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Multiple Stable Periodic Solutions in a Model for Hormonal Control of the Menstrual Cycle

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This study presents a nonlinear system of delay differential equations to model the concentrations of five hormones important for regulation and maintenance of the menstrual cycle. Linear model components for the ovaries and pituitary were previously analyzed and reported separately. Results for the integrated model are now presented here. This model predicts serum levels of ovarian and pituitary hormones which agree with data in the literature for normally cycling women. In addition, the model indicates the existence and stability of an abnormal cycle. Hence, the model may be used to simulate the effects of external hormone therapies on abnormally cycling women as well as the effects of exogenous compounds on normally cycling women. Such simulations may be helpful in understanding the role of xenobiotics in fertility problems, in predicting successful hormone therapies, and for testing hormonal methods of birth control.

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1. INTRODUCTION

Control and regulation of the menstrual cycle in adult women depends on the coordinated actions and reactions of ovarian and pituitary hormones. Follicle stimulating hormone (FSH) and luteinizing hormone (LH), which are produced by the pituitary gland, initiate the development of ovarian follicles and regulate the phases of the ovary and the production of ovarian hormones, [see Yen (1980, 1999) Hotchkiss and Knobil (1994) and Zeleznik and Benyo (1994)]. Simultaneously, at least three ovarian hormones, estradiol (E_2), progesterone (P_4), and inhibin (Ih), affect the synthesis and release of LH and FSH via the hypothalamus and the pituitary. We are developing a physiologically based model which describes the roles of these five hormones in this dual control system and which predicts serum concentrations of these hormones consistent with data in the literature for normally cycling women [see Selgrade and Schlosser (1999), Schlosser and Selgrade (2000), Harris (2001) and Selgrade (2001)].

McLachlan and Korach (1995) and Daston *et al*. (1997) have suggested that the estrogenic activity of environmental substances may disrupt the sexual endocrine systems in both humans and animals. This activity may be contributing to the increased incidence of breast cancer (Davis *et al*., 1993), to declines in sperm counts (Sharpe and Skakkebaek, 1993), and to developmental abnormalities (McLachlan, 1985). In addition, many fertility problems in women are coincident with abnormal serum levels of the ovarian and pituitary hormones. For instance, polycystic ovarian syndrome (PCOS) is usually accompanied by acyclic E_2 concentration and a higher than normal ratio of LH concentration to FSH concentration [see Yen (1999)]. Our mathematical model can be used to investigate the existence and stability of abnormal cycles and to simulate the effects of external hormone therapies on abnormally cycling women as well as the effects of exogenous compounds on normally cycling women. Such simulations may be helpful in understanding the role of xenobiotics in fertility problems, in predicting successful hormone therapies, and in testing hormonal methods of birth control which function by suppressing the mid-cycle surge in LH.

Here we present a model consisting of 13 nonlinear, delay, differential equations. In Section 2, we briefly discuss the modeling process and review two preliminary linear models for the production of the ovarian hormones (Selgrade and Schlosser, 1999) and for the production of the pituitary hormones (Schlosser and Selgrade, 2000). To validate our new nonlinear model, we show that it has an asymptotically stable periodic solution which closely approximates data in McLachlan *et al*. (1990) for 33 normally cycling women. This data set contains daily averages of the five hormones for 31 consecutive days and these averages were computed by centering data from each individual woman about the day of her LH surge. Using Hopf bifurcation theory and the software of Engelborghs *et al*. (2000), *DDE-BIFTOOL*, we exhibit another stable periodic solution for the same parameter values for which the solution that approximates normal hormonal levels exists.

This new solution may describe some biologically feasible 'abnormal' condition in women and has some similarities to PCOS. Exogenous progesterone treatments are presented which perturb the system from the 'abnormal' cycle to the normal cycle. In addition, we demonstrate exogenous estrogen inputs which cause disruption to the normal cycle and which ultimately result in abnormal cycling. Hence, this model illustrates the possibility of environmental endocrine disruption.

2. MODEL DEVELOPMENT

A normal menstrual cycle for an adult woman ranges anywhere from 25 to 35 days in duration (Ojeda, 1992) and consists of two phases, the follicular phase and the luteal phase, separated by ovulation. The pituitary, responding to signals from the hypothalamus, synthesizes and releases the gonadotropin hormones, LH and FSH. Although these hormones have a pulsatile secretion pattern, we assume that the ovary responds to average serum levels of LH and FSH (Odell, 1979), so our model tracks daily average hormone concentrations. Concurrently, 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.

Chávez-Ross (1999) 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 (1970), Bogumil *et al*. (1972a,b), McIntosh and McIntosh (1980), Plouffe and Luxenberg (1992)] 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 try to link the terms in our differential equations model to physiological mechanisms.

Our modeling approach is divided into three steps. The first two steps developed linear, time-dependent systems for the production of the pituitary hormones [see Schlosser and Selgrade (2000)] and for the production of the ovarian hormones [see Selgrade and Schlosser (1999)]. The third step carried out in this work creates a 13-dimensional, highly nonlinear, autonomous system by merging these two simpler components. Using the linear bidiagonal structure of the pituitary and ovarian systems, Selgrade and Schlosser (1999) showed that if each linear system has periodic hormone inputs of the same period then the system has a unique, globally asymptotically stable periodic solution of that period. However, this strong result for both linear systems does not imply any stability properties for the nonlinear system formed by merging these linear component systems. In fact, here we exhibit two locally, asymptotically stable periodic solutions for the merged system.

