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A new chaotic model for glucose-insulin regulatory system

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ABSTRACT

For non-invasively investigating the interaction between insulin and glucose, mathematical modeling is very helpful. In this paper, we propose a new model for insulin-glucose regulatory system based on the well-known prey and predator models. The results of previous researches demonstrate that chaos is a common feature in complex biological systems. Our results are in accordance with previous studies and indicate that glucose-insulin regulatory system has various dynamics in different conditions. One interesting feature of this new model is having hidden attractor for some set of parameters. The result of this paper might be helpful for better understanding of regulatory system that contains glucose, insulin, and diseases such as diabetes, hypoglycemia, and hyperinsulinemia.

1. Introduction

Many researchers have tried to investigate the interactions between glucose and insulin by using mathematical models [1,2]. Based on previous studies, mathematical models are powerful tools to gain an insight into such interaction. Apart from experimental research, developing bilateral interplay mathematical models of glucose-insulin has played an important part in advancing the scientist vision and saving time and money.

Diabetes Mellitus (DM), also called diabetes, is one of the most common metabolic disorders [2]. In patients with diabetes, there is a high level of sugar in blood and the sugar level can't be controlled [2]. Researches indicate that the number of diabetic patients is increasing around the world [3]. From 2012 to 2015, there are almost 1.5 to 5.0 million people die each year from diabetes [4,5]. As of 2015, it was estimated that about 415 million people, approximately 8.3% of the adult population of the world, suffer from diabetes [5]. Some of the diabetes symptoms are increased thirst and hunger, which can cause longstanding complications, including heart disease and kidney failure [2]. Some of the elements that can cause this irregular behavior in body are as follows: Genetic factors that can fertilize the body so that other factors of the disease could disrupt the metabolic system [6]; Overweight caused by malnutrition as a consequent of modern lifestyle; Side effects of some drugs like Glucocorticoids and Thyroid hormone; advancement of other diseases; and many other elements that cannot be fully discussed [6].

Scientists can develop meditative procedures by understanding the causes of a disease. Insulin is a peptide hormone, which controls the blood sugar. In diabetes, insulin is either not secreted or the body cells ignore its presence [7]. Diabetes mellitus is classified into three types. In the first type (type1 DM), insulin is not produced enough by pancreas, so it couldn't control the blood sugar level. In most of the patients with this type of diabetes, the insulin releasing cells, called beta cells, are intercepted, and killed by body's immune system [8]. Five to ten percent of diabetic patients are suffering from this type. The second type of diabetes (type 2 DM), occurs when body cannot use insulin in the right way, because of overweight, and lack of enough exercise. This type accounts for 90% to 95% of diabetics [9]. The third type of diabetes, namely the gestational diabetes, is a temporary situation that occurs during pregnancy, as the blood sugar level increases. Approximately it affects two to four percent of all pregnant women [8, 9]. Other elements like stress, anger, and nourishing habits can affect the blood glucose and insulin levels.

In previous studies, linear models of diabetes show the relationship between glucose and insulin concentration in isolation from other factors [10]. However, in nonlinear models it can be presumed that the relationship between these components is not always linear and it could be affected by the initial blood glucose level; also the statistical properties of the profile of some patients can change significantly [10,11]. The glucose-insulin system is a part of human complex system, in which the interactions between the components determine the overall behavior of the system. The insulin secretion system is a negative feedback controller operat-

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ing between the pancreatic β-cells and plasma glucose concentration. For instance, when a person eats a snack the body secretes more insulin to decrease the glucose level in the blood by increasing the consumption rate of sugar or beginning the storage process. On the contrary, when there is a low level of glucose in blood, the body stops the secretion of insulin, in which the metabolic system's condition shifts from absorptive to post-absorptive [12–14]. In order to have a good understanding of this metabolic interaction, researchers have proposed different mathematical models to simulate the relationship between plasma glucose concentration and plasma insulin concentration more precisely [15,16]. Many scientists have focused on the analysis of chaotic dynamics, since it provides a successful method for investigating biological systems [17–21]. Furthermore, this innovative excellent point of studying biological phenomena has made significant effects on advancing biological models [22–25].

In the next section, the theoretical model of the system is introduced and its dynamical properties are presented. After that, Section 3 illustrates the results and discusses the model. At last conclusion remarks are given in Section 4.

2. Mathematical model

2.1. Previous mathematical models for insulin-glucose regulatory system

Some mathematical models have been proposed to study the relationship between the blood glucose and insulin concentration. The mathematical model (1) consists of two linear differential equations for modeling glucose-insulin tolerance test, which is proposed by *Ackerman et al* in 1964 [16].

$$\begin{aligned}\frac{dx}{dt} &= a_1 y(t) - a_2 x(t) + C_1\\ \frac{dy}{dt} &= -a_3 y(t) - a_4 x(t) + C_2 + I(t)\end{aligned} \tag{1}$$

Where $x(t)$ and $y(t)$ represent insulin and glucose concentrations respectively. $I(t)$ indicates the increase rate of blood glucose due to absorption in the gastrointestinal system.

