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A Possibility of Taking into Consideration of Insulin "Age Structure" for Modeling Blood Glucose Dynamics

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Abstract. A system of two nonlinear difference-differential equations which is a mathematical model of self-regulation of glucose level in blood with time delay into consideration of insulin "age structure" is presented. 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 glucose" in normal and pathological cases.

Key words: mathematical modeling, blood glucose level, insulin, diabetes mellitus.

1. Introduction

The self-regulation of glucose level in blood can be interpreted (Švitra, 1989; Basov and Švitra, 1998) as "predator-prey" type interaction, where the "predator" is insulin, and the "prey" is glucose. In the paper (Basov *et.al*, 1999) was proposed the system of two nonlinear difference-differential equations which is a mathematical model of self-regulation of glucose level in blood:

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

$$\dot{G}(t) = r_G \left\{ 1 + b\Big[1 - \frac{I(t)}{K_I}\Big] - \frac{G(t)}{K_G} \right\} G(t). \tag{2}$$

Here $I(t)$ is the level of insulin in the blood plasma at the time moment t and K_I is its mean; $G(t)$ is the level of blood glucose and K_G is its mean; h is the time necessary for the production of insulin in β-cells of the pancreas; $r_I > 0$ chracterizes the linear rate of production of insulin; $r_G > 0$ shows the linear growth of the level of glucose in the blood; with the help of parameters a and b a feedback is realized. Parameter a controls the rate of insulin production and parameter b regulated the level of glucose in blood.

The research shows a sufficiently good agreement between the results obtained investigating model (1)–(2) and the experimental date (Basov *et. al.*, 1999).

From the general scheme of the blood glucose regulation (Švitra, 1989), it follows that there exists a certain "age structure" of insulin, where "younger" proinsulin by its activity yields considerably to "older" insulin. It is possible to calculate insulin "age structure" in mathematical model (1)–(2), replacing differential equation (1) by the following equation:

$$\dot{I}(t) = r_I\left\{\frac{G(t)}{K_G} + a\Big[1 - \frac{G(t)}{K_G}\Big] - \frac{pI(t-h_p) + (1-p)I(t-h)}{K_I}\right\}I(t). \tag{3}$$

In (3) h_p is the time necessary for proinsulin biosynthesis and the parameter $p \geqslant 0$ reflects a contribution of proinsulin fractions into a total amount of insulin produced in β-cells.

Investigating system (2)–(3), we assume that

$$\frac{r_I}{K_I} = c_1, \quad \frac{r_G}{K_G} = c_2, \tag{4}$$

where the c_1 and c_2 are positive constant. Equations (4) mean that the resistance of the exterior of the medium is a biological constant of the organism (Kolesov, 1985).

2. Stability of Equilibrium States

2.1. *Linear Analysis*

The system of nonlinear differential equations (2)–(3) has the following states of equilibrium with nonnegative coordinates:

$$I(t) \equiv 0, \quad G(t) \equiv 0; \tag{5}$$
$$I(t) \equiv 0, \quad G(t) \equiv K_G(1+b); \tag{6}$$
$$I(t) \equiv K_I a, \quad G(t) \equiv 0; \tag{7}$$
$$I(t) \equiv K_I, \quad G(t) \equiv K_G. \tag{8}$$

The states of equilibrium (5)–(6) are always unstable. Below we study the stability of interior state of equilibrium (8). In the original system of differential equations (2)–(3) we make the change of variables

$$I(t) = K_I\big[1 + x(t)\big], \quad G(t) = K_G\big[1 + y(t)\big]. \tag{9}$$

As a result we get the system of differential equations

$$\dot{x}(t) = -\big[r_I p x(t-h_p) + r_I(1-p)x(t-h) + r_I(1-a)y(t)\big]\big[1 + x(t)\big], \tag{10}$$
$$\dot{y}(t) = r_G\big[-bx(t) - y(t)\big]\big[1 + y(t)\big]. \tag{11}$$

The characteristic quasipolinomial of the linear part of system (10)–(11) is the function

$$P(\lambda) = \Big\{\lambda + r_I\big[p\mathrm{e}^{-\lambda h_p} + (1-p)\mathrm{e}^{-\lambda h}\big]\Big\}(\lambda + r_G) + r_I r_G b(1-a). \tag{12}$$

The disposition of roots of (12) in the complex plane depends on values of the parameters h_p, h, r_I, r_G, a, b and p. All they are positive according to their biological meanings (Švitra, 1989).

