Nonlinear Control of a Dynamic Model of HIV-1

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***Abstract*—Highly active antiretroviral therapy (HAART) reduces the viral burden in human immunodeficiency virus type 1 (HIV-1) infected patients. The 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 original system is first regrouped into two subsystems, then a nonlinear global controller is presented by designing two controllers over two complementary zones: a local controller on a finite region and a global controller over its complement. The local controller is designed to guarantee nonnegativty, and avoids the problem of control singularity within the neighborhood of the origin Ω. The complementary controller is designed via backstepping for both subsystems over the complementary region. The closed-loop system is globally stable at nominal values through the introduction of a novel bridging virtual control, and the resulting controller is singularity free and guarantees nonnegativity. In this paper, simulations are conducted in discrete-time with sampling time T_s to show the effectiveness of the proposed method.**

***Index Terms*—Backstepping, HIV-1 infection, nonlinear control, periodical sampling.**

I. Introduction

OVER the last few years, there have been great advances in our understanding of the HIV-1 infection. Of the drugs developed to treat HIV-1, there are six reverse transcriptase inhibitors (AZT, ddI, ddC, d4T, 3TC, and nevirapine), and three protease inhibitors (saquinavir, indinavir and ritonavir), all of which are currently approved by the Food and Drug Administration [1], [2]. These potent drugs inhibit viral replication and lead to a rapid decline in viral abundance. Highly active antiretroviral therapy (HAART), which consists of the use of multiple anti-HIV drugs, is prescribed for many HIV-positive people [3]. The inhibition of the replication of HIV-1 by HAART has been proven to be extremely effective at reducing the amount of virus in the blood and tissues of infected patients. From studies on the immune system, the population of the Leukocyte surface molecules [assigned as the "Cluster of Differentiation" (CD) number] as indicated by antibodies [4], needs to be analyzed during therapies.

It is well known that HIV-1 production in an infected individual is largely the result of a dynamic process [5], [6]. Several mathematical models that incorporate the effects of therapy on HIV-infected individuals have been developed. In a series of papers [7]–[9], the timing, frequency and intensity of AZT treatment were investigated. Descriptive models for the competitive interaction of AZT-sensitive and AZT-resistant strains of HIV have been analyzed in [10] and [11]. In [12], it is 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 increase of CD4 cell following drug treatment is responsible for the resurgence of virus. In [13], a nonlinear dynamic model is presented for HIV-1 in the human body, and the interplay between CD4+ T-cells and CD8+ T-cells is investigated. The increase in the number of cases of AIDS has led to the development of new mathematical models to describe the dynamical behavior of the viral load on $CD4^+$ T-cells counts as well as the effects of treatment strategies [14], [15]. At the same time, certain cases that are related to increases in $CD4^+$ T-cells and destruction of the viral load have been the subjects of intense clinical research [16], [17].

As a matter of fact, feedback control of HIV-1 is difficult by the inherent nonlinear nature of the involved mechanisms. Noticing the fact that the inherent structures of both CD4 equation and CD8 equation are identical, the original system, which is not in strict feedback form, is regrouped into two subsystems in strict feedback form for which backstepping design and its variants can be applied. Our studies in this paper focus on those solutions that evolve in the nonnegative sets $R^n_{\geq 0}$, within which the subsystems are analyzed on two separate compact sets $\Omega \subset R^n_{\geq 0}$ and its complement $\Omega_c = R^n_{\geq 0} - \Omega \subset R^n_{\geq 0}$.

1) In region Ω, which is of fixed size and includes the origin, a singularity free control is developed by using decoupled Lyapunov design to guarantee nonnegativity. In contrast to cancellation based design, our design decouples y_i from y_{i+1} using Young's inequality and seeks the boundedness of y_{i+1} in the next step [18], [19]. There is no need for the introduction of virtual control and coordinate transformation.
2) In the complementary set Ω_c, a new control law is designed to achieve stability over the whole region. Though there is no control singularity and nonnegativity problem in this region, the introduction of a new bridging virtual control, α, is essential to stabilize the first equation of both subsystems simultaneously, and to cancel all the unstable terms in the last step. This method allows us to extend the stability from the local sense to the global sense. The combination of the controllers in Ω and Ω_c gives a global controller.

II. Preliminaries and Dynamic Model

A. Mathematical Preliminaries

In order to study the dynamical properties of system (2), some standard notations are defined as follows [20].

1) $R_{\geq 0}(R_+)$: nonnegative (positive) real numbers.
2) $R^n_{\geq 0}(R^n_+)$: n-column vectors with entries on $R_{\geq 0}(R_+)$.

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3) R_0^n: boundary of $R_{\geq 0}^n$, set vectors $x \in R_{\geq 0}^n$ such that at least one element of $x = 0$.

Definition 2.1 [20], [21]: Set $S \subset R^n$ is said to be forward invariant with respect to the differential equation $\dot{x} = f(x)$, if, with $x(0) \in S$, each solution $x(t) \in S$ for all positive t in the domain of $x(\cdot)$.

It is clear 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 field $f(x)$ [22], [23]. 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 to solve the control problem proposed in the paper.

Lemma 2.1 [18], [19]: Let function $V(t) \geq 0$ be a continuous function defined $\forall t > 0$ and $V(0)$ bounded. If the following inequality:

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

holds and $y(t)$ is square integrable, then $x(t)$ is also square integrable. In addition, if $\dot{x}$ is bounded, 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 as described in [13]

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

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 listed in Table I. Their physical properties and interactions are explained as follows [13], [24].

1) HIV-1 utilizes CD4 cells to replicate itself, and their growth rates are inversely proportional to each other.
2) The growth rate of CD8 cells increases in response to an increase of the HIV-1 load, causing CD8 cells to attack the virus.
3) The growth rate of HIV-1 increases with increased growth in the HIV-1 and CD4 populations.
4) The growth rate of HIV-1 decreases with decreased growth in the HIV-1 and CD4 populations.

