LOCAL STABILITY ANALYSIS OF THE MATHEMATICAL MODEL FOR MENSTRUAL CYCLE

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Abstract

The menstrual cycle is the scientific term for the physiological changes that can occur in fertile women. The menstrual cycle, under controlling of the endocrine system, is necessary for reproduction. It is commonly divided into three phases: the follicular phase, ovulation, and the luteal phase. In this study, we analyze a mathematical model of the population of the human menstrual cycle. The equilibrium point of the model and its stability are show.

Keywords: menstrual cycle, mathematical model , equilibrium point , stability

Introduction

Menstrual cycle is the scientific term for physiological changes that can occur in fertile women. This article focuses on the human menstrual cycle. Menstrual cycle, under controlling of the endocrine system, is necessary for reproduction. It is commonly divided into three phases: the follicular phase, ovulation, and the luteal phase; although some sources use a different set of phases: menstruation, proliferative phase, and secretory phase.[1] Menstrual cycles are counted from the first day of menstrual bleeding. Hormonal contraception interferes with the normal hormonal changes with the aim of preventing reproduction. Stimulated by gradually increasing amounts of estrogen in the follicular phase, discharges of blood (menses) slow then stop, and the lining of the uterus thickens. Follicles in ovary begin developing under influence of a complex interplay of hormones, and after several days one or occasionally two become dominant (non-dominant follicles atrophy and die). Approximately mid-cycle, 24–36 hours after the Luteinizing Hormone (LH) surges, the dominant follicle releases an ovum, or egg in an event called ovulation. After ovulation, an egg only lives for 24 hours or less without fertilization while the remaining of dominant follicle in ovary become a corpus luteum; this body has a primary function of producing large amounts of progesterone. Under the influence of progesterone, the endometrium (uterine lining) changes to prepare for potential implantation of an embryo to establish a pregnancy. If implantation does not occur within about two weeks, the corpus luteum will involute, causing sharp drops in levels of both progesterone and estrogen. The drops of these hormones cause uterus to shed its lining and egg in a process termed menstruation.Menstruation is the blood caused by sloughing of uterus' lining. There are two types of hormones Estrogen and Progesterone Control and peel off the lining of the uterus. The two levels are related to ovulation from the ovary. Each cycle has a duration of approximately 26-30 days, depending on the individual. The average time is a month.

In the period of 1-14 months ; the creation and growth of egg is fully cooked and will be called Follicular phase hormone, follicle stimulating hormone (FSH) stimulates ovaries to make estrogen to control the creation and growth of eggs the estrogen levels are increasing.
In the period of 14-28 months ; Luteinizing hormone (LH), which is a hormone that stimulates the ovarian hormones progesterone and LH levels to be high before the date of ovulation, because the hormone LH stimulate ovulation and progesterone hormones to control the thickness of uterus' lining for fertilized eggs. Thus, the progesterone levels are high, if egg is not mixed, the progesterone levels are low. The thickness of uterus' lining decays within a month.The menarche is one of the later stages of puberty in girls. The average age of menarche in humans is 12–13 years, but is normal anywhere between ages 8 and 16. Factors such as heredity, diet and overall health can accelerate or delay menarche.[2] The cessation of menstrual cycles at the end of a woman's reproductive period is termed menopause. The average age of menopause in women is 52 years in industrialised countries such as the UK, with anywhere between 45 and 55 being common. Menopause before age 45 is considered premature in industrialised countries.[3] The age of menopause is largely a result of genetics; however, illnesses, certain surgeries, or medical treatments may cause menopause to occur earlier.[4]

