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Modeling Influence of Raltegravir Intensification on Viral Dynamics: Stability and Hopf Bifurcation*

Jiemei Li[1,†], Xiaofei Wei[1] and Jianmei Zhang[1]

Abstract In this paper, we propose an ordinary differential equation model with logistic target cell growth to describe influence of raltegravir intensification on viral dynamics. The basic reproduction number R_0 is established. The infection-free equilibrium E_0 is globally attractive if $R_0 < 1$, while virus is uniformly persistent if $R_0 > 1$. In addition, we find that Hopf bifurcation can occur at around the positive equilibrium within certain parameter ranges. Numerical simulations are performed to illustrate theoretical results.

Keywords Multi-stage models, Logistic target cell growth, Stability, Hopf bifurcation.

MSC(2010) 26A33, 34B15, 34K30.

1. Introduction

It is widely known that CD4+ T cells have been considered as the primary target cells for human immunodefficiency virus (HIV) infection. However, as yet AIDS is still an illness for which there is no vaccine since some latent viruses can reside in memory CD4+ T cells. In recent years, HIV infection is treated with a combination therapy, known as highly active anti-retroviral therapy (HAART) (see, e.g. [1, 2]), which can effectively control HIV replication in infected individuals by stopping the virus from replicating and restore their immune system [3] and reduced the number of AIDS deaths reported from potent antiretroviral medications. In the absence of antiretroviral therapy, the viral load in infected individuals soared to the peak level, followed by a decline to reach an viral set-point level during chronic infection, and thereby infect the susceptible CD4+ T cells [4].

New drug classes result from investigation of up-and-coming drug targets for the treatment of HIV infection. The integrase inhibitor raltegravir was authorized for the treatment of HIV infection [5]. More drugs such as entry inhibitor, reverse-transcriptase (RT) inhibitor, integrase inhibitor(II), and protease inhibitor(PI) have been developed to act at specific stages for clinical development [6]. For instance,

†the corresponding author.
Email address: lijiemei81@126.com(J. Li), xiaofei288199@126.com(X. Wei), 19893171158@163.com(J. Zhang)
[1]Department of Mathematics, Lanzhou Jiaotong University, Lanzhou, Gansu 730070, China
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RT inhibitor can block the process of reverse transcription. II can block process of virus DNA integrate into the host cell's DNA.

The study of dynamics for viral infection dynamical models have made excellent insights into the pathogenesis and treatment of diseases [7–14]. In [8, 9, 11], some basic three-dimensional viral dynamical models with drug treatment were proposed. Then in [4, 9, 15], some researchers have incorporated the effect of latently infected stage into the mathematical model since latently infected stage of cells can be activated by related enzymes to become the productively infected. Lloyd proposed a comprehensive model including multiple stages with treatment from different classes drug approach to analyze the dynamics of HIV decay [16, 17]. Sedaghat et al. developed a mathematical model including two stages employed to study the question of the viral load decay with RT inhibitor or integrase inhibitor in patients under treatment [18]. A number of models discussing the efficacy of antiviral treatment by insights of time-varying can be found in [19–21]. Several other models were developed to analyze the question of the rapid decay of plasma viral load after application of integrase inhibitors (see, e.g. [4, 22–25]).

In recent years, to explore the effect influence of raltegravir intensification, Wang et al. [26] established a mathematical model, in which CD4+ T cells are unlimited growth. In biology, it is more realistic to assume that the population of the CD4+ T cell has a logistic growth function [27, 28]. Motivated by the aforementioned works, in this paper, we propose an HIV infection dynamical model with logistic target cell growth to explore the effect influence of raltegravir intensification:

$$
\begin{cases}
\dfrac{dT}{dt} = sT(t)\left[1 - \dfrac{T(t)+I_1(t)}{T_M}\right] - (1-\varepsilon_{RT})\beta V_I(t)T(t),\\
\dfrac{dI_1}{dt} = (1-\varepsilon_{RT})\beta V_I(t)T(t) - d_1 I_1(t) - (1-\varepsilon_{II})k_1 I_1(t) - k_2 I_1(t),\\
\dfrac{dI_2}{dt} = (1-f)(1-\varepsilon_{II})k_1 I_1(t) - \delta I_2(t) + aL(t),\\
\dfrac{dI_3}{dt} = k_2 I_1(t) - d_3 I_3(t),\\
\dfrac{dL}{dt} = f(1-\varepsilon_{II})k_1 I_1(t) - d_L L(t) - aL(t),\\
\dfrac{dV_I}{dt} = (1-\varepsilon_{PI})N\delta I_2(t) - cV_I(t),\\
\dfrac{dV_{NI}}{dt} = \varepsilon_{PI}N\delta I_2(t) - cV_I(t).
\end{cases}
\tag{1.1}
$$

