

Nonlinear Physiological Model of Insulin-Glucose Regulation System in Type 1 Diabetes Mellitus

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Abstract : Mathematical modeling is very effective method to investigate interaction between insulin and glucose. In this paper, a new mathematical model for insulin-glucose regulation system is introduced based on well-known Lokta-Volterra model. Chaos is a common property in complex biological systems in the previous studies. The results here are in accordance with previous ones and indicating that insulin-glucose regulating system has many dynamics in different situations. The overall result of this paper may be helpful for better understanding of diabetes mellitus regulation system including diseases such as hyperinsulinemia and Type1 DM.

Index Terms— Biological mathematical modeling. Nonlinear chaotic systems. Chaos. Diabetes therapy.

I. INTRODUCTION

Due to increase in life expectancy, lethargic lifestyles and obesity in last decades, Diabetes Mellitus (DM) has become a global epidemic around the world. In 1961 Bolie found that the effective coefficients of insulin and glucose due to liver, pancreas and tissues play an important role in physiological mathematical model in insulin-glucose tolerance test[1]. In 1964 Ackerman et al. made a description of the response for the person to high doses and introduced response of the blood glucose concentration as function of time with sixteen constants[2]. In 1965, Ackerman et al. proposed linearized model of insulin-glucose system which in turns gives much reliable valuation of the glucose tolerance test curves of diagnostic than the semiquantitative and morphologic criteria [3]. Gatewood in 1968 shows the complex control system for glucose-insulin includes many interactions between endocrine systems and metabolic species [4]. Lacy et al. studied the direct effect of specific representatives on insulin secretion and these studies obviously show that islets isolated by sedimentation technique and its utilization in vitro investigation [5]. In 1970 Corte et al. tracked the cogency of

Ackerman's possibility on the glucose intestinal absorption has been proven and not statistically changed the diabetic mellitus but decrease with the age [6]. Sluiter et al. studied dose response between insulin-glucose relation after an oral glucose intake to reduce effective parameter in β -cell response [7]. Sluiter et al. illustrate the increase of insulin activity "A" and glucose tolerance "GT" after weight reduction and the decrease of "A" and "GT" by cortisone acetate premedication [8]. Bergman et al. in 1979 estimation a nonlinear mathematical model described many superiors[9]. Cobelli et al. suggested nonlinear organism model of blood glucose regulation system and glucagon dynamics [10]. A nonlinear model predictive controller developed to maintain normoglycemia in persons with (DMT1) during the fasting conditions [11]. Cobelli and Thomaseth studied linear compartment model discuss the measurements of various design factors like equienergy and equidose for input depending on the time intervals [12]. Cobelli and Thomaseth studied the design and estimating optimal inputs of the model metabolic parameters and proposed the identification of the model [13]. Both pancini and Bergman proposed an approach to measure insulin

sensitivity utilized (FSIGT) which is a minimal modeling approach [14]. A nonlinear mathematical model for both β -cell kinetics and insulin-glucose feedback system suggested by Bajaj et al. depending both plasma glucose and insulin concentrations [15]. Mathematical optimization techniques used to describe blood-glucose dynamics including infusion term depending linear model of Ackerman [16]. Fisher suggested mathematical modeling of dynamics of glucose-insulin regulation system by using theoretical analysis for controlling glucose [17]. Quon and Campfield studied mathematical model of cell surface insulin receptor regulation where the system structure model is based on mechanisms suggested by vivo and vitro experimental evidences [18]. And in 1991 Quon et al. suggested mathematical model of insulin sensitive glucose regulation system that is able to represent many facilities in glucose regulation process [19]. Greevan et al. suggested nonlinear mathematical model involving (4D) and several constants and parameters [20]. Wash et al. suggested mathematical model for absorption of injected insulin and such model introduces diffusion equilibrium between dimeric insulin, hexameric and absorption of insulin molecules [21]. Trajanoski and Wash et al. suggested mathematical fuzzy logic for glucose regulatory system. This fuzzy system can be viable for estate estimation with noisy circumstances [22]. Lehmann et al. developed a prototype computer system employing a model of carbohydrate metabolism which can be predict blood glucose and regulate insulin-dependent diabetic mellitus (IDDM) [23]. Kroll proved that the deterministic behavior in biological variation of glucose and insulin that include chaos is important because it gives the others ability of prediction [24]. Derouich and Boutayeb studied the effect of physical activity parameters of the mathematical model which allows the blood glucose in normal and study the other cases such as (T1DM) and (T2DM) [25]. Parker et al. suggested model-based predictive control algorithm to study normoglycemia in (T1DM) persons utilizing closed-loop insulin infusion pump [26]. Tolic et al. studied an oscillation supply of insulin compared to a constant supply at the same average

