

Luteinizing Hormone Dynamics in Menstruation

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Abstract — Menstruation is a finely-controlled cycle that responds to the prevailing endocrine and paracrine environment. Various hormones signal the beginning and end of notable mechanisms. Luteinizing hormone (LH) is a major player in ovulation, corpus luteum function, and the stimulation of other key hormones. Due to its pathophysiological relevance to important menstrual events, LH is the ideal candidate to model as a control system. Utilizing parameters and kinetic equations in the existing literature, a transfer function was derived. MATLAB SimuLink yielded the corresponding block diagram, output responses and Bode plot; such a model can provide key insight into the downstream effects and upstream causes of LH various concentrations. System stability analysis revealed three conclusions about the LH system: ¹⁾ the system is stable, ²⁾ the system will be less stable when the loop is closed, and ³⁾ the system is underdamped.

Overall, the LH model, if utilized in conjunction with models for other major hormones, such as FSH, progesterone, and GnRH, could be used to analyze and understand the larger control system of menstruation. Social stigma has led to inadequate menstrual literacy. The poorly understood mechanisms of menstruation ultimately lead to suboptimal healthcare treatment and services to biological females, culminating in a physical, financial and emotional burden. Understanding a smaller subsection of LH dynamics in the larger control system of menstruation can therefore lead to a greater understanding of menstruation and be utilized to improve therapeutics and research for women's health.

Key Terms — Menstruation; LH; control systems; SimuLink

I. INTRODUCTION

Menstruation, the cyclic shedding of the uterine layer, is a complex control system. Relevant hormones dictate numerous negative and positive feedback mechanisms to determine the latency, duration and intensity of each menstrual stage [1]. Consequently, engineers can model the larger control system of menstruation into subsections for each key hormone in order to elucidate the cascading effects and causes of each menstrual event.

The hypothalamus, pituitary gland and ovaries produce and deliver the key hormones via the bloodstream [2]. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the pituitary gland to release luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH, in turn, stimulates the release of progesterone. The interactions of these four major hormones - GnRH, LH, FSH, and progesterone - play a major role in menstrual regulation. The menstrual cycle has two main phases: follicular and luteal [3]. The follicular phase lasts about 14 days, during which the levels of GnRH increase, the levels of FSH initially increase and then decrease, and the levels of LH remain

low and steady. During the luteal phase, the levels of GnRH decrease in response to ovulation, causing levels of FSH and LH to decrease as well. The levels of LH are determined by the concentration of estrogen in the blood and the phase of the menstrual cycle. During the follicular phase, low levels of estrogen have a negative feedback relationship with LH and explain the decreasing levels of FSH and low levels of LH. On the other hand, during the luteal phase, high levels of estrogen have a positive feedback relationship with LH and consequently results in an exponential increase in LH.

The glycoprotein LH was identified as the ideal candidate to model and analyze because of its comparative consistency in the face of normal physiological actions such as circadian rhythm [4], predictive potential for relevant events such as ovulation or menopause, and mathematical presence in current literature. LH stimulates ovulation, the release of the egg from the follicle; the secretion of progesterone by the corpus luteum, in order to sustain pregnancy; and the production of estradiol [5], and therefore is of key clinical relevance. The applications of our LH model will be discussed in greater detail in the conclusion. To define our control system, the biological boundary between the control system is marked by the inputs and outputs of the LH system (*Figure 1*).

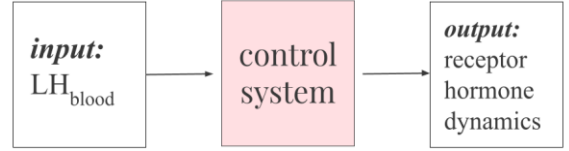


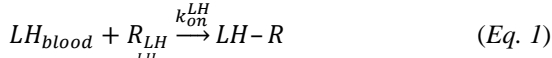
Figure 1: LH Conceptual Control System. The system's input is the concentration of luteinizing hormone in the blood and the output is the concentration of receptor-hormone complex.

