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Effect of time delays in an HIV virotherapy model with nonlinear incidence

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In this paper, we propose a mathematical model for HIV infection with delays in cell infection and virus production. The model examines a viral therapy for controlling infections through recombining HIV with a genetically modified virus. For this model, we derive two biologically insightful quantities (reproduction numbers) $\mathcal{R}_0$ and $\mathcal{R}_z$, and their threshold properties are discussed. When $\mathcal{R}_0 < 1$, the infection-free equilibrium E_0 is globally asymptotically stable. If $\mathcal{R}_0 > 1$ and $\mathcal{R}_z < 1$, the single-infection equilibrium E_s is globally asymptotically stable. When $\mathcal{R}_z > 1$, there occurs the double-infection equilibrium E_d, and there exists a constant R_b such that E_d is asymptotically stable if $1 < \mathcal{R}_z < R_b$. Some simulations are performed to support and complement the theoretical results.

1. Introduction

Acquired immune deficiency syndrome (AIDS) was first recognized by the United States Centers for Disease Control and Prevention in 1981 [1]. AIDS is caused by infection with human immunodeficiency virus (HIV), which is transmitted primarily via unprotected sexual contact, contaminated blood transfusions, hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding. With no cure or vaccine in sight, HIV disease continues to be a serious health issue for parts of the world. According to the report [2] by UNAIDS, there were approximately 36.9 (34.3–41.4) million people living with HIV around the world at the end of 2014, and 1.2 (1.0–1.5) million people died from HIV-related causes in 2014. For more information about AIDS, we refer the reader to [1–3] and references therein.

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As its name suggests, AIDS causes deficiency of the human immune system, making people infected by HIV more susceptible to common infections that do not usually affect people with a working immune system, because the number of $CD4^+$ T cells declines below a centre critical level owing to HIV infection. The entry of HIV into $CD4^+$ T cells begins with the interaction between gp120 on its surface with receptor CD4, and coreceptors CCR5 and CXCR4 on the target membrane. Then, the tips of gp41 are inserted into the target membrane, and viral and cellular membranes fuse together [4]. After HIV has bound to the target cell, the HIV RNA and various enzymes are injected into the cell, including reverse transcriptase and integrase. Reverse transcriptase copies the positive single-stranded RNA genome into a complementary DNA molecule, which together with its complement forms a double-stranded viral DNA. The viral DNA is then transported into the cell nucleus, and is integrated into the host cell's genome by another viral enzyme integrase [5]. To produce the virus, the integrated DNA provirus is transcribed into mRNA, and viral proteins are produced by translation of mRNA. Viral genome and proteins assemble together, bud out of the host cell, and a mature HIV virion is produced. During viral replication, $CD4^+$ T cells infected with HIV are killed. For the mechanism of $CD4^+$ T cell death in HIV infection, see [6,7].

A general model system for HIV infection is described by the following differential equations

$$\left.\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - f(x(t), v(t)), \\ \dot{y}(t) &= \mathrm{e}^{-a_1\tau_1} f(x(t-\tau_1), v(t-\tau_1)) - a_1 y(t) \\ \text{and} \qquad \dot{v}(t) &= k\mathrm{e}^{-a_2\tau_2} y(t-\tau_2) - pv(t), \end{aligned}\right\} \tag{1.1}$$

where $x(t)$, $y(t)$, $v(t)$ is the density of virus-free host cells (mostly corresponding to $CD4^+$ T cells), infected cells and the free HIV at time t, respectively. In the model (1.1), the healthy host cells are assumed to be produced at rate λ, and to die at rate d per cell. Host cells are contacted by the virus at rate $f(x, v)$. It is assumed that it takes an average time τ_1 for the contacting virions to enter cells, which means that the contacted cells become actively affected. Then, after an average time τ_2, the infected cells start to create and release new virions at rate k. The death rate for infected cells and free virus is a_1 and p, respectively. The death rate factor for the latent period and the virus production period is $\mathrm{e}^{-a_1\tau_1}$ and $\mathrm{e}^{-a_2\tau_2}$, respectively. Realistically, a_2 may differ from a_1.

The simplest and earliest form of system (1.1) was derived in [8,9], where $f(x, v) = \beta xv$, $\tau_1 = \tau_2 = 0$. The corresponding basic reproduction number $\mathfrak{R}_0$ was identified in [10,11], and it was proved that when $\mathfrak{R}_0 < 1$, the disease-free equilibrium is globally asymptotically stable, and when $\mathfrak{R}_0 > 1$, the disease-free equilibrium becomes unstable, and the infection equilibrium is globally asymptotically stable. When delays are added into the modelling, e.g. [12–14], it has been shown that ignoring delays leads to overestimation of the basic reproduction number. Besides the bilinear incidence rate $f(x, v) = \beta xv$, nonlinear incidence rates were also studied, for instance the saturated incidence rate $f(x, v) = \beta xv/(1 + b_1 v)$ in [15–17], and the Beddington–DeAngelis infection rate $f(x, v) = \beta xv/(1 + b_0 x + b_1 v)$ in [18–21]. For the models mentioned above with these specific nonlinear incidence rates, the corresponding basic reproduction number was identified and its threshold property was discussed.

Based on model (1.1), various HIV models are developed to investigate drug resistance, immune responses and effects of antiretroviral therapy. These researches have contributed to the understanding of HIV biology [22]. We focus on an HIV virotherapy, which is offered by generic engineering to control HIV infections via introducing recombinant virus [23–25]. One application of genetically modified viruses is cell targeting. For instance, the so-called reverse genetics systems can be used to recover rhabdoviruses from cDNA, which makes it possible to genetically engineer rhabdoviruses [23]. In this case, the recombinant virus is targeted to cells infected by HIV, because the recombinant virus is capable of infecting and killing $CD4^+$ T cells previously infected by HIV, and does no harm to healthy cells. For example, in [25], a recombinant vesicular stomastitis virus lacking the glycoprotein gene and expressing CD4 and CXCR4 is developed with the property that this virus is unable to infect normal cells, and the cells first

infected with HIV-1 are rapidly superinfected with this virus, and killed before high levels of HIV-1 are released.

To model the virotherapy, we add the recombinant virus w and double-infected cells z into system (1.1), and propose the following model

$$\left.\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - f(x(t), v(t)),\\
\dot{y}(t) &= \mathrm{e}^{-a_1\tau_1} f(x(t-\tau_1), v(t-\tau_1)) - a_1 y(t) - \alpha y(t) w(t),\\
\dot{v}(t) &= k\mathrm{e}^{-a_2\tau_2} y(t-\tau_2) - pv(t),\\
\dot{z}(t) &= \alpha y(t) w(t) - bz(t)\\
\text{and}\quad \dot{w}(t) &= cz(t) - qw(t).
\end{aligned}\right\} \tag{1.2}$$

In the model (1.2), the cells previously infected by HIV (single-infected cells) are infected by recombinant virus at a rate αwy, before turning into double-infected cells. Double-infected cells die at a rate bz and release recombinant virus at rate c per cell. The death rate of recombinant virus is q. We assume that the recombinant virus infection is much faster than HIV infection. So delays are not considered for z or w in this model.

To the best of our knowledge, only the case $f(x, v) = \beta xv$ has been considered in the literature, such as [26,27]. In [26,27], the corresponding ordinary differential system of (1.2) was studied. Only the structure of the equilibria was analysed in [27], and some numerical simulations were presented. The authors in [26] gave a dynamical analysis on the stability of all three equilibria. The effects of delay τ_1 on the dynamical behaviour were investigated in [28].

In model (1.2), we suppose that the incidence rate depends on x and v, and is given by a continuous function $f(x, v)$ with continuous derivatives. To be biologically feasible, $f(x, v)$ must satisfy the conditions

$$f(x, 0) = f(0, v) = 0, \tag{1.3}$$

$$f_x(x, v) = \frac{\partial f(x, v)}{\partial x} > 0, \quad f_v(x, v) = \frac{\partial f(x, v)}{\partial v} > 0 \tag{1.4}$$

and

$$f_{vv}(x, v) = \frac{\partial^2 f(x, v)}{\partial v^2} \leq 0, \tag{1.5}$$

for all $x, v > 0$. For the biological meaning, the first two conditions (1.3) and (1.4) are obvious. The third one (1.5) means that the incidence rate is a concave function with respect to the number of free HIV. That could be realistic, because when the number of free HIV is so high that any host cells in contact with HIV is virtually certain, the incidence rate will respond more slowly than linearly to the increase in v.

Our main goal in this paper is to study the impact of two time delays on lowering the HIV load and increasing the CD4$^+$ T cell count. We obtain two reproduction numbers $\mathcal{R}_0$ and $\mathcal{R}_z$ for (1.2), and discuss their threshold properties. As a corollary of the main results in this paper, we prove the threshold property of the corresponding basic reproduction number for system (1.1) with the general incidence rate $f(x, v)$.

The rest of this paper is organized as follows. In §2, for system (1.2), we will discuss the well-posedness of the solutions, and the existence of different equilibria. In addition, in order to properly define biologically meaningful equilibria, two reproduction numbers $\mathcal{R}_0$ and $\mathcal{R}_z$ will be defined. In §§3–5, we analyse the stability of the three equilibria: disease-free equilibrium E_0, single-infection equilibrium E_s and double-infection equilibrium E_d. It will be shown that E_0 is globally asymptotically stable for $\mathcal{R}_0 < 1$, E_s is globally asymptotically stable for $\mathcal{R}_0 > 1$ and $\mathcal{R}_z < 1$, and E_d is asymptotically stable for $1 < \mathcal{R}_z < R_b$, where R_b is a number larger than 1. A numerical example is presented in §6 to demonstrate the theoretical predictions and to show Hopf bifurcation at E_d. Finally, conclusion and discussion are drawn in §7.

2. Well-posedness and existence of equilibrium points

We introduce the Banach space $X = C([-\tau, 0]; R^5_+)$ equipped with the sup-norm, where $\tau = \max\{\tau_1, \tau_2\}$. We let $\mathbf{x}_t \in X$ be defined by $\mathbf{x}_t(\theta) = \mathbf{x}(t+\theta)$ for $\theta \in [-\tau, 0]$ for any $t \in [0, A]$, when $A \geq 0$ and $\mathbf{x} \in C([-\tau, A]; R^5_+)$.

It is biologically reasonable to consider initial conditions $\phi \in X$ for system (1.2). Using the fundamental theory of functional differential equations [29], we have that there is a unique solution $\mathbf{x}(t, \phi) = (x(t, \phi), y(t, \phi), v(t, \phi), z(t, \phi), w(t, \phi))$ to system (1.2) with $\mathbf{x}(0, \phi) = \phi$. Theorem 2.1 establishes the non-negativity and boundedness of solutions to (1.2).

Theorem 2.1. *Let $\mathbf{x}(t, \phi)$ be a solution of system (1.2) satisfying $\mathbf{x}(0, \phi) = \phi \in X$. Then, $\mathbf{x}(t, \phi)$ is non-negative and uniformly bounded for $t \geq 0$. More precisely, we have*

$$\limsup_{t \to +\infty} (x(t), y(t), v(t), z(t), w(t)) \leq \frac{\lambda}{m} e^{-a_1 \tau_1} \left(e^{a_1 \tau_1}, 1, \frac{2k}{a_1} e^{-a_2 \tau_2}, 1, \frac{2c}{b} \right), \tag{2.1}$$

where $m = \min\{a_1/2, b/2, d, p, q\}$. Furthermore, the solution semiflow $\Phi(t) = \mathbf{x}_t(\cdot) : X \to X$ has a compact global attractor.

