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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.