

The Mathematical Model of the Female Menstrual Cycle and its Modifications

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Abstract. This article is an introduction to the simplest mathematical model, which describes the hormone interaction during the menstrual cycle. Modifications of the mathematical model of the menstrual cycle including the mathematical model with the time delay depending on function researched and the mathematical model with the dispersed time delay are researched and described here. A numerical investigation was conducted, during which solutions for the above mentioned models were calculated. The solutions found are compared mutually and with the clinical data.

Key words: mathematical modeling, time delay, menstrual cycle.

1. Introduction

At the beginning of the 20th century much attention was paid for the female reproductive system. After invention of the steroidal hormones their functioning mechanisms were started explained. For the solution of this problem mathematical models were employed. In 1972 R. Bogumil with co-authors (Bogumil *et al.*, 1972) offered a very detailed mathematical model of the menstrual cycle, which contains 34 non-linear equations, but the large number of equations makes it difficult to find the expression for its solution.

Referring to the scheme of hormone interaction during the menstrual cycle (Švitra *et al.*, 1998), 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 (Švitra and Grigolienė, 1998a):

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

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

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

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

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

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

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

This mathematical model is researched in works (Švitra and Grigolienė, 1997; Švitra and Grigolienė, 1998a).

The production of hormone E_- has the main role in the analyzed system (Grigolienė *et al.*, 1999). If the secretion of E_- before the ovulation is normal, then after the ovulation production of E_+ will be not disturbed. And *vice versa* if the production of E_- by follicle is not sufficient, then during the post ovular phase secretion of the yellow corpuscle hormones will be disturbed. Clinical data confirms this interrelation (Speroff *et al.*, 1989).

2. Modifications of the Mathematical Model of the Menstrual Cycle

2.1. The Mathematical Model of Menstrual Cycle with Time Delay Depending on the Searched Function

The changing physiological quantities such as sleeping cycle, health condition, metabolic, physiological and many other factors all have influence on the hormone changes, and it influences hormone secretion in pituitary and ovary. So, the hormone concentration at the given moment later influences the 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 the certain time moment.

Behavior of the solution of the non-linear equation system (1)–(6) depends on behavior of the solutions of (2) and (5) equations system. It was found during the analysis of the equation system (1)–(6) (Švitra and Grigolienė, 1998a). As we mentioned before, E_- production plays the main role in the analyzed system.

Let's say that time delay in preovular phase h_{E_-} depends on searched function $E_-(t)$, then we put down the equation system (1)–(6) as follows:

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

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

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

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

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

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

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

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

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

The choice of the time delay expression is not casual here and it has its biological sense: when hormone concentration in blood is high, its synthesis is slowing down and vice versa (Grigolienė *et al.*, 1999). Let's analyze the modified mathematical model (7)–(12).

Linear Analysis. Let's say that parameters reflecting feedback $a = c = \alpha = 0$. Then behavior of the solutions of the equation system (7)–(12) will be described by the following behavior of the solutions of the equation 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) follows, that $0 < \Delta(E_-) \leq h_{E_-} \exp d$.

The equation system (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 will analyze the stability of (19) equilibrium state. We change variables $E_-(t) = K_{E_-}(1+x(\frac{t}{h_{E_-}}))$, $E_+(t) = K_{E_+}(1+y(t))$ 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 equation system (20)–(21)

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

has the before researched properties (Švitra and Grigolienė, 1998a). When $dr_{E_-} h_{E_-} < \frac{\pi}{2}$ and $r_{E_+} h_{E_+} < \frac{\pi}{2}$ then all roots of the equation $P(\lambda) = 0$ have negative real parts, and when $dr_{E_-} h_{E_-} = \frac{\pi}{2}$ 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. *When $0 < dr_{E_-} h_{E_-} < \frac{\pi}{2}$ and $0 < r_{E_+} h_{E_+} < \frac{\pi}{2}$ then equilibrium state (19) of the differential equation system (14)–(16) is locally asymptotically stable.*

Nonlinear Analysis. We have the system of the non-linear differential equations (20) and (21). Correct is that $dr_{E_-} h_{E_-} < \frac{\pi}{2}$ and $r_{E_+} h_{E_+} < \frac{\pi}{2}$. Referring to the Chatchinson's equation modification properties (Švitra, 1989), the following statement is correct.

