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Effect of Glucose intake on the Stability of a Dynamical Model used for the study of diabetes mellitus.

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ABSTRACT

Recently, the minimal model mostly used for the physiological study of diabetes mellitus was modified because it has some drawbacks. So a new dynamic model was proposed by De Gaetano and Arino [6] for the study of intravenous glucose tolerance test. In 2001, Jiaxu and Kuang [12] modified the way time delay was incorporated in [6] model. Some other people has also try to improve on the models to address some of the drawbacks identifies in some of the dynamic model. The objective of this paper is to present a dynamic model that will take into account the glucose intake which has not be considered in the previous models in literature. We show that the model has a unique solution for all t>0 and that the equilibrium point is globally asymptotically stable. We also perform some numerical simulation based on the data from the literature to consider the effect of glucose intake on a diabetic's subject.

Keywords: Glucose, insulin, Dynamical models, Diabetes Mellitus, Equilibrium point, Hyperglycemia.

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, hearts, and blood vessels. Several pathogenic processes are involved in the development of diabetes these range from autoimmune destruction of the β-cells (i.e. beta cell) of the pancreas with consequent insulin deficiency to abnormalities that result in resistance in insulin action. The basis of the abnormalities in carbohydrates, fats, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue response to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently co-exist in the same patients and it is often unclear which abnormality, if either alone is the primary cause of the hyperglycemia. [3,10,11].

Diabetes is a condition in which the body cannot properly use the energy from the food that has been eaten. Foods when eaten get broken down into a form of sugar called glucose; glucose is the body's main fuel. This sugar (glucose) enters the blood and goes to the cells where it is used as energy [15]. How does persistent high blood sugar damage the body? Excess glucose spurs an elevated production of "glycated proteins" which are proteins that have been damaged by binding with sugar. Such glycated proteins react with oxygen to form superoxide free radicals that can damage collagen, the structural matrix of our body. They also trigger an escalating accumulation of " advanced glycation end-products", one of the hallmarks of aging. Even worse, glycated proteins can also transform themselves into hydrogen peroxide and hydroxyl radicals, which are more potent free radicals than superoxides and far more destructive to the proteins of our tissues, organs, immune system, and muscles. Studies have shown that elevated blood sugar levels are a major cause of kidney failure, cardiovascular disease, and arteriosclerosis. Perhaps this is one of the reasons why diabetics have twice the mortality risk as non-diabetics. Moreover, diabetics with poorly controlled blood sugar have over four times the risk of dying. How do you balance blood sugar blood sugar levels to maintain a constant supply of energy to the cell without glucose overkill? This can be achieved by eating a low-glycemic and high-fiber diet. This results in a steady stream of glucose into the blood. In fact, eating the right foods can have a bigger impact on blood sugar control and lifespan than either insulin or hypoglycemic drugs, such as sulfonylureas. The glycemic index measures the impact a food has on blood sugar levels two or three hours after ingestion. The lower the glycemic index of a food, the lower the rise in blood sugar levels a food causes [19].

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic, hyperosmolar syndrome. Diabetes mellitus has been classified into four (4) namely:

1) **Type 1 Diabetes Mellitus:** Type 1 diabetes mellitus (formerly called IDDM or juvenile diabetes) is characterized by beta cell destruction caused by an autoimmune process usually leading to absolute insulin deficiency. The onset is usually acute developing over a period of a few days to weeks, over 95% of person with type 1 diabetes mellitus develop the disease before the age of 25.In this form of diabetes the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and / or ketoacidosis in the presence of infection or other stress. Still others particularly adults may retain residual beta (β)-cell functions sufficient to prevent ketoacidosis for many years; such individual eventually becomes dependent on insulin for survival and are at risk for ketoacidosis. At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma c-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8^{th} and 9^{th} decades of life.

2) **Type 2 Diabetes Mellitus:** Type 2 diabetes mellitus (formerly called NIDDM or adult onset) is characterized by insulin resistance in peripheral tissue and an insulin secretary defect of the beta cell. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. Defective beta cells become exhausted further fueling the cycle of glucose intolerance and hyperglycemia. The etiology of type 2 diabetes mellitus is multifactor and probably genetically based but it also has strong behavioral components.

Patients with type 2 diabetes encompasses individual who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. At least initially and often throughout their lifetime these individuals do not need insulin treatment to survive.

Most patients with this form of diabetes are obese. Obesity itself causes some degree of insulin resistance. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stage is often not severe enough for the patients to notice any of the classic symptoms of diabetes nevertheless such patients are at increased risk of developing micro vascular complications. Insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and / or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing this form of diabetes increases with age, obesity and lack of physical activity.

3) **Other specific types:** This includes types of diabetes mellitus of various known etiologies for instance persons with genetic defects of beta cell functions (this type of diabetes was formerly called MODY or maturity onset diabetes in youth) or with minimal defects of insulin action. Abnormalities at six genetic loci on different chromosomes have been identified to date the most common form which is associated with mutations in chromosome 12 in a hepatic

transcription factor referred to as hepatocyte nuclear factor (HNF) -1 alpha (α).The second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule.Glucokinase coverts glucose to glucose -6- phosphate the metabolism of which in turn stimulate insulin secretion by the beta (β)- cell. This glucokinase serves as the "glucose sensor" for the Beta-cell, because of defects in the glucokinase gene, increased plasma levels of glucose is necessary to elicit normal levels of insulin secretion. Point mutations in mitochondrial DNA have been found to be associated with diabetes mellitus and deafness. Genetic abnormalities that result in the inability to convert pro-insulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. The resultant glucose intolerance is mild.

Also there are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Many genetics syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down's syndrome, klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin – deficient diabetes and the absence of B-cell at autopsy. Additional manifestation includes diabetes insipidus, hypogonadism optic atrophy and neural deafness.

(4) Gestational diabetes: Gestational diabetes mellitus is an operational classification (rather than a pathophysiology condition) identifying women who develop diabetes mellitus during gestation [1,3,7,8,9,11,16].

In section 1 of this paper, we give a comprehensive physiological definitions and classification of diabetes mellitus. In section 2, we did some literature review of mathematical models for the study of diabetes mellitus. Section 3 contains our proposed dynamic model, derivation of the equilibrium point of the dynamic model, existence and uniqueness of solution and global stability results. In section 4 we discussed local stability of the equilibrium points by method of linearization and in section 5 we did local stability analysis of the equilibrium point through hopf bifurcation theory. Section 6 and 7 is the results of our numerical simulation and discussion of results respectively.

