http://dx.doi.org/10.5455/sf.83052

Science Forum (Journal of Pure and Applied Sciences)

journal homepage: www.atbuscienceforum.com

Mathematical model for the dynamics of $\beta-cell$ mass, insulin-glucose kinetics incorporating the effect of cortisol, epinephrine and physiological delay

Usman Alani Solomon[1*], Ibrahim Isa Adamu[2], Abimaje Okolo Suleiman[1], Safiyanu Adamu[2], John Samuel Zira[2], Hanifa Umar Yusuf[2]

[1]*National Center for Remote Sensing, National Space Research and Development Agency (NARSDA), Jos, Nigeria*

[2]*Department of Mathematics, Modibbo Adama University of Technology, Yola, Nigeria*

ABSTRACT

This work presents 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 define 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 consists of a system of three non-linear ordinary differential equations. The model is use to investigate the combine effect of cortisol and epinephrine with physiological delay on glucose, insulin, and beta-cell mass dynamics. The results of the study show that: In the combined presence of cortisol and epinephrine, the blood glucose increase more and the blood insulin decrease due to suppression by the hormone, despite the fact that there is increase in beta-cell mass, the system remains extremely hyperglycemic. The analytical results further show that continuous, stress, excitement, and/or trauma lead to constant secretion of cortisol and epinephrine into the blood stream. Frequent secretion of cortisol and epinephrine increases the risk of diabetes in humans.

ARTICLE INFO

Article history:
Received 22 May 2021
Received in revised form
22 May 2021
Accepted 22 May 2021
Published 12 October 2021
Available online 12 October 2021

KEYWORDS

Diabetes
Cortisol
Epinephrine
Equilibrium points
Jacobian
Stability analysis

1. Introduction

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 et al., 2011). Diabetes mellitus can also be defined as a disease of glucose regulatory system characterized by fasting and/or postprandial hyperglycemia (Topp et al., 2000).

According to Topp et al. (2000), there are two types of diabetes namely

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

Type 1 diabetes (also referred to as juvenile onset or insulin-dependent diabetes) is due to autoimmune attack on the insulin secreting β-cells (Topp et al., 2000). Type 1 diabetes affects people under the age of 40, and represents 10%–15% of the diabetic population (Boutayeb et al., 2004). Patients with type 1 diabetes are recommended to take insulin injection (Ahlam and Alaa, 2014).

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

* **Corresponding author** Usman Alani Solomon ✉ alanisolomon34@gmail.com ✉ National Center for Remote Sensing, Jos, Nigeria.

blood glucose level with reduced insulin secretion and resistance to the action of insulin (Topp et al., 2000). Type 2 diabetes represents 85%–90% of the diabetic population (Boutayeb et al., 2004).

Topp et al. (2000) developed a mathematical model for *β–cell mass*, insulin, and glucose kinetics to study the glucose regulatory system. The results of their investigation show 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 *β–cell* mass which could drive glucose levels down (dynamical hyperglycemia).

Ibrahim et al. (2014) developed Mathematical model for the dynamics of glucose regulatory system under the combined effect of dieting and physical activity. 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.

Mohammed et al. (2019) developed a Mathematical model for the dynamics of *β–cell* mass, insulin-glucose kinetics by incorporating the effect of epinephrine due to trauma, stress and/or excitement. 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 their findings, they 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.

2. Formulation of the 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., arterial blood, venous blood, cerebral spinal fluid, interstitial fluid).

The following assumptions were made:

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 *β–cell* increases with increasing glucose and formation of *β–cell* 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.

2.1. Derivation of the model equations

By considering the model assumptions, stated variables and parameters, the ordinary nonlinear differential equation which describe the dynamics of *β–cell* mass, insulin-glucose kinetics incorporating the effect of cortisol, epinephrine and physiological delay become

$$\frac{dG}{dt} = R_o + G_e + G_c(t-\tau) - (E_{GO} + S_I I)G \tag{2.1}$$

$$\frac{dI}{dt} = \frac{\beta\sigma G^2}{\alpha + G^2} - (\rho + \rho_c + K)I \tag{2.2}$$

$$\frac{d\beta}{dt} = (-d_o + r_1 G - r_2 G^2)\beta \tag{2.3}$$

Table 1 below shows the notations and descriptions of the stated variables and parameters. Figure 1 shows the flow diagram of the model.

Table 1. Notations and descriptions of state variables and parameters

$G(t)$:	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:	Constant beta cell glucose tolerance ranges.
ρ:	Epinephrine effectiveness in suppressing insulin secretion.
ρ_c:	Cortisol effectiveness in suppressing insulin secretion.
P_0:	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.

