MATHEMATICAL MODEL FOR THE DYNAMICS OF $\beta - cell$ MASS, INSULIN-GLUCOSE KINETICS INCORPORATING THE EFFECT OF CORTISOL, EPINEPHRINE AND PHYSIOLOGICAL DELAY

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A THESIS SUBMITTED TO THE DEPARTMENT OF MATHEMATICS, SCHOOL OF PHYSICAL SCIENCES, YOLA, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTER DEGREE OF SCIENCE IN MATHEMATICS OF THE MODIBBO ADAMA UNIVERSITY OF TECHNOLOGY, YOLA

FEBRUARY, 2020

DECLARATION PAGE

I hereby declare that this project thesis was written by me and it is a record of my own research work. It has not been presented before in any previous application for a higher degree. All references cited have been duly acknowledge.

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USMAN, Solomon Alani Date

DEDICATION

I dedicate this research work to my late father MWO Usman Alani (rtd) and my beloved mother Mrs. Mero Usman.

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ABSTRACT

In this work, we present a mathematical model for the dynamics of β-cell mass, insulin-glucose kinetics incorporating the effect of cortisol, epinephrine and physiological delay. Parameter ρ_c is defined and incorporated in this work to represent the effectiveness of cortisol in suppressing insulin, also the parameter $G_c(t-\tau)$ is define and incorporated to represent cortisol induced glucose increase with τ representing physiological delay as the factor that affect glucose-insulin homeostasis. The model which consists of a system of three non-linear ordinary differential equations is used to investigate the effect of cortisol and physiological delay on glucose, insulin and beta-cell mass dynamics. The results of the study show that; in the presence of cortisol, the blood glucose increases and the blood insulin decreases due to suppression by the hormone, despite the fact that there is increase in beta-cell mass, the system remain extremely hyperglycemic. Further, the result of the numerical experiment carried out indicate that frequent cortisol secretion into the blood induce prolong and extreme hyperglycemia. Frequent cortisol and epinephrine secretions increases the risk of diabetes in humans.

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CHAPTER ONE

INTRODUCTION

1.1 Background of the study

Diabetes mellitus is the disease of the metabolism, which is characterized by very high insufficient supply of the insulin. One of the most finely tuned mechanisms of the human body is the regulation of sugar in the blood stream. A delicate balance is normally maintained between the amount of glucose and insulin in the bloodstream (Kwacha, Ongati, & Simwa, 2011). Diabetes mellitus can also be defined as a disease of glucose regulatory system characterized by fasting and/or postprandial hyperglycemia (Mohammed, Adamu, & Barka, 2019).

According to Mohammed *et al*. (2019), there are two types of diabetes namely;

i. Types 1 diabetes T1DM.
ii. Types 2 diabetes T2DM.

1.1.1 The type 1 diabetes T1DM

Type 1 diabetes (also referred to as juvenile onset or insulin-dependent diabetes) is due to autoimmune attack on the insulin secreting β-cells (Mohammed *et al*., 2019). Type 1 diabetes affects people under the age of 40, and represents 10-15% of the diabetic population (Boutayeb, Twizell, Acouayb & Chetouni, 2004). Patients with type 1 diabetes are recommended to take insulin injection (Ahlam & Alaa, 2014).

1.1.2 The type 2 diabetes T2DM

Type 2 diabetes (also referred to as adult onset or non-insulin-dependent diabetes) is associated with a deficit in the mass of β-cells due to extreme elevated blood glucose level with reduced insulin secretion and resistance to the action of insulin (Mohammed *et al*., 2019). Type 2 diabetes represents 85-90% of the diabetic population (Boutayeb *et al*., 2004).

The pre-disposing historical high-risk factors for T2DM include increasing age (old age), central obesity, dietary polyphagia of animal fat, carbonated drinks, lack of physical exercise, familiar genetic factor, history of gestational diabetes, polycystic ovary syndrome, severe mental illness, presence of hypertension, hyperlipidaemia, ethnicity and cardio-metabolic factors. Recent emerging risk factors include sleeping deprivation, drug-induced metabolic changes, environmental pollutants, low birth weight and fatal malnutrition (Frank & Mingxian, 2015). Gestational diabetes can occur temporarily during pregnancy which is due to hormonal changes and usually begins in the fifth or sixth month of pregnancy (between the 24^{th} and 28^{th} weeks). Gestational diabetes usually resolves once the baby is born. However, 25-50% of women with gestational diabetes will eventually develop diabetes later in their life, especially in those who require insulin during pregnancy and those who are overweight after delivery (Ahlam & Alaa, 2014).

1.1.3 Aetiology and progression of diabetes

Diabetes mellitus, commonly known as diabetes, is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels known as Hyperglycemia (Hussain & Zendeng, 2014).

Blood glucose levels are regulated by two negative feedback loops. In the short term, hyperglycemia stimulates a rapid increase in insulin release from the pancreatic β-cells. The associated increase in blood insulin levels causes increased glucose uptake and decrease glucose production by the liver leading to reduction in blood glucose

(Mohammed *et al*., 2019). Recent evidence suggests that chronic hyperglycemia may contribute to a second negative feedback loop by increasing the mass of insulin secreting β-cells, through changes in the rates of β-cells replication and death (Mohammed *et al*., 2019). An increase in β-cells represents an increase an increase capacity for insulin secretion which, in turn, would lead to decrease in blood glucose. Type 2 diabetes has been associated with defects in components of both the short-term and chronic negative feedback loops. Although type 2 diabetes is associated with insulin resistance, insulin secretory defects, and insulin β-cells mass. Each of these defects can also be found in people without diabetes.

Insulin-stimulated glucose disposal is reduced to 50-100% in patients with type 2 diabetes as compared to non-diabetic controls. However, insulin resistance of a similar magnitude also has been documented in many no-diabetic individuals including obese subjects, or during pregnancy, puberty, and aging (Mohammed *et al*., 2019). Thus, normoglycemia can be maintained in subjects with insulin resistance via increase in blood insulin levels. Defect of insulin secretion have been demonstrated in some people with type 2 diabetes (Mohammed *et al*., 2019). Even more severe defects in insulin secretion are present in patients with type 2 diabetes following islet transplantation, when normoglycemia is maintained in the absence of exogenous insulin treatment (Mohammed *et al*., 2019). This suggests that glucose homeostasis can be maintained despite significant loss of β-cell function when an individual has normal insulin sensitivity. Mohammed *et al*. (2019) observed that β-cell mass is reduced by 40-50% in patients with type 2 diabetes when compared with weight matched non-diabetic subjects. In comparison, approximately 80-90% of the β-cell mass is lost before the onset of hyperglycemia in individuals who develop type 1 diabetes, suggesting that a greater β-cell mass is required in the presence of insulin resistance (Mohammed *et al*., 2019). This is also consistent with the observation of a 43% higher β-cell mass in normoglycemia for subjects with insulin resistance due to obesity (Mohammed *et al*., 2019). Although these data suggest that multiple defects are required for the onset of type 2 diabetes, it is unclear if these defects have single casual origin or if they occur independently. Experimental induction of insulin resistance using either high fat feeding, glucocorticoid administration, or genetically induced obesity has been shown to cause type 2 diabetes under certain circumstances. This support the hypothesis that insulin resistance can cause β-cell defects, and hence diabetes, either by over working the β-cell (β-cell exhaustion) or by toxic effects of hyperglycemia on the β-

cell (glucose toxicity). However, the existence of normoglycemia in humans and animals highly resistant to insulin, suggests independent defects in insulin sensitivity and β-cell function are required for type2 diabetes. Finally, hyperglycemia is known to induce insulin resistance. This supports the hypothesis that a primary insulin secretory defect that causes hyperglycemia could lead to hyperglycemia could lead to insulin resistance and diabetes via increased glucose levels (Mohammed *et al*., 2019).

1.1.4 Symptoms of diabetes

According to report by Temitope (2016), the symptoms of diabetes are as follows:

1. Frequent urination and excessive thirst
2. Disproportionate thirst
3. Intense hunger
4. Weight gain
5. Unusual weight loss
6. Increase fatigue
7. Irritability
8. Blurred vision
9. Sexual dysfunction among men
10. Numbness or tingling, especially in feet or hands etc

1.1.5 Diabetes complications

Diabetes if not controlled it will lead to the following complications:

1. Kidney failure.
2. Blindness.
3. Amputation.
4. Cardiovascular diseases (Boutayeb *et al*., 2004).

1.2 Statement of the Problem

Mohammed *et al*. (2019) extended the work of Topp, Promislaw, Devries, Miura, & Finegood, (2000) by incorporating the effect of epinephrine due to trauma, stress and/or excitement. Mohammed *et al.* (2019) did not incorporate the joint effect of cortisol & epinephrine, and physiological delay in the sensing and secretion of glucose and insulin due to trauma, stress and/or excitement in their work.

In this work, we set out to develop a mathematical model for $\beta - cell$ mass, insulin and glucose kinetics under the combined influence of cortisol and epinephrine by incorporating physiological delay.

1.3 Aim and Objectives of the Study

The aim of this work is to develop a mathematical model for the dynamics of β-cell mass, insulin-glucose kinetics incorporating the effect of cortisol, epinephrine and physiological delay.

The objectives of our study are to:

i. extend the Mohammed *et al.* (2019) model, by incorporating the combine effect of cortisol with physiological delay and epinephrine on β-cell mass, insulin and glucose dynamics.
ii. obtain the equilibrium of the modified model.
iii. analyse stability of the modified model.
iv. carry out numerical experiments on the modified model.
v. compare the performance of the existing and modified models from the results of the numerical experiments.

1.4 Significance of the Study

This model will help Mathematic modelers have a good understanding of the dynamics of insulin-glucose kinetics under the influence of stress, excitement, and trauma. This is because this model incorporates the combine effect of cortisol with physiological delay and epinephrine.

1.5 Scope of the Study

The study is limited to the study of glucose regulatory system under the influence of trauma, excitement and/stress by extending the model of Mohammed *et al.* (2019).

1.6 Definitions of Operational Terms

1.6.1 Insulin: A hormone secreted by the pancreatic β-cells, it facilitates tissues uptake of glucose.

1.6.2 Glucagon: A hormone secreted by the pancreatic α-cells, it increases the breakdown of glycogen into glucose.

1.6.3 Epinephrine: A hormone secreted by the adrenal medulla, it is part of emergency mechanism to quickly increase the glucose concentration in the blood. It increases the rate of breakdown of glycogen into glucose.

1.6.4 Cortisol: Cortisol is a life sustaining adrenal hormone essential to the maintenance of homeostasis. Called "the stress hormone," cortisol influences, regulates or modulates many of the changes that occur in the body in response to stress including, but not limited to:

i. Blood sugar (glucose) levels

ii. Fat, protein and carbohydrate metabolism to maintain blood glucose (gluconeogenesis).

1.6.5 β-cell Mass: An amount of β-cells in the pancreas that is responsible for production of insulin.

1.6.6 β-cell: A pancreatic cell that is responsible for secreting glucagon.

1.6.7 Endogenous: Glucose or insulin secretion from within the body.

1.6.8 Exogenous: Glucose or insulin intake from outside the body.

1.6.9 Mathematical modeling: This is the art of transforming problem from its real-life situation to mathematical formation.

1.6.10 Hyperglycemia: This refers to high level of glucose in the blood.

1.6.11 Hypoglycemia: This refers to low level of glucose in the blood.

1.6.12 Sigmoid function: A sigmoid function is a bounded, differentiable, real function that is defined for all real input values and has a non-negative derivative at each point. It is a mathematical function having characteristic "S"-shaped curve or sigmoid curve.

1.6.13 Aetiology: The cause, set of causes, or manner of causation of a disease or condition.

1.6.14 Postprandial hyperglycemia (PPHG): High blood sugar following a meal.

CHAPTER TWO

LITERATURE REVIEW

2.1 Mathematical modeling

Topp *et al*., (2000) developed a mathematical model for $\beta - cells\ mass$, Insulin, and Glucose kinetics to study the glucose regulatory system. In developing the model, they assumed (among others) that: in post absorptive state, the glucose is released into the blood by the liver and kidneys, removed from the interstitial fluid by all the cells of the body and distributed into many physiological compartments (arterial blood, venous blood, cerebral spinal fluid, interstitial fluid) , the rate of glucose production and uptake depend on blood glucose and insulin levels and are normalized by the volume of glucose distribution, the rate of insulin clearance is proportional to blood insulin levels. Replication rate for $\beta - cells$ increases with increasing glucose. On the basis of these assumptions, they developed a novel model for $\beta - cell$ mass, Insulin, and Glucose Dynamics. The result of their study revealed that for normal parameter values, the model has stable fixed points (representing physiological and pathological steady states), separated on a slow manifold by a saddle point. They further found out that mild hyperglycemia leads to the growth of the $\beta - cells$ mass (negative feedback) while extreme hyperglycemia leads to the reduction of the $\beta - cells$ mass (positive feedback). Their work predicted that there were three pathways to diabetes in prolong hyperglycemia as follows:

i. Physiological fixed point can be shifted to a hyperglycemia level (regulated hyperglycemia)
ii. The physiological and saddle points can be eliminated (bifurcation)
iii. Progressive defects in glucose or insulin dynamics can drive glucose levels up at a rate faster than the adaptation of the $\beta - cell$ mass which could drive glucose levels down (dynamical hyperglycemia).

Boutayeb *et al*., (2004) developed a mathematical model for the burden of diabetes and its complications. The model was proposed to deal with the dynamics of population of diabetes. In developing their model, they assumed that: the rates of developing of complications (λ) , recovery from complication (γ), severely disable from complications (ν), natural death(μ), and death due to complication (δ) were constant, and these rates of changes were formalized by the ordinary differential equations (ODEs). On the basis of

these assumptions, they developed a model for the burden of diabetes and its complications. The result of their work from different scenarios suggested that it is important to control the incidence of diabetes and its complications and hence to convince decision makers that investment in the healthcare is cost effective.

Li, Kuang, and Clinton (2006) developed a model: Mathematical modeling of the glucose-insulin regulatory system and ultradian insulin secretory oscillation with two explicit time delay. In developing the model they assumed that: Insulin can only be produced from $\beta - cell$ secretion, mainly response to elevated glucose concentration. Insulin is cleared by all insulin sensitive tissues while degradation is mediated primarily by insulin receptor. They further assumed that; glucose production either by endogenous or exogenous production and the infusion rate are constant. On the basis of this assumption, they developed a model of glucose-insulin regulatory system and ultradian insulin secretory oscillations with two-time delays. The results of their work revealed many unique features of this time delay model under study. Based on this intensive simulation, they suspected that one of the possible many causes of ultradian insulin secretion oscillations was the time delay of the insulin secretion stimulated by the elevated glucose concentration.

