Abstract

HARRIS, LEONA ANN. Differential Equation Models for the Hormonal Regulation of the Menstrual Cycle. (Under the direction of James F. Selgrade.)

There are growing concerns about the effects of environmental substances on the sexual endocrine system. It is believed that estrogenic substances may disrupt the sexual endocrine system by initiating or promoting such adverse effects as cancer, developmental disorders, and the reduction of fertility [17, 40]. While these effects appear to be more imminent during high levels of exposure to estrogenic substances, concerns are increasing because low levels of exposure to estrogenic substances occur more frequently for longer periods of time; in our diets (phytoestrogens), in the environment (pesticides), and in contraception (spermicides and birth control pills) and hormonal therapies [17, 40]. These effects might have a profound effect on the menstrual cycle. Therefore, mathematical models that accurately predict the serum levels of hormones that control the menstrual cycle would be useful tools in evaluating the effects of environmental substances.

The human menstrual cycle is controlled by the pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the ovarian hormones, estradiol (E_2), progesterone (P_4), and inhibin (Ih). The pituitary hormones stimulate the growth of ovarian follicles that secrete hormones and work to produce a fertilized ovum. The mathematical models to be presented in this work predict the blood levels

of these five hormones as they interact to regulate and maintain the menstrual cycle.

The unmerged model has a pituitary component and an ovarian component consisting of linear systems of ordinary differential equations with time dependent coefficients. The pituitary systems describe the synthesis, release, and clearance of LH and FSH during the menstrual cycle, based on their response to E_2, P_4 and Ih. Functions representing the ovarian hormones are used as inputs into these systems. The ovarian system describes the roles of FSH and LH in the development of ovarian follicles and the production of E_2, P_4 and Ih during the menstrual cycle. Functions representing the pituitary hormones are used as inputs into this system. The merged model is formed by merging the pituitary and ovarian systems together. The merged system is a highly nonlinear system of delay differential equations that describes the interactions between the five hormones throughout the menstrual cycle. This model predicts reasonably accurate blood levels of these hormones observed in normally cycling women as reported in the literature.

The merged system is shown to have two stable periodic solutions for the same parameter set, a large amplitude solution that fits data found in the literature for normally cycling women and a small amplitude solution arising from Hopf bifurcation in the system parameters. The small amplitude cycle possesses many similarities to the menstrual cycle disorder referred to as polycystic ovarian syndrome (PCOS). Hormonal treatments for this abnormality are simulated and the large amplitude cycle fitting the data for normally cycling women is successfully recovered. In addition, simulations of exogenous estrogen exposure show that the large amplitude cycle can be perturbed into the small amplitude cycle. Therefore, in this modeling environment, an exogenous estrogen input disrupts the normal menstrual cycle.

DIFFERENTIAL EQUATION MODELS FOR THE HORMONAL REGULATION OF THE MENSTRUAL CYCLE

BY

LEONA A. HARRIS

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To my mother,
you have truly been my inspiration through it all.
Thank you!

Biography

Leona Ann Harris was raised in Queens, New York. She attended public schools in New York through her tenth grade year and in May 1991, graduated from St. Catherine's School, a boarding school in Richmond, Virginia. She then attended Spelman College in Atlanta, Georgia where she participated in the Scholars in Mathematics at Spelman (SIMS) Program. She graduated magna cum laude from Spelman in May 1995 with a Bachelor of Science degree in Mathematics. She earned a Master of Science degree in Applied Mathematics in December 1999 and a Doctor of Philosophy degree in Applied Mathematics in December 2001 from North Carolina State University in Raleigh, North Carolina. She has accepted a postdoctoral research position with the National Health and Environmental Effects Research Laboratory of the U.S. Environmental Protection Agency in Research Triangle Park, North Carolina.

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"With men this is impossible; but with God all things are possible." Matthew 19:26

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Chapter 1

Introduction

Ovarian and pituitary hormones work together to regulate and maintain the menstrual cycle in adult women. The menstrual cycle is made up of two phases: the follicular phase and the luteal phase separated by ovulation and menstruation. During the menstrual cycle, the pituitary secretes hormones that stimulate the growth and development of ovarian follicles. Consequently, these follicles secrete hormones which control the secretion of pituitary hormones. The pituitary and ovarian hormones work together to release an ovum (egg) to be fertilized. If fertilization does not occur, the cycle is repeated. The menstrual cycle is an integral part of the sexual endocrine system, therefore many clinical studies have been performed to better understand the mechanisms controlling this process. The behavior of the hormones that control the menstrual cycle can be modeled mathematically using differential equations that describe their interactions throughout the cycle.

In this work a model that predicts the blood concentrations of five hormones produced in the ovary and the pituitary as they interact to regulate and maintain the menstrual cycle will be presented. The model has three components: the pituitary component, the ovarian component, and the merged component. The first two components of the model were first developed by Schlosser and Selgrade in [50, 54]. The

first component of the model consists of systems of ordinary differential equations that describe the synthesis, release, and clearance of the pituitary hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) during the menstrual cycle, based on their response to the ovarian hormones estradiol (E_2), progesterone (P_4), and inhibin (Ih). Functions representing the ovarian hormones are used as inputs into these systems. The input functions were approximated using data from the literature [41] for the serum levels of E_2, P_4, and Ih during the menstrual cycles of 33 normally cycling women. The second component of the model is a system of ordinary differential equations that describes the roles of FSH and LH in the development of ovarian follicles and the production of the ovarian hormones, E_2, P_4, and Ih, during the menstrual cycle. Functions representing the pituitary hormones are used as inputs into this system. The final component of the model is the merged system formed by merging the pituitary and ovarian components together. This system is a nonlinear system of delay differential equations that describes the interactions between the five hormones throughout the menstrual cycle.

There are growing concerns about the effects of environmental substances on the sexual endocrine system. It is believed that substances that mimic the effects of estradiol and other estrogens may disrupt the sexual endocrine system by initiating or promoting such adverse effects as breast cancer, ovarian cancer, developmental disorders, and even the lowering of sperm counts [17, 40]. While these effects appear to be more imminent during high levels of exposure to estrogenic substances, concerns are increasing because low levels of exposure to estrogenic substances occur more frequently for longer periods of time; in our diets (phytoestrogens), in the environment (pesticides), and in contraception (spermicides and birth control pills) and hormonal therapies [17, 40]. These concerns have led to many clinical studies to determine the plausibility of such hypotheses. A disruption of the sexual endocrine system caused by estrogenic compounds may have a profound effect on the menstrual cycle.

Therefore a mathematical model that accurately predicts the serum levels of hormones that control the menstrual cycle would be a useful tool in evaluating the effects of exogenous compounds on the sexual endocrine system. In addition, such a model could be used to test the effects of various hormonal methods of birth control such as birth control pills, skin implants, and liquid injectables [33].

A review of various mathematical models of the human menstrual cycle from the literature can be found in [12]. Many of these models are descriptive rather than predictive and do not rely upon physiological mechanisms that control the cycle. In addition, many models only address certain aspects of the menstrual cycle. For example, models describing the effect of estradiol on serum levels of LH and FSH and vice versa during the menstrual cycle that do not address the effects of progesterone and inhibin [12, 35]. The model to be presented in this work is based on the physiolgical mechanisms in the hypothalamus, the pituitary, and the ovary that regulate and maintain the menstrual cycle through the synthesis and release of hormones, the development of ovarian follicles, and the positive and negative feedback relationships of hormones during the cycle.

This dissertation is organized as follows. In Chapter 2 we provide a description of the hypothalalmus-pituitary-ovarian axis and its role in the regulation of the human menstrual cycle. In Chapter 3 we examine the model assumptions and structure of the unmerged model consisting of the pituitary component and the ovarian component as presented in [50, 54]. The ovarian component is reformulated to include dimensional quantities that replace the concept of follicular "capacity" [54]. In Chapter 4 we provide theoretical results for the existence and uniqueness of solutions to the pituitary and ovarian systems. The parameter estimation problem is discussed and numerical and stability results are presented using parameter values identified by a numerical method of optimizing parameters. In Chapter 5 we merge the pituitary and ovarian components together and explore issues of existence and uniqueness for

this nonlinear system of delay differential equations. We also study the existence of periodic solutions and present results which give evidence for the existence of two stable periodic solutions; a large amplitude solution that fits the data for normally cycling women and a small amplitude solution arising from Hopf bifurcation in the system parameters. In Chapter 6 we further analyze the small amplitude cycle and demonstrate its similarities to PCOS, a common menstrual cycle abnormality. We simulate possible hormonal treatments for this abnormality and successfully recover the large amplitude cycle. We also show that exposure to exogenous estrogen for long periods of time can disrupt the normal menstrual cycle. Finally, in Chapter 7 we transform the merged system into a dimensionless system using the nondimensionalization procedure to determine whether the number of system parameters can be reduced.

Chapter 2

The Biological System

2.1 The Hypothalamus-Pituitary-Ovarian Axis

The endocrine system is a communication system of glands that regulate certain body functions through the secretion of hormones into interstitial tissue. Hormones are chemical molecules produced in the cells of endocrine glands which send messages to other cells in target organs [45, 49]. Most hormones are carried to their target organs by the blood, while some hormones act on cells within the organ in which they are produced [49]. The hypothalamus, the pituitary, and the ovary are all endocrine glands that communicate with each other to regulate a woman's reproductive system. The hypothalamus is the part of the brain that connects the central nervous system to the endocrine system via the Hypothalamus-Pituitary-Ovarian Axis (HPO). By releasing the hormone Gonadotropin-Releasing Hormone (GnRH) into the blood, the hypothalamus signals the anterior lobe of the pituitary gland to produce the hormones, Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) [34]. FSH and LH are called gonadotropins because they stimulate the gonads, the human reproductive glands.

In women the gonadal gland is the ovary. FSH and LH control the development

of the ovarian follicles and the corpus lutea, and hence play an important role in the production of ovarian hormones. Through negative and positive feedback loops to the hypothalamus and/or the pituitary, the ovarian hormones regulate the production of LH and FSH [34]. This hormonal control system is illustrated in Figure 2.1. A similar control system exists in men, but will not be discussed in this work.

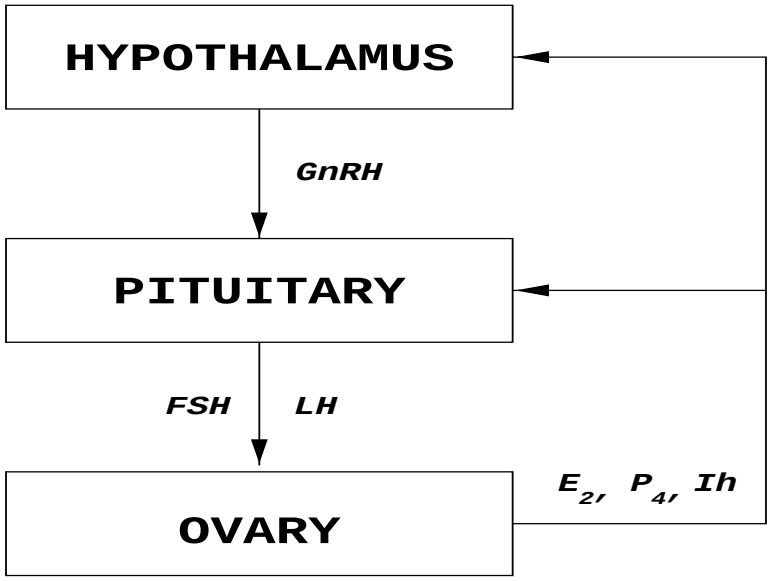

Figure 2.1: Hypothalamus - Pituitary - Ovarian Axis

A female's reproductive system begins to develop as early as 9 weeks after gestation when the ovaries are differentiated [49]. The ovaries have two important roles: gametogenesis, the production and development of ova (eggs) to be fertilized, and steroidogenesis, the production of sex steroids, particularly estrogens, progestins, and androgens [49]. Ovarian follicles are the functional compartments of the ovary which nurture and release the eggs and produce hormones in response to changing serum levels of LH and FSH. At birth, there are approximately 1-2 million inactive follicles in the ovaries [25, 49]. The number of inactive follicles decreases to zero by the onset

of menopause because some of these follicles are selected to undergo several stages of growth and development, while the rest are left to undergo atresia, a process of degeneration. On average, only about 400 growing follicles will be chosen to ovulate in an woman's lifetime [49].

2.2 The Menstrual Cycle

Before puberty, the hormonal control mechanism described in the previous section is not functioning. Therefore the production of LH and FSH in the pituitary is "irregular" (non-cyclic) [45]. The beginning of a woman's reproductive years marks a change in the production of the gonadotropins and a change in the ovaries' responsiveness to them [49]. At this time, the cyclic process called the menstrual cycle begins. This process is regulated by the secretion of GnRH from the hypothalamus, LH and FSH from the pituitary, and estradiol (E_2), progesterone (P_4), and inhibin (Ih) from the ovary. A normal menstrual cycle lasts for 25-32 days [41] and consists of two phases, the follicular phase and the luteal phase separated by ovulation and menstruation, respectively. A schematic diagram of the menstrual cycle is shown in Figure 2.2.

During the follicular phase of the cycle, the gonadotropins stimulate follicles to grow and produce hormones, and a dominant follicle is chosen from the growing follicles to be the one that will ovulate. Ovulation is defined to be the rupturing of the dominant follicle and the release of the egg that awaits fertilization. Ovulation initiates the luteal phase of the cycle in which the ruptured follicle is transformed into the corpus luteum. The corpus luteum is a gland that is stimulated by the gonadotropins to grow and produce hormones that inhibit the pituitary's secretion. If fertilization does not occur the corpus luteum undergoes a process of degeneration called luteolysis, thereby taking away the inhibitory effect that it has on the pituitary. A rise in gonadotropin secretion initiates menstruation and the follicular phase of the

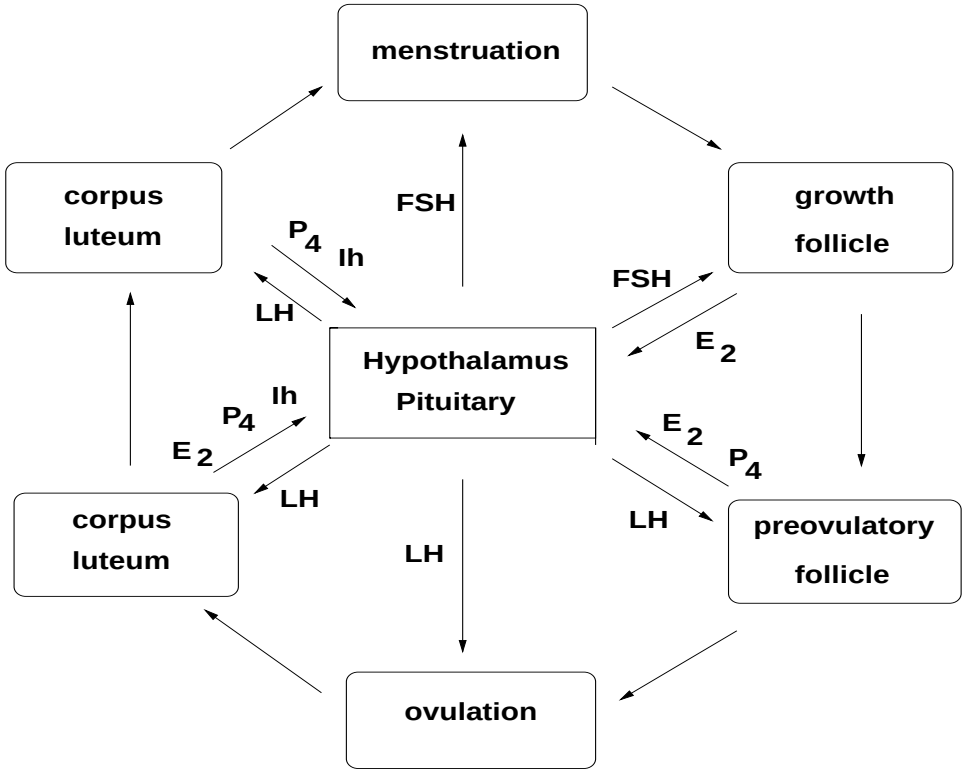

Figure 2.2: The Phases of the Menstrual Cycle: Appeared in the Fields Institute Communications, Volume 21, 1999, Selgrade and Schlosser.

next cycle [53].

The menstrual cycle, continuing throughout a woman's reproductive years, is temporarily interrupted by pregnancy and terminated by menopause. The normal cyclicity of the menstrual cycle can also be disrupted by exposure to certain environmental substances and hormonal imbalances due to endocrine disorders. The ovaries become inactive once all of its follicles have undergone atresia. This marks the onset of menopause, the end of a woman's reproductive years. At this time the feedback loops from the ovaries to the pituitary and the hypothalamus no longer exist and the hormonal control of the menstrual cycle is terminated.

Before each menstrual cycle, several inactive follicles called primordial follicles are selected to grow into primary follicles. The growth of primordial follicles into primary follicles does not depend on hormonal secretion from the pituitary [49], therefore we will not discuss that process in this work. Primary follicles consist of an egg surrounded by a single layer of granulosa cells, and a basement membrane. The granulosa cells inside the follicles have FSH receptors. Receptors are proteins formed on the membrane of a cell or within the cell which bind to hormones targeting that cell. These receptors are needed for a hormonal stimulus to take effect [45, 61].

The follicular phase of the menstrual cycle can be divided into three stages of follicular growth and development: the menstrual follicular (MsF) stage, the secondary follicular (SeF) stage, and the preovulatory follicular (PrF) stage. At the beginning of each menstrual cycle, rising levels of FSH stimulate the growth of about 6-12 primary follicles [49]. We will call this group of follicles, menstrual follicles, as they are selected to grow during menstruation. During this stage of follicular growth, a layer of theca cells called the theca interna where LH receptors are found, is formed outside of the basement membranes of the menstrual follicles. These follicles are stimulated by FSH and LH to grow into secondary follicles, which are characterized by an increase in the size and number of granulosa cells and the formation of a layer of theca cells called the theca externa. The theca cells of a follicle provide the follicle with its source of blood flow and allow estradiol to rapidly enter general circulation [45, 61]. Stimulated by FSH and LH, the growth of the secondary follicles increases the production of estradiol. At the end of the secondary follicular stage, one follicle is selected from the secondary follicles to be the one that will ovulate and the others undergo atresia. This preovulatory follicle grows rapidly and secretes estradiol in large amounts. During the preovulatory follicular stage, estradiol peaks and stimulates FSH and LH to surge. The LH surge induces ovulation, the rupturing of the primary follicle and the release of the egg to be fertilized. This marks the onset of the luteal

phase. During this phase of the cycle the ruptured follicle is transformed in the corpus luteum. The granulosa cells and theca cells become luteal cells which are stimulated to grow by LH [49]. As the corpus luteum grows it begins to produce progesterone and inhibin in large amounts, while continuing its production of estradiol. Inhibin and progesterone secretion is important in the luteal phase because these hormones inhibit the production of FSH and LH, respectively. If fertilization of the released egg occurs, the corpus luteum secretes hormones in preparation for pregnancy. If fertilization does not occur, the corpus luteum undergoes luteolysis, thereby taking away the inhibitory effect it has on the pituitary. The decrease in hormone secretion from the corpus luteum causes menstruation and a rise in the production of FSH and LH. This initiates the beginning of the next cycle.

Chapter 3

The Unmerged Model: Model Assumptions and Structure

In this chapter we will discuss the mathematical structure of the unmerged model which has two components: the pituitary component and the ovarian component. The pituitary component depicts the ovary's hormonal control of the pituitary, while the ovarian component depicts the pituitary's hormonal control of the ovary. The first two components were presented in [50, 54] by Schlosser and Selgrade. The authors focused on the hormonal structure of the HPO axis and the qualitative behavior of the five hormones that regulate the menstrual cycle. In this work we will: (i) optimize the model parameters so that the output yields good approximations to data found in literature, (ii) study the stability of model simulations, and (iii) validate the model by merging the first two components together and testing the effects of external forcing on the output. The merged model will describe the hormonal interaction between the pituitary and the ovary throughout the menstrual cycle. This model will be discussed in detail in Chapter 5.

3.1 The Pituitary Component

The pituitary component describes the synthesis, release, and clearance of FSH and LH based on the pituitary's response to serum levels of E_2, P_4, and, Ih. This component consists of two systems, the FSH system and the LH system, of 2-dimensional ordinary differential equations with time dependent coefficients. Each system is linear in its state variables, however the time dependent coefficients are nonlinear functions of the ovarian hormones. Equations representing the serum levels of the ovarian hormones during a menstrual cycle are used as inputs into the pituitary systems in order to predict the serum levels of the pituitary hormones during that cycle. The input functions are chosen so that they approximate the data for serum levels of E_2, P_4, and Ih found in the McLachlan *et al.* paper [41] and that the resulting levels of FSH and LH also fit the data in this paper.

This data was used throughout this modeling process because this was the only paper we could find that presented the full hormone profiles for each of the five hormones we are modeling. The hormone profiles presented in the McLachlan paper are illustrated in Figures 3.1 and 3.2 and the approximate serum levels are listed in Table A.1 in Appendix A. The authors of [41] describe an experiment that was performed on 33 normally cycling women whose hormone levels were recorded each day for a complete cycle. The data values for each woman were then normalized around the day of her LH surge so that the data for all 33 women could be averaged together to get the daily mean serum levels in Table A.1 [41]. This lumped data is used to represent the blood levels of the pituitary and ovarian hormones during a normal menstrual cycle.

The data for the ovarian and pituitary hormones found in the McLachlan paper are given for days 0 to 30. However, in order to determine whether each system accurately predicts the normal periodic behavior of the hormones during the menstrual cycle it

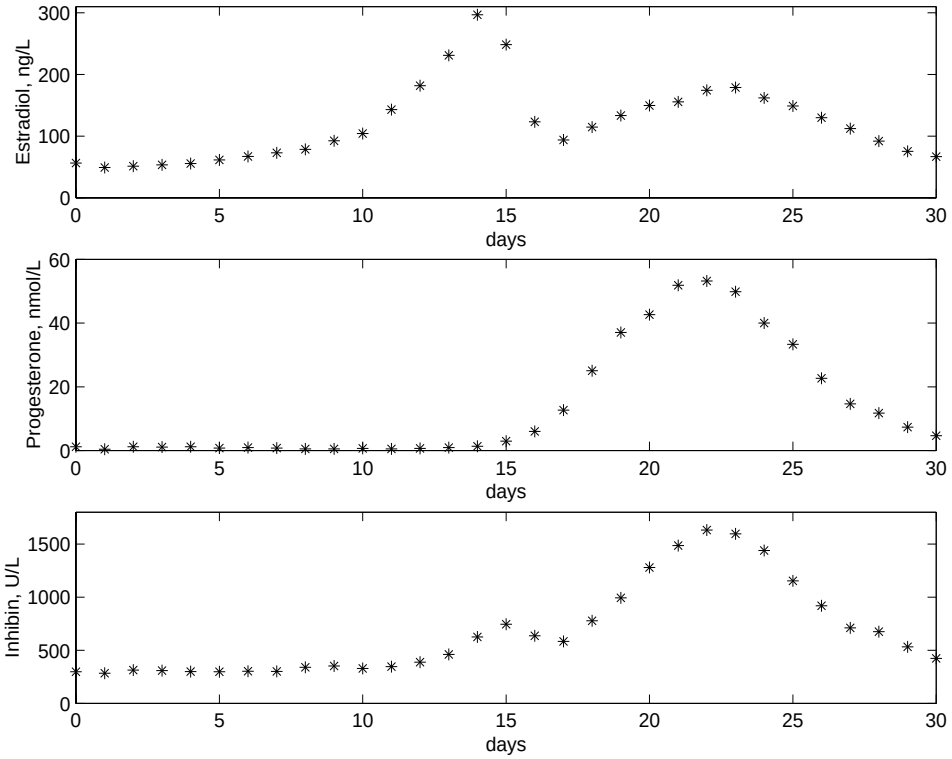

Figure 3.1: Daily mean serum levels of estradiol, progesterone, and inhibin of 33 normally cycling women. Appeared in McLachlan *et al.* [41].

is necessary to assume that the hormone data is periodic. The period is chosen to be $p = 31$ for the following reasons: (i) the blood concentration of each hormone at day 30 is greater than the level on day 0, and (ii) the slope of the tangent line of the data points at day 30 is negative (ie. the data is decreasing at day 30). Therefore we make the assumption that the hormone levels at day 31 are equal to those at day 0 and that the serum levels repeat every 31 days.

The FSH and LH systems are two-compartment models consisting of the pituitary and the blood. FSH and LH are synthesized in the pituitary and held on reserve in a releasable pool to be released into the blood. $RP_{FSH}(t)$ and $RP_{LH}(t)$

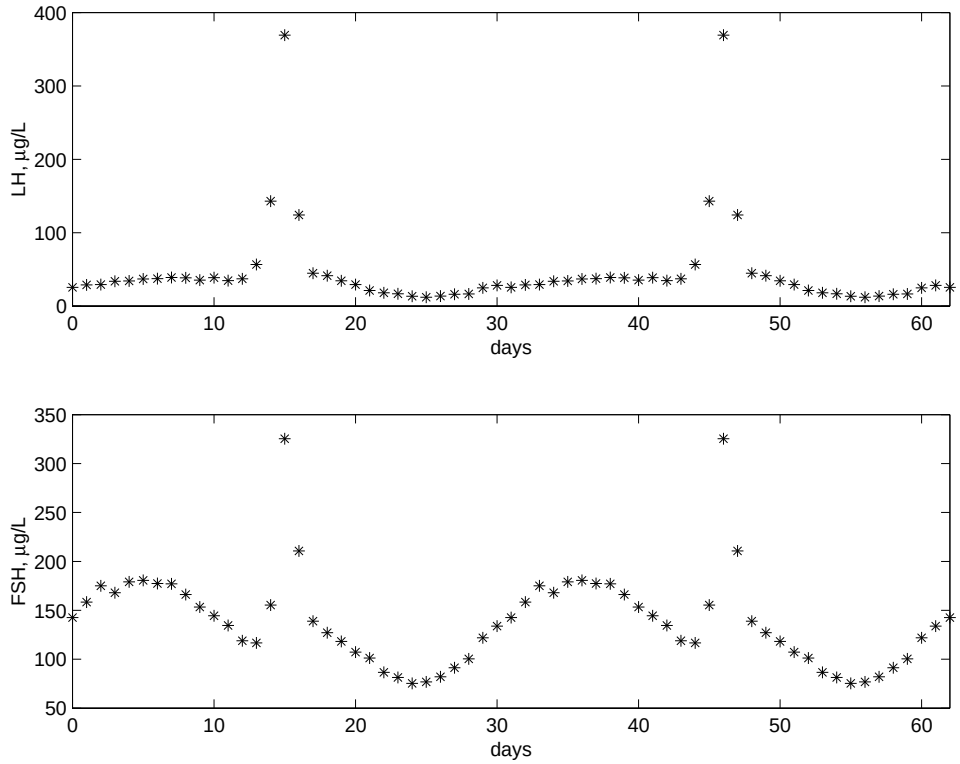

Figure 3.2: Daily mean serum levels of FSH and LH of 33 normally cycling women. Appeared in McLachlan *et al.* [41].

are state variables in the pituitary systems representing the amount of FSH and LH held on reserve in the pituitary at time t days and $FSH(t)$ and $LH(t)$ are the state variables representing the concentrations of FSH and LH in the blood at time t. $E_2(t)$, $P_4(t)$, and $Ih(t)$ are the functions describing the blood levels of the ovarian hormones at time t that are inputted into the pituitary systems. Under the assumption that the blood levels are periodic, input functions which approximate periodic data are used in the systems. The input function for E_2 over one period is the sum of a constant term and two "Gaussian" type exponential terms characterizing the two peaks present in the estradiol profile, the largest one occurring on day 14 just

before midcycle and the other occuring on day 23 during the luteal phase of the cycle. Similarly, the input functions for P_4 and Ih over one period contain a constant term and one exponential term characterizing the peak of each of these hormones on day 22 during the luteal phase of the cycle. In order to approximate periodic data, exponential terms are added to the input functions to characterize the peaks for as many periods as we wish to consider. The input functions used to approximate the ovarian hormone data over two periods of data are as follows:

$$E_2(t) = e_0 + e_1 e^{-\frac{(t-14)^2}{e_2}} + e_3 e^{-\frac{(t-23)^2}{e_4}} + e_1 e^{-\frac{(t-45)^2}{e_2}} + e_3 e^{-\frac{(t-54)^2}{e_4}}, \tag{3.1}$$

$$P_4(t) = pr_0 + pr_1 e^{-\frac{(t-22)^2}{pr_2}} + pr_1 e^{-\frac{(t-53)^2}{pr_2}}, \tag{3.2}$$

$$Ih(t) = h_0 + h_1 e^{-\frac{(t-22)^2}{h_2}} + h_1 e^{-\frac{(t-53)^2}{h_2}}. \tag{3.3}$$

The functions in (3.1)-(3.3) were chosen to approximate the input data because they are differentiable, non-oscillatory functions that rise and fall with the data. We attempted to use other techniques to approximate the data, such as truncated Fourier series approximation and spline interpolation. However, these techniques did not yield favorable results. While these approximation techniques have the advantage that they yield exact values for the data points and approximations for the points in between, using them in the model presented several disadvantages. For instance, function evaluations took much more time than for the exponential approximations. This increased computation time was too costly during parameter estimation. Since the truncated Fourier series and spline interpolation yield exact values for each data point, the input functions using these approximations to the data were not smooth enough to yield smooth solutions using a differential equation solver in MatLab.

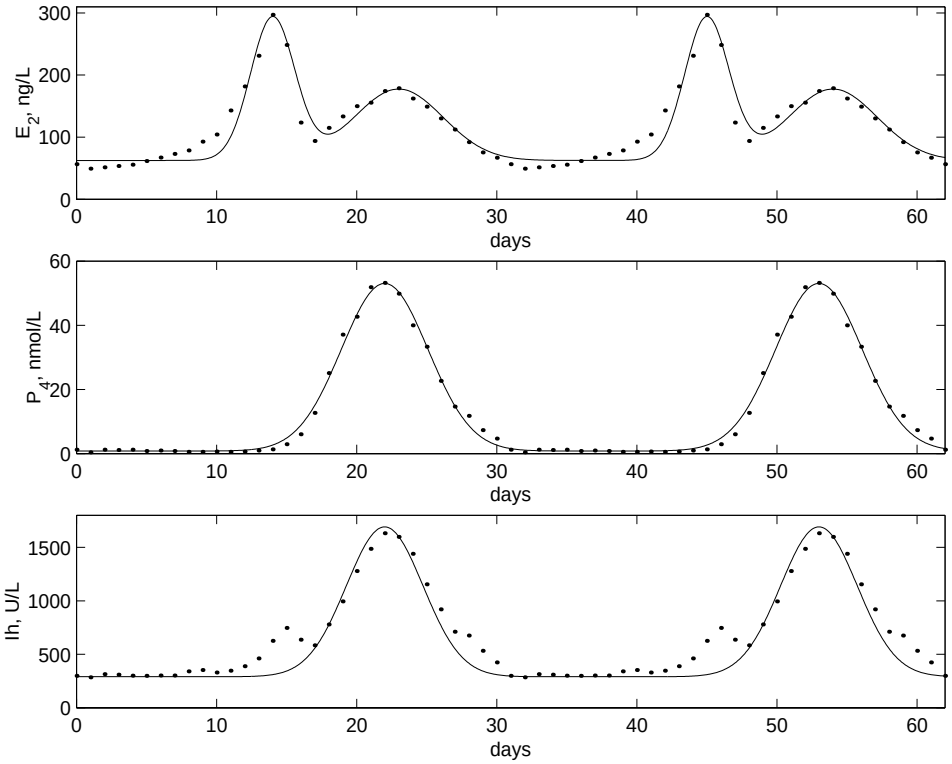

Figure 3.3: The ovarian hormone input functions used in the pituitary component of the model as compared to the data in the McLachlan paper.

Functions representing one period of data are presented in [50, 54]. The input functions presented in this work are different from the functions presented in [50, 54] in the following ways: (i) the functions in (3.1)-(3.3) approximate two periods of data, (ii) a exponential term is used in the estradiol function to approximate the first peak instead of a quadratic rational function, and (iii) the parameter values are not the same. The ovarian input function parameters that were estimated to fit the data in the McLachlan paper are listed in Table A.2. For a review of the estimation techniques used, see Section 4.2. The input functions used in the pituitary systems are shown in Figure 3.3.

In this model, gonadotropin synthesis and gonadotropin release are treated as separate processes [50, 54]. This is an important feature of the model because these processes have different control mechanisms. Synthesis refers to hormone production and the formation of a releasable pool in secretory vesicles [50], while release refers to secretion into the blood. The pituitary secretes FSH and LH into the blood in response to GnRH. However, due to the complex nature of GnRH synthesis and release, this model lumps together the direct regulation of the pituitary and the indirect regulation of the pituitary via GnRH release from the hypothalamus as one control mechanism [50, 54]. Therefore the ovary's indirect regulation of the pituitary, characterized by the release of GnRH in response to the serum levels of the ovarian hormones, appears implicitly in the FSH and LH release terms of the pituitary systems. FSH and LH are secreted in a pulsatile manner, however, it is assumed that the ovary responds to average blood levels of FSH and LH [43]. Therefore, the systems in the pituitary component predict the average blood concentrations of FSH and LH throughout the menstrual cycle [54].

The FSH system consists of two coupled differential equations, one corresponding to RP_{FSH} in the pituitary and the other corresponding to FSH in the blood. Changes in $\mathrm{RP}_{FSH}(t)$ are determined by the amount of FSH synthesized in the pituitary and the amount of FSH released into the blood. Similarly, changes in $\mathrm{FSH}(t)$ are determined by the amount of FSH released into the blood and the amount cleared from the blood. The synthesis, release, and clearance rates for FSH are denoted by syn_{FSH}, rel_{FSH}, $clear_{FSH}$, respectively. Therefore the FSH system is of the form:

$$\frac{d}{dt}RP_{FSH} = syn_{FSH} - rel_{FSH} \tag{3.4}$$

$$\frac{d}{dt}FSH = \frac{1}{v_{dis}}\, rel_{FSH} - clear_{FSH} \tag{3.5}$$

The parameter v_{dis} represents the volume of distribution which is the portion of the blood throughout which hormones are circulated after release. It is this proportionality constant which relates the concentration of a hormone in the blood and the amount of that hormone produced in the body by the relation [32, 59]:

$$\text{Concentration} = \frac{\text{Amount}}{\text{Volume of Distribution}}.$$

The synthesis and release rates of FSH are modeled by rational functions of ovarian hormones in which stimulatory effects appear in the numerators and inhibitory effects appear in the denominators. A study by Chang and Jaffe [10] showed that progesterone stimulates the release of FSH and LH when estradiol blood levels are in a normal range during the late follicular phase. Tsai and Yen [58] demonstrated that blood levels of FSH and LH decline after the administration of ethinyl estradiol. This suggests that estradiol inhibits the release of FSH and LH into circulation. In fact, their studies also showed that estradiol has a greater inhibitory effect on FSH release than on LH release [58]. A preovulatory decline in FSH blood levels, not present in the LH profile, provides further evidence of the greater inhibitory effect of rising estradiol levels in the late follicular phase of the cycle. Therefore second order inhibition of estradiol is used in the FSH release term, while a first order inhibition of estradiol is used in the LH release term [50, 54]. The release rate of FSH is assumed

to be proportional to amount of FSH on reserve in the pituitary, therefore

$$rel_{FSH} = rel_{FSH}(E_2, P_4, RP_{FSH}).$$

There is evidence that inhibin has an inhibitory effect on FSH synthesis [26, 30, 41, 52]. Therefore the synthesis rate of FSH is assumed to be a function of inhibin concentrations, that is

$$syn_{FSH} = syn_{FSH}(Ih).$$

The period of time between changes in inhibin blood levels and changes in the synthesis rates of FSH is captured by incorporating a time delay, δ_{Ih}, into the input function $Ih(t)$ [50]. Finally, the clearance rate of FSH is assumed to be proportional to FSH blood levels. Therefore the FSH system is of the form:

$$\frac{d}{dt}RP_{FSH} = syn_{FSH}(Ih) - rel_{FSH}(E_2, P_4, RP_{FSH}) \tag{3.6}$$

$$\frac{d}{dt}FSH = \frac{1}{v_{dis}} rel_{FSH}(E_2, P_4, RP_{FSH}) - clear_{FSH}(FSH) \tag{3.7}$$

where

$$syn_{FSH}(Ih) = \frac{n}{1 + \dfrac{Ih(t - \delta_{Ih})}{p}} \tag{3.8}$$

$$rel_{FSH}(E_2, P_4, RP_{FSH}) = \frac{q(1 + rP_4(t))}{1 + sE_2(t)^2} RP_{FSH} \tag{3.9}$$

and

$$clear_{FSH}(FSH) \;=\; cl_F\, FSH \tag{3.10}$$

The compartmental structure of the LH system is identical to that of the FSH system with state variables RP_{LH} and LH. However there are variations in the synthesis and release terms because LH responds differently to ovarian hormone secretion. Recall that estradiol and progesterone have a similar effect on LH release as they have on FSH release, with the exception that estradiol has a greater inhibitory effect on FSH release. Therefore a first order inhibitory effect of estradiol on LH release is used instead of the second order effect used in the FSH system.