Detailed biological considerations of the parameters of the model (1.1) can be found in Table 1. We observe that variables I_3 and V_{NI} are decoupled from the other equations of model (1.1). Therefore, we only need to analyze the dynamical behavior

Table 1. Summary of model parameters

Para.	Description
T	The counts of uninfected cells
I_1	The counts of infected cells have finished the process of reverse transcription
I_2	The counts of infected cells and these cells can produce virus(finished the process of reverse transcription)
I_3	The counts of infected cells that fail the DNA integration and contain 2-LTR DNA circles
L	The counts of latently infected cells (L)
V_{NI}	Non-infectious viral particles owing to efficacy of protease inhibitors
V_I	Infectious viral particles
s	Generation rate of uninfected cells
d	Death rate of uninfected cells
β	A rate at which the virus infects uninfected cells
d_1	Death rate of cells in the I_1 class
k_1	A Rate at which I_1 cells move to I_2
k_2	Rate at which I_1 cells move to I_3
f	A small fraction of infected cells become latently infected
δ	Death rate of infected cells in the I_2 class
d_3	Death rate of infected cells in the I_3 class
d_L	Death rate of L
a	A rate of productively infected cells which L are activated by their relevant antigens
$N\delta$	Generation rate of virus release form an infected cell per unit time
c	Viral clearance rate
ε_{RT}	Drug efficacy of reverse transcriptase inhibitor
ε_{II}	Drug efficacy of integrase inhibitor
ε_{PI}	Drug efficacy of protease inhibitor

of the solutions of the following subsystem

$$\begin{cases} \dfrac{dT}{dt} = sT(t)\left[1 - \dfrac{T(t)+I_1(t)}{T_M}\right] - (1-\varepsilon_{RT})\beta V_I(t)T(t), \\ \dfrac{dI_1}{dt} = (1-\varepsilon_{RT})\beta V_I(t)T(t) - d_1 I_1(t) - (1-\varepsilon_{II})k_1 I_1(t) - k_2 I_1(t), \\ \dfrac{dI_2}{dt} = (1-f)(1-\varepsilon_{II})k_1 I_1(t) - \delta I_2(t) + aL(t), \\ \dfrac{dL}{dt} = f(1-\varepsilon_{II})k_1 I_1(t) - d_L L(t) - aL(t), \\ \dfrac{dV_I}{dt} = (1-\varepsilon_{PI})N\delta I_2(t) - cV_I(t). \end{cases} \tag{1.2}$$

We rescale model (1.2) for mathematical convenience as follows

$$\begin{aligned} &u(t) = \frac{T(t)}{T_M}, \quad \omega_1(t) = \frac{I_1(t)}{T_M}, \quad \omega_2(t) = \frac{I_2(t)}{T_M}, \quad l(t) = \frac{L(t)}{T_M}, \\ &v(t) = \frac{1}{(1-\varepsilon_{PI})N}\frac{V_I(t)}{T_M}, \quad \widetilde{t} = \delta t, \quad \rho = \frac{(1-\varepsilon_{PI})(1-\varepsilon_{RT})\beta N T_M}{\delta}, \\ &\rho_1 = \frac{s}{\delta}, \quad \rho_2 = \frac{d_1}{\delta}, \quad \rho_3 = \frac{(1-\varepsilon_{II})k_1}{\delta}, \quad \rho_4 = \frac{k_2}{\delta}, \\ &\rho_5 = \frac{(1-f)(1-\varepsilon_{II})k_1}{\delta}, \quad \rho_6 = \frac{a}{\delta}, \quad \rho_7 = \frac{f(1-\varepsilon_{II})k_1}{\delta}, \quad \rho_8 = \frac{d_L}{\delta}, \ \rho_9 = \frac{c}{\delta}. \end{aligned}$$

Then the rescaled model has the form

$$\begin{cases} \dfrac{du(t)}{dt} = \rho_1 u(t)[1 - u(t) - \omega_1(t)] - \rho v(t)u(t), \\ \dfrac{d\omega_1(t)}{dt} = \rho v(t)u(t) - \rho_2\omega_1(t) - \rho_3\omega_1(t) - \rho_4\omega_1(t), \\ \dfrac{d\omega_2(t)}{dt} = \rho_5\omega_1(t) - \omega_2(t) + \rho_6 l(t), \\ \dfrac{dl(t)}{dt} = \rho_7\omega_1(t) - \rho_8 l(t) - \rho_6 l(t), \\ \dfrac{dv(t)}{dt} = \omega_2(t) - \rho_9 v(t). \end{cases} \tag{1.3}$$

