ISTANBUL TECHNICAL UNIVERSITY
ELECTRIC - ELECTRONICS FACULTY

Modeling and Control of Biological Systems
2021 Spring
(CRN: 22920)

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Final Project

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1) Introduction

In this study, the production of ovarian hormones (estradiol, progesterone, and inhibin) is modeled. Firstly, these hormones are expressed with a 9-dimensional system of ordinary differential equations using a well-fitting gonadotropin hormones model (luteinizing hormone and follicle-stimulating hormone) as inputs. This model is acceptable when compared with real-life occurrences, however, since it begins and ends at different values of hormones in a 30-day period, the model cannot express the real menstrual cycle for over 30 days. Secondly, the first model is extended to a 13-dimensional system of ordinary differential equations. The model extension has been made with the addition of the gonadotropin hormones' synthesis, release, and clearance model. This 13- dimensional model gives a more sensitive approximation of the ovarian hormones and it gives a periodic signal which makes it viable for any number of days.

2) Menstrual cycle and hormones

The menstrual period of an adult human woman lasts 30 days. This is the follicular phase of the first part of the cycle. In this cycle, the follicle grows and develops. When the development of the follicle is completed, ovulation begins. The follicle turns into corpus luteum. The new cycle is called the luteal phase, and the corpus luteum begins to secrete hormones for pregnancy. When pregnancy does not occur, the corpus luteum becomes ineffective and is excreted from the body. This cycle can be seen in Figure 1.

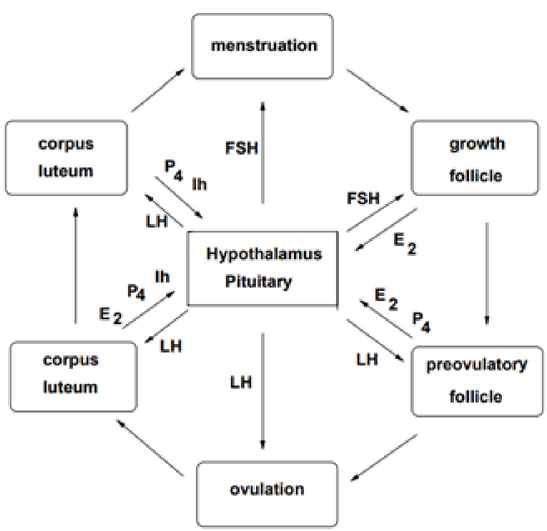

Figure 1: Menstrual cycle

Figure 1 shows a model of producing five hormones during this cycle. These hormones are divided into the groups: Gonadotropins and Ovarian hormones. There are two gonadotropin hormones: Luteinizing hormone (LH) and Follicle-Stimulating Hormone (FSH). Hormones are secreted from the anterior lobe of the pituitary, regulating the functions of the ovaries in women and the testicles in men. FSH helps the maturation of ovarian follicles in females and the production and maturation of spermatozoa in males. When viewed from men, LH seems to play an important role in the regular secretion of the testosterone hormone. It has an important role in initiating ovulation in women and taking part in the chain reaction for reproduction.

This study deals with three Ovarian hormones, as seen in Figure 1: Estradiol (E2), Progesterone (P4), and Inhibin (Ih). For these hormones to be secreted from the ovary, FSH and LH hormones must be secreted adequately and regularly from the pituitary.

Three types of estrogen hormones are produced in the human body. Estrone(E1), estriol(E3), and estradiol(E2) hormones are named estradiol, which is the form of estrogen that is active in the period from puberty (adolescence) to menopause.

Progesterone is a hormone that roughly prepares women for pregnancy and is secreted by the ovaries in cycles each month in a healthy, reproductive-age woman. Progesterone is produced during ovulation when an egg is released in the middle of the menstrual cycle. Progesterone begins to thicken the uterus wall to allow a fertilized egg (embryo) to attach or attach to the uterine wall. In other words, it prepares the uterine wall like a bed for the development of the embryo. However, if the egg is not fertilized within the appropriate time, the body decreases the secretion of progesterone, and the uterine wall is destroyed and excreted, that is, menstrual bleeding (menstruation) occurs.