2.1. ***Pituitary model.*** Firstly, Schlosser and Selgrade (2000) derived two systems of linear ordinary differential equations which describe the pituitary's syn-

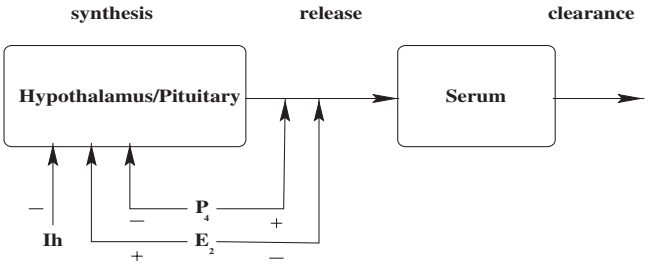

Figure 1. Control of the pituitary's synthesis and release of LH and FSH. Compartments represent the brain and the blood. The plus or minus arrows indicate stimulatory or inhibitory effects of ovarian hormones on synthesis and release.

thesis and release of LH and FSH as controlled by the ovarian hormones. Data from McLachlan *et al*. (1990) were used to obtain input functions for serum levels of E_2, P_4, and Ih. The state variables are pituitary and serum levels of LH and FSH and the differential equations are linear in these variables but, since the inputs are functions of time, the systems are nonautonomous. To obtain the LH and the FSH systems we assume that gonadotopin synthesis occurs in the pituitary, and the hormones are held in a reserve pool for release into the blood stream [see Wang *et al*. (1976)]. The stimulatory and inhibitory effects of the ovarian hormones on this process are indicated in Fig. 1.

Let $\mathrm{RP_{LH}}$ denote the state variable which represents the amount of LH in the reserve pool and let LH denote the serum concentration of LH. The system of differential equations governing the synthesis (s_{LH}), release (r_{LH}) and clearance (c_{LH}) of LH has the form

$$\begin{aligned} \frac{d}{dt}\mathrm{RP_{LH}} &= s_{\mathrm{LH}}(E_2, P_4) - r_{\mathrm{LH}}(E_2, P_4, \mathrm{RP_{LH}}) \\ \frac{d}{dt}\mathrm{LH} &= \frac{1}{v} r_{\mathrm{LH}}(E_2, P_4, \mathrm{RP_{LH}}) - c_{\mathrm{LH}}(\mathrm{LH}) \end{aligned} \tag{1}$$

where

$$s_{\mathrm{LH}}(E_2, P_4) = \frac{V_{0,\mathrm{LH}} + \frac{V_{1,\mathrm{LH}}[E_2(t)]^8}{[Km_{\mathrm{LH}}]^8 + [E_2(t)]^8}}{1 + P_4(t - d_P)/Ki_{\mathrm{LH},P}}, \tag{1a}$$

$$r_{\mathrm{LH}}(E_2, P_4, \mathrm{RP_{LH}}) = \frac{k_{\mathrm{LH}}[1 + c_{\mathrm{LH},P} P_4(t)]\mathrm{RP_{LH}}}{1 + c_{\mathrm{LH},E} E_2(t)}, \tag{1b}$$

and

$$c_{\mathrm{LH}}(\mathrm{LH}) = a_{\mathrm{LH}}\mathrm{LH}. \tag{1c}$$

In (1), $E_2(t)$ and $P_4(t)$ are the inputs which are explicit functions of time approximated from the data for serum concentrations of E_2 and P_4. The term $s_{\mathrm{LH}}(E_2, P_4)$

captures the effects of E_2 and P_4 on LH synthesis. Clinical experiments [e.g., Tsai and Yen (1971), Swerdloff *et al*. (1972), Karsch *et al*. (1973a,b), Liu and Yen (1983), Clarke and Cummins (1984)] have indicated that LH exhibits a biphasic response to E_2 concentrations of various strengths and durations. To model this response, Schlosser and Selgrade (2000) assumed that the effect of E_2 on LH synthesis is different than the effect on LH release, i.e., E_2 inhibits release [see the denominator in (1b)] but at high levels E_2 significantly promotes synthesis [see the Hill function in the numerator of (1a)]. The release term $r_{\mathrm{LH}}(E_2, P_4, \mathrm{RP}_{\mathrm{LH}})$ is the product of $\mathrm{RP}_{\mathrm{LH}}$ and a function which includes the inhibitory effect of E_2 on the release of LH into the blood. This term divided by blood volume v appears in the differential equation for the state variable LH, which also contains a linear clearance term. The parameters in (1a)–(1c) are named according to the traditional scheme for chemical reactions, e.g., V represents the velocity of the reaction [see Keener and Sneyd (1998)]. The time-delay parameter d_P, which is assumed only for the synthesis term, describes the period between the time when changes in serum levels of P_4 occur and the time when subsequent changes in LH synthesis rates occur. A similar delay for E_2 was initially included (Schlosser and Selgrade, 2000) but recent parameter identification (Harris, 2001) indicated that it was insignificant.

