Stability and oscillations of time-delayed model for the testosterone regulation

T. Tanutpanit, P. Pongsumpun* ,and I. M. Tang

***Abstract*—** In this paper, we develop the mathematical model with a time delay to describe the feedback mechanisms concerning of cyclicity of the male hormonal balance on the influence of variations in the sex hormone-binding globulin (SHBG) concentration. We show that a Hopf bifurcation occurs when a time delay τ passes through a critical value. Numerical simulations are performed to illustrate the analytical results. Moreover, this model can explain the pulsatile secretion of hormones in male.

***Keywords*—**Hormone, Time delay, Oscillation, Testosterone, SHBG, Hormonal regulation.

I. INTRODUCTION

IN males, testosterone (T) is the primary sex hormone that has many direct effects on the anatomy and metabolism. The biosynthesis of testosterone is controlled with hormonal interactions via feedback and feedforward relationships in the complex dynamical system. The hypothalamus and pituitary gland are important for regulation the amount of testosterone produced by the male testes. Testosterone levels rise and then fall over the short term (2-3 hours) in humans [1]. To stimulate testosterone production**,** The gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the anterior pituitary to produce luteinizing hormone (LH) which travels in the bloodstream to the testes. LH influences activity in the Leydig cells [2,3], where cholesterol is gradually changed into a series of compounds until it becomes testosterone. When high testosterone level is reached, the level of testosterone production is regulated by a negative-feedback to inhibit GnRH secretion which leads to a reduction in the frequency and amount of pulsatile LH release. As a result, testosterone production is dropped [1]. Once testosterone is transported in the blood, a large fraction of the circulating testosterone (~ 50%) 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 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 (BioT) [5,6,7]. SHBG is a protein produced primarily in the liver. The level of SHBG is one factor that determines the total testosterone level [8,9] because it binds with high affinity to a large fraction of the testosterone in circulation therefore high concentrations of SHBG reduce the level of bioavailable testosterone. Consequently, the total concentration of testosterone increases to maintain adequate levels of bioavailable testosterone [10].

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 [11], 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 $T(t)$. 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 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 [12] 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

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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.

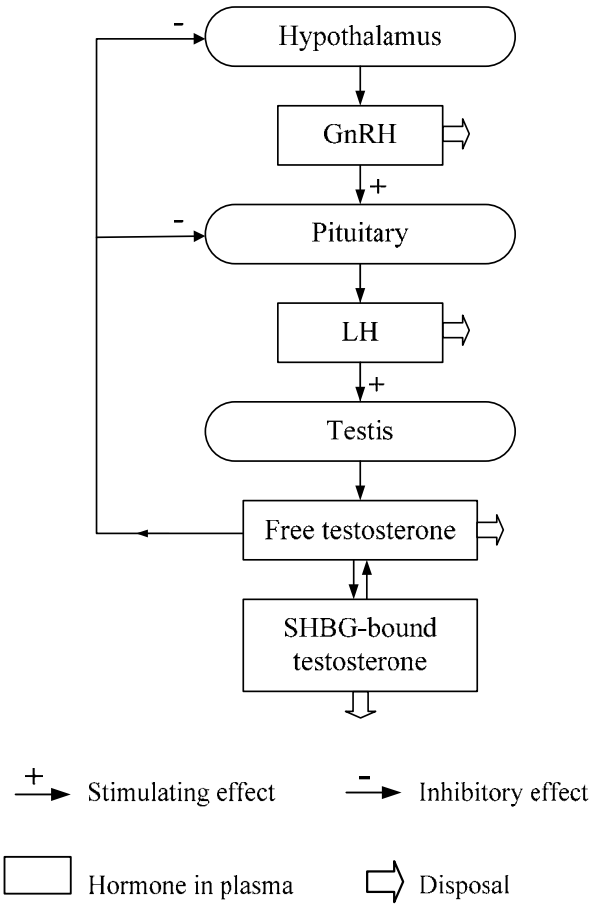

Fig.1. The flow and interactions block diagram of the hypothalamo-pituitary-gonadal axis in men.

