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Mathematical Modeling of The Effect of Epinephrine And Insulin On Blood Glucose Concentration

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Abstract *- In this research, we modeled the interaction between blood glucose and insulin, with epinephrine as treatment of diabetes. Diabetes is a syndrome of disordered metabolism, due to the combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels. Different hormones in human body such as insulin, growth hormone, and glucagon control blood glucose concentration levels, epinephrine best known as adrenaline, glucocorticoids and thyroxin. The two most common forms of diabetes are due to either a diminished production of insulin (Type 1 diabetes), or diminished response by the body to 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. The problem was modeled, solved and can be used to explain the dynamics of hormone, insulin is activation and how it affects glucose levels in blood. The results obtained are in line with those proposed by Hussian and Zadeng (2014), however, the previous researcher never considered constant supply of an epinephrine and other treatment, which give rise to the proposed models. The proposed models are in homogenous ordinary differential equations form, with the initial condition. In order to study the effect of insulin and epinephrine on the glucose concentration, we differentiated blood glucose concentration equation and substitute the insulin and epinephrine equations into the resulting equation from the glucose differentiation and simplified. The reduced nonlinear differential equation was solved using the method of variation of parameters where we obtained the particular solution. The numerical simulation was done using Mathematica, version 10 and the basic entry parameters were varied to study their effect on blood glucose concentration.*

Keywords *- Modeling, Blood, Glucose, Concentration, Epinephrine, Diabetes*

I. INTRODUCTION

Mathematical modeling is defined as the translation of real life problems into mathematical problems, formulating mathematical models necessary for solving a problem and interpretation of the results (Berry and Nyman, 2002; Bukova-Guzel, 2011). It involves solving the mathematical problems and interpreting these solutions in the language of the real world, validating the conclusions by comparing them with the situation, and then either improving the model or, if it is acceptable, and applying the model to similar situations for evaluation and refinement.

Diabetes affects the levels in insulin and glucose in the bloodstream, hence it's very important to investigate. This numerical analysis of the model by Hussain and Zadeng (2014) allows medical professionals and mathematicians alike to better understand the interaction and regulation of insulin and glucose in the bloodstream. By using different methods to analyze, the model relationship can be further demonstrated and behaviors can be better predicted.

Ali and Tahir (2019) investigated the interaction of insulin and glucose regulation in Type 1 diabetes mellitus based on Lokta-Volterra model. The results of the research indicated that insulin-glucose regulating system has many dynamics in different situations. Joseph (2016) formulated models to study type 1 diabetes in mice at the University of British Columbia. He deduced that diabetes mellitus results from the loss of β-cells, an auto - immune disease, the case where insulin production is severely reduced. American Diabetes Association, (2005) Type 2 diabetes is the most common form of 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.

Cooke *et al*, (2008) said Type 1 diabetes, is an autoimmune disease, and represents only 10% of all cases of diabetes. They further stated that Type1 diabetes is a hereditary disease, which occurs in about 4-20 per 100,000 people with peak occurrence around 14 years of age.

Tai (1994) developed a mathematical model for the determination of total areas under glucose tolerance and other metabolic

