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Globally Stable Nonlinear Control of HIV-1 Systems

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***Abstract*— This paper addresses the problem of controlling the predator-prey like model of the interaction among CD4$^+$ T-cell, CD8$^+$ T-cell and HIV-1 by an external drug agency. By exploring the dynamic properties of the system, the origin system is £rst regrouped into two subsystems, then a nonlinear global controller is presented by designing two controllers over two complimentary zones: a local controller on a £nite region and a global boundary controller over its compliment. The local controller is developed to guarantee the nonnegative properties and avoid control singularity problem within the neighborhood of origin Ω. The complimentary controller is designed via backstepping for both the subsystems respectively over the complimentary region. The closed-loop system is globally stable at nominal values, the resulting controller is singularity free and guarantee the nonnegative properties. Simulation results are demonstrated to show the effectiveness of the proposed methods.**

I. INTRODUCTION

Over last few years, the understanding of HIV-1 infection has been greatly advanced. There are six reverse transcriptase inhibitors (AZT, ddI, ddC, d4T, 3TC and nevirapine) and three protease inhibitors (saquinavir, indinavir and ritonavir) in the current approval by Food and Drug Adminstration [1][2]. These potent drugs inhibit viral replication and lead to a rapid decline in viral abundance. Highly active antiretroviral therapy (HAART), composed of multiple anti-HIV drugs, is prescribed to many HIV-positive people [3]. HAART inhibits the replication of HIV-1, has proven to be extremely effective at reducing the amount of virus in the blood and tissues of infected patients. In the development of a better understanding of the dynamics of the immune system, much can be learnt from the approaches and tools used by the ecologist to explore the population dynamics and evolution of single and multi-species communities.

It is well known that HIV-1 production in infected indivituals is largely the result of a dynamic process [4][5].Several mathematical models that incorporate the effects of therapy on HIV-infected individuals has been developed. In a series of papers [6][7][8], the timing, frequency and intensity of AZT treatment are investigated. Descriptive models for the competitive interaction of AZT-sensitive and AZT-resistant strains of HIV has been analyzed in [9]. In [10], it proposed that the short term effect of AZT treatment is due to the predator-prey like interaction between virus and host cells and that the CD4 cell increase following drug treatment is responsible for the resurgence of virus. In [11], a nonlinear dynamic model is presented for HIV-1 in the human body and investigated the interplay between CD4+ T-cells and CD8+ T-cells. The increase in the number of cases of AIDS has led to the development of new mathematical models which describe the dynamical behavior of the viral load on CD4$^+$ T-cells counts as well as the effects of treatment strategies [12][13]. On the other hand, some cases were related to improvements in CD4$^+$ T-cells and destruction of the viral load. Intense clinical research has been carried out [14][15].

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As a matter of fact, the feedback control of HIV-1 is a problem which is made dif£cult by the inherent nonlinear nature of the involved mechanisms. The origin system is not in the strict-feedback form. By noticing that the inherent structures of both CD4 equation and CD8 equations are identical, the original system is regrouped into two subsystems, for which backstepping design and its variants can be applied. Our studies in this paper focus on those solutions evolving in the nonnegative sets $R^n_{\geq 0}$, where the subsystems are analyzed on two separate compact set $\Omega \subset R^n_{\geq 0}$ and its compliment $\Omega_c = R^n_{\geq 0} - \Omega \subset R^n_{\geq 0}$ respectively.

The main contributions of the paper lie in:

(i) The introduction of two complement regions for global control system design that enable us to handle the singularity and nonnegativity problem individually;
(ii) The recomposition of the original system such that each subsystem is in strict feedback form, for which backstepping design can be applied; and
(iii) The design of a novel bridging virtual control which serves as a bridge to stabilize the two subsystem simultaneously.

The organization of this paper is as follows. Some mathematical preliminary results and a detailed presentation predator-prey like model of HIV-1 [11] is introduced in Section III. In Section III, a new Lyapunov based method is presented to design a controller for both subsystems over two complementary regions. Section IV contains the numerical experiment of the controlled HIV-1 model. Finally, some concluding remarks are given in Section V.

