Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

MBE, 17(5): 4527–4543.
DOI: 10.3934/mbe.2020250
Received: 03 March 2020
Accepted: 16 June 2020
Published: 29 June 2020

Research article

Global stability for a class of HIV virus-to-cell dynamical model with Beddington-DeAngelis functional response and distributed time delay

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Abstract: A HIV virus-to-cell dynamical model with distributed delay and Beddington-DeAngelis functional response is proposed in this paper. Using the characteristic equations and analytical means, the principle reproduction number R_0 on the local stability of infection-free and chronic-infection equilibria is established. Furthermore, by constructing suitable Lyapunov functionals and using LaSalle invariance principle, we show that if $R_0 \leq 1$ the infection-free equilibrium is globally asymptotically stable, while if $R_0 > 1$ the chronic-infection equilibrium is globally asymptotically stable. Numerical simulations are presented to illustrate the theoretical results. Comparing the effects between discrete and distributed delays on the stability of HIV virus-to-cell dynamical models, we can see that they could be same and different even opposite.

Keywords: distributed delay; principle reproduction number; Beddington-DeAngelis functional response; Lyapunov functional; globally asymptotical stability

1. Introduction

In the past decades, the research on virus dynamical models has attracted great many medical scientists and bio-mathematicians for its important potential applications on prediction and prevention and control of many fatal diseases, e.g., Ebola, Zika, measles, schistosomiasis (see, e.g., [1–7]) etc. As well known, AIDS is a serious infectious disease caused by HIV viruses which choose the $CD4^+T$ lymphocytes in the human immune system as the mainly attacking target. HIV viruses increasingly destroy the $CD4^+T$ lymphocytes in large quantities till depriving of efficacy of immune system in human body, at the same time, turn the infected $CD4^+T$ lymphocytes into HIV viruses. Nowak and Bangham [8] initiatively applied a parasite model proposed by Anderson and May [9] to investigate

the virus-to-cell dynamics as follows:

$$\begin{cases} \dfrac{dx}{dt} = s - dx(t) - \beta x(t)v(t), \\ \dfrac{dy}{dt} = \beta x(t)v(t) - py(t), \\ \dfrac{dz}{dt} = ky(t) - uv(t). \end{cases} \tag{1.1}$$

Here x, y, v represent the concentration of uninfected CD4$^+$T cells, infected CD4$^+$T cells and HIV viruses at time t, respectively. s ($s > 0$) is the rate of newborn CD4$^+$T cells, d, p, u are the death rates of uninfected CD4$^+$T cells, infected CD4$^+$T cells and removed rate of HIV virus particles from the system respectively. The constant β is the infection (or contact) rate between uninfected CD4$^+$T cells and HIV viruses. Criteria on the globally asymptotical stability of infection-free and chronic-infection equilibria were established. Recently, a lots of significant works on the HIV dynamical models were achieved based on model (1.1). The primary issues are: computation of the principle reproduction number R_0 under different incidence functions (e.g., bilinear, saturation, Beddington-DeAngelis, nonlinear incidence, etc.) with cell-to-cell transmission and virus-to-cell transmission (or mixed transmission), stability of infection-free equilibrium, extinction of infection, existence and stability of chronic-infection equilibrium, persistence of infection (see, e.g., [10–15] and references cited therein) etc.

However, as we know that the conversion of uninfected (or infected) CD4$^+$T cells into infected CD4$^+$T cells (or HIV viruses) will often not respond immediately to change, but rather will do so after a time lag. Therefore, many authors introduced the time delays into HIV dynamic models (see, e.g., [16–18]). Meanwhile, Beddington-DeAngelis functional response is more realistic to characterize the dynamic evolution process of susceptible cells and viruses (e.g., [19–22]). Huang et al. [20], Nakata [21] introduced Beddington-DeAngelis functional response and discrete delay into the above model (1) as follows

$$\begin{cases} \dfrac{dx}{dt} = s - dx(t) - \dfrac{\beta x(t)v(t)}{1 + ax(t) + bv(t)}, \\ \dfrac{dy}{dt} = \dfrac{e^{-p\tau}\beta x(t-\tau)v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)} - py(t), \\ \dfrac{dz}{dt} = ky(t) - uv(t). \end{cases} \tag{1.2}$$

Here function $\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}$ denotes the Beddington-DeAngelis infection rate between uninfected CD4$^+$T cells x and HIV viruses v, a, b are positive constants, $\tau > 0$ represents the requisite time for conversion of uninfected CD4$^+$T cells x into infected CD4$^+$T cells y. Many important results about the globally asymptotical stability of infection-free and chronic-infection equilibria were obtained. Furthermore, it has been proven that distributed delay is more proper to model the long-term infectious process than

discrete delay (e.g., [23–25]). Xu [23] introduced distributed delay into model (1.1) as follows

$$\begin{cases} \dfrac{dx}{dt} = s - dx(t) - \beta x(t)v(t), \\ \dfrac{dy}{dt} = \beta \displaystyle\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau - ay(t), \\ \dfrac{dz}{dt} = k \displaystyle\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau - uv(t). \end{cases} \tag{1.3}$$

Criteria based on principle reproduction number R_0 were obtained on the globally asymptotical stability of infection-free and chronic-infection equilibria. Motivated by the above considerations, in this paper, we incorporate Beddington-DeAngelis functional response and distributed delay into model (1.2) as follows

$$\begin{cases} \dfrac{dx}{dt} = s - dx(t) - \dfrac{\beta x(t)v(t)}{1 + ax(t) + bv(t)}, \\ \dfrac{dy}{dt} = \displaystyle\int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1 + ax(t-\sigma) + bv(t-\sigma)}d\sigma - py(t), \\ \dfrac{dz}{dt} = ky(t) - uv(t). \end{cases} \tag{1.4}$$

The integral term $\int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma$ represents the total quantity of target CD4$^+$T cells x exposed to the HIV viruses v and still survive and convert into infected CD4$^+$T cells y within time intervals $[0, \tau]$. Here, $f(\sigma) : [0, \tau] \to [0, \infty)$ is the distribution function which accounts for the variance of infected cells to become productively infected from individual to individual, assumed to be compact support, $f(\sigma) \geq 0$ and $\int_0^\tau f(\sigma)d\sigma = 1$ (refer to [11]).

