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A New Time Delay Model For Glucose-Insulin Regulatory Chaotic System

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Abstract The mathematical modeling is very helpful for non-invasive investigation of glucose-insulin interaction. In this paper a new mathematical model for glucose-insulin endocrine metabolic regulatory feedback system incorporating the β-cell dynamic and function for regulating and maintaining bloodstream insulin level, with time delay has been proposed. The model includes the insulin degradation due to glucose interaction. The dynamical behavior of the model is analyzed and two dimensional bifurcation diagram is 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 easily induced rise to complex dynamics such as periodic oscillation consistent with the biological experiments results and periodic doubling cascade and chaos state which represent metabolic disorder may lead to diabetes mellitus.

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1 Introduction

Diabetes mellitus (DM), which is commonly known as diabetes is a syndrome of dysfunctional metabolism, 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 are 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 an epidemic 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 estimates that 436 million people around the world live with diabetes corresponding to 1 to 11 of the 20-79 adult's population. The figure is expected to hit the 592 million people in 2035 [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 blood insulin concentration causes increased glucose removal and decrease glucose production by the liver leading to a reduction in blood glucose [4,5]. From 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 rep-

resents an increase capacity for insulin secretion which, in turn, would lead to a decrease in blood glucose.

The mathematical modeling for studying the glucose metabolism and insulin secretion or glucose-insulin interaction have a longstanding history. The mathematical models continue to be more accurate and clinically feasible. And evolve to be a useful resource for clinical investigation; and play an important roll in understanding the governing mechanisms 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 by Ker R.B et al [12] in 1939 where they proposed the first approach to measure the insulin sensitivity in vivo. Mathematical models were used to estimate the glucose clearance and glucose-insulin dynamics in general. Bolie V.W. [13] in 1961 is also one of the earliest in this field, formulating a simple ordinary differential equations system. Ackreman et al [14] in 1979 proposed a simple linear model the glucose tolerance test using two linear ordinary differential equations. The real start of mathematical modeling of glucose-insulin system is thought to be the so called minimal model proposed by Bergman et al in 1979 [15]. This mathematical model is widely used in physiological scientific research on the metabolism of the glucose. In 1987 J. S. Bajaj suggested a nonlinear mathematical model incorporated the kinetic of the β-cell and glucose-insulin regulatory system [9], which is based on Turner et al [16] to incorporate the β-cell dynamics. The analysis of the dynamical model of Bajaj shown that only damped oscillation can occur in response to glucose charge. However, several research have shown persistent oscillation pattern in the blood glucose level and insulin concentration [16,17]. Brain et al [18] 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. The model has two stable fixed points representing pathological and physiological steady states, separated by a saddle point on a slow manifold.The importance of understanding the whole-body glucose regulation mechanism, was described using various mathematical models proposed for glucose regulation in the human body, and discuss the difficulty and limitation in reproducing real processes of glucose regulation in [19]. A review of some of mathematical models proposed in the literature for use in the glucose-insulin feedback system related to diabetes is given in [20], enhanced with a survey on available software.

The usage of ordinary or partial differential equations to model biological systems has a long history, beginning from Mathus, Verhulst, Lotka and Voltera [21]. Due to the complexity of these phenomena it is becoming clear that these model cannot show the rich dynamics existed in the natural systems. so, there is a new approach to deal with these complexities one of them is the use of time delay parts in the differential equations. The lags or simply the delays can simply lump complicated biological processes together [22] representing only for the time required for these processes to occur. Delay model become more common and widely used in many biological modeling branches. Delay model have appeared in studying of chemostat model [23], epidemiology [24] circadian rhythms [25], tumor growth [26,27], neural network [28,29] and genetic regulatory networks model [30].

The inclusion of time delay in the glucose-insulin feedback system appeared in research work [31,32,33,34]. Two significant time lags are considered the first is the glucose triggered insulin production lag τ_g and the second is the hepatic glucose response lag τ_i. Based on Lenbury model suggested in [11], Sarika [34] and Chuedoung [35] proposed mathematical models which are incorporating the two time lags τ_g and τ_i. These models tried to give a qualitative framework [35] to understand the delayed responsive mechanism due to glucose stimulation and the secreted insulin requires a certain amount of time before increasing in the plasma.