As discussed in [24], it is easy to verify that there are two equilibriums: one is on the boundary of $R_{\geq 0}^3$ and stands as a saddle point; and the other is an interior equilibrium that is attractive within R_+^3 (see Appendix). The class of systems which we consider is basically 'forward invariant' as defined in [20]. The forward invariant class provides a means to guarantee the nonnegative properties of the biomedical system. These definitions are useful, as our study will be focused on the solution of (2) that evolves in $R_{\geq 0}^3$.

Lemma 2.2 [20]: Both R_0^3 and R_+^3 are forward invariant sets with respect to system (2).

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

Lemma 2.3 [20]: For each $\xi \in R_{\geq 0}^3$, there is a unique solution $x(t)$ of (2) with $x(0) = \xi$, defined for all $t \geq 0$.

TABLE I
DESCRIPTION OF VARIABLES AND PARAMETER

Variables and Parameters	Description
x_1	CD4+ T-cells population
x_2	CD8+ T-cells population
x_3	HIV-1 viral load
p_1	death rate of CD4+ T-cells
p_2	rate of infection of CD4+ cells by virus
p_3	death rate of CD8+ T-cells
p_4	rate of increase of CD8+ T-cells in response to increased HIV-1 load
p_5	rate of increase of Viral load
p_6	rate of decrease of Viral load
x_{10}	CD4+ T-cells unperturbed equilibrium value
x_{20}	CD8+ T-cells unperturbed equilibrium value

III. CONTROLLER DESIGN

Let $x_0 = [x_{10}\ x_{20}\ 0]^T$ denote the healthy value. For convenience of control design, define the state variables as

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

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 defined in [24], we introduce the external control agent u to reduce the viral load. The state equations are

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

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 first two equations, it is noted that:

a) if $y_1(0) < 0$, then $y_1(t) < 0\ \forall t > 0$;
b) if $y_2(0) > 0$, then $y_2(t) > 0\ \forall t > 0$.

These can be easily verified 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 $y_1(t)$ approaches 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 $y_2(t)$ approaches 0. The observation is not only useful for control system design, but also realistic. In an HIV infected human lymphatic system, CD4 count is much less than the healthy value, i.e., $y_1(t) < 0$, and CD8 count is much more than the healthy value, i.e., $y_2(t) > 0$.

Examining system (4), it can be seen that the system is not in the standard backstepping design form. Thus, backstepping procedure cannot be directly applied. However, it is well known from [25], [26] that:

1) backstepping allows flexibility in exploiting the properties of the physical system, i.e., avoiding cancellations;
2) stability of nonlinear systems are investigated using Lyapunov theory fundamentally, including backstepping;
3) 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 understandings provide the inspiration to:

1) re-group the system into different subsystems for the convenience of applying backstepping design;
2) combine the design procedure to obtain the final control design for the original physical system.

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

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

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

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 $*_{i,j}$ denote the jth variable or constant of the ith subsystem, unless otherwise defined.

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

1) *Nonnegativity:* The controller should ensure nonnegativity of the state variables.
2) *Control singularity:* The control singularity problem should be avoided, as the states converge to zero.
3) *Global control:* The control design should ensure global stability rather than a local one.

By exploiting the physical properties of the system, control system design can be carried out in two separate zones. For ease of discussion, let us define sets $\Omega \subset R^3_{\geq 0}$ and Ω_c as follows:

$$\Omega := \left\{ y \in R^3_{\geq 0} : y_3 < \frac{p_3}{p_4} \right\} \tag{7}$$

$$\Omega_c := R^3_{\geq 0} - \Omega \tag{8}$$

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

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

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

In this section, the controller design is developed based on backstepping. Backstepping is a standard design procedure for handling systems in strict feedback form, and usually contains n steps [25], [27], [28]. The design of control law is based on the following change of coordinates: $z_1 = x_1$, $z_i = x_i - \alpha_{i-1}$, $i = 2, \ldots, n$, where $\alpha_i(t)$ is an intermediate control function 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 exploiting the physical properties of the system, global control is constructed over two complementary regions: Ω and Ω_c. In Section III-A, asymptotic control is presented using decoupled iterative Lyapunov design [19] to overcome the nonnegativity and singularity problem. In Section III-B, 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 carrying out decoupled iterative Lyapunov design based on the natural system description directly, without the introduction of any virtual control [18], [19].

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

Step 1) Let us consider the first 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:

$$V_{1,1} = \frac{1}{2} y_1^2. \tag{9}$$

Its derivative is given by

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

Using Young's inequality

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

we have

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

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

Remark 2: Since $y_3 \geq 0$, if we choose $\epsilon_1 < p_1$, then $-(p_1 - \epsilon_1 + p_2 y_3) y_1^2$ 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 $\dot{V}_{1,1}$ 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 y_1 is ensured, according to Lemma 2.1.

Step 2) In this step, we will design a controller u_1 that makes 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

$$V_{1,2} = \frac{1}{2} y_3^2. \tag{13}$$

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

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

Considering the following controller

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

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

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

Since $\dot{V}_{1,2}$ is negative semi-definite, it follows from (16) y_3 is square integrable. Applying Lemma 2.1 backward to the 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. Let us rewrite Σ_2 as

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

Step 1) Consider the Lyapunov function candidate

$$V_{2,1} = \frac{1}{2}y_2^2. \tag{17}$$

Its derivative is given by

$$\begin{aligned} \dot{V}_{2,1} &= y_2\dot{y}_2 = -p_3y_2^2 + p_4(y_2 + x_{10})y_2y_3 \\ &= -p_3y_2^2 + p_4y_3y_2^2 + p_4x_{10}y_2y_3. \end{aligned} \tag{18}$$

Since our region of interest is within Ω, i.e., $y_3 < p_3/p_4$, we have

$$p_4x_{10}y_2y_3 < p_3x_{10}y_2. \tag{19}$$

Accordingly, we have

$$\dot{V}_{2,1} < -k_{2,1}y_2^2 + k_{2,2}y_2 \tag{20}$$

where $k_{2,1} = p_3 - p_4y_3 > 0$, and $k_{2,2} = p_3x_{10} > 0$. It is obvious that y_2 is bounded.

