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A Cascade Control Approach for a Class of Biomedical Systems

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Abstract An approach for the robust feedback control of a class of biomedical systems in chained form is presented. The control approach is based on modeling error compensation techniques and a recursive cascade scheme. Numerical simulations on three biomedical models of VIH-1, cancer and glucose systems are provided to illustrate our findings.

I. Introduction

IN the recent years, considerable effort has been directed toward the development of control schemes for biomedical systems aimed to both assist to the physicians with drug dosification regimes and to provide some general guidelines that may prove helpful to clinicians and the pharmaceutical industry [1], [2], [4], [8]. Both, new discoveries in biology that provide new actuators and sensors as well as improved understanding of biological functions and the developments in mathematical models for biomedical systems have been impulsed such control applications in biomedical sciences [1], [4]-[8].

A large class of models of biomedical systems can be written as a nonlinear dynamical system in a chained form [4]-[7]. In this paper we focus on the model-based control of chained models of biomedical systems, and assume, as is common in biomedical systems, that the control corresponds to drug dosification of certain external input. Model-based control of biomedical systems is a challenging problem due to the lack of an accurate mathematical model of such systems. The proposed control is based on the application of a recursive cascade control scheme that exploits the chained form of certain class of biomedical systems, and the use of modeling error compensation techniques to derive a robust feedback control scheme.

This work is organized as follows: In the next section, the class of biomedical systems is introduced. In Section 3, the robust cascade feedback control approach is developed. In section 4 we applied the proposed control method to three biomedical systems. Finally, in Section 5 we close this work with some concluding remarks.

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II. A class of biomedical systems

Consider biomedical systems which, possibly after a change of coordinates, can be described by

$$\begin{aligned} \dot{x}_i &= f_i(x) + g_i(x)x_{i+1} \qquad 1 \le i \le n-1 \\ \dot{x}_n &= f_n(x) + g_n(x)u \end{aligned} \tag{1}$$

where x are the states of the system and u is the control input (drug). The functions f_i and g_i, $1 \le i \le n$, are smooth nonlinear functions. Note that the dynamical system (1) is in the so called chained form [1].

The control objective is to stabilize one state x_k ($1 \le k \le n$-1) of system (1) about a given reference $x_{k,ref}$ of system (1) under the following assumptions:

A.1 The full states x are measured.

A.2 The functions f_i and g_i, $1 \le i \le n$, are uncertain.

It is not hard to see that several well-known models of biomedical system, including a certain class of prey-predator models [4]-[7], can be described by (1).

III. A robust cascade feedback control approach

Cascade control is a common control configuration in process control, which can be thought of as partial state feedback [9]. A typical cascade control structure has two feedback controllers with the output of the primary (master) controller changing the set point of the secondary (slave) controller. We exploit the chained form of system (1) to design a recursive cascade procedure to control certain class of biomedical systems. Since biomedical system has several terms that are in general uncertains or unknowns, we will follow a robust feedback control approach based on modeling error compensation techniques (MEC) to deal with such uncertain terms [8], [9]. In the following we describe our robust feedback control approach.

Since functions f_j and g_j are uncertain, we introduce modeling error functions η_j associated to the uncertain functions

$$\eta_j = -[\overline{f}_j(x) - f_j(x)] - [\overline{g}_j(x) - g_j(x)] \tag{2}$$

where $j = k,\ldots,n$, $x_{j+1} = u_i$, and when $j = n$ then $x_{j+1} = u$. Then system (1) can be written as

$$\dot{x}_i = \overline{f}_j(x) + \overline{g}_j(x)x_{j+1} + \eta_j \tag{3}$$

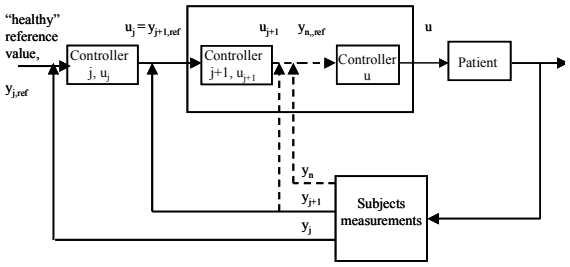

Fig. 1. Recursive cascade control scheme for biomedical systems.

