Hopf Bifurcation and Chaos in Time-Delay Model of Glucose-Insulin Regulatory System

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Abstract

Mathematical modeling is very helpful for non-invasive investigation of glucose-insulin interaction. In this paper a new time delay mathematical model for glucose-insulin endocrine metabolic regulatory feedback system incorporating the β-cell dynamic and function for regulating and maintaining bloodstream insulin level, has been proposed. The proposed model includes the mathematical representation of an important biological fact that the moderate hyperglycemia leads to the growth of the β-cell number (negative feedback) while extreme hyperglycemia leads to the reduction of the β-cell number (positive feedback). The dynamical behavior of the model is analyzed analytically using Hopf bifurcation theorem and numerically such as two dimensional bifurcation diagrams with respect to two essential parameters of the model are obtained. The results show that the time delay in insulin secretion in response to blood glucose level, and the delay in glucose drop due to increased insulin concentration can give rise to complex dynamics, such as periodic oscillation consistent with the biological findings and periodic doubling cascade and chaotic state which represent metabolic disorder that may lead to diabetes mellitus.

Keywords: Glucose, Insulin, Metabolic regulatory system, β-cell, Time delay, Hopf bifurcation, Chaos

1. Introduction

Diabetes mellitus (DM), which is a chronic disease, known commonly as diabetes is a syndrome of metabolic system dysfunctions, usually due to a combination of hereditary and environmental causes, causing abnormal high blood plasma sugar levels known as hyperglycemia. Glucose concentration in the plasma of a normal subject lies in the range of 80-110 [mg/dl] [1]. Plasma glucose level is controlled by complex interactions of multiple hormones and chemicals in the body, including the insulin produced in the pancreatic β-cells. Diabetes mellitus has become a disease with considerable complications such as nephropathy, retinopathy, peripheral neuropathy and blindness [2]. The number of subjects with diabetes in the world is increasing continuously every year. International Diabetes Federation (IDF) estimates that 463 million people around the world live with diabetes corresponding to 1 to 11 of the 20-79 adult population. The figure is expected to hit the 700 million people in 2045 [3].

Blood plasma glucose level is regulated by two negative feedback control loops where hyperglycemia stimulates a rapid increase in insulin charge from the pancreatic β-cells. The associated increase in plasma insulin concentration causes increased glucose removal and decreased its production by the liver which leads to a reduction in plasma glucose [4, 5]. On the other side, hyperglycemia contributes to a second negative feedback control loop by increasing the number of insulin secreting β-cells, by changing the rates of β-cell replication and death [5]. An increased β-cell number represents an increase capacity for insulin secretion which, in turn, would lead to a decrease in blood glucose.

Mathematical modeling for studying the glucose metabolism and insulin secretion or glucose-insulin interaction have a longstanding history. Mathematical models continue to become more and more accurate and clinically feasible, and evolve to be a useful resource for clinical investigation; thus playing an important role in understanding the governing mechanisms

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of the glucose-insulin regulatory [6]. Due to the great complexity of the regulatory system many mathematical models have been suggested [7, 8, 9, 10, 11] to investigate the relationship between the concentrations of plasma glucose and insulin in response to glucose charge or increase. One of the pioneer work was done in 1939 by Himsworth and his coworkers [12] where they proposed the first approach to measure the insulin sensitivity in vivo. Ackerman et al. [8] suggested a simple linear model for representing glucose tolerance test using two linear ordinary differential equations. A fundamental milestone of mathematical modeling of glucose-insulin system is thought to be the so called minimal model proposed by Bergman and coworkers [13]. This mathematical model is widely used in physiological scientific research on the metabolism of the glucose.

In 1987 Bajaj suggested a nonlinear mathematical model incorporating the kinetic of the β-cell and glucose-insulin regulatory system [9], which is based on Turner et al. [14] to incorporate the β-cell dynamics. The analysis of the dynamical model of Bajaj was shown that only damped oscillation can occur in response to glucose charge. However, several researches have shown persistent oscillation pattern in the blood glucose level and insulin concentration [14, 15]. Topp [4] developed a novel mathematical model incorporating the β-cell dynamics, insulin, and glucose kinetics, where the dynamics of the glucose and insulin are considered relatively fast compared to β-cell mass dynamics. Whole body glucose regulation mechanism was described using various mathematical models proposed for glucose regulation in the human body, which also show the difficulty and limitation in reproducing real processes of glucose regulation [16].

A new approach to deal with the glucose-insulin system complexities is the use of time-delay in the differential equations. The lags or simply the delays can lump complicated biological processes together [17] representing only the time required for these processes to occur. Time-delay models become more common and widely used in many biological modeling branches [18]. Time-delay models have appeared in theory of chemostat model [19], epidemiology [20] circadian rhythms [21], neural networks [22, 23] and genetic regulatory networks [24]. The inclusion of time delay in the glucose-insulin feedback system appeared in research work [25, 26, 27, 28]. Chuedoung et al. [29] expressed the glucose and insulin dynamic system as a one-compartment model to study the oscillatory behavior of the system. They considered the existence of two explicit time-delays, the first is the glucose triggered insulin production lag τ_g and the second time-delay is the hepatic glucose response lag τ_i. They proposed that the combined effect of the two time-delays influenced the dynamics of the glucose-insulin regulatory mechanism, but not each individual delay. They concluded that there was a critical composite delay τ affects the oscillatory behavior of the glucose-insulin homeostasis. They revealed two dynamical states related to the regulatory system, where below the critical composite time-delay the system is asymptotically stable toward fixed points and have oscillatory behavior otherwise.

In this paper, we proposed a nonlinear mathematical model for the endocrine glucose-insulin metabolic regulatory feedback system consisting of delay differential equations modified from the model studied by Chuedoung [29]. The new model considers the representation of an important biological fact not included in the model before, which is related to the hyperglycemia or high glucose concentration level that triggers and increases the death rate of the β-cell. The nonlinear model is then analyzed analytically using Hopf bifurcation theorem to capture different dynamical behaviors, including the stable dynamics, the existence of periodic solutions and sustained oscillations, and derived the appropriate conditions for the system to undergo these behaviors. Moreover, we investigated the inherent chaotic state and hidden pattern dynamics which are not presented in the work of [29]. These dynamics have an important biological implications and attracted many scientific researches to investigate behavior complexity of the biological systems [30, 31, 32].
This paper is organized as follows. In Sec. 2, we describe the proposed glucose-insulin metabolic regulatory system. Sec. 3, includes the mathematical system analysis and appropriate conditions for Hopf bifurcation are given. In Sec. 4, we present numerical simulation. Then a discussion of the results are given in Sec. 5.

