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Research Article

A new application of fractional glucose-insulin model and numerical solutions

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ABSTRACT

Along with the developing technology, obesity and diabetes are increasing rapidly among people. The identification of diabetes diseases, modeling, predicting their behavior, conducting simulations, studying control and treatment methods using mathematical methods has become of great importance. In this paper, we have obtained numerical solutions by considering the glucose-insulin fractional model. This model consists of three compartments: the blood glucose concentration (G), the blood insulin concentration (I) and the ready-to-absorb glucose concentration (D) in the small intestine. The fractional derivative is used in the sense of Caputo. By performing mathematical analyzes for the Glucose-Insulin fractional mathematical model, numerical results were obtained with the help of the Euler method and graphs were drawn.

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INTRODUCTION

Most of the food we eat, especially the food that contains carbohydrates, is converted into glucose to be used for energy in the body. Pancreas, an organ built into the back of the stomach, produces a hormone called insulin, which allows our muscles and other tissues to take glycose from the blood and use it as energy. Glucose, which passes through nutrients to blood, enters the cells through insulin hormones. Cells use glucose as fuel. Glucose is the main energy source of the body, and if the amount of glucose is more than the body needs fuel, it is stored in the liver in the fat tissue [1].

Insulin is a hormonal release in beta cells in the pancreas, an organ in the back of the stomach in our body. It separates the sugar in the blood from the blood, allowing it to enter the cell. So the sugar level in the blood is reduced. All body cells need glucose for energy, but some of them (brain, red blood cells and reproductive organs) can only

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meet energy needs with glucose. To do this, the blood glucose level must always be sufficient. The blood sugar level is controlled by hormones released from a pancreas called insulin and glukagon. The rise of blood sugar and the fall are dangerous to the body [2].

The main purpose of mathematical modeling is to explain the process by mathematically articating real life problems. However, it is also important that the modeled process can be controlled. Mathematical models have been developed to help explain a system, examine the effects of its various components and make predictions about their behavior [3].

Models with fractional derivatives deliver better results than models from integer steps in the theory of control of various physical and biological processes and dynamic systems. It is a convenient approach to use fractional operators to explain the memory and quality characteristics of many substances and processes, as such features are ignored from the whole step to the derivative. In population models, the future state of a population depends on its past status. It's called the memory effect. The memory effect of the population can be examined by adding a latency term or by using a fractional derivative in the model [5,6].

The mathematical problems including fractional differential equations play a significant role in analysis and modelling of various scientific processes such as damping laws, electrical circuits, fluid mechanics, and relaxation processes since fractional derivative is nonlocal operator. Fractional mathematical problems attract a growing attention of numerous scientist from diverse branches of science [16-19]. The adversity of fractional differential equations is that solving them analytically is hard or impossible. Therefore, numerous numerical methods such as reduced differential transform method, Adomian decomposition method, homotopy perturbation method, variational iteration method, homotopy analysis method , fractional difference method, Euler Method, Runge-Kutta Method and new iterative method have been developed to establish numerical solution in series form [20-22]. Different from the numerical solutions, numerous analytical solutions of fractional models can be seen in literature [23-27].

This paper consists of five parts. The first chapter provides information on the importance of fractional mathematical modeling, application of fractional differential equations, analytical solutions and glucose-insulin mechanism. In the second part, the formation of a fractional Glucose-Insulin model and the Generalized Euler Method were given. In the third part, a new application of the fractional Glucose-Insulin model was made to obtain numerical results and graph them. The fourth chapter included the discussion. In the fifth part, the results were given.

MATERIALS AND METHODS

Fractional Derivation and Fractional Glucose-Insulin Model

The most commonly used definitions of the fractional derivative are Riemann-Liouville, Caputo, Atangana-Baleanu and the Conformable derivative. In this study, because the classical initial conditions are easily applicable and provide ease of calculation, the Caputo derivative operator was preferred and modeling was created. The definition of the Caputo fractional derivative is given below.