curves. The model allows flexibility in experimental conditions, which means, in the case of the glucose-response curve, samples can be taken with differing time intervals and total area under the curve can still be determined with precision.
De Gaetano and Arino (2000) proposed an aggregated delay differential model called the dynamic model which solves the problems found in the minimal model. The dynamic model was also observed to have positive, bounded solutions and to be globally asymptotically stable around the pre-injection equilibrium blood glucose and insulin concentrations.
Mukhopadhyay *et al*. (2004) concluded that dynamical model has been shown to allow simultaneous estimation of both insulin secretion and glucose uptake parameters. They proposed an extension by introducing a generic weight function in the delay integral kernel for the pancreatic response to glucose. Boutayeb *et al.* (2004) used ordinary differential equations and numerical approximations to monitor the size of populations of diabetes with and without complications. Li *et al.* (2006) proposed a mathematical model to study the glucose-insulin regulatory system with two explicit time delays applying the mass conservation law. They suspected that one of the possible many causes of ultrafine insulin secretion oscillations is the time delay of the insulin secretion simulated by the elevated glucose concentration.
Adewal *et al*. (2007) presented a new generalized mathematical model for the study of diabetes mellitus. The model accounted for all glucose intake and insulin injected (administered) as a function of the molecular weight of carbohydrate and protein intake, respectively. They used the model to monitor the blood plasma glucose level in non-diabetic and suspected diabetic subjects.
De Gaetano *et al*. (2008) formulated a model of the pancreatic islet compensation, presented its physiological assumptions, established some fundamental qualitative characteristics of its solutions, extensively discussed the numerical values assigned to its parameters, simulated its performance over the span of a lifetime under various conditions, including worsening insulin resistance and primary replication defects. Singh *et al*. (2014) formulated a mathematical model to describe the performance of Blood Glucose Regulating System (BRGS) during Glucose Tolerance Test (GTT). And they concluded that a value of less than four hours for at the initial time frame, the corresponding period to the natural frequency of the system indicated normalcy while appreciably more than four hours implied mild diabetes. Aliukonis *et al.* (2009) proposed a mathematical model to study the impact of physical exercises on glycemic regulation. They performed linear, nonlinear and numerical analysis of glycemic regulation and they also applied the simulating modeling program for modeling. On introducing two external periodical functions defining diet and physical exercise in normal and diabetic cases, their numerical analysis showed that their model reflects glycemia and insulin dynamics of a healthy person and a diabetic person rather exactly.
Li and Zheng (2010) proposed a general model following the dynamic model which includes single delay model and one of the models in Li *et al.* (2001) as a special case. Their model admits globally stable equilibrium under certain conditions of the parameter. Their model is shown to admit oscillating behavior due to the existence of Hopf-bifurcation. However, Sadhya and Kumar (2011) proposed a new mathematical model for the study of diabetes which takes into account plasma glucose concentration, generalized insulin and plasma insulin concentration. Their model showed the difference of glucose-insulin regulatory system between a normal person and a diabetic person. They found that the glucose concentration of diabetic patient does not come down after a certain time which showed the evidence that the person suffer from diabetes. Bunonyo *et al*. (2020) investigated blood flow through a channel with treatment and magnetic field.
Many researchers have modeled the interaction of insulin and glucose in the bloodstream of those afflicted with diabetes. For instance, Gaetano and Arino (2000) presented a dynamic system, simple delay differential model which was created based on a minimal model from the early 1980s that was largely used in physiological research. According to their investigation, the model is both desirable and practical in that it appropriately demonstrates the body's physiological interactions with glucose and insulin. However, the general model presented by Hussain and Zadeng was based on not only this model by Gaetano and Arino earlier research. In view of the aforementioned literatures we've reviewed so far, and the recent model by Hussain and Zadeng (2014), we present our proposed models to study the interaction between glucose concentration, insulin in the blood stream and epinephrine as treatment in the system.

II. MATHEMATICAL FORMULATION

In formulating mathematical models to study the interaction between glucose and insulin, and the consideration of epinephrine as the treatment for Type 1 and Type 2, diabetes, we shall first consider the previous models that investigated the glucose concentration; we consider research by Hussain and Zadeng (2014).

A. Previous Models

According to Hussain and Zadeng (2014), the glucose concentration and insulin relationship in bloodstream is:

$$\frac{dx}{dt} = -a_1 x - a_2 y + a_3 x \tag{3.1}$$

$$\frac{dy}{dt} = b_1 x - b_2 y \tag{3.2}$$

$$x \geq 0, y \geq 0$$

B. Modified Models

Following Hussain and Zadeng (2014), we introduced the epinephrine treatment effect on equation (3.1)–(3.2), and present the modified system as follows:

$$\frac{dx}{dt} = -a_1 x - a_2 y + a_3 x + a_4 w \tag{3.3}$$

$$\frac{dy}{dt} = b_1 x - b_2 y + b_3 w \tag{3.4}$$

$$\frac{dw}{dt} = \mu_0 + b_3 w - a_5 x - b_4 y \tag{3.5}$$

III. MATHEMATICAL ANALYSIS

Recalling the modified system in our mathematical analysis, we have them written as:

$$\frac{dx}{dt} = -a_1 x - a_2 y + a_3 x + a_4 w \tag{3.3}$$

$$\frac{dy}{dt} = b_1 x - b_2 y + b_3 w \tag{3.4}$$

$$\frac{dw}{dt} = \mu_0 + b_3 w - a_5 x - b_4 y \tag{3.5}$$

To solve equation (3.3)-(3.5), we first differentiate equation (3.3), which we have as:

$$\frac{d^2x}{dt^2} = -a_1 \frac{dx}{dt} - a_2 \frac{dy}{dt} + a_3 \frac{dx}{dt} + a_4 \frac{dw}{dt} \tag{3.6}$$

Substituting equation (3.4) to (3.5) into equation (3.6), we have the following:

$$\frac{d^2x}{dt^2} = \left(a_3 - a_1\right)\frac{dx}{dt} - \left(a_2 b_1 + a_4 a_5\right)x + \left(a_2 b_2 - a_4 b_4\right)y + \left(a_4 b_3 - a_2 b_3\right)w + \mu_0 a_4 \tag{3.7}$$

Assuming $y(0) = 0$, then equation (3.3) is reduced to:

$$w = \frac{1}{a_4}\frac{dx}{dt} + \frac{\left(a_1 - a_3\right)}{a_4}x \tag{3.8}$$

Substitute equation (3.8) into equation (3.7), we have:

$$\frac{d^2x}{dt^2} = \left(a_3 - a_1\right)\frac{dx}{dt} - \left(a_2 b_1 + a_4 a_5\right)x + \left(a_4 b_3 - a_2 b_3\right)\left(\frac{1}{a_4}\frac{dx}{dt} + \frac{\left(a_1 - a_3\right)}{a_4}x\right) + \mu_0 a_4 \tag{3.9}$$

Simplifying equation (3.9), we have:

$$\frac{d^2x}{dt^2} + \left(\left(a_1 - a_3\right) + \frac{\left(a_4 b_3 - a_2 b_3\right)}{a_4}\right)\frac{dx}{dt} + \left(\frac{\left(a_3 - a_1\right)\left(a_4 b_3 - a_2 b_3\right)}{a_4} - \left(a_2 b_1 + a_4 a_5\right)\right)x = -\mu_0 a_4 \tag{3.10}$$

Let $2\alpha = \left(\left(a_1 - a_3\right) + \frac{\left(a_4 b_3 - a_2 b_3\right)}{a_4}\right)$ and $\omega_0^2 = \left(\frac{\left(a_3 - a_1\right)\left(a_4 b_3 - a_2 b_3\right)}{a_4} - \left(a_2 b_1 + a_4 a_5\right)\right)$, so that equation (3.10) is reduced to:

$$\frac{d^2x}{dt^2}+2\alpha\frac{dx}{dt}+\omega_0^2x=-\mu_0a_4 \tag{3.11}$$

Solving equation (3.11), we let $x=e^{\lambda t}$, so that the homogenous equation (3.11) can be written as:

$$\lambda^2+2\alpha\lambda+\omega_0^2=0 \tag{3.12}$$

The solution to equation (3.12) is obtained as:

$$\lambda_1=\frac{-2\alpha+\sqrt{4\alpha^2-4\omega_0^2}}{2} \text{ and } \lambda_2=\frac{-2\alpha-\sqrt{4\alpha^2-4\omega_0^2}}{2} \tag{3.13}$$

The roots of equation (3.13) can be rewritten as:

$$\lambda_1=-\alpha+\sqrt{-\left(\omega_0^2-\alpha^2\right)} \text{ and } \lambda_2=-\alpha-\sqrt{-\left(\omega_0^2-\alpha^2\right)} \tag{3.14}$$

