jafari, M. Perc, *et al.*, 2019 Effects of partial time delays on synchronization patterns in izhikevich neuronal networks. The European Physical Journal B **92**: 1–7.

Singh, H. K. and D. N. Pandey, 2021 Stability analysis of a fractional-order delay dynamical model on oncolytic virotherapy. Mathematical Methods in the Applied Sciences **44**: 1377–1393.

Sprott, J. C., 2015 Strange attractors with various equilibrium types. The European Physical Journal Special Topics **224**: 1409–1419.

Statista, 2019 Countries with the highest number of diabetics worldwide in 2019. https://www.statista.com/statistics/281082/countries-with-highest-number-of-diabetics/, Accessed: 2021-07-30.

Tasaka, Y., F. Nakaya, H. Matsumoto, and Y. Omori, 1994 Effects of aminoguanidine on insulin release from pancreatic islets. Endocrine journal **41**: 309–313.

Teka, W. W., R. K. Upadhyay, and A. Mondal, 2018 Spiking and bursting patterns of fractional-order izhikevich model", journal = "communications in nonlinear science and numerical simulation **56**: 161 – 176.

Yao, Z. and B. Tang, 2021 Further results on bifurcation for a fractional-order predator-prey system concerning mixed time delays. Discrete Dynamics in Nature and Society **2021**.

Zambrano-Serrano, E., J. M. Munoz-Pacheco, L. C. Gómez-Pavón, A. Luis-Ramos, and G. Chen, 2018 Synchronization in a fractional-order model of pancreatic β -cells. The European Physical Journal Special Topics **227**: 907–919.

How to cite this article: Fernández-Carreón, B., Munoz-Pacheco, J.M., Zambrano-Serrano, E., Felix-Beltrán, O.G. Analysis of a Fractional-Order Glucose-Insulin Biological System with Time Delay. Chaos Theory and Applications, 4(1), 10-18, 2022.