A stabilizing control function for system (3) is

$$x_{j+1} = -[\overline{f_j}(x) + \eta_j + \varpi_{cj}(x_j - x_{j,ref})]\overline{g_j}(x)^{-1} \qquad (4)$$

where ω_{cj} are control design parameters. Since the modeling error functions η_j contain uncertain terms, the following observers are introduced in order to use approximate modeling error functions:

$$\dot{\overline{\eta_j}} = \varpi_{ej}(\eta_j - \overline{\eta_j})$$

where ω_{ej} are estimation design parameters. From (3) we have that

$$\eta_j = \dot{x}_i - \overline{f}_j(x) - \overline{g}_j(x)x_{j+1}$$

which allows to represent the modeling error functions in terms of measured signals, their derivatives and rough available estimates, of the uncertain functions $f_j(x)$ and $g_j(x)$,

$$\dot{\overline{\eta_j}} = \varpi_{ej}(\dot{x}_j - \overline{f_j}(x) - \overline{g_j}(x)x_{j+1} - \overline{\eta_j})$$

A realizable version of the above estimator is given by

$$\begin{aligned} \dot{\omega}_j &= -\overline{f_j}(x) - \overline{g_j}(x)x_{j+1} - \overline{\eta_j} \\ \overline{\eta_j} &= \varpi_{ej}(\omega_j + x_j) \end{aligned} \qquad (5)$$

The resulting control approach is given by the following feedback function

$$x_{j+1} = -[\overline{f_j}(x) + \overline{\eta_j} + \varpi_{cj}(x_j - x_{j,ref})]\overline{g_j}(x)^{-1} \qquad (6)$$

and the modeling estimators (5). It can be seen that the cascade control approach is based on the design of intermediate control functions $u_{i..}$ The design is recursive because the computation of u_{i+1} requires the computation of u_i. Figure 1 shows the recursive cascade control approach.

The following comments are in order:

- Each single control loop has only two control design parameters, *i.e.*, ω_c and ω_e. The closed-loop parameter ω_c can be chosen as the inverse of the mean time of the open-loop dynamics. On the other hand, the estimation parameter $\omega_e > 0$, which determines the smoothness of the modeling error and can be chosen as $\omega_e < 0.5\ \omega_c$ [9].
- Stability must be preserved in the context of both structured uncertainties in the parameters as well as unstructured errors in modeling. The stability analysis of the closed-loop systems is beyond of the scope of this paper. However, this can be borrowed with stability arguments from singular perturbation theory [9].
- We have assumed that the full state is available from measurements. This is not met in general. To overcome this disadvantage of our control approach, we can introduce state observers for unmeasured states.

IV. Examples

In this section, simulation results are presented for three biomedical systems: *(i)* regulation of HIV-1 dynamics, *(ii)* suppression of cancer tumor cells, and *(iii)* regulation of glucose levels with application of exogenous insulin.

A. HIV-1 Biodynamical Model

AIDS is the disease that has affected the whole world in the 20 years since it was first detected. It is caused by HIV. HIV largely exerts its effect on the immune system by destroying CD4+ T cells that are critical in helping the body fight infections [3]. There are a number of control techniques that can be utilized to design dynamical therapies for HIV [3]-[4]. HIV dynamic models provide a global picture of the virus elimination and production process during antiviral treatments for each individual patient. These models typically consider the dynamics of the CD4+ T cell and virus populations as well as the effects of drug therapy [3]. In some of these models other immune system populations, such as macrophages or CD8+ cells, have been included. In this work, we consider a nonlinear dynamical type prey-predator model of HIV-1 given by [4]

$$\begin{aligned} \dot{x}_1 &= p_1(x_{10} - x_1) - p_2 x_1 x_3 \\ \dot{x}_2 &= p_3(x_{20} - x_2) + p_4 x_2 x_3 \\ \dot{x}_3 &= x_3(p_5 x_1 - p_6 x_2) - u \end{aligned} \qquad (7)$$

where x_1 and x_2 are the CD4 and CD8 lymphocyte populations respectively, x_3 is the HIV-1 viral load, p_1 - p_6 are parameters and u is an external control agent (e.g., an antiretroviral drug agent). Since the growth rate of HIV-1

