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Computational model of insulin-glucose regulatory system to represent type 1 diabetes mellitus, hypoglycemia and hyperinsulinemia

Ahmed Mohammed Ali[a] and Fadhil Rahma Tahir

Department of Electrical Engineering, University of Basrah, Basrah, Iraq

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Abstract. Diabetes mellitus (DM) is probably one of the most popular diseases among people. In this disorder, a malfunction occurs in the insulin-glucose regulatory system. To model the DM pathophysiology, we propose a computational model for the insulin-glucose regulatory system. In this differential equation model, the complex behavior of this biological system has been considered. This model shows chaos and bifurcating properties which have been seen in dynamical diseases. We have analyzed static and dynamical properties of the proposed model to show its strength and capability to represent different types of diabetes and other dysfunction in the insulin-glucose system.

1 Introduction

Glucose, in the group of carbohydrate known as simple sugars, plays a critical role in providing energy for the brain and red blood cells. To keep the level of glucose in its narrow standard range, the pancreas releases two endocrine hormones with inhibitory and excitatory effects; Glucagon, excitatory, and insulin, inhibitory, hormones which are released form α and β-cells respectively [1,2]. Dysfunction of this system causes the blood sugar to increase and decrease, which yields respectively diabetes and hypoglycemia. Diabetes is one of the most prevalent diseases studies of which show that 23 million U.S. adults have been diagnosed with diabetes until 2016 [3].

There are three main categories of diabetes mellitus; Type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM) [4]. In type 1 diabetes mellitus, insulin secretion is impaired due to the selective autoimmune destruction of the pancreatic β-cells in genetically susceptible people [5]. This type of DM is also called insulin-dependent diabetes. Type 2 diabetes is associated with resistance to insulin, so inadequate insulin secretion happens in this condition. This disorder, which is also named non-insulin-dependent diabetes, becomes more common with increasing age, obesity and weight gain [6]. To have insight about the prevalence of these two types of the DM, in 2016, type 1 and type 2 diabetes accounted for approximately 6% and 91% of all cases of diagnosed diabetes, respectively [3]. Glucose intolerance onset or first recognition during pregnancy is defined as gestational diabetes mellitus [7], which increases the risk of type 2 diabetes compared with those who had a normal pregnancy [8]. Also, other disorders in the insulin-glucose regulatory system, e.g.

[a] e-mail: ahmed.m.ojiemy@gmail.com

hypoglycemia [4,9], hyperglycemia [4,10] and hyperinsulinemia [4,11] can be studied in computational models which consider the insulin and glucose relationship.

Computational models of natural systems can be used to explain, predict and control the systems without practical experiments. In biological cases, one can test the effect of the different drugs without experiments and probable undesired side effects on a living sample. In 1964, Ackerman et al. [12] proposed two linear differential equations to describe the feedback relationships between the blood glucose and insulin concentrations of experimental data. The parameters of their model were physiologically meaningful. To model the β-cell effects on releasing insulin, Bajaj et al. proposed three differential equations which also was a nonlinear model [13]. Their results matched with the experimental observations of both normal and protein malnutrition groups. In this case, some researchers considered delay differential equations to model the time delay for the insulin production and effect of insulin on glucose production [14–16]. Also, gastrointestinal absorption term of glucose is considered in some models which yield chaotic responses in these systems [17]. [18] considers three differential equations which can generate chaotic behavior to model the insulin-glucose regulatory system. Chaotic and fuzzy analyses are also used to predict maximum fasting blood glucose [19]. To control the insulin-regulatory system which has uncertain time-delays and chaotic behavior, adaptive sliding mode control is used in [20].

Some complex nonlinear systems show strange or chaotic attractors for particular values of their parameters [21]. Most of the biological systems are in the group of complex and nonlinear systems, so expected to see chaotic responses in experimental analyses of these systems. The evidence shows chaos in some biological systems like brain [22–24], heart [25,26], kidney [27] and eye [28] in both physiological and pathophysiological conditions. In dynamical diseases in which the responses of the considered system change as the biological parameters change, the disease can be divided into different distinct phases [29]. With regard to the experimental evidence being normal, pre-disease or disease phases can have chaos or periodic responses in dynamical disorders.

