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Local and global analysis of endocrine regulation as a non-cyclic feedback system *

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Abstract

To understand the sophisticated control mechanisms of the human's endocrine system is a challenging task that is a crucial step towards precise medical treatment of many dysfunctions and diseases. Although mathematical models describing the endocrine system as a whole are still elusive, recently some substantial progress has been made in analyzing theoretically its subsystems (or *axes*) that regulate the production of specific hormones. Secretion of many vital hormones, responsible for growth, reproduction and metabolism, is orchestrated by feedback mechanisms that are similar in structure to the model of simple genetic oscillators, proposed first by B.C. Goodwin. Unlike the celebrated Goodwin's model, the endocrine regulation mechanisms are in fact known to have *non-cyclic* structures and involve multiple feedbacks; a Goodwin-type model thus represents only a part of such a complicated mechanism. In this paper, we examine a non-cyclic feedback system of hormonal regulation, obtained from the classical Goodwin's oscillator by introducing an additional negative feedback. We establish global properties of this model and show, in particular, that the *local* instability of its unique equilibrium implies that almost all system's solutions oscillate; furthermore, under additional restrictions these solutions converge to periodic or homoclinic orbits.

Key words: Biomedical systems; Stability; Periodic solutions; Oscillations.

1 Introduction

Hormones are signaling molecules that are secreted by glands, transported by blood, and involved in many vital bodily functions. Sophisticated mechanisms of interactions between glands and hormones couple them into the *endocrine system*, whose mathematical modeling remains a challenging problem. However, visible progress has been made in modeling some of its subsystems (or *axes*), responsible for the secretion of specific hormones. In particular, the general control mechanisms in hypothalamic-pituitary (HP) neurohormonal axes,

maintaining processes of growth, metabolism, reproduction and stress resistance, have been revealed (Evans et al. 2009, Stear 1975). Regulatory centers in hypothalamus produce neurohormones, called *releasing hormones* or *releasing factors* (Stear 1975). Each of these hormones stimulates the secretion of the corresponding *tropic* hormone by the pituitary gland, which, in turn, stimulates some target gland or organ to release the *effector* hormone (Fig. 1b). Besides its direct signaling functions, the effector hormone inhibits the production of the corresponding releasing and tropic hormones. These negative feedback loops maintain the concentrations of all three hormones within certain limits.

The understanding of hormonal (in particular, testosterone and cortisol) regulation mechanisms leads to the possibilities of efficient diagnosing and treatment of hormonal dysfunctions and diseases caused by them, such as reproductive failures and prostate cancer (Evans et al. 2009), obesity and aging (Veldhuis 1999) and disorders
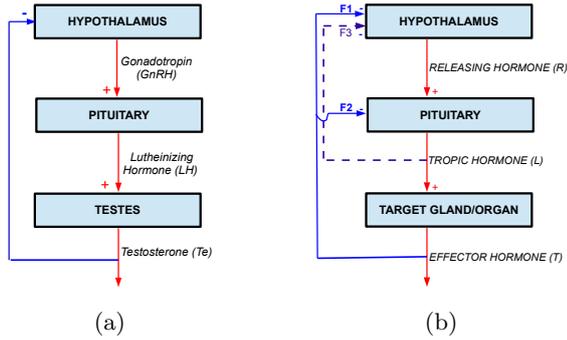
Fig. 1. (a) The cyclic system of testosterone regulation (Churilov et al. 2009, Smith 1980); (b) The structure of a hypothalamic-pituitary axis (Stear 1975).

of the central nervous system (Bairagi et al. 2008). This motivates the development of mathematical models, portraying the complex behavior of hormonal axes.

The blood levels of hormones exhibit both circadian (24-hour) and short-period oscillations (Keenan et al. 2000), resembling the dynamics of the celebrated *Goodwin's oscillator* (Goodwin 1965). Considered as a "prototypical biological oscillator" (Gonze & Abou-Jaoude 2013), Goodwin's model has been extensively used to describe the dynamics of HP axes, e.g. testosterone regulation (Smith 1980). For Goodwin's model and more general *cyclic* feedback systems, profound mathematical results have been established, ensuring the existence of periodic orbits (Hastings et al. 1977, Hori et al. 2011) in the case where the (unique) system's equilibrium is unstable. For the classical model from (Goodwin 1965) such an instability appears to be a restrictive condition; for example, the feedback is described by the conventional Hill function (Gonze & Abou-Jaoude 2013) with the corresponding Hill constant being required to be greater than 8 (Smith 1980, Thron 1991). This restriction can be relaxed, taking into account transport delays (Murray 2002), *pulsatile* secretion of neurohormones (Churilov et al. 2014, 2009, Evans et al. 2009) and stochastic noises (Keenan et al. 2000).

