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Research Article

Dynamical Analysis of a Delayed HIV Virus Dynamic Model with Cell-to-Cell Transmission and Apoptosis of Bystander Cells

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In this paper, a delayed viral dynamical model that considers two different transmission methods of the virus and apoptosis of bystander cells is proposed and investigated. The basic reproductive number R_0 of the model is derived. Based on the basic reproductive number, we prove that the disease-free equilibrium E_0 is globally asymptotically stable for $R_0 < 1$ by constructing suitable Lyapunov functional. For $R_0 > 1$, by regarding the time delay as bifurcation parameter, the existence of local Hopf bifurcation is investigated. The results show that time delay can change the stability of endemic equilibrium and cause periodic oscillations. Finally, we give some numerical simulations to illustrate the theoretical findings.

1. Introduction and Model Formulation

AIDS is a serious immune-mediated disorder caused by human immunodeficiency virus (HIV) infection. Continuous high-level HIV replication leads to a chronic fatal infection. By destroying important cells in the human immune system, such as helper T cells (especially $CD4^+$T cells), macrophages, and dendritic cells, HIV destroys or damages the functions of various immune cells in the immune system, resulting in a wide range of immune abnormalities [1]. With the development of infection, the human immune system begins to weaken, which leads to the extreme decline of the body's resistance, leading to a variety of opportunistic infections, such as herpes zoster, tuberculosis, *Pneumocystis carinii* pneumonia, toxoplasmosis, microsporidia, and so on [2, 3].

Since its first discovery in the United States in 1981, AIDS has spread very rapidly. By 2018, AIDS has been found in almost every country in the world. According to the latest UNAIDS report, approximately 37.9 million people worldwide have been infected with HIV by 2018; approximately 23.3 million people are receiving antiretroviral treatment; nearly 770,000 people have died of AIDS-related diseases [4]. AIDS has become one of the most intractable infectious diseases in today's society, posing a huge threat to the survival and further development of mankind. Especially with the globalization of human activities, the increasing frequency of people's communication and the continuous evolution of HIV virus pose new challenges to the prevention and treatment of AIDS. Due to several unique characteristics of HIV replication and transmission, such as two transmission mechanisms of the virus and the lack of proofreading mechanisms, effective vaccines and specific medicines that can completely cure AIDS have not been developed until now [5]. Only prophylactic blockers have been developed that can be used before and after the onset of high-risk behavior, and this antiretroviral drug can only delay the progression of the disease. Therefore, a more in-depth study of the HIV virus is very important.

Mathematical modeling plays an important role in the study of biological systems. Mathematical models can

provide a more typical, more refined, and more quantitative description of complex systems [6–18]. Due to the uncertainty of clinical measurement, the low quality of samples, and the high risk of repeated trials, the use of mathematical models to describe the infection process qualitatively and quantitatively, to study the mechanism of AIDS infection and the treatment of AIDS, is of great significance to the control of HIV infection [19–21].

In 1996, Nowak et al. [22] proposed a virus infection model of ordinary differential equation describing the relationship among infected cells, uninfected cells, and free viruses as follows:

$$\begin{cases} \dot{x}(t) = s - \mathrm{d}x(t) - \beta x(t)v(t), \\ \dot{y}(t) = \beta x(t)v(t) - py(t), \\ \dot{v}(t) = ky(t) - uv(t), \end{cases} \tag{1}$$

where $x(t)$, $y(t)$, and $v(t)$ are the concentrations of uninfected CD4$^+$T cells, infected CD4$^+$T cells, and the free virus particles, respectively. s is the rate at which new uninfected CD4$^+$T cells are produced, and d is the natural mortality of uninfected CD4$^+$T cells. p is the mortality of infected CD4$^+$T cells infected with virus or immune system, β is the probability of uninfected CD4$^+$T cells infected with the free virus, k is the rate of CD4$^+$T cells producing free virus, and u is the rate at which the body's immune system clears the virus. The authors derived the basic reproductive number $R_0 = \beta\lambda k/\mathrm{adu}$ and proved that when $R_0 < 1$, the infection will not spread and the system will return to the uninfected state, and when $R_0 > 1$, the number of infected cells will increase, while the number of uninfected cells will decrease, and the system will converge to the disease-free equilibrium. In the model, the term βxv is the rate that infected cells are produced by the contact of uninfected cells and free virus; usually this transmission method is called cell-free virus spread. Based on model (1), large mathematical models considering cell-free virus transmission and different functional responses have been proposed and analyzed, for example, $\beta xv/(x+y)$ in [23], $\beta xv/(1+bv)$ in [24, 25], $\beta xv/(1+ax+bv)$ in [26], $\beta xv/(1+ax+bv+abxv)$ in [27], and general nonlinear functional response [28–30].

Perelson and Nelson [31], Wang and Li [32], and Hu et al. [33] extended model (1) by introducing logistic growth for susceptible CD4$^+$ T cells. However, many research studies have shown that virus can be transmitted directly from cell to cell by virological synapses, i.e., cell-to-cell transmission [34–41]. Then recently, Lai and Zou [42] proposed a viral dynamical model that combines both cell-free virus transmission and cell-to-cell transmission as follows:

$$\begin{cases} \dot{x}(t) = rx(t)\left(1 - \dfrac{x(t) + \alpha y(t)}{x_M}\right) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t), \\ \dot{y}(t) = \beta_1 x(t)v(t) + \beta_2 x(t)y(t) - \mathrm{d}_y y(t), \\ \dot{v}(t) = \gamma y(t) - \mathrm{d}_v v(t), \end{cases} \tag{2}$$

where r is the target cell growth rate limited by the carrying capacity of the target cell x_M and the constant α indicates the restriction of infected cells that are usually applied to the growth of cells of target cells, $\alpha \gg 1$. They found that if $R > 1$, then the infection will persist and the Hopf bifurcation will occur within a certain range of parameters, where R is the basic reproductive number.

What is interesting is that there are some differences between the above models about the decrease of uninfected cells. The decrease of uninfected cells x in model (1) is due to the natural death or the infection by free virus, while in model (2), the decrease of x is caused by the density-dependent mortality or the infection by free virus or the infection by infected cells. However, recent research studies have shown that apoptosis is an important factor of the decrease of uninfected cells [43], and HIV can produce apoptosis signals that induce apoptosis in uninfected CD4$^+$T cells [44, 45]. Then, by taking into account the time delay in HIV virus from HIV infection to produce new viral particles [34] and apoptosis of bystander cells, Cheng et al. [46] proposed a virus model for HIV infection with discrete delay as follows:

$$\begin{cases} \dot{x}(t) = s - \mathrm{d}x(t) - cx(t)y(t) - \beta x(t)v(t), \\ \dot{y}(t) = e^{-\lambda\tau}\beta x(t-\tau)v(t-\tau) - py(t), \\ \dot{v}(t) = ky(t) - uv(t), \end{cases} \tag{3}$$

where c is the apoptotic rate of uninfected cells induced by infected CD4$^+$T cells and $e^{-\lambda\tau}$ represents the probability of survival of infected cells during the incubation period from virus particles entering cells to releasing new virus particles. They proved that when the basic reproductive number $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable, and when $R_0 > 1$, the infected equilibrium is locally asymptotically stable and the system is uniformly persistent. Guo and Ma [47] extended model (3) by using a general functional response and obtained the global properties of the model. Ji et al. [48] expanded model (3) by considering a full logistic growth of uninfected cells.

