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Mathematical Modeling of Tissue regeneration in Diabetic Foot

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Abstract: *In the present work the model of the dynamics insulin-glucose is indicated 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. It presents the model corresponding to the process of regeneration of diabetic foot tissues, distinguishing the case in which the tissues are added and when this process is decreasing; and a qualitative study of the solutions of the corresponding equations is made and conclusions are drawn regarding the future behavior of the process, indicating those cases when the process is irreversible and when the tissues are regenerated.*

Key words: *Insulin, glucose, diabetic, hormones.*

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I. Introduction

Hormones are chemicals produced by glands of the endocrine system or by specialized neurons, are of utmost 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 dynamics of 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 lack of insulin and / or the inability of insulin to properly exercise its effects, causing an increase of glucose (sugar) in the blood.

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 in cases of 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 the 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 still more from the qualitative point of view, [3].

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 not always able to regulate the use of glucose.

"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', [3].

In Brazil, one of the first modeling works in teaching was by Aristides Camargo Barreto, from Rio de Janeiro's PUC, in the 1970s. The consolidation and diffusion were carried out by several teachers, in particular, by Professor Rodney Bassanezi [10].], of Unicamp of Campinas-SP and its orientandos.

"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 which, along with its intrinsic, logical been useful tools in solving scientific and technological problems of the utmost importance, "[2].

Thus, mathematical models seek to capture the essence of dynamics, that is, the algorithm capable of describing the exercise of mathematical induction, being of importance in the development of the capacity to solve problems, to formulate and test hypotheses. methodologies, when judging by the studied subject, which, in most cases, are related through the compartmental analysis.

"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 exact" [10]. 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 the one presented in [9], when dealing with sexually transmitted diseases, a topic also treated in Brazil by the Epidemiological Bulletin Syphilis [1].

In [8] a study of the insulin-glucose dynamics is made, indicating in particular the pre-diabetic patients. In the doctoral thesis Roy, A [11] a study of the dynamics insulin-glucose is made and the influence of the exercises in the control of glucose is indicated.

In [6], [7] and [17] are treated the social effects that could appear in people as consequences of diabetes.

The treatment that we will make in this case corresponds with other models presented in the researches of other diseases, especially the case of sicklemia, quite treated and with many models already developed, only some of these works will be mentioned. In [12], [13], [14], and [15] the qualitative study of different models in an autonomous and non-autonomous form of polymer formation is discussed.

Our goal in this work is to study the dynamics of insulin-glucose for a diabetic person, indicating the corresponding model; which will be simplified to arrive at conclusions regarding the disease for the critical case in which the matrix of the linear part presents a pair of pure imaginary eigenvalues.

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.

II. 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 too 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 [10] diabetes mellitus is a disease of a generic nature, characterized by hyperglycemia of dependence on lack of insulin. It 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 main regulating hormone in the glucose level.

For the writing of the context, the data are based on 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. It may be that you or someone close to you has diabetes. Learn more and learn to live well with the disease, making it one more reason to take care of health.

When the person has diabetes, however, the body does not produce enough insulin and can not use the glucose properly. The level of glucose in the blood is high, taking place the famous hyperglycemia. If this condition persists for long periods, there may be damage to organs, blood vessels and nerves.

In some people, the immune system mistakenly attacks the beta 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 activity 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 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 rate of glycemia. About 90% of people with diabetes have type 2. It manifests most often in adults, but children can also present. Depending on the severity, it 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 attentive if:

- Has a diagnosis of pre-diabetes - decreased glucose tolerance or impaired fasting glucose;
- You have high blood pressure;
- You have high cholesterol or changes in the blood triglyceride rate;
- 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.
- Has been diagnosed with some psychiatric disorders, such as schizophrenia, depression, bipolar disorder.

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 increased risk of subsequent development of diabetes for both mother and baby, the type is Gestational Diabetes.

III. 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 $\bar{g}$ and $\bar{h}$ 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 the time t.
- $\hat{h}(t)$ the concentration of insulin at the time t.

