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# A mathematical model of glucose-insulin interaction

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## Abstract

In this paper, we present a mathematical model of diabetes mellitus, which is a metabolic disease concerned with the regulation process of glucose in the body by the pancreatic insulin. This paper considers the disappearance of glucose due to insulin action (insulin-dependent) as well as the disappearance of glucose due to tissue uptake such as the brain and nerve cells (insulin-independent) and rise in glucose level due to infusion through meal intake, oral glucose intake, continuous nutrition absorption and constant infusion. The linear and non-linear cases are considered and the model is analyzed using Lyapunov's method. Conditions for local as well as global stability are obtained. Numerical simulations are carried out and graphs are also generated to indicate the role of insulin in the regulation process of glucose in the human body.

**Key words**: Diabetes mellitus; insulin; stability; Lyapunov; Jacobian. *sphinx*; Lengteng; nectar-feeding; pollination.

## Introduction

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. Glucose concentration in the blood of a normal person lies in the range of 80-110 mg/dl under fasting condition.[1] Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormones glucagon and insulin produced in the alpha and beta cells of the pancreas respectively. Diabetes has become an epidemic with considerable complications such as retinopathy, nephropathy, peripheral neuropathy and blindness.[2] The number of diabetics in the world is increasing every year. International Diabetes Federation estimates that in 2013, 382 million people around the world have diabetes and the figure is expected to hit the 592 million by the year 2035 (http://www.idf.org).

Many researchers have used mathematical models to understand and predict the behaviour of biological systems.[3-5] The study of glucose-insulin interaction dates back as early as the sixties[6,7] and since then has been studied extensively by many researchers. The most widely used model in the study of diabetes is the mini-

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mal model which is used in the interpretation of the intravenous glucose tolerance test (IVGTT).[8] This model consists of three equations which may be considered to be divided into two separate parts. In order to overcome the difficulties of the coupled minimal model and to remove the artificial non-observable variable $X(t)$, Gaetano and Arino[9] have proposed a simpler model called the dynamic model.

Following the dynamic model, several authors[10-17] have proposed more popular, general and realistic models with results consistent with physiology. The modelling of the glucose-insulin system has become an interesting topic and several models have been proposed and studied with the purpose of understanding the system better, investigating possible pathways to diabetes as well as providing better insulin administration practices. Many models have been presented as described in a survey by Makroglou *et al.*[18] as well as in the review by Boutayeb and Chetouni[19] in which most of the models proposed existing in literature can be found.

## Modelling the Glucose-regulatory System

In the glucose regulatory system, the main two players are the pancreatic hormones insulin and glucagon. Insulin and glucagon act together to balance metabolism. The pancreas releases glucagon when blood sugar (glucose) level falls too low. Glucagon causes the liver to convert stored glycogen into glucose, which is released in the bloodstream. Glucagon raises blood glucose levels and insulin organizes the use of fuels for either storage or oxidation. Elevated glucose concentrations of glucose in blood stimulate the release of insulin, and insulin acts on cells throughout the body to stimulate uptake, storage and utilization of glucose.

In this paper, we propose the following general model for the interaction of glucose and insulin

$$\dot{x} = -a_1 x - a_2 xy + a_3,$$

$$\dot{y} = b_1 x - b_2 y \qquad (1)$$

Where $x \geq 0, y \geq 0$
$x$ represents glucose concentration
$y$ represents insulin concentration
$a_1$ is the rate constant which represents insulin-independent glucose disappearance
$a_2$ is the rate constant which represents insulin-dependent glucose disappearance
$a_3$ is the glucose infusion rate
$b_1$ is the rate constant which represents insulin production due to glucose stimulation
$b_2$ is the rate constant which represents insulin degradation

## Equilibrium Points

Consider

$$\dot{x} = 0 \Rightarrow -a_1 x - a_2 xy + a_3 = 0$$
$$\dot{y} = 0 \Rightarrow b_1 x - b_2 y = 0 \qquad (2)$$

The equilibrium point $(x^*, y^*)$ exists for the above model.

