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MINIMAL MODEL MODIFIED OF THE DIABETES TO SIMULATE GLUCOSE AND INSULIN LEVELS

MODELO MÍNIMO MODIFICADO DE LA DIABETES PARA SIMULAR NIVELES DE GLUCOSA E INSULINA

Alejandro Duitama Leal,[1] Andrei Alain González Galeano,[2] y Javier Hernán Gil Gómez[3]

Abstract: Due to the importance that diabetes is nowadays, a disease that is worldwide nominated as a pandemic, it is necessary to study and understand from different disciplines the processes that are involved in a better identification and treatment of it. Thus the mathematical modeling of the glucose and insulin levels present in the body was done making a modification of the minimal model, to consider exogenous variations of the glucose and insulin levels. For that, the study was based on the work done by Ackerman and the minimal model, and the system of differential equations connected (SDEC) was modified in order to include a gradual exogenous increase of the glucose and insulin amount. The approximate solution of the SDEC was obtained using the Runge Kutta method of fourth order and it was compared with the reported experimental results, finding a good behavior. Based on the experimental curve, different cases were modeled where the insulin and glucose amount varies, and for each case, the group of corresponding curves was analyzed according to

1 BSc. In Physics, Universidad Nacional de Colombia, Colombia. MSc. In Geophysics, Universidad Nacional de Colombia, Colombia. Current position: professor Universidad El Bosque, Colombia. E-mail: aduitamal@unal.edu.co
2 BSc. In Mathematics, Universidad Nacional de Colombia, Colombia. MSc. In Applied Mathematics, Universidad EAFIT, Colombia. Current position: professor Universidad El Bosque, Colombia. E-mail: aagonzalez@unal.edu.co
3 BSc. In Mathematics, Universidad Pedagógica Nacional, Colombia. MSc. In Applied Mathematics, Universidad EAFIT, Colombia. Current position: profesor, Universidad El Bosque, Colombia. E-mail: Javiher26@gmail.com

the insulin and glucose amount respectively. It was found that small increases of the glucose amount causes an increase of the insulin production and this is because the body increases the insulin production to regulate it to the normal levels.

Key Words: Diabetes, Glucose, Insulin, Ackerman Model, Minimal Model.

Resumen*:* Debido a la importancia que actualmente tiene la diabetes como enfermedad que se perfila ser una pandemia a nivel mundial, se hace necesario estudiar y comprender, desde diferentes disciplinas, los procesos que se involucran para una mejor identificación y tratamiento de la misma. El presente artículo describe el modelamiento matemático de los niveles de glucosa e insulina presentes en el cuerpo basado en el trabajo de Ackerman realizando una modificación del sistema de ecuaciones diferenciales acopladas (SEDA) en el modelo mínimo incluyendo un aumento gradual exógeno para considerar variaciones exógenas de tales niveles. A partir de la curva experimental se consideraron diferentes casos, de manera que cada familia de curvas correspondiente se analizó en función de la cantidad de glucosa e insulina, respectivamente. La solución aproximada del SEDA se obtuvo usando el método de Runge Kutta de cuarto orden y se comparó con resultados experimentales reportados. Se encontró que pequeños aumentos en la cantidad de Glucosa produce un incremento en la Insulina debido a que el cuerpo aumenta su producción para regularla a niveles normales.

Palabras clave: Diabetes, Glucosa, Insulina, Modelo de Ackerman, Modelo mínimo.

1. Introduction

Diabetes mellitus (DM) is a disease that is characterized by presenting high glucose concentrations in the blood. The American Diabetes Association, classifies the Diabetes mellitus in three types: “Diabetes mellitus type 1, in which there is a total destruction of the β cells, which entails an absolute insulin deficiency; Diabetes mellitus Type 2 generated as a consequence of a progressive defect of the insulin secretion, the gestational diabetes, which is diagnosed during the pregnancy; and other types of diabetes caused by different causes. Several disruptions cause it, being the main ne the low production of the insulin hormone, secreted by the β cells. Diabetes mellitus constitutes an important cause of public health concern" [1].

Diabetes is mostly diagnosed by different types of tests; one of these is the Glucose Tolerance Test (GTT). For this test the patient goes to the hospital after a night fasting and a high dose of glucose is given. During the next three to five hours, several measurements of the glucose concentration in the patient's blood is done, and these measurements are used in the diabetes diagnose. Its model is based on the following elementary biology concepts taken from [2].

