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Global Stability in a Viral Infection Model with Lytic and Nonlytic Immune Responses

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Abstract—This paper investigates the global stability of a viral infection model with lytic and nonlytic immune responses. If the basic reproductive ratio of the virus is less than or equal to one, by the LaSalle's invariance principle and center manifold theorem, the disease-free steady state is globally asymptotically stable. If the basic reproductive ratio of the virus is greater than one, then the virus persists in the host and the disease steady state is locally asymptotically stable. Furthermore, by the method of Lyapunov function, the global stability of the disease steady state is established. At the same time, if we neglect the efficacy of the lytic component, using a geometrical approach, we obtain a different type of conditions for the global stability of the disease steady state.

Keywords—Virus dynamics, Immune responses, Global stability, Uniform persistence, Center manifold.

1. INTRODUCTION

Mathematical models can provide insights into the dynamics of viral load *in vivo*. A simple model may play a significant role in the development of a better understanding of the disease and the

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various drug therapy strategies used against it. Recently, there has been a lot of papers on virus dynamics within-host, some include the immune response directly (e.g., [1–5]), and others don't contain the immune responses (e.g., [6–11]). Being different from the epidemic compartment models (e.g., [12,13] and references cited therein), in which individuals are partitioned into some classes and the transmission dynamics of infectious diseases in host populations is studied, virus models focus on the disease dynamics within an infected individual.

During viral infections, the host immune system reacts with innate and antigen-specific immune responses. Both types of responses can be subdivided broadly into lytic and nonlytic components. Lytic components kill infected cells, whereas the nonlytic inhibit viral replication through soluble mediators. As a part of the innate response, natural killer cells can lyse infected cells and cytokines (e.g., interferon α (IFN-α) and IFN-β) secreted by various cell types can inhibit viral replication in a nonlytic fashion. In an antigen-specific response, cytotoxic T lymphocytes (CTLs) kill infected cells, whereas antibodies neutralize free virus particles and thus, inhibit the infection of susceptible cells. In addition, CD4+ and CD8+ T cells can secrete cytokines that inhibit viral replication (e.g., IFN-γ and tumor necrosis factor α (TNF-α)). In order to investigate the role of direct lytic and nonlytic inhibition of viral replication by immune cells in viral infections, Bartholdy *et al.* [1] and Wodarz *et al.* [5] constructed a mathematical model describing the basic dynamics of the interaction between susceptible host cells, a virus population, and immune responses, which is described by the following differential equations,

$$\begin{aligned} x' &= \lambda - dx - \frac{\beta xy}{1+qz}, \\ y' &= \frac{\beta xy}{1+qz} - ay - pyz, \\ z' &= cy - bz, \end{aligned} \tag{1.1}$$

$$x(0) > 0, \qquad y(0) > 0, \qquad z(0) > 0,$$

where $x(t)$ is the number of susceptible host cells, $y(t)$ is the number of virus population and $z(t)$ is the number of immune responses; susceptible host cells are generated at a rate λ, die at a rate dx and become infected by virus at a rate βxy without the immune responses; to model nonlytic antiviral activity, viral replication is inhibited by the immune responses at a rate $1+qz$; infected cells die at a rate ay and are killed by the immune system at a rate pyz for modelling lytic effector mechanisms; the immune responses are assumed to get stronger at a rate proportional to the number of infected cells, cy, and also decay exponentially at a rate proportional to its current strength, bz. Note that the variable z represents the total immunity that can be generated in response to virus infection. The parameter p expresses the strength of the lytic component, whereas the parameter q expresses the efficacy of the nonlytic component.

Note that system (1.1) has not included the dynamics of free virus explicitly. This is because [1,5] assume that the turnover of free virus is much faster than that of infected cells. This allows them to make a quasi steady-state assumption, whereby the amount of free virus is simply proportional to the number of infected cells. Hence, the number of infected cells y can be considered also a measure of virus load.

Since the global dynamics of (1.1) is very useful in investigating the fundamental question of which type of responses is required to combat different types of viral infection, in the present paper, we focus on the mathematical analysis of the global dynamics of (1.1). We will show that if the basic reproductive ratio $R_0 \leq 1$, the disease-free steady state is globally asymptotically stable, corresponding to which the virus is cleared and the disease dies out; if $R_0 > 1$, the virus persists in the host and the disease steady state is locally asymptotically stable. Furthermore, the global stability of the disease steady state is established by Lyapunov function. When the efficacy of the lytic component is neglected, simple sufficient conditions for the global stability of the disease steady state is also obtained by geometrical approach of Li and Muldowney [24].

Our paper is organized as follows, in the next section, we give the conditions of stability of the disease-free steady state. The stability of the disease steady state is analyzed in Section 3. The paper ends with some numerical simulation in Section 4 and a brief discussion in Section 5.

2. DISEASE-FREE STEADY STATE

In [1,5], the basic reproductive ratio of the virus for system (1.1) is given by $R_0 = \lambda\beta/ad$. This ratio describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process. It is easy to see that if $R_0 \leq 1$, the disease-free steady state $E_0 = (\lambda/d, 0, 0)$ is the unique steady state, corresponding to the extinction of the free virus; if $R_0 > 1$, in addition to the disease-free steady state, there is only one disease steady state $E_1 = (\bar{x}, \bar{y}, \bar{z})$, corresponding to the survival of the free virus, described by the following expressions

$$\begin{aligned}
\bar{x} &= \frac{(a + p\bar{z})(1 + q\bar{z})}{\beta} = \frac{c\lambda(1 + q\bar{z})}{cd + (b\beta + cdq)\bar{z}}, \\
\bar{y} &= \frac{b\bar{z}}{c}, \\
\bar{z} &= \frac{-(pcd + ab\beta + acdq) + \sqrt{(pcd + ab\beta + acdq)^2 - 4p(b\beta + cdq)(acd - c\lambda\beta)}}{2(bp\beta + cdpq)}.
\end{aligned} \tag{2.1}$$

The objective of this section is to perform a global analysis to the disease-free steady state E_0. First, we show that solutions of system (1.1) are positive and ultimately bounded.

THEOREM 2.1. *All solutions of system (1.1) are positive for $t > 0$ and there exists $M > 0$, such that all the solutions satisfy $x(t), y(t), z(t) < M$ for all large t.*

PROOF. Because $y = 0$ is the constant solution of system (1.1), by the uniqueness and continuity of the solutions for initial conditions, we get $y(t) > 0$ for any $t > 0$. Next, we prove that $x(t)$ and $z(t)$ are positive for all $t > 0$. Suppose, for example, $x(t)$ is not always positive. Then, let $\tau > 0$ be the first time such that $x(\tau) = 0$. By the first equation of (1.1) we have $x'(\tau) = \lambda > 0$. This means $x(t) < 0$, for $t \in (\tau - \varepsilon, \tau)$, where ε is an arbitrarily small positive constant. This is a contradiction. It follows that $x(t)$ is always positive. In the same way, we see that $z(t)$ is always positive.

Next, we sketch the ultimate boundedness argument. Since all solutions of (1.1) are positive, by the first equation of (1.1) we have $x' = \lambda - dx - \beta xy/(1 + qz) < \lambda - dx$. Therefore, we have $x(t) < \lambda/d + 1$ for all large t, say $t > t_0$. Adding the first two equations gives $x' + y' = \lambda - dx - ay - pyz < \lambda - dy$. Let $A > 0$ such that $dA > \lambda + 1$. Then, so long as $x(t) + y(t) \geq A + \lambda/d + 1$ and $t > t_0$, we have $x' + y' < -1$. Clearly, there must exist $t_1 > t_0$ such that $x(t) + y(t) < A + \lambda/d + 1$ for all $t > t_1$.

The asymptotic bound for $y(t)$, namely, $y(t) < A + \lambda/d + 1$, together with the differential inequality $z' < c(A + \lambda/d + 1) - bz$, which holds for large t, leads immediately to the asymptotic bound $z(t) \leq c/b\ (A + \lambda/d + 1)$. ∎

To be concise, let $f(T)$ denotes the vector field of (1.1), where $T = (x, y, z)$. The Jacobian matrix J of (1.1) at T is

$$J = \begin{bmatrix} -d - \dfrac{\beta y}{1 + qz} & -\dfrac{\beta x}{1 + qz} & \dfrac{q\beta xy}{(1 + qz)^2} \\ \dfrac{\beta y}{1 + qz} & -a - pz + \dfrac{\beta x}{1 + qz} & -py - \dfrac{q\beta xy}{(1 + qz)^2} \\ 0 & c & -b \end{bmatrix}. \tag{2.2}$$

Now, we consider the stability of (1.1) at the disease-free steady state E_0. By Routh-Hurwitz criterion and center manifold theorem [25, Chapter 2, Theorem 2.7.2], we obtain the following.