Theorem 2. *When $\varepsilon = dr_{E_-} h_{E_-} - \frac{\pi}{2} > 0$ is sufficiently small, then equation (20) has its stable periodic solution*

$$x(\tau) = \xi x_1(\tau) + \xi^2 x_2(\tau) + \dots, \quad (23)$$

where

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

$$\begin{aligned} \sigma \left(1 + \frac{c_2}{b_2} \varepsilon + \dots \right) &= \frac{2}{2h_{E_-}}, \\ b_2 &= \frac{6\pi - 4 + 4\pi(1 + \pi) - 5\pi(3 + \pi)d^2}{80}, \\ c_2 &= \frac{4 - 4\pi d + 5\pi(3 + \pi)d^2}{40\pi}, \end{aligned} \quad (25)$$

$$\xi = \sqrt{\frac{dr_{E_-} h_{E_-} - \frac{\pi}{2}}{b_2}},$$

$$\tau = \frac{t}{h_{E_-} (1 + c_2 \xi^2)}.$$

Properties of function $b_2(d)$, when $d = a$ are described by (Švitra, 1989).

When $r_{E_+} h_{E_+} < \frac{\pi}{2}$ then the differential equation (21) will have the only stable periodic solution as well.

$$y(\tau) = \xi y_1(\tau) + \xi^2 y_2(\tau) + \dots \quad (26)$$

Accordingly, the differential equations (14) and (16) will have the periodic solutions.

Theorem 3. When $0 < r_{E_-} h_{E_-} - \frac{\pi}{2} = \varepsilon \ll 1$ and when $0 \leq d \leq d_0$ the system (14)–(16) in the equilibrium state (19) will have the stable periodic solution

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

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

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

here $y_1(\tau), y_2(\tau), \sigma, \tau$ and ξ are calculated in the same way (Švitra and Grigolienė, 1998a).

2.2. The Mathematical Model of Menstrual Cycle with Distributed Time Delay

We may interpret the time delay during the menstrual cycle as a function dispersed according to the certain law. Referring to the above-presented comments we will change the equation (2) of the equation system (1)–(6) to the equation with distributed time delay. Then we may write down the equation system (1)–(6)

$$\dot{F}(t) = r_F \left[1 + a \left(1 - \frac{E_-(t-1)}{K_{E_-}} \right) - \frac{F(t)}{K_F} \right] F(t), \tag{29}$$

$$\dot{E}_-(t) = r_{E_-} \left[1 - \frac{1}{K_{E_-}} \int_{h_{E_- \min}}^{h_{E_- \max}} H(s) E_-(t-s) ds \right] E_-(t), \tag{30}$$

$$\dot{L}(t) = r_L \left[1 + c \left(\frac{E_-(t-1)}{K_{E_-}} - \frac{P(t)}{K_P} \right) - \frac{L(t)}{K_L} \right] L(t), \tag{31}$$

$$\dot{P}(t) = r_P \left[\alpha \frac{L(t-h_{E_-})}{K_L} + (1-\alpha) \frac{E_+(t-h_{E_-})}{K_{E_+}} - \frac{P(t)}{K_P} \right] P(t), \tag{32}$$

$$\dot{E}_+(t) = r_{E_+} \left[\frac{E_-(t)}{K_{E_-}} - \frac{E_+(t-h_{E_+})}{K_{E_+}} \right] E_+(t), \tag{33}$$

$$E(t) = E_-(t) + E_+(t-h_{E_-}). \tag{34}$$

The differential equation (30) is a generalization of the equation (2). By its biological sense $h_{E_- \max} > h_{E_- \min}$, and non-negative function $H(s)$ is a characteristic of the age structure of the concentration of the hormone E_- . Additionally $\int_{h_{E_- \min}}^{h_{E_- \max}} H(s) ds = 1$.

Let's make an analysis of the mathematical model (29)–(34) of the menstrual cycle.

