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# A within-host virus model with multiple infected stages under time-varying environments

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ABSTRACT

HIV-1 infection and treatment may occur in the non-constant environment due to the time-varying drug susceptibility and growth of target cells. In this paper, we propose a within-host virus model with multiple stages for infected cells under time-varying environments, to study how the multiple infected stages affect on the counts of viral load and $CD4^+$-T cells. We establish the sufficient conditions for both persistent HIV infection and clearance of HIV infection based on two positive constants $R_*$, $R^*$. When the system is under persistent infection, we further obtained detailed estimates of both the lower and upper bounds of the viral load and the counts of $CD4^+$-T cells. Furthermore, numerical simulations are carried out to verify our analytical results and demonstrate the combined effects of multiple infected stages and non-constant environments, and reflect that both persistence and clearance of infection are possible when $R_* < 1 < R^*$ holds. In particular, the numerical results exhibit the viral load of system with multiple infected stages may be less than that with single infected stage, and simulate the effect of time-varying environment of the autonomous system with multiple infected stages. We expect that our theoretical and simulation results can provide guidance for clinical therapy for HIV infections.



## 1. Introduction

Over the last two decades there has been extensive research on modeling and analysis of the human immunodeficiency virus (HIV) infection ([1–4,5–9]). Most HIV infection models focus on the single-infected stage for infected cells. The standard technique for developing mathematical descriptions of HIV infection between virus particles and uninfected $CD4^+$ T-cells is to model the system with single-infected stage as a set of autonomous ordinary differential equations. This approach has led to many insights into the factors that affect HIV infection and control. The infection remains asymptomatic for years, the population of $CD4^+$-T cells falls to low levels and the virus load sufficiently increases leading to the development of AIDS. However, it is very important to establish an appropriate HIV model for HIV antiviral therapy and control, thus consideration of following factors should attract more attention.

Firstly, multiple infected stages and treatment for infected cells are more interesting. As noted in [11–21], they investigated that an infected individual enters the first infectious stages at the moment of infection and then progresses through all these stages until the last one, with the infectiousness of a person depending upon his current disease stage. In [17], Hyman et al.

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suggested that some infected individuals could pass through four infection stages: (1) the highly infectious acute stage in the first few weeks; (2) the low infectivity early chronic stage; (3) the high infectivity late chronic stage; (4) the AIDS stage. And Sedaghat et al. [21] established two-stages infection model based on three different kinds of levels of virus during the chronic phase of infection. Samanta [20] investigated a non-autonomous stage-structured HIV/AIDS epidemic model with two stages between HIV/AIDS patients not the host cells in the body, established some sufficient conditions on the permanence and extinction of the disease, and obtained the explicit formula of the eventual lower bounds of infected individuals. Thus, additional multiple infected stages and treatment for infected cells are important and realistic to model for HIV-1 pathogenesis and drug treatment dynamics.

On the other hand, the non-autonomous phenomenon, are familiar features in virus infection models, such as varying infection rate (see [22–29]), and especially the periodic drug therapy and periodic drug effectiveness, occur in many realistic within-host models, relevant to our study here are the works [30–34] and so on.

Motivated by these factors above, especially multiple infected stages were introduced in the non-autonomous HIV infection model, to give a more appropriate model and better understanding of the antiretroviral drug during HIV-1 virus infection. Our primary goals of this paper are to establish such precise estimates of the viral load using the lower and upper bounds of coefficients, and to investigate what happens if the model including multiple infected stages.

In this paper, we will provide some sufficient conditions on the permanence and extinction of system (1), which are different from the popular technique of uniform persistence theory to address the virus dynamic system in a periodic environment [38]. To our best knowledge, if the system is a periodic system, we can obtain the threshold values by using the theory of uniform persistence for periodic systems developed by Prof. Xiaoqiang Zhao (see [10,25]); if the system is almost periodic without delay, then the conditions of the threshold values may be weakened, as shown in [28]. Our system is a general non-autonomous model (not necessarily periodic) with multiple infected stages. The standard techniques to address periodic (or almost periodic) systems, such as the basic reproduction ratio derivation and the persistence theory of periodic (or almost periodic) systems, are not applicable here. Fortunately, the analysis techniques in [34] (with single-infected stage) provided a tool so that one can do this simple non-autonomous HIV infection model, which make it possible for us to consider the model with multi-stage infection and treatment. Thereupon, the research of non-autonomous HIV infection model multiple infected stages is not only interesting but also necessary, and more challenging than the single-infected stage [34].

This article is organized as follows. The next section presents a non-autonomous HIV-1 model with multiple infected stages and gives some preliminaries lemmas. Our main results on permanence and extinction of system (1) are completely determined by the threshold values and obtained in Section 3. In Section 4, numerical simulations are considered to illustrate our main results. We also investigate the impact of multiple infected stages on HIV infection through the sensitivity analysis of $R_*$ and comparisons between delayed non-autonomous HIV-1 models with single-infected stage and three infected stages. A brief conclusion is given in Section 5.

## 2. Model formulation and preliminaries

HIV replication cycle may contain much stages, such as reverse transcription, integration, assembly and viral release and so on. Different drug classes act on specific stages. A comprehensive model including multiple stages may be more accurate in studying the dynamics of HIV decay under treatment from different drug classes. There are some clinical and experimental data that show that drugs acting on later stages of viral replication cycle may lead to a more rapid viral load decline. A model including two stages have been developed to study the dynamics under treatment in Sedaghat et al. [21]. They showed that the stage in the HIV-1 life cycle at which a drug acts may affect the observed decay dynamics, which is the later in the life cycle an inhibitor acts, the more rapid the decay in viremia. In this section, based on the works of [11,17,21,35–37], we formulate a general multistage infection progression model between uninfected CD4$^+$ T-cells and virus particles which traverses $n$ different stages during its life-cycle. We distinguish the host populations into the following compartments: uninfected cells $x(t)$, a succession of infected cells $y_i(t),\ i = 1, 2, \ldots, n$, whose members are in the $i$th stage of the infection progression, and virus particles $v(t)$. Based on the above assumptions and Section 1, a non-autonomous HIV-1 model with multiple stages for infected cells can be considered as follows:

$$\begin{cases} \dot{x}(t) = \lambda(t) - \mu(t)x(t) - \beta(t)x(t)v(t), \\ \dot{y}_1(t) = \beta(t)x(t)v(t) - k_1(t)y_1(t), \\ \dot{y}_2(t) = \widetilde{k}_1(t)y_1(t) - k_2(t)y_2(t), \\ \dot{y}_3(t) = \widetilde{k}_2(t)y_2(t) - k_3(t)y_3(t), \\ \qquad\qquad \cdots \\ \dot{y}_n(t) = \widetilde{k}_{n-1}(t)y_{n-1}(t) - k_n(t)y_n(t), \\ \dot{v}(t) = \widetilde{k}_n(t)y_n(t) - \delta(t)v(t), \end{cases} \tag{1}$$

where

$$\begin{aligned} &k_i(t) = \widetilde{k}_i(t) + \delta_i(t), \quad \widetilde{k}_i(t) = (1 - \varepsilon_{II}(t))k_i(t), \quad i = 1, \ldots, n-1, \\ &\widetilde{k}_n(t) = (1 - \varepsilon_{PI}(t))N(t)k_n(t), \quad \beta(t) = (1 - \varepsilon_{RT}(t))k(t), \end{aligned} \tag{2}$$

and the meanings of functions $\lambda(t)$, $\mu(t)$, $k_i(t)$, $\delta_i(t)$ $(i = 0, 1, \ldots, n)$, $k(t)$, $\delta(t)$, $N(t)$, $\varepsilon_{RT}(t)$, $\varepsilon_{II}(t)$ and $\varepsilon_{PI}(t)$ appeared in (2) are in accordance with the corresponding autonomous system parameters $\lambda$, $\mu$, $k_j$, $k$, $\delta$, $N$, $\varepsilon_{RT}$, $\varepsilon_{II}$ and $\varepsilon_{PI}$, respectively.

The initial condition of system (1) is given by

$$x(0) > 0, \quad y_i(0) > 0 \text{ for some } i \in \{1, 2, \dots, n\}. \tag{3}$$

In the following, we will give some assumptions and notations for system (1)

($A_1$) Functions $\lambda(t), \mu(t), \beta(t), k_i(t), \delta_i(t), \widetilde{k}_i(t)$ $(i = 1, \dots, n)$ and $\delta(t)$ are positive continuous bounded and have positive lower bounds.

($A_2$) If $f(t)$ is a continuous bounded function defined on $[0, +\infty)$, then we set

$$f^l = \liminf_{t\to+\infty} f(t) \quad f^u = \limsup_{t\to+\infty} f(t).$$

**Definition 1.** The system (1) is said to be permanent if there exists positive constants $q_0, \widetilde{q}_1, \dots, \widetilde{q}_{n+1}$ and $\widetilde{L}_0, \widetilde{L}_1, \dots, \widetilde{L}_{n+1}$ such that

$$q_0 \le \liminf_{t\to+\infty} x(t) \le \limsup_{t\to+\infty} x(t) \le \widetilde{L}_0,$$
$$\widetilde{q}_i \le \liminf_{t\to+\infty} y_i(t) \le \limsup_{t\to+\infty} y_i(t) \le \widetilde{L}_i, \quad i = 1, 2, \dots, n,$$
$$\widetilde{q}_{n+1} \le \liminf_{t\to+\infty} v(t) \le \limsup_{t\to+\infty} v(t) \le \widetilde{L}_{n+1},$$

hold for any solution $(x(t), y_1(t), \dots, y_n(t), v(t))$ of system (1) with initial condition (3). Here $q_0, \widetilde{q}_1, \dots, \widetilde{q}_{n+1}, \widetilde{L}_0, \widetilde{L}_1, \dots, \widetilde{L}_{n+1}$ are independent of (3).

