

MODELING HORMONAL CONTROL OF THE MENSTRUAL CYCLE

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Abstract

This study presents a strategy for developing a mathematical model describing the concentrations of five hormones important for regulation and maintenance of the menstrual cycle. Models which correctly predict the serum levels of ovarian and pituitary hormones may assist the experimentalist by indicating directions of investigation. In addition, model simulations may be helpful for evaluating the effects of exogenous compounds on the sexual endocrine system of adult women, for testing hormonal methods of birth control, and for understanding the phenomenon of menstrual cycle synchronization.

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1. Introduction

The complex interplay between ovarian and pituitary hormones is the key ingredient for regulating and maintaining the menstrual cycle in adult women. That the pituitary gland plays a crucial role in the control of the menstrual cycle was not known until this century (see Greep [13] for a history of research on hormones of the pituitary). Although much research (e.g., see Hotchkiss and Knobil [15], Yen [47, 48], and Zeleznik and Benyo [49]) has been done to understand the physiological mechanisms involved in the regulation of the primate menstrual cycle, not all aspects are completely understood. There are significant experimental difficulties in determining these mechanisms, especially at the level of the hypothalamus and pituitary. Mathematical models which correctly predict the serum levels of ovarian and pituitary hormones during the cycle may assist the experimentalist by indicating directions of investigation.

Recent reports (e.g., McLachlan and Korach [27] or Daston *et al.* [9]) have suggested that environmental substances which have estrogenic activity may disrupt the sexual endocrine systems in both humans and animals. In particular, such compounds may be contributing to the increased incidence of breast cancer [10], to declines in sperm counts [42], and to developmental abnormalities [26]. However, there is considerable scientific debate about the plausibility of this hypothesis (e.g., Safe [37]; Kramer and Giesy [18]). Mathematical models can be used to simulate the effects of exogenous compounds on the sexual endocrine system of adult women. Simulations of this type may be helpful in evaluating hypotheses about the role of xenoestrogens in breast and ovarian cancers and may be useful for testing hormonal methods of birth control which function by suppressing the mid-cycle surge in luteinizing hormone. Finally, simulations and experimentation with versions of these models coupled appropriately should help in understanding the phenomenon of menstrual cycle synchronization (e.g., Schank and McClintock [38]).

Here a strategy is presented for developing a mathematical model describing the concentrations of five hormones important for regulation and maintenance of the cycle. There are three steps to this modeling process. The first step describes the pituitary's synthesis and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which are controlled by the ovarian hormones, estradiol (E_2), progesterone (P_4), and inhibin (Ih). Data from the literature (McLachlan *et al.* [28]) are used to obtain input functions for serum levels of E_2 , P_4 , and Ih and the state variables are

pituitary and serum levels of LH and FSH . The second step models the effects of the pituitary hormones, LH and FSH , on the growth and development of ovarian follicles and on the production of the ovarian hormones, E_2 , P_4 , and Ih . Here the input functions are the serum concentrations of LH and FSH and the state variables are the capacities of follicular and luteal tissue during various stages of the cycle to produce E_2 , P_4 , and Ih . In the first two steps, systems of ordinary differential equations are obtained which are linear in the state variables with time-dependent, periodic, coefficient functions depending on the input functions. Selgrade and Schlosser [41] showed analytically that if either system has input functions of period T then that system has a globally, asymptotically stable solution of period T . Clinical data will be used to optimize the model parameters in these two systems. The final step is to merge the models from the first two steps creating a highly nonlinear system of differential equations where serum concentrations of pituitary and ovarian hormones are the state variables. As yet, this step has not been implemented. Various positive and negative feedback mechanisms supported by experimental data are incorporated into the model.

Validation of the model may be accomplished by forcing the system with doses of E_2 and P_4 which mimic clinical studies where estrogen and progesterone were given exogenously, e.g., Liu and Yen [24], Odell and Molitch [30] and Weick *et al.* [45]. If the model responses are similar to the results of clinical experiments then that would indicate that the model could be used to predict the responses of the normal menstrual cycle to exogenous inputs.

