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Mathematical Model for the Detection and Control of Diabetes

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Abstract

Diabetes mellitus is a chronic condition in which the body cannot make or use available insulin effectively. Diabetes is one of the biggest diseases in western world today. Many millions suffer from it and do not know they have the disease. This work presents an extension of an earlier model for the detection of diabetes in the blood. The new model incorporates physical exercise which facilitates the utilization of glucose, the effectiveness of insulin and the release of epinephrine concentrations in the blood. The existence and stability of the equilibria of the model is investigated and the only equilibrium state was found to be uniformly asymptotically stable. It is shown using Ackerman criteria for detecting diabetes that, the new model can be used for the interpretation of the result from a Glucose Tolerance Test (GTT). A computer program is also developed to simulate the null-clines of the model equations to study the effect of physical exercise on glucose, insulin and epinephrine concentrations in the blood, and it is found that as the rate of physical exercise increases, the excess glucose, insulin and epinephrine concentrations returned to their equilibrium levels with time. The above results confirm that physical exercise is useful in the control of diabetes and is therefore recommended for diabetic patients.

Keywords: Diabetes; Glucose; Insulin; Epinephrine; Glucose Tolerance Test; Physical Exercise.

1.0 Introduction

Historically, diabetes is a Greek word meaning a siphon. The word was used to connote a condition of passing water (urine) like siphon. Mellitus is a Latin word meaning sweetened or honey-like. Put together, the term Diabetes Mellitus was literally used to denote a disease condition associated with persistent passing of sweetened urine [1]. Diabetes Mellitus is a chronic condition in which the body cannot make or use available insulin effectively. So Diabetic Patients require supplements of insulin in the form of regular injection and tablets in addition to modified diet to regulate glucose input [2]. According to WHO [3], there are three types of diabetes;*Type 1 diabetes*(lack of insulin), *Type 2 diabetes*(insulin not working properly), and*Type 3 diabetes*(also known as *gestational*occurs in pregnancy and usually disappears after child birth).Symptoms of diabetes include;Thirst, hunger, frequent urine, tiredness,Vaginal discharge in women and erectile dysfunction in men,Unusual sensations such as tingling in your fingers, toes, Blurred vision, weight loss, andGum problem, or itching, or sores that do not heal quickly[4-5].Diabetes can be detected through some of the following tests;Intra Venous Glucose Tolerance Test (IVGTT),Oral Glucose Tolerance Test (OGTT) or simply Glucose Tolerance Test (GTT), andFrequently Sampled Intra Venous Glucose Tolerance Test (FSIVGTT) [6].

Over the years, mathematical models have been used to understand and predict the spread of many diseases, relating important public health questions to basic infection parameters [6].Many mathematical models have been developed to better understand the mechanisms of the glucose-insulin regulatory system [7-9]. Many of the models considered only two variables, glucose and insulin concentrations in the blood. An improved model over the earlier models has been formulated by Kwach *et al.* [6] in which a third variable, epinephrine concentration in the blood, is included. The importance of this third variable lies in its ability to help in conducting a reliable test for detecting diabetes in the blood. Kwach *et al.*[6] found their model to be asymptotically stable. Furthermore, the resonance period of their model was far less than the resonance period for the existing models. This shows that the glucose concentration returns to normal levels within a shorter time.

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Research has shown that physical exercise can lower blood glucose and blood pressure, improve the body's ability to use insulin and increase epinephrine concentrations [10-13]. Glucose commonly called sugar is a carbohydrate that comes from the food we eat.It is an important energy source that is needed by all the cells and organs of the body. Insulin is a hormone secreted by the beta cells of the pancreas that is essential especially for the metabolism of carbohydrates and the regulation of glucose levels in the blood and that when insufficiently produced results in diabetes mellitus. Epinephrine is a hormone secreted by the adrenal medulla that is part of an emergency mechanism to quickly increase the concentration of glucose in the blood in times of extreme hypoglycaemia. It increases the rate of breakdown of glycogen into glucose and directly inhibits glucose uptake by muscle tissue. It acts directly on the pancreas to inhibit insulin secretion, and it aids in the conversion of lactate to glucose in the liver.The motivation for this study lies in the role that physical exercise can play in the control of diabetes as mentioned above.To this end, we improve on the model by Kwach *et al.*[6] by including the role of physical exercise in the control of diabetes.