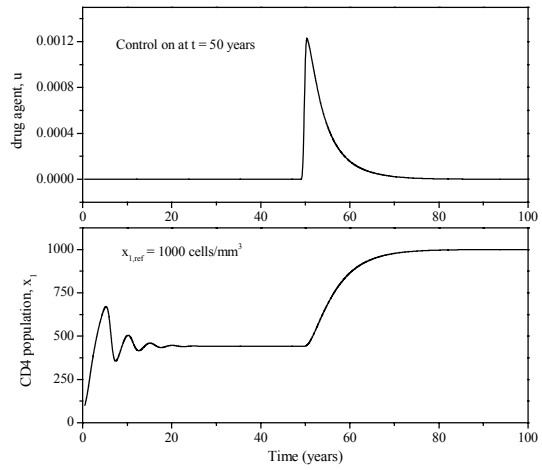

Fig 2. Controlled behavior of HIV-1 dynamics.

decreases with decreased growth in the HIV-1 and CD4 populations we choose as the control objective the regulation of x_1 to a desired "healthy" reference $x_{1,ref}$. Parameters are: x_{10} = 1000 cells/mm³, x_{20} = 550 cells/mm³, [p_1-p_6] = [0.25, 50.0, 0.25, 10.0, 0.01, 0.006], and the initial conditions x_{10} = x_{10}, x_{20} = x_{20} and x_{30} = 300 virus copies/ml [4].

The control scheme is given by,

$$
\begin{aligned}
u_1 &= -\frac{1}{\overline{p_2}\overline{x_1}}[\overline{p_1}(\overline{x_{10}} - x_1) + \overline{\eta_1} + \varpi_{c1}(x_1 - x_{1,ref})] \\
u &= -[\overline{x_3}(\overline{p_5}x_1 - \overline{p_6}x_2) + \overline{\eta_2} + \varpi_{c2}(x_3 - u_1)] \\
\dot{\omega}_1 &= -\overline{p_1}(\overline{x_{10}} - x_1) + \overline{p_2}x_1u_1 - \overline{\eta_1} \qquad \overline{\eta_1} = \varpi_{e1}(\omega_1 + x_1) \\
\dot{\omega}_2 &= x_3(\overline{p_5}x_1 - \overline{p_6}x_2) + u - \overline{\eta_2} \qquad \overline{\eta_2} = \varpi_{e2}(\omega_2 + x_3)
\end{aligned}
\tag{8}
$$

It can be seen from Figure 2 that we can successfully

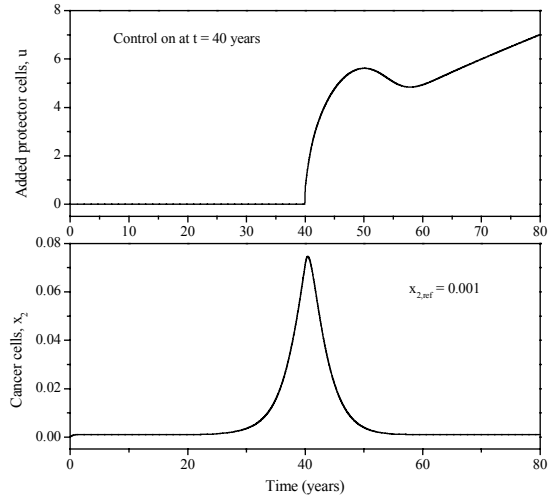

Fig 3. Controlled behavior of growth of cancer cells.