Over eight hundred million people menstruate every day [5]. Despite its high prevalence, however, the pathophysiology of menstruation and its effects are poorly understood. Academia has traditionally underserved women's health, and menstruation in particular, because of social stigma related to a woman's reproductive and sexual health. The unexplored hormonal fluctuations associated with menstruation have historically been used as justification to exclude women in clinical trials for therapeutics, toxicology, and translational research [5]. Such systematic discrimination can significantly impact a woman's access to quality healthcare. Subsequently, deepening our understanding of the underlying mechanisms of menstruation can improve personalized care not only in regards to reproductive and sexual health, but all spheres of women's health.

II. DERIVATION

The chemical reaction kinetics describing LH-receptor binding over a small amount of time can be modeled by *Eqs. 1,2*,

and 3 [2]. The physiological representation of each rate constant and parameter is listed in **Tables 1** and 2, respectively.



The rate constants in **Table 1** represent the binding, formation and desensitization rates that govern the chemical kinetics of LH. The effects of changes can be understood conceptually. Increasing the binding rate of hormone to receptor would create an initial spike in the total amount of receptor-hormone complex, but would eventually settle to a final saturated concentration as a result of control mechanisms. In contrast, increasing the formation rate of free LH receptors or decreasing the desensitization rate of receptors to LH would raise the final “saturated” concentration.

The role of each of the three kinetic equations in modeling LH can now be explained. The first kinetic equation (**Eq. 1**) represents the binding of LH to receptors. The second kinetic equation (**Eq. 2**) represents the desensitization of receptors to LH. The third kinetic equation (**Eq. 3**) represents the formation of free LH receptors.

$$\frac{d}{dt}R_{LH}(t) = k_{recy}^{LH} \cdot R_{LH,des}(t) - k_{on}^{LH} \cdot LH_{blood}(t) \cdot R_{LH}(t) \quad (Eq. 4)$$

$$\frac{d}{dt}LH-R(t) = k_{on}^{LH} \cdot LH_{blood}(t) \cdot R_{LH}(t) - k_{des}^{LH} \cdot LH-R(t) \quad (Eq. 5)$$

$$\frac{d}{dt}R_{LH,des}(t) = k_{des}^{LH} \cdot LH-R(t) - k_{recy}^{LH} \cdot R_{LH,des}(t) \quad (Eq. 6)$$

The corresponding differential equations (**Eqs. 4, 5, 6**) are derived from the kinetic equations (**Eqs. 1, 2, 3**) [2]. The equation of particular clinical interest describes the formation of the receptor-hormone complex (**Eq. 4**). The binding of LH with its receptor is necessary to initiate signal transduction and downstream biological processes; therefore, this equation can be most closely associated with relevant physiological effects. With the differential equations (**Eqs. 4, 5, 6**) and parameters (**Tables 1, 2**), the transfer function and SimuLink model can be derived.

Table 1: Summary of Rate Constants [2]

| Rate Constant | Physiological Representation | Value |
|---------------------|----------------------------------|----------------|
| $x = k_{recy}^{LH}$ | Free LH receptor formation rate | 68.9491/day |
| $y = k_{on}^{LH}$ | Hormone to Receptor Binding Rate | 2.143 L/day·IU |
| $z = k_{des}^{LH}$ | LH receptor desensitization rate | 183.36/day |

Table 2. Summary of Initial Conditions [2]

| Parameter | Physiological Representation | Initial Values |
|---------------------|--|-----------------------|
| $a(t) = R_{LH}$ | Concentration of LH Receptor | $A_0 = 7.304$ nmol/L |
| $b(t) = R_{LH,des}$ | Concentration of Desensitized LH Receptor | $B_0 = 1.5032$ nmol/L |
| $c(t) = LH_{blood}$ | Concentration of LH in Blood | $C_0 = 6.619$ IU/L |
| $d(t) = LH-R$ | Concentration of LH Receptor-Hormone Complex | $D_0 = 0.565$ nmol/L |

III. EXPERIMENTAL METHODS

A. Building a Transfer Function

To model this system and perform subsequent analysis, a transfer function must be derived. The parameter input $a(t)$, which represents the concentration of LH receptors, and the parameter output $d(t)$, which represents the concentration of receptor-hormone complexes, can be linearized. The assumption that allows for linearization is that the behavior of $a(t)$ and $d(t)$ is approximately linear for small signals around the steady-state operating point. Such an assumption is reasonable because the endocrine system does not experience extreme levels of hormone flux, since signal transduction often follows cascading pathways that magnify minute concentration changes. The Laplace transform of the linearized ODEs yields **Eqs. 7, 8, 9**.