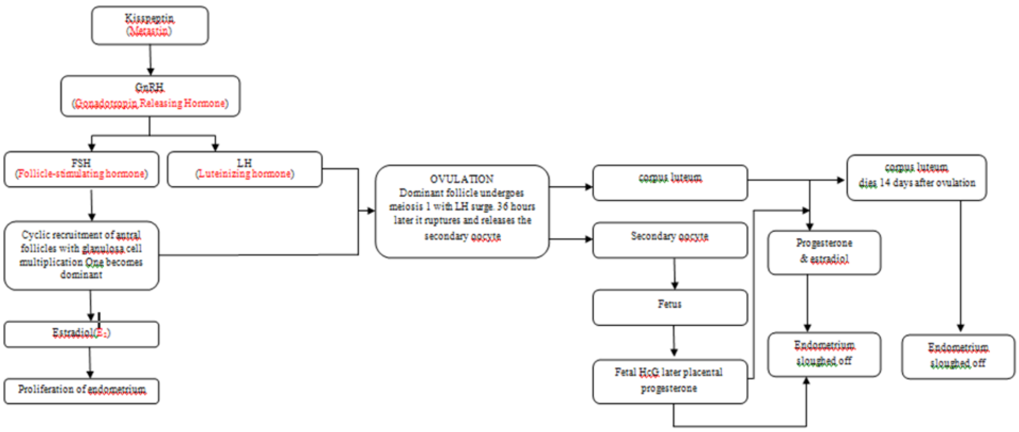
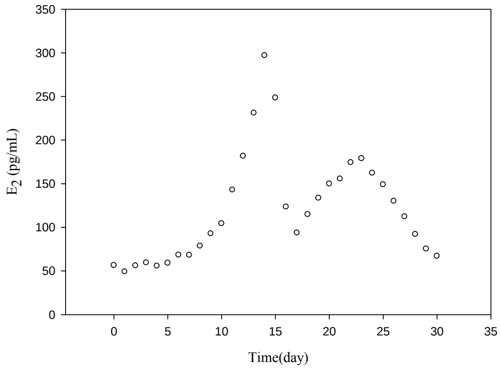
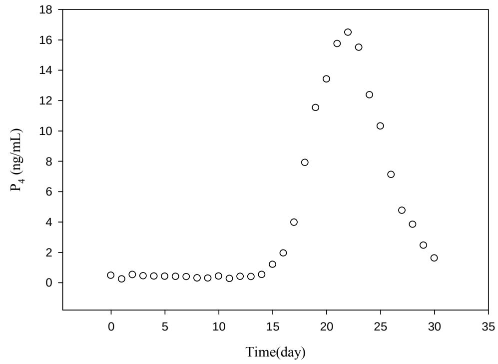


Figure 1 menstrual cycle[5]

Mathematical Model

A successful model of the pituitary's synthesis and release of the gonadotropin hormones must capture the biphasic response of LH to E_2 concentrations of various as follows :