Keh-Dong, and Fouad (2010) developed a computational model of the human glucose-insulin regulatory system. In developing the model, they assumed that:

i. each variable, g (difference between blood glucose concentration) and i (difference between plasma insulin concentration), has various influences upon the appropriate change speed with a negative feedback (i.e., utilization or clearance) process, which is shown as the parameters -p1 and -p4 (p are constants) in both equations.
ii. an increase in blood glucose levels provokes an increase of insulin secretion, which is expressed as the positive feedback (i.e., stimulation) parameter +p3 in the second equation.
iii. an increase of hormone insulin secretion leads to a reduction in blood glucose levels, which is formulated as the negative feedback (i.e., utilization) parameter -p2 in the first equation.

The results of their investigation showed that the conventional parameters estimation methods, such as the Gauss-Newton method, usually have the drawback of singular inverted matrix. The main purpose of their approach is to develop a simple, stable and formula-derivation-free computational program and, most importantly, to avoid divergence

problem. Furthermore, there are no bounded constraints applied, and thus the movements of all equations' parameters during their entire computer simulation are absolutely free. Clinically speaking, in order to determine whether or not a subject has pre-diabetes or diabetes, health care providers usually conduct a Glucose Tolerance Test (GTT) and apply standard HOMA and QUICKI methods.

Dimplekumar, and Andrew (2014) developed the model Mathematical analysis of insulin-glucose feedback system of diabetes. In developing the model, they assumed that: Two concentrations adequately describe the performance of the blood glucose regulatory system (BGRS).

a. Concentration of glucose in the Blood (G)
b. Net Hormonal Concentration (H)

The results of their investigation show that three Insulin-Feedback models analyze the efficiency of Insulin in regulating glucose dependency upon how insulin is introduced into the individual. The models analyze the infusion upon the hypoglycemic attributes of glucose in the blood, analyses the mechanism of slow ultradian oscillation infusions of insulin into individuals with varying levels of infusion with respect to time, and finally utilizes a time delay over short intervals which create a pulsatile effect in the infusion of glucose.

Ntaganda (2014) developed the Hopf Bifurcation of a two-delay mathematical model of glucose and insulin during physical activity. In developing the model, they assumed that: the flow plasma glucose and insulin in liver (LC) and pancreas (PC) compartments are delayed by two positive constants τ_g and τ_i respectively. As the cardiovascular respiratory system is regulated by heart rate H and alveolar ventilation V_A via arterial pressure (P_A) and venous pressure (P_v). Base on these assumptions, they developed a mathematical model of Hopf Bifurcation of a two-delay mathematical model of glucose and insulin during physical activity. The results of their investigation on Bifurcation for mathematical model revealed that plasma glucose and the plasma insulin responses to cardiovascular and respiratory controls (heart rate and alveolar ventilation). An algorithm is used to find delay parameters of stability, instability and Hopf bifurcation for a 30 years old woman during three different physical activities which are walking, jogging, and running. The results show that Hopf bifurcations are the intermediate oscillation solutions from stability to instability regions.

Ibrahim, Haruna, and Garba (2014) developed Mathematical model for the dynamics of glucose regulatory system under the combined effect of dieting and physical activity. In developing the model, they assumed that: Glucose concentration change is not rapid, extreme physiological and chemically induced trauma is excluded so that the rate of neogenesis and transdifferentiation is negligible. They incorporated dieting and physical exercise through a control parameter, defined and introduced the parameter denoted byh as a ratio of physical activity (amount of calories burnt through exercise) denoted by EX, and dieting (amount of calorie intake) denoted by d. The results of their investigation show that for type I diabetes, physical exercise has very negligible effect in improving plasma glucose disposal when β-cell mass deteriorates, hence the need for an exogenous insulin therapy for survival. Whereas for type II diabetes, it was shown that physical exercise alone (with insulin sensitivity>>0) can be used to improve glucose disposal, and thus enhancing plasma glucose regulation. In the event where insulin sensitivity≈0, Physical exercise which improves insulin effectiveness can improve glucose disposal, and thus enhancing plasma glucose regulation.

Boutayeb, Mohamed, Boutayeb and Mohamed (2014) developed Mathematical modeling and simulation of β-cell mass, insulin and glucose dynamics: effect of genetic predisposition to diabetes. In developing the model, they assumed that: The β-cell dynamics depends on genetic predisposition to diabetes. The results of their investigation show that in absence of predisposition to diabetes (ε = 0) the pathological equilibrium point is unstable and evolution will be towards the stable physiological equilibrium state (G = 82.6, I = 23, β = 900). Assuming that physical exercise can increase insulin sensitivity by 36% whereas overweight/obesity and other factors may decrease insulin induced glucose uptake in both diabetic and nondiabetic subjects, simulations were carried out with different values of the parameters c, d and K. The model shows that increased insulin sensitivity (higher value of c) due to physical exercise leads to a physiological equilibrium point with normoglycaemia and a low value of β-cell mass when ε = 1 and a value of glucose approaching normoglycaemia (G = 72) and a normal value of β-cell mass when ε=0. On the other hand, insulin resistance (lower value of c) can be compensated by an increased β-cell insulin secretory rate (d) or by an increased level of β-cell carrying capacity (K). In particular, when both the values of K and d are increased, the model gives a physiological equilibrium point with nearly the same values of G, I and β for all values of ε. Consequently, the model stresses, as shown by experimental studies, the fact that not all

people with insulin resistance develop diabetes. More interestingly, the model confirms the idea that non diabetic and especially pre-diabetic people may avoid the evolution towards type 2 diabetes T2DM by acting on the risk factors, especially physical activity and overweight/ obesity.

Ntaganda *et al*. (2018) developed simplified mathematical model of glucose-insulin system. In developing the model, they assumed that: They modified the Sorensen model to consider the tissue compartment as set of brain, kidney, gut and periphery. So that the blood from those elements passes through the tissue compartment to flow into the heart and lungs compartments. The results of their investigation shows that a three compartmental mathematical model that describes the variation of glucose and insulin for human being provide interesting answers to the question of determining the global mathematical model with lower number of equations for glucose-insulin system. Numerical results show that the proposed model is adaptable to data. The proposed mathematical model can also be used to adjust diabetes mellitus type I or type II for diabetic patients.

De Gaetano and Hardy (2019) developed a mathematical model titled: "A novel fast-slow model of diabetes progression: Insights into mechanisms of response to the interventions in the Diabetes Prevention Program". In their work the acknowledge the fact several models for the long-term development of type 2 diabetes (T2DM) already exist, focusing on the dynamics of the interaction between glycemia, insulinemia and β-cell. They further added that current models consider representative (fasting or daily average) glycemia and insulinemia as characterizing the compensation state of the subject at some instant in low time. Which clearly showed that only these representative levels can be followed through time and that the role of fast glycemic oscillations is neglected. They arrived at an improved model (DPM15) for the long- term progression of T2DM, introducing separate peripheral and hepatic (liver and kidney) insulin actions. The DPM15 model no longer uses near-equilibrium approximation to separate fast and slow time scales, but rather describes, at each step in slow time, a complete day in the life of the virtual subject in fast time. The model can thus represent both fasting and post-prandial glycemic levels and describe the effect of interventions acting on insulin-enhanced tissue glucose disposal or on insulin-inhibited hepatic glucose output, as well as on insulin secretion and β-cell replicating ability. Their model can simulate long-term variations of commonly used clinical indices (HOMA-B, HOMA-IR, insulinogenic index) as well as of Oral Glucose Tolerance or

Euglycemic Hyperinsulinemic Clamp test results. Their model has been caliberated against observational data from the Diabetes Prevention Program study: It showed good adaptation to observations as a function of very plausible values of their parametres describing the effect of such interventions as Placebo, Intensive LifeStyle and Metformin administration.

Amparo, Pau, Jorge and Pantelis (2019) modeled the effect of the cephalic phase of insulin secretion on glucose metabolism. They observed that the nervous system has a significant impact in glucose homeostasis and endocrine pancreatic secretion in humans, especially during the cephalic phase of insulin release (CPIR); that is, before a meal is absorbed. However, the underlying mechanisms of this neural-pancreatic interaction are not well understood and therefore often neglected, despite their significance to achieving an optimal glucose control. As a result, the dynamics of insulin release from the pancreas are currently described by mathematical models that reproduce the behavior of the β cells using exclusively glucose levels and other hormones as inputs. To bridge this gap, they have combined, for the first time, metabolic and neural mathematical models in a unified system to reproduce to a great extent the ideal glucoregulation observed in healthy subjects. Their results satisfactorily replicate the CPIR and its impact during the post-absorptive phase. Furthermore, their model gives insight into the physiological interaction between the brain and the pancreas in healthy people and suggests the potential of considering the neural information for restoring glucose control in people with diabetes. In conclusion, the results of their work gives insight into the physiological basis of the nervous control of the pancreatic secretion and suggests the potential benefit of considering the neural information for restoring glucose control in people with diabetes.

Mohammed *et al*. (2019) developed a Mathematical model for the dynamics of $\beta - cell$ mass, insulin-glucose kinetics by incorporating the effect of epinephrine due to trauma, stress and/or excitement. The model is an improvement on the work by Topp *et al.* (2000). They defined and incorporated a parameter ρ to represent the effectiveness of epinephrine in suppressing insulin secretion and a parameter G_e representing epinephrine induced glucose increase as the factors that affect glucose and insulin homeostasis. The result of their study showed that; In the presence of epinephrine, the blood glucose increased and the blood insulin decreased due to suppression by the hormone, despite the fact that there is an increase in beta-cell mass the system remained extremely hyperglycemic. The result of their numerical experiment carried out further indicated that frequent epinephrine secretion into the blood induced prolong and extreme hyperglycemia. Frequent epinephrine secretion

increases the risk of diabetes in humans. In view of the findings of this study, we recommend that there should be massive and continuous health education, especially for communities living in the areas where the stated agents (trauma, excitement and stress) of epinephrine secretion are common.

From the above available literature review, we see that the combined effect of cortisol and epinephrine due to trauma, excitement and/or stress with physiological delay was not considered in modeling glucose, insulin, and $\beta - cell$ mass dynamics to study their effects on the system.

CHAPTER THREE

METHODOLOGY

3.1 Existing Model

3.1.1 Assumptions of existing model

In post-absorptive state, the glucose is released into the blood stream by the liver and kidneys, removed from the interstitial fluid by all the cells of the body, and distributed into many physiological compartments (e.g aeterial blood, venous blood, cerebral spinal fluid, interstitial fluid).

i. The rates of glucose production and utilization depend on blood glucose and insulin levels and the rate of glucose and utilization are normalized by the volume of glucose distribution to obtain the proper unit.
ii. The rate of insulin clearance is proportional to blood insulin levels when the system is near steady state and secretion and clearance rate are normalized by insulin's volume of distribution.
iii. The rate of insulin secretion is sigmoidal function of glucose production.
iv. Replication rates for $\beta - cells$ increases with increasing glucose and formation of $\beta - cells$ be equal to replication.
v. Only trauma, excitement and/stress are factors that triggers epinephrine from the kidneys.
vi. Epinephrine induced glucose production from kidney is negligible and ignored.
vii. Epinephrine induced glucose production from the liver is considered. Epinephrine effectiveness in suppressing insulin secretion is constant.
viii. Blood insulin level will also be decreased by epinephrine suppression on insulin secretion.

Table 1: Variables and parameters of existing model

Variables/ Parameters	**Description**
$G(\mathrm{t})$	Blood glucose concentration at time t.
$I(t)$	Blood insulin concentration at time t.
$\beta(t)$	Beta cell mass at time t.
R_0	The net rate of glucose production at zero glucose level.
E_{G0}	Total glucose effectiveness at zero insulin.
S_i	Total insulin sensitivity.
δ	Maximum rate of insulin secretion.
α	Inflection point of sigmoidal function.
K	Insulin clearance rate for muscles, liver and kidney.
d_0	Beta cell natural death rate.
r_1 and r_2	Constant beta cell glucose tolerance ranges.
ρ	Epinephrine effectiveness in suppressing insulin secretion.
G_e	Amount of glucose increase due to Epinephrine secretion at time t.

3.1.2 Existing model equation

Mohammed *et al.* (2019) obtained the model equations describing $\beta - cells\ mass$, insulin-glucose kinetics by incorporating the effect of epinephrine due to trauma, stress and/or excitement as follows:

$$\frac{dG}{dt} = R_o + G_e - (E_{GO} + S_i I)G$$

$$\frac{dI}{dt} = \frac{\beta \sigma G^2}{\alpha + G^2} - (\rho + K)I \qquad (3.2)$$

$$\frac{d\beta}{dt} = (-d_o + r_1 G - r_2 G^2)\beta$$

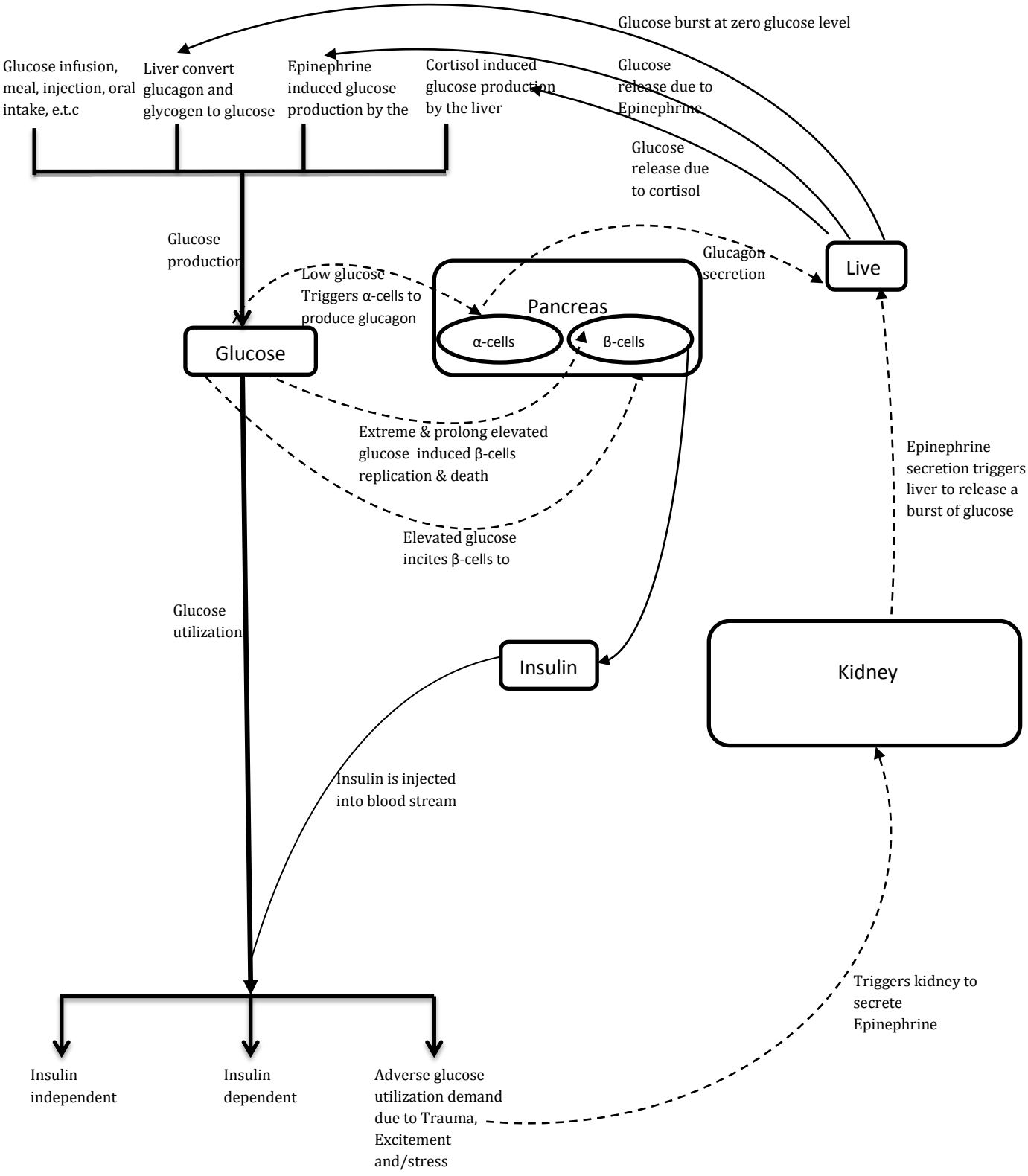

Figure 1: Flow diagram of existing model

3.2 The Modified Model

In this section, we present the extended model of Mohammed *et al*. (2019) by incorporating the idea of delay from Ntaganda (2014), and cortisol hormone.

