Hindawi
International Journal of Differential Equations
Volume 2018, Article ID 9818372, 7 pages
https://doi.org/10.1155/2018/9818372

Research Article

Qualitative Analysis of a Generalized Virus Dynamics Model with Both Modes of Transmission and Distributed Delays

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Received 11 August 2017; Revised 14 December 2017; Accepted 18 December 2017; Published 1 February 2018

Academic Editor: Samir H. Saker

We propose a generalized virus dynamics model with distributed delays and both modes of transmission, one by virus-to-cell infection and the other by cell-to-cell transfer. In the proposed model, the distributed delays describe (i) the time needed for infected cells to produce new virions and (ii) the time necessary for the newly produced virions to become mature and infectious. In addition, the infection transmission process is modeled by general incidence functions for both modes. Furthermore, the qualitative analysis of the model is rigorously established and many known viral infection models with discrete and distributed delays are extended and improved.

1. Introduction

Viruses are microscopic organisms that need to penetrate into a cell of their host to duplicate and multiply. Many human infections and diseases are caused by viruses such as the human immunodeficiency virus (HIV) that is responsible for acquired immunodeficiency syndrome (AIDS), Ebola that can cause an often fatal illness called Ebola hemorrhagic fever, and the hepatitis B virus (HBV) that can lead to chronic infection, cirrhosis, or liver cancer.

In viral dynamics, infection processes and virus production are not instantaneous. In reality, there are two kinds of delays: one in cell infection and the other in virus production. In the literature, these delays are modeled by discrete time delays [1–6], by finite distributed delays [7–9], and by infinite distributed delays [9–12]. The delay in cell infection can be modeled by an explicit class of latently infected cells (see, e.g., [13–15]).

On the other hand, viruses can spread by two fundamental modes, one by virus-to-cell infection through the extracellular space and the other by cell-to-cell transfer involving direct cell-to-cell contact [16–19]. For these reasons, we propose the following generalized virus dynamics model with both modes of transmission and distributed delays:

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - f(x(t), y(t), v(t))\, v(t) \\
&\quad - g(x(t), y(t))\, y(t), \\
\dot{y}(t) &= \int_0^\infty h_1(\tau) \\
&\quad \cdot e^{-\alpha_1 \tau} \left[f(x(t-\tau), y(t-\tau), v(t-\tau))\, v(t-\tau) \right. \\
&\quad \left. + g(x(t-\tau), y(t-\tau))\, y(t-\tau) \right] d\tau - ay(t), \\
\dot{v}(t) &= k \int_0^\infty h_2(\tau)\, e^{-\alpha_2 \tau} y(t-\tau)\, d\tau - \mu v(t),
\end{aligned} \tag{1}$$

where $x(t)$, $y(t)$, and $v(t)$ are the concentrations of uninfected cells, infected cells, and free virus particles at time t, respectively. The uninfected cells are produced at rate λ, die at rate dx, and become infected either by free virus at rate $f(x, y, v)v$ or by direct contact with an infected cell at rate $g(x, y)y$. Hence, the term $f(x, y, v)v + g(x, y)y$ denotes

the total infection rate of uninfected cells. The parameters a and μ are, respectively, the death rates of infected cells and free virus. k is the production rate of free virus by an infected cell. In this proposed model, we assume that the virus or infected cell contacts an uninfected target cell at time $t-\tau$, and the cell becomes infected at time t, where τ is a random variable taken from a probability distribution $h_1(\tau)$. The term $e^{-\alpha_1\tau}$ represents the probability of surviving from time $t-\tau$ to time t, where α_1 is the death rate for infected but not yet virus-producing cells. Similarly, we assume that the time necessary for the newly produced virions to become mature and infectious is a random variable with a probability distribution $h_2(\tau)$. The term $e^{-\alpha_2\tau}$ denotes the probability of surviving the immature virions during the delay period, where $1/\alpha_2$ is the average life time of an immature virus. Therefore, the integral $\int_0^\infty h_2(\tau)e^{-\alpha_2\tau}y(t-\tau)d\tau$ describes the mature viral particles produced at time t.

