

A Delay Mathematical Model for the Operating Characteristics of the Male Hormonal Regulation

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Abstract: A mathematical model describing the feedback mechanisms of the male hormonal regulation is presented. The mathematical models with a time delay are performed in order to explain the relationship between the concentrations of the hormones in the hypothalamic-pituitary-gonadal axis with the concentration of sex hormone-binding globulin (SHBG). Moreover, we determine new parameter values to exhibit the change in testosterone level which is due to the lower SHBG level that observed in obese men.

Keywords: hormone, time delay, testosterone, SHBG, hormonal regulation.

1. Introduction

The gonadal sex hormone, testosterone (T), is synthesized and secreted primarily by the interstitial cells of the testes. It plays important roles in the development and regulation of bodily functions; therefore, the testosterone production is carefully controlled to maintain balanced levels in blood. The body has a system for controlling androgen; testosterone biosynthesis is operated by the endocrine hormone in the complex dynamical system. It occurs via the negative feedback loops within the hypothalamus-pituitary-gonadal axis (HPG-axis). The gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of luteinizing hormone (LH) at the pituitary gland in pulses. LH, in turn, stimulates androgen production in the Leydig cells [1, 2], in which cholesterol the enzymatic conversion are where cholesterol is gradually changed into a series of compounds until it becomes testosterone. When high testosterone level is reached, in the hypothalamic-pituitary unit, the production and secretion of GnRH and LH have been controlled by a negative-feedback which leads to reduce the frequency and amount of pulsatile LH release. As a result, testosterone production is dropped [3]. Testosterone levels rise and then fall over the short term (2-3 hours) in humans [3]. Once testosterone is transported in the blood, most testosterone is bound; 50% of testosterone is tightly bound to sex hormone-binding globulin (SHBG) and is therefore physiologically inactive [4]. A further approximately 48% circulates bound weakly to albumin and only a small percentage (~ 2%) of testosterone is unbound or free testosterone (FT). Circulating bound and free testosterone is collectively referred to as total testosterone. The free testosterone and albumin-bound testosterone, which are physiologically available to the body tissues resulting in an effect on the cell, are known as the bioavailable testosterone [5, 6, and 7].

Sex hormone-binding globulin (SHBG), which is a protein produced primarily in the liver, binds to and transports sex hormones in the bloodstream. Since SHBG binds with high affinity to a large fraction of the testosterone, high concentrations of SHBG will reduce the level of bioavailable testosterone (BioT) in circulation. As a result, testosterone need to be further released in order to maintain adequate levels of BioT [8], so the level of SHBG is a significant factor that determines the total testosterone level [9,10]. The normal range of SHBG levels in adult males is between 0.674 to 5.620 micrograms per deciliter ($\mu\text{g}/\text{dL}$). A decrease in testosterone level can impact many of the body's systems. A deficiency in male sex hormone is due to hypogonadism. In men, low testosterone and low SHBG are associated with higher rates of obesity and diabetes [11-13].

Mathematical models for the regulation of male sex hormone have been widely studied and developed in order to understand the interaction of hormones in dynamic biological system for a long time. A simple mathematical model describing the hypothalamic-pituitary-gonadal system is proposed by Smith [14]. It is generalized to explain the pulsatile hormone regulation in the GnRH-LH-T axis. We denote the concentrations

of the GnRH, LH and T respectively by $R(t)$, $L(t)$ and $T(t)$, respectively. Smith's model comprises three differential equations

$$\begin{aligned}\frac{dR}{dt} &= f(T) - b_1(R), \\ \frac{dL}{dt} &= g_1(R) - b_2(L), \\ \frac{dT}{dt} &= g_2(L) - b_3(T).\end{aligned}\tag{1}$$

The positive function b_1, b_2, b_3 refer to clearing rates of the hormones and g_1, g_2, f describe the hormone secretion rates, where b_1, b_2, b_3, g_1 and g_2 are the monotonic increasing functions and the negative feedback function f is a monotonic decreasing function. In 1983, Smith [15] enlarged this model by using a time delay τ in the T -equation as a period for traveling the LH hormone from pituitary gland to the target cells and actions of gonadotrophins in the gonads. the model is represented as delay differential equations

$$\begin{aligned}\frac{dR}{dt} &= f(T) - b_1(R), \\ \frac{dL}{dt} &= g_1(R) - b_2(L), \\ \frac{dT}{dt} &= g_2(L(t-\tau)) - b_3(T).\end{aligned}\tag{2}$$

Where τ is a delay associated with the blood circulation time in the body.