Remark 3: Note that inequality (20) is not unique. By using Young's inequality, we can also obtain

$$\begin{aligned} \dot{V}_{2,1} &< -(p_3 - p_4y_3)y_2^2 + \epsilon_2y_2^2 + \frac{p_4^2x_{10}^2}{4\epsilon_2}y_3^2 \\ &= -k_{2,1}^*y_2^2 + k_{2,2}^*y_3^2 \end{aligned} \tag{21}$$

where $k_{2,1}^* = p_3 - p_4y_3 - \epsilon_2 > 0$, $k_{2,2}^* = (p_4^2x_{10}^2/4\epsilon_2)$, and $\epsilon_2 > 0$.

We have to choose the zone as $\Omega^* = \{y \in R_{\geq 0}^3 : y_3 < p_3/p_4 - \epsilon_2/p_4\}$ rather than $\Omega = \{y \in R_{\geq 0}^3 : y_3 < p_3/p_4\}$. Apparently, it is much tighter than Ω.

Step 2) Consider the Lyapunov function

$$V_{2,2} = \frac{1}{2}y_3^2 \tag{22}$$

and the control law

$$u_2 = k_{2,3}y_3 + f_{2,2}(y_1, y_2), \quad k_{2,3} > 0 \tag{23}$$

we have

$$\dot{V}_{2,2} = y_3\left[f_{2,2}(y_1, y_2) - u_2\right] = -k_{2,3}y_3^2. \tag{24}$$

Similar to the previous discussion, we know that both y_2 and y_3 are square integrable.

Stage 3: Additive Lyapunov Design: Fundamentally, we only need to stabilize the third equation of (4), i.e., the 2nd equation of both subsystems Σ_1 and Σ_2. We have also chosen the same Lyapunov function for both subsystems Σ_1 and Σ_2, i.e., $V_{1,2} = V_{2,2}$. It should be a good Lyapunov function candidate for the third equation of the original system (4) as well.

Accordingly, let us consider the Lyapunov function candidate

$$V = \frac{1}{2}y_3^2. \tag{25}$$

From stages 1 and 2, we have

$$\dot{V} = y_3^2\phi(y_1, y_2) - uy_3. \tag{26}$$

Considering the regional control law

$$u = u_r = y_3\phi(y_1, y_2) + k_3y_3, \quad k_3 > 0 \tag{27}$$

we have

$$\dot{V} = -k_3y_3^2, \quad \forall y \in \Omega \tag{28}$$

which shows that the origin $(\mathrm{y} = 0)$ is asymptotically stable. As y is continuous, hence, a direct application of Barbalat's Lemma [29] gives $\lim_{t\to\infty}|y(t)| = 0$, which implies, in particular, that $\lim_{t\to\infty}|x(t) - x_0| = 0$.

Theorem 3.1: Consider the closed-loop system (4) with the compact set (7). If the control law (27) 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 obtained by following the previous design procedures from Stages 1–3. Δ

To ensure nonnegativity of y_3 which denotes the concentration of the viral load, let us check the closed-loop system (4) and (27). After the cancellation of the nonlinear term $y_3[p_5(y_1 + x_{10}) - p_6(y_2 + x_{20})]$, it gives

$$\dot{y}_3 = -ky_3. \tag{29}$$

As stated in Lemma 2.2, y_3 is said to be a nonnegative variable with $y_3(0) \in R_{\geq 0}$.

B. Complementary Control

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

Step 1: Let us consider subsystem Σ_1 first. Define $z_{1,1} = y_1$. Its derivative is given by

$$\dot{z}_{1,1} = \dot{y}_1 = -p_1z_{1,1} - p_2(z_{1,1} + x_{10})(z_{1,2} + \alpha) \tag{30}$$

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

$$V_{1,1} = \frac{1}{2}z_{1,1}^2. \tag{31}$$

Its derivative is given by

$$\begin{aligned} \dot{V}_{1,1} &= z_{1,1}\dot{z}_{1,1} = z_{1,1}\left[-p_1y_1 - p_2(y_1 + x_{10})\right]y_3 \\ &= -p_1z_{1,1}^2 - p_2z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha). \end{aligned} \tag{32}$$

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 first 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

$$\alpha = \alpha_1 + \alpha_2 \tag{33}$$

where α_i is used to stabilize subsystem $\Sigma_i (i = 1, 2)$. From (33), (32) can be rewritten as

$$\begin{aligned}\dot{V}_{1,1} = &-p_1 z_{1,1}^2 - p_2 z_{1,1}(z_{1,1} + x_{10})\alpha_1 \\ &-p_2 z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha_2).\end{aligned} \tag{34}$$

Apparently, by choosing $\alpha_1 = c_{1,1} y_1/(y_1 + x_{10})$ and noting that $z_{1,1} = y_1$, we have

$$\dot{V}_{1,1} = -(p_1 + c_{1,1}p_2) z_{1,1}^2 - p_2 z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha_2). \tag{35}$$

The first term is stabilizing because both $p_1, p_2 > 0$, and the second term $-p_2 z_{1,1}(z_{1,1} + x_{10})(z_{1,2} + \alpha_2)$ will be handled in the next step. The closed-loop form of (30) with (33) is

$$\dot{z}_{1,1} = -(p_1 + c_{1,1}p_2) z_{1,1} - p_2 (z_{1,1} + x_{10})(z_{1,2} + \alpha_2). \tag{36}$$

