

A Model for the Production of Ovarian Hormones during the Menstrual Cycle

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Abstract. In this study, a mathematical model is developed for the production of the ovarian hormones (estradiol, progesterone, and inhibin) with input functions which represent blood levels of the gonadotropin hormones (luteinizing hormone and follicle stimulating hormone). A 9-dimensional system of linear, nonautonomous, ordinary differential equations tracks the capacities of 9 stages of the ovary to synthesize hormones. The model predicts blood levels of these ovarian hormones which match reasonably well data in the literature collected from normally cycling women. In addition, given input functions fitting the data for the gonadotropin hormones and of a fixed period, the system of differential equations is shown to have a globally asymptotically stable solution with the same period. This model will be merged with a similar model for the gonadotropin hormones to obtain a nonlinear system with delay describing the concentrations of five hormones important for regulation and maintenance of the menstrual cycle. Such a model may be useful for predicting the effects of hormonally active environmental substances on the menstrual cycle.

1. INTRODUCTION

Recent reports (e.g., McLachlan and Korach [1995] or Daston *et al.* [1997]) 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 have contributed to the increase in breast cancer (Davis *et al.* [1993]), to declines in sperm counts (Sharpe and Skakkebaek [1993]), and to developmental abnormalities (McLachlan [1985]). At present, it is not clear what levels of exposure to estrogenic substances produce toxic effects in humans.

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In order to test the effects of exogenous compounds on the human menstrual cycle in a modelling environment, we intend to develop a mathematical model of the normal menstrual cycle which consists of a system of ordinary differential equations describing the concentrations of five hormones important for regulation and maintenance of the cycle. There are two primary components to this model. The first component is 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). The derivation and rationale for the equations of the first component of the model are contained in Schlosser and Selgrade [1997] and will be reviewed below. This paper studies the second component of the model, which describes the effects of LH and FSH on the growth and development of the ovary and on the production of the ovarian hormones, E_2 , P_4 and Ih . Various positive and negative feedback mechanisms that are supported by experimental data are incorporated into the model. A 9-dimensional system of linear, nonautonomous ordinary differential equations tracks the capacities of 9 stages of the ovary to synthesize hormones. This system of equations describes the qualitative features of the circulatory concentrations of ovarian hormones. Comparisons with data in McLachlan *et al.* [1990] indicate that the peaks and valleys of our model simulations correspond precisely to those in the data. In addition, given input functions fitting the data for the gonadotropin hormones and of a fixed period, we show that the model has a unique, globally asymptotically stable solution with the same period. Hence, our model predicts that women with the same gonadotropin blood profiles will have the same ovarian hormone profiles.

The primary focus of this work is the structural aspects of the ovarian component of the model and its qualitative behavior. Integrating the two components into one system where all hormone concentrations are phase variables, estimating model parameters from clinical data, and validation of the model by comparing its predictions to clinical data will be the topics of future work.

2. BACKGROUND AND MODEL STRUCTURE

2.1. Outline of the Menstrual Cycle.

The normal menstrual cycle (Figure 1) for an adult female is approximately 30 days in duration. Briefly, the first half of the cycle is called the follicular phase, during which the primary follicle develops and matures. Then ovulation occurs and the primary follicle is transformed into the corpus luteum. The luteal phase of the cycle follows, during which the corpus luteum produces hormones in preparation for pregnancy. If pregnancy does not occur, the corpus luteum becomes inactive and the cycle repeats.