ovary produces E_2 , P_4 , and Ih , which control the pituitary's synthesis and release of the gonadotropin hormones during the various stages of the cycle. The follicular phase begins with the first day of menstrual flow. During menstruation, the serum levels of FSH are increasing and promote the growth of early antral follicles. The preantral and early antral follicles are developing during the two previous menstrual cycles but are too immature to produce significant amounts of E_2 . These follicles possess cell surface receptors for FSH but not LH [50]. Under the influence of increasing FSH , 6 to 12 follicles develop into secondary follicles by adding layers of granulosa cells [29]. During the second third of the follicular phase, the production of E_2 increases due to the growth of these secondary follicles, which possess both FSH and LH receptors. A primary follicle is selected to continue its development and FSH begins to decrease. The physiological mechanism responsible for the selection of a primary follicle is not known. However, several mathematical models of the follicle selection process have been proposed, e.g., see Lacker and Peskin [22], Lacker *et al.* [21], and Chávez-Ross *et al.* [6]. We do not include follicle selection in our model. During the preovulatory follicular stage, the primary follicle grows rapidly and produces E_2 in large amounts. LH levels are roughly constant during the first two-thirds of the follicular phase. However, because of stimulation due to high E_2 concentration, the pituitary begins to secrete gonadotropins at a faster rate. The concentration of E_2 peaks and one day later LH peaks at approximately eight times its early follicular concentration and then rapidly subsides. This rise and fall of LH over a period of 5 days is referred to as the LH surge. After a significant decrease during the second half of the follicular phase, FSH also surges concurrently with LH .

Ovulation commences 16 to 24 hours after the LH surge [32]. The action of LH transforms the primary follicle into the corpus luteum over a period of 5 or 6 days [49]. The corpus luteum ("yellow body") is characterized by increased fat storage in the theca and granulosa cells and increased secretion of E_2 , P_4 , and Ih . Approximately two days before the LH surge, serum levels of P_4 begin to increase and reach a maximum midway through the luteal phase. The Ih profile is similar to that of P_4 . P_4 and Ih appear to inhibit the secretion of LH and FSH , respectively, during the luteal phase (see [23, 19, 28, 35, 36]). The corpus luteum grows during the first half of the luteal phase and reaches its maximal size roughly by the middle of the luteal phase. LH is needed to maintain the normal function of the corpus luteum throughout this period

[49]. If fertilization occurs then the coordinated effects of LH and chorionic gonadotropin produced by the placenta sustain the corpus luteum and permit continued secretion of E_2 and P_4 in preparation for pregnancy. Otherwise, the corpus luteum decreases in size and steroid secretion and becomes inactive by the end of the menstrual cycle. The decline of the corpus luteum results in a decrease in P_4 and Ih serum levels and, consequently, the removal of the inhibition on LH and FSH synthesis. The resulting gradual rise in LH and FSH levels at the end of the month initiates the next cycle.

Chávez-Ross [5] reviewed much of the literature on mathematical models of the menstrual cycle and the estrus cycle of rodents, including models of follicle growth and selection as well as cycle regulation. Previous models of cycle regulation (e.g., Schwartz [40], Bogumil *et al.* [3, 4], McIntosh and McIntosh [25], and Plouffe and Luxenberg [34]) have useful components but also contain elements which are not based on biological mechanisms. For instance, they may contain a switch to turn on the LH surge or convolution integrals which weight the effects of E_2 concentrations over time. We make every effort to link the terms in our differential equations model to physiological mechanisms.

In order to estimate parameters and obtain input functions for steps one and two of our model, we use data for serum hormone concentrations in McLachlan *et al.* [28] for 33 normally cycling women. The output of model simulations will also be compared to these data. The concentrations in Table 1 are approximated from the graphs [28, Fig.1, page 43]. Table 1 contains 31 data points for each hormone representing a 30 day cycle. However, these data are not periodic. In order to obtain periodic cycling of the hormones in our model, we need periodic data for the input functions and for parameter estimation. Notice that the data for E_2 , P_4 , and Ih are decreasing on day 30 but are still larger than the values on day 0. The data for LH and FSH are increasing on day 30 and the FSH value is less than the value on day 0. The LH value on day 0 is not consistent with this pattern and may be spurious. Hence, to obtain data of period 31 we augment Table 1 by repeating the values for day 0 at the bottom of the table.

3. System for the Pituitary Hormones

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

Time day	E_2 pg/mL	P_4 ng/mL	LH ng/mL	FSH ng/mL	Ih U/L
0	56.387	0.468	25.34	142.5	297.90
1	49.168	0.227	28.74	158.3	284.10
2	56.087	0.519	29.36	175.1	313.80
3	59.465	0.43	33.71	168	308.70
4	55.76	0.417	34.29	179.1	299.30
5	59.138	0.406	36.78	180.6	298.70
6	68.4	0.392	37.35	177.3	302.20
7	68.236	0.379	38.88	177	301.50
8	78.696	0.292	38.52	166.1	339.80
9	92.67	0.279	35.28	153.4	352.00
10	104.3	0.418	38.71	144.4	329.70
11	143.04	0.254	34.54	134.5	346.30
12	181.75	0.393	37.02	118.9	388.80
13	231.05	0.381	56.62	116.6	461.70
14	296.92	0.52	142.9	155.3	625.40
15	248.43	1.189	369.2	325.4	745.80
16	123.4	1.934	124	210.7	636.90
17	93.76	3.966	44.63	138.9	584.20
18	114.82	7.897	41.39	127.1	778.30
19	133.5	11.52	34.32	118.2	993.90
20	149.85	13.401	29.18	107.3	1279.0
21	155.57	15.741	21.18	101.2	1486.0
22	174.28	16.483	17.95	86.53	1632.0
23	178.83	15.486	16.64	81.36	1597.0
24	162.19	12.366	13.38	75.29	1440.0
25	149.06	10.306	12.02	76.79	1154.0
26	130.04	7.111	13.54	82.1	919.50
27	112.23	4.749	16.02	91.23	711.10
28	92.044	3.827	16.56	100.4	675.80
29	75.373	2.45	24.72	121.9	532.20
30	66.983	1.604	28.2	133.9	423.40