It has been shown that high blood levels of estradiol promote rapid LH synthesis, therefore the numerator of the LH synthesis term contains a Hill function to reflect estradiol's stimulatory effect on LH. This effect is most evident in the late follicular phase of the menstrual cycle when large amounts of estradiol are secreted by the preovulatory follicle, inducing the LH surge. The Hill function is a fractional expression of estradiol concentrations of the form:

$$\frac{vE_2(t)^h}{w^h + E_2(t)^h}, \tag{3.11}$$

where v is the maximal induction of E_2 on the production rate of LH, w is the level of E_2 at half-max, and h is the Hill coefficient. These parameters need to be chosen so that the Hill function increases rapidly as estradiol concentrations vary in a normal range for late follicular phase levels. The Hill coefficient determines the rate of increase. Based on the data for normally cycling women, Schlosser and Selgrade chose a range of 200 and 600 ng/L [50]. This range includes normal and elevated levels of estradiol and therefore the model can be used to monitor the effects of administering

exogenous estrogens to existing estradiol levels.

In the luteal phase of the cycle estradiol blood levels peak for a second time, however, this peak is not as substantial as the late follicular phase peak. It is believed that at this time progesterone blood levels inhibit LH synthesis [53]. As with $\mathrm{Ih}(t)$ in the FSH synthesis term, the time delays δ_E and δ_P, are used in the input functions $\mathrm{E}_2(t)$ and $\mathrm{P}_4(t)$ which appear in the LH synthesis term. Therefore the LH system has the form:

$$\begin{aligned} \frac{d}{dt}RP_{LH} &= syn_{LH}(E_2, P_4) - rel_{LH}(E_2, P_4, RP_{LH}) && (3.12) \\ \frac{d}{dt}LH &= \frac{1}{v_{dis}}\, rel_{LH}(E_2, P_4, RP_{LH}) - clear_{LH}(LH) && (3.13) \end{aligned}$$

where

$$syn_{LH}(E_2, P_4) = \frac{u + \dfrac{vE_2(t-\delta_E)^h}{w^h + E_2(t-\delta_E)^h}}{1 + \dfrac{P_4(t-\delta_P)}{w_1}}, \qquad (3.14)$$

$$rel_{LH}(E_2, P_4, RP_{LH}) = \frac{y(1 + zP_4(t))}{1 + z_1E_2(t)}\, RP_{LH}, \qquad (3.15)$$

and

$$clear_{LH}(LH) = cl_L\, LH. \qquad (3.16)$$

A description of the 8 FSH system parameters and the 10 LH system parameters

used in the pituitary component of the model and a discussion on how these parameters can be estimated to fit the data found in the McLachlan paper is provided in Section 4.2.

3.2 The Ovarian Component

The ovarian component of the unmerged model describes the role of the pituitary hormones in the development of ovarian follicles and the production of ovarian hormones during the menstrual cycle. Due to the fast time scale of the release and clearance of ovarian hormones [54], the ovarian component is not set up as a two-compartmental model between the ovary and blood as in the pituitary component. Instead, the ovarian component is a 9-dimensional system of ordinary differential equations which track the capacity of the ovary to produce hormones throughout the various stages of the menstrual cycle. The ovary's capacity at each stage of the cycle is assumed to be proportional to the mass of the follicles or corpus lutea at that stage [54]. In this work we reformulate the ovarian component of the model as presented in [54] to provide a physical meaning to the concept of follicular "capacity". Here the state variables are chosen to represent the mass of the "active" follicular or luteal tissue during the corresponding stage of the cycle. By "active" mass we mean mass that is growing and secreting hormones.

The ovarian component divides the menstrual cycle into 9 distinct stages of follicular and luteal development. The follicular phase of the cycle is divided into three stages:

i. Menstrual Follicular Stage (MsF), representing the stimulation of several immature (menstrual) follicles by FSH;

ii. Secondary Follicular Stage (SeF), representing the growth of the secondary follicles induced by FSH and LH; and

iii. Preovulatory Follicular Stage (PrF), representing the selection and growth of the dominant follicle stimulated by LH.

The period separating the follicular and luteal phases is divided into two stages:

i. Ovulatory Scar 1 (Sc_1), representing ovulation; and

ii. Ovulatory Scar 2 (Sc_2), representing luteinization.

The luteal phase is divided into four stages of luteal development:

$$\mathrm{Lut}_i \text{ for } i = 1, \ldots, 4.$$

A schematic diagram (adapted from a graph by Dr. Paul Schlosser) outlining the effect of gonadotropin secretion on the nine stages of follicular and luteal development is shown in Figure 3.4. The ovarian system is linear in its state variables with time dependent coefficients that are nonlinear functions of the pituitary hormones. $MsF(t)$, $SeF(t)$, $PrF(t)$, $Sc_1(t)$, $Sc_2(t)$, $Lut_1(t)$, $Lut_2(t)$, $Lut_3(t)$, and $Lut_4(t)$, are the state variables in this system representing the mass of the follicular and/or luteal secretory tissue which is active during the corresponding stage of the cycle.

Equations representing the serum levels of the pituitary hormones during a menstrual cycle are used as inputs into the ovarian system in order to predict the serum levels of the ovarian hormones during that cycle. Using the superposition of "Gaussian" type exponential terms to approximate the data for FSH and LH was somewhat cumbersome due to their sharp peaks at day 15 (midcycle) and basal levels throughout the remainder of the cycle. Therefore several exponential terms were used to achieve

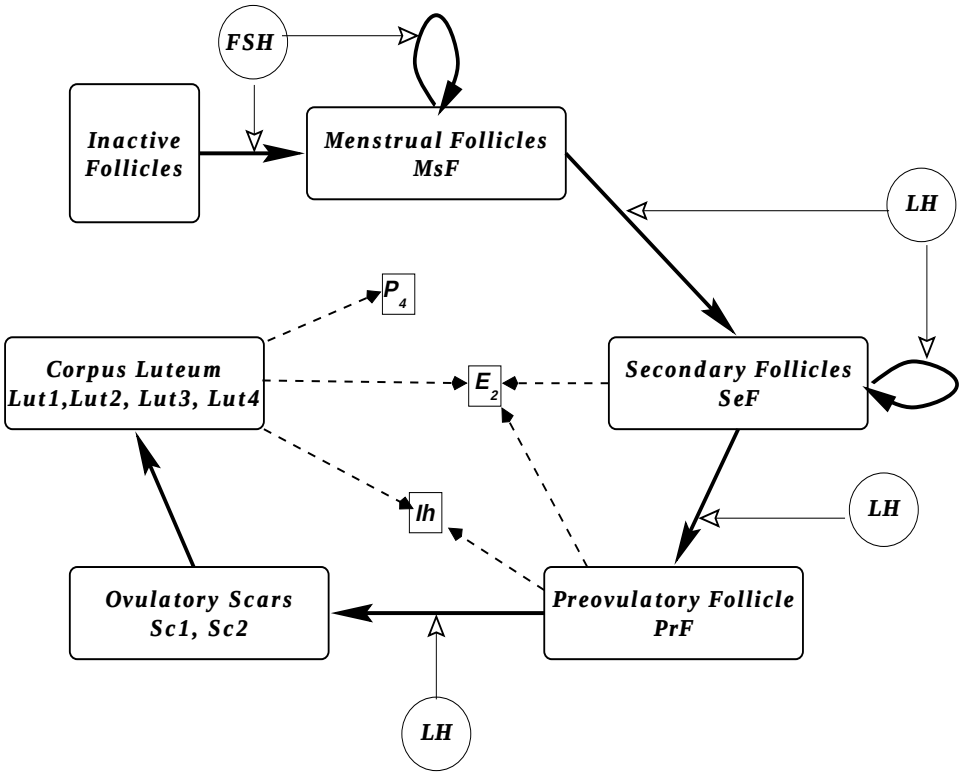

Figure 3.4: Stages of follicular and luteal development throughout the menstrual cycle.

a good approximation. The input functions we used to approximate two periods of pituitary data are:

$$\begin{aligned} FSH(t) &= f_1 e^{\frac{-(t-5)^2}{f_2}} + f_3 e^{\frac{-(t-15)^2}{f_4}} + f_5 e^{\frac{-(t-18)^2}{f_6}} + f_7 e^{\frac{-(t-36)^2}{f_8}} \\ &\quad f_9 e^{\frac{-(t-46)^2}{f_{10}}} + f_5 e^{\frac{-(t-49)^2}{f_6}} + f_7 e^{\frac{-(t-67)^2}{f_{11}}}, \end{aligned} \tag{3.17}$$

$$\begin{aligned} LH(t) &= l_0 + l_1 e^{\frac{-(t-7)^2}{l_2}} + l_3 e^{\frac{-(t-15)^2}{l_4}} + l_5 e^{\frac{-(t-18)^2}{l_6}} + l_1 e^{\frac{-(t-38)^2}{l_2}} \\ &\quad + l_3 e^{\frac{-(t-46)^2}{l_4}} + l_5 e^{\frac{-(t-49)^2}{l_6}} + l_1 e^{\frac{-(t-69)^2}{l_2}}. \end{aligned} \tag{3.18}$$

Using the parameters values found in Table A.3, the input functions used in the ovarian system are graphed against the data from the McLachlan paper in Figure 3.5.

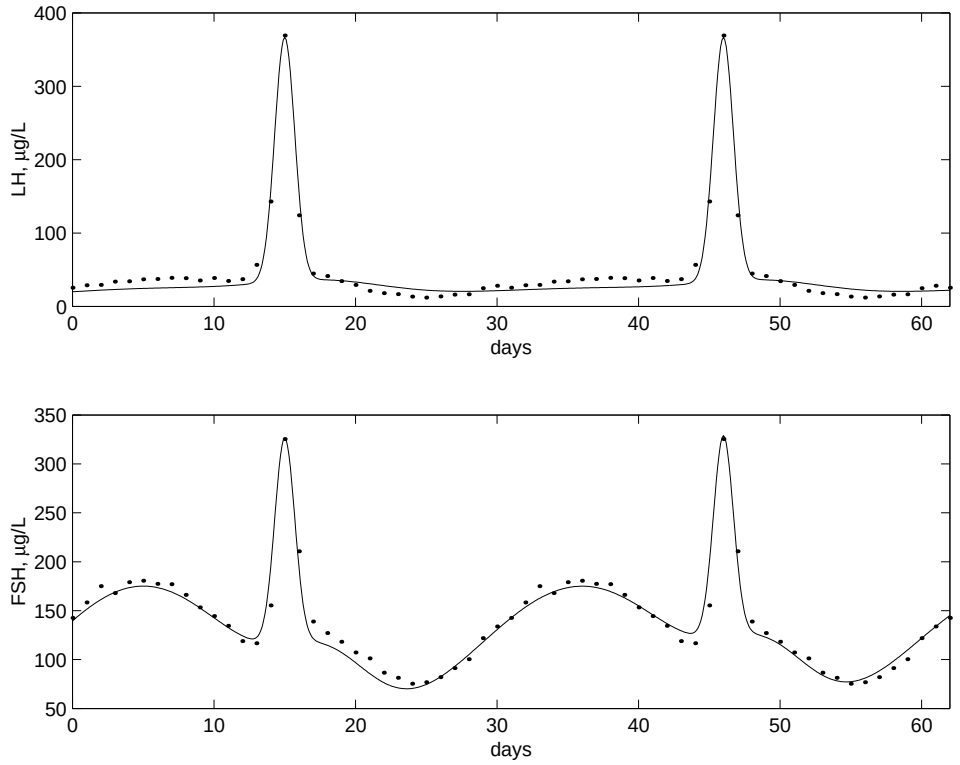

Figure 3.5: The pituitary hormone input functions used in the ovarian component of the model as compared to the data in the McLachlan paper.

Each of the nine variables in the ovarian system is a continuous function of time with the following behavior:

a) it increases as the mass corresponding to that stage of development becomes active,

b) it reaches a peak during its highest level of activity, and then

c) it decreases as the active mass in that stage becomes inactive.

A transfer of activity occurs from each stage to the next. For example, one follicle is chosen from the growing secondary follicles to be the dominant follicle that continues to grow until it ovulates. This represents a transfer of activity from the Secondary Follicular Stage to the Preovulatory Follicular Stage. Hence, as the SeF(t) is decreasing because the mass in that stage is becoming inactive, the function PrF(t) is increasing because the mass in that stage is becoming active.

In revising the model in [54], we opted to add an additional parameter to the system equations, LH_0, for dimensional consistency in the case when the exponents of LH are fractions. The parameter LH_0 will have the same units as LH as it will represent a unit of measurement of LH. Therefore the ovarian system has the form:

$$\frac{d}{dt}MsF = b\,FSH(t) + \left[c_1\,FSH(t) - c_2\left(\frac{LH(t)}{LH_0}\right)^{\alpha}\right]MsF \tag{3.19}$$

$$\frac{d}{dt}SeF = c_2\left(\frac{LH(t)}{LH_0}\right)^{\alpha}MsF + \left[c_3\left(\frac{LH(t)}{LH_0}\right)^{\beta} - c_4\left(\frac{LH(t)}{LH_0}\right)\right]SeF \tag{3.20}$$

$$\frac{d}{dt}PrF = c_4\left(\frac{LH(t)}{LH_0}\right)SeF - c_5\left(\frac{LH(t)}{LH_0}\right)^{\gamma}PrF \tag{3.21}$$

$$\frac{d}{dt}Sc_1 = c_5\left(\frac{LH(t)}{LH_0}\right)^{\gamma}PrF - d_1\,Sc_1 \tag{3.22}$$

$$\frac{d}{dt}Sc_2 = d_1\,Sc_1 - d_2\,Sc_2 \tag{3.23}$$

$$\frac{d}{dt}Lut_1 = d_2\,Sc_2 - k_1\,Lut_1 \tag{3.24}$$

$$\frac{d}{dt}Lut_2 = k_1\,Lut_1 - k_2\,Lut_2 \tag{3.25}$$

$$\frac{d}{dt}Lut_3 = k_2\,Lut_2 - k_3\,Lut_3 \tag{3.26}$$

$$\frac{d}{dt}Lut_4 = k_3\,Lut_3 - k_4\,Lut_4 \tag{3.27}$$

As in the estrogen model presented by Keener and Sneyd [35,Chapter 19], the rate

of change of each of the ovarian hormone concentrations can be written as:

$$\frac{d\,C}{d\,t} = \frac{1}{v_{dis}} \sum_{i=1}^{9} s_i\, F_i(t) - \delta\, C, \tag{3.28}$$

where C represents the hormone's blood concentration, F_i represents the active mass of follicular or luteal tissue in the i^{th} stage of the ovarian system, s_i represents the hormone's secretion rate during the i^{th} stage of the cycle, and δ represents the hormone's clearance rate. We assume that the clearance of the ovarian hormones from the blood is rapid compared to the development of follicles and corpus lutea (*ie.* the time scale is much faster) [35] and, hence, δ is large. Dividing through by δ in equation (3.28) yields the left hand side $\epsilon \frac{dC}{dt}$, where $\epsilon = \frac{1}{\delta}$. Therefore the system in (3.19)-(3.27), together with the differential equation in (3.28) can be written as:

$$\frac{dF}{dt} = g(F,t), \tag{3.29}$$

$$\epsilon \frac{dC}{dt} = h(F,C,t), \tag{3.30}$$

where $F = (MsF, SeF, PrF, Sc_1, Sc_2, Lut_1, Lut_2, Lut_3, Lut_4)$ and ϵ is small [2]. Using the "pseudo-steady state" hypothesis [2, 35, 42], we assume that $\epsilon \frac{dC}{dt} \approx 0$ and hence equation (3.28) reduces to:

$$C(t) \approx \sum_{i=1}^{9} C_i\, F_i(t), \tag{3.31}$$

where the coefficient $C_i = \frac{s_i}{\delta\, v_{dis}}$ weights the i^{th} stage's contribution to the total amount of hormone produced throughout the cycle.

Estradiol is secreted mainly by the secondary follicles and the preovulatory follicle and partially by the corpus luteum. Therefore the concentration of E_2 denoted by

Est(t) may be written as a linear combination of SeF, PrF, and Lut_4, that is:

$$Est(t) = e_1 + e_2\, SeF(t) + e_3\, PrF(t) + e_4\, Lut_4(t). \tag{3.32}$$

Progesterone and inhibin are secreted mainly in the luteal phase by the corpus luteum, however inhibin is also secreted by the preovulatory follicle. Therefore the concentrations of P_4 and Ih denoted by Prog(t) and Inh(t) may be written as:

$$Prog(t) = pr_1\, Lut_3(t) + pr_2\, Lut_4(t), \text{and} \tag{3.33}$$

$$Inh(t) = h_1 + h_2\, PrF(t) + h_3\, Lut_3(t) + h_4\, Lut_4(t). \tag{3.34}$$

Equations (3.32)-(3.34) are referred to as auxiliary equations. A description of the 12 system parameters and 10 auxiliary equation parameters used in the ovarian component of the model and a discussion on how these parameters can be estimated to fit the data found in the McLachlan paper is provided in Section 4.2.

Chapter 4

Analyzing the Unmerged Model

The unmerged model consists of three systems of ordinary differential equations, the FSH system, the LH system, and the ovarian system. In order to determine whether these systems accurately predict the blood levels of the pituitary and ovarian hormones during the menstrual cycle, we must first find estimates for the system parameters. In this chapter, we provide theoretical results for the existence and uniqueness of solutions and a description of the parameter optimization techniques used in this project. We also present numerical and stability results obtained from using the parameter values in the pituitary and ovarian systems.

4.1 Theoretical Results for the Pituitary and Ovarian Systems

Each of the pituitary and ovarian systems can be written in the form [54]:

$$X' = A(t)\,X + B(t) \tag{4.1}$$

where $A(t)$ is a continuous matrix on $[0, \infty)$ and $B(t)$ is a continuous vector on $[0, \infty)$. The following theorem ensures the existence and uniqueness of a solution to the system in (4.1) with $X(0) = X_0$.

THEOREM 4.1. ***Existence and Uniqueness of Linear, Non-autonomous Systems of Ordinary Differential Equations.*** *If $A(t)$ and $B(t)$ are continuous on $[0, \infty)$ and $||X_0|| < \infty$, then the system in (4.1) has a unique solution $X(t)$ on $[0, \infty)$ that satisfies the initial condition $X(0) = X_0$ [8].*

Using the variations of constants formula [8, 46] for linear, non-autonomous systems of ordinary differential equations, these systems can be solved explicitly. The closed form solutions for each system will be presented in this section.

The FSH System

If we let $X = (X_1, X_2) = (RP_{FSH}, FSH) \in \mathbb{R}^2$, then the FSH system in (3.6)-(3.7) can be written as:

$$X' = A_F(t)\, X + B_F(t), \tag{4.2}$$

where

$$A_F(t) = \begin{pmatrix} a_{11}^F(t) & a_{12}^F(t) \\ a_{21}^F(t) & a_{22}^F(t) \end{pmatrix} = \begin{pmatrix} -\frac{q(1+rP_4(t))}{1+sE_2(t)^2} & 0 \\ \\ \frac{q(1+rP_4(t))}{v_{dis}(1+sE_2(t)^2)} & -cl_F \end{pmatrix}, \tag{4.3}$$

and

$$B_F(t) = \begin{pmatrix} b_1^F(t) \\ b_2^F(t) \end{pmatrix} = \begin{pmatrix} \frac{n}{1+Ih(t-\delta_{Ih})/p} \\ 0 \end{pmatrix}. \tag{4.4}$$

$A_F(t)$ is a continuous matrix and $B_F(t)$ is a continuous vector, provided that the input

functions $E_2(t)$, $P_4(t)$, and $Ih(t)$ are all continuous. By the variations of constant formula [8, 46], if $\Phi_F(t)$ is a fundamental matrix of the system,

$$X' \;=\; A_F(t)\; X, \tag{4.5}$$

then the solution of (4.2) with the initial condition $X(0) = X_0$ is given by:

$$X(t) = \Phi_F(t)\; \Phi_F^{-1}(0)\; X_0 + \Phi_F(t)\; \int_0^t \Phi_F^{-1}(\tau) B_F(\tau) d\tau. \tag{4.6}$$

A fundamental matrix of the system in (4.5) is a nonsingular, solution matrix. This system can be rewritten as:

$$X_1' \;=\; a_{11}^F(t)\; X_1 \tag{4.7}$$

$$X_2' \;=\; a_{21}^F(t)\; X_1 + a_{22}^F(t)\; X_2. \tag{4.8}$$

A fundamental matrix, $\Phi_F(t)$, satisfying $\Phi_F(0) = I$, can be found by solving the first equation and then substituting the result into the second equation and solving.

Using the integrating factor $e^{-\int_0^t a_{11}^F(\tau)d\tau}$ the following solution to (4.7) is obtained:

$$X_1(t) = X_1(0)\; e^{\int_0^t a_{11}^F(\tau)d\tau}. \tag{4.9}$$

After substituting this equation into (4.8) for $X_1(t)$ we obtain:

$$X_2' - a_{22}^F(t)\; X_2 = a_{21}^F(t)\; X_1(0)\; e^{\int_0^t a_{11}^F(\tau)d\tau}. \tag{4.10}$$

Multiplying both sides by the integrating factor $e^{-\int_0^t a_{22}^F(\tau)d\tau}$ yields:

$$\frac{d}{dt}\left(X_2 e^{-\int_0^t a_{22}^F(\tau)d\tau} \right) = a_{21}^F(t)\; X_1(0)\; e^{\int_0^t [a_{11}^F(\tau) - a_{22}^F(\tau)]d\tau}. \tag{4.11}$$

Integrating both sides of (4.11) from 0 to t we obtain the solution:

$$\begin{aligned} X_2(t) &= X_2(0)e^{\int_0^t a_{22}^F(\tau)d\tau} \\ &+ X_1(0)e^{\int_0^t a_{22}^F(\tau)d\tau}\int_0^t a_{21}^F(s)e^{\int_0^s [a_{11}^F(\tau)-a_{22}^F(\tau)]d\tau}ds \end{aligned} \tag{4.12}$$

Therefore the solution matrix of (4.5) with $\Phi_F(0) = I$ has the form:

$$\Phi_F(t) = \begin{pmatrix} e^{\int_0^t a_{11}^F(s)ds} & 0 \\ \\ e^{\int_0^t a_{22}^F(\tau)d\tau}\int_0^t a_{21}^F(s)e^{\int_0^s [a_{11}^F(\tau)-a_{22}^F(\tau)]d\tau}ds & e^{\int_0^t a_{22}^F(s)ds}. \end{pmatrix} \tag{4.13}$$

To check whether $\Phi_F(t)$ is a fundamental matrix we need to determine the $det\,\Phi_F(t)$. By Abel's formula [8, 46],

$$det\,\Phi_F(t) = det\,\Phi_F(0)\,e^{\int_0^t \sum_{i=1}^2 a_{ii}^F(\tau)d\tau}. \tag{4.14}$$

Therefore $det\,\Phi_F(t) = e^{\int_0^t \sum_{i=1}^2 a_{ii}^F(\tau)d\tau} \neq 0$ since $det\,\Phi_F(0) = det(I) = 1$ and $e^x \neq 0$ for any x. Hence $\Phi_F(t)$ is a fundamental matrix of (4.5) with $\Phi_F(0) = I$.

The LH System

Similarly, if we let $Y = (y, Y_2) = (RP_{LH}, LH) \in \mathbb{R}^2$, then the LH system in (3.12)-(3.13) can be written as:

$$Y' = A_L(t)\,Y + B_L(t), \tag{4.15}$$

where

$$A_L(t) = \begin{pmatrix} a_{11}^L(t) & a_{12}^L(t) \\ a_{21}^L(t) & a_{22}^L(t) \end{pmatrix} = \begin{pmatrix} -\dfrac{y(1+zP_4(t))}{1+z_1E_2(t)} & 0 \\ \dfrac{y(1+zP_4(t))}{v_{dis}(1+z_1E_2(t))} & -cl_L \end{pmatrix}, \tag{4.16}$$

and

$$B_L(t) = \begin{pmatrix} b_1^L(t) \\ b_2^L(t) \end{pmatrix} = \begin{pmatrix} u + \dfrac{vE_2(t-\delta_E)^h}{w^h + E_2(t-\delta_E)^h} \\ \dfrac{}{1+P_4(t-\delta_P)/w_1} \\ 0 \end{pmatrix}. \tag{4.17}$$

$A_L(t)$ is a continuous matrix and $B_L(t)$ is a continuous vector, provided that the input functions, $E_2(t)$ and $P_4(t)$, are both continuous. Therfore by the variations of constant formula, the solution of (4.15) with the initial condition $Y(0) = Y_0$ is given by:

$$Y(t) = \Phi_L(t)\ \Phi_L^{-1}(0)\ Y_0 + \Phi_L(t)\ \int_0^t \Phi_L^{-1}(\tau) B_L(\tau) d\tau, \tag{4.18}$$

where

$$\Phi_L(t) = \begin{pmatrix} e^{\int_0^t a_{11}^L(s)ds} & 0 \\ e^{\int_0^t a_{22}^L(\tau)d\tau} \int_0^t a_{21}^L(s) e^{\int_0^s [a_{11}^L(\tau) - a_{22}^L(\tau)]d\tau} ds & e^{\int_0^t a_{22}^L(s)ds}. \end{pmatrix} \tag{4.19}$$

is a fundamental matrix of the system $Y' = A_L(t)\, Y$ with $\Phi_L(0) = I$.

The Ovarian System

The ovarian system is different from the pituitary systems in that it is a 9-dimensional system of differential equations. However, a closed form solution is

obtained using a fundamental matrix in the variation of constants formula in the same way as above. If we let

$$Z = (MsF, SeF, PrF, Sc_1, Sc_2, Lut_1, Lut_2, Lut_3, Lut_4) \in \mathbb{R}^9,$$

then the ovarian system in (3.19)-(3.27) can be written as:

$$Z' \;=\; A_{Ov}(t)\; Z + B_{Ov}(t), \tag{4.20}$$

where

$$A_{Ov}(t) \;=\; \begin{pmatrix} a_{11}^{Ov}(t) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{21}^{Ov}(t) & a_{22}^{Ov}(t) & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{32}^{Ov}(t) & a_{33}^{Ov}(t) & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{43}^{Ov}(t) & a_{44}^{Ov}(t) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{54}^{Ov}(t) & a_{55}^{Ov}(t) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{65}^{Ov}(t) & a_{66}^{Ov}(t) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & a_{76}^{Ov}(t) & a_{77}^{Ov}(t) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a_{87}^{Ov}(t) & a_{88}^{Ov}(t) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{98}^{Ov}(t) & a_{99}^{Ov}(t) \end{pmatrix}, \tag{4.21}$$

and

$$B_{Ov}(t) = \begin{pmatrix} b_1^{Ov}(t) \\ b_2^{Ov}(t) \\ b_3^{Ov}(t) \\ b_4^{Ov}(t) \\ b_5^{Ov}(t) \\ b_6^{Ov}(t) \\ b_7^{Ov}(t) \\ b_8^{Ov}(t) \\ b_9^{Ov}(t) \end{pmatrix} = \begin{pmatrix} b\,FSH(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{4.22}$$

The matrix $A_{Ov}(t)$ can be broken into 4 blocks in the following way:

$$A_{Ov}(t) = \begin{pmatrix} A_{Ov}^1(t) & A_{Ov}^2(t) \\ 0 & A_{Ov}^3(t) \end{pmatrix}, \tag{4.23}$$

where

$$A_{Ov}^1(t) = \begin{pmatrix} c_1 FSH(t) - c_2 \left(\frac{LH(t)}{LH_0}\right)^{\alpha} & 0 & 0 \\ c_2 \left(\frac{LH(t)}{LH_0}\right)^{\alpha} & c_3 \left(\frac{LH(t)}{LH_0}\right)^{\beta} - c_4 \left(\frac{LH(t)}{LH_0}\right) & 0 \\ 0 & c_4 \left(\frac{LH(t)}{LH_0}\right) & -c_5 \left(\frac{LH(t)}{LH_0}\right)^{\gamma} \\ 0 & 0 & c_5 \left(\frac{LH(t)}{LH_0}\right)^{\gamma} \end{pmatrix}, \tag{4.24}$$

$$A_{Ov}^2(t) = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ -d_1 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{4.25}$$

and

$$A^3_{Ov}(t) = \begin{pmatrix} d_1 & -d_2 & 0 & 0 & 0 & 0 \\ 0 & d_2 & -k_1 & 0 & 0 & 0 \\ 0 & 0 & k_1 & -k_2 & 0 & 0 \\ 0 & 0 & 0 & k_2 & -k_3 & 0 \\ 0 & 0 & 0 & 0 & k_3 & -k_4 \end{pmatrix}. \tag{4.26}$$

$A_{Ov}(t)$ is a continuous matrix and $B_{Ov}(t)$ is a continuous vector, provided that the input functions, $FSH(t)$ and $LH(t)$, are both continuous. Therefore by the variations of constant formula, the solution of (4.20) satisfying $Z(0) = Z_0$ is given by:

$$Z(t) = \Phi_{Ov}(t)\ \Phi^{-1}_{Ov}(0)\ Z_0 + \Phi_{Ov}(t)\ \int_0^t \Phi^{-1}_{Ov}(\tau) B_{Ov}(\tau) d\tau, \tag{4.27}$$

where $\Phi_{Ov}(t)$ is a fundamental matrix of the system

$$Z' \ = \ A_{Ov}(t)\, Z \tag{4.28}$$

with $\Phi_{Ov}(0) = I$.

This system can be rewritten as:

$$\begin{aligned}
Z_1' &= a_{11}^{Ov}(t)\ Z_1 && (4.29)\\
Z_2' &= a_{21}^{Ov}(t)\ Z_1 + a_{22}^{Ov}(t)\ Z_2, && (4.30)\\
Z_3' &= a_{32}^{Ov}(t)\ Z_2 + a_{33}^{Ov}(t)\ Z_3, && (4.31)\\
Z_4' &= a_{43}^{Ov}(t)\ Z_3 + a_{44}^{Ov}(t)\ Z_4, && (4.32)\\
Z_5' &= a_{54}^{Ov}(t)\ Z_4 + a_{55}^{Ov}(t)\ Z_5, && (4.33)\\
Z_6' &= a_{65}^{Ov}(t)\ Z_5 + a_{66}^{Ov}(t)\ Z_6, && (4.34)\\
Z_7' &= a_{76}^{Ov}(t)\ Z_6 + a_{77}^{Ov}(t)\ Z_7, && (4.35)\\
Z_8' &= a_{87}^{Ov}(t)\ Z_7 + a_{88}^{Ov}(t)\ Z_8, && (4.36)\\
Z_9' &= a_{98}^{Ov}(t)\ Z_8 + a_{99}^{Ov}(t)\ Z_9. && (4.37)
\end{aligned}$$

To find $\Phi_{Ov}(t)$ we will solve each of the equations in (4.30)-(4.37) by substituting the previous equation's solution and integrating from 0 to t. The integrating factors for the system equations are $e^{-\int_0^t a_{ii}^{Ov}(\tau)d\tau}$ for $i = 1, \ldots, 9$. Therefore the solution to the first differential equation in (4.29) is:

$$Z_1(t) = Z_1(0)\ e^{\int_0^t a_{11}^{Ov}(\tau)d\tau}. \tag{4.38}$$

After substituting (4.38) into (4.30) for Z_1 and solving we obtain:

$$\begin{aligned}
Z_2(t) &= Z_2(0)e^{\int_0^t a_{22}^{Ov}(\tau)d\tau} + e^{\int_0^t a_{22}^{Ov}(\tau)d\tau}\int_0^t a_{21}^{Ov}(s)Z_1(s)e^{\int_0^s -a_{22}^{Ov}(\tau)d\tau}ds && (4.39)\\
&= Z_2(0)e^{\int_0^t a_{22}^{Ov}(\tau)d\tau} + Z_1(0)e^{\int_0^t a_{22}^{Ov}(\tau)d\tau}\int_0^t a_{21}^{Ov}(s)e^{\int_0^s [a_{11}^{Ov}(\tau)-a_{22}^{Ov}(\tau)]d\tau}ds
\end{aligned}$$

Continuing this process for $i = 3, \ldots, 9$ we obtain the following closed form solution

for $Z_i(t)$:

$$Z_i(t) = Z_i(0)e^{\int_0^t a_{ii}^{Ov}(\tau)d\tau} + e^{\int_0^t a_{ii}^{Ov}(\tau)d\tau} \int_0^t a_{i,i-1}^{Ov}(s)Z_{i-1}(s)e^{\int_0^s -a_{ii}^{Ov}(\tau)d\tau}ds. \tag{4.40}$$

Due to the large number of nested integrals that appear in the fundamental matrix $\Phi_{Ov}(t)$ derived from (4.38)-(4.40), we will not present the matrix elements explicitly. However, we should note that $\Phi_F(t)$, $\Phi_L(t)$, and $\Phi_{Ov}(t)$ are all lower triangular matrices with diagonal entries:

$$\phi_{ii}^F(t) = e^{-\int_0^t a_{ii}^F(\tau)d\tau}, \quad \phi_{ii}^L(t) = e^{-\int_0^t a_{ii}^L(\tau)d\tau}, \quad \text{and} \quad \phi_{ii}^{Ov}(t) = e^{-\int_0^t a_{ii}^{Ov}(\tau)d\tau} \tag{4.41}$$

respectively. These entries will become important in Section 4.3 when we discuss the stability of periodic solutions of the pituitary and ovarian systems in (4.2), (4.15), and (4.20).

4.2 Estimating Model Parameters

We wish to determine whether the pituitary and ovarian systems accurately predict data values for the blood concentrations of FSH, LH, E_2, P_4, and Ih during a normal menstrual cycle. To achieve this goal we must find estimates for all of the parameters in the model. Some of the parameters have been found experimentally and are presented in literature, however many of the parameters are unknown. In each of the pituitary systems there are two sets of parameters that need to be estimated, the input function parameters and the system parameters. However the ovarian system has an additional set of parameters to be estimated, the auxiliary equation parameters.

In order to find optimal estimates for the unknown model parameters, we need a numerical optimization technique that will identify these values. Each parameter set was optimized using a "least squares" curve fitting technique. The goal of the technique is to find the set of parameters that minimizes a "least squares" cost function. For the pituitary systems, we wish to find the set of parameters that minimizes:

$$C = \sum_{i=0}^{62} |f(t_i) - H_i|^2, \tag{4.42}$$

where H_i represents the hormone's blood level given by the data in McLachlan *et al.* [41] at time $t_i = 0, \ldots, 62$ days (see Table A.1), $f(t)$ represents the hormone's approximated blood level at time t. Note that the approximated hormone level represents the input function value or the solution value corresponding to a given hormone. To estimate the parameters in the ovarian input functions, a cost function for each of the ovarian hormones is minimized in which the input functions in (3.1), (3.2), and (3.3) are substituted into (4.42) for $f(t)$. The pituitary system parameters were estimated by solving the differential equations in (3.6)-(3.7) and (3.12)-(3.13) and then substituting the solutions for FSH and LH into (4.42) for $f(t)$. When estimating the

system parameters, the cost function represents the solution error of the differential equations. In each minimization procedure the data values listed in Table A.1 are repeated over two periods and substituted into (4.42) for $H_i,\ i = 1, \ldots, 62$.

For the ovarian system, the minimization procedure used to estimate the input function parameters is the same as the procedure described above. The input functions for FSH and LH given by (3.17) and (3.18) are substituted into (4.42) for $f(t)$. A problem arises when attempting to estimate the ovarian system parameters because there is no data available corresponding to the mass of "active" follicular tissue throughout the menstrual cycle. Therefore a different cost function must be used to estimate the remaining parameters. The auxiliary equations in (3.32), (3.33), and (3.34) are used to approximate the blood levels of the ovarian hormones during the cycle. Therefore, we must use a cost function that calculates the error obtained from the auxiliary equations, which are linear combinations of the ovarian system state variables. The "least squares" cost function we used superposed the error for all of the ovarian hormones in the following way:

$$C = \sum_{i=0}^{62} |Est(t_i) - E_i|^2 + |Prog(t_i) - P_i|^2 + |Inh(t_i) - I_i|^2, \tag{4.43}$$

where $Est(t)$, $Prog(t)$, and $Inh(t)$ are the auxiliary equations in (3.32)-(3.34) and E_i, P_i, and I_i, are the data values for estradiol, progesterone, and inhibin listed in Table A.1 repeated over two periods.