Linear analysis. Let's say parameters of the reflecting feedback mechanism are $a = c = \alpha = 0$. Then behavior of the solutions of the equation system (29)–(34) will be

described by the following behavior of the equation system solutions:

$$\dot{E}_-(t) = r_{E_-} \left[1 - \frac{1}{K_{E_-}} \int_{h_{E_- \min}}^{h_{E_- \max}} H(s) E_-(t-s) ds \right] E_-(t), \quad (35)$$

$$\dot{E}_+(t) = r_{E_+} \left[\frac{E_-(t)}{K_{E_-}} - \frac{E_+(t-h_{E_+})}{K_{E_+}} \right] E_+(t). \quad (36)$$

The equation system (35)–(36) will have the equilibrium states (17), (18), (19).

Obviously the equilibrium states (17) and (18) are not stable. We will further research system of the equations (35) and (36) in the environment of its equilibrium state (19).

We can judge about the local asymptotic stability of the equilibrium state (19) of the equation system (35)–(36) after the research of the characteristic quasipolynomial of the equation system (35)–(36)

$$P(\lambda) = \left[\lambda + r_{E_-} \int_{h_{E_- \min}}^{h_{E_- \max}} H(s) \exp(-\lambda s) ds \right] [\lambda + r_{E_+} \exp(-\lambda h_{E_+})] \quad (37)$$

roots positioning in the complex plain surface.

Positioning of the quasipolynomial $P(\lambda) = \lambda + r_{E_+} \exp(-\lambda h_{E_+})$ roots in the complex plain surface has been already researched (Švitra and Grigolienė, 1998a). We will find positioning of the quasipolynomial

$$P(\lambda) = \lambda + r_{E_-} \int_{h_{E_- \min}}^{h_{E_- \max}} H(s) \exp(-\lambda s) ds \quad (38)$$

roots in the complex plain surface. We will use the D -partitioning method.

Quasiplnomial (38) has the zero root when

$$p = -r_{E_-}. \quad (39)$$

The straight line (39) is one of the lines making the D -partitioning boundaries of the plain surface $p = r_{E_-}$.

Let's say $\lambda = i\sigma$ ($\sigma > 0$), then from the equation

$$\lambda + r_{E_-} \int_{h_{E_- \min}}^{h_{E_- \max}} H(s) \exp(-\lambda s) ds = 0 \quad (40)$$

we will get the remaining equations of the D -partitioning curves in the parametric form

$$r_{E_-} = \frac{\sigma}{\int_{h_{E_- \min}}^{h_{E_- \max}} H(s) \sin \sigma s ds}, \quad (41)$$

$$p = -r_{E-} \int_{h_{E-\min}}^{h_{E-\max}} H(s) \cos \sigma s ds. \tag{42}$$

As $\sigma \rightarrow 0$ we determine the so-called cups $A(p_0, r_{E-0})$, whose coordinates are:

$$r_{E-0} = \frac{1}{\int_{h_{E-\min}}^{h_{E-\max}} H(s) s ds}, \tag{43}$$

$$p_0 = -r_{E-0}. \tag{44}$$

Referring to the available clinical data and recommendations (Speroff *et al.*, 1989; Bogumil *et al.*, 1972; Švitra, 1989), let's say that

$$H(s) = a \exp \left[-\frac{1}{2} (s - h_*)^2 \right], \tag{45}$$

where $a > 0$, $h_* = \frac{h_{E-\min} + h_{E-\max}}{2}$, $h_{E-\min} = 5$ days, $h_{E-\max} = 9$ days.

In Fig. 1 the D -partitioning of the plane surface $p r_{E-}$ is made. Area D_0 is the area of asymptotic stability, in the area D_2 two roots with positive real part appears, and so on.