We study by the method of D-partitions (Neimark, 1948) the disposition in the complex plane of roots of the equation

$$P(\lambda; r_I, a) = 0, \tag{13}$$

where $P(\lambda; r_I, a)$ is quasipolynomial (12) for the some fixed values of the parameters h_p, h, r_G, b and p.

For $\lambda = 0$ from (13) we get lines $a = 1 + \frac{1}{b}$ and $r_I = 0$. Further, for $\lambda = i\sigma$ $(\sigma > 0)$ we get equations in the parametric form of remaining curves of the D-partition on the plane $r_I a$:

$$r_I = \frac{r_G \sigma}{r_G \varphi_1(\sigma) - \sigma \varphi_2(\sigma)}, \tag{14}$$

$$a = \frac{r_G \varphi_2(\sigma) + \sigma \varphi_1(\sigma)}{r_G b} + 1 - \frac{1}{r_I} \frac{\sigma^2}{r_G b}, \tag{15}$$

where

$$\varphi_1(\sigma) = p \sin \sigma h_p + (1-p) \sin \sigma h, \tag{16}$$

$$\varphi_2(\sigma) = p \cos \sigma h_p + (1-p) \cos \sigma h. \tag{17}$$

As $\sigma \to 0$ from (14)–(15) we determine the so-called cups $M(r_I^M, a^M)$, whose coordinates are

$$r_I^M = \frac{r_G}{r_G \big[p h_p + (1-p)h\big] - 1}, \quad a^M = 1 + \frac{1}{b}. \tag{18}$$

In the case of diabetes mellitus, for the values of parameters (Švitra, 1989)

$$h_p = 3, \quad h = 4, \quad r_G = 6.6, \quad b = 0.34, \quad p = 0.8, \tag{19}$$

the interesting to us part of the D-partition on the plane $r_I a$ is constructed on Fig. 1.

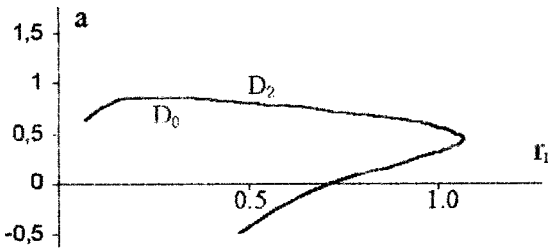

Fig. 1. The D-partition on the plane of the parameters r_I and a in the case of diabetes mellitus.

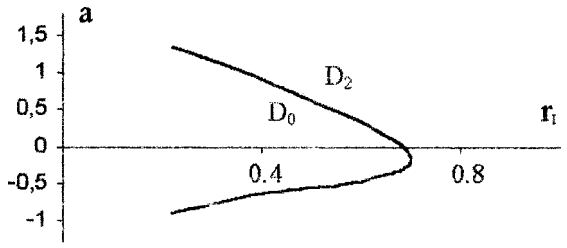

Fig. 2. The D-partition on the plane of the parameters r_I and a in the normal case.

In the case where the normal regulation r_G is sufficiently small, the parameter b is sufficiently large and the values of parameters are taken as follows

$$h_p = 3, \quad h = 5, \quad r_G = 2.8, \quad b = 1.5, \quad p = 0.2, \tag{20}$$

the corresponding D-partition on the plane $r_I a$ is presented on Fig. 2. In both the cases it is simple to show that in the domain D_0 all the roots of (13) have negative real parts, and passing from D_0 to D_2 acquire two complex conjugate roots of (13) with positive real parts. Thus, if the point (r_I, a) is located in D_0, the inner equilibrium state (8) is asymptotically stable, while if the point (r_I, a) goes into the domain D_2, in circles (8) there may appear stable periodic behavior of system (2)–(3).

2.2. *Nonlinear Analysis*

The general investigation of the nonlinear problem is rather complicated. Thus, in order to simplify the problem, we use some biological assumption. In case of diabetes mellitus r_G is large, i.e., $r_G \gg r_I$. From (2) and the well known theorem of Tikhonov (Tikhonov, 1948) one gets the approximate equation

$$\frac{G(t)}{K_G} = 1 + b\Big[1 - \frac{I(t)}{K_I}\Big]. \tag{21}$$

Then from (21) and (3) it follows

$$\dot{I}(t) = r_I\Big\{1 + b(1-a)\Big[1 - \frac{I(t)}{K_I}\Big] - \frac{pI(t-h_p) + (1-p)I(t-h)}{K_I}\Big\}I(t). \tag{22}$$

After the substitution

$$I(t) = K_I\big[1 + x(t)\big] \tag{23}$$

we get the differential equation

$$\dot{x}(t) = -r_I\big[\alpha x(t) + px(t-h_p) + (1-p)x(t-h)\big]\big[1 + x(t)\big], \tag{24}$$

where $\alpha = b(1-a)$.

