Research Article

Global Dynamics of a Virus-Immune System with Virus-Guided Therapy and Saturation Growth of Virus

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We considered a piecewise virus-immune dynamic model to investigate the effectiveness of the HIV virus loads-guided structured treatment interruptions (STIs). To better describe the biological reality, we extended the existing models by taking the carrying capacity of the virus loads into consideration to indicate the saturated growth of virus loads. We initially investigated the sliding dynamics of the proposed model and then obtained the global dynamics of the proposed model. Our main results showed that the system can exhibit very complex and diverse dynamic behaviors including a globally asymptotically stable equilibrium, bistable equilibria, and tristable equilibria, depending on the dynamics of the subsystems and the threshold level. In particular, an interesting result indicated that, with a proper threshold condition, the virus-guided therapy policy can successfully control the virus loads far below its carrying capacity and maintain the activity of the immune system for the case that the effector cells always go to zero without therapy or with continuous therapy. The finding suggested that the optimal strategy should be individual-based due to coexistence of multiple stable steady states, depending on the threshold conditions and the initial levels of viral loads and effector cells of the patients.

1. Introduction

Highly active antiretroviral therapy (HAART) plays significant roles in improving survival and reducing morbidity and mortality in HIV patients [1, 2]. Nevertheless, lifelong HAART confronts many complicated problems such as adherence difficulties and the evolution of drug resistance [3–6]. Structured treatment interruptions (STIs), the alternative strategies, have been designed to effectively achieve sustained specific immunity for early therapy in HIV infection. Indeed, STIs are beneficial for some chronically infected individuals who may need to take drugs throughout their lives as well as the reconstruction of patients' immune system when they are not taking the drugs [7].

Since the first HIV patient received the structured antiretroviral therapy in 1999 [8], STIs have been widely investigated by many researchers. Basically, it includes two kinds of treatment regimes: carrying out the therapies at fixed moments or depending on the CD4 cell counts and/or viral loads. For example, some studies designed a scheduled treatment that therapy was initiated only when the CD4

cell counts decreased below 350 cells/ μL [9–12]. Aiming to maintain CD4 cell counts higher than 350 cells/ μL and HIV virus loads less than 100,000 copies/ μL , Ruiz et al. designed an experiment to evaluate the safety of CD4 cell and HIV virus-guided STIs [13]. Many works have been done to compare the STIs with the continuous antiretroviral therapy (ART), but conflicting results have been reported [7, 11, 13–17]. In particular, Maggiolo et al. made a conclusion that the structured treatment can result in the similar benefits for the patients with the continuous therapies [7], while the SMART study group found that STIs may also endanger the patients' life if their immune responses are not sufficiently stimulated [18]. STI is still an important topic since lifelong ART brings great challenges to all HIV positive individuals. Moreover, as immune therapy arises, combining the ART with immune therapy (such as interleukin-2 (IL-2) treatment) may be a good choice for treating HIV patients [19]. Modelling and quantifying the efficacy of the combination of STIs and immune therapy remains unclear and falls within the scope of this study.

Mathematical models are useful tools for investigating the dynamics of HIV-1 infection [20, 21]. Although many studies modelled the continuous therapy for HIV-infected patients [22–24], few attempts studied the STIs through mathematical modelling. In 2000, using a standard population model, Bonhoeffer et al. argued the benefits and risk generated from STIs [25]. In the study [26], Adams et al. analyzed the efficacy of STIs with fixed moments through the optimal control theory. Further, Rosenberg et al. pointed out that it is needed to include drug resistance and CD4 cell counts when making the structured treatment [27]. In 2006, Park et al. developed a mathematical model to investigate the impact of finite times of structured treatment guided by CD4 cell counts on HIV patients [28]. Then, Tang et al. [29] formulated a piecewise system to describe the CD4 cell-guided STIs, quantitatively explored STI strategies, and explained some controversial conclusions from different clinical studies. To further model immune therapy, Tang et al. [30] proposed a piecewise virus-immune dynamic model considering the combined antiretroviral therapy with interleukin-2 (IL-2) treatment. The model is given as follows:

$$\begin{aligned}\dot{x} &= rx - pxy - \varepsilon_1 \Phi x, \\ \dot{y} &= \frac{cxy}{1 + \omega x} - qxy - \delta y + \varepsilon_2 \Phi y,\end{aligned}\quad (1)$$

with

$$\Phi = \begin{cases} 0, & \text{if } H(x) = x - V_T < 0, \\ 1, & \text{if } H(x) = x - V_T > 0, \end{cases}\quad (2)$$

where x and y represent the HIV virus loads and the effector cells, respectively. Note that a critical value of virus loads, denoted by V_T , is set to trigger the combined therapy. That is, only when the virus loads exceed the threshold, we carry out the antiretroviral therapy and immune therapy (such as the interleukin-2 (IL-2) treatment) simultaneously for the patients, with ε_1 being the elimination rate of HIV virus due to antiretroviral therapy and ε_2 representing the growth rate of the effector cells due to immune therapy. Here, r is the growth rate of HIV virus which incorporates both their multiplication and death, δ is the death rate of the effector cells, p denotes the rate of binding of the effector cells to the virus loads, q represents the rate of inactivation of the effector cells, and $cx/(1 + \omega x)$ denotes that effector cell multiplication due to immune response has a maximum value as the HIV virus loads become large sufficiently.

In [30], the authors mainly discussed the global dynamics of system (1), and they further considered the efficacy of the effector cell-guided or both the effector cell and the HIV virus-guided piecewise therapies [31, 32]. Their results indicated that HIV virus can be controlled under some conditions with virus or effector cell-guided therapy, but still there are some parameter regions that the threshold policy can not prevent HIV from growing infinitely. As we can see from model (1), they simply assumed the linear growth of HIV virus. However, this is not what the thing looks like. Some clinical facts indicate that there should be “saturation effects” for the growth of HIV virus [33, 34]. The linear growth of HIV virus is unreasonable. Note that including the

saturated growth of the HIV virus makes the model more natural but significantly changes the dynamics of the basic immune-virus system. Little is known about whether HIV virus-guided therapy based on this more natural description of its growth can completely control the growth of HIV and falls within the scope of this study.

The main purpose of this paper is to propose a piecewise model with the saturated growth for virus loads to describe HIV virus-guided therapy and then evaluate the effectiveness of the threshold policy through analyzing the global dynamics of the proposed model. The remaining parts of this paper are organized as follows. In Section 2, we initially propose the model, give some basic definitions of the Filippov system and also briefly conclude the dynamic behaviors of two subsystems. In Section 3, we mainly discuss the sliding mode and sliding dynamics, including the existence of the sliding domain and the pseudoequilibrium. In Section 4, we investigate the global dynamics of the proposed model. Finally, we provide the discussion and some biological conclusions.

2. Filippov Model and Preliminaries

In this paper, we extend model (1) by including the saturated growth of HIV virus, and hence we propose the following model:

$$\begin{aligned}\dot{x} &= rx(1 - \eta x) - pxy - \varepsilon_1 \Phi x, \\ \dot{y} &= \frac{cxy}{1 + \omega x} - qxy - \delta y + \varepsilon_2 \Phi y,\end{aligned}\quad (3)$$

with

$$\Phi = \begin{cases} 0, & \text{if } H(x) = x - V_T < 0, \\ 1, & \text{if } H(x) = x - V_T > 0. \end{cases}\quad (4)$$

Here, $1/\eta$ represents the carrying capacity of virus loads.

Letting $Z = (x, y)^T$,

$$\begin{aligned}F_{R_1}(Z) &= \left(rx(1 - \eta x) - pxy, \frac{cxy}{1 + \omega x} - qxy - \delta y \right)^T, \\ F_{R_2}(Z) &= \left(rx(1 - \eta x) - pxy - \varepsilon_1 x, \frac{cxy}{1 + \omega x} - qxy \right. \\ &\quad \left. - \delta y + \varepsilon_2 y \right)^T.\end{aligned}\quad (5)$$

Then system (3) with (4) can be rewritten as the following general planar Filippov system [35–37]:

$$Z(t) = \begin{cases} F_{R_1}(Z), & Z \in R_1, \\ F_{R_2}(Z), & Z \in R_2. \end{cases}\quad (6)$$

with $R_1 = \{Z \in R_+^2 \mid H(Z) < 0\}$ and $R_2 = \{Z \in R_+^2 \mid H(Z) > 0\}$. Additionally, we describe the discontinuity boundary Σ separating the two regions R_1 and R_2 as $\Sigma = \{Z \in R_+^2 \mid H(Z) = 0\}$, where $H(Z)$ is a smooth scale function

nonvanishing on Σ . For convenience, we denote Filippov system (6) defined in region R_1 as system S_1 and that defined in region R_2 as system S_2 . Then we let

$$\sigma(Z) = \langle H_Z(Z), F_{R_1}(Z) \rangle \langle H_Z(Z), F_{R_2}(Z) \rangle, \quad (7)$$

where $\langle \cdot \rangle$ represents the standard scalar product and $H_Z(Z) = (1, 0)^T$ denotes the nonvanishing gradient of H on Σ . In the following, we replace $\langle H_Z(Z), F_{R_i}(Z) \rangle$ with the notation $F_{R_i}H(Z)$ for $i = 1, 2$.