Solving (2), we get

$$x^* = \frac{-a_1 b_2 + \sqrt{(a_1 b_2)^2 + 4a_2 b_2 a_3 b_1}}{2b_1 a_2}$$
$$y^* = \frac{-a_1 b_2 + \sqrt{(a_1 b_2)^2 + 4a_2 b_2 a_3 b_1}}{2b_2 a_2}$$

The interior-equilibrium point $(x^*, y^*)$ exists unconditionally as $x^*$ and $y^*$ are always positive as all the parameters are considered positive.

## Linearization of the Model

Consider the Jacobian matrix of (1) given by

$$J = \begin{pmatrix} -a_1 - a_2 y & -a_2 x \\ b_1 & -b_2 \end{pmatrix}$$

At $(x^*, y^*)$,

$$J^* = \begin{pmatrix} -a_1 - a_2 y^* & -a_2 x^* \\ b_1 & -b_2 \end{pmatrix}$$

We now use the transformation $x = X + x^*, y = Y + y^*$ and then linearize the system

$$\begin{pmatrix} \dot{X} \\ \dot{Y} \end{pmatrix} = J^* \begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} -a_1 - a_2 y^* & -a_2 x^* \\ b_1 & -b_2 \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}$$

We get the linearized system

$$\dot{X} = -a_1X - a_2y^*X - a_2x^*Y$$
$$\dot{Y} = b_1X - b_2Y$$

## Stability Analysis

***Theorem 1:*** *The interior-equilibrium point* $(x^*, y^*)$ *is locally asymptotically stable if*

$$(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2y^*)$$

***Proof:*** Consider the Lyapunov function

$$V = \frac{1}{2}(X^2 + Y^2)$$

Hence, $\dot{V} = -(a_1 + a_2y^*)X^2 + (b_1 - a_2x^*)XY - b_2Y^2$

$$= -\frac{1}{2}AX^2 + BXY - \frac{1}{2}CY^2$$

Where $A = 2(a_1 + a_2y^*)$

$$B = b_1 - a_2x^*$$
$$C = 2b_2$$

The sufficient condition for $\dot{V}$ to be negative definite is that

$$B^2 < AC$$

i.e. $(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2y^*)$

which is the condition that the parameters must satisfy so that the critical point $(x^*, y^*)$ is locally asymptotically stable.

***Lemma 1:*** *The set* $\Omega = \left\{(x, y): 0 \le x + y \le \frac{a_3}{\delta} + ce^{-\delta t},\ \delta = min(a_1 - b_1, b_2),\ c\ is\ a\ constant\right\}$ *is a region of attraction for all solutions initiating in the positive quadrant*

***Proof:*** From our model we have

$$\frac{dx}{dt} = -a_1x - a_2xy + a_3$$

And $\frac{dy}{dt} = b_1x - b_2y$

Therefore, $\frac{d(x+y)}{dt} = -a_1x - a_2xy + a_3 + b_1x - b_2y$

$$\le -a_1x + a_3 + b_1x - b_2y$$
$$= -(a_1 - b_1)x + a_3$$
$$- b_2y\}$$
$$< -\min\{(a_1 - b_1), b_2\}(x + y) + a_3$$

Let $\delta = \min\{(a_1 - b_1), b_2\}$

Thus $x + y < \frac{a_3}{\delta} + ce^{-\delta t}$

***Theorem2:*** *The interior-equilibrium point* $(x^*, y^*)$ *is globally asymptotically stable if* $(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2\bar{y})$ *where* $\bar{y} = \frac{1}{2}\left(\frac{a_3}{\delta} + ce^{-\delta t}\right)$