β-cell shortage leads to hyperglycemia and diabetes [30]. These cells show bursting electrical activity in Islet of Langerhans [31]. To describe these complex behaviors, calcium-activated potassium (K-Ca) channel is utilized in Chay-Keizer model [32,33]. Improved Chay-Keizer models can model both isolated cells and clusters of cells tightly coupled by gap junctions [34]. It should be noted that complex and chatic activity of these important agents complicate the insulin-glucose regulatory system's activity.

In this article, we propose a new model to explain the glucose, insulin and β-cell dynamics in the regulatory system in Section 2.1. We analyze both statistical and dynamical properties of this system using the stability analysis and bifurcation diagram. In this case, different disorders in the regulatory system can be analyzed using the bifurcation diagram of the system for related and physiologically meaningful parameters of the system. Finally, the conclusion of the article has been discussed in Section 4.

2 The proposed model and its linear stability analysis

2.1 Chaotic model of the insulin-glucose regulatory system

To propose a new model, we consider the dynamical relationship between insulin, glucose and β-cells concentrations. In this context, physiologically meaningful parameters have been considered to suggest a three-dimensional differential equation.

Table 1. Values of the model parameters.

R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
1.00	2.17	0.41	1.00	0.79	−1.00	1.48	0.16	−0.80	5.53
R_{11}	R_{12}	R_{13}	R_{14}	R_{15}	R_{16}	R_{17}	R_{18}	R_{19}	
−0.29	0.27	1.59	−2.98	3.27	2.13	−0.92	5.30	0.00	

It should be noted that the proposed model will be expected to show behavioral responses to the insulin-glucose regulatory system. So the values of the parameters should be set as these responses will be meaningful. For example, all three variables of this system show concentrations of the particular materials in the body, so their values should be positive in time which make the basin of the parameters limited. Also, the existence of quadratic and cubic terms in the model will give it the potential to show complex behavior and transitions.

The proposed computational model for the insulin-glucose regulatory system is as follows:

$$\begin{aligned}\frac{dx}{dt} &= -R_1x + R_2y + R_3y^2 + R_4z + R_5z^2 + R_6z^3 + R_{17}\\ \frac{dy}{dt} &= -R_7x - R_8x^2 - R_9x^3 - R_{10}z - R_{11}z^2 - R_{12}z^3 + R_{18}\\ \frac{dz}{dt} &= R_{13}y + R_{14}y^2 + R_{15}y^3 - R_{16}z - R_{19}\end{aligned} \tag{1}$$

where $x(t)$ is insulin concentration, $y(t)$ is blood glucose concentration and $z(t)$ is the population density of β-cells. Also, R_1 represents the reduction rate of insulin concentration, which is based on its current level. R_2 and R_3 show the increase rate of insulin when glucose concentration increases. R_4, R_5 and R_6 show the increase rate of insulin concentration when the β-cells' level increases. R_7, R_8 and R_9 represent the rate of glucose reduction in response to increasing the insulin level. R_{10}, R_{11} and R_{12} show the reduction rate of glucose concentration because of β-cells' activity. R_{13}, R_{14} and R_{15} represent the rate of increase in β-cells due to the increase in glucose concentration. R_{16} shows the rate of decrease in β-cells due to its current level. R_{17} represents the rate of increase in insulin in the absence of insulin and glucose and R_{18} shows increase in the rate of glucose in the absence of insulin and β-cells. Also, R_{19} shows decrease rate of β-cells in the absence of insulin and glucose.

2.2 Stability analysis of the proposed system

To study this system, we consider the value of the parameters as Table 1. Figure 1 shows time response of the insulin, 2D phase space of glucose vs. insulin concentration, 2D phase space of β-cells vs. insulin concentration and 3D phase space of all three variables of the system. The chaotic response of the system can be seen both in time and phase plane.

If we change $R_1 = 2$ and the other parameters remain the same as Table 1, this system has one equilibrium at $E^* = (x^*, y^*, z^*) = (1.22, 0.99, 0.86)$. The Jacobian matrix of the system is as follows:

$$J = \begin{pmatrix} -R_1 & R_2 + 2R_3y & R_4 + 2R_5z + 3R_6z^2 \\ -R_7 - 2R_8x - 3R_9x^2 & 0 & -R_{10} - 2R_{11}z - 3R_{12}z^2 \\ 0 & R_{13} + 2R_{14}y + 3R_{15}y^2 & -R_{16} \end{pmatrix} \tag{2}$$

