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Mathematical Modeling of Nonlinear Dynamics of Blood Hormones

Gabriela Urbina[1] **and Daniel N. Riahi**[2]

Abstract

In this paper, mathematical modeling of nonlinear dynamics of blood hormones regulatory system, which includes glucose, insulin and glucagon hormones and with the presence of the secreted insulin due to the pancreatic beta cells, is developed and investigated. This model considers the time evolution of nonlinear dynamics of the equations for the blood hormones that represent glucose, glucagon and insulin concentrations plus insulin and glucagon actions as well as secreted insulin due to the pancreatic beta cells. Using both theoretical and numerical procedures, we determine such quantities by examining some data for the case of one patient at three different times of the day as well as the case of three patients at the same time of the day and for different values of the parameters. We find that the nonlinear effects due to the time-dependent interactions between these hormones can be notable and affect the resulting values for each hormone for given instant in time. For the present nonlinear dynamical system, there are parameters whose values differ for different diabetes patients and their roles to determine the values of the glucose, glucagon and insulin concentrations in the patient's blood and the responses that arise due to the insulin and glucagon actions can be notable. We find, in particular, that the cases with relatively moderate or smaller values of the parameters, which represent kinetics of the insulin action, insulin sensitivity, rate for the glucagon action and the glucagon sensitivity, can lead to moderate or smaller values of the plasma glucose concentration.

Keywords: Blood glucose, Glucose dynamics, Blood hormones.

[1] School of Mathematical & Statistical Sciences, University of Texas Rio Grande Valley.
[2] School of Mathematical & Statistical Sciences, University of Texas Rio Grande Valley.

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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 of highly importance 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 transport the glucose you eat into your cells as an energy source; this hormone is called insulin. More specifically, the individual's immune system attacks and destroys the pancreatic cells that help 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 use insulin properly, which also leads to a higher glucose level in the bloodstream than normal. Whenever this is the case, an individual would be diagnosed with diabetes. On the other hand, pre-diabetes is a condition where the blood sugar is higher than normal, yet it is not high enough to be diagnosed as diabetes. Individuals with pre-diabetes are at higher risk of developing diabetes if it is left untreated.

As mentioned previously, diabetes can lead to several health complications, including heart problems and death. Therefore, early detection is trivial for the health of diabetic patients. There are blood tests that can help to detect whether an individual has diabetes or not. Researchers have discovered that the dynamics of interaction between different hormones in the regulatory system can be modeled by a system of nonlinear differential equations.

Bergman and Cobelli [1] developed a novel approach that is referred to as minimal models to take into account the two main blood hormones, namely glucose and insulin for the diabetes patients and estimated the corresponding insulin sensitivity when the glucose concentration in the plasma can be minimized.

More recently, Herrero et al. [2] extended a minimal model to take into account presence of glucagon hormone and by using three sets of data, they were able to find agreement between their model and the experimental data. Their results could be useful for further progress on type 1 diabetes mellitus management.

In the present paper, the purpose of our research work was first to develop a mathematical model, which is an extension of the so-called minimal model due to authors in [1] that is simple enough so that the biological complexities are minimized, but the main qualitative aspects of the mechanism for the insulin glucose

regulatory system is retained. Our present model extended the previous models [1, 3-4] by taking into consideration specific nonlinear system of equations for the time evolution of the hormones in the human's blood that represent plasma glucose concentration, insulin excitable tissue glucose uptake activity, which refers to as insulin action, plasma insulin concentration, glucagon concentration, glucagon action [2] and also take into consideration the secreted insulin due to the pancreatic beta cells, which becomes effective if the plasma glucose concentration is elevated beyond some value. Glucagon is a blood hormone that is generated by the alpha-cells. It causes liver to convert stores of some other hormone (glycogen) into glucose and releases it to blood flow. Next, we used both theoretical and numerical procedures to determine the solutions 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 find some interesting results. In particular, we find that the nonlinear effect due to the nonlinear system for the glucose-insulin-glucagon dynamics can be significant for both hormones concentration in the plasma and for the hormone action such as the insulin action. Thus, nonlinear dynamics of the blood hormones regulatory system need to be taken into account in the modeling of such a system that can more accurately describe the hormones interactions affecting the health of the diabetes patients.

2. Modeling System for Blood Hormones Dynamics

Our modeling system for the dynamics of the blood hormones in an extensional of the so-called minimal system [1] that is simple enough with no notable biological complexities. The original minimal model has been applied by several authors including those due to [5-7] for noninvasive insulin sensitivity evaluation. In the present paper we apply an extension of such system by making use some part on the modeling of glucagon [2] plus taking into account externally taken energy by the patient and include beta cells effect to generate additional insulin due to the significant elevation of glucose. Our governing modeling system is given below

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

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

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

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

$$dY/dt = -P_7 Y(t) + P_8 [N(t) - N_b], \quad (1e)$$

$$dN/dt = -P_9 N(t) + Z_2(t)/(V_N \quad t_{max}), \quad (1f)$$

$$dZ_2/dt = [Z_1(t) - Z_2(t)]/t_{max}, \; d Z_1/dt = w + Z_1(t)/t_{max}, \quad (1g\text{-}h)$$

$$G = G_b , \; I = I_b , \; N = N_b, \; X = Y = 0, \; r = 0 \text{ at } t = 0, \quad (1i)$$

where for any function $f(t)$, $[\,f\,] = f$ if $f > 0$ and 0 otherwise.

Here G is glucose concentration in plasma with basal value G_b, X is insulin action, I is plasma insulin concentration with basal value I_b, N is glucagon concentration with basal value N_b, Y is glucagon action, r is the secreted insulin by the pancreatic beta cells in response to alteration in plasma concentration, Z_1 and Z_2 are a two compartment chain that represent absorption of subcutaneously administered glucagon which initial values are taken as zero in this paper, P_1 and P_2 are positive constants representing, respectfully, kinetics of glucose and insulin action, P_3 is a positive constant representing insulin sensitivity coefficient, P_4 is a positive constant representing contribution to the plasma insulin concentration by 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, P_7 is the constant rate describing glucagon ability to enhance glucose production by liver, (P_8 /P_7) is a constant representing glucagon sensitivity that measures the glucagon ability to enhance production by liver, P_9 is a constant decay rate of the plasma glucagon, and w is a subcutaneous glucagon infusion rate whose expression is a lengthy expression involving glucose, time rate of change of glucose and glucagon concentration, and our computational data indicated that its value should be taken as zero based on the condition described in [2] that we adopted in the present study. In addition, V_N is a constant representing distribution volume of the plasma glucagon, t_{max} is a constant time to maximum glucagon absorption, $D(t)$ is a form of imported food or performed a competitive sport, which can represent glucose absorption rate in blood by the food intake, and here we 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 representing 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.