THEOREM 2.2. *The disease-free steady state E_0 is locally asymptotically stable if $R_0 \leq 1$ and is unstable if $R_0 > 1$.*

PROOF. The characteristic equation associated with the Jacobian matrix (2.2) at the disease-free steady state E_0 is given by

$$H_{E_0}(\omega) = (\omega + d)\left(\omega + a - \frac{\lambda\beta}{d}\right)(\omega + b) = 0. \tag{2.3}$$

Therefore, all roots of equation (2.3) are negative when $R_0 < 1$, i.e., the disease-free steady state E_0 is locally asymptotically stable. If $R_0 > 1$, $\omega = (\lambda\beta - da)/d > 0$ is a root of equation (2.3), thus, the disease-free steady state E_0 is unstable.

To consider the case $R_0 = 1$, we set $\tilde{x} = x - \lambda/d$, $\tilde{y} = y$, $\tilde{z} = z$. Under this transformation, equation (1.1) becomes

$$\begin{aligned} x' &= -dx - \frac{\beta xy}{1+qz} - \frac{\beta\lambda y}{d(1+qz)}, \\ y' &= \frac{\beta xy}{1+qz} + \frac{\beta\lambda y}{d(1+qz)} - ay - pyz, \\ z' &= cy - bz, \end{aligned} \tag{2.4}$$

where we substitute x, y, z for $\tilde{x}, \tilde{y}, \tilde{z}$. The disease-free steady state E_0 is shifted to $\mathbf{0} = (0,0,0)$. The Jacobian matrix at $\mathbf{0}$ of (2.4) is

$$J_0 = \begin{bmatrix} -d & -\dfrac{\beta\lambda}{d} & 0 \\ 0 & 0 & 0 \\ 0 & c & -b \end{bmatrix}$$

when $R_0 = 1$. The matrix J_0 has eigenvalues $-d, 0, -b$, thus, the center manifold is a curve tangent to the y-axis. In order to obtain the approximative expression of the center manifold, we set

$$\begin{aligned} x &= m_1 y + m_2 y^2 + O\left(y^2\right), \\ z &= n_1 y + n_2 y^2 + O\left(y^2\right). \end{aligned} \tag{2.5}$$

It follows that

$$\begin{aligned} x' &= m_1 y' + 2m_2 y y' + O(y), \\ z' &= n_1 y' + 2n_2 y y' + O(y). \end{aligned} \tag{2.6}$$

In order to find the unknown coefficients, $m_1, m_2, n_1, n_2, \ldots$, we substitute (2.4) and (2.5) into (2.6) and obtain

$$\begin{aligned} (a + dm_1)\, y + \left(\beta m_1 + \beta m_1^2 + dm_2 - aqn_1 - pm_1 n_1 - aqm_1 n_1\right) y^2 + O\left(y^2\right) &= 0, \\ (bn_1 - c)\, y + \left(\beta m_1 n_1 - pn_1^2 - aqn_1^2 + bn_2\right) y^2 + O\left(y^2\right) &= 0. \end{aligned} \tag{2.7}$$

Comparing the coefficients of y, y^2 in (2.7), we find that

$$\begin{aligned} m_1 &= -\frac{a}{d}, \qquad m_2 = \frac{acq}{bd} - \frac{acq}{bd^2} - \frac{a^2cq}{bd^2} + \frac{a\beta}{d^2} - \frac{a^2\beta}{d^3}, \\ n_1 &= \frac{c}{b}, \qquad n_2 = \frac{ac\beta}{b^2 d} + \frac{c^2(p+aq)}{b^3}. \end{aligned}$$

Then, substituting (2.5) into (2.4), we have

$$y' = -\left(\frac{acq}{b} + \frac{cp}{b} + \frac{a\beta}{d}\right) y^2 + O\left(y^3\right). \tag{2.8}$$

Clearly, the zero point $y = 0$ of (2.8) is locally asymptotically stable, then the zero point $y = 0$ of (2.4), or equivalently, the zero point $y = 0$ of (1.1) is also locally asymptotically stable. Thus, the disease-free steady state E_0 is locally asymptotically stable when $R_0 = 1$. ∎

For the global stability of E_0, we have the following.

THEOREM 2.3. *The disease-free steady state E_0 is globally asymptotically stable if $R_0 \leq 1$.*

PROOF. Define a Lyapunov function,

$$V = \frac{1}{2}\left(x - \frac{\lambda}{d}\right)^2 + ny + kz,$$

where $n = \lambda/d$ and

$$k = \begin{cases} \dfrac{\lambda}{cd}\left(a - \dfrac{\lambda\beta}{d}\right) - \varepsilon > 0, & \text{if } R_0 < 1, \\ 0, & \text{if } R_0 = 1. \end{cases}$$

Along the trajectories of system (1.1), we have

$$\begin{aligned} V'|_{(1.1)} &= \left(x - \frac{\lambda}{d}\right)\left[-d\left(x - \frac{\lambda}{d}\right) - \frac{\beta xy}{1+qz}\right] + \frac{n\beta xy}{1+qz} - any - npyz + cky - bkz \\ &= -d\left(x - \frac{\lambda}{d}\right)^2 - \frac{\beta xy}{1+qz}\left(x - \frac{\lambda}{d}\right) + \frac{n\beta xy}{1+qz} - (an - ck)\, y - npyz - bkz. \end{aligned}$$

Since

$$\frac{\beta xy}{1+qz} = \frac{\beta y}{1+qz}\left(x - \frac{\lambda}{d}\right) + \frac{\beta\lambda y}{d(1+qz)},$$

we have

$$\begin{aligned} V'|_{(1.1)} &= -d\left(x - \frac{\lambda}{d}\right)^2 - \frac{\beta y}{1+qz}\left(x - \frac{\lambda}{d}\right)^2 - \frac{\beta\lambda y}{d(1+qz)}\left(x - \frac{\lambda}{d}\right) + \frac{n\beta y}{1+qz}\left(x - \frac{\lambda}{d}\right) \\ &\quad + \frac{n\beta\lambda y}{d(1+qz)} - (an - ck)\, y - npyz - bkz \\ &= -\left(d + \frac{\beta y}{1+qz}\right)\left(x - \frac{\lambda}{d}\right)^2 - \frac{(\lambda - nd)\,\beta y}{d(1+qz)}\left(x - \frac{\lambda}{d}\right) \\ &\quad + \frac{n\beta\lambda y - dy\,(an - ck)\,(1+qz)}{d(1+qz)} - npyz - bkz \\ &= -\left(d + \frac{\beta y}{1+qz}\right)\left(x - \frac{\lambda}{d}\right)^2 - \frac{(\lambda - nd)\beta y}{d(1+qz)}\left(x - \frac{\lambda}{d}\right) \\ &\quad + \frac{(n\beta\lambda - d\,(an - ck))\, y}{d(1+qz)} - \frac{q\,(an - ck)\, yz}{1+qz} - npyz - bkz. \end{aligned}$$

Since $n = \lambda/d, k = (\lambda/cd)(a - \lambda\beta/d) - \varepsilon$, we have $\lambda - nd = 0$, $n\beta\lambda - d(an - ck) = -cd\varepsilon$ and $q(an - ck) = q\beta\lambda^2/d^2 + cq\varepsilon$. Thus,

$$\begin{aligned} V'|_{(1.1)} = &-\left(d + \frac{\beta y}{1+qz}\right)\left(x - \frac{\lambda}{d}\right)^2 - \frac{c\varepsilon y}{1+qz} - \frac{q\left(\beta\lambda^2/d^2 + c\varepsilon\right) yz}{1+qz} \\ &- \frac{\lambda pyz}{d} - b\left(\frac{\lambda}{cd}\left(a - \frac{\lambda\beta}{d}\right) - \varepsilon\right) z. \end{aligned} \tag{2.9}$$

Note that x, y, z are positive. All terms of the right in (2.9) are nonpositive when $R_0 < 1$, i.e., $V' \leq 0$ and $V' = 0$ if and only if $x = \lambda/d$, $y = 0$, $z = 0$. Therefore, the maximal invariant set in $\{(x, y, z) : V' = 0\}$ is the singleton $\{E_0\}$.

