A NEW MATHEMATICAL MODEL OF HUMAN GLUCOSE REGULATORY SYSTEM

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Abstract

In this research, we present a mathematical model of the glucose in the body that depends on the insulin produced in the pancreas, which allows us to study the biological causes of diabetes mellitus. This study is focused on glucose absorption due to direct intravenous of insulin. Glucose is absorbed by tissue cells such as the brain and neurons and the increasing glucose level is contemplated from food intake and oral glucose intake. From the foregoing, it can be summarized as a mathematical model of the glucose-insulin system by linear mathematical analysis; Lyapunov's method with local stable conditional cases. Finally, conclusive analysis of insulin function was performed using numerical with graph presentation to confirm the results in glycemic control processes in humans.

Keywords: Glucose, Insulin, Lyapunov's function, Stability, Diabetes mellitus

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Nattacha Nuwaboot

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Notation/Symbols

$\dot{x}$	is glucose concentration in the body at time t respectively.
$\dot{y}$	is insulin concentration in the body at time t respectively.
a_1	is represented by insulin independent with glucose disappearance, the rate of constant.
a_2	is represented by insulin dependent on glucose disappearance
a_3	is the glucose infusion rate after meal
a_4	is represented by intravenous insulin injection when glucose concentration is high, the rate of constant.
b_1	is represented by insulin production due to glucose stimulation, the rate of constant.
b_2	is represented by insulin degradation, the rate of constant.

Chapter 1

Introduction

In this section, the background is mentioned in relation to researching mathematical models for the human glucose regulatory system, the significance of the glucose-insulin regulatory system and the objectives we hope to achieve. We would like to point out the benefits of this study.

1.1 Research Motivation

Currently, one of the five deadliest diseases that kill Thai people the most is diabetes. (5 serious diseases are cancer, heart disease, diabetes, high blood pressure, and kidney disease) In 2018, the survey found that 425 million people had diabetes worldwide, which was projected to increase to 642 million people worldwide within 2040 and may be increased the number every year. In 2012, estimated 1.5 million deaths were attributed primarily to diabetes as reported by WHO [1].

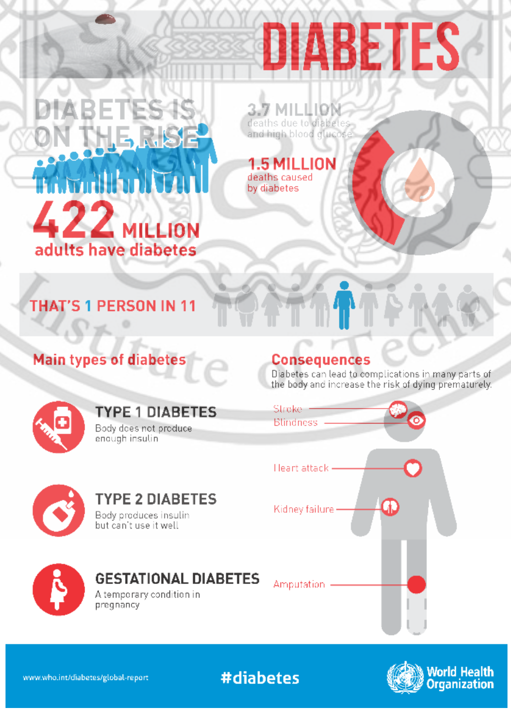

Figure 1.1 Basic information on the number of people with diabetes [1].

1.1.1 Types of diabetes

Diabetes is a chronic disease caused by the metabolism of blood sugar levels. The normal blood glucose concentration level in humans is in a narrow range (70–110 mg / dl). If the concentration is higher than the specified, it indicates diabetes. There are three main types of diabetes. The most common types of diabetes are:

Type 1 diabetes mellitus or T1DM is a chronic decease in which the pancreas produces little or no insulin by itself. Approximately 5-10% of the patients belong to T1DM. Symptoms of T1DM usually develops rapidly. It’s usually diagnosed in all ages. Patient is going to need to take insulin every day to survive.

type 2 diabetes mellitus or T2DM, usually in adults rise when the body be able to oppose to insulin or doesn't produce enough insulin. About 90-95% of people with diabetes have type 2. T2DM can be hindered or delayed by redirecting healthcare, such as eating clean food, and exercise.

Type 3 diabetes mellitus or T3DM, Gestational diabetes develops in pregnant who have never had diabetes. Gestational diabetes usually goes away after giving birth but increases risk for T2DM later in life. Baby is liable to have overweight as a child or teen, and more likely to develop type 2 diabetes later in life too [2].

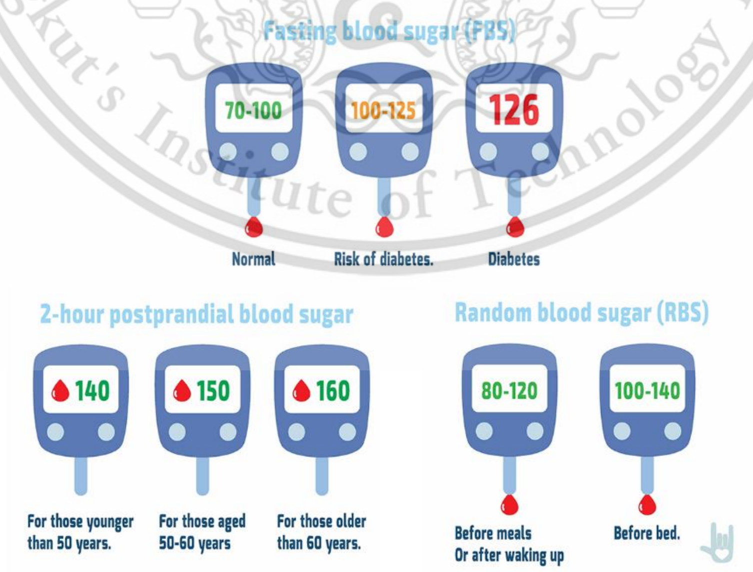

Figure 1.2: Testing blood sugar levels with a meter [3].

1.1.2 Complications

External factors that affect the blood glucose concentration level include meal intake, the rate of digestion, activity, reproductive conditions. Complications such as kidney failure, leg amputation, vision loss and nerve damage. An extremely high risk of a heart attack and stroke in adults with diabetes. In pregnancy, if diabetes is poorly controlled, it increases the risk of fetal death and other problems [4].

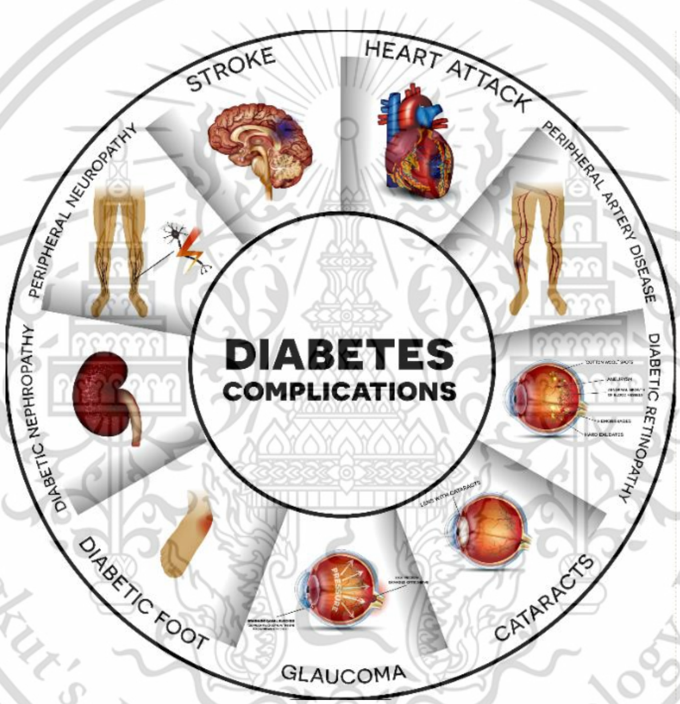

Figure 1.3: Complications of Diabetes Mellitus [4]

1.1.3 Intra Venous Glucose Tolerance Test (IVGTT)

Many scientists are interested in mathematical models to realize and forecast the biological behavior of the glucose–insulin metabolic control system. The experimental model used to study diabetes was the intravenous glucose tolerance test (IVGTT). The IVGTT consists in rapidly injecting a bolus of glucose intravenously. The IVGTT allows [15].

