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Global dynamics of a delayed within-host viral infection model with both virus-to-cell and cell-to-cell transmissions☆

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ABSTRACT

A within-host viral infection model with both virus-to-cell and cell-to-cell transmissions and three distributed delays is investigated, in which the first distributed delay describes the intracellular latency for the virus-to-cell infection, the second delay represents the intracellular latency for the cell-to-cell infection, and the third delay describes the time period that viruses penetrated into cells and infected cells release new virions. The global stability analysis of the model is carried out in terms of the basic reproduction number $\mathcal{R}_0$. If $\mathcal{R}_0 \leq 1$, the infection-free (semi-trivial) equilibrium is the unique equilibrium and is globally stable; if $\mathcal{R}_0 > 1$, the chronic infection (positive) equilibrium exists and is globally stable under certain assumptions. Examples and numerical simulations for several special cases are presented, including various within-host dynamics models with discrete or distributed delays that have been well-studied in the literature. It is found that the global stability of the chronic infection equilibrium might change in some special cases when the assumptions do not hold. The results show that the model can be applied to describe the within-host dynamics of HBV, HIV, or HTLV-1 infection.

1. Introduction

When a virus enters the human body, it targets cells with specific receptors. The viral capsid protein binds to the specific receptors on the host cellular surface and injects its core. For example, human immunodeficiency virus (HIV) infects vital cells in the human immune system such as helper T cells (specifically CD4+ T-cells). Its surface protein, gp120, specifically interacts with the chemokine receptors on the surface of CD4+ T-cells. Once bound to the target cell, the HIV RNA and various enzymes are injected into the cell. The hepatitis B virus (HBV) gains entry into the cell by binding to the surface receptor NTCP on the surface. Because HBV multiplies via RNA made by a host enzyme, the viral genomic DNA is transferred to the cell nucleus by host proteins called chaperones. After an intracellular period associated with transcription, integration, and the production of capsid proteins, the infected cell releases hundreds of virions that can infect other cells.

Mathematical models have been developed to describe the within-host dynamics of various viral infections, mostly focusing on virus-to-cell spread in the bloodstream, such as human immunodeficiency virus (HIV) (Kirschner and Webb [23], Müller et al. [30], Nowak and Bangham [34], Nowak and May [35], Perelson et al. [37], Perelson and Nelson [38], Wodarz et al. [48]), hepatitis C virus (HCV) (Dixit et al. [12], Neumann et al. [33], Dahari et al. [8], DebRoy et al. [9]), human T-cell lymphotropic virus I (HTLV-1) (Stilianakis and Seydel [45], Wodarz et al. [49]), etc. The basic within-host viral infection model consists of three components: uninfected target cells, infected target cells and free virus (Bonhoeffer et al. [5], Nowak and May [35]).

On the other hand, great attention has also been paid to the study of *in vitro* cell-to-cell spread of virus since many features are easier to determine experimentally in tissue cultures than in the bloodstream. For example, HIV is thought to be active in areas such as the lymph nodes and the brain where cell-to-cell spread would be a much more important mode of infection than virus-to-cell spread (Dimitrov et al. [11], Sturdevant et al. [47]). The data of Gummuluru et al. [18] demonstrate that cell-to-cell spread of HIV is the predominant route of viral spread since viral replication in a system with rapid cell turnover kinetics depends on cell-to-cell transfer of virus. Sigal et al. [43] examined replication from cell-to-cell spread of HIV in the presence of clinical drug concentrations using a stochastic infection model and found that replication is intermittent without substantial accumulation of mutations. Also, Bangham [2] reported that HTLV-I infection is achieved primarily through cell-to-cell contact. Cell-to-cell

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spread not only facilitates rapid viral dissemination but may also promote immune evasion and influence disease (Sattentau [41]). Based on these observations, researchers have constructed within-host viral infection models for the dynamics of cell-to-cell transmission of HIV (Culshaw et al. [7]).

Upon infection with viruses, there is a short intracellular "eclipse phase", during which the cell is infected but has not yet begun producing virus. For HIV infection, Spouge et al. [44] pointed out that there are two methods to model this eclipse phase, by a time delay or by an explicit class of latently infected cells, but did not consider it in their models. Perelson et al. [37] studied a system with an explicit class of latently infected cells. Herz et al. [21] assumed that cells become productively infected τ time units after initial infection and found that including an intracellular delay did change the estimates of the viral clearance rate but did not change the productively infected T cell loss rate. Culshaw and Ruan [6] showed that such an intracellular delay did not change the stability of the infected steady state for clinically reported parameter values. Mittler et al. [29] assumed that the intracellular delay was continuous and varied according to a gamma distribution and observed dramatic changes in the estimates of viral clearance. See also Banks et al. [3], Dixit et al. [13], Grossman et al. [15–17], Lloyd [28], Nelson et al. [31,32], Lai and Zou [25], Li and Shu [26], Pawelek et al. [36], Shu et al. [42], Wang et al. [46], and Zhu and Zou [50] for HIV infection model with delay; Katri and Ruan [22] for HTLV-1 infection models with delay; and Eikenberry et al. [14] for HBV infection models with delay.

Culshaw et al. [7] proposed a two-dimensional model of cell-to-cell spread of HIV in tissue cultures, in which the intracellular incubation period is modeled by a gamma distribution, and found out that, differing from the cell-to-free virus spread models, the cell-to-cell spread models can produce infective oscillations in typical tissue culture parameter regimes and the latently infected cells are instrumental in sustaining the infection.