3.2.1 Assumptions of the modified model

In post-absorptive state, the glucose is released into the blood stream by the liver and kidneys, removed from the interstitial fluid by all the cells of the body, and distributed into many physiological compartments (e.g aeterial blood, venous blood, cerebral spinal fluid, interstitial fluid).

i. The rates of glucose production and utilization depend on blood glucose and insulin levels and the rate of glucose and utilization are normalized by the volume of glucose distribution to obtain the proper unit.
ii. The rate of insulin clearance is proportional to blood insulin levels when the system is near steady state and secretion and clearance rate are normalized by insulin's volume of distribution.
iii. The rate of insulin secretion is sigmoidal function of glucose production.
iv. Replication rates for $\beta - cells$ increases with increasing glucose and formation of $\beta - cells$ be equal to replication.
v. Only trauma, excitement and/stress are factors that triggers epinephrine and cortisol hormone from the kidneys.
vi. Cortisol effectiveness in suppressing insulin secretion is constant.
vii. Epinephrine effectiveness in suppressing insulin secretion is constant.
viii. A physiological delay τ in the secretion of cortisol hormone by the kidney.

Table 2: Variables and parameters of modified model

Variables/ Parameters	**Description**
$G(\mathrm{t})$	Blood glucose concentration at time t.
$I(t)$	Blood insulin concentration at time t.
$\beta(t)$	Beta cell mass at time t.
R_0	The net rate of glucose production at zero glucose level.
E_{G0}	Total glucose effectiveness at zero insulin.
S_i	Total insulin sensitivity.
δ	Maximum rate of insulin secretion.
α	Inflection point of sigmoidal function.
K	Insulin clearance rate for muscles, liver and kidney.
d_0	Beta cell natural death rate.
r_1 and r_2	Constant beta cell glucose tolerance ranges.
ρ	Epinephrine effectiveness in suppressing insulin secretion.
ρ_c	Cortisol effectiveness in suppressing insulin secretion.
P_o	The rate of glucose production at zero glucose level.
E_{G0p}	The glucose effectiveness at zero insulin for production.
S_{ip}	Insulin sensitivity for production.
U_0	The rate if glucose utilization at zero glucose level.
E_{G0u}	Glucose effectiveness at zero insulin for utilization.
S_{iu}	Insulin sensitivity for utilization.

$G_e(t)$	Amount of glucose increase due to Epinephrine secretion at time t.
$G_c(t)$	Amount of glucose increase due to cortisol secretion at time t .
τ	Time lag in cortisol secretion.

3.2.2 Dynamics of the glucose regulatory system

3.2.2.1 Glucose-Insulin dynamics

Glucose is produced and absorbed into the blood stream after meal injection, glucose infusion or oral intake of glucose. The elevated blood glucose incites β-cell of the pancreas to secrete insulin, helping to return the glucose concentration to the normal level (Li, Kuang, & Clinton 2006), as the glucose concentration level decreases the secretion drops gradually (Li, Kuang, & Clinton, 2006). Glucose is removed (utilized) from the interstitial fluid by the cell of the body and distribute into many physiological compartment (Mohammed *et al*., 2019). This utilization of glucose normally is insulin driven or independent of insulin (Mohammed *et al*., 2019). On the other hand, low glucose incites α-cells of the pancreas to secrete glucagon to convert glycogen to glucose and inject it into blood stream (Li, Kuang, & Clinton, 2006).

The stress system relies on two key hormones: Epinephrine and Cortisol (Sapolsky, 2003). In an emergency situation (induced trauma, excitement and/stress), the adrenal medulla of the kidney is triggered to secrete Epinephrine (Kwacha *et al*., 2011). The secretion of epinephrine influences the adrenal medulla of the kidney to also secrete (slowly) a continuous amount of cortisol hormone (Tracie, 2013). Epinephrine and cortisol incite the liver to release a burst of glucose into the blood stream at different time intervals. As the levels of epinephrine start coming down, so rises the amount of cortisol flowing through the veins. Moreover, cortisol has a much larger momentum than epinephrine which means that even though it builds up slowly, it also takes a long time to go back to normal (Sapolsky, 2003)**.**

3.2.2.2 β-Cells dynamics

β -cells changes depend on glucose concentration with increase glucose levels, β-cells replication is reduced while β-cells death is increased or remain constant (Mohammed *et al*., 2019).

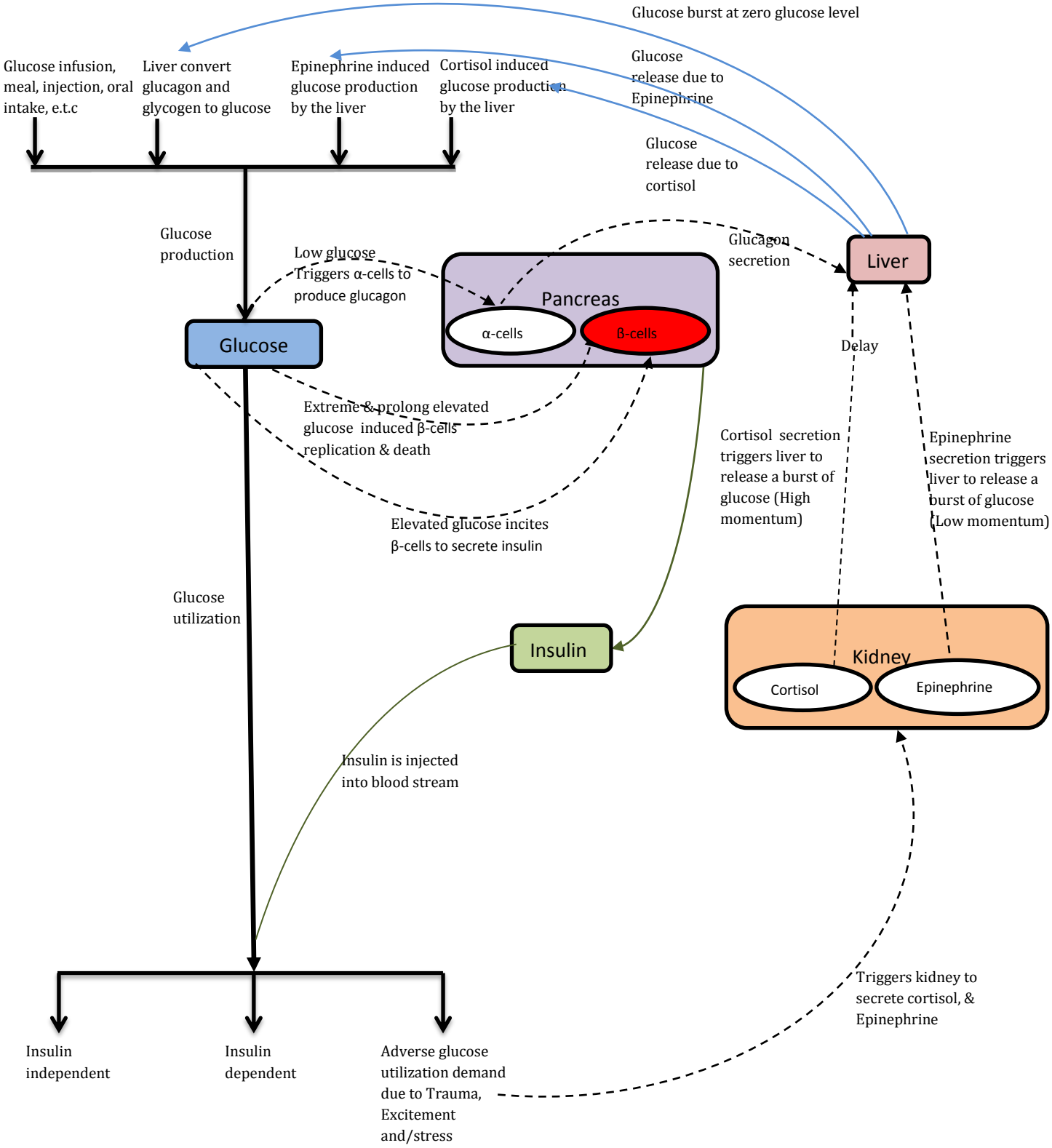

Figure 2: Flow diagram of modified model

3.3 Derivation of the Modified Model Equations

3.3.1 Glucose dynamics

In post-absorptive state, the glucose is released into the blood stream by the liver and kidneys, removed from the interstitial fluid by all the cells of the body, and distributed into many physiological compartments (e.g aeterial blood, venous blood, cerebral spinal fluid, interstitial fluid). This study suggests that a single compartment model is appropriate when glucose kinetics is relatively slow. Since we are primarily concerned with the evolution of testing blood glucose levels over a time-scale of days to years, glucose dynamics are modeled with a single compartment mass balance equation (Mohammed *et al*., 2019)

$$\frac{dG}{dt} = production - utilization \tag{3.4}$$

where G is the concentration of glucose in the blood at time t (measured in days).

3.3.1.1 Glucose production

Mohammed *et al.* (2019) gave the glucose production as;

$$\text{Production}=P_o - (E_{G0p} + S_{ip}\text{I})G \tag{3.5}$$

However, cortisol and epinephrine increases the glucose concentration in the blood stream by $G_c(t-\tau)$ and G_e respectively. Thus

$$\text{production} = P_0 + G_e + G_c(t-\tau) - (E_{G0p} + S_{ip}\text{I})G \tag{3.6}$$

3.3.1.2 Glucose utilization

Mohammed *et al.* (2019) gave the glucose utilization function as;

$$Utilization = U_0 + (E_{G0u} + S_{iu}\text{I})G \tag{3.7}$$

We use the same function in our model. This is because cortisol and epinephrine do not have effect on glucose utilization.

Therefore, the rate of change of glucose with time is given below from equation (3.4)

$$\frac{dG}{dt} = P_0 + G_e(t) + G_c(t-\tau) - (E_{G0p} + S_{ip}\text{I})G - [U_0 + (E_{G0u} + S_{iu}\text{I})G]$$

$$\frac{dG}{dt} = (P_0 - U_0) + G_e(t) + G_c(t-\tau) - [(E_{G0p} + E_{G0u}) + (S_{ip} + S_{iu})\mathrm{I}]G$$

Hence, the equation of glucose dynamics under the influence of cortisol and epinephrine hormones which is secreted in response to trauma, excitement and/stress is given by

$$\frac{dG}{dt} = R_o + G_e + G_c(t-\tau) - (E_{GO} + S_i I)G \tag{3.8}$$

where $R_0 = P_0 - U_0$, $E_{G0} = E_{G0p} + E_{G0u}$, $S_i\mathrm{I} = (S_{ip} + S_{iu})\mathrm{I}$

3.3.2 Insulin dynamics

Mohammed *et al.* (2019) gave the equation for insulin dynamics as

$$\frac{dI}{dt} = \mathrm{sec}\,retion - clearance \tag{3.9}$$

3.3.2.1 Insulin secretion

Mohammed *et al.* (2019) gave the insulin production equation below

$$\frac{dI}{dt} = \frac{\beta\sigma G^2}{\alpha + G^2}$$

Since cortisol and epinephrine suppresses insulin secretion by ρ_e (epinephrine effectiveness) and ρ_c (cortisol effectiveness), in this work we incorporate the effects of cortisol and epinephrine in insulin secretion.

$$Amount\,of\,insulin\ \ \mathrm{sec}\,retion\ \mathrm{sup}\,pressed = -\rho I - \rho_c I$$

$$= (\rho + \rho_c)I \tag{3.10}$$

Therefore, equation (3.9) in the presence of cortisol and epinephrine is given by

$$\frac{dI}{dt} = \frac{\beta\sigma G^2}{\alpha + G^2} - (\rho + \rho_c)I \tag{3.11}$$

3.3.2.2 Insulin clearance

Mohammed *et al.* (2019) gave the equation for insulin clearance function as

$$Insulin\ clearance = KI \tag{3.12}$$

In this work, we use the same expression in equation (3.12). This is because cortisol and epinephrine do not affect insulin clearance.

Hence, the equation (3.9) for insulin dynamics is given below

$$\frac{dI}{dt} = \frac{\beta \sigma G^2}{\alpha + G^2} - (\rho + \rho_c)I - KI$$

$$\frac{dI}{dt} = \frac{\beta \sigma G^2}{\alpha + G^2} - (\rho + \rho_c + K)I \tag{3.13}$$

3.3.3 $\beta - cells\ mass$ dynamics

Mohammed *et al.* (2019) gave the $\beta - cells\ mass$ dynamics below as

$$\frac{d\beta}{dt} = Formation - Loss \tag{3.14}$$

3.3.3.1 $\beta - cells$ formation (Replication)

Mohammed *et al.* (2019) gave the $\beta - cells$ formation (replication) function as

$$\text{Formation} = (r_{1a}G - r_{2a}G^2)\beta \tag{3.15}$$

In this work, we are using the same functional relation in equation (3.15). This is because cortisol and epinephrine do not have effect on the formation (replication) of $\beta - cells$.

3.3.3.2 $\beta - cells$ death (Loss)

Mohammed *et al.* (2019) gave the $\beta - cells$ death (loss) function below as

$$\text{Death} = (d_o - r_{1b}G + r_{2b}G^2)\beta \tag{3.16}$$

In this work, we are using the same functional relation as in equation (3.16). This is because cortisol and epinephrine do not have effect on the death (loss) of $\beta - cells$.

Hence, the equation (3.14) for the $\beta - cells\ mass$ dynamics gives

$$\frac{d\beta}{dt} = (r_{1a}G - r_{2a}G^2)\beta - (d_o - r_{1b}G + r_{2b}G^2)\beta$$

$$\frac{d\beta}{dt} = (-d_o + r_1 G - r_2 G^2)\beta \tag{3.17}$$

where $r_1 = r_{1a} + r_{1b}$ and $r_2 = r_{2a} + r_{2b}$ are constants related to $\beta - cell$ dynamic.

