Analysis of Human Glucose Regulatory System Model by Lypunov's Method

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***Abstract* - In this research, we present a mathematical model of diabetes mellitus showing how glucose metabolism in the body is related to pancreatic insulin. We looked at the breakdown of glucose due to direct injection of insulin into the vein, and the breakdown of glucose due to the uptake of tissues such as the brain and neurons, and also considered the increased glucose level coming from consuming food and eating glucose directly. From this behavior, we can summarize it as a mathematical model of the system of glucose. Then, we used linear and nonlinear mathematical theorem analysis by Lyapunov's method with conditional and local stability and global stability cases respectively. Finally, a numerical approach along with a graph presentation was used to confirm the conclusive analysis of the role that insulin works in the process of regulating the blood sugar level in the human body.**

***Keywords* - Diabetes mellitus, Glucose-insulin, stability, Lypunov**

I. INTRODUCTION

Diabetes mellitus is a disorder associated with the metabolism of the body. It is caused by genetics and environment. The patient is unable to produce the insulin enough. Thus a condition that results in abnormally high blood sugar levels is called "hyperglycemia". The normal blood glucose concentration range is followed an overnight fast (70 - 110 mg/dl) . For a normal subject, after an overnight fast, the basal plasma insulin is in the range of 5 - 10 μU/ml and as large as 30 - 150 μU/ml during meal consumption while the glucose concentration level is high (Ahren and Taborsky,2002). The blood glucose level is regulated by the interaction of the glucagon and insulin in the pancreas.

Besides, the Diabetics may have complications such as retinopathy, nephropathy, peripheral, neuropathy and blindness [1]. There is an increasing number of people with diabetes every year. It is estimated that 592 million people will be affected by 2035, according to the web site. (http://idf.org) .For theses reasons, many researchers are interested in mathematical models to understand and to predict the biological behavior of the glucose–insulin endocrine metabolic regulatory system. An experimental model used to study diabetes was the intravenous glucose tolerance test (IVGTT). Gaetano and Arino proposed a simpler model called the dynamic model.

Modeling Glucose-insulin has become an exciting topic and there are many models. Each model aims to better understand glucose and insulin interaction. It also can examine the possibility of diabetes as well as find better methods for using insulin. Several models were presented by Makroglou et al,and reviewed by Boutayeb and Chetouni. Most of models can be found in conventional experiments.

II. PRELIMINARY

A. The Glucose-Insulin Interaction

Normal blood glucose concentration level in humans is in a narrow range (70–110 mg / dl). Exogenous factors that affect the blood glucose concentration level include food intake, rate of digestion, and exercise. The pancreatic endocrine hormones insulin and glucagon are responsible for keeping the glucose concentration level in check and secreted from β -cells and α -cells respectively, which are contained in the so-called Langerhans islets scattered in the pancreas. When the blood glucose concentration level is high, the β -cells release insulin which results in lowering the blood glucose concentration level by inducing the uptake of the excess glucose by the liver and other cells and by inhibiting hepatic glucose production. When the blood glucose level is low, the α -cells release glucagon, which results in increasing the blood glucose level by acting on liver cells and causing them to release glucose into the blood (seeFigure1)

According to Andrea De Gaetano's research [4] The dynamical model of the glucose-insulin system to be studied is therefore:

$$0 = -b_1 G_b + b_4 I_b G_b + b_7$$

and

$$0 = -b_2 I_b + b_6 G_b$$

In fact, assuming the subject is at equilibrium at [4]. From the above equation It has been analyzed, edited and further studied in order to further understand the system by Hussain J [11].

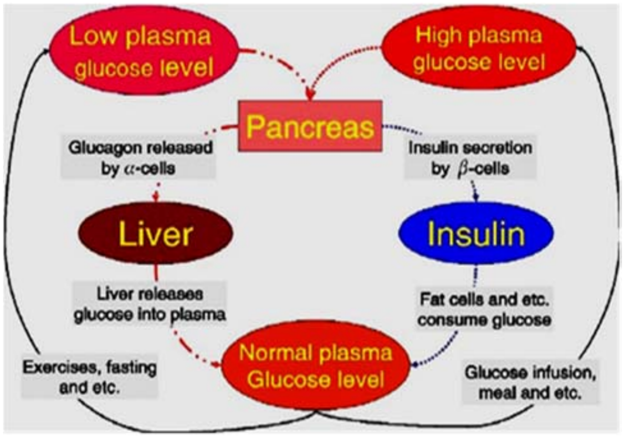

Figure1. Physiological glucose-insulin regulatory system, Makroglou A (2006) [7]