Then, based on model (3) and motivated by [32, 47, 48], considering the time delay in HIV virus from HIV infection to produce new viral particles and the time delay in the cell-to-cell transmission and the apoptosis effect of uninfected $CD4^+T$ cells, we propose a delayed viral model as follows:

$$\begin{cases} \dot{x}(t) = s + rx(t)\left(1 - \dfrac{x(t) + y(t)}{T}\right) - \mathrm{d}x(t) - \beta x(t)v(t) - \alpha x(t)y(t) - cx(t)y(t), \\ \dot{y}(t) = \delta x(t-\tau)v(t-\tau) + \eta x(t-\tau)y(t-\tau) - py(t), \\ \dot{v}(t) = ky(t) - uv(t), \end{cases} \tag{4}$$

where x, y, and v are the concentrations of uninfected cells, infected cells, and free virus. s is the rate that new uninfected cells are produced, r is the intrinsic growth rate, and T is the maximum level of $CD4^+T$ cells. d, p, and u are the natural mortalities of uninfected cells, infected cells, and free virus, respectively. α is the probability of healthy cells being infected by infected cells, δ represents the survival rate of infected cells before effective infection, c is the apoptotic rate of uninfected cells induced by infected $CD4^+T$ cells, and η is the survival rate of healthy cells before effective infection by infected cells.

The remainder of the paper is organized as follows. In Section 2, we will give the initial conditions of model (4) and some preliminary properties. In Section 3, we will discuss the stability of the equilibria. In Section 4, we illustrate the main results by some numerical simulations. Finally, we give a brief conclusion and topics for further research in the future.

2. Basic Reproductive Number and the Equilibria

Let $C = C([-\tau, 0]; R_3)$ be the Banach space of continuous functions mapping from interval $[-\tau, 0]$ to R_3 equipped with the sup-norm. The initial condition of the model (4) is given as follows:

$$x(\theta) = \phi_1(\theta), y(\theta) = \phi_2(\theta), v(\theta) = \phi_3(\theta), \quad (\theta \in [-\tau, 0]), \tag{5}$$

where $\phi = (\phi_1, \phi_2, \phi_3) \in C$ such that $\phi_i(\theta) \geq 0 (\theta \in [-\tau, 0], i = 1, 2, 3)$. About the boundedness and non-negativity of the solutions of model (4), by using the method in [49], we can prove the following lemma.

Lemma 1. *The solution $(x(t), y(t), v(t))$ of model (4) with initial condition (5) is existent, unique, and non-negative on $[0, +\infty)$ and also ultimately bounded. Moreover,*

$$\begin{aligned} \limsup_{t \longrightarrow +\infty} x(t) &\coloneqq x_0, \\ \limsup_{t \longrightarrow +\infty} (x(t) + y(t+\tau)) &\coloneqq \frac{s + rx_0}{d_1}, \\ \limsup_{t \longrightarrow +\infty} v(t) &\coloneqq \frac{k(s + rx_0)}{d_1 u}, \end{aligned} \tag{6}$$

where $d_1 = \min\{d, p\}$ and $x_0 = T/2r(r - d + \sqrt{(d-r)^2 + 4rs/T})$.

The basic reproductive number of model (4) is $R_0 = ((\delta k + \eta u)/pu)x_0$. Then, model (4) always has a virus-free equilibrium $E_0 = (x_0, 0, 0)$, where $x_0 = T/2r(r - d + \sqrt{(d-r)^2 + 4rs/T})$, and if $R_0 > 1$, there exists a unique epidemic equilibrium $E^* = (x^*, y^*, v^*)$, where

$$\begin{aligned} x^* &= \frac{pu}{\delta k + \eta u}, \\ y^* &= \frac{s + x^*(r - (rx^*/T) - d)}{x^*((r/T) + (\beta k/u) + \alpha + c)}, \\ v^* &= \frac{ky^*}{u}. \end{aligned} \tag{7}$$

3. Stability for E_0 and E^*

In this section, we will discuss the stability for E_0 and E^* with the increase of R_0. We start with $R_0 < 1$.

Theorem 1. *For model (4), if $R_0 < 1$, E_0 is globally asymptotically stable for any time delay $\tau > 0$.*

Proof. We consider the linearization system of model (4) at E_0 as follows:

$$\begin{cases} \dot{x}(t) = \left(r - d - \dfrac{2rx_0}{T}\right)x(t) - \left(\dfrac{r}{T} + \alpha + c\right)x_0 y(t) - \beta x_0 v(t), \\ \dot{y}(t) = (\eta x_0 - p)y(t-\tau) + \delta x_0 v(t-\tau), \\ \dot{v}(t) = ky(t) - uv(t). \end{cases} \tag{8}$$

The characteristic equation for E_0 is given as

$$\left(\lambda - r + d + \frac{2r}{T}x_0\right)\left[\left(\lambda + p - \eta x_0 e^{-\lambda\tau}\right)(\lambda + u) - k\delta x_0 e^{-\lambda\tau}\right] = 0. \tag{9}$$

It is easy to see that (9) has a root:

$$\lambda_1 = r - d - \frac{2r}{T}x_0 = -\sqrt{(d-r)^2 - \frac{4rs}{T}} < 0. \tag{10}$$

Then, we only need to discuss the distribution of the roots of

$$\left(\lambda + p - \eta x_0 e^{-\lambda\tau}\right)(\lambda + u) - k\delta x_0 e^{-\lambda\tau} = 0. \tag{11}$$

Obviously, equation (11) can be written as

$$\lambda^2 + (p+u)\lambda - \eta x_0 e^{-\lambda\tau}\lambda + pu - (\eta u + k\delta)x_0 e^{-\lambda\tau} = 0. \tag{12}$$

When $R_0 < 1$, $pu - (\eta u + k\delta)x_0 > 0$; therefore, $\lambda = 0$ is not a root of (12). If (12) has a pair of pure imaginary root $\lambda = i\omega\,(\omega > 0)$ for any $\tau > 0$, substituting it into (12), we can get that

$$\begin{aligned} i\omega(p+u) + \left(pu - \omega^2\right) = {} & i\left[\omega\eta x_0 \cos(\omega\tau) - x_0(\eta u + k\delta)\sin(\omega\tau)\right] \\ & + \left[\omega\eta x_0 \sin(\omega\tau) + x_0(\eta u + k\delta)\cos(\omega\tau)\right], \end{aligned} \tag{13}$$

and then separating its real and imaginary parts, one gets

$$\begin{cases} \omega(p+u) = \omega\eta x_0 \cos(\omega\tau) - x_0(\eta u + k\delta)\sin(\omega\tau), \\ pu - \omega^2 = \omega\eta x_0 \sin(\omega\tau) + x_0(\eta u + k\delta)\cos(\omega\tau). \end{cases} \tag{14}$$