It has been discovered that β-cells have an essential role in regulating glucose and insulin concentration, which was not mentioned in Ackerman model. The main function of β-cells is to store and release insulin. Mathematical model (2) for insulin-glucose regulatory system, proposed by Bajaj and Rao in 1987 [26], consists of three differential equations and incorporates β-cells.

$$\begin{aligned}\frac{dx}{dt} &= R_1 y - R_2 x + C_1\\ \frac{dy}{dt} &= \frac{R_3 N}{z} - R_4 x + C_2\\ \frac{dz}{dt} &= R_5 y(T - z) + R_6 z(T - z) - R_7 z\end{aligned} \tag{2}$$

Where $x(t)$ is insulin concentration, $y(t)$ is blood glucose concentration and z(t) is the population density of β-cells. T is total density of β-cells. R_1 represents the rate of increase in insulin concentration in response to blood glucose increase. R_2 shows the rate of insulin reduction which is independent from glucose concentration and is based on its current level. R_4 indicates the decrease rate of glucose in response to insulin secretion. R_5 shows the rate of increase in dividing β-cells due to interaction between blood glucose above the fasting level and the non-dividing β-cells, R_6 is the rate of increase in β-cells due to interaction between dividing and non-dividing β-cells, R_7 shows the decrease rate of β-cells due to its current level, C_1 accounts for the rate of increase of x in the absence of x and y and C_2 shows increase rate of y in the absence of x and z. Mentioned models treat the system as an isolated environment, omitting many factors that may affect the insulin-glucose relationship.

2.2. Mathematical model of prey and predator

Predation, by means of biological expressions, is defined as the interaction between a predator and a prey in an ecosystem [27]. *Vito Volterra* was the pioneer mathematician who introduced the first model composed of two simple differential equations describing the behavior of population dynamics of the aforementioned genres in terms of measurable variables in 1926. The model (3) is known as *Lotka–Volterra* model [22].

$$\begin{aligned}\frac{dx}{dt} &= ax(1 - x) - bxy\\ \frac{dy}{dt} &= -cy + dxy\end{aligned} \tag{3}$$

Where $x(t)$ is the population density of prey and $y(t)$ is the population density of predator. It is noteworthy to say that *a, b, c* and *d* are all positive parameters.

2.3. New mathematical model for insulin-glucose regulatory system

As it can be conceived, the relationship between glucose and insulin is like prey and predator; therefore, we propose a continuous nonlinear model for insulin-glucose regulatory system using prey and predator model proposed by *Vito Volterra* in [22]. The bilateral influence of the components has also been taken into account in order to preserve the comprehensiveness and accuracy of the model. In the proposed model, it has been assumed that the derivatives of the variables are cubic function of the variables themselves. Using cubic function of variables enhances the accuracy of model and can convincingly mimic the insulin glucose regulatory system. In addition to normal state, the new model is capable of showing the state of glucose-insulin regulatory system in abnormal metabolic conditions, which was the blind spot of the previous models. These capabilities will be explained in next sections. The mathematical relationships for the model are formulated as follows:

$$\begin{aligned}\frac{dx}{dt} &= -a_1 x + a_2 xy + a_3 y^2 + a_4 y^3 + a_5 z + a_6 z^2 + a_7 z^3 + a_{20}\\ \frac{dy}{dt} &= -a_8 xy - a_9 x^2 - a_{10} x^3 + a_{11} y(1 - y) - a_{12} z\\ &\quad -a_{13} z^2 - a_{14} z^3 + a_{21}\\ \frac{dz}{dt} &= a_{15} y + a_{16} y^2 + a_{17} y^3 - a_{18} z - a_{19} yz\end{aligned} \tag{4}$$

Where $x(t)$ is the population density of predator (insulin), $y(t)$ is the population density of prey (glucose) and $z(t)$ is the population density of β-cells; $-a_1$ represents the natural reduction of insulin concentration in absence of glucose; a_2 shows the propagation rate of insulin in presence of glucose; $-a_8$ represents the effect of insulin on glucose and a_{11} indicates the natural growth of glucose in absence of insulin. These terms are determined through prey and predator model; meanwhile, it is vital that these four parameters be positive. a_3 and a_4 show the increase rate of insulin when there is an increase in glucose concentration. a_5, a_6 and a_7 show the increase rate of insulin level secreted by β-cells and are independent from other components. a_9 and a_{10} represent the rate of glucose reduction in response to insulin secretion. a_{12}, a_{13} and a_{14} show the reduction rate of glucose concentration due to insulin secreted by β-cells. a_{15}, a_{16} and a_{17} represent the rate of increase in β-cells caused by the increase in glucose concentration. a_{18} and a_{19} show the rate of decrease in β-cells due to its current level.

