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# A MATHEMATICAL MODEL FOR THE STUDY OF GLYCAEMIC HOMEOSTASY

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**Abstract**. A mathematical model for the blood-glucose homeostasis is built in this paper, using the previous models. The results of this paper concern the stability of the equilibrium solutions of a nonlinear differential system which govern the model.

## 1. Introduction

Here, we propose the study of some properties of the mechanisms which are involved in the blood glucose concentration homeostasis. We have in view the models which have been elaborated up to the present and we build a model for the glycaemic homeostasy. In 1965 Ackerman, Gatewood, Rosevear and Molnar [1] have been proposed a model described by a differential linear system in plane where the parameters are the glucose deviation from his constant value (harvested in blood in the morning after fasts overnight) and the similar deviation of a well-balanced average concentration of hormones (insulin, glucagon, growth hormone, epinephrine, cortisone). The destination of the model is to understand the treatment of diabetics in assumption of the administer of some hypoglicaemiant medicine and of glucose. The nonhomogeneous differential system which govern this model is the following:

$$\begin{cases} g^{'} = -m_1 g - m_2 h + J \\ h^{'} = -m_3 h + m_4 g + K \end{cases}$$

where, $m_1, m_2, m_3, m_4$ are positive constant, $J(t)$ is the rate of infusion from the intestines (or intravenously) of the glucose, $K(t)$ is the intravenous rate of infusion of the insulin, $g = G - G_0, h = H - H_0$. Here, $G = G(t)$ is the blood glucose concentration, $H = H(t)$ is the glucose-regulation hormones concentration in the blood and $G_0, H_0$ are the constant levels of this concentrations. We can see in the above system that the action of the hormonal concentration, $h$, is prevalent of the insulin type. In [1], some assumptions are used about the $J$ and $K$ functions and about the constants $m_i$, $i = \overline{1,4}$ (for instance, $(m_1 + m_3)^2 < 4m_1m_3 + 4m_2m_4$) which permit to solve the system and to obtain the solution in a damping oscillatory form round about the $G_0$ and $H_0$ levels.

Afterwards, was been elaborated some models which contain the distinct action of the hyperglicaemiant hormones. A summary presentation of these models can be found in [3]. For instance the Automonov model contain three status parameters

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(insulin and epinephrine concentrations and the glucose concentration in three compartments) and lead to a system with 6 linear differential equations. In [3], starting to the former models, the author build a model (together with the Rhode Island Hospital research workers) considering the blood glucose concentration and the plasmatic levels of hormones (insulin, glucagon, growth hormone, cortisone, thyroxin, epinephrine) and of the free fatty acids and aminoacids. From these result a nonlinear neutral system with 5 differential equations, which also describe various processes included negative feedbacks. Some arguments for nonlinearity are exposed in [3] (we use these arguments and other arguments in this article)

In [4] some algorithms are proposed for the mathematical modelling in glycaemic evolution of diabetics, with applications in treatment schemes. Here, are considered the advanced diabetic cases which present the phenomena of glycosuria, proposing a model with two status parameters : glycaemia and the sugar concentration in urine.

In the construction of the model, in this article, we consider the hypotheses from [1] and [3] and the assertions from the medical monography [2]. Here, we consider the effect of the interaction between the glucose and the hormones concerning on the speed of glycaemic changes and we obtain a nonlinear differential system. Because the glycaemic homeostasy contain negative feedback processes (in accord with [1], [2], [3]), in each equation there is such terms. It is known that the mechanisms of glycaemic homeostasy are so delicacy, and then the effect of the interaction between the glucose and the hormones is attenuated by the great glycaemic values. This effect will be appear in the first equation through the nonlinear term, $\frac{axy}{x+G_0}$.

## 2. **The construction of the model**

The status parameters are the plasmatic concentrations of the glucose, $G(t)$, of the insulin, $I(t)$, and of the average of hyperglycaemiant hormones, $H(t)$ (glucagon, cortisone, tyroxin, ACTH, growth hormone, epinephrine). Using the reasonings from [1] and [3] we consider that $G, I, H$ are derivable with continuous derivative functions on an interval of $[0, \infty)$. Let $G_0, I_0, H_0$ be the values of these functions at the initial moment, $t_0 \in [0, \infty)$ , which can be known by blood harvesting in the morning after fasts overnight. Our aim is to obtain results using the classification of the singular points in the plane and therefore we consider two dependent variables, $x(t) = G(t) - G_0, y(t) = H(t) - H_0 - (I(t) - I_0)$. Then, the new status parameters are the glycaemic deviation from his equilibrium value and the difference of such deviations for insulin and hyperglycaemiant hormones.