In this paper, we study a nonlinear mathematical model for the glucose-insulin regulatory feedback control system consisting of delay-differential equations modified from model studied by Chuedoung [35]. The new model system is consider the addition of new part representing the insulin degradation term. The nonlinear model is then analyzed to capture different dynamic behavior including the existence of of periodic solutions and sustained oscillation, and investigate the inherent chaotic behavior and dynamics which is attracted many scientific researches and great effort in studying biological systems and phenomena [36,37,38].

2 Mathematical Model

Besides the paramount and distinctive importance of experimental researches for developing effective treatment protocols, studying and developing mathematical models of glucose-insulin bilateral interplay have had an essential role in accelerating the research processes and making breakthroughs in this field by saving both money and time. Conventionally, it was believed that

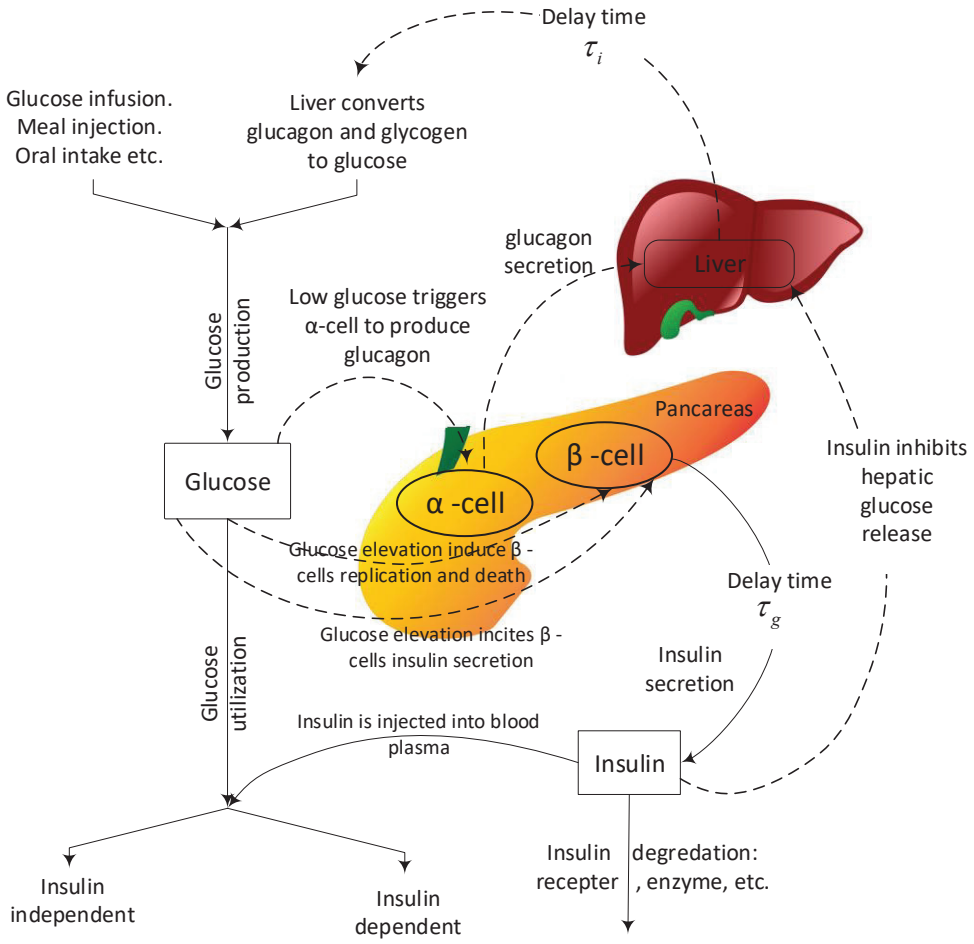


Fig. 1: A scheme of the dynamics of glucose, insulin and β-cell

a linear relationship defines the mechanism of glucose-insulin negative feedback system. A linear model for diabetes assumes that the relationship between glucose and insulin concentration could be studied in isolation from other components. In contrast, nonlinear models proposed in previous studies assume that the relationship between components is not always linear and it could depend on initial blood glucose level; moreover, they revealed the fact that statistical properties of the profile in some patients could alter substantially [39]. In glucose-insulin regulatory system, interactions between its components are responsible for the overall behavior of the system, which makes this regulatory system a complex one.