The rest of the paper is organizes as follows: In section 2, the formulation of the extended model is explained, the analysis of the new model is considered in section 3, while in section 4 the results and discussion of the model is presented. Finally, the conclusion and recommendations is done in section 5.

2.0 Model Formation

Since the aim of this work is to extend the Kwach *et al.*[6] model for detecting diabetes in the blood (which is to help in the interpretation of the Glucose Tolerance Test (GTT)), the existing model is first presented.

2.1 Assumptions of the Existing Model

The assumptions according to the existing model are as follows:

(i) An increase in glucose in the blood stimulates tissue uptake of glucose and glycogen storage in the liver,
(ii) An increase in insulin facilitates the uptake of glucose in tissues and the liver,
(iii) An increase in blood glucose results in the release of insulin,
(iv) An increase in insulin only results in increased metabolism of excess insulin,
(v) An increase in epinephrine stimulates tissue uptake of glucose,
(vi) An increase in epinephrine facilitates the utilization of insulin.

2.2 Definition of Variables of the Existing Model

$\boldsymbol{g}(\mathbf{t}) =$ Excess glucose concentration in the blood at time t,
$\boldsymbol{h}(\mathbf{t}) =$ Excess insulin concentration in the blood at time t,
$\boldsymbol{e}(\mathbf{t}) =$ Excess epinephrine concentration in the blood at time t.

2.3 Definition of the Parameters of the Existing Model

The parameters of the existing model were not defined in biological term. Theparameters of the existing model are defined as follows:

a = The rate of glucose consumption in tissues,
b = The rate at which insulin facilitates the uptake of glucose by the body tissues,
c =The rate at which insulin is secreted in the body by the pancreas,
d =The rate at which insulin is used up in the body tissues,
f = The rate at which epinephrine inhibits glucose uptake by muscle tissues,
k =The rate at which epinephrine acts on the pancreas to inhibit insulin secretion,
l =The rate of change in plasma epinephrine concentration as a result of low glucose concentration,
m =The change in plasma epinephrine concentration as a result of low insulin concentration,
n =The rate at which epinephrine is secreted in the blood.

2.4 The Existing Model Equations

With these assumptions, variables and parameters above, the existing model by Kwach *et al.* [6] is given as follows:

$$\frac{dg}{dt} = -ag - bh + fe \quad (1)$$
$$\frac{dh}{dt} = cg - dh + ke \quad (2)$$
$$\frac{de}{dt} = -lg - mh + ne \quad (3)$$

where a, b, c, d, f, k, l, m and n are positive quantities, defined above.

2.5 The Extended Model

The model (1) – (3) is extended by including physical exercise as a measure of control for diabetes under the following additional assumptions and parameters:

2.6 Assumptions of the Extended Model

(i) Physical exercise results in the burning of calories, which facilitates the utilization of glucose by muscles and liver,

(ii) Physical exercise results in the burning of calories, which increases the utilization of insulin,
(iii) Physical exercise results in the utilization of glucose, which facilitates the release of plasma epinephrine concentration.

2.7 Parameters of the Extended Model

Based on the new assumptions, the following parameters are introduced and will be used in conjunction with the existing parameters

p =The rate at which glucose concentration is used up due to physical exercise,
q = The rate at which insulin concentration is used up in the body as a result of physical exercise,
r =The rate at which epinephrine is released for energy as a result of physical exercise.

2.8 The Extended Model Equations

Based on the above assumptions, definition of variables, parameters above, the extended model equations are given as follows:

$$\frac{dg}{dt} = -(a+p)g - bh + fe \quad (4)$$

$$\frac{dh}{dt} = cg - (d+q)h + ke \quad (5)$$

$$\frac{de}{dt} = -lg - mh + (n+r)e \quad (6)$$

where *p*, *q* and *r* are as defined above.

