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ORIGINAL ARTICLE

Resonance of Periodic Combination Antiviral Therapy and Intracellular Delays in Virus Model

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Abstract

There is a substantial interest in detailed models of viral infection and antiviral drug kinetics in order to optimize the treatment against viruses such as HIV. In this paper, we study within-viral dynamics under general intracellular distributed delays and periodic combination antiviral therapy. The basic reproduction number R_0 is established as a global threshold determining extinction versus persistence, and spectral methods are utilized for analytical and numerical computation of R_0. We derive the critical maturation delay for virus and optimal phase difference between sinusoidally varying drug efficacies under various intracellular delays. Furthermore, numerical simulations are conducted utilizing realistic pharmacokinetics and gamma-distributed viral production delays for HIV. Our results demonstrate that the relative timing of the key viral replication cycle steps and periodic antiviral treatment schedule involving distinct drugs all can interact to critically affect the overall viral dynamics.

Keywords Antiviral therapy · Intracellular delays · Virus model · Basic reproduction number · Spectral analysis

Mathematics Subject Classification 92B05 · 37N25

1 Introduction

Modeling within-host virus dynamics has been an extensive area of research in mathematical biology. For example, models of HIV dynamics under antiretroviral therapy (ART) have been utilized to gain insight on the kinetics of HIV infection and promising treatment strategies (Adams et al. 2005; Wei et al. 1995; Perelson et al. 1996; Rong

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et al. 2007). ART typically consists of a combination of antiviral medications acting at different stages of the viral replication stages. In particular, reverse-transcriptase inhibitors (RTIs) block reverse transcription (RT) after cell infection and before viral production, whereas protease inhibitors (PIs) target the cell's production of viable viral particles. Although ART has been remarkably successful in controlling HIV, ongoing viral replication can persist during therapy, and drug side effects and adherence continue to be issues. Thus, an important motivation for mathematical models is optimization of combination drug therapies acting on distinct phases of the viral replication cycle.

Viral infection is most simply captured by the standard virus model (Perelson and Nelson 1999); a nonlinear system of three ordinary differential equations (ODEs) incorporates target cells, infected cells and free virus particles as the state variables. A more detailed description involves consideration of the replication stages between virus-cell entry and new (mature) viral production by the infected cell. To account for the time lag between viral entry of a target cell and subsequent initiation of viral production from the newly infected cell, known as the *eclipse phase*, Perelson et al. included discrete and distributed delays in the standard model (Nelson and Perelson 2002). Building upon the delay model, many authors consider virus models with age structure in the infected cell compartment where the death (lysis) and viral production rate can vary with age since the infection of the cell (Browne and Pilyugin 2013; Nelson et al. 2004; Rong et al. 2007; Huang et al. 2012).

Given that cell infection and viral production are the fundamental steps in the replication cycle, perhaps the most effective way to incorporate heterogeneity in infected cell processes is to assume that both the eclipse and viral production phases are distributed delays (Shu et al. 2013). Here, we extend previous models by generalizing an age-structured system, with eclipse and virus-producing stages, to an infinite-delay system with probability distributions describing the time taken in each of these stages. In this way, recent experimental estimates of these distributions (Beauchemin et al. 2017) can be accurately quantified in the virus models. Also, the kinetics of distinct classes of drugs can be incorporated in relation to their timing with respect to the key viral replication stages, building upon previous virus models with antiviral therapy (Rong et al. 2007; Wang et al. 2016). In addition, the probability distributions of eclipse and viral production stage are convenient for threshold dynamics analysis in the case of periodic antiviral therapy.

Periodicity in antiviral efficacies occurs as a consequence of the discrete nature of drug intake for patients. The magnitude of fluctuations in antiviral drug efficacy within patients depends upon dosing regimen, adherence and pharmacodynamic properties of the medication (Shen et al. 2008; Vaidya and Rong 2017). Several works have explored the dynamics of virus models with time-varying combination antiviral therapy, treatment optimization with respect to minimizing the reproduction number R_0 and the threshold quantity determining viral extinction versus persistence (De Leenheer 2009; Vaidya and Rong 2017; Wang et al. 2014). The phase difference between distinct antiviral efficacies was found to critically affect R_0 for the standard ODE virus model with periodic drug efficacy functions as small amplitude perturbations from constant level (Browne and Pilyugin 2012), "bang–bang" (Browne and Pilyugin 2016) and more realistic pharmacokinetic functions (Wang and Zhao 2013). Furthermore, Neagu et

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al. (2018) argued that inherent delays in the viral replication cycle can substantially affect viral dynamics during periodic (single-drug) antiviral treatment. Here, we further these previous results by rigorous analysis of R_0 and resulting threshold dynamics in a general distributed delay virus model with periodic antiviral drug efficacies. In particular, utilizing the definition of R_0 in the periodic infinite-dimensional setting (Bacaër and Ouifki 2007; Bacaër and Abdurahman 2008; Bacaër and Dads 2012; Posny and Wang 2014; Zhao 2017a), we develop analytical and numerical methods to optimize periodic combination therapy for viral infections with a variety of viral intracellular delay distributions. Our results demonstrate that the relative timing of the key viral replication cycle steps, periodic antiviral treatment schedule and phase difference between distinct drugs all can interact to critically affect the overall viral dynamics.

2 The Model

We begin by considering the following extension of an age-structured virus model originally proposed by Nelson et al. (2004):

$$\begin{aligned} S'(t) &= \lambda - \delta S(t) - kS(t)V(t), \\ \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) j(t,\tau) &= -(\mu_1(\tau) + \gamma(\tau)) j(t,\tau), \quad j(t,0) = kS(t)V(t), \\ \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) i(t,a) &= -\mu_2(a) i(t,a), \quad i(t,0) = \int_0^\infty \gamma(\tau) j(t,\tau) \mathrm{d}\tau, \\ V'(t) &= \int_0^\infty q(a) i(t,a) \mathrm{d}a - \mathrm{d}V(t). \end{aligned} \tag{1}$$

Here, $S(t)$ is the population size of healthy cells, $j(t,\tau)$ is the density of infected cells in eclipse phase (before viral production begins) with respect to age since cell infection τ, $i(t,a)$ is the density of productively infected cell concentration with respect to time elapsed since initiation of viral production, a, and $V(t)$ is the viral load concentration. The healthy cells replenish with constant recruitment rate λ and per capita death rate δ. In the absence of viral infection, the healthy cells will reach at the equilibrium $\bar{S} = \lambda/\delta$. The infection of healthy cells is modeled by a mass action term kSV, where k is the infectivity rate. The death rate of infected cells in the eclipse phase is $\mu_1(\tau)$, and the rate at which infected cells transition to viral production stage is $\gamma(\tau)$, and both depend on time since cell infection τ. Additionally, $\mu_2(a)$ and $q(a)$ are the age-dependent death rate and viral production rate for productively infected cells. System (1) directly extends the ordinary differential equation virus model with infected cells to be divided into eclipse and virus-producing stages (Buonomo and Vargas-De-León 2012), by introducing continuous age structures in each class. We are interested in a detailed description of the progression of infected cells during typical replication

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cycle; thus, we do not consider the small fraction of infected cells, which are in the resting state, and form the latent reservoir (Rong and Perelson 2009).

Next, we incorporate time-varying combination antiviral treatment into (1):

$$S'(t) = \lambda - \delta S(t) - (1 - \eta_1(t))kS(t)V(t), \tag{2}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) j(t,\tau) = -(\mu_1(\tau) + \gamma(\tau))j(t,\tau), \quad j(t,0) = (1 - \eta_1(t))kS(t)V(t),$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) i(t,a) = -\mu_2(a)i(t,a), \quad i(t,0) = \int_0^\infty \gamma(\tau)j(t,\tau)\mathrm{d}\tau,$$

$$V'(t) = (1 - \eta_2(t)) \int_0^\infty q(a)i(t,a)\mathrm{d}a - \mathrm{d}V(t), \tag{3}$$

where $\eta_1(t)$ and $\eta_2(t)$ are the efficacies of reverse-transcriptase inhibitors (RTIs) and protease inhibitors (PIs), respectively. An extension of system (3) with more detailed model of the action of the RTI is discussed at the end of this section, in Remark 1.

We assume that the drug efficacies, $\eta_1(t)$ and $\eta_2(t)$, are at least piecewise continuous periodic functions with a common period T, representative of a periodic therapy, and $\eta_1(t), \eta_2(t) \in [0, 1]$ for all $t \in \mathbb{R}$. Two particular examples of periodic drug efficacies we consider in this paper for explicit analytical and numerical results are:

1. *Sinusoidal perturbations from constant efficacy* (Browne and Pilyugin 2012)

$$\eta_i(t) = e_i + \varepsilon a_i \cos \omega t, \tag{4}$$

   where e_i is the constant (mean) drug efficacy, εa_i is amplitude of small amplitude oscillation, and $\omega = 2\pi/T$ with T being the period of drug administration.
2. *Classical dose–response with impulse and exponential decays* (Shen et al. 2008)

$$\eta_i(t) = \frac{1}{1 + \left(\frac{\mathrm{IC}_{50_i}}{D_i(t)}\right)^{m_i}}, \quad D_i(t) = C_i \left(\mathrm{e}^{-r_i(t \bmod T)} + \sum_{n=1}^{\infty} \delta(t - nT)\right), \tag{5}$$

   where $D_i(t)$ is the drug concentration in the blood, IC_{50_i} is the concentration at 50% target inhibition, m_i is a slope parameter analogous to the Hill coefficient, $C_i = C_{\max_i}/(1 - \mathrm{e}^{-r_i T})$ with $C_{\max_i}$ is the maximal concentration achieved in the blood, r_i is the decay rate of drug concentration, and $\delta(t)$ is the Dirac delta function.

The first example, small amplitude sinusoidal drug efficacies, will allow for analytic approximation of R_0 and also can resemble small variations in antiviral drug efficacy under daily periodic dosing. The second example has been utilized to model pharmacodynamics of antiviral medications (Vaidya and Rong 2017).