In order to consider the trajectory of the Filippov vector field $(F_{R_1}(Z), F_{R_2}(Z))$, through a point $Z \in \Sigma$, we distinguish the following regions on Σ according to whether or not the vector field points towards it:

(a) Crossing region:

$$\Sigma_c = \{Z \in \Sigma \mid F_{R_1}H(Z) \cdot F_{R_2}H(Z) > 0\}, \quad (8)$$

(b) Sliding region:

$$\Sigma_s = \{Z \in \Sigma \mid F_{R_1}H(Z) > 0, F_{R_2}H(Z) < 0\}, \quad (9)$$

(c) Escaping region:

$$\Sigma_e = \{Z \in \Sigma \mid F_{R_1}H(Z) < 0, F_{R_2}H(Z) > 0\}. \quad (10)$$

Further, we can define a scalar differential equation on the sliding domain by employing the Filippov method. Let

$$g(Z) = \lambda F_{R_1} + (1 - \lambda) F_{R_2}, \quad \lambda = \frac{\langle H_Z, F_{R_2} \rangle}{\langle H_Z, F_{R_2} - F_{R_1} \rangle} \quad (11)$$

with $0 < \lambda < 1$. Then, we have that

$$Z' = g(Z), \quad Z \in \Sigma_s \quad (12)$$

describes the dynamics of system (6) on the sliding segment Σ_s . In what follows, we give the definitions of two types of equilibria of Filippov system (6).

Definition 1. A point Z^* is referred to as a real equilibrium of system (6) if $F_{R_1}(Z^*) = 0, H(Z^*) < 0$, or $F_{R_2}(Z^*) = 0, H(Z^*) > 0$. A point Z^* is called a virtual equilibrium of system (6) if $F_{R_1}(Z^*) = 0, H(Z^*) > 0$, or $F_{R_2}(Z^*) = 0, H(Z^*) < 0$. Both the real equilibrium and virtual equilibrium are called regular equilibria.

Definition 2. A point Z^* is referred to as a pseudoequilibrium if it is an equilibrium of the sliding mode of system (6); i.e., the equilibrium of the equation $Z' = g(Z) = 0$ satisfies $H(Z^*) = 0$.

Before exploring the global dynamics of the Filippov system (3), it is essential to have a clear view of the dynamics of two basic subsystems. Thus, we first briefly make some conclusions on the dynamics of subsystem S_1 and subsystem S_2 .

For subsystem S_1 , there always exists a trivial equilibrium $E_{10} = (0, 0)$ and a boundary equilibrium $E_{1\eta} = (x_{1\eta}, 0) = (1/\eta, 0)$. The positive equilibrium (x^*, y^*) of subsystem S_1 satisfies the following equations:

$$\begin{aligned} r(1 - \eta x^*) - py^* &= 0, \\ \frac{cx^*}{1 + \omega x^*} - qx^* - \delta &= 0. \end{aligned} \quad (13)$$

Let

$$\begin{aligned} f(x) &\doteq cx - (qx + \delta)(1 + \omega x) \\ &= -q\omega x^2 + (c - q - \delta\omega)x - \delta, \end{aligned} \quad (14)$$

and $\Delta_1 = c - q - \delta\omega - 2\sqrt{q\omega\delta}$. It is easy to verify that if $\Delta_1 > 0$ holds true, then $f(x) = 0$ has two positive roots which are given as

$$\begin{aligned} x_{11} &= \frac{c - q - \delta\omega - \sqrt{(c - q - \delta\omega)^2 - 4q\omega\delta}}{2q\omega}, \\ x_{12} &= \frac{c - q - \delta\omega + \sqrt{(c - q - \delta\omega)^2 - 4q\omega\delta}}{2q\omega}. \end{aligned} \quad (15)$$

Particularly, we know $f(x) > 0$ for $x \in (x_{11}, x_{12})$ and $f(x) < 0$ for $x \in (0, x_{11})$ or $x \in (x_{12}, +\infty)$. Substituting x_{11} or x_{12} into the first equation of (13), we get

$$\begin{aligned} y_{11} &= \frac{r}{p}(1 - \eta x_{11}), \\ y_{12} &= \frac{r}{p}(1 - \eta x_{12}). \end{aligned} \quad (16)$$

Thus, if

$$\begin{aligned} \frac{c - q - \delta\omega \mp \sqrt{(c - q - \delta\omega)^2 - 4q\omega\delta}}{2q\omega} &< \frac{1}{\eta} \\ \left(\text{i.e., } x_{1i} < \frac{1}{\eta}, \quad i = 1, 2 \right) \end{aligned} \quad (17)$$

holds true, then $E_{1i}(x_{1i}, y_{1i}), i = 1, 2$, are positive equilibria of system S_1 .

Next, we briefly investigate the stability of the equilibria of system S_1 . $E_{1\eta}$ is locally stable if $(c/\eta)/(1 + \omega/\eta) - q/\eta - \delta < 0$, which is equivalent to $\Delta_1 < 0$ or $\Delta_1 > 0, y_{11} < 0$ or $\Delta_1 > 0$, and $y_{12} > 0$. Define a function $K(x, y) = 1/xy$, and calculate

$$L = \frac{\partial}{\partial x} \left(K(x, y) \frac{dx}{dt} \right) + \frac{\partial}{\partial y} \left(K(x, y) \frac{dy}{dt} \right) = -\frac{r\eta}{y}, \quad (18)$$

where dx/dt and dy/dt are defined in system S_1 . Since all the parameters are positive and solutions to system S_1 initiating from R_+^2 are nonnegative, L does not change its sign in the first quadrant. Hence according to Dulac-Bendixson criterion, we get that there are no limit cycles or homoclinic connections for system S_1 . Therefore, if there is no positive equilibrium, then the boundary equilibrium $E_{1\eta}$ is globally asymptotically stable because system S_1 is bounded. Further, if $\Delta_1 > 0$ and $x_{11} < 1/\eta < x_{12}$ hold true, it is easy to verify that $f(1/\eta) > 0$, and hence the boundary equilibrium $E_{1\eta}$ is unstable. Therefore, under this scenario, positive equilibrium E_{11} is

globally asymptotically stable. When there are two positive equilibria of system S_1 , the dynamics of system S_1 have been shown in [38] that the equilibrium E_{12} is always an unstable saddle and E_{11} and $E_{1\eta}$ are bistable. Then the dynamics of system S_1 can be concluded as follows.

Proposition 3. *System S_1 always has a trivial equilibrium E_{10} and a boundary equilibrium $E_{1\eta}$. If $\Delta_1 < 0$ or $\Delta_1 > 0$ and $x_{11} > 1/\eta$ hold true, then there is no positive equilibrium, and the boundary equilibrium $E_{1\eta}$ is globally asymptotically stable; If $\Delta_1 > 0$ and $x_{11} < 1/\eta < x_{12}$, there is one and only one positive equilibrium E_{11} which is globally asymptotically stable; If $\Delta_1 > 0$ and $x_{12} < 1/\eta$, there are two positive equilibria E_{11} and E_{12} , and E_{11} and $E_{1\eta}$ are bistable.*

If $r > \varepsilon_1$ and $\delta > \varepsilon_2$, system S_2 has similar properties to system S_1 . Denote $\Delta_2 = c - q - (\delta - \varepsilon_2)\omega - 2\sqrt{q\omega(\delta - \varepsilon_2)}$ and

$$x_{2i} = \frac{c - q - (\delta - \varepsilon_2)\omega \mp \sqrt{(c - q - (\delta - \varepsilon_2)\omega)^2 - 4q\omega(\delta - \varepsilon_2)}}{2q\omega}, \quad (19)$$

$$y_{2i} = \frac{r}{p}(1 - \eta x_{2i}) - \frac{\varepsilon_1}{p},$$

$$i = 1, 2.$$

Similarly, if

$$\frac{c - q - (\delta - \varepsilon_2)\omega \mp \sqrt{(c - q - (\delta - \varepsilon_2)\omega)^2 - 4q\omega(\delta - \varepsilon_2)}}{2q\omega} < \frac{r - \varepsilon_1}{r\eta} \quad \left(\text{i.e., } x_{2i} < \frac{r - \varepsilon_1}{r\eta}, i = 1, 2 \right) \quad (20)$$

holds true, then $E_{2i}(x_{2i}, y_{2i}), i = 1, 2$, are positive equilibria of system S_2 . Then we can conclude the dynamics of system S_2 as follows.

