Modelling System of Two Insulin-Glucose Delays to Achieve the Dynamics of Glucose Changes

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ABSTRACT

Background: Due to the increased prevalence of diabetes and the irreparable complications of this disease, it is important to measure and monitor the blood glucose levels of diabetic patients. The only way to treat type 1 diabetes is monitoring insulin, and in this type of diabetes, insulin should be injected into the body in order to reduce the patient's blood glucose as prescribed by the physician at certain times. In addition, the only way to treat type 2 diabetes is through diet and exercise daily.

Objective: We aim to use an ordinary differential equation model with two-delays to control the rate of changes in blood glucose levels throughout the day, based on the amount of food that the person consumes.

Material and Methods: In this analytical study, we extended an *ODE* model which is parameterized by data collected in this study to capture dynamics of glucose and insulin. We used global sensitivity analysis method to assess model robustness with respect to parameter perturbations.

Results: Our results have shown that utilizing the dynamics of changes in blood glucose levels throughout the day can be used to prevent hypoglycemia and hyperglycemic in the diabetic patients.

Conclusion: Dynamic modeling can help us to prevent hypoglycemia and hyperglycemia in the diabetic patients.

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Keywords

Glucose-Insulin; Dynamic; Sensitivity; Hypoglycemia; Hyperglycemia; Diabetes Type 1; Diabetes Type 2; Insulin

Introduction

Diabetes is a type of disorder in the body. In this disorder, the ability of the body to consume and metabolize whole sugars decreases in the body, thereby leading to an increase in blood glucose in the body [1].

The prevalence of diabetes in the world is increasing in recent years. In 2007, the American Diabetes Organization stated that about 17.5 million people in the United States suffer from diabetes [2] that is 45% more than 2002. About 5% to 10% of these patients suffer from type 1 diabetes. In addition, according to the financial statistics on diabetes, the economic burden of diabetic patients increased from $132 billion in 2002 to $174 billion in 2007 [3].

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According to studies, in 2011, there were more than 6 million diabetic patients in Iran, and the prevalence of diabetes was 8-11%; the highest prevalence of diabetes was reported in Yazd province in Iran [4-5]. According to the International congress on diabetes, by 2040, the number of diabetic people will reach 72 million and 643 million in the Middle East and the world, respectively [5].

β-cells of the pancreas accelerates blood flow to tissues by secreting insulin [6-8]. Diabetes is the result of partial malfunction in the insulin secretion system by the pancreas (type 1 diabetes), and malfunction of the insulin receptor cells to absorb insulin (type 2 diabetes) [7, 9]. Long-term effects of diabetes are generally due to increased blood glucose levels. These effects may result in loss of vision, cardiovascular diseases, kidney diseases and sexual dysfunction [10].

Anticoagulant effects of diabetes often occur because of a decrease in blood glucose levels. These effects may lead to dizziness, numbness or death [6].

Activities and rest everyday have a great influence on insulin sensitivity [11]. In a normal person, the amount of insulin injection is well proportional to produced glucose from the liver and the amount of glucose needed for a person's vital balance [12].

Insulin sensitivity is very high and effective in healthy people, while it is less susceptible to diabetic patients. The human body needs a blood glucose level of 70 to 109 mg/dL [13].

In 2002, *Ahren* and *Taborsky* found that plasma insulin levels for a healthy person ranged from 5 to 10 μU/ml. In 2002, *Simo*n and *Brandenberger* stated that it could be in the range of 10-40 μU/ml at a constant feeding time.

The first simple models are presented by Boolean [14] and Ackerman [15]. In this model, only two components of insulin and blood glucose were examined and had a linear structure. *Later*, in 1979, *Bergman* [16] and his first-generation colleagues presented the lowest Bergman model, which was performed on 9 dogs based on venous glucose test [17]. In 1991, *Sturgis* and colleagues [18] presented an ODE model [19-20]. The purpose of this model was to find the origin of ultradian oscillations and show that insulin secretion from the pancreas was oscillating and these oscillations were at three fast rates, including a period of about 10 seconds, a sharp period of 5 to 15 minutes and a slow period of 50 to 150 minutes. These slow fluctuations may be known as ultradian fluctuations based on two negative feedbacks, which is related to the effect of insulin on glucose consumption and the glucose effect on insulin secretion [21].

In 1995, *Drozdov* and his colleagues introduced a model for describing fluctuations of insulin production in humans [22]. *Parker* and colleagues first used a precursor controller to control blood glucose levels in type 1 diabetic patients [23]. They used the *Soren Sen* model as a diabetic patient's body simulator [24]. They applied a rich signal to the patient's body and identified the appropriate barometric reading for use in the pre-controller [21]. *Eren-orukl et al*. used two GPC2 and LQC1 techniques to control blood glucose in type 1 diabetic patients. In 2006, the two-point model was expressed by Li and *Kuang* [21], which considered two delays in this model as follows: a delay since glucose concentration increases until insulin is transmitted to intercellular space and another delay, since insulin is produced until changes in the production of liver glucose [4].

Generally, due to type 1 diabetes, the insulin injection system fails. Its treatment involves insulin injections and constant blood glucose control [3]. Therefore, in these patients, insulin is injected three to four times manually. Blood glucose levels in type 1 diabetic patients vary widely, which can lead to hyperglycemia ($G(t)> 120$ mg/dl) or hypoglycemia ($G(t) <65$ mg / dl) [25].

Type 1 diabetes is an insulin-dependent diabetes, because in this type of diabetes, the body cann't produce the insulin needed to reduce

the patient's blood glucose. Therefore, insulin should be injected into the patient's body to reduce blood glucose levels [1, 13]. Type 2 diabetes is an insulin dependent diabetes, because you have enough insulin in this type of diabetes, but there are few insulin-receptors in the body [1, 13].