The main purpose of this paper is to explore the effect of distributed delay and Beddington-DeAngelis functional response on the dynamical behavior of HIV virus-to-cell dynamical model (1.4). Furthermore, by introducing the principle reproduction number R_0 to discuss the locally and globally asymptotical stability of free-infection equilibrium E_0 and chronic-infection equilibrium E^* by constructing proper Lyapunov functionals and LaSalle invariance principle.

The organization of this paper is as follows. In the second section, we discuss the positivity and boundedness of solutions of system (1.4). In the section 3, criteria are obtained on the local stability of infection-free equilibrium E_0 if principle reproduction number $R_0 < 1$, and chronic-infection equilibrium E^* if $R_0 > 1$. In the section 4, we further establish criteria on the globally asymptotical stability of infection-free equilibrium E_0 if $R_0 \leq 1$, and chronic-infection equilibrium E^* if $R_0 > 1$. In the section 5, the theoretical results are illustrated by numerical simulations and discussion. Comparing of effects between discrete delay and distributed delay on the stability with models (1.2) and (1.4), we can see that they would be complete different even opposite if the same values of delay is taken within a proper interval. In the last section, a brief conclusion is presented.

2. Positivity and boundedness of solutions

The initial conditions of model (1.4) are given as

$$x(\theta) = \varphi_1(\theta), \quad y(\theta) = \varphi_2(\theta), \quad v(\theta) = \varphi_3(\theta), \quad \theta \in [-\tau, 0]. \tag{2.1}$$

Where $\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in C([-\tau, 0], R^3_+)$ such that $\varphi_i(\theta) \geq 0 (\tau \leq \theta \leq 0, i = 1, 2, 3)$, and C be the Banach space of continuous functions from $[-\tau, 0]$ to R^3 equipped with the sup-norm.

With respect to the positivity and boundedness of solutions for models (1.4), we have the following result.

Theorem 2.1. *Let $(x(t), y(t), v(t))^T$ be any solution of model (1.4) with initial conditions (2.1), we have that all solutions $(x(t), y(t), v(t))^T$ of model (1.4) are non-negative on $[0, +\infty)$ and ultimately bounded.*

Proof. Assume $x(t)$ is not positive on the maximum existing interval $[0, T)$, then there exists a $t_1 \in [0, T)$ such that $x(t_1) = 0$ and $x(t) > 0$ for all $t \in [0, t_1)$, therefore, we can easily see that $\dot{x}(t_1) \leq 0$. On the other hand, from the first equation of model (1.4), we can see $\dot{x}(t_1) = s > 0$. This leads to a contradiction. Therefore, $x(t)$ is always nonnegative for all $t \in [0, T)$. From the other two equations of model (1.4), we have

$$\begin{aligned} y(t) =& y(0)e^{-dt} + \int_0^t \int_0^\tau f(\sigma) \frac{e^{-d\sigma}\beta x(\theta - \sigma)v(\theta - \sigma)}{1 + ax(\theta - \sigma) + bv(\theta - \sigma)} d\sigma e^{-d(t-\theta)} d\theta \\ v(t) =& v(0)e^{-ut} + \int_0^t k y(\theta) e^{-u(t-\theta)} d\theta. \end{aligned}$$

Therefore, it is easy to see that $y(t)$ and $v(t)$ are all non-negative for all $t \in [0, T)$.

Next, we prove the boundedness of the system, from the first equation of system (1.4) we can obtain

$$\dot{x}(t) = s - dx(t) - \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)} \leq s - dx(t).$$

By comparison theorem, we obtain $\lim_{t \to +\infty} \sup x(t) \leq \frac{s}{d}$, so $x(t)$ is bounded on $[0, T)$. Define

$$F(t) = \int_0^\tau f(\sigma) e^{-d\sigma} x(t - \sigma) d\sigma + y(t),$$

and $\delta = \min\{d, p\}$. We have

$$\begin{aligned} \frac{dF(t)}{dt} =& \int_0^\tau f(\sigma) e^{-d\sigma} [s - dx(t - \sigma) - \frac{\beta x(t - \sigma)v(t - \sigma)}{1 + ax(t - \sigma) + bv(t - \sigma)}] d\sigma \\ &+ \int_0^\tau f(\sigma) \frac{e^{-d\sigma}\beta x(t - \sigma)v(t - \sigma)}{1 + ax(t - \sigma) + bv(t - \sigma)} - py(t) \\ =& s \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma - d \int_0^\tau f(\sigma) e^{-d\sigma} x(t - \sigma) d\sigma - py(t) \\ \leq& s \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma - \delta F(t). \end{aligned} \tag{2.2}$$

This implies that $F(t)$ is bounded, therefore $y(t)$ is bounded too. By the third equation of system (1.4), $v(t)$ is also bounded. Because all solution $(x(t), y(t), v(t))$ of model (1.4) is bounded on $[0, T)$, therefore, we can see that $T = +\infty$. This completes the proof of Theorem 2.1.

3. Local stability of equilibria

In this part, we discuss the local stability of the equilibria of model (1.4). Obviously, there is always a infection-free equilibrium $E_0(s/d, 0, 0)$ for model (1.4). Next, we will analyze the positive chronic-

infection equilibrium $E^* = (x^*, y^*, v^*)$ of model (1.4). Consider the following equations

$$\begin{cases} s - dx^* - \dfrac{\beta x^* v^*}{1 + ax^* + bv^*} = 0, \\ \displaystyle\int_0^\tau f(\sigma) e^{-d\sigma} d\sigma \frac{\beta x^* v^*}{1 + ax^* + bv^*} - py^* = 0, \\ ky^* - uv^* = 0. \end{cases} \tag{3.1}$$

We have

$$x^* = \frac{pu + kbs \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma}{(bkd + \beta k) \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma - apu}, \quad v^* = \frac{k}{pu}(s - dx^*) \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma, \quad y^* = \frac{u}{k} v^*. \tag{3.2}$$

For the positivity of the chronic-infection equilibrium $E^* = (x^*, y^*, v^*)$, we need $x^* > 0$, which means

$$(bkd + \beta k) \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma - apu > 0. \tag{3.3}$$

Denote

$$R_0 = \frac{k\beta s \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma}{pu(d + as)}.$$

when $R_0 > 1$, Eq (3.3) is always true, meanwhile $v^* > 0$ also holds.

