

## Research Article

# Global Properties of Virus Dynamics Models with Multitarget Cells and Discrete-Time Delays

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We propose a class of virus dynamics models with multitarget cells and multiple intracellular delays and study their global properties. The first model is a 5-dimensional system of nonlinear delay differential equations (DDEs) that describes the interaction of the virus with two classes of target cells. The second model is a  $(2n + 1)$ -dimensional system of nonlinear DDEs that describes the dynamics of the virus,  $n$  classes of uninfected target cells, and  $n$  classes of infected target cells. The third model generalizes the second one by assuming that the incidence rate of infection is given by saturation functional response. Two types of discrete time delays are incorporated into these models to describe (i) the latent period between the time the target cell is contacted by the virus particle and the time the virus enters the cell, (ii) the latent period between the time the virus has penetrated into a cell and the time of the emission of infectious (mature) virus particles. Lyapunov functionals are constructed to establish the global asymptotic stability of the uninfected and infected steady states of these models. We have proven that if the basic reproduction number  $R_0$  is less than unity, then the uninfected steady state is globally asymptotically stable, and if  $R_0 > 1$  (or if the infected steady state exists), then the infected steady state is globally asymptotically stable.

## 1. Introduction

Nowadays, various types of viruses infect the human body and cause serious and dangerous diseases. Mathematical modeling and model analysis of virus dynamics have attracted the interests of mathematicians during the recent years, due to their importance in understanding the associated characteristics of the virus dynamics and guiding in developing efficient anti-viral drug therapies. Several mathematical models have been proposed in the literature to describe the interaction of the virus with the target cells [1]. Some of these models are given

by a system of nonlinear ordinary differential equations (ODEs). Others are given by a system of nonlinear delay differential equations (DDEs) to account the intracellular time delays. The basic virus dynamics model with intracellular discrete time delay has been proposed in [2] and given by

$$\dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t), \quad (1.1)$$

$$\dot{y}(t) = e^{-m\tau} \beta x(t - \tau)v(t - \tau) - ay(t), \quad (1.2)$$

$$\dot{v}(t) = py(t) - cv(t), \quad (1.3)$$

where  $x(t)$ ,  $y(t)$ , and  $v(t)$  represent the populations of uninfected target cells, infected cells, and free virus particles at time  $t$ , respectively. Here,  $\lambda$  represents the rate of which new target cells are generated from sources within the body,  $d$  is the death rate constant, and  $\beta$  is the infection rate constant. Equation (1.2) describes the population dynamics of the infected cells and shows that they die with rate constant  $a$ . The virus particles are produced by the infected cells with rate constant  $p$ , and are removed from the system with rate constant  $c$ . The parameter  $\tau$  accounts for the time between viral entry into the target cell and the production of new virus particles. The recruitment of virus-producing cells at time  $t$  is given by the number of cells that were newly infected cells at time  $t - \tau$  and are still alive at time  $t$ . The probability of surviving the time period from  $t - \tau$  to  $t$  is  $e^{-m\tau}$ , where  $m$  is the constant death rate of infected cells but not yet virus-producing cells.

A great effort has been made in developing various mathematical models of viral infections with discrete or distributed delays and studying their basic and global properties, such as positive invariance properties, boundedness of the model solutions and stability analysis [3–19]. In [20–24], multiple intracellular delays have been incorporated into the virus dynamics model. Most of the existing models are based on the assumption that the virus attacks one class of target cells (e.g.,  $CD4^+$  T cells in case of HIV or hepatic cells in case of HCV and HBV). Since the interactions of some types of viruses inside the human body is not very clear and complicated, therefore, the virus may attack more than one class of target cells. Hence, virus dynamics models describing the interaction of the virus with more than one class of target cells are needed. In case of HIV infection, Perelson et al. [25] observed that the HIV attack two classes of target cells,  $CD4^+$  T cells and macrophages. In [26, 27], an HIV model with two target cells has been proposed. In very recent works [28–30], we have proposed several HIV models with two target cells and investigated the global asymptotic stability of their steady states. In [31], we have proposed a class of virus dynamics models with multitarget cells. However, the intracellular time delay has been neglected in [26–31].

The purpose of this paper is to propose a class of virus dynamics models with multi-target cells and establish the global stability of their steady states. The first model considers the interaction of the virus with two classes of target cells. In the second model, we assume that the virus attacks  $n$  classes of target cells. The third model generalizes the second one by assuming that the infection rate is given by saturation functional response. We incorporate two types of discrete time delays into these models describing (i) the time between the target cell is contacted by the virus particle and the contacting virus enters the cell, (ii) the time between the virus has penetrated into a cell and the emission of infectious (mature) virus particles. The global stability of these models is established using Lyapunov functionals, which are similar in nature to those used in [11, 20]. We prove that the global dynamics of these models are determined by the basic reproduction number  $R_0$ . If  $R_0 \leq 1$ , then

the uninfected steady state is globally asymptotically stable (GAS). If  $R_0 > 1$  (or if the infected steady state exists), then the infected steady state is GAS for all time delays.

## 2. Virus Dynamics Model with Two Target Cells and Delays

In this section, we introduce a mathematical model of virus infection with two classes of target cells. This model can describe the HIV dynamics with two classes of target cells, CD4<sup>+</sup> T cells and macrophages [26, 27]. This model can be considered as an extension of the models given in [11, 26, 27]:

$$\dot{x}_1(t) = \lambda_1 - d_1 x_1(t) - \beta_1 x_1(t)v(t), \quad (2.1)$$

$$\dot{y}_1(t) = e^{-m_1 \tau_1} \beta_1 x_1(t - \tau_1)v(t - \tau_1) - a_1 y_1(t), \quad (2.2)$$

$$\dot{x}_2(t) = \lambda_2 - d_2 x_2(t) - \beta_2 x_2(t)v(t), \quad (2.3)$$

$$\dot{y}_2(t) = e^{-m_2 \tau_2} \beta_2 x_2(t - \tau_2)v(t - \tau_2) - a_2 y_2(t), \quad (2.4)$$

$$\dot{v}(t) = e^{-n_1 \omega_1} p_1 y_1(t - \omega_1) + e^{-n_2 \omega_2} p_2 y_2(t - \omega_2) - cv(t), \quad (2.5)$$

where  $x_1$  and  $x_2$  represent the populations of the two classes of uninfected target cells;  $y_1$  and  $y_2$  are the populations of the infected cells. The population of the target cells are described by (2.1) and (2.3), where  $\lambda_1$  and  $\lambda_2$  represent the rates of which new target cells are generated,  $d_1$  and  $d_2$  are the death rate constants, and  $\beta_1$  and  $\beta_2$  are the infection rate constants. Equations (2.2) and (2.4) describe the population dynamics of the two classes of infected cells and show that they die with rate constants  $a_1$  and  $a_2$ . The virus particles are produced by the two classes of infected cells with rate constants  $p_1$  and  $p_2$  and are cleared with rate constant  $c$ . Here the parameter  $\tau_i$  accounts for the time between the target cells of class  $i$  are contacted by the virus particle and the contacting virus enters the cells. The recruitment of virus-producing cells at time  $t$  is given by the number of cells that were newly infected cells at times  $t - \tau_i$  and are still alive at time  $t$ . Also,  $m_i$  is assumed to be a constant death rate for infected target cells, but not yet virus-producing cells. Thus, the probability of surviving the time period from  $t - \tau_i$  to  $t$  is  $e^{-m_i \tau_i}$ ,  $i = 1, 2$ . The time between the virus has penetrated into a target cell of class  $i$  and the emission of infectious (matures) virus particles is represented by  $\omega_i$ . The probability of survival of an immature virus is given by  $e^{-n_i \omega_i}$ , where  $n_i$  is constant.

### 2.1. Initial Conditions

The initial conditions for system (2.1)–(2.5) take the form

$$\begin{aligned} x_1(\theta) &= \varphi_1(\theta), & y_1(\theta) &= \varphi_2(\theta), & x_2(\theta) &= \varphi_3(\theta), & y_2(\theta) &= \varphi_4(\theta), & v(\theta) &= \varphi_5(\theta), \\ \varphi_i(\theta) &\geq 0, & \theta &\in [-\max\{\tau_1, \tau_2, \omega_1, \omega_2\}, 0], & i &= 1, \dots, 5, \end{aligned} \quad (2.6)$$

where  $(\varphi_1(\theta), \dots, \varphi_5(\theta)) \in C([-\max\{\tau_1, \tau_2, \omega_1, \omega_2\}, 0], \mathbb{R}_+^5)$ , the Banach space of continuous functions mapping the interval  $[-\max\{\tau_1, \tau_2, \omega_1, \omega_2\}, 0]$  into  $\mathbb{R}_+^5$ , where  $\mathbb{R}_+^5 = \{(z_1, z_2, \dots, z_5) : z_i \geq 0\}$ .

