Stability of a Glucose-Insulin and Externally (G-I-E) Regulatory System Model

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***Abstract* - A mathematical model for glucose-insulin regulatory system is presented. The glucose-insulin regulatory system has been introduced with a new variable which is ingested glucose. The ingested glucose is the external source of glucose that is coming from source of food and assumed to follow the logistic growth model. In addition, we analyze glucose constant value consumed from medicine. With the introduction of ingested glucose a three variable model is established. The stability of the model is analyzed by construction of Lyapunov function and conditions for stability have been derived. Numerical simulations are used to validate and describe the stability of the proposed model.**

Keywords - Glucose-Insulin, Stability, Lyapunov Function, Numerical Simulation

I. INTRODUCTION

An Irregular Glucose insulin regulator system in human can lead to diabetes. The disease can be caused by environmental and genetic factors. The diabetes causes an imbalance in the insulin; the body is unable to produce enough insulin to carry glucose from food to cells to generate energy more efficiently. In general, the diabetes can be categorized into two groups: Type 1 diabetes and Type 2 diabetes. Normal blood glucose concentration level in humans is in a narrow range 3.9 mmol/L-6.1 mmol/L (70-110 mg/dL). There were more than 422 million people with diabetes worldwide in 2014 but only 108 million had diabetics in 1980.

At the beginning of 20th century, mathematical modeling of different diseases; asthma, cancer and diabetes, were started. Many more clinical and nonclinical models have been designed and analyzed for diseases. Some diabetic models had established and derived with glucose and insulin regulator. In the middle of 1960, Ackerman and other research [2] developed:

$$\dot{g} = -ag - bh \tag{1}$$
$$\dot{h} = cg - dh \tag{2}$$

Where a, b, c and d are constants

Two equations were based on a simple model for the blood glucose regulatory system.

In 1961, Bolie [3] had some confusion of normal blood glucose regulation. The model was:

$$\dot{G} = -a_1 G - a_2 I + p \tag{3}$$
$$\dot{I} = -a_3 G - a_4 I \tag{4}$$

From 2016 to 2018, Devi and other researchers [4], [5], [7] had developed a Glucose-Insulin-External G-I-E model where externally ingested glucose was assumed to be logistic growth, and insulin was assumed to be a constant amount of glucose and insulin in the body.

II. MATHEMATICAL MODEL

A. The Glucose-Insulin-External Interaction Process

According to Devi and friend [4], the new G-I-E system of equations was added by adding a new variable, the externally-derived glucose constant in external equation. The system can be described in Figure 1 below.

During eating sweet foods, more carbohydrate or diabetic drug, the digestive system is in the process. This glucose is released and sent into the bloodstream in the body.