Therefore, from the assumption, description and schematic diagram of the modified model in *figure 1*, we derived the following modified model equations:

$$\frac{dG}{dt} = R_o + G_e + G_c(t - \tau) - (E_{GO} + S_i I)G \tag{3.18}$$

$$\frac{dI}{dt} = \frac{\beta \sigma G^2}{\alpha + G^2} - (\rho + \rho_c + K)I \tag{3.19}$$

$$\frac{d\beta}{dt} = (-d_o + r_1 G - r_2 G^2)\beta \tag{3.20}$$

CHAPTER FOUR

RESULTS AND DISCUSSION

In this section, we carried out analytical and numerical studies on the modified model which is an extension of Mohammed *et al.* (2019) model as indicated in the following ways below:

4.1 Equilibrium points of the system

We studied the equilibrium solution of the modified model equations by splitting the glucose regulatory system into subsystems; the slow (β-cell mass) subsystem and fast (glucose/insulin) subsystem.

4.1.1 Equilibrium of the slow subsystem β-cell mass

Setting $\frac{d\beta}{dt} = 0$ from equation (3.20)

We have

$$(-d_o + r_1 G - r_2 G^2)\beta = 0$$

Either

$$\beta = 0 \text{ or } -d_o + r_1 G - r_2 G^2 = 0 \tag{4.1}$$

which can also be written as

$$r_2 G^2 - r_1 G + d_o = 0 \tag{4.2}$$

Solving for *G* in equation (4.1) by using quadratic formula $G_{1,2} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$.

where $a = r_2$, $b = -r_1$, and $c = d_o$

$$G_{1,2} = \frac{-(-r_1) \pm \sqrt{(-r_1)^2 - 4 r_2 d_o}}{2 r_2}$$

$$G_{1,2} = \frac{r_1 \pm \sqrt{r_1^2 - 4 r_2 d_o}}{2 r_2}$$

$$G_1 = \frac{r_1 - \sqrt{r_1^2 - 4 r_2 d_o}}{2 r_2} \tag{4.3}$$

or

$$G_2 = \frac{r_1 + \sqrt{r_1^2 - 4 r_2 d_o}}{2 r_2} \tag{4.4}$$

For the slow (β-cell mass) subsystem, we have the following either $\beta = 0$ or $r_2 G^2 - r_1 G + d_o$. Thus, the eigen-value $\lambda = -(r_2 G^2 - r_1 G + d_o)$.

The slow (β-cell mass) subsystem is locally and asymptotically stable since the Eigenvalue is negative, and $r_2 G^2 + d_o > r_1 G$

4.1.2 Equilibrium of fast (glucose/insulin) subsystem

For insulin dynamics at equilibrium, we have $\frac{dI}{dt} = 0$ from equation (3.19), this implies that

$$\frac{\beta \sigma G^2}{\alpha + G^2} - (\rho + \rho_c + K) I = 0 \tag{4.5}$$

Making insulin *I* the subject of equation (4.5), hence equation (4.5) gives

$$-(\rho + \rho_c + K) I = -\frac{\beta \sigma G^2}{\alpha + G^2}$$

$$(\rho + \rho_c + K) I = \frac{\beta \sigma G^2}{\alpha + G^2}$$

$$I = \frac{\beta \sigma G^2}{\alpha + G^2} \times \frac{1}{\rho + \rho_c + K} \tag{4.6}$$

From equation (4.1), we saw that $\beta = 0$ .By substituting the value of β into equation (4.6), we have

$$I = 0 \tag{4.7}$$

Glucose dynamics at equilibrium, we have set $\frac{dG}{dt} = 0$ from equation (3.18). This implies that

$$R_o + G_e + G_c(t-\tau) - (E_{GO} + S_i I)G = 0 \tag{4.8}$$

Substituting the value of I from equation (4.7) into equation (4.8), we have

$$R_o + G_e + G_c(t-\tau) - (E_{GO} + S_i \times 0)G = 0$$

$$R_o + G_e + G_c(t-\tau) - E_{GO}G = 0 \tag{4.9}$$

Making *G* the subject of equation (4.9)

$$-E_{GO}G = -(R_o + G_e + G_c(t-\tau))$$

$$E_{Go}G = R_o + G_e + G_c(t-\tau)$$

$$G = \frac{R_o + G_e + G_c(t-\tau)}{E_{GO}}$$

Therefore, the equilibrium point of the fast (glucose/insulin) subsystem is given by

$$E_0(G^*, I^*) = \left(\frac{R_o + G_e + G_c(t-\tau)}{E_{GO}}, 0 \right) \tag{4.10}$$

4.2 Stability Analysis

We test the stability of the fast (glucose/insulin) subsystem from equation (3.17) and (3.18) by using the Jacobian matrix

$$J = \begin{bmatrix} \frac{\partial F_1}{\partial G} & \frac{\partial F_1}{\partial I} \\ \frac{\partial F_2}{\partial G} & \frac{\partial F_2}{\partial I} \end{bmatrix} \tag{4.11}$$

Let

$$F_1 = R_o + G_e + G_c(t-\tau) - (E_{GO} + S_i I)G$$

$$F_2 = \frac{\beta\sigma G^2}{\alpha + G^2} - (\rho + \rho_c + K)I$$

Thus, the Jacobian matrix in (4.11) becomes

$$J = \begin{bmatrix} -(E_{GO} + S_i I) & S_i G \\ \dfrac{2\alpha\beta\sigma G^2}{\left(\alpha + G^2\right)^2} & -(\rho + \rho_c + K) \end{bmatrix}$$

At equilibrium of the fast subsystem

$$J(E_o) = \begin{bmatrix} -(E_{Go} + S_i \times 0) & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \\ 0 & -(\rho + \rho_c + K) \end{bmatrix}$$

$$J(E_o) = \begin{bmatrix} -E_{Go} & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \\ 0 & -(\rho_e + \rho_c + K) \end{bmatrix}$$

Using the characteristics equation, we have

$$\left| J(E_o) - \lambda I \right| = 0$$

Substituting the Jacobian $J(E_0)$ into the characteristic's equation

$$\left| J(E_o) - \lambda I \right| = \left| \begin{bmatrix} -E_{Go} & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \\ 0 & -(\rho + \rho_c + K)I \end{bmatrix} - \lambda \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \right| = 0$$

$$\left| J(E_o) - \lambda I \right| = \left| \begin{bmatrix} -E_{Go} & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \\ 0 & -(\rho + \rho_c + K)I \end{bmatrix} - \begin{bmatrix} \lambda & 0 \\ 0 & \lambda \end{bmatrix} \right| = 0$$

$$\left| J(E_o) - \lambda I \right| = \begin{vmatrix} -E_{Go} - \lambda & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \\ 0 & -(\rho + \rho_c + K) - \lambda \end{vmatrix} = 0$$

$$(-E_{G0} - \lambda)[-(\rho_c + \rho + K) - \lambda] = 0$$

$$-E_{G0} - \lambda = 0 \; or \; -(\rho_c + \rho + K) - \lambda = 0$$

$$\lambda_1 = -E_{G0} \; and \; \lambda_2 = -(\rho_c + \rho + K)$$

We have seen that for the fast (glucose/insulin) subsystems, all eigen-values of $\lambda_i < 0 \; for \; i = 1,2$ are negative. Thus the subsystem is locally and asymptotically stable.

Analyzing the system as a whole, we test for stability by considering equations (3.18), (3.19), and (3.20) above.

Let

$$F_1 = R_o + G_e + G_c(t - \tau) - (E_{GO} + S_i I)G$$

$$F_2 = \frac{\beta \sigma G^2}{\alpha + G^2} - (\rho + \rho_c + K)I$$

$$F_3 = (-d_o + r_1 G - r_2 G^2)\beta$$

Thus, the Jacobian matrix of the above system is given by

$$J = \begin{bmatrix} \frac{\partial F_1}{\partial G} & \frac{\partial F_1}{\partial I} & \frac{\partial F_1}{\partial \beta} \\ \frac{\partial F_2}{\partial G} & \frac{\partial F_2}{\partial I} & \frac{\partial F_2}{\partial \beta} \\ \frac{\partial F_3}{\partial G} & \frac{\partial F_3}{\partial I} & \frac{\partial F_3}{\partial \beta} \end{bmatrix} \qquad (4.12)$$

The Jacobian matrix (4.12) become

$$J = \begin{bmatrix} -E_{Go} & S_i G & 0 \\ 0 & -(\rho + \rho_c + K) & \frac{\sigma G^2}{\alpha + G^2} \\ 0 & 0 & -d_o + r_1 G - r_2 G^2 \end{bmatrix}$$

At equilibrium of the whole system we have

$$J(E_o) = \begin{bmatrix} -E_{Go} & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} & 0 \\ 0 & -(\rho + \rho_c + K) & \dfrac{\sigma \left(\dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \right)^2}{\alpha + \left(\dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \right)^2} \\ 0 & 0 & -d_o + r_1 \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} - r_2 \left(\dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} \right)^2 \end{bmatrix}$$

$$J(E_o) = \begin{bmatrix} -E_{Go} & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} & 0 \\ 0 & -(\rho + \rho_c + K) & \dfrac{\sigma \left(R_o + G_e + G_c(t-\tau) \right)^2}{\alpha \left(E_{GO} \right)^2 + \left(R_o + G_e + G_c(t-\tau) \right)^2} \\ 0 & 0 & -d_o + r_1 \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} - r_2 \dfrac{\left(R_o + G_e + G_c(t-\tau) \right)^2}{\left(E_{GO} \right)^2} \end{bmatrix}$$

The characteristics equation is given by

$$\left| J(E_o) - \lambda I \right| = 0$$

$$\left| J(E_o) - \lambda I \right| = \left| \begin{bmatrix} -E_{Go} & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} & 0 \\ 0 & -(\rho + \rho_c + K) & \dfrac{\sigma \left(R_o + G_e + G_c(t-\tau) \right)^2}{\alpha \left(E_{GO} \right)^2 + \left(R_o + G_e + G_c(t-\tau) \right)^2} \\ 0 & 0 & -d_o + r_1 \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} - r_2 \dfrac{\left(R_o + G_e + G_c(t-\tau) \right)^2}{\left(E_{GO} \right)^2} \end{bmatrix} - \lambda \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \right| = 0$$

$$\left| J(E_o) - \lambda I \right| = \left| \begin{bmatrix} -E_{Go} & S_i \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} & 0 \\ 0 & -(\rho + \rho_c + K) & \dfrac{\sigma \left(R_o + G_e + G_c(t-\tau) \right)^2}{\alpha \left(E_{GO} \right)^2 + \left(R_o + G_e + G_c(t-\tau) \right)^2} \\ 0 & 0 & -d_o + r_1 \dfrac{R_o + G_e + G_c(t-\tau)}{E_{GO}} - r_2 \dfrac{\left(R_o + G_e + G_c(t-\tau) \right)^2}{\left(E_{GO} \right)^2} \end{bmatrix} - \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{bmatrix} \right| = 0$$

$$\left|J(E_o)-\lambda I\right|=\begin{vmatrix} -E_{Go}-\lambda & S_i\dfrac{R_o+G_e+G_c(t-\tau)}{E_{GO}} & 0 \\ 0 & -(\rho+\rho_c+K)-\lambda & \dfrac{\sigma\left(R_o+G_e+G_c(t-\tau)\right)^2}{\alpha\left(E_{GO}\right)^2+\left(R_o+G_e+G_c(t-\tau)\right)^2} \\ 0 & 0 & -d_o+r_1\dfrac{R_o+G_e+G_c(t-\tau)}{E_{GO}}-r_2\dfrac{\left(R_o+G_e+G_c(t-\tau)\right)^2}{\left(E_{GO}\right)^2}-\lambda \end{vmatrix}=0$$

$$-E_{Go}-\lambda=0 \text{ or } -(\rho+\rho_c+K)-\lambda=0 \text{ or}$$

$$-d_o+r_1\frac{R_o+G_e+G_c(t-\tau)}{E_{GO}}-r_2\frac{\left(R_o+G_e+G_c(t-\tau)\right)^2}{\left(E_{GO}\right)^2}-\lambda=0$$

The eigen-values

$$\lambda_1=-E_{Go},\ \lambda_2=-(\rho+\rho_c+K), \text{ and}$$

$$\lambda_3=-\left(r_2\frac{\left(R_o+G_e+G_c(t-\tau)\right)^2}{\left(E_{GO}\right)^2}-r_1\frac{R_o+G_e+G_c(t-\tau)}{E_{GO}}+d_o\right)$$

The initial condition for this system consists of a function defined on $-\tau \le t \le 0$. Thus, for small enough τ and for $\tau = 0$, the whole system for for values of $\lambda_i < 0$ $(for\ i = 1,2,3)$ is locally and asymptotically stable otherwise it is unstable.

4.3 Numerical Experiments

Some numerical experiments were performed using MATLAB R2015a to study the behaviors of the system under the influence of trauma, excitement and stress with physiological delay. The initial value of the variables: Glucose, Insulin and β-cell mass were assumed and varies. Apart from three parameters which values were obtained from other literatures, all other parameters values used in the experiment were obtained from the literature by Mohammed *et al.* (2019), and are given in table 3.

Given the values in table 3 for the parameters of the model. We compute initial values of glucose increase and insulin suppression due to epinephrine and cortisol hormones, using the equilibrium solution for glucose and insulin for the experiment as follows:

With $\tau = 0$

i. Blood glucose in the absence of cortisol and epinephrine
ii. Blood glucose in the presence of cortisol and epinephrine
iii. Blood insulin in the absence of cortisol and epinephrine
iv. Blood insulin in the presence of cortisol and epinephrine
v. Beta cell mass in the absence of cortisol and epinephrine
vi. Beta cell mass in the presence of cortisol and epinephrine

With $\tau = 0.01$

i. Blood glucose in the absence of cortisol and epinephrine
ii. Blood glucose in the presence of cortisol and epinephrine
iii. Blood insulin in the absence of cortisol and epinephrine
iv. Blood insulin in the presence of cortisol and epinephrine
v. Beta cell mass in the absence of cortisol and epinephrine
vi. Beta cell mass in the presence of cortisol and epinephrine
vii. We experimented the effect of cortisol and epinephrine at varying β-cell mass as follows:

With $\tau = 0$

i. Glucose and insulin dynamics in the absence of cortisol and epinephrine at β=300, 600, 900
ii. Glucose and insulin dynamics in the presence of cortisol and epinephrine at β=300, 600, 900
iii. Glucose, insulin and β-cell mass (at β=300) in the absence of cortisol and epinephrine
iv. Glucose, insulin and β-cell mass (at β=300) in the presence of cortisol and epinephrine
v. β-cell mass replication and death dynamics in the absence of cortisol and epinephrine
vi. β-cell mass replication and death dynamics in the presence of cortisol and epinephrine

With $\tau = 0.01$

i. Glucose and insulin dynamics in the absence of cortisol and epinephrine at β=300, 600, 900

ii. Glucose and insulin dynamics in the presence of cortisol and epinephrine at β=300, 600, 900
iii. Glucose, insulin and β-cell mass (at β=300) in the absence of cortisol and epinephrine
iv. Glucose, insulin and β-cell mass (at β=300) in the presence of cortisol and epinephrine
v. β-cell mass replication and death dynamics in the absence of cortisol and epinephrine
vi. β-cell mass replication and death dynamics in the presence of cortisol and epinephrine

Glucose (G) in the slow beta-cell mass subsystem

The values of $d_o = 6 \times 10^{-2},\ r_1 = 8.4 \times 10^{-4}, r_2 = 2.4 \times 10^{-6}$ are in table 4. Substituting the values in equation (4.1), we have

$$-6 \times 10^{-2} + 8.4 \times 10^{-4} G - 2.4 \times 10^{-6} G^2 = 0$$

$$24G^2 - 8400G + 600000 = 0$$

Solving for G,we have

$$G_{1,2} = \frac{8400 \pm \sqrt{8400^2 - 4 \times 24 \times 600000}}{2 \times 24}$$

Either

$$G_1 = \frac{1200}{48}$$

$$= 250$$

Or

$$G_1 = \frac{8400}{48}$$

$$= 100$$

The one-dimensional subsystem has three steady state solutions which are where β=0, G=100 and G=250. These three steady states are referred to as the pathological, physiological, and unstable steady state respectively (Mohammed *et al.*, 2019).