3. Solutions, Results & Discussion

In this section, we consider the system of equation (1a)-(1h) and their corresponding initial conditions given in (1i). We carried out our investigation using both analytical and numerical methods to determine the solutions for the stated system.

3.1 Analytical solutions

As was explained earlier in section 2, our numerical results indicated that the value of w term in (1h) is for all the values of t that we used in our computations. Using simple separation of variables approach to solve (1g-h), which is subjected to zero conditions at t=0, we find Z_1=Z_2=0.

Using these results in (1e-f) and using method of separation of variable as well as taking into account solution as sum of general homogeneous solution plus particular non-homogeneous solution for (1f), we determine the following analytical solutions for the glucagon concentration and glucagon action:

$N=N_b\ exp\ (-P_9\ t)$, $Y=e_1\ exp\ (-P_7\ t)+P_8\ N_b\ \{[1/(P_7\ -P_9)]exp(-P_9\ t)-(1/P_7)$, (2a-b)

where

$e_1\ =P_8\ N_b\ [1/P_7\ -1/(P_7\ -P_9)]$. (2c)

These results indicate that glucagon delivery is passive here, and the glucagon concentration decays as time goes on.
For $G \leq P_5$, we consider both linear and nonlinear versions of the system (1a-c) and (1i), and we solve 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 $G \leq P_5$ and $G<G_b+\theta$ hold starting at the initial time $t=0$, then we find that the linear version of the system (1a-c) and (1i) yield the following solutions:

$G=G_b\ +[a_0\ /(P_1\ -b_0)][exp(-b_0\ t)-exp(-P_1\ t)]$, $I=I_b$, $X=0$, $r=0$ for $G\leq P_5$ and $G<G_b\ +\theta$ at $t=0$. (2d-g)

The nonlinear solutions for X, I and r remain the same as that given in (2e-g), but the nonlinear solution for G will be described later. It can be seen from these solutions 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 value of 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 trigger extra insulin production to counter the presence of glucose concentration in the plasma.

If $G\leq P_5$ 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 using the same type of stated analytical approach yields the following solutions for the linear case:

$I=I_b+I_0\ exp[P_6\ (t_0\ -t)]$, $r\ =r_0\ exp[a(t_0\ -t)]$, $X=e_2\ exp(-P_2\ t)+e_4\ exp(-P_6\ t)+e_5\ exp$

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

(2h-k)

where

$e_4 =[(I_0 - I_b)P_3 \exp(P_6 t_0)]/(P_2 - P_6)$, $e_5 =[r_0 P_3 \exp(a t_0)]/(P_2 - a)$, $e_2 = X_0 \exp(P_2 t) - e_4 \exp[(P_2 - P_6) t_0] - e_5 \exp[(P_2 - a)t_0]$, $e_7 = G_b e_2/(P_1 - P_2)$, $e_8 = G_b e_4/(P_1 - P_6)$, $e_9 = G_b e_5/(P_1 - a)$, $e_{10} = a_0/(P_1 - b_0)$, $e_6 =(G_0 - G_b)\exp(P_1 t_0) - e_7 \exp[(P_1 - P_2)t_0] - e_8 \exp[(P_1 - P_6)t_0] - e_9 \exp[(P_1 - a)t_0] - e_{10} \exp[(P_1 - b_0)t_0]$. (2l-s)

For nonlinear system, the solutions for r, I and X remain the same as those given in (2h-j). However, the solution for G for either the case $t_0 >0$ or $t_0 =0$ needs to be found using a different analytical method. We applied the method of integration factor [8] to determine the expression for $G(t)$. It is given below:

$$G(t)=G_b + \{[\int_0^t \mu(t)R(t)dt] + (G_0 - G_b)\mu(t_0)\}/[\mu(t)], \quad (2t)$$

where

$\mu(t)=\exp\{[P_1 + P_8 N_b/P_7]t - (e_2/P_2)\exp(-P_2 t) - (e_4/P_6)\exp(-P_6 t) - (e_5/a)\exp(-a t) + (e_1/P_7)\exp(-P_7 t) + [P_8 N_b/(P_7 P_9 - P_9^2)]\exp(-P_9 t)\}$, $R(t)=G_b [X(t) - Y(t)] + a_0 \exp(-b_0 t)$. (2u-v)

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

3.2 Numerical solutions and results

For both $G<P_5$ and $G\geq P_5$ as well as $G<G_b+\theta$ and $G\geq G_b+\theta$, the system is also solved numerically for both linear and nonlinear cases using Euler's method [9]. In the case of $G< P_5$ and $G<G_b+\theta$ we checked our numerical results versus solution given in this section to verify the numerical solutions as well as to see the reasonable value of the mesh distance, and we find very good agreement between numerical and analytical solutions. Thus, it also verified our constructed code as well as showed quite reasonable value of 0.05 for the mesh distance.

Since the analytical solutions for N and Y are already given in (2a-c), the present system of equations and initial conditions that need to be solved numerically 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 hormones (glucose and insulin concentrations in plasma, secreted insulin by beta cells together with the insulin action.

We need to determine that already given dependent variables along with the interaction terms for the dependent variables, etc. To obtain these calculations, we used some collected data for both cases of one diabetes patient at three different time period of a day and three diabetic patients at a given time interval of a day [2] in order to analysis the blood hormones dynamics in the regulatory system of these patients. The values of the parameters and constants for three patients as well as for a patient at a given time interval were collected from [2], which are for the cases where the secreted insulin by the beta-cells was not provided. For the parameter values that are given in the equation (1d) for r, we used the values as given in [3], which are a=0.13, β=0.05 and two values 0 and 80 for θ.

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 [9]. In the case of $G< P_5$, we did check our numerical results versus solution given in (2) to verify the numerical solutions as well as to see the reasonable value of the mesh distance, and we find very good agreement between numerical and analytical solutions. Thus, it also verified our constructed code as well as showed quite reasonable value of 0.05 for the mesh distance.

The present system of equations and initial conditions are for time evolution of G, I and X versus t. This system of differential equations represents the time rate of change of two hormones (glucose and insulin concentrations in plasma) together with the insulin action with the blood as dependent variables along with the interaction terms for dependents variables, etc. To obtain these calculations, we used some collected data for both healthy and diabetic patients in order to analysis the glucose-insulin dynamics in the regulatory system of these patients.