3.0 Model Analysis

In this section, the new model (4) – (6) for the detection of diabetes and also for the control of diabetes is analysed.Since the only concern is to measure glucose concentration in the blood for detecting diabetes, the model (4) – (6) is transformed into a second order ordinary differential equation in terms of glucose concentration as follows:

Taking the second derivative of equation (4) with respect to *t* gives

$$\frac{d^2g}{dt^2} + (a+p)\frac{dg}{dt} + b\frac{dh}{dt} - f\frac{de}{dt} = 0 \quad (7)$$

Substituting for $\frac{dh}{dt}$ and $\frac{de}{dt}$ in (7), and assuming that there is no excess insulin concentration in the blood($h = 0$)as in Kwach *et al*. [6], then

$$\frac{d^2g}{dt^2} + (a+p)\frac{dg}{dt} + (bc+fl)g + \big(bk - f(r+n)\big)e = 0 \quad (8)$$

From equation (4), $e = \frac{1}{f}(\frac{dg}{dt} + (a+p)g)$.

Substituting this in (8) and simplifying results to

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + \omega_0^2 g = 0 \quad (9)$$

where, $\alpha = \frac{1}{2}\left(a + p + \frac{bk}{f} - (n+r)\right)$, and (10)

$$\omega_0^2 = \left(bc + fl + (a+P)\frac{bk}{f} - (a+p)r - (a+p)n\right) \quad (11)$$

Equation (9) is a second order differential equation representing a **Simple Harmonic Motion.**

3.1 Analytical Solution of the Extended Model

The characteristic equation of (9) is given as follows;

$$\lambda^2 + 2\alpha\lambda + \omega_0^2 = 0 \quad (12)$$

The eigenvalues of the characteristic equation using the quadratic formula is given as

$$\lambda_{1,2} = -\alpha \pm \sqrt{\alpha^2 - \omega_0^2} \quad (13)$$

With any Simple Harmonic Motion, three cases are involved: the overdamped case:($\alpha^2 - \omega_0^2 > 0$), the critically damped case: ($\alpha^2 - \omega_0^2 = 0$) and underdamped case:($\alpha^2 - \omega_0^2 < 0$).

From basic differential equations, if the characteristic equation has only positive real coefficients, then the eigenvalues are either complex with negative real parts or both eigenvalues are negative and real.We assume that $\alpha^2, \omega_0^2 > 0$. This means that the eigenvalues are assumed to be complex with negative real parts.

Therefore, the general solution of (9) is given by

$$g(t) = e^{-\alpha t}(c_1 cos\omega t + c_2 sin\omega t) \quad (14)$$

where $c_1 and c_2$ are constants

If we take $c_1 = A\sin\delta, c_2 = A\cos\delta$, then an alternative solution of (9) is as follows [14].

$$g(t) = Ae^{-\alpha t} sin(\omega t + \delta) \quad (15)$$

Here, A is the amplitude of the system, and δ is the phase angle.

If there is a small perturbation in the glucose concentration, then

$\mathrm{G(t)} = \mathrm{G}_0 + g(t)$

$\Rightarrow \mathrm{G(t)} = \mathrm{G}_0 + \mathrm{A}e^{-\alpha t}\sin(\omega t + \delta)$ (16)

therefore, the solution of (9) is given by

$\mathrm{G(t)} = \mathrm{G}_0 + \mathrm{A}e^{-\alpha t}\sin(\omega t + \delta)$ (17)

where G_0 is the equilibrium blood sugar level, α is the ability of the system to return to equilibrium state after perturbation, and ω is a response to perturbations. Equation (17) is also referred to as a GTT model.

α, which is expected to be the primary measure of whether someone is diabetic, was found to have errors from the many subjects tested by Ackerman *et al.* [15]. A more reliable measure was the use of the natural frequency of the system.

