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HIV Infection Control Design With the Form of Constant or State Function

WEN-JUNE WANG, (Fellow, IEEE), AND YI DING
Department of Electrical Engineering, National Central University, Taoyuan 32001, Taiwan
Corresponding author: Wen-June Wang (wjwang@ee.ncu.edu.tw)

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ABSTRACT Antiviral therapy widely used in HIV treatment has obtained some achievements in public health. In this study, an HIV infection dynamic mathematical model is considered and three types of the control strategy for this model are designed. On the basis of the Lyapunov theory, we propose three main theorems in which three types of the control strategy for drug treatments $u_1(t)$ or/and $u_2(t)$ are designed to push all states to the infection-free equilibrium point E_1. Theorem 1 or Theorem 2 proposes the monotherapy with $u_1(t)$ only or with $u_2(t)$ only. The combination therapy with $u_1(t)$ and $u_2(t)$ together is constructed in Theorem 3. In these three theorems, $u_1(t)$ or/and $u_2(t)$ can be a function of states or a fixed constant within a certain range. Finally, there are several simulation results to illustrate that the proposed controls are effective to treat the HIV infection. In the simulation section, there is a detailed discussion about the state responses with the proposed three types of control strategy for drug treatments.

INDEX TERMS HIV infection, antiviral therapy, mathematical model, Lyapunov theory, control strategy, equilibrium point, drug treatments.

I. INTRODUCTION

Nowadays acquired immunodeficiency syndrome (AIDS) is playing an evil role to systematically damage public hygiene developments in many countries. AIDS is one of the serious infectious diseases, which causes a series of social and health problems to push the whole nation into a dangerous situation. Human immunodeficiency virus (HIV) is a type of Lentivirus which can give rise to HIV infection and AIDS with time finally [1], [2]. HIV mainly owns several transmissible routes that contain mother-to-fetus transmission, blood exposure, and sexual exposure. In addition, active drug users always share syringes/needles and this is a big problem which has to face for many countries. It is obvious that unclean syringes/needles can easily make HIV transmission acquire a fast transmission rate, that condition is not our need. The infection mechanism of HIV is to intrude CD4+T cells in vivo, that means the virus attacks healthy CD4+T cells and uses them to realize the reproductive purpose [3]. In addition, the count of CD4+T cells will be reduced substantially to result in the human immunodeficiency condition, after then, the defense shield and protective capability of the immune system in the human body will be destroyed and eroded until the patient totally loses protection and waits to die. After widespread uses of anti-viral therapy, the prevalence of HIV infection has been effectively controlled in many developed countries, but it still endangers or damages a lot of developing and undeveloped countries. Clinical treatment popularly applies highly active antiretroviral therapy (HAART) that involves several anti-retroviral drugs at the same time in order to lead the counts of viral load to have a substantial reduction [4], [5] and furthermore extend the duration of drug efficacies and delay the drug resistance or side effects [6], [7]. Reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) are the worldwide chose to end this epidemic [8], [9]. It is recognized that combination therapy is the best choice to overcome HIV infection in clinical treatment [10], [11]. Although there are several successful medical services provided in clinical to suppress the virus, unfortunately, because of drug resistance and drug side-effects, HIV study still needs enough financial support to explore it and then invent HIV vaccines or synthesize a series of new drugs.

Medical clinic and laboratory studies are the most direct way to disclose the truth of HIV infection and transmission [12], [13], and many clinic and experiment-based data

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can be collected via these studies. Recently, instead of the traditional mind, dynamic mathematical modeling becomes a significant method in the research area of infectious disease. Furthermore, a suitable HIV dynamic mathematical model can facilitate us to discover new therapy and estimate/forecast the progress of drug resistance, side-effect or drug effect. A simplified HIV dynamic mathematical model normally involves several state variables such as uninfected CD4+T cells, infected CD4+T cells and free virus [14]–[17]. Along with the progress of research, some researchers introduced a new concept to divide infected CD4+T cells into two parts to the original HIV model [18]–[20] in order to enhance the accuracy of the study result.

In fact, applying a mathematical method to study disease is an inexpensive and worthy method since it can break through limitations in order to more extensively and flexibly utilize scientific and social resources. In [21], the authors proposed a pulse control to an HIV model with delay terms and switching parameters, where the value of the control was chosen as 0 or 1. In [22], a Markov chain-based HIV model was studied to eradicate HIV by solving a system of linear equations. In [23], a modified HIV infection model was considered. By using Lyapunov functions and LaSalle's invariance principle, the stability was analyzed, and the drug treatments m and n were given with two constants to make all states converge to the infection-free equilibrium point. In [24] and [25], the drug treatments of the HIV-infected model were set as either 0 or 1 so that they were easy to result in a discontinuous therapeutic effect. Besides HIV study, other mathematical models such as the hepatitis B virus (HBV), dengue fever, rabies, and cancer were extensively studied by applying control theories and mathematical methods to disclose the viral behaviors. In [26], vaccine efficacy α and a fraction of newborns vaccinated p were regarded as two controls to be designed so that all states of the modified model converge to their desired condition. Similarly, in [27] and [28], the authors considered two dynamic models about rabies between dog and human. They discussed the control strategy of the culling rate and immunization rate, such that disease transmission was cut off and the number of infected people was minimized. In practical, [29] claimed that the drug treatment for HIV should be scheduled dynamically with time by means of the model's varying states rather than be a fixed value.

The fundamental difference of this study compared with the previous related papers is that the proposed control strategy can be designed as a function of states or be chosen as a constant within certain limits. These controls can make all states of HIV model return to the infection-free equilibrium point E_1 finally. In other words, the state of illness for HIV-infected patients will recover to their health situations. In Theorem 1, Theorem 2 and Theorem 3, three types of control strategy for drug treatment $u_1(t)$ alone, drug treatment $u_2(t)$ alone, and combination therapy $u_1(t)$ and $u_2(t)$ together, respectively, are designed with the form of constant or state function.

