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Model of the Dynamics Insulin-Glucose

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Abstract: *In the present work a study of the dynamics of insulin-glucose is performed for both a healthy person and a patient who has already contracted diabetes; The different types of diabetes are indicated as well as the symptoms that characterize it. The models that simulate the insulin-glucose dynamics for a healthy person are presented, and later the corresponding changes are made to simulate the process in a diabetic; The system is simplified in correspondence with the critical case considered, if a qualitative study of the system of equations is made and conclusions are made regarding the future behavior of the disease.*

Keywords: *Insulin, glucose, diabetic, hormones.*

1. INTRODUCTION

Hormones are chemicals produced by glands in the endocrine system or by specialized neurons. They are of extreme importance for the control of the functioning of the human body. Several hormones are produced in our body, each of which has a specific effect; some hormones act as a kind of chemical messenger, carrying information between cells, others act with the function of regular organ and body regions. Insulin is a hormone produced by the pancreas, whose function is to reduce blood glucose (blood glucose). It is responsible for the absorption of glucose by the cells.

When the dynamic insulin-glucose is not the natural one in the human organism, it can be produced to diabetes; this disease is a metabolic syndrome of multiple origin, due to the lack of insulin and / or the inability of insulin to properly exercise its effects, causing an increase of glucose (sugar) in the blood. Diabetes happens because the pancreas is not able to produce the hormone insulin enough to meet the needs of the body, or because the hormone is not able to act properly (insulin resistance). Insulin promotes the reduction of glycemia by allowing the sugar that is present in the blood to penetrate into the cells to be used as a source of energy. Therefore, if there is lack of this hormone, or even if it does not act correctly, there will be increased blood glucose and hence diabetes.

Physical activity is essential in the treatment of diabetes to keep blood sugar levels under control, and thus rule out the risks of weight gain. Exercise should be performed three to five times a week, there is a restriction on hypoglycaemia. Thus, people with very low blood glucose should not start physical activity, at risk of further lowering levels. On the other hand, if diabetes is uncontrolled, with very high glycemia, exercise can cause the release of counterregulatory hormones, further increasing glycemia. In all cases, patients with diabetes should always agree with their doctors on the best options. Remembering that the ideal is to favor light physical activities, because when the caloric expenditure is greater than the replacement of nutrients after the training, there may be hypoglycaemia.

The functioning of the human organism and the components of the physiological system in normal and healthy state can be described in a simplified way assuming that the physiological system will remain in a state of equilibrium. When one studies a real problem or phenomenon, it inevitably has to be simplified, idealized, taking into account only those essential factors that act on the process, neglecting the less significant ones. The question inevitably arises whether or not the simplifying assumptions have been correctly chosen. It is possible that the factors not considered strongly influence the studied phenomenon, changing its quantitative characteristics and even more from the qualitative point of view. (Ruiz A.I, 2016, p 177).

When a meal is ingested and absorbed by the digestive system, the level of glucose in the blood increases and induces insulin synthesis; Individuals with diabetes have the ability to produce insulin naturally but are not always able to regulate glucose use. (CIANNELLA, ANDRADE, SILVA, p.1).

"The recognition of a scientific theory has the necessary condition that it can be expressed in mathematical language. Mathematics itself has undergone a substantial evolution in correspondence with the demands of the various research areas, thus appearing new mathematical theories".(RUIZ A.I, 2016, p. 9)

In the last three decades, modeling has been gaining ground in several countries, in the discussions on teaching and learning, with positions for and against, its use as a strategy for teaching mathematics. In Brazil, one of the first modeling works in teaching was by Professor Aristides Camargo Barreto, from Rio de Janeiro's PUC, in the 1970's. The consolidation and diffusion were carried out by several teachers, in particular, by Professor Rodney Bassanezi (2004), of Unicamp of Campinas-SP and its orientandos. (BIEMBENGUT and HEIN, 2003, p.7).

