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GLOBAL PROPERTIES OF A VIRUS DYNAMICS MODEL WITH SELF-PROLIFERATION OF CTLS

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Abstract. A viral infection model with self-proliferation of cytotoxic T lymphocytes (CTLs) is proposed and its global dynamics is obtained. When the per capita self-proliferation rate of CTLs is sufficient large, an infection-free but immunity-activated equilibrium always exists and is globally asymptotically stable if the basic reproduction number of virus is less than a threshold value, which means that the immune effect still exists though virus be eliminated. Qualitative numerical simulations further indicate that the increase of per capita self-proliferation rate may lead to more severe infection outcome, which may provide insight into the failure of immune therapy.

1. Introduction

Outbreaks of viral infection have become a major global health concern. Different kinds of virus, such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Ebola Virus and Zika Virus, have been associated with severe outcomes. A great deal of effort has been put toward to understand the life cycle of these virus. With the development of biomedical research, mathematical models also play an increasingly important role to provide insights into virus infection and dynamics, as well as on how an infection can be reduced or even eradicated. For example, on HBV infection, Nowak et al. [13] first proposed a basic three-dimensional viral infection model within-host. Note that immune responses play a critical part in the process of viral infections. Nowak et al. [14] further proposed the following four-dimensional system with the cytotoxic T lymphocytes (CTLs) population based on the basic model:

$$\begin{cases} x' = s - \beta xv - d_1 x, \\ y' = \beta xv - d_2 y - pyz, \\ v' = ky - uv, \\ z' = cyz - d_3 z. \end{cases} \tag{1.1}$$

Here $x(t), y(t), v(t)$ and $z(t)$ represent uninfected target cells, infected cells, free virus and CTLs, respectively. Uninfected cells are produced at a constant rate s, die at rate $d_1 x$, and become infected at rate βxv. Infected cells are produced at rate βxv and die at rate $d_2 y$. Free virus are produced from infected cells at rate ky and die at rate uv. CTLs are produced at rate cyz due to the stimulation of infected cells, and die at rate $d_3 z$. Infected cells are eliminated by CTLs at rate pyz. After that, based on the basic models, many studies were carried out to analysis of the dynamics of various virus infection within-host, such as [1, 9, 12, 15, 16, 17, 22, 23, 25] and the reference therein.

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Recent studies on the production mechanism of immune cells show that its self-proliferation cannot be neglected besides the stimulation of infected cells in [7]. Thus, to understand the effect of self-proliferation, based on the system (1.1) and [7], we propose the following new virus infection model:

$$\begin{cases} x' = s - \beta xv - d_1 x, \\ y' = \beta xv - d_2 y - pyz, \\ v' = ky - uv, \\ z' = cyz + rz(1 - \frac{z}{m}) - d_3 z. \end{cases} \tag{1.2}$$

Here the logistic proliferation term $rz(1 - z/m)$ describes the self-proliferation of CTLs, in which parameter r denotes a per capita self-proliferation rate, and m means the capacity of CTLs population.

When $r = 0$, i.e., without self-proliferation of CTLs, (1.2) has been completely analyzed in [10] if there is not explicit dynamics of free virus under a plausible quasi steady-state assumption. To explore the effects of the recruitment of immune responses on virus infection, the main contribution of the present paper is to obtain the complete global properties of (1.2) when $r > 0$.

2. Global dynamics analysis

Since we are interested in the dynamics of viral infection, and not the initial processes of infection, we assume that the initial condition of (1.2) has the form $x(0) > 0, y(0) > 0, v(0) > 0$ and $z(0) > 0$. Based on the initial conditions, it is easy to show that the solutions of system (1.2) are non-negative and ultimately bounded. The equilibria of (1.2) are the solutions of the following algebraic equations:

$$\begin{cases} s - \beta xv - d_1 x = 0, \\ \beta xv - d_2 y - pyz = 0, \\ ky - \mu v = 0, \\ cyz + rz(1 - \frac{z}{m}) - d_3 z = 0. \end{cases} \tag{2.1}$$

Clearly, system (1.2) always has infection-free equilibrium $E_0 = (\frac{s}{d_1}, 0, 0, 0)$. According to the definition and algorithm of the basic reproduction number of virus in [4], we can obtain the basic reproduction number of virus $R_0 = \frac{\beta sk}{d_1 d_2 \mu}$. Using the fourth equation of (2.1), we have $z = 0$ or

$$z = \frac{m}{r}(r - d_3 + cy). \tag{2.2}$$

When $z = 0$, based on the first three equations of (2.1), it is easy to obtain that the immunity-inactivated infection equilibrium $E_1 = (\frac{s}{d_1 R_0}, \frac{d_1\mu(R_0-1)}{\beta k}, \frac{d_1(R_0-1)}{\beta}, 0)$ always exists if $R_0 > 1$.

