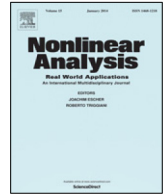




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# An age-structured virus model with two routes of infection in heterogeneous environments



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## ABSTRACT

On the basis of the complexity of the human body, we explore viral dynamics by using a two-compartment model incorporating the age since infection of infected cells and both virus-to-cell infection and cell-to-cell transmission routes. The basic reproduction number,  $\mathcal{R}_0$ , of the system is formulated from two mechanisms: one is the potential trigger from a single infection route in a compartment and the other is the synergistic effect of a viral infection in two compartments. Accordingly, we prove that the infection-free equilibrium is globally asymptotically stable (GAS) if  $\mathcal{R}_0 < 1$ , whereas virus persists uniformly with respect to the initial infection if  $\mathcal{R}_0 > 1$ . From the viewpoint of a predominant infection route incorporated with another mild infection route, we demonstrate global convergence to the infected equilibrium by applying a theory of perturbation on the globally stable steady state.

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## 1. Introduction

The concepts of virus-to-cell infection and cell-to-cell transmission have been extensively studied to explore the viral dynamics and accordingly develop possible drug therapies. The two infection routes are individually supported by experimental evidence or theoretical investigations, mostly for targeted pathologies. Studies have regarded the host as a single compartment and simultaneously discussed both infection routes for specific viruses. On the basis of the complexity of the human body, with multiple tissues and organs, considering multiple compartments within the host and exploring possible infection routes in different parts are necessary.

The virus-to-cell infection process in a compartment such as the bloodstream occurs in the following steps: (1) viruses such as the human immunodeficiency virus (HIV) and human T-cell lymphotropic virus

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I (HTLV-1) bind to a receptor on the surface of a CD4+ T cell, (2) the fusion of a virus with a host cell results in the release of genetic material, (3) the integration and transcription of genetic material occur in an infected cell, and (4) the new virus buds through the membrane of an infected cell [1,2]. The cell-to-cell transmission process was used to describe a viral infection in a compartment such as the lymph node and the brain because CD4+ T lymphocytes are densely aggregated and frequently interact in lymphoid tissues, and HIV can disseminate through direct transmission from infected cells to uninfected cells according to the concept of the HIV virological synapse [3,4]. Recent studies [5–7] have considered both mechanisms in viral infections within a single compartment. However, the human body is composed of both the blood and lymphatic systems and contains numerous physiological tissues. Therefore, a viral infection may spread in multiple fields and not in a single compartment within the host. This indicates the need to model viral dynamics by using multiple compartments. For example, Qesmi et al. [8] modeled a two-compartment system including a new liver and the entire blood system for hepatitis B virus (HBV) during the post-transplant period. It helps in predicting the level of viral infection in the blood system and timely providing drug therapy to prevent reinfection in a new liver after transplantation. Nevertheless, only the route of virus-to-cell infection was examined in this study. How the two aforementioned routes manage the viral infection in different compartments with variant physiological features is an important issue to explore the viral dynamics according to heterogeneous environments of the human body.

A feature of viral dynamics is the heterogeneous structure of the infected cell population, which may lead to variant infectivity and infection reduced motility in different ages [9–12]. Early models of viral infection were developed in the form of ordinary differential equations [1,13], in which the intracellular reaction was assumed to be simultaneous and the infected cell produced viruses after contacting the virus particles. Among the studies considering the delayed intracellular reaction, Herz et al. [14] explored HIV infection by using a delayed differential equation model. Thieme and Castillo-Chaves [15] studied the effect of infection-age-dependent infectivity on the dynamics of HIV transmission within a population group. Another study [11] developed an age-structured model of HIV infection in vivo, in which the production rate of viral particles and the death rate of productively infected cells were accordingly assumed to depend on the age.

On the basis of previous considerations, we propose the following partial differential equation model incorporating the age-since-infection structure for infected cells and both infection routes in a two-compartment environment:

$$\begin{aligned}
 \frac{dT_1(t)}{dt} &= f_1(T_1(t)) - \beta_{11}T_1(t)V(t) - \beta_{12}T_1(t) \int_0^\infty p_1(a)i_1(t, a)da, \\
 \frac{\partial i_1(t, a)}{\partial t} + \frac{\partial i_1(t, a)}{\partial a} &= -(\delta_1(a) + m_1)i_1(t, a), \\
 \frac{dT_2(t)}{dt} &= f_2(T_2(t)) - \beta_{21}T_2(t)V(t) - \beta_{22}T_2(t) \int_0^\infty p_2(a)i_2(t, a)da, \\
 \frac{\partial i_2(t, a)}{\partial t} + \frac{\partial i_2(t, a)}{\partial a} &= -(\delta_2(a) + m_2)i_2(t, a), \\
 \frac{dV(t)}{dt} &= \int_0^\infty q_1(a)i_1(t, a)da + \int_0^\infty q_2(a)i_2(t, a)da - \mu V(t),
 \end{aligned} \tag{1.1}$$

with the boundary condition:

$$i_j(t, 0) = \beta_{j1}T_j(t)V(t) + \beta_{j2}T_j(t) \int_0^\infty p_j(a)i_j(t, a)da, \quad j = 1, 2, \tag{1.2}$$

and the initial condition:

$$T_1(0) = T_{10}, \quad i_1(0, a) = i_{10}(a), \quad T_2(0) = T_{20}, \quad i_2(0, a) = i_{20}(a), \quad V(0) = V_0, \tag{1.3}$$

satisfying  $T_{10}, T_{20} > 0, V_0 \in \mathbb{R}_+, i_{10}(\cdot), i_{20}(\cdot) \in L^1_+$ , where  $\mathbb{R}_+ = [0, \infty)$  and  $L^1_+ = L^1((0, \infty), \mathbb{R}_+)$ , which is the nonnegative cone of  $L^1 = L^1((0, \infty), \mathbb{R})$ . In the  $j$ th compartment, at time  $t$ ,  $T_j(t)$  denotes the

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