The pair of differential equations for synthesis and release of FSH (see M3 and M4) have a form similar to (1) and are discussed in detail in Schlosser and Selgrade (2000) where

$$s_{\mathrm{FSH}}(Ih) = \frac{V_{\mathrm{FSH}}}{1 + Ih(t - d_{Ih})/Ki_{\mathrm{FSH},Ih}}, \tag{2a}$$

$$r_{\mathrm{FSH}}(E_2, P_4, \mathrm{RP}_{\mathrm{FSH}}) = \frac{k_{\mathrm{FSH}}[1 + c_{\mathrm{FSH},P}P_4(t)]\mathrm{RP}_{\mathrm{FSH}}}{1 + c_{\mathrm{FSH},E}[E_2(t)]^2}, \tag{2b}$$

and

$$c_{\mathrm{FSH}}(\mathrm{FSH}) = a_{\mathrm{FSH}}\mathrm{FSH}. \tag{2c}$$

Both the LH and FSH systems are linear and time-dependent differential equations with 17 parameters in total. The clearance rates and the volume of distribution v were found in the literature but the other parameters were crudely estimated in Schlosser and Selgrade (2000) using the data from McLachlan *et al*. (1990). Harris (2001) applied a Nelder-Meade minimizer in a least squares routine to reparameterize the LH and FSH systems and to obtained the improved values listed in Table 1.

2.2. ***Ovarian model.*** To describe the production of E_2, P_4, and Ih in the ovary, Selgrade and Schlosser (1999) derived a linear, time-dependent system of nine ordinary differential equations [see (M5) through (M13) in the merged system (M1)–(M13) below] to represent nine distinct stages of the ovary based on the

Table 1. Parameter values for the LH and FSH equations.

LH equation (1)		
k_{LH}	2.49	day^{-1}
a_{LH}	14.0	day^{-1}
$V_{0,\mathrm{LH}}$	1263.4	$\mu\mathrm{g\ day}^{-1}$
$V_{1,\mathrm{LH}}$	91 000	$\mu\mathrm{g\ day}^{-1}$
Km_{LH}	360	$\mathrm{ng\ L}^{-1}$
$Ki_{\mathrm{LH},P}$	31.22	$\mathrm{nmol\ L}^{-1}$
$c_{\mathrm{LH},E}$	0.0049	$\mathrm{L\ ng}^{-1}$
$c_{\mathrm{LH},P}$	0.07	$\mathrm{L\ nmol}^{-1}$
d_P	1.00	day

FSH equation		
V_{FSH}	5700	$\mu\mathrm{g\ day}^{-1}$
a_{FSH}	8.21	day^{-1}
k_{FSH}	7.29	day^{-1}
d_{Ih}	2.00	days
$c_{\mathrm{FSH},E}$	0.16	$(\mathrm{L/ng})^2$
$Ki_{\mathrm{FSH},Ih}$	641	$\mathrm{U\ L}^{-1}$
$c_{\mathrm{FSH},P}$	644	$\mathrm{L\ nmol}^{-1}$
v	2.50	L

capacity of each stage to produce hormones. The dependence on time appears in the gonadotropin input functions, LH(t) and FSH(t), which were obtained from the data in McLachlan *et al*. (1990). The capacity to produce hormones is assumed proportional to the mass of each stage, so the state variables represent the masses of the 'active' follicular or luteal tissues during the corresponding stages of the cycle (see Fig. 2). The follicular phase of the cycle consists of the follicle recruitment stage, RcF, the secondary follicular stage, SeF, and the preovulatory follicular stage, PrF. The transitional period between the follicular phase and the luteal phase is divided into two stages referred to as ovulatory scars, Sc_1 and Sc_2. The luteal phase consists of four stages, Lut_i for $i = 1, \ldots, 4$. The gonadotropins promote tissue growth within a stage and the transformation of tissue from one stage to the next as indicated in Fig. 2.

Since clearance from the blood of the ovarian hormones is on a fast timescale, we assume that serum levels of E_2, P_4, and Ih are at quasi-steady state [see Keener and Sneyd (1998) as did Bogumil *et al*. (1972a)]. Hence, we take these concentrations to be proportional to the tissue masses during the appropriate stages of the cycle giving the following three auxiliary equations for serum levels of E_2, P_4 and Ih as functions of time:

$$E_2(t) = e_0 + e_1\mathrm{SeF}(t) + e_2\mathrm{PrF}(t) + e_3\mathrm{Lut}_4(t), \tag{3a}$$

$$P_4(t) = p_1\mathrm{Lut}_3(t) + p_2\mathrm{Lut}_4(t) \qquad \text{and} \tag{3b}$$

$$Ih(t) = h_0 + h_1\mathrm{PrF}(t) + h_2\mathrm{Lut}_3(t) + h_3\mathrm{Lut}_4(t). \tag{3c}$$

The first term on the right in (M5), bFSH, represents the pituitary's stimulation of premature follicles and initiates the cyclic changes within the ovary. Follicle growth rates during the follicular phase are assumed proportional to the FSH and LH serum levels, see Odell (1979). The transition from the secondary follicular stage to the preovulatory follicular stage corresponds to the selection of the dominant follicle and depends on LH. The dominant follicle secretes large amounts