Table 1: Daily hormone concentrations from McLachlan *et al.* [28]

strengths and durations [16]. Clinical experiments (e.g., [7, 16, 17, 24, 43, 44]) have indicated that administration of exogenous E_2 causes an immediate decrease in serum LH and FSH . But if the E_2 is administered at a high enough dose over a long enough period of time then, after the initial dip, there is a significant increase in serum LH above basal level. It is widely accepted [15] that the large quantity of E_2 produced during the preovulatory follicular stage elicits the LH surge and, hence, ovulation. However, the physiological mechanism which switches E_2 inhibition of LH to E_2 stimulation of LH is not known.

In an attempt to explain this switch, Schlosser and Selgrade [39] assumed that the effect of E_2 on LH synthesis is different than the effect on LH release, i.e., they assumed that E_2 has a positive effect on synthesis but a negative effect on release. The idea that gonadotropin synthesis and release are differentially regulated was described first by Yen [47]. There is experimental evidence for this in the work of Clayton *et al.* [8] on rats and Hotchkiss *et al.* [14] on the rhesus monkey. Hotchkiss *et al.* [14] showed that the amount of LH in the pituitary during the growth-follicular stage increased as E_2 increased while the serum concentration of LH was roughly constant. Hence, although E_2 is inhibiting LH release during this stage, it is not suppressing LH synthesis and, in fact, may be promoting synthesis. In addition, Ördög *et al.* [33] showed that the removal of E_2 inhibition on LH release does not trigger the LH surge. Finally, numerical simulations by Schlosser and Selgrade [39] indicated that removing E_2 inhibition on LH release resulted in a rebound effect but not of the magnitude of the LH surge. Such evidence led Schlosser and Selgrade [39] to hypothesize that high serum concentrations of E_2 stimulate the synthesis of LH . This effect is incorporated into the model discussed below.

There are other plausible explanations for the biphasic LH response. For example, Ördög (personal communication and [33]) suggests that there may be three different biological mechanisms involved at the cellular level in the pituitary. One mechanism results in the inhibition of LH release [16, 44] and accounts for the suppression of LH concentrations in adult women throughout their normal cycles. This inhibition is not present in postmenopausal women where typical E_2 levels are lower and, hence, LH levels are higher than before menopause. A second mechanism promotes the synthesis of LH at a rate which increases as E_2 increases [14]. These two mechanisms are similar to that assumed by Schlosser and Selgrade [39]. However, according to Ördög, the positive effect

on LH synthesis alone is unlikely to cause the LH surge because the requirements for E_2 stimulation of LH biosynthesis and “surge-mode” release are different, with release occurring only after the pituitary has been exposed to 200-400 pg/mL for at least 36 hours [17]. On the other hand, low (less than 100 pg/mL) E_2 levels, while stimulating LH synthesis, as inferred from the amplitude of the LH rebound following treatments with an estrogen receptor antagonist [33], cannot induce a surge regardless of how long these levels are maintained [17]. In other words, insufficient accumulation of LH in the pituitary is not likely to explain the lack of the LH peak under these circumstances. It is more likely that the negative feedback action of E_2 on LH release changes to a positive effect on LH release. This third mechanism results in significant LH release (the LH surge) which depletes the LH stores in the pituitary. This biological hypothesis has not yet been proven experimentally nor modeled mathematically.

To model the scenario that E_2 promotes LH synthesis and inhibits LH release, Schlosser and Selgrade [39] used a system of 2-dimensional ordinary differential equations to represent a two compartment model consisting of the pituitary and the blood which captures the processes of LH synthesis, release, and clearance. Gonadotropin synthesis occurs in the pituitary where it is held in a reserve pool for release into the blood stream. $RP_{LH}(t)$ denotes the function of time which represents the amount of LH in the releasable pool. $LH(t)$ denotes the serum concentration. The effects of P_4 are incorporated into the synthesis and release terms of the system. The increased size and duration of E_2 induced surges in hypogonadal women, when P_4 is infused during the surge as compared to E_2 treatment alone [24], implies that P_4 promotes LH release. Low serum levels of LH during the luteal phase in spite of a second increase in E_2 indicates that the high P_4 concentrations during the luteal phase suppress LH synthesis. The differential equation for $RP_{LH}(t)$ contains terms for synthesis and for release; the differential equation for $LH(t)$ contains terms for assimilation and for clearance. Both equations are linear in the state variables, $RP_{LH}(t)$ and $LH(t)$, with time-dependent coefficients which are functions of the ovarian hormones, i.e., E_2 and P_4 . The LH system is given by:

$$\begin{aligned} \frac{d}{dt} RP_{LH} &= syn_{LH}(E_2, P_4) - rel_{LH}(E_2, P_4, RP_{LH}) \\ \frac{d}{dt} LH &= \frac{1}{v_{dis}} rel_{LH}(E_2, P_4, RP_{LH}) - clear_{LH}(LH), \end{aligned} \tag{LHeq}$$

where

$$syn_{LH}(E_2, P_4) = \frac{V_{0,LH} + \frac{V_{1,LH} [E_2(t - d_E)]^a}{[Km_{LH}]^a + [E_2(t - d_E)]^a}}{1 + P_4(t - d_P)/Ki_{LH,P}}, \quad (LHsyn)$$

$$rel_{LH}(E_2, P_4, RP_{LH}) = \frac{k_{LH} [1 + c_{LH,P} P_4(t)] RP_{LH}}{1 + c_{LH,E} E_2(t)}, \quad (LHrel)$$

$$\text{and} \quad clear_{LH}(LH) = r_{LH} LH. \quad (LHcl)$$

The 12 parameters (V 's, K 's, c 's, d 's, k_{LH} , r_{LH} , v_{dis} and $a = 8$) in this system have been obtained either from clinical data or chosen so that the output of numerical simulation fits the data of Table 1. The input functions, $E_2(t)$ and $P_4(t)$ are approximated from Table 1, see Schlosser and Selgrade [39]. The time-delays $d_E = 0.42$ days and $d_P = 2.9$ days are parameters which describe the period between the time when changes in serum levels of the ovarian hormones occur and the time when subsequent changes in LH synthesis rates occur. The progesterone delay of 2.9 days is unrealistically long and should be improved by optimizing parameters. The volume of distribution, $v_{dis} = 2.5$ L, appears in the second equation to account for LH assimilation into the blood stream. The synthesis term ($LHsyn$) contains an increasing function of E_2 in the numerator. This fractional expression is called a Hill function and it increases rapidly as E_2 varies between 200 and 600 pg/mL to reflect the positive effect of large estradiol concentration on the synthesis of LH .

The FSH system has a similar form:

$$\begin{aligned} \frac{d}{dt} RP_{FSH} &= syn_{FSH}(Ih) - rel_{FSH}(E_2, P_4, RP_{FSH}) \\ \frac{d}{dt} FSH &= \frac{1}{v_{dis}} rel_{FSH}(E_2, P_4, RP_{FSH}) - clear_{FSH}(FSH), \end{aligned} \quad (FSHeq)$$

where

$$syn_{FSH}(Ih) = \frac{V_{FSH}}{1 + Ih(t - d_{Ih})/Ki_{FSH,Ih}}, \quad (FSHsyn)$$

$$rel_{FSH}(E_2, P_4, RP_{FSH}) = \frac{k_{FSH} [1 + c_{FSH,P} P_4(t)] RP_{FSH}}{1 + c_{FSH,E} [E_2(t)]^2}, \quad (FSHrel)$$

$$\text{and} \quad \text{clear}_{FSH}(FSH) = r_{FSH} FSH. \quad (FSHcl)$$

The presurge dip in FSH as E_2 increases and the size of the FSH surge suggest that the FSH surge may be a rebound effect, and our release term ($FSHrel$) captures this behavior with second order inhibition of E_2 on FSH release. The term ($FSHsyn$) reflects the negative effect of inhibin $Ih(t)$ on FSH synthesis, (see [1] and [12]), which has a time-delay $d_{Ih} = 2$ days.

The LH and FSH systems have a total of 20 parameters, see Table 2. Those which were not available in the literature were estimated by fitting numerical simulations to the LH and FSH data of Table 1. These parameters have not been optimized.

<i>LH</i>	
k_{LH}	3 day ⁻¹
r_{LH}	14 day ⁻¹
a	8
$V_{0,LH}$	1400 μg/day
$V_{1,LH}$	95900 μg/day
Km_{LH}	360 ng/L
$Ki_{LH,P}$	26 nmol/L
$c_{LH,E}$	0.008 L/ng
$c_{LH,P}$	0.024 L/ng
d_E	0.42 day
d_P	2.9 day
v_{dis}	2.5 L

<i>FSH</i>	
V_{FSH}	4400 μg/day
r_{FSH}	8.21 day ⁻¹
k_{FSH}	45 day ⁻¹
d_{Ih}	2 day
$c_{FSH,E}$	0.005 (L/ng) ²
$Ki_{FSH,Ih}$	1176.5 U/L
$c_{FSH,P}$	3 L/nmol
v_{dis}	2.5 L

Table 2: Parameter values for the *LH* and *FSH* systems.