Definition. [4] Let $f(t)$ be a function that can be continuously differentiable n times. The value of the function $f(t)$ for the value of α that satisfies the condition $n - 1 < \alpha < n$. The Caputo fractional derivative of α th order $f(t)$ is defined by ${}_a^C Dt^\alpha = \frac{1}{\Gamma(n-\alpha)} \int_\alpha^t (t-x)^{n-\alpha-1} f^n(x) dx$.

Fractional Glucose-Insulin Model

The fractional Glucose-Insulin model consists of three compartments. The first is the concentration of glucose in the blood (G), the second is the concentration of insulin in the blood (I) and the third is the concentration of ready-for-absorption glucose in the small intestine (D). It should be fractional differential equation system of the fractional glucose-insulin model is as follows:

$$\begin{aligned} \frac{d^\alpha I}{dt^\alpha} &= k_1 G - k_6 I \\ \frac{d^\alpha G}{dt^\alpha} &= -k_4 (I - I_{pi}) - k_2 I - k_3 + k_0 D \\ \frac{d^\alpha D}{dt^\alpha} &= -k_a D \end{aligned} \tag{1}$$

where $\frac{d^\alpha}{dt^\alpha}$ is the Caputo fractional derivative with respect to time t and $0 < \alpha \leq 1$.

Initial values are given as,

$$I(0) = I_0 \, , G(0) = G_0, D(0) = D_0.$$

Because fractional-order models have a memory feature in events related to a time variable, they show more realistic and accurate results than integer-order models. Therefore, the established model was created as a fractional order [5-14]. In the system of (1), we reduce the fractional-order differential equation to a full-order differential equation by taking $\alpha = 1$. The compartment and parameters of the spell are shown in Table 1 and Table 2.

Firstly, since the absorption of glucose in the small intestine during fasting decreases over time, the equation should be as follows:

$$\frac{d^\alpha D}{dt^\alpha} = -k_a D \tag{2}$$

Table 1. Variables used in the systems and their meanings

Variables used in the systems	Meanings
$I(t)$	the concentration of insulin in the blood at time t
$G(t)$	the concentration of glucose in the blood at time t
$D(t)$	the concentration of ready-for-absorption glucose in the small intestine at time t

Table 2. Parameters and their meanings

Parameters	Meanings
k_0	The rate of glucose in the blood at the time of fasting
k_1	The rate of insulin secretion from the pancreas
k_2	The rate of glucose elevation in tissues due to insulin
k_3	The rate of glucose elevation in tissues regardless of insulin
k_4	The rate of increase of glucose production in the liver
k_6	The rate of insulin passage into the blood
k_a	Glucose absorption parameter
l_{pi}	The change in insulin in the blood, which is due to the changed production of glucose in the liver

Since, with this absorption, the amount of glucose in the blood during fasting will begin to increase over time, the equation should be as follows:

$$\frac{d^{\alpha}G}{dt^{\alpha}} = k_0 D \tag{3}$$

Glucose that enters the blood will eventually pass to the brain and other organs and reduce the concentration of glucose due to insulin in organs other than the brain and regardless of insulin in the brain. On the other hand, since the liver is the organ responsible for glucose production, it is necessary to express the effect of the glucose rise rate due to it on reducing insulin separately. If glucose production continues in the liver, accordingly, the concentration of insulin in the blood will increase over time. If $l_{pi} < 0$ the amount of insulin increases and if $l_{pi} > 0$ the amount of insulin will decrease, the equation should be as follows:

$$\frac{d^{\alpha}G}{dt^{\alpha}} = -k_4(I - I_{pi}) - k_2 I - k_3 + k_0 D \tag{4}$$

Depending on the increase in glucose in the blood, there will be an increase in the amount of insulin secreted from the pancreas and over time, depending on this equation, the amount of insulin passing into the blood will decrease, so the equation should be as follows:

$$\frac{d^{\alpha}I}{dt^{\alpha}} = k_1 G - k_6 I \tag{5}$$

it is obtained [10].

