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MATHEMATICAL MODEL FOR DETERMINING DIABETES IN CAPE COAST

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Abstract
Diabetes is said to be one of the rising killer diseases globally, claiming one life every eight seconds and a limb lost at every 30 seconds. This has become a burden in the country as the situation has the tendency to weaken the workforce of the nation if much awareness is not induced. The aim of this project is to find out how our body's metabolism is linked to the disease by modeling the interaction between insulin and glucose. The objective is to use the model to analyse a clinical test for the determining of various forms of diabetes. A nonlinear least square method is used to determine the coefficient parameters of the system based on actual data from Glucose Tolerance test (GTT). The simulations also provide an indicator to diagnose a diabetic condition. Central Regional Teaching Hospital was used as the population and three patients were selected at random for the studies of which one was hyperglycemic (subject B), diabetic (subject C) and the other non-diabetic (subject A). The error between the simulated data and the experimental data was calculated to be very small in subject A and subject C. The case with subject B indicate that our model described above can only be used to diagnose mild diabetes or pre-diabetes, since it was assumed throughout that the deviation of g of G from its optimal value G_o is small.
Keywords: differential equation, diabetes, glucose, insulin.

INTRODUCTION

Shim and Siegel (2010) define mathematical model as a mathematical representation of reality that attempts to explain the behavior of some aspect of it. The mathematical model serves the following purposes: (1) to find an optimal solution to a planning or decision problem; (2) to answer a variety of what-if questions; (3) to establish understandings of the relationships among the input data items within a model; and (4) to attempt to extrapolate past data to derive meaning. Many everyday activities carried out without a thought are uses of mathematical models.

This paper seeks to model the test for detecting diabetes. One area of modeling that involves the interaction of two separate variables is called compartment models.

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. A compartment model could represent an ecological system where the material could be energy, the compartments could represent different species of animals and plants, and the flow between compartments could account for uptake and loss of food (or energy).

Compartment models 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 project the materials are glucose and insulin and the compartment is the blood.

Diabetes is a worldwide concern now and many developed countries are making it their national concern in fighting it. Some developing countries are making an attempt to fight it. In Ghana, about four million people may be affected with diabetes mellitus, which is a group of metabolic diseases in which a person has high blood sugar, a condition which could be attributed to a situation where either the body does not produce enough insulin or because cells do not respond to the insulin that is produced; but it could be controlled and managed with little injections of insulin (Bagbin, 2012). Many individuals have little or no knowledge about the disease and the extent of damage it can cause both to the individual and the nation as a whole. Muoio, and Newgard (2008) noted that 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, and glucagon control blood glucose levels, epinephrine best known as adrenaline, glucocorticoids and thyroxin. Diabetes is a disease that is characterized by excessive glucose in the blood stream. Currently, there is an epidemic of diabetes that has resulted from unhealthy lifestyles, which are dramatically different from how humans survived many years ago when food was difficult to find. There are two forms of diabetes, Type 1, often called juvenile diabetes, and Type 2, often referred to as adult onset diabetes (which now occurs in children as young as 5). Type 1 diabetes, is an autoimmune disease, and represents only 10% of all cases of diabetes. Type 1 diabetes is a hereditary disease, which occurs in about 4-20 per 100,000 people with peak occurrence around 14 years of age (Cooke et al, 2008).
Type 1 diabetes occurs when someone who is genetically predisposed to the disease incurs some unknown environmental assault that initiates the auto-immune system to attack their own β-cells. When the β-cells are destroyed, they boost the immune system to further attack more β-cells, leaving the body without the ability to produce insulin. This severely limits its ability to regulate glucose and results in the onset of diabetes. Because of the immune response, the body cannot regenerate new β-cells nor can transplants succeed. (Cooke et al, 2008).

The normal range of blood glucose concentration should be maintained within narrow limits throughout the day. The average is 70–140 mg/dl, lower in the morning and higher after the meals.

