# GLOBAL DYNAMICS OF TWO EPIDEMIC MODELS

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# Global Dynamics of Two Epidemic Models

by

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## Abstract

Mathematical studies of infectious disease involve delay differential equations which are more accurate in representing models with gestation times, incubation periods, or intracellular delays, and periodic equations which account for impact of seasonal, or diurnal environments. The purpose of this thesis is to investigate the global dynamics of a time-delayed dengue transmission model and a periodic within-host virus model.

We begin with mathematical preliminaries for this thesis. We provide some mathematical definitions and theorems related to the theory of cooperative delay differential equation, uniform persistence and coexistence states, chain transitive sets, and basic reproduction numbers.

In Chapter 2, we present a time-delayed dengue transmission model with age structure for the vector population. We first introduce the basic reproduction number, and show that the disease persists when $\mathcal{R}_0 > 1$. It is also shown that the disease will die out if $\mathcal{R}_0 < 1$, provided that the invasion intensity is not strong. We further establish a set of sufficient conditions for the existence and global attractivity of the endemic equilibrium by the method of fluctuations. Numerical simulations are performed to illustrate our analytic results.

Chapter 3 is devoted to the investigation of the effects of periodic drug treatment on standard within-host virus model. We first introduce the basic reproduction ratio for the model, then show that the infection free equilibrium is globally asymptotically stable and the disease eventually disappears if $\mathcal{R}_0 < 1$, while there exists at least one positive periodic state and the disease persists when $\mathcal{R}_0 > 1$. We also consider

optimization problems by shifting the phase of these drug efficacy functions. It turns out that shifting the phase can certainly affect the stability of the infection free steady state. A numerical study is performed to illustrate our analytic results.

At last, we summarize the results in this thesis, and also point out some problems for future investigation in Chapter 6.

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# Chapter 1

# Preliminaries

In this chapter, we present some definitions and known theorems which will be used in the rest of this thesis. They are involved in cooperative delay differential equations, uniform persistence and coexistence states, chain transitive sets and basic reproduction number.

## 1.1 Cooperative delay differential equations

Let $Y$ be a Banach space with an order cone $Y_+$ with nonempty interior $\mathrm{Int}Y_+$. For $x, y \in Y$, we write $x \leq y$ if $y - x \in Y_+$, $x < y$ if $y - x \in \mathrm{Int}Y_+ \setminus \{0\}$, and $x \ll y$ if $y - x \in \mathrm{Int}Y_+$.

For delay differential equation, let $r$ denotes the maximum delay appearing in the equation, then the space $C := C([-r, 0], \mathbb{R}^n)$ is a natural choice of state space. Define $C_+ := \{\phi \in C : \phi(\theta) \geq 0, -r \leq \theta \leq 0\}$. The notation $<$, $\leq$, $\ll$ will be used for the order relations on $C$ generated by $C_+$. In particular, $\phi \leq \psi$ in $C$ if and only if $\phi(s) \leq \psi(s)$ holds in $\mathbb{R}^n$ for every $s \in [-r, 0]$.

Consider system

$$\frac{dx(t)}{dt} = f(t, x_t), \tag{1.1}$$

where $f : \mathbb{R} \times D \to \mathbb{R}^n$ is continuous and $D \subset C$ is open. It is also assumed that $f$ is Lipschitz in its second argument on each compact subset of $\mathbb{R} \times D$ so that initial value problem associated with (1.1) has unique solutions.

**Theorem 1.1.1.** ([29, THEOREM 5.2.1]) *Assume that if $\phi \in D$ satisfies $\phi \geq 0$, $\phi_i(0) = 0$ for some $i$ and $t \in \mathbb{R}$, then $f_i(t, \phi) \geq 0$. If $\phi \in D$ satisfies $\phi \geq 0$ and $t_0 \in \mathbb{R}$, then $x(t, t_0, \phi) \geq 0$ for all $t \geq t_0$ in its maximal interval of existence.*

**Definition 1.1.1.** *$f$ is said to be quasimonotone if for any $\phi \leq \psi$ with $\phi_i(0) = \psi_i(0)$ for some $i$, we have $f_i(\phi) \leq f_i(\psi)$.*

**Theorem 1.1.2.** ([29, THEOREM 5.1.1]) *Let $f, g : \Omega \to \mathbb{R}^n$ be continuous, Lipschitz on each compact subset of $\Omega$, and assume that either $f$ or $g$ satisfies the quasimonotone condition. Assume also that $f(t, \phi) \leq g(t, \phi)$ for all $(t, \phi) \in \Omega$. If $(t_0, \phi)$, $(t_0, \psi) \in \Omega$ satisfy $\phi \leq \psi$, then*

$$x(t, t_0, \phi, f) \leq x(t, t_0, \psi, g)$$

*holds for all $t \geq t_0$ for which both are defined.*

Next we consider the general nonautonomous linear system

$$\frac{dx(t)}{dt} = L(t)x_t,$$

where $L : \mathbb{R} \to L(C, \mathbb{R}^n)$ is continuous and $L(C, \mathbb{R}^n)$ is the space of bounded linear maps from $C$ to $\mathbb{R}^n$. Let $L_i(t)\phi$ denote the $i$-th component of $L(t)\phi$. Then $L(t)$ satisfies the quasimonotone condition if and only if the following condition holds:

(K) If $\phi \geq 0$ and $\phi_i(0) = 0$, then $L_i(t)\phi \geq 0$.

**Theorem 1.1.3.** ([29, LEMMA 5.1.2]) *(K) holds if and only if there exists $a_i(t) \in \mathbb{R}$ for $1 \leq i \leq n$ and positive Borel measures $\eta_{ij}(t)$ for $1 \leq i, j \leq n$ such that*

$$L_i(t)\phi = a_i(t)\phi_i(0) + \sum_{j=1}^{n} \int_{-r_j}^{0} \phi_j(\theta) d_\theta \eta_{ij}(t, \theta) \tag{1.2}$$

*and $\eta_{ii}(t)\{0\} = 0$. Moreover, if (K) holds, then the representation (1.2) is unique and $a_i(t)$ and $\eta_{ij}(t)$ are continuous functions of $t$.*

**Definition 1.1.2.** *Matrix $A = (a_{ij})_{n\times n}$ is said to be irreducible if for every nonempty proper subset $I$ of the set $N = \{1, 2, \ldots, n\}$, there is an $i \in I$ and $j \in J = N \setminus I$ such that $a_{ij} \neq 0$.*

We then introduce the following condition:

(I) The matrix $A(L)(t)$ defined by

$$A(L)(t) = col(L(t)\hat{e}_1, L(t)\hat{e}_2, \ldots, L(t)\hat{e}_n)$$

is irreducible, where $\hat{e}_i \in C$ is the element with $i$-th component 1 and the other component 0 for all $\theta \in [-r, 0)$.

**Definition 1.1.3.** *System (1.1) is said to be cooperative if $D$ is order convex and $df(\phi)$ satisfies the condition (K) for each $\phi \in D$.*

If system (1.1) is cooperative, then the derivative $df(\phi)$ can be represented as in (1.2) where $a_i = a_i(\phi)$ and $\eta_{ij} = \eta_{ij}(\phi)$ are continuous functions of $\phi \in D$.

**Definition 1.1.4.** *System (1.1) is said to be cooperative and irreducible if it is cooperative and the following conditions hold:*

*(1) For any $\phi \in D$, $df(\phi)$ satisfies (I);*

*(2) For every $j$ for which $r_j > 0$, there exists $i$ such that for all $\phi \in D$,*

$$\eta_{ij}(\phi)([-r_j, -r_j + \varepsilon)) > 0$$

*for all small $\varepsilon > 0$.*

To present some results about the stability of an equilibrium of system (1.1), we assume $f$ is continuously differentiable and cooperative in a domain $D$. Suppose $\bar{v}$ is an equilibrium of (1.1), that is $\bar{v} \in \mathbb{R}^n$ is such that $f(\bar{v}) = 0$. Then the linear variational system corresponding to $\bar{v}$ is

$$y'(t) = Ly_t, \qquad L = df(\bar{v}). \tag{1.3}$$

**Definition 1.1.5.** *The stability modulus of $L$ is defined as*

$$s(L) = \max\{\Re\lambda : Det\Delta(\lambda) = 0\}$$

*where $\Re\lambda$ denotes the real part of $\lambda$.*

Suppose system (1.1) is cooperative and irreducible. Then we can define a cooperative and irreducible system of ordinary differential equations by ignoring any delays which appear in (1.1). This leads to the following system

$$x' = F(x), \qquad F(x) = f(\hat{x}). \tag{1.4}$$

where $\hat{}$ denote the inclusion $\mathbb{R}^n \to C$ by $x \to \hat{x}$, $\hat{x}_i(\theta) \equiv x_i$, for all $\theta \in [-r, 0)$, $i = 1, \ldots, n$. Observe that (1.4) has the same equilibria as (1.1).

**Theorem 1.1.4.** ([29, Corallary 5.5.2]) *$s(L) < 0$ ($s(L) > 0$) if and only if $s(DF(v)) < 0$ ($s(DF(v)) > 0$).*

Next we introduce some notations about matrices. For matrices $A$ and $B$, $0 \leq A$, $0 < A$ means that $A$ is entry-wise nonnegative, positive, respectively. $A \leq B$ means that $0 \leq B - A$. $A$ is quasi-positive means all of its off-diagonal entries are nonnegative. The exponential of a square matrix $A$ is expressed as $\exp[A]$. Let $\rho(A)$ be the spectral radius of the matrix $A$. The following standard results (see, e.g., [9]) will be used later.

**Theorem 1.1.5.** *The following statements are valid:*

*(1) If $A$ is quasi-positive and $A \leq B$ but $A \neq B$, then $0 \leq \exp[tA] \leq \exp[tB]$ but $\exp[tA] \neq \exp[tB]$, $\forall t > 0$.*

*(2) if $A > 0$ and $B \geq 0$ has no zero row or zero column, then $AB > 0$ and $BA > 0$.*

*(3) if $0 < A \leq B$ but $A \neq B$, then $\rho(A) < \rho(B)$.*

## 1.2 Uniform persistence and coexistence states

Suppose $X$ is a metric space with metric $d$. Let $f : X \to X$ be a continuous map and $X_0 \subset X$ an open set. Define $\partial X_0 := X \setminus X_0$, and $M_\partial := \{x \in \partial X_0, f^n(x) \in \partial X_0, \ \forall n \geq 0\}$.

**Definition 1.2.1.** *A bounded set $A$ is said to attract a bounded set $B$ in $X$ if*

$$\lim_{n\to\infty} \sup_{x\in B}\{d(f^n(x), A)\} = 0.$$

*A subset $A \subset X$ is said to be an attractor if $A$ is nonempty compact and invariant ($f(A) = A$), and $A$ attracts some open neighborhood of itself. A global attractor for $f : X \to X$ is an attractor that attracts every point in $X$. For a nonempty invariant*

*set $M$, the set $W^s(M) = \{x \in X : \lim_{n\to\infty} d(f^n(x), M) = 0\}$ is called the stable set of $M$.*

**Definition 1.2.2.** *A continuous map $f : X \to X$ is said to be point dissipative if there is a bounded set $B_0$ in $X$ such that $B_0$ attracts each point in $X$.*

**Theorem 1.2.1.** ([42, THEOREM 1.3.1]) *If $f : X \to X$ is compact and point dissipative, then there is a connected global attractor $A$ that attracts each bounded set in $X$.*

**Theorem 1.2.2.** ([42, THEOREM 1.3.1 AND REMARK 1.3.1]) *Assume that*

*(C1) $f(X_0) \subset X_0$ and $f$ has a global attractor $A$;*

*(C2) There exists a finite sequence $\mathcal{M} = \{M_1, \ldots, M_k\}$ of disjoint, compact, and isolated invariant sets in $\partial X_0$ such that*

*(a) $\Omega(M_\partial) := \cup_{x\in M_\partial} \omega(x) \subset \cup_{i=1}^k M_i$;*

*(b) No subset of $\mathcal{M}$ forms a cycle in $\partial X_0$;*

*(c) $M_i$ is isolated in $X$;*

*(d) $W^s(M_i) \cap X_0 = \emptyset$ for each $1 \le i \le k$.*

*Then $f$ is uniformly persistent with respect to $(X_0, \partial X_0)$ in the sense that there exists an $\eta > 0$ such that $\liminf_{n\to\infty} d(f^n(x), \partial X_0) \ge \eta$ for all $x \in X_0$.*

Recall that a family of mappings $\Phi(t), t \ge 0$ on $X$ is called a continuous-time semiflow provided that $\Phi(0) = I$, $\Phi(t)x$ is continuous jointly in $(t, x)$, and $\Phi(t)\circ\Phi(s) = \Phi(t + s)$ for all $t, s \ge 0$.

**Definition 1.2.3.** *A continuous function $p : X \to [0, \infty)$ is called a generalized distance function for $\Phi(t)$ if it has the property that $p(\Phi(t)x) > 0$ for $t > 0$ if either $p(x) = 0$ and $x \in X_0$ or if $p(x) > 0$.*

**Theorem 1.2.3.** ([31, THEOREM 3]) *Let $p$ be a generalized distance function for the given semiflow $\Phi(t)$. Assume that*

*(P1)* *$\Phi(t)$ has a global attractor;*

*(P2)* *There exists a finite sequence $M = \{M_1, M_2, \ldots, M_k\}$ of pairwise disjoint, compact and isolated invariant sets in $\partial X_0$ with the following properties*

*a)* *$\cup_{x \in M_0} \omega(x) \subset \cup_{i=1}^{k} M_i$;*

*b)* *No subset of $M$ forms a cycle in $\partial X_0$;*

*c)* *$M_i$ is isolated in $X$;*

*d)* *$W^s(M_i) \cap p^{-1}(0, \infty) = \emptyset$ for all $1 \leq i \leq k$, where $W^s(M_i)$ is the stable set of $M_i$.*

*Then there exists $\eta > 0$ such that $\liminf_{t \to \infty} p(\Phi(t)x) \geq \eta$ for all $x \in X_0$.*

Assume $X$ is a closed subset of Banach space $E$, and that $X_0$ is a convex and relatively open subset in $X$. Then $\partial X_0$ is relatively closed in $X$. We have the following result.

**Theorem 1.2.4.** ([42, THEOREM 1.3.6]) *Let $S : X \to X$ be a continuous map with $S(X_0) \subset X_0$. Assume that*

*(1)* *$S : X \to X$ is point dissipative;*

*(2) $S$ is compact;*

*(3) $S$ is uniformly persistent with respect to $(X_0, \partial X_0)$;*

*Then there exists a global attractor $A_0$ for $S$ in $X_0$ that attracts strongly bounded sets in $X_0$ and $S$ has a coexistence state $x_0 \in A_0$.*

Let $\omega > 0$. A family of mappings $\Phi(t) : X \to X$, $t \geq 0$, is called an $\omega$-periodic semiflow on $X$ if it has the following properties:

(1) $\Phi(0) = I$, where $I$ is the identity map on $X$;

(2) $\Phi(t + \omega) = \Phi(t) \circ \Phi(\omega)$, $\forall t \geq 0$;

(3) $\Phi(t)x$ is continuous in $(t, x) \in [0, \infty) \times X$.

The mapping $\Phi(\omega)$ is called the Poincaré map (period map) associated with this periodic semiflow.

**Theorem 1.2.5.** ([42, THEOREM 3.1.1]) *Let $\Phi(t)$ be a $\omega$-periodic semiflow on $X$ with $\Phi(t)X_0 \subset X_0$, $\forall t \geq 0$. Assume that $S = \Phi(\omega)$ satisfies the following conditions:*

*1) $S$ is point dissipative in $X$;*

*2) $S$ is compact;*

*Then uniform persistence of $S$ with respect to $(X_0, \partial X_0)$ implies that of $\Phi(t) : X \to X$.*

## 1.3 Chain transitive sets

Let $\Phi(t), t \geq 0$, be a continuous-time semiflow on a metric space $X$ with metric $d$. We say $e \in X$ is an equilibrium of $\Phi(t)$ if $\Phi(t)e = e$ for all $t \geq 0$.

**Definition 1.3.1.** *Let $A \subset X$ be a nonempty, invariant set for $\Phi(t)$. We say $A$ is internally chain transitive if for any $a$, $b \in A$ and any $\varepsilon > 0$, $t_0 > 0$, there is a finite sequence $\{x_1 = a, x_2, \ldots, x_{m-1}, x_m = b; t_1, \ldots, t_{m-1}\}$ with $x_i \in A$ and $t_i \geq t_0$, $1 \leq i \leq m-1$, such that $d(\Phi(t_i)x_i, x_{i+1}) < \varepsilon$ for all $1 \leq i \leq m-1$.*

**Theorem 1.3.1.** ([42, LEMMA 1.2.1′]) *Let $\Phi(t) : X \to X$, $t \geq 0$, be a continuous time semiflow. Then the omega (alpha) limit set of any precompact positive (negative) orbit is internally chain transitive.*

**Theorem 1.3.2.** ([42, THEOREM 1.2.2 AND REMARK 1.3.2]) *Assume that each equilibrium of $\Phi(t)$ is an isolated invariant set, that there is no cyclic chain of equilibria, and that every precompact orbit converges to some equilibrium of $\Phi(t)$. Then any internally chain transitive set is an equilibrium of $\Phi(t)$.*

## 1.4 Basic reproduction number

Basic reproduction number of an infectious disease is a fundamental and important concept in the study of disease control. It is defined as the expected number of secondary infections arising from a single individual during his or her entire infectious period, in a population of susceptible. Usually, the basic reproduction number serves as a threshold parameter in the sense that the disease dies out if the basic reproduction number is less than unity, and the disease persists in the population if it is greater than unity. Thus, in order to control the disease, we need to reduce $\mathcal{R}_0$ to be less than 1. The explicit formula of $\mathcal{R}_0$ was given in [34] for a large class of autonomous compartmental epidemic models. In this section, we present the theory of basic

reproduction ratios for compartmental epidemic models in periodic environments, which was developed in [36].

We consider a heterogeneous population whose individuals can be grouped into $n$ homogeneous compartments. Let $x = (x_1, \ldots, x_n)^T$, with each $x_i \geq 0$, be the state of individuals in each compartment. Assume that the compartments can be divided into two types: infected compartments, labeled by $i = 1, \ldots, m$, and uninfected compartments, labeled by $i = m+1, \ldots, n$. Denote $X_s$ to be the set of all disease-free states:

$$X_s := \{x \geq 0 : x_i = 0,\ \forall i = 1, \ldots, m\}.$$

Let $\mathcal{F}_i(t, x)$ be the input rate of newly infected individuals in the $i$th compartment, $\mathcal{V}_i^+(t, x)$ be the input rate of individuals by other means (for example, births, immigrations), and $\mathcal{V}_i^-(t, x)$ by the rate of transfer of individuals out of compartment $i$ (for example, deaths, recovory and emigrations). Thus, the disease transmission model is governed by an autonomous ordinary differential system:

$$\frac{dx_i}{dt} = \mathcal{F}_i(t, x) - \mathcal{V}_i(t, x) := f_i(t, x),\ i = 1, \ldots, n. \tag{1.5}$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. We assume that the model (1.5) admits a disease-free periodic solution $x^0(t) = (0, \ldots, 0, x_{m+1}^0(t), \ldots, x_n^0(t))^T$ with $x_i^0(t) \geq 0$, $m+1 \leq i \leq n$ for all $t$. Let $f = (f_1, \ldots, f_n)^T$, and define

$$F(t) := \left(\frac{\partial \mathcal{F}_i(t, x^0(t))}{\partial x_j}\right)_{1 \leq i,j \leq m},\ V(t) := \left(\frac{\partial \mathcal{V}_i(t, x^0(t))}{\partial x_j}\right)_{1 \leq i,j \leq m},$$
$$M(t) := \left(\frac{\partial \{_i(t, x^0(t))}{\partial x_j}\right)_{m+1 \leq i,j \leq n}.$$

It then follows that

$$D_x\mathcal{F}(t,x^0(t))=\begin{pmatrix}F(t) & 0\\ 0 & 0\end{pmatrix},\ D_x\mathcal{V}(t,x^0(t))=\begin{pmatrix}V(t) & 0\\ J(t) & -M(t)\end{pmatrix}$$

where $J(t)$ is an $(n-m)\times n$ matrix. Denote $\Phi_A(t)$ be the monodromy matrix of the linear $\omega$-periodic system $\frac{dz}{dt}=A(t)z$. We make the following assumptions:

(A1) For each $1\le i\le n$, the function $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$, and $\mathcal{V}_i^-(t,x)$ are nonnegative and continuous on $\mathbb{R}\times\mathbb{R}^n_+$ and continuously differential with respect to $x$.

(A2) There is a real number $\omega>0$ such that for each $1\le i\le n$, the function $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$, and $\mathcal{V}_i^-(t,x)$ are $\omega$-periodic in $t$.

(A3) If $x_i=0$, then $\mathcal{V}_i^-=0$. In particular, if $x\in X_s$, then $\mathcal{V}_i^-=0$ for $i=1,\dots,m$.

(A4) $\mathcal{F}_i=0$ if $i>m$.

(A5) If $x\in X_s$, then $\mathcal{F}_i(x)=\mathcal{V}_i^+(x)=0$ for $i=1,\dots,m$.

(A6) $\rho(\Phi_M(\omega))<1$, where $\rho(\Phi_M(\omega))$ is the spectral radius of $\Phi_M(\omega)$.

(A7) $\rho(\Phi_{-V}(\omega))<1$.

Let $Y(t,s)$, $t>s$, be the evolution operator of the linear $\omega$-periodic system

$$\frac{dy}{dt}=-V(t)y.$$

That is, for each $s\in\mathbb{R}$, the $m\times m$ matrix $Y(t,s)$ satisfies

$$\frac{d}{dt}Y(t,s)=-V(t)Y(t,s),\ \forall t\le s,\ Y(s,s)=I,$$

where $I$ is the $m\times m$ identity matrix. Set $C_\omega$ be the ordered Banach space of all $\omega$-periodic functions from $\mathbb{R}$ to $\mathbb{R}^m$ equipped with the maximum norm and the positive

cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0,\ \forall t \geq 0\}$. Then we can define a linear operator $L : C_\omega \to C_\omega$ by

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

We call $L$ the next infection operator, and define the spectral radius of $L$ as the basic reproduction ratio

$$\mathcal{R}_0 := \rho(L)$$

for the periodic epidemic model (1.5).

Let $W(t, s, \lambda)$, $t \geq s$, $s \in \mathbb{R}$, be the evolution operator of the following linear system

$$\frac{dw}{dt} = \big(-V(t) + \frac{1}{\lambda}F(t)\big)w,\ t \in \mathbb{R}. \tag{1.6}$$

The following theorem is useful to numerically compute the basic reproduction ratio $\mathcal{R}_0$.