Proposition 4. *System S_2 has a trivial equilibrium $E_{20} = (0, 0)$ and a boundary equilibrium $E_{2\eta} = (x_{2\eta}, 0) = ((r - \varepsilon_1)/r\eta, 0)$. If $\Delta_2 < 0$ or $\Delta_2 > 0$ and $x_{21} > (r - \varepsilon_1)/r\eta$, system S_2 has no positive equilibrium, and the boundary equilibrium $E_{2\eta}$ is globally asymptotically stable; if $\Delta_2 > 0$ and $x_{22} < (r - \varepsilon_1)/r\eta < x_{21}$ hold true, there is one and only one positive equilibrium E_{21} of system S_2 which is globally asymptotically stable; if $\Delta_2 > 0$ and $x_{22} < (r - \varepsilon_1)/r\eta$ hold true, there are two positive equilibria E_{21} and E_{22} , and both E_{21} and $E_{2\eta}$ are bistable.*

3. Sliding Dynamics

According to the definition of $\sigma(Z)$ in Section 2, we have

$$\begin{aligned} \sigma(Z) &= (rx(1 - \eta x) - pxy)(rx(1 - \eta x) - pxy - \varepsilon_1 x). \end{aligned} \quad (21)$$

Let $\sigma(Z) < 0$, and one yields

$$\frac{r}{p}(1 - \eta x) - \frac{\varepsilon_1}{p} < y < \frac{r}{p}(1 - \eta x). \quad (22)$$

It is reasonable to assume that the therapy should be done before virus growing and approaching its carrying capacity; therefore, in this study, we always assume that $V_T < 1/\eta$ holds true. Then, if $(1 - \varepsilon_1/r)/\eta < V_T < 1/\eta$ (i.e., $x_{2\eta} < V_T < x_{1\eta}$), the sliding segment is $\Sigma_s^1 = \{(x, y) \mid x = V_T, 0 \leq y \leq (r/p)(1 - \eta V_T)\}$; if $0 < V_T < x_{2\eta}$, then the sliding segment is $\Sigma_s^2 = \{x, y \mid x = V_T, (r/p)(1 - \eta V_T) - \varepsilon_1/p \leq y \leq (r/p)(1 - \eta V_T)\}$.

Next, we employ Utkin's equivalent control method introduced in [39] to examine the sliding dynamics in the region Σ_s . It follows from $H(x) = 0$ and the first equation of system (3) that

$$\frac{dH}{dt} = \frac{dx}{dt} = rx(1 - \eta x) - pxy - \Phi \varepsilon_1 x = 0. \quad (23)$$

Solving (23) with respect to Φ yields

$$\Phi = \frac{r}{\varepsilon_1}(1 - \eta x) - \frac{p}{\varepsilon_1}y. \quad (24)$$

Then substituting Φ into the second equation of system (3) gives

$$\begin{aligned} \frac{dy}{dt} &= y \left(-\frac{\varepsilon_2}{\varepsilon_1}py + \frac{\varepsilon_2}{\varepsilon_1}r(1 - \eta V_T) + \frac{cV_T}{1 + \omega V_T} - qV_T - \delta \right) \\ &\triangleq Q_s(V_T, y). \end{aligned} \quad (25)$$

Then, the sliding dynamics of system (3) can be described as (25). Let $Q_s(V_T, y) = 0$, and we obtain two roots

$$\begin{aligned} y_0 &= 0, \\ y_p &= \frac{r}{p}(1 - \eta V_T) + \frac{\varepsilon_1}{\varepsilon_2 p} \left(\frac{cV_T}{1 + \omega V_T} - qV_T - \delta \right). \end{aligned} \quad (26)$$

This indicates that there are two possible pseudoequilibria $E_0 = (V_T, 0)$ and $E_p = (V_T, y_p)$. In order to verify whether they are located at the sliding segment, we consider two situations $0 < V_T < x_{2\eta}$ and $x_{2\eta} < V_T < x_{1\eta}$.

It is easy to see that E_0 can not be a pseudoequilibrium when $0 < V_T < x_{2\eta}$, while it is always a pseudoequilibrium for $x_{2\eta} < V_T < x_{1\eta}$. Thus, we only need to analyze the existence of E_p . First, we prove the following lemmas.

Lemma 5. *If $\Delta_1 > 0$ and $\Delta_2 > 0$ hold true, then we have $x_{21} < x_{11} < x_{12} < x_{22}$.*

Proof. Let

$$\begin{aligned} g_1(z) &= c - q - \omega z - \sqrt{(c - q - \omega z)^2 - 4q\omega z}, \\ &\quad \text{(with } z > 0). \end{aligned} \quad (27)$$

To ensure the function to be well defined, we need $c - q - \omega z > 2\sqrt{q\omega z}$ (i.e., $\Delta_1 > 0$). Further, we know

$$\begin{aligned} c - q - \omega z &> 2\sqrt{q\omega z} \iff \\ c - q - \omega z &> 0, \\ (c - q - \omega z)^2 - 4q\omega z &> 0 \iff \\ z &< \frac{c - q}{\omega}, \\ 0 &< z < \frac{c + q - 2\sqrt{qc}}{\omega} \\ \text{or } z &> \frac{c + q + 2\sqrt{qc}}{\omega}. \end{aligned} \quad (28)$$

Definitely, we have $(c - q)/\omega < (c + q + 2\sqrt{qc})/\omega$, and $(c - q)/\omega > (c + q - 2\sqrt{qc})/\omega$ hold true. Therefore, the domain for $g_1(z)$ is $(0, (c + q - 2\sqrt{qc})/\omega)$, which is a continuous interval. Through simple calculation, we obtain

$$g'_1(z) = -\omega + \omega \frac{c + q - \omega z}{\sqrt{(c - q - \omega z)^2 - 4q\omega z}}. \quad (29)$$

Then, we have

$$\begin{aligned} g'_1(z) &> 0 \iff \\ c + q - \omega z &> \sqrt{(c - q - \omega z)^2 - 4q\omega z} \iff \\ 4qc &> 0. \end{aligned} \quad (30)$$

Because all the parameters are positive, $g'_1(z) > 0$ always holds true in its domain. Then, according to $\Delta_1 > 0$, $\Delta_2 > 0$, and $\delta > \delta - \varepsilon_2 > 0$, we have $x_{21} < x_{11}$. Similarly, let

$$g_2(z) = c - q - \omega z + \sqrt{(c - q - \omega z)^2 - 4q\omega z}. \quad (31)$$

which is also defined in the interval $0 < z < (c - q - 2\sqrt{qc})/\omega$. Note that $g'_2(z) < 0$ is equivalent to $c + q - \omega z > 0$. Further, it is obvious that $c + q - \omega z > c - q - \omega z > 0$. This means that $g'_2(z) < 0$ always holds true in its domain. Thus, we obtain that $x_{12} < x_{22}$ because $\Delta_1 > 0$, $\Delta_2 > 0$ and $\delta > \delta - \varepsilon_1 > 0$. In conclusion, we have $x_{21} < x_{11} < x_{12} < x_{22}$ if $\Delta_1 > 0$ and $\Delta_2 > 0$. The proof is completed. $\square$

Lemma 6. If $\Delta_1 < 0$ (or $\Delta_2 < 0$) holds true, then we have $y_p < (r/p)(1 - \eta V_T)$ (or $y_p < (r/p)(1 - \eta V_T) - \varepsilon_1/p$). If $\Delta_1 > 0$ and $\Delta_2 > 0$, then we have that $(r/p)(1 - \eta V_T) - \varepsilon_1/p < y_p < (r/p)(1 - \eta V_T)$ for $x_{21} < V_T < x_{11}$ or $x_{12} < V_T < x_{22}$; $y_p < (r/p)(1 - \eta V_T) - \varepsilon_1/p$ for $0 < V_T < x_{21}$ or $V_T > x_{22}$; and $y_p > (r/p)(1 - \eta V_T)$ for $x_{11} < V_T < x_{12}$.