**Lemma 1.** *([38]) Consider the following non-autonomous linear equation*

$$\dot{w}(t) = \lambda(t) - \mu(t)w(t). \tag{4}$$

*Suppose that assumptions ($A_1$) and ($A_2$) hold, then we have the following result:*

(i) *Denote the ultimate limit of all the solutions of Eq. (4) with the initial value $w(0) > 0$ by $w^*(t)$, where $w^*(t)$ is bounded and globally uniformly attractive on $R_+$.*
(ii) *There exist $m, M > 0$, such that $m < \liminf_{t\to+\infty} w(t) \le \limsup_{t\to+\infty} w(t) < M$.*
(iii) *If $\mu(t) > 0$ for all $t \ge 0$ and*

$$0 < \liminf_{t\to+\infty} \frac{\lambda(t)}{\mu(t)} \le \limsup_{t\to+\infty} \frac{\lambda(t)}{\mu(t)} < +\infty,$$

*then for any solution $w(t)$ of Eq. (4) with the initial condition $w(0) > 0$, we have*

$$\liminf_{t\to+\infty} \frac{\lambda(t)}{\mu(t)} = \left(\frac{\lambda(t)}{\mu(t)}\right)^l < \liminf_{t\to+\infty} w(t) \le \limsup_{t\to+\infty} w(t) < \left(\frac{\lambda(t)}{\mu(t)}\right)^u = \limsup_{t\to+\infty} \frac{\lambda(t)}{\mu(t)}.$$

**Lemma 2.** *The solution $(x(t), y_1(t), \dots, y_n(t), v(t))$ of system (1) with initial condition (3) is positive and bounded for all $t \ge 0$.*

**Proof.** Since the right hand side of system (1) is completely continuous, so the solution $(x(t), y_1(t), \dots, y_n(t), v(t))$ of (1) with initial condition (3) exists and is unique.

By system (1), we obtain

$$\begin{cases} x(t) = x(0)e^{-\int_0^t (\mu(s)+\beta(s)v(s))ds} + \displaystyle\int_0^t \lambda(s)e^{\int_t^s (\mu(\theta)+\beta(\theta)v(\theta))d\theta} ds, \\ y_1(t) = y_1(0)e^{-\int_0^t k_1(s)ds} + \displaystyle\int_0^t \beta(s)x(s)v(s)e^{\int_t^s k_1(\theta)d\theta} ds, \\ y_i(t) = y_i(0)e^{-\int_0^t k_i(s)ds} + \displaystyle\int_0^t \widetilde{k}_{i-1}(s)y_{i-1}(s)e^{\int_t^s k_i(\theta)d\theta} ds, \quad i = 2, 3, \dots, n. \\ v(t) = v(0)e^{-\int_0^t \delta(s)ds} + \displaystyle\int_0^t \widetilde{k}_n(s)y_n(s)e^{\int_t^s \delta(\theta)d\theta} ds. \end{cases} \tag{5}$$

Similar to Lemma 2.3 in [34], we easily obtain $x(t), y_1(t), \dots, y_n(t), v(t) > 0$ for all $t \ge 0$ since $x(0), y_1(0), \dots, y_n(0), v(0) > 0$.

Now, we will show that $(x(t), y_1(t), \dots, y_n(t), v(t))$ are bounded for all $t \ge 0$. Let

$$\begin{aligned} H(t) &= x(t) + \frac{\beta^l}{\beta^u} y_1(t) + \frac{\beta^l k_1^l}{2\beta^u \widetilde{k}_1^u} y_2(t) + \frac{\beta^l k_1^l k_2^l}{2^2 \beta^u \widetilde{k}_1^u \widetilde{k}_2^u} y_3(t) \\ &\quad + \dots + \frac{1}{2^{n-1}} \cdot \frac{\beta^l}{\beta^u} \cdot \prod_{i=1}^{n-1} \left(\frac{k_i^l}{\widetilde{k}_i^u}\right) y_n(t) + \frac{1}{2^n} \cdot \frac{\beta^l}{\beta^u} \cdot \prod_{i=1}^{n} \left(\frac{k_i^l}{\widetilde{k}_i^u}\right) v(t). \end{aligned} \tag{6}$$

Then, we can compute the time derivative of $H(t)$ along the solution of (1) as follows:

$$\begin{aligned}
\dot{H}(t) &= \lambda(t) - \mu(t)x(t) - \beta(t)x(t)v(t) + \frac{\beta^l}{\beta^u}[\beta(t)x(t)v(t) - k_1(t)y_1(t)] + \frac{\beta^l k_1^l}{2\beta^u \widetilde{k}_1^u}[\widetilde{k}_1(t)y_1(t) - k_2(t)y_2(t)] \\
&\quad + \frac{\beta^l k_1^l k_2^l}{2^2\beta^u \widetilde{k}_1^u \widetilde{k}_2^u}[\widetilde{k}_2(t)y_2(t) - k_3(t)y_3(t)] + \cdots + \frac{1}{2^{n-1}}\cdot\frac{\beta^l}{\beta^u}\cdot\prod_{i=1}^{n-1}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right) \times [\widetilde{k}_{n-1}(t)y_{n-1}(t) - k_n(t)y_n(t)] \\
&\quad + \frac{1}{2^n}\cdot\frac{\beta^l}{\beta^u}\cdot\prod_{i=1}^{n}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right)[\widetilde{k}_n(t)y_n(t) - \delta(t)v(t)] \\
&\le \lambda(t) - \mu(t)x(t) - \frac{\beta^l}{2\beta^u}k_1^l y_1(t) - \frac{1}{2^2}\cdot\frac{\beta^l k_1^l}{\beta^u \widetilde{k}_1^u}\cdot k_2^l y_2(t) - \cdots - \frac{1}{2^{n-1}}\cdot\frac{\beta^l}{\beta^u}\cdot\prod_{i=1}^{n-2}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right)\cdot k_{n-1}^l y_{n-1}(t) \\
&\quad - \frac{1}{2^n}\cdot\frac{\beta^l}{\beta^u}\cdot\prod_{i=1}^{n-1}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right)\cdot k_n^l y_n(t) - \frac{1}{2^n}\cdot\frac{\beta^l}{\beta^u}\cdot\prod_{i=1}^{n}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right)\delta^l v(t) \\
&\le \lambda(t) - \sigma H(t),
\end{aligned} \tag{7}$$

here $\sigma = \min\{\mu^l, \frac{k_1^l}{2}, \frac{k_2^l}{2}, \dots, \frac{k_n^l}{2}, \delta^l\}$. By (7) and Lemma 1, we have

$$\limsup_{t\to+\infty} H(t) \le \frac{\lambda^u}{\sigma}. \tag{8}$$

Thus, we easily have that

$$\begin{aligned}
&\limsup_{t\to+\infty} y_1(t) \le \frac{\beta^u\lambda^u}{\beta^l\sigma} \triangleq \widetilde{L}_1, \\
&\limsup_{t\to+\infty} y_2(t) \le \frac{2\beta^u\lambda^u}{\beta^l\sigma}\frac{\widetilde{k}_1^u}{k_1^l} \triangleq \widetilde{L}_2, \\
&\quad\cdots \\
&\limsup_{t\to+\infty} y_n(t) \le \frac{2^{n-1}\beta^u\lambda^u}{\beta^l\sigma}\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right) \triangleq \widetilde{L}_n, \\
&\limsup_{t\to+\infty} v(t) \le \frac{2^n\beta^u\lambda^u}{\beta^l\sigma}\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right) \triangleq \widetilde{L}_{n+1},
\end{aligned}$$

where $\triangleq$ means "is defined as".

Furthermore, from the first equation of (1), $\dot{x}(t) \le \lambda(t) - \mu(t)x(t) \le \lambda^u - \mu^l x(t)$, which implies that

$$\limsup_{t\to+\infty} x(t) \le \frac{\lambda^u}{\mu^l} \triangleq \widetilde{L}_0. \tag{9}$$

So, $x(t), y_1(t), y_2(t), \dots, y_n(t), v(t)$ are bounded for all $t \ge 0$ since $H(t)$ is bounded for all $t \ge 0$ since $H(t)$ is bounded. This completes the proof of Lemma 2. □

**Lemma 3.** *The solution $(x(t), y_1(t), \dots, y_n(t), v(t))$ of system (1) with initial condition (3) satisfies*

$$\liminf_{t\to+\infty} x(t) \ge q_0, \tag{10}$$

*where*

$$q_0 = \left(\frac{\lambda(t)}{\mu(t) + 2^n\beta(t)\cdot\frac{\beta^u}{\beta^l}\prod_{i=1}^{n}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right)\frac{\lambda^u}{\sigma}}\right)^l.$$

**Proof.** By Lemma 2, for any $\varepsilon > 0$, there exists a $t_0 > 0$ large enough such that

$$v(t) \le \frac{2^n\beta^u}{\beta^l}\prod_{i=1}^{n}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right)\frac{\lambda^u}{\sigma} + \varepsilon, \quad t \ge t_0.$$

Thus, by the first equation of system (1),

$$\dot{x}(t) \geq \lambda(t) - \left[\mu(t) + \beta(t)\left(\frac{2^n\beta^u}{\beta^l}\prod_{i=1}^{n}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right)\frac{\lambda^u}{\sigma} + \varepsilon\right)\right]x(t), \quad t \geq t_0,$$

which means that $\liminf_{t\to+\infty} x(t) \geq q_0$. This completes the proof of Lemma 4.

