Stabilization of a Class of Biomedical Systems via Stability Preservation

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Abstract. We present a method for stabilization of a class of nonlinear systems. The notion of stability preservation is exploited to prove that a transformation allows to find a stabilizer. The nonlinear systems have uncontrollable linearized system. From this fact, we propose a method that departs from a controllable linearized system to a linear transformation. The linear transformation allows to take the uncontrolled system preserving the stability properties of the controlled one. Thus, the resulting controller is able to stabilize biomedical systems. Type I diabetes mellitus and HIV-I diseases are used to show the potential of method. Numerical simulations for this cases illustrate the performance of closed-loop approach.
Keywords: Stability Preservation, Stabilization, Biomedical Systems

1 Introduction

Stabilization of an equilibrium point is a classical and common problem in control theory. The stabilization of nonlinear systems is still a problem under study and investigation. The stabilization of dynamical systems is used in several research areas, for instance, in control of manipulators, mechanical systems, chaos synchronization and more recently in biomedical systems or complex networks. The stabilization of nonlinear systems has been studied using various theories with some promising results, see [1],[2],[3] and references therein. In [1], the author proposed a method to find a stabilizing control law for feedback output. A strong assumption is stated about the system has to be at least weakly detectable to construct a state estimator. Then a stabilizer is derived. If this controller stabilizes the estimated system, it stabilizes the original system. On the other hand, authors in [2], extended the Q-parametrization theorem but for nonlinear systems. They assumed that the closed-loop system is well-posed and as the system plant P is stable or incrementally stable, then the closed-loop system is stable if and only if there exists a stable matrix Q such that the controller is given by $C = Q(I - PQ)^{-1}$ for some stable Q. This result requires that the nonlinear

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plant be strongly stabilizable in order to a compensator be determined. Finally, authors in [3], proposed a linearization at origin. Then, studying the resulting linear matrix (which has uncontrollable modes), they performed the stabilization analyzing the properties of a center manifold and normal forms. Behtash and Sastry [3] considered the case when the linearized part has uncontrollable modes on the imaginary axis. Compared with the previous results, we are interested in stabilizing equilibrium for a class of biomedical systems that presents unstable modes. Our proposal neither ask for weakly detectabillity of the system nor uses an state estimator; it is not required that the plant be strongly stabilizable; as an additional contribution the class of systems studied has not only models at the imaginary axis. But modes with positive real component.

Our proposed method is used on biomedical systems. The biomedical systems are of relevant interest in the scientific community, Type I diabetes mellitus (TIDM) and Type I Human Immunodeficiency Virus (HIV-I). TIDM is a chronic disease characterized by self destruction of pancreatic cells which are responsible of insulin secretion. In absence of insulin, blood glucose levels in patient are increased up to 200 mg/dl. This last provoke hyperglycemia which carries out several illnesses, among others atherosclerosis, retinopathy,etc.In order to regulate blood glucose, in TIDM external doses of insulin are necessary. Hence, a closed-loop of the blood glucose level is the best strategy to maintain it regulated in permitted values. To this aim, a controller that calculate this external doses of insulin must be synthesized [4]. By other hand, HIV-I infection is a disease that provoke thousand of deaths last three decades. Over the last two decades tremendous effort has been applied to the mathematical modeling of the epidemiology and immunology dynamics of HIV. There are several approaches to the modeling of the infectious diseases at the cellular level to describe the immune system and the hostpathogen interaction. These models describe the dynamics between white blood cells (CD4+ T cells),the infected cells and concentration of free virion [5]. The idea here is quite similar than in TIDM, this is, synthesized a feedback-controller in order to stabilizes the propagation of concentration of free virion to avoid the infection od CD4+T cells.

