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Threshold dynamics of an HIV-1 virus model with both virus-to-cell and cell-to-cell transmissions, intracellular delay, and humoral immunity☆

Jiazhe Lin, Rui Xu*, Xiaohong Tian

Institute of Applied Mathematics, Shijiazhuang Mechanical Engineering College, Shijiazhuang 050003, PR China

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ABSTRACT

Direct cell-to-cell transmission of HIV-1 is proved to be a more efficient means of virus infection than virus-to-cell transmission. In this paper, we incorporate both virus-to-cell and cell-to-cell transmissions into an HIV-1 virus model, which also contains intracellular delay and humoral immunity. By analyzing the characteristic equations, the local stability of feasible equilibria is established. By using Lyapunov functionals and LaSalle's invariance principle, it is verified that global threshold dynamics of the model can be explicitly described by immune-inactivated reproduction rate and immune-activated reproduction rate. Numerical simulations are carried out to illustrate the corresponding theoretical results.

1. Introduction

Human immunity is consist of humoral immunity and cellular immunity, which are mainly associated by B-lymphocyte and T-lymphocyte, respectively. In [1–5], dynamical behavior of virus models with cellular immunity has been studied more. Recently, Virgin and Walker [6] and Roederer et al. [7] revealed that humoral immunity plays an important role in the whole human immunity and considered that only by understanding the both two immune responses in unprecedented depth can we develop a protective HIV vaccine. Hence, mathematical modeling and analysis of virus dynamics with humoral immunity can be helpful to design treatment strategies and to provide insights on evaluating effective antiviral drug therapies. Some authors have made their efforts on researching the dynamical behavior of virus models with humoral immunity, for example, Wang and Zou [8] and Murase et al. [9] considered an basic HIV-1 virus model with humoral immunity:

$$\begin{cases} \dot{x}(t) = \Lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) = \beta x(t)v(t) - ay(t), \\ \dot{v}(t) = ky(t) - uv(t) - pv(t)z(t), \\ \dot{z}(t) = cv(t)z(t) - bz(t), \end{cases} \tag{1.1}$$

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* Corresponding author.
E-mail address: xur2020meu@163.com (R. Xu).

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where $x(t)$ denotes uninfected cells (susceptible cells) which are produced at rate Λ and die at rate d, $y(t)$ denotes infected cells, $v(t)$ denotes virus, and $z(t)$ denotes B cells; β is infection rate of virus transmission; a, u and b are death rates of infected cells, virus and B cells, respectively; k denotes the number of free virus particles produced by per infected cell. $pv(t)z(t)$ and $cv(t)z(t)$ are used to describe the virus killed by B cells and the new B cells produced by antigenic stimulation, respectively.

However, the models above include virus-to-cell transmission only. In fact, cell-to-cell transmission has great influence on virus infection, which can not be ignored. In [10], Sigal et al. proved that cell-to-cell spread is the major route of infection as for HIV-1. Some mathematical analysis of virus models with cell-to-cell transmission has been performed. For instance, Li and Wang [11] dealt with the global dynamics of an HIV infection model which incorporated direct cell-to-cell transmission. Meanwhile, Lai and Zou [12,13] studied the effect of cell-to-cell transfer of HIV-1 on the virus dynamics. Lately, Wang et al. [14] have investigated age-structured viral infection models with cell-to-cell transmission and obtained the threshold conditions for the global stability of feasible equilibria.

In addition, model (1.1) did not consider the time between viral entry into a cell and the production of new virus particles, which exists in most diseases. In [15], Elaiw and Alshamrani included the latently infected cells into the model and analysed two nonlinear viral infection models with humoral immune response. Besides, Xu [16] discussed an HIV-1 infection model with an intracellular delay, carried out a complete mathematical analysis of the model and established its global dynamics. Furthermore, Wang and Hu et al. [17] introduced a general incidence rate $f(x(t-\tau), v(t-\tau))$ to denote the average number of cells which are infected by each virus in unit time.

Motivated by the works of Wang and Zou [8], Murase et al. [9] and Lai and Zou [12,13], in the present paper, we are concerned with the effect of both virus-to-cell and cell-to-cell transmissions and intracellular delay on the global dynamics of HIV-1 infection model. To this end, we consider the following delay differential equations:

$$\begin{cases} \dot{x}(t) = \Lambda - dx(t) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t), \\ \dot{y}(t) = \beta_1 e^{-m\tau} x(t-\tau)v(t-\tau) + \beta_2 e^{-m\tau} x(t-\tau)y(t-\tau) - ay(t), \\ \dot{v}(t) = ky(t) - uv(t) - pv(t)z(t), \\ \dot{z}(t) = cv(t)z(t) - bz(t), \end{cases} \tag{1.2}$$

where β_1 and β_2 are infection rates of virus-to-cell transmission and cell-to-cell transmission, respectively; the delay τ represents the time between viral entry into a cell and the production of new free virus or the time between infected cells spreading virus into uninfected cells and the production of new free virus; m is assumed to be a constant death rate for infected but not yet virus-producing cells. Thus, the probability of surviving the time period from $t-\tau$ to t is $e^{-m\tau}$. All parameters are assumed to be positive.

The initial condition for systems (1.2) take the form

$$x(\theta) = \phi_1(\theta), \quad y(\theta) = \phi_2(\theta), \quad v(\theta) = \phi_3(\theta), \quad z(\theta) = \phi_4(\theta), \tag{1.3}$$

where it satisfies that

$$\phi_i(\theta) \geq 0, \quad \theta \in [-\tau, 0), \quad \phi_i(0) > 0, \quad i = 1, 2, 3, 4,$$

where $\phi_i \in C([-\tau, 0], R^4_{+0})$, $i = 1, 2, 3, 4$, the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into R^4_{+0}, where $R^4_{+0} = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1, 2, 3, 4\}$.

It can be proved by the fundamental theory of functional differential equations [18] that system (1.2) has a unique solution $(x(t), y(t), v(t), z(t))$ satisfying the initial condition (1.3). It is easy to show that all solutions of system (1.2) with initial condition (1.3) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

This paper is organized as follows. In Section 2, we verify the existence of feasible equilibria and the boundedness of solutions to system (1.2). In Section 3, the local asymptotic stability of feasible equilibria is established. In Section 4, we investigate the global asymptotic stability of feasible equilibria. In Section 5, we present numerical simulations to illustrate our results and study the effect of cell-to-cell transmission, viral production rate and viral remove rate on viral dynamics, respectively. Besides, we shall perform a sensitivity analysis of immune-inactivated reproduction rate and immune-activated reproduction rate, respectively. The conclusions of our paper will be given in Section 6.

2. Feasible equilibria and boundedness of solutions

Clearly, system (1.2) always has an infection-free equilibrium $E_0(\Lambda/d, 0, 0, 0)$. Denote

$$\mathcal{R}_0 = \frac{(\beta_1 k + \beta_2 u)\Lambda}{aud} e^{-m\tau},$$

here, $\mathcal{R}_0$ is called immune-inactivated reproduction rate of system (1.2), which represents the number of newly infected cells produced by one infected cell during its lifespan [19]. It is easy to show that if $\mathcal{R}_0 > 1$, system (1.2) has an immunity-