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ROLES OF SEX HORMONE-BINDING GLOBULIN ON PULSATILE SECRETION OF TESTOSTERONE BY MATHEMATICAL MODELING

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TAREERAT TANUTPANIT

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หัวข้อวิทยานิพนธ์	บทบาทโกลบูลินที่จับกับฮอร์โมนเพศในกลไกการหลั่งฮอร์โมนเพศชายโดยแบบจำลองทางคณิตศาสตร์
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บทคัดย่อ

เทสโทสเทอโรนเป็นฮอร์โมนที่มีลักษณะการหลั่งแบบเป็นจังหวะภายในกลไกการควบคุมแบบย้อนกลับบนแกนไฮโปทาลามิก-พิทูอิทารี-โกนาดอล ในการศึกษานี้ได้พัฒนาแบบจำลองทางคณิตศาสตร์เพื่อใช้ศึกษารูปแบบการหลั่งในกระบวนการสร้างฮอร์โมนเทสโทสเทอโรนเพื่อรักษาสภาวะสมดุลของร่างกายในเพศชาย โดยพิจารณาถึงความล่าช้าของเวลาที่เกิดจากการเดินทางของฮอร์โมน Luteinizing hormone จากต่อมใต้สมองไปยังเซลล์สร้างฮอร์โมนเทสโทสเทอโรน แบบจำลองที่สร้างขึ้นนี้ได้พัฒนามาจากแบบจำลองทางคณิตศาสตร์ของ David Greenhalgh และ Qamar J.A Khan (2009) ทั้งนี้ในแบบจำลองทางคณิตศาสตร์แรกถูกสร้างขึ้นเพื่อศึกษากระบวนการหลั่งฮอร์โมนที่มีการรักษาสมดุลของระดับเทสโทสเตอโรนในสภาวะที่มีการเปลี่ยนแปลงของระดับโปรตีน Sex hormone-binding globulin (SHBG) ที่จะจับกับฮอร์โมนเทสโทสเตอโรนในเลือด และในแบบจำลองทางคณิตศาสตร์ที่สองถูกใช้ในการศึกษาการเปลี่ยนแปลงของระดับ SHBG-bound testosterone หลังจากเทสโทสเทอโรนถูกปล่อยออกสู่กระแสเลือด เมื่อวิเคราะห์แบบจำลองด้วยวิธีการของการจำลองเชิงพลวัตมาตรฐานทำให้ได้เงื่อนไขที่จำเป็นของพารามิเตอร์สำหรับการเกิดผลเฉลยที่มีลักษณะเป็นคาบ ในส่วนของการจำลองเชิงตัวเลขพบว่าแบบจำลองที่สร้างขึ้นให้ผลเฉลยที่มีลักษณะสอดคล้องกับพฤติกรรมการหลั่งของฮอร์โมนเทสโทสเตอโรน ซึ่งจะถูกนำไปพัฒนาเพื่อศึกษาปัจจัยที่ทำให้เกิดความเปลี่ยนแปลงของระดับฮอร์โมนที่ผิดปกติ

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Thesis	Roles of Sex Hormone-Binding Globulin on Pulsatile Secretion of Testosterone by Mathematical Modeling
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Abstract

In males, testosterone is the primary sex hormone that is secreted in a pulsatile manner. The biosynthesis of testosterone is controlled with hormonal interactions via feedback and feedforward relationships in the complex dynamical system. Mathematical models for the regulation of male sex hormone have been studied to understand the interaction of hormones in biological system. In this study, the modified mathematical models with a time delay were developed from the mathematical model proposed by Greenhalgh and Khan (2009). In the first model, the mathematical model was constructed to describe the feedback mechanisms concerning of the cycle of the male hormonal balance on the influence of variations in the sex hormone-binding globulin (SHBG) concentration. For the second model, the relations which explain the rate of binding SHBG to testosterone was conducted into the mathematical model in order to investigate the change of SHBG-bound testosterone at the time that testosterone is released into the bloodstream and then bind to SHBG. The standard dynamical modeling method was used to analyse the mathematical models that include a delay in order to obtain the conditions under which bifurcation phenomenon occurs. Numerical simulations were performed to illustrate the analytical results which correspond to the behavior of testosterone secretion. In addition, the models will be developed to study factors causing hormone imbalance.

Keywords : Hypothalamis-Pituitary-Gonadal axis, Mathematical modeling, Testosterone, Homeostasis, Gonadal steroid hormones.

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Miss Tareerat Tanutpanit

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Chapter 1
Introduction

1.1 Statement and Significant of the Problems

Mathematics plays an important role in other fields of science. In biology, mathematical modeling is the application of mathematics. It is an efficient tool to enhance the understanding of the behavior of complex biological systems. There are the uses of mathematical models in endocrinology. Many modeling studies of endocrine systems have been published since the 1960s [1,2]. These models have been used to describe a chain of chemical reaction corresponding to the physiological and biochemical structures.

Hormones are chemical substances which are produced by the glands in the bodily system. It has many functions including controlling and regulation the activity of certain tissues or organs. In the reproductive system, sex hormones are responding to control the development of primary and secondary sexual characteristics.

In male, testosterone is the majority of sex hormone secreted into the bloodstream by the male sex gland. This male sex hormone is synthesized and secreted primarily by Leydig cells in the testis. It plays a crucial role in the development and maintenance of many male characteristics. The body carefully regulates the production of testosterone in order to ensure normal development and regulation of male reproductive system [3]. Testosterone synthesis is controlled by biological mechanism in the reproductive hormonal axis which contains three main components: the hypothalamus, the pituitary gland and the gonads. Hormones which are produced in this axis include gonadotropinreleasing hormone (GnRH), luteinizing hormone (LH) and testosterone (T). These hormones are implicated in regulation of reproductive operation via a complex feedback loop. GnRH is released by the hypothalamus in an episodic manner. It then triggers the pituitary gland to produce and secret LH into the blood, which activates the enzymatic conversion of cholesterol into testosterone in the Leydig cells. Testosterone is secreted in pulsatile

pattern. Its levels have rapidly acting feedback activity at both hypothalamic level and pituitary level in order to maintain adequate levels of the hormones in the male reproductive system [4,5]. Furthermore, as testosterone circulates in the blood it mostly binds to plasma proteins called sex hormone binding globulin, or SHBG. SHBG-bound testosterone is so tightly bound that it is not biologically active. High concentrations of SHBG will reduce the level of bioavailable testosterone in circulation. Thus, levels of SHBG can have a role in determining levels of testosterone.

As direct measurements of hormones in the human are difficult to implement due to ethical reasons. Mathematical models for the regulation of male sex hormone have been widely used for a long time and have been studied in order to understand the interaction of hormones in dynamic biological system.

In this study, mathematical models with time delay is required and will be developed. Modeling is performed with ordinary differential equations in order to explain the operation of negative feedback in the endocrine system of testosterone regulation in the male. The variations in the SHBG level will be considered in these models. Furthermore, the obtained theoretical results are validated through simulation and numerical calculations.

1.2 Objectives of the study

The major objectives of this thesis are to modify the mathematical model of time-delayed feedback in the male hypothalamic-pituitary-gonadal (HPG) axis, which is originally presented by Khan and Greenhalgh. They described the biological mechanism responsible for the regulation of testosterone in the GnRH-LH-T axis. Standard analytical techniques are used to analyse the modified mathematical models in order to obtain the conditions under which bifurcation phenomenon occurs. Moreover, numerical simulations are performed to illustrate concentration curves of the hormones and interesting dynamical behavior depending on the delay parameter. The specific objectives are:

1) To analyse the keeping testosterone concentration within a certain range on the influence of variations in the sex hormone-binding globulin (SHBG) concentration.
2) To investigate the correlation between total testosterone level and SHBG-bound testosterone level.
3) To use the results of mathematical models for analyzing the impact of changing on the male hormonal regulation.

1.3 Scope of the study

The goals and objectives are as follows:

1) To construct a mathematical model with a time delay for testosterone hormonal regulation. The variation in the SHBG level is a factor also considered in this model.
2) To develop a mathematical model of the testosterone homeostatic mechanism to account for the correlation between total testosterone level and SHBG-bound testosterone level in HPG-axis.
3) To analyze the results from the models and develop mathematical model for the estimation of the endocrine system of testosterone regulation.
4) To illustrate that the constructed mathematical models in this study can explain the regular fluctuations of the hormones in hormonal regulation of the male reproductive system.

1.4 Process of the study

The processes of the study are

1) Study the human anatomy and physiology in the endocrine system of male hormonal regulation.
2) Study definitions, theoretical background and review the related literatures.
3) Set up the mathematical models.
4) Analyze the mathematical models.
5) Develop the mathematical models.

6) Compare the analytical results and discussion.

1.5 Benefits

This study gives us a better understanding of the interaction of hormones in dynamic biological system. The resulting model can be used to study the secretory pattern of hormones in dynamic biological system. So it can be developed to investigate factors affecting on imbalancing in the reproductive hormonal system.

Chapter 2
Literature Reviews

2.1 The male hormonal regulation

Many hormones are made by the glands of the body. They are produced and secreted in one part of the body and then travel to other body tissues in which they reduce their effects. Testosterone (T) belongs to a class of male hormones called androgens, which are sometimes called steroids or anabolic steroids. It is synthesized and secreted primarily by the interstitial cells of the testes, small quantities are also produced by the adrenal glands. Both men and women produce this hormone, which is presented in much greater levels in men than women. Testosterone are secreted in pulsatile patterns in male mammals. Its levels rise and then fall over the short term (2-3 hours) in humans [8-11].

Testosterone is responsible for many of the physical characteristics specific to adult males. It plays important roles in the development and regulation of bodily functions; therefore, the regulation of testosterone production is tightly controlled to maintain concentrations of circulating hormones required for normal development and function in the body. Thus 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 [12,13], where cholesterol is gradually changed into a series of compounds until it becomes testosterone. Testosterone synthesis is under the tight control of the pituitary gonadotrophin luteinizing hormone. In the HPG-axis, negative feedback activity is primarily responsible for minimizing hormonal perturbations and maintaining homeostasis [14] , that is , as blood levels of testosterone is too high, in the hypothalamic-pituitary unit, the production and secretion of GnRH and LH have

been controlled by a negative-feedback which lead to reduce the frequency and amount of pulsatile LH release. As a result, testosterone production is dropped [8] as shown in figure 2.1.

The secretion of the LH follows an episodic pattern resulting in there being fluctuations of the level of testosterone levels in the circulating blood [15,16]. To maintain the level of testosterone at some equilibrium levels, There are also feedback mechanism that regulate the production and release of GnRH and LH , i.e., 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.

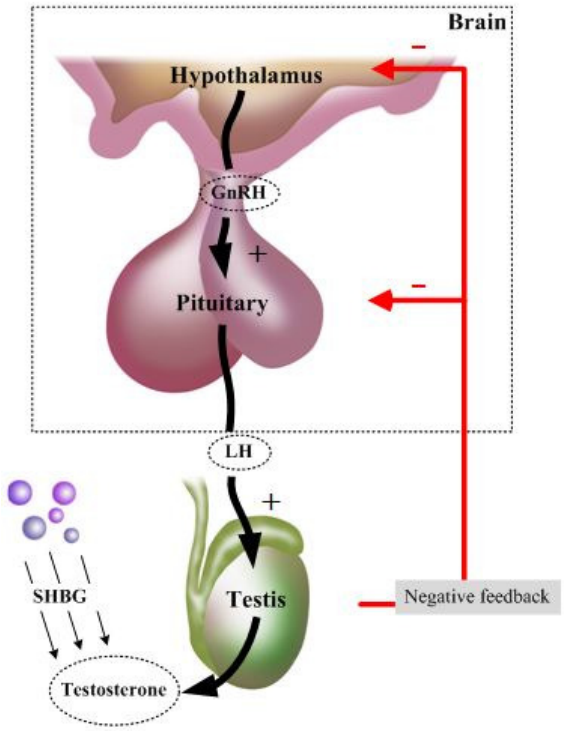

Figure 2.1 The normal regulation of the hypothalamus down to the testis in the negative feedback mechanism. Hypothamic hormone (GnRH) secreted in plusatile pattern by the hypothalamus triggers the production of LH in pituitary gland. After LH is released to the bloodstream, it travels to the testis for stimulation of the testosterone secretion. The testosterone in turn acts to modulate GnRH and LH secretion by negative feedback.

After testosterone is secreted into the bloodstream, 96-98 % will be bound to various carrier proteins. One of these will be the sex hormone-binding globulin (SHBG). This protein is produced primarily in the liver. The entry of SHBG into hypothalamus-pituitary-gonadal axis is shown in the lower left corner of figure 2.1. SHBG plays an important role in determining the testosterone for its endocrinology activity. Because SHBG can tightly bind to the testosterone making them physiologically inactive [17-19]. A large fraction (~ 60-70%) of the testosterone will be of this type. Another 28 - 38% will be bound to albumin, the bind between albumin and testosterone is weak and readily dissociates in order to create free testosterone when it need. Only a small percentage (~ 2%) of testosterone will be unbound. These will be considered to be free testosterone (FT). Only the free testosterone (FT) is capable of entering a cell and activating the receptor on SHBG

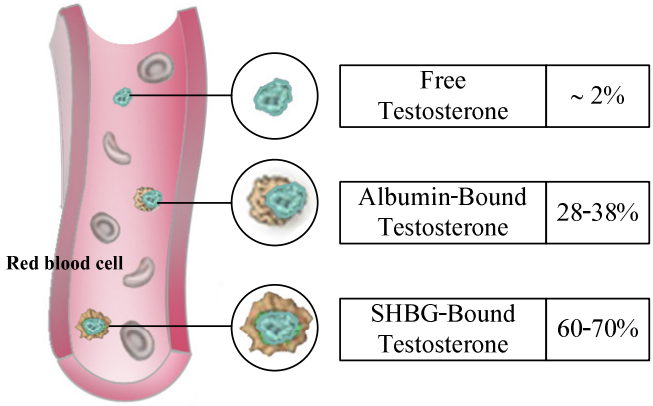

Figure 2.2 Testosterone fractions in the blood.

gene on chromosome and turning it on. The circulating bound and free testosterone are collectively referred to the total testosterone. The free testosterone and the albumin-bound testosterone are physiologically available to the body tissues. These are known as bioavailable testosterone (BioT) [20]. The level of SHBG becomes one factor that determines the total testosterone level [21-24]. High concentrations of SHBG reduce the level of bioavailable testosterone. Consequently, the total concentration of testosterone must increase to maintain adequate levels of bioavailable testosterone [25].

There are several reviews of the experimental data corresponding to the validity of the GnRH-LH-T system [26-28]. An important recurrent observation in many experiments in adult males is that the level of both LH and testosterone undergo cyclic fluctuations of the same period. Nankin and Troen [29] measured LH concentration in men and found regular cyclic periods of 1-3 hours. The LH fluctuations in the blood vary in amplitude from to 1.8 to 8.6 IU/l in adult men [30]. The standard range of testosterone is about 300 -1000 ng/dl with an average level of 642 ng/dl [31] in adult men. In addition, some researchers suggest that the healthy men have testosterone levels between 400-600 ng/dl. Blood testosterone fluctuate over the short term (2-3 hours) in human male [32]. Furthermore, the basic range of SHBG, the principle blood protein that ties up androgenic hormone, is 0.674-5.620 μg/dl [33].

2.2 Literature Reviews

Mathematical models for the regulation of male sex hormone have been widely used for a long time and have been studied in order to understand the interaction of hormones in dynamic biological system. Denoting the concentrations of GnRH, LH and Testosterone, respectively, by $R(t)$, $L(t)$ and $T(t)$. Smith (1980) proposed a simple negative feedback compartment model involving the three hormones GnRH, LH and T [34]. It is represented schematically as shown in Figure 2.3. This model is generalized to explain the pulsatile hormone regulation in the GnRH-LH-T axis.

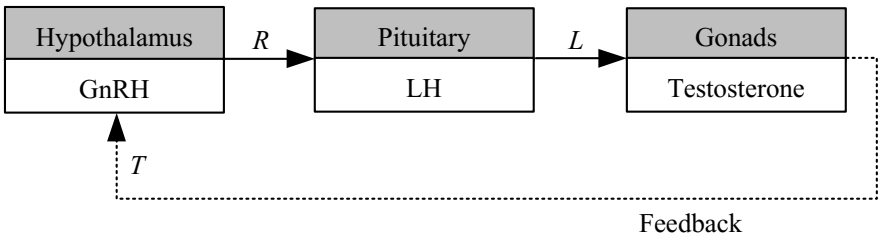

Figure 2.3 Compartmental model for the regulation of testosterone production in the male. The solid lines denote activation, dashed line denotes inhibition control to the hypothalamus from the testes.

Smith's model, which reflect the scheme in Figure 2.3, comprises three differential equations as follows

$$\begin{aligned} \frac{dR}{dt} &= f(T) - b_1(R) \ , \\ \frac{dL}{dt} &= g_1(R) - b_2(L) \ , \\ \frac{dT}{dt} &= g_2(L) - b_3(T) \ . \end{aligned} \tag{2.1}$$

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 [35] 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

$$\begin{aligned} \frac{dR}{dt} &= f(T) - b_1(R) \ , \\ \frac{dL}{dt} &= g_1(R) - b_2(L) \ , \\ \frac{dT}{dt} &= g_2\big(L(t-\tau)\big) - b_3(T) \end{aligned} \tag{2.2}$$

where τ is a delay associated with the blood circulation time in the body. From the model (2.1), Murray [34] suggested a simple delay model

$$\begin{aligned} \frac{dR}{dt} &= f(T) - b_1 R \ , \\ \frac{dL}{dt} &= g_1 R - b_2 L \ , \\ \frac{dT}{dt} &= g_2 L - b_3 T \ . \end{aligned} \tag{2.3}$$

Here b_1, b_2, b_3, g_1 and g_2 are positive constants. Murray exhibited that there is a critical time delay τ_c such that the positive steady state of the model (2.3) is linearly unstable with growing oscillations. Limit cycle periodic solutions could take place with certain parameter values.

Ruan and Wei [36] modified the model of Smith [37] which contains a time delay. They exhibit that a unique positive equilibrium point of this model is locally asymptotically stable for certain parameter whatever the value of the time delay. But there is a critical time delay such that this unique positive equilibrium point is locally asymptotically stable when the time delay is less than the critical value. When the time delay passes through the critical value, Hopf bifurcation occurs and the steady state becomes unstable. In sum, this model can describe the cyclic fluctuations of three hormones for certain parameter values.

In addition, Cartwright and Husain [32] suggested the model which is based on more recent experimental results with further delays. This model also incorporates inhibitory effect which control to the hypothalamus from the pituitary and testes. They proposed differential equations as follows:

$$\begin{aligned}
\frac{dR}{dt} &= r_R H\left[2-\frac{L(t-\tau_A)}{L_0}-\frac{T(t-\tau_B)}{T_0}\right]-d_R R\,,\\
\frac{dL}{dt} &= r_L R(t-\tau_C)-d_L L\,,\\
\frac{dT}{dt} &= r_T L(t-\tau_D-\tau_E)-d_T T\,.
\end{aligned} \tag{2.4}$$

where d_R, d_L, d_T, r_R, r_L and r_T are all rate constants. $\tau_A, \tau_B, \tau_C, \tau_D$ and τ_E are all time delays. And, $H(x)$ is the Heaviside step function, which is defined as

$$H(x) = \begin{cases} 0\,, & x<0 \\ \frac{1}{2}\,, & x=0 \\ 1\,, & x>0 \end{cases}\,.$$

This model can interpret the characteristics of the male hormonal regulation and fluctuations of the level of GnRH and LH after castration.

In order to produce the model more realistic, experimental results need to be considered as much as possible in it. The effects of LH on the hypothalamus were observed by Gay [38] and the effects of testosterone on the hypothalamus were observed by Steiner et al. [39].

In 2009, Greenhalgh and Khan [40] proposed their model in order to interpret the population dynamics of the hypothalamic hormone, the pituitary hormone and testosterone in the male hormonal regulation system. They used realistic parameter values to exhibit that their model can predict the regular oscillations observed in concentrations of GnRH, LH and testosterone. Greenhalgh and Khan introduced the delay differential equation mathematical model which improved on previously simpler models by taking into account observed experimental facts. The delay-differential equation model is therefore formulated as follows:

$$\begin{aligned} \frac{dR}{dt} &= \frac{b_1 R}{L + b_3 T} - b_2 R\,, \\ \frac{dL}{dt} &= \frac{c_1 R L}{R + b_5 T} - c_2 L\,, \\ \frac{dT}{dt} &= b_6 L(t-\tau) T - b_4 T\,. \end{aligned} \tag{2.5}$$

where $b_1, b_2, \ldots, b_6, c_1$ and c_2 are strictly positive constants.

This model can interpret the cyclic release of three major hormones in the endocrinology processes of testosterone regulation. It also took into account a time delay between stimulation of the testis by LH and the rise in testosterone in the bloodstream.

In this thesis, we introduce biomathematical models which are enlarged from the mathematical model proposed by Greenhalgh and Khan [40]. The aim of this study is to discuss and evaluate the relations between total testosterone, SHBG and SHBG-bound testosterone. The modified nonlinear system models are utilized to provide wider understanding about the role of sex hormone-binding globulin in the process of pulsatile endocrine regulation of testosterone.

Chapter 3

Mathematical Modeling of the Testosterone Regulation Including the Role of Sex Hormone-Binding Globulin

In this chapter, we introduce the mathematical model with a time delay is developed from the mathematical model proposed by Greenhalgh and Khan [40] in order to study the interaction of hormones in balancing the endocrine system of testosterone regulation.

3.1 Mathematical model

We now construct the mathematical model in order to investigate blood concentrations in testosterone hormonal regulation on the influence of variations in the SHBG concentration.

