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GLOBAL STABILITY OF A MULTIPLE DELAYED VIRAL INFECTION MODEL WITH GENERAL INCIDENCE RATE AND AN APPLICATION TO HIV INFECTION

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Abstract. In this paper, the dynamical behavior of a viral infection model with general incidence rate and two time delays is studied. By using the Lyapunov functional and LaSalle invariance principle, the global stabilities of the infection-free equilibrium and the endemic equilibrium are obtained. We obtain a threshold of the global stability for the uninfected equilibrium, which means the disease will be under control eventually. These results can be applied to a variety of viral infections of disease that would make it possible to devise optimal treatment strategies. Numerical simulations with application to HIV infection are given to verify the analytical results.

1. **Introduction.** In the past decades, mathematical models have been paid much attention to investigate the viral infection of disease in vivo. A proper model can not only provide important quantitative insights into the pathogenesis, but also lead to design treatment strategies which would more effectively bring the infection under control [9]. Due to the fact that actions and reactions take time to take effect in real-life problems, many biological models considered time delays in the variables being modeled [4, 6, 10, 12, 15, 16, 18, 19, 20, 21]. But many models were constructed with only one time delay.

In modelling the viral infection of disease, the incidence rate plays a critical role in describing the population dynamics of viral load in vivo. Based on different practical backgrounds, some nonlinear incidence rates have been considered [1, 7, 8, 11, 13, 14, 22]. Gang Huang et al. [7] discussed a delayed model with Beddington-DeAngelis functional response

$$\begin{cases} x' = s - dx - \dfrac{\beta xv}{1+ax+bv}, \\ y' = \dfrac{\beta x(t-\tau)v(t-\tau)}{1+ax(t-\tau)+bv(t-\tau)}e^{-\alpha\tau} - ay, \\ v' = ky - uv. \end{cases} \tag{1}$$

Where uninfected cells x are assumed to be produced at the constant rate s, die at the rate of dx and become infected at the rate of $\frac{\beta xv}{1+ax+bv}$. Infected cells y are produced at the rate of $\frac{\beta x(t-\tau)v(t-\tau)}{1+ax(t-\tau)+bv(t-\tau)}e^{-\alpha\tau}$ and die at the rate of ay, where τ represents the time needed for infected cells to produce virions after viral entry.

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Free virions v are generated from infected cells at the rate of ky and decay at the rate of uv.

It is easy to see that when $a = 0, b > 0$, model (1) is the delayed model with saturation response which was discussed by Rui Xu [22]. When $a > 0, b = 0$, model (1) is the delayed model with Holling type II functional response. When $a = 0, b = 0$, model (1) is the delayed model with the bilinear incidence rate (Holling type I functional response).

Recently, Hattaf et al. [5] proposed a nonlinear incidence rate with the form of $f(x, y, v)v$. Tian and Liu [17] studied a generalization of the Hattaf's model with the form of $f(x, y, v)$. The general incidence rate can help us gain the unification results by the omission of unessential details. However, the effect of the time delay on the dynamics of viral infection should be considered.

Motivated by the work above, we consider the following DDE model with two time delays:

$$\begin{cases} x' = s - dx - f(x, y, v), \\ y' = f(x(t-\tau_1), y(t-\tau_1), v(t-\tau_1))e^{-\alpha_1\tau_1} - ay, \\ v' = ky(t-\tau_2)e^{-\alpha_2\tau_2} - uv. \end{cases} \tag{2}$$

Where τ_1 represents the time necessary for infected cells to produce new virions. The term $e^{-\alpha_1\tau_1}$ accounts for cells that are infected at time t but die before becoming productively infected τ_1 time units later. τ_2 represents the time for the newly produced virions to become mature. The term $e^{-\alpha_2\tau_2}$ accounts for the probability of survival of immature virions. The incidence $f(x, y, v)$ is assumed to be continuously differentiable in R^3_+ and satisfies the following hypotheses [17]:

(H_1) $f(0, y, v) = 0$, for all $y \geqslant 0$ and $v \geqslant 0$; $f(x, y, 0) = 0$, for all $x \geqslant 0$ and $y \geqslant 0$.

(H_2) $\dfrac{\partial f}{\partial x}(x, y, v) > 0$, for all $x \geqslant 0, y \geqslant 0$ and $v > 0$.

(H_3) $\dfrac{\partial f}{\partial y}(x, y, v) \leqslant 0$, for all $x \geqslant 0, y \geqslant 0$ and $v \geqslant 0$.

(H_4) $\dfrac{\partial f}{\partial v}(x, y, v) \geqslant 0$, $v\dfrac{\partial f}{\partial v}(x, y, v) - f(x, y, v) \leqslant 0$, for all $x \geqslant 0, y \geqslant 0$ and $v \geqslant 0$.