II. PRELIMINARIES AND DYNAMIC MODEL

A. Mathematical Preliminaries

In order to study the dynamical properties of system (2), some standard notations to be used are listed below [16]:

(i) $R_{\geq 0}$=nonnegative real numbers;
(ii) R^n_+=n-column vectors with entries on R_+; similarly for $R_{\geq 0}$;
(iii) R^n_0=boundary of $R^n_{\geq 0}$, set vectors $x \in R_{\geq 0}$ such that at least one element of $x = 0$.

De£nition 1: [16] Set $S \subset R^n$ is said to be forward invariant with respect to the differential equation $\dot{x} = f(x)$

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if with $x(0) \in S$ each solution $x(t) \in S$ for all positive t in the domain of de£nition of $x(\cdot)$.

It is clear to note that the forward invariant property of a nonlinear system depends on the initial state $x(0)$.

Let $L_f h_j := (\partial h_j/\partial x) f(x)$ denote the directional derivative (Lie derivative) of a scalar function h_j with respect to the vector £eld $f(x)$ [17]. Further, let $L_f^i h_j := L_f(L_f^{i-1} h_j) \forall j = 1, 2, \ldots, m$, with $L_f^0 h_j := h_j$.

The following Lemma is essential in solving the control problem proposed in the paper, in particular, the control problem without virtual control.

Lemma 1: [18], [19] Let function $V(t) \geq 0$ be a continuous function de£ned $\forall t \in R^+$ and $V(0)$ bounded. If the following inequality.

$$\dot{V}(t) \leq -c_1 x^2(t) + c_2 y^2(t), \quad \text{constants} \quad c_1, c_2 > 0 \quad (1)$$

holds and $y(t)$ is square integrable, then $x(t)$ is also square integrable. In addition, if $\dot{x}$ is bound, then $x \to 0$ as $t \to \infty$.

B. Dynamics and Properties of the HIV-1 System

In this paper, we shall investigate the problem of controlling the predator-prey like model described as [11]:

$$\begin{aligned} \dot{x}_1 &= p_1(x_{10} - x_1) - p_2 x_1 x_3 \\ \dot{x}_2 &= p_3(x_{20} - x_2) + p_4 x_2 x_3 \\ \dot{x}_3 &= x_3(p_5 x_1 - p_6 x_2), \end{aligned} \quad (2)$$

where x_1, x_2 and x_3 are the states, $p_1, p_2, \ldots, p_6$ are positive constants and their detailed explanations are explained in [11][20]

The system has two equilibriums: one is on the boundary of $R^3_{\geq 0}$ stands as a saddle point, the other is an interior equilibrium that is attractive within R^3_+ (see [21]). The class of systems which we consider is basically 'forward invariant' as de£ned in [16]. The forward invariant provides a method to guarantee the nonnegative properties of the biomedical system. These de£nitions are useful, as our study will be focused on the solution of (2) that evolves in $R^3_{\geq 0}$.

Lemma 2: [16] Both R^3_0 and R^3_+ are forward-invariant sets with respect to system (2).

These properties are simple consequences of the fact that, because the ith component of the solution of (2) will satisfy $\dot{x}_i(t) \geq 0$ whenever $x_i(t) = 0$.

Lemma 3: [16] For each $\xi \in R^3_{\geq 0}$, there is a unique solution $x(t)$ of (2) with $x(0) = \xi$, de£ned for all $t \geq 0$.

III. Controller Design

Let x_0 denotes the nominal healthy value. For the convenience of control design, choose the state variables as

$$y = \begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} = \begin{bmatrix} x_1 - x_{10} \\ x_2 - x_{20} \\ x_3 \end{bmatrix} \quad (3)$$

so that the desired equilibrium point is located at the origin of the state space. Consequently, the control objective is to force x converge to x_0. As de£ned in [20], we introduce the external control agent u to reduce the viral load. The state equation is

$$\begin{aligned} \dot{y}_1 &= -p_1 y_1 - p_2(y_1 + x_{10}) y_3 \\ \dot{y}_2 &= -p_3 y_2 + p_4(y_2 + x_{20}) y_3 \\ \dot{y}_3 &= y_3[p_5(y_1 + x_{10}) - p_6(y_2 + x_{20})] - u, \end{aligned} \quad (4)$$

where $y_1 + x_{10} = x_1 > 0$, $y_2 + x_{20} = x_2 > 0$, and $y_3 = x_3 \geq 0$.

