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Analyzing global stability of a viral model with general incidence rate and cytotoxic T lymphocytes immune response

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Abstract The global dynamics of a viral model with general incidence rate and CTL immune response is investigated. We derive the basic reproduction number for viral infection R_0 and the immune response reproduction number R_{CTL} for the viral infection model and establish the global dynamics completely determined by the values of R_0 and R_{CTL}. By constructing Lyapunov functions and using LaSalle invariance principle, the disease-free equilibrium E_0 is globally asymptotically stable when the basic reproduction number for viral infection $R_0 < 1$, and there exists a unique CTL-inactivated infection equilibrium E_1 which is globally stable and the infection becomes endemic with no sustained immune response when $R_{\mathrm{CTL}} \leq 1 < R_0$, and then, the CTL-activated infection equilibrium E^* of the model exists and is also globally attractive when the immune response reproduction number $R_{\mathrm{CTL}} > 1$.

Keywords Viral model · Immune response · Time delay · Global asymptotic stability

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1 Introduction

Researching the viral infectious has been an increasingly complex issue in recent years. For better understanding of the virus dynamics, mathematical models have been witnessed to be used rapidly. Many mathematical models have been used to describe the infection process with humoral immune response such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and human T-cell leukemia virus type 1 (HTLV-1) in [3,4,7,13]. In fact, cytotoxic T lymphocytes (CTL) immune response is universal and necessary to eliminate or control the disease after viral infection. Therefore, Nowak and Bangham [5] constructed a mathematical model to investigate dynamics of the interaction between susceptible cells, infected cells, viruses and immune cells with CTL immune response.

We introduce the standard viral infection model in Nowak [5].

$$\begin{aligned} x'(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ y'(t) &= \beta x(t)v(t) - ay(t) - py(t)z(t), \\ v'(t) &= ky(t) - uv(t), \\ z'(t) &= cy(t)z(t) - bz(t). \end{aligned} \tag{1}$$

where $x(t)$ denotes the number of healthy target cells, $y(t)$ denotes the number of actively infected target cells, $v(t)$ denotes the number of mature viruses and $z(t)$ denotes the number of CTL cells. Uninfected target cells are assumed to be generated at a constant rate

λ and die at rate d. Infection of target cells by free virus is assumed to occur at rate β. Infected cells die at rate a and are removed at rate p by the CTL immune response. New virus is produced from infected cells at rate k and dies at rate u. The average lifetime of uninfected cells, infected cells and free virus is thus given by $1/d$, $1/a$ and $1/u$, respectively. c denotes rate at which the CTL response is produced, and b denotes death rate of the CTL response, respectively, with given constants $\lambda, \beta, a, p, d, k, u, c, b > 0$.

Then, we assume our viral dynamics model with general incidence rate $xf(v)$. Here, the function $f(v)$ is assumed to be continuous on $v \in [0, +\infty)$ and continuously differentiable on $v \in (0, +\infty)$ and satisfies

$$\begin{cases} f(0) = 0, \\ f'(v) > 0, \quad \text{for all } v \geq 0, \\ f''(v) < 0, \quad \text{for all } v \geq 0. \end{cases} \tag{2}$$

With these assumptions, we have the following viral model

$$\begin{aligned} x'(t) &= \lambda - dx(t) - x(t)f(v(t)), \\ y'(t) &= x(t)f(v(t)) - ay(t) - py(t)z(t), \\ v'(t) &= ky(t) - uv(t), \\ z'(t) &= cy(t)z(t) - bz(t). \end{aligned} \tag{3}$$

with the initial conditions of model (3) which is $x(0) > 0$, $y(0) > 0$, $v(0) > 0$ and $z(0) > 0$.

It is easy to check that class of functions $f(v)$ satisfies (2). For instance, if $f(v) = v$, then the incidence rate with time delay is used in Li and Shu [2] who have studied global dynamics of an in-host viral model with intracellular delay. And if $f(v) = \frac{v}{1+av}$, then the incidence rate is used in Zhou [13] who mainly has obtained sufficient conditions for the asymptotical stability of a disease-free equilibrium, an immune-free equilibrium and an endemic equilibrium.

The paper is organized as follows. In Sect. 2, we deal with some basic properties, e.g., positivity and boundedness of solutions, basic reproduction number and existence of equilibria. In Sect. 3, we prove the global dynamics of the disease-free equilibrium when $R_0 < 1$. In Sect. 4, we establish the global stability of the CTL-inactivated infection equilibrium E_1 when $R_{\text{CTL}} < 1 < R_0$. In Sect. 5, we establish the global attractivity of the CTL-inactivated infection equilibrium E^* when $R_{\text{CTL}} > 1$.

2 Basic properties

2.1 Positivity and boundedness

The dynamics of system (3) will be investigated in a suitable phase space and a bounded feasible region. Initial conditions for system (3) are chosen as

$$\varphi \in \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+, \quad \varphi(0) > 0. \tag{4}$$

Proposition 1 *Under initial conditions in (4), all solutions of system (3) are nonnegative and ultimately bounded in $\mathbb{R} \times \mathbb{R} \times \mathbb{R} \times \mathbb{R}$. Furthermore, all feasible solutions of the system (3) enter the region*

$$\Omega = \left\{ (x, y, v, z) \in \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+ : \|x\| \leq \frac{\lambda}{d}, \|x + y + \frac{p}{c}z\| \leq \frac{\lambda}{\tilde{\mu}}, \|v\| \leq \frac{\lambda k}{u\tilde{\mu}} \right\},$$

where $\tilde{\mu} = \min\{d, a, b\}$.