Table 1 Blood glucose levels chart

Person's Category	Fasting State		Postprandial
	Glucose minimum value(mg/dl)	Glucose maximum value(mg/dl)	2-3 hours after eating (mg/dl)
Hypoglycemia	-	<59	<60
Early Hypoglycemia	60	79	60-70
Normal	80	100	<140
Early diabetes	101	126	140-200
Diabetic	<126	-	<200

For most normal persons, the glucose levels are between 80 mg/dl and 100 mg/dl in a fasting state that occurs when a person has not eaten or drunk anything for at least eight hours. Table 1 shows the glucose levels for different people categories with the minimum and maximum value of the glucose level for each category. After eating, the glucose level rises above the normal level and should fall back to the original starting point within two to three hours. If the glucose level does not fall, the person is classified as diabetic or at the early diabetes stage. However, the glucose level should not fall below 60 mg/dl as this is typically the symptom of hypoglycemia.
The classical symptoms of diabetes are increased hunger (Polyphagia), increased thirst (Polydipsia), and frequent urination (Polyuria) (Cooke et al, 2008). These symptoms tend to develop rapidly (weeks or months) in Type 1 diabetes. The frequent urination results from the poor water re-absorption in the kidney because of the osmotic imbalance of glucose in the blood. The dehydration from frequent and dilute urine causes the symptom of being thirsty. Other symptoms include blurred vision caused by glucose absorption in the lenses of the

eyes, fatigue, weight loss, and poor wound healing. Type 1 diabetes may result is diabetic ketoacidosis, where the urine smells of acetone.

The onset of type 1 diabetes is most common in children or young adults and accounts for around 10% or less of the total number of people with diabetes. Type 2 diabetes accounts for almost all of the remaining cases of diabetes as the other forms are rare. Type 2 diabetes is a condition that predominantly affects middle-aged and older people but prevalence is increasing among children and young adults in countries with a high prevalence of obesity (WHO, 2003).

Diabetes prevalence studies in southern Ghana have recorded a steady increase. The earliest studies in the 1960s recorded 0.2% prevalence in a population of men in Ho (Ghana Medical, 1964). Diabetes screening conducted by the Ghana Diabetes Association in the early 1990s suggested 2–3% prevalence in urban areas in southern Ghana; in the late 1990s a prevalence rate of 6.4% for diabetes and 10.7% for impaired glucose tolerance (IGT) was recorded in a community in Accra (Amoah et al, 2002). At Korle-Bu hospital, the percentage of medical admissions due to diabetes increased almost two-fold from 3.5 in the mid-1970s to 6.4% in the mid-1980s (Adubofuor et al, 1993).

The level of glucose inside the human being body changes significantly in response to food intake and other physiological and environment conditions. It is necessary to derive mathematics models to capture such dynamics for control design. Over the years, many mathematical models have been developed to describe the dynamic behavior of the human glucose-insulin system. Such models are highly nonlinear and usually very complex. The most commonly used and simplified model is the minimal model introduced by Bergman in 1979.

The majority of mathematical models were devoted to the dynamics of glucose-insulin, including Intra Venous Glucose Tolerance Test (IVGTT), Oral Glucose Tolerance Test (OGTT) and Frequently Sampled Intra Venous Glucose Tolerance Test (FSIVGTT). So far, all the existing models were based on two variables only: glucose and insulin. The minimal model of glucose and insulin was formulated to be the easiest model with which to deal. This has been shown to be the simplest physiologically based representations that can respectively account for the observed glucose kinetics when the plasma insulin values are supplied and for the observed insulin kinetics when the plasma glucose values are supplied. The minimal model is capable of describing the dynamics of the diabetic patient.

Problem

A recent study conducted by Diabetes Care in the United States was to estimate the prevalence of diabetes and the number of people of all ages with diabetes for years 2000 and 2030. According to their studies, Ghana has its diabetics age 25 years and above out of a sample size of 4733 (Wild et al, 2004). The rate at which diabetes is sweeping our middle aged group can affect our nation's manpower. Apparently this disease is all over the nation affecting both the rich and the poor, young and old. Upon the many researches that had been on Ghana's diabetes it points out that the disease is increasing at a fast rate and this has become a national issue.

Objectives

The goal of this study is

1. To model the interaction between glucose and insulin in the body.
2. To use the model to discuss a clinical test for the detection of various forms of 1.0 diabetes.

