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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]:

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

$$\begin{aligned}
\frac{dT_1^*(t)}{dt} &= (1-\eta_{RT}(t))k_1V(t)T_1(t) - \delta_1 T_1^*(t),\\
\frac{dT_2(t)}{dt} &= f_2(T_2) - (1-\sigma\eta_{RT}(t))k_2V(t)T_2(t),\\
\frac{dT_2^*(t)}{dt} &= (1-\sigma\eta_{RT}(t))k_2V(t)T_2(t) - \delta_2 T_2^*(t),\\
\frac{dV(t)}{dt} &= (1-\eta_P(t))(\delta_1 N_1 T_1^*(t) + \delta_2 N_2 T_2^*(t)) - \gamma V(t).
\end{aligned} \tag{2.1}$$

The variables and parameters are described in Table 1. Here we use general growth rate functions, $f_1(T_1)$ and $f_2(T_2)$, to describe the growth of healthy CD4$^+$ cells and macrophages, respectively. $f_1(T_1)$ and $f_2(T_2)$ are assumed to be smooth and satisfy the next condition:

(A1) There exists $T_{i0} > 0$ such that $f_i(T_i)(T_i - T_{i0}) < 0$ for $T_i \neq T_{i0}$ and $f_i'(T_{i0}) < 0$, $i = 1, 2$.

By this assumption, the class of admissible $f(T)$ is quite large, and includes two most popular choices

(1) Perelson and Nelson [17]: $f(T) = a - bT + pT(1 - \frac{T}{T_{max}})$;

(2) Nowak and May [15]: $f(T) = a - bT$.

As discussed in the Introduction section, we assume the drug efficacy functions, $\eta_{RT}(t)$, $\eta_P(t) : \mathbb{R}_+ \to [0, 1]$, to be periodic with common period ω. For realistic consideration, we assume $\eta_{RT}(t)$, $\eta_P(t) \not\equiv 0$, or 1. Clinical observation shows that the RT-inhibitors are more effective in the CD4$^+$ cells than in macrophages. Thus, $\sigma \in [0, 1]$ describes this fact.

Table 1. Variables and parameters for system (2.1).

Variables and parameters	Description
Dependent variables	
T_1	Concentration of the uninfected CD4$^+$ cells
T_1^*	Concentration of the infected CD4$^+$ cells
T_2	Concentration of the uninfected macrophages
T_2^*	Concentration of the infected macrophages
V	Concentration of the free virus particles
Parameters	
$f_1(T_1)$ $(a_1 - b_1T_1)$	Net growth rate of uninfected CD4$^+$ cells
$f_2(T_2)$ $(a_2 - b_2T_2)$	Net growth rate of uninfected macrophages
k_1	Infection rate of uninfected CD4$^+$ cells by virus
k_2	Infection rate of uninfected macrophages by virus
δ_1	Death rate of uninfected CD4$^+$ cells
δ_2	Death rate of uninfected macrophages
N_1	Rate of the virus particles produced by the infected CD4$^+$ cells
N_2	Rate of the virus particles produced by the infected macrophages
γ	Rate at which the virus cleared from the plasma
$\eta_{RT}(t)$	Drug efficacy function of the RT inhibitor
$\eta_P(t)$	Drug efficacy function of the P inhibitor
σ	Fraction of the effectiveness of the RT inhibitors to the macrophages

Remark 2.1. Usually, different RT inhibitors and P inhibitors have different dosage interval. Therefore, $\eta_{RT}(t)$ and $\eta_P(t)$ can have different periods, ω_1 and ω_2, respectively. If $\frac{\omega_1}{\omega_2}$ is a rational number, we can choose ω to be the minimum multiple of ω_1

and ω_2, and then regard the system as an ω-periodic system. If $\frac{\omega_1}{\omega_2}$ is an irrational number, one cannot find a common period for $\eta_{RT}(t)$ and $\eta_P(t)$. However, such a case is rare in reality.

Clearly, condition (A1) and the continuity of f_i implies that $f_i(T_{i0}) = 0$, $i = 1, 2$. It then follows that $E_0 = (T_{10}, 0, T_{20}, 0, 0)$ is the unique infection free equilibrium point of (2.1).

Theorem 2.1. *System (2.1) has a unique and bounded solution with initial value in $\mathbb{R}^5_+$. Further, the compact set*

$$\mathcal{D} := \big\{(T_1, T_1^*, T_2, T_2^*, V) \in \mathbb{R}^5_+ : \ T_1 \le T_{10}, \ T_1^* \le A_1 + T_{10} + 1, \\ T_2 \le T_{20}, T_2^* \le A_2 + T_{20} + 1, V \le L\big\}$$

is positively invariant and attracts all positive orbits in $\mathbb{R}^5_+$. Here $A_i > 0$ satisfies that $\delta_i A_i > S_i + 1$ with $S_i = \max_{T\ge 0} f_i(T)$, $i = 1, 2$,
and $L = \frac{\delta_1 N_1(A_1+T_{10}+1)+\delta_2 N_2(A_2+T_{20}+1)}{\gamma}$.

Proof. We use the argument similar to that in the proof of [14, Lemma 3.1]. By [19, Theorem5.2.1], it follows that for any $(T_1(0), T_1^*(0), T_2(0), T_2^*(0), V(0)) \in \mathbb{R}^5_+$, system (2.1) has a unique local nonnegative solution $(T_1(t), T_1^*(t), T_2(t), T_2^*(t), V(t))$ through the initial value $(T_1(0), T_1^*(0), T_1(0), T_1^*(0), V(0))$.

Since $\frac{dT_1(t)}{dt} \le f_1(T_1)$, $\forall t \ge 0$, we see that $\limsup_{t\to\infty} T_1(t) \le T_{10}$. Then for large t, say $t > t_0$, we have $T_1(t) < T_{10} + 1$. Let $S_1 = \max_{T\ge 0} f_1(T)$. By the first two equations of system (2.1), we obtain that $\frac{d}{dt}(T_1(t) + T_1^*(t)) = f_1(T_1) - \delta_1 T_1^* \le S_1 - \delta_1 T_1^*$. Let $A_1 > 0$ be such that $\delta_1 A_1 > S_1 + 1$. Then as long as $T_1(t) + T_1^*(t) > A_1 + T_{10} + 1$ and $t > t_0$, we have $\frac{d}{dt}(T_1(t) + T_1^*(t)) < -1$. Clearly, there exists $t_1 > t_0$ such that $T_1(t) + T_1^*(t) < A_1 + T_{10} + 1$ for all $t \ge t_1$. Therefore, $T_1^*(t) < A_1 + T_{10} + 1$ for all $t \ge t_1$. By similar argument for the (T_2, T_2^*) population, we have that: there exists a large $t_2 > 0$ such that $\limsup_{t\to\infty} T_2(t) \le T_{20}$ and $T_2^*(t) < A_2 + T_{20} + 1$ for all $t > t_2$, where $A_2 > 0$ satisfies $\delta_2 A_2 > S_2 + 1$ and $S_2 = \max_{T\ge 0} f_2(T)$. Then we have $\frac{dV(t)}{dt} \le \delta_1 N_1(A_1 + T_{10} + 1) + \delta_2 N_2(A_2 + T_{20} + 1) - \gamma V < L\gamma - \gamma V$ for all $t \ge \max\{t_1, t_2\}$, where L is defined as in the theorem. It then follows that $\lim_{t\to\infty} V(t) \le L$. Thus, we conclude that the solution is ultimately bounded. Hence, the solutions of system (2.1) exist globally on the interval $[0, \infty)$, and $\mathcal{D}$ is positively invariant and attracts all positive orbits in $\mathbb{R}^5_+$. □