Glucose (G) in the absence of cortisol and epinephrine from equation (4.8)

We have

$$G = \frac{R_o}{E_{Go} + S_i I}$$

Thus

$$G = \frac{1487}{1.44 + 0.72 \times 23}$$

$$= 82.61$$

$$\approx 83\, mg / dl (milligrams / decilitres)$$

For glucose (G) in the presence of cortisol and epinephrine, we obtained the parameter(G_c) and (G_e) respectively from the following

At basal level, blood glucose is 90mg/dl Roger, Lerner and Daniel (1971). Since cortisol and epinephrine quickly increase glucose concentration in the blood from 90mg/dl to as high as 140mg/dl Didier and Raymond (1998). To that effect we have 140 mg/dl − 90 mg/dl =50mg/dl cortisol and epinephrine induced increase in the blood. Converting 50mg/dl glucose increase due to cortisol and epinephrine rate at which glucose is secreted from the liver at zero glucose levels. We have the following: Net rate of glucose production at zero glucose level.

G_e = Amount of glucose production due to epinephrine due to trauma, excitement and stress.

G_c = Amount of glucose production due to cortisol due to trauma, excitement and stress at $\tau = 0$

Therefore, net glucose production in the presence of cortisol and epinephrine

$$\frac{Net\ change\ of\ glucose\ due\ to\ cortisol\ and\ epinephrine\ as\ a\ result\ of\ trauma, excitement\ and\ stress}{Total\ glucose\ production\ due\ to\ cortisol\ and\ epinephrine\ as\ a\ result\ of\ trauma, excitement\ and\ stress} \times Net\ rate\ of\ glucose\ production\ at\ zero\ glucose\ level$$

$$= \frac{140 - 90}{140} \times 1487$$

$$= 0.357 \times 1487$$

$$= 530.859\, mg / dl$$

Therefore, amount of glucose production due to cortisol and epinephrine is 530.859 mg/dl

4.3.1 Variable and parameters values of the existing and modified models

Table 4: Variables and parameters values

Variables/ Parameters	**Value**	**Unit**	
$G(\mathrm{t})$	82.6	mg/dl	Boutayeb *et al*. (2014)
$I(t)$	23	mU/L	Boutayeb *et al*. (2014)
$\beta(t)$	300	mg/dl	Mohammed *et al.* (2019)
R_0	864	mg/dl	Assumed
E_{G0}	1.44	d^{-1}	Mohammed *et al.* (2019)
S_i	0.72	m$l\mu/dU$	Mohammed *et al.* (2019)
δ	43.2	$\mu Um/dl$	Mohammed *et al.* (2019)
α	20,000	mg^2/dl^2	Mohammed *et al.* (2019)
K	432	d^{-1}	Mohammed *et al.* (2019)
d_0	6×10^{-2}	d^{-1}	Mohammed *et al.* (2019)
r_1	8.4×10^{-4}	mg/dl	Mohammed *et al.*

			(2019)
r_2	2.4×10^{-6}	mg/dl	Mohammed *et al.* (2019)
G_e	308.75	mg/dl	Mohammed *et al.* (2019)
G_c	1.5×10^{-2}	mg/dl	Abercrombic,Kalin,& Davidson (2005)

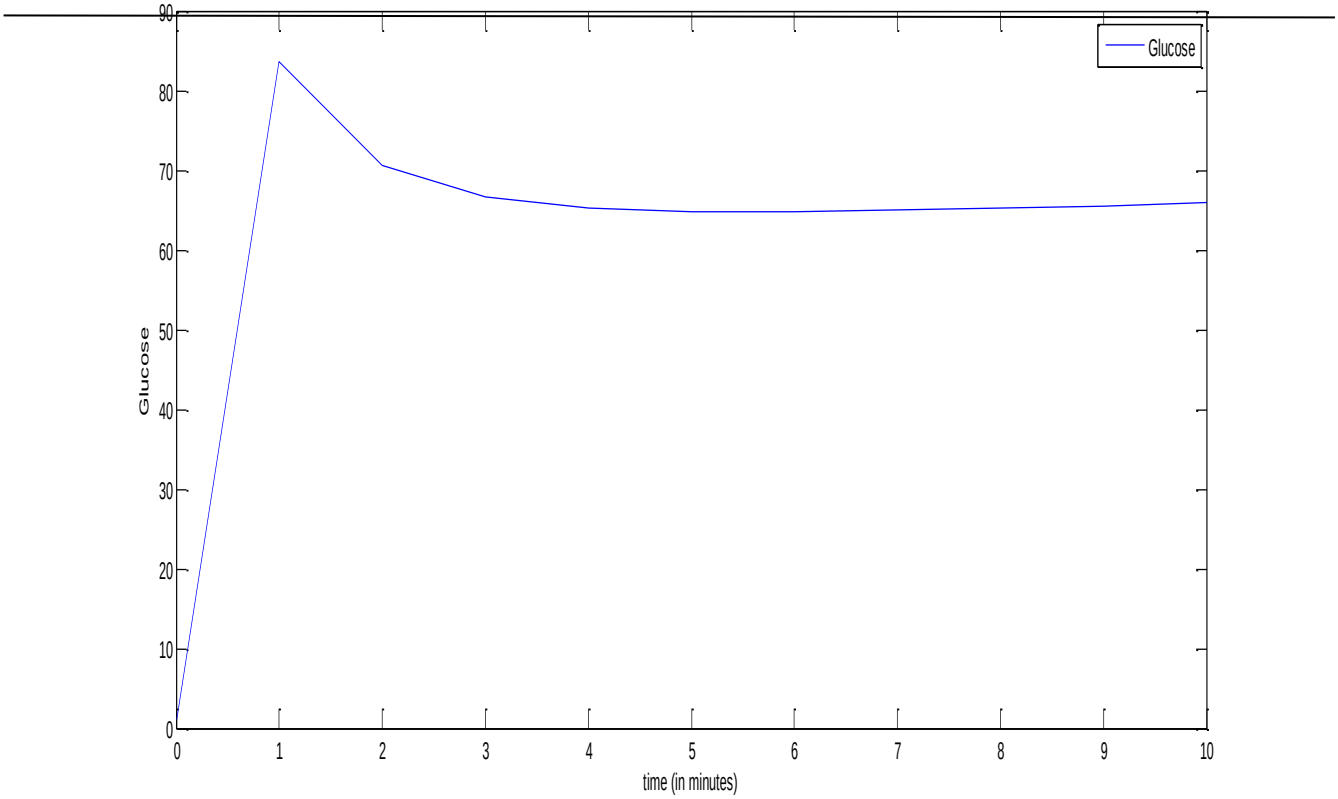

Figure 3: Glucose in the absence of cortisol and insulin

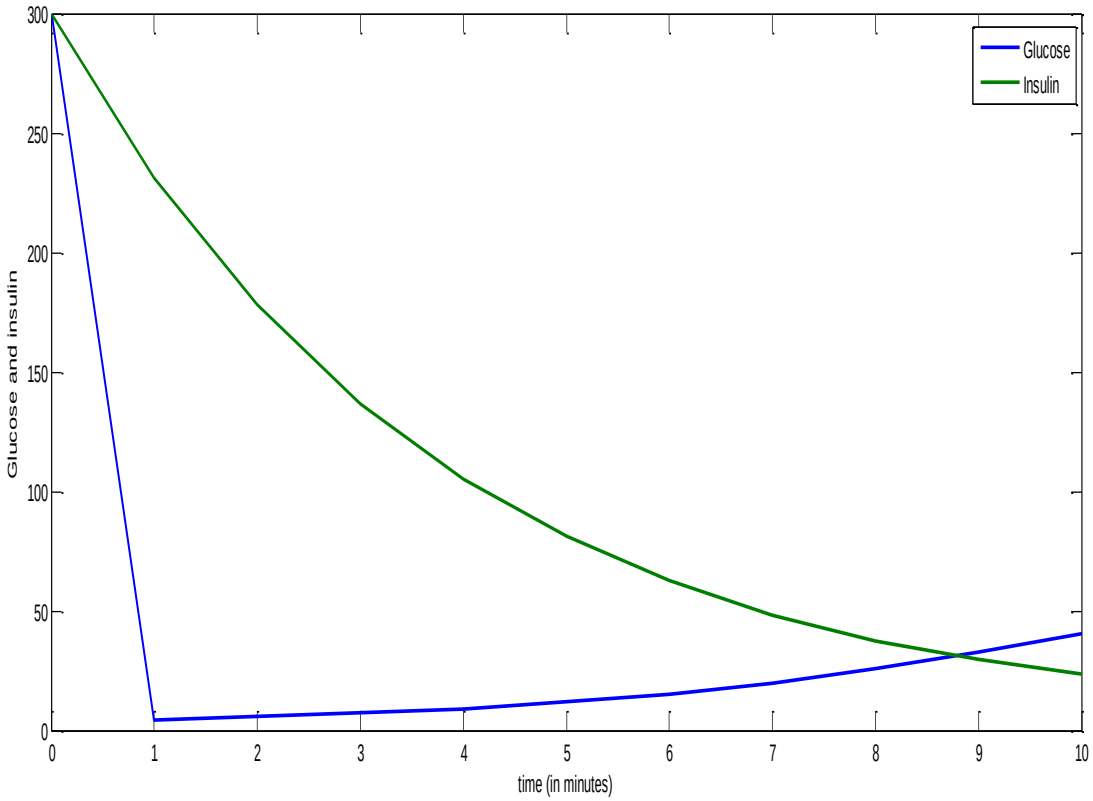

Figure 4: Glucose and insulin dynamics in the presence of cortisol and epinephrine at β =300

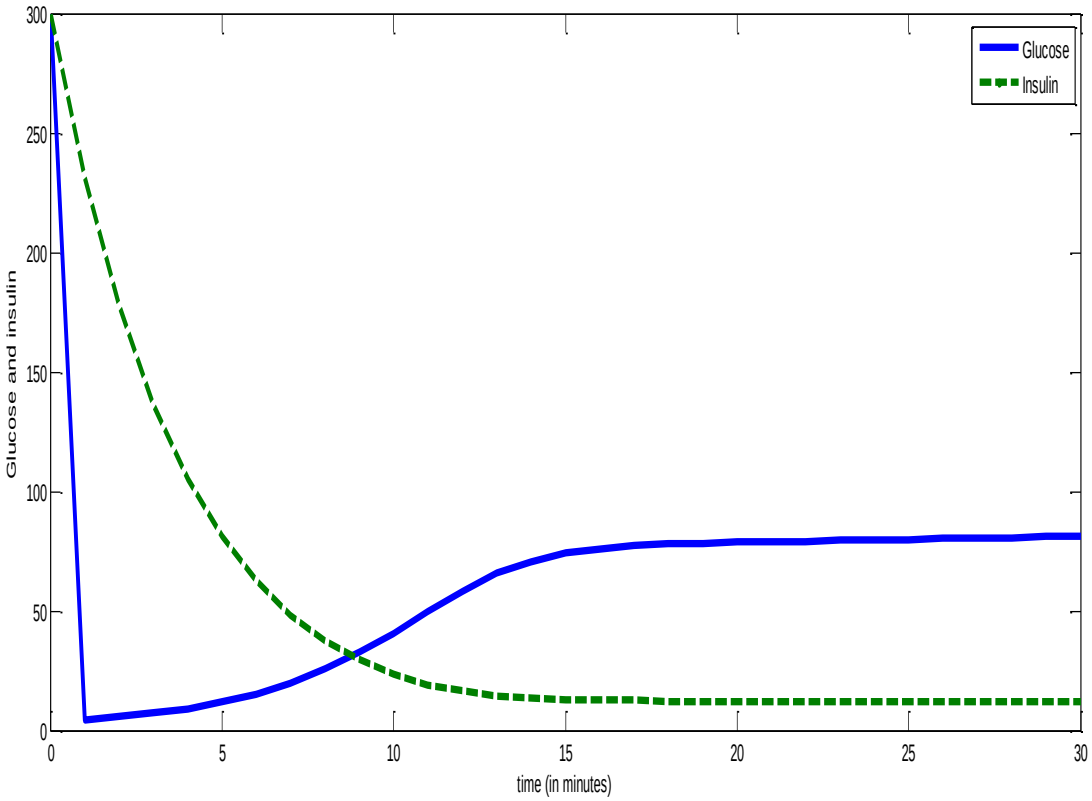

Figure 5: Glucose and insulin dynamics in the presence of cortisol and epinephrine at β =1