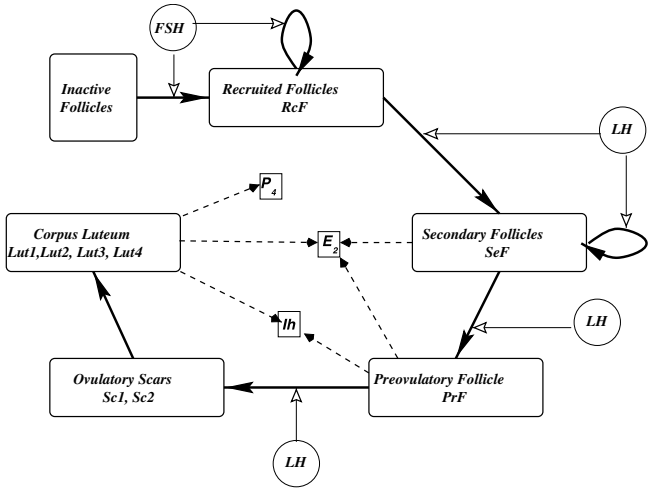

Figure 2. Diagram of the stages of the ovary. Compartments represent follicular or luteal tissue in each stage. Solid arrows indicate transformation of tissue from one stage to another or growth within a stage when pointing back to the same compartment. Open arrows indicate induction by gonadotropins. Dotted arrows indicate synthesis of ovarian hormones.

of E_2 as reflected in (3a), see Baird (1976). Ovulation and luteinization are not instantaneous events (Odell, 1979) and are represented by two stages 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 stages. The primary source of P_4 and Ih is the corpus luteum as indicated in (3b) and (3c).

To improve on the parameter estimation for the ovarian system and the auxiliary equations in Selgrade and Schlosser (1999), Harris (2001) used Nelder–Meade with least squares to obtain Table 2.

2.3. ***Merged model.*** The final step of this modeling process is to merge the pituitary and ovarian systems into a single 13-dimensional system of nonlinear, delay differential equations (M1)–(M13) with the three auxiliary equations (3). While the two model components were described previously, results for this merged system are presented for the first time here. In the merged system the functions LH and FSH are state variables and the functions E_2, P_4, and Ih are linear combinations of the ovarian state variables via the auxiliary equations. Hence, system (M1)–(M13) is autonomous since there are no time-dependent inputs as there were in the pituitary and ovarian systems. In addition, (M1-M13) is highly nonlinear, e.g., the first term in (M1) contains a rational function of degree 8 in the state variables. Discrete delays are present in the FSH and LH synthesis terms. The inhibitory effect of P_4 on LH synthesis present in (M1) results in delay

Table 2. Parameter values for ovarian and auxiliary equations.

Ovarian equations (M5)–(M13)		
b	0.0040	L day^{-1}
c_1	0.0058	L μg^{-1} day^{-1}
c_2	0.0480	day^{-1}
c_3	0.0040	day^{-1}
c_4	0.0061	day^{-1}
c_5	1.2655	day^{-1}
d_1	0.6715	day^{-1}
d_2	0.7048	day^{-1}
k_1	0.6876	day^{-1}
k_2	0.6900	day^{-1}
k_3	0.6891	day^{-1}
k_4	0.7093	day^{-1}
α	0.7736	
β	0.1566	
γ	0.0202	

Auxiliary equation (3)		
e_0	48.000	ng L^{-1}
e_1	0.1044	1 kL^{-1}
e_2	0.1659	1 kL^{-1}
e_3	0.2309	1 kL^{-1}
p_1	0.0500	nmol L^{-1} μg^{-1}
p_2	0.0500	nmol L^{-1} μg^{-1}
h_0	274.28	U L^{-1}
h_1	0.4064	U L^{-1} μg^{-1}
h_2	0.4613	U L^{-1} μg^{-1}
h_3	2.1200	U L^{-1} μg^{-1}

affecting two state variables via (3b) and a similar effect of Ih on FSH in (M3) affects three state variables via (3c). To study the dynamical behavior of (M1)–(M13), we use the delay differential equation solver *DDE23* of Shampine and Thompson (2001).

$$\frac{d}{dt}\mathrm{RP_{LH}} = \frac{V_{0,\mathrm{LH}} + \frac{V_{1,\mathrm{LH}}E_2^8}{Km_{\mathrm{LH}}^8 + E_2^8}}{1 + P_4(t-d_P)/Ki_{\mathrm{LH},P}} - \frac{k_{\mathrm{LH}}[1 + c_{\mathrm{LH},P}P_4]\mathrm{RP_{LH}}}{1 + c_{\mathrm{LH},E}E_2} \tag{M1}$$

$$\frac{d}{dt}\mathrm{LH} = \frac{1}{v}\frac{k_{\mathrm{LH}}[1 + c_{\mathrm{LH},P}P_4]\mathrm{RP_{LH}}}{1 + c_{\mathrm{LH},E}E_2} - a_{\mathrm{LH}}\mathrm{LH} \tag{M2}$$

$$\frac{d}{dt}\mathrm{RP_{FSH}} = \frac{V_{\mathrm{FSH}}}{1 + Ih(t-d_{Ih})/Ki_{\mathrm{FSH},Ih}} - \frac{k_{\mathrm{FSH}}[1 + c_{\mathrm{FSH},P}P_4]\mathrm{RP_{FSH}}}{1 + c_{\mathrm{FSH},E}E_2^2} \tag{M3}$$