Remark 1: From the £rst two equations, we £nd that

(i) if $y_1(0) < 0$, then $y_1(t) < 0 \ \forall t > 0$.
(ii) if $y_2(0) > 0$, then $y_2(t) > 0 \ \forall t > 0$.

These are easily veri£able as follows. Because $x_1 = y_1 + x_{10} > 0$, $y_3 > 0$ and all the parameters p_1 and p_2 are positive constants, we know that $\dot{y}_1(t) < 0$ whenever $y_1(t)$ approach 0. Similarly, because $x_2 = y_2 + x_{20} > 0$, $y_3 > 0$ and all the parameters p_3 and p_4 are positive constants, we know that $\dot{y}_2(t) > 0$ whenever $y_2(t)$ approach 0. The observation is not only useful for control system design, but also the case in reality. In an HIV infected human lymphatic system, CD_4 count is much less than the nominal value, i.e., $y_1(t) < 0$, and CD_8 count is much more than the nominal value , i.e., $y_2(t) > 0$.

Examining system (4), we know that it is not in the standard backstepping design form, and the backstepping procedure cannot be directly applied. However, it is well known that [22] backstepping allows ¤exibility in exploiting the properties of the physical system, i.e. avoiding cancellations; stability of nonlinear systems are investigated using Lyapunov theory fundamentally, including backstepping; Lyapunov functions are additive, like energy, i.e., Lyapunov functions for combinations of subsystems may be derived by adding the Lyapunov functions of the subsystems.

The above ideas motivate us to re-group the system into two subsystems that are in strict feedback form for the convenience of applying backstepping design; sum up the design procedure together for the original physical system for the £nal control design, as will be demonstrated here for the systematic understanding to demonstrated the main idea.

Let us divide system (4) into two subsystems Σ_1 and Σ_2 in strict feedback forms:

$$\Sigma_1 \begin{cases} \dot{y}_1 &= f_{1,1}(y_1, y_2) + g_{1,1}(y_1, y_2) y_3 \\ \dot{y}_3 &= f_{1,2}(y_1, y_2) - u_1 \end{cases} \quad (5)$$

$$\Sigma_2 \begin{cases} \dot{y}_2 &= f_{2,1}(y_1, y_2) + g_{2,1}(y_1, y_2) y_3 \\ \dot{y}_3 &= f_{2,2}(y_1, y_2) - u_2 \end{cases} \quad (6)$$

where

$$\begin{aligned} f_{1,1}(y_1, y_2) &= -p_1 y_1 \\ g_{1,1}(y_1, y_2) &= -p_2(y_1 + x_{10}) \\ f_{2,1}(y_1, y_2) &= -p_3 y_2 \\ g_{2,1}(y_1, y_2) &= p_4(y_2 + x_{20}) \\ f_{1,2}(y_1, y_2) &= f_{2,2}(y_1, y_2) = y_3 \phi(y_1, y_2), \end{aligned}$$

with $\phi(y_1, y_2) = p_5(y_1 + x_{10}) - p_6(y_2 + x_{20})$.

For convenience of discussion, let $*_{i,j}$ denotes the jth variable or constant of the ith subsystem, unless otherwise de£ned.

For the control design, the following technical problems should be addressed:

(i) Nonnegative problem: The controller should ensure the nonnegative properties of the state variables.
(ii) Control singularity: The states converge to zero causing control singularity problem, which should be avoided in control design.
(ii) Global control: The control design should ensure global stability rather than a local one.