2. Literature Review.

We considered the models of Boutayeb [5] that used the modified version of the glucose-insulin dynamics minimal model proposed by Bergon and Cobelli in Early eighties to consider the effect of physical exercise on the dynamics of glucose and insulin.

The model is given as:

$$\frac{dG(t)}{dt} = -(1+q_2)X(t)G(t) + (p_1+q_1)(G_b - G(t)) \qquad (2.1)$$

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$$\frac{dI(t)}{dt} = -p_2 X(t) + (p_3 + q_3)(I(t) - I_b)$$

(i) $(I(t) - I_b)$ Represents the difference between the plasma insulin concentration and the basal insulin.
(ii) X(t) is the interstitial insulin.
(iii) $(G_b - G(t))$ Is the difference between the basal glucose concentration and the plasma glucose.
q1: the effect of the physical exercise in accelerating the utilization of glucose by muscles and the liver.
q2: the effect of the physical exercise in increasing the muscular and liver sensibility to the action of the insulin.
q3: the effect of the physical exercise in increasing the utilization of insulin.
p_1, p_2 *and* p_3 are parameters.

In 2004, Mukhopadhyay et.al [13] used the following dynamic model of the glucose-insulin system to studied the intra-venous glucose tolerance test. The model is given as;

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7 \qquad (2.2)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 \int_0^{\infty} w(s) G(t-s) ds$$

$$G(t) \equiv G_b \ \textit{for every} \ t \in [-\infty, 0), G(0) = G_b + b_0 \ \ I(0) = I_b + b_3 b_0$$

This model extends the scope of the previously model by introducing a generic weight function w in the delay integral kernel for the pancreatic response to glucose, in place of the previously used specific rectangular weighting function (constant over a finite interval, zero otherwise), [13].

In 2001, Jiaxu and Kuang proposed the following specific models of glucose-insulin interaction.

$$\frac{dG(t)}{dt} = G'(t) = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7 \qquad (2.3)$$

$$\frac{dI(t)}{dt} = I'(t) = -b_2 I(t) + b_6 G(t - b_5) \qquad \text{(For Discrete time delay)}$$

$$\frac{dG(t)}{dt} = G'(t) = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7 \qquad (2.4)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{-b_5}^{0} G(t + \theta) d\theta \qquad \text{(For Distributed time delay)}$$

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The initial condition is

$G(0) = G_b + b_0, I(0) = I_b + b_3 b_0, and G(t) \equiv G_b, \ for\ t \in [-b_5, 0)$,
Where $G_t(\theta) = G(t+\theta), t > 0, \theta \in [-b_5, 0]$.
The models has a unique equilibrium point (G^*, I^*).
The pioneer in this field was Bolie, who proposed in 1961 the simple model

$$\frac{dG}{dt} = -a_1 G - a_2 I + p \qquad (2.5)$$
$$\frac{dI}{dt} = -a_3 G - a_4 I$$

The term $b_4 I(t) G(t)$ in model (2.2) assumes mass law action applies here, but model (2.3) and (2.4) assume instead that that insulin- dependent net glucose tissue uptake takes the more general and realistic Michaelis-menten form $\frac{G(t)}{(\alpha G(t)+1)}$ which has a maximum capacity $\frac{b_4}{\alpha}$. The parameter α in the response function $\frac{G(t)}{(\alpha G(t)+1)}$ is a non negative. $\frac{1}{\alpha}$ is the half saturation constant. The reason for this is simply due to the limit of time and the capacity of insulin's ability of digesting glucose.

3.1. The Model Preliminaries.

In this paper, our aim is to present a model for the study of diabetes mellitus which takes into account further glucose intake. So we extend the Mukhopadhyay et.al. and Jiaxu et.al models as follows;

$$\frac{dG(t)}{dt} = -(b_1 + q_1)G(t) - \frac{b_4 I(t) G(t)}{(\alpha G(t)+1)} + b_7 G^{n}{}_{in}, \qquad G(0) = G_0,\ G^0 = 1 \qquad (3.1)$$
$$\frac{dI(t)}{dt} = -b_2 I(t) + (b_6 + q_3)\int_0^{\infty} w(s) G(t-s)\,ds, \qquad I(0) = I_0$$
$$G(t) \equiv G_b \ for\ every\ t \in [-\infty, 0), G(0) = G_b + b_0 \ \ I(0) = I_b + b_3 b_0$$

Where n could take any value in the non-negative real axis. We note that n=0 coincides the model in literature (see [12,13]). This model assumes further food intake which manifests in further glucose release $G^n\ (n > 0)$.

G [mg/dl] is the glucose plasma concentration;
Gb[mg/dl] is the basal (pre-injection) plasma glucose concentration;
I [pM] is the insulin plasma concentration;
Ib[pM] is the basal (pre-injection) insulin plasma concentration;

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$b_0[mg/dl]$ is the theoretical increase in plasma concentration over basal glucose concentration at time zero after instantaneous administration of glucose bolus;
$b_2[\min^{-1}]$ is the apparent first-order disappearance rate constant for insulin;
$b_4[\min^{-1} pM^{-1}]$ is the constant amount of insulin-dependent glucose disappearance rate constant per pm of plasma insulin concentration;
$b_6[\min^{-1} pM/(mg/dl)]$ is the constant amount of second-phase insulin release rate per (mg/dl) of average plasma glucose concentration per unit time;
$b_7[(mg/dl)^{1-n} \min^{-1}]$ is the constant increase in plasma glucose concentration due to constant base line liver glucose release; Here we have assumed b_7 is a constant as in [12,13]
q_1 is the effect of the physical exercise in accelerating the utilization of glucose by muscles and the liver [5].
q_3 is the effect of the physical exercise in increasing the utilization of insulin [5].