Our proposal consists in finding a transformation from a controllable nonlinear system [6]; which we refer to as CS. For CS system, we calculate a stabilizing controller, which makes stable the linear part of the system. The next step is to propose the same controller with system having UMS via a transformation of the linear part of the unstable system. Thus, this procedure consists in finding an invertible transformation for the linear part of the system with UMS, such that it is equal under the transformation to the linear part of CS. Therefore, the system with UMS is stabilizable via a controller containing the transformation. In this sense we say that the stability of CS is preserved and exploited to stabilize system with UMS. This can be seen like a stabilizability condition for the UMS provided that there exists a stable system from where preservation of stability is claimed. We illustrate the result in two well known biomedical systems, departing from an other well known dynamical systems which is stabilizable via a simple controller.

2 Problem Formulation

The class of biomedical systems considered for stabilization are given by the the TIDM

$$\begin{aligned} \dot{G} &= -X(G+G_B)+p(t) \\ \dot{X} &= -p_2X+p_3I \\ \dot{I} &= -n(I+I_B) \\ y_D &= G \end{aligned} \tag{1}$$

this system has three modes given by $\Lambda_{TIDM} = \{0, -0.025, -0.0926\}$ for the system parameters $G_B = 4.5, p_2 = 0.025, p_3 = 1.3000 \times 10^{-5}, n = 0.0926$, note that one of the modes is unstable. On the other hand, the HIV-I infection system is given by the following set of equations

$$\begin{aligned} \dot{T} &= s - dT - bTV \\ \dot{T}_{ip} &= bTV - \mu_1 T_{ip} \\ \dot{V} &= gT_{pi} - \mu_2 V \\ y_H &= T - s/d \end{aligned} \tag{2}$$

this system has three modes given by $\Lambda_{HIV} = \{-0.007, 0.5589, -0.8589\}$ with parameter values $s = 7.0, d = 0.007, b = 4 \times 10^{-6}, \mu_1 = 0.3, \mu_2 = 0.6, g = 75$ the system (2) has one unstable mode. A natural approach to control this class of systems is the geometrical nonlinear control theory [6], [7]. To verify if both systems can be controlled we determine the relative degree. The relative degree involves the reachability and detectability for nonlinear systems. It is said that a system $\dot{x} = f(x) + g(u)u$ with output $y = h(x)$ has relative degree ρ at x^0 if (i) $L_g L_f^k h(x) = 0$, for $k < \rho - 1$, and for all x in the neighborhood of x^0, (ii) $L_g L_f^{\rho-1} h(x^0) \neq 0$. Therefore from this condition if function in (ii) is well defined then the system is reachable and detectable and there exists a control law that controls the system at the point x^0. The relative degree for the system (1) is $\rho = 3$ and has the relative degree function $L_g L_f^2 h(x^0) = -G_B P_3 = 5.85 \times 10^{-3}$ note that this value depends only on the parameters and does not depend on the system states, this is, it is always constant. Moreover, the value is closed to zero, this means that the relative degree is not well defined practically, since the control law is as $u = \frac{1}{-G_B P_3}\left(-L_f^3 h(x) + \nu\right)$. In this sense the control action presents an excessive overshoot and is undesirable for this class of biomedical systems. For the system (2), the case is almost the same, the relative degree is $\rho = 3$ and the function $L_g L_f^2 h(x^0) = bTg = 3 \times 10^{-4} T$. In this case the relative degree function depends on one state, again the control law is not well defined practically, leading a high overshoot. In this sense, the geometric approach is not recommended to stabilize this class of biomedical systems.

To overcome this problem we propose the stabilization of the nonlinear system considering the stabilization of the linear part of the linearization, provided

that the nonlinear terms be at least locally Lipschitz. To this end, the problen can be formulated as follows. Let us consider systems that can be written as

$$\begin{aligned} \dot{x}_u &= A_u x_u + \Phi_u(x_u) \\ y_u &= C_u x_u \end{aligned} \tag{3}$$

where the subscript u and s stand for the unstable and stable characteristic respectively, $x_u \in \mathbb{R}^n$ is the system state vector, $A_u \in \mathbb{R}^{n\times n}$ is the Jacobian unstable matrix for the linearization, $\Phi_u : \mathbb{R}^n \to \mathbb{R}^n$ is a smooth vector field which comprises the nonlinear terms, $C_u \in \mathbb{R}^{1\times n}$ defines the system output state and $u_s : \mathbb{R}^n \to \mathbb{R}$ is a stabilizing controller, which should determined provided that does it exist, the subscript u stands for the unstable characteristic.