By the fundamental theory of functional differential equations [32], system (2.1)–(2.5) has a unique solution  $(x_1(t), y_1(t), x_2(t), y_2(t), v(t))$  satisfying the initial conditions (2.6).

## 2.2. Nonnegativity and Boundedness of Solutions

In the following, we establish the nonnegativity and boundedness of solutions of (2.1)–(2.5) with initial conditions (2.6).

**Proposition 2.1.** *Let  $(x_1(t), y_1(t), x_2(t), y_2(t), v(t))$  be any solution of (2.1)–(2.5) satisfying the initial conditions (2.6), then  $x_1(t)$ ,  $y_1(t)$ ,  $x_2(t)$ ,  $y_2(t)$ , and  $v(t)$  are all nonnegative for  $t \geq 0$  and ultimately bounded.*

*Proof.* From (2.1) and (2.3), we have

$$x_i(t) = x_i(0)e^{-\int_0^t (d_i + \beta_i v(\xi)) d\xi} + \lambda_i \int_0^t e^{-\int_\eta^t (d_i + \beta_i v(\xi)) d\xi} d\eta, \quad i = 1, 2, \quad (2.7)$$

which indicates that  $x_1(t) \geq 0$ ,  $x_2(t) \geq 0$  for all  $t \geq 0$ . Now from (2.2), (2.4), and (2.5), we have

$$\begin{aligned} y_i(t) &= y_i(0)e^{-a_i t} + e^{-m_i \tau_i} \int_0^t \beta_i x_i(\eta - \tau_i) v(\eta - \tau_i) e^{-a_i(t-\eta)} d\eta, \quad i = 1, 2, \\ v(t) &= v(0)e^{-ct} + \int_0^t [e^{-n_1 \omega_1} p_1 y_1(\eta - \omega_1) + e^{-n_2 \omega_2} p_2 y_2(\eta - \omega_2)] e^{-c(t-\eta)} d\eta, \end{aligned} \quad (2.8)$$

confirming that  $y_1(t) \geq 0$ ,  $y_2(t) \geq 0$ ,  $v(t) \geq 0$  for all  $t \in [0, \max\{\tau_1, \tau_2, \omega_1, \omega_2\}]$ . By a recursive argument, we obtain  $y_1(t) \geq 0$ ,  $y_2(t) \geq 0$ ,  $v(t) \geq 0$  for all  $t \geq 0$ .

To show the boundedness of the solutions, we let  $X_1(t) = e^{-m_1 \tau_1} x_1(t - \tau_1 - \omega_1) + y_1(t - \omega_1)$  and  $X_2(t) = e^{-m_2 \tau_2} x_2(t - \tau_2 - \omega_2) + y_2(t - \omega_2)$ , then

$$\begin{aligned} \dot{X}_1(t) &\leq \lambda_1 e^{-m_1 \tau_1} - \sigma_1 X_1(t), \\ \dot{X}_2(t) &\leq \lambda_2 e^{-m_2 \tau_2} - \sigma_2 X_2(t), \end{aligned} \quad (2.9)$$

where  $\sigma_1 = \min\{d_1, a_1\}$  and  $\sigma_2 = \min\{d_2, a_2\}$ . Hence,  $\limsup_{t \rightarrow \infty} X_1(t) \leq L_1$ , and  $\limsup_{t \rightarrow \infty} X_2(t) \leq L_2$ , where  $L_1 = \lambda_1 e^{-m_1 \tau_1} / \sigma_1$  and  $L_2 = \lambda_2 e^{-m_2 \tau_2} / \sigma_2$ . On the other hand,

$$\dot{v}(t) \leq e^{-n_1 \omega_1} p_1 L_1 + e^{-n_2 \omega_2} p_2 L_2 - cv, \quad (2.10)$$

then  $\limsup_{t \rightarrow \infty} v(t) \leq L_3$ , where  $L_3 = (e^{-n_1 \omega_1} p_1 L_1 + e^{-n_2 \omega_2} p_2 L_2) / c$ . It follows that the solution  $(x_1(t), y_1(t), x_2(t), y_2(t), v(t))$  is ultimately bounded.  $\square$

## 2.3. Steady States

It will be explained in the following that the global behavior of model (2.1)–(2.5) crucially depends on the basic reproduction number given by

$$R_0 = \frac{e^{-(m_1 \tau_1 + n_1 \omega_1)} p_1 \beta_1 a_2 x_1^0 + e^{-(m_2 \tau_2 + n_2 \omega_2)} p_2 \beta_2 a_1 x_2^0}{a_1 a_2 c}, \quad (2.11)$$

where  $x_1^0 = \lambda_1/d_1$  and  $x_2^0 = \lambda_2/d_2$ . We observe that  $R_0$  can be written as

$$R_0 = R_1 + R_2, \quad (2.12)$$

where

$$R_1 = \frac{e^{-(m_1\tau_1+n_1\omega_1)}p_1\beta_1\lambda_1}{a_1d_1c}, \quad R_2 = \frac{e^{-(m_2\tau_2+n_2\omega_2)}p_2\beta_2\lambda_2}{a_2d_2c} \quad (2.13)$$

are the basic reproduction numbers of each class of target cell dynamics separately (see [28]).

Following the same line as in [28], we can show that if  $R_0 \leq 1$ , then system (2.1)–(2.5) has only one steady state  $E_0 = (x_1^0, 0, x_2^0, 0, 0)$  which is called uninfected steady state, and if  $R_0 > 1$ , then system (2.1)–(2.5) has two steady states  $E_0$  and infected steady state  $E_1 = (x_1^*, y_1^*, x_2^*, y_2^*, v^*)$ . The coordinates of the infected steady state are given by

$$\begin{aligned} x_1^* &= \begin{cases} \frac{\alpha_5 c}{\alpha_1 \alpha_5 + \alpha_2 \alpha_3}, & \text{if } \alpha_4 = 0, \\ \frac{-(\alpha_1 \alpha_5 + \alpha_2 \alpha_3 - \alpha_4 c) + \sqrt{(\alpha_1 \alpha_5 + \alpha_2 \alpha_3 - \alpha_4 c)^2 + 4\alpha_1 \alpha_4 \alpha_5 c}}{2\alpha_1 \alpha_4}, & \text{if } \alpha_4 \neq 0, \end{cases} \\ x_2^* &= \begin{cases} \frac{\alpha_3 c}{\alpha_1 \alpha_5 + \alpha_2 \alpha_3}, & \text{if } \alpha_4 = 0, \\ \frac{c}{\alpha_2} + \frac{(\alpha_1 \alpha_5 + \alpha_2 \alpha_3 - \alpha_4 c) - \sqrt{(\alpha_1 \alpha_5 + \alpha_2 \alpha_3 - \alpha_4 c)^2 + 4\alpha_1 \alpha_4 \alpha_5 c}}{2\alpha_2 \alpha_4}, & \text{if } \alpha_4 \neq 0, \end{cases} \\ y_1^* &= \frac{d_1}{a_1 e^{m_1 \tau_1}} \left( \frac{x_1^0}{x_1^*} - 1 \right) x_1^*, \quad y_2^* = \frac{d_2}{a_2 e^{m_2 \tau_2}} \left( \frac{x_2^0}{x_2^*} - 1 \right) x_2^*, \quad v^* = \frac{d_1}{\beta_1} \left( \frac{x_1^0}{x_1^*} - 1 \right), \end{aligned} \quad (2.14)$$

where

$$\begin{aligned} \alpha_1 &= \frac{e^{-(n_1\omega_1+m_1\tau_1)}p_1\beta_1}{a_1}, \quad \alpha_2 = \frac{e^{-(n_2\omega_2+m_2\tau_2)}p_2\beta_2}{a_2}, \quad \alpha_3 = \lambda_2\beta_1, \\ \alpha_4 &= \beta_1 d_2 - \beta_2 d_1, \quad \alpha_5 = \lambda_1\beta_2. \end{aligned} \quad (2.15)$$

## 2.4. Global Stability

In this section, we prove the global stability of the uninfected and infected steady states of system (2.1)–(2.5). The strategy of the proof is to use suitable Lyapunov functionals which are similar in nature to those used in [11, 20]. Next we will use the following notation:  $z = z(t)$ , for any  $z \in \{x_1, y_1, x_2, y_2, v\}$ . We also define a function  $H : \mathbb{R}_{>0} \rightarrow \mathbb{R}_{\geq 0}$  as

$$H(z) = z - 1 - \ln z. \quad (2.16)$$

It is clear that  $H(z) \geq 0$  for any  $z > 0$  and  $H$  has the global minimum  $H(1) = 0$ .

