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An impulsive model of endocrine regulation with two negative feedback loops ⋆

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Abstract: Whereas obtaining a global model of the human endocrine system remains a challenging problem, visible progress has been demonstrated in modeling its subsystems (*axes*) that regulate production of specific hormones. The axes are typically described by Goodwin-like cyclic feedback systems. Unlike the classical Goodwin oscillator, obeying a system of ordinary differential equations, the feedback mechanisms of brain-controlled hormonal regulatory circuits appear to be pulsatile, which, in particular, exclude the possibility of equilibrium solutions. The recent studies have also revealed that the regulatory mechanisms of many vital hormones (including e.g. testosterone and cortisol regulation) are more complicated than Goodwin-type oscillators and involve multiple negative feedback loops. Although a few "multi-loop" extensions of the classical Goodwin model have been studied in literature, the analysis of *impulsive* endocrine regulation models with additional negative feedbacks has remained elusive. In this paper, we address one of such models, obtained from the impulsive Goodwin-type oscillator by introducing an additional *linear* feedback. Since the levels of hormones' concentrations oscillate periodically, examination of endocrine regulation circuits is primarily focused on periodic solutions. We prove the existence and uniqueness of periodic solutions of a special type, referred to as 1-cycles and featured by the unique discontinuous point in each period. Procedures for computing such a solution and testing its stability are discussed. The results are confirmed by numerical simulations.

Keywords: Biomedical systems; Oscillations; Periodic solutions; Impulse signals.

1. INTRODUCTION

Hormones are products of glands, playing essential roles in vital bodily functions such as metabolism, reproduction and growth. This motivates the study of interactions between glands and hormones that can be described by many feedback and feedforward controls, resulting in a complex system called the *endocrine system*. Due to the complexity of the endocrine system, obtaining a mathematical model to describe all features of the endocrine system is a challenging problem. To obtain instructive mathematical models of hormonal regulation, the endocrine system is usually decoupled into subsystems, called *axes*, capturing only known essential characteristics and interactions.

One of the most studied axes of the endocrine system regulates the production of testosterone (Te) hormone in males and involves also the Gonadotropin-Releasing Hormone (GnRH) and the Luteinizing Hormone (LH). GnRH, secreted in hypothalamus, facilitates the secretion of LH in the pituitary gland, stimulating, in turn, the release of Te in the testes. Te inhibits the secretion of GnRH and LH, thus closing a negative feedback loop. The GnRH-LH-Te axis regulates reproductive functions and some aging processes (Mulligan et al., 1997; Veldhuis, 1999).

The testosterone regulation mechanism serves as a "benchmark" in mathematical modeling of hormonal regulation; however, "neurohormone" regulatory circuits, controlled by the brain regulatory centers, are in fact based on the same principles (Keenan et al., 2000). One of the relatively simple deterministic models for hormonal regulation was proposed by Smith (1980) who suggested that GnRH, LH and Te concentrations follow the conventional Goodwin's oscillator model (Goodwin, 1965), where the negative feedback is described by Hill nonlinearity (Gonze and Abou-Jaoudé, 2013). Such a model, however, imposes a number of restrictions, since the oscillatory solutions exist only for Hill exponents of greater than 8, which are considered to be unrealistic for most biochemical reactions (Murray, 2002; Heuett and Qian, 2006).

Although Goodwin's model can have oscillatory solutions for smaller Hill constants, taking inevitable delays into account (Smith, 1983; Das et al., 1994), there is a growing belief that the main factor, responsible for oscillation, is

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the *discontinuity* of the feedback mechanism. The GnRH hormone secretion in the hypothalamus is closely related to the neural dynamics and is not continuous but *pulsatile* (Krsmanović et al., 1992; Keenan and Veldhuis, 1997; Keenan et al., 2000). So a continuous Hill-type nonlinearity should be replaced by a discontinuous map such as a Heaviside function (Cartwright and Husain, 1986). A more complicated model, based on the Goodwin oscillator, has been proposed in Churilov et al. (2009). The feedback from Te to GnRH is described by a pulse-amplitude-frequency modulator (Gelig and Churilov, 2012), where the modulating amplitude function can be a Hill nonlinearity. Recently this model has been validated by experimental data (Mattsson and Medvedev, 2013).