B. Mathematical Model of the Glucose-Insulin Interaction

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

$$\dot{x} = -a_1 x - a_2 xy + a_3 + a_4 y, \quad (2.1)$$
$$\dot{y} = b_1 x - b_2 y \quad (2.2)$$

Where x $\geqslant$ 0, y $\geqslant$ 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 after meal
a_4 is the rate constant of insulin injection when glucose concentration is high levels
b_1 is the rate constant which represents insulin production due to glucose stimulation
b_2 is the rate constant which represents insulin degradation

C. Equilibrium Points

Consider

$$\dot{x} = 0 \Rightarrow -a_1 x - a_2 xy + a_3 + a_4 y = 0 \quad (2.3)$$
$$\dot{y} = 0 \Rightarrow b_1 x - b_2 y = 0 \quad (2.4)$$

The equilibrium point (x∗, y∗) exists for the above model. Equation (3),(4) is solved by following:

$$x^* = \frac{-a_1 b_2 + a_4 b_1 + \sqrt{(a_1 b_2 - a_4 b_1)^2 + 4(a_2 b_1 a_3 b_2}}{2 a_2 b_1} \quad (2.5)$$

$$y^* = \frac{-a_1 b_2 + a_4 b_1 + \sqrt{(a_1 b_2 - a_4 b_1)^2 + 4(a_2 b_2 a_3 b_1}}{2 a_2 b_2} \quad (2.6)$$

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

D. Linearization

Consider the Jacobian matrix of (2.1), (2.2) given by:

$$J = \begin{bmatrix} -a_1 - a_2 y & -a_2 x + a_4 \\ b_1 & -b_2 \end{bmatrix}$$

At (x∗, y∗) following:

$$J^* = \begin{bmatrix} -a_1 - a_2 y^* & -a_2 x^* + a_4 \\ b_1 & -b_2 \end{bmatrix}$$

We now use the transformation x = X + x∗, y = Y + y∗ and then linearize the system.

We get the linearized system:

$$\dot{X} = -a_1 X - a_2 y^* X - a_2 x^* Y + a_4 Y \quad (2.7)$$
$$\dot{Y} = b_1 X - b_2 Y \quad (2.8)$$

E. Stability Analysis

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

(b1 + a4 − a2x∗)2 < 4b2(a1 + a2y∗)

Proof: Consider The Lyapunov function:

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

Hence,

$$\dot{V} = -(a_1 + a_2 y^*)X^2 + (b_1 + a_4 - a_2 x^*)XY - b_2 Y^2$$
$$= -\frac{1}{2}AX^2 + BXY - \frac{1}{2}CY^2$$

Where $A = 2(a_1 + a_2 y^*)$, $B = b_1 + a_4 - a_2 x^*$, $C = 2b_2$

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

$B^2 < AC$

i.e. $(b_1 + a_4 - a_2x^*)^2 < 4b_2(a_1 + a_2y^*)$

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

Lemma 1: The set $\Omega = \{(x, y) : 0 \le x + y \le a3 + ce^{-\delta t}, \delta = \min(a1 - b1, b2 - a4), a4)$, *c is a constant, is a region of attraction for all solutions initiating in the positive quadrant*

Proof: From our model we have:

$$\frac{dx}{dt} = -a_1x - a_2xy + a_3 + a_4$$

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

Therefore,

$$\begin{aligned}\frac{d(x+y)}{dt} &= -a_1x - a_2xy + a_3 + a_4y + b_1x - b_2y \\ &\le -a_1x + a_3 + a_4y + b_1x - b_2y \\ &= -(a_1 - b_1)x + a_3 - (b_2 - a_4)y \\ &< -min\{(a_1 - b_1), (b_2 - a_4)\}(x, y) + a_3\end{aligned}$$

Let $\delta = min\ \{(a1 - b1), (b2 - a4)\}$

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

Theorem 2: The interior-equilibrium point (x∗, y∗) is globally asymptotically stable if:

$$(a_4 - a_2x^* + b_1)^2 < 4b_2(a_1\bar{y}) \quad \text{where} \quad \bar{y} = \frac{1}{2}\left(\frac{a_3}{\delta}\right) + ce^{-\delta t}$$

Proof: Consider the Lyapunov function:

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

Then

$$\begin{aligned}\dot{V} &= (x - x^*)\dot{x} + (y - y^*)\dot{y} \\ &= (-a_1 - a_2y)(x - x^*)^2 + (a_4 - a_2x^* \\ &\quad + b_1)(x - x^*)(y - y^*) - b_2(y - y^*)^2 \\ &= -\frac{1}{2}A_{11}(x - x^*)^2 + A_{12}(x - x^*) \\ &\quad (y - y^*) - \frac{1}{2}A_{22}(y - y^*)^2\end{aligned}$$

Where A11 = 2(a1 + a2y), A12 = (a4 − a2x∗ + b1), A22 = 2b2

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

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

i.e. $(a_4 - a_2x^* + b_1)^2 < 4b_2(a_1 + a_2\bar{y})$

Thus, the interior-equilibrium point is globally asymptotically stable.