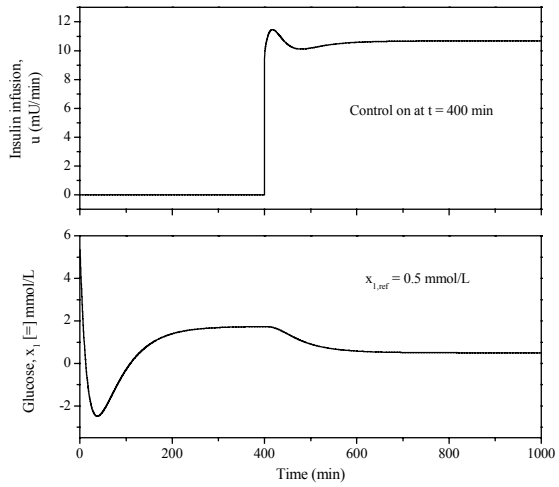

Fig 4. Controlled behavior of glucose dynamics.

perform the regulation of the x_1 state to a healthy state via the control scheme (8). Control parameters were set as ω_{ci} = [0.2 0.667] and ω_{ei} = [0.5 0.2]. It can be seen from Figure 2 that in order to regulate the CD4 population to a constant reference value, the required control input is an impulse-type external input of u which can be realized in practice.

B. Prey-Predator-Protector Cancer Model

Cancer is one of the greatest killers in the world and the control of tumor growth requires special attention. Thus, it is important to design treatment strategies that ensure a desired rate of tumor cell kill. Mathematical models may serve in cancer treatments. Mathematical models for cancer treatments have a long history in mathematical biology. One class of model, developed and analyzed by Stein [5], is the so-called prey-predator-protector model, which is in the chained form described by (1). The model consists of three equations which represents the growth rates of the normal (prey) x_1, cancer (predator) x_2 and the protecting (protector) cells x_3.

$$
\begin{aligned}
\dot{x}_1 &= x_1(p_1 - p_2x_1 - p_3x_2) \\
\dot{x}_2 &= x_2(p_4 + p_5x_1 - p_6x_3) \\
\dot{x}_3 &= x_3(p_7 - p_8x_3) + u
\end{aligned}
\tag{9}
$$

where p_1 - p_8 are all positive constant parameters [1001.0 1.0 1000.0 5.0 1.0 4.0×10^{-3} 1.0 1.0]. The parameter p_7 is related to the growth rate of the protector cells. With the protectors decreasing, the predators begin increasing. The prey also begin to decrease. A ratio of normal cells/cancer cells ≤10000 is set where the subject dies [5]. In order to control the growth of cancer cells and prolong the subject life two alternatives are possible [5]: *(i)* removal of cancer cells by means of surgery and *(ii)* addition of protectors to counteract their deterioration. Keeping in mind the above biological scenario, the addition of protectors via our

feedback control scheme will be addressed. We consider that the tumor cells growth due a decrease of parameter p_7 in some stage of a subjects life. In this case, our feedback control approach is given by

$$\begin{aligned} u_1 &= -\frac{1}{\overline{p_6 x_2}}[x_2(\overline{p_4}+\overline{p_5}x_1)+\overline{\eta_1}+\varpi_{c1}(x_2-x_{2,ref})] \\ u &= -[x_3(\overline{p_7}-\overline{p_8}x_3)+\overline{\eta_2}+\varpi_{c2}(x_3-u_1)] \\ \dot{\omega}_1 &= -x_2(\overline{p_4}+\overline{p_5}x_1)+\overline{p_6}x_2u_1-\overline{\eta_1} \qquad \overline{\eta_1}=\varpi_{e1}(\omega_1+x_2) \\ \dot{\omega}_2 &= x_3(\overline{p_7}-\overline{p_8}x_3)-u-\overline{\eta_2} \qquad \overline{\eta_2}=\varpi_{e2}(\omega_2+x_3) \end{aligned} \tag{10}$$

Control parameters were set as ω_{ci} = [0.4 1.0] and ω_{ei} = [2.0 8.0]. Other simulation parameter values are x_{10} = 100.0, x_{20} = 2.0×10^{-4} and x_{30} = 1.0. Figure 3 shows that after the progressive addition of protector cells, the growth of malignant tumor cells can be controlled.

