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ORIGINAL ARTICLE

Global stability of a virus dynamics model with cure rate and absorption

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Abstract In this paper, we investigate a mathematical model which takes account the cure of infected cells and the loss of viral particles due to the absorption into uninfected cells. The global stability of the model is determined by using the direct Lyapunov method for disease-free equilibrium, and the geometrical approach for chronic infection equilibrium.

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1. Introduction

The aim of this work is to study the dynamical behavior of the following model describing the interaction between the susceptible host cells (x), infected cells (y) and free virus (v), this model is formulated by the following nonlinear system of differential equations:

$$\begin{aligned} \dot{x} &= \lambda - dx - f(x,y,v)v + \rho y, \\ \dot{y} &= f(x,y,v)v - (a+\rho)y, \\ \dot{v} &= ky - uv - if(x,y,v)v, \end{aligned} \tag{1}$$

where the susceptible host cells are produced at a rate λ, die at a rate dx and become infected by virus at a rate $f(x,y,v)v$. Infected cells may be killed because of viral or immune effects, or they may be lost by noncytolytic elimination of the cccDNA in their nucleus. The loss rate of infected cells is given by $a+\rho$, where a is the death rate of infected cells and ρ is the reversion rate into the uninfected state. The term ρy into first equation of (1) gives a measure of the uninfected cells which are created through "cure", per unit time. Recently, this cure of infected cells is considered by several works [1–6]. Finally, free virus is produced by infected cells at a rate ky, decays at a rate uv and the parameter i takes only the values 0 or 1. When $i=0$ corresponds to the system treated by Hattaf et al. in [6], and $i=1$ takes account the loss of viral particles when it enters the target cells. Note that, when a pathogen enters an

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uninfected cell, the number of pathogens in the blood decreases by one. This is called the absorption effect, which is considered in [9–11] and is ignored by many authors such as [1–8]. As in [6–8], we assume that the function $f(x,y,v)$ is continuously differentiable in the interior of $\mathbb{R}^3_+$ and satisfies:

$$f(0,y,v)=0, \text{ for all } y\geqslant 0 \text{ and } v\geqslant 0, \tag{H$_1$}$$

$$\frac{\partial f}{\partial x}(x,y,v)>0, \text{ for all } x>0,\ y\geqslant 0 \text{ and } v\geqslant 0, \tag{H$_2$}$$

$$\frac{\partial f}{\partial y}(x,y,v)\leqslant 0 \text{ and } \frac{\partial f}{\partial v}(x,y,v)\leqslant 0,\ \forall\ x,y,v\geqslant 0. \tag{H$_3$}$$

The rest of our paper is organized as follows. Section 2 deals with some preliminary results concerning positivity and boundedness of solutions, basic reproduction number and existence of equilibria. In Section 3, we discuss the stability of equilibria. The paper ends with some applications in Section 4.

2. Preliminaries

In this section, we establish the positivity and boundedness of solutions, basic reproduction number and existence of equilibria.

2.1. Positive invariance and boundedness

Theorem 2.1. *The octant* $\mathbb{R}^3_+=\{(x,y,v)\in\mathbb{R}^3: x\geqslant 0,\ y\geqslant 0,\ v\geqslant 0\}$ *is positively invariant with respect* (1). *Moreover, all solutions of* (1) *are uniformly bounded in the compact subset* $\Gamma=\left\{(x,y,v)\in\mathbb{R}^3_+:\ x+y\leqslant\frac{\lambda}{\delta},\ v\leqslant\frac{k\lambda}{u\delta}\right\}$, *where* $\delta=min\{a,d\}$.

Proof. The positive invariance of the positive orthant is trivial. It remains to show that the system (1) is uniformly bounded. Let $(x(t),y(t),v(t))$ be any solution with positive initial conditions (x_0,y_0,v_0). Adding the first two equations of the system (1) gives, $\frac{d}{dt}(x+y)=\lambda-dx-ay\leqslant\lambda-\delta(x+y)$, with $\delta=min\{a,d\}$. Then we obtain that $\limsup_{t\to\infty}(x+y)\leqslant\frac{\lambda}{\delta}$. On the other hand, from the third equation of the system, it is easy to see that $\limsup_{t\to\infty}v\leqslant\frac{\lambda k}{u\delta}$. Hence, all solutions of the system (1) which start in $\mathbb{R}^3_+$ are eventually confined in the region Γ. This completes the proof. □

2.2. Basic reproduction number and equilibria

By a simple calculation, system (1) has always one disease-free equilibrium $E_f\left(\frac{\lambda}{d},0,0\right)$. Therefore, the basic reproduction number of (1) is given by

$$R_0=\frac{(k-(a+\rho)i)f\left(\frac{\lambda}{d},0,0\right)}{u(a+\rho)}. \tag{2}$$

Using the same technique in [6], we deduce that there exists a unique endemic equilibrium when $R_0>1$. Hence, we have the following result.