Greenhalgh and Khan [16] attempted to enhance on the models of Smith [15] and of Cartwright and Husain [3] by using different response functions which incorporated more qualitatively observed biological behaviors.

In this study, we use the model of Tanutpanit et al. [17], which was modified from the model of Greenhalgh and Khan in order to describe the relation of the sex hormone-binding globulin (SHBG) and hypothalamic-pituitary-gonadal hormones, by determining new parameter values that concern with the change of SHBG production rate observed in obese men to exhibit the changes in testosterone levels.

2. Mathematical Model

Tanutpanit et al. [17] proposed a modified mathematical model with a time delay to consider the mechanism for maintaining the balance of testosterone levels in bloodstream.

They presented the differential equation model as follows:

$$\begin{aligned}\frac{dG}{dt} &= \frac{r_1 G}{Lh + r_2 Te} - \mu_1 G \\ \frac{dLh}{dt} &= \frac{r_3 G}{G + r_4 Te} Lh - \mu_2 Lh \\ \frac{dTe}{dt} &= a_1 Lh(t-\tau) Te + a_2 S \cdot Te - \mu_3 Te \\ \frac{dS}{dt} &= \frac{a_3 S}{1 + a_4 Te} - \mu_4 S\end{aligned}\tag{3}$$

Where $G(t)$, $Lh(t)$, $Te(t)$ and $S(t)$ as plasma concentrations of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), testosterone (T) and sex hormone-binding globulin (SHBG), respectively. In the system (3), the parameters $r_1, r_2, r_3, r_4, a_1, a_2, a_3, a_4$ are strictly positive and the positive constants $\mu_1, \mu_2, \mu_3, \mu_4$ refer to clearing rates of four hormones which are proportional to their concentration.

This model can explain the mechanism of testosterone regulation in the male reproductive system shown in Fig 1. GnRH is released in a pulsatile manner from the hypothalamus [18], which in turn leads to act as a signal to the pituitary gland for the pulsatile LH secretion into the blood stream. LH travels to the testes to stimulate the Leydig cells for the testosterone production. The pulsatile LH releasing conduces to fluctuations in the levels of testosterone [19,20]. To maintain the level of the testosterone at some equilibrium level, the hypothalamus gland signals the pituitary gland to limit the amount of LH to be released when the concentration of the testosterone in the blood is above a certain level. This of course will reduce the production of testosterone in the testis.

