Mathematical model for blood glucose detection of diabetes

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Abstract

Our body contain a number of hormones, including glucagon, growth hormone, insulin, epinephrine, sometimes known as adrenaline, glucocorticoids, and thyroxine, which regulate blood sugar levels. In this paper, we use compartment modeling to detect diabetes in blood. Nonlinear Least Squares Method were used to estimate the unknown parameters of the differential equations that describe the glucose-insulin dynamics.

Keywords : diabetes, blood glucose, mathematical model, compartment model.

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1 Introduction

Diabetes is a syndrome of excessively high blood sugar levels brought on by a malfunctioning metabolism, which is typically brought on by a combination of inherited and environmental factors. The two most common forms of diabetes are Type 1 diabetes and Type 2 diabetes which can be categorized as follows.

- Type 1 diabetes is due to diminished production of insulin, this is also called insulin - dependent diabetes or juvenile-type diabetes. The patient of type 1 diabetes is considered hypoglycemic.
- Type 2 diabetes is caused by the decreased insulin production by the beta cells of pancreas and an increased insulin resistance by peripheral tissues. This causes hyperglycemia, or high blood glucose level in the body. Therefore they are not insulin dependent but may require some exogenous form of insulin to help maintain normal blood glucose levels. Insulin is needed by the peripheral tissues to use the glucose in the body for energy. Without insulin the body is unable to use glucose causing body cells to starve and may result in complications in other parts of the body.

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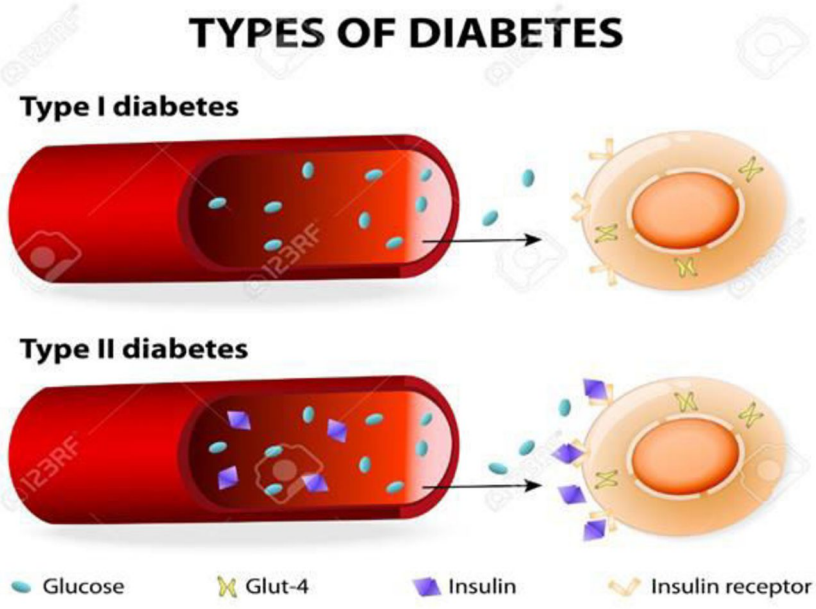
TYPES OF DIABETES
Type I diabetes
Type II diabetes
Glucose
Glut-4
Insulin
Insulin receptor

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Differential equation is a mathematical concept that perfectly explains mathematical modeling. Many mathematicians and biologists have used differential equations to model diseases and epidemics such as the model of lake pollution, bacteria growth, enzyme kinetics and many more. One area of modeling that involves the interaction of two separate variables is called compartment models.

Diabetic patients require supplement of insulin in the form of regular injections and tablets in addition to modified diet to regulate glucose input, Krimmel et al [6]. Glucose plays an important role in the food metabolism of any vertebrate tissue since it is a source of energy for all tissues and organs, Middleman [7].

In section 2, we formulate the compartment model and determine the signs of constants. In section 3, we determine the solution and in section 4, we estimate the parameter and analyze the results. Finally, we provide conclusion with recommendations for further study.

2 Formulation and signs of constants

2.1 Formulation of the model

Compartment models are often used to describe transport of material in biological systems. A compartment model contains a number of compartments, each containing well mixed material. Compartments exchange material with each other following certain rules. Material can either flow from one compartment to another, it can be added from the outside through the source, or it can be removed through the drain. Most compartment models have more that one compartments and equations for such a model are obtained by describing a conservation laws for each compartment.