1. Glucose is fundamental in any vertebrate metabolism since it is an energy source for all the tissues and organs. There is an ideal blood glucose concentration for each individual, and any excessive deviation of this maximum concentration leads to serious pathological conditions [3] [1].

2. While the glucose levels in the blood trend to be self-regulated, they are influenced as well by a wide range of hormones, of which we will make a graphical analysis of their behavior [3] [1].

According to the former, several models have been proposed in order to modeling the behavior of the glucose and insulin, based on the parameters that are easily measured [1]. One of these is the Ackerman model that predicts with a low number of parameters the behavior of the glucose and insulin levels, but also it has the inconvenience that ignores quantities that affect directly the levels, thus the minimal model appears [1] [4] [5], which incorporates an auxiliary quantity denominated active insulin, which allows a good description of the behavior of these two levels, and that is why that this model is used as a theoretical model basis for the study done. The minimal model is expressed by the following differential equations:

$$\frac{dG(t)}{dt} = -p_1(G(t) - G_b) - X(t)G(t) + J_G \qquad G(0) = p_0 \qquad (1)$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b) \qquad X(0) = 0 \qquad (2)$$

$$\frac{dI(t)}{dt} = p_4(G(t) - p_5)t - p_6(I - I_b) + J_I \qquad I(0) = p_5 + I_b \qquad (3)$$

Where each parameter and variable included is described in Table 1 with their respective unit. It is necessary to mention that the differential equations are connected and the method that was used to model the glucose-insulin system was the Runge-Kutta of fourth order. The first equation describes the glucose G absorption and elimination. The second one expresses the active insulin levels and the third one represents the insulin.

$p_0(mg/dl)$	**Glucemia teórica en $t = 0$ después del bolo de glucosa**
$p_1(min^{-1})$	**Tasa de eliminación de la glucosa independiente de la insulina**
$p_2(min^{-1})$	**Tasa de eliminación de insulina activa (disminución de la absorción)**
$p_3(min^{-2}(\mu UI\ /ml)^{-1})$	**Incremento en la capacidad de Absorción debido a la insulina**
$p_4((\mu UI\ /ml)\ (mg/dl)^{-1}min^{-1})$	**Tasa de liberación pancreática después del bolo**
$p_5(mg/dl)$	**Glucemia objetivo del páncreas**
$p_6(min^{-1})$	**Tasa de decaimiento para la insulina en el plasma**
$p_7(\mu UI\ /ml)$	**Concentración teórica de insulina en el plasma en el tiempo $t = 0$**
$G_B(mg/dl)$	**Glucemia basal del sujeto**
$I_B(\mu UI\ /ml)$	**Insulinemia basal del sujeto**
$G(t)(mg/dl)$	**Concentración de glucosa en la sangre en el instante t**

I(t) $(\mu UI\ /ml)$	**Concentración de insulina en la sangre en el instante t**
X(t) (min^{-1})	**Insulina activa en el instante t**

Table 1. Parameters of the Simulation [1].

The parameters of the Gaussian equation $J_G(t)$ y $J_I(t)$ that represent the exogenous contributions of glucose and insulin are given the following way:

$$J_G(t) = A_G e^{-k_G(t-t_G)^2} \tag{4}$$

$$J_I(t) = A_I e^{-k_I(t-t_I)^2} \tag{5}$$

And their values are given in table 2.

$A_G(\mathrm{mg}/(\mathrm{dl}\cdot\mathrm{min}))$	50
$k_G(1/\mathrm{min})$	0.005
$t_G(\mathrm{min})$	10
$A_I\ (\mu UI\ /(ml\cdot min))$	50
$k_I(1/\mathrm{min})$	0.005
$t_I(\mathrm{min})$	12

Table 2. Parameters of the Exogenous Agents. Source: own.

According to these parameters the numerical values of the parameters worked during the simulation are given. See table 3.

$p_1(min^{-1})$	4.4488×10^{-2}
$p_2(min^{-1})$	0.8304×10^{-2}
$p_3(min^{-2}(\mu UI\ /ml)^{-1})$	3.9739×10^{-6}

$p_4((\mu UI\ /ml)\ \ (mg/dl)^{-1}min^{-1})$	4.772×10^{-3}
$p_5(mg/dl)$	8.67768×10^{1}
$p_6(min^{-1})$	3.0551×10^{-1}
$p_7(\mu UI\ /ml)$	3.9903×10^{2}
G(t)(mg/dl)	3.1986×10^{2}
I(t) $(\mu UI\ /ml)$	4.0803×10^{2}
X(t) (min^{-1})	0

Table 3. Parameters of the Simulation [1].