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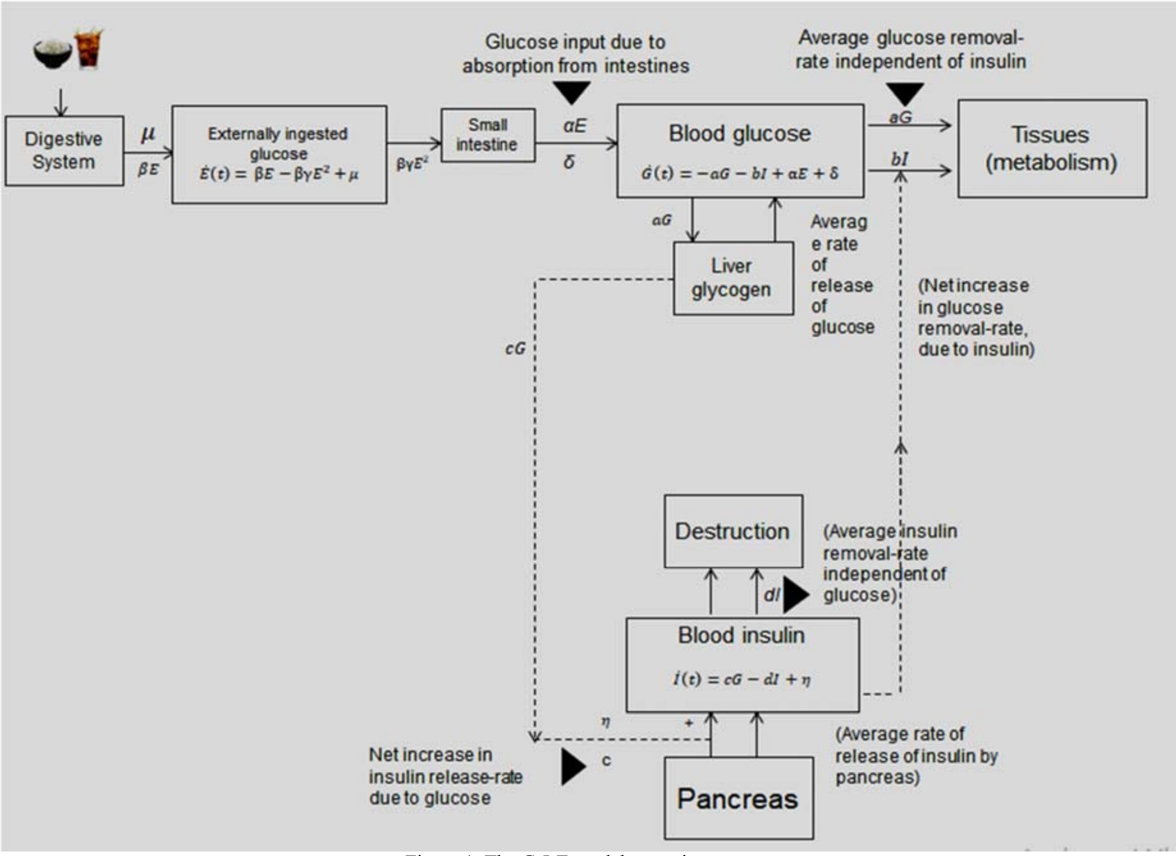

Figure 1. The G-I-E model operation process

B. Mathematical Model of The Glucose-insulin -External

In this paper, we define:

$G(t)$: denote the glucose concentration in the body at time t.
(t) : denote the insulin concentration in the body at time t.
and
$E(t)$: denote the externally ingested glucose at time t which is coming from the source of food to the body. The model is

$$\dot{G}(t) = -aG - bI + \alpha E + \delta \quad (5)$$
$$\dot{I}(t) = cG - dI + \eta \quad (6)$$
$$\dot{E}(t) = \beta E(1-\gamma E) + \mu \quad (7)$$

where, $G \geqslant 0, I \geqslant 0$ and $E \geqslant 0$

δ: Constant amount of glucose present in the body
η: Constant amount of insulin present in the body
a: Rate constant representing insulin independent glucose disappearance
b: Rate constant representing insulin dependent glucose disappearance
c: Rate constant representing insulin production due to glucose stimulation
d: Rate constant representing glucose independent insulin degradation
α: Rate constant representing increase of glucose level due to ingested glucose
β: Intrinsic growth constant of ingested glucose
$\frac{1}{\gamma}$: Carrying capacity of ingested glucose
μ: Constant amount of glucose from externally ingested glucose in the form of medication.

III. MODEL ANALYSIS

A. Equilibrium points

Consider equations (5), (6) and (7). We first find two equilibrium points. The equations (7) $\dot{E}(t) = 0$, we get E two values that are:

$$E_1 = \frac{\beta - \sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{2\beta\gamma} \text{ and } E_2 = \frac{\beta + \sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{2\beta\gamma}$$

Consider at $E_1 = \frac{\beta - \sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{2\beta\gamma}$
we get the G_1 and I_1 values respectively as follows:

$$G_1 = \frac{\frac{d\alpha}{\gamma} - \frac{d\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2d\delta - 2b\eta}{2(bc+ad)},$$

$$I_1 = \frac{\frac{c\alpha}{\gamma} - \frac{c\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2c\delta + 2a\eta}{2(bc+ad)}$$

So the first equilibrium is (G_1, I_1, E_1).