In addition, using the third and first equation of (2.1), we have

$$v = \frac{k}{\mu} y \ \text{ and } \ x = \frac{s}{\beta v + d_1} = \frac{s\mu}{\beta k y + d_1 \mu}. \tag{2.3}$$

After that, using the second equation and (2.3), we have

$$\frac{\beta k}{\mu} xy - d_2 y - pyz = 0. \tag{2.4}$$

Thus, when $y = 0$, using (2.2), we know that an infection-free but immunity-activated equilibrium $E_2 = (\frac{s}{d_1}, 0, 0, \frac{m(r-d_3)}{r})$ will appear if $r > d_3$. Otherwise, using (2.2), (2.3) and (2.4), we have

$$f(y) \equiv \frac{\beta k}{\mu} x - d_2 - pz = \frac{\beta k s}{\beta k y + d_1 \mu} - d_2 - \frac{mp}{r}(r - d_3 + cy) = 0.$$

Clearly, $f(+\infty) < 0$ and function $f(y)$ is monotonically decreasing since $f'(y) < 0$ always valid. As a result, $f(y) = 0$ has a unique positive root if

$$f(0) = \frac{\beta k s}{d_1 \mu} - d_2 - \frac{mp}{r}(r - d_3) = d_2[R_0 - 1 - \frac{mp}{r d_2}(r - d_3)] > 0,$$

i.e., $R_0 > 1 + \frac{mp}{rd_2}(r - d_3)$.

When $r < d_3$, according to (2.2), in order to keep the positive of z, we need

$$f(\frac{d_3 - r}{c}) = \frac{\beta ksc}{\beta k(d_3 - r) + d_1\mu} - d_2 > 0$$

is valid, i.e., $R_0 > 1 + \frac{\beta k(d_3 - r)}{cd_1\mu}$.

In summary, we have the following proposition.

Proposition 2.1. *The following hold.*

(i) *If $R_0 > 1$, the immunity-inactivated infection equilibrium E_1 always exists. Especially, an infection-free but immunity-activated equilibrium E_2 will appear if $r > d_3$.*

(ii) *Suppose that $0 \le r \le d_3$. If $R_0 > 1 + \frac{\beta k(d_3 - r)}{cd_1\mu}$, system (1.2) has a unique immunity-activated infection equilibrium $E_3 = (x_3, y_3, v_3, z_3)$, where*

$$x_3 = \frac{s\mu}{\beta k y_3 + d_1\mu}, \quad v_3 = \frac{k}{\mu} y_3, \quad z_3 = \frac{m}{r}(r - d_3 + cy_3),$$

and y_3 is the unique positive root of $f(y) = 0$ in this case.

(iii) *Suppose that $r > d_3$. If $R_0 > 1 + \frac{pm(r - d_3)}{rd_2}$, system (1.2) has a unique immunity-activated infection equilibrium $E_4 = (x_4, y_4, v_4, z_4)$, where*

$$x_4 = \frac{s\mu}{\beta k y_4 + d_1\mu}, \quad v_4 = \frac{k}{\mu} y_4, \quad z_4 = \frac{m}{r}(r - d_3 + cy_4),$$

and y_4 is the unique positive root of $f(y) = 0$ in this case.

In order to obtain the stability of above mentioned equilibria, we first give the Jacobian matrix J of system (1.2) at (x, y, v, z),

$$J = \begin{pmatrix} -\beta v - d_1 & 0 & -\beta x & 0 \\ \beta v & -d_2 - pz & \beta x & -py \\ 0 & k & -\mu & 0 \\ 0 & cz & 0 & cy + r - d_3 - \frac{2rz}{m} \end{pmatrix}. \tag{2.5}$$

So we have the following results.

Theorem 2.2. *The following hold.*

(i) *When $0 \le r \le d_3$, the infection-free equilibrium E_0 is globally asymptotically stable if $R_0 < 1$, and it is unstable when $R_0 > 1$.*

(ii) *When $r > d_3$, the infection-free equilibrium E_0 is always unstable.*

Proof. According to (2.5), we have the characteristic equation of system (1.2) at E_0

$$(\lambda + d_1)(\lambda - (r - d_3))H_0(\lambda) = 0, \tag{2.6}$$

where $H_0(\lambda) = \lambda^2 + (d_2 + \mu)\lambda + d_2\mu(1 - R_0)$. It is easy to show that $\lambda_1 = -d_1 < 0$ and $\lambda_2 = r - d_3$ are the roots of (2.6). Further, we can get all roots of $H_0(\lambda)$ are negative real part if $R_0 < 1$, and there is one positive real root if $R_0 > 1$.