***Proof:*** Consider the Lyapunov function

$$V = \frac{1}{2}(x - x^*)^2 + \frac{1}{2}(y - y^*)^2$$

Then, $\dot{V} = (x - x^*)\dot{x} + (y - y^*)\dot{y}$

$$= (x - x^*)(-a_1x - a_2xy + a_3 + a_1x^* + a_2x^*y^* - a_3 + a_2x^*y - a_2x^*y)$$
$$+(y - y^*)(b_1x - b_2y - b_1x^* - b_2y^*)$$
$$= (x - x^*)\{-a_1(x - x^*) - a_2y(x - x^*) - a_2x^*(y - y^*)\}$$
$$+(y - y^*)\{b_1(x - x^*) + b_2(y - y^*)\}$$
$$= (-a_1 - a_2y)(x - x^*)^2 + (-a_2x^* + b_1)(x - x^*)(y - y^*) - b_2(y - y^*)^2$$
$$= -\frac{1}{2}A_{11}(x - x^*)^2 + A_{12}(x - x^*)(y - y^*) - \frac{1}{2}A_{22}(y - y^*)^2$$

Where $A_{11} = 2(a_1 + a_2y)$

$$A_{12} = -a_2x^* + b_1$$
$$A_{22} = 2b_2$$

The condition for $\dot{V}$ to be negative definite is that

$$A_{12}{}^2 < A_{11}A_{22}$$

i.e., $(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2\bar{y})$ where $\bar{y} = \frac{1}{2}\left(\frac{a_3}{\delta} + ce^{-\delta t}\right)$, say.

Thus, the interior-equilibrium point $(x^*, y^*)$ is globally asymptotically stable if $(b_1 - a_2x^*)^2 < 4b_2(a_1 + a_2\bar{y})$ where $\bar{y} = \frac{1}{2}\left(\frac{a_3}{\delta} + ce^{-\delta t}\right)$

## Numerical Simulation

In a clinical experiment conducted and reported in Gaetano *et al.*[9] ten healthy volunteers (5 males and 5 females) participated, all of whom had no family or personal history of diabetes and other endocrine diseases. They were not on any medication and had maintained