A compartment model could represent an ecological system where the material could be energy, the compartments could represents different species of animals and plants, and the flow between compartments could account for uptake and loss of food(or energy). Compartment model also arise in physiology, where the material could be oxygen that is transported with the blood between different organs (compartments) in the body. In this work the materials are glucose and insulin and the compartment is the blood.

Glucose, an end product of carbohydrate digestion is converted into energy in the cells of the body. A hormone secreted by the pancreas facilitates the absorption of glucose by cells other than those of the brain and nervous system. A delicate balance is normally maintained between the amounts of glucose and insulin in the bloodstream. If the insulin concentration is too low then too little glucose is absorbed from the bloodstream; the unabsorbed glucose is then lost in the urine along with other nutrients. If on the other hand, the insulin

concentration is too high, then too much glucose is absorbed by cells other than those of the brain and nervous system; lack of glucose available to the cells of the brain then impairs its function.

The main features that a model of the glucose-insulin regulation system must take into account are as follows:

1. A rise in concentration of glucose in blood stream results in liver absorbing more of the glucose, which converts and stores as glycogen, a drop in the concentration of glucose reverse the process.

$$\frac{dg}{dt} = -ag,$$

where g represents glucose concentration, t represents time and a, a constant.

2. A rise in concentration of glucose in the bloodstream stimulates the pancreas to produce insulin at a faster rate, a drop in the glucose concentration lowers the rate of insulin production.

$$\frac{dg}{dh} = -bh,$$

where h represents insulin concentration and b, a constant.

3. There is an external rate at which the blood concentration is being increased.

$$\frac{dg}{dt} = J(t),$$

4. A rise in the concentration of insulin in the bloodstream enables the glucose to pass more readily through the membranes of the cells in the skeletal muscle, resulting in greater absorption of glucose in the blood stream.

$$\frac{dh}{dt} = cg,$$

where c, a constant.

5. Insulin produced by the pancreas, is constantly being degraded by the liver.

$$\frac{dh}{dt} = -eh,$$

where e, a constant.

The general model is written as

$$\frac{dG}{dt} = f_1(G, H) + J(t) \quad (1)$$

$$\frac{dH}{dt} = f_2(G, H) \quad (2)$$

where $J(t)$ is ingested source of glucose, f_1 and f_2 are functions of G and H. The homeostasis assumption means that we want to consider a local perturbation of the dynamical system away from equilibrium. Thus, we create the perturbation variables.

$$\begin{aligned} g(t) &= G(t) - G_0 \\ h(t) &= H(t) - H_0 \end{aligned}$$

G_0 and H_0 are equilibrium values for blood glucose and insulin concentration. $G(t)$ and $H(t)$ are displacement of glucose and insulin from their respective from their respective base values. Thus,

$$f_1(G_0, H_0) = f_2(G_o, H_0) = 0.$$

The general model (1) and (2) is expanded to linear terms yielding the linearized perturbation model given by

$$\frac{dg}{dt} = \delta \frac{f_1(G_0, H_0)g}{dg} + \delta \frac{f_1(G_0, H_0)h}{dh} \tag{3}$$

$$\frac{dh}{dt} = \delta \frac{f_2(G_0, H_0)g}{dg} + \delta \frac{f_2(G_0, H_0)h}{dh} \tag{4}$$

where $g(t)$ and $h(t)$ now represent the linearized perturbed variables. By examining the partial derivative of the equation (3) and (4) and simplifying we obtain

$$\frac{dg}{dt} = -ag - bh + J(t) \tag{5}$$

$$\frac{dh}{dt} = -ch + eg \tag{6}$$

where a, b, c, e are constants.

2.2 Signs of constants

To determine how the solutions of the differential equation behave, one must have some information about the coefficients a, b, c and d.

- From model component (1) it follows that $\frac{dg}{dt}$ is negative. for $g > 0$ and $h = 0$, since the blood glucose concentration will be decreasing through tissue uptake of glucose and the storing of excess glucose in the liver in the form of glycogen.Then in turn makes the constant a positive.
- From model component (2) it follows that $\frac{dg}{dt}$ is negative since a positive value of h tends to decrease blood glucose level by facilitating tissue uptake of glucose and by increasing the rate at which glucose is converted to glycogen. This makes b a positive.

- Model component (4) depicts that $\frac{dh}{dt}$ must be positive since a positive value of g causes the endocrine glands to secrete those hormones which tend to increase H. This makes the constant e positive also.
- Finally model component (5) follows that $\frac{dg}{dt}$ must be negative since the concentration of hormones in the blood decreases through hormone metabolism. This leaves constant c to be positive.