2. Proposed Model

Nonlinear models of the glucose-insulin regulatory system consider that the relationship between components is not always linear and it could depend on plasma glucose initial level; moreover, they showed the fact that the patients profiles statistical properties could alter substantially [33]. The interactions between different components of the glucose-insulin regulatory system are responsible for the comprehensive behavior of the system dynamics, making this biological regulatory system a complex one. We propose a nonlinear mathematical model for endocrine glucose-insulin regulatory feedback system which starts from the model of [29], and modified to model the fact that

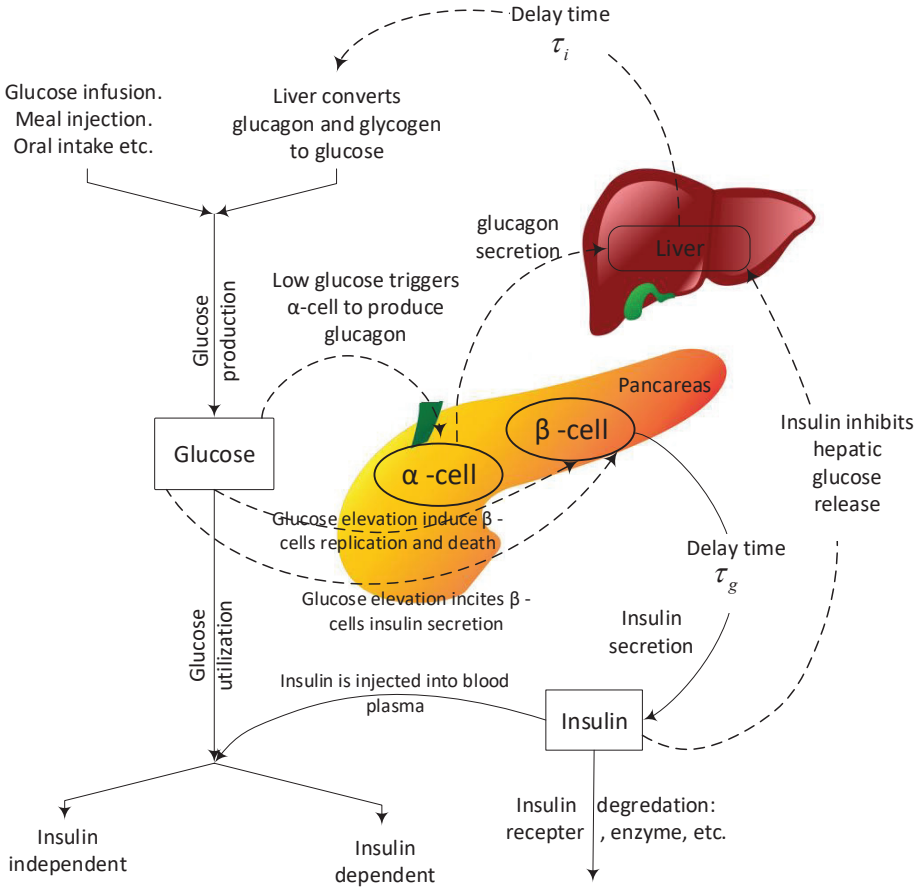


Figure 1: A scheme of the dynamics of glucose, insulin and β-cell.

β-cell replication and death rates vary nonlinearly with glucose concentration level according to in *vitro* studies [34, 35] which demonstrate that the β-cells amount subjected to replication varies as a nonlinear function of glucose level concentration in the medium. The rate of replication of β-cells increases when the glucose levels increasing; however, at high glucose level or extreme hyperglycemia, β-cell replication may be reduced [34, 35]. This modification is rendering the new proposed model more biologically realistic. The model equations then become time delay differential equations model, the dynamics scheme showing the main elements and components is presented in Fig. 1 and then formulated by the following delay differential equations system:

$$\begin{aligned}
\dot{x}(t) &= r_1 z(t-\tau_g) y(t-\tau_g) - r_2 x(t) + c_1 z(t-\tau_g) \\
\dot{y}(t) &= R_3 N/z(t) - R_4 x(t-\tau_i) + c_2 \\
\dot{z}(t) &= R_5(y(t)-\hat{y})(T-z(t)) + R_6 z(t)(T-z(t)) - \\
&\quad R_7 z(t) - R_8 y^2(t) z(t)
\end{aligned} \tag{1}$$

where $x(t)$ is the insulin concentration above its basal level, $y(t)$ is the glucose concentration above its basal level and $z(t)$ is β-cells number according to Bajaj [9] definition, and $\widehat{y}$ stands for the difference between glucose basal level and glucose fasting level. τ_g is the time delay of insulin secretion stimulated by plasma glucose level change, and τ_i is the time-delay in glucose reduction caused by insulin concentration increase. The term $r_1 y(t-\tau_g) z(t-\tau_g)$ represents the insulin concentration increase in response to previous increase in plasma glu-

cose at time-delay τ_g.

Since insulin is a hormone, it has to be degraded like any other hormone. Apart from its degradation as it helps in the conversion of the excess glucose to glycogen, it is being used for other activities and these activities degrade it. r_2x is the decreasing rate of insulin independent of glucose, $c_1z(t-\tau_g)$ is the increase of plasma insulin level secreted by β-cells and it is independent from the remaining components.

System (1) embraces two time delays included in the glucose-insulin regulatory system; therefore, it is more realistic and more representative of behavior of the glucose-insulin biological regulatory system in different time delays. Previous mathematical models cannot show the rich dynamics of the aforementioned biological system with respect to time delays. According to the model proposed by Molnar et al. [7], if there is a decrease in insulin secretion due to a reduction to $1/N$ of the normal number, n, of β-cells, the basal plasma glucose increases until nearly normal basal insulin levels are obtained [9]. So, the plasma glucose concentration is a function of the β-cells capacity N/n.

$R_4x(t-\tau_i)$ is the reduction rate of glucose concentration in response to insulin secretion with the time delay τ_i. T parameter in the model represents the total density of β-cells, and the term $R_5(y-\widehat{y})(T-z)$ represents the increase of dividing β-cells due to the interplay between blood glucose above the fasting level and the nondividing β-cells. The term $R_6z(T-z)$ represents the rate of increase of z caused by bilateral interaction between dividing and nondividing β-cells, and the term R_7z represents the reduction in z due to β-cell current level. β-cells can be formed by the replication of existing β-cells, neogenesis (replication and differentiation) from stem cells, and transdifferentiation of other cells. Presently, it is not possible to quantify rates of neogenesis and transdifferentiation. However, calculations suggest indirectly that they make a negligible contribution to β-cell mass dynamics except during development and in response to extreme physiological or chemically induced trauma [36, 37, 38]. In *vitro* studies demonstrate that the amount of β-cells undergoing replication varies nonlinearly with glucose level concentration in the medium. Rate of β-cell mass replication increases with glucose level elevation. However, at excessive hyperglycemia, β-cells replication may be reduced [34, 35]. Moreover, β-cells can be lost by apoptosis (regulated cell death), necrosis (unregulated cell death). In *vitro*, β-cells death has been shown to vary as a nonlinear function of glucose concentration level. Increasing the blood glucose concentration from 0 to about 11 mM in medium surrounding cultured β-cells, reduced the rate of β-cells death. When the glucose level above 11 [mM], the death rate of β-cells either remained low or increased [39, 40]. We have modeled this behavior with term $R_8y^2(t)z(t)$, changing the existed growth rate of the β-cells to be in logistic form. This is rendering the model to be more consistent with the biological studies. The above model then can somewhat abstractly be written as a system of three differential equation in the following form:

$$\begin{aligned}
\dot{x}(t) &= r_1z_{\tau_g}y_{\tau_g} - r_2x + c_1z_{\tau_g} \\
\dot{y}(t) &= R_3N/z - R_4x_{\tau_i} + c_2 \\
\dot{z}(t) &= R_5(y-\hat{y})(T-z) + R_6z(T-z) - R_7z - R_8y^2z
\end{aligned} \tag{2}$$

where

$$\begin{aligned}
x_{\tau_i} &\equiv x(t-\tau_i) \\
y_{\tau_g} &\equiv y(t-\tau_g) \\
z_{\tau_g} &\equiv z(t-\tau_g)
\end{aligned} \tag{3}$$

3. Dynamical Analysis

In order to study the effect of the two time delays and the existence of periodic and chaotic dynamics in the proposed model, assume that the system steady state point is (x_s, y_s, z_s). Letting $X = x - x_s$, $Y = y - y_s$ and $Z = z - z_s$, so this will lead to the following linearized model of the proposed system (1):

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = J \begin{bmatrix} X \\ Y \\ Z \end{bmatrix} \tag{4}$$

where J is the Jacobian matrix evaluated at the steady state point (x_s, y_s, z_s) and can be written as in (5). Then, the corresponding transcendental polynomial characteristic equation of J can be written as in (6).

$$J = \begin{bmatrix} -r_2 & r_1z_se^{-\lambda\tau_g} & (r_1y_s + c_1)e^{-\lambda\tau_g} \\ -R_4e^{-\lambda\tau_i} & 0 & -\dfrac{R_3}{z_s^2}N \\ 0 & R_5(T-z_s) - 2R_8y_sz_s & -R_5(y_s-\widehat{y}) + R_6(T-2z_s) - R_7 - R_8y_s^2 \end{bmatrix} \tag{5}$$

$$F(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + [a_3 + a_4\lambda]e^{-\lambda\tau} - a_5 \quad (6)$$

where
$\tau = \tau_i + \tau_g$
$a_1 = A_6 - A_5,$
$a_2 = -A_1A_3 - A_5A_6,$
$a_3 = A_1A_4 + A_5A_7,$
$a_4 = A_7,$
$a_5 = A_1A_2,$

with
$A_1 = R_5(T - z_s) - 2R_8Y_sZ_s,$
$A_2 = -\frac{r_2R_3}{z_s^2}N,$
$A_3 = -\frac{R_3}{z_s^2}N,$
$A_4 = R_4(r_1y_s + c_1),$
$A_5 = -R_5(y_s - \widehat{y}) + R_6(T - 2z_s) - R_7 - R_8y_s^2,$
$A_6 = r_2,$
$A_7 = R_4r_1z_s.$

An important approach to gain preliminarily insight into the properties and behavior of a dynamic system is to carry a bifurcation analysis. To find the appropriate conditions on the model (1) that ensure the occurrence of Hopf bifurcation, assume $\lambda(\tau) = \sigma(\tau) + j\mu(\tau)$ where $\sigma(\tau)$ and $\mu(\tau)$ both depend on the time delay, and substitute into (6), get:

$$\begin{aligned}&(\sigma(\tau) + j\mu(\tau))^3 + a_1(\sigma(\tau) + j\mu(\tau))^2 + a_2(\sigma(\tau) + j\mu(\tau))\\ &+ \exp(-\sigma\tau)(\cos(\mu\tau) - jsin(\mu\tau))(a_3 + a_4(\sigma(\tau) + j\mu(\tau)))\\ &+a_5 = 0\end{aligned} \quad (7)$$

Now suppose that $\sigma(\tau_c) = 0$ for some $\tau_c > 0$ and $\sigma(\tau) < 0$ for vaules of $0 < \tau < \tau_c$. Then the equilibrium point of the system (1) may lose its stability at τ_c, where $\lambda(\tau) = j\mu(\tau_c)$. However, $j\mu(\tau_c)$ is a solution of (6) if and only if

$$\begin{aligned}&-j\mu^3 - a1\mu^2 + ja2\mu + (a_3 + a_4j\mu)(cos(\mu\tau) - jsin(\mu\tau))\\ &+a5 = 0\end{aligned} \quad (8)$$

Equating to zero, both the real part and imaginary part in (8), yields:

$$a_1\mu^2 - a_5 = a_3cos(\mu\tau) + a_4\mu sin(\mu\tau), \quad (9)$$

$$-\mu^3 + a_2\mu = -a_4\mu cos(\mu\tau) + a_3sin(\mu\tau). \quad (10)$$

Squaring and adding (9) and (10), we obtain:

$$(a_1\mu^2 - a_5)^2 + (a_2\mu - \mu^3)^2 = a_3^2 + a_4^2\mu^2 \quad (11)$$

$$\mu^6 + (a_1^2 - 2a_2)\mu^4 + (a_2^2 - 2a_1a_5 - a_4^2)\mu^2 + (a_5^2 - a_3^2) = 0 \quad (12)$$

Letting $\theta = \mu^2$ in (12) we obtain:

$$F(\theta) \equiv \theta^3 + b_1\theta^2 + b_2\theta + b_3 = 0 \quad (13)$$

where b_1, b_2 and b_3 are defined as follows:
$b_1 = a_1^2 - 2a_2,$
$b_2 = a_2^2 - 2a_1a_5 - a_4^2,$
$b_3 = a_5^2 - a_3^2.$
For such polynomial (13), the following lemma is applicable based on [41, 42].