**Theorem 2.2.** (i) If  $R_0 \leq 1$ , then  $E_0$  is GAS for any  $\tau_1, \tau_2, \omega_1, \omega_2 \geq 0$ .  
(ii) If  $R_0 > 1$ , then  $E_1$  is GAS for any  $\tau_1, \tau_2, \omega_1, \omega_2 \geq 0$ .

*Proof.* (i) We consider a Lyapunov functional

$$W_1 = W_{11} + W_{12} + W_{13}, \quad (2.17)$$

where

$$\begin{aligned} W_{11} &= e^{-m_1\tau_1} x_1^0 H\left(\frac{x_1}{x_1^0}\right) + y_1 + \gamma \left( e^{-m_2\tau_2} x_2^0 H\left(\frac{x_2}{x_2^0}\right) + y_2 \right) + \frac{a_1}{p_1} e^{n_1\omega_1} v, \\ W_{12} &= e^{-m_1\tau_1} \int_0^{\tau_1} \beta_1 x_1(t-\theta)v(t-\theta)d\theta + \gamma e^{-m_2\tau_2} \int_0^{\tau_2} \beta_2 x_2(t-\theta)v(t-\theta)d\theta, \\ W_{13} &= a_1 \int_0^{\omega_1} y_1(t-\theta)d\theta + \gamma a_2 \int_0^{\omega_2} y_2(t-\theta)d\theta, \end{aligned} \quad (2.18)$$

where  $\gamma = (p_2 a_1 / p_1 a_2) e^{n_1\omega_1 - n_2\omega_2}$ . We note that  $W_1$  is defined, continuous, and positive definite for all  $(x_1, y_1, x_2, y_2, v) > 0$ . Also, the global minimum  $W_1 = 0$  occurs at the uninfected steady state  $E_0$ .

The time derivatives of  $W_{11}$  and  $W_{12}$  are given by

$$\begin{aligned} \frac{dW_{11}}{dt} &= e^{-m_1\tau_1} \left( 1 - \frac{x_1^0}{x_1} \right) \dot{x}_1 + \dot{y}_1 + \gamma \left( e^{-m_2\tau_2} \left( 1 - \frac{x_2^0}{x_2} \right) \dot{x}_2 + \dot{y}_2 \right) + \frac{a_1}{p_1} e^{n_1\omega_1} \dot{v}, \\ \frac{dW_{12}}{dt} &= e^{-m_1\tau_1} \int_0^{\tau_1} \frac{d}{dt} \beta_1 x_1(t-\theta)v(t-\theta)d\theta + \gamma e^{-m_2\tau_2} \int_0^{\tau_2} \frac{d}{dt} \beta_2 x_2(t-\theta)v(t-\theta)d\theta \\ &= -e^{-m_1\tau_1} \int_0^{\tau_1} \frac{d}{d\theta} \beta_1 x_1(t-\theta)v(t-\theta)d\theta - \gamma e^{-m_2\tau_2} \int_0^{\tau_2} \frac{d}{d\theta} \beta_2 x_2(t-\theta)v(t-\theta)d\theta \\ &= e^{-m_1\tau_1} (\beta_1 x_1 v - \beta_1 x_1(t-\tau_1)v(t-\tau_1)) + \gamma e^{-m_2\tau_2} [\beta_2 x_2 v - \beta_2 x_2(t-\tau_2)v(t-\tau_2)]. \end{aligned} \quad (2.19)$$

Similarly,  $dW_{13}/dt$  is given by

$$\frac{dW_{13}}{dt} = a_1 (y_1 - y_1(t-\omega_1)) + \gamma a_2 (y_2 - y_2(t-\omega_2)). \quad (2.20)$$

It follows that

$$\begin{aligned} \frac{dW_1}{dt} &= e^{-m_1\tau_1} \left( 1 - \frac{x_1^0}{x_1} \right) (\lambda_1 - d_1 x_1 - \beta_1 x_1 v) + e^{-m_1\tau_1} \beta_1 x_1(t-\tau_1)v(t-\tau_1) - a_1 y_1 \\ &\quad + \gamma \left[ e^{-m_2\tau_2} \left( 1 - \frac{x_2^0}{x_2} \right) (\lambda_2 - d_2 x_2 - \beta_2 x_2 v) + e^{-m_2\tau_2} \beta_2 x_2(t-\tau_2)v(t-\tau_2) - a_2 y_2 \right] \\ &\quad + \frac{a_1}{p_1} e^{n_1\omega_1} [e^{-n_1\omega_1} p_1 y_1(t-\omega_1) + e^{-n_2\omega_2} p_2 y_2(t-\omega_2) - cv] \end{aligned}$$

$$\begin{aligned}
& + e^{-m_1\tau_1} [\beta_1 x_1 v - \beta_1 x_1(t - \tau_1)v(t - \tau_1)] + \gamma e^{-m_2\tau_2} [\beta_2 x_2 v - \beta_2 x_2(t - \tau_2)v(t - \tau_2)] \\
& + a_1 [y_1 - y_1(t - \omega_1)] + \gamma a_2 [y_2 - y_2(t - \omega_2)] \\
= & e^{-m_1\tau_1} \lambda_1 \left[ 2 - \frac{x_1^0}{x_1} - \frac{x_1}{x_1^0} \right] + e^{-m_2\tau_2} \gamma \lambda_2 \left[ 2 - \frac{x_2^0}{x_2} - \frac{x_2}{x_2^0} \right] + e^{-m_1\tau_1} \beta_1 x_1^0 v \\
& + e^{-m_2\tau_2} \gamma \beta_2 x_2^0 v - \frac{a_1 c}{p_1} e^{n_1 \omega_1} v \\
= & e^{-m_1\tau_1} \lambda_1 \left[ 2 - \frac{x_1^0}{x_1} - \frac{x_1}{x_1^0} \right] + e^{-m_2\tau_2} \gamma \lambda_2 \left[ 2 - \frac{x_2^0}{x_2} - \frac{x_2}{x_2^0} \right] + \frac{a_1 c e^{n_1 \omega_1}}{p_1} (R_0 - 1) v.
\end{aligned} \tag{2.21}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then the first two terms of (2.21) are less than or equal to zero. Therefore, if  $R_0 \leq 1$ , then  $dW_1/dt \leq 0$  for all  $x_1, x_2, v > 0$ . By Theorem 5.3.1 in [32], the solutions of system (2.1)–(2.5) limit to  $M$ , the largest invariant subset of  $\{dW_1/dt = 0\}$ . Clearly, it follows from (2.21) that  $dW_1/dt = 0$  if and only if  $x_1 = x_1^0, x_2 = x_2^0, v = 0$ . Noting that  $M$  is invariant, for each element of  $M$  we have  $v = 0, \dot{v} = 0$ . From (2.5) we drive that

$$0 = \dot{v} = e^{-n_1 \omega_1} p_1 y_1(t - \omega_1) + e^{-n_2 \omega_2} p_2 y_2(t - \omega_2). \tag{2.22}$$

Since  $y_1(t - \theta) \geq 0$  and  $y_2(t - \theta) \geq 0$  for all  $\theta \in [0, \max\{\tau_1, \tau_2, \omega_1, \omega_2\}]$ , then  $e^{-n_1 \omega_1} p_1 y_1(t - \omega_1) + e^{-n_2 \omega_2} p_2 y_2(t - \omega_2) = 0$  if and only if  $y_1(t - \omega_1) = y_2(t - \omega_2) = 0$ . Hence,  $dW_1/dt = 0$  if and only if  $x_1 = x_1^0, x_2 = x_2^0, y_1 = y_2 = v = 0$ . From LaSalle's invariance principle,  $E_0$  is GAS for any  $\tau_1, \tau_2, \omega_1, \omega_2 \geq 0$ .

