Mathematical Model of ingested glucose in Glucose-Insulin Regulation

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Abstract

Here, we develop a mathematical model for glucose-insulin regulatory system. The model includes a new parameter which is the amount of ingested glucose. Ingested glucose is an external glucose source coming from digested food. We assume that the external glucose or ingested glucose decays exponentially with time. We establish a system of three linear ordinary differential equations with this new parameter, derive stability analysis and the solution of this model.

Keywords

Mathematical model, Diabetes mellitus, Linear system, Ingested glucose, Glucose tolerance test, Natural time period, Stability analysis.

1 Introduction

Glucose which we get from food is very important for the human body because it is like fuel and energy source for cells as well as the human body. However diabetes is a condition when blood glucose level exceeds the normal range (75 -110 mg/dl) for a long period of time. In 2017, 4 million people died due to diabetes and approximately 425 million adults in the world had diabetes. Statistics says that by 2045 the number of people with diabetes will rise to 629 million. More than 1,106,500 children have type 1 diabetes and more than 21 million births are affected by diabetes during pregnancy (2017). Around 352 million people have risk to develop type 2 diabetes [1]. India was ranked up from 11th (2005) to 7th (2016) due to number of deaths by diabetes and there are 70 million people who suffered from diabetes and statistics says these numbers will grow more than double in the next decade [2]. For normal person blood glucose level reaches to a homeostasis with the help of two types of hormones, first which reduces blood glucose level like Insulin, Amylin, Somatostatin and second which raises blood glucose level like Glucagon, Epinephrine (adrenaline), Growth Hormone, Thyroxine [3]. However when there is a disorder in secretion of Insulin or cells becomes resistant of Insulin or both, then lower amount of glucose reaches to the cells and blood glucose level is very high than fasting blood glucose level for a long period of time. Since the lower amount of glucose reaches the cells, body weakens and person become diabetic [4].

There are mainly three types of diabetes :

- **Type 1 diabetes mellitus** - Type 1 diabetes mellitus previously known as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". Almost 10% of worldwide diabetics have type 1 diabetes and most of them are children. This type of diabetes caused due to deficiency of insulin in blood. Feeling very thirsty, urinating frequently, feeling very tired, weight loss, constant hunger are the main symptoms of type 1 diabetes. [5, 6, 7]

- **Type 2 diabetes mellitus -** Type 2 diabetes mellitus previously known as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult onset diabetes". Almost 90% of worldwide diabetics have type 2 diabetes and most of them are adults. This type of diabetes is caused due to the insulin resistance in the cells of the body (may be due to problem in insulin receptors in the cells). Symptoms are almost similar as type 1 diabetes. However people who suffers from type 2 diabetes are often obese. [5, 6, 7]

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- **Gestational diabetes -** Gestational diabetes is a type of diabetes which develops in some women when they are pregnant. Most of the time, this type of diabetes goes away after the baby is born. However they and their children have increased risk of type 2 diabetes. Gestational diabetes is mainly diagnosed through parental screening rather than through symptoms. [5, 6, 7]

Mathematical models are very important to understand the dynamic behavior of complex biological systems. There are various mathematical models, statistical methods and algorithms to understand different aspects of diabetes. Models can be classified between two categories :

- **Clinical models** - Clinical models are developed to understand a disease more accurately so that we can find a better cure of it. There are various existing models for diagnostics like GTT (glucose tolerance test), IVGTT (intravanous glucose tolerance test), OGTT (oral glucose tolerance test), FSIVGTT (frequently sampled intravenous glucose tolerance test). [4, 8, 9]

- **Non-clinical models -** Non-clinical models are developed from the partial knowledge of the system. There are various non-clinical models to understand insulin-glucose dynamics and also there are many different types of non-clinical models. [4, 8, 9]

Since diabetes is very complex in nature, these models needs to be upgraded with respect to the experimental knowledge. Here we present a realistic model by considering a new parameter which represents ingested glucose (External glucose which is acquired from intake food).

The paper is arranged in the following way : importance of glucose and insulin and their role in the human body, discussion of the previous model (briefly) and the new model, analysis of stability and calculation for model, model fitting of a data-set and finally concluding remarks.