First, about the local stability (or un-stability) for infection-free equilibrium E_0 of model (1.4), we have the following result.

Theorem 3.1. *The infection-free equilibrium E_0 of model (1.4) is locally asymptotically stable (or unstable) if $R_0 < 1$ (or $R_0 > 1$).*

Proof. For the infection-free equilibrium E_0, we can obtain the characteristic equation of system (1.4) as follows:

$$(\lambda + d)[(\lambda + p)(\lambda + u) - \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma \frac{k\beta s}{d + as} e^{-\lambda\tau}] = 0.$$

Because of $\lambda = -d < 0$, so the stability of E_0 depends on

$$h(\lambda) = (\lambda + p)(\lambda + u) - \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma \frac{k\beta s}{d + as} e^{-\lambda\tau}.$$

Case 1: $R_0 < 1$, from

$$h(\lambda) = (\lambda + p)(\lambda + u) - \int_0^\tau f(\sigma) e^{-d\sigma} d\sigma \frac{k\beta s}{d + as} e^{-\lambda\tau} = 0,$$

it follows that

$$G(\lambda) = \frac{\int_0^\tau f(\sigma) e^{-d\sigma} d\sigma \frac{k\beta s}{d+as} e^{-\lambda\tau}}{(\lambda + p)(\lambda + u)} = 1.$$

Let $\lambda = x + iy$ $(x, y \in R)$, if $x \geq 0$, we obtain

$$\begin{aligned} 1 =\mid G(\lambda) \mid &= \frac{\mid \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta s}{d+as}e^{-\lambda\tau} \mid}{\mid (\lambda+p)(\lambda+u) \mid} \\ &\leq \frac{\mid \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta s}{d+as}e^{-x\tau} \mid}{\mid (x+p)(x+u) \mid} \\ &\leq \frac{\mid \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta s}{d+as} \mid}{\mid pu \mid} \\ &= \frac{k\beta s\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma}{pu(d+as)} = R_0 < 1, \end{aligned} \tag{3.4}$$

which is a contradiction. Thus, if $R_0 < 1$, then $x < 0$, and hence E_0 is locally asymptotically stable.
Case 2: If $R_0 > 1$, we obtain

$$h(0) = pu - \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta s}{d+as} < 0,$$

and $\lim_{\lambda\to\infty} h(\lambda) = +\infty$. Therefore, $h(\lambda) = 0$ has at least one non-negative root. Hence, if $R_0 > 1$, then E_0 is unstable. This completes the proof of Theorem (3.1).

Next, about the local stability for chronic-infection equilibrium E^* of model (1.4), we have the following result.

Theorem 3.2. *If $R_0 > 1$, then the chronic-infection equilibrium E^* of model (1.4) is locally asymptotically stable.*

Proof. We can obtain that the characteristic equation at the chronic-infection equilibrium E^* as follow:

$$\begin{aligned} &(\lambda + d + \frac{\beta v^*(1+bv^*)}{(1+ax^*+bv^*)^2})[(\lambda+p)(\lambda+u) - \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta x^*(1+ax^*)}{(1+ax^*+bv^*)^2}e^{-\lambda\tau}] \\ &+ \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{\beta v^*(1+bv^*)}{(1+ax^*+bv^*)^2}\frac{k\beta x^*(1+ax^*)}{(1+ax^*+bv^*)^2}e^{-\lambda\tau} = 0. \end{aligned} \tag{3.5}$$

That is

$$(\lambda+p)(\lambda+u) = \frac{(\lambda+d)\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta x^*(1+ax^*)}{(1+ax^*+bv^*)^2}e^{-\lambda\tau}}{\lambda + d + \frac{\beta v^*(1+bv^*)}{(1+ax^*+bv^*)^2}}. \tag{3.6}$$

Let

$$L = (\lambda+p)(\lambda+u), \quad R = \frac{(\lambda+d)\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta x^*(1+ax^*)}{(1+ax^*+bv^*)^2}e^{-\lambda\tau}}{\lambda + d + \frac{\beta v^*(1+bv^*)}{(1+ax^*+bv^*)^2}}.$$

If λ is a root of (3.2) with nonnegative real part, it follows

$$\mid L \mid =\mid (\lambda+p)(\lambda+u) \mid \geq pu.$$

Furthermore, from (3.1), we can have

$$\begin{aligned} \mid R \mid =& \mid \frac{(\lambda+d)\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{k\beta x^*(1+ax^*)}{(1+ax^*+bv^*)^2}e^{-\lambda\tau}}{\lambda+d+\frac{\beta v^*(1+bv^*)}{(1+ax^*+bv^*)^2}} \mid \\ =& \mid \frac{(\lambda+d)\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma k\beta x^*(1+ax^*)e^{-\lambda\tau}}{(\lambda+d)(1+ax^*+bv^*)^2+\beta v^*(1+bv^*)} \mid \\ <& \mid \frac{\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma k\beta x^*(1+ax^*)e^{-\lambda\tau}}{(1+ax^*+bv^*)^2} \mid \\ =& \ pu \mid \frac{\beta x^* v^*(1+ax^*)e^{-\lambda\tau}}{(s-dx^*)(1+ax^*+bv^*)^2} \mid \\ <& \ pu \mid \frac{1+ax^*}{1+ax^*+bv^*} \mid \\ <& \ pu. \end{aligned} \tag{3.7}$$

Consequently, we obtain $\mid L \mid > \mid R \mid$, which leads to a contradiction. Therefore, we can get that (3.5) cannot have any root with positive real part. Hence, the chronic-infection equilibrium E^* is locally asymptotic stable as $R_0 > 1$. This completes the proof of Theorem 3.2.

4. Global stability of equilibria

In this section, we will prove the globally asymptotical stability of infection-free equilibrium E_0 and chronic-infection equilibrium E^* for model (1.4). First for the globally asymptotical stability of E_0, we have the following result.