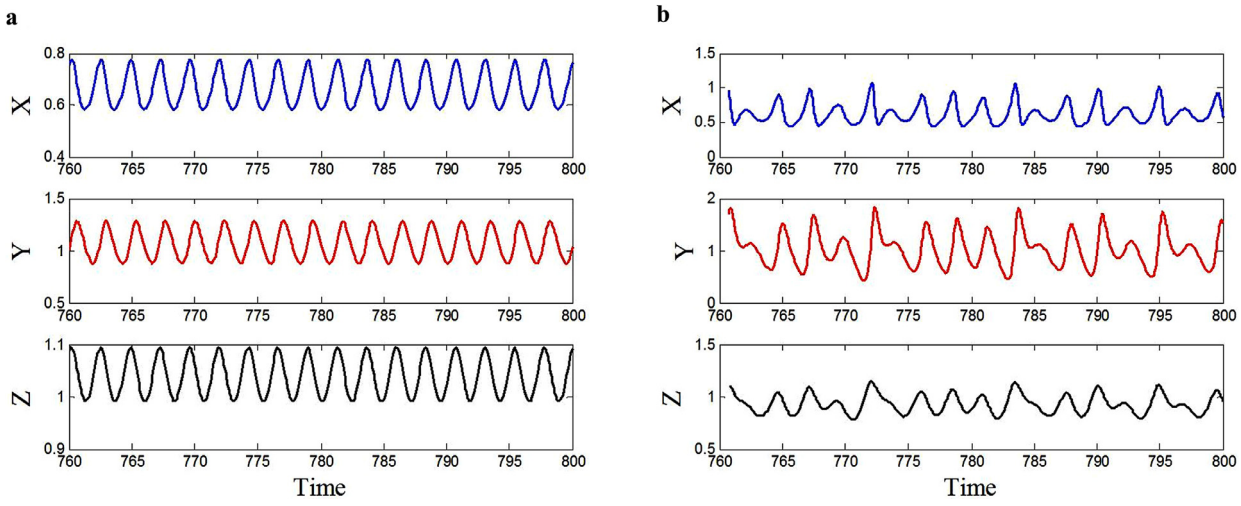

Fig. 1. a) Time series of the System (4) with initial condition of $x_0 = 0.53,\ y_0 = 1.31,\ z_0 = 1.03$ for the parameters given in Table 1 and parameter $a_1 = 3$. b) Time series of the System (4) with initial condition of $x_0 = 0.53,\ y_0 = 1.31,\ z_0 = 1.03$ for the parameters given in Table 1. (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

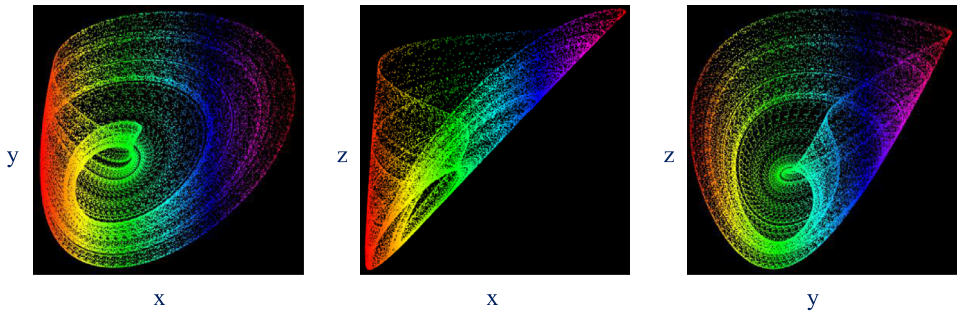

Fig. 2. Different projection of the visualization of chaotic attractor of System (4) by trajectory with initial condition of $x_0 = 0.53,\ y_0 = 1.31,\ z_0 = 1.03$ for the parameters given in Table 1.

3. Results and discussion

3.1. Time series and state space

The available experimental data is only based on glucose concentration which were acquired during the execution of experiments whose timescale is not sufficiently long for the purpose of verifying numerical models [15]. Furthermore, most models do not conform to known physiological data. In contemporary research methods, matching numerical results to experimental outcomes and choosing the best coinciding curve is not adequate for verifying numerical models. A model is pretended to be accurate if it demonstrates the same dynamic performance as observed in real data as well. To be more precise, if a fluctuating pattern is perceptible from experimental data, an appropriate model showing the same data fluctuation trend must be proposed. In the current model, it is expected to observe periodic behavior under normal metabolic conditions and chaotic behavior under faulty status of metabolic system. It is noteworthy that these expectations are in line with previous studies in the field revealing that a chaotic behavior of a system is a sign of an existing disorder in the system [28,29].

In this research, the behavior of System (4) for different quantity of parameters is investigated. The proposed model comprises a number of parameters whose values are essential in changing the behavior of the system. Figs. 1 and 2 indicate the time-series and state space trajectories of the proposed system, respectively. Computer simulation of the Figs. 1 and 2 is performed through taking the model coefficients as following table:

As it can be conceived, the value of insulin, glucose and β-cells' concentration can't be negative. Time series of the System (4)s are all positive. Fig. 1a indicates time series of the variables of the proposed model, which are all periodic, under normal condition. Several studies have reported persistent cyclic patterns in plasma glucose and insulin concentrations in man and monkeys in normal condition [30]. The results obtained from Kroll's experiment demonstrated proofs of chaotic behavior in glucose and insulin time-series [31]. As can be seen in Fig. 1b, the outcomes of another study ran by Molnar et al. by making an observation of 48 hours under the condition that immunoreactive insulin measurements were made from ambulatory-fed subjects, indicated chaotic behavior in plasma insulin and glucose patterns as well [32]. Fig. 1b shows time series of the variables of the proposed model in abnormal conditions which are all chaotic. It has been proven in the next section that these time-series are chaotic.