3 Solution of the model

Equations (1),(2),(3) and (4) are two first-order differential equations for g and h. However,since only the concentration of glucose in the blood is measured it is likely that variable h is removed. This can be accomplished as follows: Differentiating (5)with respect to t gives

$$\frac{d^2g}{dt^2} = -a\frac{dg}{dt} - b\frac{dh}{dt} + \frac{dJ(t)}{dt}. \tag{7}$$

Substituting (6) into (7) and rearranging the terms we get

$$\frac{d^2g}{dt^2} = -a\frac{dg}{dt} + c(bh) - bdg + \frac{dJ(t)}{dt}. \tag{8}$$

Using (5) and Simplifying further we get

$$\frac{d^2g}{dt^2} + (a+c)\frac{dg}{dt} + (ac+bd)g = cJ(t) + \frac{dJ(t)}{dt}. \tag{9}$$

Let

$$\begin{aligned} \alpha &= \frac{a+c}{2} \\ {\omega_0}^2 &= ac+bd \\ S(t) &= cJ(t) + \frac{dJ(t)}{dt}. \end{aligned}$$

Then (9) becomes,

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + {\omega_0}^2 g = S(t). \tag{10}$$

For the purpose of this study, let $t = 0$ be the time at which the glucose load has been completely ingested, thus making $S(t) = 0$. Then,for $t \geq 0$, $g(t)$ satisfies the linear second-order constant coefficient homogeneous equation.

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + {\omega_0}^2 g = 0. \tag{11}$$

This model certainly conforms to reality in predicting that the glucose concentration tends to return eventually to its optimal/basal concentration after initial

ingestion. Let $g = Ae^{mt}$ be one of the solutions of equation (11). Then (11) becomes

$$Am^2e^{mt} + 2\alpha Ame^{mt} + {\omega_0}^2 Ae^{mt} = 0. \quad (12)$$

$$Ae^{mt} \neq 0. \quad (13)$$

Solving (12), we arrive at

$$m = -\alpha \pm \sqrt{\alpha^2 - {\omega_0}^2}. \quad (14)$$

The solution of $g(t)$ depends on the sign of $\alpha^2 - {\omega_0}^2$. This generates three cases of solution.

Case:1 Over damped

In this case, $\alpha^2 - {\omega_0}^2 \geq 0$ and the solution for $g(t)$ is

$$g(t) = e^{-\alpha t}(Ae^{\gamma t} + Be^{-\gamma t}), \quad (15)$$

where $\gamma = \alpha^2 - {\omega_0}^2$

Case:2 Critically damped

In this case $\alpha^2 - {\omega_0}^2 = 0$ and the equation has the general solution

$$g(t) = e^{-\alpha t}(A + Bt), \quad (16)$$

Case:3 Under damped

In this case, $\alpha^2 - {\omega_0}^2 \leq 0$ and the solution for $g(t)$ is

$$g(t) = e^{-\alpha t}(Ccos\beta t + iDsin\beta t), \quad (17)$$

where $\beta = \alpha^2 - {\omega_0}^2$. As

$$cos\delta = \frac{C}{\sqrt{C^2 + D^2}}$$

and if $K = \sqrt{C^2 + D^2}$, the general solution becomes

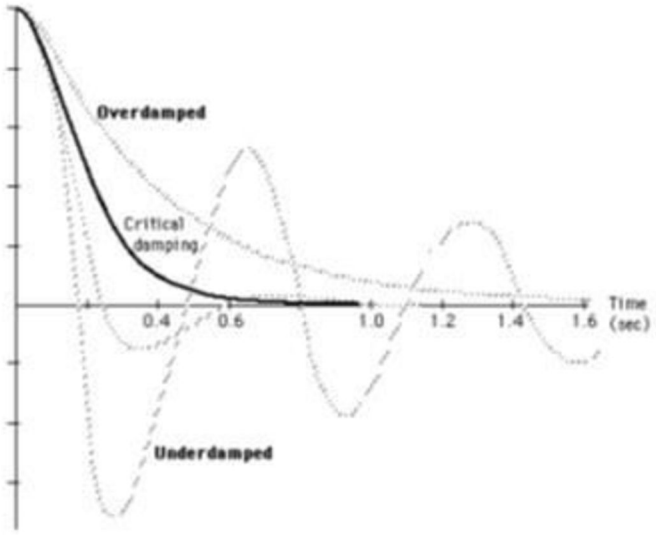
$$g(t) = Ke^{-\alpha t}cos(\beta t - \delta). \quad (18)$$