Although relatively well studied, cyclic models of HP axes are restrictive, assuming the presence of only one negative feedback loop, as illustrated by the models of testosterone regulation (Fig. 1a), examined in (Churilov et al. 2009, Smith 1980). The actual mechanism of an HP axis in fact involves multiple feedback loops (Stear 1975): the effector hormones inhibit the secretion of *both* releasing and tropic hormones, closing thus the *long* negative feedback loops (F1, F2 in Fig. 1b). Besides them, the *short* feedback loop (F3) also exists, whose effect, however, is ignored by most of the existing mathematical models of endocrine regulation (Bairagi et al. 2008, Greenhalgh & Khan 2009, Liu & Deng 1991, Sriram et al. 2012, Vinther et al. 2011) since it is much weaker than the long feedbacks and "most vulnerable" (Stear 1975) among the three types of feedback mechanisms.

Mathematical models, taking the existence of multiple feedback loops into account, have been proposed for the testosterone (Greenhalgh & Khan 2009, Liu & Deng 1991, Tanutpanit et al. 2015) and cortisol regulation (Bairagi et al. 2008, Sriram et al. 2012, Vinther et al. 2011). Similar models with multiple feedback loops have been reported to describe the dynamics of some metabolic pathways (Ghomsi et al. 2014, Sinha & Ramaswamy 1987). Unlike the classical Goodwin's oscillator, these models do not have the cyclic structure, which makes the relevant results, ensuring the existence or absence of periodic solutions (Hastings et al. 1977, Hori et al. 2011, Thron 1991), inapplicable. Mathematical studies of such models have been limited to analysis of local stability and Hopf bifurcations.

In this paper, we examine a model of hormonal regulation with two negative feedbacks, originally proposed in (Bairagi et al. 2008) to describe the mechanism of cortisol regulation in the adrenal axis (hypothalamus-pituitary-adrenal cortex). Our simulations (Section 5) show its applicability to testosterone regulation modeling. The model is similar in structure to the classical Goodwin's oscillator, but involves two the negative feedbacks (F1, F2 in Fig. 1b) from the effector hormone to the releasing and tropic hormones. Unlike the original model in (Bairagi et al. 2008), we do not restrict these nonlinearities to be identical or Hill functions. To keep the analysis concise, in this paper we neglect the transport delays, discontinuities, describing the pulsatile secretion of neurohormones, and the effects of stochastic noises. For the model in question, we develop the "global" theory, showing that its properties are similar to those of the Goodwin's oscillator, e.g. under some assumptions, the *local* instability of the equilibrium implies the existence of periodic orbits and, furthermore, the convergence of *almost any* solution to such an orbit.

This paper is organized as follows. Section 2 introduces the model in question, whose local stability properties are examined in Section 3. Section 4 presents the main results of the paper, concerned with global properties of the system. Section 5 illustrates the model in question by numerical simulations. The results of the paper are proved in Section 6. Section 7 concludes the paper.

2 The Goodwin-Smith model and its extension

We start with the conventional Goodwin's model (Goodwin 1965), describing a self-regulating system of three chemicals, whose concentrations are denoted by R, L and T and evolve in accordance with the following equations

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

Our notation follows (Smith 1980), where Goodwin's oscillator was proposed for modeling of the gonadal axis in male (Fig. 1a) and R, L, T stood, respectively, for the blood levels of the gonadotropin-releasing hormone (GnRH), lutheinizing hormone (LH) and testosterone (Te). The constants $b_1, b_2, b_3 > 0$ are the clearing rates of the corresponding chemicals, whereas the constants $g_1, g_2 > 0$ and the nonnegative decreasing function $f(T)$ determine their production rates. Often $f(\cdot)$ stands for the *Hill function* (Gonze & Abou-Jaoude 2013)

$$f(T) = \frac{K}{1 + \beta T^n}, \qquad K, \beta, n > 0. \qquad (2)$$

The releasing factor (R) drives the production of the tropic hormone (L), which in turn stimulates the secretion of the effector hormone (T). The effector hormone *inhibits* the production of the releasing factor: an increase in T reduces the production rate $\dot{R}$, and vice versa.

