Global stability of a viral dynamics model with multi-target cells and nonlinear incidence rate

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Abstract: In this paper, we investigate the dynamical behavior of a virus dynamics model with multi-target cells. The incidence rate of infection is given by a nonlinear function. The model is a $2n+1$ -dimensional nonlinear ODEs that describes the population dynamics of the virus, n classes of uninfected target cells and n classes of infected cells. Using the method of Lyapunov function, we have proven that if $R_0 \le 1$, then the uninfected steady state is globally asymptotically stable (GAS), and if the infected steady state exists, it is GAS.
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1. Introduction

Mathematical modeling and model analysis of virus infection such as human immunodeficiency virus (HIV) [1-16], hepatitis B virus (HBV) [17] and hepatitis C virus (HCV) [18] have attracted the interests of mathematicians during the recent years. The basic model of viral infection is given by [1-2]:

$$\dot{x} = \lambda - dx - \beta xv, \quad (1)$$

$$\dot{y} = \beta xv - ay, \quad (2)$$

$$\dot{v} = py - cv, \quad (3)$$

where x, y and v are the populations of the uninfected target cells, infected cells and free virus particles, respectively. The uninfected cells are generated from sources within the body at rate λ, die with rate constant d and become infected at rate βxv, where β is the infection rate constant. The infected cells are produced at rate βxv and die with rate constant a. The virus particles are produced by the infected cells with rate constant p, and are removed from the system with rate constant c.

In model (1)-(3), it is assumed that the virus attack one class of target cells (CD4+ T cells in case of HIV or hepatic cells in case of HCV and HBV) and the infection rate is given by bilinear incidence rate.
The purpose of this paper is to propose a virus infection model with multi-target cells and establish the global stability of its steady states. The incidence rate is assumed to be nonlinear. We prove that if $R_0 \le 1$, then the uninfected steady state is globally asymptotically stable (GAS), and if the infected steady state exists then it is GAS.

2. The model

In the literature, the infection process in most virus infection models is characterized by bilinear incidence rate βxv. However, the actual incidence rate is probably not linear over the entire range of x and v [22-23]. In this section we make a generalization of the basic virus infection model (1)-(3) by assuming that the virus attacks n classes of target cells and the incidence rate is nonlinear.

$$\dot{x}_i = \lambda_i - d_i x_i - \frac{\beta_i x_i^{q_i} v}{1 + k_i v}, \ i = 1,...,n \quad (4)$$

$$\dot{y} = \frac{\beta_i x_i^{q_i} v}{1 + k_i v} - a_i y_i, \qquad i = 1,...,n \quad (5)$$

$$\dot{v} = \sum_{i=1}^{n} p_i y_i - cv, \quad (6)$$

where $q_i > 0, k_i \ge 0, i = 1,...,n$. All the variables and other parameters have the same meaning as given in model (1)-(3).

2.1. Positive invariance

We note that model (4)-(6) is biologically acceptable in the sense that no population goes negative. It is straightforward to check the positive

invariance of the non-negative orthant R_+^{2n+1} by model (4)-(6). In the following, we prove that there always exists a compact positively invariant set for model (4)-(6).

Proposition 1. There exist positive numbers $L_i, i=1,...,n$ and M such that the compact set

$$\Omega = \{(x_i, y_i, v, i=1,...,n) \in R_+^{2n+1}, \quad 0 \le x_i, y_i \le L_i, \quad i=1,...,n, \quad 0 \le v \le M\}.$$

Proof. Let $T_i = x_i + y_i, i=1,...,n$, then $\dot{T}_i \le \lambda_i - \sigma_i T_i$,

where $\sigma_i = \min\{d_i, a_i\}$. Hence $0 \le T_i(t) \le \frac{\lambda_i}{\sigma_i}$ for all $t \ge 0$ if $T_i(0) \le \frac{\lambda_i}{\sigma_i}$. It follows that $0 \le x_i(t), y_i(t) \le L_i$ for all $t \ge 0$ if $x_i(0) + y_i(0) \le L_i$ where $L_i = \frac{\lambda_i}{\sigma_i}$. On the other hand,

$$\dot{v} \le \sum_{i=1}^{n} p_i L_i - cv.$$

Then $0 \le v(t) \le M$ for all $t \ge 0$ if $v(0) \le M$ where $M = \sum_{i=1}^{n} \frac{p_i L_i}{c}$.