3. The global dynamics

We then consider the stability of E_0, and the global dynamical behavior of system (2.1). First, we derive the basic reproduction ratio $\mathcal{R}_0$ for system (2.1) by applying the next generation operator approach (see [2, 22]). The linearized system of (2.1) at the infection free equilibrium point E_0 is (we only list the equations for infected cells and free virus particles)

$$\begin{aligned}
\frac{dT_1^*(t)}{dt} &= (1-\eta_{RT}(t))k_1T_{10}V - \delta_1T_1^*,\\
\frac{dT_2^*(t)}{dt} &= (1-\sigma\eta_{RT}(t))k_2T_{20}V - \delta_2T_2^*,\\
\frac{dV(t)}{dt} &= (1-\eta_P(t))(\delta_1N_1T_1^* + \delta_2N_2T_2^*) - \gamma V.
\end{aligned} \tag{3.1}$$

Define

$$F(t) := \begin{pmatrix} 0 & 0 & (1-\eta_{RT}(t))k_1T_{10}\\ 0 & 0 & (1-\sigma\eta_{RT}(t))k_2T_{20}\\ N_1(1-\eta_P(t))\delta_1 & N_2(1-\eta_P(t))\delta_2 & 0 \end{pmatrix},$$

and

$$G(t) := \begin{pmatrix} \delta_1 & 0 & 0\\ 0 & \delta_2 & 0\\ 0 & 0 & \gamma \end{pmatrix}.$$

Let $\Phi_A(t)$ and $\rho(\Phi_A(\omega))$ be the monodromy matrix of the linear ω-periodic system $\frac{dx(t)}{dt} = A(t)x$ and the spectral radius of $\Phi_A(\omega)$, respectively. Let $Y(t,s)$, $t \geq s$, be the evolution operator of the linear ω-periodic system

$$\frac{dy}{dt} = -G(t)y, \tag{3.2}$$

that is, for each $s \in \mathbb{R}$, the 2×2 matrix $Y(t,s)$ satisfies

$$\frac{dY(t,s)}{dt} = -G(t)Y(t,s),\ \forall t \geq s,\ Y(s,s) = I,$$

where I is the 3×3 identity matrix. Thus, the monodromy matrix $\Phi_{-G}(t)$ of system (3.2) equals to $Y(t,0)$, $t \geq 0$.

In view of the periodic environment, we assume that $\phi(s)$, ω-periodic in s, is the initial distribution of infectious individuals. Then $F(s)\phi(s)$ is the rate of new infectious produced by the infected individuals who where introduced at time s. Given $t \geq s$, $Y(t,s)F(s)\phi(s)$ gives the distribution of those infected individuals who were newly infected at time s and remain in the infected compartments at time t. It follows that

$$\Psi(t) := \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da$$

is the distribution of accumulative new infectious at time t produced by all those infected individuals $\phi(s)$ introduced at time previous to t.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, which is equipped with the maximum norm $\|\cdot\|$ and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0, \forall t \in \mathbb{R}\}$. Then we can define a linear operator L: $C_\omega \to C_\omega$ by

$$(L\phi)(t) = \int_0^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da,\ \forall t \in \mathbb{R},\ \phi \in C_\omega. \tag{3.3}$$

Following [22], we call L the next generation operator and define the basic reproduction ratio as $\mathcal{R}_0 := \rho(L)$, the spectral radius of L.

In a special case of $\eta_{RT}(t) \equiv \eta_{RT}$ and $\eta_P(t) \equiv \eta_P$, for all $t \geq 0$, we obtain $F(t) \equiv F$. By Van Den Driessche and Watmough [9], we have an explicit expression for $\mathcal{R}_0$:

$$\mathcal{R}_0 = \rho(FG^{-1}) = (1-\eta_P)\frac{N_1(1-\eta_{RT})k_1T_{10} + N_2(1-\sigma\eta_{RT})k_2T_{20}}{\gamma}.$$

In the periodic case, let $W(t,\lambda)$ be the monodromy matrix of the linear ω-periodic system

$$\frac{dw}{dt} = \Big(-G(t) + \frac{1}{\lambda}F(t)\Big)w,\ t \in \mathbb{R}. \tag{3.4}$$

with parameter $\lambda \in (0,\infty)$. Since $F(t)$ is nonnegative and $-G(t)$ is cooperative, it follows that $\rho(W(\omega,\lambda))$ is continuous and nonincreasing in $\lambda \in (0,\infty)$ and $\lim_{\lambda\to\infty}\rho(W(\omega,\lambda)) < 1$. It is easy to verify that system (2.1) satisfies assumptions $(A_1)-(A_7)$ in [22]. Thus, we have the following two results.

Lemma 3.1. ([22, Theorem 2.1]) *The following statements are valid:*

(i) *If $\rho(W(\omega,\lambda)) = 1$ has a positive solution λ_0, then λ_0 is an eigenvalue of operator L and hence $\mathcal{R}_0 > 0$.*

(ii) *If $\mathcal{R}_0 > 0$, then $\lambda = \mathcal{R}_0$ is the unique solution of $\rho(W(\omega,\lambda)) = 1$.*

(iii) *$\mathcal{R}_0 = 0$ if and only if $\rho(W(\omega,\lambda)) < 1$ for all $\lambda > 0$.*

Lemma 3.2. ([22, Theorem 2.2]) *The following statements are valid:*

(i) *$\mathcal{R}_0 = 1$ if and only if $\rho(\Phi_{F-G}(\omega)) = 1$.*

(ii) *$\mathcal{R}_0 > 1$ if and only if $\rho(\Phi_{F-G}(\omega)) > 1$.*

(iii) *$\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-G}(\omega)) < 1$.*

Thus, the infection free equilibrium E_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

Theorem 3.1. *If the basic reproduction ratio $\mathcal{R}_0 < 1$, then the unique infection free equilibrium E_0 is globally asymptotically stable.*

Proof. By Lemma 3.2, we know that when $\mathcal{R}_0 < 1$, E_0 is locally asymptotically stable. Therefore, we only need to prove the global attractivity of E_0 for $\mathcal{R}_0 < 1$.

By Theorem 2.1, it follows that for any $\varepsilon > 0$, there exists a large $t_0 > 0$ such that $T_i(t) < T_{i0} + \varepsilon$ $(i = 1, 2)$ when $t > t_0$. Therefore, when $t > t_0$, we have

$$\begin{aligned}
\frac{dT_1^*(t)}{dt} &\leq (1-\eta_{RT}(t))k_1(T_{10}+\varepsilon)V - \delta_1 T_1^*,\\
\frac{dT_2^*(t)}{dt} &\leq (1-\sigma\eta_{RT}(t))k_2(T_{20}+\varepsilon)V - \delta_2 T_2^*,\\
\frac{dV(t)}{dt} &= (1-\eta_P(t))(\delta_1 N_1 T_1^* + \delta_2 N_2 T_2^*) - \gamma V.
\end{aligned}$$

Considering the following comparison system

$$\frac{dh(t)}{dt} = (F(t) - G(t) + M_\varepsilon)h(t). \tag{3.5}$$

where

$$M_\varepsilon = \begin{pmatrix} 0 & 0 & (1-\eta_{RT}(t))k_1\varepsilon \\ 0 & 0 & (1-\sigma\eta_{RT}(t))k_2\varepsilon \\ 0 & 0 & 0 \end{pmatrix}.$$

By Lemma 3.2, we know that $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-G}(\omega)) < 1$. We can choose ε small enough such that $\rho(\Phi_{F-G+M_\varepsilon}(\omega)) < 1$.