Generally, the task of insulin in your body is to collect sugar from the body and store it in the liver as glycogen, which reduces the blood glucose in the individual [9].

Material and Methods

In this section we aim to construct and analytical ODE based model to predict dynamics of blood glucose and insulin in body, therefore, as shown in Figure 1, we determined the sources of sugar production in the blood as well as the use of sugars.

Glucose changes = input sugar + glucose released from the liver – insulin independent glucose - insulin dependent glucose (1)

Block diagram (Figure 1) shows the changes in blood glucose.

Since people with type 1 diabetes do not produce almost any type of insulin, in this model, insulin changes should be considered as follows:

Insulin changes = injected insulin - consumed insulin (2)

Body model

To model the body, we must have a formula for production and consumption in different parts of the body. The empirical formulas extracted for different parts are:

1. Glucose used by insulin-independent cells Nervous cells and a number of endocrine cells without insulin can absorb glucose in the blood. Consequently, equation 3 should be used. According to equation 3, it can be said that the insulin-independent of glucose level can be varied by the three parameters, including U_b, C_2, and V_g.

$$f_2(G) = \frac{U_b}{1 - e^{-\frac{G}{C_2 \times V_g}}} \quad (3)$$

2. Glucose used by insulin-dependent cells.

Muscle cells and fatty acids need insulin to remove glucose from the blood. Without insulin, almost no glucose is removed from these cells. This is as follows: this formula has two parts and the insulin passage section is another part of the sugar import. According to equation 4, the number of glucose consumed by insulin-dependent cells can be varied with the two parameters C_3 and V_g.

$$f_3(G) = \frac{G}{C_3 \times V_g} \quad (4)$$

$$f_4(I) = \frac{U_0 + (U_m - U_0)}{1 + e^{-\beta \times In\left(\frac{1}{C_4 \times \left(\frac{X}{V_i} + \frac{1}{E \times t_i}\right)}\right)}} \quad (5)$$

$$Glucose\,used\,by\,insulin - \text{dependent cells} = f_3(G) \times f_4(I) \quad (6)$$

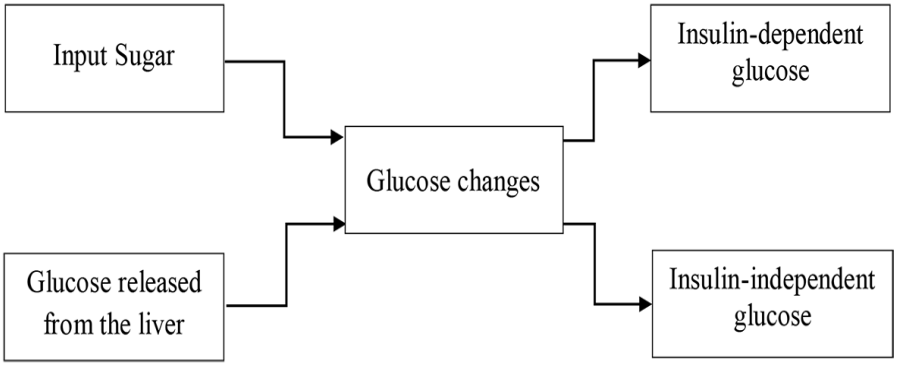

Figure 1: Block diagram below showing the changes in blood glucose.

Regarding equations 3 and 4, due to the use in both the equations, V_g can be a candidate for constant assumption because it is independent of glucose used by insulin-independent cells and glucose used by insulin-dependent cells; consequently, the process causes coefficients to be chosen easier. However, these two parts cannot be explicitly considered independently. Therefore, the changes in insulin-independent consumption remain the two coefficients of U_b and C_2. The constant assumption of C_2 and the variable coefficient assumption of U_b is very convenient because the formula is linear with the U_b coefficient.

In equation 6, which has two parts, the part f_3 is related to the number of changes in glucose consumption based on sugar change and the part f_4 is related to the number of changes in glucose consumption based on insulin. In the first section, with the constant assuming V_g, only the C_3 remains; thus, C_3 can be considered as one of the variable coefficients. In the second part, the number of coefficients is high. The formula for the coefficients U_0 and U_m is linear and the coefficients β, C_4, V_i, E, and t_i are nonlinear.

3. Glucose released from the liver with insulin control

When glucose in the plasma decreases, the liver releases the glycogen stored within itself as glucose in the blood. This reaction is controlled by insulin and decreases by increasing insulin secretion. The relationship is as follows.

$$f_5(I)=\frac{R_g}{1+e^{\alpha(\frac{1}{V_i}-C_5)}} \quad (7)$$

Given the equations 1, 3, 6 and 7, we have:

$$\frac{dG}{dt}(t)=G_{in}-f_2(G(t))-f_3(G(t))\times f_4(I(t))+f_5(I(t-\tau_2)) \quad (8)$$

In the case of equation 7, the formula with coefficient R_g is linear and with other coefficients is nonlinear. Therefore, R_g is a variation coefficient and α is nonlinear coefficients also it has more effect on nonlinear coefficients.

This model covers almost all the blood glucose interactions of a healthy person.

In different people, according to the physical and mental conditions, and even in a person in different conditions, the amount of intake and production of sugar in blood is different.

Insulin-dependent sugar consumption is more in neurons and brain cells, resulting in insulin-dependent glucose consumption to increase in people with brain activity compared to insulin-dependent glucose consumption in muscle cells and non-brain cells. In people who have a lot of physical activity or exercise, most glucose used by insulin-dependent cells.

Therefore, in present study, we tried to change the coefficients according to the conditions of each person in the formulas related to different parts of the model and to make a special model for each person. The coefficients that must be changed to determine each specific person's model are as follows:

1. Independent glucose consumption of insulin:

As previously mentioned, cells that use glucose no need for insulin are mostly neurons and brain cells. According to equation 3, the amount of independent glucose of insulin by three parameters U_b, C_2 and V_g can be changed.