If $R_0 = 1$, then

$$V'|_{(1.1)} = -d\left(x - \frac{\lambda}{d}\right)^2 - \frac{\beta y}{1+qz}\left(x - \frac{\lambda}{d}\right)^2 - \frac{q\beta\lambda^2 yz}{d^2(1+qz)} - \frac{\lambda pyz}{d}.$$

Thus, $V' \leq 0$ and $V' = 0$ if and only if $x = \lambda/d$, $yz = 0$. By LaSalle's invariance principle, any solution of system (1.1) tends to M, where $M \subset \{(x, y, z) : x = \lambda/d,\ yz = 0\}$ is the largest invariant subset of system (1.1). By the expression of system (1.1), $M = \{E_0\}$ is a singleton set.

The globally asymptotical stability of E_0 when $R_0 \leq 1$ follows from LaSalle's invariance principle [26, Chapter 2, Theorem 6.4] and Theorem 2.2. ∎

3. DISEASE STEADY STATE

In this section, we analyze the global stability of the disease steady state. First, we study the local stability of the disease steady state.

THEOREM 3.1. *The disease steady state E_1 is locally asymptotically stable if $R_0 > 1$.*

PROOF. After tedious calculations, the characteristic equation associated with the Jacobian matrix (2.2) at E_1 is given by

$$H_{E_1}(\omega) = \omega^3 + A_1\omega^2 + A_2\omega + A_3 = 0, \tag{3.1}$$

where

$$\begin{aligned} A_1 &= b + \frac{\lambda}{\bar{x}} > 0, \\ A_2 &= \frac{\beta^2\bar{x}\bar{y}}{(1+q\bar{z})^2} + cp\bar{y} + \frac{cq\beta\bar{x}\bar{y}}{(1+q\bar{z})^2} + \frac{b\lambda}{\bar{x}} > 0, \\ A_3 &= \frac{b\beta^2\bar{x}\bar{y}}{(1+q\bar{z})^2} + \frac{cq\lambda\beta\bar{x}\bar{y}}{(1+q\bar{z})^2} + \frac{cp\lambda\bar{y}}{\bar{x}} - \frac{cq\beta^2\bar{x}\bar{y}^2}{(1+q\bar{z})^3}. \end{aligned} \tag{3.2}$$

Using the first expression of (2.1), we have $\beta\bar{x} = (a + p\bar{z})(1 + q\bar{z})$. Thus,

$$\begin{aligned} A_3 &= \frac{\beta\bar{y}}{(1+q\bar{z})^2}\left[b\beta\bar{x} + cq\lambda - \frac{cq\beta\bar{x}\bar{y}}{1+q\bar{z}}\right] + \frac{cp\lambda\bar{y}}{\bar{x}} \\ &= \frac{\beta\bar{y}}{(1+q\bar{z})^2}\left[b\left(a+p\bar{z}\right)\left(1+q\bar{z}\right) + cq\lambda - cq\bar{y}\left(a+p\bar{z}\right)\right] + \frac{cp\lambda\bar{y}}{\bar{x}} \\ &= \frac{\beta\bar{y}}{(1+q\bar{z})^2}\left[b\left(a+p\bar{z}\right) + cq\lambda\right] + \frac{cp\lambda\bar{y}}{\bar{x}} > 0. \end{aligned}$$

To finish the proof, we need to show that

$$\Delta_2 = \begin{vmatrix} A_1 & 1 \\ A_3 & A_2 \end{vmatrix} = A_1A_2 - A_3 > 0.$$

Using (3.2), we have

$$A_1A_2 = \frac{b\beta^2\bar{x}\bar{y}}{(1+q\bar{z})^2} + cbp\bar{y} + \frac{cqb\beta\bar{x}\bar{y}}{(1+q\bar{z})^2} + \frac{b^2\lambda}{\bar{x}} + \frac{\lambda\beta^2\bar{y}}{(1+q\bar{z})^2} + \frac{cp\lambda\bar{y}}{\bar{x}} + \frac{cq\lambda\beta\bar{y}}{(1+q\bar{z})^2} + \frac{b\lambda^2}{\bar{x}^2}.$$

Hence,

$$\Delta_2 = cbp\bar{y} + \frac{b^2\lambda}{\bar{x}} + \frac{b\lambda^2}{\bar{x}^2} + \frac{\lambda\beta^2\bar{y} + cqb\beta\bar{x}\bar{y}}{(1+q\bar{z})^2} + \frac{cq\beta^2\bar{x}\bar{y}^2}{(1+q\bar{z})^3} > 0.$$

Therefore, all roots of equation (3.1) have negative real parts by Routh-Hurwitz criterion. It follows that the disease steady state E_1 is locally asymptotically stable. ∎

Next, we deal with the uniform persistence of (1.1).

THEOREM 3.2. *If $R_0 > 1$, then system (1.1) is uniformly persistent, i.e., there exists $\varepsilon > 0$ (independent of initial conditions), such that $\liminf_{t\to+\infty} x(t) > \varepsilon$, $\liminf_{t\to+\infty} y(t) > \varepsilon$, and $\liminf_{t\to+\infty} z(t) > \varepsilon$.*

PROOF. The result follows from an application of Theorem 4.6 in [27], with $X_1 = \text{int}(R^3_+)$ and $X_2 = bd(R^3_+)$. Since the proof is similar to that of Lemma 3.5 in [9], we only sketch the modifications that E_0 is a weak repeller for X_1.

Since $R_0 > 1$, there exists $\varepsilon > 0$ such that $\beta((\lambda/d) - \varepsilon)/(1 + q\varepsilon) - a - p\varepsilon > \varepsilon$. Suppose there exists a solution $(x(t), y(t), z(t))$ such that $(x(t), y(t), z(t)) \to (\lambda/d, 0, 0)$. Thus, when t is sufficient large, we have

$$\frac{\lambda}{d} - \varepsilon < x(t) < \frac{\lambda}{d} + \varepsilon, \qquad y(t) \le \varepsilon, \qquad z(t) \le \varepsilon.$$

By the second equation of system (1.1), we have

$$y' = \frac{\beta xy}{1+qz} - ay - pyz \geq \frac{\beta\left((\lambda/d)-\varepsilon\right)y}{1+q\varepsilon} - ay - p\varepsilon y > \varepsilon y.$$

Then $y(t)$ tends to infinity when t tends to infinity. This is a contradiction to that $y(t)$ tends to zero. Thus, E_0 is a weak repeller for X_1. ∎

The following results study the global stability of the disease steady state E_1.

THEOREM 3.3. *The disease steady state E_1 is globally asymptotically stable if $R_0 > 1$ and*

$$4bdp\left(1+q\bar{z}\right)^2 + 2bdq\beta\bar{x}\left(1+q\bar{z}\right) \geq cq^2\beta^2\bar{x}\bar{y}^2. \tag{3.3}$$

PROOF. Define a Lyapunov function,

$$V = \frac{1}{2}\left(x-\bar{x}\right)^2 + n\left(y-\bar{y}-\bar{y}\ln\frac{y}{\bar{y}}\right) + \frac{k}{2}\left(z-\bar{z}\right)^2,$$

where $n = \bar{x}$,

$$k = \frac{p\bar{x}}{c} + \frac{q\beta\bar{x}^2}{c\left(1+q\bar{z}\right)\left(1+qz\right)}.$$

Along the trajectories of system (1.1), we have

$$\begin{aligned} V'|_{(1.1)} &= \left(x-\bar{x}\right)\left[-d\left(x-\bar{x}\right) - \left(\frac{\beta xy}{1+qz} - \frac{\beta\bar{x}\bar{y}}{1+q\bar{z}}\right)\right] \\ &+\bar{x}\left(y-\bar{y}\right)\left[\left(\frac{\beta x}{1+qz} - \frac{\beta\bar{x}}{1+q\bar{z}}\right) - p\left(z-\bar{z}\right)\right] + \left(p\bar{x} + \frac{q\beta\bar{x}^2}{\left(1+q\bar{z}\right)\left(1+qz\right)}\right)\left(y-\bar{y}\right)\left(z-\bar{z}\right) \\ &- \left(\frac{bp\bar{x}}{c} + \frac{bq\beta\bar{x}^2}{c\left(1+q\bar{z}\right)\left(1+qz\right)}\right)\left(z-\bar{z}\right)^2 - \frac{q^2\beta\bar{x}^2\left(cy-bz\right)}{2c\left(1+q\bar{z}\right)\left(1+qz\right)^2}\left(z-\bar{z}\right)^2. \end{aligned}$$