By [26, Lemma 2.1], it follows that there exists a positive, ω-periodic function $\bar{h}(t)$ such that $h(t) = e^{\theta t}\bar{h}(t)$ is a solution of system (3.5), where $\theta = \frac{1}{\omega}\ln\rho(\Phi_{F-G+M_\varepsilon}(\omega))$. Since $\rho(\Phi_{F-G+M_\varepsilon}(\omega)) < 1$, θ is a negative constant. Therefore, we have $h(t) \to 0$ as $t \to \infty$. For any nonnegative initial value $(T_1^*(0), T_2^*(0), V(0))^T$ for system (2.1), there is a sufficiently large $M^* > 0$, such that $(T_1^*(0), T_2^*(0), V(0))^T \le M^*\bar{h}(0)$ holds. By the comparison principle [20, Theorem B.1], we have $(T_1^*(t), T_2^*(t), V(t))^T \le M^*h(t)$, for all $t \ge 0$, where $M^*h(t)$ is also a solution for system (3.5). Therefore, we get $T_1^*(t) \to 0$, $T_2^*(t) \to 0$ and $V(t) \to 0$ as $t \to \infty$. By asymptotically autonomous semiflows [21], it then follows that $T_i(t) \to T_{i0}$, $i = 1, 2$ as $t \to \infty$. □

Define

$$X_0 := \{(T_1, T_1^*, T_2, T_2^*, V) \in \mathbb{R}^5_+ : \ T_1^* > 0, T_2^* > 0, V > 0\}, \quad \partial X_0 := \mathbb{R}^5_+ \setminus X_0.$$

Let $P : \mathbb{R}^5_+ \to \mathbb{R}^5_+$ be the Poincaré map associated with system (2.1), that is

$$P(x_0) = u(\omega, x_0), \ \forall x_0 \in \mathbb{R}^5_+,$$

where $u(t, x_0)$ is the unique solution of system (2.1) with initial value $u(0, x_0) = x_0$. It is easy to see that

$$P^m(x_0) = u(m\omega, x_0), \ \forall m > 0.$$

Lemma 3.3. *If $\mathcal{R}_0 > 1$, then there exists a $\alpha^* > 0$, such that for any $x_0 \in X_0$, we have*

$$\limsup_{m\to\infty} d(P^m(x_0), E_0) \ge \alpha^*. \tag{3.6}$$

Proof. Since $\mathcal{R}_0 > 1$, by Lemma 3.2, we have $\rho(\Phi_{F-G}(\omega)) > 1$. Then we can choose $\varepsilon > 0$ small enough such that $\rho(\Phi_{F-G-M_\varepsilon}(\omega)) > 1$.

Note that the system, for $i = 1$, or $i = 2$,

$$\tilde{T}_i'(t) = f_i(\tilde{T}_i) - \alpha k_i\tilde{T}_i, \tag{3.7}$$

admits a unique globally asymptotically stable positive equilibrium point, denoted as $\tilde{T}_{i0}(\alpha)$, when α is sufficiently small, and $\tilde{T}_{i0}(\alpha) \to T_{i0}$ as $\alpha \to 0$. We then fix α small enough such that $\tilde{T}_{i0}(\alpha) > T_{i0} - \varepsilon$. Denote $\tilde{T}_i(t, \alpha)$ be solution of (3.7) with initial value $\tilde{T}_i(0)$.

By the continuity of solutions with respect to initial condition, for $\alpha > 0$, there exists a $\alpha^* = \alpha^*(\alpha)$ such that for all $x_0 \in X_0$ with $\|x_0 - E_0\| \le \alpha^*$, there holds $\|u(t, x_0) - u(t, E_0)\| = \|u(t, x_0) - E_0\| < \alpha$, $\forall t \in [0, \omega)$.

Assume, by contradiction, that $\limsup_{m\to\infty} d(P^m(x_0), E_0) < \alpha^*$ for some $x_0 \in X_0$. Without loss of generality, we assume that $d(P^m(x_0), E_0) < \alpha^*$, $\forall m \ge 0$. It then follows that

$$\|u(t, P^m(x_0)) - u(t, E_0)\| < \alpha, \ \forall t \in [0, \omega], \ \forall m \ge 0.$$

For any $t \geq 0$, let $t = m\omega + t'$, where $t' \in [0, \omega)$, m is the largest integer less than or equal to t/ω. Therefore we have

$$\begin{aligned}&\|u(t, x_0 - u(t, E_0)\| \\ &= \|u(t', P^m(x_0) - u(t', E_0)\| < \alpha, \ \forall t \geq 0.\end{aligned}$$

Note that $(T_1(t), T_1^*(t), T_2(t), T_2^*(t), V(t)) = u(t, x_0)$. It then follows that $T_1^*(t) < \alpha$, $T_2^*(t) < \alpha$, $V(t) < \alpha$, $\forall t \geq 0$. From the equations of $T_1(t)$ and $T_2(t)$ in system (2.1), we have

$$\begin{aligned}T_1'(t) &\geq f_1(T_1) - \alpha(1 - \eta_{RT}(t))k_1T_1 \geq f_1(T_1) - \alpha k_1T_1, \\ T_2'(t) &\geq f_2(T_2) - \alpha(1 - \sigma\eta_{RT}(t))k_2T_2 \geq f_2(T_2) - \alpha k_2T_2.\end{aligned}$$

Since $\tilde{T}_{i0}(\alpha)$ is globally asymptotically stable for system (3.7) and $\tilde{T}_{i0}(\alpha) > T_{i0} - \varepsilon$, we obtain for T_1^*, T_2^* and V populations of system (2.1) that, for sufficiently large t,

$$\begin{aligned}T_1^{*\prime}(t) &\geq (1 - \eta_{RT}(t))k_1(T_{10} - \varepsilon)V - \delta_1T_1^*, \\ T_2^{*\prime}(t) &\geq (1 - \sigma\eta_{RT}(t))k_2(T_{20} - \varepsilon)V - \delta_2T_2^*, \\ V'(t) &= (1 - \eta_P(t))(\delta_1N_1T_1^* + \delta_2N_2T_2^*) - \gamma V.\end{aligned} \tag{3.8}$$

Next we consider the following system

$$\begin{aligned}\tilde{T}_1^{*\prime}(t) &= (1 - \eta_{RT}(t))k_1(T_{10} - \varepsilon)V - \delta_1\tilde{T}_1^*, \\ \tilde{T}_2^{*\prime}(t) &= (1 - \sigma\eta_{RT}(t))k_2(T_{20} - \varepsilon)V - \delta_2\tilde{T}_2^*, \\ \tilde{V}'(t) &= (1 - \eta_P(t))(\delta_1N_1\tilde{T}_1^* + \delta_2N_2\tilde{T}_2^*) - \gamma\tilde{V}.\end{aligned} \tag{3.9}$$

By [26, Lemma 2.1], we know that there exists a positive ω-periodic function $(\bar{T}_1^*(t), \bar{T}_2^*(t), \bar{V}(t))^T$ such that $(\tilde{T}_1^*(t), \tilde{T}_2^*(t), \tilde{V}(t))^T = e^{\zeta t}(\bar{T}_1^*(t), \bar{T}_2^*(t), \bar{V}(t))^T$ is a solution of system (3.9), where $\zeta = \frac{1}{\omega}\ln\rho(\Phi_{F-G-M_\varepsilon}(\omega))$. Since $\rho(\Phi_{F-G-M_\varepsilon}(\omega)) > 1$, ζ is a positive constant. Let $t = n\omega$ and n be nonnegative integer, then we get

$$(\tilde{T}_1^*(n\omega), \tilde{T}_2^*(n\omega), \tilde{V}(n\omega))^T = e^{\zeta n\omega}(\bar{T}_1^*(t), \bar{T}_2^*(t), \bar{V}(t))^T \to (\infty, \infty)$$

as $n \to \infty$, since $\omega\zeta > 0$ and $(\bar{T}_1^*(t), \bar{T}_2^*(t), \bar{V}(t))^T > 0$. For any nonnegative initial condition $(T_1^*(0), T_2^*(0), V(0))^T$ of system (3.8), there exists a sufficiently small $m^* > 0$ such that $(T_1^*(0), T_2^*(0), V(0))^T \geq m^*(\bar{T}_1^*(0), \bar{T}_2^*(0), \bar{V}(0))^T$. By the comparison principle [20, Theorem B.1], we have

$$(T_1^*(t), T_2^*(t), V(t))^T \geq m^*(\tilde{T}_1^*(t), \tilde{T}_2^*(t), \tilde{V}(t))^T \ \textit{for all } t > 0.$$

where $m^*(\tilde{T}_1^*(t), \tilde{T}_2^*(t), \tilde{V}(t))^T$ is also a solution for (3.9). Thus we have $T_1^*(n\omega) \to \infty$, $T_2^*(n\omega) \to \infty$ and $V(n\omega) \to \infty$ as $n \to \infty$, which is a contradiction. □

Theorem 3.2. *When $\mathcal{R}_0 > 1$, there exists a $\xi > 0$ such that any solution $(T_1(t),\ T_1^*(t),\ T_2(t),\ T_2^*(t),\ V(t))$ of system (2.1) with initial value $(T_1(0),\ T_1^*(0),\ T_2(0),\ T_2^*(0),\ V(0)) \in X_0$ satisfies*

$$\liminf_{t\to\infty}(T_1^*(t), T_2^*(t), V(t)) > (\xi, \xi, \xi).$$

and system(2.1) admits at least one positive periodic solution.