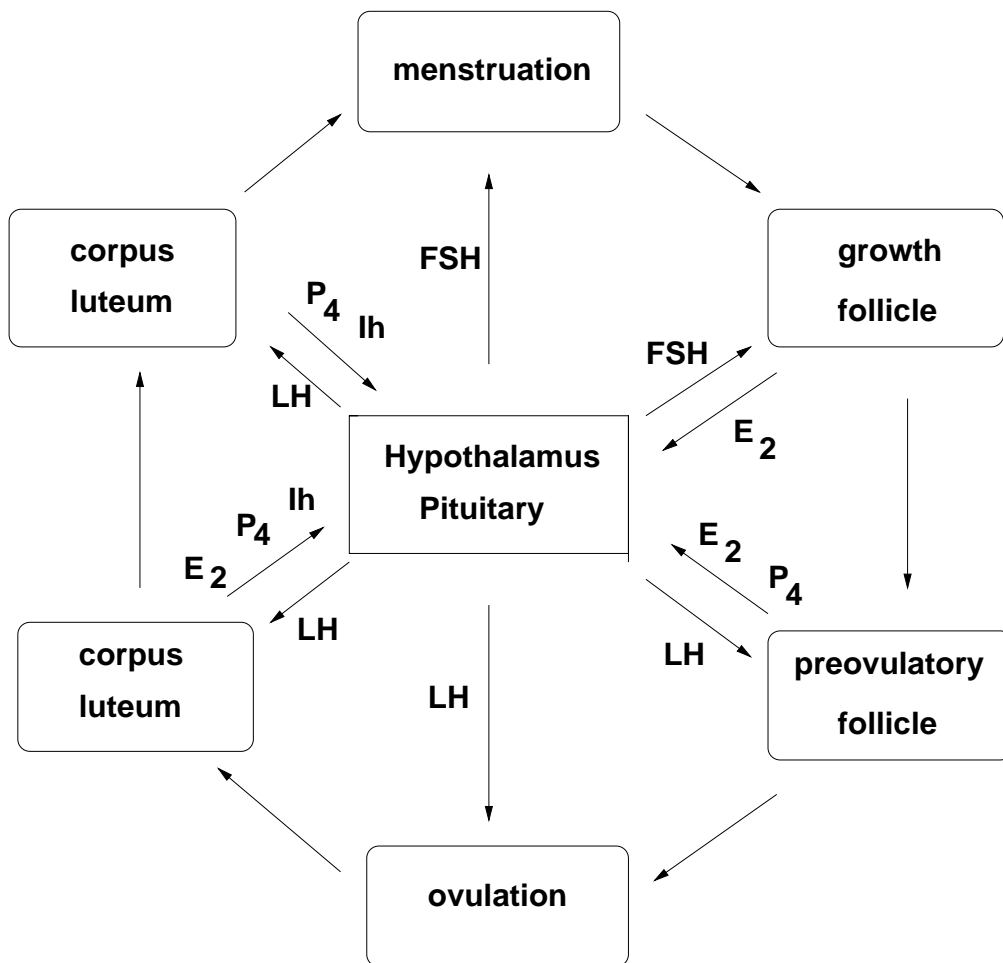


Figure 1: Phases of the menstrual cycle with gonadotropin hormones, LH and FSH , and ovarian hormones, E_2 , P_4 and Ih .

Here we focus on five primary hormones produced during the month which are important for regulating and maintaining the cycle. The pituitary, in conjunction with the hypothalamus, synthesizes and releases the gonadotropin hormones, FSH and LH . Although these hormones have a pulsatile secretion pattern, we assume that the ovary responds to average blood levels of LH and FSH (Odell [1979]), so we track their average concentrations in the blood. As part of its normal function, the 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, as depicted in Figure 1.

The cycle begins with the first day of menstrual flow. During menstruation, the blood levels of FSH are rising and promoting the growth of immature follicles. Usually 6 to 12 follicles develop into secondary follicles by adding layers of granulosa cells (Odell [1979]). During the second third of the follicular phase, the production of E_2 increases due to the growth of the secondary follicles and a primary follicle is selected to continue its development and ultimately to release its ovum. We refer to this time period as the growth follicle stage (see Figure 1). We do not try to model the follicle selection process,

but models have been developed, e.g., see Lacker and Peskin [1981], Lacker *et al.* [1987], and Chavez-Ross *et al.* [1997]. During the growth follicle stage, *FSH* reaches a maximum and secondary follicles begin to atrophy. As the cycle passes into the preovulatory follicular stage, the primary follicle grows more rapidly and produces E_2 in large amounts. During the first two-thirds of the follicular phase, *LH* levels are constant. As E_2 increases toward a maximum, E_2 primes the pituitary for gonadotropin synthesis, so *LH* and *FSH* levels begin to rise. E_2 peaks and one day later *LH* peaks at approximately 8 times its early follicular concentration. This rapid rise and fall of *LH* over a period of 5 days is referred to as the *LH* surge and is necessary for ovulation, which occurs within 16 to 36 hours after the surge. The day of the *LH* peak is considered the midpoint of the menstrual cycle. After a significant decrease during the preovulatory follicular stage, *FSH* also surges concurrently with *LH*.

The *LH* surge followed by ovulation transforms the primary follicle into the corpus luteum. 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*. A low P_4 concentration during the follicular phase begins to increase approximately 2 days before the *LH* surge and continues to increase to 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 synthesis of *LH* and *FSH*, respectively, during the luteal phase in spite of a second increase in E_2 (see Legacé *et al.* [1980], Krey and Kamel [1990], McLachlan *et al.* [1990], and Rivier *et al.* [1990,1991]). The corpus luteum grows during the first half of the luteal phase, reaching its maximal size roughly by the middle of the luteal phase. If fertilization does not occur then the corpus luteum decreases in size and hormone 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* secretion 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.

Previous models of the menstrual cycle or the estrus cycle in mice and rats (see Schwartz [1970], Bogumil *et al.* [1972a], Bogumil *et al.* [1972b], McIntosh and McIntosh [1980], and Plouffe and Luxenberg [1992]) have useful components but also contain elements which are not based on biological mechanisms. For example, they may contain a switch to turn on the *LH* surge, separate sources for tonic and surge *LH* levels, or convolution integrals which weight the effects of hormone levels in past time. We make every effort to link the terms in our differential equations model to physiological mechanisms.

2.2. Equations for the Pituitary Model.

In Schlosser and Selgrade [1997], we develop systems of differential equations for the concentrations of the gonadotropin hormones with the ovarian hormones considered as input functions. The precise form of these inputs are obtained from data in McLachlan *et al.* [1990] for 33 normally cycling women. A novel feature of this portion of our model is that we separate the processes of gonadotropin synthesis and gonadotropin release. Synthesis refers to the production of mature proteins and sequestering of these proteins into secretory vesicles, producing a releasable pool. The release of these proteins into circulation is treated as a separate step, whose regulation differs from the regulation of synthesis. The idea that gonadotropin synthesis and release are differentially regulated was described first by Yen [1980].

Two systems of 2-dimensional ordinary differential equations are used to model both the *LH* and *FSH* processes of synthesis, release, and clearance. Each system is a two compartment model consisting of the pituitary and the blood. Gonadotropin synthesis occurs in the pituitary where it is held in a reserve pool for release into the blood stream. $RP_{LH}(t)$ and $RP_{FSH}(t)$ denote the functions of time which represent the amounts of *LH* and *FSH*, respectively, in the releasable pool. $LH(t)$ and $FSH(t)$ denote the concentrations in the blood. The differential equations for $RP_{LH}(t)$ and $RP_{FSH}(t)$ contain terms for synthesis and for release; the differential equations for $LH(t)$ and $FSH(t)$ contain terms for

assimilation and for clearance. Both these systems are linear in the phase variables, $RP_{LH}(t)$, $LH(t)$, $RP_{FSH}(t)$, and $FSH(t)$, with time-dependent coefficients which are functions of the ovarian hormones, i.e., E_2 , P_4 , and Ih . We use the following explicit functions of time t days for $E_2(t)$, $P_4(t)$, and $Ih(t)$ which approximate the data in McLachlan *et al.* [1990] reasonably well (see Schlosser and Selgrade [1997]):

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

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

$$Ih(t) = 300 + 1330 \exp\left(-\frac{(t-7)^2}{19}\right).$$

Here “exp” denotes exponentiation base “ e ”.