C. Glucose-Insulin Interaction Model

Diabetes mellitus is a chronic metabolic disease characterized by the uncoupling of blood glucose levels and insulin secretion, causing abnormal glycemic excursions [6], [7]. Type 1 diabetes is characterized by a complete insulin deficiency [7]. The most important strategy in the prevention of diabetic complications is the implementation of frequent blood glucose monitoring coupled with a well-planned regimen of insulin delivery [7]. Insulin-glucose dynamics are nonlinear and of high order. We consider the Bergman's minimal model, which is a simple diabetic model of a mathematically tractable size [6]. Bergman's minimal model has been used in physiological research on the metabolism of glucose and most importantly this model has been verified and tested in clinical environment [6]. The model equations are [7]

$$\begin{aligned} \dot{x}_1 &= -p_1x_1 - x_2(x_1+x_{1b}) + d \\ \dot{x}_2 &= -p_2x_2 + p_3x_3 \\ \dot{x}_3 &= -\eta(x_3+x_{3b}) + u/V_i \end{aligned} \tag{11}$$

where x_1 and x_2 represents the differences of plasma glucose concentration and free plasma insulin concentration from their basal values respectively, x_3 is proportional to the concentration of insulin in the remote compartment, x_{1b} and x_{3b} are basal values of plasma glucose concentration and free plasma insulin concentration respectively, V_i is the insulin distribution volume, n is the fractional disappearance rate of insulin, d and u are the rates of infusion of exogenous glucose and insulin respectively. Parameter values for a typical subject are [6]: p_1 - p_3 = [0.028 0.025 1.3×10^{-5}], n= (5/54), V_i = 12.0, x_{1b} = 4.5 and x_{3b} = 15.0. For parameter d, the fisher model was chosen, *i.e.*, d = 0.5exp(0.05t) [6]. We consider the regulation of the plasma glucose level $x_{1,ref}$ via an infusion of exogenous insulin u. We have the following recursive cascade control scheme:

$$\begin{aligned} u_1 &= -\frac{1}{x_1+\overline{x_{1b}}}[\overline{p_1}x_1 - d - \overline{\eta_1} - \varpi_{c1}(x_1-x_{1,ref})] \\ u_2 &= \frac{1}{\overline{p_3}}[\overline{p_2}x_2 - \overline{\eta_2} - \varpi_{c2}(x_2-u_1)] \\ u &= \overline{V_i}[\overline{\eta}(x_3+\overline{x_{3b}}) - \overline{\eta_3} - \varpi_{c3}(x_3-u_2)] \end{aligned} \tag{12}$$

$$\begin{aligned} \dot{\omega}_1 &= \overline{p_1}x_1 + x_2(x_1+\overline{x_{1b}}) - d - \overline{\eta_1} \qquad \overline{\eta_1} = \varpi_{e1}(\omega_1+x_1) \\ \dot{\omega}_2 &= \overline{p_2}x_2 - \overline{p_3}x_3 - \overline{\eta_2} \qquad \overline{\eta_2} = \varpi_{e2}(\omega_2+x_2) \\ \dot{\omega}_3 &= \overline{\eta}(x_3+\overline{x_{3b}}) - u/\overline{V_i} - \overline{\eta_3} \qquad \overline{\eta_3} = \varpi_{e3}(\omega_3+x_3) \end{aligned} \tag{13}$$

Initial conditions were chosen as: x_{10} = 5.5, x_{20} = 0.0, and x_{30} =10.0. The control law is set with ω_{ci} = [0.02 0.04 0.0667] and ω_{ei} = [2.0 10.0 20.0]. In general, the main objectives while deciding the control parameter settings were no overshoot (as an overshoot could be dangerous from a physiological point of view), smooth regulation, and minimum response time, in that order of preference. The results obtained with the above control scheme are illustrated in Figure 4.

V. Conclusions

By means of modeling error compensation techniques we have derived a robust model-based feedback control approach for a class of biomedical systems. Numerical simulations shown the control performance. One of the goals to design control schemes in biomedical processes is to gain insight into how design drug dosification regimes to assist to physicians in clinical treatments. At the level of biomedical sciences the problem is to supply specific drug regimes with certain dynamics to the organism such that the biomedical system achieves a specified healthy state with reduced side effects. At the level of control theory the biomedical problem amounts to the construction of control schemes such the biomedical control objectives can be achieved.

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