Theorem 2.2.

(i) *If* $R_0\leqslant 1$, *then the system* (1) *has a unique disease-free equilibrium of the form* $E_f\left(\frac{\lambda}{d},0,0\right)$.

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

3. Local and global stability of equilibria

The Jacobian matrix of (1) at an arbitrary point is given by

$$J=\begin{pmatrix} -d-\frac{\partial f}{\partial x}v & -\frac{\partial f}{\partial y}v+\rho & -\frac{\partial f}{\partial v}v-f \\ \frac{\partial f}{\partial x}v & \frac{\partial f}{\partial y}v-(a+\rho) & \frac{\partial f}{\partial v}v+f \\ -i\frac{\partial f}{\partial x}v & k-i\frac{\partial f}{\partial y}v & -u-i\left(f+\frac{\partial f}{\partial v}v\right)\end{pmatrix}. \tag{3}$$

Based on Jacobine matrix approach by evaluating (3) at E_f and E^*, we can obtain the following results.

Theorem 3.1. *The disease-free equilibrium* E_f *is locally asymptotically stable if* $R_0<1$ *and it is unstable if* $R_0>1$.

Theorem 3.2. *Suppose that* $R_0>1$. *If* $i=0$ *or if* $i=1$ *and the function f satisfies the following hypothesis*

$$\left(f(x,y,v)+v\frac{\partial f}{\partial v}\right)\geqslant 0,\quad \text{for all } x,y,v\geqslant 0, \tag{H$_4$}$$

then the chronic infection equilibrium E^* *is locally asymptotically stable.*

Remark 3.3. The assumption (H$_4$) is verified by different types of the incidence rate including the mass action, the standard incidence, the saturation incidence, Beddington-DeAngelis incidence function, Crowley-Martin incidence function and the more generalized incidence function proposed by Hattaf el al. (see Section 5 in [8]).

Based on the following Lyapunov functional $V(t)=\frac{k}{a+\rho}y(t)+v(t)$, it is not hard to establish the following theorem.

Theorem 3.4. E_f *is globally asymptotically stable in* Γ *if* $a\geqslant d$ *and* $R_0\leqslant 1$.

In order to establish the global stability of the chronic infection equilibrium E^* when $R_0>1$, we need first to show the following lemma.

Lemma 3.5. *If* $R_0>1$, *the system* (1) *is uniformly persistent.*

Proof. This lemma follows from a uniform persistence result, Theorem 4.3 in [12]. To show that system (1) satisfies all the conditions of Theorem 4.3 in [12] if $R_0>1$, we choose $X=\mathbb{R}^3$ and the set $E=\Gamma$. The maximal invariant set M on the boundary $\partial\Gamma$ is the singleton E_f and is isolated. By Theorem 4.3 in [12], we can see that the uniform persistence of system (1) is equivalent to the unstability of the disease-free equilibrium E_f. Hence, by Theorem 3.1, we know if $R_0>1$, the system (1) is uniform persistence. □

Next, we establish a set of conditions which are sufficient for the global stability of the chronic infection equilibrium E^*. According to Lemma 3.5, we know if $R_0>1$, the system (1) is uniform persistence. Hence, there exists a compact

absorbing set $K \subset \Gamma$ [15]. Along each solution $(x(t), y(t), v(t))$ of (1) such that $X_0 = (x(0), y(0), v(0)) \in K$, we put

$$\bar{p}_1 = \limsup_{t\to\infty} \sup_{X_0\in K} \frac{1}{t}\int_0^t \left(-\frac{\partial f}{\partial y}y(s) - \frac{\partial f}{\partial v}v(s)\right)ds,$$

$$\bar{q}_1 = \limsup_{t\to\infty} \sup_{X_0\in K} \frac{1}{t}\int_0^t \left(\frac{\partial f}{\partial x}y(s) - \frac{\partial f}{\partial y}y(s) - \frac{\partial f}{\partial v}v(s)\right)ds.$$

