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Stability properties of the Goodwin-Smith oscillator model with additional feedback ⋆

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Abstract: The Goodwin oscillator is a simple yet instructive mathematical model, describing a wide range of self-controlled biological and biochemical processes, among which are self-inhibitory metabolic pathways and genetic circadian clocks that lead to important applications, such as the *hormonal* cycles modeling. Indeed, one of the first models of hormonal rhythm, squarely based on the conventional Goodwin oscillator, was suggested by W.R. Smith to describe the testosterone regulation in male and is often referred to as the Goodwin-Smith model. The Goodwin-Smith model describes an endocrine regulatory circuit, consisting of three hormones. Gonadotropin-releasing hormone controls the secretion of the luteinizing hormone, which influences the secretion of testosterone. In its turn, testosterone inhibits the secretion of gonadotropin, which effect is represented by the nonlinear *feedback*. Further theoretical and experimental works on hormonal regulation revealed that the structure of this control circuit is in fact more complicated, since the testosterone directly influences the secretion of both precursor hormones. This motivates us to consider the modified Goodwin-Smith model with some additional negative feedback loop. The potential applications of such an extended model are not limited to hormonal regulation; similar models, where extra feedbacks can be either positive or negative, arise in metabolic reactions. We show that many basic properties of the Goodwin-Smith model retain their validity, after introducing an additional feedback, which include the existence and uniqueness of equilibria, Hopf bifurcation, and the existence of periodic solutions.

Keywords: Hormonal regulation, Goodwin-Smith model, Stability, Hopf Bifurcation

1. INTRODUCTION

In the seminal paper Goodwin (1965) a simple yet instructive model of a self-regulating biochemical system was proposed, which consists of a chain of biochemical reactions. The product of each reaction in the chain activates the next reaction, whereas the last product inhibits the first reaction in the chain, closing thus a *negative feedback* loop. The original model from Goodwin (1965), referred to as the *Goodwin oscillator*, describes a chain of three reactions; this chain is modeled by Lur'e type-system, i.e. the feedback interconnection of a linear part and nonlinearity. The linear part stands for the system of biochemical reactions, whereas the nonlinearity, described by the Hill function Murray (2002), represents the inhibitory feedback. The Goodwin oscillator, along with its extensions, is used to model genetic oscillatory circuits and circadian clocks Murray (2002); Gonze et al. (2005) and metabolic pathways Costalat and Burger (1996). One of the most important applications of the Goodwin oscillators is the model of a hormonal cycle, originating from the seminal works Smith (1980, 1983) and often referred to as the *Goodwin-Smith* model Churilov and Medvedev (2014).

The study of hormonal regulatory processes and their mathematical modeling are essential for identification of the culprits in their disfunction and the corresponding effective prophylaxis and medical treatment. More important for systems and control scientists, hormonal regulatory processes are complex dynamical biological systems interacting through feedback (inhibitory) and feed-forward (stimulatory) controls Veldhuis (1999). The papers Smith (1980, 1983) proposed a model for the testosterone regulation in male. The testosterone is an extremely important hormone whose regular imbalance can cause dramatic changes Murray (2002) such as reproductive failures and prostate cancer; its regulation is believed to play an important role in the aging process Veldhuis (1999). Smith investigated a three-dimensional dynamical system, where the elements of the state vector stand for chemical concentrations of the Gonadotropin-Releasing Hormone (GnRH), Luteinising Hormone(LH) and Testosterone (Te). GnRH, secreted in hypothalamus, controls the secretion of LH in the pituitary gland; LH stimulates the secretion of testosterone in testes which, in its turn, inhibits the secretion of

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GnRH. To model this endocrine feedback circuit, called GnRH-LH-Te axis, the conventional Goodwin oscillator was used and, later, its delayed extension Smith (1983).

Further experimental studies of the testosterone regulation revealed that in the testosterone regulation circuit another negative feedback exists, namely, Te directly inhibits LH Veldhuis et al. (2009); Sheckter et al. (1989); Bing-Zheng and Gou-Min (1991). This motivates to consider the extended Goodwin-Smith model, incorporating the direct negative feedback from Te to LH. Usually, the negative feedback is represented by a Hill-type nonlinearity, however, as will be shown, in fact one can use any positive strictly decreasing function. Furthermore, it appears that introduction of this feedback *does not* change many basic properties of the Goodwin-Smith model such as e.g. the existence and uniqueness of the positive equilibrium point, the Hopf bifurcation as its stability switches to instability and the existence of periodic solutions when the equilibrium is unstable. This differs our model from other models of testosterone regulations with addition feedback from Te to LH, e.g. that proposed in Greenhalgh and Khan (2009). The model from Greenhalgh and Khan (2009) has no positive equilibrium, removing the direct feedback from Te to LH, and even in presence of such a feedback the equilibrium exists only for special choice of parameters.