The LH system is:

$$\frac{d}{dt} RP_{LH} = \text{syn}_{LH}(E_2, P_4) - \text{rel}_{LH}(E_2, P_4, RP_{LH}) \quad (2.1a)$$

$$\frac{d}{dt} LH = \frac{1}{v_{dis}} \text{rel}_{LH}(E_2, P_4, RP_{LH}) - \text{clear}_{LH}(LH), \quad (2.1b)$$

where

$$\text{syn}_{LH}(E_2, P_4) = \frac{1400 + \frac{95900 [E_2(t-d_E)]^8}{[360]^8 + [E_2(t-d_E)]^8}}{1 + P_4(t-d_P)/26}, \quad (2.1c)$$

$$\text{rel}_{LH}(E_2, P_4, RP_{LH}) = \frac{3 [1 + 0.024 P_4(t)] RP_{LH}}{1 + 0.008 E_2(t)}, \quad \text{and} \quad (2.1d)$$

$$\text{clear}_{LH}(LH) = 14 LH. \quad (2.1e)$$

The 12 parameters in system (2) have been chosen so that the output of numerical simulation fits the data of McLachlan *et al.* [1990] qualitatively. However, these parameters have not been optimized using that data. 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 blood levels of the ovarian hormones occur and the time when subsequent changes in LH synthesis rates occur. The volume of distribution, $v_{dis} = 2.5L$, appears in the second equation to account for LH assimilation into the blood stream.

Experimental evidence from women (Tsai and Yen [1971]) and from animals (Swerdlhoff *et al.* [1972] and Clarke and Cummins [1984]) indicate that the effect of estradiol on LH synthesis is different than the effect on LH release. For instance, experimental infusion of estradiol is followed by an immediate decrease in serum LH levels, i.e., LH release is inhibited by E_2 . However, after a period of days, if the E_2 concentration is large enough, there is a substantial increase in serum LH — much larger than a simple rebound effect would indicate. In addition, the absence of any presurge dip in LH during the normal menstrual cycle indicates the the surge is much more than a rebound effect (Liu and Yen [1983]). Both the size of the LH surge and the lack of a presurge LH dip provide evidence for a positive effect of E_2 on LH synthesis; see Schlosser and Selgrade [1997] for a complete discussion. Hence, the synthesis term (2.1c) 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 250 and 600 ng/L to reflect the

positive effect of large estradiol concentration on the synthesis of LH . The denominator of the release term (2.1d) provides for the inhibitory effect of E_2 on LH release. Progesterone has the opposite effects on LH synthesis and release as indicated by the positions of the P_4 terms in (2.1c) and (2.1d). The term $clear_{LH}$ is a first order LH clearance term.

The FSH system has a similar form, i.e.:

$$\frac{d}{dt} RP_{FSH} = syn_{FSH}(Ih) - rel_{FSH}(E_2, P_4, RP_{FSH}) \quad (2.2a)$$

$$\frac{d}{dt} FSH = \frac{1}{v_{dis}} rel_{FSH}(E_2, P_4, RP_{FSH}) - clear_{FSH}(FSH), \quad (2.2b)$$

where

$$syn_{FSH}(Ih) = \frac{3800}{1 + Ih(t - d_{Ih})/1430}, \quad (2.2c)$$

$$rel_{FSH}(E_2, P_4, RP_{FSH}) = \frac{65 [1 + 4 P_4(t)] RP_{FSH}}{1 + 0.007 [E_2(t)]^2}, \quad \text{and} \quad (2.2d)$$

$$clear_{FSH}(FSH) = 8.21 FSH. \quad (2.2e)$$

There does not seem to be strong evidence of a positive effect of E_2 on FSH synthesis, only a negative effect on FSH release (Tsai and Yen [1971]). In fact, the presurge dip in FSH as E_2 increases suggests that the FSH surge may be a rebound effect, and our release term (2.2d) captures this behavior with second order inhibition of E_2 on FSH release. The syn_{FSH} term (2.2c) reflects the negative effect of inhibin $Ih(t)$ on FSH synthesis, (see Franchimont *et al.* [1981] and Anderson and DePaolo [1981]), which has a time-delay $d_{Ih} = 2$ days.

3. SYSTEM FOR THE OVARY

In our model for the production of ovarian hormones, we use a 9-dimensional system of differential equations with explicit functions of t as inputs for the gonadotropin hormones. The forms of these input functions are determined by the data in McLachlan *et al.* [1990] which are depicted in Figures 2 and 3. To obtain the FSH function, which exhibits two distinctly different rising profiles during the month, we superpose a rational function and two negative exponential function (Figure 2):

$$FSH(t) = 250 - \frac{250(t-15)^4}{1+(t-15)^4} + 175 \exp\left(-\frac{(t-5)^2}{120}\right) + 150 \exp\left(-\frac{(t-35)^2}{160}\right). \quad (3.1)$$