Simplifying the above formula and letting $\kappa = \omega^2$, we have

$$f(\kappa) = \kappa^2 + \left(p^2 + u^2 - x_0^2\eta^2\right)\kappa + p^2u^2 - x_0^2(\eta u + k\delta)^2 = 0. \tag{15}$$

On the one hand, it is easy to get that

$$p^2u^2 - x_0^2(\eta u + k\delta)^2 = p^2u^2\left(1 - R_0^2\right) > 0. \tag{16}$$

On the other hand,

$$p^2 + u^2 - x_0^2\eta^2 = \left(\frac{1}{R_0^2} - 1\right)x_0^2y^2 + \frac{1}{R_0^2}\left(\frac{\delta^2k^2}{u^2} + \frac{2\delta ky}{u}\right)x_0^2 + u^2 > 0, \tag{17}$$

where $R_0 = ((\delta k + \eta u)/pu)x_0 < 1$ is used.

Clearly, it indicates that $f(\kappa) > 0$, which is in conflict with $f(\kappa) = 0$. This shows that all the roots of (8) have negative real parts for any time delay $\tau \geq 0$. Therefore, the disease-free equilibrium E_0 is locally asymptotically stable for any time delay $\tau \geq 0$.

Next, let us prove that if $R_0 < 1$, E_0 is globally attractive for any time delay $\tau \geq 0$. Define

$$G = \left\{\phi = (\phi_1, \phi_2, \phi_3) \in C \,\middle|\, x_0 \geq \phi_1 \geq 0, \phi_2 \geq 0, \phi_3 \geq 0\right\}. \tag{18}$$

It is easy to show that G attracts all solutions of model (4) and is also positively invariant with respect to model (4). If $R_0 < 1$, let us choose a functional $W(\phi)$ on G as follows:

$$W(\phi) = m\phi_2(0) + \phi_3(0) + n\int_{-\tau}^{0}\phi_2(\theta)\mathrm{d}\theta + \varepsilon\int_{-\tau}^{0}\phi_3(\theta)\mathrm{d}\theta, \tag{19}$$

where $m = k/(p - \eta x_0), n = m\eta x_0 = k\eta x_0/(p - \eta x_0), n + k = mp$, and $\varepsilon > 0$ is a constant to be chosen later. Since $R_0 < 1$, we have $m, n > 0$. It can be found that $W(\phi)$ is continuous on the subset $\overline{G}$ in C. From the invariance of G, for any $\phi \in G$, the solution $(x(t), y(t), v(t))$ of model (4) satisfies $x(t) \leq x_0$ for any $t \geq 0$. It follows from (4) that

$$\begin{aligned} \dot{W}(\phi) &= m\left[\delta\phi_1(-\tau)\phi_3(-\tau) + \eta\phi_1(-\tau)\phi_2(-\tau)\right] - mp\phi_2(0) + k\phi_2(0) - u\phi_3(0) \\ &\quad + n\left(\phi_2(0) - \phi_2(-\tau)\right) + \varepsilon\left(\phi_3(0) - \phi_3(-\tau)\right) \\ &\leq m\left[\delta\phi_1(-\tau)\phi_3(-\tau) + \eta x_0\phi_2(-\tau)\right] - mp\phi_2(0) + k\phi_2(0) - u\phi_3(0) \\ &\quad + n\left(\phi_2(0) - \phi_2(-\tau)\right) + \varepsilon\left(\phi_3(0) - \phi_3(-\tau)\right) \\ &= m\delta\left(\phi_1(-\tau)\phi_3(-\tau)\right) + n\phi_2(0) + k\phi_2(0) - mp\phi_2(0) - u\phi_3(0) \\ &\quad + \varepsilon\left(\phi_3(0) - \phi_3(-\tau)\right) \\ &= m\delta\phi_1(-\tau)\phi_3(-\tau) - u\phi_3(0) + \varepsilon\left(\phi_3(0) - \phi_3(-\tau)\right) \\ &= \phi_3(-\tau)\left(m\delta\phi_1(-\tau) - \varepsilon\right) + \phi_3(0)(\varepsilon - u) \\ &\leq \phi_3(-\tau)\left(m\delta x_0 - \varepsilon\right) + \phi_3(0)(\varepsilon - u). \end{aligned} \tag{20}$$

Since $R_0 < 1$, it is possible that we can choose the parameter $\varepsilon > 0$ such that $m\delta x_0 < \varepsilon < u$. Thus, it has $\dot{W}(\phi) \leq \phi_3(0)(\varepsilon - u) \leq 0$, for any $\phi \in G$. All these manifest that $W(\phi)$ is a Lyapunov functional on the subset G. By using Lyapunov–LaSalle invariance principle, the disease-free equilibrium E_0 of model (4) is globally asymptotically stable.

Next, let us analyze the stability of the epidemic equilibrium E^*. And the linearized system of model (4) at E^* is

$$\begin{cases} \dot{x}(t) = -\left(\frac{s}{x^*} + \frac{rx^*}{T}\right)x(t) - \left(\frac{r}{T} + \alpha + c\right)x^* y(t) - \beta x^* v(t), \\ \dot{y}(t) = \delta(v^* x(t-\tau) + x^* v(t-\tau)) + \eta\left(y^* x(t-\tau) + x^* y(t-\tau)\right) - py(t), \\ \dot{v}(t) = ky(t) - uv(t). \end{cases} \tag{21}$$

The characteristic equation for E^* is given as

$$\left(\lambda + \frac{s}{x^*} + r\frac{x^*}{T}\right)\left[\left(\lambda + p - \eta x^* e^{-\lambda\tau}\right)(\lambda + u) - k\delta x^* e^{-\lambda\tau}\right] + e^{-\lambda\tau}(\delta v^* + \eta y^*)\left[x^*\left(\frac{r}{T} + \alpha + c\right)(\lambda + u) + k\beta x^*\right] = 0. \tag{22}$$