rate by introducing a mathematical model of insulin- glucose regulation [27]. Brian Topp et al. suggested a novel model of β -cell insulin, mass and insulin-glucose dynamics that consists of three dimensions [28]. Mari suggested modeling method to study insulin secretion, insulin-glucose and glucose metabolism [29]. Stevens et al. proposed mathematical model that able to describe ageing effect to the raise of the glycemia with time for diagnosis of diabetes [30]. Boutayeb et al. suggested mathematical model consists of ordinary differential equations and approximations numerically discussed with a set of dynamic parameters [31]. Kansal made selection of models available for studying of diabetes and focus on the types of problems and for which each model is well studied [32]. Picchini et al. developed mathematical model that allows greatest amount of information data, making it easier to understand insulin resistance in obese versus normal persons [33]. Li et al. introduced unique features model with two delays for better understanding of insulin-glucose regulatory system by employing mass conservation law and with such model oscillations in insulin secretion can stimulated by elevated glucose level [34]. De Gaetano et al. presented model of pancreatic islet compensation with its physiological parameters and simulated under various conditions so the model is proposed as a realistic and robust [35]. Smith et al. described a model considered six compartments that represent brain, heart, lungs, gut, liver, kidney and skeletal muscle and this model considered energy balance and body fat [36]. Kang et al. suggested three oscillatory modes of insulin secretion and this mathematical mode exhibits distinct period ranges :fast, slow, and ultradian as well as the behavior of membrane potential and calcium concentration in the β -cells [37]. Depending on both (OGTT) and (IVGTT), Overgaard et al. evaluated a new approach of insulin secretion in order to approximate a model for quantifying β -cell function [38]. Makroglou et al. introduced an overview of some mathematical models appearing the literature for the use of insulin-glucose regulatory systems where the models are ODE, PDE, DPDE and integro-differential equations with computational ones [39]. Wang et al. proposed a new model for

insulin therapy for both T1DM and T2DM [40]. Kwach et al. described blood glucose regulation system (BGRS) as (3D) system and analyzed for both equilibrium and stability to prove the blood glucose concentration for diabetic and non-diabetic persons [41]. Pie et al. suggested a modified an original physiological model of an artificial pancreas utilization insulin secretion time delay and rich dynamics such as periods, quasi period and chaotic behavior are introduced [42]. Shi et al. proposed novel approach for modeling time delay model in (IVGTT) and this mathematical model uses two parameters to simulate discrete time delay and distributed time delay [43]. McKnight et al. developed a mathematical model to describe glucose kinetics in both steady and non-steady states [44]. Palumbo et al. focused on the important clinical tests performed to understand glucose homeostasis and to present disease progression in terms of β -cells dynamics [45]. Hussain and Zadeng proposed mathematical model of insulin-glucose interaction that considers the disappearance of glucose with insulin action and raise in glucose concentration due to oral intake and meal digestion [46]. Adamu et al. proposed mathematical model under dieting conditions and physical activity, it is an extended and updated version of Brian et al. in 2000 [47][28]. Henquin proposed dynamics of glucose-induced insulin secretion in normal human islets and their identification through vitro comparisons of islets from diabetic and control persons [48]. Singh and Kumar proposed a generalized mathematical model that studied the effect of the physical activities on insulin-glucose regulatory system for diabetic and non-diabetic persons [49]. Zhao et al. suggested mathematical model of hepatic insulin that can exhibits many temporal patterns and introduce bistable switch on and switch off under the control of insulin receptors IRS1 and IRS2[50]. Fessel et al. presented solution for the minimal model which allows for separating the glucose and insulin dynamics with the same system and identifying patient parameters of glucose from IVGTT [51]. Kang et al. described various mathematical models proposed for glucose regulation within human body and studied the difficulties in reproducing real glucose regulation[52][53]. Keenan et al.