The model from Churilov et al. (2009) inherits the cyclic structure of the classical Goodwin oscillator. When applied to describe the GnRH-LH-Te axis, it implies that Te inhibits the secretion of GnRH directly, and influences the production of LH indirectly. In this paper, we extend this model by introducing another negative feedback from Te to LH, whose existence was reported in the literature and strongly supported by experiments (Bagatell et al., 1994; Veldhuis, 1999; Veldhuis et al., 2009). It should be noticed that up to now only a few Goodwin-like models with multiple feedbacks have been studied in the literature, and most of them deal with continuous dynamics (Tanutpanit et al., 2015; Bairagi et al., 2008; Greenhalgh and Khan, 2009; Taghvafard et al., 2016, 2017). An exception is a very general stochastic model from Keenan and Veldhuis (1997); Keenan et al. (2000), whose rigorous analysis remains a non-trivial and challenging problem.

Although the existence of multiple feedback loops in testosterone and other hormonal regulation systems is commonly accepted in the literature, there is no consensus on mathematical description of the respective feedback controls. The important property of the model, developed in Churilov et al. (2009), is the possibility to represent it in the Lur'e form with a single scalar nonlinearity (standing for the pulsatile feedback from Te to GnRH). To use the benefits of the framework from Churilov et al. (2009), we suppose that the additional feedback does not destroy this structure, that is, the additional feedback from Te to LH is linear. This structure introduces only one uncertain parameter (a scalar feedback gain is introduced), compared to the previous model from Churilov et al. (2009), which makes it possible to suggest an identification procedure, similar to (Mattsson and Medvedev, 2013). Using the model with a negative linear feedback, one however faces a problem of the solution feasibility: some solutions may escape from the positive octant.

Dealing with hormonal regulation models, one is mainly interested in *periodic* solutions; as discussed in Churilov et al. (2009), experiments show that usually such solutions are featured by the existence of one or two pulses over one period (called, respectively, 1-cycles and 2-cycles). As shown in Churilov et al. (2009), the 1-cycle always exists and is unique. For such a solution an efficient criterion of local stability can be given. We extend this result to the system with the additional feedback.

The paper is organized as follows. Section 2 introduces the model in question. Section 3 presents the main result, concerned with the existence and positivity of periodic solutions. Section 4 offers the numerical simulations, supporting the main result. Section 5 concludes the paper.

2. THE IMPULSIVE MODEL OF ENDOCRINE REGULATION

We consider the following model of endocrine regulation

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

Here R, L and T stand for the concentration of three hormones. Dealing with testosterone regulation in males, they are, respectively, serum concentrations of GnRH, LH and Te. The constants $b_i > 0$ determine the clearing rates of the corresponding hormones, while the constants $g_i, k > 0$ and the decreasing function $\xi(\cdot) > 0$ represent their secretion rates. Unlike the classical Goodwin-Smith model (Goodwin, 1965; Smith, 1980), model (1) involves an additional negative feedback loop from T to L, described by the feedback gain k; the cyclic model from Smith (1980) corresponds to the case where $k = 0$.

It is convenient to rewrite system (1) in Lur'e form

$$\begin{aligned} \dot{x} &= Ax + B\xi, \\ y &= Cx, \end{aligned} \tag{2}$$

where $x = [R,\ L,\ T]^\top$, $y = T$, and

$$A = \begin{bmatrix} -b_1 & 0 & 0 \\ g_1 & -b_2 & -k \\ 0 & g_2 & -b_3 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \quad C^\top = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}. \tag{3}$$

Following Churilov et al. (2009), we now replace the nonlinear map $\xi(\cdot)$ in (1) by a pulse-amplitude-frequency modulator (Gelig and Churilov, 2012), formally written as

$$\xi(t) = \sum_{n=0}^{\infty} \lambda_n \delta(t - t_n), \tag{4}$$

where $\delta(t)$ is a Dirac delta-function. The generalized function $\xi(t)$ is determined by the times t_n at which GnRH pulses are fired with the amplitudes λ_n. Suppose that the GnRH firing time t_n and the amplitude λ_n are given by

$$\begin{gathered} t_{n+1} = t_n + \tau_n, \quad \tau_n = \Phi(y(t_n^-)), \quad \lambda_n = \Psi(y(t_n^-)), \\ t_0 = 0, \quad y(0^-) = y(0). \end{gathered} \tag{5}$$

where $\Phi(\cdot)$ and $\Psi(\cdot)$ stand, respectively, for the frequency and amplitude modulation characteristics. Hereafter $y(t_n^-)$ stands for the left-side limits of $y(t)$ at t_n; similarly, $y(t_n^+)$ stands for the right-side limit.