On the other hand, (22) is equivalent to

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0, \tag{23}$$

where

$$P(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3, \tag{24}$$

$$Q(\lambda) = b_1\lambda^2 + b_2\lambda + b_3, \tag{25}$$

with

$$\begin{aligned} a_1 &= p + u + B, \\ a_2 &= pu + pB + Bu, \\ a_3 &= puB, \\ b_1 &= -I, b_2 = GE - BI - uI - kH, \\ b_3 &= GEu + GkF - kBH - BIu \\ &= G(Eu + kF) - B(kH + Iu), \\ B &= \frac{s}{x^*} + r\frac{x^*}{T}, \\ E &= x^*\left(\frac{r}{T} + \alpha + c\right), \\ F &= \beta x^*, \\ G &= \delta v^* + \eta y^*, \\ H &= \delta x^*, \\ I &= \eta x^*. \end{aligned} \tag{26, 27}$$

When $\tau = 0$, (12) reduces to

$$\lambda^3 + (a_1 + b_1)\lambda^2 + (a_2 + b_2)\lambda + a_3 + b_3 = 0. \tag{28}$$

Notice that

$$\begin{aligned} a_1 + b_1 &= p + u + B - I \\ &> p + u - I \\ &= p + u - \eta x^* \\ &= \frac{kp\delta + ku\delta + \eta u^2}{k\delta + \eta u} > 0, \\ a_2 + b_2 &= B(p + u - I) + GE + pu - uI - kH \\ &= B(p + u - I) + GE > 0, \\ a_3 + b_3 &= puB + G(Eu + kF) - B(kH + Iu) \\ &= G(Eu + kF) > 0, \\ H_1 &= a_1 + b_1 > 0, \\ H_2 &= (a_1 + b_1)(a_2 + b_2) - (a_3 + b_3) \\ &= B(p + u - I)^2 + GE(p + u - I) + B^2(p + u - I) \\ &\quad + G(EB - Eu - kF). \end{aligned} \tag{29}$$

Therefore, if $R_0 > 1$ and $H_2 > 0$ hold, by the Routh–Hurwitz criterion, the epidemic equilibrium E^* is locally asymptotically stable for any time delay $\tau = 0$.

Next, let us investigate the stability of E^* when $\tau > 0$. Since $a_3 + b_3 = puB + G(Eu + kF) - B(kH + Iu) = G(Eu + kF) > 0$, $\tau = 0$ is not the root of (23). For $\tau > 0$, we assume that (23) has the pure imaginary root $\lambda = i\omega(\omega > 0)$, and substituting it into (23), we can get that

$$-i\omega^3 - a_1\omega^2 + ia_2\omega + a_3 + \left(-b_1\omega^2 + ib_2\omega + b_3\right) \cdot (\cos\omega\tau - i\sin\omega\tau) = 0, \tag{30}$$

and then separating its real and imaginary parts, we get

$$\begin{aligned} \omega^3 - a_2\omega &= \left(b_1\omega^2 - b_3\right)\sin(\omega\tau) + b_2\omega\cos(\omega\tau), \\ a_1\omega^2 - a_3 &= \left(b_3 - b_1\omega^2\right)\cos(\omega\tau) + b_2\omega\sin(\omega\tau). \end{aligned} \tag{31}$$

Clearly, it is equivalent to

$$\omega^6 + \left(a_1^2 - b_1^2 - 2a_2\right)\omega^4 + \left(a_2^2 - b_2^2 - 2b_1b_3\right)\omega^2 + \left(a_3^2 - b_3^2\right) = 0. \tag{32}$$

Let $c_1 = a_1^2 - b_1^2 - 2a_2, c_2 = a_2^2 - b_2^2 - 2a_1a_3 - 2b_1b_3$, and $c_3 = a_3^2 - b_3^2$; (22) can be written as

$$\omega^6 + c_1\omega^4 + c_2\omega^2 + c_3 = 0. \tag{33}$$

Let $\varpi = \omega^2$; (33) is equivalent to

$$\varpi^3 + c_1\varpi^2 + c_2\varpi + c_3 = 0. \tag{34}$$

Define

$$g(\varpi) = \varpi^3 + c_1\varpi^2 + c_2\varpi + c_3, \tag{35}$$

and thus

$$g'(\varpi) = 3\varpi^2 + 2c_1\varpi + c_2. \tag{36}$$

We consider that

$$3\varpi^2 + 2c_1\varpi + c_2 = 0, \tag{37}$$

and it has two real roots, given as $\varpi_1 = (-c_1 + \sqrt{\Delta})/3$ and $\varpi_2 = (-c_1 - \sqrt{\Delta})/3$, where $\Delta = c_1^2 - 3c_2$. Next, we get the following lemma from [50]. □

Lemma 2. *For polynomial (34), the following conclusions are given:*

(i) If $c_3 < 0$, (34) has at least one positive root.

(ii) If $c_3 \geq 0$ and $\Delta < 0$, (34) has no real root.

(iii) If $c_3 \geq 0$ and $\Delta > 0$ and if and only if $\varpi_1 = (-c_1 + \sqrt{\Delta})/3 > 0$ and $g(\varpi_1) \leq 0$, (34) has real roots.

Assume that $g(\varpi) = 0$ has positive real roots; therefore, we can suppose that (34) has $k\,(1 \leq k \leq 3)$ positive real roots, denoted as ϖ_1, ϖ_2, and ϖ_3. Moreover, (33) has positive real roots $\omega_k = \sqrt{\varpi_k}$. From (31), we can get that

$$\cos(\omega\tau) = \frac{(b_2 - a_1b_1)\omega^4 + (a_1b_3 + a_3b_1 - a_2b_2)\omega^2 - a_3b_3}{b_2^2\omega^2 + (b_3 - b_1\omega^2)^2}. \tag{38}$$

In addition, we get the corresponding $\tau_k^{(n)} > 0$ such that (33) has pure imaginary $\lambda = i\omega_k$, where

$$\tau_k^{(n)} = \frac{1}{\omega_k}\left\{\arccos\left(\frac{(b_2 - a_1b_1)\omega_k^4 + (a_1b_3 + a_3b_1 - a_2b_2)\omega_k^2 - a_3b_3}{b_2^2\omega_k^2 + \left(b_3 - b_1\omega_k^2\right)^2}\right) + 2n\pi\right\}, \tag{39}$$

in which $k = 1, 2, 3$, $n = 0, 1, 2, \ldots$

Define

$$\tau^* = \min_{k\in[1,2,3]}\left\{\tau_k^{(0)}\right\}. \tag{40}$$

Differentiating the two sides of (15) with respect to τ, it follows that

$$\begin{aligned}&\left(3\lambda^2 + 2a_1\lambda + a_2\right)\frac{d\lambda}{d\tau} + (2b_1\lambda + b_2)e^{-\lambda\tau}\frac{d\lambda}{d\tau}\\ &-\left(b_1\lambda^2 + b_2\lambda + b_3\right)e^{-\lambda\tau}\left(\lambda + \tau\frac{d\lambda}{d\tau}\right) = 0,\end{aligned} \tag{41}$$

and therefore,

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1}_{\lambda=i\omega_k} &= \frac{(a_2 - 3\omega_k^2) + 2a_1\omega_k i}{\left(a_2\omega_k^2 - \omega_k^4\right) + \left(a_1\omega_k^3 - a_3\omega_k\right)i}\\ &+ \frac{2b_1\omega_k i + b_2}{-b_2\omega_k^2 + \left(b_3\omega_k - b_1\omega_k^3\right)i} - \frac{\tau}{\omega_k i}.\end{aligned} \tag{42}$$