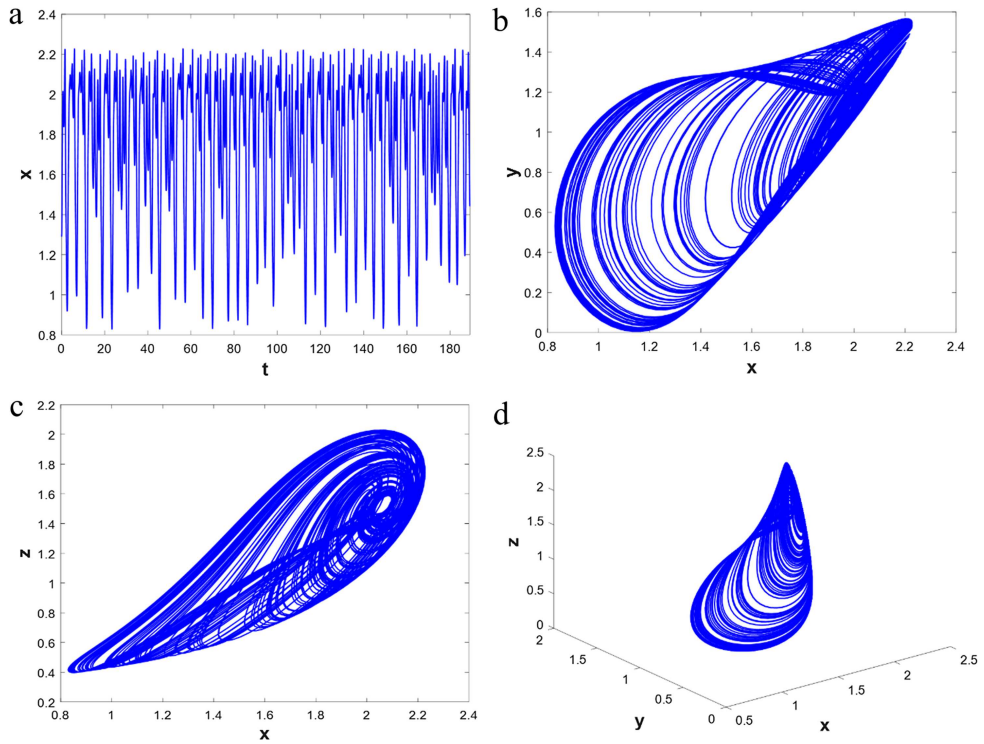

Fig. 1. (a) Insulin concentration, (b) chaotic response in x-y space, (c) x-z space and (d) 3D view of the chaotic response of the insulin-glucose regulatory system. The value of the parameters are $[R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}] = [1.00, 2.17, 0.41, 1.00, 0.79, -1.00, 1.48, 0.16, -0.80, 5.53, -0.29, 0.27, 1.59, -2.98, 3.27, 2.13, -0.92, 5.30, 0.00]$ and initial conditions are chosen as $(x(0), y(0), z(0)) = (1.29, 0.7, 0.44)$.

which yields eigenvalues as:

$$\begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \end{pmatrix} = \begin{pmatrix} -1.10 - 4.86i \\ -1.10 + 4.86i \\ -1.92 \end{pmatrix}. \tag{3}$$

So, stability analysis shows that it is a stable equilibrium. Figure 2 shows the response of the system which displays this stable equilibrium. To analyze the existence of any hidden attractor in the system, we derive the basin of attraction of the system when there is a stable equilibrium. Figure 3 shows basin of attraction of the system. As seen, the system goes to stable equilibrium when $[\mathrm{R}_1, \mathrm{R}_2, \mathrm{R}_3, \mathrm{R}_4, \mathrm{R}_5, \mathrm{R}_6, \mathrm{R}_7, \mathrm{R}_8, \mathrm{R}_9, \mathrm{R}_{10}, \mathrm{R}_{11}, \mathrm{R}_{12}, \mathrm{R}_{13}, \mathrm{R}_{14}, \mathrm{R}_{15}, \mathrm{R}_{16}, \mathrm{R}_{17}, \mathrm{R}_{18}, \mathrm{R}_{19}] = [2.00, 2.17, 0.41, 1.00, 0.79, -1.00, 1.48, 0.16, -0.80, 5.53, -0.29, 0.27, 1.59, -2.98, 3.27, 2.13, -0.92, 5.30, 0.00]$.

