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Mathematical modeling of nonlinear blood glucose-insulin dynamics with beta cells effect

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Abstract

We consider mathematical modeling of blood glucose-insulin regulatory system with the additional effect of the secreted insulin by the pancreatic beta cells and in the presence of an external energy input to such system. Such modeling system is investigated to determine the time-dependent nonlinear dynamics that take place by the quantities, which represent the glucose and insulin concentrations in the blood, insulin action as well as in the absence or presence of secreted insulin due to the pancreatic beta cells. Using both analytical and numerical procedures, we determine such quantities versus time for both diabetes patients and normal human and for different values of the parameters. We find that the nonlinear effect of the dynamics of the investigated regulatory system increases the values of the insulin action and the glucose and insulin concentrations. In the absence of the beta cells effects, which can correspond to the case of severe type 1 diabetes, the plasma glucose is higher and the insulin action and the insulin concentration are less active than the corresponding ones for the case in the presence of beta cells, which is relevant for type 2 diabetes or moderate type 1 diabetes patients. For the present system, smaller values of the parameters of the model, which represent kinetics of the glucose and insulin action, insulin sensitivity, insulin secretion enhancement and the plasma insulin decay rate, can lead to notably lower values of the glucose concentration. In the presence of the secreted insulin by the pancreatic beta cells the insulin action and the insulin concentration are more effective to reduce the blood glucose, which can help to improve the diabetes patient's health.

Keywords: Blood glucose; Insulin concentration; Glucose-insulin dynamics; Blood hormones

AMS-MSC 2010 No: 37M99, 92B05

1. Introduction

Diabetes is a critical health problem among Americans. In 2015, diabetes was the seventh leading cause of death in the U.S., according to the Centers for Disease and Prevention. A most recent report showed that approximately more than 100 million U.S. adults have diabetes or pre-diabetes. Diabetes and pre-diabetes are medical conditions that can affect an individual at any age and must be diagnosed and treated promptly. However, many Americans failed to treat this condition. Only about 11.6 percent of Americans with pre-diabetes were aware of their conditions and approximately, 1 in 4 adults did not know that they had diabetes. An early diagnosis is highly important as pre-diabetes can lead to type 2 diabetes and diabetes can lead to heart problems and death.

Diabetes is known to be a health condition where the blood glucose levels are too high. This medical problem can be caused by different reasons. One of the reasons might be by a failure of an individual's pancreas to produce a hormone that helps transporting the glucose that the person eats into the body's cells as an energy source; and this hormone is called insulin. More clearly, under the early stage of the diabetes illness, the individual's immune system can often attack and damage or destroy the pancreatic cells that help to regulate the level of glucose in the blood. As a result, the glucose builds up in the individual's bloodstream. If this is the case, an individual would be diagnosed with type 1 diabetes. Another reason might be that an individual's body might not produce enough insulin or not be able to use insulin properly, which also can lead to a higher glucose level in bloodstream than the normal glucose level. Whenever this is the case, an individual would be diagnosed with type 2 diabetes.

On the other hand, pre-diabetes is a condition where the blood sugar is higher than normal, but it is not high enough to be diagnosed as diabetes. Individuals with pre-diabetes are at higher risk of developing type 2 diabetes if it is left untreated. As we referred to before, diabetes can lead to several health complications including heart problems and death. Therefore, early detection is important for the health recovery of the diabetic patients. There are blood tests that can help to detect whether an individual has diabetes or not.

In the last several decades there have been a number of research studies on the diabetes illness, which can be of the type 1 diabetes or type 2 diabetes, and the associated blood hormones using different approaches (Bergman et al. 1979, 1980; Bergman and Cobelli 1980; Toffolo et al. 1980; Ni et al. 1997; Mitsis et al. 2009; Gyorgy et al. 2015; Mourad et al. 2015; Rietschoten et al. 2015; Turksoy et al. 2016; Sara and Annette 2016; Hassan et al. 2017; Gomez et al. 2017; Forlenza et al. 2019). Bergman et al. (1979) and Bergman and Cobelli (1980) developed a model for the motion of the glucose and insulin hormones. It has been referred to as the minimal model since it was simple enough with the least amount of the biological complexities. The minimal model is often referred to as an open-loop model since it does not contain an equation for the insulin secretion due to the pancreatic beta cells, which can operate when the glucose plasma concentration is elevated.

Mitsis et al. (2009) considered, in particular, a so-called closed-loop model that combined part of the minimal model with an equation for the insulin secretion by the beta cells. These authors developed a Volterra type computational model that was tested versus their closed-loop model, which did not include an equation for the plasma insulin concentration. Instead, in their computational model they used a collection of data points to represent the plasma insulin concentration term in the retained part of the minimal model. Closed-loop system can also be due to an external source for the insulin injection or for pumping insulin by a device attached to the diabetes patient's body as in the case of artificial pancreas device system described by Sara and Annette (2016). These authors described the operation by such device, which consists of an insulin pump and a glucose monitor all controlled by a digital controller. Such device has been used mainly for the patients with very severe type 1 diabetes, where the pancreatic beta cells are completely inactive or destroyed.

Hassan et al. (2017) studied a closed-loop type system that was based on a modified minimal model, where they added an external insulin function to the equation for the plasma insulin concentration. They carried out some computational work to determine the amount of insulin input that may be needed for a patient with specified glucose concentration.

In the present paper we develop a new mathematical model to determine the nonlinear dynamics of the blood hormones in the regulatory system of humans. Our model is an extension of the minimal model and the previous models due to Mitsis et al. (2009) and Hassan et al. (2017). It takes into consideration for the first time the specific nonlinear system of differential equations for the time evolution of the plasma glucose concentration, insulin excitable tissue due to glucose uptake activity, which refers to as insulin action, plasma insulin concentration and also the secreted insulin due to the pancreatic beta cells that becomes effective if the plasma glucose concentration is elevated beyond some value. In addition, the equation for the plasma glucose of our modeling system contains a source function that provides external energy input to the patient's body.

Thus, our modeling system is a closed-loop system. In the presence of the pancreatic beta cells, our system is a closed-loop system that provides for the first time the external energy input for the glucose as well as internal insulin input due to the pancreatic beta cells so that our model can be applicable to both type 2 diabetes and moderate type 1 diabetes patients cases, where the pancreatic beta cells can operate. In the absence of the pancreatic beta cells that we also considered in the present study in order to determine the results in the absence of the beta cells, our modeling system is also a closed-loop system due to presence of the external energy input, but then the modeling system can be only relevant to the severe type 1 diabetes patient case.

