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The mathematical model of the menstrual cycle with time delay depending on the researched function

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Introduction

The endocrine system is one of the main systems, which determins harmony and coordination of physiological processes of organism. Endocrinical glands produce biologically active matters, the hormones, by which homeostasis is supported, i.e., the stability of the organism inner medium, independently of the changes in the external surroundings. That is why the most important problem in endocrinology is to find out the hormone actions. The method of mathematical modeling [1] helps us to solve those problems, too. With the all of mathematical models one may find new trends in experimental and clinical researches, based on new quantitative hypotheses. Referring to the scheme of hormone interaction during the menstrual cycle [7], interrelations of the analyzed system were interpreted as an ecological problem "predator – prey". Then we describe the dynamics of the sexual hormones during the menstrual cycle by the following mathematical model [6]:

$$\dot{F}(t) = r_F\left[1 + a\left(1 - \frac{E_-(t-1)}{K_{E-}}\right) - \frac{F(t)}{K_F}\right]F(t), \tag{1}$$

$$\dot{E}_-(t) = r_{E-}\left[1 + b\left(1 - \frac{F(t)}{K_F}\right) - \frac{E_-(t-h_{E-})}{K_{E-}}\right]E_-(t), \tag{2}$$

$$\dot{L}(t) = r_L\left[1 + c\left(\frac{E_-(t-1)}{K_{E-}} - \frac{P(t)}{K_P}\right) - \frac{L(t)}{K_L}\right]L(t), \tag{3}$$

$$\dot{P}(t) = r_P\left[\alpha\frac{L(t-h_{E-})}{K_L} + (1-\alpha)\frac{E_+(t-h_{E-})}{K_{E+}} - \frac{P(t)}{K_P}\right]P(t); \tag{4}$$

$$\dot{E}_+(t) = r_{E+}\left[\frac{E_-(t)}{K_{E-}} - \frac{E_+(t-h_{E+})}{K_{E+}}\right]E_+(t), \tag{5}$$

$$E(t) = E_-(t) + E_+(t-h_{E-}). \tag{6}$$

Here, $L(t), F(t), P(t)$ are concentrations of LH (luteinising hormone), FSH (follicle stimulating hormone), and progesterone P in blood at the time moment t; respectively $E_-(t)$, $E_+(t)$ is the concentration of estradiol E in blood at the time t in the pre- and post ovular phase, respectively; $K_{E-}, K_{E+}, K_P, K_L, K_F$ - is that of estradiol E (in the pre- and post-ovular phase), and progesterone P, LH, FSH are respective average concentrations in blood. The parameters $r_{E-}, r_{E+}, r_P, r_L, r_F$ characterize the growth rate of the corresponding hormone concentration, and the parameters a, b, c realize regulation, which takes place through the feedback mechanism.

This mathematical model is researched in [5, 8].

The production of hormone E_- plays the main role for the system analyzed in [2]. If the secretion of E_- before the ovulation is normal, then after the ovulation the production of E_+ will not be disturbed. And *vice versa*, if the production of E_- by follicle is in sufficient, then in the post-ovular phase, the secretion of the yellow corpuscle hormones will be disturbed. Clinical data confirm this interrelation [3].

Mathematical model

The changing physiological quantities, such as the sleeping cycle, health condition, metabolic, physiological and many other factors, all of them have influence on the hormone changes, and they also influence hormone secretion in pituitary and ovary. So, the hormone concentration at the given moment influences the pasterior hormone concentration. Thus, speaking about the time delay in the female menstrual cycle, we can claim that, in this system, it depends on the searched function, i.e., the hormone concentration in blood at a certain time moment.

The behavior of solution of the non linear system of equations (1)–(6) depends on the behavior of the solutions of system (2) and (5). This relation was found during the analysis of the system of equations (1)–(6) [8]. As mentioned before, E_- production plays the main role in the system analyzed.