The preservation stability objective is to keep intact the stability properties of a system stabilized with a linear controller $u_s = K_s y_s$ such that the system (3), with unstable matrix A_u, is stabilized as well. This is, we design a u_s able to lead the trajectories of the system distinct to (3) to lead trajectories x_u to neighborhood of the equilibrium; i.e., $\| x \| \leq \delta$ for some Euclidean norm and the small $\delta > 0$ stands for the neighborhood radius.

3 Stability preservation to stabilization

We focus our attention on the class of systems with uncontrollable linearization (3). To begin with, let us consider that there exists a system which is detectable and reachable (controllable and observable) via the control command $u_s = K_s y_s$

$$\begin{aligned} \dot{x}_s &= A x_s + \Phi_s(x_s) + B_s u_s \\ y_s &= C_s x_s \end{aligned} \tag{4}$$

where the closed-loop matrix $A_s = (A + B_s K_s C_s)$, $A_s \in \mathbb{R}^{n\times n}$, $B_s \in \mathbb{R}^n$, $\Phi_s \in \mathbb{R}^n$ note that $A_s \neq A_u$, $B_s \neq B_u$, $\Phi_s \neq \Phi_u$ and $C_s \neq C_u$. Thereafter, to investigate stabilizability for system (3) let us consider the following proposition.

Proposition 1. Let x_s^* and x_u^* be equilibrium points for the nonlinear systems $\dot{x}_s = F_s(x_s)$ and $\dot{x}_u = F_u(x)$, respectively, where $F_s : D_s \to \mathbb{R}^n$ and $F_u : D_u \to \mathbb{R}^n$ are continuously differentiable vector fields and $D_s, D_u \subset \mathbb{R}^n$ are neighborhoods of the origin. Let

$$A_s = \frac{\partial F_s}{\partial x_s}(x_s), A_u = \frac{\partial F_u}{\partial x_u}(x_u) \tag{5}$$

be the Jacobian matrices of CS and system with UMS, respectively. Consider the following decomposition

$$\begin{aligned} \dot{x}_s &= F_s(x_s) = (A + B_s K_s C_s)\, x_s + \Phi_s(x_s) \\ \dot{x}_u &= F_u(x_u) = A_u x_u + \Phi_u(x_u) \end{aligned} \tag{6}$$

with continuously differentiable vector fields $\Phi_s : D_s \to \mathbb{R}^n$ and $\Phi_u : D_u \to \mathbb{R}^n$. Suppose that there exists a transformation $\mathbb{T} : \mathbb{R}^{n\times n} \to \mathbb{R}^{n\times n}$ such that preserves

eigenvalues of $(A + B_s K_s C_s)$ with negative real part and $\mathbb{T}\{(A_s + B_s K_s C_s)\} = A_u$, then the origin of the nonlinear system $\dot{x}_u = F_u(x_u)$ is asymptotically stable if $Re\lambda_{i_s} < 0$ for all eigenvalue of $(A + B_s K_s C_s)$ and Φ_u continuously differentiable such that $\frac{\|\Phi_u(x_u)\|_2}{\|x_u\|_2} \to 0$ as $\|x_u\|_2 \to x_u^*$. The proof of this statement has been reported in [8].

