Mathematical Model for Blood Glucose Invention During Fasting and Post Pandial

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Abstract

Diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels. Various hormones in our body such as insulin, growth hormone, glucagon control blood glucose levels, epinephrine best known as adrenaline, glucocorticoids and thyroxine. The two most common forms of diabetes are due to either a diminished production of insulin (Type 1 diabetes), or decreased response by the body of insulin (Type 2 and gestational diabetes).Both lead to hyperglycemia, which largely causes the acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. We will explain how each hormone is initiated and how its impact the glucose levels in blood. We present a mathematical model that determines diabetes in patients based in the results on the glucose intolerance test of 5 hours. Our model extends the one suggested by E.Ackerman2 (1969) to include three instead of two hormones concentrations. In particular we include concentrations for glucose, glucagon and a global variable that includes other hormones such as insulin. The model is based on a 3×3 system of non –homogenous ordinary differential equation. A nonlinear least square method is used to find the coefficient parameters of the system based on actual from data GTT. The simulations also provide an indicator similar to the one proposed by E. Ackerman (1969), to diagnose a diabetic condition. Additionally, we develop a graphical user interface to facilitate the entering of the patient's data and the visualization of the results.

Keywords: Differential Equations, Diabetes, Simulations, Graphical User Interface

I. INTRODUCTION

How do you find out that you have Type 2 diabetes? Often, because there may not be noticeable symptoms, the diagnosis is made during an annual physical or checkup. Your doctor may order a Fasting Blood Sugar (FBS), or an Oral Glucose Tolerance Test (OGTT) better known as GTT to help determine whether you have diabetes, what do these tests mean?

The FBS is a fasting test, meaning that you can't eat for 8-10hours before you have your blood drawn. Most people like to go for the test first thing in the morning after fasting all night. A fasting blood glucose of 70mg/dl to 100 mg/dl is normal. If your fasting blood glucose level comes back between 100 mg/dl and 125 mg/dl then you are considered to have impaired fasting glucose or pre-diabetes. A fasting glucose over 125mg/dl indicates that you have Type 2 diabetes. Most doctors like to get a fasting blood sugar on two separate occasions to make sure of the diagnosis. Expected measurements can be found in Table 1.

The GTT is a glucose challenge test. A fasting blood glucose is usually taken first to establish a baseline level. Then you are given a 75 grams glucose drink. Two hours later another blood sample is drawn to check your glucose level. If your blood glucose is under 140 mg/dl then your glucose tolerance is considered normal. If it is 140mg/dl to 200 mg/dl, then you have impaired glucose tolerance or pre-diabetes. If your glucose is over 200mg/dl then a diagnosis of type 2 diabetes is made. Again, your doctor will usually perform this test on two different occasions before a definite diagnosis is made. A very serious difficulty associated with this method of diagnosis is that no universal accepted criterion exists for interpreting the results of the GTT. Diabetes mellitus is the most common endocrine disorder. The diagnosis requires a fasting plasma glucose of (>140 mg/dl) on two occasions. Following ingestion of 75 grams of glucose, the finding of a venous plasma glucose of (>120mg/dl) after two hours and on at least another occasion during the two hour test is suggestive. In the case of diagnosing hypoglycemia, it requires a plasma glucose (<45-70 mg/dl) no more than two occasions.

II. PRELIMINARIES

Blood glucose levels are controlled by various hormones in our body such as insulin, growth hormone, glucagon, epinephrine best known as adrenaline, glucocorticoids and thyroxine. Our model's goal is to determine if a patient has diabetes taking in consideration the glucose intolerance test (GTT)and the normal glucose levels that the patient should present (Table1).The model

will determine how much the different hormones influence in those levels of sugar in blood. Therefore an explanation on how each hormone is activated and how it affects glucose levels in blood is now given.