In women, inhibin acts to inhibit the synthesis and secretion of follicle-stimulating hormones. It stimulates the release of follicle-stimulating hormone, actually an inhibitor; therefore, the second hormone is part of a feedback mechanism to prevent overgrowth of the follicle-stimulating hormone.

3) Models for the hormonal control of the menstrual cycle

a) The 9-Dimensional model

Ovarian hormones have time-dependent coefficients. Estradiol, progesterone and, inhibin can be mathematically expressed as,

$$E_2(t) \ = 300 - \frac{240(t+1)^2}{3+(t+1)^2} + 90 \exp\left(-\frac{(t-8)^2}{10}\right)$$

$$P_4(t) \ = 52 \exp\left(-\frac{(t-7)^2}{18}\right)$$

$$Ih(t) = 300 + 1330\exp\left(-\frac{(t-7)^2}{18}\right)$$

Also, for 9-dimensional model LH hormones are modeled as,

$$\frac{d}{dt}RP_{LH} = syn_{LH}(E_2, P_4) - rel_{LH}(E_2, P_4, RP_{LH})$$

$$\frac{d}{dt}LH = \frac{1}{v_{dis}} rel_{LH}(E_2, P_4, RP_{Lh}) - clear_{LH}(LH),$$

Where,

$$syn_{LH}(E_2, P_4) = \frac{1400 + \frac{95900[E_2(t) - d_E]^8}{[360]^8 + [E_2(t) - d_E]^8}}{1 + P_4(t - d_P)/26}$$

$$syn_{LH}(E_2, P_4) = \frac{1400 + \frac{95900[E_2(t) - d_E]^8}{[360]^8 + [E_2(t) - d_E]^8}}{1 + P_4(t - d_P)/26}$$

$$rel_{LH}(E_2, P_4, RP_{LH}) = \frac{3[1 + 0.024P_4(t)]RP_{LH}}{1 + 0.008E_2(t)}$$

$$clear_{LH}(LH) = 14\ LH$$

Furthermore, for the 9-dimensional model FSH hormones are modeled as,

$$\frac{d}{dt}RP_{FSH} = syn_{FSH}(LH) - rel_{FSH}(E_2, P_4, RP_{FSH}),$$

$$\frac{d}{dt}FSH = \frac{1}{v_{dis}} rel_{LH}(E_2, P_4, RP_{Lh}) - clear_{FSH}(FSH),$$

$$syn_{FSH}(Ih) = \frac{3800}{1 + Ih(t - d_{Ih})/1430}$$

$$rel_{FSH}(E_2, P_4, RP_{FSH}) = \frac{65[1 + 4P_4(t)]RP_{FSH}}{1 + 0.007[E_2(t)]^2}$$

$$clear_{FSH}(FSH) = 8.21\, FSH$$

b) System for the Ovary

During ovulation, FSH and LH hormones can be modeled as,

$$FSH(t) = 250 - \frac{250(t-15)^4}{(t-15)^4})$$

$$+175 \exp\left(-\frac{(t-5)^2}{120}\right) + 150\exp\,(-\frac{(t-35)^2}{160}))$$

$$LH(t) = 380 - \frac{352(t-15)^4}{1 + \ (t-15)^4}$$

c) Model for Ovarian Hormones

The follicular phase consists of the menstrual stage, $MsF(t)$, the growth follicle stage, Gr$F(t)$, and the preovulatory stage, $PrF(t)$. Follicular phase and luteral phase are divided into two stages referred to as ovulatory scar, $Sc_1(t)$ and $Sc_2(t)$. The luteral phase consists of four stages, Lut_i, for $i \ = \ 1, 2, 3, 4$.