In the current brief, we proposed a nonlinear mathematical model for glucose-insulin regulatory feedback system by incorporating the enhanced delay differential equations embracing β-cells proposed by the model presented by [35]. The dynamics scheme is presented in Fig. 1, and formulated by the following delay differential equations system as follow:

$$\begin{aligned}
\dot{x}(t) &= r_1 z(t-\tau_g) y(t-\tau_g) - r_2 x - r_3 xy + c_1 z(t-\tau_g) \\
\dot{y}(t) &= R_3 N/z - R_4 x(t-\tau_i) + c_2 \\
\dot{z}(t) &= R_5(y-\hat{y})(T-z) + R_6 z(T-z) - R_7 z
\end{aligned} \tag{1}$$

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 the number of β-cells according to Bajaj [9] definition, and $\widehat{y}$ is the difference between glucose basal level and its fasting level. τ_g is the delay in insulin secretion in response to blood glucose level, and τ_i is the delay in glucose drop due to increased insulin concentration. The term $r_1 y(t-\tau_g) z(t-\tau_g)$ shows the increase in insulin concentration in response to previous blood glucose increase at the 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. It has been shown that the level of degradation of insulin vary from person to person and from male to female. Even in women, pregnant women degrades insulin more than the non-pregnant ones.In general, insulin degradation occurs in two ways: reduction and proteolytic. The reduction process is encountered when insulin takes part in reaction or used up by cells as they act as enzymes in reactions in the body [40]. This activity therefore reduces the amount of the insulin available for further reactions. Also certain enzymes in the body inactivate the biological activity of insulin. Such enzymes are called 'insulinase' and they are considered to be proteolytic in nature. An example of such enzyme is 'protein-disulphide-reductase (glucathione)'. It inactivates insulin by catalysing the reduction of the disulphate bonds of insulin and thus splitting of the insulin molecules [41]. This glucathione also inactivates proinsulin and at the same time the reactivation of reduced and randomly oxidised proinsulin [42]. However, excess inactivation of the insulin is controlled by another enzyme called the glucagon. Other growth hormones also contribute in the control of insulin degradation. These enzymes help in the adjustment in the rate of insulin degradation to changing rate of insulin secretion and requirements. r_2x is the rate of insulin decrease independent of glucose, and r_3xy will represent the insulin degradation related to the glucose current concentration level including this will enhance the model to be more biologically realistic and feasible and $c_1z(t-\tau_g)$ is the increase of insulin level secreted by β-cells and is independent from other components. System (3) considers two time lags in insulin-glucose regulatory system; therefore, it is more realistic and is capable of showing the behavior of insulin-glucose regulatory system in different time delays. Previous models cannot display the behavior of aforementioned biological system with respect to time delays. According to the model presented by Molnar et al. [43], if insulin secretion decreases to $1/N$ of the number of β-cells, designated increases until insulin levels are restored to nearly normal standards. So the plasma glucose concentration is a function of the β-cells capacity N/n. N is the normal number of β-cells. $R_4x(t)-\tau_i$ is the rate of glucose reduction in response to insulin secretion with the time delay τ_i. T is the total density of β-cells, and the term $R_5(y-\widehat{y})(T-z)$ represents the increase in dividing β-cells caused by the interaction between blood glucose above the fasting level and the nondividing β-cells. The term $R_6z(T-z)$ represents the increase in z due to interaction between dividing and nondividing β-cells, and the term R_7z represents the reduction in z due to its current level. The above model can then be written for simplicity as a system of three differential equation in the form:

$$\begin{aligned} \dot{x}(t) &= f \\ \dot{y}(t) &= g \\ \dot{z}(t) &= h \end{aligned} \tag{2}$$

where

$$\begin{aligned} f &= r_1 z_{\tau_g} y_{\tau_g} - r_2 x - r_3 xy + c_1 z_{\tau_g} \\ g &= R_3 N/z - R_4 x_{\tau_i} + c_2 \\ h &= R_5(y-\hat{y})(T-z) + R_6 z(T-z) - R_7 z \end{aligned} \tag{3}$$

with

$$\begin{aligned} x_{\tau_i} &\equiv x(t-\tau_i) \\ y_{\tau_g} &\equiv y(t-\tau_g) \\ z_{\tau_g} &\equiv z(t-\tau_g) \end{aligned} \tag{4}$$

2.1 Dynamical Analysis

In order to investigate the effect of the two delays on the possibility 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):

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = J \begin{bmatrix} X \\ Y \\ Z \end{bmatrix} \tag{5}$$

where J is the Jacobian matrix evaluated at the steady state point $(x_s, y_s, z_s) = (3.1394, 1.6477, 0.9610)$ and can be written as in 6. Then, the corresponding characteristic equation of J can be written as in 7.

The proposed model dynamics stability behavior can be determined by finding the eigenvalues of the Jacobian matrix J at the equilibrium point. The equilibrium point for the given system parameters in Table 1 is evaluated, and the eigenvalues for different values of lags are calculated and given in Table 2.

$$J = \begin{bmatrix} (-r_3 y_s - r_2) & (-r_3 x_s + r_1 z_s e^{-\lambda\tau_g}) & (r_1 y_s + c_1)e^{-\lambda\tau_g} \\ -R_4 e^{-\lambda\tau_i} & 0 & -\dfrac{R_3}{z_s^2} N \\ 0 & R_5(T - z_s) & \dfrac{R_5(y-\widehat{y})T - R_6 z_s^2}{z_s} \end{bmatrix} \tag{6}$$

Table 1: Coefficients of the proposed model

Paramters	r_1	r_2	r_3	R_3	R_4	R_5	R_6	R_7	c_1	c_2	$\widehat{y}$	T	N
Value	0.472	0.2275	0.025	0.82	0.6	0.3	0.3	0.2	0.1	0.8	1.42	1.5	1.27

Table 2: Eigenvalues at $\tau_i = 0.05$

τ_g	λ_1	λ_2	λ_3 ...
0.40	-0.008-0.638i	-0.008+0.638i	-0.532
0.46	0.000-0.634i	0.000+0.634i	-0.535
0.60	0.017-0.624i	0.017+0.624i	-0.541

$$F(\lambda) = \lambda^3 + a_1\lambda^2 + [\lambda + 1]a_2 e^{-\lambda\tau_i} - [a_3\lambda + a_3 - a_4]e^{-\lambda\tau} - a_5\lambda - a_6 \tag{7}$$

where
$\tau = \tau_i + \tau_g$
$a_1 = A_6 - A_5,$
$a_2 = A_5 A_2,$
$a_3 = A_5 A_7,$
$a_4 = A_1 A_4,$
$a_5 = A_1 A_3 + A_5 A_6,$
$a_6 = A_1 A_3 A_6,$
with
$A_1 = R_5(T - z_s),$
$A_2 = R_4(-r_3 x_s),$
$A_3 = -\frac{R_3}{z_s^2} N,$
$A_4 = R_4(r_1 y_s + c_1),$
$A_5 = \frac{R_5(y - \widehat{y})T - R_6 z_s^2}{z_s},$
$A_6 = -r_3 y_s - r_2,$
$A_7 = R_4 r_1 z_s,$

2.2 Bifurcation Diagram

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. 2, based on the system parameter in Table 1. The 2D-bifurcation diagram is color-coded depending on the periodicity of the attractor [44]. 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 feed as initial value for the second iteration.