In all the calculations that were used to produce figures, we set $a_0=b_0=1$, a=0.13, β=0.05 and θ=0. In the following figures 1-6, we made use of the data provided in [2] for a patient referred to this reference as subject-117 for meals given in 3 intervals in time of a day as breakfast, lunch and dinner times. The values of the parameters and constants for this patient are as given in Table 1 below:

Table 1: Parameters and constants for patient-117 at three-time intervals

Parameters/Constants	**Breakfast, 80*g***	**Lunch, 80*g***	**Dinner, 108*g***
P_1	0.014	0.014	0.014
P_2	0.0039	0.021	0.012
P_3/P_2	0.000855	0.000632	0.000773
P_4	0.0039	0.0039	0.0039
P_5	79.035	79.035	79.035
P_6	0.265	0.265	0.265
P_7	0.016	0.139	0.017
P_8/P_7	0.000196	0.0000810	0.000138
P_9	0.62	0.62	0.62
I_b	11.01	11.01	11.01
N_b	46.30	46.30	46.30
G_b	100	100	100

In the present study, we also investigated only cases where the initial conditions for the glucose concentration, insulin concentration and glucagon concentrations are the same as their basal values.

Figure 1 presents plasma glucose concentration versus time for the patient-117 given meals at three intervals of time (breakfast, lunch & dimmer) and with the values of the parameters and constants as given in table 1. It can be seen from Figure 1 that initially plasma glucose concentration increases from its basal value due to the intake energy such as food taken by the patient plus the energy generated by disturbances or competitive exercise by the patient's body, which correspond to the case where magnitude of $D(t)$ in (1a). This then leads quickly to higher values of the plasma glucose concentration, and then the glucose decreases as the amount of

the intake energy is consumed by the patient's body. Then the amount of the glucose concentration decreases at a higher rate as time goes on as can be seen in Figure 1. However, as can be seen in this figure very shortly after the initial time, the values of the glucose concentration at lunch time become smaller as compare to those at breakfast and dinner times, which turn out to be due to the larger insulin action that is responded due to the larger intake energies taken during that day. The values of the glucose at dinner time is mostly higher than those during the breakfast and lunch because the amount of intake energy at dinner time was higher.

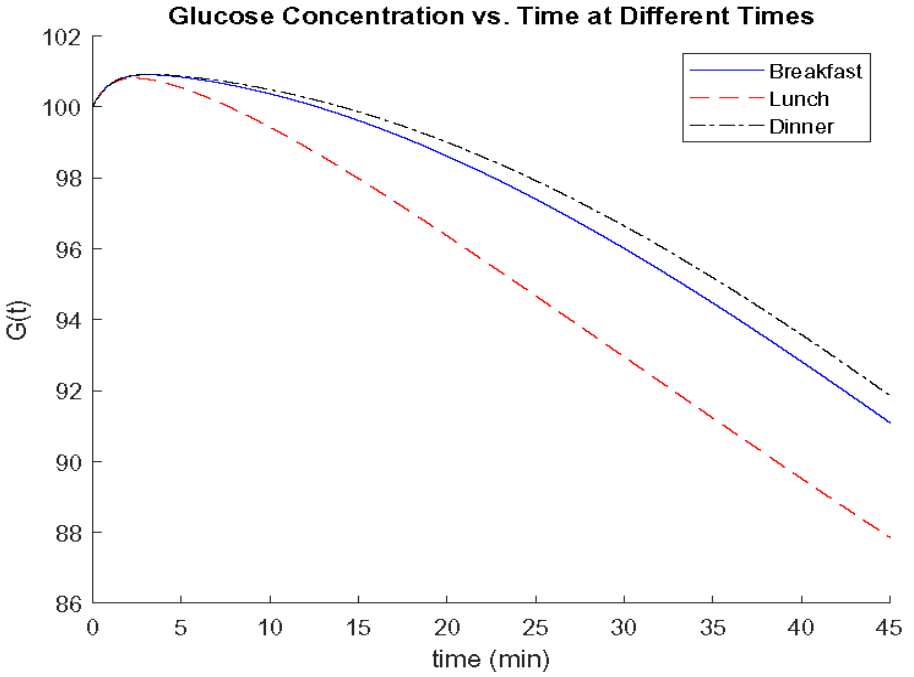

Figure 1: Plasma glucose concentration versus time for the case of patient-117 at given meals at three-time intervals (breakfast, 80*g*; lunch, 80*g*; & dinner, 108*g*)

Figure 2 presents plasma insulin concentration versus time and for the same patient and three meals cases, as in Figure 1. It can be seen from this Figure that, in particular, the value of the insulin concentration at the dinner time interval is mostly higher than the corresponding values during the other two meals, which is due to the higher energy taken during the dinner time that leads to higher glucose concentrations, and so the plasma insulin concentration needs to build up to counteract the higher rise in the plasma glucose concentration.

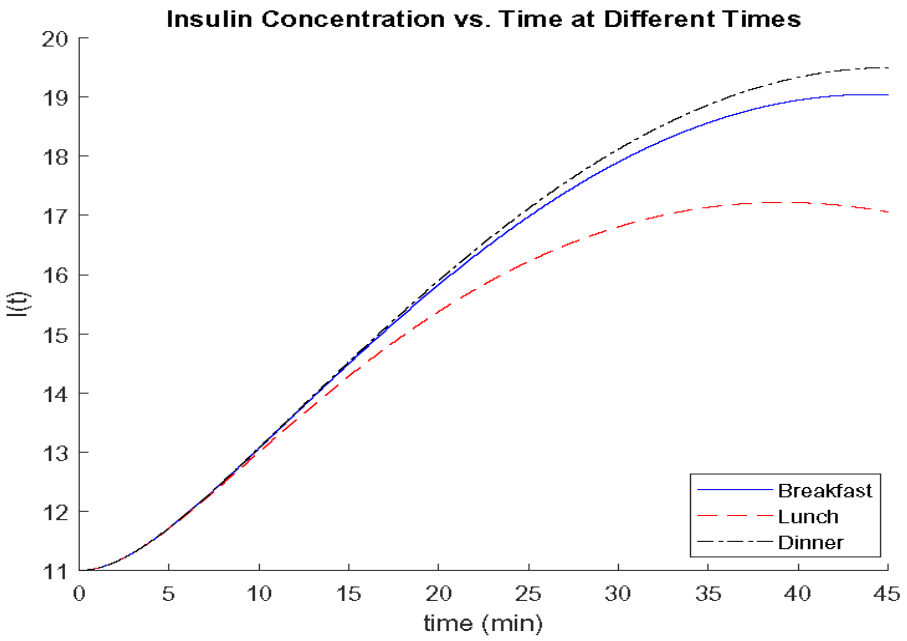

Figure 2: The same as in Figure 1 but for the insulin concentration

Figure 3 is the same as in Figure 1 but for insulin action versus time. It can be seen from this Figure that insulin action is stronger during the lunch time based on the same reason that was explained in regard to lower values of the plasma glucose concentration shown in Figure 1.