It is easy to show that the incidence rate $f(x, y, v)$ generalizes many common forms such as βxv, $\frac{\beta xv}{x+y}$, $\frac{\beta xv}{1+\alpha v}$, $\frac{\beta xv}{1+ax+bv}$ and $\frac{\beta xv}{1+ax+bv+abxv}$.

In this paper, our primary goal is to study the effect of the two delays on the dynamics of model (2) and give a mathematical analysis of its global stability.

The rest of this paper is organized as follows. In Section 2, we introduce some preliminary results of model (2). The existence and uniqueness of positive equilibrium of model (2) are also discussed. In Section 3, we study the global stability of the infection-free equilibrium by using the Lyapunov functional and LaSalle invariance principle. The stability of the endemic equilibrium is analyzed in Section 4. In Section 5, numerical simulations are given to verify the analytical results. Finally, concluding remarks are given in Section 6.

2. **Preliminary results.**

In this section, for biological reasons, we will show the positivity and boundedness of solutions of model (2) and the existence and uniqueness of the positive equilibrium.

We denote the Banach space of continuous functions $\varphi : [-\tau, 0] \to \mathbb{R}^3$ by C with norm $\|\varphi\| = \sup\limits_{-\tau\leqslant\theta\leqslant 0} |\varphi(\theta)|$, where $\tau = \max(\tau_1, \tau_2)$. The nonnegative cone of C is defined by $C_+ = C([-\tau, 0], \mathbb{R}^3_+)$. The initial conditions of model (2) are

$(0,\varphi), \varphi \in C^+$ and $\varphi(0) > 0$. A solution of model (2) is denoted by $(x(t), y(t), v(t))$. We will give the following basic results of model (2).

2.1. **Positivity and boundedness of solutions.** The proof of positive solution is easy, we only show the boundedness of solutions as follows.

Theorem 2.1. *There is an $M > 0$, such that, for any positive solution $(x(t), y(t), v(t))$ of model (2), we have $x(t) < M$, $y(t) < M$, $v(t) < M$.*

Proof. Consider the following function

$$\begin{aligned} N(t) &= x(t) + y(t) + \frac{a}{2k}v(t) + \int_{t-\tau_1}^{t} f(x(\theta), y(\theta), v(\theta))e^{-\alpha_1(t-\theta)}d\theta \\ &\quad + \frac{a}{2}\int_{t-\tau_2}^{t} y(\theta)e^{-\alpha_2(t-\theta)}d\theta. \end{aligned}$$

Calculating the derivative of N along the solutions of model (2) gives

$$\begin{aligned} N'(t) &= s - d\cdot x - \frac{a}{2}\cdot y - u\cdot\frac{a}{2k}v - \alpha_1\cdot\int_{t-\tau_1}^{t} f(x(\theta), y(\theta), v(\theta))e^{-\alpha_1(t-\theta)}d\theta \\ &\quad -\alpha_2\cdot\frac{a}{2}\int_{t-\tau_2}^{t} y(\theta)e^{-\alpha_2(t-\theta)}d\theta \\ &\leqslant s - \min\{d, \frac{a}{2}, u, \alpha_1, \alpha_2\}N(t). \end{aligned}$$

Denote $h = \min\{d, \frac{a}{2}, u, \alpha_1, \alpha_2\}$, it follows that

$$N'(t) \leqslant s - hN(t).$$

Further

$$N(t) \leqslant \frac{s}{h} + (N(0) - \frac{s}{h})e^{-ht}.$$

Hence, $N(t)$ is bounded. Then we can conclude that $x(t)$, $y(t)$ and $v(t)$ are eventually bounded. Thus, there exists an $M > 0$ such that $x(t) < M, y(t) < M, v(t) < M$. This completes the proof. □

Define

$$D = \{(x,\ y,\ v) \in R^3_+|\ \ 0 < x(t) \leqslant \frac{s}{d}, 0 \leqslant y(t), v(t) \leqslant M\}.$$

If $x(0) \leqslant \frac{s}{d}$, then from the first equation of model (2), we have $x(t) \leqslant \frac{s}{d}$ when $t > 0$. It is easy to see that D is a positively invariant region for model (2).

2.2. **Existence and uniqueness of the positive equilibrium.** Obviously, $Q_1 = (\frac{s}{d}, 0, 0)$ is the infection-free equilibrium of model (2), which represents the extinction of the free virus.

Following the concept of next generation matrix given by Diekmann et al. [2] and the reproduction number given by van den Driessche and Watmough in [3], we can compute the basic reproduction number of model (2) as

$$R_0 = \frac{k}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}\frac{\partial f(\frac{s}{d}, 0, 0)}{\partial v},$$

which describes the average number of secondary infections produced by a single infected cell during the period of infection when all other cells are uninfected.

As for the existence and uniqueness of the positive equilibrium, we have the following theorem.