Theorem 3.6. *Assume $R_0 > 1$ and (H_4) hold. If $\max\{\frac{ky}{v} - i\frac{\partial f}{\partial y}y, i\frac{\partial f}{\partial x}y\} = \frac{ky}{v} - i\frac{\partial f}{\partial y}y$ and $i\bar{p}_1 < \delta$ or if $i\bar{q}_1 < \delta$, then E^* is globally asymptotically stable.*

Proof. To investigate the global stability of E^*, we apply the geometrical approach developed by Li and Muldowney in [13]. The second additive compound matrix of the Jacobian matrix J, given by (3), is defined by

$$J^{[2]} = \begin{pmatrix} j_{11}+j_{22} & j_{23} & -j_{13} \\ j_{32} & j_{11}+j_{33} & j_{12} \\ -j_{31} & j_{21} & j_{22}+j_{33} \end{pmatrix}, \tag{4}$$

where j_{kl} is the (k,l)th entry of J. Let $P = diag\left(1, \frac{v}{v}, \frac{v}{v}\right)$. Then

$$P_f P^{-1} = diag\left(0, \frac{\dot{y}}{y} - \frac{\dot{v}}{v}, \frac{\dot{y}}{y} - \frac{\dot{v}}{v}\right),$$

where matrix P_f is obtained by replacing each entry p_{ij} of P by its derivative in the direction of solution of (1). In addition, we have

$$B = P_f P^{-1} + PJ^{[2]}P^{-1} = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix},$$

where

$$B_{11} = -(a+d+\rho) - \frac{\partial f}{\partial x}v + \frac{\partial f}{\partial y}v,$$

$$B_{12} = \begin{pmatrix} \frac{v}{y}\left(\frac{\partial f}{\partial v}v + f(x,y,v)\right) & \frac{v}{y}\left(\frac{\partial f}{\partial v}v + f(x,y,v)\right) \end{pmatrix},$$

$$B_{21} = \begin{pmatrix} \left(k - i\frac{\partial f}{\partial y}v\right)\frac{v}{v} \\ i\frac{\partial f}{\partial x}y \end{pmatrix}, \quad B_{22} = \begin{pmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{pmatrix},$$

which

$$b_{11} = \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - u - d - \frac{\partial f}{\partial x}v - i\left(f + \frac{\partial f}{\partial v}v\right), \quad b_{12} = \rho - \frac{\partial f}{\partial y}v,$$

$$b_{21} = \frac{\partial f}{\partial x}v, \quad b_{22} = \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - a - \rho - u + \frac{\partial f}{\partial y}v - i\left(f + \frac{\partial f}{\partial v}v\right).$$

Let (w_1, w_2, w_3) denote the vector in $\mathbb{R}^3$, choose a norm in $\mathbb{R}^3$ as $|w_1, w_2, w_3| = \max\{|w_1|, |w_2| + |w_3|\}$ and let μ be the Lozinskii measure with respect to this norm. Then we have the following estimate, see [14]:

$$\mu(B) \leqslant \sup\{g_1, g_2\}, \tag{5}$$

where $g_1 = \mu_1(B_{11}) + |B_{12}|$ and $g_2 = |B_{21}| + \mu_1(B_{22})$, here μ_1 denotes the Lozinskii measure with respect to l_1 vector norm, $|B_{12}|$ and $|B_{21}|$ are matrix norms with respect to l_1 norm. Moreover, we have

$$g_1 = \frac{\dot{y}}{y} - d + \frac{v^2}{y}\frac{\partial f}{\partial v} - \frac{\partial f}{\partial x}v + \frac{\partial f}{\partial y}v \leqslant \frac{\dot{y}}{y} - \delta. \tag{6}$$

and

$$g_2 = \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - \delta + \max\left\{\frac{ky}{v} - i\frac{\partial f}{\partial y}y, i\frac{\partial f}{\partial x}y\right\} - u - i\left(f + \frac{\partial f}{\partial v}v\right). \tag{7}$$

If $\max\left\{\frac{ky}{v} - i\frac{\partial f}{\partial y}y, i\frac{\partial f}{\partial x}y\right\} = \frac{ky}{v} - i\frac{\partial f}{\partial y}y$, then

$$g_2 = \frac{\dot{y}}{y} - \delta - i\left(\frac{\partial f}{\partial y}y + \frac{\partial f}{\partial v}v\right). \tag{8}$$