Algorithms were created in MATLAB, a software by MathWorks Inc., to optimize the unknown parameter sets using the "least squares" fit to the data as described above. A key component of the algorithms is the MATLAB function call,

$$\bar{x} \ = \ fmins('costfunc', \bar{x}_0, options),$$

which uses the Nelder-Mead Simplex Method to find a local minimizer $\bar{x}$ of a cost function, $costfunc$, starting with an initial guess, x_0. The Nelder Mead Simplex Method is called a direct search method because it systematically searches through many points $\bar{x} \in R^n$ until the minimum of a function $f(\bar{x}) \in \mathbb{R}$ is found [39, 60]. This optimization procedure creates a search pattern by iteratively choosing simplices to test. A simplex is a generalized triangle with $(n+1)$ vertices in $n-$space [39]. The method starts with an initial simplex, orders the points on the simplex by their corresponding function values from smallest to largest, and then replaces the worst point (the point on the simplex with the largest function value) with a new point having a lower function value. The new point is obtained by reflecting, expanding, contracting, and/or shrinking the simplex with respect to the worst point. Once the new point is found, it replaces the old point creating a new simplex. The process is continued iteratively until a minimum is found. An outline of the two variable case will follow.

An initial simplex (triangle) is created with a user-defined guess as one of its vertices. The other vertices are selected in the first step of the optimization procedure [39]. The function $f(x, y)$ is evaluated at each vertex and the vertices are ordered by their function values, *ie.* V_1 yields the best or lowest value, V_2 yields the next lowest value, and V_3 yields the worst or largest value [39]. Therefore we have the following relation:

$$f(V_1) \leq f(V_2) \leq f(V_3). \tag{4.44}$$

A diagram illustrating the choices for the next simplex is shown in Figure 4.1. The steps for creating the new simplex from the initial simplex are as follows [39, 60]:

1. **Reflect.** Reflect the worst vertex V_3 about the best line segment $\overline{V_1V_2}$ to get the point R.

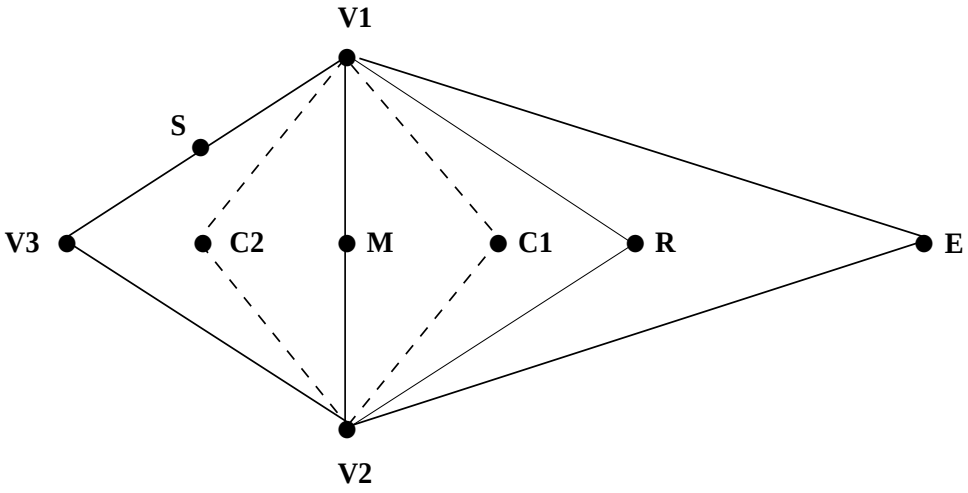

Figure 4.1: These are the choices of the next simplex outlined in Steps 1 and 2.

(a) If $f(V_1) \leq f(R) < f(V_2)$ then replace the worst point V_3 with R forming the new triangle V_1V_2R.

(b) Else if $f(R) < f(V_1)$, then **expand** R to E.

i. If $f(E) < f(R)$, then replace V_3 with E instead of R forming the new triangle V_1V_2E.

ii. Else if $f(E) \geq f(R)$, then form the new triangle with R, V_1V_2R.

(c) Otherwise, $f(R) \geq f(V_2)$. Go to Step 2: Contract.

2. **Contract.** If $f(R) \geq f(V_2)$, then contract between the midpoint M of $\overline{V_1V_2}$ and the worst point V_3 and the reflection point R, whichever one yields a smaller function value.

(a) If $f(V_2) \leq f(R) < f(V_3)$, then contract outside to C_1, the midpoint of $\overline{MR}$.

i. If $f(C_1) \leq f(R)$, then replace V_3 with C_1 forming the new triangle

$V_1V_2C_1$.

ii. Else if $f(C_1) > f(R)$, go to Step 3: Shrink.

(b) Else if $f(V_3) \leq f(R)$, then contract inside to C_2, the midpoint of $\overline{MV_3}$.

i. If $f(C_2) \leq f(V_3)$, then replace V_3 with C_2 forming the new triangle $V_1V_2C_2$.

ii. Else if $f(C_2) > f(V_3)$, go to Step 3: Shrink.

3. **Shrink.** If $f(C_1) > f(R)$, or $f(C_2) > f(V_3)$, then shrink the triangle $V_1V_2V_3$ to V_1MS where M is the midpoint of $\overline{V_1V_2}$ and S is the midpoint of $\overline{V_1V_3}$. The new simplex is V_1MS. Evaluate f at each vertex and order the vertices, renaming them. Then repeat Step 1.

Pituitary System Parameters

Three parameters used in the pituitary systems were not estimated using the optimization procedure described above. The volume of distribution in (3.7) and (3.13) is estimated to be $v_{dis} = 2.5\,L$ because the average woman has $4-5\,L$ of blood, 55% of which consists of blood plasma and the other 45% consisting of blood cells. Therefore the volume of distribution is approximately $2.5L$. [32, 59]. Estimates for the clearance rates for FSH and LH, cl_F and cl_L, were derived from measurements presented in Coble *et al.* [13] and Kohler *et al.* [47]. These authors measured the metabolic clearance rates for FSH and LH of pre-menopausal women, ages 20-27, and obtained their average metabolic clearance rates: $MCR_{FSH} = 14.2 \pm 1.1\,mL/min$ and $MCR_{LH} = 24.4 \pm 1.8\,mL/min$. To obtain values for cl_F and cl_L, we scaled MCR_{FSH} and MCR_{LH} by the volume of distribution and converted to a time scale of days. Therefore,

$$cl_F = MCR_{FSH} \times \frac{1}{v_{dis}} \times \frac{1440 \text{ min}}{1 \text{ day}} \approx 8.2\,\text{day}^{-1}, \tag{4.45}$$

and

$$cl_F = MCR_{LH} \times \frac{1}{v_{dis}} \times \frac{1440 \text{ min}}{1 \text{ day}} \approx 14 \, \text{day}^{-1}. \tag{4.46}$$

The remainder of the system parameters were unknown, therefore the Nelder Mead Simplex Method was used to estimate them. For the FSH system in (3.6)-(3.7), there were 6 unknown parameters: n, the maximal production rate of FSH; p, the inhibition constant for the synthesis of FSH; q, the rate constant for the release of FSH into circulation; r, the induction constant for the effect of P_4 on the release of FSH; s, the inhibition constant for the effect of E_2 on the release of FSH; and δ_{Ih}, the time delay of $\text{Ih}(t)$. The optimal estimates that we obtained for these parameters are listed in Table 4.1.

Table 4.1: **Estimates for the FSH System Parameters**

Parameter	**Value**	
n	5700	$\mu g/\text{day}$
p	641	U/L
q	7.29	$1/\text{day}$
r	644	$L/nmol$
s	0.160	$(L/ng)^2$
δ_{Ih}	2.00	days

These parameters, along with the ovarian input function parameters listed in Table A.2, were used to solve the FSH system in (3.6)-(3.7). A graph of the solution compared to the data in the McLachlan paper is presented in Figure 4.2.

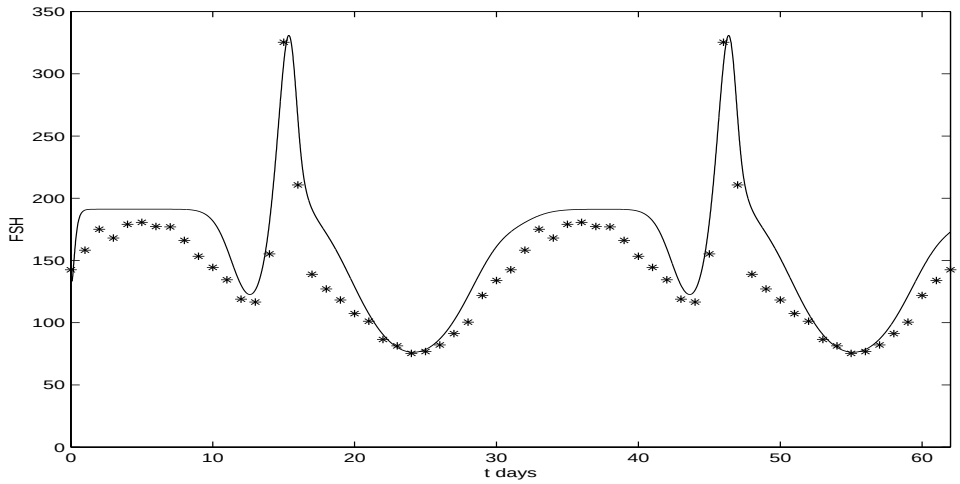

Figure 4.2: Graph of FSH serum concentrations as predicted by the FSH system where $\star$ represents the data points and — represents the solution curve.

For the LH system in (3.12)-(3.13), there were 10 unknown parameters: u, the non-induced maximal production rate of LH; v, the maximal induction on LH synthesis; w, level at half-max; h, the Hill coefficient; w_1, inhibition constant for the synthesis of LH; y, the rate constant for the release of LH; z, the induction constant for the effect of P_4 on the release of LH; z_1, the inhibition constant for the effect of E_2 on the release of LH; δ_E, the time delay of $E_2(t)$; and δ_P, the time delay of $P_4(t)$. The optimal estimates that we obtained for these parameters are listed in Table 4.2. These parameters, along with the ovarian input function parameters, were used to solve the LH system. A graph of the solution compared to the data is presented in Figure 4.3.

Table 4.2: **Estimates for the LH System Parameters**

Parameter	**Value**	
u	1263.4	μg/day
v	91000	μg/day
w	360	ng/L
w_1	31.22	$L/nmol$
y	2.49	1/day
z	0.07	$L/nmol$
z_1	0.0049	L/ng
δ_E	0	days
δ_P	1	days
h	8	dimensionless

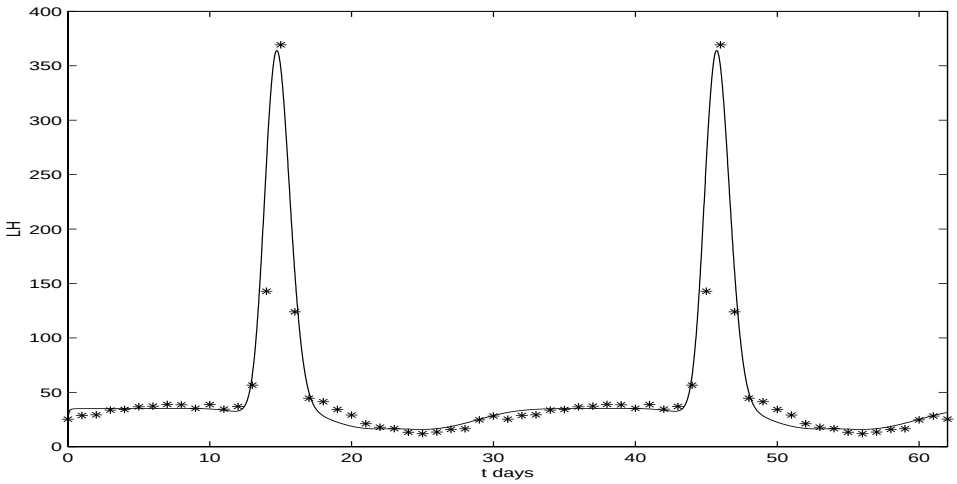

Figure 4.3: Graph of LH serum concentrations as predicted by the LH system where $\star$ represents the data points and — represents the solution curve.

Ovarian System and Auxiliary Equation Parameters

The ovarian system in (3.19)-(3.27) and (3.32)-(3.34) has two sets of unknown parameters to be estimated, the system parameters and the auxiliary equation parameters. There are 15 system parameters and 10 auxiliary equation parameters. The system parameters are: b, the rate constant for the recruitment of inactive follicles induced by FSH; c_1, the rate constant for the growth of menstrual follicles induced by FSH; c_2, the rate constant for the transfer of menstrual follicles into secondary follicles; c_3, the rate constant for the growth of secondary follicles; c_4, the rate constant for the transfer of secondary follicles into preovulatory follicles; c_5, the rate constant for the induction of ovulation by LH; d_1, the rate constant for the transition from ovulation to luteinization; d_2, k_1, k_2, k_3, and k_4, the rate constants for the growth of the corpus luteum during the luteal phase of the cycle; and $\alpha, \beta,$ and γ, the fractional exponents of LH stimulation in the follicular phase of the cycle. Section 3.1.

The auxiliary equation parameters are: e_1, the concentration of E_2 at basal level; e_2 the rate at which the secondary follicles contribute to the total amount of estradiol in the blood; e_3, the rate at which the preovulatory follicle contributes to E_2; e_4, the rate at which the corpus luteum contributes to E_2; pr_1 and pr_2, the rates at which the corpus luteum contributes to the total amount of progesterone in the blood; h_1, the the concentration of Ih at basal level; h_2 the rate at which the preovulatory follicle contributes to the total amount of inhibin in the blood; and h_3 and h_4, the rates at which the corpus luteum contributes to Ih.

The minimization procedure using the "least squares" cost function in (4.43) did not yield optimal estimates for these parameters (*ie.* the resulting parameter set did not yield a good approximation to the data). We found two reasons for such behavior: (i) this system has a large number of parameters to estimate at one time; and/or (ii) the magnitudes of the errors in the cost function vary greatly and the

error corresponding to one hormone (*eg.* inhibin) overshadows the error of the others preventing the minimization procedure from succeeding. We opted to modify the cost function to fit the ovarian system to estradiol. The modified cost function is:

$$C_E = \sum_{i=0}^{62} |Est(t_i) - E_i|^2, \tag{4.47}$$

where $Est(t)$ is the auxiliary equation in (3.32), and E_i for $i = 0, .., 62$ are the data values for estradiol listed in Table A.1 repeated over two periods. Using this approach there are 15 system parameters and only 4 auxiliary equation parameters to be estimated. We felt that this was a sufficient approach to identify system parameters because estradiol plays a more significant role throughout the menstrual cycle than the other ovarian hormones. Estimates for the optimal system parameters are listed in Table 4.3.

Once the system parameters were found, they were used to obtain estimates for the remaining auxiliary equation parameters using the cost functions:

$$C_P = \sum_{i=0}^{62} |Prog(t_i) - P_i|^2, \tag{4.48}$$

and

$$C_I = \sum_{i=0}^{62} |Inh(t_i) - I_i|^2, \tag{4.49}$$

where $Prog(t)$ and $Inh(t)$ are the auxiliary equations in (3.33), and (3.34) and P_i and I_i are the data values for progesterone and inhibin listed in Table A.1 repeated over two periods. Estimates for the optimal parameters in the auxiliary equations for estradiol, progesterone, and inhibin are listed in Table 4.4.

Table 4.3: **Estimates for the Ovarian System Parameters**

Parameter	Value
b	0.0040 L/day
c_1	0.0058 $(L/\mu g)$/day
c_2	0.0480 1/day
c_3	0.0040 1/day
c_4	0.0061 1/day
c_5	1.2655 1/day
d_1	0.6715 1/day
d_2	0.7048 1/day
k_1	0.6876 1/day
k_2	0.6900 1/day
k_3	0.6891 1/day
k_4	0.7093 1/day
α	0.7736 (dimensionless)
β	0.1566 (dimensionless)
γ	0.0202 (dimensionless)

Table 4.4: **Estimates for the Parameters in the Ovarian Auxiliary Equations**

Parameter	Value	Parameter	Value
e_1	48.000 ng/L	pr_2	0.0500 $(nmol/L)/\mu g$
e_2	0.1044 $1/kL$	h_1	274.28 U/L
e_3	0.1659 $1/kL$	h_2	0.4064 $(nmol/L)/\mu g$
e_4	0.2309 $1/kL$	h_3	0.4613 $(U/L)/\mu g$
pr	0.0500 $(nmol/L)/\mu g$	h_4	2.1200 $(U/L)/\mu g$

Recall that each state variable in the system represents the mass of the follicular and/or luteal secretory tissue which is active during the corresponding stage of the cycle. Each state variable is represented by a continuous function of time which increases to a peak as the mass of that stage reaches its highest level of (secretory) activity and then decreases as the stage's mass becomes inactive. The "capacity" to produce hormones is transferred to the next stage, at which time the next state variable is increasing. A graph of the nine state variables MsF, SeF, PrF, Sc_1, Sc_2, Lut_1, Lut_2, Lut_3, and Lut_4, is shown in Figure 4.4.

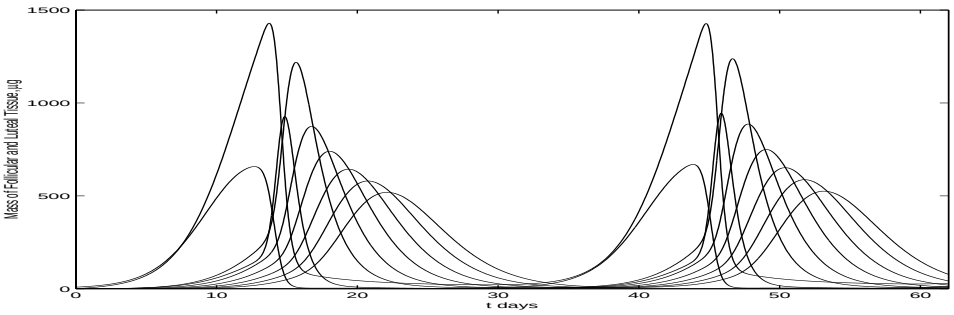

Figure 4.4: Graphs of the ovarian state variables predicted by the ovarian system.

To get a closer look at each phase of the cycle, the state variables are graphed by phase in Figure 4.5. The first graph illustrates the transfer of "capacity" between the stages of the follicular phase. Notice that the slopes of the hormone capacities (as the stages become active) are increasing during this phase. This indicates that as the menstrual follicles are growing into secondary follicles and then into preovulatory follicles, they are becoming "active" faster and hence secreting hormones at a faster rate. The SeF peak is much higher than the MsF peak due to the stimulation of growth by LH. However, the PrF peak is lower because it represents the hormone "capacity" of the preovulatory follicle (one of the secondary follicles chosen to be the one that will ovulate). The second graph in Figure 4.5 illustrates an increase in

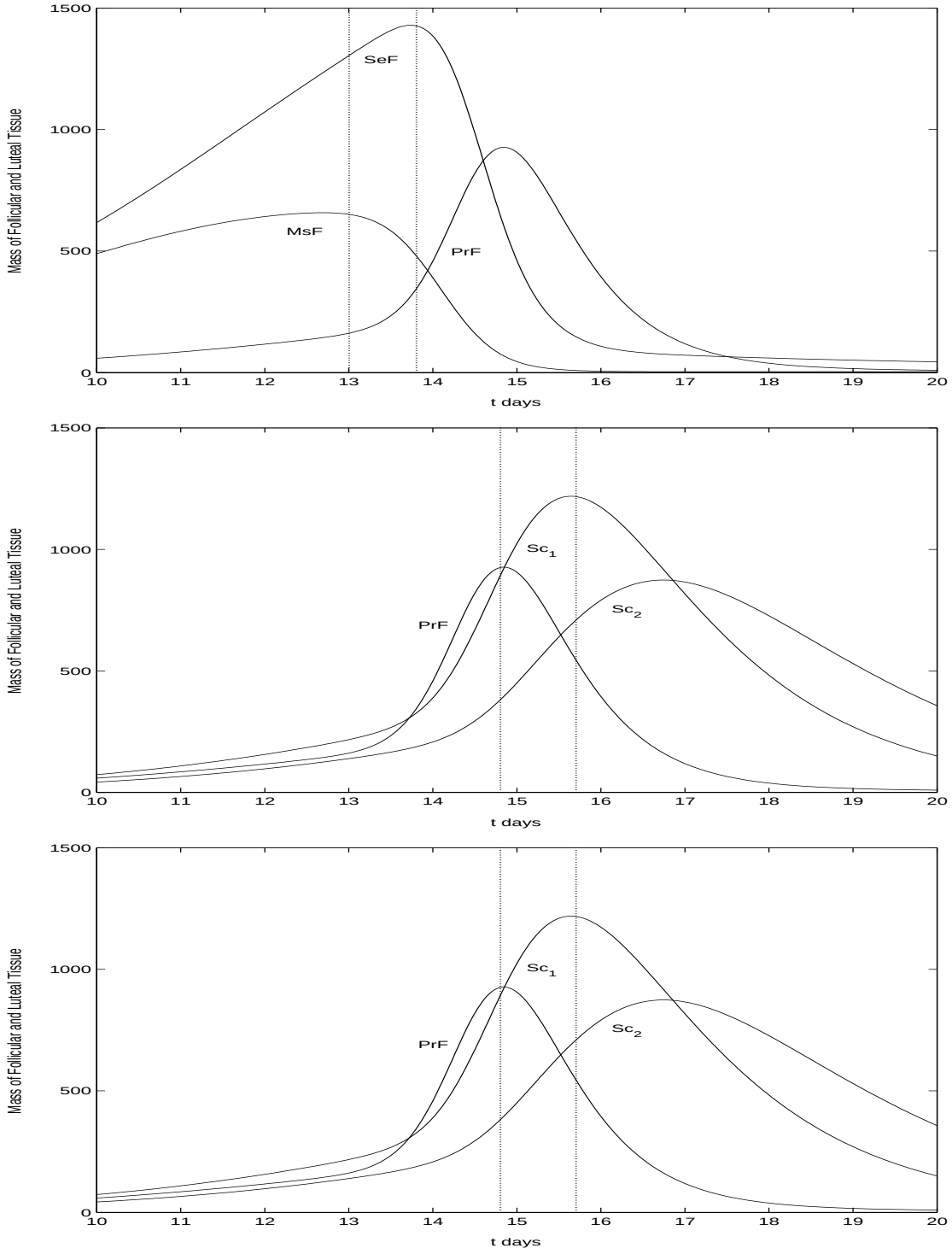

Figure 4.5: Stages of Follicular and Luteal Development.

hormone "capacity" just before ovulation due to the rapid growth of the preovulatory follicle. The auxiliary equations for estradiol, progesterone, and inhibin in (3.32)-(3.34) are graphed in Figures 4.6-4.8.

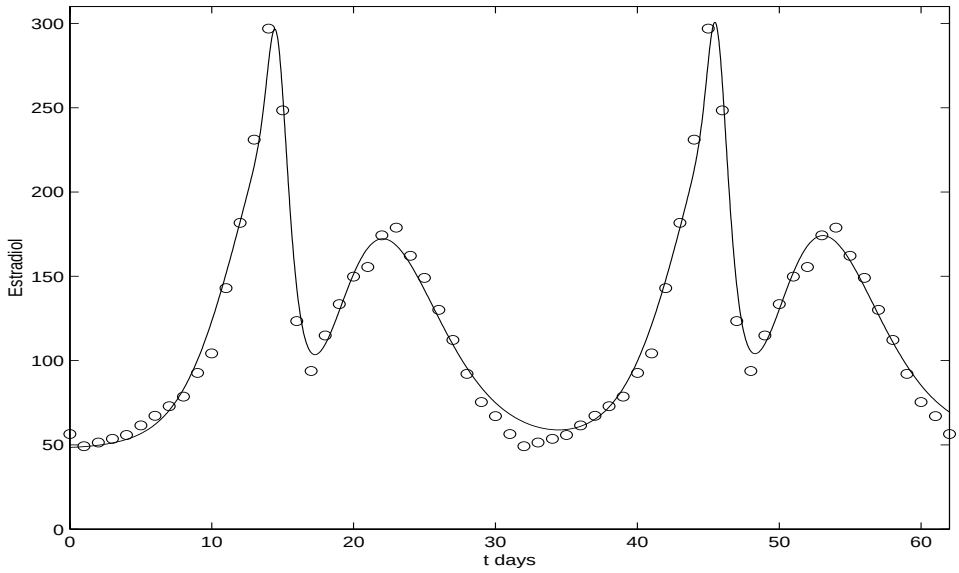

Figure 4.6: Graph of E_2 serum concentrations as predicted by the ovarian system where the ∘ represent data points and the — represents the solution curve.

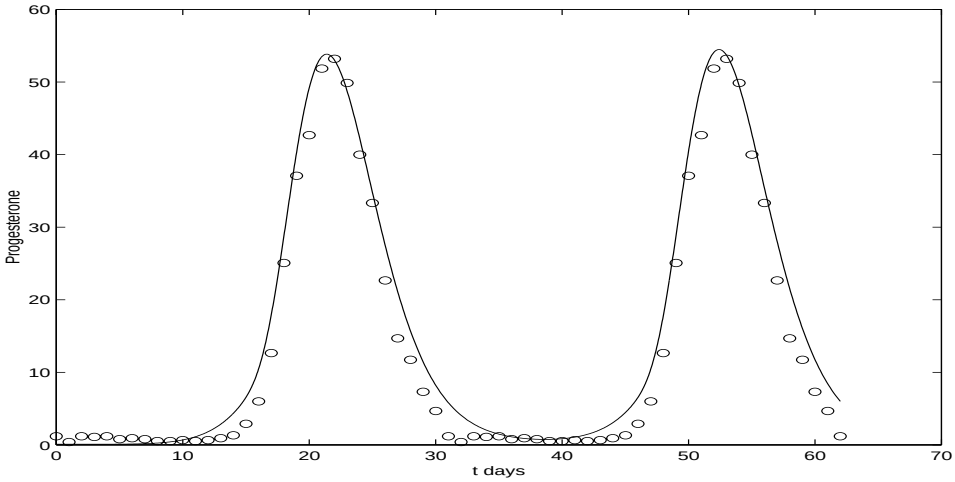

Figure 4.7: Graph of P_4 serum concentrations as predicted by the ovarian system where the ∘ represent data points and the — represents the solution curve.

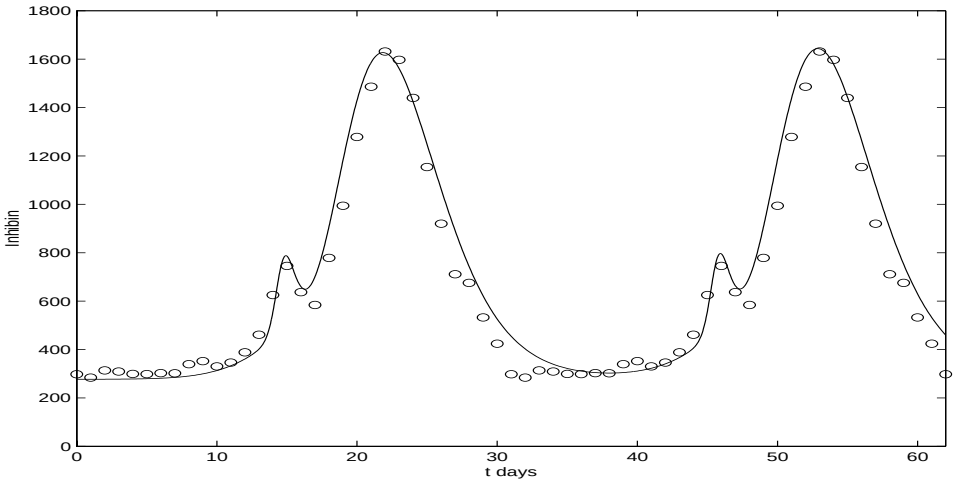

Figure 4.8: Graph of Ih serum concentrations as predicted by the ovarian system where the ∘ represent data points and the — represents the solution curve.

4.3 Stability Results

In this section we will give evidence which suggests that the solutions of the pituitary and ovarian systems presented in the previous section are locally asymptotically stable. We will then show that using periodic input functions and the parameter estimates listed in Tables (4.1)-(4.4), we can find periodic solutions of these systems that are globally asymptotically stable.

4.3.1 Varying Initial Conditions in the Pituitary and Ovarian Systems

By varying the initial conditions for the systems in (3.6)-(3.7), (3.12)-(3.13), and (3.19)-(3.27), we wish to determine whether each system has a locally asymptotically stable solution. For the FSH system we used the original initial condition $[RP_{FSH}(0), FSH(0)] = [352, 142.5]$ and 8 other initial conditions that greatly varied the values for $RP_{FSH}(0)$ and $FSH(0)$. The initial conditions we used to solve the FSH system are listed in Table 4.5

Table 4.5: Varying the initial conditions in the FSH system.

$RP_{FSH}(0)$	$FSH(0)$
0	140
0	1400
0	10
1	1
600	600
140	0
1400	0
10	0

For the LH system, we used the original initial condition $[RP_{LH}(0), LH(0)] =$

$[600, 25.34]$ and initial conditions listed in Table 4.5 to vary the values of $RP_{LH}(0)$ and $LH(0)$. Figure 4.9 shows that even for a wide range of initial values the solutions to the FSH and LH systems all converge to the same solution within 2 days, *ie.* each of the pituitary systems has a locally asymptotically stable solution.

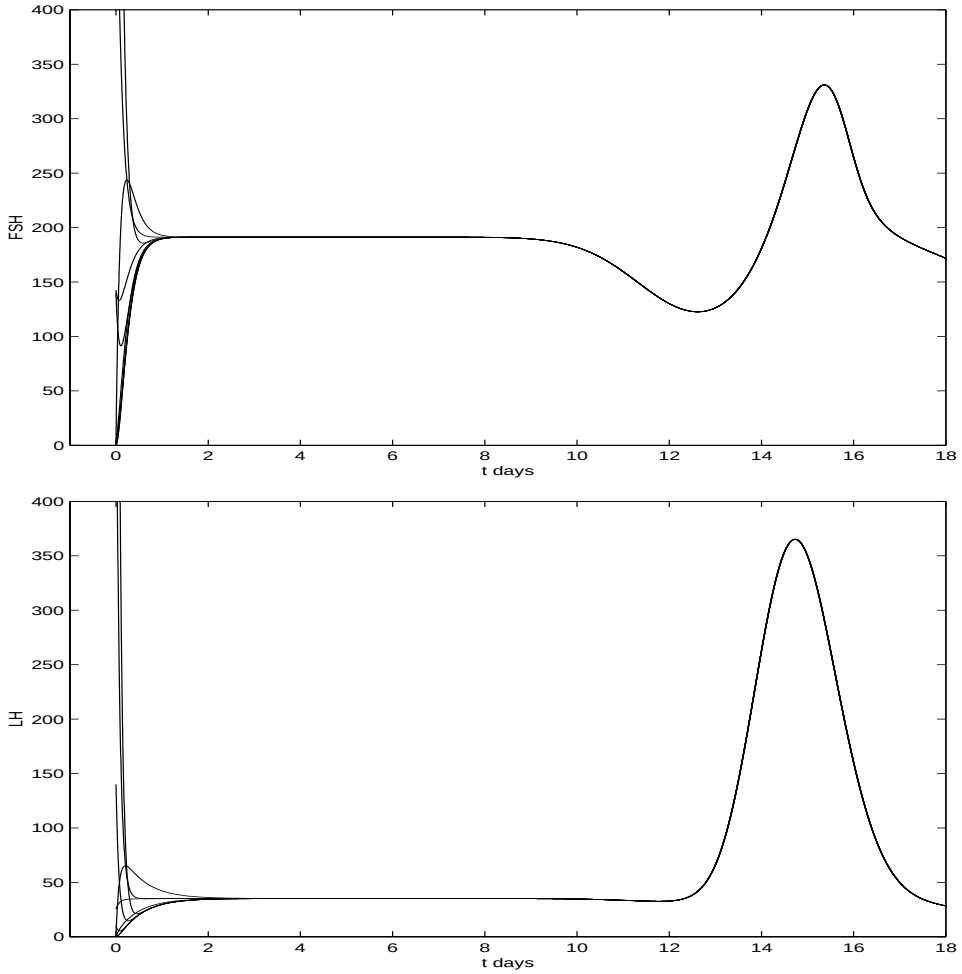

Figure 4.9: Results of varying initial conditions in the pituitary systems.

The ovarian system has 9 equations, therefore there were too many initial conditions to vary to get a good feel for the stability of a solution. Therefore we chose to observe the behavior of estradiol when varying the initial conditions of the state variable which contribute to $Est(t)$. These state variables are SeF, PrF, and Lut_4. The original initial condition is $[9, 1, 1, 1, 1, 1, 1, 1, 1]$. The initial conditions we used to solve the FSH system are listed in Table 4.6. The first set of initial conditions

Table 4.6: Varying the initial conditions in the ovarian system.

$MsF(0)$	$SeF(0)$	$PrF(0)$	$Sc_1(0)$	$Sc_2(0)$	$Lut_1(0)$	$Lut_2(0)$	$Lut_3(0)$	$Lut_4(0)$
9	0	1	1	1	1	1	1	1
9	10	1	1	1	1	1	1	1
9	100	1	1	1	1	1	1	1
9	1	0	1	1	1	1	1	1
9	1	20	1	1	1	1	1	1
9	1	200	1	1	1	1	1	1
9	1	1	1	1	1	1	1	0
9	1	1	1	1	1	1	1	15
9	1	1	1	1	1	1	1	30
9	0	0	0	0	0	0	0	0
9	10	0	0	0	0	0	0	0
1	500	1	1	1	1	1	1	1
1	1	300	1	1	1	1	1	1
1	1	1	50	1	1	1	1	50
30	1	1	30	30	30	1	1	30

varied the values of $SeF(0)$, $PrF(0)$, and $Lut_4(0)$ while fixing the initial conditions for the other state variables. The second set of initial conditions were chosen at random to vary some of the other state variable's starting points. The resulting solutions are graphed in Figure 4.10. The first set of solutions are shown in the first graph and all of the solutions appear in the second graph. From these graphs we see that when we only vary the initial conditions of the state variables that contribute to estradiol, the

solutions are converging to the same solution very quickly. We also see that when we begin to vary the initial conditions for all of the state variables, solutions still seem to converge to the same solution but it is taking longer when the initial conditions are "far" from that solution.

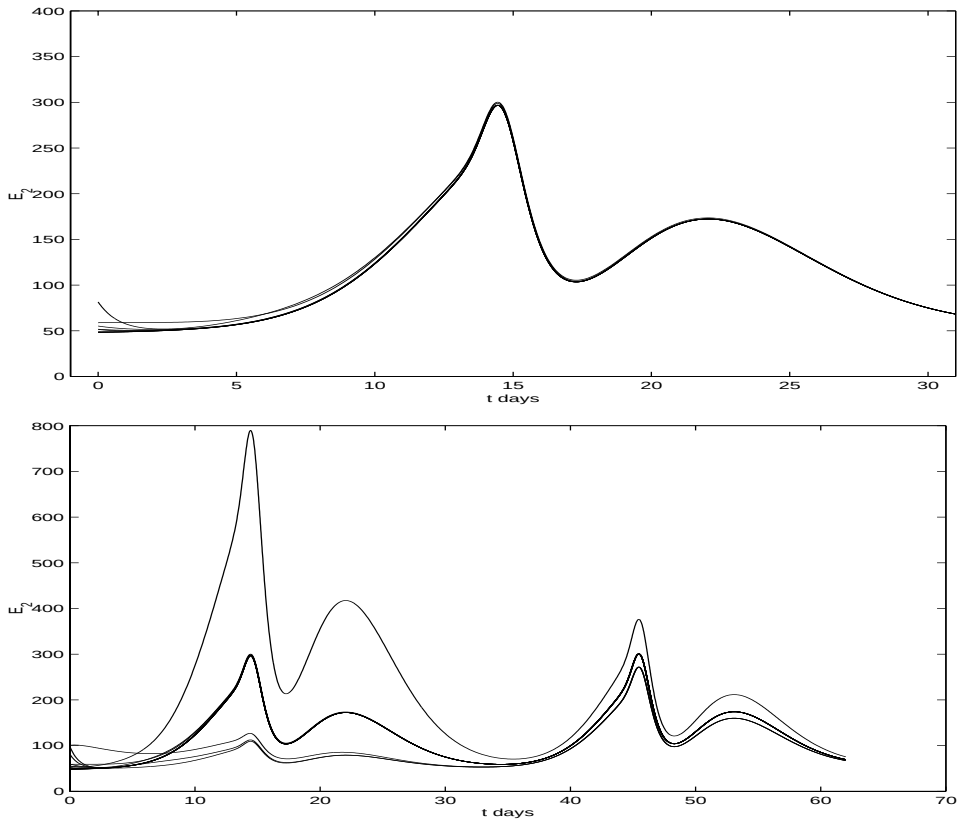

Figure 4.10: Results of varying initial conditions in the ovarian system.

The second graph shows that the ovarian system is sensitive to large variations in the initial conditions. This suggests that there is a weak attraction to a stable solution. The graphs in Figures 4.9 and 4.10 provide evidence that each of the pituitary and ovarian systems has a locally asymptotically stable solution that yields a

good approximation to the data found in the literature. The results also suggest that even for large variations in the initial conditions, convergence occurs. Next we will investigate whether these solutions are globally asymptotically stable.

