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Analysis of an HIV infection model with logistic target-cell growth and cell-to-cell transmission

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ABSTRACT

This paper deals with the global dynamics of an HIV infection model, which incorporates a logistic mitosis term for the uninfected target cells and direct cell-to-cell transmission. It is assumed that beside the diffusion-limited cell-free virus, the infection directly occurs from infected cells to healthy cells. The existence of Hopf bifurcation are discussed by identifying the recruitment rate and mitosis rate of $CD4^+$ T cells as bifurcation parameter. In the case where taking intrinsic mitosis as bifurcation parameter, the direction, stability and period of Hopf bifurcation are investigated by computing normal form. The effect of cell-to-cell transmission rate on viral dynamics are also addressed. Some numerical examples are provided to illustrate our results.

1. Introduction

During the past decades, several different formulations of mathematical models for HIV infection have been extensively investigated based on the basic viral infection models proposed in [5,12–16]. These formulations include systems of ordinary differential equations (ODEs), delay differential equations (DDEs) and partial differential equations (PDEs). The main issues studied in these papers focus on the following points: (i) the mechanisms that cause gradual depletion of $CD4^+$ T cell in an infected individual; (ii) the immunological response to HIV infection; (iii) the possible mechanisms and outcomes of the viral infection process. In the light of these studies, we can get a full understanding of the viral dynamics.

The classical and basic HIV model is typically composed of three variables: susceptible $CD4^+$ T cells, infected $CD4^+$ T cells and free virus. If a free virus particle encounters a susceptible cell, it has a chance to infect the cell, enabling the virus to spread through its target cell population [6]. Denoting by $T(t)$ the concentration of $CD4^+$ T cells at time t. The following target cells dynamics has been proposed by many literatures (see, for example [9,14,16,22] and the references cited therein),

$$\frac{dT}{dt} = \lambda - dT + rT\left(1 - \frac{T}{K}\right). \tag{1.1}$$

Biologically, it is based on the following assumptions:

- $CD4^+$ T cells is produced from precursors at a constant rate λ (recruitment rate), and have a natural turn-over rate d;
- Once stimulated by antigen, the mitosis of $CD4^+$ T cells multiply through intrinsic mitosis with a rate r, $rT(1 - \frac{T}{K})$, where K is the maximum level of $CD4^+$ T cells maintained by homeostasis in the body.

This target cells dynamics (1.1) also have been extended to a full logistic growth term for the growth of $CD4^+$ T cell (see, [10,21]). HIV infection will interrupt the normal $CD4^+$ T cell dynamics. Denote by $T^*(t)$ and $V(t)$ the populations of infected target cells that produce virus and free virus particles,

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respectively. Parameters δ and c are turnover rate of $T^*(t)$ and $V(t)$, respectively. Denote by $\beta_1 T(t)V(t)$ the incidence of HIV infection for CD4$^+$ T cells, where β_1 is the infection rate by free viruses. Constant N is assumed to be the average number of virus particles produced by each infected cell (termed as the burst size). In order to be more realistic, incorporating time delays to represent that the recruitment of virus-producing cells at time t given by the number of cells that were newly infected at time $t-\tau$ and are still alive at time t (see, [8,9]). In [9], Li and Shu proposed the following DDEs to understand joint effects of target cells and intracellular delay on viral dynamics in vivo:

$$\begin{cases} \dfrac{dT}{dt} = \lambda - dT + rT\left(1-\dfrac{T}{K}\right) - \beta_1 TV, \\ \dfrac{dT^*}{dt} = \beta_1 e^{-s\tau} T(t-\tau)V(t-\tau) - \delta T^*, \\ \dfrac{dV}{dt} = N\delta T^* - cV, \end{cases} \tag{1.2}$$

where the delay τ presents the lag from the time of initial infection to the production of new virions by infected CD4$^+$ cells. Constant s is the death rate of infected but not yet virus-producing cells, and $e^{-s\tau}$ describes the probability of infected target cells surviving the period of intracellular delay from $t-\tau$ to t. It is often of interest to study whether Hopf bifurcations can occur for the case where the target-cell dynamics having a mitosis component given by a logistic term. Mathematically, the main results on (1.2) in [9,22] reveal that

- Time delay τ can destabilize the infection equilibrium, and can lead to periodic oscillations from Hopf bifurcation only when r is positive and sufficiently large. Sustained oscillations were observed from infected equilibrium through numerical simulations.