We define the variables in our model as follows:

$\frac{dR}{dt}$ is the rate of change for plasma concentration of gonadotropin-releasing hormone (GnRH)

$\frac{dL}{dt}$ is the rate of change for plasma concentration of luteinizing hormone (LH)

$\frac{dT}{dt}$ is the rate of change for plasma concentration of testosterone (T)

$\frac{dS}{dt}$ is the rate of change for plasma concentration of sex hormone-binding globulin (SHBG)

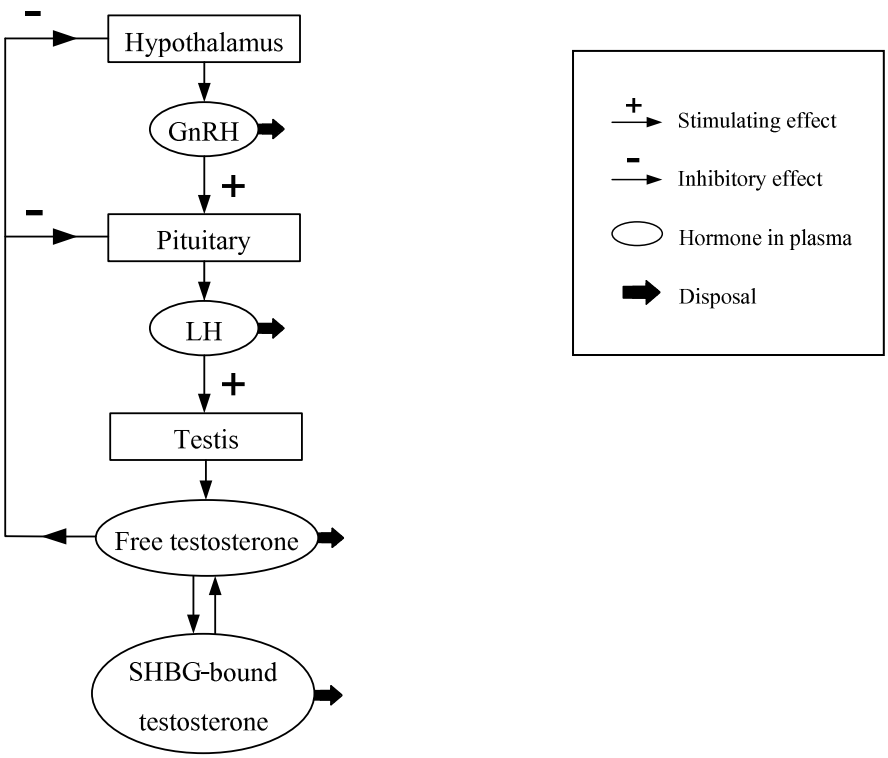

Figure 3.1 The flow and interactions block diagram of the hypothalamo-pituitary-gonadal axis in men.

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

$$\frac{dR}{dt} = \frac{r_1 R}{L + r_2 T} - \mu_1 R \qquad (3.1)$$

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

$$\frac{dL}{dt} = \frac{a_1 RL}{R + a_2 T} - \mu_2 L \tag{3.2}$$

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

$$\frac{dT}{dt} = g_1 L(t-\tau)T - \mu_3 T \tag{3.3}$$

In order to take into account the influence of variations in the SHBG concentration on the testosterone production. Equations (3.1) - (3.3) are modified to be as the following equations.

$$\frac{dR}{dt} = \frac{r_1 R}{L + r_2 T} - \mu_1 R \tag{3.4}$$

$$\frac{dL}{dt} = \frac{a_1 RL}{R + a_2 T} - \mu_2 L \tag{3.5}$$

$$\frac{dT}{dt} = g_1 L(t-\tau)T + g_2 ST - \mu_3 T \tag{3.6}$$

$$\frac{dS}{dt} = \frac{e_1 S}{1 + e_2 T} - \mu_4 S \tag{3.7}$$

The term $g_2 ST$ is added into (3.6) 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. [6]. Moreover, the first term on the right-hand side of (3.7) represents the rate of the SHBG production which is assumed for decreasing the hepatic production of SHBG by testosterone [25]. Each hormone is cleared from the bloodstream at a rate proportional to its concentration. In the system (3.4)-(3.7), the parameters μ_1, μ_2, μ_3, μ_4 refer to the clearance rates of the all four hormones which is proportional to their concentration and r_1, r_2, a_1, a_2, g_1, g_2, e_1, e_2 are strictly positive.

3.2 Analysis of the mathematical model

3.2.1 The steady state solutions

In order to find steady states of the equations (3.4)-(3.7), we let $E\left(R^*, L^*, T^*, S^*\right)$ be an equilibrium point of the system and then set the right hand side of equations (3.4) to (3.7) to zero.

$$\frac{r_1 R^*}{L^* + r_2 T^*} - \mu_1 R^* = 0 \tag{3.8}$$

$$\frac{a_1 R^* L^*}{R^* + a_2 T^*} - \mu_2 L^* = 0 \tag{3.9}$$

$$g_1 L^* T^* + g_2 S^* T^* - \mu_3 T^* = 0 \tag{3.10}$$

$$\frac{e_1 S^*}{1 + e_2 T^*} - \mu_4 S^* = 0. \tag{3.11}$$

From equation (3.8), we get $R^* = 0$ or

$$\frac{r_1}{L^* + r_2 T^*} - \mu_1 = 0. \tag{3.12}$$

Considering $R^* = 0$ in equation (3.9), we have

$$L^* = 0.$$

Substituting $L^* = 0$ in equation (3.10), we get

$$T^* = 0 \quad \text{or} \quad S^* = \frac{\mu_3}{g_2}. \tag{3.13}$$

Considering $T^* = 0$ in equation (3.11), we have the first equilibrium point of the system, $E_1\left(R_1^*, L_1^*, T_1^*, S_1^*\right) = (0,0,0,0)$. Moreover, we obtain the second equilibrium point by substituting $S^* = \frac{\mu_3}{g_2}$ into equation (3.11), therefore $E_2\left(R_2^*, L_2^*, T_2^*, S_2^*\right) = \left(0, 0, \frac{1}{e_2}\left(\frac{e_1}{\mu_4} - 1\right), \frac{\mu_3}{g_2}\right)$.

From equation (3.12), we can rewrite equation (3.10) in the form

$$\left[g_1\left(\frac{r_1}{\mu_1} - r_2 T^*\right) + g_2 S^* - \mu_3 \right] \cdot T^* = 0 . \qquad (3.14)$$

That is

$$T^* = 0 \quad \text{or} \quad S^* = \frac{1}{g_2}\left[\mu_3 - g_1\left(\frac{r_1}{\mu_1} - r_2 T^*\right)\right]$$

Thus, we get the other equilibriums points as follows:

$$E_3\left(R_3^*, L_3^*, T_3^*, S_3^*\right) = \left(\frac{a_2(\frac{e_1}{\mu_4} - 1)}{e_2(\frac{a_1}{\mu_2} - 1)}, \frac{r_1}{\mu_1} - \frac{r_2}{e_2}(\frac{e_1}{\mu_4} - 1), \frac{1}{e_2}(\frac{e_1}{\mu_4} - 1), \frac{1}{g_2}(\mu_3 - g_1(\frac{r_1}{\mu_1} - \frac{r_2}{e_2}(\frac{e_1}{\mu_4} - 1))) \right)$$

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

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

$$\frac{e_1}{\mu_4} > 1 \ , \ \frac{a_1}{\mu_2} > 1 \ , \ \frac{r_1}{\mu_1} - \frac{r_2}{e_2}\left[\frac{e_1}{\mu_4} - 1\right] > 0 \ \text{ and } \ \mu_3 - g_1\left(\frac{r_1}{\mu_1} - \frac{r_2}{e_2}\left[\frac{e_1}{\mu_4} - 1\right]\right) > 0 .$$

We can see that only the equilibrium point E_3 is physically relevant because it has all hormones present. Thus, in the next section, we will only consider the stability of the system (3.4)-(3.7) about the equilibrium E_3.

3.2.2 Local stability Analysis

In this section, we study the stability of the steady state and its bifurcation behavior for the equations (3.4)-(3.7). We look for solution of the system in the form

$$\begin{bmatrix} R(t) \\ L(t) \\ T(t) \\ S(t) \end{bmatrix} = C_0 e^{\lambda t}$$

where $C_0 = \begin{bmatrix} c_1 & c_2 & c_3 & c_4 \end{bmatrix}^T$ is constant vector and λ is an eigenvalue of a Jacobian matrix. It is direct to show that the stability matrix of the system linearized about the positive equilibrium E_3 is

$$\mathbf{J} = \begin{bmatrix} -\lambda & -\dfrac{r_1 R_3^*}{\left(L_3^* + r_2 T_3^*\right)^2} & -\dfrac{r_1 r_2 R_3^*}{\left(L_3^* + r_2 T_3^*\right)^2} & 0 \\ \dfrac{a_1 a_2 T_3^* L_3^*}{\left(R_3^* + a_2 T_3^*\right)^2} & -\lambda & -\dfrac{a_1 a_2 R_3^* L_3^*}{\left(R_3^* + a_2 T_3^*\right)^2} & 0 \\ 0 & g_1 T_3^* e^{-\lambda\tau} & g_1 L_3^* \left(e^{-\lambda\tau} - 1\right) - \lambda & g_2 T_3^* \\ 0 & 0 & -\dfrac{e_1 e_2 S_3^*}{\left(1 + e_2 T_3^*\right)^2} & -\lambda \end{bmatrix} \tag{3.15}$$

The matrix (3.15) can be written as

$$\mathbf{J} = \begin{bmatrix} -\lambda & -\phi_1 & -\phi_2 & 0 \\ \varepsilon_1 & -\lambda & -\varepsilon_2 & 0 \\ 0 & \beta_1 e^{-\lambda\tau} & \beta_2 \left(e^{-\lambda\tau} - 1\right) - \lambda & \beta_3 \\ 0 & 0 & -\delta & -\lambda \end{bmatrix} \tag{3.16}$$

where

$$\phi_1 = \frac{r_1 R_3^*}{\left(L_3^* + r_2 T_3^*\right)^2} \ , \ \phi_2 = \frac{r_1 r_2 R_3^*}{\left(L_3^* + r_2 T_3^*\right)^2} \ , \ \varepsilon_1 = \frac{a_1 a_2 T_3^* L_3^*}{\left(R_3^* + a_2 T_3^*\right)^2} \ , \ \varepsilon_2 = \frac{a_1 a_2 R_3^* L_3^*}{\left(R_3^* + a_2 T_3^*\right)^2}$$

$$\beta_1 = g_1 T_3^* \ , \ \beta_2 = g_1 L_3^* \ , \ \beta_3 = g_2 T_3^* \ , \ \delta = \frac{e_1 e_2 S_3^*}{\left(1 + e_2 T_3^*\right)^2}$$

The eigenvalues are gained by solving the characteristic equation; $\det(\mathbf{J} - \lambda \mathbf{I}_4) = 0$ where $\mathbf{I}_4$ is the identity matrix dimension 4x4. The corresponding characteristic equation is given by

$$\begin{aligned} \lambda^4 - \left(\beta_2 \left(e^{-\lambda\tau} - 1\right)\right) \lambda^3 + \left(\delta\beta_3 + \varepsilon_2 \beta_1 e^{-\lambda\tau} + \varepsilon_1 \phi_1\right) \lambda^2 \\ + \left(\varepsilon_1 \beta_1 \phi_2 e^{-\lambda\tau} - \varepsilon_1 \phi_1 \beta_2 \left(e^{-\lambda\tau} - 1\right)\right) \lambda + \delta\varepsilon_1 \phi_1 \beta_3 = 0 \end{aligned} \tag{3.17}$$

In the absence of delay, (3.17) becomes

$$\lambda^4 + \left(\delta\beta_3 + \varepsilon_1 \phi_1\right) \lambda^2 + \varepsilon_1 \beta_1 \phi_2 \ \lambda + \delta\varepsilon_1 \phi_1 \beta_3 = 0 \tag{3.18}$$

By using the Routh-Hurwitz criteria, it shows that this equilibrium is unstable when $\tau = 0$.

We now study the stability of the equilibrium in the presence of a delay. Here, we attend to identify whether there exists a critical delay τ^* so that the real part of the eigenvalue λ is positive for $\tau > \tau^*$. In other words, the real part of the eigenvalue λ is zero at $\tau = \tau^*$, at which the equilibrium loses its stability when τ passes through a critical value τ^*.

For the equilibrium E_3, we let $\lambda(\tau) = u(\tau) + i\,v(\tau)$ where u, v are real. Therefore we have $u(\tau) < 0$ for values of τ such that $0 < \tau < \tau^*$, that is, this equilibrium remains stable for these values of τ. The characteristic equation (3.17) is now in the form

$$\begin{aligned}(u+iv)^4 - \left(\beta_2\left(e^{-(u+iv)\tau} - 1\right)\right)(u+iv)^3 \; + \; & \left(\delta\beta_3 + \varepsilon_1\phi_1 + \varepsilon_2\beta_1 e^{-(u+iv)\tau}\right)(u+iv)^2 \\ & + \left(\varepsilon_1\beta_1\phi_2 e^{-(u+iv)\tau} - \varepsilon_1\phi_1\beta_2\left(e^{-(u+iv)\tau} - 1\right)\right)(u+iv) \; + \; \delta\varepsilon_1\phi_1\beta_3 \; = \; 0\end{aligned} \tag{3.19}$$

The equation (3.19) can be rewritten as

$$\begin{aligned}u^4 + 4iu^3v - 6u^2v^2 - 4iuv^3 + v^4 \; - & \left(\beta_2\left(e^{-(u+iv)\tau} - 1\right)\right)\left(u^3 + 3iu^2v - 3uv^2 - iv^3\right) \\ & + \left(\delta\beta_3 + \varepsilon_1\phi_1 + \varepsilon_2\beta_1 e^{-(u+iv)\tau}\right)\left(u^2 + 2iuv - v^2\right) \\ & + \left(\varepsilon_1\beta_1\phi_2 e^{-(u+iv)\tau} - \varepsilon_1\phi_1\beta_2\left(e^{-(u+iv)\tau} - 1\right)\right)(u+iv) + \delta\varepsilon_1\phi_1\beta_3 \; = \; 0\end{aligned}$$

By using Euler's equation and then equating real and imaginary parts of this equation to zero, we deduce that

$$\begin{aligned}& u^4 + v^4 - 6u^2v^2 + \beta_2 u^3 - 3\beta_2 uv^2 + \left(\delta\beta_3 + \varepsilon_1\phi_1\right)\left(u^2 - v^2\right) + u + \delta\varepsilon_1\phi_1\beta_3 \\ & + \left[2uv\varepsilon_2\beta_1 - \beta_2\left(3u^2v - v^3\right) - v\varepsilon_1\left(\phi_1\beta_2 - \beta_1\phi_2\right)\right] e^{-u\tau}\sin\left(v\tau\right) \\ & + \left[u\varepsilon_1\left(\beta_1\phi_2 - \phi_1\beta_2\right) - \beta_2\left(u^3 - 3uv^2\right) + \varepsilon_2\beta_1\left(u^2 - v^2\right)\right] e^{-u\tau}\cos\left(v\tau\right) \;\; = \;\; 0\end{aligned} \tag{3.20}$$

$$\begin{aligned}& 4u^3v - 4uv^3 + 2\left(\delta\beta_3 + \varepsilon_1\phi_1\right)uv + \beta_2\left(3u^2v - v^3\right) + v \\ & + \left[u\varepsilon_1\left(\phi_1\beta_2 - \beta_1\phi_2\right) + \beta_2\left(u^3 - 3uv^2\right) - \varepsilon_2\beta_1\left(u^2 - v^2\right)\right] e^{-u\tau}\sin\left(v\tau\right) \\ & + \left[v\varepsilon_1\left(\beta_1\phi_2 - \phi_1\beta_2\right) - \beta_2\left(3u^2v - v^3\right) + 2\varepsilon_2\beta_1 uv\right] e^{-u\tau}\cos\left(v\tau\right) \;\; = \;\; 0\end{aligned} \tag{3.21}$$

To determine the existence of a critical dealay τ^*. We consider that $u(\tau^*)=0$ and $\lambda(\tau^*)=iv(\tau^*)$ for some $\tau^*>0$, equation (3.20) and (3.21) become

$$v^{*2}\varepsilon_2\beta_1\cos(v^*\tau^*)+\left[v^*\varepsilon_1(\phi_1\beta_2-\beta_1\phi_2)-\beta_2 v^{*3}\right]\sin(v^*\tau^*) = v^{*4}-v^{*2}(\delta\beta_3+\varepsilon_1\phi_1)+\delta\varepsilon_1\phi_1\beta_3 \quad (3.22)$$

$$\left[v^*\varepsilon_1(\beta_1\phi_2-\phi_1\beta_2)+v^{*3}\beta_2\right]\cos(v^*\tau^*)+v^{*2}\varepsilon_2\beta_1\sin(v^*\tau^*) = v^{*3}\beta_2-v^* \quad (3.23)$$

Adding up the squares of both equations. Hence, equations (3.22) and (3.23) reduce to

$$\begin{aligned} v^{*8}+v^{*6}\left(-2(\delta\beta_3+\varepsilon_1\phi_1)\right)+v^{*4}\left(2\varepsilon_1\phi_1\delta\beta_3+(\delta\beta_3+\varepsilon_1\phi_1)^2-2\beta_2-\varepsilon_2^2\beta_1^2-2\varepsilon_1\beta_2\left[\beta_1\phi_2-\phi_1\beta_2\right]\right) \\ +v^{*2}\left(1-2\varepsilon_1\phi_1\delta\beta_3(\delta\beta_3+\varepsilon_1\phi_1)-\varepsilon_1^2\left[\beta_1\phi_2-\phi_1\beta_2\right]^2\right)+\varepsilon_1^2\phi_1^2\delta^2\beta_3^2 = 0 \end{aligned}$$

Suppose $w=v^{*2}$, we obtain

$$f(w) = w^4+k_1w^3+k_2w^2+k_3w+k_4 = 0 \quad (3.24)$$

where

$$\begin{aligned} k_1 &= -2(\delta\beta_3+\varepsilon_1\phi_1) \\ k_2 &= 2\varepsilon_1\phi_1\delta\beta_3+(\delta\beta_3+\varepsilon_1\phi_1)^2-2\beta_2-\varepsilon_2^2\beta_1^2-2\varepsilon_1\beta_2\left[\beta_1\phi_2-\phi_1\beta_2\right] \\ k_3 &= 1-2\varepsilon_1\phi_1\delta\beta_3(\delta\beta_3+\varepsilon_1\phi_1)-\varepsilon_1^2\left[\beta_1\phi_2-\phi_1\beta_2\right]^2 \\ k_4 &= \varepsilon_1^2\phi_1^2\delta^2\beta_3^2 \end{aligned}$$

Since $k_4>0$, $f(w)$ has at least one positive root when there is $\alpha_i>0$ for some i such that $f(\alpha_i)<0$ and α_i is one of the three turning points of $f(w)$.

We can solve for the critical time delays τ^* by substituting $v^*>0$ into equation (3.22) and (3.23). We obtain

$$\tau^* = \frac{1}{v^*}\arcsin\left(\frac{m_1v^{*7}+m_2v^{*5}+m_3v^{*3}-m_4v^*}{n}\right)+\frac{2\pi(k-1)}{v^*} \quad (3.25)$$

where

$$\begin{aligned} m_1 &= -\beta_2 \\ m_2 &= \varepsilon_2\beta_1\beta_2+\beta_2(\delta\beta_3+\varepsilon_1\phi_1)-\varepsilon_1(\beta_1\phi_2-\phi_1\beta_2) \\ m_3 &= \varepsilon_1(\delta\beta_3+\varepsilon_1\phi_1)(\beta_1\phi_2-\phi_1\beta_2)-\varepsilon_2\beta_1-\delta\varepsilon_1\phi_1\beta_2\beta_3 \\ m_4 &= \delta\varepsilon_1^2\phi_1\beta_3\left[\beta_1\phi_2-\phi_1\beta_2\right] \\ n &= \left(\varepsilon_2\beta_1v^{*2}\right)^2+\left(\beta_2v^{*3}+\varepsilon_1(\beta_1\phi_2-\phi_1\beta_2)v^*\right)^2 \quad \text{and} \quad k=0,1,2,\ldots. \end{aligned}$$

Theorem 3.1 Suppose that $4w^3+3k_1w^2+2k_2w+k_3\neq 0$ then the system of delay differential equations (3.4)-(3.7) with the critical value τ^* as in (3.25) behaves the Hopf bifurcation when the value of time delay τ passes through the critical value τ^*.

Proof. We now show that

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

From equation (3.20) and (3.21), 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

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} P + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} Q = R \tag{3.26}$$

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} (-Q) + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} P = S \tag{3.27}$$

where

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

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

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

$$S = -\varepsilon_2\beta_1 v^{*3}\cos(v^*\tau^*)+\left[\beta_2 v^{*4}+v^{*2}\varepsilon_1(\beta_1\phi_2-\phi_1\beta_2)\right]\sin(v^*\tau^*).$$

To find for $\left.\frac{du}{d\tau}\right|_{\tau=\tau^*}$, by solving equations (3.26) and (3.27) , we deduce that

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} = \frac{PR-QS}{P^2+Q^2}. \tag{3.28}$$

Consider

$$\begin{aligned}
PR-QS = & \left[1-3\beta_2 v^2+\left[3\beta_2 v^2+\varepsilon_2\beta_1\tau v^2+\varepsilon_1\left(\beta_1\phi_2-\phi_1\beta_2\right)\right]\cos(v\tau)\right. \\
& \left.+\left[2\varepsilon_2\beta_1 v-\tau\beta_2 v^3-\tau v\varepsilon_1\left(\beta_1\phi_2-\phi_1\beta_2\right)\right]\sin(v\tau)\right] \\
& \cdot\left(\left(-v^4\beta_2-\varepsilon_1 v^2\left(\beta_1\phi_2-\phi_1\beta_2\right)\right)\cos(v\tau)-\varepsilon_2\beta_1 v^3\sin(v\tau)\right) \\
& -\left[4v^3-2v\left(\delta\beta_3+\varepsilon_1\phi_1\right)+\left[-2v\varepsilon_2\beta_1+\tau\beta_2 v^3+\tau\varepsilon_1 v\left(\beta_1\phi_2-\phi_1\beta_2\right)\right]\cos(v\tau)\right. \\
& \left.+\left[3\beta_2 v^2+\varepsilon_2\beta_1\tau v^2+\varepsilon_1\left(\beta_1\phi_2-\phi_1\beta_2\right)\right]\sin(v\tau)\right] \\
& \cdot\left(-\varepsilon_2\beta_1 v^3\cos(v\tau)+\left(v^4\beta_2+\varepsilon_1 v^2\left(\beta_1\phi_2-\phi_1\beta_2\right)\right)\sin(v\tau)\right)
\end{aligned}$$

$$\begin{aligned}
= & -2\varepsilon_2^2\beta_1^2 v^4-3\beta_2^2 v^6-4\varepsilon_1\beta_2\left(\beta_1\phi_2-\phi_1\beta_2\right)v^4-\varepsilon_1^2\left(\beta_1\phi_2-\phi_1\beta_2\right)^2 v^2 \\
& +\left[-v\left(v^3\beta_2-v\right)+3\beta_2 v^3\left(v^3\beta_2-v\right)\right] \\
& +\left[4v^4\left(v^4+\delta\varepsilon_1\phi_1\beta_3-v^2\left(\delta\beta_3+\varepsilon_1\phi_1\right)\right)-2v^2\left(\delta\beta_3+\varepsilon_1\phi_1\right)\left(v^4+\delta\varepsilon_1\phi_1\beta_3-v^2\left(\delta\beta_3+\varepsilon_1\phi_1\right)\right)\right]
\end{aligned}$$

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

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

From equation (3.24), we get

$$PR-QS = v^{*2}\left(4w^3+3k_1w^2+2k_2w+k_3\right). \qquad (3.29)$$

We then have

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

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

Therefore for $\tau = 0$ the model (3.4)-(3.7) is unstable and whenever τ passes through a value τ^* corresponding to $v^* = \sqrt{w^*}$, where w^* is a simple root of $f(w) = 0$, Hopf bifurcation occurs.