$$\frac{d}{dt}\mathrm{FSH} = \frac{1}{v}\frac{k_{\mathrm{FSH}}[1 + c_{\mathrm{FSH},P}P_4]\mathrm{RP_{FSH}}}{1 + c_{\mathrm{FSH},E}E_2^2} - a_{\mathrm{FSH}}\mathrm{FSH} \tag{M4}$$

$$\frac{d}{dt}\mathrm{RcF} = b\mathrm{FSH} + [c_1\mathrm{FSH} - c_2\mathrm{LH}^{\alpha}]\mathrm{RcF} \tag{M5}$$

$$\frac{d}{dt}\mathrm{SeF} = c_2\mathrm{LH}^{\alpha}\mathrm{RcF} + [c_3\mathrm{LH}^{\beta} - c_4\mathrm{LH}]\mathrm{SeF} \tag{M6}$$

$$\frac{d}{dt}\mathrm{PrF} = c_4\mathrm{LH}\,\mathrm{SeF} - c_5\mathrm{LH}^{\gamma}\mathrm{PrF} \tag{M7}$$

$$\frac{d}{dt}Sc_1 = c_5\mathrm{LH}^{\gamma}\mathrm{PrF} - d_1Sc_1 \tag{M8}$$

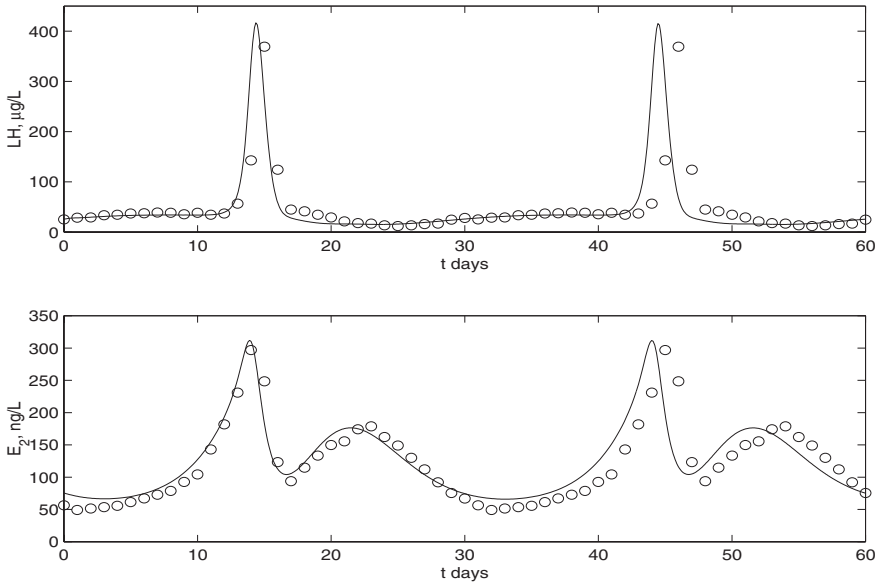

Figure 3. The solid curves (normal cycle) represent serum concentrations of LH and E_2 for normally cycling women as predicted by the merged system (M1)–(M13) and ○'s represent the daily mean serum levels of LH and E_2 for 33 women in McLachlan *et al*. (1990).

$$\frac{d}{dt}Sc_2 = d_1 Sc_1 - d_2 Sc_2 \tag{M9}$$

$$\frac{d}{dt}\mathrm{Lut}_1 = d_2 Sc_2 - k_1 \mathrm{Lut}_1 \tag{M10}$$

$$\frac{d}{dt}\mathrm{Lut}_2 = k_1 \mathrm{Lut}_1 - k_2 \mathrm{Lut}_2 \tag{M11}$$

$$\frac{d}{dt}\mathrm{Lut}_3 = k_2 \mathrm{Lut}_2 - k_3 \mathrm{Lut}_3 \tag{M12}$$

$$\frac{d}{dt}\mathrm{Lut}_4 = k_3 \mathrm{Lut}_3 - k_4 \mathrm{Lut}_4. \tag{M13}$$

3. RESULTS

Simulations of system (M1)–(M13) were run using the parameter values in Tables 1 and 2 without further adjustment to the parameters. The initial conditions for FSH and LH were chosen to correspond to the initial data values in McLachlan *et al*. (1990) and the initial conditions for the other state variables were chosen as a result of numerical experiments with the pituitary and ovarian systems. For these initial conditions, we observe a locally asymptotically stable periodic solution (Fig. 3) which approximates the data of McLachlan *et al*. (1990) and we refer to this