2.2. Steady states

It is easy to show that, system (4)-(6) has an uninfected steady state $E^0 = (x_i^0, y_i^0, v^0, i=1,...,n)$ where $x_i^0 = \lambda_i / d_i, y_i^0 = 0, v^0 = 0$. The system can also has a positive infected steady state $E^* = (x_i^*, y_i^*, v^*, i=1,...,n)$. The coordinates of the infected steady state, if they exist, satisfy the equalities:

$$\lambda_i = d_i x_i^* + \frac{\beta_i (x_i^*)^{q_i} v^*}{1 + k_i v^*}, \quad i=1,...,n \qquad (7)$$

$$a_i y_i^* = \frac{\beta_i (x_i^*)^{q_i} v^*}{1 + k_i v^*}, \qquad i=1,...,n \qquad (8)$$

$$cv^* = \sum_{i=1}^{n} p_i y_i^*. \qquad (9)$$

We define the basic reproduction number for system (4)-(6)

$$R_0 = \sum_{i=1}^{n} R_{0,i} = \sum_{i=1}^{n} \frac{p_i \beta_i (x_i^0)^{q_i}}{a_i c}.$$

where $R_{0,i}$ is the basic reproduction number for the dynamics of the interaction of the virus only with the target cells of class i.

2.3 Global stability

In this section, we prove the global stability of the uninfected and infected steady states of system (4)-(6) employing the method of Lyapunov function [24]. We define a function

$$H(s) = 1 + \frac{s^r - rs}{r-1}, \; r > 0, \; r \ne 1, \; s \ge 0$$

Clearly $H(0) = 1$ and

$$H'(s) = \frac{r(s^{r-1} - 1)}{r-1} \Rightarrow H'(1) = 0$$

$$H''(s) = rs^{r-2} \Rightarrow H''(1) = r > 0.$$

Then H has the global minimum at $s=1$, $H(1) = 0$. It follows that $H(s) \ge 0$ for all $s \ge 0$. We also define the following function

$$F(s) = s - 1 - \ln(s).$$

It is clear that $F(s) \ge 0$ for any $s > 0$ and F has the global minimum $F(1) = 0$.

Theorem 1. If $R_0 \le 1$, then E^0 is GAS.

Proof. Assume that $q_i \ne 1$. Define a Lyapunov function W_0 as follows:

$$W_0 = \sum_{i=1}^{n} \frac{p_i}{a_i} \left[x_i H\left(\frac{x_i^0}{x_i}\right) + y_i \right] + v.$$

The time derivative of W_0 along the trajectories of (4)-(6) satisfies

$$\frac{dW_0}{dt}=\sum_{i=1}^{n}\frac{p_i}{a_i}\left[\left(1-\left(\frac{x_i^0}{x_i}\right)^{q_i}\right)\left(\lambda_i-d_ix_i-\frac{\beta_i x_i^{q_i}v}{1+k_iv}\right)+\frac{\beta_i x_i^{q_i}v}{1+k_iv}-a_iy_i\right]+\sum_{i=1}^{n}p_iy_i-cv,$$

$$=\sum_{i=1}^{n}\frac{p_i\lambda_i}{a_i}\left(1-\left(\frac{x_i^0}{x_i}\right)^{q_i}\right)\left(1-\frac{x_i}{x_i^0}\right)+cv\left(\sum_{i=1}^{n}\frac{p_i\beta_i\left(x_i^0\right)^{q_i}}{a_ic(1+k_iv)}-1\right)$$

$$=\sum_{i=1}^{n}\frac{p_i\lambda_i}{a_i}\left(1-\left(\frac{x_i^0}{x_i}\right)^{q_i}\right)\left(1-\frac{x_i}{x_i^0}\right)+cv\left(R_0-1\right)-c\sum_{i=1}^{n}\frac{k_iR_{0,i}}{1+k_iv}v^2.$$

Let $g_i=x_i/x_i^0$, then

$$\frac{dW_0}{dt}=\sum_{i=1}^{n}\frac{p_i\lambda_i}{a_i}\left(1-g_i\right)\left(1-\frac{1}{g_i^{q_i}}\right)+cv\left(R_0-1\right)-c\sum_{i=1}^{n}\frac{k_iR_{0,i}}{1+k_iv}v^2.$$

We have

$$\left(1-g_i\right)\left(1-\frac{1}{g_i^{q_i}}\right)\le 0, \text{ for all } q_i, g_i>0.$$

Then if $R_0\le 1$ then $\frac{dW_0}{dt}\le 0$ for all $(x_i,v)>0$. The solutions of system (4)-(6) limit to, the largest invariant subset of $\left\{\frac{dW_0}{dt}=0\right\}$. Clearly, $\frac{dW_0}{dt}=0$ if and only if $x_i=x_i^0$ and $v=0$. Noting that Q is invariant, for each element of Q we have $v=0$, then $\dot{v}=0$.

From Eq. (6) we drive that

$$0=\dot{v}=\sum_{i=1}^{n}p_iy_i. \qquad (10)$$

Since $y_i\ge 0$, then from Eq. (10) we have $y_i=0$. This yields $\frac{dW_0}{dt}=0$ at the steady state E^0. Hence from LaSalle's Invariance Principle, E^0 is GAS.

Theorem 2. If E^* exists then it is GAS.