Let $\omega^2=\left(\omega_0^2-\alpha^2\right)$, so that the roots are reduced to:

$$\lambda_1=-\alpha+i\omega \text{ and } \lambda_2=-\alpha-i\omega \tag{3.15}$$

So, the homogenous solution of equation (3.11) is:

$$x_c=e^{-\alpha t}\left(A_1cos\omega t+B_1sin\omega t\right)=A_1e^{-\alpha t}cos\omega t+B_1e^{-\alpha t}sin\omega t \tag{3.16}$$

where

$$x_1=e^{-\alpha t}cos\omega t, x_2=e^{-\alpha t}sin\omega t \tag{3.17}$$

We apply the method of variation of parameters to obtain the particular solution of equation (3.11), which is:

$$x_p\left(t\right)=A_1\left(t\right)e^{-\alpha t}cos\omega t+B_1\left(t\right)e^{-\alpha t}sin\omega t \tag{3.18}$$

So that

$$A_1\left(t\right)=\mu_0a_4\int\frac{\left(e^{-\alpha t}sin\omega t\right)}{W\left(x_1,x_2\right)} \text{ and } B_1\left(t\right)=-\mu_0a_4\int\frac{\left(e^{-\alpha t}cos\omega t\right)}{W\left(x_1,x_2\right)} \tag{3.19}$$

The Wronskian is calculated as follows"

$$W\left(x_1,x_2\right)=\begin{vmatrix} e^{-\alpha t}cos\omega t & e^{-\alpha t}sin\omega t \\ -\alpha e^{-\alpha t}cos\omega t-\omega e^{-\alpha t}sin\omega t & \omega e^{-\alpha t}cos\omega t-\alpha e^{-\alpha t}sin\omega t \end{vmatrix} \tag{3.20}$$

Simplifying equation (3.20), we have:

$$W\left(x_1,x_2\right)=\omega e^{-2\alpha t} \tag{3.21}$$

Substituting the result in equation (3.21) into equation (3.19), we have:

$$A_1\left(t\right)=\frac{\mu_0a_4}{\omega}\int\left(e^{\alpha t}sin\omega t\right)dt \text{ and } B_1\left(t\right)=-\frac{\mu_0a_4}{\omega}\int\left(e^{\alpha t}cos\omega t\right)dt \tag{3.22}$$

By applying integration by part on equation (3.22), we have:

$$\begin{aligned} A_1\left(t\right)&=\frac{\mu_0a_4}{\omega}\int\left(e^{\alpha t}sin\omega t\right)dt=\frac{\mu_0a_4e^{\alpha t}}{\omega}\left(\frac{\omega cos\left(\omega t\right)+\alpha sin\left(\omega t\right)}{\alpha^2+\omega^2}\right) \\ B_1\left(t\right)&=-\frac{\mu_0a_4}{\omega}\int\left(e^{\alpha t}cos\omega t\right)dt=\frac{\mu_0a_4e^{\alpha t}}{\omega}\left(\frac{\alpha cos\left(\omega t\right)-\omega sin\left(\omega t\right)}{\alpha^2+\omega^2}\right) \end{aligned} \tag{3.23}$$

Now, we substitute equation (3.23) into equation (3.18), we have the particular solution as:

$$x_p\left(t\right)=\left(\frac{\mu_0a_4}{\omega}\left(\frac{\omega cos\left(\omega t\right)+\alpha sin\left(\omega t\right)}{\alpha^2+\omega^2}\right)\right)cos\omega t+\left(\frac{\mu_0a_4}{\omega}\left(\frac{\alpha cos\left(\omega t\right)-\omega sin\left(\omega t\right)}{\alpha^2+\omega^2}\right)\right)sin\omega t \tag{3.24}$$

