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Dynamic behaviors of a delayed HIV model with stage-structure ☆

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ABSTRACT

Inspired by a simulation specific to a delayed HIV model with stage-structure, some dynamic behaviors are studied in this paper, including global stability of disease-free equilibrium and local Hopf bifurcation when taking the delay as a parameter. The corresponding characteristic equation is a transcendental equation, with the parameters delay-dependent, thus we use the conventional analysis introduced by Beretta and Kuang to obtain sufficient conditions to the existence of Hopf bifurcation. Then some properties of Hopf bifurcation such as direction, stability and period are determined, and several examples illustrate our results.

1. Introduction

Since AIDS was found in America in 1981, it spreads worldwide which has caused great attention from physicians, biologists, mathematicians and physicists. In recent years, HIV dynamics model has become a hot topic in the field of HIV therapeutics studies. When HIV enters the body, it targets cells with $CD4^+$ receptors, including the $CD4^+$ T-cells, the main driver of the immune response. Through infection and eventual killing of these cells, HIV damages the immune system, leading to humoral and cellular immune function loss (which leads to AIDS), making the body susceptible to opportunistic infections [1].

The basic mathematical model [2] of HIV pathogenesis in-host describes interactions of the immune system and the virus by including uninfected and infected $CD4^+$ T-cells (T and T^*) and infectious virus (V) as follows:

$$\begin{aligned} \frac{d}{dt}T(t) &= \xi - dT(t) - \beta T(t)V(t), \\ \frac{d}{dt}T^*(t) &= \beta T(t)V(t) - \delta T^*(t), \\ \frac{d}{dt}V(t) &= kT^*(t) - cV(t). \end{aligned} \tag{1}$$

Here ξ is the source of uninfected cells from precursors; infectious viruses attack uninfected cells at the rate of β and make the uninfected cells into infected ones; d, δ and c are the death rates of uninfected cells, infected cells and infectious virus, respectively. Much has been learned regarding the pathogenesis of HIV in-host using this basic model, and many extensions

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have furthered our understanding of this pathogen. Wang and Li [3] added a full logistic term $rT(t)\left(1-\frac{T(t)+T^*(t)}{T_{max}}\right)$ based on (1), they established the global dynamics of their model. Further more, Li and Shu [4] considered the following model:

$$\begin{aligned}
\frac{d}{dt}T(t) &= \xi - dT(t) - \beta T(t)V(t),\\
\frac{d}{dt}T^*(t) &= \beta e^{-m\tau}T(t-\tau)V(t-\tau) - \delta T^*(t),\\
\frac{d}{dt}V(t) &= kT^*(t) - cV(t).
\end{aligned} \tag{2}$$

In [4] they assume that virus production occurs after the virus entry by a constant delay τ. Therefore, the recruitment of virus producing cells at time t is given by the number of cells that were newly infected at time $t-\tau$ and are still alive at time t. Thus the survival rate during this period is $e^{-m\tau}$ in case m is the death rate for infected cells. Besides stability of equilibrium, the authors also show that for intercellular delays to generate sustained oscillations in in-host models it is necessary to have a logistic mitosis term in target-cell compartments. Then in 2011, Li and Shu [5] considered a model adding a simplified logistic growth term $rT(t)(1-\frac{T(t)}{T_{max}})$ in (2), and studied the joint effects of τ and r on the dynamic behavior. Besides the previous two models, we can see that the appearance of delay is common in HIV models such as [6–8]. Especially [5] showed that τ can lead to Hopf bifurcations and stability switches under certain condition. Meanwhile in [7,8], the effect of the time delay on the stability of the endemically infected equilibrium is studied. Wang et al. [1] also proposed the following model involving logistic growth of the uninfected cells and a time delay:

$$\begin{aligned}
\frac{d}{dt}T(t) &= \xi - dT(t) + rT(t)\left(1-\frac{T(t)}{T_{max}}\right) - \beta T(t)V(t),\\
\frac{d}{dt}T^*(t) &= \beta T(t-\tau)V(t-\tau) - \delta T^*(t),\\
\frac{d}{dt}V(t) &= kT^*(t) - cV(t).
\end{aligned} \tag{3}$$

They show that time delay has no effect on the local asymptotic stability of the uninfected steady state, but can destabilize the infected steady state, leading to periodic oscillations from Hopf bifurcations in the realistic parameter ranges. Furthermore, (3) is modified as follows in [1] by including full logistic proliferation and a varying bud rate,

$$\begin{aligned}
\frac{d}{dt}T(t) &= \xi - dT(t) + rT(t)\left(1-\frac{T(t)+T^*(t)}{T_{max}}\right) - \beta T(t)V(t),\\
\frac{d}{dt}T^*(t) &= \beta e^{-m\tau}T(t-\tau)V(t-\tau) - \delta T^*(t),\\
\frac{d}{dt}V(t) &= kT^*(t) - cV(t).
\end{aligned} \tag{4}$$

For (4), periodic solutions are also observed through numerical simulations. However, theoretical study for explaining this periodic oscillations is more challenging and remains unknown.

In this paper, we will provide a detailed analysis in (4). For delayed models, it is always a complexity to examine the distribution of the roots of their transcendental characteristic equations at a certain equilibrium, especially for those model whose parameters are delay-dependent. In [9], practical guidelines that combine graphical information with analytical work are provided to deal with the models with delay-dependent parameters. Therefore, we will employ the techniques in [9] to analyze (4), showing that the periodic solutions found in [1] are the results of Hopf bifurcations.

The structure of the paper is as follows. We first raise a question of existence of Hopf bifurcation by a simulation. In Section 3, we find the positively invariant feasible region, consider the equilibria and their stabilities in the light of the guidelines in [9]. Under appropriate conditions, the unique positive equilibrium can be destabilized through a Hopf bifurcation and stability switches of stability-instability-stability occur. In Section 4, we use the normal form method and the center manifold theory in [10] to analyze the direction, stability and the period of the bifurcating periodic solution. In Section 5, four sets of numerical simulations will be provided to illustrate our results.

2. Example and forecast

By the inspiration of Wang [1], several sets of parameters on system (4) are chosen to find some conceivable dynamic behavior of (4), fortunately, when we choose

$$\xi = 10,\ d = 0.03,\ m = 0.03,\ r = 0.95,\ T_{max} = 1500,\ \beta = 0.0011,\ \delta = 0.26,\ k = 3.9,\ c = 3 \tag{5}$$

we obtain the following figures in phase space.

As we can see from Fig. 1 that when $\tau = 1.5$ sustained oscillation occurs, but whether the periodic solution caused by Hopf bifurcation needs our deeper research. In the next section we will discuss the existence of Hopf bifurcation.