Mathematically, equations (2) and (4) are treated as follows. At time t_n the pulse is fired, corresponding to the release of GnRH hormone, which is described as the jump of its concentration $x_1(t_n^+) = x_1(t_n^-) + \lambda_n$ yet not affecting the two remaining hormones $x_2(t_n^-) = x_2(t_n^+)$, $x_3(t_n^-) = x_3(t_n^+)$. Equivalently, in the vector form

$$x(t_n^+) = x(t_n^-) + \lambda_n B. \tag{6}$$

Here the amount of the released hormone λ_n and the time of the next release t_{n+1} depend on the output $y(t_n)$ (the concentration of Te). Between the consecutive instants t_n and t_{n+1}, the dynamics of (2) is linear, i.e.,

$$\dot{x} = Ax, \qquad t_n < t < t_{n+1}. \tag{7}$$

When the concentration of testosterone increases, the pulses of GnRH become sparser and their amplitude decreases (Veldhuis, 1999). Following Churilov et al. (2009), we assume that $\Phi(y)$ and $\Psi(y)$ are respectively, non-decreasing and non-increasing for $y \geq 0$; these functions are also uniformly positive and bounded, that is

$$\Phi : [0, \infty) \to [\Phi_1, \Phi_2], \quad \Psi : [0, \infty) \to [\Psi_1, \Psi_2], \quad (8)$$

where $\Phi_j > 0$ and $\Psi_j > 0$ $(j = 1, 2)$ are some constants. The condition (8) implies that the instants of consecutive pulses are separated by a positive dwell-time $t_{n+1} - t_n \geq \Psi_1$, so the Zeno behavior is not possible. On the other hand, since the jump (6) occurs on each interval of length λ_n and $\lambda_n \geq \Psi_1 > 0$, the system has no equilibria.

Since the elements $x_i(t)$ stand for chemical concentrations, only non-negative solutions of the closed-loop system (6), (7) are meaningful in practice. In the case where $k = 0$, addressed in Churilov et al. (2009), the solution starting in the positive octant $x(0) \in \mathbb{R}^3_+$ automatically remains there since the matrix A is Metzler, and thus neither the linear dynamics (7) nor the jumps (6) are able to move the solution outside the positive octant $\mathbb{R}^3_+$. This, however, does not hold for the case where $k > 0$ since the matrix A is not Metzler and thus the state vector $x(t)$, obeying (7), may escape from $\mathbb{R}^3_+$ between two pulses. Henceforth, by a solution of the system we always mean a *non-negative* solution which does not leave $\mathbb{R}^3_+$ between consecutive jumps. Similar to (Churilov et al., 2009), one can prove that any such solution is infinitely prolongable and remains bounded, since A is Hurwitz stable, and $\Phi(\cdot)$ and $\Psi(\cdot)$ are bounded.

In this paper, we are primarily interested in *periodic* solutions of the closed-loop system, which describe the periodic fluctuations of the hormones' concentrations (Murray, 2002). We show that, under natural assumptions, such a solution always exists and, moreover, has the only discontinuity point t_n over periods, so-called "1-cycle" (Churilov et al., 2009).

3. EXISTENCE OF PERIODIC SOLUTIONS

By definition, we call a (non-negative) solution τ-*periodic* (where $\tau > 0$) if $x(s_1^-) = x(s_2^-)$ whenever $s_1 \geq 0$ and $s_2 = s_1 + \tau$. It can be easily shown that for such a solution on each interval $[t; t + \tau)$ the same number of pulses are fired, whose number is *finite* due to (5) and (8) (the time between two consecutive pulses is no less than $\Phi_1 > 0$). Following Zhusubaliyev and Mosekilde (2003), we call a periodic solution of (2)-(5) *m-cycle* if m pulses are fired over the least period. As shown in Churilov et al. (2009), in the case where $k = 0$ the 1-cycle exists and is unique. By using an efficient numerical procedures, such a solution can be found and tested for local stability. For existence of 2-cycles, to the best of the authors' knowledge, only sufficient conditions exist (Churilov et al., 2009), whereas m-cycles with $m \geq 3$ are rarely observed in experiments and their existence, in general, remains an open problem.

In this section, we offer a sufficient condition for the existence and uniqueness of 1-cycle solutions in the presence of additional linear feedback $k > 0$. It can be easily shown (Churilov et al., 2009) that for 1-cycle solution, one has $t_{n+1} - t_n = \tau_0 \, \forall n$, where $\tau_0 > 0$ is the least period and thus $y(t_n^-) = y_0 := y(0)$ and $\lambda_n = \lambda_0$ for all $n \geq 0$.