(i) When $0 \le r < d_3$, we have $\lambda_2 < 0$. As a result, the infection-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and $0 \le r < d_3$, and is unstable if $R_0 > 1$. When $r = d_3$, $\lambda_2 = 0$. Thus, the center manifold is a curve tangent to the z-axis. In this case, settling a transformation

$\tilde{x} = x - x_0, \tilde{y} = y, \tilde{v} = v, \tilde{z} = z$, we know (1.2) becomes

$$\begin{cases} x' = -\beta xv - \dfrac{\beta s}{d_1}v - d_1 x, \\ y' = \beta xv + \dfrac{\beta s}{d_1}y - d_2 y - pyz, \\ v' = ky - \mu v, \\ z' = cyz - \dfrac{r}{m}z^2, \end{cases} \tag{2.7}$$

where we substitute x, y, v, z for $\tilde{x}, \tilde{y}, \tilde{v}, \tilde{z}$. To obtain the approximative expression of the center manifold, we set

$$\begin{aligned} x &= k_2 z^2 + k_3 z^3 + O(z^3), \\ y &= n_2 z^2 + n_3 z^3 + O(z^3), \\ v &= b_2 z^2 + b_3 z^3 + O(z^3), \end{aligned} \tag{2.8}$$

and obtain

$$\begin{aligned} \frac{dx}{dt} &= [2k_2 z + 3k_3 z^2 + O(z^2)]\frac{dz}{dt}, \\ \frac{dy}{dt} &= [2n_2 z + 3n_3 z^2 + O(z^2)]\frac{dz}{dt}, \\ \frac{dv}{dt} &= [2b_2 z + 3b_3 z^2 + O(z^2)]\frac{dz}{dt}. \end{aligned} \tag{2.9}$$

Substituting (2.7) and (2.8) into (2.9), we have

$$\begin{cases} -(\dfrac{\beta s}{d_1}b_2 + d_1 k_2)z^2 - (\dfrac{\beta s}{d_1}b_3 + d_1 k_3 - \dfrac{2r}{m}k_2)z^3 + O(z^3) = 0, \\ -(\dfrac{\beta s}{d_1}n_2 + d_2 n_2)z^2 - (\dfrac{\beta s}{d_1}n_3 + d_2 n_3 - \dfrac{2r}{m}n_2)z^3 + O(z^3) = 0, \\ (kn_2 - \mu b_2)z^2 + (kn_3 - \mu b_3 + \dfrac{2r}{m}b_2)z^3 + O(z^3) = 0. \end{cases} \tag{2.10}$$

Comparing the coefficients of z and z^2 in (2.10), we have

$$k_2 = k_3 = n_2 = n_3 = b_2 = b_3 = 0.$$

As a result, substituting (2.8) into the last equation of (2.7), we have

$$\frac{dz}{dt} = -\frac{r}{m}z^2 + O(z^3). \tag{2.11}$$

Thus, the zero point $z = 0$ of (2.11) is locally asymptotically stable, then E_0 is locally asymptotically stable if $R_0 < 1$ and $r = d_3$.

Let

$$L_0 = x - x_0 - x_0 \ln\frac{x}{x_0} + y + \frac{d_2}{k}v + \frac{p}{c}z.$$

Taking the time derivative of L_0 along the solution of system (1.2), we have

$$\begin{aligned} L_0' =& (1 - \frac{x_0}{x})(s - \beta xv - d_1 x) + \beta xv - d_2 y - pyz \\ &+ \frac{d_2}{k}(ky - \mu v) + \frac{p}{c}\left(cyz + rz(1 - \frac{z}{m}) - d_3 z\right) \\ =& d_1 x_0(2 - \frac{x}{x_0} - \frac{x_0}{x}) + \frac{d_2\mu}{k}(R_0 - 1)v - \frac{prz^2}{cm} + \frac{p(r - d_3)z}{c} \leq 0 \end{aligned}$$

if $R_0 < 1$ and $0 \le r \le d_3$, and $L_0' = 0$ only if $x = x_0, v = 0$ and $z = 0$ simultaneously, i.e., the maximal invariant subset in $\{(x, y, v, z) : L_0'|_{(1.2)} = 0\}$ is the singleton $\{E_0\}$. As a result, E_0 is globally asymptotically stable based on the LaSalle's invariance principle.