By exploring the physical properties, control system design to be conducted in two separate zones. For ease of discussion, let us de£ne set $\Omega \subset R^3_{\geq 0}$ and Ω_c as follows:

$$\Omega \;:=\; \{y \in R^3_{\geq 0} :\; y_3 < p_3/p_4\} \quad (7)$$
$$\Omega_c \;:=\; R^3_{\geq 0} - \Omega. \quad (8)$$

" $-$ " in (8) is used to denote the complement of set B in set A as follow

$$A - B := \{x | x \in A \; and \; x \notin B\}.$$

As p_3 and $p_4 > 0$, Ω is not empty. We £rst focus our study in Ω, to solve the nonnegative problem and avoid control singularity problem. Then, we generalize our local result to global stability via backstepping design, where no singularity and nonnegative problem present.

In this section, the controller design is developed based on backstepping. Backstepping design is a standard design procedure now in handing systems in strict feedback, and usually contains n steps [23]. The design of control law is based on the following change of coordinates: $z_1 = x_1$, $z_i = x_i - \alpha_{i-1}$, $i = 2, ..., n$, where $\alpha_i(t)$ is an intermediate control functions developed for the ith-subsystem based on an appropriate Lyapunov function $V_i(t)$. The control law $u(t)$ is designed in the last step.

By exploring the physical problem of the system, global control is constructed over two complementary regions: Ω and its complement Ω_c. In Subsection III-A, asymptotic control is presented using decoupled iterative Lyapunov design to overcome the nonnegativity and singularity problem. In Subsection 3.2, we employ the backstepping design with bridging virtual control to realize the global result in Ω_c.

A. Region Control

In region Ω which includes the origin, stable control can be easily constructed by exploiting the properties of the system through a process of decoupled iterative Lyapunov design on the natural description directly, without the introduction of any virtual control.

For convenience of discussion, control system design is developed in three stages – while the £rst two stages are for each subsystems, the third stage is to sum up the results obtained in stages 1 and 2 in order to conclude any results for the whole system.

Stage 1: Subsystem Σ_1: As subsystem Σ_1 is of 2nd order, the design consists of 2 steps.

Step 1 Let us £rst consider the £rst equation of Σ_1, i.e.,

$$\dot{y}_1 = f_{1,1}(y_1, y_2) + g_{1,1}(y_1, y_2) y_3.$$

Choose the following Lyapunov function candidate

$$V_{1,1} = \frac{1}{2} y_1^2. \quad (9)$$

Its derivative is given by

$$\begin{aligned} \dot{V}_{1,1} &= y_1 \dot{y}_1 = -p_1 y_1^2 - p_2 (y_1 + x_{10}) y_1 y_3 \quad (10) \\ &= -p_1 y_1^2 - p_2 y_3 y_1^2 - p_2 x_{10} y_1 y_3, \end{aligned}$$

Using Young's inequality,

$$-p_2 x_{10} y_1 y_3 \leq \epsilon_1 y_1^2 + \frac{p_2^2 x_{10}^2}{4\epsilon_1} y_3^2, \quad \epsilon_1 > 0, \quad (11)$$

we have

$$\begin{aligned} \dot{V}_{1,1} &\leq -p_1 y_1^2 - p_2 y_3 y_1^2 + \epsilon y_1^2 + \frac{p_2^2 x_{10}^2}{4\epsilon_1} y_3^2 \quad (12) \\ &= -(p_1 - \epsilon_1 + p_2 y_3) y_1^2 + k_{1,1} y_3^2, \end{aligned}$$

where $k_{1,1} = \frac{p_2^2 x_{10}^2}{4\epsilon_1} > 0$.

Remark 2: Since $y_3 \geq 0$, if we choose $\epsilon_1 < p_1$, $-(p_1 - \epsilon_1 + p_2 y_3) y_1^2$ is a stabilizing item and there is no need to cancel it. Unlike the argument of classical Lyapunov design where the stabilization of y_1 relies on the cancellation of the coupling term $y_1 y_3$ in $\dot{V}_1$ in the next step, the stabilization of y_1 relies on the proof of the stability of y_3 in the following step. If we could prove that y_3 is square integrable, then the stability of the y_1 is ensured, according to Lemma 1.