2.0 BASIC DEFINITIONS AND CONCEPT

1. Diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels. The two most common forms of diabetes are Type 1 diabetes and Type 2 (Muoio, and Newgard, 2008).
2. Type 1 diabetes is due to a diminished production of insulin, this is also called insulin-dependent diabetes or juvenile-type diabetes. The patient of type 1 diabetes is considered hypoglycemic.
3. Type 2 diabetes is caused by the decreased insulin production by the beta cells of the pancreas and an increased insulin resistance by the peripheral tissues. This causes hyperglycemia, or high blood glucose levels 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.
Kwach et al (2011) presented a new mathematical model for Blood Glucose Regulatory System (BGRS) which include epinephrine as a third variable in the form

Y = AY, and whose solution has been analyzed for equilibrium and stability to provide the blood glucose concentrations for diabetics and non-diabetics. They established that the final model is asymptotically stable compared to the existing models (Kwach et al, 2011)
Mahaffy, (2006) deduced that diabetes mellitus results from the loss of β-cells, an auto - immune disease, the case where insulin production is severely reduced. It's a hereditary disease and the peak diagnosis occurs around age 14. He explains that 10% of diabetes cases are Type 1, while 90% are Type 2(where cells become insulin resistant, mostly in obese individual).
Rosado, (2009) explains how the various hormones in our body; insulin, growth hormone and glucagon control blood glucose levels and how they are activated. He also presented a mathematical model that determines the diabetes in patients based in the results on the glucose tolerance test of 5 hours. His model extended from the one proposed by (Ackerman, et al, 1969) which included three hormones instead of two.
(Stahl, et al, 2008) worked on Diabetes mellitus modeling and short term prediction based on blood glucose measurement. Here an attempt is made to show how system identification and control may be used to estimate predictive quantitative models to be used in the design of optimal insulin regimens. The system was divided into three subsystems, the insulin subsystem, the glucose subsystem and the insulin-glucose interaction. The insulin subsystem aims to describe the absorption of injected insulin from the subcutaneous depots and the glucose subsystem the absorption of glucose from the gut following a meal.
Diabetes care in the United States under took a study to estimate the prevalence of diabetes and the number of people of all ages with diabetes for years 2000 and 2030. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. (Wild, et al, 2004).
Boutayeb et al, (2004) noted on the burden and complications of diabetes on the individual and the society as a whole. They observed three levels of estimating the cost of diabetes namely: (1) Cost directly related to the diagnosis and management of diabetes without complications. This includes the in-patient and out-patient care, means of treatment by insulin or tablets and the equipment of self-control (blood and urine testing). (2) Costs generated by complications of diabetes. These are difficult to quantify because diabetes is linked to micro and macro vascular diseases such as heart disease, kidney failure, eye disease and

amputation. Moreover, diabetes may add a cost of care by complicating other unrelated medical situations like infections, accidents and surgery. (3). Indirect costs correlated to the quality of life and the economic productivity which can be somehow estimated by the degree of disability (Boutayeb, et al, 2004).

Type 2 diabetes is the most common form of type 2 diabetes accounting for around 90% of all diabetics. Approximately 18.2 million people in the United States have diabetes, or about 6.3% of the population. An exact number is not available due to many people that are undiagnosed and living with type 2 diabetes. Approximately 13 million people are diagnosed with diabetes and approximately 5.2 million people are undiagnosed (American Diabetes Association, 2005).

There is not one single risk factor that causes an individual to develop type 2 diabetes, but it is having multiple risk factors that put an individual at risk. The risk factors for developing type- 2 diabetes are: · Being overweight or obese; · Having a history of type 2 diabetes in your family ;Having high triglyceride levels, or low levels of HDL cholesterol (the "good" cholesterol); Having a history of gestational diabetes or the first recognition of diabetes during pregnancy.

Nutrition is a key component in maintaining near normal blood glucose levels. Limiting calories and fat to achieve a 5-10% weight loss, consuming less salt and watching how many carbohydrates are eaten are all important in the nutritional management of type 2 diabetes (Mahan, 2004). It is important to control portion sizes, eat nutrient dense foods, and include a variety of foods that are unprocessed. Eating a variety of foods including fruits, vegetables, complex carbohydrates, non-fat dairy, lean meats, beans, poultry, and fish are all important in a healthy diet (American Diabetes Association, 2005).