Theorem 4.1. *The infection-free equilibrium E_0 of model (1.4) is globally asymptotically stable if $R_0 \leq 1$.*

Proof. Define a Lyapunov functional V_1 as follows:

$$V_1(x,y,v) = \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{x_0}{1+ax_0}(\frac{x(t)}{x_0}-1-\ln\frac{x(t)}{x_0})+y(t)+\frac{p}{k}v(t)+U^-(t).$$

Where $x_0 = \frac{s}{d}$, and

$$U^-(t) = \int_0^\tau\int_{t-\sigma}^t f(\sigma)\frac{e^{-d\sigma}\beta x(\xi)v(\xi)}{1+ax(\xi)+bv(\xi)}d\xi d\sigma.$$

Derivative $U^-(t)$ on both sides, we have:

$$\begin{aligned} \frac{dU^-(t)}{dt} &= \int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t)v(t)}{1+ax(t)+bv(t)}d\sigma - \int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma \\ &= \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)} - \int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma. \end{aligned} \tag{4.1}$$

Therefore, we obtain that

$$\begin{aligned}
\frac{dV_1}{dt} &= \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{1}{1+ax_0}(1-\frac{x_0}{x})\dot{x}(t)+\dot{y}(t)+\frac{p}{k}\dot{v}(t)+\frac{dU^-(t)}{dt}\\
&= \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{1}{1+ax_0}(1-\frac{x_0}{x})\Big[s-dx(t)-\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}\Big]\\
&\quad+\int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma-py(t)\\
&\quad+\frac{p}{k}(ky(t)-uv(t))+\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}\\
&\quad-\int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma\\
&= \int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{1}{1+ax_0}(1-\frac{x_0}{x(t)})\Big[dx_0-dx(t)-\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}\Big]\\
&\quad-\frac{pu}{k}v(t)+\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}\\
&= -\frac{d\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma}{x(t)(1+ax_0)}(x(t)-x_0)^2\\
&\quad+\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\frac{1+ax(t)}{1+ax_0}\times\frac{\beta x_0 v(t)}{1+ax(t)+bv(t)}-\frac{pu}{k}\\
&= -\frac{d\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma}{x(t)(1+ax_0)}(x(t)-x_0)^2+\frac{puv(t)}{k}\times\frac{1+ax(t)}{1+ax(t)+bv(t)}(R_0-1)\\
&\quad-\frac{pub}{k(1+ax(t)+bv(t))}v^2(t).
\end{aligned}\tag{4.2}$$

Therefore, when $R_0 \le 1$ we have $\frac{dV_1}{dt} \le 0$. And $\frac{dV_1}{dt} = 0$ if and only if $x = x_0, v = 0$. Let M be the largest invariant set $\{(\phi_1,\phi_2,\phi_3)^T \in R^3_+, \dot{V}_1 = 0\}$, we have $M = \{E_0\}$. It follows from LaSalle invariance principle, when $R_0 \le 1$, then E_0 is globally asymptotically stable. This completes the proof of Theorem 4.1.

Next, about the globally asymptotical stability of $E^* = (x^*, y^*, v^*)$ of system (1.4), we have the following result:

Theorem 4.2. *If $R_0 > 1$, the chronic-infection E^* of model (1.4) is globally asymptotically stable.*

Proof. We define Lyapunov functional V_2 as follows:

$$V_2(x,y,v) = U(t) + py^*U^+(t), \tag{4.3}$$

$$\begin{aligned}
U(t) =&(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)^2\Big[x(t)-x^*-\int_{x^*}^{x(t)}\frac{1+a\theta+bv^*}{1+ax^*+bv^*}\times\frac{x^*}{\theta}d\theta\Big]\\
&+\Big[(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)(y(t)-y^*-y^*\ln\frac{y(t)}{y^*})\Big]\\
&+\Big[(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\frac{p}{k}(v(t)-v^*-v^*\ln\frac{v(t)}{v^*})\Big],
\end{aligned}\tag{4.4}$$

and

$$U^+(t) = \int_0^\tau \int_{t-\sigma}^t f(\sigma)e^{-d\sigma}\Big[(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\frac{\beta x(\xi)v(\xi)}{py^*(1+ax(\xi)+bv(\xi))} - 1 - \ln(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\frac{\beta x(\xi)v(\xi)}{py^*(1+ax(\xi)+bv(\xi))}\Big]d\xi d\sigma. \tag{4.5}$$

We can find that

$$\begin{aligned}\frac{dU^+(t)}{dt} =& \int_0^\tau (\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\frac{f(\sigma)e^{-d\sigma}\beta x(t)v(t)}{py^*(1+ax(t)+bv(t))}d\sigma \\ &- \int_0^\tau (\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\frac{f(\sigma)e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{py^*(1+ax(t-\sigma)+bv(t-\sigma}))d\sigma \\ &+ \int_0^\tau e^{-d\sigma}\ln\Big(\frac{x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}\times\frac{1+ax(t)+bv(t)}{x(t)v(t)}\Big)d\sigma \\ =&\frac{1}{py^*}(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)^2\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)} \\ &- \frac{1}{py^*}(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma \\ &+ \int_0^\tau f(\sigma)e^{-d\sigma}\ln\Big(\frac{x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}\times\frac{1+ax(t)+bv(t)}{x(t)v(t)}\Big)d\sigma.\end{aligned} \tag{4.6}$$