Assume that initial conditions for model (1.3) are given as follows

$$\begin{cases} u(0) = u_0 > 0, \ \omega_1(0) = \omega_{10} > 0, \ \omega_2(0) = \omega_{20} > 0, \\ l(0) = l_0 > 0, \ v(0) = v_0 > 0, \ u_0 + \omega_{10} \le 1. \end{cases} \tag{1.4}$$

The rest of the paper is organized as follows. In Section 2, we address positivity and boundedness of solution of model (1.3). In Section 3, we discuss global stability of IFE(infection-free equilibrium). In Section 4, we prove the uniform persistence in the case of $R_0 > 1$. In Section 5, we analyze stability of IE(infection equilibrium) and Hopf bifurcation, and Section 6 is devoted to illustrating numerical simulation. In Section 7, we further give some conclusions and discussions.

2. Positivity and boundedness of solutions

It is easy to see that model (1.3) always has an infection-free equilibrium $E_0 = (1, 0, 0, 0, 0)$. Simple computations yield the basic reproduction number

$$R_0 = \frac{\rho[\ \rho_5(\rho_6+\rho_8)+\rho_6\rho_7\ ]}{(\rho_2+\rho_3+\rho_4)(\rho_6+\rho_8)\rho_9}.$$

If $R_0 > 1$, model (1.3) has a positive equilibrium $E^* = (u^*,\ \omega_1^*,\ \omega_2^*,\ l^*,\ v^*)$, where

$$u^* = \frac{1}{R_0},\quad \omega_1^* = \frac{\rho_1(R_0-1)}{R_0[\rho_1+R_0(\rho_2+\rho_3+\rho_4)]},\quad \omega_2^* = \frac{\rho_9(\rho_2+\rho_3+\rho_4)R_0}{\rho}\omega_1^*,$$
$$l^* = \frac{\rho_7}{\rho_6+\rho_8}\omega_1^*,\quad v^* = \frac{(\rho_2+\rho_3+\rho_4)R_0}{\rho}\omega_1^*.$$

Theorem 2.1. *Let $(u(t),\ \omega_1(t),\ \omega_2(t),\ l(t),\ v(t))$ be the solution of model (1.3) satisfying the initial conditions (1.4). Then the solution is positive and bounded:*

$$0 < u(t) \le 1,\quad 0 < \omega_1(t) \le 1,\quad 0 < \omega_2(t) \le \omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6\rho_7}{\rho_8+\rho_6},$$
$$0 < l(t) \le l_0 + \frac{\rho_7}{\rho_8+\rho_6},\quad 0 < v(t) \le v_0 + \frac{1}{\rho_9}\left(\omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6\rho_7}{\rho_8+\rho_6}\right).$$

Furthermore, $u(t) + \omega_1(t) \le 1$ for all $t \ge 0$.

Proof. To prove the positivity of solutions, by way of contradiction, we assume that t_i $(i = 1,\ 2,\ 3,\ 4,\ 5)$ are the first times such that $u(t) = 0,\ \omega_1(t) = 0,\ \omega_2(t) = 0,\ l(t) = 0$ and $v(t) = 0$ respectively. Let $t_0 = \min\{t_1,\ t_2,\ t_3,\ t_4,\ t_5\}$.

First, if $t_0 = t_1$, then $u(t_1) = 0$ and $u(t) > 0,\ \omega_1(t) > 0,\ \omega_2(t) > 0,\ l(t) > 0,\ v(t) > 0$ for $t \in [0,\ t_1)$. Then for all $t \in [0, t_1]$, we have

$$\frac{d}{dt}[u(t)+\omega_1(t)] = \rho_1 u(t)[1-(u(t)+\omega_1(t))] - \rho_2\omega_1(t) - \rho_3\omega_1(t) - \rho_4\omega_1(t).$$

It is easy to see that $u(t) + \omega_1(t) \le 1$ for $t \in [0, t_1]$. In fact, for any $t^* \in [0,\ t_1]$ such that $u(t^*) + \omega_1(t^*) = 1$, we get

$$\frac{d}{dt}[u(t)+\omega_1(t)]|_{t=t^*} = -(\rho_2+\rho_3+\rho_4)\omega_1(t^*) < 0.$$