Proof. By Theorem 2.1, the discrete-time system $\{P^m\}_{m\geq 0}$ admits a global attractor in $\mathbb{R}^5_+$, and $\mathbb{R}^5_+$ is positively invariant. By the second and third equations of system (2.1), we have

$$\begin{aligned}\frac{dT_1^*(t)}{dt} &\geq -\delta_1 T_1^*,\\ \frac{dT_2^*(t)}{dt} &\geq -\delta_2 T_2^*,\\ \frac{dV(t)}{dt} &\geq -\gamma V.\end{aligned}$$

By the comparison principle, we get that $T_1^*(t) > 0$, $T_2^*(t) > 0$, and $V(t) > 0$, $\forall t \geq 0$ if $T_1^*(0) > 0$, $T_2^*(0) > 0$, $V(0) > 0$, which implies that X_0 is positively invariant. Now we prove that $\{P^m\}_{m\geq 0}$ is uniformly persistent with respect to $(X_0, \partial X_0)$.

From the first and third equations of (2.1), we get

$$\frac{dT_i(t)}{dt} \geq -k_i V(t) T_i,\ i = 1, 2. \tag{3.10}$$

By the comparison principal, we get $T_i(t) > 0$ for all $t \geq 0$ if $T_i(0) > 0$. When $T_i(0) = 0$, we have

$$\frac{dT_i(0)}{dt} = f_i(0) > 0,$$

then we have $T_i(t) > 0$ for $0 < t \ll 1$, then by (3.10) and the comparison principle, we get that when $T_i(0) = 0$, $T(t) > 0$ for $t > 0$. Then we have for all initial value in X_0, that

$$T_i(t) > 0,\ \forall t > 0,\ i = 1, 2. \tag{3.11}$$

Define

$$M_\partial := \big\{x_0 \in \partial X_0 :\ P^m(x_0) \in \partial X_0,\ \forall m \geq 0\big\}.$$

We now show that

$$M_\partial := \big\{(T_1, 0, T_2, 0, 0) :\ T_1 \geq 0, T_2 \geq 0\big\}.$$

Clearly $\big\{(T_1, 0, T_2, 0, 0) :\ T_1 \geq 0, T_2 \geq 0\big\} \subset M_\partial$. It suffices to prove that for any $(T_1(0), T_1^*(0), T_2(0), T_2^*(0), V(0)) \in M_\partial$, we have $T_1^*(m\omega) = T_2^*(m\omega) = V(m\omega) = 0$, $\forall m \geq 0$. If it is not true, for some initial value $(T_1(0), T_1^*(0), T_2(0), T_2^*(0), V(0)) \in M_\partial$, there exists an $m_1 \geq 0$ such that $(T_1^*(m_1\omega), T_2^*(m_1\omega), V(m_1\omega)) > 0$. If $(T_1^*(m_1\omega), T_2^*(m_1\omega), V(m_1\omega)) \gg 0$, by the positive invariance of X_0, we have $(T_1^*(t), T_2^*(t), V(t)) \gg 0$ for any $t > m_1\omega$, which is a contradiction. Therefore, we only need to consider the following six cases:

Case 1: $T_1^*(m_1\omega) = 0$, $T_2^*(m_1\omega) > 0$ and $V(m_1\omega) > 0$.

According to the above analysis and $T_2^*(m_1\omega) > 0$, $V(m_1\omega) > 0$, we obtain that $T_2^*(t),\ V(t) > 0$, for all $t \geq m_1\omega$. Therefore, we obtain

$$\begin{aligned}T_1^{*\prime}(m_1\omega) &= (1 - \eta_{RT}(m_1\omega))k_1 V(m_1\omega) - \sigma_1 T_1^*(m_1\omega)\\ &= (1 - \eta_{RT}(m_1\omega))k_1 V(m_1\omega).\end{aligned}$$

Table 2. Six cases such that $(T_1^*(m_1\omega), T_2^*(m_1\omega), V(m_1\omega)) > 0$.

Cases	1	2	3	4	5	6
$T_1^*(m_1\omega)$	0	+	+	0	0	+
$T_2^*(m_1\omega)$	+	0	+	0	+	0
$V(m_1\omega)$	+	+	0	+	0	0

If $\eta_{RT}(m_1\omega) \neq 1$, $T_1^{*\prime}(m_1\omega) > 0$ for $t > m_1\omega + \epsilon$ with ϵ sufficiently small. Then by the positively invariance of X_0, we have $T_1^{*\prime}(m_1\omega) > 0$ for all $t > m_1\omega$.

If $\eta_{RT}(m_1\omega) = 1$, thus, $T_1^{*\prime}(m_1\omega) = 0$. By the assumption of $\eta_{RT}(t) \neq 1$ for all $t \in [0, \omega)$, define t^* as $t^* = \inf\{t \in [0,\omega),\ \eta_{RT}(t + m_1\omega) \neq 1\}$. Therefore, we have $T_1^*(m_1\omega) > 0$ for $t > t^* + m_1\omega + \epsilon$ for some ϵ sufficiently small.

Case 5: $T_1^*(m_1\omega) = 0$, $T_2^*(m_1\omega) > 0$ and $V(m_1\omega) = 0$.

In this case, we have for the free virus population that

$$\begin{aligned} V'(m_1\omega) &= N(1 - \eta_P(m_1\omega))(\delta_1 T_1^*(m_1\omega) + \delta_2 T_2^*(m_1\omega)) - \gamma V(m_1\omega) \\ &= N(1 - \eta_P(m_1\omega))\delta_2 T_2^*(m_1\omega) \end{aligned}$$

If $\eta_P(m_1\omega) \neq 1$, $V^{*\prime}(m_1\omega) > 0$ for $t > m_1\omega + \epsilon$ with ϵ sufficiently small. Then by the positively invariance of X_0, we have $V^{*\prime}(m_1\omega) > 0$ for all $t > m_1\omega$.

If $\eta_P(m_1\omega) = 1$, by similar analysis as for case 1, we have that $V^{*\prime}(m_1\omega) > 0$ for some $t > m_1\omega + \bar{t}$.

The analysis for case 2, 3, 4, and 6 are similar. Thus, we have that $(T_1(t), T_1^*(t), T_2(t), T_2^*(t), V(t)$ finally enters X_0 with an initial condition in M_∂, which is a contradiction. Thus, we conclude that $M_\partial := \{(T_1, 0, T_2, 0, 0) :\ T_1 \geq 0, T_2 \geq 0\}$.