Theorem 2.2. *If $R_0 > 1$, then model (2) has a unique endemic equilibrium of the form $Q_2 = (x^*, y^*, v^*)$ with $0 < x^* < \frac{s}{d}, y^* > 0$ and $v^* > 0$.*

Proof. At any equilibrium, we have:

$$\begin{cases} s - dx - f(x, y, v) = 0, \\ f(x, y, v)e^{-\alpha_1\tau_1} - ay = 0, \\ kye^{-\alpha_2\tau_2} - uv = 0. \end{cases} \tag{3}$$

By the first and the second equation of (3), we have

$$y = \frac{1}{ae^{\alpha_1\tau_1}}(s - dx),$$

and

$$f(x, y, v) = ae^{\alpha_1\tau_1}y.$$

From the third equation, we get

$$v = \frac{ky}{ue^{\alpha_2\tau_2}} = \frac{k(s - dx)}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}.$$

Obviously, if $x > \dfrac{s}{d}$, there is no positive equilibrium.

Now, we consider the following function $F(x)$ defined on the interval $[0, \frac{s}{d}]$:

$$F(x) = f(x, y, v) - ae^{\alpha_1\tau_1}y,$$

where $y = \dfrac{1}{ae^{\alpha_1\tau_1}}(s - dx)$ and $v = \dfrac{k(s - dx)}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}$.

Then,

$$\begin{aligned} F'(x) &= \left(\frac{\partial f}{\partial x} + \frac{\partial f}{\partial y}(-\frac{d}{ae^{\alpha_1\tau_1}}) + \frac{\partial f}{\partial v}(-\frac{kd}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}})\right) - ae^{\alpha_1\tau_1}(-\frac{d}{ae^{\alpha_1\tau_1}}) \\ &= \frac{\partial f}{\partial x} - \frac{d}{ae^{\alpha_1\tau_1}}\frac{\partial f}{\partial y} + \left(d - \frac{kd}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}\frac{\partial f}{\partial v}\right). \end{aligned}$$

Clearly, $F(0) = 0 - ae^{\alpha_1\tau_1}\dfrac{1}{ae^{\alpha_1\tau_1}}s = -s < 0$, $F(\dfrac{s}{d}) = f(\dfrac{s}{d}, 0, 0) = 0$. Notice that $f(x, y, 0) = 0$, so $\dfrac{\partial f}{\partial x}(\dfrac{s}{d}, 0, 0) = 0$ and $\dfrac{\partial f}{\partial y}(\dfrac{s}{d}, 0, 0) = 0$. Therefore,

$$\begin{aligned} F'(\frac{s}{d}) &= \frac{\partial f}{\partial x}(\frac{s}{d}, 0, 0) - \frac{d}{ae^{\alpha_1\tau_1}}\frac{\partial f}{\partial y}(\frac{s}{d}, 0, 0) + \left(d - \frac{kd}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}\frac{\partial f}{\partial v}(\frac{s}{d}, 0, 0)\right) \\ &= d(1 - R_0). \end{aligned}$$

Hence, we get $F'(\dfrac{s}{d}) < 0$ when $R_0 > 1$. Therefore, there exists at least one positive equilibrium $Q_2 = (x^*, y^*, v^*)$ with $0 < x^* < \frac{s}{d}, y^* > 0$ and $v^* > 0$.

Next, we will proof the uniqueness of the positive equilibrium. Observe the third term of $F'(x^*)$. Since $f(x^*, y^*, v^*) = ae^{\alpha_1\tau_1}y^*$ and $v^* = \dfrac{ky^*}{ue^{\alpha_2\tau_2}} = \dfrac{kf(x^*, y^*, v^*)}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}$ at

any positive equilibrium, we have

$$\begin{aligned} & d - \frac{kd}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}\frac{\partial f}{\partial v}(x^*,y^*,v^*) \\ = \; & d - d\frac{v^*}{f(x^*,y^*,v^*)}\frac{\partial f}{\partial v}(x^*,y^*,v^*) \\ = \; & \frac{d}{f(x^*,y^*,v^*)}\left(f(x^*,y^*,v^*) - v^*\frac{\partial f}{\partial v}(x^*,y^*,v^*)\right). \end{aligned}$$

Since $f(x,y,v) - v\dfrac{\partial f}{\partial v}(x,y,v) \geqslant 0$, we get $F'(x^*) > 0$ at any positive equilibrium. Suppose there are at least two positive equilibria of $F(x) = 0$ in $(0, \dfrac{s}{d})$, then there must be $F'(x^*) < 0$ at some equilibrium, which is a contradiction. Therefore, if $R_0 > 1$, there exists a unique endemic equilibrium $Q_2 = (x^*, y^*, v^*)$ with $0 < x^* < \frac{s}{d}, y^* > 0$ and $v^* > 0$. This completes the proof. □

3. **Global stability of the infection-free equilibrium Q_1.** In this section, we will study the global stability of the infection-free equilibrium Q_1. We have the following theorem.