The solution to equation (3.11) is the sum of equation (3.16) and equation (3.24), which is:

$$x(t)=\left(\begin{array}{l} A_1e^{-\alpha t}cos\omega t+B_1e^{-\alpha t}sin\omega t+\left(\frac{\mu_0a_4}{\omega}\left(\frac{\omega cos(\omega t)+\alpha sin(\omega t)}{\alpha^2+\omega^2}\right)\right)cos\omega t \\ +\left(\frac{\mu_0a_4}{\omega}\left(\frac{\alpha cos(\omega t)-\omega sin(\omega t)}{\alpha^2+\omega^2}\right)\right)sin\omega t \end{array}\right) \tag{3.25}$$

To solve for the constant coefficient, we considered the initial glucose concentration at $t=0$ $x(0)=x_0$ and the concentration at $t=T$ which is $x(T)=x_T$ so that

$$x(t)=\left(\begin{array}{l} A_1e^{-\alpha t}cos\omega t+B_1e^{-\alpha t}sin\omega t+\left(\frac{\mu_0a_4}{\omega}\left(\frac{\omega cos(\omega t)+\alpha sin(\omega t)}{\alpha^2+\omega^2}\right)\right)cos\omega t \\ +\left(\frac{\mu_0a_4}{\omega}\left(\frac{\alpha cos(\omega t)-\omega sin(\omega t)}{\alpha^2+\omega^2}\right)\right)sin\omega t \end{array}\right) \tag{3.26}$$

where $A_1=x_0-\left(\left(\frac{\mu_0a_4}{\alpha^2+\omega^2}\right)\right)$

$$B_1=\left[\begin{array}{l} \frac{x_Te^{\alpha t}}{\sin\omega T}-\left(\frac{\mu_0a_4e^{\alpha t}}{\omega}\left(\frac{\alpha\cos(\omega T)-\omega\sin(\omega T)}{\alpha^2-\omega^2}\right)\right)- \\ \left(\left(\frac{x_0}{\sin\omega T}-\frac{1}{\sin\omega T}\left(\frac{\mu_0a_4}{\alpha^2+\omega^2}\right)\right)+\frac{\mu_0a_4e^{\alpha T}}{\omega\sin\omega T}\left(\frac{\omega\cos(\omega T)+\alpha\sin(\omega T)}{\alpha^2+\omega^2}\right)\right)\cos\omega T \end{array}\right]$$

IV. RESULTS AND DISCUSSION

We formulated the interaction between blood glucose concentration and insulin level, with epinephrine model. The system of equation was solved and simulation carried out using Mathematica, and the data used are obtained from Hussain and Zadeng (2014). The results are presented as Figure 1 to Figure 4, the graphical results are as follows:

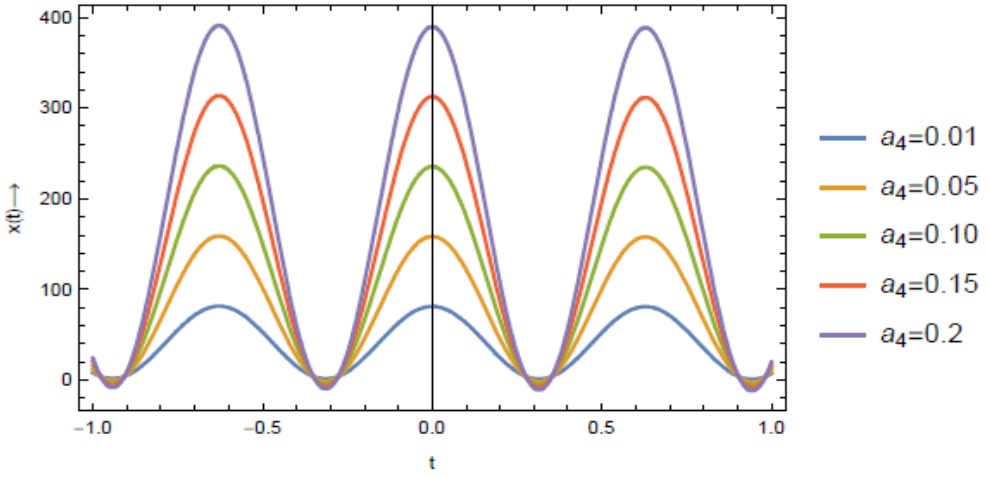

Figure 1 Effect of a_4 on blood glucose concentration $x(t)$

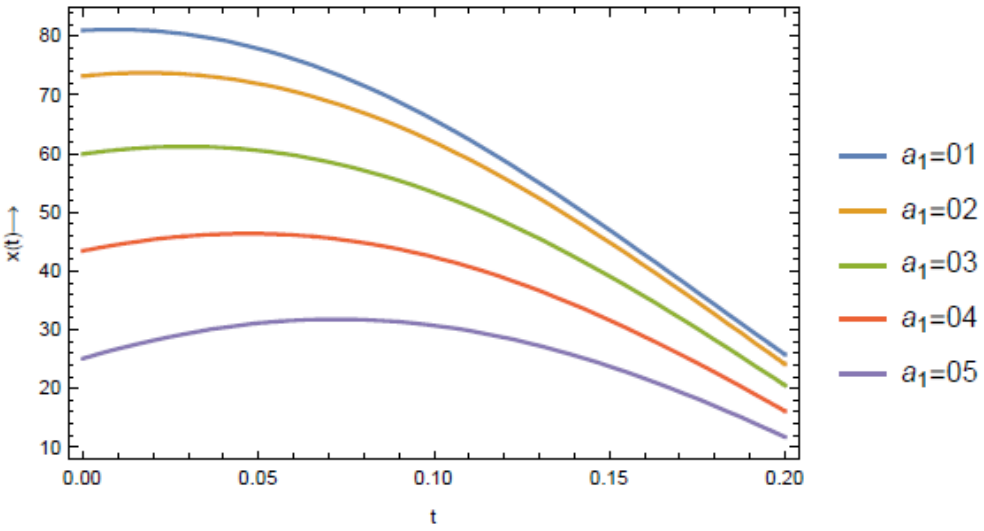

Figure 2 Effect of $\alpha(a_1)$ on blood glucose concentration $x(t)$

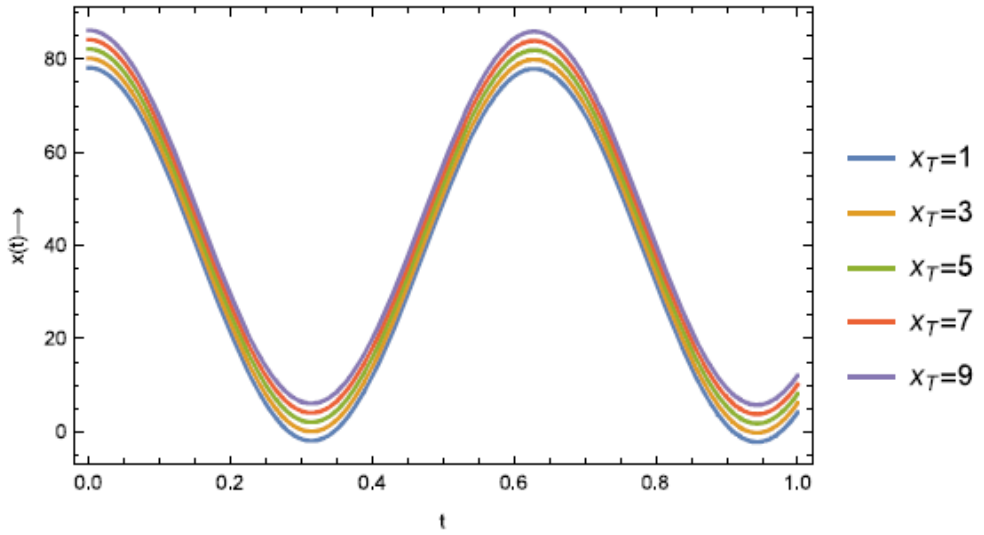

Figure 3 Effect of x_T on blood glucose concentration $x(t)$

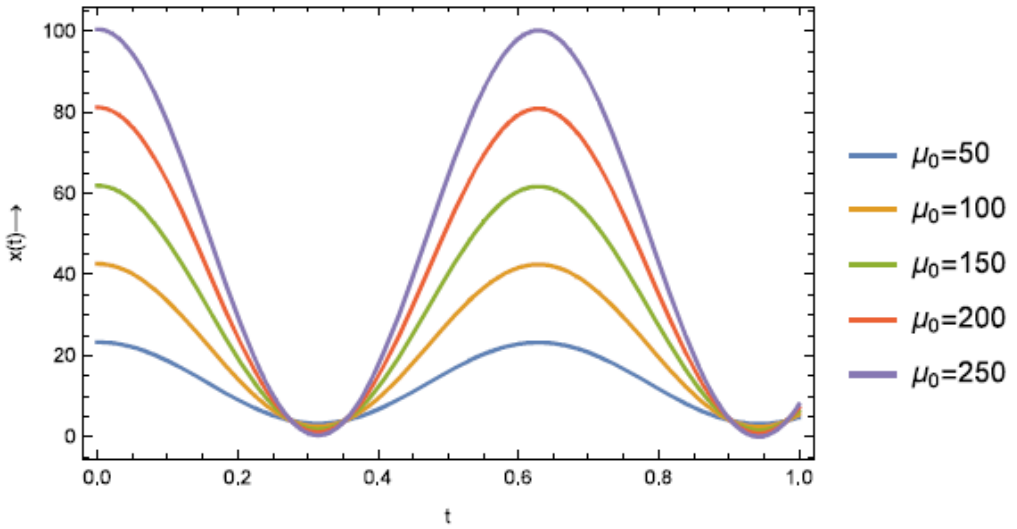

Figure 4 Effect of μ_0 on blood glucose concentration $x(t)$

IV. DISCUSSION OF RESULTS

We have formulated our model to investigate the impact of epinephrine treatment on the glucose level by solving the dynamics system of equation for the glucose concentration interaction with insulin and treatment through the use of epinephrine, an adrenaline related medication, and we found the following observations:

i. Figure 1 shows that the glucose concentration increases, as the pancreatic beta cell cause an increase in insulin level.
ii. The increase in the insulin independent disappearance rate causes a decrease in blood glucose concentration level, as illustrated in Figure 2
iii. Figure 3 depicts a scenario where blood glucose concentration increases for the different concentration level at time $t \to T$ increase, that is, as x_T increases.
iv. Figure 4 clearly shows an increase in blood glucose concentration, for the increase in constant supply of epinephrine μ_0.