Proof We now show that $x(t) > 0$ for all $t \geq 0$. In fact, assuming the contrary, and letting $t_1 > 0$ be the first time such that $x(t_1) = 0$, then by the first equation of system (3) we obtain $x'(t_1) = \lambda > 0$, and hence $x(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$, where $\varepsilon > 0$ is enough small. This contradicts $x(t) > 0$ for $t \in (0, t_1)$. Then, we obtain $x(t) > 0$ for $t > 0$. The right-hand side of the fourth equation of system (3) for z effectively contains a factor of $z(t)$. Positivity for $z(t)$ therefore follows by standard arguments. As same as $x(t)$, we can verify the positivity of solution $v(t)$ under initial conditions in (4). For $v(t)$ of system (3), we let $t_2 > 0$ be the first time such that $v(t_2) = 0$. By the second equation of system (3), we get

$$y'(t_2) = y(t_2)(-a - pz(t_2)).$$

Then, we obtain $y(t_2) > 0$. It follows that $v'(t_2) > 0$, and hence $v(t) < 0$ for $t \in (t_2 - \varepsilon, t_2)$, where $\varepsilon > 0$ is enough small. This contradicts $v(t) > 0$ for $t \in (0, t_2)$, and hence, $v(t)$ is positive for $t > 0$ and

$$y(t) = \left(y(0) + \int_0^t x(\theta) f(v(\theta)) \mathrm{e}^{(a+pz(t))\theta} d\theta \right) \times \mathrm{e}^{-(a+pz(t))t} > 0.$$

Next, we show that positive solutions of (3) are ultimately bounded for $t \geq 0$. For the first equation of system (3), we obtain $x'(t) \leq \lambda - dx(t)$, and thus $\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{d}$. By system (3), we get

$$\dot{x}(t) + \dot{y}(t) + \frac{p}{c}\dot{z}(t) \leq \lambda - \tilde{\mu}\left(x(t) + y(t) + \frac{p}{c}z(t)\right).$$

where $\tilde{\mu} = \min\{d, a, b\}$. Consequently, $\limsup_{t\to\infty}(x(t) + y(t) + \frac{p}{c}z(t)) \le \frac{\lambda}{\tilde{\mu}}$. For $v(t)$,

$$\dot{v}(t) \le k\frac{\lambda}{\tilde{\mu}} - uv(t),$$

then $\limsup_{t\to\infty} v(t) \le \frac{k\lambda}{\tilde{\mu}u}$. Therefore, every solution of system (3) is ultimately bounded.

2.2 Basic reproduction number and existence of equilibria

For studying existence of equilibria, the equilibria equations for model (3) are given by

$$\begin{aligned} &\lambda - d\bar{x} - \bar{x}f(\bar{v}) = 0,\\ &\bar{x}f(\bar{v}) - a\bar{y} - p\bar{y}\bar{z} = 0,\\ &k\bar{y} - u\bar{v} = 0,\\ &c\bar{y}\bar{z} - b\bar{z} = 0. \end{aligned} \tag{5}$$

Obviously, for system (3), there always exists an infection-free equilibrium $E_0 = (x_0, y_0, v_0, z_0) = (\frac{\lambda}{d}, 0, 0, 0)$. In addition to E_0, the system may have two types of chronic-infection equilibria $E_1 = (x_1, y_1, v_1, 0)$ and $E^* = (x^*, y^*, v^*, z^*)$ in Ω, where $x_1, y_1, v_1, x^*, y^*, v^*, z^*$ are all strictly positive. E_1 is known as a CTL-inactivated equilibrium (CTL-IE) if it exists and E^* is known as a CTL-activated equilibrium (CTL-AE) if it exists. At a CTL-inactivated equilibrium, the disease is persistent with a constant $v_1 > 0$, whereas the CTL response is absent. This corresponds to an asymptomatic carrier. At a CTL-activated equilibrium, the viral load and the CTL response persist at the level of v^* and z^*, respectively.

The global dynamics of model (3) is determined by the basic reproduction number R_0 for viral infection:

$$R_0 = \frac{k\lambda f'(0)}{aud}.$$

and R_{CTL} for the CTL response:

$$R_{\mathrm{CTL}} = \frac{kx^*f(v^*)}{auv^*}.$$

Here, we can see that $R_{\mathrm{CTL}} < R_0$ always holds.

Proposition 2 *System (3) always has a disease-free equilibrium E_0. Moreover, if $R_{\mathrm{CTL}} < 1 < R_0$, then system (3) has a unique chronic-infection equilibrium $E_1 = (x_1, y_1, v_1, 0)$ satisfying (5). If $R_{\mathrm{CTL}} > 1$, then system (3) has a unique CTL-activated equilibrium E^* satisfying (5).*

Proof By (5), chronic-infection equilibrium E_1 should satisfy the following equations

$$\begin{aligned} &\lambda - dx_1 - x_1f(v_1) = 0,\\ &x_1f(v_1) - ay_1 = 0,\\ &ky_1 - uv_1 = 0. \end{aligned} \tag{6}$$

We consider the following function $H(v)$ defined by

$$H(v) = \lambda - \frac{dau}{k}\frac{v}{f(v)} - \frac{au}{k}v, \tag{7}$$

and we know

$$H'(v) = -\frac{au}{k} - \frac{dau}{k}\frac{f(v) - vf'(v)}{f^2(v)}.$$

From the properties of the function $f(v)$ by (2), in particular, from $f(0) = 0$ and $f''(v) < 0$, it illustrates that $f(v) - vf'(v) > 0$ for all $v > 0$, and we have $H'(v) < 0$. Therefore, there exists a positive root of $H(v) = 0$ when $R_0 > 1$, $H(v)$ has to satisfy $H(0) > 0$, i.e.,

$$H(0) = \lambda - \frac{dau}{kf'(0)} = \lambda\left(1 - \frac{1}{R_0}\right).$$

Secondly, the CTL-AE equilibrium $E^* = (x^*, y^*, v^*, z^*)$ satisfies (5), and then, the CTL-AE equilibrium E^* exists as the following form

$$x^* = \frac{\lambda}{d + f(v^*)} > 0, \quad y^* = \frac{b}{c} > 0, \quad v^* = \frac{k}{u}y^* > 0,$$
$$z^* = \frac{x^*f(v^*) - ay^*}{py^*} = \frac{a}{p}\left(R_{\mathrm{CTL}} - 1\right).$$

if and only if $R_{\mathrm{CTL}} > 1$.