Theorem 3.1. *If $R_0 < 1$, then the infection-free equilibrium Q_1 is globally asymptotically stable.*

Proof. Consider the following Lyapunov functional

$$V = e^{\alpha_1\tau_1}y + \frac{a}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}v + \int_{t-\tau_1}^{t} f(x(\theta),y(\theta),v(\theta))d\theta + ae^{\alpha_1\tau_1}\int_{t-\tau_2}^{t} y(\theta)d\theta.$$

Calculating the derivative of V along the solutions of model (2) gives

$$\begin{aligned} V'(t) &= f(x(t-\tau_1),y(t-\tau_1),v(t-\tau_1)) - ae^{\alpha_1\tau_1}y \\ &\quad + \frac{a}{k}\left(ke^{\alpha_1\tau_1}y(t-\tau_2) - ue^{\alpha_1\tau_1+\alpha_2\tau_2}v\right) + f(x,y,v) \\ &\quad - f(x(t-\tau_1),y(t-\tau_1),v(t-\tau_1)) + ae^{\alpha_1\tau_1}\left(y - y(t-\tau_2)\right) \\ &= f(x,y,v) - \frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}v. \end{aligned}$$

Notice that $\dfrac{\partial f}{\partial x}(x,y,v) > 0$, $\dfrac{\partial f}{\partial y}(x,y,v) \leqslant 0$. Meanwhile, $f(x,y,v) - v\dfrac{\partial f}{\partial v}(x,y,v) \geqslant 0$, which indicates $\dfrac{f(x,y,v)}{v}$ is decreasing for v. Similar with the proof in [17], we have

$$\begin{aligned} V'(t) &\leqslant f(x_0,0,v) - \frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}v \\ &= \left(\frac{f(x_0,0,v)}{v} - \frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}\right)v \\ &\leqslant \left(\lim_{v\to 0^+}\frac{f(x_0,0,v)}{v} - \frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}\right)v \\ &= \left(\frac{\partial f(x_0,0,0)}{\partial v} - \frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}\right)v \\ &= \frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}(R_0-1)v. \end{aligned}$$

Since $R_0 < 1$, then $V'(t) \leqslant 0$ and $V'(t) = 0$ if and only if $v = 0$. For each point in E, the largest invariant subset of $\{(x,\ y,\ v)|V'(t) = 0\}$, we have $v'(t) = 0$, and $y = 0$. Since E is invariant, from the first equation of model (2), it is easy to prove that all solutions approach the infection-free equilibrium Q_1. This completes the proof. □

Remark 1. Notice the fact that the reproduction number R_0 is a decreasing function for the time delays τ_1 and τ_2. $R_0 = \dfrac{k}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}\dfrac{\partial f(\frac{s}{d},0,0)}{\partial v} \leqslant \dfrac{k}{au}\dfrac{\partial f(\frac{s}{d},0,0)}{\partial v} = R^*$. The delay independent R^* is the basic reproduction number of the nondelayed model in [17]. Hence, ignoring the two time delays in real-life problems will overestimate the threshold R_0.

4. **Stability of the endemic equilibrium Q_2.** In this section, we will study the stability of the endemic equilibrium $Q_2 = (x^*, y^*, v^*)$. It is often difficult to handle the global stability of the endemic equilibrium for a delayed differential model mathematically. In the following, we will consider the incidence rate $f(x, y, v)$ with the form of $f(x, v)$, which covers many common forms such as βxv, $\frac{\beta xv}{1+\alpha v}$, $\frac{\beta xv}{1+ax+bv}$ and $\frac{\beta xv}{1+ax+bv+abxv}$.

To simplify the presentation, we will use the following notation: $z_{\tau_i} = z(t-\tau_i)$ for any $z \in \{x, y, v\}$ and $i = 1, 2$. We have the following theorem.

Theorem 4.1. *If $R_0 > 1$, then the endemic equilibrium Q_2 is globally asymptotically stable.*

Proof. Consider the following Lyapunov functional

$$\begin{aligned} V &= x - x^* - \int_{x^*}^{x} \frac{f(x^*,v^*)}{f(\theta,v^*)}d\theta + e^{\alpha_1\tau_1}y^*H(\frac{y}{y^*}) + \frac{a}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}v^*H(\frac{v}{v^*}) \\ &\quad + \int_{t-\tau_1}^{t} f(x^*,v^*)H(\frac{f(x(\theta),v(\theta))}{f(x^*,v^*)})d\theta + ae^{\alpha_1\tau_1}\int_{t-\tau_2}^{t} y^*H(\frac{y(\theta)}{y^*})d\theta, \end{aligned}$$

where $H(x) = x - 1 - \ln x$.