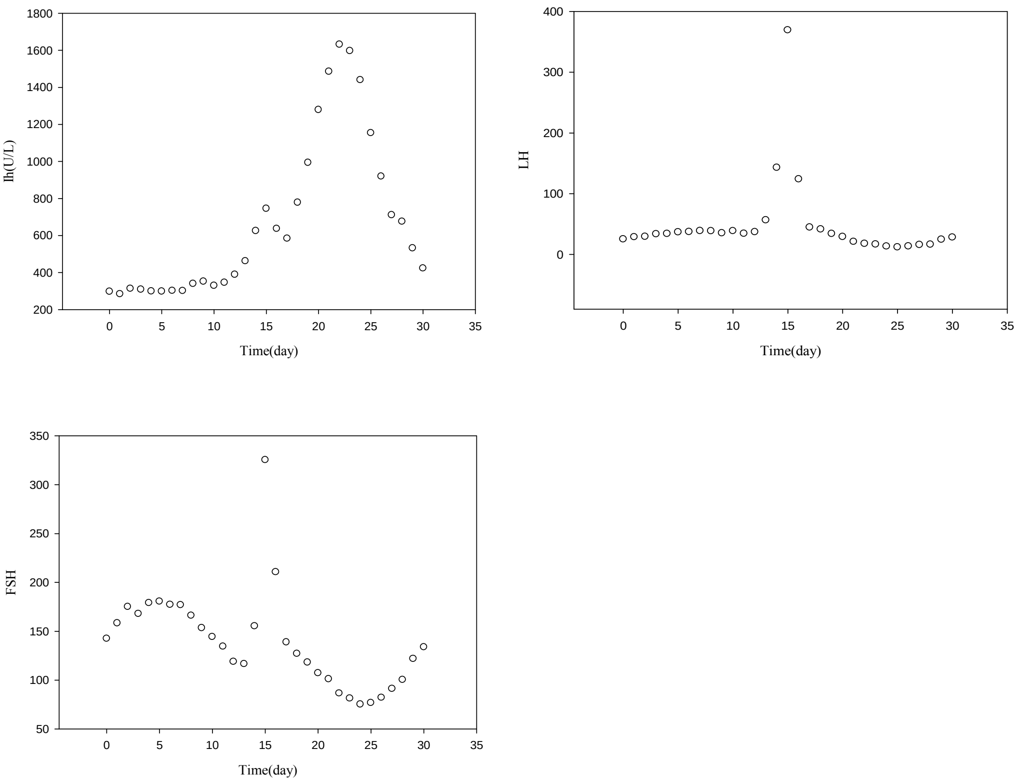


Figure 2 Daily hormone concentrations from McLachlan et al. [6]

The dynamical equations of system for the Hormones can be explained as follows [7]-[8]

System for the Pituitary Hormones

The system of differential equations governing the synthesis (s_{LH}), release (r_{LH}) and clearance (c_{LH}) of LH has the form

$$\frac{d}{dt}P_{LH} = s_{LH}\left(E_2, P_4\right) - r_{LH}\left(E_2, P_4, P_{LH}\right) \qquad (1)$$

$$\frac{d}{dt}LH = \frac{1}{v}r_{LH}\left(E_2, P_4, P_{LH}\right) - c_{LH}\left(LH\right) \qquad (2)$$

The pair of differential equations for synthesis and release of FSH have a form similar to (1)-(2) has the form

$$\frac{d}{dt}P_{FSH} = s_{FSH}\left(Ih\right) - r_{FSH}\left(E_2, P_4, P_{FSH}\right) \qquad (3)$$

$$\frac{d}{dt}FSH = \frac{1}{v}r_{FSH}\left(E_2, P_4, P_{FSH}\right) - c_{FSH}\left(FSH\right) \qquad (4)$$

where

$$s_{LH}(E_2,P_4)=\frac{V_{0,LH}+\dfrac{V_{1,LH}\left[E_2(t)\right]^8}{\left[K_{mLH}\right]^8+\left[E_2(t)\right]^8}}{1+P_4(t\text{-}dp)/K_{iLH,p}}$$

$$r_{LH}(E_2,P_4,P_{LH})=\frac{k_{LH}\left[1+c_{LH,p}P_4(t)\right]P_{LH}}{1+c_{LH,E}E_2(t)}$$

$$c_{LH}(LH)=a_{LH}LH$$

and

$$s_{FSH}(Ih)=\frac{V_{FSH}}{1+Ih\left(t\text{-}d_{Ih}\right)/K_{iFSH,Ih}}$$

$$r_{FSH}(E_2,P_4,P_{FSH})=\frac{k_{FSH}\left[1+c_{FSH,p}P_4(t)\right]P_{FSH}}{1+c_{FSH,E}\left[E_2(t)\right]^2}$$

$$c_{FSH}(FSH)=a_{FSH}FSH$$

where P_{LH},LH, P_{FSH} and FSH are the mass of stored LH in the pituitary , luteinizing hormone , mass of stored FSH in the pituitary and follicle stimulating hormone , respectively. The parameters in the above equations are defined as follows:

E_2 is the estradiol
P_4 is the progesterone
Ih is the inhibin concentration in the blood
v is the blood volume
$\alpha,\beta,\gamma,b,o_1,o_2,o_3,o_4,o_5,o_6,o_7,o_8,o_9,o_{10},o_{11}$ is the parameters for the ovary
$e_0, e_1, e_2, e_3, p_1, p_2, h_1, h_2, h_3, h_4$ is the parameters for these auxiliary equations

System for the Ovarian Hormones

The model for the ovary divides the follicular phase and the luteal phase into 9 distinct states based on the capacity of each state to produce hormones.
Before ovulation until the date of ovulation (follicular phase).