$$sA(s) - a_0 = xB(s) - ya_0C(s) - yc_0A(s) \quad (Eq. 7)$$

$$sD(s) - d_0 = ya_0C(s) + yc_0A(s) - zD(s) \quad (Eq. 8)$$

$$sB(s) - b_0 = zD(s) - xB(s) \quad (Eq. 9)$$

In order to determine the corresponding transfer relationship, an additional assumption must be posited: the initial conditions for $a(t)$, $b(t)$ and $d(t)$ are negligible. While the system will never start with having no LH receptors, desensitized or not, a transfer function for the system will still reveal insights about LH and receptor behavior. Thus, we will make these assumptions so that the following transfer relationship (**Eq. 10**) and subsequent transfer function (**Eq. 11**) may be derived.

$$\left(s + z - \frac{yc_0xz}{(s+yc_0)(s+x)}\right)D(s) = \left(ya_0 + \frac{y^2c_0a_0}{s+yc_0}\right)C(s) \quad (Eq. 10)$$

$$tf = \frac{D(s)}{C(s)} = \frac{(ya_0(s+yc_0) - y^2a_0c_0)(s+x)}{(s+2)(s+x)(s+yc_0) - yc_0xz} \quad (Eq. 11)$$

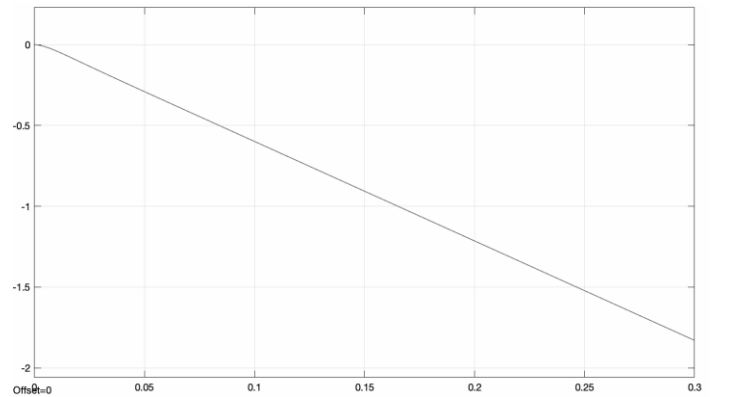


Figure 2. The transfer function response. The SimuLink response for **Eq. 11** validates a step response as the input of the LH control system.

For the purposes of this model, we assume that the pituitary gland constantly maintains constant LH levels in the blood. Indeed, LH levels stay approximately constant during the period of menses within a typical menstrual cycle [3]. From the negative slope of the transfer function response (**Figure 2**), we can determine that the concentration of the LH-receptor complex decreases over time. Such a trend makes conceptual sense, as we expect the feedback mechanisms caused by desensitization of the

receptors and the lack of formation of new receptors to drive the output concentration downwards. Because the simulation is not limited by biological constraints, it becomes negative.

B. Simulation Using Simulink

The LH-receptor complex dynamics can be modeled using the MathWorks application Simulink on MATLAB (*Figure 3*). The resulting block diagram models the transfer function (*Eq. 11*) for the input parameter of the concentration of LH in the blood, $c(t)$, and the output parameter of the concentration of the LH-receptor complex, $d(t)$. As previously mentioned, a step response is used as the input concentration of LH in the blood because during onset of menses, which signifies the start of the menstrual cycle, LH is released at an approximately constant level, resulting in the values described in *Table 1* and *2*.

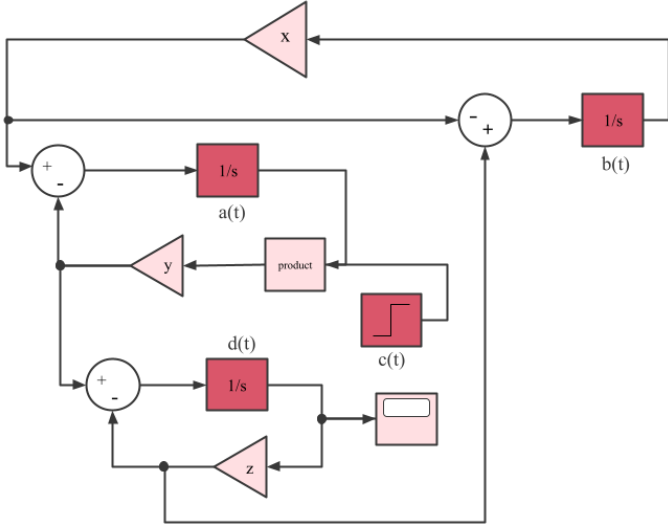


Figure 3. Block diagram in Simulink modeling LH-receptor complex dynamics. The block diagram models a system with the input, $c(t)$, as the concentration of LH in the blood, and the output, $d(t)$, as the concentration of the LH-receptor complex.