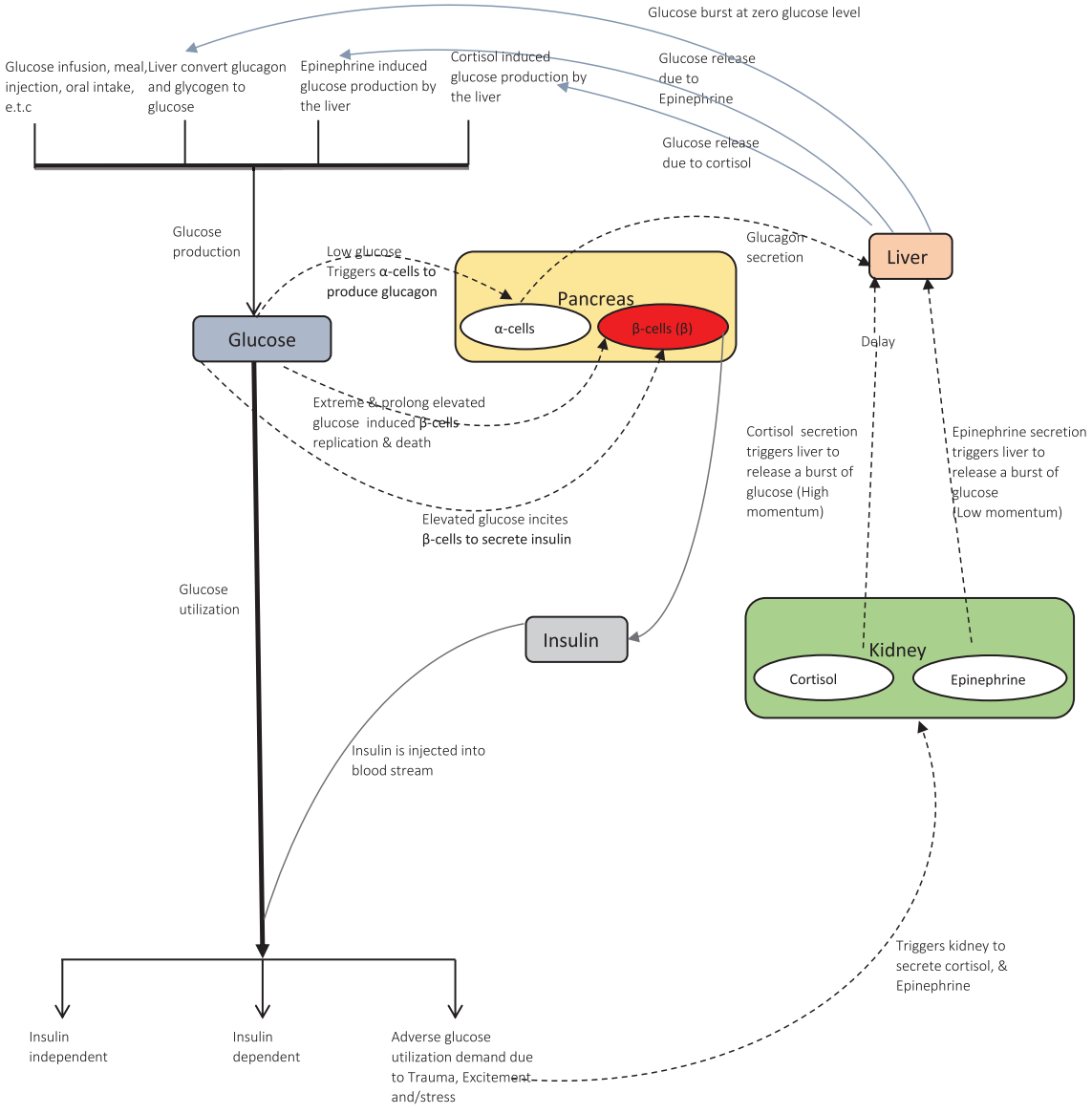

Figure 1. Flow diagram of the model.

3. Analysis of the Model

In this section, we are going to analyze the system of model in Equations (2.1)–(2.3). This involves; equilibrium points and stability analysis of the system of equations.

3.1. 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.

3.1.1. Equilibrium of the slow subsystem *β*-cell mass

Setting $\frac{d\beta}{dt}=0$ from Equation (2.3)

We have

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

Either

$$\beta = 0 \text{ or } -d_o + r_1 G - r_2 G^2 = 0 \tag{3.1}$$

which can also be written as

$$r_2 G^2 - r_1 G + d_o = 0 \tag{3.2}$$

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 $c = d_o$

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

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

$$G_1 = \frac{r_1 - \sqrt{r_1^2 - 4r_2 d_o}}{2r_2} \tag{3.3}$$

or

$$G_2 = \frac{r_1 + \sqrt{r_1^2 - 4r_2 d_o}}{2r_2} \tag{3.4}$$

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 eigenvalue $\lambda = -(r_2 G^2 - r_1 G + d_o)$.