$$\frac{d}{dt}MsF = bFSH(t) + \{c_1FSH(t) - c_2[LH(t)]^a MsF\}$$

$$\frac{d}{dt}GrF = c_2[LH(t)]^a MsF \ + \{c_3[LH(t)]^a - c_4LH(t)\}GrF$$

$$\frac{d}{dt}PrF = c_4LH(t)\}GrF - \ c_5[LH(t)]^a PrF$$

$$\frac{d}{dt}Sc_1 = \ c_5[LH(t)]^a PrF - d_1Sc_1$$

$$\frac{d}{dt}Sc_2 = \ d_1Sc_1 - d_2Sc_2$$

$$\frac{d}{dt}Lut_1 = \ d_2Sc_2 - k_1Lut_1$$

$$\frac{d}{dt}Lut_2 = \ k_1Lut_1 - k_2Lut_2$$

$$\frac{d}{dt}Lut_3 = \ k_2Lut_2 - k_3Lut_3$$

$$\frac{d}{dt}Lut_4 = \ k_3Lut_3 - k_4Lut_4$$

Parameter values of the model is as follows,

a	0.6		e_0	48
b	0.004		e_1	0.7
c_1	0.0045		e_2	2.1
c_2	0.077		e_3	1.7
c_3	0.006		p_1	0.55
c_4	0.008		p_2	0.45
c_5	0.045		h_0	270
d_1	0.5		h_1	2.5
d_2	0.8		h_2	2
k_1	0.6		h_3	10
k_2	0.5		h_4	14
k_3	0.6			
k_4	0.65			

Table 1: Parameter values for the model

d) The 13-Dimensional model

In the first stage, the first four of two-dimensional systems of differential equations describe the synthesis, release, and clearance of gonadotropin hormones. Furthermore, these equations contain specific input functions of time t for the ovarian hormones.

$$\frac{d}{dt}RP_{LH} = \frac{V_{0,LH} + \dfrac{V_{1,LH} * E_2^8}{K_{m_{LH}}^8 + E_2^8}}{1 + \dfrac{P_4}{K_{i_{LH,P}}}} - \frac{k_{LH} * \left[1 + c_{LH,p} * P_4\right] * RP_{LH}}{1 + c_{LH,E} * E_2}$$

$$\frac{d}{dt}LH = \frac{1}{v}\frac{k_{LH} * \left[1 + c_{LH,p} * P_4\right] * RP_{LH}}{1 + c_{LH,E} * E_2} - a_{LH} * LH$$

$$\frac{d}{dt}RP_{FSH} = \frac{V_{FSH}}{1 + \dfrac{Inh(t)}{K_{i_{FSH,Inh}}}} - \frac{k_{FSH} * \left[1 + c_{FSH,P} * P_4\right] * RP_{FSH}}{1 + c_{FSH,E} * E_2^2}$$

$$\frac{d}{dt}FSH = \frac{1}{v} * \frac{k_{FSH} * \left[1 + c_{FSH,p} * P_4\right] * RP_{FSH}}{1 + c_{FSH,E} * E_2^2} - a_{FSH} * FSH$$

In the second stage, there is a 9-dimensional system of differential equations for monthly development of the ovary.

$$\frac{d}{dt}ReF = b * FSH + [c_1 * FSH - c_2 * LH^{\alpha}] * ReF$$

$$\frac{d}{dt}SeF = c_2 * LH^{\alpha} * ReF + \left[c_3 * LH^{\beta} - c_4 * LH\right] * SeF$$

$$\frac{d}{dt}PrF = c_4 * LH * SeF - c_5 * LH^{\gamma} * PrF$$

$$\frac{d}{dt}Ov_1 = c_5 * LH^{\gamma} * PrF - d_1 Ov_1$$

$$\frac{d}{dt}Ov_2 = d_1 Ov_1 - d_2 Ov_2$$

$$\frac{d}{dt}Lut_1 = d_2 Ov_2 - k_1 Lut_1$$

$$\frac{d}{dt}Lut_2 = k_1 Lut_1 - k_2 Lut_2$$

$$\frac{d}{dt}Lut_3 = k_2 Lut_2 - k_3 Lut_3$$

$$\frac{d}{dt}Lut_4 = k_3 Lut_3 - k_4 Lut_4$$

Using Euler approximation these differential equations will be solved to calculate the ovarian hormones given with

$$E_2 = e_0 + e_1 SeF + e_2 PrF + e_3 Lut_4$$

$$P_4 = p_0 + p_1 Lut_3 + p_2 Lut_4$$

$$Inh = h_0 + h_1 PrF + h_2 Lut_2 + h_3 Lut_3$$

4) Simulations

a) The 9-Dimensional model

The simulation results using the 9-dimensional model can be seen in Figure 2 and Figure 3. Here since [1] did not share the initial values of the states, they were all chosen as 0. Choosing the initial values of the states as 0 does not affect the stability of the system, it only changes the values of hormone levels and they can be tuned to real-life occurrences just by changing the initial values.

