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Impulsive model of endocrine regulation with a local continuous feedback

Hadi Taghvafard[a], Alexander Medvedev[*,b], Anton V. Proskurnikov[c,d], Ming Cao[a]

[a] Engineering and Technology Institute, University of Groningen, Groningen, the Netherlands
[b] Uppsala University, Uppsala, Sweden
[c] Delft Center for Systems and Control, Delft University of Technology, Delft, the Netherlands
[d] Institute for Problems in Mechanical Engineering of the Russian Academy of Sciences, St. Petersburg, Russia

A B S T R A C T

Whereas development of mathematical models describing the endocrine system as a whole remains a challenging problem, visible progress has been demonstrated in modeling its subsystems, or *axes*. Models of hormonal axes portray only the most essential interactions between the hormones and can be described by low-order systems of differential equations. This paper analyzes the properties of a novel model of a hypothalamic-pituitary axis, portraying the interactions in a chain of a release hormone (secreted by the hypothalamus), a tropic hormone (produced by the pituitary gland) and an effector hormone (secreted by a target gland). This model, unlike previously published ones, captures two prominent features of neurohormonal regulation systems, namely, the pulsatile (episodic) production of the release hormone and a complex non-cyclic feedback mechanism that maintains the involved hormone concentrations within certain biological limits. At the same time, the discussed model is analytically tractable; in particular, the existence of a so-called 1-cycle featured by a single pulse over one period is proven mathematically.

1. Introduction

Hormones are chemical blood-borne substances produced in an organism by glands that regulate vital functions such as metabolism, reproduction, and growth. The endocrine system of an organism is the collection of glands communicating through hormone molecules as messengers, see e.g. [1]. The interacting glands can be considered as a dynamical system with numerous feed-forward and feedback control mechanisms, corresponding to stimulatory and inhibitory couplings between the hormones. The operation of endocrine glands is orchestrated by the brain, in particular the hypothalamus and the pituitary gland (hypophysis). The former produces concentration pulses of so-called release hormones (releasing factors) that communicate control information to the glands through pulse amplitude and frequency, see e.g. [2]. The neuroendocrine control loop incorporating the hypothalamus and the involved endocrine glands gives thus an example of *impulsive* (pulse-modulated) control system [3] and constitutes a special case of *hybrid* system [4], involving both continuous-time and discrete-time dynamics.

1.1. Endocrine axes

Given the complexity and multiscale nature of the underlying biological structure, to devise a mathematical model that describes the operation of the endocrine system in the extensive detail is a challenging problem. Tractable mathematical models are usually obtained by decoupling the endocrine system into subsystems, called axes, capturing only essential characteristics and interactions [5].

One of the most studied endocrine axes is the one that regulates the production of testosterone (Te) in the male, where the Gonadotropin-Releasing Hormone (GnRH) and the Luteinizing Hormone (LH) play crucial roles. This axis is called the GnRH-LH-Te (or the Hypothalamo-Pituitary-Reproductive) axis. GnRH, produced in the hypothalamus, stimulates the pituitary gland that responds by the secretion of LH that, in turn, stimulates the production of Te in the testes. This cascade of stimulation from GnRH to Te is then closed by two negative feedback loops from Te to GnRH and LH [5,6]. The feedback from Te to LH is a somewhat intricate matter. It is fundamentally enabled by the presence of Te receptors in the pituitary but its strength apparently differs between species [7].

The mathematical construction used to portray the mechanism of Te regulation serves as a *benchmark* in modeling of endocrine regulation, because much of the structure is widely applicable to some other neuroendocrine regulatory circuits controlled by the hypothalamus and the pituitary gland [8,9]. The structure and function of the pulsatile feedback mechanism from Te to GnRH is similar to the function of some other releasing hormones, such as in the endocrine axes of cortisol, growth, adrenal and parathyroid hormones [10,11]. The schematic

* Corresponding author.
E-mail addresses: taghvafard@gmail.com (H. Taghvafard), alexander.medvedev@it.uu.se (A. Medvedev), anton.p.1982@ieee.org (A.V. Proskurnikov), m.cao@rug.nl (M. Cao).

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diagram of these mechanisms, including two[1] negative feedback loops, is shown in Fig. 1.

Cortisol (C) is a hormone involved in the response to stress and inflammation as well as in metabolism. Similar to the case of Te regulation, the C regulation loop essentially comprises two more hormones [14–17]. Corticotropin-releasing hormone (CRH) is secreted in the hypothalamus in pulses and stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland to the bloodstream. Further, ACTH stimulates the secretion of C from the adrenal glands. Neither the amplitude nor the frequency of the CRH pulses are constant: the amplitude increases under stress, and the frequency varies from one to three CRH release episodes per hour. There are two feedback loops in the axis. C inhibits the secretion of CRH in the hypothalamus, both pulse mass and timing, through a negative "outer" impulsive feedback; C also inhibits the ACTH secretion through a continuous local feedback [18].

Another clinically important and often studied example of pulsatile endocrine axis is presented by the regulation of growth hormone (GH) that is secreted in the pituitary in response to pulses of growth hormone-releasing hormone (GHRH) produced in the hypothalamus. The third hormone in the chain is growth hormone-inhibiting hormone (GHIH), also known as somatostatin, which is secreted at several locations in the digestive system. The secretion of GHIH is stimulated by GH and inhibits the secretion of GHRH, thus closing the negative regulation loop. GHIH also inhibits GH secretion in a dose-dependent manner through a local feedback [19].

1.2. Mathematical modeling

For some endocrine regulation circuits, e.g. the GnRH-LH-Te axis in the male, very detailed and realistic models have been constructed [5,8], taking into account nonlinear interactions between the hormones, the hybrid dynamics of the system, and uncertainty of the model parameters captured by stochastic processes. The high complexity of these models makes their thorough analysis challenging; even the proof of solution existence requires non-trivial mathematical tools [8]. At the same time, visible progress has been made in analysis of simplified models that can be divided into several major classes.