The framework of this paper is as follows: In Section 2, the model and the problem of the HIV model are presented. Section 3 introduces the control strategy design for the drug to treat HIV infection. Some simulation results are shown and discussed in Section 4. Finally, a conclusion is given.

II. THE SYSTEM MODEL AND PROBLEM DESCRIPTION FOR HIV INFECTION

A. SYSTEM MODEL

Consider the following HIV infection model [18], [20]

$$\begin{aligned}\dot{x}_1(t) &= \lambda - d_1 x_1(t) - k_1 x_1(t) x_4(t) + b x_2(t)\\ \dot{x}_2(t) &= k_1 x_1(t) x_4(t) - (b + k_2 + d_2)\, x_2(t)\\ \dot{x}_3(t) &= k_2 x_2(t) - d_3 x_3(t)\\ \dot{x}_4(t) &= a x_3(t) - d_4 x_4(t)\end{aligned} \tag{1}$$

where $x_1(t)$, $x_2(t)$, $x_3(t)$ and $x_4(t)$ represent the counts of uninfected CD4+T cells, infected CD4+T cells in the eclipse phase, productively infected CD4+T cells and free virus, respectively. All parameters of model (1) are positive constants in this article. λ is the natural production rate of uninfected CD4+T cells, inversely, d_1 is the natural death rate of uninfected CD4+T cells. b is the rate that some infected CD4+T cells in the eclipse phase will recover to the uninfected cells. k_1 is the production rate of infected CD4+T cells in the eclipse phase, and die at rate d_2. Similarly, productively infected CD4+T cells are produced at rate k_2, and die at d_3. The free virus is produced at rate a and dies at rate d_4. The above model (1) has a basic reproduction number R_0 which is regarded as the number of one infected case who can averagely diffuse to otherwise healthy people over the whole infectious period [18], [20]. Its form is

$$R_0 = \frac{a k_1 k_2 \lambda}{(b + k_2 + d_2)\, d_1 d_3 d_4}. \tag{2}$$

It is well known that if $R_0 \leq 1$, the uninfected status is globally asymptotically stable; but if $R_0 > 1$, the infected status is globally asymptotically stable [20], [23], [30]. The strict description of R_0 is that a patient's condition is recovering to a healthy period if $R_0 \leq 1$, inversely, the disease will continue existing if $R_0 > 1$.

In fact, not all latent infected cells will be activated to become infected cells or anew revert back to uninfected cells, in other words, the state is similar to a memory T cell state with integrated provirus,moreover, they are able to resume virus production in blood after reactivation [23], [31]. Thus, the term $b x_2(t)$ will actually be neglected. Besides, during the period of HIV infection, uninfected CD4+T cells and free virus have some relation such that the term $k_1 x_1(t) x_4(t)$ of model (1) may be replaced by $k_1 x_1(t) x_4(t)/(x_1(t) + x_4(t))$ [23]

$$\begin{aligned}\dot{x}_1(t) &= \lambda - d_1 x_1(t) - \frac{k_1 x_1(t) x_4(t)}{x_1(t) + x_4(t)}\\ \dot{x}_2(t) &= \frac{k_1 x_1(t) x_4(t)}{x_1(t) + x_4(t)} - (k_2 + d_2)\, x_2(t)\\ \dot{x}_3(t) &= k_2 x_2(t) - d_3 x_3(t)\\ \dot{x}_4(t) &= a x_3(t) - d_4 x_4(t)\end{aligned} \tag{3}$$

Therefore, the modified basic reproduction number [23] is

$$R_0^m = \frac{ak_1k_2}{(k_2+d_2)\,d_3d_4}. \tag{4}$$

If $R_0^m \le 1$, the infection-free steady situation is

$$E_1 = [x_0\ 0\ 0\ 0]^T = [\lambda/d_1\ 0\ 0\ 0]^T \tag{5}$$

where E_1 is the infection-free equilibrium point. But, if $R_0^m > 1$, there exists an infected steady situation [23]

$$E_2 = \begin{bmatrix} x_1^* \\ x_2^* \\ x_3^* \\ x_4^* \end{bmatrix} = \begin{bmatrix} \dfrac{\lambda R_0^m}{k_1\left(R_0^m-1\right)+d_1R_0^m} \\ \dfrac{d_3d_4}{ak_2}x_4^* \\ \dfrac{d_4}{a}x_4^* \\ \left(R_0^m-1\right)x_1^* \end{bmatrix}, \tag{6}$$

where E_2 is the equilibrium point of the infected state. According to the natural rules, all state variables $x_1(t)$, $x_2(t)$, $x_3(t)$ and $x_4(t)$ in model (3) are always nonnegative for all $t \ge 0$. Meanwhile, all of them are bounded in the subset $\Theta(t \ge 0)$ [20], [23]

$$\Theta = \left\{0 \le x_1(t), x_2(t), x_3(t) \le \frac{\lambda}{d_1}, 0 \le x_4(t) \le \frac{a\lambda}{d_1d_4}\right\}. \tag{7}$$

B. THE MODEL WITH DRUG TREATMENT

In terms of model (3), the anti-HIV mathematical model with medical care is given as follows [23]

$$\begin{aligned}
\dot{x}_1(t) &= \lambda - d_1x_1(t) - (1-\eta_1u_1(t))\,\frac{k_1x_1(t)x_4(t)}{x_1(t)+x_4(t)} \\
\dot{x}_2(t) &= (1-\eta_1u_1(t))\,\frac{k_1x_1(t)x_4(t)}{x_1(t)+x_4(t)} - (k_2+d_2)\,x_2(t) \\
\dot{x}_3(t) &= k_2x_2(t) - d_3x_3(t) \\
\dot{x}_4(t) &= (1-\eta_2u_2(t))\,ax_3(t) - d_4x_4(t)
\end{aligned} \tag{8}$$

where $u_1(t)$ and $u_2(t)$ are regarded as the control actions of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs), respectively. η_1 and η_2 denote the maximal effects of the drug therapy and both of them are almost approaching 1. Two types of antiretroviral drugs $u_1(t)$ and $u_2(t)$ are used in model (8) to defense against viral infection, which are widely utilized in clinical research and therapy worldwide, *i.e.,* blocking new infections and suppressing new viruses. Here, the range of $u_1(t)$ and $u_2(t)$ must be between 0 (no medication) and 1 (full medication).