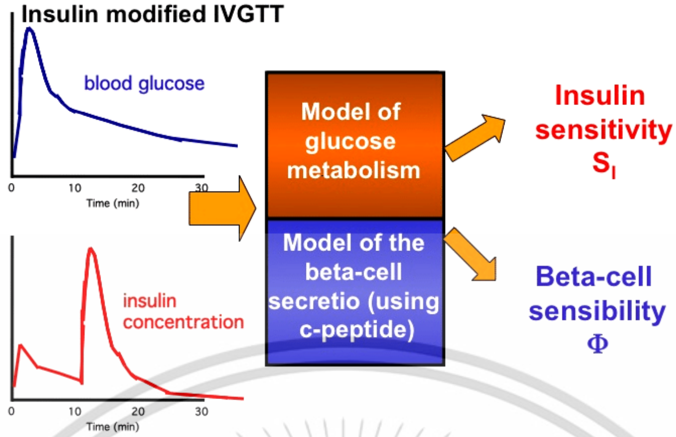

Figure 1.4: Intra Venous Glucose Tolerance Test (IVGTT) [15]

1.1.4 Mathematical Model of Glucose - Insulin System

The investigator to clearly distinguished the first-phase insulin secretion, for these reasons Gaetano and Arino presented a simple model. The simple form of the glucose-insulin regulatory system to be studied is as follows [8].

$$0 = -b_1 G_b + b_4 I_b G_b + b_7, \quad (1.1)$$

$$0 = -b_2 I_b + b_6 G_b \quad (1.2)$$

When (G_b, I_b) is assumed to be an equilibrium point [8]. It has been analyzed, edited and further worked in order to understand the system by Hussain J [14].

$$\dot{x} = -a_1 x - a_2 xy + a_3, \quad (1.3)$$

$$\dot{y} = b_1 x - b_2 y. \quad (1.4)$$

1.2 Objectives of the study

1. To study a mathematical model for glucose-Insulin interaction
2. To modify a new model for glucose-insulin interaction under the Insulin injection directly into a vein.
3. To create the stability theorem for this new model using a technique of Lyapunov's function

1.3 Scope of the study

1. For normal cases in human, study principle of model for glucose-insulin interaction.
2. Modify a new glucose – insulin interaction model under the insulin injection directly into a vein.
3. Lyapunov function is used to check stability of the model.
4. Numerical methods are used to analyze the behavior of models.
5. Finally, get a new theorem for stability case in this model.

1.4 Research methodology

1. Study the incidence of diabetes and related research.
2. Study the mathematical model of diabetes and the true origins of the human body.
3. Study the behavior of blood sugar - insulin with normal people.
4. Modified the model by increasing the injected insulin constant.
5. Numerical simulations are used to analyze the modified model.
6. Use graphs to analyze the new model.
7. Conclusions - reviews and suggestions

1.5 Benefits of the study

1. To know the factors and symptoms of diabetes.
2. Conceptual understanding of a system of linear differential equations and can be applied to the diabetic system
3. A new model was obtained for the glucose-insulin interaction analysis for use in the future

Chapter 2

Basic knowledge and Literature Reviews

In this chapter, it is some basis about the blood glucose-insulin, some mathematical model of the glucose - insulin metabolic regulatory system, some of the numerical analyzes are used in models and reviews of literature related to the model.

2.1 Basic knowledge about blood glucose-insulin

2.1.1 Blood Glucose Regulation

The concentration of glucose is regulated by the interaction of the pancreatic endocrine hormone's insulin and glucagon, which is roughly described as β-cells and α-cells, which are both activated by some factors causing insulin and glucagon to be secreted respectively. Both cells are scattered in the pancreas called Islets of Langerhans [11].

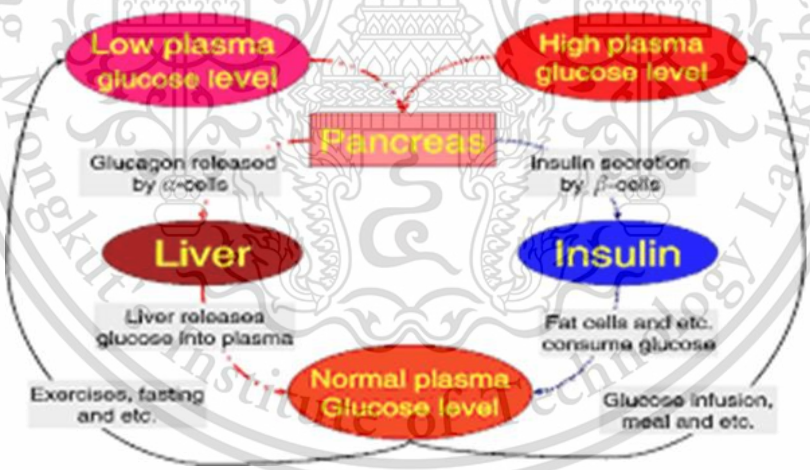

Figure 2.1 Physiological glucose-insulin regulatory system [11].

There are 2 cases to explain, 1st when blood sugar levels are raised, and another low plasma glucose level has occurred. When blood sugar levels are raised, pancreas in human body will use β cells and β cells are stimulated to secrete insulin. This insulin shall be regulated for resulting in higher than normal blood sugar concentrations level. After the process, normal plasma glucose level, the liver and other cells (e.g., muscle) can be excessive absorption. The second case, a low sugar levels is taken. Pancreas will use α-cells to stimulate the releasing glucagon hormone by acting in the liver cells and causing glucose to spread into a vein. The blood of normal people range is 70–110 mg/dl. Normally, a person has a problem with the level of glucose that can occur for 2 reasons, namely hyperglycemia or hypoglycemia. Diabetes is a disease of the glucose-insulin regulating system, which is called hyperglycemia (See Figure 2.1 for plasma glucose-insulin interaction loops.) [11]

2.1.2 Nonlinear systems and Linearization

We will be only interested in nonlinear systems, for example:

$$\frac{dx}{dt} = \sin x$$

$$\frac{dx}{dt} = -0.15y + 0.5xy \tag{2.1}$$

are nonlinear systems.

We are always able to find an explicit solution of the linear system for the form given the general autonomous linear system of two first-order equations.

2.1.3 Equilibrium Points

An equilibrium of a dynamical system is a value of the state variables where the state variables do not change. In other words, an equilibrium is a solution that does not change with time. This means if the systems start at an equilibrium, the state will remain at the equilibrium forever. In a discrete dynamical system, such as

$$x_{n+1} = f(x_n) \tag{2.2}$$

(in function iteration form) or

$$x_{n+1} - x_n = g(x_n) \tag{2.3}$$

(in difference form), one can fine the equilibria by substituting in the same quantity for x_n and x_{n+1}, such as substituting $x_{n+1} = x_n = E$. One must then solve the equation

$$E = f(E) \tag{2.4}$$

or

$$0 = g(E) \tag{2.5}$$

to determine the values E such that $x_n = E$ is an equilibrium of the dynamical system. In a continuous dynamical system, such as

$$\frac{dx}{dt} = f(x), \tag{2.6}$$

one can fine the equilibrium by setting $\frac{dx}{dt} = 0$. One must then solve the equation

$$0 = f(E) \tag{2.7}$$

to determine values E such that $x(t) = E$ is an equilibrium of the dynamical system.