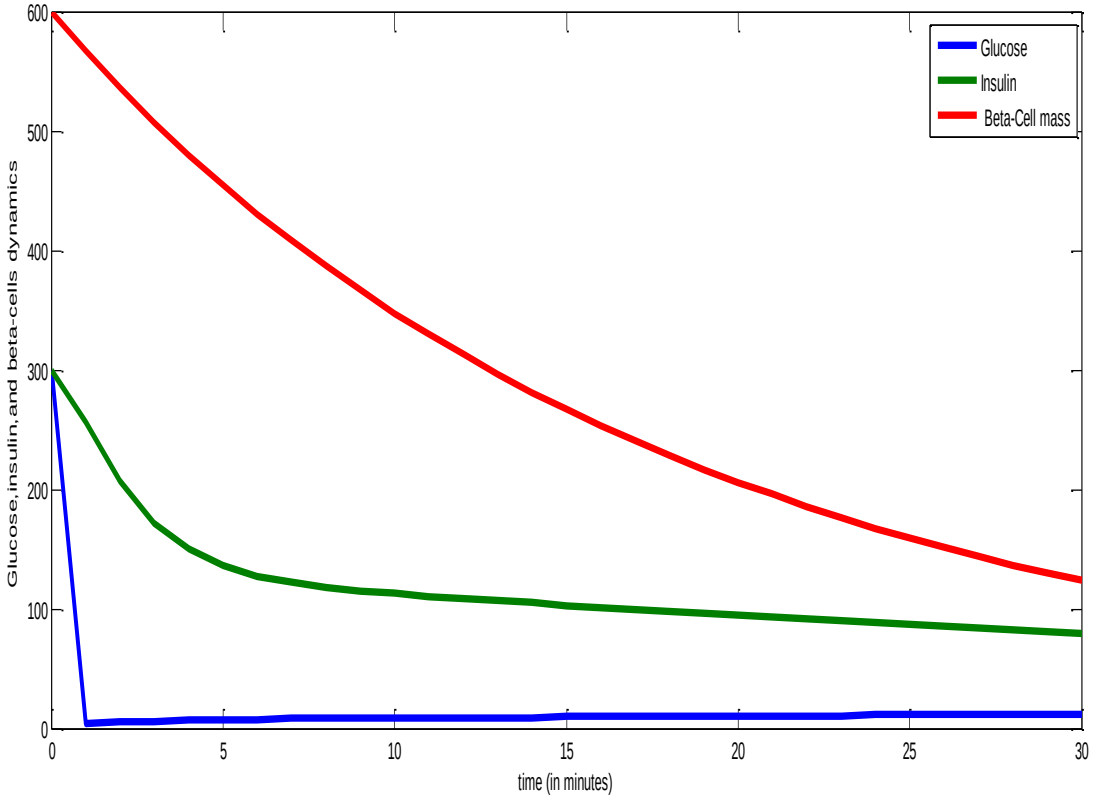

Figure 6: Glucose and insulin dynamics in the absence of cortisol and epinephrine at β =600

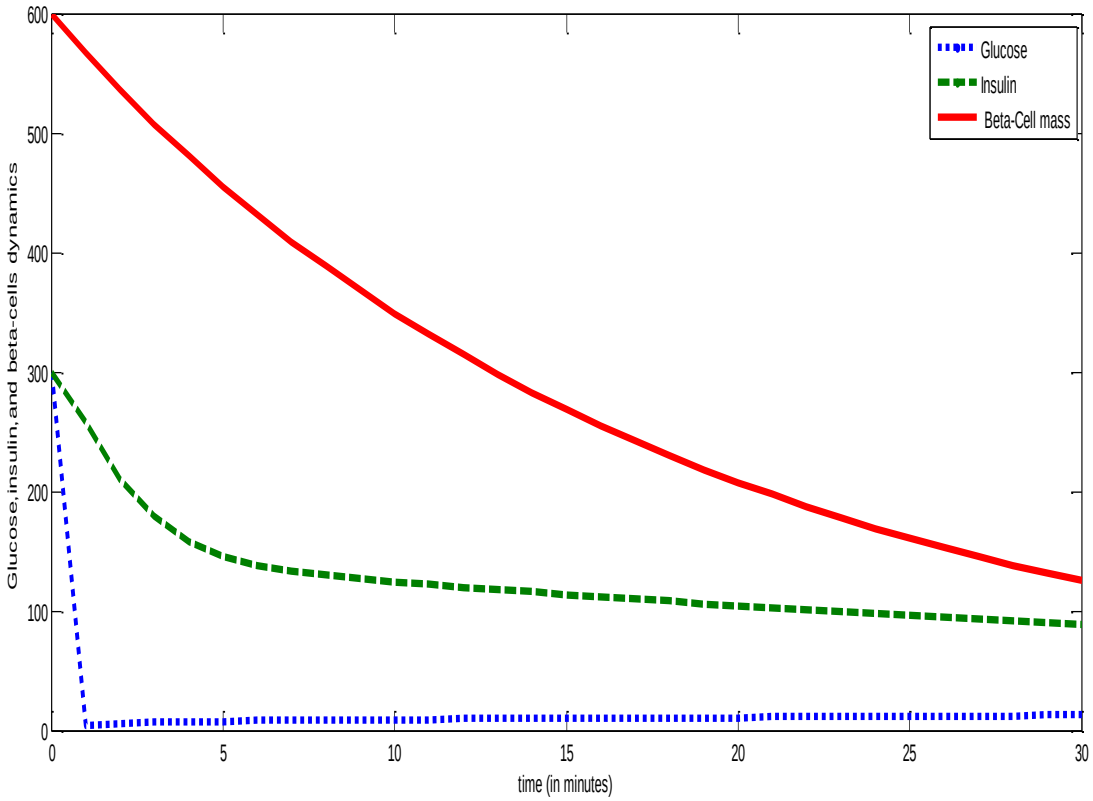

Figure 7: Glucose, insulin, and β-cell mass dynamics in the presence of cortisol and epinephrine at β =600

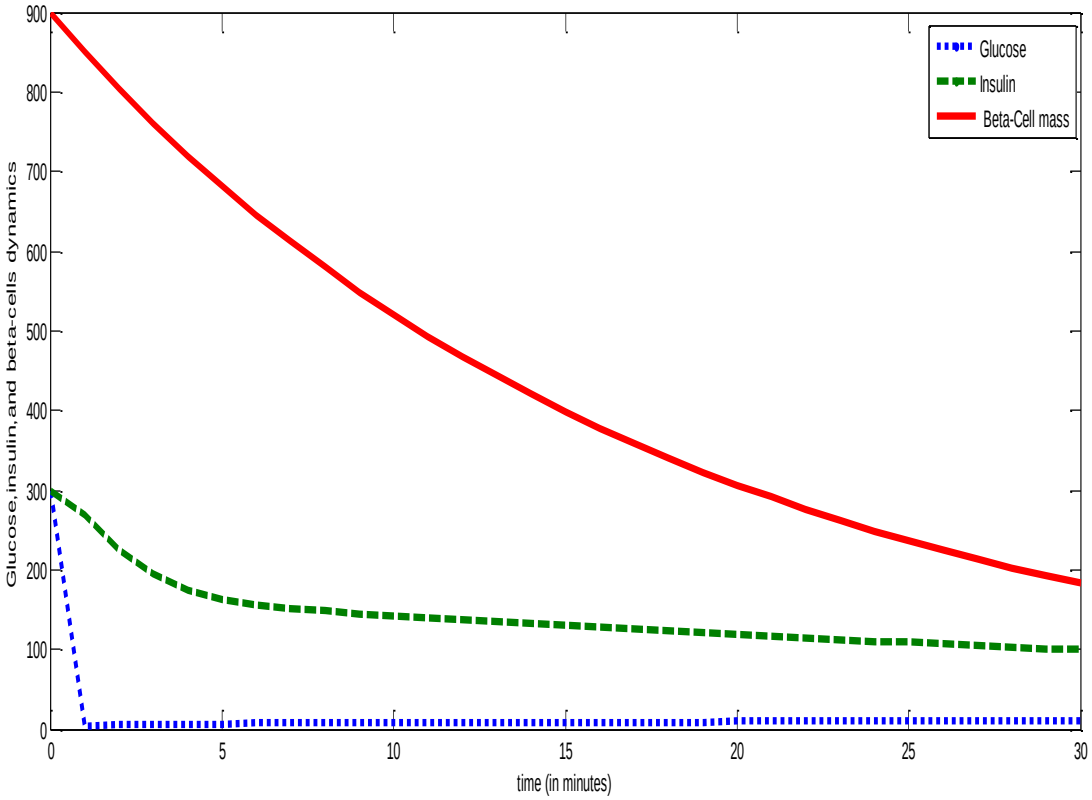

Figure 8: Glucose and insulin dynamics in the presence of cortisol and epinephrine at β =900

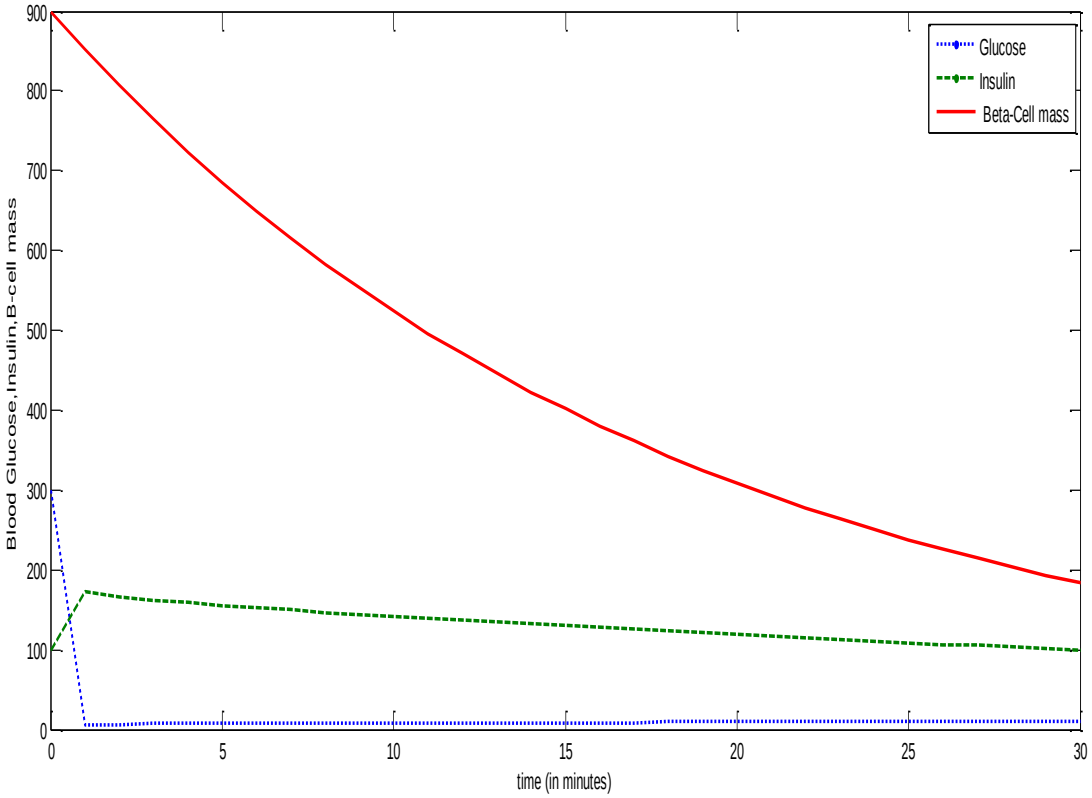

Figure 9: Glucose and insulin dynamics in the presence of cortisol and epinephrine at β =900 and delay=0.01

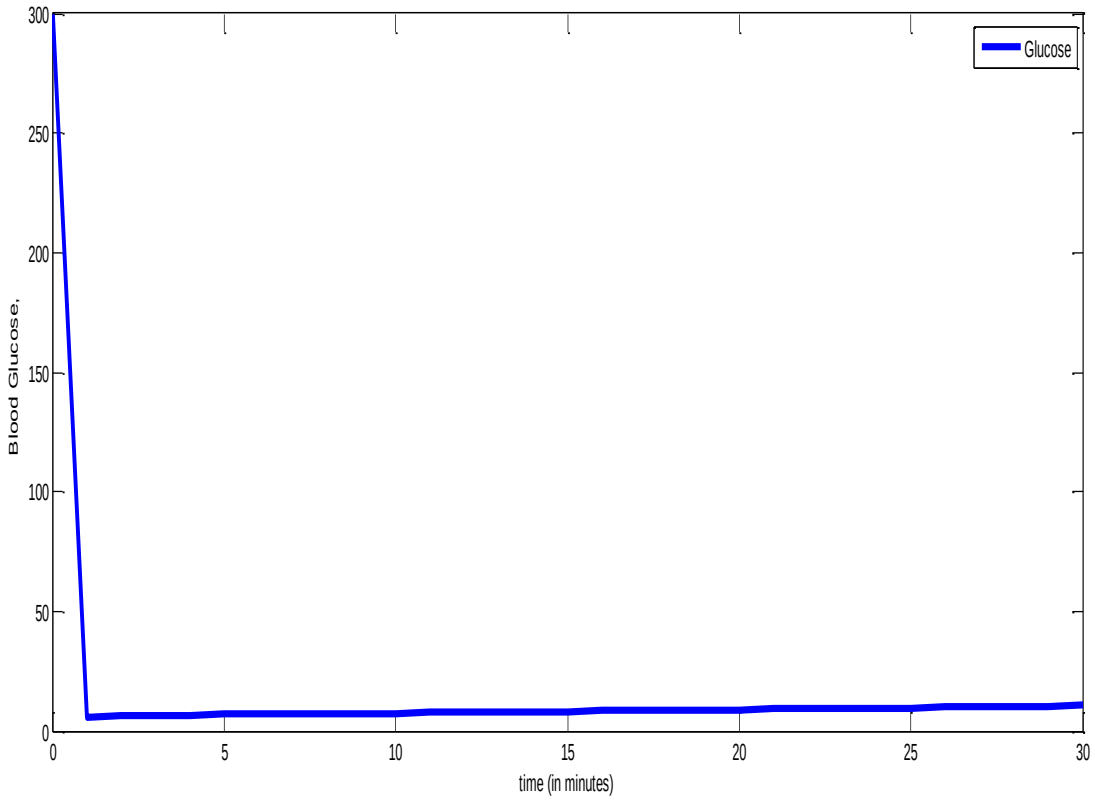

Figure 10: Glucose in the absence of cortisol and epinephrine at β =300 and delay=0.01

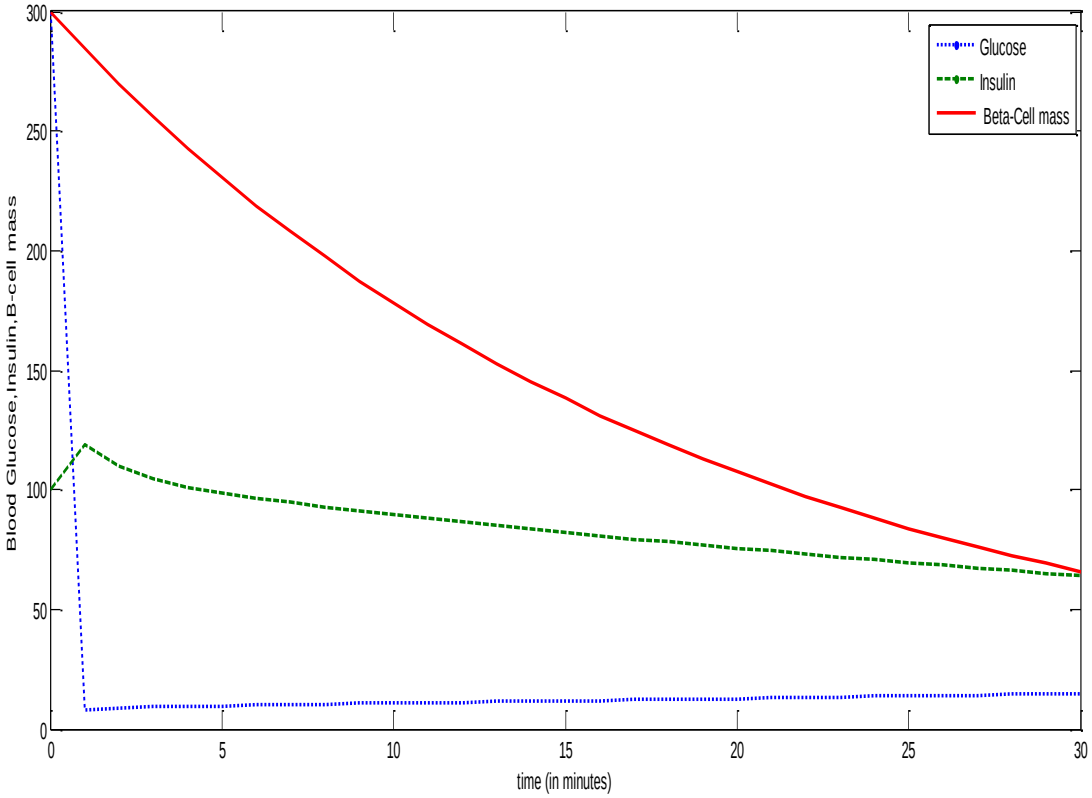

Figure 11: Glucose and insulin dynamics in the absence of cortisol and epinephrine at β =300 and delay=0.01