Hence, combining the above inequality and the initial condition $u_0 + \omega_{10} \le 1$, we can obtain $u(t) + \omega_1(t) \le 1$. So $u(t) \le 1$ and $\omega_1(t) \le 1$ hold for all $t \in [0, t_1]$. From model (1.3), we get

$$\frac{dl(t)}{dt} \le \rho_7 - (\rho_8+\rho_6)l(t),\quad t \in [0, t_1],$$

which implies

$$l(t) \le e^{-(\rho_8+\rho_6)t}\left[l_0 + \frac{\rho_7}{\rho_8+\rho_6}\left(e^{(\rho_8+\rho_6)t}-1\right)\right] \le l_0 e^{-(\rho_8+\rho_6)t} + \frac{\rho_7}{\rho_8+\rho_6}$$
$$\le l_0 + \frac{\rho_7}{\rho_8+\rho_6},$$

for $t \in [0,\ t_1]$. Then

$$\frac{d\omega_2(t)}{dt} \le \rho_5 - \omega_2(t) + \rho_6 \left(l_0 + \frac{\rho_7}{\rho_8 + \rho_6} \right),$$

which implies

$$\begin{aligned} \omega_2(t) &\le e^{-t} \left[\omega_{20} + \left(\rho_5 + \rho_6 l_0 + \frac{\rho_6 \rho_7}{\rho_8 + \rho_6} \right) (e^t - 1) \right] \\ &\le \omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6 \rho_7}{\rho_8 + \rho_6}, \quad t \in [0,\ t_1]. \end{aligned}$$

From model (1.3), we have

$$\frac{dv(t)}{dt} \le \omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6 \rho_7}{\rho_8 + \rho_6} - \rho_9 v(t),$$

which implies

$$v(t) \le v_0 + \frac{1}{\rho_9} \left(\omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6 \rho_7}{\rho_8 + \rho_6} \right), \quad t \in [0,\ t_1].$$

Again from the first equation in model (1.3), we get

$$u(t) \ge u_0 e^{-\int_0^t [\rho_1 \omega_1(s) + \rho v(s)] ds}, \quad t \in [0,\ t_1].$$

Hence

$$u(t_1) \ge u_0 e^{-\left[\rho_1 + \rho v_0 + \frac{\rho}{\rho_9} \left(\omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6 \rho_7}{\rho_8 + \rho_6} \right) \right] t_1} > 0,$$

which contradicts $u(t_1) = 0$.

Second, if $t_0 = t_2,\ \omega_1(t_2) = 0,\ u(t_2) \ge 0,\ \omega_2(t_2) \ge 0,\ l(t_2) \ge 0,\ v(t_2) \ge 0$ and $u(t) > 0,\ \omega_1(t) > 0,\ \omega_2(t) > 0,\ l(t) > 0,\ v(t) > 0$ for $t \in [0,\ t_2)$, then from the second equation in (1.3), we get

$$\frac{d\omega_1(t)}{dt} \ge -(\rho_2 + \rho_3 + \rho_4)\omega_1(t), \quad t \in [0,\ t_2],$$

thus $\omega_1(t_2) \ge \omega_{10} e^{-(\rho_2 + \rho_3 + \rho_4) t_2} > 0$, which is in contradiction to $\omega_1(t_2) = 0$.

Third, if $t_0 = t_3,\ \omega_2(t_3) = 0,\ u(t_3) \ge 0,\ \omega_1(t_3) \ge 0,\ l(t_3) \ge 0,\ v(t_3) \ge 0$ and $u(t) > 0,\ \omega_1(t) > 0,\ \omega_2(t) > 0,\ l(t) > 0,\ v(t) > 0$ for $t \in [0, t_3)$, then from the third equation in (1.3), we have $\omega_2(t_3) \ge \omega_{20} e^{-t_3} > 0$, which is in contradiction to $\omega_2(t_3) = 0$.

Fourth, if $t_0 = t_4,\ l(t_4) = 0,\ u(t_4) \ge 0,\ \omega_1(t_4) \ge 0,\ \omega_2(t_4) \ge 0,\ v(t_4) \ge 0$ and $u(t) > 0, \omega_1(t) > 0, \omega_2(t) > 0, l(t) > 0, v(t) > 0$ for $t \in [0,\ t_4)$. Similarly, we have

$$l(t_4) \ge l_0 e^{-(\rho_8 + \rho_6) t_4} > 0,$$

which is a contradiction.

Finally, if $t_0 = t_5,\ v(t_5) = 0,\ u(t_5) \ge 0,\ \omega_1(t_5) \ge 0,\ \omega_2(t_5) \ge 0,\ l(t_5) \ge 0,$ and $u(t) > 0,\ \omega_1(t) > 0,\ \omega_2(t) > 0,\ l(t) > 0,\ v(t) > 0$ for $t \in [0,\ t_5)$. one gets $v(t_5) \ge v_0 e^{-\rho_9 t_5} > 0$.