2.1.4 Linearization

If f is a function of a single variable x and differentiable at x_1, then an equation of the tangent line to the graph at $(x_1, f(x_1))$ is

$$y = f(x_1) + f'(x_1)(x - x_1), \tag{2.8}$$

The tangent line, which we write as

$$L(x) = f(x_1) + f'(x_1)(x - x_1) \tag{2.9}$$

is said to be a linearization of f and x_1. When x is close to x_1 and the tangent line is close to the graph of f, we can approximate the functional value $f(x)$ using the corresponding y coordinate on the tangent line. We say that $f(x) \approx L(x)$ is a local linear approximation of $f(x)$. Similarly, if is a function of two variables x and y that has continuous first partial derivatives in a neighborhood of (x_1, y_1), then using an equations of the tangent plane at $(x_1, y_1, f, (x_1, y_1))$, the linearization of f at (x_1, y_1) is

$$L(x, y) = f(x_1, y_1) + f_x(x_1, y_1)(x - x_1) + f_y(x_1, y_1)(y - y_1) \tag{2.10}$$

Where f_x and f_y denote the first partial derivatives. Thus when (x, y) is close to (x_1, y_1),

$$f(x, y) \approx L(x, y) \tag{2.11}$$

is a local linear approximation of $f(x, y)$

Definition: Assume that $f_y(x, y)$ and $f_2(x, y)$ are functions of the independent variables x and y we got Jacobian matrix $J(x, y)$ followed by:

$$\begin{bmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{bmatrix} \quad (2.12)$$

2.1.5 Lyapunov's Function

A Lyapunov's function is commonly used to prove the stability of the equilibrium point, which is a scalar function defined on the phase space. The Lyapunov method was applied to study the stability of differential equations and systems. Below, we restrict ourselves to the autonomous systems

$$\dot{X} = f(x) \ or \ \frac{dx_i}{dt} = f_i(x_1, x_2, \dots, x_n), \quad i = 1,2, \dots, n; \quad (2.13)$$

With the equilibrium $X \equiv 0$

We assume that we can get the differential function continuously.

$$V(x) = V(x_1, x_2, \dots, x_n), \quad (2.14)$$

Example $$V(x_1, y_2) = ax_1^2 + bx_2^4 \ , a, b > 0 \quad (2.15)$$

We fine the total derivative of the function $V(x)$ with respect to time t:

$$\frac{dV}{dt} = \frac{\partial V}{\partial x_1}\frac{dx_1}{dt} + \frac{\partial V}{\partial x_2}\frac{dx_2}{dt} + \cdots + \frac{\partial V}{\partial x_n}\frac{dx_n}{dt} \quad (2.16)$$

Given $V(x)$ is smooth function in a neighborhood U of the origin. When $V(x)$ is called Lyapunov's function for an autonomous system

$$\dot{X} = f(x), \quad (2.17)$$

If according to statements, then;

1. $V(X) > 0 \ for \ all \ X \ \in U\{0\}$;
2. $V(0) = 0$;
3. $\frac{dv}{dt} \leq 0 \ for \ all \ X \ \in U$.

2.1.6 Stability Theorems

Stability theorem in terms of Lyapunov. If in a neighborhood U of a zero solution $X = 0$ of an autonomous system there is a Lyapunov function $V(x)$, then the equilibrium points $X = 0$ of the system is Lyapunov stable.

Theorem on asymptotic stability.

If in a neighborhood U of a zero solution $X = 0$ of an autonomous system, there is a Lyapunov function $V(x)$ with a negative definite derivative $\frac{dV}{dt} < 0$ for all $X \in U\{0\}$, then the equilibrium point $X = 0$ of the system is asymptotically stable.

As it can be seen, the total derivative $\frac{dV}{dt}$ must be strictly negative (negative definite) in a neighborhood of the origin for the asymptotic stability of a zero solution.

2.2 Literature Reviews

In 1939, Himsworth and Ker studied the type of diabetes. There are two types of diabetes: insulin-sensitive and non-insulin-sensitive. A mathematical model was created to study and simulate glucose-insulin for the first time

In 1965, Ackerman and Gatewood discovered a mathematical model. It's a simple linear model. That was developed for the blood sugar control system, the test was performed by the oral glucose tolerance test and Intravenous glucose tolerance test. The model presents a large physiological control system. Which has been used in a variety of applications and has been successfully developed into a simulate dynamics with more complexity.

In 2000, Gaetano and Arino created a mathematical model of the glucose-insulin interaction. Based on the intravenous glucose tolerance test (IVGTT) in normal people without disease.

In 2014, Hussain and Zadeng, A mathematical model of the glucose-insulin interaction was tested for stability by Lyapunov's function and the results were analyzed by numerical methodology.

In this study, the mathematical model of the glucose-insulin system was modified by adding a new variable to the equation: the rate constant of insulin injection when glucose concentration is high in the case that the patient is a normal person without disease. The meal is consumed which is described as shown in **Figure** 2.2. When we consume food through digestive

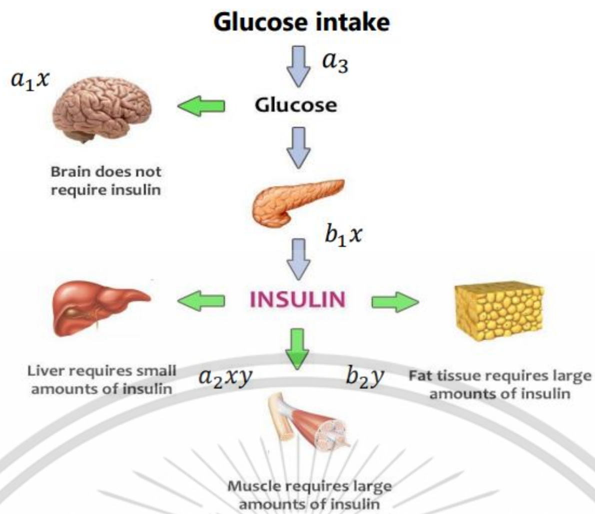

Figure 2.2: Biological behavior of the glucose–insulin metabolism in the body system[11].

The description of the biological behavior of the glucose – insulin metabolism in the body is starting to take glucose in the body while we consume food through the digestive system. It is digested into glucose at the rate of a_3, the brain can absorb glucose to use without insulin as an intermediary, resulting in a_1x rate. The pancreas is stimulated to produce insulin by the remaining glucose at the rate of b_1x. Fat cells and muscle cells use insulin as a intermediary for glucose uptake at the a_2xy rate. Residual insulin is eliminated by the liver at the rate of b_2y. Finally, a simulation of intravenous insulin at the rate of a_4y was performed. The model describes in **Figure** 2.2.

We get the system equation as follows.

$$\dot{x} = -a_1x - a_2xy + a_3 + a_4y, \tag{2.18}$$

$$\dot{y} = b_1x - b_2y \tag{2.19}$$

When $\dot{x}$ and $\dot{y}$ is glucose and insulin concentration in the body at time t respectively.

a_1 is represented by insulin independent with glucose disappearance, the rate of constant.

a_2 is represented by insulin dependent on glucose disappearance

a_3 is the glucose infusion rate after meal

a_4 is represented by intravenous insulin injection when glucose concentration is high, the rate of constant.

b_1 is represented by insulin production due to glucose stimulation, the rate of constant.

b_2 is represented by insulin degradation, the rate of constant.

A new mathematical system model of human glucose regulation is (2.18) and (2.19). Mathematical methods are used to find the equilibrium point of the model. After that finding the stability of the model by differential equation system technique, we can get a new theorem. The simulation was done by constructing the Lyapunov's function to prove the condition. Stability is described in the next chapter.