Introducing the "discrete map" (Churilov et al., 2009)

$$P(x) := e^{A\Phi(Cx)}[x + \Psi(Cx)B], \quad (9)$$

the states $x^n := x(t_n^-)$ obey the discrete-time equation

$$x^{n+1} = P(x^n). \quad (10)$$

The equation (10) is immediate from (5), (6) and (7) since

$$x^{n+1} = e^{A(t_{n+1}-t_n)}x(t_n^+) = e^{A(t_{n+1}-t_n)}[x^n + \lambda_n B]$$
$$= e^{A\tau_n}\left[x^n + \Psi(Cx^n)B\right] = e^{A\Phi(Cx^n)}\left[x^n + \Psi(Cx^n)B\right].$$

Obviously, 1-cycle, starting at $x^0 := x(0) \in \mathbb{R}^3_+$, corresponds to a *fixed point* of $P(x)$. Indeed, $x^1 = x^0$ and thus

$$P(x^0) = x^0. \quad (11)$$

On the other hand, suppose that (11) has a solution $x^0 \in \mathbb{R}^3_+$. Denoting τ_0, t_1, λ_0 from (5) with $n = 0$ and defining the function $x(t)$ on $(t_0; t_1)$ from (7) and the initial condition $x(t_0^+) = x^0 + \lambda_0 B$, one has $x(t_1^-) \overset{(10)}{=} P(x^0) = x^0$. Denoting $t_2 := t_1 + \tau_0$ and $x(t_1^+) = x^0 + \lambda_0 B$, one prolongs the function $x(t)$ to $(t_1; t_2)$ and shows that $x(t_2^-) = x^0$, and so on; so one may *formally* construct a τ_0-periodic 1-cycle. However, this formal procedure may lead to unfeasible solution since starting from the initial condition $x(t_n^+) = x^0 + \lambda_0 B$, the trajectory may leave the positive octant during the interval $(t_n; t_{n+1})$. Hence, to find all (non-negative) 1-cycles, one has to perform the following procedure:

Algorithm 1. (Hunting for 1-cycles)

(1) find all (non-negative) solutions of (11) and the corresponding periods $\tau_0 = \Phi(Cx^0)$;
(2) for each of these solutions, consider the function $x(t) = e^{tA}(x^0 + \lambda_0 B)$, $t \in (0; \tau_0)$;
(3) (non-negative) 1-cycles correspond to those points x^0 for which $x(t) \geq 0 \quad \forall t \leq \tau_0$.

As demonstrated in Churilov et al. (2009), in the case $k = 0$, the equation (11) always has a unique (non-negative) solution, which corresponds to 1-cycle (for $k = 0$, steps (2) and (3) can be omitted since the trajectory automatically remains positive). We show that this result remains valid, under natural assumptions, if the gain k is positive yet bounded by some known constant

$$0 \leq k < k^0 := \frac{(b_3 - b_2)^2}{4g_2}. \quad (12)$$

Namely, the following assumptions is adopted hereafter.

As reported in the literature (Cartwright and Husain, 1986; Keenan and Veldhuis, 1998), in the testosterone regulation circuit the clearing rates of the three hormones satisfy the condition $b_1 > b_3 > b_2$. Our main result guarantees the existence and uniqueness of 1-cycle solution under this condition. Later it will be shown that the restriction on b_i can in fact be relaxed, which may be potentially useful for other hormonal axes.

Theorem 1. Suppose that $b_1 > b_3 > b_2$ and (12) holds. Then the equation (11) has a unique solution $x^0 \in \mathbb{R}^3_+$, and this solution corresponds to a (non-negative) 1-cycle. Furthermore, x^0 can be found from the system of equations

$$y^0 = \tilde{P}(y^0) := \Psi(y^0)C(e^{-A\Phi(y^0)} - I)^{-1}B, \quad (13)$$

$$x^0 = \Psi(y^0)(e^{-A\Phi(y^0)} - I)^{-1}B. \quad (14)$$

The function $\tilde{P}$ in (13) is non-negative, bounded and non-increasing, and hence the unique solution $y^0 \geq 0$ of (13) can be found via the bisection method.

Proof. We follow four steps to prove this theorem. First, we prove that (11) is equivalent to (13) and (14). Second, we prove the last statement of Theorem 1, which implies that (13) has a unique positive solution. Third, we demonstrate that the corresponding vector x^0 is also non-negative. Fourth, we show that the step (2) of Algorithm 1, applied to x^0, gives a non-negative function $x(t)$.