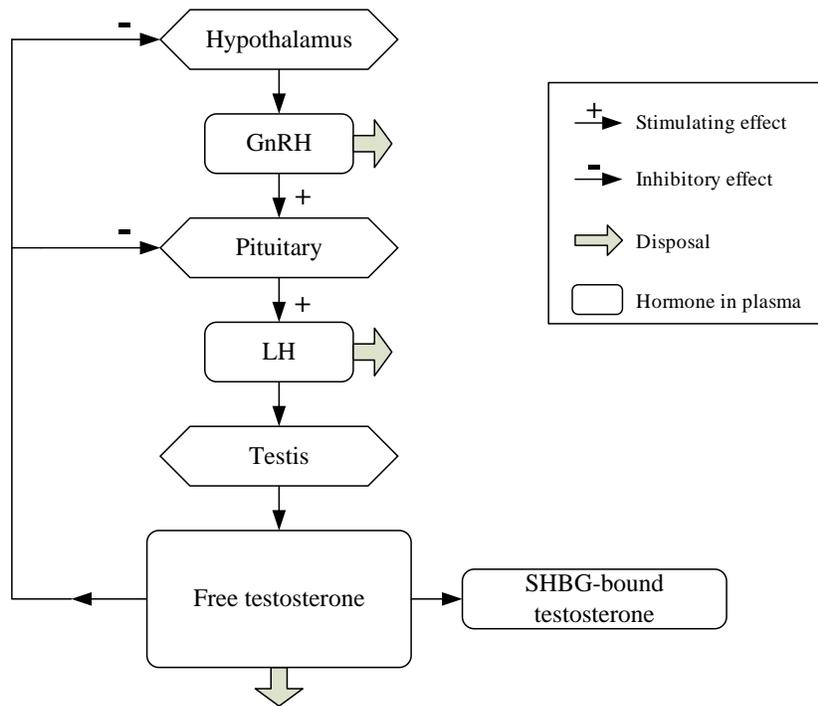


Fig. 1: The flow and interactions block diagram of the hypothalamo-pituitary-gonadal axis in men.

The only possible equilibrium state $E(G^*, Lh^*, Te^*, S^*)$ of the system (3) is given by

$$G^* = \frac{r_4 \mu_2}{r_3 - \mu_2} \cdot Te^* = \frac{r_4 \mu_2}{r_3 - \mu_2} \cdot \left(\frac{a_3 - \mu_4}{a_4 \mu_4} \right),$$

$$LH^* = \frac{r_1}{\mu_1} - r_2 Te^* = \frac{r_1}{\mu_1} - r_2 \cdot \left(\frac{a_3 - \mu_4}{a_4 \mu_4} \right),$$

$$Te^* = \frac{a_3 - \mu_4}{a_4 \mu_4},$$

and
$$S^* = \frac{1}{a_2} (\mu_3 - a_1 Lh^*) = \frac{1}{a_2} \left(\mu_3 - a_1 \left(\frac{r_1}{\mu_1} - r_2 \left(\frac{a_3 - \mu_4}{a_4 \mu_4} \right) \right) \right)$$

Which also satisfies the conditions

$$a_3 > \mu_4, r_3 > \mu_2, \frac{r_1}{\mu_1} > r_2 \cdot \left(\frac{a_3 - \mu_4}{a_4 \mu_4} \right) \text{ and } \mu_3 - a_1 \left(\frac{r_1}{\mu_1} - r_2 \left(\frac{a_3 - \mu_4}{a_4 \mu_4} \right) \right) > 0.$$

3. Numerical Results

In order to show the quantitative behavior of the hormones in the hypothalamic-pituitary-gonadal axis, including the concentration of sex hormone-binding globulin (SHBG) We conduct numerical simulations with the same realistic parameter values that Greenhalgh and Khan [16] used in simulation. For the other parameters, we take $a_2 = 0.0092$ /min, $a_3 = 6$ /min, $a_4 = 0.3$ and $\mu_4 = 0.031$ /min which correspond to the steady state E and the normal range of hormone levels. Fig.2 shows that the equilibrium E is asymptotically stable where $\tau = 120$,