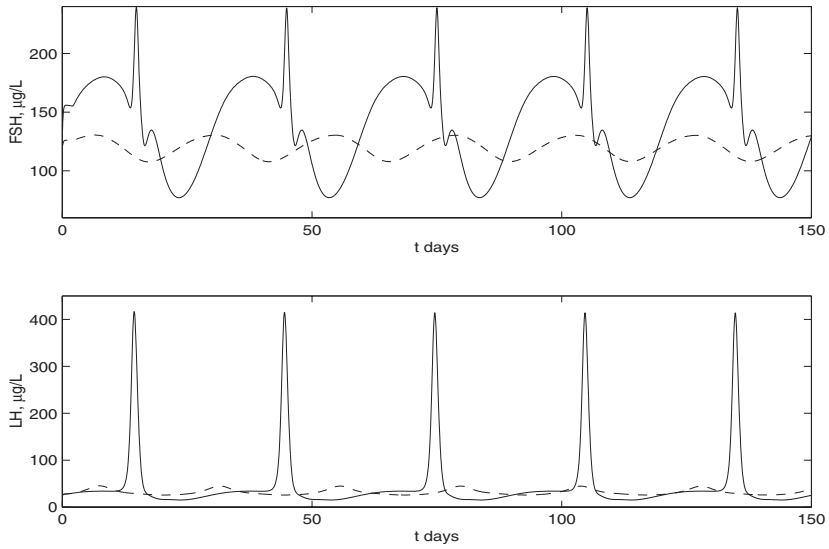

Figure 4. Pituitary hormones, FSH and LH, for the simulated normal cycle (solid curve) and the simulated abnormal cycle (dashed curve).

solution as the *normal* cycle. The period of this normal cycle is roughly 29.5 days as compared to the period of the data which we assume is 31 days.

For this same set of parameter values, there exists another locally asymptotically stable periodic solution of period 24 days, which we call the *abnormal* cycle. We discovered this solution using the theory of Hopf bifurcations and the software of Engelborghs *et al*. (2000), *DDE-BIFTOOL*, to track periodic solutions as parameters change from the values where Hopf bifurcation occurs. Numerical simulations indicate that the domain of attraction of this solution is smaller than that of the normal cycle [see Harris (2001)]. A detailed study of the domains of attraction will be the topic of future work. The abnormal cycle may describe some abnormal condition in women and, in fact, has some similarities to PCOS. Figures 4 and 5 compare the hormone profiles of the normal and abnormal cycles for 150 days.

For the abnormal cycle, the E_2 levels vary only slightly throughout a period, FSH and P_4 concentrations are lower than those of the normal cycle, and the average LH concentration is slightly higher except at the time of the surge. Hence, the ratio of LH to FSH is elevated above that for the normal cycle. These characteristics are present in many PCOS individuals, see Yen (1999) and Marshall *et al*. (2001).

3.1. ***P_4 treatment.*** Since PCOS is the leading cause of female infertility in the United States (Nestler *et al*., 1998), clinical and experimental treatments have been implemented to correct hormonal imbalances in PCOS women, e.g., Petsos *et al*. (1986), Anttila *et al*. (1992), Buckler *et al*. (1992), Fiad *et al*. (1996) and Nestler *et al*. (1998). One cause of these imbalances may be that

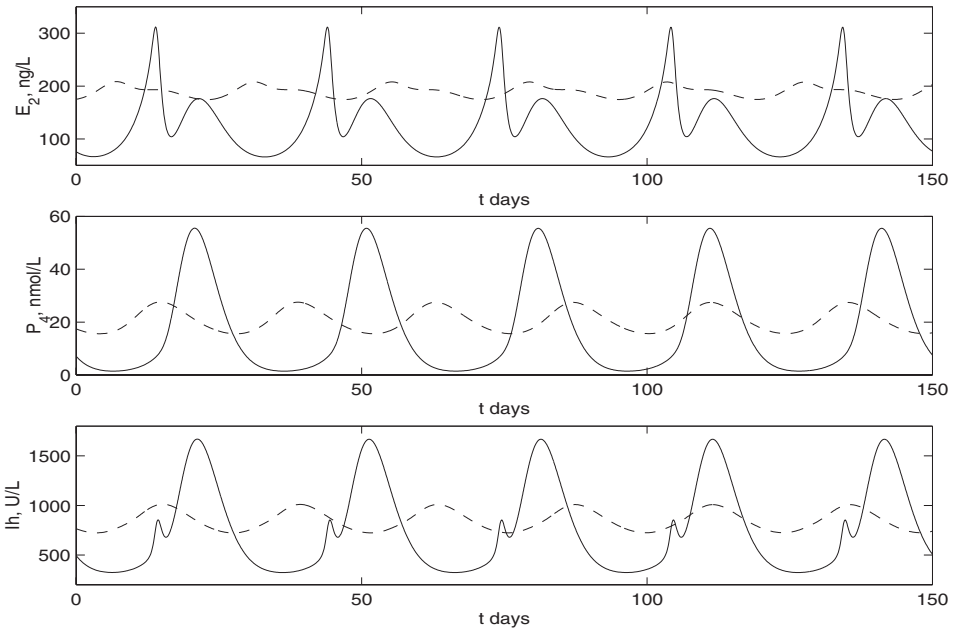

Figure 5. Ovarian hormones, E_2, P_4 and Ih, for the simulated normal cycle (solid curve) and the simulated abnormal cycle (dashed curve).