(ii) Define a Lyapunov functional as

$$\begin{aligned}
W_2 = & e^{-m_1\tau_1} x_1^* H\left(\frac{x_1}{x_1^*}\right) + y_1^* H\left(\frac{y_1}{y_1^*}\right) + \gamma \left[ e^{-m_2\tau_2} x_2^* H\left(\frac{x_2}{x_2^*}\right) + y_2^* H\left(\frac{y_2}{y_2^*}\right) \right] \\
& + \frac{a_1}{p_1} e^{n_1 \omega_1} v^* H\left(\frac{v}{v^*}\right) + e^{-m_1\tau_1} \beta_1 x_1^* v^* \int_0^{\tau_1} H\left(\frac{x_1(t - \theta)v(t - \theta)}{x_1^* v^*}\right) d\theta \\
& + e^{-m_2\tau_2} \gamma \beta_2 x_2^* v^* \int_0^{\tau_2} H\left(\frac{x_2(t - \theta)v(t - \theta)}{x_2^* v^*}\right) d\theta + a_1 y_1^* \int_0^{\omega_1} H\left(\frac{y_1(t - \theta)}{y_1^*}\right) d\theta \\
& + \gamma a_2 y_2^* \int_0^{\omega_2} H\left(\frac{y_2(t - \theta)}{y_2^*}\right) d\theta.
\end{aligned} \tag{2.23}$$

Differentiating with respect to time yields

$$\frac{dW_2}{dt} = e^{-m_1\tau_1} \left( 1 - \frac{x_1^*}{x_1} \right) (\lambda_1 - d_1 x_1 - \beta_1 x_1 v) + \left( 1 - \frac{y_1^*}{y_1} \right) (e^{-m_1\tau_1} \beta_1 x_1(t - \tau_1)v(t - \tau_1) - a_1 y_1)$$

$$\begin{aligned}
& + \gamma \left[ e^{-m_2 \tau_2} \left( 1 - \frac{x_2^*}{x_2} \right) (\lambda_2 - d_2 x_2 - \beta_2 x_2 v) \right. \\
& \quad \left. + \left( 1 - \frac{y_2^*}{y_2} \right) (e^{-m_2 \tau_2} \beta_2 x_2 (t - \tau_2) v (t - \tau_2) - a_2 y_2) \right] \\
& + \frac{a_1}{p_1} e^{n_1 \omega_1} \left( 1 - \frac{v^*}{v} \right) (e^{-n_1 \omega_1} p_1 y_1 (t - \omega_1) + e^{-n_2 \omega_2} p_2 y_2 (t - \omega_2) - cv) \\
& + e^{-m_1 \tau_1} \left[ \beta_1 x_1 v - \beta_1 x_1 (t - \tau_1) v (t - \tau_1) + \beta_1 x_1^* v^* \ln \left( \frac{x_1 (t - \tau_1) v (t - \tau_1)}{x_1 v} \right) \right] \\
& + \gamma e^{-m_2 \tau_2} \left[ \beta_2 x_2 v - \beta_2 x_2 (t - \tau_2) v (t - \tau_2) + \beta_2 x_2^* v^* \ln \left( \frac{x_2 (t - \tau_2) v (t - \tau_2)}{x_2 v} \right) \right] \\
& + a_1 \left[ y_1 - y_1 (t - \omega_1) + y_1^* \ln \left( \frac{y_1 (t - \omega_1)}{y_1} \right) \right] \\
& + a_2 \gamma \left[ y_2 - y_2 (t - \omega_2) + y_2^* \ln \left( \frac{y_2 (t - \omega_2)}{y_2} \right) \right] \\
& = e^{-m_1 \tau_1} \left( 1 - \frac{x_1^*}{x_1} \right) (\lambda_1 - d_1 x_1) + e^{-m_1 \tau_1} \beta_1 x_1^* v - e^{-m_1 \tau_1} \frac{y_1^* \beta_1 x_1 (t - \tau_1) v (t - \tau_1)}{y_1} + a_1 y_1^* \\
& + \gamma \left[ e^{-m_2 \tau_2} \left( 1 - \frac{x_2^*}{x_2} \right) (\lambda_2 - d_2 x_2) + e^{-m_2 \tau_2} \beta_2 x_2^* v - e^{-m_2 \tau_2} \frac{y_2^* \beta_2 x_2 (t - \tau_2) v (t - \tau_2)}{y_2} \right. \\
& \quad \left. + a_2 y_2^* \right] - a_1 \frac{v^* y_1 (t - \omega_1)}{v} - \gamma a_2 \frac{v^* y_2 (t - \omega_2)}{v} - \frac{a_1 c}{p_1} e^{n_1 \omega_1} v + \frac{a_1 c}{p_1} e^{n_1 \omega_1} v^* \\
& + e^{-m_1 \tau_1} \beta_1 x_1^* v^* \ln \left( \frac{x_1 (t - \tau_1) v (t - \tau_1)}{x_1 v} \right) + \gamma e^{-m_2 \tau_2} \beta_2 x_2^* v^* \ln \left( \frac{x_2 (t - \tau_2) v (t - \tau_2)}{x_2 v} \right) \\
& + a_1 y_1^* \ln \left( \frac{y_1 (t - \omega_1)}{y_1} \right) + \gamma a_2 y_2^* \ln \left( \frac{y_2 (t - \omega_2)}{y_2} \right).
\end{aligned} \tag{2.24}$$

Using the infected steady state  $E_1$  conditions

$$\begin{aligned}
\lambda_1 & = d_1 x_1^* + \beta_1 x_1^* v^*, & \lambda_2 & = d_2 x_2^* + \beta_2 x_2^* v^*, & a_1 y_1^* e^{m_1 \tau_1} & = \beta_1 x_1^* v^*, \\
a_2 y_2^* e^{m_2 \tau_2} & = \beta_2 x_2^* v^*, & cv^* & = p_1 e^{-n_1 \omega_1} y_1^* + p_2 e^{-n_2 \omega_2} y_2^*,
\end{aligned} \tag{2.25}$$

we obtain

$$\begin{aligned}
\frac{dW_2}{dt} & = e^{-m_1 \tau_1} \left[ d_1 x_1^* + a_1 y_1^* e^{m_1 \tau_1} - d_1 x_1 - \frac{x_1^*}{x_1} (d_1 x_1^* + a_1 y_1^* e^{m_1 \tau_1} - d_1 x_1) \right] \\
& + e^{-m_1 \tau_1} \beta_1 x_1^* v^* \left( \frac{v}{v^*} \right) - a_1 y_1^* \frac{y_1^* x_1 (t - \tau_1) v (t - \tau_1)}{y_1 x_1^* v^*} + 2a_1 y_1^* \\
& + \gamma \left[ e^{-m_2 \tau_2} (d_2 x_2^* + a_2 y_2^* e^{m_2 \tau_2} - d_2 x_2) - e^{-m_2 \tau_2} \frac{x_2^*}{x_2} (d_2 x_2^* + a_2 y_2^* e^{m_2 \tau_2} - d_2 x_2) \right]
\end{aligned}$$



$$\begin{aligned}
& + e^{-m_2\tau_2} \beta_2 x_2^* v^* \left( \frac{v}{v^*} \right) - a_2 y_2^* \frac{y_2^* x_2(t-\tau_2)v(t-\tau_2)}{y_2 x_2^* v^*} + 2a_2 y_2^* \Big] \\
& - a_1 y_1^* \frac{v^* y_1(t-\omega_1)}{v y_1^*} - \gamma a_2 y_2^* \frac{v^* y_2(t-\omega_2)}{v y_2^*} - \frac{a_1 c}{p_1} e^{n_1 \omega_1} v^* \left( \frac{v}{v^*} \right) \\
& + a_1 y_1^* \ln \left( \frac{x_1(t-\tau_1)v(t-\tau_1)}{x_1 v} \right) + \gamma a_2 y_2^* \ln \left( \frac{x_2(t-\tau_2)v(t-\tau_2)}{x_2 v} \right) \\
& + a_1 y_1^* \ln \left( \frac{y_1(t-\omega_1)}{y_1} \right) + \gamma a_2 y_2^* \ln \left( \frac{y_2(t-\omega_2)}{y_2} \right) \\
= & e^{-m_1\tau_1} d_1 x_1^* \left( 2 - \frac{x_1}{x_1^*} - \frac{x_1^*}{x_1} \right) - a_1 y_1^* \frac{x_1^*}{x_1} - a_1 y_1^* \frac{y_1^* x_1(t-\tau_1)v(t-\tau_1)}{y_1 x_1^* v^*} \\
& - a_1 y_1^* \frac{v^* y_1(t-\omega_1)}{v y_1^*} + 3a_1 y_1^* + a_1 y_1^* \ln \left( \frac{x_1(t-\tau_1)v(t-\tau_1)y_1(t-\omega_1)}{x_1 v y_1} \right) \\
& + \gamma \left[ e^{-m_2\tau_2} d_2 x_2^* \left( 2 - \frac{x_2}{x_2^*} - \frac{x_2^*}{x_2} \right) - a_2 y_2^* \frac{x_2^*}{x_2} - a_2 y_2^* \frac{y_2^* x_2(t-\tau_2)v(t-\tau_2)}{y_2 x_2^* v^*} \right. \\
& \quad \left. - a_2 y_2^* \frac{v^* y_2(t-\omega_2)}{v y_2^*} + 3a_2 y_2^* + a_2 y_2^* \ln \left( \frac{x_2(t-\tau_2)v(t-\tau_2)y_2(t-\omega_2)}{x_2 v y_2} \right) \right] \\
& + \frac{a_1}{p_1} e^{n_1 \omega_1} (e^{-n_1 \omega_1} p_1 y_1^* + e^{-n_2 \omega_2} p_2 y_2^* - c v^*) \frac{v}{v^*}.
\end{aligned} \tag{2.26}$$