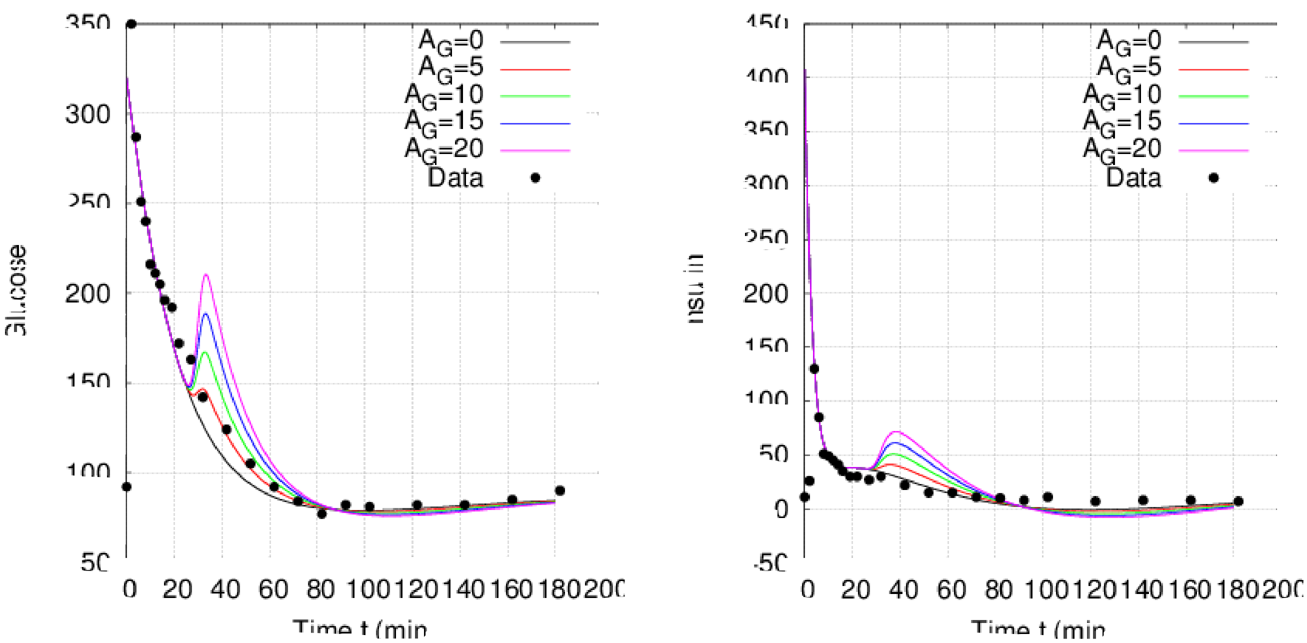
2. Methodology

The system of equations obtained with the equations (1), (2) y (3), is solved using the Runge-Kutta method of fourth order and it is developed a code in c++ that allows it to make the necessary iterations on time until obtain an approximated solution of the lineal equations system. From there the code is validated, and for that the experimental data reported [6] are used, in order to obtain a comparison with data in accordance with studies that have already been done. With the validated program, the following simulations where done:

The first group of simulations consisted in obtaining the group of glucose, insulin, and active insulin curves, from the pattern curves of each one, when the exogenous agent is a glucose cud. For the second group of simulation, the same family of curves was obtained but the external agent is the amount of insulin that is introduced in the body.

3. Results and discussion

According to the methodology, the family of curves that was obtained for the first group of simulations was the following: In figure 1, a decline is observed both for the glucose and insulin levels with the pass of time, and these levels trend to the reference values. It is shown that when $A_G = 0$, the insulin and glucose behaviors approximate to the reported values by [6] which in the curves of figure 1 (a) and (b) correspond to the back dots. This means that the code and the equations system mostly model the results that are reported in the literature.



(a) **(b)**

Figure 1. Variation of the glucose (a) and insulin (b) levels, based on time for different exogenous quantities of glucose. The experimental data were reported and taken from [6].

Now an exogenous quantity of glucose is introduced, which can mean that a glucose cud or any food with high sugar levels is introduced. This is shown in the range of the Gaussian that represents the exogenous agent that increases the glucose levels.