3 Global stability when $R_0 < 1$

Furthermore, it is important to analyze the stability of trivial equilibrium (see [6,8,11,12]), as it will indicate whether the virus will die out eventually, or it will persist for all time. The characteristic equation associated with the linearization of the system (3) near the steady state E_0 gives

$$(\xi + d)(\xi + b)\left[(\xi + a)(\xi + u) - kx_0f'(0)\right] = 0. \tag{8}$$

the eigenvalues are $\xi_1 = -d < 0$ and $\xi_2 = -b < 0$, and the steady state E_0 is locally asymptotically stable if all eigenvalues of

$$(\xi + a)(\xi + u) - kx_0f'(0) = 0. \tag{9}$$

All eigenvalues of Eq. (9) have negative real parts. That is, we need that

$$\xi^2 + (a+u)\xi + au - kx_0 f'(0) = 0$$

has negative real parts.

Obviously, when $R_0 < 1$, $au - kx_0 f'(0) < 0$. All eigenvalues of Eq. (9) have negative real parts.

We arrive at the following result.

Theorem 1 *If $R_0 < 1$, then the disease-free equilibrium E_0 of system (3) is locally asymptotically stable. Moreover, if $R_0 > 1$, then the disease-free equilibrium E_0 of system (3) is unstable.*

Next, we analyze the global stability of disease-free equilibrium by constructing Lyapunov function.

Theorem 2 *If $R_0 < 1$, then the disease-free equilibrium E_0 of system (3) is globally asymptotically stable in Ω.*

Proof We construct the following Lyapunov function $V : \mathbb{R} \times \mathbb{R} \times \mathbb{R} \times \mathbb{R} \to \mathbb{R}$:

$$V(t) = x_0 g\left(\frac{x(t)}{x_0}\right) + y(t) + \frac{a}{k}v(t) + \frac{p}{c}z(t). \quad (10)$$

where $g(x) = x - 1 - \ln x$, $x \in \mathbb{R}_+$, has the global minimum at $x = 1$ and $g(1) = 0$.

We easily obtain the Lyapunov function V is non-negative and defined in Ω with respect to the trivial equilibrium E_0.

We calculate the time derivative of $V(t)$ along the solutions of system (3) and obtain

$$\begin{aligned}
\frac{\mathrm{d}V}{\mathrm{d}t}|_{(3)} &= \left(1 - \frac{x_0}{x}\right)\dot{x}(t) + \dot{y}(t) + \frac{a}{k}\dot{v}(t) + \frac{p}{c}\dot{z}(t) \\
&= \lambda - dx(t) - \frac{x_0}{x}(\lambda - dx(t)) \\
&\quad + x_0 f(v(t)) - \frac{au}{k}v(t) - \frac{pb}{c}z(t) \\
&= dx_0\left(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)}\right) \\
&\quad + \frac{au}{k}v(t)\left(\frac{kx_0 f(v(t))}{auv(t)} - 1\right) - \frac{pb}{c}z(t) \\
&\le dx_0\left(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)}\right) \\
&\quad + \frac{au}{k}v(t)\,(R_0 - 1) - \frac{pb}{c}z(t). \qquad (11)
\end{aligned}$$

From $x(t) > 0$, we obtain

$$2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)} \le 0.$$

Hence, $\dot{V}|_{(3)} \le 0$. From (11), we know that $\dot{V}|_{(3)} = 0$ if and only if $x(t) = \lambda/d$, $v(t) = 0$ and $z(t) = 0$. Let

$$S = \{(\lambda/d, \varphi_1, 0, 0) \in \bar{\Omega} | \dot{V}|_{(3)} = 0\},$$

and M is the largest positive invariant set in S, where $\bar{\Omega}$ is the closure of Ω.

From system (3), we get $y(t) = 0$. Thus, it follows that $M = \{(\lambda/d, 0, 0, 0)\} = \{E_0\}$. By the LaSalle invariance principle [1], E_0 is globally attractive. This confirms the globally asymptotical stability of E_0 in Ω.

4 Global attractivity when $R_{\mathrm{CTL}} < 1 < R_0$

In this section, we show that the CTL-inactivated equilibrium E_1 of system (3) is globally attractivity if $R_{\mathrm{CTL}} < 1 < R_0$ by using a Lyapunov function.

For confirming result on dynamics of CTL-IE E_1, we require a additional assumptions.

(H) $b - cy_1 > 0$.

Theorem 3 *Assume that (H) is satisfied. If $R_{\mathrm{CTL}} < 1 < R_0$, then the CTL-inactivated equilibrium E_1 of system (3) is globally attractive.*

Proof We construct the following Lyapunov function $V : \mathbb{R} \times \mathbb{R} \times \mathbb{R} \times \mathbb{R} \to \mathbb{R}$:

$$\begin{aligned}
V(t) &= x(t) - x_1 - \int_{x_1}^{x(t)} \frac{x_1}{\xi}\mathrm{d}\xi + y_1 g\left(\frac{y(t)}{y_1}\right) \\
&\quad + \frac{a}{k}v_1 g\left(\frac{v(t)}{v_1}\right) + \frac{p}{c}z(t).
\end{aligned}$$

where $g(x) = x - 1 - \ln x$, $x \in \mathbb{R}_+$, has the global minimum at $x = 1$ and $g(1) = 0$.