With this importance, modeling has been increasingly characterized as a way of understanding and acting in the world and the knowledge that is being generated in this area will be fruit in our human construction, be it natural, social and cultural. "Mathematics is a living science, not only in the daily lives of citizens, but also in universities and research centers, where today there is an impressive production of new knowledge that, along with its intrinsic, logical been instrumental in solving scientific and technological problems of the greatest importance"(PCNs, 1998, 24)

The model does not always express all the details of the phenomenon, because it is not always possible due to the complexity of the phenomenon, or if it is possible it is not always feasible due to the difficulty of working with complex models mathematically. "Modeling is efficient from the moment we are aware that we are working with approximations of reality, so the prognostics in general will not be accurate." Rodney (2004). For example, when forecasting the population of the upper Solimões in the year 2020 will always be a roughly approximate value of the real figure, we are taking a growth rate that is not stable, because in the populations there are unexpected migrations.

The process researched here is modeled by means of a second-order system similar to that presented in Repilado, JA, Ruiz, IA, and Bernal, A. (1998), in treating sexually transmitted diseases, a topic also treated in Brazil, by the Syphilis Epidemiological Bulletin (2015).

In Leigh P, Temprosa M, Mather KJ. (2014) a study of the dynamics of insulin-glucose, indicating in particular the pre-diabetic patients. In Roy's doctoral thesis, A (2008) studies the dynamics of insulin-glucose and indicates the influence of exercises on glucose control.

In Huang Xue-fang, Song Lei, LI (2001), Hu Yi-ping, Zhang Ji-jia (2007) and Zhou Hua-lin, Qi Wen-bo (2006) are addressed the social effects that could appear in people as consequences of diabetes.

The treatment that we will do in this case corresponds to other models presented in the researches of other diseases, especially the case of sicklemia, quite treated and with a large number of already developed models, only some of these works will be mentioned. In Sánchez, S., Fernández, G. A. A., Ruiz. A. I. (2012) and Sánchez, S., Fernández, G. A. A., Ruiz. A. I., & Carvalho, E. F (2016) is the qualitative study of different models in an autonomous and non-autonomous form of polymer formation.

Our objective in this work is to study the dynamics of insulin-glucose, indicating the corresponding models where the model corresponding to the diabetic case will be included, which are simplified to reach conclusions regarding the disease for different critical cases presented.

People with diabetes should avoid the simple sugars present in sweets and simple carbohydrates such as pasta and breads as they have a very high glycemic index. When a food has low glycemic index, it slows the absorption of glucose. But when the rate is high, this absorption is fast and speeds up the increase in blood glucose rates. Carbohydrates should make up 50% to 60% of the total calories consumed by the person with diabetes, preferring complex carbohydrates (nuts, nuts, whole grains) that will be absorbed more slowly.

2. Development

Those who have diabetes may also suffer from hypoglycemia. When exercising, it is important to check the glycemic control before starting the activity, to choose the best food; if glycemia is very low, it is advisable to give preference to carbohydrates, as well as avoid them if you are high. The choice of food also depends on the type of exercise: long-term aerobic exercise (such as running and swimming) tends to lower blood glucose levels, requiring a greater intake of food.

According to Rodney Carlos Bassanezi (2004) diabetes mellitus is a hereditary transmission disease, diagnosed through the presence of glucose in the urine. Diagnostic tests are based on decreased glucose tolerance or in the presence of hyperglycaemia. The treatment is by means of injection of insulin or substance that stimulates its secretion.

A simple model for interpreting the results of a GTT (Glucose Tolerance Test) is based on the following biological information:

- Glucose is a source of energy for all organs and systems, being very important in the metabolism of any vertebrate. For each individual there is an optimum concentration and any excessive deviation of this concentration leads to severe pathological conditions.
- The blood glucose level tends to be self regulatory. This level is influenced and controlled by a wide variety of hormones and other metabolites. Insulin, secreted by pancreatic cells, is the major regulating hormone in the glucose level.

For the writing of the context, the data are based on the information provided by the Brazilian Society of Diabetes, located at Rua Afonso Braz, 579, Salas 72/74 - Vila Nova Conceição, in the city of São Paulo - SP. It indicates that, today, in Brazil, there are more than 13 million people living with diabetes, which represents 6.9% of the population. And that number is growing. In some cases, the diagnosis is delayed, favoring the appearance of complications.

When the person has diabetes, however, the body does not produce enough insulin and can not use the glucose properly. The blood glucose level gets high, giving rise to hyperglycemia. If this condition continues for long periods, there may be damage to organs, blood vessels and nerves.