4.3.2 Periodic Attractors in the Pituitary and Ovarian Systems

Recall that the pituitary and ovarian systems in (3.6)-(3.7), (3.12)-(3.13), and (3.19)-(3.27) have the form:

$$\frac{dX}{dt}(t) = A(t)\,X(t) + B(t), \tag{4.50}$$

where

$$A(t) = \begin{pmatrix} a_{11}(t) & 0 & 0 & \cdots & 0 \\ a_{21}(t) & a_{22}(t) & 0 & \cdots & 0 \\ 0 & a_{32}(t) & a_{33}(t) & \cdots & 0 \\ \vdots & & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & a_{n,n-1}(t) & a_{nn}(t) \end{pmatrix} \tag{4.51}$$

is a continuous matrix in $\mathbb{R}^{n\times n}$ and $X(t)$ and $B(t)$ are continuous vectors in $\mathbb{R}^n$. In this section we will show that if A and B are periodic with period $\omega > 0$, then the system in (4.50) has a unique periodic solution $X_\omega(t)$ which has period ω and is globally asymptotically stable. That is, we wish to show that $X(t) \to X_\omega(t)$ as $t \to \infty$, where $X(t)$ is any other solution of the system. In each of these systems $A(t)$ and $B(t)$ are functions of one or more of the five hormones, FSH, LH, E_2, P_4, and Ih. If we assume that each input function is a periodic function of time with period $\omega = 31$, then $A(t)$ and $B(t)$ are periodic with period ω. Selgrade and Schlosser [54] proved the existence a unique $\omega-$periodic solution $X_\omega(t)$ of the system in (4.50) provided that the input functions are $\omega - \textit{periodic}$ and $\int_0^\omega a_{ii}(\tau)d\tau \neq 0,\ i = 1,\ldots,n$, where

the initial condition $X_\omega(0)$ is given by:

$$X_\omega(0) = [I - \Phi(\omega)]^{-1}\, \Phi(\omega) \int_0^\omega \Phi(s)^{-1} B(s) ds$$

and $\Phi(t)$ is a fundamental matrix of the differential equation

$$\frac{dx}{dt}(t) = A(t)x(t) \tag{4.52}$$

such that $\Phi(0) = I$. Let $X_\omega(t)$ be that solution. Selgrade and Schlosser also proved that $X_\omega(t)$ is globally asymptotically stable if $\int_0^\omega a_{ii}(\tau)d\tau < 0,\ i = 1, \ldots, n$ [53, 54]. We will show that when negative, these integrals determine the exponential rate of approach to the globally asymptotically stable solution. Let $X(t)$ be any solution of the system in (4.50) such that $X(0) = X_0$ is not on X_ω. If we define $Y(t) = X(t) - X_\omega(t)$, then $Y(t)$ is a solution of the differential equation in (4.52) such that $Y(t) = \Phi(t)Y_0$. The following theorem taken from [8] gives us a way to represent $\Phi(t)$ as the product of a periodic matrix and an exponential matrix.

THEOREM 4.2. ***Floquet's Theorem.*** *Let $A(t)$ be a continuous periodic matrix with period ω and let $\Phi(t)$ be a fundamental matrix of the system in (4.52). There exists a continuous, periodic matrix $P(t)$ that is nonsingular and has period ω and a constant matrix R such that*

$$\Phi(t) = P(t)e^{Rt}. \tag{4.53}$$

The function $P(t)$ has the property that

$$P(\omega) = P(0) = \Phi(0) = I,$$

since $P(t)$ has period ω. Therefore

$$\Phi(\omega) = P(\omega)\, e^{R\omega} = e^{R\omega},$$

and hence, the eigenvalues of $\Phi(\omega)$ are the eigenvalues of $e^{R\omega}$. The eigenvalues of $e^{R\omega}$ are called the characteristic multipliers of the system in (4.52). If we can show that the characteristic multipliers all have magnitudes less than 1, then all solutions of (4.52) converge to 0 as $t \to \infty$ (see [8] for further details). Therefore if the eigenvalues of $e^{R\omega}$ all have magnitudes less than 1, then $Y(t) = X(t) - X_\omega(t) \to 0$ (that is, $X(t) \to X_\omega(t)$ as $t \to \infty$). In order to determine the magnitudes of the characteristic multipliers, we will find the eigenvalues of $\Phi(\omega)$ for the pituitary and ovarian systems since we found fundamental matrices for each system in Section 4.1.

In Section 4.1 we showed that the fundamental matrices $\Phi_F(t)$, $\Phi_L(t)$, and $\Phi_{Ov}(t)$ were all lower triangular matrices. Therefore the diagonal entries:

$$\phi_{ii}^F(t) = e^{\int_0^t a_{ii}^F(\tau)d\tau}, \quad i = 1, 2, \tag{4.54}$$

$$\phi_{ii}^L(t) = e^{\int_0^t a_{ii}^L(\tau)d\tau}, \quad i = 1, 2, \text{and} \tag{4.55}$$

$$\phi_{ii}^{Ov}(t) = e^{\int_0^t a_{ii}^{Ov}(\tau)d\tau}, \quad i = 1, 2, \ldots, 9, \tag{4.56}$$

are their eigenvalues. Hence the characteristic multipliers of the system in (4.52) are of the form:

$$\lambda_i = e^{\int_0^\omega a_{ii}(s)ds} \quad \text{for} \quad i = 1, \ldots, n. \tag{4.57}$$

We know that if $\lambda = e^{\omega\rho}$ is a real eigenvalue of $e^{R\omega}$, then ρ is an eigenvalue of R. Therefore the eigenvalues of R are of the form:

$$\rho_i = \frac{1}{\omega}\int_0^{\omega} a_{ii}(s)ds \quad \text{for} \quad i = 1, \ldots, n. \tag{4.58}$$

These are called the characteristic exponents of (4.52). If we can show that all of the characteristic exponents are negative, then the characteristic multipliers in (4.54)-(4.54) all have magnitudes less than 1 and $X(t) \to X_\omega(t)$ as $t \to \infty$ in each system. And hence, there is a unique periodic solution $X_\omega(t)$ for each of the pituitary and ovarian systems which is globally asymptotically stable. We will show that the integrals in (4.58) are in fact negative for all of the systems.

Characteristic Exponents for the Pituitary Systems

The characteristic exponents of (4.52) are the convergence rates of the periodic attractors of (4.50). The FSH and LH systems each have two characteristic exponents. Let ρ_i^{FSH} for $i = 1, 2$, denote the characteristic exponents corresponding to the FSH system and ρ_i^{LH} for $i = 1, 2$, denote the characteristic exponents corresponding to the LH system. Then the characteristic exponents for the FSH system have the form:

$$\rho_1^{FSH} = \frac{1}{\omega}\int_0^{\omega} -\frac{q(1 + rP_4(s))}{1 + sE_2(s)^2}ds, \tag{4.59}$$

and

$$\rho_2^{FSH} = \frac{1}{\omega}\int_0^{\omega} -cl_F ds = -8.21. \tag{4.60}$$

The characteristic exponents for the LH system have the form:

$$\rho_1^{LH} = \frac{1}{\omega}\int_0^{\omega} -\frac{y(1 + zP_4(s))}{1 + z_1E_2(s)}ds, \tag{4.61}$$

and

$$\rho_2^{LH} = \frac{1}{\omega}\int_0^{\omega} -cl_L ds = -14. \tag{4.62}$$

In order to obtain estimates for the characteristic exponents ρ_1^{FSH} and ρ_1^{LH} in (4.59) and (4.61), the integrals need to be approximated. Using a quadrature integration technique in MATLAB to calculate the integrals and the parameter fits from Section 4.2, the following estimates were obtained:

$$\rho_1^{FSH} \approx -17.72, \text{ and } \rho_1^{LH} \approx -1.612. \tag{4.63}$$

This shows that all of the characteristic exponents of the pituitary systems are negative. Therefore there exists globally asymptotically stable periodic solutions, $X_\omega^{FSH}(t)$ and $X_\omega^{LH}(t)$, for the FSH and LH systems, respectively. It can also be shown that there exists $K_L, K_F > 0$ such that

$$|Y^{FSH}(t)| = |X^{FSH}(t) - X_\omega^{FSH}(t)| \leq K_F e^{-17.72t}$$

and

$$|Y^{LH}(t)| = |X^{LH}(t) - X_\omega^{LH}(t)| \leq K_L e^{-1.612t}.$$

Therefore it will take at most $t_{FSH} = 2.808$ and $t_{LH} = 14.39$ days for any solutions to converge within 10^{-10} to the periodic solutions of the FSH and LH systems. These estimates were determined by finding t so that $e^{-\rho t} = 1 \times 10^{-10}$.

Characteristic Exponents for the Ovarian System

The ovarian system has nine characteristic exponents. Let ρ_i^{Ov} for $i = 1, 2, \ldots, 9$, denote the characteristic exponents corresponding to the ovarian system. These characteristic exponents have the form:

$$\rho_1^{Ov} = \frac{1}{\omega}\int_0^{\omega}\left(c_1 FSH(s) - c_2\left(\frac{LH(s)}{LH_0}\right)^{\alpha}\right)ds, \tag{4.64}$$

$$\rho_2^{Ov} = \frac{1}{\omega}\int_0^{\omega}\left(c_3\left(\frac{LH(s)}{LH_0}\right)^{\beta} - c_4\left(\frac{LH(s)}{LH_0}\right)\right)ds, \tag{4.65}$$

$$\rho_3^{Ov} = \frac{1}{\omega}\int_0^{\omega} -c_5\left(\frac{LH(s)}{LH_0}\right)^{\gamma} ds, \tag{4.66}$$

$$\rho_4^{Ov} = -d_1 = -0.6715, \tag{4.67}$$

$$\rho_5^{Ov} = -d_2 = -0.7048, \tag{4.68}$$

$$\rho_6^{Ov} = -k_1 = -0.6876, \tag{4.69}$$

$$\rho_7^{Ov} = -k_2 = -0.6900, \tag{4.70}$$

$$\rho_8^{Ov} = -k_3 = -0.6891, \tag{4.71}$$

$$\rho_9^{Ov} = -k_4 = -0.7093. \tag{4.72}$$

We have to approximate the integrals in (4.64)-(4.66) to make sure that they are negative. The following estimates were obtained using MATLAB:

$$\rho_1^{Ov} \approx -0.06, \;\; \rho_2^{Ov} \approx -0.2728, \;\; \text{and} \;\; \rho_3^{Ov} \approx -1.357. \tag{4.73}$$

This shows that all of the characteristic exponents of the ovarian systems are all negative. Therefore there exists a globally asymptotically stable periodic solution $X_\omega^{Ov}(t)$ for the ovarian system. It can also be shown that there exists $K_{Ov} > 0$ such that $|Y^{Ov}(t)| = |X^{Ov}(t) - X_\omega^{Ov}(t)| \leq K_{Ov}e^{-0.06t}$. Therefore it will take at most $t_{Ov} = 384$ days for any solution to converge to the $X_\omega^{Ov}(t)$ (within 10^{-10}).

Chapter 5

The Merged Model: Assumptions and Analysis

The merged model is obtained by merging the pituitary and ovarian systems together into a 13-dimensional, autonomous system of delay differential equations that is highly nonlinear. Our goal is to determine whether the estimated parameters from the pituitary and ovarian components can be used in the merged model to reproduce the hormone levels found in the data without using any inputs into the system. The state variables from the pituitary and ovarian systems are the state variables in the merged system. In addition, the pituitary inputs in the ovarian equations are replaced with the state variables FSH and LH and the ovarian inputs in the pituitary equations are replaced with the auxiliary equations for E_2, P_4, and Ih in (3.32)-(3.34) which are linear combinations of state variables. In this chapter, we provide theoretical results for the existence and uniqueness of solutions of nonlinear, delay differential equations (dde's) and present numerical results for the merged system obtained using a dde solver in MatLab. We also study the stability of steady state and periodic solutions.

5.1 Theoretical Results for the Merged System

Results for existence and uniqueness of solutions of nonlinear systems of delay differential equations are similar to those for ordinary differential equations. However, when delays are introduced into the system the method of finding solutions and studying the stability of those solutions is more difficult. Utilizing existence and uniqueness results for ordinary differential equations a technique called the **method of steps** can be used to determine whether a system of delay differential equations has a unique solution [18]. In this section we will provide an outline of the method of steps, followed by a simple example using the method. We will then show how the method of steps can be used to establish the existence and uniqueness of solutions of the merged system.

The Method of Steps

Consider the following system of delay differential equations with constant time delays:

$$x'(t) = f(t,\, x(t),\, x(t-\delta_1),\, x(t-\delta_2), \ldots, x(t-\delta_m)) \qquad \text{for } t \geq 0, \quad (5.1)$$

$$x(t) = \phi(t) \qquad \text{for } t \in [-\delta\,,\, 0], \quad (5.2)$$

where $f,\, \phi \in \mathbb{R}^n$ are continuous, $\delta_1,\, \delta_2,\, \ldots,\, \delta_m \geq 0$, and $\delta = \max_{i=1,\ldots,m}\{\delta_i\}$ [18, 36].

Step 1: Solve the system in (5.1)-(5.2) for $t \in [0\,,\, \widehat{\delta}]$ where $\widehat{\delta} = \min_{i=1,\ldots,m}\{\delta_i\}$.

If $t \in [0\,,\, \widehat{\delta}]$, then $t - \delta_i \in [-\delta\,,\, 0]$ for $i = 1, \ldots, m$. By (5.2) we see that

$$x(t-\delta_i) = \phi(t-\delta_i) \qquad \text{for } i = 1, \ldots, m.$$

Therefore, for $t \in [0\,,\,\widehat{\delta}]$ the system in (5.1)-(5.2) reduces to the ode:

$$x'(t) = f(t,\, x(t),\, \phi(t-\delta_1),\, \phi(t-\delta_2), \ldots, \phi(t-\delta_m)) \equiv g(t, x(t)), \quad (5.3)$$

$$x(0) = \phi(0), \quad (5.4)$$

where g is a continuous function in t and in x. If g is locally Lipschitz with respect to x, then by the Picard-Lindelöf theorem [29] there exists a unique solution $x(t)$ that satisfies (5.3)-(5.4) for $t \in [0\,,\,\widehat{\delta}]$. A useful way to check whether a function $g(t, x(t))$ is locally Lipschitz in x is to determine whether g has continuous first partial derivatives in x [29]. Note that $\partial g/\partial t$ may not be continuous, but this is not needed for the existence and uniqueness of solutions.

Step 2: Solve the system in (5.1)-(5.2) for $t \in [\widehat{\delta}\,,\,2\,\widehat{\delta}]$.

If $t \in [\widehat{\delta}\,,\,2\,\widehat{\delta}]$, then $-\delta < \widehat{\delta} - \delta_i \leq t - \delta_i \leq \widehat{\delta}$ for $i = 1, \ldots, m$.
There are two cases:
(i) $t - \delta_i \in [-\delta\,,\,0]$ in which case $x(t-\delta_i) = \phi(t-\delta_i)$, or
(ii) $t - \delta_i \in [0\,,\,\widehat{\delta}\,]$ in which case $x(t-\delta_i)$ is determined by the solution $x(t)$ on $t \in [0\,,\,\widehat{\delta}]$ found in Step 1. In either case, the equation in (5.1) reduces to the system of ordinary differential equations:

$$x'(t) \equiv h(t, x(t)) \qquad \text{for each } t \in [\widehat{\delta}\,,\,2\,\widehat{\delta}], \quad (5.5)$$

where the initial condition is determined by the initial function ϕ or by the solution of (5.3) found in Step 1. Further, the function $h(t, x(t))$ is continuous in t and in x. If h is locally Lipschitz with respect to x, then the solution of (5.5) on $[\widehat{\delta}\,,\,2\,\widehat{\delta}]$ exists and is unique.

$$\vdots$$

Step n (for n $\geq$ 3): Solve the system in (5.1)-(5.2) for $t \in [(n-1)\,\widehat{\delta}\,,\, n\,\widehat{\delta}]$ using the results obtained in the previous steps.

Continue this process inductively stepping through intervals $[(n-1)\,\delta\,,\, n\,\delta]$ for $n = 1, 2, \ldots$ to obtain a unique solution defined on the desired interval $[0\,,\, \beta]$. Notice that if $m = 1$ there is only one delay δ_1 and hence $\delta = \max_{i=1,\ldots,m}\{\delta_i\} = \min_{i=1,\ldots,m}\{\delta_i\} = \widehat{\delta}$.

The following example illustrates how the method of steps is used to solve a simple linear delay differential equation. Consider the system

$$x'(t) \;=\; a\,x(t) \,+\, b\,x(t-d) \qquad \text{for } t \geq 0, \tag{5.6}$$

$$x(t) \;=\; c \qquad \text{for } t \in [-d\,,\, 0], \tag{5.7}$$

$$\begin{aligned}
\text{If } t \in [0, d] \text{ then } t - d \in [-d, 0]. \;&\Longrightarrow\; x(t-d) = c. \\
&\Longrightarrow\; x'(t) - a\,x(t) \;=\; b\,c. \\
&\Longrightarrow\; \frac{d}{dt}\left[x(t)\,e^{-a\,t}\right] \;=\; b\,c\,e^{-a\,t}. \\
&\Longrightarrow\; \text{Integrating both sides from 0 to } t \text{ we obtain:} \\
&\qquad x(t) = e^{a\,t}\left(c \,+\, \frac{b\,c}{a}\right) \,-\, \frac{b\,c}{a} \text{ for } t \in [0, d].
\end{aligned}$$

$$
\begin{aligned}
\text{If } t \in [d, 2d] \text{ then } t - d \in [0, d]. \quad &\Longrightarrow \quad x(t-d) = e^{a\,(t-d)} \left(c \,+\, \frac{b\,c}{a} \right) \,-\, \frac{b\,c}{a}. \\
&\Longrightarrow \quad x'(t) - a\,x(t) \,=\, b \left[e^{a\,(t-d)} \left(c \,+\, \frac{b\,c}{a} \right) \,-\, \frac{b\,c}{a} \right]. \\
&\Longrightarrow \quad \frac{d}{dt} \left[x(t)\, e^{-a\,t} \right] = \left[b\,c\, e^{-a\,d} \left(1 + \frac{b}{a} \right) - \frac{b^2\,c}{a} e^{-a\,t} \right]. \\
&\Longrightarrow \quad \text{Integrating both sides from } d \text{ to } t \text{ we obtain:} \\
&\qquad\qquad x(t) = \left[b\,c \left(1 \,+\, \frac{b}{a} \right) \,(t-d) \,-\, \frac{b^2\,c}{a^2} \right] \, e^{a\,(t-d)} \\
&\qquad\qquad + e^{a\,(t+d)} \left(c \,+\, \frac{b\,c}{a} \right) \,-\, \frac{b\,c}{a}\, e^{a\,t} \,+\, \frac{b^2\,c}{a^2}.
\end{aligned}
$$

Continue this process for $t \in [2d, 3d], [3d, 4d], [4d, 5d], \ldots$ as far as desired using this method of stepping through intervals of length d.

The Merged System

The merged system is the 13-dimensional system of delay, differential equations given by:

$$\frac{d}{dt} RP_{FSH} \;=\; \frac{n}{1 + \dfrac{Ih(t-\delta_{Ih})}{p}} \;-\; \frac{q(1+rP_4)}{1+sE_2^2}\, RP_{FSH}, \tag{5.8}$$

$$\frac{d}{dt} FSH \;=\; \frac{1}{v_{dis}} \frac{q(1+rP_4)}{1+sE_2^2}\, RP_{FSH} \;-\; cl_F FSH, \tag{5.9}$$

$$\frac{d}{dt} RP_{LH} \;=\; \frac{u + \dfrac{vE_2(t-\delta_E)^h}{w^h + E_2(t-\delta_E)^h}}{1 + \dfrac{P_4(t-\delta_P)}{w_1}} \;-\; \frac{y(1+zP_4)}{1+z_1E_2}\, RP_{LH}, \tag{5.10}$$

$$\frac{d}{dt} LH \;=\; \frac{1}{v_{dis}} \frac{y(1+zP_4)}{1+z_1E_2}\, RP_{LH} \;-\; cl_L LH, \tag{5.11}$$

$$\frac{d}{dt} MsF \;=\; bFSH + \left[c_1 FSH - c_2 \left(\frac{LH}{LH_0} \right)^{\alpha} \right] \, MsF, \tag{5.12}$$

$$\frac{d}{dt}SeF = c_2\left(\frac{LH}{LH_0}\right)^{\alpha} MsF + \left[c_3\left(\frac{LH}{LH_0}\right)^{\beta} - c_4\left(\frac{LH}{LH_0}\right)\right] SeF, \quad (5.13)$$

$$\frac{d}{dt}PrF = c_4\left(\frac{LH}{LH_0}\right) SeF - c_5\left(\frac{LH}{LH_0}\right)^{\gamma} PrF, \quad (5.14)$$

$$\frac{d}{dt}Sc_1 = c_5\left(\frac{LH}{LH_0}\right)^{\gamma} PrF - d_1 Sc_1, \quad (5.15)$$

$$\frac{d}{dt}Sc_2 = d_1 Sc_1 - d_2 Sc_2, \quad (5.16)$$

$$\frac{d}{dt}Lut_1 = d_2 Sc_2 - k_1 Lut_1, \quad (5.17)$$

$$\frac{d}{dt}Lut_2 = k_1 Lut_1 - k_2 Lut_2, \quad (5.18)$$

$$\frac{d}{dt}Lut_3 = k_2 Lut_2 - k_3 Lut_3, \quad (5.19)$$

$$\frac{d}{dt}Lut_4 = k_3 Lut_3 - k_4 Lut_4, \quad (5.20)$$

where

$$E_2(t) = e_1 + e_2\, SeF(t) + e_3\, PrF(t) + e_4\, Lut_4(t), \quad (5.21)$$

$$P_4(t) = pr\, Lut_3(t) + pr_2\, Lut_4(t), \text{and} \quad (5.22)$$

$$Ih(t) = h_1 + h_2\, PrF(t) + h_3\, Lut_3(t) + h_4\, Lut_4(t). \quad (5.23)$$

This system can be rewritten as:

$$x'(t) = f(t,\, x(t),\, x(t-\delta_E),\, x(t-\delta_P),\, x(t-\delta_I)), \quad (5.24)$$

where $x = (RP_{FSH}, FSH, RP_{LH}, LH, MsF, SeF, PrF, Sc_1, Sc_2, Lut_1, Lut_2, Lut_3, Lut_4)$. If we define

$$f \equiv f(t,\, x^0,\, x^1,\, x^2,\, x^3)$$

where $x^j = x(t-\delta_j)$ for $\delta_0 = 0,\ \delta_1 = \delta_E,\ \delta_2 = \delta_P,$ and $\delta_3 = \delta_I,$ then f can be written as [20]:

$$f(t,\, x^0,\, x^1,\, x^2,\, x^3) = \begin{pmatrix} \dfrac{n}{1+(Ih^3/p)} \;-\; \dfrac{q(1+rP^0)}{1+s(E^0)^2}\, x_1^0 \\ \\ \dfrac{1}{v_{dis}} \dfrac{q(1+rP^0)}{1+s(E^0)^2}\, x_1^0 \;-\; cl_F x_2^0 \\ \\ \dfrac{u+v(E^1)^h/(w^h+(E^1)^h)}{1+(P^2/w_1)} \;-\; \dfrac{y(1+zP^0)}{1+z_1E^0}\, x_3^0 \\ \\ \dfrac{1}{v_{dis}} \dfrac{y(1+zP^0)}{1+z_1E^0}\, x_3^0 \;-\; cl_L x_4^0 \\ \\ b\, x_2^0 + \left[c_1\, x_2^0 - c_2 \left(\dfrac{x_4^0}{LH_0} \right)^{\alpha} \right] x_5^0 \\ c_2 \left(\dfrac{x_4^0}{LH_0} \right)^{\alpha} x_5^0 + \left[c_3 \left(\dfrac{x_4^0}{LH_0} \right)^{\beta} - c_4 \left(\dfrac{x_4^0}{LH_0} \right) \right] x_6^0 \\ c_4 \left(\dfrac{x_4^0}{LH_0} \right) x_6^0 - c_5 \left(\dfrac{x_4^0}{LH_0} \right)^{\gamma} x_7^0 \\ c_5 \left(\dfrac{x_4^0}{LH_0} \right)^{\gamma} x_7^0 - d_1\, x_8^0 \\ d_1\, x_8^0 - d_2\, x_9^0 \\ d_2\, x_9^0 - k_1\, x_{10}^0 \\ k_1\, x_{10}^0 - k_2\, x_{11}^0 \\ k_2\, x_{11}^0 - k_3\, x_{12}^0 \\ k_3\, x_{12}^0 - k_4\, x_{13}^0 \end{pmatrix}. \tag{5.25}$$

In (5.25), $E^0(t) = E_2(t)$ and $P^0(t) = P_4(t)$ are defined by the auxiliary equations without delay given as:

$$E^0 = e_1 + e_2x_6^0 + e_3x_7^0 + e_4x_{13}^0, \tag{5.26}$$

$$P^0 = prx_{12}^0 + pr_2x_{13}^0, \tag{5.27}$$

and $E^1(t) = E_2(t-\delta_E)$, $P^2(t) = P_4(t-\delta_P)$, and $Ih^3(t) = Ih(t-\delta_I)$ are defined by the auxiliary equations with delayed variables given as:

$$E^1 = e_1 + e_2x_6^1 + e_3x_7^1 + e_4x_{13}^1, \tag{5.28}$$

$$P^2 = prx_{12}^2 + pr_2x_{13}^2, \tag{5.29}$$

$$Ih^3 = h_1 + h_2x_7^3 + h_3x_{12}^3 + h_4x_{13}^3. \tag{5.30}$$

This notation will become useful in keeping track of the delayed variables.

We will use the method of steps to guarantee the existence and uniqueness of a solution $x(t)$ of (5.24) for all $t \geq 0$ given a continuous initial function $\phi(t)$ such that

$$x(t) = \phi(t) \qquad \text{for } t \in [-\delta\,,\,0], \tag{5.31}$$

where $\delta = max\{\delta_E, \delta_P, \delta_I\}$ and $\widehat{\delta} = min\{\delta_E, \delta_P, \delta_I\}$. The function $\phi(t)$ is called the history of $x(t)$. For $t \in [0\,,\,\widehat{\delta}]$, the system in (5.24) reduces to:

$$x'(t) = f(t,\, x(t),\, \phi(t-\delta_E),\, \phi(t-\delta_P), \phi(t-\delta_I)) = g(t, x(t)), \tag{5.32}$$

$$x(0) = \phi(0), \tag{5.33}$$

where g is a continuous function in t and in x. If g is locally Lipschitz with respect to x, then by the Picard-Lindelöf theorem there exists a unique solution $x(t)$ that satisfies (5.32)-(5.33) for $t \in [0\,,\,\widehat{\delta}]$. A useful way to check whether a function $g(t, x(t))$ is

locally Lipschitz in x is to determine whether g has continuous first partial derivatives in x [29]. To find the partial derivatives of g, we will differentiate f with respect to its first dependent variable, x^0.

$$\frac{\partial f_1}{\partial x_1^0} = -\frac{q(1+rP^0)}{1+s(E^0)^2} \qquad \frac{\partial f_2}{\partial x_1^0} = \frac{1}{v_{dis}}\frac{q(1+rP^0)}{1+s(E^0)^2}$$

$$\frac{\partial f_1}{\partial x_2^0} = 0 \qquad \frac{\partial f_2}{\partial x_2^0} = -cl_F$$

$$\frac{\partial f_1}{\partial x_3^0} = 0 \qquad \frac{\partial f_2}{\partial x_3^0} = 0$$

$$\frac{\partial f_1}{\partial x_4^0} = 0 \qquad \frac{\partial f_2}{\partial x_4^0} = 0$$

$$\frac{\partial f_1}{\partial x_5^0} = 0 \qquad \frac{\partial f_2}{\partial x_5^0} = 0$$

$$\frac{\partial f_1}{\partial x_6^0} = \frac{2q(1+rP^0)sE^0e_2x_1^0}{(1+s(E^0)^2)^2} \qquad \frac{\partial f_2}{\partial x_6^0} = -\frac{1}{v_{dis}}\frac{2q(1+rP^0)sE^0e_2x_1^0}{(1+s(E^0)^2)^2}$$

$$\frac{\partial f_1}{\partial x_7^0} = \frac{2q(1+rP^0)sE^0e_3x_1^0}{(1+s(E^0)^2)^2} \qquad \frac{\partial f_2}{\partial x_7^0} = -\frac{1}{v_{dis}}\frac{2q(1+rP^0)sE^0e_3x_1^0}{(1+s(E^0)^2)^2}$$

$$\frac{\partial f_1}{\partial x_8^0} = 0 \qquad \frac{\partial f_2}{\partial x_8^0} = 0$$

$$\frac{\partial f_1}{\partial x_9^0} = 0 \qquad \frac{\partial f_2}{\partial x_9^0} = 0$$

$$\frac{\partial f_1}{\partial x_{10}^0} = 0 \qquad \frac{\partial f_2}{\partial x_{10}^0} = 0$$

$$\frac{\partial f_1}{\partial x_{11}^0} = 0 \qquad \frac{\partial f_2}{\partial x_{11}^0} = 0$$

$$\frac{\partial f_1}{\partial x_{12}^0} = -\frac{qrprx_1^0}{1+s*(E^0)^2} \qquad \frac{\partial f_2}{\partial x_{12}^0} = \frac{1}{v_{dis}}\frac{qrprx_1^0}{1+s*(E^0)^2}$$

$$\frac{\partial f_1}{\partial x_{13}^0} = -\frac{qrpr_2x_1^0}{1+s(E^0)^2} + \frac{2q(1+rP^0)s(E^0)e_4x_1^0}{(1+s(E^0)^2)^2} \qquad \frac{\partial f_2}{\partial x_{13}^0} = -\frac{1}{v_{dis}}\frac{2q(1+rP^0)sE^0e_4x_1^0}{(1+s(E^0)^2)^2} + \frac{1}{v_{dis}}\frac{qrpr_2x_1^0}{1+s(E^0)^2}$$

$$\frac{\partial f_3}{\partial x_1^0} = 0 \qquad \frac{\partial f_4}{\partial x_1^0} = 0$$

$$\frac{\partial f_3}{\partial x_2^0} = 0 \qquad \frac{\partial f_4}{\partial x_2^0} = 0$$

$$\frac{\partial f_3}{\partial x_3^0} = -\frac{y(1+zP^0)}{1+z_1E^0} \qquad \frac{\partial f_4}{\partial x_3^0} = -cl_L$$

$$\frac{\partial f_3}{\partial x_4^0} = 0 \qquad \frac{\partial f_4}{\partial x_4^0} = 0$$

$$\frac{\partial f_3}{\partial x_5^0} = 0 \qquad \frac{\partial f_4}{\partial x_5^0} = 0$$

$$\frac{\partial f_3}{\partial x_6^0} = \frac{y(1+zP^0)z_1e_2x_3^0}{(1+z_1E^0)^2} \qquad \frac{\partial f_4}{\partial x_6^0} = -\frac{1}{v_{dis}}\frac{y(1+zP^0)z_1e_2x_3^0}{(1+z_1E^0)^2}$$

$$\frac{\partial f_3}{\partial x_7^0} = \frac{y(1+zP^0)z_1e_3x_3^0}{(1+z_1E^0)^2} \qquad \frac{\partial f_4}{\partial x_7^0} = -\frac{1}{v_{dis}}\frac{y(1+zP^0)z_1e_3x_3^0}{(1+z_1E^0)^2}$$

$$\frac{\partial f_3}{\partial x_8^0} = 0 \qquad \frac{\partial f_4}{\partial x_8^0} = 0$$

$$\frac{\partial f_3}{\partial x_9^0} = 0 \qquad \frac{\partial f_4}{\partial x_9^0} = 0$$

$$\frac{\partial f_3}{\partial x_{10}^0} = 0 \qquad \frac{\partial f_4}{\partial x_{10}^0} = 0$$

$$\frac{\partial f_3}{\partial x_{11}^0} = 0 \qquad \frac{\partial f_4}{\partial x_{11}^0} = 0$$

$$\frac{\partial f_3}{\partial x_{12}^0} = -\frac{yzprx_3^0}{1+z_1E^0} \qquad \frac{\partial f_4}{\partial x_{12}^0} = \frac{1}{v_{dis}}\frac{yzprx_3^0}{1+z_1E^0}$$

$$\frac{\partial f_3}{\partial x_{13}^0} = -\frac{yzpr_2x_3^0}{1+z_1E^0} + \frac{y(1+zP^0)z_1e_4x_3^0}{(1+z_1E^0)^2} \qquad \frac{\partial f_4}{\partial x_{13}^0} = \frac{1}{v_{dis}}\left[\frac{yzpr_2x_3^0}{1+z_1E^0} - \frac{y(1+zP^0)z_1e_4x_3^0}{(1+z_1E^0)^2}\right]$$

where E^0 and P^0 are defined by the equations in (5.26)-(5.27).