In this paper, we consider a generalization of Goodwin's oscillator (1), including *two* negative feedbacks

$$\begin{aligned}
\dot{R} &= -b_1 R + f_1(T), \\
\dot{L} &= g_1 R - b_2 L + f_2(T), \qquad (3) \\
\dot{T} &= g_2 L - b_3 T.
\end{aligned}$$

A special case of (3), where f_1 and f_2 stand for the Hill nonlinearities with the same Hill constant n has been proposed in (Bairagi et al. 2008) to describe the dynamics of *adrenal* axis: R, L, T stand, respectively, for the levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol. The nonlinearities f_1 and f_2 describe respectively the negative feedbacks F1 and F2 in Fig. 1b; the effect of short negative feedback (F3) is neglected. Unlike (Bairagi et al. 2008), these nonlinear maps are *not necessarily* identical or Hill functions. As discussed in (Vinther et al. 2011), dealing with a similar model of cortisol regulation, the natural assumptions on these functions are their non-negativity (which prevents the solutions from leaving the domain where $R, L, T \geq 0$). Moreover, it is natural to assume that $f_1(T) > 0$ since "the feedbacks must not shut down hormone production completely" (Vinther et al. 2011). Similar to the Goodwin's model, two feedbacks are inhibitory, which implies that f_1 and f_2 are non-increasing. We thus adopt the following assumption.

Assumption 1 *The functions $f_1 : [0; \infty) \to (0; \infty)$ and $f_2 : [0; \infty) \to [0; \infty)$ are continuously differentiable and non-increasing, i.e. $f_1'(T), f_2'(T) \leq 0$ for any $T \geq 0$. The parameters $b_1, b_2, b_3, g_1, g_2 > 0$ are constant.*

Notice that we allow that $f_2(T) \equiv 0$; all of the results, obtained below, are thus applicable to the classical Goodwin's oscillator (1). However, we are mainly interested in the case where $f_2 \not\equiv 0$, which leads to the *non-cyclic*

structure of the system and makes it impossible to use mathematical tools developed for cyclic systems, such as criteria for global stability and the existence of periodic solutions existence (Hastings et al. 1977, Hori et al. 2011, Thron 1991). Unlike the existing works on multi-feedback models of hormonal regulation (Bairagi et al. 2008, Greenhalgh & Khan 2009, Liu & Deng 1991, Sriram et al. 2012, Tanutpanit et al. 2015, Vinther et al. 2011), our examination of model (3) is not limited to local stability and bifurcation analyses. We are primarily interested in the *interplay* between local and global properties, revealed for the classical Goodwin's oscillator, namely, the existence of oscillatory solutions, provided that the (only) system's equilibrium is unstable.

3 Equilibria and local stability properties

Since R, L and T stand for the chemical concentrations, one is interested in the solutions, staying in the positive octant $R(t), L(t), T(t) \geq 0$. Since $f_i(T) \leq f_i(0)$ for all $T > 0$, all solutions are bounded and exist up to ∞.

The following properties of the system's equilibrium can be proved (Taghvafard et al. 2016). Assumption 1 implies that (3) has a unique equilibrium point $E^0 = (R^0, L^0, T^0)$, where $T^0 > 0$ is the unique root of

$$\frac{b_1 b_2 b_3}{g_1 g_2} T^0 - \left[f_1(T^0) + \frac{b_1}{g_1} f_2(T^0) \right] = 0, \qquad (4)$$

and $R^0 = \frac{1}{b_1} f_1(T^0), L^0 = \frac{b_3}{g_2} T^0$. Denoting

$$\begin{aligned}
\Theta_0 &\triangleq a_3 - a_1 a_2 + g_2 \left[(b_2 + b_3) f_2'(T^0) - g_1 f_1'(T^0) \right], \\
a_1 &\triangleq b_1 + b_2 + b_3, a_2 \triangleq b_1 b_2 + b_1 b_3 + b_2 b_3, a_3 \triangleq b_1 b_2 b_3, \\
& \qquad (5)
\end{aligned}$$

the local stability properties of the equilibrium are given by the following lemma (Taghvafard et al. 2016).

Lemma 2 *System (3) has the unique equilibrium E^0 in the positive octant. In both cases of $\Theta_0 < 0$ and $\Theta_0 > 0$, the equilibrium E^0 is hyperbolic [1] . If $\Theta_0 = 0$, then the two eigenvalues are complex-conjugated imaginary numbers.*

In general biochemical systems locally stable equilibria may coexist with periodic solutions. At the same time, for Goodwin's oscillator (1) the necessary and sufficient for local stability and sufficient conditions of the *global* stability are in fact very close (Thron 1991), so the equilibrium's instability is often considered as the requirement of the biological feasibility. It is known, for instance, that Goodwin's oscillators with unstable equilibria have periodic orbits (Hastings et al. 1977, Hori

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[1] An equilibrium p of the system $\dot{x} = f(x)$ is *hyperbolic* if the Jacobian $f'(p)$ has no eigenvalues with zero real parts.