We calculate the time derivative of V along the positive solutions of system (3). Firstly, we have

$$\begin{aligned}
&\dot{V}(t)|_{(3)} \\
&= \dot{x}(t) - \frac{x_1}{x(t)}\dot{x}(t) + \dot{y}(t) - \frac{y_1}{y(t)}\dot{y}(t) \\
&\quad + \frac{a}{k}\left(\dot{v}(t) - \frac{v_1}{v(t)}\dot{v}(t)\right) + \frac{p}{c}\dot{z}(t) \\
&= \lambda - dx(t) - \frac{x_1}{x(t)}(\lambda - dx(t) - x(t)f(v(t))) \\
&\quad - \frac{y_1}{y(t)}(x(t)f(v(t)) - ay(t)) \\
&\quad + py_1 z(t) - \frac{au}{k}v(t) - \frac{a}{k}\frac{v_1}{v(t)}(kv(t) \\
&\quad - uv(t)) - \frac{pb}{c}z(t) \qquad (12)
\end{aligned}$$

Using $\lambda = dx_1 + x_1 f(v_1)$, $x_1 f(v_1) = ay_1$ and $ky_1 = uv_1$, we obtain

$$\begin{aligned}
&\dot{V}(t)|_{(3)}\\
&= dx_1\left(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}\right) + ay_1 - ay_1\frac{v(t)}{v_1}\\
&\quad - ay_1\frac{x_1}{x(t)} + ay_1\frac{f(v(t))}{f(v_1)}\\
&\quad - ay_1\frac{y_1}{y(t)}\frac{x(t)}{x_1}\frac{f(v(t))}{f(v_1)} + ay_1\\
&\quad - ay_1\frac{v_1}{v(t)}\frac{y(t)}{y_1} + ay_1 + pz(t)\left(y_1 - \frac{b}{c}\right)\\
&= dx_1\left(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}\right)\\
&\quad + ay_1\left(1 - \frac{x_1}{x(t)} + \frac{f(v(t))}{f(v_1)}\right)\\
&\quad + ay_1\left(1 - \frac{y_1}{y(t)}\frac{x(t)}{x_1}\frac{f(v(t))}{f(v_1)}\right)\\
&\quad + ay_1\left(1 - \frac{v(t)}{v_1} - \frac{v_1}{v(t)}\frac{y(t)}{y_1}\right) + pz(t)\left(y_1 - \frac{b}{c}\right)\\
&= dx_1\left(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}\right)\\
&\quad + ay_1\left(-1 - \frac{v(t)}{v_1} + \frac{f(v(t))}{f(v_1)} + \frac{v(t)}{v_1}\frac{f(v_1)}{f(v(t))}\right)\\
&\quad + ay_1\left(4 - \frac{x_1}{x(t)} - \frac{y_1}{y(t)}\frac{x(t)}{x_1}\frac{f(v(t))}{f(v_1)} - \frac{v_1}{v(t)}\frac{y(t)}{y_1}\right.\\
&\quad \left. - \frac{v(t)}{v_1}\frac{f(v_1)}{f(v(t))}\right) + pz(t)\left(y_1 - \frac{b}{c}\right) \qquad (13)
\end{aligned}$$

Because of satisfying the conditions (H) and

$$\begin{aligned}
&2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)} \le 0,\\
&-1 - \frac{v(t)}{v_1} + \frac{f(v(t))}{f(v_1)} + \frac{v(t)}{v_1}\frac{f(v_1)}{f(v(t))} \le 0,\\
&4 - \frac{x_1}{x(t)} - \frac{y_1}{y(t)}\frac{x(t)}{x_1}\frac{f(v(t))}{f(v_1)} - \frac{v_1}{v(t)}\frac{y(t)}{y_1}\\
&- \frac{v(t)}{v_1}\frac{f(v_1)}{f(v(t))} \le 0.
\end{aligned}$$

thus $\dot{V}(t) \le 0$ holds. Hence, the solutions of system (3) must converge to M, the largest positive invariant set of $M = \{\dot{V}(t) = 0\}$.

Next, we analyze that M consists of only the interior equilibrium E_1. We see that $\dot{V}(t) = 0$ if and only if $x(t) = x_1$, $y(t) = y_1$, $v(t) = v_1$. From system (3), we get $z_1 = 0$. Thus, it follows that $M = \{E_1\}$. By the LaSalle invariance principle [1], E_1 is globally attractive.

5 Global attractivity when $R_{\mathrm{CTL}} > 1$

We have proved in above sections that, if $R_{\mathrm{CTL}} > 1$, the CTL-AE E^* exists in the interior of Ω. We will investigate the attractivity of E^* in following section.

Theorem 4 *If $R_{\mathrm{CTL}} > 1$, then the CTL-activated equilibrium E^* is globally attractive.*

Proof We construct the following Lyapunov function $V : \mathbb{R} \times \mathbb{R} \times \mathbb{R} \times \mathbb{R} \to \mathbb{R}$:

$$\begin{aligned}
V(t) &= x(t) - x^* - \int_{x^*}^{x(t)} \frac{x^*}{\xi}\mathrm{d}\xi\\
&\quad + y^* g\left(\frac{y(t)}{y^*}\right) + \frac{a + pz^*}{k}v^* g\left(\frac{v(t)}{v^*}\right)\\
&\quad + \frac{p}{c}z^* g\left(\frac{z(t)}{z^*}\right),
\end{aligned}$$

where $g(x) = x - 1 - \ln x$, $x \in \mathbb{R}_+$, has the global minimum at $x = 1$ and $g(1) = 0$.