2 Glucose-Insulin dynamics in the human body

In this section we will discuss briefly, how glucose-insulin plays an important role in the human body. We start with a simple block diagram which represents importance of glucose in the human body.
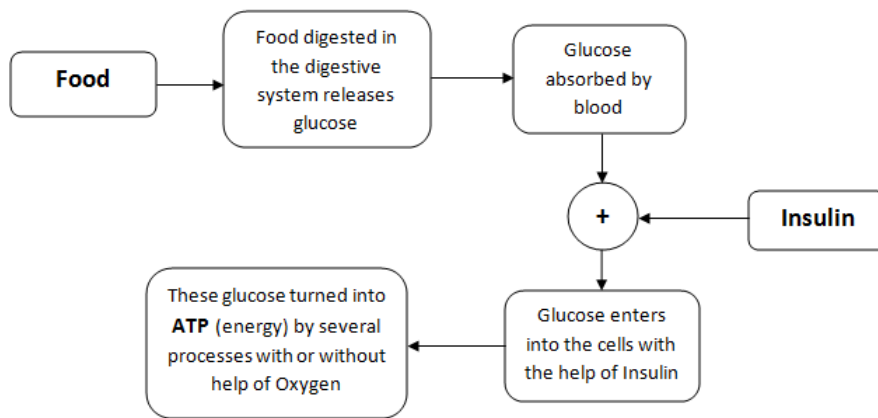

Figure 1: Block diagram to show how glucose is converted to energy.

Glucose is converted to energy (ATP) in the cells by glycolysis and other processes. In some cells glucose turns into energy with the help of oxygen and in some cells it turns into energy without oxygen [10]. Also insulin is very important, because with the help of insulin glucose can enter into cells. If there is less insulin or the body cells are insulin resistant then glucose cannot enter into the cells, and it remains in the blood creating different complications [3, 6].
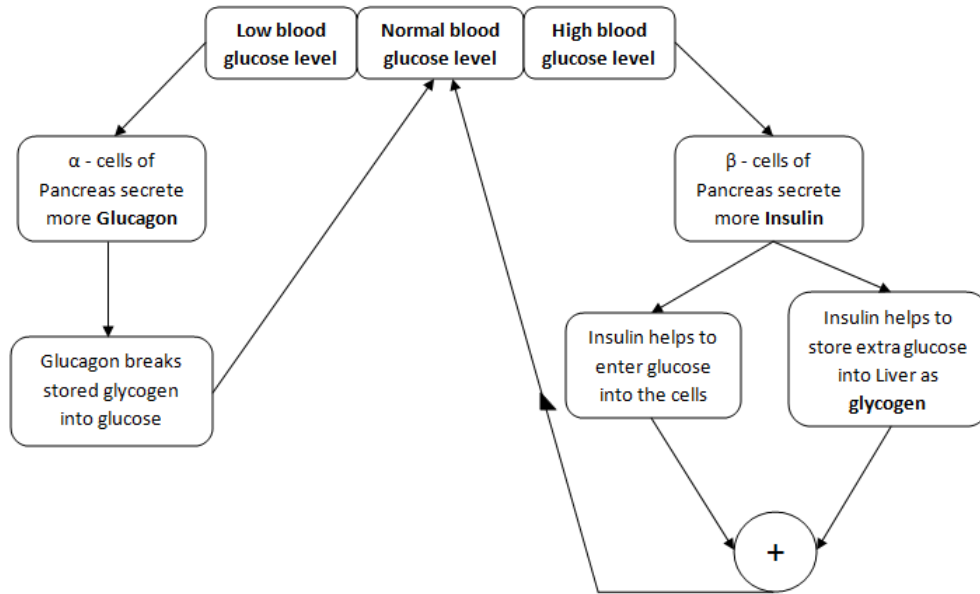
Figure 2: Block diagram to show how homeostasis is maintained for a normal person.