et al. 2011). After the publication of the seminal Goodwin's paper (Goodwin 1965), it was noticed (Griffith 1968, Smith 1980, Thron 1991) that for the Hill nonlinearity (2) the equilibrium can be unstable (for some choice of the parameters b_i, g_i) if and only if $n > 8$. The following theorem extends the latter result to the generalized system (3) and arbitrary decreasing functions $f_1(T), f_2(T)$. We introduce an auxiliary function

$$M(T) \triangleq -T f_1'(T)/f_1(T) > 0, \qquad \forall T > 0. \quad (6)$$

Theorem 3 *Let the functions f_1, f_2 satisfy Assumption 1. Then the following statements hold:*

(1) if $M(T) < 8 \, \forall T > 0$ then $\Theta_0 < 0$ for any choice of $b_i, g_i > 0$: the equilibrium of (3) is stable;

(2) if $M(T) \leq 8 \, \forall T > 0$ then $\Theta_0 \leq 0$ for any $b_i, g_i > 0$; the inequality is strict if $f_2(T) > 0$ for any $T > 0$;

(3) if $M(T) > 8$ for some $T > 0$ then there exist parameters b_i, g_i such that the equilibrium is unstable ($\Theta_0 > 0$) and, furthermore, the system has at least one non-constant periodic solution.

Theorem 3 will be proved in Section 6. For the usual Goodwin-Smith model (1) it has been established in (Smith 1980). The existence of periodic solutions in statement (3) is based on the Hopf bifurcation theorem (Poore 1976). However, the proof substantially differs from most of the existing results on the Hopf bifurcation analysis in *delayed* biological oscillators (Greenhalgh & Khan 2009, Sun et al. 2016), proving the bifurcations at the "critical" delay values, under which the equilibrium loses its stability. In the undelayed case, it is non-trivial to construct a one-parameter family of systems (3), satisfying the conditions of the Hopf bifurcation theorem. For model (1), such a parametrization has been proposed in (Smith 1980), however, the complete proof of the bifurcation existence has remained elusive.

Remark 4 *Theorem 3 does not imply that a periodic solution exists for **any** system (3) with unstable equilibrium. The corresponding strong result holds for cyclic systems (Hastings et al. 1977, Hori et al. 2011). In Section 4 we extend it to the broad class of system (3), whose nonlinearities $f_2(\cdot)$ satisfy a special slope restriction.*

Remark 5 *Although the conditions ensuring the equilibrium's global attractivity in the positive octant are close to the local stability, the Hopf bifurcation analysis in Section 6 shows that in the case where $M(T) > 8$, there always exists a set of parameters b_i and g_i, for which (3) has a periodic solution in spite of the locally stable equilibrium. The existence of cycles for $M(T) \leq 8$ seems to be an open problem even for the Goodwin's model (1).*

Applying Theorem 3 to the case where $f_1(T)$ is the Hill function (2), one has $M(T) = -\frac{T f_1'(T)}{f_1(T)} = n \frac{\beta T^n}{1 + \beta T^n}$ and

the condition $M(T) > 8$ reduces to the well-known condition $n > 8$. Although Hill's exponents $n > 4$ are often considered to be non-realistic, Goodwin's models with $n > 8$ adequately describe some metabolic reactions and also arise from *model reduction* procedures (Gonze & Abou-Jaoude 2013), approximating a long chain of chemical reactions by a lower-dimensional system.

4 Oscillatory properties of the solutions

In the case of the classical Goodwin-Smith model (1) ($f_2 \equiv 0$), it is widely known that the local instability implies the existence of at least one periodic trajectory. A general result from (Hastings et al. 1977) establishes this for a general *cyclic* system (with a sufficiently smooth right-hand side). The cyclic structure of the system and the equilibrium's instability imply the existence of an *invariant toroidal domain* (Hastings et al. 1977), and closed orbits in it correspond to fixed points of the Poincaré map. This result, however, is not applicable to system (3). Another approach, used in (Hori et al. 2011) to examine oscillations in genetic regulatory circuits, employs elegant results by Mallet-Paret (Mallet-Paret & Sell 1996, Mallet-Paret & Smith 1990), extending the Poincaré-Bendixson theory to Goodwin-type systems.

At the same time, when $\Theta_0 > 0$, one is able to prove that almost all solutions are oscillatory in the sense that they are bounded yet non-convergent. This oscillatory property was introduced by V.A. Yakubovich (Yakubovich 1973).

4.1 Yakubovich-oscillatory solutions

We start with the definition (Pogromsky et al. 1999).