There are many tools or suggestions that one can use when trying to maintain normal blood glucose levels. One tool is the "Rate Your Plate", which is a great tool to use when you are trying to control portion sizes. One-fourth of the plate should be filled with whole grains, one-fourth should be protein, and half of the plate should be non-starchy vegetables. Other tools also include carbohydrate counters or exchange lists, which is when you count the carbohydrates or exchanges in each meal (American Diabetes Association, 2005).

Diabetes prevalence studies in southern Ghana have recorded a steady increase. The earliest studies in the 1960s recorded 0.2% prevalence in a population of men in Ho. Diabetes screening conducted by the Ghana Diabetes Association in the early 1990s suggested 2–3% prevalence in urban areas in southern Ghana; in the late 1990s a prevalence rate of 6.4% for diabetes and 10.7% for impaired glucose tolerance (IGT) was recorded in a community in Accra. At Korle-Bu hospital, the percentage of medical admissions due to diabetes increased almost two-fold from 3.5 in the mid-1970s to 6.4% in the mid-1980s. (Aikins, 2007).

Diabetes mellitus can be classified into four principal types .This includes type 1 diabetes, type 2 diabetes, other specific types of diabetes, and gestational diabetes mellitus. The most common types of diabetes seen in Sub-Saharan Africa are type 2 and type 1 diabetes mellitus. Although type 1 diabetes is not caused by the adverse effects of lifestyle, as type 2 can be, the chronic complications of both type 1 and type 2 diabetes on the eyes, cardiovascular system, nerves, and kidneys are similar (WHO 1999).

(Lynch and Bequette, 2002) tested the glucose minimal model of Bergman (1979) to design a Model Predictive Control (MPC) to control the glucose level in a diabetic patient. The insulin secretion term ($\gamma*(g-h)*t$) of the differential equation of the minimal model was replaced by a constant term which makes the infusion of the insulin to be constant and independent of the glucose level.

Fisher, (1991) used the glucose insulin minimal model of Bergman (1979) to design a semi-closed loop insulin infusion algorithm based on plasma glucose samplings taken over a three hours' time span. The study concentrates on the glucose level and did not take into

consideration some important factors such as free plasma insulin concentration and the rate at which insulin is produced as the level of glucose rises.

Furler, et al. (1985) modified the glucose insulin minimal model of Bergman (1970) by removing the insulin secretion and adding insulin antibodies to the model. The algorithm calculates the insulin infusion rate as a function of the measured plasma glucose concentration. The linear interpolation was used to find the insulin rate. The algorithm neglected some important variations in insulin concentration and other model variables. Also, it took more than two hours to bring the glucose level to the neighborhood of the glucose basal level.

METHODOLOGY

The Central Regional Teaching Hospital was used as the population for the study with few patients randomly selected. One patient known to be highly diabetic was selected while others were chosen at random.

Mathematical models will be derived from the interaction between glucose and insulin in the blood. The model will take the form as

$$\frac{dg}{dt} = F_1(g,h)$$

$$\frac{dh}{dt} = F_2(g,h)$$

where F_1 and F_2 are some functions, g is glucose, h is insulin and t is time. Since the level of glucose inside the human being body changes significantly up or down based on the amount and the kind of food, it is a nonlinear model. One major key problem in nonlinear system identification is to estimate the unknown parameters. Estimating the unknown parameters of a mathematical model requires the input-output data and the class of model. The parameters estimation problem can be formulated as an optimization problem where the best model is the model that best fits the data according to the given criterion. The parameters are chosen or guessed so that the output of the model is the best match with respect to the experimental data. Nonlinear models require iterative methods that start with an initial guess of the unknown parameters. The iteration alters the current guess until the algorithm converges. Experimental data will be collected from a medical clinic or hospital that will be used to check the accuracy of the model. A MATLAB, a programmable software and Excel spreadsheet will be used in the estimation of the parameters.