Consider at $E_2 = \frac{\beta+\sqrt{\beta}\sqrt{\beta+4\mu\gamma}}{2\beta\gamma}$

we get the G_2 and I_2 values respectively as follows:

$$G_2 = \frac{\frac{d\alpha}{\gamma} + \frac{d\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2d\delta - 2b\eta}{2(bc+ad)},$$

$$I_2 = \frac{\frac{c\alpha}{\gamma} + \frac{c\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2c\delta + 2a\eta}{2(bc+ad)}$$

So the second equilibrium is $(G_2, I_2, E_2) =$

$$\left(\frac{\frac{d\alpha}{\gamma} + \frac{d\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2d\delta - 2b\eta}{2(bc+ad)}, \frac{\frac{c\alpha}{\gamma} + \frac{c\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2c\delta + 2a\eta}{2(bc+ad)}, \frac{\beta+\sqrt{\beta}\sqrt{\beta+4\mu\gamma}}{2\beta\gamma}\right)$$

B. Stability analysis

Performing search the eigenvalues to explain the solutions of equations about equilibrium. The stability of the equilibrium can be found from the eigenvalues of the Jacobian matrix. Since the first equilibrium point, the Jacobian matrix is:

$$J = \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & -\beta\gamma E + \beta(1-\gamma E) \end{pmatrix}_{(G_1,I_1,E_1)}$$
$$= \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & \sqrt{\beta}\sqrt{\beta+4\mu\gamma} \end{pmatrix}$$

We have:

$$\lambda_1 = \sqrt{\beta}\sqrt{\beta+4\mu\gamma}, \quad \lambda_{2,3} = \frac{-(a+d)\pm\sqrt{(a-d)^2-4bc}}{2}$$

The G-I-E model is stabilized around the first equilibrium point when $\forall\lambda_i < 0$ for $i = 1,2,3$.

From eigenvalue $\lambda_1 = \sqrt{\beta}\sqrt{\beta+4\mu\gamma} \nless 0$, so the model G-I-E unstable around:

$(G_1, I_1, E_1) =$

$$\left(\frac{\frac{d\alpha}{\gamma} - \frac{d\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2d\delta - 2b\eta}{2(bc+ad)}, \frac{\frac{c\alpha}{\gamma} - \frac{c\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2c\delta + 2a\eta}{2(bc+ad)}, \frac{\beta-\sqrt{\beta}\sqrt{\beta+4\mu\gamma}}{2\beta\gamma}\right)$$

Consider the second equilibrium points:

$(G_2, I_2, E_2) =$

$$\left(\frac{\frac{d\alpha}{\gamma} + \frac{d\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2d\delta - 2b\eta}{2(bc+ad)}, \frac{\frac{c\alpha}{\gamma} + \frac{c\alpha\sqrt{\beta+4\mu\gamma}}{\sqrt{\beta}\gamma} + 2c\delta + 2a\eta}{2(bc+ad)}, \frac{\beta+\sqrt{\beta}\sqrt{\beta+4\mu\gamma}}{2\beta\gamma}\right)$$

the Jacobian matrix is:

$$J = \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & -\beta\gamma E + \beta(1-\gamma E) \end{pmatrix}_{(G_2,I_2,E_2)}$$
$$= \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & -\sqrt{\beta}\sqrt{\beta+4\mu\gamma} \end{pmatrix}$$

We have:

$$\lambda_1 = -\sqrt{\beta}\sqrt{\beta+4\mu\gamma}, \quad \lambda_{2,3} = \frac{-(a+d)\pm\sqrt{(a-d)^2-4bc}}{2}$$

Therefore, the G-I-E model is stable around the point (G_2, I_2, E_2) $\forall\lambda_i < 0$ for $i = 1,2,3$