From (2.25), we see that the last term in (2.26) vanishes. Then, using the following equalities:

$$\begin{aligned}
\ln \left( \frac{x_1(t-\tau_1)v(t-\tau_1)y_1(t-\omega_1)}{x_1 v y_1} \right) &= \ln \left( \frac{x_1^*}{x_1} \right) + \ln \left( \frac{y_1(t-\omega_1)v^*}{y_1^* v} \right) \\
& \quad + \ln \left( \frac{y_1^* x_1(t-\tau_1)v(t-\tau_1)}{y_1 x_1^* v^*} \right), \\
\ln \left( \frac{x_2(t-\tau_2)v(t-\tau_2)y_2(t-\omega_2)}{x_2 v y_2} \right) &= \ln \left( \frac{x_2^*}{x_2} \right) + \ln \left( \frac{y_2(t-\omega_2)v^*}{y_2^* v} \right) \\
& \quad + \ln \left( \frac{y_2^* x_2(t-\tau_2)v(t-\tau_2)}{y_2 x_2^* v^*} \right),
\end{aligned} \tag{2.27}$$

we can rewrite (2.26) as

$$\begin{aligned}
\frac{dW_2}{dt} &= e^{-m_1\tau_1} d_1 x_1^* \left( 2 - \frac{x_1}{x_1^*} - \frac{x_1^*}{x_1} \right) + e^{-m_2\tau_2} \gamma d_2 x_2^* \left( 2 - \frac{x_2}{x_2^*} - \frac{x_2^*}{x_2} \right) \\
& - a_1 y_1^* \left[ H \left( \frac{x_1^*}{x_1} \right) + H \left( \frac{y_1(t-\omega_1)v^*}{y_1^* v} \right) + H \left( \frac{y_1^* x_1(t-\tau_1)v(t-\tau_1)}{y_1 x_1^* v^*} \right) \right] \\
& - \gamma a_2 y_2^* \left[ H \left( \frac{x_2^*}{x_2} \right) + H \left( \frac{y_2(t-\omega_2)v^*}{y_2^* v} \right) + H \left( \frac{y_2^* x_2(t-\tau_2)v(t-\tau_2)}{y_2 x_2^* v^*} \right) \right].
\end{aligned} \tag{2.28}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then the first two terms of (2.28) are less than or equal to zero. It is easy to see that if  $x_1^*, y_1^*, x_2^*, y_2^*, v^* > 0$ , then  $dW_2/dt \leq 0$ . By [32, Theorem 5.3.1], the solutions of system (2.1)–(2.5) limit to  $M$ , the largest invariant subset of  $\{dW_2/dt = 0\}$ . It can be seen that  $dW_2/dt = 0$  if and only if  $x_1 = x_1^*$ ,  $x_2 = x_2^*$ ,  $v = v^*$ , and  $H = 0$ , that is,

$$\frac{y_1(t - \omega_1)v^*}{y_1^*v} = \frac{y_2(t - \omega_2)v^*}{y_2^*v} = \frac{y_1^*x_1(t - \tau_1)v(t - \tau_1)}{y_1x_1^*v^*} = \frac{y_2^*x_2(t - \tau_2)v(t - \tau_2)}{y_2x_2^*v^*} = 1. \quad (2.29)$$

If  $v = v^*$ , then from (2.29), we have  $y_1 = y_1^*$  and  $y_2 = y_2^*$ , and hence  $dW_2/dt$  equal to zero at  $E_1$ . LaSalle's invariance principle implies global stability of  $E_1$ .  $\square$

### 3. Basic Virus Dynamics Model with Multitarget Cells and Delays

In this section, we propose a virus dynamics model which describes the interaction of the virus with  $n$  classes of target cells. Two types of discrete-time delays ( $\tau_i$ ,  $\omega_i$ ,  $i = 1, \dots, n$ ) are incorporated into the model. The model is a generalization of those of one class of target cells and two classes of target cells models presented, respectively, in [26, 33]. Moreover, it can be seen that when  $n = 1$  and  $\omega_1 = 0$ , then the following model leads to the model presented in [11].

$$\begin{aligned} \dot{x}_i &= \lambda_i - d_i x_i - \beta_i x_i v, \quad i = 1, \dots, n, \\ \dot{y}_i &= e^{-m_i \tau_i} \beta_i x_i(t - \tau_i) v(t - \tau_i) - a_i y_i, \quad i = 1, \dots, n, \\ \dot{v} &= \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i(t - \omega_i) - cv, \end{aligned} \quad (3.1)$$

where  $x_i$  and  $y_i$  represent the populations of the uninfected target cells and infected cells of class  $i$ , respectively,  $v$  is the population of the virus particles. All the parameters of the model have the same biological meaning as given in the previous section.

The initial conditions for system (3.1) take the form

$$\begin{aligned} x_j(\theta) &= \varphi_j(\theta), \quad j = 1, \dots, n, \\ y_j(\theta) &= \phi_{j+n}(\theta), \quad j = 1, \dots, n, \\ v(\theta) &= \varphi_{2n+1}(\theta), \\ \varphi_j(\theta) &\geq 0, \quad j = 1, \dots, 2n + 1, \quad \theta \in [-\max\{\tau_1, \dots, \tau_n, \omega_1, \dots, \omega_n\}, 0], \end{aligned} \quad (3.2)$$

where  $(\varphi_1(\theta), \varphi_2(\theta), \dots, \varphi_{2n+1}(\theta)) \in C$  and  $C = C([-\max\{\tau_1, \dots, \tau_n, \omega_1, \dots, \omega_n\}, 0], \mathbb{R}_+^{2n+1})$  is the Banach space of continuous functions mapping the interval  $[-\max\{\tau_1, \dots, \tau_n, \omega_1, \dots, \omega_n\}, 0]$  into  $\mathbb{R}_+^{2n+1}$ .

Similar to the previous section, the nonnegativity and the boundedness of the solutions of system (3.1) can be shown.

### 3.1. Steady States

It is clear that system (3.1) has an uninfected steady state  $E_0 = (x_1^0, \dots, x_n^0, y_1^0, \dots, y_n^0, v^0)$ , where  $x_i^0 = \lambda_i/d_i$ ,  $y_i^0 = 0$ ,  $i = 1, \dots, n$ , and  $v^0 = 0$ . The system can also have a positive infected steady state  $E_1(x_1^*, \dots, x_n^*, y_1^*, \dots, y_n^*, v^*)$ . The coordinates of the infected steady state, if they exist, satisfy the equalities:

$$\lambda_i = d_i x_i^* + \beta_i x_i^* v^*, \quad i = 1, \dots, n, \quad (3.3)$$

$$a_i y_i^* = e^{-m_i \tau_i} \beta_i x_i^* v^*, \quad i = 1, \dots, n, \quad (3.4)$$

$$c v^* = \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i^*. \quad (3.5)$$

The basic reproduction number of system (3.1) is given by

$$R_0 = \sum_{i=1}^n R_i = \sum_{i=1}^n \frac{e^{-(m_i \tau_i + n_i \omega_i)} \beta_i p_i \lambda_i}{a_i d_i c}, \quad (3.6)$$

where  $R_i$  is the basic reproduction number for the dynamics of the interaction of the virus only with the target cells of class  $i$ .

### 3.2. Global Stability

In the following theorem, the global stability of the uninfected and infected steady states of system (3.1) will be established.

**Theorem 3.1.** (i) If  $R_0 \leq 1$ , then  $E_0$  is GAS for any  $\tau_i, \omega_i \geq 0$ ,  $i = 1, \dots, n$ .

(ii) If  $E_1$  exists, then it is GAS for any  $\tau_i, \omega_i \geq 0$ ,  $i = 1, \dots, n$ .