2. Insulin-dependent glucose consumption:

This type of consumption is in all cells of the body, except neurons and brain cells, and it is calculated from equation 6. According to equation 6, thus the amount of Insulin-dependent glucose consumption by parameters U_b, C_3, U_o, U_m, β, C_4, V_i and E can change.

3. The consumption of released glucose from the liver with insulin control:

The released glucose from the liver with insulin control is different for every person. To calculate it, equation 7 is used. According to equation 7, the amount of released glucose from the liver with insulin control is changing by the parameters R_g, α, V_i, and C_5.

4. Consumption insulin:

The body of each person needs a different amount of insulin. Therefore, it should be for

each individual to consider the coefficients, in order to determining the insulin changes in the body using equation 9:

$$\frac{dI}{Dt}(t) = f_1\left(G\left(t-\tau_1\right)\right) + KI_{in} - d_i I(t) \qquad (9)$$

5. Insulin production:

The amount of insulin secretion in reaction to increment of blood glucose in the individual is proportional to equation 10. According to equation 7, the amount of released glucose from the liver with insulin control is changing by the parameters R_m, C_1, V_g and a_1.

$$f_1(G) = \frac{R_m}{1+e^{\frac{C_1-\frac{G}{V_g}}{a_1}}} \qquad (10)$$

Two-delay model

In the body, during normal state, changes in glucose and insulin are accomplished with two delays:

1. Delay in the production of insulin after increasing blood glucose.

2. Delay in the effect of insulin on inhibition of blood glucose.

In the natural body model, insulin with an effect on the liver inhibits the amount of release glucose and increasing the consumption of glucose in the cells. In the proposed model, there is a second delay, such as the normal body, because the delay is related to the structure of the liver and the cells of the body and in patients with diabetes, the liver and other cells have normal activity. However, the first delay is different from the natural body model since it does not produce insulin in the body and should be injected into the body at certain times.

In this model, considering that insulin gradually enters the bloodstream after injection, the delay in producing insulin in a person is equal to the needed time for insulin to reach its maximum of 5%.

As a result, we summarize all the coefficients in Table 1, which are independent or dependent coefficients.

The third column of the Table 1 represents the variable coefficients used to estimate the genetic algorithm so that optimal parameters are estimated, so that the dynamics of the model for these parameters with the data obtained during the invasive data processing with the glucometer are compatible. In fact, the difference between the output of the model and the data obtained is considered as the cost of the genetic algorithm.

In this paper, considering that the subjects under study were healthy people and had no illness, the parameter k should be removed from equation 9 since it is the amount of insulin injected into the body. In addition, di is the amount of insulin secreted by pancreatic cells to reduce the blood glucose of an individual in the case of abnormal glucose levels.

In this paper, constant parameters are considered in accordance with Table 2.

The simulated model in MATLAB software is shown in Figure 2.

Table 1: Determination of constant and variable coefficients

Constant coefficients	Variable coefficients	
C_2, V_g	U_b	Independent glucose consumption of Insulin
C_4, U_0, V_g, t_i, E, V_i	U_m, C_3, β	Insulin-dependent glucose consumption
C_5, V_i	R_g, α	The consumption of glucose released from the liver with insulin control
R_m, C_1, α_1, V_g	-	Insulin production
k	d_i	Insulin independent glucose Consumption

Table 2: Parameters of constant values

Parameters	Assumed value	Unit
C_1	2000	mgl^{-1}
α_1	300	mgl^{-1}
R_m	210	mU min^{-1}
V_g	10	l
C_2	144	mgl^{-1}
C_4	80	mUl^{-1}
U_0	940	mg min^{-1}
t_i	100	min
E	0.2	$lmin^{-1}$
V_i	11	l
C_5	26	mUl^{-1}
K	0	-

Results

In this paper, a two-delay model has been used to model blood glucose changes and insulin changes, which is described in detail in the previous section.

As shown in the relationships of previous section, there are many parameters that cannot be considered as variables because of the complexity of the subject. With the implementation of the insulin-glucose model for the constant and variable parameters mentioned in Table 1, results that are presented below.

The research model was implemented in MATLAB software simulation and the dynamics of blood glucose and insulin was obtained according to the above-mentioned relationships in the previous sections.

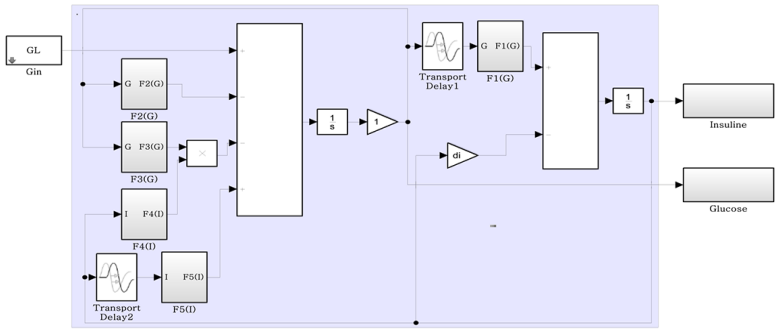

Figure 2: Model implemented using MATLAB software.

With the implementation of equation 3, we have obtained the following graph according to the values of Table 2.

As shown in Figure 3, these cells can't have an effect on glucose, so glucose levels is very high and can't be reduced insulin levels.

With the implementation of equation 4, we have obtained the following graph according to the values of Table 2.

According to Figure 4, muscle cells and fat cells require with insulin to remove glucose from the blood. Without insulin, almost no glucose is removed by these cells. As you can see, in these cells, insulin are secreted proportional to the amount of glucose and insulin prevents blood glucose from rising.