The modified basic reproductive number [23] with $u_1(t)$ only is

$$R_1 = \frac{(1-\eta_1u_1(t))\,ak_1k_2}{(k_2+d_2)\,d_3d_4}; \tag{9}$$

with $u_2(t)$ only is

$$R_2 = \frac{(1-\eta_2u_2(t))\,ak_1k_2}{(k_2+d_2)\,d_3d_4}; \tag{10}$$

or with combination therapy $u_1(t)$ and $u_2(t)$ is

$$R_3 = \frac{(1-\eta_1u_1(t))\,(1-\eta_2u_2(t))\,ak_1k_2}{(k_2+d_2)\,d_3d_4}. \tag{11}$$

The state variables of HIV model (8) can reach and maintain the infection-free equilibrium point $E_1 = \left(\lambda/d_1,\ 0,\ 0,\ 0\right)$, if $R_1 \le 1$, $R_2 \le 1$, or $R_3 \le 1$, respectively [20], [23], [30].

C. PROBLEM DESCRIPTION

It is well-known that HIV-infected patients may evolve to AIDS and finally go to death if they cannot receive enough and necessary treatments to extend their life-span. In model (8), most previous papers applied fixed values of $u_1(t)$ or/and $u_2(t)$ for the drug treatments [24], [25]. In this study, we will design two types of the control $u_1(t)$ and $u_2(t)$, in which one type is a function of state variables and the other type is also a constant, such that all states approach their healthy situation asymptotically. Ordinarily, it is reasonable that the doses of drug injection and intake can be adjusted by the doctor based on the patient's state of illness, therefore the treatment control can depend on the states of the model (8). On the other hand, the treatment control can be a constant too but must satisfy some condition. It is seen that $u_1(t)$ is used to treat uninfected CD4+T cells $x_1(t)$ and infected CD4+T cells $x_2(t)$ in the first two equations of the model (8). Similarly, $u_2(t)$ targets the free virus $x_4(t)$ in the fourth equation of model (8). In the following section, the control strategy will be designed to solve the above-mentioned problem.

III. CONTROL STRATEGY DESIGN

A. CONTROL DESIGN FOR MONOTHERAPY

According to the model (8), it is apparent that $u_1(t)$ deals with $x_1(t)$ and $x_2(t)$, and $u_2(t)$ targets the free virus $x_4(t)$. However, these four states are dependent on each other. In the following, we will investigate the monotherapy in the first two theorems and then the combination therapy will be studied in the third theorem.

Firstly, let us consider using one control $u_1(t)$ only (*i.e.*$u_2(t) = 0$) to treat the HIV-infected patient.

Theorem 1: Suppose $R_0^m > 1$, the states of model (8) with one control $u_1(t)$ only (*i.e.*$u_2(t) = 0$) can converge to the infection-free equilibrium point E_1 asymptotically, if the control $u_1(t)$ is chosen as

$$u_1(t) = \begin{cases} 0, & \text{if } \tilde{u}_1(t)+\varphi \le 0; \\ \tilde{u}_1(t)+\varphi, & \text{if } 0 < \tilde{u}_1(t)+\varphi < 1; \\ 1, & \text{Otherwise.} \end{cases} \tag{12}$$

in which

$$\tilde{u}_1(t) = \frac{1}{\eta_1}\left[1 - \frac{(\mathrm{T}_1(t)+\mathrm{T}_2(t))\,(x_1(t)+x_4(t))}{(q_1+q_2)\,k_1x_1(t)x_4(t)}\right], \tag{13}$$

$$\mathrm{T}_1(t) = q_1\,(\lambda - d_1x_1(t))\,, \tag{14}$$

$$\mathrm{T}_2(t) = q_2\,(k_2+d_2)\,x_2(t), \tag{15}$$

and parameters q_1 and q_2 are two suitably chosen positive constants. In addition, φ is a very small constant satisfying$0 < \tilde{u}_1(t)+\varphi < 1$; or if $u_1(t)$ is a constant to satisfy

$$\frac{1}{\eta_1}\left(1 - \frac{1}{R_0^m}\right) \le u_1(t) \le 1. \tag{16}$$

Proof: Let us consider a Lyapunov $V_1(t)$ as follows

$$V_1(t) = q_1\left(\frac{\lambda}{d_1} - x_1(t)\right) + q_2 x_2(t) \tag{17}$$

where q_1 and q_2 are positive constants. Note that the Lyapunov function $V_1(t)$ is constructed by $x_1(t)$ and $x_2(t)$ due to $u_1(t)$ has directly impacted them. Next, the derivative of $V_1(t)$ is

$$\begin{aligned}\dot{V}_1(t) &= -q_1\dot{x}_1(t) + q_2\dot{x}_2(t)\\ &= -q_1\left[\lambda - d_1x_1(t) - (1-\eta_1u_1(t))\frac{k_1x_1(t)x_4(t)}{x_1(t)+x_4(t)}\right]\\ &\quad + q_2\left[(1-\eta_1u_1(t))\frac{k_1x_1(t)x_4(t)}{x_1(t)+x_4(t)} - (k_2+d_2)x_2(t)\right]\\ &= -q_1(\lambda - d_1x_1(t)) - q_2(k_2+d_2)x_2(t)\\ &\quad + (q_1+q_2)(1-\eta_1u_1(t))\frac{k_1x_1(t)x_4(t)}{x_1(t)+x_4(t)}.\end{aligned} \tag{18}$$