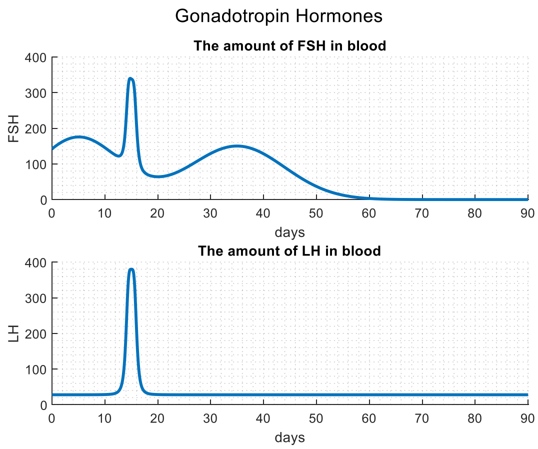

Figure 2: Gonadotropin Hormones (9-dimensional model):

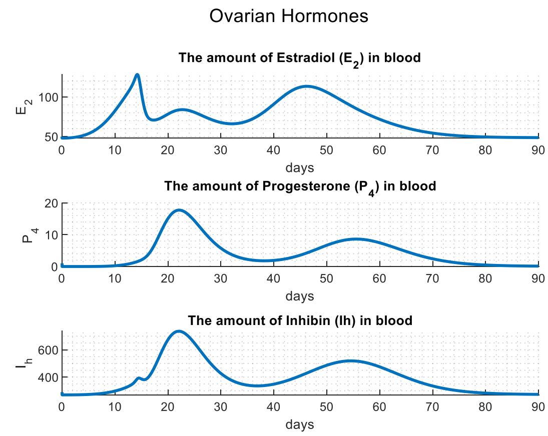

Figure 3: Ovarian Hormones (9-dimensional model)

b) The 13-Dimensional model

The simulation results using the 13-dimensional model can be seen in Figure 4 and Figure 5. Here initial state values are chosen to be

$$\{40, 12, 20, 11, 5, 1, 1, 1, 1, 1, 1, 1, 1\}$$

as in [3]

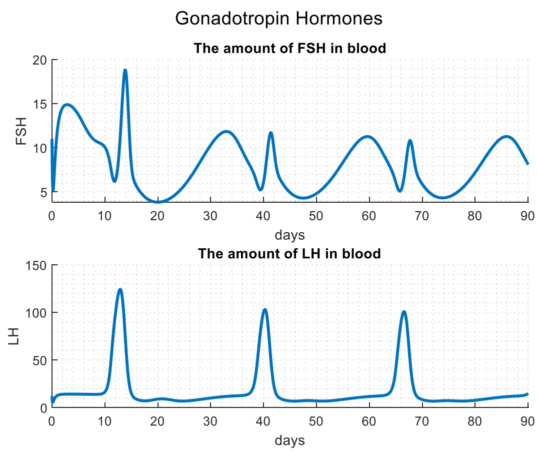

Figure 4: Gonadotropin Hormones (13-dimensional model)

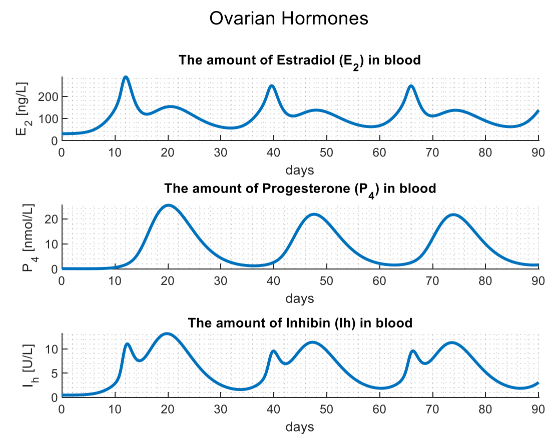

Figure 5: Ovarian Hormones (13-dimensional model)

Furthermore, hormone levels for initial state values

$$\{29.65, 6.86, 8.47, 6.15, 3.83, 11.51, 5.48, 19.27, 45.65, 100.73, 125.95, 135.84, 168.71\}$$

as in [2] the results can be seen in Figure 6 and Figure 7.