Proof. System (1.2) can be rewritten as $\dot{\mathbf{x}}(t) = \mathbf{F}(\mathbf{x}_t)$, where

$$\mathbf{F}(\phi) = \begin{pmatrix} \lambda - d\phi_1(0) - f(\phi_1(0), \phi_3(0)) \\ e^{-a_1 \tau_1} f(\phi_1(-\tau_1), \phi_3(-\tau_1)) - a_1 \phi_2(0) - \alpha \phi_2(0) \phi_5(0) \\ k e^{-a_2 \tau_2} \phi_2(-\tau_2) - p\phi_3(0) \\ \alpha \phi_2(0) \phi_5(0) - b\phi_4(0) \\ c\phi_4(0) - q\phi_5(0) \end{pmatrix}$$

for $\phi = (\phi_1, \phi_2, \ldots, \phi_5) \in X$. It is easy to see that for any $\phi \in X$, $\phi_i(0) = 0$ for some i, we have $\mathbf{F}_i(\phi) \geq 0$. Therefore, according to theorem 2.1 in [30, ch. 5], we know that $\mathbf{x}(t, \phi) \geq 0$ for all $t \geq 0$ in its maximal interval of existence.

For the boundedness of the solution, we define

$$B(t) = e^{-a_1 \tau_1} x(t) + y(t + \tau_1) + \frac{a_1}{2k} e^{a_2 \tau_2} v(t + \tau_1 + \tau_2) + z(t + \tau_1) + \frac{b}{2c} w(t + \tau_1). \tag{2.2}$$

Differentiating $B(t)$ with respect to time along the solution of (1.2) yields

$$\begin{aligned} \left. \frac{dB(t)}{dt} \right|_{(1.2)} &= e^{-a_1 \tau_1} [\lambda - dx(t) - f(x(t), v(t))] + e^{-a_1 \tau_1} f(x(t), v(t)) - a_1 y(t + \tau_1) \\ &\quad - \alpha y(t + \tau_1) w(t + \tau_1) + \frac{a_1}{2} y(t + \tau_1) - \frac{a_1}{2k} e^{a_2 \tau_2} p v(t + \tau_1 + \tau_2) \\ &\quad + \alpha y(t + \tau_1) w(t + \tau_1) - bz(t + \tau_1) + \frac{b}{2} z(t + \tau_1) - \frac{b}{2c} q w(t + \tau_1) \\ &= \lambda e^{-a_1 \tau_1} - e^{-a_1 \tau_1} dx(t) - \frac{a_1}{2} y(t + \tau_1) - \frac{b}{2} z(t + \tau_1) \\ &\quad - \frac{a_1}{2k} e^{a_2 \tau_2} p v(t + \tau_1 + \tau_2) - \frac{b}{2c} q w(t + \tau_1) \\ &\leq \lambda e^{-a_1 \tau_1} - mB(t). \end{aligned}$$

Then, we know

$$\limsup_{t \to +\infty} B(t) = \frac{\lambda e^{-a_1 \tau_1}}{m}.$$

On the other hand, it has been proved that $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $w(t)$ are non-negative. Then, from (2.2) for any $t \geq -\tau$, we have $e^{-a_1 \tau_1} x(t) \leq B(t)$, which implies

$$\limsup_{t \to +\infty} x(t) \leq \limsup_{t \to +\infty} e^{a_1 \tau_1} B(t) = \frac{\lambda}{m}.$$

Using the similar argument for $y(t)$, $z(t)$, $v(t)$ and $w(t)$, we get their boundedness listed in (2.1).

Because of the boundedness of the solution, the semiflow $\Phi(t) = \mathbf{x}_t(\cdot)$ of system (1.2) is point dissipative. By [31, theorem 3.6.1], $\Phi(t)$ is compact for any $t > \tau$. On the basis of theorem 3.4.8 in [32], we obtain that $\Phi(t)$ has a compact global attractor in X. The proof of the theorem is completed. ■

Next, we address the basic reproduction number for the model system (1.2) by the next-generation operator approach [33,34]. It is easy to see that system (1.2) has a disease-free equilibrium $E_0 = (x_0, 0, 0, 0, 0)$, where $x_0 = \lambda/d$. Linearizing the system at E_0, we obtain the following two disease-related equations for variables y and v

$$\dot{y}(t) = -a_1 y(t) + \mathrm{e}^{-a_1\tau_1} f_v(x_0, 0) v(t - \tau_1),$$
$$\dot{v}(t) = k\mathrm{e}^{-a_2\tau_2} y(t - \tau_2) - pv(t).$$

Denote u_1 and u_2 be the number of infected cells and HIV at time $t = 0$, respectively. Then, the remaining numbers of infected cells and HIV at time t are given by

$$u_1(t) = u_1\mathrm{e}^{-a_1 t} \quad \text{and} \quad u_2(t) = u_2\mathrm{e}^{-pt}.$$

The total numbers of newly infected cells and produced HIV are

$$\bar{u}_1 = \int_{\tau_1}^{\infty} \mathrm{e}^{-a_1\tau_1} f_v(x_0, 0) u_2(t - \tau_1)\,\mathrm{d}t = \frac{\mathrm{e}^{-a_1\tau_1}}{p} f_v(x_0, 0) u_2$$

and

$$\bar{u}_2 = \int_{\tau_2}^{\infty} k\mathrm{e}^{-a_2\tau_2} u_1(t - \tau_2)\,\mathrm{d}t = \frac{k\mathrm{e}^{-a_2\tau_2}}{a_1} u_1,$$

which can be rewritten as

$$\begin{pmatrix} \bar{u}_1 \\ \bar{u}_2 \end{pmatrix} = M_0 \begin{pmatrix} u_1 \\ u_2 \end{pmatrix}, \quad \text{where } M_0 = \begin{pmatrix} 0 & \dfrac{\mathrm{e}^{-a_1\tau_1}}{p} f_v(x_0, 0) \\ \dfrac{k\mathrm{e}^{-a_2\tau_2}}{a_1} & 0 \end{pmatrix}.$$

Then, the matrix M_0 is the next infection operator. As usual, the spectral radius of M_0 is called the basic reproduction number $\mathcal{R}_0$, which is

$$\mathcal{R}_0 = \sqrt{\frac{k\mathrm{e}^{-a_1\tau_1 - a_2\tau_2}}{a_1 p} f_v(x_0, 0)}.$$

Biologically, $\mathcal{R}_0^2 = (k/p)\mathrm{e}^{-a_1\tau_1} \cdot (\mathrm{e}^{-a_2\tau_2}/a_1) f_v(x_0, 0)$ gives the average number of virions caused by one virion, where $(k/p)\mathrm{e}^{-a_1\tau_1}$ is the mean number of host cells infected by each virion, and $(\mathrm{e}^{-a_2\tau_2}/a_1) f_v(x_0, 0)$ is the average number of HIV virions produced by one single-infected cell.

Now, we want to find the other equilibria of system (1.2), beside the disease-free equilibrium point E_0. From the last three equations in (1.2), we get

$$w(\alpha c y - qb) = 0, \quad z = \frac{q}{c} w \quad \text{and} \quad y = \frac{p}{k\mathrm{e}^{-a_2\tau_2}} v. \tag{2.3}$$

The first equation in (2.3) yields (i) $w = 0$ or (ii) $y = (bq)/(c\alpha)$.

(i) If $w = 0$, then $z = 0$, and the first two equations in (1.2) yields

$$\mathrm{e}^{-a_1\tau_1}(\lambda - dx) - \frac{a_1 p}{k\mathrm{e}^{-a_2\tau_2}} v = 0 \tag{2.4}$$

and

$$F(x, v) = 0, \quad \text{where } F(x, v) = \mathrm{e}^{-a_1\tau_1} f(x, v) - \frac{a_1 p}{k\mathrm{e}^{-a_2\tau_2}} v. \tag{2.5}$$

First, we consider the case $\mathcal{R}_0 < 1$. If there exists a positive solution (x, v) in (2.4) and (2.5), then $0 \le x < x_0$ from (2.4). Further, we can show that $F(x, v) < 0$ for $0 \le x < x_0$ and $v > 0$. In fact, from

$$F_v(x, v) = \mathrm{e}^{-a_1\tau_1} f_v(x, v) - \frac{a_1 p}{k\mathrm{e}^{-a_2\tau_2}} \quad \text{and} \quad F_{vv}(x, v) = \mathrm{e}^{-a_1\tau_1} f_{vv}(x, v) \le 0 \text{ owing to (1.5)},$$

we have $F_v(x_0,0)=(a_1p)/(k\mathrm{e}^{-a_2\tau_2})(\mathcal{R}_0^2-1)<0$ when $\mathcal{R}_0<1$, and $F_v(x_0,v)<F_v(x_0,0)<0$ for all $v>0$. Noting that $F(x_0,0)=0$, together with $F_v(x_0,v)<0$, yields $F(x_0,v)<0$ for all $v>0$. Finally, we obtain $F(x,v)<0$ for $0\le x<x_0$ and $v>0$ owing to $F_x(x,v)=\mathrm{e}^{-a_1\tau_1}f_x(x,v)>0$ from (1.4). Therefore, when $\mathcal{R}_0<1$, equations (2.4) and (2.5) do not have positive solutions, which means no equilibrium points.

For the case $\mathcal{R}_0>1$, we shall prove that there exists a function $x=h(v)$ satisfying (2.5), and $h'(v)\ge 0$. Then that proving the existence of positive solutions (x,v) for (2.4) and (2.5) is converted to showing that the curve $x=h(v)$ intersects with the straight line $L: x=x_0-(a_1p)/(dk\mathrm{e}^{-a_1\tau_1-a_2\tau_2})v$ defined by (2.4), as shown in figure 1.

We first show $h'(v)\ge 0$ when $x=h(v)$ exists. Noting that, from the mean value theorem, for any x and $v>0$ there exists $v^*\in(0,v)$ such that

$$f(x,v)=f(x,v)-f(x,0)=f_v(x,v^*)v. \tag{2.6}$$

Then, substituting (2.6) into (2.5) yields

$$f_v(x,v^*)=\frac{a_1p}{ka^{-a_1\tau_1-a_2\tau_2}}.$$

Hence, from (1.5), we have

$$f_v(x,v)\le f_v(x,v^*)=\frac{a_1p}{ka^{-a_1\tau_1-a_2\tau_2}},\quad 0<v^*<v, \tag{2.7}$$

for any x and v satisfying $x=h(v)$. On the other hand, from (2.5), we have

$$h'(v)=\frac{\mathrm{d}x}{\mathrm{d}v}=\frac{(a_1p)/(k\mathrm{e}^{-a_2\tau_2})-\mathrm{e}^{-a_1\tau_1}f_v(x,v)}{\mathrm{e}^{-a_1\tau_1}f_x(x,v)}.$$

Therefore, $h'(v)\ge 0$ is straightforward from (2.7).

To prove the existence of function $x=h(v)$ satisfying $F(h(v),v)=0$, we expand $F(x,v)$ for $x>0$ in the form

$$F(x,v)=\left(\mathrm{e}^{-a_1\tau_1}f_v(x,0)-\frac{a_1p}{k\mathrm{e}^{-a_2\tau_2}}\right)v+O(v^2),\quad 0<v\ll 1. \tag{2.8}$$

When $\mathcal{R}_0>1$, i.e. $\mathrm{e}^{-a_1\tau_1}f_v(x_0,0)-(a_1p)/(k\mathrm{e}^{-a_2\tau_2})>0$, from (2.8) we have $F(x_0,v)>0$ for $v\in(0,\varepsilon)$, $\varepsilon\ll 1$. Note that $F(0,v)<0$ for $v>0$. Then given that $F(x,v)$ is an increasing function in x from (1.4), for any $v\in(0,\varepsilon)$, there exists only one $x\in(0,x_0)$ satisfying $F(x,v)=0$. Then, $x=h(v)$ exists for $v\in(0,\varepsilon)$ and $x\in(0,x_0)$.