**Theorem 1.4.1.** ([36, THEOREM 2.1]) *Let (A1)-(A7) hold. Then the following statements are valid:*

*(1) If $W(\omega, 0, \lambda)$ has a positive solution $\lambda_0$, then $\lambda_0$ is an eigenvalue of $L$, and hence $\mathcal{R}_0 > 0$.*

*(2) If $\mathcal{R}_0 > 0$, then $\lambda_0 = \mathcal{R}_0$ is the unique solution of $\rho(W(\omega, 0, \lambda)) = 1$.*

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

The following result shows that $\mathcal{R}_0$ is a threshold parameter for the local stability of a disease-free periodic solution $x^0(t)$.

**Theorem 1.4.2.** ([36, THEOREM 2.2]) *Assume that (A1)-(A7) hold. Then the following statements are valid:*

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

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

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

*Thus,* $x^0(t)$ *is asymptotically stable if* $\mathcal{R}_0 < 1$, *and unstable if* $\mathcal{R}_0 > 1$.

Finally, we give a numerical algorithm for the computation of $\mathcal{R}_0$ (see [44]).

Let $\Phi(t, \lambda)$, $t \geq 0$, be the standard fundamental matrix solution of (1.6) with $\Phi(0, \lambda) = I$. For any given $\lambda > 0$, we can numerically compute all eigenvalues of $\Phi(\omega, \lambda)$ by Matlab, or Maple, and hence, the spectral radius, $\rho(\Phi(\omega, \lambda))$, of $\Phi(\omega, \lambda)$.

Let $f(\lambda) := \rho(\Phi(\omega, \lambda))$. Since $F(t)$ is nonnegative and $-V(t)$ is cooperative, it follows that $f(\lambda)$ is continuous and nonincreasing in $\lambda \in (0, \infty)$. Further, $\lim_{\lambda \to \infty} f(\lambda) = \rho(\Phi_{-V}(\omega)) < 1$. By the following four steps, we can numerically calculate $\mathcal{R}_0$.

(1) Choose two positive numbers $a_0 < b_0$ such that $f(a_0 > 1 > f(b_0))$. If there is no such $a_0$, then Theorem 1.4.1(iii) implies that $\mathcal{R}_0 = 0$.

(2) Define two sequences $a_n$ and $b_n$ by inductions if $f(\frac{a_n + b_n}{2}) \geq 1$, define $a_{n+1} = \frac{a_n + b_n}{2}$, and $b_{n+1} = b_n$; otherwise, define $a_{n+1} = a_n$, and $b_{n+1} = \frac{a_n + b_n}{2}$. It follows that $a_n \leq b_n$, $a_{n+1} \geq a_n$, $b_{n_1} \leq b_n$, and $f(a_n) \geq 1 \geq f(b_n)$ for all $n$.

(3) By step (2), we have $[a_{n+1}, b_{n+1}] \subset [a_n, b_n]$ and $b_n - a_n = \frac{1}{2^n}(b_0 - a_0)$. Thus $\lim_{n \to \infty} a_n = \lim_{n \to \infty} b_n = \lambda_0 > 0$. Since $f(a_n) \geq 1 \geq f(b_n)$ for all $n$, we have $f(\lambda_0) \geq 1 \geq f(\lambda_0)$, and hence $f(\lambda_0) = 1$. Consequently, we have $\mathcal{R}_0 = \lambda_0$.

(4) Since $a_n \leq \mathcal{R}_0 \leq b_n$, we see that $\mid a_n - \mathcal{R}_0 \mid \leq b_n - a_n = \frac{1}{2^n}(b_0 - a_0)$, and $\mid b_n - \mathcal{R}_0 \mid \leq b_n - a_n = \frac{1}{2^n}(b_0 - a_0)$. Given an error tolerance $\varepsilon$, we can choose an $N > 0$ such that $\frac{1}{2^N}(b_0 - a_0) \leq \varepsilon$. Thus, we have $\mathcal{R}_0 \approx a_N$ or $\mathcal{R}_0 \approx b_N$.

# Chapter 2

# A Time-Delayed Dengue Transmission Model

## 2.1 Introduction

Dengue fever is the most common viral disease spread to humans by mosquitos, and has become an international public health concern. Dengue is caused by a group of four antigenically distinct flavivirus serotypes: DEN-1, DEN-2, DEN-3, and DEN-4; and is primarily transmitted by Aedes mosquitos, particularly A. aeqypti mosquitos. Dengue is found in tropical and subtropical regions around the world, predominately in urban and peri-urban areas. The incidence of dengue has grown dramatically around the world in recent decades. It is endemic in more than 110 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. It infects 50 to 100 million people worldwide a year, leading to 50 million hospitalizations, and approximately 12,500 to 25,000 deaths a year [6, 7, 27, 37].

The human is the main amplifying host of the virus, although studies have shown that in some part of the world monkeys may become infected and perhaps serve as a source of virus for uninfected mosquitos [6]. Human may get infected by a bite from the infected mosquitos, and A. aegypti mosquitos may acquire the virus when they feed on an infectious individual. Much have been done in terms of modeling and analysis of disease transmission with structured vector population. Wang and Zhao [35] proposed a nonlocal and time-delayed reaction-diffusion model of dengue fever, and established a threshold dynamics in terms of the basic reproduction number $\mathcal{R}_0$. Lou and Zhao [22] presented a malaria transmission model with structured vector population, and also established a threshold type result, which states that when $\mathcal{R}_0 < 1$ and the disease invasion is not strong, the disease will die out; when $\mathcal{R}_0 > 1$, the disease will persist.

In this chapter, we incorporate the stage structure of mosquitos (see, e.g., [22]), since the development stages of mosquitos have a profound impact on the transmission of disease: first, the immature mosquitos do not fly and bite human, so they do not participate in the infection cycle; second, mature mosquitos are quite different from immature mosquitos from biological and epidemiological perspectives. In view of realistic consideration, we take these different stages into account. We also include the time delay to describe the incubation periods of mosquitos and the human populations, which is important because there are incubation realistically and the time period is not small. In fact, from the expression of $\mathcal{R}_0$ in section 3, we can see those delays reduce the values of $\mathcal{R}_0$. Therefore, the neglect of the delays overestimated the infection risk.

The purpose of this chapter is to study the global dynamics of a time-delayed

dengue transmission model. In section 2, we present the model system and prove its wellposedness. In section 3, we first introduce the basic reproduction number $\mathcal{R}_0$, and then show that the disease is uniformly persistent when $\mathcal{R}_0 > 1$ by appealing to the theory developed in [5, 31]. Under certain conditions, we also obtain the nonlocal stability of the disease-free equilibrium when $\mathcal{R}_0 < 1$. In section 4, we obtain a set of sufficient conditions for the endemic equilibrium to be globally attractive by the method of fluctuations. In section 5, we perform numerical simulations to illustrate our analytic results.

## 2.2 The model

In this section, following the ideas in [35], we present an age-structure dengue model with time delay for the cross infection between mosquitos and human individuals. We divide the mosquito population into two subclasses: aquatic population and winged population. Winged female A. aegypti mosquitoes lay eggs in unattended water. Eggs may develop into larvae from two days up to one week. The larvae spend up to three days to pass through four instars to enter the pupal stage. The pupa develops into an adult after about two days. The immature mosquitos live in aquatic habitats and mature mosquitos disperse to search for food. Let $A$ denote the density of aquatic population of mosquitos, $W$ be the density of winged population of mosquitos, and $\tau_A$ be the length of immature stage of mosquitos. Following the model to formulate a stage-structured population in Aiello and Freedman [2], we suppose the dynamics

of mosquitos is described by

$$\begin{aligned}\frac{dA(t)}{dt} &= B((W(t))W(t) - aA(t) - e^{-a\tau_A}B(W(t-\tau_A))W(t-\tau_A),\\ \frac{dW(t)}{dt} &= e^{-a\tau_A}B(W(t-\tau_A))W(t-\tau_A) - \mu_w W(t),\end{aligned}$$

where $B$ is the per capita birth rate of adult mosquitos, $a$ is the per capita death rate of aquatic mosquitos, and $\mu_w$ is the death rate of adult mosquitos. Following [35], we assume that the function of $B(W)W$ is the logistic growth rate:

$$rW[1-W/K]_+ = \begin{cases} rW[1-W/K] & , \quad if\ 0 \le W \le K \\ 0 & , \quad if\ W > K \end{cases}$$

For the dynamics of human population, we assume that the density $N$ of the human population obeys

$$\frac{dN}{dt} = H - \mu_h N,$$

where $H$ is a constant recruitment rate and $\mu_h$ is the death rate.

To consider dengue transmission between mosquitos and human individuals, we let $W_1$, $W_e$ and $W_2$ denote the density of susceptible, exposed, and infectious mosquitos of winged population, respectively; and divide the human population into four compartments: susceptible ($S$), exposed ($E$), infectious ($I$) and recovered ($R$). Let $\tau_w$ be the incubation period of dengue virus within mosquitos and $\tau_h$ be the incubation period of dengue virus within hosts. Following Chowell et al. [8], we suppose that the infection rates of susceptible mosquitos and susceptible human individuals are described by

$$bp\frac{I}{N}W_1,\ bq\frac{S}{N}W_2,$$

respectively, where $b$ is the mean rate of mosquito bites per mosquito, $p$ is the probability that a bite by a susceptible mosquito to an infectious host will cause infections,

$q$ is the probability that a bite by an infectious mosquito to a susceptible host will cause infection to the host, and $N = S + E + I + R$ is the total density of human population. Since an infectious mosquito may have lower fecundity than a susceptible mosquito, we let $\sigma \in [0, 1]$ denote the relative fecundity of an infected mosquito to a susceptible mosquito. Specifically, the infectious mosquito has the same reproduction rate as a susceptible mosquito if $\sigma = 1$, and have lower reproduction rate if $\sigma < 1$. Then we have the following model:

$$\begin{aligned}
\frac{dA(t)}{dt} &= r[1 - \frac{W(t)}{K}]_+ W_\sigma(t) - aA(t) - re^{-a\tau_A}[1 - \frac{W(t-\tau_A)}{K}]_+ W_\sigma(t-\tau_A), \\
\frac{dW_1(t)}{dt} &= re^{-a\tau_A}[1 - \frac{W(t-\tau_A)}{K}]_+ W_\sigma(t-\tau_A) - \mu_w W_1(t) - \beta_w \frac{I(t)}{N(t)} W_1(t),
\end{aligned} \tag{2.1}$$

$$W_e(t) = \int_{t-\tau_w}^{t} e^{-\mu_w(t-s)} \beta_w \frac{I(s)}{N(s)} W_1(s) ds, \tag{2.2}$$

$$\frac{dW_2(t)}{dt} = \beta_w e^{-\mu_w \tau_w} \frac{I(t-\tau_w)}{N(t-\tau_w)} W_1(t-\tau_w) - (\mu_w + \varepsilon_w) W_2(t), \tag{2.3}$$

$$\frac{dS(t)}{dt} = H - \mu_h S(t) - \beta_h W_2(t) \frac{S(t)}{N(t)}, \tag{2.4}$$

$$E(t) = \int_{t-\tau_h}^{t} e^{-\mu_h(t-s)} \beta_h \frac{S(s)}{N(s)} W_2(s) ds, \tag{2.5}$$

$$\frac{dI(t)}{dt} = \beta_h e^{-\mu_h \tau_h} W_2(t-\tau_h) \frac{S(t-\tau_h)}{N(t-\tau_h)} - (\mu_h + \varepsilon_h + \gamma) I(t), \tag{2.6}$$

$$\frac{dR(t)}{dt} = \gamma I(t) - \mu_h R(t), \tag{2.7}$$

where $W(t) = W_1(t) + W_e(t) + W_2(t)$, $W_\sigma(t) = W_1(t) + W_e(t) + \sigma W_2(t)$, $\beta_w = bp$, $\beta_h = bq$, $\gamma$ is the recovery rate of infected human individuals, $\varepsilon_w$ and $\varepsilon_h$ are the infection-induced death rates of infected mosquitos and human individuals, respectively.

Note that the equation for aquatic population of mosquitos is decoupled from the other equations. It then suffices to consider system (2.1)-(2.7) which is an integro-

differential equation system. Differentiating (2.2) and (2.5) gives

$$\frac{dW_e(t)}{dt} = \beta_w \frac{I(t)}{N(t)} W_1(t) - \mu_w W_e(t) - \beta_w e^{-\mu_w \tau_w} \frac{I(t-\tau_w)}{N(t-\tau_w)} W_1(t-\tau_w), \tag{2.8}$$

$$\frac{dE(t)}{dt} = \beta_h W_2(t) \frac{S(t)}{N(t)} - \mu_h E(t) - \beta_h e^{-\mu_h \tau_h} W_2(t-\tau_h) \frac{S(t-\tau_h)}{N(t-\tau_h)}. \tag{2.9}$$

The system consisting of (2.1), (2.8), (2.3), (2.4), (2.9), (2.6) and (2.7) is an ordinary differential system with time delays. For simplicity, we will refer to this system as "the model system" in the rest of this chapter.

Let $\tau = \max\{\tau_A, \tau_w, \tau_h\}$, and define $C := C([-\tau, 0], \mathbb{R}^7)$. For $\phi = (\phi_1, \phi_2, \cdots, \phi_7) \in C$, define $\| \phi \| = \sum_{i=1}^{7} \| \phi_i \|_\infty$, where $\| \phi_i \|_\infty = \max_{\theta \in [-\tau, 0]} | \phi_i(\theta) |$. Then $C$ is a Banach space. Define $C_+ = \{\phi \in C : \phi_i(\theta) \geq 0, \forall 1 \leq i \leq 7, \theta \in [-\tau, 0]\}$. Then $C_+$ is a normal cone of $C$ with nonempty interior in $C$. For a continuous function $u : [-\tau, \sigma_\phi) \to \mathbb{R}^7$ with $\sigma_\phi > 0$, we define $u_t \in C$ for each $t \geq 0$ by $u_t(\theta) = u(t + \theta)$, $\forall \theta \in [-\tau, 0]$.

In view of (2.2) and (2.5), we choose the initial data for the model system in $\mathcal{X}_\delta$, which is defined as

$$\mathcal{X}_\delta = \left\{ \phi \in C_+ : \sum_{i=4}^{7} \phi_i(s) \geq \delta, \forall s \in [-\tau, 0], \phi_2(0) = \int_{-\tau_w}^{0} e^{\mu_w s} \beta_w \frac{\phi_6(s)\phi_1(s)}{\sum_{i=4}^{7} \phi_i(s)} ds, \right.$$
$$\left. \phi_5(0) = \int_{-\tau_h}^{0} e^{\mu_h s} \beta_h \frac{\phi_4(s)\phi_3(s)}{\sum_{i=4}^{7} \phi_i(s)} ds \right\}$$

for small $\delta \in \left(0, \frac{H}{\varepsilon_h + \mu_h}\right)$. The following result shows that the model system is well-posed in $\mathcal{X}_\delta$, and the solution semiflow admits a global attractor on $\mathcal{X}_\delta$.

**Theorem 2.2.1.** *For any $\phi \in \mathcal{X}_\delta$, the model system has a unique nonnegative solution $u(t, \phi)$ satisfying $u_0 = \phi$. Furthermore, the solution semiflow $\Phi(t) = u_t(\cdot) : \mathcal{X}_\delta \to \mathcal{X}_\delta$ has a compact global attractor.*

*Proof.* Given $\phi \in \mathcal{X}_\delta$, define

$$G(\phi) := (G_1(\phi), G_2(\phi), G_3(\phi), G_4(\phi), G_5(\phi), G_6(\phi), G_7(\phi)),$$

where

$$\begin{aligned}
G_1(\phi) &= re^{-a\tau_A}[1 - \frac{\sum_{i=1}^{3}\phi_i(-\tau_A)}{K}]_+(\phi_1(-\tau_A) + \phi_2(-\tau_A) + \sigma\phi_3(-\tau_A)) \\
&\quad -\mu_w\phi_1(0) - \beta_w\frac{\phi_6(0)}{\sum_{i=4}^{7}\phi_i(0)}\phi_1(0), \\
G_2(\phi) &= \beta_w\frac{\phi_6(0)}{\sum_{i=4}^{7}\phi_i(0)}\phi_1(0) - \mu_w\phi_2(0) - \beta_w e^{-\mu_w\tau_w}\frac{\phi_6(-\tau_w)}{\sum_{i=4}^{7}\phi_i(-\tau_w)}\phi_1(-\tau_w), \\
G_3(\phi) &= \beta_w e^{-\mu_w\tau_w}\frac{\phi_6(-\tau_w)}{\sum_{i=4}^{7}\phi_i(-\tau_w)}\phi_1(-\tau_w) - (\mu_w + \varepsilon_w)\phi_3(0), \\
G_4(\phi) &= H - \mu_h\phi_4(0) - \beta_h\frac{\phi_4(0)}{\sum_{i=4}^{7}\phi_i(0)}\phi_3(0), \\
G_5(\phi) &= \beta_h\frac{\phi_4(0)}{\sum_{i=4}^{7}\phi_i(0)}\phi_3(0) - \mu_h\phi_5(0) - \beta_h e^{-\mu_h\tau_h}\frac{\phi_4(-\tau_h)}{\sum_{i=4}^{7}\phi_i(-\tau_h)}\phi_3(-\tau_h), \\
G_6(\phi) &= \beta_h e^{-\mu_h\tau_h}\frac{\phi_4(-\tau_h)}{\sum_{i=4}^{7}\phi_i(-\tau_h)}\phi_3(-\tau_h) - (\mu_h + \varepsilon_h + \gamma)\phi_6(0), \\
G_7(\phi) &= \gamma\phi_6(0) - \mu_h\phi_7(0).
\end{aligned}$$

Note that $\mathcal{X}_\delta$ is closed in $C$, and for all $\phi \in \mathcal{X}_\delta$, $G(\phi)$ is continuous and Lipschitz in $\phi$ in each compact set in $\mathbb{R} \times \mathcal{X}_\delta$. By [16, Theorem 2.3], it then follows that for any $\phi \in \mathcal{X}_\delta$, there is an unique solution of the model system through $(0, \phi)$ on its maximal interval $[0, \sigma_\phi)$ of existence.

Since $G_i(\phi) \geq 0$ whenever $\phi \in \mathcal{X}_\delta$ with $\phi_i(0) = 0$, Theorem 1.1.1 implies that the solutions of the model system are nonnegative for all $t \in [0, \sigma_\phi)$. Note that the total host population satisfies

$$\frac{dN(t)}{dt} = H - \mu_h N(t) - \varepsilon_h I(t) \geq H - (\mu_h + \varepsilon_h)N(t).$$

For system $\frac{dy}{dt} = H - (\mu_h + \varepsilon_h)y(t)$, the equilibrium $\frac{H}{\mu_h + \varepsilon_h}$ is globally asymptotically stable. For any $0 < \delta < \frac{H}{\mu_h + \varepsilon_h}$, $\frac{dy}{dt}|_{y=\delta} = H - (\mu_h + \varepsilon_h)\delta > 0$. So if $y(0) \geq \delta$, then

$y(t) \geq \delta$, for any $t \geq 0$. From (2.8), we get

$$e^{\mu_w t}(W_e'(t) + \mu_w W_e(t)) = e^{\mu_w t}(\beta_w \frac{I(t)}{N(t)} W_1(t) - \beta_w e^{-\mu_w \tau_w} \frac{I(t-\tau_w)}{N(t-\tau_w)} W_1(t-\tau_w))$$

By integrating on both sides from 0 to $t$, we obtain

$$\begin{aligned}
& e^{\mu_w t} W_e(t) - W_e(0) \\
&= \int_0^t e^{\mu_w s} \beta_w \frac{I(s)}{N(s)} W_1(s) ds - \int_0^t e^{\mu_w (s-\tau_w)} \beta_w \frac{I(s-\tau_w)}{N(s-\tau_w)} W_1(s-\tau_w) ds \\
&= \int_0^t e^{\mu_w s} \beta_w \frac{I(s)}{N(s)} W_1(s) ds - \int_{-\tau_w}^{t-\tau_w} e^{\mu_w s} \beta_w \frac{I(s)}{N(s)} W_1(s) ds \\
&= \int_{t-\tau_w}^t e^{\mu_w s} \beta_w \frac{I(s)}{N(s)} W_1(s) ds - \int_{-\tau_w}^0 e^{\mu_w s} \beta_w \frac{I(s)}{N(s)} W_1(s) ds
\end{aligned}$$

Therefore, if $W_e(0) = \int_{-\tau_w}^0 e^{\mu_w s} \beta_w \frac{I(s)}{N(s)} W_1(s) ds$ is satisfied, then

$$W_e(t) = \int_{t-\tau_w}^t e^{-\mu_w (t-s)} \beta_w \frac{I(s)}{N(s)} W_1(s) ds.$$

Similarly, if $E(0) = \int_{-\tau_h}^0 e^{\mu_h s} \beta_h \frac{W_2(s) S(s)}{N(s)} ds$ is satisfied, then

$$E(t) = \int_{t-\tau_h}^t e^{-\mu_h (t-s)} \beta_h \frac{S(s)}{N(s)} W_2(s) ds.$$

This implies that $u_t \in \mathcal{X}_\delta$, $\forall t \in [0, \sigma_\phi)$.

Note that

$$\frac{dN(t)}{dt} = H - \mu_h N(t) - \varepsilon_h I(t) \leq H - \mu_h N(t).$$

For system

$$\frac{d\bar{N}(t)}{dt} = H - \mu_h \bar{N}(t), \tag{2.10}$$

the equilibrium $N^* = \frac{H}{\mu_h}$ is globally asymptotically stable. By the comparison principle, it follows that

$$\limsup_{t \to \infty} N(t) \leq N^*. \tag{2.11}$$

Regarding the total vector population, we have

$$\begin{aligned}\frac{dW(t)}{dt} &= re^{-a\tau_A}[1-\frac{W(t-\tau_A)}{K}]_+W_\sigma(t-\tau_A)-\mu_wW(t)-\varepsilon_wW_2(t)\\ &\leq re^{-a\tau_A}[1-\frac{W(t-\tau_A)}{K}]_+W(t-\tau_A)-\mu_wW(t)\\ &\leq re^{-a\tau_A}\frac{K}{4}-\mu_wW(t).\end{aligned}$$

For system $\frac{dy}{dt}=re^{-a\tau_A}\frac{K}{4}-\mu_wy(t)$, the equilibrium $\frac{re^{-a\tau_A}K}{4\mu_w}$ is globally asymptotically stable. By the comparison principle, it follows that

$$\limsup_{t\to\infty}W(t)\leq\frac{re^{-a\tau_A}K}{4\mu_w}. \tag{2.12}$$

By (2.11) and (2.12), it follows that $\sigma_\phi=\infty$, all the solutions exist globally, and are ultimately bounded. Moreover, when $N(t)>\max\{\frac{H}{\mu_h},\frac{re^{-a\tau_A}K}{4\mu_w}\}$ and $W(t)>\max\{\frac{H}{\mu_h},\frac{re^{-a\tau_A}K}{4\mu_w}\}$, we have

$$\frac{dN(t)}{dt}<0,\frac{dW(t)}{dt}<0$$

which implies that all solutions are uniformly bounded. Therefore , the solution semiflow $\Phi(t)=u_t(\cdot):\mathcal{X}_\delta\to\mathcal{X}_\delta$ is point dissipative. By [16, Theorem 3.6.1], $\Phi(t)$ is compact for any $t>\tau$. Thus, [17, Theorem 3.4.8] implies that $\Phi(t)$ has a compact global attractor in $\mathcal{X}_\delta$. □

## 2.3 Threshold dynamics

In this section, we establish the threshold dynamics for the model system in terms of the basic reproduction number.