3.2. Stability analysis

The dynamical behavior of the proposed system can be determined by evaluating the eigenvalues of corresponding Jacobian matrix at each of the equilibrium points. Due to the biological meaning of the variables (the time series should be positive), only

Table 1
Coefficients of proposed model.

	a_1	a_2	a_3	a_4	a_5	a_6	a_7	a_8	a_9	a_{10}	a_{11}
Model Coefficients	2.04	0.1	1.09	−1.08	0.03	−0.06	2.01	0.22	−3.84	−1.2	0.3
	a_{12}	a_{13}	a_{14}	a_{15}	a_{16}	a_{17}	a_{18}	a_{19}	a_{20}	a_{21}	
Model Coefficients	1.37	−0.3	0.22	0.3	−1.35	0.5	−0.42	−0.15	−0.19	−0.56	

Table 2
Eigenvalues and equilibria of System (4).

Equilibria (x_0, y_0, z_0)	Eigen values
(0.805, 1.815, 1.319)	$\lambda_1 = 1.3802$, $\lambda_{2,3} = -1.7563 \pm 7.5090i$
(0.624, 0.935, 0.877)	$\lambda_1 = -2.8372$, $\lambda_{2,3} = 0.5262 \pm 2.3472i$

Due to λ values, both of these equilibrium points are saddle, since both have positive and negative eigenvalues.

stability analysis of positive fixed points is done. The Jacobian matrix of the System (4) is given by:

$$J = \begin{pmatrix} -a_1 + a_2 y & a_2 x + 2a_3 y + 3a_4 y^2 & a_5 + 2a_6 z + 3a_7 z^2 \\ -a_8 y - 2a_9 x - 3a_{10} x^2 & -a_8 x + a_{11}(1 - 2y) & -a_{12} - 2a_{13} z - 3a_{14} z^2 \\ 0 & a_{15} + 2a_{16} y + 3a_{17} y^2 - a_{19} z & -a_{18} - a_{19} y \end{pmatrix} \quad (5)$$

The System (4) has two positive fixed points for parameter set in Table 1 and $a_1 = 3$, which are given in Table 2.

3.3. Bifurcation diagrams

In this section, bifurcation diagrams of the System (4) for different parameters are plotted and the biological meanings of these diagrams are discussed. In a bifurcation diagram, the quantities gained or approached asymptotically by a system (fixed points, periodic orbits, or chaotic attractors) is plotted against a bifurcation variable in the system. As it has been observed in previous studies, whenever a chaotic behavior is demonstrated by a system, it signifies the existence of some disorders [28,29]. In the present study, whenever system acts chaotically we specify it as some kind of disorder. Four common disorders related to insulin-glucose regulatory system is simulated by the proposed mathematical model.

3.3.1. Type2 diabetes

If the effect of insulin on glucose concentration is declined or cells of the body become insulin-resistant, insulin cannot track glucose and the concentration of blood glucose rises, which results in type 2 diabetes disorder. We expect the system to show chaotic manner in this situation, this expectation is in line with the decrease in a_8 parameter. This parameter represents the effect of secreted insulin on glucose concentration. When this parameter decreases, it means that body cells resist on accepting insulin. Fig. 3 is the bifurcation diagram of the system based on different values of a_8. In order to plot the bifurcation diagrams of the system for each value of control parameter the system is first allowed to settle down and then the local maxima of time series (X_{max}) are plotted for a few thousand iterations. Fig. 3 shows that if body cells resist on accepting insulin, which is the main cause of type 2 diabetes, the system behaves chaotically. System is stable for large values of parameter a_8 but as this parameter decreases system acts in chaotic behavior. As it can be seen small changes in quantities of the parameters of the model cause overall changes in the behavior of the system.

Lenbury et al. showed that the key elements specifying dynamic behaviors of insulin-glucose regulatory system are shape and volume of the cells. This fact was discovered by investigating channel conductance related parameters during the clinical observation of electrical activities of cells. It has been well established that such electrical activities are closely related to insulin secretion and the regulation of plasma glucose [33].