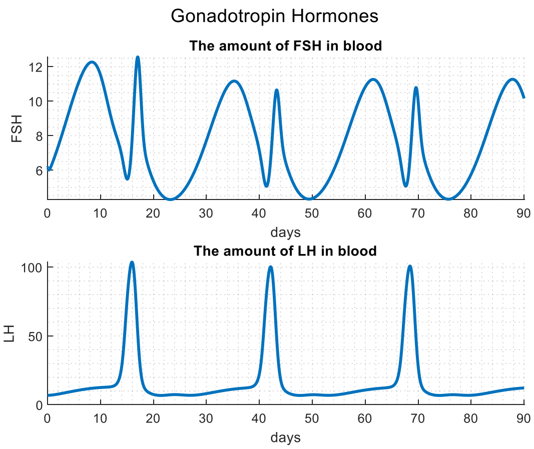

Figure 6: Gonadotropin Hormones for new initial conditions (13-dimensional model)

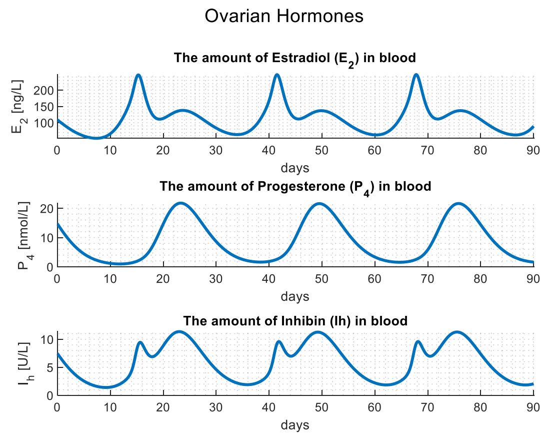

Figure 7: Ovarian Hormones for new initial conditions (13-dimensional model)

As it was mentioned before, the 13-dimensional hormone model can create a periodic signal unlike the 9-dimensional model as long as the initial conditions are chosen in the stable interval. Furthermore, the system is significantly sensitive to parameters c_2 and Km_{LH} and a bifurcation analysis can be made to see the effects of changing these parameters but this paper does not include this analysis. Instead of it, this paper inspects the effects of Km_{LH} analyzing hormone levels. For $c_2 = 0.07$, the values of gonadotropin and ovarian hormones can be seen in Figure 8 and Figure 9.

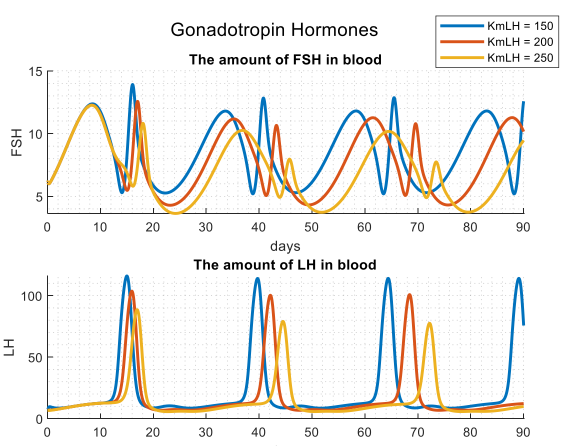

Figure 8: Gonadotropin Hormones for different values of Km_{LH} (13-dimensional model)

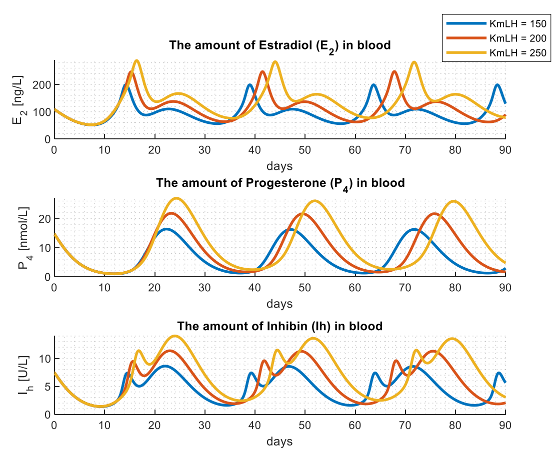

Figure 9: Ovarian Hormones for different values of Km_{LH} (13-dimensional model)