Greenhalgh and Khan [14] proposed the delay differential equation model which explains the population dynamics of GnRH, LH and T. This model was modified from the models of Smith [6,15] and Cartwright and Husain [1] by taking into account experimental findings about the hypothalamic-pituitary-gonadal system. In this model, the only one of four equilibrium where all three hormones were presented. They analyzed the stability and Hopf bifurcation of the equilibrium. It is therefore unstable with no time delay, and Hopf bifurcation occurs repeatedly as the time delay increases through an infinite sequence of positive values.

In this paper, a mathematical model for the hormonal regulation of testosterone production in the mechanism of the hypothalamic-pituitary-gonadal system which was proposed by Greenhalgh & Khan (2009) is enlarged by taking into account the influence of variations in the SHBG concentration on testosterone level. This system incorporates a discrete delay in the time that LH requires to travel through the bloodstream to reach its site of action at the gonads [8]. In addition, the existence and stability of steady states of the system are considered as well.

II. Mathematical Model for The Testosterone Regulaion

A. Mathematical Model

To develop a mathematical model for testosterone hormonal regulation on the influence of variations in the SHBG concentration. We represent $R(t)$, $L(t)$, $T(t)$ and $S(t)$ as plasma concentrations of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), testosterone (T) and sex hormone-binding globulin (SHBG), respectively.

In order to balance the level of hormones in the bloodstream .Firstly, the merged effect of T and LH influence the production of GnRH by the hypothalamus. At low concentrations of T and LH , there is an increase in the production of GnRH with increasing GnRH concentration and it is the other way around when concentrations of T and LH are high. Hence, the secretion rate of GnRH is assumed in the form

$$\frac{dR}{dt} = \frac{r_1 R}{L + r_2 T} - \mu_1 R \tag{3}$$

Secondly, the pituitary secretion of LH is under controlling of the positive and negative feedback from GnRH and T, respectively. The secretion of LH will be decreased when the level of GnRH drops to the low level and T rises to the high level. Conversely, the secretion of LH will be increased as the GnRH concentration is high and the level of T is low. Therefore, the secretion rate of LH is assumed in the form

$$\frac{dL}{dt} = \frac{a_1 RL}{R + a_2 T} - \mu_2 L \tag{4}$$

Additionally, as the reason that LH stimulates leydig cells to convert cholesterol to T in that it incorporates the time delay corresponding to the time for traveling the LH hormone from pituitary gland to stimulate the production of T in the

gonads. Hence, The dynamics of testosterone level described by the following equation

$$\frac{dT}{dt} = g_1 L(t-\tau)T - \mu_3 T \quad (5)$$

In order to take into account the influence of variations in the SHBG concentration on the testosterone production. Equations (3) - (5) are modified as the following equations

$$\frac{dR}{dt} = \frac{r_1 R}{L + r_2 T} - \mu_1 R \quad (6a)$$

$$\frac{dL}{dt} = \frac{a_1 RL}{R + a_2 T} - \mu_2 L \quad (6b)$$

$$\frac{dT}{dt} = g_1 L(t-\tau)T + g_2 ST - \mu_3 T \quad (6c)$$

$$\frac{dS}{dt} = \frac{e_1 S}{1 + e_2 T} - \mu_4 S \quad (6d)$$

The term $g_2 ST$ is added into (6c) to support the dynamics of testosterone in the reason that the production of testosterone will be increased in order to maintain adequate levels of bioavailable testosterone as the levels of SHBG elevated. This is supported by experimental study described by Winters et al. [12]. Moreover, the first term on the right-hand side of (6d) represents the rate of the SHBG production which is assumed for decreasing the hepatic production of SHBG by testosterone [10]. In the system (6), the parameters r_1, r_2, a_1, a_2, g_1, g_2, e_1, e_2, are strictly positive and the positive constants μ_1, μ_2, μ_3, μ_4 refer to clearing rates of the all four hormones which is proportional to their concentration.