3.2.3 Numerical results

We now consider numerical simulations to see whether our model can predict the regular oscillations observed in levels of GnRH, LH, testosterone and SHBG in blood. 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 [23] used in simulation. For the other parameters, we take $g_1 = 0.0092$/min, $g_2 = 0.002$/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 $E_3(1.08, 4.95, 652.22, 3.09)$ where $\tau > \tau^* \approx 123.47$.

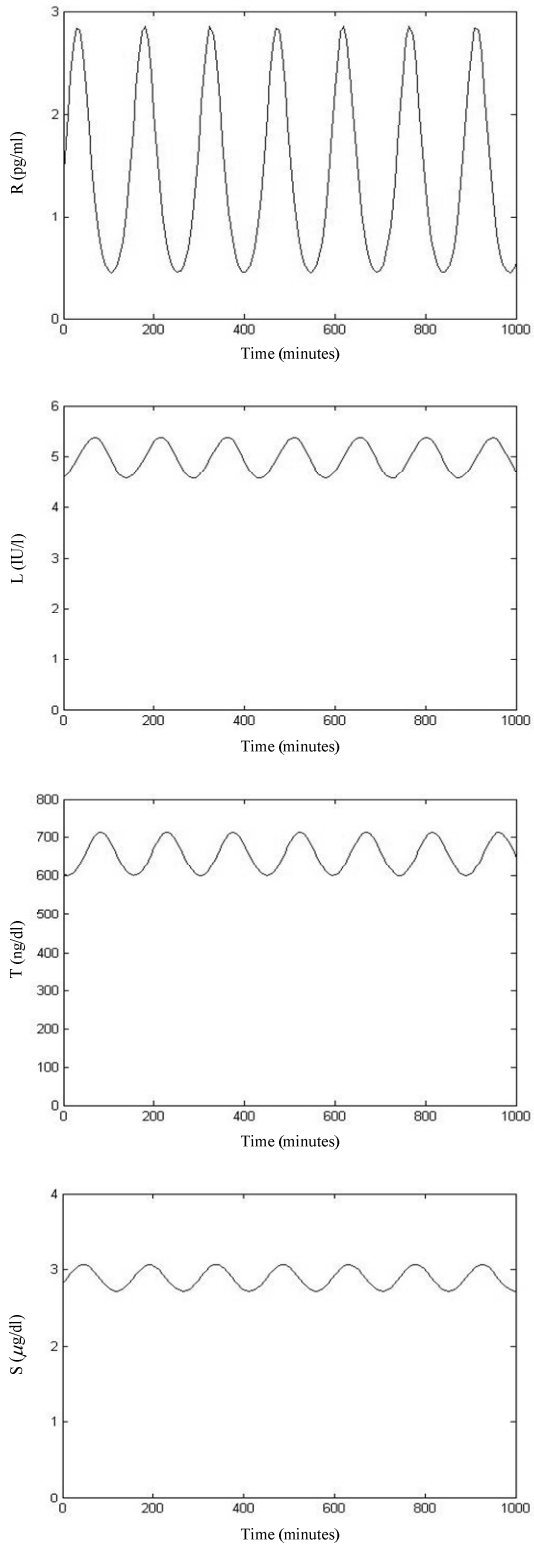

Figure 3.2 Numerical simulations for the equation (3.4)-(3.7) with $\tau = 124$. Hopf bifurcation occurs from the positive equilibrium. The initial value is (1, 5.7, 500, 2).

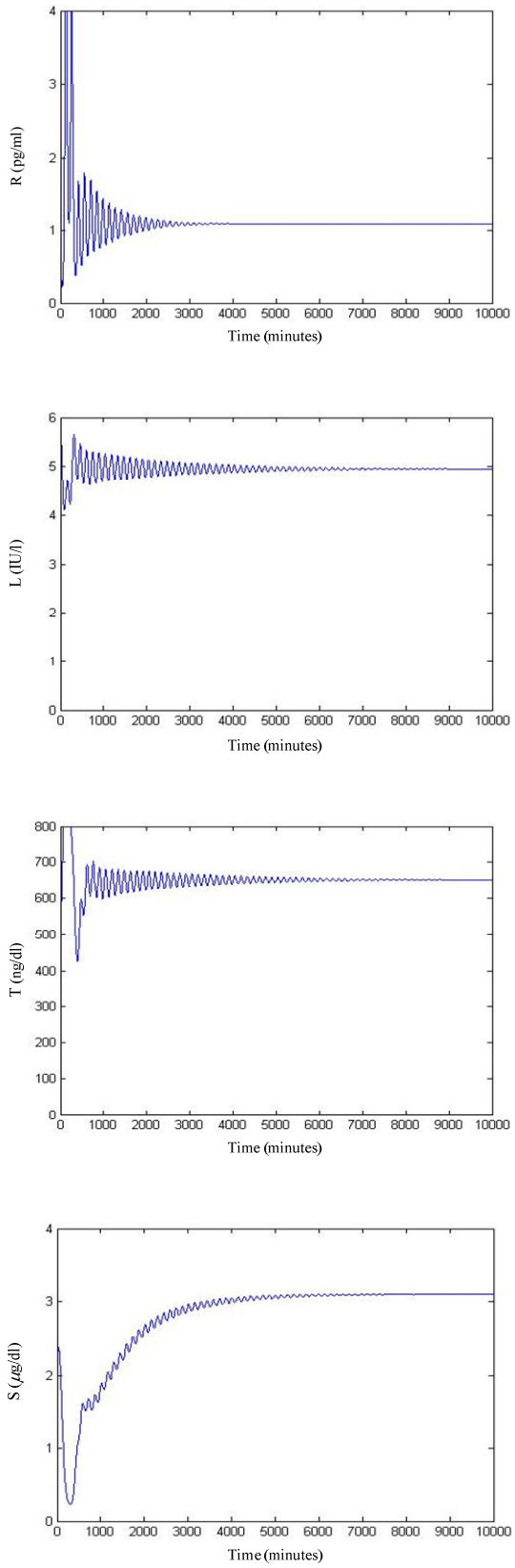

Figure 3.3 Numerical simulations for equation (3.4)-(3.7) with $\tau = 120$. The positive equilibrium is asymptotically stable. The initial value is (1, 5.7, 500, 2).

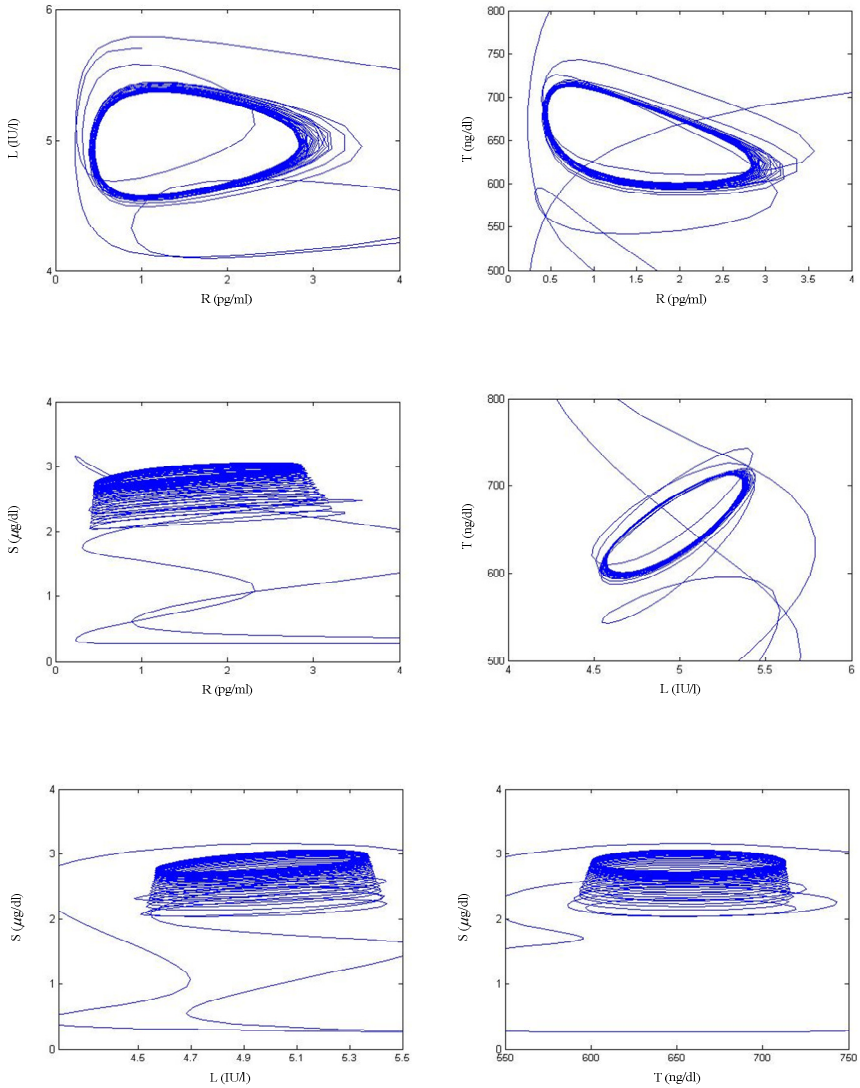

Figure 3.4 Numerical simulations demonstrate the solution trajectories which projected into the 2D-space for equations (3.4)-(3.7) with $\tau = 124$ min. The initial value is (1, 5.7, 500, 2).

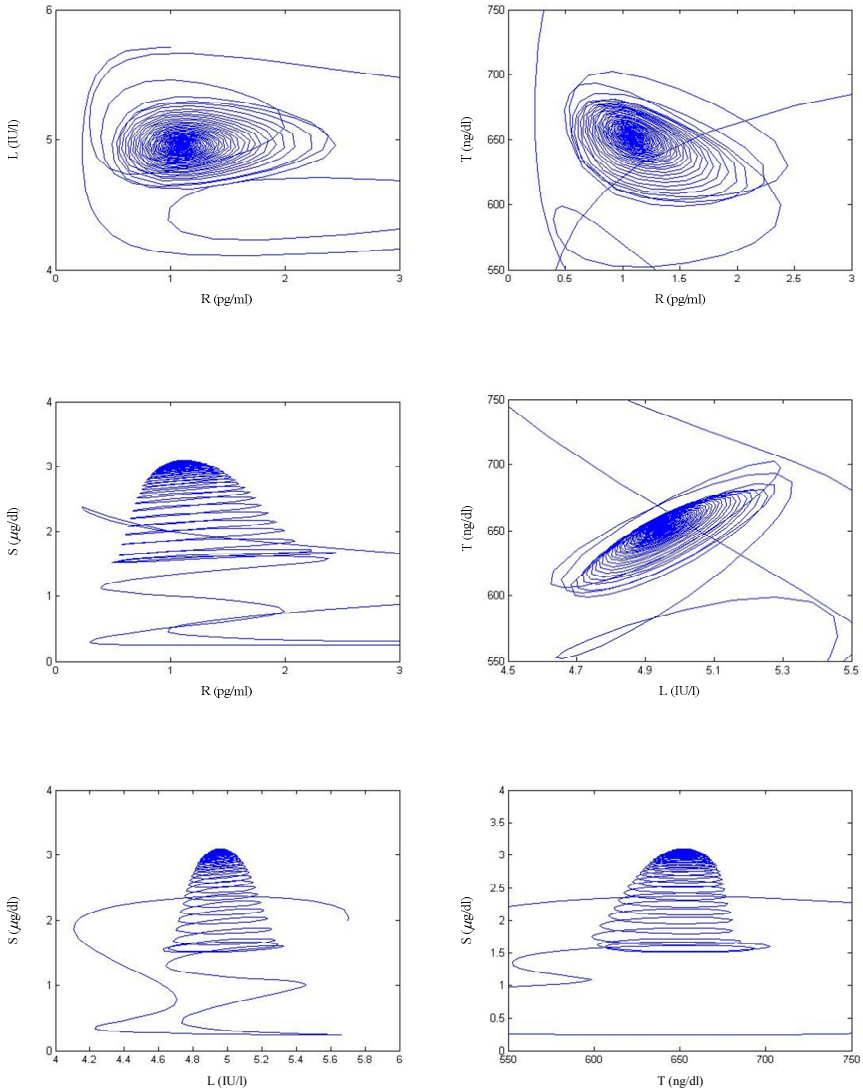

Figure 3.5 Numerical simulations demonstrate the solution trajectories which projected into the 2D-space for equations (3.8)-(3.11) with $\tau = 120$ min. The initial value is (1, 5.7, 500, 2).

The mathematical model developed in this section describes the feedback mechanisms in consideration of cyclicity of the male sex hormone balanced on the influence of variations in the SHBG concentration. Levels of total testosterone can be directly affected by changes in levels of SHBG to maintain an optimal concentration of free testosterone which is biologically active for the cells in the body. 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 variations in the SHBG concentration on the testosterone production. This model can explain the pulsatile secretion of the hormones in the human male GnRH-LH-T axis. The oscillatory characteristics of hormones regulation agree well with experimental data and other simulated hormone fluctuation levels.

The association between obesity and low SHBG is well established and the reduction of SHBG contributes significantly to the reduction in circulating total testosterone level in obese men. As SHBG binds testosterone with high affinity, reduction in circulating SHBG decreases circulating T and therefore delivery of T to peripheral tissues.

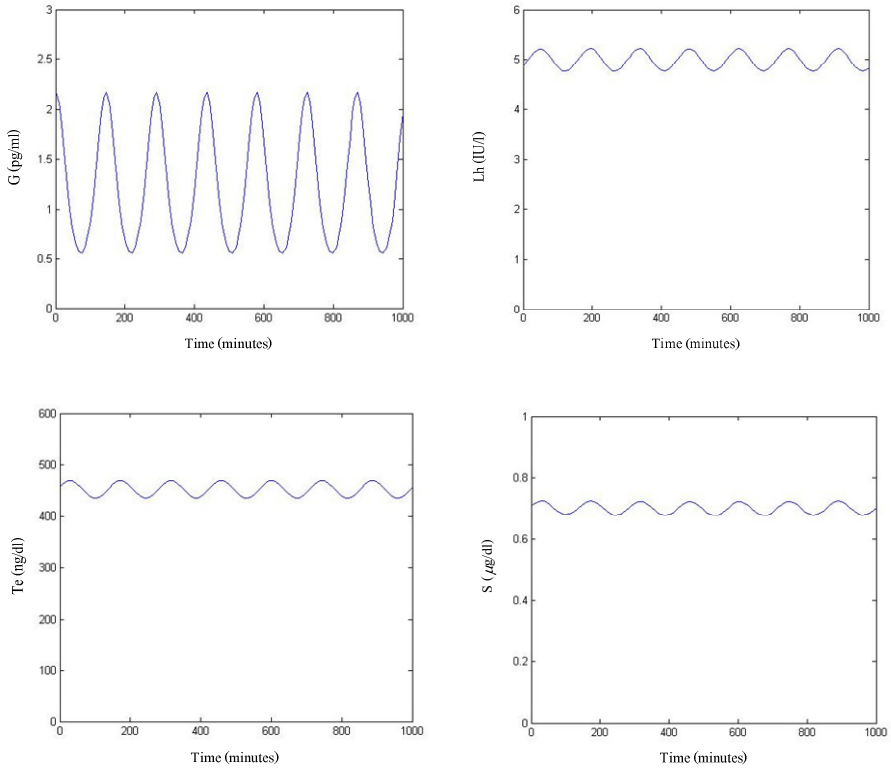

Figure 3.6 Numerical simulations for the equation (3.4)-(3.7) with $\tau = 124$. Hopf bifurcation occurs from the positive equilibrium. The initial value is (1, 5.7, 500, 2) with the value of parameters $e_1 = 5.5$/min, $e_2 = 0.3$/min.

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 Figure 3.6, indicate that the total testosterone levels diminish with decreasing SHBG levels that appears in men with obesity [42,43].

Chapter 4

A Model for the Testosterone Regulation Taking into Account the Presence of Two Types of Testosterone Hormones

4.1 Mathematical model

As described in chapter 2, After testosterone is secreted into the bloodstream, 96-98 percent will be bound to various carrier proteins. One of these will be the sex hormone-binding globulin (SHBG). This protein is produced primarily in the liver. The entry of SHBG into hypothalamus-pituitary-gonadal axis is shown in the lower left corner of figure 2.1. SHBG plays an important role in determining the availability of the testosterone for its endocrinology activity. The reason for this is SHBG can tightly bind to the testosterone making them physiologically inactive. A large fraction (~ 60-70%) of the testosterone will be of this type. Another 28 - 38% will be weakly bond to albumin. Only a small percentage (~ 2%) of testosterone will be unbound. These will be considered to be free testosterone (FT). Only the free testosterone (FT) is capable of entering a cell and activating the receptor on SHBG gene on chromosome and turning it on. The circulating bound and free testosterone are collectively referred to as the total testosterone. The free testosterone and the albumin-bound testosterone are physiologically available to the body tissues. These are known as bioavailable testosterone (BioT). The level of SHBG becomes one factor that determines the total testosterone level. High concentrations of SHBG reduce the level of bioavailable testosterone. Consequently, the total concentration of testosterone must increase to maintain adequate levels of bioavailable testosterone.

In this section, we construct the mathematical model by improving the previous model proposed by Greenhalgh and Khan in order to explore the presence of two types of testosterone hormones, total testosterone and SHBG-bound testosterone, in the endocrinology processes of testosterone regulation. We now allow the SHBG level to vary. This makes the revised model more medically correct.

In humans, the levels of SHBG may depend on the medical condition of the person. The SHBG levels are decreased when the person suffers from hypothyroidism, diabetes, obesity or the Cushing's syndrome. The levels are elevated when the person suffers from hyperthyroidism, cirrhosis of the liver and is pregnant. Inclusion of the SHGB is necessary since an increase in the SHBG level leads to an increase in total testosterone level.

By defining the variables in our model as follows:

$\frac{dR}{dt}$ is the rate of change for plasma concentration of gonadotropin-releasing hormone (GnRH).

$\frac{dL}{dt}$ is the rate of change for plasma concentration of luteinizing hormone (LH).

$\frac{dT}{dt}$ is the rate of change for plasma concentration of testosterone (T).

$\frac{dT_S}{dt}$ is the rate of change for plasma concentration of SHBG bound testosterone.

We assume that only free testosterones are bioavailable for the production of the hormone, we must differentiate between the two and so each needs its own individual designation. In this study, we will investigate the following delay differential equations

$$\frac{dR}{dt} = \frac{q_1 R}{L + q_2 T} - \mu_1 R \tag{4.1}$$

$$\frac{dL}{dt} = \left(\frac{d_1 R}{R + d_2 T}\right) \cdot L - \mu_2 L \tag{4.2}$$

$$\frac{dT}{dt} = a \cdot L(t-\tau)T + \frac{r_3}{1 + r_4 T_s} T - \mu_3 T \tag{4.3}$$

$$\frac{dT_S}{dt} = \left(\frac{e_1 T}{1 + e_2 T}\right) \cdot T_S - \mu_4 T_S \tag{4.4}$$

where $q_1, q_2, d_1, d_2, a, p_1, p_2, e_1, e_2$ are strictly positive parameters and $\mu_1, \mu_2, \mu_3, \mu_4$ are defined as the metabolic clearance rates of all four hormones.

As we have said, the gonadotropin-releasing hormone R is released by hypothalamus. As pointed out in reference [40], the release of *R* is influenced by the combined effect of both the *L* and the testosterone hormones. The response function used in (4.1) reflects this. The release of *L* hormone by the pituitary gland should be high when the level of T is low and the level of R is Low. The release of *L* should be low then the level of T is high and the level of *R* is high. The response function used in (4.2) exhibits two different behaviors for R greater of less than *L*. In (4.4), we use a hyperbolic function $\varphi(T) = e_1 T / (1 + e_2 T)$ to describe the change of SHBG-bound testosterone level. $\varphi(T)$,which is an increasing and bounded function where $T > 0$, is used to explain the rise in the level of SHBG-bound testosterone at the time that testosterone is released into the bloodstream and then bind to SHBG.

4.2 Analysis of the mathematical model

4.2.1 The steady state solutions

In order to find steady states, we set the right hand side of Eq. (4.1) to (4.4) to zero. We see that the above equations admit the nonzero steady state $\bar{E}\left(\bar{R}, \bar{L}, \bar{T}, \bar{T}_S\right)$ where

$$\bar{R} = \frac{d_2\mu_2}{d_1 - \mu_2}\left(\frac{\mu_4}{e_1 - e_2\mu_4}\right) = \frac{d_2\mu_2}{d_1 - \mu_2}\bar{T},$$

$$\bar{L} = \frac{q_1}{\mu_1} - q_2\left(\frac{\mu_4}{e_1 - e_2\mu_4}\right) = \frac{q_1}{\mu_1} - q_2\bar{T},$$

$$\bar{T} = \frac{\mu_4}{e_1 - e_2\mu_4},$$

and

$$\bar{T}_S = \frac{1}{r_4}\left(\frac{r_3}{\mu_3 - a\left(\frac{q_1}{\mu_1} - q_2\left(\frac{\mu_4}{e_1 - e_2\mu_4}\right)\right)} - 1\right) = \frac{1}{r_4}\left(\frac{r_3}{\mu_3 - a\,\bar{L}} - 1\right).$$

Obviously, this steady state is positive if and only if

$$d_1 - \mu_2 > 0, \quad \frac{q_1}{\mu_1} - \frac{q_2\mu_4}{e_1 - e_2\mu_4} > 0, \quad e_1 - e_2\mu_4 > 0 \text{ and } \frac{r_3}{\mu_3 - a\,\bar{L}} - 1 > 0.$$

In order to analyse the stability of the steady state $\bar{E}$, we consider the system (4.1) to (4.4) in the general form

$$\begin{aligned}
\frac{dR}{dt} &= f\left(R(t),L(t),T(t),T_S(t)\right)\\
\frac{dL}{dt} &= g\left(R(t),L(t),T(t),T_S(t)\right)\\
\frac{dT}{dt} &= h\left(R(t),L(t),T(t),T_S(t)\right)\\
\frac{dT_S}{dt} &= k\left(R(t),L(t),T(t),T_S(t)\right)
\end{aligned} \tag{4.5}$$

with the transformations

$$w = R-\bar{R},\ x = L-\bar{L},\ y = T-\bar{T},\ z = T_S-\bar{T}_S \text{ and } x_1 = L_1-\bar{L},$$

where $L_1(t) = L(t-\tau)$.