The first mathematical models postulated to describe the hormonal regulation, namely, secretion of thyroid hormones [20] and Te regulation in the male [21], constitute special cases of the so-called *Goodwin's oscillator*, which has been proposed in [22] to describe enzymatic control processes in cells. Goodwin's model portrays sustained oscillations in a cyclic feedback system of three chemicals (Fig. 2) that in e.g., [21] stand for the GnRH, LH and Te hormones. Chemical A stimulates the production of B, which in turn stimulates the production of chemical C, which represses the activity of A thus closing the negative feedback loop. The cascade of corresponding biochemical interactions is described by a third-order system of differential equations. In the simplest and most studied situation [21,22], the kinetics of each reaction are described by a linear equation, and the only nonlinear term in the system represents the negative feedback from C to A. Models of endocrine regulation that are squarely based on Goodwin's model inherit its principal limitations. First, oscillatory behavior is observed only for special choices of the model parameters. For instance, if the negative feedback is parameterized by the Hill nonlinearity, it has been observed that periodic solutions exist only for the Hill constants greater than[2] 8, which are usually considered as biologically infeasible [25,26].

[1] Although the third "short" feedback from pituitary to hypothalamus also exists [9], its effect is much weaker than the influences of the "long" feedbacks and is often neglected to reduce the models' complexity [12,13].

[2] For Hill constants less than 8, the equilibrium of the model is known to be locally stable [21], whereas global stability, suggested by extensive computer simulations, has been proved only in special situations [23,24].

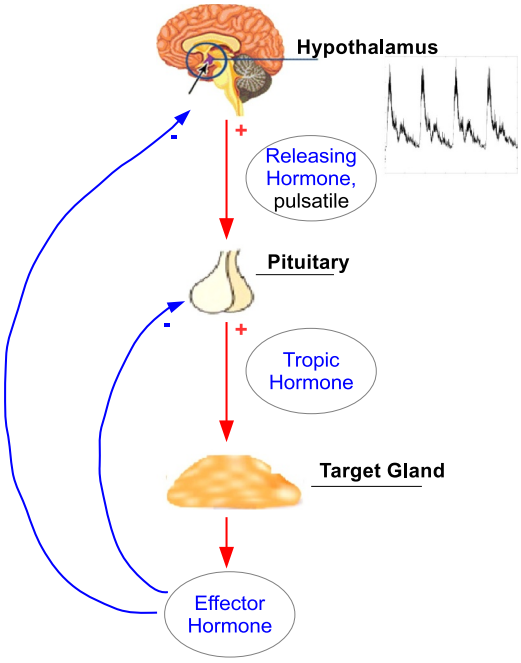

Fig. 1. A hypothalamus-pituitary endocrine axis.

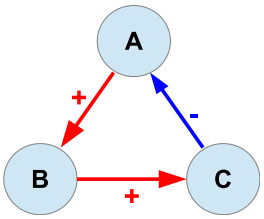

Fig. 2. The scheme of Goodwin's oscillator as a cyclic feedback system.

Second, Goodwin's model does not capture the full feedback mechanism of a hormonal axis, since it neglects the "local" feedback from the target gland to the pituitary and cannot explain pulsatile secretion of the releasing hormone.

The mentioned limitations have given rise to two classes of models extending conventional Goodwin's oscillator. Models of the first type [12,13,27–32] abandon the restrictive cyclic structure of Goodwin's oscillator and consider more complex interactions between the hormones that obey nonlinear ordinary or delay-differential equations. Their continuous dynamics, inherited from the Goodwin oscillator, enable one to use well-developed techniques of ordinary differential equations, from the local stability analysis and Hopf bifurcations to recent extensions of Poincaré-Bendixson theorems [33].

The second class of models, developed in [10,34–39] for Te regulation in the male, preserve the cyclic structure of Goodwin's system (Fig. 2) and focus on the pulsatile mechanism of the release hormone's secretion, whose existence is established by numerous experimental studies [5,40,41]. To cope with the hybrid (impulsive) dynamics of such models, special techniques have been developed from theory of impulsive control systems [3]. Unlike the Goodwin's oscillator with a continuous nonlinearity, the hybrid model of [35] has no equilibria and is proved to have periodic trajectories. In particular, a unique solution with one pulse over the period (1-cycle) exists [35]; periodic solutions with $m \geq 2$ pulses per period (m-cycles) may also exist [39].

Both Te and C impulsive regulation loops are subject to circadian rhythm. The mechanisms of entrainment of the endogenous hormone concentration oscillations to an exogenous periodic force, e.g. the circadian rhythm, are studied in [42], with respect to the impulsive Goodwin's oscillator, and in [43], where they are compared to those in

the classical continuous one.

1.3. The model under consideration

Recapitulating the overview of mathematically tractable models that portray dynamics of the hypothalamus-pituitary axes, one notices that the effects of multiple feedback loops and discontinuous feedback mechanisms have been studied *separately*. The examples of pulsatile neuroendocrine regulation loops in Section 1.1 motivate to introduce study a generic third-order system with a local feedback from the target gland to pituitary and the outer (intrinsic) pulse-modulated loop from the gland to hypothalamus. To study the mathematical properties of such a system is the main objective of this paper. A natural question arises on whether such a system enjoys the properties that are established for the impulsive Goodwin's oscillator without local feedback, e.g. the existence of cycles.

The local feedback, whose function is supported by sufficient experimental evidence [5,8,9,12,29,40], can be reasonably assumed to be continuous, as it does not pass through hypothalamus that applies pulsatile neurally implemented regulation. There is, however, no consensus on the mathematical description of the respective feedback control law. Whereas one could in principle suppose that this feedback mechanism is nonlinear and can be described by a Hill-type or other decreasing nonlinear function, this paper considers a model, where the negative local feedback is represented by an *affine* function (first-order polynomial). Similar to the impulsive Goodwin oscillator [35], the dynamics of such a system between two consecutive pulses are affine, and this property is beneficial in two aspects. First, it allows to extend the theory developed in [35] to the case of non-cyclic endocrine regulatory circuit with two feedbacks. Second, it enables the use of efficient identification methods [10,37] that are still more developed for systems whose dynamics depend linearly on unknown parameters (regressor form). From experimental data, the feedback typically cannot be observed in its full domain of definition [44]; beyond the saturation intervals of extreme hormone concentration, the Hill-type nonlinearity can be well approximated by an affine function.

Unlike the Hill-type nonlinearity, strictly decreasing polynomial functions cannot remain positive on the positive semi-axis. In contrast to both the original Goodwin's oscillator and its impulsive counterpart, the model considered in this paper does not enjoy the global positivity property (the positive orthant is not forward invariant). Whereas a positive value of each state variable corresponds to the *actual* serum concentrations of the respective hormones, a negative value may be interpreted as the amount of hormone that the system *is lacking* for normal functioning. The biologically available pool of a hormone in a gland is limited at any moment and can be less than an instantaneous demand for it. In the long run, lack of releasable hormone is known to lead to endocrine diseases such as type II diabetes and adrenal depletion. From a biological viewpoint, negative solutions can thus be feasible, standing however for pathological behaviors of the system.

