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Stability Analysis for a Delayed Viral Infection Model with Lytic Immune Response

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Abstract: A class of more general delayed viral infection model with lytic immune response is proposed based on some important biological meanings. The sufficient criteria for local and global asymptotic stabilities of the viral free equilibrium are given, and the sufficient conditions of local asymptotic stability of the infected equilibrium are given too. And the effects of time delay on stabilities of the viral infection model have been studied.

Key words: viral infection model; time delay; lytic immune response; asymptotic stability

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一类具有溶菌性免疫反应的时滞病毒感染模型的稳定性分析

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摘 要:基于一些重要的生物学意义,提出一类更常见的具有溶菌性免疫反应的时滞病毒感染模型.给出了无感染平衡点的局部和全局渐近稳定性的充分条件,还得到感染平衡点的局部渐近稳定性的充分条件.并且研究了时滞对该病毒感染模型的稳定性影响.

关键词:病毒感染模型;时滞;溶菌性免疫反应;渐近稳定性

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0 Introduction

The research of mathematical models can provide insights into the dynamics of viral load in vivo and is very helpful for clinical treatment. The population dynamics of target cells is not completely understood. Nevertheless, a reasonable model for this population of cells is

$$\frac{dx}{dt} = s - dx + kx\left(1 - \frac{x}{x_{max}}\right), \tag{1}$$

where $x(t)$ is the number of susceptible T cells, s represents the rate at which new T cells are created by proliferation of existing T cells. Here we represent the proliferation by a logistic function in which k is the maximum proliferation rate of target cells. x_{max} is the T population density at which proliferation shuts off. d is death rate of the T cells.

Recently, there has been a lot of papers on virus dynamics within-host, some include the immune response directly[1-5]. 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[3] constructed a mathematical model describing the basic dynamics of the interaction between susceptible host cells, a virus population, and immune response. By the similar theoretical analysis to population dynamical systems and epidemic models[6] time delays should be consider in viral models[5], and Buric' et al[7] considered the effects of the time delay for immune response on two-dimensional system which consists of infected cells and CTLs and Kaifa Wang[5] studied the effects of the time delay for immune response on the three-dimensional system with $\dot{z} = cy(t-\tau) - bz$. In this paper, we consider the following model with delay between the time a cell begin to be infected and the time of emission of virus particles from this cell

$$\begin{cases} \dot{x} = s - dx + kx\left(1 - \dfrac{x}{x_{max}}\right) - \beta xy, \\ \dot{y} = \beta e^{-m\tau} x(t-\tau) y(t-\tau) - ay - pyz, \\ \dot{z} = cy - bz, \end{cases} \tag{2}$$

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where $y(t)$ is the number of virus population and $z(t)$ is the number of immune responses; susceptible host cells become infected by virus at rate of βxy; infected cells die at a rate ay and killed by the immune system at a rate pyz for modelling lytic effector mechanisms; the lytic immune response is activated at a rate proportional to the number of infected cells, cy, and also decays exponentially at a rate proportional to its current strength, bz. In model(2) the term $e^{-m\tau}$ accounts for the proportion of infected cells which still alive τ time units later.

1 Preliminaries

We denote by C the Banach space of continuous functions $\phi: [-\tau, 0] \to R^3$ with norm

$$\|\phi\| = \sup_{-\tau \le \theta \le 0} \{|\phi_1(\theta)|, |\phi_2(\theta)|, |\phi_3(\theta)|\},$$

where $\phi = (\phi_1, \phi_2, \phi_3)$. Further, let

$C_+ = \{\phi = (\phi_1, \phi_2, \phi_3) \in C: \phi_i \ge 0$ for all $\theta \in [-\tau, 0]$, $i = 1, 2, 3\}$.

The initial condition for system (2) is given as

$$x(\theta) = \phi_1(\theta),\ y(\theta) = \phi_2(\theta),\ z(\theta) = \phi_3(\theta),\ -\tau \le \theta \le 0, \tag{3}$$

where $\phi = (\phi_1, \phi_2, \phi_3)$.

Lemma 1 Suppose that $(x(t), y(t), z(t))$ is a solution of system (2) with initial conditions (3), then $x(t) \ge 0$, $y(t) \ge 0$, $z(t) \ge 0$ for all $t \ge 0$.

