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Research Article

Dynamics of a Viral Infection Model with General Contact Rate between Susceptible Cells and Virus Particles

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This paper investigates the dynamic behavior of a viral infection model with general contact rate between susceptible host cells and free virus particles. If the basic reproduction number of the virus is less than unity, by LaSalle's invariance principle, the disease-free equilibrium is globally asymptotically stable. If the basic reproduction number of the virus is greater than unity, then the virus persists in the host and the endemic equilibrium is locally asymptotically stable.

1. Introduction

Viral infection within-host, such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infections, is a complicated kinetic process, and mathematical model is always important, which can give a hand to understand the complexity between the responses of the body and variant conditions [1–6].

The basic viral infection model contains three variables, susceptible host cells (x), infected host cells (y), and free virus particles (v), which can be formulated by the following differential equations [7, 8]:

$$\begin{aligned} \frac{dx}{dt} &= r - mx - \beta xv, \\ \frac{dy}{dt} &= \beta xv - ay, \\ \frac{dv}{dt} &= ky - uv, \end{aligned} \tag{1}$$

in which susceptible host cells are produced at a constant rate, r, die at the rate of mx, and become infected with the rate of βxv. Infected host cells are produced at the rate of βxv and die at the rate of ay. Free virus particles are released from infected host cells at the rate of ky and die at the rate of uv. It is assumed that parameters r, m, β, a, k, and u are all positive constants.

Note that there is an assumption that the infection term is based on the *mass-action principle*, which means that there is a constant contact rate (β) between susceptible host cells and virus particles in (1). However, many experiments of microparasitic infections suggest the infection rate may be a nonlinear relationship [3, 9–11], such as dose-dependent infection rate. Thus, to meet more biological practice, we replace the constant contact rate (β) with a general contact rate ($f(v)$) between susceptible cells and virus particles and obtain the following modified viral infection model:

$$\begin{aligned} \frac{dx}{dt} &= r - mx - f(v)\, xv, \\ \frac{dy}{dt} &= f(v)\, xv - ay, \\ \frac{dv}{dt} &= ky - uv, \end{aligned} \tag{2}$$

where the contact rate function $f(v)$ satisfy the following assumption (**H1**):

(**H1**) $f(v) : \mathbb{R}_+ \to \mathbb{R}_+$, continuous and differentiable, $f(0) = \beta$, $f'(v) < 0$ and $f(\infty) = 0$.

The primary goal of this paper is to carry out a mathematical analysis of system (2) and predict whether the infection

disappears or survives. The organization of this paper is as follows. In the next section, some preliminary results are given, including the dissipativity of system (2), the definition of basic reproduction number of the virus, and the existence of the disease-free equilibrium and endemic equilibrium. In Section 3, by analyzing the corresponding characteristic equations, we study the local stability of the equilibria. In Section 4, by using suitable Lyapunov function and LaSalle's invariance principle [12], we first prove that if the basic reproduction number is less than unity, the disease-free equilibrium is globally asymptotically stable. Then using Theorem 4.6 in [13], we obtain the uniform persistence of (2) if the basic reproduction number is greater than unity. A brief discussion is given in Section 5 to conclude this work.

2. Preliminary Results

In this section, we first show that all solutions of system (2) are positive and ultimately bounded. Then the existence of feasible equilibria is given under the condition of basic reproduction number of the virus.

Because of the biological meaning of the components $(x(t), y(t), v(t))$, we focus on the model in the first octant of $\mathbb{R}^3$ and consider system (2) with initial conditions

$$x(0) > 0, \qquad y(0) > 0, \qquad v(0) > 0. \tag{3}$$

The following result shows that system (2) is dissipative.

Theorem 1. *Under the initial conditions* (3)*, all solutions of system* (2) *are positive for* $t > 0$ *and there exists a constant* $M > 0$*, such that all solutions satisfy* $x(t) < M$*,* $y(t) < M$*, and* $v(t) < M$ *for all sufficiently large* t*.*

Proof. Note that $x'|_{x=0} = r > 0$, $y'|_{y=0} = f(v)xv$ and $V'|_{v=0} = ky$. This implies that $(x(t), y(t), v(t)) \in \mathbb{R}^3_+$ for all $t > 0$, provided that $(x(0), y(0), v(0)) \in \mathbb{R}^3_+$. Suppose that $x(t)$ is not always positive. Let $\tau > 0$ be the first time such that $x(\tau) = 0$. By the first equation of (2) we have $x'(\tau) = r > 0$, which implies $x(t) < 0$ for $t \in (\tau - \varepsilon, \tau)$ for sufficiently small $\varepsilon > 0$, a contradiction. Thus, $x(t)$ is positive for all $t > 0$. In addition, by the second and third equations of (2), we have

$$\begin{aligned} y(t) &= \left(y(0) + \int_0^t f(v(s))\, x(s)\, v(s)\, e^{as} ds \right) e^{-at} \\ &\geq y(0)\, e^{-at} > 0, \\ v(t) &= \left(v(0) + \int_0^t ky(s)\, e^{us} ds \right) e^{-ut} \geq v(0)\, e^{-ut} > 0, \end{aligned} \tag{4}$$

for all $t > 0$. Therefore, it is easy to see that $y(t)$ and $v(t)$ are positive with initial conditions (3).