Theorem. $\forall t \geq 0$ $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $D(0) = D_0 \geq 0$, the solutions of the system in (1) with initial conditions $(I(t), G(t), D(t)) \in R_+^3$ are not negative [6-8-17].

Generalized Euler Method

In this paper, we use the Generalized Euler method to solve the initial value problem with the Caputo fractional derivative. Many of the mathematical models consist of non-linear systems, and finding solutions to these systems can be quite difficult. Analytical solutions cannot be found in most cases and a numerical approach should be considered for this. One of these approaches is the Generalized Euler method [15].

Let $D^{\alpha}y(t) = f(t, y(t))$, $y(0) = y_0$, $0 < \alpha \leq 1$, $0 < t < a$ be the initial value problem. Let $[0, a]$ the interval over which we want to find the solution of the problem. For convenience subdivide the $[0, a]$ into n sub-intervals $[t_j, t_{j+1}]$, where $h = \frac{a}{n}$ $j = 0, 1, \ldots, n\text{-}1$. Suppose that $y(t)$, $D^{\alpha}y(t)$ and $D^{2\alpha}y(t)$ are continuous in range $[0, a]$ and using the generalized Taylor's formula, the following equality is obtained [15].

$$y(t_1) = y(t_0) + \frac{h^{\alpha}}{\Gamma(\alpha + 1)} f(t_0, y(t_0))$$

This process will be repeated to create an array. Let $t_{j+1} = t_j + h$ $t$such that

$$y(t_{j+1}) = y(t_j) + \frac{h^{\alpha}}{\Gamma(\alpha + 1)} f(t_j, y(t_j))$$

$j = 0, 1, \ldots, n\text{-}1$. the generalized formula in the form is obtained. For every $k = 0, 1, \ldots, n\text{-}1$ with step size h we get

$$I(k+1) = I(k) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(k_1 G - k_6 I)$$

$$G(k+1) = G(k) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(-k_4(I - I_{pi}) - k_2 I - k_3 + k_0 D) \quad (6)$$

$$D(k+1) = D(k) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(-k_a D).$$

Numerical Simulation of the Fractional Glucose-Insulin Model

In this section, numerical simulation and graphs of the fractional Glucose-Insulin model will be shown. Now let's get a numerical simulation of the fractional Glucose-Insulin model using the Generalized Euler method. It is also possible to change the value of the parameters and to control changes in exploration.Taking into account the past studies on the glucose and insulin system, the fractional state of the model created by Mercedes Lamborte in 2013 was considered and numerical results were obtained using the Generalized Euler method [10]. Consider the parameters $k_0 = 0.01$, $k_1 = 0.7$, $k_2 = 0.0005$, $k_3 = 1$, $k_4 = 0.05$, $k_6 = 0.5$ $k_a = 0.15$, $l_{pi} = 800$ according to the data in [10].

$G = 150$, $= 90$, $D = 50$ to be arbitrary let's take size of step $h = 0{,}01$. Using the Euler method, the following table is obtained.

In Table 3, Table 4 and Table 5, the changes of *I, G* and *D* are observed for different states of α. According to the results obtained, if the α parameter is changed, the values of the *I, G* and *D* compartments become different. According to the initial conditions and parameters taken, it is seen that the change in compartments *I, G* and *D* is different for = 1, $\alpha = 0.9$ and $\alpha = 0.8$

Although the difference in the values obtained may seem small, in fact, these differences may have important medical consequences. Graphs of the data in table 3, table 4 and table 5 were shown in figure-1, figure-2 and figure-3.

By the above figures, we observe the following highlights:

* It is observed that the concentration of insulin in the blood will increase over time (see Figure 1).

* It is observed that the concentration of glucose in the blood will increase over time for $\alpha = 1$, $\alpha = 0.9$ and it will rise faster for $\alpha = 0.8$ (Figure 2).