Calculating the derivative of V along the solutions of model (2) gives

$$\begin{aligned} V'(t) &= \left(1 - \frac{f(x^*,v^*)}{f(x,v^*)}\right)x' + e^{\alpha_1\tau_1}(1-\frac{y^*}{y})y' + \frac{a}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}(1-\frac{v^*}{v})v' \\ &\quad + f(x,v) - f(x_{\tau_1},v_{\tau_1}) - f(x^*,v^*)\ln\frac{f(x,v)}{f(x_{\tau_1},v_{\tau_1})} \\ &\quad + ae^{\alpha_1\tau_1}\left(y - y_{\tau_2} - y^*\ln\frac{y}{y_{\tau_2}}\right) \\ &= d(x^*-x)\left(1-\frac{f(x^*,v^*)}{f(x,v^*)}\right) + f(x^*,v^*) - f(x,v) - f(x^*,v^*)\frac{f(x^*,v^*)}{f(x,v^*)} \\ &\quad + f(x,v)\frac{f(x^*,v^*)}{f(x,v^*)} + f(x_{\tau_1},v_{\tau_1}) - ae^{\alpha_1\tau_1}y - \frac{y^*}{y}f(x_{\tau_1},v_{\tau_1}) + ae^{\alpha_1\tau_1}y^* \\ &\quad + ae^{\alpha_1\tau_1}y_{\tau_2} - \frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}v - ae^{\alpha_1\tau_1}\frac{v^*}{v}y_{\tau_2} + \frac{auv^*}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2} + f(x,v) \\ &\quad - f(x_{\tau_1},v_{\tau_1}) - f(x^*,v^*)\ln\frac{f(x,v)}{f(x_{\tau_1},v_{\tau_1})} + ae^{\alpha_1\tau_1}\left(y - y_{\tau_2} - y^*\ln\frac{y}{y_{\tau_2}}\right). \end{aligned}$$

Notice that $f(x^*,v^*)=ae^{\alpha_1\tau_1}y^*=\frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}v^*$ and $y^*=\frac{u}{k}e^{\alpha_2\tau_2}v^*$, we get

$$\begin{aligned}
V'(t) &= d(x^*-x)\left(1-\frac{f(x^*,v^*)}{f(x,v^*)}\right)+3f(x^*,v^*)-f(x^*,v^*)\frac{f(x^*,v^*)}{f(x,v^*)}\\
&\quad +f(x,v)\frac{f(x^*,v^*)}{f(x,v^*)}-f(x^*,v^*)\frac{y^*}{f(x^*,v^*)y}f(x_{\tau_1},v_{\tau_1})-\frac{au}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}v\\
&\quad -ae^{\alpha_1\tau_1}\frac{v^*}{v}y_{\tau_2}-f(x^*,v^*)\ln\frac{f(x,v)}{f(x_{\tau_1},v_{\tau_1})}-ae^{\alpha_1\tau_1}y^*\ln\frac{y}{y_{\tau_2}}\\
&= d(x^*-x)\left(1-\frac{f(x^*,v^*)}{f(x,v^*)}\right)-f(x^*,v^*)\left(\frac{f(x^*,v^*)}{f(x,v^*)}-1-\ln\frac{f(x^*,v^*)}{f(x,v^*)}\right)\\
&\quad -f(x^*,v^*)\left(\frac{y^*f(x_{\tau_1},v_{\tau_1})}{f(x^*,v^*)y}-1-\ln\frac{y^*f(x_{\tau_1},v_{\tau_1})}{f(x^*,v^*)y}\right)\\
&\quad -f(x^*,v^*)\left(\frac{ky_{\tau_2}}{ue^{\alpha_2\tau_2}v}-1-\ln\frac{ky_{\tau_2}}{ue^{\alpha_2\tau_2}v}\right)\\
&\quad -f(x^*,v^*)\left(\frac{vf(x,v^*)}{v^*f(x,v)}-1-\ln\frac{vf(x,v^*)}{v^*f(x,v)}\right)\\
&\quad +\frac{f(x^*,v^*)v}{f(x,v^*)f(x,v)}\left(f(x,v^*)-f(x,v)\right)\left(\frac{f(x,v^*)}{v^*}-\frac{f(x,v)}{v}\right).
\end{aligned}$$

Since $\dfrac{\partial f}{\partial x}>0$, it is easy to prove

$$d(x^*-x)\left(1-\frac{f(x^*,v^*)}{f(x,v^*)}\right)\leqslant 0.$$

Notice that $\dfrac{\partial f}{\partial v}\geqslant 0$, which indicates f is increasing with respect to v. Meanwhile, $f-v\dfrac{\partial f}{\partial v}\geqslant 0$, which indicates $\dfrac{f}{v}$ is decreasing with respect to v. Therefore,

$$\left(f(x,v^*)-f(x,v)\right)\left(\frac{f(x,v^*)}{v^*}-\frac{f(x,v)}{v}\right)\leqslant 0.$$

Hence, $V'(t)\leqslant 0$ and $V'(t)=0$ if and only if $x=x^*,y=y^*$ and $v=v^*$. By the Lyapunov - Lasalle Theorem, solutions in D approach the largest positively invariant subset of the set E where $V'(t)=0$. All solutions in the set D approach the endemic equilibrium Q_2. This completes the proof. □

5. **Numerical simulations.** In this section, we will give numerical simulations of model (2). Let $f(x,y,v)=\frac{\beta xv}{1+\alpha v}$.