The possible non-negative equilibria of system (2) are viral free equilibrium $E_0 = (x_0, 0, 0)$ and infected equilibrium $E_1 = (\bar{x}, \bar{y}, \bar{z})$, where

$$x_0 = \frac{x_{\max}}{2k}\left[k - d + \sqrt{(k-d)^2 + \frac{4ks}{x_{\max}}}\right],$$

$$\bar{x} = \frac{-(d - k - \frac{ab\beta}{cp}) + \sqrt{(d - k - \frac{ab\beta}{cp})^2 + 4s(\frac{k}{x_{\max}} + \frac{b\beta^2 e^{-m\tau}}{cp})}}{2(\frac{k}{x_{\max}} + \frac{b\beta^2 e^{-m\tau}}{cp})},$$

$$\bar{y} = \frac{b(\beta \bar{x} e^{-m\tau} - a)}{cp},$$

$$\bar{z} = \frac{c\bar{y}}{b}. \tag{4}$$

The basic reproductive number is given as

$$R_0 = \frac{s\beta e^{-m\tau} + ak(1 - \frac{a}{\beta x_{\max} e^{-m\tau}})}{ad}.$$

Lemma 2 For any solution $(x(t), y(t), z(t))$ of (4), we have that

$$\limsup_{t \to +\infty} x(t) \le x_0 = \frac{x_{\max}}{2k}\left[k - d + \sqrt{(k-d)^2 + \frac{4ks}{x_{\max}}}\right].$$

Lemma 3

$$R_0 < 1 \Rightarrow \beta x_0 e^{-m\tau} - a < 0,$$

$$R_0 = 1 \Rightarrow \beta x_0 e^{-m\tau} - a = 0,$$

$$R_0 > 1 \Rightarrow \beta x_0 e^{-m\tau} - a > 0.$$

Now, we will begin to analysis the geometric properties of the equilibria of system (2). Let $\tilde{E}$ be any arbitrary equilibrium of system (2). Then te characteristic equation about $\tilde{E}$ is given by

$$(\lambda + b)(\lambda + a + p\tilde{z})(\lambda + d - k + \frac{2k\tilde{x}}{x_{\max}} + \beta\tilde{y}) + cp\tilde{y}(\lambda + d - k + \frac{2k\tilde{x}}{x_{\max}} + \beta\tilde{y}) - \beta\tilde{x}(\lambda + b)(\lambda + d - k + \frac{2k\tilde{x}}{x_{\max}})e^{-m\tau}e^{-\lambda\tau} = 0. \tag{5}$$

2 Stability analysis of the viral free equilibrium E_0

In this section, we shall consider the stability for the infection free equilibrium E_0 of system (2). We have the following main results

Theorem 1 If $R_0 < 1$, then the viral free equilibrium E_0 is locally asymptotically stable for any time delay $\tau \ge 0$; If $R_0 > 1$, then the viral free equilibrium E_0 is unstable; If $R_0 = 1$, it is a critical case.

Proof For equilibrium $E_0(x_0, 0, 0)$, transcendental equation (5) reduces to

$$(\lambda + b)(\lambda + d - k + \frac{2kx_0}{x_{\max}})(\lambda + a - \beta x_0 e^{-m\tau}e^{-\lambda\tau}) = 0. \tag{6}$$

It is clear that the transcedental equation (6) has negative roots

$$\lambda_1 = -b,$$

$$\lambda_2 = -(d - k + \frac{2kx_0}{x_{\max}}) = -\sqrt{(d-k)^2 + \frac{4ks}{x_{\max}}},$$

and from Lemma 3, we have that $\lambda_3 = \beta x_0 e^{-m\tau} - a < 0$, for $R_0 < 1$. Hence, when $R_0 < 1$ the viral free equilibrium E_0 is locally asymptotically stable for any time dealy $\tau \ge 0$.

If $R_0 > 1$, by Lemma 3 we can see that $\lambda_3 = \beta x_0 e^{-m\tau} - a > 0$, then E_0 is unstable. Therefore our results in this theorem are proved.

Theorem 2 If $R_0 \le 1$, then the viral free equilibrium E_0 of system (2) is globally asymptotically stable for any time delay $\tau \ge 0$.

Proof Define

$G = \{\phi = (\phi_1, \phi_2, \phi_3) \in G_+ \mid x_0 \ge \phi_1 \ge 0, \phi_2 \ge 0, \phi_3 \ge 0\}$.