Due to the fact that endocrine regulation processes exhibit self-sustained oscillations, the main concern in securing model feasibility is the existence of periodic solutions in the system. The key finding in [35] dealing with the impulsive Goodwin's oscillator is the existence and uniqueness of a special periodic solution ("1-cycle"), having only one pulse over the (minimal) period. In general, the system may have other periodic solutions; the clinical data suggest the existence of cycles with multiple pulses over the period.

For the cyclic model presented in [35], the existence and uniqueness of 1-cycle solution along with its local stability are given. In this work, similar results are obtained with respect to a system with an additional feedback. Note that the positivity of 1-cycle solutions of the cyclic model in [35] holds automatically, while it is not true for the extended system. So another contribution of this paper is the disclosure of sufficient conditions for positivity of the 1-cycle solution.

The rest of the paper is organized as follows. In Section 2, the impulsive Goodwin' oscillator proposed in [35,45–47] is recapitulated and an extension to it is introduced, which is the main contribution of this work. The mathematical properties of this model are discussed in Section 3. In Section 4, these results are illustrated by numerical simulations. In Section 5, conclusions are drawn.

2. Impulsive Goodwin's oscillator and its extension

In this section, the model of impulsive (or hybrid) Goodwin's oscillator, proposed in [35,45–48] to portray the pulsatile feedback mechanism of the testosterone regulation in the male, is extended to include a local continuous feedback. This extension is supported by biological facts and is also shown to impact the assumptions that are critical for the use of the readily available model analysis. For the reader's convenience, the original model's properties are summarized in the next section.

2.1. The impulsive Goodwin's oscillator

The model in [35] describes the dynamics of three variables $R(t)$, $L(t)$, $T(t)$, standing, respectively, for the serum concentrations of the release, tropic and effector hormones. In the case of Te regulation, these hormones are GnRH, LH and Te. Similar to the classical (continuous) Goodwin oscillator [22], the *feedforward* couplings in Fig. 1 are described by a chain of linear first-order blocks as follows

$$\begin{aligned}&\dot{L}(t) = g_1 R(t) - b_2 L(t),\\ &\dot{T}(t) = g_2 L(t) - b_3 T(t),\\ &b_2, b_3, g_1, g_2 > 0.\end{aligned} \tag{1}$$

The release hormone R initiates the chain by stimulating the production of the tropic hormone L, which in turn drives the production of the effector hormone T. The model from Churilov et al. [35] ignores the presence of the local feedback from T to L, whereas the "long" *pulsatile* feedback mechanism obeys the equations[3]

$$\begin{aligned}&\dot{R}(t) = -b_1 R(t), \quad t \in (t_n, t_{n+1}]\\ &R(t_n^+) = R(t_n) + \lambda_n, \quad n = 0, 1, ...\end{aligned} \tag{2}$$

The instantaneous jumps in the hormone concentration are caused by short release hormone pulses. The pulses are fired by a pulse-modulation mechanism, implementing the "long" feedback from the effector to the release hormone (Fig. 1). The sequences of pulse instants t_n and amplitudes λ_n depend on a specific solution of the model given by (1) and (2). An important assumption, based on experimental evidence [49], is that, in this feedback mechanism[4], the amplitude λ_n and the inter-pulse interval $(t_{n+1} - t_n)$ depend only on the state of the system at time t_n, but not on the previous trajectory. More precisely,

$$\lambda_n = \Psi(T(t_n)), \quad t_{n+1} = t_n + \Phi(T(t_n)), \quad t_0 = 0, \tag{3}$$

where the functions Φ, Ψ are strictly positive and bounded

$$\begin{aligned}&\Phi\colon \mathbb{R} \to [\Phi_1, \Phi_2], \qquad \Psi\colon \mathbb{R} \to [\Psi_1, \Psi_2],\\ &0 < \Phi_1 < \Phi_2 < \infty, \quad 0 < \Psi_1 < \Psi_2 < \infty.\end{aligned} \tag{4}$$

The assumption $t_0 = 0$ does not reduce generality and means that the system operation starts with the first pulse.

The amplitude modulation characteristic Ψ is supposed to be *non-increasing*, while the frequency modulation characteristic Φ is assumed to be *non-decreasing*. In testosterone regulation mechanism, an increase of Te level decreases the frequency of GnRH pulses and reduces their

[3] Given a function $f\colon [0, \infty) \to \mathbb{R}$, we use $f(t^+)$ to denote the right limit $\lim_{s \downarrow 0} f(t + s)$. Henceforth all piecewise-continuous functions, without loss of generality, are supposed to be left continuous, so $f(t) = \lim_{s \downarrow 0} f(t - s)\ \forall\ t > 0$.

[4] Such a feedback mechanism is referred to as a pulse amplitude-frequency modulator of the first kind [3] or an impulsive self-triggered control [50].

amplitudes [6], thus also suppressing the bursts of LH. This agrees with the inverse relation between the frequency of GnRH pulses and amplitudes of (major) LH pulses, documented in the literature [51].

2.2. The main properties of the impulsive Goodwin's oscillator

Introducing the continuous state vector $x(t) = [R(t), L(t), T(t)]^\top$ and the matrices

$$A = \begin{bmatrix} -b_1 & 0 & 0 \\ g_1 & -b_2 & 0 \\ 0 & g_2 & -b_3 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \quad C = [0, 0, 1], \tag{5}$$

model (1)–(3) can be rewritten as follows

$$\begin{aligned} \dot{x}(t) = Ax(t),\ y(t) &= Cx(t), \quad t \in (t_n, t_{n+1}], \\ x(t_n^+) &= x(t_n) + B\lambda_n, \end{aligned} \tag{6}$$

$$\lambda_n = \Psi(y(t_n)), \quad t_{n+1} = t_n + \Phi(y(t_n)), \quad t_0 = 0. \tag{7}$$

The equations of (6) can be also written as follows

$$\begin{aligned} x(t) &= e^{tA}x(0) + \sum_{n:\, t_n<t} e^{(t-t_n)A}B\lambda_n, \\ x(t^+) &= x(t) + B\begin{cases} 0, & t \notin \{t_k\}_{k\geq 1} \\ \lambda_n, & t = t_n. \end{cases} \end{aligned} \tag{8}$$

or, using the formalism of Dirac δ-functions

$$\dot{x}(t) = Ax(t) + B\xi(t), \quad \xi(t) = \sum_{n=0}^{\infty} \lambda_n \delta(t - t_n). \tag{9}$$

Eq. (9)resembles the well-known Goodwin's oscillator [22,32] with the only principal difference that the static nonlinear feedback of the latter is replaced by a nonlinear pulse modulator of (7). The system (1)–(3) or, equivalently, (6) and (7) is henceforth referred to as the *impulsive (or hybrid) Goodwin oscillator*. Due to the persistent pulses, this system has no equilibria and always has periodic solutions (possibly, unstable) [35].