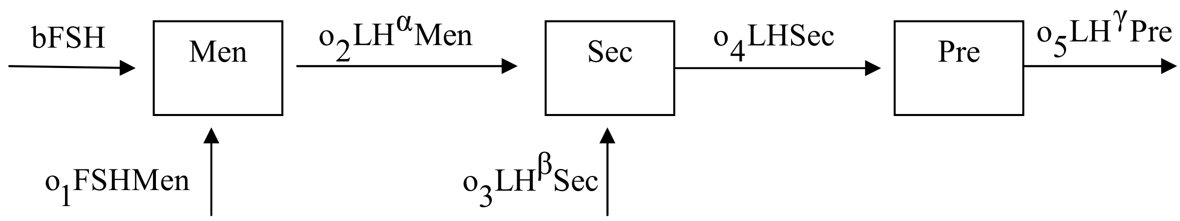


Figure 3 Diagram of the hormone before ovulation until the day of ovulation (follicular phase).

The dynamical equations of the hormone before ovulation until the day of ovulation (follicular phase) are described by

$$\frac{d}{dt}\mathrm{Men}=b\mathrm{FSH}+\left[o_1\mathrm{FSH}-o_2\mathrm{LH}^{\alpha}\right]\mathrm{Men} \tag{5}$$

$$\frac{d}{dt}\mathrm{Sec}=o_2\mathrm{LH}^{\alpha}\mathrm{Men}+\left[o_3\mathrm{LH}^{\beta}-o_4\mathrm{LH}\right]\mathrm{Sec} \tag{6}$$

$$\frac{d}{dt}\mathrm{Pre}=o_4\mathrm{LHSec}-o_5\mathrm{LH}^{\gamma}\mathrm{Pre} \tag{7}$$

where Men , Sec and Pre are the Menstrual , secondary , preovulatory follicle state , respectively.

During the transition period before ovulation until the day of ovulation (follicular. phase) to the period after ovulation until the day before menstruation (luteal phase).

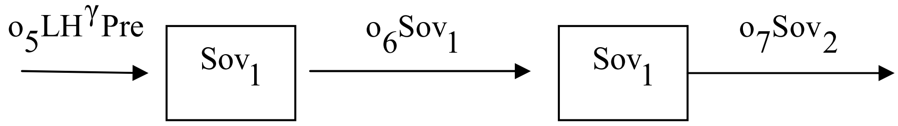


Figure 4 Diagram of the hormonal changes of ovulation prior to the date of ovulation (follicular phase) to the period after ovulation until the day before menstruation (luteal phase).

The dynamical equations of the hormonal changes of ovulation prior to the date of ovulation (follicular phase) to the period after ovulation until the day before menstruation (luteal phase) are described by

$$\frac{d}{dt}\mathrm{Sov}_1=o_5\mathrm{LH}^{\gamma}\mathrm{Pre}-o_6\mathrm{Sov}_1 \tag{8}$$

$$\frac{d}{dt}\mathrm{Sov}_2=o_6\mathrm{Sov}_1-o_7\mathrm{Sov}_2 \tag{9}$$

where Sov_1 and Sov_2 are the early and late ovulatory scar, respectively.

After ovulation until the day before menstruation (luteal phase).

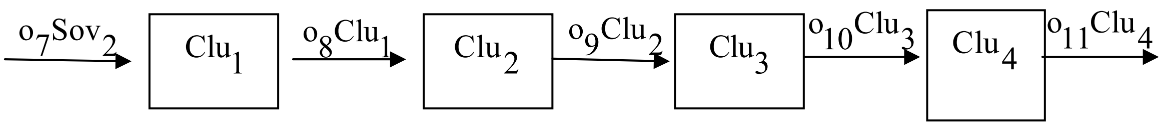


Figure 5 Diagram of the hormone after ovulation until the day before menstruation (luteal phase).