We define the "diseased classes" as the mosquito and human populations that are either exposed or infectious, i.e. $W_e$, $W_2$, $E$ and $I$. To get the disease-free equilibrium,

letting $W_e = W_2 = E = I = 0$, we then get $R = 0$ and

$$\begin{aligned}
\frac{dW_1(t)}{dt} &= re^{-a\tau_A}[1 - \frac{W_1(t-\tau_A)}{K}]_+ W_1(t-\tau_A) - \mu_w W_1(t), \qquad (2.13)\\
\frac{dS(t)}{dt} &= H - \mu_h S(t). \qquad (2.14)
\end{aligned}$$

$E_0 = (0, 0, 0, N^*, 0, 0, 0)$ and $E_1 = (W^*, 0, 0, N^*, 0, 0, 0)$ are two disease free equilibria, where $W^* = \frac{K(re^{-a\tau_A} - \mu_w)}{re^{-a\tau_A}}$. By [43, Proposition 4.1], for system (2.13), the equilibrium $W^*$ is globally asymptotically stable if the following condition is satisfied

(H1) $\mu_w < re^{-a\tau_A} \leq 3\mu_w$.

Linearizing the model system at the disease free equilibrium $E_1$, we obtain the following system (here we only write down the equations for the diseased classes):

$$\begin{aligned}
\frac{dW_e(t)}{dt} &= \beta_w \frac{W^*}{N^*} I(t) - \mu_w W_e(t) - \beta_w e^{-\mu_w \tau_w} \frac{W^*}{N^*} I(t-\tau_w),\\
\frac{dW_2(t)}{dt} &= \beta_w e^{-\mu_w \tau_w} \frac{W^*}{N^*} I(t-\tau_w) - (\mu_w + \varepsilon_w) W_2(t),\\
\frac{dE(t)}{dt} &= \beta_h W_2(t) - \mu_h E(t) - \beta_h e^{-\mu_h \tau_h} W_2(t-\tau_h),\\
\frac{dI(t)}{dt} &= \beta_h e^{-\mu_h \tau_h} W_2(t-\tau_h) - (\mu_h + \varepsilon_h + \gamma) I(t).
\end{aligned}$$

Following the idea in [38], we introduce the basic reproduction number for the model system. Denote $x_1$, $x_2$, $x_3$ and $x_4$ be the number of each diseased class at time $t = 0$, and $x_1(t)$, $x_2(t)$, $x_3(t)$ and $x_4(t)$ be the remaining populations of each class at time $t$, respectively, then we obtain

$$\begin{aligned}
x_2(t) &= x_2 e^{-(\mu_w + \varepsilon_w)t},\\
x_4(t) &= x_4 e^{-(\mu_h + \varepsilon_h + \gamma)t}.
\end{aligned}$$

The total number of newly infected in each diseased class is

$$\begin{aligned}
\bar{x}_1 &= \int_0^\infty \frac{\beta_w W^*}{N^*} x_4(t)dt = \frac{\beta_w W^*}{N^*(\mu_h+\varepsilon_h+\gamma)} x_4, \\
\bar{x}_2 &= \int_{\tau_w}^\infty \frac{\beta_w e^{-\mu_w \tau_w} W^*}{N^*} x_4(t-\tau_w)dt = \frac{\beta_w e^{-\mu_w \tau_w} W^*}{N^*(\mu_h+\varepsilon_h+\gamma)} x_4, \\
\bar{x}_3 &= \int_0^\infty \beta_h x_2(t)dt = \frac{\beta_h}{\mu_w+\varepsilon_w} x_2, \\
\bar{x}_4 &= \int_{\tau_h}^\infty \beta_h e^{-\mu_h \tau_h} x_2(t-\tau_h)dt = \frac{\beta_h e^{-\mu_h \tau_h}}{\mu_w+\varepsilon_w} x_2.
\end{aligned}$$

Since

$$\begin{pmatrix} \bar{x}_1 \\ \bar{x}_2 \\ \bar{x}_3 \\ \bar{x}_4 \end{pmatrix} = \begin{pmatrix} 0 & 0 & 0 & \frac{\beta_w W^*}{N^*(\mu_h+\varepsilon_h+\gamma)} \\ 0 & 0 & 0 & \frac{\beta_w e^{-\mu_w \tau_w} W^*}{N^*(\mu_h+\varepsilon_h+\gamma)} \\ 0 & \frac{\beta_h}{\mu_w+\varepsilon_w} & 0 & 0 \\ 0 & \frac{\beta_h e^{-\mu_h \tau_h}}{\mu_w+\varepsilon_w} & 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix}$$

We can see that the $2 \times 2$ matrix:

$$M_0 = \begin{pmatrix} 0 & 0 & 0 & \frac{\beta_w W^*}{N^*(\mu_h+\varepsilon_h+\gamma)} \\ 0 & 0 & 0 & \frac{\beta_w e^{-\mu_w \tau_w} W^*}{N^*(\mu_h+\varepsilon_h+\gamma)} \\ 0 & \frac{\beta_h}{\mu_w+\varepsilon_w} & 0 & 0 \\ 0 & \frac{\beta_h e^{-\mu_h \tau_h}}{\mu_w+\varepsilon_w} & 0 & 0 \end{pmatrix}$$

is the next infection operator. As usual, we define the spectral radius of the matrix $M_0$ as the basic reproduction number $\mathcal{R}_0$ for the model system. It then follows that

$$\mathcal{R}_0 = \sqrt{\frac{\beta_w \beta_h e^{-(\mu_w \tau_w + \mu_h \tau_h)} W^*}{N^*(\mu_w+\varepsilon_w)(\mu_h+\varepsilon_h+\gamma)}}.$$

Our first result shows that the disease is uniformly persistent if $\mathcal{R}_0 > 1$.

**Theorem 2.3.1.** *Let (H1) hold. If $\mathcal{R}_0 > 1$, then there is an $\eta > 0$ such that any solution $u(t, \phi)$ of the model system with $\phi \in \mathcal{X}_\delta$, $\phi_3(0) \neq 0$ and $\phi_6(0) \neq 0$ satisfies*

$$\liminf_{t \to \infty} (W_2(t), I(t)) \geq (\eta, \eta).$$

*Proof.* Define

$$X_0 = \{\phi = (\phi_1, \phi_2, \ldots, \phi_7) \in \mathcal{X}_\delta : \ \phi_3(0) \neq 0, \ \textit{and} \ \phi_6(0) \neq 0\}.$$

Clearly, we have

$$\partial X_0 = \mathcal{X}_\delta \setminus X_0 = \{\phi \in \mathcal{X}_\delta : \ \phi_3(0) = 0, \ \textit{or} \ \phi_6(0) = 0\}.$$

Define

$$M_\partial = \{\phi \in \mathcal{X}_\delta : \Phi(t)\phi \in \partial X_0, \forall t \geq 0\}.$$

**Claim 1.** *There exists a $\delta_1 > 0$, such that for any $\phi \in X_0$, $\limsup_{t\to\infty} \| \Phi(t)\phi - E_0 \| \geq \delta_1$.*

Since $\mu_w < re^{-a\tau_A}$, we can choose $\varepsilon_0 > 0$ and $\delta_1 > 0$ sufficiently small, such that

$$\frac{a_3}{a_1 + a_2 + a_3 + a_4} < \varepsilon_0, \ \forall \mid (a_1, a_2, a_3, a_4) - (N^*, 0, 0, 0) \mid < \delta_1, \tag{2.15}$$

$$\mu_w + \beta_w \varepsilon_0 < re^{-a\tau_A}(1 - \frac{3\delta_1}{K}). \tag{2.16}$$

where $(a_1, a_2, a_3, a_4) \in \mathbb{R}^4_+$.

For any $\phi \in \mathcal{X}_\delta$, since $\phi_3(0) \neq 0$, and $\phi_6(0) \neq 0$, it follows from Theorem 1.1.1, we get

$$W_2(t) > 0, \ I(t) > 0, \forall t > 0. \tag{2.17}$$

Next we show that there exists a $t_0 \geq 0$, such that $W_1(t_0, \phi) > 0$, for all $\phi \in X_0$. Otherwise, there exists $\psi \in X_0$, such that $W_1(t, \psi) = 0$, for all $t \geq 0$. From (2.2), we get $W_e(t) \equiv 0$ for all $t \geq \tau_w$, then from (2.1), we get $W_2(t) \equiv 0$, for all $t \geq \tau_w$, a contradiction with (2.17). Then, by Theorem 1.1.1, $W_1(t) > 0$, for all $t \geq t_0$.

Suppose, by contradiction, that $\limsup_{t\to\infty} \| \Phi(t)\psi - E_0 \| < \delta_1$ for some $\psi \in X_0$. Thus, $\| \Phi(t)\psi - E_0 \| < \delta_1$ holds for all large $t$.

Then we can choose large number $t_1 > t_0$, such that for all $t \geq t_1$, there holds that

$$\frac{dW_1(t)}{dt} \geq re^{-a\tau_A}(1 - \frac{3\delta_1}{K})W_1(t - \tau_A) - (\mu_w + \beta_w\varepsilon_0)W_1(t).$$

Consider the next linear and monotone time-delayed system

$$\frac{dw(t)}{dt} = re^{-a\tau_A}(1 - \frac{3\delta_1}{K})w(t - \tau_A) - (\mu_w + \beta_w\varepsilon_0)w(t). \tag{2.18}$$

Let $\lambda_0$ be the principal eigenvalue of the corresponding eigenvalue problem of equation (2.18). Since for any $\phi \in C([-\tau, 0], \mathbb{R}_+)$ with $\phi(0) = 0$, we have $re^{-a\tau_A}(1 - 3\delta_1/K)\phi(-\tau_A) \geq 0$. Therefore, (2.18) is cooperative. Then we consider the auxiliary system

$$\frac{d\tilde{w}(t)}{dt} = \big(re^{-a\tau^A}(1 - 3\delta_1/K) - (\mu_w + \beta_w\varepsilon_0)\big)\tilde{w}(t). \tag{2.19}$$

By (2.16), the eigenvalue $\lambda_0'$ of system (2.19) is $re^{-a\tau^A}(1 - 3\delta_1/K) - (\mu_w + \beta_w\varepsilon_0) > 0$. By Theorem 1.1.4, we get $\lambda_0 > 0$ if and only if $\lambda_0' > 0$. Therefore, $\lambda_0 > 0$.

We can choose $l > 0$ small enough such that $le^{\lambda_0 t} \leq W_1(t), \forall t \in [t_1, t_1 + \tau_A]$. Clearly, $le^{\lambda_0 t}$ satisfies (2.18) for all $t \geq t_1$. Then by the comparison principle, we get

$$le^{\lambda_0 t} \leq W_1(t), \ \forall t \geq t_1 + \tau_A,$$

Since $\lambda_0 > 0$ and $l > 0$, $le^{\lambda_0 t} \to \infty$ as $t \to \infty$. Thus, $\lim_{t\to\infty} W_1(t) = \infty$, a contradiction.

**Claim 2.** *There exists a $\delta_2 > 0$, such that for any $\phi \in X_0$, $\limsup_{t\to\infty} \| \Phi(t)\phi - E_1 \| \geq \delta_2$.*

First we consider the following linear cooperative system

$$\begin{aligned}\frac{d\hat{W}_2(t)}{dt} &= \beta_w e^{-\mu_w\tau_w}(\frac{W^*}{N^*}-\varepsilon)\hat{I}(t-\tau_w)-(\mu_w+\varepsilon_w)\hat{W}_2(t),\\ \frac{d\hat{I}(t)}{dt} &= \beta_h e^{-\mu_h\tau_h}(1-\varepsilon)\hat{W}_2(t-\tau_h)-(\mu_h+\varepsilon_h+\gamma)\hat{I}(t).\end{aligned} \tag{2.20}$$

For sufficiently small $\varepsilon > 0$, let $\lambda_1(\varepsilon)$ be the principle eigenvalue of system (2.20). For any $\hat{\phi} = (\hat{\phi}_1, \hat{\phi}_2) \in C([-\tau, 0], \mathbb{R}^2_+)$. First, we define

$$f(\hat{\phi}) = \begin{pmatrix} \beta_w e^{-\mu_w\tau_w}(\frac{W^*}{N^*}-\varepsilon)\hat{\phi}_2(-\tau_w)-(\mu_w+\varepsilon_w)\hat{\phi}_1(0) \\ \beta_h e^{-\mu_h\tau_h}(1-\varepsilon)\hat{\phi}_1(-\tau_h)-(\mu_h+\varepsilon_h+\gamma)\hat{\phi}_2(0)\end{pmatrix}$$

It is easy to see that $f$ is continuously differentiable cooperative in the sense that for any $\hat{\psi} \in C([-\tau, 0], \mathbb{R}^2_+)$, the linear operator $L := df(\hat{\psi})$ satisfies $L_i(\hat{\phi}) \geq 0$ whenever $\hat{\phi} \in C([-\tau, 0], \mathbb{R}^2_+)$ with $\hat{\phi}_i(0) = 0$ for some $1 \leq i \leq 2$. Then we consider the auxiliary system

$$\begin{aligned}\frac{d\hat{\hat{W}}_2(t)}{dt} &= \beta_w e^{-\mu_w\tau_w}(\frac{W^*}{N^*}-\varepsilon)\hat{\hat{I}}(t)-(\mu_w+\varepsilon_w)\hat{\hat{W}}_2(t),\\ \frac{d\hat{\hat{I}}(t)}{dt} &= \beta_h e^{-\mu_h\tau_h}(1-\varepsilon)\hat{\hat{W}}_2(t)-(\mu_h+\varepsilon_h+\gamma)\hat{\hat{I}}(t).\end{aligned} \tag{2.21}$$

Let $\lambda_1'(\varepsilon)$ be the principal eigenvalue of eigenvalue problem of system (2.21). By calculation, it follows that $\lambda_1'(\varepsilon) > 0$ if and only if $\alpha(\varepsilon) := \frac{\beta_w\beta_h e^{-(\mu_w\tau_w+\mu_h\tau_h)}}{(\mu_w+\varepsilon_w)(\mu_h+\varepsilon_h+\gamma)}(\frac{W^*}{N^*}-\varepsilon)(1-\varepsilon) > 1$. When $\varepsilon = 0$, $\alpha(\varepsilon) = \mathcal{R}_0^2 > 1$. Since $\alpha(\varepsilon)$ is continuous with respect to $\varepsilon$, we can choose $\varepsilon$ small enough such that $\alpha(\varepsilon) > 1$, thus $\lambda_1'(\varepsilon) > 0$. By Theorem 1.1.4, $\lambda_1(\varepsilon) > 0$ if and only if $\lambda_1'(\varepsilon) > 0$. Thus, we can restrict $\varepsilon$ small enough such that $\lambda_1(\varepsilon) > 0$.

For this small $\varepsilon$, there exists $\delta_2 = \delta_2(\varepsilon) > 0$, such that

$$\begin{aligned}&\frac{b_4}{b_4+b_5+b_6+b_7} > 1-\varepsilon > 0, \ \textit{and}\\ &\frac{b_1+b_2+b_3}{b_4+b_5+b_6+b_7} > \frac{W^*}{N^*}-\varepsilon > 0, \ \forall \mid (b_1, b_2, \cdots, b_7) - E_1 \mid < \delta_2.\end{aligned}$$

Assume, by contradiction, that $\limsup_{t\to\infty} \parallel \Phi(t)\phi - E_1 \parallel < \delta_2$ for some $\phi \in X_0$. Then there exists a large number $t_2$, such that for all $t \geq t_2$,

$$\parallel \Phi(t)\phi - E_1 \parallel < \delta_2.$$

Then we can further choose $t_3 > t_2$ large enough, such that for all $t \geq t_3$,

$$\frac{W(t)}{N(t)} \geq \frac{W^*}{N^*} - \varepsilon, \ \frac{S(t)}{N(t)} \geq 1 - \varepsilon.$$

That is, when $t \geq t_3$, we have

$$\begin{aligned} \frac{dW_2(t)}{dt} &\geq \beta_w e^{-\mu_w \tau_w}(\frac{W^*}{N^*} - \varepsilon)I(t-\tau_w) - (\mu_w + \varepsilon_w)W_2(t), \\ \frac{dI}{dt} &\geq \beta_h e^{-\mu_h \tau_h}(1-\varepsilon)W_2(t-\tau_h) - (\mu_h + \varepsilon_h + \gamma)I(t). \end{aligned}$$

Let $v = (v_1, v_2)^T$ be the positive right eigenvector associated with $\lambda_1(\varepsilon)$ for system (2.20), choose $l > 0$ small enough such that

$$\begin{aligned} l v_1 e^{\lambda_1(\varepsilon)t} &\leq W_2(t), \forall t \in [t_3, t_3 + \tau], \\ l v_2 e^{\lambda_1(\varepsilon)t} &\leq I(t), \forall t \in [t_3, t_3 + \tau], \end{aligned}$$

Clearly, $l e^{\lambda_1(\varepsilon)t}(v_1, v_2)^T$ satisfies (2.20) for $t \geq t_3$. Then by the comparison principle, we get

$$(W_2(t), I(t)) \geq l e^{\lambda_1(\varepsilon)t}(v_1, v_2), \forall t \geq t_3 + \tau.$$

Since $\lambda_1(\varepsilon) > 0$, letting $t \to \infty$, we obtain

$$\lim_{t\to\infty} W_2(t) = \infty, \ \lim_{t\to\infty} I(t) = \infty$$

a contradiction.

Let $\omega(\phi)$ be the omega limit set of the orbit of $\Phi(t)$ through $\phi \in \mathcal{X}_\delta$.

**Claim 3.** $\cup_{\phi\in M_\partial}\omega(\phi) = E_0 \cup E_1$.

For any $\phi \in M_\partial$, i.e. $\Phi(t)\phi \in \partial X_0$, we have $W_2(t,\phi) \equiv 0$, or $I(t,\phi) \equiv 0$. If $W_2(t,\phi) \equiv 0$, then from the equations of $S$, $E$ and $I$, we have $\lim_{t\to\infty} S(t,\phi) = N^*$, $\lim_{t\to\infty} E(t,\phi) = 0$ and $\lim_{t\to\infty} I(t,\phi) = 0$. Let $\Phi(t)$ be the solution semiflow of the model system, which is defined as

$$\Phi(t)\phi = (W_1(t,\phi), W_e(t,\phi), W_2(t,\phi), S(t,\phi), E(t,\phi), I(t,\phi), R(t,\phi)),\ \forall \phi \in \mathcal{X}_\delta.$$

Following from Theorem 2.2.1, $\Phi(t)$ is compact for any $t > \tau$. Let $\omega = \omega(\phi)$ be the omega limit set of $\Phi(t)\phi$. It then follows from Theorem 1.3.1 that $\omega$ is an internally chain transitive set for $\Phi(t)$. Hence, we have

$$\omega = \omega_1 \times \left\{(0, N^*, 0, 0)\right\} \times \omega_2$$

for some $\omega_1 \in C([-\tau, 0], \mathbb{R}^2_+)$ and $\omega_2 \in C([-\tau, 0], \mathbb{R}_+)$. It is easy to see that

$$\Phi(t)\mid_\omega (\psi_1, \psi_2, 0, N^*, 0, 0, \psi_7) = (\Psi_1(t)(\psi_1, \psi_2), 0, N^*, 0, 0, \Psi_2(t)\psi_7)$$

where $\psi_1,\ \psi_2,\ \psi_7 \in C([-\tau, 0], \mathbb{R}_+)$, $\Phi_1(t)$ is the solution semiflow associated with the following system

$$\begin{aligned}
\frac{d\tilde{W}_1(t)}{dt} &= re^{-a\tau_A}[1 - \frac{\tilde{W}_1(t-\tau_A) + \tilde{W}_e(t-\tau_A)}{K}]_+(\tilde{W}_1(t-\tau_A) + \tilde{W}_e(t-\tau_A)) \\
&\quad -\mu_w\tilde{W}_1(t), \qquad (2.22)\\
\frac{d\tilde{W}_e(t)}{dt} &= -\mu_w\tilde{W}_e(t). \qquad (2.23)
\end{aligned}$$

and $\Phi_2(t)$ is the solution semiflow associated with

$$\frac{d\tilde{R}(t)}{dt} = -\mu_h\tilde{R}(t). \qquad (2.24)$$

Since $\omega$ is an internally chain transitive set for $\Phi(t)$, it then follows that $\omega_1$, $\omega_2$ are also internally chain transitive sets for $\Phi_1(t)$, $\Phi_2(t)$, respectively. For system

(2.24), $\{0\}$ is the unique equilibrium point and globally asymptotically stable. Let $\tilde{W} = \tilde{W}_1(t) + \tilde{W}_2(t)$, system (2.22)(2.23) is equivalent to

$$\begin{aligned} \frac{d\tilde{W}(t)}{dt} &= re^{-a\tau_A}[1 - \frac{\tilde{W}(t-\tau_A)}{K}]_+(\tilde{W}(t-\tau_A) - \mu_w\tilde{W}(t), \qquad (2.25) \\ \frac{d\tilde{W}_e(t)}{dt} &= -\mu_w\tilde{W}_e(t). \end{aligned}$$

By [43, Proposition 4.1], $W^*$ and 0 are globally asymptotically stable for system (2.25) and (2.23), respectively. So $(W^*, 0)^T$ is globally asymptotically stable for system (2.22) and (2.23) in $C([-\tau, 0], \mathbb{R}^2_+) \setminus \{(0,0)\}$. Therefore, by Theorem 1.3.2, we get $\omega_1 = \{(W^*, 0)\}$ or $\{(0,0)\}$, and $\omega_2 = \{0\}$. Thus, we have $\omega = \{(W^*, 0, 0, N^*, 0, 0, 0)\}$ or $\{(0, 0, 0, N^*, 0, 0, 0)\}$.