*Proof.* (i) Define a Lyapunov functional  $W_1$  as follows:

$$W_1 = \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} x_i^0 H \left( \frac{x_i}{x_i^0} \right) + y_i + e^{-m_i \tau_i} \beta_i \int_0^{\tau_i} x_i(t-\theta) v(t-\theta) d\theta + a_i \int_0^{\omega_i} y_i(t-\theta) d\theta \right] + \frac{a_1}{p_1} e^{n_1 \omega_1} v, \quad (3.7)$$

where  $\gamma_i = (a_1 p_i / a_i p_1) e^{n_1 \omega_1 - n_i \omega_i}$ . The time derivative of  $W_1$  along the solution of system (3.1) satisfies

$$\begin{aligned} \frac{dW_1}{dt} = \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( 1 - \frac{x_i^0}{x_i} \right) (\lambda_i - d_i x_i - \beta_i x_i v) + e^{-m_i \tau_i} \beta_i x_i (t - \tau_i) v(t - \tau_i) - a_i y_i \right. \\ \left. + e^{-m_i \tau_i} (\beta_i x_i v - \beta_i x_i (t - \tau_i) v(t - \tau_i)) + a_i (y_i - y_i(t - \omega_i)) \right] \end{aligned}$$

$$\begin{aligned}
& + \frac{a_1}{p_1} e^{n_1 \omega_1} \left( \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i(t - \omega_i) - c v \right) \\
& = \sum_{i=1}^n e^{-m_i \tau_i} \gamma_i \lambda_i \left[ 2 - \frac{x_i}{x_i^0} - \frac{x_i^0}{x_i} \right] + \frac{a_1 c}{p_1} e^{n_1 \omega_1} \left( \sum_{i=1}^n \frac{e^{-(m_i \tau_i + n_i \omega_i)} p_i \beta_i x_i^0}{a_i c} - 1 \right) v \\
& = \sum_{i=1}^n e^{-m_i \tau_i} \gamma_i \lambda_i \left[ 2 - \frac{x_i}{x_i^0} - \frac{x_i^0}{x_i} \right] + \frac{a_1 c}{p_1} e^{n_1 \omega_1} (R_0 - 1) v.
\end{aligned} \tag{3.8}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then the first term of (3.8) is less than or equal to zero. Therefore, if  $R_0 \leq 1$ , then  $dW_1/dt \leq 0$  for all  $x_i, y_i, v > 0$ . Similar to the previous section, one can show that the maximal compact invariant set in  $\{dW_1/dt = 0\}$  is the singleton  $\{E_0\}$  when  $R_0 \leq 1$ . The global stability of  $E_0$  follows from LaSalle's invariance principle.

To prove (ii), we consider the Lyapunov functional

$$\begin{aligned}
W_2 = & \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} x_i^* H\left(\frac{x_i}{x_i^*}\right) + y_i^* H\left(\frac{y_i}{y_i^*}\right) + e^{-m_i \tau_i} \beta_i x_i^* v^* \int_0^{\tau_i} H\left(\frac{x_i(t - \theta)v(t - \theta)}{x_i^* v^*}\right) d\theta \right. \\
& \left. + a_i y_i^* \int_0^{\omega_i} H\left(\frac{y_i(t - \theta)}{y_i^*}\right) d\theta \right] + \frac{a_1}{p_1} e^{n_1 \omega_1} v^* H\left(\frac{v}{v^*}\right).
\end{aligned} \tag{3.9}$$

Differentiating with respect to time yields

$$\begin{aligned}
\frac{dW_2}{dt} = & \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( 1 - \frac{x_i^*}{x_i} \right) (\lambda_i - d_i x_i - \beta_i x_i v) + \left( 1 - \frac{y_i^*}{y_i} \right) (e^{-m_i \tau_i} \beta_i x_i(t - \tau_i) v(t - \tau_i) - a_i y_i) \right. \\
& + e^{-m_i \tau_i} (\beta_i x_i v - \beta_i x_i(t - \tau_i) v(t - \tau_i)) + e^{-m_i \tau_i} \beta_i x_i^* v^* \ln\left(\frac{x_i(t - \tau_i) v(t - \tau_i)}{x_i v}\right) \\
& \left. + a_i (y_i - y_i(t - \omega_i)) + a_i y_i^* \ln\left(\frac{y_i(t - \omega_i)}{y_i}\right) \right] \\
& + \frac{a_1 e^{n_1 \omega_1}}{p_1} \left( 1 - \frac{v^*}{v} \right) \left( \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i(t - \omega_i) - c v \right) \\
= & \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( \lambda_i - d_i x_i - \frac{\lambda_i x_i^*}{x_i} + d_i x_i^* + \beta_i x_i^* v \right) - e^{-m_i \tau_i} \beta_i x_i(t - \tau_i) v(t - \tau_i) \frac{y_i^*}{y_i} + a_i y_i^* \right. \\
& \left. + e^{-m_i \tau_i} \beta_i x_i^* v^* \ln\left(\frac{x_i(t - \tau_i) v(t - \tau_i)}{x_i v}\right) + a_i y_i^* \ln\left(\frac{y_i(t - \omega_i)}{y_i}\right) \right] \\
& - \frac{a_1 c e^{n_1 \omega_1}}{p_1} v - \frac{v^*}{v} \sum_{i=1}^n \gamma_i a_i y_i(t - \omega_i) + \frac{a_1 c e^{n_1 \omega_1}}{p_1} v^*.
\end{aligned} \tag{3.10}$$

Using the infected steady state conditions (3.3)–(3.5), and the following equality:

$$\frac{a_1 c e^{n_1 \omega_1}}{p_1} v^* = \frac{a_1 e^{n_1 \omega_1}}{p_1} \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i^* = \sum_{i=1}^n \gamma_i a_i y_i^*, \quad (3.11)$$

we obtain

$$\begin{aligned} \frac{dW_2}{dt} &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( d_i x_i^* + e^{m_i \tau_i} a_i y_i^* - d_i x_i - \frac{x_i^*}{x_i} (d_i x_i^* + e^{m_i \tau_i} a_i y_i^*) + d_i x_i^* \right) \right. \\ &\quad \left. - a_i y_i^* \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i)}{y_i x_i^* v^*} + 2a_i y_i^* - a_i y_i^* \frac{v^* y_i(t - \omega_i)}{v y_i^*} \right. \\ &\quad \left. + a_i y_i^* \ln \left( \frac{x_i(t - \tau_i) v(t - \tau_i)}{x_i v} \right) + a_i y_i^* \ln \left( \frac{y_i(t - \omega_i)}{y_i} \right) \right] \\ &\quad + \left( \sum_{i=1}^n e^{-m_i \tau_i} \gamma_i \beta_i x_i^* - \frac{a_1 c e^{n_1 \omega_1}}{p_1} \right) v \\ &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} d_i x_i^* \left( 2 - \frac{x_i^*}{x_i} - \frac{x_i}{x_i^*} \right) - a_i y_i^* \frac{x_i^*}{x_i} - a_i y_i^* \frac{v^* y_i(t - \omega_i)}{v y_i^*} \right. \\ &\quad \left. - a_i y_i^* \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i)}{y_i x_i^* v^*} + 3a_i y_i^* + a_i y_i^* \ln \left( \frac{x_i(t - \tau_i) v(t - \tau_i) y_i(t - \omega_i)}{x_i v y_i} \right) \right] \\ &\quad + \frac{a_1 e^{n_1 \omega_1}}{p_1} \left( \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i^* - c v^* \right) \frac{v}{v^*}. \end{aligned} \quad (3.12)$$

From (3.5), we can see that the last term in (3.12) vanishes. Then, by using the following equality:

$$\ln \left( \frac{x_i(t - \tau_i) v(t - \tau_i) y_i(t - \omega_i)}{x_i v y_i} \right) = \ln \left( \frac{x_i^*}{x_i} \right) + \ln \left( \frac{v^* y_i(t - \omega_i)}{v y_i^*} \right) + \ln \left( \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i)}{y_i x_i^* v^*} \right), \quad (3.13)$$

we can rewrite (3.12) as

$$\begin{aligned} \frac{dW_2}{dt} &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} d_i x_i^* \left( 2 - \frac{x_i^*}{x_i} - \frac{x_i}{x_i^*} \right) - a_i y_i^* \left( H \left( \frac{x_i^*}{x_i} \right) + H \left( \frac{v^* y_i(t - \omega_i)}{v y_i^*} \right) \right. \right. \\ &\quad \left. \left. + H \left( \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i)}{y_i x_i^* v^*} \right) \right) \right]. \end{aligned} \quad (3.14)$$

It is easy to see that if  $x_i^*, y_i^*, v^* > 0$ ,  $i = 1, \dots, n$ , then  $dW_2/dt \leq 0$  for all  $(x_i, y_i, v) > 0$  (the arithmetical mean is greater than or equal to the geometrical mean and  $H \geq 0$ ). Clearly,

the singleton  $\{E_1\}$  is the only invariant set in  $\{dW_2/dt = 0\}$ . LaSalle's invariance principle implies global stability of  $E_1$ .  $\square$

#### 4. Virus Dynamics Model with Saturation Infection Rate

In this section, we proposed a virus dynamics model which describes the interaction of the virus with  $n$  classes of target cells taking into account the saturation infection rate and multiple intracellular delays:

$$\begin{aligned} \dot{x}_i(t) &= \lambda_i - d_i x_i(t) - \frac{\beta_i x_i(t)v(t)}{1 + \alpha_i v(t)}, \quad i = 1, \dots, n, \\ \dot{y}_i(t) &= \frac{e^{-m_i \tau_i} \beta_i x_i(t - \tau_i)v(t - \tau_i)}{1 + \alpha_i v(t)} - a_i y_i(t), \quad i = 1, \dots, n, \\ \dot{v}(t) &= \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i(t - \omega_i) - cv(t), \end{aligned} \quad (4.1)$$

where  $\alpha_i$ ,  $i = 1, \dots, n$  are positive constants. The variables and parameters of the model have the same definitions as given in Section 2. We mention that if  $n = 1$  and  $\omega_1 = 0$ , then model (4.1) leads to the model presented in [9], and if  $n = 2$  and  $\omega_1 = \omega_2 = 0$ ,  $\alpha_1 = \alpha_2 = 1$ , then model (4.1) leads to the model presented in [34].