Consequently,

$$g(t) = g_0 + Ke^{-\alpha t}cos(\beta t - \delta). \quad (19)$$

Where g_0 ,is the patient's blood glucose concentration before the glucose load is ingested. This is determined by measuring the patients blood glucose concentration immediately upon arrival at the hospital. After which the patient is given an amount of glucose to take,then four additional measurements $g_1; g_2; g_3$ and g_4 of the patient's blood glucose concentration at times $t_1; t_2; t_3$ and t_4 are recorded. These measurements will be used to determine the unknowns K, α, β and ω from four equations:

$$g_j = g_0 + Ke^{-\alpha t_j}cos(\beta t_j - \delta), \quad j = 1, 2, 3, 4. \quad (20)$$


Overdamped
Critical
damping
0.4
0.6
1.0
1.2
1.4
1.6
Time
(sec.)
Underdamped

8

This solution has four unknown parameters to be fitted in the data. The parameters represent g_0 the equilibrium blood sugar level, α measures the ability of the system to return to equilibrium state after being perturbed, and β gives a frequency response to perturbations. It is expected that measuring α should be the primary measure of whether someone was diabetic, as people with diabetic should not be able to return rapidly to normal equilibrium levels. These parameters can be determined by minimizing the least square error of the equation

$$E = \sum_{j=1}^{n} \left[g_j - g_0 + Ke^{-\alpha t_j} cos(\beta t_j - \delta) \right]^2 \tag{21}$$

4 Parameter Estimation and Data Analysis

Parameter estimation is a common problem in many areas of process modeling.The goal is to determine values of model parameters that provide the best fit to measured data, generally based on some type of least squares or maximum likelihood criterion.Parameter estimation can be described as a model that is able to take control of a model running it as many times as it needs while adjusting its parameters until the discrepancies between selected model outputs and a set of data or laboratory measurements are reduced to a minimum in the weighted least square sense.

The method of least squares assumes that the best-fit curve of a given set of data is the curve that has the minimal sum of the derivatives squared (least squares error) from a given set of data.

In general,the Relative Error,(RE) indicates how good an estimate is, in relative to the true values.Although absolute errors are useful, they do not necessarily give an indication of the importance of an error. If the experimental value is denoted by g_{ex} and the estimated (or simulated) value is denoted by g_{est}, then the relative error is defined as

$$RE = \frac{g_{ex} - g_{est}}{g_{ex}}$$

And the Square Relative Error,(SRE) can be expressed as

$$SRE = \left[\frac{g_{ex_i} - g_{est_i}}{g_{ex_i}} \right]^2 .$$

When the data is sampled over a certain period of time, the Mean Square Relative Error(MSRE)can be used. The MSRE is defined as

$$MSRE = \frac{1}{n} \sum_{i=1}^{n} \left[\frac{g_{ex_i} - g_{est_i}}{g_{ex_i}} \right]^2$$

for $i = 1, 2, 3, 4$ where g_{ex_i} is the experimental value at sample i, g_{est-i} is the estimated value at sample i, and where n is the number of samples of a data set.

4.1 Data Collection

Using the conversion 1millimole/liter=18.18 milligram/decilitre the gathered data was converted from millimole/litre to milligram/decilitre. As can be seen in the subsequent tables individuals whose data were collected was categorized into the following subjects.
Subject A:Is an individual with a normal glucose-insulin interaction.
Subject B:Is an individual with type 1 diabetes(hyperglycemic).
Subject C:Is an individual with a mild form of diabetes(pre-diabetic).

Table 1 : Data on Subject A

Time (hr)	Glucose Con.(mm/I)	Glucose Con.(mg/dI)
0	4.7	85.446
1	6.6	119.988
2	5.1	92.718
3	4.7	85.446
4	4.6	83.628

Table 2 : Data on Subject B

Time (hr)	Glucose Con.(mm/I)	Glucose Con.(mg/dI)
0	10.7	194.526
1	33.3	605.394
2	33.3	605.394
3	33.0	559.94
4	32.4	589.032
5	19.7	358.146

The patient recorded a high glucose level in the first hour after which he was administered 10ml of insulin. The glucose level did not drop after next hour upon given the insulin so a dosage of 5ml insulin was administered to him.