B. Steady state

In order to find steady states, we set the right hand side of equations (6a) to (6d) to zero. We obtain the four possible equilibrium states :

i) $E_1\left(R_1^*, L_1^*, T_1^*, S_1^*\right) = (0,0,0,0)$

ii) $E_2\left(R_2^*, L_2^*, T_2^*, S_2^*\right) = \left(0,\ 0,\ \frac{1}{e_2}\left(\frac{e_1}{\mu_4}-1\right),\ \frac{\mu_3}{g_2}\right)$

iii) $E_3\left(R_3^*, L_3^*, T_3^*, S_3^*\right) =$

$$\left(\frac{a_2\left(\frac{e_1}{\mu_4}-1\right)}{e_2\left(\frac{a_1}{\mu_2}-1\right)},\ \frac{r_1}{\mu_1}-\frac{r_2}{e_2}\left(\frac{e_1}{\mu_4}-1\right),\ \frac{1}{e_2}\left(\frac{e_1}{\mu_4}-1\right),\ \frac{1}{g_2}\left(\mu_3 - g_1\left(\frac{r_1}{\mu_1}-\frac{r_2}{e_2}\left(\frac{e_1}{\mu_4}-1\right)\right)\right)\right)$$

iv) $E_4\left(R_4^*, L_4^*, T_4^*, S_4^*\right) = \left(\frac{a_2\left[\frac{r_1}{\mu_1}-\frac{\mu_3}{g_1}\right]}{r_2\left[\frac{a_1}{\mu_2}-1\right]},\ \frac{\mu_3}{g_1},\ \frac{1}{r_2}\left[\frac{r_1}{\mu_1}-\frac{\mu_3}{g_1}\right],\ 0\right)$.

As we see, there is only the steady state E_3 that has all four hormones presented. It is the positive steady state of our equations where

$$\frac{e_1}{\mu_4} > 1\ ,\ \frac{a_1}{\mu_2} > 1\ ,\ \frac{r_1}{\mu_1} - \frac{r_2}{e_2}\left[\frac{e_1}{\mu_4} - 1\right] > 0 \text{ and}$$

$$\mu_3 - g_1\left(\frac{r_1}{\mu_1} - \frac{r_2}{e_2}\left[\frac{e_1}{\mu_4} - 1\right]\right) > 0\,.$$

By physically meaning, we will consider only the steady state E_3.

C. Local Stability and local Hopf bifurcation analysis

Based on the theory of differential equations, we consider the Jacobian matrix of our equations evaluated at the positive equilibrium E_3, that is

$$J = \begin{bmatrix} 0 & -\phi_1 & -\phi_2 & 0 \\ \varepsilon_1 & 0 & -\varepsilon_2 & 0 \\ 0 & \beta_1 e^{-\lambda\tau} & \beta_2\left(e^{-\lambda\tau} - 1\right) & \beta_3 \\ 0 & 0 & -\delta & 0 \end{bmatrix}$$

where

$$\phi_1 = \frac{r_1 R_3^*}{\left(L_3^* + r_2 T_3^*\right)^2}\ ,\ \phi_2 = \frac{r_1 r_2 R_3^*}{\left(L_3^* + r_2 T_3^*\right)^2},$$

$$\varepsilon_1 = \frac{a_1 a_2 T_3^* L_3^*}{\left(R_3^* + a_2 T_3^*\right)^2}\ ,\ \varepsilon_2 = \frac{a_1 a_2 R_3^* L_3^*}{\left(R_3^* + a_2 T_3^*\right)^2},$$

$$\beta_1 = g_1 T_3^*\ ,\ \beta_2 = g_1 L_3^*\ ,\ \beta_3 = g_2 T_3^*,$$

$$\delta = \frac{e_1 e_2 S_3^*}{\left(1 + e_2 T_3^*\right)^2}$$

Therefore the characteristic equation is given by

$$\lambda^4 - \left(\beta_2\left(e^{-\lambda\tau} - 1\right)\right)\lambda^3 + \left(\delta\beta_3 + \varepsilon_2\beta_1 e^{-\lambda\tau} + \varepsilon_1\phi_1\right)\lambda^2 + \left(\varepsilon_1\beta_1\phi_2 e^{-\lambda\tau} - \varepsilon_1\phi_1\beta_2\left(e^{-\lambda\tau} - 1\right)\right)\lambda + \delta\varepsilon_1\phi_1\beta_3 = 0 \quad (7)$$