From Lemma 2, we see that G attracts all solutions of (2). For any $\phi = (\phi_1, \phi_2, \phi_3) \in G$, let $(x(t), y(t), z(t))$ be the solution of (2) with the initial function (3). Then we can claim that for any $t \ge 0$ $x(t) \le x_0$. Hence, G is a positively invariant with respect to (2). If $R_0 < 1$, let us define a functional W on G as follows,

$$W(t) = \phi_2(0) + \eta \int_{-\tau}^{0} \phi_2(\theta)\, d\theta, \tag{7}$$

here $\eta > 0$ is a constant to be chosen later. It is clear that $W(t)$ is continuous on the subset G in G_+. From the invariance of G, for any $\phi \in G$, the solution $(x(t), y(t), z(t))$ of (2) with the initial function (3) satisfies $x(t) \leq x_0$ for any $t \geq 0$. It follows from (2) and (7) that

$$\dot{W}(t)|_{(2)} \leq \phi_2(-\tau)(\beta x_0 e^{-m\tau} - \eta) - \phi_2(0)(a - \eta) - p\phi_2(0)\phi_3(0).$$

By $R_0 < 1$, we can choose η such that $\beta x_0 e^{-m\tau} < \eta < a$. Hence, we have that

$$\dot{W}(t)|_{(2)} \leq -p\phi_2(0)\phi_3(0), \quad (8)$$

for any $\phi \in G$. Hence, $W(\phi)$ is a Lyapunov function on the subset G in G_+. The classical Lyapunov-LaSalle invariance principal shows that $(x_0, 0, 0)$ is globally attractive. Since it has been shown that, if $R_0 < 1$, $(x_0, 0, 0)$ is locally asymptotically stable for any time delay $\tau \geq 0$. Hence, $(x_0, 0, 0)$ is globally asymptotical stability for any time delay $\tau \geq 0$.

If $R_0 = 1$, let us consider the following function on G,

$$W(t) = \phi_2(0) + \beta x_0 e^{-m\tau} \int_{-\tau}^{0} \phi_2(\theta)\, d\theta. \quad (9)$$

Clearly $W(t)$ is also continuous on subset G in C_+. From the invariance of G, for any $\phi \in G$, the solution $(x(t), y(t), z(t))$ of (2) with the initial function (3) satisfies $x(t) \leq x_0$ for all $t > 0$. From (2) and (9), we also have that

$$\dot{W}|_{(2)} = \beta e^{-m\tau}\phi_2(-\tau)(\phi_1(-\tau) - x_0) - \phi_2(0)(a - \beta x_0 e^{-m\tau}) - p\phi_2(0)\phi_3(0).$$

By $R_0 = 1$ and $x(t) \leq x_0$ for all $t > 0$, we have that $\dot{W}|_{(2)} \leq -p\phi_2(0)\phi_3(0)$, for any $\phi \in G$. Hence, $W(\phi)$ is a Lyapunov function on the subset G in G_+. By the same proof as the case of $R_0 < 1$, we can show that when $R_0 = 1$ the viral free equilibrium E_0 is also globally asymptotically stable for any time delay $\tau \geq 0$. Hence, $(x_0, 0, 0)$ is globally asymptotically stable for any time delay $\tau \geq 0$. Thus Theorem 2 is proved.

3 Stability analysis of the infected equilibrium E_1

In this section we shall regard τ as a parameter to study the stability of the infected equilibrium E_1.

The characteristic of the linearized system of (2) near the infected equilibrium E_1 is given by

$$P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0, \quad (10)$$

where

$$P(\lambda, \tau) = \lambda^3 + b_1(\tau)\lambda^2 + b_2(\tau)\lambda + b_3(\tau),$$
$$Q(\lambda, \tau) = b_4(\tau)\lambda^2 + b_5(\tau)\lambda + b_6(\tau), \quad (11)$$

and

$$b_1(\tau) = (b + \beta\bar{x}e^{-m\tau}) + (d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y}),$$
$$b_2(\tau) = (b + \beta\bar{x}e^{-m\tau})(d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y}) + (b\beta\bar{x}e^{-m\tau} + cp\bar{y}),$$
$$b_3(\tau) = (d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y})(b\beta\bar{x}e^{-m\tau} + cp\bar{y}),$$
$$b_4(\tau) = -\beta\bar{x}e^{-m\tau},$$
$$b_5(\tau) = -(b + d - k + \frac{2k\bar{x}}{x_{max}})\beta\bar{x}e^{-m\tau},$$
$$b_6(\tau) = -b\beta\bar{x}e^{-m\tau}(d - k + \frac{2k\bar{x}}{x_{max}}).$$

When $\tau = 0$, the equation (10) becomes $\lambda^3 + a_1(0)\lambda^2 + a_2(0)\lambda + a_3(0) = 0$, where

$$a_1(0) = b_1(0) + b_4(0) = b + d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y} > 0,$$
$$a_2(0) = b_2(0) + b_5(0) = d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y} + cp\bar{y} + \beta^2\bar{x}\bar{y},$$
$$a_3(0) = b_3(0) + b_6(0) = b\beta^2\bar{x}\bar{y} + cp\bar{y}(d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y}) > 0.$$

We also have

$$a_1(0)a_2(0) - a_3(0) = bcp\bar{y} + (d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y})(b + d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y} + \beta^2\bar{x}\bar{y}) > 0.$$

By Routh-Hurwitz criterion, we have the following Theorem 3.