Step 2 In this step, we will design a controller u_1 that make y_3 square integrable. This is fundamentally different from the commonly understood backstepping designs, where control system design is carried out for the transformed system in z space, rather than in the y space directly. Consider the Lyapunov candidate

$$V_{1,2} = \frac{1}{2} y_3^2. \quad (13)$$

Noticing the 2nd equation of Σ_1 in (5), its derivative is given by

$$\dot{V}_{1,2} = y_3 \dot{y}_3 = y_3 [f_{1,2}(y_1, y_2) - u_1]. \quad (14)$$

Considering the following controller

$$u_1 = k_{1,2} y_3 + f_{1,2}(y_1, y_2), \quad (15)$$

with constant $k_{1,2} > 0$, equation (14) can be rewritten as

$$\dot{V}_{1,2} = -k_{1,2} y_3^2 \leq 0. \quad (16)$$

Since $\dot{V}_3$ is negative semi-de£nite, it follows from y_3 is square integrable. Applying Lemma 1 backward to equation of y_1, we know that y_1 is also bounded, and moreover, $\lim_{t\to\infty} |y_i| = 0$, for $i = 1, 3$.

Stage 2: Subsystem Σ_2: As the structure of Σ_1 is identical to that of Σ_2, similar analysis can be carried out without any problem. For detail explanation, see [21].

Stage 3: Additive Lyapunov Design: Fundamentally, we only need to stabilize the third equation of (4), i.e., the 2nd equation of both subsystem Σ_1 and Σ_2. Further noticing that the choice of Lyapunov functions for the second equations in the previous analysis, we have chosen the same Lypunov function for both subsystem Σ_1 and Σ_2 , i.e., $V_{1,2} = V_{2,2}$. It should be a good Lypunov function candidate for the third equation of the original system (4) as well.

Accordingly, let us consider the Lyapunov function candidate

$$V = \frac{1}{2}y_3^2. \tag{17}$$

From stage 1 and stage 2, we have

$$\dot{V} = y_3^2\phi(y_1, y_2) - uy_3. \tag{18}$$

Considering the regional control law

$$u = u_r = y_3\phi(y_1, y_2) + k_3y_3, \quad k_3 > 0, \tag{19}$$

we have

$$\dot{V} = -k_3y_3^2, \quad \forall y \in \Omega, \tag{20}$$

which shows that the origin (y=0) is asymptotically stable. As y is continuous, hence, a direct application of Barbalat's Lemma [24] gives that $\lim_{t\to\infty} |y(t)| = 0$, which implies, in particular, that $\lim_{t\to\infty} |x(t) - x_0| = 0$. We summarize our conclusion in the Theorem 1.

Theorem 1: Consider the closed-loop system (4) with the compact set (7. If the control law (19) is applied, then, $\forall y(0) \in \Omega$, $y(t) \in \Omega$ $\forall t \geq 0$, and $y \to 0$ as $t \to \infty$.

Proof: The proof can be easily completed by following the previous design procedures from Stage 1 to Stage 3. Δ

B. Complementary Control

In this subsection, within Ω_c, no nonnegativity problem exists. Because the virtual control law should be same for the second equations of subsystems Σ_i, i=1, 2, we shall develop the control system in distinct steps as backstepping design, but with more complexity.

Step 1 : Let us consider Subsystem Σ_1 £rst. De£ne $z_{1,1} = y_1$. Its derivative is given by

$$\dot{z}_{1,1} = \dot{y}_1 = -p_1z_{1,1} - p_2(z_{1,1} + x_{10})(z_{1,2} + \alpha), \tag{21}$$

where $z_{1,2} = y_3 - \alpha$, and α will be de£ned later. Choose the following Lyapunov function candidate

$$V_{1,1} = \frac{1}{2}z_{1,1}^2. \tag{22}$$

Its derivative is given by

$$\begin{aligned}\dot{V}_{1,1} &= z_{1,1}\dot{z}_{1,1} = z_{1,1}[-p_1y_1 - p_2(y_1 + x_{10})]y_3 \\ &= -p_1z_{1,1}^2 - p_2z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha). \quad (23)\end{aligned}$$