* It is observed that the concentration of ready-for-absorption glucose in the small intestine will decrease over time for $\alpha = 1$, $\alpha = 0.9$ and decrease faster for $\alpha = 0.8$ (Figure 3).

Table 3. The values of *I, G* and *D* at the moment *t* for $\alpha = 1$

t	*I*(*t*)	*G*(*t*)	*D*(*t*)
0	90	150	50
1	90,95	150,55	49,88
2	91,9	151,1	49,76
3	92,84	151,65	49,64
4	93,79	152,21	49,52
5	94,74	152,76	49,4
6	95,68	153,31	49,29
7	96,62	153,86	49,17
8	97,56	154,41	49,05
9	98,5	154,95	48,94
10	99,44	155,5	48,82
11	100,38	156,05	48,7
12	101,32	156,59	48,59
13	102,25	157,14	48,47
14	103,18	157,68	48,36

Table 4. The values of *I, G* and *D* at the moment *t* for $\alpha = 0.9$

t	*I*(*t*)	*G*(*t*)	*D*(*t*)
0	90,00	150,00	50,00
1	90,98	150,57	49,87
2	91,97	151,15	49,59
3	92,96	151,72	49,39
4	93,94	152,29	49,19
5	94,92	152,87	48,99
6	95,9	153,44	48,79
7	96,88	154,01	48,6
8	97,86	154,58	48,4
9	98,84	155,15	48,2
10	99,82	155,72	48,01
11	100,79	156,29	47,81
12	101,76	156,85	47,62
13	102,73	157,42	47,43
14	103,7	157,98	47,24

Table 5. The values of *I, G* and *D* at the moment *t* for $\alpha = 0.8$

t	*I*(*t*)	*G*(*t*)	*D*(*t*)
0	90,00	150,00	50,00
1	91,61	150,94	49,79
2	93,23	151,88	49,59
3	94,84	152,82	49,39
4	96,44	153,75	49,19
5	98,05	154,69	48,99
6	99,64	155,62	48,79
7	101,24	156,55	48,6
8	102,83	157,47	48,4
9	104,41	158,4	48,2
10	106	159,32	48,01
11	107,58	160,24	47,81
12	109,15	161,16	47,62
13	110,72	162,08	47,43
14	112,29	162,99	47,24

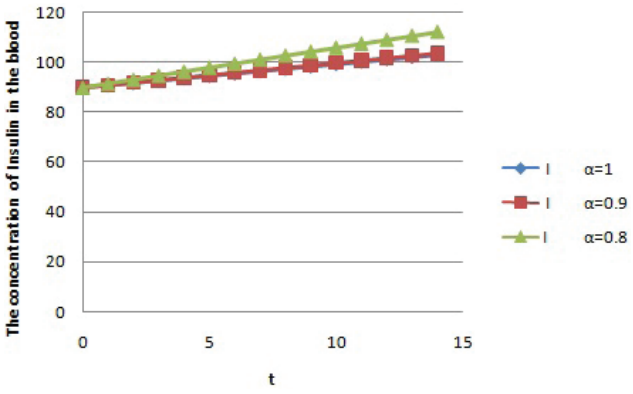

Figure 1. The graph of change of the *I* compartment model.

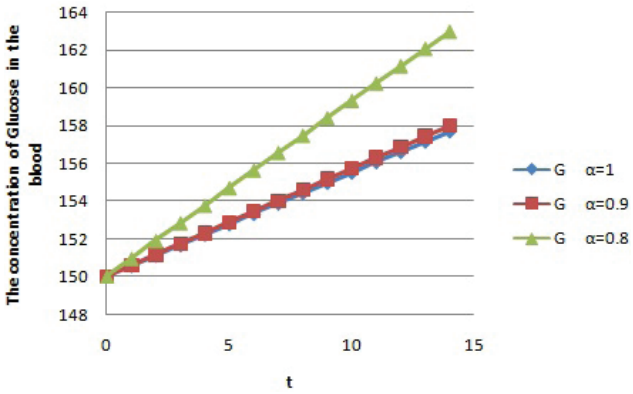

Figure 2. The graph of change of the *G* compartment model.