Proof. Let $f_1(x) = cx/(1 + \omega x) - qx - \delta$, and we know that $f_1(x) < 0$ if $\Delta_1 < 0$. Therefore, it follows from the formula of y_p that when $\Delta_1 < 0$, then $y_p < (r/p)(1 - \eta V_T)$. If $\Delta_1 > 0$, we get $f_1(x) > 0$ for $x_{11} < x < x_{12}$, and $f_1(x) < 0$ for $0 < x < x_{11}$ or $x > x_{12}$. This means that, when $\Delta_1 > 0$, we get $y_p >$

$(r/p)(1 - \eta V_T)$ for $x_{11} < V_T < x_{12}$, and $y_p < (r/p)(1 - \eta V_T)$ for $0 < V_T < x_{11}$ or $V_T > x_{12}$. Rearranging the formula of y_p yields

$$\begin{aligned} y_p &= \frac{r}{p} (1 - \eta V_T) - \frac{\varepsilon_1}{p} \\ &+ \frac{\varepsilon_1}{\varepsilon_2 p} \left(\frac{c V_T}{1 + \omega V_T} - q V_T - \delta + \varepsilon_2 \right). \end{aligned} \quad (32)$$

Therefore, applying similar analysis we have that when $\Delta_2 < 0$, then $y_p < (r/p)(1 - \eta V_T) - \varepsilon_1/p$; when $\Delta_2 > 0$, then $y_p > (r/p)(1 - \eta V_T) - \varepsilon_1/p$ for $x_{21} < V_T < x_{22}$, and $y_p < (r/p)(1 - \eta V_T) - \varepsilon_1/p$ for $0 < V_T < x_{21}$ or $V_T > x_{22}$. This completes the proof. $\square$

Lemma 7. If $\Delta_1 > 0$ and $\Delta_2 > 0$, then we have $y_p > \min\{y_{21}, y_{11}\}$ for $x_{21} < V_T < x_{11}$.

Proof. Taking the derivative of y_p with respect to V_T gives

$$\frac{dy_p}{dV_T} = -\frac{r}{p}\eta + \frac{\varepsilon_1}{\varepsilon_2 p} \left(\frac{c}{(1 + \omega V_T)^2} - q \right). \quad (33)$$

Let $(dy_p/dV_T) > 0$, we have $-(1/\omega)\sqrt{c\varepsilon_1/(r\eta\varepsilon_2 + q\varepsilon_1)} - 1/\omega < V_T < (1/\omega)\sqrt{c\varepsilon_1/(r\eta\varepsilon_2 + q\varepsilon_1)} - 1/\omega$.

Thus, if $(1/\omega)\sqrt{c\varepsilon_1/(r\eta\varepsilon_2 + q\varepsilon_1)} - 1/\omega > 0$, $y_p(V_T)$ is increasing for $0 < V_T < (1/\omega)\sqrt{c\varepsilon_1/(r\eta\varepsilon_2 + q\varepsilon_1)} - 1/\omega$ and decreasing for $V_T > (1/\omega)\sqrt{c\varepsilon_1/(r\eta\varepsilon_2 + q\varepsilon_1)} - 1/\omega$; if $(1/\omega)\sqrt{c\varepsilon_1/(r\eta\varepsilon_2 + q\varepsilon_1)} - 1/\omega < 0$, then $y_p(V_T)$ is decreasing for $V_T > 0$. Therefore, when $x_{11} < V_T < x_{21}$, there may be three cases: (a) $y_p(V_T)$ is always decreasing as V_T increases, which means $y_p > y_p(x_{11}) = y_{11}$; (b) $y_p(V_T)$ is always increasing as V_T increases, then $y_p > y_p(x_{21}) = y_{21}$; (c) $y_p(V_T)$ is initially increasing and then decreasing as V_T increases, and hence $y_p > \min\{y_p(x_{21}), y_p(x_{11})\} = \min\{y_{21}, y_{11}\}$. This completes the proof. $\square$

It is easy to verify that if $\Delta_2 < 0$, then we have $\Delta_1 < 0$, which means that there can not be $\Delta_1 > 0$ when $\Delta_2 < 0$. According to the existence of possible equilibria of subsystems S_1 or S_2 , we consider the following cases to discuss the existence of the pseudoequilibrium E_p .

Case A1. There is no positive equilibrium for subsystem S_2 . Then, we have three subcases:

(i) **There is no positive equilibrium for subsystem S_1 (denoted by Case A11).** Hence, there could be

$$\Delta_1 < 0,$$

$$\Delta_2 < 0;$$

$$\text{or } \Delta_1 < 0,$$

$$\Delta_2 > 0,$$

$$x_{21} > \frac{(r - \varepsilon_1)}{r\eta};$$

$$\begin{aligned}
&\text{or } \Delta_1 > 0, \\
&x_{11} > \frac{1}{\eta}, \\
&\Delta_2 > 0, \\
&x_{21} > \frac{(r - \varepsilon_1)}{r\eta}.
\end{aligned} \tag{34}$$

It follows from Lemma 6 that for Case A11 there is always $y_p < (r/p)(1 - \eta V_T) - \varepsilon_1/p$ for $0 < V_T < x_{2\eta}$. This means that there is no pseudoequilibrium for $0 < V_T < x_{2\eta}$. Then, we mainly consider $x_{2\eta} < V_T < x_{1\eta}$. Now, there is $(r/p)(1 - \eta V_T) - \varepsilon_1/p < 0$. Therefore, we have $y_p < (r/p)(1 - \eta V_T) - \varepsilon_1/p < 0$ for the first subcase of Case A11 (i.e., $\Delta_1 < 0, \Delta_2 < 0$), which means E_p is not feasible. For the other two subcases, if $x_{21} > x_{1\eta}$, E_p is not feasible as well. However, if $x_{2\eta} < x_{21} < x_{1\eta}$, then the sign of y_p is not determined for the whole interval $x_{2\eta} < V_T < x_{1\eta}$. We denote

$$\begin{aligned}
(H_1): \quad &\frac{r}{p}(1 - \eta V_T) + \frac{\varepsilon_1}{\varepsilon_2 p} \left(\frac{cV_T}{1 + \omega V_T} - qV_T - \delta \right) > 0 \\
&\quad \quad \quad (\text{i.e., } y_p > 0); \\
(H_2): \quad &\frac{r}{p}(1 - \eta V_T) + \frac{\varepsilon_1}{\varepsilon_2 p} \left(\frac{cV_T}{1 + \omega V_T} - qV_T - \delta \right) < 0 \\
&\quad \quad \quad (\text{i.e., } y_p < 0).
\end{aligned} \tag{35}$$

Therefore, E_p is feasible for (H_1) , while it is not feasible for (H_2) .

(ii) **There is a unique equilibrium for subsystem S_1 (denoted by Case A12);** that is,

$$\begin{aligned}
&\Delta_1 > 0, \\
&x_{11} < \frac{1}{\eta} < x_{12}, \\
&\Delta_2 > 0, \\
&x_{21} > \frac{(r - \varepsilon_1)}{r\eta}.
\end{aligned} \tag{36}$$

For such case, there is no pseudoequilibrium for $0 < V_T < x_{2\eta}$. There are two pseudoequilibria E_0 and E_p for (H_1) and $x_{21} < V_T < x_{11}$, and there is only one pseudoequilibrium E_0 for $x_{2\eta} < V_T < x_{21}$ or $x_{11} < V_T < x_{1\eta}$ or (H_2) and $x_{21} < V_T < x_{11}$.

(iii) **There are two equilibria for subsystem S_1 (denoted by Case A13);** that is,

$$\begin{aligned}
&\Delta_1 > 0, \\
&x_{12} < \frac{1}{\eta}, \\
&\Delta_2 > 0, \\
&x_{21} > \frac{(r - \varepsilon_1)}{r\eta}.
\end{aligned} \tag{37}$$

Similar to Case A12, there is no pseudoequilibrium for $0 < V_T < x_{2\eta}$. E_p is feasible for (H_1) , $x_{21} < V_T < x_{11}$, or (H_1) , $x_{12} < V_T < \min\{x_{1\eta}, x_{22}\}$.

Case A2. There is one positive equilibrium for subsystem S_2 . Then, consider the following:

(i) **There is no positive equilibrium for subsystem S_1 (denoted by Case A21).** Then, there should be

$$\begin{aligned}
&\Delta_1 < 0, \\
&\Delta_2 > 0, \\
&x_{21} < \frac{(r - \varepsilon_1)}{r\eta} < x_{22}; \\
&\text{or } \Delta_1 > 0, \\
&x_{11} > \frac{1}{\eta}, \\
&\Delta_2 > 0, \\
&x_{21} < \frac{(r - \varepsilon_1)}{r\eta} < x_{22}.
\end{aligned} \tag{38}$$

It follows from Lemma 6 that if $\Delta_1 < 0$ or $\Delta_1 > 0, y_{11} < 0$, then we have $y_p < (r/p)(1 - \eta V_T)$ for $0 < V_T < x_{1\eta}$. Further, because $\Delta_2 > 0, y_{22} < 0 < y_{21}$, according to Lemma 6, there is no pseudoequilibrium for $0 < V_T < x_{21}$ while E_p is feasible for $x_{21} < V_T < x_{2\eta}$. Similarly, for $x_{2\eta} < V_T < x_{1\eta}$, the sign of y_p can not be determined. Thus, when $x_{2\eta} < V_T < x_{1\eta}$, there might be either two pseudoequilibria E_0 and E_p for (H_1) , or one pseudoequilibrium E_0 for (H_2) . Especially, if $x_{22} < x_{1\eta}$, then E_p is not feasible for $x_{22} < V_T < x_{1\eta}$.