Since A is Hurwitz and Metzler,[5] the matrix e^{tA} has nonnegative entries and exponentially decays as $t \to \infty$. Moreover, it can be shown that the vector $e^{tA}B$ is strictly positive for any $t \geq 0$. Using (4),(7) and (8), it is shown [35] that

$$0 < V_i \leq \varliminf_{t\to+\infty} x_i(t) \leq \varlimsup_{t\to+\infty} x_i(t) \leq H_i < \infty \quad \forall\, i = 1, 2, 3, \tag{10}$$

where the constants V_i, H_i can be found explicitly and depend on the bounds Φ_i, Ψ_i in (4) and constants b_i, g_i as follows

$$\begin{aligned} V_1 &= \frac{\Psi_1}{e^{b_1\Phi_2} - 1}, \quad V_2 = \frac{g_1 V_1}{b_2}, \quad V_3 = \frac{g_1 g_2 V_1}{b_2 b_3} \\ H_1 &= \frac{\Psi_2}{1 - e^{-b_1\Phi_2}}, \quad H_2 = \frac{g_1 H_1}{b_2}, \quad H_3 = \frac{g_1 g_2 H_1}{b_2 b_3}. \end{aligned} \tag{11}$$

Note that in view of (8) the system is *positive*: if the components of $x(0)$ are non-negative, the same holds for $x(t)$, $t \geq 0$. Inequalities (10) show that the feedback mechanism adjusts the hormone levels around a normal physiological pattern that belongs to an attractor, not necessarily a periodic one, Zhusubaliyev et al. [36]. It is also obvious from (10) that each trajectory is uniformly positive (after a transient period) and bounded.

As known from Churilov et al. [35], the system always has *1-cycle*, i.e. a special periodic solution, such that the (minimal) period contains only a single pulse. This result is based on the fact that the sequence $X_n = x(t_n)$ obeys the recursion

$$X_{n+1} = Q(X_n), \quad Q(x) := e^{A\Phi(Cx)}(x + \Psi(Cx)B), \tag{12}$$

and the complete inter-sample behavior of the (hybrid) solutions can be reconstructed from it.

Theorem 1 ([35]). *For any non-increasing function Ψ and non-decreasing function Φ that are C^1-smooth and satisfy (4), the mapping Q has a unique fixed point $x^0 > 0$ corresponding to the unique 1-cycle solution to impulsive system (6) and (7).*

It can be shown [35] that (12) is, for the case of 1-cycle, equivalent to the transcendental equation for $y^0 = Cx^0$

$$y^0 = C\left(I - e^{A\Phi(y^0)}\right)^{-1} e^{A\Phi(y^0)}\Psi(y^0)B, \quad y^0 > 0, \tag{13}$$

whose right-hand side appears to be a *non-increasing* function of y^0 [35]. The inverse matrix exists since A is a Hurwitz matrix and $\Phi(\cdot)$ is uniformly positive.

Notice also that the biology of the system precludes identical half-life times in an endocrine axis, i.e. b_i, $i = 1, 2, 3$ are all distinct. In this generic situation, the latter equation can be further simplified as follows

$$\begin{aligned} y^0 &= g_1 g_2 \Psi(y^0) \sum_{i=1}^{3} \frac{\alpha_i}{e^{b_i\Phi(y^0)} - 1}, \\ \alpha_i &= \prod_{\substack{j=1 \\ j\neq i}}^{3} \frac{1}{b_j - b_i}, \quad i = 1, 2, 3. \end{aligned} \tag{14}$$

In general, the 1-cycle solution can be unstable; its *orbital* stability is determined by the eigenvalues of the Jacobian $Q'(x_0)$ ("multipliers"): if these eigenvalues $\lambda_{1,2,3} \in \mathbb{C}$ lie in the open unit circle $|\lambda_j| < 1$, the 1-cycle is orbitally stable [35]. Finally, the hybrid Goodwin oscillator can have other periodic solutions that correspond to the fixed points of Q with period $m \geq 2$, i.e.

$$\begin{aligned} Q^{(m)}(x_0) &= \underbrace{Q\circ Q\circ \ldots \circ Q}_{m \text{ times}}(x_0) = x_0, \\ Q^{(j)}(x_0) &\neq x_0 \quad \forall\, j = 1, \ldots, m-1, \end{aligned}$$

where $\circ$ denotes composition of functions, i.e. $Q\circ Q(x) = Q(Q(x))$. Such solutions are referred to as *m-cycles* [52] and characterized by m pulses fired during the (minimal) period.

2.3. Model extension with local feedback

This paper primarily addresses an extension of the impulsive Goodwin's oscillator that takes into account the *local* feedback from the effector hormone T to the tropic hormone L. As has been discussed in Introduction, there is no consensus in the literature on what function should be used to describe this feedback. It is henceforth assumed that the feedback can be represented by the *affine* function $\mu - kT$, where μ, $k \geq 0$, so that the linear equations in (1) are replaced by

$$\begin{aligned} \dot{L}(t) &= g_1 R(t) - b_2 L(t) - kT(t) + \mu, \\ \dot{T}(t) &= g_2 L(t) - b_3 T(t), \end{aligned} \tag{15}$$

where the pulsatile mechanism of release hormone secretion is given by (2) and (3). All other parameters describing the production and clearing rates of the hormones are supposed to satisfy the same assumptions as in Section 2.1.

Obviously, Eq. (1) is a special case of (15) with $k = \mu = 0$. The constant $k \geq 0$ in (15) stands for the *control gain*, regulating the dependence between the level of the effector hormone (e.g. testosterone) and the secretion of the tropic hormone in the pituitary gland. The constant μ may be considered as a characteristic of the hormone's basal level,[6] i.e. the result of the hormone secretion outside the feedback

[5] A real square matrix is called *Hurwitz* if all its eigenvalues λ_j have negative real parts $Re\lambda_j < 0$ and *Metzler* if all its off-diagonal elements are nonnegative.