Initial conditions are important in chaotic systems and coexistence of attractors may occur in complex systems. Moreover, they are important in biological systems as they may show genetic of the patients. So, in Figure 4, basin of attraction of the system is considered when $[\mathrm{R}_1, \mathrm{R}_2, \mathrm{R}_3, \mathrm{R}_4, \mathrm{R}_5, \mathrm{R}_6, \mathrm{R}_7, \mathrm{R}_8, \mathrm{R}_9, \mathrm{R}_{10}, \mathrm{R}_{11}, \mathrm{R}_{12}, \mathrm{R}_{13}, \mathrm{R}_{14}, \mathrm{R}_{15}, \mathrm{R}_{16}, \mathrm{R}_{17}, \mathrm{R}_{18}, \mathrm{R}_{19}] = [1.00, 2.17, 0.41, 2.69, 0.79, -1.00, 1.48, 0.16, -0.80, 5.53, -0.29, 0.27, 1.59, -2.98, 3.27, 2.13, -0.92, 5.30, 0.00]$. Chaotic (black), periodic (green) and unbounded (red) attractors are seen in this figure.

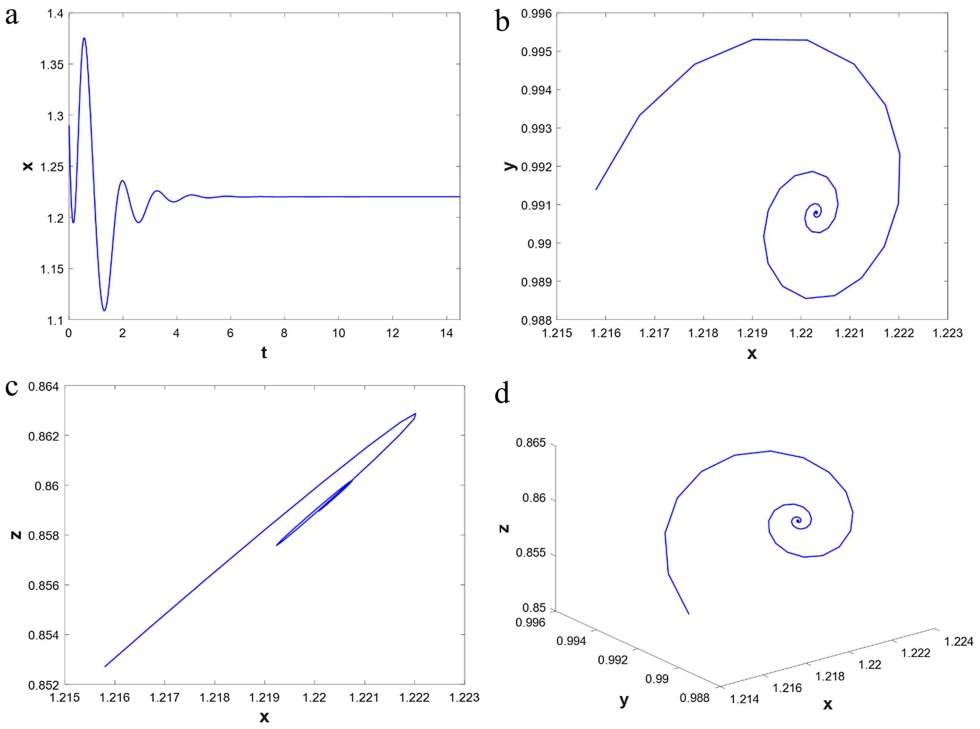

Fig. 2. (a) Insulin concentration, (b) stable equilibrium in x-y space, (c) x-z space and (d) 3D view of the response of the insulin-glucose regulatory system. The value of the parameters are the same as Figure 1 but $R_1 = 2$ and initial conditions are chosen as $(x(0), y(0), z(0)) = (1.29,0.7,0.44)$.