the persistent rapid pulses of gonadotropin releasing hormone (GnRH) during the luteal phase of the cycle favor LH synthesis instead of FSH synthesis (Marshall *et al*., 2001). Sustained levels of P_4 during the luteal phase of the normal cycle inhibit the amplitude and frequency of GnRH secretion. Hence, the administration of exogenous progesterone has been used to elevate serum P_4 to normal luteal levels and, subsequently, to reduce the LH/FSH ratio [see Petsos *et al*. (1986), Anttila *et al*. (1992), Buckler *et al*. (1992) and Fiad *et al*. (1996)]. In our model, the administration of exogenous progesterone may be implemented easily by adding a term to the progesterone auxiliary equation (3b). Our P_4 therapy (see the middle graph of Fig. 6) adds 80 nmol L^{-1} to (3b) for 5 days at the beginning of the luteal phase of the abnormal cycle. Because of a slight rise in LH around day 8 (Fig. 4) and decreasing E_2 at that time (Fig. 5), we assume that the luteal phase of the abnormal cycle begins on day 8 and we administer P_4 from day 8 to day 13. This treatment increases serum P_4 by 80 nmol L^{-1} for those 5 days and results in normal P_4 concentrations in the next cycle (see the bottom graph of Fig. 6), as well as normal levels of the other hormones. Figure 7 shows that, during the treatment period, LH initially spikes because P_4 promotes LH release but then decreases to normal luteal phase levels for the duration of the treatment because P_4 inhibits LH synthesis. This behavior is consistent with what has been observed in clinical experiments, see Buckler *et al*. (1992).

Mathematically, a perturbation to the abnormal cycle caused by the addition of 80 nmol L^{-1} of P_4 results in the solution leaving the domain of attraction

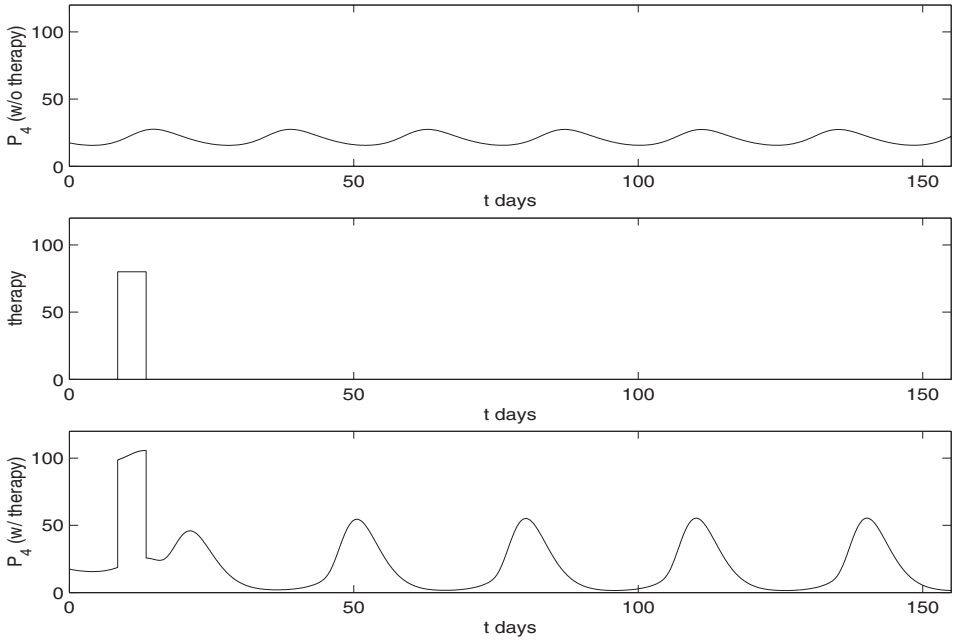

Figure 6. Progesterone treatment restores the normal circulation of hormones. The top graph depicts P_4 serum levels for the abnormal cycle. Administering progesterone for the first 5 days of the luteal phase (middle graph) of the abnormal cycle so that P_4 levels are elevated by 80 nmol L^{-1} rapidly recovers the normal cycle (bottom graph).

of the abnormal cycle and rapidly approaching the normal cycle. If a treatment of 50 nmol L^{-1} for 5 days is administered then it takes approximately 120 days (four normal cycle lengths) for the normal cycle to be attained. With a treatment of only 30 nmol L^{-1} for 5 days, the normal cycle will not be recovered. A complete dose–response analysis for P_4 administration will be carried out in the future.

3.2. ***E_2 disruption.*** There is increasing concern that environmental substances with estrogenic activity may disrupt the sexual endocrine system in humans and animals, [e.g., see McLachlan and Korach (1995) or Daston *et al*. (1997)]. The effects of exogenous estrogen on the dynamical behavior of our model may be tested by adding a term to the estrogen auxiliary equation (3a). The middle graph in Fig. 8 depicts an exogenous E_2 exposure of 50 ng L^{-1} for one complete cycle ($\sim$30 days), followed by a cycle with no exposure and then followed by another 30 day period of exposure. This periodic disruption is applied at the beginning of the normal cycle. After the first 30 day exposure, E_2 levels return to near normal ranges for a complete month (see the third graph in Fig. 8). However, the second E_2 exposure results in an E_2 profile which never reaches a level sufficient to elicit an LH surge. Hence, after about 90 days from the beginning of exposure, the disrupted solution lies in the domain of attraction of the abnormal cycle but it takes another 180 days (6 normal cycles) for this disrupted solution to become quite close