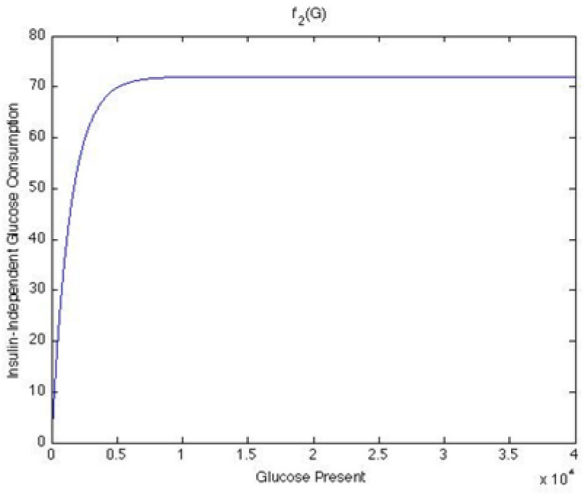

Figure 3: The rate of independent glucose consumption of insulin

According to Figure 5, when blood glucose of body increases, body cells release insulin to lower blood glucose, but when so increase blood glucose, insulin secretion can't control blood glucose levels. As a result, insulin should be injected into the body.

With the implementation of equation 5, we have obtained the following graph according to the values of Table 2.

With the implementation of equation 7, we have obtained the following graph according to the values of Table 2.

When glucose in the plasma decreases, glycogen stored in the liver as glucose is released in the blood. This reaction is controlled by insulin and decreases glucose by increasing insulin secretion. According to Figure 6, when the body needs with sugar and doesn't enter the body from the outside, the liver begins to produce glucose, and according to Figure 7 at this time insulin secretion controls the process of producing glucose by the liver to prevent high of glucose production.

In order to obtain the dynamics of blood glu-

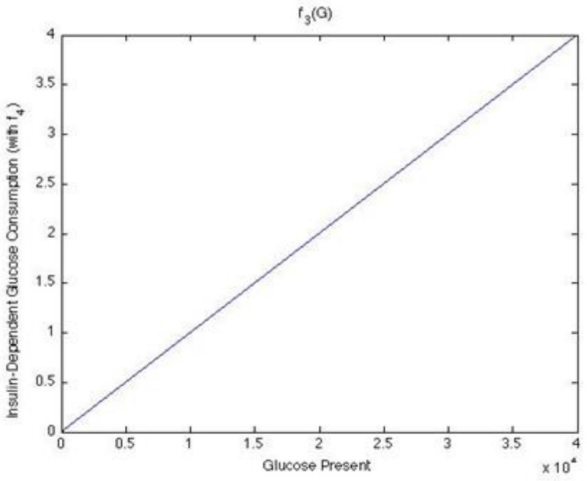

Figure 4: Absorption of glucose by insulin dependent cells

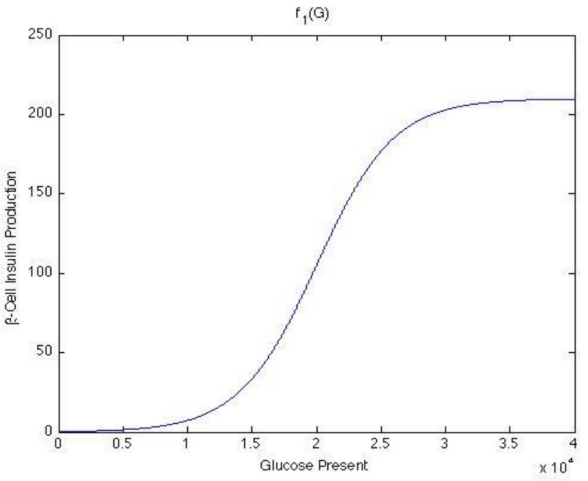

Figure 5: The rate of insulin secretion in response to increased blood glucose

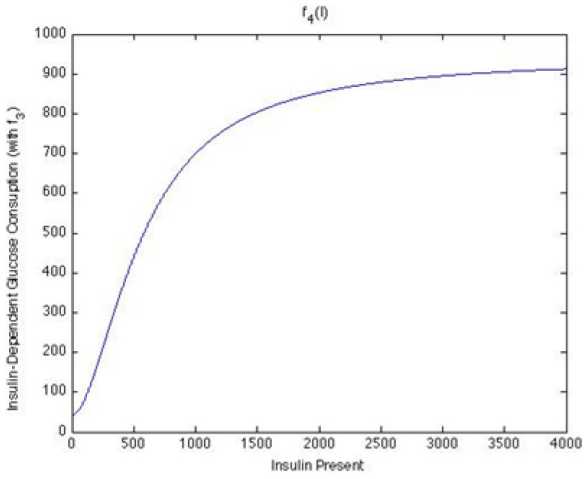

Figure 6: Absorption of glucose by cells with the presence of insulin

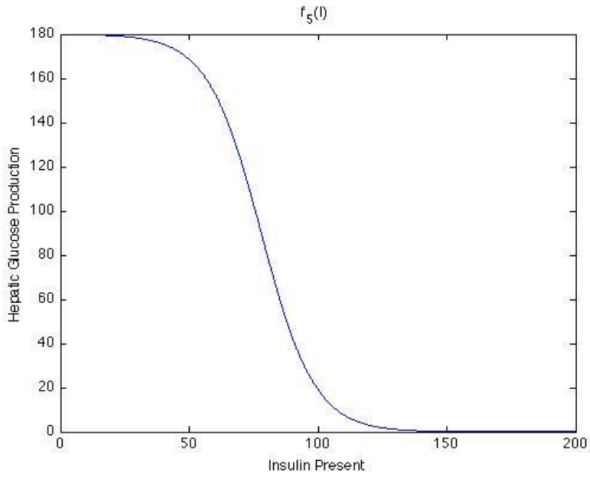

Figure 7: The amount of released glucose consumption with insulin control by the liver

cose according to the biological reality and its use in control systems, need to obtain human data that was done with the following description. To determine the amount of glucose from the food to the blood, the amount of glucose in each meal must first be determined. The amount of glucose in the food (usually absorbed in the healthy gastrointestinal tract) can be obtained from a site linked to the American Food and Drug Administration [5].