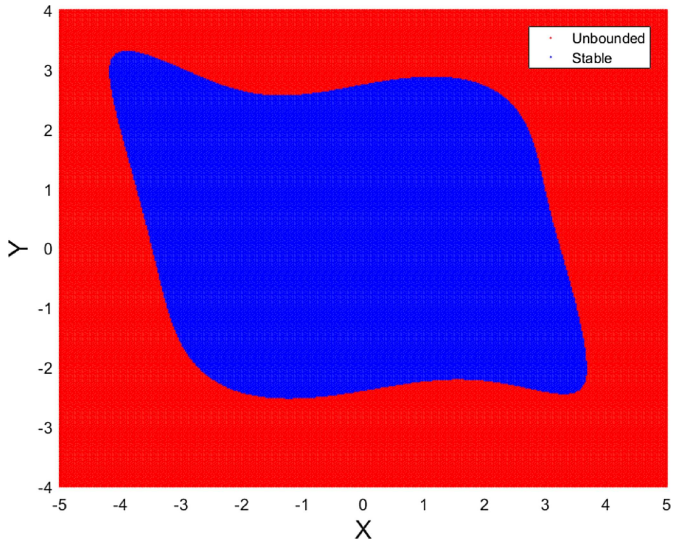

Fig. 3. This figure shows the basin of attraction of the system in $z = 0.44$. It shows that there isn't any hidden chaotic attractors.

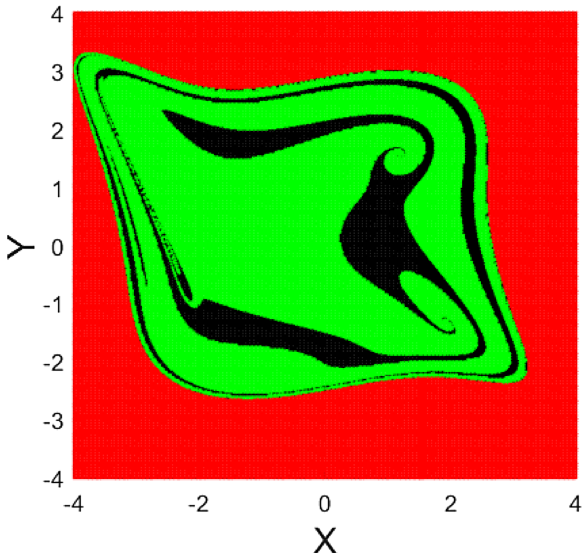

Fig. 4. Basin of attraction of the system when $[R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}] = [1.00, 2.17, 0.41, 2.69, 0.79, -1.00, 1.48, 0.16, -0.80, 5.53, -0.29, 0.27, 1.59, -2.98, 3.27, 2.13, -0.92, 5.30, 0.00]$. In this condition, chaotic (black), periodic (green) and unbounded (red) attractors are seen.

3 Results and discussion

In this section, we analyze the dynamical results of our proposed model. To consider different types of DM and other disorders in this system, we derive the bifurcation diagram of the system for different physiologically meaningful parameters of the system. In the bifurcation diagram, we consider the response of the system as the control parameter increases (or decreases). Changing the range and type of system response indicates the sensitivity of the system to the considered control parameter.

3.1 Type 1 diabetes

In type 1 diabetes, an autoimmune process of the body yields to decreasing the β-cells concentration [5]. As the number of β-cells decreases, secretion of insulin reduces too. To consider dynamical changes in the system in this type of diabetes, we can consider parameter R_{19} in β-cells' changing rate equation, $\dot{z}$. This parameter shows the constant decreasing rate of β-cells' concentration. As we consider this decreasing parameter grows, dynamical changes of the glucose, insulin and β-cells during type 1 diabetes can be derived.

Figure 5 shows the bifurcation diagram of the insulin concentration as parameter R_{19} increases. With regard to Figure 5, the insulin concentration has chaotic attractor while the decreasing rate of β-cells is low. In our hypothesis, these chaotic variations are normal and in the physiological limits as the insulin level changes in a day. However, in the case of more destruction of β-cells, these variations vanish and insulin dynamics becomes ordered through period halving bifurcation.