In order to find the local stability of the steady state, we consider the case without delay time τ. Setting $\tau = 0$ in (7), we have the characteristic equation

$$\lambda^4 + \left(\delta\beta_3 + \varepsilon_2\beta_1 + \varepsilon_1\phi_1\right)\lambda^2 + \varepsilon_1\beta_1\phi_2\lambda + \delta\varepsilon_1\phi_1\beta_3 = 0. \quad (8)$$

By using the Routh-Hurwitz criteria, the non-trivial steady state is unstable for $\tau = 0$.

We now return to the analysis of equation (7) for $\tau \geq 0$. In order to determine the conditions on the parameters for Hopf bifurcation. For the steady state E_3, we let $\lambda(\tau) = u(\tau) + iv(\tau)$ where u and v are real. The equation (7) becomes

$$\begin{aligned}&(u+iv)^4 - \left(\beta_2\left(e^{-\tau(u+iv)} - 1\right)\right)(u+iv)^3 \\ &+ \left(\delta\beta_3 + \varepsilon_2\beta_1 e^{-\tau(u+iv)} + \varepsilon_1\phi_1\right)(u+iv)^2 \\ &+ \left(\varepsilon_1\beta_1\phi_2 e^{-\tau(u+iv)} - \varepsilon_1\phi_1\beta_2\left(e^{-\tau(u+iv)} - 1\right)\right)(u+iv) \\ &+ \delta\varepsilon_1\phi_1\beta_3 = 0\end{aligned} \quad (9)$$

Separating the real and imaginary parts, we obtain

$$\begin{aligned}&u^4 + v^4 - 6u^2v^2 + u + \delta\varepsilon_1\phi_1\beta_3 + 2uv\varepsilon_2\beta_1 e^{-u\tau}\sin(v\tau) \\ &- \beta_2 e^{-u\tau}(3u^2v - v^3)\sin(v\tau) \\ &- v\varepsilon_1 e^{-u\tau}(\phi_1\beta_2 - \beta_1\phi_2)\sin(v\tau) \\ &+ u\varepsilon_1 e^{-u\tau}(\beta_1\phi_2 - \phi_1\beta_2)\cos(v\tau) \\ &+ (u^2 - v^2)(\delta\beta_3 + \varepsilon_1\phi_1 + \varepsilon_2\beta_1 e^{-u\tau}\cos(v\tau)) \\ &- \beta_2(u^3 - 3uv^2)(e^{-u\tau}\cos(v\tau) - 1) = 0\end{aligned} \quad (10)$$

and

$$\begin{aligned}&4u^3v - 4uv^3 + v + \beta_2 e^{-u\tau}(u^3 - 3uv^2)\sin(v\tau) \\ &- \varepsilon_2\beta_1(u^2 - v^2)e^{-u\tau}\sin(v\tau) \\ &- \beta_2(3u^2v - v^3)(e^{-u\tau}\cos(v\tau) - 1) \\ &+ 2uv(\delta\beta_3 + \varepsilon_1\phi_1 + \varepsilon_2\beta_1 e^{-u\tau}\cos(v\tau)) \\ &+ v\varepsilon_1 e^{-u\tau}(\beta_1\phi_2 - \phi_1\beta_2)\cos(v\tau) \\ &+ u\varepsilon_1 e^{-u\tau}(\phi_1\beta_2 - \beta_1\phi_2)\sin(v\tau) = 0\end{aligned} \quad (11)$$

To determine the existence of a critical delay τ^*, the value of τ such that $u(\tau^*) = 0$ at which the switch of stability appears. We set $\tau = \tau^*$ and denote $v(\tau^*)$ as v^*, Equation (10) and (11) become

$$\begin{aligned}&v^{*2}\varepsilon_2\beta_1\cos(v^*\tau^*) - \left(v^*\varepsilon_1\left[\beta_1\phi_2 - \phi_1\beta_2\right] + v^{*3}\beta_2\right)\sin(v^*\tau^*) \\ &= v^{*4} + \delta\varepsilon_1\phi_1\beta_3 - v^{*2}\left(\delta\beta_3 + \varepsilon_1\phi_1\right)\end{aligned} \quad (12)$$

and

$$\begin{aligned}&\left(v^*\varepsilon_1(\beta_1\phi_2 - \phi_1\beta_2) + v^{*3}\beta_2\right)\cos(v^*\tau^*) \\ &+ v^{*2}\varepsilon_2\beta_1\sin(v^*\tau^*) = v^{*3}\beta_2 - v^*\end{aligned} \quad (13)$$