III. MAIN RESULTS

A. Numerical Simulation

In a clinical experiment conducted and reported in Gaetano et al [4]. Ten healthy volunteers 5 males and 5 females participated. All subjects had negative family and personal histories for diabetes mellitus and other endocrine diseases.

The parameters values for the 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 [4] and found that it fit well with the conditions for existence and the stability of the interior-equilibrium.

Taking the data of their first subject:

$a_1 = 0.0226$, $a_2 = 3.80e - 08$, $a_3 = 3.842$, $a_4 = -0.065$,
$b_1 = 0.0022$, $b_2 = 0.0437$

We get $x^* = 148.4969$ and $y^* = 7.4758$

The condition for local stability for (x∗, y∗) is also satisfied as:

$(b_1 + a_4 - a_2x^*)^2 = 0.0039 < 4b_2(a_1 + a_2y^*) = 0.0040$

We consider the particular case:

$$y = \frac{a_3}{\delta} = \frac{3.842}{0.0204} = 188.3333$$

We see that the interior equilibrium point (x*, y*)

Also, graphs are generated for two different values of a4, the rate constant which rep- resents insulin injection. We see that when a4 = -0.065 the curve for glucose concentration show that peak to 148.4969 mg/dl and glucose concentration is lower as 69.43 mg/dl when a4 = -

0.6567 .This shown that insulin an important role in the regulation process of the level of glucose in the human body.

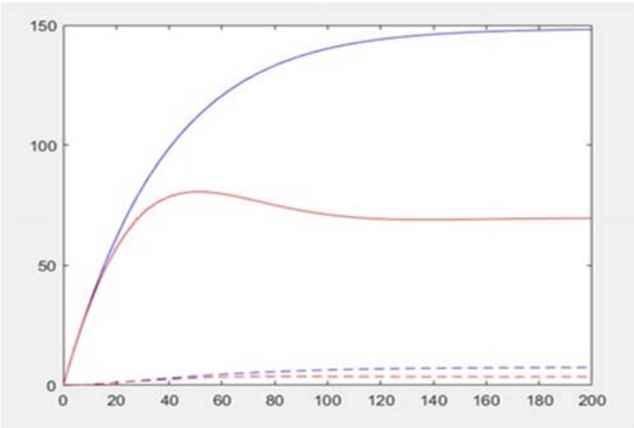

Figure 2: glucose concentration as a4 = −0.065(model: Blue line), glucose concentration as a4 = −0.6567(model: red line) and insulin concentration (model: dashed lines)

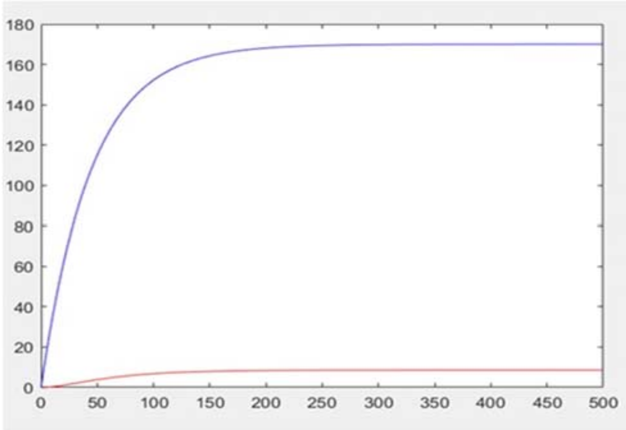

Figure 3: Glucose-insulin equilibrium after consumption with original dynamical model, Hussain J (2014) [10].

TABLE I. DYNAMICAL MODEL, ANDRES DE GAETANO (2000) [4]

Table 1. Dynamical model results: anthropometric characteristics and dynamical model parameter values found for each experimental subject, together with their sample mean, standard deviation, standard error and coefficient of variation. BW is body weight, LBM is lean body mass, FBM is fat mass, bas. gluc. is basal blood glucose, bas. insul. is basal plasma insulin, R^2 is the (unweighted data) coefficient of determination.