Table – 1
Goals for Blood Glucose in the Control of Diabetes

Goal	*Aceptable*	*Ideal*
	mg/dL	*mg/dL*
Fasting	*60-130*	*70-110*
Post Prandial (2hr)	*70-180*	*70-140*

A. Insulin

The hormone insulin is made in the beta cells of the pancreas and is secreted when the body presents high blood sugar levels. When only $10-20\%$ of beta cells are working properly then the sings of diabetes tend to show. Insulin causes most of the body's cells to take up glucose from the blood (including liver, muscle and fat tissue cells), storing it as glycogen in the liver and muscle, and stops use of fat as an energy source. When insulin is absent (or low), glucose is not taken up by most body cells and the body begins to use fat as an energy source (ie, transfer of lipids from adipose tissue to the liver for mobilization as an energy source).When sugar levels are high in the body then the insulin hormone is segregated. When control of insulin levels fail, diabetes mellitus results. On the other hand, an excess of insulin results in hypoglycemia.

B. Glucagon

Glucagon is an important hormone involved in carbohydrate metabolism. Produced by the alpha cells in the pancreas, it is released when the glucose level in the blood is low (hypoglycemia), causing the liver to convert stored glycogen into glucose and release it into the bloodstream. The action of glucagon is thus opposite to that of insulin, which instructs the body's cells to take in glucose from the blood in times of satiation. In this action if there is no sufficient glucose in blood the glucagon takes the reserves of glucose stored in the liver.

C. Adrenaline

Also known as epinephrine is a hormone is released from the adrenal glands when danger threatens or in an emergency. The hormone boosts the supply of oxygen and glucose to the brain and muscles, while suppressing other non-emergency bodily processes (digestion in particular). It increases heart rate and stroke volume, dilates the pupils, and constricts arterioles in the skin and gastrointestinal tract while dilating arterioles in skeletal muscles. In times of extreme hypoglycemia it elevates the blood sugar level by increasing catabolism (breakdown) of glycogen to glucose in the liver, and at the same time begins the breakdown of lipids in fat cells. It is important to note that adrenaline mobilizes the glucose reserves in the liver and muscles while glucagon only access the liver reserves. It is important to note that adrenaline is not the automatic response of the body in case of hypoglycemia and therefore we will concentrate in study glucagon segregation that will be given by the glucose level in blood.

D. Thyroxine

Thyroxine is the major hormone secreted by the follicular cells of the thyroid gland. It is important to note that is involved in controlling the rate of metabolic processes in the body and influencing physical development. Diabetic patients have a higher prevalence of thyroid disorders compared with the normal population [3].The presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirements. In patients without any thyroid dysfunction it normally segregates the tryroxine hormone which influence in the metabolism of the body ergo it can either increased or decreased blood sugar levels.

E. Glucocorticoids

Glucocorticoids is the hormone secreted by the adrenal cortex and plays an important role in the metabolism of carbohydrates. The name "glucocorticoid" derives from early observations that these hormones were involved in glucose metabolism. In the fasted state, glucocorticoid stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood.

The metabolic effects include the inhibition of glucose uptake in muscle and adipose tissue: A mechanism to conserve glucose and stimulation of gluconeogenesis, particularly in the liver. Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon.

The vast majority of gluconeogenesis takes place in the liver and, to a smaller extent in the cortex of kidneys. This process occurs during periods of fasting, starvation, or intense exercise and is highly energetic. Gluconeogenesis is often associated with ketosis. Gluconeogenesis is also a target of therapy for type II diabetes, such as metformin, which inhibit glucose formation and stimulate glucose uptake by cells.

F. Growth Hormone (Somatotropin)

The growth hormone or somatotropin in segregated by the delta cells in the pancreas. It intervenes directly on the regulation of glycemic and the segregation depends on the high levels of glucose, amino acids and glucagon. In addition to increasing height in

children and adolescents, growth hormone has many other effects on the body. This is to reduce liver uptake of glucose and promote gluconeogenesis in the liver, therefore it increases the glucose levels in blood.

It is important to note when the growth hormone is segregated it increases blood sugar levels. It is believed that the growth hormone decreases the sensitivity of muscle and adipose membrane to insulin, thereby reducing the effectiveness of insulin in promoting glucose uptake[1].