3.2. Equilibrium points of the dynamic model

$$\frac{dG(t)}{dt} = -(b_1+q_1)G(t) - \frac{b_4 I(t)G(t)}{(\alpha G(t)+1)} + b_7 G^{n}_{in}, \qquad G(0)=G_0,\ G^0=1$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + (b_6+q_3)\int_0^{\infty} w(s)G(t-s)ds, \qquad I(0)=I_0$$

$G(t) \equiv G_b$ *for every* $t \in [-\infty, 0), G(0) = G_b + b_0$ $I(0) = I_b + b_3 b_0$

Set $\frac{dG(t)}{dt} = 0$ *and* $\frac{dI(t)}{dt} = 0$

We have $0 = -(b_1+q_1)G(\alpha G+1) - b_4 IG + \alpha G b_7 G^{n}_{in} + b_7 G^{n}_{in}$,

$$b_7 G^{n}_{in}, \ = (b_1+q_1)G(\alpha G+1) + b_4 IG - \alpha G b_7 G^{n}_{in} \qquad (3.2)$$

Also,

$$0 = -b_2 I + (b_6+q_3)G\int_0^{\infty} w(s)ds,$$

since $G(t) = G_b$ *forevery* $t \in [-\infty, 0)$

Now, by the mean value theorem for definite integral

$$\int_0^{\alpha} w(s)ds = 1$$

So the second equation of (3.1) becomes

$$0 = -b_2 I + (b_6+q_3)G$$

$$b_2 I = (b_6+q_3)G$$

$$\therefore I = \frac{(b_6+q_3)G}{b_2} \qquad (3.3)$$

Putting (3.3) into (3.2), we have

$$(b_1+q_1)G(\alpha G+1)+\frac{b_4(b_6+q_3)G^2}{b_2}-\alpha G b_7 G^{n}{}_{in}-b_7 G^{n}{}_{in},=0 \qquad (3.4)$$

Hence, the equilibrium points is given as

$$G_+^{*}=\frac{\left(-((b_1+q_1)-\alpha b_7 G^{n}{}_{in})+\sqrt{((b_1+q_1)-\alpha b_7 G^{n}{}_{in})^2+4b_7 G^{n}{}_{in}(\alpha(b_1+q_1)+\frac{b_4(b_6+q_3)}{b_2}}\right)}{2\left(\alpha(b_1+q_1)+\frac{b_4(b_6+q_3)}{b_2}\right)}$$ Whi

$$I^{*}=\frac{(b_6+q_3)}{b_2}G^{*}$$

ch we may rewrite as

$$G^{*}=\frac{2b_7 G^{n}{}_{in}}{\left(((b_1+q_1)-\alpha b_7 G^{n}{}_{in})+\sqrt{((b_1+q_1)-\alpha b_7 G^{n}{}_{in})^2+4b_7 G^{n}{}_{in}(\alpha(b_1+q_1)+\frac{b_4(b_6+q_3)}{b_2}}\right)}$$ For

$$I^{*}=\frac{(b_6+q_3)}{b_2}G^{*}$$

convenience of analysis we define

$$b_1+q_1=h, b_2=z, b_6+q_3=q\frac{b_4 IG}{\alpha G+1}=g(G,I), and \int_0^{\infty} w(s)ds=L(G_t).$$

Functions g,h,q,z satisfy the following general conditions.

(i) $h(0)=0, h(\infty)=\infty, h'(x)>0$

(ii) $g(0,0)=0, g_x(x,y)>0, g_y(x,y)>0,$
$g(x,0)=0, g(0,y)=0, g(\infty,y)<\infty, g(x,\infty)=\infty \; when \; x\neq 0$

(iii) $z(0)=0, z(\infty)=\infty, z'(x)>0$

(iv) $q(x)=0$, if and only if $x=0; q(L(G_t+\varphi_t))>q(L(G_t)) \; for \; \varphi_t\in C[-\infty,0]$ with $\varphi_t(\theta)>0, \theta\in[-\infty,0]$.

3.3. Existence and Uniqueness of Solution

We need the following proposition and theorem to study the existence and uniqueness of solution of the model.

Proposition 3.1: All solution of model (3.1) exists for all t > 0, and are positive and bounded.

Theorem (William's) 3.1: Considered the initial value system

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$$x_1' = f_1(t, x_1, x_2, \ldots, x_n), \qquad x_1(t_0) = x_{10},$$
$$x_2' = f_2(t, x_1, x_2, \ldots x_n), \qquad x_2(t_0) = x_{20},$$
$$\vdots$$
$$x_n' = f_n(t, x_1, x_2, \ldots, x_n), \qquad x_n(t_0) = x_{n0}$$
$$\Rightarrow x' = f(t, x), \qquad x_n(t_0) = x_{n0} \qquad (3.5)$$

Let D denotes the region [in (n+1)-dimensional space, one dimension for t and n dimension for the vector x], $|t - t_0| \le a, \quad \|x - x_0\| \le b.$

and suppose the partial derivatives

$\frac{\partial f_i}{\partial f_j}$, $i, j = 1,2,\ldots,n.$ are continuous in D. Then there is a constant $\delta > 0$ such that there exists a unique continuous vector solution $x(t)$ of the system (3.5) in the interval $|t - t_0| \le \delta.$ [18].

Theorem 3.2: There exists a unique solution of (3.1) for
$|t - t_0| \le a, \quad \|G - G_0\| \le b \, and \, \|I - I_0\| \le b.$

Proof: By proposition (3.1) we show that there exist a solution for all $t > 0$.

Let $(G(t), I(t))$ be a solution of (2.1). If $G(t_0) = 0$ for some t_0>0, then $G'(t_0) \le 0.$ However, at t_0 due to the assumption that $h(0) = g(0, y) = 0,$ we have

$G'(t_0) = -h(G(t_0)) - g(G(t_0), I(t_0)) + b_7 G^n{}_{in} = b_7 G^n{}_{in} > 0$.This contraction shows that $G(t) > 0$ for all t in the interval of existence.

If $I(t_0) = 0$, for some $t_0 > 0$, then $I'(t_0) \le 0$ and

$0 \ge I'(t_0) = -z(I(t_0)) + q(L(G_{t_0})) = q(L(G_{t_0}))$

Since $G_{t_0}(\theta) > 0, \, for \, \theta \in [-\infty, 0], q(L(G_{t_0})) > 0$ by (iv) and thus $I(t) > 0$ for all t in the interval of existence.

As for the boundedness of $G(t),$ by the first equation of (3.1),

$G'(t) = -h(G(t)) - g(G(t), I(t)) + b_7 G^n{}_{in} \le -h(G(t)) + b_7 G^n{}_{in}$

Thus $G(t),$ is bounded by $M_G = \max\{G_b + b_0, h^{-}'(b_7 G^n{}_{in})\}$.

And hence I(t) is bounded by $M_I = \max\{I_b + b_0 b_3, z^{-}'(q(M_G))\}$ due to $I'(t) = -z(I(t)) + q(G_t) \le -z(I(t)) + q(M_G)$.

