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Analysis of an age structured HIV infection model with virus-to-cell infection and cell-to-cell transmission☆

Jinliang Wang[a], Jiying Lang[a], Xingfu Zou[b,c,*]

[a] School of Mathematical Science, Heilongjiang University, Harbin 150080, PR China
[b] Department of Applied Mathematics, University of Western Ontario, London, Ontario, Canada, N6A 5B7
[c] College of Mathematics and Statistics, Central South University, Changsha, Hunan 410083, PR China

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ABSTRACT

Recent studies reveal that cell-to-cell transmission via formation of virological synapses can contribute significantly to virus spread, and hence, may play a more important role than virus-to-cell infection in some situations. Age-structured models can be employed to study the variations w.r.t. infection age in modeling the death rate and virus production rate of infected cells. Considering the above characteristics for within-host dynamics of HIV, in this paper, we formulate an age-structured hybrid model to explore the effects of the two infection modes in viral production and spread. We offer a rigorous analysis for the model, including addressing the relative compactness and persistence of the solution semiflow, and existence of a global attractor. By subtle construction and estimates of Lyapunov functions, we show that the global attractor actually consists of an singleton, being either the infection free steady state if the basic reproduction number is less than one, or the infection steady state if the basic reproduction number is larger than one.

1. Introduction

Over the past decade, significant progress has been made in the mathematical modeling of HIV infection and antiretroviral therapy. It has been realized that mathematically modeling within-host virus dynamics may significantly contribute to the understanding of the effects of antiretroviral drugs treatment. Much of the work on this and related topics builds upon the pioneering work of Ho et al. [1] and Perelson et al. [2] where a three-dimensional system of ordinary differential equations (ODEs) was used to describe the inter-

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* Corresponding author at: Department of Applied Mathematics, University of Western Ontario, London, Ontario, Canada, N6A 5B7.
E-mail addresses: jinliangwang@hlju.edu.cn (J. Wang), xzou@uwo.ca (X. Zou).

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action of uninfected target cells, infected cells, and free virus particles. Since [1,2], there have been a lot of efforts in modifying/improving the model by incorporating various factors.

Nelson et al. [3] formulated a model for HIV infection in the form of initial–boundary-value problem, allowing death rate and virus production rate of infected cells to be infection-age-dependent, denoted by $\theta(a)$ and $p(a)$ respectively, the model reads

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = h - dT(t) - \beta_1 T(t)V(t), \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right) i(a,t) = -\theta(a) i(a,t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty p(a) i(a,t)\mathrm{d}a - cV(t), \\ i(0,t) = \beta_1 T(t)V(t), \\ T(0) = T_s, \qquad i(a,0) = i_s(a), \quad \text{and} \quad V(0) = V_s, \end{cases} \tag{1.1}$$

where $T(t)$ denotes the concentration of uninfected target T cells at time t, $i(a,t)$ denotes the concentration of infected T cells of infection age a at time t, and $V(t)$ denotes the concentration of infectious virus at t. The parameters of model (1.1) are explained as below: h is the constant recruitment rate, β_1 is the rate at which an uninfected cell becomes infected by an infectious virus, d is the natural death rate of uninfected cells, $\theta(a)$ is the infection-age-dependent per capita death rate of infected cells, c is the clearance rate of virions, and $p(a)$ is the viral production rate of an infected cell with infection age a. Mathematically, for a specific form of $p(a)$ and constant $\theta(a)$, Nelson et al. [3] analyzed the *local* stability of the model without or with drug treatment, respectively. They also performed some numerical simulations to illustrate that the time to reach the peak viral level depends not only on the initial conditions but also on the speed at which viral production achieves its maximum value. Subsequently, Rong et al. [4] and Feng and Rong [5] further modified this age-structured model by including three different classes of drugs to assess the effects of different combination of therapies on viral dynamics. They also extended the *local* stability analysis in [3] for general forms of both $p(a)$ and $\theta(a)$ by reformulating the system to a system of Volterra integral equations. However, the *global* behavior is left as an open problem in the above works. Actually, *global* stability is one of the challenging problems in the analysis of biological models and yet it is essential to rule out other dynamical scenarios such as periodic solutions. By constructing suitable Lyapunov functions, Huang et al. [6] were able to complete a global analysis for the model (1.1) without (or with) drug treatment. The age-structured model (1.1) was also used by Qesmi et al. [7] to study the dynamical behaviors of hepatitis B or C virus.

On the other hand, recent experimental work shows that direct cell-to-cell spread via formation of virological synapses can contribute significantly to virus spread in vivo [8]. In fact, the high efficiency of infection by large numbers of virions is likely to result in a transfer of multiple virions to a target cell [8]. The cell-to-cell infection mechanism through transfer of viral particles from infected cells to uninfected cells has also been investigated by some other researchers, among which are [9,10] and [11] from the virological view points. More specifically, in [9], Dimitrov et al. found that the infection rate constant is the critical parameter that affects the kinetics of HIV-1 infection, and furthermore, the infectivity of HIV-1 during cell-to-cell transmission is greater than the infectivity of cell-free viruses; in [10], Sigal et al. claimed that cell-to-cell spread of HIV-1 does reduce the efficacy of antiretroviral therapy, because cell-to-cell infection can cause multiple infections of target cells, which can in turn reduce the sensitivity to the antiretroviral drugs; in [11], Sattentau showed that Herpes simplex virus type-1 (HSV-1) can spread between a fibroblast and a T cell via a virological synapse while it can also move between fibroblasts by assembling and budding at basolateral intercellular junctions.

The above works suggest that the cell-to-cell transmission mechanism is significant. In response to these evidences, there have been some recent works by mathematical models quantitatively exploring the effect of the co-existence of the two modes on the virus dynamics. For example, [12–17] all used ordinary differential