As in [20], the incidence functions $f(x,y,v)$ and $g(x,y)$ for the two modes are continuously differentiable and satisfy the following hypotheses:

- (H_0) $g(0,y)=0$, for all $y\geq 0$; $(\partial g/\partial x)(x,y)\geq 0$ (or $g(x,y)$ is a strictly monotone increasing function with respect to x when $f\equiv 0$) and $(\partial g/\partial y)(x,y)\leq 0$, for all $x\geq 0$ and $y\geq 0$.
- (H_1) $f(0,y,v)=0$, for all $y\geq 0$ and $v\geq 0$.
- (H_2) $f(x,y,v)$ is a strictly monotone increasing function with respect to x (or $(\partial f/\partial x)(x,v,y)\geq 0$ when $g(x,y)$ is a strictly monotone increasing function with respect to x), for any fixed $y\geq 0$ and $v\geq 0$.
- (H_3) $f(x,y,v)$ is a monotone decreasing function with respect to y and v.

Biologically, the four hypotheses are reasonable and consistent with the reality. For more details on the biological significance of these four hypotheses, we refer the reader to the works [20–22]. Further, the general incidence functions $f(x,y,v)$ and $g(x,y)$ include various types of incidence rates existing in the literature.

The probability distribution functions $h_1(\tau)$ and $h_2(\tau)$ are assumed to satisfy $h_i(\tau)\geq 0$ and $\int_0^\infty h_i(\tau)d\tau=1$ for $i=1,2$. When $h_1(\tau)=\delta(\tau-\tau_1)$ and $h_2(\tau)=\delta(\tau-\tau_2)$, where $\delta(\cdot)$ is the Dirac delta function, system (1) becomes a model with two discrete time delays τ_1 and τ_2 which is the generalization of the models presented in [2–6]. When $f(x,y,v)=\beta_1 x$ and $g(x,y)=0$, where β_1 is the virus-to-cell infection rate, we get the HIV infection model with distributed intracellular delays investigated by Xu [11]. On the other hand, the model proposed by Lai and Zou [23] is a special case of our model (1) when $f(x,y,v)=\beta_1 x$, $g(x,y)=\beta_2 x$, and $h_2(\tau)=\delta(\tau)$, where β_2 is the cell-to-cell transmission rate. It is important to note that the model studied by Nelson and Perelson in [10] is a particular case of [23].

The main objective of this work is to investigate the dynamical behavior of system (1). For this end, we start with the existence, the positivity, and boundedness of solutions, which implies that our model is well posed. After that, we determine the basic reproduction number and steady states of the model. The global stability of the disease-free equilibrium and the chronic infection equilibrium is established in Sections 3 and 4 by constructing appropriate Lyapunov functionals. An application of our results is presented in Section 5. Finally, the conclusion is summarized in Section 6.

2. Well-Posedness and Equilibria

For biological reasons, we suppose that the initial conditions of system (1) satisfy

$$\begin{aligned} x(\theta)&=\phi_1(\theta)\geq 0,\\ y(\theta)&=\phi_2(\theta)\geq 0,\\ v(\theta)&=\phi_3(\theta)\geq 0,\\ &\theta\in(-\infty,0]. \end{aligned} \tag{2}$$

Define the Banach space for fading memory type as follows:

$$\begin{aligned} C_\alpha=\Big\{&\varphi\in C\left((-\infty,0],\mathbb{R}_+^3\right):\varphi(\theta)\\ &\cdot e^{\alpha\theta}\text{ is uniformly continuous on }(-\infty,0],\ \|\varphi\|\\ &=\sup_{\theta\leq 0}|\varphi(\theta)|e^{\alpha\theta}<\infty\Big\}, \end{aligned} \tag{3}$$

where α is a positive constant and $\mathbb{R}_+^3=\{(x_1,x_2,x_3):x_i\geq 0,\ i=1,2,3\}$.

Theorem 1. *For any initial condition $\phi=(\phi_1,\phi_2,\phi_3)\in C_\alpha$ satisfying (2), system (1) has a unique solution on $[0,+\infty)$. Furthermore, this solution is nonnegative and bounded for all $t\geq 0$.*

Proof. By the fundamental theory of functional differential equations [24–26], system (1) with initial condition $\phi\in C_\alpha$ has a unique local solution on $(0,T_{\max})$, where $T_{\max}$ is the maximal existence time for solution of system (1).