If $\alpha = p = 0$ and $r_1 = \frac{\pi}{2h} + \varepsilon$, the characteristic quasipolinomial of the linear part of (24) has two simple roots $\tau(\varepsilon) \pm i\sigma(\varepsilon)$, satisfying the conditions $\tau(0) = 0,\ \sigma(0) = \sigma_0 = \frac{\pi}{2h},\ (0 \leqslant \varepsilon \ll 1)$ and (Švitra, 1989)

$$\tau_0' = \frac{2\pi}{\pi^2+4},\ \sigma_0' = \frac{4}{\pi^2+4}. \tag{25}$$

All other roots of it have negative real parts. Further, let $r_I\alpha = \alpha_0\varepsilon,\ r_Ip = \beta_0\varepsilon$. Then the characteristic quasipolinomial

$$P(\lambda;\varepsilon) = \lambda + \alpha_0\varepsilon + \beta_0\varepsilon \mathrm{e}^{-\lambda h_p} + [\sigma_0 + \varepsilon(1-\beta_0)]\mathrm{e}^{-\lambda h} \tag{26}$$

of the linear part of (24) has the simple roots $\eta(\varepsilon) \pm i\omega(\varepsilon)$, satisfying the conditions $\eta(0) = 0,\ \omega(0) = \sigma_0$,

$$\eta_0' = -(\tau_0' \mathrm{Im}\, P_{0\varepsilon}' + \sigma_0' \mathrm{Re}\, P_{0\varepsilon}'), \tag{27}$$

$$\omega_0' = \tau_0' \mathrm{Re}\, P_{0\varepsilon}' - \sigma_0' \mathrm{Im}\, P_{0\varepsilon}'), \tag{28}$$

where $\eta_0' = \eta'(\varepsilon)$, $\omega_0' = \omega'(\varepsilon)$ at $\varepsilon = 0$, $P_{0\varepsilon}' = P_\varepsilon'(\lambda;\varepsilon)$ at $\varepsilon = 0$, $\lambda = i\sigma_0$, and τ_0' and σ_0' are determined by (25). From (26) it follows, that

$$\mathrm{Re}\, P_{0\varepsilon}' = \alpha_0 + \beta_0 \cos\sigma_0 h_p, \quad \mathrm{Im}\, P_{0\varepsilon}' = -\big[1 - \beta_0(1 - \sin\sigma h_0)\big]. \tag{29}$$

From the above consideration and the results of Švitra (Švitra, 1989) we conclude the following

Theorem 1. *Let $0 < r_I - \sigma_0 = \varepsilon \ll 1$ and let the positive variable η_0' is determined by formula* (27)*. Then in a sufficiently small neighborhood of zero the difference-differential equation* (22) *at $r_I\alpha = \alpha_0\varepsilon$, $r_Ip = \beta_0\varepsilon$ has a unique (up to translation of time) stable periodic solution $I(t)$, for which on any segment of time of order ε^{-1} one has the asymptotic representation*

$$I(t) = K_I\big[1 + \xi\cos\sigma_0\tau + \xi^2 x_2(\tau) + \mathrm{O}\,(\xi^3)\big], \tag{30}$$

$$\xi = \sqrt{\frac{\varepsilon}{b_2}}, \quad \tau = \frac{t}{1 + c\xi^2}, \tag{31}$$

where

$$x_2(t) = \frac{1}{10}\sin 2\sigma_0\tau + \frac{1}{5}\cos 2\sigma_0\tau, \tag{32}$$

$$c_2 = c_0 + \frac{\omega_0' d_0}{\eta_0'\sigma_0}, \quad b_2 = -\frac{d_0}{\eta_0'}, \tag{33}$$

ω_0 is determined by formula (28) *and*

$$d_0 = -\frac{\sigma_0(3\pi - 2)}{10(\pi^2 + 4)}, \quad c_0 = \frac{\pi + 6}{10(\pi^2 + 4)}, \tag{34}$$

with $\sigma_0 = \frac{\pi}{2h}$ (Švitra,1989).