The dynamical equations of the hormone after ovulation until the day before menstruation (luteal phase) are described by

$$\frac{d}{dt}Clu_1 = o_7 Sov_2 - o_8 Clu_1 \qquad (10)$$

$$\frac{d}{dt}Clu_2 = o_8 Clu_1 - o_9 Clu_2 \qquad (11)$$

$$\frac{d}{dt}Clu_3 = o_9 Clu_2 - o_{10} Clu_3 \qquad (12)$$

$$\frac{d}{dt}Clu_4 = o_{10} Clu_3 - o_{11} Clu_4 \qquad (13)$$

where Clu_1, Clu_2, Clu_3 and Clu_4 are the development stages of corpus luteum .
More conditions :

$$\begin{aligned} E_2(t) &= e_0 + e_1 Sec + e_2 Pre + e_3 Clu_4 \\ P_4(t) &= p_1 Clu_3 + p_2 Clu_4 \\ Ih(t) &= h_0 + h_1 Pre + h_2 Clu_3 + h_3 Clu_4 \end{aligned} \qquad (14)$$

Since the data of Table 1 is assumed to have a period of 31 days, compared to the data to illustrate the periodic behavior of the solutions. The mathematical structure of systems (1) -(4) is such that each system has a globally asymptotically stable solution of period 31 .

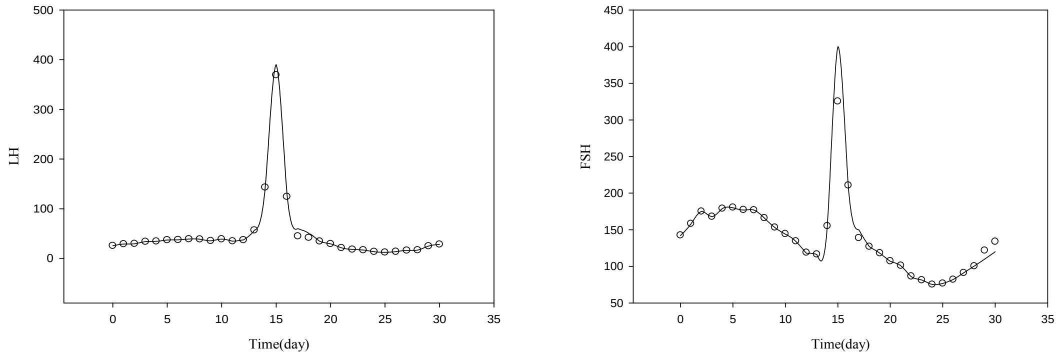
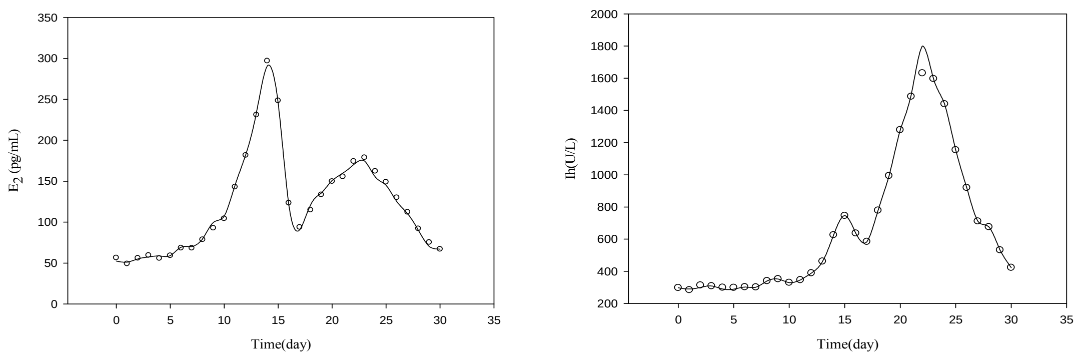


Figure 6 Graphs of LH and FSH predicted by equations (1) -(4) and data from figure 1 for comparison.



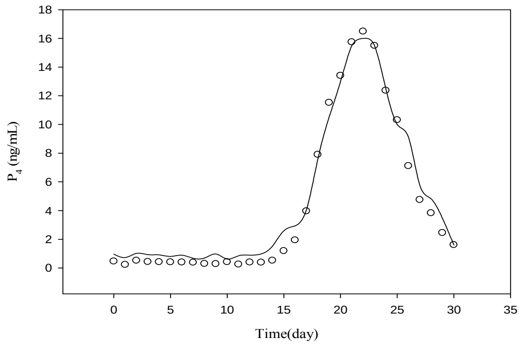


Figure 7 Graphs of E_2 , Ih and P_4 predicted by equations (5) -(14) and data from figure 1 for comparison.