Table 3 : Data on Subject C

Time (hr)	Glucose Con.(mm/I)	Glucose Con.(mg/dI)
0	5.50	100
1	12.10	220
2	9.62	175
3	5.50	100
4	4.67	85
5	4.95	90

4.2 Data Analysis

The data in the tables are fit to the model equation

$$g(t) = g_0 + Ke^{-\alpha t}cos(\beta t - \delta).$$

A least square best fit is performed and a table of the best fitting parameters for each of the subjects and the least sum of square errors are shown below:

The tables are arranged in the following columns:
Column 1:Time.
Column 2:Observed glucose concentration.
Column 3:Predicted glucose concentration.
Column 4:Square of the difference that is the square of the difference between the predicted value and the observed value.
Column 5:Square Relative Error(SRE).
Column 6:Mean Square Relative Error(MSRE).
The tables also include the Mean Square Relative Error percentage and parameter estimates.

Table 4 : Analysis of Subject A

Parameters	Initial Values
g	85.446
K	1
α	1
β	1
δ	1

Table 5 : Results of Subject A

Time(hr)	Glu.Con.	Glu.Con.	D.Sqr	SRE	MSRE	MSRE%
0	85.446	85.43881971	5.15566E-05	7.062E-09	8.062E-06	0.00081
1	119.988	119.8739354	1.3010728E-05	9.037E-07		
2	92.718	92.75207858	1.16135E-03	1.351E-07		
3	85.446	85.01541599	1.85402593E-01	2.539E-05		
4	83.628	83.93945414	9.7003679E-02	1.387E-05		

Sum of Difference Squared=2.96629906E-01.

Substituting these parameters into equation (19) gives

$$g(t) = 83.95 + 287.7e^{-1.74t}cos(0.79t - 1.57). \qquad (22)$$

Now

$$\begin{aligned} \omega_0 &= \sqrt{\beta^2 + \alpha^2} \\ &= 1.913678. \end{aligned}$$

And

$$\begin{aligned} T_0 &= \frac{2\pi}{\omega_0} \\ &= 3.284. \end{aligned}$$

Since $T_0 < 4$ it implies that person is normal.

Table 6 : Parameter Estimates

Parameters	Values
g	83.94540986
K	287.7098641
α	1.743175135
β	0.789623301
δ	1.565605623

Table 7 : Analysis of Subject B

Parameters	Initial Values
g	194.526
K	1
α	1
β	1
δ	1

Table 8 : Results of Subject B

Time(hr)	Glu.Con.	Glu.Con.	D.Sqr	SRE	MSRE	MSRE%
0	194.526	194.5122614	0.00018875	4.9880E-09	0.053006	5.300573
1	605.394	551.5721503	2896.791507	7.9038E-03		
2	605.394	551.5721715	2896.789219	7.9038E-03		
3	599.94	551.5721715	1.85402593E-01	6.4997E-03		
4	589.032	551.5721715	9.7003679E-02	4.0443E-03		
5	358.146	551.5721715	37413.68384	2.9168E-01		

Sum of Difference Squared=46949.95

Substituting these parameters into equation (19) gives

$$g(t) = 551.57 + 786.28e^{-17.4t}cos(0.91t - 4.24). \qquad (23)$$

Now

$$\begin{aligned} \omega_0 &= 17.43207774 \\ T_0 &= 0.36048 \end{aligned}$$

Since $T_0 < 4$ it implies that person is normal.

Table 9 : Parameter Estimates

Parameters	Values
g	551.5721715
K	786.2821511
α	17.40826645
β	0.910820217
δ	4.241014072

Table 10 : Analysis of Subject C

Parameters	Initial Values
g	100
K	1
α	1
β	1
δ	1

Table 11 : Results of Subject C

Time(hr)	Glu.Con.	Glu.Con.	D.Sqr	SRE	MSRE	MSRE%
0	100	99.79420264	0.042352553	4.2352E-06	0.0000674	0.067391
1	220	220.8929173	0.797301314	1.6473E-05		
2	175	172.5304381	6.098736136	1.9914E-04		
3	100	103.7998814	14.43909902	1.4439E-03		
4	85	81.20734359	14.38424266	1.9908E-03		
5	90	91.77464209	3.149354537	3.8880E-04		

Sum of difference squared=38.91108622.