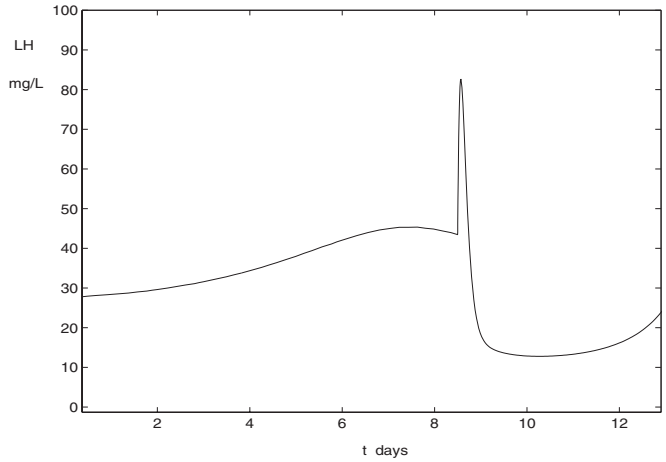

Figure 7. Effect of P_4 treatment on the LH of the abnormal cycle. LH spikes between days 8 and 9 and then decreases to normal luteal phase levels for the duration of the treatment because P_4 inhibits LH synthesis.

to the abnormal cycle (day 270 in Fig. 8). Surprisingly, a continuous E_2 exposure of 50 ng L^{-1} for 60 days (two cycles) will not disrupt the normal cycle. However, continuous exposures at higher levels will cause cycle disruption. A strength and duration study for this phenomenon will be the subject of future work.

4. SUMMARY AND CONCLUSIONS

Here we have presented a model for hormonal control of the menstrual cycle which involves five hormones essential to this process. The system of 13 delay differential equations (M1)–(M13) has 42 parameters (Tables 1 and 2) which were identified using data from the literature. For these parameters, the model exhibits at least two locally asymptotically stable periodic solutions. One solution approximates the data and we suggest that the other solution represents some abnormal condition in women, possibly PCOS. An exhaustive study of state space needs to be done to determine if there are other stable solutions. Also, the domains of attraction of stable solutions need to be mapped. The abnormal cycle may be obtained from a supercritical Hopf bifurcatioin by varying a single parameter. Hence, if only one parameter in Tables 1 and 2 is changed, system (M1)–(M13) has a stable equilibrium. We intend to investigate the physiological significance of this equilibrium solution.

In clinical experiments, progesterone treatment has been used to normalize the gonadotropin levels of PCOS patients. We illustrate a P_4 therapy which perturbs the abnormal cycle to the normal cycle within 1 month. Also, we present an exogenous estrogen exposure which disturbs the normal cycle enough that the system ultimately oscillates abnormally. Other P_4 treatments and E_2 disruptions are possible and will be the subjects of future studies.

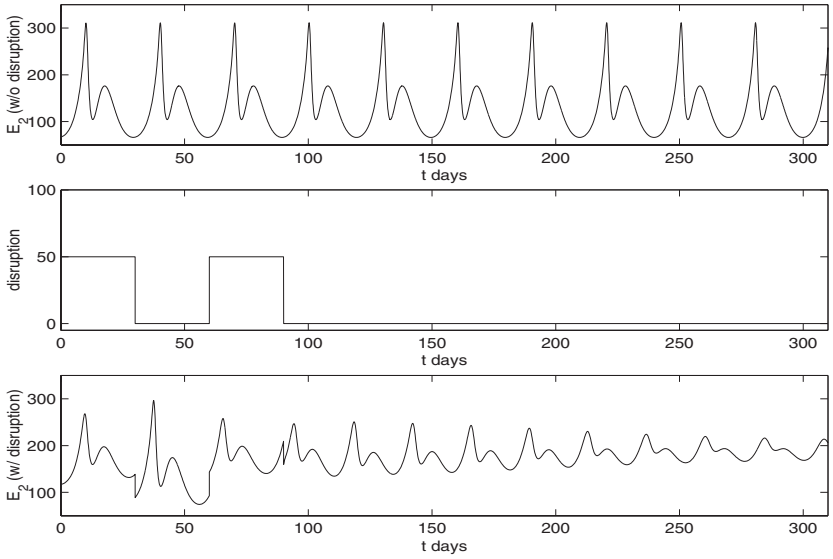

Figure 8. Exogenous estrogen exposure can lead to abnormalities in the normal menstrual cycle. The top graph depicts E_2 serum levels for the normal cycle. Exposing the normal cycle to 50 ng L^{-1} of exogenous estrogen for a full cycle, followed by a full cycle with no exposure and then another full cycle of exposure (middle graph), disrupts the normal circulation of hormones (bottom graph).

Finally, this model may certainly be improved by including greater biological realism. For instance, the data of McLachlan *et al*. (1990) were collected before the assay distinguishing inhibin A and inhibin B was available. With data for inhibin A and B now in the literature (Groome *et al*., 1996) both should be included in the model. The inhibin profile in the present model is similar to inhibin A while inhibin B is prominent during the follicular phase of the cycle. The present model lumps together the pituitary and hypothalamus and does not describe the role of GnRH. However, we have mentioned that the ovarian hormones may affect gonadotropin secretion by modulating the GnRH pulse frequency and amplitude. Hence, the present model may be improved by developing and integrating a specific model for GnRH.

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