3.2 Parameter Estimation

We obtained the parameters $G_0,\ A,\ \alpha, \omega and \delta$ as follows:

The data in Table 1from Rohan [16] is fitted to the GTT model (Equation (17)). A least square best fit[17] is performed using an inbuilt excel tool solver to minimize the least square error in order to obtain the optimal values for the parameters. The Table of values for the parameters generated and the least sum of the square errors is presented in Table 2.

T**able 1:** Data from Glucose Tolerance Test Conducted on Two Individuals by [16]. (For the purpose of this research work, the two individuals shall be referred to as subject A and subject B)

t (hr)	**G(t) (mg/dl)Subject A**	**G(t) (mg/dl) Subject B**
0.00	70	100
0.50	150	185
0.75	165	210
1.00	145	220
1.50	90	195
2.00	75	175
2.50	65	105
3.00	75	100
4.00	80	85
6.00	75	90

Table 2: Parameter Values for the GTT Model

Para-meters	subject A	subject B	Mean Square Error (MSRE)for subject A	(MSRE)% for subject A	Mean Square Error (MSRE) for subject B	(MSRE)% for subject B
G_0	77.0369757	95.2123549	0.003352191	3.35219E-06	0.005209183	5.21E-06
A	179.564621	263.1528475				
α	1.02763759	0.633490626				
ω	1.72436666	1.030365222				
δ	0	0.008722147				

Table 3: Values for the Null-Clines of the Model Equations

p	*g(p)*	*r*	*e(r)*	*q*	*h(q)*
0.0475	3.7019	0.0025	32.0333	0.076	6.1386
0.5475	3.1681	0.5025	15.0008	0.576	2.0347
1.0475	2.7689	1.0025	9.3406	1.076	1.0149
1.5475	2.459	1.5025	6.5946	1.576	0.609
2.0475	2.2115	2.0025	5.0052	2.076	0.4064
2.5475	2.0092	2.5025	3.9839	2.576	0.2907
3.0475	1.8409	3.0025	3.2799	3.076	0.2184
3.5475	1.6986	3.5025	2.7695	3.576	0.1701
4.0475	1.5767	4.0025	2.3849	4.076	0.1363
4.5475	1.4711	4.5025	2.0863	4.576	0.1117
5.0475	1.3788	5.0025	1.8486	5.076	0.0932
5.5475	1.2974	5.5025	1.6557	5.576	0.0789
6.0475	1.225	6.0025	1.4965	6.076	0.0677
6.5475	1.1603	6.5025	1.363	6.576	0.0588
7.0475	1.1021	7.0025	1.2498	7.076	0.0515
7.5475	1.0495	7.5025	1.1528	7.576	0.0454
8.0475	1.0016	8.0025	1.0687	8.076	0.0404
8.5475	0.958	8.5025	0.9953	8.576	0.0362
9.0475	0.9179	9.0025	0.9308	9.076	0.0326
9.5475	0.8811	9.5025	0.8736	9.576	0.0295

Theorem 1: Stability Criteria [17]
Suppose that the $n-$ square matrix A has eigenvalues $\lambda_i, i = 1,2,\ldots,n$. Then the stability of a solution of the linear system of ordinary differential equations
$x' = Ax$
is determined according to the following criteria:
(i) If $\mathrm{Re}(\lambda_i) < 0$, for all i then there is uniform asymptotic stability,
(ii) If $\mathrm{Re}(\lambda_i) \leq 0$, for any i or algebraic multiplicity equals geometric multiplicity whenever $\lambda_i = 0$, for any i, then there is uniform stability,
(iii) If $\mathrm{Re}(\lambda_i) > 0$, for any i or the algebraic multiplicity is greater than the geometric multiplicity whenever $\lambda_i = 0$ for any i, then there is instability.

