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A HIV Infection Model with Periodic Multidrug Therapy

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Abstract This paper investigates the effects of periodic drug treatment on a HIV infection model with two co-circulation populations of target cells. We first introduce the basic reproduction ratio for the model, and then show that the infection free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$, while the infection persists and there exists at least one positive periodic state when $\mathcal{R}_0 > 1$. Therefore, $\mathcal{R}_0$ serves as a threshold parameter for the infection. We then consider an optimization problem by shifting the phase of drug efficacy functions, which corresponds to change the dosage time of drugs in each time interval. It turns out that shifting the phase affect critically on the stability of the infection free steady state. Finally, exhaustive numerical simulations are carried out to support our theoretical analysis and explore the optimal phase shift.

Keywords HIV infection, periodic drug treatment, basic reproduction ratio, global stability, optimization.

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1. Introduction

Recently, a great many mathematical models have been developed to study the dynamics of human immunodeficiency virus (HIV) infection with drug treatment (see, e.g [1, 4, 5, 8, 10, 13, 14, 17, 23, 24]). Most of these models considered a three dimensional equation which described the interaction of the HIV and the $CD4^+$ cells. For example, [5,13,14] considered the stability (local or global) of the infection free equilibrium of the three dimensional within-host model with constant drug efficacies. [4,8,24] extended the work to with periodic drug efficacy functions since the drugs are most commonly to be prescribed at a fixed dose and fixed time interval in the process of treatment.

Perelson et cl. [16] observed that after the dosage of the anti-HIV drugs the load of HIV experienced initially a rapid exponential decline (first phase), then a slower exponential decline (second phase). The second phase in the decay profile is probably due to not considering other sources of HIV-1 in the analysis, such as infected macrophages, activation of latently infected lymphocytes, and so on. Therefore, other HIV models considered the interaction process of the HIV not

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only with CD4$^+$ cells, but also with macrophages (see, e.g [1,10,17,23]). Elaiw [10] studied some of the basic properties of the following two co-circulation populations of target cells:

$$\begin{aligned}
\frac{dT_1(t)}{dt} &= a_1 - b_1T_1(t) - k_1T_1(t)V(t)\\
\frac{dT_1^*(t)}{dt} &= k_1T_1(t)V(t) - \delta_1T_1^*(t)\\
\frac{dT_2(t)}{dt} &= a_2 - b_2T_2(t) - k_2T_2(t)V(t)\\
\frac{dT_2^*(t)}{dt} &= k_2T_2(t)V(t) - \delta_2T_2^*(t)\\
\frac{dV(t)}{dt} &= N(T_1^*(t) + T_2^*(t)) - \gamma V(t)
\end{aligned}$$

where the state variables and parameters are described in Table 1.

To consider the drug treatment, we first give a brief introduction of the mechanism of the available anti-HIV drugs. Due to clinical experiments, "drug cocktails", a combination of multiple drugs, have been proved to be useful and effective, and become a standard procedure in the treatment of HIV infection. Most of the available anti-HIV drugs fall into two categories: reverse transcriptase (RT) inhibitors and protease (P) inhibitors. Invading a CD4* target cell and then duplicating its RNA genome is a crucial part of the viral life cycle. RT inhibitors prevent HIV RNA from making a DNA copy, thus blocking the integration of the viral code into the target cells. P inhibitors target on the final step of the viral production: preventing the cutting of the viral proteins before their release from the infected cells. P inhibitors, therefore, effectively reduce the number of infectious virus particles released from a infected cell.

In this paper, we consider a HIV infection model with two co-circulation populations of target cells and periodic drug efficacy functions. The model studied is adapted from the previous models used in [10, 24]. We improve the model in [10] in the following few ways. First, we adopt general growth functions for the CD4$^+$ cell and macrophage population, $f_1(T), f_2(T)$ (see section 2 for details), instead of fixed ones $(a - bT)$. Second, we also allow that the CD4$^+$ cell and macrophage produce different numbers of virus after infection (N_1, N_2). Third, the drug efficacy functions are assumed to be periodic instead of fixed constants. Comparing to [24], we introduce the macrophage population, by which we obtain a more realistic and accurate model.

The organization of this paper is as follows. In section 2, we formulate the mathematical model, and study the existence, uniqueness and boundedness of solutions. In section 3, we define the basic reproduction ratio, $\mathcal{R}_0$, and established a threshold type result with respect to $\mathcal{R}_0$. Furthermore, we introduce the optimization problem of the phase shift. Exhaustive numerical simulations are performed in section 4 to support our analytical analysis, and explore the optimal phase shift numerically.

2. The model

The model we use is adapted from the model used in [10, 24]:

$$\frac{dT_1(t)}{dt} = f_1(T_1) - (1 - \eta_{RT}(t))k_1V(t)T_1(t),$$