Therefore, $\dot{V}_1(t) < 0$ can be guaranteed, if

$$\begin{aligned}-q_1(\lambda - d_1x_1(t)) + (q_1+q_2)(1-\eta_1u_1(t))\frac{k_1x_1(t)x_4(t)}{x_1(t)+x_4(t)}\\ - q_2(k_2+d_2)x_2(t) < 0.\end{aligned} \tag{19}$$

Therefore, if (12) holds with (13)-(15), $u_1(t)$ is nonnegative and (19) is satisfied. It is noted that $\tilde{u}_1(t) \geq 1$ is impossible since $T_1(t) > 0$ and $T_2(t) > 0$. Thus, $x_1(t)$ and $x_2(t)$ will approach $x_0 = \lambda/d_1$ and 0 finally, respectively. Since $x_2(t)$ approaches zero finally, then the third equation of model (8) will make $x_3(t)$ converge to zero finally too. Consequently, it is obvious that, from the fourth equation of model (8), $x_4(t)$ will approach zero along with other states in model (8).

On the other hand, let $u_1(t)$ be chosen to satisfy (16) so that $R_1 \leq 1$, that means

$$R_1 = \frac{(1-\eta_1u_1(t))ak_1k_2}{(k_2+d_2)d_3d_4} = (1-\eta_1u_1(t))R_0^m \leq 1. \tag{20}$$

Hence, according to the knowledge in [20], [23], and [30], the infection-free equilibrium point E_1 can be reached finally. The proof is completed.

Remark 1: The parameters q_1 and q_2 present the weights of two terms in (17), respectively. They denote the degrees of importance of state variables $x_1(t)$ and $x_2(t)$ to be concerned and chosen by the designer, respectively, in model (8). Further, their values may impact the convergence rate of $V_1(t)$. For instance, if $q_1 > q_2$, that means the designer cares about $x_1(t)$ much more than $x_2(t)$, and the convergence rate of $V_1(t)$ depends on $x_1(t)$ approaching λ/d_1 much more than $x_2(t)$ approaching 0.

Secondly, let us consider using one control $u_2(t)$ only (*i.e.*$u_1(t) = 0$) to suppress HIV infection and viral reproduction in vivo.

Theorem 2: Suppose $R_0^m > 1$, the states of model (8) with one control $u_2(t)$ only (*i.e.*$u_1(t) = 0$) can converge to the infection-free equilibrium point E_1 asymptotically, if the control $u_2(t)$ is chosen as

$$u_2(t) = \begin{cases} 0, & \text{if } \tilde{u}_2(t)+\gamma \leq 0;\\ \tilde{u}_2(t)+\gamma, & \text{if } 0 < \tilde{u}_2(t)+\gamma < 1;\\ 1, & \text{Otherwise.}\end{cases} \tag{21}$$

in which

$$\tilde{u}_2(t) = \frac{1}{\eta_2}\left[1 - \frac{d_4x_4(t)}{ax_3(t)}\right] \tag{22}$$

and γ is a constant satisfying $0 < \tilde{u}_2(t)+\gamma < 1$; or if $u_2(t)$ is a constant to satisfy

$$\frac{1}{\eta_2}\left(1 - \frac{1}{R_0^m}\right) \leq u_2(t) \leq 1. \tag{23}$$

Proof: Let us consider a Lyapunov function $V_2(t)$ as follows

$$V_2(t) = h_1x_4(t) \tag{24}$$

where h_1 is a positive constant. Note that the Lyapunov function $V_2(t)$ is formed by $x_4(t)$ due to $u_2(t)$ has directly impacted the forth equation of model (8). Then, the derivative of $V_2(t)$ is

$$\begin{aligned}\dot{V}_2(t) &= h_1\dot{x}_4(t)\\ &= h_1(1-\eta_2u_2(t))ax_3(t) - h_1d_4x_4(t).\end{aligned} \tag{25}$$

Here, $\dot{V}_2(t) < 0$ if

$$(1-\eta_2u_2(t))ax_3(t) - d_4x_4(t) < 0. \tag{26}$$

Therefore, if (21) holds with (22), it is obvious that $u_2(t)$ is nonnegative and (26) is satisfied. It is noted that $\tilde{u}_2(t) \geq 1$ is impossible due to $d_4x_4(t)/ax_3(t) \geq 0$. Thus, $x_4(t)$ will approach 0 finally. Since $x_4(t)$ approaches zero finally, then the first and second equations of model (8) will make $x_1(t)$ and $x_2(t)$ converge to x_0 and zero finally too. Consequently, it is obvious that, from the third equation of model (8), $x_3(t)$ after all will approach zero too.

Secondly, let $u_2(t)$ be chosen to satisfy (23) then

$$R_2 = \frac{(1-\eta_2u_2(t))ak_1k_2}{(k_2+d_2)d_3d_4} = (1-\eta_2u_2(t))R_0^m \leq 1. \tag{27}$$

Hence, according to the knowledge in [20], [23], and [30], the state variables can arrive at the infection-free equilibrium point E_1 at last. The proof is completed.

Remark 2: The parameter h_1 can be any positive constant which does not appear in the form of the designed control. It can be set to 1.

B. CONTROL DESIGN FOR COMBINATION THERAPY

In comparison with the above monotherapy, combination therapy can obviously surpass the single medicine or single therapeutic approach in durable or long-term treatment. Combination therapy also can prolong the time-span to slow down the risk of drug resistance or side effect in the course of the patient's treatment [32]. Thus, $u_1(t)$ and $u_2(t)$ will be considered simultaneously in the following theorem.