Define

$$W(t) = y_1(t) + \frac{k_1^u}{\widetilde{k}_1^l}y_2(t) + \frac{k_1^u k_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}y_3(t) + \cdots + \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)y_n(t) + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)v(t), \tag{11}$$

and

$$G(t) = y_1(t) + \frac{k_1^l}{\widetilde{k}_1^u}y_2(t) + \frac{k_1^l k_2^l}{\widetilde{k}_1^u\widetilde{k}_2^u}y_3(t) + \cdots + \prod_{i=1}^{n-1}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right)y_n(t) + \prod_{i=1}^{n}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right)v(t). \tag{12}$$

□

Thus, we obtain the following Lemma.

**Lemma 4.** *For any t large enough, then we have*

*(i)*

$$W(t) \leq a_1y_1(t) + a_2y_2(t) + \cdots + a_ny_n(t) + av(t), \tag{13}$$

*where*

$$a_1 = 1, \quad a_j = \prod_{i=1}^{j-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right), \quad j = 2, 3, \ldots, n, \quad a = \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right).$$

*(ii)*

$$G(t) \leq b_1y_1(t) + b_2y_2(t) + \cdots + b_ny_n(t) + bv(t) \leq W(t), \tag{14}$$

*where*

$$b_1 = 1, \quad b_j = \prod_{i=1}^{j-1}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right), \quad j = 2, 3, \ldots, n, \quad b = \prod_{i=1}^{n}\left(\frac{k_i^l}{\widetilde{k}_i^u}\right).$$

## 3. Permanence and extinction of system (1)

Denote

$$R_* = \frac{\beta^l\lambda^l}{\delta^u\mu^u}\cdot\prod_{i=1}^{n}\left(\frac{\widetilde{k}_i^l}{k_i^u}\right) \quad R^* = \frac{\beta^u\lambda^u}{\delta^l\mu^l}\cdot\prod_{i=1}^{n}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right). \tag{15}$$

Then we have the following theorem.

**Theorem 1.** *The system (1) with initial condition (3) is permanent provided that $R_* > 1$. Namely, we have the following results:*

$$\begin{aligned}
\widetilde{q}_1 &\leq \liminf_{t\to+\infty} y_1(t) \leq \limsup_{t\to+\infty} y_1(t) \leq \widetilde{L}_1,\\
\widetilde{q}_2 &\leq \liminf_{t\to+\infty} y_2(t) \leq \limsup_{t\to+\infty} y_2(t) \leq \widetilde{L}_2,\\
\widetilde{q}_3 &\leq \liminf_{t\to+\infty} y_3(t) \leq \limsup_{t\to+\infty} y_3(t) \leq \widetilde{L}_3,\\
&\cdots\\
\widetilde{q}_n &\leq \liminf_{t\to+\infty} y_n(t) \leq \limsup_{t\to+\infty} y_n(t) \leq \widetilde{L}_n,\\
\widetilde{q}_{n+1} &\leq \liminf_{t\to+\infty} v(t) \leq \limsup_{t\to+\infty} v(t) \leq \widetilde{L}_{n+1},
\end{aligned}$$

*where $\widetilde{q}_i$ and $\widetilde{L}_i$, $i = 1, 2, \ldots, n+1$ are defined in (43), (44) and Lemma 2, respectively.*

**Proof.** Combining with Lemma 2 and the following Proposition 1, we will complete the proof of this theorem. □

**Proposition 1.** *If $R_* > 1$ holds, then for any positive solution $(x(t), y_1(t), \ldots, y_n(t), v(t))$ of system (1) with (3), we have*

$$\liminf_{t\to+\infty} y_i(t) \geq \widetilde{q}_i, \quad i = 1, 2, \ldots, n \qquad \liminf_{t\to+\infty} v(t) \geq \widetilde{q}_{n+1}, \tag{16}$$

*where $\widetilde{q}_1, \widetilde{q}_2, \ldots, \widetilde{q}_n$ and $\widetilde{q}_{n+1}$ are defined in (43) and (44).*

**Proof.** Here we only show that it is true by the following four steps.

Step I. We will prove that for any solution of system (1), there exist

$$q_1 = \min\left\{\frac{1}{2}\frac{\mu^u\delta^l}{\beta^u\widetilde{k}_n^u}(R_*-1)\prod_{i=1}^{n-1}\left(\frac{k_{i+1}^l}{\widetilde{k}_i^u}\right),\ \frac{1}{2}\frac{\mu^u}{\beta^u\alpha}(R_*-1)\prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\right\},$$

$$q_2 = \frac{1}{2}\frac{\mu^u\delta^l}{\beta^u\widetilde{k}_n^u}(R_*-1)\prod_{i=2}^{n-1}\left(\frac{k_{i+1}^l}{\widetilde{k}_i^u}\right),$$

$$\cdots$$

$$q_{n-1} = \frac{1}{2}\frac{\mu^u\delta^l}{\beta^u\widetilde{k}_n^u}(R_*-1)\frac{k_n^l}{\widetilde{k}_{n-1}^u},$$

$$q_n = \frac{1}{2}\frac{\mu^u\delta^l}{\beta^u\widetilde{k}_n^u}(R_*-1),$$

$$\alpha = 1+\frac{k_1^u\widetilde{k}_1^u}{\widetilde{k}_1^lk_2^l}+\prod_{i=1}^{2}\left(\frac{k_i^u\widetilde{k}_i^u}{\widetilde{k}_i^lk_{i+1}^l}\right)+\cdots+\prod_{i=1}^{n-2}\left(\frac{k_i^u\widetilde{k}_i^u}{\widetilde{k}_i^lk_{i+1}^l}\right)+\prod_{i=1}^{n-1}\left(\frac{k_i^u\widetilde{k}_i^u}{\widetilde{k}_i^lk_{i+1}^l}\right), \tag{17}$$

such that $\limsup_{t\to+\infty} y_1(t)\geq q_1,\quad \limsup_{t\to+\infty} y_2(t)\geq q_2,\ldots,\quad \limsup_{t\to+\infty} y_n(t)\geq q_n$, respectively. If they are not true, without loss of generality, we assume that $\limsup_{t\to+\infty} y_1(t) < q_1$, from the third equation of system (1), we have

$$\dot{y}_2(t) = \widetilde{k}_1(t)y_1(t) - k_2(t)y_2(t) \leq \widetilde{k}_1q_1 - k_2^ly_2(t),$$

by Lemma 1, $\limsup_{t\to+\infty} y_2(t) \leq \frac{\widetilde{k}_1^u}{k_2^l}q_1$. Similarly, from the last $(n-1)$ equations of system (1), we get

$$\limsup_{t\to+\infty} y_3(t)\leq\frac{\widetilde{k}_1^u\widetilde{k}_2^u}{k_2^lk_3^l}q_1,\ldots,\quad \limsup_{t\to+\infty} y_n(t)\leq\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_i^u}{k_{i+1}^l}\right)q_1,\quad \limsup_{t\to+\infty} v(t)\leq\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_i^u}{k_{i+1}^l}\right)\frac{\widetilde{k}_n^u}{\delta^l}q_1.$$

Thus, by the first equation of system (1), we obtain

$$\dot{x}(t) = \lambda(t)-\mu(t)x(t)-\beta(t)x(t)v(t)\geq\lambda^l-\left[\mu^u+\beta^u\cdot q_1\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_1^u}{k_{i+1}^l}\right)\left(\frac{\widetilde{k}_n^u}{\delta^l}\right)\right]x(t),$$

it follows from Lemma 1 that

$$\liminf_{t\to+\infty} x(t)\geq\frac{\lambda^l}{\mu^u+\beta^u\cdot q_1\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_i^u}{k_{i+1}^l}\right)\left(\frac{\widetilde{k}_n^u}{\delta^l}\right)}\triangleq h(q_1). \tag{18}$$

Note that the definition of $W(t)$, we obtain

$$\begin{aligned}\dot{W}(t) &= \beta(t)x(t)v(t)+\frac{k_1^u}{\widetilde{k}_1^l}\widetilde{k}_1(t)y_1(t)-k_1(t)y_1(t)+\frac{k_1^uk_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}\widetilde{k}_2(t)y_2(t)-\frac{k_1^u}{\widetilde{k}_1^l}k_2(t)y_2(t)+\cdots\\ &\quad+\prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left[\frac{k_n^u}{\widetilde{k}_n^l}\widetilde{k}_n(t)y_n(t)-k_n(t)y_n(t)\right]-\prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta(t)v(t)\\ &\geq \beta(t)x(t)v(t)-\prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta(t)v(t)\\ &\geq\left(\beta^lh(q_1)-\prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u\right)v(t)>0,\end{aligned} \tag{19}$$

from (15), (17) and (19) , then

$$\begin{aligned}\dot{W}(t) &\geq\left(\beta^l\frac{\lambda^l}{\mu^u+\beta^u\cdot q_1\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_i^u}{k_{i+1}^l}\right)\left(\frac{\widetilde{k}_n^u}{\delta^l}\right)}-\prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u\right)v(t)\\ &\geq\left(\frac{\beta^l\lambda^l}{\mu^u+\frac{\mu^u}{2}(R_*-1)}-\prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u\right)v(t)\end{aligned}$$

$$= \delta^u \prod_{i=1}^{n} \left( \frac{k_i^u}{\widetilde{k}_i^l} \right) \frac{R_* - 1}{R_* + 1} v(t) > 0, \quad \text{if } R_* > 1, \tag{20}$$

which implies that $W(t)$ is increasing, using Lemma 4, $W(t)$ is positive bounded, so there must exist a constant $W^* > 0$ such that $W(t) \to W^*$ when $t \to +\infty$, which means that $\dot{W}(t) \to 0$ when $t \to +\infty$, this reduces that $v(t) \to 0, y(t) \to 0$ as $t \to +\infty$. So $W(t) \to 0$ as $t \to +\infty$, which reduces a contradiction. Thus $\limsup_{t\to+\infty} y_1(t) \geq q_1$. Similarly, we can easily obtain

$$\limsup_{t\to+\infty} y_2(t) \geq q_2, \quad \limsup_{t\to+\infty} y_3(t) \geq q_3, \ldots, \quad \limsup_{t\to+\infty} y_n(t) \geq q_n.$$

Step II. Secondly, we will show that there exists a constant $\gamma = \alpha q_1 e^{-(\tau+2p)\delta^u} > 0$ such that $W(t) \geq \gamma$.

