

Modeling endocrine regulation of the menstrual cycle using delay differential equations



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ABSTRACT

This article reviews an effective mathematical procedure for modeling hormonal regulation of the menstrual cycle of adult women. The procedure captures the effects of hormones secreted by several glands over multiple time scales. The specific model described here consists of 13 nonlinear, delay, differential equations with 44 parameters and correctly predicts blood levels of ovarian and pituitary hormones found in the biological literature for normally cycling women. In addition to this normal cycle, the model exhibits another stable cycle which may describe a biologically feasible “abnormal” condition such as polycystic ovarian syndrome. Model simulations illustrate how one cycle can be perturbed to the other cycle. Perturbations due to the exogenous administration of each ovarian hormone are examined. This model may be used to test the effects of hormone therapies on abnormally cycling women as well as the effects of exogenous compounds on normally cycling women. Sensitive parameters are identified and bifurcations in model behavior with respect to parameter changes are discussed. Modeling various aspects of menstrual cycle regulation should be helpful in predicting successful hormone therapies, in studying the phenomenon of cycle synchronization and in understanding many factors affecting the aging of the female reproductive endocrine system.

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1. Introduction

Complex endocrine signaling between the brain and the ovaries is crucial for regulating and maintaining the female reproductive system of many mammals and birds. Abnormal levels of reproductive hormones often result in cycle irregularities. For instance, polycystic ovarian syndrome (PCOS), a leading cause of infertility in women [1,2,53], is usually associated with hormonal imbalances. Many PCOS women exhibit high androgen and low progesterone levels and their estrogen fluctuates little during the month at levels which may be contraceptive [53]. Another example of cycle irregularities in mammals is implied by the observation that the breeding of dairy cows to maximize milk production is concurrent with a decrease in bovine fertility [33,36,37,47]. There is evidence that high milk yield cows have lower amounts of progesterone and luteinizing hormone than cows which are not genetically modified. Also, there is concern [10,26,38,51] that

environmental substances with estrogenic activity may disrupt the sexual endocrine system and, hence, may contribute to the increased incidence of breast cancer [11], to declines in sperm counts [45], and to developmental abnormalities [25]. Modeling various aspects of menstrual and estrous cycle regulation may be helpful in understanding the roles of the many components of the reproductive endocrine system. Also, mathematical models may be used to simulate the effects of exogenous compounds and hormonal treatments on the reproductive system.

Over the last 10–15 years, we have developed and analyzed mechanistic, deterministic, mathematical models [14,15,17,23,32,39,41–44] which predict average serum concentrations of reproductive hormones that agree with data in the biological literature for normally cycling adult women [27,50]. This article reviews the procedure which we and other modelers, e.g., Boer et al. [3], Bogumil et al. [4,5], Chen and Ward [7], Reinecke and Deuflhard [34], Röblitz et al. [35], and Zeeman et al. [55], have found effective for modeling hormonal regulation of the female reproductive system. This approach may be described as **dual control** and captures the effects of hormones secreted by several glands over **multiple time scales**. A more general review article by Vetharaniam et al. [48] describes a variety of models for

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hormonal control of the female reproductive cycle of humans and animals.

Most mathematical models of cycle regulation track blood levels of hormones produced by the brain and the ovaries during the follicular and luteal phases of the cycle (Fig. 1). Follicle stimulating hormone (FSH) and luteinizing hormone (LH), which are produced by the pituitary gland, initiate the development of ovarian follicles and promote ovulation and the formation of the corpus luteum (see [19,54,56]). Simultaneously, at least three ovarian hormones, estradiol (E2), progesterone (P4), and inhibin (Inh), affect the synthesis and release of LH and FSH (see [20,22,49]). Pulses of gonadotropin-releasing hormone (GnRH) are produced by the hypothalamus on a time scale of minutes and hours and these pulses modulate the pituitary's secretion of FSH and LH (see Clayton et al. [9]). Because only data for daily blood levels of FSH and LH are available [27,50] and because the ovaries respond to average daily blood levels [29], our models lump the effects of the hypothalamus and the pituitary together and we consider the synthesis and release of FSH and LH on a time scale of days and months. As part of their normal function, the ovaries produce E2, P4, and Inh, which control the pituitary's synthesis and release of FSH and LH during the various stages of the cycle (see Fig. 1). Because the clearance of the ovarian hormones from the blood is rapid compared to the clearance of the pituitary hormones and compared to the time scale for ovarian development, we assume that the blood levels of the ovarian hormones are at quasi-steady state [21] and their concentrations are modeled as linear combinations of the appropriate ovarian stages of the cycle (see Section 2.3). These simplifications avoid issues of multiple time scales and permit the use of a daily time scale to track hormonal variation during the cycle.