To have a better and complete understanding of the within-host infection dynamics inside the whole body, it is necessary to take both virus-to-cell and cell-to-cell transmissions into consideration in modeling viral infections. In fact, recently Lai and Zou [25] proposed a delay differential equations model to include both infection modes of viral infection and spread, in which infection ages via viruses and infected cells are described by two distributed delays. They observed that the basic reproduction number of their model might be underevaluated if either cell-to-cell spread or virus-to-cell infection is neglected. Pourbashash et al. [39] used ordinary differential equations to model the two mechanisms of viral infection and conducted the local and global stability analysis of the model. In general, there are very few studies considering both virus-to-cell and cell-to-cell transmissions on viral infections.

In this paper we consider a within-host viral infection model with both virus-to-cell and cell-to-cell transmissions and three distributed delays, in which the first distributed delay describes the intracellular latency for the virus-to-cell infection (Mittler et al. [29]), the second delay represents the intracellular latency for the cell-to-cell infection (Culshaw et al. [7]), and the third delay describes the time period that viruses penetrated into cells and infected cells release new virions (Nelson and Perelson [32]). The mathematical model is constructed in Section 2. In Section 3, preliminaries are introduced, including the positivity and boundedness of solutions, as well as the existence of an infection-free equilibrium and a chronic infection equilibrium. The global stability of equilibria is obtained in Section 4. Finally, examples and numerical simulations for several special cases of the main model are presented, including various within-host dynamics models with discrete or distributed delays that have been well-studied in the literature. Besides the stability of equilibria under some conditions, it is also shown that periodic oscillations occur via Hopf bifurcations.

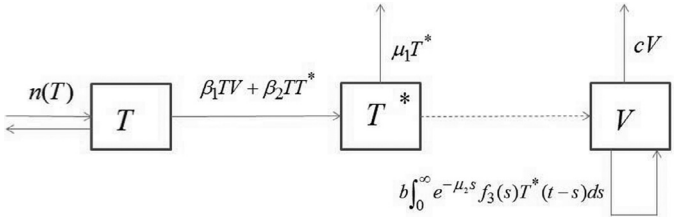

Fig. 1. Transfer diagram of the within-host viral infection.

2. Mathematical model

The compartmental model includes the concentrations of healthy target cells $T(t)$ which are susceptible to infection, infected cells $T^*(t)$ that produces viruses, and viruses $V(t)$. As assumed in De Leenheer and Smith [10], if there is no infection in the healthy target cells, the dynamics of T satisfy the equation

$$\frac{dT(t)}{dt} = n(T(t)), \tag{2.1}$$

where $n(T)$ is a function describing the natural change (including both production and turnover) of healthy target cells. Furthermore, the function $n(T)$ is assumed to satisfy the following properties:

(H_1) $n(T)$ is continuously differentiable and there exists $T^0 > 0$ such that $n(T^0) = 0$ and $n(T)(T - T^0) < 0,\ \forall T \neq T^0$;
(H_2) $n'(T) < 0, \forall T \in [0, T^0]$.

There are two typical functions for $n(T)$: $n(T) = h - d_T T$ and $n(T) = h - d_T T + rT(1 - \frac{T}{K})$ with $h, d_T, r, K > 0$, see Culshaw and Ruan [6], Li and Shu [26], Nowak and Bangham [34], Perelson and Nelson [38], Shu et al. [42], Wang et al. [46], for example.

Let β_1 be the virus-to-cell infection rate, β_2 be the cell-to-cell infection rate, μ_1 and c be death rates of actively infected cells and viruses, respectively. $e^{-\mu_1 s_1}$ is the survival rate of cells that are infected by viruses at time t and become activated infected s_1 time later with a probability distribution $f_1(s_1)$. Then $\int_0^\infty \beta_1 T(t - s_1)V(t - s_1)f_1(s_1)e^{-\mu_1 s_1}ds_1$ describes the newly activated infected target cells which are infected by free viruses s_1 time ago (Mittler et al. [29]). Similarly, $\int_0^\infty \beta_2 T(t - s_2)T^*(t - s_2)f_2(s_2)e^{-\mu_1 s_2}ds_2$ represents the newly activated infected target cells which are infected by infected cells s_2 time ago (Culshaw et al. [7]). Let s_3 be the random variable that is the time between viral RNA transcription and viral release and maturation with a probability distribution $f_3(s_3)$. The integral $\int_0^\infty e^{-\mu_2 s_3} f_3(s_3)T^*(t - s_3)ds_3$ describes the mature viral particles produced at time t (Nelson and Perelson [32]). b is the average number of viruses that bud out from an infected cell, and $e^{-\mu_2 s_3}$ is the survival rates of cells that start budding from activated infected cells at time t and become free mature viruses s_3 time later. Note that s_1, s_2, and s_3 are all integration variables, without loss of generality, they all will be represented by s.

A transfer diagram for the vivo infection of viruses is shown in Fig. 1. The model is given as follows:

$$\begin{aligned}
\frac{dT(t)}{dt} &= n(T(t)) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t),\\
\frac{dT^*(t)}{dt} &= \int_0^\infty \beta_1 T(t - s)V(t - s)f_1(s)e^{-\mu_1 s}ds\\
&\quad + \int_0^\infty \beta_2 T(t - s)T^*(t - s)f_2(s)e^{-\mu_1 s}ds - \mu_1 T^*(t),\\
\frac{dV(t)}{dt} &= b\int_0^\infty e^{-\mu_2 s} f_3(s)T^*(t - s)ds - cV(t).
\end{aligned} \tag{2.2}$$

$f_i(s) : [0, \infty) \to [0, \infty)$ are probability distributions with compact support, $f_i(s) \geq 0$, and $\int_0^\infty f_i(s)ds = 1,\ i = 1, 2, 3$. The distribution was