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A Mathematical Model of Glucose - Insulin regulation under the influence of externally ingested glucose (G-I-E model)

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Abstract:*Here, we present a mathematical model for glucose- insulin regulatory system. 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. With the introduction of ingested glucose, a three variable model is established. Stability of the model has been analyzed under various equilibrium conditions. Numerical simulations are used to validate and describe the stability of the proposed model.*

AMS Subject Classification*: 90C31, 93A30, 93D99, 00A71, 00A72, 34D20*
***KEYWORDS*:** *Modelling, mathematical modelling, diabetes mellitus, glucose-insulin regulatory system, stability, Jacobian , logistic growth model*

I. INTRODUCTION

It has been surveyed that globally in every six seconds one person dies from diabetes (5 million deaths). One in every eleven adults is suffering from diabetes (415 million), one in every seven births is affected by gestational diabetes. Around 542000 children have type-1 diabetes i.e. 20-79 in every 1000 (2015). Three quarter of the people with diabetes are living in low and middle income countries. 12% of the global health expenditure is spent on diabetes ($ 673 billion), 46.5% of adults with diabetes are undiagnosed [1]. In India about 63 million people are suffering from diabetes and this figure is likely to increase up to 80 million by 2025. By 2040, one adult in every ten peoples (642 million) will have diabetes [2]. Assam is a state of India where around 4% people are suffering from diabetes [3].

Diabetes mellitus also commonly known as diabetes is a metabolic disorder in human body due to some hereditary and environmental causes. Diabetes is a chronic condition in which glucose (sugar) level in blood exceeds the normal range i.e. 80-110 mg/dl. It is a disease of glucose-insulin endocrine disorder characterised by hyperglycaemia resulting from imbalance in insulin secretion, insulin in action or both. Like insulin the other hormones such as growth hormone (somatotropin), glucagon control blood sugar levels, epinephrine best known as adrenaline, glucocorticoids and thyroxin. When we take food the body breaks down all the sugars and starches into glucose, which is the basic fuel for the cells in the body. The blood always has some glucose in it because body needs glucose for energy. Insulin takes the glucose from the blood and act on cells through receptors. In pancreas the beta cells secrete insulin and amylin, alpha cells secrete glucagon, delta cells secrete somatostatin, gamma cells secrete pancreatic polypeptide When there is no supply of insulin or if it is insufficient or the quality is poor or abnormal or sometimes body cells cannot respond to insulin very well, then the glucose cannot enter into the cells. And glucose builds up in the blood instead of going to the cells. Consequently, there is not enough energy to run a body and leads to diabetes mellitus.

The two most common forms of diabetes are due to either a diminished production of insulin also known as type-1 diabetes or diminished response by the body to insulin also known as type-2 diabetes. Both lead to hyperglycaemia, which largely causes the acute signs of diabetes, excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy and changes in energy metabolism. In 1980, expert committee of WHO proposed classification of diabetes mellitus and named it as IDDM (insulin dependent diabetes mellitus) or type-1 and NIDDM (non-insulin dependent diabetes mellitus) or type-2. But in 1985 type-1 and type-2 names are omitted and only IDDM and NIDDM were known as the types of diabetes mellitus [4].

Another type of diabetes is Gestational diabetes, which occurred in pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type-2 diabetes. Some other forms of diabetes are congenital diabetes, which is genetic defects of insulin secretion, cystic fibrosis related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenetic diabetes. All forms of diabetes have been treatable since insulin is available since 1921 and type-2

diabetes may be controlled with medications. Both type-1 and type-2 are chronic conditions those cannot be cured permanently.

Diabetes is associated with a large number of abnormalities in insulin metabolism, ranging from an absolute deficiency to a combination of deficiency and resistance, causing an inability to dispose glucose from the blood stream. As referred by Pacini and Bergman the three main factors those play an important role for glucose disposal are insulin sensitivity, glucose effectiveness and pancreatic responsiveness [15]. Failure in any of these may lead to impaired glucose tolerance, or if severe, diabetes.

The literature dealing with modelling for diabetes is mainly concerned with glucose and insulin dynamics. There are various models based on glucose insulin interaction. These models are valid under certain conditions and assumptions. These models may be useful for further mathematical treatment.