Adding up the squares of both equations. Hence, equations (12) and (13) reduce to

$$f(w) = w^4 + k_1w^3 + k_2w^2 + k_3w + k_4 = 0 \quad (14)$$

where $w = v^{*2}$ and

$$k_1 = -2\left(\delta\beta_3 + \varepsilon_1\phi_1\right)$$

$$k_2 = 2\varepsilon_1\phi_1\delta\beta_3 + \left(\delta\beta_3 + \varepsilon_1\phi_1\right)^2 - 2\beta_2 - \varepsilon_2^2\beta_1^2 - 2\varepsilon_1\beta_2\left[\beta_1\phi_2 - \phi_1\beta_2\right]$$

$$k_3 = 1 - 2\varepsilon_1\phi_1\delta\beta_3\left(\delta\beta_3 + \varepsilon_1\phi_1\right) - \varepsilon_1^2\left[\beta_1\phi_2 - \phi_1\beta_2\right]^2$$

$$k_4 = \varepsilon_1^2\phi_1^2\delta^2\beta_3^2$$

The value of critical delay τ^* is determined by the necessity that $u(\tau^*) = 0$, then the existence of purely imaginary eigenvalues depend on whether equation (14) has at least one positive real root. To follow this necessity, we state the conditions to ensure that equation (14) has a positive real root.

Lemma. Let $f(w)$ has the three turning points denoted by $\alpha_1, \alpha_2, \alpha_3$.

(i) If $k_4 < 0$, then $f(w)$ has at least one positive real root

(ii) If $k_4 \geq 0$ and there is $\alpha_i > 0$ for some i such that $f(\alpha_i) < 0$, then $f(w)$ has exactly two positive real roots.

(iii) If $f(\alpha_i) > 0$ for all i, then $f(w)$ has no the positive real roots.

Thus, if the solution of the equation (14) exists, we can solve for the critical time delays τ^* by substituting v^* into equation (12) and (13). We obtain

$$\tau^* = \frac{1}{v^*}\arcsin\left(\frac{m_1 v^{*7} + m_2 v^{*5} + m_3 v^{*3} - m_4 v^*}{n} \right) + \frac{2\pi(k-1)}{v^*} \tag{15}$$

where

$$m_1 = -\beta_2$$
$$m_2 = \varepsilon_2\beta_1\beta_2 + \beta_2(\delta\beta_3 + \varepsilon_1\phi_1) - \varepsilon_1[\beta_1\phi_2 - \phi_1\beta_2]$$
$$m_3 = \varepsilon_1(\delta\beta_3 + \varepsilon_1\phi_1)[\beta_1\phi_2 - \phi_1\beta_2] - \varepsilon_2\beta_1 - \delta\varepsilon_1\phi_1\beta_2\beta_3$$
$$m_4 = \delta\varepsilon_1^2\phi_1\beta_3[\beta_1\phi_2 - \phi_1\beta_2]$$
$$n = (\varepsilon_2\beta_1 v^{*2})^2 + (\beta_2 v^{*3} + \varepsilon_1[\beta_1\phi_2 - \phi_1\beta_2]v^*)^2$$

and $k = 0,1,2,\ldots$.