If $W_2(t, \phi) \not\equiv 0$, then there exists $t_0 \geq 0$, such that $W_2(t_0, \phi) > 0$. We then obtain that $W_2(t, \phi) > 0$ for all $t \geq t_0$, and $I(t, \phi) \equiv 0$. From the equations of $W_e$, $W_2$ and $R$, we have $\lim_{t\to\infty} W_e(t, \phi) = 0$, $\lim_{t\to\infty} W_2(t, \phi) = 0$, and $\lim_{t\to\infty} R(t, \phi) = 0$. Hence, we have

$$\omega = \omega_3 \times \{(0,0)\} \times \omega_4 \times \{(0,0)\}$$

for some $\omega_3 \in C([-\tau, 0], \mathbb{R}_+)$ and $\omega_4 \in C([-\tau, 0], \mathbb{R}^2_+)$. It is easy to see that

$$\Phi(t) \mid_\omega (\psi_1, 0, 0, \psi_4, \psi_5, 0, 0) = (\Phi_3(t)\psi_1, 0, 0, \Phi_4(t)(\psi_4, \psi_5), 0, 0)$$

where $\psi_1,\ \psi_4,\ \psi_5 \in C([-\tau, 0], \mathbb{R}_+)$, $\Phi_3(t)$ is the solution semiflow associated with the following system

$$\frac{d\bar{W}(t)}{dt} = re^{-a\tau_A}[1 - \frac{\bar{W}(t-\tau_A)}{K}]_+\bar{W}(t-\tau_A) - \mu_w\bar{W}(t), \qquad (2.26)$$

and $\Phi_4(t)$ is the solution semiflow associated with

$$\begin{aligned} \frac{d\bar{S}(t)}{dt} &= H - \mu_h\bar{S}(t), \qquad (2.27) \\ \frac{d\bar{E}(t)}{dt} &= -\mu_h\bar{I}(t). \qquad (2.28) \end{aligned}$$

By [43, Proposition 4.1], $W^*$ is globally asymptotically stable for system (2.26) in $C([-\tau, 0], \mathbb{R}_+) \setminus \{0\}$. Clearly, $N^*$ and 0 are globally asymptotically stable for system (2.27) and (2.28), respectively. Theorem 1.3.2 implies that $\omega_3 = \{W^*\}$ or$\{0\}$, $\omega_4 = \{(N^*, 0)\}$. Therefore, we have $\omega = \{(W^*, 0, 0, N^*, 0, 0, 0)\}$ or $\{(0, 0, 0, N^*, 0, 0, 0)\}$. Consequently, we have $\cup_{\phi \in M_\partial} \omega(\phi) = E_0 \cup E_1$.

Define a continuous function $p : \mathcal{X}_\delta \to \mathbb{R}_+$ by

$$p(\phi) = \min\{\phi_3(0), \phi_6(0)\}, \forall \phi \in \mathcal{X}_\delta.$$

Clearly, $p^{-1}(0, \infty) \subset X_0$. It follows from (2.17) that $p$ has the property that if either $p(\phi) = 0$ and $\phi \in X_0$, or $p(\phi) > 0$, then $p(\Phi(t)\phi) > 0$, for all $t > 0$. Thus $p$ is a generalized distance function for the semiflow $\Phi(t) : \mathcal{X}_\delta \to \mathcal{X}_\delta$. By claim 3, we get that any forward orbit of $\Phi(t)$ in $M_\partial$ converges to $E_0$ or $E_1$, by claim 1 and claim 2, we conclude that $E_0$ and $E_1$ are two isolated invariant sets in $\mathcal{X}_\delta$, and $(W^s(E_0) \cup W^s(E_1)) \cap X_0 = \emptyset$. Moreover, it is easy to see that no subset of $\{E_0, E_1\}$ forms a cycle in $\partial X_0$. By Theorem 1.2.3, it then follows that there exists $\eta > 0$ such that $\liminf_{t \to \infty} p(\Phi(t)\phi) \geq \eta$ for all $\phi \in X_0$, which implies the uniform persistence stated in the theorem. □

The subsequent result shows that the disease dies out if $\mathcal{R}_0 < 1$, provided there is only a small invasion in the $W_2$ and $I$ classes. For any given $M > 0$, denote

$$\begin{aligned}
\mathcal{X}_\delta^M &= \Big\{ \phi \in C([-\tau, 0], [0, M]^7) : \sum_{i=4}^{7} \phi_i(s) \geq \delta, \forall s \in [-\tau, 0], \\
&\phi_2(0) = \int_{-\tau_w}^{0} e^{\mu_w s} \beta_w \frac{\phi_6(s)\phi_1(s)}{\sum_{i=4}^{7} \phi_i(s)} ds, \\
&\phi_5(0) = \int_{-\tau_h}^{0} e^{\mu_h s} \beta_h \frac{\phi_4(s)\phi_3(s)}{\sum_{i=4}^{7} \phi_i(s)} ds \Big\}.
\end{aligned}$$

Then we have the following result.

**Theorem 2.3.2.** *Let (H1) hold. If $\mathcal{R}_0 < 1$, then for every $M > \max\{\frac{H}{\mu_h}, \frac{re^{-a\tau_A}K}{4\mu_w}\}$, there exists a $\zeta = \zeta(M) > 0$ such that for any $\phi \in \mathcal{X}_\delta^M \setminus E_0$ with $(\phi_3(s), \phi_6(s)) \in [0,\zeta]^2$, for any $s \in [-\tau, 0]$, the solution $u(t,\phi)$ of the model system through $\phi$ satisfies* $\lim_{t\to\infty} \parallel u(t,\phi) - E_1 \parallel = 0$.

*Proof.* Let $M > \max\{\frac{H}{\mu_h}, \frac{re^{-a\tau_A}K}{4\mu_w}\}$ be given. From the prove of Theorem 2.2.1, we see that $\mathcal{X}_\delta^M$ is positively invariant for the solution semiflow of the model system. We then have

$$u(t,\phi) \in [0,M]^7, \quad \forall t \geq 0, \phi \in \mathcal{X}_\delta^M.$$

Consider the following linear and monotone system

$$\begin{aligned} \frac{d\tilde{W}_2(t)}{dt} &= \beta_w e^{-\mu_w\tau_w}(\frac{W^\star+\varepsilon}{N^\star-\varepsilon})\tilde{I}(t-\tau_w) - (\mu_w+\varepsilon_w)\tilde{W}_2(t), \\ \frac{d\tilde{I}(t)}{dt} &= \beta_h e^{-\mu_h\tau_h}\tilde{W}_2(t-\tau_h) - (\mu_h+\varepsilon_h+\gamma)\tilde{I}(t). \end{aligned} \tag{2.29}$$

For sufficiently small $\varepsilon > 0$, let $\lambda_2(\varepsilon)$ be the principle eigenvalue of this eigenvalue problem. Clearly, system (2.29) is cooperative. Then we consider the next auxiliary system

$$\begin{aligned} \frac{d\tilde{\tilde{W}}_2(t)}{dt} &= \beta_w e^{-\mu_w\tau_w}(\frac{W^\star+\varepsilon}{N^\star-\varepsilon})\tilde{\tilde{I}}(t-\tau_w) - (\mu_w+\varepsilon_w)\tilde{\tilde{W}}_2(t), \\ \frac{d\tilde{\tilde{I}}(t)}{dt} &= \beta_h e^{-\mu_h\tau_h}\tilde{\tilde{W}}_2(t-\tau_h) - (\mu_h+\varepsilon_h+\gamma)\tilde{\tilde{I}}(t). \end{aligned} \tag{2.30}$$

Let $\lambda_2'(\varepsilon)$ be the principal eigenvalue of the corresponding eigenvalue problem of system (2.30). Then we get $\lambda_2'(\varepsilon) < 0$ if and only if $\beta(\varepsilon) := \frac{\beta_w\beta_h e^{-(\mu_w\tau_w+\mu_h\tau_h)}}{(\mu_w+\varepsilon_w)(\mu_h+\varepsilon_h+\gamma)}\frac{W^\star+\varepsilon}{N^\star-\varepsilon} < 1$. When $\varepsilon = 0$, $\beta(0) = \mathcal{R}_0^2 < 1$. Since $\beta(\varepsilon)$ is continuous with respect to $\varepsilon$, we can choose $\varepsilon$ small enough, such that $\beta(\varepsilon) < 1$, therefore, $\lambda_2'(\varepsilon) < 0$. Following from Theorem 1.1.4, we get $\lambda_2(\varepsilon) < 0$ if and only if $\lambda_2'(\varepsilon) < 0$. Thus, we can restrict $\varepsilon$ small enough

such that $\lambda_2(\varepsilon) < 0$. Let $(e_1, e_2)^T$ be positive right eigenvector associated with $\lambda_2(\varepsilon)$.

Now we consider the following equations:

$$\frac{d\check{W}}{dt} = re^{-a\tau_A}[1 - \frac{\check{W}(t-\tau_A)}{K}]_+\check{W}(t-\tau_A) - \mu_w\check{W}(t) - \varepsilon_w\xi_1, \tag{2.31}$$

$$\frac{d\check{N}}{dt} = H - \mu_h\check{N}(t) - \varepsilon_h\xi_1. \tag{2.32}$$

Choose small $\xi_1 > 0$ and large $T = T(M) > 0$ such that for any solutions of $(\check{W}(t,\phi), \check{N}(t,\phi))$. We then have

$$\check{W}(t) < W^* + \varepsilon,\ \check{N}(t) > N^* - \varepsilon,\ \forall t \geq T.$$

Denote the solution of system (2.29) by $\tilde{u}(t,\phi) = (\tilde{W}_2(t), \tilde{I}(t))$ with respect to initial data $\tilde{\phi} = (\tilde{\phi}_1, \tilde{\phi}_2) \in C([-\tau, 0], [0, M]^2)$. Then for system (2.29), for $\xi_1 > 0$, there exists $\xi_2 > 0$, such that if $(\xi_2 e_1, \xi_2 e_2) \ll (\xi_1, \xi_1)$. Since $\lambda_2(\varepsilon) < 0$, we get that

$$(\xi_2 e_1 e^{\lambda_2(\varepsilon)t}, \xi_2 e_2 e^{\lambda_2(\varepsilon)t}) \ll (\xi_1, \xi_1)), \forall t \geq 0. \tag{2.33}$$

For every solution of the model system through $\phi$, there exists a $\zeta = \zeta(M) > 0$ such that

$$(W_2(t,\phi), I(t,\phi)) \ll (\xi_1, \xi_1), \forall t \in [0, T_1] \tag{2.34}$$

provided that $(\phi_3(s), \phi_6(s)) < (\zeta, \zeta)$.

We further claim that (2.34) holds for all $t \geq 0$. Suppose, by contradiction, that the claim is not true. Then there exists a $T_2 = T_2(\phi) > T_1$ such that $(W_2(t,\phi), I(t,\phi)) \ll (\xi_1, \xi_1)$, for all $t \in [0, T_2)$, and $W_2(T_2, \phi) = \xi_1$ or $I(T_2, \phi) = \xi_1$. By the comparison principle, for $t \in [T_1, T_2]$, we have

$$(W_2(t,\phi), I(t,\phi) \leq (\tilde{W}_2(t,\phi), \tilde{I}(t,\phi) \ll (\xi_1, \xi_1) \tag{2.35}$$

a contradiction. So (2.34) holds for all $t \geq 0$. From (2.33) and (2.35), we see that $\lim_{t\to\infty}(W_2(t,\phi), I(t,\phi)) = (0,0)$. Let $\Phi(t)$ be the solution semiflow of the model system, and let $\omega = \omega(\phi)$ be the omega limit set of $\Phi(t)\phi$, which is an internally chain transitive set for $\Phi(t)$. Hence, we have

$$\omega = \omega_5 \times \{0\} \times \omega_6 \times \{0\} \times \omega_7$$

for some $\omega_5,\ \omega_6 \in C([-\tau, 0], \mathbb{R}^2_+)$ and $\omega_7 \in C([-\tau, 0], \mathbb{R}_+)$. It is easy to see that

$$\Phi(t) \mid_\omega (\psi_1, \psi_2, 0, \psi_4, \psi_5, 0, \psi_7) = (\Phi_5(t)(\psi_1, \psi_2), 0, \Phi_6(t)(\psi_4, \psi_5), 0, \Phi_7(t)\psi_7)$$

where $\psi_1,\ \psi_2,\ \psi_4,\ \psi_5,\ \psi_7 \in C([-\tau, 0], \mathbb{R}_+)$, $\Phi_5(t)$ is the solution semiflow associated with the following system

$$\begin{aligned}
\frac{d\tilde{W}_1(t)}{dt} &= re^{-a\tau_A}[1 - \frac{\tilde{W}_1(t-\tau_A) + \tilde{W}_e(t-\tau_A)}{K}]_+(\tilde{W}_1(t-\tau_A) + \tilde{W}_e(t-\tau_A)) \\
&\quad -\mu_w\tilde{W}_1(t), \\
\frac{d\tilde{W}_e(t)}{dt} &= -\mu_w\tilde{W}_e(t).
\end{aligned}$$

$\Phi_6(t)$ is the solution semiflow associated with

$$\begin{aligned}
\frac{d\bar{S}(t)}{dt} &= H - \mu_h\bar{S}(t), \\
\frac{d\bar{E}(t)}{dt} &= -\mu_h\bar{E}(t).
\end{aligned}$$

and $\Phi_7(t)$ is the solution semiflow associated with

$$\frac{d\tilde{R}(t)}{dt} = -\mu_h\tilde{R}(t).$$

It then follows that $\omega_5,\ \omega_6,\ \omega_7$ are internally chain transitive sets for $\Phi_5(t)$, $\Phi_6(t)$, and $\Phi_7(t)$, respectively. By the analysis of system (2.22), (2.23), (2.27) and (2.24), we get $\omega_5 = \{(W^*, 0)\}$, $\omega_6 = \{(N^*, 0)\}$, and $\omega_7 = \{0\}$. Thus, we have $\omega = \{(W^*, 0, 0, N^*, 0, 0, 0)\}$. It follows that $\lim_{t\to\infty} u(t,\phi) = (W^*, 0, 0, N^*, 0, 0, 0)$. □

## 2.4 Global attractivity

In this section, we study the global attractivity in the model system in the case where the disease-induced death rates of infected mosquitos and human individuals are zero, and the fecundity of infected mosquitos is the same as the susceptible mosquitos. In this case, the model system becomes

$$\begin{aligned}
\frac{dW_1(t)}{dt} &= re^{-a\tau_A}[1-\frac{W(t-\tau_A)}{K}]_+W(t-\tau_A)-\mu_wW_1(t)-\beta_w\frac{I(t)}{N(t)}W_1(t)\\
\frac{dW_e(t)}{dt} &= \beta_w\frac{I(t)}{N(t)}W_1(t)-\mu_wW_e(t)-\beta_we^{-\mu_w\tau_w}\frac{I(t-\tau_w)}{N(t-\tau_w)}W_1(t-\tau_w),\\
\frac{dW_2(t)}{dt} &= \beta_we^{-\mu_w\tau_w}\frac{I(t-\tau_w)}{N(t-\tau_w)}W_1(t-\tau_w)-\mu_wW_2(t),\\
\frac{dS(t)}{dt} &= H-\mu_hS(t)-\beta_hW_2(t)\frac{S(t)}{N(t)},\\
\frac{dE(t)}{dt} &= \beta_hW_2(t)\frac{S(t)}{N(t)}-\mu_hE(t)-\beta_he^{-\mu_h\tau_h}W_2(t-\tau_h)\frac{S(t-\tau_h)}{N(t-\tau_h)}.\\
\frac{dI(t)}{dt} &= \beta_he^{-\mu_h\tau_h}W_2(t-\tau_h)\frac{S(t-\tau_h)}{N(t-\tau_h)}-(\mu_h+\gamma)I(t),\\
\frac{dR(t)}{dt} &= \gamma I(t)-\mu_hR(t).
\end{aligned} \tag{2.36}$$

It is clear that when $\mathcal{R}_0 < 0$, system (2.36) has only two equilibria $E_0$ and $E_1$. However, system (2.36) admits a equilibrium $E^* := (W_1^*, W_e^*, W_2^*, S^*, E^*, I^*, R^*)$ when $\mathcal{R}_0 > 1$, where

$$\begin{aligned}
S^* &= \frac{H(\mu_h\beta_w+\mu_w(\mu_h+\gamma)e^{\mu_h\tau_h})}{\mu_h(\mu_h\beta_w+\mu_w(\mu_h+\gamma)e^{\mu_h\tau_h}\mathcal{R}_0^2)},\\
I^* &= \frac{H\mu_w(\mathcal{R}_0^2-1)}{\mu_h\beta_w+\mu_w(\mu_h+\gamma)e^{\mu_h\tau_h}\mathcal{R}_0^2}.
\end{aligned}$$

and

$$\begin{aligned}
W_2^* &= \frac{(\mu_h+\gamma)N^* e^{\mu_h \tau_h} I^*}{\beta_h S^*},\\
W_1^* &= \frac{\mu_w N^* e^{\mu_w \tau_w} W_2^*}{\beta_w I^*},\\
W_e^* &= (e^{\mu_w \tau_w}-1)W_2^*,\\
E^* &= \frac{(e^{\mu_h \tau_h}-1)(\mu_h+\gamma)I^*}{\mu_h},\\
R^* &= \frac{\gamma I^*}{\mu_h}.
\end{aligned}$$

The following two results show the global attractivity of system (2.36).

**Theorem 2.4.1.** *Let (H1) hold. If $\mathcal{R}_0 < 1$, $\sigma = 1$, and $\varepsilon_w = \varepsilon_h = 0$, then the disease-free equilibrium $E_1$ of the model system is globally attractive in $\mathcal{X}_\delta \setminus E_0$.*

*Proof.* If $\sigma = 0$ and $\varepsilon_w = \varepsilon_h = 0$, the whole mosquitos and human populations admit the following two equations:

$$\begin{aligned}
\frac{dW(t)}{dt} &= re^{-a\tau_A}[1-\frac{W(t-\tau_A)}{K}]_+ W(t-\tau_A) - \mu_w W(t),\\
\frac{dN(t)}{dt} &= H - \mu_h N(t).
\end{aligned}$$

Since $W^*$ and $N^*$ is globally asymptotically stable for the above two equations, respectively, there exists $T = T(\varepsilon) > 0$ such that

$$W(t) \le W^* + \varepsilon,\ N(t) \ge N^* - \varepsilon,\ \forall t \ge T.$$

Thus, when $t \ge T$, we have

$$\begin{aligned}
\frac{dW_2(t)}{dt} &\le \beta_w e^{-\mu_w \tau_w}(\frac{W^*+\varepsilon}{N^*-\varepsilon})I(t-\tau_w) - (\mu_w+\varepsilon_w)W_2(t),\\
\frac{dI}{dt} &\le \beta_h e^{-\mu_h \tau_h} W_2(t-\tau_h) - (\mu_h+\varepsilon_h+\gamma)I(t).
\end{aligned}$$

When $\mathcal{R}_0 < 1$, $\varepsilon$ small enough, by the analysis of system (2.29) and the comparison principle, we then have

$$\lim_{t\to\infty}(W_2(t), I(t)) = (0, 0).$$

It then follows from the theory of asymptotically semiflows (see [32]) that

$$\lim_{t\to\infty}(W_1(t), W_c(t), S(t), E(t), R(t)) = (W^*, 0, N^*, 0, 0).$$

This completes the proof. □

To obtain the global attractivity of the endemic equilibrium, we need the following additional assumption:

(H2) $\beta_w\mu_h \geq \mu_w(\mu_h + \gamma)e^{\tau_h\mu_h}$.

**Theorem 2.4.2.** *Let (H1) and (H2) hold. If $\mathcal{R}_0 > 1$ and $\varepsilon_w = \varepsilon_h = 0$, $\sigma = 1$, then for any $\phi \in \mathcal{X}_\delta$ with $\phi_3(0) \neq 0$, $\phi_6(0) \neq 0$, we have $\lim_{t\to\infty} u(t, \phi) = E^*$.*

*Proof.* When $\varepsilon_w = \varepsilon_h = 0$, $\sigma = 1$, we have

$$\begin{aligned} \frac{dW(t)}{dt} &= re^{-a\tau_A}[1 - \frac{W(t-\tau_A)}{K}]_+ W(t-\tau_A) - \mu_w W(t), \\ \frac{dN(t)}{dt} &= H - \mu_h N(t). \end{aligned} \tag{2.37}$$

When (H1) holds, $(W^*, N^*)$ is globally asymptotically stable for system (2.37). Hence, we have the following limiting system:

$$
\begin{aligned}
\frac{dW_1(t)}{dt} &= A - \mu_w W_1(t) - \beta'_w I(t) W_1(t), \\
\frac{dW_e(t)}{dt} &= \beta'_w I(t) W_1(t) - \mu_w W_e(t) - \beta'_w e^{-\mu_w \tau_w} I(t-\tau_w) W_1(t-\tau_w), \\
\frac{dW_2(t)}{dt} &= \beta'_w e^{-\mu_w \tau_w} I(t-\tau_w) W_1(t-\tau_w) - \mu_w W_2(t), \\
\frac{dS(t)}{dt} &= H - \mu_h S(t) - \beta'_h W_2(t) S(t), \\
\frac{dE(t)}{dt} &= \beta'_h W_2(t) S(t) - \mu_h E(t) - \beta'_h e^{-\mu_h \tau_h} W_2(t-\tau_h) S(t-\tau_h), \\
\frac{dI(t)}{dt} &= \beta'_h e^{-\mu_h \tau_h} W_2(t-\tau_h) S(t-\tau_h) - (\mu_h + \gamma) I(t), \\
\frac{dR(t)}{dt} &= \gamma I(t) - \mu_h R(t).
\end{aligned} \tag{2.38}
$$

where $A = W^* \mu_w$, $\beta'_w = \beta_w / N^*$, $\beta'_h = \beta_h / N^*$.