Nonlinear Analysis. With an aim to simplify the calculations and remembering properties of δ functions, we can change expression $\int_{h_{E-\min}}^{h_{E-\max}} H(s) E_-(t-s) ds$ in the equation (30) into expression $E_-(t-h_*)$. When there is a low dispersion then h_* is close to 7. Then

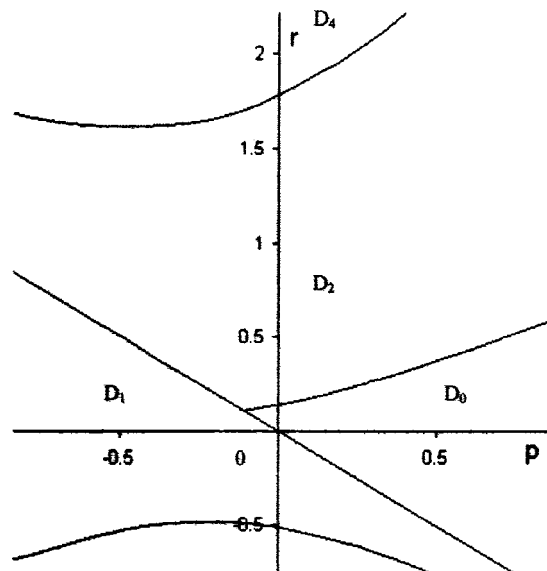


Fig. 1. The D -partition on the plane of parameters p and r_{E-} .

nonlinear analysis of the equation system (29)–(34) is analogous to nonlinear analysis of the simplest mathematical model of the menstrual cycle (Švitra and Grigolienė, 1998a).

3. Results of Numerical Investigation

We proceed directly numerical investigation of the mathematical models (1)–(6) and (7)–(12) and comparison of the results obtained with the experimental data (Speroff *et al.*, 1989). The expressions of the stable periodic solutions are presented in (Švitra and Grigolienė, 1998a) and in (27), (28).

Referring to the methodology offered by (Švitra, 1989) and experimental data, quantitative meaning of parameters are $r_{E_-} = 0,33$; $r_{E_+} = 0,15$; $r_P = 0,49$; $r_L = 5,5$ and $r_F = 5,6$. Average meanings of the parameters K_{E_-} , K_{E_+} , K_P , K_L ir K_F are known from the experimental data. We refer to (Speroff *et al.*, 1989) and find $K_{E_-} = 150$ pg/ml, $K_{E_+} = 100$ pg/ml, $K_P = 2$ ng/ml, $K_L = 35$ μ U/ml ir $K_F = 20$ μ U/ml. For the feedback parameters we ascribe the following meanings $a = -0.23$, $b = -0.1$, $c = 0.135$ ir $\alpha = 0.15$.

Time delays h_{E_-} and h_{E_+} introduced in the equation system (1)–(6) characterize the time period, which is necessary to mature follicle and start producing estradiol. Estradiol E_- concentration depends on degree of follicle maturity: the younger follicle the less estrogen are produced and vice versa, i.e., in the preovular phase changes in E_- concentration at the time moment t depend on concentration at the time moment $t - h_{E_-}$. Analogously the time delay h_{E_+} is interpreted in post ovular phase. Referring to the experimental data from (Bogumil *et al.*, 1972) we will consider that $h_{E_-} > h_{E_+}$, because in yellow corpuscle cell the typical structure of cells – steroid producers – is created; for that reason biosynthesis in post ovular phase is shorter; therefore $h_{E_-} = 7$ days, $h_{E_+} = 2$ days.

With the help of imitational modeling system ModelMaker v. 3.0 solutions of the simplest mathematical model (1)–(6) of the menstrual cycle were calculated. Fig. 2 shows female hormone dynamics during the menstrual cycle.

Solving the (7)–(12) equation system using numerical methods quantitative meanings of parameters r_{E_+} , r_P , r_L , r_F , average meanings of parameters K_{E_-} , K_{E_+} , K_P , K_L , K_F , meanings of feedback parameters a , b , c , α remain the same as in the first case. Parameter $r_{E_-} = 0,29$. Using the same method and the expressions (27), (28) we get the estradiol dynamics during menstrual cycle in equation system (7)–(12) case.