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The equations in model (3) can be converted to a delay differential equation system. By standard application of method of characteristics, we obtain

$$j(t,\tau) = k(1-\eta_1(t-\tau))S(t-\tau)V(t-\tau)\mathrm{e}^{-\int_0^\tau(\mu_1(s)+\gamma(s))\mathrm{d}s},$$

$$i(t,a) = \int_0^\infty \gamma(\tau)\beta(t-a-\tau)S(t-a-\tau)V(t-a-\tau)\mathrm{e}^{-\int_0^\tau(\mu_1(s)+\gamma(s))\mathrm{d}s}\mathrm{d}\tau$$
$$\mathrm{e}^{-\int_0^a\mu_2(s)\mathrm{d}s},$$

where $\beta(t) = k(1-\eta_1(t))$. Define $p(t) = 1-\eta_2(t)$. Substituting this into the equation for $V'(t)$ yields

$$V'(t) = p(t)\int_0^\infty\int_0^\infty q(a)\gamma(\tau)\beta(t-a-\tau)S(t-a-\tau)V(t-a-\tau)$$
$$\mathrm{e}^{-\int_0^\tau(\mu_1(s)+\gamma(s))\mathrm{d}s}\mathrm{e}^{-\int_0^a\mu_2(s)\mathrm{d}s}\mathrm{d}\tau\mathrm{d}a - \mathrm{d}V(t). \tag{6}$$

Equations (2) and (6) together with the initial conditions for viral load $V(t)$ on $(-\infty, 0]$ can formulate a closed system with time delay. Assuming that $V(-\infty)$ is bounded, we rewrite (6) as an integral equation

$$V(t) = \int_0^\infty \mathrm{e}^{-\mathrm{d}s}p(t-s)\int_0^\infty\int_0^\infty q(a)\gamma(\tau)\beta(t-s-a-\tau)$$
$$S(t-s-a-\tau)V(t-s-a-\tau)$$
$$\mathrm{e}^{-\int_0^\tau(\mu_1(s)+\gamma(s))\mathrm{d}s}\mathrm{e}^{-\int_0^a\mu_2(s)\mathrm{d}s}\mathrm{d}\tau\mathrm{d}a\mathrm{d}s. \tag{7}$$

We now seek to extend the viral model by allowing more general distributed delays with respect to the key stages in the viral replication cycle. Several previous works (Culshaw and Ruan 2000) have assumed there is a fixed intracellular delay τ_0, so that $\gamma(\tau) = \delta(\tau-\tau_0)$ where $\delta(\tau)$ is the Dirac delta function. Others have assumed an exponentially distributed eclipse phase, in particular the extended classical virus ODE model with additional eclipse (or latent) infection compartment (Buonomo and Vargas-De-León 2012). A more general approach that has been studied is to consider a distributed delay according to a kernel, which we denote here by $\pi(\tau)$, describing the probability density function for the age τ that a (surviving) infected cell becomes productive (Shu et al. 2013). If $P(\tau)$ is the survival rate during the eclipse phase, then $\theta := \int_0^\infty P(\tau)\pi(\tau)\mathrm{d}\tau$ is the probability of an infected cell becoming productive and $f(\tau) = (P(\tau)\pi(\tau))/\theta$ is the conditional probability density for the age τ that a cell becomes productive. Note that this description of the eclipse phase generalizes the age-structured model which considers the exponential distributions $\pi(\tau) = \gamma(\tau)\mathrm{e}^{-\int_0^\tau\gamma(s)\mathrm{d}s}$ and $P(\tau) = \mathrm{e}^{-\int_0^\tau\mu_1(s)\mathrm{d}s}$. Similarly, we can generalize the

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productively infected cell kinetics by assuming an arbitrary survival probability distribution $\sigma(a)$ with $g(a) = (q(a)\sigma(a))/N$ corresponding to the conditional probability of producing infectious virus arising a units of time after the cell becomes productively infected where $N = \int_0^\infty q(a)\sigma(a)\mathrm{d}a$ is the burst size (average # of virus produced during infected cell life). For the age-structured model (3), we choose $\sigma(a) = \mathrm{e}^{-\int_0^a \mu_2(s)\mathrm{d}s}$. With these features in mind, we extend the delay differential system (2)–(6) as

$$S'(t) = \lambda - \delta S(t) - \beta(t)S(t)V(t), \tag{8}$$

$$V'(t) = \theta N p(t) \int_0^\infty \int_0^\infty g(a) f(\tau)\beta(t-a-\tau)S(t-a-\tau)V(t-a-\tau)\mathrm{d}\tau\mathrm{d}a - \mathrm{d}V(t). \tag{9}$$

The integral equation (7) can then be generalized by writing (9) as follows:

$$V(t) = \theta N \int_0^\infty \int_0^\infty \int_0^\infty \mathrm{e}^{-\mathrm{d}s} p(t-s)g(a)f(\tau)\beta(t-s-a-\tau)S(t-s-a-\tau)V(t-s-a-\tau)\mathrm{d}\tau\mathrm{d}a\mathrm{d}s. \tag{10}$$

It is obvious that any PDE in the age-structured model can be converted into the above DDE by setting

$$\theta = \int_0^\infty \gamma(\tau)\mathrm{e}^{-\int_0^\tau [\gamma(s)+\mu_1(s)]\mathrm{d}s}\mathrm{d}\tau, \quad f(\tau) = \frac{1}{\theta}\gamma(\tau)\mathrm{e}^{-\int_0^\tau [\gamma(s)+\mu_1(s)]\mathrm{d}s},$$

$$N = \int_0^\infty q(a)\mathrm{e}^{-\int_0^a \mu_2(s)\mathrm{d}s}\mathrm{d}a, \quad g(a) = \frac{1}{N}q(a)\mathrm{e}^{-\int_0^a \mu_2(s)\mathrm{d}s}.$$

However, the above relation is not necessarily invertible in the sense that any DDE (8), (9) can be converted into the PDE with age structure. Besides being more general, the DDE formulation in terms of probability distributions, $f(\tau)$ and $g(a)$, has also advantages in the spectral analysis to come in this paper. Furthermore, from a biological point of view, it is convenient to formulate the kinetics of the main phases of the infected cell cycle as distributions which can be matched to experimental data.

Another generalization of model (1) was proposed in Wang and Dong (2018). Our model differs from that in Wang and Dong (2018) in the sense that we incorporate periodic antiviral treatment and our model system is nonautonomous. In general, it is a challenge to compute the basic reproduction number and study the model dynamics for periodic systems with time delays.

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The dynamics of (8), (9) (equivalently (10)) will be analyzed in what follows; however, we also remark here that the system can be extended with respect to modeling reverse transcription (RT) in infected cells as described below.

Remark 1 A more detailed description of antiviral action with respect to infected cell life can take into account that RT inhibitors act during the eclipse phase interfering with RT transcriptase, a necessary step for viral replication. In "Appendix A", we extend the age-structured model by adding an extra compartment explicitly tracking the process of RT during the eclipse phase of infected cell. In the special case that RT occurs at a fixed time, r, after viral entry, then the delay differential equation for the virus, $V(t)$, reduces to (9) with $\beta(t)$ shifted by r units of time, i.e., $\beta(t+r)$. In particular, all of the formulae we will derive in Sect. 4.2 concerning reproduction number dependent on the periodic forcing hold in the extended model with the RT delay r shifting the effective infection rate as $\beta(t+r)$.

3 Threshold Analysis of Model

3.1 Boundedness

Throughout this paper, we assume that $g(a)$ and $f(\tau)$ are probability density functions on $\mathbb{R}_+$ with exponentially decay rate at infinity.

(H) *There exists* $\alpha_0 > 0$ *such that both* $g(t)\mathrm{e}^{\alpha_0 t} \to 0$ *and* $f(t)\mathrm{e}^{\alpha_0 t} \to 0$ *as* $t \to \infty$.

To study the model system with the infinite delay, we first introduce the weighted continuous function space. For a given $\alpha \in (0, \alpha_0)$, we define C_α to be the subspace of $C(\mathbb{R}_-, \mathbb{R})$ such that $\phi(\theta)\mathrm{e}^{\alpha\theta}$ is uniformly continuous on $\mathbb{R}_- = (-\infty, 0]$ and the norm

$$\|\phi\|_\alpha := \sup_{\theta\in\mathbb{R}_-} |\phi(\theta)\mathrm{e}^{\alpha\theta}|$$

is finite. It is easily seen that C_α is a Banach space equipped with the norm $\|\cdot\|_\alpha$, and system (8), (9) is well-posed in $C_\alpha \times C_\alpha$.

Let C_α^+ be the nonnegative cone collecting all nonnegative functions in C_α. We intend to show that if the initial profile is contained in the $C_\alpha^+ \times C_\alpha^+$, so is the solution for any $t > 0$. It can be proved by contradiction that $S(t) \geq 0$. If $t_0 \geq 0$ is the infimum of all t with $S(t) < 0$, then $S(t_0) = 0$ and $S'(t_0) \leq 0$, which obviously contradict Eq. (8). Actually, we have $S(t) > 0$ for all $t > 0$. Next, we integrate (9) to obtain

$$V(t) = \mathrm{e}^{-\mathrm{d}t}V(0) + \theta N \int_0^t \int_0^\infty \int_0^\infty \mathrm{e}^{-\mathrm{d}(t-s)} p(s)g(a)f(\tau)$$
$$\beta(s-a-\tau)S(s-a-\tau)V(s-a-\tau)\mathrm{d}\tau\mathrm{d}a\mathrm{d}s,$$

from which nonnegativity of $V(t)$ follows. If, further, $V(0) > 0$, it is easy to show that $V(t) > 0$ for all $t > 0$.

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We also want to show that the solution of the model system with nonnegative initial conditions is bounded above. From (8), we have $S'(t) \leq \lambda - \delta S(t)$. By comparison principle, we obtain $\limsup_{t\to\infty} S(t) \leq \lambda/\delta$. Furthermore, if $S(t) \leq \lambda/\delta$ for some $t = t_0$, then $S(t) \leq \lambda/\delta$ for all $t \geq t_0$. Define an auxiliary function

$$U(t) = \theta N \int_t^\infty \int_0^\infty \int_0^\infty \mathrm{e}^{-\mathrm{d}(t-s)} p(s)g(a)f(\tau)\beta(s-a-\tau) S(s-a-\tau)V(s-a-\tau)\mathrm{d}a\mathrm{d}\tau\mathrm{d}s.$$

It is readily seen that $U(t) \geq 0$ for all $t \geq 0$, and

$$U'(t) = -\theta N p(t) \int_0^\infty \int_0^\infty g(a)f(\tau)\beta(t-a-\tau) S(t-a-\tau)V(t-a-\tau)\mathrm{d}a\mathrm{d}\tau - \mathrm{d}U(t).$$

Add this equation to (8) and (9) yields

$$S'(t) + U'(t) + V'(t) = \lambda - \delta S(t) - \beta(t)S(t)V(t) - \mathrm{d}U(t) - \mathrm{d}V(t).$$

By comparison principle, we have $\limsup_{t\to\infty}[S(t) + U(t) + V(t)] \leq \lambda/\min\{\delta, d\}$.

Note that system (8), (9) is a nonautonomous with a periodic solution semiflow $U(t, s)$ on $C_\alpha \times C_\alpha$ satisfying $U(t, t) = I$, $U(t, s)U(s, r) = U(t, r)$ and $U(t + T, s + T) = U(t, s)$. To construct an equivalent autonomous semigroup, we use the idea in Saperstone (1981) (see also Rebelo et al. 2014; Zhao and Hutson 1994) to introduce the compact metric space

$$\mathbb{R}_T := \mathbb{R}/T\mathbb{Z} = \{r \in \mathbb{R} : r_1 \sim r_2 \Leftrightarrow (r_1 - r_2)/T \in \mathbb{Z}\}$$

equipped with the distance $d(r_1, r_2) = |\mathrm{e}^{2i\pi r_1/T} - \mathrm{e}^{2i\pi r_2/T}|$. Define a semigroup $\Psi(t)$ on $X = C_\alpha \times C_\alpha \times \mathbb{R}_T$ as

$$\Psi(t)(\phi, r) = (U(t + r, r)\phi, t + r), \quad \phi = (u, v) \in C_\alpha \times C_\alpha, \quad r \in \mathbb{R}_T.$$

$\Psi(t)$ is well-defined since

$$\Psi(t)(\phi, r + T) = (U(t + r + T, r + T)\phi, t + r + T) = (U(t + r, r)\phi, t + r) = \Psi(t)(\phi, r).$$

It is also easy to verify that $\Psi(0) = I$ and

$$\Psi(t)\Psi(s)(\phi, r) = (U(t + s + r, s + r)U(s + r, r)\phi, t + s + r) = (U(t + s + r, r)\phi, t + s + r) = \Psi(t + s)(\phi, r).$$

The argument in the preceding paragraph indicates that $\Psi(t)$ is point dissipative. Moreover, for any constant $C > \lambda/\min\{\delta, d\}$, the bounded region $\Gamma_C := \{(u, v, r) \in$

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$X : \|u\|_\alpha \le C,\ \|v\|_\alpha \le C\}$ is absorbing in the sense that it contains all possible attractors of $\Psi(t)$.