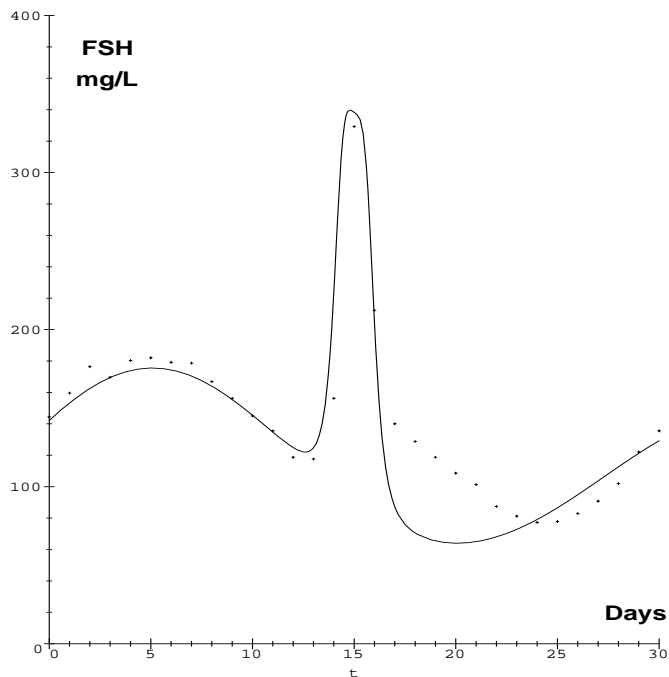


Figure 2: Graph of the $FSH(t)$ input function (3.1) and data (\dots) from McLachlan *et al.* [1990] for comparison.

For $LH(t)$, we capture the surge with a rational function centered at day 15 (Figure 3):

$$LH(t) = 380 - \frac{352(t-15)^4}{1+(t-15)^4}. \quad (3.2)$$

Functions in this form are handled easily by the numerical software package we use (*XPP*, the UNIX version of PhasePlane, Ermentrout [1990]). In addition, explicit input functions allow us to calculate certain integral conditions derived in Section 4 for the existence and stability of periodic solutions of our system of differential equations.

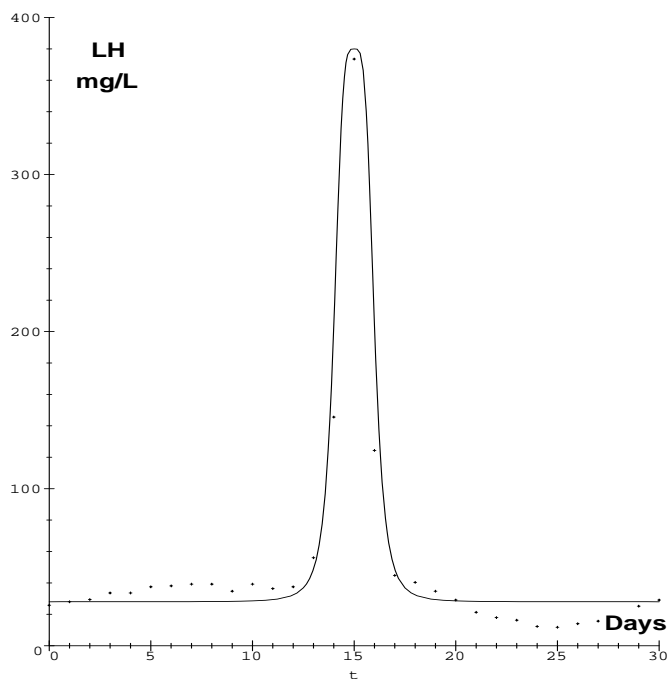


Figure 3: Graph of the $LH(t)$ input function (3.2) and data (\dots) from McLachlan *et al.* [1990] for comparison.

Our model for the ovary divides the follicular phase and the luteal phase into 9 distinct stages based on the capacity of each stage to produce hormones. We use ordinary differential equations to track this capacity as it is transferred from one stage to the next stage during the cycle. We assume the capacity at each stage is proportional to the mass of that stage. The follicular phase consists of the menstrual stage, $MsF(t)$, the growth follicle stage, $GrF(t)$, and the preovulatory stage, $PrF(t)$. We divide the transitional period between the follicular phase and the luteal phase into two stages referred to as ovulatory scar, $Sc_1(t)$ and $Sc_2(t)$. The luteal phase consists of four stages, Lut_i for $i = 1, \dots, 4$. The system of differential equations we obtain is:

$$\begin{aligned}
\frac{d}{dt} MsF &= b FSH(t) + \{c_1 FSH(t) - c_2 [LH(t)]^a\} MsF \\
\frac{d}{dt} GrF &= c_2 [LH(t)]^a MsF + \{c_3 [LH(t)]^a - c_4 LH(t)\} GrF \\
\frac{d}{dt} PrF &= c_4 LH(t) GrF - c_5 [LH(t)]^a PrF \\
\frac{d}{dt} Sc_1 &= c_5 [LH(t)]^a PrF - d_1 Sc_1 \\
\frac{d}{dt} Sc_2 &= d_1 Sc_1 - d_2 Sc_2 \\
\frac{d}{dt} Lut_1 &= d_2 Sc_2 - k_1 Lut_1 \\
\frac{d}{dt} Lut_2 &= k_1 Lut_1 - k_2 Lut_2 \\
\frac{d}{dt} Lut_3 &= k_2 Lut_2 - k_3 Lut_3 \\
\frac{d}{dt} Lut_4 &= k_3 Lut_3 - k_4 Lut_4.
\end{aligned} \tag{3.3a}$$

Since clearance from the blood of the ovarian hormones is on a fast time scale, we assume that the blood levels of E_2 , P_4 , and Ih are essentially at steady-state as in Bogumil *et al.* [1972a]. Hence, we take these concentrations to be proportional to the hormone capacities at the appropriate stages of the cycle, i.e., we take:

$$E_2(t) = e_0 + e_1 GrF(t) + e_2 PrF(t) + e_3 Lut_4(t), \tag{3.3b}$$

$$P_4(t) = p_1 Lut_3(t) + p_2 Lut_4(t) \quad \text{and} \tag{3.3c}$$

$$Ih(t) = h_0 + h_1 PrF(t) + h_2 Lut_2(t) + h_3 Lut_3(t) + h_4 Lut_4(t). \tag{3.3d}$$