4. Conclusions

The offered theoretical models give a good description of the real situation in the long period (28 days) cycle. Their precision is confirmed by the correspondence between theoretically and practically calculated hormone concentrations in patients' blood during all phases of the menstrual cycle. The main regulator in these models is the mechanism of feedback (positive and negative) and parameters regulating it, therefore the model reflects

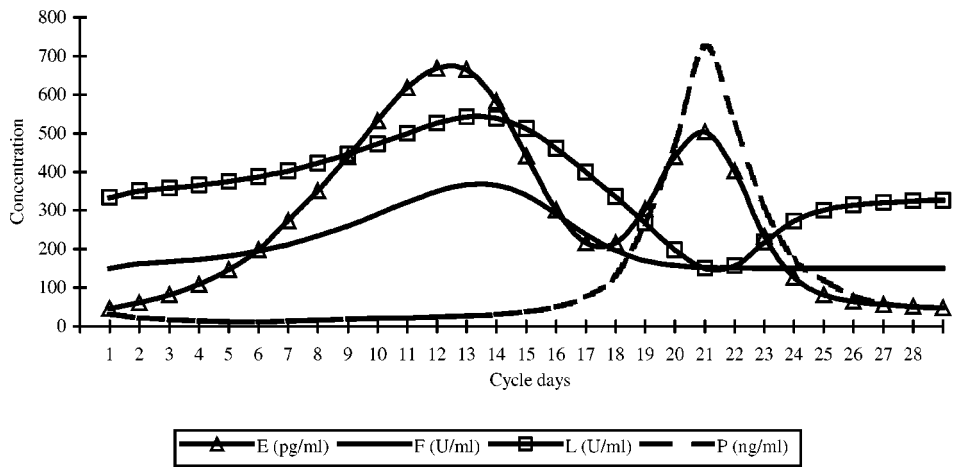


Fig. 2. Sexual hormones dynamics in main case.

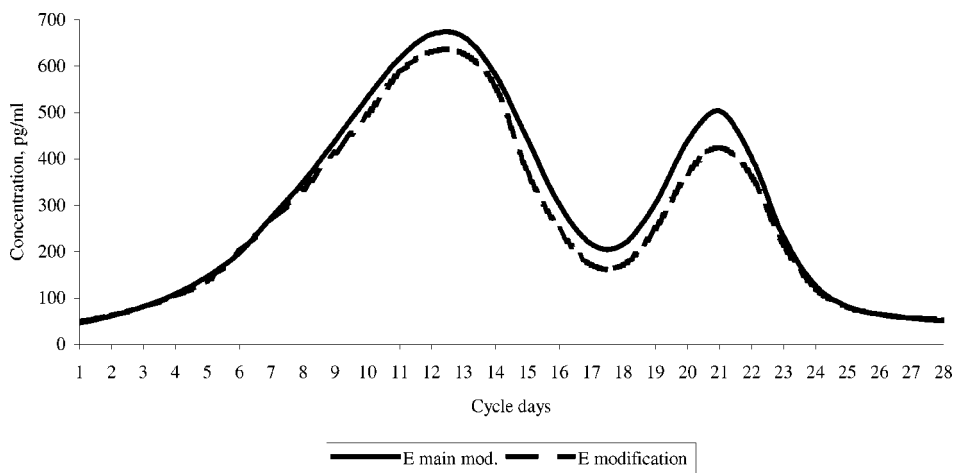


Fig. 3. E dynamics in main case and in modification.

the shifts in hormone levels during the deviations of the menstrual cycle. In Fig. 3 estradiol $E_$ dynamics is shown in the preovular phase calculated using each mathematical model. The meanings of the simplest mathematical model of the menstrual cycle and mathematical model with time delay depending on the searched function are not much different from each other.

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Moters ovuliacinio ciklo matematinis modelis ir jo modifikacijos

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Straipsnyje supažindinama su paprasčiausiu matematiniu modeliu, aprašančiu hormonų sąveiką ovuliacinio ciklo metu. Pasiūlytos ir ištirtos ovuliacinio ciklo matematinio modelio modifikacijos – matematinis modelis su vėlavimu, priklausančiu nuo ieškomos funkcijos, bei matematinis modelis su pasiskirsčiusiu vėlavimu. Atliktas skaitinis eksperimentas, kurio metu rasti minėtų modelių sprendiniai. Gauti sprendiniai palyginti su klinikiniais duomenimis bei tarpusavyje.