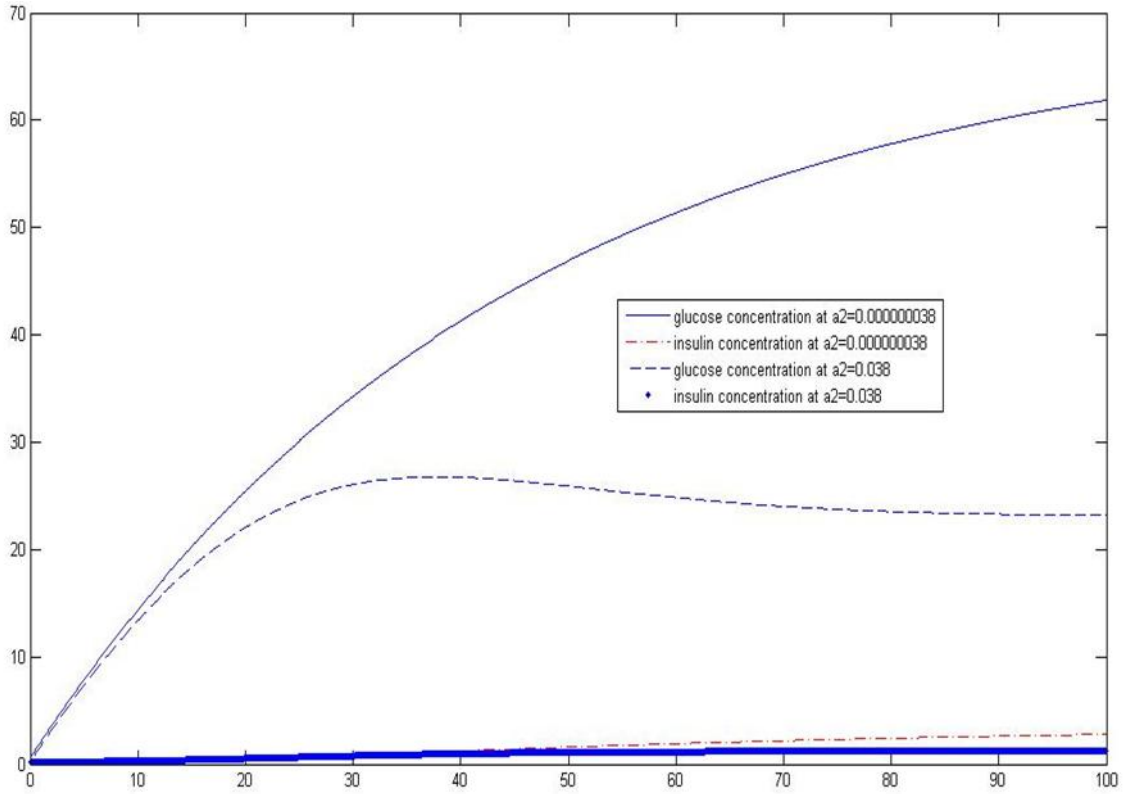


Figure 1. Insulin-glucose equilibrium.

constant weight for the six months preceding the experiment. The parameters values for the volunteers are listed in their Table 1.[9] They were able to show that the dynamic model does produce solutions that fit well with the data collected from their experiment. We fit the data from Table 1[9] and found that it fit well with the conditions for existence and the stability of the interior-equilibrium except for sixth and seventh subjects[9] which were also observed by Li *et al.*[14]

Taking the data of their first subject:

$$a_1 = 0.0226\,,\ a_2 = 3.80e-08\,,$$
$$a_3 = 1.56\,, b_1 = 0.0022\,, b_2 = 0.0437\,.$$

We get $x^* = 69.0261,\ y^* = 3.5540$

The condition for local stability for $(x^*, y^*)$ is also satisfied as

$$(b_1 - a_2x^*)^2 = 5.0505e-06 < 4b_2(a_1 + a_2y^*) = 0.0040$$

For validation of the global stability condition, we consider the case when $t \to 0$, i.e when $\bar{y} < \frac{a_3}{\delta} + c$. We again consider the particular case $\bar{y} = \frac{a_3}{\delta} = \frac{1.56}{0.0204} = 76.4706$. We see that the interior-equilibrium point $(x^*, y^*)$ is globally asymptotically stable.

Also, graphs are generated for two different values of $a_2$, the rate constant which represents insulin-dependent glucose disappearance. We see that when $a_2 = 0.038$, the curve for glucose cencentration shows that peak glucose concentration is lower (between 20-30 units) as compared to smaller values of $a_2 = 0.000000038$ where glucose concentration level reaches more than 60 units over the same interval of time. This shows that insulin plays an important role in the regulation process of the level of glucose in the human body.

## CONCLUSION

In this paper, a mathematical model has been proposed and analyzed to study the dynamics of glucose and insulin in the human body. The model was formulated by a system of ordinary differential equations and two cases viz., linear and non-linear cases were considered. Both cases are validated by numerical simulations and the importance of the role of insulin in the disappearance of glucose has been shown by graph which depicts the situation for two different values of $a_2$, the rate constant representing insulin-dependent glucose disappearance. When $a_2$ value was lower (3.8e-08), glucose level was significantly high (62 units approx.) and when $a_2$ was higher (0.038), glucose level was lower (23 units approx.) which indicates that insulin plays a vital role in regularizing glucose concentration in the human body. The interior-equilibrium point is shown to exist without any condition and is consistent with the human physiology. It is shown to be locally as well as globally stable under certain conditions on the system parameters and for a bounded y (insulin concentration), using Lyapunov's direct method. From the above results, we conclude that the model is physiologically consistent and may be a useful tool for further research on diabetes.

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