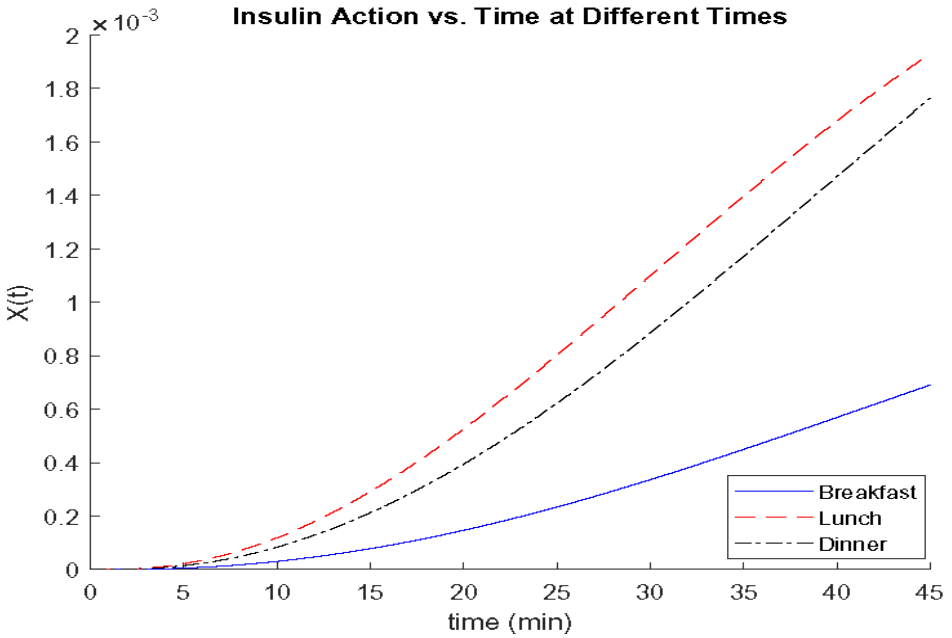

Figure 3: The same as in Figure 1 but for the insulin action

Figure 4 is the same as in Figure 1 but for the secreted insulin due to the beta-cells. It can be seen from this Figure that the insulin secretation by the pancreatic beta-cells is, in particlar, highrt at the dinner time, which a reaction to the higher amount of glucose generated due to the higher intake energy at the dinner interval. For sufficiently large time that the amount of the glucose concentration reduces considerably, then the beta-cells become passive and the amount of the insulin secretion diminshes to zero.

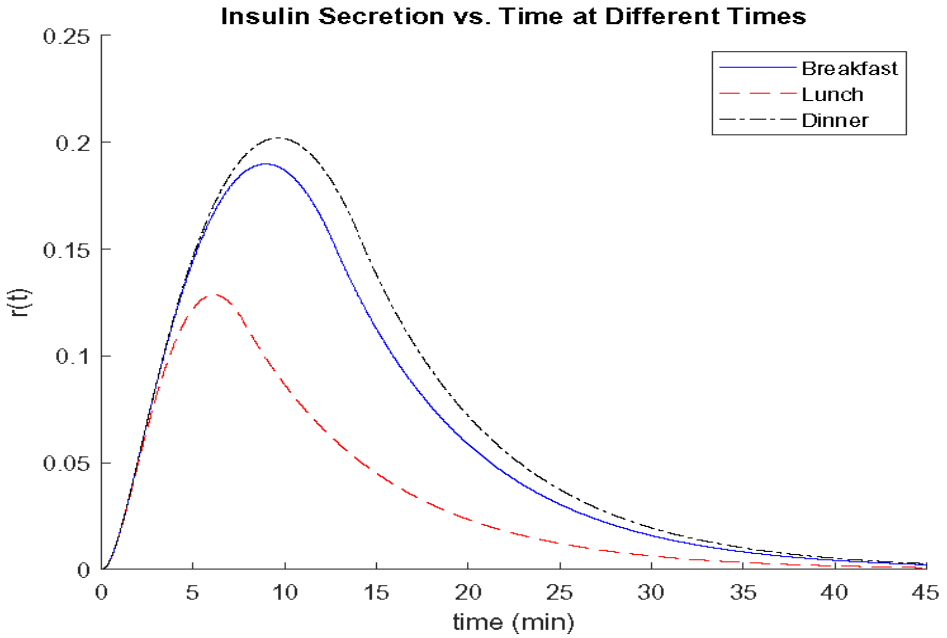

Figure 4: The same as in Figure 1 but for secreted insulin due to beta-cells.

Figure 5 presents plasma glucagon concentration and for the same parameters, constants and conditions as those for Figure 1. It can be seen from this Figure that the glucagon concentration begins at its basal value and then its values decrease with increasing the tine, which is due to the present case that the glucagon delivery is passive for the zero initial values for the absorption of the subcutaneously administered glucagon assume in the present study. The values of the glucagon concentration for all the three meals intervals appear to be the same since as can be seen from the equation (1f), the time rate of change of the plasma glucagon concentration does not depends for the other hormones concentration since the subcutaneous glucagon infusion rate w was found to be zero in the present investigation.

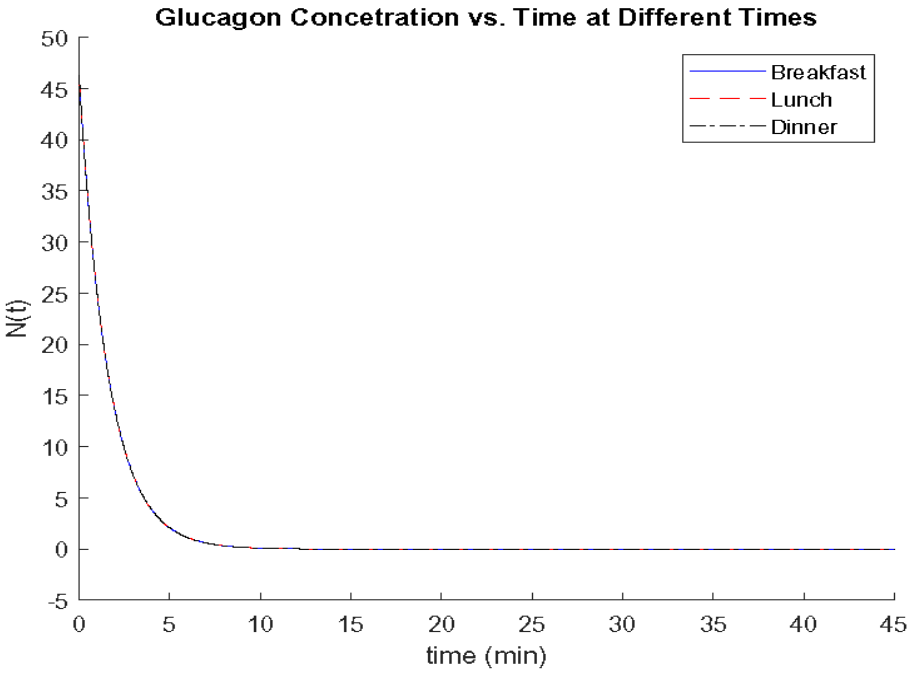

Figure 5: The same as in Figure 1 but for plasma glucagon concentration.