Let $g(t-\tau_w) = W_1(t-\tau_w) + e^{\mu_w \tau_w} W_2(t)$, that is $g(t) = W_1(t) + e^{\mu_w \tau_w} W_2(t+\tau_w)$. It follows that

$$
\begin{aligned}
g'(t) &= W'_1(t) + e^{\mu_w \tau_w} W'_2(t+\tau_w) \\
&= A - \mu_w (W_1(t) + e^{\mu_w \tau_w} W_2(t+\tau_w)) \\
&= A - \mu_w g(t).
\end{aligned}
$$

Then the equilibrium $A/\mu_w = W^*$ is globally asymptotically stable. For system (2.38), we then consider the following limiting system:

$$
\frac{d\bar{W}_2(t)}{dt} = \beta'_w e^{-\mu_w \tau_w} \bar{I}(t-\tau_w)(W^* - e^{\mu_w \tau_w} \bar{W}_2(t)) - \mu_w \bar{W}_2(t), \tag{2.39}
$$

$$
\frac{d\bar{S}(t)}{dt} = H - \mu_h \bar{S}(t) - \beta'_h \bar{S}(t) \bar{W}_2(t), \tag{2.40}
$$

$$
\frac{d\bar{I}(t)}{dt} = \beta'_h e^{-\mu_h \tau_h} \bar{S}(t-\tau_h) \bar{W}_2(t-\tau_h) - (\mu_h + \gamma) \bar{I}(t). \tag{2.41}
$$

**Claim.** *The set* $\mathcal{D} := C([-\tau, 0], [0, W^* e^{-\mu_w \tau_w}] \times \mathbb{R}^2_+)$ *is positively invariant for system (2.39)-(2.41).*

To prove this claim, we define $F(\psi) :=$

$$\begin{pmatrix} \beta'_w e^{-\mu_w \tau_w} \psi_3(-\tau_w)(W^* - e^{\mu_w \tau_w} \psi_1(0)) - \mu_w \psi_1(0) \\ H - \mu_h \psi_2(0) - \beta'_h \psi_1(0) \psi_2(0) \\ \beta'_h e^{-\mu_h \tau_h} \psi_1(-\tau_h) \psi_2(-\tau_h)) - (\mu_h + \gamma) \psi_3(0) \end{pmatrix}, \ \forall \psi \in \mathcal{D}.$$

Note that $\mathcal{D}$ is relatively closed in $C([-\tau, 0], \mathbb{R}^3)$, and $F(\psi)$ is continuous and Lipschitz in $\psi$ in each compact set in $\mathbb{R} \times \mathcal{D}$. By [16, Theorem 2.3], it follows that for all $\psi \in \mathcal{D}$, there is an unique solution of system (2.39)-(2.41) through $(0, \psi)$ on its maximal interval of existence. Since $F_i(\psi) \geq 0$ whenever $\psi \in \mathcal{D}$ with $\psi_i(0) = 0$, Theorem 1.1.1 implies that the solution of (2.39)-(2.41) are nonnegative for all $t$ in its maximal interval of existence. Furthermore, if $\psi_1(0) = W^* e^{-\mu_w \tau_w}$, then $F_1(\psi) \leq 0$. It follows by [29, Remark 5.2.1] that $\bar{W}_2(t, \psi) \leq W^* e^{-\mu_w \tau_w}$ for all $t > 0$. Thus, $\mathcal{D}$ is positively invariant.

By the arguments similar to those in Theorem 2.3.1, it easily follows that system (2.39)-(2.41) is uniformly persistent in the sense that there exists a $\eta_1 > 0$ such that for any given $\psi = (\psi_1, \psi_2, \psi_3) \in \mathcal{D}$ with $\psi_1(0) \neq 0$, $\psi_3(0) \neq 0$, the solution $(\bar{W}_2(t, \psi), \bar{S}(t, \psi), \bar{I}(t, \psi))$ of (2.39)-(2.41) satisfies

$$\liminf_{t \to \infty} (\bar{W}_2(t, \psi), \bar{I}(t, \psi)) \geq (\eta_1, \eta_1).$$

For any given $\psi \in \mathcal{D}$ with $\psi_1(0) \neq 0$ and $\psi_3(0) \neq 0$, let $(\bar{W}_2(t), \bar{S}(t), \bar{I}(t)) = (\bar{W}_2(t, \psi), \bar{S}(t, \psi), \bar{I}(t, \psi))$. In order to use the method of fluctuations (see, e.g., [18, 33, 39]) for system (2.39)-(2.41), we define

$$\begin{aligned} \bar{W}_2^\infty &= \limsup_{t \to \infty} \bar{W}_2(t), \ \bar{W}_{2\infty} = \liminf_{t \to \infty} \bar{W}_2(t); \\ \bar{S}^\infty &= \limsup_{t \to \infty} \bar{S}(t), \ \bar{S}_\infty = \liminf_{t \to \infty} \bar{S}(t); \\ \bar{I}^\infty &= \limsup_{t \to \infty} \bar{I}(t), \ \bar{I}_\infty = \liminf_{t \to \infty} \bar{I}(t). \end{aligned}$$

Clearly, $\bar{W}_2^\infty \geq \bar{W}_{2\infty} \geq \eta_1 > 0$, $\bar{S}^\infty \geq \bar{S}_\infty$ and $\bar{I}^\infty \geq \bar{I}_\infty \geq \eta_1 > 0$. Further, there exist sequences $t_n^i \to \infty$ and $\sigma_n^i \to \infty$, $i = 1, 2, 3$, such that

$$\begin{aligned}
\lim_{n\to\infty} \bar{W}_2(t_n^1) &= \bar{W}_2^\infty, \bar{W}_2'(t_n^1) = 0, \forall n \geq 1;\\
\lim_{n\to\infty} \bar{W}_2(\sigma_n^1) &= \bar{W}_{2\infty}, \bar{W}_2'(\sigma_n^1) = 0, \forall n \geq 1;\\
\lim_{n\to\infty} \bar{S}(t_n^2) &= \bar{S}^\infty, \bar{S}'(t_n^2) = 0, \forall n \geq 1;\\
\lim_{n\to\infty} \bar{S}(\sigma_n^2) &= \bar{S}_\infty, \bar{S}'(\sigma_n^2) = 0, \forall n \geq 1;\\
\lim_{n\to\infty} \bar{I}(t_n^3) &= \bar{I}^\infty, \bar{I}'(t_n^3) = 0, \forall n \geq 1;\\
\lim_{n\to\infty} \bar{I}(\sigma_n^3) &= \bar{I}_\infty, \bar{I}'(\sigma_n^3) = 0, \forall n \geq 1.
\end{aligned}$$

Let $m_1 = \beta_w e^{-\mu_w \tau_w} W^*/N^*$ and $m_2 = \beta_h e^{-\mu_h \tau_h}/N^*$. It then follows from (2.39) and the above claim that

$$\begin{aligned}
\bar{I}^\infty(m_1 - \beta_w' \bar{W}_2^\infty) - \mu_w \bar{W}_2^\infty \geq 0 \geq \bar{I}_\infty(m_1 - \beta_w' \bar{W}_2^\infty) - \mu_w \bar{W}_2^\infty,\\
\bar{I}^\infty(m_1 - \beta_w' \bar{W}_{2\infty}) - \mu_w \bar{W}_{2\infty} \geq 0 \geq \bar{I}_\infty(m_1 - \beta_w' \bar{W}_{2\infty}) - \mu_w \bar{W}_{2\infty},
\end{aligned}$$

and hence,

$$\bar{I}^\infty \geq \frac{\mu_w \bar{W}_2^\infty}{m_1 - \beta_w' \bar{W}_2^\infty} \geq \frac{\mu_w \bar{W}_{2\infty}}{m_1 - \beta_w' \bar{W}_{2\infty}} \geq \bar{I}_\infty. \tag{2.42}$$

By (2.40), we have

$$\begin{aligned}
H - \bar{S}^\infty(\mu_h + \beta_h' \bar{W}_{2\infty}) \geq 0 \geq H - \bar{S}^\infty(\mu_h + \beta_h' \bar{W}_2^\infty),\\
H - \bar{S}_\infty(\mu_h + \beta_h' \bar{W}_{2\infty}) \geq 0 \geq H - \bar{S}_\infty(\mu_h + \beta_h' \bar{W}_2^\infty),
\end{aligned}$$

which implies that

$$\frac{H}{\mu_h + \beta_h' \bar{W}_{2\infty}} \geq \bar{S}^\infty \geq \bar{S}_\infty \geq \frac{H}{\mu_h + \beta_h' \bar{W}_2^\infty}. \tag{2.43}$$

In view of (2.41), we obtain

$$m_2\bar{S}^\infty\bar{W}_2^\infty - (\mu_h+\gamma)\bar{I}^\infty \geq 0 \geq m_2\bar{S}_\infty\bar{W}_{2\infty} - (\mu_h+\gamma)\bar{I}^\infty,$$
$$m_2\bar{S}^\infty\bar{W}_2^\infty - (\mu_h+\gamma)\bar{I}_\infty \geq 0 \geq m_2\bar{S}_\infty\bar{W}_{2\infty} - (\mu_h+\gamma)\bar{I}_\infty,$$

and hence,

$$\frac{m_2\bar{S}^\infty\bar{W}_2^\infty}{\mu_h+\gamma} \geq \bar{I}^\infty \geq \bar{I}_\infty \geq \frac{m_2\bar{S}_\infty\bar{W}_{2\infty}}{\mu_h+\gamma}. \tag{2.44}$$

Therefore, combining (2.43) and (2.44) together, we get

$$\frac{H}{\mu_h+\beta_h'\bar{W}_{2\infty}}\frac{m_2\bar{W}_2^\infty}{\mu_h+\gamma} \geq \bar{I}^\infty \geq \bar{I}_\infty \geq \frac{H}{\mu_h+\beta_h'\bar{W}_2^\infty}\frac{m_2\bar{W}_{2\infty}}{\mu_h+\gamma}. \tag{2.45}$$

Comparing (2.42) with (2.45), we obtain

$$\frac{H}{\mu_h+\beta_h'\bar{W}_{2\infty}}\frac{m_2\bar{W}_2^\infty}{\mu_h+\gamma} \geq \frac{\mu_w\bar{W}_2^\infty}{m_1-\beta_w'\bar{W}_2^\infty};$$
$$\frac{H}{\mu_h+\beta_h'\bar{W}_2^\infty}\frac{m_2\bar{W}_{2\infty}}{\mu_h+\gamma} \leq \frac{\mu_w\bar{W}_{2\infty}}{m_1-\beta_w'\bar{W}_{2\infty}}.$$

Simplifying the above two inequalities, we get

$$\beta_w\mu_h(\bar{W}_2^\infty - \bar{W}_{2\infty}) \leq \mu_w(\mu_h+\gamma)e^{-\tau_h\mu_h}(\bar{W}_2^\infty - \bar{W}_{2\infty})$$

Since condition $(H2)$ holds, we have $W_2^\infty = W_{2\infty}$. By (2.43) and (2.45), we get $S^\infty = S_\infty$ and $I^\infty = I_\infty$. It follows that $\lim_{t\to\infty}(\bar{W}_2(t), \bar{S}(t), \bar{I}(t)) = (W_2^*, S^*, I^*)$ for any $\psi \in \mathcal{D}$ with $\psi_1(0) \neq 0$ and $\psi_3(0) \neq 0$.

Now we define for system (2.38) that

$$\begin{aligned}\omega^* \quad := \quad & \{(\phi_3,\phi_4,\phi_6) \in C([-\tau,0],\mathbb{R}^3_+), \lim_{n\to\infty}(W_2(t_n+\cdot), S(t_n+\cdot), I(t_n+\cdot)) = \\ & (\phi_3,\phi_4,\phi_6) \ for \ some \ t_n \to \infty \ as \ n \to \infty\}.\end{aligned}$$

By similar arguments as in Theorem 2.2.1, it follows that $\omega^*$ is a nonempty and compact subset of $C([-\tau, 0], \mathbb{R}^3_+)$. Since for any $t_n$,

$$W^* = \lim_{t_n \to \infty} g(t_n - \tau_w) = \lim_{t_n \to \infty} (W_1(t_n - \tau_w) + e^{\mu_w \tau_w} W_2(t_n))$$

Thus, we have

$$\lim_{t_n \to \infty} W_2(t_n) \leq W^* e^{-\mu_w \tau_w}.$$

Therefore, we obtain that $\omega^* \subset \mathcal{D}$.

By the above claim and the continuous-time version of [42, Lemma 1.2.2], it follows that $\omega^*$ is an internally chain transitive set for the solution semiflow of system (2.39)-(2.41) on the positively invariant set $\mathcal{D}$. Then by Theorem 1.3.2, $\omega^* = \{(W_2^*, S^*, I^*)\}$ or $\{(0, N^*, 0)\}$. By similar argument of Theorem 2.3.1, $\omega^* \neq \{(0, N^*, 0)\}$. Therefore, $\omega^* = \{(W_2^*, S^*, I^*)\}$. Hence, we have, for system (2.38),

$$\begin{aligned} \lim_{n \to \infty} W_1(t_n + \cdot) &= \lim_{n \to \infty} (g(t_n + \cdot) - e^{\mu_w \tau_w} W_2(t_n + \tau_w + \cdot)) \\ &= W^* - e^{\mu_w \tau_w} W_2^* = W_1^*, \ \forall t_n \to \infty \ as \ n \to \infty. \end{aligned}$$

Let $\Phi'(t)$ be the solution semiflow of system (2.38). By similar argument as Theorem 2.2.1 for the model system, we obtain that $\Phi'(t)$ is compact for any $t > \tau$. Let $\omega' = \omega'(\phi)$ be the omega limit set of $\Phi'(t)\phi$. It then follows from Theorem 1.3.1 that $\omega'$ is an internally chain transitive set for $\Phi'(t)$. Hence, we have

$$\omega' = W_1^* \times \omega_1' \times \{(W_2^*, S^*)\} \times \omega_2' \times \{I^*\} \times \omega_3'.$$

for some $\omega_i' \in C([-\tau, 0], \mathbb{R}_+)$, $i = 1, 2, 3$. It is easy to see that

$$\Phi'(t) \mid_{\omega'} (W_1^*, \psi_2, W_2^*, S^*, \psi_5, I^*, \psi_7) = (W_1^*, \Psi'(\psi_2), W_2^*, S^*, \Psi'(\psi_5), I^*, \Psi'(\psi_7)).$$

where $\psi_1,\ \psi_2,\ \psi_7 \in C([-\tau,0],\mathbb{R}_+)$, $\Phi_1'(t)$ is the solution semiflow associated with

$$\frac{du_1(t)}{dt} = \beta_w' I^* W_1^*(1 - e^{-\mu_w \tau_w}) - \mu_w u_1(t), \tag{2.46}$$

$\Phi_2'(t)$ is the solution semiflow associated with

$$\frac{du_2(t)}{dt} = \beta_h' S^* W_2^*(1 - e^{-\mu_h \tau_h}) - \mu_w u_2(t), \tag{2.47}$$

and $\Phi_3'(t)$ is the solution semiflow associated with

$$\frac{du_3(t)}{dt} = \gamma I^* - \mu_h u_3(t). \tag{2.48}$$

Since $\omega'$ is an internally chain transitive set for $\Phi'(t)$, it then follows that $\omega_1'$, $\omega_2'$, $\omega_3'$ are also internally chain transitive sets for $\Phi_1'(t)$, $\Phi_2'(t)$, $\Phi_3'(t)$, respectively. Clearly, $W_c^*$, $E^*$, $R^*$ are the unique equilibrium point and globally asymptotically stable for (2.46), (2.47) and (2.48), respectively. Therefore, by Theorem 1.3.2, we get $\omega_1' = \{W_c^*\}$, $\omega_2' = \{E^*\}$, and $\omega_3' = \{R^*\}$. Thus, we have $\omega' = E^*$. □

## 2.5 Numerical simulations

In this section, we carry out numerical simulations to illustrate our analytic results.

In view of [35], we fix $\tau_A = 10$, $\tau_w = 10$, $\tau_h = 5$, and then take three sets of values of other parameters to perform the numerical simulations.

First, we take $\beta_w = 0.06$, $\beta_h = 0.15$, $r = 1$, $a = 0.2$, $\gamma = 0.15$, $\mu_w = 0.1$, $\mu_h = 0.0001$, $H = 0.001$, $K = 10$, $\sigma = 0.8$, $\varepsilon_w = 0.01$, $\varepsilon_h = 0.0001$. It is easy to verify that condition (H1) holds, and $\mathcal{R}_0 = 0.174$, $W^* = 2.61$, $N^* = 10$. It follows from Theorem 3.2 that when $W_2(s)$ and $I(s)$, $s \in [-\tau, 0]$, are small, the disease will die out (see Figure 2.1).

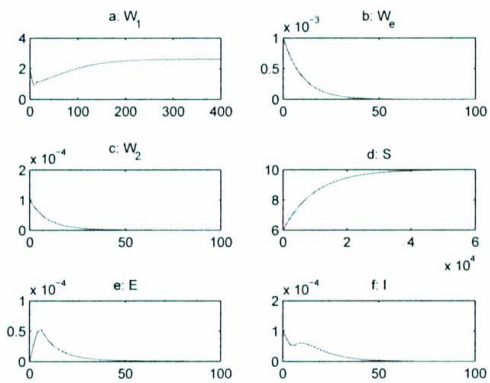


Figure 2.1: *Long-term behavior of the population of each class when* $\mathcal{R}_0 < 1$ *and the invasion is small.*

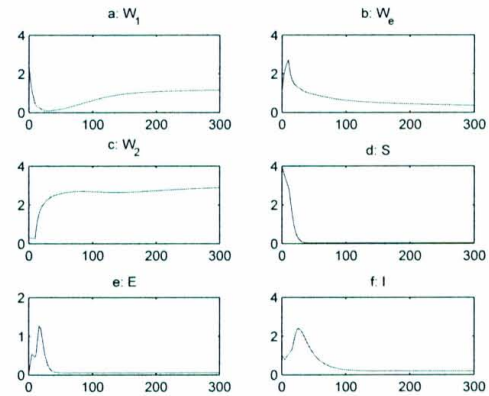


Figure 2.2: $E^*$ *is globally asymptotically attractive when* $\mathcal{R}_0 > 1$ *and conditions (H1) and (H2) hold.*

Second, we take $\beta_w = 0.9$, $\beta_h = 0.5$, $r = 1$, $a = 0.4$, $\gamma = 0.05$, $\mu_w = 0.01$, $\mu_h = 0.001$, $H = 0.1$, $K = 10$, $\sigma = 1$, $\varepsilon_w = \varepsilon_h = 0$. Then we get that (H1) and (H2) hold, and $\mathcal{R}_0 = 17.509$, $W^* = 4.540$, $N^* = 10$. By Theorem 2.4.2, we obtain

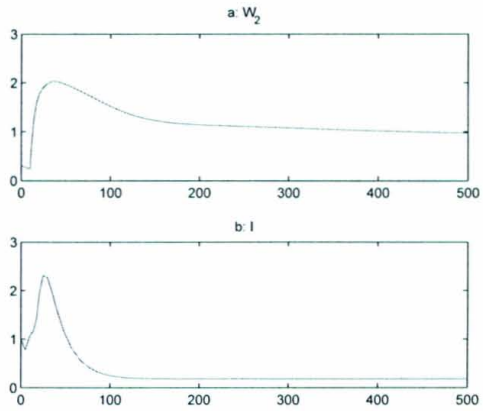


Figure 2.3: *Persistence of infected mosquitos and human individuals.*

$E^* = (1.655, 0.275, 2.610, 0.076, 0.049, 0.1936, 9.681)$ is globally attractive (see Figure 2.2).

Third, we take $\beta_w = 0.9$, $\beta_h = 0.5$, $r = 1$, $a = 0.4$, $\gamma = 0.05$, $\mu_w = 0.01$, $\mu_h = 0.001$, $H = 0.1$, $K = 10$, $\sigma = 0.8$, $\varepsilon_w = 0.01$, $\varepsilon_h = 0.0001$, we get $\mathcal{R}_0 = 11.462$. We can see that the disease is uniform persistence. Figure 2.3 indicates the behavior of the infectious mosquitos and infectious human population.

# Chapter 3

# A Within-Host Virus Model with Periodic Multidrug Therapy

## 3.1 Introduction

In recent years, mathematical models have shown great values in the understanding of within-host viral infections. In particular, periodic models are always formulated to account for impact of seasonal, or diurnal environmental drivers on host-pathogen interactions such as seasonal changes in host social behavior and contact rates, annual pulses of host births and deaths changes, and changes in host immune defense system [1].

Perelson and Nelson [26], Nowak and May [25] provide a standard model, comprised of three state variables corresponding to concentration of uninfected target cells, productively infected cells and free virus particles. Antiviral medicines used to treat these infections can be incorporated into mathematical models and the effect of

the drugs on the dynamics of the system is an interesting and practical problem to investigate. In the treatment, the drugs are most commonly prescribed to be taken on a fixed dose, fixed time-interval basis. For example, in HIV treatment the P-inhibitor ritonavir is usually taken once every 12 hours, and the RT-inhibitor tenofovir DF is usually taken once every 24 hours [12]. Therefore, the drug efficacy functions are periodic in time. De Leenheer [9] and Browne and Pilyugin [4] took the drug efficacy function of the bang-bang type, that is, at each moment during the period of the treatment cycle, the drug is either active at a fixed efficiency level or it is inactive. The drug is thus characterized by two parameters: its efficiency level when active, and the duration of the activity. Papers [12, 28] provide detailed pharmacokinetic models, and characterize the drug efficacy functions by a quick rise of the efficacy to a peak value right after drug intake, followed by a slower decay.

As a starting point, we consider a classical within-host virus model [26, 25] with periodic multidrug treatment. Note that, we focus primarily on HIV models here but, following by [4, 9], the basic model applies to many other important infections such as hepatitis B [14] and C [15], influenza [13] and malaria parasite P. *falciparum* [24].

A brief review of the salient features of HIV in the disease will be helpful. HIV is a RNA virus. First, the HIV enters its target, CD4+ cell. Inside this cell, it makes a DNA copy of its RNA genome. In this process, it needs the enzyme reverse transcriptase (RT). This DNA copy is then integrated into the DNA of the infected cell. The viral DNA, called the provirus, is then duplicated with the cell's DNA every time the cell divided, and henceforth, the viral particles can bud off the cell to infect other healthy cells. Once infected, a cell remains infected for life. Before leaving the host cell, the virus particle is equipped with protease, an enzyme used to

cleave a long protein chain. If this feature is lost, the virus particle is not capable of successfully infecting other T cells, and the P-inhibitors are the drugs that target this step. Currently, there are four classes of antiretroviral drugs available in the treatment of HIV infected patients: nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and entry/fusion inhibitors [4]. The main drugs are RT-inhibitor and R-inhibitor, and in practice, cocktails of several of these drugs have been very common and most successful [12].

In this chapter, we employ the theory of basic reproduction ratios and uniform persistence for periodic systems, which are two important techniques to address the disease dynamics in a periodic environment. The basic reproduction number $R_0$ is defined as the expected number of secondary infections arising from a single individual during his or her entire infectious period, in a population of susceptible. The concept of next generation matrix was used in [11, 34] to define $R_0$ for autonomous epidemic models, and was further extended in [3, 36] to periodic epidemic models, and the developed theory has been applied to various scenarios such as HIV [21], malaria [22], tuberculosis [19] and rabies [40]. Persistence theory addresses a long term survival of the pathogen in a system, and can be used to show that the pathogen remains endemic when the basic reproduction ratio is great than one.