The first term of the equation for MsF in (3.3a) represents the FSH initiation of the development of premature follicles. This input from the pituitary begins the cyclic changes within the ovary. The follicle growth rate during this stage is assumed proportional to the FSH blood levels (Odell [1979]). The transition into the stage of development of the secondary follicles is promoted by LH via the term $c_2 [LH(t)]^a MsF$. We allow for a parameter a , $0 < a \leq 1$, to weaken slightly the LH effect. As the secondary follicles grow, E_2 synthesis increases and therefore a GrF term is included in (3.3b). The transition from the growth follicle stage to the preovulatory follicle stage corresponds to the selection of the primary follicle and depends on the full effect of LH . During the preovulatory stage, the primary follicle is secreting large amounts of E_2 , (Baird [1976]), as reflected in (3.3b). Ovulation and luteinization are not instantaneous events (Odell [1979]) but occur over a period of 16 to 36 hours after the LH surge. We represent this transition with two stages referred to as ovulatory scars. We assume that there is little hormone synthesis during this period. The transition is promoted by LH as reflected by the first term in the equation for Sc_1 . Then, in our model the capacity to produce hormones cascades through four luteal stages. Odell [1979] suggested that low concentrations of LH are required to maintain normal corpus luteum function as depicted in Figure 1. However, our LH input function (Figure 3) is essentially constant during the luteal phase, so we assume constant growth rates in (3.3a) for our luteal stages. The choice of four stages allows us to position capacity peaks at times which correspond to the data in McLachlan *et al.* [1990] for the luteal phase without using delays in the differential equations.

Although delays pose no problem for the mathematical analysis of the present ovarian model, when the ovarian and the pituitary models are merged to yield a nonlinear system of differential equations eliminating delays will simplify that nonlinear system. The primary source of P_4 and Ih is the corpus luteum as indicated in (3.3c) and (3.3d).

In Section 4, we obtain complicated analytic expressions for the solutions to (3.3a). However, these formulas do not provide insight into the qualitative behavior of the hormone profiles nor do they lend themselves to parameter estimation. Hence, we examine solution profiles using the UNIX simulation package of Ermentrout [1990]. Some numerical experimentation was used to obtain the following tables of parameter values:

Eq. (3.3a)		Eqs. (3.3b,c,d)	
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 ovarian model (3.3).

The parameters of Table 1 are used to produce the profiles of ovarian hormones in Figure 4 below. As in Bogumil *et al.* [1972a], we assume that a basal level for E_2 is produced by the adrenal gland and the ovary, and we take it to be 48 ng/L because that is the minimum of the data values in McLachlan *et al.* [1990]. The majority of the E_2 produced during a normal cycle is contributed by the growth and preovulatory stages in the follicular phase and the fourth luteal stage, with the largest portion produced by the primary follicle. Notice that the behavior of the simulated solution $E_2(t)$ in Figure 4 is not as sharp as the data in McLachlan *et al.* [1990], but the peaks and valleys occur at precisely the same times during the cycle. The follicular E_2 peak occurs on day 14 and the luteal peaks for the ovarian hormones occur on days 22 and 23. In order to approximate data in McLachlan *et al.* [1990], which is not periodic, we choose initial conditions which result in simulated solutions which are not periodic. The profiles of all three hormones are higher on day 30 than at the beginning of the cycle. In our model, P_4 is produced by the third and fourth luteal stages in approximately equal proportions. We assume a basal level for Ih and take the majority of Ih to be synthesized during the second, third, and fourth luteal stages. Also, notice that the Ih data have a small spike on day 15 which we attribute to the primary follicle (see (3.3d)).