Therefore, we can obtain

$$\begin{aligned}\frac{dV_2}{dt} =&(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)^2(1-\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\times\frac{x^*}{x})\dot{x}(t) \\ &+(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)(1-\frac{y^*}{y})\dot{y}(t) \\ &+(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\frac{p}{k}(1-\frac{v^*}{v(t)})\dot{v}(t)+py^*\frac{dU^+(t)}{dt} \\ =&(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)^2(1-\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\times\frac{x^*}{x})\Big[dx^*-dx(t) \\ &+\frac{\beta x^*v^*}{1+ax^*+bv^*}-\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}\Big] \\ &+(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)(1-\frac{y^*}{y})\Big[\int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma \\ &-py(t)\Big]+(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)\frac{p}{k}(1-\frac{v^*}{v})[ky(t)-uv(t)]+py^*\frac{dU^+(t)}{dt} \\ =&(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma)^2(1-\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\times\frac{x^*}{x})\Big[-d(x(t)-x^*) \\ &+\frac{\beta x^*v^*}{1+ax^*+bv^*}-\frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}\Big]\end{aligned}$$

$$
\begin{aligned}
&+ \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)\Big(1-\frac{y^*}{y(t)}\Big)\Big[\int_0^\tau f(\sigma)\frac{e^{-d\sigma}\beta x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma - py(t)\Big]\\
&+ \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)\frac{p}{k}\Big(1-\frac{v^*}{v(t)}\Big)[ky(t)-uv(t)] + py^*\frac{dU^+(t)}{dt}\\
=&-\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)^2\frac{d(1+bv^*)}{x(t)(1+ax^*+bv^*)}(x(t)-x^*)^2 + \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)py^*\\
&-\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)py^*\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\frac{x^*}{x(t)} + \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)py^*\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\frac{v(t)}{v^*}\\
&-py^*\frac{y^*(1+ax^*+bv^*)}{y(t)x^*v^*}\int_0^\tau f(\sigma)\frac{e^{-d\sigma}x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma + \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)py^*\\
&-\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)py^*\frac{v(t)}{v^*} - \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)py^*\frac{y(t)v^*}{y^*v(t)} + \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)py^*\\
&+py^*\int_0^\tau f(\sigma)e^{-d\sigma}\ln\Big(\frac{x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}\times\frac{1+ax(t)+bv(t)}{x(t)v(t)}\Big)d\sigma\\
=&-\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)^2\frac{d(1+bv^*)}{x(t)(1+ax^*+bv^*)}(x(t)-x^*)^2\\
&+py^*\Big[3\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big) - \Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\frac{x^*}{x(t)}\\
&-\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)\times\frac{y(t)v^*}{y^*v(t)} - \frac{y^*(1+ax^*+bv^*)}{y(t)x^*v^*}\int_0^\tau f(\sigma)\frac{e^{-d\sigma}x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}d\sigma\Big]\\
&+py^*\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)\Big(-\frac{v(t)}{v^*}+\frac{v(t)}{v^*}\frac{1+ax(t)+bv^*}{1+ax(t)+bv(t)}\Big)\\
&+py^*\int_0^\tau f(\sigma)e^{-d\sigma}\ln\Big(\frac{x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}\frac{1+ax(t)+bv(t)}{x(t)v(t)}\Big)d\sigma\\
=&-\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)^2\frac{d(1+bv^*)}{x(t)(1+ax^*+bv^*)}(x(t)-x^*)^2\\
&+py^*\int_0^\tau f(\sigma)e^{-d\sigma}\Big[1-\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\frac{x^*}{x(t)}+\ln\Big(\frac{1+ax(t)+bv^*}{1+ax^*+bv^*}\frac{x^*}{x(t)}\Big)\Big]d\sigma\\
&+py^*\int_0^\tau f(\sigma)e^{-d\sigma}\Big(1-\frac{y(t)v^*}{y^*v(t)}+\ln\frac{y(t)v^*}{y^*v(t)}\Big)d\sigma\\
&+py^*\int_0^\tau f(\sigma)e^{-d\sigma}\Big[1-\frac{y^*(1+ax^*+bv^*)}{y(t)x^*v^*}\times\frac{x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}\\
&\qquad+\ln\Big(\frac{y^*(1+ax^*+bv^*)}{y(t)x^*v^*}\times\frac{x(t-\sigma)v(t-\sigma)}{1+ax(t-\sigma)+bv(t-\sigma)}\Big)\Big]d\sigma\\
&\qquad+py^*\int_0^\tau f(\sigma)e^{-d\sigma}\Big(1-\frac{1+ax(t)+bv(t)}{1+ax(t)+bv^*}+\ln\frac{1+ax(t)+bv(t)}{1+ax(t)+bv^*}\Big)d\sigma\\
&\qquad+py^*\Big(\int_0^\tau f(\sigma)e^{-d\sigma}d\sigma\Big)\Big(-1-\frac{v(t)}{v^*}+\frac{1+ax(t)+bv(t)}{1+ax(t)+bv^*}+\frac{v(t)}{v^*}\frac{1+ax(t)+bv^*}{1+ax(t)+bv(t)}\Big).
\end{aligned}
\tag{4.7}
$$

$$
\tag{4.8}
$$

For any $\eta(t) > 0$, the function

$$H(t) = 1 - \eta(t) + \ln \eta(t)$$

is always non-positive, and $H(t) = 0$ if and only if $\eta(t) = 1$.

Furthermore, we have

$$\begin{aligned} &-1-\frac{v(t)}{v^*}+\frac{1+ax(t)+bv(t)}{1+ax(t)+bv^*}+\frac{v(t)}{v^*}\frac{1+ax(t)+bv^*}{1+ax(t)+bv(t)} \\ =&\frac{-b(1+ax)(v(t)-v^*)^2}{v^*(1+ax+bv)(1+ax+bv^*)}\leq 0. \end{aligned} \tag{4.9}$$

Hence, we can see that $\frac{dV_2}{dt} \leq 0$. And $\frac{dV_2}{dt} = 0$ if and only if $x(t) = x^*, y(t) = y^*, v(t) = v^*$. From the Lyapunov-LaSalle invariance principle, it indicates that when $R_0 > 1$, the chronic-infection equilibrium E^* is globally asymptotically stable. This completes the proof of Theorem 4.2.

5. Numerical simulations and discussion

In this paper, we studied a class of HIV virus-to-cell dynamic model with distributed delay and Beddington-DeAngelis functional response, by analysis methods and constructing proper Lyapunov functionals, threshold criteria of principle reproduction number R_0 for model (1.4) were established. We see that if $R_0 \leq 1$ the infection-free equilibrium $E_0 = (s/d, 0, 0)$ is globally asymptotically stable, while if $R_0 > 1$ the chronic-infection equilibrium $E^* = (x^*, y^*, v^*)$ is globally asymptotically stable. Now, we will use numerical simulations to illustrate our results, for convenience, we take

$$f(\sigma) = \frac{1}{\tau}, \quad 0 \leq \sigma \leq \tau. \tag{5.1}$$

Obviously, we have

$$\int_0^\tau f(\sigma)d\sigma = \int_0^\tau \frac{1}{\tau}d\sigma = 1.$$

We take the values of parameters in both model (1.2) and (1.4) as in the following Table 1.