As expected, since Km_{LH} represents the level of E_2 sufficient for significant LH synthesis and the LH surge, the peak values of ovarian hormones have increased as Km_{LH} increases. Moreover, the system is not able to tolerate after a certain value of Km_{LH} which is found to be around 253. As an example, hormone levels in the menstrual cycle for $Km_{LH} = 256$ can be seen in Figure 10 and Figure 11.

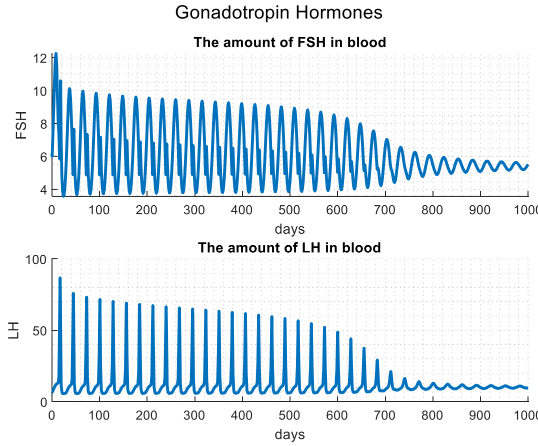

Figure 10: Gonadotropin Hormones for Km_{LH} = 256 (13-dimensional model)

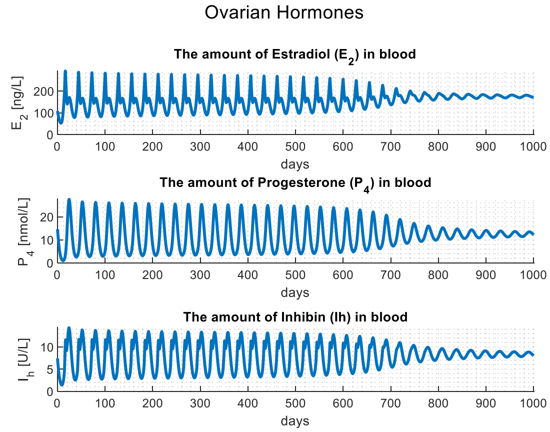

Figure 11: Ovarian Hormones for Km_{LH} = 256 (13-dimensional model)

Since this analysis can be done to analyze the lower and upper limits of both Km_{LH} and c_2 and each of their graphs will take a lot of space, the tables below have been created to show the stability range of the system only depending on Km_{LH} and c_2 (fixing one of them). c_2 and Km_{LH} are chosen as 0.07 and 200 respectively as fixed values because they are the actual measured values from women.

c_2	Km_{LH}
0.07	$87 < Km_{LH} < 253$

Table 2: Stability interval of Km_{LH} for fixed c_2

Km_{LH}	c_2
200	$0.0162 < c_2 < 0.0912$

Table 3: Stability interval of c_2 for fixed Km_{LH}

5) Conclusion

In this study, it was shown that the level of hormones involved in the menstrual cycle can be modeled using 9- and 13-dimensional ordinary differential equations. Furthermore, the benefits of using the 13-dimensional model are discussed. Lastly, the stability range of the system has been determined for the most critical parameters in the model. For future study, we advise a detailed bifurcation analysis for some of the parameters in the model.

6) References

[1] J. Selgrade and P. Schlosser, "A model for the production of ovarian hormones during the menstrual cycle," *Differential Equations with Applications to Biology*, pp. 429–446, 1998.

[2] A. Margolskee and J. F. Selgrade, "Dynamics and bifurcation of a model for hormonal control of the menstrual cycle with inhibin delay," *Mathematical Biosciences*, vol. 234, no. 2, pp. 95–107, 2011.

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7) Appendix

Github

https://github.com/Bubuyson/Ovarian-model