(ii) When $r > d_3$, the eigenvalue $\lambda_2 = r - d_3 > 0$. So the infection-free equilibrium E_0 is always unstable. □

Theorem 2.3. *Suppose that immunity-inactivated infection equilibrium E_1 exists, i.e., $R_0 > 1$.*

(i) *When $0 \le r < d_3$, E_1 is globally asymptotically stable if $1 < R_0 < 1 + \frac{\beta k(d_3 - r)}{cd_1\mu}$, and it is unstable when $R_0 > 1 + \frac{\beta k(d_3 - r)}{cd_1\mu}$.*

(ii) *When $r \ge d_3$, E_1 is always unstable.*

Proof. Let $x_1 = \frac{s}{d_1 R_0}, y_1 = \frac{d_1\mu(R_0-1)}{\beta k}, v_1 = \frac{d_1(R_0-1)}{\beta}$. According to (2.5), we have the following characteristic equation of system (1.2) at E_1

$$(\lambda - cy_1 - r + d_3)H_1(\lambda) = 0,$$

where $H_1(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$, and

$$a_1 = d_2 + \mu + d_1 R_0 > 0, \quad a_2 = d_1(d_2 + \mu)R_0 > 0, \quad a_3 = d_1 d_2 \mu(R_0 - 1) > 0.$$

Here we use $\beta v_1 = d_1(R_0 - 1), \beta k x_1 = d_2\mu$. Further, we have

$$a_1 a_2 - a_3 = R_0^2 d_1^2(d_2 + \mu) + d_1 d_2 \mu(R_0 + 1) + R_0 d_1(d_2^2 + \mu^2) > 0.$$

Clearly, $\lambda_1 = r - d_3 + cy_1 = r - d_3 + \frac{cd_1\mu(R_0-1)}{\beta k}$ is an eigenvalue at E_1 of system (1.2), and the real parts of $H_1(\lambda)$ are negative according to Routh-Hurwitz criterion.

(i) When $0 \le r < d_3$, we know $\lambda_1 < 0$ if $R_0 < 1 + \frac{\beta k(d_3 - r)}{cd_1\mu}$, i.e., E_1 is locally asymptotically stable in this case. Otherwise, it is unstable.

Let

$$L_1 = x - x_1 - x_1 \ln\frac{x}{x_1} + y - y_1 - y_1 \ln\frac{y}{y_1} + \frac{\beta x_1 v_1}{k y_1}(v - v_1 - v_1 \ln\frac{v}{v_1}) + \frac{p}{c}z.$$

Taking the time derivative of L_2 along the solution of system (1.2), and using $s = \beta x_1 v_1 + d_1 x_1, \beta x_1 v_1 = d_2 y_1$ and $k y_1 = \mu v_1$, we have

$$\begin{aligned} L_1' =& (1 - \frac{x_1}{x})(s - \beta x v - d_1 x) + (1 - \frac{y_1}{y})\left(\beta x v - d_2 y - pyz\right) \\ &+ (1 - \frac{v_1}{v})\frac{\beta x_1 v_1}{k y_1}(ky - \mu v) + \frac{p}{c}\left(cyz + rz(1 - \frac{z}{m}) - d_3 z\right) \\ =& d_1 x_1\left(2 - \frac{x_1}{x} - \frac{x}{x_1}\right) + \beta x_1 v_1\left(3 - \frac{x_1}{x} - \frac{y_1 x v}{y x_1 v_1} - \frac{v_1 y}{v y_1}\right) \\ &+ \frac{p d_1 \mu}{\beta k}\left(R_0 - 1 - \frac{\beta k(d_3 - r)}{cd_1\mu}\right)z - \frac{prz^2}{cm} \le 0 \end{aligned}$$

if $R_0 < 1 + \frac{\beta k(d_3 - r)}{cd_1\mu}$, and $L_1' = 0$ only if $x = x_1, \frac{y}{y_1} = \frac{v}{v_1}$ and $z = 0$. In this case, it is easy to obtain that the maximal invariant subset in $\{(x, y, v, z) : L_1'|_{(1.2)} = 0\}$ is the singleton $\{E_1\}$. As a result, E_1 is globally asymptotically stable based on the LaSalle's invariance principle.

(ii) When $r \ge d_3$, $\lambda_1 = r - d_3 + cy_1 > 0$ is always valid. So E_1 is always unstable. □

Theorem 2.4. *Suppose that $r > d_3$. The infection-free but immunity-activated equilibrium E_2 is globally asymptotically stable if $R_0 < 1 + \frac{pm(r - d_3)}{rd_2}$ and unstable if $R_0 > 1 + \frac{pm(r - d_3)}{rd_2}$.*

Proof. According to (2.5), we have the following characteristic equation of system(1.2) at E_2

$$(\lambda + d_1)(\lambda + r - d_3)H_3(\lambda) = 0,$$

where $H_3(\lambda) = \lambda^2 + (d_2 + \mu + pz_2)\lambda + d_2\mu(1 + \frac{pm(r-d_3)}{rd_2} - R_0)$. It is easy to obtain that $\lambda_1 = -d_1 < 0, \lambda_2 = -r + d_3 < 0$ are the eigenvalues at E_2 of system(1.2), and all roots of $H_3(\lambda)$ are negative real part if $R_0 < 1 + \frac{pm(r-d_3)}{rd_2}$. Thus, E_2 is locally asymptotically stable if $R_0 < 1 + \frac{pm(r-d_3)}{rd_2}$. Otherwise, it is unstable.