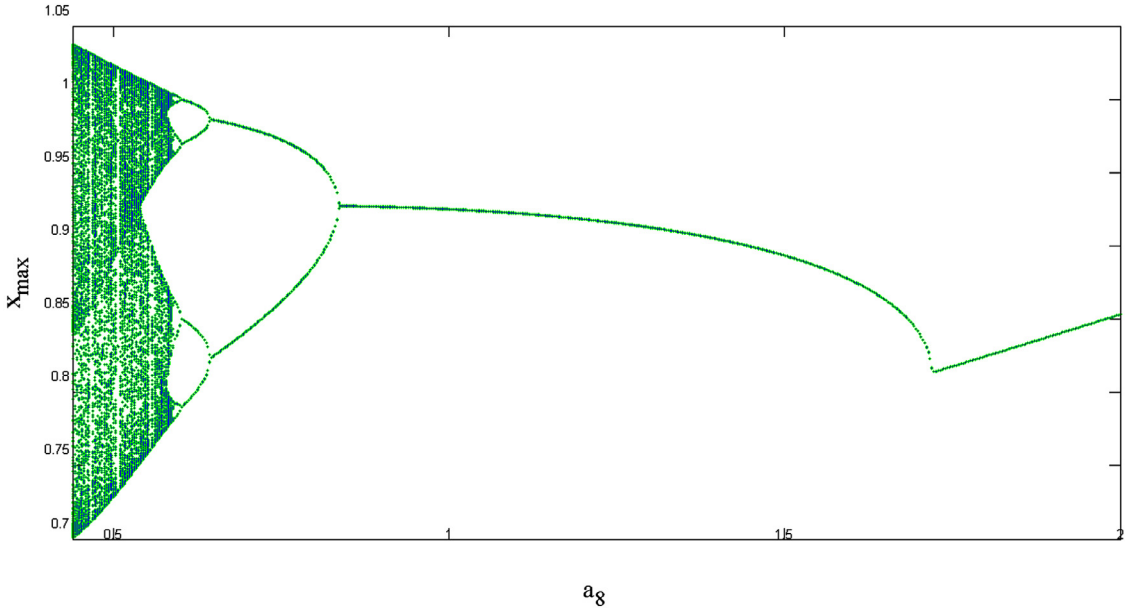

Fig. 3. The System (4) bifurcation diagram based on different values of parameter a_8.

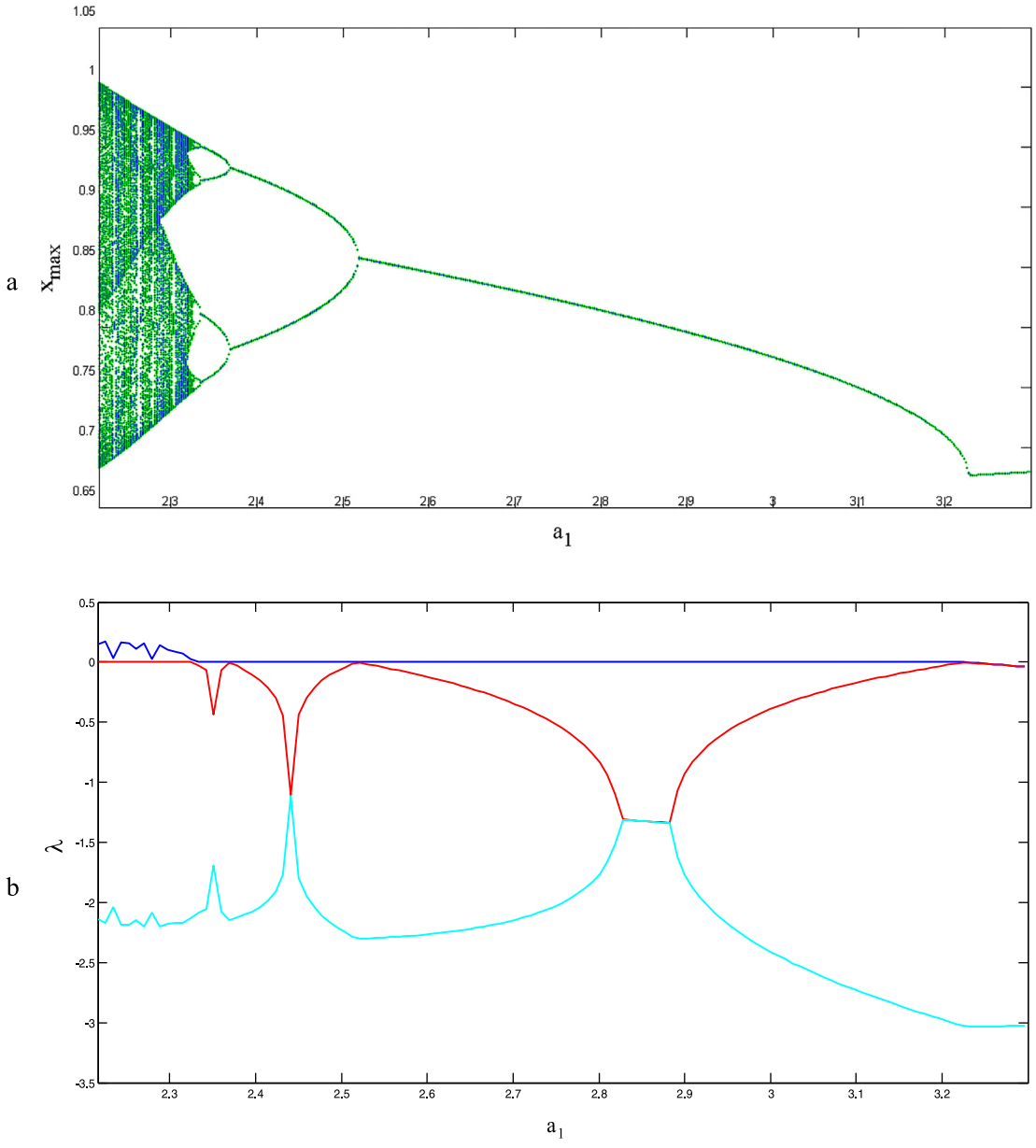

Fig. 4. a) Bifurcation diagram of System (4) based on different values of parameter a_1. b) The Lyapunov exponent diagram of System (4) based on parameter a_1.