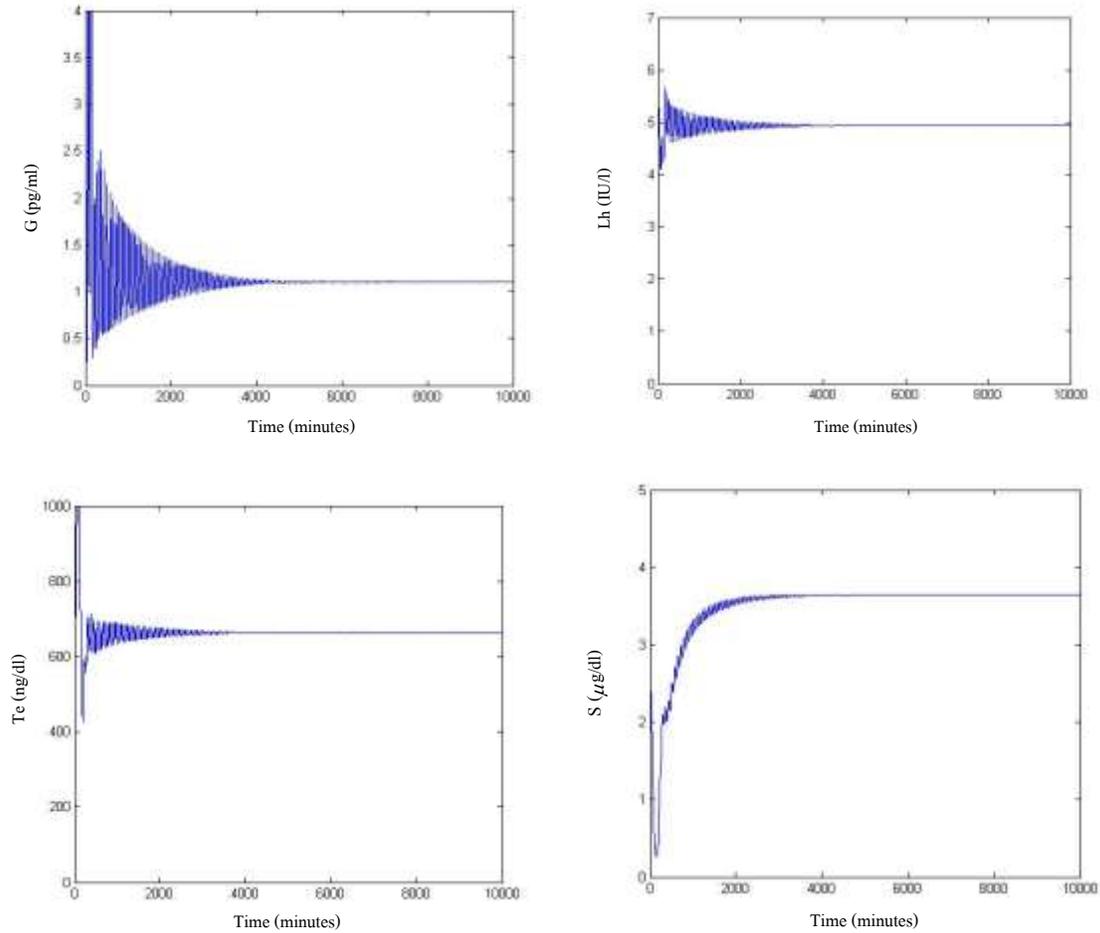


Fig. 2: Numerical simulations for eqs.(3) with $\tau = 120$. The positive equilibrium is asymptotically stable. The initial value is (1, 5, 642, and 3).