In some people, the immune system mistakenly attacks cells. Soon, little or no insulin is released into the body. As a result, glucose stays in the blood instead of being used as energy. This is the process that characterizes Type 1 diabetes, which concentrates between 5% and 10% of the total people with the disease. Type 1 usually appears in childhood or adolescence, but can be diagnosed in adults as well. This variety is always treated with insulin, medications, food planning and physical activities to help control blood glucose levels.

It is already known that there is a genetic influence, having a close relative with the disease greatly increases the chances of you having it too. But there is still no conclusive research on risk factors for Type 1 Diabetes.

Type 2 appears when the body can not properly use the insulin it produces; or does not produce enough insulin to control the glycemic rate. About 90% of people with diabetes have type 2, it manifests most often in adults, but children can also present; depending on severity, the disease can be controlled with physical activity and food planning, in other cases it requires the use of insulin and / or other medications to control glucose.

People who have risk factors for the development of Type 2 Diabetes should make periodic medical visits and checkups frequently.

You should be more aware if:

- Has a diagnosis of pre-diabetes, decreased glucose tolerance or altered fasting glucose;
- You have high blood pressure;
- You have high cholesterol or changes in blood triglyceride levels;
- You are overweight, especially if the fat is concentrated around the waist;
- Has a parent or sibling with diabetes;
- Has any other health condition that may be associated with diabetes, such as chronic kidney disease.

Between Type 1 and Type 2, Autoimmune Latent Adult Diabetes (LADA) was also identified. Some people who are diagnosed with Type 2 develop an autoimmune process and end up losing beta cells from the pancreas. And there is also gestational diabetes, a temporary condition that occurs during pregnancy. It affects between 2% and 4% of all pregnant women and implies risk, increasing the later development of diabetes for both mother and baby, the type is Gestational Diabetes.

3. Formulation of the Model

Initially we will give some basic principles that we will take into account in the writing of the model; let's denote by $\overline{g}$ and $\overline{h}$ the optimal glucose and hormone insulin values for a normal person, and we will indicate the following other variables to consider:

- $\hat{g}(t)$ the glucose concentration at time t.

- $\hat{h}(t)$ the insulin concentration at time t.

In the system we will consider the variables g and h defined as follows $g = \hat{g}(t) - \overline{g}$ and $h = \hat{h}(t) - \overline{h}$ so when $(g,h) \to (0,0)$ So $(\hat{g}(t), \hat{h}(t)) \to (\overline{g}, \overline{h})$.

The proposed method simply establishes the interaction between insulin and glucose under normal conditions: by the interaction between glucose and hormone in the body of a healthy person, if the concentration of glucose decreases proportional to its concentration and decreases proportionally the concentration of the hormones, however the concentration of the hormones is proportional to the concentration of glucose, because in a healthy individual this is a self regulatory process, and decreases proportional to its own concentration, since its increase is as necessary; so the basic model of this process is described analytically by the following system of equations:

$$\begin{cases} \dfrac{dg}{dt} = -ag - bh + G(g,h,t) \\ \dfrac{dh}{dt} = cg - dh + H(g,h,t) \end{cases} \tag{1}$$

With the initial condition (g_0, h_0).

The functions $G(g,h,t)$ and $H(g,h,t)$ they represent external disturbances of glucose and blood hormone concentrations, that is, they represent disturbances in the system (1), and will depend on momentary unforeseen events (a food, news, or any emotional state).

It is clear that this system models the dynamics of insulin-glucose for a healthy person, for whatever the non-linear functions, the total insulin and glucose concentrations will tend to the optimum concentrations, since the equation characteristic of the linear part of the system 1) has the form:

$$\begin{vmatrix} -a-k & -b \\ c & -d-k \end{vmatrix} = 0 \Rightarrow k^2 + (a+d)k + (ad+bc) = 0 \tag{2}$$

Since the coefficients of the matrix are positive, then the eigenvalues have a negative real part, so that the null solution of the system (1) is asymptotically stable, and therefore the insulin and glucose concentrations will tend to the optimum concentrations, thus the patient at no time will contract the disease in the meantime if the existing conditions remain.