Data Analysis

The data in the table are fit to the model equation $g(t) = g_o + Ke^{-\alpha t}\cos(\beta t - \delta)$

A least square best fit is performed using Excel. An inbuilt tool, Solver was used to minimize the Least square error in order to obtain the optimal values for $g_o, K, \alpha, \beta and \delta$ .A table of the best fitting parameters for each of the subjects and the least sum of square errors are shown below in table 4.1.1.

4.1.1.Analysis on subject A

Subject A shows the results of a normal (non-diabetic) patient.

Table 4.1.1

Subject A- normal						
Time (hour)	Observed Glucose Concentration (mg/dl)	Predicted Glucose Concentration (mg/dl)	difference squared	SRE	MSRE	MSRE%
0	85.446	85.43881971	5.15566E-05	7.062E-09	8.062E-06	0.00081
1	119.988	119.8739354	0.013010728	9.037E-07		
2	92.718	92.75207858	0.00116135	1.351E-07		
3	85.446	85.01541599	0.185402593	2.539E-05		
4	83.628	83.93945414	0.097003679	1.387E-05		
				4.031E-05		
		sum of diff^2	0.296629906			
Parameters						
g	83.94540986					
K	287.7098641					
α	1.743175135					
β	0.789623301					
δ	1.565605623					

Substituting these parameters into equation (24) gives

$$g(t) = 83.95 + 287.7e^{-1.74t}\cos(0.79t - 1.57) \quad \text{...} \quad (28)$$

Figure 4.1 shows the graph of time against glucose concentration for table 4.1.1. On the graph the predicted points are shown in red whiles the observed points are shown in blue.

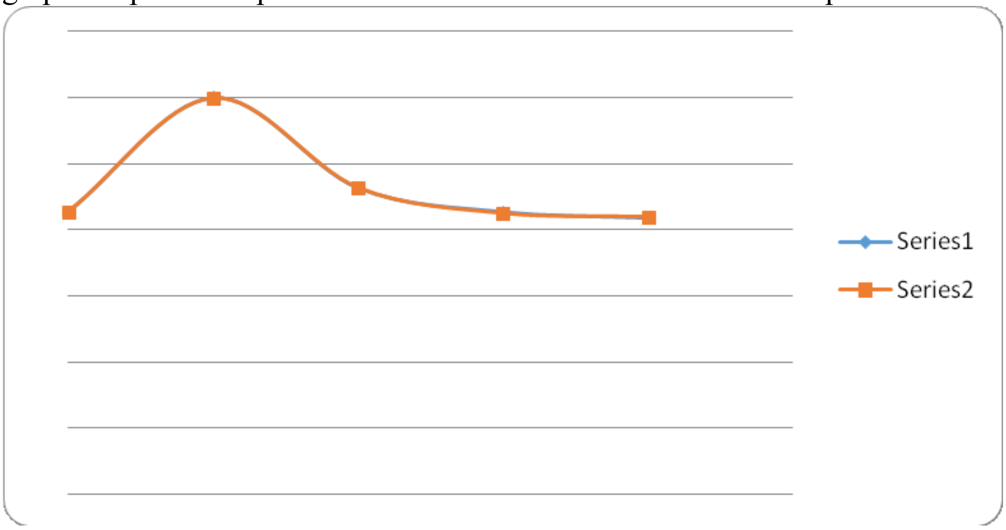

Figure 4.1.1 graph of subject A

Using the criterion set by Ackerman et al the natural period of the system can be calculated as follows;

From equation (27)

$$\omega_o = \sqrt{\beta^2 + \alpha^2} = \sqrt{0.789^2 + (-1.743)^2} = 1.913678$$

And $T_o = \dfrac{2\pi}{\omega_o} = \dfrac{2*\pi}{1.914} = 3.284$

Since $T_o < 4$ it implies that the person is normal.