Because $h'(v)\ge 0$, $\lim_{v\to 0^+}h(v)$ must exist. Let $x_*=\lim_{v\to 0^+}h(v)$. Then, $x_*<x_0$, because $x=h(v)<x_0$ for $v\in(0,\varepsilon)$. In order to make sure that the curve $x=h(v)$ can intersect with the straight line L, we still need to study the maximal interval of existence for the function $x=h(v)$.

Let $\lim_{v\to\varepsilon^-}h(v)=x_\varepsilon$. If x_ε is infinite, then $(0,\varepsilon)$ is the largest interval we can find. Otherwise, we have $F(x_\varepsilon,\varepsilon)=0$ from the continuousness of $F(x,v)$ in x and v. Because $(\partial F/\partial x)(x_\varepsilon,\varepsilon)=\mathrm{e}^{-a_1\tau_1}f_x(x_\varepsilon,\varepsilon)>0$ from (1.4), by implicit function theorem, we have $\delta>0$ such that function $x=\tilde{h}(v)$ for $v\in(\varepsilon-\delta,\varepsilon+\delta)$ exists and satisfies $F(\tilde{h}(v),v)=0$, and $h(v)=\tilde{h}(v)$ for $v\in(\max\{\varepsilon-\delta,0\},\varepsilon]$. Hence, the function $x=h(v)$ can be extended to interval $(0,\varepsilon+\delta)$. Using this process repeatedly, we can find the maximal interval $(0,N)$ for $x=h(v)$. Denote $x^*=\lim_{v\to N^-}h(v)$. Then, from the argument above, we can see at least one of x^* or N is infinite.

Then, we claim that if $\mathcal{R}_0>1$, there must exist a unique intersection point $(v_\mathrm{s},x_\mathrm{s})$ in figure 1 for the curves defined by (2.4) and (2.5). Therefore, if $\mathcal{R}_0>1$, then a single-infection equilibrium $E_\mathrm{s}=(x_\mathrm{s},y_\mathrm{s},v_\mathrm{s},0,0)$ exists, where $y_\mathrm{s}=(p)/(k\mathrm{e}^{-a_2\tau_2})v_\mathrm{s}$, x_s and v_s satisfy equations (2.4) and (2.5).

(ii) Next, we consider the case $y=(bq)/(c\alpha)\triangleq y_\mathrm{d}$ and $w>0$. Let $v_\mathrm{d}=(k\mathrm{e}^{-a_2\tau_2}/p)y_\mathrm{d}$. The first two equations in (1.2) yield

$$\mathrm{e}^{-a_1\tau_1}(\lambda-\mathrm{d}x)-a_1y_\mathrm{d}-\alpha y_\mathrm{d}w=0,\quad \lambda-\mathrm{d}x-f(x,v_\mathrm{d})=0. \tag{2.9}$$

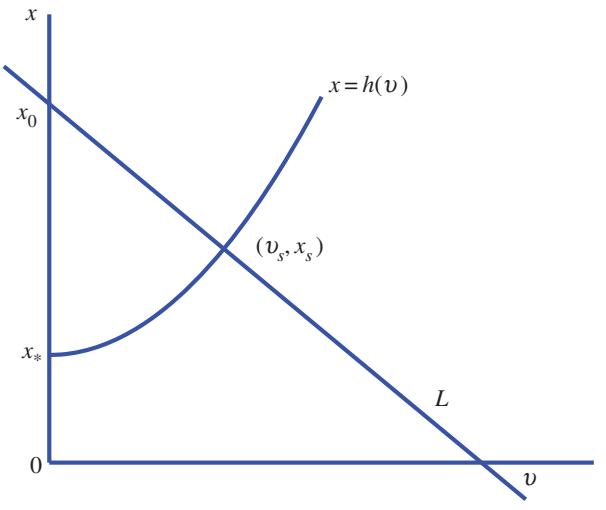

Figure 1. The curves defined by equations (2.4) and (2.5). (Online version in colour.)

Let $g_1(x,w)=\mathrm{e}^{-a_1\tau_1}(\lambda-\mathrm{d}x)-a_1y_\mathrm{d}-\alpha y_\mathrm{d}w$, $g_2(x)=\lambda-\mathrm{d}x-f(x,v_\mathrm{d})$. From the first equation in (2.9), we see that $w>0$ if and only if $g_1(x,0)>0$, which yields

$$x<M,\quad \text{where } M=\frac{\lambda}{d}-\frac{a_1y_\mathrm{d}}{d\mathrm{e}^{-a_1\tau_1}}. \tag{2.10}$$

Note that $g_2(x)$ is a decreasing function in x, and $g_2(0)=\lambda>0$. Then, equations in (2.9) have positive solutions satisfying (2.10) if and only if $M>0$ and $g_2(M)<0$, that is

$$f(M,v_\mathrm{d})>\frac{a_1y_\mathrm{d}}{\mathrm{e}^{-a_1\tau_1}}. \tag{2.11}$$

Before we simplify the condition (2.11), we shall first show that equilibrium E_s exists when (2.11) holds. From (1.3) and the mean value theorem in multiple variables, there exists $\theta\in(0,1)$ such that

$$f(M,v_\mathrm{d})=f\left(\frac{\lambda}{d}-\frac{a_1y_\mathrm{d}}{d\mathrm{e}^{-a_1\tau_1}},v_\mathrm{d}\right)-f\left(\frac{\lambda}{d},0\right)=-f_x(x_\theta,v_\theta)\frac{a_1y_\mathrm{d}}{d\mathrm{e}^{-a_1\tau_1}}+f_v(x_\theta,v_\theta)v_\mathrm{d}, \tag{2.12}$$

where $x_\theta=\lambda/d-(\theta a_1y_\mathrm{d})/(d\mathrm{e}^{-a_1\tau_1})$, $v_\theta=\theta v_\mathrm{d}$. Because $v_\mathrm{d}=(k\mathrm{e}^{-a_2\tau_2}/p)y_\mathrm{d}$ and $f(\lambda/d,0)=0$, from (2.11) and (2.12), we can obtain $\mathcal{R}_0>R_1$, where

$$R_1=\frac{f_v(x_0,0)}{f_v(x_\theta,v_\theta)}\left(1+\frac{f_x(x_\theta,v_\theta)}{d}\right). \tag{2.13}$$

From (1.3) and (1.4), we get $f_{vx}(x,0)\geq 0$, and further with (1.5) we have $f_v(x_\theta,v_\theta)\leq f_v(x_\theta,0)\leq f_v(x_0,0)$ for $x_\theta<x_0$ and $v_\theta>0$. Then, $R_1>1$ from (2.13). Hence, inequality (2.11) implies $\mathcal{R}_0>R_1>1$, and then E_s exists.

On the other hand, (2.11) could be rewritten as

$$\mathrm{e}^{-a_1\tau_1}(\lambda-dM)-\frac{a_1p}{k\mathrm{e}^{-a_2\tau_2}}v_\mathrm{d}=0\quad\text{and}\quad \mathrm{e}^{-a_1\tau_1}f(M,v_\mathrm{d})-\frac{a_1p}{k\mathrm{e}^{-a_2\tau_2}}v_\mathrm{d}>0. \tag{2.14}$$

Comparing (2.14) with (2.4) and (2.5), from figure 1, we see that the point (v_d,M) satisfying (2.14) is on the straight line L and above the curve $x=h(v)$, which means that (2.11) is equivalent to $v_\mathrm{d}<v_\mathrm{s}$. Because $y_\mathrm{d}=(p)/(k\mathrm{e}^{-a_2\tau_2})v_\mathrm{d}$ and $y_\mathrm{s}=(p)/(k\mathrm{e}^{-a_2\tau_2})v_\mathrm{s}$, we have $y_\mathrm{d}<y_\mathrm{s}$, i.e. $\mathcal{R}_z=y_\mathrm{s}/y_\mathrm{d}>1$. Hence, $\mathcal{R}_z>1$ is equivalent to condition (2.11). We also can see that $\mathcal{R}_z>1$ implies $M>0$, because

$$d\mathrm{e}^{-a\tau_1}M=\lambda\mathrm{e}^{-a_1\tau_1}-\frac{a_1pv_\mathrm{d}}{k\mathrm{e}^{-a_2\tau_2}}>\mathrm{e}^{-a_1\tau_1}(\lambda-\mathrm{d}x_\mathrm{s})-\frac{a_1pv_\mathrm{s}}{k\mathrm{e}^{-a_2\tau_2}}=0\quad\text{from (2.4).}$$

Therefore, if and only if $\mathcal{R}_z>1$, then (2.9) has only one positive solution $(x_\mathrm{d},w_\mathrm{d})$ for (x,w), and system (1.2) has a double-infection equilibrium $E_\mathrm{d}=(x_\mathrm{d},y_\mathrm{d},v_\mathrm{d},z_\mathrm{d},w_\mathrm{d})$, where $z_\mathrm{d}=(q/c)w_\mathrm{d}$.

For the biological meaning of $\mathcal{R}_z$, we rewrite $\mathcal{R}_z = c/q \cdot \alpha y_s/b$, because $y_d = (bq)/(c\alpha)$. It is easy to see that c/q is the average number of recombinant virus that a double-infected cell produces, and $\alpha y_s/b$ gives the mean number of double-infected cells caused by each recombinant virus when the number of single-infected cells stabilizes at y_s. Then, $\mathcal{R}_z$ is the average number of recombinant virus caused by one recombinant virus.

Obviously, as $\mathcal{R}_z \to 1^+$, $y_d \to y_s^-$ and $v_d \to v_s^-$. Because both (x_d, v_d) and (x_s, v_s) satisfy $\lambda - dx - f(x, v) = 0$ from the first equation in system (1.2), we get $x_d \to x_s^+$ as $v_d \to v_s^-$ from condition (1.4). Further, when $x_d \to x_s^+$ and $y_d \to y_s^-$, we have $w_d \to 0^+$, and then $z_d \to 0^+$. Hence, we can see that equilibrium point E_d bifurcates from E_s at $\mathcal{R}_z = 1$.

Summarizing the above discussion, we have the following theorem.

Theorem 2.2. *System (1.2) has three possible biologically meaningful equilibria: disease-free equilibrium* $E_0 = (x_0, 0, 0, 0, 0)$, *with* $x_0 = \lambda/d$, *single-infection equilibrium* $E_s = (x_s, y_s, v_s, 0, 0)$, *with* $y_s = (p)/(ke^{-a_2\tau_2})v_s$, x_s *and* v_s *satisfy (2.4) and (2.5), and double-infection equilibrium* $E_d = (x_d, y_d, v_d, z_d, w_d)$, *with* $y_d = (bq)/(c\alpha)$, $v_d = (ke^{-a_2\tau_2}/p)y_d$, $z_d = (q/c)w_d$, x_d *and* w_d *satisfy (2.9). More specifically, (i) if* $\mathcal{R}_0 < 1$, E_0 *is the only equilibrium; (ii) if* $\mathcal{R}_0 > 1$, *the single-infection equilibrium* E_s *exists* and *(iii) the double-infection equilibrium* E_d *exists if and only if* $\mathcal{R}_z > 1$.

3. Global stability of equilibrium E_0

Here, we shall study the global stability of the disease-free equilibrium point E_0. We have the following theorem.