Similar analysis can be carried out for subsystem Σ_2. Define $z_{2,1} = y_2$. Its derivative is given by

$$\begin{aligned}\dot{z}_{2,1} = \dot{y}_2 &= -p_3 y_2 + p_4 (y_2 + x_{20}) y_3 \\ &= -p_3 z_{2,1} + p_4 (z_{2,1} + x_{20})(z_{2,2} + \alpha)\end{aligned} \tag{37}$$

where $z_{2,2} = y_3 - \alpha$, ensures that $z_{1,2} = z_{2,2}$. Furthermore, we have to apply the same virtual control, which is essential to solve the proposed problem at the last stage. Consider the Lyapunov function

$$V_{2,1} = \frac{1}{2} z_{2,1}^2. \tag{38}$$

From (37), its derivative is given by

$$\begin{aligned}\dot{V}_{2,1} = z_{2,1}\dot{z}_{2,1} &= z_{2,1}\left[-p_3 y_2 + p_4 (y_2 + x_{20})\right] y_3 \\ &= -p_3 z_{2,1}^2 + p_4 z_{2,1}(z_{2,1} + x_{20})\alpha_2 \\ &\quad + p_4 z_{2,1}(z_{2,1} + x_{20})(z_{2,2} + \alpha_1).\end{aligned} \tag{39}$$

By choosing $\alpha_2 = -c_{2,1} y_2/(y_2 + x_{20})$, we obtain

$$\dot{V}_{2,1} = -(c_{2,1}p_4 + p_3) z_{2,1}^2 + p_4 z_{2,1}(z_{2,1} + x_{20})(z_{2,2} + \alpha_1). \tag{40}$$

The nonlinear term $p_4 z_{2,1}(z_{2,1} + x_{20})(z_{2,2} + \alpha_1)$ will be canceled in the last step. The closed-loop form of (37) with (33) is

$$\dot{z}_{2,1} = -(c_{2,1}p_4 + p_3) z_{2,1} + p_4 (z_{2,1} + x_{20})(z_{2,2} + \alpha_1). \tag{41}$$

Step 2: For convenience, let us define

$$g(y) = L_{y_1}\alpha_1 + L_{y_2}\alpha_2. \tag{42}$$

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

$$\dot{z}_{1,2} = \dot{y}_3 - g(y). \tag{43}$$

For subsystems (30) and (43), we shall now design a control law u_1 to render the time derivative of a Lyapunov function negative definite. Following the standard backstepping design, consider the Lyapunov function candidate

$$V_{1,2} = V_{1,1} + \frac{1}{2} z_{1,2}^2. \tag{44}$$

Its derivative is

$$\begin{aligned}\dot{V}_{1,2} = \dot{V}_{1,1} + z_{1,2}\dot{z}_{1,2} &= -(p_1 + c_{1,1}p_2) z_{1,1}^2 + z_{1,2} - p_2 z_{1,1}(z_{1,1} + x_{10}) \\ &\quad \times (z_{1,2} + \alpha_2)(f_{1,2} - u_1 - g(y)) \\ &= -(p_1 + c_{1,1}p_2) z_{1,1}^2 - p_2 z_{1,1}(z_{1,1} + x_{10})\alpha_2 \\ &\quad + z_{1,2}(f_{1,2} - u_1 - p_2 z_{1,1}(z_{1,1} + x_{10}) - g(y)).\end{aligned} \tag{45}$$

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

$$u_1 = -g(y) - \left(1 + \frac{\alpha_2}{z_{1,2}}\right) p_2 z_{1,1}(z_{1,1} + x_{10}) + c_{1,2} z_{1,2} + f_{1,2}(y) \tag{46}$$

leads to

$$\dot{V}_{1,2} = -(c_{1,1}p_2 + p_1) z_{1,1}^2 - c_{1,2} z_{1,2}^2. \tag{47}$$

Since $\dot{V}_{1,2}$ is negative, it follows from LaSalle–Yoshizawa Theorem that the equilibrium $z = 0$ is globally asymptotically stable [29]. Note that u_1 and α are smooth functions 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 derivative of $z_{2,2}$ is expressed as

$$\dot{z}_{2,2} = f_{2,2} - u_2 - g(y). \tag{48}$$

For subsystems (41) and (48), we now design a control law u_2 to provide global stability. Consider the Lyapunov function

$$V_{2,2} = V_{2,1} + \frac{1}{2} z_{2,2}^2. \tag{49}$$

Noting (41) and (48), we have

$$\begin{aligned}\dot{V}_{2,2} = \dot{V}_{2,1} + z_{2,2}\dot{z}_{2,2} &= -(c_{2,1}p_4 + p_3) z_{2,1}^2 + z_{2,2}(f_{2,2} - u_2 - g(y)) \\ &\quad + p_4 z_{2,1}(z_{2,1} + x_{20})(z_{2,2} + \alpha_1) \\ &= -(c_{2,1}p_4 + p_3) z_{2,1}^2 + p_4 z_{2,1}(z_{2,1} + x_{20})\alpha_1 \\ &\quad + z_{2,2}(f_{2,2} - u_2 + p_4 z_{2,1}(z_{2,1} + x_{20}) - g(y)).\end{aligned} \tag{50}$$

Similarly, we know that $z_{2,2} = y_3 - \alpha > p_3/p_4 > 0$. Consider the well defined control law

$$u_2 = -g(y) + \left(1 + \frac{\alpha_1}{z_{2,2}}\right) p_4 z_{2,1}(z_{2,1} + x_{20}) + c_{2,2} z_{2,2} + f_{2,2}(y). \tag{51}$$

Substituting (51) into (50), we have

$$\dot{V}_{2,2} = -(c_{2,1}p_4 + p_3) z_{2,1}^2 - c_{2,2} z_{2,2}^2. \tag{52}$$

Since $\dot{V}_{2,2} \leq 0$, it follows from LaSalle-Yoshizawa Theorem that the equilibrium $z = 0$ is globally asymptotically stable [29]. Note that $u_2(y_0, z)$ and α_2 are smooth functions and satisfy $u_2(y_0, 0) = 0$, $\forall x_0 \in R_+^2$, and $\alpha_2(x_0, 0) = 0$, $\forall x_0 \in R_+^2$. Thus, we can conclude that $y = 0$ is globally asymptotically stable.