Since $qz/(1+qz) < 1$, we have

$$\frac{bq^2\beta\bar{x}^2 z}{2c(1+q\bar{z})(1+qz)^2} < \frac{bq\beta\bar{x}^2}{2c(1+q\bar{z})(1+qz)}.$$

Furthermore, we have

$$\begin{aligned} \frac{\beta xy}{1+qz} - \frac{\beta\bar{x}\bar{y}}{1+q\bar{z}} &= \frac{\beta y\left(x-\bar{x}\right)}{1+qz} + \frac{\beta\bar{x}\left(y-\bar{y}\right)}{1+qz} - \frac{q\beta\bar{x}\bar{y}\left(z-\bar{z}\right)}{\left(1+qz\right)\left(1+q\bar{z}\right)}, \\ \frac{\beta x}{1+qz} - \frac{\beta\bar{x}}{1+q\bar{z}} &= \frac{\beta\left(x-\bar{x}\right)}{1+qz} - \frac{q\beta\bar{x}\left(z-\bar{z}\right)}{\left(1+qz\right)\left(1+q\bar{z}\right)}. \end{aligned}$$

Thus,

$$\begin{aligned} V'|_{(1.1)} &< -\left(d + \frac{\beta y}{1+qz}\right)\left(x-\bar{x}\right)^2 + \frac{q\beta\bar{x}\bar{y}}{\left(1+qz\right)\left(1+q\bar{z}\right)}\left(x-\bar{x}\right)\left(z-\bar{z}\right) \\ &- \left(\frac{bp\bar{x}}{c} + \frac{q\beta\bar{x}^2\left(b\left(1+qz\right)+cqy\right)}{2c\left(1+q\bar{z}\right)\left(1+qz\right)^2}\right)\left(z-\bar{z}\right)^2 \\ &\equiv -A_1\left(x-\bar{x}\right)^2 + A_2\left(x-\bar{x}\right)\left(z-\bar{z}\right) - A_3\left(z-\bar{z}\right)^2, \end{aligned} \tag{3.4}$$

where

$$\begin{aligned} A_1 &= d + \frac{\beta y}{1+qz} > 0, \\ A_2 &= \frac{q\beta\bar{x}\bar{y}}{\left(1+qz\right)\left(1+q\bar{z}\right)} > 0, \\ A_3 &= \frac{bp\bar{x}}{c} + \frac{q\beta\bar{x}^2\left(b\left(1+qz\right)+cqy\right)}{2c\left(1+q\bar{z}\right)\left(1+qz\right)^2} > 0. \end{aligned}$$

When $(x-\bar{x})(z-\bar{z}) \leq 0$, then from (3.4), we have $V' < 0$ is always true. When $(x-\bar{x})(z-\bar{z}) > 0$, since the arithmetical mean is greater than or equal to the geometrical mean, we have $V' < 0$ if $A_2^2 \leq 4A_1A_3$, i.e.,

$$cq^2\beta^2\bar{x}\bar{y}^2 \leq 4\left(d+\frac{\beta y}{1+qz}\right)\left(bp+\frac{q\beta\bar{x}\left(b\left(1+qz\right)+cqy\right)}{2\left(1+q\bar{z}\right)\left(1+qz\right)^2}\right)\left(1+qz\right)^2\left(1+q\bar{z}\right)^2. \tag{3.5}$$

Note that

$$\begin{aligned}
&4\left(d+\frac{\beta y}{1+qz}\right)\left(bp+\frac{q\beta\bar{x}\left(b\left(1+qz\right)+cqy\right)}{2\left(1+q\bar{z}\right)\left(1+qz\right)^2}\right)\left(1+qz\right)^2\left(1+q\bar{z}\right)^2\\
&\quad = 4bdp\left(1+q\bar{z}\right)^2\left(1+qz\right)^2+2bdq\beta\bar{x}\left(1+q\bar{z}\right)\left(1+qz\right)\\
&\qquad +2\beta y\left(1+q\bar{z}\right)\left(bq\beta\bar{x}+2bp\left(1+q\bar{z}\right)\left(1+qz\right)+c\bar{x}q^2\left(d+\frac{\beta y}{1+qz}\right)\right)\\
&\quad > 4bdp\left(1+q\bar{z}\right)^2+2bdq\beta\bar{x}\left(1+q\bar{z}\right).
\end{aligned}$$

It follows that (3.5) is valid when (3.3) holds, i.e., $V' < 0$, which concludes the proof. ∎

In fact, the condition (3.3) of Theorem 3.3 can be rewritten as a form of R_0. Using (2.1), we have

$$\bar{x} = \frac{c\lambda(1+q\bar{z})}{cd+(b\beta+cdq)\bar{z}}, \qquad \bar{y} = \frac{b\bar{z}}{c}.$$

Thus, (3.3) is equivalent to

$$(4dpq(b\beta+cdq)-b\lambda q^2\beta^2)\bar{z}^2+(8cpqd^2+4bdp\beta+2cd\beta\lambda q^2)\bar{z}+4cpd^2+2cdq\beta\lambda \geq 0. \tag{3.6}$$

When

$$\lambda \leq \frac{4dp(b\beta+cdq)}{bq\beta^2},$$

i.e.,

$$R_0 \leq \frac{4p(b\beta+cdq)}{abq\beta} \equiv R^*,$$

inequality (3.6) is always valid. When $R_0 > R^*$, let

$$f(z) = B_1z^2+B_2z+B_3,$$

where $B_1 = 4dpq(b\beta+cdq)-b\lambda q^2\beta^2 < 0$, $B_2 = 8cpqd^2+4bdp\beta+2cd\beta\lambda q^2$, $B_3 = 4cpd^2+2cdq\beta\lambda$. By the figure of equation $f(z)=0$, we see that the sufficient and necessary condition of inequality (3.6) is $\bar{z} \leq z^*$, where

$$z^* = \frac{-B_2-\sqrt{B_2^2-4B_1B_3}}{2B_1}$$

is the positive root of $f(z)=0$. Thus, we obtain the following corollary.

COROLLARY 3.1. *If $1 < R_0 \leq R^*$, then the disease steady state E_1 is globally asymptotically stable; if $R_0 > R^* \geq 1$, then the disease steady state E_1 is globally asymptotically stable when $\bar{z} \leq z^*$.*

Now, we study the influence of the different immune responses. In the absence of the efficacy of the nonlytic component, i.e., $q=0$, inequality (3.6) is always true. In the absence of the efficacy

of the lytic component, i.e., $p = 0$, the expressions of $E_1 = (\bar{x}, \bar{y}, \bar{z})$ in (2.1) is changed to the following,

$$\begin{aligned}
\bar{x} &= \frac{a(1+q\bar{z})}{\beta} = \frac{c\lambda(1+q\bar{z})}{cd+(b\beta+cdq)\bar{z}},\\
\bar{y} &= \frac{b\bar{z}}{c},\\
\bar{z} &= \frac{-(2acdq+ab\beta-cq\lambda\beta)+\sqrt{(2acdq+ab\beta-cq\lambda\beta)^2-4acq(b\beta+cdq)(ad-\lambda\beta)}}{2aq(b\beta+cdq)}.
\end{aligned} \tag{3.7}$$

Inequality (3.6) becomes to following,

$$-bq\beta\bar{z}^2+2cdq\bar{z}+2cd\geq 0 \tag{3.8}$$

and the positive root of $f(z) = 0$ is

$$z^* = \frac{cdq+\sqrt{cdq(cdq+2b\beta)}}{bq\beta}.$$

Thus, inequality (3.8) is true when $\bar{z} \leq z^*$. Let $C_1 = b\beta + cdq, C_2 = 2acdq + ab\beta - cq\lambda\beta$, using equation (3.7), we know that $\bar{z} \leq z^*$ is equivalent to

$$R_0 \leq 1+\frac{aC_1\left(cdq+\sqrt{cdq\,(b\beta+C_1)}\right)^2+b\beta C_2\left(cdq+\sqrt{cdq\,(b\beta+C_1)}\right)}{acdqb^2\beta^2} \equiv R_0^1.$$

In order to ensure

$$aC_1\left(cdq+\sqrt{cdq\,(b\beta+C_1)}\right)^2+b\beta C_2\left(cdq+\sqrt{cdq\,(b\beta+C_1)}\right)>0,$$

we need

$$R_0 < 2+\frac{b\beta}{cdq}+\frac{C_1\left(cdq+\sqrt{cdq(b\beta+C_1)}\right)}{bcdq\beta} \equiv R_0^2.$$

Thus, let $R^{**} = \max\{R_0^1, R_0^2\}$, we have the following corollary.