It should be noticed that the potential applications of such an extended model are not limited to hormonal regulation; similar Goodwin-like models with "extra" feedbacks may arise in some metabolic reactions Ghomsi et al. (2014).

2. THE EXTENDED GOODWIN-SMITH MODEL WITH ADDITIONAL FEEDBACK

The original Goodwin-Smith model for testosterone regulation Smith (1980) describes the dynamics of of three hormones GnRH (gonadotropin release hormone), LH (luteinizing hormone) and Te (testosterone). Denoting the respective serum concentrations with R, L and T, the dynamics obeys the conventional model Goodwin (1965)

$$\begin{cases} \dot{R} = -b_1 R + f_1(T), \\ \dot{L} = g_1 R - b_2 L, \\ \dot{T} = g_2 L - b_3 T, \end{cases} \tag{1}$$

Here b_1, b_2 and b_3 are positive constants, describing clearing rates of GnRH, LH and Te respectively. The constants $g_1, g_2 > 0$ and a positive decreasing function $f_1(\cdot)$ stand for the corresponding secretion rates. Usually, the function $f_1(T)$ is the Hill-type nonlinearity Murray (2002), that is

$$f_1(T) = \frac{K}{1 + \beta T^n}, \tag{2}$$

where $K, \beta, n > 0$. The number n, often chosen natural, is referred to as the *Hill constant*, which has a chemical interpretation Gonze and Abou-Jaoude (2013).

The Goodwin-Smith model has been extensively studied; the central result, valid in fact for much more general cyclic feedback systems Hori et al. (2011), states that *instability* of (the only) equilibrium point implies the existence of a stable periodic solution. As will be discussed later, in fact almost any solution converges to a periodic orbit, whose uniqueness, however, seems to be an open problem. The stable equilibrium switches to instability via the Hopf bifurcation Smith (1980). The existence of periodic solutions when the equilibrium is *stable* is another open problem; for global stability only *sufficient* conditions exist Arcak and Sontag (2006). However, the case of locally stable equilibrium is usually considered as "unfeasible" Murray (2002), and main effort was focused on establishing conditions where the equilibrium is strictly locally *unstable*. For a general cyclic feedback system, conditions for instability are given by the *secant criterion* Thron (1991); Arcak and Sontag (2006), which in the case of the model (1) implies Smith (1980) the condition

$$-\frac{T f_1'(T)}{f_1(T)} > 8. \tag{3}$$

In the case where the feedback is described by the Hill function (2), this shapes into the well-known constraint $n > 8$, which has been criticized in many works as unrealistic Murray (2002); Gonze and Abou-Jaoude (2013).

To overcome this limitations and get an oscillatory system under smaller Hill coefficients, the Goodwin-Smith system can be modified in different ways, e.g. by introducing sufficiently large delays Smith (1983); Murray (2002), discontinuous pulsatile nonlinearities $f_1(T)$ Churilov et al. (2009), or nonlinear reaction rates, described by the Mikhaelis-Menten nonlinearities Gonze et al. (2005).

In this paper, we consider another modification of the Goodwin-Smith system, based on the experimental fact that testosterone *directly* inhibits LH Veldhuis et al. (2009), Sheckter et al. (1989), Nagayama (1977), Caminos-Torres et al. (1977), Bing-Zheng and Gou-Min (1991). Although the full physiological process of testosterone regulation is not yet completely understood Murray (2002), a natural idea is introduce an additional negative feedback from Te to LH, arriving thus at the model

$$\begin{cases} \dot{R} = -b_1 R + f_1(T), \\ \dot{L} = g_1 R - b_2 L + f_2(T), \\ \dot{T} = g_2 L - b_3 T. \end{cases} \tag{4}$$

Unlike (1), the model (4) involves a function $f_2(T)$ which will be assumed positive and decreasing (for instance, this can be another Hill function). A natural question arises if taking the additional feedback into account yields in a system with principally different properties than the original system (1). As will be shown in the next section, in fact the basic properties of the usual Goodwin-Smith models retain their validity for (4). This result, in fact, can be considered as both positive and negative. The "positive" part states that choosing a more realistic model for the testosterone regulation, one does not loose the well-studied properties of the Goodwin oscillator, such as the existence of unique equilibrium and criteria for the periodic solutions existence. The bad news is that the extra feedback cannot help to overcome the basic restriction (3).

3. THE PROPERTIES OF THE EXTENDED MODEL

In this section, we study the basic properties of the model (4). Notice first that, since $f_1, f_2 > 0$, the solutions of the dynamical system (4), starting in the positive octant $R \geq 0, L \geq 0, T \geq 0$, remains positive. Furthermore, since $0 < f_1(T) \leq f_1(0)$ and $0 < f_2(T) \leq f_2(0)$,