Next, we used both analytical and numerical procedures to determine the solution for such nonlinear system under particular conditions for different levels of diabetes in patients, while analyzing the interaction of the considered hormones in the regulatory system. We found that the nonlinear effect due to the nonlinear modeling system for the glucose-insulin dynamics can be notable. Our modeling system provided details of the nonlinear dynamics of the considered blood hormones and the roles play by the glucose concentration, insulin action, insulin concentration, insulin secretion of the pancreatic beta cells and the external energy input during the time evolution of the hormones.

2. Modeling system

Our modeling system for the glucose-insulin dynamics is partially based on a so-called minimal model (Bergman et al. 1979) that is simple enough with least biological complexities. The original minimal model has been applied by several authors in the past including notable ones due to Bergman and Cobelli (1980), Toffolo et al. (1980) and Bergman et al. (1980) for the noninvasive insulin sensitivity evaluation. In the present paper we make use of such model and include additional important effects of external energy input and presence of the pancreatic beta cells that can generate additional insulin due to the high elevation of glucose.

Our governing modeling system is given below

$$dG/dt = -[P_1 + X(t)]G(t) + P_1 G_b + D(t), \tag{1a}$$

$$dX/dt = -P_2 X(t) + P_3 [I(t) - I_b + r(t)], \tag{1b}$$

$$dI/dt = P_4[G(t) - P_5]^+ t - P_6[I(t) - I_b], \tag{1c}$$

$$dr/dt = -a\, r(t) + \beta[G(t) - G_b - \theta]^+, \tag{1d}$$

$$G = G_b,\ I = I_b,\ X = 0,\ r = 0 \ \text{ at } t = 0, \tag{1e}$$

where for any function $f(t)$, we designate that $[f]^+ = f$ if $f > 0$ and 0 otherwise. Here G is the glucose concentration in the plasma with basal value G_b, where basal values are those that were measured during a fasting period for the diabetes patient, X is the insulin action, I is the plasma insulin concentration with basal value I_b, r is the secreted insulin by the pancreatic beta cells in response to alteration in plasma glucose concentration, P_1 and P_2 are positive constants that are referred to as, respectfully, kinetics of glucose and insulin action, P_3 is a positive constant that is referred to as insulin sensitivity coefficient, P_4 is a positive constant representing contribution to the plasma insulin concentration by the internal regulatory system, P_5 is a positive constant above which insulin is secreted, P_6 is a positive constant representing plasma insulin decay rate, $D(t)$ is an external energy input to the patient's body, which can be a form of imported food, and can represent glucose absorption rate in the blood by the food intake, and here we use a modeling form of it as $a_0\, exp(-b_0\, t)$, where a_0 and b_0 are two positive constants of order unity, a is a positive constant that is referred to as a kinetic constant, β is a positive constant that determines rate of insulin secretion and θ is a non-negative constant with value above which insulin due to beta cells is operative.

The form that we chose for the input energy $D(t)$ can be a reasonable modeling one for the qualitative aspects of the glucose absorption rate in the blood as in the case of a meal taken by the patient, when the impact of the energy input to the patient's digestive system is higher first and then its impact decreases with increasing time.

The modeling equations (1a)-(1d) contain the non-negative constants parameters P_1 –P_6, a, θ and β that were defined above and include those defined in the minimal model (Mitsis et al. 2009; Hassan et al. 2017) and in the pancreatic beta cells model (Mitsis et al. 2009). They are measurable constants with the physiological range of values (Ni et al. 1997; Mitsis et al. 2009), where the actual values can vary for different normal and patient cases.

In the following paragraphs, we provide some explanation of the modeling system (1a)-(1e), but it should be noted that the equations (1a)-(1c) in the absence of both the external energy input term $D(t)$ and the governing equation for the insulin secretion r are basically equivalent to the minimal model (Bergman et al. 1979) that we described before in the section 1.

The left-hand-side of the equation (1a) represents the time rate of change of the plasma glucose concentration, and it balances with the sum of three terms in the right-hand-side of (1a). The first term $[-P_1 (G-G_b)]$ represents the contribution of the glucose excess over its basal value on the rate of change of the glucose, while the second term is the nonlinear (bilinear) term $(–P_1 X G)$ that describes the effect of the insulin action to reduce the plasma glucose and, thus, has a negative contribution to the rate of change of the glucose. The last term is the external energy input that has a positive contribution to the rate of change of the glucose.

The left-hand-side of the equation (1b) represents the time rate of change of the insulin action, and it balances with sum of three terms in the right-hand-side of (1b). The first term $(-P_2 X)$ represents the contribution of the insulin action alone on the rate of change of the insulin action and has a negative contribution. The second term $[P_3 (I-I_b)]$ represents the contribution of the insulin concentration excess over its basal value on the rate of change of the insulin action. It has a positive contribution only if the insulin concentration is above its basal value. The last term $(P_3 r)$ is the positive contribution on the rate of change of the insulin action by the secreted insulin due to the pancreatic beta cells.

The left-hand-side of the equation (1c) represents the time rate of change of the plasma insulin concentration, and it balances with sum of two terms in the right-hand-side of (1c). The first term $[P_4 (G-P_5)]^+ t$ represents a positive contribution by the glucose to the time rate of increase of the insulin concentration if the blood glucose is sufficiently large $(G>P_5)$, while the second tem $[P_6 (I-I_b)]$ represents contribution by the deviation of insulin concentration from its basal value to its time rate of change.

The left-hand-side of the equation (1d) is the time rate of change of the secreted insulin by the pancreatic beta cells, and it balances with the sum of two terms in the right-hand-side in (1d). The first term $(-a r)$ represents the contribution of the secreted insulin alone on its time rate of change, while the second term $\beta(G-G_b -\theta)$ represent a positive contribution by the deviation of the glucose from its basal value to the time rate of increase of the secreted insulin if this glucose excess from its basal value is sufficiently large $(G-G_b>\theta)$.