proposed novel method to quantify the loss of homeostasis among glucose, insulin and glucagon secretion pattern. This new developed method avoids many difficulties that played an important estimation of insulin-glucose sensitivity [54]. Al Ali et al. introduced mathematical model that describing the effect of growth hormone on the glucose homeostasis by extending existing model [55]. Chakrabarty et al. in 2019 described feedback control model based on an experimental canine information that can be generate more reliable effective control algorithms which regarded as promising step towards automated and implantable artificial pancreas systems [56]. In this paper, we propose a new model to explain the glucose, insulin and β -cells dynamics in the regulatory system. In Sec.III we analyze both statistical and dynamical properties of this system using the stability analysis, bifurcation diagram and Lyapunov exponents of the system for related physiologically meaningful parameters of the system. Finally, the conclusion of the paper has been discussed in Sec.V.

II. MATHEMATICAL MODEL

A. Prey-Predator Model

Volterra was a major mathematician that proposed the prey-predator model that composed of two simple differential equations which in turn can describe the behavior dynamics in terms of measurable variables which is known as Lotka-Volterra model [57].

$$\begin{aligned}\frac{dG}{dt} &= aG(t)(1 - G) - bG(t)I(t) \\ \frac{dI}{dt} &= -cI(t) + dG(t)I(t)\end{aligned}\quad (1)$$

where $G(t)$ is the population density of prey, $I(t)$ is the population density of predator and a,b,c and d are parameters.

B. Historical Mathematical model of insulin-glucose physiological systems

Many scientists in different fields have been proposed studying the interaction and the relationship between insulin and glucose into the body and made predictions for diabetic therapy. The mathematical model (2) suggested by Ackerman in 1964 with six constants [2].

$$\begin{aligned} \frac{dG}{dt} &= -a_1G(t) + a_2I(t) + C_1 \\ \frac{dI}{dt} &= -a_3I(t) + a_4G(t) + a_5 + T(t) \end{aligned} \quad (2)$$

where $G(t)$ is glucose concentration, $I(t)$ is insulin concentration and $T(t)$ is rate of increase of blood glucose due to absorption in GIT system. Also, a_1 represent average rate of glucose removal independent of insulin. a_2 rate of released glucose into blood. c_1 represent net increase in average rate of glucose. a_3 insulin removal independent of glucose. a_4 net increase of rate of insulin due to glucose. a_5 release of insulin by pancreas independent of glucose.

Later, it has been discovered that the main function of β -cell is to store and secret insulin. So the mathematical model (3) proposed by Bajaj studied three ODE's that embody β -cells.

$$\begin{aligned} \frac{dG}{dt} &= R_1G(t) - R_2I(t) + C_1 \\ \frac{dG}{dt} &= \frac{R_3N}{z} - R_4I(t) + C_2 \\ \frac{dz}{dt} &= R_5G(t)(T - z(t)) + R_6z(T - z(t)) - R_7z(t) \end{aligned} \quad (3)$$

where $G(t)$ is insulin concentration, $I(t)$ is glucose concentration and $z(t)$ is the population density of β -cell. R_1 represents the increase rate of insulin concentration in response to the blood glucose increase. R_2 represents the rate of insulin reduction which is independent of glucose concentration and based on the current level. R_3 shows the decrease rate of glucose in response to insulin secretion. R_4 shows the rate of increase in β -cells dividing due to interaction between blood glucose level above the fasting level. R_5 shows the increase of β -cells due to interaction between dividing and non-dividing β -cells. R_6 is the decrease rate of β -cells

toward its current level. C_1 is the rate of increase of G in the absence of G and I . C_2 is the increase rate of I in the absence of G and Z . Mentioned models have a common properties which they are omitting many factors that may affect the insulin-glucose interaction and all of them are suggested to in an isolated environment.