Lemma 1. *Let* $\theta^* = \frac{-b_1 + \sqrt{b_1^2 - 3b_2}}{3}$. *If* $b_2 < 0$ *and* $F(\theta^*) < 0$, *then (13) has at least one positive solution.*

Proof. Since $b_3 > 0$, $F(0) = b_3 > 0$. By equating the derivative of $F(\theta)$ to 0, the critical points of $F(\theta)$ can be obtained as follows:

$$3\theta^2 + 2b_1\theta^2 + b_2 = 0$$

whose roots are

$$\theta_{1,2} = \frac{-b_1 \pm \sqrt{b_1^2 - 3b_2}}{3}.$$

If $b_2 < 0$, then we have

$$\theta^* = \frac{-b_1 + \sqrt{b_1^2 - 3b_2}}{3} > 0$$

But $F(\theta^*) < 0$ and $F(\theta^*) \to \infty$ as $\theta \to \infty$. This shows that at least the plot of $F(\theta)$ is crossing the right hand side horizontal axis at least once. Then $F(\theta)$ has one positive solution at least. □

It is clear that if the conditions presented in Lemma (1) hold, then polynomial (13) has one positive solution at least. Depending on the coefficients values of the polynomial (13) b_i where , $i = 1, 2, 3$, (13) can have up to three positive solutions. Without loss of generality, the positive solutions of equation (13) may be denoted by θ_1, θ_2, and θ_3. Then, writing $\mu_i = \sqrt{\theta_i}, i = 1, 2, 3$ and substituting $\mu = \mu_i$ in equations (9) and (10), we obtain

$$a_1\mu_i^2 - a_5 = a_3cos(\mu_i\tau) + a_4\mu_i sin(\mu_i\tau)$$

$$\mu_i^3 - a_2\mu_i = -a_4\mu_i cos(\mu_i\tau) + a_3sin(\mu_i\tau)$$

Solving for τ,

$$\frac{a_1\mu_i^2 - a_5}{-\mu_i^3 + a_2\mu_i} = \frac{a_3cos(\mu_i\tau) + a_4\mu_i sin(\mu_i\tau)}{-a_4\mu_i cos(\mu_i\tau) + a_3sin(\mu_i\tau)},$$

which yields

$$tan(\mu_i\tau) = \frac{(a_1\mu_i^2 - a_5)a_4\mu_i - a_3(\mu_i^3 + a_2\mu_i)}{(a_1\mu_i^2 - a_5)a_3 + a_4\mu_i(\mu_i^3 - a_2\mu_i)}, i = 1, 2, 3$$

Therefore

$$\tau_i^{(n)} = \frac{1}{\mu_i} tan^{-1}\left[\frac{(a_1\mu_i^2 - a_5)a_4\mu_i - a_3(\mu_i^3 + a_2\mu_i)}{(a_1\mu_i^2 - a_5)a_3 + a_4\mu_i(\mu_i^3 - a_2\mu_i)}\right] + \frac{2\pi(n-1)}{\mu_i} \quad (14)$$

where $i = 1, 2, 3$ and $n = 1, 2, 3, ...$

Let $\tau_c > 0$ denotes the smallest of such τ, namely

$$\tau_c = min\left\{\tau_i^{(n)} > 0, 1 < i < 3, n >= 1\right\},$$

Denote the value of μ at τ_c as μ_c. To prove that the model exhibit Hopf bifurcation, the following condition should be satisfied:

$$\left.\frac{d(\mathrm{Re}\lambda)}{d\tau}\right|_{\tau=\tau_c} \neq 0 \quad (15)$$

For the purpose of abstraction and convenience, define the parameters as follows:

$$\begin{aligned}
\phi_1 &= a_2 - 3\mu_c^2 - a_4\mu_c\tau_c sin(\mu_c\tau_c) + (a_4 - a_3\tau_c)cos(\mu_c\tau_c),\\
\phi_2 &= 2a_1\mu_c - a_4\mu_c\tau_c cos(\mu_c\tau_c) - (a_4 - a_3\tau_c)sin(\mu_c\tau_c),\\
\phi_3 &= a_3\mu_c,\\
\phi_4 &= a_4\mu_c^2,
\end{aligned} \quad (16)$$

$$\begin{aligned}
\psi_1 &= \phi_1\phi_3 + \phi_2\phi_4,\\
\psi_2 &= \phi_2\phi_3 - \phi_1\phi_4,
\end{aligned} \quad (17)$$

Theorem 2. *Suppose that the conditions in Lemma (1) hold at the critical time delay τ_c and the associated μ_c. Moreover, let the following conditions are satisfied:*

i. $\phi_1 \neq 0$;

ii. $\phi_2 \neq 0$;

iii. $\psi_1 sin(\mu_c\tau_c) + \psi_2 cos(\mu_c\tau_c) \neq 0$.

Then (15) holds, and the model dynamics exhibit a Hopf bifurcation as τ passed through a critical value τ_c.

Proof. By equating to zero the real and imaginary parts of (7), we get:

$$\sigma^3 - 3\sigma\mu^2 + a_1\sigma^2 - a_1\mu^2 + a_5 + a_2\sigma + \exp(-\sigma\tau)(a_4\mu sin(\mu\tau) + (a_3 + a_4\sigma)cos(\mu\tau)) = 0, \quad (18)$$

$$3\sigma^2\mu - \mu^3 + 2a_1\sigma\mu + a_2\mu + \exp(-\sigma\tau)(a_4\mu sin(\mu\tau) + (a_3 + a_4\sigma)cos(\mu\tau)) = 0, \quad (19)$$

where the coefficients $a_i, i = 1, 2, ..., 5$, are defined as before. Differentiating (18) with respect to τ and evaluating at $\tau = \tau_c$, we obtain

$$\begin{aligned}
&(a_2 - 3\mu_c^2)\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c} - 2a_1\mu_c\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c} =\\
&[(a_4\mu_c\tau_c)sin(\mu_c\tau_c) - (a_4 - a_3\tau_c)cos(\mu_c\tau_c)]\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c}\\
&- [(a_4\mu_c\tau_c)cos(\mu_c\tau_c) - (a_4 - a_3\tau_c)sin(\mu_c\tau_c)]\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c}\\
&+ [a_3\mu_c sin((\mu_c\tau_c) - a_4\mu_c^2 cos((\mu_c\tau_c)].
\end{aligned} \quad (20)$$

or equivalently:

$$\phi_1\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c} - \phi_2\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c} = \phi_3 sin(\mu_c\tau_c) - \phi_4 cos(\mu_c\tau_c). \quad (21)$$

Similarly, from (19) we have

$$\begin{aligned}
&(a_2 - 3\mu_c^2)\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c} + 2a_1\mu_c\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c} =\\
&[(a_4\mu_c\tau_c)sin(\mu_c\tau_c) - (a_4 - a_3\tau_c)cos(\mu_c\tau_c)]\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c}\\
&+ [(a_4\mu_c\tau_c)cos(\mu_c\tau_c) + (a_4 - a_3\tau_c)sin(\mu_c\tau_c)]\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c}\\
&+ [a_3\mu_c cos((\mu_c\tau_c) - a_4\mu_c^2 sin(\mu_c\tau_c)].
\end{aligned} \quad (22)$$

or equivalently

$$\phi_1\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c} - \phi_2\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c} = \phi_4 sin(\mu_c\tau_c) - \phi_3 cos(\mu_c\tau_c). \quad (23)$$

by solving (21) and (23) to obtain $\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c}$, we get

$$(\phi_1^2 + \phi_2^2)\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c} = (\phi_1\phi_3 + \phi_2\phi_4)sin(\mu_c\tau_c) + (\phi_2\phi_3 - \phi_1\phi_4)cos(\mu_c\tau_c).$$

Therefore using (17) we have

$$\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c} = \frac{\psi_1 sin(\mu_c\tau_c) + \psi_2 cos(\mu_c\tau_c)}{(\phi_1^2 + \phi_2^2)}. \quad (24)$$

Thus according to conditions (i)-(iii), it is clear that $\left.\frac{d\sigma}{d\tau}\right|_{\tau=\tau_c} \neq 0$. Therefore, a Hopf bifurcation occurs in the dynamics when time lag τ passes through the critical time delay τ_c, and this end the proof. □

Table 1: Coefficients of the proposed model.