We calculate the time derivative of V along the positive solutions of system (3). Firstly, we have

$$\begin{aligned}
&\dot{V}(t)|_{(3)}\\
&= \dot{x}(t) - \frac{x^*}{x(t)}\dot{x}(t) + \dot{y}(t) - \frac{y^*}{y(t)}\dot{y}(t)\\
&\quad + \frac{a + pz^*}{k}\left(\dot{v}(t) - \frac{v^*}{v(t)}\dot{v}(t)\right)\\
&\quad + \frac{p}{c}\left(\dot{z}(t) - \frac{z^*}{z(t)}\dot{z}(t)\right)\\
&= \lambda - dx(t) - \frac{x^*}{x(t)}(\lambda - dx(t) - x(t)f(v(t)))\\
&\quad - \frac{y^*}{y(t)}(x(t)f(v(t)) - ay(t))\\
&\quad + py^*z(t) - \frac{au}{k}v(t) - \frac{pz^*u}{k}v(t)\\
&\quad - \frac{a}{k}\frac{v^*}{v(t)}(ky(t) - uv(t))\\
&\quad - \frac{pz^*}{k}\frac{v^*}{v(t)}(ky(t) - uv(t)) - \frac{pb}{c}z(t) + \frac{pb}{c}z^*\\
&= \lambda - dx(t) - \frac{x^*}{x(t)}(\lambda - dx(t) - x(t)f(v(t)))\\
&\quad - \frac{y^*}{y(t)}x(t)f(v(t)) + ay^*
\end{aligned}$$

$$-\frac{au}{k}v(t)-\frac{pz^*u}{k}v(t)-a\frac{v^*}{v(t)}y(t)+a\frac{u}{k}v^*$$
$$-pz^*\frac{v^*}{v(t)}y(t)+pz^*\frac{u}{k}v^*+pz^*\frac{b}{c} \tag{14}$$

Using $\lambda = dx^* + x^*f(v^*)$, $x^*f(v^*) = ay^* + pz^*y^*$ and $ky^* = uv^*$, we obtain

$$\begin{aligned}
\dot{V}(t)|_{(3)} &= dx^* + x^*f(v^*) - dx(t) - \frac{x^*}{x(t)}(dx^* + x^*f(v^*)\\
&\quad - dx(t)) - x^*f(v(t))\\
&\quad - \frac{y^*}{y(t)}x(t)f(v(t)) + ay^* - \frac{au}{k}v(t)\\
&\quad - \frac{pz^*u}{k}v(t) - a\frac{v^*}{v(t)}y(t)\\
&\quad + ay^* - pz^*\frac{v^*}{v(t)}y(t) + 2pz^*y^*\\
&= dx^*\left(2 - \frac{x(t)}{x^*} - \frac{x^*}{x(t)}\right) + x^*f(v^*)\\
&\quad - \frac{x^*}{x(t)}x^*f(v^*) + x^*f(v^*)\frac{v(t)}{v^*}\\
&\quad - x^*f(v^*)\frac{y^*}{y(t)}\frac{x(t)f(v(t))}{x^*f(v^*)} + 2x^*f(v^*)\\
&\quad - \frac{au}{k}v(t) - \frac{pz^*u}{k}v(t)\\
&\quad - a\frac{v^*}{v(t)}y(t) - pz^*\frac{v^*}{v(t)}y(t)\\
&= dx^*\left(2 - \frac{x(t)}{x^*} - \frac{x^*}{x(t)}\right)\\
&\quad + x^*f(v^*)\left(1 - \frac{x^*}{x(t)} + \frac{f(v(t))}{f(v^*)}\right)\\
&\quad + x^*f(v^*)\left(1 - \frac{y^*}{y(t)}\frac{x(t)}{x^*}\frac{f(v(t))}{f(v^*)}\right)\\
&\quad + x^*f(v^*)\left(1 - \frac{v(t)}{v^*} - \frac{v^*}{v(t)}\frac{y(t)}{y^*}\right)\\
&= x^*f(v^*)\left(2 - \frac{x(t)}{x^*} - \frac{x^*}{x(t)}\right)\\
&\quad + x^*f(v^*)\left(-1 - \frac{v(t)}{v^*} + \frac{f(v(t))}{f(v^*)}\right.\\
&\quad \left. + \frac{v(t)}{v^*}\frac{f(v^*)}{f(v(t))}\right)\\
&\quad + x^*f(v^*)\left(4 - \frac{x^*}{x(t)} - \frac{y^*}{y(t)}\frac{x(t)}{x^*}\frac{f(v(t))}{f(v^*)}\right.\\
&\quad \left. - \frac{v^*}{v(t)}\frac{y(t)}{y^*} - \frac{v(t)}{v^*}\frac{f(v^*)}{f(v(t))}\right).
\end{aligned} \tag{15}$$

Because of satisfying the following conditions

$$2 - \frac{x(t)}{x^*} - \frac{x^*}{x(t)} \le 0,$$
$$-1 - \frac{v(t)}{v^*} + \frac{f(v(t))}{f(v^*)} + \frac{v(t)}{v^*}\frac{f(v^*)}{f(v(t))} \le 0,$$
$$4 - \frac{x^*}{x(t)} - \frac{y^*}{y(t)}\frac{x(t)}{x^*}\frac{f(v(t))}{f(v^*)} - \frac{v^*}{v(t)}\frac{y(t)}{y^*} - \frac{v(t)}{v^*}\frac{f(v^*)}{f(v(t))} \le 0.$$

thus $\dot{V}(t) \le 0$ holds. Hence, the solutions of system (3) must converge to M, the largest positive invariant set of $M = \{\dot{V}(t) = 0\}$.

Next, we analyze that M consists of only the interior equilibrium E^*. We see that $\dot{V}(t) = 0$ if and only if $x(t) = x^*$, $y(t) = y^*$, $v(t) = v^*$. Thus, it follows that $M = \{E^*\}$. From system (3), we get $z(t) = z^*$. By the LaSalle invariance principle [1], E^* is globally attractive.