The following hypotheses are used in the construction of the model :

a) Each status variable have influence upon the proper speed of changes into a negative feedback process.

b) An increase of hyperglycaemiant hormones secretion provoke the increase of glycaemia, and the release of insulin secretion lead to a diminution of glycaemia. A glycaemic increase provoke the increase of insulin secretion and the decrease of hyperglycaemiant hormones secretion.

c) The interaction between the glucose and hormones determine a moderate modification of glycaemia. This hypothesis introduce in the first equation of the system a nonlinear term. The intestinal absorption of the alimentary glucose under

the action of the intestinal glucagon (a hyperglycaemiant hormone) can be described by this nonlinear term too. This is the reason because the model can be described by an autonomous differential system:

$$(1) \quad \begin{cases} x' = a\dfrac{xy}{x+G_0} - bx + my \\ y' = -cx - dy \end{cases} , a, b, c, d, m > 0$$

with initial conditions:

$$(2): \quad x(0) = 0, y(0) = 0.$$

The terms $-bx$ and $-dy$ represent the negative feedback according to the hypothesis a), the terms $my$ and $-cx$ are introduced by the hypothesis b) and the term $a\dfrac{xy}{x+G_0}$ is the nonlinear term from the hypothesis c). We can see that $x+G_0 = G > 0$, because the glycaemic values are always positive. The constant values $a, b, c, d, m$ and $G_0, H_0, I_0$ are specific to each person. The constant $b, c, d, m$ have the same signification as in [1] and $a$ is a coefficient of hormonal efficiency. For the most persons we can consider the condition $ac \geq bd + mc$, be fulfilled.

## 3. **First approximation stability**

We consider the open semiplane, $D = \{(x, y) \in \mathbb{R}^2 : x > -G_0\}$ and the functions

$U, V : D \longrightarrow \mathbb{R}$, given by

$$U(x, y) = a\frac{xy}{x+G_0} - bx + my, V(x, y) = -cx - dy.$$

It can see that $U, V \in C^1(D)$ and so there are locally Lipschitz on $D$. Then each Cauchy problem, (1)+(2) with initial conditions in $D$, has a unique maximal solution. About the stability of equilibrium solutions of the system (1) we obtain :

**Theorem 3.1.** *For each positive values of $a, b, c, d, m, G_0$ the system (1) has in the set $D$ two echilibrium solutions $P_1(0, 0)$ and $P_2(x_2, y_2)$ , with $x_2 < 0, y_2 > 0$ , such that $P_1(0, 0)$ is asymptotically stable, and $P_2(x_2, y_2)$ is saddle point. If $(b-d)^2 < 4mc$ then $P_1(0, 0)$ is focus.*

*Proof.* The equilibrium solutions of the system (1) are the solutions of the algebraic system :

$$\begin{cases} U(x, y) = 0 \\ V(x, y) = 0 \end{cases} \iff \begin{cases} \dfrac{axy}{x+G_0} - bx + my = 0 \\ -cx - dy = 0 \end{cases} ,$$

that is $x_1 = 0, y_1 = 0$ and

$$x_2 = \frac{-G_0(bd + mc)}{ac + bd + mc}, y_2 = \frac{cG_0(bd + mc)}{d(ac + bd + mc)}.$$

For the first approximation stability of the equilibrium solutions $P_1(0, 0)$ and $P_2(x_2, y_2)$ we compute the eigenvalues of the Jacobi matrix for the vectorial field $(U, V)$ in these points. In this sense, for $P_1(0, 0)$ :

$$\det(J_{U,V}(0, 0) - \lambda I) = \begin{vmatrix} \dfrac{\partial U(0,0)}{\partial x} - \lambda & \dfrac{\partial U(0,0)}{\partial y} \\ \dfrac{\partial V(0,0)}{\partial x} & \dfrac{\partial V(0,0)}{\partial y} - \lambda \end{vmatrix} = \begin{vmatrix} -b - \lambda & m \\ -c & -d - \lambda \end{vmatrix} =$$

$$= 0 \Longleftrightarrow \lambda^2 + (b+d)\lambda + mc + bd = 0.$$

Because $b + d > 0$ and $bd + mc > 0$ we infer that $\mathrm{Re}\lambda_1 < 0, \mathrm{Re}\lambda_2 < 0$. Then $P_1(0,0)$ is asymptotically stable (uniform, because the system is autonomous). If $(b-d)^2 - 4mc \geq 0$ then, this equilibrium point is a node and if $(b-d)^2 - 4mc < 0$ , is focus. The condition $(b-d)^2 - 4mc < 0$, is priori asserted in [1], using some experiments, where the values of $b$ and $d$ are greater than $m$ and $c$, but such that $|b-d| < 2mc$. For the equilibrium point $P_2(x_2, y_2)$ ,