Paramters	r_1	r_2	R_3	R_4	R_5	R_6	R_7	R_8	c_1	c_2	$\widehat{y}$	T	N
Value	0.472	0.25	0.82	0.6	0.45	0.3	0.3	0.0123	0.1	0.8	1.42	1.5	1.27

Table 2: Eigenvalues at $\tau_i = 0.05$ for several values of τ_g

τ_g	λ_1	λ_2	$\lambda_3 \ldots$
0.300	-0.019+j0.666	-0.019+j0.666	-0.525
0.441	0.000+j0.657	0.000-j0.657	-0.532
0.600	0.019+j0.645	0.019-j0.645	-0.541

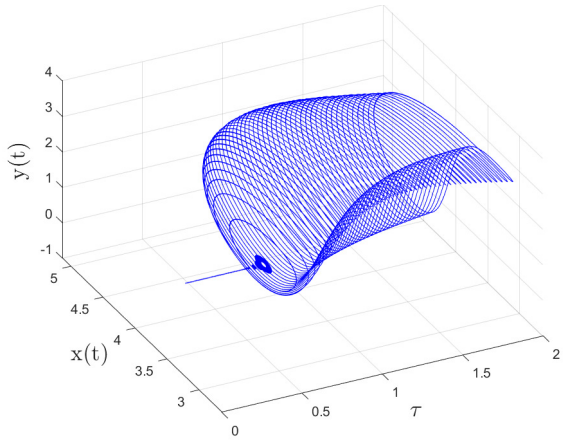


Figure 2: Hopf Bifurcation of system (1)

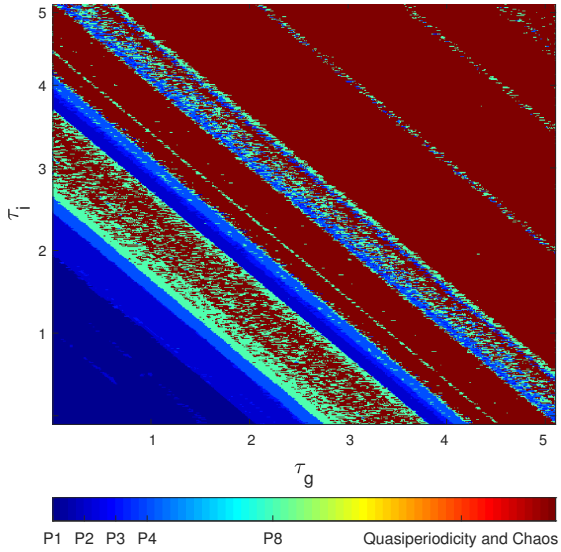


Figure 3: 2D Bifurcation Diagram of system (1) where the color code represents the system periodicity.

4. Simulation Results

By opting the composite time delay τ as a bifurcation parameter, and fixing the system (1) other parameters as given in Table 1 adapted from Cheudoung et al. [29], the periodic solutions in phase plane are plotted for different values of τ as shown in Fig. 2. The first part of the plot show steady state solution then the periodic solution is bifurcate at τ_c, the radius of the limit cycle is changing with τ. Moreover, the stability behavior of the equilibrium point can be shown by finding the eigenvalues of the Jacobian matrix J. Here, we fix the parameters of the model (1) as in Table 1, and considering different values for the time-delay τ_g. the results are given in Table 2. It is worth noting that the equilibrium stability depends on both τ_i and τ_g. Although other choices of the parameters are possible to obtain chaotic dynamics, here we focus on the different dynamical behavior induced by the time-delays.

To reveal the behavior of the proposed mathematical model and obtain the bifurcation structure when the two time delays are varied, the two-dimensional bifurcation diagram is plotted in Fig. 3, based on the system parameter in Table 1. The 2D-bifurcation diagram is color-coded depending on the periodicity of the attractor [43]. The diagram is produced by varying the two time delays (τ_i, τ_g), then one-dimensional bifurcation diagrams are consequently obtained fixing one delay and changing the second. The final state of the model is feed as initial value for the next iteration.

To show the effect of individual time-delay on the system behavior and to provide more information about the dependence of the system dynamics on a certain parameters, one-dimensional bifurcation diagram is good tool that used usually to reveal the attractor type, to which the system dynamics finally settle down after transient phase. So, one-dimensional bifurcation diagram is evaluated for chosen values of time delay from Fig. 3. By increasing the insulin secretion time-delay (τ_g), the system becomes chaotic. The chaotic behavior arises through a period-doubling route-to-chaos, followed by a crisis and a second cascade of period doubling leading to a second region of chaotic behavior as it can be observed in Fig. 4 for different values of