Finally, we show that the set of trajectories $\gamma^+(\Gamma_C) = \bigcup_{\phi\in\Gamma_C}\gamma^+(\phi)$ is also bounded. To see this, we consider the auxiliary system with (8) replaced with

$$S'(t) = \lambda - \delta S(t). \tag{11}$$

The differential equation for $V(t)$ is still (9). Any initial condition (ϕ, r) in Γ_C is bounded by (S_0, V_0, r) with $S_0(\theta) = V_0(\theta) = Ce^{-\alpha\theta}$ for $\theta \in \mathbb{R}_-$. Thus, by comparison principle, $U(t,r)\phi \le U(t,r)(S_0, V_0)$. We can use a similar argument as in the proof of point dissipativeness of $\Psi(t)$ to find a constant $\bar{C} > 0$ (which depends on C) such that $\gamma^+(\Gamma_C) \subset \Gamma_{\bar{C}}$.

3.2 Basic Reproduction Number

Following Bacaër and Ouifki (2007), Bacaër and Abdurahman (2008), Bacaër and Dads (2012), Zhao (2017a), we can define the reproduction number for the renewal type Eq. (10) as the spectral radius of the next-generation operator, $R_0 = \rho(L)$, where

$$(L\phi)(t) = \theta N\bar{S}\int_0^\infty\int_0^\infty\int_0^\infty e^{-ds}\,p(t-s)g(a)f(\tau)\beta(t-s-a-\tau)\phi(t-s-a-\tau)\mathrm{d}\tau\mathrm{d}a\mathrm{d}s, \tag{12}$$

acting on the space of continuous $T-$periodic functions on $\mathbb{R}$, denoted as $\mathbb{P}_T$. For any infinite sequence of continuous and uniformly bounded $\phi_n \in \mathbb{P}_T$, we can show that both $L\phi_n$ and $(L\phi_n)'$ are uniformly bounded (since g, f are probability distributions and $\beta(t)$, $p(t)$ are periodic functions). By the Arzela–Ascoli theorem, L is a compact operator on $\mathbb{P}_T$. Obviously, L is a positive operator on the cone of nonnegative functions in $\mathbb{P}_T$. If $p(t) > 0$ and $\beta(t) > 0$ for all $t \in \mathbb{R}$, then L is strongly positive and Krein–Rutman theorem (Du 2006, Theorem 1.2) implies that $R_0 = \rho(L)$ is an eigenvalue of the operator L with a corresponding positive eigenfunction $u(t)$; that is,

$$R_0u(t) = \theta N\bar{S}\int_0^\infty\int_0^\infty\int_0^\infty e^{-ds}\,p(t-s)g(a)f(\tau)\beta(t-s-a-\tau)u(t-s-a-\tau)\mathrm{d}\tau\mathrm{d}a\mathrm{d}s. \tag{13}$$

Observe that the definition of R_0 in (13) involves an eigenvalue equation for an infinite-dimensional operator. In Sect. 15, we investigate a formulation of R_0 amenable to analytical methods, and we will develop different numerical methods to compute R_0 in Sect. 4.3.

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3.3 Extinction and Persistence of Infection

In the following theorem, we state that the basic reproduction number is the threshold parameter for the model dynamics. First, we demonstrate that if $R_0 < 1$, then the disease-free equilibrium $E_0 = \{\bar{S}, 0\}$ with $\bar{S} = \lambda/\delta$ is globally attractive in X.

Theorem 2 *Assume* (H). *If* $R_0 < 1$, *there exists* $\alpha_1 \in (0, \alpha_0)$ *such that, for any* $\alpha \in (0, \alpha_1)$, *the disease-free equilibrium* $E_0 = \{\bar{S}, 0\}$ *is globally attractive in* $C_\alpha^+ \times C_\alpha^+$.

Proof Recall that $\mathbb{P}_T$ is the Banach space of continuous $T-$periodic functions on $\mathbb{R}$ equipped with the supremum norm. We introduce the following parametrized compact operator on $\mathbb{P}_T$:

$$(L_\mu \phi)(t) = \theta N \bar{S} \int_0^\infty \int_0^\infty \int_0^\infty \mathrm{e}^{\mu(s+a+\tau)-\mathrm{d}s} p(t-s) g(a) f(\tau) \beta(t-s-a-\tau)\phi(t-s-a-\tau)\mathrm{d}\tau \mathrm{d}a\mathrm{d}s, \tag{14}$$

for all real $\mu < \min\{d, \alpha_0\}$. Obviously, $\rho(L_0) = \rho(L) = R_0 < 1$; see (12). Moreover, $\rho(L_\mu)$ is continuous (Degla 2008, Theorem 2.1) and increasing (Burlando 1991, Theorem 1.1) in μ. Hence, there exists a small $\nu > 0$ such that $\rho(L_\nu) < 1$. Krein–Rutman theorem implies that the principal eigenfunction $\phi \in \mathbb{P}_T$ is positive. Let $\varepsilon = \bar{S}/\rho(L_\nu) - \bar{S} > 0$ and $v(t) = \mathrm{e}^{-\nu t}\phi(t)$. It follows that

$$v(t) = \theta N(\bar{S}+\varepsilon) \int_0^\infty \int_0^\infty \int_0^\infty \mathrm{e}^{-\mathrm{d}s} p(t-s) g(a) f(\tau) \beta(t-s-a-\tau) v(t-s-a-\tau)\mathrm{d}\tau \mathrm{d}a\mathrm{d}s.$$

Differentiating both sides gives a periodic renewal equation

$$v'(t) = -\mathrm{d}v(t) + \theta N(\bar{S}+\varepsilon) p(t) \int_0^\infty \int_0^\infty \beta(t-a-\tau) g(a) f(\tau) v(t-a-\tau)\mathrm{d}a\mathrm{d}\tau.$$

The above equation is also a perturbation of the linearization of (7). Now, we choose $\alpha_1 = \min\{\nu/2, \alpha_0/2\}$ and let $\{S(t), V(t)\}$ be any solution of (8), (9) with the initial condition in $C_\alpha \times C_\alpha$, where $\alpha \in (0, \alpha_1)$. Since $\limsup_{t\to\infty} S(t) \le \bar{S}$, there exists $t_0 > 0$ such that $S(t) < \bar{S} + \varepsilon$ for all $t > t_0$. In view of $2\alpha < \nu$, the functions $V(t)\mathrm{e}^{\nu t}$ and $S(t)V(t)\mathrm{e}^{\nu t}$ are uniformly bounded for all $t \in \mathbb{R}_-$. Consequently, there exists $C > 0$ such that $Cv(t) \ge V(t)$ and $(\bar{S}+\varepsilon)Cv(t) \ge S(t)V(t)$ for all $t \le t_0$. Denote

$$F(t) = \theta N(\bar{S}+\varepsilon) p(t) \iint_{\tau+a \ge t-t_0} \beta(t-a-\tau) g(a) f(\tau) C v(t-a-\tau)\mathrm{d}a\mathrm{d}\tau.$$

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It is easily seen that

$$Cv'(t) = -\mathrm{d}Cv(t) + \theta N(\bar{S}+\varepsilon)p(t)\iint_{\tau+a\le t-t_0}\beta(t-a-\tau)g(a)f(\tau)Cv(t-a-\tau)\mathrm{d}a\mathrm{d}\tau + F(t),$$

for $t \ge t_0$. On the other hand, from the choice of C we have

$$V'(t) \le -\mathrm{d}V(t) + \theta N(\bar{S}+\varepsilon)p(t)\iint_{\tau+a\le t-t_0}\beta(t-a-\tau)g(a)f(\tau)V(t-a-\tau)\mathrm{d}a\mathrm{d}\tau + F(t)$$

for all $t \ge t_0$. By comparison principle, $Cv(t) \ge V(t)$ for all $t \ge t_0$. Especially, $V(t) \to 0$ as $t \to \infty$. It then follows from (8) that $S(t) \to \bar{S}$ as $t \to \infty$. □

Remark 3 Since the delay is not finite, the Poincaré map for the linearization of (7) may not be compact on C_α. Thus, one cannot use a similar argument as in the proof of Xu and Zhao (2005), Proposition 2.1, to find an upper solution which converges to zero as t approaches infinity.

When $R_0 > 1$, we prove in "Appendix" the following theorem stating that system (8), (9) is uniformly persistent.

Theorem 4 *Assume* (H) *and* $\alpha \in (0, \alpha_0)$. *If* $R_0 > 1$, *then there exists* $\delta_0 > 0$ *such that for any initial condition* $(u_0, v_0) \in C_\alpha \times C_\alpha$ *with* $v_0(0) > 0$, *the solution* (S, V) *of* (8), (9) *satisfies* $\liminf_{t\to\infty} S(t) > \delta_0$ *and* $\liminf_{t\to\infty} V(t) > \delta_0$.

4 Computing R_0

4.1 Fourier Analysis

In a similar spirit to Bacaër (2007), we consider Fourier expansions of the $T-$periodic functions $u(t)$, $p(t)$ and $\beta(t)$:

$$u(t) = \sum_{j\in\mathbb{Z}} c_j \mathrm{e}^{ij\omega t}, \quad \frac{\beta(t)}{\langle\beta\rangle} = \sum_{j\in\mathbb{Z}} \beta_j \mathrm{e}^{ij\omega t}, \quad \frac{p(t)}{\langle p\rangle} = \sum_{j\in\mathbb{Z}} p_j \mathrm{e}^{ij\omega t}, \tag{15}$$

where $\omega = \frac{2\pi}{T}$, $\langle\beta\rangle := \frac{1}{T}\int_0^T \beta(t)\,\mathrm{d}t$ and $\langle p\rangle := \frac{1}{T}\int_0^T p(t)\,\mathrm{d}t$. The eigenfunction $u(t)$ can also be normalized so that $c_0 = \langle c\rangle = 1$. Substituting (15) into (13), the eigenvalue

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equation expands as follows:

$$\frac{R_0}{\theta N \bar{S}\langle\beta\rangle\langle p\rangle}\sum_{j\in\mathbb{Z}} c_j \mathrm{e}^{ij\omega t} = \sum_{m\in\mathbb{Z}}\sum_{l\in\mathbb{Z}}\sum_{n\in\mathbb{Z}} \beta_l p_m c_n \mathrm{e}^{i(m+l+n)\omega t}\int_0^\infty \mathrm{e}^{-\mathrm{d}s}\mathrm{e}^{-i(m+n+l)\omega s}\mathrm{d}s$$

$$\int_0^\infty g(a)\mathrm{e}^{-i(l+n)\omega a}\mathrm{d}a\int_0^\infty f(\tau)\mathrm{e}^{-i(l+n)\omega\tau}\mathrm{d}\tau.$$

$$= \sum_{j\in\mathbb{Z}}\sum_{k\in\mathbb{Z}}\sum_{n\in\mathbb{Z}} \beta_{k-n} p_{j-k} c_n \mathrm{e}^{ij\omega t}\frac{F_k}{d+ij\omega},$$

where in the last step we make changes of indices $j = l + m + n$ and $k = l + n$. and

$$F_k := \int_0^\infty g(a)\mathrm{e}^{-ik\omega a}\mathrm{d}a\int_0^\infty f(\tau)\mathrm{e}^{-ik\omega\tau}\mathrm{d}\tau. \tag{16}$$

We denote

$$\gamma = \frac{d}{\theta N \bar{S}\langle\beta\rangle\langle p\rangle}, \quad H_j = \frac{d}{d+ij\omega}. \tag{17}$$

It is readily seen that

$$\gamma R_0 c_j = H_j \sum_{k\in\mathbb{Z}}\sum_{n\in\mathbb{Z}} F_k \beta_{k-n} p_{j-k} c_n. \tag{18}$$

Note that F_k is the product of characteristic functions corresponding to probability distributions g and f evaluated at $-k\omega$ and H_j is the characteristic function of the exponential distribution evaluated at $-j\omega$. Also, recall the product of characteristic functions is equal to the characteristic function of sum of independent random variables with corresponding probability distributions. Thus, coefficients determining the effect of periodicity on reproduction number are influenced by how the periodic drug efficacies interact with the probability kernels describing delays in the replication cycle.