Furthermore, for all $t \geq 0$, we have

$$u(t) + \omega_1(t) \leq 1, \quad l(t) \leq l_0 + \frac{\rho_7}{\rho_8 + \rho_6}, \quad \omega_2(t) \leq \omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6\rho_7}{\rho_8 + \rho_6},$$
$$v(t) \leq v_0 + \frac{1}{\rho_9}\left(\omega_{20} + \rho_5 + \rho_6 l_0 + \frac{\rho_6\rho_7}{\rho_8 + \rho_6}\right).$$

The proof is complete. □

The following set

$$\mathbb{Y} := \Big\{(u,\ \omega_1,\ \omega_2,\ l,\ v) \in \mathbb{R}^5 \ \Big|\ u > 0,\ \omega_1 \geq 0,\ \omega_2 \geq 0,\ l \geq 0,\ v \geq 0,\ u + \omega_1 \leq 1, l \leq \frac{1}{\rho_8 + \rho_6}\Big\}$$

is invariant for the solution semi-flow of (1.3).

3. Stability of the IFE

Theorem 3.1. *If $R_0 < 1$, the IFE E_0 is globally attractive.*

Proof. We have to prove that

$$\lim_{t\to+\infty}(u(t),\ \omega_1(t),\ \omega_2(t),\ l(t),\ v(t)) = (1,\ 0,\ 0,\ 0,\ 0).$$

Since $u(t) \leq 1$ for all $t \geq 0$, we have

$$\begin{cases} \dfrac{d\omega_1(t)}{dt} \leq \rho v(t) - \rho_2\omega_1(t) - \rho_3\omega_1(t) - \rho_4\omega_1(t), \\ \dfrac{d\omega_2(t)}{dt} \leq \rho_5\omega_1(t) - \omega_2(t) + \rho_6 l(t), \\ \dfrac{dl(t)}{dt} \leq \rho_7\omega_1(t) - \rho_8 l(t) - \rho_6 l(t), \\ \dfrac{dv(t)}{dt} \leq \omega_2(t) - \rho_9 v(t). \end{cases}$$

For the linear cooperative system

$$\begin{cases} \dfrac{d\widetilde{\omega_1}(t)}{dt} = \rho\widetilde{v}(t) - \rho_2\widetilde{\omega_1}(t) - \rho_3\widetilde{\omega_1}(t) - \rho_4\widetilde{\omega_1}(t), \\ \dfrac{d\widetilde{\omega_2}(t)}{dt} = \rho_5\widetilde{\omega_1}(t) - \widetilde{\omega_2}(t) + \rho_6\widetilde{l}(t), \\ \dfrac{d\widetilde{l}(t)}{dt} = \rho_7\widetilde{\omega_1}(t) - \rho_8\widetilde{l}(t) - \rho_6\widetilde{l}(t), \\ \dfrac{d\widetilde{v}(t)}{dt} = \widetilde{\omega_2}(t) - \rho_9\widetilde{v}(t), \end{cases} \tag{3.1}$$

there exists a principal eigenvalue λ_0 associated with strictly positive eigenvector ξ_0 [29]. Given $M > 0$, it follows that the linear system (3.1) admits a solution

$$(\widetilde{\omega_1}(t),\ \widetilde{\omega_2}(t),\ \widetilde{l}(t),\ \widetilde{v}(t)) = Me^{\lambda_0 t}\xi_0.$$

Choosing $M > 0$ such that $(\omega_1(0),\ \omega_2(0),\ l(0),\ v(0)) \le M(\widetilde{\omega_1}(0),\ \widetilde{\omega_2}(0),\ \widetilde{l}(0),\ \widetilde{v}(0))$, one gets, for $t \ge 0$,

$$(\omega_1(t),\ \omega_2(t),\ l(t),\ v(t)) \le Me^{\lambda_0 t}\xi_0.$$

We see that $\lambda_0 < 0$ if $R_0 < 1$. Thus if $R_0 < 1$, we have

$$\lim_{t\to+\infty}\omega_1(t) = 0,\quad \lim_{t\to+\infty}\omega_2(t) = 0,\quad \lim_{t\to+\infty} l(t) = 0,\quad \lim_{t\to+\infty} v(t) = 0.$$

Then the first equation in (1.3) is asymptotic to the following equation

$$\frac{d\widetilde{u}(t)}{dt} = \rho_1\widetilde{u}(t)[1-\widetilde{u}(t)],$$

which is the logistic equation. Since $\rho_1 > 0$, by the asymptotic autonomous semi-flow theory [30] , it is easy to see that $\lim_{t\to+\infty} u(t) = 1$.