The boundedness statement implies that solutions exist for all t >0.

We shall now use theorem (3.1) above to show that the solution is unique.

Let $$G'(t) = f_1(G, I) = -(b_1 + q_1)G(t) - \frac{b_4 I(t) G(t)}{(\alpha G(t) + 1)} + b_7 G^n{}_{in} \qquad (3.6)$$

$$I'(t) = f_2(G, I) = -b_2 I + (b_6 + q3)\int_0^\infty w(s) G(t - s) ds$$

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Considering the partial derivatives of (3.6), we have

$$\frac{\partial f_1}{\partial G} = -(b_1 + q_1) - \frac{b_4 I}{(\alpha G + 1)^2}$$

$$\frac{\partial f_1}{\partial I} = -\frac{b_4 G}{(\alpha G + 1)}$$

$$\frac{\partial f_2}{\partial G} = (b_6 + q_3)$$

$$\frac{\partial f_2}{\partial I} = -b_2$$

Now

$$\left|\frac{\partial f_1}{\partial G}\right| = \left|-(b_1 + q_1) - \frac{b_4 I}{(\alpha G + 1)^2}\right|$$

$$\left|\frac{\partial f_1}{\partial I}\right| = \left|-\frac{b_4 G}{(\alpha G + 1)}\right|$$

$$\left|\frac{\partial f_2}{\partial G}\right| = \left|(b_6 + q_3)\right|$$

$$\left|\frac{\partial f_2}{\partial I}\right| = \left|-b_2\right|$$

This implies that $\left|\frac{\partial f_i}{\partial x_j}\right|$, $i = 1,2,\ x_j = G, I$ are bounded. Hence there exists a unique solution of (3.1). This completes the proof.

Also, we shall state the fluctuation lemma without proof. This lemma shall be use to establish the fact that model (3.1) is always uniformly persistent, which implies that both components of solutions of the model are eventually bounded by positive constants from both above and below. Such bound are independent of the initial conditions.

Fluctuation lemma: Let $f : R \to R$ be a differentiable function. If

$l = \liminf_{t\to\infty} f(t) < \limsup f(t) = L$, then there are sequence $\{t_k\} \uparrow \infty \{s_k\} \uparrow \infty$ such that for all k,

$$f'(t_k) = f'(s_k) = 0 \ \lim_{k\to\infty} f(s_k) = l \ and \lim_{k\to\infty} f(t_k) = L$$

Lemma (3.1): Consider model (3.1), If $I_\infty < I^\infty$,

Then, $-z^-(q(G_\infty)) \le I_\infty \le I^\infty \le -z^-(q(G^\infty))$

If $G_\infty < G^\infty$, then

$-h(G_\infty) - g(G_\infty, I^\infty) + b_7 G^n{}_{in} \le 0 \, and - h(G^\infty) - g(G^\infty, I_\infty) + b_7 G^n{}_{in} \ge 0$.

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Proof: Since $I_\infty < I^\infty$, then by the fluctuation lemma A above, there exist $\{t_k\} \uparrow \infty \{s_k\} \uparrow \infty$ such that $I'(t_k) = I'(s_k) = 0 \lim_{k\to\infty} I(s_k) = I_\infty \; and \lim_{k\to\infty} I(t_k) = I^\infty$. Since $(G(t), I(t))$ is a solution of (3.1), then we have

$0 = I'(t_k) = -z(I(t_k)) + q(L(G_{t_k}))$ for all k.

For any $\delta > 0$, there exist $k_0 > 0$ such that $G^\infty + \delta > G_{t_k}(\theta), \theta \in [-\infty, 0]$ for all $k > k_0$.

Hence condition (IV) implies that $q(L(G_{t_k})) \le q(G^\infty + \delta) \; for \; k > k_0$. Therefore,

$0 = -z(I(t_k)) + q(L(G_{t_k})) \le -z(I(t_k)) + q(G^\infty + \delta)$.

By letting $k \to \infty, \delta \to 0$, we have

$z(I^\infty) \le q(G^\infty)$. (1*)

Similarly,

$0 = I'(s_k) = -z(I(s_k)) + q(L(G_{s_k}))$ for all k.

For any $\delta > 0$, there exist $k_0 > 0$ such that $G_\infty + \delta < G_{s_k}(\theta), \theta \in [-\infty, 0]$ for all $k > k_0$.

Hence,

$q(L(G_{s_k})) \ge q(G_\infty + \delta) \; for \; k > k_0$

Therefore, $0 = -z(I(s_k)) + q(L(G_{s_k})) \ge -z(I(s_k)) + q(G_\infty + \delta)$.

By letting $k \to \infty, \delta \to 0$, we have $z(I_\infty) \ge q(G_\infty)$. (1**)

Combining (1*) and (1**), we have

$-z^-(q(G_\infty)) \le I_\infty \le I^\infty \le -z^-(q(G^\infty))$.

Also if $G_\infty < G^\infty$, by fluctuation lemma, there exist $\{t'_k\} \uparrow \infty \{s'_k\} \uparrow \infty$ such that $G'(t'_k) = G'(s'_k) = 0 \lim_{k\to\infty} G(s'_k) = G_\infty \; and \lim_{k\to\infty} I(t'_k) = G^\infty$.

Thus we have

$0 = G'(t'_k) = -h(G(t'_k)) - g(G(t'_k), I(t'_k)) + b_7 G^n{}_{in}$

and $0 = G'(s'_k) = -h(G(s'_k)) - g(G(s'_k), I(s'_k)) + b_7 G^n{}_{in}$

for all k. Assuming $\lim_{k\to\infty} I(s'_k) \; and \lim_{k\to\infty} I(t'_k)$ exist, we have

$0 = \lim_{k\to\infty}(-h(G(t'_k)) - g(G(t'_k), I(t'_k))) + b_7 G^n{}_{in}$

$= -h(G^\infty) - g(G^\infty, \lim_{k\to\infty} I(t'_k)) + b_7 G^n{}_{in} \le -f(G^\infty) - g(G^\infty, I_\infty) + b_7 G^n{}_{in}$.

$0 = \lim_{k\to\infty}(-h(G(s'_k)) - g(G(s'_k), I(s'_k))) + b_7 G^n{}_{in}$

$= -h(G_\infty) - g(G_\infty, \lim_{k\to\infty} I(s'_k)) + b_7 G^n{}_{in} \ge -f(G_\infty) - g(G_\infty, I^\infty) + b_7 G^n{}_{in}$.