Table 1. Values of parameters.

models	a	b	d	s	β	p	k	u
(1.2) and (1.4)	0.6	0.8	0.1	0.8	0.8	0.5	0.3	0.2

We have the following results for model (1.4):

Case 1, we take $\tau = 40$ with other values of parameters in Table 1, we can easily get $R_0 = 0.8124 < 1$. From the Theorem 4.1, we can see that the infection-free equilibrium $E_0 = (8, 0, 0)$ of model (1.4) is globally asymptotically stable (see Figure 1(a) and (b)).

Case 2, we take $\tau = 0.2$ with other values of parameters in Table 1, we can easily obtain $R_0 = 3.2775 > 1$. From the Theorem 4.2 we, can see that the chronic-infection equilibrium $E^* = (1.4405, 1.2989, 1.9483)$ of model (1.4) is globally asymptotically stable (see Figure 1(c) and (d)).

Furthermore, we will compare the effects between discrete delay and distributed delay on the stability of the virus-to-cell dynamical models, i.e., models (1.2) and (1.4). According to [20], the

principle reproduction number of model (1.2) is

$$R_0^* = \frac{k\beta s e^{-p\tau}}{pu(d+as)}.$$

The principle reproduction number of model (1.4) is

$$R_0 = \frac{k\beta s(1-e^{-d\tau})}{\tau dpu(d+as)}.$$

In the case of values of parameters in Table 1, we have the following conclusions:

$$\begin{cases} R_0^* \geq 1, R_0 > 1, if & 0 < \tau \leq 2.3941. \\ R_0^* < 1, R_0 \geq 1, if & 2.3942 < \tau \leq 31.715. \\ R_0^* < 1, R_0 < 1, if & \tau > 31.716. \end{cases} \tag{5.2}$$

By calculation, we can see that the two equilibria of model (1.2) are

$$E_0^* = (s/d, 0, 0), \bar{E}^* = (\frac{sbk + pue^{p\tau}}{k\beta + bdk - apue^{p\tau}}, \frac{s\beta ke^{-p\tau}(1-\frac{1}{R_0^*})}{p(k\beta + bdk - apue^{p\tau})}, \frac{s\beta k^2 e^{-p\tau}(1-\frac{1}{R_0^*})}{pu(k\beta + bdk - apue^{p\tau})}).$$

And

$$E_0 = (s/d, 0, 0), E^* = (x^* = \frac{dpu + (1-e^{-d\tau})kbs}{\tau(1-e^{-d\tau})(bkd + \beta k) - a\tau dpu}, y^* = \frac{u}{k}v^*, v^* = \frac{k}{\tau dpu}(s - dx^*)(1-e^{-d\tau}))$$

are the infection-free and chronic-infection equilibria of system (1.4), respectively.

We take the values of parameters as in the Table 1 for both models (1.2) and (1.4). If the delay $\tau = 0.2$ is taken for both models (1.2) and (1.4), we can see $R_0^* = 2.9953 > 1$, by [20], the chronic-infection equilibrium $\bar{E}^* = (1.5303, 1.1708, 1.7562)$ of model (1.2) is globally asymptotically stable (see Figure 2(a),(b)). And $R_0 = 3.2775 > 1$, the chronic-infection equilibrium $\bar{E}^* = (1.4405, 1.2989, 1.9483)$ of model (1.4) is globally asymptotically stable (see Figure 1(c),(d)). If delay $\tau = 2.8$ is taken for both models (1.2) and (1.4), we can see $R_0^* = 0.8163 < 1$, by [20] the infection-free equilibrium $E_0^* = (8, 0, 0)$ of model (1.2) is globally asymptotically stable (see Figure 2(e) and (f)). While $R_0 = 2.8873 > 1$, the chronic-infection equilibrium $E^* = (1.5709, 1.1215, 1.6822)$ of model (1.4) is globally asymptotically stable (see Figure 1(e),(f)). If delay $\tau = 40$ is taken for both models (1.2) and (1.4), we can see $R_0^* = 6.8231 \times 10^{-9} < 1$, by [20] the infection-free equilibrium $E_0^* = (8, 0, 0)$ of model (1.2) is globally asymptotically stable (see Figure 2(c) and (d)). While $R_0 = 0.8124 > 1$, the infection-free equilibrium $E_0^* = (8, 0, 0)$ of model (1.2) is globally asymptotically stable (see Figure 1(a),(b)).

The details of above numerical simulations for both models (1.2) and (1.4) are as follows:

Table 2. Numerical simulations of the models (1.2) and (1.4).

τ	R_0^*	E_0^*	$\bar{E}^*$	R_0	E_0	E^*
0.2	2.9953	–	GAS (Figure 2(a), (b))	3.2775	–	GAS (Figure 1(c), (d))
2.8	0.8163	GAS (Figure 2(e), (f))	–	2.8873	–	GAS (Figure 1(e), (f))
40	6.231×10^{-9}	GAS (Figure 2(c), (d))	–	0.8124	GAS (Figure 1(a), (b))	–

[1] Here, GAS=globally asymptotically stable.