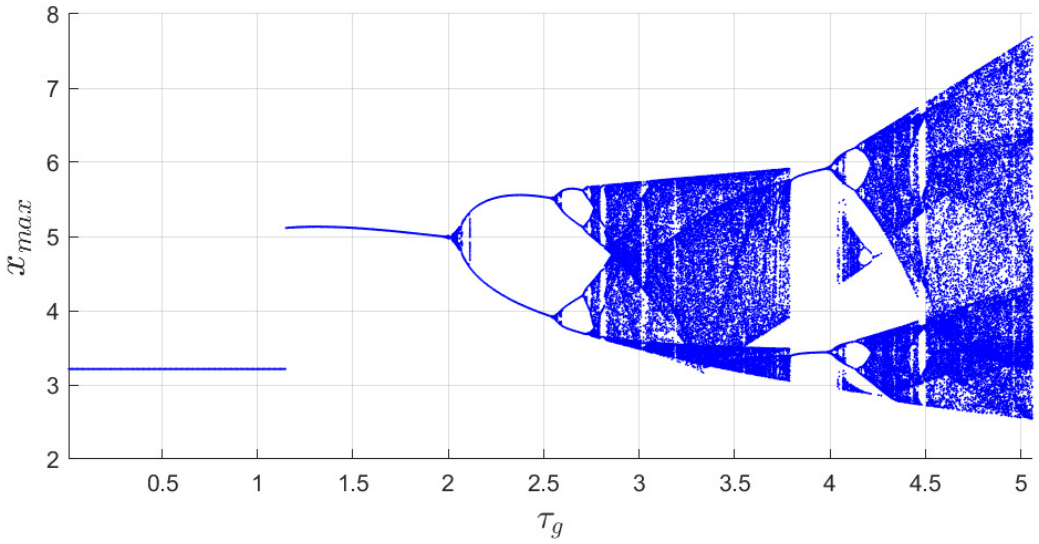
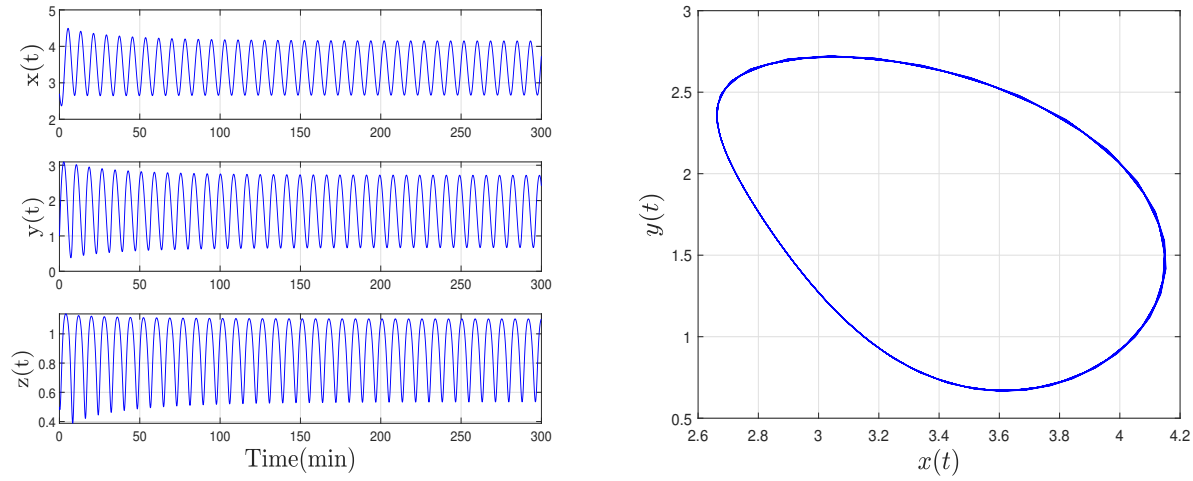


Figure 4: One-dimensional bifurcation diagram of system (1) for τ_i=0.05 and different values of insulin secretion time τ_g.

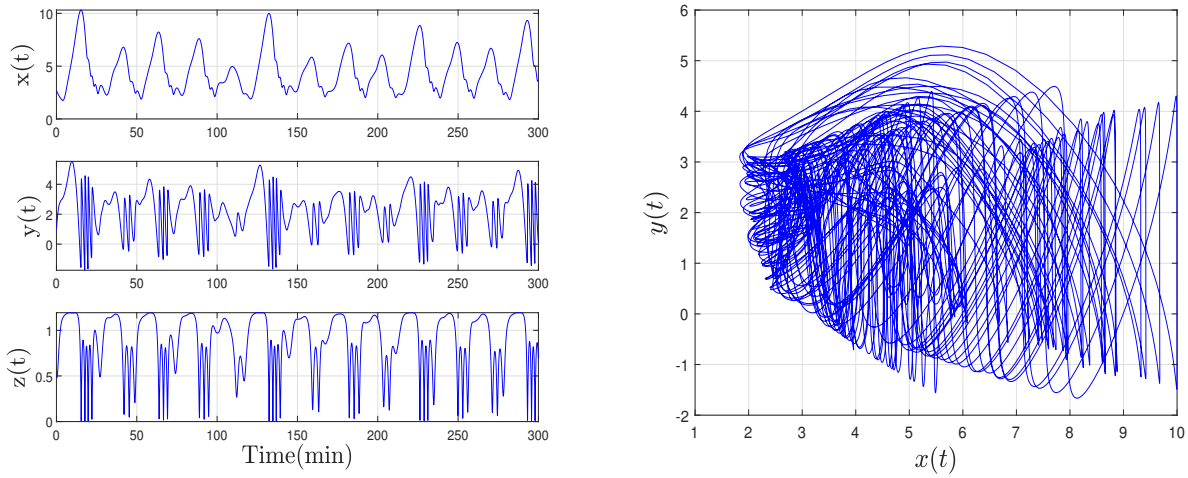


(a) (b)

Figure 5: Periodic behavior in system (1): (a) Time series of insulin, glucose and β-cell respectively; (b) Corresponding attractor in the phase plane.

(τ_g). It is clear that due to the increase in the delay, the insulin cannot track the blood plasma glucose change which results in a metabolic disorder. Fig. 5, shows the corresponding time evolution of the insulin concentration above its basal level $x(t)$ and glucose concentration above its basal level $y(t)$ and β-cells number at $\tau_i = 0.05$ and $\tau_g = 0.46$. For these parameters a periodic solution is obtained. This parallel the periodic behavior for the biological variables of insulin and glucose that has been experimentally reported for normal endocrine metabolic system in various researches as [15, 27, 7] and many others. The tight coupling between glucose and insulin oscillations suggest that these oscillations represent a dynamic property of the insulin-glucose feedback loop and that periodically modulated signals are more effective than constant, stochastic or chaotic stimuli in producing a sustained physiological response in the target cells.

Fig. 6, shows the time series of system (1) where the system behavior is chaotic for the given parameters as



(a) (b)

Figure 6: Chaotic behavior in system (1) : (a) Time series of insulin, glucose and β-cell respectively, (b) Corresponding attractor in the phase plane.

in Table 1 and $\tau_i = 3.5$ and $\tau_g = 3.5$. The results are in line with literature in the field revealing that a chaotic behavior in the system is a sign of an existing disorder in the biological system [30, 31, 32]. Molnar's [7] and Kroll's [44] showing experiments reporting the chaotic behavior in glucose-insulin waveforms. So, due to the chaotic behavior, stabilizing blood glucose level for diabetic subjects is a challenge, the patient continues to avoid hypoglycemia and hyperglycemia. Generally, the analysis of plasma glucose concentration measurements is one of the most crucial tasks in order to support the glucose metabolic control. As a consequence, the blood glucose evolution level of diabetic subjects, possibly, can be predicted with a range of confidence. Out of this range the process is chaotic, where, according to chaos theory, the system is deterministic but long-term unpredictable due to sensitive to initial conditions. The sensitivity to initial conditions has been numerically confirmed by calculating the largest Lyapunov exponent with the algorithm discussed in Appendix A, the value obtained is $LLE = 0.009$. The algorithm is applied to mathematical model (1), with the parameters as in Table 1 selecting a time delay in the chaotic region such as $\tau_i = \tau_g = 3.5$. The value of the LLE is found positive, which is clearly the signature of a chaotic behavior.

