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GLYCEMIA MONITORING

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Abstract

Here a system of two non-linear difference–differential equations, which is mathematical model of self-regulation of the sugar level in blood, is investigated. The analysis carried out by qualitative and numerical methods allows us to conclude that the mathematical model explains the functioning of the physiological system "insulin–blood sugar" in both normal and pathological cases, i.e. diabetes mellitus and hyperinsulinism.

1. GLYCEMIA REGULATION SYSTEM

Metabolism and exchange of energy are the basis of the vital activity of all higher organisms. Metabolism is regulated by the central nervous system and multiple links of it, as well as by chemical combinations circulating in blood and produced by endocrine glands. The major source of energy is one of the representatives of carbohydrates: glucose, which enters into blood with food during the meal admittance. Continuous supply of glucose governs the system that controll sugar level in blood and permitt for an organism to accumulatand mobilise energy in accordance with the need of tissues.

The normal sugar level in a healthy organism is not constant, but oscillating [1,2] within limits, that guarantee optimal conditions of providing sugar to tissues and, first of all, to the nervous system. A significant decrease of level of sugar in blood leads to serious hypoglycemical disorders, which reflect seriously on the state of the entire organism. Expressed crudely, a protracted increase of level of sugar in blood leads to the development of diabetes. Thus, the study of the mechanism of self-regulation of the sugar level in blood is one of the most important problems of medicine.

Two principal parts of regulation of the sugar level in blood, i.e. the neural (neurohumoral) and local (humoral) are illustrated in Fig.1.

Neurohumoral, or indirect regulation, is carried out by adrenalin, i.e. a hormone of the brain substance of adrenal glands. The basic role in humoral (local) regulation is played by hormones produced by Langerhan's islets: insulin, glucagon and somatostatin.

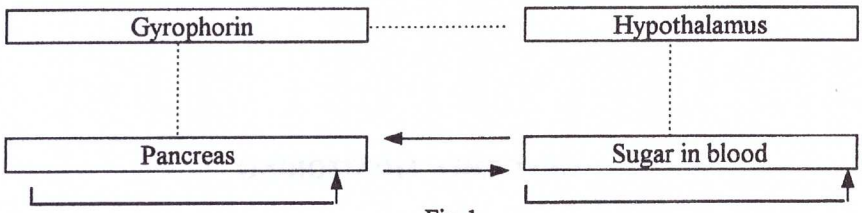

Fig. 1

The principal controller of glycemia is insulin. It is secreted by β-cells of Langerhan's islets dependingly on the content of sugar in blood. The increased level of sugar in blood stimulates the production of insulin and its entering into blood plasma, which causes the decrease of sugar level in blood. The insufficient level of insulin in blood results is diabetes mellitus.

The increase of the sugar level in blood in a healthy organism (for example, during eating) does not result in undesirable effects. In the consequence of the action of insulin, sugar is directed into two depots: liver, where it is stored as glycogen, and peripheric tissues. Therefore, the level of sugar in blood of healthy organism slightly increases.

If the level of sugar in blood declines, but its consumption continues then insulin stops to be produced. α-cells of the Langerhan's islets start secreting another hormone – glucagon. Under its influence the liver glycogen is converted back into sugar and enters into blood. Thus, the constant level of sugar in certain limits is secured both by interaction "insulin - glucagon" and by the activity of liver. The stock of sugar in liver is large enough to sustain its normal level in blood, despite occasional long breaks in nutrition.

Somatostatin, that is produced by δ-cells of pancreas, controls the secretion of glucagon and insulin. Sharp and rapid gyperglycemic effects are caused by above mentioned adrenalin. It is the main hormone sustaining the sugar level in blood, if it is flattened by insulin or starvation.

Insulin in blood can exist freely or in combination with proteins. The free insulin directly decreases sugar content, while the connected one acts only when freed from proteins. At present, it is possible to measure only gross amount of insulin in blood, so-called immunoreactive insulin (IRI). Research [3] shows, that there are rhythmical oscillations of the level of insulin in blood and they are related to the oscillations of level of sugar.