Definition 6 *A bounded function $\varrho : [0; \infty) \to \mathbb{R}$ is called Y-oscillatory (Yakubovich-oscillatory), if $\varliminf_{t \to \infty} \varrho(t) < \varlimsup_{t \to \infty} \varrho(t)$. A bounded map $x : [0; \infty) \to \mathbb{R}^m$ is Y-oscillatory if some its element $x_i(\cdot)$ is Y-oscillatory.*

Using Theorem 1 in (Pogromsky et al. 1999), and Lemma 2, the following result is derived.

Lemma 7 *Suppose that system (3) has an unstable equilibrium ($\Theta_0 > 0$). Then for any initial condition $(R(0), L(0), T(0))$, except for the points from some set of zero Lebesgue measure, the corresponding solution $(R(t), L(t), T(t))$ is Y-oscillatory as $t \to \infty$.*

Any periodic solution is Y-oscillatory, and the same holds for solutions converging to periodic orbits. In general, a dynamical system can have other Y-oscillatory solutions, e.g. showing chaotic behavior. It is known, however, that solutions of the conventional Goodwin-Smith model (1) and many other cyclic feedback systems (Hori et al. 2011) in fact exhibit a very regular

behavior, similar to that of planar (two-dimensional) systems (Mallet-Paret & Sell 1996, Mallet-Paret & Smith 1990). A natural question, addressed in the next subsection, is the applicability of the Mallet-Parret's theory to the extended model (3).

4.2 The Mallet-Parret theorem for the extended Goodwin-Smith model: the structure of ω-limit set

The widely-known Poincaré-Bendixson theory for planar autonomous (time-invariant) systems states that the ω-limit set of a bounded solution can be a closed orbit, an equilibrium point or union of several equilibria and heteroclinic[2] trajectories, converging to them (it is possible that $\omega(x)$ is a union of an equilibrium and homoclinic trajectory, converging to it). Although this result is not applicable to the system of order 3 or higher, it remains valid for *cyclic* systems (Hori et al. 2011, Mallet-Paret & Smith 1990) and some tridiagonal systems (Elkhader 1992, Mallet-Paret & Sell 1996). For the reader's convenience, we formulate the corresponding result.

Consider the dynamical system of order $N + 1$, where $N \geq 2$, described by the equations

$$
\begin{aligned}
\dot{x}_0 &= h_0(x_0, x_1) \\
\dot{x}_i &= h_i(x_{i-1}, x_i, x_{i+1}), \quad i = 1, \dots, N-1 \quad (7) \\
\dot{x}_N &= h_N(x_{N-1}, x_N, x_0),
\end{aligned}
$$

Here the functions $h_0(\xi, \zeta)$ and $h_i(\eta, \xi, \zeta)$, $(i = 1, \dots, N)$, are C^1-smooth and *strictly* monotone in ζ; the functions $h_i(\eta, \xi, \zeta)$ for $i = 1, \dots, N$ are also nonstrictly monotone in η. That is, the ith chemical (where $i \geq 1$) influences the production rate of the $(i-1)$th one, and the 0th chemical influences the production of the Nth one. Chemical i (where $i < N$) may influence the production of chemical $(i + 1)$, however, it is allowed that $\frac{\partial h_{i+1}}{\partial x_i} \equiv 0$. The central assumption is that if the influences between "adjacent" chemicals are *equally signed* (being either both stimulatory or inhibitory)

$$
\frac{\partial h_{i+1}}{\partial x_i} \frac{\partial h_i}{\partial x_{i+1}} \geq 0, \qquad \forall i = 0, 1, \dots, N-1. \quad (8)
$$

Applying a simple change of variables, without loss of generality (Mallet-Paret & Sell 1996) assume that

$$
\frac{\partial h_i(\eta, \xi, \zeta)}{\partial \eta} \geq 0, \; \delta_i \frac{\partial h_i(\eta, \xi, \zeta)}{\partial \zeta} > 0, \delta_i = \begin{cases} 1, & i < N, \\ \pm 1, & i = N. \end{cases} \quad (9)
$$

We are interested in tridiagonal systems (7) with a single equilibrium, for which the result of (Mallet-Paret & Sell 1996, Theorem 2.1) reduces[3] to the following lemma.

Lemma 8 *Let the C^1-smooth nonlinearities h_i in (7) satisfy the conditions (8) and the system has only one equilibrium. Then the ω-limit set of any bounded solution can have one of the following structural types: (a) closed orbit; (b) union of the equilibrium point and a homoclinic trajectory; (c) the equilibrium point (singleton).*

Note that the "sign-symmetry" assumption (8) is violated in system (3): the effector hormone's (T) production is driven by the tropic hormone (L) and, at the same time, inhibits the secretion of L (Fig. 1a). So Lemma 8 cannot be *directly* applied to system (3). To overcome this problem, we show that there exists a one-to-one mapping $(R, L, T) \to (x_0, x_1, x_2)$ which transforms system (3) into the "canonical" form (9) with $N = 3$ and $\delta_N = -1$. This allows to prove our main result.

