Model of Dynamic Insulin-Glucose in Diabetic

D. Rodríguez, M. Lacort, R. Ferreira, S. Sánchez, F. Chagas, Z. Ribeiro, A. I. Ruiz

Abstract - **In the present work a study of the dynamic insulin-glucose in a healthy person is made; the different types of diabetes are indicated as well as the symptoms that characterize each one of them. The model that simulates the insulin-glucose dynamics for a person with diabetes is presented, and for the critical case of a pair of pure imaginary eigenvalues of the matrix of the linear part of the system, the system is simplified, a qualitative study is done of the system of equations and conclusions are given on the future behavior of the disease.**

Key words - Insulin, glucose, diabetic, hormones.

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 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 origins, 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.

The problem of insulin-glucose dynamics has been well researched and there are interesting models of this dynamics; [13], the authors deduce the model and treat the critical case when it has a null value in the linear part matrix.

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. [7].

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. [8].

"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 "[6].

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 [1], of Unicamp of Campinas-SP and its orientandos. [2].

"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 "[4].

The mathematical criteria must be chosen for the verification of the dynamics, that is, the algorithm of selection of exercises in the same way, form of problems, formulate and test hypotheses, for this, are for different methodological processes, judging by the studied subject, which, most of the times, are related to compartmental analysis.

"Modeling is efficient from the moment we are aware that we are working with approximations of reality, so the prognostics in general are not accurate" [1]. For example, predicting the high-season population in the year 2020 will always be a roughly approximate value of the real figure, we are applying a growth rate that is not stable since the main variables can be migrated.

The process researched here is modeled by a second order model similar to the one presented in [12], when treating as sexually transmitted diseases, a subject also treated in Brazil by the [3].

In [11] a study of the dynamics of insulin-glucose, indicating in particular the pre-diabetic patients.

In [9] and [10] are addressed the social effects that could appear in people as consequences of diabetes.

DOI: http://dx.doi.org/10.24018/ejers.2019.4.3.1150

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 [14] and [15] is the qualitative study of different models in an autonomous and non-autonomous form of polymer formation.

Our goal in this work is to do a study of 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

According to [1] diabetes 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 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 insulin and can not use the glucose properly. The blood glucose level gets high, and hyperglycemia appears. 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.

Type 2 appears when the body cannot 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, but it most often manifests in adults, but children can also have it. 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 1 and 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 pancreatic cells. 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.[5].

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 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

DOI: http://dx.doi.org/10.24018/ejers.2019.4.3.1150

$g = \hat{g}(t) - \overline{g}$ 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:

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

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:

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

Since the coefficients of the matrix are positive, then the eigenvalues have a real negative part, this causes the null solution of the system (1) to be asymptotically stable, and therefore the insulin and glucose concentrations will tend to the optimum concentrations, thus the patient in no time will contract the disease.

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.

IV. 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 that of course the total concentrations will always converge to the optimal concentrations, both in glucose and in insulin; but it may be the case that even though the concentration variation of the concentrations is proportional to its concentration of either glucose or insulin that does not present 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.

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

Note: In the case where insulin is proportional to its concentration, system (1) exchanges the h in the second equation and the qualitative analysis for both systems are similar.

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 insulin-glucose dynamics for a healthy person, since the total concentrations tend to the optimum concentrations, since the conditions of the first approximation theorem for asymptotic stability are satisfied.

- If $a > d$ or $bc < ad$ the system describes the insulin-glucose dynamics for a diabetic person, since the total concentrations will not tend to optimum concentrations, because in this case the conditions of the first approximation theorem for instability are satisfied.

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

- If takes place to relations $a = d$ and $bc > ad$ the matrix of the linear part of the system (3) has a pair of pure imaginary eigenvalues, and the first approximation theorem is not applicable, which will be treated next.

To arrive at conclusions in this situation we will transform the system to the normal form, suppose that these imaginary own values have the form and; in this situation the matrix can be reduced to the diagonal form by applying a non-degenerate linear transformation, resulting in the following system.

$$\begin{cases} g_1' = \sigma i g_1 + G(g_1, h_1) \\ h_1' = -\sigma i h_1 + H(g_1, h_1) \end{cases} \quad \textbf{(4)}$$

This problem for an autonomous case was dealt with in, [15], but here it is the non-autonomous case.