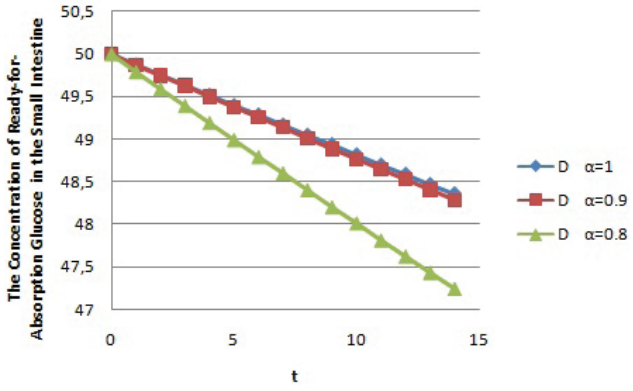

Figure 3. The graph of change of the *D* compartment model.

RESULTS AND DISCUSSION

One of the shortcomings of the model is that the effects of glucagon may not be investigated at various different glucose and insulin concentrations, since the effects of glucagon are implicit, hidden in the effects of insulin on liver glucose production. Second, this model adopts the rodent β-cell model, albeit modified for the human insulin secretion pattern. There is also a lot of room for improvements in the detailed description of plasma insulin extraction, in Deciphering the complex network of interactions between glucose regulatory components, for example, in refining the assumption of three-stage insulin effects on liver glucose production.

Despite these shortcomings, whole-body glucose regulation models are generally useful for understanding glucose homeostasis. In particular, they have raised the possibility of predicting blood glucose changes under insulin secretion defects or insulin resistance, which could generate the elevation of blood glucose or abnormal oscillation patterns of plasma glucose and insulin.

Besides this, it is possible to consider the case of anorexia or obesity, with the assumption that the amount of glucose stored in the body is determined by the liver glucose production rate and the peripheral glucose utilization rate. This model is used to measure the kinetics of glucose and the effect of insulin on them.

The main disadvantages of the mentioned models lie in the large number of parameters and the complex metabolic studies that should be performed to estimate them. This compels to work with average values that decrease the validity of the results and the applicability of the models.

The advantage of this model lies in the possibility of obtaining all the parameters for each person. In addition, the parameters are obtained from blood glucose and insulin levels, common biochemical measurements.

When the pancreatic organ in the human body could not secrete enough insulin hormones, the glucose in our body, insulin and glucose change in the intestine were analyzed using a mathematical model using Caputo fractional derivative.

The parameters used in this study differ according to the person used. In order to find these parameters, various statistical methods were used and then this model was expressed in the form of a system of differential equations in the relevant article. As a result, the model we have examined has been simplified and its boundaries have been narrowed compared to previous models. This form of models its study and development will offer solutions for obesity, which is a disease of the next generation.

CONCLUSION

In this study, a new application was made using the Generalized Euler method of the fractional glucose-insulin model and graphs were drawn with the help of numerical results obtained. In this study, the mathematical modeling of the diabetic change in the body has been studied. Many problems in real life are analyzed by the help of fractional derivative differential equations, resulting in more realistic results. The modeling used in the field of medicine also contributes significantly to the treatment of these diseases. In the graphs obtained, the change of insulin concentration in the blood, glucose concentration in the blood and the

absorption-ready glucose concentration in the small intestine were examined over time. Glucose-Insulin models are especially important for diabetics. With this study, a mathematical modeling of the change in the amount of glucose in the body of a person suffering from diabetes, the state of insulin and the concentration of ready-for-absorption glucose in the small intestine over time was carried out. This model might be a helpful tool for the experimental design of diabetes drugs research. Also, it enables the design and development of mechanisms for the control of glycaemia in order to improve the quality of life of diabetic patients.

AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

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