COROLLARY 3.2. *If $R_0 > 1$ and $q = 0$, then the disease steady state E_1 is globally asymptotically stable; if $1 < R_0 < R^{**}$ and $p = 0$, then the disease steady state E_1 is globally asymptotically stable.*

REMARK. By Corollary 3.2, when the efficacy of the nonlytic component is neglected, i.e., $q = 0$, which is very common in virus dynamics models (e.g., [2–4]), the disease steady state E_1 is globally stable only if it exists.

In the following, using the geometrical approach of Li and Muldowney in [24], we obtain simple sufficient conditions that the disease steady state E_1 is globally asymptotically stable when $p = 0$. At first, we give a brief outline of this geometrical approach.

Let $x \mapsto f(x) \in \mathbb{R}^n$ be a C^1 function for x in an open set $D \subset \mathbb{R}^n$. Consider the differential equation,

$$x' = f(x). \tag{3.9}$$

Denote by $x(t, x_0)$ the solution to (3.9) such that $x(0, x_0) = x_0$. We make the following two assumptions.

(H_1) There exists a compact absorbing set $K \subset D$.

(H_2) Equation (3.9) has a unique equilibrium $\bar{x}$ in D.

The equilibrium $\bar{x}$ is said to be globally stable in D if it is locally stable and all trajectories in D converge to $\bar{x}$. For $n \geq 2$, by a *Bendixson criterion* we mean a condition satisfied by f which precludes the existence of nonconstant periodic solutions of (3.9). The classical Bendixson's condition $\operatorname{div} f(x) < 0$ for $n = 2$ is robust under C^1 local perturbations of f. For higher-dimensional systems, the C^1 robust properties are discussed in [24,28,29].

A point $x_0 \in D$ is *wandering* for (3.9) if there exists a neighborhood U of x_0 and $T > 0$ such that $U \cap x(t, U)$ is empty for all $t > T$. Thus, for example, all equilibria and limit points are nonwandering. The following global-stability principle is established in [24] for autonomous systems in any finite dimension.

THEOREM 3.4. *Suppose that Assumptions (H_1) and (H_2) hold. Assume that (3.9) satisfies a Bendixson criterion that is robust under C^1 local perturbations of f at all nonequilibrium nonwandering points for (3.9). Then, $\bar{x}$ is globally stable in D provided it is stable.*

The following Bendixson criterion is given in [24] and shown to have the robustness required by Theorem 3.4. Let $x \mapsto P(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 for $x \in D$. Assume that $P^{-1}(x)$ exists and is continuous for $x \in K$, the compact absorbing set. A quantity $\bar{q}_2$ is defined as

$$\bar{q}_2 = \limsup_{t \to \infty} \sup_{x_0 \in K} \frac{1}{t} \int_0^t \mu \left(B \left(x \left(s, x_0 \right) \right) \right) ds, \tag{3.10}$$

where

$$B = P_f P^{-1} + P \frac{\partial f^{[2]}}{\partial x} P^{-1}, \tag{3.11}$$

the matrix P_f is obtained by replacing each entry p of P by its derivative in the direction of f, p_{ij_f}, and $\mu(B)$ is the *Lozinskiĭ measure* of B with respect to a vector norm $|\cdot|$ in $\mathbb{R}^N$, $N = \binom{n}{2}$, defined by [30, p. 41]

$$\mu(B) = \lim_{h \to 0^+} \frac{|I + hB| - 1}{h}.$$

It is shown in [24] that, if D is simply connected, the condition $\bar{q}_2 < 0$ rules out the presence of any orbit that gives rise to a simple closed rectifiable curve that is invariant for (3.9), such as periodic orbits, homoclinic orbits, and heteroclinic cycles. Moreover, it is robust under C^1 local perturbations of f near any nonequilibrium point that is nonwandering. In particular, the following global-stability result is proved in [24].

THEOREM 3.5. *Assume that D is simply connected and that the Assumptions (H_1) and (H_2) hold. Then, the unique equilibrium $\bar{x}$ of (3.9) is globally stable in D if $\bar{q}_2 < 0$.*

Now, we study the global stability of the disease steady state E_1, and obtain the following.

THEOREM 3.6. *If $R_0 > 1$, $p = 0$, $2a < b + 2d$, and $cq\lambda < \min\{b\beta, (b + 2d - 2a)\beta\}$, then the disease steady state E_1 is globally asymptotically stable.*

PROOF. The Jacobian matrix J associated with a general solution to (1.1) is as (2.2), its second additive compound matrix $J^{[2]}$ is

$$J^{[2]} = \begin{bmatrix} -a - d - \dfrac{\beta y}{1+qz} + \dfrac{\beta x}{1+qz} & -\dfrac{q\beta xy}{(1+qz)^2} & -\dfrac{q\beta xy}{(1+qz)^2} \\ c & -b - d - \dfrac{\beta y}{1+qz} & -\dfrac{\beta x}{1+qz} \\ 0 & \dfrac{\beta y}{1+qz} & -a - b + \dfrac{\beta x}{1+qz} \end{bmatrix}. \tag{3.12}$$

A comprehensive survey on compound matrices and their relations to differential equations is given in [31]. Set the function,

$$P(x, y, z) = \begin{bmatrix} f_1 & 0 & 0 \\ 0 & f_2 & 0 \\ 0 & f_2 & f_2 \end{bmatrix},$$

where $f_1 = 1 + qz$, $f_2 = qx$. Then,

$$P_f P^{-1} = \operatorname{diag}\left\{\frac{f_1'}{f_1}, \frac{f_2'}{f_2}, \frac{f_2'}{f_2}\right\}$$

and the matrix $B = P_f P^{-1} + P\frac{\partial f}{\partial x}^{[2]} P^{-1}$ in (3.11) can be written in block form,

$$B = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix},$$

where

$$B_{11} = \frac{f_1'}{f_1} - a - d + \frac{\beta x}{1+qz} - \frac{\beta y}{1+qz}, \qquad B_{12} = \begin{bmatrix} 0 & -\dfrac{\beta y}{1+qz} \end{bmatrix},$$

$$B_{21} = \begin{bmatrix} \dfrac{cqx}{1+qz} \\ \dfrac{cqx}{1+qz} \end{bmatrix}, \qquad B_{22} = \begin{bmatrix} \dfrac{f_2'}{f_2} - b - d + \dfrac{\beta x}{1+qz} - \dfrac{\beta y}{1+qz} & -\dfrac{\beta x}{1+qz} \\ a - d & \dfrac{f_2'}{f_2} - a - b \end{bmatrix}.$$

Let (u, v, w) denotes the vectors in $\mathbb{R}^3 \cong \mathbb{R}^{\binom{n}{2}}$, we select a norm in $\mathbb{R}^3$ as $|(u, v, w)| = \max\{|u|, |v| + |w|\}$ and let μ denotes the Lozinskiĭ measure with respect to this norm. Following the method in [32], we have the estimate $\mu(B) \leq \sup\{g_1, g_2\}$, where

$$g_1 = \mu_1(B_{11}) + |B_{12}|, \qquad g_2 = |B_{21}| + \mu_1(B_{22}),$$

$|B_{12}|$, $|B_{21}|$ are matrix norms with respect to the l_1 vector norm, and μ_1 denotes the Lozinskiĭ measure with respect to the l_1 norm, see [30, p.41]. More specifically, $\mu_1(B_{11}) = f_1'/f_1 - a - d + \beta x/(1+qz) - \beta y/(1+qz)$, $|B_{12}| = \beta y/(1+qz)$, $|B_{21}| = cqx/(1+qz)$. To calculate $\mu_1(B_{22})$, add the absolute value of the off-diagonal elements to the diagonal one in each column of B_{22}, and then take the maximum of two sums, see [30, p. 41]. From Theorem 2.1, 3.2, and $2a < b + 2d$, we have

$$\begin{aligned} \mu_1(B_{22}) &= \max\left\{\frac{f_2'}{f_2} - b - d + \frac{\beta x}{1+qz} - \frac{\beta y}{1+qz} + |a-d|, \frac{f_2'}{f_2} - a - b + \frac{\beta x}{1+qz}\right\} \\ &\leq \frac{f_2'}{f_2} + \frac{\beta x}{1+qz} - a - \min\{b + 2d - 2a, b\}. \end{aligned}$$