Theorem1: The exchange of variables,

$$\begin{cases} g_1 = g_2 + H_1(g_2, h_2) \\ h_1 = h_2 + H_2(g_2, h_2) \end{cases} \quad \textbf{(5)}$$

It reduces the system (4) in the normal form,

$$\begin{cases} g_2' = \sigma i g_2 + g_2 P(g_2 h_2) \\ h_2' = -\sigma i h_2 + h_2 \overline{P}(g_2 h_2) \end{cases} \quad \textbf{(6)}$$

Demonstration: By deriving the transformation (5) along the trajectories of systems (4) and (6) we obtain the system of equations,

$$\begin{cases} (p_1 - p_2 - 1)\sigma i H_1 + g_2 P(g_2 h_2) = \\ G(g_2 + H_1, h_2 + H_2) - \dfrac{\partial H_1}{\partial g_2} g_2 P - \dfrac{\partial H_1}{\partial h_2} h_2 \overline{P} \\ (p_1 - p_2 + 1)\sigma i H_2 + h_2 \overline{P}(g_2 h_2) = \\ H(g_2 + H_1, h_2 + H_2) - \dfrac{\partial H_2}{\partial g_2} g_2 P - \dfrac{\partial H_2}{\partial h_2} h_2 \overline{P} \end{cases} \quad \textbf{(7)}$$

As in the two equations of the system (7) there is the possibility of resonance, from the first equation it is deduced that if $p_1 - p_2 - 1 \neq 0$, so H_1 is determined in a unique way and in this case $P = 0$, because the case is not resonant. If, on the contrary, $p_1 - p_2 - 1 = 0$, is arbitrary, and to ensure uniqueness it is $H_1 = 0$, and from this we deduce the form indicated above for P; similarly proceed to determine H_2 and $\overline{P}$ from the second equation.

In the system (6) that the unknown functions are complex conjugated, that is to say, we have to $h_2 = \overline{g_2}$, and, moreover, the series P has the following representation,

$$P(g_2 h_2) = \sum_{n=k}^{\infty} a_n (g_2 h_2)^n + i \sum_{n=l}^{\infty} b_n (g_2 h_2)^n$$

Theorem 2: If $a_k < 0$, then the trajectories of the system (6) are asymptotically stable, otherwise they are unstable.

Demonstration: Consider the positively defined Lyapunov function,

$$V(g_2, h_2) = g_2 h_2$$

We have that its derivative along the trajectories of the system (6) has the following expression,

$$V'(g_2, h_2) = a_k (g_2 h_2)^{k+1} + R(g_2, h_2)$$

This function is defined as negative because in R potencies of degrees higher than those indicated in the initial part of the expression of the derivative of V, this allows us to state that the equilibrium position is asymptotically stable.

V. CONCLUSIONS

1. From the characteristics of the problem considered it is natural for the critical case to appear, in which the matrix of the linear part has a pair of pure imaginary eigenvalues.
2. The normal form allows great difficulties, make a qualitative study of the trajectories of the system.
3. Theorem 1 gives the methodology to follow so that the original system is simplified in order to find a better treatment to the studied process.
4. If $a_k < 0$, the patient will remain in the basal state at a later time than the analysis performed.

5. If $a_k > 0$ it is necessary to take the prophylactic measures necessary to change the clinical picture and prevent a fatal outcome as a consequence of the disease, since the patient has altered the relation insulin-glucose, and therefore if he does not have diabetes at that moment will contract soon.

REFERENCES

[1] Bassanezi, Rodney Carlos. Teaching-Learning with Mathematical Modeling, São Paulo: Context, 2004.
[2] Biembengut, Maria Salett e HEIN, Nelson. *Modelagem Matemática no Ensino*, São Paulo: Contexto, 2003.

[3] Brazil. Epidemiological Bulletin Syphilis. Brasília: Ministry of Health, Department of Health Surveillance - Department of STD, AIDS and Viral Hepatitis,IV, n. 1, 2015.

[4] Brazil. National Curricular Parameters - Third and Fourth Cycle of Elementary Education: Mathematics / Fundamental Education Secretariat. Brasilia: MEC/SEF, 1998.

[5] Brazil. Ministry of Health. Health Surveillance Secretariat. National STD and AIDS Program. Manual of Control of Sexually Transmitted Diseases / Ministry of Health, Secretariat of Health Surveillance, National STD and AIDS Program. Brasília: Ministry of Health.2005.

[6] Chaveco, Antonio Iván Ruiz. Application of Differential Equations in Mathematical Modeling, Curitiba: CRV, 2016.

[7] Chaveco, A; Domínguez, S e Garcías A. Mathematical modeling of the polymerization of hemoglobin S. LAP LAMBERT Academic Publishing. Germany. 2015.

[8] Ciannella, S.; Andrade, R. N.; Silva, N. Use of the Simulink Tool to Evaluate Controllers Feedback on the Problem of Glucose Control in Type-I Diabetic Patients.

DOI: http://dx.doi.org/10.24018/ejers.2019.4.3.1150

[9] Huang Xue-fang,Song Lei,LI "The Effect of Social Support on Type II Diabetes with Depression" Chinese_Journal_of_Clinical Psychology (2001).
[10] Hu Yi-ping,Zhang Ji-jia "Effect of Community Comprehensive Psychological and Behavioral Intervention on Glucose Metabolism of Type 2 Diabetes Patients Complicated with Depression". Chinese General Practice (2007).