Next, we sketch the arguments for ultimate boundedness of solution of (2). Let $N_1(t) = x(t) + y(t)$, $N_2(t) = x(t) + y(t) + (av(t)/k)$, $d_1 = \min\{m, a\}$, and $d_2 = \min\{m, a, u\}$. Since all solutions of (2) are positive, we have

$$\begin{aligned} N_1' &= r - mx - ay < r - d_1 N_1, \\ N_2' &= r - mx - \frac{au}{k} v < 2r - d_2 N_2. \end{aligned} \tag{5}$$

Therefore, $N_1(t) < 2r/d_1$ and $N_2(t) < 3r/d_2$ for all sufficiently large t, and hence, $x(t)$, $y(t)$, and $v(t)$ are ultimately bounded by some positive constant M. □

Note that a free virus particle has an average lifetime of $1/u$ and parameter k is the burst size, which means the total number of virions produced by an infected cell during its life span. Thus, at the beginning of the infectious process, the average number of newly virus particles generated from one virus particle, which is the basic reproduction number of virus by [14, 15], can be defined as

$$R_0 = \frac{rkf(0)}{aum} = \frac{rk\beta}{aum}. \tag{6}$$

Now, we begin to find the equilibria of model (2) by the following algebraic system

$$\begin{aligned} r - mx - f(v)\, xv &= 0, \\ f(v)\, xv - ay &= 0, \\ ky - uv &= 0. \end{aligned} \tag{7}$$

Solving the third algebraic equation of (7), we can obtain $y = uv/k$. By combining this equality with the second equation of (7), we have $x = au/kf(v)$ or $v = 0$. When $v = 0$, it is easy to have $y = 0$ and $x = r/m$ by the third and first equations of (7); that is, system (2) always has a disease-free equilibrium state, denoted as $E_0 = (r/m, 0, 0)$. If $v \neq 0$, substituting $x = au/kf(v)$ in the first equation of (7), we have

$$\varphi_1(v) \equiv r - \frac{au}{k} v = \frac{amu}{kf(v)} \equiv \varphi_2(v). \tag{8}$$

Note that

$$\begin{aligned} &\varphi_1(0) = r, \qquad \varphi_2(0) = \frac{aum}{k\beta}, \qquad \varphi_1'(v) = -\frac{au}{k} < 0, \\ &\varphi_2'(v) = -\frac{aumkf'(v)}{(kf(v))^2} > 0. \end{aligned} \tag{9}$$

Thus, if $\varphi_1(0) > \varphi_2(0)$, that is, $R_0 > 1$, there is a unique positive root for (8).

We summarize the above analyses in the following result.

Proposition 2. *For system* (2)*, the disease-free equilibrium* $E_0 = (r/m, 0, 0)$ *always exists. Furthermore, the unique endemic equilibrium* $E_1 = (x^*, y^*, v^*)$ *exists only if* $R_0 > 1$*; here* $x^* = au/kf(v^*)$*,* $y^* = uv^*/k$*, and* v^* *is the unique positive root of* (8)*.*

3. Local Stability

In this section, we study the local stability of each of feasible equilibria of system (2) by analyzing the corresponding characteristic equations, respectively.

The Jacobian matrix J of (2) at (x, y, v) is

$$J = \begin{bmatrix} -m - vf(v) & 0 & -xf(v) - xvf'(v) \\ f(v)v & -a & xf(v) + xvf'(v) \\ 0 & k & -u \end{bmatrix}. \quad (10)$$

At disease-free equilibrium E_0,

$$J_{E_0} = \begin{bmatrix} -m & 0 & -\dfrac{\beta r}{m} \\ 0 & -a & \dfrac{\beta r}{m} \\ 0 & k & -u \end{bmatrix}. \quad (11)$$

Clearly, the determinant of the lower right-hand 2×2 matrix is positive and its trace is negative only if $R_0 < 1$, so its eigenvalues have negative real parts in this case. Thus, E_0 is locally asymptotically stable if and only if $R_0 < 1$.