The oscillations of level of sugar in blood are found to have clearly expressed time hierarchy. The consequence of neurohumoral regulation are the high-frequency oscillations in the range of minutes [4–6], while the humoral regulation results in low-frequency oscillations, in a range of hours [7,8]. Thus, we meet both rapid and slow processes. The works of authors, investigating high-frequency oscillations [4–6] show, that the various amplitudes of oscillations with periods 400–500 and 30–40 seconds subsist among different individuals. Though, the slow processes are of greater interest,

because their investigation can shed light on various pathologies related to disturbance of carbohydrate exchange. As the values of high-frequency oscillations are averaged, we make only the slowly passing processes to be the object of our modelling.

Low-frequency oscillations were detected while measuring the level of sugar in blood at various times of a day, during which the samples of blood were taken several times. The derived results allow to conclude the presence of the day-night oscillations of level of sugar in blood with the period of 24 hours.

2. ELEMENTARY MATHEMATICAL MODEL TAKING INTO ACCOUNT THE NUTRIMENT REGIME

The review of coexisting mathematical models of glycemia regulation is produced in the study [9]. Wherein D. Švitra offered a model interpreting the self-regulation of sugar level in blood as "predator - prey" type interaction, where the predator is insulin, and the prey is sugar. One of modifications of the model is a system of the following 4 difference–differential equations:

$$\dot{I}(t) = r_I \left\{ \frac{G(t)}{K_G} + a\left[\frac{G(t)}{K_G} - \frac{I_A(t)}{K_{IA}} \right] - \frac{I(t-h)}{K_I} \right\} I(t), \tag{1}$$

$$\dot{I}_A(t) = r_{IA} \left\{ \frac{G(t)}{K_G} + b\left[\frac{G(t)}{K_G} - \frac{I(t)}{K_I} \right] - \frac{I_A(t)}{K_{IA}} \right\} I_A(t), \tag{2}$$

$$\dot{G}(t) = r_G \left\{ 1 + c\left[1 - \frac{I_A(t)}{K_{IA}} \right] - \frac{G(t)}{K_G} \right\} G(t), \tag{3}$$

$$\dot{I}_S(t) = r_{IS} \left\{ \frac{I(t)}{K_I} + d\left[\frac{I(t)}{K_I} - \frac{I_A(t)}{K_{IA}} \right] - \frac{I_S(t)}{K_{IS}} \right\} I_S(t) \tag{4}$$

Here $I(t)$ is the total amount of insulin, produced by β-cells of pancreatic gland, $I_A(t)$ and $I_S(t)$ are the levels of active and bonded insulin in the blood plasma at the moment of time t, resp.; K_I, K_{IA} and K_{IS} – their averages, h – the time, necessary for production of insulin, and $G(t)$ – the level of sugar in blood, K_G – mean level of it. Value $r_I > 0$ defines the linear rate of production of insulin and r_{IA}, r_{IS}, r_G are the linear runup of concentrations of active insulin, bonded insulin and sugar in blood, resp., and parameters a, b, c, d accomplish feedback. The model reflects actual situation [9].

The functionality of increase rising of sugar level in blood related to admittance of food, i. e. functionality of alimentary hyperglycemia, still is not ascertained. Certain results of clinical experiments show that regime of nutriment can "synchronize" the dynamics of sugar level in blood [10], in such a way concealing the individual biorhythm of sugar level in blood.

Alimentary hyperglycemia is sufficiently vividly expressed process, which occurs as an influence of certain periodic external force on sugar in the blood system.

Therefore it is necessary to take into account the regime of nutriment. For model (1)–(4) this is done in [9]. However, clinical findings about the dynamics of basic variables are apparently deficient. Therefore we suggest the simplified version of the model (1)–(4) of regulation of sugar level in blood taking into account the regime of nutriment a consisting of 2 differential equations:

$$\dot{I}(t) = r_I\left[\frac{G(t)}{K_G} + a\left(1-\frac{G(t)}{K_G}\right) - \frac{I(t-h)}{K_I}\right]I(t), \tag{5}$$

$$\dot{G}(t) = r_G\left[1+g(t)+b\left(1-\frac{I(t)}{K_I}\right) - \frac{G(t)}{K_G}\right]G(t). \tag{6}$$

Notation is the same as in model (1)–(4). Function $g(t) = g(t+r)$ governs the nutriment regime.