Theorem 3.3: For model (3.1), If $g(x, z^-(q(y))) - g(y, z^-(q(x))) \ge 0$ for all $x \ge y > 0$, then the unique equilibrium point (G^*, I^*) of (3.1.) is globally asymptotically stable.

Proof: If $I_\infty < I^\infty$, by lemma (3.1),

we have shown that $-z^-(q(G_\infty)) \le I_\infty \le I^\infty \le -z^-(q(G^\infty))$

Thus $G_\infty < G^\infty$ and

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$$-h(G_\infty)-g(G_\infty,z^-(q(G^\infty)))+b_7G^n{}_{in}\le -h(G_\infty)-g(G_\infty,I^\infty)+b_7G^n{}_{in}\le 0, \qquad (2^*)$$

$$-h(G^\infty)-g(G^\infty,z^-(q(G_\infty)))+b_7G^n{}_{in}\ge -h(G^\infty)-g(G^\infty,I_\infty)+b_7G^n{}_{in}\ge 0 \qquad (2^{**})$$

(2*) –(2**), we have

$$h(G^\infty)-h(G_\infty)+(g(G^\infty,z^-(q(G_\infty)))-g(G_\infty,z^-(q(G^\infty)))\le 0$$

If $g(x,z^-(q(y)))-g(y,z^-(q(x)))\ge 0$ then,

$$g(G^\infty,z^-(q(G_\infty)))-g(G_\infty,z^-(q(G^\infty)))\ge 0,$$

Therefore, $h(G^\infty)-h(G_\infty)\le 0$.

Again (2**)-(2*), we have

$$h(G_\infty)-h(G^\infty)+(g(G_\infty,z^-(q(G^\infty)))-g(G^\infty,z^-(q(G_\infty)))\ge 0$$

Therefore, $h(G_\infty)-h(G^\infty)\ge 0$.

Which indicates that $G_\infty=G^\infty$ and thus $I_\infty=I^\infty$. Since (G^*,I^*) is the only equilibrium point of (3.1), we have $\lim_{k\to\infty} G(t)=G^*$ *and* $\lim_{k\to\infty} I(t)=I^*$.

4. Local stability of the equilibrium points of the dynamic model.

Theorem 4.1: The equilibrium point (G^*,I^*) is locally asymptotically stable.

Proof:

We translate the equilibrium to the origin using a state transformation $X_1=G-G^*$ *and* $X_2=I-I^*$ to have

$$X_1=G-\frac{\left(-(b_1+q_1)-\alpha b_7G^n{}_{in})+\sqrt{((b_1+q_1)-\alpha b_7G^n{}_{in})^2+4b_7G^n{}_{in}(\alpha(b_1+q_1)+\frac{b_4(b_6+q_3)}{b_2}}\right)}{2\left(\alpha(b_1+q_1)+\frac{b_4(b_6+q_3)}{b_2}\right)}$$

$$X_2=I-\frac{\left(-(b_1+q_1)-\alpha b_7G^n{}_{in})+\sqrt{((b_1+q_1)-\alpha b_7G^n{}_{in})^2+4b_7G^n{}_{in}(\alpha(b_1+q_1)+\frac{b_4(b_6+q_3)}{b_2}}\right)}{2\left(\alpha(b_1+q_1)+\frac{b_4(b_6+q_3)}{b_2}\right)}\left(\frac{b_6+q_3}{b_2}\right)$$

to get an equivalent system

$$\frac{dX_1}{dt}=-(b_1+q_2)(X_1+G^*)(\alpha(X_1+G^*)+1)-b_4(X_1+G^*)(X_2+I^*) \qquad (4.1)$$
$$+\alpha b_7G^n{}_{in}(X_1+G^*)+\alpha b_7G^n{}_{in}$$

$$\frac{dX_2}{dt}=-b_2(X_2+I^*)+(b_6+q_3)\int_0^\infty w(s)(X_1+G^*)(t-s)ds \qquad (4.2)$$

$$\frac{dX_2}{dt}=-b_2X_2-b_2I_1+(b_6+q_3)[\int_0^\infty w(s)X_1(t-s)ds+\int_0^\infty w(s)G_1(t-s)ds]$$

Now

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$$\int_0^\infty w(s)ds = 1$$

$$\frac{dX_2}{dt} = -b_2X_2 - b_2I^* + (b_6+q_3)\int_0^\infty w(s)X_1(t-s)ds + (b_6+q_3)G^*$$

$$\frac{dX_2}{dt} = -b_2X_2 + (b_6+q_3)\int_0^\infty w(s)X_1(t-s)ds$$

Putting $(b_1+q_1)G(\alpha G+1) + \frac{b_4(b_6+q_3)G^2}{b_2} - \alpha G b_7 G^n{}_{in} = b_7 G^n{}_{in}$ into (4.1) we have

$$\frac{dX_1}{dt} = [-(b_1+q_2)(2\alpha G^*+1) - b_4I^* + \alpha b_7 G^n{}_{in}]X_1 - b_4X_1X_2 - (b_1+q_2)\alpha X_1{}^2 - b_4G^*X_2$$

Now consider the linearized system around the equilibrium point (G^*, I^*). We have

$$\frac{dX_1}{dt} = [-(b_1+q_2)(2\alpha G^*+1) - b_4I^* + \alpha b_7 G^n{}_{in}]X_1 - b_4G^*X_2 \qquad (4.3)$$

$$\frac{dX_2}{dt} = -b_2X_2 + (b_6+q_3)\int_0^\infty w(s)X_1(t-s)ds \qquad (4.4)$$

Let $Y = \begin{pmatrix} X_1 \\ X_2 \end{pmatrix}$

The system of equation above becomes

$$\frac{dY}{dt} = \begin{bmatrix} [-(b_1+q_2)(2\alpha G^*+1) - b_4I^* + \alpha b_7 G^n{}_{in}] & -b_4G^* \\ (b_6+q_3)\int_0^\infty w(s)(t-s)ds & -b_2 \end{bmatrix} \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} \qquad (4.5)$$