The human body needs to maintain homeostasis (dynamic equilibrium in human body) of blood glucose level. To maintain this homeostasis, mainly insulin and glucagon work together. Insulin is released from the β-cells of pancreas, and glucagon is released from the α-cells of pancreas. Figure 2 shows how human body maintains homeostasis with the help of these two hormones. When blood glucose level of the human body is higher than the normal level, the pancreas secretes more insulin. Insulin helps glucose to enter the cells. This also helps the extra glucose to get stored into the liver as glycogen, thus reducing the blood glucose level to maintain the homeostasis. However, when blood glucose level is low, the pancreas secretes glucagon which breaks stored glycogen into glucose and increases blood glucose level to normal level [4, 7, 11].
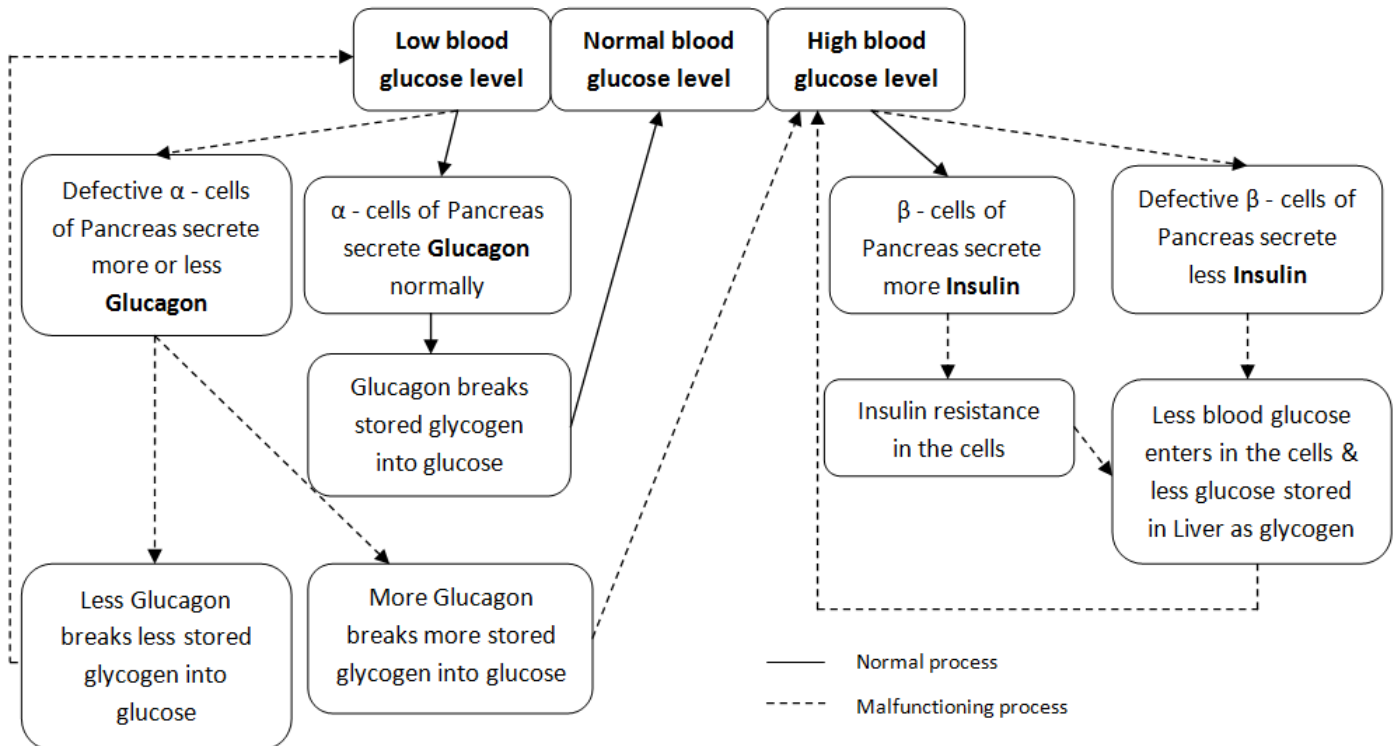

Figure 3: Block diagram to show how glucose level varies for diabetic person.

However for a diabetic person, the human body cannot maintain homeostasis of blood glucose level [Figure 3]. In type-1 diabetes, β-cells of pancreas are destroyed by ones own immune system (T-cells). Thus less insulin is produced and for this

insulin deficiency blood glucose level is high for a very long period.

In type-2 diabetes, cells of the human body becomes insulin resistant. So, insufficient amount of blood glucose enters into the cells. Also low amount of blood glucose gets stored into liver in the form of glycogen. To overcome this situation pancreas secretes excess insulin. If this excess insulin is enough to bring back blood glucose level to the normal level then the person is pre-diabetic. However if this excess insulin is not enough then the person is type-2 diabetic. Other reason for which blood glucose level can be high is due to malfunctioning α-cells of pancreas. In this case they produce excess amount of glucagon [4, 6, 7].

3   Modeling glucose-insulin dynamics

In this section we first discuss a model suggested by previous authors. Next we go on to discuss the relevant factors that we have introduced into our model.

In 1964, E. Ackerman, J. W. Rosevear and W. F. McGuckin developed a mathematical model of Glucose-tolerance test [12]. In this model they have considered $G(t)$ as blood-glucose concentration and $H(t)$ as blood-insulin concentration. Here G_b and H_b were defined as fasting blood glucose level and fasting hormone (insulin) level respectively. $D_2(t)$ and $h(t)$ were defined as difference of the blood-glucose level and blood-hormone (insulin) level from the fasting levels respectively. So, $D_2(t) = G(t) - G_b$ and $h(t) = H(t) - H_b$. The main equations used in that model are,

$$\frac{dD_2}{dt} = -a_1 D_2 - a_2 h + I,$$
$$\frac{dh}{dt} = b_1 D_2 - b_2 h.$$

Where,

a_1 =Rate constant of glucose removal independent of insulin.

a_2 =Rate constant of glucose removal dependent of insulin.

b_1 =Rate constant of insulin release due to glucose.

b_2 =Rate constant of insulin removal independent of glucose.

$I(t)$= Rate of increase of blood glucose due to absorption of glucose from intestines.