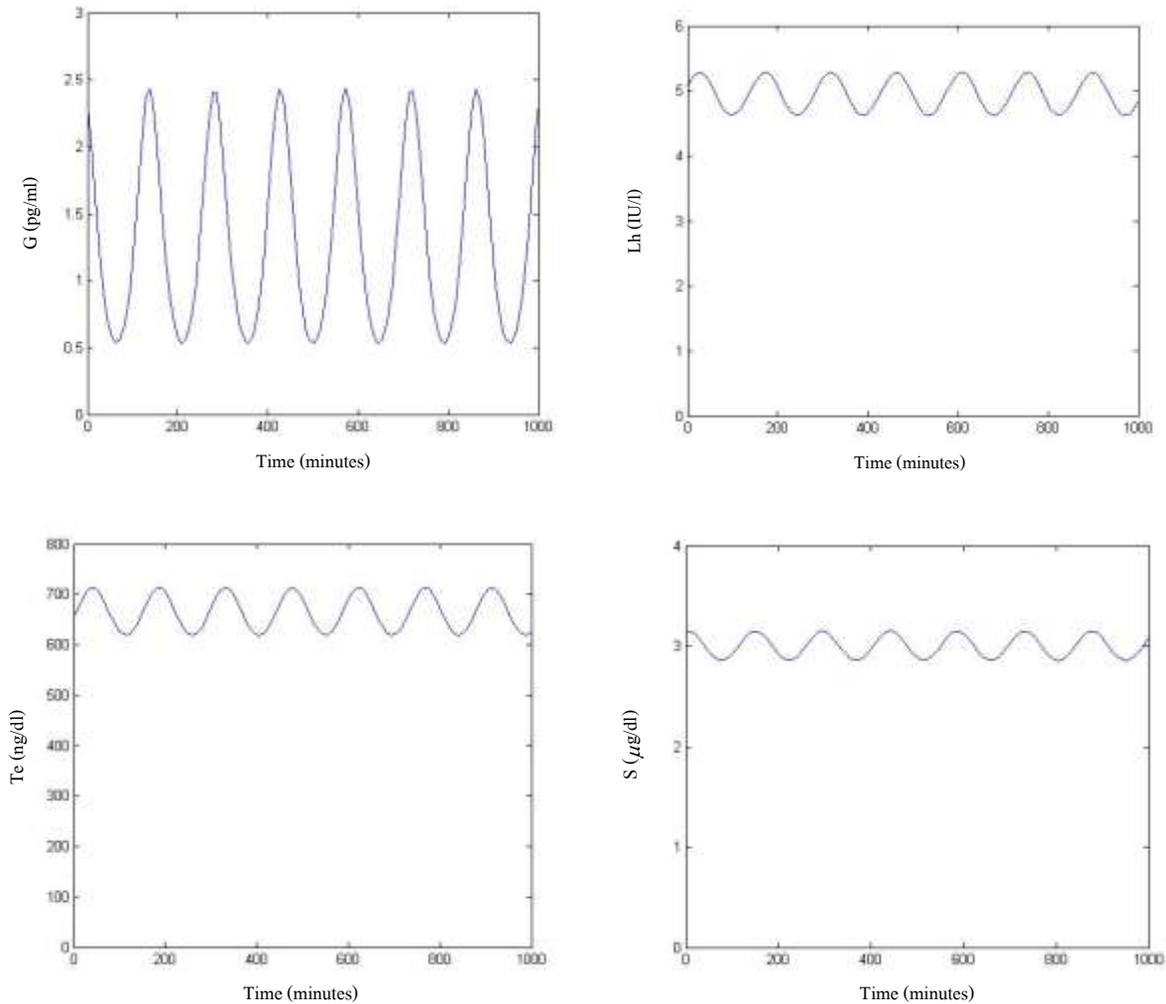


Fig. 3: Numerical simulations of equation (3) exhibit the oscillating levels of four main hormones in the system with $\tau = 124$. The initial value is $(1, 5, 642, 3)$. The values of parameters are $r_1 = 2.8$, $r_2 = 0.001$, $r_3 = 0.016$, $r_4 = 0.001$, $a_1 = 0.0092$, $a_2 = 0.0016$, $a_3 = 6$ and $a_4 = 0.3$ /min.

The behavior of the trajectories tending to the steady state $E^*(1.10, 4.94, 663.33, 3.64)$ As shown in Fig. 3 and 4, the system undergoes a Hopf bifurcation occurs near the positive equilibrium E where $\tau = 124$.

4. Conclusion

In this study we postulate new parameter values in the system in order to exhibit the quantitative behavior of testosterone when the hepatic SHBG production declines, which is associated with obesity. The oscillatory characteristics of hormone levels, as shown in Fig.3 and 4, indicate that the total testosterone levels diminish with decreasing SHBG levels that appears in men with obesity [21, 22].

