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Viral infection model with periodic lytic immune response

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Abstract

Dynamical behavior and bifurcation structure of a viral infection model are studied under the assumption that the lytic immune response is periodic in time. The infection-free equilibrium is globally asymptotically stable when the basic reproductive ratio of virus is less than or equal to one. There is a non-constant periodic solution if the basic reproductive ratio of the virus is greater than one. It is found that period doubling bifurcations occur as the amplitude of lytic component is increased. For intermediate birth rates, the period triplication occurs and then period doubling cascades proceed gradually toward chaotic cycles. For large birth rate, the period doubling cascade proceeds gradually toward chaotic cycles without the period triplication, and the inverse period doubling can be observed. These results can be used to explain the oscillation behaviors of virus population, which was observed in chronic HBV or HCV carriers.

1. Introduction

Mathematical models can provide insights into the dynamics of viral load in vivo. Basic models of viral dynamics contain three variables, which are functions of time t: the populations of uninfected cells, $x(t)$, infected cells that produce virus, $y(t)$, and free virus particles, $v(t)$ (e.g., [2,13]). Without the treatment of drugs, Bartholdy et al. [1] and Wodarz et al. [23] found that the turnover of free virus is much faster than that of infected cells, which allowed them to make a quasi steady-state assumption, whereby the amount of free virus is simply proportional to the number of infected cells. Hence, the number of infected cells $y(t)$ can also be considered as a measure of virus load $v(t)$.

During viral infections, especially with non-cytopathic viruses, the lytic CTL response has been shown to be necessary to eliminate or control the disease (e.g., [8,17,18]). Thus, many papers considered the dynamics of a virus population with lytic immune response (see [11,12,24] and references cited therein). In their models, infected cells become

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lysed by CTLs (z) at a rate pyz, where the parameter p expresses the strength of the lytic component and is a positive constant.

However, as one of organismic physiological systems, like the other circadian rhythms, the immune system is modulated by endogenic center and peripheral mechanism of all levels, including the modulation of centric oscillator and nervous incretion. Many works on immune circadian rhythms have been done by experimental immunologists for the aspects of immunocyte, immunoresponsion and immunomodulation (see [6,7,15]). These experiments verified that the amount of lymphocytes in peripheral blood shows circadian rhythms, which may be modulated by the circadian rhythms of the secretion of cortin. For example, the amount of lymphocytes in peripheral blood, including T cells, $CD4^+$T cells, $CD8^+$T cells and B cells, is lower in the daytime than that at night, and it reaches the peak value at 23:00–3:00, and the foot value at 11:00–14:00. Furthermore, experiments confirmed that the circadian oscillation of lymphocytes is mainly caused by the oscillation of T lymphocytes, not by B lymphocytes.

Based on the experimental data of human immune circadian rhythms, Li and Qi [10] obtained the formulations of T lymphocytes in lymphoid tissues and peripheral blood in the form of a sinusoidal function

$$T(t) = k_0 + k_1 \cos(2\pi t - \varphi)$$

with a period of one day. Their model can be used to explain the stationary oscillation behavior of T lymphocytes in lymphoid tissues and peripheral blood and the numerical results are in agreement with human immune circadian rhythm experimental data. Here we assume that the strength of the lytic component is in (direct) proportion to the amount of T lymphocytes in lymphoid tissues and peripheral blood, thus the strength of the lytic component coefficient, p, is also taken in the form of a sinusoidal function as

$$p(t) = \beta_0 + \beta_1 \cos(2\pi t - \varphi), \tag{1.1}$$

where β_0 is the basic strength of the lytic component, the amplitude β_1 ($0 \leqslant \beta_1 < \beta_0$) measures the degree of oscillation, and φ is the acrophase. The time is scaled in units of days, so the period is just one.

For a quantitative analysis of the dynamics between virus replication and the periodic CTL response, we design a simple mathematical model based on susceptible host cells, $x(t)$, a virus population, $y(t)$, and a CTL response, $z(t)$. Susceptible host cells are generated at a rate λ, die at a rate dx and become infected by virus at a rate βxy. Infected cells die at a rate ay and are killed by the CTL response at a rate $p(t)yz$. This corresponds to lytic effector mechanisms. The coefficient $p(t)$ expresses the strength of the lytic component, which is a general continuous, bounded, positive, periodic of period ω, and not identically zero function of time. The CTL response expands in response to viral antigen derived from infected cells at a rate cy and decay in the absence of antigenic stimulation at a rate bz. Then the model, which details the changes in host-cell number and strength of the immune response as the infection develops over time, is described by the following non-autonomous ordinary differential equations:

$$\begin{cases} x' = \lambda - dx - \beta xy, \\ y' = \beta xy - ay - p(t)yz, \\ z' = cy - bz, \\ x(0) > 0, \quad y(0) > 0, \quad z(0) > 0. \end{cases} \tag{1.2}$$

The main purpose of our investigations in this article is to study the effect of periodic variation in the strength of the lytic component $p(t)$. The organization of this paper is as follows. In Section 2, we give the analytic analysis on system (1.2), and obtain the conditions for the extinction of the virus population and the existence of the non-constant periodic solution, respectively. In Section 3, computer simulations of the system (1.2) are given. Finally, a summary and discussion for the results of analytic analysis and computer simulation are presented.

2. Analytic analysis

It is straightforward to show that with a non-constant strength $p(t)$ our model (1.2) has one and only one steady state

$$E_0 \equiv (x^*, 0, 0) = (\lambda/d, 0, 0),$$

which represents the infection-free equilibrium. The basic reproductive ratio of the virus is given by $R_0 = \lambda\beta/ad$. This ratio describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process. Intuitively, we expect that the disease becomes endemic if $R_0 > 1$, whereas the disease dies out it $R_0 \leqslant 1$. In this section we shall formally state and prove some of these results. First of all, we shall show that system (1.2) is dissipative.