Theorem 2: Ackerman Criteria for Testing Diabetes from the result of GTT [15]
Given a Simple Harmonic equation in y, of the type:
$y'' + 2\alpha y' + \omega_0^2 y = 0$
where, α measures the ability of the system to return to equilibrium state after being perturbed and $\omega_0 = \sqrt{\omega^2 + \alpha^2}$ is the natural frequency of the system and
$T_0 = \frac{2\pi}{\omega_0}$ is the natural period of the system
If
$T_0 < 4$ hours, then the subject does not have diabetes,
$T_0 > 4$ hours, then the subject has diabetes.
The parameter values on Table 2 are substituted in the GTT model equation (17) to obtain equations (18) and (19). The graphs of glucose concentration using (18) and (19) are presented in Figure 1.

Subject A
$$G(t) = 77.0369757 + 179.564621e^{-1.02763759t}\sin(1.72436666t) \quad (18)$$
Subject B
$$G(t) = 95.2123549 + 263.1528475e^{-0.633490626t}\sin(1.030365222t + 0.008722147) \quad (19)$$

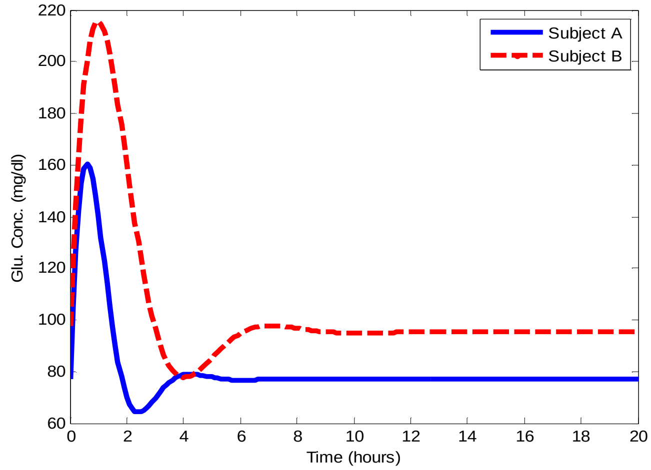

Figure 1: Graphs ofGTT

3.3 Stability of the Extended Model

Using equation (13) and the parameter values on Table 2 we obtain the following results:

Subject A

$$\lambda_{1,2} = -1.0276 \pm 1.7260i$$

Subject B

$$\lambda_{1,2} = -0.6335 \pm 1.0303i$$

Since the eigenvalues are both complex with negative real parts, it follows from Theorem 1that the system (4) – (6) is uniformly asymptotically stable.

3.4 Testing for Diabetes (GTT)

Subject A

Using the parameter values in Table 2 we get

$\omega_0 = \sqrt{\omega^2 + \alpha^2} = \sqrt{(1.72436666)^2 + (1.02763759)^2} = 2.0074$, and

$$\mathrm{T}_0 = \frac{2\pi}{\omega_0} = \frac{2\pi}{2.0074} = 3.1301$$

Subject B

Using the parameter values in Table 2 we get

$\omega_0 = \sqrt{\omega^2 + \alpha^2} = \sqrt{(1.030365222)^2 + (0.633490626)^2} = 1.2095$, and

$$\mathrm{T}_0 = \frac{2\pi}{\omega_0} = \frac{2\pi}{1.2095} = 5.1947$$

4.0 Results and Discussion

4.1 Numerical Simulation and Results

Thenull-clines of the extended model equations were simulated (hypothetically) to study the effect of physical exercise on the dynamics of glucose, insulin and epinephrine concentrations in the blood. The null-clines of the extended model equations (equations of glucose, insulin and epinephrine) are;

$$-(a+p)g - bh + fe = 0 \quad (20)$$

$$cg - (d+q)h + ke = 0 \quad (21)$$

$$-lg - m\square + (n+r)e = 0 \quad (22)$$

Or

$$g(p) = \frac{fe-bh}{a+p} \quad (23)$$

$$h(q) = \frac{cg+ke}{d+q} \quad (24)$$

$$e(r) = \frac{lg+m\square}{n+r} \quad (25)$$

A computer program is developed to simulate equations (23) – (25). The values generated from the simulation are presented in Table 3 andthe graphs obtained from the Table are presented in Figure 2.