In paper [16], Song et al. studied a HIV infection model with one time delay. Clinical experiments give us biologically reasonable ranges for parameter values in model (2). For example, since the infected CD4$^+$ T cells live less than 1-2 days, we can choose the death rate of infected T cells, a, to be values between 0.5 and 1.0 [16]. To illustrate our theoretical analysis results, we choose the parameter values of model (2) as those in paper [16] with $s=5$ mm^{-3} day^{-1}, $d=0.01$ day^{-1}, $\alpha=1\times10^{-6}$ mm^3, $\alpha_1=1.2$ day^{-1}, $\alpha_2=3.4$ day^{-1}, $a=0.5$ day^{-1}, $k=1200$ day^{-1} , $u=5$ day^{-1}. We will regard β as a parameter to study the stability of equilibria of model (2).

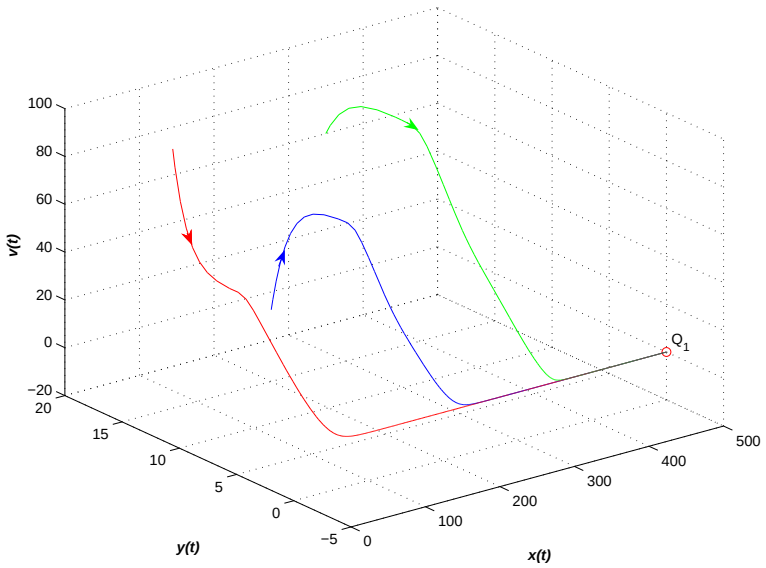

FIGURE 1. The infection-free equilibrium $Q_1 = (500, 0, 0)$ is globally asymptotically stable, when $\beta = 2 \times 10^{-4}, \tau_1 = 1, \tau_2 = 1.2$. The basic reproduction number $R_0 = 0.244 < 1$.

Note that the basic reproduction number is given by $R_0 = \dfrac{\beta sk}{adue^{\alpha_1\tau_1+\alpha_2\tau_2}}$. If β is small enough such that $R_0 < 1$, then the virus eventually dies out. Let $\beta = 2\times10^{-4}$. We will study the effects of the two delays on the dynamics of model (2). Firstly, we choose $\tau_1 = 1, \tau_2 = 1.2$, then the basic reproduction number $R_0 = 0.244 < 1$. The initial conditions are chosen as $(x(0), y(0), v(0)) = (350, 20, 60), (200, 15, 10)$ and $(25, 12, 98)$ respectively. As can be seen from Figure 1, numerical simulations confirm that the infection-free equilibrium Q_1 is globally stable if $R_0 < 1$. Secondly, we choose $\tau_1 = 0.8, \tau_2 = 1.8$ and do not change the other parameter values. We can calculate $R_0 = 0.04 < 1$. In Figure 2, numerical simulations show that the infection-free equilibrium Q_1 is also globally stable if $R_0 < 1$. Figure 1 and Figure 2 demonstrate our theoretical analysis that the infection-free equilibrium Q_1 is globally asymptotically stable if $R_0 < 1$ and the virus is cleared. The two delays have no direct effects on the stability of the viral dynamics if $R_0 < 1$.

With the increase of β, the endemic equilibrium occurs if $R_0 > 1$. According to Theorem 4.1, the endemic equilibrium Q_2 is globally asymptotically stable. To verify the above analytic results about Q_2, we choose $\beta = 2 \times 10^{-3}$. We will study the effects of the two delays on the dynamics of model (2). Firstly, we choose $\tau_1 = 1, \tau_2 = 1.2$, then the basic reproduction number $R_0 = 2.44 > 1$. Figure 3 shows that the endemic equilibrium Q_2 is globally stable if $R_0 > 1$. Secondly, we choose $\tau_1 = 0.8, \tau_2 = 1.5$ in Figure 4, then $R_0 = 1.12 > 1$ and Q_2 is also globally stable. Figure 3 and Figure 4 demonstrate that the endmic equilibrium Q_2 is globally asymptotically stable if $R_0 > 1$ and the virus persists in the host.