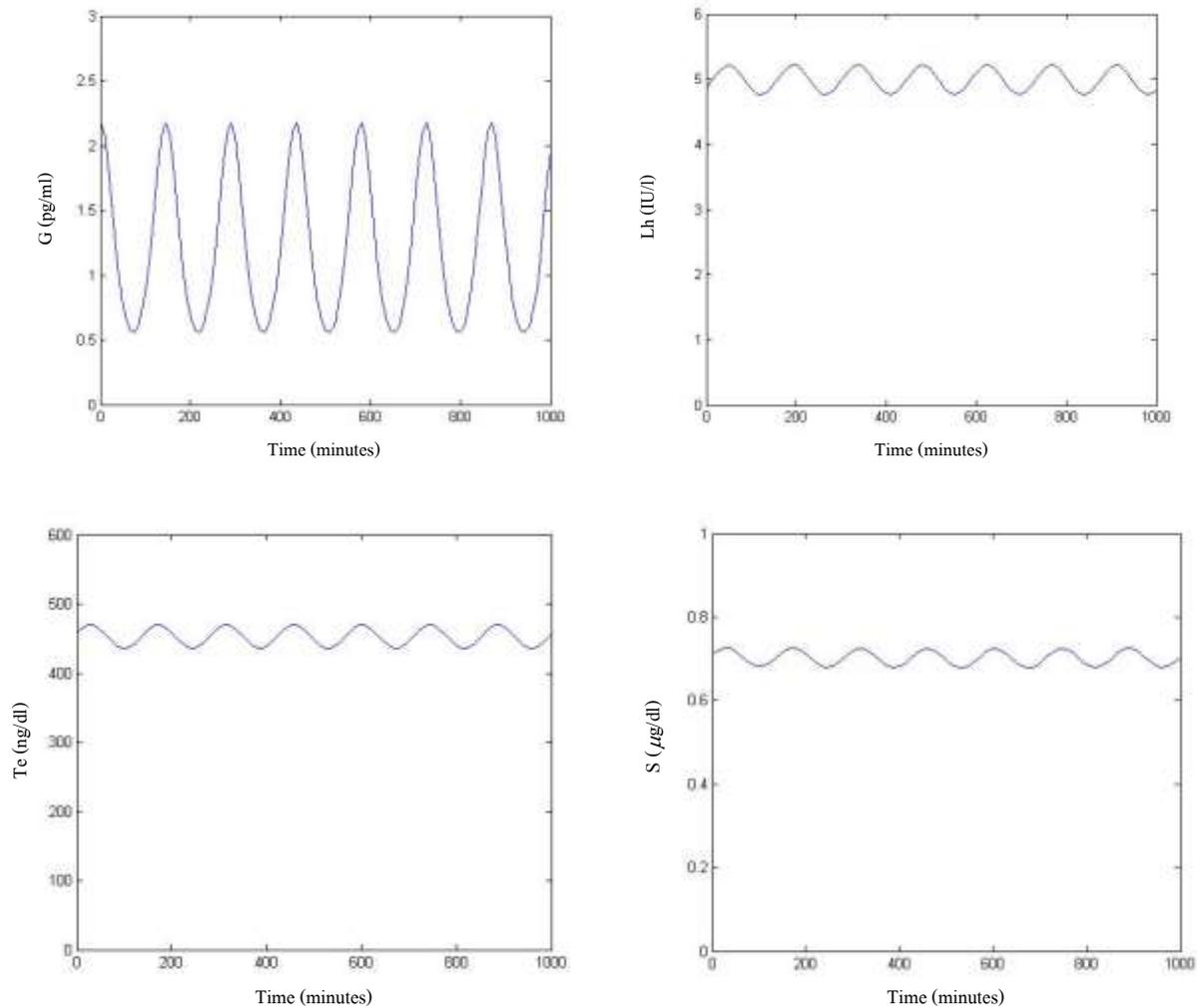


Fig. 4: Numerical simulations of equation (3) exhibit the oscillating levels of four main hormones in the system with $\tau = 124$. The initial value is (1, 5, 642, 3). The values of parameters are $r_1 = 2.8$, $r_2 = 0.001$, $r_3 = 0.016$, $r_4 = 0.001$, $a_1 = 0.0092$, $a_2 = 0.0016$, $a_3 = 5.5$ and $a_4 = 0.3$ /min.

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