The initial conditions that are given in (1e) for the glucose and insulin concentrations in the plasma are taken to be their corresponding basal values, which are usually those values measured during the fasting conditions. We choose these basal values as the initial values of these quantities by ignoring very short “transient” phase between the fasting and starting times of the

motion (Mitsis et al. 2009). The initial conditions for X and r that are given in (1e) are taken as zero since initially there is no action taken by the insulin and no secreted insulin is generated at t=0.

As we already explained in the section 1, our modeling system (1a)-(1e) is a novel one that for the first time investigates the nonlinear dynamics of four nonlinear differential equations for the time-dependent motion due to the plasma glucose concentration, plasma insulin concentration, insulin action and the secreted insulin by the pancreatic beta cells. In addition, our modeling system includes the effect of an external energy input to the patient's body. Thus, the results of our dynamical investigation can be relevant for the motion of the hormones in the regulatory systems for type 2 diabetes and moderate type 1 diabetes patients, where pancreatic beta cells can operate.

Also to detect the dynamical results due to the presence of active pancreatic beta cells alone, we also investigated the modeling system in the absence of the beta cells, where the corresponding results can be relevant to severe type 1 diabetes patient case. We then compared the results between the case in the presence of beta cells and the case in the absence of the beta cells, and we were able to determine the effects due to the beta cells alone. In the previous section we already reviewed the previous studies on the related subject, and in the section 4 we have explained the significance of the present work as compared to the previous related studies.

3. Solution, results & discussion without beta cells effect

In this section we consider the system of equations (1a)-(1c) and the corresponding initial conditions given in (1e) but with no presence of the beta cells effect on the insulin action, so that r=0 in (1b). Thus, here we consider the case that the pancreatic beta cells of the patient are completely inactive and cannot operate, which corresponds to the case of patient with severe type 1 diabetes. We carried out our investigation using both analytical and numerical methods to determine the solution for the stated system.

3.1. Analytical solution & results

For $G \leq P_5$, we considered both linear and nonlinear versions of the stated system, and we solved them analytically which was done easily using separated variables approach for the homogenous part of each equation plus a simple non-homogeneous term if the equation is non-homogeneous. If $G \leq P_5$ holds initially at t=0, then we find that both linear and nonlinear version of the system yield

$$G=G_b+[a_0/(P_1-b_0)][exp(-b_0 t)-exp(-P_1 t)],\ I=I_b,\ X=0 \quad \text{for } G\leq P_5 \text{ at } t=0. \qquad (2a\text{-}c)$$

By direct substitution, the solution given by (2a-c) was verified to be the solution of the linear version of the system (1a)-(1c) and (1e).

It can be seen from this solution that the plasma insulin concentration stays at its basal value and the insulin action remains zero. These results indicate that for the value of plasma glucose concentration less than or equal to a threshold value, the insulin action as well as insulin concentration are not effective since glucose in the plasma is not large enough to trigger extra insulin production for countering the presence of the glucose concentration in the plasma.

If $G \le P_5$ begins to hold at some value $t_0 > 0$ where $G=G_0$, $X=X_0$ and $I=I_0$, then using the same type of the stated analytical approach, we find the following solution for the linear case:

$$I=I_b+I_0\, exp[P_6\,(t_0 - t)],\ X=c_2\, exp(-P_2\, t)+c_4\, exp(-P_6\, t), \tag{2d-e}$$

$$G=G_b+ c_6\, exp(-P_1\, t)+c_7\, exp(-P_2\, t)+c_8\, exp(-P_6\, t)+c_{10}\, exp(-b_0\, t), \tag{2f}$$

where

$$c_4 =[(I_0 - I_b)P_3\, exp(P_6\, t_0)]/(P_2 - P_6),\ c_2= X_0\, exp(\, P_2\, t_0)-c_4\, exp[(P_2 - P_6\,)\, t_0], \tag{2g-h}$$

$$c_7 =G_b\, c_2/(P_1 - P_2),\ c_8=G_b\, c_4/(P_1 - P_6\,),\ c_{10} =a_0\, /(P_1 - b_0), \tag{2i-k}$$

$$c_6 =(G_0 - G_b)exp(P_1\, t_0)-c_7\, exp[(P_1 - P_2)t_0]-c_8\, exp[(P_1 - P_6)t_0]-c_{10}\, exp\,[\,(P_1 - b_0\,)t_0\,]. \tag{2l}$$

By direct substitution to the governing system, we proved that (2d-f) is the solution to the linear version of (1a-e).

For the nonlinear system, the solution for I and for X remain the same as the ones given in (2d-e). However, the solution for G needs to be found using a different analytical method. We applied the method of integration factor (Pontryagin 1962) to determine the expression for $G(t)$. It is given below:

$$G(t)=G_b +\{[\textstyle\int_0^t \mu(t)R(t)\mathrm{d}t]+(G_0 - G_b)\mu(t_0)\}/[\mu(t)], \tag{2m}$$

where

$$\mu(t)=exp[P_1\, t+(c_2/P_2)exp(-P_2\, t)+(c_4\, /P_6)exp(-P_6\, t)],\ R(t)=G_b\, X(t)+a_0\, exp(-b_0\, t). \tag{2n-o}$$

3.2. Numerical solution & results

For both $G<P_5$ and $G \ge P_5$, the system is also solved numerically for both linear and nonlinear cases using Euler's method (Ascher et al. 1995). In the case of $G< P_5$, we did check our numerical results versus the solution given in (2) to verify the numerical solution as well as to check the reasonable value of the mesh distance, and we find very good agreement between the numerical and analytical solutions. Thus, it was verified the correctness of our constructed code, and, in addition, it showed the step size of 0.05 that we used in the simulation was quite reasonable.

The present system of equations and initial conditions are for the time evolution of G, I and X versus t. This system of differential equations represents the time rate of change of glucose and insulin concentrations in the plasma together with the insulin action as the dependent variables.