Then,

$$\begin{aligned}&\left(\frac{d(\mathrm{Res}(\lambda))}{d\tau}\right)^{-1}_{\lambda=i\omega_k}\\ &= \frac{(a_2 - 3\omega_k^2)\left(a_2\omega_k^2 - \omega_k^4\right) + 2a_1\omega_k\left(a_1\omega_k^3 - a_3\omega_k\right)}{\left(a_2\omega_k^2 - \omega_k^4\right) + \left(a_1\omega_k^3 - a_3\omega_k\right)}\\ &+ \frac{2b_1\omega_k\left(b_3\omega_k - b_1\omega_k^3\right) - b_2^2\omega_k^2}{b_2^2\omega_k^4 + \left(b_3\omega_k - b_1\omega_k^3\right)^2}.\end{aligned} \tag{43}$$

From (31), we have

$$\left(\omega^3 - a_2\omega\right)^2 + \left(a_1\omega - a_3\right)^2 = b_2^2\omega^2 + \left(b_1\omega^2 - b_3\right)^2. \tag{44}$$

Hence,

$$\begin{aligned}\left(\left(\frac{d(\mathrm{Res}(\lambda))}{d\tau}\right)\right)^{-1}_{\lambda=i\omega_k} &= \frac{3\varpi_k^3 + 2c_1\varpi_k^2 + c_2\varpi_k}{\omega_k^2\left[b_2^2\omega_k^2 + \left(b_1\omega_k^2 - b_3\right)^2\right]}\\ &= \frac{\omega_k g'(\varpi_k)}{\omega_k^2\left[b_2^2\omega_k^2 + \left(b_1\omega_k^2 - b_3\right)^2\right]}.\end{aligned} \tag{45}$$

Since $\omega_k > 0$, this is enough to demonstrate that $\mathrm{Re}(d\lambda(\tau)/d\tau)|_{\tau=\tau_k^{(n)}}$ and $g'(\varpi_k)$ have the same sign. Combining Lemma 2 with (45), we have the following conclusions.

Theorem 2. *If $R_0 > 1$, the following results hold:*

(i) If $c_3 \geq 0$ and $\Delta \leq 0$, then the epidemic equilibrium $E^* = (x^*, y^*, v^*)$ is locally asymptotically stable.

(ii) If $c_3 \geq 0$ or $c_3 < 0$ and $\Delta > 0$, then the epidemic equilibrium $E^* = (x^*, y^*, v^*)$ is asymptotically stable when $\tau \in [0, \tau^*)$ and unstable when $\tau > \tau^*$.

(iii) If the conditions of (ii) are all satisfied and $g'(\varpi_k) \neq 0$, then model (1) undergoes a Hopf bifurcation at E^* when $\tau > \tau_k^{(n)}$ $(n = 0, 1, 2, \ldots)$.

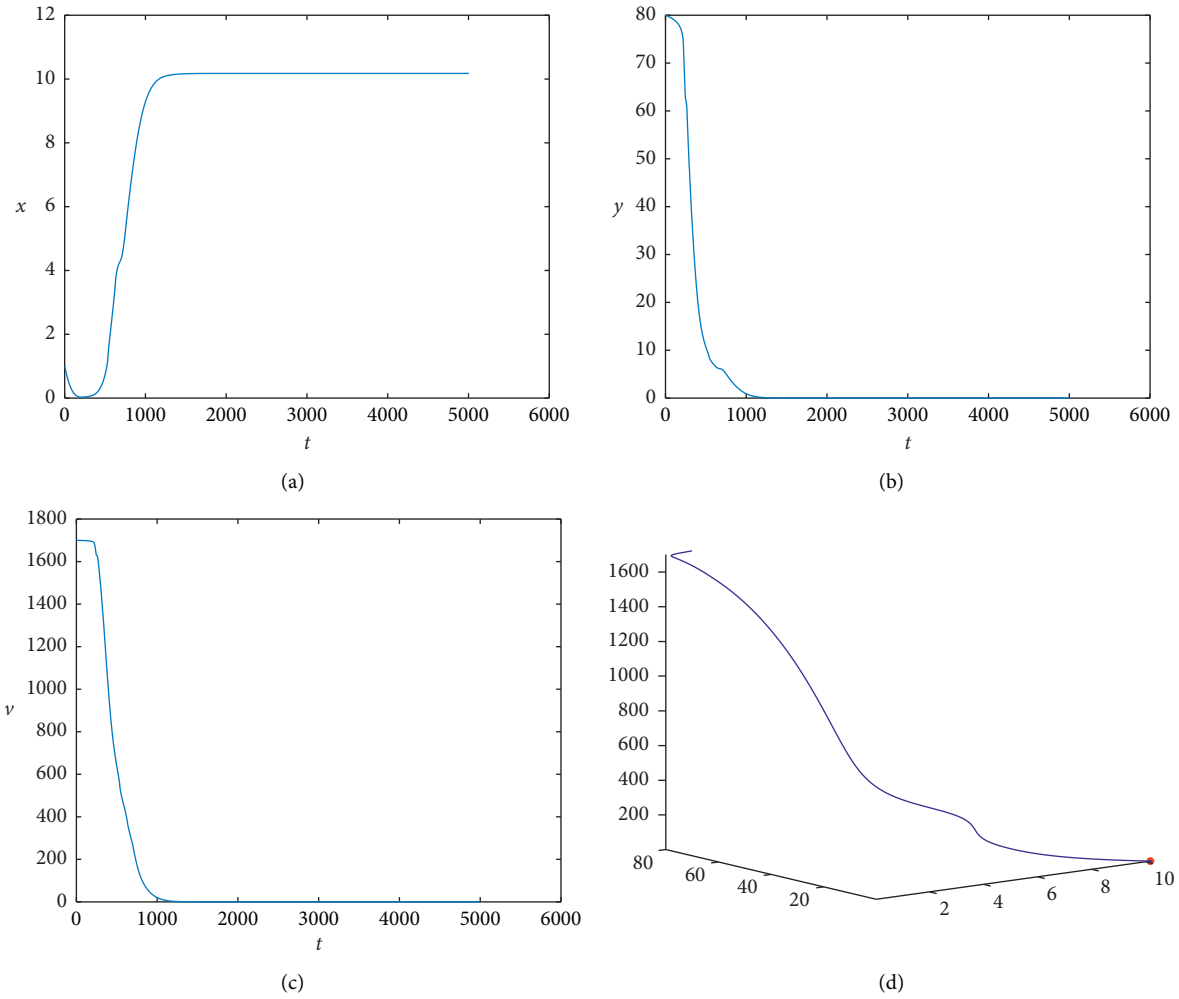


FIGURE 1: Illustration of basic behavior of solutions of system (4) with initial condition I_3, where $\mathscr{R} = 0.8548 < 1$: (a) time series of $x(t)$, (b) time series of $y(t)$, (c) time series of $v(t)$, and (d) phase trajectories of $x(t)$, $y(t)$, and $v(t)$.

