J. Math. Anal. Appl. 442 (2016) 642–672

Contents lists available at ScienceDirect

Journal of Mathematical Analysis and Applications

www.elsevier.com/locate/jmaa

Stability analysis in delayed within-host viral dynamics with both viral and cellular infections

Shyan-Shiou Chen [a], Chang-Yuan Cheng [b,*], Yasuhiro Takeuchi [c]

[a] *Department of Mathematics, National Taiwan Normal University, Taipei 11677, Taiwan*
[b] *Department of Applied Mathematics, National Pingtung University, Pingtung 90003, Taiwan*
[c] *Department of Physics and Mathematics, Aoyama Gakuin University, Sagamihara 252-5258, Japan*

ARTICLE INFO

Article history:
Received 8 April 2016
Available online 9 May 2016
Submitted by W. Sarlet

Keywords:
Virus-to-cell transfer
Cell-to-cell transfer
Immune response
Time delay
Hopf bifurcation

ABSTRACT

We consider a within-host viral model by incorporating (i) mitosis of the healthy target cells which is described by the logistic term; (ii) two routes of infection via, respectively, binding of a virus to a receptor on the surface of a target cell to start genetic reactions (virus-to-cell infection), and the direct transmission from infected cells to uninfected cells through the concept of virological synapse in vivo (cell-to-cell infection); (iii) three time delays accounting, respectively, for a period of the chemical reaction in the virus-to-cell infection, an intracellular incubation period in the cell-to-cell infection and a period of the immune lag incurred by antigenic activation and selection. First, we prove the threshold dynamics of the proposed model, allowing either global convergence to the infection-free equilibrium or uniform persistence of the virus. In addition, global convergence to the infected equilibrium is also derived under a certain criterion in the case without immune delay. Second, to deal with the local stability of the infected equilibrium under a general case with all delay times being positive, we extend an existing geometric method for a new application on the resulted characteristic equation. When the three delays are positive, we showed that incorporation of the immune delay and the intracellular delays in both routes of infection may lead to stability switches of the infected equilibrium according to instinct strength of the logistic growth of the target cells and the transmission rates along both routes of infection.

1. Introduction

Time delay, which occurs in variant mechanisms such as intracellular reactions and immune responses, and virus transmission procedures is one of the key factors in viral dynamics. Virus-to-cell transmission and in vivo cell-to-cell transmission are two main routes of viral infection in within-host dynamics [27,30,31,33]. The virus-to-cell transmission process can be decomposed into several steps: the binding of human

* Corresponding author.
E-mail addresses: sschen@ntnu.edu.tw (S.-S. Chen), cycheng@mail.nptu.edu.tw (C.-Y. Cheng), takeuchi@gem.aoyama.ac.jp (Y. Takeuchi).

http://dx.doi.org/10.1016/j.jmaa.2016.05.003
0022-247X/

immunodeficiency virus (HIV) to a receptor on the surface of a CD4+ T cell, the fusion of HIV with a host cell and the release of genetic material, the integration and transcription of genetic material in an infected cell, the assembly of a new virus, and budding through the membrane of an infected cell [27]. The cell-to-cell transmission process is described as follows: Because CD4+ T lymphocytes are densely aggregated and frequently interact in lymphoid tissues, HIV can disseminate by direct transmission from infected cells to uninfected cells through the concept of HIV virological synapse in vivo [13,44]. In recent years, several mathematical models have been proposed for describing viral infections through a single route for certain disease expression. For example, several models have been developed from the perspective of virus-to-cell transmission for describing HIV type I (HIV-I), hepatitis C virus, hepatitis B virus, and human T-cell lymphotropic virus I (HTLV-I) [5,11,18,24,26,28,29], and models involving cell-to-cell transmission in HIV-I and HTLV-I infections have also been implemented [7,19,36]. Moreover, both mechanisms underlying certain diseases and mathematical models have been proposed for describing viral infection via both routes [15,43].

The work in [8] was one of the first to explore oscillations in viral dynamics. The authors showed that the model, involving the considerations of virus particles, uninfected and infected T cells (a type of virus-to-cell transmission), is equivalent to a competitive system in dimension 3 and obeys a generalized Poincaré–Bendixson theorem which helps to investigate the existence of asymptotically stable periodic orbits. However, further consideration on either the cell-to-cell transmission or the immune response will destroy the competitive property. In addition, time delay can play a role to induce oscillations in several biological systems. On the basis of a previous multistep virus conversion process that occurs before the formation of productively infected cells, intracellular time delays were incorporated into mathematical models in [6,7,10,12,18,24,25,31,42]. The immune response during an infection period must be considered for controlling the development of a virus and the stimulation of antigens for generating immune responses such as cytotoxic T lymphocytes (CTLs) for a specific period. Therefore, time delay was also considered in formulating the immune response in [4,5,12,19,21,23,28,35,39,41]. Immune delay often leads to complex dynamics such as stability switches, periodic oscillations, and even chaotic behaviors. In particular, when the power spectral density and sensitive dependence were calculated under the initial conditions in [41], the immune delay time facilitated the onset of complicated dynamic behaviors whenever susceptible host cells assumed a linear growth and the birth rate was greater than a critical value. On the other hand, the researchers in [35] numerically characterized chaotic behaviors in viral dynamics involving the logistic growth of susceptible host cells. The researchers in [19] also theoretically demonstrated the existence of multiple stable periodic oscillations in a model involving delayed CTL response to HTLV-I infection by showing an overlap of multiple stable Hopf branches.

Stability switches of an equilibrium mean existence of numerous changes in local stability and the instability of this equilibrium because of an increase in the value of a parameter in the system. In the field of virus dynamics, two mechanisms generate switches in the stability of equilibria. The first mechanism is attributable to a delayed immune response [41], whereas the second mechanism is due to exponentially decayed delay-dependent parameters [20,43]. The second mechanism was proposed in [24] to describe the cellular delay between the initial viral infection and the consequent viral production. This mechanism can be described by the following equation:

$$\beta e^{-a\tau} x(t-\tau) y(t-\tau), \tag{1}$$

where x and y are the target cells and virus resource, respectively; τ is the time delay, a is the death rate of infected cells before virus production, and $e^{-a\tau}$ is the probability of infected target cells surviving in the eclipse period. This mechanism can be used to derive characteristic equations with delay-dependent parameters in certain models [20,43], and the geometric method presented in [2], by which one can indicate the existence of pure imaginary roots, facilitates the process of evaluating the stability of an equilibrium.