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# ABOUT DISTRIBUTED CONTROL IN MODEL OF TESTOSTERONE REGULATION

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ABSTRACT. In the paper, stability of integro-differential equation is studied. The model of testosterone regulation is considered. The model describes an interaction of: the concentration of hormone (GnRH) which will be denoted as $x_1$, with the concentration of the hormone (LH)-$x_2$ and the concentration of testosterone (Te)-$x_3$ and can be written in the form

$$\begin{cases} x_1'(t) + b_1 x_1(t) = 0, \\ x_2'(t) + b_2 x_2(t) - g_1 x_1(t) = 0, \\ x_3'(t) + b_3 x_3(t) - c_1 \int\limits_0^t e^{-\alpha_1 (t-s)} x_2(s)\, ds = 0, \ t \geq 0 \ . \end{cases}$$

The values $b_i$, $i = 1, 2, 3$ correspond to the respective half-life times of GnRH, LH and Te. The aim of the work is to propose a concept to hold the concentration of testosterone above a corresponding level. In order to achieve this, distributed input control in the form of integral term is used.

## 1. Introduction

The non-autonomous integro-differential equations (IDEs)

$$y'(t) + A(t)y(t) + \int\limits_0^t k(t,s)y(s)\, ds = 0, \qquad y(t) \in R^n, \quad t \in [0, +\infty), \qquad (1.1)$$

where $A(t)$ and $k(t,s)$ are $n \times n$ matrices with continuous coefficients, model many processes in applications.

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It was demonstrated in the works [1], [2] that these equations can be used to model endocrine regulation in correspondence to the delay incurred by transport of hormone molecules from the secretion site to receptors. This is typically motivated in [3] that signals of the receptors sensitive to the stimulating hormone depends on the mean value of the hormone concentration over a certain period, rather than the instantaneous value. The affinity of a receptor to bind a hormone molecule within a given time interval can be defined by the kernel function $k(t, s)$. Although the distributed input control is a frequently appearing challenge, only a few papers are devoted to this problem. See, for example, the recent papers [4], [5]. Noise in the feedback delay control is the main obstacle appearing in mathematical models with distributed inputs: it is impossible to base the control on the value of the process $X(t_j)$ at a moment $t_j$ only, such that we have to make an average value of the process $X(t)$ at a corresponding neighborhood of $t_j$. Another way for arranging integral delay terms is, for example, the time required for assimilation of medicine. The integral term with a kernel defining a weight of every value adopts this role. It points out in [6] that such models with distributed inputs can appear, for example, in population dynamics, in propellant rocket motors and in networked control systems. IDE (1.1) was considered in many well-known works [9], [10], [12], [13]. In the paper [7] a new approach to study of IDE is proposed. The main idea is to reduce the analysis of IDE to one of a corresponding system of ordinary differential equations (ODE). The number of equations in this new ODE system will be bigger than in the given one, but analysis will be significantly easier. We demonstrate the use of this method to the problem of testosterone regulation.

## 2. Description of model

Consider the model of testosterone regulation integrated into the paper [8] modeling of a hereditary feedback system and based on the concepts presented in [10]–[13]. The model describes an interaction of: the concentration of hormone (GnRH) which will be denoted as $x_1$, with the concentration of the hormone (LH)-$x_2$ and the concentration of testosterone (Te-$x_3$ and can be written in the form

$$\begin{cases} x_1'(t) + b_1 x_1(t) = 0, \\ x_2'(t) + b_2 x_2(t) - g_1 x_1(t) = 0, \\ x_3'(t) + b_3 x_3(t) - c_1 \displaystyle\int_0^t e^{-\alpha_1 (t-s)} x_2(s)\, ds = 0, \ t \geq 0. \end{cases} \tag{2.1}$$

The values $b_i$, $i = 1, 2, 3$ correspond to the respective half-life times of GnRH, LH and Te and can be calculated according to the biomedical data for typical hormones levels as provided in the literature [8]:

$$b_1 = 0.4, \quad b_2 = 0.01, \quad b_3 = 0.046, \quad g_1 = 2, \quad c_1 = 4. \tag{2.2}$$

We set the control in the form

$$u(t) = -c_2 \int_0^t e^{-\alpha_2(t-s)} \{x_3(s) - T(s)\}\, ds \tag{2.3}$$

in the right-hand side of the second equation. The function $T(t)$ in the difference under the integral presents the concentration of testosterone which we wish to hold. It is clear that the integral term increases the concentration of hormone LH if the concentration $x_3(t)$ of Te is less than $T(t)$. The control (2.3) appears reasonable and could be realized according to opinions of clinical experts. By substituting this control into the second equation we obtain the system

$$\begin{cases} x_1'(t) + b_1 x_1(t) = 0, \\ x_2'(t) + b_2 x_2(t) - g_1 x_1(t) + c_2 \displaystyle\int_0^t e^{-\alpha_2(t-s)} x_3(s)\, ds = f(t), \\ x_3'(t) + b_3 x_3(t) - c_1 \displaystyle\int_0^t e^{-\alpha_1(t-s)} x_2(s)\, ds = 0, \ t \geq 0, \end{cases} \tag{2.4}$$

where

$$f(t) = c_2 \int_0^t e^{-\alpha_2(t-s)} T(s)\, ds. \tag{2.5}$$

## 3. Main result

**Theorem 3.1.** *If* $b_2 b_3 \alpha_2 \alpha_1 - c_1 c_2 > 0$, *then the system* (2.4) *is exponentially stable.*

Proof. Using the idea of the reduction of IDE to the system of ODE proposed in [7], the system (2.4) can be reduced to the system