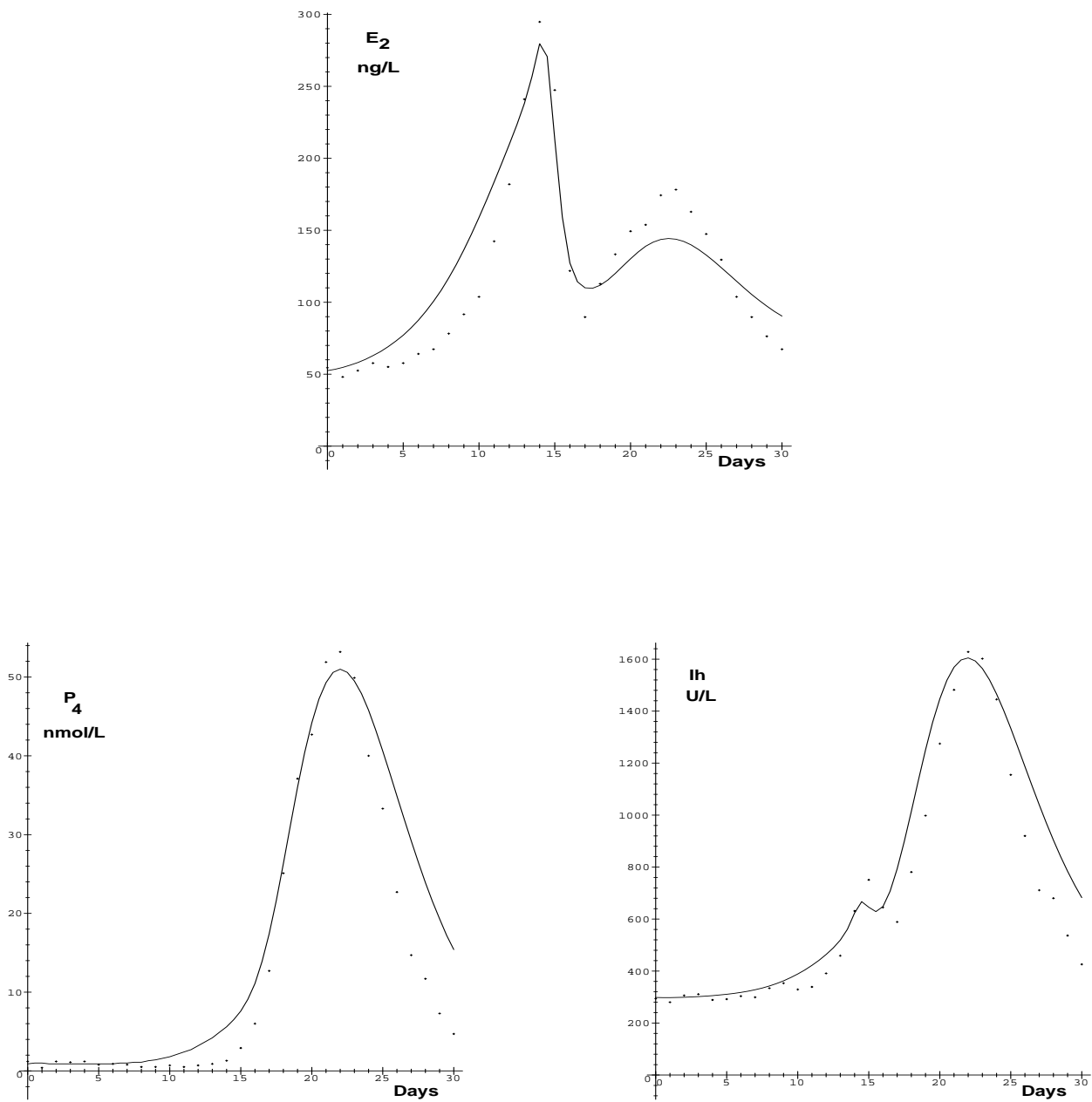


Figure 4: Graphs of $E_2(t)$, $P_4(t)$, and $lh(t)$ simulations of (3.3) and data (\dots) from McLachlan *et al.* [1990] for comparison.

4. MATHEMATICAL ANALYSIS

Let $X(t) = (x_1(t), x_2(t), \dots, x_n(t))$ denote a n -dimensional, differentiable vector function of time $t \geq 0$. If δ is a vector of delays then let $W(t, \delta)$ be a continuous vector function of time and δ . Assume that $A(t)$ represents a $n \times n$ -matrix of continuous functions of time. The systems of differential equations for *LH* (2.1), *FSH* (2.2), and the ovary (3.3) are linear and nonautonomous with the general form:

$$X'(t) = A(t)X(t) + W(t, \delta). \quad (4.1)$$

where $'$ denotes the derivative with respect to time. For a given initial condition, a solution to (4.1) exists and is unique. If $\Phi(t)$ is a fundamental solution matrix of the homogeneous linear system $X'(t) = A(t)X(t)$ then the solution to (4.1) satisfying the initial condition $X(0)$ is given by

$$X(t) = \Phi(t)\Phi(0)^{-1}X(0) + \Phi(t)\int_0^t \Phi(s)^{-1}W(s, \delta)ds. \quad (4.2)$$

Equation (4.2) is the variation of constants formula which may be found in any standard text on ordinary differential equations, e.g., Brauer and Nohel [1969], Coddington and Levinson [1955], or Hale [1969].

If $A(t)$ and $W(t, \delta)$ are periodic functions of period T then (4.1) has a solution of period T if and only if $X(T) = X(0)$, (e.g., see Brauer and Nohel [1969]). Using this fact in (4.2) yields

$$[I - \Phi(T)\Phi(0)^{-1}]X(0) = \Phi(T)\int_0^T \Phi(s)^{-1}W(s, \delta)ds, \quad (4.3)$$

where I is the $n \times n$ identity matrix. If $[I - \Phi(T)\Phi(0)^{-1}]$ has an inverse then the unique T -periodic solution to (4.1) has initial condition given by

$$X(0) = [I - \Phi(T)\Phi(0)^{-1}]^{-1}\Phi(T)\int_0^T \Phi(s)^{-1}W(s, \delta)ds. \quad (4.4)$$

If $\Phi(0)^{-1} = I$, which is the case in our models, then the properties of $\Phi(t)$ determine the existence, the uniqueness, and the stability of periodic solutions.

Because of the form of (2.1), (2.2), and (3.3), we assume that $A(t)$ has the bidiagonal form:

$$A(t) = \begin{bmatrix} a_{11}(t) & 0 & 0 & \cdots \\ a_{21}(t) & a_{22}(t) & 0 & \cdots \\ 0 & \ddots & \ddots & \\ \cdots & 0 & a_{n,n-1}(t) & a_{nn}(t) \end{bmatrix}. \quad (4.5)$$

A fundamental matrix for $X'(t) = A(t)X(t)$ may be obtained by repeated integration as outlined in the following proposition.

Lemma 1. *Let $A(t)$ have the bidiagonal form given by (4.5). The fundamental matrix $\Phi(t) = (\phi_{ij}(t))$ for $X'(t) = A(t)X(t)$ with $\Phi(0) = I$ is lower triangular with diagonal entries, for $i = 1, \dots, n$, defined by*

$$\phi_{ii}(t) = e^{\int_0^t a_{ii}(s)ds}, \quad (4.6)$$

and the remaining nonzero entries recursively defined in terms of the previous row by

$$\phi_{ij}(t) = \phi_{ii}(t)\int_0^t a_{i,i-1}(s)\phi_{i-1,j}(s)\phi_{ii}^{-1}(s)ds \quad \text{for } j < i. \quad (4.7)$$

Proof First integrate the equation $x_1' = a_{11}(t)x_1$ to get $x_1(t) = x_1(0)e^{\int_0^t a_{11}(s) ds}$. Hence $\phi_{11}(t)$ is given by (4.6). Proceed by induction on the row index i .