C. Linearization

We take a system of nonlinear differential equations into a system of linear equations near the 2nd equilibrium point. From the Jacobian matrix around the point (G_2, I_2, E_2):

$$J = \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & -\beta\gamma E + \beta(1-\gamma E) \end{pmatrix}_{(G_2,I_2,E_2)}$$
$$= \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & -\sqrt{\beta}\sqrt{\beta+4\mu\gamma} \end{pmatrix}\begin{pmatrix} G-G_2 \\ I-I_2 \\ E-E_2 \end{pmatrix}$$

Consider transformation of:

$G = X + G_2, I = Y + I_2$ and $= Z + E_2$,

so that:

$$\begin{pmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{pmatrix} = \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & -\sqrt{\beta}\sqrt{\beta+4\mu\gamma} \end{pmatrix}\begin{pmatrix} X \\ Y \\ Z \end{pmatrix}$$

Thus, the system of linear equations of the G-I-E model is:

$$\dot{X} = -aX - bY + \alpha Z$$

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$$\dot{Y} = cX - dY$$
$$\dot{Z} = -\sqrt{\beta}\sqrt{\beta + 4\mu\gamma}Z$$

D. Lyapunov Function

Consider a system of equations to determine the stability of an equilibrium using Lyapunov function,

$$V = AX^2 + BY^2 + CZ^2 + 2DXZ$$

Therefore,

$$\begin{aligned}\dot{V} &= 2AX\dot{X} + 2DZ\dot{X} + 2BY\dot{Y} + 2CZ\dot{Z} + 2DX\dot{Z} \\ &= -2aAX^2 - 2BdY^2 - \left(2C\sqrt{\beta}\sqrt{\beta + 4\mu\gamma} - 2D\alpha\right)Z^2 \\ &\quad -(2Ab - 2Bc)XY - 2DbYZ \\ &\quad -\left(2Da - 2A\alpha + 2D\sqrt{\beta}\sqrt{\beta + 4\mu\gamma}\right)XZ \qquad (8)\end{aligned}$$

Obviously, the coefficient of X^2, Y^2 and YZ is clearly negative. Let $D = 1$ by substituting it in the system of equations (8), so the result will be as follows:

$$A = \frac{a + \sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{\alpha}, B = \frac{ab + b\sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{c\alpha}, C = \frac{\alpha}{\sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}$$

and get

$$\dot{V} = -\left(\frac{2a^2 + 2a\sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{\alpha}\right)X^2 - \left(\frac{2abd + 2bd\sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{c\alpha}\right)Y^2$$

$$-\left(\frac{2a + 2\sqrt{\beta}\sqrt{\beta + 4\mu\gamma} - 2ab - 2b\sqrt{\beta}\sqrt{\beta + 4\mu\gamma}}{\alpha}\right)XY - 2bYZ \qquad (9)$$

Therefore, it is definitely negative only if:

$$\left(a + \sqrt{\beta}\sqrt{\beta + 4\mu\gamma}\right) - b\left(a + \sqrt{\beta}\sqrt{\beta + 4\mu\gamma}\right) > 0$$

$$(1 - b)\left(a + \sqrt{\beta}\sqrt{\beta + 4\mu\gamma}\right) > 0 \rightarrow b < 1 \qquad (10)$$

Finally, the conditions are stable. The G-I-E model is locally asymptotically stable for a equilibrium point. This corresponds to the definition of the Lyapunov function.

IV. NUMERICAL SIMULATIONS

All conditions for this new G-I-E model are found and known that the stability of the model is under condition:

$b < 1$.