We now show that the system of delay differential equations (6a)-(6d) exhibits the Hopf bifurcation as the value of time delay τ passes through the critical value τ^* by showing that

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} \neq 0$$

From equation (10) and (11), we find the differentiation with respect to τ and evaluate at $\tau = \tau^*$ for which $u(\tau^*) = 0$ and $v(\tau^*) = v^*$. We then obtain

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} P + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} Q = R \tag{16}$$

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} (-Q) + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} P = S \tag{17}$$

where

$$\begin{aligned} P =\ & 1 - 3\beta_2 v^{*2} \\ & + \left[3\beta_2 v^{*2} + \varepsilon_2\beta_1\tau^* v^{*2} + \varepsilon_1(\beta_1\phi_2 - \phi_1\beta_2)\right]\cos(v^*\tau^*) \\ & + \left[2\varepsilon_2\beta_1 v^* - \beta_2\tau^* v^{*3} - \tau^* v^* \varepsilon_1(\beta_1\phi_2 - \phi_1\beta_2)\right]\sin(v^*\tau^*) \end{aligned}$$

$$\begin{aligned} Q =\ & 4v^{*3} - 2v^*(\delta\beta_3 + \varepsilon_1\phi_1) \\ & + \left[\beta_2\tau^* v^{*3} - 2\varepsilon_2\beta v^*_1 + \tau^* v^* \varepsilon_1(\beta_1\phi_2 - \phi_1\beta_2)\right]\cos(v^*\tau^*) \\ & + \left[3\beta_2 v^{*2} + \varepsilon_2\beta_1\tau^* v^{*2} + \varepsilon_1(\beta_1\phi_2 - \phi_1\beta_2)\right]\sin(v^*\tau^*) \end{aligned}$$

$$\begin{aligned} R =\ & \left(-v^{*4}\beta_2 - \varepsilon_1 v^{*2}(\beta_1\phi_2 - \phi_1\beta_2)\right)\cos(v^*\tau^*) \\ & - \varepsilon_2\beta_1 v^3 \sin(v^*\tau^*) \end{aligned}$$

$$\begin{aligned} S =\ & -\varepsilon_2\beta_1 v^{*3}\cos(v^*\tau^*) \\ & + \left(\beta_2 v^{*4} + v^{*2}\varepsilon_1(\beta_1\phi_2 - \phi_1\beta_2)\right)\sin(v^*\tau^*) \end{aligned}$$

By solving equations (16) and (17) , we have

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} = \frac{PR - QS}{P^2 + Q^2} \tag{18}$$

Consider

$$\begin{aligned} PR - QS =\ & 4v^{*8} - 6(\delta\beta_3 + \varepsilon_1\phi_1)v^{*6} \\ & + (4\delta\varepsilon_1\phi_1\beta_3 + 2(\delta\beta_3 + \varepsilon_1\phi_1)^2 - 2\varepsilon_2^2\beta_1^2 \\ & - 4\varepsilon_1\beta_2(\beta_1\phi_2 - \phi_1\beta_2) - 4\beta_2)v^{*4} \\ & + (1 - \varepsilon_1^2(\beta_1\phi_2 - \phi_1\beta_2)^2 - 2\delta\varepsilon_1\phi_1\beta_3(\delta\beta_3 + \varepsilon_1\phi_1))v^{*2} \end{aligned}$$

$$\begin{aligned} =\ & v^{*2}(4v^{*6} - 6(\delta\beta_3 + \varepsilon_1\phi_1)v^{*4} \\ & + (4\delta\varepsilon_1\phi_1\beta_3 + 2(\delta\beta_3 + \varepsilon_1\phi_1)^2 - 2\varepsilon_2^2\beta_1^2 \\ & - 4\varepsilon_1\beta_2(\beta_1\phi_2 - \phi_1\beta_2) - 4\beta_2)v^{*2} \\ & + (1 - 2\delta\varepsilon_1\phi_1\beta_3(\delta\beta_3 + \varepsilon_1\phi_1) - \varepsilon_1^2(\beta_1\phi_2 - \phi_1\beta_2)^2)) \end{aligned}$$

$$= v^{*2}\left(4w^3 + 3k_1 w^2 + 2k_2 w + k_3\right)$$

$$= v^{*2} \cdot \left.\frac{df(w)}{dw}\right|_{w=v^{*2}}$$

Since $\frac{df(w)}{dw}$ equal to zero where w is the turning point of f. Following on from the Lemma, we see that $\left.\frac{df(w)}{dw}\right|_{w=v^{*2}} \neq 0$. Thus, we can conclude that

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} = \frac{PR-QS}{P^2+Q^2} \neq 0 \qquad (19)$$

Therefore, the Hopf bifurcation arises as τ passes through the critical value τ^*.