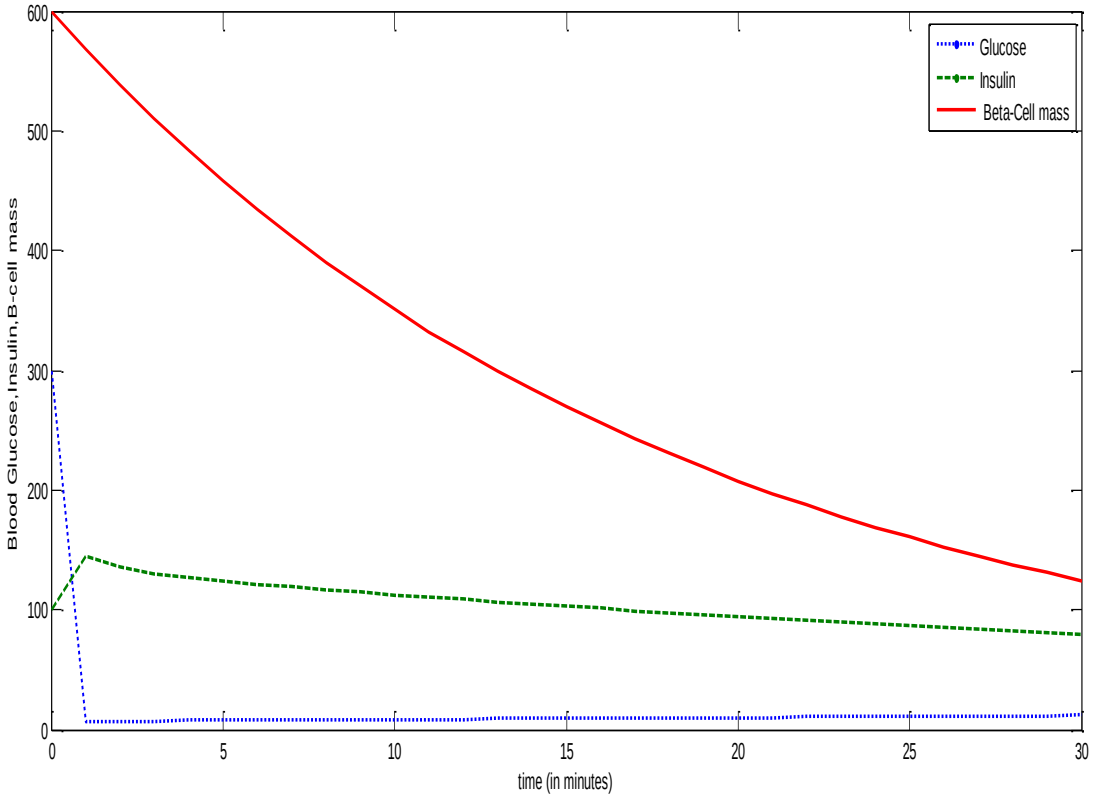

Figure 12: Glucose and insulin dynamics in the absence of cortisol and epinephrine at β =600 and delay=0.01

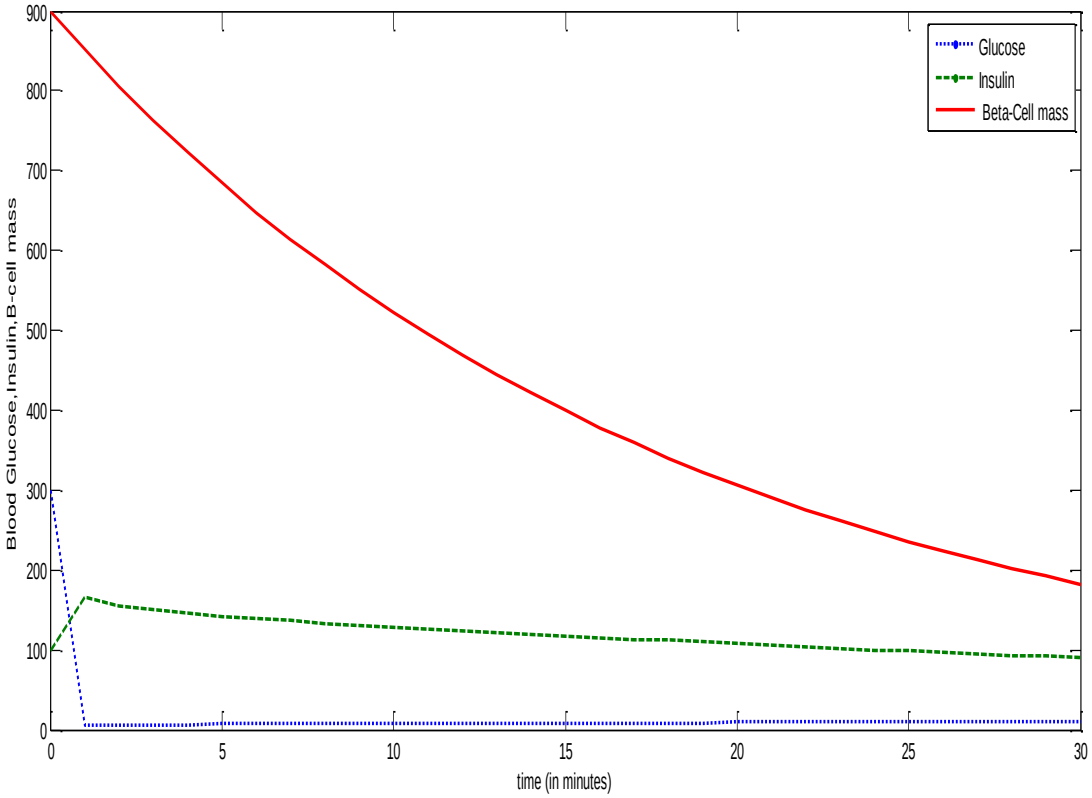

Figure 13: Glucose and insulin dynamics in the absence of cortisol and epinephrine at β =900 and delay=0.01

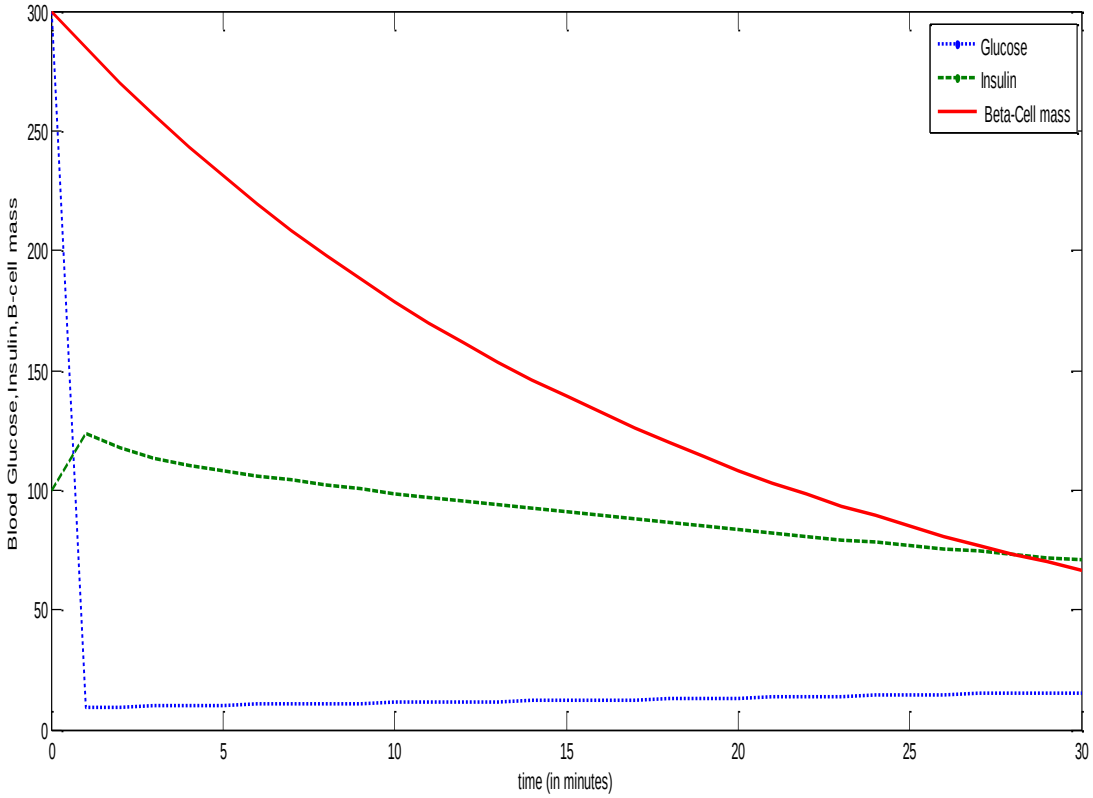

Figure 14: Glucose and insulin dynamics in the presence of cortisol and epinephrine at β =300 and delay=0.01

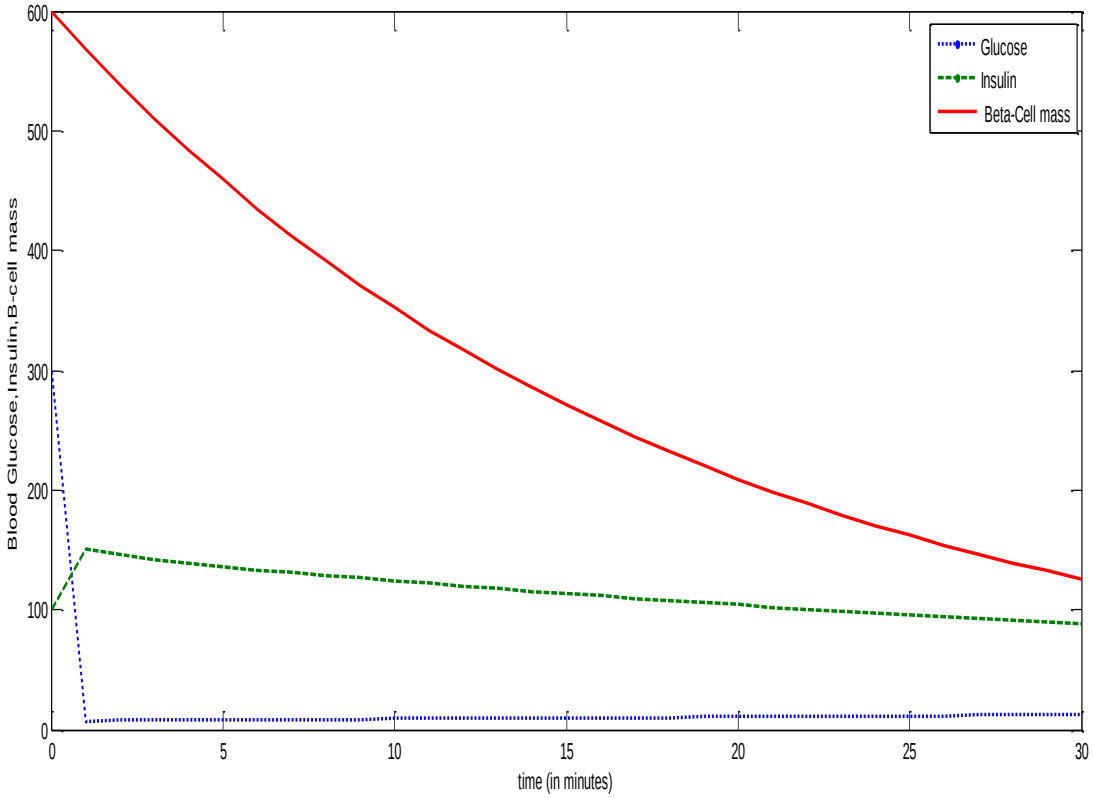

Figure 15: Glucose and insulin dynamics in the presence of cortisol and epinephrine at β =600 and delay=0.01

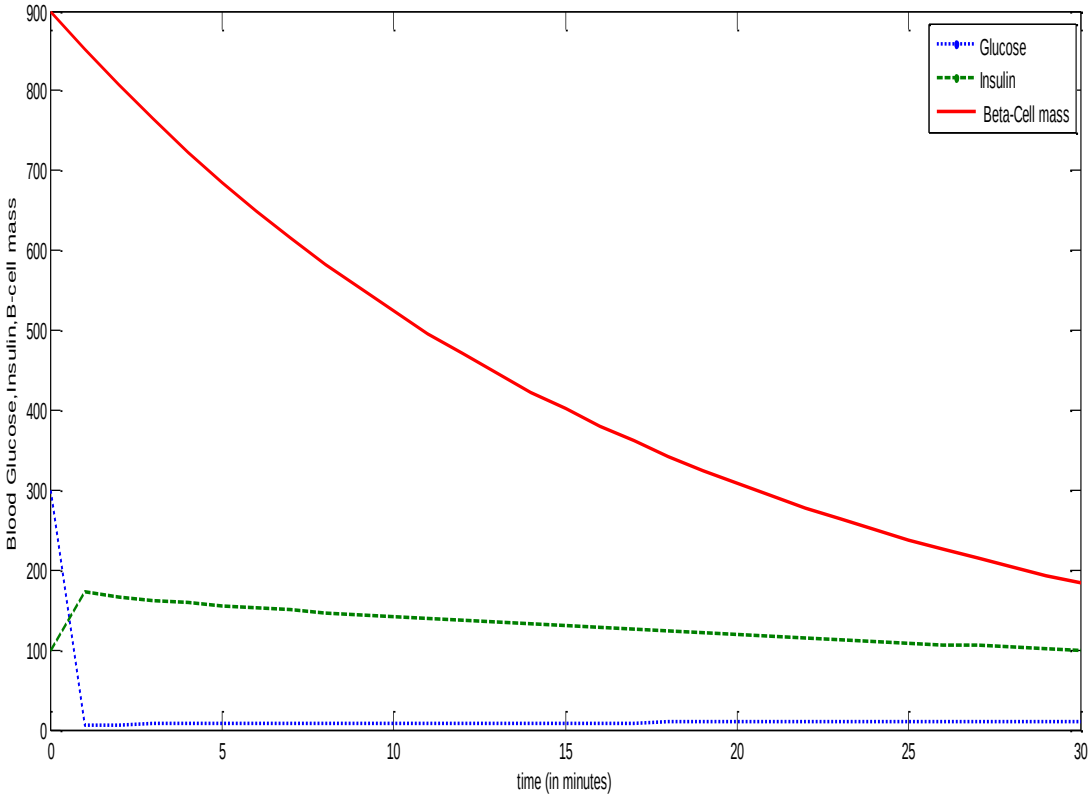

Figure 16: Glucose and insulin dynamics in the presence of cortisol and epinephrine at β =900 and delay=0.01

4.3.1 Discussion of the Results

Discussion of the results is presented as follows:

Case1: Glucose in the Absence of Cortisol and Epinephrine

Figure 4.1 shows the net rate of glucose production at basal glucose level in the absence of cortisol and epinephrine. This result was obtained by implementing the model under normal glucose, the α-cells of the pancreas produce glucagons which trigger the liver to convert stored glycogen into glucose and release it into the blood stream.