Moreover, we can obtain an interesting phenomenon if we increase the time delays with $\tau_1 = 1.5, \tau_2 = 1.5$ and do not change the other parameter values of Figure 4. As shown in Figure 5, the infection-free equilibrium Q_1 becomes stable again. The reason lies in that the basic reproduction number $R_0 = 0.4837 < 1$. Figure 5

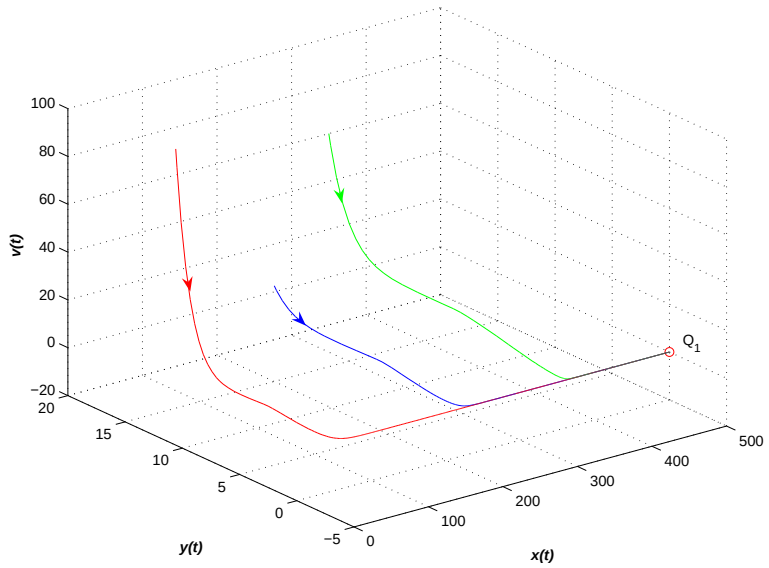

FIGURE 2. The infection-free equilibrium $Q_1 = (500, 0, 0)$ is globally asymptotically stable, when $\beta = 2 \times 10^{-4}, \tau_1 = 0.8, \tau_2 = 1.8$. The basic reproduction number $R_0 = 0.04 < 1$.

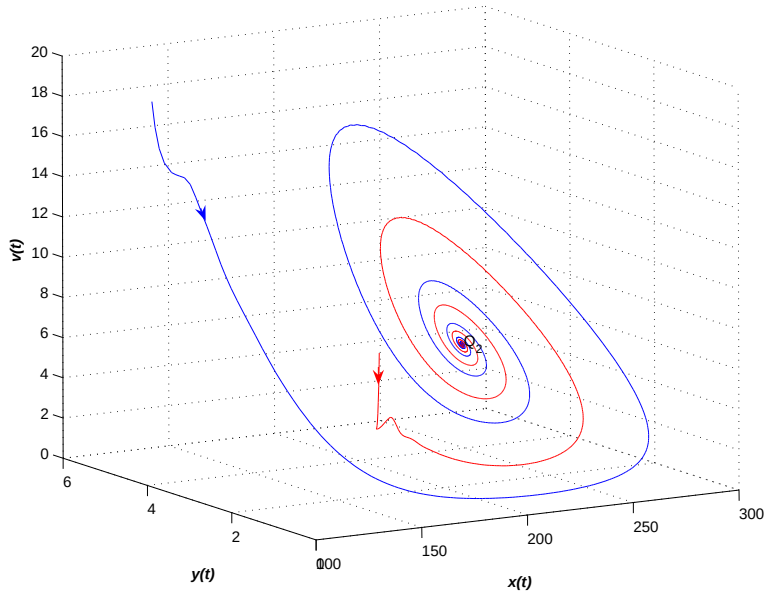

FIGURE 3. The endemic equilibrium $Q_2 = (204.55, 1.78, 7.23)$ is globally asymptotically stable, when $\beta = 2 \times 10^{-3}, \tau_1 = 1, \tau_2 = 1.2$. The basic reproduction number $R_0 = 2.44 > 1$.