The subjects tested the amount of food consumed per meal in grams, enters the amount of material on the site, the amount of glucose enters into the body through eating the food, they are given as inputs to the model.

Clearly, the amount of glucose in the food doesn't enter into the bloodstream pulp because the digestive process is time consuming. Blood glucose consider as pulse because the body needs enough time to produce insulin. This balance exists in the absorption of glucose by the digestive system and the production of insulin by the body.

After eating, food start digesting in the stomach. When digestion starts, glucose begins to be absorbed in the body. By increasing digestion in the stomach, the process of absorption of food in the body increases. Finally, by reducing the amount of glucose in the food, the process of absorption is reduced of course the type of data is collected from healthy individual. To model the food intake, used a pattern according to Figure 8.

The parameters in Figure 8 are explained below:

t_1: The initial delay is the time to begin absorbing food glucose.

t_2: It is the time when most food is digested and glucose is absorbed to its maximum.

t_3: It is when almost all food glucose are absorbed in the stomach and intestines.

G: The maximum absorbance value is calculated from the following equation 11.

$$G = \frac{Total\ \ sugar\ \ in\ \ the\ \ food}{\left(\frac{t_3 - t_1}{2}\right)} \qquad (11)$$

Finally, the amount of glucose entered from food through the blood, which was calculated through the site, is in accordance with Table 3,

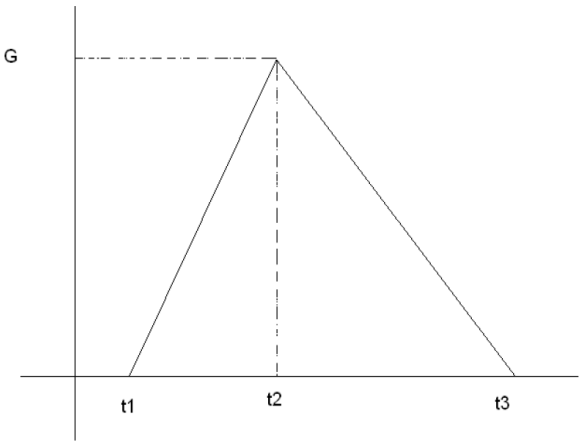

Figure 8: Modelling the intake of glucose from food to blood

Table 3: The amount of glucose intake from food to blood

First subject		Second subject		Third subject	
Time	**Input glucose (*mg*)**	**Time**	**Input glucose (*mg*)**	**Time**	**Input glucose (*mg*)**
11:45	16000	09:50	18000	10:45	13500
14:30	16400	13:30	16000	13:00	17000
18	10000	19:00	10000	17:00	14000
21:45	164000	23:00	10600	20:30	20000

which is used in the model of this study.

Given that the genetic algorithm has been used to estimate the 7-parameter value, each chromosome contains 7 genes. The number of chromosomes is 200, the percentage of crossover is 80% and the percentage of mutation is 50%. The selection of the parents for the crossover was based on the suitability or fitness of the chromosomes. The cost function of the genetic algorithm is the square of the difference between the levels of blood glucose obtained from the individual model with the human datacollected with a glucometer. Therefore, the genetic algorithm seeks to achieve the highest matching between the output of the individual's blood glucose level and the level of glucose obtained from the individual's mathematical model, so that in 6 or 7 blood glucose records (for three individuals involved in the process of data analysis, registration blood glucose was different). During the time of data acquisition, it would have a high adaptation to the dynamics of the model.

Using the MATLAB software, for estimating the variable parameters using the genetic algorithm, the constant parameters were considered according to Table 2 and the results were obtained according to Table 4.

The inputs of this model are the invasive measurements of blood glucose at specified times (usually 30 minutes after eating) by the glucometer, as shown in Table 5.

Now, according to Table 4, the variable parameters estimated by the genetic algorithm

Table 4: Estimation of variable parameters by genetic algorithm

Variable parameters	First subject	Second subject	Third subject	Unit
R_g	128.2	72.9	230.1	$\mu U min^{-1}$
α	0.3	0.1	0.08	lpU^{-1}
β	0.29	0.96	0.85	-
U_m	520.8	319.8	152.9	$mgmin^{-1}$
U_b	10.09	22.9	46.6	$mgmin^{-1}$
C_3	509.5	311.4	120.9	mgl^{-1}
d_i	0.1	0.63	0.68	μU

Table 5: The measured blood glucose levels of the subjects tested using a glucometer device

First subject		Second subject		Third subject	
Time	Blood glucose ($mg.dl^{-1}$)	Time	Blood glucose ($mg.dl^{-1}$)	Time	Blood glucose ($mg.dl^{-1}$)
07:33	100	09:10	100	11:00	96
12:08	122	12:23	120	13:20	116
14:47	117	15:32	119	16:30	112
15:05	114	17:14	110	20:30	105
18:54	108	20:20	130	23:00	116
22:20	107	23:20	120	-	-

are analysed in the model application and performance of the model.

• Implementing the model for the first subject Figure 9.

As shown in Figure 9, the model has been able to track almost all points measured with a glow (red star). There are four peak in the glucose chart that if pay attention to these course in the insulin chart, you will find that glucose in the blood (peak area) of the insulin is secreted with a delayed time, and thus causes a decrease in blood glucose levels.

• Implementing the model for the second subject Figure 10.