Chapter 3

Research Methodology

The research operation has the following steps: finding the equilibrium point of our model and the model's stability analysis are detailed below.

3.1 Equilibrium points

Find the equilibrium point from equations (2.18) and (2.19). Performing the nonlinear differential equations of the mathematical model equal to zero, $x = 0$ and $y = 0$. The glucose and insulin concentrations are obtained as follows:

Consider

$$\dot{x} = 0 \rightarrow -a_1x - a_2xy + a_3 + a_4y = 0, \quad (3.1)$$

$$\dot{y} = 0 \rightarrow b_1x - b_2y \qquad = 0 \quad (3.2)$$

The equilibrium point (x^*, y^*) exists for the above model. In equation (3.1),(3.2) is solved by following :

Finding x^* from (3.2) we will get: $y = \frac{b_1x}{b_2}$

Replace y back in (3.1) we will get;

$$\begin{aligned} 0 &= -a_1x - a_2x\left(\frac{b_1x}{b_2}\right) + a_3 + a_4\left(\frac{b_1x}{b_2}\right), \\ &= -a_1b_2x - a_2b_1x^2 + a_3b_2 + a_4b_1x, \\ &= -a_2b_1x^2 + (-a_1b_2 + a_4b_1)x + a_3b_2 \end{aligned} \quad (3.3)$$

finding solutions from $x^* = \frac{-b \pm \sqrt{b^2-4ac}}{2a}$ we got:

$$x^* = \frac{-a_1b_2 + a_4b_1 + \sqrt{(a_1b_2 - a_4b_1)^2 + 4(a_2b_1a_3b_2)}}{2a_2b_1} \quad (3.4)$$

Finding y^* from (3.2) we will get: $x = \frac{b_2y}{b_1}$

Replace x back in (3.1) we will get:

$$\begin{aligned} 0 &= -a_1\left(\frac{b_2y}{b_1}\right) - a_2y\left(\frac{b_2y}{b_1}\right) + a_3 + a_4y, \\ &= -a_1b_2y - a_2b_2y^2 + a_3b_1 + a_4b_1y, \end{aligned} \quad (3.5)$$

$$= -a_2 b_2 y^2 + (-a_1 b_2 + a_4 b_1) y + a_3 b_1$$

finding solutions from $y^* = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$ we got:

$$y^* = \frac{-a_1 b_2 + a_4 b_1 + \sqrt{(a_1 b_2 - a_4 b_1)^2 + 4(a_2 b_2 a_3 b_1)}}{2 a_2 b_2} \tag{3.6}$$

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

3.2 Linearization

Consider the Jacobian matrix of (3.18),(3.19) given by

$$J = \begin{bmatrix} -a_1 - a_2 y & -a_2 x + a_4 \\ b_1 & -b_2 \end{bmatrix}, \tag{3.7}$$

At (x^*, y^*) following :

$$J = \begin{bmatrix} -a_1 - a_2 y^* & -a_2 x^* + a_4 \\ b_1 & -b_2 \end{bmatrix} \tag{3.8}$$

Let $x = X + x^*, y = Y + y^*$ be the transformation and then derive linear system. Therefore, we get the following linear equation:

$$\dot{X} = -a_1 X - a_2 y^* X - a_2 x^* Y + a_4 Y, \tag{3.9}$$

$$\dot{Y} = b_1 X - b_2 Y \tag{3.10}$$

3.3 Stability Analysis

Theorem1: The interior-equilibrium point (x^*, y^*) is locally asymptotically stable of (3.9) , (3.10) if

$$(b_1 + a_4 - a_2 x^*)^2 < 4 b_2 (a_1 + a_2 y^*) \tag{3.11}$$

Proof: Consider the Lyapunov's function

$$V = \frac{1}{2}(x^2 + y^2) \tag{3.12}$$

Let (x^{*}, y^{*}) be the internal equilibrium point. We found the total derivative of the function $V(x, y)$

$$\dot{V} = V_x + V_y \tag{3.13}$$

we will have

$$V_x = \left(\frac{\partial v}{\partial x}\right) \cdot \frac{dx}{dt} = \nabla V \cdot f(x) = -a_1 X^2 - a_2 y^{*} X^2 - a_2 x^{*} XY + a_4 XY, \tag{3.14}$$

and

$$V_y = \left(\frac{\partial v}{\partial y}\right) \cdot \frac{dy}{dt} = \nabla V \cdot f(y) = b_1 XY - b_2 y^2, \tag{3.15}$$

thus,

$$\begin{aligned} \dot{V} &= -(a_1 + a_2 y^{*})X^2 + (b_1 + a_4 - a_2 x^{*})XY - b_2 Y^2, \\ &= -\frac{1}{2}AX^2 + BXY - \frac{1}{2}CY^2 \end{aligned} \tag{3.16}$$

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

According to the asymptomatic local stability theorem, if the function $V(x, y)$ is always positive and $\dot{V}(x, y)$ is always negative. From Equation (3.14) we get that :

$$B^2 - AC < 0$$

then

$$B^2 < AC$$

thus,

$$(b_1 + a_4 - a_2 x^{*})^2 < 4b_2(a_1 + a_2 y^{*}) \tag{3.17}$$

If such conditions are met, the internal equilibrium point (x^{*}, y^{*}) is locally asymptotically stable. The glucose-insulin interaction model was concluded to have intrinsic stability of the equilibrium point. This corresponds to the definition of the Lyapunov's function. Numerical methods are used to check stability conditions, resulting in a graph which is described in the next chapter.

Chapter 4

Simulations and Discussion

According to the analysis, it was found that the stability of the glucose – insulin interaction model was subject to conditions (3.17).

4.1 Numerical Simulation

Parameters were summarized in the following table1. The parameters for those who can show that dynamic models create solutions are consistent with the data collected by their experiment. We fit the information based on table 1 and found that it is well compatible with the conditions for existence and stability of the internal balance [8].

Table 1 : Dynamical results [8].

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

Taking the data of their first subject:

Table 2 : Parameter setting

Parameters	a_1	a_2	a_3	a_4	b_1	b_2
Value	0.0226	3.80e – 08	3.842	- 0.065	0.0022	0.0437

Considering equation (3.4) and (3.6) we get equilibriums point (x^*, y^*), in which value.

$$x^* = \frac{-a_1 b_2 + a_4 b_1 + \sqrt{(a_1 b_2 - a_4 b_1)^2 + 4(a_2 b_1 a_3 b_2)}}{2a_2 b_1} = 148.4969$$

and

$$y^* = \frac{-a_1 b_2 + a_4 b_1 + \sqrt{(a_1 b_2 - a_4 b_1)^2 + 4(a_2 b_2 a_3 b_1)}}{2a_2 b_2} = 7.4758$$

Therefore, $x^* = 148.4969$ and $y^* = 7.4758$

From theorem 1, it can be seen that ; $(b_1 + a_4 - a_2 x^*)^2 < 4b_2(a_1 + a_2 y^*)$

$$0.0039 < 0.0040$$

Since, the values are reversed, the condition is fulfilled according to theorem1, the equilibrium point (x^*, y^*) is locally asymptotically stable. The glucose-insulin interaction which follows this new dynamic model can be done. In the body of a normal person when food enters the body processes in the body take carbohydrates to digest 1-2 hours after eating. This causes the sugar level in the body to rise after eating for at least 2 hours. The post-meal glucose concentration curve was simulated by Table 1, showing that after 1-2 hours of eating, the glucose concentration rose to 170 mg/dl as shown in **Figure** 4.1.

Table 3: Showing of increased glucose concentrations after meals at different times (step 30).