(ii) **There is a unique positive equilibrium for subsystem S_1 (denoted by Case A22);** that is,

$$\begin{aligned}
&\Delta_1 > 0, \\
&x_{11} < \frac{1}{\eta} < x_{12}, \\
&\Delta_2 > 0, \\
&x_{21} < \frac{(r - \varepsilon_1)}{r\eta} < x_{22}.
\end{aligned} \tag{39}$$

For such case, it follows from Lemmas 6 and 7 that E_p is feasible for $x_{21} < V_T < x_{11}$. Especially, if $x_{11} > x_{2\eta}$, then there are two pseudoequilibria E_0 and E_p for $x_{2\eta} < V_T < x_{11}$, and there is no pseudoequilibrium for $0 < V_T < x_{21}$.

(iii) **There are two positive equilibria for subsystem S_1 (denoted by Case A23);** that is,

$$\begin{aligned}
&\Delta_1 > 0, \\
&x_{12} < \frac{1}{\eta},
\end{aligned}$$

$$\begin{aligned}\Delta_2 &> 0, \\ x_{21} &< \frac{(r - \varepsilon_1)}{r\eta} < x_{22}.\end{aligned}\quad (40)$$

Here, we consider three subcases: $x_{12} < x_{2\eta}$, $x_{11} < x_{2\eta} < x_{12}$, or $x_{11} > x_{2\eta}$ in terms of the relationship of $x_{2\eta}$ to x_{11} and x_{12} . If $x_{12} < x_{2\eta}$, then E_p is feasible for $x_{21} < V_T < x_{11}$ or $x_{12} < V_T < x_{2\eta}$ or (H_1) and $x_{2\eta} < V_T < \min\{x_{22}, x_{1\eta}\}$. If $x_{11} < x_{2\eta} < x_{12}$, then E_p is feasible for $x_{21} < V_T < x_{11}$ or (H_1) and $x_{12} < V_T < \min\{x_{22}, x_{1\eta}\}$. If $x_{11} > x_{2\eta}$, then it follows from Lemma 7 that E_p is feasible for $x_{21} < V_T < x_{11}$ or (H_1) and $x_{12} < V_T < \min\{x_{22}, x_{1\eta}\}$.

Case A3. There are two positive equilibria for subsystem S_2 . Under this case, there can not be a unique positive equilibrium for subsystem S_1 according to Lemma 5. Then, consider the following:

(i) **There is no positive equilibrium for subsystem S_1 (denoted by Case A31);** that is,

$$\begin{aligned}\Delta_1 &< 0, \\ \Delta_2 &> 0, \\ x_{22} &< \frac{(r - \varepsilon_1)}{r\eta}.\end{aligned}\quad (41)$$

It follows from Lemma 6 that E_p is feasible for $x_{21} < V_T < x_{22}$.

(ii) **There are two positive equilibria for subsystem S_1 (denoted by Case A32);** that is,

$$\begin{aligned}\Delta_1 &> 0, \\ x_{12} &< \frac{1}{\eta}, \\ \Delta_2 &> 0, \\ x_{22} &< \frac{(r - \varepsilon_1)}{r\eta}.\end{aligned}\quad (42)$$

Similarly, according to Lemma 6, E_p is a pseudoequilibrium for $x_{21} < V_T < x_{11}$ or $x_{12} < V_T < x_{22}$.

Having discussed the existence of the pseudoequilibria, we take the derivative of Q_s with respect to y to analyze the stability of the pseudoequilibria. Note that

$$\begin{aligned}\frac{dQ_s}{dy} &= \left(-\frac{\varepsilon_2}{\varepsilon_1}py + \frac{\varepsilon_2}{\varepsilon_1}r(1 - \eta V_T) + \frac{cV_T}{1 + \omega V_T} - qV_T - \delta \right) \\ &\quad - \frac{\varepsilon_2}{\varepsilon_1}py.\end{aligned}\quad (43)$$

Then, we have $(dQ_s/dy)|_{E_0} = (\varepsilon_2/\varepsilon_1)r(1 - \eta V_T) + cV_T/(1 + \omega V_T) - qV_T - \delta = (\varepsilon_2/\varepsilon_1)py_p$ and $(dQ_s/dy)|_{E_p} = -(\varepsilon_2/\varepsilon_1)py_p$.

FIGURE 1: Phase plane x - y for Filippov epidemic model (3), showing the switching line ($x = V_T$), sliding segment $\overline{A_1A_2}$, and the diagrams C_1 and C_2 split from the limit cycle C by the switching line.

Therefore, if (H_1) holds true, then the pseudoequilibrium E_p is locally stable on the sliding segment when it is feasible, and E_0 is unstable; if (H_2) holds true, then E_p becomes infeasible and the pseudoequilibrium E_0 is locally stable on the sliding segment when it exists.

4. Global Dynamics of System (3)

In this section, we will investigate the global dynamics of Filippov system (3). Initially, we shall rule out the existence of limit cycle for system (3). Here, we take Case A11 as an example to illustrate that there is not any limit cycles. The detailed proof is given in the appendix. Note that, for the other cases, we can prove the nonexistence of limit cycle for system (3) using the similar methods, and here we omit the detailed proof.

Lemma 8. For Case A11, there is no limit cycle for Filippov system (3).

Corresponding to the discussion of the sliding dynamics, we then consider the following cases to examine the global dynamics of system (3).

Case A1. There is no positive equilibrium for subsystem S_2 .

(i) **There is no positive equilibrium for subsystem S_1 (i.e., Case A11).** Then, we discuss the global dynamics of the Filippov system by considering the following subsituations:

(a) If $0 < V_T < x_{2\eta}$, then we know that $E_{2\eta}$ is a real equilibrium which is stable while $E_{1\eta}$ is a virtual equilibrium which is unstable. As we mentioned above, there is no limit cycle for system (3), and moreover there is not any other stable equilibrium, thus the local stability of $E_{2\eta}$ indicates that $E_{2\eta}$ is globally asymptotically stable (shown in Figure 2(a)).

FIGURE 2: Phase portraits of Filippov system (3) for Case A11 with different threshold conditions. (a) The boundary equilibrium $E_{2\eta}$ is globally asymptotically stable, here $V_T = 2.5$; (b) the pseudoequilibrium E_0 is globally asymptotically stable, here $V_T = 5.2$; (c) the pseudoequilibrium E_p is globally asymptotically stable, here $V_T = 5.5$. The other parameter values are fixed as $r = 10$, $p = 0.8$, $\omega = 0.23$, $c = 2$, $q = 0.3$, $\delta = 3.26$, $\eta = 0.16$, $\varepsilon_1 = 2$, and $\varepsilon_2 = 0.1$.

(b) If $x_{2\eta} < V_T < x_{1\eta}$ and (H_2) hold true, then we have that $E_{2\eta}$ becomes a virtual equilibrium. It follows from the discussion in Section 3 that the pseudoequilibrium E_0 is stable on the sliding segment Σ_s^1 . Similarly, system (3) does not have any limit cycle. Therefore, the local stability of E_0 indicates that E_0 is globally asymptotically stable (shown in Figure 2(b)).

(c) If $x_{2\eta} < V_T < x_{1\eta}$ and (H_1) hold true, then there are two pseudoequilibria E_0 and E_p on the sliding segment Σ_s^1 . As we proved in Section 3, E_p is locally stable while E_0 is unstable. Similar to subcase (b), we have that E_p is globally asymptotically stable (shown in Figure 2(c)).

Based on the above discussions, the global dynamics of system (3) can be concluded as follows.

Theorem 9. For Case A11, if $0 < V_T < x_{2\eta}$, then the boundary equilibrium $E_{2\eta}$ is globally asymptotically stable; if $x_{2\eta} < V_T < x_{1\eta}$, then the pseudoequilibrium E_0 is globally asymptotically stable for (H_2) being satisfied, while the pseudoequilibrium E_p is globally asymptotically stable for (H_1) being satisfied.

(ii) **There is a unique positive equilibrium for subsystem S_1 (i.e., Case A12).** If $0 < V_T < x_{2\eta}$, $E_{1\eta}$ and E_{11} are virtual equilibria, and $E_{2\eta}$ is a real equilibrium which is stable. As mentioned above, under this scenario, there is no limit cycle or no pseudoequilibrium for Filippov system (3), and thus $E_{2\eta}$ is globally stable. If $x_{2\eta} < V_T < x_{21}$, $E_{2\eta}$ becomes a virtual equilibrium, and there emerges the stable pseudoequilibrium E_0 on the sliding segment Σ_s^1 . If $x_{21} < V_T < x_{11}$, the same results hold compared with the case $x_{2\eta} < V_T < x_{21}$ if (H_2) holds true, while there are two pseudoequilibria E_0 (unstable) and E_p (stable) on Σ_s^1 if (H_1) holds true. Furthermore, if $x_{11} < V_T < x_{1\eta}$, E_{11} becomes a real equilibrium which is locally

stable. There is a pseudoequilibrium E_0 on Σ_s^1 which is unstable. Then, the global dynamics of Filippov system (3) are concluded as follows.