III. Numerical Results

Testosterone is altered by the hormonal milieu. In order to show the quantitative behavior of the three hormones involved in Testosterone regulation with relation to circulating SHBG levels. We conduct numerical simulations with the same realistic parameter values that Greenhalgh and Khan[14] used in simulation. For the other parameters, we take $g_2 = 0.0092$ /min, $e_1 = 5.9$ /min, $e_2 = 0.3$ and $\mu_4 = 0.031$ /min which correspond to the steady state E_3 and the normal range of hormone levels. After hundreds of numerical simulations, we find that the system is asymptotically stable when $\tau < \tau^* \approx 123.47$. Fig.2 shows that the equilibrium E_3 is asymptotically stable where $\tau = 120$. As shown in Fig. 3, the system undergoes a Hopf bifurcation occurs near the positive equilibrium $E_3(1.07, 4.95, 641.83, 1.28)$ where $\tau > \tau^* \approx 123.47$. The oscillatory characteristics of hormone regulations agree well with experimental data and other simulated hormone fluctuation levels.

IV. Conclusion

The mathematical model developed in this paper describes the feedback mechanisms in consideration of cyclicity of the male hormonal balance on the influence of variations in the SHBG concentration. Levels of total testosterone can, therefore, be directly affected by changes in levels of SHBG to maintain a constant concentration of free testosterone. In addition, we used a time delay τ in the model to explain a period for traveling the LH hormone from pituitary gland to the target cells and actions of gonadotrophins in the gonads.

We investigated our equations that incorporate a discrete delay in the time. In order to show that Hopf bifurcation can occur, the numerical simulations are given to explain the analytical results. We found that a family of periodic solutions bifurcate from the equilibrium when τ passes through a critical value. Moreover, this model predicts the changes in the cycle in correspondence with the influence of