This makes finding the numerical simulations to confirm the stability case:

$a = 1, b = 0.00475, c = 1.5, d = 2.05, \alpha = 0.01$
$\beta = 1, \gamma = 0.2353, \delta = 4.7245, \eta = 0.425, \mu = 0.005$

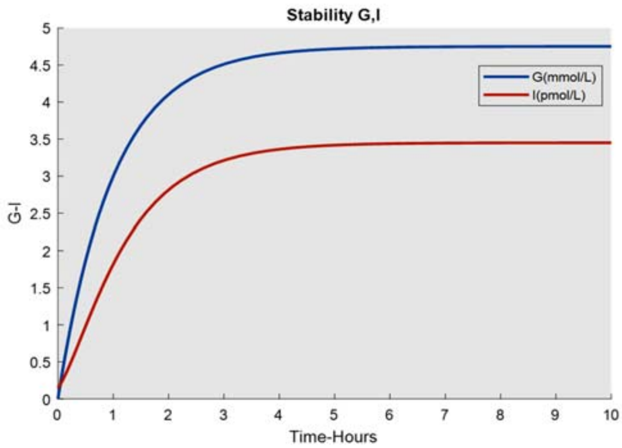

Figure 2. Stability of blood glucose-insulin under the influence of externally ingested glucose

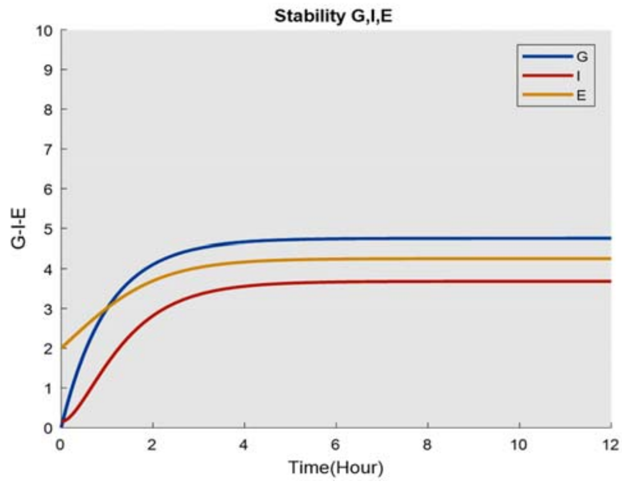

Figure 3. The behavior of glucose-insulin and externally ingested glucose under the condition.

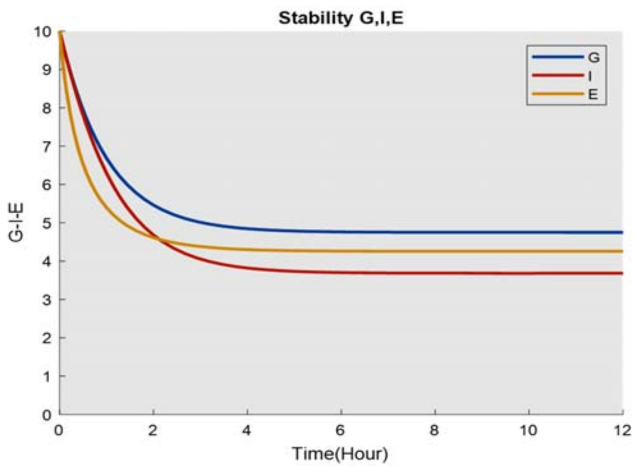

Figure 4. The behavior of glucose-insulin and externally ingested glucose over the condition.