As subsystems Σ_1 and Σ_2 should be fundamentally simultaneously stabilized using one single input, the virtual control α should be the same for the £rst equations of the two systems, so that the transformed coordinates in the next step for the two subsystems are the same, i.e., $z_{1,2} = z_{2,2}$. Consider the virtual control

$$\alpha = \alpha_1 + \alpha_2, \tag{24}$$

where α_i is used to stabilize the subsystem Σ_i. Noticing (24), (23) can be rewritten as

$$\begin{aligned}\dot{V}_{1,1} &= -p_1z_{1,1}^2 - p_2z_{1,1}(z_{1,1} + x_{10})\alpha_1 \quad (25)\\ &\quad -p_2z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha_2).\end{aligned}$$

Apparently, by choosing $\alpha_1 = \frac{c_{1,1}y_1}{y_1+x_{10}}$ and noticing that $z_{1,1} = y_1$, we have

$$\begin{aligned}\dot{V}_{1,1} &= -(p_1 + c_{1,1}p_2)z_{1,1}^2 \quad (26)\\ &\quad -p_2z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha_2).\end{aligned}$$

The £rst term is stabilizing because both $p_1, p_2 > 0$, and the second term $-p_2z_{1,1}(z_{1,1}+x_{10})(z_{1,2}+\alpha_2)$ will be handled in the next step. The closed-loop form of (21) with (24) is

$$\dot{z}_{1,1} = -(p_1+c_{1,1}p_2)z_{1,1} - p_2(z_{1,1}+x_{10})(z_{1,2}+\alpha_2). \tag{27}$$

Similar analysis can be carried out for subsystem Σ_2. for complete deduction, see [21]

Step 2: For convenience, let us de£ne

$$g(y) = L_{y_1}\alpha_1 + L_{y_2}\alpha_2. \tag{28}$$

The derivative of $z_{1,2}$ is expressed as

$$\dot{z}_{1,2} = \dot{y}_3 - g(y). \tag{29}$$

For subsystem (21) and (29), we now design a control law u_1 to render the time derivative of a Lyapunov function negative de£ne. Following the standard backstepping design, consider the Lyapunov function candidate

$$V_{1,2} = V_{1,1} + \frac{1}{2}z_{1,2}^2. \tag{30}$$

Its derivative for (29) is

$$\begin{aligned}\dot{V}_{1,2} &= \dot{V}_{1,1} + z_2\dot{z}_2 \quad (31)\\ &= z_{1,2}\Big(f_{1,2} + u_1 - g(y)\Big) - (p_1 + c_{1,1}p_2)z_{1,1}^2 \\ &\quad -p_2z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha_2) \\ &= -(p_1 + c_{1,1}p_2)z_{1,1}^2 - p_2z_{1,1}(z_{1,1} + x_{10})\alpha_2 \\ &\quad +z_{1,2}\Big(f_{1,2} - u_1 - p_2z_{1,1}(z_{1,1} + x_{10}) - g(y)\Big).\end{aligned}$$

Since within Ω_c, $z_{1,2} = y_3 - \alpha > p_3/p_4 > 0$, it is easy to see that the choice of control

$$\begin{aligned}u_1 &= c_{1,2}z_{1,2} + f_{1,2}(y) - g(y) \quad (32)\\ &\quad -(1 + \frac{\alpha_2}{z_{1,2}})p_2z_{1,1}(z_{1,1} + x_{10}),\end{aligned}$$

which is well de£ned, leads to

$$\dot{V}_{1,2} = -(c_{1,1}p_2 + p_1)z_{1,1}^2 - c_{1,2}z_{1,2}^2, \tag{33}$$

which means that the equilibrium $z = 0$ is globally asymptotically stable, since $\dot{V}_{1,2}$ is negative, it follows from LaSalle-Yoshizawa theorem [24]. Note that u_1 and α are smooth function and satisfy $u(0) = 0$, and $\alpha \to 0$ as $t \to \infty$, $\forall y(0) \in R_+^2$. Thus, we can conclude that $y = 0$ is globally asymptotically stable.