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

$$V = V_{1,2} + V_{2,2}. \tag{53}$$

From (45) and (50), we have

$$\begin{aligned}\dot{V} &= \dot{V}_{1,2} + \dot{V}_{2,2} \\ &= -(c_{1,1}p_2 + p_1)z_{1,1}^2 - p_2 z_{1,1}\alpha_2(z_{1,1} + x_{10}) \\ &\quad + z_{1,2}\{f_{1,2} - u - p_2 z_{1,1}(z_{1,1} + x_{10}) - g(y)\} \\ &\quad - (c_{2,1}p_4 + p_3)z_{2,1}^2 + p_4 z_{2,1}\alpha_1(z_{2,1} + x_{20}) \\ &\quad + z_{2,2}\{f_{2,2} - u + p_4 z_{2,1}(z_{2,1} + x_{20}) - g(y)\}. \quad (54)\end{aligned}$$

In Ω_c, because the same virtual control α is used, we know that $z_{1,2} = z_{2,2} > 0$, (54) can be rewritten as

$$\begin{aligned}\dot{V} &= -(c_{1,1}p_2+p_1)z_{1,1}^2 - (c_{2,1}p_4+p_3)z_{2,1}^2 \\ &\quad + z_{1,2}\left[f_{1,2} - u - \left(1+\frac{\alpha_2}{z_{1,2}}\right)p_2 z_{1,1}(z_{1,1}+x_{10}) - g(y)\right] \\ &\quad + z_{2,2}\left[f_{2,2} - u + \left(1+\frac{\alpha_1}{z_{2,2}}\right)p_4 z_{2,1}(z_{2,1}+x_{20}) - g(y)\right] \quad (55) \\ &= -(c_{1,1}p_2+p_1)z_{1,1}^2 - (c_{2,1}p_4+p_3)z_{2,1}^2 + z_{1,2} \\ &\quad \times \left[f_{1,2} - \left(1+\frac{\alpha_2}{z_{1,2}}\right)p_2 z_{1,1}(z_{1,1}+x_{10}) + f_{2,2}\right. \\ &\quad \left. + \left(1+\frac{\alpha_1}{z_{2,2}}\right)p_4 z_{2,1}(z_{2,1}+x_{20}) - 2g(y) - 2u\right]. \quad (56)\end{aligned}$$

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

$$\begin{aligned}u &= u_c \\ &= -g(y) + c_{1,2}z_{1,2} \\ &\quad - \frac{1}{2}\left[\left(1+\frac{\alpha_2}{z_{1,2}}\right)p_2 z_{1,1}(z_{1,1}+x_{10}) - f_{1,2}\right. \\ &\quad \left. - \left(1+\frac{\alpha_1}{z_{2,2}}\right)p_4 z_{2,1}(z_{2,1}+x_{20}) - f_{2,2}\right] \quad (57)\end{aligned}$$

leads to

$$\dot{V} = -(c_{1,1}p_2 + p_1)z_{1,1}^2 - (c_{2,1}p_4 + p_3)z_{2,1}^2 - c_{1,2}z_{1,2}^2. \quad (58)$$

Since V is negative definite, it follows that the system is asymptotically stable at the origin.

Theorem 3.2: Consider the closed-loop system consisting of (4), the set (8) and the control law (57). Then, for any initial conditions $y(0) \in \Omega_c$, the solution of system (4) $y(t) \to \Omega$ as $t \to \infty$ asymptotically.

Proof: The proof of Theorem 3.2 can be derived from Stages 1–3. Δ

Remark 4: For clarity, the control law (57) is clearly derived from (56). By examining (56), and noting the expression of (46) and (51), we know that the control in (57) can be conveniently written as

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

with u_c denoting control in the complement region, and with u_1 and u_2 defined in (46) and (51), respectively.

Remark 5: The design difficulties mainly come from the fact that the system is not in strict feedback form. In contrast to traditional backstepping design, we divide the system into two subsystems, and use a bridging virtual control α derived from both of the subsystems. Noting (54), if the subsystems are handled independently, i.e., $z_{1,2} \neq z_{2,2}$, it is difficult to seek a suitable control u. For clarity, let us rewrite (54) using different virtual controls

$$\begin{aligned}\dot{V} &= -(c_{1,1}+p_1)z_{1,1}^2 - (c_{2,1}+p_3)z_{2,1}^2 \\ &\quad + z_{1,2}[z_{1,1} + f_{1,2}(y_1, y_2) - u - \dot{\alpha}_1] \\ &\quad + z_{2,2}[z_{2,1} + f_{2,2}(y_1, y_2) - u - \dot{\alpha}_2] \quad (59)\end{aligned}$$

where $z_{1,2} = y_3 - \alpha_1$ and $z_{2,2} = y_3 - \alpha_2$. In the case where $z_{1,2} \neq z_{2,2}$, it would be difficult to design u to guarantee the Lyapunov stability condition, i.e., we will not able to find a control unless $z_{1,2} = z_{2,2}$.