Theorem 3 If $\tau = 0$ and $R_0 > 1$, then the infected equilibrium E_1 is locally asymptotically stable.

Theorem 4 If $\tau = 0$ and $R_0 > 1$, then the infected equilibrium E_1 is globally asymptotically stable.

Proof Define a Lyapunov function $V = (x - \bar{x}\ln x) + (y - \bar{y}\ln y) + \frac{p}{2c}(z - \bar{z})^2$. When $\tau = 0$, calculating the derivative of V along the solutions of system (2), we find

$$\dot{V}(t) = -\frac{s}{x\bar{x}}(x - \bar{x})^2 - \frac{k}{x_{max}}(x - \bar{x})^2 - \frac{bp}{c}(z - \bar{z})^2.$$

Thus, $\dot{V} \leq 0$ and $\dot{V} = 0$ if and only if $x = \bar{x}$, $z = \bar{z}$. By LaSalle's invariance principle, when $\tau = 0$, any solution of system (2) tends to M, where $M \subset \{(x, y, z) \mid x = \bar{x}, z = \bar{z}\}$ is the largest invariant subset of system (2). By the third equation of (2) we can see that $M = \{E_1\}$ is a singleton set. Follows from LaSalle's invariance principle and Theorem 3, the infected equilibrium E_1 is globally asymptotically stable when $\tau = 0$ and $R_0 > 1$.

For $\tau > 0$, we have the following results.

Theorem 5 If $R_0 > 1$, $a_1(\tau) > 0$, $a_2(\tau) > 0$, and $a_3(\tau) > 0$, then the infected equilibrium E_1 is locally asymptotically stable.

Proof From Theorem 3, we have that any root of (10) has negative real part for $\tau = 0$.

If $\lambda = i\omega$ $(\omega > 0)$ be a root of equation (10), and from which we have

$$-b_3(\tau) + b_1(\tau)\omega^2 = -b_5(\tau)\omega\sin\omega\tau + (b_4(\tau)\omega^2 -$$

$$b_6(\tau))\cos\omega\tau,$$

$$\omega^3 - b_2(\tau)\omega = -(b_4(\tau)\omega^2 - b_6(\tau))\sin\omega\tau - b_5(\tau)\omega\cos\omega\tau. \quad (12)$$

Let $\omega^2 = h$, we have

$$F(h) = h^3 + a_1 h^2 + a_2 h + a_3 = 0, \quad (13)$$

where

$$a_1 = b^2 - 2cp\bar{y} + (d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y})^2,$$

$$a_2 = (d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y})(b^2 - 2cp\bar{y}) + cp\bar{y} + 2b\beta\bar{x}e^{-m\tau}) + \beta^3\bar{x}^2\bar{y}e^{-m\tau}[2(d - k + \frac{2k\bar{x}}{x_{max}}) + \beta\bar{y}],$$

$$a_3 = (b_3(\tau) - b_6(\tau))[cp\bar{y}(d - k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y}) + b\beta\bar{x}e^{-m\tau}(-k + \frac{2k\bar{x}}{x_{max}} + \beta\bar{y})].$$

We can see that if $a_1(\tau) > 0$, $a_2(\tau) > 0$, and $a_3(\tau) > 0$, then $F(h) > 0$, which contradicts $F(h) = 0$. This shows that all the roots of the characteristic equation (10) have negative real parts for any time delay. This completes the proff of Theorem 5.

4 Conclusions

In this paper, a class of more general viral infection model with time delay and lytic immune response is considered. The delay between the time a cell begin to be infected and the time of emission of virus particles from this cell is taken into account. Then, a detailed analysis on the asymptotic stabilities of the equilibrium of the viral infection model is carried out. It is show that, if $R_0 < 1$, the viral free equilibrium E_0 is locally asymptotically stable for any time delay $\tau \geq 0$, and that, if $R_0 = 1$, the linearized system of the viral infection model at the E_0 is stable for any time delay $\tau \geq 0$. Furthermore, it has also been show that, if $R_0 \leq 1$, the viral free equilibrium E_0 is globally asymptotically stable for any time delay $\tau \geq 0$. The results show that, the time delay has no effect on both local and global asymptotic properties of the viral free equilibrium E_0 of the viral infection model. If $R_0 > 1$, then E_0 becomes unstable and the infected equilibrium E_1 is locally asymptotically stable for some conditions.

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