C. New Mathematical Chaotic Model for 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 three-dimensional differential equations.

It should be noted that the proposed model will be expected to show behavioral responses of 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 body. The proposed computational model for the insulin-glucose regulatory system is as follows:

$$\begin{aligned} \frac{dI}{dt} &= -R_1I(t) + R_2G(t) + R_3G^2(t) + R_4G^3(t) + R_5z(t) + R_6z^2(t) + R_7z^3(t) + R_{18} \\ \frac{dG}{dt} &= -R_8I(t) - R_9I^2(t) - R_{10}I^3(t) - R_{11}z(t) - R_{12}z^2(t) - R_{13}z^3(t) + R_{19} \\ \frac{dz}{dt} &= R_{14}G(t) + R_{15}G^2(t) + R_{16}G^3(t) - R_{17}z(t) \end{aligned} \quad (4)$$

where $I(t)$ is insulin concentration, $G(t)$ 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 , R_3 and R_4 show the increase rate of insulin when glucose concentration increases. R_5 , R_6 and R_7 show the increase rate of insulin concentration when the β -cells' level increases. R_8 , R_9 and R_{10} represent the rate of glucose reduction in response to increasing the insulin level. R_{11} , R_{12} and R_{13} show the reduction rate of glucose concentration because of β -cells' activity. R_{14} , R_{15} and R_{16} represent the rate of increase in β -cells due to the increase in glucose concentration. R_{17} shows the rate of

decrease in β –cells due to its current level. R_{18} represents the decrease rate of β -cells and R_{19} shows increase rate of glucose in the absence of insulin and β -cells.

III. STABILITY ANALYSIS OF THE PROPOSED SYSTEM

To study the dynamic system, we regard Table1 firstly. The dynamical behavior of the chaotic system can be tracked by evaluating the eigenvalues of corresponding Jacobian matrix at each equilibrium points. Because of the biological meaning of the variables, so the only positive fixed points (Time series must be positive). The system has only one positive equilibrium point which is at $E^* = (I^*, G^*, z^*) = (1.687, 0.894, 1.426)$. The Jacobian matrix of the system in (5) which yields an eigenvalues as $\lambda_1 = 2.5576, \lambda_2 = -0.4138 + j4.7890, \lambda_3 = -0.4138 - j4.789$. So, stability analysis indicates that it is a stable equilibrium.

A. Bifurcations and Lyapunov Exponents Diagrams

In this section, both bifurcation and Lyapunov exponents diagrams for R_8 are plotted and the biological meaning of such parameter is discussed as shown in Fig.1. As it has been observed in previous studies, whenever a chaotic behavior is demonstrated by a system, it yields and introduces some disorders [58]. In the present study, the system exhibits some chaotic behavior. That we specify it as biological disorder. According to both bifurcation and Lyapunov exponents, whenever the insulin decreasing may cause such biological disorder as shown in Fig.1. Lyapunov exponents spectrum is away to analysis nonlinear behavior of dynamical system. Which measure the exponential rates of the divergence and convergence of nearby trajectories in phase space of chaotic system. If there is at least one positive Lyapunov exponent, the system is chaotic [59][60]. The chaotic attractor and the tendency of the state variables identical to this suitable set of parameters. It can be realized that any small fluctuation in model parameters leads to undesired behavior of the

system. We discovered in bifurcation diagram of the system that the appearance of a period doubling rout to chaos is similar to prey and predator model.