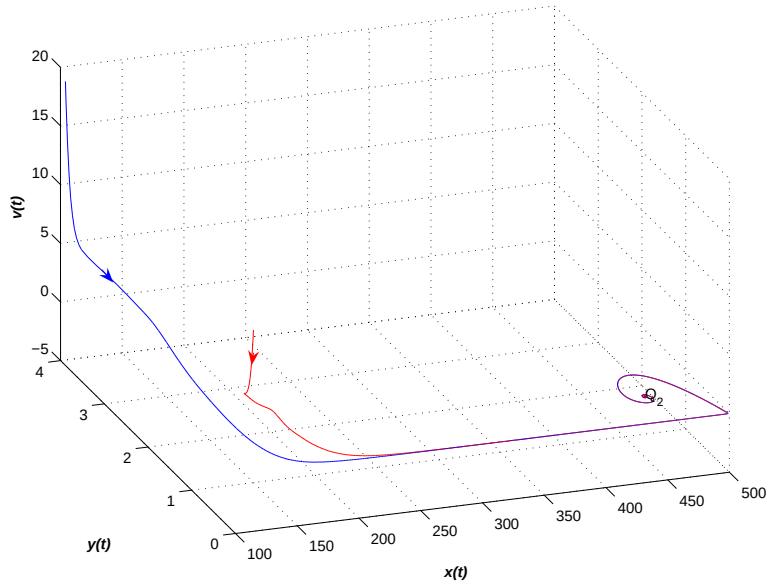

FIGURE 4. The endemic equilibrium $Q_2 = (446.29, 0.41, 0.60)$ is globally asymptotically stable, when $\beta = 2 \times 10^{-3}, \tau_1 = 0.8, \tau_2 = 1.5$. The basic reproduction number $R_0 = 1.12 > 1$.

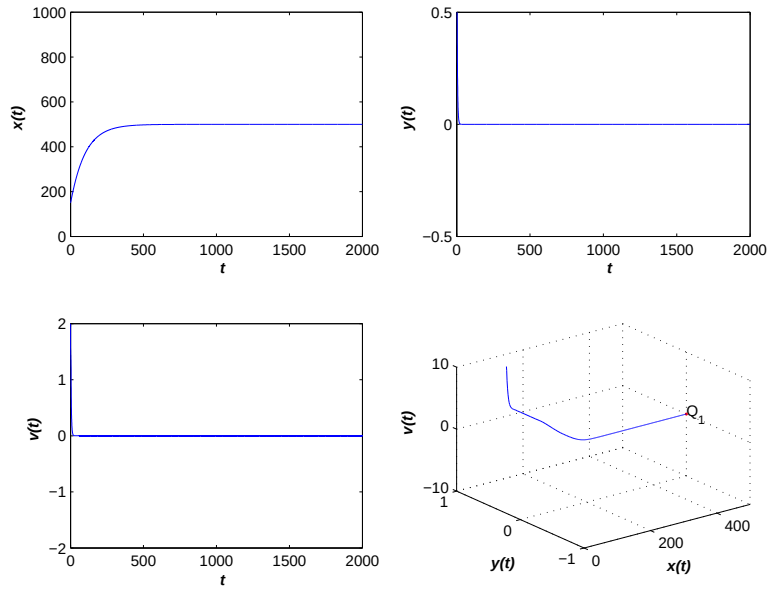

FIGURE 5. The infection-free equilibrium $Q_1 = (500, 0, 0)$ becomes stable again, when $\beta = 2 \times 10^{-3}, \tau_1 = 1.5, \tau_2 = 1.5$. The basic reproduction number $R_0 = 0.4837 < 1$.

demonstrates our theoretical result again that the infection-free equilibrium Q_1 is globally asymptotically stable if $R_0 < 1$ and the virus is cleared eventually.

6. **Conclusions.** Due to the fact that actions and reactions often take time to take effect in real-life problems, many papers propose viral models with one time delay. To cover a variety of incidence functions and time delays in many models, we establish a viral infection model with general incidence rate and two kinds of delays in this paper. The boundedness of solutions and the existence and uniqueness of endemic equilibrium for the general model (2) have been proved. By using the Lyapunov functional and LaSalle invariance principle, we obtain the conditions of global stabilities of the infection-free equilibrium and the endemic equilibrium of model (2).

It is easy to see that when $\tau_2 = 0, f(x, y, v) = \frac{\beta x v}{1+ax+bv}$, model (2) is the delayed model with Beddington-DeAngelis functional response which was discussed by Gang Huang et al.[7]. In paper [17], Tian and Liu studied a generalization of the Hattaf's model [5] with the form of $f(x, y, v)$. The general incidence rate can help us gain the unification results by the omission of unessential details. However, the effect of the time delays on the dynamics of viral infection was not been considered in paper [5, 17]. The basic reproduction number of the nondelayed model in [17] is $R^* = \dfrac{k}{au}\dfrac{\partial f(\frac{s}{d}, 0, 0)}{\partial v}$. Notice the fact that the reproduction number of model (2) $R_0 = \dfrac{k}{aue^{\alpha_1\tau_1+\alpha_2\tau_2}}\dfrac{\partial f(\frac{s}{d}, 0, 0)}{\partial v} \leqslant R^*$. Hence, ignoring the two time delays in real-life problems will overestimate the threshold of the basic reproduction number.

Moreover, the basic reproduction number R_0 is a decreasing function for the two time delays τ_1 and τ_2. When the time delays are long enough, the endemic equilibrium disappears and the virus is cleared in the host. For example, if the time delays $\tau_1 = \tau_2 > 1.35$ day^{-1} in Figure 5, then $R_0 < 1$. This can help to develop drug treatment strategies which would more effectively bring the infection under control.

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