6 Simulations

In this section, we carry out some numerical simulations to support our theoretical analysis. Reasonable choices for $f(v)$ include the case $f(v) = \beta v (\beta > 0)$. The following viral model is

$$\begin{aligned}
x'(t) &= \lambda - dx(t) - \beta x(t)v(t),\\
y'(t) &= \beta x(t)v(t) - ay(t) - py(t)z(t),\\
v'(t) &= ky(t) - uv(t),\\
z'(t) &= cy(t)z(t) - bz(t).
\end{aligned} \tag{16}$$

Then, $R_0 = \frac{k\lambda\beta}{aud}$ and $R_{\mathrm{CTL}} = \frac{kx^*\beta}{au}$.

Corollary 1 *(i) If $R_0 < 1$, then the disease-free equilibrium E_0 of system (16) is globally asymptotically stable in Ω;*

(ii) Assume that (H) is satisfied. If $R_{\mathrm{CTL}} < 1 < R_0$, then the CTL-inactivated equilibrium E_1 of system (16) is globally attractive;

(iii) If $R_{\mathrm{CTL}} > 1$, then the CTL-activated equilibrium E^* of system (16) is globally attractive.

Next, we consider three sets of parameters values:

(1) $\lambda = 165$, $\beta = 0.001$, $d = 0.015$, $a = 1.64$, $u = 0.18$, $p = 0.2$, $c = 0.2$, $k = 0.25$, $b = 0.05$ and $R_0 = 0.4695 < 1$.

(2) $\lambda = 165$, $\beta = 0.001075$, $d = 0.15$, $a = 1.64$, $u = 0.18$, $p = 0.2$, $c = 0.2$, $k = 0.25$, $b = 0.05$ and $R_{\mathrm{CTL}} < 1 < R_0$.

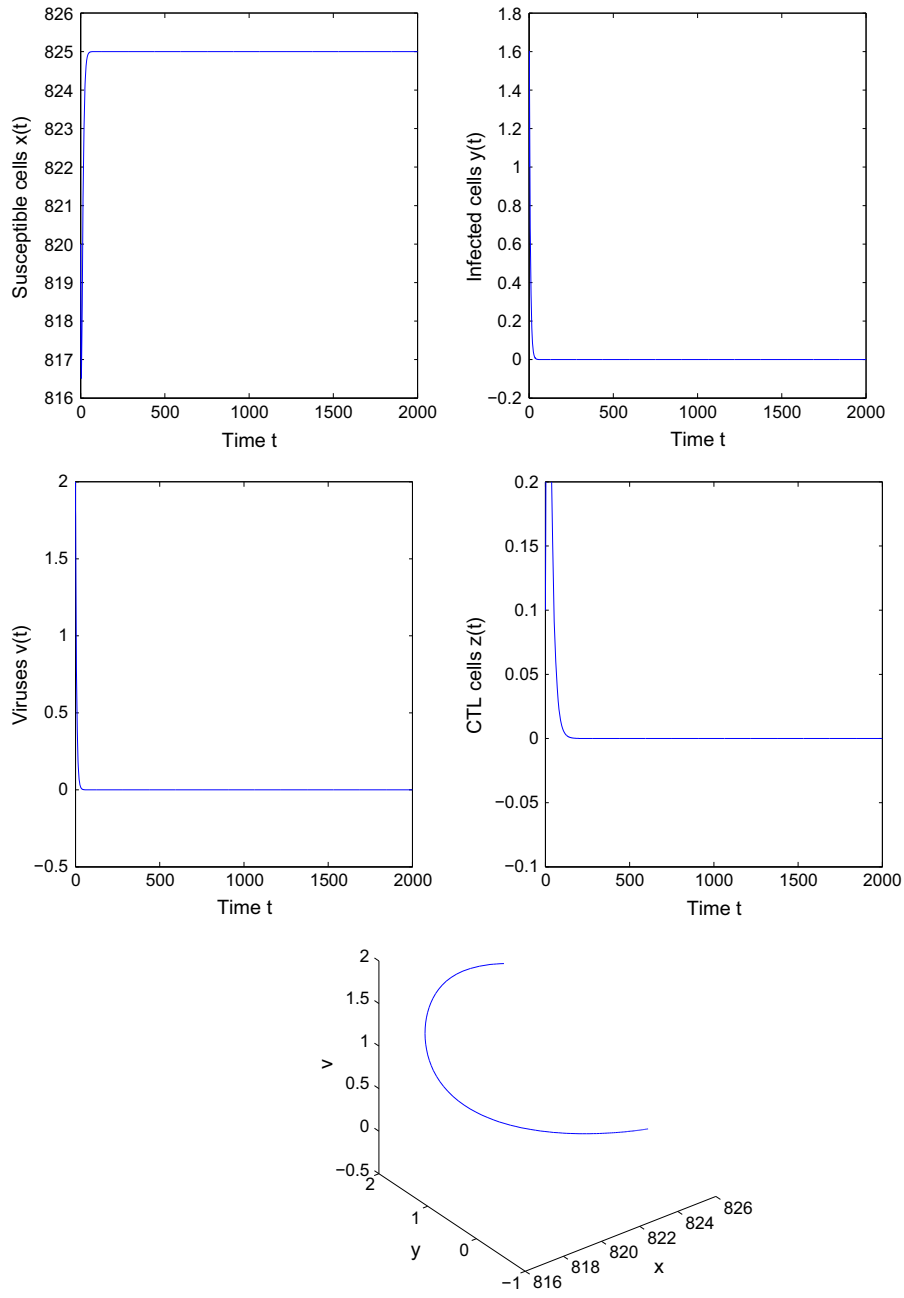

Fig. 1 Numerical simulations for system (16) with $\lambda = 165$ cells/mm^3/day, $\beta = 0.001\,\text{mm}^3$/cells/day, $d = 0.015\,\text{day}^{-1}$, $a = 1.64\,\text{day}^{-1}$, $u = 0.18\,\text{day}^{-1}$, $p = 0.2\,\text{mm}^3$/cells/day, $c = 0.2\,\text{mm}^3$/cells/day, $k = 0.25\,\text{day}^{-1}$, $b = 0.05\,\text{day}^{-1}$ and $R_0 = 0.932 < 1$, then the corresponding solution converges to the viral-free equilibrium E_0, and it indicates that the virus will die out eventually

(3) $\lambda = 165$, $\beta = 0.002$, $d = 0.15$, $a = 1.64$, $u = 0.18$, $p = 0.2$, $c = 0.2$, $k = 0.25$, $b = 0.05$ and $R_{\text{CTL}} > 1$.