By Step I, we obtain that for any $t_0 > 0$,

$$W(t) < \left( 1 + \frac{k_1^u \widetilde{k}_1^u}{\widetilde{k}_1^l k_2^l} + \prod_{i=1}^{2} \left( \frac{k_i^u \widetilde{k}_i^u}{\widetilde{k}_i^l k_{i+1}^l} \right) + \cdots + \prod_{i=1}^{n-2} \left( \frac{k_i^u \widetilde{k}_i^u}{\widetilde{k}_i^l k_{i+1}^l} \right) + \prod_{i=1}^{n-1} \left( \frac{k_i^u \widetilde{k}_i^u}{\widetilde{k}_i^l k_{i+1}^l} \right) \right) q_1 \triangleq \alpha q_1$$

is impossible for all $t \geq t_0$. Hence, we will consider the two possibilities as follows:

(i) $W(t) \geq \alpha q_1$ for all $t$ large enough;
(ii) $W(t)$ oscillates about $\alpha q_1$ for all $t$ large enough.

Obviously, we only need to consider the second case. Let $t_1$ and $t_2$ be sufficiently large times satisfying

$$W(t_1) = W(t_2) = \alpha q_1, \quad W(t) < \alpha q_1, \quad \forall t \in (t_1, t_2),$$

If $t_2 - t_1 \leq 2p$, where

$$p = \frac{1}{\mu^u (R_* + 1)} \ln \frac{4R_*}{R_* - 1} > 0. \tag{21}$$

From (11), we obtain

$$\prod_{i=1}^{n} \left( \frac{k_i^u}{\widetilde{k}_i^l} \right) v(t) \leq W(t) < \alpha q_1, \quad \forall t \in (t_1, t_2),$$

that is

$$v(t) \leq \alpha q_1 \prod_{i=1}^{n} \left( \frac{\widetilde{k}_i^l}{k_i^u} \right), \quad \forall t \in (t_1, t_2).$$

It follows that from the first equation of system (1), we get

$$\begin{aligned} \dot{x}(t) &= \lambda(t) - \mu(t)x(t) - \beta(t)x(t)v(t) \\ &\geq \lambda^l - \left( \mu^u + \beta^u \alpha q_1 \prod_{i=1}^{n} \left( \frac{\widetilde{k}_i^l}{k_i^u} \right) \right) x(t), \quad \forall t \in (t_1, t_2). \end{aligned} \tag{22}$$

For any $\forall t \in (t_1, t_2)$, integrating the inequality (22) from $t_1$ to $t_2$, we have

$$\begin{aligned} x(t) &\geq x(t_1) \exp\left( - \int_{t_1}^{t} \left( \mu^u + \beta^u \alpha q_1 \prod_{i=1}^{n} \left( \frac{\widetilde{k}_i^l}{k_i^u} \right) \right) ds \right) + \int_{t_1}^{t} \lambda^l \exp\left( - \int_{s}^{t} \left( \mu^u + \beta^u \alpha q_1 \prod_{i=1}^{n} \left( \frac{\widetilde{k}_i^l}{k_i^u} \right) \right) d\theta \right) ds \\ &\geq \frac{\lambda^l}{\mu^u + \beta^u \alpha q_1 \prod_{i=1}^{n} \left( \frac{\widetilde{k}_i^l}{k_i^u} \right)} \left( 1 - \exp\left( - \left( \mu^u + \beta^u \alpha q_1 \prod_{i=1}^{n} \left( \frac{\widetilde{k}_i^l}{k_i^u} \right) \right) (t - t_1) \right) \right). \end{aligned} \tag{23}$$

Thus, we have

$$x(t) \geq \frac{\lambda^l}{\mu^u + \beta^u \alpha q_1 \prod_{i=1}^{n} \left( \frac{\widetilde{k}_i^l}{k_i^u} \right)} - \varepsilon_0 \triangleq x_\Delta > 0, \quad \forall t \in (t_1 + p, t_2), \tag{24}$$

where

$$\varepsilon_0 = \frac{1}{2} \frac{\delta^u}{\beta^l} \prod_{i=1}^{n} \left( \frac{k_i^u}{\widetilde{k}_i^l} \right) \frac{R_* - 1}{R_* + 1} = \frac{1}{2} \frac{\lambda^l}{\mu^u} \frac{R_* - 1}{R_* (R_* + 1)} > 0.$$

According to (11), (17) and (19), we further obtain

$$\begin{aligned}\dot{W}(t) &\geq \left(\beta^l x(t) - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u\right)v(t) > -\prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u v(t) \\ &\geq -\delta^u W(t), \quad \forall t \in (t_1, t_2).\end{aligned} \tag{25}$$

Noting that $t_2 - t_1 < 2p$, then

$$W(t) \geq W(t_1)e^{-\int_{t_1}^{t}\delta^u ds} = \alpha q_1 e^{-\delta^u(t-t_1)} \geq \alpha q_1 e^{-2p\delta^u} \triangleq \gamma. \tag{26}$$

If $t_2 - t_1 > 2p$, clearly, when $t \in [t_1, t_1 + 2p]$, $W(t) \geq \gamma$ holds; when $t \in [t_1 + 2p, t_2]$, from (19),

$$\begin{aligned}\dot{W}(t) &\geq \beta(t)x(t)v(t) - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta(t)v(t) \\ &\geq \left(\beta^l x_\Delta - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u\right)v(t) > 0, \quad \text{if } R_* > 1,\end{aligned}$$

then we have

$$W(t) \geq W(t_1 + 2p) \geq \gamma, \quad \forall t \in [t_1 + 2p, t_2].$$

Therefore, if $R_* > 1$, then for all $t$ large enough, we obtain $W(t) \geq \gamma > 0$, this means that

$$a_1 y_1(t) + a_2 y_2(t) + \cdots + a_n y_n(t) + av(t) \geq \gamma > 0. \tag{27}$$

Step III. Next, we will prove that there exists

$$\begin{aligned}&\overline{\gamma} = \frac{\beta^l q_0 \gamma}{a\bar{c}}, \quad \gamma_1 = \frac{\beta^l q_0 k_1^u \gamma}{a\bar{c}a_1\bar{c}_1}, \quad \gamma_2 = \frac{k_1^u}{\widetilde{k}_1^l}\frac{k_1^u k_2^u}{a_1 a_2 \bar{c}_1 \bar{c}_2}\frac{\beta^l q_0 \gamma}{a\bar{c}}, \quad \ldots, \\ &\gamma_{n-1} = \left(\frac{k_1^u}{\widetilde{k}_1^l}\right)^{n-2}\left(\frac{k_2^u}{\widetilde{k}_2^l}\right)^{n-1}\cdots\left(\frac{k_{n-2}^u}{\widetilde{k}_{n-2}^l}\right)\cdot\prod_{i=1}^{n-1}\left(\frac{k_i^u}{a_i\bar{c}_i}\right)\frac{\beta q_0 \gamma}{a\bar{c}},\end{aligned}$$

such that

$$\begin{aligned}&\liminf_{t\to+\infty}\widetilde{P}_1(t) = \liminf_{t\to+\infty}(a_1y_1(t) + a_2y_2(t) + \cdots + a_ny_n(t)) > \overline{\gamma} > 0, \\ &\liminf_{t\to+\infty}\widetilde{W}_1(t) = \liminf_{t\to+\infty}(a_2y_2(t) + a_3y_3(t) + \cdots + a_ny_n(t) + av(t)) > \gamma_1 > 0, \\ &\liminf_{t\to+\infty}\widetilde{W}_2(t) = \liminf_{t\to+\infty}(a_3y_3(t) + a_4y_4(t) + \cdots + a_ny_n(t) + av(t)) > \gamma_2 > 0, \\ &\quad\ldots \\ &\liminf_{t\to+\infty}\widetilde{W}_{n-1}(t) = \liminf_{t\to+\infty}(a_ny_n(t) + av(t)) > \gamma_{n-1} > 0.\end{aligned} \tag{28}$$