Figure 6 presents the same as Figure 1 but for glucagon action versus time. It is seen clearly the role of such action whose magnitude is negatively intensified, which due to the time decaying effect by the glucagon concentration that we described above. The differences of the graphs for different meal intervals are due to the value of the constant parameter that represent rate for the dynamics of the glucagon action that its value differs for different meal interval.

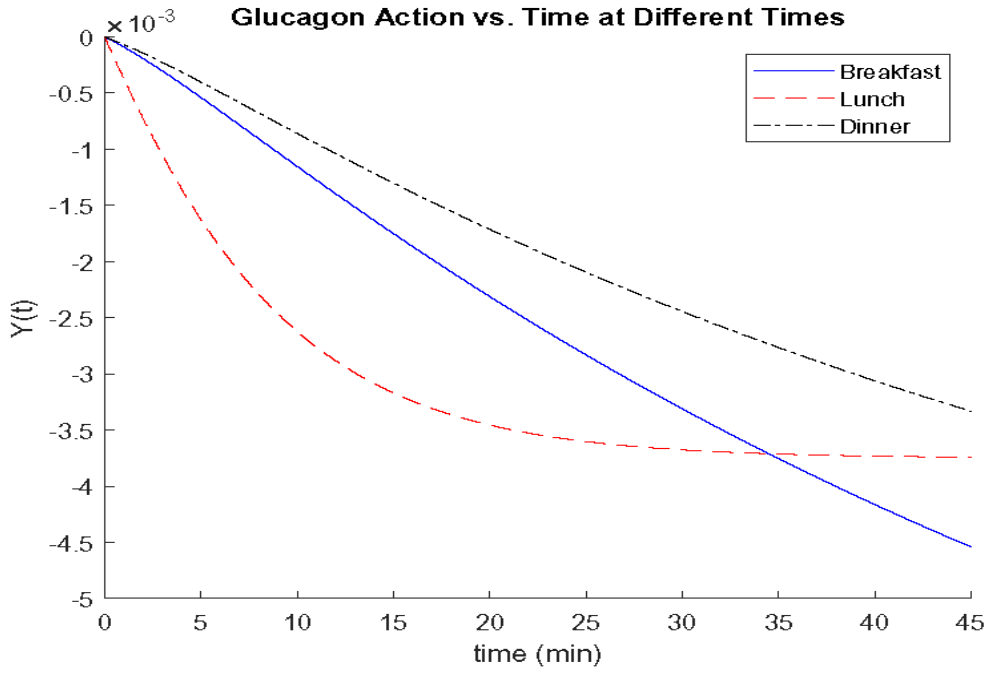

Figure 6: The same as Figure 1 but for glucagon action.

From the results presented so far, it should be noted that the roles of the nonlinear interaction terms that are more noticeable in (1a) leads to decaying the glucose concentration in time by both the insulin action and the glucagon action, which in the present case has a negative effect to produce glucose.

From the results presented by Figures 1-6, it can be seen that for relatively larger values of the four parameters that represent kinetics of the insulin action, insulin sensitivity, rate for glucagon action dynamics and glucagon sensitivity, which are a lunch time, lead to mostly smaller values of hormones concentrations and, in particular, smaller values of the glucose concentration. Relatively moderate values of the first three of these parameters, which are at dinner time, lead to mostly larger hormones concentrations. Relatively smaller values of the first three of these parameters, which are at breakfast time, lead to mostly moderate values of the hormones concentration.

In the second part of the present results, we consider three sets of data that in [2] were called subjects 117, 126, and 128. We refer to each of there as a patient and make use of their data at dinner time. Table 2 below provides values of the parameters and constants for this part of our calculation.

Table 2: Parameters and constants for three patients-117, -126 & -128 at one time interval

Parameters & Constants	Patient-117	Patient-126	Patient-128
P_1	0.014	0.014	0.014
P_2	0.012	0.057	0.0048
P_3	$9.276\ e^{-6}$	$1.288\ e^{-5}$	$4.032\ e^{-6}$
P_4	0.0039	0.0039	0.0039
P_5	79.035	79.035	79.035
P_6	0.265	0.265	0.265
P_7	0.017	0.022	0.0108
P_8 /P_7	0.000138	0.0000896	0.000119
P_9	0.62	0.383	0.735
I_b	11.01	19.78	10.03
N_b	46.30	48.13	59.23
G_b	100	100	100

Figure 7 presents plasma glucose concentration versus time for three patients at dinner time interval and for the parameters and basal values that are given in table 2. It can be seen from this Figure that initially the blood glucose is raised up at the same rate for the three patients, but shortly afterward the glucose concentration decrease with increasing time due to the insulin effect, and the rate of decrease with respect to time of the glucose is notably higher for the patient-117 than those for the

other two patients which is turns out to be due to the higher amount of the insulin action.