By expanding f, g, h and k in the Taylor series about a steady state $\bar{E}$ and retaining only the first order terms. We have the linearized system of (4.1) to (4.4) as follows :

$$\frac{dw}{dt} = -\left(\frac{r_1\bar{R}}{\left(\bar{L}+r_2\bar{T}\right)^2}\right)x - \left(\frac{r_1 r_2\bar{R}}{\left(\bar{L}+r_2\bar{T}\right)^2}\right)y \tag{4.6}$$

$$\frac{dx}{dt} = \left(\frac{a_1a_2\ \bar{L}\cdot\bar{T}}{\left(\bar{R}+a_2\bar{T}\right)^2}\right)w - \left(\frac{a_1a_2\ \bar{L}\cdot\bar{R}}{\left(\bar{R}+a_2\bar{T}\right)^2}\right)y \tag{4.7}$$

$$\frac{dy}{dt} = \left(g_1\bar{T}\right)x_1 - \left(\frac{r_3r_4}{\left(1+r_4\bar{T}_S\right)^2}\bar{T}\right)z \tag{4.8}$$

$$\frac{dz}{dt} = \left(\frac{e_1\bar{T}_S}{\left(1+e_2\bar{T}\right)^2}\right)y\ . \tag{4.9}$$

Now, looking for solutions of (4.6)-(4.9) in the form

$$\begin{bmatrix} w(t)\\ x(t)\\ y(t)\\ z(t)\end{bmatrix} = C_1e^{\lambda t}$$

where C_1 is a constant vector.

Then the linear system of Eq.(4.6)-(4.9) can be expressed as

$$\begin{bmatrix} \frac{dw}{dt} \\ \frac{dx}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{bmatrix} = \begin{bmatrix} 0 & -\frac{q_1\bar{R}}{\left(\bar{L}+q_2\bar{T}\right)^2} & -\frac{q_1 q_2\bar{R}}{\left(\bar{L}+q_2\bar{T}\right)^2} & 0 \\ \frac{d_1 d_2\,\bar{L}\cdot\bar{T}}{\left(\bar{R}+d_2\bar{T}\right)^2} & 0 & -\frac{d_1 d_2\,\bar{L}\cdot\bar{R}}{\left(\bar{R}+d_2\bar{T}\right)^2} & 0 \\ 0 & g_1\bar{T}e^{-\lambda\tau} & 0 & -\frac{r_3 r_4}{\left(1+r_4\bar{T}_S\right)^2}\bar{T} \\ 0 & 0 & \frac{e_1\bar{T}_S}{\left(1+e_2\bar{T}\right)^2} & 0 \end{bmatrix} \begin{bmatrix} w \\ x \\ y \\ z \end{bmatrix} \qquad (4.10)$$

For convenience, letting

$$\eta_1 = -\frac{q_1\bar{R}}{\left(\bar{L}+q_2\bar{T}\right)^2}\ ,\ \eta_2 = -\frac{q_1 q_2\bar{R}}{\left(\bar{L}+q_2\bar{T}\right)^2}\ ,$$

$$\eta_3 = \frac{d_1 d_2\,\bar{L}\cdot\bar{T}}{\left(\bar{R}+d_2\bar{T}\right)^2}\ ,\quad \eta_4 = -\frac{d_1 d_2\,\bar{L}\cdot\bar{R}}{\left(\bar{R}+d_2\bar{T}\right)^2}\ ,$$

$$\eta_5 = a\bar{T}\ ,\ \eta_6 = -\frac{r_3 r_4}{\left(1+r_4\bar{T}_S\right)^2}\bar{T}\ \text{ and }\ \eta_7 = \frac{e_1\bar{T}_S}{\left(1+e_2\bar{T}\right)^2}.$$

The system (4.10) becomes

$$\begin{bmatrix} \frac{dw}{dt} \\ \frac{dx}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{bmatrix} = \begin{bmatrix} 0 & \eta_1 & \eta_2 & 0 \\ \eta_3 & 0 & \eta_4 & 0 \\ 0 & \eta_5 e^{-\lambda\tau} & 0 & \eta_6 \\ 0 & 0 & \eta_7 & 0 \end{bmatrix} \begin{bmatrix} w \\ x \\ y \\ z \end{bmatrix} \qquad (4.11)$$

Let

$$A = \begin{bmatrix} 0 & \eta_1 & \eta_2 & 0 \\ \eta_3 & 0 & \eta_4 & 0 \\ 0 & \eta_5 e^{-\lambda\tau} & 0 & \eta_6 \\ 0 & 0 & \eta_7 & 0 \end{bmatrix}$$

be the coefficient matrix of the the linear system with λ being an eigenvalue of the matrix A. The eigenvalues are gained by solving the characteristic equation; $\det(A - \lambda \mathrm{I}_4) = 0$ where I_4 is the identity matrix dimension 4x4. The corresponding characteristic equation is given by

$$\lambda^4 - (\eta_1\eta_3 + \eta_6\eta_7)\lambda^2 + \eta_1\eta_3\eta_6\eta_7 - (\eta_4\eta_5\lambda^2 + \eta_2\eta_3\eta_5\lambda)e^{-\lambda\tau} = 0 \qquad (4.12)$$

In the absence of delay, that is, $\tau = 0$, the equation (4.12) becomes

$$\lambda^4 - (\eta_1\eta_3 + \eta_4\eta_5 + \eta_6\eta_7)\lambda^2 - \eta_2\eta_3\eta_5\lambda + \eta_1\eta_3\eta_6\eta_7 = 0 \qquad (4.13)$$

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

Now, we return to the analysis of equation (4.12) in case $\tau > 0$. We rewrite the equation in a form as

$$\lambda^4 + p_1\lambda^2 + p_2 + (q_1\lambda^2 + q_2\lambda)e^{-\lambda\tau} = 0 \qquad (4.14)$$

where

$$p_1 = -(\eta_1\eta_3 + \eta_6\eta_7)\ ,\ p_2 = \eta_1\eta_3\eta_6\eta_7\ ,\ q_1 = -\eta_4\eta_5 \text{ and } q_2 = -\eta_2\eta_3\eta_5.$$

For the steady state $\bar{E}$, we let $\lambda(\tau) = u(\tau) + iv(\tau)$ where u and v are real. The equation (4.14) becomes

$$(u+iv)^4 + p_1(u+iv)^2 + p_2 + \left(q_1(u+iv)^2 + q_2(u+iv)\right)e^{-(u+iv)\tau} = 0 \qquad (4.15)$$

The equation (4.15) can be rewritten as follow

$$\begin{aligned}(u^4 + 4iu^3v - 6u^2v^2 - 4iuv^3 + v^4) + p_1(u^2 + 2iuv - v^2) + p_2 \\ + \left[q_1(u^2 + 2iuv - v^2) + q_2(u+iv)\right]e^{-(u+iv)\tau} = 0\end{aligned} \qquad (4.16)$$

By using the Euler's equation , $e^{i\theta} = \cos\theta + i\sin\theta$, we get

$$\begin{aligned}&\left(u^4 + 4iu^3v - 6u^2v^2 - 4iuv^3 + v^4\right) + p_1\left(u^2 + 2iuv - v^2\right) + p_2 \\ &\quad + \left[q_1\left(u^2 + 2iuv - v^2\right) + q_2\left(u + iv\right)\right]\left(e^{-u\tau}\left[\cos\left(v\tau\right) - i\sin\left(v\tau\right)\right]\right) = 0\end{aligned} \tag{4.17}$$

Equating real and imaginary parts of this equation to zero, we deduce that

$$\begin{aligned}&u^4 - 6u^2v^2 + v^4 + p_1\left(u^2 - v^2\right) + p_2 \\ &+e^{-u\tau}\left[\left(q_1\left(u^2 - v^2\right) + q_2u\right)\cos\left(v\tau\right) + \left(q_2v + 2q_1uv\right)\sin\left(v\tau\right)\right] = 0\end{aligned} \tag{4.18}$$

$$\begin{aligned}&4u^3v - 4uv^3 + 2p_1uv \\ &\quad + e^{-u\tau}\left[\left(q_2v + 2q_1uv\right)\cos\left(v\tau\right) - \left(q_1\left(u^2 - v^2\right) + q_2u\right)\sin\left(v\tau\right)\right] = 0\end{aligned} \tag{4.19}$$

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^*, Eq. (4.18) and (4.19) become

$$q_1v^{*2}\cos\left(v^*\tau^*\right) - q_2v^*\sin\left(v^*\tau^*\right) = v^{*4} - p_1v^{*2} + p_2 \tag{4.20}$$

and

$$q_2v^*\cos\left(v^*\tau^*\right) + q_1v^{*2}\sin\left(v^*\tau^*\right) = 0. \tag{4.21}$$

We sum the squares of both equations. Hence, equations (4.20) and (4.21) reduce to

$$v^{*8} - 2p_1v^{*6} + \left(2p_2 + p_1^2 - q_1^2\right)v^{*4} - \left(2p_1p_2 + q_2^2\right)v^{*2} + p_2^2 = 0. \tag{4.22}$$

We define

$$A(s) = s^4 - 2p_1s^3 + (2p_2 + p_1^2 - q_1^2)s^2 - \left(2p_1p_2 + q_2^2\right)s + p_2^2 \tag{4.23}$$

where $A\left(s = v^{*2}\right) = 0$ and

$$a_1 = -2p_1,\ a_1 = 2p_2 + p_1^2 - q_1^2,\ a_1 = -\left(2p_1p_2 + q_2^2\right) \text{ and } a_4 = p_2^2$$

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 (4.22) has at least

one positive real root. From (4.20) and (4.21), the equations can be written in the form

$$\cos\left(v^*\tau^* + \theta_1\right) = \frac{v^{*4} - p_1 v^{*2} + p_2}{v^*\sqrt{\left(q_1 v^*\right)^2 + q_2^2}} \quad \text{and} \quad \sin\left(v^*\tau^* + \theta_1\right) = 0 \tag{4.24}$$

where θ_1 is in the interval $\left[0, \frac{\pi}{2}\right)$,

$$\cos\left(\theta_1\right) = \frac{q_1 v^*}{\sqrt{\left(q_1 v^*\right)^2 + q_2^2}} \quad \text{and} \quad \sin\left(\theta_1\right) = \frac{q_2}{\sqrt{\left(q_1 v^*\right)^2 + q_2^2}} \tag{4.25}$$

Therefore, if the equation (4.22) has a positive real root, we can solve for the critical time delays τ^* from

$$\tau^* = \frac{1}{v^*}\left[2k\pi - \arcsin\frac{q_2}{\sqrt{\left(q_1 v^*\right)^2 + q_2^2}}\right] \quad \text{for } k \in I^+ \text{ and } v^* \neq 0. \tag{4.26}$$

Theorem 4.1 Suppose that $4s^3 + 3a_1 s^2 + 2a_2 s + a_3 \neq 0$ then the system of delay differential equations (4.1)-(4.4) with the critical value τ^* as in (4.26) behaves the Hopf bifurcation when the value of time delay τ passes through the critical value τ^*.

Proof. We now show that

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

From equations (4.18) and (4.19), we find the differentiation with respect to τ and evaluate at $\tau = \tau^*$ for which $u\left(\tau^*\right) = 0$ and $v\left(\tau^*\right) = v^*$. We then obtain

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} P + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} Q = R \tag{4.27}$$

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} (-Q) + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} P = S \tag{4.28}$$

where

$$\begin{aligned}
P &= q_1 v^{*2}\tau \cos\left(v^*\tau^*\right) + q_2 \cos\left(v^*\tau^*\right) - q_2\tau^* v^* \sin\left(v^*\tau^*\right) + 2q_1 v^* \sin\left(v^*\tau^*\right) \\
&= \left[q_1 v^{*2}\tau^* \cos\left(v^*\tau^*\right) + q_2 \cos\left(v^*\tau^*\right)\right] + \left[2q_1 v^* \sin\left(v^*\tau^*\right) - q_2\tau^* v^* \sin\left(v^*\tau^*\right)\right] \\
&= \left[q_2 + q_1 v^{*2}\tau^*\right]\cos\left(v^*\tau^*\right) + \left[2q_1 - q_2\tau^*\right]v^* \sin\left(v^*\tau^*\right)
\end{aligned}$$

$$\begin{aligned}
Q &= 4v^{*3} - 2p_1 v^* + v^{*2} q_1\tau^* \sin\left(v^*\tau^*\right) - 2q_1 v^* \cos\left(v^*\tau^*\right) \\
&\quad + q_2 v^*\tau^* \cos\left(v^*\tau^*\right) + q_2 \sin\left(v^*\tau^*\right) \\
&= 4v^{*3} - 2p_1 v^* + \left[q_2 + v^{*2} q_1\tau^*\right]\sin\left(v^*\tau^*\right) + \left[q_2\tau^* - 2q_1\right]v^* \cos\left(v^*\tau^*\right)
\end{aligned}$$

$$R = -q_2 v^{*2} \cos\left(v^*\tau^*\right) - q_1 v^{*3} \sin\left(v^*\tau^*\right)$$

$$S = q_2 v^{*2} \sin\left(v^*\tau^*\right) - q_1 v^{*3} \cos\left(v^*\tau^*\right).$$

To find for $\left.\frac{du}{d\tau}\right|_{\tau=\tau^*}$, by solving Equations (4.27) and (4.28) , we deduce that

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} = \frac{PR - QS}{P^2 + Q^2}. \tag{4.29}$$

Consider

$$\begin{aligned}
PR - QS &= \left(\left[q_2 + q_1 v^{*2}\tau^*\right]\cos\left(v^*\tau^*\right) + \left[2q_1 - q_2\tau^*\right]v^* \sin\left(v^*\tau^*\right)\right) \\
&\quad \cdot \left(-q_2 v^{*2} \cos\left(v^*\tau^*\right) - q_1 v^{*3} \sin\left(v^*\tau^*\right)\right) \\
&\quad - \left(4v^{*3} - 2p_1 v^* + \left[q_2 + v^{*2} q_1\tau^*\right]\sin\left(v^*\tau^*\right) + \left[q_2\tau^* - 2q_1\right]v^* \cos\left(v^*\tau^*\right)\right) \\
&\quad \cdot \left(q_2 v^{*2} \sin\left(v^*\tau^*\right) - q_1 v^{*3} \cos\left(v^*\tau^*\right)\right) \\
&= -\left(\begin{array}{r} q_2^2 v^{*2} + q_1 q_2 v^{*4}\tau^* + 2q_1^2 v^{*4} - q_1 q_2 v^{*4}\tau^* + 4v^{*4}\left(q_2 v^* \sin\left(v^*\tau^*\right) - q_1 v^{*2} \cos\left(v^*\tau^*\right)\right) \\ + 2p_1 v^{*2}\left(q_1 v^{*2} \cos\left(v^*\tau^*\right) - q_2 v^* \sin\left(v^*\tau^*\right)\right) \end{array} \right) \\
&= -\left(q_2^2 v^{*2} + 2q_1^2 v^{*4} + 4v^{*4}\left(-v^{*4} + p_1 v^{*2} - p_2\right) + 2p_1 v^{*2}\left(v^{*4} - p_1 v^{*2} + p_2\right)\right) \\
&= 4v^{*8} - 4p_1 v^{*6} - 2p_1 v^{*6} + 4p_2 v^{*4} - 2q_1^2 v^{*4} + 2p_1^2 v^{*4} - 2p_1 p_2 v^{*2} - q_2^2 v^{*2} \\
&= 4v^{*8} - 6p_1 v^{*6} + \left(4p_2 - 2q_1^2 + 2p_1^2\right)v^{*4} - \left(2p_1 p_2 + q_2^2\right)v^{*2} \\
&= v^{*2}\left(4v^{*6} - 6p_1 v^{*4} + \left(4p_2 - 2q_1^2 + 2p_1^2\right)v^{*2} - \left(2p_1 p_2 + q_2^2\right)\right)
\end{aligned}$$

$$= \quad v^{*2}\left(4s^3 - 6p_1 s^2 + \left(4p_2 - 2q_1^2 + 2p_1^2\right)s - \left(\ 2p_1 p_2 + q_2^2\right)\right)$$

$$= \quad v^{*2}\left(4s^3 + 3a_1 s^2 + 2a_2 s + a_3\right)$$

$$\neq \quad 0\,.$$

We have just shown that the numerator of the expression on the right-hand side of Eq. (4.29) is not equal to zero and looking at the definitions of P and Q given below Eq. (4.28), we see that P and Q are both finite quantities and so $P^2 + Q^2 \neq 0$. We can therefore conclude that

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} \quad = \quad \frac{PR - QS}{P^2 + Q^2} \quad \neq \quad 0 \qquad (4.30)$$

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

□

4.2.2 Numerical results

To gain a quantitative sense of the behavior of the hormones in our model for the regulation of testosterone when there are two types of testosterones present, we have simulated the behaviors by numerically solving equations (4.1)-(4.4) using routine dde23 in MATLAB. Most of the realistic values of the parameters are taken from Greenhalgh and Khan. The values of the other parameters used in the simulation are $r_3 = 0.023$/min, $r_4 = 1.47$/min, $e_1 = 0.004$/min, $e_2 = 0.08$/min and $\mu_4 = 0.0491$/min. These values when substituted into the expressions for the steady values of the components, $\bar{R}, \bar{L}, \bar{T}$ and $\bar{T}_S$ yield normal range of values of the hormone levels, i.e., $\bar{E}\left(1.07, 4.95, 645.39, 373.96\right)$. Since (4.22) satisfies the conditions of one of the Theorems in Ref. [44] regarding whether the fourth order (in $s = v^{*2}$) algebraic, Equation (4.22) has at least one real positive value. This would be the value of v^*. Substituting this value into (4.22), we would get the critical delay at which the Hopf bifurcation occurs. For the values of the parameters used in our numerical calculations, $\tau^* = 121.236$ min.

For $\tau = 120$ min which is less than τ^*, the values of the *R*, *L*, *T* and T_S would converge to the steady state values as $t \to \infty$. For $\tau = 123.47$ min which is greater than τ^*, the values of the four variable would not converge to the steady state values, but would instead oscillate about the steady state values. Figures 4.2 and 4.3 show

the time evolutions of R, L, T and T_S obtained from the numerical solutions of Equations (4.1)-(4.4) for $\tau = 120$ min and 123.47 min, respectively. As we see, the plots of R, L, T and T_S show that of R, L, T and T_S approach the steady state as $t \to \infty$ (Figure 4.2). Figure 4.3 shows the time evolution of R, L, T and T_S when $\tau = 123.47$. As we see, R, L, T and T_S do not approach the steady state as $t \to \infty$. Instead, the values of R, L and T oscillate about the steady state values without the amplitude of oscillation getting smaller as $t \to \infty$. To see this better, we have plotted the solutions in a 2D space when $\tau = 123.47$ (Figure 4.4). All the figures are of limit cycle behaviors which are what was predicted by Theorem 2.2. To complete the story, we have plotted R, L and T against each other for $\tau = 120$ min on Figure 4.5. We see that the trajectories are spirals which converge to the steady state values.

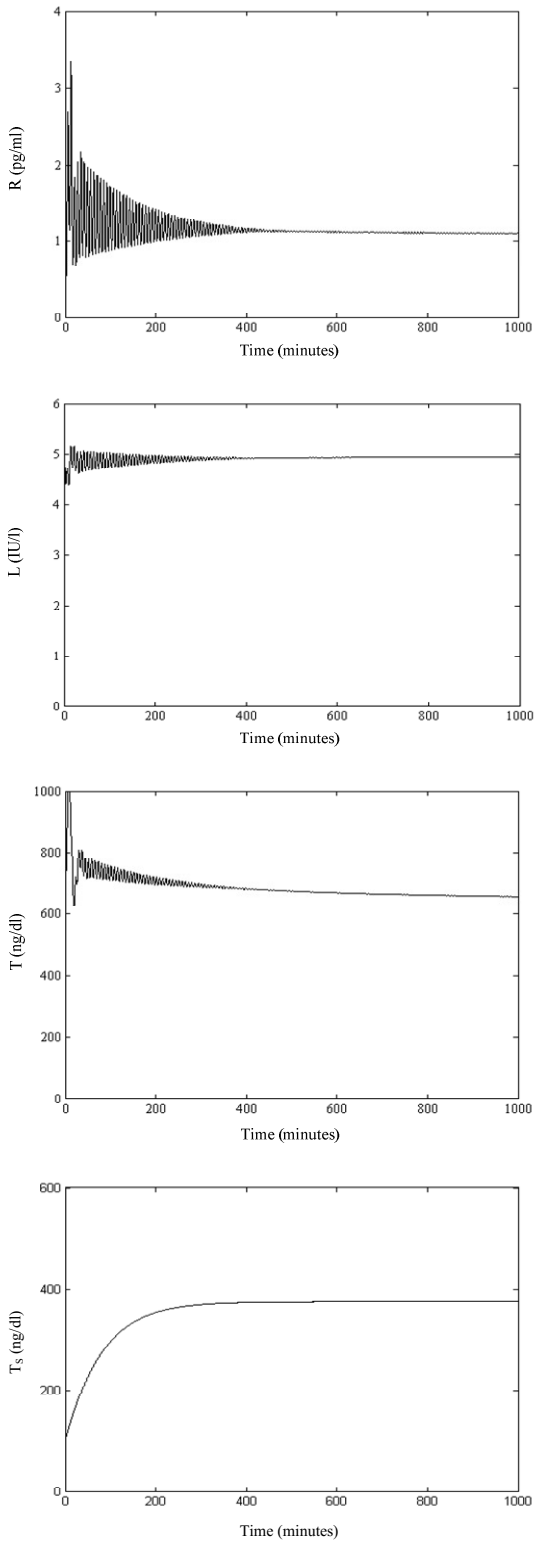

Figure 4.1. Numerical simulation for equations (4.1)-(4.4) with $\tau = 120$ min. The positive equilibrium is asymptotically stable. The initial value is (1, 5.3, 645, 100).