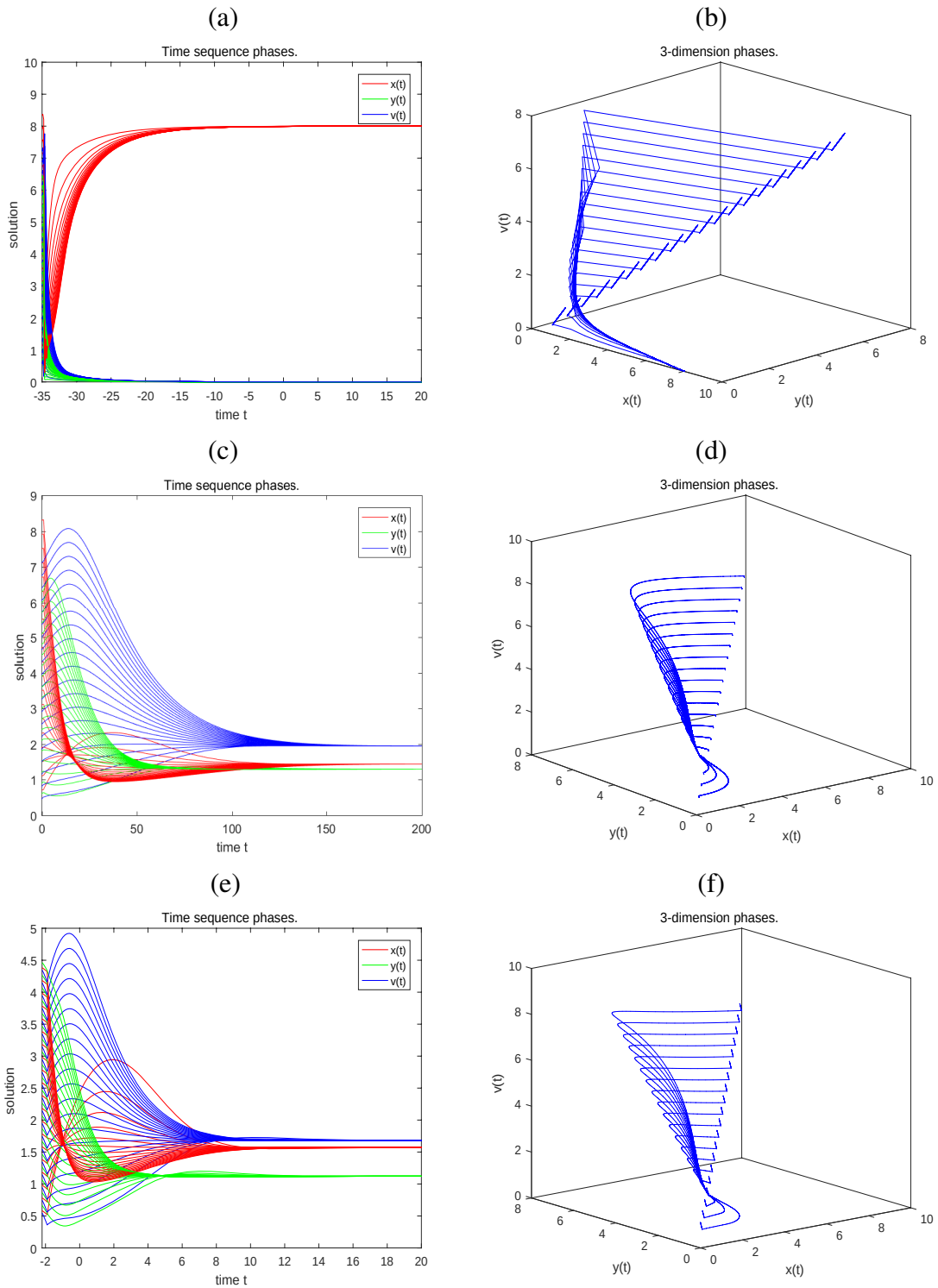

Figure 1. (a), (b): Time series and 3-dimension phases of solutions $(x(t), y(t), v(t))$ of system (1.4) in case 1 with initial functions: $(x(\theta), y(\theta), v(\theta)) = (0.3 + 0.1 * sin(\theta) + 0.4 * k, 0.3 + 0.2 * sin(\theta) + 0.3 * k, 0.1 + 0.3 * sin(\theta) + 0.35 * k)$, $k = 1, 2, \cdots, 20$, for all $\theta \in [-40, 0]$, respectively. (c), (d): Time series and 3-dimension phases of solutions $(x(t), y(t), v(t))$ of system (1.4) in case 2 with initial functions: $(x(\theta), y(\theta), v(\theta)) = (0.3 + 0.1 * sin(\theta) + 0.4 * k, 0.3 + 0.2 * sin(\theta) + 0.3 * k, 0.1 + 0.3 * sin(\theta) + 0.3 * k)$, $k = 1, 2, \cdots, 20$, for all $\theta \in [-0.2, 0]$, respectively. (e), (f): Time series and 3-dimension phases of solutions $(x(t), y(t), v(t))$ of system (1.4) with initial functions: $(x(\theta), y(\theta), v(\theta)) = (0.3 + 0.1 * sin(\theta) + 0.2 * k, 0.3 + 0.2 * sin(\theta) + 0.2 * k, 0.1 + 0.3 * sin(\theta) + 0.2 * k)$, $k = 1, 2, \cdots, 20$, for all $\theta \in [-2.8, 0]$, respectively.