Substituting these parameters into equation (19) gives

$$g(t) = 104.86 + 230.5e^{-0.5t}cos(1.06t - 1.59). \qquad (24)$$

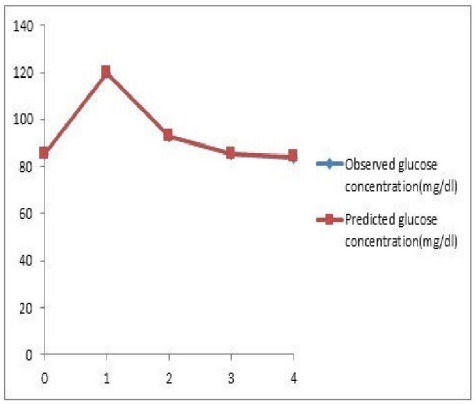
Now

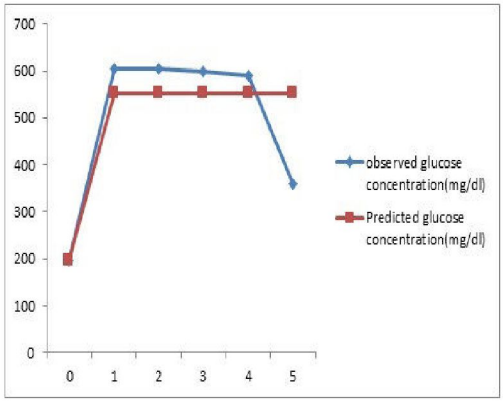
$$\begin{aligned} \omega_0 &= 71.191 \\ T_0 &= 5:278 \end{aligned}$$

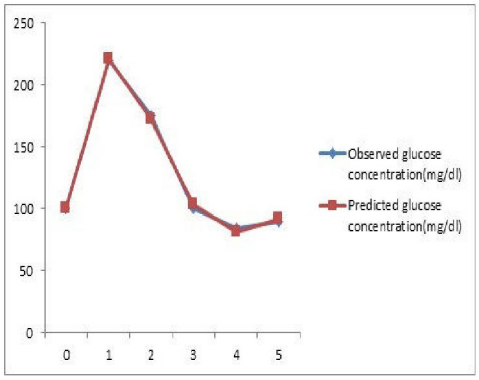
Since $T_0 > 4$ it implies that person is diabetic.

Table 12 : Parameter Estimates

Parameters	Values
g	104.8558461
K	230.5246798
α	0.538558627
β	1.062200113
δ	1.5927551448


140
120
100
80
60
40
20
0
0
1
2
3
4
Observed glucose concentration(mg/dl)
Predicted glucose concentration(mg/dl)


700
600
500
400
300
200
100
0
0
1
2
3
4
5
observed glucose concentration(mg/dl)
Predicted glucose concentration(mg/dl)


250
200
150
100
50
0
0
1
2
3
4
5
Observed glucose concentration(mg/dl)
Predicted glucose concentration(mg/dl)

5 Conclusion

This work aid in the detection of the disease at an early stage. It is worth noting that the model developed in this study only considered an internal rate at which blood glucose concentration is being increased. Future research may take into account an external rate at which blood glucose concentration is being increased. Variables such as epinephrine and glucagon should be included as separate variables in future models describing glucose-insulin dynamics. Evidence indicates that levels of epinephrine may rise dramatically during the recovery phase of the GTT response, when glucose levels have been lowered below fasting levels.

References

[1] Cooke, D. W., Plotnick, L., Type 1 diabetes mellitus in pediatrics., *Pediatr Rev*, 29 (11): 37484 (2008).

[2] 3. Ackerman, E., Rosevear, J. W., and McGuckin, W. F. (1964), A mathematical model of the glucose tolerance test, *Phys. Med. Biol.*, 9, 202-213.

[3] Furler, S. M., Kraegen, E. W., Smallwood, R. H., and Chisholm, D. J., Blood glucose control by intermittent loop closure in the basal mode: computer simulation studies with a diabetic model, *Diabetes care*, 1985, vol 8, pp. 553 561.

[4] Bergman, R.N, Ider, Y.Z., Bowden, C.R., and Cobelli, C., Quantitative estimation of insulin sensitivity, *Am. J. Physiol.*, 1979, vol. 236, pp. E667-E677.

[5] Braun, Martin, Differential Equations and Their Applications, *An Introduction to Applied Mathematics*, Springer, New York, 1975.

[6] Krimmel E, Krimmel P, (1992). The Low Blood Sugar Handbook, *Franklin Publishers*, 67-69.

[7] Middleman, (1972). Transport Phenomena in the Cardiovascular System, *Willey Interscience*, New York.

[8] Narayanan S,Manickavasagam Pillai T K, Differential Equations and its Applications, *S.Viswanathan (Printers and Publishers),PVT.,LTD*, 2008.