Automatica 91 (2018) 190–196

Contents lists available at ScienceDirect

Automatica

journal homepage: www.elsevier.com/locate/automatica

Brief paper

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

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ARTICLE INFO

Article history:
Received 17 October 2016
Received in revised form 16 October 2017
Accepted 1 December 2017

Keywords:
Biomedical systems
Stability
Periodic solutions
Oscillations

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.

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, Farhy & Johnson, 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 of the central nervous system (Bairagi, Chatterjee & Chattopadhyay, 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, Sun, & Veldhuis, 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

☆ The material in this paper was partially presented at the 6th IFAC International Workshop on Periodic Control Systems (PSYCO'16) June 29–July 1, 2016 Eindhoven, The Netherlands. This paper was recommended for publication in revised form by Associate Editor Jun-ichi Imura under the direction of Editor Thomas Parisini.

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https://doi.org/10.1016/j.automatica.2018.01.035
0005-1098/

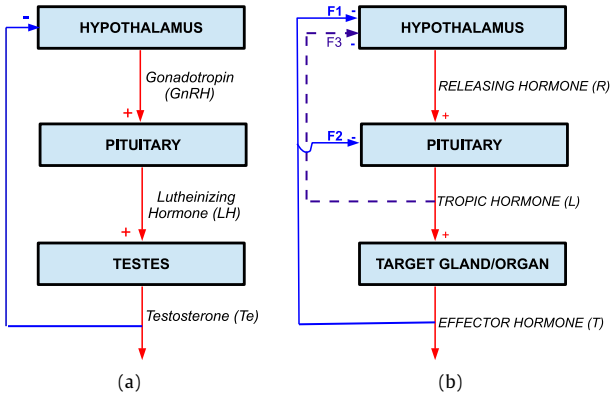

Fig. 1. (a) The cyclic system of testosterone regulation (Churilov, Medvedev & Shepeljavyi, 2009; Smith, 1980); (b) The structure of a hypothalamic-pituitary axis (Stear, 1975).

general *cyclic* feedback systems, profound mathematical results have been established, ensuring the existence of periodic orbits (Hastings, Tyson, & Webster, 1977; Hori, Kim, & Hara, 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, Medvedev, & Mattsson, 2014; Churilov et al., 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) and 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, Rodriguez-Fernandez, & Doyle, 2012; Vinther, Andersen, & Ottesen, 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, Pongsumpun, & Tang, 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, Kakmeni, Kofane & Tchawoua, 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), luteinizing 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)

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

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

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

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