Theorem 3: Suppose $R_0^m > 1$, the states of model (8) with combination therapy $u_1(t)$ and $u_2(t)$ can converge to the infection-free equilibrium point E_1 asymptotically, if the controls $u_1(t)$ and $u_2(t)$ are chosen to satisfy

$$u_1(t) = \begin{cases} 0, & \text{if } u_1^*(t) + \delta_1 \le 0; \\ u_1^*(t) + \delta_1, & \text{if } 0 < u_1^*(t) + \delta_1 \le 0; \\ 1, & \text{Otherwise.} \end{cases} \quad (28)$$

and

$$u_2(t) = \begin{cases} 0, & \text{if } u_2^*(t) + \delta_2 \le 0; \\ u_2^*(t) + \delta_2, & \text{if } 0 < u_2^*(t) + \delta_2 < 1; \\ 1, & \text{Otherwise} \end{cases} \quad (29)$$

respectively, in which

$$u_1^*(t) = \frac{1}{\eta_1}\left[1 - \frac{(H_1(t) + H_2(t))\,(x_1(t) + x_4(t))}{(p_1 + p_2)\,k_1 x_1(t) x_4(t)}\right], \quad (30)$$

$$u_2^*(t) = \frac{1}{\eta_2}\left[1 - \frac{d_4 x_4(t)}{a x_3(t)}\right], \quad (31)$$

$$H_1(t) = p_1\,(\lambda - d_1 x_1(t))\,, \quad (32)$$

$$H_2(t) = p_2\,(k_2 + d_2)\,x_2(t), \quad (33)$$

and the parameters p_1 and p_2 are some positive constants. δ_1 and δ_2 are very small constants satisfying $0 < u_1^*(t) + \delta_1 < 1$ and $0 < u_2^*(t) + \delta_2 < 1$, respectively; or if $u_1(t)$ and $u_2(t)$ are constants to satisfy

$$0 \le (1 - \eta_1 u_1(t))\,(1 - \eta_2 u_2(t)) \le \frac{1}{R_0^m}. \quad (34)$$

Proof: Let us define a Lyapunov function $V(t)$ as

$$V_3(t) = p_1\left(\frac{\lambda}{d_1} - x_1(t)\right) + p_2 x_2(t) + p_3 x_4(t) \quad (35)$$

where p_1, p_2 and p_3 are three positive constants. After then,

$$\begin{aligned} \dot{V}_3(t) &= -p_1 \dot{x}_1(t) + p_2 \dot{x}_2(t) + p_3 \dot{x}_4(t) \\ &= -p_1\left[\lambda - d_1 x_1(t) - (1 - \eta_1 u_1(t))\,\frac{k_1 x_1(t) x_4(t)}{x_1(t) + x_4(t)}\right] \\ &\quad + p_2\left[(1 - \eta_1 u_1(t))\,\frac{k_1 x_1(t) x_4(t)}{x_1(t) + x_4(t)} - (k_2 + d_2)\,x_2(t)\right] \\ &\quad + p_3\left[(1 - \eta_2 u_2(t))\,a x_3(t) - d_4 x_4(t)\right] \\ &= -p_1\,(\lambda - d_1 x_1(t)) \\ &\quad + (p_1 + p_2)\,(1 - \eta_1 u_1(t))\,\frac{k_1 x_1(t) x_4(t)}{x_1(t) + x_4(t)} \\ &\quad - p_2\,(k_2 + d_2)\,x_2(t) \\ &\quad + p_3\,(1 - \eta_2 u_2(t))\,a x_3(t) - p_3 d_4 x_4(t). \end{aligned} \quad (36)$$

$\dot{V}_3(t) < 0$ can be guaranteed, if

$$-p_1\,(\lambda - d_1 x_1(t)) + (p_1 + p_2)\,(1 - \eta_1 u_1(t))\,\frac{k_1 x_1(t) x_4(t)}{x_1(t) + x_4(t)} - p_2\,(k_2 + d_2)\,x_2(t) < 0 \quad (37)$$

and

$$(1 - \eta_2 u_2(t))\,a x_3(t) - d_4 x_4(t) < 0. \quad (38)$$

Thus, if $u_1(t)$ and $u_2(t)$ are the forms of (28) and (29), respectively, then (37) and (38) will be satisfied. It is noted that $u_1^*(t) \ge 1$ or/and $u_2^*(t) \ge 1$ is/are impossible since the last term of (30) is positive.

On the other hand, let $u_1(t)$ and $u_2(t)$ be chosen to satisfy (34), that means

$$\begin{aligned} R_3 &= \frac{(1 - \eta_1 u_1(t))\,(1 - \eta_2 u_2(t))\,a k_1 k_2}{(k_2 + d_2)\,d_3 d_4} \\ &= (1 - \eta_1 u_1(t))\,(1 - \eta_2 u_2(t))\,R_0^m \le 1. \end{aligned} \quad (39)$$

Finally, the state variables can converge to the infection-free equilibrium point E_1. The proof is completed.

Remark 3: The values of p_1, p_2 and p_3 are the weights of three terms in (35), respectively. They denote the degrees of $x_1(t)$, $x_2(t)$ and $x_4(t)$, respectively, to be concerned by the designer in model (8). Furthermore, their values can impact the convergence rate of $V_3(t)$.

Remark 4: From the above theorems, it shows that the control design can be a function of states or be a constant within a certain range. What is the difference in the treatment performance between these two kinds of control? Which kind will be better for the treatment of HIV infection? The following simulation results may give us some reflections.

IV. SIMULATION RESULTS

Actually, the purpose of this article is to design controls $u_1(t)$ and $u_2(t)$ as the drug treatments to drive model states approaching the infection-free equilibrium point E_1. In this example, suppose the parameters of HIV-infected model are given as follows: $\lambda = 13.9$, $d_1 = 0.0139$, $d_2 = 0.0495$, $d_3 = 0.5776$, $d_4 = 2.3$, $k_1 = 0.5$, $k_2 = 1.1$ and $a = 30$ (adopted from the reference papers [23], [31], [33]–[35]). Here we set $\eta_1 = \eta_2 = 0.98$. The initial values are set as follows: $x_1(0) = 10^3$, $x_2(0) = 0$, $x_3(0) = 0$ and $x_4(0) = 10^2$ [20]. Moreover, let the control action of drug treatment be activated at $t \ge 5$.