Time (x) mins.	0	30	60	90	120	150	200	230	260
Glucose (y) mg/dl.	0	86	128	149	160	165	170	≈170	≈170

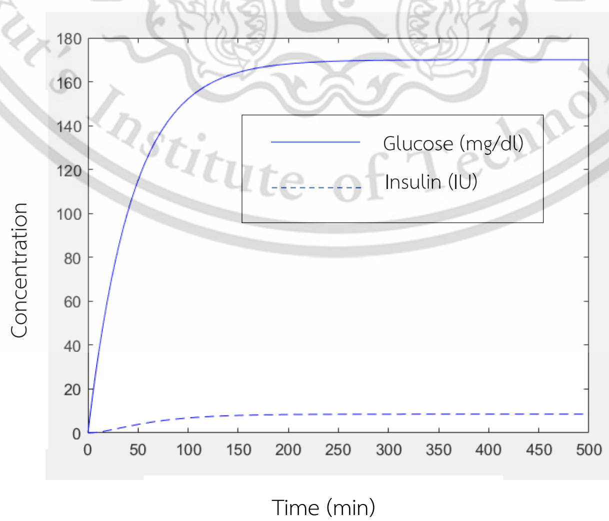

Figure 4.1: Simulation of glucose – insulin function after meal with parameters in Table 2.

Time axis in Figure 4.1, Table3 is shown step 30 up for the values of glucose concentration after eating foods. This confirms the reasons after eating at least an hour, high glucose concentration level occurs.

Also, graphs are generated for two different values of a_4 is a constant rate, which represents an intravenous of insulin. Considered at a_4 = - 0.065 the curve for glucose concentration was shown to peak to 148.4969 mg/dl shown in **Figure** 4.2 and glucose concentration was reduced to 69.43 mg/dl when a_4 = - 0.6567 shown in **Figure** 4.3. This indicated that insulin is important for the metabolism of the regulatory process of glucose level in the human.

Table 4: Glucose concentrations with insulin injections at a_4 = -0.065.

Time (x) mins.	0	30	60	90	120	150	200	230	260
Glucose (y) mg/dl	0	86	120	137	144	147	148	≈148.50	≈148.50

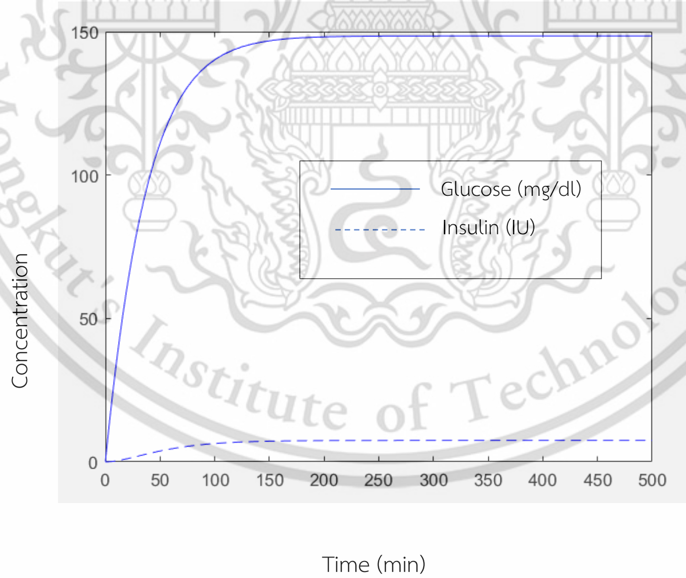

Figure 4.2: Simulation of Glucose – Insulin function after receiving meal with a_4 = - 0.065.

Table 5: Glucose concentrations with insulin injections at a_4 = -0.6567.

Time (x) mins.	0	30	60	90	120	150	200	230	260
Glucose (y) mg/dl	0	72	79	72	68	69	69.4	≈69.43	≈69.43

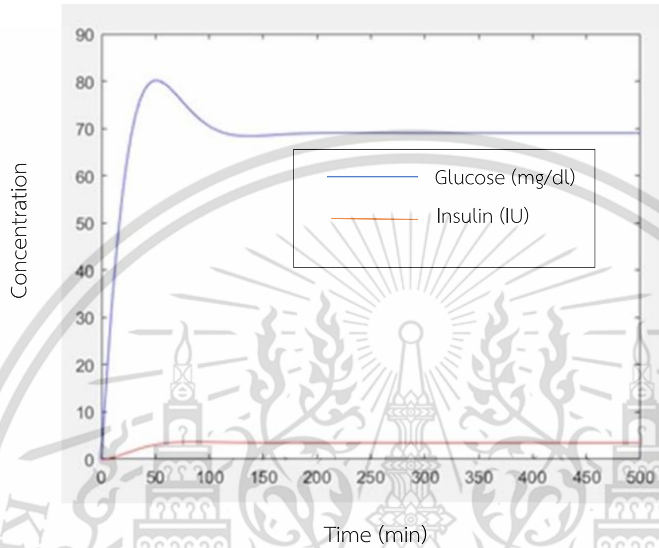

Figure 4.3: Simulation of glucose – insulin function after receiving meal with a_4 = - 0.6567.

Chapter 5

Conclusions

The content of this chapter is a summary of research findings and recommendations, which has the following details.

5.1 Conclusions

Dynamic modeling of the glucose-insulin interaction was developed based on research by Hussain J [14], adding the insulin injection factor to the original equation. Therefore, the equation is nonlinear a new equation system model is (2.18) and (2.19). We converted (2.18) and (2.19) to a linear equation based on equations (3.7) and (3.8). Then, we used the Lyapunov function for analyzing the stability with the conditions with having Theorem 1, and used numerical simulations to test the conditions in Theorem 1 results in conditions hypothesized in the theorem are accurate. Therefore, the glucose-insulin reaction equation is stable.

The model constructed using a linear differential equation showing the importance of insulin to glucose breakdown is represented by simulated curves of two different a_4 values, where a_4 is the insulin infusion constant at a_4 = -0.065, the glucose concentration was as high as 148 mg/dl, and at a_4 = -0.6567, we found that it reduced the glucose level to 69 mg/dl. Insulin plays a role in normalizing the concentration of glucose in the body. The study concluded that this new glucose-insulin model is physiologically consistent. Finally, this study could be helpful for further diabetes research. In the body of a normal person when food enters the body processes in the body take carbohydrates to digest 1-2 hours after eating. This causes the sugar level in the body to rise after eating for nearly 2 hours.

5.2 Suggestion

In this work we shown a solution using the Lyapunov function $V = \frac{1}{2}(x^2 + y^2)$ to determine the stability condition and use all three numerical cases to simulate solution of the glucose-insulin equation system model. Its other researchers are interested, you can improve other models, adding effective terms of co-glucose-insulin or taking time delay. Or using another numerical method to simulate and comparison