4. Numerical Simulations

In this section, we give some numerical simulations to validate our main results in Section 3. The basic parameters are set as follows [51]: $s = 2, r = 10, T = 10, d = 0.02, \beta = 0.000027, \alpha = 0.000024, c = 0.001, \delta = 0.002, \eta = 0.002, p = 0.5, k = 10$, and $u = 0.5$. Direct calculations with Maple 14 show that $\mathscr{R} = 0.8548 < 1$ and $E_0 = (10.1765, 0, 0)$. Figure 1 shows that virus-free equilibrium E_0 of the system is stable.

In the following, we change T to 100, and direct calculations show system (4) has two equilibria, i.e., $E_0 = (10.1765, 0, 0)$ and $E_1 = (11.9048, 88.1959, 1763.9171)$ ($\mathscr{R} = 8.4 > 1$). We easily get

$$\begin{aligned} a_3 &= 0.3396, \\ b_3 &= 1.8997, \\ g(0) = c_3 &= a_3^2 - b_3^2 = -3.4937 < 0. \end{aligned} \tag{46}$$

Then, equation (31) has one positive root $u = 3.165$, equation (28) has one positive root $\omega_0 = 1.779$, and the Hopf bifurcation value is $\tau_0 = 0.5304$. First, let $\tau = 0.52 < \tau_0$ and select three different initial values $I_1 = (1, 0.01, 1700)$, $I_2 = (1, 80, 0.01)$, and $I_3 = (1, 80, 1700)$, respectively. Numerical simulations show that the solutions of system converge to the same equilibrium, respectively (see Figures 2, 3, and 4). In the biological sense, tiny presence of infected cells or virus can lead to the disease transmission. Next, let $\tau = 0.54 > \tau_0$; Figure 5 shows that periodic

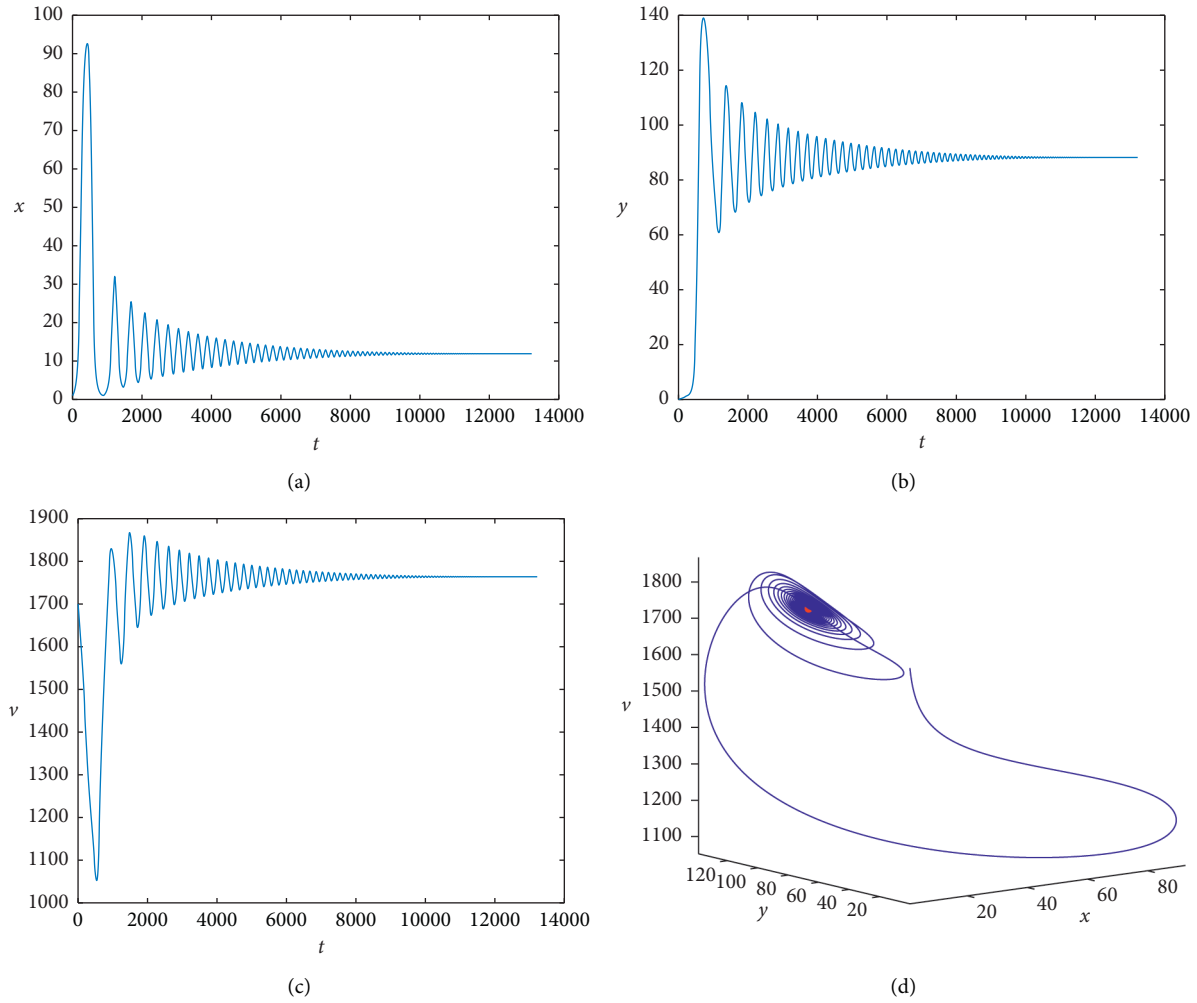


Figure 2: Illustration of basic behavior of solutions of system (4) with $\tau = 0.52$, where $\mathscr{R} = 8.4 > 1$ (the initial condition is (1, 0.01, 1700)): (a) time series of $x(t)$, (b) time series of $y(t)$, (c) time series of $v(t)$, and (d) phase trajectories of $x(t)$, $y(t)$, and $v(t)$.