In conclusion, we have been able to formulate the interaction between blood glucose and insulin, considering constant supply of epinephrine in addition to the epinephrine model which was not considered by Hussain and Zadeng (2014). The system was solved comprehensively using the method of variation of parameter (VPM), and obtained the exact the solution. And our result oscillatory behaviors strongly agrees with Li and Zheng (2010).

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Definition of parameters

$\frac{dx}{dt}$ The rate change of glucose concentration over time

$\frac{dy}{dt}$ The rate of change of insulin concentration over time

$\frac{dw}{dt}$ The rate of change of epinephrine concentration over time

μ_0 Constant supply of epinephrine into the bloodstream

α Pancreatic a_4 cells increase, results to an increase in α

a_1 The rate constant which represents insulin-independent glucose disappearance rate

a_2 The rate constant which represents insulin-dependent glucose disappearance rate

a_3 Is the glucose infusion rate

a_4 The rate of pancreatic β cell increase insulin after glucose injection

a_5 The threshold value of glucose above which the pancreatic β cell increase insulin

b_1 The rate constant which represent insulin production due to glucose stimulation

b_2 The rate constant which represent insulin degradation

b_3 Insulin concentration increase per mg/dl increase in concentration of glucose

b_4 The constant amount of insulin dependent glucose disappearance rate

x_0 The initial amount of blood glucose concentration at $t = 0$

x_T The amount of glucose concentration at $t = T \equiv 100\text{sec}$