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

The proposed method simply establishes the interaction between insulin and glucose under normal conditions: let g be the concentration of glucose in the blood and h the concentration of liquid hormones; by the interaction between glucose and hormone in the body of a healthy person, one has to that the concentration of glucose decreases proportional to its concentration and decreases proportional the concentration of the hormones, however the concentration of the hormones adds proportional to the concentration of glucose, since in an individual healthy this is a self regulatory process and decreases proportional to its own concentration, since its increase is according to what is needed to act as regulator of glucose; so the basic model of this process is described analytically by the following system of equations:

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

The function $G(g,h,t)$ and $H(g,h,t)$ represent external rates of variation of the concentrations of glucose and hormones in the blood, that is, they represent disturbances in the system(1), and will depend on momentary unforeseen events, this problem was addressed in [4].

IV. Model Corresponding To Diabetic

The model presented in both the linear and the nonlinear case corresponds to the normal behavior of the body of a person who does not have diabetes, since it is perceived that both glucose and insulin concentrations tend to the optimal values, but as we have seen in the beginning this is a disease of multiple causes, that is to say, it can appear by the excessive production of glucose or by insufficient production of the hormone insulin; this means that in our model to be able to adequately contemplate these possibilities, it is necessary to make some adjustments, that is to say, to change the signs of the coefficients a and c, or simply one of them, thus leaving in one of the possible case, this model in the following way,

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

Observação: Aqui se tem a situação de um paciente que apresenta um rápido crescimento da concentração de glicose, só isso não é suficiente para dizer que corresponde a um diabético; pois se a produção de insulina pelo pâncreas se corresponde com esse acréscimo da glicose, se teria uma pessoa sana, masse além do crescimento da glicose, a produção de insulina não é a adequada se produziria a diabetes.
Em [5] os autores dão conclusões com relação à situação da doença reduzindo o sistema forma normal, o que permitiu dar conclusões do comportamento futuro e da situação do paciente.

V. Regeneration Of Diabetic Pie Fabrics

When diabetes is very advanced, there may be changes in the membranous tissues of the feet, often producing deep wounds or ulcers that at times may have very critical manifestations for the patient; this process is known as diabetic foot, and our objective now is to analyze the procedure before such a situation to achieve the regeneration of the tissues, that is, the control of the infection that this disease has produced.

The process of regenerating the tissues in the diabetic foot can be approached in different ways, as in this case they are equivalent to the healing of ulcers or wounds, or the reduction of contaminated masses. It is known that to carry out the study of a model that simulates the process of varying the contaminated mass of a diabetic foot, or equivalently, the decrease of the surface area of the ulcers, it is necessary to see how these will change with time; here will be analyzed when they are in the process of growing or decreasing as a consequence of treatment,[16].

We will use the following notation, x(t) will represent the contaminated mass at time t, it is also necessary to take into account that from the moment a particular contaminated mass appears in the patient, will vary between a minimum value and a maximum value, but will not be completely eliminated.

$$R = \{(t,x) \in R^2 / t > 0, m \leq x \leq M\}$$

When the contaminated mass is close to the maximum value, that is, there are deep ulcers, stage of development of gangrene, the process becomes irreversible and, in general, the solution is partial or total amputation of the affected part.

$$R_1 = \{(t,x) \in R^2 / t > 0, M - \beta_1 \leq x \leq M\}$$

The region $R_1$is called the region of irreversibility.

If the contaminated mass is close to the minimum value, the patient is in a comfort phase, that is, under these conditions there is no possibility of risk.

$$R_2 = \{(t,x) \in R^2 / t > 0, m \leq x \leq m + \beta_2\}$$

The region $R_2$is called the region of comfort.

There is an intermediate amount of contaminated mass, from which it can be transformed into an irreversible process that passes to the comfort phase in correspondence with external factors or the attention that the patient is receiving, or the concern of himself with regard to his disease.

$R_3 = \{(t,x) \in R^2 / t > 0, m + \beta_2 \leq x \leq M - \beta_1\}$

The region$R_3$is called a region of doubt or transit, subject to constant changes.

The process of simulating the variation of the contaminated mass are moments in which this mass can increase, or the influence of the treatment could diminish, aspects that must be present in the model.