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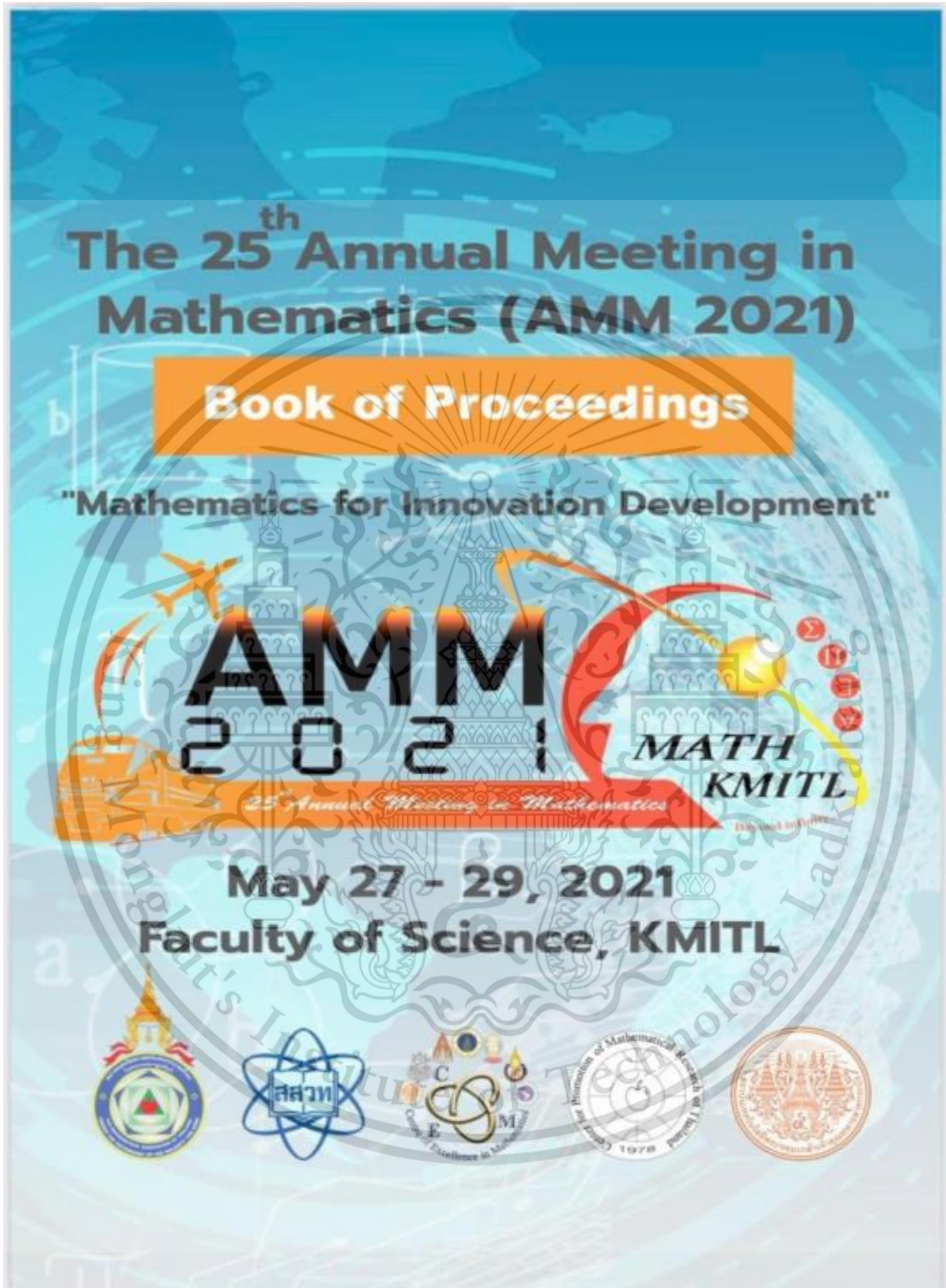
Appendix

Appendix A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ตัวแบบเชิงคณิตศาสตร์สำหรับระดับน้ำตาลกลูโคสในมนุษย์

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กรุงเทพมหานคร 10520

บทคัดย่อ

งานวิจัยนี้นำเสนอแบบจำลองเชิงคณิตศาสตร์ของโรคเบาหวาน ที่แสดงเกี่ยวกับกระบวนการเผาผลาญกลูโคสในร่างกายที่สัมพันธ์กับฮอร์โมนอินซูลินในตับอ่อน งานวิจัยนี้จะพิจารณาการสลายของน้ำตาลกลูโคสเนื่องจากการฉีดอินซูลินเข้าไปในหลอดเลือดดำโดยตรง และพิจารณาการสลายของน้ำตาลกลูโคสเนื่องจากการดูดซึมของเนื้อเยื่อ เช่น สมอง และ เซลล์ประสาท และระดับของกลูโคสที่เพิ่มขึ้นมาจากการรับประทานอาหาร และ ทานกลูโคสโดยตรง จากลักษณะการทำงานนี้ สามารถสรุปเป็นแบบจำลองทางคณิตศาสตร์ของระบบการทำงานของกลูโคส จากนั้นใช้การวิเคราะห์ด้วยทฤษฎีบททางคณิตศาสตร์โดยระเบียบวิธีเลียปูนอฟที่มีเงื่อนไขและกรณีเป็นไปตามเสถียรภาพเฉพาะที่กับกับ สุดท้ายใช้วิธีเชิงตัวเลขร่วมกับการนำเสนอด้วยกราฟเพื่อยืนยันผลการวิเคราะห์ที่สรุปชัดแจ้งเกี่ยวกับบทบาทการทำงานของอินซูลินในกระบวนการควบคุมระดับน้ำตาลในร่างกายมนุษย์

คำสำคัญ: โรคเบาหวาน , กลูโคส-อินซูลิน , ความเสถียรภาพ , เลียปูนอฟ

1 บทนำ

โรคเบาหวานเป็นโรคที่เกี่ยวข้องกับความผิดปกติของระบบการเผาผลาญในร่างกาย มักมีสาเหตุมาจากพันธุกรรมและสิ่งแวดล้อม ผู้ป่วยที่เป็นโรคเบาหวานจะมีปัญหาที่ร่างกายไม่สามารถผลิตฮอร์โมนอินซูลินได้เอง จึงทำให้เกิดภาวะที่ส่งผลให้ระดับน้ำตาลในเลือดสูงขึ้นผิดปกติ ที่เรามักจะเรียกว่า "ไฮเพอร์ไกลซีเมีย" โดยความเข้มข้นของกลูโคสในเลือดของคนปกติจะอยู่ในช่วง 70 - 110 มิลลิกรัม/เดซิลิตร เมื่อไม่ได้รับประทานอาหารเป็นเวลานาน (อดอาหารประมาณ 12 ชม.) เช่นเดียวกับระดับความเข้มข้นของอินซูลินเมื่ออดอาหารความเข้มข้นอยู่ในช่วง 5-10 ไมโครยูนิต/มิลลิลิตร ระดับน้ำตาลกลูโคสในเลือดจะถูกควบคุมโดยการทำงานร่วมกันของฮอร์โมนกลูคากอนและฮอร์โมนอินซูลินที่ถูกผลิตในตับอ่อน

โรคเบาหวานก่อให้เกิดภาวะแทรกซ้อนมากมาย เช่น จอประสาทตา , โรคไต และ ตาบอด ผู้ป่วยที่เป็นโรคเบาหวานมีจำนวนเพิ่มขึ้นทุกปี และคาดว่าจำนวนผู้ป่วยโรคนี้จะเพิ่มขึ้นสูงถึง 592 ล้านคนทั่วโลกภายในปี 2035 อ้างอิงจากเว็ปไซต์ (http://www.idf.org) เนื่องด้วยเหตุนี้ทำให้นักวิจัยหลายคนสนใจศึกษาเกี่ยวกับแบบจำลองเชิงคณิตศาสตร์เพื่อทำความเข้าใจและทำนายพฤติกรรมทางชีวภาพของการควบคุมการเผาผลาญกลูโคส-อินซูลิน รูปแบบการทดลองที่ใช้ในการศึกษาโรคเบาหวานคือการทดสอบความทนทานต่อกลูโคสทางหลอดเลือดดำ(IVGTT) โดย Gaetano and Arino ได้นำเสนอแบบจำลองอย่างง่ายขึ้นมาเรียกว่า แบบจำลองไดนามิก
\indent\indent การสร้างแบบจำลองกลูโคส – อินซูลินกลายเป็นหัวข้อที่น่าสนใจและมีแบบจำลองหลากหลาย เป้าหมายของแบบจำลองต่างๆเพื่อทำความเข้าใจการทำงานร่วมกันของกลูโคส-อินซูลินและสามารถตรวจสอบความ

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เป็นไปได้ของการเป็นโรคเบาหวาน ตลอดจนการหาวิธีที่ดีกว่าในการรักษาด้วยอินซูลิน โดย Makroglo ได้ทำการศึกษาและนำเสนอแบบจำลองเหล่านี้ และถูกนำมาวิจารณ์โดย Boutayed and Chetouni