Theorem 3.1. *If* $\mathcal{R}_0 < 1$, *the disease-free equilibrium* $E_0 = (x_0, 0, 0, 0, 0)$ *is globally asymptotically stable, implying that none of the two virus can invade, regardless of the initial load. If* $\mathcal{R}_0 > 1$, *then* E_0 *becomes unstable.*

Proof. First, we recall that E_0 is the only equilibrium when $\mathcal{R}_0 < 1$. To prove the global stability of E_0, we construct the following Lyapunov function:

$$V_0 = e^{-a_1\tau_1}\left(x - f_v(x_0, 0)\int_{x_0}^{x}\frac{dx}{f_v(x, 0)}\right) + y + \frac{a_1}{ke^{-a_2\tau_2}}v + z + \frac{b}{c}w$$
$$+ e^{-a_1\tau_1}\int_{t-\tau_1}^{t} f(x(\eta), v(\eta))\,d\eta + a_1\int_{t-\tau_2}^{t} y(\eta)\,d\eta.$$

Then, the derivative of V_0 with respect to time t along the solution of system (1.2) can be expressed as

$$\begin{aligned}\left.\frac{dV_0}{dt}\right|_{(1.2)} &= e^{-a_1\tau_1}\left(1 - \frac{f_v(x_0, 0)}{f_v(x, 0)}\right)(\lambda - dx - f(x, v)) + e^{-a_1\tau_1}f(x(t-\tau_1), v(t-\tau_1)) - a_1 y - \alpha y w \\ &\quad + \frac{a_1}{ke^{-a_2\tau_2}}(ke^{-a_2\tau_2}y(t-\tau_2) - pv) + \alpha y w - bz + \frac{b}{c}(cz - qw) \\ &\quad + e^{-a_1\tau_1}(f(x, v) - f(x(t-\tau_1), v(t-\tau_1))) + a_1(y - y(t-\tau_2)) \\ &= e^{-a_1\tau_1}dx_0\left(1 - \frac{x}{x_0}\right)\left(1 - \frac{f_v(x_0, 0)}{f_v(x, 0)}\right) + \frac{a_1 p}{ke^{-a_2\tau_2}}\left(\frac{f(x, v)}{f_v(x, 0)}\mathcal{R}_0^2 - v\right) - \frac{bq}{c}w.\end{aligned}$$

Because $f_{vx}(x, 0) \geq 0$, we have $f_v(x, 0) \geq f_v(x_0, 0)$ if $x \geq x_0$, and $f_v(x, 0) \leq f_v(x_0, 0)$ if $x \leq x_0$. Then

$$\left(1 - \frac{x}{x_0}\right)\left(1 - \frac{f_v(x_0, 0)}{f_v(x, 0)}\right) \leq 0.$$

From (1.5) and (2.6), we see $f(x, v) = f_v(x, v^*)v \leq f_v(x, 0)v$, $0 \leq v^* \leq v$. Then

$$\frac{f(x, v)}{f_v(x, 0)}\mathcal{R}_0^2 - v \leq (\mathcal{R}_0^2 - 1)v \leq 0, \quad \text{when } \mathcal{R}_0 < 1.$$

Hence, $dV_0/dt|_{(1.2)} \leq 0$ and the equality holds for $x = x_0$, $v = w = 0$. Thus, by LaSalle's invariance principle [35], we conclude that E_0 is globally asymptotically stable.

For the unstability of E_0, we have the linearized system of (1.2) at E_0 given by

$$\begin{aligned}\dot{x}(t) &= -dx(t) - f_v(x_0, 0)v(t),\\ \dot{y}(t) &= -a_1 y(t) + e^{-a_1\tau_1} f_v(x_0, 0)v(t-\tau_1),\\ \dot{v}(t) &= ke^{-a_2\tau_2} y(t-\tau_2) - pv(t),\\ \dot{z}(t) &= -bz(t),\\ \dot{w}(t) &= cz(t) - qw(t),\end{aligned}$$

for which the characteristic equation is

$$(\xi + d)(\xi + b)(\xi + q)[\xi^2 + (a_1 + p)\xi + a_1 p(1 - \mathcal{R}_0^2 e^{-(\tau_1+\tau_2)\xi})] = 0.$$

Obviously, for the local stability of E_0, it suffices to only consider the zeros of the following function

$$D_0(\xi) = \xi^2 + (a_1 + p)\xi + a_1 p(1 - \mathcal{R}_0^2 e^{-(\tau_1+\tau_2)\xi}). \tag{3.1}$$

When $\mathcal{R}_0 > 1$, we have

$$D_0(0) = a_1 p(1 - \mathcal{R}_0^2) < 0, \quad \lim_{\xi\to+\infty} D_0(\xi) = +\infty,$$

which means that there exists at least one positive real root for (3.1). Therefore, if $\mathcal{R}_0 > 1$, the infection-free equilibrium E_0 is unstable. ■

4. Global stability of the single-infection equilibrium E_s

From the analysis given in §2, we know the single-infection equilibrium $E_s = (x_s, y_s, v_s, 0, 0)$ exists when $\mathcal{R}_0 > 1$. Before we discuss the global stability of E_s, we have the following persistence result.

Theorem 4.1. *Let* $X_0 = \{\phi = (\phi_1, \phi_2, \ldots, \phi_5) \in X : \phi_2(0) > 0$ *and* $\phi_3(0) > 0\}$, *and denote* $\partial X_0 = X \setminus X_0 = \{\phi \in X : \phi_2(0) = 0$ *or* $\phi_3(0) = 0\}$. *When* $\mathcal{R}_0 > 1$, *system (1.2) is uniformly persistent with respect to* $(X_0, \partial X_0)$ *in the sense that there exists some* $\eta > 0$ *such that* $\liminf_{t\to\infty}(y(t), v(t)) > \eta$.

Proof. By the form of system (1.2), it is easy to see that X_0 is positively invariant. We set $M_\partial = \{\phi \in X : \Phi(t)\phi \in \partial X_0, \forall t \geq 0\}$. Clearly, $M_\partial = \{\phi \in X : \phi_2(0) = 0, \phi_3(0) = 0\}$.

We claim that $W^s(E_0) \cap X_0 = \emptyset$. Assume that, on the contrary, there exists $\psi \in X_0$ such that $\lim_{t\to\infty} \Phi(t)\psi = E_0$. Then, for any sufficiently small $\varepsilon > 0$, there exists a positive constant $T_0 = T_0(\varepsilon)$, such that for $\mathbf{x}(t, \psi)$ we have $x(t) > x_0 - \varepsilon$, $v(t) < \varepsilon$ and $w(t) < \varepsilon$ for all $t \geq T_0$. Here, because $\mathcal{R}_0 > 1$, we can choose ε small enough such that

$$\varepsilon\alpha p + a_1 p\left(1 - \frac{f_v(x_0 - \varepsilon, \varepsilon)}{f_v(x_0, 0)}\mathcal{R}_0^2\right) < 0. \tag{4.1}$$

Furthermore, when $t \geq T_0 + \tau_1$, for $\mathbf{x}(t, \psi)$, we have

$$\left.\begin{aligned} &f(x(t-\tau_1), v(t-\tau_1)) \geq f(x_0 - \varepsilon, v(t-\tau_1)) \quad \text{from (1.4)}\\ \text{and}\quad &f(x_0 - \varepsilon, v(t-\tau_1)) \geq f_v(x_0 - \varepsilon, \varepsilon)v(t-\tau_1) \quad \text{from (1.5) and (2.6).}\end{aligned}\right\} \tag{4.2}$$

Consequently, for $t \geq T_0 + \tau_1$, from (4.2), we have

$$\begin{aligned}\dot{y}(t) &\geq e^{-a_1\tau_1} f_v(x_0 - \varepsilon, \varepsilon)v(t-\tau_1) - (a_1 + \varepsilon\alpha)y(t),\\ \dot{v}(t) &= ke^{-a_2\tau_2} y(t-\tau_2) - pv(t).\end{aligned}$$

Suppose ξ_0 is the principal eigenvalue of the following linear cooperative system

$$\left.\begin{aligned} &\dot{u}_1(t) = -(a_1 + \varepsilon\alpha)u_1(t) + e^{-a_1\tau_1} f_v(x_0 - \varepsilon, \varepsilon)u_2(t-\tau_1)\\ \text{and}\quad &\dot{u}_2(t) = ke^{-a_2\tau_2} u_1(t-\tau_2) - pu_2(t).\end{aligned}\right\} \tag{4.3}$$

Through computing the characteristics polynomial and using (4.1), we find that the origin is a saddle point in the corresponding ordinary differential equations of system (4.3) simply by

ignoring delays in (4.3). Thus, $\xi_0 > 0$ from [30, corollary 5.5.2]. Let $u_s = (u_y, u_v)^T$ be the positive right eigenvector associated with ξ_0 for system (4.3). We choose $l > 0$ small enough such that $lu_y e^{\xi_0 t} \le y(t,\psi)$, $lu_v e^{\xi_0 t} \le v(t,\psi)$, for all $t \in [T_0 + \tau, T_0 + 2\tau]$. Obviously, $le^{\xi_0 t}u_s$ satisfies (4.3) for all $t \ge T_0 + \tau$. Then by the comparison principle, we get $(y(t,\psi), v(t,\psi))^T \ge le^{\xi_0 t}u_s$ for all $t \ge T_0 + \tau$. Because $lu_s > 0$ and $\xi_0 > 0$, letting $t \to \infty$, we obtain

$$\liminf_{t\to\infty} y(t,\psi) = \infty, \quad \liminf_{t\to\infty} v(t,\psi) = \infty,$$

a contradiction.

Define a continuous function $p_1 : X \to R_+$ by $p_1(\phi) = \min\{\phi_2(0), \phi_3(0)\}$, $\phi \in X$. Then, $p_1^{-1}(0,\infty) \subset X_0$ and $p_1(\Phi(t)\phi) > 0$ if either $p_1(\phi) = 0$ and $\phi \in X_0$, or if $p_1(\phi) > 0$. Thus, p_1 is a generalize distance function for the solution semiflow $\Phi(t)$ [36]. We obtain that E_0 is a compact and isolated invariant sets in ∂X_0, and $\bigcup_{x\in M_\partial} \omega(x) \subset E_0$. Furthermore, no subset of E_0 forms a cycle in ∂X_0. From the claim above, E_0 is isolated in X, and $W^s(E_0) \cap X_0 = \emptyset$. By [36, theorem 3], it follows that there exists $\eta > 0$ such that $\liminf_{t\to\infty} p_1(\Phi(t)\phi) \ge \eta$ for all $\phi \in X_0$, which implies $\Phi(t)$ is uniformly persistent with respect to $(X_0, \partial X_0)$. Thus, we have $\omega(\phi) \subset X_0$ for any $\phi \in X_0$. ■

Further, we have the following result of the global stability at E_s.