4.1.2. Analysis on Subject B

Subject B - diabetes						
Time (hour)	Observed Glucose concentration (mg/dl)	Predicted Glucose Concentration (mg/dl)	Difference Squared	SRE	MSRE	MSRE%
0	194.526	194.5122614	0.00018875	4.98807E-09	0.053006	5.300573
1	605.394	551.5721503	2896.791507	0.007903892		
2	605.394	551.5721715	2896.789219	0.007903886		
3	599.94	551.5721715	2339.44683	0.006499763		
4	589.032	551.5721715	1403.238748	0.004044397		
5	358.146	551.5721715	37413.68384	0.291682425		
		sum of diff^2	46949.95033	0.318034369		
Parameter						
g	551.5721715					
K	786.2821511					
α	17.40826645					
β	0.910820217					
δ	4.241014072					

Substituting the parameters into equation (24)

$$g(t) = 551.57 + 786.28e^{-17.4t}\cos(0.91t - 4.24) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (29)$$

Correspondingly $\omega_o = 17.43207774$ and $T_o = 0.360484854$

The value of T_o indicates that with subject B time is not an essence, the individual can maintain a high glucose level for a long period of time until insulin is injected to begin to reduce the glucose .

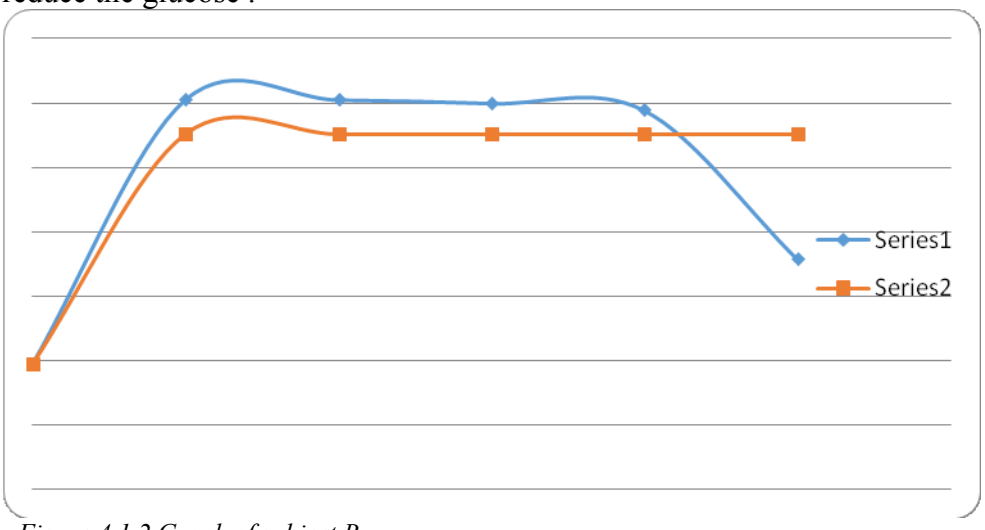

Figure 4.1.2 Graph of subject B

From the figure it is observed that the predicted points are the red and the observed points are the blue.

4.2.3 Analysis on Subject C

By substituting the parameters into equation (24) the general solution becomes

$$g(t) = 104.86 + 230.5e^{-0.5t}\cos(1.06t - 1.59) \qquad (30)$$

Also $\omega_o = \sqrt{0.538^2 + 1.06^2} = 1.191$ and $T_o = \frac{2\pi}{\omega_o} = \frac{2*\pi}{1.191} = 5.278$

Since $T_o > 4$ it implies that subject C is a diabetic.

Table 4.1.3 Analysis on subject C

Subject C						
Time (hour)	**Observed Glucose Concentration (mg/dl)**	**Predicted Glucose Concentration (mg/dl)**	**Difference squared**	**SRE**	**MSRE**	**MSRE%**
0	100	99.79420264	0.042352553	4.23526E-06	0.000674	0.067391
1	220	220.8929173	0.797301314	1.64732E-05		
2	175	172.5304381	6.098736136	0.000199142		
3	100	103.7998814	14.43909902	0.00144391		
4	85	81.20734359	14.38424266	0.001990899		
5	90	91.77464209	3.149354537	0.000388809		
		sum of diff^2	38.91108622			
				0.004043469		
Parameters						
g	104.8558461					
K	230.5246798					
α	0.538558627					
β	1.062200113					
δ	1.592755148					

Figure 4.1.3 shows the graph of subject C. From the figure the predicted points are shown in red whiles the observed points are in blue.