Let A=$[(b_1+q_2)(2\alpha G^*+1) + b_4I^* - \alpha b_7 G^n{}_{in}]$, B=b_4G*,

C=$(b_6+q_3)\int_0^\infty w(s)(t-s)ds$, D=b_2. Therefore, (4.5) becomes

$$X_1'(t) = -AX_1(t) - BX_2(t)$$
$$X_2'(t) = CX_1(t) - DX_2(t) \qquad (4.6)$$

Let the Jacobian matrix J evaluated at a fixed point (G^*, I^*) be

$$J = \begin{bmatrix} -A & -B \\ C & -D \end{bmatrix}$$

From the Jacobian matrix J, We have

Trace (P)=$-(A+D)$

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$\Delta J = Q = AD + BC$

Then the characteristic equation is given as

$|J - \lambda I| = 0$

$$\Rightarrow \begin{vmatrix} -A-\lambda & -B \\ C & -D-\lambda \end{vmatrix} = 0$$

$\Delta(\lambda) = \lambda^2 - P\lambda + Q$ which gives

$$\lambda_+ = \frac{P + \sqrt{P^2 - 4Q}}{2} \quad \text{and} \quad \lambda_- = \frac{P - \sqrt{P^2 - 4Q}}{2}$$

Clearly, the trace P<0 and Q>0 since all the parameters in the model are positive. This shows that the hyperbolic fixed points, (G^*, I^*) is stable (attractors).

Again, from (4.5) we have

$$A = \begin{bmatrix} [-(b_1+q_1)(2\alpha G^* + 1) - b_4 I^* + \alpha b_7 G^{n}{}_{in}] & -b4G^* \\ (b_6+q_3)\int_0^\infty w(s)(t-s)ds & -b_2 \end{bmatrix}$$

The characteristic equation is given as $|A - \lambda I| = 0$

$$\Rightarrow \begin{bmatrix} [-(b_1+q_2)(2\alpha G^* + 1) - b_4 I^* + \alpha b_7 G^{n}{}_{in}] - \lambda & -b4G^* \\ (b_6+q_3)\int_0^\infty w(s)(t-s)ds & -b_2 - \lambda \end{bmatrix} = 0 \qquad (4.6)$$

$$= \left[\{-(b_1+q_2)(2\alpha G^* + 1) - b_4 I^* + \alpha b_7 G^{n}{}_{in}) - \lambda\}\{-b_2 - \lambda\}\right] + \left[b_4 G_1 (b_6+q_3) w(\lambda)\right] = 0$$

Where, $w(\lambda) = \int_0^\infty e^{-\lambda s} w(s)ds$.

$$\Rightarrow \lambda^2 + [(b_1+q_2)(2\alpha G^* + 1) + b_4 I^* + b_2 - \alpha b_7 G^{n}{}_{in}]\lambda + [(b_1+q_2)(2\alpha G^* + 1) + b_4 I^* - \alpha b_7 G^{n}{}_{in}]b_2 + b_4 G^* (b_6+q_3) w(\lambda) = 0 \qquad (4.7)$$

Let $[(b_1+q_2)(2\alpha G^* + 1) + b_4 I^* + b_2 - \alpha b_7 G^{n}{}_{in}]$ =a,

$[(b_1+q_2)(2\alpha G^* + 1) + b_4 I^* - \alpha b_7 G^{n}{}_{in}]b$ =c and $b_4 G^* (b_6+q_3)$ =d.

So we rewrite (4.7) as

$$\Delta(\lambda) = \lambda^2 + a\lambda + c + dw(\lambda) = 0 \qquad (4.8)$$

$$\lambda' s = \frac{-a \pm \sqrt{a^2 - 4(c + dw(\lambda))}}{2} \qquad (4.9)$$

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$w(\lambda)=\int_0^{\infty} e^{-\lambda s}w(s)ds$ since, $\int_0^{\alpha} w(s)ds=1$, then $w(\lambda)=\int_0^{\infty} e^{-\lambda s}w(s)ds=\tau$

Where τ is the average time delay and $\tau=\frac{w(s)}{\lambda}$, where w(s) is the weight function which is non negative. From (4.9), for some $\tau\in[0,\infty)$ the real roots are negative since all the parameters are positive. This implies that the model is locally asymptotically stable.

5. Local stability analysis: We observed that $\lambda=0$ cannot be a root of the characteristics equation since from (4.8) $\Delta(\lambda)=c+d\neq 0$. So the only possibility for instability is through a Hopf bifurcation. So we define a parameter region where no stability switch can take place as $R(\lambda)$.

Theorem 5.1: If R(0) > 1, then the equilibrium (G^*,I^*) is locally asymptotically stable.

Proof:

Let (G_1^*,I_1^*) be the equilibrium. We show that the only possibility for the instability is through Hopf bifurcation theory by investigating whether there exist a real $\mu\succ 0$, so that $\lambda=i\mu$ is a real root of $\Delta(\lambda)=0$.

Let $i=\sqrt{-1}$, substituting $\lambda=i\mu$ in $\Delta(\lambda)=0$, we have

$-\mu^2+i(b_1(2\alpha G^*+1)+b_4I^*+b_2-\alpha b_7)\mu+(b_1(2\alpha G^*+1)+b_4I^*-\alpha b_7)b_2+b_4G^*(b_6)w(i\mu)=0$

We make $w(i\mu)$ subject of the formula

$$w(i\mu)=\frac{\mu^2-i(b_1(2\alpha G^*+1)+b_4I^*+b_2-\alpha b_7)\mu-(b_1(2\alpha G^*+1)+b_4I_1^*-\alpha b_7)b_2}{b_4G_1^*b_6} \quad (5.1)$$

Now

$|w(i\mu)|\leq\int_0^{\infty} w(s)|e^{-i\mu s}|ds=1$

$|w(i\mu)|\leq 1$

Let

$R(\mu)=\frac{\{\mu^2-[(b_1(2\alpha G^*+1)+b_4I^*-\alpha b_7)b_2]\}^2+\{(b_1(2\alpha G^*+1)+b_4I^*+b_2-\alpha b_7)\}^2\mu^2}{(b_4G_1^*b_6)^2}$ and

$$R(0)=\frac{((b_1(2\alpha G^*+1)+b_4I_1^*-\alpha b_7)b_2)^2}{(b_4G_1^*b_6)^2} \quad (5.2)$$

Substituting $I^*=\frac{b_6}{b_2}G^*$ we have

$$\frac{((b_2b_1(2\alpha G^*+1)+b_4(b_6+q_3)G_1^*-\alpha b_7b_2)b_2)^2}{(b_4G_1^*b_6)^2}\succ 1$$

$$\frac{dR(\mu)}{d\mu}=\frac{4\mu(\mu^2-(b_1(2\alpha G^*+1)+b_4I^*-\alpha b_7)b_2)+(b_1(2\alpha G^*+1)+b_4I^*+b_2-\alpha b_7)^2 2\mu}{(b_4G_1^*b_6)^2}$$