Theorem 4.2. *If $\mathcal{R}_0 > 1$ and $\mathcal{R}_z < 1$, then the single-infection equilibrium E_s is globally asymptotically stable, implying that the recombinant virus cannot survive but the pathogen virus can. E_s becomes unstable when $\mathcal{R}_z > 1$.*

Proof. We construct the Lyapunov function $V_s = V_1 + e^{-a_1\tau_1} f(x_s, v_s) V_2$, where

$$V_1 = e^{-a_1\tau_1}\left(x - f(x_s,v_s)\int_{x_s}^{x} \frac{dx}{f(x,v_s)}\right) + (y - y_s \ln y) + \frac{a_1}{ke^{-a_2\tau_2}}(v - v_s \ln v) + z + \frac{b}{c}w,$$

$$V_2 = \int_{t-\tau_1}^{t}\left(\frac{f(x(\eta),v(\eta))}{f(x_s,v_s)} - \ln\frac{f(x(\eta),v(\eta))}{f(x_s,v_s)}\right)d\eta + \int_{t-\tau_2}^{t}\left(\frac{y(\eta)}{y_s} - \ln\frac{y(\eta)}{y_s}\right)d\eta.$$

Note that E_s satisfies the following relations

$$\lambda = dx_s + f(x_s,v_s), \quad a_1 y_s = e^{-a_1\tau_1} f(x_s,v_s) \quad \text{and} \quad \frac{a_1 p}{ke^{-a_2\tau_2}} v_s = e^{-a_1\tau_1} f(x_s,v_s).$$

Using the above equalities, we have

$$\begin{aligned}
\frac{\partial V_1}{\partial x}\dot{x} &= e^{-a_1\tau_1}\left(1 - \frac{f(x_s,v_s)}{f(x,v_s)}\right)(\lambda - dx - f(x,v)) \\
&= e^{-a_1\tau_1} dx_s \left(1 - \frac{x}{x_s}\right)\left(1 - \frac{f(x_s,v_s)}{f(x,v_s)}\right) \\
&\quad + e^{-a_1\tau_1} f(x_s,v_s)\left(1 - \frac{f(x,v)}{f(x_s,v_s)} - \frac{f(x_s,v_s)}{f(x,v_s)} + \frac{f(x,v)}{f(x,v_s)}\right), \\
\frac{\partial V_1}{\partial y}\dot{y} &= \left(1 - \frac{y_s}{y}\right)(e^{-a_1\tau_1} f(x(t-\tau_1), v(t-\tau_1)) - a_1 y - \alpha y w) \\
&= e^{-a_1\tau_1} f(x_s,v_s)\left(\frac{(y-y_s) f(x(t-\tau_1), v(t-\tau_1))}{y f(x_s,v_s)} - \frac{y}{y_s} + 1\right) - \alpha(y - y_s)w, \\
\frac{\partial V_1}{\partial v}\dot{v} &= \frac{a_1}{ke^{-a_2\tau_2}}\left(1 - \frac{v_s}{v}\right)(ke^{-a_2\tau_2} y(t-\tau_2) - pv) \\
&= e^{-a_1\tau_1} f(x_s,v_s)\left(\frac{y(t-\tau_2)}{y_s} - \frac{v}{v_s} - \frac{v_s y(t-\tau_2)}{v y_s} + 1\right), \\
\frac{\partial V_1}{\partial z}\dot{z} &= \alpha y w - bz, \\
\frac{\partial V_1}{\partial w}\dot{w} &= \frac{b}{c}(cz - qw) = bz - \frac{bq}{c}w
\end{aligned}$$

and for V_2,

$$\frac{\mathrm{d}V_2}{\mathrm{d}t}=\frac{f(x,v)}{f(x_\mathrm{s},v_\mathrm{s})}-\frac{f(x(t-\tau_1),v(t-\tau_1))}{f(x_\mathrm{s},v_\mathrm{s})}+\ln\frac{f(x(t-\tau_1),v(t-\tau_1))}{f(x,v)}+\frac{y}{y_\mathrm{s}}-\frac{y(t-\tau_2)}{y_\mathrm{s}}+\ln\frac{y(t-\tau_2)}{y},$$

which yields

$$\begin{aligned}\left.\frac{\mathrm{d}V_s}{\mathrm{d}t}\right|_{(1.2)}&=\frac{\partial V_1}{\partial x}\dot{x}+\frac{\partial V_1}{\partial y}\dot{y}+\frac{\partial V_1}{\partial v}\dot{v}+\frac{\partial V_1}{\partial z}\dot{z}+\frac{\partial V_1}{\partial w}\dot{w}+\mathrm{e}^{-a_1\tau_1}f(x_\mathrm{s},v_\mathrm{s})\frac{\mathrm{d}V_2}{\mathrm{d}t}\\&=\mathrm{e}^{-a_1\tau_1}dx_\mathrm{s}\left(1-\frac{x}{x_\mathrm{s}}\right)\left(1-\frac{f(x_\mathrm{s},v_\mathrm{s})}{f(x,v_\mathrm{s})}\right)+\frac{bq}{c}(\mathcal{R}_z-1)w\\&\quad+\mathrm{e}^{-a_1\tau_1}f(x_\mathrm{s},v_\mathrm{s})\left(3-\frac{f(x_\mathrm{s},v_\mathrm{s})}{f(x,v_\mathrm{s})}+\frac{f(x,v)}{f(x,v_\mathrm{s})}-\frac{y_\mathrm{s}f(x(t-\tau_1),v(t-\tau_1))}{yf(x_\mathrm{s},v_\mathrm{s})}\right.\\&\quad\left.-\frac{v}{v_\mathrm{s}}-\frac{v_\mathrm{s}y(t-\tau_2)}{vy_\mathrm{s}}+\ln\frac{f(x(t-\tau_1),v(t-\tau_1))}{f(x,v)}+\ln\frac{y(t-\tau_2)}{y}\right)\\&=\mathrm{e}^{-a_1\tau_1}dx_\mathrm{s}\left(1-\frac{x}{x_\mathrm{s}}\right)\left(1-\frac{f(x_\mathrm{s},v_\mathrm{s})}{f(x,v_\mathrm{s})}\right)+\frac{bq}{c}(\mathcal{R}_z-1)w\\&\quad+\mathrm{e}^{-a_1\tau_1}f(x_\mathrm{s},v_\mathrm{s})\left(4-\frac{f(x_\mathrm{s},v_\mathrm{s})}{f(x,v_\mathrm{s})}-\frac{f(x,v_\mathrm{s})v}{f(x,v)v_\mathrm{s}}-\frac{y_\mathrm{s}f(x(t-\tau_1),v(t-\tau_1))}{yf(x_\mathrm{s},v_\mathrm{s})}\right.\\&\quad\left.-\frac{v_\mathrm{s}y(t-\tau_2)}{vy_\mathrm{s}}+\ln\frac{f(x(t-\tau_1),v(t-\tau_1))}{f(x,v)}+\ln\frac{y(t-\tau_2)}{y}\right)\\&\quad+\mathrm{e}^{-a_1\tau_1}f(x_\mathrm{s},v_\mathrm{s})\left(1-\frac{f(x,v_\mathrm{s})}{f(x,v)}\right)\left(\frac{f(x,v)}{f(x,v_\mathrm{s})}-\frac{v}{v_\mathrm{s}}\right).\end{aligned}$$

From (1.4), $f(x,v_\mathrm{s})\geq f(x_\mathrm{s},v_\mathrm{s})$ when $x\geq x_\mathrm{s}$, and $f(x,v_\mathrm{s})\leq f(x_\mathrm{s},v_\mathrm{s})$ when $x\leq x_\mathrm{s}$. Then

$$\left(1-\frac{x}{x_\mathrm{s}}\right)\left(1-\frac{f(x_\mathrm{s},v_\mathrm{s})}{f(x,v_\mathrm{s})}\right)\leq 0.$$

Furthermore, we know that $f(x,v)$ is a concave function in v from (1.5). Then for any $v>0$ and any s in $(0,1]$, $f(x,(1-s)0+sv)\geq(1-s)f(x,0)+sf(x,v)$, which implies

$$\frac{f(x,sv)}{f(x,v)}\geq s\quad\text{and}\quad\frac{f(x,v)}{f(x,sv)}\leq\frac{1}{s}.$$

From the above inequalities and (1.4), $f(x,v)$ should satisfy

$$\left(1-\frac{f(x,v_\mathrm{s})}{f(x,v)}\right)\left(\frac{f(x,v)}{f(x,v_\mathrm{s})}-\frac{v}{v_\mathrm{s}}\right)\leq 0\quad\text{for all } x,v>0.$$

The following inequality

$$\sum_{i=1}^{n}\left(1-\frac{b_i}{a_i}+\ln\frac{b_i}{a_i}\right)=n-\sum_{i=1}^{n}\frac{b_i}{a_i}+\ln\prod_{i=1}^{n}\frac{b_i}{a_i}\leq 0,$$

holds for any positive a_i and b_i, because the function $g_s(x)=x-1-\ln x\geq 0$ for all $x>0$, and $g_s(x)=0$ if and only if $x=1$. Thus, we have

$$\begin{aligned}&4-\frac{f(x_\mathrm{s},v_\mathrm{s})}{f(x,v_\mathrm{s})}-\frac{f(x,v_\mathrm{s})v}{f(x,v)v_\mathrm{s}}-\frac{y_\mathrm{s}f(x(t-\tau_1),v(t-\tau_1))}{yf(x_\mathrm{s},v_\mathrm{s})}\\&\quad-\frac{v_\mathrm{s}y(t-\tau_2)}{vy_\mathrm{s}}+\ln\frac{f(x(t-\tau_1),v(t-\tau_1))}{f(x,v)}+\ln\frac{y(t-\tau_2)}{y}\leq 0,\end{aligned}$$

because

$$\begin{aligned}&\ln\frac{f(x(t-\tau_1),v(t-\tau_1))}{f(x,v)}+\ln\frac{y(t-\tau_2)}{y}\\&=\ln\left(\frac{f(x_\mathrm{s},v_\mathrm{s})}{f(x,v_\mathrm{s})}\cdot\frac{f(x,v_\mathrm{s})v}{f(x,v)v_\mathrm{s}}\cdot\frac{y_\mathrm{s}f(x(t-\tau_1),v(t-\tau_1))}{yf(x_\mathrm{s},v_\mathrm{s})}\cdot\frac{v_\mathrm{s}y(t-\tau_2)}{vy_\mathrm{s}}\right).\end{aligned}$$

Therefore, $\mathrm{d}V_s/\mathrm{d}t|_{(1.2)} \leq 0$ when $\mathcal{R}_z < 1$, and the equality holds when $x = x_s$, $y = y_s$, $v = v_s$ and $w = 0$. Then by LaSalle's invariance principle [35], we conclude that E_s is globally asymptotically stable when $\mathcal{R}_0 > 1$ and $\mathcal{R}_z < 1$.

When $\mathcal{R}_z > 1$, for the local unstability of E_s, we calculate the linearized system of (1.2) at E_s, and obtain

$$\begin{aligned}
\dot{x}(t) &= -(d + f_x(x_s, v_s))x(t) - f_v(x_s, v_s)v(t),\\
\dot{y}(t) &= \mathrm{e}^{-a_1\tau_1} f_x(x_s, v_s)x(t-\tau_1) - a_1 y(t) + \mathrm{e}^{-a_1\tau_1} f_v(x_s, v_s)v(t-\tau_1) - \alpha y_s w(t),\\
\dot{v}(t) &= k\mathrm{e}^{-a_2\tau_2} y(t-\tau_2) - pv(t),\\
\dot{z}(t) &= -bz(t) + \alpha y_s w(t) \quad \text{and}\\
\dot{w}(t) &= cz(t) - qw(t).
\end{aligned}$$

Then, the characteristic equation is given by $D_1(\xi)D_2(\xi) = 0$, where

$$\begin{aligned}
D_1(\xi) &= (\xi + b)(\xi + q) - c\alpha y_s,\\
D_2(\xi) &= \xi^3 + (a_1 + p + d + f_x(x_s, v_s))\xi^2 + ((a_1 + p)(d + f_x(x_s, v_s)) + a_1 p)\xi\\
&\quad + a_1 p(d + f_x(x_s, v_s)) - k f_v(x_s, v_s)(\xi + d)\mathrm{e}^{-a_1\tau_1 - a_2\tau_2}\mathrm{e}^{-(\tau_1+\tau_2)\xi}.
\end{aligned}$$

Because the quadratic polynomial $D_1(\xi)$ in ξ can be expanded as

$$D_1(\xi) = \xi^2 + (b + q)\xi + bq(1 - \mathcal{R}_z),$$

it is easy to see that $D_1(\xi) = 0$ has two zeros with negative real part if and only if $\mathcal{R}_z < 1$. When $\mathcal{R}_z > 1$, $D_1(\xi)$ has two real roots with different signs. Therefore, E_s is unstable if $\mathcal{R}_z > 1$. ■

From the proof of theorems 3.1 and 4.2, it is easy to get the following corollary.