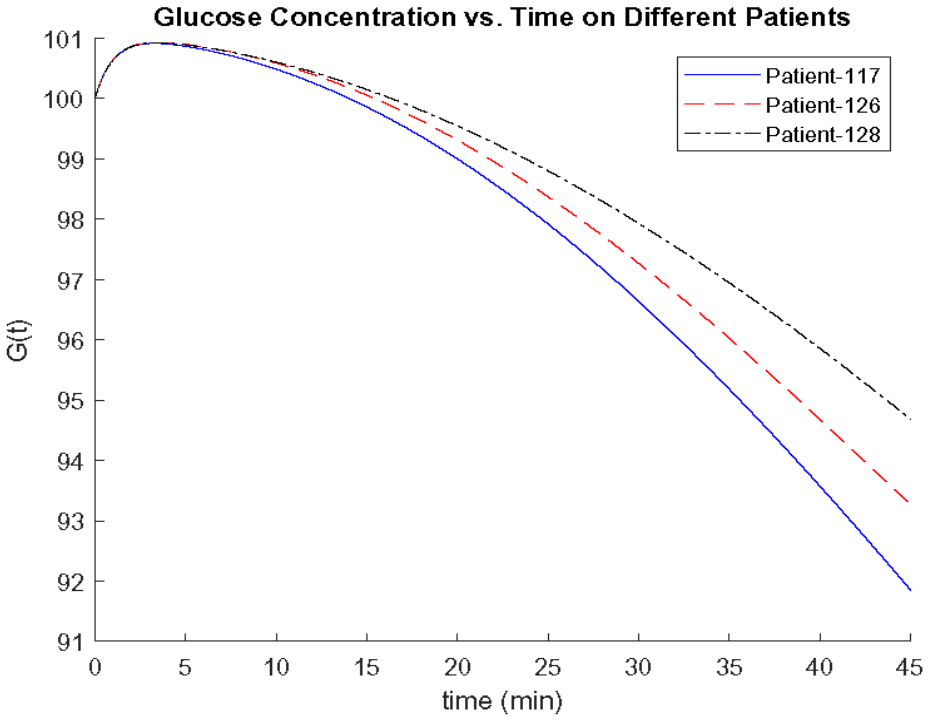

Figure 7: Blood glucose concentration versus time for the three patients and for the parameters and basal values the same as those listed in the Table 2.

Figure 8 presents the same case with parameter and basal values as those given in Figure 7 but for plasma insulin concentration. It can be seen from this Figure that the values of the insulin concentration for the patient-126 is notably higher than those for the other two patients, which is due to the higher basal value for this patient. It is also seen that for sufficiently large values of the time variable the insulin concentration for the patient-117 is smaller as compare with the values for the other patients that is in agreement with the results shown in Figure 7.

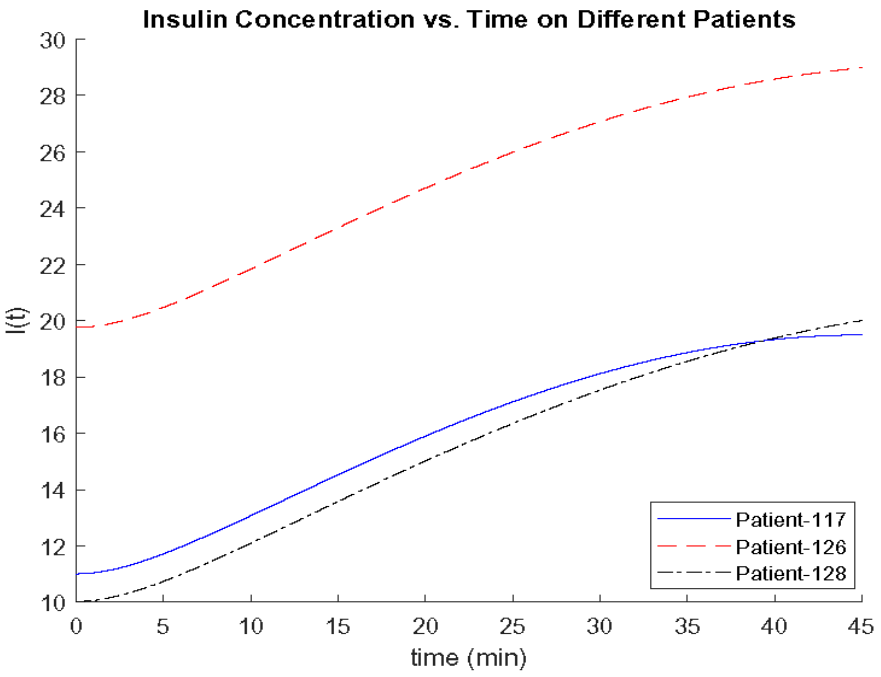

Figure 8: The same as Figure 7 but for plasma insulin concentration

Figure 9 presents insulin action versus time for the three patients and the same parameter and basal values as those described for Figure 7. It can be seen from this figure that in analog to the results presented in Figure 7 for the plasma glucose, the insulin action for the patient-117 actually dominates over those for the other two patients for sufficiently large time.

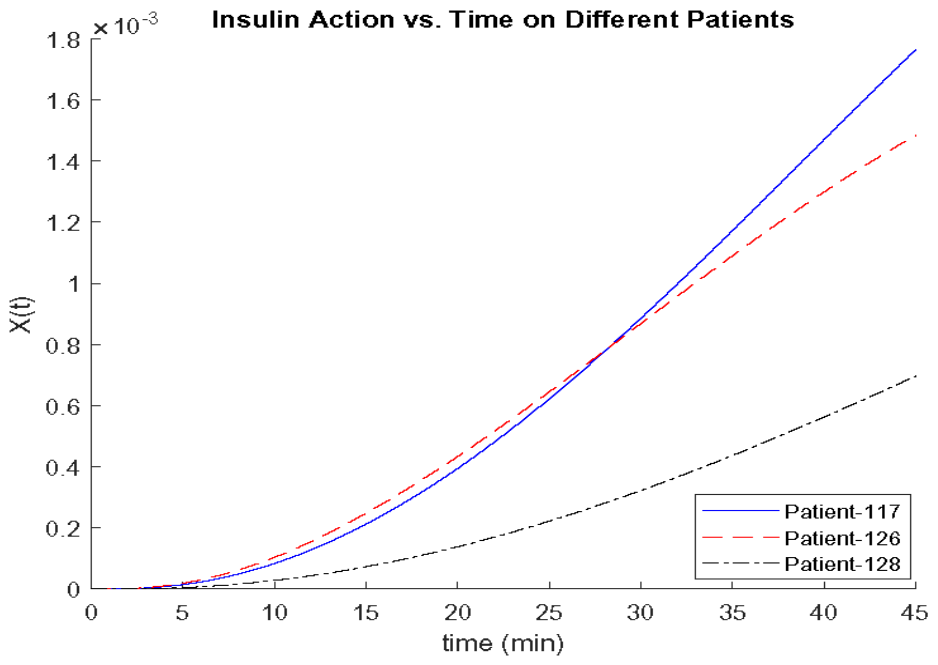

Figure 9: The same as in figure 7 but for insulin action

Figure 10 presents secreted insulin by the pancreatic beta-cells for the three patients versus time and for the same parameter and basal values as those for Figure 7. As be seen in this Figure that the insulin secretion for each patient starts to increase, reach a maximum at a relatively small value and then decrease with increasing time until it is basically reaches its zero value. The value of the insulin secretion for the patient-117 is mostly smaller than those for the other two patients, which is reasonable due to the smaller plasma glucose concentration for this patient.