Clearly, there is exactly one fixed point E_0 of P in M_∂. According to Lemma 3.3, we obtain that E_0 is an isolated invariant set, and $W^s(E_0) \cap X_0 = \emptyset$. Note that every orbit in M_∂ approaches to E_0, and E_0 is acyclic in M_∂. [27, Remark 1.3.1] implies that P is uniformly persistent with respect to $(X_0, \partial X_0)$. By [27, Theorem 3.1.1], it follows that the solutions of system (2.1) are uniformly persistent with respect to $(X_0, \partial X_0)$, which means that there exists a $\xi > 0$ such that any solution $(T_1(t), T_1^*(t), T_2(t), T_2^*(t), V(t))$ of system (2.1) with initial condition $(T_1(0), T_1^*(0), T_2(0), T_2^*(0), V(0)) \in X_0$ satisfies

$$\liminf_{t\to\infty}(T_1^*(t), T_2^*(t), V(t)) > (\xi, \xi, \xi).$$

Furthermore, by the coexistence theorem [27, Theorem 1.3.6], we have that P has a fixed point, denoted as $E_* = (T_{1*}(0), T_{1*}^*(0), T_{2*}(0), T_{2*}^*(0), V_*(0)) \in X_0$. Obviously, we have $T_{i*}(0) \geq 0$, $T_{i*}^*(0) > 0$ and $V_*(0) > 0$, $i = 1, 2$. We then prove that the ω-periodic solution for system (2.1), denoted as $(T_{1*}(t), T_{1*}^*(t), T_{2*}(t), T_{2*}^*(t), V_*(t))$, which corresponds to E_*, is positive. It is suffice to prove that $T_{i*}(t) > 0$ for all $t > 0$ by the positively invariance of X_0. By the periodicity of $T_{i*}(t)$, we only need to prove that $T_{i*}(\bar{t}) > 0$ for some $\bar{t} \in [0, \omega)$. If it is not true, we have $T_{i*}(t) \equiv 0$ for all $t \geq 0$. By the equations for $T_i(t)$, we obtain that

$$0 = T_{i*}' = f_i(0) > 0,$$

which is a contradiction. Thus, $(T_{1*}(t), T_{1*}^*(t), T_{2*}(t), T_{2*}^*(t), V_*(t))$ is a positive ω-periodic solution of system (2.1). □

By Theorems 3.1 and 3.2, we conclude that to determine whether the viral persists in an individual, we only need to determine the value of $\mathcal{R}_0$. Thus, $\mathcal{R}_0$ serves as a threshold parameter. Zhao [28] gives a detailed algorithm for numerical computation of $\mathcal{R}_0$, which is used in the numerical studies in section 4.

All the previous analysis is with the assumption that the two different kinds of drugs are taken at the the same time every day. Browne and Pilyugin [4], and Wang and Zhao [24] analyzed the phase shift problem, and showed that shifting the phase of the drug efficacy functions, which corresponds to changing daily drug administration time, can critically effect the stability of infectious-free steady state. Inspired by their work, we then consider the phase shift problem with $\psi_1, \psi_2 \in [0, \omega)$:

$$\begin{aligned}
\frac{dT_1(t)}{dt} &= f_1(T_1) - (1 - \eta_{RT}(t - \psi_1))k_1 V T_1, \\
\frac{dT_1^*(t)}{dt} &= (1 - \eta_{RT}(t - \psi_1))k_1 V T_1 - \delta_1 T_1^*, \\
\frac{dT_2(t)}{dt} &= f_2(T_2) - (1 - \sigma\eta_{RT}(t - \psi_1))k_2 V T_2, \\
\frac{dT_2^*(t)}{dt} &= (1 - \sigma\eta_{RT}(t - \psi_1))k_2 V T_2 - \delta_2 T_2^*, \\
\frac{dV(t)}{dt} &= (1 - \eta_P(t - \psi_2))(\delta_1 N_1 T_1^* + \delta_2 N_2 T_2^*) - \gamma V.
\end{aligned} \tag{3.12}$$

Therefore, the linearized system of system (3.12) at E_0 are (we only list the equations for the infected cells and free virus particles):

$$x' = B(t, \psi_1, \psi_2)x, \tag{3.13}$$

where $x = (T_1^*, T_2^*, V)^T$, and

$$B(t, \psi_1, \psi_2) = \begin{pmatrix} -\delta_1 & 0 & (1-\eta_{RT}(t-\psi_1))k_1 T_{10} \\ 0 & -\delta_2 & (1-\sigma\eta_{RT}(t-\psi_1))k_2 T_{20} \\ N_1(1-\eta_P(t-\psi_2))\delta_1 & N_2(1-\eta_P(t-\psi_2))\delta_2 & -\gamma \end{pmatrix}.$$

Define

$$F(t, \psi_1, \psi_2) = \begin{pmatrix} 0 & 0 & (1-\eta_{RT}(t-\psi_1))k_1 T_{10} \\ 0 & 0 & (1-\sigma\eta_{RT}(t-\psi_1))k_2 T_{20} \\ N_1(1-\eta_P(t-\psi_2))\delta_1 & N_2(1-\eta_P(t-\psi_2))\delta_2 & 0 \end{pmatrix}.$$

and

$$G(t, \psi_1, \psi_2) = G(t) = \begin{pmatrix} \delta_1 & 0 & 0 \\ 0 & \delta_2 & 0 \\ 0 & 0 & \gamma \end{pmatrix}.$$

By similar argument for system (3.1), we define the basic reproduction ratio for system (3.13):

$$\mathcal{R}_0(\psi_1, \psi_2) := \rho(L_{\psi_1, \psi_2})$$

where

$$(L_{\psi_1,\psi_2}\phi)(t) = \int_0^\infty Y(t, t-a)F(t-a, \psi_1, \psi_2)\phi(t-a)da, \ \forall t \in \mathbb{R}, \ \phi \in C_\omega.$$

By [24, Lemma 2.4], we have the next similar result.

Lemma 3.4. *$\mathcal{R}_0(\psi_1, \psi_2) = \mathcal{R}_0(0, \psi)$, where $\psi = (\psi_2 - \psi_1)$ modulo ω, that is, ψ is determined by $\psi_2 - \psi_1 = m\omega + \psi$, $\psi \in [0, \omega)$, $m \in \mathbb{Z}$.*

Proof. The proof is similar to the proof for [24, Lemma 2.4]. Therefore, we omit the proof here. □

For simplicity, denote $\mathcal{R}_0(0, \psi) = \mathcal{R}_0(\psi)$. We observe that the map $\psi \to \mathcal{R}_0(\psi)$ is a ω-periodic function in $\mathbb{R}$. Therefore, instead of considering the optimization problem of finding optimal ψ_1 and ψ_2 for $\eta_{RT}(t)$ and $\eta_P(t)$, we only need to find the optimal phase shift ψ for $\eta_P(t - \psi)$. Therefore, we only need to consider the time difference between administrated dosages of the RT inhibitors and P inhibitors.

4. Case studies

In this section, we numerically study the effect of phase shift to the basic reproduction ratio, $\mathcal{R}_0$, and then determine its effect to the viral states in an individual. To start with a simple case of drug efficacy functions and also as a comparison to the numerical studies in [4] and [24], we choose the drug efficacy function to be of the bang-bang type with same duration of activation, and then with different efficacy levels and different durations of activity. Then using the numerical fitting results in [24], we simulate the case with drug efficacy functions based on actual pharmocokinetic models.

4.1. Drug efficacies of the bang-bang type

As in [4] and [24], we first choose $\eta_{RT}(t), \eta_P(t) : \mathbb{R} \to [0, 1)$ as following

$$\eta_{RT}(t) = \begin{cases} e_{RT} & , \text{ if } t \in [0, \frac{1}{2}], \\ 0 & , \text{ if } t \in (\frac{1}{2}, 1) \end{cases}, \quad \eta_P(t) = \begin{cases} e_P & , \text{ if } t \in [0, \frac{1}{2}], \\ 0 & , \text{ if } t \in (\frac{1}{2}, 1). \end{cases}$$

where e_{RT}, $e_P \in [0, 1]$ are fixed constants. Therefore, we have $\omega = 1$(day), and the RT-inhibitor and P-inhibitor are active with efficacy e_{RT} and e_P, respectively, for the first 12 hours of a day, and 0 for the next 12 hours.