We start with introducing some notations. Let

$$\alpha := \frac{b_2+b_3}{2}, \qquad \beta := \frac{\sqrt{(b_3-b_2)^2-4kg_2}}{2},$$
$$\gamma := (b_3-b_1)(b_2-b_1)+kg_2, \tag{15}$$
$$\nu := (b_3-b_2)(b_1-b_3)+2kg_2, \tag{16}$$
$$\eta_1 := \frac{1}{\gamma}, \qquad \eta_2 := \frac{\mu_1-\mu_3}{2\gamma\beta}, \qquad \eta_3 := \frac{\mu_2-\mu_1}{2\gamma\beta}, \tag{17}$$
$$\mu_1 := b_1, \qquad \mu_2 := \alpha-\beta, \qquad \mu_3 := \alpha+\beta. \tag{18}$$
$$\zeta_1 := \frac{b_3-b_1}{\gamma}, \qquad \zeta_2 := \frac{\nu-2\beta(b_3-b_1)}{4\gamma\beta}, \tag{19}$$
$$\zeta_3 := \frac{-\nu-2\beta(b_3-b_1)}{4\gamma\beta}, \quad \zeta_4 := \frac{2\beta+b_2-b_3}{4\beta}, \tag{20}$$
$$\zeta_5 := \frac{2\beta+b_3-b_2}{4\beta}, \qquad \zeta_6 = \frac{c}{2\beta}. \tag{21}$$

Step 1. (*The equivalence of* (11) *and* (13),(14).) Let x^0 stand for the solution of (11). Denoting $y^0 = Cx^0$, the pair y^0, x^0 is a solution to (13),(14). On the other hand, if x^0 satisfies (14), where y^0 is a solution to (13) then, obviously, $y^0 = Cx^0$. Substituting this into (14), one proves that (11) holds.

Step 2. (*The last statement of Theorem 1.*) Our goal is to show that the right-hand side of (13) is non-negative, bounded and non-increasing. Notice that this function can be represented as $\tilde{P}(y^0) = \Psi(y^0)F(\Phi(y^0))$, where $F(y) := C(e^{-yA}-I)^{-1}B$. Since Ψ is non-increasing and Φ is non-decreasing, both being uniformly positive and bounded, it remains to prove that $F(y)$ is non-increasing and positive as $y \geq 0$. It is verified that

$$F(y) = g_1g_2\sum_{j=1}^{3}\frac{\eta_j}{e^{\mu_j y}-1}, \tag{22}$$

with the parameters η_i and μ_i defined in (17) and (18). Now we prove that $F'(y) \leq 0$ for every $y > 0$. A straightforward computation shows that

$$F'(y) = g_1g_2\sum_{j=1}^{3}(-\eta_j)\psi_y(\mu_j), \ \psi_y(\mu) := \frac{\mu e^{\mu y}}{(e^{\mu y}-1)^2}. \tag{23}$$

Since $b_1 > b_3 > b_2$, one concludes that $\gamma > 0$ and hence $\eta_1 > 0$. Moreover, due to the fact that $b_1 > b_3$, we have $\eta_2 > 0$ and $\eta_3 < 0$. Using (23), we know that $F'(y) \leq 0$ if

$$-\eta_3\psi_y(\mu_3) \leq \eta_1\psi_y(\mu_1)+\eta_2\psi_y(\mu_2). \tag{24}$$

Define $\theta := \frac{\eta_1}{-\eta_3}$. Since $\eta_1+\eta_2+\eta_3 = 0$, we have $0 < \theta < 1$. In addition, it is verified that $\mu_3 = \theta\mu_1+(1-\theta)\mu_2$. Therefore, inequality (24) is equivalent to

$$\psi_y(\theta\mu_1+(1-\theta)\mu_2) \leq \theta\psi_y(\mu_1)+(1-\theta)\psi_y(\mu_2).$$

On the other hand, we know that $\mu_j > 0, j = 1,2,3$. Since the second derivative of $\psi_y(\mu)$ is positive for every $y, \mu > 0$, we conclude that $\psi_y(\mu)$ is convex and hence $F'(y) \leq 0$. This shows that F is non-decreasing on $\mathbb{R}_+$. To show that $F(y) \geq 0 \, \forall y \geq 0$, it remains to notice that

$$F(y) = C(e^{-Ay}-I)^{-1}B = C(I-e^{Ay})^{-1}e^{Ay}B \xrightarrow[y\to+\infty]{} 0,$$

since matrix A is Hurwitz stable.