Let

$$L_2 = x - x_2 - x_2 \ln \frac{x}{x_2} + y + \frac{d_2}{k} R_0 v + \frac{p}{c}(z - z_2 - z_2 \ln \frac{z}{z_2}),$$

where $x_2 = \frac{s}{d_1}, z_2 = \frac{m(r-d_3)}{r}$. Taking the time derivative of L_2 along the solution of system (1.2), we have

$$\begin{aligned} L_2' =& (1 - \frac{x_2}{x})(s - \beta x v - d_1 x) + \beta x v - d_2 y - pyz + \frac{d_2}{k} R_0 (ky - \mu v) \\ &+ \frac{p}{c}(1 - \frac{z_2}{z})\left(cyz + rz(1 - \frac{z}{m}) - d_3 z\right) \\ =& d_1 x_2 (2 - \frac{x}{x_2} - \frac{x_2}{x}) + d_2(R_0 - 1 - \frac{pm(r-d_3)}{rd_2})y - \frac{rp}{cm}(z - z_2)^2 \leq 0 \end{aligned}$$

if $R_0 < 1 + \frac{pm(r-d_3)}{rd_2}$, and $L_2' = 0$ only if $x = x_2, y = 0$ and $z = z_2$, i.e., the maximal invariant subset in $\{(x, y, v, z) : L_2'|_{(1.2)} = 0\}$ is the singleton $\{E_2\}$. As a result, E_2 is globally asymptotically stable based on the LaSalle's invariance principle. □

Theorem 2.5. *The following hold.*

(i) *When $0 \leq r \leq d_3$, the immunity-activated infection equilibrium E_3 is globally asymptotically stable as long as it appears, i.e., $R_0 > 1 + \frac{\beta k(d_3 - r)}{cd_1\mu}$.*

(ii) *When $r > d_3$, the immunity-activated infection equilibrium E_4 is globally asymptotically stable as long as it appears, i.e., $R_0 > 1 + \frac{pm(r-d_3)}{rd_2}$.*

Proof. For the sake of description, the equilibria E_3 and E_4 are uniformly denoted as $E_* = (x_*, y_*, v_*, z_*)$. First, we discuss the local stability of E_*, according to (2.5), we have

$$J(E_*) = \begin{pmatrix} -d_1 - \sigma & 0 & -\frac{\alpha\mu}{k} & 0 \\ \sigma & -\alpha & \frac{\alpha\mu}{k} & -py^* \\ 0 & k & -\mu & 0 \\ 0 & cz_* & 0 & -\frac{r}{m} z_* \end{pmatrix},$$

where $\sigma = \beta v_* > 0, \alpha = d_2 + pz_* > 0, \frac{\alpha\mu}{k} = \beta x_* > 0$. The characteristic equation of system (1.2) at E_* is

$$\lambda^4 + \hat{a}_1\lambda^3 + \hat{a}_2\lambda^2 + \hat{a}_3\lambda + \hat{a}_4 = 0,$$

in which

$$\begin{aligned} \hat{a}_1 &= \frac{r}{m} z_* + \alpha + \mu + \varpi > 0, \\ \hat{a}_2 &= cpz_* y_* + \frac{r}{m} z_*(\alpha + \mu + \varpi) + \varpi(\alpha + mu) > 0, \\ \hat{a}_3 &= cpz_* y_*(\mu + \varpi) + \frac{r}{m} z_* \varpi(\alpha + \mu) + \alpha\mu\sigma > 0, \\ \hat{a}_4 &= c\mu p z_* y_* \varpi + \alpha\mu\sigma \frac{r}{m} z_* > 0, \\ \varpi &= d_1 + \sigma. \end{aligned}$$

After some calculations, we have

$$\begin{aligned}\hat{a}_1\hat{a}_2-\hat{a}_3=&cpz_*y_*(\frac{r}{m}z_*+\alpha)+(\alpha+\mu+\varpi)\frac{r^2}{m^2}z_*^2+\frac{r}{m}z_*(\alpha+\mu+\varpi)^2\\&+\alpha(\alpha\varpi+2d_1\mu+\mu\sigma+\varpi)+\mu\varpi(\mu+\varpi)>0,\end{aligned}$$