From the second equation of (1.1) when $p = 0$, we have

$$\frac{y'}{y} = \frac{\beta x}{1+qz} - a.$$

From Theorem 2.1, 3.2, and the first equation of (1.1), we have

$$\frac{cqx}{1+qz} < cqx < \frac{cq\lambda}{\beta}.$$

Since $cq\lambda < \min\{b\beta, (b + 2d - 2a)\beta\}$, take $\varepsilon = \min\{b\beta, (b + 2d - 2a)\beta\} - cq\lambda > 0$ is a constant, we have

$$\begin{aligned} g_1 &= \frac{f_1'}{f_1} - a - d + \frac{\beta x}{1+qz} \\ &= \frac{f_1'}{f_1} + \frac{y'}{y} - d, \\ g_2 &\leq \frac{f_2'}{f_2} + \frac{y'}{y} + \frac{cqx}{1+qz} - \min\{b + 2d - 2a, b\} \\ &< \frac{f_2'}{f_2} + \frac{y'}{y} + \frac{cq\lambda}{\beta} - \min\{b + 2d - 2a, b\} \\ &= \frac{f_2'}{f_2} + \frac{y'}{y} - \frac{\varepsilon}{\beta}. \end{aligned}$$

Using the variation of constants formula for inhomogeneous linear ordinary differential equations, we write the solutions to the first and the third equality of system (1.1) in the form of

$$x(t) = x(0)\, e^{-\int_0^t (d+\beta y(s)/(1+qz(s)))\, ds} + \frac{\int_0^t \left(\lambda e^{\int_0^s (d+\beta y(\tau)/(1+qz(\tau)))\, d\tau}\right) ds}{e^{\int_0^t (d+\beta y(s)/(1+qz(s)))\, ds}}$$

and

$$z(t) = z(0)\, e^{-bt} + \frac{\int_0^t cy(s)\, e^{bs}\, ds}{e^{bt}}.$$

Thus,

$$\left| x(t) - \frac{\lambda}{d + \beta y(t)/(1+qz(t))} \right| \to 0$$

and

$$\left| z(t) - \frac{cy(t)}{b} \right| \to 0, \qquad \text{as } t \to \infty$$

are valid. Note that

$$\frac{f_1'}{f_1} = \frac{q(cy - bz)}{1+qz},$$
$$\frac{f_2'}{f_2} = \frac{\lambda - dx}{x} - \frac{\beta y}{1+qz}.$$

We can choose t_1 large enough such that

$$g_1 \le \frac{y'}{y} - (d - \delta),$$
$$g_2 < \frac{y'}{y} - \left(\frac{\varepsilon}{\beta} - \delta\right)$$

for $t \ge t_1$, where δ can be chosen arbitrarily small.

Therefore,

$$\mu(B) \le \frac{y'}{y} - \bar{b}$$

for $t \ge t_1$, where $\bar{b} = \min\{d - \delta, \varepsilon/\beta - \delta\} > 0$ is a constant. Along each solution $(x(t), y(t), z(t))$ of equation (1.1) with $(x(0), y(0), z(0)) \in K$, where K is the compact absorbing set and exists by Theorems 2.1 and 3.2, we have

$$\frac{1}{t}\int_0^t \mu(B)\, ds = \frac{1}{t}\int_0^{t_1} \mu(B)\, ds + \frac{1}{t}\int_{t_1}^t \mu(B)\, ds \le \frac{1}{t}\int_0^{t_1} \mu(B)\, ds + \frac{1}{t}\log\frac{y(t)}{y(t_1)} - \bar{b},$$

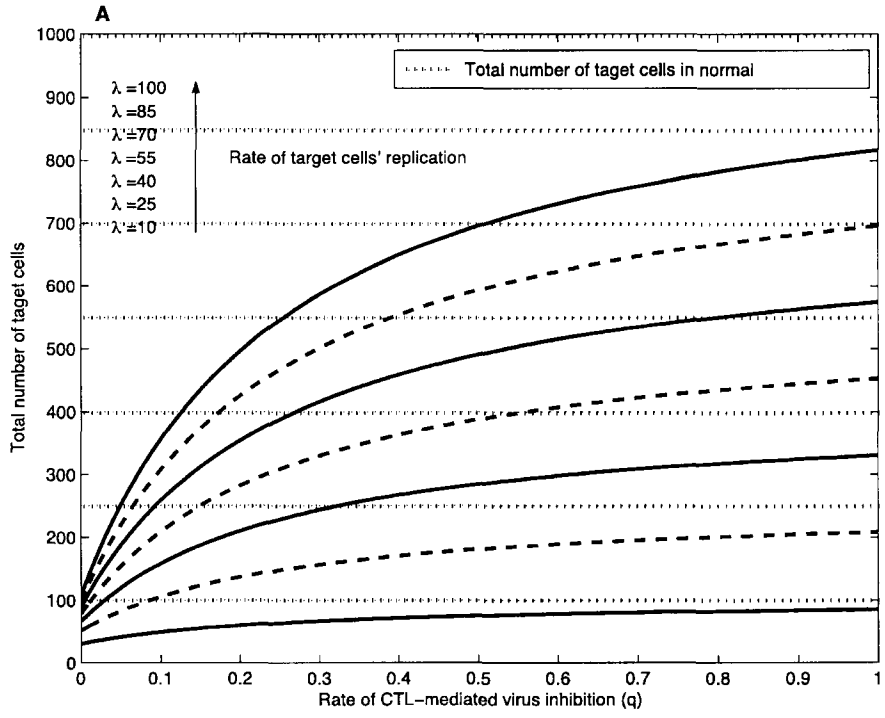
which implies that $\bar{q}_2 \le -\bar{b}/2 < 0$ from (3.10). This complete the proof. ∎

REMARK 3.2. In Corollary 3.2 and Theorem 3.6, the conditions of the global stability of E_1 when $p = 0$ is not same and cannot include each other.

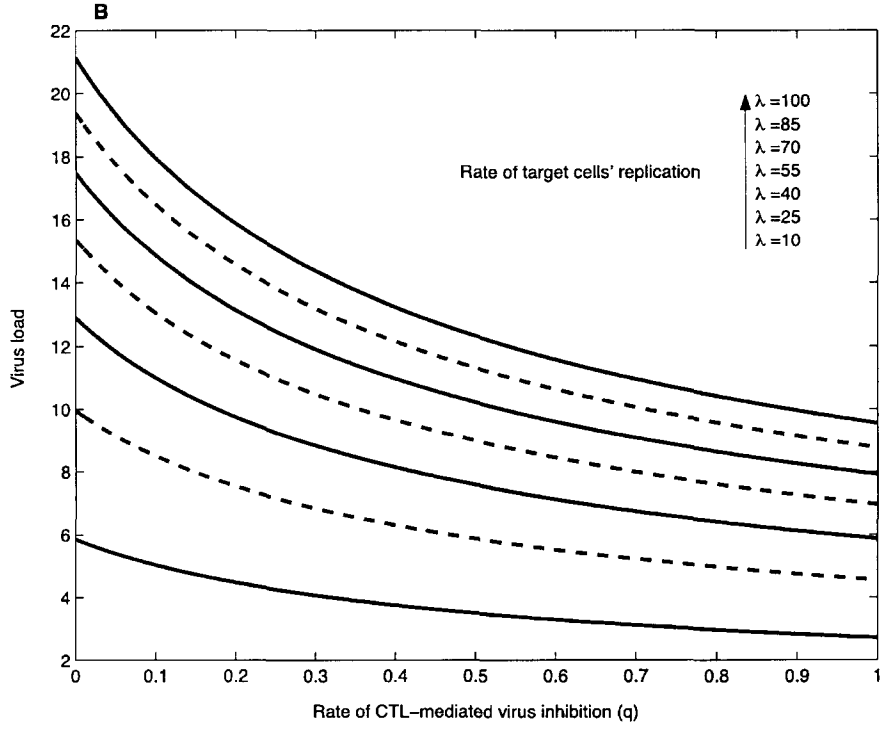
4. SIMULATION

In this section, to investigate whether the above findings could be explained in simple quantitative terms, we used the numerical simulation to analyze the effect of the dynamics between the rate of CTL-mediated virus inhibition (q) and the rate of target cells' replication (λ). The parameters were fixed by

$$d = 0.1, \qquad \beta = 0.05, \qquad a = 0.1, \qquad c = 0.2, \qquad b = 0.1, \qquad p = 0.1.$$