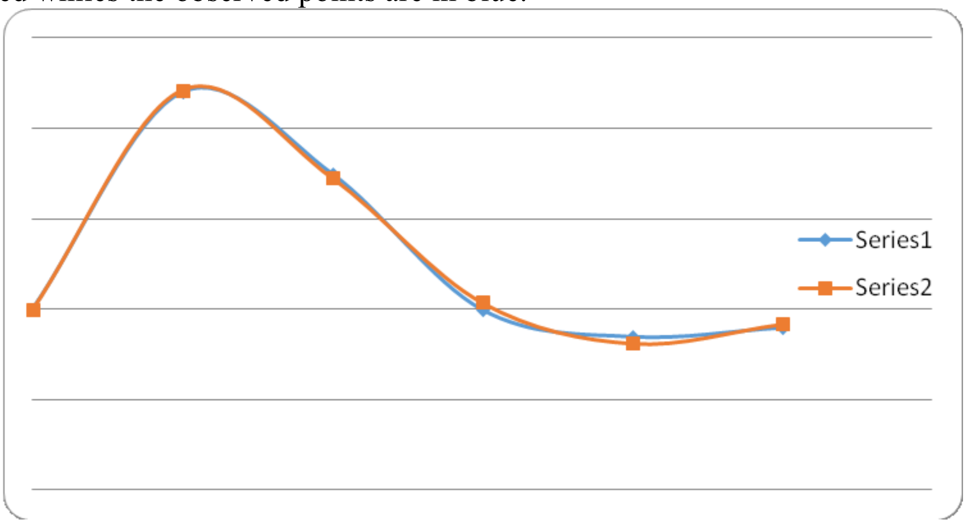

Figure 4.1.3 Graph of subject C

Discussion of results

Comparing figures 4.1.1, 4.1.2 and 4.1.3 it could noticed that figure 4.1.1 produced the best fit curve. The predicted values fall exactly on the observed or measured values and this

means that the values are good. It continues to make equation (28) the best model for detecting diabetes.
Figure 4.1.3 is the next best fit curve since the predicted values were just too close to the measured values. The natural period calculated for subject C shows that it is pre-diabetic that is a mild form of diabetes. Equation (30) of subject C also becomes a good model for detecting diabetes.
Figure 4.1.2 shows an advanced form of diabetes where the patients' blood glucose shown on the graph seems not to fall. This is called a hyperglycemic, a situation where the patient maintains a high level of glucose over a period of time unless is given insulin to help step down the glucose level.

CONCLUSION

In this paper a model for detecting diabetes Mellitus in the blood was derived given by the equation (23). Data collected on patients from the Central Regional Hospital and the Nonlinear Least Squares Method were used to estimate the unknown parameters of the differential equations that describe the glucose-insulin dynamics with the help of Excel spreadsheet inbuilt optimization tool called solver. The simulation diagram of the proposed mathematical model with the estimated parameters was constructed. The error between the simulated data and the experimental data was calculated to be very small in subject A and subject C. The case with subject B indicate that our model described above can only be used to diagnose mild diabetes or pre-diabetes, since it was assumed throughout that the deviation of g of G from its optimal value G_o is small. Very large deviations of G from G_o usually indicate severe diabetes or diabetes insipidus, which is a disorder of the posterior lobe of the pituitary gland (Ackerman et al, 1969).

Limitations

One shortcoming of this model is that it sometimes yields a poor fit to the data in the time period three to five hours after ingestion of glucose load. This indicates of course that variables such as epinephrine and glucagon play an important role in this time period. Also the five-hour Glucose Tolerance test (GTT) is no longer used in our hospitals and clinics. What is now commonly used is the Random Glucose Test. This made it difficult to obtain any secondary data fit for this thesis rather primary data was acquired of hand from three volunteers including myself. One being a normal person (non-diabetic), the other pre-diabetic and the last a strong diabetic (hyperglycemic).

Recommendation

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 Glucose Tolerance test (GTT) response, when glucose levels have been lowered below fasting levels.

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