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$$= \frac{2\mu(2\mu^2 + {b_2}^2 + (b_1(2\alpha G^* + 1) + b_4 I^* - \alpha b_7)^2)}{(b_4 {G_1}^* b_6)^2} \quad (5.3)$$

Substituting $I^* = \frac{b_6}{b_2} G^*$ we have

$$= \frac{2\mu(2\mu^2 + {b_2}^2 + (b_2 b_1(2\alpha G^* + 1) + b_4 b_6 G^* - \alpha b_7 b_2)^2)}{(b_4 {G_1}^* b_6)^2} \geq 0 \quad (5.4)$$

This shows that $R(\mu)$ is an increasing function of μ since $R(0) > 1$. It follows that; $R(\mu) > 1$ *for every* $\mu \geq 0$. Thus, $|w(i\mu)| > 1, \forall\ \mu > 0$, but $|w(i\mu)| < 1 \forall \mu > 0$. Hence there is no possibility of stability switching so the system is locally asymptotically stable.

6. Numerical Simulation.

Numerical simulations of the dynamics model were carried out by Matlab 6.5, using the set of parameter values in table 1. It should be emphasized that the parameters in table 1 is a modified results of experiment in a clinical study of ten healthy volunteers subjects as reported by Jiaxu and Kuang [12]. Also, by definition, Foods when eaten get broken down into a form of sugar called glucose. The common table sugar known as sucrose is produce by combining glucose and fructose to produce a molecule of sucrose and a molecule of water. So for the purpose of this study our $G^n{}_{in}$ was chosen from the nutrition fact of Rogers Berry sugar. Also for the purpose of the studies we assume that the subject does not do any exercise, so $q_1 = q_2 = 0$.

Table 1:

P	G_b	I_b	b_0	b_1	b_2	b_3	b_4	b_5	b_6	b_7	$G^n{}_{in}$
U	Mg/dl	pM	Mg/dl	$\min^{-1}$	$\min^{-1}$	$\frac{dlpM}{mg}$	$\min^{-1}\ pM^{-1}$	min	$\frac{dlpM}{mg\ \min}$	$\frac{mg}{dl\ \min}$	g
V	88	68.8	209	0.0002	0.0422	1.64	1.09E-04	23	0.033	0.68	4

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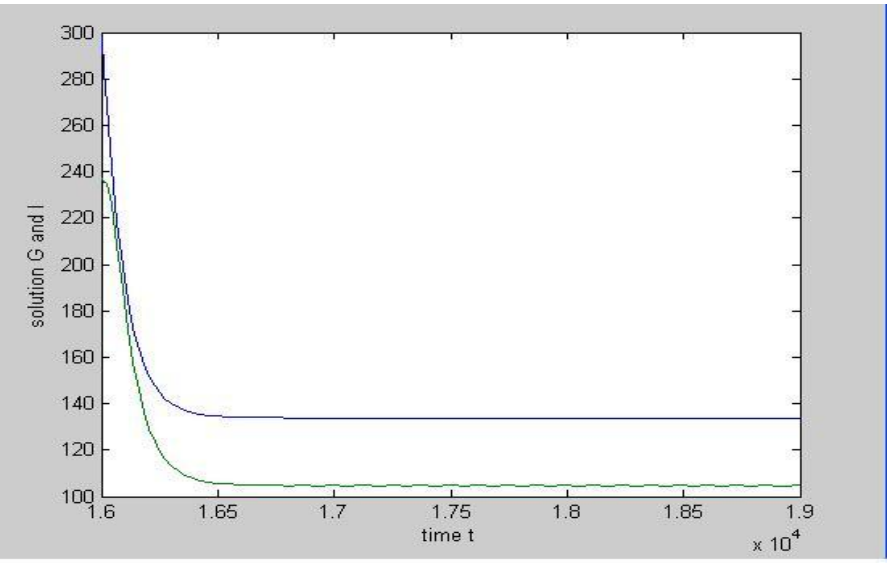

FIGURE 1: Graph of Glucose and insulin concentration against time. The upper concentration curve represent glucose and the lower represent insulin. Here $\alpha = 0.01, n = 0$

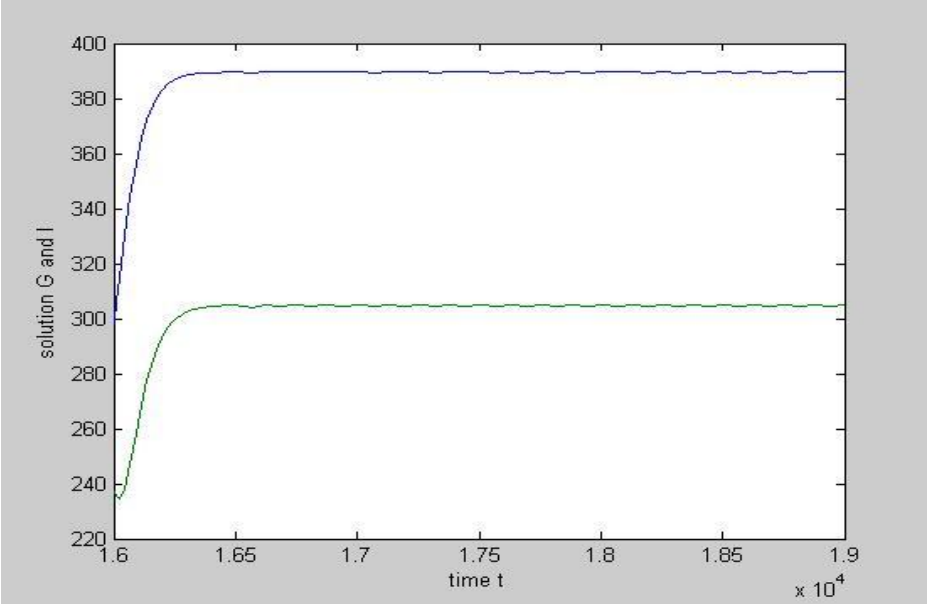

FIGURE 2: Graph of Glucose and insulin concentration against time. The upper concentration curve represent glucose and the lower represent insulin. Here $\alpha = 0.01, n = 1$