[11] Leigh P, Temprosa M, Mather KJ. Regression From Prediabetes to Normal Glucose Regulation Is Associated With Reduction in Cardiovascular Risk: Results From the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2014;37(9):2622-31. DOI: 10.2337/dc14-0656.
[12] Repilado, J. A., Ruiz, I. A., & Bernal, A. Analysis and identification of a mathematical model of the transmission of infectious diseases. (1998). Cienc. Mat., 16 (1), 65 - 69.
[13] Rodíguez D, Sánchez S, Leão L, Ribeiro Z, Lacort M., Ferreira R, Ruiz A I. "Model of insulin-glucose dynamics". International Journal of Innovative Research in Electronics and Communications.Volume 5, Issue 4, 2018, Page No: 1-8
[14] Sánchez, Sandy; Ruiz, Antonio I.; Fernández, Adolfo. "Un modelo de los procesos moleculares de la polimerización y cristalización de la Hemoglobina S", Rev. Ciencias Matemáticas. 26 (2012), No. 1, pp 53 - 57.
[15] Sánchez, S., Fernández, G. A. A., Ruiz. A. I., & Carvalho, E. F." Modelo de la sicklemia con coeficientes periódicos en la función de polimerización".Ciencia e TecnicaVitivinicolaJournal, (2016).

Antonio Iván Ruiz Chaveco.
Mathematics course. You have more than 40 articles published in specialized journals. He is author of the book "Mathematical Modeling of the Polymerization of Hemoglobin S" published by Lap Lambert of Germany in 2015. He published the book "Calculation with Historical Facts: Functions of Various Variables" in the CRV publisher in 2016. He published the book "Application of Difficult Aquaculations in Mathematical Modeling "at the CRV publishing house in 2017. He supervised three doctoral theses and several master's and specializations in Mathematics. He has coordinated several extension projects, including six international scientific events. He was the coordinator of 8 specialization projects in Mathematics teaching developed in the municipalities of the interior of Amazonas; has more than 20 complete articles published in annals of international events.

Esp. Zequias Ribeiro Montalvão Filho.
Graduated in Mathematics Degree from the State University of Amazonas-UEA, Specialist in Methodology of Teaching Mathematics from the Faculdade Integrada do Brasil-FAIBRA. Professor at the State University of Amazonas at the Center for Higher Studies of Tabatinga-CESTB and the Municipal Government of Tabatinga. Has research with articles published in Modeling and Problem Solving. Participation of a book published by CRV in 2016. Member of the Research Group: Amazonian Education and Diversity - GPEDA.

Fabiana Chagas de Andrade
She is currently a PhD student in the Mathematics Teaching Program at UFRJ, an effective teacher at CEFET - RJ Uned Itaguaí, teaching subjects for the Mechanical Engineering and Production courses and distance tutor of the CEDERJ-UFF consortium, in math. He holds a Master's degree in Mathematics from UNIRIO (2014) and a degree in Mathematics from the University of Grande Rio (2010). Postgraduate course in New Technologies of Teaching Mathematics (NTEM) of LANTE-UFF. Has experience in Mathematics, with emphasis on Mathematics Education and Digital Technologies. She was an effective professor of Mathematics at the Center for Reference in Training and Distance Education (CEFOR) of the Federal Institute of Espírito Santo (IFES), assistant professor of mathematics at the Department of Mathematics Federal Rural University of Rio de Janeiro. state and municipal networks of RJ from 2011 to 2015.

Sandy Sánchez Domínguez.
Professor Sandy Sanchez Dominguez. sandys@uo.edu.cu MD trained as a mathematician from 2015 onwards, currently directs the Department of Mathematics of the Universidad de Oriente in Santiago de Cuba, in his academic history he has 17 scientific publications in refereed journals and presented papers in 8 scientific events countries. He has taught 6 postgraduate courses and was a director of 7 thesis specialization in Mathematics and a Master's thesis, is an active member of the Cuban Society of Mathematics and Computer Science, she received two national awards and developed a stay of research at the Jaume I de la Plana University, Spain.

Marcelo Lacortt.
Graduated in Mathematics (2008) and Master in Engineering (2011), both by the University of Passo Fundo, UPF. Assistant Professor of University of the State of Amazonas, UEA.

Rainey Ferreira do Nascimento.
Graduated in Mathematics (2006) and Specialization in Methodology of Teaching Mathematics (2009), both by the University of the State of Amazonas, UEA. Assistant Professor at the State University of Amazonas, UEA.

Daniela Rodríguez
Graduated in the Mathematics course at the University of Oriente Cuba in the year 2017. At the present time she is professor of the department of Mathematics of the University of the East. He is doing a Masters in Mathematics at the University of Havana Cuba.