To obtain the numerical solution of this system, we used some collected data values for the constant parameters of the governing system for both healthy person and diabetic patients. The values of the parameters and constants for three patients and one normal person cases were collected from some references (Ni et al. 1997; Mitsis et al. 2009; Hassan et al. 2017) that are given below in Table 1:

Table 1. Parameters for a normal person and three diabetes patients

Parameter	**Normal**	**Patient 1**	**Patient 2**	**Patient3**
P_1	0.031	0	0	0
P_2	0.012	0.011	0.007	0.014
P_3	0.00000492	0.0000053	0.00000216	0.00000994
P_4	0.0039	0.0042	0.0038	0.0046
P_5	79.035	80.2	77.578	82.937
P_6	0.265	0.26	0.246	0.281
G_b	70-80	70-80	70-80	70-80
I_b	7	7	7	7
G_0	291.2	220	200	180
I_0	364.8	50	55	60

In the present study we investigated only the cases where the initial conditions for the glucose concentration and insulin concentration are the same as their basal values. For the case that the initial conditions for the glucose and insulin concentrations can be different from the corresponding basal values, then other initial conditions for G and I can be those that are given in Table 1 as G_0 and I_0 (Hassan et al. 2017), but we did not consider such case in the present study.

For the analytical solution that was given in (2a) for $G(t)$, which we found to agree very well with the corresponding numerical solution for $G < P_5$, we present here such result graphically as is shown in Figure 1 for a normal person and for different values of the constant coefficients a_0 and b_0 in the expression for the energy input function $D(t)$, which represents the glucose absorption rate to the blood of the particular normal person with the values of the parameters and the constants as given in table 1.

It can be seen from this Figure that initially the plasma glucose concentration increases from its basal value due to the intake energy. The glucose concentration increases quickly with increasing the magnitude of the energy input and then the glucose decreases with increasing t as the amount of the intake energy is consumed by the person's body. For sufficiently large values of t, the glucose concentration then reaches its equilibrium value, which is its basal value.

As stated earlier and as a test of our numerical code, we also compared our numerical solution for plasma glucose concentration, plasma insulin concentration and the insulin action subjected to the same parameter and constant values as the corresponding ones that were considered for the analytical solution (2a-c), and we found excellent agreement between the numerical solution and the corresponding the analytical solution.

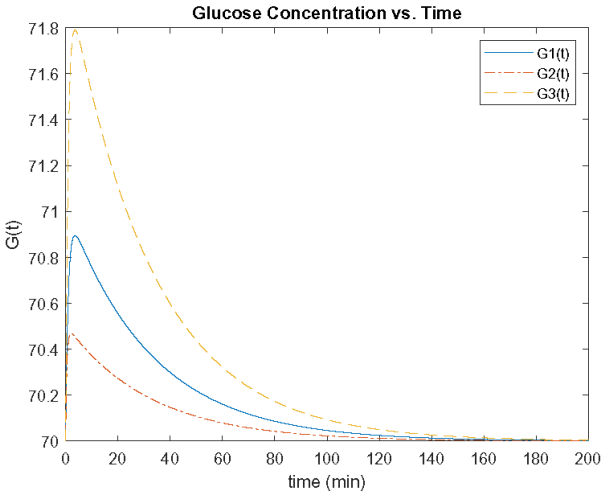

Figure 1. Glucose versus time for normal person, where G_1, G_2 and G_3 correspond, respectively, to the values of $(a_0, b_0) = (1, 1), (1, 2)$ and $(2, 1)$

Figure 2 presents the numerical solution for the glucose concentration versus time for the normal person and for the same parameters values as those for Figure 1, but here the basal value for the glucose is chosen as 80 since we wanted to determine the results for $G > P_5$ that requires the numerical approach be implemented as was explained before. It can be seen from this Figure that the glucose concentration is raised up very quickly, reaches a maximum and then decreases

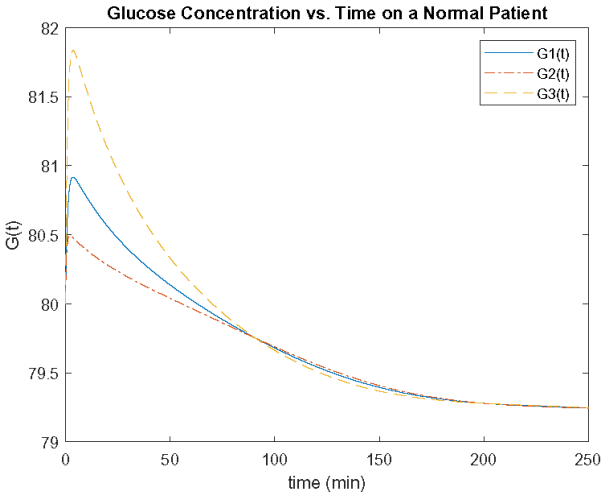

Figure 2. The same as in Figure 1 but for basal value of 80

sharply with increasing t. Its initial sharp increase in value is due to the presence of the energy input, which is highest initially but decreases with increasing time. Then, a short time later, the glucose concentration decreases with increasing time, which is due to the reduction in the value of the energy input as well as the presence of insulin that increase quickly to reduce the presence of high glucose.

Figure 3 is the same as Figure 2 but for insulin action versus time. It can be seen from this Figure

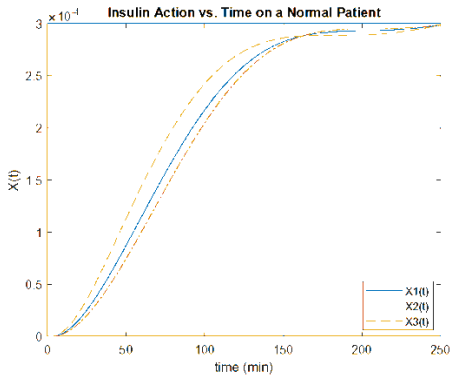

Figure 3. The same as in Figure 2 but for insulin action

that the insulin action arises to counteract the presence of the glucose and is stronger for the case where the glucose concentration is higher in the plasma, and the rate of increase of the insulin action is also higher for higher glucose concentration, which are expected biomedically.

Figure 4 is the same as Figure 2 but for the plasma insulin concentration. It can be seen from this

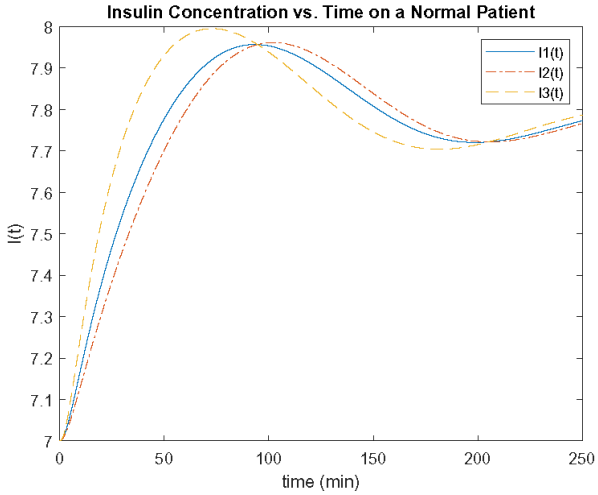

Figure 4. The same as in Figure 2 but for insulin concentration

Figure that initially the insulin concentration increases with time and is higher for higher glucose concentration until at some value in time when it begins to decrease with increasing time. Initially insulin concentation increases strongly with time in order to reduce the glucose concentration that was built up initially and reaches a maximum due to the energy input, and then the insulin concentration decreases at later time since the amount of glucose is reduced due to the insulin impact, and the energy input also is reduced at such later in time.