If the functions $G(g,h,t)$ and $H(g,h,t)$ are linear, the system can be integrated and determine the values corresponding to the unknown functions directly, this is the case generally treated in the previous bibliography; but if these functions are non-linear, in general this system is not integrable and therefore it is necessary to make a qualitative study to draw conclusions.

4. Proportional Growth at its Concentration

The model presented above corresponds to the normal behavior of the body of a person who does not have diabetes, and who of course the total concentrations will always converge to the optimal concentrations, both in glucose and in insulin; but it is possible to present the case in which, even though the concentration variation of the concentrations is proportional to its concentration, either glucose or insulin and that there is no diabetes, since if the variation of the other concentration is adequate there would be no diabetes; for example, when the glucose variation is proportional to its concentration the model would look like this.

$$\begin{cases} \dfrac{dg}{dt} = ag - bh + G(g,h,t) \\ \dfrac{dh}{dt} = cg - dh + H(g,h,t) \end{cases} \tag{3}$$

Note: In the case where insulin is proportional to its concentration, in system (1) the coefficient signal of the second equation is changed and the qualitative analysis for both systems is similar, so only one of the systems.

The equation characteristic of the linear part of the system (3) has the form:

$$\begin{vmatrix} a-k & -b \\ c & -d-k \end{vmatrix} = 0 \Rightarrow k^2 + (d-a)k + (bc-ad) = 0$$

From this characteristic equation it can be seen that for the model (3), the following situations can be presented:

- If $a < d$ and $bc > ad$ the system describes the dynamic insulin-glucose for a healthy person, since the total concentrations tend to the optimal concentrations, being satisfied the conditions of the first approximation theorem.

- Whether relationships take place $a = d$ and $bc > ad$ the linear part matrix of the system (3) has a pair of pure imaginary eigenvalues, and the first approximation theorem is not applicable.

- If $a < d$ and $bc = ad$ the matrix of the linear part of the system would have a unique null value and a negative value, and therefore a critical case would exist for which its stability could not be decided using the first approximation system, which will be dealt with in the next section.

5. Case which Appears Um Nulo Property Value

Within the general process particular cases are interesting for which you can arrive at clearer conclusions of the state of the process studied; in this system appear critical cases to be studied independently; suppose that the system (3) is such that the matrix of the linear part has a unique null value and the other negative, ie if it satisfies the conditions, $a < d$ and $bc = ad$, for the study of this case the autonomous system will be considered and written as follows,

$$\begin{cases} x_1' = ax_1 - bx_2 + X_1(x_1, x_2) \\ x_2' = cx_1 - dx_2 + X_2(x_1, x_2) \end{cases}$$

Through non-degenerate linear transformation $x = Sy$, at where $x = col(x_1, x_2)$, $y = col(y_1, y_2)$, the system 3 is reduced to the shape,

$$\begin{cases} y_1' = Y_1(y_1, y_2) \\ y_2' = \lambda_1 y_2 + Y_2(y_1, y_2) \end{cases} \tag{4}$$

Note: Here the matrix is reduced to the canonical form of Jordan which in this case is a diagonal matrix.

Teorema1: There is the exchange of variables,

$$y_i = z_i + h_i(z_1), (i = 1,2) \tag{5}$$

which reduces the system (4) to the normal shape on invariant surface, (FNSI),

$$\begin{cases} z_1' = Z_1(z_1) + \tilde{Z}_1(z_1, z_2) \\ z_2' = \lambda_1 z_2 + \tilde{Z}_2(z_1, z_2) \end{cases} \tag{6}$$

where the series h_i are determined in a unique way and $\tilde{Z}_i(z_1, 0) = 0, (i = 1,2)$. Thus, for $z_2 = 0$, one has the normal form, $z_1' = Z_1(z_1)$.