From (5), (6) and (8), we get $\mu(B) \leqslant \frac{\dot{y}}{y} - \delta - i\left(\frac{\partial f}{\partial y}y + \frac{\partial f}{\partial v}v\right)$, Hence,

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{X_0\in K} \frac{1}{t}\int_0^t \mu(B)ds \leqslant -\delta + i\bar{p}_1 < 0.$$

In general case, we have

$$g_2 = \frac{\dot{y}}{y} - \delta + i\left(\frac{\partial f}{\partial x}y - \frac{\partial f}{\partial y}y - \frac{\partial f}{\partial v}v\right). \tag{9}$$

From (5), (6) and (9), we get $\mu(B) \leqslant \frac{\dot{y}}{y} - \delta + i\left(\frac{\partial f}{\partial x}y - \frac{\partial f}{\partial y}y - \frac{\partial f}{\partial v}v\right)$. Consequently,

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{X_0\in K} \frac{1}{t}\int_0^t \mu(B)ds \leqslant -\delta + i\bar{q}_1 < 0.$$

By Theorem 3.5 in [13], E^* is globally asymptotically stable. □

From Theorem 3.6, we obtain the following result.

Corollary 3.7. *Assume $R_0 > 1$ and (H_4) hold. If $i = 0$, then E^* is globally asymptotically stable.*

4. Applications

Here, we give some examples of incidence functions for which we apply our theoretical results concerning the global stability of E^* when $R_0 > 1$.

Example 1. Mass Action when $f(x,y,v) = \beta x$. In this case, the hypotheses H_1, H_2,H_3 and H_4, are satisfied. In addition,

$$\int_0^t \left(\frac{\partial f}{\partial x}y(s) - \frac{\partial f}{\partial y}y(s) - \frac{\partial f}{\partial v}v(s)\right)ds = \int_0^t \beta y(s)ds.$$

Since $\dot{x} + \dot{y} = \lambda - dx - ay$, we have

$$\int_0^t \beta y(s)ds \leqslant \frac{\beta\lambda}{a}t - \frac{\beta}{a}(x(t) + y(t) - x(0) - y(0)).$$

Thus $\bar{q}_1 \leqslant \frac{\beta\lambda}{a}$. By applying Theorem 3.6, we deduce that E^* is globally asymptotically stable if $i = 0$ or if $i = 1$ and $\beta\lambda < \delta a$.

Example 2. Standard Incidence when $f(x,y,v) = \frac{\beta x}{x+y}$. In the same, the hypotheses H_1, H_2, H_3 and H_4 are satisfied. Moreover,

$$\int_0^t \left(\frac{\partial f}{\partial x}y(s) - \frac{\partial f}{\partial y}y(s) - \frac{\partial f}{\partial v}v(s)\right)ds = \int_0^t \frac{\beta y(s)}{x(s)+y(s)}ds \leqslant \beta t.$$

Then $\bar{q}_1 \leqslant \beta$. From Theorem 3.6, E^* is globally asymptotically stable if $i = 0$ or if $i = 1$ and $\beta < \delta$.

Example 3. Saturation Incidence when $f(x, y, v) = \frac{\beta x}{1+v}$. Then H_1,H_2,H_3 and H_4 are satisfied and $\frac{\partial f}{\partial x} y(s) = \frac{\beta y}{1+v} \leqslant \frac{\beta y}{v}$. If we suppose that $\beta < k$, we get $\max\left\{\frac{ky}{v} - \frac{\partial f}{\partial y} y, \frac{\partial f}{\partial x} y\right\} = \frac{ky}{v}$. Further,

$$\int_0^t \left(-\frac{\partial f}{\partial y} y(s) - \frac{\partial f}{\partial v} v(s)\right) ds = \int_0^t \frac{\beta x(s) v(s)}{(1 + v(s))^2} ds \leqslant \int_0^t \beta x(s) ds.$$

Since $\dot{x} + \dot{y} = \lambda - dx - ay$, we have

$$\int_0^t \beta x(s) ds \leqslant \frac{\beta\lambda}{d} t - \frac{\beta}{d}(x(t) + y(t) - x(0) - y(0)).$$

Hence $\bar{p}_1 \leqslant \frac{\beta\lambda}{d}$. By Theorem 3.6, we deduce that E^* is globally asymptotically stable if $i = 0$ or if $i = 1$ and $\beta < \min(k, \frac{\delta d}{\lambda})$.

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