##### 4.1. Steady States

It is clear that system (4.1) has an uninfected steady state  $E_0 = (x_1^0, \dots, x_n^0, y_1^0, \dots, y_n^0, v^0)$ , where  $x_i^0 = \lambda_i/d_i$ ,  $y_i^0 = 0$ , and  $v^0 = 0$ . The system can also have a positive infected steady state  $E_1(x_1^*, \dots, x_n^*, y_1^*, \dots, y_n^*, v^*)$ . The coordinates of the infected steady state, if they exist, satisfy the equalities:

$$\begin{aligned} \lambda_i &= d_i x_i^* + \frac{\beta_i x_i^* v^*}{1 + \alpha_i v^*}, \quad i = 1, \dots, n, \\ a_i y_i^* &= e^{-m_i \tau_i} \frac{\beta_i x_i^* v^*}{1 + \alpha_i v^*}, \quad i = 1, \dots, n, \\ cv^* &= \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i^*. \end{aligned} \quad (4.2)$$

The basic reproduction number  $R_0$  for system (4.1) is the same as given by (3.6).

##### 4.2. Global Stability

In this section, we study the global stability of the uninfected and infected steady states of system (4.1).

**Theorem 4.1.** (i) If  $R_0 \leq 1$ , then  $E_0$  is GAS for any  $\tau_i, \omega_i \geq 0$ ,  $i = 1, \dots, n$ .  
(ii) If  $E_1$  exists, then it is GAS for any  $\tau_i, \omega_i \geq 0$ ,  $i = 1, \dots, n$ .

*Proof.* (i) Define a Lyapunov functional  $W_1$  as follows:

$$W_1 = \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} x_i^0 H \left( \frac{x_i}{x_i^0} \right) + y_i + e^{-m_i \tau_i} \beta_i \int_0^{\tau_i} \frac{x_i(t-\theta)v(t-\theta)}{1 + \alpha_i v(t-\theta)} d\theta + a_i \int_0^{\omega_i} y_i(t-\theta) d\theta \right] + \frac{a_1 e^{n_1 \omega_1}}{p_1} v, \quad (4.3)$$

The time derivative of  $W_1$  along the trajectories of (4.1) satisfies

$$\begin{aligned} \frac{dW_1}{dt} &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( 1 - \frac{x_i^0}{x_i} \right) \left( \lambda_i - d_i x_i - \frac{\beta_i x_i v}{1 + \alpha_i v} \right) + e^{-m_i \tau_i} \frac{\beta_i x_i (t - \tau_i) v (t - \tau_i)}{1 + \alpha_i v (t - \tau_i)} - a_i y_i \right. \\ &\quad \left. + e^{-m_i \tau_i} \left( \frac{\beta_i x_i v}{1 + \alpha_i v} - \frac{\beta_i x_i (t - \tau_i) v (t - \tau_i)}{1 + \alpha_i v (t - \tau_i)} \right) + a_i (y_i - y_i (t - \omega_i)) \right] \\ &\quad + \frac{a_1 e^{n_1 \omega_1}}{p_1} \left( \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i (t - \omega_i) - c v \right) \\ &= \sum_{i=1}^n \gamma_i e^{-m_i \tau_i} \left[ \lambda_i - d_i x_i - \lambda_i \frac{x_i^0}{x_i} + d_i x_i^0 + \frac{\beta_i x_i^0 v}{1 + \alpha_i v} \right] - \frac{a_1 c e^{n_1 \omega_1}}{p_1} v \\ &= \sum_{i=1}^n \gamma_i e^{-m_i \tau_i} \lambda_i \left[ 2 - \frac{x_i}{x_i^0} - \frac{x_i^0}{x_i} \right] - \frac{a_1 c e^{n_1 \omega_1}}{p_1} v + \frac{a_1 c e^{n_1 \omega_1}}{p_1} \sum_{i=1}^n \frac{e^{-(m_i \tau_i + n_i \omega_i)} p_i \beta_i x_i^0 v}{a_i c (1 + \alpha_i v)} \\ &= \sum_{i=1}^n \gamma_i e^{-m_i \tau_i} \lambda_i \left[ 2 - \frac{x_i}{x_i^0} - \frac{x_i^0}{x_i} \right] - \frac{a_1 c e^{n_1 \omega_1}}{p_1} v + \frac{a_1 c e^{n_1 \omega_1}}{p_1} \sum_{i=1}^n \frac{R_i v}{1 + \alpha_i v} \\ &= \sum_{i=1}^n \gamma_i e^{-m_i \tau_i} \lambda_i \left[ 2 - \frac{x_i}{x_i^0} - \frac{x_i^0}{x_i} \right] + \frac{a_1 c e^{n_1 \omega_1}}{p_1} (R_0 - 1) v - \frac{a_1 c e^{n_1 \omega_1}}{p_1} \sum_{i=1}^n \frac{R_i \alpha_i v^2}{1 + \alpha_i v}. \end{aligned} \quad (4.4)$$

It is clear that if  $R_0 \leq 1$ , then  $dW_1/dt \leq 0$  for all  $x_i, y_i, v > 0$ , where equality occurs at  $E_0$ . The global stability of  $E_0$  follows from LaSalle's invariance principle.

To prove (ii), we consider the Lyapunov functional:

$$\begin{aligned} W_2 &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} x_i^* H \left( \frac{x_i}{x_i^*} \right) + y_i^* H \left( \frac{y_i}{y_i^*} \right) \right. \\ &\quad \left. + e^{-m_i \tau_i} \frac{\beta_i x_i^* v^*}{1 + \alpha_i v^*} \int_0^{\tau_i} H \left( \frac{x_i(t-\theta)v(t-\theta)(1 + \alpha_i v^*)}{x_i^* v^* (1 + \alpha_i v(t-\theta))} \right) d\theta \right. \\ &\quad \left. + a_i y_i^* \int_0^{\omega_i} H \left( \frac{y_i(t-\theta)}{y_i^*} \right) d\theta \right] + \frac{a_1 e^{n_1 \omega_1}}{p_1} v^* H \left( \frac{v}{v^*} \right). \end{aligned} \quad (4.5)$$