The main idea in the above Proposition is to find the transformation $\mathbb{T} = A_u(A + B_s K_s C_s)^{-1}$. In this way, it is possible to find a transformation which preserves stability of the system (4). Afterwards, a family of stabilizing controllers u_s for system (3) can be calculated based on the existence of the transformation $\mathbb{T}$. To this end, let us assume that there exists the matrix $(A + B_s K_s C_s)^{-1}$ and we can write the system (3) as follows

$$\begin{aligned} \dot{x}_u &= \mathbb{T}(A + B_s K_s C_s) x_u + B_u u_s + \Phi_u(x_u) \\ &= \{\mathbb{T}(A + B_s K_s C_s) + B_u K_u C_u\} x_u + \Phi_u(x_u) \\ y_u &= C_u x_u \end{aligned} \tag{7}$$

From this system it is possible to assign the closed-loop system poles, provided that $Re\lambda_i < 0$ where λ_i are the aigenvalues of $\{\mathbb{T}(A + B_s K_s C_s) + B_u K_u C_u\}$ and $\frac{\|\Phi_u(x_u)\|_2}{\|x_u\|_2} \to 0$ as $\|x_u\|_2 \to x_s^*$.

4 Stabilization of biomedical systems

In order to illustrate the stabilization of a class of biomedical system, let us consider a nonlinear system as CS, i.e., its linear part is controllable and observable. The CS is given by the Rössler equation

$$\begin{aligned} \dot{x}_1 &= -(x_2 + x_3) \\ \dot{x}_2 &= x_1 + a x_2 \\ \dot{x}_3 &= b + x_3(x_1 - c) + u \\ y &= C_s x_1 \end{aligned} \tag{8}$$

Notice that the Rössler system has no biomedical interpretation. This fact intentionally used to exaggerate the differences between CS and the system with UMS. The system (8)is stabilizable via the feedback $u_s = K_s C_s x_1$, moreover, it can be written as $\dot{x} = A_s x + \Phi_s(x)$ and the matrix A_s has eigenvalues with negative real parts. The method is implemented to two well-known biomedical systems, which are presented next.

4.1 Type I Diabetes Mellitus

The Type I Diabetes Mellitus (TIDM) is an immunologic disease characterized by the self-destruction of the pancreatic β-cells implying the lost of the pancreatic insulin secretion. A direct consequence of TIDM is the hyperglycemia, which

is defined as a blood glucose concentration above 120 mg/dl, the hyperglycemia causes diverse consequences, among others, polyuria, thirst, dehydration and slimming.

In absence of an insulin therapy, these facts can lead the patient to intense metabolic ketoacidosis and, possibly, to the death [9]. Due to the illness effects, the principal objective of the (traditional) TIDM therapy consists to avoid the long-terms hyperglycemic periods via exogenous insulin infusion, which is usually injected after a carbohydrate ingesta. Nevertheless, some results show that even if the traditional therapy is prescribed to a patient, diverse complications can arise. Hence, the need of automatic controllers including delivery devices is imperative. Because of this need, the control community has begun the study of the blood glucose regulation as a control problem via feedback. The incursions have provided feedback controllers to compute the insulin amount required to avoid long-term hyperglycemic conditions from fuzzy logic [13], predictive-model algorithms [14] and H_∞ theory [4].

Now, we consider the dynamical system for the TIDM given (1)

$$\begin{aligned} \dot{G} &= -X(G+G_B)+p(t) \\ \dot{X} &= -p_2X+p_3I \\ \dot{I} &= -n(I+I_B) \\ y_D &= G \end{aligned} \tag{9}$$

Note diabetes model has no control input. As was discuss above this model has a zero mode, therefore this is a candidate to be stabilized via the preservation of stability using system (8). We look for a transformation $\mathbb{T}$, from matrices A_s and A_u which are given by

$$A_s = \begin{pmatrix} 0 & -1 & -1 \\ 1 & a & 0 \\ K & 0 & -c \end{pmatrix} \tag{10}$$

$$A_u = \begin{pmatrix} 0 & -G_B & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -n \end{pmatrix} \tag{11}$$

which are respectively derived from Rössler system and system (1). From these matrices we can compute a transformation which preserves stability as stated in Proposition 1 as $\mathbb{T}(A_s+B_sK_sC_s)=A_u$, this means that there exists a matrix $\mathbb{T}$ such that $A_u=\mathbb{T}(A_s+B_sK_sC_s)$ from where we have

$$\mathbb{T} = \frac{1}{K_sa-c}\begin{pmatrix} -G_Bc & -G_BK_s & G_B \\ -p_2c-p_3K_sa & -p_2K_s-p_3K_s & p_2+p_3 \\ nK_sa & nK_s & -n \end{pmatrix} \tag{12}$$