$$\frac{\partial f_5}{\partial x_1^0} = 0 \qquad \frac{\partial f_6}{\partial x_1^0} = 0$$

$$\frac{\partial f_5}{\partial x_2^0} = b + c_1 x_5^0 \qquad \frac{\partial f_6}{\partial x_2^0} = 0$$

$$\frac{\partial f_5}{\partial x_3^0} = 0 \qquad \frac{\partial f_6}{\partial x_3^0} = 0$$

$$\frac{\partial f_5}{\partial x_4^0} = \frac{-c_2\alpha}{LH_0}\left(\frac{x_4^0}{LH_0}\right)^{\alpha-1} x_5^0 \qquad \frac{\partial f_6}{\partial x_4^0} = \frac{c_2\alpha}{LH_0}\left(\frac{x_4^0}{LH_0}\right)^{\alpha-1} x_5^0 + \left[\frac{c_3\beta}{LH_0}\left(\frac{x_4^0}{LH_0}\right)^{\beta-1} - \frac{c_4}{LH_0}\right] x_6^0$$

$$\frac{\partial f_5}{\partial x_5^0} = c_1 x_2^0 - c_2\left(\frac{x_4^0}{LH_0}\right)^{\alpha} \qquad \frac{\partial f_6}{\partial x_5^0} = c_2\left(\frac{x_4^0}{LH_0}\right)^{\alpha}$$

$$\frac{\partial f_5}{\partial x_6^0} = 0 \qquad \frac{\partial f_6}{\partial x_6^0} = c_3\left(\frac{x_4^0}{LH_0}\right)^{\beta} - c_4\frac{x_4^0}{LH_0}$$

$$\frac{\partial f_5}{\partial x_7^0} = 0 \qquad \frac{\partial f_6}{\partial x_7^0} = 0$$

$$\frac{\partial f_5}{\partial x_8^0} = 0 \qquad \frac{\partial f_6}{\partial x_8^0} = 0$$

$$\frac{\partial f_5}{\partial x_9^0} = 0 \qquad \frac{\partial f_6}{\partial x_9^0} = 0$$

$$\frac{\partial f_5}{\partial x_{10}^0} = 0 \qquad \frac{\partial f_6}{\partial x_{10}^0} = 0$$

$$\frac{\partial f_5}{\partial x_{11}^0} = 0 \qquad \frac{\partial f_6}{\partial x_{11}^0} = 0$$

$$\frac{\partial f_5}{\partial x_{12}^0} = 0 \qquad \frac{\partial f_6}{\partial x_{12}^0} = 0$$

$$\frac{\partial f_5}{\partial x_{13}^0} = 0 \qquad \frac{\partial f_6}{\partial x_{13}^0} = 0$$

$$\frac{\partial f_7}{\partial x_1^0} = 0 \qquad \frac{\partial f_8}{\partial x_1^0} = 0$$

$$\frac{\partial f_7}{\partial x_2^0} = 0 \qquad \frac{\partial f_8}{\partial x_2^0} = 0$$

$$\frac{\partial f_7}{\partial x_3^0} = 0 \qquad \frac{\partial f_8}{\partial x_3^0} = 0$$

$$\frac{\partial f_7}{\partial x_4^0} = \frac{c_4}{LH_0} x_6^0 - \frac{c_5 \gamma}{LH_0} \left(\frac{x_4^0}{LH_0} \right)^{\gamma - 1} x_7^0 \qquad \frac{\partial f_8}{\partial x_4^0} = \frac{c_5 \gamma}{LH_0} \left(\frac{x_4^0}{LH_0} \right)^{\gamma - 1} x_7^0$$

$$\frac{\partial f_7}{\partial x_5^0} = 0 \qquad \frac{\partial f_8}{\partial x_5^0} = 0$$

$$\frac{\partial f_7}{\partial x_6^0} = c_4 \left(\frac{x_4^0}{LH_0} \right) \qquad \frac{\partial f_8}{\partial x_6^0} = 0$$

$$\frac{\partial f_7}{\partial x_7^0} = -c_5 \left(\frac{x_4^0}{LH_0} \right)^{\gamma} \qquad \frac{\partial f_8}{\partial x_7^0} = c_5 \left(\frac{x_4^0}{LH_0} \right)^{\gamma}$$

$$\frac{\partial f_7}{\partial x_8^0} = 0 \qquad \frac{\partial f_8}{\partial x_8^0} = -d_1$$

$$\frac{\partial f_7}{\partial x_9^0} = 0 \qquad \frac{\partial f_8}{\partial x_9^0} = 0$$

$$\frac{\partial f_7}{\partial x_{10}^0} = 0 \qquad \frac{\partial f_8}{\partial x_{10}^0} = 0$$

$$\frac{\partial f_7}{\partial x_{11}^0} = 0 \qquad \frac{\partial f_8}{\partial x_{11}^0} = 0$$

$$\frac{\partial f_7}{\partial x_{12}^0} = 0 \qquad \frac{\partial f_8}{\partial x_{12}^0} = 0$$

$$\frac{\partial f_7}{\partial x_{13}^0} = 0 \qquad \frac{\partial f_8}{\partial x_{13}^0} = 0$$

$$
\begin{array}{lllll}
\frac{\partial f_9}{\partial x_1^0} = 0 & \frac{\partial f_{10}}{\partial x_1^0} = 0 & \frac{\partial f_{11}}{\partial x_1^0} = 0 & \frac{\partial f_{12}}{\partial x_1^0} = 0 & \frac{\partial f_{13}}{\partial x_1^0} = 0 \\
\frac{\partial f_9}{\partial x_2^0} = 0 & \frac{\partial f_{10}}{\partial x_2^0} = 0 & \frac{\partial f_{11}}{\partial x_2^0} = 0 & \frac{\partial f_{12}}{\partial x_2^0} = 0 & \frac{\partial f_{13}}{\partial x_2^0} = 0 \\
\frac{\partial f_9}{\partial x_3^0} = 0 & \frac{\partial f_{10}}{\partial x_3^0} = 0 & \frac{\partial f_{11}}{\partial x_3^0} = 0 & \frac{\partial f_{12}}{\partial x_3^0} = 0 & \frac{\partial f_{13}}{\partial x_3^0} = 0 \\
\frac{\partial f_9}{\partial x_4^0} = 0 & \frac{\partial f_{10}}{\partial x_4^0} = 0 & \frac{\partial f_{11}}{\partial x_4^0} = 0 & \frac{\partial f_{12}}{\partial x_4^0} = 0 & \frac{\partial f_{13}}{\partial x_4^0} = 0 \\
\frac{\partial f_9}{\partial x_5^0} = 0 & \frac{\partial f_{10}}{\partial x_5^0} = 0 & \frac{\partial f_{11}}{\partial x_5^0} = 0 & \frac{\partial f_{12}}{\partial x_5^0} = 0 & \frac{\partial f_{13}}{\partial x_5^0} = 0 \\
\frac{\partial f_9}{\partial x_6^0} = 0 & \frac{\partial f_{10}}{\partial x_6^0} = 0 & \frac{\partial f_{11}}{\partial x_6^0} = 0 & \frac{\partial f_{12}}{\partial x_6^0} = 0 & \frac{\partial f_{13}}{\partial x_6^0} = 0 \\
\frac{\partial f_9}{\partial x_7^0} = 0 & \frac{\partial f_{10}}{\partial x_7^0} = 0 & \frac{\partial f_{11}}{\partial x_7^0} = 0 & \frac{\partial f_{12}}{\partial x_7^0} = 0 & \frac{\partial f_{13}}{\partial x_7^0} = 0 \\
\frac{\partial f_9}{\partial x_8^0} = d_1 & \frac{\partial f_{10}}{\partial x_8^0} = 0 & \frac{\partial f_{11}}{\partial x_8^0} = 0 & \frac{\partial f_{12}}{\partial x_8^0} = 0 & \frac{\partial f_{13}}{\partial x_8^0} = 0 \\
\frac{\partial f_9}{\partial x_9^0} = -d_2 & \frac{\partial f_{10}}{\partial x_9^0} = d_2 & \frac{\partial f_{11}}{\partial x_9^0} = 0 & \frac{\partial f_{12}}{\partial x_9^0} = 0 & \frac{\partial f_{13}}{\partial x_9^0} = 0 \\
\frac{\partial f_9}{\partial x_{10}^0} = 0 & \frac{\partial f_{10}}{\partial x_{10}^0} = -k_1 & \frac{\partial f_{11}}{\partial x_{10}^0} = k_1 & \frac{\partial f_{12}}{\partial x_{10}^0} = 0 & \frac{\partial f_{13}}{\partial x_{10}^0} = 0 \\
\frac{\partial f_9}{\partial x_{11}^0} = 0 & \frac{\partial f_{10}}{\partial x_{11}^0} = 0 & \frac{\partial f_{11}}{\partial x_{11}^0} = -k_2 & \frac{\partial f_{12}}{\partial x_{11}^0} = k_2 & \frac{\partial f_{13}}{\partial x_{11}^0} = 0 \\
\frac{\partial f_9}{\partial x_{12}^0} = 0 & \frac{\partial f_{10}}{\partial x_{12}^0} = 0 & \frac{\partial f_{11}}{\partial x_{12}^0} = 0 & \frac{\partial f_{12}}{\partial x_{12}^0} = -k_3 & \frac{\partial f_{13}}{\partial x_{12}^0} = k_3 \\
\frac{\partial f_9}{\partial x_{13}^0} = 0 & \frac{\partial f_{10}}{\partial x_{13}^0} = 0 & \frac{\partial f_{11}}{\partial x_{13}^0} = 0 & \frac{\partial f_{12}}{\partial x_{13}^0} = 0 & \frac{\partial f_{13}}{\partial x_{13}^0} = -k_4
\end{array}
$$

$\frac{\partial g}{\partial x} = \frac{\partial f}{\partial x^0}$ is a continuous matrix. Therefore g is Lipschitz in x, and the system in (5.32)-(5.33) has a unique solution $x(t)$ on $[0\,,\,\widehat{\delta}]$. The method of steps guarantees the existence and uniqueness of a solution $x(t)$ for all $t \geq 0$ by stepping through intervals of length $\widehat{\delta} = min\{\delta_E, \delta_P, \delta_I\}$. For each interval the history is known and continuous and the partial derivatives (listed above) remain the same. Therefore the merged system has a unique solution $x(t)$ for all $t \in [0, \infty)$.

5.2 Numerical Solutions of the Merged System

Now that we have established the existence and uniqueness of solutions of the merged system when a continuous history is given, we can solve the system numerically in MatLab. A delay differential equation solver, dde23 [56], was used to solve the merged system using the parameter values obtained in Chapter 4 (see Tables 4.1, 4.2, 4.3, and 4.4). We opted to use a constant history $\phi(t) = \phi_0$ since $\phi(t)$ is defined for at most 2 days ($\delta = max\{\delta_E, \delta_P, \delta_I\} \leq 2$). We used the initial conditions from the pituitary and ovarian systems to form ϕ_0 since they yielded good approximations to the data. Graphs of the pituitary and ovarian hormones as predicted by the merged system are presented in Figures 5.1, 5.2 and 5.3.

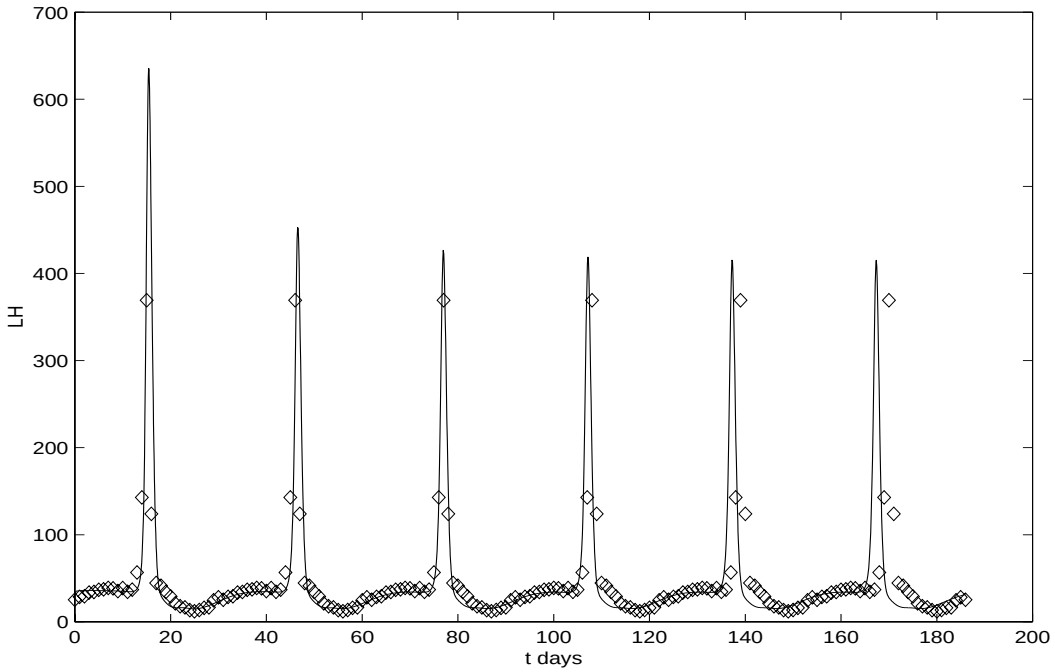

Figure 5.1: Graph of LH as predicted by the merged system where ∘ represent the data and — represents the solution curve.

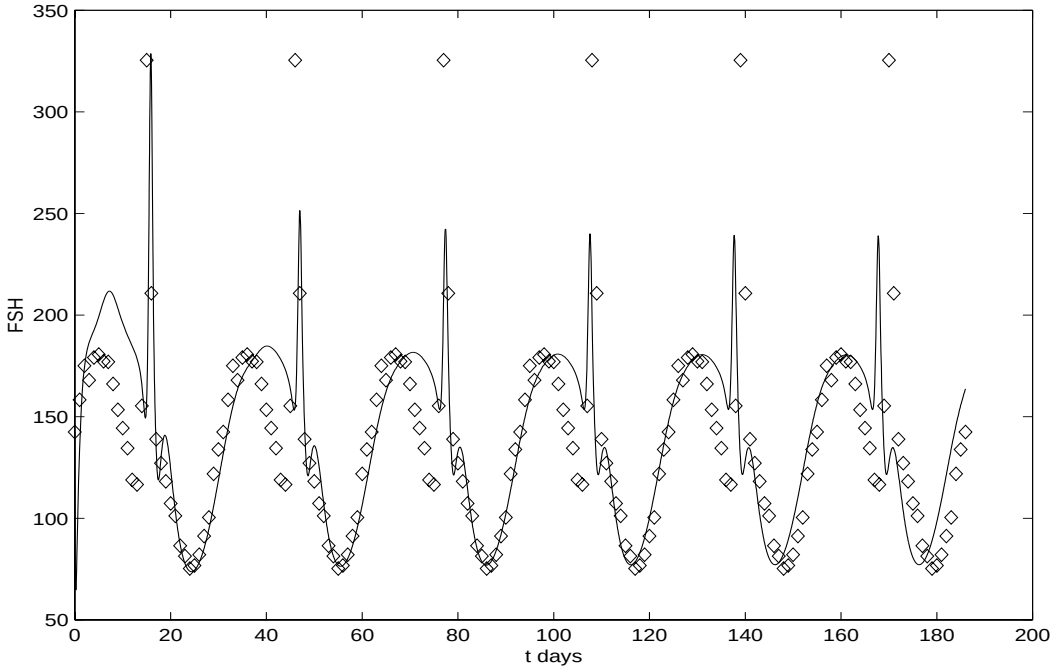

Figure 5.2: Graph of FSH as predicted by the merged system where ∘ represent the data and — represents the solution curve.

These graphs show that using the parameters and initial conditions from the unmerged model, the merged system reproduces the blood levels of the LH, E_2, P_4, and Ih presented in the McLachlan paper. However, the merged system does not reproduce the FSH profile very well near midcycle. During the late follicular phase (just before the gonadotropins surge) FSH blood levels do not decrease fast enough and do not drop low enough to match the data, and the FSH surge is not nearly as high as in the data. However, the merged system yields a good fit to the FSH data during the early-mid follicular phase and the luteal phase. Also notice that there is a second rise in FSH blood levels during the luteal phase as a result of the initial decline in inhibin blood levels at the end of the follicular phase (see Figure 5.3). Recall that the dependence of FSH on inhibin blood levels is delayed by two days.

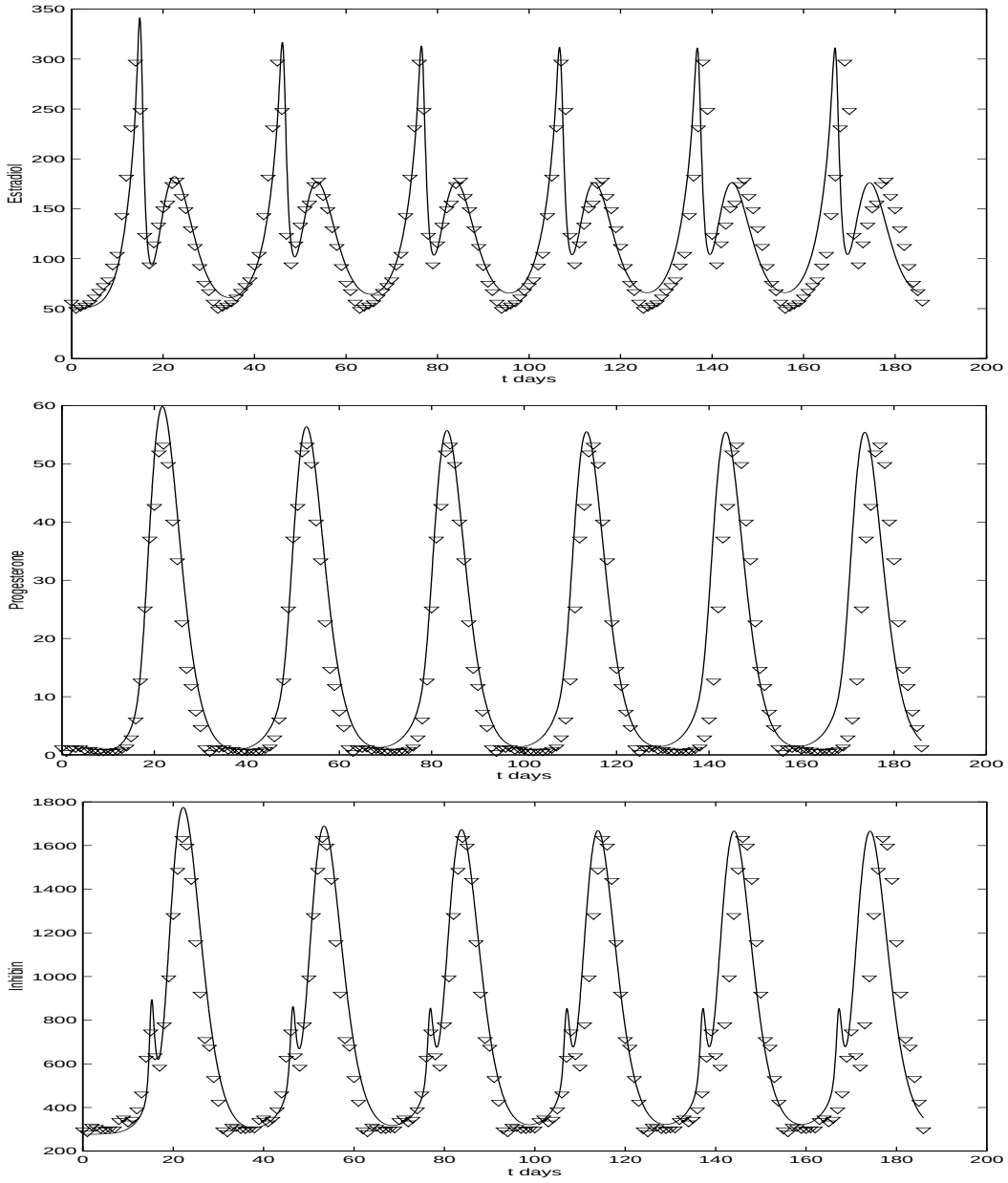

Figure 5.3: Graphs of the ovarian hormones predicted by the merged system where ∘ represent the data and — represents the solution curve.

The parameters used to solve the merged system were estimated over two periods of data using periodic input functions with period $\omega = 31$. However, the graphs in Figures 5.1, 5.2 and 5.3 suggest that solutions are converging to a periodic solution with period $\omega = 29.5$ (not $\omega = 31$ as we expected). The length $\omega = 29.5$ is consistent with the duration of an average menstrual cycle [3]. Incidentally, this period length is the length of a lunar month. Many researchers believe that there is some correlation between the lunar month and the menstrual cycle [16]. Since the FSH profile is different from what we expected, particularly the FSH surge, we decided to take a closer look at the FSH synthesis and release terms in (3.8)-(3.9) for the unmerged and merged systems. The graphs in Figure 5.4 compare the terms syn_{FSH} and rel_{FSH}

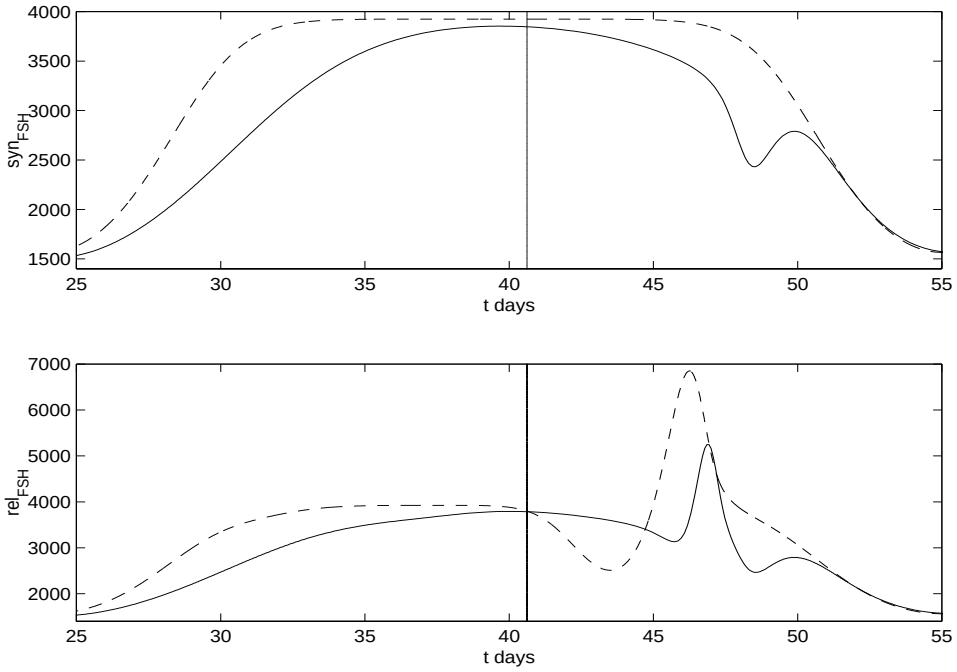

Figure 5.4: **Comparison of syn_{FSH} and rel_{FSH} in the unmerged FSH system and the merged system where the dashed curve represents the unmerged system and the solid curve represents the merged system.**

from the unmerged and merged systems. Here we see that in the unmerged (FSH) system, the late follicular phase is marked by a buildup of FSH in the pituitary caused by fairly constant synthesis rate and a decreasing release rate. In the merged system, however, a decreasing synthesis rate and a fairly constant release rate reduces the amount of FSH stored in the pituitary. The amount of FSH released into the blood is proportional to the amount held on reserve in the pituitary. Therefore a decline in estradiol blood levels induces the release of the FSH buildup and the surge of FSH blood levels at midcycle. For the merged system, the release of FSH into the bloodstream is slower and not as great as in the FSH system since the reserve pool is smaller.

5.3 Stability of Periodic Solutions

In this section we will provide evidence for the existence of a locally asymptotically stable periodic solution of the merged system that yields a good fit to the data in the McLachlan paper [41]. The graphs in Figures 5.1, 5.2, and 5.3 suggests that solutions of the merged system may be converging to such a periodic solution with period $\omega \approx 29.5$.

Recall that the merged system is a nonlinear, autonomous system of delay differential equations of the form:

$$x'(t) = f(x(t),\, x(t-\delta_1),\, x(t-\delta_2), \ldots, x(t-\delta_m)) \qquad \text{for } t \geq 0. \tag{5.34}$$

The linearization of (5.34) about a solution $x^*(t)$ is given by [20]:

$$x'(t) = A_0(t)\; x(t) + \sum_{i=1}^{m} A_i(t)\; x(t-\delta_i), \tag{5.35}$$

where

$$A_i(t) = \frac{\partial f}{\partial x^i}\,\Big|_{(x^*(t),x^*(t-\delta_1),\ldots,x^*(t-\delta_m)),} \qquad i = 0, \ldots, m. \tag{5.36}$$

In (5.36) the arguments of f are rewritten as $x^i(t) = x(t-\delta_i)$ for $i = 0, \ldots, m$ and $\delta_0 = 0$. The linear system in (5.35), called the **variational equation**, is used to determine the stability of steady state and periodic solutions of (5.34) [20].

A solution $x^*(t)$ of (5.34) is ω-periodic if $x^*(t+\omega) = x^*(t)$ for all t. Given an ω-periodic solution $x^*(t)$, the linearized system in (5.35) has time dependent coefficients with period ω. That is,

$$A_i(t+\omega) = A_i(t), \qquad i = 0, \ldots, m. \tag{5.37}$$

Let $x_\omega(t)$ be an $\omega-$periodic solution of the system in (5.34) with the initial function $x(t) = \phi(t)$ for $t \in [-\delta, 0]$ where $\delta = \max_{i=1}^{m} \delta_i$. The solution $x_\omega(t)$ depends on the initial condition $z_0 = \phi(0)$, therefore we can write $x_\omega(t) = x_\omega(t; z_0)$. The **monodromy matrix** M of the periodic solution is defined to be [22, 38, 55]:

$$M = \frac{\partial x_\omega(\omega; z_0)}{\partial z}. \tag{5.38}$$

The eigenvalues of the monodromy matrix are called the characteristic multipliers of the linearized system in (5.35) with respect to the periodic solution $x_\omega(t; z_0)$. In autonomous systems, 1 is always an eigenvalue of the monodromy matrix [20, 55]. It can be shown that if the other $n-1$ (nontrivial) eigenvalues of M all have moduli less than 1, then the zero solution of (5.35) is locally asymptotically stable (see [28] for a proof of this result). It can also be shown that if the zero solution of the linearized equation in (5.35) is locally asymptotically stable, then the $\omega-$periodic solution $x_\omega(t)$ of (5.34) is also locally asymptotically stable.

Therefore, we can determine the stability of a given periodic solution of (5.34) by calculating the monodromy matrix and finding its eigenvalues. In practice, a periodic solution of a nonlinear system of delay differential equations cannot be found explicitly. Instead, we must rely on numerical approximations to analyze the stability of periodic solutions. In order to determine the stability of a periodic solution of (5.34) we must follow these steps [21]:

1. Obtain an approximation of the unknown periodic solution $x_\omega(t)$ using a numerical method for solving boundary value problems (eg. collocation methods). Collocation methods approximate a solution $y(t)$ of (5.35) using functions of the form

$$u = \alpha_1 u_1 + \alpha_2 u_2 + \cdots + \alpha_k u_p \tag{5.39}$$

in terms of a basis u_i which spans the space of admissible functions [55, 57]. A mesh of p collocation points $\{t_k\}$ where $0 = t_0 < t_1 < \cdots < t_p = \omega$ are chosen so that the equation (5.35) is satisfied exactly at each point. Therefore the method of collocation is reduced to solving the p linear equations:

$$\sum_{j=1}^{p} \alpha_j \, u_j'(t_k) = \sum_{j=1}^{p} \alpha_j \sum_{i=0}^{m} A_i(t_k) \, u_j(t_k - \delta_i), \qquad k = 1, \ldots p, \tag{5.40}$$

for the coefficients $\alpha_1, \alpha_2, \ldots, \alpha_p$ [57].

2. Using the periodic solution from the first step, compute a discrete approximation of the monodromy matrix M and then find its eigenvalues [22, 38].

We will not perform such calculations in this work as they can be cumbersome and would divert attention from the focus of this section. Instead we will investigate the stability of the periodic solution by perturbing the original initial conditions used to solve the merged system. Table 5.1 lists the initial conditions used to solve the merged system. The initial conditions for the FSH, LH, and ovarian systems from Tables 4.5 and 4.6 were put together to form the merged system initial conditions.

Table 5.1: Varying the Initial Conditions in the Merged System

I.C.	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	x_{10}	x_{11}	x_{12}	x_{13}
1	0	140	0	1400	9	0	1	1	1	1	1	1	1
2	0	1400	0	10	9	10	1	1	1	1	1	1	1
3	0	10	1	1	9	100	1	1	1	1	1	1	1
4	1	1	600	600	9	1	0	1	1	1	1	1	1
5	600	600	140	0	9	1	20	1	1	1	1	1	1
6	140	0	1400	0	9	1	200	1	1	1	1	1	1
7	1400	0	10	0	9	1	1	1	1	1	1	1	0
8	10	0	0	140	9	1	1	1	1	1	1	1	15
9	352	142.5	600	25.34	9	0	0	0	0	0	0	0	0
10	352	142.5	600	25.34	9	10	0	0	0	0	0	0	0
11	352	142.5	600	25.34	1	500	1	1	1	1	1	1	1
12	352	142.5	600	25.34	1	1	300	1	1	1	1	1	1
13	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 5.5 shows that for a wide range of initial values the solutions to the merged system converge to the same periodic solution. Most of the solutions converge quickly, however there are a few that take up to 6 cycles to approach the periodic attractor. For example, initial condition #11 yields the solution with lower concentrations and initial condition #13 yields the solution with higher concentrations; both taking a longer time to approach the attractor. These numerical results suggest that there exists a periodic solution $x_\omega(t)$ with $\omega \approx 29.5$ that is locally asymptotically stable, however it would be very difficult to determine a region of stability in $\mathbb{R}^{13}$. Therefore in the next section we will further analyze the dynamics of the merged system by considering possible steady state solutions and bifurcations.

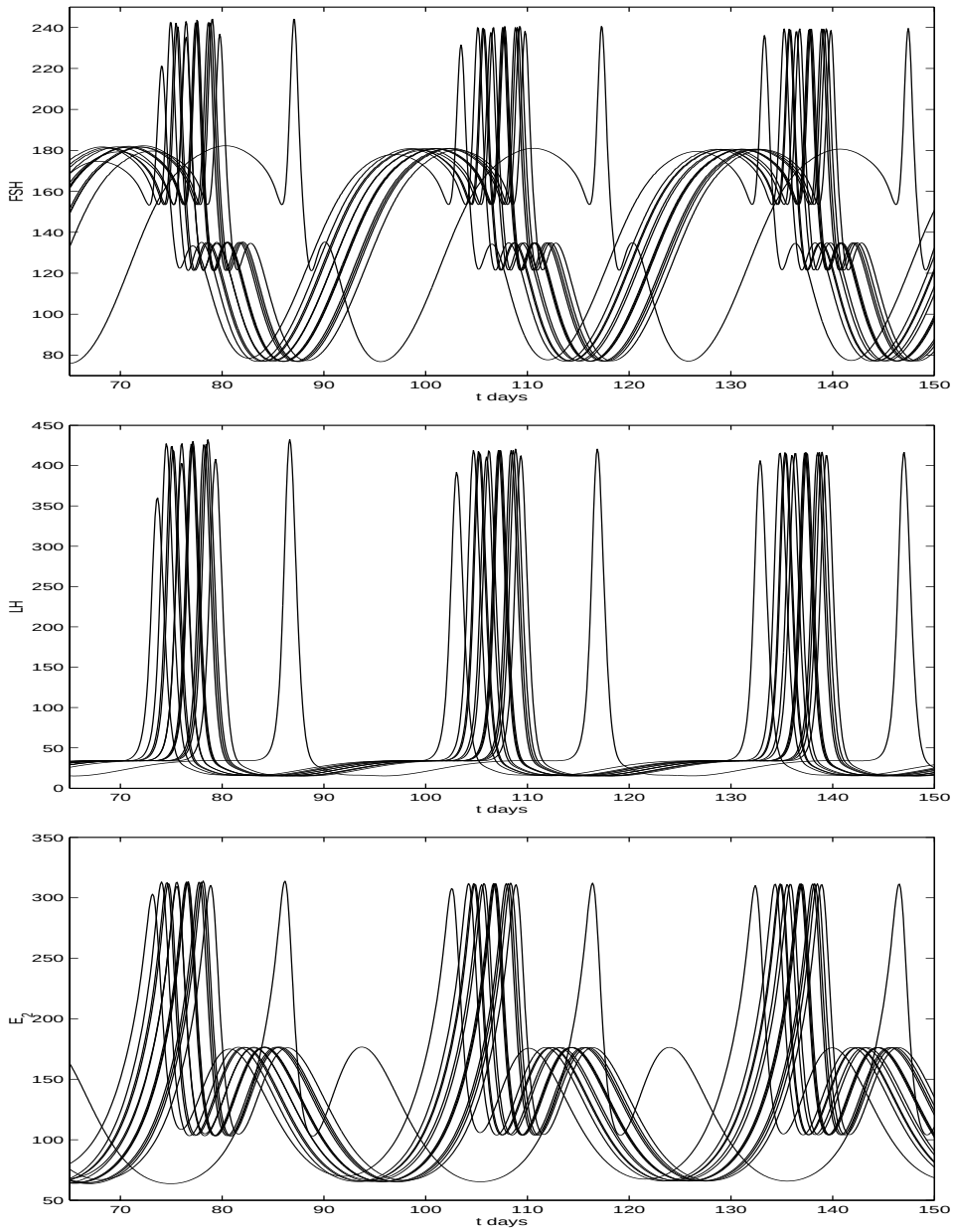

Figure 5.5: FSH, LH, and estradiol blood levels as a result of varying initial conditions in the merged system.

5.4 Stability of Steady States and Bifurcation Analysis

In this section we will study the existence of steady state solutions of the merged system and investigate whether bifurcations arise when certain parameters are varied. When we consider the existence of bifurcations we are concerned with changes in the stability of steady states solutions.

The merged system is a system of delay differential equations of the form (5.34), however the right hand side of (5.34) also depends on the parameters in the system. Therefore (5.34) can be rewritten in terms of the parameters $\rho = (\rho_1, \rho_2, \ldots, \rho_p)$ in the following way:

$$x'(t) = f(x(t),\, x(t-\delta_1),\, x(t-\delta_2), \ldots, x(t-\delta_m); \rho) \qquad \text{for } t \geq 0. \tag{5.41}$$

A solution $x^*(t)$ is called a steady state solution of (5.41) if $x^*(t) = x^*$ for all t and $f(x^*, x^*, \ldots, x^*; \rho) = 0$. In this case, the linearization in (5.35) becomes a linear system of delay differential equations with constant coefficients of the form [20, 21]:

$$x'(t) = A_0(\rho)\, x(t) + \sum_{i=1}^{m} A_i(\rho)\, x(t-\delta_i), \tag{5.42}$$

where

$$A_i(\rho) = \frac{\partial f}{\partial x^i}|_{(x^*,\ldots,x^*,\rho)}, \qquad i = 0, \ldots, m. \tag{5.43}$$

As with ordinary differential equations, we seek exponential solutions of the linearized system in (5.42)-(5.43) to determine the stability of steady state solutions of (5.41).

Suppose that $x(t) = e^{\lambda t}\, c$, $c \neq \vec{0}$ is a solution of (5.42).

$$\begin{aligned} x(t) = e^{\lambda t}\, c \text{ is a solution of (5.42).} &\iff \lambda e^{\lambda t} c = A_0(\rho)\, e^{\lambda t} c + \sum_{i=1}^{m} A_i(\rho)\, e^{\lambda(t-\delta_i)} c. \\ &\iff \lambda\, c = A_0(\rho)\, c + \sum_{i=1}^{m} A_i(\rho)\, e^{-\lambda\delta_i} c. \\ &\iff \left(\lambda\, - A_0(\rho) + \sum_{i=1}^{m} A_i(\rho)\, e^{-\lambda\delta_i}\right) c = 0. \\ &\iff \det(\lambda\, I - A_0(\rho) + \sum_{i=1}^{m} A_i(\rho)\, e^{-\lambda\delta_i}) = 0. \end{aligned}$$

The derived equation given by [20, 21]:

$$\det\left(\lambda\, I\; -\; A_0(\rho)\; +\; \sum_{i=1}^{m} A_i(\rho)\, e^{-\lambda\delta_i}\right) = 0 \tag{5.44}$$

is called the **characteristic equation** for the linearized system in (5.42). The stability of the steady state solution x^* of (5.41) is equivalent to the stability of the zero solution of (5.42). Therefore, the roots of the characteristic equation in (5.44) determine the stability of the steady state solution x^*. The characteristic equation has an infinite number of complex roots [18], hence the thought of determining the stability of a steady state might seem like an impossible task. However, the following results show that it is only necessary to find a finite number of roots. For proofs of these results see [18, 28].

THEOREM 5.1. *If there is a sequence $\{\lambda_j\}$ of solutions to the characteristic equation in (5.44) such that $|\lambda_j| \to \infty$ as $j \to \infty$, then $\Re e(\lambda_j) \to -\infty$ as $j \to \infty$. Thus, there exists an $\alpha \in \mathbb{R}$ such that all solutions of (5.44) satisfy $\Re e(\lambda) < \alpha$. In addition, given any $\mu \in \mathbb{R}$, the equation in (5.44) has no more than a finite number of roots λ such that $\Re e(\lambda) \geqq \mu$ (Driver [18], Hale [28]).*

THEOREM 5.2. *If* $\Re e(\lambda) < 0$ *for every solution of the characteristic equation, then* $\exists\ M > 0$ *and* $\gamma > 0$ *such that* $\|y(t)\| \leq M\|\phi\|e^{-\gamma t}\ \forall t \geq 0$ *provided that* $y(t) = \phi(t)$ *for* $t \in [-\delta, 0]$ *(Driver [18]).*

The merged system is a 13-dimensional nonlinear system, therefore it is difficult and often impossible to solve for steady state solutions explicitly. Numerically, it is even more difficult to latch onto an unstable steady state since approximations of the steady state would approach any stable attractors of the system. It is possible to vary some of the parameters in the system in search of a parameter set that yields a stable steady state solution. In this model we are concerned with oscillatory solutions, therefore we will determine whether Hopf bifurcations occur when varying parameters. A Hopf bifurcation occurs as a parameter is varied when a pair of eigenvalues corresponding to a branch of steady state solutions crosses the imaginary axis and leads to a branch of periodic solutions [21]. In this work we are concerned with stable periodic solutions of the merged system, therefore we will search for supercritical bifurcations. When a branch of steady state solutions loses stability at bifurcation giving rise to a branch of stable periodic solutions, the bifurcation is called **supercritical** [55].

When searching for bifurcations one parameter $\tilde{\rho} = \rho_i$ is varied while the others, $\rho_j\ \ j \neq i$, remain fixed. Therefore (5.41) can be written in terms of the parameter to be varied as:

$$x'(t) = f(x(t),\, x(t-\delta_1),\, x(t-\delta_2), \ldots, x(t-\delta_m); \tilde{\rho}) \qquad \text{for } t \geq 0. \tag{5.45}$$

A Hopf bifurcation occurs when the following hypotheses are satisfied [28]:

(H1) There exists an $x^* \in \mathbb{R}^n$ such that $f(x^*, \ldots, x^*, \tilde{\rho_0}) = 0$ for some $\tilde{\rho_0} \in \mathbb{R}$.

(H2) The characteristic equation in (5.44) has a single pair of purely imaginary roots $\lambda(\tilde{\rho_0}) = \pm\, i\, \beta_0$.

(H3) $\frac{d}{d\tilde{\rho}}\Re e\lambda(\tilde{\rho}_0) \neq 0$ in some neighborhood of $\tilde{\rho}_0$.

If (H1)-(H3) are satisfied, a branch of periodic solutions arises with increasing amplitudes. The periodic solution which appears just after bifurcation has small amplitude and an initial period of approximately $\frac{2\pi}{\beta_0}$ [28]. The value at which bifurcation occurs, $\tilde{\rho}_0$, is called the Hopf point.