Theorem 9 *Suppose that Assumption 1 holds and*

$$
\sup_{T \geq 0} |f_2'(T)| \leq \frac{(b_3 - b_2)^2}{4g_2}. \quad (10)
$$

Then any solution of (3) has the ω-limit set of one of the three types, listed in Lemma 8. If the equilibrium is unstable, then almost any solution converges to either a periodic orbit or the closure of a homoclinic trajectory.

It should be noticed that (10) automatically holds for the classical Goodwin's oscillator (1) (and, more generally, when f_2 is constant); Furthermore, if the equilibrium is unstable, system (1) cannot have homoclinic orbits (Hori et al. 2011). This leads to the following corollary.

Corollary 10 *If system (1) has an unstable equilibrium, then it also has a (non-trivial) periodic orbit. Moreover, almost any solution converges to such an orbit.*

Whereas the first statement of Corollary 10 has been established for a very broad class of cyclic systems (Hastings et al. 1977), the second statement, confirmed by numerical simulations, still has not been proved mathematically. For a general system (3), the inequality (10) restricts the slope of the nonlinear function $f_2(\cdot)$. Numerical experiments, shown in Section 5, show that this condition is only sufficient, and the solutions' may converge to the periodic orbit even when it is violated.

---

[2] Given a dynamical system $\dot{x} = f(x) \in \mathbb{R}^m$, its *heteroclinic* solution is a globally defined non-constant solution $x(t) : (-\infty; \infty) \to \mathbb{R}^m$, whose limits at ∞ and $-\infty$ are equilibria. If these limits coincide, the solution is called *homoclinic*.

[3] Formally, the paper (Mallet-Paret & Sell 1996) deals with delay systems, explicitly assuming that the delay is non-zero. The results are, however, valid for tridiagonal systems (7) without delays; as mentioned in (Mallet-Paret & Sell 1996, p. 442), the corresponding result (under some additional restrictions) has been established in (Elkhader 1992).

5 Numerical simulation

In this section, we give a numerical simulation, which allows to compare the behaviors of systems (1) and (3). The model parameters $b_1 = 0.1$ min^{-1}, $b_2 = 0.015$ min^{-1}, $b_3 = 0.023$ min^{-1}, $g_1 = 5$ min^{-1} and $g_2 = 0.01$ min^{-1} are chosen to comply with the experimental data reported in (Cartwright & Husain 1986, Das et al. 1994).

The functions $f_1(T), f_2(T)$ are chosen of the Hill-type. Following (Das et al. 1994), the parameters of f_1 are considered to be $K_1 = \beta_1 = n = 20$. To show the effect of the additional feedback f_2 on the oscillations of hormones, its parameters are chosen to be $K_2 = n = 20$ and $\beta_2 = 10$. A straightforward calculation shows that the equilibria of systems (1) and (3) are given by $E^{GS} = (0.0098, 3.2529, 1.4143)$ and $E^{New} = (0.0094, 3.2589, 1.4169)$, respectively. Moreover, the quantity Θ_0, defined in (5), for systems (1) and (3) is given by $\Theta_0^{GS} = 1.5207 \times 10^{-4}$ and $\Theta_0^{New} = 1.1590 \times 10^{-4}$, confirming the instability of equilibria. Both systems (1) and (3) are plotted in Fig. 2 for a time period of 24 hours with the same parameters and initial conditions $(R(0), L(0), T(0)) = (1\ pg/ml,\ 6\ ng/ml,\ 2\ ng/ml)$. Although nonlinearity f_2 considered in the example does not satisfy condition (10), system (3) still have oscillatory behavior for parameters b_i and g_i considered above. As it is observed in Fig. 2, after some time, both amplitude and period of the oscillations of R, L and T in system (3) become less than the corresponding ones in system (1). The amplitudes of oscillation for systems (1) and (3), calculated numerically, are given by $A^{GS} \approx (52\ pg/ml,\ 3.64\ ng/ml,\ 0.58\ ng/ml)$, and $A^{New} \approx (41.75\ pg/ml,\ 3.04\ ng/ml,\ 0.46\ ng/ml)$, respectively. Furthermore, the periods of oscillation for systems (1) and (3) are given by $P^{GS} \approx 1.870$ and $P^{New} \approx 1.755$. So the feedback $f_2(\cdot)$ influences both the amplitude and period of oscillations.