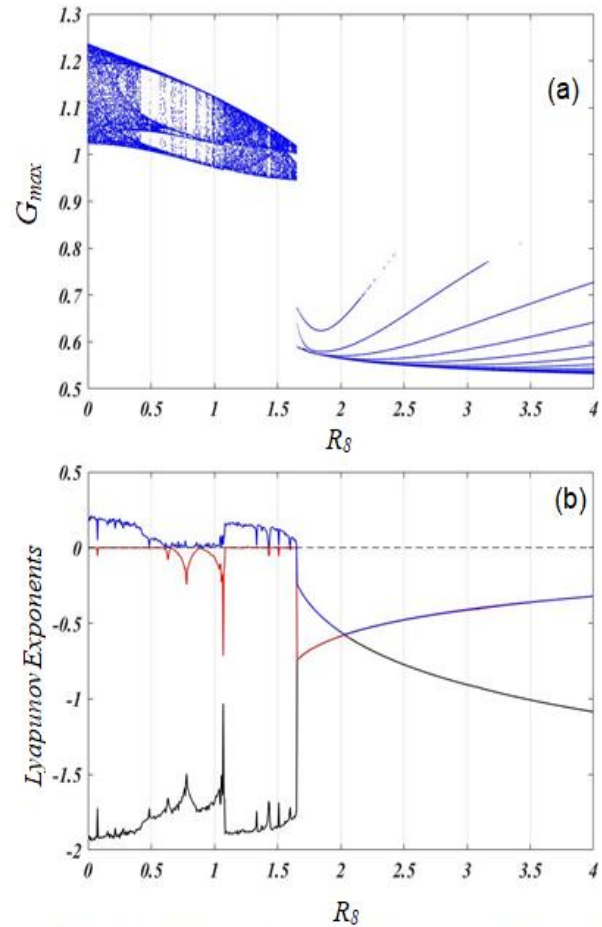


Figure 1:(a) Bifurcation diagram of the system with G_{max} as the parameter R_8 changes (b) Lyapunov diagram with respect to R_8 . This parameter shows the decrease rate of insulin concentration may cause biological disorder.

TABLE I
PARAMETERS OF PROPOSED CHAOTIC SYSTEM

Parameter	Value	Parameter	Value
R_1	0.30	R_{11}	1.95
R_2	0.69	R_{12}	0.75
R_3	0.27	R_{13}	-0.02
R_4	0.92	R_{14}	0.83
R_5	0.98	R_{15}	1.01
R_6	-0.62	R_{16}	1.25
R_7	-0.10	R_{17}	1.43
R_8	1.24	R_{18}	-0.83
R_9	-1.06	R_{19}	1.93
R_{10}	-0.29		