We have modified the above model taking into account the contribution of the ingested glucose in the form of an additional differential equation. We explain this model using a block diagram where various parts of the human body represented by compartments. [Figure 4]
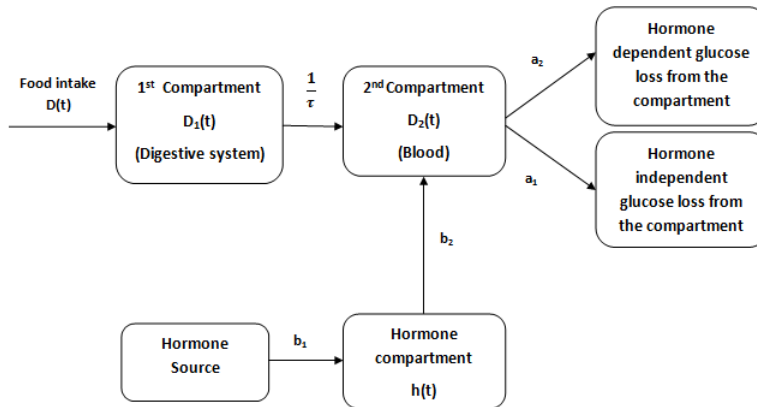

Figure 4: Diagram of simplified model of blood glucose regulatory system.

Let at time t glucose disturbance of the digestive system (1st compartment) is $D_1(t)$. In this system we assume that the fasting glucose level is zero, thus glucose level and glucose disturbance is same. Let at time t the blood (2nd compartment) glucose level is $G(t)$ and the effective hormone level is $H(t)$. By the term effective hormone level means the net effect of all hormones (like insulin, glucagon) which can increase or decrease blood glucose level. The fasting blood glucose and the effective hormone levels G_b and H_b respectively. Let, $D_2(t)$ and $h(t)$ are the disturbances of the blood glucose level and the effective hormone level at time t respectively. Thus we can write $D_2(t) = G(t) - G_b$ and $h(t) = H(t) - H_b$. [12, 13]

In this model we make following assumptions :

- Rate of decrease in glucose disturbance in digestive system is proportional to its glucose disturbance ($D_1(t)$) at time t.

- Rate of increase in glucose disturbance in blood is proportional to the glucose which enters blood from digestive system $(D_1(t))$ at time t.

- Rate of hormone independent decrease of glucose disturbance in blood is proportional to its glucose disturbance $(D_2(t))$ at time t.

- Rate of hormone dependent decrease of glucose disturbance in blood is proportional to the effective hormone disturbance $(h(t))$ at time t.

- Rate of increase in effective hormone disturbance is proportional to the glucose disturbance in blood $(D_2(t))$ at time t.

- Rate of decrease in effective hormone disturbance is proportional to the effective hormone disturbance $(h(t))$ at time t.

Using these assumptions the model equations can be written as,

$$\frac{dD_1}{dt} = -\frac{D_1}{\tau}, \qquad\qquad D_1(0) = A_G D, \tag{1}$$

$$\frac{dD_2}{dt} = \frac{D_1}{\tau} - a_1 D_2 - a_2 h, \qquad D_2(0) = 0, \tag{2}$$

$$\frac{dh}{dt} = b_1 D_2 - b_2 h, \qquad\qquad h(0) = 0. \tag{3}$$

τ =Time constant of decreasing glucose level in the digestive system, which is the total time to decrease glucose level to $1/e$ of the maximum value.

a_1 =Rate constant of the hormone independent decrease of glucose level in the blood.

a_2 =Rate constant of the hormone dependent decrease of glucose level in the blood.

b_1 =Rate constant of release of the hormone due to blood glucose disturbance.

b_2 =Rate constant for the removal of the hormone due to disturbance of the blood hormone level.

D =Amount of food that has been taken.

A_G =Percentage of glucose obtained in the body from the food that has been taken.

4 Stability analysis of this model

To determine fixed points we can write,

$$\frac{dD_1}{dt} = \frac{dD_2}{dt} = \frac{dh}{dt} = 0.$$

Substituting $\frac{dD_1}{dt} = 0$ in equation (1) we get,

$$D_1 = 0 = D_{10}. \tag{4}$$

Now making $\frac{dD_2}{dt} = 0$ and $\frac{dh}{dt} = 0$ and putting D_{10} in equation (2) we get,

$$\frac{D_{10}}{\tau} - a_1 D_{20} - a_2 h_0 = 0,$$

$$a_1 D_{20} + a_2 h_0 = 0. \tag{5}$$

From equation (3) we get,

$$b_1 D_{20} - b_2 h_0 = 0. \tag{6}$$

Solving equation (5), (6) we get,

$$D_{20} = 0 \tag{7}$$

and

$$h_0 = 0. \tag{8}$$

So the fixed point is $(D_{10}, D_{20}, h_0) = (0, 0, 0)$. Thus equations (1), (2) and (3) can be written in the matrix form as,

$$
\begin{pmatrix} \frac{dD_1}{dt} \\ \frac{dD_2}{dt} \\ \frac{dh}{dt} \end{pmatrix} = \begin{pmatrix} -\frac{1}{\tau} & 0 & 0 \\ \frac{1}{\tau} & -a_1 & -a_2 \\ 0 & b_1 & -b_2 \end{pmatrix} \begin{pmatrix} D_1 \\ D_2 \\ h \end{pmatrix}
$$