First, we prove that $x(t)>0$ for all $t\in(0,T_{\max})$. In fact, supposing the contrary, let $t_1>0$ be the first time such that $x(t_1)=0$ and $\dot{x}(t_1)\leq 0$. From the first equation of system (1), we have $\dot{x}(t_1)=\lambda>0$ which is a contradiction. Then $x(t)>0$ for all $t\in(0,T_{\max})$.

From the second and third equations of system (1), we get

$$\begin{aligned} y(t)&=\phi_2(0)e^{-at}+\int_0^t e^{-a(t-s)}\int_0^\infty h_1(\tau)\\ &\cdot e^{-\alpha_1\tau}\left[f\left(x(s-\tau),y(s-\tau),v(s-\tau)\right)v(s-\tau)\right.\\ &\left.+g\left(x(s-\tau),y(s-\tau)\right)y(s-\tau)\right]d\tau\,ds,\\ v(t)&=\phi_3(0)e^{-\mu t}+k\int_0^t e^{-\mu(t-s)}\int_0^\infty h_2(\tau)e^{-\alpha_2\tau}y(s\\ &-\tau)\,d\tau\,ds, \end{aligned} \tag{4}$$

which implies that $y(t)$ and $v(t)$ are nonnegative for all $t\in(0,T_{\max})$.

Now, we prove the boundedness of the solutions. From the first equation of (1), we have $\dot{x}(t) \leq \lambda - dx(t)$ which implies that

$$\limsup_{t\to+\infty} x(t) \leq \frac{\lambda}{d}. \tag{5}$$

Then $x(t)$ is bounded. Let

$$T(t) = y(t) + \int_0^{\infty} h_1(\tau)\, e^{-\alpha_1\tau} x(t-\tau)\, d\tau. \tag{6}$$

Since $x(t)$ is bounded and $\int_0^{\infty} h_1(\tau)d\tau = 1$, the integral in $T(t)$ is well defined and differentiable with respect to t. Hence,

$$\begin{aligned}\frac{dT(t)}{dt} &= \lambda \int_0^{\infty} h_1(\tau)\, e^{-\alpha_1\tau} d\tau \\ &\quad - d\int_0^{\infty} h_1(\tau)\, e^{-\alpha_1\tau} x(t-\tau)\, d\tau - ay(t) \\ &\leq \lambda\eta_1 - \delta T(t),\end{aligned} \tag{7}$$

where $\delta = \min\{a, d\}$ and

$$\eta_i = \int_0^{\infty} h_i(\tau)\, e^{-\alpha_i\tau} d\tau, \quad i = 1, 2. \tag{8}$$

Thus, $T(t) \leq M := \max\{T(0), \lambda\eta_1/\delta\}$, which implies that $y(t)$ is bounded.

It remains to prove that $v(t)$ is bounded. By third equation of system (1) and the boundedness of $y(t)$, we deduce that

$$\dot{v}(t) \leq kM\eta_2 - \mu v(t). \tag{9}$$

Then $v(t) \leq \max\{v(0), kM\eta_2/\mu\}$. Therefore, $v(t)$ is also bounded. We have proved that all variables of system (1) are bounded which implies that $T_{\max} = +\infty$ and the solution exists globally. □

If in addition to (2) we assume that $\phi_i(0) > 0$ for all $i = 1, 2, 3$, we easily obtain the following result.

Remark 2. When $\phi = (\phi_1, \phi_2, \phi_3) \in C_\alpha$ satisfying (2) with $\phi_i(0) > 0$ $(i = 1, 2, 3)$, all solution of (1) with initial condition ϕ is positive for all $t \geq 0$.