Theorem 10. For Case A12, if $0 < V_T < x_{2\eta}$, then $E_{2\eta}$ is globally asymptotically stable (shown in Figure 3(a)); if $x_{2\eta} < V_T < x_{21}$, then E_0 is globally asymptotically stable (shown in Figure 3(b)); if $x_{21} < V_T < x_{11}$, then E_0 is globally asymptotically stable for (H_2) being satisfied and E_p is globally asymptotically stable for (H_1) being satisfied (shown in Figure 3(c)); if $x_{11} < V_T < x_{1\eta}$, then E_{11} is globally asymptotically stable (shown in Figure 3(d)).

(iii) **There are two positive equilibria for subsystem S_1 (i.e., Case A13).** If there is only one steady state (boundary equilibrium or positive equilibrium or pseudoequilibrium), then it is globally stable. We can analyze the dynamics of system (3) under the same scenario using the similar methods. However, there is a different situation for such case. That is, if $x_{12} < V_T < \min\{x_{1\eta}, x_{22}\}$ holds true, then E_{11} is a real equilibrium; hence it is locally stable. Furthermore, E_0 is a locally stable pseudoequilibrium if (H_2) holds true, but if (H_1) holds true, E_0 lose its stability and E_p becomes a locally stable pseudoequilibrium. In conclusion, if $x_{12} < V_T < \min\{x_{1\eta}, x_{22}\}$, E_{11} is bistable with E_0 (or E_p) for (H_2) (or (H_1)) being satisfied. Based on the discussion above, the global dynamics of system (3) for Case A13 can be concluded as follows.

Theorem 11. For Case A13, if $0 < V_T < x_{2\eta}$, then $E_{2\eta}$ is globally asymptotically stable (shown in Figure 4(a)); if $x_{2\eta} < V_T < x_{21}$, then E_0 is globally asymptotically stable (shown in Figure 4(b)); if $x_{21} < V_T < x_{11}$, then E_0 (or E_p) is globally

FIGURE 3: Phase plane of Filippov system (3) for Case A12 with different threshold conditions. (a) The boundary equilibrium $E_{2\eta}$ is globally asymptotically stable, here $V_T = 3$; (b) the pseudo-equilibrium E_0 is globally asymptotically stable, here $V_T = 4$; (c) the pseudo-equilibrium E_p is globally asymptotically stable, here $V_T = 4.7$; (d) the regular equilibrium E_{11} is globally asymptotically stable, here $V_T = 5.5$. Parameter values are $r = 10$, $p = 0.8$, $\omega = 0.23$, $c = 2.05$, $q = 0.3$, $\delta = 3.26$, $\eta = 0.16$, $\varepsilon_1 = 4$, and $\varepsilon_2 = 0.1$.

asymptotically stable for (H_2) (or (H_1)) being satisfied (shown in Figure 4(c) (or Figure 4(d))); if $x_{11} < V_T < x_{12}$, then E_{11} is globally asymptotically stable (shown in Figure 4(e)); if $x_{12} < V_T < \min\{x_{1\eta}, x_{22}\}$, then E_0 and E_{11} are bistable for (H_2) being satisfied and E_p and E_{11} are bistable for (H_1) being satisfied (shown in Figure 4(f)). In particular, E_0 and E_{11} are always bistable for $x_{22} < V_T < x_{1\eta}$.

Cases A2 (A21, A22, and A23) and A31. All the dynamics of system (3) for four cases are similar to the former three cases, and thus we just omit the proof here. The global dynamics of these cases are summarized in Table 1 with the dynamical behaviors shown in Figures 5–8, respectively.

Case A32. There are two positive equilibria for both subsystems S_1 and S_2 , respectively. And the horizontal compartments of these equilibria satisfy $x_{21} < x_{11} < x_{12} < x_{22}$. In

terms of the existence and stability of the positive equilibria, the dynamics of the subsystems are similar to the focused situation in study [30]. Thus, based on the relationships of V_T with respect to x_{21} , x_{11} , x_{12} , and x_{22} , we can analyze the dynamics of system (3) through the following subcases.

If the threshold condition is relatively small, i.e., $0 < V_T < x_{21}$, only $E_{2\eta}$, E_{21} , and E_{22} are real equilibria. It follows from the dynamics of system S_2 that both $E_{2\eta}$ and E_{21} are stable, and thus they are bistable for the Filippov system (3). If V_T increases and satisfies $x_{21} < V_T < x_{11}$, E_{21} becomes a virtual equilibrium while the locally stable pseudo-equilibrium E_p emerges, and thus $E_{2\eta}$ and E_p are bistable. Further, we can conclude that E_{11} is bistable with $E_{2\eta}$ when $x_{11} < V_T < x_{12}$ or $x_{22} < V_T < x_{2\eta}$, while it is bistable with E_0 when $x_{2\eta} < V_T < x_{1\eta}$. If $x_{12} < V_T < x_{22}$, E_{11} and $E_{2\eta}$ are stable while there also exists pseudo-equilibrium E_p which is locally stable as well.

FIGURE 4: Solution trajectories of Filippov system (3) for Case A13 with different threshold conditions. (a) The boundary equilibrium $E_{2\eta}$ is globally asymptotically stable, here $V_T = 3.5$; (b) the pseudoequilibrium E_0 is globally asymptotically stable, here $V_T = 4.4$; (c) the pseudoequilibrium E_0 is globally asymptotically stable, here $V_T = 4.43$; (d) the pseudoequilibrium E_p is globally asymptotically stable, here $V_T = 5$; (e) the regular equilibrium E_{11} is globally asymptotically stable, here $V_T = 6.5$; (f) the regular equilibrium E_{11} and the pseudoequilibrium E_p are bistable, here $V_T = 7$. Parameter values are chosen as follows: $r = 10$, $p = 0.8$, $\omega = 0.24$, $c = 1.848$, $q = 0.3$, $\delta = 2.735$, $\eta = 0.12$, $\varepsilon_1 = 5.6$, and $\varepsilon_2 = 0.1$.

Thus, based on the above discussions, we have the following conclusions.

Theorem 12. For Case A32, if $0 < V_T < x_{21}$, then equilibrium E_{21} and the boundary equilibrium $E_{2\eta}$ are bistable (shown in Figure 9(a)); if $x_{21} < V_T < x_{11}$, then E_p and $E_{2\eta}$ are bistable (shown in Figure 9(b)); if $x_{11} < V_T < x_{12}$, then E_{11} and $E_{2\eta}$ are bistable (shown in Figure 9(c)); if $x_{12} < V_T < x_{22}$, then E_p , E_{11} , and $E_{2\eta}$ are locally tristable (shown in Figure 9(d)); if $x_{22} < V_T < x_{2\eta}$, $E_{2\eta}$ and E_{11} are bistable (shown in Figure 9(e)); if $x_{2\eta} < V_T < x_{1\eta}$, then E_0 and E_{11} are bistable (shown in Figure 9(f)).

5. Conclusion and Discussion

Based on the basic immune-virus model, we considered the threshold policy depending on virus loads for the

HIV-infected patients and obtained a nonsmooth system. Compared with the model in [30], we extend it by taking the saturated growth of virus into consideration, and hence our model is better in line with the biological reality. Meanwhile, our model also includes a piecewise elimination rate of HIV virus and growth rate of the effector cells to indicate that the antiretroviral therapy and interleukin-2 (IL-2) treatment are carried out simultaneously once the HIV virus loads increase above a threshold level.

We first briefly concluded the dynamics of two subsystems. Based on the properties of the subsystems, we discussed the sliding mode and sliding dynamics with different threshold conditions. In more detail, the sliding segments are $\Sigma_s^1 = \{(x, y) \mid x = V_T, 0 \leq y \leq (r/p)(1 - \eta V_T)\}$, for $x_{2\eta} < V_T < x_{1\eta}$, and $\Sigma_s^2 = \{(x, y) \mid x = V_T, (r/p)(1 - \eta V_T) - \varepsilon_1/p \leq y \leq (r/p)(1 - \eta V_T)\}$ for $0 < V_T < x_{2\eta}$. We note that

TABLE I: Dynamics of system (3) for Cases A11–A32.