The purpose of this chapter is to study the impact of periodic drug treatment on the dynamic behavior of a standard within-host virus model. Mathematically, we obtain a nonlinear periodic ordinary differential system, define the basic reproduction ratio, and establish a threshold result in terms of the basic reproduction ratio (Section 3). Motivated by [4], we further investigate the optimizing phase shifts of the RT-inhibitor and P-inhibitor drug efficacy functions (optimal in the sense of minimizing

the basic reproduction ratio). If only one drug is used in a treatment, shifting the phase of the drug efficacy function does not change the dynamics of the model system. If, however, both the RT-inhibitor and P-inhibitor are used, then these phase shifts can completely change the dynamics. In the numerical study (Section 4), we first consider a simple case of HIV treatment, where the efficacy functions are of the bang-bang type. Then we investigate the case of using the actual pharmacokinetic models of the drug efficacies. A brief discussion section completes the chapter.

## 3.2 The global dynamics

We first give a brief review on the classical within-host model [26, 25]:

$$\begin{aligned} \frac{dT}{dt} &= f(T) - kVT, \\ \frac{dT^*}{dt} &= kVT - \beta T^*, \\ \frac{dV}{dt} &= N\beta T^* - \gamma V. \end{aligned} \tag{3.1}$$

Here $T$, $T^*$, $V$ denote the concentrations of healthy and infected cells, and free virus particles, respectively. All parameters are assumed to be positive. $\beta$ and $\gamma$ are the decay rates of infected cells and virus particles, respectively. $kVT$, a term of mass action type, models the rate at which free virus infects a healthy cell, and $N$ is the average number of virus particles budding off an infected cell during its lifetime. The (net) growth rate of healthy cell population is given by a smooth function $f(T) : \mathbb{R}_+ \to \mathbb{R}$, which has the property that there exists $T_0 > 0$, such that $f(T)(T - T_0) < 0$, for all $T \neq T_0$ and $f'(T_0) < 0$. The class of admissible $f(T)$ is quite large, and contains two most popular choices:

1) Pereson and Nelson [26]: $f(T) = f_1(T) = a - bT + pT(1 - \frac{T}{T_{max}})$;

2) Nowak and May [25]: $f(T) = f_2(T) = a - bT$.

Clearly, the continuity of $f$ implies that $f(T_0) = 0$. It then follows that $E_0 = (T_0, 0, 0)$ is the unique infection free equilibrium of (3.1). System (3.1) also admits a positive equilibrium (endemic equilibrium), $\bar{E} = (\bar{T}, \bar{T}^*, \bar{V})$, provided that $f(\frac{\gamma}{kN}) > 0$, where $\bar{T} = \frac{\gamma}{kN}$, $\bar{T}^* = \frac{f(\bar{T})}{\beta}$, $\bar{V} = \frac{f(\bar{T})}{k\bar{T}}$. By considering the fate of a single productively infected cell in an otherwise healthy individual with normal target cell level $T = T_0$, we can determine the basic reproduction number $\bar{\mathcal{R}}_0$ for model (3.1): The infected cell produces $N$ virions, each with life span $\gamma^{-1}$, which will infect $\frac{kT_0N}{\gamma}$ healthy target cells. Hence, $\bar{\mathcal{R}}_0 = \frac{kT_0N}{\gamma}$. In terms of $\bar{\mathcal{R}}_0$, [10] gives an excellent analysis of the global dynamics of system (3.1).

**Theorem 3.2.1.** ([10, LEMMAS 3.2 AND 3.5])
*If $\bar{\mathcal{R}}_0 > 1$, then $E_0$ is unstable and the infection persists in the sence that there exists $\epsilon > 0$ such that $\liminf_{t\to\infty}(T(t), T^*(t), V(t)) > (\epsilon, \epsilon, \epsilon)$ for initial condition satisfying $T^*(0) + V(0) > 0$. If $\bar{\mathcal{R}}_0 < 1$, then $E_0$ is globally asymptotically stable.*

Assuming that currently the HIV cannot be eradicated in an individual, that is, $\bar{\mathcal{R}}_0 > 1$. Then we incorporate a treatment of two types of drugs, RT-inhibitor and P-inhibitor, and modify the model as following:

$$\begin{aligned} \frac{dT(t)}{dt} &= f(T) - k(1 - \eta_{RT}(t))VT, \\ \frac{dT^*(t)}{dt} &= k(1 - \eta_{RT}(t))VT - \beta T^*, \\ \frac{dV(t)}{dt} &= N(1 - \eta_P(t))\beta T^* - \gamma V. \end{aligned} \tag{3.2}$$

where $\eta_{RT}(t)$, $\eta_P(t) : \mathbb{R} \to [0,1]$ are the drug efficacy functions of the RT-inhibitor and P-inhibitor, respectively. For realistic consideration, we assume $\eta_{RT}(t)$, $\eta_P(t) \not\equiv 0$, or 1, and suppose that both $\eta_{RT}(t)$ and $\eta_P(t)$ are periodic and share a common period $\omega$.

**Theorem 3.2.2.** *System (3.2) has a unique and bounded solution with initial value in $\mathbb{R}^3_+$. Further, the compact set*

$$\mathcal{D} := \left\{ (T, T^*, V) \in \mathbb{R}^3_+ : T \le T_0, T^* \le A + T_0 + 1, V \le \frac{N\beta(A + T_0 + 1)}{\gamma} \right\}$$

*is positively invariant and attracts all positive orbits in $\mathbb{R}^3_+$.*

*Proof.* We use the argument similar to that in the proof of [10, Lemma 3.1]. By Theorem 1.1.1, it follows that for any $(T(0), T^*(0), V(0)) \in \mathbb{R}^3_+$, system (3.2) has a unique local nonnegative solution $(T(t), T^*(t), V(t))$ through the initial value $(T(0), T^*(0), V(0))$.

Since $\frac{dT(t)}{dt} \le f(T)$, $\forall t \ge 0$, we see that $\limsup_{t\to\infty} T(t) \le T_0$. Then for large $t$, say $t > t_0$, we have $T(t) < T_0 + 1$. Let $S = \max_{T\ge 0} f(T)$. By the first two equations of system (3.2), we obtain that $\frac{d}{dt}(T(t) + T^*(t)) = f(T) - \beta T^* \le S - \beta T^*$. Let $A > 0$ be such that $\beta A > S + 1$. Then as long as $T(t) + T^*(t) > A + T_0 + 1$ and $t > t_0$, we have $\frac{d}{dt}(T(t) + T^*(t)) < -1$. Clearly, there exists $t_1 > t_0$ such that $T(t) + T^*(t) < A + T_0 + 1$ for all $t \ge t_1$. Clearly, $T^*(t) < A + T_0 + 1$ for all $t \ge t_1$. Then we have $\frac{dV(t)}{dt} \le N\beta T^* - \gamma V < N\beta(A + T_0 + 1) - \gamma V$ for all $t \ge t_1$. Then we have $\lim_{t\to\infty} V(t) \le \frac{N\beta(A+T_0+1)}{\gamma}$. It concludes that the solution is ultimately bounded. Hence, the solutions of system (3.2) exist globally on the interval $[0, \infty)$, and $\mathcal{D}$ is positively invariant and attracts all positive orbits in $\mathbb{R}^3_+$. □

We then introduce the basic reproduction ratio $\mathcal{R}_0$ for system (3.2) by using the next generation operators approach (see [3, 36]). By previous analysis, system (3.2)

has exactly one infection free equilibrium $E_0$. The equations for infected cells and virus particles of the linearized system for (3.2) at $E_0$ are

$$\begin{aligned} \frac{dT^*(t)}{dt} &= k(1-\eta_{RT}(t))T_0V - \beta T^*, \\ \frac{dV(t)}{dt} &= N(1-\eta_P(t))\beta T^* - \gamma V. \end{aligned} \tag{3.3}$$

Set

$$F(t) := \begin{pmatrix} 0 & k(1-\eta_{RT}(t))T_0 \\ N\beta(1-\eta_P(t)) & 0 \end{pmatrix}, \quad G(t) := \begin{pmatrix} \beta & 0 \\ 0 & \gamma \end{pmatrix}.$$

Let $\Phi_A(t)$ and $\rho(\Phi_A(\omega))$ be the monodromy matrix of the linear $\omega$-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 $\omega$-periodic system

$$\frac{dy}{dt} = -G(t)y, \tag{3.4}$$

that is, for each $s \in \mathbb{R}$, the $2 \times 2$ 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 $2 \times 2$ identity matrix. Thus, the monodromy matrix $\Phi_{-G}(t)$ of system (3.4) equals to $Y(t,0)$, $t \geq 0$.

In view of the periodic environment, we assume that $\phi(s)$, $\omega$-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 $C_\omega$ be the ordered Banach space of all $\omega$-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

$$(L\phi)(t) = \int_0^\infty Y(t, t-a)F(t-a)\phi(t-a)da, \ \forall t \in \mathbb{R}, \ \phi \in C_\omega. \tag{3.5}$$

Following [36], 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 the special case of $\eta_{RT}(t) = \eta_{RT}$, $\eta_P(t) = \eta_P$, $\forall t \geq 0$, we obtain

$$F = \begin{pmatrix} 0 & k(1-\eta_{RT})T_0 \\ N\beta(1-\eta_P) & 0 \end{pmatrix}, \ and \ G = \begin{pmatrix} \beta & 0 \\ 0 & \gamma \end{pmatrix}.$$

It then follows from [34] that

$$\mathcal{R}_0 = \rho(FG^{-1}) = \sqrt{\frac{kNT_0(1-\eta_{RT})(1-\eta_P)}{\gamma}}.$$

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

$$\frac{dw}{dt} = \Big( -G(t) + \frac{1}{\lambda}F(t) \Big) w, \ t \in \mathbb{R}. \tag{3.6}$$

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 (3.2) satisfies assumptions $(A_1)-(A_7)$ in [36]. Thus, we have the two results as in Theorems 1.4.1 and 1.4.2 corresponding to our system.

**Theorem 3.2.3.** *If the basic reproduction number $\mathcal{R}_0 < 1$, then the unique infection free equilibrium $E_0$ is globally asymptotically stable.*

*Proof.* By Theorem 1.4.2, we know that when $\mathcal{R}_0 < 1$, $E_0$ is locally asymptotically stable. It suffices to prove that $E_0$ is globally attractive if $\mathcal{R}_0 < 1$.

By Theorem 3.2.2, it follows that for any $\varepsilon > 0$, there exists large $t_0 > 0$ such that $T(t) < T_0 + \varepsilon$ when $t > t_0$. Then for system (3.2), we have, when $t > t_0$, that

$$\begin{aligned} \frac{dT^*(t)}{dt} &\leq k(1-\eta_{RT}(t))(T_0+\varepsilon)V - \beta T^*, \\ \frac{dV(t)}{dt} &= N(1-\eta_P(t))\beta T^* - \gamma V. \end{aligned}$$

Considering the following comparison system

$$\frac{dh(t)}{dt} = (F(t) - G(t) + M_\varepsilon)h(t). \tag{3.7}$$

where

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

By Theorem 1.4.2, we know that $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-G}(\omega)) < 1$. We can choose $\varepsilon$ small enough such that $\rho(\Phi_{F-G+M_\varepsilon}(\omega)) < 1$.

By [41, Lemma 2.1], it follows that there exists a positive, $\omega$-periodic function $\bar{h}(t)$ such that $h(t) = e^{\theta t}\bar{h}(t)$ is a solution of system (3.7), where $\theta = \frac{1}{\omega}\ln\rho(\Phi_{F-G+M_\varepsilon}(\omega))$. Since $\rho(\Phi_{F-G+M_\varepsilon}(\omega)) < 1$, $\theta$ is a negative constant. Therefore, we have $h(t) \to 0$ as $t \to \infty$. For any nonnegative initial value $(T^*(0), V(0))^T$ for system (3.2), there is a sufficiently large $M^* > 0$, such that $(T^*(0), V(0))^T \leq M^*\bar{h}(0)$ holds. By the comparison principle [30, Theorem B.1], we have $(T^*(t), V(t))^T \leq M^*h(t)$, for all $t \geq 0$, where $M^*h(t)$ is also a solution for system (3.7). Therefore, we get $T^*(t) \to 0$

and $V(t) \to 0$ as $t \to \infty$. By asymptotically autonomous semiflows [32], it then follows that $T(t) \to T_0$ as $t \to \infty$. □

Define

$$X_0 := \{(T, T^*, V) \in \mathbb{R}^3_+ : \ T^* > 0, V > 0\}, \quad \partial X_0 := \mathbb{R}^3_+ \setminus X_0.$$

Let $P : \mathbb{R}^3_+ \to \mathbb{R}^3_+$ be the Poincaré map associated with system (3.2), that is

$$P(x_0) = u(\omega, x_0), \ \forall x_0 \in \mathbb{R}^3_+,$$

where $u(t, x_0)$ is the unique solution of system (3.2) with $u(0, x_0) = x_0$. It is easy to see that

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

**Lemma 3.2.1.** *If $\mathcal{R}_0 > 1$, then there exists a $\sigma^* > 0$, such that for any $x_0 \in X_0$, we have*

$$\limsup_{m\to\infty} d(P^m(x_0), E_0) \geq \sigma^*. \tag{3.8}$$

*Proof.* Since $\mathcal{R}_0 > 1$, by Theorem 1.4.2, 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

$$\frac{d\tilde{T}(t)}{dt} = f(\tilde{T}) - k\sigma\tilde{T}, \tag{3.9}$$

admits a unique globally asymptotically stable positive equilibrium point, denoted as $\tilde{T}_0(\sigma)$, when $\sigma$ sufficiently small, and $\tilde{T}_0(\sigma) \to T_0$ as $\sigma \to 0$. We fix $\sigma$ small enough such that $\tilde{T}_0(\sigma) > T_0 - \varepsilon$. Denote $\tilde{T}(t, \sigma)$ be solution of (3.9) with initial value $\tilde{T}(0)$.

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

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

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

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 $t/\omega$. Therefore we have

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

Note that $(T(t), T^*(t), V(t)) = u(t, x_0)$. It then follows that $T^*(t) < \sigma$, $V(t) < \sigma$, $\forall t \geq 0$. From the first equation of system (3.2), we have

$$\frac{dT(t)}{dt} \geq f(T) - k(1 - \eta_{RT}(t))\sigma T \geq f(T) - k\sigma T.$$

Since $\tilde{T}_0(\sigma)$ is globally asymptotically stable for system (3.9) and $\tilde{T}_0(\sigma) > T_0 - \varepsilon$, we obtain for the second and third equations of system (3.2) that, for sufficiently large $t$,

$$\begin{aligned} \frac{dT^*(t)}{dt} &\geq k(1 - \eta_{RT}(t))(T_0 - \varepsilon)V - \beta T^*, \\ \frac{dV(t)}{dt} &= N(1 - \eta_P(t))\beta T^* - \gamma V. \end{aligned} \tag{3.10}$$

Next we consider the following system

$$\begin{aligned}\frac{d\tilde{T}^*(t)}{dt} &= k(1-\eta_{RT}(t))(T_0-\varepsilon)\tilde{V}-\beta\tilde{T}^*,\\ \frac{d\tilde{V}(t)}{dt} &= N(1-\eta_P(t))\beta\tilde{T}^*-\gamma\tilde{V}.\end{aligned} \tag{3.11}$$

By [41, Lemma 2.1], we know that there exists a positive $\omega$-periodic function, denoting as $(\bar{T}^*(t),\bar{V}(t))^T$, such that $(\tilde{T}^*(t),\tilde{V}(t))^T = e^{\zeta t}(\bar{T}^*(t),\bar{V}(t))^T$ is a solution of system (3.11), where $\zeta = \frac{1}{\omega}\ln\rho(\Phi_{F-G-M_\varepsilon}(\omega))$. Since $\rho(\Phi_{F-G-M_\varepsilon}(\omega)) > 1$, $\zeta$ is a positive constant. Let $t = n\omega$ and $n$ be nonnegative integer, then we get

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

as $n\to\infty$, since $\omega\zeta > 0$ and $(\bar{T}^*(t),\bar{V}(t))^T > 0$. For any nonnegative initial condition $(T^*(0),V(0))^T$ of system (3.10), there exists a sufficiently small $m^* > 0$ such that $(T^*(0),V(0))^T \geq m^*(\bar{T}^*(0),\bar{V}(0))^T$. By the comparison principle [30, Theorem B.1], we have

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

where $m^*(\tilde{T}^*(t),\tilde{V}(t))^T$ is also a solution for (3.11). Thus we have $T^*(n\omega)\to\infty$, $V(n\omega)\to\infty$ as $n\to\infty$, which is a contradiction. □

**Theorem 3.2.4.** *When $\mathcal{R}_0 > 1$, there exists a $\delta > 0$ such that any solution of system (3.2), $(T(t),T^*(t),V(t))$, with initial value $(T(0),T^*(0),V(0)) \in X_0$ satisfies*

$$\liminf_{t\to\infty}(T^*(t),V(t)) > (\delta,\delta).$$

*and system(3.2) admits at least one positive periodic solution.*

*Proof.* By Theorem 3.2.2, the discrete-time system $\{P^m\}_{m\geq 0}$ admits a global attractor in $\mathbb{R}^3_+$, and $\mathbb{R}^3_+$ is positively invariant. By the second and third equations of system

(3.2), we have

$$\begin{aligned} \frac{dT^*(t)}{dt} &\geq -\beta T^*, \\ \frac{dV(t)}{dt} &\geq -\gamma V. \end{aligned}$$

By the comparison principle, we get that $T^*(t) > 0$, $V(t) > 0$, $\forall t \geq 0$ if $T^*(0) > 0$, $V(0) > 0$, 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 equation of system (3.2), we get

$$\frac{dT(t)}{dt} \geq -kV(t)T, \tag{3.12}$$

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

$$\frac{dT(0)}{dt} = f(0) > 0,$$

then we have $T(t) > 0$ for $0 < t \ll 1$, then by (3.12) and the comparison principle, we get that when $T(0) = 0$, $T(t) > 0$ for $t > 0$. Then we have for all initial value in $X_0$, we have

$$T(t) > 0, \ \forall t > 0. \tag{3.13}$$

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

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

Clearly $\{(T,0,0) : T \geq 0\} \subset M_\partial$. It suffices to prove that for any $(T(0), T^*(0), V(0)) \in M_\partial$, we have $T^*(m\omega) = V(m\omega) = 0$, $\forall m \geq 0$. If it is not true, for some initial value $(T(0), T^*(0), V(0)) \in M_\partial$, there exists an $m_1 \geq 0$ such that $(T^*(m_1\omega), V(m_1\omega)) > 0$. If $(T^*(m_1\omega), V(m_1\omega)) \gg 0$, by the positive invariance of $X_0$, we have $(T^*(t), V(t)) \gg 0$ for any $t > m_1\omega$, which is a contradiction. Therefore, we have $T^*(m_1\omega) > 0$ and $V(m_1\omega) = 0$ or $T^*(m_1\omega) = 0$ and $V(m_1\omega) > 0$. First we consider the case that $T^*(m_1\omega) > 0$ and $V(m_1\omega) = 0$. Since $T^*(m_1\omega) > 0$, $T^*(t) > 0$, for all $t \geq m_1\omega$. By the assumption of $\eta_P(t)$, there exists $t' \in [0, \omega)$ such that $\eta_P(t') < 1$. At $t = t' + m_1\omega$,

$$\frac{d}{dt}V(t' + m_1\omega) \geq N\beta(1 - \eta_P(t' + m_1\omega))T^*(t' + m_1\omega) > 0,$$

Then there exists $\epsilon > 0$ sufficiently small such that $V(t) > 0$ for $t' + m_1\omega < t < t' + m_1\omega + \epsilon$. Then by the comparison principle, we get $V(t) > 0$ for all $t \geq t' + m_1\omega$, which is a contradiction. Similarly, when $T^*(m_1\omega) = 0$ and $V(m_1\omega) > 0$, we get a contradiction, which implies that $M_\partial := \{(T,0,0) : T \geq 0\}$.

Clearly, there is exactly one fixed point $E_0$ of $P$ in $M_\partial$. Lemma 3.2.1 implies that $E_0$ is an isolated invariant set in $\mathbb{R}^3_+$ and $W^s(E_0) \cap X_0 = \emptyset$. Note that, every orbit in $M_\partial$ approaches to $E_0$, and $E_0$ is acyclic in $M_\partial$. By Theorem 1.2.2, it follows that $P$ is uniformly persistent with respect to $(X_0, \partial X_0)$. By Theorem 1.2.5, the solutions of system (3.2) are uniformly persistent with respect to $(X_0, \partial X_0)$. That is, there exists a $\delta > 0$ such that any solution $(T(t), T^*(t), V(t))$ of system (3.2) with initial value $(T(0), T^*(0), V(0)) \in X_0$ satisfies

$$\liminf_{t\to\infty}(T^*(t), V(t)) > \delta.$$

Furthermore, Theorem 1.2.4 implies that $P$ has a fixed point, denoted as

$(T_*(0), T_*^*(0), V_*(0)) \in X_0$. Then $T_*(0) \geq 0$, $T_*^*(0) > 0$ and $V_*(0) > 0$. We further claim that $T_*(\bar{t}) > 0$ for some $\bar{t} \in [0, \omega]$. If it is not true, then $T_*(t) \equiv 0$, $\forall t \geq 0$, due to the periodicity of $T_*(t)$. From the first equation of (3.2), we get

$$0 = \frac{dT_*(t)}{dt} = f(0) > 0,$$

a contradiction. Then we have $T_*(t) > 0$, for all $t \geq 0$. And the positive invariance of $X_0$ implies that $(T_*(t), T_*^*(t), V_*(t)) \in \text{Int}(\mathbb{R}^3_+)$, $\forall t \geq 0$. Therefore, $(T_*(t), T_*^*(t), V_*(t))$ is a positive $\omega$-periodic solution of system (3.2). □

From Theorems 3.2.3 and 3.2.4, we see that $\mathcal{R}_0$ is a threshold parameter to determine whether or not the viral persists in an individual.

In the rest of this section, we investigate the effect that phase shifts of these drug efficacy functions have on the dynamics of system (3.2). Assume that the drugs is taken at the same time every day. Then shifting the phase of a drug efficacy function corresponds to changing the daily drug administration time [4].