6 Proofs of Theorems 3 and 9

We start with the proof of Theorem 3, extending the proofs from (Griffith 1968) and (Smith 1980). The proof employs the widely known McLaurin's inequality for the case of three variables implies (Smith 1980) that

$$\frac{(b_1 + b_2 + b_3)(b_1 b_2 + b_1 b_3 + b_2 b_3)}{b_1 b_2 b_3} \geq 9. \qquad (11)$$

Another result, used in the proof, is the Hopf bifurcation theorem (Poore 1976). This theorem deals with a one-parameter family of dynamical systems

$$\dot{x} = F(x, \mu), \quad \mu \in (-\varepsilon; \varepsilon). \qquad (12)$$

It is assumed that for $\mu = 0$, the system has an equilibrium at x_0, for which $F(x, \mu)$ is C^1-smooth in the vicin-
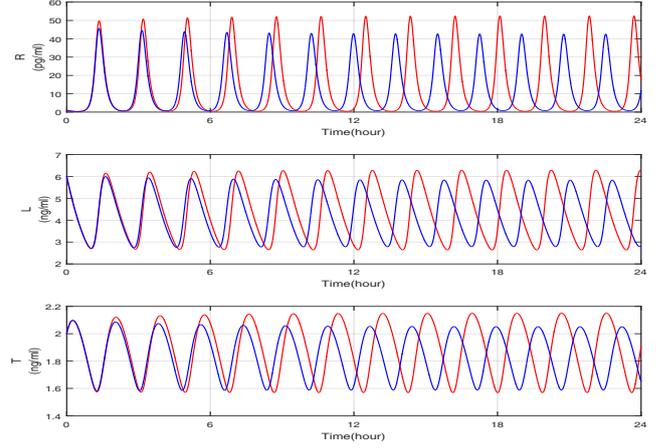

Fig. 2. Red and blue plots show numerical simulations of systems (1) and (3), respectively, with the same initial conditions and parameter values.

ity of $(x_0, 0)$, the Jacobian matrix $D_x F(x_0, 0)$ has a pair of simple imaginary eigenvalues $\pm \imath \omega_0$ (where $\omega_0 \neq 0$) and all other eigenvalues have non-zero real parts. The implicit function theorem implies that for $\mu \approx 0$ there exists an equilibrium point $x(\mu)$ of system (12) such that $x(0) = x_0$. The corresponding Jacobian $D_x F(x(\mu), \mu)$ has a pair of complex-conjugated eigenvalues $\alpha(\mu) \pm \imath \omega(\mu)$ with $\alpha(0) = 0$ and $\omega(0) = \omega_0$. The Hopf bifurcation theorem is as follows (Poore 1976, Theorem 2.3).

Theorem 11 *If $\alpha'(0) \neq 0$, the dynamical system (12) undergoes the Hopf bifurcation at $\mu = 0$, that is, there exist $\varepsilon_0 > 0$ such that for any $\mu \in (-\varepsilon_0, \varepsilon_0) \setminus \{0\}$ system (12) has a non-trivial periodic solution.*

Proof of Theorem 3. Let (R^0, L^0, T^0) be an equilibrium of (3) for some choice of $b_i, g_i > 0$. Using (4), one has

$$g_2 = \frac{b_1 b_2 b_3 T^0}{g_1 f_1(T^0) + b_1 f_2(T^0)}. \qquad (13)$$

Substituting (13) into (5) and dividing by $(b_1 b_2 b_3)$, the inequality (11) and Assumption 1 imply the following

$$\frac{\Theta_0}{b_1 b_2 b_3} = \underbrace{\frac{T^0 (b_2 + b_3) f_2'(T^0)}{g_1 f_1(T^0) + b_1 f_2(T^0)}}_{\leq 0} + \underbrace{\frac{g_1 (-T^0 f_1'(T^0))}{g_1 f_1(T^0) + b_1 f_2(T^0)}}_{\leq M(T^0)}$$
$$- \frac{(b_1 + b_2 + b_3)(b_1 b_2 + b_1 b_3 + b_2 b_3)}{b_1 b_2 b_3} + 1 \leq M(T^0) - 8. \qquad (14)$$

The inequality (14) is strict unless $b_1 = b_2 = b_3$ and $f_2(T^0) = f_2'(T^0) = 0$, implying thus statements 1 and 2.