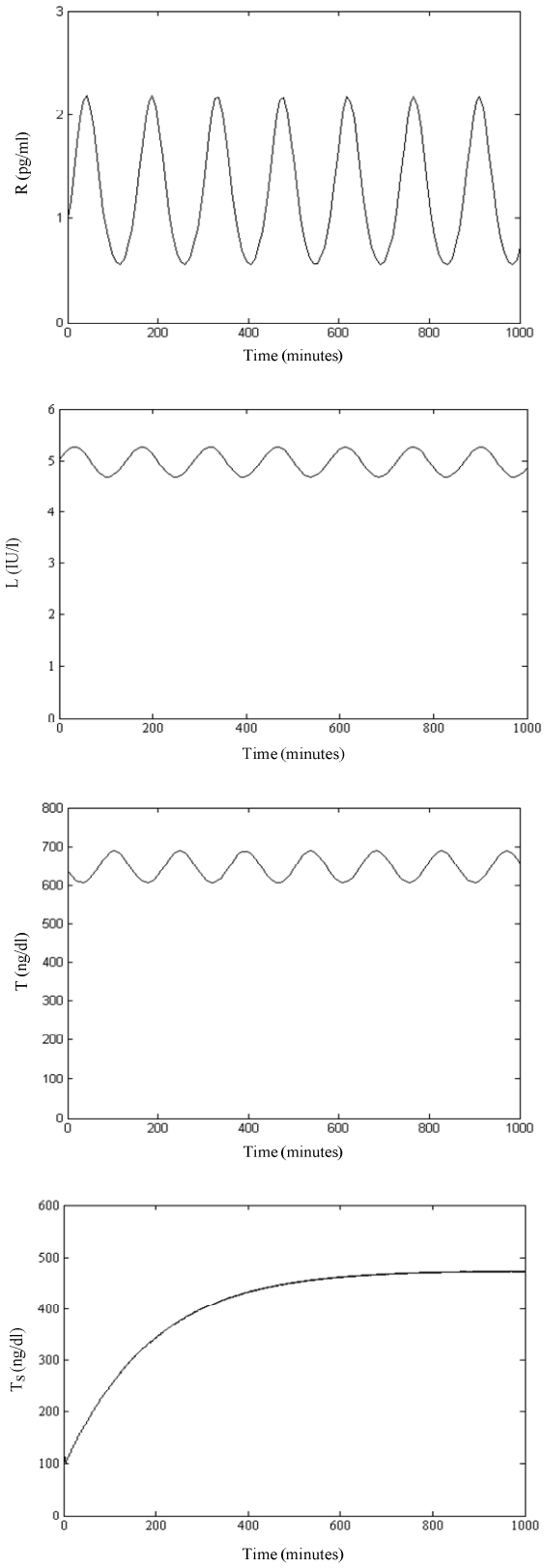

Figure 4.2. Numerical simulations of equations (4.1)-(4.4) exhibits the oscillating levels of three main hormones and the boosting level of SHBG bound testosterone in the system with $\tau = 123.47$ min. The initial value is (1, 5.3, 645, 100).

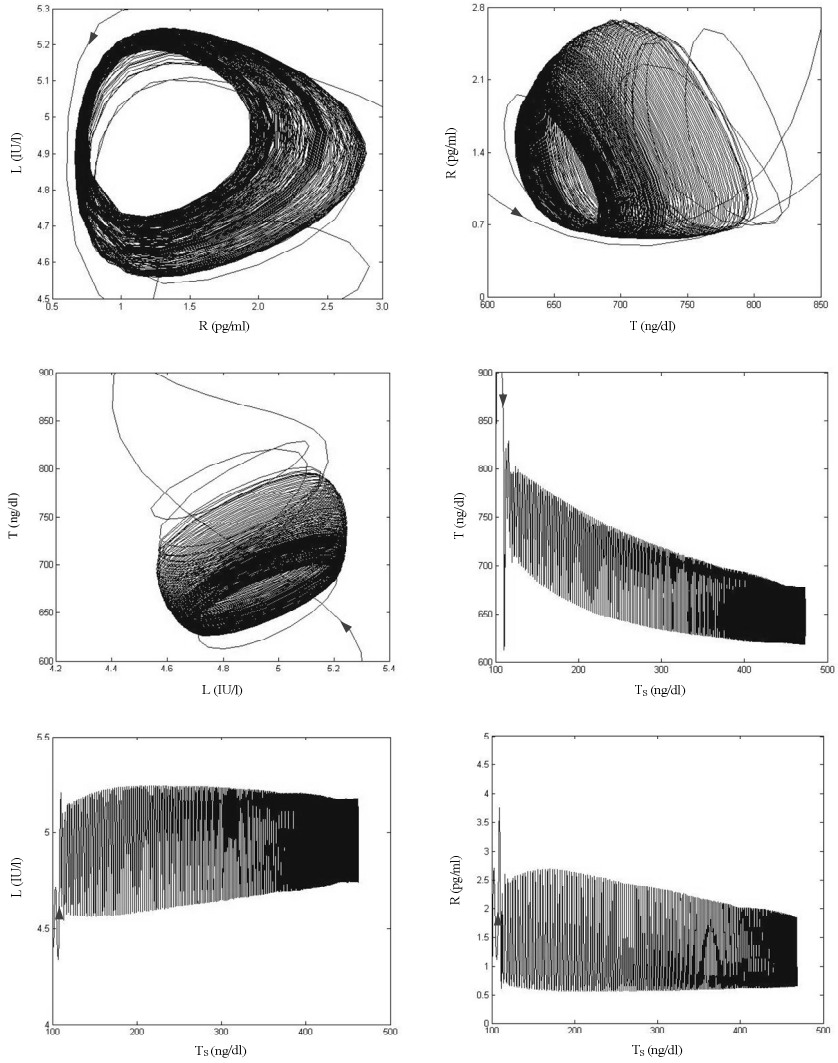

Figure 4.3. Numerical simulations demonstrate the solution trajectories which projected into the 2D-space for equations (4.1)-(4.4) with $\tau = 123.47$ min. The initial value is (1, 5.3, 645, 100).

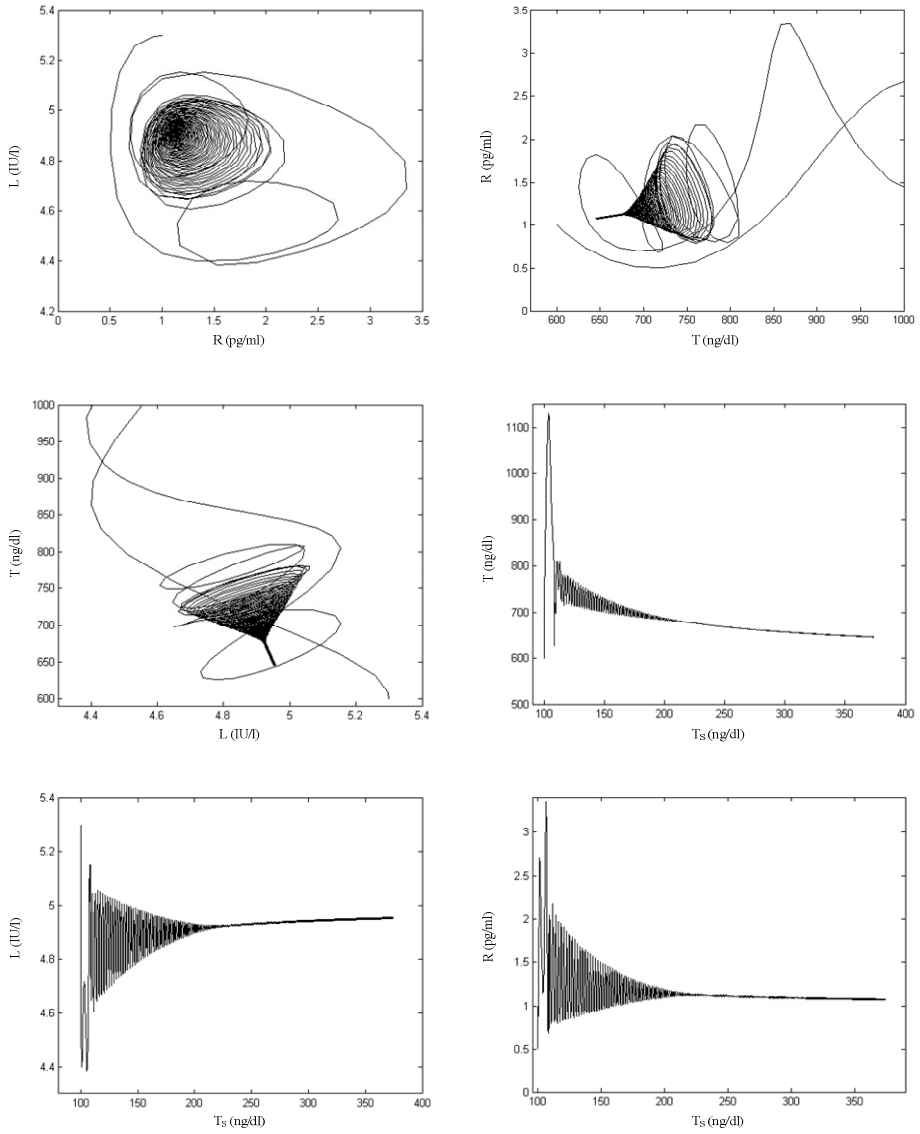

Figure 4.4. Numerical simulations demonstrate the solution trajectories which projected into the 2D-space for equations (4.1)-(4.4) with $\tau = 120$ min. The initial value is (1, 5.3, 645, 100). The positive equilibrium is asymptotically stable.

In this study, we developed a mathematical model in order to examine the characteristics of the male hormonal regulation which is effected by the binding of testosterone to SHBG in the male hormonal balancing system. The numerical simulations show the episodic pattern of three main hormone levels and exhibit the boosting level of SHBG bound testosterone in the system. Also, as time passes, we see the stability in the level of T_S although the binding of testosterone to SHBG still proceeds in the bloodstream. This result is in agreement with the format of hormone

balancing in the system. In addition, we showed the impact of different time delays to demonstrate that the periodic solutions bifurcate from the equilibrium when τ passes through a critical value. Moreover, this can explain the pulsatile secretion of hormones in males and the concentration curves which correspond to the data well.

Chapter 5
Conclusions and Suggestions

In this thesis, we purpose the mathematical models to explore the mechanism of testosterone regulation with analyzing the phenomenon of periodic fluctuations in the concentrations of hormones. The models are modified from the proposed model [40], that is able to explain the regular fluctuations of the three hormones in the hypothalamic-pituitary-gonadal endocrine cycle which regulates the production of the male hormone testosterone.

As a reason that the levels of testosterone in the actual endocrine system is also related to event outside the GnRH-LH-T loop [3]. That is, after testosterone is released in the bloodstream, it will be bound to various carrier proteins, resulting in a change of bioavailble testosterone level. Large amounts of total circulating testosterone are bound to sex hormone binding globulin (SHBG). Thus, SHBG-bound testosterone is biologically inactive. So it such plays an important role in regulating the amount of free testosterone in the male body. The levels of bioavailable testosterone are inversely related to the levels of SHBG. Therefore, as the level of SHBG is elevated, the body will increasingly stimulate the production of testosterone in the Leydig cells in order to maintain the optimal level of testosterone.

We studied the mathematical models to describe the fluctuations of the hormones in hormonal regulation of the male reproductive system having been linked to changes in SHBG levels. We formulated the differential equation models with a time delay corresponding to the time for traveling the LH hormone from pituitary gland to stimulate the production of testosterone in the gonads. We used standard dynamical modeling method to discover and analyze the equilibrium points, the jacobian matrices and their stability. We gain the conditions for periodical solutions and stability of the mathematical models.

The mathematical model presented in Chapter 3 extends the ability of the model of Greenhalgh and Khan [40] in order to explain serum hormone levels in the GnRH-LH-Testosterone system corresponding to SHBG. It is regulated and maintained by a balance of positive and negative feedback loops. We see that there is a unique equilibrium with all four hormones present. It is unstable when the time delay is

zero and as the time delay τ increases passing through the critical value τ^*. In simulation, we performed experiments on the model with realistic parameter values to illustrate quantitatively similar patterns of cyclic hormone fluctuations as detailed in Chapter 2 and the previous works. The hormone levels show oscillatory patterns about the equilibrium point in case of instability. The phenomenon of periodic fluctuations of the hormone levels supports and conforms to the data in the experimental results.

The model in Chapter 4 consisted of four nonlinear differential equations. We like to construct the mathematical model that can explain the mechanism of male hormone regulation and can exhibit the relation between the levels of total testosterone and SHBG-bound testosterone. The model is enlarged from the previous model given in [40]. To investigate the characteristics of the male hormonal regulation which is impacted by the binding of testosterone to SHBG in the male hormonal balancing system. We found that a unique equilibrium is unstable when the time delay is zero and whenever τ passes through a value τ^* , Hopf bifurcation occurs. The numerical simulations show the oscillating levels of three main hormones as observed biologically and the boosting level of SHBG bound testosterone in the system. Also, we found the very small change of SHBG-bound testosterone level in time. This result is in agreement with the format balancing in the system.

Furthermore, we wish that our study will represent a step forward in the development of the mathematical models. Next, we will develop a model including other factors that impact on male sex hormone in order to describe blood levels of hormones important for controlling the male sex hormone.

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Appendices

Appendix A

A. Theoretical Background

In this section, we introduce some theoretical background which is used to derive and characterize the properties of solutions of dynamical system in our models. As we have seen that our biological problems encountered in dynamical system modeling are nonlinear in structure. It can be proceeded to analyse the solution which visualizes the behavior of the real system [6].

Consider the system of ordinary differential equations as follows:

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \\ \frac{dy}{dt} &= g(x,y) \end{aligned} \tag{A.1}$$

where f and g are nonlinear functions.

Definition A.1 A point (x_0, y_0) is call a *steady state solution* or *equilibrium* of the system (A.1) when

$$f(x_0, y_0) = g(x_0, y_0) = 0$$

Definition A.2 The Jacobian matrix of the system (A.1) evaluated at (x_0, y_0) is defined by

$$J(x_0, y_0) = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}_{(x_0, y_0)}$$

Theorem A.3 An equilibrium (x_0, y_0) of the differential equation system (A.1) is stable if all the eigenvalues of $J(x_0, y_0)$, have negative real parts. The equilibrium point is unstable if at least one of the eigenvalues has a positive real part.

The equilibrium (x_0, y_0) of the system (A.1) can be classified based on their eigenvalues of $J(x_0, y_0)$:

- If the eigenvalues of $J(x_0, y_0)$ are complex with positive real parts, the point (x_0, y_0) is called an unstable focus.

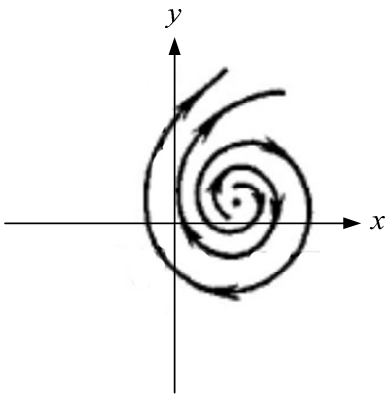

Figure A.1 An unstable focus.

- If the eigenvalues of $J(x_0, y_0)$ are complex with negative real parts, the point (x_0, y_0) is called a stable focus.

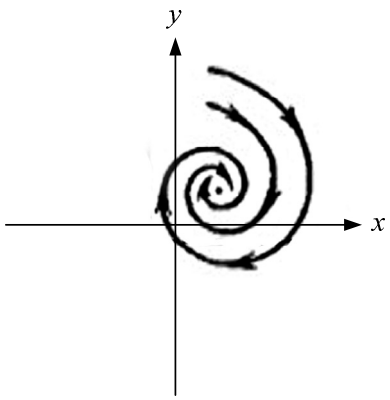

Figure A.2 A stable focus.

- If all eigenvalues of $J(x_0, y_0)$ are real and positive, the point (x_0, y_0) is called an unstable node

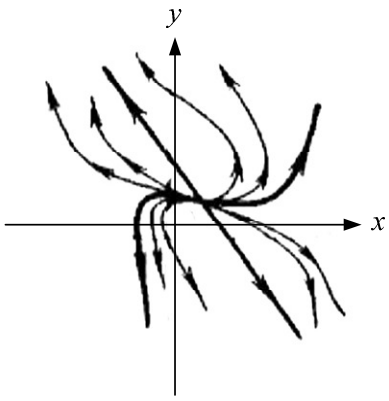

Figure A.3 An unstable node.

- If all eigenvalues of $J(x_0, y_0)$ are real and negative, the point (x_0, y_0) is called a stable node

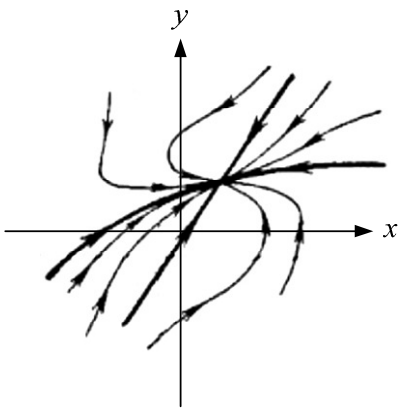

Figure A.4 A stable node.

- If the eigenvalues of $J(x_0, y_0)$ have opposite signs, the point (x_0, y_0) is called a saddle point

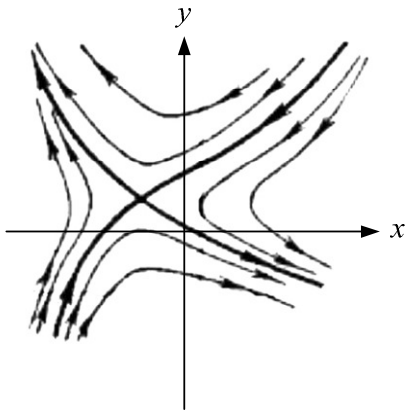

Figure A.5 A saddle point.

Now, we use the above ideas to consider a system with populations $X_1, X_2, ..., X_k$ as follows:

$$\begin{aligned} \frac{dX_1}{dt} &= f_1(X_1, X_2, ..., X_k), \\ \frac{dX_2}{dt} &= f_2(X_1, X_2, ..., X_k), \\ &\vdots \\ \frac{dX_k}{dt} &= f_k(X_1, X_2, ..., X_k). \end{aligned} \tag{A.2}$$

or in the form of vector notation

$$\frac{d\,\mathrm{X}}{dt} = \mathrm{F(X)} \tag{A.3}$$

for $\mathrm{X} = (X_1, X_2, ..., X_k)$, $\mathrm{F} = (f_1, f_2, ..., f_k)$, where each of the function $f_1, f_2, ..., f_k$ depend on all or some $X_1, X_2, ..., X_k$. A point $\bar{\mathrm{X}} = (X_1^*, X_2^*, ..., X_k^*)$ is called the equilibrium point when it satisfies $\mathrm{F}(\bar{\mathrm{X}}) = 0$. In the same way, next step is to determine stability properties of the steady state. In linearizing equation (A.3), the Jacobian of $\mathrm{F(X)}$ is obtained by setting

$$J = \frac{\partial \mathrm{F}}{\partial \mathrm{X}}(\bar{\mathrm{X}}) \tag{A.4}$$

or

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial X_1} & \frac{\partial f_1}{\partial X_2} & \cdots & \frac{\partial f_1}{\partial X_k} \\ \frac{\partial f_2}{\partial X_1} & \frac{\partial f_2}{\partial X_2} & \cdots & \frac{\partial f_2}{\partial X_k} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_k}{\partial X_1} & \frac{\partial f_k}{\partial X_2} & \cdots & \frac{\partial f_k}{\partial X_k} \end{bmatrix}_{\bar{\mathrm{X}}} \tag{A.5}$$

Here, J is a $k \times k$ matrix. Eigenvalues λ of this matrix satisfy

$$\det(J - \lambda I) = 0. \tag{A.6}$$

We obtain a characteristic equation of the form

$$\lambda^k + a_1\lambda^{k-1} + a_2\lambda^{k-2} + \ldots + a_{k-1}\lambda + a_k = 0. \tag{A.7}$$

The stability of the equilibrium point can be determined without solving the actual values of eigenvalues by using the Routh-Hurwitz criteria.

Theorem A.4 (Routh-Hurwitz criteria for local asymptotical stability)

Given the characteristic equation (2.7), define k matrices as follows:

$$\mathrm{H}_1 = [a_1],$$

$$\mathrm{H}_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix},$$

$$\mathrm{H}_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix},$$

$$\mathrm{H}_4 = \begin{bmatrix} a_1 & 1 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 \\ a_5 & a_4 & a_3 & a_2 \\ a_7 & a_6 & a_5 & a_4 \end{bmatrix},$$

and $$\mathrm{H}_k = \begin{bmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_k \end{bmatrix}.$$

Then all eigenvalues have negative real parts, i.e., the equilibrium point $\bar{\mathrm{X}}$ is stable if and only if the determinants of all Hurwitz matrices are positive that is

$$\det \mathrm{H}_j > 0 \qquad \text{for} \quad j = 1,2,...,k$$

Here,

$$\det \mathrm{H}_4 = a_1a_2a_3a_4 + a_2a_3a_5 + 2a_1a_4a_5 + a_1^2a_2a_6 + a_3a_7 - a_3^2a_4 - a_1^2a_4^2 - a_1a_2^2a_5 - a_5^2 - a_1a_3a_6 - a_1a_2a_7$$

The conditions of Routh-Hurwitz criteria for local asymptotical stability in 4th order characteristic polynomial equation:

i) $a_1 > 0$

ii) $a_3 > 0$

iii) $a_4 > 0$

iv) $a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0$

In the following theorem, we discuss the Hopf bifurcation theorem [7].

Theorem A.5 For a system of first order differential equations given by

$$\frac{d\,\mathrm{X}}{dt} = \mathrm{F}(\mathrm{X};\tau)$$

where $\mathbf{X}$ is a column vector. If

(i) $\mathbf{F}(\mathbf{X};\tau) = 0$ for τ in an open interval containing τ^* and $\mathbf{X}_e$ is an equilibrium point of $\mathbf{F}$.

(ii) $\mathbf{F}$ is analytic in $\mathbf{X}$ and τ in a neighborhood of $(\mathbf{X}_e, \tau^*)$.

(iii) the Jacobian matrix $J(\tau) = D_{\mathbf{X}}\mathbf{F}(\mathbf{X}_e, \tau)$ has a pair of complex conjugate eigenvalues λ and $\overline{\lambda}$ such that

$$\lambda(\tau) = u(\tau) + iv(\tau)$$

where

$$v(\tau^*) = v^* > 0, \quad u(\tau^*) = 0, \quad \left.\frac{du}{d\tau}\right|_{\tau=\tau^*} \neq 0$$

for the critical value of bifurcation parameter τ^*.

(iv) The remaining eigenvalues of $J(\tau)$ have strictly negative real parts,

then the system $\frac{d\mathbf{X}}{dt} = \mathbf{F}(\mathbf{X};\tau)$ has a family of periodic solutions that means there is a loss of linear stability of the equilibrium point $\mathbf{X}_e$ as τ crosses τ^*.

A limit cycle is an isolated closed trajectory which neigbouring trajectories are not closed but spiral away or toward the limit cycle. A limit cycle can be stable, unstable, or half-stable.