Corollary 4.3. *When $\mathcal{R}_0 < 1$, the infection-free equilibrium $\tilde{E}_0 = (x_0, 0, 0)$ is asymptotically stable for system (1.1); when $\mathcal{R}_0 > 1$, $\tilde{E}_0$ becomes unstable, and the equilibrium $\tilde{E}_s = (x_s, y_s, v_s)$ is asymptotically stable for system (1.1).*

5. Stability of the double-infection equilibrium E_d

The double-infection equilibrium E_d comes into existence for $\mathcal{R}_z > 1$. To discuss the local stability of E_d, for any quantity A involving τ_1 and τ_2 in the paper, we denote by $\mathring{A}$ the value of A when $\tau_1 = \tau_2 = 0$. We have the following result for the local stability of E_d.

Theorem 5.1. *For system (1.2), there exists an $R_b > 1$ such that the double-infection equilibrium E_d is asymptotically stable for $1 < \mathcal{R}_z < R_b$.*

Proof. First, we recall that E_d exists if and only if $\mathcal{R}_z > 1$. The linearized system of (1.2) at $E_d = (x_d, y_d, v_d, z_d, w_d)$ is

$$\left.\begin{aligned}
\dot{x}(t) &= -F_d x(t) - f_v(x_d, v_d)v(t),\\
\dot{y}(t) &= \mathrm{e}^{-a_1\tau_1}(f_x(x_d, v_d)x(t-\tau_1) + f_v(x_d, v_d)v(t-\tau_1)) - A_w y(t) - \alpha y_d w(t),\\
\dot{v}(t) &= k\mathrm{e}^{-a_2\tau_2} y(t-\tau_2) - pv(t),\\
\dot{z}(t) &= \alpha w_d y(t) - bz(t) + \alpha y_d w(t)\\
\text{and}\quad \dot{w}(t) &= cz(t) - qw(t),
\end{aligned}\right\} \tag{5.1}$$

where $F_d = d + f_x(x_d, v_d)$ and $A_w = a_1 + \alpha w_d$.

By straightforward but tedious algebraic manipulations, we obtain the characteristic equation of (5.1), given by

$$D(\xi) = (\xi + p)(\xi + F_d)[\xi(\xi + b + q)(\xi + A_w) + bq\alpha w_{\mathrm{d}}] - A_w p\mathcal{R}_d \xi(\xi + d)(\xi + b + q)\mathrm{e}^{-\xi(\tau_1+\tau_2)}$$
$$= \xi^5 + \sum_{i=0}^{4} A_i \xi^i - \sum_{i=1}^{3} B_i \xi^i \mathrm{e}^{-\xi(\tau_1+\tau_2)} = 0, \tag{5.2}$$

where $\mathcal{R}_d = (k\mathrm{e}^{-a_1\tau_1 - a_2\tau_2})/(A_w p) f_v(x_{\mathrm{d}}, v_{\mathrm{d}})$ and

$$A_4 = A_w + F_d + p + b + q,$$
$$A_3 = A_w F_d + (p + b + q)(A_w + F_d) + p(b + q),$$
$$A_2 = (p + b + q)A_w F_d + p(b + q)(A_w + F_d) + bq\alpha w_{\mathrm{d}},$$
$$A_1 = p(b + q)A_w F_d + (F_d + p)bq\alpha w_{\mathrm{d}},$$
$$A_0 = F_d pbq\alpha w_{\mathrm{d}} \quad \text{and}$$
$$B_3 = A_w p\mathcal{R}_d, \quad B_2 = (d + b + q)B_3, \quad B_1 = d(b + q)B_3.$$

When $\tau_1 = \tau_2 = 0$, (5.2) becomes

$$\xi^5 + C_4\xi^4 + C_3\xi^3 + C_2\xi^2 + C_1\xi + C_0 = 0, \tag{5.3}$$

where

$$C_4 = \mathring{A}_w + \mathring{F}_d + p + b + q,$$
$$C_3 = (\mathring{A}_w + p)\mathring{F}_d + (b + q)(\mathring{A}_w + \mathring{F}_d + p) + \mathring{A}_w p(1 - \mathring{\mathcal{R}}_d),$$
$$C_2 = (b + q)(\mathring{A}_w + p)\mathring{F}_d + (\mathring{F}_d - d)\mathring{A}_w p + \mathring{A}_w p(d + b + q)(1 - \mathring{\mathcal{R}}_d) + bq\alpha\mathring{w}_d,$$
$$C_1 = \mathring{A}_w p(b + q)(\mathring{F}_d - d) + \mathring{A}_w pd(b + q)(1 - \mathring{\mathcal{R}}_d) + bq(\mathring{F}_d + p)\alpha\mathring{w}_d,$$
$$C_0 = \mathring{F}_d pbq\alpha\mathring{w}_d.$$

The necessary and sufficient conditions for all zeros of (5.3) to have negative real part are given by

$$\Delta_1 = C_4 > 0,$$
$$\Delta_2 = C_3C_4 - C_2 > 0,$$
$$\Delta_3 = C_2\Delta_2 - C_4(C_1C_4 - C_0) > 0,$$
$$\Delta_4 = C_1\Delta_3 - C_0\big[C_3\Delta_2 - (C_1C_4 - C_0)\big] > 0 \quad \text{and}$$
$$\Delta_5 = C_0\Delta_4 > 0.$$

Then, we need only to check the signs of Δ_i, $i = 2, 3, 4$, because $C_0 > 0$ and $C_4 > 0$. But it is not easy to determine them for general $\mathring{w}_d$ when $\mathcal{R}_z > 1$. Hence, we use a continuity argument here. When $\mathcal{R}_z = 1$ or $\mathring{w}_d = 0$, we have

$$\Delta_2|_{\mathcal{R}_z=1} = (a_1 + \mathring{F}_s + p)(\mathring{F}_s p + (b + q)(a_1 + \mathring{F}_s + p + b + q))$$
$$+ (a_1 + \mathring{F}_s)a_1\mathring{F}_s + a_1 dp + a_1 p(\mathring{F}_s - d + a_1 + p)(1 - \mathring{\mathcal{R}}_s),$$
$$\Delta_3|_{\mathcal{R}_z=1} = [\mathring{F}_s(a_1^2 + (a_1 + p)(\mathring{F}_s + p)) + a_1 dp + a_1 p(\mathring{F}_s - d + a_1 + p)(1 - \mathring{\mathcal{R}}_s)]$$
$$\times [(b + q)(\mathring{F}_s + b + q)(a_1 + p + b + q) + a_1 p(\mathring{F}_s - d)$$
$$+ a_1 p(b + d + q)(1 - \mathring{\mathcal{R}}_s)],$$
$$\Delta_4|_{\mathcal{R}_z=1} = (a_1 p(b + q)(\mathring{F}_s - d) + a_1 pd(b + q)(1 - \mathring{\mathcal{R}}_s))\Delta_3|_{\mathcal{R}_z=1},$$

where

$$F_s = d + f_x(x_s, v_s) \quad \text{and} \quad \mathcal{R}_s = \frac{k e^{-a_1\tau_1 - a_2\tau_2}}{a_1 p} f_v(x_s, v_s). \tag{5.4}$$

Because $y_s = (p)/(k e^{-a_2\tau_2})v_s$, from the second equation in (1.2) we have $(a_1 p)/(k e^{-a_1\tau_1 - a_2\tau_2})v_s - f(x_s, v_s) = 0$. Then, $\mathcal{R}_s \le 1$ when we take into account $f(x_s, v_s) \ge f_v(x_s, v_s)v_s$ from (1.5) and (2.6). Thus, from (5.4) and (1.4) $\Delta_i|_{\mathcal{R}_z=1} > 0$, $i = 2, 3, 4$. Because C_i, $i = 0, \ldots, 4$, are meaningful only for $\mathcal{R}_z > 1$, because of the continuity there exists a neighbourhood $(1, R_\varepsilon)$ around $\mathcal{R}_z = 1$ such that $\Delta_i > 0$ when $\mathcal{R}_z \in (1, R_\varepsilon)$, $i = 2, 3, 4$. Therefore, all roots of (5.3) have negative real part when $1 < \mathcal{R}_z < R_\varepsilon$.

If at least one of $\tau_i \neq 0$ for $i = 1, 2$, it is easy to see $\xi = 0$ is not a zero of (5.2) because $A_0 > 0$. Moreover, there are no roots for (5.2) existing as $\xi \to \infty$, because $\limsup\{|Q_3(\xi)/P_4(\xi)| : |\xi| \to \infty, \mathrm{Re}\,\xi \ge 0\} < 1$ (see [37]), where

$$Q_3(\xi) = -A_w p \mathcal{R}_d \xi(\xi + d)(\xi + b + q) \quad \text{and}$$
$$P_4(\xi) = (\xi + p)(\xi + F_d)[\xi(\xi + b + q)(\xi + A_w) + bq\alpha w_\mathrm{d}].$$

Because all roots of (5.2) continuously depend on τ_1 and τ_2, the only possibility that the roots of (5.2) enter into the right half plane is to cross the imaginary axis as τ_1 and τ_2 increase. Suppose a purely imaginary number $\xi = \mathrm{i}\varpi$, $(\varpi > 0)$, is a root of (5.2). Then substituting $\xi = \mathrm{i}\varpi$, $\varpi > 0$ into $D(\xi) = 0$ yields

$$\mathrm{i}\varpi^5 + A_4\varpi^4 - \mathrm{i}A_3\varpi^3 - A_2\varpi^2 + \mathrm{i}A_1\varpi + A_0 = (-\mathrm{i}B_3\varpi^3 - B_2\varpi^2 + \mathrm{i}B_1\varpi)\, \mathrm{e}^{-\mathrm{i}(\tau_1+\tau_2)\varpi}.$$

Computing the modulus on the both sides gives $H(\varpi^2) = \varpi^{10} + h_1\varpi^8 + h_2\varpi^6 + h_3\varpi^4 + h_4\varpi^2 + h_5 = 0$, with

$$\begin{aligned}
h_1 &= A_4^2 - 2A_3 = F_d^2 + A_w^2 + p^2 + (b+q)^2,\\
h_2 &= 2A_1 - 2A_2A_4 + A_3^2 - B_3^2 = (b+q)^2(A_w^2 + F_d^2 + p^2) + (A_w^2 + p^2)F_d^2\\
&\quad + A_w^2p^2(1 - \mathcal{R}_d^2) - 2(A_w + b + q)bq\alpha w_\mathrm{d},\\
h_3 &= 2A_0A_4 - 2A_1A_3 + A_2^2 + 2B_1B_3 - B_2^2\\
&= (b+q)^2(A_w^2 + p^2)F_d^2 + (F_d^2 - d^2)A_w^2p^2 + A_w^2p^2((b+q)^2 + d^2)(1 - \mathcal{R}_d^2)\\
&\quad + b^2q^2\alpha^2w_\mathrm{d}^2 - 2(F_d^2 + p^2)(A_w + b + q)bq\alpha w_\mathrm{d},\\
h_4 &= A_1^2 - 2A_0A_2 - B_1^2 = (b+q)^2(F_d^2 - d^2)A_w^2p^2 + A_w^2p^2d^2(b+q)^2(1 - \mathcal{R}_d^2)\\
&\quad + (F_d^2 + p^2)b^2q^2\alpha^2w_\mathrm{d}^2 - 2F_d^2p^2(A_w + b + q)bq\alpha w_\mathrm{d}\\
h_5 &= A_0^2 = F_d^2p^2b^2q^2\alpha^2w_\mathrm{d}^2.
\end{aligned}$$

Clearly, $h_1 > 0$ and $h_5 > 0$. For h_i, $i = 2, 3, 4$, we use the continuity argument again, and have $h_i|_{\mathcal{R}_z=1} > 0$. Similarly, there exits $R_{\hat{b}} > 1$ such that for $1 < \mathcal{R}_z < R_{\hat{b}}$ all $h_i > 0$, $i = 1, \ldots, 5$, which implies that $H(\varpi^2)$ does not have any positive real roots. Therefore, combining with the condition $1 < R_z < R_\epsilon$, let $R_b = \min\{R_\epsilon, R_{\hat{b}}\}$, then for any $\mathcal{R}_z \in (1, R_b)$, the roots of (5.2) stay in the left half complex plane and E_d is locally asymptotically stable. ■

Besides the local stability of E_d, we have the following uniform persistence result with respect to the recombinant virus and double-infected cells.