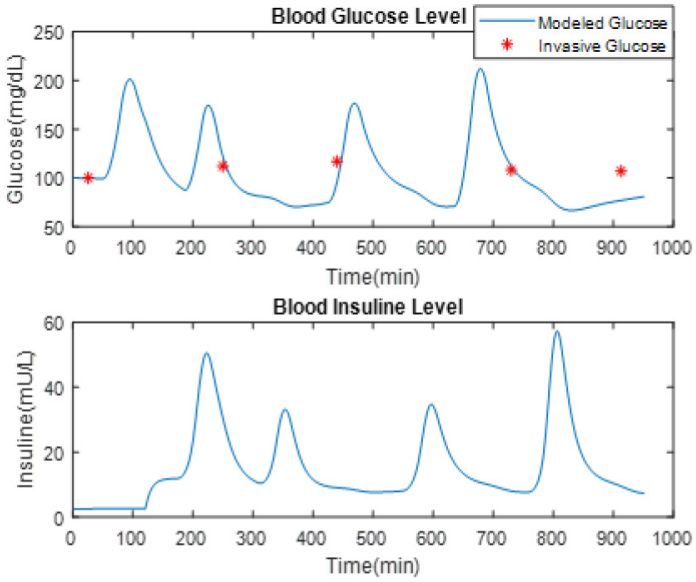

Figure 9: Output diagram of the two-delayed glucose-insulin model with the measured value through the glucometer for the first subject

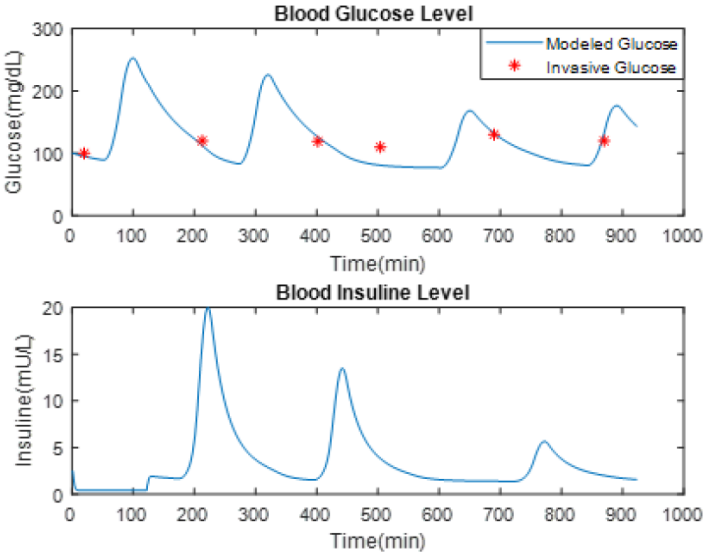

Figure 10: Output diagram of the two-delayed glucose-insulin model with the measured value through the glucometer for the second subject

As shown in Figure 10, the model has been able to track almost all points measured with a glow (red star). There are four peak in the glucose chart. It is observed that glucose in the blood after the rise (insulin) is secreted with a delayed glucose, resulting in a decrease in the amount of blood glucose in a person's body. It should only be noted that the last peak that occurred for the glucometer did not appear on the insulin chart, because the duration of this model was 1000 minutes, while we know that after the peak occurred in the glucose chart, peak in the insulin chart appears with a delay that occurs after 1000 minutes and therefore the model has failed to show it.

• Implementing the model for the third subject Figure 11.

As observed in Figure 11, the model has been able to follow almost all points measured with a glow (red star). There are four peak in the glucose chart, and peaks in the insulin chart denoting that glucose is secreted with a delay after increasing blood glucose (peak order), thereby reducing the amount of blood glucose. The advantage of this model is that insulin is proportional to the level of glucose in your body. This can be clearly deduced in the third quarter of this chart.

Now, for the sensitivity of each of these parameters to be measured in the model, it should be done as follows:

First, have to run the model for a long time, so that the dynamics of insulin and glucose reach their steady state, in which time a long time of 5000 seconds was considered and the model was implemented.

Also, the parameters that were estimated by the genetic algorithm should be considered in order to analyze the dynamic sensitivity of the model, consider the model with parameters 0.01 × Parameter up to 100 × Parameter and divide this interval into 500 parts and execute the model for each of the parameter values (each 500 times) to target constant glucose and insulin measurement.

Therefore, the sensitivity of the model to the parameters estimated by the genetic algorithm should be obtained. Of course, the sensitivity results are given only for the first person in this study.

• Calculate the sensitivity of the model to the first subject Figure 12.

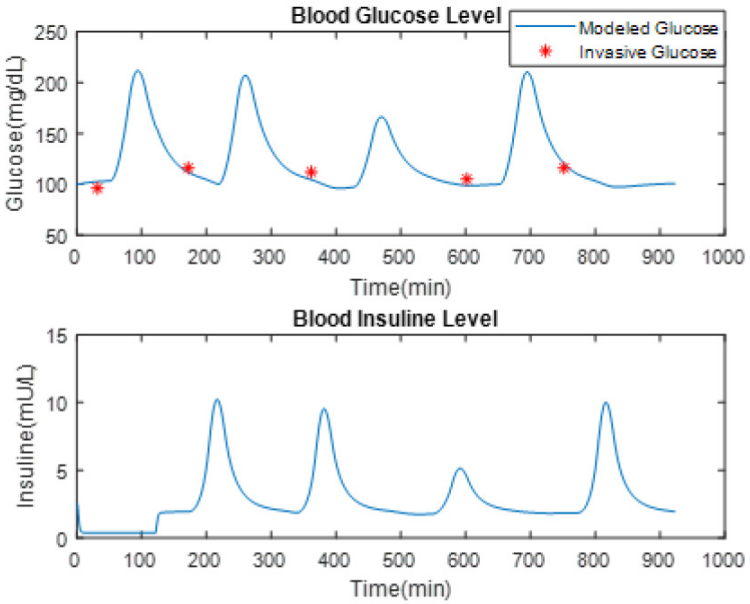

Figure 11: Output diagram of the two-delayed glucose-insulin model with the measured value through the glucometer for the third subject