2.1. Equilibria. Obviously, system (1) has always one disease-free equilibrium of the form $E_f(\lambda/d, 0, 0)$. Therefore, the basic reproduction R_0 of system (1) can be defined by

$$R_0 = \frac{k\eta_1\eta_2 f(\lambda/d, 0, 0) + \mu\eta_1 g(\lambda/d, 0)}{a\mu}. \tag{10}$$

As in [20], R_0 can be rewritten as $R_0 = R_{01} + R_{02}$, where $R_{01} = k\eta_1\eta_2 f(\lambda/d, 0, 0)/a\mu$ is the basic reproduction number corresponding to virus-to-cell infection mode and $R_{02} = \eta_1 g(\lambda/d, 0)/a$ is the basic reproduction number corresponding to cell-to-cell transmission mode.

Theorem 3.

(i) *If $R_0 \leq 1$, then system (1) has a unique disease-free equilibrium of the form $E_f(\lambda/d, 0, 0)$.*

(ii) *If $R_0 > 1$, the disease-free equilibrium is still present and system (1) has a unique chronic infection equilibrium of the form $E^*(x^*, y^*, v^*)$ with $x^* \in (0, \lambda/d)$, $y^* > 0$, and $v^* > 0$.*

Proof. It is clear that $E_f(\lambda/d, 0, 0)$ is the unique steady state of system (1) when $R_0 \leq 1$. To find the other equilibria, we resolve the following system:

$$\begin{aligned}\lambda - dx - f(x, y, v)\, v - g(x, y)\, y &= 0, \\ \eta_1\left(f(x, y, v)\, v + g(x, y)\, y\right) - ay &= 0, \\ k\eta_2 y - \mu v &= 0.\end{aligned} \tag{11}$$

From (11), we obtain the equation

$$\begin{aligned}&k\eta_1\eta_2 f\left(x, \frac{\eta_1(\lambda - dx)}{a}, \frac{k\eta_1\eta_2(\lambda - dx)}{a\mu}\right) \\ &\quad + \mu\eta_1 g\left(x, \frac{\eta_1(\lambda - dx)}{a}\right) = a\mu.\end{aligned} \tag{12}$$

We have $y = (\eta_1(\lambda - dx))/a \geq 0$, which implies that $x \leq \lambda/d$. Thus, there is no biological equilibrium when $x > \lambda/d$.

Define the function ψ_1 on the interval $[0, \lambda/d]$ by

$$\begin{aligned}\psi_1(x) &= k\eta_1\eta_2 f\left(x, \frac{\eta_1(\lambda - dx)}{a}, \frac{k\eta_1\eta_2(\lambda - dx)}{a\mu}\right) \\ &\quad + \mu\eta_1 g\left(x, \frac{\eta_1(\lambda - dx)}{a}\right) - a\mu.\end{aligned} \tag{13}$$

Clearly, $\psi_1(0) = -a\mu < 0$, $\psi_1(\lambda/d) = a\mu(R_0 - 1)$, and

$$\begin{aligned}\psi_1'(x) &= k\eta_1\eta_2\left(\frac{\partial f}{\partial x} - \frac{d\eta_1}{a}\frac{\partial f}{\partial y} - \frac{kd\eta_1\eta_2}{a\mu}\frac{\partial f}{\partial v}\right) \\ &\quad + \mu\eta_1\left(\frac{\partial g}{\partial x} - \frac{d\eta_1}{a}\frac{\partial g}{\partial y}\right) > 0.\end{aligned} \tag{14}$$

Hence, if $R_0 > 1$, there exists another biologically meaningful equilibrium $E^*(x^*, y^*, v^*)$ with $x^* \in (0, \lambda/d)$, $y^* > 0$, and $v^* > 0$. This completes the proof. □

3. Stability of the Disease-Free Equilibrium

In this section, we establish the stability of the disease-free equilibrium.

Theorem 4. *The disease-free equilibrium E_f is globally asymptotically stable when $R_0 \leq 1$ and becomes unstable when $R_0 > 1$.*

Proof. To study the global stability of E_f, we consider the following Lyapunov functional:

$$V(t) = \frac{1}{\eta_1} y(t) + \frac{f(\lambda/d, 0, 0)}{\mu} v(t) + \frac{1}{\eta_1} \int_0^\infty h_1(\tau) \cdot e^{-\alpha_1 \tau} \int_{t-\tau}^t \left(f(x(s), y(s), v(s)) v(s) + g(x(s), y(s)) y(s) \right) ds\, d\tau + \frac{kf(\lambda/d, 0, 0)}{\mu} \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} \int_{t-\tau}^t y(s)\, ds\, d\tau. \tag{15}$$