Proof. Assume that $q_i\ne 1$. Define a Lyapunov function W_1 as follows:

$$W_1=\sum_{i=1}^{n}\frac{p_i}{a_i}\left[x_iH\left(\frac{x_i^*}{x_i}\right)+y_i^*F\left(\frac{y_i^*}{y_i}\right)\right]+v^*F\left(\frac{v^*}{v}\right).$$

The time derivative of W_1 along the trajectories of (4)-(6) satisfies

$$\frac{dW_1}{dt}=\sum_{i=1}^{n}\frac{p_i}{a_i}\left[\left(1-\left(\frac{x_i^*}{x_i}\right)^{q_i}\right)\left(\lambda_i-d_ix_i-\frac{\beta_ix_i^{q_i}v}{1+k_iv}\right)+\left(1-\frac{y_i^*}{y_i}\right)\left(\frac{\beta_ix_i^{q_i}v}{1+k_iv}-a_iy_i\right)\right]+\left(1-\frac{v^*}{v}\right)\left(\sum_{i=1}^{n}p_iy_i-cv\right)$$

$$=\sum_{i=1}^{n}\frac{p_i}{a_i}\left[\lambda_i-d_ix_i-\lambda_i\left(\frac{x_i^*}{x_i}\right)^{q_i}+d_ix_i^*\left(\frac{x_i^*}{x_i}\right)^{q_i-1}+\frac{\beta_i\left(x_i^*\right)^{q_i}v}{1+k_iv}-\frac{y_i^*}{y_i}\frac{\beta_ix_i^{q_i}v}{1+k_iv}+a_iy_i^*-a_iy_i\frac{v^*}{v}\right]-cv+cv^*.$$

Using the infected steady state conditions (7)-(9), we obtain

$$\frac{dW_1}{dt}=\sum_{i=1}^{n}\frac{p_i}{a_i}\left[d_i x_i^*-d_i x_i-(d_i x_i^*+a_i y_i^*)\left(\frac{x_i^*}{x_i}\right)^{q_i}\right.$$
$$+d_i x_i^*\left(\frac{x_i^*}{x_i}\right)^{q_i-1}+a_i y_i^*\frac{v(1+k_i v^*)}{v^*(1+k_i v)}+3a_i y_i^*$$
$$-a_i y_i^*\left(\frac{x_i}{x_i^*}\right)^{q_i}\frac{y_i^* v(1+k_i v^*)}{y_i v^*(1+k_i v)}$$
$$\left.-a_i y_i^*\frac{y_i v^*}{y_i^* v}-a_i y_i^*\frac{v}{v^*}\right]$$
$$=\sum_{i=1}^{n}\frac{p_i}{a_i}\left[d_i x_i^*\left(1-\frac{x_i}{x_i^*}-\left(\frac{x_i^*}{x_i}\right)^{q_i}+\left(\frac{x_i^*}{x_i}\right)^{q_i-1}\right)\right.$$
$$+a_i y_i^*\left(-1-\frac{v}{v^*}+\frac{v(1+k_i v^*)}{v^*(1+k_i v)}+\frac{1+k_i v}{1+k_i v^*}\right)$$
$$+a_i y_i^*\left(4-\left(\frac{x_i^*}{x_i}\right)^{q_i}-\left(\frac{x_i}{x_i^*}\right)^{q_i}\frac{y_i^* v(1+k_i v^*)}{y_i v^*(1+k_i v)}\right.$$
$$\left.\left.-\frac{y_i v^*}{y_i^* v}-\frac{1+k_i v}{1+k_i v^*}\right)\right]. \qquad (11)$$

Let $h_i=x_i/x_i^*$ then Eq. (11) can be rewritten as

$$\frac{dW_1}{dt}=\sum_{i=1}^{n}\frac{p_i}{a_i}\left[d_i x_i^*(1-h_i)\left(1-\frac{1}{h_i^{q_i}}\right)\right.$$
$$-a_i y_i^*\frac{k_i(v-v^*)^2}{v^*(1+k_i v)(1+k_i v^*)}$$
$$+a_i y_i^*\left(4-\left(\frac{x_i^*}{x_i}\right)^{q_i}-\left(\frac{x_i}{x_i^*}\right)^{q_i}\frac{y_i^* v(1+k_i v^*)}{y_i v^*(1+k_i v)}\right.$$
$$\left.\left.-\frac{y_i v^*}{y_i^* v}-\frac{1+k_i v}{1+k_i v^*}\right)\right]. \qquad (12)$$

From Eq. (12) we drive that, if $(x_i^*, y_i^*, v^*)>0$, then $\frac{dW_1}{dt}\le 0$ where the equality occurs at then E^* The global stability of E^* follows from LaSalle's Invariance Principle.

3. Conclusion

In this paper we have proposed a virus infection model with multi-target cells. The model describes the interaction of the virus with n classes of target cells. In this model, the incidence rate is assumed to be nonlinear. The global stability of the uninfected and infected steady states of the model is established by direct Lyapunov method. We have proven that, if $R_0\le 1$, then the uninfected steady state is GAS, and if the infected steady state exists then it is GAS.

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