Firstly, based on Theorem 1, let $q_1 = 10^{-4}$, $q_2 = 10^{-4}$ and $\varphi = 0.05$. Then the control $u_1(t)$ is given from (12). From Theorem 2, let $\gamma = 2.2 \times 10^{-3}$. Then the control $u_2(t)$ is given from (21). Based on Theorem 3, let $p_2 = 10^{-4}$, $p_3 = 10^{-4}$, $\delta_1 = 0.05$ and $\delta_2 = 2.675 \times 10^{-3}$. Then the combination therapy $u_1(t)$and$u_2(t)$ is given from (28) and (29). Therefore, $u_1(t) = 0.95$ or/and $u_2(t) = 0.95$ are fixed values of drug treatments and satisfy $0.926 \le u_1(t) \le 1$ in (16) or $0.926 \le u_2(t) \le 1$ in (23), and $0 \le (1 - \eta_1 u_1(t))\,(1 - \eta_2 u_2(t)) \le 1/R_0^m$ in (34). In order to show the effect of treatment, let the control action of drug treatment be activated at $t \ge 5$. The simulation results with treatment and without treatment are shown in Fig. 1-7, respectively.

In Fig. 1, we can see any control can make $x_1(t)$ approach λ/d_1, but the brown curve is the situation without treatment. In Fig. 2 and Fig. 3, all controls are activated at $t \ge 5$ and all of them make $x_2(t)$ approach zero finally, but monotherapy $u_2(t)$ from (21) has slower performance since it does not control $x_2(t)$ directly. Similarly, in Fig. 4 and Fig. 5, all controls can make $x_3(t)$ approach zero finally, but monotherapy $u_2(t)$

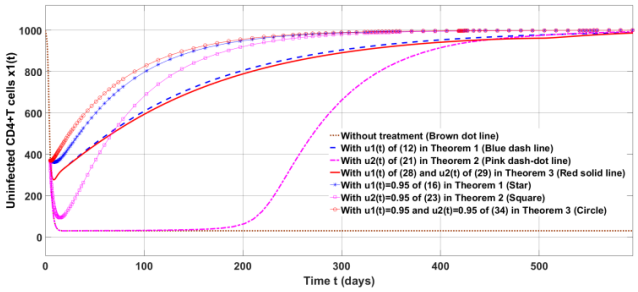

FIGURE 1. State trajectories of uninfected cells $x_1(t)$.

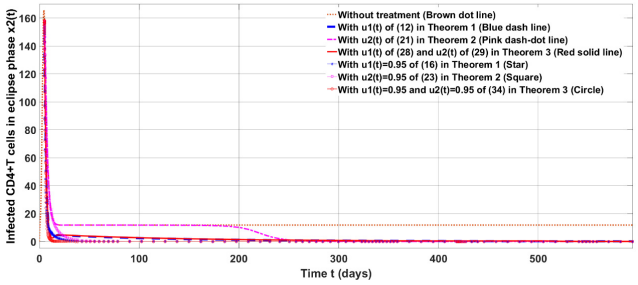

FIGURE 2. State trajectories of infected CD4+T cells in the eclipse phase $x_2(t)$.

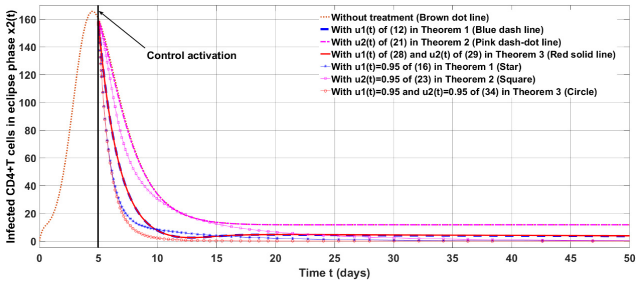

FIGURE 3. State trajectories of infected CD4+T cells in the eclipse phase $x_2(t)$ before $t = 50$.

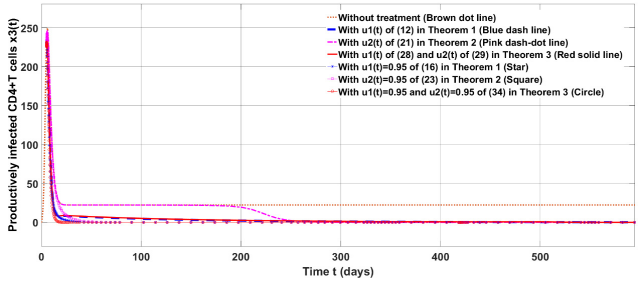

FIGURE 4. State trajectories of productively infected CD4+T cells $x_3(t)$.

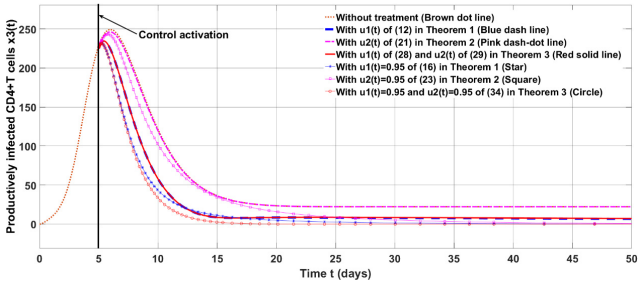

FIGURE 5. State trajectories of productively infected CD4+T cells $x_3(t)$ before $t = 50$.