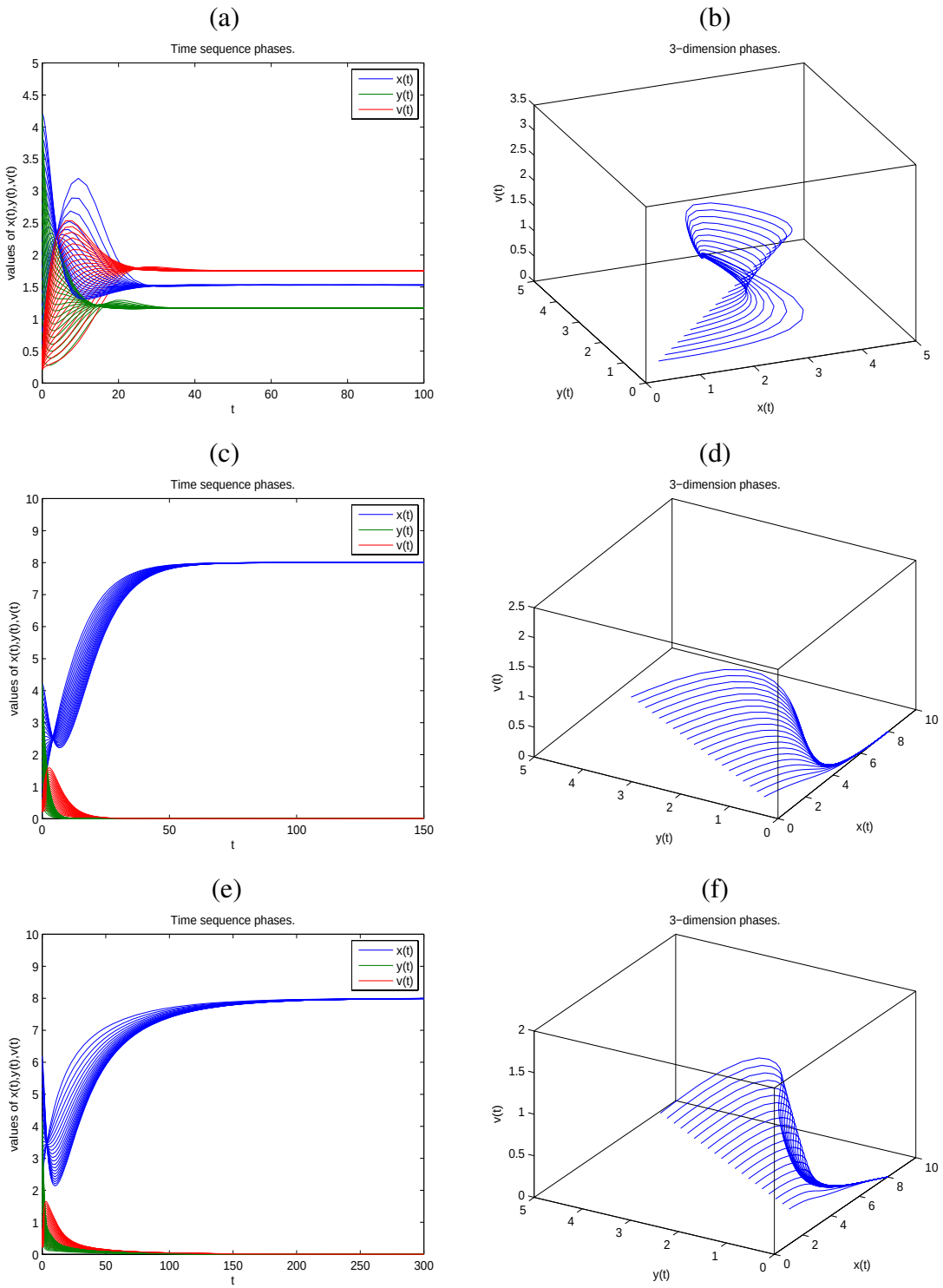

Figure 2. (a), (b): Time series and 3-dimension phases of solutions $(x(t), y(t), v(t))$ of system (1.2) when delay $\tau = 0.2$ and with initial functions: $(x(\theta), y(\theta), v(\theta)) = (0.2+0.2*k, 0.2+0.2*k, 0.2+0.01*k),\ k = 1, 2, \cdots, 20,$ for all $\theta \in [-0.2, 0]$, respectively.(c), (d): Time series and 3-dimension phases of solutions $(x(t), y(t), v(t))$ of system (1.2) when delay $\tau = 40$ and with initial functions: $(x(\theta), y(\theta), v(\theta)) = (0.2+0.2*k, 0.2+0.2*k, 0.2+0.01*k),\ k = 1, 2, \cdots, 20,$ for all $\theta \in [-40, 0]$, respectively. (e), (f): Time series and 3-dimension phases of solutions $(x(t), y(t), v(t))$ of system (1.2) when delay $\tau = 2.8$ and with initial functions: $(x(\theta), y(\theta), v(\theta)) = (2.2+0.2*k, 0.2+0.2*k, 0.2+0.01*k),\ k = 1, 2, \cdots, 20,$ for all $\theta \in [-2.8, 0]$, respectively.

Based on the above comparison, we can draw a conclusion: for HIV virus-to-cell dynamical models (1.2) and (1.4), the effects of discrete and distributed delays on stability could be similar and different even opposite. If $0 < \tau \leq 2.3941$ and with the same values of parameters in Table 1, the basic reproduction number $R_0^* > 1$ and $R_0 > 1$ both hold corresponding to models (1.2) and (1.4), both $\bar{E}^*$ and E^* are globally asymptotically stable. However, if $2.3942 < \tau \leq 31.715$ and with the same values of parameters, the basic reproduction number $R_0^* < 1$ holds for model (1.2), while $R_0 > 1$ holds for model (1.4). Meanwhile, the stability on the E_0, E^* of model (1.4) and E_0^*, $\bar{E}^*$ of model (1.2) presents completely opposite results. Furthermore, if $\tau > 31.716$ and with the same values of parameters, the basic reproduction number $R_0^* < 1$ and $R_0 < 1$ both hold corresponding to models (1.2) and (1.4), both E_0^* and E_0 are globally asymptotically stable. Briefly, under the same set of parameters, when the same values are taken for both discrete and distributed delays of models (1.2) and (1.4) within a properly interval respectively, if the infection-free equilibrium of model (1.2) with discrete delay is globally asymptotically stable, then the chronic-infection equilibrium of model (1.4) with distributed delay could be globally asymptotically stable. In other word, if the virus turn to extinct with discrete time delay, it could be persistent with distributed time delay for HIV virus-to-cell infectious models. However, if the same values of parameters are taken for discrete and distributed delays in other intervals respectively, both models (1.2) and (1.4) have the same results about stability.

6. Conclusions

In this paper, a class of HIV virus-to-cell dynamics model with Beddington-DeAngelis functional response and distribution delay is studied. The principle reproduction number R_0 is obtained, by which threshold values on the globally asymptotical stability of infection-free equilibrium E_0 and chronic-infection equilibrium E^* of model (4) are established. If $R_0 \leq 1$ the infection-free equilibrium E_0 is globally asymptotically stable, while $R_0 > 1$ the chronic-infection equilibrium E^* is globally asymptotically stable. Comparing with the effects of discrete and distributed delays on the stability of HIV virus-to-cell dynamic models, they could be same and different even opposite, the HIV virus could be more persistent in a distributed delay model than a discrete delay model.

Acknowledgments

We are grateful to the handling editor and anonymous reviewers for their valuable comments and suggestions that greatly improved the readability of this paper. This work is supported by the National Natural Science Foundation of China (Grant Nos. 11861065, 11771373, 11702237), the Natural Science Foundation of Xinjiang Province (2019D01C076, 2017D01C082).

Conflict of interest

The authors declare no conflicts of interest.

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