System (2.1) contains numerous parameters that must be assigned before numerical computation. In order to compare the numerical results with the ones did in [24] which studied the interaction of HIV infection and the CD4$^+$ cells, we apply two sets of parameters here (Table 3). In parameter set I, the parameters for the CD4$^+$ cell population are the same as in [4, 24]. The parameter set II are extract from the parameter values as in [**?**, 3, 5]. Note that $f_i(T_i) = a_i - b_iT_i$, $i = 1, 2$.

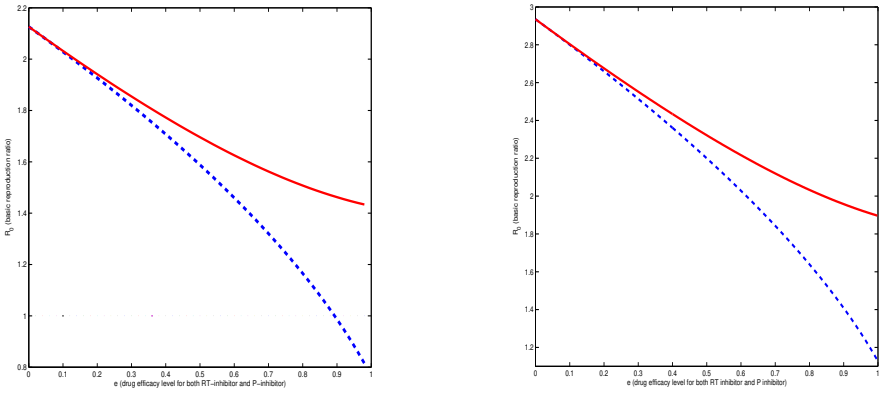
We first study the relation between $\mathcal{R}_0$ and the drug efficacy level, e_{RT}, and e_P. Figure 1 shows the plot of $\mathcal{R}_0$ as a function of e for both parameter sets, where $e = e_{RT} = e_P$: the red solid curve describes the in-phase case ($\psi = 0$), while the blue dashed curve is for the out of phase case ($\psi = 0.5$). Remember that the infection free equilibrium E_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$

Table 3. Two sets of parameter values used for simulations of system (2.1).

Parameter	Value for parameter set I	Value for parameter set II	Units
a_1	10000	10000	cells/mL·day
b_1	0.01	0.01	1/day
δ_1	1	0.7	1/day
k_1	2.4×10^{-8}	8.0×10^{-7}	mL/virious·day
a_2	31.98	31.98	cells/mL·day
b_2	0.01	0.01	1/day
σ	0.34 ($\in [0,1]$)	0.34 ($\in [0,1]$)	—
δ_2	0.7	0.7	1/day
k_2	10000	10000	mL/virious·day
N_1	3000	100	virions/cell
N_2	100	100	virions/cell
γ	23	13	1/day

and unstable if $\mathcal{R}_0 > 1$. Thus, for parameter set I, the in-phase treatment cannot clear the infection, while the out of phase treatment can clear the infection when $e > 0.89$ (approximately). Notice that, Figure 1 in [24] showed that the out of phase treatment can clear the infection when $e > 0.7$ (approximately) without considering the macrophage population. Therefore, we conclude that, it may underestimate the value of $\mathcal{R}_0$, thus, underestimate the level of infection if the macrophage population is not considered. For parameter set II, neither the in-phase and out of phase treatment can clear the infection from an individual's system. However, the out of phase treatment greatly reduces the value of $\mathcal{R}_0$, which means that it can slow down the process of infection.

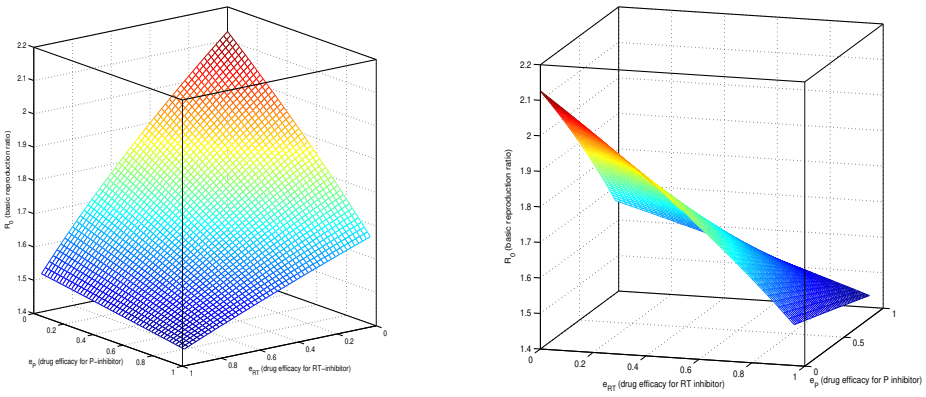
Figures 2, 3, 4, and 5 show the 3D plot of $\mathcal{R}_0$ as a function of e_{RT} and e_P for both parameter sets. Comparing the in-phase plot and the out of phase plot, we further conclude that the phase shift helps clear the infection out.



(a) **(b)**

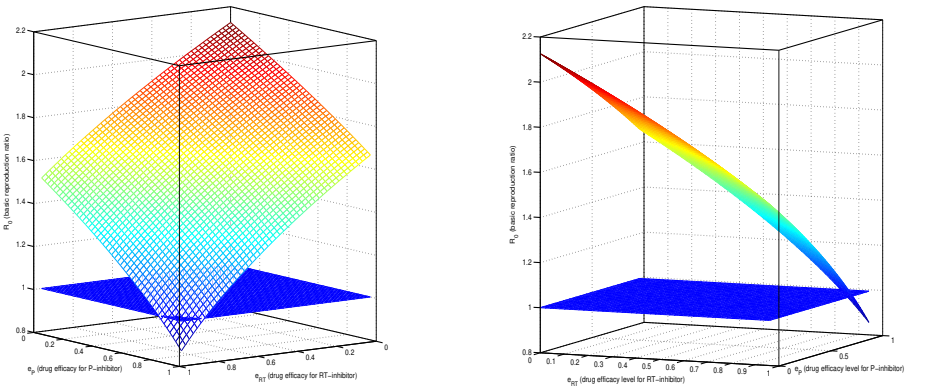
Figure 1. Basic reproduction ratio $\mathcal{R}_0$ vs. efficacy for in-phase (red solid curve) and out of phase treatments (blue dashed curve). (a) Parameter set I; (b) Parameter set II

To better understand the relation of $\mathcal{R}_0$ and ψ, we then plot $\mathcal{R}_0$ as a function of



(a) **(b)**

Figure 2. Basic reproduction ratio $\mathcal{R}_0$ vs. e_{RT} and e_P with parameter set I: in-phase treatment ($\psi = 0$): two different views

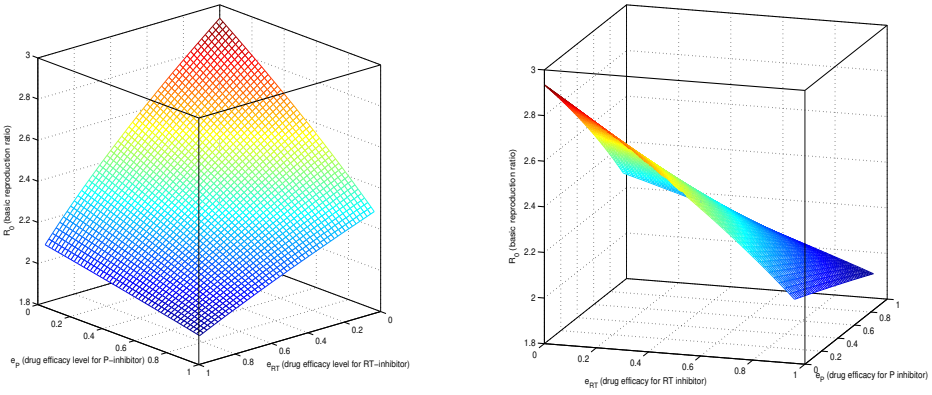


(a) **(b)**

Figure 3. Basic reproduction ratio $\mathcal{R}_0$ vs. e_{RT} and e_P with parameter set I: out of phase treatment ($\psi = 0.5$): two different views