Theorem 5.2. *If $\mathcal{R}_z > 1$, then there is an $\eta > 0$ such that any solution $\mathbf{x}(t, \phi)$ of the system (1.2) with $\phi \in X$, $\phi_4(0) > 0$ and $\phi_5(0) > 0$ satisfies*

$$\liminf_{t\to+\infty}(z(t, \phi), w(t, \phi)) \ge (\eta, \eta).$$

Proof. Define $Y_0 = \{\phi \in X : \phi_4(0) > 0 \text{ and } \phi_5(0) > 0\}$. Then, we have $\partial Y_0 = X \setminus Y_0 = \{\phi \in X : \phi_4(0) = 0 \text{ or } \phi_5(0) = 0\}$. Define $N_\partial = \{\phi \in X : \Phi(t)\phi \in \partial Y_0,\ \forall t \ge 0\}$.

By a similar argument as that in the proof of theorem 4.1, we can show that when $\mathcal{R}_0 > 1$, we have $W^s(E_0) \cap Y_0 = \emptyset$. We also claim that there exists a $\delta > 0$, such that any $\phi \in Y_0$, $\limsup_{t\to\infty} \|\Phi(t)\phi - E_s\| \geq \delta$.

Again, assume that on the contrary, there exists $\psi \in Y_0$ such that $\lim_{t\to\infty} \Phi(t)\psi = E_s$. Then for any sufficiently small $\varepsilon > 0$, there exists a positive constant $T_1 = T_1(\varepsilon)$, such that $y(t) > y_s - \varepsilon$ for all $t \geq T_1$. Here, because $\mathcal{R}_z > 1$, we can choose ε small enough such that

$$\varepsilon c\alpha + bq(1 - \mathcal{R}_z) < 0. \tag{5.5}$$

Then for $t \geq T_1$, in (1.2) we have $\dot{z} = \alpha y w - bz \geq \alpha(y_s - \varepsilon)w - bz$ and $\dot{w} = cz - qw$. It is easy to see that the following linear system

$$\dot{u}_1 = -bu_1 + \alpha(y_s - \varepsilon)u_2 \quad \text{and} \quad \dot{u}_2 = cu_1 - qu_2, \tag{5.6}$$

has a saddle point at the origin when (5.5) holds. Suppose that $\xi_1 > 0$ is the positive eigenvalue, and $u_d = (u_z, u_w)^T$ be the corresponding positive right eigenvector. We choose $l > 0$ small enough such that $lu_z e^{\xi_1 t} \leq z(t)$, $lu_w e^{\xi_1 t} \leq w(t)$, for all $t \in [T_1, T_1 + \tau]$. Obviously, $le^{\xi_1 t}u_d$ satisfies (5.6) for all $t \geq T_1$. Then by the comparison principle, we get $(z(t), w(t))^T \geq le^{\xi_1 t}u_d$ for all $t \geq T_1 + \tau$. Because $lu_d > 0$ and $\xi_1 > 0$, letting $t \to \infty$, we obtain $\liminf_{t\to\infty} z(t) = \infty$, $\liminf_{t\to\infty} w(t) = \infty$, which is a contradiction. Therefore, we have $W^s(E_s) \cap Y_0 = \emptyset$, when $\mathcal{R}_z > 1$.

Next, we claim $\bigcup_{\phi\in N_\partial} \omega(\phi) = E_0 \cup E_s$. For any $\phi \in N_\partial$, i.e. $\Phi(t)\phi \in \partial Y_0$, we have $z(t, \phi) \equiv 0$, or $w(t, \phi) \equiv 0$. From the w equation in system (1.2), we have $\lim_{t\to\infty} w(t) = 0$ if $z(t) \equiv 0$, or $\lim_{t\to\infty} z(t) = 0$ if $w(t) \equiv 0$. Hence, we have $\omega(\phi) = \omega_1 \times \{(0, 0)\}$ for some $\omega_1 \in C([-\tau, 0]; R^3_+)$, and

$$\Phi(t)|_\omega(\phi_1, \phi_2, \phi_3, 0, 0) = (\Phi_1(t)(\phi_1, \phi_2, \phi_3), 0, 0),$$

where $\Phi_1(t)$ is the solution semiflow associated with system (1.1). From corollary 4.3, we have that ω_1 is either $\tilde{E}_0$ or $\tilde{E}_s$. Hence, $\bigcup_{\phi\in N_\partial} \omega(\phi) = E_0 \cup E_s$.

Define a continuous function $p_2 : X \to R_+$ by $p_2(\phi) = \min\{\phi_4(0), \phi_5(0)\}$, $\phi \in X$. Then, $p_2^{-1}(0, \infty) \subset Y_0$, and p_2 is also a generalize distance function for the solution semiflow $\Phi(t)$. From the proof above, we conclude that any forward orbit of $\Phi(t)$ in N_∂ converges to E_0 or E_s, that E_0 and E_s are two isolated invariant sets in X, and $(W^s(E_0) \cap W^s(E_1)) \cup Y_0 = \emptyset$. Moreover, it is easy to see that no subset of $\{E_0, E_s\}$ forms a cycle in ∂Y_0. By [36, theorem 3], it follows that there exist $\eta > 0$ such that $\liminf_{t\to\infty} p_2(\Phi(t)\phi) \geq \eta$ for all $\phi \in Y_0$, which implies $\Phi(t)$ is uniformly persistent with respect to $(Y_0, \partial Y_0)$. ■

6. Numerical simulations

In the above discussions, owing to the general form of $f(x, v)$, we cannot obtain the explicit form of R_z. Consequently, we are not able to either prove the global stability of the third equilibrium point E_d or determine whether there are other dynamic phenomena around E_d for $\mathcal{R}_z > 1$. So in this section, using numerical simulation we show some dynamical behaviour around E_d, including the convergence of orbits to E_d and the existence of Hopf bifurcation for system (1.2).

Because there are more parameters involved in the model if a nonlinear incidence function is used, we cannot find the proper value range for the new parameter in the literature. A non-reliable parameter value could damage the biological interpretation of the numerical simulations. So we chose a bilinear incidence function $f(x, v) = \beta xv$, where β is the constant rate at which a T cell is contacted by the virus, which is widely used in other papers. Then $\mathcal{R}_0^2 = (k\beta\lambda)/(a_1 dp)e^{-a_1\tau_1 - a_2\tau_2}$ and $\mathcal{R}_z = (\alpha cdp)/(\beta bkq)(\mathcal{R}_0^2 - 1)$.

For computer simulation, we set the parameter values as the following: $\lambda = 1\,\text{cell}\,\text{mm}^{-3}$, $d = \frac{1}{180}\,\text{day}^{-1}$, $\alpha = \beta = \frac{1}{260}\,\text{vir}\,\text{mm}^{-3}\,\text{day}^{-1}$, $\tau_2 = \frac{9}{20}\,\text{day}$, $a_1 = 0.5\,\text{day}^{-1}$, $b = 2\,\text{day}^{-1}$, $p = q = 3\,\text{day}^{-1}$, $k = 80\,\text{vir}\,\text{cell}^{-1}$, $c = 1800\,\text{vir}\,\text{cell}^{-1}$, see [27,38]. Let τ_1 be the bifurcation parameter.

The disease-free equilibrium E_0 is now given by $E_0 = (180, 0, 0, 0, 0)$, which is globally asymptotically stable from theorem 3.1 for $\tau_1 > \tau_s \approx 6.76767349288$, i.e. $\mathcal{R}_0 < 1$. When $\tau_1 < \tau_s$, E_0 becomes unstable, and the single-infection equilibrium E_s exists, given by $E_s =$

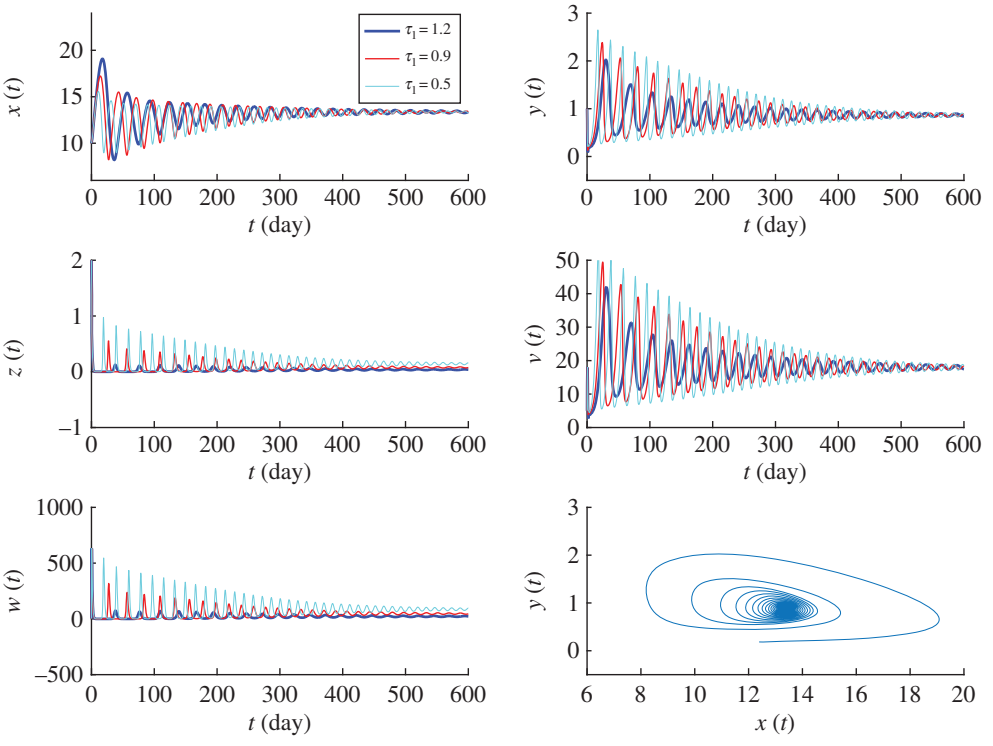

Figure 2. Simulation of (1.2) for $\tau_1 = 0.5, 0.9, 1.2$, taken from the interval $\tau_1 \in (\tau_h, \tau_d)$, showing convergence to the equilibrium E_d. (Online version in colour.)

$(\frac{39}{8}e^{\tau_1/2+9/40}, 2e^{-\tau_1/2} - \frac{13}{240}e^{9/40}, \frac{160}{3}e^{-\tau_1/2-9/40} - \frac{13}{9}, 0, 0)$, which is globally asymptotically stable from theorem 4.2 for $\tau_s > \tau_1 > \tau_d \approx 1.5217799236$.