The results of simulations of systems (*LHeq*) and (*FSHeq*) with the parameter values of Table 2 are shown in Figure 2. Since the data of Table 1 is assumed to have a period of 31 days, the simulations were run for 62 days and compared to the data to illustrate the periodic behavior of the solutions. The mathematical structure of systems (*LHeq*) and (*FSHeq*) is such that each system has a globally asymptotically stable solution of period 31 as discussed in section 5.

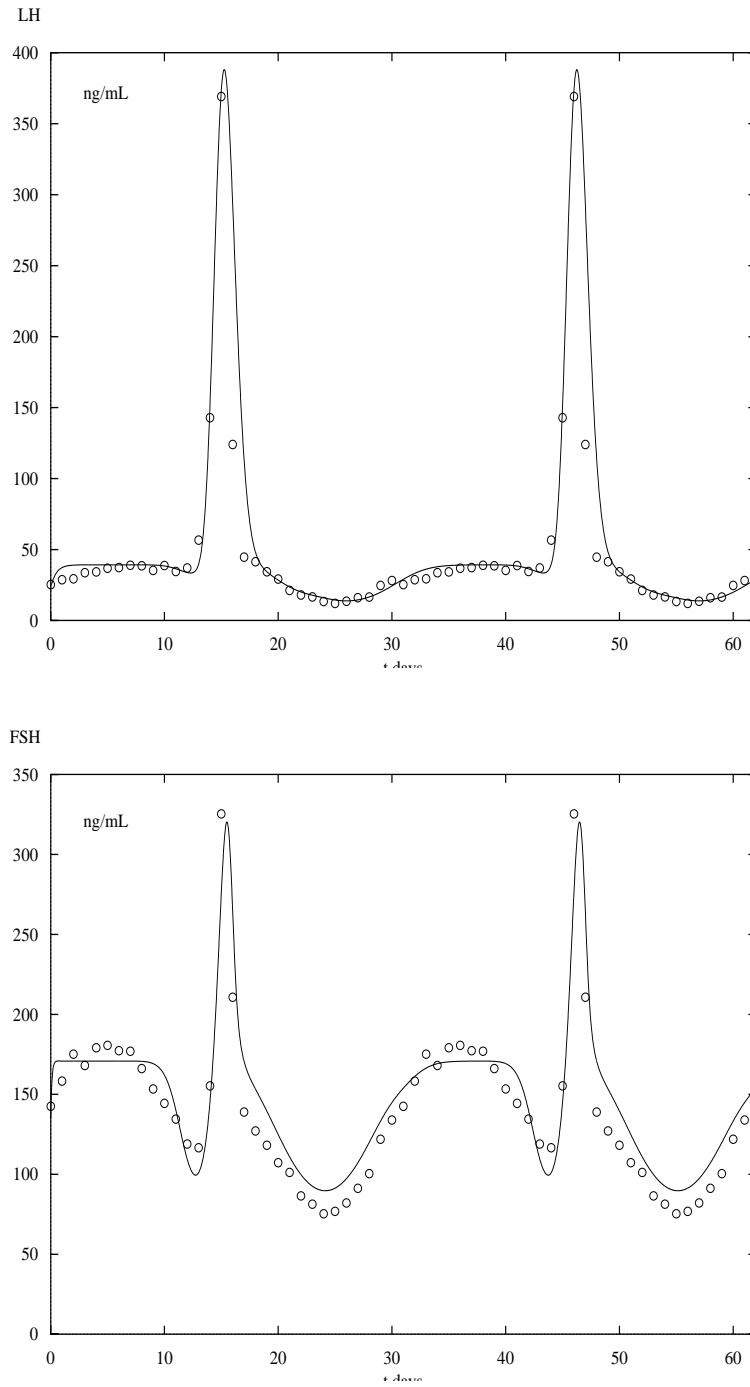


Figure 2: Graphs of LH and FSH predicted by equations ($LHeq$) and ($FSHeq$) and data \circ from Table 1 for comparison.

To validate this step of the model, Schlosser and Selgrade [39] ran simulations in an attempt to mimic the experiments of Liu and Yen [24] and Tsai and Yen [44] on normal women in midfollicular phase and similar experiments on castrate female rats reported in Odell and Molitch [30]. Under gradual administration of exogenous estradiol or ethinyl estradiol, experimental observations indicated an immediate decrease in serum levels of LH and FSH . After a period of approximately 4 days when serum levels of E_2 had increased sufficiently, a LH surge was observed [24, 44, 30]. In [39] the E_2 input function for systems (LH_{eq}) and (FSH_{eq}) was adjusted to approximate the E_2 serum level measured in the experiments of Liu and Yen [24] and simulations were run. Model output closely resembled the experimental results (see Figure 7 in [39]). A small P_4 infusion after several days of E_2 administration resulted in accentuation of LH and FSH surges in experiments [24] and similar behavior was produced by model simulations [39].