Analysis of the mathematical model

Equilibrium Points

The equilibrium points are obtained by setting the right hand side of $(1)-(13)$ equal to zero. We get an equilibrium point $\left(LH^*, P^*_{LH}, FSH^*, P^*_{FSH}, Men^*, Sec^*, Pre^*, Sov^*_1, Sov^*_2, Clu^*_1, Clu^*_2, Clu^*_3, Clu^*_4\right)$

Where

$$LH^* = \left[\frac{V_{0,LH} + \dfrac{V_{1,LH}\left[E_2(t)\right]^8}{\left[K_{mLH}\right]^8 + \left[E_2(t)\right]^8}}{1+P_4(t\text{-}dp)/K_{iLH,p}}\right]\left[\frac{1}{va_{LH}}\right] \tag{15}$$

$$P^*_{LH} = \left[\frac{V_{0,LH} + \dfrac{V_{1,LH}\left[E_2(t)\right]^8}{\left[K_{mLH}\right]^8 + \left[E_2(t)\right]^8}}{1+P_4(t\text{-}dp)/K_{iLH,p}}\right]\left[\frac{1+c_{LH,E}E_2(t)}{k_{LH}\left[1+c_{LH,p}P_4(t)\right]}\right] \tag{16}$$

$$FSH^* = \left[\frac{1}{va_{FSH}}\right]\left[\frac{V_{FSH}}{1+Ih(t\text{-}d_{Ih})/K_{iFSH,Ih}}\right] \tag{17}$$

$$P^*_{FSH} = \left[\frac{V_{FSH}}{1+Ih(t\text{-}d_{Ih})/K_{iFSH,Ih}}\right]\left[\frac{1+c_{FSH,E}\left[E_2(t)\right]^2}{k_{FSH}\left[1+c_{FSH,p}P_4(t)\right]}\right] \tag{18}$$

$$Men^* = \frac{bFSH^*}{o_2(LH^*)^{\alpha} - o_1FSH^*} \tag{19}$$

$$Sec^* = \frac{bFSH^* o_2(LH^*)^{\alpha}}{\left(o_1FSH^* \text{-} o_2(LH^*)^{\alpha}\right)\left(o_3(LH^*)^{\beta} \text{-} o_4LH^*\right)} \tag{20}$$

$$Pre^{*} = \frac{o_4 bFSH^{*} o_2 (LH^{*})^{1+\alpha-\gamma}}{o_5 \left(o_1 FSH^{*} - o_2 (LH^{*})^{\alpha} \right)\left(o_3 (LH^{*})^{\beta} - o_4 LH^{*} \right)} \qquad (21)$$

$$Sov_1^{*} = \frac{o_4 bFSH^{*} o_2 (LH^{*})^{1+\alpha}}{o_6 \left(o_1 FSH^{*} - o_2 (LH^{*})^{\alpha} \right)\left(o_3 (LH^{*})^{\beta} - o_4 LH^{*} \right)} \qquad (22)$$

$$Sov_2^{*} = \frac{o_4 bFSH^{*} o_2 (LH^{*})^{1+\alpha}}{o_7 \left(o_1 FSH^{*} - o_2 (LH^{*})^{\alpha} \right)\left(o_3 (LH^{*})^{\beta} - o_4 LH^{*} \right)} \qquad (23)$$

$$Clu_1^{*} = \frac{o_4 bFSH^{*} o_2 (LH^{*})^{1+\alpha}}{o_8 \left(o_1 FSH^{*} - o_2 (LH^{*})^{\alpha} \right)\left(o_3 (LH^{*})^{\beta} - o_4 LH^{*} \right)} \qquad (24)$$

$$Clu_2^{*} = \frac{o_4 bFSH^{*} o_2 \left(LH^{*} \right)^{1+\alpha}}{o_9 \left(o_1 FSH^{*} - o_2 \left(LH^{*} \right)^{\alpha} \right)\left(o_3 \left(LH^{*} \right)^{\beta} - o_4 LH^{*} \right)} \qquad (25)$$

$$Clu_3^{*} = \frac{o_4 bFSH^{*} o_2 \left(LH^{*} \right)^{1+\alpha}}{o_{10} \left(o_1 FSH^{*} - o_2 \left(LH^{*} \right)^{\alpha} \right)\left(o_3 \left(LH^{*} \right)^{\beta} - o_4 LH^{*} \right)} \qquad (26)$$

$$Clu_4^{*} = \frac{o_4 bFSH^{*} o_2 \left(LH^{*} \right)^{1+\alpha}}{o_{11} \left(o_1 FSH^{*} - o_2 \left(LH^{*} \right)^{\alpha} \right)\left(o_3 \left(LH^{*} \right)^{\beta} - o_4 LH^{*} \right)} \qquad (27)$$