In fact, we denote
(i)

$$\begin{aligned}P_1(t) = y_1(t) &+ \frac{k_1^u}{\widetilde{k}_1^l}\left(y_2(t) + \int_t^t \widetilde{k}_1(s)y_1(s)ds\right) + \frac{k_1^u k_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}\left(y_3(t) + \int_t^t \widetilde{k}_2(s)y_2(s)ds\right) + \cdots \\ &+ \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(y_n(t) + \int_t^t \widetilde{k}_{n-1}(s)y_{n-1}(s)ds\right),\end{aligned} \tag{29}$$

by Lemma 4, then we get

$$\begin{aligned} P_1(t) &\le y_1(t) + a_2y_2(t) + a_3y_3(t) + \cdots + a_ny_n(t) \\ &\le a_1y_1(t) + a_2y_2(t) + a_3y_3(t) + \cdots + a_ny_n(t) = \widetilde{P}_1(t), \end{aligned}$$

and

$$\begin{aligned} \dot{\widetilde{P}}_1(t) &\ge \dot{P}_1(t) = \beta(t)x(t)v(t) - k_1(t)y_1(t) + \frac{k_1^u}{\widetilde{k}_1^l}\widetilde{k}_1(t)y_1(t) + \frac{k_1^uk_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}\widetilde{k}_2(t)y_2(t) \\ &\quad - \frac{k_1^u}{\widetilde{k}_1^l}k_2(t)y_2(t) + \cdots + \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)(\widetilde{k}_{n-1}(t)y_{n-1}(t) - k_n(t)y_n(t)) \\ &\ge \beta(t)x(t)v(t) - \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)k_n(t)y_n(t) \\ &\ge \beta^lq_0v(t) - \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)k_n^uy_n(t). \end{aligned} \tag{30}$$

It follows from (27) that

$$v(t) \ge \frac{\gamma - (a_1y_1(t) + a_2y_2(t) + \cdots + a_ny_n(t))}{a}.$$

So, we have

$$\begin{aligned} \dot{\widetilde{P}}_1(t) &\ge \frac{\beta^lq_0\gamma}{a} - \frac{\beta^lq_0}{a}(a_1y_1(t) + a_2y_2(t) + \cdots + a_ny_n(t)) - \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)k_n^uy_n(t) \\ &\ge \frac{\beta^lq_0\gamma}{a} - \frac{\beta^lq_0}{a}(a_1y_1(t) + a_2y_2(t) + \cdots + a_{n-1}y_{n-1}(t)) - \left(\frac{\beta^lq_0}{a} + k_n^u\right)a_ny_n(t) \\ &\ge \frac{\beta^lq_0\gamma}{a} - \bar{c}\widetilde{P}_1(t), \end{aligned}$$

where

$$\bar{c} = \max\left\{\frac{\beta^lq_0}{a} + k_n^u, \frac{\beta^lq_0}{a}\right\} = \frac{\beta^lq_0}{a} + k_n^u,$$

which implies that $\liminf\limits_{t\to+\infty}\widetilde{P}_1(t) \ge \frac{\beta^lq_0\gamma}{a\bar{c}} = \overline{\gamma}$, then

$$a_1y_1(t) + a_2y_2(t) + \cdots + a_ny_n(t) \ge \overline{\gamma}. \tag{31}$$

(ii) Next, we denote

$$\begin{aligned} W_1(t) &= \frac{k_1^u}{\widetilde{k}_1^l}y_2(t) + \frac{k_1^uk_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}\left(y_3(t) + \int_t^t\widetilde{k}_2(s)y_2(s)ds\right) \\ &\quad + \prod_{i=1}^{3}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(y_4(t) + \int_t^t\widetilde{k}_3(s)y_2(s)ds\right) + \cdots + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(v(t) + \int_t^t\widetilde{k}_n(s)y_n(s)ds\right). \end{aligned} \tag{32}$$

Similarly, by Lemma 4, we have

$$\begin{aligned} W_1(t) &\le \frac{k_1^u}{\widetilde{k}_1^l}y_2(t) + a_3y_3(t) + a_4y_4(t) + \cdots + a_ny_n(t) + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)v(t) \\ &\le a_2y_2(t) + a_3y_3(t) + a_4y_4(t) + \cdots + a_ny_n(t) + av(t) \triangleq \widetilde{W}_1(t), \end{aligned}$$

and

$$\begin{aligned} \dot{\widetilde{W}}_1(t) &\ge \dot{W}_1(t) = \frac{k_1^u}{\widetilde{k}_1^l}(\widetilde{k}_1(t)y_1(t) - k_2(t)y_2(t)) + \frac{k_1^uk_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}(\widetilde{k}_2(t)y_2(t) - k_3(t)y_3(t)) + \cdots \\ &\quad + \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)(\widetilde{k}_{n-1}(t)y_{n-1}(t) - k_n(t)y_n(t)) + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)(\widetilde{k}_n(t)y_n(t) - \delta(t)v(t)) \\ &\ge \frac{k_1^u}{\widetilde{k}_1^l}\widetilde{k}_1^ly_1(t) - \frac{k_1^uk_2^u}{\widetilde{k}_1^l}y_2(t) + \frac{k_1^uk_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}(\widetilde{k}_2^ly_2(t) - k_3^uy_3(t)) + \cdots + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)(\widetilde{k}_n^ly_n(t) - \delta^uv(t)) \\ &\ge k_1^uy_1(t) - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^uv(t), \end{aligned} \tag{33}$$

it follows from (31) that

$$y_1(t) \geq \frac{\overline{\gamma} - (a_2y_2(t) + a_3y_3(t) + \cdots + a_ny_n(t))}{a_1},$$

thus we have

$$\begin{aligned}\dot{\widetilde{W}}_1(t) &\geq \frac{k_1^u\overline{\gamma}}{a_1} - \frac{k_1^u}{a_1}(a_2y_2(t) + a_3y_3(t) + \cdots + a_ny_n(t)) - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u v(t)\\ &\geq \frac{k_1^u\overline{\gamma}}{a_1} - \frac{k_1^u}{a_1}(a_2y_2(t) + a_3y_3(t) + \cdots + a_ny_n(t)) - \delta^u a v(t)\\ &\geq \frac{k_1^u\overline{\gamma}}{a_1} - \bar{c}_1\widetilde{W}_1(t),\end{aligned}$$

where $\bar{c}_1 = \max\{\frac{k_1^u}{a_1}, \delta^u\}$, which means that

$$\liminf_{t\to+\infty}\widetilde{W}_1(t) \geq \frac{k_1^u\overline{\gamma}}{a_1\bar{c}_1} = \frac{\beta^l q_0 k_1^u\gamma}{aa_1\overline{c}c_1} \triangleq \gamma_1. \tag{34}$$

(iii) Denote

$$\begin{aligned}W_2(t) = \frac{k_1^uk_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}y_3(t) + \prod_{i=1}^{3}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(y_4(t) + \int_t^t \widetilde{k}_3(s)y_3(s)ds\right) + \prod_{i=1}^{4}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(y_5(t) + \int_t^t \widetilde{k}_4(s)y_4(s)ds\right) + \cdots\\ + \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(y_n(t) + \int_t^t \widetilde{k}_{n-1}(s)y_{n-1}(s)ds\right) + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(v(t) + \int_t^t \widetilde{k}_n(s)y_n(s)ds\right).\end{aligned} \tag{35}$$

Using Lemma 4, we have

$$\begin{aligned}W_2(t) &\leq \frac{k_1^uk_2^u}{\widetilde{k}_1^lk_2^l}y_3(t) + a_4y_4(t) + \cdots + a_ny_n(t) + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)v(t)\\ &\leq a_3y_3(t) + a_4y_4(t) + \cdots + a_ny_n(t) + av(t) \triangleq \widetilde{W}_2(t),\end{aligned}$$

and

$$\begin{aligned}\dot{\widetilde{W}}_2(t) \geq \dot{W}_2(t) &= \frac{k_1^uk_2^u}{\widetilde{k}_1^l\widetilde{k}_2^l}(\widetilde{k}_2(t)y_2(t) - k_3(t)y_3(t)) + \prod_{i=1}^{3}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)(\widetilde{k}_3(t)y_3(t) - k_4(t)y_4(t)) + \cdots\\ &\quad + \prod_{i=1}^{n-1}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)(\widetilde{k}_{n-1}(t)y_{n-1}(t) - k_n(t)y_n(t)) + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)(\widetilde{k}_n(t)y_n(t) - \delta(t)v(t))\\ &\geq \frac{k_1^uk_2^u}{\widetilde{k}_1^l}y_2(t) - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u v(t).\end{aligned} \tag{36}$$

Noting that (35), then

$$y_2(t) \geq \frac{\gamma_1 - (a_3y_3(t) + a_4y_4(t) + \cdots + a_ny_n(t) + av(t))}{a_2}.$$

So, we have

$$\begin{aligned}\dot{\widetilde{W}}_2(t) &\geq \frac{k_1^uk_2^u\gamma_1}{\widetilde{k}_1^la_2} - \frac{k_1^uk_2^u}{\widetilde{k}_1^la_2}(a_3y_3(t) + a_4y_4(t) + \cdots + a_ny_n(t) + av(t)) - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u v(t)\\ &\geq \frac{k_1^uk_2^u\gamma_1}{\widetilde{k}_1^la_2} - \bar{c}_2\widetilde{W}_2(t),\end{aligned}$$

where $\bar{c}_2 = \max\left\{\frac{k_1^uk_2^u}{\widetilde{k}_1^la_2}, \frac{k_1^uk_2^u}{\widetilde{k}_1^la_2} + \delta^u\right\} = \frac{k_1^uk_2^u}{\widetilde{k}_1^la_2} + \delta^u$, by Lemma 1, then we obtain

$$\liminf_{t\to+\infty}\widetilde{W}_2(t) \geq \frac{k_1^uk_2^u\gamma_1}{\widetilde{k}_1^la_2\bar{c}_2} = \frac{\beta^l q_0}{a}\frac{(\widetilde{k}_1^u)^2k_2^u\gamma}{\widetilde{k}_1^la_1a_2\bar{c}_1\bar{c}_2\overline{c}} \triangleq \gamma_2. \tag{37}$$