2 ความรู้พื้นฐาน

ความรู้พื้นฐานที่ใช้นำมาจาก [4],[7],[10]

2.1 งานวิจัยที่เกี่ยวข้อง

2.1.1 การทำงานร่วมกันของกลูโคสและอินซูลิน

ระดับความเข้มข้นของน้ำตาลกลูโคสในเลือดของคนปกติอยู่ในช่วง 70 – 110 mg/dl ปัจจัยภายนอกที่มีผลต่อระดับความเข้มข้นของกลูโคสในเลือด ได้แก่ การบริโภคอาหาร , อัตราการย่อยอาหาร และ การออกกำลังกาย ฮอร์โมนอินซูลินและกลูคากอนถูกผลิตจากเบต้าเซลล์ และ แอลฟาเซลล์ ที่อยู่ในตับอ่อนตามลำดับ
มีหน้าที่ในการตรวจวัดระดับความเข้มข้นของกลูโคส เมื่อกลูโคสมีระดับความเข้มข้นสูงขึ้น เบต้าเซลล์จะถูกกระตุ้นให้หลั่งอินซูลินออกมา เพื่อให้กลูโคสส่วนเกินสามารถถูกดูดซึมไปยังตับและเซลล์ต่างๆเมื่อระดับความเข้มข้นของกลูโคสต่ำลงมาก แอลฟาเซลล์จะถูกกระตุ้นให้กลูคากอนทำงาน โดยไปกระตุ้นให้ตับผลิตกลูโคสทำให้ความเข้มข้นของกลูโคสในเลือดเพิ่มขึ้นเป็นไปตาม รูปภาพที่ 1

รูปภาพที่ 1. ลักษณะทางกายภาพระบบการทำงานของกลูโคส-อินซูลิน ,Makroglou A (2006) [7]

2.1.2 แบบจำลองเดิม

จากการวิจัยของ Andrea De Gaetano [4] การศึกษาแบบจำลองพลวัตของระบบกลูโคส - อินซูลินเป็นดังนี้

$$0 = -b_1G_b + b_4I_bG_b + b_7 \text{ และ } 0 = -b_2I_b + b_6G_b$$

ในความเป็นจริงสมมติว่าวัตถุอยู่ในสภาวะสมดุลที่ (G_b, I_b) [4]. จากสมการข้างต้นได้รับการวิเคราะห์แก้ไขและศึกษาเพิ่มเติมเพื่อทำความเข้าใจระบบโดย Hussain J [10].

2.2 แบบจำลองเชิงคณิตศาสตร์ของกลูโคสอินซูลิน

ในงานวิจัยนี้ เรานำเสนอแบบจำลองทั่วไปของการทำงานร่วมกันของกลูโคส-อินซูลิน เป็นไปตามสมการดังต่อไปนี้

$$\dot{x} = -a_1x - a_2xy + a_3 + a_4y \quad (2.1)$$

$$\dot{y} = b_1x - b_2 \quad (2.2)$$

เมื่อ $x, y \geq 0$

x คือ ความเข้มข้นของกลูโคส

y คือ ความเข้มข้นของอินซูลิน

a_1 คือ อัตราค่าคงที่ของอินซูลินที่ไม่แปรผันตามกลูโคสที่สลายไป

a_2 คือ อัตราค่าคงที่ของอินซูลินที่แปรผันตามกลูโคสที่หายไป

a_3 คือ อัตราความเข้มข้นของกลูโคสหลังจากบริโภค

a_4 คือ อัตราการฉีดอินซูลินหลังจากบริโภค

b_1 คือ อัตราค่าคงที่ของอินซูลินที่ถูกผลิตขึ้นเนื่องจากกลูโคส

b_2 คือ อัตราค่าคงที่การย่อยสลายของอินซูลิน

2.3 ระเบียบวิธีดำเนินการ

2.3.1 จุดดุลยภาพ

พิจารณา

$$\dot{x} = 0 \Rightarrow -a_1x - a_2xy + a_3 + a_4y = 0 \qquad (2.3)$$

$$\dot{y} = 0 \Rightarrow b_1x - b_2y = 0 \qquad (2.4)$$

กำหนดให้จุดดุลยภาพคือจากสมการ (2.1)(2.2) จะได้ว่า

$$x^* = \frac{-a_1b_2 + a_4b_1 + \sqrt{(a_1b_2 - a_4b_1)^2 + 4(a_2b_1a_3b_2)}}{2a_2b_1} \qquad (2.5)$$

$$y^* = \frac{-a_1b_2 + a_4b_1 + \sqrt{(a_1b_2 - a_4b_1)^2 + 4(a_2b_2a_3b_1)}}{2a_2b_2} \qquad (2.6)$$

2.3.2 การทำให้เป็นระบบเชิงเส้น

พิจารณาจากเมทริกซ์จาโคเบียนของสมการ (2.1),(2.2) ดังนี้

$$J = \begin{pmatrix} -a_1 - a_2y & -a_2x + a_4 \\ b_1 & -b_2 \end{pmatrix}$$

ที่จุด (x^*, y^*) จะได้ว่า

$$J^* = \begin{pmatrix} -a_1 - a_2y^* & -a_2x^* + a_4 \\ b_1 & -b_2 \end{pmatrix}$$

เนื่องจากการแปลง กำหนดให้ $x = X + x^*, y = Y + y^*$ สามารถทำให้เป็นระบบสมการเชิงเส้นได้ดังต่อไปนี้:

$$\begin{pmatrix} \dot{X} \\ \dot{Y} \end{pmatrix} = J^* \begin{pmatrix} X \\ Y \end{pmatrix} = \begin{pmatrix} -a_1 - a_2y^* & -a_2x^* + a_4 \\ b_1 & -b_2 \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}$$

ดังนั้นจะได้ระบบสมการดังนี้:

$$\dot{X} = -a_1X - a_2y^*X - a_2x^* + a_4Y \qquad (2.7)$$

$$\dot{Y} = b_1X - b_2Y \qquad (2.8)$$

2.3.3 การวิเคราะห์ความเสถียรภาพ

ทฤษฎีบท 1: จุดดุลยภาพภายใน (x^*,y^*) เป็นเสถียรภาพเฉพาะที่กำกับ(locally asymptotical stable) ถ้า

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

พิสูจน์ : จากฟังก์ชันเลียปูนอฟ

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

กำหนดให้ (x^*,y^*) เป็นเสถียรภาพเฉพาะที่กำกับ (Locally asymptotical stable)

พิจารณา $$\dot{V} = V_x + V_y$$

จะได้ว่า $$V_x = \left(\frac{dv}{dx}\right) f(x) = -a_1X^2 - a_2y^*X^2 - a_2x^*XY + a_4XY$$

และ $$V_y = \left(\frac{dv}{dy}\right) f(y) = b_1XY - b_2y^2$$

ดังนั้นจะได้

$$\dot{V} = -(a_1 + a_2y^*)X^2 + (b_1 + a_4 - a_2x^*)XY - b_2Y^2$$
$$= -\frac{1}{2}AX^2 + BXY - \frac{1}{2}CY^2$$

เมื่อ $A = 2(a_1 + a_2y^*)$, $B = b_1 + a_4 - a_2x^*$, $C = 2b_2$

จากทฤษฎีบทความเสถียรภาพเลียปูนอฟ (x^*,y^*) เป็นเสถียรภาพเฉพาะที่กำกับแล้ว $\dot{V}(x,y)$ เป็นค่าลบเสมอ