Calculating the time derivative of V along the positive solution of system (1), we get

$$\dot{V}(t)\Big|_{(1)} = \left(f(x, y, v) - f\left(\frac{\lambda}{d}, 0, 0\right) \right) v + \frac{a}{\eta_1} y \left(\frac{k\eta_1\eta_2 f(\lambda/d, 0, 0) + \mu\eta_1 g(x, y)}{a\mu} - 1 \right). \tag{16}$$

We have $\limsup_{t\to\infty} x(t) \le \lambda/d$, which implies that all omega limit points satisfy $x(t) \le \lambda/d$. Thus, it is sufficient to consider solutions for which $x(t) \le \lambda/d$. By (10) and (H_1)–(H_3), we obtain

$$\dot{V}(t)\Big|_{(1)} \le \left(f(x, 0, 0) - f\left(\frac{\lambda}{d}, 0, 0\right) \right) v + \frac{a}{\eta_1} (R_0 - 1) y \le \frac{a}{\eta_1} (R_0 - 1) y. \tag{17}$$

Therefore, $\dot{V}|_{(1)} \le 0$ when $R_0 \le 1$. In addition, it is not hard to verify that the largest compact invariant set in $\{(x, y, v) \mid \dot{V} = 0\}$ is the singleton $\{E_f\}$. From LaSalle invariance principle [27], we deduce that the disease-free equilibrium E_f is globally asymptotically stable when $R_0 \le 1$.

On the other hand, the characteristic equation at E_f is given by

$$(\xi + d) \left[(\xi + \mu) \left(\xi + a - \overline{\eta}_1(\xi)\, g\left(\frac{\lambda}{d}, 0\right) \right) - \overline{\eta}_1(\xi)\, \overline{\eta}_2(\xi)\, kf\left(\frac{\lambda}{a}, 0, 0\right) \right] = 0, \tag{18}$$

where $\overline{\eta}_i(\xi) = \int_0^\infty h_i(\tau) e^{-(\xi+\alpha_i)\tau} d\tau$. Define a function ψ_2 on $[0, +\infty)$ by

$$\psi_2(\xi) = (\xi + \mu) \left(\xi + a - \overline{\eta}_1(\xi)\, g\left(\frac{\lambda}{d}, 0\right) \right) - \overline{\eta}_2(\xi)\, \overline{\eta}_2(\xi)\, kf\left(\frac{\lambda}{d}, 0, 0\right). \tag{19}$$

We have $\psi_2(0) = a\mu(1 - R_0) < 0$ and $\lim_{\xi\to+\infty} \psi_2(\xi) = +\infty$, which implies that ψ_2 has a positive real root. Consequently, E_f is unstable for $R_0 > 1$. □

4. Stability of the Chronic Infection Equilibrium

In this section, we investigate the global stability of the chronic infection equilibrium E^* by assuming that $R_0 > 1$ and the functions f and g satisfy, for all $x, y, v > 0$, the following hypothesis:

$$\left(1 - \frac{f(x, y, v)}{f(x, y^*, v^*)}\right) \left(\frac{f(x, y^*, v^*)}{f(x, y, v)} - \frac{v}{v^*}\right) \le 0, \quad \left(1 - \frac{f(x^*, y^*, v^*)\, g(x, y)}{f(x, y^*, v^*)\, g(x^*, y^*)}\right) \cdot \left(\frac{f(x, y^*, v^*)\, g(x^*, y^*)}{f(x^*, y^*, v^*)\, g(x, y)} - \frac{y}{y^*}\right) \le 0. \tag{H_4}$$

Therefore, we get the following result.