At this point we can found a value for the stabilizing control gain K_u such that $Re\lambda_i \{\mathbb{T}(A + B_s K_s C_s) + B_u K_u C_u\} < 0$.

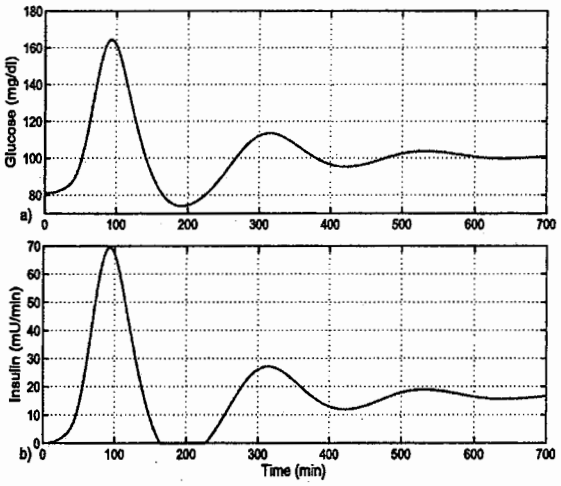

Fig. 1. Synchronization of the network in a chaotic attractor.

In order to show stabilization via stability preservation of diabetes system, the following parameter were chosen $G_B = 4.5, p_2 = 0.025, p_3 = 1.3000 \times 10^{-5}, n = 0.0926$ for the Diabetes model and $a = 0.2, b = 0.2, c = 5.7$ for the Rössler system. The result is shown in Figure 1, controller was activated at $t_c = 100$. Figure 1(a) illustrates the stabilization of the Glucose level at the point $G^* = 100mg/dl$. Figure 1(b) is the control action, it is the insulin rate to counteract the glucose level.

4.2 HIV-I disease

Infection by human immunodeficiency virus-type 1 (HIV-1) has many puzzling quantitative features. For example, there is an average lag of nearly 10 years between infection with the virus and the onset of AIDS in adults. The reason for this time lag remains largely unknown, although it seems tied to changes in the number of circulating $CD4^+$ T cells. The major target of HIV-I infection is a class of lymphocytes, or white blood cells, known as $CD4^+$ T cells. These cells secrete growth and differentiation factors that are required by other cell populations in the immune system, and hence these cells are also called "helper

T cells". When the $CD4^+$ T cell count, which is normally around 1000 mm^{-3}, reaches 200 mm^{-3} or below in an HIV-I infected patient, then that person is classified as having AIDS. Because of the central role of $CD4^+$ T cells in immune regulation, their depletion has widespread deleterious effects on the functioning of the immune system as a whole and leads to the immunodeficiency that characterizes AIDS [5].

The model for the HIV-I infection is given by the following set of equations

$$\begin{aligned} \dot{T} &= s - dT - bTV \\ \dot{T}_{ip} &= bTV - \mu_1 \\ \dot{V} &= gT_{pi} - \mu_2 V \\ y_H &= T_{pi} \end{aligned} \tag{13}$$

where T represents the uninfected lymphocytes $CD4^+$, T_{ip} are the infected lymphocytes $CD4^+$ and V represent the virus, for more details see [5] and [15]. As in diabetes case, the system (13) has no control input. Parameter values were considered as $s = 8$, $d = 0.008$, $b = 0.000004$, $\mu_1 = 0.3$, $\mu_2 = 0.6$ and $g = 75$, with initial conditions $T(0) = 1000 cells/mm^3$, $T_{ip}(0) = 0$ and $V(0) = 0$.