In reality, we also generalize the results into discrete time. Then the controller, using a digital sampler, can be expressed as

$$\begin{aligned}u &= u_d(kT_{s,c}) \\ &= \frac{1}{2}\left(u_1(kT_{s,c}) + u_2(kT_{s,c})\right), \\ &\quad t \in [kT_{s,c}, (k+1)T_{s,c}), \quad (60)\end{aligned}$$

where $T_{s,c} > 0$ is a sampling period of complementary control, $k = 1, 2, 3, \ldots$. In the preceding discussion, we have designed two controllers for states $y \subset \Omega$ and $y \subset \Omega_c$ respectively. Thus, we obtain the following proposition.

Proposition 3.1: Consider the closed-loop system (4) and the control law

$$u(t) = \begin{cases} u_r : y \in \Omega \\ u_c : y \in \Omega_c \end{cases} \quad (61)$$

where u_r and u_c are defined in (27) and (57) respectively. Then, system (4) is asymptotically stable at the origin for any $y(0) \subset R_{\geq 0}$.

IV. Numerical Experiment

To simulate the dynamics $CD4^+$ T-cell, $CD8^+$ T-cell and HIV-1, the values of the parameters used are: $x_{10} = 1000\ \text{cell/mm}^3$, $x_{20} = 550\ \text{cell/mm}^3$, $p_1 = 0.25$, $p_2 = 50$, $p_3 = 0.25$, $p_4 = 10.0$, $p_5 = 0.01$ and $p_6 = 0.006$ [24]. Note that $0 < x_1 < x_{10}$ and $x_2 > x_{20}$. In order to show the control effectiveness, let us define

$$\lambda_{x_1} = \frac{\text{Min}(x_1)}{\text{Healthy}(x_1)}100\% \quad (62)$$

$$\lambda_{x_2} = \frac{\text{Max}(x_2)}{\text{Healthy}(x_2)}100\% \quad (63)$$

where x_1 and x_2 denote for the concentrations of $CD4^+$ T-cells and $CD8^+$ T-cells respectively, and $\text{Healthy}(x_1) = x_{10}$ and $\text{Healthy}(x_2) = x_{20}$.

A. Periodic Sampling

As indicated in [30], for actual medical practice, blood is first sampled from the patient and then antibodies and HIV are tested on a weekly basis in a periodical manner. Fixed medications are then given for the same period, where it is assumed that the concentration of the drug in blood is maintained for its effectiveness.

As such, simulations are carried out to model the practice, i.e., control signal is assumed to be fixed for the sampling interval using a digital sampler with a period of T_s. Since HAART is a

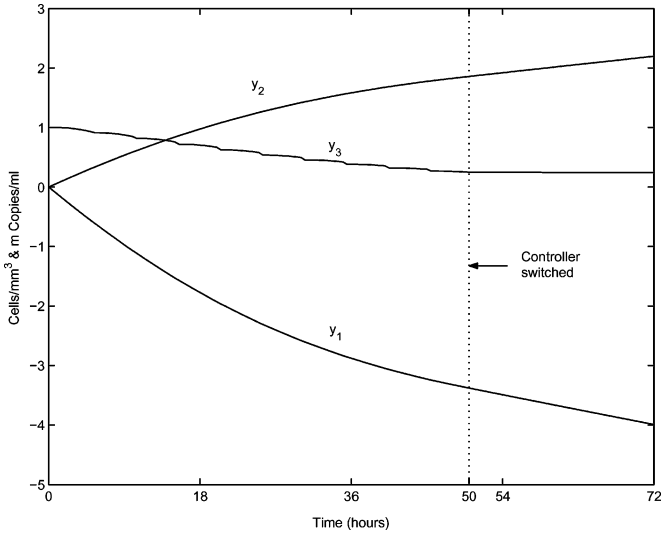

Fig. 1. The system states with sampling time $T_{s,c} = 5$ h in the first 72 h.

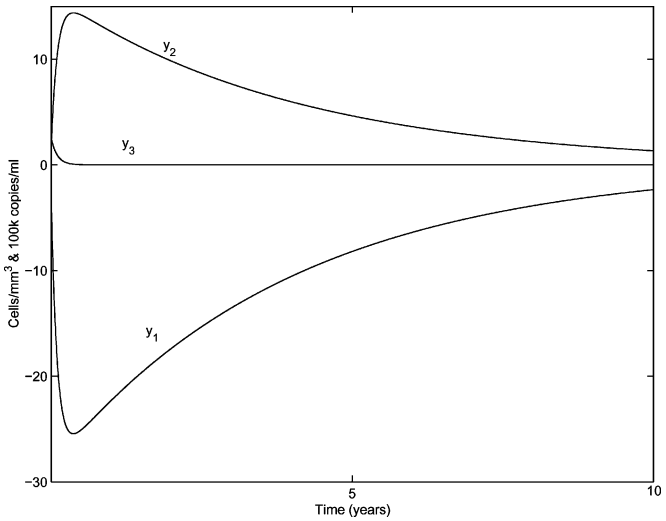

Fig. 2. The system states with sampling time $T_{s,c} = 1$ week in the first 10 years.

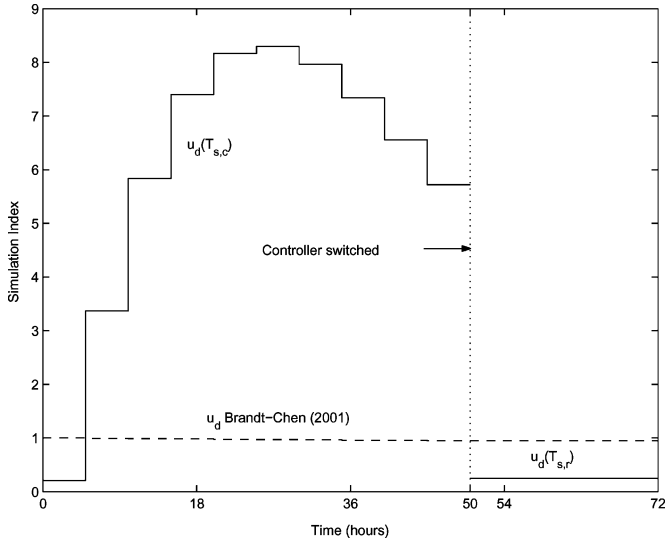

Fig. 3. The control action with periodic sampling $T_{s,c} = 5$ h.