Case 2: Glucose and Insulin Dynamics in the Presence of Cortisol and Epinephrine at β =300

Figure 4.2 shows the rate of glucose production at basal glucose level in the presence of trauma, excitement and stress. These results was obtained by implementing the model under normal glucose, insulin dynamics with cortisol and epinephrine as a result of trauma and excitement and stress. At basal glucose level, the adrenal medulla of the kidney produces cortisol and epinephrine which trigger the liver to emergently produce a burst of glucose and release them into the blood.

Case 3: Glucose and Insulin Dynamics in the Presence of Cortisol and Epinephrine at β =1

Figure 4.3 shows the effect of β-cell mass on insulin secretion and glucose utilization in the presence of trauma, excitement and stress at a negligible β=1. We notice that the insulin decreases as the blood glucose increases.

Case 4**:** Glucose and Insulin Dynamics in the Absence of Cortisol and Epinephrine at β =600

Figure 4.4 shows the effect of β-cell mass on insulin secretion and glucose utilization in the absence of trauma, excitement and stress at β=600. We observe that glucose level decreases and blood insulin level increases in β-cell mass. The insulin and the β-cell mass gradually drops as the glucose level gradually gets to equilibrium. We also observe that the insulin level is around 70-80.

Case 5: Glucose, Insulin, and β -Cell Mass Dynamics in the Presence of Cortisol and Epinephrine at β =600

Figure 4.5 shows the effect of β-cell mass on insulin secretion and glucose utilization in the presence of trauma, excitement and stress at β=600. In this, both blood glucose and blood insulin levels increases but insulin increase is insignificant to reduce the blood glucose level to homeostasis due to effect of epinephrine and cortisol of increasing glucose and suppression of insulin secretion. It is observed that the insulin level is around 90-100.

Case 6: Glucose and Insulin Dynamics in the Presence of Cortisol and Epinephrine at β =900

Figure 4.6 shows the effect of β-cell mass on insulin secretion and glucose utilization in the presence of trauma, excitement and stress at β=900. In this the blood glucose level remain high while insulin level increase but not enough to reduce blood glucose level due to homeostasis. We observed that the insulin level is slightly above 100.

Case 7: Glucose and insulin Dynamics in the Presence of Cortisol and Epinephrine at β =900 and τ =0.01

Figure 4.6 shows the effect of β-cell mass on insulin secretion and glucose utilization in the presence of trauma, excitement and stress at β=900 and τ=0.01. In this the blood glucose level remain high while insulin level increases insignificantly as a result of the delay but not enough to reduce blood glucose level due to homeostasis. We observe that the insulin is at 100 as a result of the effect of the delay on the system.

Case 8: Glucose in the Absence of Cortisol and Epinephrine at β =300 and τ =0.01

Figure 4.9 shows the rate of glucose production at basal glucose level in the presence of trauma, excitement and stress β=300 and τ=0.01. At basal glucose level, the adrenal medulla of the kidney produces zero cortisol and epinephrine. Thus glucose increase gradually in the blood stream.

Case 9: Glucose and Insulin Dynamics in the Absence of Cortisol and Epinephrine at β =300 and τ =0.01

Figure 4.9 shows the rate of glucose production at basal glucose level in the presence of trauma, excitement and stress β=300 and τ=0.01. At basal glucose level, the adrenal medulla of the kidney produces zero cortisol and epinephrine. Thus glucose increase gradually in the blood stream. The beta-cell mass reduces with a corresponding effect on the insulin thereby causing the insulin to get to equilibrium.

Case 10: Glucose and Insulin Dynamics in the Absence Of Cortisol and Epinephrine at β =600 and τ =0.01

Figure 4.10 shows the effect of β-cell mass on insulin secretion and glucose utilization in the absence of trauma, excitement, and stress at β=600 and delay τ=0.01. in this case, glucose level decreases and blood insulin level increase because of increase in β-cell mass. The beta-cell mass dropped to as low as 120.

Case 11: Glucose and Insulin Dynamics in the Absence of Cortisol and Epinephrine at β =900 and τ =0.01

Figure 4.11 shows the effect of β-cell mass on insulin secretion and glucose utilization in the absence of trauma, excitement and stress at β=900 and τ=0.01. We observe that glucose level decreases and blood insulin level increases in β-cell mass. The beta-cell mass only dropped to a low 190 in this case.

Case 12: Glucose and Insulin Dynamics in the Presence of Cortisol and Epinephrine at β =300 and τ =0.01

Figure 4.12 shows the effect of β-cell mass on insulin secretion and glucose utilization in the presence of trauma, excitement and stress at β=300 and τ=0.01. In this, both blood glucose and blood insulin levels increases but insulin increase is insignificant to reduce the blood glucose level to homeostasis due to effect of epinephrine and cortisol of increasing glucose and suppression of insulin secretion.

Case 13: Glucose and Insulin Dynamics in the Presence Of Cortisol and Epinephrine at β =600 and τ =0.01

Figure 4.13 shows the effect of β-cell mass on insulin secretion and glucose utilization in the presence of trauma, excitement and stress at β=600. In this, both blood glucose and blood insulin levels increases but insulin increase is insignificant as a result of the delay τ=0.01 to reduce the blood glucose level to homeostasis due to effect of epinephrine and cortisol of increasing glucose and suppression of insulin secretion.

Case 14: Glucose and Insulin Dynamics in the Presence Of Cortisol and Epinephrine at β =900 and τ =0.01

Figure 4.14 shows the effect of β-cell mass on insulin secretion and glucose utilization in the presence of trauma, excitement and stress at β=900. In this the blood glucose level gradually increases, the insulin also reduces gradually while β-cell mass reduces drastically due to homeostasis.

CHAPTER FIVE

SUMMARY, CONCLUSION AND RECOMMENDATION

5.1 Summary

Diabetes mellitus is the disease of the metabolism, which is characterized by very high insufficient supply of the insulin. One of the most finely tuned mechanisms of the human body is the regulation of sugar in the blood stream. In understanding the dynamics of insulin-glucose kinetics, mathematics modelers develop mathematical models. In our model, we incorporated a parameter ρ_c by defining it as effectiveness of cortisol in suppressing insulin secretion and a parameter $G_c(t-\tau)$ by defining it as cortisol induced glucose with delay τ denoting the time lag before the secretion of cortisol. Where $G_c(t-\tau)$ and ρ_c is the increase factors that affect glucose and insulin homeostasis respectively. The model which consist of a system of three nonlinear ordinary differential equations was used to investigate the effect of epinephrine on glucose and β-cell mass dynamics. The results of the study showed that in the presence of cortisol there is increase in blood glucose level and increase in β-cell mass which increase blood insulin level but not enough to bring down blood glucose into homeostasis. As a result, there is an extreme hyperglycemia in all three distinct state. Furthermore, the results of the numerical experiment carried out indicated that cortisol and epinephrine secretion into the blood induced prolong and extreme hyperglycemia. An extreme hyperglycemia induced both β=cell death and insulin resistance which will lead to diabetes.

5.2 Conclusion

We modified the work of Mohammed *et al.* (2019), Mathematical model for the dynamics of glucose, insulin, and beta-cell mass under the effect of trauma, excitement and stress by incorporating $G_c(t-\tau)$ and ρ_c as the rate of glucose production due to cortisol with physiological delay τ and cortisol effectiveness in suppressing insulin secretion to examine the effect of two parameters on glucose regulatory system respectively. Analytical studies were carried out using Jacobian matrix. The equilibrium points were obtained and our

results showed that the equilibrium point of the system is locally and asymptotically stable since all the eigen-values are negative. This shows that the diseases can be controlled to avoid further spread. The result of the numerical experiment carried out indicated that frequent cortisol secretion into the blood induced prolong and extreme hyperglycemia. An extreme hyperglycemia induced both beta-cells death and insulin resistance that could lead to both type1 and type2 diabetes.

5.3 Recommendation

In view of the findings of this study, we recommend that Mathematics modelers should add delay functions in either equation (3.19) or equation (3.20) for the insulin dynamics or β-cell mass dynamics respectively in order to test the behavior of the new system of equations.

5.4 Contribution to Knowledge

We are able to develop a mathematical model for the dynamics of glucose-insulin kinetics incorporating the effect of cortisol, epinephrine and physiological delay.

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APPENDIX I

GLUCOSE AND INSULIN DYNAMICS IN THE PRESENCE OF CORTISOL AND EPINEPHRINE AT β =900

```
function yprime=Alani(t,y)
yprime=zeros(3,1);
lamda = 2000; sigma1 = 308.75; sigma2 = 0.015; epsilon = 0.44; gamma = 2.072; rho1 = 0.06; rho2 = 0.002;
kappa = 0.2; delta = 43.2; mu = 0.06; ar1 = 0.00084; ar2 = 0.0000024; alpha = 40000; tee = 0.0002; tau = 3000;
yprime(1) = lamda + sigma1 + sigma2 * (tee - tau) - (epsilon + gamma * y(2)) * y(1);
yprime(2) = ((y(3) * delta * y(1)^2) / (alpha + y(1)^2)) - (rho1 + rho2 + kappa) * y(2);
yprime(3) = -(mu - ar1 * y(1) + ar2 * y(1)^2) * y(3);
```

APPENDIX II

GLUCOSE AND INSULIN DYNAMICS IN THE PRESENCE OF CORTISOL AND EPINEPHRINE AT β =900 AND DELAY=0.01

```
function yprime=Alani(t,y)

yprime=zeros(3,1);
lamda = 2000; sigma1 = 308.75; sigma2 = 0.015; epsilon = 1.44; gamma = 2.072; rho1 = 0.06; rho2 = 0.002;
kappa = 0.2; delta = 43.2; mu = 0.06; ar1 = 0.00084; ar2 = 0.0000024; alpha = 40000; tee = 1; tau = 0.01;
yprime(1) = lamda + sigma1 + sigma2 * (tee - tau) - (epsilon + gamma * y(2)) * y(1);
yprime(2) = ((y(3) * delta * y(1)^2) / (alpha + y(1)^2)) - (rho1 + rho2 + kappa) * y(2);
yprime(3) = -(mu - ar1 * y(1) + ar2 * y(1)^2) * y(3);
```

APPENDIX III

GLUCOSE IN THE ABSENCE OF CORTISOL AND EPINEPHRINE AT β=300 AND DELAY=0.01

```
function yprime=Alani(t,y)
yprime=zeros(3,1);
lamda = 2000; sigma1 = 0; sigma2 = 0; epsilon = 1.44; gamma = 2.072; rho1 = 0.06; rho2 = 0.002;
kappa = 0.2; delta = 43.2; mu = 0.06; ar1 = 0.00084; ar2 = 0.0000024; alpha = 40000; tee = 1; tau = 0.01;
yprime(1) = lamda + sigma1 + sigma2 * (tee - tau) - (epsilon + gamma * y(2)) * y(1);
yprime(2) = ((y(3) * delta * y(1)^2) / (alpha + y(1)^2)) - (rho1 + rho2 + kappa) * y(2);
yprime(3) = -(mu - ar1 * y(1) + ar2 * y(1)^2) * y(3);
```

APPENDIX IV

GLUCOSE AND INSULIN DYNAMICS IN THE ABSENCE OF CORTISOL AND EPINEPHRINE AT β =300 AND DELAY=0.01

```
function yprime=Alani(t,y)
yprime=zeros(3,1);
lamda = 2000; sigma1 = 0; sigma2 = 0; epsilon = 1.44; gamma = 2.072; rho1 = 0.06; rho2 = 0.002;
kappa = 0.2; delta = 43.2; mu = 0.06; ar1 = 0.00084; ar2 = 0.0000024; alpha = 40000; tee = 1; tau = 0.01;
yprime(1) = lamda + sigma1 + sigma2 * (tee - tau) - (epsilon + gamma * y(2)) * y(1);
yprime(2) = ((y(3) * delta * y(1)^2) / (alpha + y(1)^2)) - (rho1 + rho2 + kappa) * y(2);
yprime(3) = -(mu - ar1 * y(1) + ar2 * y(1)^2) * y(3);
```

APPENDIX V

GLUCOSE AND INSULIN DYNAMICS IN THE ABSENCE OF CORTISOL AND EPINEPHRINE AT β =900 AND DELAY=0.01

```
function yprime=Alani(t,y)
yprime=zeros(3,1);
lamda = 2000; sigma1 = 0; sigma2 = 0; epsilon = 1.44; gamma = 2.072; rho1 = 0.06; rho2
= 0.002;
kappa = 0.2; delta = 43.2; mu = 0.06; ar1 = 0.00084; ar2 = 0.0000024; alpha = 40000; tee =
1; tau = 0.01;
yprime(1) = lamda + sigma1 + sigma2 * (tee - tau) - (epsilon + gamma * y(2)) * y(1);
yprime(2) = ((y(3) * delta * y(1)^2) / (alpha + y(1)^2)) - (rho1 + rho2 + kappa) * y(2);
yprime(3) = -(mu - ar1 * y(1) + ar2 * y(1)^2) * y(3);
```

APPENDIX VI

GLUCOSE AND INSULIN DYNAMICS IN THE PRESENCE OF CORTISOL AND EPINEPHRINE AT β=300 AND DELAY=0.01

```
function yprime=Alani(t,y)
yprime=zeros(3,1);
lamda = 2000; sigma1 = 308.75; sigma2 = 0.015; epsilon = 1.44; gamma = 2.072; rho1 = 0.06; rho2 = 0.002;
kappa = 0.2; delta = 43.2; mu = 0.06; ar1 = 0.00084; ar2 = 0.0000024; alpha = 40000; tee = 1; tau = 0.01;
yprime(1) = lamda + sigma1 + sigma2 * (tee - tau) - (epsilon + gamma * y(2)) * y(1);
yprime(2) = ((y(3) * delta * y(1)^2) / (alpha + y(1)^2)) - (rho1 + rho2 + kappa) * y(2);
yprime(3) = -(mu - ar1 * y(1) + ar2 * y(1)^2) * y(3);
```