$$\begin{aligned}\hat{a}_3(\hat{a}_1\hat{a}_2-\hat{a}_3)-\hat{a}_1^2\hat{a}_4=&\mu\alpha c^2p^2z_*^2y_*^2+c^2p^2\mu\frac{r}{m}z_*^3y_*^2+c^2p^2z_*^2y_*^2\varpi(\frac{r}{m}z_*+\alpha)\\&+cp\frac{r^2}{m^2}z_*^3y_*\big[\alpha(2\varpi+\mu)+(\varpi+\mu)^2\big]+cp\frac{r}{m}z_*^2y_*\big[(2\varpi\\&+\mu)\alpha^2+\mu(3d_1+2\mu+4\sigma)+2\varpi^2\big]\alpha+(\mu+\varpi)(\varpi^2+\mu^2)\big]\\&+c\alpha pz_*y_*\big[(\varpi^2+\mu\sigma)\alpha+\varpi(\varpi+d_1\mu))\big]-c\alpha\mu^2p\sigma z_*y_*\\&+\big[\frac{r^3}{m^3}z_*^3+\frac{r^2}{m^2}z_*^2(\alpha+\mu+\varpi)+\frac{r}{m}z_*\varpi(\alpha+\mu)\big]\big[\varpi\alpha^2\\&+\alpha(\varpi^2+2d_1\mu+\mu\sigma)+\mu\varpi(\mu+\varpi)\big]+\alpha\mu\sigma\big[\varpi\alpha^2+(\varpi^2\\&+2d_1\mu+\mu\sigma)\alpha+\mu(\varpi^2+d_1\mu)\big]+\alpha\mu^3\sigma^2.\end{aligned}$$

Notice that this only has one negative term. Using the first and the last terms, and this negative term, we have

$$\alpha\mu(c^2p^2z_*^2y_*^2-c\mu p\sigma z_*y_*+\mu^2\sigma^2)\geq\alpha\mu(2cp\mu\sigma z_*y_*-c\mu p\sigma z_*y_*)>0,$$

thus, $\hat{a}_3(\hat{a}_1\hat{a}_2-\hat{a}_3)-\hat{a}_1^2\hat{a}_4>0$. Moreover, it follows from the Routh-Hurwitz criterion that E_* is locally asymptotically stable.

In order to obtain the global stability of E_*, let

$$L_*=x-x_*-x_*\ln\frac{x}{x_*}+y-y_*-y_*\ln\frac{y}{y_*}+\frac{\beta x_*v_*}{ky_*}(v-v_*-v_*\ln\frac{v}{v_*})+\frac{p}{c}(z-z_*-z_*\ln\frac{z}{z_*}).$$

Taking the time derivative of L_* along the solution of system(1.2), we get

$$\begin{aligned}L_*'=&(1-\frac{x_*}{x})(s-\beta xv-d_1x)+(1-\frac{y_*}{y})(\beta xv-d_2y-pyz)\\&+(1-\frac{v_*}{v})\frac{\beta x_*v_*}{ky_*}(ky-\mu v)+\frac{p}{c}(1-\frac{z_*}{z})\bigg(cyz+rz(1-\frac{z}{m})-d_3z\bigg).\end{aligned}$$

Using $s=\beta x_*v_*+d_1x_*$, $\beta x_*v_*=d_2y_*+py_*z_*$, $ky_*=\mu v_*$ and $y_*=\dfrac{rz_*+m(d_3-r)}{mc}$, we have

$$\begin{aligned}L_*'=&2d_1x_*-d_1x-d_1x_*\frac{x_*}{x}+\beta x_*v_*+\beta x_*v-\beta x_*v_*\frac{x_*}{x}-\beta xv\frac{y_*}{y}\\&+\beta x_*v_*-py_*z_*+py_*z+pyz_*-\beta x_*v-\beta x_*v_*\frac{v_*y}{vy_*}+\beta x_*v_*\\&+\frac{p}{c}\bigg(rz(1-\frac{z}{m})-d_3z\bigg)-pyz_*-\frac{p}{c}\bigg(rz_*(1-\frac{z}{m})-d_3z_*\bigg)\\=&d_1x_*(2-\frac{x_*}{x}-\frac{x}{x_*})+\beta x_*v_*(3-\frac{x_*}{x}-\frac{xvy_*}{x_*v_*y}-\frac{v_*y}{vy_*})-\frac{pr}{mc}(z-z_*)^2\leq0,\end{aligned}$$

and $L_*'=0$ only if $x=x_*$, $\frac{y}{y_*}=\frac{v}{v_*}$ and $z=z_*$. In this case, it is easy to obtain that the maximal invariant subset in $\{(x,y,v,z):L_*'|_{(1.2)}=0\}$ is the singleton $\{E_*\}$. As a result, E_* is globally asymptotically stable if it exists based on the LaSalle's invariance principle. □

For the convenience of reading, we summarize the complete global properties of system (1.2) as shown in Figure 1.