Local Asymptotical Stability

The local stability of an equilibrium point is determined from the signs of eigenvalues of the Jacobian matrix of the right hand side of the above set of differential equations.
For equations $(1)-(13)$, the Jacobian matrix evaluated at ($LH^{*}, P_{LH}^{*}, FSH^{*}, P_{FSH}^{*}, Men^{*}, Sec^{*}, Pre^{*}, Sov_1^{*}, Sov_2^{*}, Clu_1^{*}, Clu_2^{*}, Clu_3^{*}, Clu_4^{*}$) is given by

$$J = \begin{bmatrix}
\frac{-k_{LH}\left[1+c_{LH,p}P_4(t)\right]}{1+c_{LH,E}E_2(t)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{k_{LH}\left[1+c_{LH,p}P_4(t)\right]}{1+c_{LH,E}E_2(t)} & -va_{LH} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{-k_{FSH}\left[1+c_{FSH,p}P_4(t)\right]}{1+c_{FSH,E}\left[E_2(t)\right]^2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{k_{FSH}\left[1+c_{FSH,p}P_4(t)\right]}{1+c_{FSH,E}\left[E_2(t)\right]^2} & -va_{FSH} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -o_2\alpha\left(LH^{*}\right)^{\alpha-1}Men^{*} & 0 & b+o_1Men^{*} & o_1FSH^{*}-o_2\left(LH^{*}\right)^{\alpha} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & o_2\alpha\left(LH^{*}\right)^{\alpha-1}Men^{*}+\left[o_3\beta\left(LH^{*}\right)^{\beta-1}-o_4\right]Sec^{*} & 0 & 0 & o_2\left(LH^{*}\right)^{\alpha} & o_3\left(LH^{*}\right)^{\beta}-o_4LH^{*} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & o_4Sec^{*}-o_5\gamma\left(LH^{*}\right)^{\gamma-1}Pre^{*} & 0 & 0 & 0 & o_4LH^{*} & -o_5\left(LH^{*}\right)^{\gamma} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & o_5\gamma\left(LH^{*}\right)^{\gamma-1}Pre^{*} & 0 & 0 & 0 & 0 & o_5\left(LH^{*}\right)^{\gamma} & -o_6 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & o_6 & -o_7 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & o_7 & -o_8 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & o_8 & -o_9 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & o_9 & -o_{10} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & o_{10} & -o_{11}
\end{bmatrix}$$

The eigenvalues are obtained by solving the characteristic equation; $\det\left(J-\lambda I_{13}\right)=0$ where I_{13} is the identity matrix dimension 13×13. The characteristic equation is given by

$$\left(\lambda+\frac{k_{LH}\left[1+c_{LH,p}P_4\left(t\right)\right]}{1+c_{LH,E}E_2\left(t\right)}\right)\left(\lambda+\frac{k_{FSH}\left[1+c_{FSH,p}P_4\left(t\right)\right]}{1+c_{FSH,E}\left[E_2\left(t\right)\right]^2}\right)\left(\lambda+va_{LH}\right)\left(\lambda+va_{FSH}\right)\left(\lambda+o_2LH^{*\alpha}-o_1FSH^{*}\right)$$
$$\left(\lambda+o_4LH^{*}-o_3LH^{*\beta}\right)\left(\lambda+o_5LH^{*\gamma}\right)\left(\lambda+o_6\right)\left(\lambda+o_7\right)\left(\lambda+o_8\right)\left(\lambda+o_9\right)\left(\lambda+o_{10}\right)\left(\lambda+o_{11}\right)=0 \qquad (28)$$