4.2 Perturbation Analysis

Next, we consider the particular case where the drug efficacies are sinusoidal perturbations from constant values, e_i, given by $\eta_i(t)$ in (4), along with a possible phase difference between the distinct drug administrations. Then, it suffices to let

$$\frac{\beta(t)}{\langle\beta\rangle} = 1 + 2\varepsilon\alpha_1\cos\omega t, \quad \frac{p(t)}{\langle p\rangle} = 1 + 2\varepsilon\alpha_2\cos[\omega(t-\phi)], \tag{19}$$

where $\alpha_i = -\frac{a_i}{2(1-e_i)}$, and $\phi \in [0, T)$ represents the phase difference between the distinct antiviral drug efficacies, i.e., $\phi = (\phi_2 - \phi_1) \mod T$, where ϕ_1 and ϕ_2 are

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the phases of two drug administrations. The phase difference inherently describes the timing between dosages of the two drugs in the periodic schedule. It follows that the Fourier coefficients for $\beta(t)$ and $p(t)$ are as follows:

$$\beta_0 = p_0 = 1, \quad \beta_1 = \beta_{-1} = \varepsilon\alpha_1, \quad p_1 = \varepsilon\alpha_2 e^{-i\omega\phi}, \quad p_{-1} = \varepsilon\alpha_2 e^{i\omega\phi},$$

and $\beta_j = p_j = 0$ for $|j| \geq 2$.

We assume $\varepsilon > 0$ is small and write γR_0 and c_j as power series expansions in ε:

$$\gamma R_0 = \sum_{k\geq 0} \rho_{0k}\varepsilon^k, \quad c_j = \sum_{k\geq 0} c_{jk}\varepsilon^k.$$

Since $\beta_j = p_j = 0$ for $|j| \geq 2$, we can simply write Eq. (18) as

$$\begin{aligned}\gamma R_0 c_j = H_j[&p_{-1}F_{j+1}(\beta_{-1}c_{j+2} + \beta_0 c_{j+1} + \beta_1 c_j)\\ &+ p_0 F_j(\beta_{-1}c_{j+1} + \beta_0 c_j + \beta_1 c_{j-1})\\ &+ p_1 F_{j-1}(\beta_{-1}c_j + \beta_0 c_{j-1} + \beta_1 c_{j-2})]\end{aligned} \tag{20}$$

By substituting these expansions into (20) and comparing the coefficients of ε^k (with $k = 0, 1, 2, 3$) on both sides, we obtain

$$\rho_{00}c_{j0} = H_j F_j c_{j0},$$

$$\rho_{01}c_{j0} + \rho_{00}c_{j1} = H_j[F_{j+1}\alpha_2 e^{i\omega\phi}c_{j+1,0} + F_j(\alpha_1 c_{j+1,0} + c_{j1} + \alpha_1 c_{j-1,0}) + F_{j-1}\alpha_2 e^{-i\omega\phi}c_{j-1,0}],$$

$$\rho_{02}c_{j0} + \rho_{01}c_{j1} + \rho_{00}c_{j2} = H_j[F_{j+1}\alpha_2 e^{i\omega\phi}(\alpha_1 c_{j+2,0} + c_{j+1,1} + \alpha_1 c_{j0}) + F_j(\alpha_1 c_{j+1,1} + c_{j2} + \alpha_1 c_{j-1,1}) + F_{j-1}\alpha_2 e^{-i\omega\phi}(\alpha_1 c_{j0} + c_{j-1,1} + \alpha_1 c_{j-2,0})],$$

$$\rho_{03}c_{j0} + \rho_{02}c_{j1} + \rho_{01}c_{j2} + \rho_{00}c_{j3} = H_j[F_{j+1}\alpha_2 e^{i\omega\phi}(\alpha_1 c_{j+2,1} + c_{j+1,2} + \alpha_1 c_{j1}) + F_j(\alpha_1 c_{j+1,2} + c_{j3} + \alpha_1 c_{j-1,2}) + F_{j-1}\alpha_2 e^{-i\omega\phi}(\alpha_1 c_{j1} + c_{j-1,2} + \alpha_1 c_{j-2,1})].$$

From the normalization condition $c_0 = 1$, we have $c_{00} = 1$ and $c_{0k} = 0$ for $k \geq 1$. It then follows from the first equation (with $j = 0, \pm 1, \pm 2, \ldots$) that $\rho_{00} = H_0 F_0 = 1$ and $c_{j0} = 0$ for $|j| \geq 1$. Substituting these into the second equation (with $j = 0, \pm 1$) yields $\rho_{01} = 0$ and

$$\begin{aligned}c_{11} &= H_1 F_1 c_{11} + H_1 F_1 \alpha_1 + H_1 \alpha_2 e^{-i\omega\phi},\\ c_{-1,1} &= H_{-1}\alpha_2 e^{i\omega\phi} + H_{-1}F_{-1}\alpha_1 + H_{-1}F_{-1}c_{-1,1}.\end{aligned} \tag{21}$$

It is easy to obtain from the second equation that $c_{j1} = 0$ for $|j| \geq 2$. Next, we set $j = 0$ in the third equation to find

$$\begin{aligned}\rho_{02} &= \alpha_2 F_1 e^{i\omega\phi}(c_{11} + \alpha_1) + \alpha_1 c_{11} + \alpha_1 c_{-1,1} + \alpha_2 F_{-1}e^{-i\omega\phi}(\alpha_1 + c_{-1,1})\\ &= \alpha_1\alpha_2(F_1 e^{i\omega\phi} + F_{-1}e^{-i\omega\phi}) + c_{11}(\alpha_2 F_1 e^{i\omega\phi} + \alpha_1) + c_{-1,1}(\alpha_2 F_{-1}e^{-i\omega\phi} + \alpha_1)\end{aligned}$$

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Note that H_1 and H_{-1}, and F_1 and F_{-1} defined in (17) are conjugates. Thus, on account of (21), we obtain

$$\rho_{02} = 2\alpha_1\alpha_2 f_1 + 2(\alpha_1^2 + \alpha_2^2) f_2, \tag{22}$$

where

$$f_1 = \mathrm{Re}\,\frac{F_1 e^{i\omega\phi} + H_1 e^{-i\omega\phi}}{1 - H_1 F_1} = \frac{A\cos(\omega\phi) + B\sin(\omega\phi)}{|1 - H_1 F_1|^2},$$

$$f_2 = \mathrm{Re}\,\frac{H_1 F_1}{1 - H_1 F_1} = \frac{\mathrm{Re}(H_1 F_1) - |H_1 F_1|^2}{|1 - H_1 F_1|^2}.$$

Here, we recall that $H_1 = \frac{d}{d+i\omega}$ and $F_1 = \int_0^\infty g(a)e^{-i\omega a}da \int_0^\infty f(\tau)e^{-i\omega\tau}d\tau$, and, for simplicity, we have denoted

$$A = (1 - |H_1|^2)\,\mathrm{Re}(F_1) + (1 - |F_1|^2)\,\mathrm{Re}(H_1),$$

$$B = -(1 - |H_1|^2)\,\mathrm{Im}(F_1) + (1 - |F_1|^2)\,\mathrm{Im}(H_1).$$

By choosing $j = \pm 1$ in the third equation, we further obtain $c_{12} = c_{-1,2} = 0$. Finally, it is easy to calculate from the fourth equation with $j = 0$ that $\rho_{03} = 0$.

We summarize the above calculation in the following theorem displaying the effect of sinusoidal drug efficacy perturbations on R_0, along with the optimal phase difference ϕ^* between the two drugs.

Theorem 5 *If $\beta(t)$ and $p(t)$ are small perturbations of constants as given in (19), then the basic reproduction number has the asymptotic formula*

$$R_0 = \frac{\theta N \bar{S}\langle\beta\rangle\langle p\rangle}{d}(1 + \rho_{02}\varepsilon^2 + O(\varepsilon^4)),$$

where ρ_{02} is given as in (22). Furthermore, ρ_{02} is minimized at the phase difference

$$\phi^* = \frac{T}{2} + \frac{T}{2\pi}\arctan\frac{B}{A} \mod T$$

if $A \geq 0$, and

$$\phi^* = \frac{T}{2\pi}\arctan\frac{B}{A} \mod T$$

if $A < 0$.

Note that ρ_{02} is the first coefficient in the expansion of R_0 corresponding to amplitude, ϵ, and therefore will control the effect of periodic perturbations on R_0. In particular, we are interested in the optimal phase difference ϕ^* which will minimize ρ_{02} and, in turn, minimize R_0.