[6] In the case of Te regulation [35], a basal level also appears in the concentration of Te. This, however, does not need a model modification since a

loop. Note here that removing μ simplifies the model, but then, for $b_2 > b_3$, the system may not have positive solutions. With $\mu \neq 0$, the dynamics of (1) are nonlinear (affine), which is a price to pay for preserving the model positivity in spite of the local feedback. Naturally, linearity can be recovered by considering μ as an additional state variable with the trivial dynamics $\dot{\mu} = 0$. However, it is more convenient to preserve the chain structure and consider μ as a constant input.

With the matrices in (5) and introducing

$$D = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}, \quad A_k = A - kD[0 \;\; 0 \;\; 1], \tag{16}$$

system (15),(2),(3) is rewritten in a matrix form as

$$\begin{aligned} \dot{x}(t) = A_k x(t) + D\mu, \; y(t) = Cx(t), \quad t \in (t_n, t_{n+1}], \\ x(t_n^+) = x(t_n) + B\lambda_n, \end{aligned} \tag{17}$$

$$\lambda_n = \Psi(y(t_n)), \quad t_{n+1} = t_n + \Phi(y(t_n)), \quad t_0 = 0. \tag{18}$$

Similar to (8), one notices that

$$\begin{aligned} x(t) &= e^{tA_k}x(0) + A_k^{-1}\left(e^{tA_k} - I\right)D\mu + \sum_{n:\, t_n<t} e^{(t-t_n)A_k}B\lambda_n \\ x(t^+) &= x(t) + B\begin{cases} 0, & t \notin \{t_k\}_{k\geq 1} \\ \lambda_n, & t = t_n. \end{cases} \end{aligned} \tag{19}$$

The matrix A_k with the characteristic polynomial

$$\begin{vmatrix} \lambda + b_1 & 0 & 0 \\ -g_1 & \lambda + b_2 & k \\ 0 & -g_2 & \lambda + b_3 \end{vmatrix} = (\lambda + b_1)[(\lambda + b_2)(\lambda + b_3) + kg_2].$$

is *Hurwitz* for any $k \geq 0$. The principal difference with the impulsive Goodwin's oscillator from Section 2.1 is that A_k is no longer Metzler, which means that the positive octant $\{x \in \mathbb{R}^3 : x_i > 0 \;\; \forall\, i\}$ is not a forward invariant set. Since the mechanism of the release hormone secretion in (2) and (3) is the same as in the impulsive Goodwin oscillator, inequalities (10) remain valid for $i = 1$ with V_1, H_1 from (11) (recall that $x_1 = R$). The remaining two variables x_2, x_3 can become negative, being however bounded in view of (19).

As has been discussed in Introduction, negative solutions can be considered as biologically meaningful, standing however for undesirable system behaviors. A natural question thus arises on whether the extended impulsive Goodwin model (17) and (18) enjoys the main property of model (6) and (7) and possesses positive periodic solutions. The domain in the space of the parameters where this can be guaranteed will be specified in the next section. For the corresponding set of the parameters, the extended model reduces in fact to a system of the same type as (6),(7), thus enabling the use of the well-developed theory for the impulsive Goodwin's oscillator.

3. Mathematical results

In this section, the main mathematical result of the paper is proved, extending the key properties of the impulsive Goodwin's oscillator from Section 2 to a more general system that is given by (17) and (18). Two key assumptions adopted to obtain this result are, first, a small gain of the local feedback k and, second, a sufficiently large μ (ensuring the solution's ultimate[7] positivity)

$$0 \leq k < k_*: = \frac{(b_2 - b_3)^2}{4g_2}, \tag{20}$$

$$\begin{aligned} \mu &> -g_1 V_1 + \max\left(\frac{g_1 g_2 \rho (H_1 - V_1)}{b_3}, 0\right), \\ \rho &: = \frac{(b_2 - b_3) - \sqrt{(b_2 - b_3)^2 - 4kg_2}}{2g_2}. \end{aligned} \tag{21}$$

Here V_1, H_1 are defined in (11). Under assumption (20), $\rho \leq 0$ if and only if $b_3 \geq b_2$; in such a situation, condition (21) holds for any $\mu \geq 0$. Obviously, (20) and (21) hold when $k = \mu = 0$. In the latter case, the system boils down to the impulsive Goodwin's oscillator, i.e. (6) and (7).

Theorem 2. *Let the functions Φ and Ψ be non-decreasing and non-increasing, respectively. If condition (20) holds, then system (17)and (18) has a unique 1-cycle solution that, in general, does not need to be strictly positive. If, additionally, the condition (21) is valid, then all solutions of system (17)and (18) are uniformly ultimately positive and bounded*

$$0 < V_i' \leq \varliminf_{t\to+\infty} x_i(t) \leq \varlimsup_{t\to+\infty} x_i(t) \leq H_i' < \infty, \quad i = 1, 2, 3, \tag{22}$$

where V_i', H_i' depend on the bounds Φ_i, Ψ_i and the coefficients b_i, g_i, k, μ. In particular, the unique 1-cycle and all other periodic solutions are strictly positive.

Notice that (21) may also hold for $\mu < 0$. Although negative value of μ does not have a clear biological interpretation (see the discussion below), the ultimate positivity of solutions can be guaranteed. Note that, unlike in the impulsive Goodwin's oscillator ($k = \mu = 0$), solutions that start in the positive octant $x > 0$ may leave it (some hormone's level can be insufficient for normal functioning of the system on some time intervals); inequalities (22) entail however that the levels of hormones return to the normal (non-negative) physiological pattern after some transient period. The proof of Theorem 2 is based on an affine transformation of the coordinates that reduces system (17) and (18) to the impulsive Goodwin's oscillator (6) and (7). This transformation is introduced in the next subsection. An alternative direct proof for the special case $\mu = 0$ and $b_3 > b_2$ was given in the conference paper [53].