Further, let $r_I = r_I^0 + \varepsilon$, $r_I p = \alpha_0 \varepsilon$. Then the characteristic quasipolinomial

$$P(\lambda; \varepsilon) = \lambda + (r_I^0 + \varepsilon)\alpha + \alpha_0 \varepsilon \mathrm{e}^{-\lambda h_p} + \left[r_I^0 + \varepsilon(1 - \alpha_0)\right]\mathrm{e}^{-\lambda h} \tag{35}$$

of the linear part of (24) in the general case has simple roots $\eta(\varepsilon) \pm i\omega(\varepsilon)$, satisfying the conditions $\eta(0) = 0, \omega(0) = \sigma_0$. The following equalities hold

$$\eta_0' = -\frac{r_I^0}{\sigma_0}(\tau_0' \mathrm{Im}\, P_{0\varepsilon}' + \sigma_0' \mathrm{Re}\, P_{0\varepsilon}'), \tag{36}$$

$$\omega_0' = \frac{r_I^0}{\sigma_0}(\tau_0' \mathrm{Re}\, P_{0\varepsilon}' - \sigma_0' \mathrm{Im}\, P_{0\varepsilon}'), \tag{37}$$

where $P_{0\varepsilon}' = P_\varepsilon'(\lambda; \varepsilon)$ at $\lambda = i\sigma_0$ and $\varepsilon = 0$, σ_0 is the root of the equation

$$\alpha + \cos \sigma_0 h = 0, \tag{38}$$

belonging to the interval $\left(0, \frac{\pi}{2h}\right)$, r_I^0 is determined by the formula

$$r_I^0 = \frac{\sigma_0}{\sin \sigma_0 h}, \tag{39}$$

and τ_0', σ_0' are determined by formulas

$$\tau_0' = \frac{h\sigma_0^2}{r_I^0\left[h^2\sigma_0^2 + (1 + \alpha h r_I^0)^2\right]}, \tag{40}$$

$$\sigma_0' = \frac{\sigma_0(1 + \alpha h r_I^0)}{r_I^0\left[h^2\sigma_0^2 + (1 + \alpha h r_I^0)^2\right]} \tag{41}$$

(Švitra, 1989). From (35) it follows that

$$\mathrm{Re}\, P_{0\varepsilon}' = \alpha_0(\alpha + \cos \sigma_0 h_p), \quad \mathrm{Im}\, P_{0\varepsilon}' = -\alpha_0 \sin \sigma_0 h_p - (1 - \alpha_0) \sin \sigma_0 h. \tag{42}$$

There holds the following (Švitra, 1989).

Theorem 2. *Let $0 < r_I - r_I^0 = \varepsilon \ll 1$ and let the variable η_0' is positive. Then differential equation* (22) *has for $r_I p = \alpha_0 \varepsilon$ (up to translations of time), a unique stable*

periodic solution $I(t)$, for which on any segment of time of order ε^{-1} one has asymptotic representation (30)*, where σ_0 is determined from equation* (38)*,*

$$x_2(\tau) = A_{2s} \sin 2\sigma_0\tau + A_{2c} \cos 2\sigma_0\tau \tag{43}$$

with

$$A_{2s} = \frac{1-2\alpha}{2(5-4\alpha)}\sqrt{\frac{1-\alpha}{1+\alpha}}, \quad A_{2c} = \frac{1-\alpha}{5-4\alpha}, \tag{44}$$

$$\xi = \sqrt{\frac{\varepsilon}{B_2}}, \quad \tau = \frac{t}{1+C_2\xi^2}, \tag{45}$$

$$B_2 = \frac{\tau_0'}{\eta_0'}b_2, \quad C_2 = c_2 + \frac{\sigma_0'}{\sigma_0}b_2 - \frac{\omega_0'}{\sigma_0}B_2, \tag{46}$$

and

$$b_2 = \frac{3hr_I^0 + 2\alpha - 1}{4h(1+\alpha)(5-4\alpha)}, \quad c_2 = \frac{1-2\alpha}{4hr_I^0(1+\alpha)(5-4\alpha)}. \tag{47}$$

η_0' and ω_0' are determined by (36)–(37)*.*

3. Results of Numerical Investigation

We proceed directly to numerical investigation of the mathematical model (2)–(3) and the comparison of the obtained results with the experimental data. Here, taking into account that the resistance of exterior medium is a biological constant of the organism both in the normal and in the pathological cases, we assume the following experimental data (Švitra, 1989): $c_1 = 0.04$, $c_2 = 0.03$.