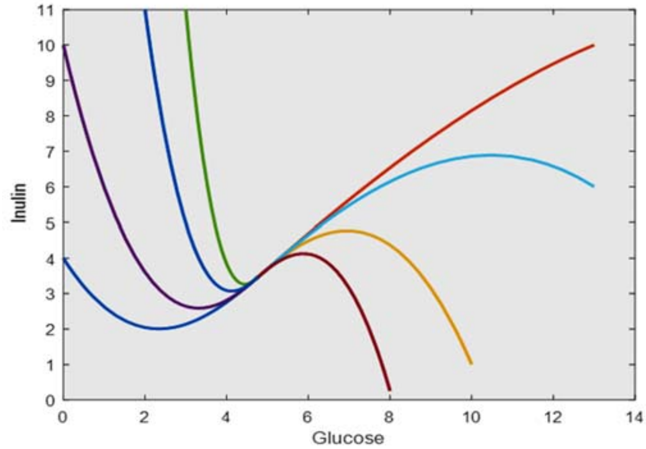

Figure 5. The phase portrait of glucose-insulin under the condition $b < 1$

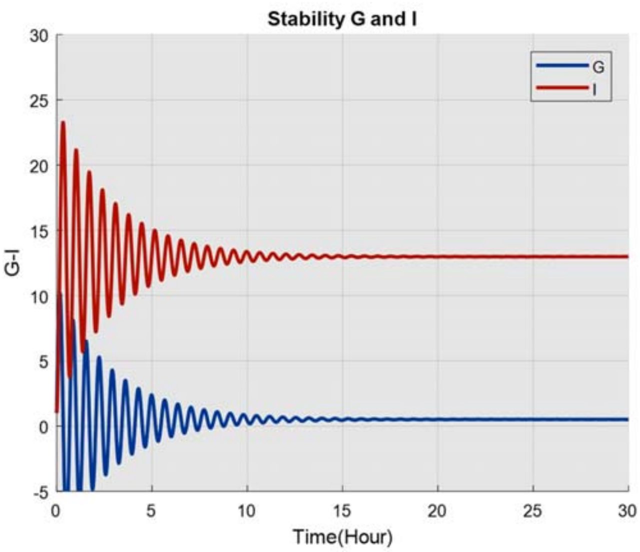

Figure 6. The stable behavior of glucose and insulin.

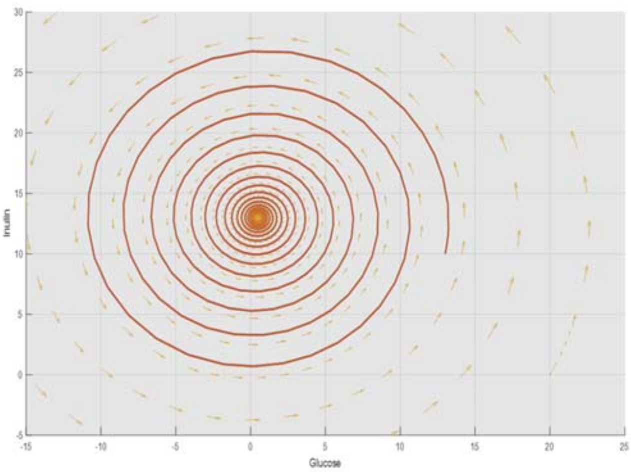

Figure 7 shows phase portraits for Glucose - Insulin.

V. DISSCUSSION AND CONCLUSION

Some exogenous glucose or drugs had been given to the normal people who have low glucose levels, the glucose in the blood gradually reached homeostasis after 2 hours; Figure 2, (Normal blood glucose concentration level is 3.9-6.1 mmol/L). Moreover, Figure 3 displays 3 variables; glucose, insulin and externally ingested glucose in the same case. In Figure 4, the behavior of glucose-insulin is demonstrated starting a higher initial glucose and being ingested in the body. The numerical simulation points out to the normal range of glucose levels after 2 hours as well. The phase portrait of our system of equations is characterized by a stable focus around the equilibrium (G_2, I_2, E_2) that gives directions in Figure 5. The parameters of Figure 6 and 7 are $a = -0.25$, $b = -8$, $\alpha = 0.6575$, $\delta = 100$, $c = 10.4275$, $d = 0.4275$ and $\eta = 0.2785$. The trajectories like decline oscillating to stability to the constant as toward normal constant indicator level in Figure 6. Finally, Figure 7 is shown for glucose and insulin represented the stability of diabetic models in which trajectories are spirals.

The new G-I-E system model; equations (5)-(7), is analyzed by Lyapunov. The numerical solutions have been confirmed all conditions for stabilities. The human body's regulating system normalized the balance of glucose, insulin and external glucose, after we had consumed food into the body at the end of 2 hours of digestion and absorption. Simulation of diabetic case is the same direction to stable, but it took much more time. The concurrently stable curve get nearly 10 hours after eating food or taking medicine into the body.

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