Step 3. (*Positivity of the starting point* x^0) In this step, we show that all components of $x^0 = [x_1^0 \ x_2^0 \ x_3^0]^\top$ are positive. From the previous step we know that $x_3^0 = y^0 > 0$. So it remains to show that $x_1^0, x_2^0 > 0$. From (14) it is verified that

$$x_1^0 = \frac{\lambda_0}{e^{b_1\tau_0}-1}, \qquad x_2^0 = \lambda_0 g_1\sum_{j=1}^{3}\frac{\zeta_j}{e^{\mu_j\tau_0}-1},$$

where μ_j and ζ_j, $j = 1,2,3$, are defined in (18), (19) and (20). Due to the positivity of λ_0, one concludes that $x_1^0 > 0$. So it remains to prove that $x_2^0 > 0$. To this end, we define the function $H(t) := \sum_{j=1}^{3}\zeta_j\varrho_t(\mu_j)$ with $\varrho_t(\mu) := \frac{1}{e^{\mu t}-1} \ \forall t > 0$, whose positivity is equivalent to the positivity of x_2^0. Since $b_1 > b_3 > b_2$, we have $\gamma, \nu > 0$ defined in (15) and (16), and hence $\zeta_1, \zeta_3 < 0$ and $\zeta_2 > 0$. Due to the fact that $\zeta_1+\zeta_2+\zeta_3 = 0$, we can rewrite

$$\begin{aligned} H(t) &= \sum_{j=1}^{3}\zeta_j\varrho_t(\mu_j) \\ &= \zeta_1[\varrho_t(\mu_1)-\varrho_t(\mu_2)]+\zeta_3[\varrho_t(\mu_3)-\varrho_t(\mu_2)] \end{aligned}$$

On one hand, we know that $\varrho_t(\cdot)$ is a decreasing function; on the other hand, it can be readily seen that $\mu_2 < \mu_3$ and $\mu_2 < \mu_1$. Therefore $\varrho_t(\mu_3) < \varrho_t(\mu_2)$ and $\varrho_t(\mu_1) < \varrho_t(\mu_2)$ which results in the positivity of $H(t)$ and hence $x_2^0 > 0$.

Step 4. (*Positivity of function* $x(t)$) Our goal now is to show that

$$x(t) = e^{tA}(x^0+\lambda_0 B), \tag{25}$$

is non-negative for $t \in [0 \ \tau_0]$ (here τ_0, λ_0 are defined from (5)). Suppose that $x(t) = [x_1(t) \ x_2(t) \ x_3(t)]^\top$.

First, we show that the output $y(t) = Cx(t)$ remains non-negative. Indeed,

$$\begin{aligned} y(t) &= Ce^{tA}(x^0+\lambda_0 B) \\ &= g_1g_2(\lambda_0+x_1^0)\sum_{j=1}^{3}\eta_j e^{-\mu_j t}+\underbrace{\frac{g_2x_2^0}{2\beta}\left[e^{-\mu_2 t}-e^{-\mu_3 t}\right]}_{\geq 0} \\ &\quad +\underbrace{y^0\left[(b_3-b_2)(e^{-\mu_2 t}-e^{-\mu_3 t})+2\beta(e^{-\mu_3 t}+e^{-\mu_2 t})\right]}_{\geq 0} \end{aligned}$$

where η_j and μ_j, $j = 1,2,3$, are defined in (17) and (18). We know that $\eta_1+\eta_2+\eta_3 = 0$, and the function $\mu \mapsto e^{-t\mu}$ is convex. So following the same steps as those in Step 2 used to prove that $F'(y) \leq 0$, one concludes that $\sum_{j=1}^{3}\eta_j e^{-\mu_j t} \geq 0$ and hence $y(t) \geq 0$ for $t \in [0, \tau_0]$.

Now we show that $x_1(t), x_2(t) > 0$. From (25) one has

$$x_1(t) = e^{-b_1 t}(x_1^0+\lambda_0), \qquad x_2(t) = H_1(t)+H_2(t),$$

with

$$H_1(t) := g_1(x_1^0 + \lambda_0)\sum_{j=0}^{3}\zeta_j e^{-\mu_j t},$$

$$H_2(t) := (\zeta_4 x_2^0 + \zeta_6 x_3^0)e^{-(\alpha+\beta)t} + (\zeta_5 x_2^0 - \zeta_6 x_3^0)e^{-(\alpha-\beta)t},$$

where μ_j and ζ_j are defined in (18), (20) and (21). From the previous steps we know that $x_1^0, \lambda_0 > 0$. Therefore $x_1(t) > 0$.