(iv) Denote

$$W_3(t) = \prod_{i=1}^{3}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)y_4(t) + \prod_{i=1}^{4}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(y_5(t) + \int_t^t \widetilde{k}_4(s)y_4(s)ds\right) + \cdots + \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\left(v(t) + \int_t^t \widetilde{k}_n(s)y_n(s)ds\right). \tag{38}$$

Thus, by Lemma 4, we have

$$W_3(t) \le a_4y_4(t) + a_5y_5(t) + \cdots + a_ny_n(t) + av(t) \triangleq \widetilde{W}_3(t),$$

and

$$\begin{aligned}\dot{\widetilde{W}}_3(t) \ge \dot{W}_3(t) &\ge \frac{k_1^uk_2^uk_3^u}{\widetilde{k}_1^l\widetilde{k}_2^l}y_3(t) - \prod_{i=1}^{n}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\delta^u v(t)\\ &\ge \prod_{i=1}^{2}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_3^u\gamma_2}{a_3} - \bar{c}_3\widetilde{W}_3(t),\end{aligned}$$

where

$$\bar{c}_3 = \max\left\{\prod_{i=1}^{2}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_3^u}{a_3} \quad \prod_{i=1}^{2}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_3^u}{a_3} + \delta^u\right\} = \prod_{i=1}^{2}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_3^u}{a_3} + \delta^u,$$

which implies that

$$\liminf_{t\to+\infty}\widetilde{W}_3(t) \ge \prod_{i=1}^{2}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_3^u\gamma_2}{a_3\bar{c}_3} \triangleq \gamma_3. \tag{39}$$

Similarly, one by one we have

$$\begin{aligned}&\liminf_{t\to+\infty}\widetilde{W}_4(t) = \liminf_{t\to+\infty}(a_5y_5(t) + \cdots + a_ny_n(t) + av(t)) \ge \prod_{i=1}^{3}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_4^u\gamma_3}{a_4\bar{c}_4} \triangleq \gamma_4,\\ &\liminf_{t\to+\infty}\widetilde{W}_5(t) = \liminf_{t\to+\infty}(a_6y_6(t) + \cdots + a_ny_n(t) + av(t)) \ge \prod_{i=1}^{4}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_5^u\gamma_4}{a_5\bar{c}_5} \triangleq \gamma_5,\\ &\qquad\cdots\\ &\liminf_{t\to+\infty}\widetilde{W}_{n-2}(t) = \liminf_{t\to+\infty}(a_{n-1}y_{n-1}(t) + a_ny_n(t) + av(t)) \ge \prod_{i=1}^{n-3}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_{n-2}^u\gamma_{n-3}}{a_{n-2}\bar{c}_{n-2}} \triangleq \gamma_{n-2},\\ &\liminf_{t\to+\infty}\widetilde{W}_{n-1}(t) = \liminf_{t\to+\infty}(a_ny_n(t) + av(t)) \ge \prod_{i=1}^{n-2}\left(\frac{k_i^u}{\widetilde{k}_i^l}\right)\frac{k_{n-1}^u\gamma_{n-2}}{a_{n-1}\bar{c}_{n-1}} \triangleq \gamma_{n-1}.\end{aligned} \tag{40}$$

Step IV. In this step, we will show that

$$\liminf_{t\to+\infty}v(t) \ge \widetilde{q}_{n+1}, \tag{41}$$

where

$$\widetilde{q}_{n+1} = \frac{1}{2}\frac{\widetilde{k}_n^l\gamma_{n-1}}{a_n\delta^u + \widetilde{k}_n^l a}.$$

If (41) is not true, then

$$\liminf_{t\to+\infty}v(t) < \widetilde{q}_{n+1},$$

by the definition of inferior limit of $v(t)$, we obtain that there exists a time-sequence $\{t_n\}_{n=1}^{\infty}$ such that $v(t_n) \le \widetilde{q}_{n+1},\ t_n \to +\infty$ as $n \to \infty$.

From Lemmas 2, 3, 4 and Step III,

$$\widetilde{W}_{n-1}(t_n) = a_ny_n(t_n) + av(t_n) \ge \gamma_{n-1},$$

thus

$$y_n(t_n) \ge \frac{\gamma_{n-1} - av(t_n)}{a_n},$$

from the last equation of system (1), we obtain

$$\begin{aligned}\dot{v}(t_n) &= \widetilde{k}_n(t_n)y(t_n) - \delta(t_n)v(t_n)\\ &\ge \widetilde{k}_n(t_n)\frac{\gamma_{n-1} - av(t_n)}{a_n} - \delta(t_n)v(t_n)\\ &\ge \frac{\widetilde{k}_n^l\gamma_{n-1}}{a_n} - \left(\delta^u + \frac{\widetilde{k}_n^l a}{a_n}\right)\widetilde{q}_{n+1}\end{aligned}$$

$$\begin{aligned}&\geq \frac{\widetilde{k}_n^l\gamma_{n-1}}{a_n}-\frac{a_n\delta^u+\widetilde{k}_n^l a}{a_n}\cdot\frac{1}{2}\frac{\widetilde{k}_n^l\gamma_{n-1}}{a_n\delta^u+\widetilde{k}_n^l a}\\&=\frac{\widetilde{k}_n^l\gamma_{n-1}}{2a_n}>0.\end{aligned} \tag{42}$$

According to (42), we will consider three cases as follows:

(i) If $v(t_n)$ oscillates about $\widetilde{q}_{n+1}$, obviously, there exists a subsequence $\{t_{n_j}\}$ such that $t_{n_j\to+\infty}$ as $j\to\infty$, and $\dot{v}(t_{n_j})=0$, then it is a contradiction since (42) holds.

(ii) If $v(t_n)<\widetilde{q}_{n+1}$ and $v(t_n)$ is ultimately increase monotonically, from (42), then there exist $T_n>0$ such that $v(T_n)\to v^*(\text{constant})\leq\widetilde{q}_{n+1}$ as $n\to\infty$, so $\dot{v}(T_n)=0$ as $n\to\infty$, but $\dot{v}(T_n)>\frac{\widetilde{k}_n^l\gamma_{n-1}}{2a_n}>0$, this reduces a contradiction.

(iii) If $v(t_n)<\widetilde{q}_{n+1}$ and $v(t_n)$ is not ultimately increase monotonically, for any $T>0$, $\exists t_T>T$ such that such that $\dot{v}(t_T)<0$ and $v(t_T)<\widetilde{q}_{n+1}$, this contradiction again. Therefore, we have

$$\liminf_{t\to+\infty}v(t)\geq\widetilde{q}_{n+1}.$$

Step V. Finally, we will show that

$$\liminf_{t\to+\infty}y_1(t)\geq\widetilde{q}_1,\ \liminf_{t\to+\infty}y_2(t)\geq\widetilde{q}_2,\ldots,\ \liminf_{t\to+\infty}y_n(t)\geq\widetilde{q}_n$$

where $\widetilde{q}_1,\ \widetilde{q}_2,\ldots,\ \widetilde{q}_n$, are defined in (43) and (44).

From the second equation of system (1) and Lemma 4, for all $t$ large enough, we get $\dot{y}_1(t)=\beta(t)x(t)v(t)-k_1(t)y_1(t)\geq\beta^l q_0\widetilde{q}_{n+1}-k_1^u y_1(t)$, according to Lemma 1, which implies that

$$\liminf_{t\to+\infty}y_1(t)\geq\frac{\beta^l q_0\widetilde{q}_{n+1}}{k_1^u}=\frac{1}{2}\frac{\beta^l q_0}{k_1^u}\frac{\widetilde{k}_n^l\gamma_{n-1}}{a_n\delta^u+\widetilde{k}_n^l a}=\widetilde{q}_1, \tag{43}$$

where

$$\begin{aligned}&\gamma_{n-1}=\left(\frac{k_1^u}{\widetilde{k}_1^l}\right)^{n-2}\left(\frac{k_2^u}{\widetilde{k}_2^l}\right)^{n-3}\cdots\left(\frac{k_{n-2}^u}{\widetilde{k}_{n-2}^l}\right)\cdot\prod_{i=1}^{n-1}\left(\frac{k_i^u}{a_i\bar{c}_i}\right)\frac{\beta^l q_0}{a\bar{c}}\gamma,\\&\gamma=\alpha q_1 e^{-2p\delta^u},\end{aligned}$$

and $q_0, a_i, a, \bar{c}, \bar{c}_i$ are defined in (10), (13) and Step III, respectively.