Meanwhile in [14,17], it is also shown that orbitally asymptotically stable periodic orbits exist and attract almost all solutions under suitable conditions for (1.2) with a compartment of latently infected T cells [14] and with nonlinear incidence rate [17], respectively. In a recent work, Li and Shu [7] gave an affirmed answer to the question that whether Hopf bifurcations in in-host models are the result of target-cell dynamics, intracellular delays, or a combination of both. They argued that the occurrence of Hopf bifurcation in in-host viral models depends critically on the target-cell dynamics, not on intracellular delays:

- If no Hopf bifurcation occurs in an in-host model without delay, incorporating intracellular delays will not produce periodic oscillations.

On the other hand, some recent studies reveal that direct cell-to-cell (infected source cell and a susceptible target cell) transmission also be vital to the in vivo spread of the virus. It is found to be a more potent and efficient means of virus propagation than the virus-to-cell infection mechanism. During cell-to-cell transmission, viral particles can be simultaneously transferred from infected CD4$^+$ T cells to uninfected ones through virological synapses. We emphasize that understanding the viral dynamics are very significant in terms of applications. There is an extensive literature dealing with studies related to target cells dynamics and cell-to-cell spread of HIV with and without delays (see e.g. [1,10,11]) and it is impossible to mention all the authors. For detailed description and derivation of the model with cell-to-cell transmission and distribution delays, we refer the reader to previous works [3,6,18,19] for more details on these concerns.

For a full understanding that whether Hopf bifurcations can occur for the case where the target cells dynamics having a mitosis component given by a logistic term, it is necessary to carry out bifurcation analysis of the following model, which incorporates diffusion-limited cell-free virus transmission and cell-to-cell transmission of HIV-1,

$$\begin{cases} \dfrac{dT}{dt} = \lambda - dT + rT\left(1-\dfrac{T}{K}\right) - \beta_1 TV - \beta_2 TT^*, \\ \dfrac{dT^*}{dt} = \beta_1 TV + \beta_2 TT^* - \delta T^*, \\ \dfrac{dV}{dt} = N\delta T^* - cV, \end{cases} \tag{1.3}$$

where β_2 is the infection rate by the cell-to-cell transmission. Before going into details, we first make the following assumptions on the parameters of (1.3).

(i) $r \geq d$: identifying the existence of the mitosis of CD4$^+$ T cells (1.1) compared to the natural growth rate $\lambda - dT$;
(ii) $\delta \geq d$: reflecting the viral burden on the infected CD4$^+$ T cells.

There is an extensive literature dealing with the dynamics of model (1.3) with various possible formulations. Although it is an ordinary differential equation, it can be used to model the infection dynamics of HIV-1, HBV and other viruses. For example, an HIV infection model similar to (1.3) but using similar growth $rT(1-\frac{T+\alpha T^*}{K})$ for susceptible CD4$^+$ T cells has been proposed in [10,21] with $\beta_1 > 0$ and in [1] with $\beta_1 = 0$. These models concluded the result that if the basic reproduction number is greater than one, the infection can persist and Hopf bifurcation can occur from the infection equilibrium within certain parameter ranges.

Of particular interest to us is that, to our knowledge, there are no previous results in the literature concerning the dynamics of model (1.3). This motivates our study in this paper. We shall carry out mathematical analysis of (1.3) to establish the global dynamics of system (1.3) and to investigate whether a logistic mitosis term in target-cell compartment and cell-to-cell transmission mode will cause rich qualitative dynamics on model (1.3). Questions such as non-negativity and boundedness of solutions of system (1.3), stability of equilibria, uniform persistence and Hopf bifurcation will be analyzed. We give examples of numerical applications of our results.

The rest of the paper is organized as follows. Non-negativity and boundedness of solutions of system (1.3) are given in Section 2. Stability of the infection-free equilibrium is discussed in Section 3. Section 4 is devoted to the uniform persistence of the infection. We consider the stability of the positive equilibrium $\overline{E}$ and Hopf bifurcation in Section 5. In Section 6, we present some numerical examples to illustrate our theoretical results. In particular, when parameter r is fixed, Hopf bifurcation occurs at $\overline{E}$ when λ passes through the unique critical value λ^*. Moreover, if λ is fixed, stable periodic solutions occur from equilibrium when r lies in suitable range. We further consider the effect of cell-to-cell