There are no general method for solving the systems of nonlinear delay differential equations, like (5)–(6), therefore for further linear analysis we put $g(t) = 0$. System (5)–(6) has 4 equilibrium states, only 2 of which can be stable in the state of so-called internal equilibrium

$$I(t) \equiv K_I,\ G(t) \equiv K_G. \tag{7}$$

Characteristic quasipolynomial of the linearized system (5)–(6) in the neighbourhood of the equilibrium state (7) is the function

$$P(\lambda) = (\lambda + r_G)(\lambda + r_1\ e^{-\lambda h}) + r_I r_G(1-a). \tag{8}$$

In case of diabetes $r_G >> r_1$. From (6) and Tichonov's theorem [9] it follows, that

$$\frac{G(t)}{K_G} = 1 + b\left(1-\frac{I(t)}{K_I}\right). \tag{9}$$

Putting (9) into equation (5) we obtain

$$\dot{I}(t) = r_I\left[1 + b(1-a)\left(1-\frac{I(t)}{K_I}\right) - \frac{I(t-h)}{K_I}\right]I(t). \tag{10}$$

This is Hatchinson's equation with internal feedback. The state $I(t) = K_I$ is a stable equilibrium state of equation (10) and the function

$$P(\lambda) = \lambda + \alpha r + r e^{-\lambda h}, \tag{11}$$

is a characteristic quasipolynomial of it where $\alpha = b\ (1-a)$.

This characteristic quasipolynomial, when linearized in the neighbourhood of the equilibrium state $I(t) = K_I$ has a single pair of imaginary roots $\pm i\sigma$, while the other roots are negative real parts at

$$r_0 = \frac{\sigma_0}{\sin \sigma_0 h}, \tag{12}$$

where σ_0 – is a unique root of equation $\alpha + \cos \sigma h = 0$, from $(0, \pi/h)$. By method of D-partition we shall investigate of roots of equation $P(\lambda, r_I, a) = 0$, where $P(\lambda, r_I, a)$ is characteristic polynomial (8). When $\lambda = 0$, from (8) we obtain a straight line $a = 1 + 1/b$; when $\lambda = \pm i\sigma$ $(\sigma > 0)$ we obtain parametrical equations

$$r_I = \frac{r_G \sigma}{r_G \sin \sigma h - \sigma \cos \sigma h}, \tag{13}$$

$$a = \frac{r_G \cos \sigma h + \sigma \sin \sigma h}{r_G b} + 1 - \frac{1}{r_I} \frac{\sigma^2}{r_G b}, \tag{14}$$

which determine the coordinates of restitution point R:

$$\lim_{\sigma \tau \to 0} r_I = \frac{1}{h - \frac{1}{r_G}}, \tag{15}$$

$$\lim_{\sigma \to 0} a = 1 + \frac{1}{b}. \tag{16}$$

In the case of diabetes, for the values of parameters

$$b = 0.34, \quad h = 5, r_G = 8.5 \tag{17}$$

the part of D-partition of the plane $r_I a$ is presented on Fig.2.

In the case of normal regulation, the values parameters can be taken like this:

$$b = 1.5, \quad h = 5, \quad r_G = 3. \tag{18}$$

The corresponding D-partition of the plane $r_I a$ is presented on Fig.3.

In the case of hyperinsulinism, the parameter b increases significantly, while the rest of the values stay virtually the same:

$$b = 4, \quad h = 5, \quad r_G = 0.6. \tag{19}$$

The corresponding D-partition of plane $r_I a$ is presented on Fig.4.

In all of these 3 cases the roots of quasipolynomial (8) satisfy the inequality $\mathrm{Re}\,\lambda < 0$ in D_0. Thereby (17), (18) and (19) hold; the point (r_I, a) resides in D_0 and internal equilibrium state (7) is asymptotically stable. If the point (r_I, a) passes onto

D_2, then the system (5)–(6) may possess a stable periodic solution in neighbourhood (7).