The reason for the fall in the T cell count is unknown as the processes that determine the rate of fall. T cells are normally replenished in the body, and the infection may affect the source of new T cells or the homeostatic processes that control T cell numbers in the body. Although HIV can kill cells that it productively infects, only a small fraction of $CD4^+$ T cells are productively infected at any one time. Thus, in addition to direct killing of T cells, HIV may have many indirect effects [5].

The antiretroviral pharmacs available for clinic purposes acts basically by means of two mechanisms: (i) Stoping the infection of new health cells (inhibers of reverse transcriptase) and (ii) Generating defective viral copies without infection capacity (inhibers of protease). The main objective of these pharmacs is to diminish the population of infected cells T_{ip} produced by infectious viral copies. A strategy used to simulate the antiretroviral drug effects, consists in apply a parameter or control function which affects directly the constant rate of infection health cells in this case the parameter b in (13).

Thus following the stability preservation method, we have that the linear part for the system (13) is

$$A_u = \begin{pmatrix} -1 & 0 & 0 \\ 0 & -\mu_1 & 0 \\ 0 & g & -\mu_2 \end{pmatrix} \tag{14}$$

from where the transformation $\mathbb{T}$ is given by

$$\mathbb{T} = \begin{pmatrix} ac & c & -a \\ -c\mu_1 & -K_s\mu_1 & \mu_1 \\ gc + a\mu_2 K_s & gK + \mu_2 K_s & -g - \mu_2 \end{pmatrix} \tag{15}$$

which can be used to attain the stabilization of HIV system provided that $Re\lambda_i < 0$, λ_i are the eigenvalues of $\mathbb{T}(A + B_s K_s C_s)$

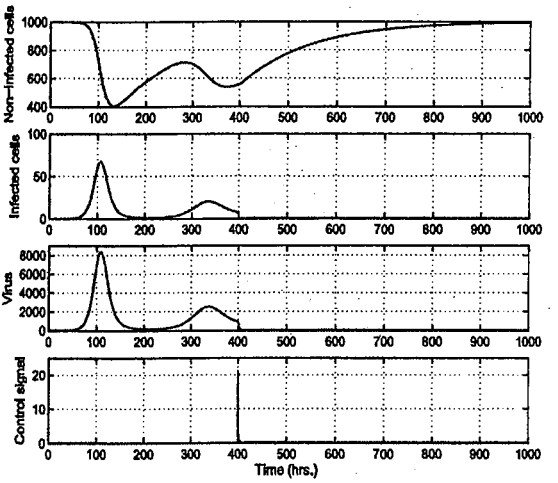

Fig. 2. Synchronization of the network in a chaotic attractor.

Figure 2 illustrates the stabilization at the origin of the infected cells T_{ip}, and therefore the virus is leaded to the origin. In this case the system parameters were chosen as $s = 7.0, d = 0.007, b = 4 \times 10^{-6}, \mu_1 = 0.3, \mu_2 = 0.6, g = 75$. The control gain $k = 3$ and was activated at $t = 400Hrs$. Figure 2 Illustrates the stabilization of the virus V and the infected cells T_{ip} therefore, the uninfected cells T tends to the noninfectious level.

5 Conclusions

In this work, we present an alternative method to stabilize a particular class of biomedical systems. The method consists in, departing from a controllable system, proposing an invertible transformation. The transformation exploits the stable properties of a controllable system to stabilize a nonlinear system with UMS. The utility of the method was illustrated using the HIV-I and the TIDM

model, in both cases the systems were stabilized at an operation point given by a healthy person. The present method is simple since it mainly consists in determine an invertible transformation from the uncontrollable system to the controllable. As example, the Rössler system is chosen to show the stability preservation even if differences between CS and unstable nonlinear system are exaggereted. This result can be extended to more complex and general systems however results in this directions are under study.

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