จะได้ว่า พิจารณาเฉพาะกรณี $B^2 - AC < 0$

ดังนั้น

$$B^2 < AC$$

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

3 ผลการศึกษา

3.1 การจำลองเชิงตัวเลข

ในการทดลองทางคลินิกของ Gaetano [4] มาจากอาสาสมัครที่มีสุขภาพดีจำนวน 10 คน เป็นผู้ชาย 5 คน และเป็นผู้หญิง 5 คน โดยครอบครัวและผู้เข้าร่วมทดลองไม่มีประวัติการเป็นโรคเบาหวาน ค่าพารามิเตอร์สำหรับการแสดงว่าแบบจำลองไดนามิกที่เหมาะสมกับข้อมูลได้มาจากข้อมูลในตารางที่ 1 ที่ปรากฏในงานวิจัย[4] และพบว่าข้อมูลที่ได้เป็นไปตามเงื่อนไขสำหรับเสถียรภาพของจุดสมดุลภายในโดยค่าพารามิเตอร์ได้มาจากข้อมูลของอาสาสมัครรายแรก ดังนี้:

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

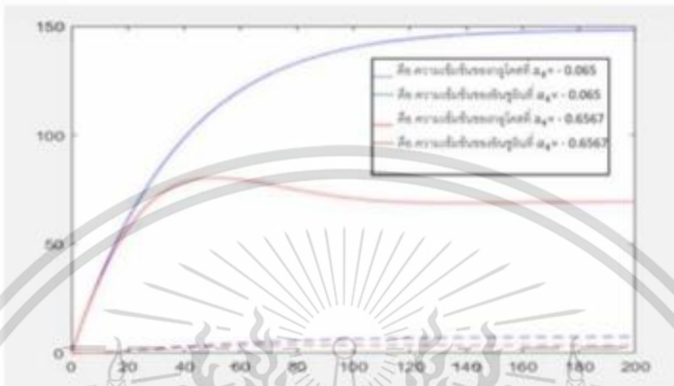
ดังนั้นจะได้ $x^* = 148.4969$ และ $y^* = 7.4758$

โดยเงื่อนไข local stability ที่ (x^*,y^*) เป็นไปตาม

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

จะเห็นว่าได้ว่า $0.0039 < 0.0040$ ซึ่งเป็นไปตามทฤษฎีบทที่ 1 นั้นคือจุดดุลยภาพภายใน (x^*,y^*) เป็นเสถียรภาพเฉพาะที่กำกับ(Locally asymptotical stable)

ดังนั้นจะได้กราฟที่สร้างจากค่าที่แตกต่างกัน 2 ค่า ของ a_4 คือ อัตราการฉีดอินซูลินหลังจากบริโภค จะได้ว่าเมื่อ a_4 = -0.065 ความเข้มข้นของกลูโคสมีระดับสูงถึง 148.4969 มิลลิกรัม/เดซิลิตร และลดลงมาอยู่ที่ 69.43 มิลลิกรัม/เดซิลิตร เมื่อ a_4 = -0.6567 นั้นแสดงว่าอินซูลินเป็นตัวช่วยลดระดับกลูโคสในร่างกาย ซึ่งมีความสำคัญต่อกระบวนการควบคุมระดับกลูโคสในร่างกาย



รูปภาพที่ 2 : ระดับความเข้มข้นของกลูโคสเมื่อ a_4 = -0.065 (กราฟ : เส้นสีน้ำเงิน) จะเห็นว่ากลูโคสมีความเข้มข้นสูงกว่าเมื่อ a_4 = -0.6567 (กราฟ : เส้นสีแดง) , และ ความเข้มข้นของอินซูลิน (กราฟ : เส้นประ)

3.2 สรุปผลการศึกษา

ในบทความนี้ได้ทำการอธิบายและวิเคราะห์แบบจำลองทางคณิตศาสตร์เพื่อศึกษาพลวัตของกลูโคสและอินซูลินในมนุษย์ โดยใช้ระบบสมการเชิงอนุพันธ์สามัญ ซึ่งจะพิจารณาเพียงกรณีแบบสมการเชิงเส้นและได้รับการทดสอบโดยการจำลองเชิงตัวเลข การหายไปของกลูโคสถูกแสดงโดยกราฟซึ่งพิจารณาค่าที่แตกต่างกันสองค่าของ a_4 คือ อัตราการฉีดอินซูลินเข้าไปโดยตรงหลังจากการบริโภค เมื่อ a_4 มีค่า -0.065 ทำให้ระดับของกลูโคสมีค่าสูงถึง 148 ยูนิต โดยประมาณ และเมื่อ a_4 มีค่า -0.6567 ระดับของกลูโคสลดต่ำลงที่ 69 ยูนิต โดยประมาณ ซึ่งบ่งชี้ว่าอินซูลินมีบทบาทในการทำให้ความเข้มข้นของกลูโคสในร่างกายมนุษย์กลับมาเป็นปกติในการใช้วิธีการเลียปูนอฟเพื่อวิเคราะห์ความเสถียรภาพ จากผลลัพธ์ข้างต้นเราสรุปได้ว่า แบบจำลองพลวัตรมีความสอดคล้องกันทางสรีรวิทยา

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Appendix B

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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

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

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].

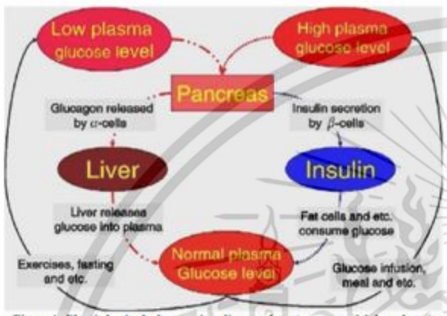

Figure1. Physiological glucose-insulin regulatory system, Makroglou A (2006) [7]

B. Mathematical Model of the Glucose-Insulin Interaction

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

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

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

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

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

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

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

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:

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

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

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The sufficient condition for 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 $\delta = min\ \{(a1 - b1), (b2 - a4)\}$

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

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 I [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.

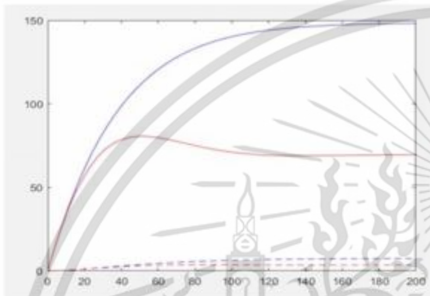

Figure 2: glucose concentration as a4 = −0.065(model: Blue line), glucose concentration as a4 = −0.6567(model: red line) and insulin concentration (model: dashed lines)

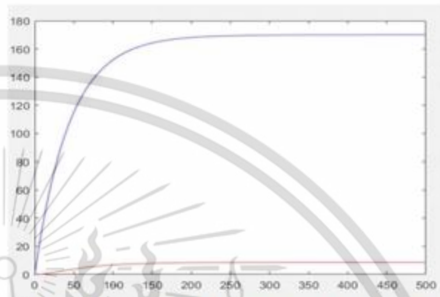

Figure 3: Glucose-insulin equilibrium after consumption with original dynamical model, Hussain J (2014) [10].

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

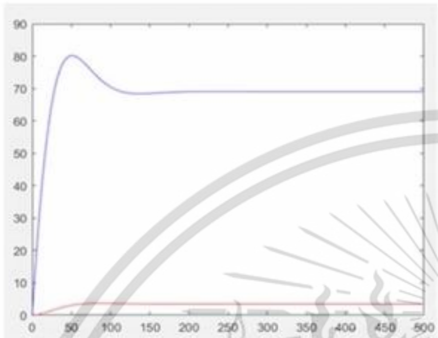

Figure 4. Glucose-insulin equilibrium after consumption with dynamical model when adding less a4 (-0.6567)

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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Academic Publication(s)

1. Nattacha Nuwaboot and Kanchana Kumnungkit. **ตัวแบบเชิงคณิตศาสตร์สำหรับระดับน้ำตาลกลูโคสในมนุษย์.** Proceeding of Annual Meeting in Mathematics 2021.(AMM 2021)
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