From numerical simulations, it is deduced that the infection rate constant β will increase the density of infected cells and of free virus particles at equilibrium condition; meanwhile, it increases the effect of CTL immune response (Figs. 1, 2, 3).

7 Summary and discussion

As we know, Nowak and Bangham [5] added the effect of CTL immune response to the classical virus model, which exists in lots of biological organisms, to obtain model (1). Meanwhile, it is difficult to obtain the global properties of a model with nonlinear function responses. Zhou [13] studied the dynamical behavior of

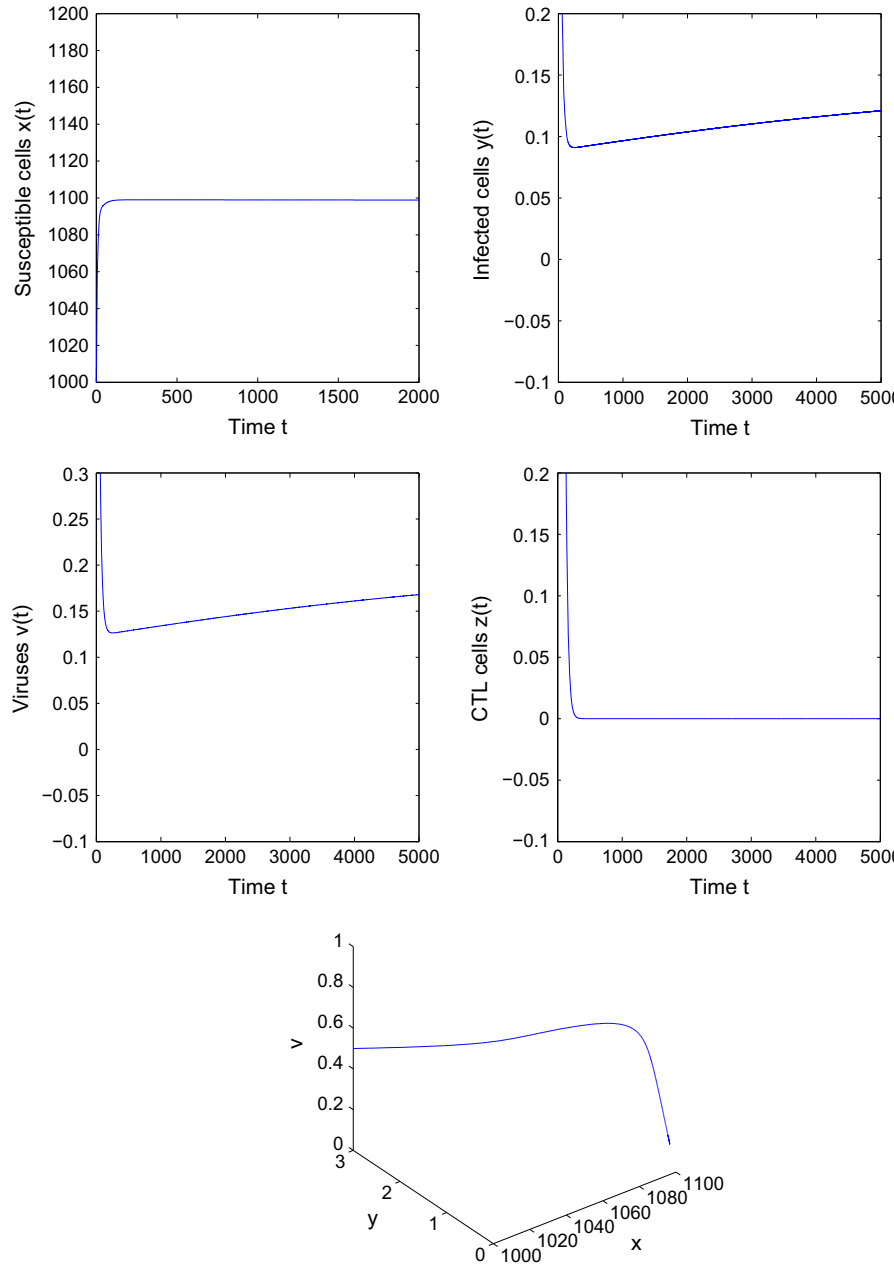

Fig. 2 Numerical simulations for system (16) with $\lambda = 165\,\text{cells/mm}^3\text{/day}$, $\beta = 0.001075\,\text{mm}^3\text{/cells/day}$, $d = 0.15\,\text{day}^{-1}$, $a = 1.64\,\text{day}^{-1}$, $u = 0.18\,\text{day}^{-1}$, $p = 0.2\,\text{mm}^3\text{/cells/day}$, $c = 0.2\,\text{mm}^3\text{/cells/day}$, $k = 0.25\,\text{day}^{-1}$, $b = 0.05\,\text{day}^{-1}$ and $R_{\text{CTL}} = 0.997 < 1 < R_0 = 1.0014$, then the corresponding solution converges to the immune-free equilibrium E_1, as it implies that the infection becomes endemic with no sustained immune responses

a virus dynamics model with CTL immune response, as the nonlinear incidence rate is $\frac{bTV}{1+aV}$, and for the model with Logistic growth, they discussed the orbital stability of bifurcating limit cycle using Poores condition. Wang [9] studied the global stability of viral dynamics model with Beddington–DeAngelis infection rate $\frac{\beta xv}{1+mx+nv}$ and CTL immune response by constructing Lyapunov functions. Wang and Elaiw [10] studied a six-dimensional human immunodeficiency virus (HIV) model with time delay and CTLs immune response, and their model described the interaction of HIV with two target cells: $CD4^+$ T cells and macrophages, and they derived that the global asymptotic attractivity of the model was completely determined by the basic reproduction number R_0 and the immune reproduction number R_0^* for the viral infection.