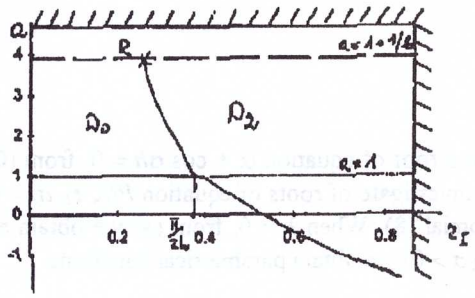

Fig.2

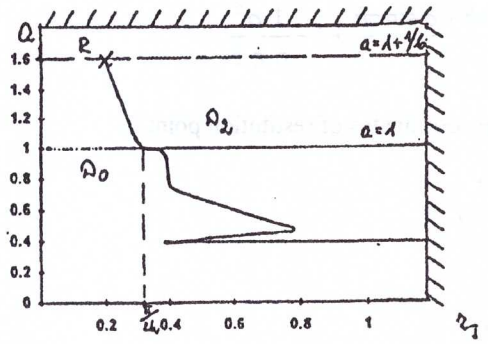

Fig.3

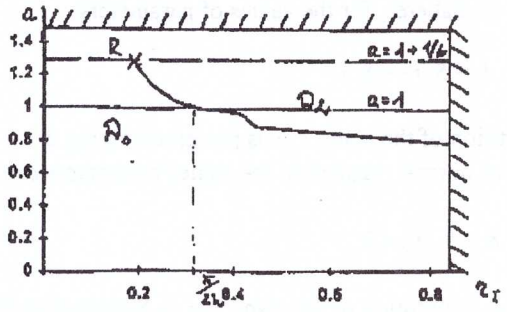

Fig.4

Nonlinear analysis has been conducted on the grounds of experimental data [11]. The selected regime of nutriment corresponds to the food admittance at 8,12,16 and 20 hrs, and the sugar content in accepted food is various.

In the case of diabetes, duration of insulin production decreases, while the amplitude of oscillations of sugar level in blood increases. Fig.5 shows the solution of system (5)–(6) in the case of values of parameters (17) and $r_1 = 0.5$, $a = 0.84$, $k_1 = 23$, $k_6 = 170$.

Fig.6 represents solution of system (5)–(6) in the case of normal regulation with the values of parameters (18) and $r_1 = 0.45$, $a = 3$, $k_1 = 28$, $k_6 = 27$.

In the case of hyperinsulinism, the amount of insulin increases, while glycemia decreases. Dependency on nutriment regime of oscillations of insulin amount is expressed vividly here. In the case of values of parameters (19) and $r_1 = 0.25$, $a = 0.55$, $k_1 = 45$, $k_6 = 31$, the solution is presented on Fig. 7.

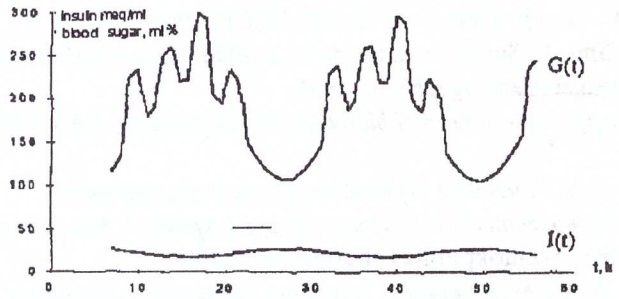

Fig.5

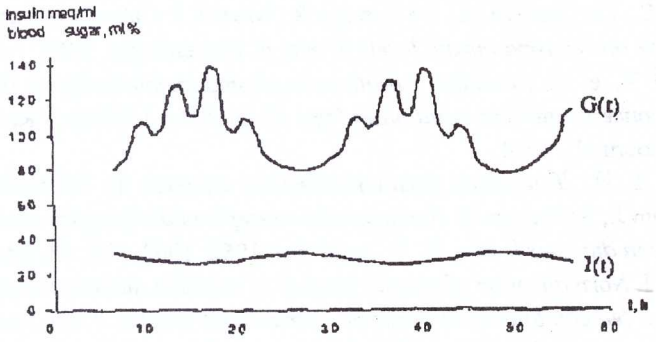

Fig.6

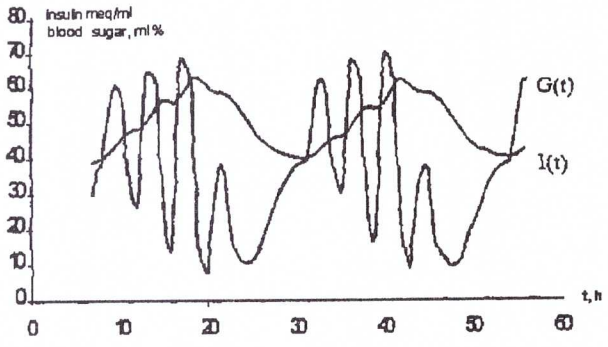

Fig.7

Comparison of the obtained theoretical curves with the data [11], as well as with the other clinical findings allow us to conclude, that in all of the 3 cases the suggested mathematical model of glycemia regulation reflects a real situation quite well and fits for various regimes of nutriment.

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