We were able to find stable steady state solutions by varying some of the system parameters in the merged system. In this section we will present the results from varying the system parameters n, k_2, and d_{inh}. Using a MatLab package called DDE-BIFTOOL [20], we were able to analyze the merged system in search of Hopf bifurcations that might arise from varying these parameters. In Figure 5.6 we see that a Hopf bifurcation exists when varying the system parameter n, the maximal production rate of FSH. A branch of stable steady state solutions exists for $n \in (4800, 4832)$ and bifurcation occurs around $n_0 = 4832\ \mu g/day$. The first graph in Figure 5.6 shows the pair of eigenvalues, $\lambda(n)$, corresponding to the branch of steady state solutions as they cross the imaginary axis causing the branch of steady states to lose stability. These eigenvalues were found using DDE-BIFTOOL. The second graph in Figure 5.6 shows the branch of stable periodic solutions that arises from the Hopf bifurcation. The y-axis in Figure 5.6 (b) measures the amplitude of the first state variable for each periodic solution along the branch. At bifurcation, the purely imaginary eigenvalues of the steady state are $\lambda(n_0) = \pm 0.2047$. Therefore the stable periodic solution that appears just after bifurcation has period $\omega \approx \dfrac{2\pi}{0.2047} = 30.69$. Notice that the periodic solutions are increasing in amplitude (in the first component) as n increases to 5400 $\mu g/day$, then the amplitudes begin to decrease to zero. This suggests the existence of another Hopf point. Figure 5.7 shows that a second Hopf bifurcation occurs as n is increased.

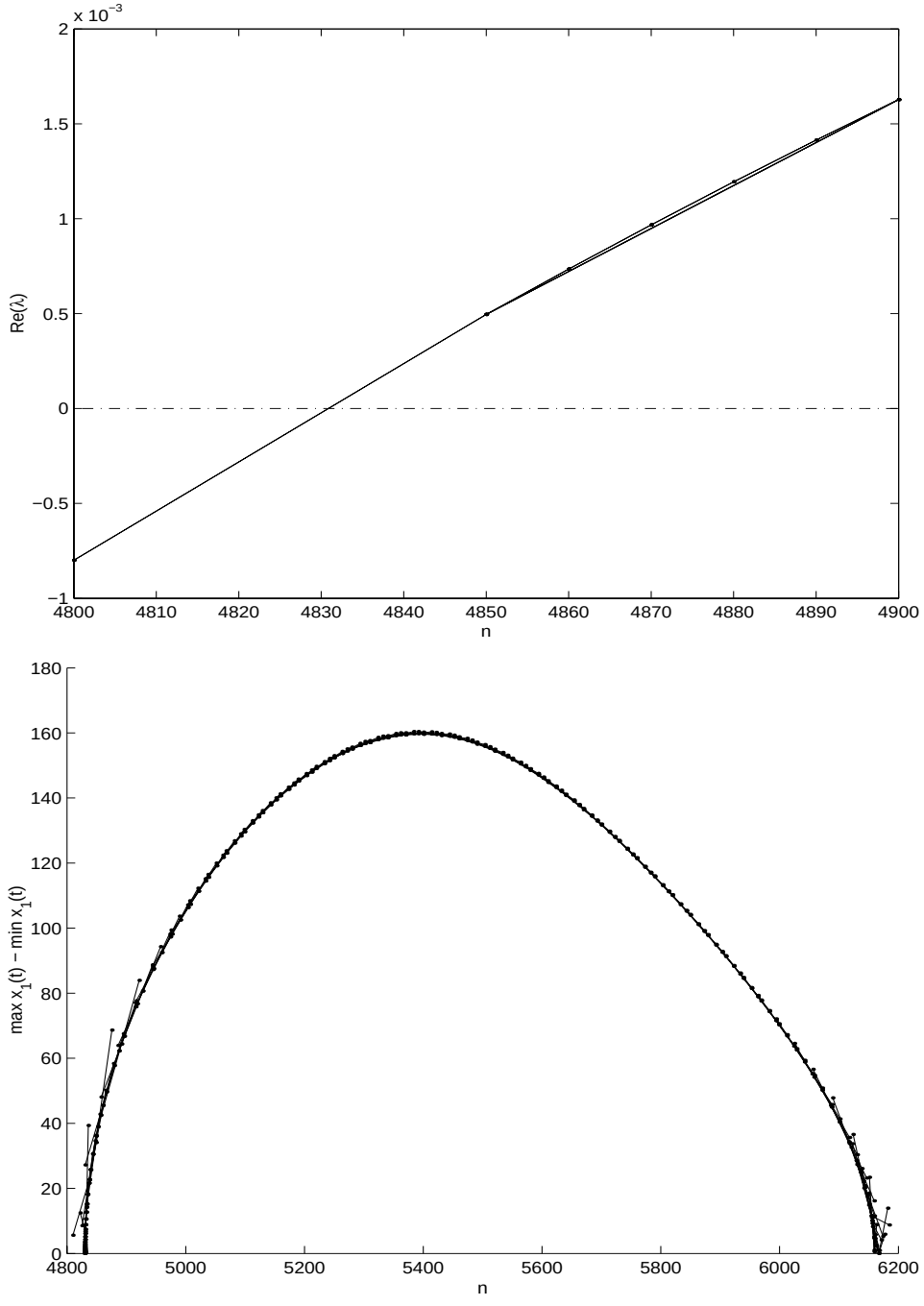

Figure 5.6: (a) Existence of Hopf bifurcation when varying n. (b) Branch of stable periodic solutions arising from the bifurcation.

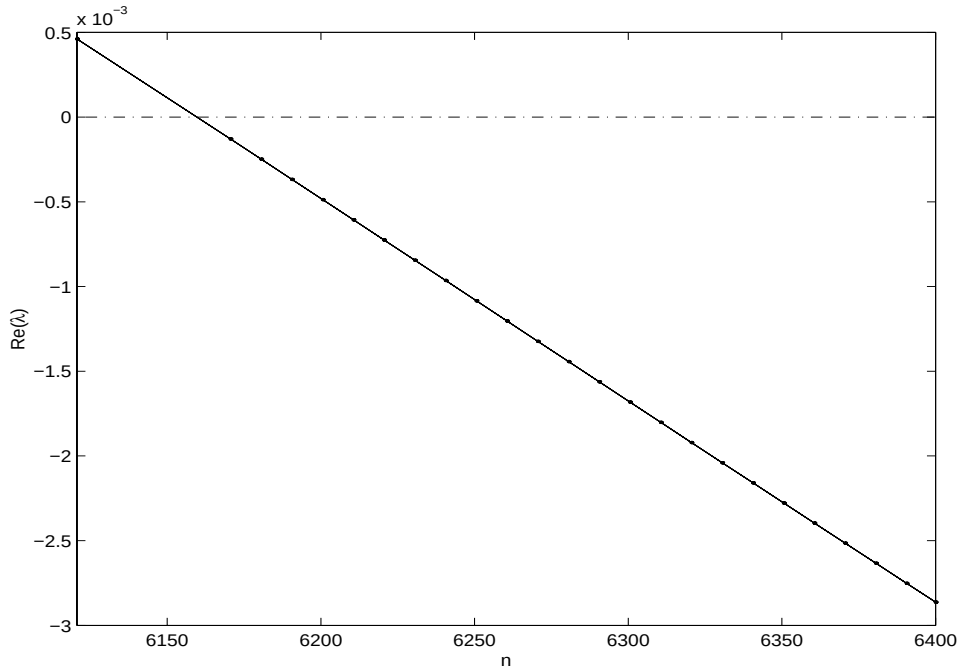

Figure 5.7: Existence of a second Hopf point when varying n.

From Figure 5.7 we see that the branch of stable periodic solutions loses stability to a branch of stable steady states around $n_1 = 6160\ \mu g/day$. This Hopf point has a pair of purely imaginary eigenvalues, $\lambda(n_1) = \pm 0.2777$, therefore the periodic solution just before bifurcation has period $\omega \approx \frac{2\pi}{0.2777} = 22.63$. (In this case, Hopf bifurcation occurs as n is decreased therefore periodic solutions arise to the left of bifurcation.) Notice that the original value of n is 5700 $\mu g/day$. Therefore the stable periodic solution arising from these Hopf bifurcations corresponding to the original parameter set has period ω such that $22.63 < \omega < 30.69$.

A Hopf bifurcation also occurs when varying k_2, a corpus luteum growth rate constant. The Hopf point is approximately $k_2 = 0.53\ day^{-1}$. The steady state at bifurcation has a pair of purely imaginary eigenvalues, $\lambda(0.53) = \pm 0.2548$. Figure 5.8 shows the branch of stable periodic solutions that arises when the branch of stable

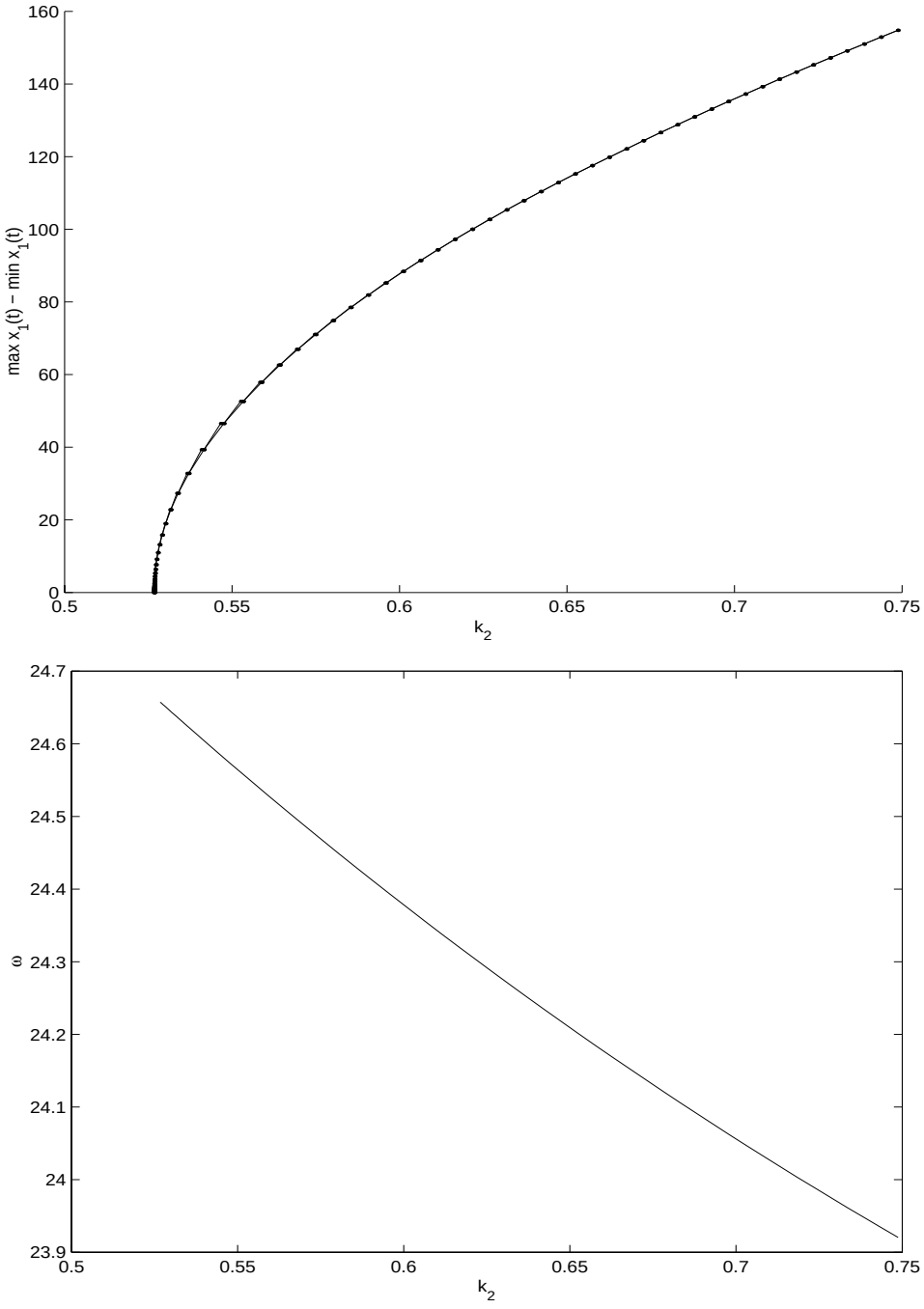

Figure 5.8: (a) Branch of stable periodic solutions arising from the bifurcation.(b) Period along branch of periodic solutions when varying k_2.

steady states loses stability. Therefore the stable periodic solution that appears just after bifurcation has period $\omega \approx \dfrac{2\pi}{0.2548} = 24.66$. A graph of the periods along the branch of stable periodic solutions is presented in Figure 5.8. Here we see that the periods along the branch are decreasing, therefore the stable periodic solution for the original parameter value $k_2 = 0.69\ day^{-1}$ arising from this bifurcation does not have period $\omega = 29.5$ as we expected. This stable periodic solution has period $\omega \approx 24.08$. These results provide evidence for the existence of a second stable periodic solution corresponding to the original merged system parameters. We will compare the two periodic solutions in Chapter 6.

It is also possible for bifurcation to arise when two merged system parameters are varied simultaneously. Figure 5.9 shows that branches of Hopf points exists in (k_2, d_{inh}) space and (n, k_2) space. The * in each graph represents the original parameter set in two space. Previously we determined that for the original parameter $k_2 = 0.69\ day^{-1}$ (along with the other fixed parameters), Hopf bifurcation occurred when varying n at $n = 4832\ \mu g/day$ and $n = 6160\ \mu g/day$. From the second graph in Figure 5.9 we see that two Hopf points exists for each k_2 in $[0.45, 0.69]$.

Remarks: The DDE-BIFTOOL package uses predictor-corrector methods to extend the branches of Hopf points and periodic solutions. For a description of these methods see [20, 38, 55].

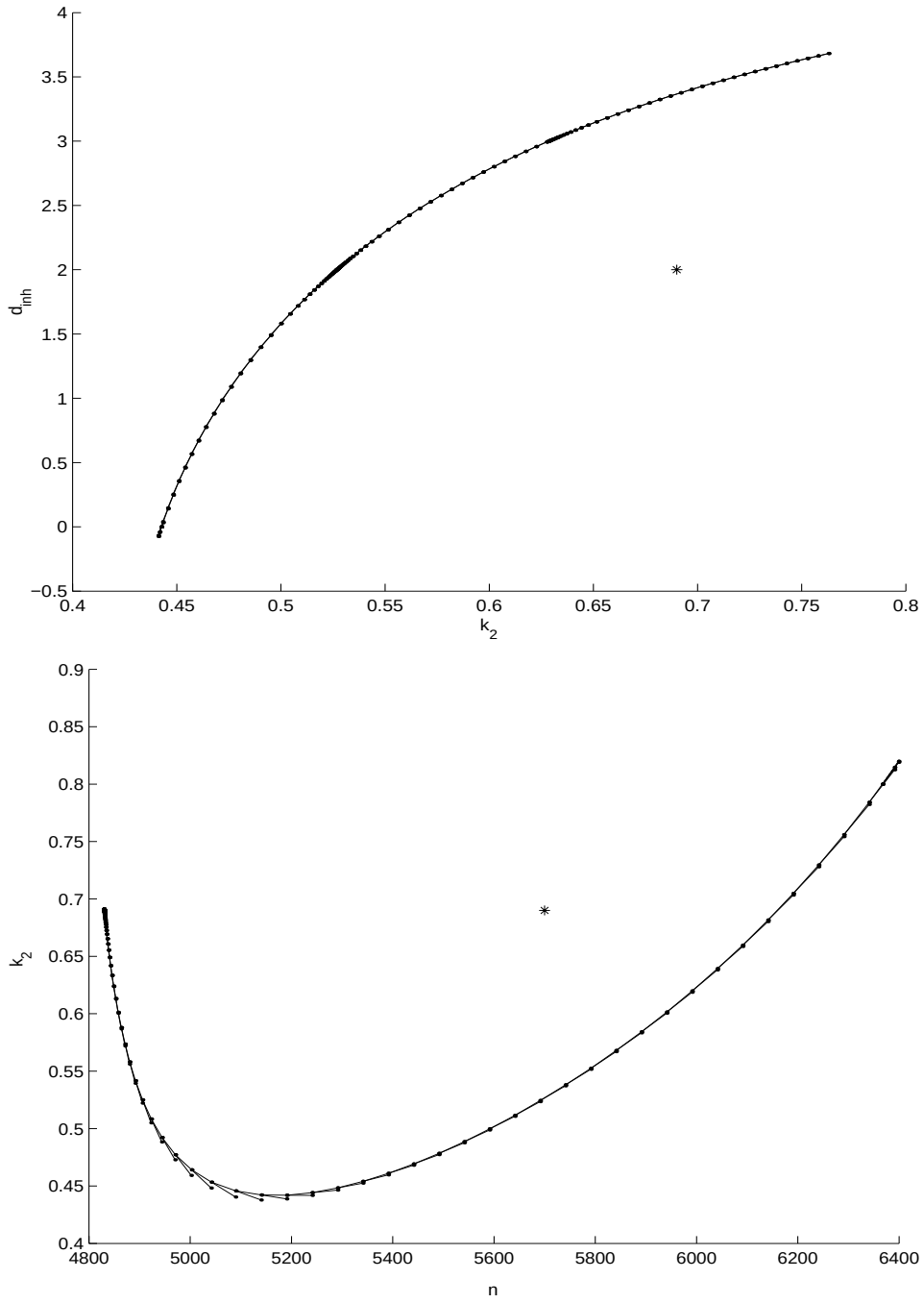

Figure 5.9: Branches of Hopf points in $[k_2, d_{inh}]$, $[n, k_2]$ space.

Chapter 6

Applications of the Merged Model

6.1 Abnormal Menstrual Cycles

In Chapter 5 we observed the existence of a second stable periodic solution other than the periodic solution that fits the data for normally cycling women. In this section we will further analyze this attractor and discuss its similarities to the results of endocrine disruptions. We will attempt to administer possible hormonal therapies to raise the hormone concentrations to normal levels.

A common abnormality of the menstrual cycle is amenorrhea, the absence of menstrual flow [45]. The infrequent occurrence of menstrual flow is called oligomenorrhea [5]. Amenorrhea is usually caused by ovulation failure due to any one of a variety of endocrine disorders, including hypo- and hyper-gonadotropic hypogonadism, and polycystic ovarian syndrome (PCOS) [5, 27]. Hypogonadotropic hypogonadism relates to a deficiency in gonadotropin secretion usually resulting from a defect of the hypothalamus and hypergonadotropic hypogonadism refers to increased secretion of FSH and/or LH due a disturbance in the negative feedback of ovarian hormones at the pituitary [5, 27]. Patients with hypergonadotropic hypogonadism fit into two categories, either menopause has occurred prematurely and ovarian follicles no longer

exist or the existing follicles are not responding to FSH and LH [27]. Polycystic ovarian syndrome is a disorder characterized by a buildup of growing ovarian follicles of which a dominant follicle is not chosen to ovulate [23]. These follicles form cysts in the ovary because the normal degenerative process for non-ovulatory follicles is disrupted. Elevated blood levels of LH, normal or low blood levels of FSH, "acyclic" or "sustained" levels of estradiol, and low levels of progesterone and inhibin are indicative of hormone abnormalities in women with PCOS [9, 63].

It has been shown that using the parameter set obtained in Section 4.2, the merged system has two stable periodic solutions. These solutions are graphed in Figures 6.1 and 6.2. The large amplitude solution fits the data for normally cycling women and the small amplitude solution arises from Hopf bifurcation in the system parameters. These solutions are a result of different initial conditions therefore the two stable periodic solutions have different domains of attraction. We believe that the small amplitude stable periodic solution is the result of an abnormality or disruption of the menstrual cycle, therefore we will refer to this cycle as the abnormal cycle. Further, we will refer to the periodic solution that fits that data of normally cycling women as the normal cycle.

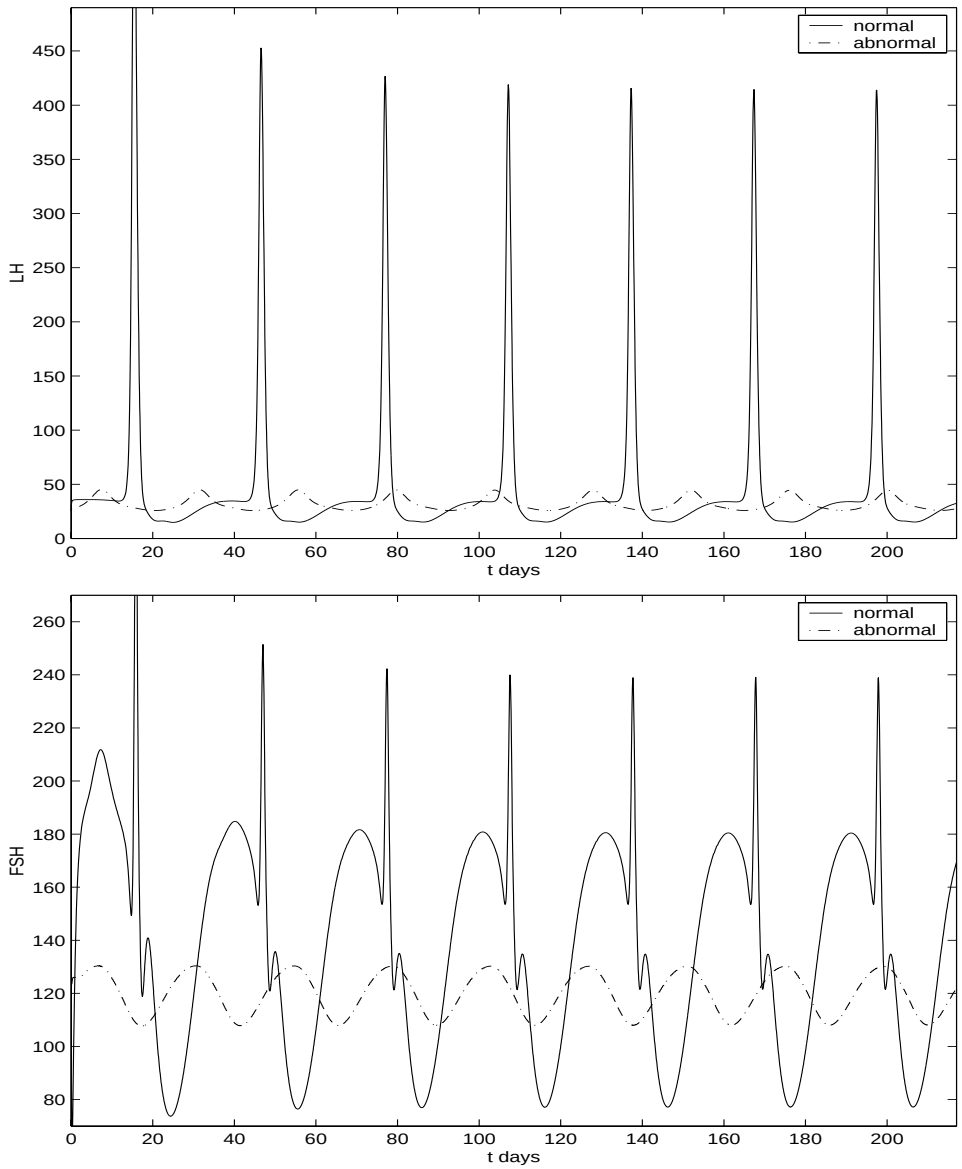

Figure 6.1: LH and FSH blood levels of the two stable periodic solutions as predicted by the merged system.

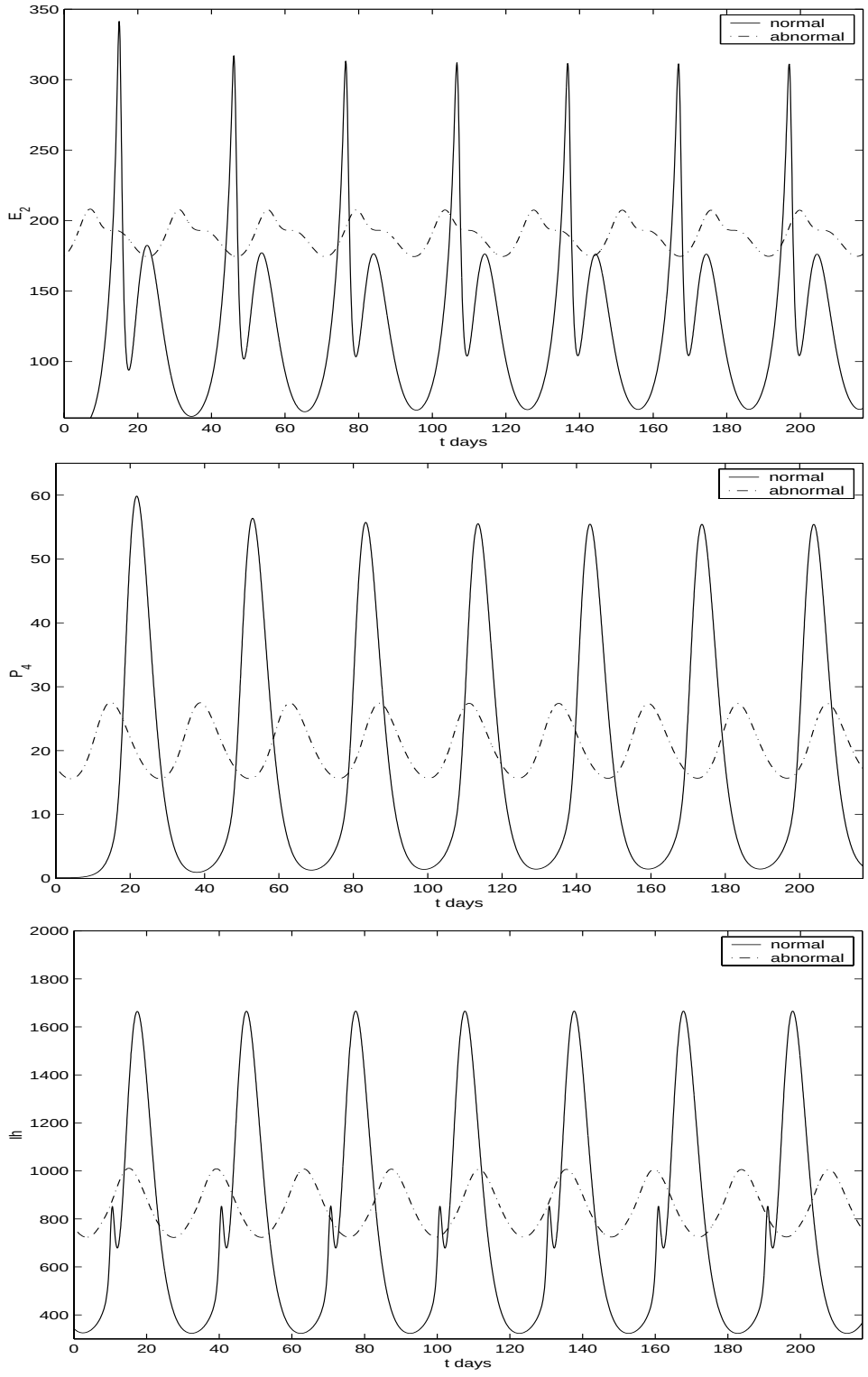

Figure 6.2: E_2, P_4, and Ih blood levels of the two stable periodic solutions as predicted by the merged system.

After conversations with Dr. Claude L. Hughes, a Reproductive Endocrinologist and Professor of Obstetrics and Gynecology at Duke University, we have determined that the hormone profiles of the abnormal cycle are characteristic of PCOS. Many women with PCOS suffer from amenorrhea and even oligomenorrhea because the mechanisms that control the menstrual cycle have been disrupted. As a result of low FSH blood levels, the growth rate of follicles selected to grow during the follicular phase of a given menstrual cycle is diminished. No dominant follicle is selected and, hence, the high E_2 synthesis rate is not achieved during the follicular phase. This effects the feedback loops to the pituitary. Gonadotropin blood levels do not surge and hence ovulation is suppressed. Women diagnosed with PCOS that have anovulatory cycles are treated with hormones that act to regulate follicular growth and the normal circulation of hormones [9, 11, 23, 48]. The hormonal profiles of the abnormal cycle of the merged system are similar to the hormonal abnormalities in women with PCOS. Therefore we will attempt to mimic progesterone treatments prescribed to PCOS patients to induce the pattern of hormone levels in the blood that occurs during a normal menstrual cycle.

6.1.1 Hormonal Therapy

Studies have shown that progesterone treatments that mimic the normal levels during the luteal phase of the cycle can restore normal ovulatory cycles [1, 9, 23, 24, 48]. In this section we will attempt to obtain normal hormone profiles as seen in the data from the administration of progesterone during the luteal phase of the abnormal cycle.

Progesterone Therapy

The abnormal cycle has an approximate period of 24 days. Estradiol levels peak on the 8th day of the cycle, therefore we assume that the follicular phase lasts for 8 days

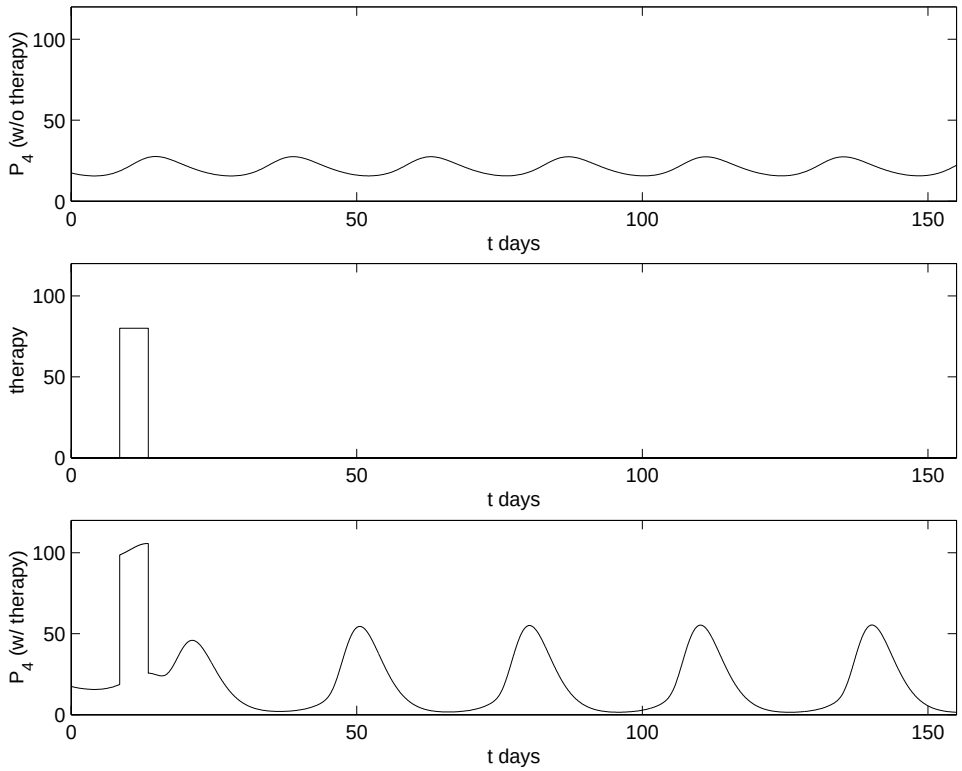

Figure 6.3: Restoring the normal circulation of hormones after 5 day progesterone treatment.

and the luteal phase lasts for 16 days. Figure 6.3 shows that administering progesterone for 5 days during the luteal phase of the cycle so that P_4 blood levels are elevated by $80\,nmol/L$ leads to the rapid recovery of the normal cycle (approximately 40 days). Figures 6.4 and 6.5 depict the changes in LH, FSH, E_2, and Ih after the treatment. Since $80\,nmol/L$ is much higher than normal levels of progesterone, we decided to lower the treatment to $50\,nmol/L$. This results in a slower recovery of the normal cycle (see Figures 6.6 and 6.7). If we reduce the treatment even further, say to $30\,nmol/L$, progesterone must be administered during the luteal phases of two consecutive cycles in order to recover the normal cycle.

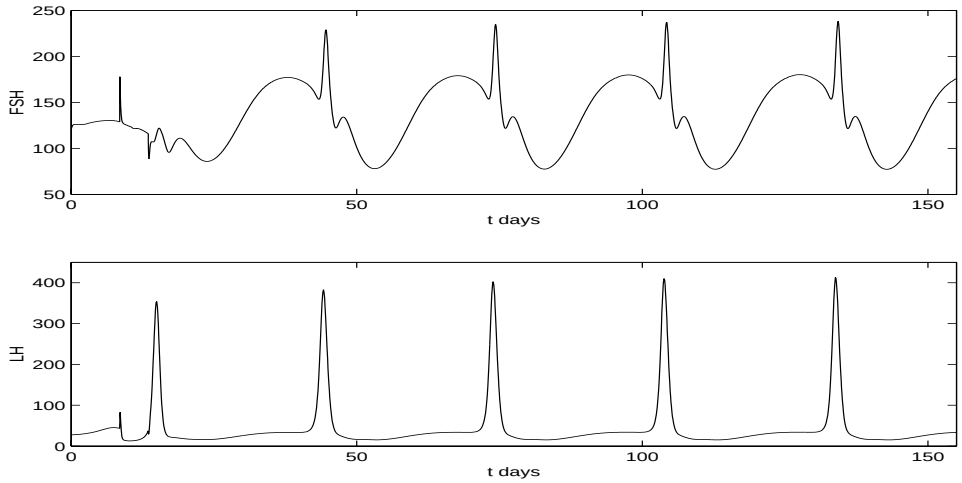

Figure 6.4: Pituitary hormones after the administration of $80\,nmol/L$ of progesterone (5 day treatment).

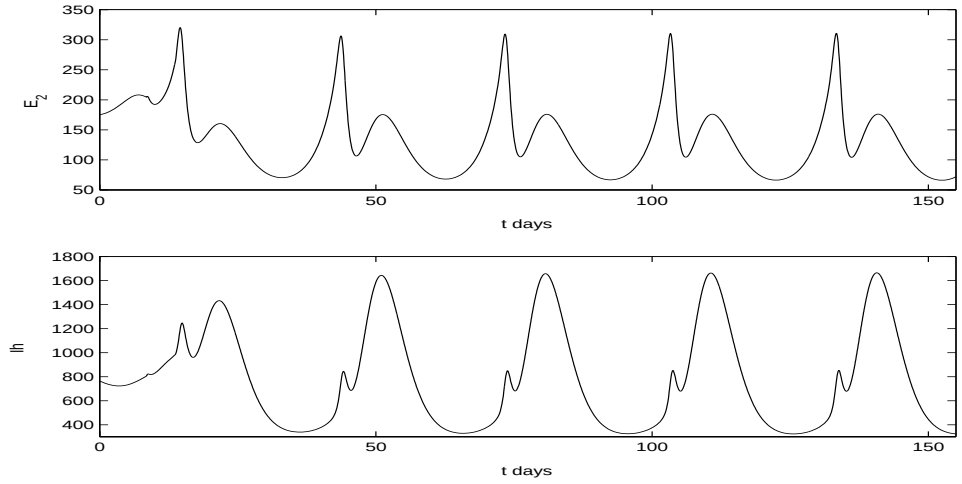

Figure 6.5: Ovarian hormones after the administration of $80\,nmol/L$ of progesterone (5 day treatment).

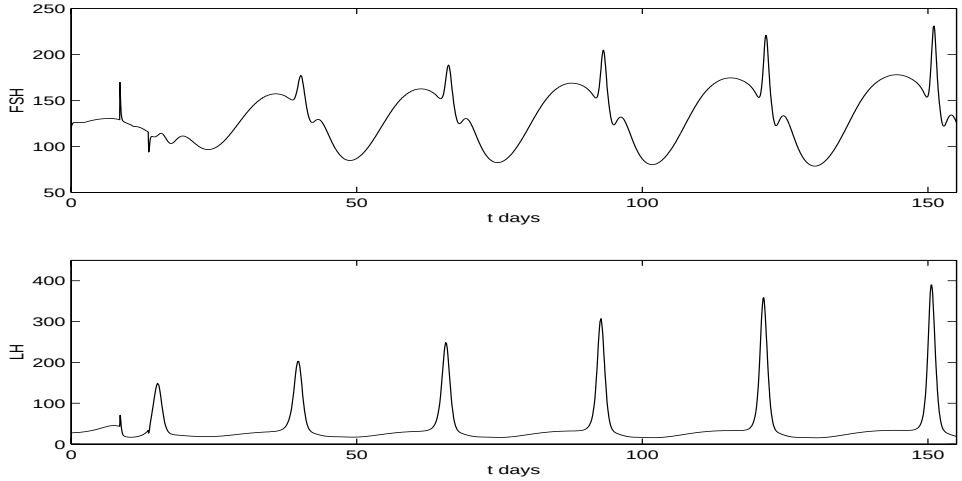

Figure 6.6: Pituitary hormones after the administration of $50\,nmol/L$ of progesterone (5 day treatment).