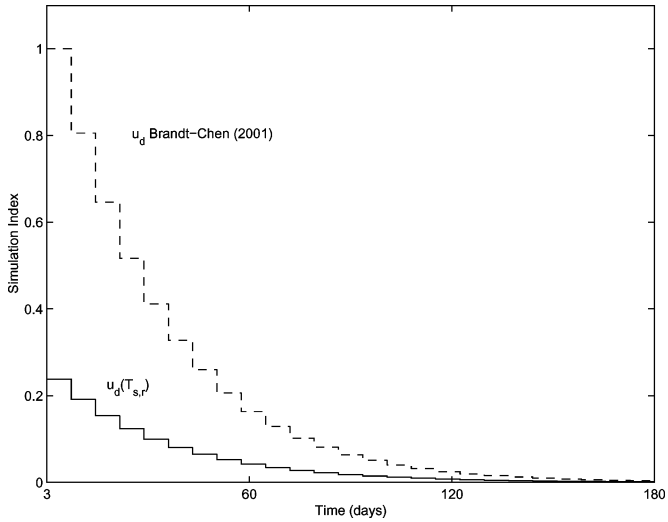

Fig. 4. The control action with periodic sampling $T_{s,r} = 1$ week.

multi-drug therapy, the control action is represented by a simulation index. If the viral load count is greater than 250 k copies/ml, then the situation is very critical, and we choose $T_{s,c} = 5$ h and apply the severe control in the complementary region, u_c. When the viral load count is reduced to less than 250 k copies/ml, the situation is less critical, and we choose $T_{s,r} = 1$ week and apply the regional control u_r. As such, the controller law (61) for $t \in [kT_s, (k+1)T_s)$ can be expressed as

$$u_d(t) = \begin{cases} u_r(kT_{s,r}) : y(kT_{s,r}) \in \Omega \\ u_c(kT_{s,c}) : y(kT_{s,c}) \in \Omega_c \end{cases} \tag{64}$$

where $T_{s,c}$ and $T_{s,r}$ are the sampling periods, and $k = 1, 2 \ldots$.

To illustrate the proposed control algorithms, we choose the design parameters as $c_{1,1} = c_{2,1} = c_{1,2} = c_{2,2} = 1$ and $k_3 = 10$. The initial conditions are chosen as $x_1(0) = 1000$ cells/mm^3, $x_2(0) = 550$ cells/mm^3 and $x_3(0) = 1000$k copies/ml. Figs. 1 –4 show the results of using controller (64) with $T_{s,r} =$ one week and $T_{s,c} = 3$ h. As shown in Fig. 1, the controller is switched at the 50th hour. Fig. 2 indicates that within the first 10 years, the virus count approaches zero and other states are kept bounded ($\lambda_{x_1} = 97.5\%$ and $\lambda_{x_2} = 102.3\%$). State $y_3(t)$ of the HIV-1 system uniformly converges to zero without rebound. However, the concentrations of the CD4$^+$ T-cell and CD8$^+$ T-cell vary at a high rate, since the viral load count is at a high level. As the viral load count is reduced to less than 250 k copies/ml, the requirement (i. e. $x_3 < p_3/p_4$) is satisfied, and the system is allowed to switch from control law (27) to (57). In Fig. 3, we find that the control action becomes very large, and the control singularity is encountered. This is the reason why we have to switch the control law as $y(t) \in \Omega$ at the 50th hour. As $y_3(t)$ goes into Ω, the regional controller continues to reduce the viral load, while the control action stays at a low level, as presented in Fig. 4.

B. Comparison With Previous Method

In Figs. 3–5, the results presented in [24] are compared with those in this paper. In Fig. 5, it is obvious that the deviation from the nominal values of the trajectories (in solid line) is much smaller than the trajectories (in dash line). λ_{x_1} and λ_{x_2} of the results in [24] are 92.5% and 108.5%, respectively. Figs. 3 and 4 present the short term and long term control action, respectively. The sampling times are the same ($T_{s,r} = 1$ week and

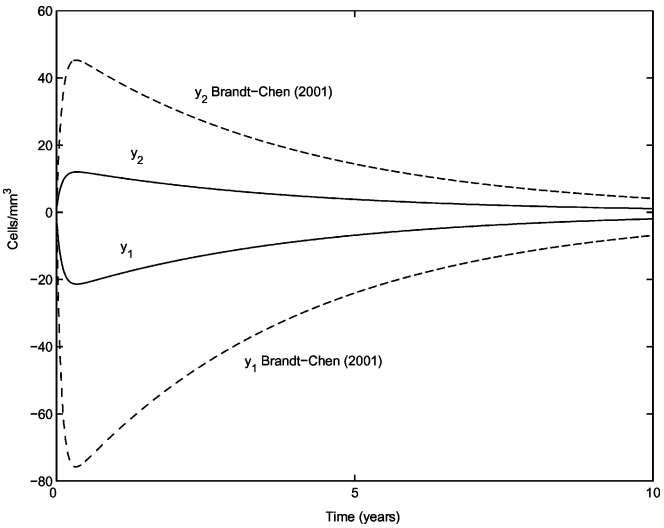

Fig. 5. System states with periodic sampling $T_{s,c} = 5$ h and $T_{s,r} = 1$ week.