Let,

$$
\begin{pmatrix} -\frac{1}{\tau} & 0 & 0 \\ \frac{1}{\tau} & -a_1 & -a_2 \\ 0 & b_1 & -b_2 \end{pmatrix} = A
$$

Now characteristic equation is given by,

$$
det(A - \lambda I) = 0
$$

Here λ is the eigen values of matrix A. So,

$$
\begin{vmatrix} (-\frac{1}{\tau} - \lambda) & 0 & 0 \\ \frac{1}{\tau} & (-a_1 - \lambda) & -a_2 \\ 0 & b_1 & (-b_2 - \lambda) \end{vmatrix} = 0
$$

From this determinant we can write,

$$
\left(-\frac{1}{\tau} - \lambda \right) \left[(a_1 + \lambda)(b_2 + \lambda) + a_2 b_1 \right] = 0.
$$

The above equation can write into two algebraic equations as, $\left(-\frac{1}{\tau} - \lambda \right) = 0$ and $\lambda^2 + (a_1 + b_2)\lambda + (a_1 b_2 + a_2 b_1) = 0$. Hence the first eigenvalue is $\lambda_1 = -\frac{1}{\tau}$ where $\tau > 0$ so $\lambda_1 < 0$ and the other two eigenvalues are

$$
\lambda_2 = \frac{-(a_1 + b_2) + \sqrt{(a_1 - b_2)^2 - 4a_2 b_1}}{2},
$$

$$
\lambda_3 = \frac{-(a_1 + b_2) - \sqrt{(a_1 - b_2)^2 - 4a_2 b_1}}{2}.
$$

If $(a_1 - b_2)^2 > 4a_2 b_1$ then $\sqrt{(a_1 - b_2)^2 - 4a_2 b_1} < (a_1 + b_2)$. So, λ_2 and λ_3 are both negative.

If $(a_1 - b_2)^2 < 4a_2 b_1$ then $\sqrt{(a_1 - b_2)^2 - 4a_2 b_1}$ is a complex quantity. Hence λ_2 and λ_3 are both complex with negative real part.
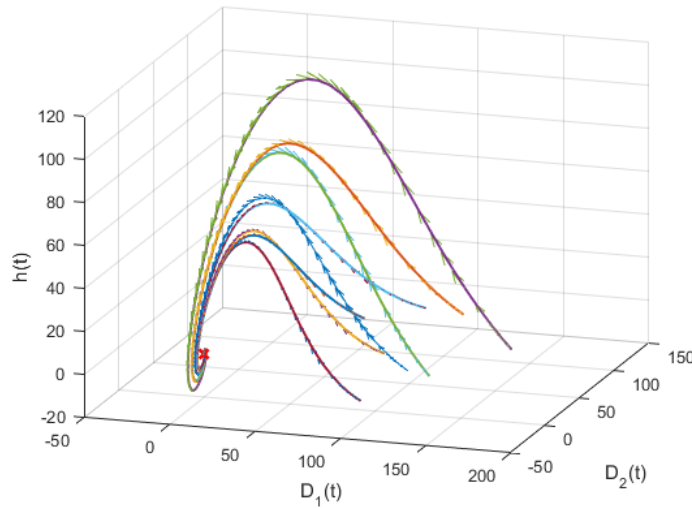
Hence the model is stable around $(0, 0, 0)$.

Figure 5: Phase portraits of these model shows it is globally stable. (0,0,0) point is represented in the plots as red ($\times$).

Figure 5 represents a three dimensional phase portrait with different initial conditions. From this plots we can see that all the trajectories converge to the point (0,0,0). Hence (0,0,0) is a stable equilibrium point and the model is globally stable.