Similarly, the analysis of subsystem Σ_2 can be similarly carried out. Due to the space limitation, the deduction is presented in [21]. Then, we choose the control law

$$\begin{aligned} u_2 &= (1 + \frac{\alpha_1}{z_{2,2}})p_4 z_{2,1}(z_{2,1} + x_{20}) \\ &+ c_{2,2}z_{2,2} + f_{2,2}(y) - g(y), \end{aligned} \tag{34}$$

which is well de£ned.

Step 3: As Lyapunov functions are additive, the sum of the Lyapunov functions for Σ_1 and Σ_2 are good candidate for the whole system. Consider the Lyapunov function candidate

$$V = V_{1,2} + V_{2,2}. \tag{35}$$

From the previous discussion, we have

$$\begin{aligned} \dot{V} &= -\sum_{i=1}^{2}(c_{i,1}p_{2i} + p_{2i-1})z_{i,1}^2 + z_{i,2}[g(y) + f_{i,2}] \quad (36) \\ &+ \sum_{i=1}^{2} z_{i,2}\Big[-u + (1 + \frac{\alpha_i}{z_{i,2}})p_{2i}z_{i,1}(z_{i,1} + x_{i0})\Big] \\ &= -\sum_{i=1}^{2}(c_{i,1}p_{2i} + p_{2i-1})z_{i,1}^2 + z_{i,2}[g(y) + f_{i,2}] \quad (37) \\ &+ z_{1,2}\sum_{i=1}^{2}\Big[-u + (1 + \frac{\alpha_i}{z_{i,2}})p_{2i}z_{i,1}(z_{i,1} + x_{i0})\Big]. \end{aligned}$$

It is clear that the control law in the complement region, u_c, of the following form

$$\begin{aligned} u &= u_c = -g(y) + c_{1,2}z_{1,2} + f_{1,2} \\ &- \frac{1}{2}\sum_{i=1}^{2}[(1 + \frac{\alpha_i}{z_{i,2}})p_{2i}z_{i,1}(z_{i,1} + x_{i0})], \end{aligned} \tag{38}$$

leads to

$$\dot{V} = -(c_{1,1}p_2 + p_1)z_{1,1}^2 - (c_{2,1}p_4 + p_3)z_{2,1}^2 - c_{1,2}z_{1,2}^2. \tag{39}$$

Since V is negative de£nite, it follows that system is asymptotically stable at the origin.

Theorem 2: Consider the closed-loop system consisting of (4), the set (8) and the control law (38). Then, for any initial conditions $y(0) \in R_{\geq 0}$, the solution of system (4) $y(t) \to 0$ as $t \to \infty$ asymptotically.

Proof: The proof of Theorem 2 can be driven from Stage 1 to Stage 3. Δ

Remark 3: For clarity, the control law (38) is clearly derived from (38). By examining (37), and noticing the expression of (32) and (34), we know that the control in (38) can be conveniently written as

$$u = u_c = \frac{1}{2}(u_1 + u_2)$$

with u_c reads as control in the complement region, and u_1 and u_2 are de£ned in (32) and (34), respectively.

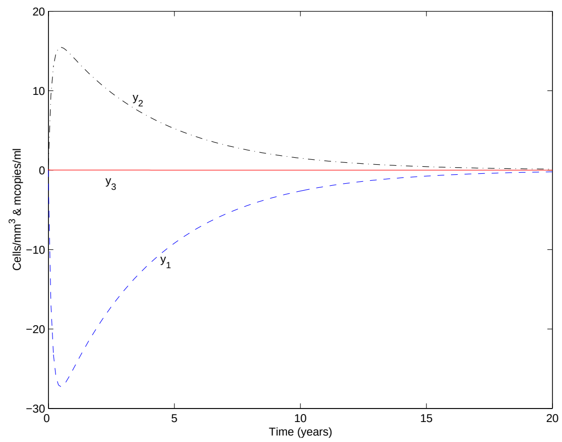

Fig. 1. System states y_1, y_2 and y_3.

Corollary 1: Consider the closed-loop system consisting of (4), the compact set (8) and the control law (38). Then, for any initial conditions $y(0) \in \Omega_c$, the solution of system (4) $y(t) \to \Omega$ in a £nite time $t^* > 0$ asymptotically.