In the same figure 1 (a) it can be observed that as this exogenous glucose quantity increases, the glucose levels in the blood hastily increase compared to the normal glucose levels in the blood. In figure 1 (b) it is shown that the insulin produced by the body increases and is precisely as a reaction to the glucose increase since the body naturally trends to regulate these quantities to normal levels. Likewise happens with the active insulin that is an auxiliary quantity of the equations system that is being worked with and whose results are shown below. See Figure 2.

In figure 2, the normal behavior of the active insulin levels present in the body ($A_G = 0$) are shown, and as the exogenous quantity of glucose hastily increases the range of the active insulin increases.

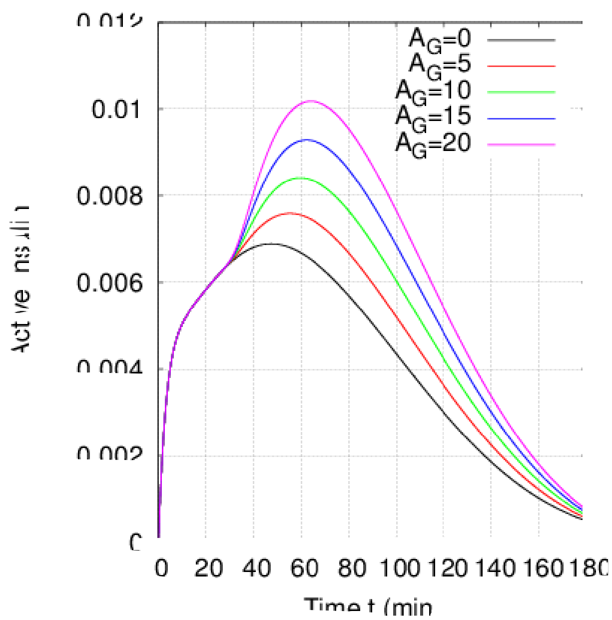
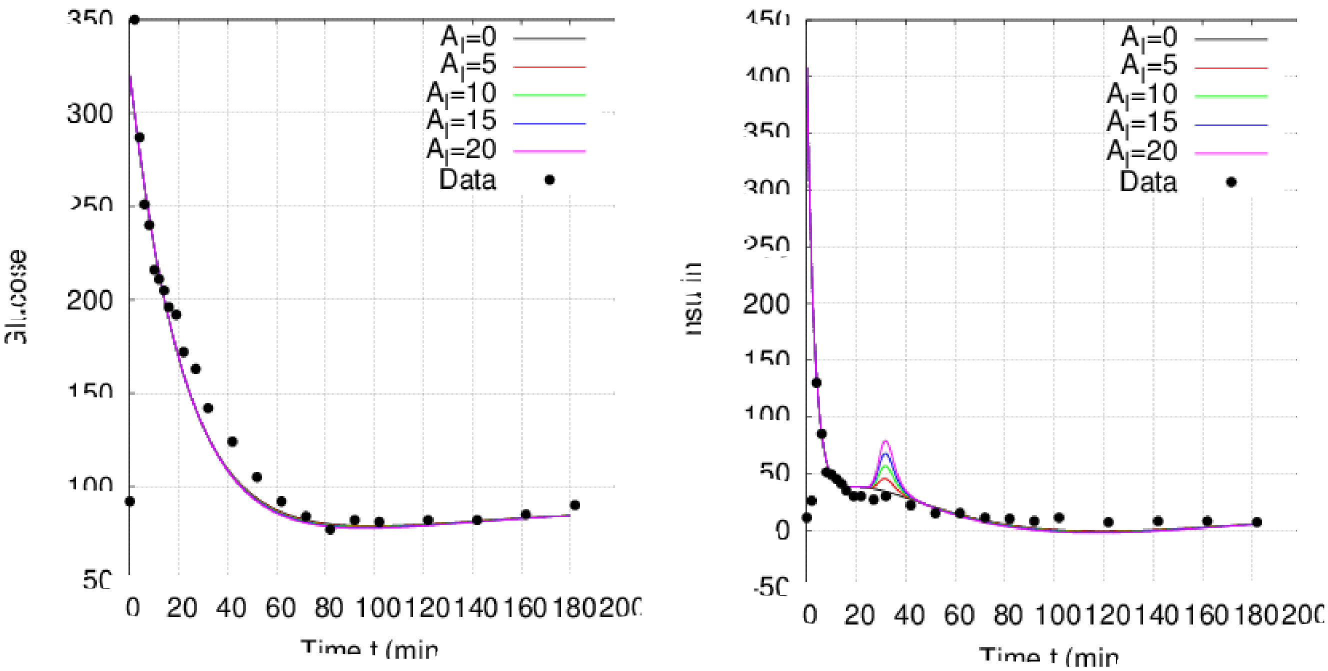


Figure 2. Variation of the active insulin levels based on time for different exogenous glucose quantities. Source: own.