Let us say that time delay, in the pre-ovular phase h_{E_-}, depends on the function $E_-(t)$, under research. Then we put down the system of equations (1)–(6) as follows:

$$\dot{F}(t) = r_F\left[1 + a\left(1 - \frac{E_-(t-1)}{K_{E-}}\right) - \frac{F(t)}{K_F}\right] F(t), \tag{7}$$

$$\dot{E}_-(t) = r_{E-}\left[1 - \frac{E_-(t - \Delta(E_-))}{K_{E_-}}\right] E_-(t), \tag{8}$$

$$\dot{L}(t) = r_L\left[1 + c\left(\frac{E_-(t-1)}{K_{E-}} - \frac{P(t)}{K_P}\right) - \frac{L(t)}{K_L}\right] L(t), \tag{9}$$

$$\dot{P}(t) = r_P\left[\alpha\frac{L(t-h_{E-})}{K_L} + (1-\alpha)\,\frac{E_+(t-h_{E-})}{K_{E+}} - \frac{P(t)}{K_P}\right] P(t); \tag{10}$$

$$\dot{E}_+(t) = r_{E+}\left[\frac{E_-(t)}{K_{E-}} - \frac{E_+(t-h_{E+})}{K_{E+}}\right] E_+(t), \tag{11}$$

$$E(t) = E_-(t) + E_+(t - h_{E-}). \tag{12}$$

where time delay $\Delta(E_-)$ depends on the function researched.

We choose the following form of the Δ dependence on $E_-(t)$

$$\Delta(E_-) = h_{E_-} \exp\left(d\left(1 - \frac{E_-}{K_{E_-}}\right)\right). \tag{13}$$

The choice of the time delay expression is not casual here and it has the biological basis: when the hormone concentration in blood is high, its synthesis is slowing down and, vice versa, [2]. Let us analyze a modified mathematical model (7)–(12).

Linear Analysis. Assume that the parameters reflecting feedback $a = c = \alpha = 0$. Then the behavior of the solutions of system of equations (7)–(12) are described by the following behavior of the solutions of the system:

$$\dot{E}_-(t) = r_{E_-}\left[1 - \frac{E_-(t - \Delta(E_-))}{K_{E_-}}\right] E_-(t), \tag{14}$$

$$\Delta(E_-) = h_{E_-} \exp\left(d\left(1 - \frac{E_-}{K_{E_-}}\right)\right), \tag{15}$$

$$\dot{E}_+(t) = r_{E+}\left[\frac{E_-(t)}{K_{E-}} - \frac{E_+(t - h_{E+})}{K_{E+}}\right] E_+(t). \tag{16}$$

From (15) it follows, that $0 < \Delta(E_-) \leqslant h_{E_-} \exp d$. The system of equations (14)–(16) has the following states of equilibrium:

$$E_-(t) = E_+(t) \equiv 0; \tag{17}$$

$$E_-(t) \equiv K_{E-}, \quad E_+(t) \equiv 0; \tag{18}$$

$$E_-(t) \equiv K_{E-}, \quad E_+(t) \equiv K_{E+}. \tag{19}$$

The states of equilibrium (17) and (18) are always unstable.

We analyze the stability of equilibrium state (19). We change variables

$$E_-(t) = K_{E_-}\left(1 + x\left(\frac{t}{h_{E_-}}\right)\right), \quad E_+(t) = K_{E+}(1 + y(t)) \quad \text{and get}$$

$$\dot{x}(t) = -r_{E_-}h_{E_-}[1 + x(t)]x(t - \exp(-dx)), \tag{20}$$

$$\dot{y}(t) = r_{E+}[x(t) - y(t - h_{E+})][1 + y(t)]. \tag{21}$$

Characteristic quasipolynomial of the linear part of the system of equations (20)–(21)

$$P(\lambda) = (\lambda + dr_{E_-} \exp(-\lambda h_{E_-}))(\lambda + r_{E+} \exp(-\lambda h_{E+})) \tag{22}$$

has the properties researched before (see [8]). If $dr_{E_-}h_{E_-} < \frac{\pi}{2}$ and $r_{E+}h_{E+} < \frac{\pi}{2}$, then all the roots of the equation $P(\lambda) = 0$ have negative real parts and, if $dr_{E_-}h_{E_-} = \frac{\pi}{2}$ and $r_{E+}h_{E+} < \frac{\pi}{2}$, a pair of imaginary roots $\pm\frac{\pi}{2}i$ appears in this equation. The following statement is correct.

Theorem 1. *If* $0 < dr_{E\_}h_{E\_} < \frac{\pi}{2}$ *and* $0 < r_{E+}h_{E+} < \frac{\pi}{2}$ *then the equilibrium state* (19) *of system of the differential equations* (14)–(16) *is locally asymptotically stable.*

Nonlinear Analysis. We have a system of non linear differential equations (20) and (21). It is true that $dr_{E\_}h_{E\_} < \frac{\pi}{2}$ and $r_{E+}h_{E+} < \frac{\pi}{2}$. Referring to the properties of the modified Chatchinson equation [4], the following statement is correct.