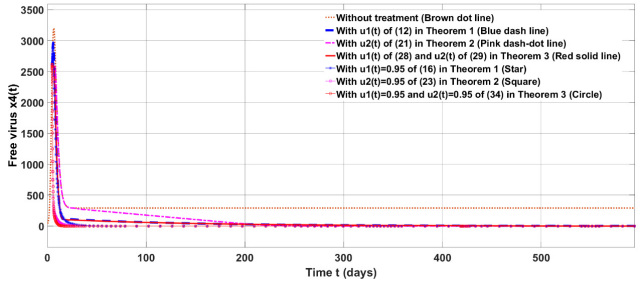

FIGURE 6. State trajectories of free virus $x_4(t)$.

from (21) has slower performance since it does not control $x_3(t)$ directly. In Fig. 6 and Fig. 7, all controls can make $x_4(t)$ approach zero finally, but monotherapy $u_2(t)$ from (21) has slower performance because $u_1(t)$ can impact $x_1(t)$ and $x_2(t)$ based on the first and second equations of model (8), $u_2(t)$ can deal with $x_4(t)$ only. The monotherapy $u_1(t)$ from (12) and combination therapy $u_1(t)$ from (28) and $u_2(t)$ from (29) own similar reduction rates to reduce $x_2(t)$, $x_3(t)$ and $x_4(t)$ in Fig. 2-7, respectively. From Figs 1-7, it is seen that the constant controls seem to have good performances and they make the states approach the equilibrium E_1 faster than the controls with states function do. But Fig. 1shows that

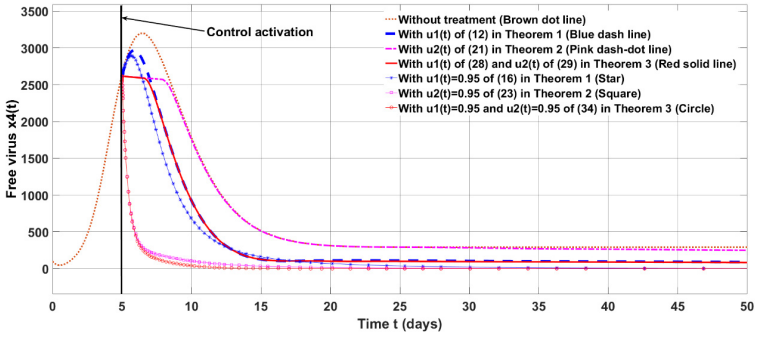

FIGURE 7. State trajectories of free virus $x_4(t)$ before $t = 50$.

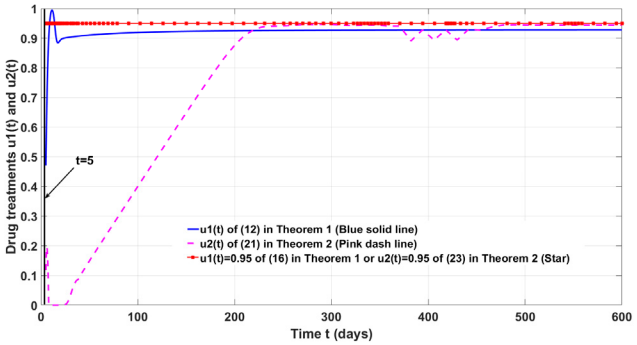

FIGURE 8. Trajectories of $u_1(t)$ in Theorem 1 and $u_2(t)$ in Theorem 2.

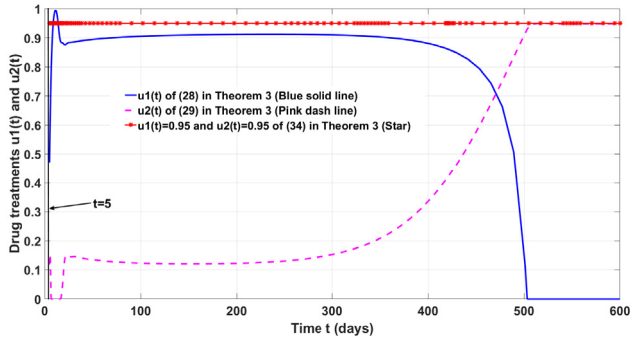

FIGURE 9. Trajectories of $u_1(t)$ and $u_2(t)$ in Theorem 3.

$u_2(t) = 0.95$ from (23) does not have a better response than $u_1(t)$ from (12) or than $u_1(t)$ from (28) and $u_2(t)$ from (29) before $t = 70$. In addition, from Fig. 2 to Fig. 5, $u_1(t) = 0.95$ and $u_2(t) = 0.95$ from (34) and $u_1(t) = 0.95$ from (16) still can obtain more perfect rate than the others, however, in Fig. 6 and Fig. 7, the reduction rate of free virus $x_4(t)$ under $u_2(t) = 0.95$ from (23) is definitely faster than the others except for the condition under $u_1(t) = 0.95$ and $u_2(t) = 0.95$ from (34) in Theorem 3, because $u_2(t)$ conducts the fourth equation of (8) and its value $u_2(t) = 0.95$ is really big.

Undeniably, $u_1(t) = 0.95$ or/and $u_2(t) = 0.95$ is/are able to make the state variables of model (8) converge to the infection-free equilibrium point E_1 asymptotically in faster rates than other proposed controls in Theorem 1, Theorem 2 and Theorem 3, and make $R_1 \leq 1$, $R_2 \leq 1$ and $R_3 \leq 1$ always. However, $u_1(t)$ or/and $u_2(t)$ using large fixed doses is like endowing overlarge treatment to the patients such that the intake can be over the need. On the other hand, using a fixed amount of drug treatment perhaps weakens the ability of flexibly customizing dosage regimens [36]. Furthermore, an infected patient always has time-varying physical conditions [29], that means, the state variables of model (8) are dynamic, therefore, the appropriateness of $u_1(t) = 0.95$ or/and $u_2(t) = 0.95$ may be doubtful. In general, every patient has his/her specific constitution and may have his/her own reaction to drug metabolism and effect [37]. Briefly, a fixed dose may be not appropriate especially when a patient is allergic or has a side effect from a large dose [37]. Consequently, $u_1(t)$ and $u_2(t)$ should be adjusted depending on the patient's condition such that the appearance of drug resistance is put off and the risk of side effect is reduced in the different process of drug treatment [32].