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4.3 Numerical Computation

We first use finite difference method (Posny and Wang 2014) to compute R_0, which is the principal eigenvalue of the linear operator L in (12). By defining

$$K(t,s) = \theta N \bar{S} \mathrm{e}^{-\mathrm{d}s} \beta(t-s) \iint_{a+\tau \le s} \mathrm{e}^{d(a+\tau)} g(a) f(\tau) p(t-s+a+\tau) \mathrm{d}a \mathrm{d}\tau, \quad (23)$$

we can rewrite (12) as $(L\phi)(t) = \int_0^\infty K(t,s)\phi(t-s)\mathrm{d}s$. Given a large integer $M > 0$, we discretize the period $[0, T]$ as $t_0 \le t_1 \le \cdots t_M$, where $t_j = j\Delta t$ with $\Delta t = T/M$. For $j > M$ or $j < 0$, we still denote $t_j = j\Delta t$. The above linear operator can be approximated by a matrix of dimension n: $(\hat{L}\hat{\phi})_j = \sum_{k=1}^{M} \hat{L}_{jk}\hat{\phi}_k$, where $\hat{\phi}$ is the numerical approximation of $\phi(x)$ and

$$\hat{L}_{jk} = \Delta t \sum_{l=0}^{\infty} K(t_j, t_{j-k+lM}). \quad (24)$$

Here, for convenience, we set $K(t,s) = 0$ if $s < 0$. The kernel $K(t_j, t_m)$ in (23) can be approximated via a standard quadrature formula:

$$K(t_j, t_m) \approx \theta N \bar{S} \mathrm{e}^{-\mathrm{d}t_m} \beta(t_{j-m}) \Delta t^2 \sum_{k+l \le m} w_{kl}(m) \mathrm{e}^{\mathrm{d}t_{k+l}} g(t_k) f(t_l) p(t_{j-m+k+l}),$$

where the quadrature weights can be chosen as $w_{kl}(m) = 1$ and $w_{0l}(m) = w_{k0}(m) = w_{kk}(m) = 1/2$ for $0 < k, l < m$; and $w_{00}(m) = w_{m0}(m) = w_{m0}(m) = 1/6$. To save the computation cost, we use the following recurrence relation to calculate the kernel function:

$$K(t_j, t_m) = \mathrm{e}^{-d\Delta t} K(t_{j-1}, t_{m-1}) + \theta N \bar{S} \mathrm{e}^{-\mathrm{d}t_m} \beta(t_{j-m}) \iint_{t_{m-1} \le a+\tau \le t_m} \mathrm{e}^{d(a+\tau)} g(a) f(\tau) p(t_{m-1} + a + \tau) \mathrm{d}a \mathrm{d}\tau,$$

where the double integral on the right-hand side can be approximated via a standard quadrature formula. If the probability density functions g and f decay rapidly at infinity, the kernel function $K(t,s)$ in (23) also decays rapidly as $s \to \infty$, and we can truncate the series in (24) as a finite sum, say, at l_m. In our simulation, we choose $l_m = 5$ and do not observe significant differences in the results with larger l_m.

Another numerical method in the computation of R_0 is based on the Fourier transform of periodic functions and spectral decomposition of linear operator L in (12). Let $M > 0$ be a large even integer. Set $\Delta t = T/M$ and $t_j = j\Delta t$ for $j \in \mathbb{N}$. We take discrete Fourier transforms

$$u(t) \approx \sum_{j=-M/2}^{M/2-1} \tilde{u}_j \mathrm{e}^{ijwt}, \quad \beta(t) \approx \sum_{j=-M/2}^{M/2-1} \tilde{\beta}_j \mathrm{e}^{ijwt}, \quad p(t) \approx \sum_{j=-M/2}^{M/2-1} \tilde{p}_j \mathrm{e}^{ijwt},$$

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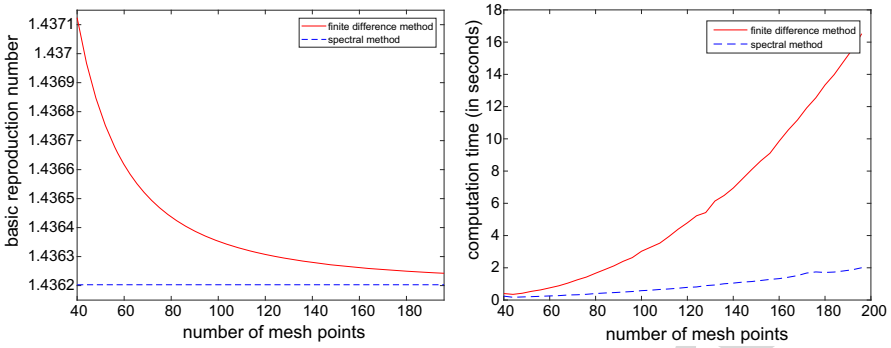

Fig. 1 Comparison of spectral method and finite difference method (Colour figure online)

where the coefficients are given by discrete inverse Fourier transform:

$$\tilde{u}_j = \frac{1}{M}\sum_{k=1}^{M} u(t_k)\mathrm{e}^{-ijwt_k}, \quad \tilde{\beta}_j = \frac{1}{M}\sum_{k=1}^{M} \beta(t_k)\mathrm{e}^{-ijwt_k}, \quad \tilde{p}_j = \frac{1}{M}\sum_{k=1}^{M} p(t_k)\mathrm{e}^{-ijwt_k}.$$

It is easily seen that $\tilde{u}_j, \tilde{\beta}_j, \tilde{p}_j$ can be extended as periodic sequence in $\mathbb{N}$ with the same period M. We use the above Fourier transforms to approximate the linear operator L in (12) as a matrix $\tilde{L}$ of dimension M:

$$\begin{aligned}(\tilde{L}\tilde{u})_j = &\sum_{\substack{m+n+l=j \\ m,n,l\in[-M/2,M/2-1]}} \theta N\bar{S}\iiint_{a,\tau,s\geq 0} \mathrm{e}^{-\mathrm{d}s+imw(t-s)+ilw(t-s-a-\tau)+inw(t-s-a-\tau)} \\ &\tilde{p}_m\tilde{\beta}_l\tilde{u}_n g(a) f(\tau)\mathrm{d}a\mathrm{d}\tau\mathrm{d}s \\ = &\frac{\theta N\bar{S}}{d+ijw}\sum_{k-n,j-k,n\in[-M/2,M/2-1]} F_k\tilde{\beta}_{k-n}\tilde{p}_{j-k}\tilde{u}_n,\end{aligned}$$

where $\tilde{u} = (\tilde{u}_{-M/2}, \ldots, \tilde{u}_{M/2-1})^T$ and F_k is given in (16).

To compare the two numerical methods, we consider a toy model:

$$\theta = 1, \quad N = 1, \quad \bar{S} = 0.1, \quad T = 2\pi, \quad d = 1, \quad g(a) = \mathrm{e}^{-a}, \quad f(\tau) = \mathrm{e}^{-\tau},$$

and $\beta(t) = (t - T/2)^2$, $p(t) = t(T - t)$ for $t \in [0, T]$. It is observed from numerical simulation (Fig. 1) that the spectral method is faster and more accurate than the finite difference method. Notice that this is only a special case with specific data. A theoretical analysis is required to justify the advantage of spectral method over finite difference method. We leave this problem for future investigation.

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4.4 Examples

In the subsection, we consider three examples: (i) bursting viral production model; (ii) budding with constant delay and viral production rate; and (iii) gamma-distributed intracellular and viral production.

Example 1 *Bursting viral production model*
Consider a simple case when the infected cells release all virus particles at a fixed age τ_0, namely $\gamma(\tau) = \delta(\tau - \tau_0)$ in the age-structured model, where $\delta(\tau)$ is the Dirac delta mass centered at $\tau = 0$. The viral production rate is also a delta function $q(a) = N\delta(a)$. It can be calculated that

$$\theta = \mathrm{e}^{-\int_0^{\tau_0} \mu_1(a)\mathrm{d}a}, \quad f(\tau) = \delta(\tau - \tau_0), \quad g(a) = \delta(a).$$

The corresponding delay differential system is

$$\begin{aligned} S'(t) &= \lambda - \delta S(t) - \beta(t)S(t)V(t), \\ V'(t) &= \theta N p(t)\beta(t - \tau_0)S(t - \tau_0)V(t - \tau_0) - \mathrm{d}V(t). \end{aligned}$$

Upon assuming $p(t)$, $\beta(t)$ are of the small amplitude sinusoidal type (19), we can utilize Theorem 5 to obtain the second-order effect on R_0 from the amplitude parameter, ε, of the periodic drug efficacies. In particular, $F_1 = \mathrm{e}^{-i\omega\tau_0}$, which implies $A = (1 - |H_1|^2)\cos(\omega\tau_0)$ and $B = (1 - |H_1|^2)\sin(\omega\tau_0)$. Note that $\arctan(B/A) = \omega\tau_0 \mod T$ if $A \geq 0$, and $\arctan(B/A) = \pi + \omega\tau_0 \mod T$ if $A < 0$. Thus, the optimal phase difference between the combination drug treatments with period T in the case of bursting virus model with intracellular delay τ_0 is $\phi^* = T/2 + \tau_0 \mod T$. The intuition for this result can be related to the previous work on the ODE virus model (Browne and Pilyugin 2016), which argues that the maximal rates of viral production and infection should be de-synchronized to antagonize the virus replication cycle.

Here we also bring to attention the recent work by Neagu et al. (2018), exploring potential viral evolution of its intracellular delay in order to "resist" antiviral treatment for a single drug with periodic efficacy. To find the critical delay from the virus perspective in the case of single-drug treatment, consider the special case $\beta(t) = 1 + 2\varepsilon\cos\omega t$ and $p(t) = 1$. Then, it follows that the first term involving ε in the expansion of $R_0(\varepsilon)$, the ε^2 coefficient ρ_{02}, can be written as:

$$\rho_{02} = \frac{2d\,[d\cos\omega\tau_0 - \omega\sin\omega\tau_0 - d]}{2d(d - d\cos\omega\tau_0 + \omega\sin\omega\tau_0) + \omega^2} = \left[-1 + \frac{\omega^2/(2d)}{d\cos\omega\tau_0 - \omega\sin\omega\tau_0 - d}\right]^{-1},$$

which achieves its maximum when $d\cos\omega\tau_0 - \omega\sin\omega\tau_0 = \sqrt{d^2 + \omega^2}$. Thus, the critical delay from the virus perspective can be calculated as $\tau_0^* = T - \arctan(\omega/d)/\omega \mod T$. At this critical value, $\rho_{02} = 2d/(\sqrt{\omega^2 + d^2} - d)$. The result concurs with simulation and informal arguments in Neagu et al. (2018) showing that the critical intracellular delay for the virus is slightly less than drug dosing period, and when

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ω/d is small, the offset is close to the (free) virus generation time $(1/d)$. Note that an objective function different from R_0 was chosen in Neagu et al. (2018) and the offset was estimated as $1/(2d)$.