Theorem 5. *Assume that (H_4) holds. If $R_0 > 1$, then the chronic infection equilibrium E^* is globally asymptotically stable.*

Proof. We define a Lyapunov functional as follows:

$$W(t) = x(t) - x^* - \int_{x^*}^{x(t)} \frac{f(x^*, y^*, v^*)}{f(s, y^*, v^*)} ds + \frac{1}{\eta_1} \cdot y^* H\left(\frac{y(t)}{y^*}\right) + \frac{f(x^*, y^*, v^*)\, v^*}{k\eta_2 y^*} v^* H\left(\frac{v(t)}{v^*}\right) + \frac{1}{\eta_1} f(x^*, y^*, v^*)\, v^* \int_0^\infty h_1(\tau) \cdot e^{-\alpha_1\tau} \int_{t-\tau}^t H\left(\frac{f(x(s), y(s), v(s))\, v(s)}{f(x^*, y^*, v^*)\, v^*}\right) ds\, d\tau + \frac{1}{\eta_1} g(x^*, y^*)\, y^* \int_0^\infty h_1(\tau) \cdot e^{-\alpha_1\tau} \int_{t-\tau}^t H\left(\frac{g(x(s), y(s))\, y(s)}{g(x^*, y^*)\, y^*}\right) ds\, d\tau + \frac{1}{\eta_2} \cdot f(x^*, y^*, v^*)\, v^* \int_0^\infty h_2(\tau) \cdot e^{-\alpha_2\tau} \int_{t-\tau}^t H\left(\frac{y(s)}{y^*}\right) ds\, d\tau, \tag{20}$$

where $H(x) = x - 1 - \ln x$, $x > 0$. Clearly, $H : (0, +\infty) \to [0, +\infty)$ attains its strict global minimum at $x = 1$ and $H(1) = 0$. Hence, $H(x) \ge 0$. Further, the functional W is nonnegative.

In order to simplify the presentation, we will use the following notations: $z = z(t)$ and $z_\tau = z(t - \tau)$ for any $z \in \{x, y, v\}$. The time derivative of W along the positive solution of system (1) is given by

$$\dot{W}(t)\Big|_{(1)} = \left(1 - \frac{f(x^*, y^*, v^*)}{f(x, y^*, v^*)}\right) \dot{x} + \frac{1}{\eta_1} \left(1 - \frac{y^*}{y}\right) \dot{y} + \frac{f(x^*, y^*, v^*)\, v^*}{k\eta_2 y^*} \left(1 - \frac{v^*}{v}\right) \dot{v} + \frac{1}{\eta_1} f(x^*, y^*, v^*)$$

$$\cdot v^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left(H\left(\frac{f(x,y,v)v}{f(x^*,y^*,v^*)v^*} \right) - H\left(\frac{f(x_\tau,y_\tau,v_\tau)v_\tau}{f(x^*,y^*,v^*)v^*} \right) \right) d\tau + \frac{1}{\eta_1} g(x^*,y^*)$$
$$\cdot y^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left(H\left(\frac{g(x,y)y}{g(x^*,y^*)y^*} \right) - H\left(\frac{g(x_\tau,y_\tau)y_\tau}{g(x^*,y^*)y^*} \right) \right) d\tau + \frac{1}{\eta_2} f(x^*,y^*,v^*)$$
$$\cdot v^* \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} \left(H\left(\frac{y}{y^*} \right) - H\left(\frac{y_\tau}{y^*} \right) \right) d\tau. \tag{21}$$

Applying $\lambda = dx^* + f(x^*,y^*,v^*)v^* + g(x^*,y^*)y^* = dx^* + (a/\eta_1)y^*$ and $k\eta_2 y^* = \mu v^*$, we obtain

$$\begin{aligned}
\dot{W}(t)\big|_{(1)} &= dx^* \left(1 - \frac{x}{x^*}\right)\left(1 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)}\right) \\
&+ \frac{1}{\eta_1} f(x^*,y^*,v^*) v^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[3 \right. \\
&- \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} + \frac{f(x,y,v)v}{f(x,y^*,v^*)v^*} - \frac{v}{v^*} \\
&- \frac{f(x_\tau,y_\tau,v_\tau)v_\tau y^*}{f(x^*,y^*,v^*)v^* y} \\
&\left. + \ln\left(\frac{f(x_\tau,y_\tau,v_\tau)v_\tau}{f(x,y,v)v} \right) \right] d\tau + \frac{1}{\eta_1} g(x^*,y^*) \\
&\cdot y^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[2 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} \right. \\
&+ \frac{f(x^*,y^*,v^*) g(x,y) y}{f(x,y^*,v^*) g(x^*,y^*) y^*} - \frac{y}{y^*} \\
&\left. + \frac{g(x_\tau,y_\tau)y_\tau}{g(x^*,y^*)y} + \ln\left(\frac{g(x_\tau,y_\tau)y_\tau}{g(x,y)y} \right) \right] d\tau \\
&- \frac{1}{\eta_2} f(x^*,y^*,v^*) v^* \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} \left[\frac{v^* y_\tau}{v y^*} \right. \\
&\left. - \ln\left(\frac{y_\tau}{y} \right) \right] d\tau.
\end{aligned} \tag{22}$$