When $R_0 > 1$, the endemic equilibrium E_1 exists, and the Jacobian matrix at E_1 is

$$J_{E_1} = \begin{bmatrix} -m - v^* f(v^*) & 0 & -x^* f(v^*) - x^* v^* f'(v^*) \\ f(v^*)v^* & -a & x^* f(v^*) + x^* v^* f'(v^*) \\ 0 & k & -u \end{bmatrix}. \quad (12)$$

The characteristic equation of (12) is given by

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0, \quad (13)$$

in which

$$\begin{aligned} A_1 &= a + u + m + v^* f(v^*) > 0, \\ A_2 &= au + (a+u)(m + v^* f(v^*)) \\ &\quad - k\left(x^* f(v^*) + x^* v^* f'(v^*)\right) \\ &= (a+u)(m + v^* f(v^*)) - kx^* v^* f'(v^*) > 0, \\ A_3 &= au(m + v^* f(v^*)) - mk\left(x^* f(v^*) + x^* v^* f'(v^*)\right) \\ &= auv^* f(v^*) - mkx^* v^* f'(v^*) > 0. \end{aligned} \quad (14)$$

Here, we used $x^* f(v^*) = au/k$ and the assumption (**H1**); that is, $f'(v) < 0$.

Because A_1 and A_3 are both positive, by Routh-Hurwitz criterion, E_1 is locally asymptotically stable if and only if $A_1A_2 - A_3 > 0$. After a simple algebraic calculation, we have that

$$\begin{aligned} &A_1A_2 - A_3 \\ &= aum - akx^* v^* f'(v^*) + (m + v^* f(v^*))\left(a^2 + au + mu\right) \\ &\quad + (u + v^* f(v^*))\left((a+u)(m + v^* f(v^*)) - kx^* v^* f'(v^*)\right) \end{aligned} \quad (15)$$

is positive because $f'(v) < 0$. Thus, E_1 is locally asymptotically stable if and only if $R_0 > 1$.

We summarize the above results and Proposition 2 in the following theorem.

Theorem 3. *If $R_0 < 1$, then only disease-free equilibrium E_0 exists and is locally asymptotically stable. When $R_0 > 1$, E_0 is unstable and the endemic equilibrium E_1 appears and is locally asymptotically stable.*

4. Global Stability and Disease Persistence

For the global stability of the equilibria, we first have the following.

Theorem 4. *The disease-free equilibrium E_0 is globally asymptotically stable if only E_0 exists; that is, $R_0 < 1$.*

Proof. Define a Lyapunov function

$$V = x - \frac{r}{m} - \ln\frac{mx}{r} + y + \frac{a}{k}v. \quad (16)$$

Along the trajectories of system (2), we have

$$\begin{aligned} V'\big|_{(2)} &= \left(1 - \frac{r}{mx}\right)x' + y' + \frac{a}{k}v' \\ &= \left(1 - \frac{r}{mx}\right)(r - mx - f(v)xv) \\ &\quad + f(v)xv - ay + ay - \frac{au}{k}v \\ &= -\frac{m}{x}\left(x - \frac{r}{m}\right)^2 - \frac{au}{k}\left(1 - \frac{krf(v)}{aum}\right)v. \end{aligned} \quad (17)$$

Based on Theorem 1, we know that all solutions of system (2) are positive for $t > 0$. Taking $\varphi(v) = 1 - krf(v)/aum$, we have $\varphi(0) = 1 - R_0$, $\varphi'(v) = -krf'(v)/aum > 0$; that is, $\varphi(v)$ is a monotone increasing function. Thus, $\varphi(v) > 0$ is always valid if $R_0 < 1$. Consequently, all terms of the right hand side of (17) are nonpositive when $R_0 < 1$, which implies that $V'|_{(2)} \le 0$ and $V'|_{(2)} = 0$ if and only if $x = r/m$ and $v = 0$. As a result, the maximal invariant set in $\{(x, y, v) : V'|_{(2)} = 0\}$ is the singleton $\{E_0\}$. According to the results in Theorem 3 and LaSalle's invariance principle [12], we have that E_0 is globally asymptotically stable if $R_0 < 1$. □

Next, we investigate the uniform persistence of (2) and have the following result.

Theorem 5. *If $R_0 > 1$, then system (2) is uniformly persistent; that is, 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 $\liminf_{t\to+\infty} v(t) > \varepsilon$ for all solutions of (2) with initial conditions (3).*

Proof. The result follows from an application of Theorem 4.6 in [13], with $X_1 = \mathrm{int}(\mathbb{R}^3_+)$ and $X_2 = \mathrm{bd}(\mathbb{R}^3_+)$. Since the proof is similar to that of Lemma 3.5 in [16], here we only sketch the modifications that E_0 is a weak repeller for X_1.