In Figure 2 a small temporary slip in which the maximum range is found. That means that as the insulin in the blood reduces the glucose, this quantity is the one left after the process of glucose regulation, since for now there has not been introduced any amount of insulin due to external agents.

Now we analyze the curves obtained from increasing the exogenous insulin levels. This situation corresponds to a person that injects himself insulin in the body. See Figure 3.



(a) **(b)**

Figure 3. Variation of the glucose a) and insulin (b) levels, based on time for different exogenous glucose quantities. The experimental data were reported and taken from [6].

In figure 3 (a) it can be seen that the behavior of the glucose levels does not undergo a big change. This is due to the insulin levels that are higher than the needed to regulate the glucose quantities. Even so, changes that are not substantially considerable are produced. In figure 2 (b) it is concluded that as the insulin levels increase, the curve presents a peak around the 30 min. the range of this maximum peak is proportional to the insulin amount that is introduced. The behavior for other times is almost the same as the pattern curve that is obtained with the data (black spots).

Finally Figure 4 was obtained, which corresponds to the active insulin levels.

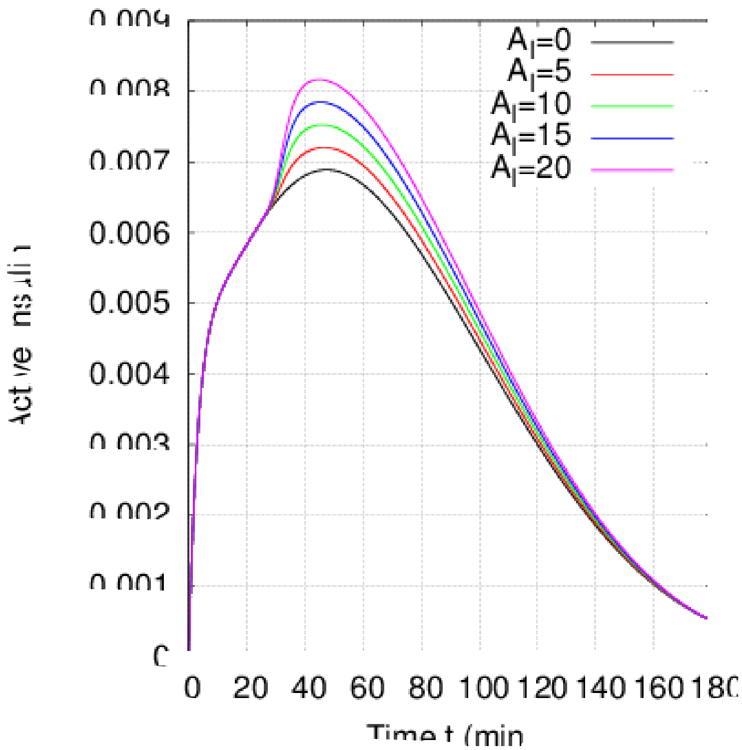


Figure 4. Variation of the active insulin levels based on time for different exogenous insulin quantities. Source: own.

In figure 4, it is concluded that the active insulin levels besides being relatively small, its range increases as the insulin introduced in the blood is higher. The increase is proportional to the exogenous amount, but the active insulin increases in lower quantities if it is compared to the increases produced by exogenous glucose quantities. The range of the active insulin is small which means that a big part of the insulin amount ends regulating the existing glucose quantity and as there are not additional contributions to the insulin levels other than the ones found in the blood and the exogenous, these values are naturally low.

4. Conclusions

The decline of the glucose and insulin levels based on time was demonstrated. This is due to the insulin regulating the glucose quantity and therefore both decrease in different amounts.

One of the interesting results is the validation of the code with reported data in the literature, from which it can be done a deeper analysis simulating gradual increases of the insulin and glucose levels, due to external agents.

According to the methodology it was found that the increase of the insulin due to the glucose increase for a sugar cud is proportional to the glucose in the cud. The amount of insulin produced trends to regulate the glucose levels.

When the exogenous insulin amount is increased, there aren't big changes of the glucose levels, since this increases due to the quantity already existing in the blood and to exogenous agents.

The active insulin is in small quantities and variations are produced when the exogenous glucose and insulin level increases. These variations in the maximum level of active insulin are higher when there are glucose increases.

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