3.1. The state transformation of the system

Consider the following transformation

$$z_1 = R, \quad z_2 = L + \rho T + \alpha, \quad z_3 = T + \beta, \tag{23}$$

where ρ is defined in (21) and α, β are two parameters to be specified. The linear part of the system given by (15) is transformed into

$$\begin{aligned} \dot{z}_2 &= g_1 z_1 - (b_2 - \rho g_2)z_2 + (\rho b_2 - \rho b_3 - \rho^2 g_2 - k)z_3 \\ &\quad + [\mu + k\beta + b_2(\alpha - \rho\beta) + \rho(g_2(\rho\beta - \alpha) + b_3\beta)], \\ \dot{z}_3 &= g_2 z_2 - (\rho g_2 + b_3)z_3 + (g_2(\rho\beta - \alpha) + b_3\beta). \end{aligned}$$

Note that $\rho b_2 - \rho b_3 - \rho^2 g_2 - k = 0$. Choosing α, β in a way that

$$\begin{cases} g_2(\rho\beta - \alpha) + b_3\beta = 0, \\ \mu + k\beta + b_2(\alpha - \rho\beta) = 0, \end{cases} \Longleftrightarrow \begin{cases} \alpha = -\dfrac{\mu(b_3 + \rho g_2)}{b_2 b_3 + k g_2}, \\ \beta = -\dfrac{\mu g_2}{b_2 b_3 + k g_2}, \end{cases} \tag{24}$$

Eq. (15) reduce to their counterparts (1), where (R, L, T) is replaced by (z_1, z_2, z_3) and b_2, b_3 are replaced by

$$\tilde{b}_2 = b_2 - \rho g_2 > 0, \quad \tilde{b}_3 = b_3 + \rho g_2 > 0. \tag{25}$$

It is easily noticed that the signs of α, β coincide with the sign of μ. The vector $z(t) = (z_1(t), z_2(t), z_3(t))^\top$ obeys the equations

$$\begin{aligned} \dot{z}(t) = \tilde{A}z(t), \; t \in (t_n, t_{n+1}], \quad z(t_n^+) = z(t_n) + B\lambda_n, \\ \lambda_n = \tilde{\Psi}(Cz(t_n)), \quad t_{n+1} = t_n + \tilde{\Phi}(Cz(t_n)), \quad t_0 = 0, \end{aligned} \tag{26}$$

(*footnote continued*)
constant bias in T can be readily incorporated in the modulation functions Φ, Ψ.

[7] A condition on the solution $x(t)$ is said to hold *ultimately* if it holds for sufficiently large $t \geq 0$. In particular, an ultimately positive solution is a solution that becomes positive as $t \to \infty$ (yet may be negative for small $t > 0$).

where B, C are the same as in (5) and

$$\tilde{A} = \begin{bmatrix} -b_1 & 0 & 0 \\ g_1 & -\tilde{b}_2 & 0 \\ 0 & g_2 & -\tilde{b}_3 \end{bmatrix}, \ \tilde{\Phi}(y) = \Phi(y-\beta), \ \tilde{\Psi}(y) = \Psi(y-\beta).$$

Obviously, the nonlinearities $\tilde{\Phi}$, $\tilde{\Psi}$ satisfy the inequalities (4) with the same bounds Φ_i, Ψ_i. In view of (25), system (26) is nothing else than a special case of the impulsive Goodwin's oscillator expressed by (6) and (7). Hence, any solution $x(t)$ of (17) and (18) corresponds to a solution of (26) and vice versa. The findings of this subsection are summarized in the following lemma.

Lemma 1. *Assume that the "small gain" condition expressed by (20) holds. Then mapping (23) establishes one-to-one correspondence between the solutions of system (17)and (18) and the solutions of (26).*

Lemma 1allows to prove the first part of Theorem 2 since the mappings $(z_1, z_2, z_3)\mapsto(R, L, T)$ and $(R, L, T)\mapsto(z_1, z_2, z_3)$ are both affine, transforming thus periodic solutions into periodic solutions and m-cycles into m-cycles for any $m \geq 1$. To compute the (unique) 1-cycle explicitly, one can use Eq. (13) (replacing A with $\tilde{A}$) that, for distinct b_1, $\tilde{b}_2$, $\tilde{b}_3$, reduces to (14). In general, neither the state transformation in (23) nor its inverse preserve positivity of solutions. Hence the 1-cycle and other positive trajectories of (26) can be mapped into solutions that leave the positive octant. To exclude these "pathological" trajectories, additional restrictions on the parameters are needed, e.g. (21).

3.2. Proof of Theorem 2

The first statement follows immediately from Lemma 1 and Theorem 1. There is one-to-one correspondence between 1-cycles of the extended system (17) and (18) and the impulsive Goodwin's oscillator (26), and the latter system has a unique 1-cycle in view of Theorem 1. To prove the second statement, recall that the solutions of (26) satisfy inequalities (10) and (11), where b_2, b_3 have to be replaced by $\tilde{b}_2$, $\tilde{b}_3$.

To prove the second statement, recall that the solutions of (26) satisfy inequalities (10), where V_i, H_i can be found from (11), replacing b_2, b_3 by $\tilde{b}_2$, $\tilde{b}_3$ respectively:

$$V_1 = \frac{\Psi_1}{e^{b_1\Phi_2}-1}, \quad \tilde{V}_2 = \frac{g_1 V_1}{\tilde{b}_2}, \quad \tilde{V}_3 = \frac{g_1 g_2 V_1}{b_2 b_3 + k g_2},$$
$$H_1 = \frac{\Psi_2}{1-e^{-b_1\Phi_2}}, \quad \tilde{H}_2 = \frac{g_1 H_1}{\tilde{b}_2}, \quad \tilde{H}_3 = \frac{g_1 g_2 H_1}{b_2 b_3 + k g_2}.$$

Note that $\tilde{b}_2\tilde{b}_3 = b_2 b_3 + k g_2$ due to (21) and (25). Since α, β depend only on the system parameters, all solutions are uniformly ultimately bounded in the sense of (22), where V_i', H_i' depend on the coefficients b_i, g_i, k, μ and the bounds Φ_i, Ψ_i. Obviously, $V_1' = V_1$ and $H_1 = H_1'$ since $x_1 = z_1$. Recalling that $T = x_3 = z_3 - \beta$, one proves (22) for $i = 3$, where

$$V_3' = \tilde{V}_3 + \frac{\mu g_2}{b_2 b_3 + k g_2} = \frac{g_2(\mu + g_1 V_1)}{b_2 b_3 + k g_2} \overset{(21)}{>} 0,$$
$$H_3' = \tilde{H}_3 + \frac{\mu g_2}{b_2 b_3 + k g_2} = \frac{g_2(\mu + g_1 H_1)}{b_2 b_3 + k g_2}.$$