Experiments of Weick *et al.* [45] indicated a refractory period of 6 to 8 days between LH surges induced by estradiol benzoate injections. However, model simulations of (LH_{eq}) with a spiked E_2 input function of 300 pg/mL repeated every 3 days produced LH surges every 3 days. This suggests that the effect of E_2 on LH synthesis in the model may be too strong and that (LH_{eq}) may need modification.

4. System for the Ovarian Hormones

Selgrade and Schlosser [41] developed a model to describe the serum concentrations of the ovarian hormones with explicit functions of time as inputs representing the serum concentrations of the gonadotropin 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. For the most part, these states correspond to the stages depicted in Figure 1. Ordinary differential equations are used to track this capacity as it is transferred from one state to the next state during the cycle. The capacity at each state is assumed proportional to the mass of that state. The follicular phase consists of the menstrual state, $MsF(t)$, the secondary follicular state, $SeF(t)$, and the preovulatory state, $PrF(t)$. The transitional period between the follicular phase and the luteal phase is divided into two states referred to as ovulatory scar, $Sc_1(t)$ and $Sc_2(t)$. The luteal phase consists of four states, $Lut_i(t)$ for $i = 1, \dots, 4$. With $LH(t)$ and $FSH(t)$ denoting the input functions, the 9-dimensional system of differential equations with 18

parameters ($\alpha, \beta, \gamma, b, c_i$'s, d_i 's and k_i 's) for the ovary is:

$$\begin{aligned}
\frac{d}{dt} MsF &= b FSH(t) + \{c_1 FSH(t) - c_2 [LH(t)]^\alpha\} MsF \\
\frac{d}{dt} SeF &= c_2 [LH(t)]^\alpha MsF + \{c_3 FSH(t) + c_4 [LH(t)]^\beta - c_5 LH(t)\} SeF \\
\frac{d}{dt} PrF &= c_5 LH(t) SeF + \{c_6 FSH(t) + c_7 LH(t) - c_8 [LH(t)]^\gamma\} PrF \\
\frac{d}{dt} Sc_1 &= c_8 [LH(t)]^\gamma PrF - d_1 Sc_1 \\
\frac{d}{dt} Sc_2 &= d_1 Sc_1 - d_2 Sc_2 \\
\frac{d}{dt} Lut_1 &= d_2 Sc_2 - k_1(LH(t)) Lut_1 \\
\frac{d}{dt} Lut_2 &= k_1(LH(t)) Lut_1 - k_2(LH(t)) Lut_2 \\
\frac{d}{dt} Lut_3 &= k_2(LH(t)) Lut_2 - k_3(LH(t)) Lut_3 \\
\frac{d}{dt} Lut_4 &= k_3(LH(t)) Lut_3 - k_4(LH(t)) Lut_4 .
\end{aligned} \tag{Ov}$$

Since clearance from the blood of the ovarian hormones is on a fast time scale, the blood levels of E_2 , P_4 , and Ih are assumed to be essentially at steady-state as in Bogumil [3]. Hence, these concentrations are taken to be proportional to the hormone capacities during the appropriate states of the cycle and 11 more parameters (e_i 's, p_i 's and h_i 's) are introduced to give three auxiliary equations:

$$E_2(t) = e_0 + e_1 SeF(t) + e_2 PrF(t) + e_3 Lut_4(t), \tag{OvE_2}$$

$$P_4(t) = p_1 Lut_3(t) + p_2 Lut_4(t) \quad \text{and} \tag{OvP_4}$$

$$Ih(t) = h_0 + h_1 PrF(t) + h_2 Lut_2(t) + h_3 Lut_3(t) + h_4 Lut_4(t). \tag{OvIh}$$

The first term of the equation for MsF in (Ov) represents the FSH stimulation of premature follicles. This input from the pituitary begins the cyclic changes within the ovary. The follicle growth rates during this state are assumed proportional to the FSH blood levels [29]. The transition into the state of development of the secondary follicles is promoted by LH . As the secondary follicles grow, E_2 synthesis increases and therefore a SeF term is included in (OvE₂). The transition from the secondary follicular state to

the preovulatory follicular state corresponds to the selection of the primary follicle and depends on LH . During the preovulatory state, the primary follicle is secreting large amounts of E_2 as reflected in (OvE_2) , see Baird [2]. Ovulation and luteinization are not instantaneous events [29] and are represented by two states referred to as ovulatory scars. Little hormone synthesis is assumed during this period. The transition is promoted by LH as reflected by the first term in the equation for Sc_1 . Then, in the model the capacity to produce hormones cascades through four luteal states. Odell [29] suggested that low concentrations of LH are required to maintain normal corpus luteum function as depicted in Figure 1. Hence, the coefficients k_i depend on the LH input function. The primary source of P_4 and Ih is the corpus luteum as indicated in (OvP_4) and $(OvIh)$.