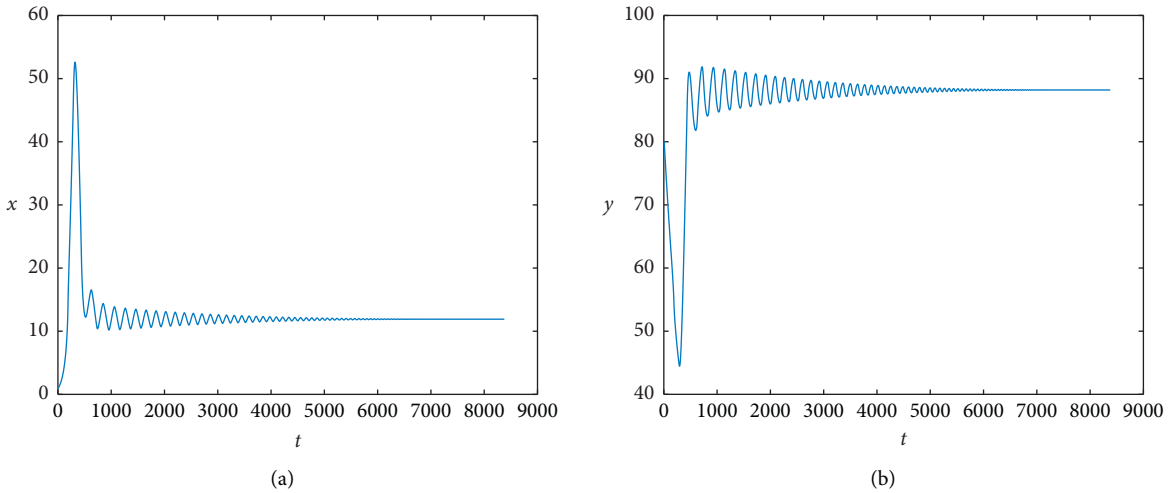
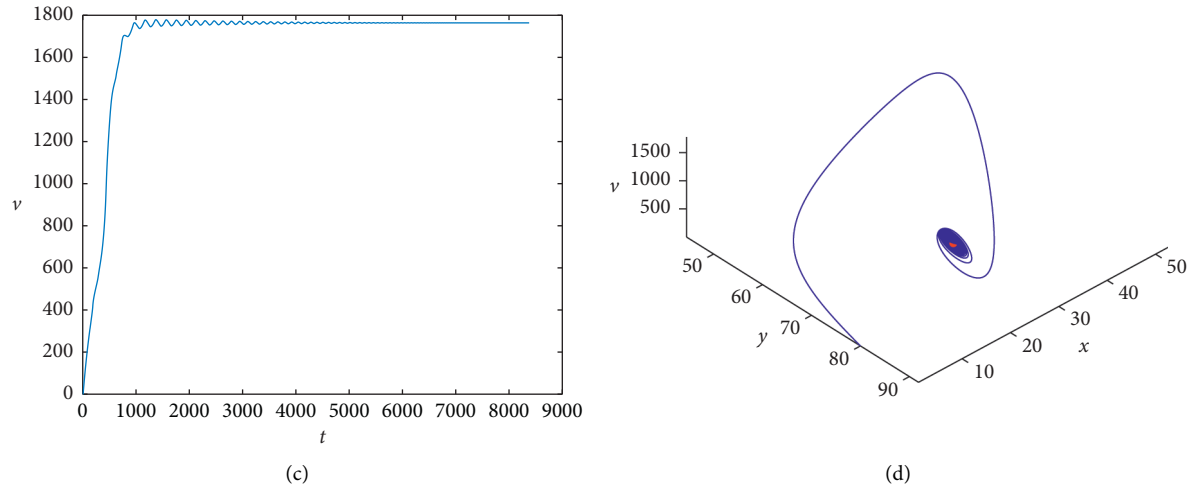
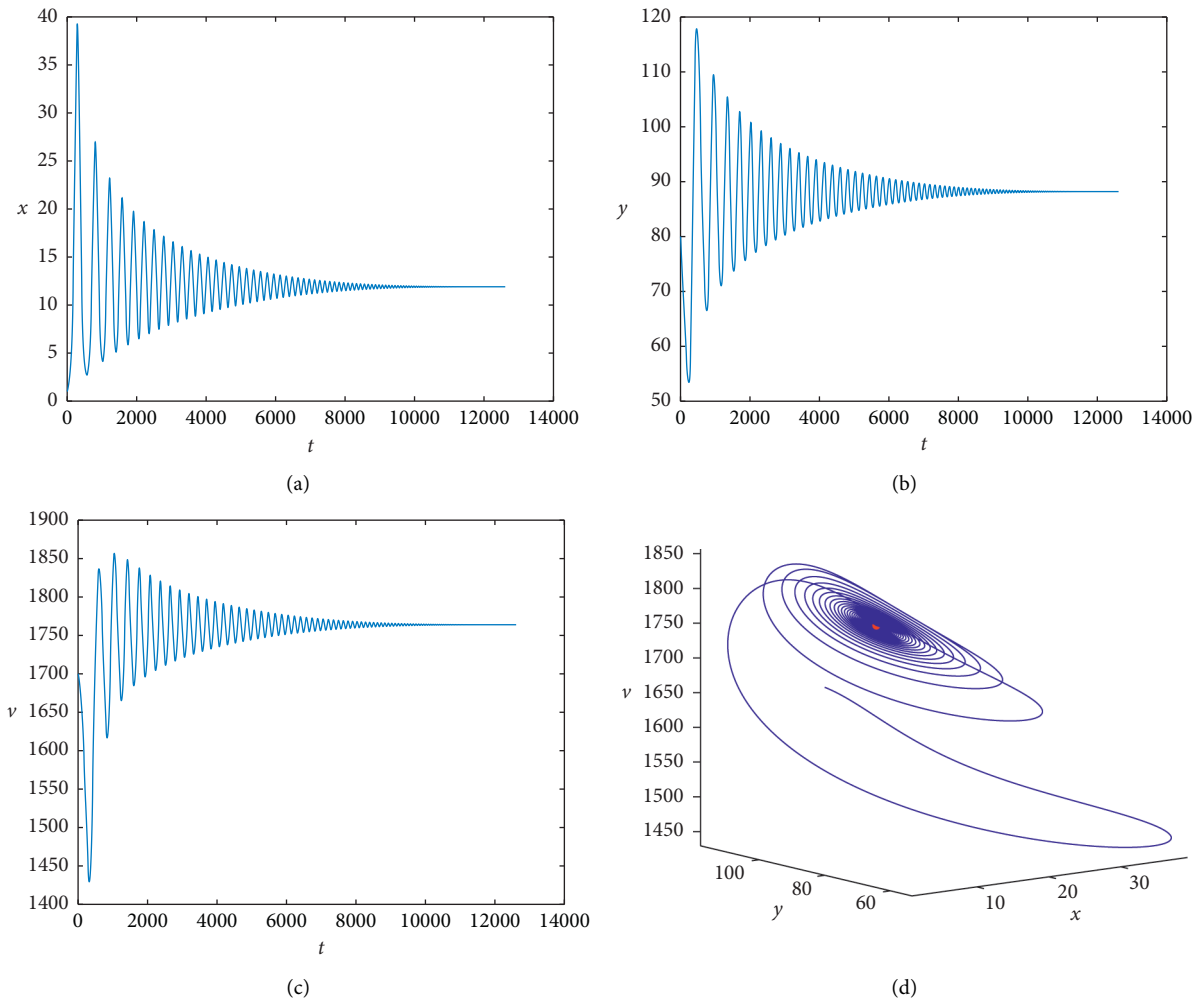


Figure 3: Continued.