Notice now that $L = x_2 = z_2 - \rho z_3 + (\alpha - \rho\beta)$, where $\alpha - \rho\beta = \mu b_3/(b_2 b_3 + k g_2)$. In the case where $b_2 \leq b_3$, one has $(-\rho) \geq 0$, entailing (22) for $i = 2$ with

$$V_2' = \tilde{V}_2 - \rho\tilde{V}_3 + \frac{\mu b_3}{b_2 b_3 + k g_2} \overset{(25)}{=} \frac{b_3(\mu + g_1 V_1)}{b_2 b_3 + k g_2} \overset{(21)}{>} 0,$$
$$H_2' = \tilde{H}_2 - \rho\tilde{H}_3 + \frac{\mu b_3}{b_2 b_3 + k g_2} \overset{(25)}{=} \frac{b_3(\mu + g_1 H_1)}{b_2 b_3 + k g_2}.$$

In the case where $b_2 > b_3$ and $\rho > 0$, (22) holds for $i = 2$ with

$$V_2' = \tilde{V}_2 - \rho\tilde{H}_3 + \frac{\mu b_3}{b_2 b_3 + k g_2} \overset{(25)}{=} \frac{b_3(\mu + g_1 V_1) + g_1 g_2(V_1 - H_1)\rho}{b_2 b_3 + k g_2}$$
$$H_2' = \tilde{H}_2 - \rho\tilde{V}_3 + \frac{\mu b_3}{b_2 b_3 + k g_2} \overset{(25)}{=} \frac{b_3(\mu + g_1 H_1) + g_1 g_2(H_1 - V_1)\rho}{b_2 b_3 + k g_2}.$$

In view of (21), one has $V_2' > 0$, which completes the proof.

Remark 1. It is obvious from the proof that condition (21) cannot be fully discarded without losing the positivity property, e.g. for $\mu < -g_1 H_1$ and $b_2 \leq b_3$ one has $H_2', H_3' < 0$, that is, *all* solutions of the system become negative. A numerical simulation, presented in Section 4 (Example 3) demonstrates that (20) cannot be dropped either: the system may even have periodic orbits that leave the positive octant.

3.3. Discussion

It is instructive to seek a control-engineering interpretation of the endocrine regulation model considered above. For the sake of simplicity, it is confined to testosterone regulation. The impulsive endocrine feedback can be assumed to pursue two goals. First, the loop has to be brought to a certain oscillation pattern, since both the frequency and amplitude of the GnRH pulse train communicate biologically significant information [2,54]. Second, the concentrations of the involved hormones have to be kept within biologically feasible bounds. Both goals are clearly fulfilled in the model at hand.

One can also assume that the local feedback from Te to LH facilitates the filtering of the pulsatile secretion of GnRH and, consequently, limits the variation of Te. This is also confirmed by numerical simulation, reported in Section 4 (Example 2). The gain of the local feedback has thus to be limited, cf (20), to allow for sufficient variation of the hormone amplitudes. As mentioned Section 2.1, both the frequency and amplitude of the GnRH pulses convey biologically significant information and the impulsive mode of the endocrine secretion is essential for the endocrine function.

As has been already discussed, the parameter μ in (17) can be interpreted in terms of the hormones' *basal levels* (for this reason, it is natural to assume that $\mu \geq 0$). The basal level of LH, here related to the value of μ, is known to be involved in sexual maturation [55] and clinically used as a puberty marker. Without GnRH stimulation, i.e. for $R(t) \equiv 0$, system (15) has equilibrium at $(L, T) = (L_b, T_b)$, whose coordinates

$$L_b = \frac{b_3\mu}{b_3 b_2 + k g_2}, \quad T_b = \frac{g_2\mu}{b_3 b_2 + k g_2},$$

constitute the basal levels of LH and Te in the model. These basal levels decrease when the local feedback gain k increases. Therefore, to maintain biologically reasonable basal levels, the gain has to be sufficiently small, cf. (20) and μ sufficiently large and positive. The choice $\mu = 0$ corresponds to negligible basal levels of the two hormones and renders the continuous part of the model at hand linear, in contrast to affine.

The matter of estimating the parameters (system identification) of the impulsive Goodwin's oscillator from experimental Te and LH data without exogenous excitation is covered in [10,37]. To account for the hybrid nature of the system, the identification is performed in two steps. First, the timing and magnitude of the GnRH pulses is evaluated from the LH data by sparse estimation relying on the technique proposed in [56]. Second, linear identification is performed to estimate the parameters of the continuous part of the model with the GnRH impulses evaluated in the first step as input and the Te concentration as the output. Despite some inherent limitations, this approach apparently produces good data fit. Yet, the approach of [10,37] cannot be directly applied to the model studied in the present paper since the local feedback in (15) is intrinsic and not identifiable from an input-output experiment. In order to recover identifiability, exogenous excitation of the

second hormone (LH) is necessary, as well known in classical closed-loop identification theory [57]. Although feasible, this is outside the scope of the present paper.

4. Numerical examples

In this section, some numerical simulations illustrating the behavior of the model at hand are presented.

Example 1. To start with, a set of parameters, partly borrowed from the model of Hypothalamic-Pituitary-Adrenal (HPA) axis in [29] is considered. The state variables *L, R, T* stand, respectively, for the concentrations of CRH, ACTH and cortisol (C) whose clearing rates are $b_1 = 0.023$, $b_2 = 0.04$ and $b_3 = 0.0083$. The secretion rates of ACTH and C are set as $g_1 = 0.032$ and $g_2 = 0.0013$, whereas the nonlinear secretion rate of CRH $\Psi(\cdot)$ and the frequency modulation functions $\Phi(\cdot)$ are chosen to be

$$\Phi(y) = \kappa_1 + \kappa_2 \frac{y^3}{1+y^3}, \qquad \Psi(y) = \kappa_3 + \kappa_4 \frac{1}{1+y^3}, \tag{27}$$

with $\kappa_1 = 60$, $\kappa_2 = 40$, $\kappa_3 = 9$ and $\kappa_4 = 0.045$. Obviously, these nonlinearities satisfy (4) with $\Phi_1 = \kappa_1$, $\Phi_2 = \kappa_1 + \kappa_2$ and $\Psi_1 = \kappa_3$, $\Psi_4 = \kappa_3 + \kappa_4$. It can be shown that conditions (20) and (21) hold when $k < 0.1932$ and $\mu > 0.1747$. The behavior of the system for $k = 0.1$ and $\mu = 0.11$ and the initial condition $(R, L, T)_{t=0} = (1, 4.5, 1)$ is shown in Fig. 3. One may see that the solution converges to a positive 1-cycle, and the patterns of oscillations are similar to those reported in [29].