From the characteristic equation (28), eigenvalues are given by

$$\lambda_1=\frac{-k_{LH}\left[1+c_{LH,p}P_4\left(t\right)\right]}{1+c_{LH,E}E_2\left(t\right)},\lambda_2=-va_{LH}\quad,\quad\lambda_3=\frac{-k_{FSH}\left[1+c_{FSH,p}P_4\left(t\right)\right]}{1+c_{FSH,E}\left[E_2\left(t\right)\right]^2}$$

$$\lambda_4=-va_{FSH}\quad,\quad\lambda_5=o_1FSH^{*}-o_2LH^{*\alpha},\lambda_6=o_3LH^{*\beta}-o_4LH^{*}$$

$$\lambda_7=-o_5LH^{*\gamma},\quad\lambda_8=-o_6\quad,\lambda_9=-o_7$$

$$\lambda_{10}=-o_8\quad,\quad\lambda_{11}=-o_9\quad,\lambda_{12}=-o_{10}\quad,\lambda_{13}=-o_{11}$$

We found that the equilibrium point is locally stable state when $o_2LH^{*\alpha}-o_1FSH^{*}>0$ and $o_4LH^{*}-o_3LH^{*\beta}>0$. The previous inequalities are shown in the following figures.

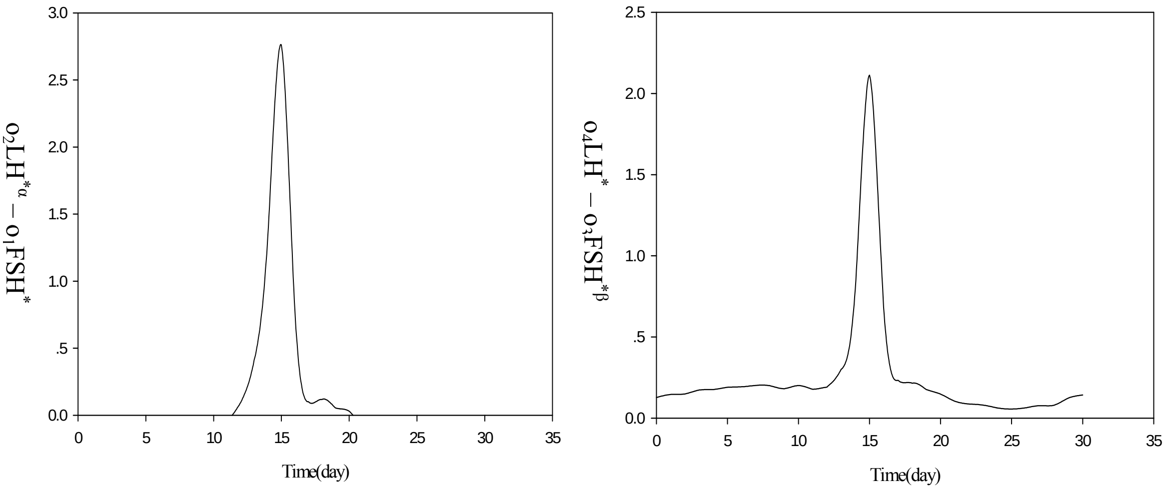


Figure 8 The parameters for this equilibrium point corresponds to a stable condition when o_1=0.0058 L /(IU day), o_2=0.048 (L/IU)$^{\alpha}$/day, o_3=0.004 (L/IU)$^{\beta}$/day, o_4=0.0061 L /(IU day), α=0.7736 , β=0.6

The equilibrium point is locally stable state because terms of eigenvalues have negative value From the above figures; $o_2 LH^{*\alpha} - o_1 FSH^{*} > 0$ and $o_4 LH^{*} - o_3 LH^{*\beta} > 0$. Thus, the equilibrium state is locally stable for $o_2 LH^{*\alpha} - o_1 FSH^{*} > 0$ and $o_4 LH^{*} - o_3 LH^{*\beta} > 0$.

Discussion and Conclusion

In this study, we analyze a mathematical model for the human menstrual cycle. The equilibrium point of mathematical model and its local stability conditions are shown. If the mathematical reasons for a loss of periodicity are understood, it might be possible to design and test therapeutic hormone strategies in this model setting and model simulations would indicate effects on the menstrual cycle.

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