3.3.2. Hypoglycemia

Existence of so much insulin in blood causes a disorder named hypoglycemia [34]. If the rate of "insulin decay", which is indicated with parameter a_1 in the model, gets low, it proceeds to hypoglycemia, thus we anticipate that the proposed system act chaotically. Fig. 4a is the bifurcation diagram of the System (4) based on different values of a_1. It can be observed in Fig. 4a that system is stable for large values of parameter a_1 but as this parameter decreases system starts to act chaotically. The numerical results of Lyapunov exponent is shown in Fig. 4b. A positive Finite-time Lyapunov exponent is an indicator of chaotic behavior [35,36]. As can be seen, the system is stable for large values of a_1, but when this parameter decreases, the system exhibits chaotic behavior. Here Lyapunov exponents are denoted by λ_{L_i}, i=1, 2, 3 with $\lambda_{L_1}>\lambda_{L_2}>\lambda_{L_3}$. Obviously, the proposed system is chaotic according to the values of the exponents bounded as $\lambda_{L_1}>0$, $\lambda_{L_2}=0$ and $\lambda_{L_3}<0$ with $|\lambda_{L_1}|<|\lambda_{L_3}|$. The fractional dimension, which presents the complexity of attractor, is defined by

$$D_{KY} = j + \frac{1}{\left|\lambda_{L_{j+1}}\right|}\sum_{i=1}^{j}\lambda_{L_i} \tag{6}$$

Where j is the largest integer satisfying $\sum_{i=1}^{j}\lambda_{L_i}\geq 0$ and $j\sum_{i=1}^{j+1}\lambda_{L_i}<0$. The calculated dimension of System (4) when $a_1=2.04$ is DKY = 2.1725 > 2. In consequence, a strange attractor is detectable in the system. (See Fig. 2)

3.3.3. Hyperinsulinemia

One of the common diseases related to insulin glucose regulatory system is hyperinsulinemia. If β-cells of pancreas secrete insulin more than particular quantities in response to the continued high blood glucose levels, hyperinsulinemia occurs [37,38]. This fact can be observed in the proposed model. The system is stable for small values of parameter a_7, which illustrates amplified rate of insulin level secreted by β-cells. As this parameter increases, the system shows chaotic behavior. Bifurcation diagram of the system

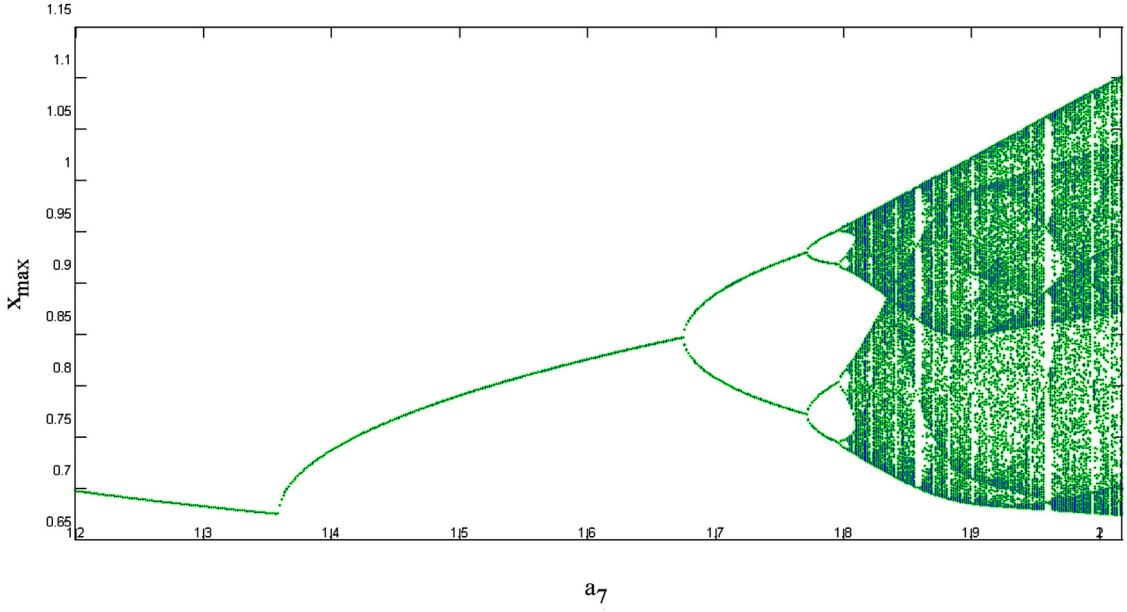

Fig. 5. The System (4) bifurcation diagram based on different values of parameter a_7.