Figure 5 presents plasma glucose concentration for both linear and nonlinear system versus time and for normal person with $a_0 = b_0 = 1$. It can be seen from this Figure that the nonlinear effect is important and lead to small increase in the value of the glucose concentration. The nonlinear effect, which is present in (1a) is due to the product of glucose concentration and the insulin action that is an effect caused by the insulin action to counteract the increase in the value of the glucose concentration that subsequently can enhance the effect of the insulin action.

Figure 6 is the same as Figure 5 but for the insulin action versus time. It is seen the role of the nonlinearity that enhances the insulin action, which we described earlier in relation to Figure 5.

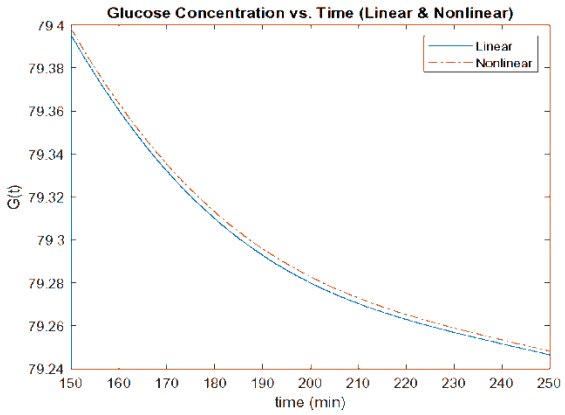

Figure 5. Glucose versus time for linear (solid line) and nonlinear (dashed line) cases for normal person with $G_b = 80$ and $a_0 = b_0 = 1.0$

However, it can be seen from this Figure that the effect of the nonlinearity is more significant for the insulin action since the insulin action is a main part of the nonlinear term in the equation (1a) that its role is to reduce the presence of the glucose concentration in the plasma whenever the value of the plasma glucose concentration becomes high enough. As a result of notable effect of the nonlinearity on the values of the insulin action shown in Figure 6, it is also expected that the values of the plasma insulin concentration become significant due to the nonlinear effect. Our next Figure 7 confirms such expectation.

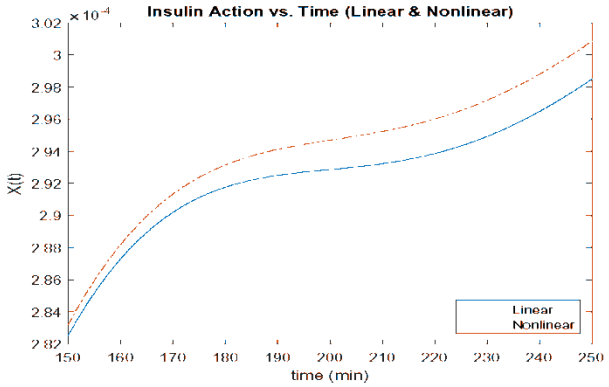

Figure 6. The same as Figure 5 but for insulin action

Figure 7 is the same as in Figure 5 but for the insulin concentration. It can be seen from this Figure that the nonlinear effect that was shown to enhance the insulin action also increase notably the value of the insulin concentration. We also generated data similar those that were shown in Figures 5-7 but for the cases of the other patients, and we found similar results about the nonlinear effect that were described above for the normal person case.

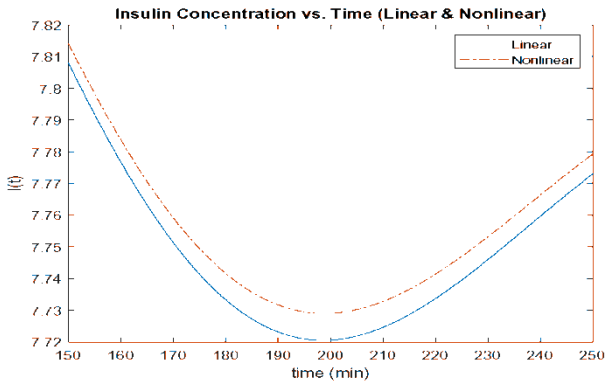

Figure 7. The same as in Figure 5 but for insulin concentration

It should be noted that while constructing graphs for linear and nonlinear systems for the case of $G > P_5$, it was noticed that the difference between these two systems is small. This is reasonable due to the fact that the values for the insulin action are relatively small and thus do not have an big impact on the nonlinear term in (1a), which represents the nonlinear interaction between the insulin action and the glucose concentration.

Figure 8 presents the plasma glucose concentration versus time for the normal person, patient 2 and patient 3, where "A" and "N" in Figure indicate the solution, respectively, by analytical and numerical procedures. It can be seen from this Figure that for the normal person the range of values for the glucose concentration is about around the basal value, which is expected. For the patient 2, the glucose concentration first increases slightly and then decreases, which is an indication of the unstable condition mainly due to the smaller values of the parameters, which include those that represent the kinetic of the glucose and insulin action, insulin sensitivity, enhancing insulin secretion and decay rate, and such smaller values tend to reduce the glucose concentration at some higher rate.

For the patient3, the values of the glucose slightly increase, which can be due to the larger values of the stated parameters, but it notably reduces the value of the insulin action. It should also be noted that in the case of patient 2, initially we had the condition of $G > P_5$, which required to determine the solution numerically for some interval in time $t<t_0$, beyond which we observed that $G \leq P_5$ that we used the available analytical solution that was given in the sub-section 3.1.