In 1939, Himsworth and Ker [5] introduced the first approach to measure the insulin sensitivity in vivo. Many of the researchers have developed different mathematical models to understand the behaviour of different biological and ecological system. The study of glucose insulin interaction started during early sixties. In mid of 1960 DrsRosevear and Molnar of the Mayo clinic and Ackerman and Gatewood [6] of the University of Minnesota discovered a fairly reliable criterion for interpreting the results of a GTT. The discovery was based on a simple model they developed for the blood glucose regulatory system (BRGS) where g is taken to be excess glucose concentration and h is excess insulin concentration at time t, which can be represented as follows

$$\dot{g} = -ag - bh \quad (1.1)$$

$$\dot{h} = cg - dh \quad (1.2)$$

with a, b, c and d as constants.

Ackerman et al [6] proposed a model which could accurately describe the blood glucose regulatory system during a glucose tolerance test and in which one or two parameters could yield the criteria for distinguishing normal individual from diabetes mellitus and pre-diabetes.

In 1961 Bolie started a mathematical model using ordinary differential equation to estimate the glucose disappearance and insulin glucose dynamics in general [7]. The model was

$$\dot{G} = -a_1 G - a_2 I + p \quad (1.3)$$

$$\dot{I} = -a_3 - a_4 I \quad (1.4)$$

Where G and I represent the glucose concentration and insulin and p, a p, a_1, a_2, a_3, a_4 are parameters.

The real start of mathematical modelling of 'glucose insulin dynamics' was started with the so called 'minimal model' proposed by the team of Bergman and Cobelli in the early eighties [Cobelli et al] . Minimal model is the most widely used model to analyse the intravenous glucose tolerance test (IVGTT) [8].Professor Bergman was awarded the Banting medal by American Diabetes Association in 2006 for his achievements in minimal model.

Several mathematical models have been derived as described in a survey by Makroglou et al. [9] and in a review by Boutayeb and Chetouni [10] for the dynamics of glucose-insulin including intravenous glucose tolerance test (IVGTT), oral glucose tolerance test (OGTT), and frequently sampled intravenous glucose tolerance test (FSIVGTT). Most of all the existing models were based on two variables only: glucose and insulin.

As stated by Bergman in 2002[11], more than 500 studies done related to the minimal model. For example, Derouich and Boutayeb modified the minimalmodel and proposed a model introducing a new parameter of physical exercise [12]. Later some drawbacks were found in the minimal model and taking into account these drawbacks De Gaetano and Arino [13, 14] proposed a delay differential model called Dynamical model.

II. MODEL DESCRIPTION

Glucose regulatory system in the body is very complex in nature. A simple mathematical model is described by Himsworth and Ker in 1939 [5] and Bolie [7]. Here, these simple models are modified to incorporate an additional variable to describe glucose-insulin system [equations (1.1)-(1.4)] under the influence of external glucose intake in the form of source of food.

Let G(t) and I(t) denote the glucose and insulin concentration in the body at time t. Let E(t)is the externally ingested glucose at time t which is coming from the source of food to the body. Thus the model for Glucose-insulin-ingested glucose is a three variable model, with the following assumptions.

(a) Degradation of glucose from body is both insulin independent and insulin dependent with different rate.
(b) Degradation of insulin from the body is glucose independent.
(c) Secretion of insulin due to glucose stimulation.
(d) The externally ingested glucose is assumed to follow logistic growth model. There is increase of glucose level due this externally ingested glucose.

(e) There is no effect of externally ingested glucose on the level of insulin
(f) A constant amount of glucose is always present in the body

2.1 MODEL EQUATIONS

With these assumptions, the mathematical model for Glucose-Insulin-Ingested glucose regulatory system can be expressed by the following sets of differential equations

$$\dot{G}(t) = -aG - bI + \alpha E + \delta \quad (2.1)$$

$$\dot{I}(t) = cG - dI \quad (2.2)$$

$$\dot{E}(t) = \beta E(1 - \gamma E) \quad (2.3)$$

Where,

δ : Constant amount of glucose 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 source of glucose
$\frac{1}{\gamma}$ *:* Carrying capacity of ingested source of glucose

III. STABILITY ANALYSIS OF THE MODEL

3.1 EQUILLIBRIUM POINTS

The equilibrium points corresponding to the equations (2.1), (2.2), (2.3) can be determined by considering $\dot{G}(t) = 0, \dot{I}(t) = 0 \; and \; \dot{E}(t) = 0$