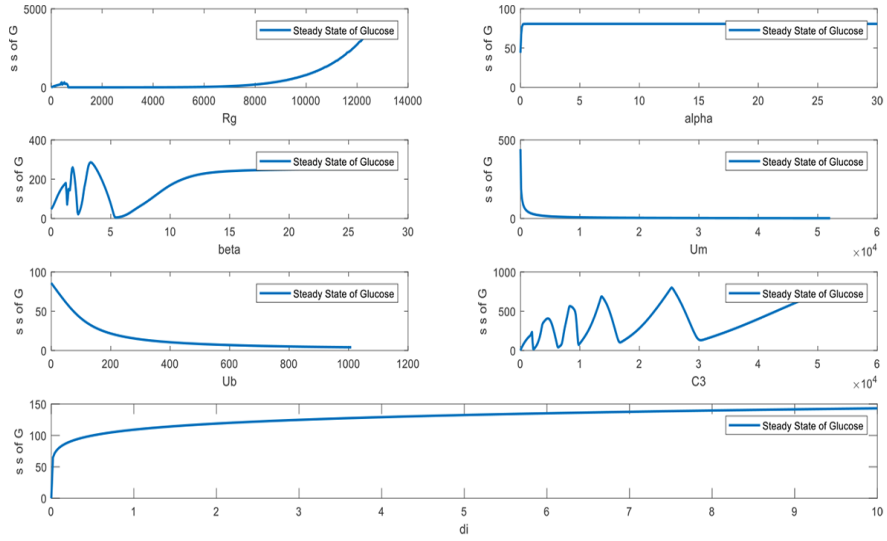

Figure 12: Sensitivity of model parameters to glucose output for the first subject

Sensitivity analysis of the model parameters is shown in Figure 12:

R_g: As shown in Figure 12, for $R_g < 8000$, the glucose state is nearly zero, which means that for the values given, the parameters R_g (values of other parameters (6 parameters) are the same as those estimated by the algorithm. The amount of glucose converges to zero, that is, for these values the glucose is not stable to this parameter, but for $R_g > 8000$ the steady state is changing rapidly, indicating that, for $R_g > 8000$ the system is very sensitive to this parameter.

α: As shown in Figure 12, the behavior of the system haven't got any sensitive to α parameter. Because of the different values of α parameter, the glucose-stable state remains almost constant.

β: As shown in Figure 12, the system behavior have sensitive to the parameter β. Because changes in the parameter β is high in the glucose-stable state of the system, for β values greater than 15, the system does not show a sensitivity to β.

U_m: As shown in Figure 12, for $U_m \approx 5$, the model shows a high sensitivity to the U_m parameter, and the amount of glucose is rapidly reduced in the range, but for $U_m > 5$, the steady-state glucose level is almost constant. It remains and does not show a sensitivity to $U_m > 5$.

U_b: As shown in Figure 12, the glucose-stable state of glucose is reduced as a function of the change in the parameters of U_b.

C_3: As shown in Figure 12, the behavior of the system is highly sensitive to the parameter C_3. Because a change in parameter C_3 causes a lot of changes in the system's glucose, so it can never be indifferent to this parameter, since with the slightest change in this parameter, the amount of glucose remaining in the state changes a lot.

d_i: As shown in Figure 12, glucose stays in glare appears to increase as a result of changing the parameter d_i.

Sensitivity analysis of the model parameters shown in Figure 13.

R_g: As shown in Figure 13, for $R_g < 3000$ stable insulin states are highly sensitive to this parameter; for these values, the parameters R_g (values of other parameters (6 parameters) are the same as those estimated by the algorithm. The amount of glucose varies greatly, but does not change for $R_g > 3000$ insulin-stable states. This means that for these values, the insulin-resistant state is not sensitive to this parameter.

α: As shown in Figure 13, the behavior of

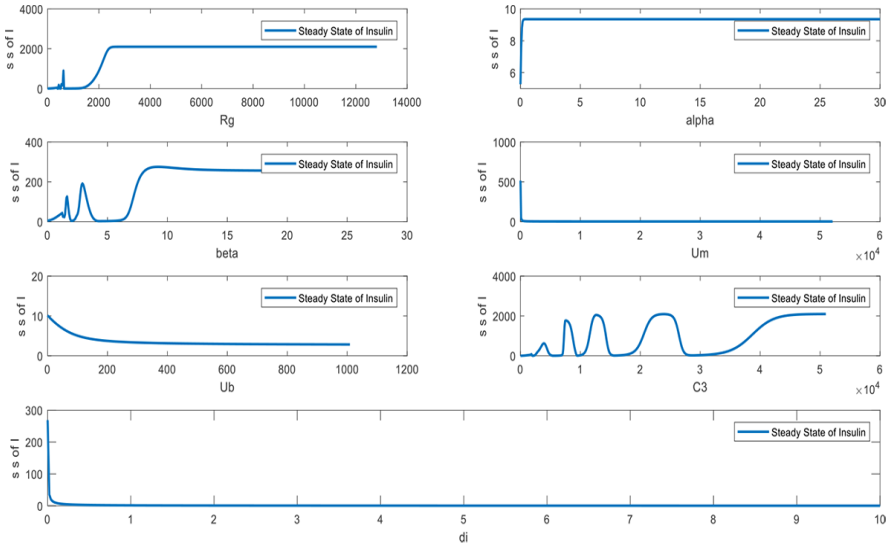

Figure 13: Sensitivity of model parameters to insulin output for the first subject

the system doesn't have a high sensitivity to α parameter. Because of the different values of the parameter α, the steady-state insulin state remains almost constant.

β: As shown in Figure 13, the behavior of the system have highly sensitive to the parameter β. Because changes in the parameter β result in large changes in the systemic stability of the system, which does not show a sensitivity to β for values of $\beta > 10$.