III. MATHEMATICAL MODEL

The model proposed serves to interpret the results of the Glucose Tolerance Test (GTT) on either normal or diabetes patients. We know that glucose plays an important role on our performance which depends on the metabolism system. Glucose provides energy to tissue and organisms but the levels provided depend on various hormones such as: insulin, growth hormone, glucagon, epinephrine best know as adrenaline, glucocorticoids and thyroxine. A standard criterion does not exist to analyze the (GTT) results which can be a problem. The model proposed in this paper will separate in three groups the hormones that influence glucose levels in blood. In this way we can group the hormones that elevate glucose levels in blood separated from those that lower them.

A. Variables

In our model we centre our attention on 3 concentrations: $G(t)$ denotes blood glucose concentrations; $E(t)$ denotes blood glucagon concentrations; $H(t)$ denotes the rest of the hormones concentrations. The equations of the model are given by:

$$\frac{dG(t)}{dt} = F_1\big(G(t), E(t), H(t)\big) + J(t) \quad (1)$$

$$\frac{dE(t)}{dt} = F_2\big(G(t), E(t), H(t)\big) \quad (2)$$

$$\frac{dH(t)}{dt} = F_3\big(G(t), E(t), H(t)\big) + K(t) \quad (3)$$

where $J(t), K(t)$ denote external rates of supplied glucose and hormones (like insulin). As it is, the model is quite general. We will consider only small perturbations or variations from a steady state or equilibrium point of the system. If (G_0, E_0, H_0) represents such a state, then it is characterized by the equations:

$$F_1(G_0, E_0, H_0) = 0,\ F_2(G_0, E_0, H_0) = 0, F_3(G_0, E_0, H_0) = 0 \quad (4)$$

We assume that G, E and H have achieved the optimal values G_0, E_0 and H_0 by the time the fasting patient has arrived at the hospital. Let

$$g(t) = G(t) - G_0,\ e(t) = E(t) - E_0, h(t) = H(t) - H_0 \quad (5)$$

Represent small variations from the corresponding optimal values. Thus we have the linearized version of equations $(1), (2)$, and (3)

$$\frac{dg(t)}{dt} = a_1 g(t) + b_1 e(t) + c_1 h(t) + J(t), \quad (6)$$

$$\frac{de(t)}{dt} = a_2 g(t) + b_2 e(t) + c_2 h(t), \quad (7)$$

$$\frac{dh(t)}{dt} = a_3 g(t) + b_3 e(t) + c_3 h(t) + K(t), \quad (8)$$

Note that glucagon, adrenaline and the growth hormone are hormones that increase blood glucose levels, and that insulin, thyroxin have the opposite effect. Considerations like these allow us to determine the signs of the coefficients in this system. For example: if glucose levels are high $(g > 0)$ and the glucagon level and other hormones low $(e = 0, h = 0)$, then the glucose level should decrease $(a_1 < 0)$ due to tissue absorption. If the glucagon levels are high $(e > 0)$ and the glucose and other hormones levels are low$(g = 0, h = 0)$, then the glucose level should increase $(b_1 > 0)$ due to glycogen conversion to glucose. Similar considerations lead us to the following inequalities:

$$a_1 < 0,\ b_1 > 0,\ c_1 < 0,\ a_2 < 0,\ b_2 < 0,\ c_2 > 0,\ a_3 > 0,\ b_3 > 0,\ c_3 < 0 \quad (9)$$

We can incorporate this signs explicitly into the system of equations (6), (7) and (8) above by re-writing it as:

$$g'(t) = -\alpha_1 g(t) + \beta_1 e(t) - \gamma_1 h(t) + J(t) \quad (10)$$

$$e'(t) = -\alpha_2 g(t) - \beta_2 e(t) + \gamma_2 h(t) \quad (11)$$

$$h'(t) = \alpha_3 g(t) + \beta_3 e(t) - \gamma_3 h(t) + K(t) \quad (12)$$

Where all the constants $\alpha_i, \beta_i, \gamma_i$ are positive number.