Thus, if $R_0 < 1$, then

$$(u(t),\ \omega_1(t),\ \omega_2(t),\ l(t),\ v(t)) \to (1,\ 0,\ 0,\ 0,\ 0), \quad \text{as } t \to +\infty.$$

The proof is complete. □

4. Uniform persistence

For $t \ge 0$, if $u_0 = 0$, the unique solution of (1.3)-(1.4) can be given by

$$\begin{aligned}
&u(t) = 0, \qquad \omega_1(t) = \omega_{10}e^{-(\rho_2+\rho_3+\rho_4)t},\\
&l(t) = e^{-(\rho_6+\rho_8)t}\left(l_0 + \frac{\rho_7\omega_{10}e^{-(\rho_2+\rho_3+\rho_4-\rho_6-\rho_8)t}}{\rho_6+\rho_8-\rho_2-\rho_3-\rho_4}\right),\\
&\omega_2(t) = e^{-t}\Big[\omega_{20} + \frac{\omega_{10}\left[\rho_5(\rho_8-\rho_2-\rho_3-\rho_4)+\rho_6(\rho_5-\rho_7)\right]e^{-t(\rho_2+\rho_3+\rho_4-1)}}{(1-\rho_2-\rho_3-\rho_4)(\rho_6+\rho_8-\rho_2-\rho_3-\rho_4)}\\
&\qquad\qquad + \frac{l_0\rho_6(\rho_6+\rho_8-\rho_2-\rho_3-\rho_4)e^{-t(\rho_8+\rho_6-1)}}{(1-\rho_6-\rho_8)(\rho_6+\rho_8-\rho_2-\rho_3-\rho_4)}\Big],\\
&v(t) = e^{-\rho_9 t}\left(v_0 + \int_0^t e^{\rho_9 s}\omega_2(s)ds\right).
\end{aligned}$$

We see that

$$\omega_1(t) \to 0,\quad \omega_2(t) \to 0,\quad l(t) \to 0,\quad v(t) \to 0,\quad \text{as}\quad t \to +\infty.$$

Hence, if $u_0 = 0$, model (1.3) cannot be persistent. In what follows, we consider the following solution space:

$$\mathbb{X} := \Big\{(u,\ \omega_1,\ \omega_2,\ l,\ v) \in \mathbb{R}^5 \\ \Big| u > 0,\ \omega_1 \ge 0,\ \omega_2 \ge 0,\ l \ge 0,\ v \ge 0,\ u+\omega_1 \le 1, l \le \frac{1}{\rho_8+\rho_6}\Big\}$$

the interior subspace of $\mathbb{X}$:

$$\mathbb{X}_0 := \left\{(u,\ \omega_1,\ \omega_2,\ l,\ v) \in \mathbb{X} \ \middle|\ \omega_1 > 0,\ \omega_2 > 0,\ l > 0,\ v > 0\right\},$$

the boundary of $\mathbb{X}_0$:

$$\partial\mathbb{X}_0 := \mathbb{X} \setminus \mathbb{X}_0 = \left\{ (u,\ \omega_1,\ \omega_2,\ l,\ v) \in \mathbb{X} \,\middle|\, \omega_1 = 0, \text{or } \omega_2 = 0,\ \text{ or } l = 0,\ \text{ or } v = 0 \right\},$$

and

$$M_\partial := \left\{ (u_0,\ \omega_{10},\ \omega_{20},\ l_0,\ v_0) \in \partial\mathbb{X}_0 \,\middle|\, \Phi_t(u_0,\ \omega_{10},\ \omega_{20},\ l_0,\ v_0) \in \partial\mathbb{X}_0,\ t \geq 0 \right\},$$

where Φ_t denotes the solution semi-flow defined by (1.3).

We easily obtain the following lemma.

Lemma 4.1. *The sets $\mathbb{X}$ and $\mathbb{X}_0$ are positively invariant for the solution semi-flow Φ_t. Moreover,*

$$M_\partial = \left\{ (\hat{u}, 0, 0, 0, 0) \,\middle|\, 0 < \hat{u} \leq 1 \right\}. \tag{4.1}$$

Lemma 4.2. *If $R_0 > 1$, the solution $(u(t),\ \omega_1(t),\ \omega_2(t),\ v(t),\ l(t))$ of model (1.3) with initial value $(u_0, \omega_{10}, \omega_{20}, v_0, l_0) \in \mathbb{X}_0$, there exsits $\eta_0 > 0$ such that*

$$\limsup_{t\to+\infty} \| (u(t), \omega_1(t), \omega_2(t), v(t), l(t)) - (1,\ 0,\ 0,\ 0,\ 0)\| \geq \eta_0.$$