To utilize the dual control nature of the system, we divide the modeling procedure into three distinct steps (see Section 2). First we derive a system of linear ordinary differential equations for the synthesis and release of FSH and LH in the pituitary which respond to the signaling of the ovarian hormones. Data [27,50] are used to obtain explicit time-periodic input functions for serum levels of E2, P4, and Inh and the unknown state variables in the system of differential equations are FSH and LH. Then the parameters of this system are estimated from the data for FSH and LH using a

numerical optimization routine. The second step reverses this process by developing a model for the monthly cyclic changes in the ovarian hormones E2, P4 and Inh under the influence of the pituitary hormones. This system of linear differential equations for the ovarian hormones contains parameters and time-periodic input functions for FSH and LH. Parameter identification is performed on this system using the data for E2, P4 and Inh. With a complete set of parameters determined, the final step is to merge these two systems into one system which is highly nonlinear because all the variables in the system are now state variables. It is important to note here that in order to fit this merged system of differential equations to the existing data, it may be necessary to re-estimate all the parameters, but the estimates already obtained serve as good starting values.

The specific model described here was originally developed by Harris [14] and Harris-Clark et al. [15]. It consists of 13 nonlinear, delay, differential equations with 44 parameters which are estimated using the data of McLachlan et al. [27]. The model is reviewed in detail in Section 2. Sections 3 and 4 discuss parameter identification, model simulations, E2 time delay, and bifurcation results. Section 5 illustrates model perturbations due to exogenous administrations of each of the ovarian hormones which have not been presented in previous publications. These examples show that timing of exposure, strength of exposure, and combinations of exposures should be carefully crafted to have therapeutic effects.

2. Biological preliminaries and model development

2.1. Biological preliminaries

Typically, a woman is born with 500,000–700,000 primordial follicles and this number decreases due to atresia with an increasing decay rate as the woman ages (e.g., see Hansen et al. [13]). During her reproductive life only a small number of these follicles develop to ovulatory status before the onset of menopause, which occurs at an average age of 51. The length of a normal menstrual cycle (Fig. 1) for an adult woman is 28 days on average but may range from 25 to 35 days [30]. The cycle is divided into the

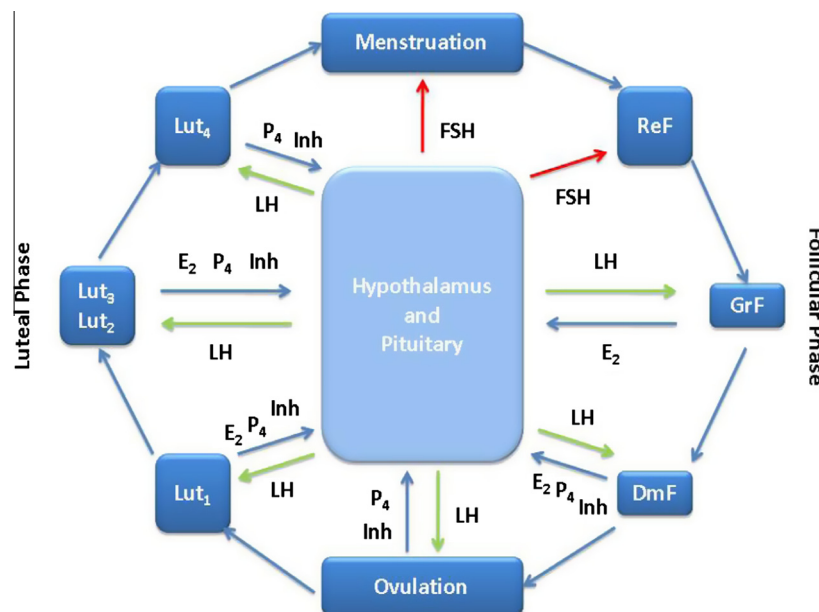


Fig. 1. The Follicular and Luteal Phases of the Menstrual Cycle. The outer ring depicts various stages of the ovaries during a monthly cycle. ReF, GrF and DmF represent the recruited, growing and dominant follicles and Lut_i , $i = 1, \dots, 4$, represent the corpus luteum. Directed arrows indicate hormonal actions.

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