During a healthy menstruation cycle, blood LH levels of 6.619 IU/L are considered standard [2]. Using this parameter value and other initial conditions from *Table 2*, this model demonstrates that the concentration of LH-receptor complex saturates rapidly (*Figure 6, Panel A*). By changing different parameter values in the block diagram, deeper analysis of the output response leads to information that has pertinent clinical implications. *Figure 4* studies the effects of changing the concentration of LH receptors (*Panels A, B*) and the effects of changing the concentration of LH in the blood (*Panels C, D*). For both, low concentrations of LH receptors or LH itself output lower saturation concentration levels of LH-receptor complex. Similarly, at high concentrations, the output response yields a higher saturation concentration of LH-receptor complex. Physiologically, this makes sense; low concentrations of LH or receptors will result in fewer complexes being formed at equilibrium. In *Figure 4*, initial overshooting and undershooting can be observed, followed by rapid settling of the response to a saturation concentration; if this behavior is undesirable, an integral controller could be implemented, as integral control is able to mitigate steady-state error.

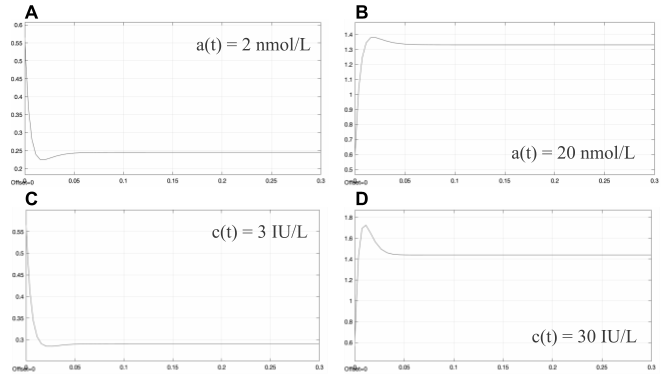


Figure 4. The resulting output response, $d(t)$, describes the concentration of LH-receptor complex present after changes to initial values for $a(t)$ and $c(t)$. (A/B) Shows the response of the system over a period of approximately 8 hours for different initial concentrations of LH receptors. By lowering this variable, the amount of LH-receptor complex decreases, and vice versa. (C/D) Shows the results over a period of approximately 8 hours for different initial concentrations of LH in the blood. By lowering the concentration of LH present, the amount of LH-receptor complex created is also lowered, and vice versa.

Similarly, the effects of studying changes to the rate constants of the system are displayed in *Figure 5*. The effects of changing the rate at which LH binds to its receptor are shown in *Panels A and B*; when the binding rate is slow, low levels of LH-receptor complex are produced, and vice versa. Similarly, the effects of changing the formation rate of free LH receptors can be seen in *Panels C and D*; when the rate at which free LH receptors are created is slow, a lower saturation concentration of LH-receptor complex is output, and vice versa. This aligns with our physiological expectations, as slow rate constants for binding and free LH receptor formation should predictably result in fewer amounts of LH-receptor complex formation. By studying the effects of changing various parameters in the block diagram, important information on menstrual cycles (e.g. menopause, malnutrition, pregnancy, fertility, etc.) can be studied.