The basic task of the blood glucose regulatory system is to bring perturbations from the steady state (G_0, E_0, H_0) back to it in time. With this in mind we look for conditions on the coefficient matrix in equations(10),(11),and (12) that guarantee that the equilibrium point (G_0, E_0, H_0) has this stability property. This will be so if all the eigenvalues of the co-efficient matrix in (10), (11) and (12) have negative real parts. A necessary condition for this is that the determinant of the coefficient matrix be negative. This determinant is given by:

$$-(\alpha_1\beta_2\gamma_3 + \alpha_2\beta_1\gamma_3 + \alpha_3\beta_2\gamma_1) + \alpha_1\beta_3\gamma_2 + \alpha_3\beta_1\gamma_2 + \alpha_2\beta_3\gamma_1 \quad (13)$$

Observe that if $\beta_{3,}\gamma_2$ are small, with the rest of the coefficients fixed, then the determinant is negative. Hence forth we consider the limiting case of $\beta_{3,}\gamma_2 = 0$ coefficient in equations (10), (11) and (12) reduces to:

$$\begin{pmatrix} -\alpha_1 & \beta_1 & -\gamma_1 \\ -\alpha_2 & -\beta_2 & 0 \\ \alpha_3 & 0 & -\gamma_3 \end{pmatrix}$$

The characteristic polynomial of this matrix is given by:

$$p(\lambda) = \lambda^3 + d_1\lambda^2 + d_2\lambda + d_3 \qquad (14)$$

Where

$$d_1 = \alpha_1 + \beta_2 + \gamma_3, \qquad d_2 = \alpha_2\beta_1 + \alpha_1\beta_2 + \alpha_1\gamma_3 + \alpha_3\gamma_1 + \beta_2\gamma_3,$$
$$d_3 = \alpha_2\beta_1\gamma_3 + \alpha_1\beta_2\gamma_3 + \alpha_3\beta_2\gamma_1 \qquad (15)$$

Note that the $d_i's$ are all positive. By the Routh-Hurwitz stability criterion[5] we get that all of the roots of $p(\lambda)$ have negative real parts if and only if $d_1 d_2 > d_3$ .To recapitulate, our problem reduces to find solutions of the system$(10) - (12)$, where all the constants $\alpha_i, \beta_i, \gamma_i$ are positive numbers such that

$$d_1 d_2 > d_3 \qquad (16)$$

Using the elimination method[4], we find the system of equations $(10) - (12)$ decouples into three equations:

$$L(g) = \hat{J}(t), \quad L(e) = \hat{M}(t), \quad L(h) = \hat{K}(t), \qquad (17)$$

where

$$L(u) = u'''(t) + d_1 u''(t) + d_2 u'(t) + d_3 u(t), \qquad (18)$$

with d_1, d_2, d_3 as above, and

$$\hat{J}(t) = J''(t) + (\beta_2 + \gamma_3)J'(t) + \beta_2\gamma_3 J(t) - \gamma_1 K'(t) - \beta_2\gamma_1 J(t),$$
$$\hat{M}(t) = -\alpha_2 J'(t) - \alpha_2\gamma_3 J(t) - \alpha_2\gamma_1 J(t), \qquad (19)$$
$$\hat{K}(t) = \alpha_3 J'(t) + \alpha_3\beta_2 J(t) + K''(t) + (\alpha_1 + \beta_2)K'(t) + (\alpha_2\beta_1 + \alpha_1\beta_2)K(t).$$

Note that the characteristic polynomial for the operator (21) is given by (14) and (15). By our assumptions on the coefficients of (14) and (15) and condition (19),we have that (14) has either three negative real roots; or one negative root and two complex conjugates roots with negative real part. Assuming the case of complex roots and taking for the moment $J = K = 0$, we have that the solution of the first equation in (10) is given by:

$$g(t) = Ae^{-at} + Be^{-bt}\cos(\omega t - \zeta), \qquad a, b > 0, \qquad (20)$$

and the blood glucose level is given by the model equation:

$$G(t) = G_{0+}Ae^{-at} + Be^{-bt}\cos(\omega t - \zeta), \qquad a, b > 0, \qquad (21)$$