Figure 9 is the same as Figure 8 but for the plasma insulin concentration versus time. It can be seen from this Figure that in analogy to the results shown in Figure 8 for the plasma glucose concentration, the insulin concentration increases slightly for the healthy person, but the rate of change of the values of the insulin concentration that increases notably over some interval in time and then decreases notably thereafter is an indication of unstable behavior in the case of the

patient 2. For the case of patient 3, the value of the insulin concentration remains basically the same as its basal value.

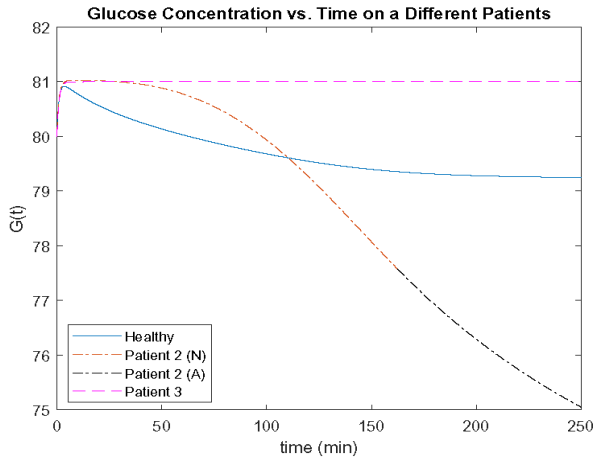

Figure 8. Glucose concentration versus time for normal person (solid line), patient 2 (dashed-dot line) and patient 3 (dashed line) for G_b =80 and a_0 =b_0 =1.0

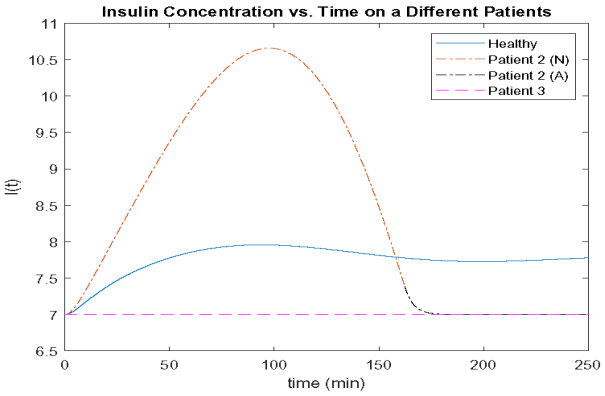

Figure 9. The same as in Figure 8 but for insulin concentration

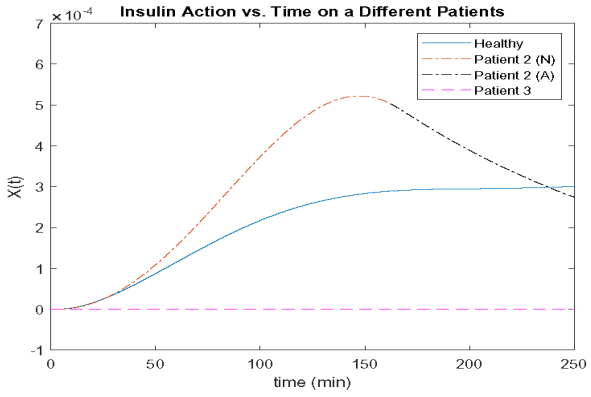

Figure 10. The same as Figure 8 but for insulin action

Figure 10 is the same as in Figure 8 but for insulin action versus time. In analogy to Figures 8-9, the insulin action increases by some relatively moderate amount for the normal person case, while it increases notably and remain at higher values for the patient 2 that indicates relatively more critical condition in this case. However, in the case of patient 3 the insulin action remains very close to its initial condition of zero value, which is due to relatively large parameters values for this patient that we described before.

4. Solution, results & discussion with beta cells effect

In this section we consider the system of equation (1a)-(1d) and their corresponding initial conditions (1e), which are for the case in the presence of beta cells effect. This means that here our modeling system can be applicable to both patients with type 2 diabetes case or with moderate type 1 diabetes case since pancreatic beta cells can operate to some levels in such cases. We carried out our investigation using both analytical and numerical methods to determine the solution for the more general stated system.

4.1. Analytical solution & results

For $G \le P_5$ and $G < G_b + \theta$, we considered both linear and nonlinear versions of the system (1a)-(1e), and we solved them analytically which was done using separated variables or integration factor approach. If $G \le P_5$ and $G < G_b + \theta$ hold starting at the initial time t=0, then we find that both linear and nonlinear version of the system yield the same solution, which is given below:

$$G=G_b+[a_0/(P_1-b_0)][exp(-b_0 t)-exp(-P_1 t)],\ I=I_b,\ X=0,\ r=0 \text{ for } G\le P_5 \text{ at } t=0. \quad (3a\text{-}d)$$

By direct substitution, we proved that (3a-d) is the solution to the system (1a-e).

It can be seen from the solution (3a-d) that the plasma insulin concentration stays at its basal value, and the insulin action and the secreted insulin by the pancreatic beta cells remain zero. These results indicate that for the value of the plasma glucose concentration less than or equal a threshold value, the insulin action, secreted insulin by beta cells as well as insulin concentration are not effective since glucose in the plasma is not large enough that triggers extra insulin production to counter the presence of glucose concentration in the plasma.

If $G \le P_5$ and $G < G_b+\theta$ initiate to hold at some value $t_0 > 0$ of time where $G=G_0$, $X=X_0$, $r = r_0$ and $I=I_0$, then the same type of stated analytical approach yields the following solutions for the linear case:

$$I=I_b+I_0\, exp[P_6 (t_0-t)],\ r=r_0\, exp[a(t_0-t)], \quad (3e\text{-}f)$$

$$X=e_2\, exp(-P_2 t)+e_4\, exp(-P_6 t)+e_5\, exp(-a t), \quad (3g)$$

$$G=G_b+ e_6\, exp(-P_1 t)+e_7\, exp(-P_2 t)+e_8\, exp(-P_6 t)+e_9\, exp(-a t)+ e_{10}\, exp(-b_0 t), \quad (3h)$$

where

$$e_4 =[(I_0 - I_b)P_3 \exp(P_6 t_0)]/(P_2 - P_6),\ e_5 =[r_0 P_3 \exp(a t_0)]/(P - a), \quad (3i\text{-}j)$$

$$e_2= X_0 \exp(P_2 t)-e_4 \exp[(P_2 - P_6) t_0]-e_5 \exp[(P_2 - a)t_0],\ e_7 =G_b c_2/(P_1 - P_2), \quad (3k\text{-}l)$$

$$e_8= G_b c_4/(P_1 - P_6),\ e_9 =G_b e_5 /(P_1 - a),\ e_{10} =a_0 /(P_1 - b_0), \quad (3m\text{-}n)$$

$$e_6 =(G_0 - G_b)\exp(P_1 t_0)-e_7 \exp[(P_1 - P_2)t_0]-e_8 \exp[(P_1 - P_6)t_0] \equiv A, \quad (3o)$$

$$A \equiv - e_9 \exp[(P_1 - a)t_0]-e_{10} \exp[(P_1 - b_0)t_0]. \quad (3p)$$

By direction substitution, we proved that the solution (3e-h) satisfies the linear version of (1a-e).