None of the 29 parameters of the (Ov) system and auxiliary equations may be obtained from the literature. It is not feasible to use a standard parameter estimator on such a complicated system. Even the somewhat simpler system in Selgrade and Schlosser [41] did not yield good parameter fits. Numerical experimentation with (Ov) has led to the following table (Table 3) of dimensionless parameters which give a reasonably accurate simulated approximation to E_2 data in Table 1, see Figure 3. Notice that the E_2 profile in Figure 3 does not match the periodic data on day 31. Hence, the parameter values of Table 3 are not exactly those which produce the periodic concentrations of ovarian hormones corresponding to the data of Table 1.

Eq. (Ov)	
b	0.004
c_1	0.0045
c_2	0.077
c_3	0
c_4	0.006
c_5	0.008
c_6	0
c_7	0
c_8	0.045

Eq. (Ov)	
d_1	0.5
d_2	0.8
k_1	0.6
k_2	0.5
k_3	0.8
k_4	4.0
α	0.6
β	0.6
γ	0.6

Eqs. (OvE_2, P_4, Ih)	
e_0	48
e_1	0.6
e_2	0.8
e_3	4.5
p_1	0.55
p_2	0.45
h_0	270
h_1	2.5
h_2	2
h_3	10
h_4	14

Table 3: Parameter values for (Ov) , (OvE_2) , (OvP_4) , and $(OvIh)$.

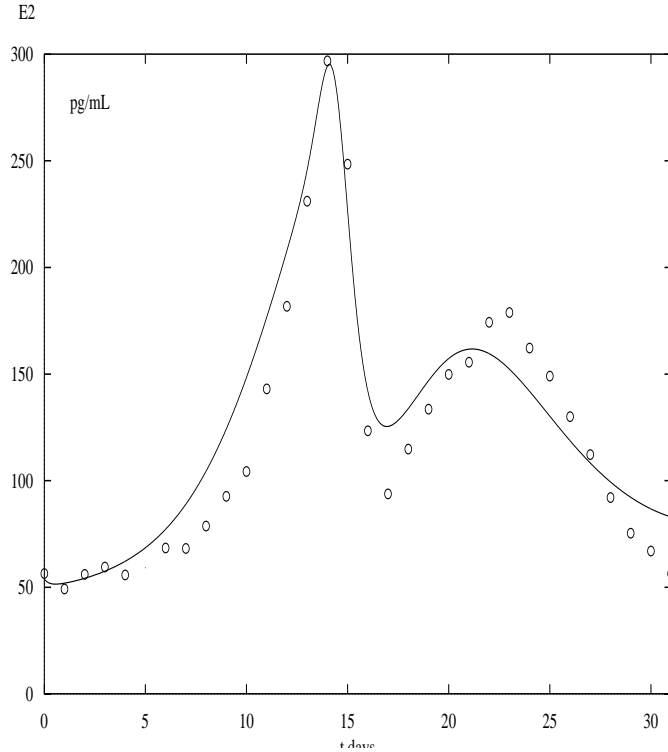


Figure 3: Graph of E_2 predicted by equations (Ov) and (Ov E_2) and data \circ from Table 1 for comparison.

5. Mathematical Analysis

The systems of differential equations (LH_{eq}), (FSH_{eq}) and (Ov) are linear and nonautonomous with bidiagonal coefficient matrices. Let $X(t) = (x_1(t), x_2(t), \dots, x_n(t))$ denote a n -dimensional differentiable vector function of time $t \geq 0$ and let $W(t)$ be a n -dimensional continuous vector function of time. Assume that $A(t)$ represents a $n \times n$ matrix of continuous functions of time. All three systems have the general form:

$$X'(t) = A(t) X(t) + W(t). \quad (5.1)$$

where “ $'$ ” denotes differentiation with respect to time and $A(t)$ has the bidiagonal form:

$$A(t) = \begin{bmatrix} a_{11}(t) & 0 & 0 & \cdots \\ a_{21}(t) & a_{22}(t) & 0 & \cdots \\ 0 & \ddots & \ddots & \\ \cdots & 0 & a_{n,n-1}(t) & a_{nn}(t) \end{bmatrix}. \quad (5.2)$$