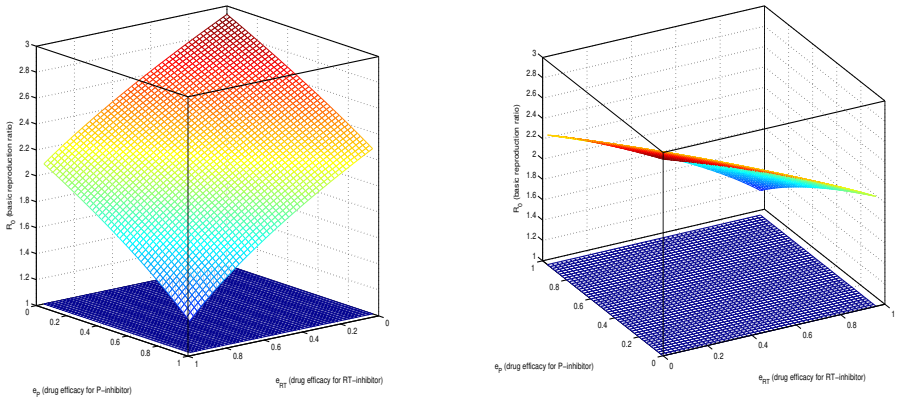
ψ with fixed e_{RT} and e_P (see Figure 6). Since $\mathcal{R}_0(\psi)$ is a ω-periodic (here $\omega = 1$) function of ψ, we only plot one period. The blue solid curve in Figure 6 depicts the case when $e_{RT} = 0.9$ and $e_P = 0.5$, while the red dot dashed curve is for the case when $e_{RT} = e_P = 0.85$. For both parameter sets, we observe that the minimum of $\mathcal{R}_0$ occurs at $\psi \approx 0.45$ which corresponds to the optimal phase shift. This optimal phase shift is exactly the same as in [24]. However, for parameter set I, the basic reproduction ratio $\mathcal{R}_0$ is less than 1 when $\psi = \psi^*$ with no consideration of the macrophage population, and greater than 1 for any ψ when the macrophage population is considered.

We further explore the case with the drug efficacy function of bang-bang type with different drug efficacy level and different duration of activation. $\eta_{RT}(t)$ and



(a) **(b)**

Figure 4. Basic reproduction ratio $\mathcal{R}_0$ vs. e_{RT} and e_P with parameter set II: in-phase treatment ($\psi = 0$): two different views



(a) **(b)**

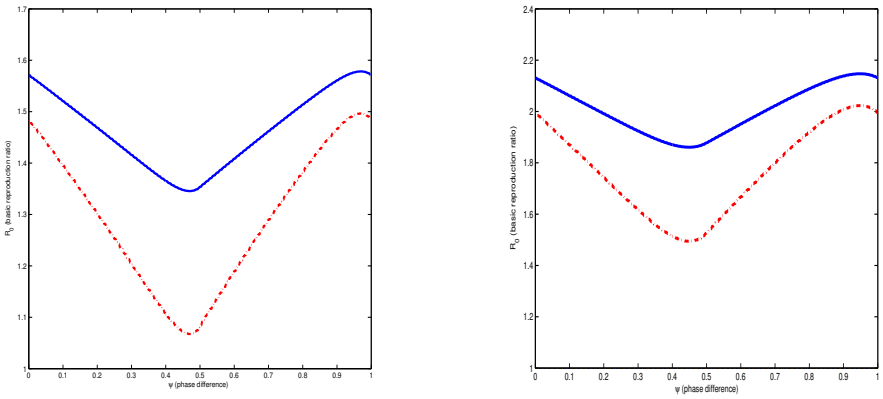
Figure 5. Basic reproduction ratio $\mathcal{R}_0$ vs. e_{RT} and e_P with parameter set II: out of phase treatment ($\psi = 0.5$): two different views

$\eta_P(t)$ then have the next form:

$$\eta_{RT}(t) = \begin{cases} e_{RT} & , \quad \text{if} \quad t \in [0, p_{RT}], \\ 0 & , \quad \text{if} \quad t \in (p_{RT}, \omega) \end{cases}, \quad \eta_P(t) = \begin{cases} e_P & , \quad \text{if} \quad t \in [0, p_P], \\ 0 & , \quad \text{if} \quad t \in (p_P, \omega). \end{cases}$$

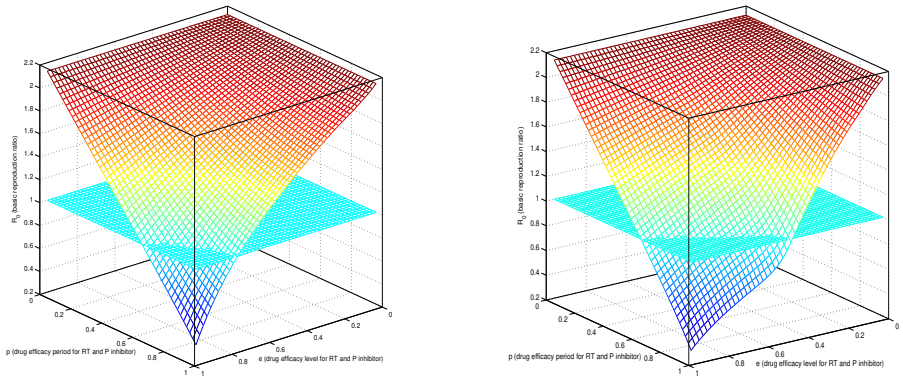
Without loss of generality, we assume that $p_{RT} < p_P$. By similar arguments as in the proof of [**?**, Theorem 3.1], we have the following result.

Theorem 4.1. *$\mathcal{R}_0$ is monotone decreasing in each of the four arguments: e_{RT}, e_P, p_{RT} and p_P.*



(a) **(b)**

Figure 6. Basic reproduction ratio $\mathcal{R}_0$ vs. phase difference ψ. (a) Parameter set I; (b) Parameter set II

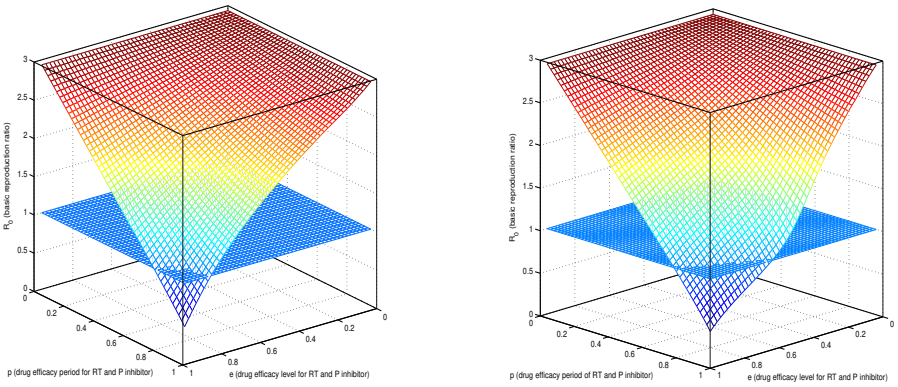


(a) **(b)**

Figure 7. Basic reproduction ratio $\mathcal{R}_0$ as a function of drug efficacy e and duration of activity p with parameter set I. The horizontal surface corresponds to $\mathcal{R}_0 = 1$. (a) In-phase case ($\psi = 0$); (b) Out of phase case ($\psi = 0.5$)

Figures 7 and 8 evaluate $\mathcal{R}_0$ as a function of e and p, where we assume that $e_{RT} = e_P = e \in [0, 1]$, and $p_{RT} = p_P = p \in [0, 1]$. Note that for both of the parameter sets, the region for e and p such that $\mathcal{R}_0 > 1$ in the out of phase case is greater than that in the in-phase case. This further supports our conclusion that the phase shift can critically affect the stability of the infection free steady state.