For the nonlinear system, the solution for each of the quantities r, I and X remain the same as the corresponding one given in (3e-g). However, the solution for G needs to be found using a different analytical method. We applied the method of integration factor (Pontryagin 1962) to determine the expression for $G(t)$. It is given below:

$$G(t)=G_b +\{[\int_0^t \mu(t)R(t)dt]+(G_0 - G_b)\mu(t_0)\}/[\mu(t)], \quad (3q)$$

where

$$\mu(t)=\exp[P_1 t+(e_2/P_2)\exp(-P_2 t)+(e_4 /P_6)\exp(-P_6 t)+(e_5 /a)\exp(-a t)], \quad (3r)$$

$$R(t)=G_b X(t)+a_0 \exp(-b_0 t). \quad (3s)$$

For $G>G_b +\theta$, then in general solutions need to be found numerically.

4.2. Numerical solution & results

For both $G<P_5$ and $G \geq P_5$, the system is also solved numerically for both linear and nonlinear cases using Euler's method (Ascher et al. 1995). In the case of $G< P_5$, we did check our numerical results versus solution given in (3) to verify the numerical solution as well as to see the reasonable value of the mesh distance, and we found very good agreement between numerical and analytical form of the solution. Thus, it also verified our constructed code.

The present system of equations and initial conditions are for the time evolution of r, G, I and X versus t. This system of differential equations represents the time rate of change of the considered dependent variables (glucose and insulin concentrations in plasma, secreted insulin).

To carry out these simulations, we used some collected data for both normal person and diabetic patients in order to determine the solution to (1a)-(1e) and then analyze the glucose-insulin dynamics in the regulatory systems of these patients.

The values of the parameters and constants for three patients as well as for the normal case were collected from some references (Ni et al. 1997; Mitsis et al. 2009; Hassan et al. 2017) and already are given mostly in table 1. For the parameter values that are given in the equation (2d)

for *r*, we used the values as given in Mitsis et al. (2009), which are a=0.13, β=0.05 and two values of 0 and 80 for θ.

Figure 11 presents the plasma glucose concentration versus time in the presence of the beta cells effect and for the normal (healthy) person, patient 1 and patient 2. It can be seen from this Figure that for the healthy person initially the plasma glucose concentration increases rapidly above its basal value due to the initial delivered energy, and then it decreases strongly with increasing time to reach its basal value and decreases further as time goes on, which is expected for a normal person.

For the patient 1, plasma glucose concentration initially increases significantly and reaches a maximum value higher than that for the normal person and then decreases less rapidly, but its value remain higher than the corresponding value for the normal case, which is an indication of some slight unstable condition mainly due to the smaller values of the parameters as compared to the corresponding values for the patient 3 (table 1).

Table 1 also includes values of those parameters that represent the kinetic of the glucose and insulin action, insulin sensitivity, enhancing insulin secretion and decay rate, and such smaller values tends to reduce the glucose concentration at higher rate. For the patient 2, the values of the glucose increase strongly at the initial stage with respect to time which can be due to the lower values of the already stated parameters. It should also be noted that in the case of the patient 2, we found the interaction between the insulin secretion due to the pancreatic beta cells and the plasma glucose concentration existed mostly through the interval in time as shown in Figure 11. This result is then led to lower values of the plasma glucose especially at higher values of time, which is the effective role of such insulin secretion generated by the pancreatic beta cells.

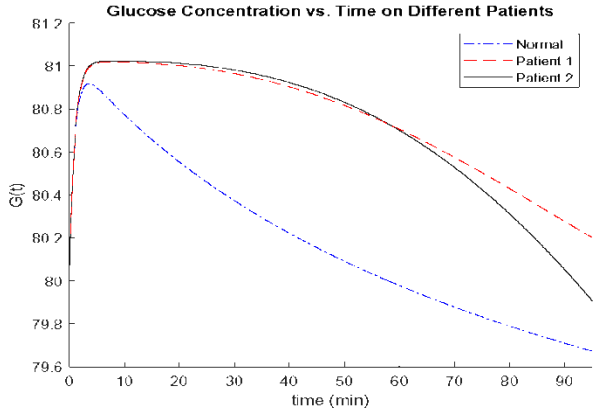

Figure 11. Glucose concentration versus time for normal person (dashed-dot line), patient 1 (dashed line), patient 2 (solid line), G_b =80 and a_0 =b_0 =1.0, a=0.13, β=0.05 and θ=0

Figure 12 is the same as Figure 11 but for the plasma insulin concentration versus time. It can be seen from this Figure that in analogy to the results based on Figure 11 that we described above, the insulin concentration increases slightly for the normal person, but the rate of change of the

values of the plasma insulin concentration for the case of patient 2 increases significantly over some interval in time and then begins to slightly increase thereafter, which is an indication of the unstable behavior in the case of the patient 2 conditions. For the case of patient 1, the value of the plasma insulin concentration appears to be small with a moderate increase with respect to time and then decreases with increasing time, which is the direct effect by the presence of the insulin secretion.