The goal hereafter is to show that $x_2(t) > 0$. Following the same steps as those in Step 3 for proving $H(t) > 0$, one can show that $H_1(t) > 0$. So it remains to prove that $H_2(t) > 0$.

We know that $H_2(0) = x_2^0 > 0$. Therefore, if

$$\zeta_5 x_2^0 - \zeta_6 x_3^0 > 0, \tag{26}$$

we have the positivity of $H_2(t)$ and hence the positivity of $x_2(t)$. From Steps 2 and 3 we know that

$$x_2^0 = \lambda_0 g_1 \sum_{j=1}^{3}\frac{\zeta_j}{e^{\mu_j\tau_0}-1}, \quad x_3^0 = \lambda_0 g_1 g_2 \sum_{j=1}^{3}\frac{\eta_j}{e^{\mu_j\tau_0}-1}.$$

Since $\zeta_5 > 0$, the inequality (26) is equivalent to

$$x_2^0 - \frac{\zeta_6}{\zeta_5}x_3^0 = \lambda_0 g_1 \sum_{j=1}^{3}\frac{\rho_j}{e^{\mu_j\tau_0}-1} > 0, \tag{27}$$

where $\rho_j := \zeta_i - \left(\frac{2kg_2}{b_3-b_2+2\beta}\right)\eta_j$. Due to the fact that $\sum_{j=1}^3 \zeta_j = \sum_{j=1}^3 \eta_j = 0$, one has $\sum_{j=1}^3 \rho_j = 0$. It is shown that

$$\rho_2 = -\rho_1 = \frac{4\beta\zeta_2}{b_3 - b_2 + 2\beta}, \qquad \rho_3 = 0. \tag{28}$$

Since $b_1 > b_3 > b_2$, we have $\zeta_2, \rho_2 > 0$, and $\mu_2 < \mu_1$. Therefore (27) can be rewritten as

$$\begin{aligned} x_2^0 - \frac{\zeta_6}{\zeta_5}x_3^0 &= \lambda_0 g_1 \sum_{j=1}^{3}\frac{\rho_j}{e^{\mu_j\tau_0}-1} \\ &= \lambda_0 g_1 \rho_2 \left(\frac{1}{e^{\mu_2\tau_0}-1} - \frac{1}{e^{\mu_1\tau_0}-1}\right) > 0. \end{aligned}$$

Therefore $H_2(t) > 0$ and hence $x_2(t) > 0$. This finishes the proof of Theorem 1.

A closer analysis of the proof reveals that in fact the inequalities $b_1 > b_3 > b_2$ can be relaxed. In fact, for the proof of the existence and uniqueness of 1-cycle solution, we used only that the numbers η_i, $i = 1, 2, 3$, are well defined and two of them are positive, whereas the remaining is negative. In the case, addressed in Theorem 2, $\eta_1, \eta_2 > 0$ and $\eta_3 < 0$. Theorem 1 can be extended to the following situations:

(1) if $b_1 < b_2 < b_3$ then $\gamma > 0, \nu < 0$, $\zeta_1, \eta_1, \zeta_3, \eta_3 > 0$ and $\zeta_2, \eta_2 < 0$;
(2) if $b_2 < b_1 < b_3$ and $k \neq k_\gamma^0 := \frac{(b_3-b_1)(b_1-b_2)}{g_2}$ (i.e. $\gamma \neq 0$), the following cases are possible:
   (a) $b_1 \in (b_2, \frac{b_2+b_3}{2}), \nu, \gamma < 0$: $\zeta_2, \eta_2, \zeta_3, \eta_3 > 0$ and $\zeta_1, \eta_1 < 0$.
   (b) $b_1 \in (b_2, \frac{b_2+b_3}{2}), \nu < 0, \gamma > 0$: $\zeta_1, \eta_1, \zeta_3, \eta_3 > 0$ and $\zeta_2, \eta_2 < 0$.
   (c) $b_1 \in \left[\frac{b_2+b_3}{2}, b_3\right), \nu, \gamma < 0$: $\zeta_2, \eta_2, \zeta_3, \eta_3 > 0$ and $\zeta_1, \eta_1 < 0$.
   (d) $b_1 \in \left[\frac{b_2+b_3}{2}, b_3\right), \nu \geq 0, \gamma < 0$: $\zeta_2, \eta_2, \zeta_3, \eta_3 > 0$ and $\zeta_1, \eta_1 < 0$.
   (e) $b_1 \in (\frac{b_2+b_3}{2}, b_3), \nu, \gamma > 0$: $\zeta_1, \eta_1, \zeta_2, \eta_2 > 0$ and $\zeta_3, \eta_3 < 0$.