Further decreasing τ_1 to pass through the critical value τ_d will cause E_s to lose its stability, and give rise to the double-infection equilibrium,

$$E_d = \left(\frac{180}{16e^{-9/40}+1}, \frac{13}{15}, \frac{208}{9}e^{-9/40}, \frac{480e^{-\tau_1/2-9/40} - 208e^{-9/40} + 13}{60(16e^{-9/40}+1)}, \right.$$
$$\left. \frac{10(480e^{-\tau_1/2-9/40} - 208e^{-9/40} + 13)}{16e^{-9/40}+1} \right).$$

Then, we can obtain the characteristic equation $D(\xi, \tau_1)$ at E_d. Solving $D(i\eta, \tau_1) = R(\eta, \tau_1) + iS(\eta, \tau_1) = 0$ yields $(\eta_h, \tau_h) \approx (\pm 0.58060139097, 0.17431498237)$. It follows from theorem 5.1 that E_d is asymptotically stable when $\tau_d > \tau_1 > \tau_h$, where $\tau_h \approx 0.17431498237$. The simulations for $\tau_1 = 0.5, 0.9, 1.2$ are shown in figure 2.

Next, we consider possible Hopf bifurcation. The following condition is held

$$\mathrm{Re}\left(\frac{d\xi}{d\tau_1}\right)\Big|_{\xi = i\eta_h, \tau_1 = \tau_h} \approx -0.031189097952 < 0.$$

Thus, $D(\xi, \tau_1) = 0$ has a pair of purely imaginary roots at $\tau_1 = \tau_h$, whose real parts become positive when $\tau_1 < \tau_h$, implying existence of a Hopf bifurcation. At the critical point, $\tau_1 = \tau_h$, E_d loses its stability through a Hopf bifurcation, giving rise to limit cycles (figure 3). When $\tau_1 = \tau_h$, we obtain $R_b = \mathcal{R}_z|_{\tau_1 = \tau_h} \approx 2.0368053805$.

To sum up, the bifurcation diagram projected on $y - \tau_1$ plane is given in figure 4, which shows what impacts the delay τ_1 could have on the dynamics around the equilibria of model (1.2).

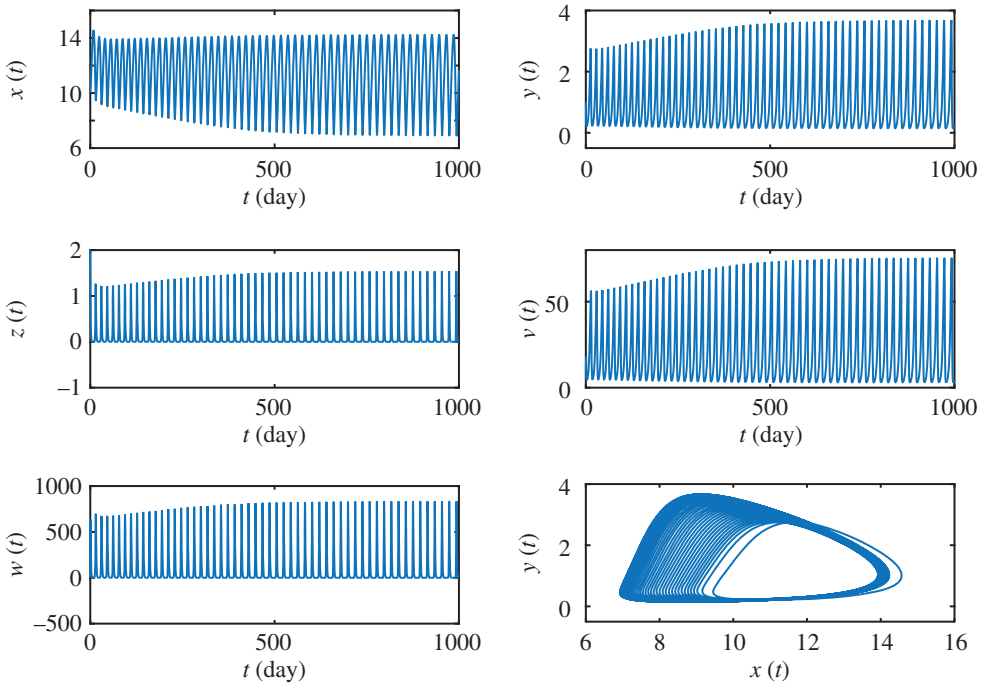

Figure 3. Simulation of (1.2) for $\tau_1 = 0.15 < \tau_h$, showing bifurcation to a limit cycle. (Online version in colour.)

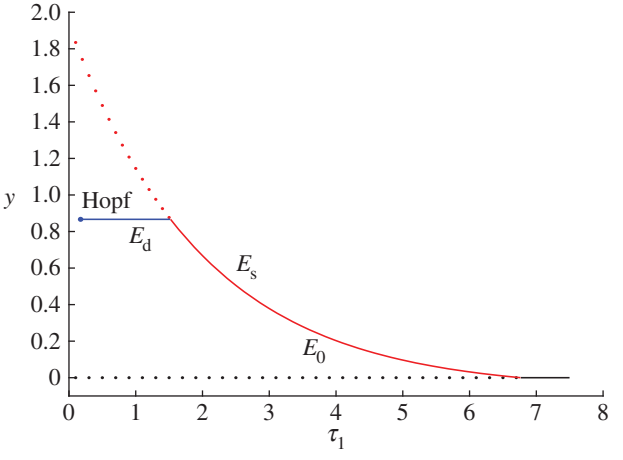

Figure 4. Bifurcation diagram projected on $y - \tau_1$ plane of model (1.2). The dotted and solid lines indicate unstable and stable equilibria, respectively. (Online version in colour.)

7. Discussion

In this paper, we propose an HIV model with a general nonlinear incidence rate and two time delays. Two production numbers $\mathcal{R}_0$ and $\mathcal{R}_z$ are obtained to determine the threshold properties. When $\mathcal{R}_0 < 1$, the disease-free equilibrium $E_0 = (x_0, 0, 0, 0, 0)$ is globally asymptotically stable. When $\mathcal{R}_0 > 1$, E_0 becomes unstable, and the single-infection equilibrium $E_s = (x_s, y_s, v_s, 0, 0)$ occurs. When $\mathcal{R}_0 > 1$ and $\mathcal{R}_z < 1$, E_s is globally asymptotically stable. At $\mathcal{R}_z = 1$, E_s bifurcates into double-infection equilibrium $E_d = (x_d, y_d, v_d, z_d, w_d)$, and E_s loses its stability for $\mathcal{R}_z > 1$. It is

shown that there exits an $\eta > 0$ such that $\liminf_{t\to\infty}(z(t,\phi), w(t,\phi)) > (\eta, \eta)$ for $\phi \in X$ with $\phi_4(0) > 0$ and $\phi_5(0) > 0$ when $\mathcal{R}_z > 1$. From theorem 5.1 and numerical simulations, we can see that E_d is asymptotically stable for $\mathcal{R}_z \in (1, R_b)$, and there may exist a Hopf bifurcation at $\mathcal{R}_z = R_b$.

From the expression of $\mathcal{R}_0$, it is easy to see that ignoring either of two delays τ_1 and τ_2 leads to overestimation of the basic reproduction number $\mathcal{R}_0$. For the effects of delays on $\mathcal{R}_z$, we first need to study the derivatives of y_s and v_s with respect to τ_1 and τ_2, respectively. From (2.4) and (2.5), we get the following equation

$$f\left(\frac{\lambda}{d} - \frac{a_1 p v_s}{dke^{-a_1\tau_1 - a_2\tau_2}}, v_s\right) - \frac{a_1 p v_s}{ke^{-a_1\tau_1 - a_2\tau_2}} \equiv 0,$$

which yields $(dv_s)/(d\tau_j) = (a_j v_s(f_x(x_s, v_s) + d))/(d(\mathcal{R}_s - 1) - f_x(x_s, v_s)) < 0$, $j = 1, 2$, where $\mathcal{R}_s$ is given in (5.4). Then, from $y_s = p/a_1 e^{-a_2\tau_2} v_s$, we have

$$\left.\begin{aligned} \frac{dy_s}{d\tau_1} &= \frac{p}{a_1 e^{-a_2\tau_2}} \frac{dv_s}{d\tau_1} < 0 \\ \text{and} \quad \frac{dy_s}{d\tau_2} &= \frac{p}{a_1 e^{-a_2\tau_2}} \left(a_2 v_s + \frac{dv_s}{d\tau_2}\right) = \frac{p}{a_1 e^{-a_2\tau_2}} \frac{a_2 v_s d\mathcal{R}_s}{d(\mathcal{R}_s - 1) - f_x(x_s, v_s)} < 0. \end{aligned}\right\} \tag{7.1}$$

Therefore, $\mathcal{R}_z = (c\alpha)/(bq) y_s$ will become larger if either τ_1 or τ_2 is not included in system (1.2). Similarly, we can easily get $dv_d/d\tau_j < 0$ and $dy_d/d\tau_j < 0$ for $j = 1, 2$.

From the simulations and figure 4, it is easy to see that choosing different values for delays could change the dynamic behaviours, not only quantitatively, but also sometimes qualitatively. So intracellular delays should be included in the modelling of HIV infection. We should mention that some results (theorems 3.1 and 4.2) in this manuscript still hold if the system has no time delay or if function f is bilinear. The new dynamics is mainly derived with the introduction of the new variables z and w, see corollary 4.3. However, when we release some conditions, e.g. (1.5) for the nonlinear incidence function f, the system will become much more complicated, multiple steady-state solutions and multistabilities may exist. This is beyond the scope of this manuscript.

Note that systems (1.1) and (1.2) share the same basic reproduction number $\mathcal{R}_0$. When $\mathcal{R}_0 < R_1$, where R_1 is given in (2.13), E_s is globally asymptotically stable in (1.2), just as $\tilde{E}_s$ in system (1.1), which means introducing the recombinant virus into the host cannot help to control the number of HIV in this case. When $\mathcal{R}_0 > R_1$, which is equivalent to $\mathcal{R}_z > 1$, the third equilibrium point E_d comes into existence. From §2, we see $x_d > x_s$, $y_d < y_s$ and $v_d < v_s$, implying that the virotherapy cannot only decrease HIV load and the number of infected cells by HIV, but also increase the healthy CD4$^+$ T cell count. So when the recombinant virus can survive, i.e. $\mathcal{R}_z > 1$, it can help to control HIV infection.

Because $\mathcal{R}_z$ can also be expressed in the form $\mathcal{R}_z = y_s/y_d$, the value of $\mathcal{R}_z$ can be used to measure the performance of the virotherapy. Larger $\mathcal{R}_z$ means more cells infected by HIV are killed and more health host cells are produced at E_d. From numerical simulations we can see that there are some phenomena we should pay attention to when $\mathcal{R}_z$ becomes larger. In figure 3, as τ_1 becomes smaller, $\mathcal{R}_z$ gets larger, and it takes more time for orbits to converge to E_d, and the amplitude of oscillations also becomes larger. Furthermore, relative large $\mathcal{R}_z$ may cause Hopf bifurcation. These two dynamics behaviours imply using this virotherapy may cause unsteadiness of the situation of patient using, if we do not choose the value range for $\mathcal{R}_z$ carefully.

On the other hand, we have $\mathcal{R}_z = (c\alpha y_s)/(bq)$, which is the mean number of recombinant virus caused by one recombinant virus when the number of single-infected cells stabilizes at y_s. Obviously, $\mathcal{R}_z$ is closely related to the parameters c, α, b and q in z and w equations. Although the explicit expression of y_s cannot obtained from system (1.2) with general nonlinear incidence function $f(x, v)$, we can see that y_s is totally determined by system (1.1). In other words, y_s is not affected with the varies of the recombinant virus w and double-infected cells z. Therefore, increasing c and α, or decreasing b and q can make $\mathcal{R}_z$ larger. This would be very helpful to develop the virotherapy to meet our expectation.

Data accessibility. This work does not have any experimental data.

Authors' contributions. The work was done when Y.T. visited Y.Y. in Memorial University. Y.T. and Y.Y. conceived the mathematical models and wrote the paper. All authors gave final approval for publication.

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