Note that the bang-bang type drug efficacy function may not be realistic. However, it is possible to improve the bang-bang type to a piecewise constant function (for example, see [4]). Moreover, every continuous function can be approximated by a piecewise constant function. Thus, the numerical study of bang-bang type drug efficacy function is necessary, and important.



(a) **(b)**

Figure 8. Basic reproduction ratio $\mathcal{R}_0$ as a function of drug efficacy e and duration of activity p with parameter set II. The horizontal surface corresponds to $\mathcal{R}_0 = 1$. (a) In-phase case ($\psi = 0$); (b) Out of phase case ($\psi = 0.5$)

4.2. Drug efficacy functions based on an actual pharmacokinetic model

After dosage, the drug concentration vary continuously due to drug absorption, distinction and metabolism of a single individual [18, 24]. [7] developed a two compartmental parmacokinetic model to determine the efficacy of two drugs: tenofovir DF (a RT-inhibitor) and retonovir (a P-inhibitor), and all the inside parameter values are based on clinic data and extensive experiments. [24] then simulated the two compartment model and gave an explicit expression for the drug efficacy function for $\eta_{RT}(t)$. In this section, we use their resulted $\eta_P(t)$ and $\eta_{RT}(t)$ for simulation.

First, for completeness of this paper, we only give a brief overview of the construction of $\eta_P(t)$ and $\eta_{RT}(t)$. Please refer to [7] for detailed explanation of the construction and parameter values. [7] used the simplest functionality to estimate the instantaneous drug efficacy:

$$\eta_X(t) = \frac{C_X(t)}{IC50_X + C_X(t)}, \tag{4.1}$$

where X is either RT or P, IC50 is the concentration at which the drug is 50% efficacious, and $C_X(t)$ is the intracellular concentration of the corresponding drug. When multiply doses of a drug are administrated continuously, the concentration of the drug in the blood is given by

$$\begin{aligned} C_b(t) = \frac{FDk_a}{V_d(k_e - k_a)} \frac{e^{-k_e t}}{e^{k_a I_d} - 1} [1 - e^{(k_e - k_a)t}(1 - e^{N_d k_a I_d}) \\ + \frac{(e^{k_e I_d} - e^{k_a I_d})(e^{(N_d - 1)k_e I_d} - 1)}{e^{k_e I_d} - 1} - e^{((N_d - 1)k_e + k_a)I_d}], \end{aligned} \tag{4.2}$$

For retonovir, the intracellular drug concentration $C_P(t)$ may be written as

$$C_P(t) = (1 - f_b)HC_b(t), \tag{4.3}$$

Therefore, we have

$$\eta_P(t) = \frac{C_P(t)}{9 \times 10^{-7} + C_P(t)} \tag{4.4}$$

with $\mathrm{IC50}_P = 9 \times 10^{-7}$.

The RT inhibitors are transported in and out the compartment in a much more completed way, [24] simulate the model established in [7], and explicitly express the intracellular concentration of tenofovir DF as

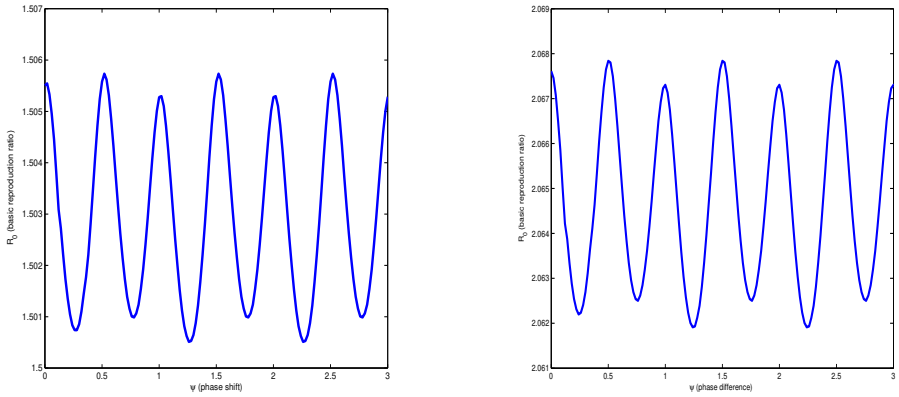
$$\begin{aligned} f(t) = {} & 17.23 + 2.251\cos(3.041s) - 30.15\sin(3.041s) - 21.58\cos(2 \times 3.041s) \\ & -3.178\sin(2 \times 3.041s) - 2.878\cos(3 \times 3.041s) + 11.92\sin(3 \times 3.041s) \\ & +4.778\cos(4 \times 3.041s) + 1.71\sin(4 \times 3.041s) + 0.6227\cos(5 \times 3.041s) \\ & -1.246\sin(5 \times 3.041s) - 0.1609\cos(6 \times 3.041s) - 0.1087\sin(6 \times 3.041s). \end{aligned}$$

where $s = \mathrm{mod}(t, 1)$. Therefore, we have

$$\eta_{RT}(t) = \frac{f(t)}{0.54 + f(t)} \tag{4.5}$$

with $\mathrm{IC50}_{RT} = 0.54$.

Figure 9 plot $\mathcal{R}_0$ as a function of the phase shift ψ with $\eta_{RT}(t)$ and $\eta_P(t)$ as in (4.5) and (4.4), respectively. From the figure, we see that $\mathcal{R}_0$ varies in a small range for all ψ ($\approx [1.500, 1.506]$ for parameter set I, and $\approx [2.062, 2.068]$ for parameter set II). Thus, the infection cannot be cleared for both parameter sets, and the phase shift does not have a significant influence on the treatment outcome. However, there exists an optimal phase shift (≈ 0.25 for both parameter sets).



(a) **(b)**

Figure 9. The basic reproduction ratio $\mathcal{R}_0$ vs. phase difference ψ. (a) Parameter set I; (b) Parameter set II

5. Conclusions and discussion

In this paper, we considered a HIV infection model with two co-circulation populations of target cells, and analyzed how periodic forcing of drug efficacies affected

the infection free equilibrium point. Mathematically, we calculated the basic reproduction ratio, $\mathcal{R}_0$, and established a threshold type result in terms of $\mathcal{R}_0$: the infection will always be cleared out if $\mathcal{R}_0 < 1$, and persist if $\mathcal{R}_0 > 1$. Therefore, by controlling the basic reproduction ratio, we can achieve the goal of control the HIV infection.

We further investigated the treatment time scale by varying the phase shift ψ in $\eta_P(\psi)$, which corresponds to change the time interval between daily dosages of the RT inhibitors and P inhibitors. Unlike other parameters, phase shift does not depend on, or affect the efficacies of the drugs. Therefore, with no consideration of the side effects of the medication, the treatment with the optimal phase shift gave the best treatment without increasing the cost. In the numerical simulation, we considered two different sets of parameter values, and two types of drug efficacy functions. Both the bang-bang type control and drug efficacy functions based on the actual pharmacokinetic models showed that the phase shift greatly reduced the value of $\mathcal{R}_0$, thus, affected critically on the clearance of the infection. Although we can not calculate optimal phase shift, the numerical simulation gave an approximation. We also observe that for a same type of drug efficacies, the optimal phase shift is almost the same for both parameter values. Therefore, we may assume that the optimal phase shift is only related to the drug efficacies, but further investigation is needed for rigorous proof.

Comparing the simulation results of parameter set I to the simulation results in [24], we found that introducing the macrophage population lead to a increasing of the value of $\mathcal{R}_0$. Macrophages played a key role in several critical aspects of HIV infection: they are the first cells infected by HIV, and perhaps the main sources of HIV production when $CD4^+$ cells become depleted [6]. Thus, not considering the macrophages resulted in underestimating the production of HIV in the system when the concentration of $CD4^+$ cells was relatively low, which agreed with the conclusion of the comparison of the numerical results.

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