Example 2 Budding with constant delay and viral production rate
Assume the infected cells mature at the age $\tau = \tau_0$ and all mature-infected cells have constant death rate and virus production rate; namely, in the age-structured model, we have $\gamma(\tau) = \delta(\tau - \tau_0)$ as before, and $\mu_2(a) = \nu$, and $q(a) = \nu N$. We then have

$$\theta = \mathrm{e}^{-\int_0^{\tau_0} \mu_1(a)\mathrm{d}a}, \quad f(\tau) = \delta(\tau - \tau_0), \quad g(a) = \nu \mathrm{e}^{-\nu a}.$$

Denote the number of productively infected cells by $I(t) = \int_0^\infty i(t, a)\,\mathrm{d}a$, we arrive at the delay differential system

$$\begin{aligned} S'(t) &= \lambda - \delta S(t) - \beta(t)S(t)V(t), \\ I'(t) &= \theta\beta(t - \tau_0)S(t - \tau_0)V(t - \tau_0) - \nu I(t), \\ V'(t) &= \nu N p(t) I(t) - dV(t). \end{aligned}$$

It is noted that the bursting case in Example 1 is the same as the limiting case of budding here in Example 2 with $\nu \to \infty$. It is easily seen that $F_1 = \nu \mathrm{e}^{-i\omega\tau_0}/(\nu + i\omega)$. Recall that $H_1 = d/(d + i\omega)$. It is easily seen that

$$\begin{aligned} A &= \frac{\omega^2}{d^2 + \omega^2} \cdot \frac{\nu[\nu\cos(\omega\tau_0) - \omega\sin(\omega\tau_0)]}{\nu^2 + \omega^2} + \frac{\omega^2}{\nu^2 + \omega^2} \cdot \frac{d^2}{d^2 + \omega^2}, \\ B &= \frac{\omega^2}{d^2 + \omega^2} \cdot \frac{\nu[\omega\cos(\omega\tau_0) + \nu\sin(\omega\tau_0)]}{\nu^2 + \omega^2} + \frac{\omega^2}{\nu^2 + \omega^2} \cdot \frac{-d\omega}{d^2 + \omega^2}. \end{aligned}$$

Consequently, the optimal phase shift of drug treatments is

$$\phi^* = \frac{T}{2} + \frac{T}{2\pi} \arctan \frac{\nu[\omega\cos(\omega\tau_0) + \nu\sin(\omega\tau_0)] - d\omega}{\nu[\nu\cos(\omega\tau_0) - \omega\sin(\omega\tau_0)] + d^2} \mod T$$

if $A \geq 0$, and

$$\phi^* = \frac{T}{2\pi} \arctan \frac{\nu[\omega\cos(\omega\tau_0) + \nu\sin(\omega\tau_0)] - d\omega}{\nu[\nu\cos(\omega\tau_0) - \omega\sin(\omega\tau_0)] + d^2} \mod T$$

if $A < 0$. Especially, when $\tau_0 = 0$ (which corresponds to the ODE virus model), the above formula reduces to $\phi^* = \frac{T}{2} + \frac{T}{2\pi} \arctan \frac{\omega(\nu - d)}{\nu^2 + d^2} \mod T$. This concurs with the result of global minimization of R_0 at $\phi^* = T/2$ obtained for bang–bang-type drug efficacies in the case of equal infected cell and viral death rates, $\nu = d$ (Browne and Pilyugin 2016).

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In order to find the critical delay from the virus perspective in the case of single-drug treatment, consider the special case $\beta(t) = 1 + 2\varepsilon \cos \omega t$ and $p(t) = 1$. We consider ρ_{02} as a function of τ_0:

$$\rho_{02} = \frac{2d\nu\left[-d\nu + (d\nu - \omega^2)\cos\omega\tau_0 - (\omega d + \omega\nu)\sin\omega\tau_0\right]}{(d\nu - \omega^2 - d\nu\cos\omega\tau_0)^2 + (\omega d + \omega\nu + d\nu\sin\omega\tau_0)^2}$$
$$= \left[-1 + \frac{\omega^2(d^2 + \omega^2 + \nu^2)/(2d\nu)}{-d\nu + (d\nu - \omega^2)\cos\omega\tau_0 - (\omega d + \omega\nu)\sin\omega\tau_0}\right]^{-1},$$

which achieves its maximum when

$$(d\nu - \omega^2)\cos\omega\tau_0 - (\omega d + \omega\nu)\sin\omega\tau_0 = \sqrt{(d\nu - \omega^2)^2 + (\omega d + \omega\nu)^2}.$$

Thus, the critical delay can be calculated as:

$$\tau_0^* = T - \frac{T}{2\pi}\arccos\frac{d\nu - \omega^2}{\sqrt{(d\nu - \omega^2)^2 + (\omega d + \omega\nu)^2}} \mod T.$$

We will use the following parameter values representative of HIV infection (Perelson and Nelson 1999) to conduct numerical simulations:

$$\lambda = 10^4, \quad \delta = 0.01, \quad \theta = 0.98, \quad k = 8 \times 10^{-7},$$
$$d = 13, \quad \tau_0 = 2, \quad T = 1, \quad N = 300. \tag{25}$$

For this example, we consider sinusoidal drug efficacies of form (4) with $\eta_1(t) = 0.945 - 2\varepsilon\cos(\omega t)$ and $\eta_2(t) = 0$, where $\varepsilon = 0.01$ and $\omega = 2\pi$. Now, we choose different values of ν and vary τ_0 to see how the time delay affects the basic reproduction number, producing the $T-$ periodic curves $R_0(\phi)$ displayed in Fig. 2. Again note that when $\nu \to \infty$, the model reduces to the one in Example 1. Observe that the amplitude of $R_0(\tau_0)$ increases and the critical delay τ_0^* shifts closer to being synchronized with the period T as $\nu \to \infty$.

Next we consider periodic combination drug therapy, setting $\eta_i(t) = 0.765 - 2\varepsilon\cos(\omega t)$ with $\varepsilon = 0.05$, and consider the effect of varying phase difference ϕ between drug efficacies, $\eta_1(t)$ and $\eta_2(t - \phi)$, on R_0. In Fig. 3a, we plot R_0 as a function of the phase shift ϕ with different values of ν for the case $\tau_0 = 1.9283$. Note that this is the critical viral delay, τ_0^*, when $\nu \to \infty$ in the case of single-drug therapy shown in Fig. 2). Notice that in the viral bursting case ($\nu \to \infty$), the phase difference ϕ substantially affects R_0. In particular, if the P-inhibitor is introduced at $\phi = 0.5$, R_0 reduces to below one, as opposed to either the single-drug (maximal R_0) or in-phase ($\phi = 0$) scenario. Thus, if the virus optimizes its R_0 under single-drug therapy as discussed in Neagu et al. (2018), it is still possible to effectively antagonize the virus with a correctly timed distinct antiviral drug. Also, observe in this case, as we decrease ν, the amplitude of $R_0(\phi)$ decreases. In Fig. 3b, we consider the case $\tau_0 = 1.6$. The curves of $R_0(\phi)$ change substantially from the prior case, showing the sensitivity of R_0 to both τ_0 and ϕ. We observe from Fig. 3 that as ν increases,

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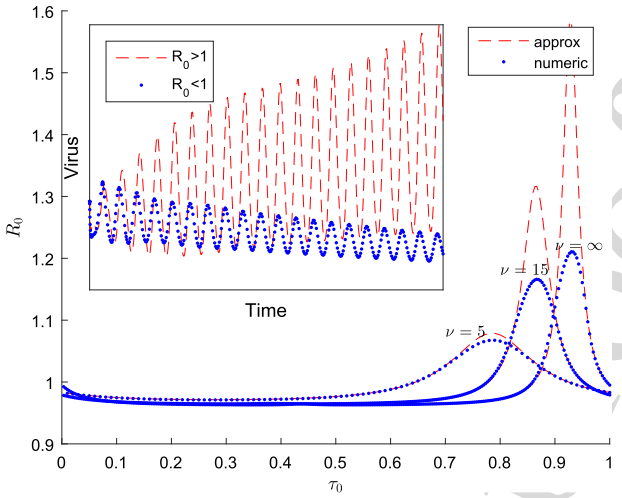

Fig. 2 The basic reproduction number R_0 as a function of the maturation delay τ_0. The numeric values are computed using both finite difference and spectral methods with sufficiently many mesh points such that the graphs obtained from both methods are almost the same. In the subfigure, we set $\nu = 15$ and choose $\tau_0 = 0.7$ (blue dotted curve) and $\tau_0 = 0.8$ (red dashed curve), respectively, to calculate the viral population along the time

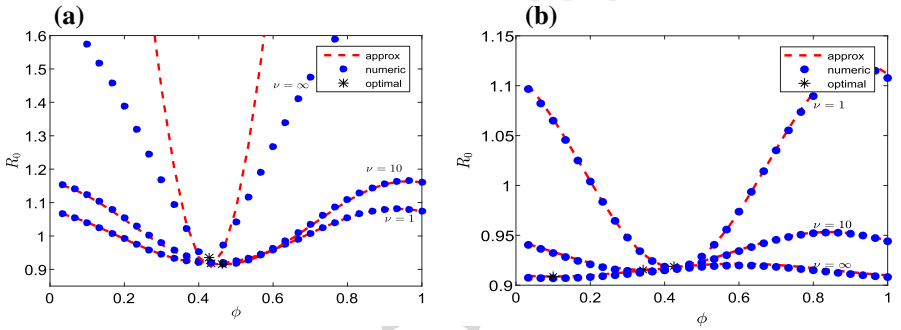

Fig. 3 The basic reproduction number R_0 as a function of the phase shift ϕ for **a** $\tau_0 = 1.9283$ and **b** $\tau_0 = 1.6$. The numeric values are computed using both finite difference and spectral methods with sufficiently many mesh points such that the graphs obtained from both methods are almost the same (Colour figure online)

both average and amplitude of R_0 decrease, and the optimal ϕ^* shifts to the left, even though the reproduction number corresponding to the case with constant drug efficacy ($\varepsilon = 0$) remains fixed.

Example 3 *Gamma-distributed intracellular and viral production*
Recent studies have shown for HIV the intracellular and viral production kernels may be gamma-distributed (Beauchemin et al. 2017). Thus, we let

$$f(\tau) = \frac{\tau^{k_1-1}\mathrm{e}^{-\tau/\theta_1}}{\Gamma(k_1)\theta_1^{k_1}}, \quad g(a) = \frac{a^{k_2-1}\mathrm{e}^{-a/\theta_2}}{\Gamma(k_2)\theta_2^{k_2}}.$$

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For illustration, we consider the simple case when $k_1 = k_2 = 1$. Define

$$I(t) = \theta\theta_2 \int_0^\infty \int_0^\infty g(a) f(\tau)\beta(t-a-\tau)S(t-a-\tau)V(t-a-\tau)\mathrm{d}\tau\mathrm{d}a$$

and $E(t) = \theta_1 \int_0^\infty f(\tau)\beta(t-\tau)S(t-\tau)V(t-\tau)\mathrm{d}\tau$. We transform the delay differential system into an ordinary differential system:

$$\begin{aligned} S'(t) &= \lambda - \delta S(t) - \beta(t)S(t)V(t), \\ E'(t) &= \beta(t)S(t)V(t) - E(t)/\theta_1, \\ I'(t) &= \theta E(t)/\theta_1 - I(t)/\theta_2, \\ V'(t) &= p(t)NI(t)/\theta_2 - \mathrm{d}V(t). \end{aligned} \tag{26}$$

This is equivalent to the age-structured PDE (3) with

$$\gamma(\tau) = \theta/\theta_1, \quad \mu_1(\tau) = (1-\theta)/\theta_1, \quad q(a) = N/\theta_2, \quad \mu_2(a) = 1/\theta_2.$$

Similarly, for any positive integers k_1 and k_2, we can use linear chain trick (Smith 2011) to obtain a system of $k_1 + k_2 + 2$ ordinary differential equations. However, we assume k_1 and k_2 are positive real numbers, and thus, the model system is in general still of infinite dimension. It can be calculated that

$$F_1 = (1 + i\theta_1\omega)^{-k_1}(1 + i\theta_2\omega)^{-k_2} = |F_1|\mathrm{e}^{-i(\omega_1 k_1 + \omega_2 k_2)},$$

where $|F_1| = [1 + (\theta_1 w)^2]^{-k_1/2}[1 + (\theta_2\omega)^2]^{-k_2/2}$, $\omega_1 = \arctan(\theta_1\omega)$ and $\omega_2 = \arctan(\theta_2\omega)$. A further computation gives

$$\begin{aligned} A &= \frac{\omega^2}{d^2+\omega^2} \cdot |F_1| \cos(\omega_1 k_1 + \omega_2 k_2) + (1 - |F_1|^2) \cdot \frac{d^2}{d^2+\omega^2}, \\ B &= \frac{\omega^2}{d^2+\omega^2} \cdot |F_1| \sin(\omega_1 k_1 + \omega_2 k_2) + (1 - |F_1|^2) \cdot \frac{-d\omega}{d^2+\omega^2}. \end{aligned}$$

Consequently, the optimal phase shift of drug treatments is

$$\phi^* = \frac{T}{2} + \frac{T}{2\pi} \arctan \frac{\omega^2|F_1| \sin(\omega_1 k_1 + \omega_2 k_2) - d\omega(1 - |F_1|^2)}{\omega^2|F_1| \cos(\omega_1 k_1 + \omega_2 k_2) + d^2(1 - |F_1|^2)} \mod T$$

if $A \geq 0$, and

$$\phi^* = \frac{T}{2\pi} \arctan \frac{\omega^2|F_1| \sin(\omega_1 k_1 + \omega_2 k_2) - d\omega(1 - |F_1|^2)}{\omega^2|F_1| \cos(\omega_1 k_1 + \omega_2 k_2) + d^2(1 - |F_1|^2)} \mod T$$

if $A < 0$.