To further investigate the system dynamic the bifurcation diagram is evaluated for chosen values of time

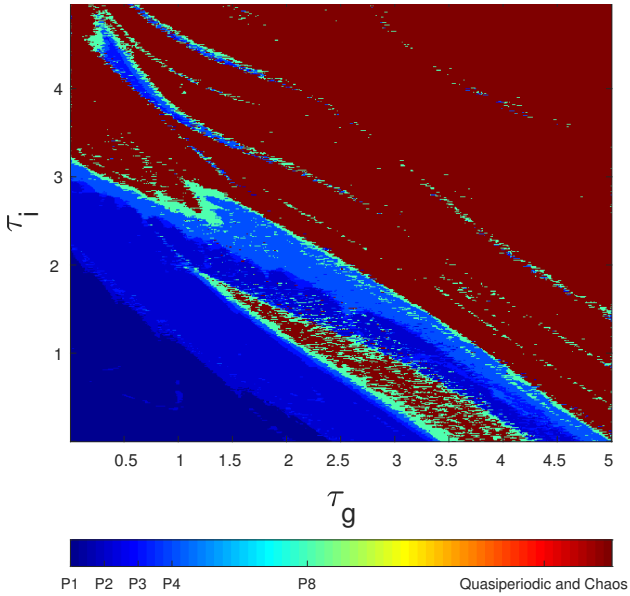


Fig. 2: 2D Bifurcation Diagram

delay from Fig. 2. By increasing the glucose delay response time caused by insulin secretion (τ_i), the system behaves chaotically as shown in Fig. 3a for different values of (τ_i). Fig. 3b show the bifurcation diagram when increasing the insulin secretion delay (τ_g) from the β-cell. and it is clear that the increase in the delay make the insulin cannot track the blood plasma glucose change which result in a metabolic disorder.

3 Simulation Results

The numerical simulation of the proposed regulatory system mathematical model 1 is implemented for the given parameters values in Table 1. Fig. 4 show the corresponding time courses 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 $\tau_g = 0.46$. where the solution trajectory tending toward limit cycle behavior and the dynamic profile of both biological variable the insulin and glucose exhibit periodic behavior which have been experimentally reported for normal endocrine metabolic system in various researches as [17,33,43] and many other literatures. The tight coupling between glucose and insulin oscillations suggest that these oscillations represent a