Hence,

$$\begin{aligned}
\dot{W}(t)\big|_{(1)} &= dx^* \left(1 - \frac{x}{x^*}\right)\left(1 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)}\right) \\
&+ f(x^*,y^*,v^*) v^* \left(-1 - \frac{v}{v^*} + \frac{f(x,y^*,v^*)}{f(x,y,v)} \right. \\
&\left. + \frac{f(x,y,v)v}{f(x,y^*,v^*)v^*} \right) + g(x^*,y^*) y^* \left(-1 - \frac{y}{y^*} \right. \\
&+ \frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} \\
&\left. + \frac{f(x^*,y^*,v^*) g(x,y) y}{f(x,y^*,v^*) g(x^*,y^*) y^*} \right) - \frac{1}{\eta_1} f(x^*,y^*,v^*) \\
&\cdot v^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[H\left(\frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} \right) \right. \\
&+ H\left(\frac{f(x_\tau,y_\tau,v_\tau)v_\tau y^*}{f(x^*,y^*,v^*)v^* y} \right) \\
&\left. + H\left(\frac{f(x,y^*,v^*)}{f(x,y,v)} \right) \right] d\tau - \frac{1}{\eta_1} g(x^*,y^*) \\
&\cdot y^* \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[H\left(\frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)} \right) \right. \\
&+ H\left(\frac{g(x_\tau,y_\tau)y_\tau}{g(x^*,y^*)y} \right) \\
&\left. + H\left(\frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} \right) \right] d\tau - \frac{1}{\eta_2} \\
&\cdot f(x^*,y^*,v^*) v^* \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} H\left(\frac{v^* y_\tau}{v y^*} \right) d\tau.
\end{aligned} \tag{23}$$

Since the function $f(x,y,v)$ is strictly monotonically increasing with respect to x, we have

$$\left(1 - \frac{x}{x^*}\right)\left(1 - \frac{f(x^*,y^*,v^*)}{f(x,y^*,v^*)}\right) \le 0. \tag{24}$$

From (H_4), we have

$$\begin{aligned}
&-1 - \frac{v}{v^*} + \frac{f(x,y^*,v^*)}{f(x,y,v)} + \frac{v}{v^*}\frac{f(x,y,v)}{f(x,y^*,v^*)} \\
&\quad = \left(1 - \frac{f(x,y,v)}{f(x,y^*,v^*)}\right)\left(\frac{f(x,y^*,v^*)}{f(x,y,v)} - \frac{v}{v^*}\right) \le 0, \\
&-1 - \frac{y}{y^*} + \frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} \\
&\quad + \frac{f(x^*,y^*,v^*) g(x,y) y}{f(x,y^*,v^*) g(x^*,y^*) y^*} \\
&\quad = \left(1 - \frac{f(x^*,y^*,v^*) g(x,y)}{f(x,y^*,v^*) g(x^*,y^*)}\right) \\
&\quad \cdot \left(\frac{f(x,y^*,v^*) g(x^*,y^*)}{f(x^*,y^*,v^*) g(x,y)} - \frac{y}{y^*}\right) \le 0.
\end{aligned} \tag{25}$$

Since $H(x) \ge 0$ for $x > 0$, we have $\dot{W}|_{(1)} \le 0$ with equality if and only if $x = x^*$, $y = y^*$, and $v = v^*$. It follows from LaSalle invariance principle that E^* is globally asymptotically stable. □