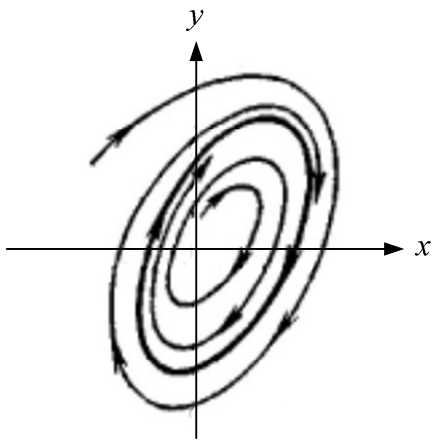

Figure A.6 A stable limit cycle.

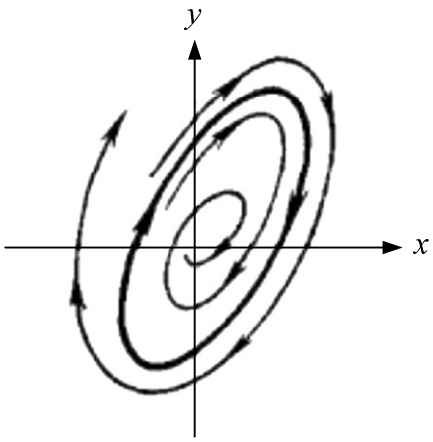

Figure A.7 An unstable limit cycle.

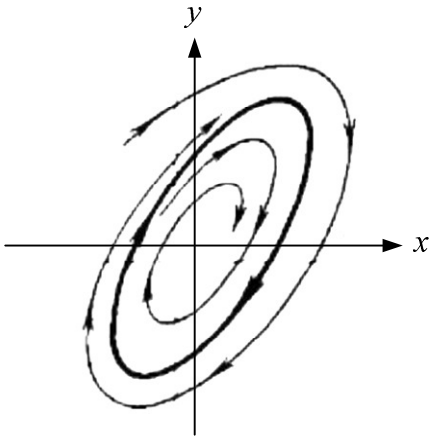

Figure A.8 A half-stable limit cycle.

Appendix B

B. Accepted Papers for Publication and Presentation

From this study, we published the following papers :

1. Tanutpanit, T. Pongsumpun, P. and Tang, I.M. 2013 "Stability and oscillations of time-delayed model for the testosterone regulation." *Journal of Mathematics and Computers in Simulation*. 4(7): 355-362.
2. Tanutpanit, T. Pongsumpun, P. and Tang, I.M. 2015 "A model for the testosterone regulation taking into account the presence of two types of testosterone hormones." *Journal of Biological Systems*. 23(2): 1-15.

Moreover, materials corresponding to the aim of the thesis are presented in the following publications :

- Tanutpanit, T. and Pongsumpun, P. 2015 "A delay mathematical model for the operating characteristics of the male hormonal regulation." International Conference on Food, Ecological and Life Sciences (FELS), Bangkok, Thailand.
- Tanutpanit, T. and Pongsumpun, P. 2015 "A modified Mathematical Model Interpreting the Quantitative Behavior of Testosterone in the Male Hormonal Regulation." International Conference on Food, Ecological and Life Sciences (FELS), Bangkok, Thailand.

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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.

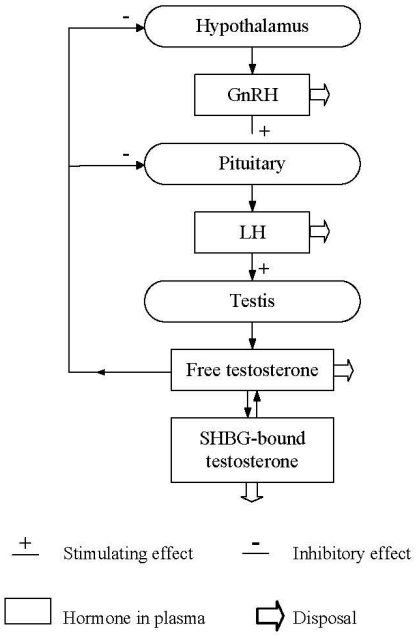

Fig.1. The flow and interactions block diagram of the hypothalamo-pituitary-gonadal axis in men.

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 equilibriums 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

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

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

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

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

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

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

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

$$\begin{aligned}k_1 &= -2\left(\delta\beta_3 + \varepsilon_1\phi_1\right) \\ k_2 &= 2\varepsilon_1\phi_1\delta\beta_3 + \left(\delta\beta_3 + \varepsilon_1\phi_1\right)^2 - 2\beta_2 \\ &\quad - \varepsilon_2^2\beta_1^2 - 2\varepsilon_1\beta_2\left[\beta_1\phi_2 - \phi_1\beta_2\right] \\ k_3 &= 1 - 2\varepsilon_1\phi_1\delta\beta_3\left(\delta\beta_3 + \varepsilon_1\phi_1\right) - \varepsilon_1^2\left[\beta_1\phi_2 - \phi_1\beta_2\right]^2 \\ k_4 &= \varepsilon_1^2\phi_1^2\delta^2\beta_3^2\end{aligned}$$

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

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

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

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

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

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

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

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

$$\begin{aligned} PR - QS &= 4v^{*8} - 6(\delta\beta_3 + \varepsilon_1\phi_1)v^{*6} \\ &\quad + (4\delta\varepsilon_1\phi_1\beta_3 + 2(\delta\beta_3 + \varepsilon_1\phi_1)^2 - 2\varepsilon_2^2\beta_1^2 \\ &\quad - 4\varepsilon_1\beta_2(\beta_1\phi_2 - \phi_1\beta_2) - 4\beta_2)v^{*4} \\ &\quad + (1 - \varepsilon_1^2(\beta_1\phi_2 - \phi_1\beta_2)^2 - 2\delta\varepsilon_1\phi_1\beta_3(\delta\beta_3 + \varepsilon_1\phi_1))v^{*2} \\ &= v^{*2}(4v^{*6} - 6(\delta\beta_3 + \varepsilon_1\phi_1)v^{*4} \\ &\quad + (4\delta\varepsilon_1\phi_1\beta_3 + 2(\delta\beta_3 + \varepsilon_1\phi_1)^2 - 2\varepsilon_2^2\beta_1^2 \\ &\quad - 4\varepsilon_1\beta_2(\beta_1\phi_2 - \phi_1\beta_2) - 4\beta_2)v^{*2} \\ &\quad + (1 - 2\delta\varepsilon_1\phi_1\beta_3(\delta\beta_3 + \varepsilon_1\phi_1) - \varepsilon_1^2(\beta_1\phi_2 - \phi_1\beta_2)^2)) \\ &= v^{*2}\left(4w^3 + 3k_1w^2 + 2k_2w + k_3\right) \\ &= v^{*2}\cdot\left.\frac{df(w)}{dw}\right|_{w=v^*} \end{aligned}$$

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 $g_1 = 0.0092$ /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 balanced on the influence of variations in the SHBG concentration. Levels of total testosterone can 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

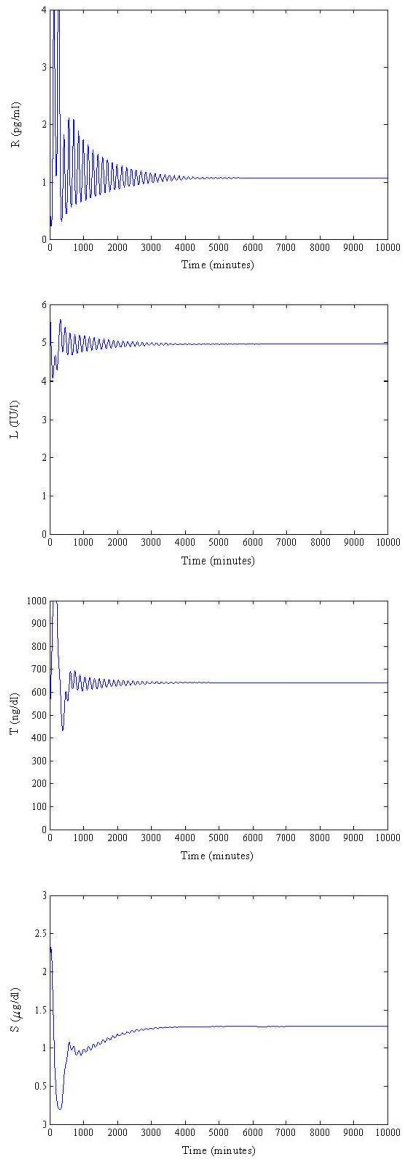

Fig 2. Numerical simulations for equation (6a)-(6d) with $\tau = 120$. The positive equilibrium is asymptotically stable. The initial value is (1, 5, 600, 1)

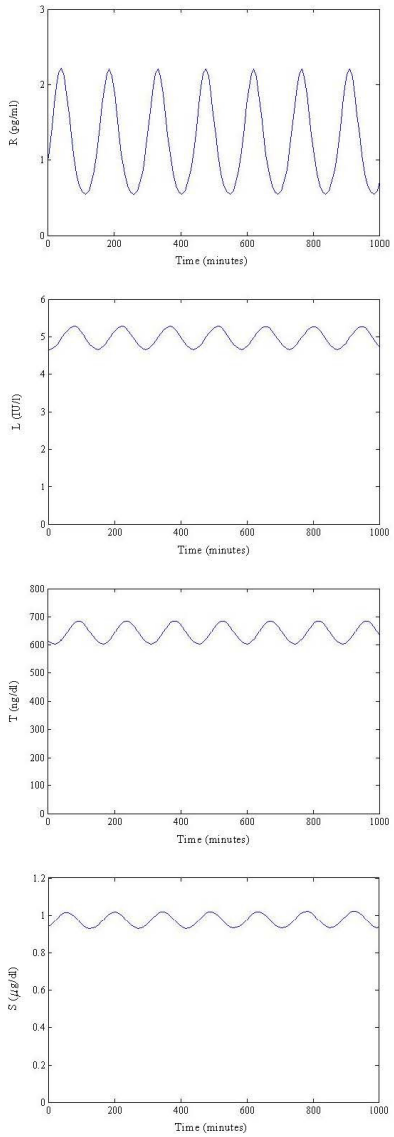

Fig 3. Numerical simulations for the equation (6a)-(6d) with $\tau = 124$. Hopf bifurcation occurs from the positive equilibrium. The initial value is (1, 5, 600, 1)

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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A MODEL FOR THE TESTOSTERONE REGULATION TAKING INTO ACCOUNT THE PRESENCE OF TWO TYPES OF TESTOSTERONE HORMONES

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The purpose of this paper is to study the effect of sex hormone binding globulin (SHBG) on the mathematical model of the hypothalamic-pituitary-gonadal (HPG) endocrine cycle which regulates the production of the male hormone testosterone. Large amounts of total circulating testosterone are bound to SHBG making them. Standard analytical techniques are used to analyze the modified mathematical model which includes a delay to account for the time required for luteinizing hormone emitted by the pituitary gland to reach the testis, to determine the steady state, its stability and the critical delay needed for the bifurcation. Numerical simulation of the solutions of the model is performed to illustrate the possible behaviors.

Keywords: Hormone; Time Delay; Oscillation; Testosterone; SHBG; Hormonal Regulation.

1. Introduction

Testosterone is an androgenic hormone which can be found in both males and females. The level of testosterone in males is about 7 to 8 times greater than that in females. In males, it plays the key role in the development of the male reproductive tissues. As an androgen, it promotes protein synthesis and as such it has an effect on the growth of muscle mass and increase in bone density. Its production in males is 20 times that in females. It is necessary for male physical development and other male processes such as beard growth and the lower pitch of the male voice.

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Testosterone is derived from cholesterol and is produced primarily by the Leydig cells in the testis. The amount of testosterone is carefully regulated by the endocrinology processes connected to the hypothalamus-pituitary-gonadal axis (HPG-axis) shown in Fig 1. Two glands close to the brain, the hypothalamus and pituitary glands regulate the secretion of the testosterone through a feedback mechanism involving hormones being secreted by the two glands. The hypothalamus releases gonadotropin-releasing hormone (GnRH) in a pulsatile manner. This acts as a signal for the pituitary gland to secret luteinizing hormone (LH) into the blood stream where it travels to the testes. Once the LH reaches the testes, it simulates the Leydig cells to produce the testosterone. The secretion of the LH follows an episodic pattern resulting in fluctuations of the level of testosterone in the circulating blood.[1,2] 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.

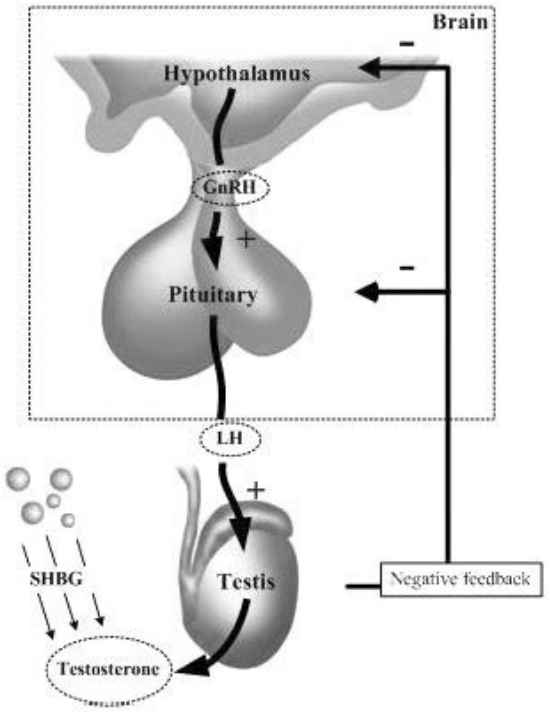

Fig. 1. A schematic overview details the steps involved in the hormonal control of male reproduction.

Mathematical models for the regulation of male sex hormone have been widely used for a long time and have been studied in order to understand the interaction of hormones in dynamic biological systems. A simple mathematical model describing the hypothalamic-pituitary-gonadal (HPG) system was first proposed by Smith.[3] It was used to explain the pulsatile hormone regulation in the GnRH–LH–T axis. Denoting the concentrations of GnRH, LH and BioT, respectively by $R(t)$, $L(t)$ and $T(t)$, Smith's model becomes

$$\begin{aligned} \frac{dR}{dt} &= f(T) - b_1(R), \\ \frac{dL}{dt} &= g_1(R) - b_2(L), \\ \frac{dT}{dt} &= g_2(L) - b_3(T), \end{aligned} \tag{1.1}$$

where the positive functions b_1, b_2, b_3 are the clearing rates of three hormones and g_1, g_2, f describe the hormone secretion rates. b_1, b_2, b_3, g_1 and g_2 are assumed to be monotonic increasing functions while the negative feedback function f is assumed to be a monotonic decreasing function. In 1983, Smith[4] made an improvement to the model by introducing a time delay τ into the T-equation since it takes time for the LH to travel from the pituitary gland to the target cells and actions of gonadotrophins in the gonads to start. The last equations for the system (1.1) would become a delay differential equation, i.e.,

$$\begin{aligned} \frac{dR}{dt} &= f(T) - b_1(R), \\ \frac{dL}{dt} &= g_1(R) - b_2(L), \\ \frac{dT}{dt} &= g_2(L(t-\tau)) - b_3(T), \end{aligned} \tag{1.2}$$

where τ is a delay caused by the time it takes the LH to reach the testis after it is released by the pituitary gland (there being a great distance between this gland and the testis).

After testosterone is secreted into the bloodstream, 96–98% will be bound to various carrier proteins. One of these will be the sex hormone-binding globulin (SHBG). This protein is produced primarily in the liver. The entry of SHBG into the hypothalamus-pituitary-gonadal axis is shown in the lower left corner of the figure. SHBG plays an important role in determining the availability of the testosterone for its endocrinology activity. The reason for this is that SHBG can tightly bind to the testosterone making it physiologically inactive.[5–7] A large fraction (∼60–70%) of the testosterone will be of this type. Another 28–38% will be weakly bound to albumin. Only a small percentage (∼2%) of testosterone will be unbound. This will be considered to be free testosterone (FT). Only the FT is capable of entering a

cell and activating the receptor on the SHBG gene on the chromosome and turning it on. The circulating bound and FT are collectively referred to as the total testosterone. The FT and the albumin-bound testosterone are physiologically available to the body tissues. These are known as bioavailable testosterone (BioT).[8] The level of SHBG becomes one factor that determines the total testosterone level.[9–12] High concentrations of SHBG reduce the level of BioT. Consequently, the total concentration of testosterone must increase to maintain adequate levels of BioT.[13,14]

Greenhalgh and Khan,[15] sought to improve on the models of Smith[4] and of Cartwright and Husain[2] by using different response functions which incorporated more qualitatively observed biological behaviors. Greenhalgh and Khan did not use the Heaviside step function to be a response function which leads to the GnRH and LH being produced when the testosterone falls below a given value. Instead they use two Michaelis-Menten-like response functions which take on different values depending on whether the feedback component biochemical is large or small. Their model included the same time delay as Smith's model. Tanutpanit *et al.*[16] improved the model of Greenhalgh and Khan by including the effects of the SHBG. As we mentioned, testosterone can bind to SHBG, making them ineffective as an endocrinology agent. Only free testosterone is important to the HPG.

In the present study, we have improved on our previous work. We now allow the SHBG level to vary. This makes the revised model more medically correct. In humans, the levels of SHBG may depend on the medical condition of the person. The SHBG levels are decreased when the person suffers from hypothyroidism, diabetes, obesity or the Cushing's syndrome. The levels are elevated when the person suffers from hyperthyroidism, cirrhosis of the liver and is pregnant. Inclusion of the SHGB is necessary since an increase in the SHBG level leads to an increase in total testosterone level.

2. Mathematical Model for the Testosterone Regulation

2.1. *Mathematical model*

Since we assume that testosterone exists in two different forms in the blood: bounded testosterone and FT. We must differentiate between the two and so each needs its own individual designation. We need to introduce four variables; R for the plasma concentration of the GnRH, LU for the LH, T for FT and T_S for SHBG bound testosterone. In this study, we will investigate the following delay differential equations

$$\frac{dR}{dt} = \frac{q_1 R}{LU + q_2 T} - \mu_1 R, \tag{2.1}$$

$$\frac{dLU}{dt} = \left(\frac{d_1 R}{R + d_2 T}\right) \cdot LU - \mu_2 LU, \tag{2.2}$$

$$\frac{dT}{dt} = a \cdot LU(t-\tau)T + \frac{r_3}{1+r_4 T_s}T - \mu_3 T, \tag{2.3}$$

$$\frac{dT_S}{dt} = \left(\frac{e_1 T}{1+e_2 T}\right) \cdot T_S - \mu_4 T_S, \tag{2.4}$$

where q_1, q_2, d_1, d_2, a, p_1, p_2, e_1, e_2 are strictly positive parameters and μ_1, μ_2, μ_3, μ_4 are defined as the metabolic clearance rates of all four hormones.

As we have said, the GnRH R is released by the hypothalamus. As pointed out in Ref. 15 the release of GnRH is influenced by the combined effect of both the LH and the testosterone hormones. The response function used in (2.1) reflects this. The release of the LH hormone by the pituitary gland should be high when the level of T is low and the level of GnRH is low. The release of LH should be low then the level of T is high and the level of GnRH is high. The response function used in (2.2) exhibits two different behaviors for R greater of less than LU. In (2.4), we use a hyperbolic function $\varphi(T) = e_1 T/(1+e_2 T)$ to describe the change of SHBG-bound testosterone level. $\varphi(T)$, which is an increasing and bounded function where $T > 0$, is used to explain the rise in the level of SHBG-bound testosterone at the time that testosterone is released into the bloodstream and then bind to SHBG.

2.2. *Steady state*

In order to find steady states, we set the right hand side of Eqs. (2.1) to (2.4) to zero. We see that the above equations admit the nonzero steady state $\bar{E}(\bar{R}, \overline{LU}, \bar{T}, \bar{T}_S)$ where

$$\bar{R} = \frac{d_2\mu_2}{d_1-\mu_2}\left(\frac{\mu_4}{e_1-e_2\mu_4}\right) = \frac{d_2\mu_2}{d_1-\mu_2}\bar{T},$$

$$\overline{LU} = \frac{q_1}{\mu_1} - q_2\left(\frac{\mu_4}{e_1-e_2\mu_4}\right) = \frac{q_1}{\mu_1} - q_2\bar{T},$$

$$\bar{T} = \frac{\mu_4}{e_1-e_2\mu_4}$$

and

$$\bar{T}_S = \frac{1}{r_4}\left(\frac{r_3}{\mu_3 - a(\frac{q_1}{\mu_1} - q_2(\frac{\mu_4}{e_1-e_2\mu_4}))} - 1\right) = \frac{1}{r_4}\left(\frac{r_3}{\mu_3 - a\overline{LU}} - 1\right).$$

Obviously, this steady state is positive if and only if

$$d_1 - \mu_2 > 0, \quad \frac{q_1}{\mu_1} - \frac{q_2\mu_4}{e_1-e_2\mu_4} > 0,$$

$$e_1 - e_2\mu_4 > 0 \quad \text{and} \quad \frac{r_3}{\mu_3 - a\overline{LU}} - 1 > 0.$$

2.3. *Local stability and local Hopf bifurcation analysis*

In order to analyze the stability of the steady state $\bar{E}$, we now use the transformations

$$w = R - \bar{R}, \quad x = LU - \overline{LU}, \quad y = T - \bar{T},$$
$$z = T_S - \bar{T}_S \quad \text{and} \quad x_1 = LU_1 - \overline{LU},$$

where $LU_1(t) = LU(t-\tau)$ and then linearize the system of (2.1)–(2.4) (See also Appendix A).