$T_{s,c} = 5$ h). In Fig. 3, the control action (solid line) goes to a maximum of 8.2 after 25–30 h. After that, the control action decreases until the controller is switched, though the control action is larger than that in [24]. In Fig. 4, we find that the control action after switching is much smaller than that proposed in [24] in the following therapy.

V. Conclusion

The dynamic properties of the prey-predator like HIV-1 model have been studied in this paper. By exploiting the system properties, the system is regrouped into two subsystems in strict feedback form, and analyzed over two complementary regions. A singularity free controller is presented for HIV-1 system using the decoupled Lyapunov over Ω. A novel bridging virtual control is applied over Ω_c for backstepping design. The proposed control can drive all the positive states asymptotically to the desired values, and guarantee the nonnegative properties of all states in the closed-loop system. The design method makes use of the flexibility of the Lyapunov design and does not lead to singular behavior with respect to the control action. The simulations also show the stability of the closed-loop system. As the viral load count decreases into Ω, the corresponding control energy can be largely reduced.

Appendix A
Proof of the Stability of the Interior Equlibrium Point E

Proof: Remark 1 shows that there exists a finite trapping region, i.e., the system states are bounded for any positive bounded initial value.

In addition, it is easy to verify that the only interior equilibrium is

$$x_e = [x_{1e}, x_{2e}, x_{3e}] \tag{65}$$

where

$$x_{1e} = \frac{p_6}{p_5} x_{2e} \tag{66}$$

$$x_{3e} = \frac{p_1(x_{10} - x_{1e})}{p_2 x_{1e}} = \frac{-p_3(x_{20} - x_{2e})}{p_4 x_{2e}}. \tag{67}$$

Substituting (66) into (67), we have

$$p_1 p_4 p_5 x_{10} + p_2 p_6 p_3 x_{20} = (p_2 p_6 p_3 + p_1 p_4 p_6) x_{2e} \tag{68}$$

then,

$$x_{1e} = \frac{p_1 p_4 p_5 x_{10} + p_2 p_6 p_3 x_{20}}{p_5(p_2 p_3 + p_1 p_4)} \tag{69}$$

$$x_{2e} = \frac{p_1 p_4 p_5 x_{10} + p_2 p_6 p_3 x_{20}}{p_6(p_2 p_3 + p_1 p_4)}. \tag{70}$$

Substituting (70) into (67), we have

$$x_{3e} = \frac{p_1 p_3(p_5 x_{10} - p_6 x_{20})}{p_1 p_4 p_5 x_{10} + p_2 p_6 p_3 x_{20}}. \tag{71}$$

From system properties, we know that $x_i > 0$, $i = 1, 2, 3$. For convenience, let us translate the origin to x_e, and choose the states $z_i = x_i - x_{ie}$, $i = 1, 2, 3$. Consider the Lyapunov function

$$\begin{aligned} V &= \frac{p_5}{p_2} x_1 + \frac{p_6}{p_4} x_2 + x_3 \\ &= \frac{p_5}{p_2}(z_1 + x_{1e}) + \frac{p_6}{p_4}(z_2 + x_{2e}) + z_3 + x_{3e} > 0 \end{aligned} \tag{72}$$

we have

$$\begin{aligned} \dot{V} &= \frac{p_5}{p_2}\dot{x}_1 + \frac{p_6}{p_4}\dot{x}_2 + \dot{x}_3 \\ &= \frac{p_5 p_1}{p_2}(x_{10} - z_1 - x_{1e}) + \frac{p_6 p_3}{p_4}(x_{20} - z_2 - x_{2e}). \end{aligned} \tag{73}$$

Substituting (69) and (70) into (73), it becomes

$$\dot{V} = -\frac{p_5 p_1}{p_2} z_1 - \frac{p_6 p_3}{p_4} z_2 \tag{74}$$

which means the system is globally attractive to the two-dimensional space

$$M = \left\{ z \in R^3 : \frac{p_5 p_1}{p_2} z_1 + \frac{p_6 p_3}{p_4} z_2 = 0 \right\}. \tag{75}$$

Thus, we are able to convert system (2) to a second-order system by using the relationship $(p_5 p_1/p_2) z_1 + (p_6 p_3/p_4) z_2 = 0$. Then, we obtain

$$\begin{aligned} \dot{z}_1 &= p_1(x_{10} - z_1 - x_{1e}) - p_2(z_1 + x_{1e})(z_3 + x_{3e}) \\ \dot{z}_3 &= \left(1 + \frac{p_1 p_4}{p_2 p_3}\right)(z_3 + x_{3e}) p_5 z_1. \end{aligned} \tag{76}$$

The Jacobian Matrix $J(0,0)$ of system (76) is

$$\begin{aligned} J &= \begin{bmatrix} -p_1 - p_2(z_3 + x_{3e}) & -p_2 \\ \left(1 + \frac{p_1 p_4}{p_2 p_3}\right)(z_3 + x_{3e}) p_5 & \left(1 + \frac{p_1 p_4}{p_2 p_3}\right) p_5 z_1 \end{bmatrix}_{(0,0)} \\ &= \begin{bmatrix} -p_1 - p_2 x_{3e} & -p_2 \\ \left(1 + \frac{p_1 p_4}{p_2 p_3}\right) x_{3e} p_5 & 0 \end{bmatrix}. \end{aligned} \tag{77}$$

Since $p_i > 0$, $i = 1, \ldots, 6$, the characteristic equation can be expressed as

$$\lambda^2 + d_1 \lambda + d_2 = 0 \tag{78}$$

where $d_1 > 0$ and $d_2 > 0$. With the Routh-Hurwitz Theorem, the stability of the open-loop system about interior equilibrium point E, which locates within the finite trapping region is guaranteed. Δ

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