Example 2. Next simulation illustrates the influence of gain k on the system's behavior. Fig. 4 illustrates the behavior of the system from Example 1 for three different gains: $k = 0$ (minimal possible value, ensuring that the feedback is negative), $k = 0.1932$ (the maximal value for which positivity is guaranteed by Theorem 2) and intermediate value $k = 0.05$. One can see that an increase in k visibly damps the oscillation amplitude and also influences the oscillation period.

Example 3. The last example shows that condition (20) cannot be discarded without losing the ultimate positivity property, moreover, for large k the system may have acquire partly negative periodic orbits. The behavior of system (17) and (18) with parameters $b_1 = 0.25$, $b_2 = 0.15$, $b_3 = 0.20$, $g_2 = 0.5$ is simulated with the nonlinearities Φ, Ψ being the same as in Example 1. The local feedback parameters are chosen as

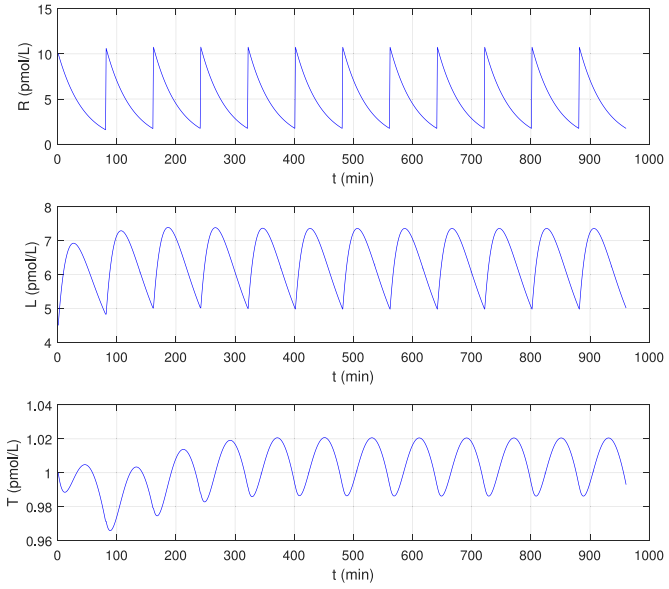

Fig. 3. A solution of the system (17) and (18) under the assumptions of Theorem 2: convergence to the positive 1-cycle.

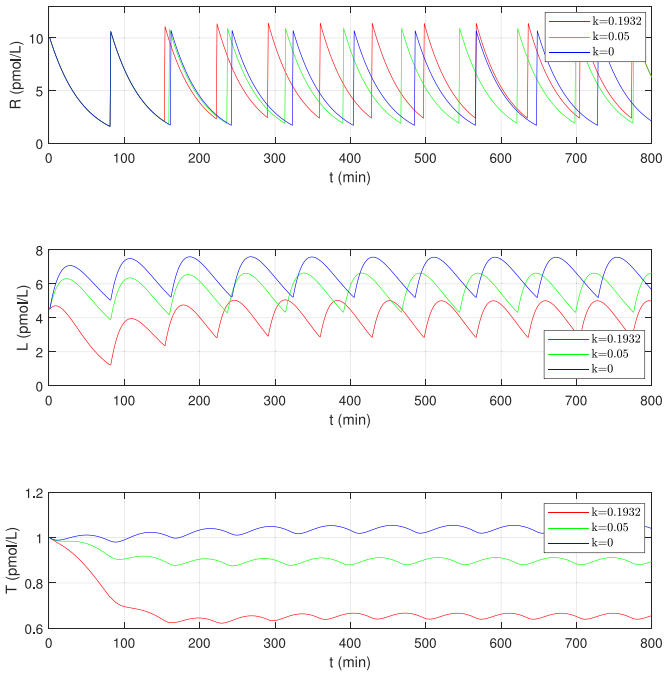

Fig. 4. The effect of local feedback gain k on the solution.

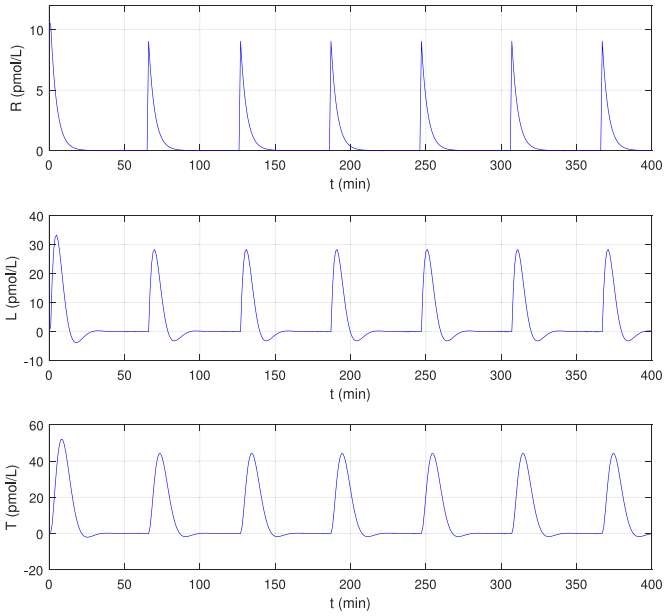

Fig. 5. A partly negative periodic orbit, arising due to violation of (20).

$\mu = 0$, satisfying thus (21) (note that $\rho < 0$) and $k = 0.1 > k_* = 0.0013$. Fig. 5 shows that the unique 1-cycle solution periodically leaves the positive octant, and hence Theorem 2 does not hold.

5. Conclusions

In this paper, a novel model of hypothalamic-pituitary hormonal axis is proposed. It is based on the previously studied model of the impulsive Goodwin's oscillator and captures the structure of the pulse-modulated neuroendocrine regulation mechanism. This mechanism comprising the pulsatile "outer" feedback from a target gland to the hypothalamus and continuous "local" feedback from the gland to the pituitary. The description of the local feedback remains an open problem; to simplify analysis of the model and make it more tractable this

feedback is chosen to be affine. It is demonstrated that the presence of this additional feedback, under natural assumptions, preserves the key property of the impulsive Goodwin's oscillator, namely, the existence of periodic solutions, in particular, the unique *1-cycle* solution featured by one pulse of the release hormone over the least period. The presence of an affine negative feedback gives rise, however, to the problem of solution positivity; in general, the positive orthant fails to be an invariant set. At the same time, natural conditions provide positivity of each periodic trajectory and *ultimate* positivity of the remaining solutions. The mathematical results are illustrated by numerical simulations.

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