We get the linear system of Eqs. (2.1)–(2.4) at $\bar{E}$ as follows:

$$\begin{bmatrix} \frac{dw}{dt} \\ \frac{dx}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{bmatrix} = \begin{bmatrix} 0 & \eta_1 & \eta_2 & 0 \\ \eta_3 & 0 & \eta_4 & 0 \\ 0 & \eta_5 e^{-\lambda\tau} & 0 & \eta_6 \\ 0 & 0 & \eta_7 & 0 \end{bmatrix} \begin{bmatrix} w \\ x \\ y \\ z \end{bmatrix}, \tag{2.5}$$

where

$$\eta_1 = -\frac{q_1\bar{R}}{(\overline{LU} + q_2\bar{T})^2}, \quad \eta_2 = -\frac{q_1 q_2 \bar{R}}{(\overline{LU} + q_2\bar{T})^2}, \quad \eta_3 = \frac{d_1 d_2 \overline{LU} \cdot \bar{T}}{(\bar{R} + d_2\bar{T})^2},$$
$$\eta_4 = -\frac{d_1 d_2 \overline{LU} \cdot \bar{R}}{(\bar{R} + d_2\bar{T})^2}, \quad \eta_5 = a\bar{T}, \quad \eta_6 = -\frac{r_3 r_4}{(1 + r_4\bar{T}_S)^2}\bar{T} \quad \text{and} \quad \eta_7 = \frac{e_1\bar{T}_S}{(1 + e_2\bar{T})^2}.$$

We obtain the corresponding characteristic equation as follows

$$\lambda^4 - (\eta_1\eta_3 + \eta_6\eta_7)\lambda^2 + \eta_1\eta_3\eta_6\eta_7 - (\eta_4\eta_5\lambda^2 + \eta_2\eta_3\eta_5\lambda)e^{-\lambda\tau} = 0. \tag{2.6}$$

To find the local stability of the steady state, we consider the case without delay time τ. Setting $\tau = 0$ in (2.6), we have the characteristic equation

$$\lambda^4 - (\eta_1\eta_3 + \eta_4\eta_5 + \eta_6\eta_7)\lambda^2 - \eta_2\eta_3\eta_5\lambda + \eta_1\eta_3\eta_6\eta_7 = 0. \tag{2.7}$$

By using the Routh–Hurwitz criteria, the nontrivial steady state is unstable for $\tau = 0$.

Now, we return to the analysis of Eq. (2.6) in case $\tau \geq 0$. We rewrite the equation in a form as

$$\lambda^4 + p_1\lambda^2 + p_2 + (q_1\lambda^2 + q_2\lambda)e^{-\lambda\tau} = 0, \tag{2.8}$$

where

$$p_1 = -(\eta_1\eta_3 + \eta_6\eta_7), \quad p_2 = \eta_1\eta_3\eta_6\eta_7, \quad q_1 = -\eta_4\eta_5 \quad \text{and} \quad q_2 = -\eta_2\eta_3\eta_5.$$

In order to determine the conditions on the parameters for Hopf bifurcation, we introduce the following theorem.[17]

Theorem 2.1. *For a system of first order differential equations given by*

$$\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}; \tau),$$

where $\mathbf{x}$ *is a column vector. If*

(i) $\mathbf{F}(\mathbf{x}; \tau) = 0$ *for* τ *in an open interval containing* τ^*, *and* $\mathbf{x}_e$ *is an equilibrium point of* $\mathbf{F}$.
(ii) $\mathbf{F}$ *is analytic in* $\mathbf{x}$ *and* τ *in a neighborhood of* $(\mathbf{x}_e, \tau^*)$.
(iii) *The Jacobian matrix* $\mathbf{J}(\tau) = D_{\mathbf{X}}\mathbf{F}(\mathbf{x}_e, \tau)$ *has a pair of complex conjugate eigenvalues* λ *and* $\bar{\lambda}$ *such that*

$$\lambda(\tau) = u(\tau) + iv(\tau),$$

where

$$v(\tau^*) = v^* > 0, \quad u(\tau^*) = 0, \quad \left.\frac{du}{d\tau}\right|_{\tau=\tau^*} \neq 0$$

for the critical value of bifurcation parameter τ^*.
(iv) *The remaining eigenvalues of* $\mathbf{J}(\tau)$ *have strictly negative real parts, then the system* $\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}; \tau)$ *has a family of periodic solutions.*

For the steady state $\bar{E}$, we let $\lambda(\tau) = u(\tau) + iv(\tau)$ where u and v are real. The Eq. (2.8) becomes

$$(u+iv)^4 + p_1(u+iv)^2 + p_2 + (q_1(u+iv)^2 + q_2(u+iv))\mathrm{e}^{-(u+iv)\tau} = 0. \tag{2.9}$$

Separating the real and imaginary parts, we get

$$u^4 - 6u^2v^2 + v^4 + p_1(u^2 - v^2) + p_2 + \mathrm{e}^{-u\tau}[(q_1(u^2 - v^2) + q_2u)\cos(v\tau) + (q_2v + 2q_1uv)\sin(v\tau)] = 0 \tag{2.10}$$

and

$$4u^3v - 4uv^3 + 2p_1uv + \mathrm{e}^{-u\tau}[(q_2v + 2q_1uv)\cos(v\tau) - (q_1(u^2 - v^2) + q_2u)\sin(v\tau)] = 0. \tag{2.11}$$

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^*, Eqs. (2.10) and (2.11) become

$$q_1v^{*2}\cos(v^*\tau^*) - q_2v^*\sin(v^*\tau^*) = v^{*4} - p_1v^{*2} + p_2 \tag{2.12}$$

and

$$q_2v^*\cos(v^*\tau^*) + q_1v^{*2}\sin(v^*\tau^*) = 0. \tag{2.13}$$

We sum the squares of both equations. Hence, Eqs. (2.12) and (2.13) reduce to

$$v^{*8} - 2p_1v^{*6} + (2p_2 + p_1^2 - q_1^2)v^{*4} - (2p_1p_2 + q_2^2)v^{*2} + p_2^2 = 0. \tag{2.14}$$

We define

$$A(s) = s^4 - 2p_1s^3 + (2p_2 + p_1^2 - q_1^2)s^2 - (2p_1p_2 + q_2^2)s + p_2^2, \tag{2.15}$$

where $A(s = v^{*2}) = 0$

The value of critical delay $\tau^*$is determined by the necessity that $u(\tau^*) = 0$, then the existence of purely imaginary eigenvalues depend on whether (2.14) has at least one positive real root. From (2.12) and (2.13), the equations can be written in the form

$$\cos(v^*\tau^* + \theta_1) = \frac{v^{*4} - p_1v^{*2} + p_2}{v^*\sqrt{(q_1v^*)^2 + q_2^2}} \quad \text{and} \quad \sin(v^*\tau^* + \theta_1) = 0, \tag{2.16}$$

where θ_1 is in the interval $[0, \frac{\pi}{2})$,

$$\cos(\theta_1) = \frac{q_1v^*}{\sqrt{(q_1v^*)^2 + q_2^2}} \quad \text{and} \quad \sin(\theta_1) = \frac{q_2}{\sqrt{(q_1v^*)^2 + q_2^2}}. \tag{2.17}$$

Thus, if Eq. (2.14) has a positive real root, we can solve for the critical time delays τ^* from

$$\tau^* = \frac{2k\pi - \theta_1}{v^*} \quad \text{for } k \in I. \tag{2.18}$$

Theorem 2.2. *Suppose that* $4s^3 + 3a_1s^2 + 2a_2s + a_3 \neq 0$ *then the system of delay differential equations* (2.1)–(2.4) *with the critical value* τ^* *as in* (2.18) *behaves the Hopf bifurcation when the value of time delay* τ *passes through the critical value* τ^*.

The proof of this theorem is given in Appendix B.

3. Numerical Results

To gain a quantitative sense of the behavior of the hormones in our model for the regulation of testosterone when there are two types of testosterones present, we have simulated the behaviors by numerically solving Eqs. (2.1)–(2.4) using routine dde23 in MATLAB. Most of the realistic values of the parameters are taken from Greenhalgh and Khan.[15] The values of the other parameters used in the simulation are $r_3 = 0.023$/min, $r_4 = 1.47$/min, $e_1 = 0.004$/min, $e_2 = 0.08$/min and $\mu_4 = 0.0491$/min. These values when substituted into the expressions for the steady values of the components, $\bar{R}, \overline{LU}, \bar{T}$ and $\bar{T}_S$ yield normal range of values of the hormone levels, i.e., $\bar{E}(1.07, 4.95, 645.39, 373.96)$. Since Eq. (2.14) satisfy the conditions of one of the Theorems in Ref. 16 regarding whether the fourth order (in $s = v^{*2}$) algebraic, Eq. (2.14) has at least one real positive value. This would be the value of v^*. Substituting this value into Eq. (2.14), we would get the critical delay at which

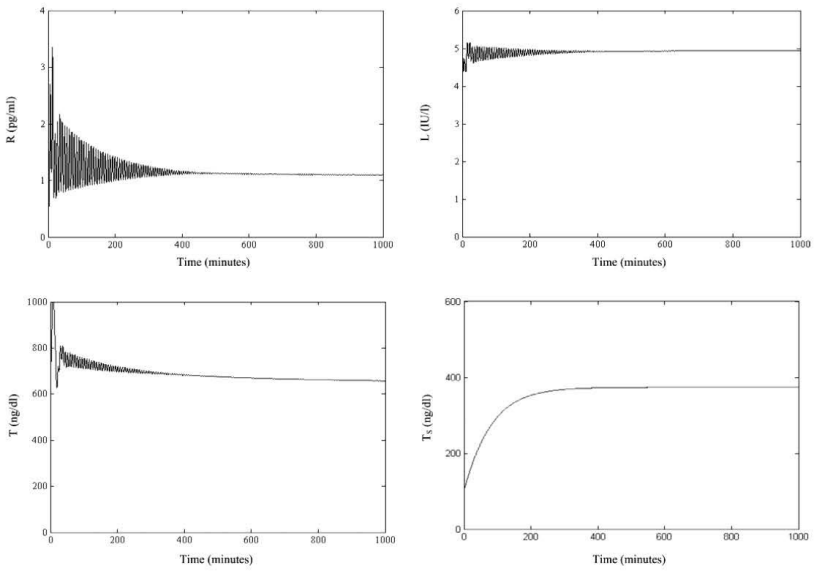

Fig. 2. Numerical simulation for Eqs. (2.1)–(2.4) with $\tau = 120$ min. The positive equilibrium is asymptotically stable. The initial value is (1, 5.3, 645, 100).

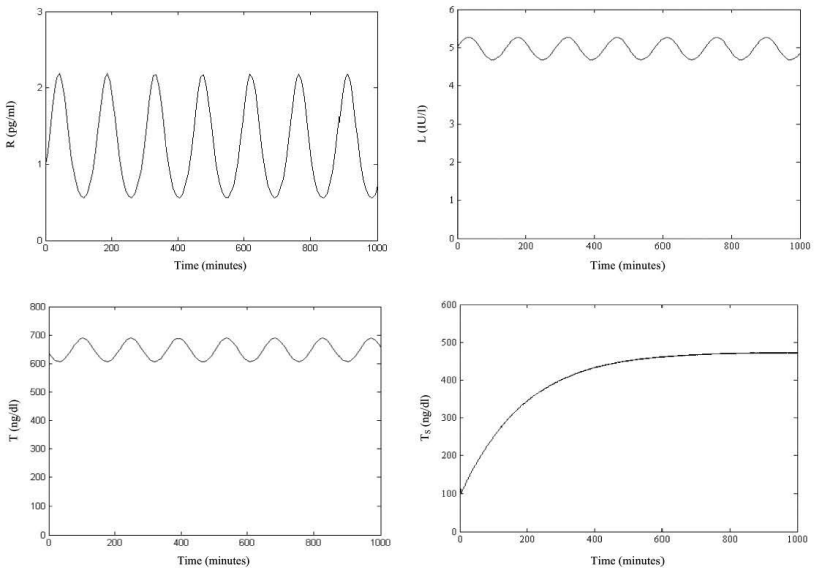

Fig. 3. Numerical simulation of equations (2.1)–(2.4) exhibits the oscillating levels of three main hormones and the boosting level of SHBG bound testosterone in the system with $\tau = 123.47$ min. The initial value is (1, 5.3, 645, 100).

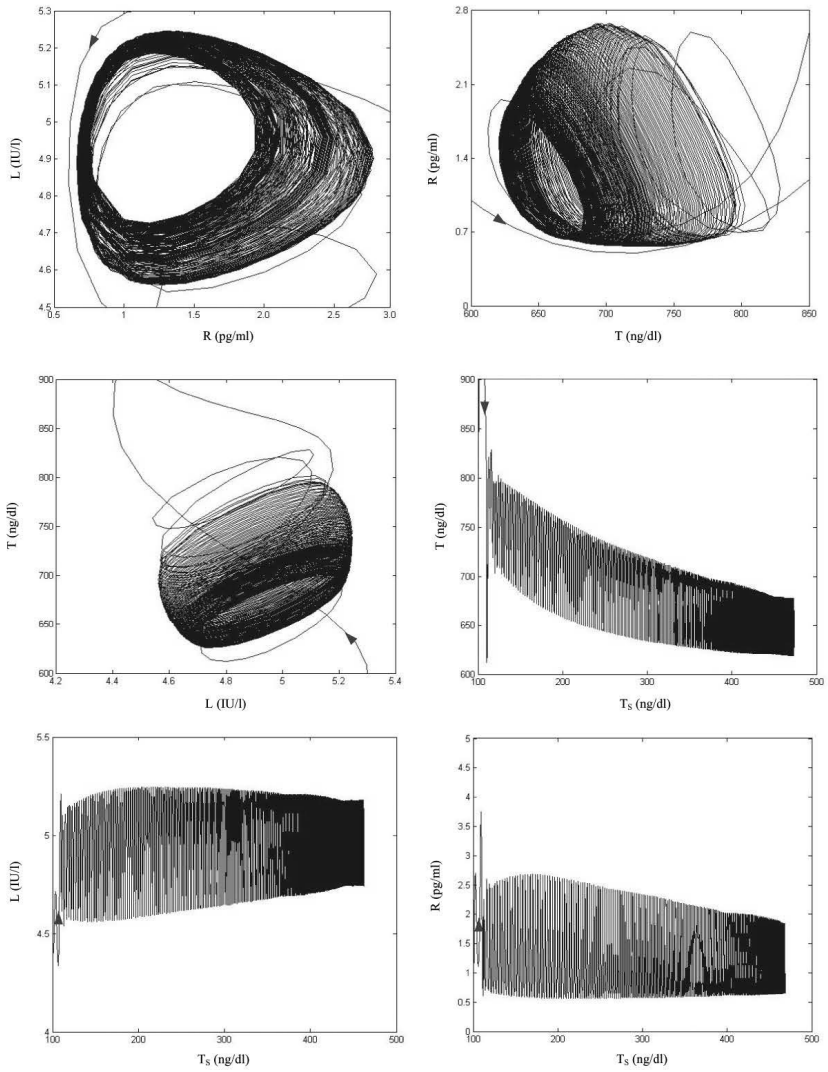

Fig. 4. Numerical simulations demonstrate the solution trajectories which projected into the 2D-space for equations (2.1)–(2.4) with $\tau = 123.47$ min. The initial value is (1, 5.3, 645, 100).

the Hopf bifurcation occurs. For the values of the parameters used in our numerical calculations, $\tau^* = 121.236$ min.

For $\tau = 120$ min which is less than τ^*, the values of the R, LU, T and T_S would converge to the steady state values as $t \to \infty$. For $\tau = 123.47$ min which is

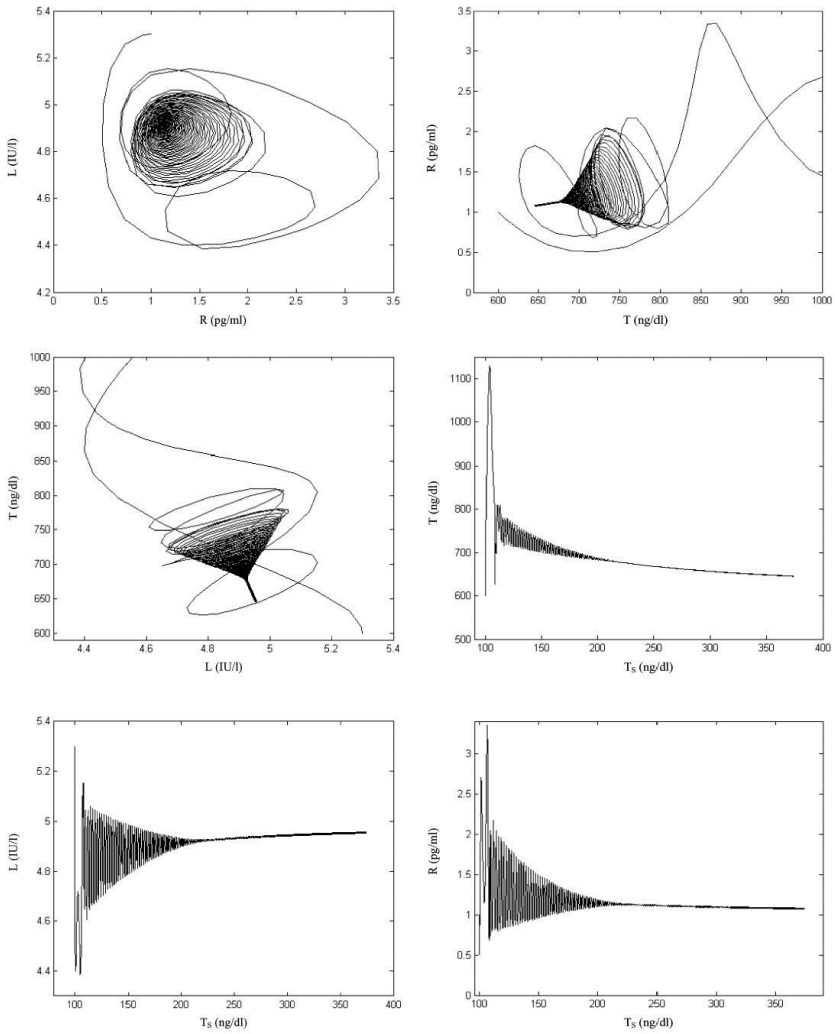

Fig. 5. Numerical simulations demonstrate the solution trajectories which projected into the 2D-space for equations (2.1)–(2.4) with $\tau = 120$ min. The initial value is (1, 5.3, 645, 100). The positive equilibrium is asymptotically stable.

greater than τ^*, the values of the four variables would not converge to the steady state values, but would instead oscillate about the steady state values. Figures 2 and 3 show the time evolutions of R, LU, T and T_S obtained from the numerical solutions of Eqs. (2.1)–(2.4) for $\tau = 120\,\text{min}$ and $123.47\,\text{min}$, respectively. As we

see, the plots of R, LU, T and T_S show that R, LU, T and T_S approach the steady state as $t \to \infty$ (Fig. 2). Figure 3 shows the time evolution of R, LU, T and T_S when $\tau = 123.47$. As we see, R, LU, T and T_S do not approach the steady state as $t \to \infty$. Instead, the values of R, LU and T oscillate about the steady state values without the amplitude of oscillation getting smaller as $t \to \infty$. To see this better, we have plotted the solutions in a 2D space when $\tau = 123.47$ (Fig. 4). All the figures are of limit cycle behaviors which are what was predicted by Theorem 2.2. To complete the story, we have plotted R, LU and T against each other for $\tau = 120$ min on Fig. 5. We see that the trajectories are spirals which converge to the steady state values.

4. Conclusion

In this study, we developed a mathematical model in order to examine the characteristics of the male hormonal regulation which is effected by the binding of testosterone to SHBG in the male hormonal balancing system. The numerical simulations show the episodic pattern of three main hormone levels and exhibit the boosting level of SHBG bound testosterone in the system. Also, as time passes, we see the stability in the level of T_S although the binding of testosterone to SHBG still proceeds in the bloodstream. This result is in agreement with the format of hormone balancing in the system. In addition, we showed the impact of different time delays to demonstrate that the periodic solutions bifurcate from the equilibrium when τ passes through a critical value. Moreover, this can explain the pulsatile secretion of hormones in males and the concentration curves which correspond to the data well.

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Appendix A. Linearization

We consider the system (2.1)–(2.4) in the general form

$$\begin{aligned}
\frac{dR}{dt} &= f(R(t), LU(t), T(t), T_S(t)) \\
\frac{dLU}{dt} &= g(R(t), LU(t), T(t), T_S(t)) \\
\frac{dT}{dt} &= h(R(t), LU(t), T(t), T_S(t)) \\
\frac{dT_S}{dt} &= k(R(t), LU(t), T(t), T_S(t))
\end{aligned} \tag{A.1}$$

with the transformations

$$\begin{aligned}
&w = R - \bar{R}, \quad x = LU - \overline{LU}, \quad y = T - \bar{T}, \\
&z = T_S - \bar{T}_S \quad \text{and} \quad x_1 = LU_1 - \overline{LU},
\end{aligned}$$

where $LU_1(t) = LU(t - \tau)$.