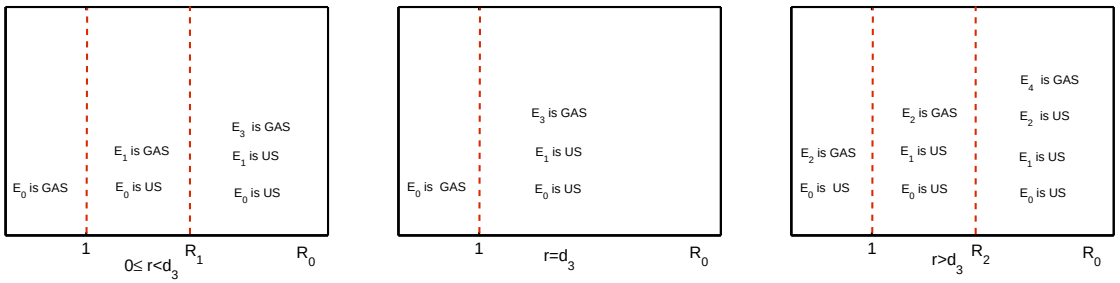

FIGURE 1. Global properties of system (1.2). Here, $E_0 = (\frac{s}{d_1}, 0, 0, 0)$, $E_1 = (\frac{s}{d_1 R_0}, \frac{d_1\mu(R_0-1)}{\beta k}, \frac{d_1(R_0-1)}{\beta}, 0)$, $E_2 = (\frac{s}{d_1}, 0, 0, \frac{m(r-d_3)}{r})$, $E_3 = (x_3, y_3, v_3, z_3)$ and $E_4 = (x_4, y_4, v_4, z_4)$ are the equilibria of system (1.2), the expression of E_3 and E_4 is shown in Proposition 2.1. $R_1 = 1 + \frac{\beta k(d_3-r)}{cd_1\mu}$ and $R_2 = 1 + \frac{pm(r-d_3)}{rd_2}$.

3. NUMERICAL SIMULATIONS

Although the complete global properties of system (1.2) have been obtained in Figure 1, it is noted that the immunity-activated infection equilibrium E_3 or E_4 is related to the parameters of self-proliferation of CTLs (r and m) from Proposition 2.1. When E_3 or E_4 is globally asymptotically stable, the infected cells (y_3 or y_4) and corresponding proportion of infected cells $\frac{y_3}{x_3+y_3}$ or $\frac{y_4}{x_4+y_4}$ are often used to describe the severity of the infection. In this section, we give numerical simulations to investigate the effect of self-proliferation of CTLs, and explore the potential significance in clinical practice. First, we fix

$$s = 1.0 \times 10^4 \text{ ml}^{-1} \cdot \text{day}^{-1},\ \beta = 3.0 \times 10^{-4} \text{ ml}^{-1} \cdot \text{day}^{-1},\ p = 0.5 \text{ ml}^{-1} \cdot \text{day}^{-1},$$
$$c = 9.6 \times 10^{-6} \text{ ml}^{-1} \cdot \text{day}^{-1},\ d_1 = 0.01 \text{ day}^{-1},\ d_2 = 1.0 \text{ day}^{-1},\ d_3 = 0.035 \text{ day}^{-1},$$
$$k = 8 \text{ virions/cell}, \quad \mu = 2.4 \text{ day}^{-1},$$

which are within the similar ranges as those ones employed in [5, 12, 17, 22]. Then, let parameters r and m change to qualitatively explore their influence on the values of E_3 or E_4, and the corresponding proportion of infected cells.

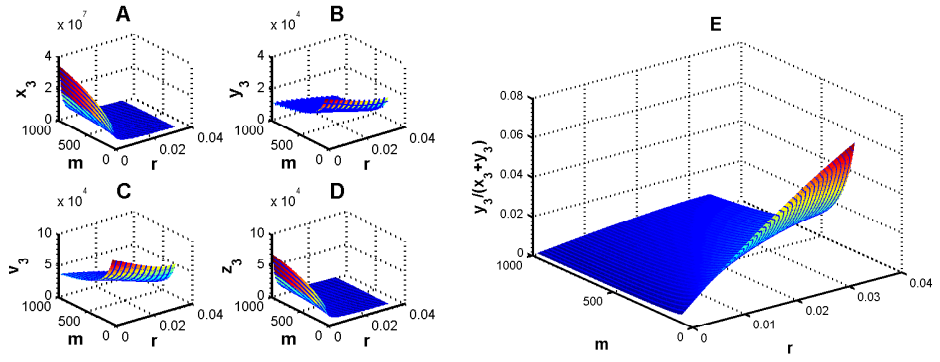

FIGURE 2. Simulations of E_3 and the corresponding proportion of y_3 when $0 \le r \le d_3$. Panel (A)-(E) are the simulated surface with two parameters changing.