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

3.1.2. Equilibrium of fast (glucose/insulin) subsystem

For insulin dynamics at equilibrium, we have $\frac{dI}{dt}=0$ from Equation (2.2), this implies that

$$\frac{\beta\sigma G^2}{\alpha + G^2} - (\rho + \rho_c + K)I = 0 \tag{3.5}$$

Making insulin I the subject of Equation (3.5), hence Equation (3.5) gives

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

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

$$I = \frac{\beta\sigma G^2}{\alpha + G^2} \times \frac{1}{\rho + \rho_c + K} \tag{3.6}$$

From Equation (3.1), we saw that $\beta = 0$.By substituting the value of β into Equation (3.6), we have

$$I = 0 \tag{3.7}$$

Glucose dynamics at equilibrium, we have set $\frac{dG}{dt}=0$ from Equation (2.1). This implies that

$$R_o + G_e + G_c(t-\tau) - (E_{GO} + S_i I)G = 0 \tag{3.8}$$

Substituting the value of I from Equation (3.7) into Equation (3.8), we have

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

$$R_o + G_e + G_c(t-\tau) - E_{GO}G = 0 \tag{3.9}$$

Making G the subject of Equation (3.9)

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

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

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

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

$$E_0(G^*, I^*) = \left(\frac{R_o + G_e + G_c(t-\tau)}{E_{GO}}, 0 \right) \tag{3.10}$$

3.2. Stability analysis

We test the stability of the fast (glucose/insulin) subsystem from Equations (2.1) and (2.2) by using the Jacobian matrix

$$J = \begin{bmatrix} \frac{\partial F_1}{\partial G} & \frac{\partial F_1}{\partial I} \\ \frac{\partial F_2}{\partial G} & \frac{\partial F_2}{\partial I} \end{bmatrix} \tag{3.11}$$

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 Equation (3.11) becomes

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

At equilibrium of the fast subsystem

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

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

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

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

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

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

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

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

$\lambda_1 = -E_{G0}$ *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 (2.1)–(2.3) 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

$$J = \begin{bmatrix} \frac{\partial F_1}{\partial G} & \frac{\partial F_1}{\partial I} & \frac{\partial F_1}{\partial \beta} \\ \frac{\partial F_2}{\partial G} & \frac{\partial F_2}{\partial I} & \frac{\partial F_2}{\partial \beta} \\ \frac{\partial F_3}{\partial G} & \frac{\partial F_3}{\partial I} & \frac{\partial F_3}{\partial \beta} \end{bmatrix} \tag{3.12}$$

The Jacobian matrix Equation (3.12) 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

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

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

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

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

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 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 for $i = 1,2,3$. This shows that diabetes can be controlled. The analytical results further show that continuous stress, excitement and/or trauma lead to constant secretion of cortisol and epinephrine into the blood stream. The constant cortisol and epinephrine in the blood stream induce prolong and extreme hyperglycemia. Extreme hyperglycemia induced beta-cells death and insulin resistance that could lead to type 1 and type 2 diabetes.

References

Ahlam AS, Alaa S. Developing a mathematical model to detect diabetes using multigene genetic programming. Adv J Artif Intell 2014; 3(10):54–59.

Boutayeb A, Chetouani A, Achouyab K, Twizell EH. Mathematical model for the burden of diabetes and its complications. Biomed Eng Online 2004; 3:20; doi:10.1186/1475-925X-3-20.

Ibrahim IA, Haruna Y, Garba EJD. Mathematical model for the dynamics of glucose regulatory system under the combined effect of dieting and physical activity. Int J Pure Appl Sci Technol 2014; 20(1):88–100.

Kwacha B, Ongati O, Simwa R. Mathematical model for detecting diabetes in the blood. Appl Math Sci 2011; 5(6):279–86.

Mohammed II, Adamu I, Barka SJ. Mathematical model for the dynamics of mass, insulin-glucose kinetics by incorporating the effect of epinephrine due to trauma, stress and/or excitement. Model Numer Simul Mater Sci 2019; 9:71–96.

Topp B, Promislaw K, de Vries G, Miura R, Finegood D. A model of mass, insulin, and glucose kinetics: pathways to diabetes. J Theor Biol 2000; 206,605–19.