$$\frac{\partial U(x_2,y_2)}{\partial x} = \frac{aG_0y_2}{(x_2+G_0)^2} - b = \frac{(bd+mc)^2 + amc^2}{acd}$$

$$\frac{\partial U(x_2,y_2)}{\partial y} = \frac{ax_2}{x_2+G_0} + m = -\frac{bd}{c}$$

$$\frac{\partial V}{\partial x} = -c, \frac{\partial V}{\partial y} = -d.$$

Then, $\det(J_{U,V}(x_2,y_2) - \lambda I) = 0 \Longleftrightarrow$

$$\lambda^2 + \left[d - \frac{(bd+mc)^2 + amc^2}{acd}\right]\lambda - \frac{(bd+mc)^2 + amc^2}{ac} - bd = 0.$$

Because $\lambda_1\lambda_2 = -\dfrac{(bd+mc)^2 + amc^2}{ac} - bd < 0, \quad \forall a, b, c, d, m \in \mathbb{R}_+^*$, we infer that $\lambda_1, \lambda_2 \in \mathbb{R}, \lambda_1 > 0, \lambda_2 < 0$ and then $P_2(x_2, y_2)$ is saddle point, (we can see that $(x_2, y_2) \in D$). The condition $ac \geq bd + mc$ lead to $x_2 \in [-\frac{G_0}{2}, 0)$, (statistical verified). □

**Remark 4.** *In the phase portrait, the unstable manifold of the saddle point is a curve through this point which arrive in the attractor $P_1(0,0)$, and the stable manifold is the frontier of the attraction basin of the origin. Here is the immediate clinical interpretations: each initial perturbation from the attraction basine of the equilibrium value $(G_0, H_0 - I_0)$ will be attract to this value, prevalent after damping oscillations. For each person there is an glycaemic unstable equilibrium value $(x_2)$, which can be considered a frontier value over there appear hypoglycaemia (sometimes coma). It can see that for the persons with great value for b and d the frontier value is far from the equilibrium value $(G_0, H_0 - I_0)$ and the return to this last value is more fast. This persons are protected by diabetes and hypoglycaemia, having a good glycaemic homeostasy.*

**Theorem 4.1.** *The system (1) has no periodic solutions.*

*Proof.* Computing the divergence of the vectorial field $(U, V)$,

$$div(U,V)(x,y) = \frac{\partial U}{\partial x} + \frac{\partial V}{\partial y} = \frac{ayG_0}{(x+G_0)^2} - b - d$$

we see that this divergence has constant sign in the inside and in the outside of the parabola :

$$y = \frac{(b+d)}{aG_0}(x+G_0)^2.$$

This parabola is in the first and in the second cadrane.., having the peak $(-G_0, 0)$. So, the origin is in the outside of this parabola and then there is no limit cycle round

about the origin, after the Bendixon theorem. Because the second singular point is saddle we infer that there is no limit cycle round about this point. □

## 5. **Stability after permanent perturbations**

Let be the perturbed system:

$$(3) \quad \begin{cases} x' = a\dfrac{xy}{x+G_0} - bx + my + R_1(t,x,y) \\ y' = -cx - dy + R_2(t,x,y) \end{cases}$$

with $R_1$ and $R_2$ continuous functions on $J \times D$, where $J \subset [0,\infty)$ is interval.

Suppose that the permanent perturbations $R_1$ and $R_2$ are bounded in average, that is they have the property: $\forall \varepsilon > 0, \forall T > 0, \exists \eta > 0$ and $\exists \varphi = (\varphi_1, \varphi_2) : J \longrightarrow \mathbb{R}^2$ such that $\int_t^{t+T} \varphi_i(s)ds < \eta, i = \overline{1,2}$ and $|R_i(t,x,y)| < \varphi_i(t), \forall t \in J, \forall (x,y) \in D$ with $\|(x,y)\| < \varepsilon, \quad i = \overline{1,2}$. Then we obtain :

**Theorem 5.1.** *The zero solution of the system (1) is stable after permanent perturbations bounded in average.*

*Proof.* Can apply the theorem 1.8′.(page95) from [5] and use the uniform asymptotic stability of the zero solution (after the first theorem), $\forall a, b, c, d.m > 0$. □

**Remark 6.** *From the previous theorem follow that the glycaemic value $G_0$ is resistant to the perturbations of impulse type with great initial values, but bounded in average and rapid estinguished. Such perturbations can be the momentary unloadings of epinephrine (in an emergency). If the permanent perturbations nonbounded in average became frequent, then can be appear some metabolic disorders. Such perturbations lead to the new glycaemic homeostasy configuration, which can be expressed by the autonomous perturbations. We study on the stability after autonomous perturbations.*

Let us consider the system:

$$(4) \quad \begin{cases} x' = a\dfrac{xy}{x+G_0} - bx + my + f(x,y) \\ y' = -cx - dy + g(x,y) \end{cases}$$

where $f, g \in C^2(D)$ with $f(0,0) = 0, g(0,0) = 0$. We study this system with the first approximation method.