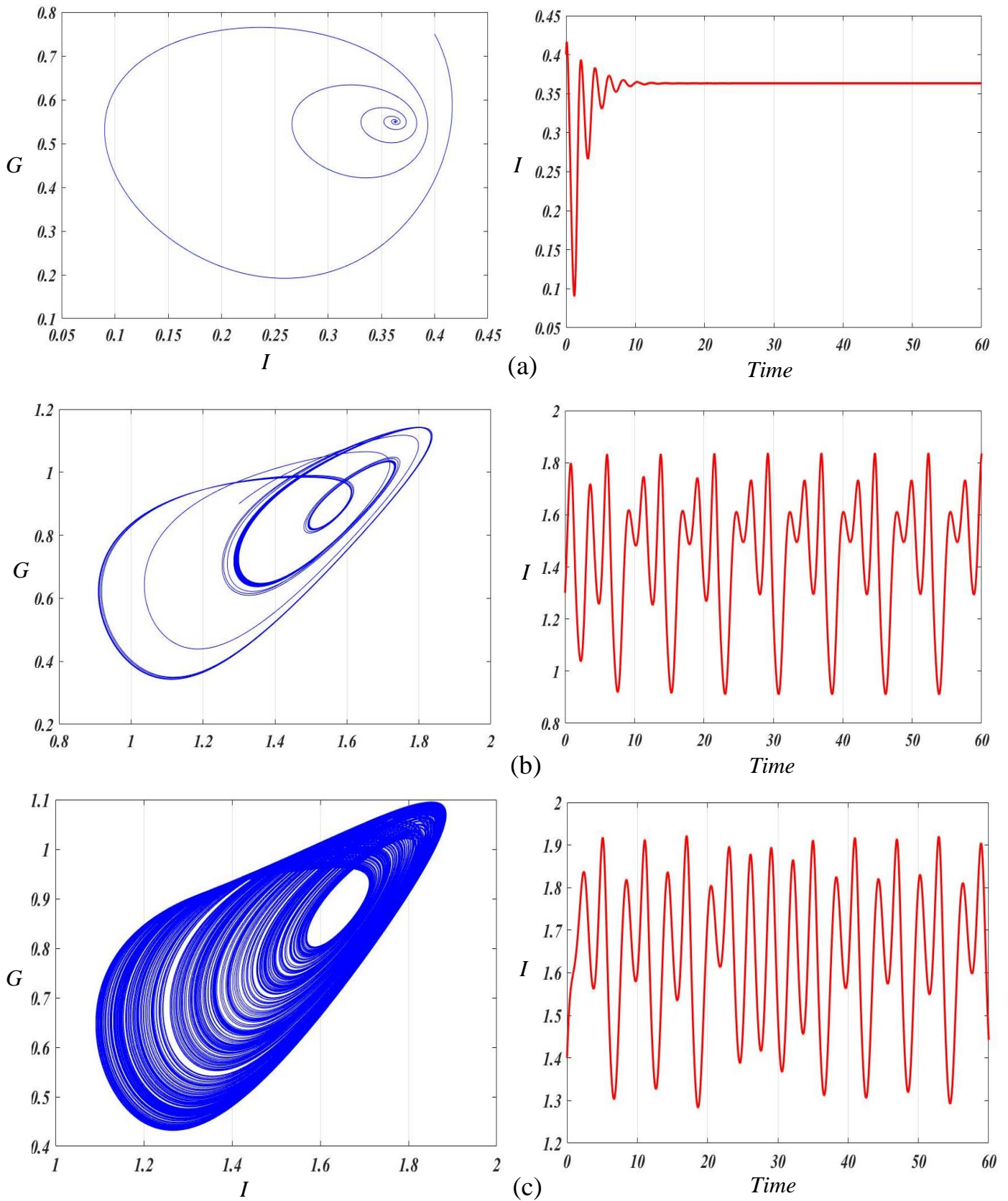


Fig. 2 Phase portrait projected on (Insulin, Glucose) plane (left column) and Insulin time response (right column): (a) Stable equilibrium point; $R_g = 2.00$, (b) Period-4 ; $R_g = 0.80$, (c) Chaotic attractor ; $R_g = 1.50$.

B. Basin of Attraction

Dynamical systems categorized into systems with self-excited and systems with hidden attractors. When an attractors basin of attraction involves equilibrium, such attractor is called “Self-excited” attractor, otherwise the attractor is hidden [61]. An attractor is called a self-excited attractor if its basin of attraction intersects with any open neighborhood of an unstable fixed point. Otherwise it is called a hidden attractor. The basin of attraction for a hidden attractor is not connected with any unstable fixed point[62].Fig.3. shows two basins of attractions of the proposed system. In Fig.3(a) it shows regions of different behavior of the system in xy -projection with $z = 1.02$ and parameters set as in Fig.2 (a) - (b). Where there is no fixed point appear, so the chaotic attractor is hidden. In Fig.3(b) unbounded region is shown in (red), periodic (limit cycle) in (green) and equasiperiodic (tours) in (black) with $z = 1.04$ and in xy -projection.

IV. TYPE 1 DIABETIC MELLITUS

Patients with type 1 diabetes must take daily insulin injections to stay alive because their β -cells do not produce any insulin. Without these injections, glucose in the body can not translate to the energy for cells or to the liver for storage. Moreover, glucose accumulation in the body causing damage of organs and tissues over the time. It is called juvenile-onset diabetes or insulin-dependent diabetes mellitus (IDDM), in which the autoimmune system’s antibodies destroy the insulin secreting β -cells in the pancreas. It is represent 5%-10% of all diabetes types and affects children and young adults [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_8 changing rate in equation \dot{G} . This parameter

shows the constant decreasing rate of insulin concentration. As we consider this decreasing parameter grows, dynamical changes of the glucose, insulin and β -cells during type 1 diabetes can be derived. Fig. 1 shows the bifurcation diagram of the insulin concentration as parameter R_8 decreases. Regards to Fig. 1, the insulin concentration has chaotic attractor while the decreasing rate of insulin secretion due to many reasons. 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 variation vanishes and insulin dynamics becomes ordered through period halving bifurcation.