U_m: As shown in Figure 13, for $U_m \approx 5$ values, the model shows a high sensitivity to the U_m parameter and the steady state insulin rate decreases rapidly in the range, but for $U_m > 5$, the steady-state insulin content is approximated. It stays constant and does not show a sensitivity to $U_m > 5$.

U_b: As shown in Figure 13, the steady-state insulin condition decreases as an exponential change in the parameters of U_b.

C_3: As shown in Figure 13, the system behavior have a high sensitivity to the C_3 parameter. Because the change in parameter C_3 causes a lot of changes in the system's insulin state, it can never be indifferent to this parameter, since with the smallest change in this parameter, the amount of insulin-resistant state is significant. But in excess of 450,000 the sensitivity of the system remains constant relative to this parameter, meaning that a change in this parameter doesn't affect the sustained state of insulin.

d_i: As shown in Figure 13, it does not change the insulin stable state of the d_i parameter.

• Dynamic glucose sensitivity analysis at specified times compared to model parameters with p value for the first subject

Since the data number is low due to the invasive of the data collection, the statistical test isn't suitable and the *PRCC* (partial rank correlation coefficient) analysis was used.

PRCC is a sensitivity analysis that statistically evaluates the correlation between dynamics and model parameters.

Glucose dynamic sensitivity analysis at specified times is shown in Figure 14 relative to the model parameters with p value.

Discussion

In this study [26], the mathematical model of an insulin-glucose system in a fuzzy and non-fuzzy (crisp) environment has been investigated.

In fact, first, ordinary differential equations [27], which have not been considered for two consecutive glucose-insulin regulatory dy-

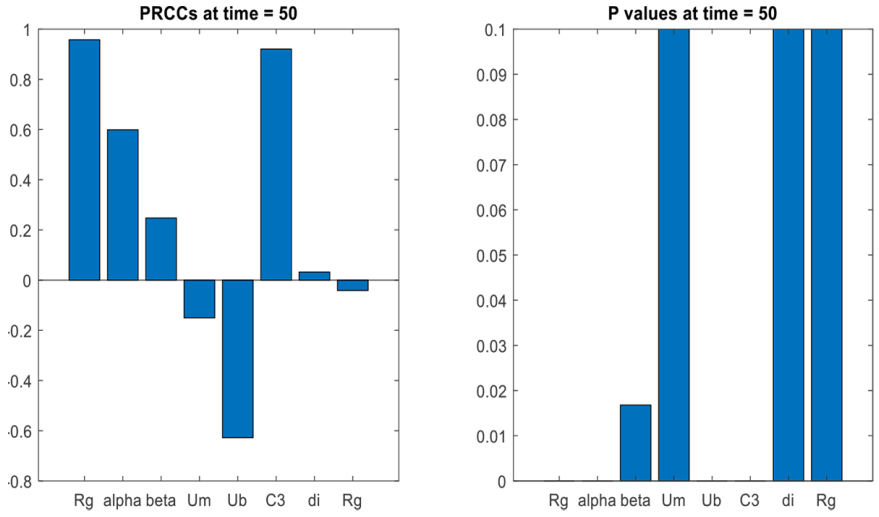

Figure 14: Glucose dynamic sensitivity analysis at specified times relative to model parameters with p value for the first subject

namics were considered, and to consider the uncertainty in the system, using derivative concepts of *Hukuhara* [28], the phase response of the model was proven.

Therefore, the benefit of this research in the study of the glucose-insulin system is the creation of an uncertainty region in the model's dynamics, which has not been considered in the model developed in the research and has examined a definite model. However, our research model is more accurate and closer to biological reality than considering the delay in glucose-insulin system dynamics.

This close proximity to the dynamics of the biologic reality model is ensured by considering the variable parameters for a precise model and their estimation using human data.

The research [21] describes the two-delayed glucose-insulin system model, which is based on this model, with the difference that some of the variable parameters described in the paper have been added. These variable parameters are used to calibrate the developed two-delayed model of this research with human data obtained using genetic algorithm to estimate these parameters. Therefore, the developed model of this study, given that the actual human data in the article is used to estimate its parameters is also able to obtain the dynamics of blood glucose in real conditions. Therefore, this model can be used in blood glucose control systems.

In this study, an accessible two-stage model of the insulin-glucose system was developed. As mentioned, some of the variable parameters of this model were estimated using data recorded by individuals. The data refers to the blood glucose levels of three individuals overnight, which were measured invasively, and the parameter estimation tool was also a genetic algorithm. The developed model, as validated with real data, can achieve the dynamics of the level of glucose in real conditions. Finally, we concluded that the two-delay model is a very good model for estimating blood sugar levels throughout the day, and can follow the pattern of blood glucose changes. The *MSE* (Mean Square Error) method was used to calculate the accuracy of the two-stroke model and the error rate and accuracy are given in Table 6.

Conclusion

In present study we extended an available *ODE* model of insulin-glucose system and parameterized it with obtained experimental

Table 6: Calculates error rate and precision with the Mean Square Error (*MSE*) method

	Error (*MSE*)	Accuracy
First subject	19	81
Second subject	20.5	79.5
Third subject	18.8	81.2

data. The calibrated model of this study can help us to predict dynamics of blood glucose daily to prevent occurrence of hypoglycemia and hyperglycemic in the patients. In the future, the two-delay model for making an insulin pump (a pump that automatically injects the amount of insulin needed to reduce the individual blood sugar and keep it within the normal range to the individual) can be used, since the amount of insulin injected by the insulin pump is injected into the body.

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Authors' Contribution

R. Vosoughi conceived the idea. Z. Sadeghi Goghari gathered data. R. Vosoughi analyzed data, drafted and revised paper. AH. Jafari supervised the study. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

This study has approved by ethical committee of Tehran University of Medical Sciences and ethical code was: IR.TUMS.MEDICINE.REC.1394.1138.

Informed consent

The data obtained from the patients were obtained with their consent.

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Conflict of Interest

None

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