The trajectories of $u_1(t)$ from (12) and $u_2(t)$ from (21) are shown in Fig. 8, and they begin to work at $t \geq 5$. Two trajectories of $u_1(t)$ from (28) and $u_2(t)$ from (29) are shown in Fig. 9, where $u_1(t)$ asymptotically approaches 0 after $t = 504$ and maintains there with time; on the other hand, $u_2(t)$ increases to its maximal value after $t = 516$ and stay there with time. In addition, according to Theorem 3, Fig. 10(a)shows a feasible region (with red color) with $R_3 \leq 1$ on $u_1(t)$ and $u_2(t)$ axis coordinates and Fig. 10(b) shows the relation among R_3, $u_1(t)$ and $u_2(t)$ for Theorem3. In Fig. 8 and Fig. 9, it is seen that $u_1(t)$ and $u_2(t)$ do not need such large values as 0.95 in some periods for the treatment of a patient. Therefore, control relying on the states may be helpful for the patient.

The conditions of $R_1 \leq 1$ in Theorem 1 and $R_3 \leq 1$ in Theorem 3 are shown in Fig. 11 after $t \approx 200$, because the values of $u_1(t)$ from (12) and $u_1(t)$ from (28) and $u_2(t)$ from (29) satisfy the feasible ranges (16) and (34), respectively. The value of R_2 with $u_2(t)$ from (21) is bigger than 1 before $t \approx 220$, and $R_2 \leq 1$ after $t \approx 220$ where the value of $u_2(t)$ maintains at the feasible range (23). It is interesting that R_3 with $u_1(t) = 0.95$ and $u_2(t) = 0.95$ from (34) always stays below 1.

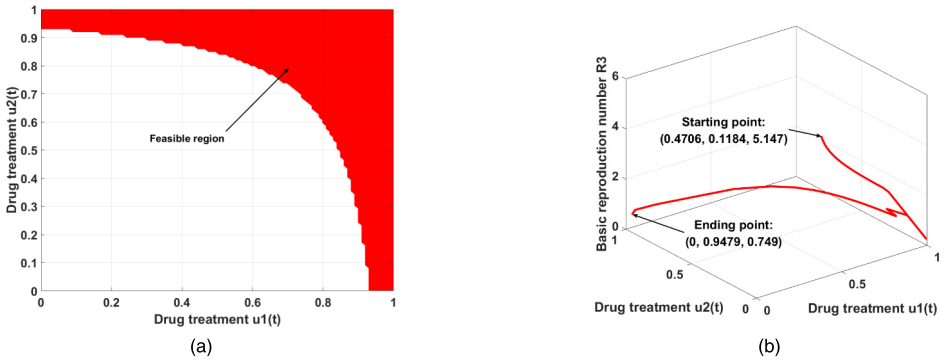

FIGURE 10. Feasible region (a) of $u_1(t)$ and $u_2(t)$ and trajectory change (b) of R_3 under $u_1(t)$ and $u_2(t)$ in Theorem 3.

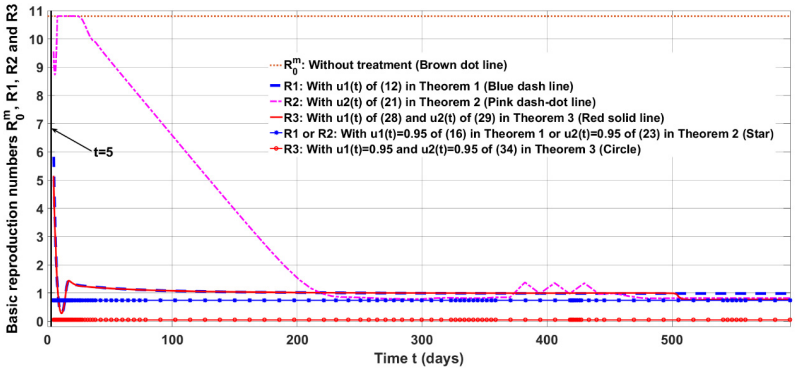

FIGURE 11. Trajectories of R_0^m, R_1, R_2 and R_3.

V. CONCLUSION

In this study, we have proposed three types of control strategy for drug treatments to make all state variables of model (8) asymptotically converge to the infection-free equilibrium point E_1 at last. Each type of control form has two choices: constant or state function. The proposed controls with the form of state function such as $u_1(t)$ of (12), $u_2(t)$ of (21) and $u_1(t)$ of (28) and $u_2(t)$ of (29) can be adjusted along with the variations of model's states. The other choice of control is that all $u_i(t)$, $i = 1, 2$, are constants which are constrained inside the proposed ranges. In the Section 4 Simulation results, it is shown that the constant controls still have pushed all states approaching the equilibrium E_1. However, many previous studies [29], [36], [37] mentioned that constant control still may have some risk or side effect for the patients. Therefore, we believe that the proposed control with the form of a state function is still valuable and informative to patients and doctors. There were some discussions about the state responses under each type of control treatment in Section 4. We believe that the combination therapy is worth being recommended in treating the HIV-infected patients; at least, it can reduce drug side effect or prolong the time of the appearance of drug resistance in the process of medical therapy.

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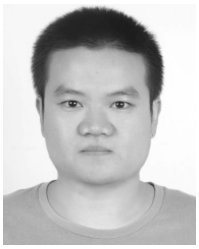
WEN-JUNE WANG (F'08) received the B.S. degree in control engineering from National Chiao-Tung University, Hsinchu, Taiwan, in 1980, the M.S. degree in electrical engineering from Tatung University, Taipei, Taiwan, in 1984, and the Ph.D. degree in electronics from National Chiao-Tung University, in 1987.

He has authored or coauthored more than 160 refereed journal papers and 160 conference papers in the areas of fuzzy systems and theorems, robust and nonlinear control in large-scale systems, and neural networks. His most significant contributions are the design of fuzzy systems and the development of robotics. His current research interests include robot control, neural networks, and pattern recognition. He was an IFSA Fellow, in 2017.



YI DING is currently pursuing the Ph.D. degree with the Department of Electrical Engineering, National Central University, Taoyuan, Taiwan.

His current research interests include systems biology, nonlinear systems, switching control, and fuzzy control.