Let $\eta_{RT}(T)$ and $\eta_P(t)$ be given $\omega$-periodic drug efficacy functions on $\mathbb{R}$. For $\psi_1$, $\psi_2 \in \mathbb{R}$, we consider the phase shift problem

$$\begin{aligned} \frac{dT(t)}{dt} &= f(T) - k(1 - \eta_{RT}(t - \psi_1))VT, \\ \frac{dT^*(t)}{dt} &= k(1 - \eta_{RT}(t - \psi_1))VT - \beta T^*, \\ \frac{dV(t)}{dt} &= N(1 - \eta_P(t - \psi_2))\beta T^* - \gamma V. \end{aligned} \tag{3.14}$$

Therefore, the equations for infected cells and virus particles of the linearizied system for system (3.14) at $E_0$ are

$$\begin{aligned}\frac{dT^*(t)}{dt} &= k(1-\eta_{RT}(t-\psi_1))T_0V-\beta T^*,\\ \frac{dV(t)}{dt} &= N(1-\eta_P(t-\psi_2))\beta T^*-\gamma V, \qquad (3.15)\end{aligned}$$

which can be rewritten as

$$x' = B(t,\psi_1,\psi_2)x, \qquad (3.16)$$

where

$$B(t,\psi_1,\psi_2) = \begin{pmatrix} -\beta & k(1-\eta_{RT}(t-\psi_1))T_0 \\ N(1-\eta_P(t-\psi_2))\beta & -\gamma \end{pmatrix}.$$

Then we have

$$F(t,\psi_1,\psi_2) = \begin{pmatrix} 0 & k(1-\eta_{RT}(t-\psi_1))T_0 \\ N(1-\eta_P(t-\psi_2))\beta & 0 \end{pmatrix}$$

and

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

Replacing $F(t)$ in (3.5) with $F(t,\psi_1,\psi_2)$, we define $L_{\psi_1,\psi_2}(\phi)(t)$, and further define $\mathcal{R}_0(\psi_1,\psi_2) = \rho(L_{\psi_1,\psi_2})$. We define $(\psi_2-\psi_1)modulo\ \omega = \psi'$, where $\psi'$ is determined by $\psi_2-\psi_1 = m\omega+\psi'$, $\psi' \in [0,\omega)$, $m \in \mathbb{Z}$.

**Lemma 3.2.2.** $\mathcal{R}_0(\psi_1,\psi_2) = \mathcal{R}_0(0,(\psi_2-\psi_1)modulo\ \omega)$.

*Proof.* Let $W(t,\psi_1,\psi_2,\lambda)$ be the monodromy matrix of the linear $\omega$-periodic system

$$\begin{aligned}\frac{dw(t)}{dt} &= (-G(t)+\frac{1}{\lambda}F(t,\psi_1,\psi_2))w,\ t\in\mathbb{R},\ \lambda\in(0,\infty).\\ &:= B(t,\psi_1,\psi_2,\lambda)w. \qquad (3.17)\end{aligned}$$

and $\rho(W(t,\psi_1,\psi_2,\lambda))$ be the spectral radius of $W(t,\psi_1,\psi_2,\lambda)$. Next we use the argument similar to that in the proof of [4, Proposition 7]. Let $\Gamma(t,\lambda)$ be the principal fundamental solution to (3.17). Let $\Phi(t,\lambda)$ be a principal fundamental solution to

$$x' = B(t+\psi_1,\psi_1,\psi_2,\lambda)x = B(t,0,(\psi_2-\psi_1)modulo\ \omega,\lambda)x.$$

Let $\tilde{\Phi}(t,\lambda) := \Phi(t-\psi_1,\lambda)$, then $\tilde{\Phi}(t,\lambda)$ is a fundamental solution of (3.17) with $\tilde{\Phi}(\psi,\lambda) = I$. Then we obtain

$$\begin{aligned}\Phi(\omega,\lambda) &= \tilde{\Phi}(\omega+\psi_1,\lambda) = \Gamma(\omega+\psi_1,\lambda)\tilde{\Phi}(0,\lambda) = \Gamma(\psi_1,\lambda)\Gamma(\omega,\lambda)\tilde{\Phi}(0,\lambda)\\ &= \tilde{\Phi}(\psi_1,\lambda)\tilde{\Phi}^{-1}(0,\lambda)\Gamma(\omega,\lambda)\tilde{\Phi}(0,\lambda) = \tilde{\Phi}^{-1}(0,\lambda)\Gamma(\omega,\lambda)\tilde{\Phi}(0,\lambda)\end{aligned}$$

Hence, for any given $\lambda > 0$, the matrix $\Phi(\omega,\lambda)$ is similar to matrix $\Gamma(\omega,\lambda)$, and hence $\rho(\Phi(\omega,\lambda)) = \rho(\Gamma(\omega,\lambda))$. If $\rho(\Phi(\omega,\lambda)) < 1$ for all $\lambda \in (0,\infty)$, then $\rho(\Gamma(\omega,\lambda)) < 1$ for all $\lambda \in (0,\infty)$. By Theorem 1.4.1(iii), we then get $\mathcal{R}_0(\psi_1,\psi_2) = \mathcal{R}_0(0,(\psi_2-\psi_1)modulo\ \omega) = 0$. If there exists $\lambda_0$ such that $\rho(\Phi(\omega,\lambda_0)) = \rho(\Gamma(\omega,\lambda_0)) = 1$, by Theorem 1.4.1(i), we get $\mathcal{R}_0(\psi_1,\psi_2)$, $\mathcal{R}_0(0,(\psi_2-\psi_1)modulo\ \omega) > 0$. By Theorem 1.4.1(ii), we further have

$$\mathcal{R}_0(\psi_1,\psi_2) = \mathcal{R}_0(0,(\psi_2-\psi_1)modulo\ \omega) = \lambda_0.$$

In conclusion, we have $\mathcal{R}_0(\psi_1,\psi_2) = \mathcal{R}_0(0,(\psi_2-\psi_1)modulo\ \omega)$. □

Denote $\mathcal{R}_0(0,\psi)$ as $\mathcal{R}_0(\psi)$. Observe that The map $\psi \mapsto \mathcal{R}_0(\psi)$ is a $\omega$-periodic function in $\mathbb{R}$. In order to optimize phase shift of $\eta_{RT}(t)$ and $\eta_P(t)$, we only need to consider phase shifts, $\psi$, where $\psi \in [0,\omega)$ and $\psi$ shifts $\eta_P(t)$ to $\eta_P(t-\psi)$. Hence, the timing between administered dosages of RT-inhibitors and P-inhibitors in the variable which affects the system dynamics.

## 3.3 Case studies

In this section, we numerically study the model with different drug efficacy functions. First, we consider the efficacy function of the bang-bang type with the same duration of activity. Second, we consider the efficacy function of the bang-bang type with different efficiency level when active and different duration of activity. At last, we investigate the case of using the actual pharmacokinetic models of the drug efficacies.

### 3.3.1 Drug efficacies of the bang-bang type

We now consider a simple case of system (3.2), where the drug efficacies are of the bang-bang type. The bang-bang type is not perfectly to model the real drug efficacy functions, but some insight can be gained on how the phase shift affect the effectiveness of the treatment. First, as in [4], we consider $\eta_{RT}(t)$ and $\eta_P(t)$ of the same type of periodic functions, and we refer to the phase shift, $\psi \in [0, \omega)$ as the phase difference between $\eta_{RT}(t)$ and $\eta_P(t-\psi)$. Following [4], we define $\eta_{RT}(t)$, $\eta_P(t) : \mathbb{R} \to [0,1)$ as periodic function with period $\omega = 1$, such that

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

where $e_{RT}$, $e_P \in [0,1]$ are fixed. Therefore the efficacy of the RT-inhibitor and P-inhibitor are $e_{RT}$ and $e_P$, respectively, for 12 hours in a day and 0 for the other 12 hours. Hence, if the phase shift $\psi \in [0, \frac{1}{2}]$, and on $[0,1)$

$$\eta_P(t-\psi) = \begin{cases} e_P & , \quad if\ t \in [\psi, \frac{1}{2} + \psi], \\ 0 & , \quad if\ t \in [0, \psi) \cup (\frac{1}{2} + \psi, 1). \end{cases}$$

If $\psi \in (\frac{1}{2}, 1)$, then on $[0, 1)$

$$\eta_P(t-\psi) = \begin{cases} e_P \quad , \quad if\ t \in [\psi, 1] \cup [0, \psi - \frac{1}{2}], \\ 0 \quad , \quad if\ t \in (\psi - \frac{1}{2}, \psi). \end{cases}$$

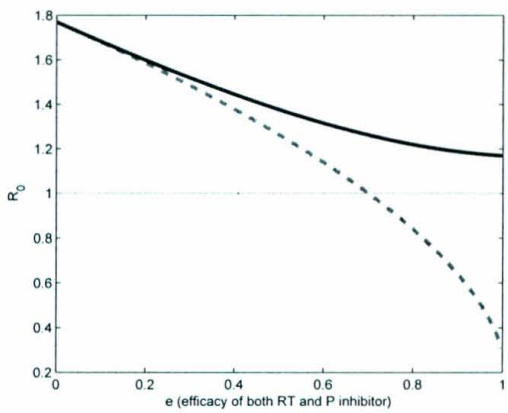


Figure 3.1: *Basic reproduction ratio $\mathcal{R}_0$ vs. efficacy for in-phase and out-of-phase treatments*

By using Theorem 1.4.1, we can numerically compute the basic reproduction ratio $\mathcal{R}_0$. We use the parameter given by Rong et al. [28], which are based on clinical data and extensive experimental evidence. The parameters are as follows: $f(T) = a - bT$ with $a = 10^4$ ml$^{-1}$ and $b = 0.01$ day$^{-1}$ (therefore, $T_0 = 10^6$ ml $^{-1}$), $k = 2.4 \times 10^{-8}$ ml day$^{-1}$, $\beta = 1$ day$^{-1}$, $N = 3000$, $\gamma = 23$ day$^{-1}$.

We first assume that $e_{RT} = e_P = e \in [0, 1]$. Then evaluate the basic reproduction ratio, $\mathcal{R}_0$, as a function of drug efficacy $e$. In figure 3.1, the solid line graphs $\mathcal{R}_0$ as a function of efficacy $e$ with $\psi = 0$. The dashed line depicts $\mathcal{R}_0$ as a function of efficacy $e$ with $\psi = 0.5$. The horizontal line is $\mathcal{R}_0 = 1$. We see that the in-phase treatments

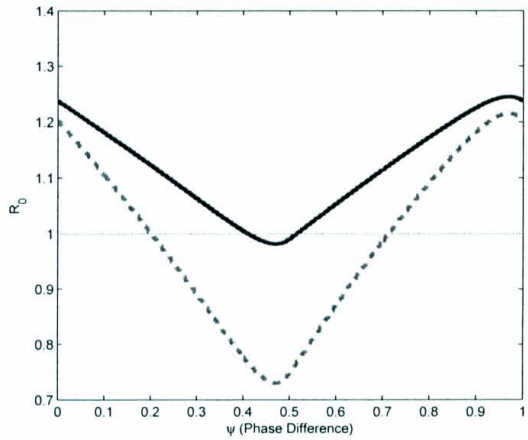


Figure 3.2: *Basic reproduction ratio $\mathcal{R}_0$ vs. phase difference $\psi$*

do not clear the infection in all circumstances, while the out-of-phase treatments do clear the infection when $e$ is relatively large.

We then fix $e_{RT}$ and $e_P$ and calculate $\mathcal{R}_0$ as a function of the phase difference $\psi$ (Figure 3.2). In Figure 3.2, the dashed curve (which is closer to 0) represents the case when $e_{RT} = e_P = 0.85$ and the solid curve represents the case when $e_{RT} = 0.9$, $e_P = 0.5$. Since $\mathcal{R}_0$ is periodic with respect to $\psi$, the minimum and maximum exist. In Figure 3.2, the minimum, which occurs just before $\psi = \frac{1}{2}$, corresponding to the optimal phase difference, $\psi^*$. From Figures 3.1 and 3.2, we can see that the phase difference plays an important role in whether or not the infection is cleared.

We now approximate the drug efficacy function with bang-bang type but different duration of activity:

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

Without loss of generality, we assume that $p_{RT} < p_P$. Motivated by [9, Proposition 2], we have the following result.

**Theorem 3.3.1.** *$\mathcal{R}_0$ is decreasing in each of the four arguments: $e_{RT}$, $e_P$, $p_{RT}$ and $p_P$.*

*Proof.* By the above definition of $\eta_{RT}$ and $\eta_P$, we rewrite (3.6) as

$$\begin{aligned}\frac{dw}{dt} &= (-G(t) + \frac{1}{\lambda}F(t))w, \\ &:= B(t, \lambda, e_{RT}, e_P, p_{RT}, p_P)w,\ t \in \mathbb{R},\ \lambda \in (0, \infty),\end{aligned}$$

and let $W(t, \lambda, e_{RT}, e_P, p_{RT}, p_P)$ be the corresponding monodromy matrix. First, we prove that $\rho(W(\omega, \lambda, e_{RT}, e_P, p_{RT}, p_P))$ is decreasing in each of the four arguments: $e_{RT}$, $e_P$, $p_{RT}$ and $p_P$.

By [9], $\rho(W(\omega, \lambda, e_{RT}, e_P, p_{RT}, p_P))$ is the spectral radius of the following matrix:

$$\begin{aligned}&\Lambda(e_{RT}, e_P, p_{RT}, p_P) = \\ &\exp[(\omega - p_P)B(0,0)] \exp[(p_P - p_{RT})B(0, e_P)] \exp[p_{RT}B(e_{RT}, e_P)],\end{aligned}$$

where

$$B(e_{RT}, e_P) = \begin{pmatrix} -\beta & \frac{k}{\lambda}(1 - e_{RT})T_0 \\ \frac{N}{\lambda}(1 - e_P)\beta & -\gamma \end{pmatrix}$$

Let $0 \leq e_{RT} < e'_{RT} < 1$ and $p_{RT} \neq 0$, then we have

$$B(e'_{RT}, e_P) \leq B(e_{RT}, e_P) \text{ and } B(e'_{RT}, e_P) \neq B(e_{RT}, e_P),$$

$$\Rightarrow \quad 0 \leq \exp[p_{RT} B(e'_{RT}, e_p)] \leq \exp[p_{RT} B(e_{RT}, e_p)]$$

$$\text{and } \exp[p_{RT} B(e'_{RT}, e_p)] \neq \exp[p_{RT} B(e_{RT}, e_p)]$$

(*by Theorem* 1.1.5(1))

$$\Rightarrow \quad 0 \leq \exp[(\omega - p_P) B(0, e_P)] \exp[(p_P - p_{RT}) B(0, e_P)] \exp[p_{RT} B(e'_{RT}, e_p)] \leq$$

$$\exp[(\omega - p_P) B(0, e_P)] \exp[(p_P - p_{RT}) B(0, e_P)] \exp[p_{RT} B(e_{RT}, e_p)],$$

$$\text{and } \exp[(\omega - p_P) B(0, e_P)] \exp[(p_P - p_{RT}) B(0, e_P)] \exp[p_{RT} B(e'_{RT}, e_p)] \neq$$

$$\exp[(\omega - p_P) B(0, e_P)] \exp[(p_P - p_{RT}) B(0, e_P)] \exp[p_{RT} B(e_{RT}, e_p)]$$

(*by Theorem* 1.1.5(1) *and* (2))

$$\Rightarrow \quad 0 \leq \Lambda(e'_{RT}, e_P, p_{RT}, p_P) \leq \Lambda(e_{RT}, e_P, p_{RT}, p_P),$$

$$\text{and } \Lambda(e'_{RT}, e_P, p_{RT}, p_P) \neq \Lambda(e_{RT}, e_P, p_{RT}, p_P),$$

$$\Rightarrow \quad \rho(\Lambda(e'_{RT}, e_P, p_{RT}, p_P)) < \rho(\Lambda(e_{RT}, e_P, p_{RT}, p_P)).$$

(*by Theorem* 1.1.5(3))

Since $\rho(\Lambda(e_{RT}, e_P, p_{RT}, p_P))$ is continuous with respect to $e_{RT}$, $e_P$, $p_{RT}$ and $p_P$, the result remains valid if $e'_{RT} = 1$. Similarly, we can prove the result with respect to $e_P$.

Let $0 \leq p_{RT} < p'_{RT} < \omega$, and $e_P \neq 0$, then

$$B(e_{RT}, e_P) \leq B(0, e_P), \text{ and } B(e_{RT}, e_P) \neq B(e_{RT}, 0)$$

$$\Rightarrow \quad 0 \leq \exp[(p'_{RT} - p_{RT})B(e_{RT}, e_P)] \leq \exp[(p'_{RT} - p_{RT})B(0, e_P)],$$

$$\text{and } \exp[(p'_{RT} - p_{RT})B(e_{RT}, e_P)] \neq \exp[(p'_{RT} - p_{RT})B(0, e_P)],$$

(*by Theorem* 1.1.5(1))

$$\Rightarrow \quad 0 \leq \exp[(p'_{RT} - p_{RT})B(e_{RT}, e_P)] \exp[p_{RT}B(e_{RT}, e_P)] \leq$$

$$\exp[(p'_{RT} - p_{RT})B(0, e_P)] \exp[p_{RT}B(e_{RT}, e_P)],$$

$$\text{and } \exp[(p'_{RT} - p_{RT})B(e_{RT}, e_P)] \exp[p_{RT}B(e_{RT}, e_P)] \neq$$

$$\exp[(p'_{RT} - p_{RT})B(0, e_P)] \exp[p_{RT}B(e_{RT}, e_P)],$$

(*by Theorem* 1.1.5(1) *and* (2))

$$\Rightarrow \quad 0 \leq \exp[(\omega - p_P)B(0,0)] \exp[(p_P - p'_{RT})B(0, e_P)]$$

$$\exp[(p'_{RT} - p_{RT})B(e_{RT}, e_P)] \exp[p_{RT}B(e_{RT}, e_P)] \leq$$

$$\exp[(\omega - p_P)B(0,0)] \exp[(p_P - p'_{RT})B(0, e_P)]$$

$$\exp[(p'_{RT} - p_{RT})B(0, e_P)] \exp[p_{RT}B(e_{RT}, e_P)],$$

$$\text{and } \exp[(\omega - p_P)B(0,0)] \exp[(p_P - p'_{RT})B(0, e_P)]$$

$$\exp[(p'_{RT} - p_{RT})B(e_{RT}, e_P)] \exp[p_{RT}B(e_{RT}, e_P)] \neq$$

$$\exp[(\omega - p_P)B(0,0)] \exp[(p_P - p'_{RT})B(0, e_P)]$$

$$\exp[(p'_{RT} - p_{RT})B(0, e_P)] \exp[p_{RT}B(e_{RT}, e_P)],$$

(*by Theorem* 1.1.5(1) *and* (2))

$$\Rightarrow \quad 0 \leq \Lambda(e_{RT}, e_P, p'_{RT}, p_P) \leq \Lambda(e_{RT}, e_P, p_{RT}, p_P),$$

$$\text{and } \Lambda(e_{RT}, e_P, p'_{RT}, p_P) \neq \Lambda(e_{RT}, e_P, p_{RT}, p_P),$$

$$\Rightarrow \quad \rho(\Lambda(e_{RT}, e_P, p'_{RT}, p_P)) < \rho(\Lambda(e_{RT}, e_P, p_{RT}, p_P)),$$

(*by Theorem* 1.1.5(3)).

Since $\rho(\Lambda(e_{RT}, e_P, p_{RT}, p_P))$ is continuous with respect to $e_{RT}$, $e_P$, $p_{RT}$ and $p_P$, the result remains valid in $p'_{RT} = \omega$. Similarly, we can prove the result with respect to $p_P$. In conclusion, it follows that for any given $\lambda > 0$, $\rho(W(\omega, \lambda, e_{RT}, e_P, p_{RT}, p_P))$ is decreasing in each of the four arguments: $e_{RT}$, $e_P$, $p_{RT}$ and $p_P$.

Now let us assume that $0 \leq e_{RT} < e'_{RT} \leq 1$. Let $\mathcal{R}_0$ be the basic reproduction ratio corresponding to $e_{RT}$, and $\mathcal{R}'_0$ as that corresponding to $e'_{RT}$. Next we prove that $\mathcal{R}_0 \geq \mathcal{R}'_0$. Since $\rho(W(t, \lambda, e_{RT}, e_P, p_{RT}, p_P))$ is decreasing with respect to $e_{RT}$, $e_P$, $p_{RT}$, $p_P$, we have

$$\rho(W(t, \lambda, e_{RT}, e_P, p_{RT}, p_P)) > \rho(W(t, \lambda, e'_{RT}, e_P, p_{RT}, p_P)).$$

If $\rho(W(t, \lambda, e_{RT}, e_P, p_{RT}, p_P)) < 1$ for all $\lambda \in (0, \infty)$, then

$$\rho(W(t, \lambda, e'_{RT}, e_P, p_{RT}, p_P)) < 1, \ \forall \lambda \in (0, \infty).$$

By Theorem 1.4.1(iii), we get $\mathcal{R}_0 = \mathcal{R}'_0 = 0$. If there exists $\lambda_0$ such that

$$\rho(W(t, \lambda_0, e_{RT}, e_P, p_{RT}, p_P)) = 1, \ \rho(W(t, \lambda, e'_{RT}, e_P, p_{RT}, p_P)) < 1, \ \forall \lambda \in (0, \infty),$$

then Theorem 1.4.1(i) implies that

$$\mathcal{R}_0 > 0 = \mathcal{R}'_0.$$

If there exist $\lambda_0$ and $\lambda'_0$ such that

$$\rho(W(t, \lambda_0, e_{RT}, e_P, p_{RT}, p_P)) = 1, \ \rho(W(t, \lambda'_0, e_{RT}, e_P, p_{RT}, p_P)) = 1,$$

we have

$$1 = \rho(W(t, \lambda_0, e_{RT}, e_P, p_{RT}, p_P)) > \rho(W(t, \lambda_0, e'_{RT}, e_P, p_{RT}, p_P)).$$

It follows that

$$\rho(W(t,\lambda_0,e'_{RT},e_P,p_{RT},p_P)) < \rho(W(t,\lambda'_0,e'_{RT},e_P,p_{RT},p_P)) = 1.$$

Since $\rho(W(t,\lambda_0,e_{RT},e_P,p_{RT},p_P))$ is nonincreasing about $\lambda$, we get $\lambda_0 > \lambda'_0$. By Theorem 1.4.1(ii), we have $\mathcal{R}_0 > \mathcal{R}'_0$. □

We illustrate Theorem 3.3.1 in Figure 3.3. Here we assume that $e_{RT} = e_P = e \in [0,1]$, and $p_{RT} = p_P = p \in [0,1]$, and evaluate the basic reproduction ratio $\mathcal{R}_0$ as a function of $e$ and $p$. Figure 3.3 shows the in-phase case with $\psi = 0$, while Figure 3.4 presents the out-of-phase case with $\psi = 0.5$. Comparing Figure 3.3 and 3.4, we see that 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 implies that the phase shift helps the clearance of the infection.

### 3.3.2 An actual pharmacokinetic model

Note that the bang-bang type control for drug efficacy may not be realistic since drug concentrations continuously vary due to drug absorption, distribution, and metabolism in the body [28]. In this section, we employ a two-compartment pharmacokinetic model developed in [12] to determine the efficacy of two drugs: tenofovir DF (a RT-inhibitor) and ritonavir (a P-inhibitor). We first briefly review this two-compartment model.