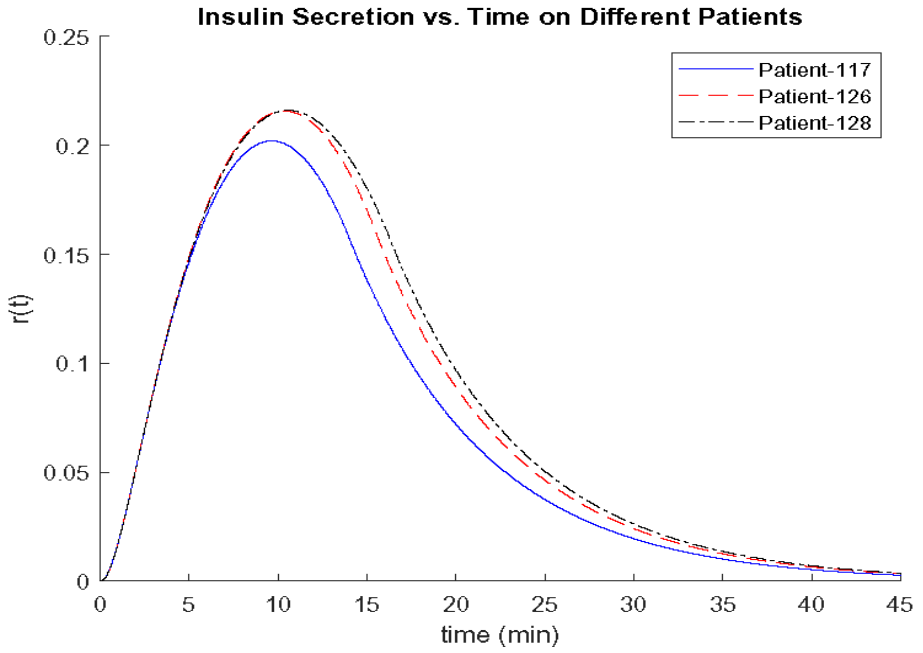

Figure 10: The same as Figure 8 but for insulin action

Figure 11 presents the plasma glucagon concentration versus time for the same three patients, parameters and basal values as those for Figure 7. It can be seen from this Figure that due to the glucagon role in the present case, the plasma glucagon concentration for each patients decays rapidly with time. The value of the glucagon concentration for all the three patients eventually becomes the same regardless of the actual basal values.

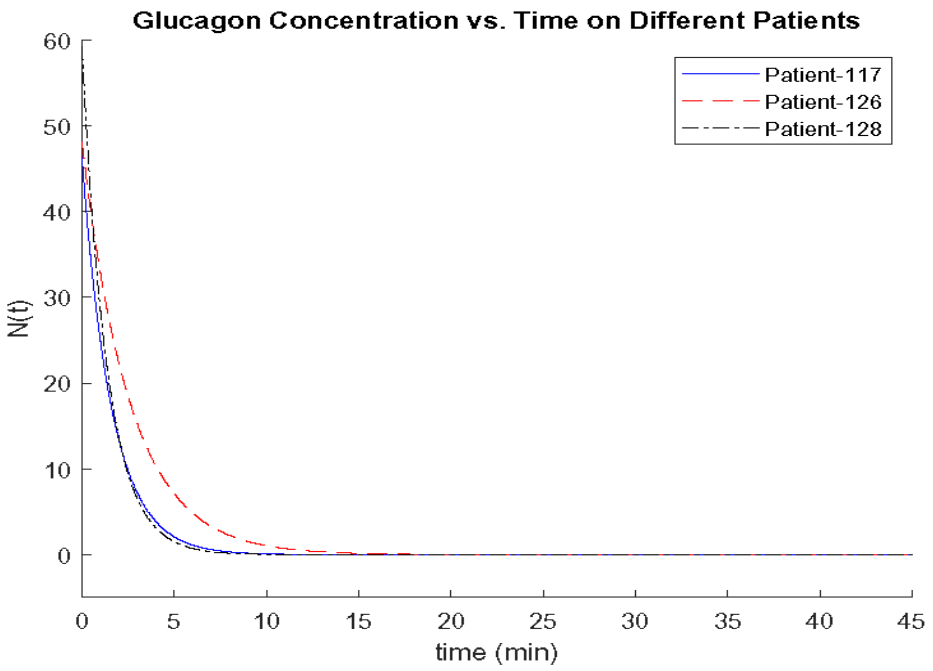

Figure 11: The same as in Figure 7 but for plasma glucagon concentration

Figure 12 present glucagon concentration versus time for the same three patients, parameters and basal values as those described for Figure 7. As can be seen from this Figure that the glucagon action is negative for each patient but has the largest magnitude for the patients-117, which is due to the fact it has highest decaying rate for rate of decrease of the glucagon concentration.

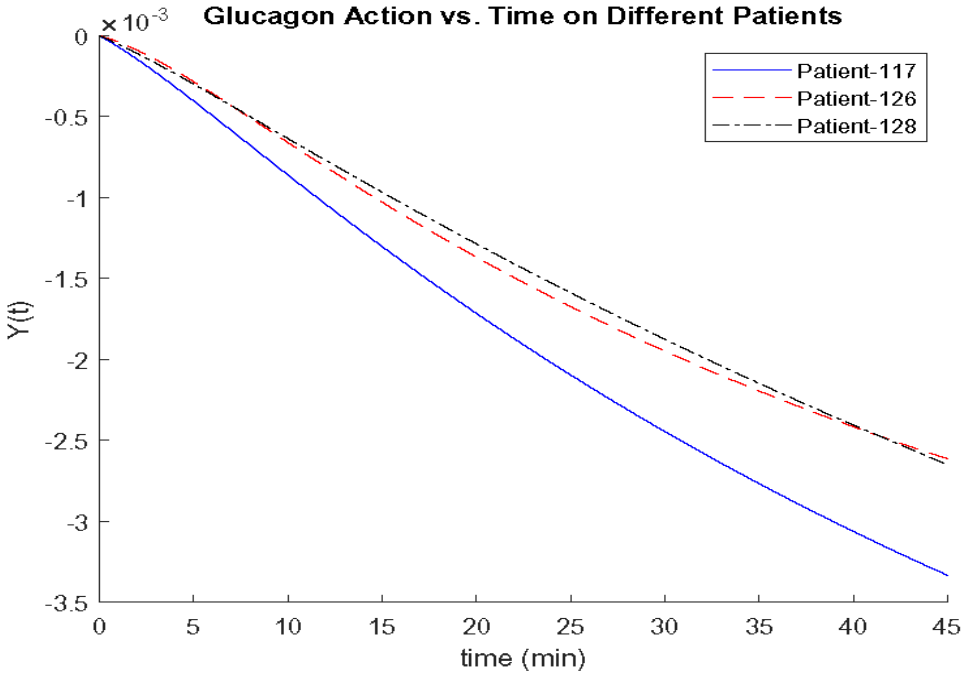

Figure 12: The same as in Figure 7 but for glucagon action.