Normal case. On Fig. 3 we have constructed a numerical solution of the system (2)–(3) in case (20) for $r_I = 0.66$ and $a = 0.55$, reflecting the regulation in the system "insulin-blood glucose" of a healthy individual. On Fig. 3, also a comparison of the experimental data (Thum *et. al.*, 1975) of the dynamics of the level of glucose in the blood of a healthy individual with the graph of the function $G(t)$ is given. It can be seen that the graph of the function $G(t)$ passes through the points of the experimental data rather well.

Case of diabetes mellitus. In this case the normal regulation breaks down and the time of production of insulin also shortens, due to which less potent insulin is made. The numerical solution of the system (2)–(3) in the case (19) and for $r_I = 0.6$, $a = 0.8$ is pictured on Fig. 4. There also, the graph of the function $G(t)$ is compared with the points of the experimental data on the dynamics of the blood glucose level of a patient with diabetes mellitus (Berger and Rodbard, 1991). It is clear, that the coincidence is rather good.

One should note that in the cases considered above the daily biorhythm of the blood glucose level is unchanged, i.e., in the course of a day we have expressions of the maximum blood glucose level.

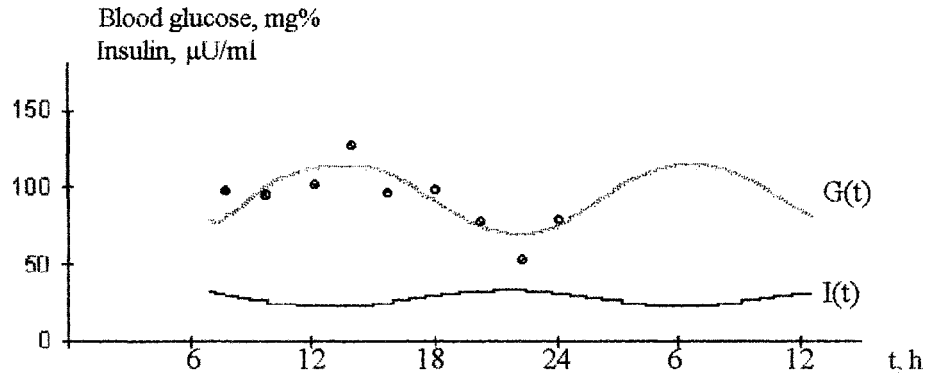

Fig. 3. Glusoce and insulin profiles in normal case.

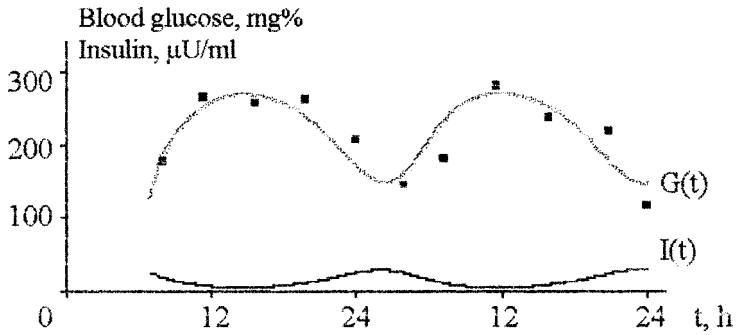

Fig. 4. Glucose and insulin profiles in case of diabetes mellitus.

4. Conclusions

Thus, by a synthesis of the methods of local analysis of nonlinear differential equations with retarded argument the methods of numerical investigation and as a result of certain biological considerations, we have succeeded in rather complete investigation of the mathematical model of self-regulation of glucose level in a blood taking into consideration the insulin "age structure". The investigation made above allows us to conclude that the mathematical model (2)–(3) clarifies the functioning of the physiological system "insulin-blood glucose" rather well both in the normal and in the pathological (diabetes mellitus) cases.

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Glikemijos dinamikos modeliavimas atsižvelgiant į insulino „amžiaus struktūrą“

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Tiriama dviejų netiesinių diferencialinių lygčių su vėlavimo argumentu sistema, kaip cukraus lygio kraujyje savaiminio reguliavimosi matematinis modelis. Modelyje atsižvelgta į tam tikrą insulino „amžiaus struktūrą“. Kokybiniais metodais, taip pat skaitmeniškai atlikta matematinė analizė leidžia padaryti išvadą, kad matematinis modelis paaiškina fiziologinės sitemos „insulinas-cukrus kraujyje“ funkcionavimą, esant jo normai ir esant patologijai – cukriniam diabetui.