(c) (d)

Figure 3: Illustration of basic behavior of solutions of system (4) with $\tau = 0.52$, where $\mathscr{R} = 8.4 > 1$ (the initial condition is (1, 80, 0.01)): (a) time series of $x(t)$, (b) time series of $y(t)$, (c) time series of $v(t)$, and (d) phase trajectories of $x(t)$, $y(t)$, and $v(t)$.



(a) (b)

(c) (d)

Figure 4: Illustration of basic behavior of solutions of system (4) with $\tau = 0.52 < \tau_0$, where $\mathscr{R} = 8.4 > 1$ (the initial condition is (1, 80, 1700)): (a) time series of $x(t)$, (b) time series of $y(t)$, (c) time series of $v(t)$, and (d) phase trajectories of $x(t)$, $y(t)$, and $v(t)$.

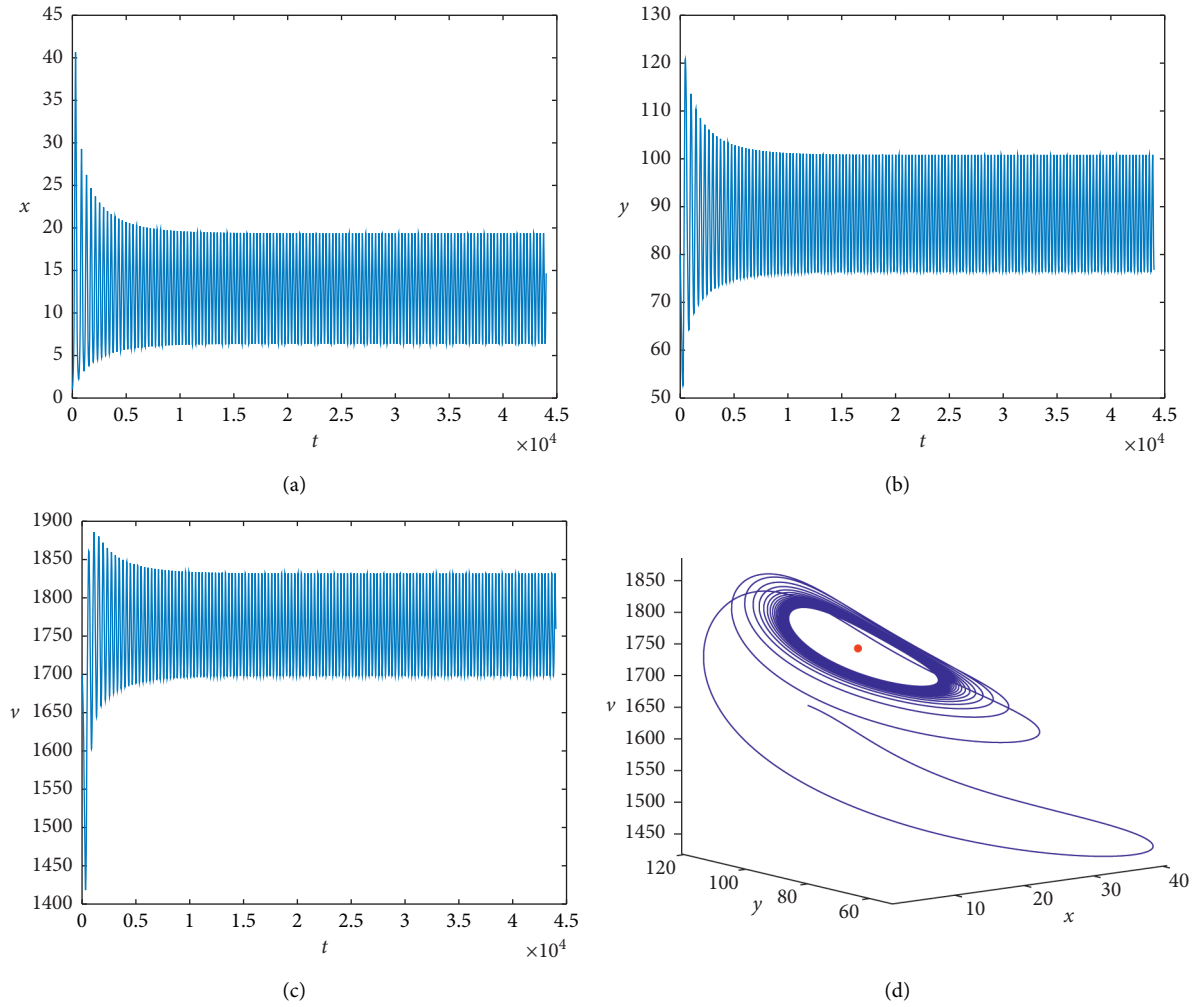


FIGURE 5: Illustration of basic behavior of solutions of system (4) with $\tau = 0.54 > \tau_0$, where $\mathscr{R} = 8.4 > 1$ (the initial condition is (1, 80, 1700)): (a) time series of $x(t)$, (b) time series of $y(t)$, (c) time series of $v(t)$, and (d) phase trajectories of $x(t)$, $y(t)$, and $v(t)$.

oscillations occur for $\tau > \tau_0$. Then, system (4) undergoes a Hopf bifurcation at E^* when $\tau = \tau_0$.

5. Conclusion

In this paper, we improved a delayed HIV virus dynamic model by introducing cell-to-cell transmission and apoptosis of bystander cells. We derived the basic reproductive number $R_0 < 1$, and based on the basic reproductive number, the stability of the equilibria of the system was investigated. The mathematical analysis showed that if $R_0 < 1$, then the disease-free equilibrium of system (4) is globally asymptotically stable, and for $R_0 > 1$, the system can produce Hopf bifurcation with the delay changing. In biology, HIV cannot successfully invade healthy cells and will be cleared by the immune system finally if $R_0 < 1$, and if $R_0 > 1$, uninfected cells, infected cells, and free virus can coexist as periodic oscillations under certain conditions.

However, it is very necessary to consider antiretroviral therapy in model (4), since it can make the model more realistic, and many scholars have noticed this topic and achieved excellent results, for example, Wang et al. [52–54] have studied the virus dynamics model with antiretroviral therapy. Their research shows that antiretroviral therapy can increase the number of uninfected T cells and decrease the number of infectious virions and is very effective for the treatment of AIDS patients. In present model, we do not consider this factor, and we will leave this for future research.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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