From the third equation of system (1) to the $(n+1)$th equation of system (1), we have

$$\begin{aligned}&\liminf_{t\to+\infty}y_2(t)\geq\frac{\widetilde{k}_1^l\widetilde{q}_1}{k_2^u}\triangleq\widetilde{q}_2,\\&\liminf_{t\to+\infty}y_3(t)\geq\frac{\widetilde{k}_2^l\widetilde{q}_2}{k_3^u}=\frac{\widetilde{k}_1^l\widetilde{k}_2^l}{k_2^u k_3^u}\widetilde{q}_1\triangleq\widetilde{q}_2,\\&\cdots\\&\liminf_{t\to+\infty}y_n(t)\geq\prod_{i=1}^{n-1}\left(\frac{\widetilde{k}_i^l}{k_{i+1}^u}\right)\widetilde{q}_1\triangleq\widetilde{q}_n,\end{aligned} \tag{44}$$

according to the methods of Theorem 3.2 in [34], we establish the sufficient conditions for the clearance of virus. □

**Theorem 2.** *If $R^*<1$, then any positive solution $(x(t),y_1(t),\ldots,y_n(t),v(t))$ of system (1) with (3) satisfies $\lim_{t\to+\infty}y_i(t)=0,\ i=1,2,\ldots,n,\ \lim_{t\to+\infty}v(t)=0$, and $\lim_{t\to+\infty}|x(t)-w^*(t)|=0$, where $w^*(t)$ is the ultimate limit of all the solutions of Eq. (4) with the initial value $w(0)>0$.*

## 4. Numerical simulations

In this section, we present computer simulations of some results of the system (1) using MATLAB 7.1. Most of these values are taken from Perelson and Nelson [5], Rong et al. [33]. To confirm our theoretical results, let us consider the following non-periodic

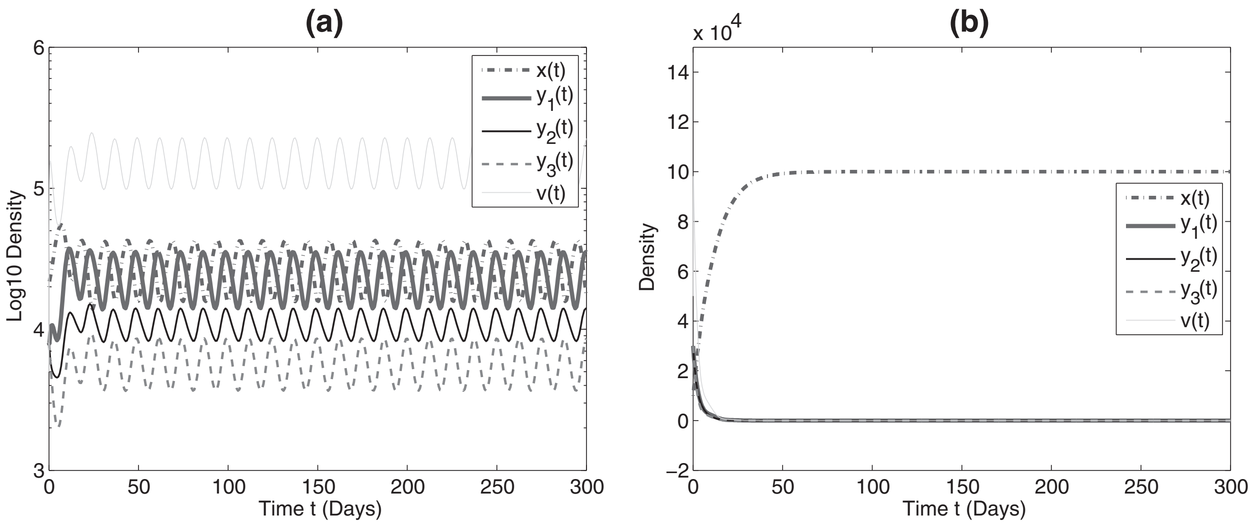


**Fig. 1.** Dynamics of uninfected cells $x(t)$, first stage of infected cells $y_1(t)$, second stage of infection $y_2(t)$, last stage of infected cells $y_3(t)$ and viral load $v(t)$ in (45): (a) with initial value (20000, 8000, 8000, 8000, 5000) and $R_* \approx 1.836 > 1$; (b) with initial value (10000, 30000, 30000, 30000, 50000) and $R^* \approx 0.64 < 1$.

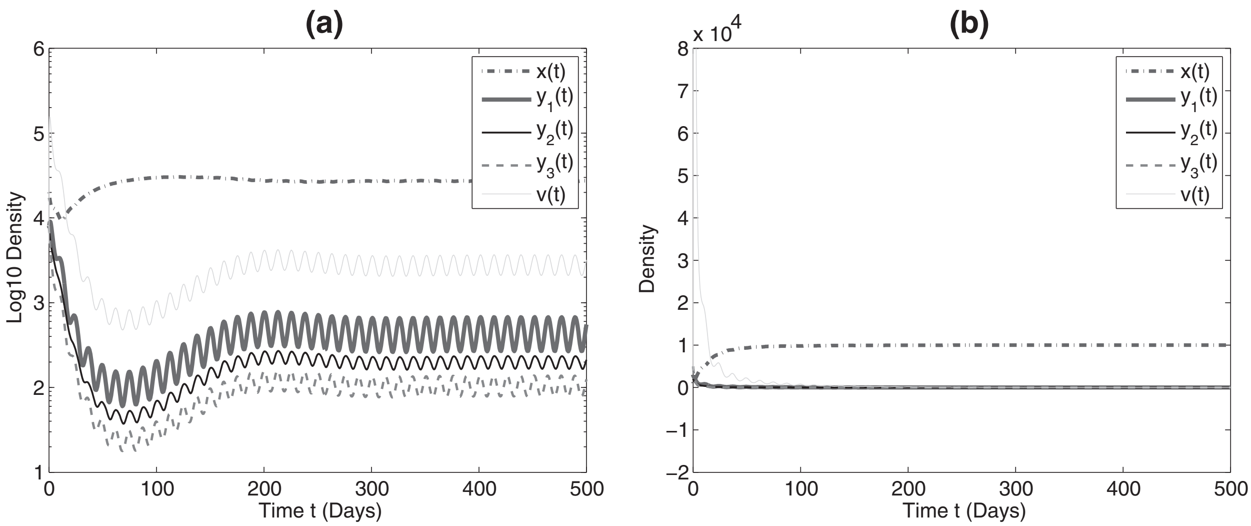


**Fig. 2.** Dynamics of uninfected cells $x(t)$, first stage of infected cells $y_1(t)$, second stage of infection $y_2(t)$, last stage of infected cells $y_3(t)$ and viral load $v(t)$ in (45): (a) with initial value (20000, 8000, 8000, 8000, 5000) and $R_* \approx 0.266 < 1 < R^* \approx 2.61$; (b) with initial value (1000, 3000, 2000, 5000, 4000) and $R_* \approx 0.199 < 1 < R^* \approx 2.455$.

within-host virus model with three infected stages (that is, $n = 3$ in system (1))

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - \beta(1 - a(0.5\sin(0.5t) + 0.6))x(t)v(t), \\ \dot{y}_1(t) = \beta(1 - a(0.5\sin(0.5t) + 0.6))x(t)v(t) - k_1 y_1(t), \\ \dot{y}_2(t) = k_1(1 - 0.6(0.3\cos(0.5t) + 0.5))y_1(t) - k_2 y_2(t), \\ \dot{y}_3(t) = k_2(1 - 0.5(0.4\sin(0.5t) + 0.6))y_2(t) - k_3 y_3(t), \\ \dot{v}(t) = N k_3 y_3(t) - \delta v(t). \end{cases} \tag{45}$$

Then we have the following results:

(I) *Persistence and extinction.* Firstly, we choose the values of parameters $\lambda = 10000,\ \mu = 0.01,\ \beta = 0.000004,\ a = 0.7,\ N = 100,\ \delta = 3,\ k_0 = 0.3,\ k_1 = 0.4,\ k_2 = 0.6,\ k_3 = 0.8$ for system (45), from Theorem 1 and (15), we have $R_* \approx 1.836 > 1$, then the system (45) is permanent (see Fig. 1(a)). If we choose the values of parameters $\lambda = 10000,\ \mu = 0.1,\ \beta = 0.000002,\ a = 0.5,\ N = 100,\ \delta = 23,\ k_0 = 0.3,\ k_1 = 0.4,\ k_2 = 0.6,\ k_3 = 0.8$ for system (45), from Theorem 2 and (15), we have $R^* \approx 0.654 < 1$, then the system (45) goes to extinct (see Fig. 1(b)).