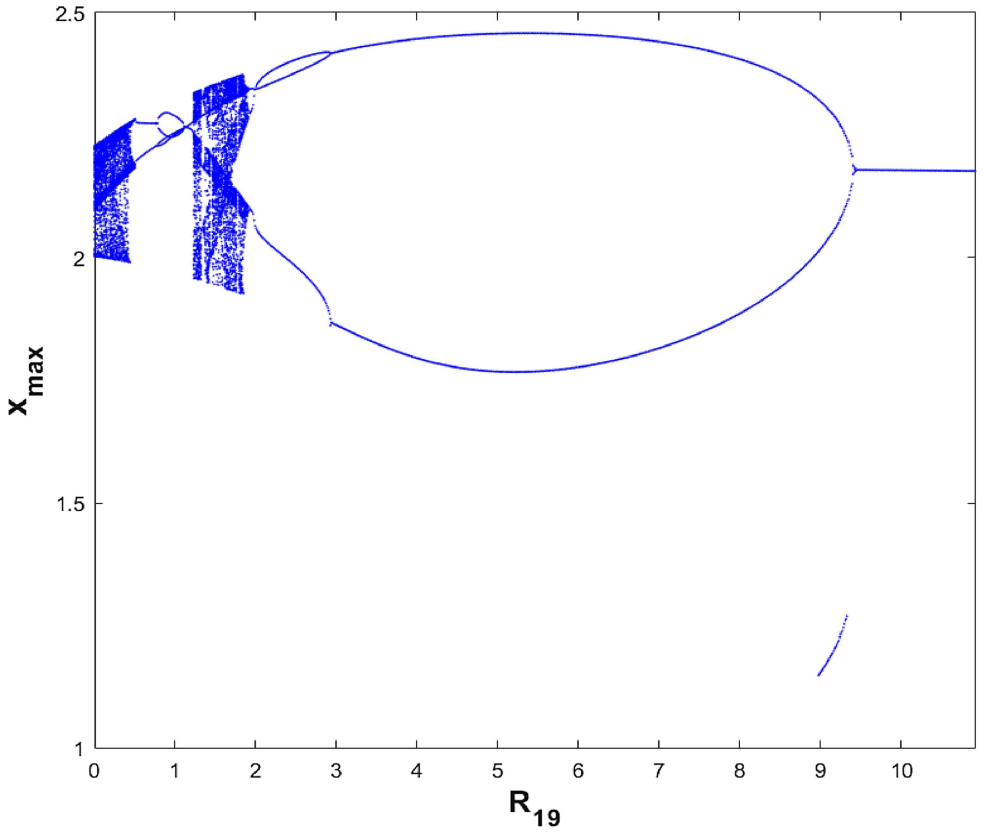

Fig. 5. Bifurcation diagram of the system as the parameter R_{19} changes. This parameter shows decrease rate of β-cells in the absence of insulin and glucose.

3.2 Hypoglycemia

The amount of blood glucose commonly falls in patients who use insulin and also have kidney failure, certain tumors, liver disease or use drugs, including alcohol [9,35]. This low blood sugar, which is identified as hypoglycemia, may result in seizures or unconsciousness. To model this disease, we consider the value of the parameter R_7 changes as this parameter shows the decreasing rate of glucose as the insulin level increases.

In Figure 6, as the controlling parameter, R_7, increases, the glucose level decreases until the dynamic of the system move from chaotic response to periodic and ordered one. As we mentioned in the previous section, the chaotic and varieties' responses in the small values of the parameter can be considered as the normal conditions which increase the parameter change it to order, vanished and small response.

3.3 Hyperinsulinemia

In the early stage of type 2 DM, a high level of insulin may exist in the blood, which is a metabolic syndrome known as hyperinsulinemia [11]. Nevertheless, it should be noted that hyperinsulinemia can be seen in other diseases like hypertension obesity [11], cancer [36] or even Alzheimer [37]. To model this condition in the insulin-glucose