5 Calculation of glucose level in blood

In this section we obtain a solution for blood glucose level from the model equations by considering all initial conditions. Solving equation (1) we get,

$$D_1 = A_0 e^{-\frac{t}{\tau}}.$$

Where A_0= Integrating constant. Substituting initial conditions,

$$D_1(0) = A_G D = A_0.$$

Hence,

$$D_1(t) = A_G D e^{-\frac{t}{\tau}}. \tag{9}$$

Differentiating equation (2),

$$\frac{d^2 D_2}{dt^2} = -a_1 \frac{dD_2}{dt} - a_2 \frac{dh}{dt} + \frac{1}{\tau}\frac{dD_1}{dt}. \tag{10}$$

Substituting the relation of $\frac{dh}{dt}$ from equation (3) in equation (10) we get,

$$\frac{d^2 D_2}{dt^2} = -a_1 \frac{dD_2}{dt} - a_2(b_1 D_2 - b_2 h) + \frac{1}{\tau}\frac{dD_1}{dt}.$$

After substituting relation of h from equation (2) in equation (11) and rearranging we get,

$$\frac{d^2 D_2}{dt^2} + (a_1 + b_2)\frac{dD_2}{dt} + (a_1 b_2 + a_2 b_1)D_2 = \frac{b_2}{\tau}D_1 + \frac{1}{\tau}\frac{dD_1}{dt}. \tag{11}$$

Now using, $a_1 + b_2 = 2\alpha$, which is sum of the rate of hormone independent glucose removal and the hormone removal and $a_1 b_2 + a_2 b_1 = \omega_0^2$ we get,

$$\frac{d^2 D_2}{dt^2} + 2\alpha\frac{dD_2}{dt} + \omega_0^2 D_2 = \frac{b_2}{\tau}D_1 + \frac{1}{\tau}\frac{dD_1}{dt}. \tag{12}$$

Substituting $D_1(t)$ from equation (9) we get,

$$\frac{d^2 D_2}{dt^2} + 2\alpha\frac{dD_2}{dt} + \omega_0^2 D_2 = \left(\frac{b_2 A_G D}{\tau} - \frac{A_G D}{\tau^2}\right)e^{-\frac{t}{\tau}}. \tag{13}$$

Using $C = \dfrac{b_2 A_G D}{\tau} - \dfrac{A_G D}{\tau^2}$

$$\frac{d^2 D_2}{dt^2} + 2\alpha\frac{dD_2}{dt} + \omega_0^2 D_2 = Ce^{-\frac{t}{\tau}}. \tag{14}$$

Solving equation (14),

$$D_2 = e^{-\alpha t}[A_1 cos(\omega t) + A_2 sin(\omega t)] + C_0 e^{-\frac{t}{\tau}}. \tag{15}$$

Where $\omega^2 = \omega_0^2 - \alpha^2$ and $\alpha^2 < \omega_0^2$ and $C_0 = \frac{A_G D(b_2\tau - 1)}{(\alpha\tau - 1)^2 + \omega^2\tau^2}$.

Now applying initial conditions $D_2(0) = 0$ and $\frac{dD_2}{dt}\big|_{t=0} = \frac{A_G D}{\tau}$ in equation (15) we get,

So finally we get $A_1 = -C_0$ and $A_2 = \frac{A_G D + C_0 - \alpha C_0 \tau}{\omega\tau}$.

So the disturbance in 2nd compartment is,

$$D_2 = e^{-\alpha t}\left[-C_0 cos(\omega t) + \frac{A_G D + C_0 - \alpha C_0 \tau}{\omega\tau}sin(\omega t)\right] + C_0 e^{-\frac{t}{\tau}}. \tag{16}$$

Hence glucose level in 2nd compartment is,

$$G(t) = G_b + D_2 = G_b + e^{-\alpha t}[-C_0 cos(\omega t) + \frac{A_G D + C_0 - \alpha C_0 \tau}{\omega \tau} sin(\omega t)] + C_0 e^{-\frac{t}{\tau}}. \tag{17}$$

From equation (16) we can see that the solution of $D_2(t)$ is like a oscillator with a small damping. $h(t)$ can have both positive and negative values. Positive $h(t)$ corresponds to the effective hormone level which decreases the blood glucose level. Similarly, negative $h(t)$ corresponds to the effective hormone level which increases the blood glucose level. As we see, α and ω can have many different values [12, 13]. So the crucial parameter turns out to be ω_0 which in other words is a natural time period $T_0 = \frac{2\pi}{\omega_0}$. If $T_0 < 4.0$ hours then the person is normal and if $T_0 \geq 4.0$ hours then the person is pre-diabetic [12, 13].

6 Modeling with experimental data

In this section, the blood glucose level $G(t)$ that is obtained from our model is fitted with a data-set and essential parameters of our model are estimated. The data-set represents a glucose vs time data for a normal (Subject A) and a diabetic (Subject B) person. This data-set is taken from "Modeling Diabetes" by Joseph M. Mahaffy (Math 636 - Mathematical Modeling) [16].

t in hour	Subject A	Subject B
0	70	100
0.5	150	185
0.75	165	210
1	145	220
1.5	90	195
2	75	175
2.5	65	105
3	75	100
4	80	85
6	75	90