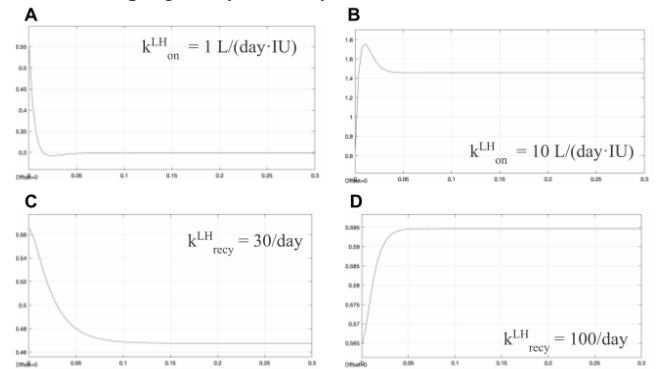


Figure 5. The resulting output response, $d(t)$, describes the concentration of LH-receptor complex present after changes to rate constants. (A/B) Shows the results of changing the LH to receptor binding rate. (C/D) Shows the results of changing the free LH receptor formation rate. Both rate constants, when set to lower values, result in an initial trough in the output before settling. When set to higher values, the output increases greatly before settling.

IV. MODEL ANALYSIS

A. System Stability

Figure 6, Panel A shows the output, $d(t)$, from the block diagram, and **Panel B** is a more realistic representation of what might happen biologically if the LH system operates with no other control system over a longer period of time. From the original ODEs, **Eq. 5** describes the dynamics of the LH-receptor complex; when the LH-receptor ($LH-R$) complex amount becomes large enough in value, $\frac{d}{dt}LH - R$ will become negative, resulting in a negative slope. Similarly, when the LH-receptor complex concentration becomes small enough in value, $\frac{d}{dt}LH - R$ will become positive, resulting in a positive slope. Together, we expect to see oscillatory behavior from the system. This behavior is seen in **Figure 6, Panel B**; physiologically, this behavior can be explained by not only the natural flux of the human body, but the receptor's "refractory period" (*i.e.* latency period) described by the desensitization of the receptor (**Eq. 6**). The latency gap may allow the system time to overshoot and undershoot equilibrium, resulting in oscillatory behavior. Additionally, this system isolates LH and thus does not describe the effects of other control systems that may affect LH-receptor dynamics. In a broader system, LH may be further modulated by other factors, such as other menstrual hormones (*e.g.* FSH or GnRH).

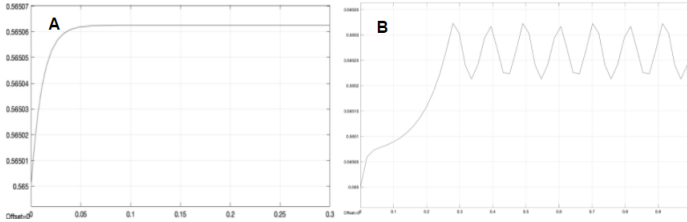


Figure 6. LH-receptor complex concentration, resulting from simulating the block diagram shown in Figure 3. (A) Shows the output from the block diagram over a period of approximately 8 hours. **(B)** Shows the output from the block diagram over 1 day.

The physiological constants listed in **Tables 1, 2** can be plugged into the transfer function (**Eq. 11**) to derive **Eq. 12**. This equation can be further simplified to **Eq. 13** by removing the negligible constant term in the denominator, as it is magnitudes lower than the other terms. The resulting Bode plots can be seen in **Figure 7**. The denominator of the simplified transfer function (**Eq. 13**) can be factored into $s(s + 113.3 + 58.3j)(s + 113.3 - 58.3j)$; from this, it can be determined that the system is stable and underdamped due to the existence of complex roots with no positive real components. Additionally, the negative phase margin (-90°) indicates that there will be stability issues when the loop is closed. This behavior may be a result of the limitations of this model, mentioned previously.

$$H(s) = \frac{-206.4s - 15086}{s^3 + 266.5s^2 + 16220s - 2.6} \quad (\text{Eq. 12})$$

$$H(s)_{\text{simplified}} = \frac{-206.4s - 15086}{s^3 + 266.5s^2 + 16220s} \quad (\text{Eq. 13})$$