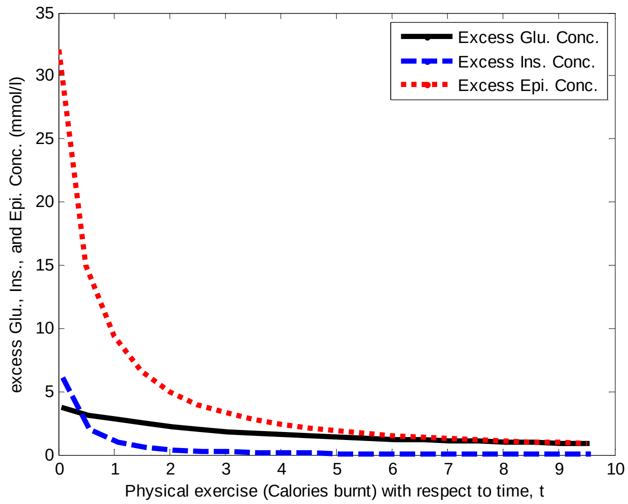

Figure 2: Effect of Physical Exercise on Glu., Ins., and Epi., Concs. in the Blood

4.2 Discussion

4.2.1 Discussion of the Analytical Results

The extended model is found to be uniformly asymptotically stable.This is a situation where the subject is normal. This result agrees with that of the existing model by Kwach *et al.*[6].

Also diabetes was tested using secondary data from a GTT of two individuals (subject A and subject B) and found the following results:

Subject A: The natural period of the system (3.1301) is less than 4 hours. This shows that the glucose concentration returns to normal level within a shorter time. This implies that the subject is normal (without diabetes). This result agrees with that of Rohan [16]with a natural period of3.0401, and Kwach *et al* [6] with a natural period of 2.9847.

Subject B: The natural period of the system (5.1947) is more than 4 hours. This shows that the glucose concentration will not return to normal within a shorter time. This implies that the subject is likely to have diabetes. This result agrees with that of Rohan [16]with a natural period of 5.1947 and Jacob [18] with a natural period of 5.2780. The above results show that the extended model can be used for the detection of diabetes.

4.2.2 Discussion of the Numerical Results

It can be seen (**Figure 1**) that the glucose concentration for subject A returns to normal (equilibrium) level within a shorter period than that of subject B. This indicates that subject A is normal, while subject B is likely to have diabetes. This result agrees with that Rohan [16].

It can also be seen (**Figure 2)** that as the effects of physical exercise on glucose, insulin and epinephrine concentrations increases, plasma glucose, insulin and epinephrine concentration returns to their equilibrium state. This is as a result of improvement in glucose uptake and utilization, insulin and epinephrine effectiveness in the body by physical exercise. This result agrees with that of Ibrahim *et al.* [13].

5.0 Conclusion and Recommendation

5.1 Conclusion

In this research work, we present a mathematical model for the detection and control of diabetes in the blood. The model is an extension of the model by Kwach *et al.* [6] where we include physical exercise as a diabetes control measure. We studied the stability of the new model and found out that it is uniformly asymptotically stable. We also tested for diabetes using secondary data from a GTT of two subjects, A and B. We found that subject A is normal (without diabetes). But subject B is likely to have diabetes. The numerical results also show that physical exercise can be used to bring blood glucose concentration, insulin concentration and epinephrine concentration to their equilibrium levels with time.The above results imply that, the extended model can be useful in the detection and control of diabetes.

Based on the results obtained from this work, we recommend the followings; Groups handling diabetes with various health services should aid in the detection of diabetes at an early stage by counselling and encouraging subjects (people) to carry out diabetes test. The Diabetes Association, in collaboration with the medical practitioners, recommend and encourage regular physical exercise for diabetic patients. Government, Diabetes Associations should improve on investment in physical exercising facilities for diabetic patients.

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