By expanding f, g, h and k in the Taylor series about a steady state $\bar{E}$ and retaining only the first order terms, we have the linearized system of (2.1)–(2.4) as

follows:

$$\frac{dw}{dt} = -\left(\frac{r_1\bar{R}}{(\overline{LU} + r_2\bar{T})^2}\right)x - \left(\frac{r_1 r_2 \bar{R}}{(\overline{LU} + r_2\bar{T})^2}\right)y, \tag{A.2}$$

$$\frac{dx}{dt} = \left(\frac{a_1 a_2 \overline{LU}\cdot\bar{T}}{(\bar{R} + a_2\bar{T})^2}\right)w - \left(\frac{a_1 a_2 \overline{LU}\cdot\bar{R}}{(\bar{R} + a_2\bar{T})^2}\right)y, \tag{A.3}$$

$$\frac{dy}{dt} = (g_1\bar{T})x_1 - \left(\frac{r_3 r_4}{(1 + r_4\bar{T}_S)^2}\bar{T}\right)z, \tag{A.4}$$

$$\frac{dz}{dt} = \left(\frac{e_1\bar{T}_S}{(1 + e_2\bar{T})^2}\right)y. \tag{A.5}$$

Now, looking for solutions of (A.2)–(A.5) in the form

$$\begin{bmatrix} w(t) \\ x(t) \\ y(t) \\ z(t) \end{bmatrix} = C_1 e^{\lambda t}$$

where C_1 is a constant vector.[11]

Then the linear system of Eqs. (A.2)–(A.5) can be expressed as

$$\begin{bmatrix} \dfrac{dw}{dt} \\ \dfrac{dx}{dt} \\ \dfrac{dy}{dt} \\ \dfrac{dz}{dt} \end{bmatrix} = \begin{bmatrix} 0 & \eta_1 & \eta_2 & 0 \\ \eta_3 & 0 & \eta_4 & 0 \\ 0 & \eta_5 \mathrm{e}^{-\lambda\tau} & 0 & \eta_6 \\ 0 & 0 & \eta_7 & 0 \end{bmatrix} \begin{bmatrix} w \\ x \\ y \\ z \end{bmatrix}, \tag{A.6}$$

where

$$\eta_1 = -\frac{q_1\bar{R}}{(\overline{LU} + q_2\bar{T})^2}, \quad \eta_2 = -\frac{q_1 q_2 \bar{R}}{(\overline{LU} + q_2\bar{T})^2}, \quad \eta_3 = \frac{d_1 d_2 \overline{LU}\cdot\bar{T}}{(\bar{R} + d_2\bar{T})^2},$$

$$\eta_4 = -\frac{d_1 d_2 \overline{LU}\cdot\bar{R}}{(\bar{R} + d_2\bar{T})^2}, \quad \eta_5 = a\bar{T}, \quad \eta_6 = -\frac{r_3 r_4}{(1 + r_4\bar{T}_S)^2}\bar{T} \quad \text{and} \quad \eta_7 = \frac{\mathrm{e}_1\bar{T}_S}{(1 + \mathrm{e}_2\bar{T})^2}.$$

Appendix B. Proof of Theorem 2.2

We now show that

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

From Eqs. (2.10) and (2.11), 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

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} P + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} Q = R, \tag{B.1}$$

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} (-Q) + \left.\frac{dv}{d\tau}\right|_{\tau=\tau^*} P = S, \tag{B.2}$$

where

$$\begin{aligned}
P &= q_1 v^{*2}\tau \cos(v^*\tau^*) + q_2 \cos(v^*\tau^*) - q_2\tau^* v^* \sin(v^*\tau^*) + 2q_1 v^* \sin(v^*\tau^*) \\
&= [q_1 v^{*2}\tau^* \cos(v^*\tau^*) + q_2 \cos(v^*\tau^*)] + [2q_1 v^* \sin(v^*\tau^*) - q_2\tau^* v^* \sin(v^*\tau^*)] \\
&= [q_2 + q_1 v^{*2}\tau^*] \cos(v^*\tau^*) + [2q_1 - q_2\tau^*] v^* \sin(v^*\tau^*) \\
Q &= 4v^{*3} - 2p_1 v^* + v^{*2} q_1 \tau^* \sin(v^*\tau^*) - 2q_1 v^* \cos(v^*\tau^*) \\
&\quad + q_2 v^*\tau^* \cos(v^*\tau^*) + q_2 \sin(v^*\tau^*) \\
&= 4v^{*3} - 2p_1 v^* + [q_2 + v^{*2} q_1 \tau^*] \sin(v^*\tau^*) + [q_2\tau^* - 2q_1] v^* \cos(v^*\tau^*) \\
R &= -q_2 v^{*2} \cos(v^*\tau^*) - q_1 v^{*3} \sin(v^*\tau^*) \\
S &= q_2 v^{*2} \sin(v^*\tau^*) - q_1 v^{*3} \cos(v^*\tau^*).
\end{aligned}$$

To solve for $\left.\frac{du}{d\tau}\right|_{\tau=\tau^*}$, by solving Eqs. (B.1) and (B.2), we deduce that

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} = \frac{PR - QS}{P^2 + Q^2}. \tag{B.3}$$

Consider

$$\begin{aligned}
PR - QS &= ([q_2 + q_1 v^{*2}\tau^*] \cos(v^*\tau^*) + [2q_1 - q_2\tau^*] v^* \sin(v^*\tau^*)) \\
&\quad \cdot (-q_2 v^{*2} \cos(v^*\tau^*) - q_1 v^{*3} \sin(v^*\tau^*)) \\
&\quad - (4v^{*3} - 2p_1 v^* + [q_2 + v^{*2} q_1 \tau^*] \sin(v^*\tau^*) + [q_2\tau^* - 2q_1] v^* \cos(v^*\tau^*)) \\
&\quad \cdot (q_2 v^{*2} \sin(v^*\tau^*) - q_1 v^{*3} \cos(v^*\tau^*)) \\
&= 4v^{*8} - 6p_1 v^{*6} + (4p_2 - 2q_1^2 + 2p_1^2) v^{*4} - (2p_1 p_2 + q_2^2) v^{*2} \\
&= v^{*2}(4v^{*6} - 6p_1 v^{*4} + (4p_2 - 2q_1^2 + 2p_1^2) v^{*2} - (2p_1 p_2 + q_2^2)) \\
&\neq 0.
\end{aligned}$$

We have just shown that the numerator of the expression on the right-hand side of Eq. (B.3) is not equal to zero and looking at the definitions of P and Q given below Eq. (B.2), we see that P and Q are both finite quantities and so $P^2 + Q^2 \neq 0$. We can therefore conclude that

$$\left.\frac{du}{d\tau}\right|_{\tau=\tau^*} = \frac{PR - QS}{P^2 + Q^2} \neq 0 \tag{B.4}$$

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

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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 (μg/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:

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

Where $\mathrm{G}(t)$, $\mathrm{Lh}(t)$, $\mathrm{Te}(t)$ and $\mathrm{S}(t)$ as plasma concentrations of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), testosterone (T) and 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 μ_1, μ_2, μ_3, μ_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.

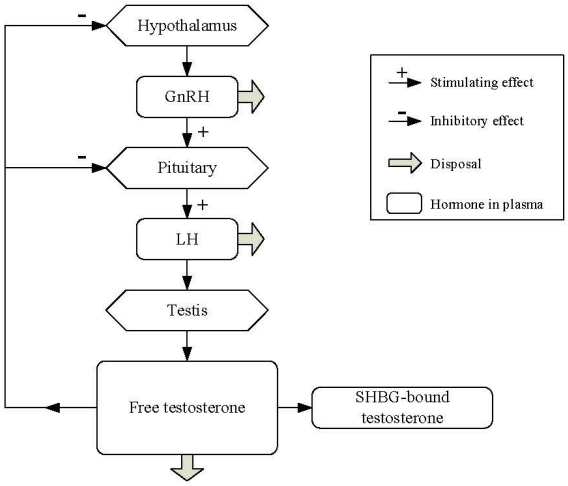

Fig. 1: The flow and interactions block diagram of the hypothalamo-pituitary-gonadal axis in men.

The only possible equilibrium state $E\left(\mathrm{G}^*, \mathrm{Lh}^*, \mathrm{Te}^*, \mathrm{S}^*\right)$ of the system (3) is given by

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

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

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

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

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 $\tau = 120$,

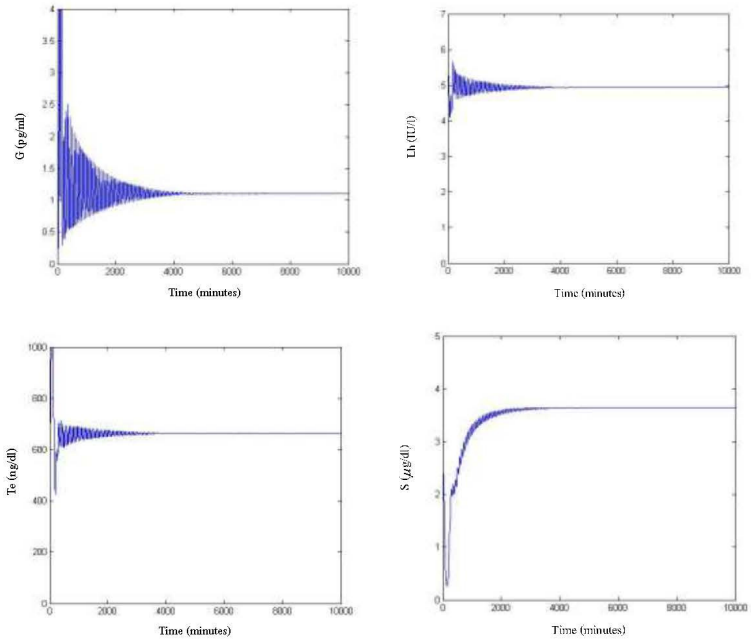

Fig. 2: Numerical simulations for eqs.(3) with $\tau = 120$. The positive equilibrium is asymptotically stable. The initial value is (1, 5, 642, and 3).

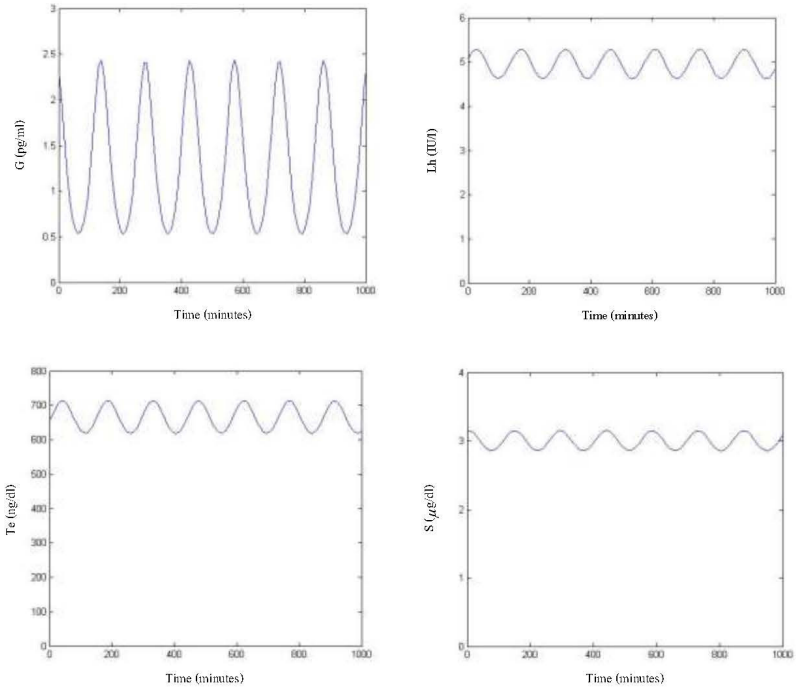

Fig. 3: Numerical simulations of equation (3) exhibit the oscillating levels of four main hormones in the system with $\tau = 124$. The initial value is (1, 5, 642, 3). The values of parameters are $r_1 = 2.8$, $r_2 = 0.001$, $r_3 = 0.016$, $r_4 = 0.001$, $a_1 = 0.0092$, $a_2 = 0.0016$, $a_3 = 6$ and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

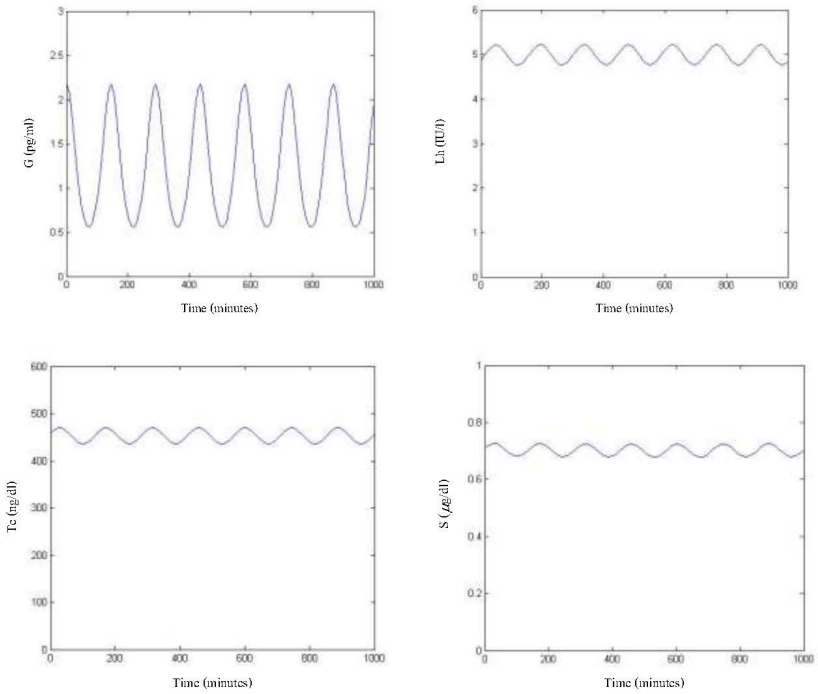

Fig. 4: Numerical simulations of equation (3) exhibit the oscillating levels of four main hormones in the system with $\tau = 124$. The initial value is (1, 5, 642, 3). The values of parameters are $r_1 = 2.8$, $r_2 = 0.001$, $r_3 = 0.016$, $r_4 = 0.001$, $a_1 = 0.0092$, $a_2 = 0.0016$, $a_3 = 5.5$ and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

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A Modified Mathematical Model Interpreting the Quantitative Behavior of Testosterone in the Male Hormonal Regulation

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Abstract: *We propose a modified mathematical model for male sex hormone regulation taking into account the quantitative behavior of two forms of testosterone hormones. The model is able to present a significant relation between total testosterone and bound testosterone levels in the hypothamic-pituitary-gonadal axis. Moreover, we show the numerical simulations of the model to illustrate the possible behaviors.*

Keywords: *Hormone, Time delay, Testosterone, SHBG, Hormonal regulation.*

1. Introduction

Hormones are chemical substances which are produced by the glands in the bodily system. It has many functions including control and regulation the activity of certain tissues or organs. In the reproductive system, sex hormones are responding to control the development of primary and secondary sexual characteristics.

In male, testosterone is the majority of sex hormone secreted into the bloodstream by the male sex gland. This male sex hormone is synthesized and secreted primarily by Leydig cells in the testis. It plays a crucial role in the development and maintenance of many male characteristics. The body carefully regulates the production of testosterone in order to ensure normal development and regulation of male reproductive system [1]. Testosterone synthesis is controlled by biological mechanism in the reproductive hormonal axis which contains three main components: the hypothalamus, the pituitary gland and the gonads. Hormones which are produced in this axis include gonadotropinreleasing hormone (GnRH), luteinizing hormone (LH) and testosterone (T). These hormones are implicated in regulation reproductive operation via a complex feedback loop. GnRH is released by the hypothalamus in a episodic manner. It then triggers the pituitary gland to produce and secret LH into the blood, which activates the enzymatic conversion of cholesterol into testosterone in the Leydig cells. Testosterone is secreted in pulsatile pattern. Its levels have rapidly acting feedback activity at both hypothalamic level and pituitary level in order to maintain adequate levels of the hormones in the male reproductive system [2,3] shown in Fig 1. In normal men, plasma levels of testosterone range from 270 to 1,070 nanogram/deciliter (ng/dl) with an average level of 679 ng/dl [4, 5]

After this male sex hormone is released, testosterone, it is principally bound to proteins in the blood, most of which is sex hormone binding globulin (SHBG). Approximately 2% of the testosterone exists in the free (unbound) forms which are the biologically active. Approximately 60% is tightly bound to SHBG. The resting testosterone is weakly bound to albumin and other proteins [6-8].

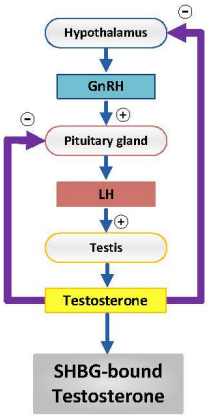

Fig. 1: The normal regulation of the hypothalamus down to the testis in the negative feedback mechanism. Hypothamic hormone (GnRH) secreted in plusatile pattern by the hypothalamus triggers the production of LH in pituitary gland. After LH is released to the bloodstream, it travels to the testis for stimulation of the testosterone secretion. The testosterone in turn acts to modulate GnRH and LH secretion by negative feedback

Mathematical models of the male sex hormone regulation have been numerously present and continuously developed over the decades. The classical model of testosterone regulation in the male is proposed by Smith [9]. The model is formed by the following differential equations

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

Where R, L and T are concentrations of GnRH, LH and Testosterone, respectively. 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 [10] improved the model in [9], he considered a period for LH hormone traveling from pituitary grand in the brain to the Leydig cells in the testis. In 1986, Cartwright and Husain [11] presented another model in order to account into the pulsatile release of the hormones within the HPG-axis, which is able to elucidate the cyclic behavior of GnRH and LH after castration. Greenhalgh and Khan [12] modified the models of Smith [10] and of Cartwright and Husain by using different response functions which incorporated more qualitatively observed biological behaviors. Tanutpanit et al. [13] extended a modified model in [12] to explain the presence of two types of testosterone hormones related with hypothalamic-pituitary-gonadal axis.

2. Mathematical Model

In this present work, the model considered in [13] is re-examined to interpret the relation of two forms of testosterone in the male hormonal regulation. Here, we need to introduce four variables; G for the plasma concentration of the gonadotropin-releasing hormone, Lh for the luteinizing hormone, Te for free testosterone and Ts for SHBG bound testosterone. We consider the change in SHBG-bound testosterone concentration is independent of itself. The model in this case can be expressed as

$$\begin{aligned}
\frac{dG}{dt} &= \frac{g_1 G}{Lh + g_2 Te} - m_1 G \,, \\
\frac{dLh}{dt} &= \left(\frac{k_1 G}{G + k_2 T}\right) Lh - m_2 Lh \,, \\
\frac{dTe}{dt} &= b \cdot Lh(t-\tau) \cdot Te + \left(\frac{k_3}{1 + k_4 \cdot Ts}\right) \cdot Te - m_3 T \,, \\
\frac{dTs}{dt} &= \frac{v_1 Te}{1 + v_2 Te} - m_4 Ts \,.
\end{aligned} \tag{2}$$

where g_1, g_2, k_1, k_2, k_3, k_4, v_1, v_2 and b are strictly positive parameters and m_1, m_2, m_3 and m_4 are defined as the metabolic clearance rates of all four hormones. We find that the above equations accord with the nonzero steady state $\overline{E}(\overline{G}, \overline{Lh}, \overline{Te}, \overline{Ts})$ where

$$\overline{G} = \frac{k_2 m_2}{k_1 - m_2}\overline{Te} \,, \quad \overline{Lh} = \frac{g_1}{m_1} - g_2 \overline{Te} \quad \text{and} \quad \overline{Ts} = \frac{v_1}{m_4}\left(\frac{\overline{Te}}{1 + v_2 \overline{Te}}\right)$$

And $\overline{Te}$ is the positive root of the quadratic equation

$$a \cdot Te^2 + b \cdot Te + c = 0$$

where

$$a = g_2 v_2 + \frac{g_2 k_4 v_1}{m_4}, \quad b = g_2 + \left(\frac{m_3}{b} - \frac{g_1}{m_1}\right)\left(v_2 + \frac{v_1 k_4}{m_4}\right) - \frac{v_2 k_3}{b} \quad \text{and} \quad c = \frac{m_1 m_3 - g_1 b - m_1 k_3}{m_1 b} \,.$$

Furthermore, because of the small change of SHBG-bound testosterone level in time[10], we such consider Ts as being in a quasi-steady-state. We invoke the steady-state approximation by setting $\frac{dTs}{dt}$ approximately equal to zero. Thus, from Ts -equation in (2) we have

$$Ts = \frac{1}{m_4}\left(\frac{v_1 Te}{1 + v_2 Te}\right) \tag{3}$$

Substituting it into eqs (2), then eqs. (2) reduces to

$$\begin{aligned}
\frac{dG}{dt} &= \frac{g_1 G}{Lh + g_2 Te} - m_1 G \,, \\
\frac{dLh}{dt} &= \left(\frac{k_1 G}{G + k_2 T}\right) Lh - m_2 Lh \,, \\
\frac{dTe}{dt} &= b \cdot Lh(t-\tau) \cdot Te + k_3 \left(\frac{1 + v_2 Te}{1 + \left(v_2 + \frac{k_4}{m_4} v_1\right) Te}\right) \cdot Te - m_3 T \,.
\end{aligned} \tag{4}$$

3. Numerical Results

Numerical simulations of the delayed system (4) are performed to exhibit the dynamical behavior depending on the delay parameter. We determine some parameter values like as in the simulation of Greenhalgh and Khan. Also, we give $v_1 = 1.5$ /min, $v_2 = 0.08$ /min, $k_4 = 1.47$ /min and $m_4 = 0.0491$ /min, which are estimated from the steady-state equation.

We used routine dde23 in MATLAB to simulate the behaviors for equation (4). Fig.2 shows the simulated results of GnRH, LH and testosterone which correspond to the steady state $\overline{E}$ that exhibits stable behavior where $\tau = 120$. Numerical simulations of the concentrations of the hormones in the system where $\tau = 125$, such varied behaviors occur in the form of periodic fluctuations, is shown in Fig.3.

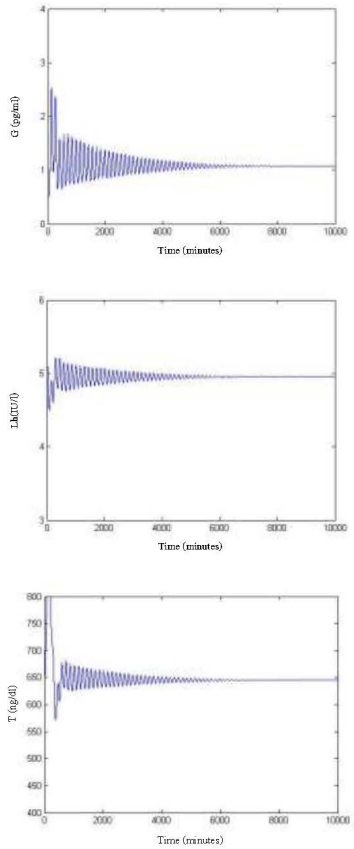

Fig. 2: The graphs show results of numerical simulations of hormone concentration $G(t)$ vs. time, $Lh(t)$ vs. time and $Te(t)$ vs. time for eqs.(4) with $\tau = 120$. Initial values are $(G_0, Lh_0, Te_0) = (1, 5.3, 600)$. The positive equilibrium is asymptotically stable.

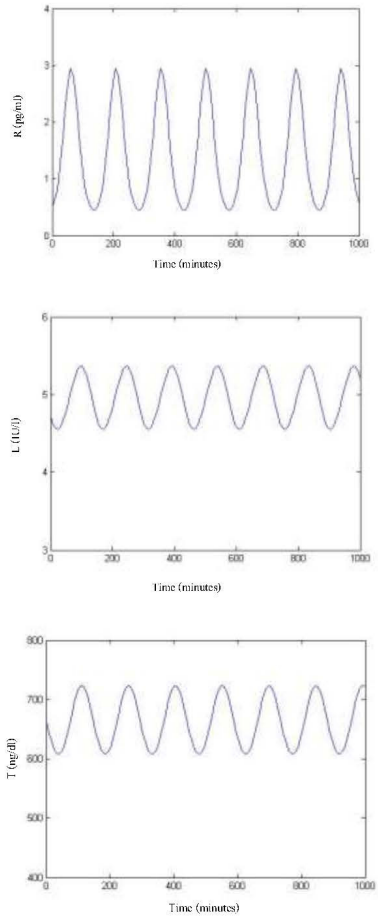

Fig. 3: The graphs show results of numerical simulations of hormone concentration $G(t)$ vs. time, $Lh(t)$ vs. time and $Te(t)$ vs. time for eqs.(4) with $\tau = 125$. Initial values are $(G_0, Lh_0, Te_0) = (1, 5.3, 600)$. The system exhibit periodic oscillations

4. Conclusion

We have modified the mathematical model of the male sex hormone regulation which explains a significant reaction between the two forms of testosterone within the hypothamic-pituitary-gonadal system. A time-delay which is corresponding to the LH secretion in the pituitary gland and travel of the hormone to the testis is considered in the model. It exhibits periodical solutions of the hormones that are consistent with the experimental data well.

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