Proof. We assume the contrary by

$$\limsup_{t\to+\infty} \|(u(t),\ \omega_1(t),\ \omega_2(t),\ v(t),\ l(t)) - (u_1,\ 0,\ 0,\ 0,\ 0)\| < \eta_0,$$

for any solution with initial value $(u_0,\ \omega_{10},\ \omega_{20},\ v_0,\ l_0) \in \mathbb{X}_0$. There exists a $t_0 > 0$ such that $u(t) > u_1 - \eta_0,\ \omega_1(t) < \eta_0,\ \omega_2(t) < \eta_0,\ l(t) < \eta_0,\ v(t) < \eta_0$, for $t \geq t_0$. From the second equation in (1.3), we have

$$\frac{d\omega_1(t)}{dt} > \rho(u_1 - \eta_0)v(t) - \rho_2\omega_1(t) - \rho_3\omega_1(t) - \rho_4\omega_1(t), \quad t \geq t_0.$$

It is easy to see that $\lambda_0(u_1 - \eta_0)$ is the principal eigenvalue of the linear cooperative system

$$\begin{cases} \dfrac{d\widetilde{\omega_1}(t)}{dt} = \rho(u_1 - \eta_0)\widetilde{v}(t) - \rho_2\widetilde{\omega_1}(t) - \rho_3\widetilde{\omega_1}(t) - \rho_4\widetilde{\omega_1}(t), \\ \dfrac{d\widetilde{\omega_2}(t)}{dt} = \rho_5\widetilde{\omega_1}(t) - \widetilde{\omega_2}(t) + \rho_6\widetilde{l}(t), \\ \dfrac{d\widetilde{l}(t)}{dt} = \rho_7\widetilde{\omega_1}(t) - \rho_8\widetilde{l}(t) - \rho_6\widetilde{l}(t), \\ \dfrac{d\widetilde{v}(t)}{dt} = \widetilde{\omega_2}(t) - \rho_9\widetilde{v}(t). \end{cases} \tag{4.2}$$

Let $(\xi_1,\ \xi_2,\ \xi_3,\ \xi_4)^T$ be the strictly positive eigenvector associated with $\lambda_0(u_1 - \eta_0)$, we then obtain

$$(\widetilde{\omega_1}(t),\ \widetilde{\omega_2}(t),\ \widetilde{l}(t),\ \widetilde{v}(t))^T = e^{\lambda_0(u_1-\eta_0)t}(\xi_1,\ \xi_2,\ \xi_3,\ \xi_4)^T$$

is a solution of (4.2). Since $\omega_1(t_0) > 0,\ \omega_2(t_0) > 0,\ l(t_0) > 0,\ v(t_0) > 0$, there exists a $\zeta > 0$ such that

$$(\omega_1(t_0),\ \omega_2(t_0),\ l(t_0),\ v(t_0))^T \geq \zeta(\widetilde{\omega_1}(t_0),\ \widetilde{\omega_2}(t_0),\ \widetilde{l}(t_0),\ \widetilde{v}(t_0))^T.$$

Then, for $t \geq t_0$, we have

$$(\omega_1(t),\ \omega_2(t),\ l(t),\ v(t))^T \geq \zeta(\widetilde{\omega_1}(t),\ \widetilde{\omega_2}(t),\ \widetilde{l}(t),\ \widetilde{v}(t))^T.$$

which implies that $\omega_1(t),\ \omega_2(t),\ v(t),\ l(t)$ are unbounded when $\lambda_0(u_1 - \eta_0) > 0$. The proof is complete. □

Theorem 4.1. *If $R_0 > 1$, the solution semi-flow Φ_t is uniformly persistent. Namely, there is a $\eta > 0$ such that any solution of model (1.3) satisfies*

$$\liminf_{t\to+\infty} \omega_1(t) \geq \eta, \quad \liminf_{t\to+\infty} \omega_2(t) \geq \eta, \quad \liminf_{t\to+\infty} l(t) \geq \eta, \quad \liminf_{t\to+\infty} v(t) \geq \eta.$$

Proof. We easily obtain that Φ_t is compact and point dissipative, it follows from [31, Theorem 1.1.3] that Φ_t has a global attractor A. Let $M = \{\ E_0\ \}$. In view of Lemma 4.1, M_∂ is the maximal compact invariant set in ∂X_0. Similar method to the proof of [32], we see that $\bigcup_{x\in M_\partial} \omega(x) = \{M\}$. Lemma 4.2 implies that M is an isolated invariant set in $\mathbb{X}$, and $W^s(M)\bigcap \mathbb{X}_0 = \emptyset$, where $W^s(M) = \{x \in \mathbb{X} \mid \lim_{t\to+\infty} d(\phi_t(x),\ M) = 0\}$. Indeed, there is no subset of M cycle forms in $\partial\mathbb{X}_0$.