Demonstration:

To prove this theorem we derive the transformation (5) along the trajectories of systems (4) and (6), so that the coefficients of the degree powers satisfy the system of equations,

$$\begin{cases} Y_1 = Z_1 + \tilde{Z}_1 + \dfrac{dh_1}{dz_1} Y_1 \\ \lambda_1 h_2 + Y_2 = \tilde{Z}_2 + \dfrac{dh_2}{dz_1} Y_1 \end{cases} \tag{7}$$

To study this system in a simpler way we will separate it in the following two cases:

Case1. When the vector p is of the form $p = (p_1, 0)$, the system (7) is reduced to:

$$\begin{cases} Y_1(z_1 + h_1, h_2) = Z_1 + \tilde{Z}_1 + \dfrac{dh_1}{dz_1} Y(z_1 + h_1, h_2) \\ \lambda h_2 + Y_2 = \dfrac{dh_2}{dz_1} Y_1(z_1 + h_1, h_2) \end{cases} \tag{8}$$

From the system (8) the series can be determined Z_1 and $h_i = 0, (i = 1,2)$.

Case2. If, however, $p = (p_1, p_2)$, at where p_2 is not null, the system (7) reduces to the following expression,

$$\begin{cases} Y_1 = \tilde{Z}_1 + \dfrac{dh_1}{dz_1} Y_1 \\ Y_2 = \tilde{Z}_2 + \dfrac{dh_2}{dz_1} Y_1 \end{cases} \tag{9}$$

Using the system (9) the series are determined $\tilde{Z}_i (i = 1,2)$, this completes the proof of the theorem.

If $\tilde{Z}_1 \equiv 0$ and $\tilde{Z}_2(z_1, 0) = 0$, the system (6) is called the quasi-normal form, which can be written as follows,

$$\begin{cases} u_1' = U_1(u_1) \\ u_2' = \lambda u_2 + \tilde{U}_2(u_1, u_2) \end{cases} \tag{10}$$

Theorem 2: There is the change of variables,

$$\begin{cases} z_1 = u_1 + h(u_1, u_2) \\ z_2 = u_2 \end{cases} \tag{11}$$

That transforms the normal form on invariant surface (6) in almost normal form (10).

Demonstration:

Deriving the transformation (11) along the trajectories of systems (6) and (10) we have that the coefficients of the powers of degree satisfy the following system of equations,

$$\begin{cases} Z_1(u_1+h) = U_1 + \dfrac{\partial h}{\partial u_1}U_1 + \dfrac{\partial h}{\partial u_2}(\lambda_1 u_2 + \tilde{U}_2) + \dfrac{\partial h}{\partial u_3}(\lambda_2 u_3 + \tilde{U}_3) \\ \tilde{Z}_2 = \tilde{U}_2 \end{cases} \quad (12)$$

Considering initially the power vector of the form $p = (p_1, 0)$, it has been that,

$$U_1(u_1) = Z(u_1)$$

Considering now the vector $p = (p_1, p_2)$, at where p_2 is not null, the system (12) reduces to the following expression,

$$\lambda h = Z_1(u_1+h) - \frac{\partial h}{\partial u_1}U_1 - \frac{\partial h}{\partial u_2}\tilde{U}_2$$

This expression allows you to calculate h. This completes the proof of the theorem.

Suppose there is $q \neq 0$ such that $U_1(u_1) = gu^N + \dots$, in this case, it is said that the system is algebraic and, if on the contrary $U_1 \equiv 0$, the system is transcendent.

Theorem3: If $q < 0$ and N is odd, then the trivial solution of the system (10) is asymptotically stable, otherwise it is unstable.

Demonstration: Following the scheme described above it is sufficient to consider the following positive definite Lyapunov function.

$$V(u_1, u_2) = u_1^2 + u_2^2$$

The derivative of V along the trajectories of the system (10) has the following form,

$$V'(u_1(t), u_2(t)) = 2qu_1^{N+1} + 2u_2^2 + R(u_1, u_2)$$

This function is defined as negative because R only contains powers of higher order in relation to those given at the beginning of the expression.

6. Conclusions

1. The critical case when the matrix of the linear part has a unique value null and the other is negative is absolutely possible.
2. The almost normal reduction in shape allowed a qualitative analysis of the trajectories of the corresponding system for the critical case treated.
3. When the matrix of the linear part of the system has a null value, and the other negative, the patient will remain in the basal state, ie no diabetes will appear, whenever the first non-zero coefficient of the normal form is negative and the corresponding power is odd, otherwise it will be necessary to review the process followed to avoid that the disease could create a critical situation in the patient.

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