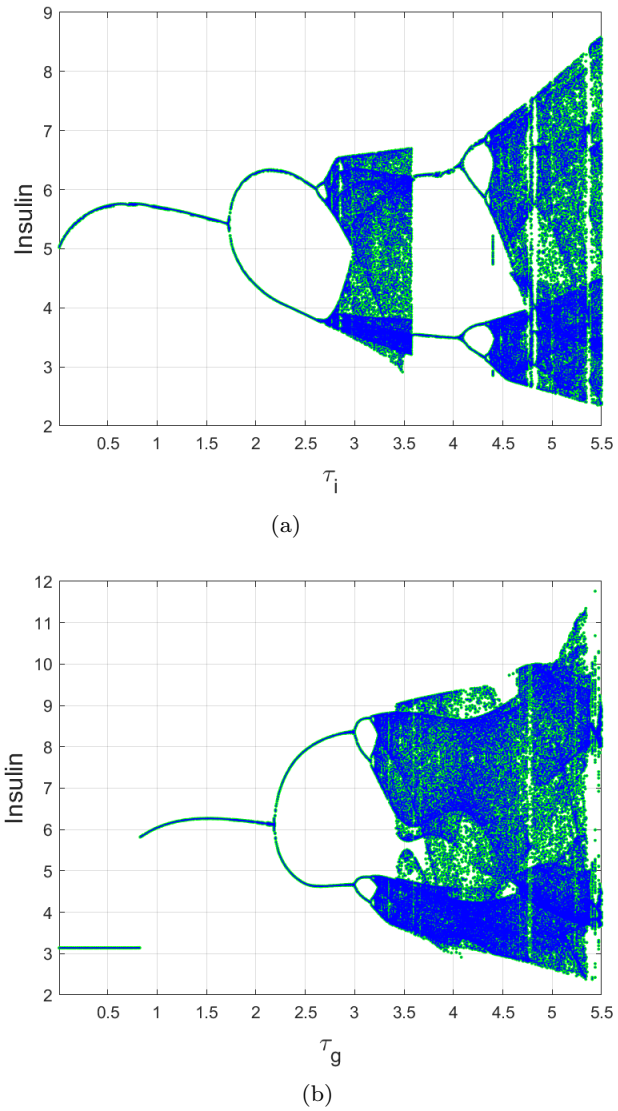


Fig. 3: The bifurcation diagram of system 1 based on different values of parameters: (a) Glucose response time, (b) Insulin secretion time.

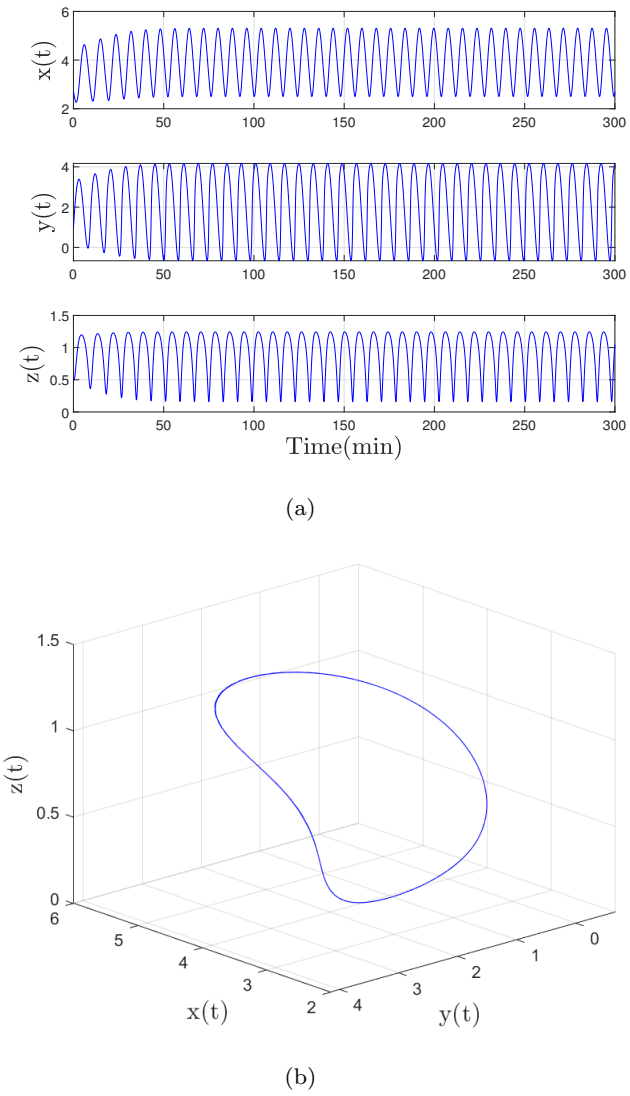
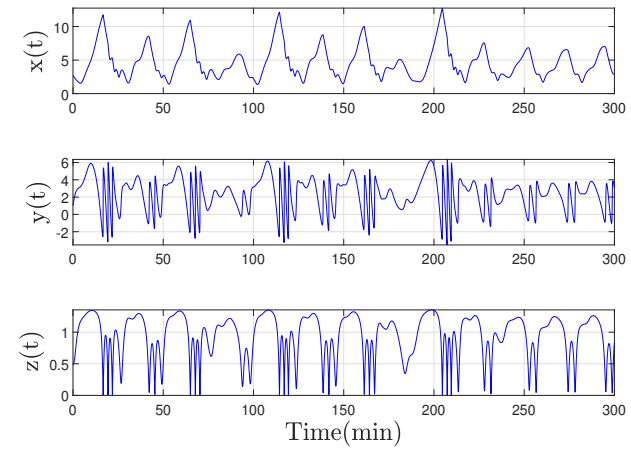