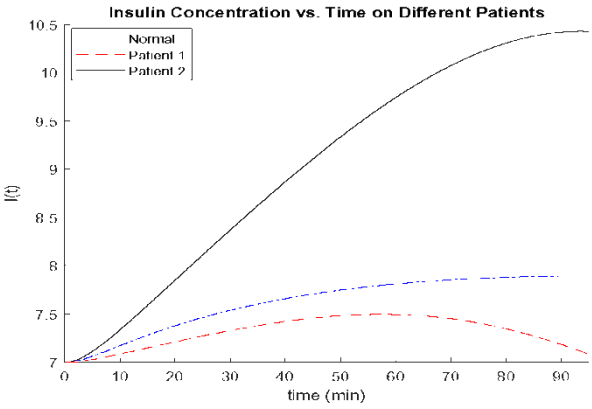

Figure 12. The same as in Figure 11 but for insulin concentration

Figure 13 presents the insulin action versus time in the presence of beta cells effect and for the same patients and parameters values as those that were for Figure 11. In analogy to Figures 11-12, the insulin action for the patient 2 ultimately becomes dominated as compared to the corresponding cases for the normal person and the patient 1. In the cases of patient 1 and the healthy person, the insulin action is relatively small because of the relatively larger values of the parameters P_2 –P_6 in the case of such cases and also because of the positive value of the glucose

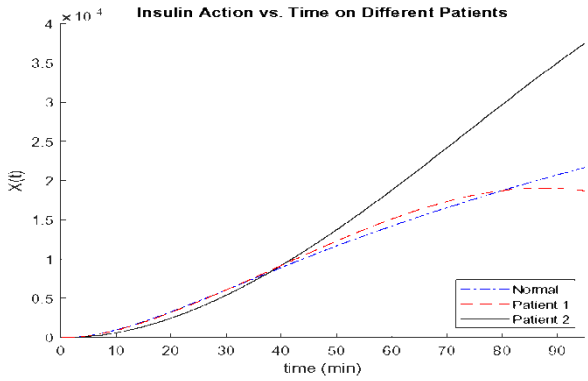

Figure 13. The same as Figure 11 but for insulin action

parameter P_1 for the healthy person that reduces the rate of increase of the glucose concentration, which subsequently reduces the insulin action.

Figure 14 is the same as Figure 11 but for the insulin secretion by the pancreatic beta cells. It can be seen from this Figure that such secreted insulin is relatively small for the healthy person since

there is no need that such secreted insulin to be significant for a normal case. However, the secreted insulin by the pancreatic beta cells is significant at least over a notable time interval for the cases of patient 1 and patient 2 in order to reduce the effect of the glucose concentration in the plasma.

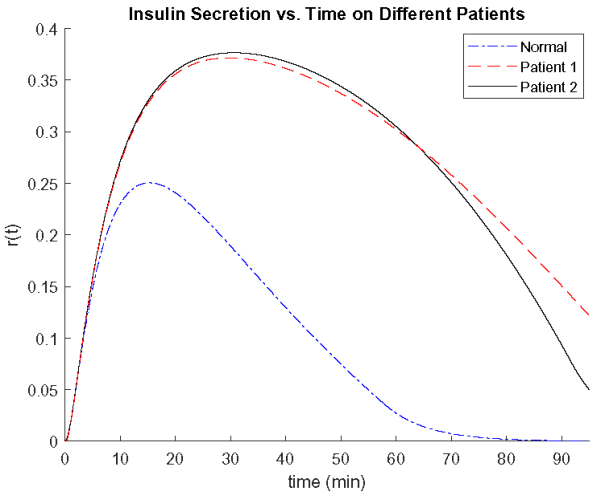

Figure 14. The same as in Figure 11 but for the insulin secretion due to the beta cells

Comparing the results that were described in this section and those in the section 3 for the same patient, we find that the maximum value for the glucose concentration becomes smaller in the presence of the beta cells than for the case in the absence of the beta cells, and then the values of the glucose decreases more rapidly with increasing time in the presence of beta cells than for the corresponding values for the case in the absence of the beta cells. The plasma insulin concentration and the insulin action increase with time and reach higher values in the presence of the beta cells. Thus, the efforts by the beta cells clearly makes the insulin more active that tends to reduce the blood glucose, which has the direct benefit for the diabetes patient's health.

4.3. Comparison with other studies

About the comparison of the present work with those of related work that were done by other authors in the past, we consider here the work due to Hassan et al. (2017) and the one due to Mitsis et al. (2009) that were already described in the section 1. Hassan et al. (2017) considered the minimal model due to Bergman and Cobelli (1980) and used a controlling approach for an external insulin delivery based on the linear version of the minimal model. Furthermore, in contrast to the present work, these authors did not present the dynamical process of the hormones and did not take into account the externally energy input, such as the one due to the consumed food, on the patients' hormones dynamics to determine the corresponding contribution to the actual results. In addition, these authors did not include the governing equation for the secreted insulin due to the pancreatic beta cells.

Mitsis et al. (2009) carried out a computational study for the glucose-insulin minimal modeling system to develop a Volterra model. However, in contrast to the present work, they did not

present the dynamical process of the hormones and did not include an equation for the insulin concentration, but instead they just used a collection of numerical values to account for such concentration. In addition, they also did not take into account any external energy input in their studies.

5. Conclusions

We investigated both analytically and numerically the time evolution of a system of nonlinear ordinary differential equations for the time-dependent variables that represented the plasma glucose concentration, insulin action, plasma insulin concentration and the insulin secretion due to the pancreatic beta cells and with externally added energy. We determined the variations of these blood hormones versus time variable and for different values of the parameters that represented different types of the patients with different health conditions. The effects of the nonlinearities in the modeling system as well as the role of the presence of the externally delivered energy to the considered glucose-insulin regulatory system were determined.

We found that the nonlinear effect in the investigated modeling system can increase the insulin action and the glucose and insulin concentrations. Presence of the externally delivered energy to the modeling system can increase the glucose concentration at some initial time interval, but the insulin action and the insulin concentration quickly increase to reduce the blood glucose that was raised up due to such added energy. In the presence of pancreatic beta cells, the glucose concentration is lower than the corresponding one in the absence of the beta cells, and both insulin action and insulin concentration appear to be more effective in the presence of the beta cells. It is also found that smaller values of the parameters that represent kinetics of the glucose and insulin concentration, insulin sensitivity and plasma insulin decay rate, can lead to relatively lower values of the glucose concentration.

It would be of interest if the present results can stimulate future research efforts in the related biomedical and biotechnological areas for developing new approach or process that could improve the heath conditions of the patients with type 1 or type 2 diabetes cases.

Future studies in this subject area can include extending the present type modeling system by including additional blood hormones in the regulatory system like those that can affect the glucose concentration and the metabolic process to determine the time evolution of these hormones in the regulatory system and how the glucose concentration is affected by the presence of such additional hormones.

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