Which implies, either $E = 0$ or $E = \frac{1}{\gamma}$

For $E = 0$, equations (2.1) and (2.2) give the following results,

$$G = \frac{d\delta}{bc + ad}, I = \frac{c\delta}{bc + ad}$$

Hence the ingested glucose free equilibrium point for the system mentioned in (2.1), (2.2) and (2.3) is

$$(\frac{d\delta}{bc + ad}, \frac{c\delta}{bc + ad}, 0)$$

For $E = \frac{1}{\gamma}$ equations (2.1) and (2.2) give the following results,

$$G = \frac{c\alpha + c\gamma\delta}{\gamma(bc + ad)}, \qquad I = \frac{d\alpha + d\gamma\delta}{\gamma(bc + ad)}$$

Hence the ingested glucose existing equilibrium point for the system mentioned in (2.1), (2.2), and (2.3) is

$$(\frac{c\alpha + c\gamma\delta}{\gamma(bc + ad)}, \frac{d\alpha + d\gamma\delta}{\gamma(bc + ad)}, \frac{1}{\gamma})$$

3.2 STABILITY ANALYSIS FOR INGESTED GLUCOSE FREE CASE

Linearising the model around $(\frac{d\delta}{bc+ad}, \frac{c\delta}{bc+ad}, 0)$ we get the following,

$$\begin{pmatrix} \dot{G} \\ \dot{I} \\ \dot{E} \end{pmatrix} = \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & \beta \end{pmatrix} \begin{pmatrix} G - \frac{d\delta}{bc + ad} \\ I - \frac{c\delta}{bc + ad} \\ E \end{pmatrix} \quad (3.1)$$

Which leads to the eigen values

$$e_1 = \beta$$

$$e_{2,3} = \frac{-(a+d) \pm \sqrt{(a-d)^2 - 4bc}}{2}$$

The model will be stable around the equilibrium point $(\frac{d\delta}{bc+ad}, \frac{c\delta}{bc+ad}, 0)$ if

$$e_i < 0, fori = 1,2,3$$

Clearly from the eigen values we have seen that $e_1 \prec 0$, hence the model is not stable around $\left(\frac{d\delta}{bc+ad}, \frac{c\delta}{bc+ad}, 0\right)$.

3.3 STABILITY ANALYSIS FOR INJESTED GLUCOSE EXISTING CASE

Linearising the model around $(\frac{c\alpha+c\gamma\delta}{\gamma(bc+ad)}, \frac{d\alpha+d\gamma\delta}{\gamma(bc+ad)}, \frac{1}{\gamma})$ we get the following,

$$\begin{pmatrix} \dot{G} \\ \dot{I} \\ \dot{E} \end{pmatrix} = \begin{pmatrix} -a & -b & \alpha \\ c & -d & 0 \\ 0 & 0 & -\beta \end{pmatrix} \begin{pmatrix} G - \frac{c\alpha + c\gamma\delta}{\gamma(bc+ad)} \\ I - \frac{d\alpha + d\gamma\delta}{\gamma(bc+ad)} \\ E - \frac{1}{\gamma} \end{pmatrix} \quad (3.2)$$

which leads to the eigen values

$$e_1 = -\beta \quad (3.3)$$

$$e_{2,3} = \frac{-(a+d) \pm \sqrt{(a-d)^2 - 4bc}}{2} \quad (3.4)$$

The model will be stable around the equilibrium point $(\frac{c\alpha+c\gamma\delta}{\gamma(bc+ad)}, \frac{d\alpha+d\gamma\delta}{\gamma(bc+ad)}, \frac{1}{\gamma})$

$$\forall\ e_i < 0, fori = 1,2,3 \quad (3.5)$$

4. ANALYSIS AND CONCLUSIONS

The initial number of glucose concentration and insulin concentration has been taken as 0.1 and 0.8. As the stability condition is depending on system parameters, the model is simulated under those stability conditions. The stability around the point ingested glucose free is not possible as one of the eigen value is always positive. The ingested glucose free equilibria gives instability is validated in Fig.1.1.