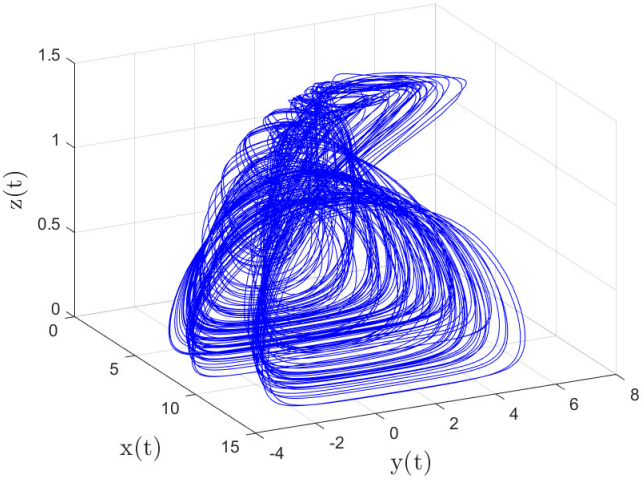
Fig. 4: The system 1 response (a) Time series of insulin, glucose and β-cell respectively, (b) corresponding phase portrait.

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. 5 shows the time series of the system 1 and the visualization of the chaotic attractor for the given parameters in Table 1 and time delay $\tau_i = 3.5$ and $\tau_g = 3.5$. The results are in line with literatures in the field reveling that a chaotic behavior in the system is a sign of an existing disorder in the biological system [36,37,38]. Molnar's [43] and Kroll's [45] experiments reported the chaotic behavior in glucose-insulin time courses. So, due to the chaotic behavior; stabilizing blood glucose level for diabetic patients is a continuous challenge, the patient tries always to avoid hyperglycemia and hypoglycemia. In fact, the analysis of blood glucose measurements is one of the most important tasks in order to assess the glucose metabolic control. And as a consequence, it is possible to define a range of confidence in which we may predict the blood glucose evolution level of diabetic patients. Out of this range the process is chaotic. Where, according to chaos theory deals with strictly deterministic dynamical systems, but have a fundamental instability phenomenon called "sensitivity to initial conditions" which modulo an additional property of recurrence, makes them un-



(a)



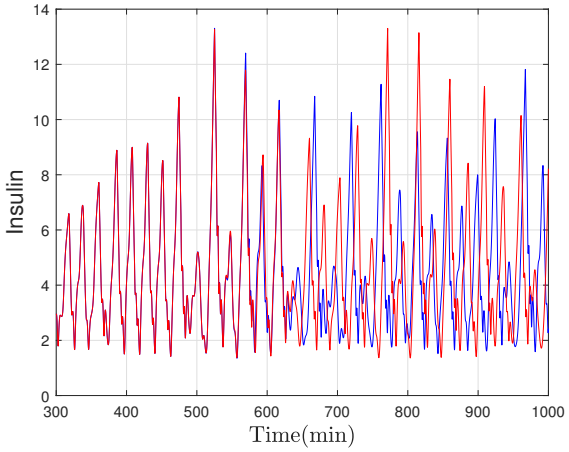
(b)

Fig. 5: The system 1 response (a) Time series of insulin, glucose and β-cell respectively, (b) corresponding phase portrait.

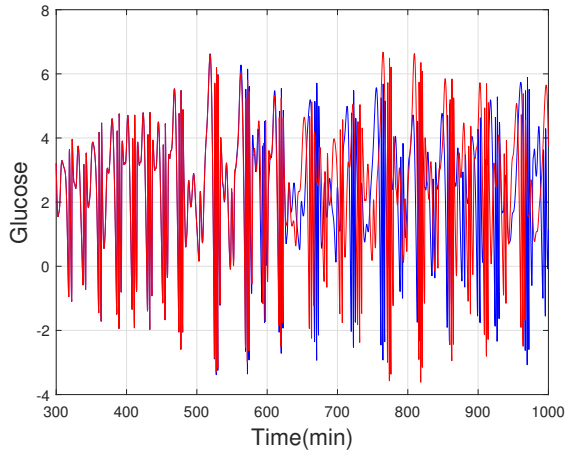
predictable in long term [46]. It has been proven in the next sections the existence of the chaotic state in the proposed model.