5. Conclusion

Glucose-insulin models start from simple linear ordinary differential equation and keep evolving toward more realistic and feasible models. The time delay differential equation model is providing a good tool to emulate the complex metabolic system by inclusion of the time delay terms in some part of the model. In this paper a crucial biological fact related to the β-cell nonlinear rate of growth and death have been taken into account, rendering the new model more realistic, accurate and more biologically feasible.

The new model has been analyzed analytically by Hopf bifurcation theorem and investigated numerically. In the proposed model, we observed a periodic behavior under normal metabolic conditions when a small time delay and chaotic behavior under faulty status or long time delay in the metabolic system. The time evolution of both the glucose and insulin reveal oscillatory behavior with a period of proximately 8 [min] which is in the accepted range 5 - 15 [min] consistent with the results reported in the biological experiments [45]. Also, the model exhibits chaos which is a measure of disorder in the biological system for other values of the parameters. The extension principle and lower bounded error are used to prove the chaotic state of the model at specific time delay range. The time delay required for the model to show chaotic behavior is about 3.5 [min], making the new system consistent with the literature [46, 47]. As direction for future work, we note that further parameters can be considered such as influence of trauma, excitement and stress and also the effect of the epinephrine in suppressing the insulin secretion and inducing the glucose increase which affects the glucose-insulin homeostasis and may lead to diabetes in human.

Appendix A

The calculation of the Largest Lyapunov Exponent LLE has been considered as one of the best method to the problem of detecting the presence of chaos in dynamical system. Lyapunov exponents measure the average divergence or convergence of nearby trajectories along certain directions in state space. In order to evaluate the Largest Lyapunov Exponent in this paper the algorithm proposed firstly by Mendes [48] is used, which is based on the concept of the lower bound error LBE introduced in [49]. This method conserve the dimensionality of the delay differential system which facilitates the calculation of the LLE, On the contrary other methods convert the DDE to high dimensional ODE system such as [50, 51]. To calculate the LLE according to this method, the system is simulated using two different interval extensions defined according to [48] as follows: An interval extension of f is an interval-valued function F of an interval variable X, with the property $F(x) = f(x)$ for real arguments, where by an interval it is meant to be a closed set of real numbers $x \in \mathbb{R}$ such that $X = [\overline{X}, \underline{X}] = \{\underline{X} \leq x \leq \overline{X}\}$. This concept is the foundation used to calculate the lower bound error. Then, the Largest Lyapunov Exponent is evaluated by least square fit to the line of the logarithm of lower bound error. The procedure is adopted from [48] and explained as follows:

1. Select two interval extensions of the mathematical model under investigation.

2. Fix exactly the same initial conditions, discretization scheme and step size, simulate the two interval extensions and get the two pseudo-orbits.

3. Use the method of least squares to find the best line fit to the slope of the logarithm curve of the absolute value of the lower bound error LBE. The slope of the line is the LLE.

References

[1] A. W. Norman, G. Litwack, Hormones, Academic Press, 1997.

[2] A. Boutayeb, M. Derouich, Age structured models for diabetes in east morocco, Mathematics and Computers in simulation 58 (3) (2002) 215–229.

[3] IDF, International diabetes federation: Diabetes facts & figures, https://www.idf.org, [Online; accessed 10-January-2020] (2019).

[4] B. Topp, K. Promislow, G. Devries, R. M. Miura, D. T Finegood, A model of β-cell mass, insulin, and glucose kinetics: pathways to diabetes, Journal of theoretical biology 206 (4) (2000) 605–619.

[5] I. I. Mohammed, I. I. Adamu, S. J. Barka, Mathematical model for the dynamics of glucose, insulin and β-cell mass under the effect of trauma, excitement and stress, Modeling and Numerical Simulation of Material Science 9 (4) (2019) 71–96.

[6] A. Mari, Mathematical modeling in glucose metabolism and insulin secretion, Current Opinion in Clinical Nutrition & Metabolic Care 5 (5) (2002) 495–501.

[7] G. Molnar, W. Taylor, A. Langworthy, Plasma immunoreactive insulin patterns in insulin-treated diabetics. studies during continuous blood glucose monitoring., in: Mayo Clinic proceedings, Vol. 47, 1972, p. 709.

[8] E. Ackerman, J. W. Rosevear, W. F. McGuckin, A mathematical model of the glucose-tolerance test, Physics in Medicine & Biology 9 (2) (1964) 203.

[9] J. Bajaj, G. S. Rao, J. S. Rao, R. Khardori, A mathematical model for insulin kinetics and its application to protein-deficient (malnutrition-related) diabetes mellitus (pddm), Journal of theoretical biology 126 (4) (1987) 491–503.

[10] C. Geevan, J. S. Rao, G. S. Rao, J. Bajaj, A mathematical model for insulin kinetics iii. sensitivity analysis of the model, Journal of theoretical biology 147 (2) (1990) 255–263.

[11] Y. Lenbury, S. Ruktamatakul, S. Amornsamarnkul, Modeling insulin kinetics: responses to a single oral glucose administration or ambulatory-fed conditions, Biosystems 59 (1) (2001) 15–25.

[12] H. Himsworth, R. Kerr, Insulin-sensitive and insulin-insensitive types of diabetes mellitus., Clinical science 4 (1939) 119–152.

[13] R. N. Bergman, Y. Z. Ider, C. R. Bowden, C. Cobelli, Quantitative estimation of insulin sensitivity., American Journal of Physiology-Endocrinology And Metabolism 236 (6) (1979) E667.

[14] R. Turner, R. Holman, D. Matthews, T. Hockaday, J. Peto, Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations, Metabolism 28 (11) (1979) 1086–1096.

[15] Y. Tasaka, F. Nakaya, H. Matsumoto, Y. Omori, Effects of aminoguanidine on insulin release from pancreatic islets, Endocrine journal 41 (3) (1994) 309–313.

[16] H. Kang, K. Han, M. Choi, Mathematical model for glucose regulation in the whole-body system, Islets 4 (2) (2012) 84–93.

[17] J. E. Forde, Delay differential equation models in mathematical biology, University of Michigan, 2005.

[18] Q. Zheng, J. Shen, Z. Wang, Pattern formation and oscillations in reaction–diffusion model with p53-mdm2 feedback loop, International Journal of Bifurcation and Chaos 29 (14) (2019) 1930040.

[19] T. Zhao, Global periodic-solutions for a differential delay system modeling a microbial population in the chemostat, Journal of mathematical analysis and applications 193 (1) (1995) 329–352.