We are now going to prove statement 3. Supposing that $M(T^0) > 8$ for some $T^0 > 0$, let $R^0 = \frac{1}{b_1} f_1(T^0)$ and $L^0 = \frac{b_3}{g_2} T^0$. It can be easily noticed from (4) that any system (3), whose parameters satisfy the condition (13),

has the equilibrium at (R^0, L^0, T^0). We are now going to design a one-parameter family of systems (3) with this equilibrium. To do this, we fix $b_1 = b_2 = b_3 = b$ (where $b > 0$ is chosen arbitrarily) and determine g_2 from (13), leaving the parameter $g_1 > 0$ free. It can be easily noticed from (14) that $\Theta_0 = \Theta_0(g_1)$ is a smooth and strict increasing function of g_1, $\lim_{g_1 \to 0} \Theta_0(g_1) < 0$ and $\lim_{g_1 \to \infty} \Theta_0(g_1) = M(T^0) - 8 > 0$. Thus for sufficiently large $g_1 > 0$, the system has an unstable equilibrium point. Furthermore, for $\varepsilon > 0$ sufficiently small, the image of $\Theta_0(\cdot)$ contains the interval $(-\varepsilon; \varepsilon)$; therefore, one can define the smooth inverse function $g_1 = g_1(\mu)$ in such a way that $\Theta_0(g_1(\mu)) = \mu$ for any $\mu = (-\varepsilon; \varepsilon)$.

We now claim that the one-parameter family of systems (3) with $b_1 = b_2 = b_3 = b > 0$, $g_1 = g_1(\mu)$ and $g_2 = g_2(\mu)$ determined by (13) satisfies the conditions of Hopf bifurcation theorem (Theorem 11). By definition, the Routh-Hurwitz discriminant (5), corresponding to a specific μ, equals $\Theta_0(g_1(\mu)) = \mu$; by Lemma 2 the system with $\mu = 0$ has a pair of pure imaginary eigenvalues. Considering the extension of these eigenvalues $\alpha(\mu) \pm \imath\omega(\mu)$ for $\mu \approx 0$, and introducing a_i by (5), it can be shown (Taghvafard et al. 2016, Appendix A) that

$$2\alpha(\mu) \left[(a_1 + 2\alpha(\mu))^2 + (a_2 - g_2(\mu)f_2'(T^0)) \right] = \mu \quad (15)$$

Differentiating (15) at $\mu = 0$ and recalling that $\alpha(0) = 0$, one shows that $\alpha'(0) = \frac{1}{2\left[a_1^2 + (a_2 - g_2(0)f_2'(T^0)\right]} > 0$. Hence for $\mu \in (0; \varepsilon_0)$ (where $\varepsilon_0 > 0$) the constructed system (3) has an unstable equilibrium at (R^0, L^0, T^0) and at least one periodic solution. Notice that for $\mu \in (-\varepsilon_0; 0)$ the system also has a periodic solution in spite of the equilibrium's local stability (see Remark 5). $\square$

Proof of Theorem 9.

The proof is based on the linear change of variables $(R, L, T) \mapsto (x_0, x_1, x_2)$, where $x_0 \triangleq T$, $x_1 \triangleq L + aT$ and $x_2 \triangleq R$ and $a \in \mathbb{R}$ is a constant to be specified later. Under this transformation, (3) shapes into (7), where

$$h_0(x_0, x_1) \triangleq g_2(x_1 - ax_0) - b_3 x_0,$$
$$h_1(x_0, x_1, x_2) \triangleq \left(a(b_2 - b_3) - a^2 g_2\right) x_0 + f_2(x_0) +$$
$$+ g_1 x_2 + (ag_2 - b_2)x_1,$$
$$h_2(x_1, x_2, x_0) \triangleq -b_1 x_2 + f_1(x_0).$$

Since $g_1, g_2 > 0$, the conditions (9) hold if $\frac{\partial h_1}{\partial x_0} \geq a(b_2 - b_3) - g_2 a^2 - \sup |f_2'(x_0)| \geq 0$. Due to the condition (10), this inequality can be provided by choosing appropriate $a \in \mathbb{R}$. Theorem 9 now follows from Lemmas 7 and 8. $\square$

7 Conclusions and future works

A mathematical model for endocrine regulation has been examined, which extends the conventional Goodwin's model by introducing an additional negative feedback. We have studied the local properties of the extended model and their relations to *global* properties, showing that the (locally) unstable equilibrium implies that almost all solutions oscillate and (under some conditions) converge to periodic orbits. The results are based on the general criterion of oscillation existence (Smith 1980) and the Mallet-Parret theory (Mallet-Paret & Sell 1996); they can be extended to many other models, e.g. the model from (Vinther et al. 2011). The relevant extensions are however beyond the scope of this manuscript due to the page limit. Further extensions of the model, including transport delays and pulsatile feedback are the subject of ongoing research.

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