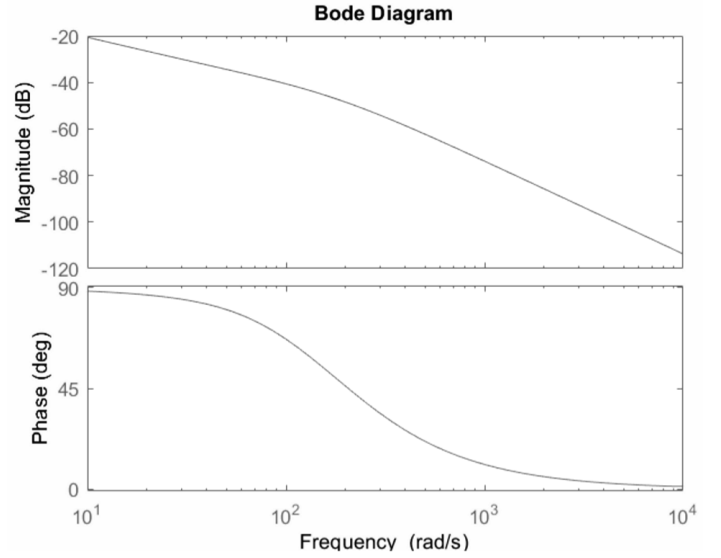


Figure 7. Bode plot resulting from the transfer function. Shows the resulting Bode plot from the full transfer function (**Eq. 12**).

V. CONCLUSION

Overall, the LH model developed in this paper holds the potential to contribute to the underserved body of women's health research and personalized care; however, we note several key limitations. In reality, the control system of menstruation consists of interconnected feedback mechanisms relying on multiple chemical messengers. Such hormones include FSH, GnRH, and progesterone, in addition to fine-tuning factors such as plasma inhibin and activin [10]. To simplify the system we focused on in this paper, our LH model minimizes the roles of these hormones within the overall menstrual cycle control system. Our more specific system can thus undergo model analysis, as seen in **Figure 6** and **Figure 7**. Given that menstruation takes place alongside other biological processes, our singular focus on LH is one of the main disadvantages. In order to fully realize the real-world applications of the LH model, it may be best interpreted alongside models of other major hormones, such as FSH, progesterone, and GnRH. Moreover, here we model the concentration of LH in the blood, $c(t)$, as a step response. Within the human body, luteinizing hormone levels in the blood fluctuate within the span of a single menstrual cycle, which lasts over the course of roughly 28 days. Thus, the model may only accurately convey what happens at certain short-term phases, such as menses, within the context of an entire cycle. We could account for these differences by changing the input $c(t)$ to an impulse or otherwise more complex signal, which would be more physiologically representative of LH dynamics at other phases within the menstrual cycle.

Given these constraints, the LH model has pertinent clinical applications: tracking pregnancy, fertility, and menopause, as well as developing therapeutics for menstruation. To start, the latency of LH peaks differs during pregnancy, and therefore can be used as a rudimentary diagnostic tool for expecting mothers [11]. In particular, LH levels will increase and reach peak (at between 25-45 mIU/mL) 24-36 hours before ovulation and drop immediately after ovulation. By modeling the effects of adding therapeutics to the LH system, we can also determine the efficacy

and toxicology of fertility treatments. Such *in silico* testing is more convenient, expedient and ethically viable than actual physiological experimentation, and can thus precede preclinical and clinical trials to save resources and prevent adverse medical events. The LH model can offer physicians a personalizable and accessible way to help patients with deciding on fertility treatments and beginning family planning.

Meanwhile, disorders related to menstruation are a common presentation in primary care. Menorrhagia, for example, afflicts about 1 in 5 American women [13]. Aberrant levels of hormones can cause or exacerbate such disorders. A central aim of pharmacology-based approaches is to identify therapeutic targets that alleviate symptoms of disorders like menorrhagia; similar to the case with fertility treatments, an *in silico* model could serve as a screening tool that precedes *in vivo* experimentation. Gaining a more quantitative understanding of Luteinizing Hormone, one of the major players involved in menstruation, can thus contribute to the development of therapeutics for similar serious and pervasive menstrual disorders. Abnormal LH cycles have also been associated with tracking the onset of menopause [12]. If an LH model, tailored to one's unique biology, could predict this onset, healthcare professionals can provide therapeutic care to alleviate patient symptoms.

Overall, menstruation remains poorly understood, despite its prevalence as a biological function. In addition to the aforementioned applications, the LH model can also be utilized to contribute to the lacking literature on women's health. Understanding the role of menstruation beyond the reproductive system could have implications within translational research. Thus, one of the strongest advantages of the LH model is its widespread applicability. The relevance of the LH model to the above scenarios - namely tracking pregnancy/fertility and menopause, treating menstrual disorders, and contributing to women's health research - would further amplify when used in conjunction with other hormone models.

VI. ACKNOWLEDGMENTS

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