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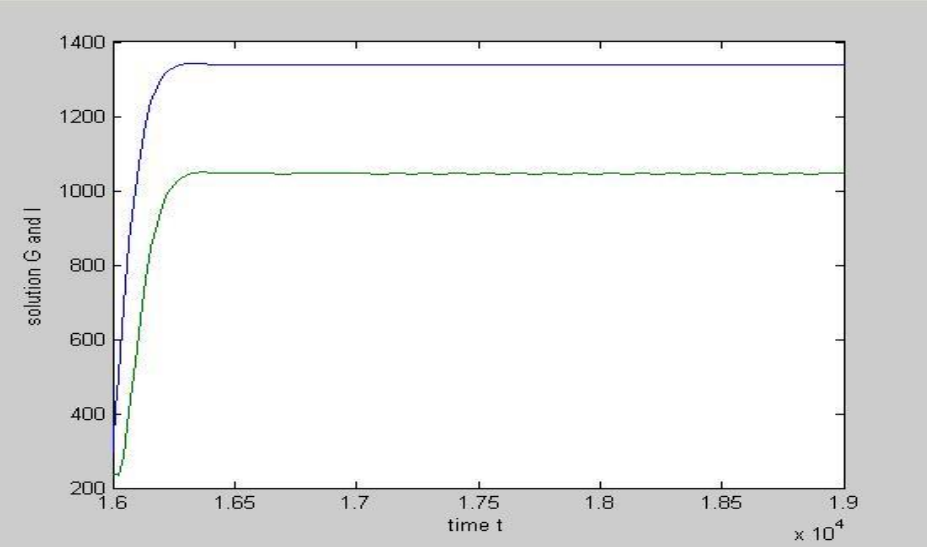

FIGURE 3: Graph of Glucose and insulin concentration against time. The upper concentration curve represent glucose and the lower represent insulin. Here $\alpha = 0.01, n = 2$

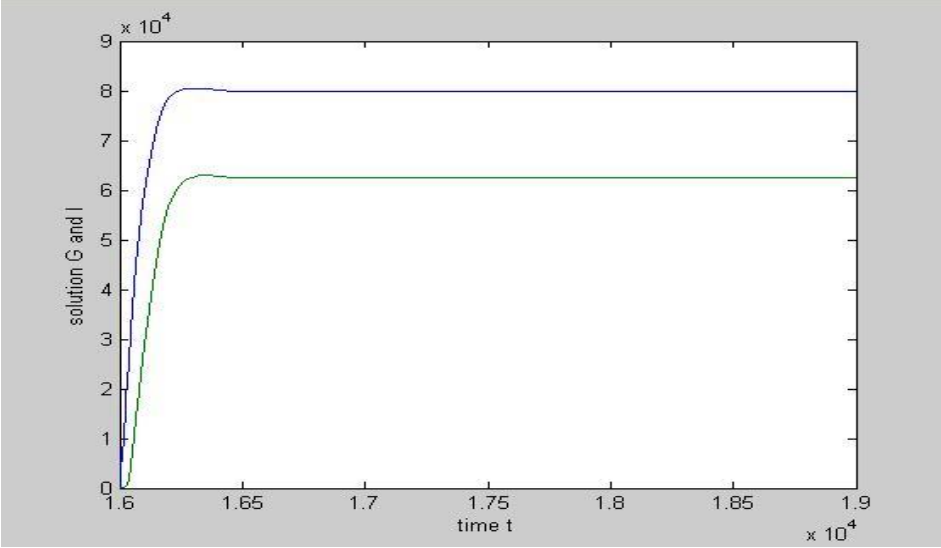

FIGURE 4: Graph of Glucose and insulin concentration against time. The upper concentration curve represent glucose and the lower represent insulin. Here $\alpha = 0.01, n = 5$

DISCUSSION OF RESULTS

We present a dynamic model which takes into account glucose intake. We show that the equilibrium point of the model is globally asymptotically stable and it is an attractor. Also there exists a unique solution of the dynamics model. We observed from the simulation results that as n increases, the glucose concentration also increases showing that when the glucose intake increases it elevate the blood plasma concentration which coincides with the clinical implications of excess intake of glucose on diabetics subjects.

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REFERENCES

[1] American Diabetes Association. Diabetes care 2004; 27: 55 – 510.
[2] Adewale SO and Ayeni RO. J Mathematical Ass Nigeria (Abacus) 2005; 32(2A):68-71.
[3] Adewale SO. Science Focus 2010; 15(2): 198-209.
[4] Bolie VW. J App Physiol 1961; 16: 783-788.
[5] Boutayeb A and Chetouani A. J BioMedical Engineering Online 2006; 5: 43-65.
[6] De Gaetano A and Arino O. Journal of Math Biol 2000; 40:136-168.
[7] Ganong WF. Review of medical physiology, Mc Graw-hill Medical Pub. U.S.A 1999.
[8] Guyton AC and Hall JE. Medical Physiol 1996; 77- 792.
[9] Harris MI: classification and diagnostic criteria for diabetes mellitus and other categories of glucose intolerance 1988; 15(2): 205 – 25.
[10] Harris MI, Hadden WC and Knowler WC, Benneth PH. Diabetes care 1987; 36:523-534.
[11] Jennifer Mayfield. Ame Fam physician 1998; 58: 6.
[12] Jiaxu L and Kuang Y. Discrete and Continuous Dynamical systems. Series B 2001; 1(1):103-124.
[13] Mukhopadhyay A, De Gaetano A, and Arino O. Discrete and continous Dynamical System Series B 2004; 4(2): 407-417.
[14] National Diabetes Data Group. Diabetes in America 2d. Ed. Bethesda. M.d. National institutes of health, national institutes of diabetes and digestive and kidney diseases, and NTH publication 1995; 95 – 1468.
[15] Report of the expert committee on diagnoses and classification of diabetes mellitus. Diabetes care 1997; 20: 1183 – 97.
[16] The expert committee on the diagnosis and classification of diabetes mellitus. follow – up report on the diagnosis of diabetes mellitus. Diabetes care 2003; 26:3160 – 3167.
[17] Strogatz, Steven H: Nonlinear Dynamics Chaos. Cambridge MA: Perseus 1994.
[18] William RD and Stanley IG. Elementary Differential Equation with Application. Addison Wesley Pub. Comp Inc. 1976.
[19] www.blood_sugar1.htm: Beware of High Blood Sugar.