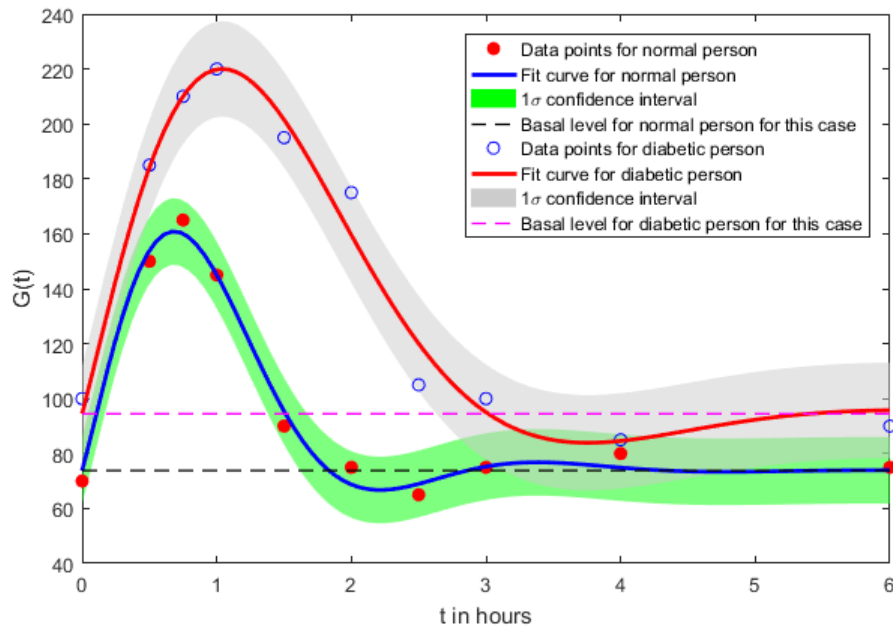Table 1: Blood glucose level data for normal (Subject A) and diabetic person (Subject B).

Figure 6: Fitted curve for normal and diabetic persons with 1σ interval.

Figure 6 shows the best fit curve with 1σ confidence interval. 1σ confidence interval confidence interval is a statistically calculated interval from a observed data-set. This interval tells us that the true value of the parameter may be lie within it. Here, 1σ confidence interval is defined as $G(t) \pm \frac{\sigma}{\sqrt{N}}$, σ=standard deviation of data and N =total number of data. If, N increases then confidence interval decreases but confidence remains same.

8

The values of the obtained parameters are,

Subject	G_b	α	ω	C_0	τ in hour
A	73.8161	1.1733	2.4128	116.4327	0.6447
B	94.4838	0.8685	1.2823	208.3634	0.6242

Table 2: Values of the fit parameters

Subject	α	ω	$\omega_0 = \sqrt{\omega^2 + \alpha^2}$	$T_0 = \frac{2\pi}{\omega_0}$ in hour
A	1.1733	2.4128	2.6829	2.3418
B	0.8685	1.2823	1.5487	4.0569

Table 3: Values of main parameters ω_0 and T_0

$G_b=$ The fasting blood glucose level. It can vary person to person.
$\alpha=$ Decay parameter of the damped oscillator.
$\omega=$ Angular frequency of damped oscillator.
From Table 2 we can see that value of both α and ω for diabetic person is less than the normal person.
$\tau=$ Time constant of decreasing glucose level in the digestive system, which is the total time to decrease glucose level to $1/e$ of the maximum value. From Table 2 we can see that the value of this parameter is nearly equal for both normal and diabetic person.
$\omega_0=$ Natural angular frequency of damped oscillator.
$T_0=$ Natural time period of damped oscillator. From Table 3 we can see that value of T_0 for normal person is small than the diabetic person.
Here we plot the data-set and fit the function with 1σ confidence interval [Figure 6]. Values of T_0 of Subject A and Subject B are 2.3418 hours and 4.0569 hours respectively [from Table 3], which indicates Subject A is normal and Subject B is mild diabetic. Thus it can be seen that the value of T_0 determines whether a person is pre-diabetic (for which $T_0 \approx 4.0$ hours) or not. This result nearly matches with the earlier model result but more accurate than the previous result to predict pre-diabetic condition. Also we found the value of a important parameter τ which is not included in the previous models. This parameter tells us how fast glucose enters in the blood from the digestive system. This parameter should be independent of the diabetes or blood glucose level at any time. From Table 2 we can see that the value of τ is nearly equal for both normal and diabetic person. So, τ is independent of diabetes and does not depend on blood glucose level.
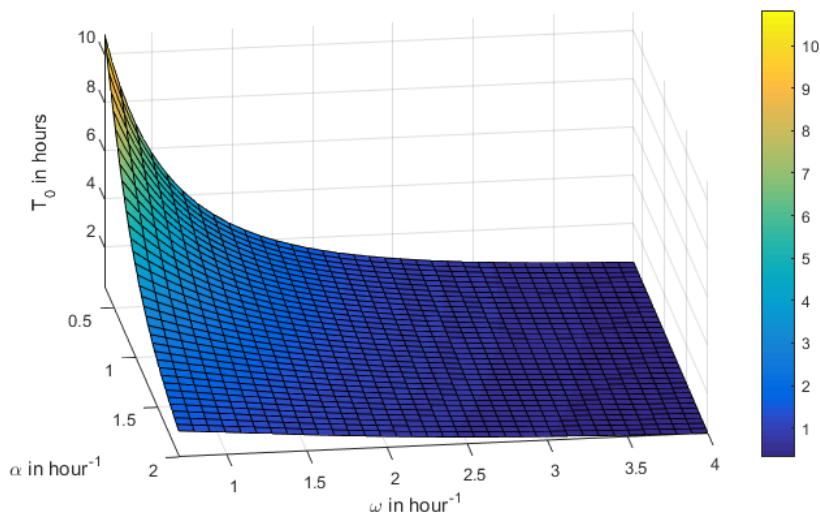