The simplest functionality to estimate the instantaneous drug efficacy is represented as

$$\eta_X(t) = \frac{C(t)}{IC50 + C(t)}, \tag{3.18}$$

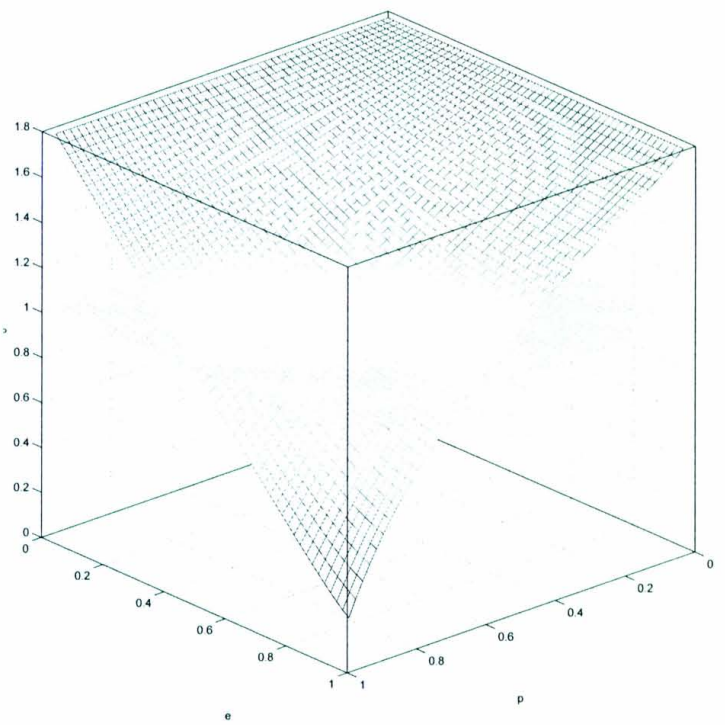


Figure 3.3: *Basic reproduction ratio $\mathcal{R}_0$ as a function of efficacy $e$ and duration $p$ with $\psi = 0$. The horizontal surface corresponds to $\mathcal{R}_0 = 1$.*

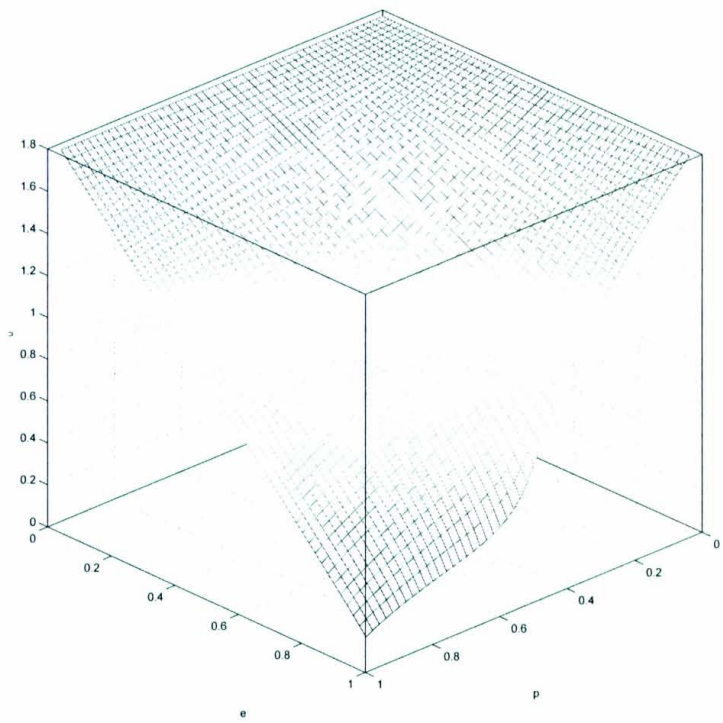


Figure 3.4: *Basic reproduction ratio $\mathcal{R}_0$ as a function of efficacy $e$ and duration $p$ with $\psi = 0.5$. The horizontal surface corresponds to $\mathcal{R}_0 = 1$.*

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

$$\begin{aligned} C_b(t) &= \frac{FDk_a}{V_d(k_e-k_a)}\frac{e^{-k_e t}}{e^{k_a I_d}-1}[1-e^{(k_e-k_a)t}(1-e^{N_d k_a I_d}) \\ &\quad + \frac{(e^{k_e I_d}-e^{k_a I_d})(e^{(N_d-1)k_e I_d}-1)}{e^{k_e I_d}-1} - e^{((N_d-1)k_e+k_a)I_d}], \end{aligned} \tag{3.19}$$

where $F$ is the bioavailability of the drug, $D$ is the mass of the drug administered in a dose, $V_d$ is the volume of the distribution, $k_a$ and $k_e$ are the absorption constant rate of the drug into the blood and the elimination rate of the drug from the blood with a drug fraction of $F$, and these two parameters can be determined from experiments. $I_d$ is the dosing interval and $N_d = integer(t/I_d) + 1$ is the number of doses until time $t$, the first dose administered at $t = 0$.

For the P-inhibitor, the intracellular drug concentration $C_c(t)$ may be written as (do not consider the resistance to drug transport across the cell boundary)

$$C_c(t) = (1 - f_b)HC_b(t), \tag{3.20}$$

where $H$ quantifies the effect of the cell membrane, $f_b$ is the fraction of the drug that is bound to plasma proteins and therefore cannot be transported into the cells. Dixit and Perelson [12] characterized ritonavir as the P-inhibitor, and the corresponding parameters were chosen as: $D = 600$ mg, $I_d = 0.5$ day, $F = 1$, $V_d = 28000$ ml, $k_a = 14.64$ day$^{-1}$, $k_e = 6.86$ day$^{-1}$, $H = 0.052$, $f_b = 0.99$ and $IC50 = 9 \times 10^{-7}$ ml$^{-1}$. The efficacy function for ritonavir are graphed in Figure 3.5.

The RT-inhibitors are transported in and out the compartment in a more complicated way: it usually must undergo three sequential phosphorylation reactions within

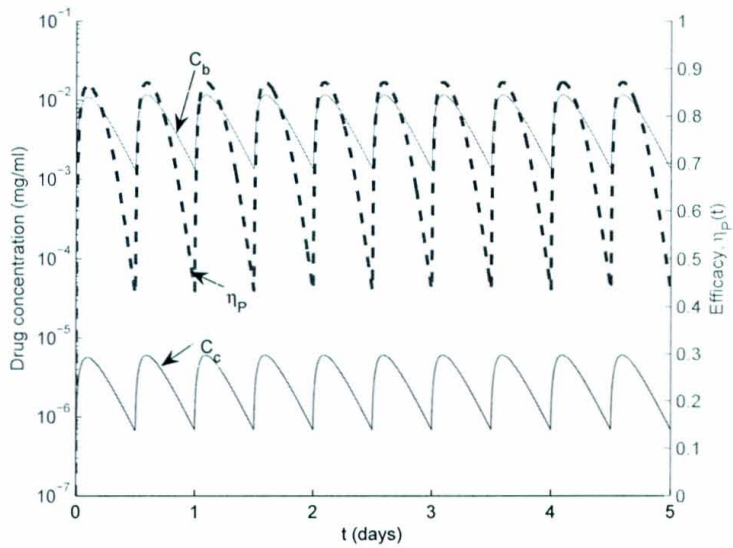


Figure 3.5: *Plasma $C_b$ (red solid line), intracellular $C_c$ (blue solid line) concentrations, and efficacy $\eta_P$ of ritonavir (green dashed line). See the text for parameter values.*

cells to their active forms. To model the phosphorylation of tenofovir DF, a recently developed drug and only two additional phosphorylation steps are essential for its activation, the authors of [12] considered the following system:

$$\begin{aligned}
\frac{dC_c}{dt} &= k_{acell}C_x - k_{ecell}C_c - k_{1f}C_c + k_{1b}C_{cp}, \\
\frac{dC_{cp}}{dt} &= -k_{ecell}C_{cp} + k_{1f}C_c - k_{1b}C_{cp} - k_{2f}C_{cp} + k_{2b}C_{cpp}, \\
\frac{dC_{cpp}}{dt} &= -k_{ecell}C_{cpp} + k_{2f}C_{cp} - k_{2b}C_{cpp},
\end{aligned} \tag{3.21}$$

where $C_c$, $C_{cp}$ and $C_{cpp}$ are the intracellular concentration of the native, monophosphorylated and diphosphorylated forms of the drug, $k_{acell}$ and $k_{ecell}$ represent the absorption and elimination rate constants, respectively. Note that $k_{1f}$, $k_{1b}$, $k_{2f}$ and $k_{2b}$ determine the rates of the phosphorylation reaction among $C_c$, $C_{cp}$ and $C_{cpp}$, and $C_x$ is given by

$$C_x = \begin{cases} (1-f_b)HC_b - C_c & , \quad if\ (1-f_b)HC_b - C_c > 0, \\ 0 & , \quad otherwise. \end{cases}$$

Solving (3.21) with initial condition $C_c(0) = C_{cp}(0) = C_{cpp}(0) = 0$, and then substituting $C_{cpp}$ for $C(t)$ in (3.18), we get the drug efficacy function for tenofovir DF, which is plotted in Figure 3.6. Here we choose parameters in [12]: $D = 300$ mg, $I_d = 1$ day, $F = 0.39$, $V_d = 87500$ ml, $k_a = 14.64$ day$^{-1}$, $k_e = 9.6$ day$^{-1}$, $H = 1800$, $f_b = 0.07$, $k_{1f} = 9.6$ day$^{-1}$, $k_{1b} = 30.3$ day$^{-1}$, $k_{2f} = 270.7$ day$^{-1}$, $k_{2b} = 95.5$ day$^{-1}$, $k_{acell} = 24000$ day$^{-1}$, $k_{ecell} = 1.1$ day$^{-1}$, $IC50 = 0.54$ ml$^{-1}$.

In order to calculate the basic reproduction ratio, we need explicit expressions for both $\eta_{RT}(t)$ and $\eta_P(t)$. For $\eta_{RT}(t)$, we use trigonometric Fourier series form

$$f(t) = a_0 + \sum_{i=1}^{6} a_i \cos(iwt) + b_i \sin(iwt)$$

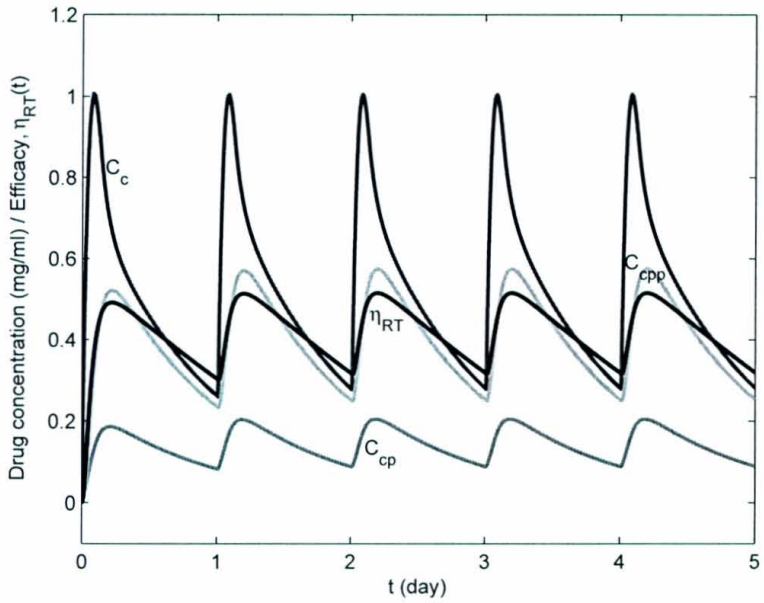


Figure 3.6: *Intracellular concentrations of the native ($C_c$)(blue), monophosphorylated ($C_{cp}$)(red), and diphosphorylated ($C_{cpp}$) (green) forms, and efficacy $\eta_{RT}$ of tenofovir DF (black). See the text for parameter values.*

to fit $C_{cpp}(t)$ which is obtained by numerically solving (3.21). Note that $C_{cpp}(t)$ is periodic in time and with period 1, and the expression $f(t)$ above is the expression for one period, that is $t \in [0, 1)$. By replacing $t$ by $\mod(t, 1)$, we obtain the periodic fitting expression for $C_{cpp}(t)$. We use the powerful software MATLAB to determine those coefficients $a_i$, $b_i$, and $w$. Therefore we obtain that

$$\begin{aligned} f(t) \;=\; & 17.23 + 2.251\cos(3.041t) - 30.15\sin(3.041t) - 21.58\cos(2 \times 3.041t) \\ & -3.178\sin(2 \times 3.041t) - 2.878\cos(3 \times 3.041t) + 11.92\sin(3 \times 3.041t) \\ & +4.778\cos(4 \times 3.041t) + 1.71\sin(4 \times 3.041t) + 0.6227\cos(5 \times 3.041t) \\ & -1.246\sin(5 \times 3.041t) - 0.1609\cos(6 \times 3.041t) - 0.1087\sin(6 \times 3.041t). \end{aligned} \tag{3.22}$$

The comparison of $C_{cpp}(t)$ and $f(t)$ is shown in Figure 3.7, from which we can see they match quite well for relatively large $t$. Substituting (3.22) to (3.18) as $C(t)$, we then get the expression for $\eta_{RT}(t)$.

By (3.19) and (3.20), we have already had an explicit expression for $eta_P(t)$, which is a quasi-periodic function. We assume the drug efficacy functions to be periodic with the same period $\omega$ ($\omega = 1$ here). Therefore, in numerical simulation, we take a period when $t$ is relatively large (which is reasonable, since we focus on the long term behavior of the model), and then by replacing $t$ with $\mod(t, 1)$, we get our new $\eta_P(t)$, which is a periodic function.

Substituting $\eta_{RT}(t)$ and $\eta_P(t)$ into system (3.2), we can numerically calculate the basic reproduction ratio $\mathcal{R}_0$. Figure 3.8 presents $\mathcal{R}_0$ as a function of phase difference. It is clear that the infection can be cleared, and the phase shift greatly influences the treatment outcome. Therefore, timing between dosages of tenofovir DF and ritonavir

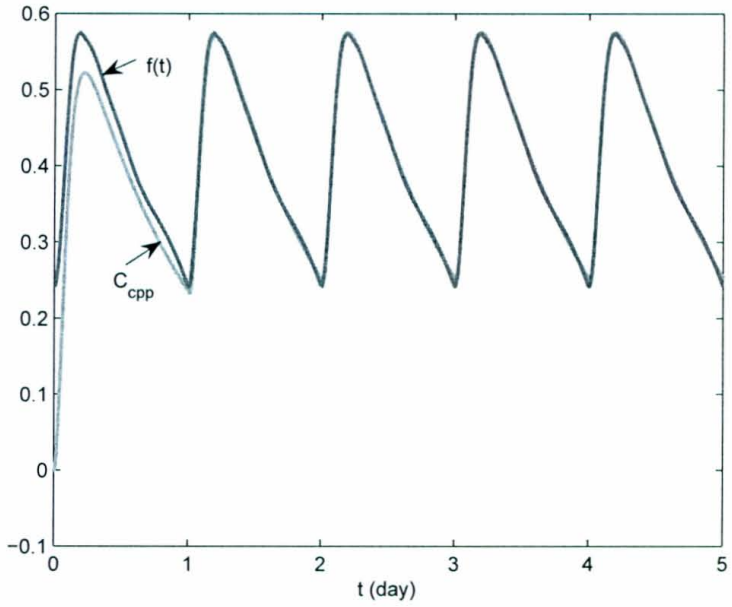


Figure 3.7: *The intracellular concentration of diphosphorylated forms of tenofovir DF, $C_{cpp}$ and its fitting curve.*

can affect treatment effectiveness.

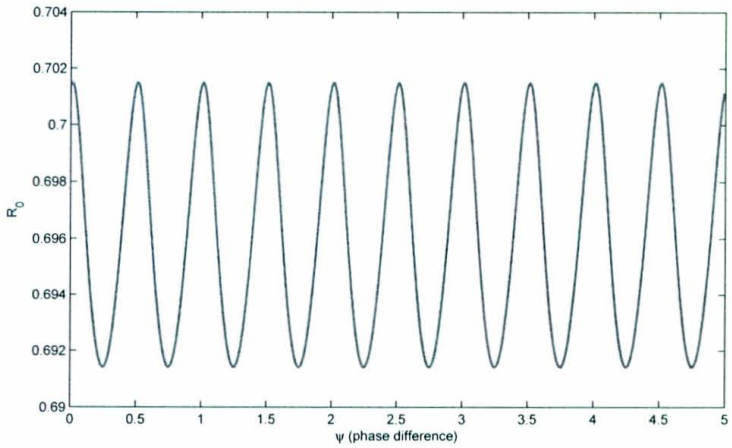


Figure 3.8: *The basic reproduction ratio $\mathcal{R}_0$ vs. phase difference $\psi$.*

## 3.4 Discussion

In general, the global dynamics of a nonlinear periodic ordinary differential system is difficult to analyze. In this chapter, we considered a within-host model with periodic drug efficacy functions. From the theoretical point of view, we have figured out the basic reproduction ratio and showed that the infection will be persist if $\mathcal{R}_0 > 1$, and will be cleared if $\mathcal{R}_0 < 1$. Moreover, the infection free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$. The threshold results indicate that the basic reproduction ratio can serve as the determining parameter on the control of infection. Although $\mathcal{R}_0$ has been evaluated for some autonomous HIV models (see, e.g., [10]), there is little work on estimating the basic reproduction ratio for HIV models with a periodic

drug efficacy functions.

In the numerical study, we considered two different types of drug efficacy functions, one of the bang-bang type and one based on actual pharmacokinetic models. In the case of bang-bang control, our results with respect to the basic reproduction ratio coincide with the results in [4] which is with respect to $\lambda_2$ (see [4] for detail). In the latter case, we use the models and parameters derived from clinical data and extensive experiments to determine the drug efficacy functions for tenofovir DF (a RT-inhibitor) and ritonavir (a P-inhibitor).

Treatments with cocktails of several drugs have been proved successful and become standard. The timing between periodic dosages of different drugs (when two or more drugs are used) may affect the treatment outcome. In this chapter, we also investigated this interesting optimal phase shift problem in the sense of minimizing the basic reproduction ratio. The numerical results shows that, for the model in this chapter, the phase difference between the dosage of RT-inhibitor and R-inhibitor can greatly influence the treatment outcome. The treatment outcome is different for the models with the same drug efficacy functions of RT-inhibitor and P-inhibitor but different phase shift. Therefore, we may easily give a better treatment scheme if we can find an optimal phase shift. However, our results should be viewed with caution, since the model we used is simplistic and probably does not capture all relevant dynamics. More realistic models for both the infection and drug efficacy function would be useful in determining how the phase shift affects the dynamics of the model system and how much the optimal phase shifts are.

# Chapter 4

# Summary and Future Work

In this chapter, we briefly summarize the results in this thesis and propose some possible problems for future investigation.

## 4.1 Research summary

In this thesis, we study the dynamics of a time-delayed dengue transmission model and a periodic within-host virus model.

Dengue is a mosquito-borne infection found in tropical and subtropical regions around the world. In recent years, transmission has increased predominantly in urban and semi-urban areas and has become a major international public health concern. Mathematical models may provide an important approach in understanding risk and planning for disease control in heterogeneous environment. Motivated by the nonlocal and time-delayed reaction diffusion dengue transmission model in [35], we considered a time-delayed model with different infection rates of susceptible mosquitos and susceptible humans. We first gave an explicit expression for the basic reproduction

number $\mathcal{R}_0$ from which we got that $\mathcal{R}_0$ is decreasing with respect to $\tau_A$, $\tau_w$, and $\tau_h$ (the length of immature stage of mosquitos, the incubation period of dengue virus within mosquitos and hosts, respectively). Our work shows that the prospects of the success of dengue control depend partly on the basic reproduction number. That is, when $\mathcal{R}_0 > 1$, the disease persists in the human population, and when $\mathcal{R}_0 < 1$ and provided the invasion is small, the disease will be cleared. This project allows us to study the trends of dengue risk.

In Chapter 3, motivated by the within-host virus model in [4, 9], we considered the case where drug efficacy function is periodic on time, and investigated the dynamics of a periodic model with two drugs (for example, P-inhibitor and PI-inhibitor for HIV). We first introduced the basic reproduction ratio, which can be numerically calculated. Then we showed that there exists an endemic periodic solution and the disease remain endemic when $\mathcal{R}_0 > 1$, and the disease dies out when $\mathcal{R}_0 < 1$. Therefore, $\mathcal{R}_0$ serves as the determining parameter on the control of infection. Furthermore, we investigated the phase shift problem, which is corresponding to change the daily time of dosage of two drugs. Our work shows that the phase shift can greatly influence the treatment outcome. Therefore, we can easily give out a better treatment scheme if we get the optimal phase shift. Note that [4] did not define the basic reproduction ratio for the model, and only studied the stability of the model with special types of drug efficacy function such as of the bang-bang type or a piecewise constant function, and they established their stability results with respect to $\lambda_2$ (see [4] for detail), while we established a threshold result with respect to the basic reproduction ratio for general periodic drug efficacy functions.

## 4.2 Future work

Following the investigations described in this thesis, a number of problems are interesting and worthy to study. In this section, we enumerate some of these possible directions.

As noted in Chapter 2, Theorem 2.3.2, the disease will die out if $\mathcal{R}_0 < 1$ provided the invasion intensity is small. However, this result may not be right when the invasion intensity is strong. In this case, reducing the basic reproduction number to be less than unity may not be enough in order to eradicate the disease. Solving this problem should be biologically interesting in the control of dengue transmission.

We have shown in Section 2.4 that there exists a unique endemic equilibrium which is globally attractive when $\mathcal{R}_0 > 1$ for a special case ($\varepsilon_w = \varepsilon_h = 0$, $\sigma = 1$). What we were not able to accomplish in this work is the existence, uniqueness, or stability of endemic equilibrium for the original model system.

Although we have shown in Theorem 3.2.4, Chapter 3 that there exists at least one positive periodic solution when the basic reproduction is greater than unity, we did not get any information on the uniqueness, multiplicity, or stability of positive periodic solution for model (3.2).

As we have indicated in Chapter 3, the model we have used is simplistic and does not capture all relevant dynamics. Model (3.2) assumes that the drug is active right after the dosage, and upon infection cells become productive (be able to produce virus) instantaneously, which is not realistic since it needs time (pharmacological delay) for drug to be absorbed and then transported and processed into an active form intracellularly, and it also requires time (intracellular delay) for an infected cell

to replicate virus (see, e.g., [20]).

In the appearance of drug treatment, for example in the treatment of HIV, emergence of drug-resistant virus is possible, which significantly increase the cost and complexity of achieving cure. According to [23], the competition between drug-resistant and wild-type strains determines which type of virus will eventually dominate the virus population during the course of AZT treatment. Therefore, antiretroviral drug resistance become a major public health problem hindering the control of HIV. The model involving pharmacological delay, intracellular delay and drug-resistant strain is biologically interesting and is part of my future work.

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