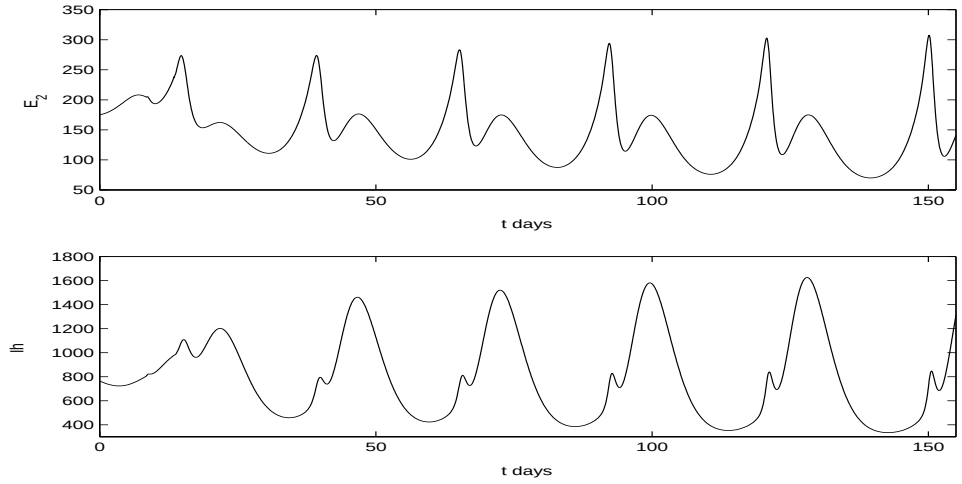

Figure 6.7: Ovarian hormones after the administration of $50\,nmol/L$ of progesterone (5 day treatment).

Estrogen Therapy

It is always possible that the abnormal cycle does not represent PCOS. Therefore we decided to look at other possible therapies. Since estradiol plays such an important role in maintaining a normal menstrual cycle, we decided to treat the abnormal cycle with estrogen during the follicular phase in an attempt to restore regular "ovulatory" behavior of the hormones. Estradiol blood levels produced by the abnormal cycle vary only slightly throughout the cycle. This suppresses the LH surge and the induction of ovulation, therefore we will administer estrogen in the follicular phase to stimulate ovulation.

Figure 6.8 shows that administering estrogen so that E_2 blood levels are elevated by $80\,ng/L$ for 5 days leads to the rapid recovery of the normal cycle (within 2 cycles).

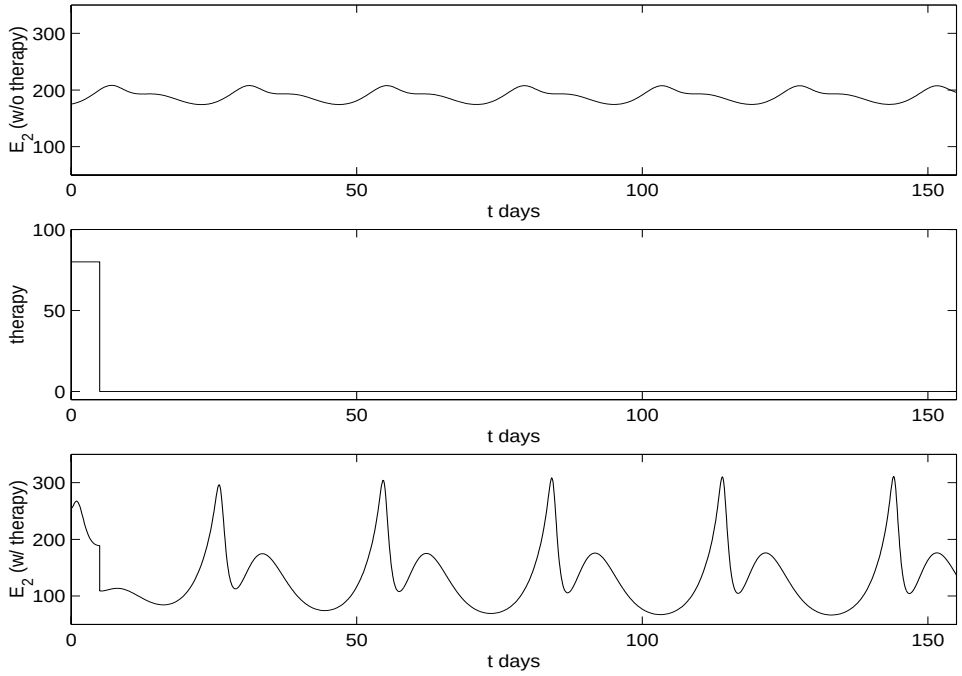

Figure 6.8: Restoring the normal circulation of hormones after 5 day estrogen treatment.

If we lower the treatment levels to $50\,ng/L$, we see that 5 days of treatment is not enough to recover the normal cycle. The number days must be increased to 10 and the recovery is still much slower than the 5 day treatment with $80\,ng/L$ (see Figure 6.9). Here the recovery time is about 8 cycles. The length of treatment can be increased

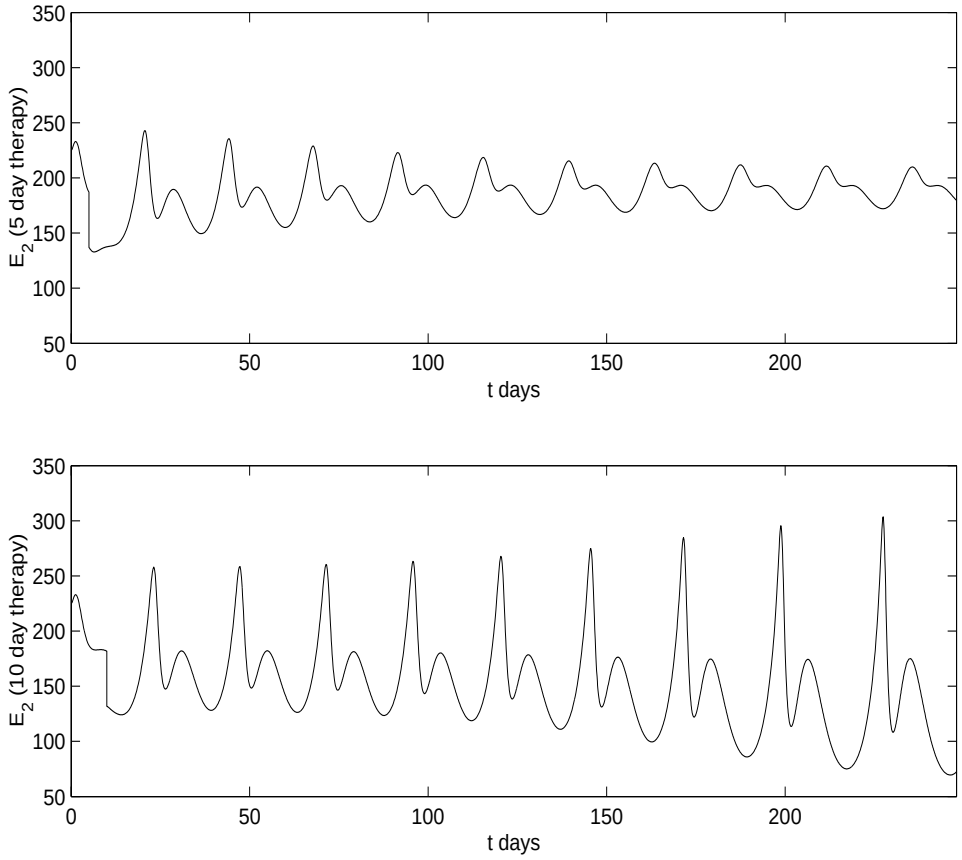

Figure 6.9: Estradiol levels after 5 and 10 day estrogen treatments ($50\,ng/L$).

to increase the recovery time, for example after 15 days of treatment the normal cycle is recovered in about 6 cycles. However, Figure 6.10 shows that if we increase the duration of the treatment to 20 days, the normal cycle is not recovered.

Here we see that exposure to exogenous estrogen for long periods of time leads to

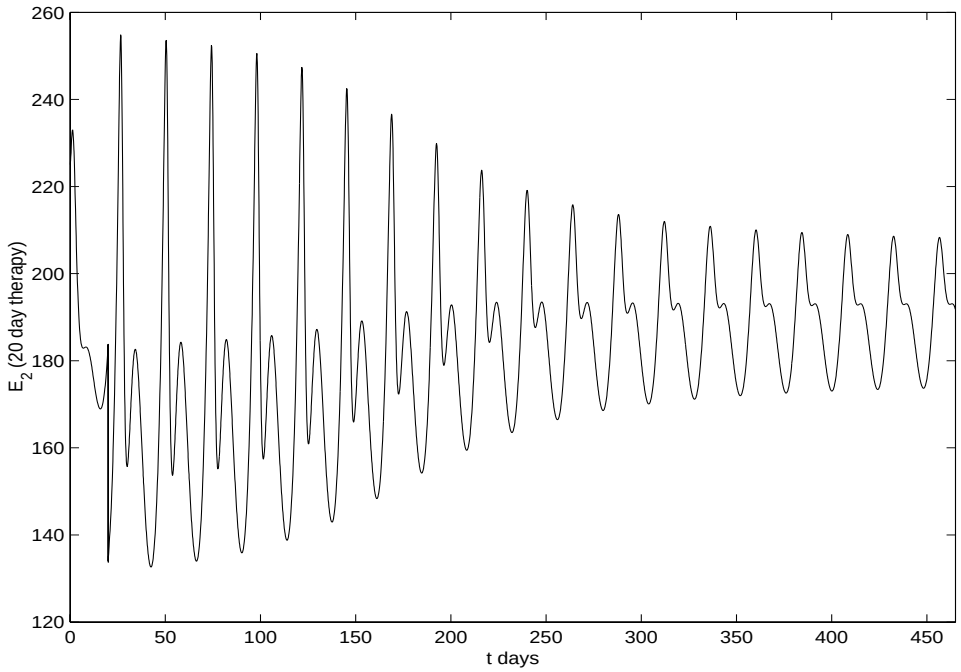

Figure 6.10: Normal cycle is not recovered after 20 day estrogen treatment.

abnormalities in the menstrual cycle. This suggests that treatments with higher doses of estrogen for shorter periods of time are more successful at recovering normal ovulatory cycles. This leads to the question of whether the normal cycle can be disrupted by an exposure to exogenous estrogen. Figure 6.11 shows that exposing the normal cycle to exogenous estrogen for a full cycle, followed by a full cycle with no exposure and then another full cycle of exposure can lead to abnormalities in the normal menstrual cycle. Notice that the length of exposure in this case is considerably greater than when the exposure occurred in the presence of abnormalities.

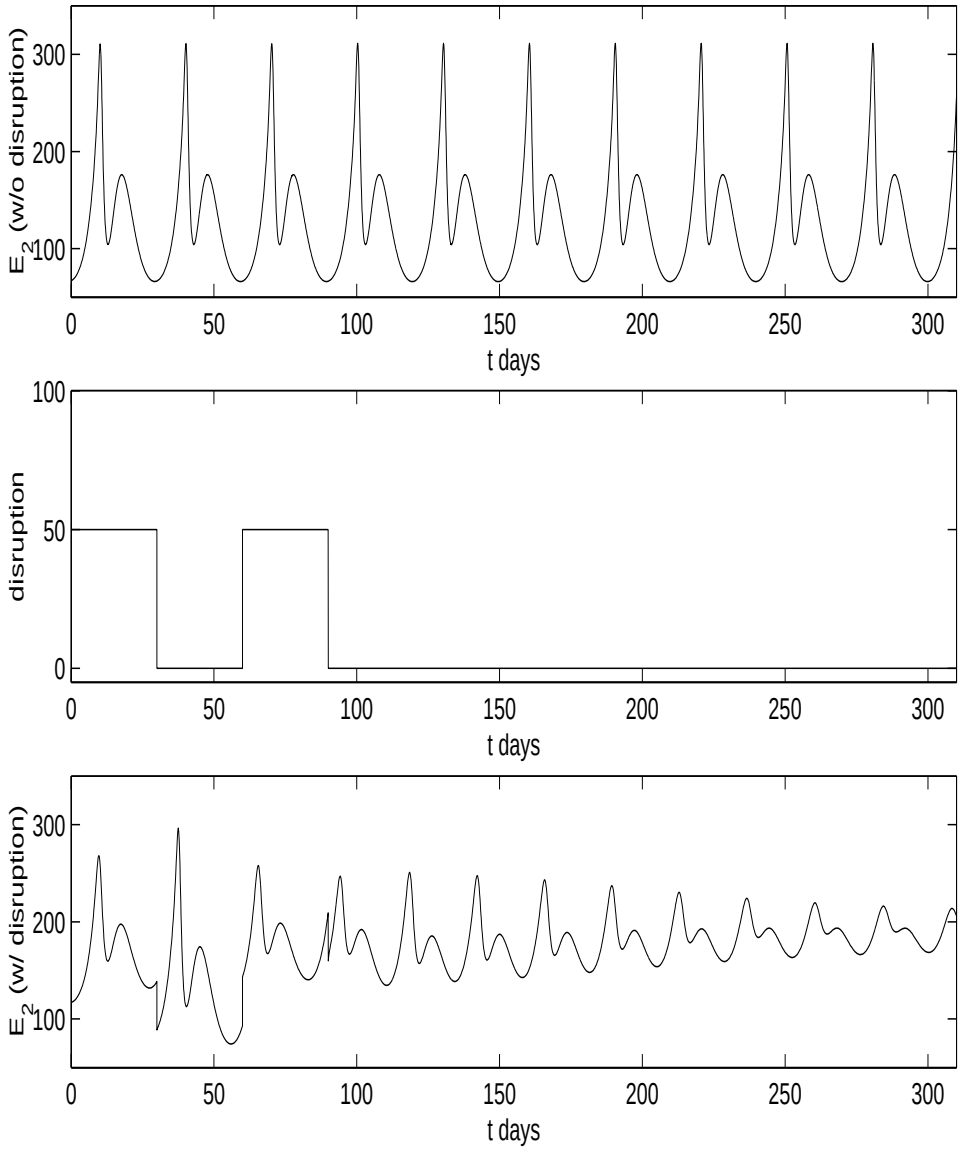

Figure 6.11: Disruption of the normal cycle by exogenous estrogen leads to abnormalities in the menstrual cycle.

Chapter 7

Dimensional Analysis and the Nondimensionalization Procedure

The process of transforming a system of differential equations with dimensional quantities into a system with dimensionless parameters and variables is called nondimensionalization. This process is performed by scaling the variables (independent and dependent) and parameters by groups of the existing system parameters [37]. There are several advantages to transforming a system of differential equations into a dimensionless system. Using a dimensionless system, one is able to determine the degrees of freedom of the system (ie. the number of independent parameters needed to define the system) [19, 31]. The degrees of freedom may turn out to be less than the number of parameters used in the original system. In that situation, the effect of varying one parameter in the original system may be compensated by varying another parameter [19]. If this is the case, nondimensionalizing the system can reduce the number of parameters used to accurately describe the behavior of the system. During this process the original parameters are not eliminated from the system. Instead, fewer dimensionless combinations of the system parameters are used to replace them [37]. In addition, the magnitudes of the dimensionless parameters can be compared to

determine whether terms may be eliminated from the system because their contribution to the overall dynamics of the system is small or negligible. In this chapter we will nondimensionalize the merged system and analyze the dimensionless system to determine whether the number of parameters and/or terms can be reduced from this system.

7.1 The Nondimensionalization Procedure

The process of nondimensionalizing a system of differential equations is outlined in the following steps [19, 37]:

Step 1. Set up charts that list the units for all of the system variables and parameters. These charts will be used to determine how the quantities in each equation should be scaled to create a dimensionless system.

Step 1a. Check that the dimensions of the left hand sides of the equations are equal to the dimensions of the right hand sides. This is called dimensional homogeneity.

Step 2. Express each dimensional variable as a dimensionless variable times a unit carrying constant. For example, given a dimensional variable $y = y(t)$, let

$$y = y^* \cdot \widehat{y},$$

where $y^* = y^*(t^*)$ is dimensionless and $\widehat{y}$ has the same dimensions as y.

Step 3. Substitute the new variables and constants into the system equations in place of the dimensional variables.

Step 4. Use the chain rule to determine the new system of equations in terms of the dimensionless ("starred") variables. By the chain rule, we have that

$$\frac{dy}{dt} = \frac{d(y^* \cdot \widehat{y})}{d(t^* \cdot \widehat{t})} = \frac{d}{dt^*}(y^* \cdot \widehat{y}) \cdot \frac{dt^*}{dt} = \widehat{y} \cdot \frac{dy^*}{dt^*} \cdot \frac{1}{\widehat{t}} = \frac{\widehat{y}}{\widehat{t}} \cdot \frac{dy^*}{dt^*}.$$

Step 5. Carefully choose values for the unit carrying ("hatted") constants.

Step 6. Create dimensionless parameters by grouping the remaining system parameters together.

Note: Reduction of the total number of parameters may be possible when the choices in Steps 5 and 6 are made wisely. The resulting system of equations consists of dimensionless variables and parameters.

7.2 The Dimensionless Merged System

In this section we will transform the merged system into a dimensionless system using the Nondimensionalization Procedure as outlined in the previous section. Charts listing the units for each quantity in the merged system can be found in Tables 7.1 and 7.2.

Table 7.1: **Description of the Merged System Variables**

Variable	**Quantity**	**Units**
RP_{FSH}	Amount(Mass) of FSH in the pituitary	μg
FSH	Concentration of FSH in the blood	$\mu g/L$
RP_{LH}	Amount(Mass) of LH in pituitary	μg
LH	Concentration of LH in the blood	$\mu g/L$
MsF	Mass of active follicular tissue during Menst. Foll. Stage	μg
SeF	Mass of active follicular tissue during Sec. Foll. Stage	μg
PrF	Mass of active follicular tissue during PreOv. Foll. Stage	μg
Sc_1	Mass of active follicular tissue during Ovulation	μg
Sc_2	Mass of active follicular tissue during Luteinization	μg
Lut_1	Mass of active luteal tissue during 1st Qtr. Luteal Stage	μg
Lut_2	Mass of active luteal tissue during 2nd Qtr. Luteal Stage	μg
Lut_3	Mass of active luteal tissue during 3rd Qtr. Luteal Stage	μg
Lut_4	Mass of active luteal tissue during 4th Qtr. Luteal Stage	μg
E_2	Concentration of E_2 in the blood	ng/L
P_4	Concentration of P_4 in the blood	$nmol/L$
Ih	Concentration of Ih in the blood	U/L

Table 7.2: **Description of the Merged System Parameters**

Parameter	**Quantity**	**Dimension**
n	maximal production rate of FSH	$\mu g/day$
p	inhibition constant for the production of FSH	U/L
q	rate constant for the release of FSH	day^{-1}
r	induction constant for the release of FSH	$L/nmol$
s	inhibition constant for the release of FSH	$(L/ng)^2$
δ_{Ih}	inhibin time delay	days
cl_F	clearance rate of FSH from the blood	day^{-1}
v_{dis}	volume of distribution	L
u	non-induced maximal production rate of LH	$\mu g/day$
v	maximal induction rate on the production of LH	$\mu g/day$
w	level of E_2 at half-max	ng/L
w_1	inhibition constant for the production of LH	$L/nmol$
y	rate constant for the release of LH	day^{-1}
z	induction constant for the release of LH	$L/nmol$
z_1	inhibition constant for the release of LH	L/ng
δ_E	estradiol time delay	days
δ_P	progesterone time delay	days
cl_L	clearance rate of LH from the blood	day^{-1}
h	Hill coefficient	dimensionless
α, β, γ	fractional exponents of LH stimulation	dimensionless
LH_0	unit of measurement of LH	$\mu g/L$
b	rate constant for the recruitment of inactive follicles	L/day
c_1	rate constant for the growth of MsF induced by FSH	$\frac{L/\mu g}{day}$

continued on the next page

Table 7.2: *continued*

Parameter	**Quantity**	**Dimension**
c_2	rate constant for the transfer of MsF into SeF	day^{-1}
c_3	rate constant for the growth of SeF	day^{-1}
c_4	rate constant for the transfer of SeF into PrF	day^{-1}
c_5	rate constant for ovulation induction	day^{-1}
d_1	rate constant for the transfer of Sc_1 into Sc_2	day^{-1}
d_2	rate constant for the transfer of Sc_2 into Lut_1	day^{-1}
k_1	rate constant for the transfer of Lut_1 into Lut_2	day^{-1}
k_2	rate constant for the transfer of Lut_2 into Lut_3	day^{-1}
k_3	rate constant for the transfer of Lut_3 into Lut_4	day^{-1}
k_4	rate constant for the degradation of Lut_4	day^{-1}
e_1	concentration of E_2 at basal level	ng/L
e_2	contribution rate of SeF to total E_2	$1/kL$
e_3	contribution rate of PrF to total E_2	$1/kL$
e_4	contribution rate of Lut_4 to total E_2	$1/kL$
pr	contribution rate of Lut_3 to total P_4	$\frac{nmol/L}{\mu g}$
pr_2	contribution rate of Lut_4 to total P_4	$\frac{nmol/L}{\mu g}$
h_1	concentration of Ih at basal level	U/L
h_2	contribution rate of PrF to total Ih	$\frac{U/L}{\mu g}$
h_3	contribution rate of Lut_3 to total Ih	$\frac{U/L}{\mu g}$
h_4	contribution rate of Lut_4 to total Ih	$\frac{U/L}{\mu g}$

Using the dimension charts in Tables 7.1 and 7.2 we need to check whether the merged system equations are dimensionally homogeneous. Recall that the merged system has

the form:

$$\frac{d}{dt}RP_{FSH} = \frac{n}{1+\dfrac{Ih(t-\delta_{Ih})}{p}} - \frac{q(1+rP_4)}{1+sE_2^2}\,RP_{FSH} \tag{7.2}$$

$$\frac{d}{dt}FSH = \frac{1}{v_{dis}}\frac{q(1+rP_4)}{1+sE_2^2}\,RP_{FSH} - cl_F FSH \tag{7.3}$$

$$\frac{d}{dt}RP_{LH} = \frac{u+\dfrac{vE_2(t-\delta_E)^h}{w^h+E_2(t-\delta_E)^h}}{1+\dfrac{P_4(t-\delta_P)}{w_1}} - \frac{y(1+zP_4)}{1+z_1E_2}\,RP_{LH} \tag{7.4}$$

$$\frac{d}{dt}LH = \frac{1}{v_{dis}}\frac{y(1+zP_4)}{1+z_1E_2}\,RP_{LH} - cl_L LH \tag{7.5}$$

$$\frac{d}{dt}MsF = bFSH + \left[c_1FSH - c_2\left(\frac{LH}{LH_0}\right)^{\alpha}\right]\,MsF \tag{7.6}$$

$$\frac{d}{dt}SeF = c_2\left(\frac{LH}{LH_0}\right)^{\alpha}MsF + \left[c_3\left(\frac{LH}{LH_0}\right)^{\beta} - c_4\frac{LH}{LH_0}\right]\,SeF \tag{7.7}$$

$$\frac{d}{dt}PrF = c_4\frac{LH}{LH_0}\,SeF - c_5\left(\frac{LH}{LH_0}\right)^{\gamma}PrF \tag{7.8}$$

$$\frac{d}{dt}Sc_1 = c_5\left(\frac{LH}{LH_0}\right)^{\gamma}PrF - d_1Sc_1 \tag{7.9}$$

$$\frac{d}{dt}Sc_2 = d_1Sc_1 - d_2Sc_2 \tag{7.10}$$

$$\frac{d}{dt}Lut_1 = d_2Sc_2 - k_1Lut_1 \tag{7.11}$$

$$\frac{d}{dt}Lut_2 = k_1Lut_1 - k_2Lut_2 \tag{7.12}$$

$$\frac{d}{dt}Lut_3 = k_2Lut_2 - k_3Lut_3 \tag{7.13}$$

$$\frac{d}{dt}Lut_4 = k_3Lut_3 - k_4Lut_4 \tag{7.14}$$

where

$$E_2 = e_1 + e_2SeF + e_3PrF + e_4Lut_4 \tag{7.15}$$

$$P_4 = prLut_3 + pr_2Lut_4 \tag{7.16}$$

$$Ih = h_1 + h_2PrF + h_3Lut_3 + h_4Lut_4 \tag{7.17}$$

By substituting the dimensions of each dimensional quantity into the system equations we will be able to determine whether the dimensions of the left hand sides of the equations are equal to the dimensions of the right hand sides. After substituting these dimensions, we obtain:

$$\frac{\mu g}{day} = \frac{d}{dt}RP_{FSH} = \frac{\frac{\mu g}{day}}{1+\frac{U/L}{U/L}} - \frac{\frac{1}{day}\cdot\left(1+\frac{L}{nmol}\cdot\frac{nmol}{L}\right)}{1+\left(\frac{L}{ng}\right)^2\cdot\left(\frac{ng}{L}\right)^2}\cdot\mu g$$

$$\frac{\mu g/L}{day} = \frac{d}{dt}FSH = \frac{1}{L}\cdot\frac{\frac{1}{day}\cdot\left(1+\frac{L}{nmol}\cdot\frac{nmol}{L}\right)}{1+\left(\frac{L}{ng}\right)^2\cdot\left(\frac{ng}{L}\right)^2}\cdot\mu g - \frac{1}{day}\cdot\frac{\mu g}{L}$$

$$\frac{\mu g}{day} = \frac{d}{dt}RP_{LH} = \frac{\frac{\mu g}{day}+\frac{\frac{\mu g}{day}\left(\frac{ng}{L}\right)^h}{\left(\frac{ng}{L}\right)^h+\left(\frac{ng}{L}\right)^h}}{1+\frac{nmol/L}{nmol/L}} - \frac{\frac{1}{day}\cdot\left(1+\frac{L}{nmol}\cdot\frac{nmol}{L}\right)}{1+\frac{L}{ng}\cdot\frac{ng}{L}}\cdot\mu g$$

$$\frac{\mu g/L}{day} = \frac{d}{dt}LH = \frac{1}{L}\cdot\frac{\frac{1}{day}\cdot\left(1+\frac{L}{nmol}\cdot\frac{nmol}{L}\right)}{1+\frac{L}{ng}\cdot\frac{ng}{L}}\cdot\mu g - \frac{1}{day}\cdot\frac{\mu g}{L}$$

$$\begin{aligned}
\frac{\mu g}{day} &= \frac{d}{dt}MsF &&= \frac{L}{day}\cdot\frac{\mu g}{L}+\left[\frac{L/\mu g}{day}\cdot\frac{\mu g}{L}-\frac{1}{day}\cdot\left(\frac{\mu g/L}{\mu g/L}\right)^{\alpha}\right]\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}SeF &&= \frac{1}{day}\cdot\left(\frac{\mu g/L}{\mu g/L}\right)^{\alpha}\cdot\mu g+\left[\frac{1}{day}\cdot\left(\frac{\mu g/L}{\mu g/L}\right)^{\beta}-\frac{1}{day}\cdot\frac{\mu g/L}{\mu g/L}\right]\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}PrF &&= \frac{1}{day}\cdot\frac{\mu g/L}{\mu g/L}\cdot\mu g-\frac{1}{day}\cdot\left(\frac{\mu g/L}{\mu g/L}\right)^{\gamma}\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}Sc_1 &&= \frac{1}{day}\cdot\left(\frac{\mu g/L}{\mu g/L}\right)^{\gamma}\cdot\mu g-\frac{1}{day}\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}Sc_2 &&= \frac{1}{day}\cdot\mu g-\frac{1}{day}\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}Lut_1 &&= \frac{1}{day}\cdot\mu g-\frac{1}{day}\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}Lut_2 &&= \frac{1}{day}\cdot\mu g-\frac{1}{day}\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}Lut_3 &&= \frac{1}{day}\cdot\mu g-\frac{1}{day}\cdot\mu g\\
\frac{\mu g}{day} &= \frac{d}{dt}Lut_4 &&= \frac{1}{day}\cdot\mu g-\frac{1}{day}\cdot\mu g
\end{aligned}$$

$$\begin{aligned}
\frac{ng}{L} &= E_2 &&= \frac{ng}{L}+\frac{1}{kL}\cdot\mu g+\frac{1}{kL}\cdot\mu g+\frac{1}{kL}\cdot\mu g\\
\frac{nmol}{L} &= P_4 &&= \frac{nmol/L}{\mu g}\cdot\mu g+\frac{nmol/L}{\mu g}\cdot\mu g\\
\frac{U}{L} &= Ih &&= \frac{U}{L}+\frac{U/L}{\mu g}\cdot\mu g+\frac{U/L}{\mu g}\cdot\mu g+\frac{U/L}{\mu g}\cdot\mu g
\end{aligned}$$

Therefore the merged system is dimensionally homogeneous and each dimensional variable can be expressed as the product of a dimensionless variable and a unit-carrying constant. The new variables and constants to be substituted into the merged system for the original dimensional variables are listed in Table 7.3.

Table 7.3: Merged System Variable Substitutions

Variable	**Dimensionless Variable**	$\times$	**Unit Carrying Constant**
t	t^*	$\times$	$\widehat{t}$
RP_{FSH}	RP^*_{FSH}	$\times$	$\widehat{RP_{FSH}}$
FSH	FSH	$\times$	$\widehat{FSH}$
RP_{LH}	RP^*_{LH}	$\times$	$\widehat{RP_{LH}}$
LH	LH^*	$\times$	$\widehat{LH}$
MsF	MsF^*	$\times$	$\widehat{MsF}$
SeF	SeF^*	$\times$	$\widehat{SeF}$
PrF	PrF^*	$\times$	$\widehat{PrF}$
Sc_1	Sc^*_1	$\times$	$\widehat{Sc_1}$
Sc_2	Sc^*_2	$\times$	$\widehat{Sc_2}$
Lut_1	Lut^*_1	$\times$	$\widehat{Lut_1}$
Lut_2	Lut^*_2	$\times$	$\widehat{Lut_2}$
Lut_3	Lut^*_3	$\times$	$\widehat{Lut_3}$
Lut_4	Lut^*_4	$\times$	$\widehat{Lut_4}$
E_2	E^*_2	$\times$	$\widehat{E_2}$
P_4	P^*_4	$\times$	$\widehat{P_4}$
Ih	Ih^*	$\times$	$\widehat{Ih}$

After making the appropriate substitutions, we obtain:

$$\frac{d(RP^*_{FSH}\cdot\widehat{RP_{FSH}})}{d(t^*\cdot\widehat{t})} = \frac{n}{1+\dfrac{\widehat{Ih}Ih^*(t^*-\delta^*_{Ih})}{p}} \;-\; \frac{q(1+rP^*_4\widehat{P_4})}{1+s(E^*_2\widehat{E_2})^2}\; RP^*_{FSH}\cdot\widehat{RP_{FSH}}$$

$$\frac{d(FSH^*\cdot\widehat{FSH})}{d(t^*\cdot\widehat{t})} = \frac{1}{v_{dis}}\frac{q(1+rP^*_4\widehat{P_4})}{1+s(E^*_2\widehat{E_2})^2}\; RP^*_{FSH}\cdot\widehat{RP_{FSH}} \;-\; cl_F FSH^*\cdot\widehat{FSH}$$

$$\frac{d(RP^*_{LH}\cdot\widehat{RP_{LH}})}{d(t^*\cdot\widehat{t})} = \frac{u+\dfrac{v(\widehat{E_2}E^*_2(t^*-\delta^*_E))^h}{w^h+(\widehat{E_2}E^*_2(t^*-\delta^*_E))^h}}{1+\dfrac{\widehat{P_4}P^*_4\,(t^*-\delta^*_P)}{w_1}} \;-\; \frac{y(1+zP^*_4\widehat{P_4})}{1+z_1E^*_2\widehat{E_2}}\; RP^*_{LH}\cdot\widehat{RP_{LH}}$$

$$\frac{d(LH^*\cdot\widehat{LH})}{d(t^*\cdot\widehat{t})} = \frac{1}{v_{dis}}\frac{y(1+zP^*_4\widehat{P_4})}{1+z_1E^*_2\widehat{E_2}}\; RP^*_{LH}\cdot\widehat{RP_{LH}} \;-\; cl_L LH^*\cdot\widehat{LH}$$

$$\frac{d(MsF^*\cdot\widehat{MsF})}{d(t^*\cdot\widehat{t})} = bFSH^*\cdot\widehat{FSH} + \left[c_1FSH^*\cdot\widehat{FSH} - c_2\left(\frac{LH^*\cdot\widehat{LH}}{LH_0}\right)^{\alpha}\right]\; MsF^*\cdot\widehat{MsF}$$

$$\frac{d(SeF^*\cdot\widehat{SeF})}{d(t^*\cdot\widehat{t})} = c_2\left(\frac{LH^*\cdot\widehat{LH}}{LH_0}\right)^{\alpha} MsF^*\cdot\widehat{MsF} + \left[c_3\left(\frac{LH^*\cdot\widehat{LH}}{LH_0}\right)^{\beta} - c_4\,\frac{LH^*\cdot\widehat{LH}}{LH_0}\right]\; SeF^*\cdot\widehat{SeF}$$

$$\frac{d(PrF^*\cdot\widehat{PrF})}{d(t^*\cdot\widehat{t})} = c_4\,\frac{LH^*\cdot\widehat{LH}}{LH_0}\; SeF^*\cdot\widehat{SeF} - c_5\left(\frac{LH^*\cdot\widehat{LH}}{LH_0}\right)^{\gamma} PrF^*\cdot\widehat{PrF}$$

$$\frac{d(Sc^*_1\cdot\widehat{Sc_1})}{d(t^*\cdot\widehat{t})} = c_5\left(\frac{LH^*\cdot\widehat{LH}}{LH_0}\right)^{\gamma} PrF^*\cdot\widehat{PrF} - d_1Sc^*_1\cdot\widehat{Sc_1}$$

$$\frac{d(Sc^*_2\cdot\widehat{Sc_2})}{d(t^*\cdot\widehat{t})} = d_1Sc^*_1\cdot\widehat{Sc_1} - d_2Sc^*_2\cdot\widehat{Sc_2}$$

$$\frac{d(Lut^*_1\cdot\widehat{Lut_1})}{d(t^*\cdot\widehat{t})} = d_2Sc^*_2\cdot\widehat{Sc_2} - k_1Lut^*_1\cdot\widehat{Lut_1}$$

$$\frac{d(Lut_2^* \cdot \widehat{Lut_2})}{d(t^* \cdot \widehat{t})} = k_1 Lut_1^* \cdot \widehat{Lut_1} - k_2 Lut_2^* \cdot \widehat{Lut_2}$$
$$\frac{d(Lut_3^* \cdot \widehat{Lut_3})}{d(t^* \cdot \widehat{t})} = k_2 Lut_2^* \cdot \widehat{Lut_2} - k_3 Lut_3^* \cdot \widehat{Lut_3}$$
$$\frac{d(Lut_4^* \cdot \widehat{Lut_4})}{d(t^* \cdot \widehat{t})} = k_3 Lut_3^* \cdot \widehat{Lut_3} - k_4 Lut_4^* \cdot \widehat{Lut_4}$$

$$E_2^* \widehat{E_2} = e_1 + e_2 \widehat{SeF} SeF^* + e_3 \widehat{PrF} PrF^* + e_4 \widehat{Lut_4} Lut_4^*$$
$$P_4^* \widehat{P_4} = pr \widehat{Lut_3} Lut_3^* + pr_2 \widehat{Lut_4} Lut_4^*$$
$$Ih^* \widehat{Ih} = h_1 + h_2 \widehat{PrF} PrF^* + h_3 \widehat{Lut_3} Lut_3^* + h_4 \widehat{Lut_4} Lut_4^*$$

where the dimensionless delays have the form:

$$\delta_E^* = \delta_E \,/\, \widehat{t}\ ,\ \delta_P^* = \delta_P \,/\, \widehat{t}\ , \text{ and } \delta_{Ih}^* = \delta_{Ih} \,/\, \widehat{t}.$$

Applying the chain rule to a variable $y = y^* \cdot \widehat{y}$, we obtain $\frac{d\,y}{d\,t} = \frac{\widehat{y}}{\widehat{t}} \cdot \frac{d\,y^*}{d\,t^*}$. Therefore we can obtain a new system of equations in terms of the dimensionless ("starred") variables by multiplying both sides of the equations by $\widehat{t}$ and dividing by the appropriate unit carrying constants. For example, multiplying the first equation by $\widehat{t}/\widehat{RP_{FSH}}$ will result in a differential equation in terms of $RP_{FSH}^* = RP_{FSH}^*(t^*)$. After multiplying each equation by the appropriate term and grouping the dimensional terms together on the right hand sides of the equations, we obtain:

$$\frac{dRP^*_{FSH}}{dt^*} = \frac{n\,\widehat{t}}{\left(1+\dfrac{\widehat{Ih}Ih^*\left(t^*-\delta_{Ih}/\widehat{t}\,\right)}{p}\right)\widehat{RP_{FSH}}} - \frac{q\widehat{t}(1+r\widehat{P_4}P_4^*)}{1+s(\widehat{E_2})^2(E_2^*)^2}\,RP^*_{FSH} \quad (7.18)$$

$$\frac{dFSH^*}{dt^*} = \frac{1}{v_{dis}}\frac{q\widehat{t}(1+r\widehat{P_4}P_4^*)}{1+s(\widehat{E_2})^2(E_2^*)^2}\,\frac{\widehat{RP_{FSH}}}{\widehat{FSH}}RP^*_{FSH} - \widehat{t}cl_F\,FSH^* \quad (7.19)$$

$$\frac{dRP^*_{LH}}{dt^*} = \frac{\left(u+\dfrac{v(\widehat{E_2})^h(E_2^*\left(t^*-\delta_E/\widehat{t}\,\right))^h}{w^h+(\widehat{E_2})^h(E_2^*\left(t^*-\delta_E/\widehat{t}\,\right))^h}\right)\widehat{t}}{\left(1+\dfrac{\widehat{P_4}P_4^*\left(t^*-\delta_P/\widehat{t}\,\right)}{w_1}\right)\widehat{RP_{LH}}} - \frac{y\widehat{t}(1+z\widehat{P_4}P_4^*)}{1+z_1\widehat{E_2}E_2^*}\,RP^*_{LH} \quad (7.20)$$

$$\frac{dLH^*}{dt^*} = \frac{1}{v_{dis}}\frac{y\widehat{t}(1+z\widehat{P_4}P_4^*)}{1+z_1\widehat{E_2}E_2^*}\,\frac{\widehat{RP_{LH}}}{\widehat{LH}}RP^*_{LH} - \widehat{t}\,cl_LLH^* \quad (7.21)$$

$$\frac{dMsF^*}{dt^*} = \widehat{t}b\frac{\widehat{FSH}}{\widehat{MsF}}FSH^* + \widehat{t}c_1\widehat{FSH}FSH^*MsF^* - \widehat{t}c_2\left(\frac{\widehat{LH}}{LH_0}\right)^{\alpha}(LH^*)^{\alpha}\;MsF^* \quad (7.22)$$

$$\frac{dSeF^*}{dt^*} = \widehat{t}c_2\frac{\left(\frac{\widehat{LH}}{LH_0}\right)^{\alpha}\widehat{MsF}}{\widehat{SeF}}(LH^*)^{\alpha}\,MsF^* + \widehat{t}c_3\left(\frac{\widehat{LH}}{LH_0}\right)^{\beta}(LH^*)^{\beta}\,SeF^* - \widehat{t}c_4\frac{\widehat{LH}}{LH_0}LH^*\;SeF^* \quad (7.23)$$

$$\frac{dPrF^*}{dt^*} = \widehat{t}c_4\,\frac{\widehat{LH}\widehat{SeF}}{LH_0\widehat{PrF}}LH^*SeF^* - \widehat{t}c_5\left(\frac{\widehat{LH}}{LH_0}\right)^{\gamma}(LH^*)^{\gamma}\,PrF^* \quad (7.24)$$

$$\frac{dSc_1^*}{dt^*} = \widehat{t}c_5\frac{\left(\frac{\widehat{LH}}{LH_0}\right)^{\gamma}\widehat{PrF}}{\widehat{Sc_1}}(LH^*)^{\gamma}\,PrF^* - \widehat{t}d_1Sc_1^* \quad (7.25)$$

$$\frac{dSc_2^*}{dt^*} = \widehat{t}d_1\frac{\widehat{Sc_1}}{\widehat{Sc_2}}Sc_1^* - \widehat{t}d_2Sc_2^* \quad (7.26)$$

$$\frac{dLut_1^*}{dt^*} = \widehat{t}d_2\frac{\widehat{Sc_2}}{\widehat{Lut_1}}Sc_2^* - \widehat{t}k_1Lut_1^* \tag{7.27}$$

$$\frac{dLut_2^*}{dt^*} = \widehat{t}k_1\frac{\widehat{Lut_1}}{\widehat{Lut_2}}Lut_1^* - \widehat{t}k_2Lut_2^* \tag{7.28}$$

$$\frac{dLut_3^*}{dt^*} = \widehat{t}k_2\frac{\widehat{Lut_2}}{\widehat{Lut_3}}Lut_2^* - \widehat{t}k_3Lut_3^* \tag{7.29}$$

$$\frac{dLut_4^*}{dt^*} = \widehat{t}k_3\frac{\widehat{Lut_3}}{\widehat{Lut_4}}Lut_3^* - \widehat{t}k_4Lut_4^* \tag{7.30}$$

$$E_2^* = \frac{e_1}{\widehat{E_2}} + \frac{e_2\cdot\widehat{SeF}}{\widehat{E_2}}SeF^* + \frac{e_3\cdot\widehat{PrF}}{\widehat{E_2}}PrF^* + \frac{e_4\cdot\widehat{Lut_4}}{\widehat{E_2}}Lut_4^*$$

$$P_4^* = \frac{pr\cdot\widehat{Lut_3}}{\widehat{P_4}}Lut_3^* + \frac{pr_2\cdot\widehat{Lut_4}}{\widehat{P_4}}Lut_4^*$$

$$Ih^* = \frac{h_1}{\widehat{Ih}} + \frac{h_2\cdot\widehat{PrF}}{\widehat{Ih}}\cdot PrF^* + \frac{h_3\cdot\widehat{Lut_3}}{\widehat{Ih}}Lut_3^* + \frac{h_4\cdot\widehat{Lut_4}}{\widehat{Ih}}Lut_4^*$$

The unit carrying ("hatted") constants may be chosen in many ways to create a dimensionless system. However, in order to determine whether a dimensionless parameter is small in comparison to other parameters the hatted constants should be chosen so that each term in the dimensionless system has unit order of magnitude (ie. the maximum over time is between 0.5 and 5) [51]. We will attempt to satisfy this condition by choosing hatted constants so that each dimensionless (dependent) variable has unit order of magnitude. The hatted constant $\widehat{t}$ is chosen to be $\widehat{t} = 1\,\text{day}$ because we want to keep the same time scale. The hatted constants for the pituitary and ovarian hormones were chosen from quantities that were related to the hormone's production or release or from quantities that represented the hormone's action on the production or release of another hormone. In addition, the hatted constants for the ovarian state variables were chosen to be the same for all of the variables. That value was chosen so that none of the dimensionless state variables would be too small and

each would have unit order of magnitude. The final unit carrying constants chosen to be substituted into equations (7.18)-(7.30) are listed in Table 7.4.