$$\begin{cases} x_1'(t) + b_1 x_1(t) = 0, \\ x_2'(t) + b_2 x_2(t) - g_1 x_1(t) + c_2 x_4(t) = f(t), \\ x_3'(t) + b_3 x_3(t) - c_1 x_5(t) = 0, \\ x_4'(t) + \alpha_2 x_4(t) - x_3(t) = 0, \\ x_5'(t) + \alpha_1 x_5(t) - x_2(t) = 0, \ t \geq 0, \end{cases} \tag{3.1}$$

with the initial conditions

$$x_4(0) = 0, \quad x_5(0) = 0. \tag{3.2}$$

Three components of solution-vector of the system (2.4) and three first components of solution-vector $\mathrm{col}\big(x_1(t), x_2(t), x_3(t), x_4(t), x_5(t)\big)$ of the system (3.1) coincide. It is clear that $x_1(t) = e^{-b_1 t}C \to 0$ when $t \to \infty$ ($C$ is a constant). Substituting $x_1(t)$ into the second equation of (3.1), we have the system

$$\begin{cases} x_2'(t) + b_2 x_2(t) + c_2 x_4(t) = f(t) + g_1 e^{-b_1 t}C, \\ x_3'(t) + b_3 x_3(t) - c_1 x_5(t) = 0, \\ x_4'(t) + \alpha_2 x_4(t) - x_3(t) = 0, \\ x_5'(t) + \alpha_1 x_5(t) - x_2(t) = 0, \ t \geq 0, \end{cases} \tag{3.3}$$

in which the right-hand side of the first equation remains bounded. Thus, we can conclude that analysis of the exponential stability of the system (3.1) is reduced to analysis of the exponential stability of the system

$$\begin{cases} x_2'(t) + b_2 x_2(t) + c_2 x_4(t) = 0, \\ x_3'(t) + b_3 x_3(t) - c_1 x_5(t) = 0, \\ x_4'(t) + \alpha_2 x_4(t) - x_3(t) = 0, \\ x_5'(t) + \alpha_1 x_5(t) - x_2(t) = 0, \ t \geq 0. \end{cases} \tag{3.4}$$

It is known that the system (3.4) is exponentially stable if the system

$$\begin{cases} x_2'(t) + b_2 x_2(t) - c_2 x_4(t) = 0, \\ x_3'(t) + b_3 x_3(t) - c_1 x_5(t) = 0, \\ x_4'(t) + \alpha_2 x_4(t) - x_3(t) = 0, \\ x_5'(t) + \alpha_1 x_5(t) - x_2(t) = 0, \ t \geq 0, \end{cases} \tag{3.5}$$

is exponentially stable. It is necessary and sufficient for the exponential stability of the system (3.5) that all components $z_2, z_3, z_4, z_5$ of the solution-vector to the algebraic system

$$\begin{cases} b_2 z_2 - c_2 z_4 = 1, \\ b_3 z_3 - c_1 z_5 = 1, \\ \alpha_2 z_4 - z_3 = 1, \\ \alpha_1 z_5 - z_2 = 1, \end{cases} \tag{3.6}$$

are positive. See, for example, in [14, Theorem 16.5].

Let us solve the system (3.6):

$$\Delta = \det\begin{pmatrix} b_2 & 0 & -c_2 & 0 \\ 0 & b_3 & 0 & -c_1 \\ 0 & -1 & \alpha_2 & 0 \\ -1 & 0 & 0 & \alpha_1 \end{pmatrix} = b_2 b_3 \alpha_2 \alpha_1 - c_1 c_2, \tag{3.7}$$

$$\Delta_1 = \det\begin{pmatrix} 1 & 0 & -c_2 & 0 \\ 1 & b_3 & 0 & -c_1 \\ 1 & -1 & \alpha_2 & 0 \\ 1 & 0 & 0 & \alpha_1 \end{pmatrix} = b_3 \alpha_2 \alpha_1 + c_2 \alpha_1 + c_2 \alpha_1 b_3 + c_1 c_2, \tag{3.8}$$

$$\Delta_2 = \det\begin{pmatrix} b_2 & 1 & -c_2 & 0 \\ 0 & 1 & 0 & -c_1 \\ 0 & 1 & \alpha_2 & 0 \\ -1 & 1 & 0 & \alpha_1 \end{pmatrix} = b_2(\alpha_1 \alpha_2 + c_1 \alpha_2) + c_1 c_2 + c_1 \alpha_2, \tag{3.9}$$

$$\Delta_3 = \det\begin{pmatrix} b_2 & 0 & 1 & 0 \\ 0 & b_3 & 1 & -c_1 \\ 0 & -1 & 1 & 0 \\ -1 & 0 & 1 & \alpha_1 \end{pmatrix} = b_2(b_3 \alpha_1 + c_1 + \alpha_1) + c_1, \tag{3.10}$$

$$\Delta_4 = \det\begin{pmatrix} b_2 & 0 & -c_2 & 1 \\ 0 & b_3 & 0 & 1 \\ 0 & -1 & \alpha_2 & 1 \\ -1 & 0 & 0 & 1 \end{pmatrix} = b_2 b_3 \alpha_2 + c_2 + b_3 \alpha_2 + b_3 c_2. \tag{3.11}$$

The conditions of Theorem 3.1 imply that all the components $z_2, z_3, z_4, z_5$ of the solution-vector are positive. According to [14, Theorem 16.5] we obtain the exponential stability of system (2.4). □

**Corollary 3.1.** *The system* (2.4) *can be always stabilized by the control in the form* (2.3).

*In order to prove this we choose* $\alpha_2 > \frac{c_1 c_2}{b_2 b_3 \alpha_1}$. *The condition of Theorem 3.1 will be fulfilled.*

Example 3.1. If $\frac{\alpha_2 \alpha_1}{c_2} > \frac{4}{0.01 \cdot 0.046}$, then the system (2.4) is exponentially stable.

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