The origin is equilibrium solution of this system having the eigenvalues equation :

$$\lambda^2 + [b + d - \frac{\partial f(0,0)}{\partial x} - \frac{\partial g(0,0)}{\partial y}]\lambda - b\frac{\partial g(0,0)}{\partial y} + \frac{\partial f(0,0)}{\partial x} \cdot \frac{\partial g(0,0)}{\partial y} +$$
$$+bd - d\frac{\partial f(0,0)}{\partial x} + mc - \frac{\partial f(0,0)}{\partial y} \cdot \frac{\partial g(0,0)}{\partial x} + c\frac{\partial f(0,0)}{\partial y} - m\frac{\partial g(0,0)}{\partial x} = 0.$$

If $\dfrac{\partial f(0,0)}{\partial y} > 0, b > \dfrac{\partial f(0,0)}{\partial x}, d > \dfrac{\partial g(0,0)}{\partial y}$ and $c > \dfrac{\partial g(0,0)}{\partial x}$ then the eigenvalues have negative real part and the solution is uniform asymptotic stable. The clinical interpretation is : if the hyperglycaemiant perturbations not succeed to modify the negative feedback characteristic of the homeostasis mechanism, then the equilibrium value is resistant to such perturbations.

If $\frac{\partial f(0,0)}{\partial x} > b$ and $\frac{\partial g(0,0)}{\partial y} > d$ then the zero solution of the system (4) is unstable. This means that the positive feedback appearance at the both components (glucose and hormones) lead to glycaemic instability.

We study now a particular case of autonomous perturbation, with $g(x,y) = yg(x), g \in C^2(I)$, $I \subset (-G_0, \infty)$, without the condition $g(0) = 0$, which means that the perturbation in the hormonal secretion speed have influence only on the hormonal feedback mechanism..

$$(5) \quad \begin{cases} x' = a\frac{xy}{x+G_0} - bx + my + f(x,y) \\ y' = -cx - dy + yg(x) \end{cases} .$$

Supposing that $0 \in I$, we can write the Taylor formula for the functions $f$ and $g$ :

$$(6) \quad \begin{array}{l} f(x,y) = \frac{\partial f(0,0)}{\partial x} \cdot x + \frac{\partial f(0,0)}{\partial y} \cdot y + \rho_1(x,y) \\ g(x) = g(0) + g'(0)x + \rho_2(x) \end{array}$$

where $\rho_1(x,y)$ and $\rho_2(x)$ contain second order derivatives. For the stability study of the zero solution of this system, after the first approximation method, the eigenvalues equation is :

$$\lambda^2 + [b + d - \frac{\partial f(0,0)}{\partial x} - g(0)]\lambda + bd + mc - d \cdot \frac{\partial f(0,0)}{\partial x} + \\ + g(0) \cdot \frac{\partial f(0,0)}{\partial x} + bg(0) + c \cdot \frac{\partial f(0,0)}{\partial y} = 0.$$

**Proposition 6.1.** *The new feedback components,* $\frac{\partial f(0,0)}{\partial x}$ *and* $g(0)$ *settle on the stability of the zero solution and* $\frac{\partial f(0,0)}{\partial y}$ *establish the shape of the solutions in a neighborhood of origin.*

*Proof.* If $\frac{\partial f(0,0)}{\partial y} \leq \frac{1}{4c}[b - d - \frac{\partial f(0,0)}{\partial x} + g(0)]^2 - m$ then the origin is a node or a saddle point. Is saddle point if $[b - \frac{\partial f(0,0)}{\partial x}] \cdot [d - g(0)] < c[m + \frac{\partial f(0,0)}{\partial y}]$, and a uniform asymptotic stable node if $[b - \frac{\partial f(0,0)}{\partial x}] \cdot [d - g(0)] > c[m + \frac{\partial f(0,0)}{\partial y}]$ and $d > g(0), b > \frac{\partial f(0,0)}{\partial x}$. The origin is unstable node if $[b - \frac{\partial f(0,0)}{\partial x}] \cdot [d - g(0)] > c[m + \frac{\partial f(0,0)}{\partial y}]$ and $d < g(0), b < \frac{\partial f(0,0)}{\partial x}$. When $\frac{\partial f(0,0)}{\partial y} \leq \frac{1}{4c}[b - d - \frac{\partial f(0,0)}{\partial x} + g(0)]^2 - m$ the eigenvalues are complex conjugated and the shape of the solutions in a neighborhood of the origin is oscillatory. In this case, the sign of $b + d - g(0) - \frac{\partial f(0,0)}{\partial x}$ decide the stability of the zero solution. □