Subject	Sex	Age (years)	Height (cm)	BW (kg)	LBM (kg)	FM (kg)	bas. gluc. (mg/dl)	bas. insul. (pM)	b_0 (mg/dl)	b_1 (min^{-1})	b_2 (min^{-1})	b_3 pM/(mg/dl)	b_4 (min^{-1}) pM^{-1}	b_5 (min)	b_6 min^{-1} pM/(mg/dl)	b_7 (mg/dl) min^{-1}	R^2
1	m	35	172	72	56	16	69	71.3	170	0.0226	0.0437	2.57	3.80E-08	20	0.045	1.56	0.865
2	f	28	155	45	36.2	8.8	79	51.7	241	0.0509	0.2062	3.55	1.29E-07	14	0.135	4.02	0.955
3	f	25	162	61	48.4	12.6	74	29.4	208	0.0309	0.1817	2.96	6.99E-07	12	0.072	2.29	0.931
4	m	32	169	68	53.5	14.5	80	56.6	355	0.0084	0.1039	4.25	7.55E-05	8	0.073	1.01	0.985
5	m	23	179	65	55	10	74	45	216	0.0273	0.0275	2.77	1.10E-07	5	0.017	2.02	0.869
6	f	27	162	65	44.5	20.5	88	68.6	209	0.0002	0.0422	1.64	1.09E-04	23	0.033	0.68	0.953
7	m	25	170	66	53	13	87	37.9	311	0.0001	0.2196	0.64	3.73E-04	23	0.096	1.24	0.957
8	f	34	158	64	42.4	21.6	78	55.8	217	0.0565	0.0438	4.39	5.70E-06	19	0.031	4.43	0.99
9	m	42	172	78	61.2	16.8	70	43.8	156	0.0135	0.2972	5.92	3.51E-08	11	0.186	0.94	0.93
10	f	55	169	67	47.4	19.6	67	37.7	184	0.0159	0.0965	2.51	8.72E-08	14	0.054	1.07	0.862
Mean		32.6	166.8	65.1	49.8	15.3	76.6	49.8	226.7	0.0226	0.1262	3.12	5.64E-05	14.9	0.074	1.93	0.93
s.d.		9.8	7.3	8.5	7.4	4.4	7.2	13.6	62.1	0.0194	0.0938	1.49	1.18E-04	6.2	0.052	1.31	0.048
s.e.		3.1	2.3	2.7	2.3	1.4	2.3	4.3	19.6	0.0061	0.0297	0.47	3.73E-05	2	0.017	0.41	0.015
c.v. (%)		9.5	1.4	4.1	4.7	9	3	8.6	8.7	27.1	23.5	15.1	66.1	13.1	22.4	21.5	1.6

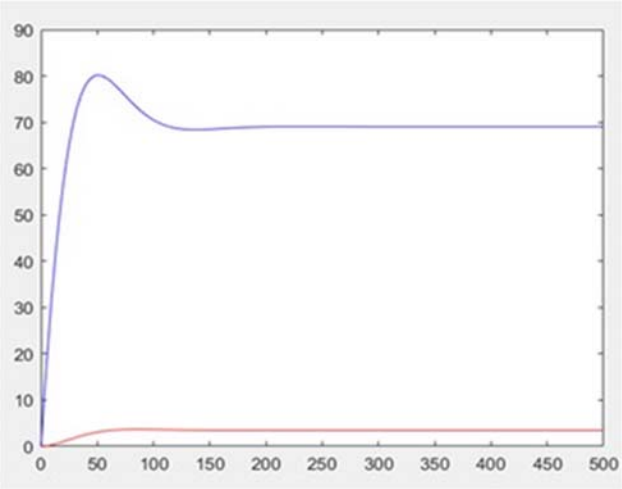

Figure 4. Glucose-insulin equilibrium after consumption with dynamical model when adding less a4 (-0.6567)

IV. CONCLUSION

In this study, a mathematical model has been proposed and analyzed to study the dynamics of glucose and insulin in the human. The model was formulated by a system of ordinary differential equation. 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 value of a4, the rate constant which represent insulin injection when glucose concentration is high level(after meal). When a4 value was higher(-0.065),glucose level was significantly high (148 units approx.) and when a4 was lower (-0.6567),glucose level was lower (69 units approx.) which indicates that insulin plays a visit role in regularizing glucose concentration in the human body. We conclude that Lyapunov's direct method is physiologically consistent and may be a useful tool for further research on diabetes. This study is especially supportive for the proper injection of insulin with expert supervision for the treatment of people with insulin resistance or type 2 diabetes mellitus to lower blood sugar levels. We sincerely hope that this study will be of great benefit to the medical profession and those interested in it.

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