When $r \in [0.0, 0.035]$ and $m \in [100, 1000]$, i.e., $0 \leq r \leq d_3$, Figure 2 shows the simulated surface of E_3 and the corresponding proportion of y_3 changing with parameters r and m. Along with the increase of parameter r, although the infected cells (y_3) and virus load (v_3) will decrease (Figure 2B and Figure 2C), the proportion of infected cells ($\frac{y_3}{x_3+y_3}$) is gradually increase (Figure 2E). In particular, the immune cells (z_3) also decrease with the increase of r (Figure 2D). These qualitatively indicate that the severity of infection may increase with the increase of r in case of $0 \leq r \leq d_3$. Along with the increase of parameter m, Figure 2A and Figure 2D show that uninfected cells (x_3) and immune cells (z_3) will increase gradually, while infected cells (y_3), virus load (v_3) and the proportion of infected cells ($\frac{y_3}{x_3+y_3}$) are decrease gradually. These qualitatively indicate that increasing parameter m can reduce the severity of virus infection.

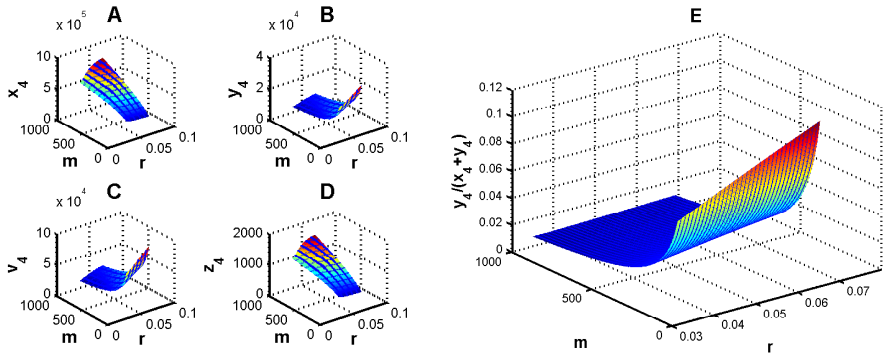

FIGURE 3. Simulations of E_4 and the corresponding proportion of y_4 when $0 \leq r \leq d_3$. Panel (A)-(E) are the simulated surface with two parameters changing.

When $r \in [0.0351, 0.07]$ and $m \in [100, 1000]$, i.e., $r > d_3$, Figure 3 shows the simulated surface of E_4 and the corresponding proportion of y_4 changing with parameters r and m. Comparing Figure 3 with Figure 2, we can find that all components of the immunity-activated infection equilibrium E_4 will increase with the increase of parameter r, including the proportion of infected cells ($\frac{y_4}{x_4+y_4}$). Along with the increase of parameter m, the variation of all components is similar to that in Figure 2.

4. Discussion

In this paper, a viral infection model with self-proliferation of CTLs is proposed and its global dynamic behavior is obtained. From Figure 1, comparing with [10], we can find the dynamic behavior of (1.2) will not change if the per capita self-proliferation rate of CTLs is insufficient, i.e., $0 < r < d_3$. However, when $r = d_3$, the immunity-inactivated infection equilibrium E_1 is always unstable if it appears. Especially, when $r > d_3$, a new steady state (named as infection-free but immunity-activated equilibrium E_2) appears and is globally asymptotically stable if the basic reproduction number is less than a threshold, which means that the immune effect still exists though virus be eliminated. This is consistent with the clinical practice of virus infection because immune cells are usually not depleted after a patient recovers. In fact, memory T cells can be maintained in lymphoid and nonlymphoid organs through self-renewal [3], including central memory T cells and effector memory T cells [18]. In particular, recent study on HBV also find that HBV specific TNF-α CD4 T cells may be in the early stage of differentiation rather than depletion of T cells [19], which suggests that the stability of immunity-inactivated infection equilibrium E_1 may be impossible in clinical practice.

On the effect of self-proliferation of immune cells, qualitative numerical simulations (Figure 2 and Figure 3) indicate that although there are different shape mode under different intensity of self-proliferation,

the increase of per capita self-proliferation rate (r) can worsen the infection, while the increase of the capacity of CTLs (m) can reduce the severity of infection. Thus, inappropriate intensity of per capita self-proliferation rate may lead to more severe infection outcome, which is similar to the effect of covalently closed circular DNA (cccDNA) self-amplification rate in HBV infection [8]. These may provide insight into the failure of immune therapy [2].

Recently, under a plausible quasi steady-state assumption, [6] ignored the direct effect of virus load, but introduced the delayed activation effect of immune cells, and the dynamics of the corresponding virus model was studied. Compared with the results of [6], we can find that quai steady-state assumption cannot affect the dynamic behavior, which is consistent with the conclusion of [20]. Note that the spatial migration of virus particles is an inherent characteristic of virus infection within-host [21, 28]. We will further analyze the effect of delay and spatial migration on the process of virus infection, such as global stability, bifurcation and the invasion speed of virus particles based on the latest research results [11, 24, 26, 27] in the future study.

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