In the case $\frac{\partial f(0,0)}{\partial y} \leq \frac{1}{4c}[b - d - \frac{\partial f(0,0)}{\partial x} + g(0)]^2 - m$ we distinguish the situations :

(i) If $b + d - g(0) - \frac{\partial f(0,0)}{\partial x} > 0$, then $\mathrm{Re}\lambda_{1,2} < 0$ and the origin is asymptotic stable focus.

(ii) If $b+d-g(0)-\dfrac{\partial f(0,0)}{\partial x}<0$, then $\mathrm{Re}\lambda_{1,2}>0$ and the origin is unstable focus.

(iii) If $b+d-g(0)-\dfrac{\partial f(0,0)}{\partial x}=0$, then

$$\lambda_{1,2}=\pm\frac{i}{2}\sqrt{4c[m+\frac{\partial f(0,0)}{\partial y}]-[b-d+g(0)-\frac{\partial f(0,0)}{\partial x}]^2}.$$

**Remark 7.** *We can realize the clinical interpretations: If the origin is a saddle point, then the negative feedback mechanism of the glucose or of the hormones is overturned and this means a transition from a moderate diabetes to an advanced diabetes.. In the case of asymptotic stable node the negative feedback is preserved and the glycaemic value $G_0$ is resistant to perturbations. The case of unstable node correspond to positive feedback and advanced diabetes.. If $\dfrac{\partial f(0,0)}{\partial y}$ increase then in the first equation of the system (5) is fortified the insulin action, which means the presence of the insulin therapy. If the origin is an asymptotic stable focus then the insulin dose is best, succeeding to maintain the glycaemy at a nondangerous level. In the case of unstable focus the treatment is inefficient.*

We note $\mu=\dfrac{\partial f(0,0)}{\partial x}$ and consider this value as a parameter and for fixed $g(0)$ let be $\mu_0=b+d-g(0)$. Suppose that $f$ and $g$ are of $C^\infty$ class and obtain the following result:

**Theorem 7.1.** *If $f\in C^\infty(D), g\in C^\infty(I), \dfrac{\partial f(0,0)}{\partial y}>0$ and $\Delta<0$, then there is a value of the $\mu$ parameter for which appear a Hopf bifurcation, corresponding to a periodic solution of the system (5).*

*Proof.* It can see that $\mathrm{Re}\lambda_{1,2}(\mu_0)=0$ si $\dfrac{\partial \mathrm{Re}\lambda_{1,2}(\mu_0)}{\partial\mu}=\frac{1}{2}>0$. Because for each other value of $\mu$ the zero solution is a focus, using the theorem of Hopf we infer that there is a periodic solution and the zero solution is a centre. The existence of a periodic solution can be proved in an other way, using the divergence of the vectorial field $(\Phi,\Psi):D\longrightarrow\mathbb{R}^2$, with

$$\Phi(x,y)=a\frac{xy}{x+G_0}-bx+my+f(x,y)$$
$$\Psi(x,y)=-cx-dy+yg(x)$$

and the curve which limit the regions from $D$ where the divergence have a constant sign, is, $y=\left[\dfrac{b+d-g(x)-\dfrac{\partial f(x,y)}{\partial x}}{aG_0}\right](x+G_0)^2$. If $\mu=\mu_0$, Then the point $(0,0)$ is on this curve, which imply that in each neighborhood of origin the divergence change the sign. Then, according to the theorem of Bendixon, there is a limit cycle round about the origin. □

**Remark 8.** *If $\mu<\mu_0$ then the origin is an asymptotic stable focus. When $\mu>\mu_0$, the origin is a unstable focus. Therefore, when $\mu$ increase crossing through $\mu_0$ appear a Hopf bifurcation and periodic solution with the loss of the stability. We can*

*observe that the periodic solutions appear only during the treatment. The bifurcation parameter can be selected also $g(0)$. For a person with hyperglycaemia the value $G_0$ is great, differing from the value of a healthy person. Therefore the value $G_0$ from the system (4) or (5) differ by the $G_0$ from the system (1).*

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