Table 7.4: Unit Carrying Constants

Equation	**Hatted Constants**
Equation 7.18:	$\widehat{t} = 1$ day
	$\widehat{Ih} = p$
	$\widehat{P_4} = w_1$
	$\widehat{RP_{FSH}} = n/q$
Equation 7.19:	$\widehat{FSH} = n/(q\ v_{dis})$
Equation 7.20:	$\widehat{E_2} = w$
	$\widehat{RP_{LH}} = u\ \widehat{t}$
Equation 7.21:	$\widehat{LH} = u\ \widehat{t}/v_{dis}$
Equations 7.22-7.24:	$LH_0 = 1\ \mu g/L$
	$\widehat{MsF} = \widehat{SeF} = \widehat{PrF} = 500\ \mu g$
Equations 7.25-7.26:	$\widehat{Sc_1} = \widehat{Sc_2} = 500\ \mu g$
Equations 7.27-7.30:	$\widehat{Lut_1} = \widehat{Lut_2} = \widehat{Lut_3} = \widehat{Lut_4} = 500\ \mu g$

After substituting these values for the hatted constants into the system equations and grouping the remaining parameters together to create dimensionless parameters, the merged system can be written in the following **dimensionless** form:

$$\frac{dRP^*_{FSH}}{dt^*} = \frac{\tilde{q}}{1 + Ih^*(t^* - \delta^*_{Ih})} \; - \; \frac{\tilde{q}\,(1 + \tilde{r}P^*_4)}{1 + \tilde{s}(E^*_2)^2}\; RP^*_{FSH} \tag{7.31}$$

$$\frac{dFSH^*}{dt^*} = \frac{\tilde{q}\,(1 + \tilde{r}P^*_4)}{1 + \tilde{s}(E^*_2)^2}\; RP^*_{FSH} \; - \; \tilde{cl}_F FSH^* \tag{7.32}$$

$$\frac{dRP^*_{LH}}{dt^*} = \frac{1 + \dfrac{\tilde{v}E^*_2(t^* - \delta^*_E)^h}{1 + E^*_2(t^* - \delta^*_E)^h}}{1 + P^*_4(t^* - \delta^*_P)} \; - \; \frac{\tilde{y}(1 + \tilde{z}P^*_4)}{1 + \tilde{z_1}E^*_2}\; RP^*_{LH} \tag{7.33}$$

$$\frac{dLH^*}{dt^*} = \frac{\tilde{y}(1 + \tilde{z}P^*_4)}{1 + \tilde{z_1}E^*_2}\; RP^*_{LH} \; - \; \tilde{cl}_L LH^* \tag{7.34}$$

$$\frac{dMsF^*}{dt^*} = \tilde{b}FSH^* + \tilde{c_1}FSH^*MsF^* - \tilde{c_2}(LH^*)^\alpha\; MsF^* \tag{7.35}$$

$$\frac{dSeF^*}{dt^*} = \tilde{c_2}(LH^*)^\alpha MsF^* + \tilde{c_3}(LH^*)^\beta SeF^* - \tilde{c_4}LH^*\; SeF^* \tag{7.36}$$

$$\frac{dPrF^*}{dt^*} = \tilde{c_4}LH^*SeF^* - \tilde{c_5}(LH^*)^\gamma PrF^* \tag{7.37}$$

$$\frac{dSc^*_1}{dt^*} = \tilde{c_5}(LH^*)^\gamma PrF^* - \tilde{d}_1 Sc^*_1 \tag{7.38}$$

$$\frac{dSc^*_2}{dt^*} = \tilde{d}_1 Sc^*_1 - \tilde{d}_2 Sc^*_2 \tag{7.39}$$

$$\frac{dLut^*_1}{dt^*} = \tilde{d}_2 Sc^*_2 - \tilde{k_1}Lut^*_1 \tag{7.40}$$

$$\frac{dLut^*_2}{dt^*} = \tilde{k_1}Lut^*_1 - \tilde{k_2}Lut^*_2 \tag{7.41}$$

$$\frac{dLut^*_3}{dt^*} = \tilde{k_2}Lut^*_2 - \tilde{k_3}Lut^*_3 \tag{7.42}$$

$$\frac{dLut^*_4}{dt^*} = \tilde{k_3}Lut^*_3 - \tilde{k_4}Lut^*_4 \tag{7.43}$$

$$E^*_2 = \tilde{e_1} + \tilde{e_1}SeF^* + \tilde{e_3}PrF^* + \tilde{e_4}Lut^*_4 \tag{7.44}$$

$$P^*_4 = \tilde{pr}Lut^*_3 + \tilde{pr}_2 Lut^*_4 \tag{7.45}$$

$$Ih^* = \tilde{h_1} + \tilde{h_2}PrF^* + \tilde{h_3}Lut^*_3 + \tilde{h_4}Lut^*_4. \tag{7.46}$$

This process of nondimensionalizing the merged system has resulted in a reduction in

the number of system parameters. Notice that the first equation could be rescaled by a factor of $1/\tilde{q}$ to eliminate the right hand side dependence on $\tilde{q}$. This would rescale RP^*_{FSH}, but it would not reduce the number of unknown parameters. Furthermore, the scale $\widehat{RP_{FSH}} = n/q$ was chosen so that RP^*_{FSH} would have have unit order of magnitude. Therefore we will not rescale the first equation. The dimensionless parameter groups are listed in Table 7.5, however the following substitutions will be made when the numerical values for the parameters in the dimensionless groups are substituted into the system:

$$\widehat{MsF} = \widehat{SeF} = \widehat{PrF} = \widehat{Sc_1} = \widehat{Sc_2} = \widehat{Lut_1} = \widehat{Lut_2} = \widehat{Lut_3} = \widehat{Lut_4} = 500\ \mu g,$$

$$LH_0 = 1\ \mu g/L, \text{ and } \widehat{t} = 1 \text{ day}.$$

Table 7.5: Dimensionless Groups of Parameters

Parameter Group	**Parameter Group**
$\tilde{q} = q\,\widehat{t}$	$\tilde{d_1} = d_1\,\widehat{t}$
$\tilde{r} = r\,w_1$	$\tilde{d_2} = d_2\,\widehat{t}$
$\tilde{s} = s\,w^2$	$\tilde{k_1} = k_1\,\widehat{t}$
$\tilde{cl_F} = cl_F\,\widehat{t}$	$\tilde{k_2} = k_2\,\widehat{t}$
$\tilde{v} = v/u$	$\tilde{k_3} = k_3\,\widehat{t}$
	$\tilde{k_4} = k_4\,\widehat{t}$
$\tilde{y} = y\,\widehat{t}$	$\tilde{e_1} = e_1/w$
$\tilde{z} = z\,w_1$	$\tilde{e_2} = e_2\,\widehat{SeF}/w$
$\tilde{z_1} = z_1\,w$	$\tilde{e_3} = e_3\,\widehat{PrF}/w$
$\tilde{cl_L} = cl_L\,\widehat{t}$	$\tilde{e_4} = e_4\,\widehat{Lut_4}/w$
$\tilde{b} = b\,n\,\widehat{t}/(q\,v_{dis}\,\widehat{MsF})$	$\tilde{pr} = pr\,\widehat{Lut_3}/w_1$
$\tilde{c_1} = c_1\,n\,\widehat{t}/(q\,v_{dis})$	$\tilde{pr_2} = pr_2\,\widehat{Lut_4}/w_1$
$\tilde{c_2} = c_2\,\widehat{t}\,(u\,\widehat{t}/(v_{dis}LH_0))^{\alpha}$	$\tilde{h_1} = h_1/p$
$\tilde{c_3} = c_3\,\widehat{t}\,(u\,\widehat{t}/(v_{dis}LH_0))^{\beta}$	$\tilde{h_2} = h_2\,\widehat{PrF}/p$
$\tilde{c_4} = c_4\,\widehat{t}\,(u\,\widehat{t}/(v_{dis}LH_0))$	$\tilde{h_3} = h_3\,\widehat{Lut_3}/p$
$\tilde{c_5} = c_5\,\widehat{t}\,(u\,\widehat{t}/(v_{dis}LH_0))^{\gamma}$	$\tilde{h_4} = h_4\,\widehat{Lut_4}/p$

7.3 Analyzing the Dimensionless System

The original parameter values can be substituted into the parameter groups in Table 7.5 to get values for the new dimensionless parameters. Table 7.6 lists these values.

Table 7.6: Dimensionless Parameter Values

Parameter	**Value**	**Parameter**	**Value**
$\tilde{q}$	7.29	$\tilde{d_1}$	0.6715
$\tilde{r}$	20106	$\tilde{d_2}$	0.7048
$\tilde{s}$	20736	$\tilde{k_1}$	0.6876
$c\tilde{l}_F$	8.21	$\tilde{k_2}$	0.6900
δ^*_{Ih}	2	$\tilde{k_3}$	0.6891
$\tilde{v}$	72.03	$\tilde{k_4}$	0.7093
$\tilde{y}$	2.49	$\tilde{e_1}$	0.13
$\tilde{z}$	2.18	$\tilde{e_2}$	0.15
$\tilde{z_1}$	1.76	$\tilde{e_3}$	0.23
$c\tilde{l}_L$	14	$\tilde{e_4}$	0.32
δ^*_E	0	$\tilde{pr}$	0.80
δ^*_P	1	$p\tilde{r}_2$	0.80
$\tilde{b}$	0.0025	$\tilde{h_1}$	0.43
$\tilde{c_1}$	1.81	$\tilde{h_2}$	0.32
$\tilde{c_2}$	5.93	$\tilde{h_3}$	0.36
$\tilde{c_3}$	0.01	$\tilde{h_4}$	1.65
$\tilde{c_4}$	3.08		
$\tilde{c_5}$	1.44		

The dimensionless merged system can be solved using these parameters and appropriately scaled initial conditions. Graphs of the pituitary and ovarian hormones as predicted by the dimensionless merged system are shown in Figures 7.1 and 7.2.

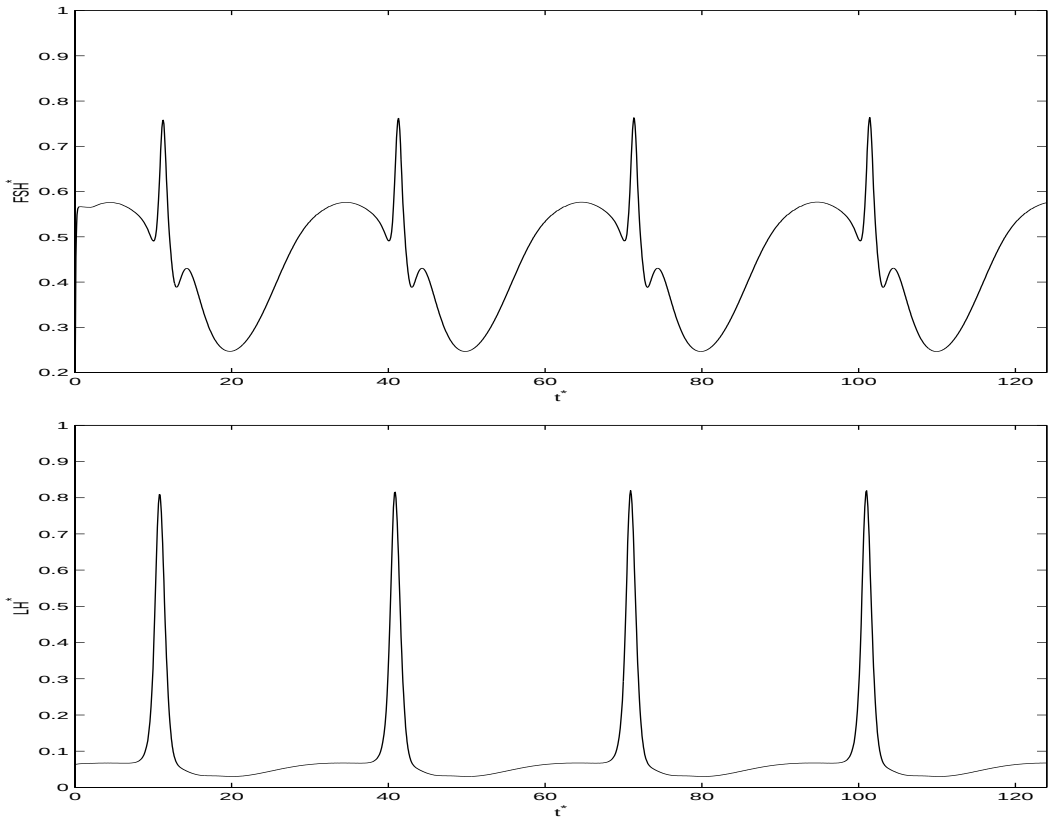

Figure 7.1: Graphs of the pituitary hormones as predicted by the dimensionless merged system.

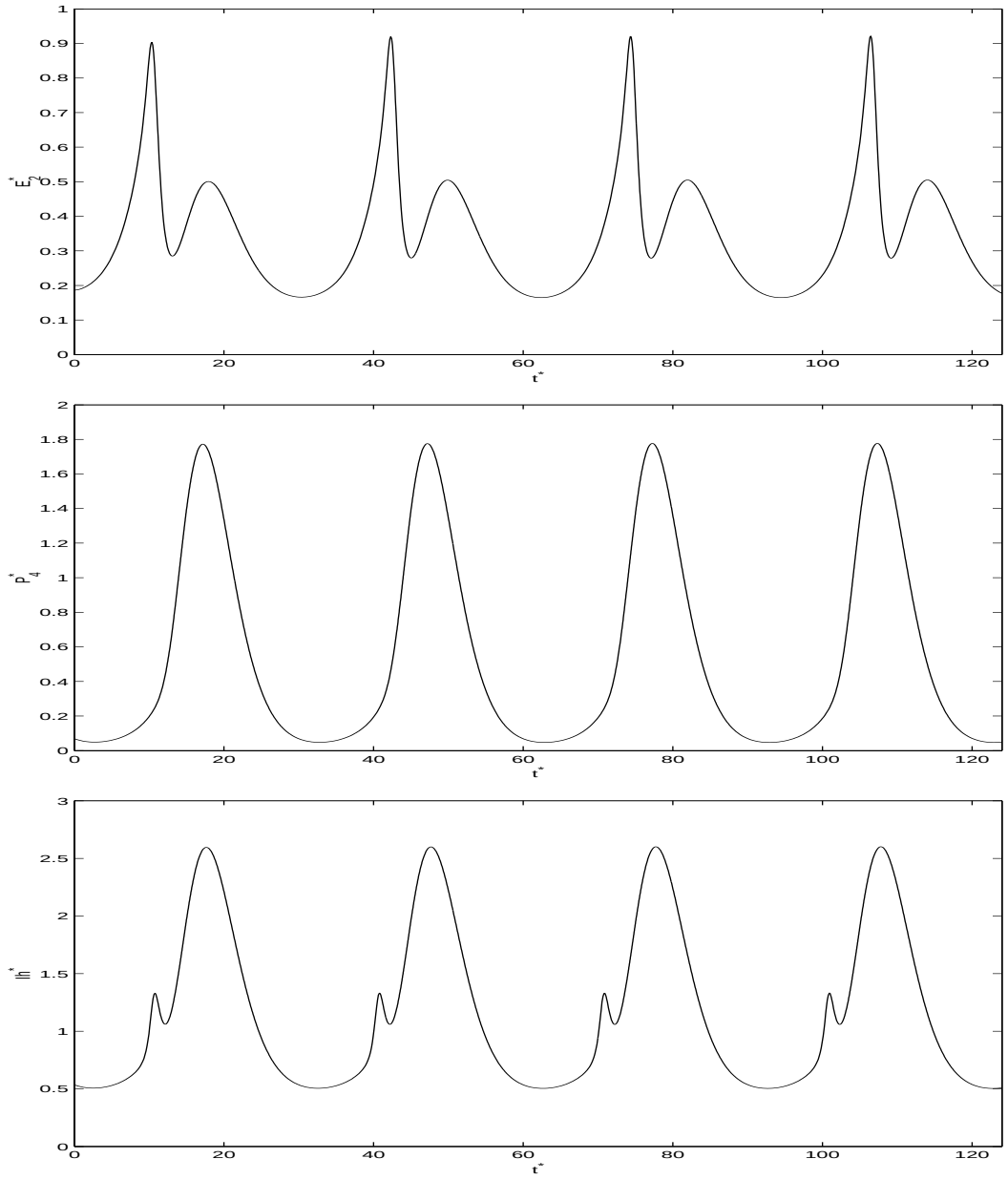

Figure 7.2: Graphs of the ovarian hormones as predicted by the dimensionless merged system.

Notice that the dimensionless blood levels for FSH, LH, and E_2 are bounded by 1 and the blood levels for P_4 and Ih are bounded by 3. Therefore all of the dimensionless hormone profiles have unit order of magnitude. In addition, the maximum levels of follicular activity are between 1 and 3 and, hence, have unit order of magnitude. Furthermore, RP^*_{FSH} has unit order of magnitude, but RP^*_{LH} does not (the maximum of RP^*_{LH} is 7.5). These bounds are useful when analyzing the magnitudes of the terms in the system. The parameters that stand out are $\tilde{r}$, $\tilde{s}$, $\tilde{b}$, and $\tilde{c_3}$. The values for $\tilde{r}$ and $\tilde{s}$ are very large compared to the other parameters, however they appear in the numerator and denominator of the same term. Therefore dividing the numerator and denominator by one of the parameters would make the remaining parameters much smaller and would yield the same effect on the release of FSH. The values for $\tilde{b}$ and $\tilde{c_3}$ are small compared to the other parameters. The maximum value of the term $\tilde{b}FSH^*$ is approximately 0.0019 and the maximum value for MsF^* is 1.4. This suggests that the effect of the term $\tilde{b}FSH^*$ on $dMsF^*/dt^*$ may not be very significant. In addition, the maximum value of the term $\tilde{c_3}(LH^*)^\beta SeF^*$ is approximately 0.0253 and the maximum of SeF^* is 2.8. The effects of these terms seem small, maybe negligible. Therefore, the possibility of eliminating these terms should be investigated.

Chapter 8

Conclusions and Future Work

8.1 Concluding Remarks

In this dissertation we develop a model for the hormonal regulation of the menstrual cycle. The model consists of three components: the pituitary component, the ovarian component, and the merged component. The pituitary component was first developed in [50] and the ovarian component in [54], however the ovarian component is reformulated in this work to provide a physical meaning to the concept of follicular "capacity". In [54] the capacity of each stage to produce hormones was assumed to be proportional to the mass at that stage. Therefore the state variables in the revised model are chosen to represent the mass of the follicular or luteal tissue that is actively secreting hormones during the corresponding stage of the cycle. In addition, the physical representations for the system parameters are formulated.

In Chapter 4 we provide theoretical results for the existence and uniqueness of solutions of the pituitary and ovarian systems. A total of 40 unknown parameters are estimated using the Nelder Mead Simplex Method and the model simulations using these parameters are compared to data for normally cycling women found in the literature. The unmerged model predictions fit the data in the McLachlan paper [41]

reasonably well using these parameter estimates. In addition, we are able to reduce the time delays in the LH synthesis term, as previously reported in [50], from 0.42 to 0 days for estradiol and from 2.9 days to 1 day for progesterone. In this chapter we also calculate the Floquet exponents numerically for the periodic attractors in the pituitary and ovarian systems. We show that the Floquet exponents are all negative, therefore given periodic input functions the pituitary and ovarian systems each have globally asymptotically stable periodic solutions which fit the data. Some of the Floquet exponents for the ovarian system are very small which indicates that the periodic solution is a weak attractor.

In Chapter 5 the merged component is implemented to determine whether the estimated parameters from the pituitary and ovarian components could be used in the merged system to reproduce the hormone levels found in the data without using any inputs into the system. The merged system predicts the blood levels of the LH, estradiol, progesterone, and inhibin reasonably well, however model predictions for the FSH blood levels near midcycle were not as good. In this chapter, we introduce the method of steps for establishing the existence and uniqueness of solutions of the merged system which is a nonlinear system of delay differential equations. By solving the system using a broad range of initial conditions, we provide evidence for the existence of a locally asymptotically stable periodic solution fitting the data for normally cycling women that has a seemingly large domain of attraction. In addition, a small amplitude, stable periodic solution arising from Hopf bifurcation in the system parameters is exhibited.

In Chapter 6 we analyze the small amplitude cycle and demonstrate its similarities to PCOS. We simulate possible hormonal treatments for this disorder and the normal cycle is successfully recovered. We also show that exposure to exogenous estrogen for long periods of time disrupts the normal menstrual cycle. Finally, in Chapter 7 the merged system is transformed into a dimensionless system to determine whether

the number of system parameters could be reduced. Appropriately scaling the state variables results in the reduction of 5 system parameters. Each equation in the dimensionless system is analyzed to determine whether there are any negligible terms due to small system parameters.

In summary, we have developed an autonomous system of delay differential equations that accurately predicts blood levels of five hormones as they interact to regulate the menstrual cycle. In addition, the model has exhibited a bistable situation, a normal cycle and an abnormal cycle. The hormone profiles of the abnormal cycle are characteristic of PCOS, therefore hormonal therapies were simulated to induce the normal hormone profiles and the normal cycle was successfully recovered. This model can be used as a tool to examine the hormonal effects of exogenous substances on the sexual endocrine system.

8.2 Future Work

The model presented in this work predicts the blood levels of LH, FSH, estradiol, progesterone, and inhibin during a normal menstrual cycle. The model predictions were reasonably accurate with the exception of predictions of FSH blood levels near midcycle. In the future, the FSH system equations should be analyzed to determine whether terms can be refined (eg. modifying the dependence of estrogen) so that the merged system would capture the FSH profile better. The dependence on inhibin blood levels should also be addressed, however it should be addressed separately.

The inhibin blood levels used in this model correspond to the levels of "total inhibin" since the data used to verify the model's accuracy dates back to 1990 when measurements for total inhibin could only be found. It has only been a few years since the first successful measurement of inhibin A (secreted by the corpus luteum) and inhibin B (secreted by developing follicles) [26, 30]. Studies suggest that these

forms of inhibin both suppress FSH [26, 30, 52], however they are secreted during different phases of the menstrual cycle and by different components of the ovary. Therefore, we will consider modifying the FSH system equations to capture the effect of inhibin A and inhibin B. This may not be possible before more studies have been performed to determine their effects on the menstrual cycle. To date the McLachlan paper has been the only paper we have found that presents all of hormone profiles that we consider in our model for an entire cycle.

The modeling approach chosen here was to determine the responses of the pituitary and ovary to known circulatory levels for normally cycling women by inputting hormonal profiles into the pituitary and ovarian systems and then using these systems as building blocks to create the final merged system. The merged system, therefore, describes how the pituitary and ovarian hormones interact throughout the menstrual cycle. A global optimization of the merged system parameters should be considered. In order to do this, one must determine how to fit the solutions to data since the observed period is shorter than the period we assumed. Another problem to consider, however, is that when using the dde solver (dde23) in MatLab the user does not have control over the time mesh. Therefore numerical schemes must be created so that when fitting to data, the solutions can be measured at desired times. Refining merged system parameters might provide the necessary fine tuning in order to capture the FSH profile accurately.

In the future we would also like to further study the domains of attraction for the normal and abnormal cycles presented in this work to better understand when a disturbance to the circulatory levels of the pituitary and ovarian hormones will completely disrupt the menstrual cycle. An in depth study on the effects of exogenous compounds on the menstrual cycle should be performed by modifying system equations. This includes simulating the effects of hormonal methods of birth control

(eg. birth control pills, skin implants, and liquid injectable). These methods administer high levels of synthetic estrogen and/or progesterone to suppress the LH surge, thereby preventing the occurrence of ovulation. In order to test the effects of these methods properly, we must determine how synthetic hormones are metabolized and absorbed in the blood so that the proper doses of these hormones can be used in model simulations.

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Appendices

Appendix A

Blood Levels of Hormones For Normally Cycling Women

A.1 Data From Clinical Studies

Table A.1: **Daily Mean Serum Levels**
(estimated from McLachlan *et al.* [41])

day	E_2 (ng/L)	P_4 (nmol/L)	Ih (U/L)	LH (μg/L)	FSH (μg/L)
0	56.387	1.2	297.9	25.34	142.5
1	49.168	0.4	284.1	28.74	158.3
2	51.3653	1.2	313.8	29.36	175.1
3	53.5627	1.113	308.7	33.71	168
4	55.76	1.2	299.3	34.29	179.1
5	61.494	0.8	298.7	36.78	180.6
6	67.228	0.933	302.2	37.35	177.3
7	72.962	0.8	301.5	38.88	177

continued on the next page

Table A.1: *continued*

day	E_2 (ng/L)	P_4 (nmol/L)	Ih (U/L)	$LH(\mu g/L)$	FSH (μg/L)
8	78.696	0.533	339.8	38.52	166.1
9	92.67	0.533	352	35.28	153.4
10	104.3	0.667	329.7	38.71	144.4
11	143.04	0.533	346.3	34.54	134.5
12	181.75	0.667	388.8	37.02	118.9
13	231.05	0.933	461.7	56.62	116.6
14	296.92	1.33	625.4	142.9	155.3
15	248.43	2.933	745.8	369.2	325.4
16	123.4	6	636.9	124	210.7
17	93.76	12.667	584.2	44.63	138.9
18	114.82	25.067	778.3	41.39	127.1
19	133.5	37.067	993.9	34.32	118.2
20	149.85	42.667	1279	29.18	107.3
21	155.57	51.867	1486	21.18	101.2
22	174.28	53.2	1632	17.95	86.53
23	178.83	49.867	1597	16.64	81.36
24	162.19	40	1440	13.38	75.29
25	149.06	33.3333	1154	12.02	76.79
26	130.04	22.667	919.5	13.54	82.1
27	112.23	14.667	711.1	16.02	91.23
28	92.044	11.733	675.8	16.56	100.4

continued on the next page

Table A.1: *continued*

day	E_2 (ng/L)	P_4 (nmol/L)	Ih (U/L)	$LH(\mu g/L)$	FSH (μg/L)
29	75.373	7.33	532.2	24.72	121.9
30	66.983	4.667	423.4	28.2	133.9

A.2 Functions Fitting the Data

Recall that the input functions used in the pituitary component of the model to approximate the data in Table A.1 for estradiol, progesterone, and inhibin blood levels over two periods are given by:

$$E_2(t) = e_0 + e_1 e^{-\frac{(t-14)^2}{e_2}} + e_3 e^{-\frac{(t-23)^2}{e_4}} + e_1 e^{-\frac{(t-45)^2}{e_2}} + e_3 e^{-\frac{(t-54)^2}{e_4}}, \quad (A.1)$$

$$P_4(t) = pr_0 + pr_1 e^{-\frac{(t-22)^2}{pr_2}} + pr_1 e^{-\frac{(t-53)^2}{pr_2}}, \quad (A.2)$$

$$Ih(t) = h_0 + h_1 e^{-\frac{(t-22)^2}{h_2}} + h_1 e^{-\frac{(t-53)^2}{h_2}}. \quad (A.3)$$

In addition, the input functions used in the ovarian component of the model to approximate the data for FSH and LH blood levels over two periods are given by:

$$\begin{aligned} FSH(t) = {} & f_1 e^{\frac{-(t-5)^2}{f_2}} + f_3 e^{\frac{-(t-15)^2}{f_4}} + f_5 e^{\frac{-(t-18)^2}{f_6}} + f_7 e^{\frac{-(t-36)^2}{f_8}} \\ & f_9 e^{\frac{-(t-46)^2}{f_{10}}} + f_5 e^{\frac{-(t-49)^2}{f_6}} + f_7 e^{\frac{-(t-67)^2}{f_{11}}}, \end{aligned} \quad (A.4)$$

$$\begin{aligned} LH(t) = {} & l_0 + l_1 e^{\frac{-(t-7)^2}{l_2}} + l_3 e^{\frac{-(t-15)^2}{l_4}} + l_5 e^{\frac{-(t-18)^2}{l_6}} + l_1 e^{\frac{-(t-38)^2}{l_2}} \\ & + l_3 e^{\frac{-(t-46)^2}{l_4}} + l_5 e^{\frac{-(t-49)^2}{l_6}} + l_1 e^{\frac{-(t-69)^2}{l_2}}. \end{aligned} \quad (A.5)$$

The functions in (A.1)-(A.5) were fit to the data using the Nelder Mead Simplex Method as described in Section 4.2. The resulting parameter values are listed in Tables A.2 and A.3.

Table A.2: **Estimates for the Parameters in the Ovarian Input Functions**

Parameter	**Value**	
e_0	62.48	ng/L
e_1	230	ng/L
e_2	5	day^2
e_3	115	ng/L
e_4	20	day^2
pr_0	0.8	nmol/L
pr_1	52.24	nmol/L
pr_2	19.15	day^2
h_0	290	U/L
h_1	1401.5	U/L
h_2	15	day^2

Table A.3: **Estimates for the Parameters in the Pituitary Input Functions**

Parameter	**Value**	
f_1	175	$\mu g/L$
f_2	110	day^2
f_3	210	$\mu g/L$
f_4	1	day^2
f_5	65	$\mu g/L$
f_6	20	day^2
f_7	174.9	$\mu g/L$
f_8	121	day^2
f_9	205	$\mu g/L$
f_{10}	1	day^2
f_{11}	130	day^2
l_0	0.156	$\mu g/L$
l_1	24.38	$\mu g/L$
l_2	230	day^2
l_3	332.12	$\mu g/L$
l_4	1	day^2
l_5	17.24	$\mu g/L$
l_6	35.16	day^2

Appendix B

Converting The Units of Progesterone and Estradiol

The units of P_4 in the McLachlan paper are $nmol/L$. In order to convert from moles to grams we need to determine the molar mass of progesterone. The molecular formula for progesterone is [15]:

$$C_{21}H_{30}O_2. \tag{B.1}$$

The molar mass of progesterone can be calculated as follows [15, 44]:

$$\begin{aligned} \text{Molar Mass of } C_{21}H_{30}O_2 &= (\#\text{ Atoms of } C \times \text{Atomic Weight of } C) \\ &+ (\#\text{ Atoms of } H \times \text{Atomic Weight of } H) \\ &+ (\#\text{ Atoms of } O \times \text{Atomic Weight of } O) \qquad \text{(B.2)} \\ &= (21 \times 12.0110) + (30 \times 1.0079) + (2 \times 15.9994) \\ &= 314.4668\, g/mol \qquad \text{(B.3)} \end{aligned}$$

Therefore 314.4668 is the mass in grams of one mole of progesterone.

The units of E_2 in the McLachlan paper are $pmol/L$. The molecular formula for

estradiol is [14]:

$$C_{18}H_{24}0_2. \tag{B.4}$$

Similarly, the molar mass of estradiol can be calculated as follows [44, 14]:

$$\begin{aligned} \text{Molar Mass of } C_{18}H_{24}0_2 &= (\#\text{ Atoms of } C \times \text{Atomic Weight of } C) \\ &+ (\#\text{ Atoms of } H \times \text{Atomic Weight of } H) \\ &+ (\#\text{ Atoms of } O \times \text{Atomic Weight of } O) \qquad \text{(B.5)} \\ &= (18 \times 12.0110) + (24 \times 1.0079) + (2 \times 15.9994) \\ &= 272.3864\, g/mol \qquad \text{(B.6)} \end{aligned}$$

Therefore 272.3864 is the mass in grams of one mole of estradiol and hence $x\,\frac{pmol}{L}$ of E_2 is equivalent to $0.2723864 \cdot x\,\frac{ng}{L}$. In this work we use ng/L as the units of estradiol. These conversions are useful in comparing the blood levels of these hormones to the other hormone levels.