Notice that although for the proof of positivity of $H(t)$ and $H_1(t)$ in Theorem 1 we used the numbers $\zeta_1, \zeta_3 < 0$ and $\zeta_2 > 0$, it is verified that for the above situations (1) and (2), the positivity of $H(t)$ and $H_1(t)$ are ensured by using the facts that the function $\mu \mapsto e^{-t\mu}$ is convex, and $\zeta_1 + \zeta_2 + \zeta_3 = 0$. Furthermore, for the positivity of $H_2(t)$ in Theorem 1, we used the positivity of ζ_5 which holds for the above cases 1 and 2 as well. Summarizing, one arrives at the following result.

Theorem 2. Theorem 1 retains valid, replacing the inequality $b_1 > b_3 > b_2$ by the three conditions $b_3 > b_2$, $b_1 \neq b_2, b_3$ and $k \neq k_\gamma^0 := \frac{(b_3-b_1)(b_1-b_2)}{g_2}$ (the latter condition always holds when $k_\gamma^0 < 0$).

The conditions of the local orbital stability for 1-cycle solutions are analogous to those obtained in Churilov et al. (2009). The solution is stable if and only the Jacobian matrix $P'(x^0)$ is Schur stable, i.e. all its eigenvalues lie strictly in the unit disk.

4. NUMERICAL SIMULATIONS

In this section, a numerical simulation is given which allows to compare the behaviors of system (2) when $k = 0$ and $k \neq 0$. Following Churilov et al. (2009), the model parameters are considered to be $b_1 = 0.025$, $b_2 = 0.15$, $b_3 = 0.2$, $g_1 = 2$, $g_2 = 0.5$, and the functions $\Phi(\cdot)$ and $\Psi(\cdot)$ are chosen to be Hill-type nonlinearities

$$\Phi(y) = \vartheta_1 + \vartheta_2\frac{(y/h)^2}{1+(y/h)^2}, \quad \Psi(y) = \vartheta_3 + \frac{\vartheta_4}{1+(y/h)^2},$$

with $\vartheta_1 = 60, \vartheta_2 = 40, \vartheta_3 = 3, \vartheta_4 = 2$ and $h = 2.7$. In order to show clearly the effect of the additional feedback, the parameter k of the additional feedback is supposed to be $k = 0.08$. Both systems, i.e. system (2) with $k = 0$ and $k = 0.08$, are plotted in Fig. 1 with the same initial conditions $R(0) = 1$, $L(0) = 3$ and $T(0) = 5$.

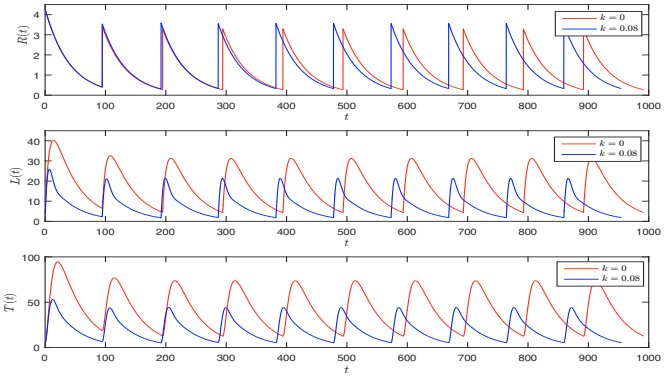

Fig. 1. Red and blue plots show numerical simulations of systems (2) when $k = 0$ and $k = 0.08$, respectively, with the same initial conditions and parameter values.

It is reported in Kandeel (2007) that exerting the feedback from Te to LH in the GnRH-LH-Te axis reduces the amplitude of serum concentration of LH. The amplitudes of oscillations of system (2) when $k = 0.08$ and $k = 0$, calculated numerically, are given respectively by $A_k \approx$

$(3.23, 19.55, 38.70)$ and $A_0 \approx (3.02, 26.92, 61.15)$ which clearly show the influence of the additional feedback on the amplitude of oscillations of system (2). Notice that the additional feedback reduces the amplitudes of oscillations of LH and Te while increases the amplitude of oscillations of GnRH.

5. CONCLUSION

A pulse-modulated model of endocrine regulation with an additional feedback has been examined. The existence and stability of periodic solutions have been presented. The extensions of the results to the cases, where conditions of Theorems 1 and 2 are failed, and the equations contain delays, are subject of ongoing research. We are also going to validate the proposed model using the results of medical experiments.

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