Figure 7: Three dimensional surface plot with different α and ω.
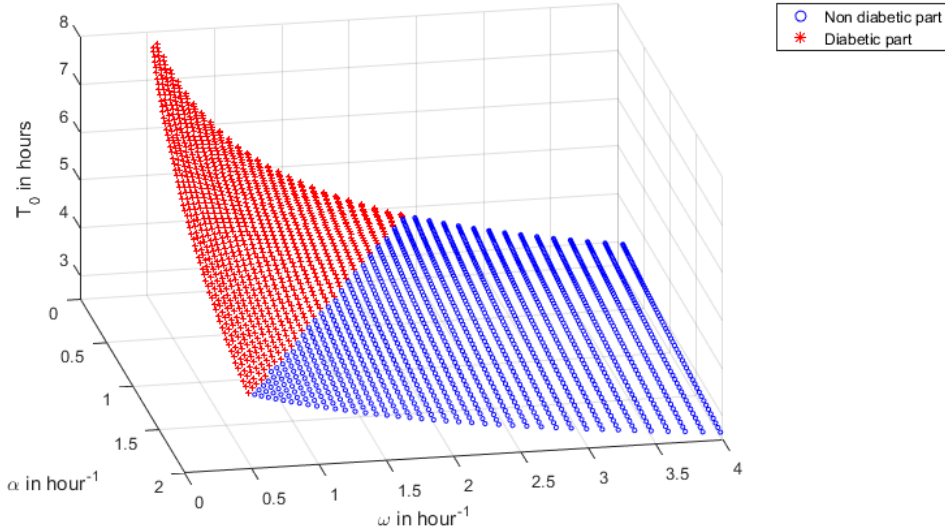
Figure 8: Three dimensional simulated scatter plot.

Figure 7 represents a three dimensional simulated surface plot which shows how T_0 varies with the possible range of α and ω. We also see as α and ω decreases, T_0 increases sharply after a point. High T_0 means that blood glucose level remains high for a long interval of time, which is the sign of a pre-diabetic case. Figure 8 represents a three dimensional simulated scatter plot. Here, blue dots represent normal cases (for which $T_0 < 4.0$ hours) and red dots represent pre-diabetic or diabetic (for which $T_0 \geq 4.0$ hours) cases. This plot shows that there exists two completely separate regions for normal and diabetic cases. It also shows that there is a large range of α and ω which can vary person to person.

7 Discussion and Conclusion

In this paper, we have modified an existing model to a more realistic one by considering ingested glucose level, which is described by an additional ordinary differential equation. Here we have assumed that the externally ingested glucose decreases exponentially with time by increasing the blood glucose level, which is modeled by a parameter τ which describes how fast ingested glucose decreases. We have found that the model is globally stable around the fixed point $(0,0,0)$. The solution imitates the behaviour of a damped harmonic oscillator and it converges to basal values normally observed in the human body. After fitting this relation to an available data-set, various fit parameters were obtained. Using these, the value of the parameter T_0, which is the natural time period of a damped oscillator, was found. To conclude, we would like to point out that the most important improvement of this model over earlier models is it's ability to predict the vulnerability of a person to be diabetic in the future. We have deduced that T_0 is less than 4 hours for a normal person and for a diabetic person, this time period is greater than 4 hours, which also matches the earlier established model predictions. Thus if a person has this natural time period T_0 of value around 4 hours, then it can be concluded that the person is susceptible to diabetes in future (pre-diabetic). However, in this model we consider that pancreas responded instantly with the blood glucose disturbance and hormone disturbance. But a small time delay of pancreatic response due to these disturbances will be more practical [32]. We can modify our model by considering this time delay. So, there is a lot of scope for further development of this model, which can enable precise and better control of this pre-diabetic stage and thus modify the quality of life of a human being.

Acknowledgment

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