V. CONCLUSION

Diabetes Mellitus (DM) 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. We propose a new model which represents the interaction of the glucose, insulin and β -cells. In this differential equations computational model, we analyze the effect of physiologically meaningful parameter (R_8) on the statistical and dynamical properties of the model. Considering bifurcation diagram of the system for one parameter of the system derives dynamical changes in Type 1 diabetes. Also Lyapunov exponents analysis had been done in order to show the exact behavior of the biological system in many different control parameters. This system shows high response. Finally, dynamical properties of the system were investigated by using basin of attraction indicating that the proposed system is newly introduced concerning hidden attractors.

$$J = \begin{pmatrix} (-R_1) & (R_2 + 2R_3G + 3R_4G^2) & (R_5 + 2R_6z + 3R_7z^2) \\ (-R_8 - 2R_9I - 3R_{10}I^2) & (0) & (-R_{11} - 2R_{12}z - 3R_{13}z^2) \\ (0) & (R_{14} + 2R_{15}G + 3R_{16}G^2) & (-R_{17}) \end{pmatrix} \quad (5)$$

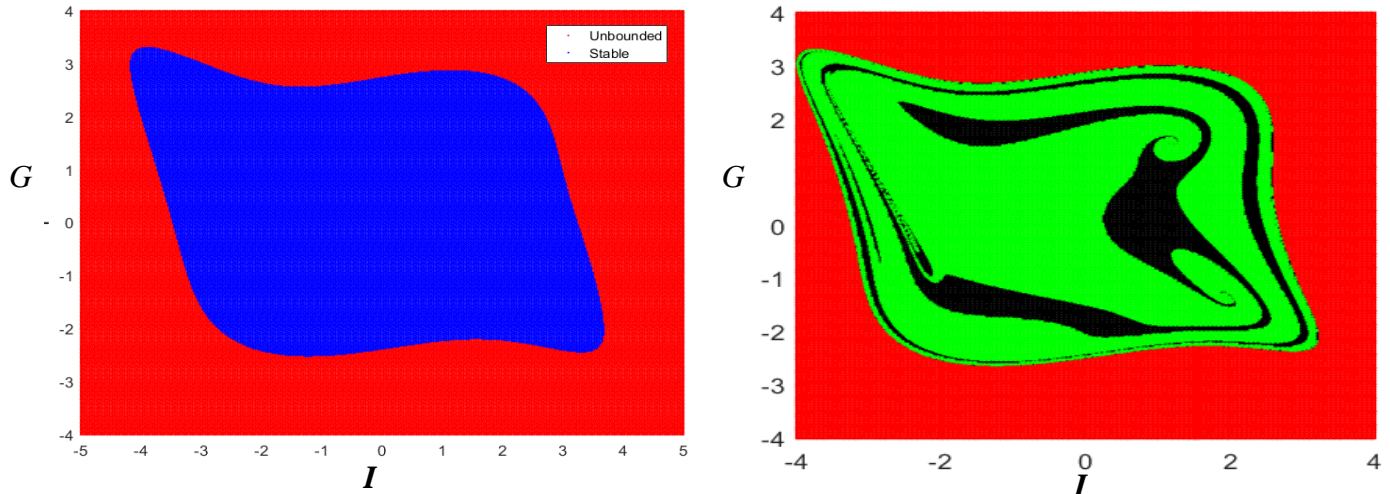


Fig.3 Hidden attractor.(a) Basin of attraction for parameters set as in Fig.2 (a)-(b) in which unbounded (red) and stable fixed point(blue).(b) Basin of attraction for parameters set as in Fig.2 (c) in which chaotic (black), periodic (green) and unbounded (red) attractors are seen.

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