[20] K. Cooke, P. Van den Driessche, X. Zou, Interaction of maturation delay and nonlinear birth in population and epidemic models, Journal of Mathematical biology 39 (4) (1999) 332–352.

[21] P. Smolen, D. A. Baxter, J. H. Byrne, A reduced model clarifies the role of feedback loops and time delays in the drosophila circadian oscillator, Biophysical journal 83 (5) (2002) 2349–2359.

[22] S. A. Campbell, R. Edwards, P. van den Driessche, Delayed coupling between two neural network loops, SIAM Journal on Applied Mathematics 65 (1) (2004) 316–335.

[23] R. Rakkiyappan, G. Velmurugan, F. A. Rihan, S. Lakshmanan, Stability analysis of memristor-based complex-valued recurrent neural networks with time delays, Complexity 21 (4) (2016) 14–39.

[24] S. Lakshmanan, F. A. Rihan, R. Rakkiyappan, J. H. Park, Stabil-

ity analysis of the differential genetic regulatory networks model with time-varying delays and markovian jumping parameters, Nonlinear analysis: Hybrid systems 14 (2014) 1–15.

[25] K. Engelborghs, V. Lemaire, J. Belair, D. Roose, Numerical bifurcation analysis of delay differential equations arising from physiological modeling, Journal of mathematical biology 42 (4) (2001) 361–385.

[26] D. L. Bennett, S. A. Gourley, Asymptotic properties of a delay differential equation model for the interaction of glucose with plasma and interstitial insulin, Applied mathematics and computation 151 (1) (2004) 189–207.

[27] J. Li, Y. Kuang, C. C. Mason, Modeling the glucose–insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays, Journal of theoretical biology 242 (3) (2006) 722–735.

[28] W. Sarikaa, Y. Lenburya, K. Kumnungkitb, W. Kunphasuruangc, Modelling glucose-insulin feedback signal interchanges involving β-cells with delays, differential equations 1 (2) (2008) 1.

[29] M. Chuedoung, W. Sarika, Y. Lenbury, Dynamical analysis of a nonlinear model for glucose–insulin system incorporating delays and β-cells compartment, Nonlinear Analysis: Theory, Methods & Applications 71 (12) (2009) e1048–e1058.

[30] P. Faure, H. Korn, Is there chaos in the brain? i. concepts of nonlinear dynamics and methods of investigation, Comptes Rendus de l'Académie des Sciences-Series III-Sciences de la Vie 324 (9) (2001) 773–793.

[31] H. Korn, P. Faure, Is there chaos in the brain ? II. Experimental evidence and related models, Comptes rendus biologies 326 (9) (2003) 787–840.

[32] G. Baghdadi, S. Jafari, J. Sprott, F. Towhidkhah, M. H. Golpayegani, A chaotic model of sustaining attention problem in attention deficit disorder, Communications in Nonlinear Science and Numerical Simulation 20 (1) (2015) 174–185.

[33] T. A. Holt, Nonlinear dynamics and diabetes control, The Endocrinologist 13 (6) (2003) 452–456.

[34] I. Swenne, The role of glucose in the in vitro regulation of cell cycle kinetics and proliferation of fetal pancreatic b-cells, Diabetes 31 (9) (1982) 754–760.

[35] S. R. Hügl, M. F. White, C. J. Rhodes, Insulin-like growth factor i (igf-i)-stimulated pancreatic β-cell growth is glucose-dependent synergistic activation of insulin receptor substrate-mediated signal transduction pathways by glucose and igf-i in ins-1 cells, Journal of Biological Chemistry 273 (28) (1998) 17771–17779.

[36] D. T. Finegood, L. Scaglia, S. Bonner-Weir, Dynamics of β-cell mass in the growing rat pancreas: estimation with a simple mathematical model, Diabetes 44 (3) (1995) 249–256.

[37] A. Fernandes, L. King, Y. Guz, R. Stein, C. Wright, G. Teitelman, Differentiation of new insulin-producing cells is induced by injury in adult pancreatic islets, Endocrinology 138 (4) (1997) 1750–1762.

[38] S. Bonner-Weir, L. A. Baxter, G. T. Schuppin, F. E. Smith, A second pathway for regeneration of adult exocrine and endocrine pancreas: a possible recapitulation of embryonic development, Diabetes 42 (12) (1993) 1715–1720.

[39] A. Hoorens, M. Van de Casteele, G. Klöppel, D. Pipeleers, Glucose promotes survival of rat pancreatic beta cells by activating synthesis of proteins which suppress a constitutive apoptotic program., The Journal of clinical investigation 98 (7) (1996) 1568–1574.

[40] I. B. Efanova, S. V. Zaitsev, B. Zhivotovsky, M. Köhler, S. Efendić, S. Orrenius, P.-O. Berggren, Glucose and tolbutamide induce apoptosis in pancreatic β-cells a process dependent on intracellular ca2+ concentration, Journal of Biological Chemistry 273 (50) (1998) 33501–33507.

[41] R. V. Culshaw, S. Ruan, A delay-differential equation model of hiv infection of cd4+ t-cells, Mathematical biosciences 165 (1) (2000) 27–39.

[42] S. Chomcheon, Y. Lenbury, W. Sarika, Stability, hopf bifurcation and effects of impulsive antibiotic treatments in a model of drug resistance with conversion delay, Advances in Difference Equations 2019 (1) (2019) 274.

[43] L. Benadero, A. El Aroudi, G. Olivar, E. Toribio, E. Gomez, Two-dimensional bifurcation diagrams: background pattern of fundamental dc–dc converters with pwm control, International Journal of Bifurcation and Chaos 13 (02) (2003) 427–451.

[44] M. H. Kroll, Biological variation of glucose and insulin includes a deterministic chaotic component, Biosystems 50 (3) (1999) 189–201.

[45] N. Pørksen, M. Hollingdal, C. Juhl, P. Butler, J. D. Veldhuis, O. Schmitz, Pulsatile insulin secretion: detection, regulation, and role in diabetes, Diabetes 51 (suppl 1) (2002) S245–S254.

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

[47] R. Bertram, M. Pernarowski, Glucose diffusion in pancreatic islets of langerhans, Biophysical journal 74 (4) (1998) 1722–1731.

[48] E. M. Mendes, E. G. Nepomuceno, A very simple method to calculate the (positive) largest lyapunov exponent using interval extensions, International Journal of Bifurcation and Chaos 26 (13) (2016) 1650226.

[49] E. Nepomuceno, S. Martins, A lower bound error for free-run simulation of the polynomial narmax, Systems Science & Control Engineering 4 (1) (2016) 50–58.

[50] J. Sprott, A simple chaotic delay differential equation, Physics Letters A 366 (4-5) (2007) 397–402.

[51] G. Hu, Hyperchaos of higher order and its circuit implementation, International Journal of Circuit Theory and Applications 39 (1) (2011) 79–89.