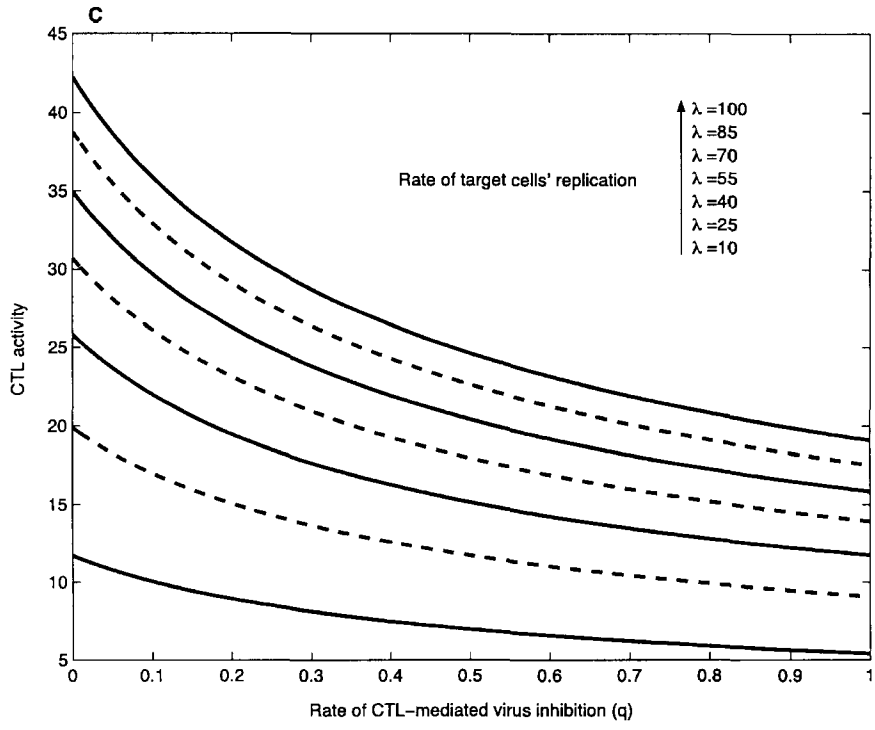


(a)



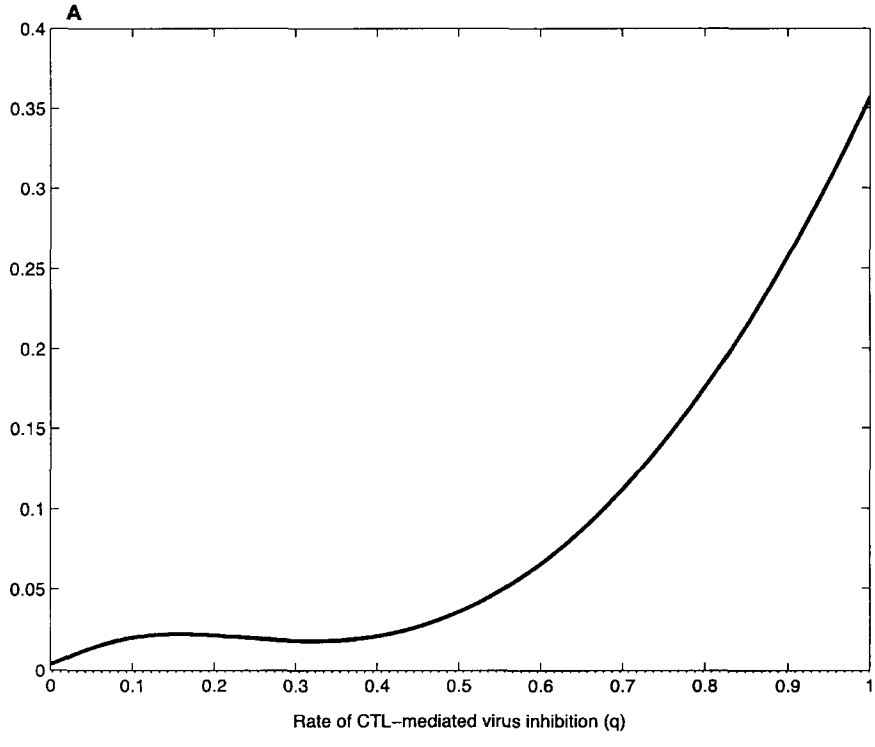
(b)

Figure 1. Effect of the rate of CTL-mediated virus inhibition (q) and the rate of target cells' replication (λ) on the outcome of viral infection, as predicted by the disease steady state E_1.



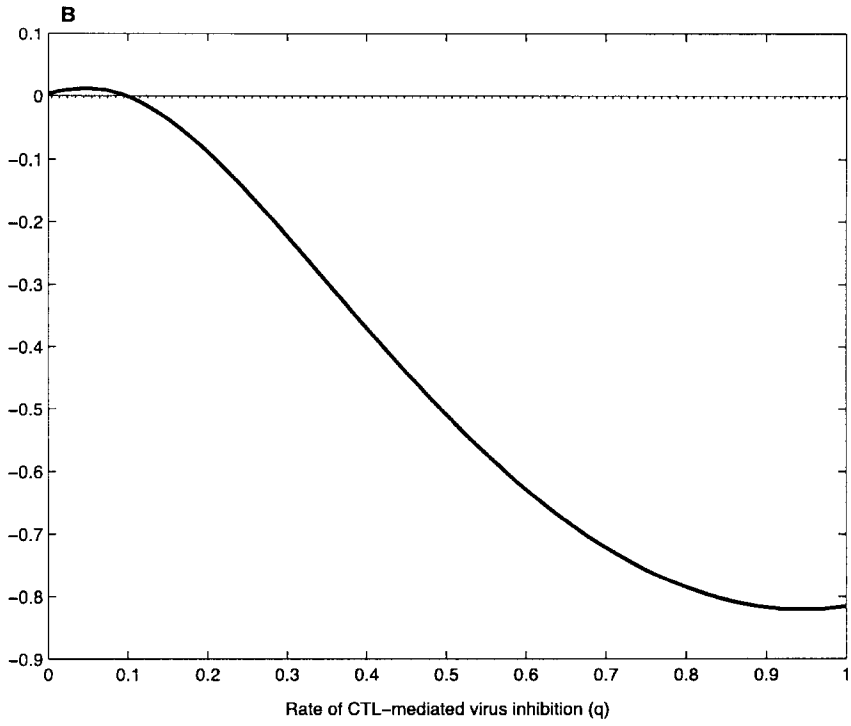
(c)

Figure 1. (cont.)



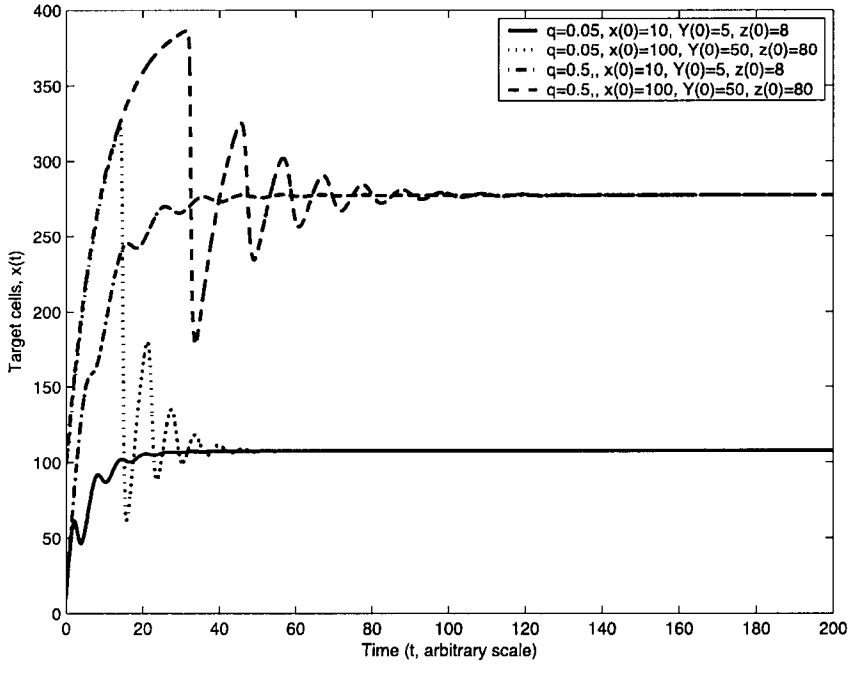
(a). $\lambda = 25$.