In the proceeding, we have design two controllers for states $y \subset \Omega$ and $y \subset \Omega_c$ respectively. Thus, we obtain the following proposition

Proposition 1: Consider the closed-loop system (4) and the control law

$$u(t) = \begin{cases} u_r & y \in \Omega \\ u_c & y \in \Omega_c \end{cases} \tag{40}$$

where u_r and u_c are de£ned in equation (19) and (38) respectively. Then, system (4) is asymptotically stable at the origin for any $y(0) \subset R_{\geq 0}$.

IV. Simulation

To verify the effectiveness of the proposed approach, the developed adaptive control is applied to system (4). To illustrate the realistic case the values of the parameters used are: $x_{10} = 1000$ cell/mm^3, $x_{20} = 550$cell/mm^3, $p_1 = 0.25$, $p_2 = 10$, $p_3 = 0.25$, $p_4 = 10.0$, $p_5 = 0.01$ and $p_6 = 0.006$. Figure 1-3 show the simulation results of applying controller (40) to system (4). The initial conditions $[y_1(0), y_2(0), y_3(0)]^T = [0, 0, 0.1]^T$, From Figure 1, it can be seen that all the states evolve in a small range ($-27 < y_1 < 0$ and $0 < y_2 < 15$) and asymptotically converge to the origin as time goes to in£nite. In Figure 2-3, we £nd that the adaptive controller is switched at the time of 14.6 hour.

V. Conclusions

The dynamics properties of the prey-predator like HIV-1 model has been studied in this paper. By exploiting the system properties, the system is regrouped into two subsystems, which are in strict feedback form, and is analyzed over two complementary regions. A singularity free controller is presented for HIV-1 system using the decoupled Lyapunov

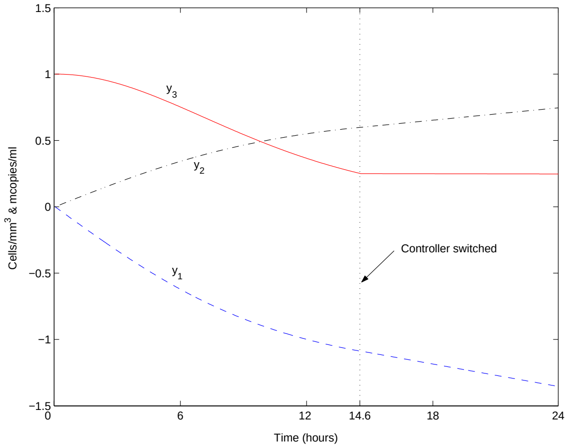

Fig. 2. System states y_1, y_2 and y_3.

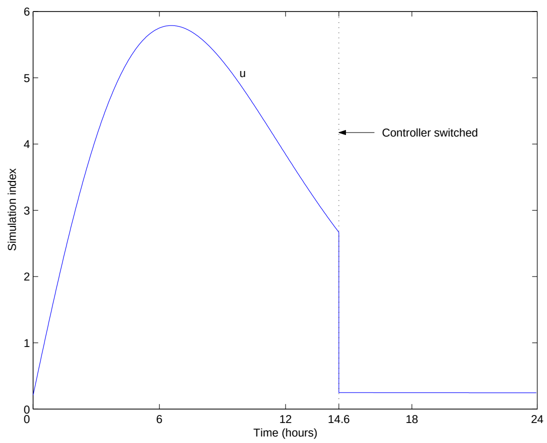

Fig. 3. Control action u.

over Ω. A novel bridging virtual control is applied over Ω_c for backstepping design. The proposed control can drive the all the positive states asymptotically converge to the desire values, and guarantee the nonnegative properties of all states in the closed-loop system. The design method make use of the ¤exibility of the Lyapunov design and does not lead to singular behavior with respect to the control action.

However, we know that every individual system has a unique set of parameters that may not be known either exactly in advance. The drugs implemented without the prori knowledge of the parameters may caused unexpected dangerous. In order to solve this problem, the estimation of HIV parameters by using adaptive observers has been proposed [25]. Adaptive control of the nonlinear HIV system has been investigated in [26].

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