Differentiating with respect to time yields

$$\begin{aligned}
\frac{dW_2}{dt} &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( 1 - \frac{x_i^*}{x_i} \right) \left( \lambda_i - d_i x_i - \frac{\beta_i x_i v}{1 + \alpha_i v} \right) \right. \\
&\quad + \left( 1 - \frac{y_i^*}{y_i} \right) \left( \frac{e^{-m_i \tau_i} \beta_i x_i (t - \tau_i) v (t - \tau_i)}{1 + \alpha_i v (t - \tau_i)} - a_i y_i \right) \\
&\quad + e^{-m_i \tau_i} \left( \frac{\beta_i x_i v}{1 + \alpha_i v} - \frac{\beta_i x_i (t - \tau_i) v (t - \tau_i)}{1 + \alpha_i v (t - \tau_i)} \right) \\
&\quad \quad \left. + \frac{\beta_i x_i^* v^*}{1 + \alpha_i v^*} \ln \left( \frac{x_i (t - \tau_i) v (t - \tau_i) (1 + \alpha_i v)}{x_i v (1 + \alpha_i v (t - \tau_i))} \right) \right) \\
&\quad + a_i (y_i - y_i (t - \omega_i)) + a_i y_i^* \ln \left( \frac{y_i (t - \omega_i)}{y_i} \right) \Big] \\
&\quad + \frac{a_1 e^{n_1 \omega_1}}{p_1} \left( 1 - \frac{v^*}{v} \right) \left( \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i (t - \omega_i) - c v \right) \\
&= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( \lambda_i - d_i x_i - \frac{\lambda_i x_i^*}{x_i} + d_i x_i^* + \frac{\beta_i x_i^* v}{1 + \alpha_i v} \right) - \frac{e^{-m_i \tau_i} \beta_i x_i (t - \tau_i) v (t - \tau_i)}{1 + \alpha_i v (t - \tau_i)} \frac{y_i^*}{y_i} + a_i y_i^* \right. \\
&\quad \left. + e^{-m_i \tau_i} \frac{\beta_i x_i^* v^*}{1 + \alpha_i v^*} \ln \left( \frac{x_i (t - \tau_i) v (t - \tau_i) (1 + \alpha_i v)}{x_i v (1 + \alpha_i v (t - \tau_i))} \right) + a_i y_i^* \ln \left( \frac{y_i (t - \omega_i)}{y_i} \right) \right] \\
&\quad - \frac{a_1 c e^{n_1 \omega_1}}{p_1} v - \frac{a_1 e^{n_1 \omega_1}}{p_1} \frac{v^*}{v} \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i (t - \omega_i) + \frac{a_1 c e^{n_1 \omega_1}}{p_1} v^*.
\end{aligned} \tag{4.6}$$

Using the infected steady state conditions (4.2), and the following equality:

$$\frac{a_1 c e^{n_1 \omega_1}}{p_1} v = \frac{a_1 c e^{n_1 \omega_1}}{p_1} v^* \frac{v}{v^*} = \frac{a_1 e^{n_1 \omega_1}}{p_1} \frac{v}{v^*} \sum_{i=1}^n e^{-n_i \omega_i} p_i y_i^* = \frac{v}{v^*} \sum_{i=1}^n \gamma_i a_i y_i^*, \tag{4.7}$$

we obtain

$$\begin{aligned}
\frac{dW_2}{dt} &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} \left( d_i x_i^* + e^{m_i \tau_i} a_i y_i^* - d_i x_i - \frac{x_i^*}{x_i} (d_i x_i^* + e^{m_i \tau_i} a_i y_i^*) + d_i x_i^* \right) + a_i y_i^* \frac{v (1 + \alpha_i v^*)}{v^* (1 + \alpha_i v)} \right. \\
&\quad - a_i y_i^* \frac{y_i^* x_i (t - \tau_i) v (t - \tau_i) (1 + \alpha_i v^*)}{y_i x_i^* v^* (1 + \alpha_i v (t - \tau_i))} + 2 a_i y_i^* - a_i y_i^* \frac{v^* y_i (t - \omega_i)}{v y_i^*} \\
&\quad \left. + a_i y_i^* \ln \left( \frac{x_i (t - \tau_i) v (t - \tau_i) y_i (t - \omega_i) (1 + \alpha_i v)}{x_i v y_i (1 + \alpha_i v (t - \tau_i))} \right) - a_i y_i^* \frac{v}{v^*} \right]
\end{aligned}$$



$$\begin{aligned}
&= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} d_i x_i^* \left( 2 - \frac{x_i^*}{x_i} - \frac{x_i}{x_i^*} \right) - a_i y_i^* \frac{x_i^*}{x_i} + 3a_i y_i^* + a_i y_i^* \left( \frac{v(1 + \alpha_i v^*)}{v^*(1 + \alpha_i v)} - \frac{v}{v^*} \right) \right. \\
&\quad - a_i y_i^* \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i) (1 + \alpha_i v^*)}{y_i x_i^* v^* (1 + \alpha_i v(t - \tau_i))} - a_i y_i^* \frac{v^* y_i(t - \omega_i)}{v y_i^*} \\
&\quad \left. + a_i y_i^* \ln \left( \frac{x_i(t - \tau_i) v(t - \tau_i) y_i(t - \omega_i) (1 + \alpha_i v)}{x_i v y_i (1 + \alpha_i v(t - \tau_i))} \right) \right] \\
&= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} d_i x_i^* \left( 2 - \frac{x_i^*}{x_i} - \frac{x_i}{x_i^*} \right) - a_i y_i^* \frac{x_i^*}{x_i} + 4a_i y_i^* - a_i y_i^* \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i) (1 + \alpha_i v^*)}{y_i x_i^* v^* (1 + \alpha_i v(t - \tau_i))} \right. \\
&\quad + a_i y_i^* \left( -1 + \frac{v(1 + \alpha_i v^*)}{v^*(1 + \alpha_i v)} - \frac{v}{v^*} + \frac{1 + \alpha_i v}{1 + \alpha_i v^*} - \frac{1 + \alpha_i v}{1 + \alpha_i v^*} \right) - a_i y_i^* \frac{v^* y_i(t - \omega_i)}{v y_i^*} \\
&\quad \left. + a_i y_i^* \ln \left( \frac{x_i(t - \tau_i) v(t - \tau_i) y_i(t - \omega_i) (1 + \alpha_i v)}{x_i v y_i (1 + \alpha_i v(t - \tau_i))} \right) \right]. \tag{4.8}
\end{aligned}$$

Then using the following equalities:

$$\begin{aligned}
\ln \left( \frac{x_i(t - \tau_i) v(t - \tau_i) y_i(t - \omega_i) (1 + \alpha_i v)}{x_i v y_i (1 + \alpha_i v(t - \tau_i))} \right) &= \ln \left( \frac{x_i^*}{x_i} \right) + \ln \left( \frac{v^* y_i(t - \omega_i)}{v y_i^*} \right) + \ln \left( \frac{1 + \alpha_i v}{1 + \alpha_i v^*} \right) \\
&\quad + \ln \left( \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i) (1 + \alpha_i v^*)}{y_i x_i^* v^* (1 + \alpha_i v(t - \tau_i))} \right), \\
-1 + \frac{v(1 + \alpha_i v^*)}{v^*(1 + \alpha_i v)} - \frac{v}{v^*} + \frac{1 + \alpha_i v}{1 + \alpha_i v^*} &= \frac{-\alpha_i (v - v^*)^2}{v^* (1 + \alpha_i v^*) (1 + \alpha_i v)}, \tag{4.9}
\end{aligned}$$

we obtain

$$\begin{aligned}
\frac{dW_2}{dt} &= \sum_{i=1}^n \gamma_i \left[ e^{-m_i \tau_i} d_i x_i^* \left( 2 - \frac{x_i^*}{x_i} - \frac{x_i}{x_i^*} \right) - a_i y_i^* \frac{\alpha_i (v - v^*)^2}{v^* (1 + \alpha_i v^*) (1 + \alpha_i v)} \right. \\
&\quad - a_i y_i^* \left( H \left( \frac{x_i^*}{x_i} \right) + H \left( \frac{v^* y_i(t - \omega_i)}{v y_i^*} \right) + H \left( \frac{1 + \alpha_i v}{1 + \alpha_i v^*} \right) \right. \\
&\quad \left. \left. + H \left( \frac{y_i^* x_i(t - \tau_i) v(t - \tau_i) (1 + \alpha_i v^*)}{y_i x_i^* v^* (1 + \alpha_i v(t - \tau_i))} \right) \right) \right]. \tag{4.10}
\end{aligned}$$

It is easy to see that if  $x_i^*, y_i^*, v^* > 0$ ,  $i = 1, \dots, n$ , then  $dW_2/dt \leq 0$  for all  $(x_i, y_i, v) > 0$ . Clearly, the singleton  $\{E_1\}$  is the only invariant set in  $\{dW_2/dt = 0\}$ . LaSalle's invariance principle implies global stability of  $E_1$ .  $\square$

## 5. Conclusion

In this paper, we have studied the global properties of a class of virus dynamics models with multitarget cells and multiple delays. First, we have introduced a model with two classes of target cells ( $CD4^+$  T and macrophages in case of HIV). Then, we have proposed a model describing the interaction of the virus with  $n$  classes of target cells. A model with multitarget cells taking into account the saturation infection rate is also studied. Two types of discrete time delays have been incorporated into these models to take into account (i) the latent period between the time the target cell is contacted by the virus particle and the time virus enters the cell, (ii) the latent period between the time the virus has penetrated into a cell and the time of the emission of infectious (mature) virus particles. The global stability of the uninfected and infected steady states has been established by using suitable Lyapunov functionals and LaSalle invariant principle. We have proven that, if the basic reproduction number  $R_0$  is less than unity, then the uninfected steady state is GAS and if  $R_0 > 1$  (or the infected steady state exists) then the infected steady state is GAS for all time delays.

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