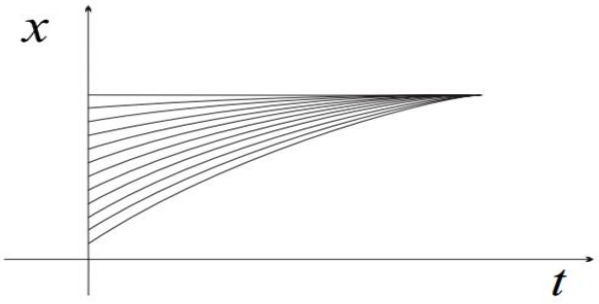
When the contaminated mass is increasing, that is, it is in the process of contamination, this growth can be expressed by means of an equation of the form,

$\frac{dx}{dt} = \propto_1 k_1 x(M - x)$ (2)

It is evident that in the equation of variation of the contaminated mass given by equation (2) the growth of that mass is considered, here$\frac{dx}{dt} > 0$because$x < M$,and the solution of this equation has the form,

$x(t) = \frac{CMe^{Mk_1 t}}{1 + Ce^{Mk_1 t}}$ (3)

The corresponding graph of the function given by expression (3) is shown below,



Pedro - 2018

This graph corresponds to the results obtained in the experimental data, when the contaminated mass is being produced.

From this expression (3) it follows that, for a sufficiently large t,$x(t) \to M$, and therefore will enter the region R_1, and therefore will enter the region of irreversibility, which should be avoided by the well being of the patient.

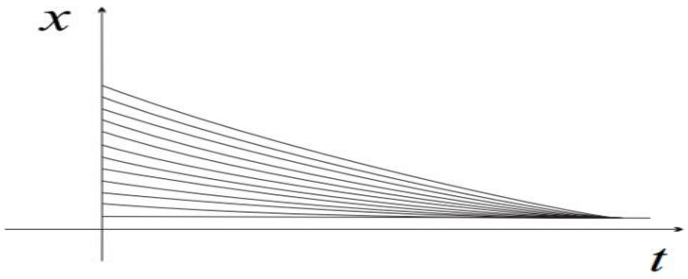
When the treatment of the patient is such that the contaminated mass is decreasing, that is, it is in the process of wound healing or ulcers; if it would have been that this variation could be expressed by means of an equation of the form,

$\frac{dx}{dt} = k_2 x(m - x)$ (4)

In this case, the equation of variation of the contaminated mass given by equation (4) shows the decrease of mass, because here $\frac{dx}{dt} < 0$,because$x < m$, and the solution of this equation has the form,

$x(t) = \frac{Cme^{mk_2 t}}{1 + Ce^{mk_2 t}}$ (5)

The graph corresponding to this assumption given by expression (5) is given below,



Pedro - 2018

This graph corresponds to the results obtained in the experimental data when the process is in the healing phase.

For a large enough t, $x(t)$will approach m and therefore will enter the comfort zone, so the patient will enjoy health, as long as there is no change in existing conditions.

In this way, our model proposal in general can be represented by the following equation,

$$\frac{dx}{dt} = \delta_1 k_1 x(M - x) + \delta_2 k_2 x(m - x) \qquad (6)$$

Here you have to$0 \leq \delta_i \leq 1 (i = 1,2)$, but the most common would be for them to take values in the binary set, that is,δ_i€$\{0,1\}$, Besides that, $\delta_1 + \delta_2 = 1$, because in the process, the contaminated mass is increasing or decreasing, being mutually exclusive for this reason.

To control the contamination process it will be necessary to determine a point set$\{t_1 , t_2 , \dots , t_n , \dots\}$such that when $x(t)$represents an arc of the curve corresponding to the function (3) such that$x(t_i)$is sufficiently close to the region of irreversibility R_1; this value will be taken as an initial condition $x(t_i)$and the solution of the Cauchy problem corresponding to equation (4) is determined with this initial condition, so the next arc will enter the comfort zone, this process will be repeated continuously, whenever adverse conditions appear, this will allow the control of the disease .

VI. Conclusion

-The system (1) simulates the dynamics of insulin-glucose for a healthy person, and always the total concentration of insulin and glucose will tend to the optimum values, but it can give the situation that still with growth of glucose concentration proportional to your concentration does not appear the disease.
-In an advanced stage the diabetic foot will often appear and in that the contaminated tissues will remain in a limited region, but will not disappear completely.
- Equation (6) simulates the process of variation of the mass of contaminated tissues in the diabetic foot, which contains as particular cases equations (2) and (4) in case of growth or decrease of the contaminated mass.
-The graphs of functions (3) and (5) correspond to the graphs of the experimental observations of the growth and decrease of the contaminated mass in a patient at an advanced stage of the disease.

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