

CHAOS SOLITONS & FRACTALS

Chaos, Solitons and Fractals 33 (2007) 234-245

www.elsevier.com/locate/chaos

# Analysis of stability and Hopf bifurcation for a viral infectious model with delay

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Accepted 13 December 2005

#### **Abstract**

In this paper, a four-dimensional viral infectious model with delay is considered. The stability of the two equilibria and the existence of Hopf bifurcation are investigated. It is found that there are stability switches and Hopf bifurcations occur when the delay  $\tau$  passes through a sequence of critical values. Using the normal form theory and center manifold argument [Hassard B, Kazarino D, Wan Y. Theory and applications of Hopf bifurcation. Cambridge: Cambridge University Press; 1981], the explicit formulaes which determine the stability, the direction and the period of bifurcating periodic solutions are derived. Numerical simulations are carried out to illustrate the validity of the main results. © 2006 Elsevier Ltd. All rights reserved.

### 1. Introduction

Lymphocytic choriomeningitis virus (LCMV) infection in mice provides an example of an extraordinarily dynamics process with an extreme sensitivity of the phenotype of infection to parameters of virus/host interaction. A mathematical model [1,2] is developed to examine the dynamics of virus-specific cytotoxic T lymphocyte (CTL) response for LCMV infection in mice. The model, considering the interacting populations of virus, precursor CTL, terminally differentiated effector CTL and the cumulative viral load is formulated by a system of non-linear delay differential equations:

$$\begin{cases} \frac{\mathrm{d}V(t)}{\mathrm{d}t} = \beta V(t) - \gamma_{\mathrm{VE}} E_{\mathrm{c}}(t) V(t), \\ \frac{\mathrm{d}E_{\mathrm{p}}(t)}{\mathrm{d}t} = \alpha_{E_{\mathrm{p}}}(E_{\mathrm{p}}^{0} - E_{\mathrm{p}}(t)) + b_{\mathrm{p}}V(t - \tau) E_{\mathrm{p}}(t - \tau), \\ \frac{\mathrm{d}E_{\mathrm{e}}(t)}{\mathrm{d}t} = b_{\mathrm{d}}V(t - \tau) E_{\mathrm{p}}(t - \tau) - \alpha_{E_{\mathrm{e}}} E_{\mathrm{e}}(t), \\ \frac{\mathrm{d}W(t)}{\mathrm{d}t} = b_{W}V(t) - \alpha_{W}W(t), \end{cases}$$

$$(1.1)$$

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Table 1 List of the model parameters

Parameter	Biological meaning
β	Replication rate constant of viruses
γve	Rate constant of virus clearance due to effector CTLs
$\alpha_{E_{\mathbf{p}}}$	Rate constant of natural death for precursor CTLs
$E_{ m p}^0$	Homeostatic concentration of LCMV-specific CTLs in spleen of unprimed mouse
$b_{\mathfrak{p}}^{P}$	Rate constant of CTL stimulation
$b_{\rm d}$	Rate constant of CTL differentiation
$\alpha_{E_c}$	Rate constant of natural death for effector CTLs
$b_W$	Rate constant of viral load increase
$\alpha_W$	Rate constant of restoration from the inhibitory effect of virus load

where V(t),  $E_p(t)$ ,  $E_e(t)$ , and W(t) denote population density of virus, precursor CTL, effector CTL, and cumulative viral load, respectively. The parameters  $\beta$ ,  $\gamma_{VE}$ ,  $\alpha_{E_p}$ ,  $E_p^0$ ,  $E_p$ ,  $E_p^0$ ,  $E_p$ ,  $E_p^0$ ,  $E_$ 

For the sake of simplicity, let x(t) = V(t),  $y(t) = E_p(t)$ ,  $z(t) = E_e(t)$  and w(t) = W(t). System (1.1) is transformed into

$$\begin{cases} \frac{\mathrm{d}x(t)}{\mathrm{d}t} = ax(t) - bx(t)z(t), \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} = c(k - y(t)) + mx(t - \tau)y(t - \tau), \\ \frac{\mathrm{d}z(t)}{\mathrm{d}t} = nx(t - \tau)y(t - \tau) - lz(t), \\ \frac{\mathrm{d}w(t)}{\mathrm{d}t} = px(t) - qw(t), \end{cases}$$

$$(1.2)$$

with the initial condition

$$(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C_+ = C((-\tau, 0], R_+^4), \quad \phi_i(0) > 0, \ i = 1, 2, 3, 4, \tag{1.3}$$

where

$$a = \beta$$
,  $b = \gamma_{VE}$ ,  $c = \alpha_{E_p}$ ,  $m = b_p$ ,  $n = b_d$ ,  $k = E_p^0$ ,  $l = \alpha_{E_e}$ ,  $p = b_W$ ,  $q = \alpha_W$ ,  $R_{\perp}^4 = \{(x, y, z, w) \in R^4, x \ge 0, y \ge 0, z \ge 0, w \ge 0\}$ .

For a long time, it has been recognized that delay may have very complicated impact on the dynamics of a system. Delay can cause the loss of stability and can bifurcate various periodic solutions. Recently, there has been extensive work dealing with time delay systems (see, for instance [3–7]).

As far as we know, the known results of the viral infectious model mainly focus on the persistence of low level virus and how other populations depend on the low level virus persistence [1,8,9], but research on the stability and direction of the bifurcating periodic solutions for this kind of system is very critical. Yang [10] and Song [11] studied the Hopf bifurcation of a two-dimensional differential system with delay and a three-dimensional differential system with delay respectively. In this paper, we extend the ideas introduced by Hassard et al. [12] to the four-dimensional viral infectious system with delay and investigate the existence and properties of Hopf bifurcation. The computation is much more complex and needs more techniques.

This paper is organized as follows. In Section 2, the stability of the equilibria and the existence of Hopf bifurcation at the positive equilibrium are studied. In Section 3, the direction of Hopf bifurcation and the stability and period of bifurcating periodic solutions on the center manifold are determined. In Section 4, some numerical simulations are performed to illustrate the analytical results found.

#### 2. Stability analysis and Hopf bifurcation

In this section, we focus on investigating the stability of the equilibria and Hopf bifurcation of the positive equilibrium of the system (1.2). System (1.2) has the boundary equilibrium  $E_0 = (0, k, 0, 0)$  and the positive equilibrium  $E_* = (x_*, y_*, z_*, w_*)$ , where

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