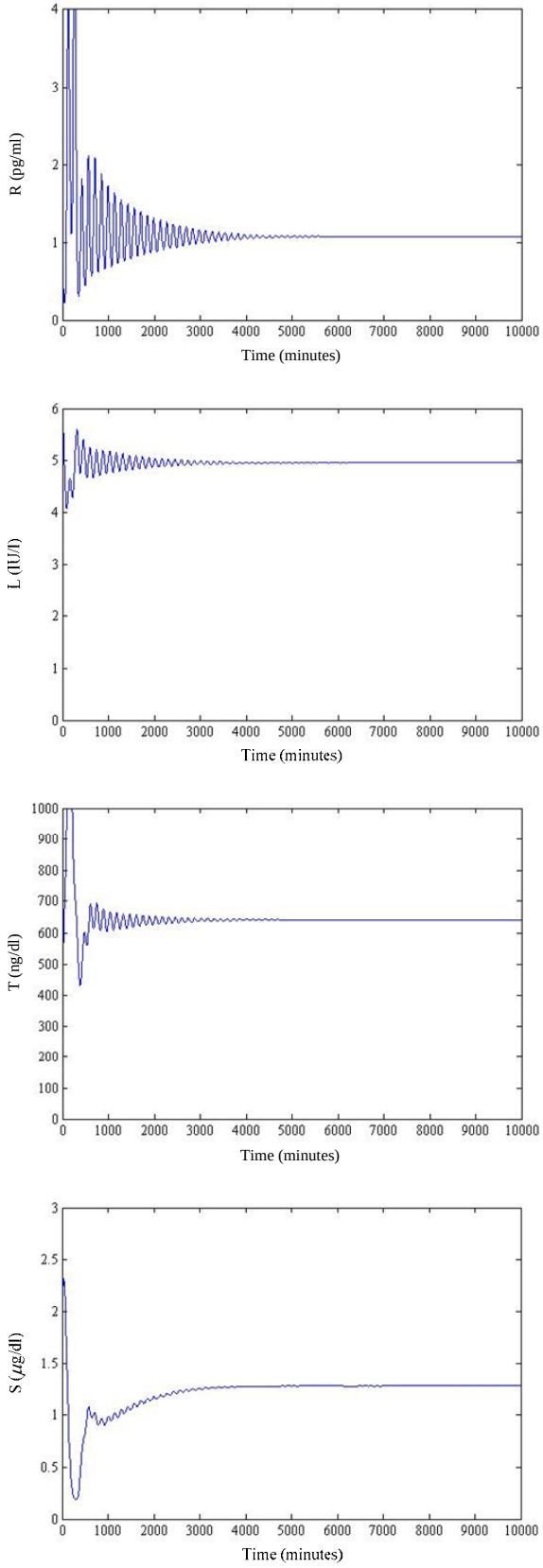

Fig 2. Numerical simulations for equation (6a)-(6d) with $\tau = 120$. The positive equilibrium is asymptotically stable. The initial value is (1, 5, 600, 1)

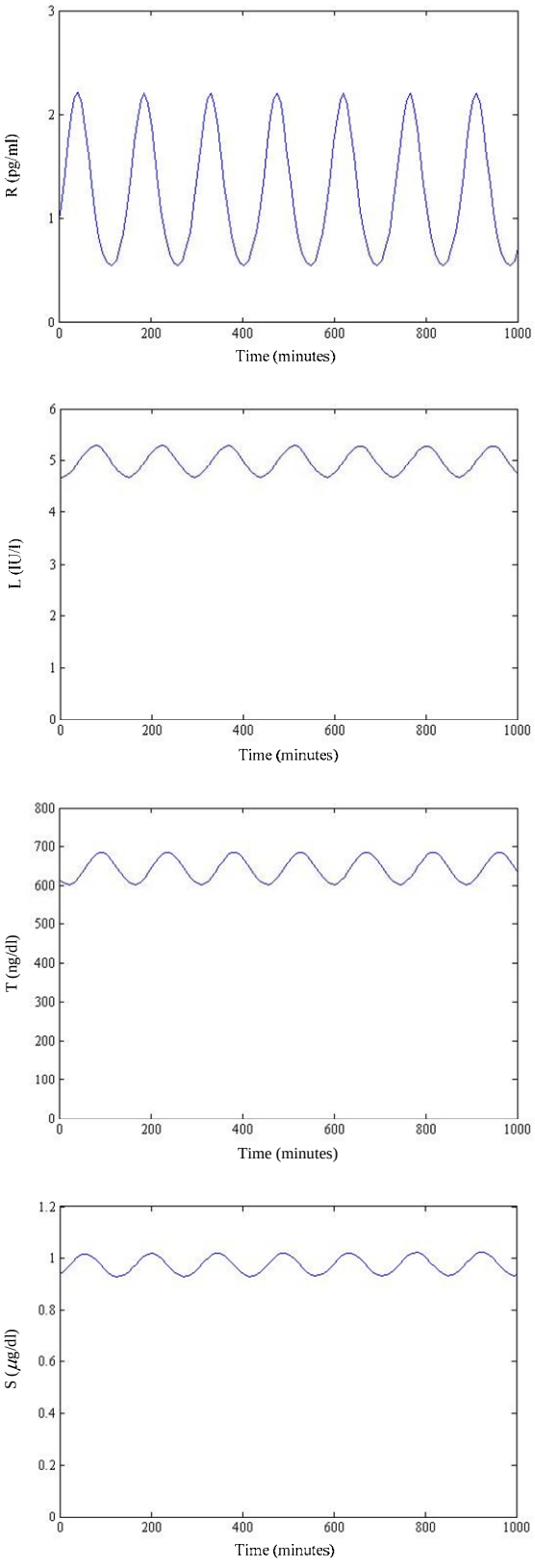

Fig 3. Numerical simulations for the equation (6a)-(6d) with $\tau = 124$. Hopf bifurcation occurs from the positive equilibrium. The initial value is (1, 5, 600, 1)

variations in the SHBG concentration on the testosterone production. This model can explain the pulsatile secretion of hormones in male [16] as well as concentration curves correspond to the experimental data well [17,18].

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