For $i = 2$, the second row of the homogeneous system is

$$x_2' = a_{21}(t)x_1 + a_{22}(t)x_2,$$

which may be solved for $x_2(t)$ in terms of $x_1(t)$ giving

$$x_2(t) = x_2(0)e^{\int_0^t a_{22}(s) ds} + e^{\int_0^t a_{22}(s) ds} \int_0^t a_{21}(s)x_1(s)e^{-\int_0^s a_{22}(u) du} ds. \quad (4.8)$$

After substituting $x_1(s) = x_1(0)\phi_{11}(s)$ into (4.8), we conclude that $\phi_{22}(t)$ is given by (4.6) and $\phi_{21}(t)$ is given by (4.7).

By induction, assume that the $(i - 1)$ row of the fundamental matrix has the desired form, i.e., the solution to the $(i - 1)$ equation of the homogeneous system is

$$x_{i-1}(t) = \sum_{j=1}^{i-1} x_j(0)\phi_{i-1,j}(t), \quad (4.9)$$

where the $\phi_{i-1,j}$ is given by (4.6) or (4.7). As with the second equation, the solution to the i -th equation may be written as

$$x_i(t) = x_i(0)e^{\int_0^t a_{ii}(s) ds} + e^{\int_0^t a_{ii}(s) ds} \int_0^t a_{i,i-1}(s)x_{i-1}(s)e^{-\int_0^s a_{ii}(u) du} ds. \quad (4.10)$$

After substituting the left side of (4.9) into (4.10) for $x_{i-1}(s)$, we see that the i -th row of $\Phi(t)$ is given by (4.6) and (4.7). \square

In the case of coefficients in (4.1) of period T , from (4.3) we see that there is a T -periodic solution if the inverse of $[I - \Phi(T)]$ exists. From Lemma 1, this is the case if none of the diagonal entries of $\Phi(T)$ are equal to 1. Hence, we obtain

Proposition 2. *Take $T > 0$ and assume that $A(t)$ and $W(t, \delta)$ have period T where $A(t)$ has the form of (4.5). Then (4.1) has a unique T -periodic solution given by (4.2) and (4.4) if for each $i = 1, \dots, n$*

$$\int_0^T a_{ii}(s) ds \neq 0.$$

If the T -periodic solution of Proposition 2 is globally asymptotically stable then, roughly speaking, women would have the same cycle if they produced the same periodic amounts of gonadotropin hormones during the cycle. Asymptotic stability holds if

$$\lim_{t \rightarrow \infty} \Phi(t) = 0. \quad (4.11)$$

To obtain (4.11) we assume that

$$\int_0^T a_{ii}(s) ds < 0. \quad (4.12)$$

From a biological perspective, (4.12) asserts that the average growth rate over the cycle for each phase of the ovary is negative. This permits the transition from one phase to the next, i.e., the decline of one phase as the next phase grows. So (4.12) precludes the continued growth of one phase throughout the cycle, which might be considered a cancerous situation. In order to see that (4.12) implies (4.11), we need bounds on the long-term behavior of the entries of $\Phi(t)$.

Lemma 3. *Take $T > 0$ and assume that $a(t)$ is a continuous T -periodic function such that $\int_0^T a(s) ds < 0$. Then there are positive constants m , M , and B such that for all $t \geq T$*

$$0 \leq m e^{-Bt} \leq e^{\int_0^t a(s) ds} \leq M e^{-Bt}, \quad (4.13)$$

Proof Let $A = -\int_0^T a(s) ds > 0$ and let $K = \int_0^T |a(s)| ds > 0$. Then for all $0 \leq t \leq T$

$$-K \leq \int_0^t a(s) ds < \int_0^t |a(s)| ds \leq K.$$

Fix $t \geq T$. There is a positive integer n so that $0 \leq t - nT < T$. Hence

$$e^{-(n+1)A} \leq e^{-At/T} \leq e^{-nA},$$

which implies that

$$e^{-nA} \leq e^A e^{-At/T} \leq e^A e^{-nA}.$$

Using the periodicity of $a(t)$, we write

$$e^{\int_0^t a(s) ds} = e^{\int_0^{nT} a(s) ds} e^{\int_{nT}^t a(s) ds} = e^{-nA} e^{\int_0^{t-nT} a(s) ds}. \quad (4.14)$$

This gives the upper bound

$$e^{\int_0^t a(s) ds} \leq e^{-nA} e^K \leq e^{A+K} e^{-At/T}.$$

Choose $B = \frac{A}{T}$ and $M = e^{A+K}$. For the lower bound, from (4.14) we have

$$e^{\int_0^t a(s) ds} \geq e^{-nA} e^{-K} \geq e^{-K} e^{-At/T}.$$

So we take $m = e^{-K}$ to obtain (4.13). \square

From Lemma 1 and Lemma 3, we obtain the following bounds for the diagonal entries of $\Phi(t)$.

Corollary 4. *Take $T > 0$ and assume that $A(t)$ has the form of (4.5) and has period T such that $\int_0^T a_{ii}(s) ds < 0$ for each i . Then there are positive constants m_i , M_i , and B_i such that for all $t \geq T$*

$$0 \leq m_i e^{-B_i t} \leq \phi_{ii}(t) \leq M_i e^{-B_i t}, \quad (4.15)$$

and

$$\phi_{ii}^{-1}(t) \leq \frac{1}{m_i} e^{B_i t}. \quad (4.16)$$

Bounds for the off-diagonal terms of $\Phi(t)$ may be recursively derived from the bounds of Corollary 4.