3.1 Largest Lyapunov Exponent

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 exponent measure the average divergence or convergence of nearby trajectories along certain directions in state space. In order to evaluate the LLE in this paper the algorithm proposed firstly by Mendes [47] will be used, which is based on the concept



(a)



(b)

Fig. 6: Derived from two interval extensions: (a) Two insulin pseudo-orbits, (b) Two glucose pseudo-orbits.

of the lower bound error LBE introduced in [48]. To calculate the LLE, the system, is simulated using two different interval extensions defined as:

Definition 1 *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 foundations used to calculate the lower bound error. Then, the largest lyapunouv exponent is evaluated by least square fit to the line of the logarithm of lower bound error. The procedure is adopted from [47] and explained as follow:

1. Choose two interval extensions of the system under investigation.

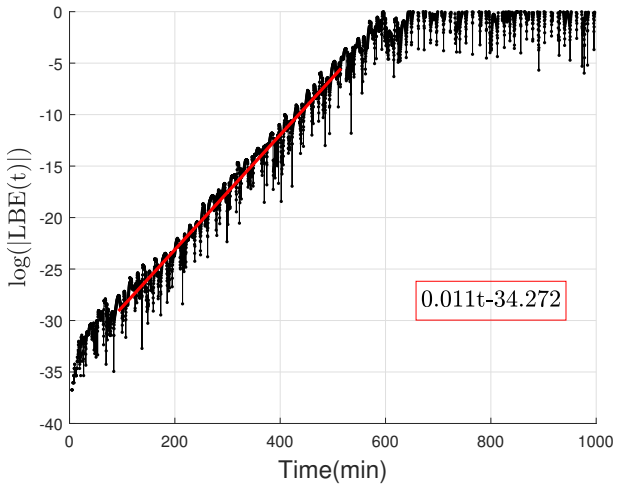


Fig. 7: The lower bound error LBE for the system 1. The red line is the least squares fit. In the figure, the equation of the line is also shown, where the first value is the estimate of the LLE.

2. With exactly the same initial conditions, step size and discretization scheme, simulate the two interval extensions.
3. Use the least squares method to fit a line 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.

The above procedure is applied to mathematical model 1, with same parameters in Table 1 selecting a time delay in the chaotic region such as $\tau_i = \tau_g = 3.5$.

Two interval extension chosen properly and the results of the simulation of the system are shown in Fig. 6a for the insulin time course while Fig. 6b shows the glucose dynamic it clear that the time courses are coincides at the beginning then begin to converge due to the trajectories expansion. Then the lower error bound is plotted in Fig. 7 and the LLE is evaluated form it. The value of the LLE is found positive and equal to the slope of the line LLE=0.011, that which is the signature of a chaotic behavior.

4 Conclusion

The mathematical modeling is an important tool to study the biological system and provide a good approach to understand the complex metabolic system. The glucose-insulin models start from simple linear ordinary differential equation and keep evolving toward more realistic and feasible model. The time delay differential equation model is providing a good tool to emulate the complex metabolic system by inclusion of the time delay term in some part of the model. New factor representing the insulin degradation due to interaction with glucose has been added, the new model has been analyzed from the stability point of view by checking the steady state point and it eigenvalues related to time delay. The bifurcation diagram and space parameter used to discover the system dynamics and reveal the oscillatory behavior with a period of proximately 8 min which is in the range 5-15 min consistent with the results reported in the biological experiments and prove the chaos existences which is a measure of disorder in the biological system. The extension principle and lower bounded error are used to prove the chaotic state of the model at specific time delay range. More parameter can be considered such as influence of trauma, excitement and stress also the effect of the epinephrine in suppressing the insulin secretion and inducing the glucose increase which affect the glucose-insulin homeostasis and may lead to diabetes in human.

Conflict of interest

The authors declare that they have no conflict of interest.

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