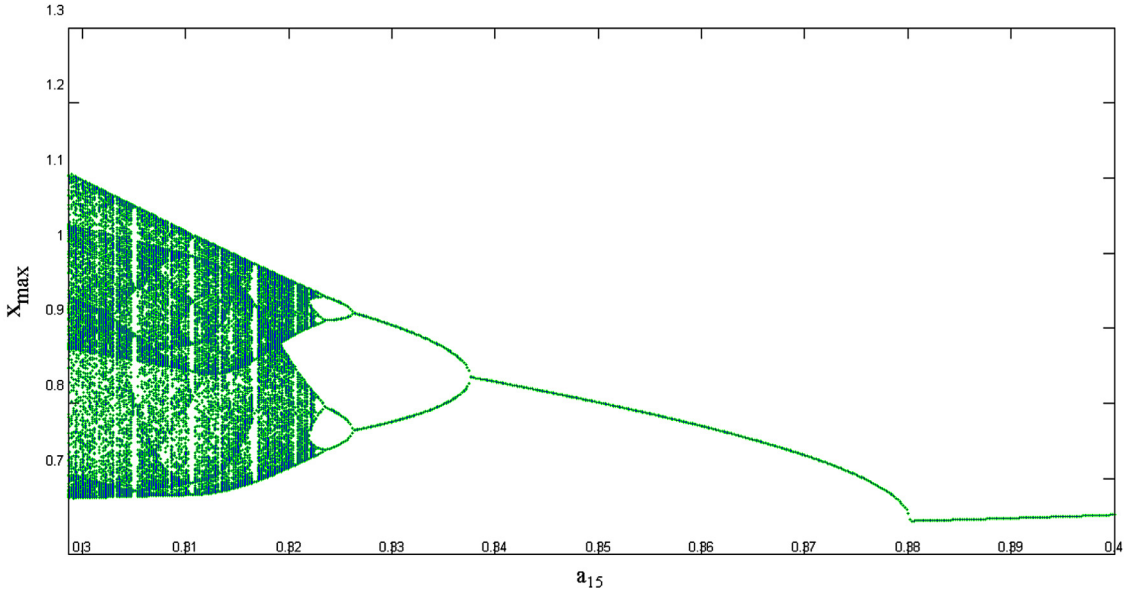

Fig. 6. The System (4) bifurcation diagram based on different values of parameter a_{15}.

for different values of a_7 is plotted in Fig. 5. System is stable for small values of parameter a_7 but as this parameter increases dynamic of the system changes to chaos. It can be realized that any small fluctuation in model parameters leads to undesired behavior of the system. We discovered in bifurcation diagrams of the system the appearance of a period doubling route to chaos, which resembles dynamics of prey and predator population model.

3.3.4. Type1 diabetes

Type 1 diabetes involves an autoimmune destruction of the insulin-producing β-cells in the pancreas. Proposed model can exhibit this disorder. If the rate of increase in population density of β-cells, represented by a_{15}, diminishes, pancreas cannot secrete enough insulin to stabilize glucose concentration level. We expect that system show chaotic behavior for small values of parameter a_{15}. Fig. 6 is the bifurcation diagram of the System (4) based on control parameter a_{15}. As can be seen the proposed system displays some kind of steady state manner for large values of control parameter a_{15} but as this parameter decreases, system starts to act chaotically which is in line with our expectation.

3.4. Basins of attraction

Recently dynamical systems were categorized into systems with self-excited attractors and systems with hidden attractors: when an attractor's basin of attraction involves equilibrium, we call that attractor "self-excited", otherwise, the attractor is hidden [39–42]. Hidden attractors exist in some real-world dynamical systems [43–45]. Rather than design, their localization and control have been of great interest in recent years [46–49]. As examples of such systems we can name systems which have surfaces of equilibria [50,51], curves of equilibria [52], stable equilibria [53], and no equilibrium points [54,55].

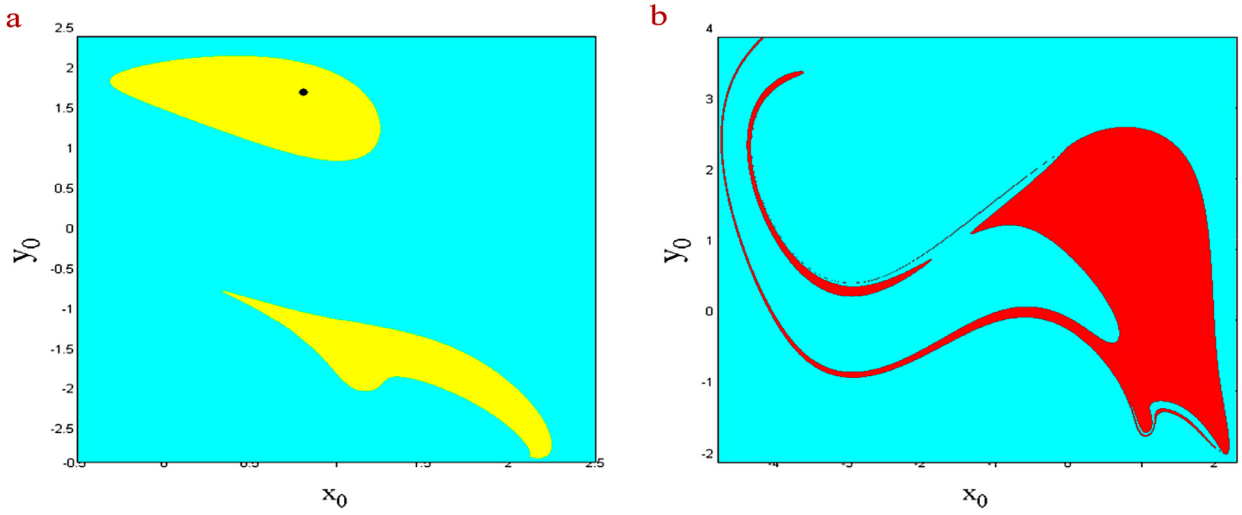

Fig. 7. a) Cross section of basin of attractions for parameter set of Fig. 1a. b) Cross section of basin of attractions for parameter set of Fig. 1b.