Cases	Conditions	$0 < V_T < x_{2\eta}$	$x_{2\eta} < V_T < x_{1\eta}$	E_0 GAS
A11	$\Delta_1 < 0, \Delta_2 < 0$ $\Delta_1 < 0, \Delta_2 > 0, x_{21} > x_{2\eta}$ $\Delta_1 > 0, x_{11} > x_{1\eta}, \Delta_2 > 0, x_{21} > x_{2\eta}$	$E_{2\eta}$ GAS	E_p GAS for (H_1) E_p GAS for (H_1)	E_0 GAS for (H_2) E_0 GAS for (H_2)
A12	$\Delta_1 > 0, x_{11} < x_{1\eta} < x_{12},$ $\Delta_2 > 0, x_{21} > x_{2\eta}$	$E_{2\eta}$ GAS	$x_{2\eta} < V_T < x_{21}$ E_0 GAS	$x_{21} < V_T < x_{11}$ E_0 GAS for (H_1) E_0 GAS for (H_2)
A13	$\Delta_1 > 0, x_{12} < x_{1\eta},$ $\Delta_2 > 0, x_{21} > x_{2\eta}$	$E_{2\eta}$ GAS	$x_{2\eta} < V_T < x_{21}$ E_0 GAS	$x_{21} < V_T < x_{11}$ E_p GAS for (H_1) E_0 GAS for (H_2) E_{11} GAS
A21	$\Delta_1 < 0, \Delta_2 > 0,$ $x_{21} < x_{2\eta} < x_{22}$ or $\Delta_1 > 0, x_{11} > x_{1\eta},$ $\Delta_2 > 0, x_{21} < x_{2\eta} < x_{22}$	E_{21} GAS (Figure 5(a))	$x_{21} < V_T < x_{2\eta}$	$x_{2\eta} < V_T < x_{1\eta}$ E_p GAS E_0 GAS (Figure 5(c)) for (H_1) (Figure 5(d)) for (H_2)
A22	$\Delta_1 > 0, x_{11} < x_{1\eta} < x_{12},$ $\Delta_2 > 0, x_{21} < x_{2\eta} < x_{22}$	E_{21} GAS (Figure 6(a))	$x_{21} < V_T < x_{11}$ E_p GAS (Figure 6(b))	$x_{11} < V_T < x_{1\eta}$ E_{11} GAS (Figure 6(c))
A23	$\Delta_1 > 0, x_{12} < x_{1\eta},$ $\Delta_2 > 0, x_{21} < x_{2\eta} < x_{22}$	E_{21} GAS (Figure 7(a))	$x_{21} < V_T < x_{11}$ E_p GAS (Figure 7(b))	$x_{12} < V_T < x_{1\eta}$ E_{11} GAS (Figure 7(c)) E_{p^p}, E_{11} BS (Figure 7(d)) for (H_1) E_0, E_{11} BS for (H_2)
A31	$\Delta_1 < 0, \Delta_2 > 0,$ $x_{22} < x_{2\eta}$	$E_{21}, E_{2\eta}$ BS (Figure 8(a))	$x_{21} < V_T < x_{22}$ $E_p, E_{2\eta}$ BS (Figure 8(b))	$x_{22} < V_T < x_{2\eta}$ $E_{2\eta}$ GAS (Figure 8(c)) E_0 GAS (Figure 8(d))
A32	$\Delta_1 > 0, x_{12} < x_{1\eta},$ $\Delta_2 > 0, x_{22} < x_{2\eta}$	$E_{21}, E_{2\eta}$ BS	$x_{21} < V_T < x_{11}$ $E_p, E_{2\eta}$ BS	$x_{12} < V_T < x_{1\eta}$ $E_{11}, E_{2\eta}$ BS $E_p, E_{11}, E_{2\eta}$ TS $E_{11}, E_{2\eta}$ BS

Note: "GAS" represents "globally asymptotically stable"; "BS" means bistable; and "TS" is tristable.

FIGURE 5: Phase portraits of Filippov system (3) for Case A21 with different threshold conditions. (a) the regular equilibrium E_{21} is globally asymptotically stable, here $V_T = 1.5$; $\varepsilon_2 = 1.5$; (b) the pseudoequilibrium E_p is globally asymptotically stable, here $V_T = 3$; $\varepsilon_2 = 2$; (c) the pseudoequilibrium E_p is globally asymptotically stable, here $V_T = 5.3$; $\varepsilon_2 = 1.5$; (d) the pseudoequilibrium E_0 is globally asymptotically stable, here $V_T = 6$; $\varepsilon_2 = 0.1$. All the other parameter values are $r = 10$, $p = 0.8$, $\omega = 0.3$, $c = 2$, $q = 0.3$, $\delta = 2.51$, $\eta = 0.16$, and $\varepsilon_1 = 2$.

there is always a pseudoequilibrium E_0 on the sliding segment Σ_s^1 . And we further discussed the existence of the other pseudoequilibrium E_p by considering eight different cases. Correspondingly, we then investigated the global dynamics of system (3) for various cases. Our main results show that the system can exhibit very rich dynamic behaviors: (a) one of the equilibria is globally asymptotically stable, which can be the pseudoequilibrium E_0 or the pseudoequilibrium E_p or the boundary equilibrium $E_{2\eta}$ of subsystem S_2 or the positive equilibrium E_{11} or E_{21} of subsystem S_1 or S_2 ; (b) two equilibria are bistable, particularly, which can be that the positive equilibrium E_{11} is bistable with E_0 (or E_p or $E_{2\eta}$), or the boundary equilibrium $E_{2\eta}$ is bistable with the pseudoequilibrium E_p (or the positive equilibrium E_{21}); (c) three equilibria are locally tristable; that is, the pseudoequilibrium E_p , the boundary equilibrium $E_{2\eta}$, and the positive equilibrium E_{11} are stable for $x_{12} < V_T < x_{22}$.

Global dynamics of our proposed model means that there is the case that the boundary equilibrium is globally stable for both the subsystems. Note that the immune-virus system without any therapy is actually system S_1 (the free system) while the immune-virus system with continuous therapy can be described by system S_2 (the control system). Comparing system S_2 with system S_1 , we can find that the continuous therapy can shrink the final density of the virus (i.e., $x_{2\eta} < x_{1\eta}$). It follows that the continuous therapy failed to maintain the activity of the immune system since the effector cell goes to zero finally. However, threshold policy indicated that, with a proper threshold condition, the STIs can not only successfully control virus loads to a previously given level which can be far below its natural carrying capacity (i.e., $x_{1\eta}$) but also maintain the activity of the immune system (corresponding to the case that the pseudoequilibrium E_p is globally stable), as Theorem 9 suggested.

FIGURE 6: Phase portraits of Filippov system (3) for Case A22 with different threshold conditions. (a) The regular equilibrium E_{21} is globally asymptotically stable, here $V_T = 1.5$; (b) the pseudoequilibrium E_p is globally asymptotically stable, here $V_T = 2.8$; (c) the regular equilibrium E_{11} is globally asymptotically stable, here $V_T = 4.2$. Parameter values are $c = 2.1$, $\delta = 2.55$, and $\varepsilon_2 = 0.6$, and other parameters are chosen as shown in Figure 5.

Moreover, according to the dynamics of subsystem S_1 for Case A21 we can see that virus loads will finally approach its carrying capacity if there is no therapy for the patients. With the continuous therapy, the virus loads of the patients can be successfully controlled far below its carrying capacity and their immune system can always maintain the activity; that is, equilibrium E_{21} is globally asymptotically stable for system S_2 . For the virus-guided threshold policy, if the threshold level is set to satisfy $x_{21} < V_T < x_{2\eta}$, then the pseudoequilibrium E_p is globally stable, and E_p will tend to E_{21} as $V_T \rightarrow x_{21}$. This means that the threshold policy can obtain the similar effects for the patients compared with the continuous therapy in terms of virus loads being controlled, which is in agreement with the clinical study [7].

It is worth mentioning that if we also assume that the two subsystems have two positive equilibria (i.e., Case A32), our model results, due to the saturated growth in model equations, show that the virus can not grow to infinity. Under this situation, we also found that the dynamics of system (3) are similar to those of the control system (system S_2) when the threshold condition is relatively small (i.e., $0 < V_T < x_{21}$); that is, the positive equilibrium E_{21} and the boundary equilibrium $E_{2\eta}$ are bistable. And if the threshold is relatively high (i.e., $V_T > x_{22}$), the dynamics of system (3) are similar to the free system S_1 . Moreover, for middle values of the threshold (i.e., $x_{12} < V_T < x_{22}$), then equilibria E_p , E_{11} , and $E_{2\eta}$ are locally tristable. Therefore, the bistability and the tristability suggest that the optimal strategy should also be individual-based by taking the initial conditions of the patients and the threshold conditions into consideration.

Appendix

Proof of Lemma 8

As mentioned in Section 2, we have precluded the existence of limit cycle for system S_1 or system S_2 . Then, we will first prove that no limit cycle exists containing part of the sliding segment $\overline{A_1 A_2}$. Thus, we consider the following situations:

(a) If $0 < V_T < x_{2\eta}$, there is no pseudoequilibrium and the sliding dynamic equation (25) satisfies $dy/dt < 0$, so the trajectory on the sliding segment $\overline{A_1 A_2}$ moves from the top to the bottom. Therefore, in the region $x > V_T$ in Figure 1, we need to show that any orbit starting from A_1 cannot hit $\overline{A_1 A_2}$ again; if it does not hold, it contradicts the stability of $E_{2\eta}$ of the subsystem S_2 . Therefore, no closed orbit containing part of the sliding segment $\overline{A_1 A_2}$ exists.