From the results presented by Figures 7-12, we find, in particular, that for moderate values of the parameters that represent kinetics of insulin action, insulin sensitivity and constant rate of glucagon action dynamics, plasma glucose concentration is relatively small. For relatively smaller values of these parameters, blood glucose is somewhat larger. For relatively similar basal values for the glucose and insulin concentration, relatively larger values of these parameters, as well as larger glucagon sensitivity, lead to smaller plasma glucose.

4. Concluding Remarks

We investigated the nonlinear dynamics of the blood hormones regulatory system in the presence of the secreted insulin by the pancreatic beta cells using the time evolution of a system of nonlinear ordinary differential equations that represent time evolution of the blood hormones for the quantities that are for the plasma glucose concentration, plasma glucagon concentration, glucagon and insulin actions in the presence of the beta cells effect and plasma insulin concentration. Aside from the dynamics played by the investigated blood hormones, our other goal has been to determine effects of various parameters that are involved in such blood hormones system versus different diabetes patients in order to uncover parameter values that can make such system relevant to patients with lower health problems. Using both theoretical and numerical methods, we determined these quantities versus time

variable, under different conditions that admit analytical solutions, and for different values of the parameters that can represent one or more than one types of patients with different health conditions. For the case of one patient alone examined at different times of a single day or the case of three patients examined at a given time interval, we found, in particular, that for patients with relatively similar basal values, relatively larger values of the parameters that represent kinetics of the glucose concentration, insulin sensitivity, constant rate of glucagon action dynamics and glucagon sensitivity, can lead to relatively lower values of the glucose concentration. During our investigation of such nonlinear dynamics of hormones, we noticed that as the glucose concentration becomes higher than its basal value, the insulin action increases as an attempt to reduce the glucose concentration in the blood, so that the plasma glucose reaches its peak value rather soon and thereafter it decreases with increasing time variable.

Future investigation can include analyzing the nonlinear dynamics of the hormones in addition to those that are for the blood glucose, insulin and glucagon action in order to determine the results on many diabetic patients with different conditions and to determine the more definite and accurate results for the roles and influences of different parameters of the governing modeling system for the hormones that, in particular, reduces the glucose levels in the bloodstream of diabetic patients.

About comparison of the present work with those of somewhat related work by other authors, we considered the work due to [4, 2-4]. Hassan et al. [4] considered the minimal model due to Bergman and Cobelli [1] and used a controlling approach for insulin delivery. However, in contrast of the present work, these authors did not take into account the delivered energy, such as one due to consumed food or involved in a competitive sport, to the patients for their actual results and, in addition, did not include glucagon hormone and also did not consider the governing equation for the secreted insulin due to the pancreatic beta cells.

Herrero et al. [2] did some composite modeling as an extension of the minimal model to include the glucose, insulin and glucagon hormones. However, in contrast to the present work, they did not include the effect due to a delivered energy such as one involved in a competitive sport, and they also did not include the governing equation for the secreted insulin due to beta-cells. In addition, their main goal was to do some testing of their model, but they did not provide the roles of the parameters of their model on the blood hormones such the plasma glucose.

Mitsis et al. [3] 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 include the glucagon hormone as well as did not 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 delivered external energy into in their Volterra model.

It is important to note that our present work and goals were totally different from those in the related work that were described above [2-4]. In addition to our first main goal to describe and present the nonlinear time-dependent evolution of

dynamics of blood hormones, our second main goal has been to detect particular domain for some main parameters of the patients, which are measurable by the diabetes patient's blood examination [10], for which glucose concentration in the patient's blood plasma retains values as the case of normal person or at least the plasma glucose be control effectively. Then such approach can open a new and effective way to potentially eliminate the diabetes illness if the values of such measurable parameters can lie in those detected domains that we referred to earlier. In addition, knowing such health recoverable domains of the patient's parameters can advance understanding to design effective transplant organs that can be used to replace the unhealthy and damaged organs in the diabetes patients' bodies.

Our present results about the nonlinear dynamics of some blood hormones and the roles played by the parameters of the governing modeling system can provide better understanding of the roles of the blood hormones in the diabetes' patients as well as can stimulate future investigations to construct other modeling systems that include additional blood hormones that can also advance biotechnological aspects in related areas such as design and production of transplants of an internal organ to be placed in the diabetes patients' bodies where such original organ is not workable anymore.

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References

[1] Bergman, R. N. and Cobelli, C. (1980). Minimal modeling, partition analysis and the estimation of insulin sensitivity, Fed. Proc. 39, 110-115.

[2] Herrero, P., Georgiou P., Oliver N., Reddy M., Johnston D. and Toumazou C. (2013). A composite model of glucagon-glucose dynamics for in silico testing of bihormonal glucose controllers, Journal of Diabetes Science and Technology, 7(4), 941-951.

[3] Mitsis, G. D., Markakis, M. G. and Marmarelis, V. Z. (2009). Nonlinear modeling of the dynamic effects of infused insulin on glucose: comparison of compartmental with Volterra models, IEEE Transactions on Biomedical Engineering, 56(10), 2347-2358.

[4] Hassan, F. U., Adil, M., Khaqan, A., Shuja, S., Tiwana, M. I., Hassan, Q. U. and Riaz, R. A. S. (2017). Closed loop blood glucose control in diabetics, Biomedical Research, 28(16), 7230-7236.

[5] Bergman, R. N., Ider, Y. Z., Bowden, G. R. and Cobelli, C. (1979). Quantitative estimation of insulin sensitivity, Am. J. Physiol. 236, E667-E677.

[6] Kwach, B., Ongati, O. and Simwa, R. (2011). Mathematical model for detecting diabetes in the blood, Applied Mathematical Sciences, 5(6), 279-286.

[7] Bergman, R. N., Bortolan, G., Cobelli, C. and Toffolo, G. (1980). Identification of a minimal model of glucose disappearance for estimating

insulin sensitivity, In Proceedings of the 5th IFAC Symposium on Identification and System Parameter Estimation (R. Isermann, Ed.), Pergamon, Oxford, 2, 883-890.

[8] Pontryagin, L. S., (1962).Ordinary differential equations, Addison-Wesley,

[9] U. M. Ascher, U. M. Mattheij and R. D. Russell, Numerical Solution of Boundary Value Problems for Ordinary Differential Equations, SIAM, Philadelphia, USA, 1995.

[10] Ni, T. C., Ader, M. and Bergman, R. N. (1997). Reassessment of glucose effectiveness and insulin sensitivity from minimal model analysis: A theoretical evaluation of the single-compartment glucose distribution assumption, Diabetes, 46, 1813-1821.