For numerical simulations in this example, we consider more realistic drug efficacies given by the impulsive exponential decay dose–response form (5) as in Vaidya and

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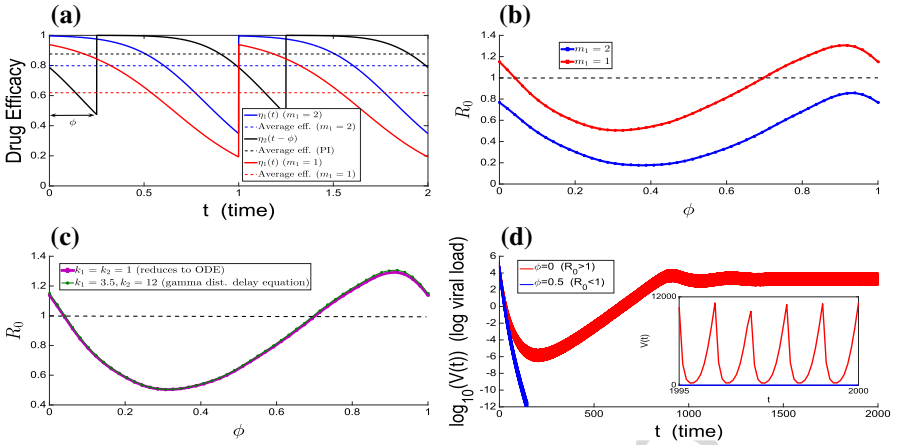

Fig. 4 **a** Impulsive exponential decay dose–response drug efficacies of RTI (blue or red) and PI (black). The pharmacodynamic parameters used in simulations from formula (5) are $m_1 = 1$ (red) or 2 (blue), $m_2 = 3$, and $r_i = 6 \ln 2$, $C_{\max_i}/IC_{50_i} = 15$ for $i = 1, 2$. **b** R_0 as a function of phase difference ϕ for the cases $m_1 = 1$ (red) or 2 (blue). The gamma distribution parameters are $k_1 = 3.5$, $k_2 = 12$ and HIV parameters are given in text. **c** R_0 as a function of phase difference ϕ when $m_1 = 1$ for gamma distribution parameters $k_1 = k_2 = 1$ and $k_1 = 3.5$, $k_2 = 12$. **d** Simulations of time-dependent solutions displaying virus level when $k_1 = k_2 = 1$ for in-phase ($\phi = 0$) and out-of-phase ($\phi = 0.5$) drug combination

Rong (2017). The pharmacodynamic parameters chosen are consistent with antiviral medications (RTIs and PIs) for HIV studied in Shen et al. (2008). For the RTI drug class, we consider two different types, NRTIs and NNRTIs, which have different slope parameters, m_1, in (5). In particular, we take $m_1 = 1$ or 2 in simulations, with the larger m_1 value increasing the drug efficacy. Figure 4a displays the periodic drug efficacies utilized for the RTI, $\eta_1(t)$ (for the 2 different m_1 values), and the PI, $\eta_2(t - \phi)$. The baseline HIV parameter values are kept as (25). Furthermore, we choose the gamma distribution parameters in line with the recent experimental estimates obtained for SIV parameters (Beauchemin et al. 2017). In particular,

$$k_1 = 3.5, \quad k_2 = 12, \quad \theta_1 = \tau_0/k_1 = 0.57, \quad \theta_2 = 1/(k_2 \nu) = 0.12.$$

In Fig. 4b, we plot the basic reproduction number as a function of the phase difference ϕ for $m_1 = 1$ and 2. Next for the case where $m_1 = 2$, in Fig. 4c, we also plot R_0 for gamma distribution parameters $k_1 = 1$, $k_2 = 1$, $\theta_1 = \tau_0/k_1 = 2$, $\theta_2 = 1/(k_2 \nu) = 1$, corresponding to the analogous ODE (26). Observe that the optimal phase shifts are almost the same and the optimal values of basic reproduction number are nearly identical. Thus, in terms of R_0, the ODE can be a good approximation of the infinite-dimensional equations corresponding to fitted parameters. The ODE case also has the advantage of relative ease in conducting numerical simulations. Thus, we display time-dependent solutions in Fig. 4d illustrating how the phase difference critically affects the outcomes of viral persistence versus extinction corresponding to whether R_0 is greater or less than unity.

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5 Discussion

In this paper, we studied within-host viral dynamics under general intracellular distributed delays and periodic combination antiretroviral therapy. Our formulation extends previous models by inclusion of eclipse and viral production stages as probability distributions, along with time-varying drug treatments. This allows us to incorporate recent experimentally derived gamma distribution parameters of HIV replication (Beauchemin et al. 2017) and pharmacodynamic models of drug therapy. Furthermore, to the best of our knowledge, we provide the first rigorous analysis establishing the basic reproduction number R_0 as a global threshold determining extinction versus persistence in an infinite-dimensional virus model with intracellular delay and periodic antiviral treatment. Although an explicit formula is not possible, we utilize Fourier analysis to provide an effective method of analytical and numerical approximation of R_0. In the proof of persistence theorem, we chose to construct an autonomous semiflow as in Saperstone (1981). It is worth mentioning that one may use another approach by considering the associated Poincaré (time-periodic) map (Zhao 2017b).

Motivated by previous results demonstrating large impacts on periodic viral dynamics induced by varying intracellular delays (Neagu et al. 2018) or phase shifts in combination drug therapy (Browne and Pilyugin 2012), we characterize how the timing of, both, viral replication cycle and combination antiviral regimen can critically affect R_0. Our analytical and numerical results show that a combination therapy can effectively neutralize a virus by optimizing phase difference ϕ between two distinct antivirals, even in the case that the virus adapts to a single drug through "synchronizing" its intracellular delay τ_0 with dosing period, as in Neagu et al. (2018). The phase difference ϕ between antiviral drug efficacies substantially affects R_0 in simulations with realistic pharmacokinetics and gamma-distributed viral production delays for HIV (Fig. 4). Thus, consideration of pharmacodynamics and dosing regimen together with viral replication kinetics may be important for the optimization of treatment.

There are several limitations to our model (9), which can be further addressed. First, as already mentioned in Remark 1, more detailed models of the viral replication cycle can allow for the precise mode of action of specific antiviral medications (e.g., RTIs). In "Appendix A", we show that assuming a fixed (discrete) intracellular delay for reverse transcription (RT) simply shifts the action of an RTI by this delay duration in our analyzed model (9); however, more general RT delay distributions will require analysis of the extended model. Additionally, although our model predicts the clearance of the virus when $R_0 < 1$, current treatment for HIV cannot eradicate the virus due to latently infected cells which are not targeted by antiviral therapy. Recent studies have modeled HIV persistence and the latent reservoir (Rong and Perelson 2009), which provides motivation for extending our model to include latency. Finally, drug resistance may be a barrier to treatment success and will be studied in future research into the optimization of antiviral therapies.

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A Extended Model with Reverse Transcription

We consider the following generalization of (3) with extra compartment explicitly tracking the process of reverse transcription (RT) during the eclipse phase of infected cell. Thus, the infected cells in the eclipse phase, $j(t,\tau)$, are separated into two classes $j_1(t,\tau_1)$ and $j_2(t,\tau_2)$ measuring infected cells τ_1 units of time after cell infection, before RT, and τ_2 units of time after RT, respectively. Then, the eclipse phase-infected cell equation in (3) is modified as follows:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial \tau_1}\right) j_1(t,\tau_1) = -(\nu_1(\tau_1)+\gamma_1(\tau_1))j(t,\tau_1), \quad j_1(t,0) = kS(t)V(t),$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial \tau}\right) j_2(t,\tau) = -(\nu_2(\tau)+\gamma_2(\tau))j_2(t,\tau),$$

$$j_2(t,0) = (1-\eta_1(t))\int_0^\infty \gamma_1(\tau_1) j_1(t,\tau_1)\mathrm{d}\tau_1,$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right) i(t,a) = -\mu(a)i(t,a), \quad i(t,0) = \int_0^\infty \gamma_2(\tau) j_2(t,\tau)\mathrm{d}\tau.$$

In the special case that $\gamma_1(\tau_1) = \delta(\tau_1 - r)$, then we have

$$j_2(t,0) = (1-\eta_1(t))\mathrm{e}^{-\int_0^r \nu_1(s)}kS(t-r)V(t-r),$$

which implies that

$$\begin{aligned} j_2(t,\tau_2) &= k(1-\eta_1(t-\tau_2))\mathrm{e}^{-\int_0^r \nu_1(s)} S(t-\tau_2-r)V(t-\tau_2-r) \\ &\quad \mathrm{e}^{-\int_0^{\tau_2}(\nu_2(s)+\gamma_2(s))\mathrm{d}s} \\ &= k(1-\eta_1(t-\tau+r))\mathrm{e}^{-\int_0^r \nu_1(s)} S(t-\tau)V(t-\tau)\mathrm{e}^{-\int_0^{\tau-r}(\nu_2(s)+\gamma_2(s))\mathrm{d}s}, \end{aligned}$$

where $\tau := \tau_2 + r$. Consequently, the differential equation for $V(t)$ becomes

$$\begin{aligned} V'(t) = p(t)\int_0^\infty\int_0^\infty & q(a)\mathrm{e}^{-\int_0^a \mu(s)\mathrm{d}s}\gamma_2(\tau)\mathrm{e}^{-\int_0^r \nu_1(s)\mathrm{d}s-\int_0^{\tau-r}(\nu_2(s)+\gamma_2(s))\mathrm{d}s}\beta(t-a-\tau+r) \\ & S(t-a-\tau)V(t-a-\tau)\mathrm{d}\tau\mathrm{d}\tau\mathrm{d}a - \mathrm{d}V, \end{aligned}$$

which is the same as Eq. (9) with the effective infection rate (affected by the RT inhibitor) shifted by r units of time, i.e., $\tilde{\beta}(t) = \beta(t+r)$. The corresponding

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relation between PDE and DDE is: $P(\tau) = \mathrm{e}^{-\int_0^r \nu_1(s)\mathrm{d}s - \int_0^{\tau-r} \nu_2(s)\mathrm{d}s}$ and $\pi(\tau) = \gamma_2(\tau)\mathrm{e}^{-\int_0^{\tau-r}\gamma_2(s)\mathrm{d}s}$, $\theta := \int_0^\infty P(\tau)\pi(\tau)\mathrm{d}\tau$, $f(\tau) = (P(\tau)\pi(\tau))/\theta$, along with $g(a) = (q(a)\sigma(a))/N$, $N = \int_0^\infty q(a)\sigma(a)\mathrm{d}a$ where $\sigma(a) = \mathrm{e}^{-\int_0^a \mu(s)\mathrm{d}s}$.