Note that there are 7 parameters to be the determined in this equation. (One can actually reduce it to 6 by requiring that $g(0) = 0$) .We compute the values of these parameters by a nonlinear least square method. If $G_1, G_2, G_3, \ldots, G_n$ are measurements of the patient's blood glucose concentration at times $t_1, t_2, t_3, \ldots, t_n$ then we find the values of $G_0, A, B, a, b, \omega, \zeta$ that minimize the mean square error functions:

$$E = \sum_{k=1}^{n} \left(G_k - G_0 - Ae^{-at_k} - Be^{-bt_k}\cos(\omega t_k - \zeta)\right)^2 \qquad (22)$$

Note that the requirement $a, b > 0$ implies that condition (19) is satisfied.

We implemented the nonlinear least square method using the functions provided by optimization toolbox in MATLAB™ .We created a graphical user interface (GUI) with MATLAB™ as well, that facilitates the entering of the patients GTT data, process it with the least square method, plots a graph of the model(24), and computes a pseudo period for this function that will be used for the diagnosis of a diabetic condition.

IV. RESULTS

Since there is not a universal criterion to diagnose diabetes two doctors evaluating a certain patients GTT results can result in two different diagnoses. Therefore, we want to determine an objective approach to analyze Glucose Intolerance Test (GTT) that can help improve a criterion to diagnose a Diabetes condition. In the model proposed by E. Ackerman (1969), the pseudo period $T = 2\pi/\omega$ was used as an indicator for a diabetic condition. Using data from a variety of sources they found that a value of less than four hours for the indicator indicated normalcy, while appreciably more than four hours implied mild diabetes. In this paper we use the same indicator to test for diabetes. We used data (provided by the oriental clinic laboratory in Humacao) from patients of the Humacao area. The data includes the fasting glucose levels at $t = 0$ and all others glucose levels every hour. We evaluated 20 patients whose name, sex or age we did not know and compare each of the results to a single diagnosis of a certain doctor. Our results are given in (Table 2).

Table – 2
Glucose Tolerance Tests of 20 Different Patients

Patient Number	*Hypothesis*			*Indicator*	*Conclusions*	
	Normal	*Diabetic*	*Pre-Diabetic*		*Diabetic*	*Normal*
	X			96-130		*X*
			X	72-144	*X*	
		X		108-194	*X*	
			X	127-292	*X*	
	X			77-124		*X*
		X		215-314	*X*	
		X		90-185	*X*	
		X		217-425	*X*	
		X		106-237	*X*	
			X	71-177	*X*	
	X			79-131		*X*
		X		194-343	*X*	
			X	69-117	*X*	
	X			102-132	*X*	
			X	107-166	*X*	
	X			115-134		*X*
			X	80-163	*X*	
		X		219-356	*X*	
			X	125-199	*X*	
		X		150-220	*X*	

V. CONCLUSIONS

The oriental clinic laboratory provided our data. The results include the fasting glucose levels at $t = 0$ and all others glucose levels every hour. We evaluated 20 patients whose name, sex, or age we did not know with our GUI and compare each of those results to a single diagnosis of a certain doctor. Our results are given in (Table 2).

We encounter that our model was correct in 4 of 20 tests. That gives us a 20% of success. Since our model only considers evaluation between normal or diabetic patients it fails to evaluate pre-diabetic patients. From the 16 patients that were pre-diabetic patients and our model diagnosed them as either normal or diabetic. Also the four hour indicator threshold might need to be re-evaluated for the Puerto Rican population due to differences in eating habits and preferences. It is important to note that large deviations of G from G_0 usually indicate severe diabetes or pre-diabetes. Our model precludes by our

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