(II) *The case $R_* < 1 < R^*$.* When the condition in neither Theorem 1 nor Theorem 2 is satisfied, we provide the simulations in Fig. 2: If we chose parameters for system (45) as in Fig. 1(a) except parameter $\mu$. That is, for system (45), we set $\mu = 0.01$,

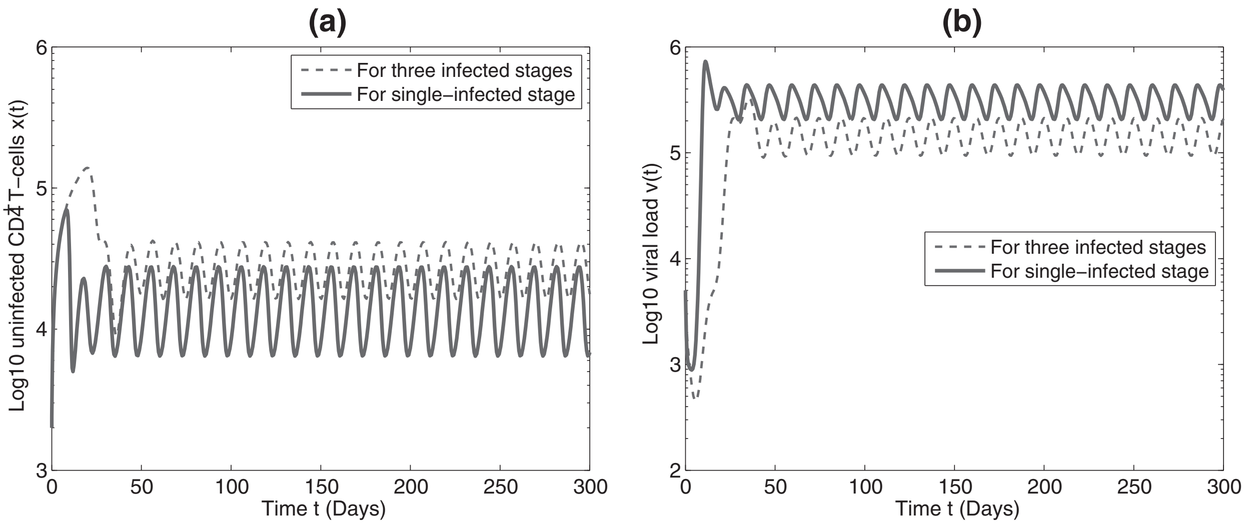


**Fig. 3.** Comparisons on the counts of uninfected CD4$^+$ T-cells of two systems (45), (46) (see (a)); the viral load of systems (45), (46) (see (b)).

we have $R_* \approx 0.266 < 1 < R^* \approx 2.61$, and the system (45) is permanent (see Fig. 2(a)); if we let $\mu = 0.1$, $N = 250$, and other parameters remain unchanged, then we have $R_* \approx 0.199 < 1 < R^* \approx 2.455$ for system (45), and the system (45) goes to extinct (see Fig. 2(b)). Thus, when $R_* < 1 < R^*$, both viral persistence and extinction are possible.

(III) *Effects of the multiple infected stages.* Here, we consider the system (1) with single-stage infected cells, which is similar to system (31) in [34] as follows:

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - \beta(1 - a(0.5\sin(0.5t) + 0.6))x(t)v(t), \\ \dot{y}_1(t) = \beta(1 - a(0.5\sin(0.5t) + 0.6))x(t)v(t) - k_1 y_1(t), \\ \dot{v}(t) = Nk_1 y_1(t) - \delta v(t). \end{cases} \tag{46}$$

We choose the values of parameters for two systems (46) and (45) as the same as (I). And we compare the counts of uninfected CD4$^+$ T-cells and viral load corresponding to two systems. From Fig. 3, new simulation results can be observed by comparisons: the counts of uninfected CD4$^+$ T-cells of a non-autonomous delayed HIV-1 infection model with three infected stages are larger than that of system with single infected stage (see Fig. 3(a)), the viral load of a non-autonomous delayed HIV-1 infection model with three stages are less than that of system with single infected stage (see Fig. 3(b)).

(IV) *Effects of the time-varying environments.* Here, we consider the system (1) with single-stage infected cells, which is similar to system (31) in [34] as follows:

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - \beta(1 - a(-0.25 + 0.6))x(t)v(t), \\ \dot{y}_1(t) = \beta(1 - a(-0.25 + 0.6))x(t)v(t) - k_1 y_1(t), \\ \dot{y}_2(t) = k_1(1 - 0.6(-0.15 + 0.5))y_1(t) - k_2 y_2(t), \\ \dot{y}_3(t) = k_2(1 - 0.5(-0.2 + 0.6))y_2(t) - k_3 y_3(t), \\ \dot{v}(t) = Nk_3 y_3(t) - \delta v(t). \end{cases} \tag{47}$$

We choose the values of parameters for (47) as the same as (I). And we compare the counts of uninfected CD4$^+$ T-cells and viral load of non-autonomous system and autonomous system with multiple stages. From Fig. 4, the counts of uninfected CD4$^+$ T-cells of a non-autonomous delayed HIV-1 infection model with three infected stages are larger than that of corresponding autonomous system with multiple stage (see Fig. 4(a)), the viral load of a non-autonomous delayed HIV-1 infection model with three stages are less than that of corresponding autonomous system with multiple stage (see Fig. 4(b)).

## 5. Conclusions

In [34], the authors have formulated a model of HIV infection incorporating non-periodic coefficients and two intracellular time delays, and have established the conditions for the permanence and extinction of the virus. From the results of [34], Wang et al. have obtained the complicated effects of the time-varying parameters on the sufficient conditions for the permanence and the extinction of the model with single infected stage. In this paper, based on the results on the system (5) with single-infected stage in [34], we proved some uniform persistent result of system (1) in Theorem 1 when the condition $R_* > 1$ holds. In Proposition 1 we obtained that explicit estimates of the lower bound of the viral load under condition $R_* > 1$. In Theorem 2, under condition $R^* < 1$, we proved that the elimination of virus infection for system (1). These results generalize the corresponding results in [34] and improve those in [34] by introducing multiple infected stages.

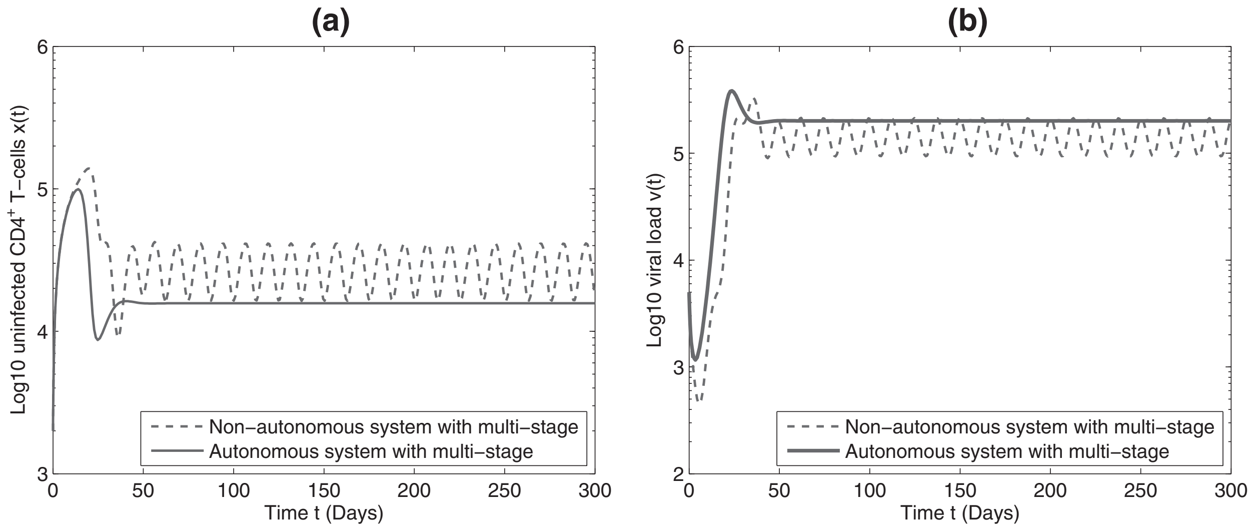


**Fig. 4.** Comparisons on the counts of uninfected CD4$^+$ T-cells of two systems (45), (47) (see (a)); the viral load of systems (45), (47) (see (b)).

We presented some numerical results for system (1) with three infected stages, respectively. Our first numerical results showed that the persistence of systems (45) when $R_* > 1$ (Fig. 1(a)) and the extinction of systems (45) when $R^* < 1$ (Fig. 1(b)); in the second numerical study, we provided the simulations in Fig. 2 when the condition in neither Theorem 1 nor Theorem 2 is satisfied (i.e., $R_* < 1 < R^*$); in the third numerical results, we investigated the comparison of the counts of uninfected CD4$^+$ T-cells and viral load corresponding to the systems with single-infected stage and three infected stages (Fig. 3). The study shows that the effects of multiple infected stages of the antiretroviral drug during HIV-1 virus infection seem to change the counts of uninfected CD4$^+$ T-cells and viral load.

Comparing to the corresponding Theorem 1 in [34] for the system (1) with single infected stage, we find that there is an extra term $\prod_{i=2}^{n}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right)$ in our permanence and extinction criteria, which exists because of the multiple infected stages. The impact of multiple infected stages hence can be explored through the sensitivity analysis of $R_*$. In fact, from the expressions of

$$R^* = \frac{\beta^u\lambda^u}{\delta^l\mu^l}\cdot\prod_{i=1}^{n}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right),$$

and (2), we can find that $\widetilde{k}_i(t) \le k_i(t)$ and $\prod_{i=1}^{n}\left(\frac{\widetilde{k}_i^u}{k_i^l}\right) \le 1$. This implies that the more infected stages the cells have, the smaller $R^*$ becomes, thus it comes from Theorem 2 that the more possibly the system will goes infection-free and hence there will be more uninfected CD4$^+$ T-cells may be retained as well.

In summary, we provided investigations of the impact of multiple infected stages on HIV virus dynamic model under time-varying environment. The interactions between HIV virus particles and different stages for infected cells are more complex compared to the autonomous (or non-autonomous) HIV infection models with single-infected stage. Moreover, we simplified our model formulations by continuous change from early stage to the final stage and did not consider mutation and drug resistance of infected cells in each stage. The present system may not completely display the real biological meanings. Therefore, it is still an open problem to study the system (1) with mutation or drug resistance which may raise more interesting and challenging mathematics problems.

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