Figure 2. Curve of $f(q;\lambda) = 4bdp(1+q\bar{z})^2 + 2bdq\beta\bar{x}(1+q\bar{z}) - cq^2\beta^2\bar{x}\bar{y}^2$.



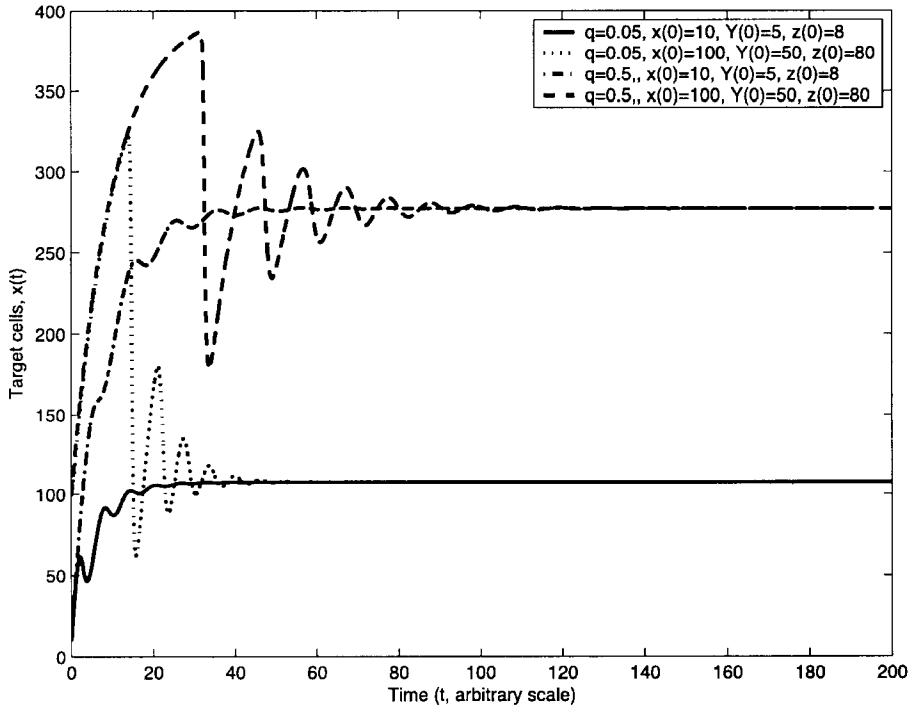
(b). $\lambda = 40$.

Figure 2. (cont.)

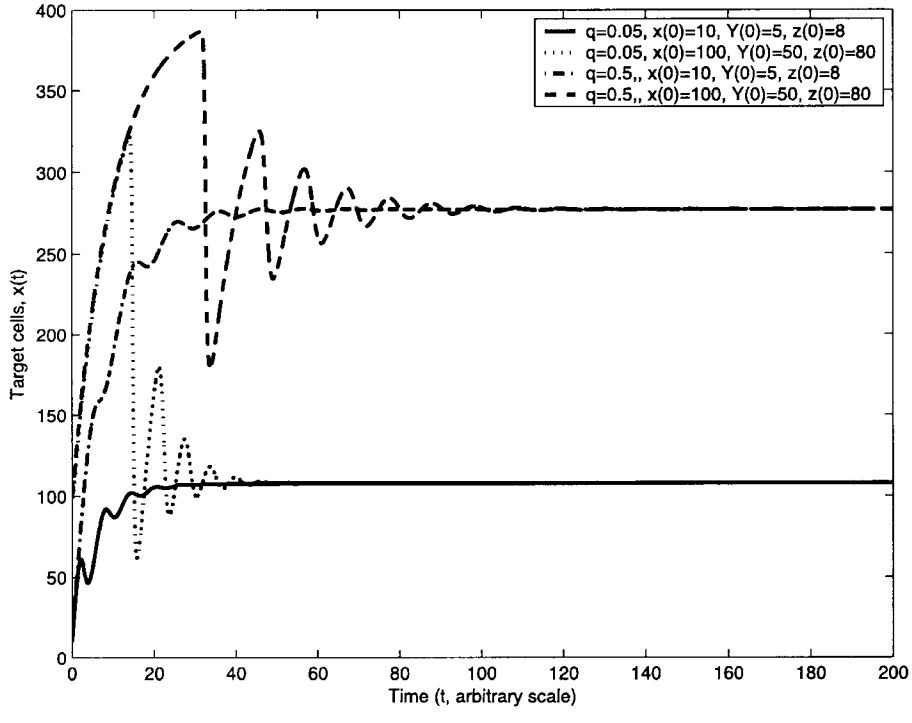


(a)

Figure 3. Time series of target cells, virus load and CTL activity in host as predicted by the model (1.1), where parameter $\lambda = 40$. When $q = 0.05$, $4bdp(1 + q\bar{z})^2 + 2bdq\beta\bar{x}(1+q\bar{z}) - cq^2\beta^2\bar{x}\bar{y}^2 = 0.01196 > 0$, whereas $q = 0.5$, $4bdp(1+q\bar{z})^2+2bdq\beta\bar{x}(1+q\bar{z}) - cq^2\beta^2\bar{x}\bar{y}^2 = -0.50857 < 0$.



(b)



(c)

Figure 3. (cont.)

Figure 1a shows the effect of pathology, measured by the total number of target cells (uninfected and infected) at the disease steady state E_1. The degree of pathology depends on the rate of CTL-

mediated virus inhibition and the rate of target cells' replication. If the rate of CTL-mediated virus inhibition at a low rate and the rate of target cells' replication is fixed, or the rate of target cells' replication at a high rate and the rate of CTL-mediated virus inhibition is fixed, then strong depletion of target cells is observed, and the host is likely to die. Figure 1b and Figure 1c show that virus load and CTL activity at the disease steady state both decline if one of the rates increase and the other is fixed.

Now, when $R_0 > 1$, we discuss the effect of q and λ on the condition (3.3) in Theorem 3.3. Figure 2a shows that the condition (3.3) is always valid if the rate of target cells' replication is at a low rate, and Figure 2b indicates that the condition (3.3) depends on the value of the rate of CTL-mediated virus inhibition when the rate of target cells' replication is at a high rate. If the rate of CTL-mediated virus inhibition is sufficient small, the condition is true.

However, Figure 3 indicates that the disease steady state E_1 is globally asymptotically stable although the condition (3.3) is not satisfied. Thus, we conjecture that the unique disease steady state E_1 is globally asymptotically stable only if the basic reproductive ratio of the virus $R_0 > 1$.

4. DISCUSSION

It has been difficult to obtain the global dynamics of the viral infection models. Recently, Korobeinikov [8], Leenheer *et al.* [9], and Wang *et al.* [11] give a global analysis of virus dynamics on the basic HIV models, which don't contain the immune responses. Since the basic HIV models can be translated to competitive systems, Leenheer *et al.* [9] and Wang *et al.* [11] used the theory of competitive system, which was initiated by Hirsch in a series of six well-known papers and was improved by Smith, of which we list [33–36]. Korobeinikov [8] constructed a class of Lyapunov function successfully, and thus obtained the global stability. However, the theory of competitive system or Korobeinikov type Lyapunov function is not fit to model (1.1).

In this paper, we present a mathematical analysis on global dynamics of the viral infections model, which is constructed by Bartholdy *et al.* [1] and Wodarz *et al.* [5] and include the immune responses directly (the efficacy of the nonlytic component and lytic component). It is rigorously established in Theorems 2.3 and 3.2 that the basic reproductive ratio of the virus R_0 is a sharp threshold parameter. If $R_0 \leq 1$, the virus is cleared and the disease dies out; if $R_0 > 1$, the virus persists in the host. Furthermore, when the efficacy of the nonlytic component $q = 0$, which is very common in virus dynamics models (e.g., [2–4]), $R_0 > 1$ means that the unique disease steady state is globally asymptotically stable. When the efficacy of the lytic component $p = 0$ or the efficacy of nonlytic component and lytic component are both present, the unique disease steady state is globally asymptotically stable if the basic reproductive ratio R_0 less than a constant, which is defined by the parameters of the model. Especially, when the efficacy of the lytic component $p = 0$, using the geometrical approach of Li and Muldowney [24], Theorem 3.6 established simple sufficient conditions for the global stability of the unique disease steady state. We expect that those approaches can be applied to solve global-stability problems in many other viral infection models.

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