B Proof of Theorem 4

We proceed in the following steps.

1. In Sect. 3.1, we have proved that $\Psi(t)$ is point dissipative and the trajectories of any given bounded set are uniformly bounded.
2. We show that $\Psi(t)$ is asymptotically smooth.
   Fix $C > \lambda/\min\{\delta, d\}$. It follows from Burton and Hutson (1989), Lemma 3.2 that the set

$$B_C := \{u \in C_\alpha^+ : \sup_{\theta\le 0} u(\theta)\mathrm{e}^{\alpha\theta/2} \le C\}$$

   is compact in C_α^+. We need to prove that $B_C \times B_C \times \mathbb{R}_T$ attracts all bounded invariant set Γ in $X = C_\alpha^+ \times C_\alpha^+ \times \mathbb{R}_T$. Fix any (S_r, V_r, r) in Γ, we denote $(S_t, V_t, t+r) = \Psi(t)(S_r, V_r, r)$ such that $(S(t), V(t)) = (S_t(0), V_t(0))$ satisfies system (8), (9) for $t > r$ with the initial condition $(S(r+\theta), V(r+\theta)) = (S_r(\theta), V_r(\theta))$ for $\theta \le 0$. Since the limit superior of $S(t)$ is bounded above by λ/δ, we have $S(t) < C$ for all large t. Let $t_0 \ge 0$ be the largest $t \ge r$ such that $S(t) \ge C$. If $S(t) < C$ for all $t \ge r$, we set $t_0 = r$. For $t > t_0$, define

$$u_t(\theta) := \begin{cases} S_t(\theta), & t_0 - t \le \theta \le 0, \\ S(t_0)\mathrm{e}^{-\alpha(\theta - t_0 + t)/2}, & \theta \le t_0 - t. \end{cases}$$

   It is readily seen that $u_t \in B_C$. Now, we intend to show that $\|u_t - S_t\|_\alpha \to 0$ as $t \to \infty$. For $\theta \in [t_0 - t, 0]$, we have $u_t(\theta) = S_t(\theta)$. As $t \to \infty$, we have

$$u_t(\theta)\mathrm{e}^{\alpha\theta} = S(t_0)\mathrm{e}^{\alpha(\theta+t_0-t)/2} \le C\mathrm{e}^{\alpha(t_0-t)} \to 0,\ \theta \le t_0 - t;$$

$$S_t(\theta)\mathrm{e}^{\alpha\theta} \le S(t+\theta)\mathrm{e}^{\alpha(t_0-t)} \le \sup_{r\le s\le t_0} S(s)\mathrm{e}^{\alpha(t_0-t)} \to 0,\ \theta \in [r-t, t_0-t];$$

$$S_t(\theta)\mathrm{e}^{\alpha\theta} = S_r(t-r+\theta)\mathrm{e}^{\alpha(\theta+t-r)}\mathrm{e}^{-\alpha(t-r)} \le \|S_r\|_\alpha \mathrm{e}^{-\alpha(t-r)} \to 0,\ \theta \le r - t.$$

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Therefore,

$$\|u_t - S_t\|_\alpha = \sup_{\theta \le t_0 - t} |u_t(\theta) - S_t(\theta)| e^{\alpha\theta}$$
$$\le C e^{\alpha(t_0 - t)} + \max\{ \sup_{r \le s \le t_0} S(s) e^{\alpha(t_0 - t)}, \|S_r\|_\alpha e^{-\alpha(t-r)} \} \to 0,$$

as $t \to \infty$. Similarly, we define

$$v_t(\theta) := \begin{cases} V_t(\theta), & t_1 - t \le \theta \le 0, \\ V(t_1) e^{-\alpha(\theta - t_1 + t)/2}, & \theta \le t_1 - t, \end{cases}$$

where t_1 is the largest $t \ge r$ such that $V(t) \ge C$; if $V(t) < C$ for all $t \ge r$, then we set $t_1 = r$. It can be shown that $v_t \in B_C$ and $\|v_t - V_t\|_\alpha \to 0$ as $t \to \infty$. Therefore, the compact set $B_C \times B_C \times \mathbb{R}_T$ attracts all bounded invariant set $\Gamma \in X$, which proves asymptotic smoothness of system (8), (9).

3. By Hale and Waltman (1989), Theorem 2.1, $\Psi(t)$ possesses a nonempty global attractor in X. Denote $X_0 = \{(u, v, r) \in X : v(0) > 0\}$ and $\partial X_0 = X \backslash X_0 = \{(u, v, r) \in X : v(0) = 0\}$. Introduce a generalized distance function $p : X \to \mathbb{R}_+$ as $p(u, v, r) = v(0)$. It is readily seen that $p^{-1}(0) = \partial X_0$ and $p^{-1}(0, \infty) = X_0$. Furthermore, by comparison principle, $p(\Psi(t)x) > 0$ for all $x \in X_0$. Hence, the condition (P) in Smith and Zhao (2001), Section 3 is verified; see also Zhao (2017b), Definition 1.3.1.

We now prove that the basin of attraction for $E_0 \times \mathbb{R}_T$ does not intersect $p^{-1}(0, \infty) = X_0$. Assume to the contrary that there exists $(S_0, V_0, t_0) \in X_0$ such that $(S(t), V(t)) \to (\bar{S}, 0)$ as $t \to \infty$, where $(S(t), V(t)) = (S_t(0), V_t(0))$ with $(S_t, V_t) = U(t, t_0)(S_0, V_0)$. Since $V(0) > 0$, comparison principle shows that $V(t) > 0$ for all $t \ge 0$. For any $\mu, \nu > 0$, we introduce a parametrized operator on $\mathbb{P}_T$:

$$(L_{\mu,\nu}\phi)(t) = \theta N \bar{S} \int_0^\infty \int_0^\infty \int_0^\infty e^{-\mu(s+a+\tau)-(d+\nu)s} p(t-s) g(a) f(\tau) \beta(t-s-a-\tau)$$
$$\phi(t-s-a-\tau) d\tau da ds.$$

Clearly, $\rho(L_{0,0}) = R_0 > 1$. It follows from continuity (Degla 2008, Theorem 2.1) and monotonicity (Burlando 1991, Theorem 1.1) of $L_{\mu,\nu}$ on both μ and ν that $\rho(L_{\delta,\delta}) > 1$ for some small $\delta > 0$. Krein–Rutman theorem guarantees that the principal eigenfunction ϕ of $L_{\delta,\delta}$ is positive. Set $\varepsilon = \bar{S} - \bar{S}/\rho(L_{\delta,\delta}) > 0$ and $v(t) = e^{\delta t}\phi(t)$. It is easily seen that

$$v(t) = \theta N(\bar{S} - \varepsilon) \int_0^\infty \int_0^\infty \int_0^\infty e^{-(d+\delta)s} p(t-s) g(a) f(\tau) \beta(t-s-a-\tau)$$
$$v(t-s-a-\tau) d\tau da ds.$$

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Differentiating both sides gives a periodic renewal equation

$$v'(t) = -(d+\delta)v(t) + \theta N(\bar{S}-\varepsilon)p(t)\int_0^\infty \int_0^\infty \beta(t-a-\tau)g(a)f(\tau) v(t-a-\tau)\mathrm{d}a\mathrm{d}\tau.$$

Since $S(t) \to \bar{S}$ as $t \to \infty$, there exists $t_0 > 0$ such that $S(t) > \bar{S} - \varepsilon$ for all $t > t_0$. Define

$$F(t) = \theta N(\bar{S}-\varepsilon)p(t)\iint_{\tau+a\geq t-t_0} \beta(t-a-\tau)g(a)f(\tau)v(t-a-\tau)\mathrm{d}a\mathrm{d}\tau.$$

It is easy to show that $F(t) \to 0$ as $t \to \infty$. On the other hand, $v(t) = \mathrm{e}^{\delta t}\phi(t) \to \infty$ as $t \to \infty$. There exists $t_1 > t_0$, such that $F(t) < \delta v(t)$ for all $t > t_1$. Consequently, we obtain

$$v'(t) \leq -dv(t) + \theta N(\bar{S}-\varepsilon)p(t)\iint_{\tau+a\leq t-t_0} \beta(t-a-\tau)g(a)f(\tau) v(t-a-\tau)\mathrm{d}a\mathrm{d}\tau$$

for all $t \geq t_1$. On the other hand,

$$V'(t) \geq -dV(t) + \theta N(\bar{S}-\varepsilon)p(t)\iint_{\tau+a\leq t-t_0} \beta(t-a-\tau)g(a)f(\tau) V(t-a-\tau)\mathrm{d}a\mathrm{d}\tau$$

for all $t \geq t_1$. Let $C = \max_{t\in[t_0,t_1]}[v(t)/V(t)]$. It follows from comparison principle that $CV(t) \geq v(t)$ for all $t \geq t_0$. This leads to a contradiction because $v(t)$ is unbounded but $V(t)$ vanishes as $t \to \infty$.

4. We demonstrate that $E_0 \times \mathbb{R}_T$ is isolated and acyclic.
Obviously, $E_0 \times \mathbb{R}_T$ is isolated. If to the contrary $E_0 \times \mathbb{R}_T$ is cyclic, namely, there exists a homoclinic orbit $\{S(t), V(t)\}$ that connects E_0 as $t \to \pm\infty$. We claim that $V(t) = 0$ for all t. Otherwise, if $V(t_0) > 0$ for some $t_0 \in \mathbb{R}$, then by (9), $V(t) > 0$ for all $t \geq t_0$. A similar argument as in the previous step shows that $V(t)$ cannot converge to 0 at infinity. Hence, $V(t) = 0$ for all t, which reduces (8) to a single ordinary equation and contradicts to the existence of homoclinic orbit.
5. All the conditions in Smith and Zhao (2001), Theorem 4.7 (see also Zhao 2017b, Theorem 1.3.2) have been verified. Therefore, there exists $\delta_0 > 0$ such that $\liminf_{t\to\infty} p(\Psi(t)x) > \delta_0$ for any $x \in X_0$. Let (S, V) be the solution of (8), (9) with the initial condition $(u_0, v_0) \in C_\alpha \times C_\alpha$ such that $v_0(0) > 0$. Denote $S_t(\theta) = S(t+\theta)$ and $V_t(\theta) = V(t+\theta)$ for all $t \geq 0$ and $\theta \leq 0$. We then have $(u_0, v_0, 0) \in X_0$ and $(S_t, V_t, t) = \Psi(t)(u_0, v_0, 0)$. The persistent of $\Psi(t)$ with respect to the distance function p implies that $\liminf_{t\to\infty} V(t) > \delta_0$. By choosing $\delta_0 > 0$ sufficiently small (and still independent of initial condition), we also obtain from (8) that $\liminf_{t\to\infty} S(t) > \delta_0$. This completes the proof.

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