In this paper, a generalized viral dynamics model with CTL immune response is studied. Based on the

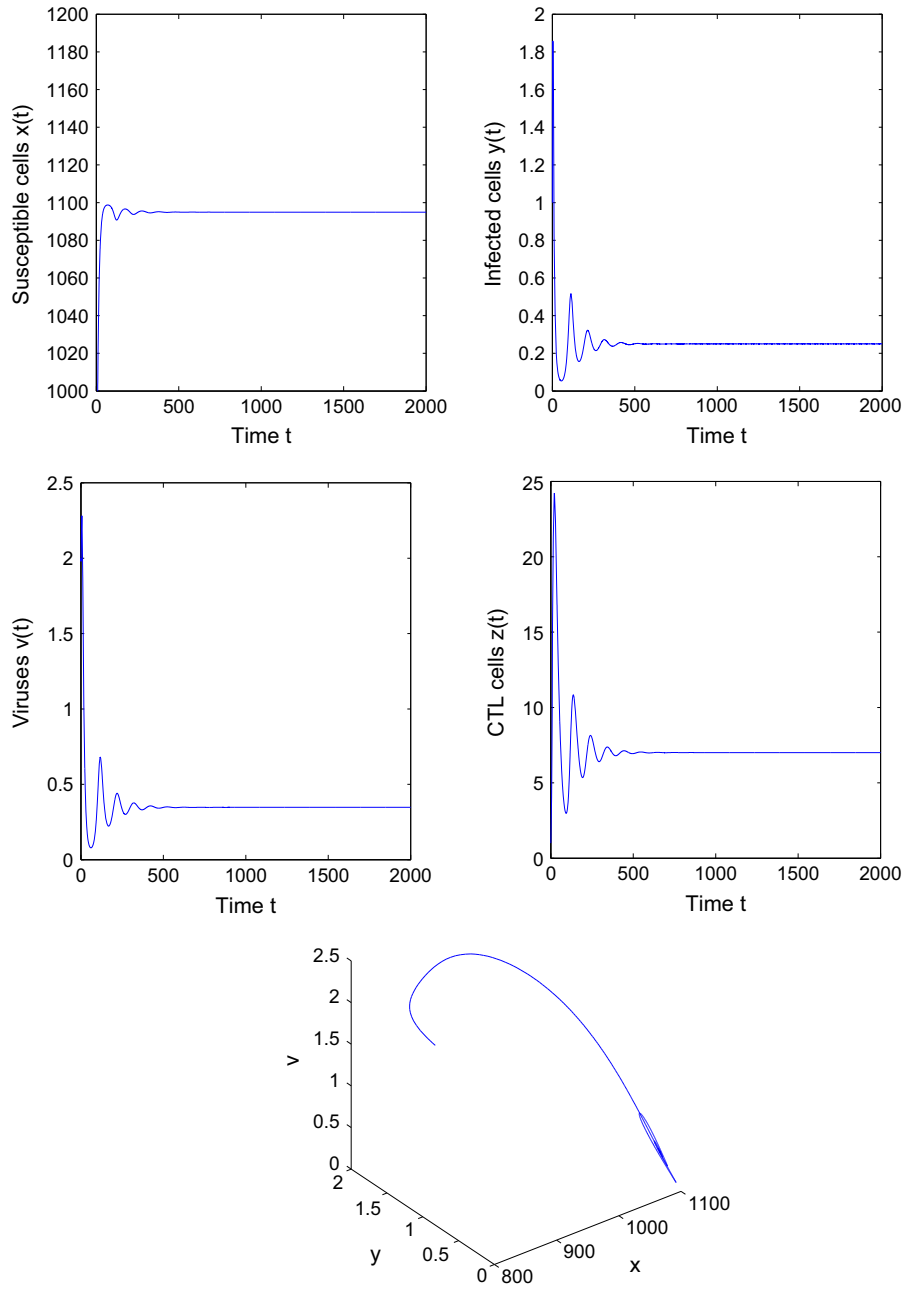

Fig. 3 Numerical simulations for system (16) with $\lambda = 165$ cells/mm^3/day, $\beta = 0.002\,\text{mm}^3$/cells/day, $d = 0.15\,\text{day}^{-1}$, $a = 1.64\,\text{day}^{-1}$, $u = 0.18\,\text{day}^{-1}$, $p = 0.2\,\text{mm}^3$/cells/day, $c = 0.2\,\text{mm}^3$/cells/day, $k = 0.25\,\text{day}^{-1}$, $b = 0.05$ day^{-1} and $R_{\text{CTL}} = 1.855 > 1$, then the corresponding solution converges to the CTL-activated infection equilibrium E^*, as it implies that the infection becomes endemic with sustained immune responses

in-host viral model with different incidence rate, we extend the known results and describe nonlinear incidence rate to be $x(t)f(v(t))$. By constructing Lyapunov functions and using Lyapunov–LaSalle invariance principle, we obtain the following results on the global behaviors of the endemic equilibria and the disease-free equilibrium:

(1) If $R_0 < 1$, then the viral-free equilibrium E_0 is globally asymptotically stable, as it indicates that the virus will die out eventually;
(2) If $R_{\text{CTL}} < 1 < R_0$, then the immune-free equilibrium E_1 is globally attractive;
(3) If $R_{\text{CTL}} > 1$, then all positive solutions converge to the chronic-infection equilibrium E^*, as it implies

that the infection becomes endemic with sustained immune responses.

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