Lemma 5. *With the same assumptions as Corollary 4, for $i = 1, \dots, n$ and for each $j < i$, there are positive constants K_{ij} and B_{ij} such that for all $t \geq T$*

$$|\phi_{ij}(t)| \leq K_{ij} e^{-B_{ij} t}. \quad (4.17)$$

Proof We argue by induction on the row index i . There are positive constants L_{ij} such that for all $t \geq 0$

$$|a_{ij}(t)| \leq L_{ij}.$$

Fix $t \geq T$. For $i = 2$ and $j = 1$, using (4.7), (4.15), and (4.16), we have

$$\begin{aligned} |\phi_{21}(t)| &\leq \phi_{22}(t) \int_0^t |a_{21}(s)| \phi_{11}(s) \phi_{22}^{-1}(s) ds \\ &\leq L_{21} \frac{M_1 M_2}{m_2} e^{-B_2 t} \int_0^t e^{(B_2 - B_1)s} ds. \end{aligned} \quad (4.18)$$

The exponential integral in (4.18) is $[e^{(B_2 - B_1)t} - 1]/(B_2 - B_1)$ if $B_2 \neq B_1$ but is t if $B_2 = B_1$. In either case, by choosing B_{21} positive and slightly less than the minimum of B_1 and B_2 and choosing K_{21} large enough, we obtain

$$|\phi_{21}(t)| \leq K_{21} e^{-B_{21}t}.$$

By induction, assume the bound of (4.17) for $\phi_{i-1,j}(t)$ and consider $\phi_{ij}(t)$. Then from (4.7)

$$\begin{aligned} |\phi_{ij}(t)| &\leq \phi_{ii}(t) \int_0^t |a_{i,i-1}(s)| |\phi_{i-1,j}(s)| \phi_{ii}^{-1}(s) ds \\ &\leq L_{i,i-1} K_{i-1,j} \frac{M_i}{m_i} e^{-B_i t} \int_0^t e^{(B_i - B_{i-1,j})s} ds. \end{aligned} \quad (4.19)$$

The appropriate bound for $|\phi_{ij}(t)|$ is obtained from (4.19). \square

Clearly, the bounds (4.15) and (4.17) imply that the fundamental matrix $\Phi(t)$ approaches 0 as $t \rightarrow \infty$. Hence we have the following result:

Theorem 6. *Take $T > 0$ and assume that $A(t)$ and $W(t, \delta)$ have period T where $A(t)$ has the form of (4.5). Then (4.1) has a unique T -periodic solution given by (4.2) and (4.4) which is globally asymptotically stable if for each $i = 1, \dots, n$*

$$\int_0^T a_{ii}(s) ds < 0. \quad (4.20)$$

We apply Theorem 6 to (3.3a) with $T=30$ days. We assume that the input functions $FSH(t)$ and $LH(t)$ have periods of 30 days and show that the integrals over a period of the diagonal coefficients in (3.3a) are negative, i.e., we verify (4.20). Most of the diagonal coefficients in (3.3a) are either negative functions or negative constants. However, the coefficients of $MsF(t)$ and $GrF(t)$ are not. In fact, for the first third of the cycle, the coefficient of $MsF(t)$ is positive. We use the software *Maple* to evaluate the integrals of these two coefficient functions and obtain:

$$\begin{aligned} \int_0^{30} \{0.0045 FSH(s) - 0.077 [LH(s)]^{0.6}\} ds &\approx -4.3257 \quad \text{and} \\ \int_0^{30} \{0.006 [LH(s)]^{0.6} - 0.008 LH(s)\} ds &\approx -11.2218. \end{aligned} \quad (4.21)$$

Hence our result for (3.3a) may be stated simply as:

Theorem 7. *If the gonadotropin input functions $FSH(t)$ and $LH(t)$ are given by (3.1) and (3.2) and have a period of 30 days then system (3.3a), which models the ovary, has a globally asymptotically stable solution and this solution has a period of 30 days.*

6. DISCUSSION.

In this study we develop a mathematical model for the synthesis of the ovarian hormones E_2 , P_4 , and Ih with input function which represent the gonadotropin hormones FSH and LH . A 9-dimensional system (3.3a) of ordinary differential equations tracks the capacities of 9 stages of the ovary to synthesize hormones — 3 stages for the follicular phase, 2 stages for ovulation and the transitional period from the follicular phase to the luteal phase, and 4 stages for the luteal phase. Since clearance from the blood is so rapid for the ovarian hormones, we assume that their blood levels are at steady-state and take these concentrations to be proportional to the hormone capacities at the appropriate stages during the cycle, see (3.3b), (3.3c) and (3.3d).

This model describes the qualitative features of the circulatory concentrations of ovarian hormones. Comparisons with data in McLachlan *et al.* [1990] in Figure 4 indicate that the peaks and valleys of our simulations correspond to those in the data although the growth and decay profiles of the data are somewhat sharper. In addition, given input functions fitting the data for the gonadotropin hormones and of period 30 days, we show that the model has a unique, globally asymptotically stable solution with a period of 30 days. Hence, our model predicts that women with the same gonadotropin blood profiles will have the same ovarian hormones profiles.

In numerical experiments with our ovarian model, we have noticed that delaying the effect of LH on the luteal stages may reduce the number of stages needed to produce correctly timed luteal hormone peaks. In particular, delay may be used to eliminate the scar stages and still get hormone peaks at 22 and 23 days. However, we have not incorporated such delay into the model because we do not have a clear physiological basis for the delay.

In order to improve model behavior, we will optimize the parameters using the data of McLachlan *et al.* [1990] for the 9-dimensional ovarian system and the systems for the synthesis and release of the gonadotropin hormones. Then we will merge the two components into one, nonlinear, autonomous system of ordinary differential equations. Because of the presence of delays in the gonadotropin component, the merged system will have delays. We intend to validate the model by seeing if it will reproduce responses to exogenous hormone administration which have been observed in clinical studies, e.g., Tsai and Yen [1971], Odell and Molitch [1974], and Clarke and Cummins [1984]. If this validation process is successful, our model should be useful in predicting the effects of environmental substances on the menstrual cycle.

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