5. Application

In this section, we consider the following HIV infection model with distributed delays:

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \frac{\beta_1 x(t) v(t)}{1+\gamma_1 v(t)} - \frac{\beta_2 x(t) y(t)}{1+\gamma_2 y(t)},\\
\dot{y}(t) &= \int_0^\infty h_1(\tau) e^{-\alpha_1 \tau} \left[\frac{\beta_1 x(t-\tau) v(t-\tau)}{1+\gamma_1 v(t-\tau)} \right.\\
&\quad \left. + \frac{\beta_2 x(t-\tau) y(t-\tau)}{1+\gamma_2 y(t-\tau)} \right] d\tau - ay(t),\\
\dot{v}(t) &= k \int_0^\infty h_2(\tau) e^{-\alpha_2 \tau} y(t-\tau)\, d\tau - \mu v(t),
\end{aligned} \tag{26}$$

where γ_1 and γ_2 are nonnegative constants that measure the saturation effect. The parameters β_1 and β_2 are the virus-to-cell infection rate and the cell-to-cell transmission rate, respectively. The other parameters have the same biological meanings as in model (1). Further, system (26) is a special case of (1) with $f(x, y, v) = \beta_1 x/(1+\gamma_1 v)$ and $g(x, y) = \beta_2 x/(1+\gamma_2 y)$. Notice that the HIV infection model presented by Lai and Zou [23] is a particular case of our model (26), it suffices to take $\gamma_1 = \gamma_2 = 0$ and $h_2(\tau) = \delta(\tau)$. In addition, system (26) always has a disease-free equilibrium $E_f(\lambda/d, 0, 0)$ and a unique chronic infection equilibrium $E^*(x^*, y^*, v^*)$ when $R_0 = \beta_1 \lambda k \eta_1 \eta_2 / da\mu + \beta_2 \lambda \eta_1 / da > 1$.

On the other hand, it is easy to see that the hypotheses (H_0)–(H_3) are satisfied. Furthermore, we have

$$\begin{aligned}
&\left(1 - \frac{f(x, y, v)}{f(x, y^*, v^*)}\right)\left(\frac{f(x, y^*, v^*)}{f(x, y, v)} - \frac{v}{v^*}\right)\\
&\quad = \frac{-\delta_1 (v - v^*)^2}{v^* (1+\delta_1 v^*)(1+\delta_1 v)} \le 0,
\end{aligned} \tag{27}$$

$$\begin{aligned}
&\left(1 - \frac{f(x^*, y^*, v^*) g(x, y)}{f(x, y^*, v^*) g(x^*, y^*)}\right)\\
&\quad \cdot \left(\frac{f(x, y^*, v^*) g(x^*, y^*)}{f(x^*, y^*, v^*) g(x, y)} - \frac{y}{y^*}\right)\\
&\quad = \frac{-\delta_2 (y - y^*)^2}{y^* (1+\delta_1 y^*)(1+\delta_1 y)} \le 0.
\end{aligned} \tag{28}$$

Consequently, the hypothesis (H_4) is satisfied. By applying Theorems 4 and 5, we get the following result.

Corollary 6.

(i) *If $R_0 \le 1$, then the disease-free equilibrium E_f of system (26) is globally asymptotically stable.*

(ii) *If $R_0 > 1$, then the disease-free equilibrium E_f becomes unstable and the chronic infection equilibrium E^* of (26) is globally asymptotically stable.*

6. Conclusion

In this work, we have proposed a mathematical model that describes the dynamics of viral infections, such as HIV and HBV, and takes into account the two modes of transmission and the two kinds of delays, one in cell infection and the other in virus production. The transmission process for both modes is modeled by two general incidence functions that include many types of incidence rates existing in the literature. Further, the two delays are modeled by infinite distributed delays. Under some assumptions on the general incidence functions, we have proved that the global stability of the proposed model is fully determined by one threshold parameter that is the basic reproduction number R_0. In addition, the viral infection models with infinite distributed delays and the corresponding results presented in several previous studies are extended and generalized.

In this study, we have neglected the mobility of cells and virus. Motivated by the works in [28–32], we will consider this mobility in our future project in order to improve our present model.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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