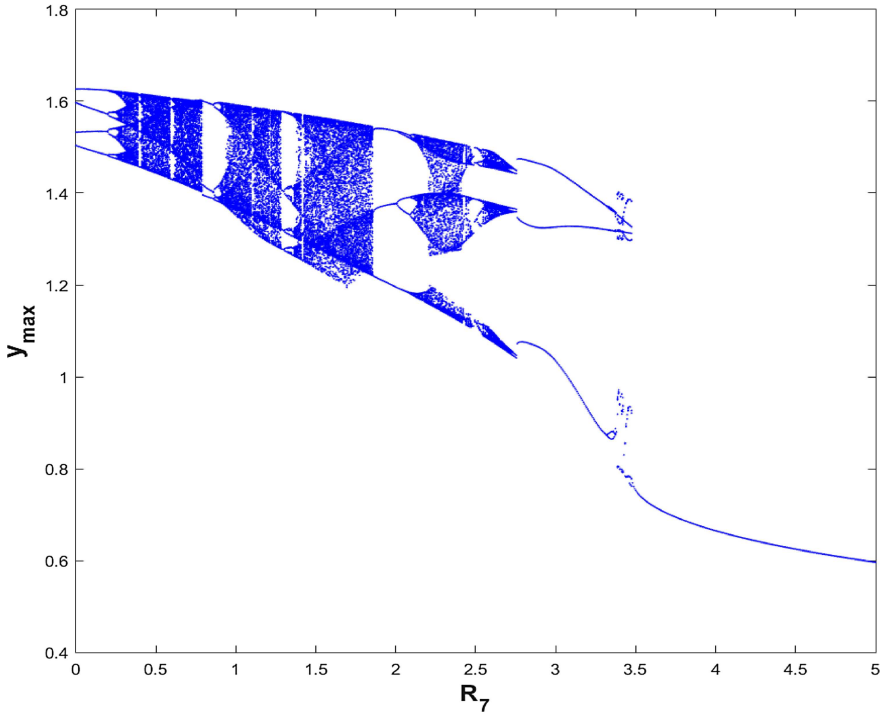

Fig. 6. Bifurcation diagram of the system as the parameter R_7 changes. This parameter shows the reduction rate of glucose in response to increasing the insulin level.

regulatory system, parameter R_4 which shows the increasing rate in insulin concentration is considered. Figure 7 shows the bifurcation of the system as the parameter R_4 changes from 1 to 4.4. For both low and high levels of the control parameter, the system shows a chaotic response. So, this disorder can be considered as a transition which occurs between two other different conditions.

As all the parameters of this system can be controllable, one can consider the efficiency of newly proposed drugs by considering the relevant parameter in this model.

4 Conclusion

Diabetes mellitus is one of the common diseases in the world. In this disease, the concentration of insulin and glucose of the blood are not in their normal range. To model diabetes and two other metabolic disorders, we present a new model which represents the interaction of the glucose, insulin and β-cells. In this differential equation computational model, we analyze the effect of physiologically meaningful parameters on the statistical and dynamical properties of the model. Considering bifurcation diagram of the system for three parameters of the system derives dynamical changes in type 1 diabetes, hypoglycemia and hyperinsulinemia. In these three diseases, we show the route to the chaotic transition of the system which represents that these disorders are in the group of dynamical diseases. To further studies, as all the parameters of this system can be controllable, one can consider the efficiency of newly proposed drugs by considering the relevant parameter in this model.

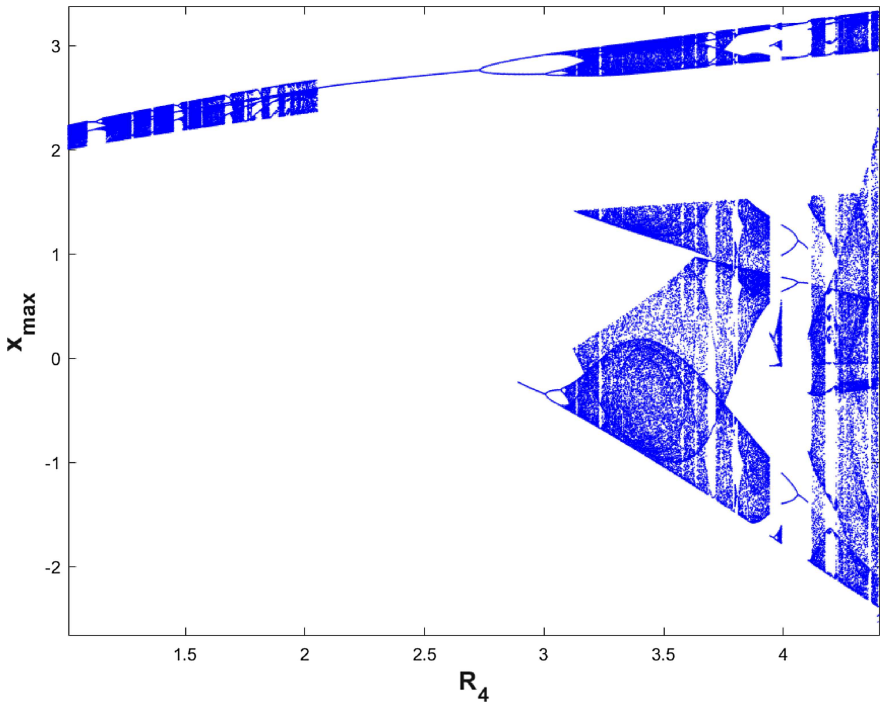

Fig. 7. Bifurcation diagram of the system as the parameter R_4 changes. This parameter shows the increase rate of insulin concentration when the β-cells' level increases.

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