Theorem 2. *If* $\varepsilon = dr_{E\_}h_{E\_} - \frac{\pi}{2} > 0$ *is sufficiently small then equation* (20) *has the stable periodic solution*

$$x(\tau) = \xi x_1(\tau) + \xi^2 x_2(\tau) + \dots, \quad \textit{where} \tag{23}$$

$$x_1(\tau) = \cos\sigma\tau, \quad x_2(\tau) = \frac{1}{10}(\sin 2\sigma\tau + 2\cos 2\sigma\tau), \tag{24}$$

$$\begin{gathered} \sigma\left(1 + \frac{c_2}{b_2}\varepsilon + \dots\right) = \frac{2}{2h_{E\_}}, \quad b_2 = \frac{6\pi - 4 + 4\pi(1+\pi) - 5\pi(3+\pi)d^2}{80}, \\ c_2 = \frac{4 - 4\pi d + 5\pi(3+\pi)d^2}{40\pi}, \quad \xi = \sqrt{\frac{dr_{E\_}h_{E\_} - \frac{\pi}{2}}{b_2}}, \quad \tau = \frac{t}{h_{E\_}(1 + c_2\xi^2)}. \end{gathered} \tag{25}$$

The properties of the function $b_2(d)$, for $d = a$, are described in [4].

If $r_{E+}h_{E+} < \frac{\pi}{2}$, then the system of differential equations (21) has only one stable periodic solution.

$$y(\tau) = \xi y_1(\tau) + \xi^2 y_2(\tau) + \dots. \tag{26}$$

Hence, the system of differential equations (14) and (16) has the periodic solutions.

Theorem 3. *If* $0 < r_{E\_}h_{E\_} - \frac{\pi}{2} = \varepsilon \iff 1$ *and* $0 \leqslant d \leqslant d_0$, *then the system* (14)–(16) *in the neighlovhood of the equilibrium state* (19) *has the stable periodic solution*

$$E_-(t) = K_{E-}\left[1 + \xi\cos\frac{\pi}{2h_{E\_}}\tau + \xi^2 x_2(\tau) + \mathrm{O}(\xi^3)\right], \tag{27}$$

where $x_2(\tau)$ *is expressed by formula* (24) *and* σ, τ, ξ *we given by formula* (25),

$$E_+(t) = K_{E_+}\left[1 + \xi y_1(\tau) + \xi^2 y_2(\tau) + \mathrm{O}(\xi^3)\right]. \tag{28}$$

Here $y_1(\tau)$, $y_2(\tau)$, σ, τ *and* ξ *are calculated in the same way* [8].

Results

We proceed directly to the numerical investigation of mathematical models (1)–(6) and (7)–(12) and comparise of the results obtained with the experimental data [3]. The expressions of the stable periodic solutions are presented in [8] and (27), (28). Fig. 1 shows E dynamics in the main case and in the modificed one.

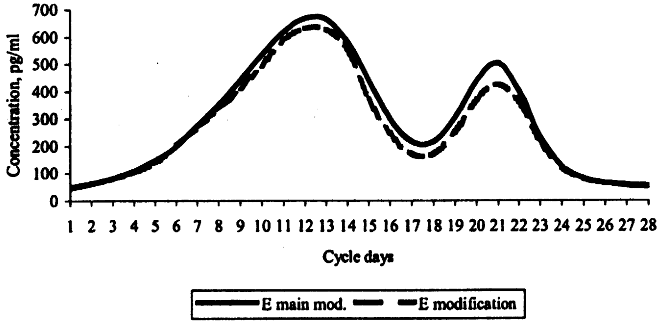

Fig. 1. E dynamics in the main case and in the modification.

Conclusions

The offered theoretical models give a good description of the real situation in the cycle of a long period (28 days). The values of the simplest mathematical model of the menstrual cycle and the mathematical model with time delay depending on the function researched differ slightly.

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Moters ovuliacinio ciklo matematinis modelis su vėlavimu, priklausančiu nuo ieškomos funkcijos

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Straipsnyje supažindinama su paprasčiausiu matematiniu modeliu, aprašančiu hormonų sąveiką ovuliacinio ciklo metu, kurį sudaro šešios netiesinės diferencialinės lygtys su vėluojančiu argumentu. Pasiūlyta ir ištirta ovuliacinio ciklo matematinio modelio modifikacija – matematinis modelis su vėlavimu, priklausančiu nuo ieškomos funkcijos. Atliktas skaitinis eksperimentas, kurio metu rasti minėtos modelio modifikacijos sprendiniai. Gauti sprendiniai palyginti su klinikiniais duomenimis bei tarpusavyje.