Available online at www.sciencedirect.com
ScienceDirect
Mathematics and Computers in Simulation 124 (2016) 87–103
MATHEMATICS AND COMPUTERS IN SIMULATION
www.elsevier.com/locate/matcom

Original articles

Analysis of HIV models with multiple target cell populations and general nonlinear rates of viral infection and cell death

Xia Wang[a,b,*], Xinyu Song[b], Sanyi Tang[a], Libin Rong[c,d]

[a] School of Mathematics and Information Sciences, Shaanxi Normal University, Xi'an, 710062, China
[b] College of Mathematics and Information Science, Xinyang Normal University, Xinyang, 464000, China
[c] Department of Mathematics and Statistics, Oakland University, Rochester, MI 48309, United States
[d] Center for Biomedical Research, Oakland University, Rochester, MI 48309, United States

Received 19 October 2013; received in revised form 16 May 2015; accepted 23 November 2015
Available online 4 February 2016

Abstract

HIV can infect different cell populations such as CD4+ T cells and macrophages. In this paper, we study the global property of the solution of an HIV model with two target cell populations. The model includes general nonlinear rates of viral infection and cell death. For each class of target cells, the time delay between viral entry into cells and viral production is included in the model. We obtain the basic reproductive number of the model, which is shown to provide a threshold condition determining the long-term behavior of the solution of the model. Specifically, we show that the infection-free equilibrium is globally asymptotically stable when the basic reproductive number is less than or equal to 1, and that the infected equilibrium is globally asymptotically stable when the basic reproductive number is greater than 1. We also extend the model with two target cell populations to a general model with n populations. Similar global properties are obtained for the general model. Numerical simulations are performed to illustrate the stability results and to evaluate the relative contribution to viral production from the two cell populations.

Keywords: Virus dynamics; Delay; Multiple target cells; Global stability; Lyapunov functional

1. Introduction

It is well known that mathematical modeling and analysis plays an important role in the study of epidemiology [1,2,15,17,20,25]. For example, Anderson and May constructed epidemic models embodying the essentials of the interaction between invertebrate hosts and their directly transmitted microparasites to study the dynamical behavior of conventional epidemiology [1]. Mathematical models have also been developed to study within-host dynamics of HIV infection, i.e., the interaction between cells, virus, and immune responses [4,22–24,26,31,36,39,40,42,50]. In [26], McLean and Kirkwood developed a mathematical model of the activation and proliferation of a clone of T helper cells in response to a replicating antigen and investigated the circumstance under which HIV can destabilize persistent infection and destroy immune memory. Rong and Perelson [39] reviewed mathematical models used to

* Corresponding author.
E-mail address: xywangxia@163.com (X. Wang).

http://dx.doi.org/10.1016/j.matcom.2015.11.011
0378-4754/

study HIV dynamics under antiretroviral therapy, low viral load persistence, the stability of latently infected cells, and the emergence of transient viral load measurements above the detection limit (so-called "viral blips"). A basic viral dynamic model of HIV infection is given below.

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) = \beta x(t)v(t) - ay(t), \\ \dot{v}(t) = py(t) - \delta v(t), \end{cases} \tag{1}$$

where x, y and v represent the densities of uninfected target cells, infected cells and virus, respectively, in blood at time t. Uninfected cells are assumed to be generated at a constant rate λ, die at a per capita rate d, and become infected at a rate βxv, where β is the infection rate. Infected cells are produced at a rate βxv and die at a per capita rate a. Virus is assumed to be produced by productively infected cells at a rate p per cell, and is removed from blood at a per capita rate δ.

The mass action term βxv is used in model (1) to describe viral infection. However, the infection may not be strictly linear in each variable over the entire range of virions v and target cells x. Nonlinear contact rate has been used in some mathematical models [9,17,18,48]. For example, Wang et al. [48] used a virus infection rate with the Beddington–DeAngelis functional response $xv/(1+kx+cv)$. Georgescu and Hsieh [9] considered a nonlinear infection rate with $c(x)f(v)$, where $c(x)$ is the contact rate function depending on susceptible cells x and $f(v)$ represents the force of infection by virus at density v. Huang et al. [14] and Korobeinikov [17,18] assumed the incidence rate to be a nonlinear function $\varphi(x, v)$. In addition, there exists a time delay between viral entry into a target cell and viral production. This intracellular time delay has been studied in many models [6,10,12,14,21,27–30,46,47,49]. In this paper, we will include a time delay τ in the general incidence of viral infection, i.e. $\varphi(x(t-\tau), v(t-\tau))$.

The death rate of productively infected cells may not follow the exponential decay described by $-ay(t)$ in model (1). Productively infected cells are mainly cleared by the immune response, which is stimulated by infected cells [5]. Thus, the death rate of productively infected cells may depend on the density of infected cells [39]. Holte et al. [13] assumed the death rate to be $a(y) = ay^{\omega}$, where ω governs the effect of the immune response on the death rate. In this paper, we will use a general nonlinear function $aG(y)$ to describe the death rate of productively infected cells.

All of the above-mentioned HIV infection models study the interaction between HIV and CD4$^+$ T cells. In addition to CD4$^+$ T cells, other cells such as macrophages [16] and dendritic cells [35] are known to be susceptible to HIV infection. HIV can infect macrophages through binding of gp120 to CD4 and CCR5 receptors, and were identified to be a highly productive source of HIV during the latter stage of viral infection [32]. Two-compartment models [5,34,39] are needed to study the interaction between HIV and two target cell populations. Elaiw and his collaborators have investigated the global asymptotic stability of the steady states of HIV models with two classes of target cells [7,8,44].

In the present paper, we study the global property of the solution of an HIV model with two target cell populations. The model includes general nonlinear rates of viral infection and cell death. Time delays between viral entry into each population of target cells and viral production are incorporated into the model. We analyze the model by deriving the basic reproductive number and proving the global stability of steady states. We also extend the model by including n target cell populations. Similar global properties are obtained for the general model and numerical simulations are performed to illustrate the theoretical results.

2. A model with two target cell populations

In this section, we introduce the following mathematical model of HIV infection with two time delays and two classes of target cells, CD4$^+$ T cells and macrophages.

$$\begin{cases} \dot{x}_1(t) = \lambda_1 - d_1 x_1(t) - \varphi_1(x_1(t), v(t)), \\ \dot{x}_2(t) = \lambda_2 - d_2 x_2(t) - \varphi_2(x_2(t), v(t)), \\ \dot{y}_1(t) = e^{-\mu_1\tau_1}\varphi_1(x_1(t-\tau_1), v(t-\tau_1)) - a_1 G_1(y_1), \\ \dot{y}_2(t) = e^{-\mu_2\tau_2}\varphi_2(x_2(t-\tau_2), v(t-\tau_2)) - a_2 G_2(y_2), \\ \dot{v}(t) = p_1 G_1(y_1(t)) + p_2 G_2(y_2(t)) - \delta v(t). \end{cases} \tag{2}$$

In the model, $x_1(t)$ and $x_2(t)$ are the populations of two classes of uninfected target cells, CD4$^+$ T cells and macrophages, respectively. $y_1(t)$ and $y_2(t)$ represent the populations of productively infected cells that can produce