(b) If $x_{2\eta} < V_T < x_{1\eta}$ and (H_1) , we have that E_p is locally asymptotically stable on the sliding segment Σ_c^1 . The local stability of E_p implies that there is no limit cycle containing part of the sliding segment $\overline{A_1 A_2}$.

(c) If $x_{2\eta} < V_T < x_{1\eta}$ and (H_2) hold true, we have that E_0 is locally asymptotically stable on the sliding segment Σ_c^1 . The local stability of E_0 on the sliding segment implies that there is no limit cycle containing part of the sliding segment $\overline{A_1 A_2}$.

Next, we preclude the limit cycle for Filippov system (3) which surrounds the sliding segment $\overline{A_1 A_2}$. Denote the right-hand side of (3) in the region $x < V_T$ (or $x > V_T$) by $f^1(z)$ (or $f^2(z)$), where $f^i(z) = (f^{i1}(z), f^{i2}(z))$. We consider that C is a limit cycle surrounding the sliding segment $\overline{A_1 A_2}$. Let C_1 (C_2) be its part on the left (right) side of the line $x = V_T$.

FIGURE 7: Solution trajectories of Filippov system (3) for Case A23 with different threshold conditions. (a) the regular equilibrium E_{21} is globally asymptotically stable, here $V_T = 1$; (b) the pseudoequilibrium E_p is globally asymptotically stable, here $V_T = 3$; (c) the regular equilibrium E_{11} is globally asymptotically stable, here $V_T = 6.5$; (d) the regular equilibrium E_{11} and the pseudoequilibrium E_p are bistable, here $V_T = 8.5$. Here $r = 10$, $p = 0.8$, $\omega = 0.23$, $c = 1.75$, $q = 0.3$, $\delta = 2.55$, $\eta = 0.1$, $\varepsilon_1 = 3$, and $\varepsilon_2 = 1$.

Denoting that the limit cycle C and the line $x = V_T$ intersect at Y_1 and Y_2 , the intersection points of C and the two auxiliary lines $x = V_T - \varepsilon$ and $x = V_T + \varepsilon$ by B_1, B_2, B_3, B_4 , respectively, are shown in Figure 1, where ε ($\varepsilon > 0$) is any sufficiently small number. Denote the region delimited by C_1 (C_2) and the segment $\overline{B_1 B_2}$ ($\overline{B_3 B_4}$) by D_1 (D_2), and the boundaries of D_1 and D_2 are denoted by E_1 and E_2 . Define the Dulac function by $K = 1/xy$ as before. From the discussions given above and Green's theorem, we have

$$\begin{aligned} & \iint_{D_1} \left(\frac{\alpha(Kf^{11})}{\alpha x} + \frac{\alpha(Kf^{12})}{\alpha y} \right) dx dy \\ &= \oint_{E_1} K(f^{11} dy - f^{12} dx) = \int_{\overrightarrow{B_1 B_2}} Kf^{11} dy, \end{aligned}$$

$$\begin{aligned} & \iint_{D_2} \left(\frac{\alpha(Kf^{21})}{\alpha x} + \frac{\alpha(Kf^{22})}{\alpha y} \right) dx dy \\ &= \oint_{E_2} K(f^{21} dy - f^{22} dx) = \int_{\overrightarrow{B_3 B_4}} Kf^{21} dy. \end{aligned} \quad (\text{A.1})$$

Let $D_0 \subset D_2$ and

$$\gamma = \iint_{D_0} \left(\frac{\alpha(Kf^{21})}{\alpha x} + \frac{\alpha(Kf^{22})}{\alpha y} \right) dx dy, \quad (\text{A.2})$$

FIGURE 8: Phase plane of Filippov system (3) for Case A31 with different threshold conditions. (a) The regular equilibrium E_{21} and the boundary equilibrium $E_{2\eta}$ are bistable, here $V_T = 3$; (b) the pseudoequilibrium E_p and the boundary equilibrium $E_{2\eta}$ are bistable, here $V_T = 5.5$; (c) the boundary equilibrium $E_{2\eta}$ is globally asymptotically stable, here $V_T = 7$; (d) the pseudoequilibrium E_0 is globally asymptotically stable. Parameter values are chosen as follows: $\delta = 2.55$, $\eta = 0.1$, and $\varepsilon_2 = 0.1$, and other parameter values are shown in Figure 5.

since $\gamma < 0$, and, furthermore,

$$\begin{aligned} & \iint_{D_1} \left(\frac{\alpha(Kf^{11})}{\alpha x} + \frac{\alpha(Kf^{12})}{\alpha y} \right) dx dy \\ & + \iint_{D_2} \left(\frac{\alpha(Kf^{21})}{\alpha x} + \frac{\alpha(Kf^{22})}{\alpha y} \right) dx dy < \gamma < 0, \end{aligned} \quad (\text{A.3})$$

and we get

$$\int_{\overrightarrow{B_1 B_2}} Kf^{11} dy + \int_{\overrightarrow{B_3 B_4}} Kf^{21} dy < \gamma < 0. \quad (\text{A.4})$$

Suppose that the ordinates of the points $Y_1, Y_2, B_1, B_2, B_3, B_4$ are $\underline{x}, \bar{x}, \underline{x} + f_1(\varepsilon), \bar{x} - f_2(\varepsilon), \bar{x} - f_3(\varepsilon), \underline{x} + f_4(\varepsilon)$, where $f_i(\varepsilon)$

is continuous and satisfies $\lim_{\varepsilon \rightarrow 0} f_i(\varepsilon) = 0$, $f_i(0) = 0$. Thus, we get

$$\begin{aligned} & \lim_{\varepsilon \rightarrow 0} \left[\int_{\overrightarrow{B_1 B_2}} Kf^{11} dy \right] \\ & = \lim_{\varepsilon \rightarrow 0} \int_{\underline{x} + f_1(\varepsilon)}^{\bar{x} - f_2(\varepsilon)} \left[\frac{r}{y} (1 - \eta x) - p \right] dy \\ & = r(1 - \eta V_T) \ln \frac{\bar{x}}{\underline{x}} - p(\bar{x} - \underline{x}). \end{aligned} \quad (\text{A.5})$$

Similarly, we have

$$\lim_{\varepsilon \rightarrow 0} \left[\int_{\overrightarrow{B_3 B_4}} Kf^{12} dy \right]$$

FIGURE 9: Phase plane of Filippov system (3) for Case A32 with different threshold conditions. (a) The regular equilibrium E_{21} and the boundary equilibrium $E_{2\eta}$ are bistable, here $V_T = 2$; (b) the pseudoequilibrium E_p and the boundary equilibrium $E_{2\eta}$ are bistable, here $V_T = 5$; (c) the regular equilibrium E_{11} and the boundary equilibrium $E_{2\eta}$ are bistable, here $V_T = 8$; (d) the regular equilibrium E_{11} , the pseudoequilibrium E_p and the boundary equilibrium $E_{2\eta}$ are locally stable simultaneously, here $V_T = 12$; (e) the regular equilibrium E_{11} and the boundary equilibrium $E_{2\eta}$ are bistable, here $V_T = 14.8$; (f) the regular equilibrium E_{11} and the pseudoequilibrium E_0 are bistable, here $V_T = 18$. We fix all other parameters as follows: $r = 10$, $p = 0.8$, $\omega = 0.18$, $c = 1.75$, $q = 0.3$, $\delta = 3.26$, $\eta = 0.05$, $\varepsilon_1 = 2$, and $\varepsilon_2 = 0.45$.

$$\begin{aligned}
 &= \lim_{\varepsilon \rightarrow 0} \int_{\bar{x}-f_3(\varepsilon)}^{\bar{x}+f_4(\varepsilon)} \left[\frac{r}{y} (1 - \eta x) - p - \frac{\delta}{x} \right] dy \\
 &= -r(1 - \eta V_T) \ln \frac{\bar{x}}{\underline{x}} + \left(p + \frac{\delta}{V_T} \right) (\bar{x} - \underline{x}).
 \end{aligned}
 \tag{A.6}$$

Therefore,

$$\lim_{\varepsilon \rightarrow 0} \left[\int_{B_1 B_2} K f^{11} dy + \int_{B_3 B_4} K f^{21} dy \right] = \frac{\delta}{V_T} (\bar{x} - \underline{x}) > 0,
 \tag{A.7}$$

which contradicts (A.4). Thus, we preclude the existence of the limit cycle C surrounding the sliding segment $\bar{A}_1 \bar{A}_2$. The proof is completed.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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