Since $R_0 > 1$, that is, $au < rkf(0)/m$, together with the continuity of the function $f(v)$, there exists a sufficiently small constant $\epsilon > 0$ such that $au < k(r/m - \epsilon) f(\epsilon)$ is valid. Suppose that there exists a solution $(x(t), y(t), v(t))$ such that $(x(t), y(t), v(t)) \to (r/m, 0, 0)$. Thus, when t is sufficiently large, we have

$$\frac{r}{m} - \epsilon < x(t) < \frac{r}{m} + \epsilon, \qquad y(t) \le \epsilon, \qquad v(t) \le \epsilon. \tag{18}$$

By the second equation of (2), we have

$$\frac{dy}{dt} = f(v)\, xv - ay \ge f(\epsilon)\left(\frac{r}{m} - \epsilon\right) v - ay. \tag{19}$$

Take an auxiliary system of (2) as

$$\begin{aligned} \frac{dy}{dt} &= f(\epsilon)\left(\frac{r}{m} - \epsilon\right) v - ay, \\ \frac{dv}{dt} &= ky - uv. \end{aligned} \tag{20}$$

Clearly, $(0, 0)$ is the unique equilibrium of (20) and the Jacobian matrix J of (20) is given by

$$J = \begin{bmatrix} -a & f(\epsilon)\left(\frac{r}{m} - \epsilon\right) \\ k & -u \end{bmatrix}. \tag{21}$$

After a simple calculation, we have that the determinant of matrix (21)

$$\det(J) = au - k\left(\frac{r}{m} - \epsilon\right) f(\epsilon) < 0 \tag{22}$$

is valid for some sufficiently small constant $\epsilon > 0$ if $R_0 > 1$. Thus, $(0, 0)$ is unstable in this case. This is a contradiction to that $(y(t), v(t)) \to (0, 0)$. As a result, E_0 is a weak repeller for X_1. □

5. Discussion

Considering the biological practice during viral or microparasitic infection [3, 9–11], we proposed a viral infection model with general contact rate between susceptible cells and virus particles, which is a generalization of the basic viral infection model [7, 8]. The biological meaning of the assumption (**H1**) is that the accumulation of free virus particles can affect the contact rate between susceptible cells and virus particles, and the contact function is gradually weaker along with the increasing of free virus particles.

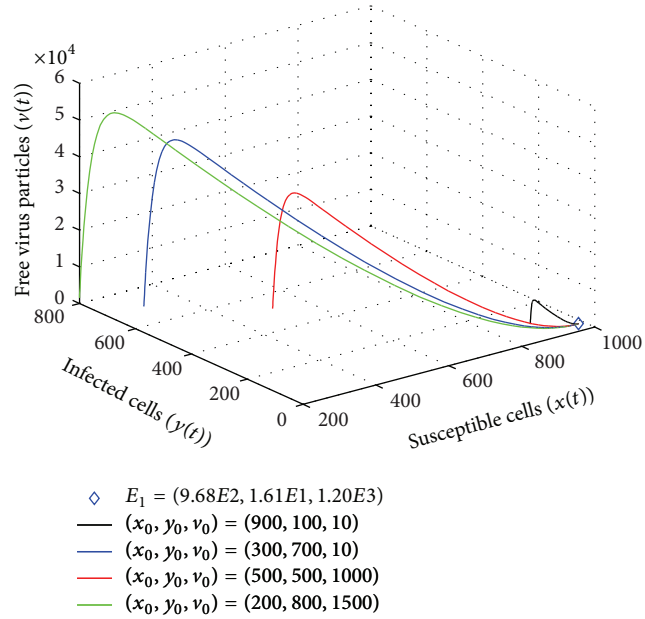

FIGURE 1: Phase diagram of system (2) under different initial conditions. Here $f(v) = \beta/(1 + bv)$ and $r = 10.0$, $m = 0.01$, $\beta = 3.60 \times 10^{-6}$, $a = 0.02$, $b = 0.01$, $k = 50$, and $u = 0.67$.

Though the rigorous analysis of stability of equilibria is obtained in [17] for the basic model, it is usually very complicated [18] and we cannot obtain the global stability of the endemic equilibrium E_1. However, we have the conditions of globally asymptotic stability of the disease-free equilibrium and persistence of virus. In addition, the phase diagram of system (2) indicates that all solutions tend to the unique disease steady state E_1 under different initial conditions (Figure 1). Thus, we conjecture that E_1 is globally asymptotically stable only if it exists even though the rigorous mathematical proof remains open.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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