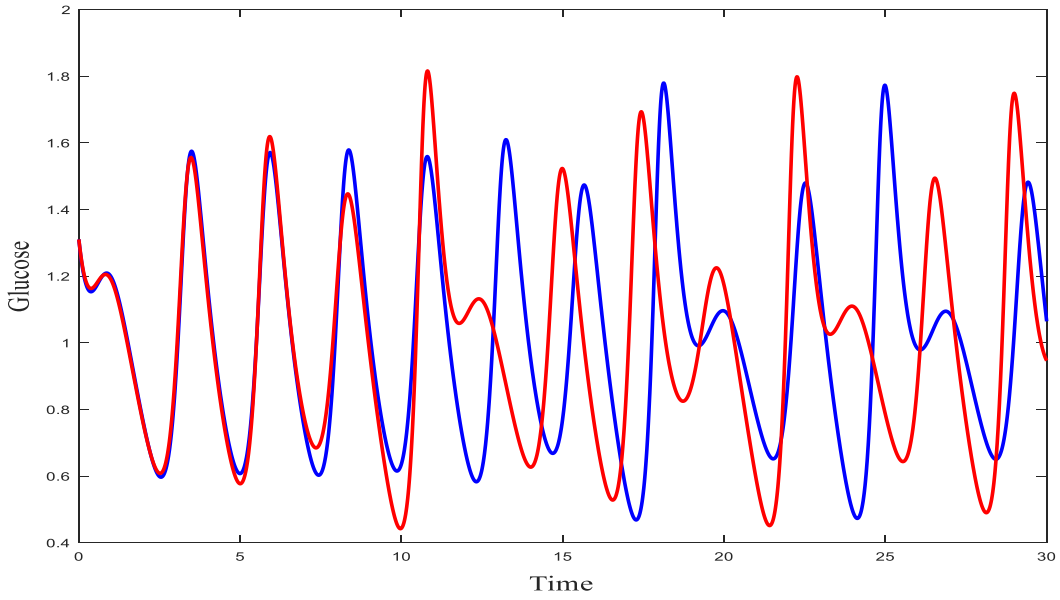

Fig. 8. Chaotic evolution of proposed system showing the effect of very small difference in the initial conditions. The initial conditions are $x_0 = 0.53$ and $x'_0 = 0.54$. ($y_0 = y'_0 = 1.31$, $z_0 = z'_0 = 1.03$).

Fig. 7 shows the two basin of attraction of System (4). Fig. 7a is the cross section of basin of attraction in xy-plane at $z = 1.31$. It shows regions of different dynamic behavior of system for parameter set of Fig. 1a. Unbounded regions are shown in light blue, periodic (limit cycle) and quasiperiodic (torus) regions are shown in yellow and black dot corresponds to fixed point. Fig. 7b shows a cross section in the xy-plane at $z = 1.03$ with parameter set of Fig. 1b. Initial conditions in the light blue region lead to unbounded orbits and those in the red region lead to strange attractor. There is no fixed point in the system for the selected parameters; therefore the chaotic attractor is hidden. The authors are not aware of any other hidden attractor in biological systems and models.

3.5. Sensitivity to initial condition

In the case of chaotic dynamics, a minor variation in initial conditions may cause significantly different dynamic behavior. Therefore, even a slight fluctuation in the insulin concentration may result in unpredictable outcomes through time.

The effect of small changes in initial insulin concentration on glucose time-series of the System (4) (variable y) can be observed in Fig. 8. It is of note that the administration of insulin through an appropriate program is difficult in some of patients. Furthermore, in such patients, using an integration of scheduled nutrition and exercise and timetabled insulin administration is purely inadequate in confining blood glucose within proper limits. Of course, the effect of apparent irregular alterations cannot be overlooked and must be taken into consideration [32]. The aforementioned phenomenon is shown in Fig. 8.

To summarize, we have proposed a new continuous nonlinear mathematical model for insulin-glucose regulatory system using the mathematical model of prey and predator, which can mimic the interaction between insulin concentration, glucose concentration and β-cells in normal and abnormal situations. In comparison with previous models proposed for insulin-glucose regulatory system, this model exhibits various behaviors for different set of parameters, such as chaos, which was clinically observed in previous researches. Previous models were capable of modeling the insulin-glucose regulatory system only in normal condition, but the pro-

posed model is able to explain the interaction between the components in both normal and abnormal conditions.

4. Conclusion

In order to describe the interactions between glucose, insulin and β-cells, a new mathematical model was presented. Dynamical analysis of this new system such as studying time-series, state space and stability was done. Bifurcation diagrams of the system for various control parameters were plotted. Results demonstrated that the system exhibits different behaviors in various conditions and is capable of explaining the interaction between glucose, insulin and β-cells in different disorders, such as type1 diabetes, type2 diabetes, hypoglycemia and hyperinsulinemia. Lyapunov exponent analysis was done in order to determine the exact behavior of the system in different control parameters. The basin of attraction plot showed that the proposed model belongs to a newly introduced category of dynamical systems: systems with hidden attractors. Finally, dynamical properties of system were investigated for different initial conditions.

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