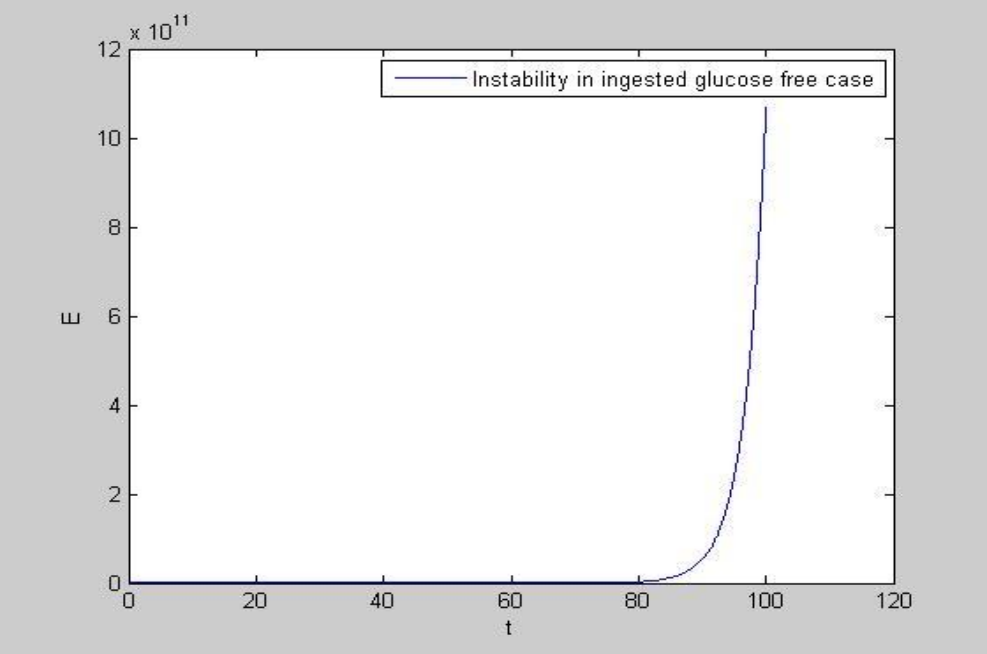

Fig.1.1. Unstable externally ingested glucose in ingested glucose free equilibrium.

With co-existing equilibria given by (3.3) and (3.4) is analysed with same parameters is analysed numerically. Fig.1.2 and Fig.1.3 represents the stability of all three variables around the coexisting equilibria. It has been also found that using different parameters and initial values for coexisting equilibria shows stability in the G-I-E model.

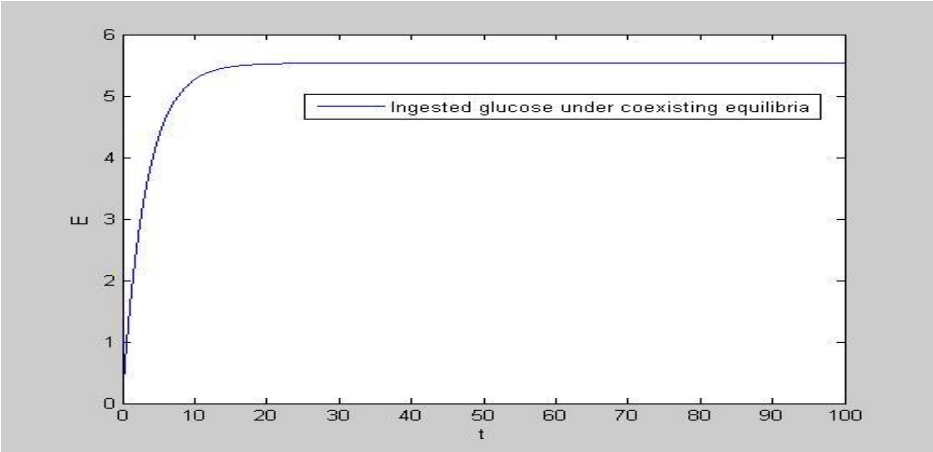

Fig.1.2. Stability of externally ingested glucose under co-existing equilibria

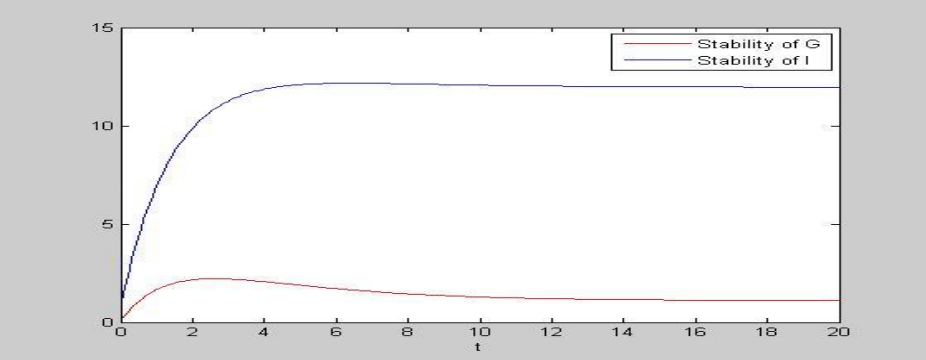

Fig.1.3.Stable glucose and insulin concentration under co-existing equilibria

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