For the model under discussion, $A(t)$ and $W(t)$ depend on the input functions which are obtained from the data of Table 1. For instance, in (LHeq) the inputs are $E_2(t)$ and $P_4(t)$, the term $\text{syn}(E_2, P_4)$ is $W(t)$ and $A(t)$ is the 2×2 matrix given by

$$\begin{bmatrix} \frac{-k_{LH} [1+c_{LH,P} P_4(t)]}{1+c_{LH,E} E_2(t)} & 0 \\ \frac{k_{LH} [1+c_{LH,P} P_4(t)]}{v_{dis} [1+c_{LH,E} E_2(t)]} & -r_{LH} \end{bmatrix}.$$

If $\Phi(t)$ is the fundamental solution matrix of the homogeneous linear system $X'(t) = A(t) X(t)$ with $\Phi(0) = I$ then the solution to (5.1) satisfying the initial condition $X(0)$ is given by

$$X(t) = \Phi(t) X(0) + \Phi(t) \int_0^t \Phi(s)^{-1} W(s) ds. \quad (5.3)$$

Because $A(t)$ is bidiagonal, it follows that $\Phi(t) = (\phi_{ij}(t))$ is lower triangular. Selgrade and Schlosser [41] computed that

$$\phi_{ii}(t) = e^{\int_0^t a_{ii}(s) ds}, \quad (5.4)$$

and recursively that

$$\phi_{ij}(t) = \phi_{ii}(t) \int_0^t a_{i,i-1}(s) \phi_{i-1,j}(s) \phi_{ii}^{-1}(s) ds \quad \text{for } j < i. \quad (5.5)$$

Using this explicit representation for $\Phi(t)$, Selgrade and Schlosser [41] proved:

Theorem. *Take $T > 0$ and assume that $A(t)$ and $W(t)$ have period T where $A(t)$ has the form of (5.2). If for each $i = 1, \dots, n$*

$$\int_0^T a_{ii}(s) ds < 0, \quad (5.6)$$

then (5.1) has a unique T -periodic solution and this solution is globally asymptotically stable.

This Theorem may be applied to the gonadotropin systems (LH_{eq}) and (FSH_{eq}) because the coefficient functions $a_{ii}(t)$ are negative for all t so (5.6) is trivially satisfied. Hence, if the serum concentrations of the ovarian hormones have a period of $T=31$ days then the Theorem predicts globally asymptotically stable solutions of period 31 days for the gonadotropes, which are depicted in Figure 2 for parameter values in Table 2. Since some of the coefficient functions in (Ov) are not always negative, to verify that the integral conditions (5.6) are satisfied for (Ov), Selgrade and Schlosser [41] used the symbolic manipulator *Maple* to evaluate the integrals. From a biological perspective, (5.6) applied to (Ov) asserts that the average growth rate over the cycle for each state of the ovary is negative. This permits the transition from one state to the next, i.e., the decline of one state as the next state grows. Thus, if the input functions $FSH(t)$ and $LH(t)$ for the gonadotropin hormones have a period of 31 days then the serum concentrations of the ovarian hormones will attain stable, oscillatory behavior of period 31 days which is independent of the initial conditions.

6. Merged Model and Conclusions

The final step of this modeling process is to merge systems (LH_{eq}), (FSH_{eq}) and (Ov) resulting in a 13-dimensional system of nonlinear ordinary differential equations with three auxiliary equations (OvE_2), (OvP_4) and ($OvIh$). Before merging these systems, the parameter values for (Ov) need to be improved so that the solutions of (Ov) match the periodic data of Table 1. Also, structural modifications may be needed in the systems of differential equations so that model outputs correspond to known experimental results.

The system of differential equations created by merging (LH_{eq}), (FSH_{eq}) and (Ov) is highly nonlinear. For instance, the Hill function in (LH_{syn}) will be an eighth degree rational function in the variable E_2 . If delay proves to be biologically significant for LH and FSH synthesis then delay terms need to be included in the nonlinear system, which complicates analysis (e.g., see Kuang [20]). For a fixed set of parameter values, the unique periodic solutions to the systems (LH_{eq}), (FSH_{eq}) and (Ov) comprise a periodic solution to the merged nonlinear system. Ideally, one would like to show that

this solution is asymptotically stable. Numerical simulations should indicate whether or not this is true but an analytical proof would be quite difficult even without delay.

Understanding how system parameters affect the dynamical properties of such a periodic solution should be helpful in understanding and predicting menstrual cycle irregularities. 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. To test the effects of hormonally active environmental substances on the menstrual cycle, terms could simply be added to the auxiliary equations (OvE_2), (OvP_4) and ($OvIh$) which would represent external sources of these hormones. Model simulations would indicate effects on the menstrual cycle. However, if the pharmacokinetics of these environmental substances are known then additional differential equations will be needed in the model to accommodate the pharmacokinetics. Successful applications of the model in this area may be useful in evaluating hypotheses about the role of hormonally active compounds in breast and ovarian cancers.

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