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

$$p(x) = \min\{\omega_{10},\ \omega_{20},\ l_0,\ v_0\}, \quad x = (u_0,\ \omega_{10},\ \omega_{20},\ l_0,\ v_0) \in \mathbb{X}.$$

Thus, p is a generalized distance function for the semi-flow Φ_t. It follows from [31, Theorem 3] that there exists an $\eta > 0$ such that for all $y \in \mathbb{X}_0$, we have $\min_{x\in\omega(y)} p(x) > \eta$. Hence

$$\liminf_{t\to+\infty} \omega_1(t) \geq \eta, \quad \liminf_{t\to+\infty} \omega_2(t) \geq \eta, \quad \liminf_{t\to+\infty} l(t) \geq \eta, \quad \liminf_{t\to+\infty} v(t) \geq \eta.$$

The proof is complete. □

5. Stability of the IE and Hopf bifurcation

Note that

$$\rho_1(1 - 2u^* - \omega_1^*) - \rho_1\omega_1^* - \rho v^* = -\rho_1 u^* = -\frac{\rho_1}{R_0},$$
$$\rho v^* = \frac{(\rho_2 + \rho_3 + \rho_4)\omega_1^*}{u^*} = R_0(\rho_2 + \rho_3 + \rho_4)\omega_1^*.$$

We easily get that the Jacobian matrix of (1.3) at E^* is given by

$$\overline{J} = \begin{pmatrix} -\frac{\rho_1}{R_0} & \frac{\rho_1}{R_0} & 0 & 0 & -\frac{\rho}{R_0} \\ aR_0\omega_1^* & -a & 0 & 0 & \frac{\rho}{R_0} \\ 0 & \rho_5 & -1 & \rho_6 & 0 \\ 0 & \rho_7 & 0 & -d & 0 \\ 0 & 0 & 1 & 0 & -\rho_9 \end{pmatrix},$$

where $a = \rho_2 + \rho_3 + \rho_4$ and $d = \rho_6 + \rho_8$.

The corresponding characteristic equation of model (1.3) at IE E^* is

$$\lambda^5 + b_1\lambda^4 + b_2\lambda^3 + b_3\lambda^2 + b_4\lambda + b_5 = 0,$$

where

$$\begin{aligned}
b_1 =&\rho_9 + a + d + \frac{\rho_1}{R_0} + 1,\\
b_2 =&\rho_1 aS + \rho_9 a + \rho_9 d + ad + \frac{\rho_1\rho_9}{R_0} + \frac{\rho_1 d}{R_0} + \rho_9 + a + d + \frac{\rho_1}{R_0},\\
b_3 =&\rho_1\rho_9 S + \rho_1 adS + \rho_1 aS + G + \frac{\rho_1\rho_9 a}{R_0} + \frac{\rho_1\rho_9 d}{R_0} + \rho_9 a + \rho_9 d + ad + \frac{\rho_1 d}{R_0},\\
b_4 =&\rho_1\rho_9 adS + \rho_1\rho_9 aS + \rho_1 adS + \rho_5 a\rho U + \frac{\rho_1\rho_9 d}{R_0},\\
b_5 =&\rho_1\rho_9 Sad + \rho_5 Ud\rho + \rho_6\rho_7 U\rho,
\end{aligned}$$

where

$$S = \frac{1}{R_0} - \omega_1^*, \quad U = a\omega_1^* - \frac{\rho_1}{R_0^2}, \quad G = \rho_9 ad - \frac{\rho_5\rho}{R_0}.$$

Assume that

(H1) $S > 0,\ U > 0,\ G > 0.$

Denote

$$\begin{aligned}
&\Delta_1 = b_1, \quad \Delta_2 = b_1b_2 - b_3, \quad \Delta_3 = b_3\Delta_2 + b_1b_5 - b_1^2b_4,\\
&\Delta_4 = b_4(\Delta_3 + b_1b_5) - b_2b_5\Delta_2 - b_5^2, \quad \Delta_5 = b_5\Delta_4, \quad \Delta_{30} = \Delta_2 b_3 - b_1^2 b_4.
\end{aligned}$$

Further, we have

$$\begin{aligned}
\Delta_1 =& \rho_9 + a + d + \frac{\rho_1}{R_0} + 1 > 0,\\
\Delta_2 =& \frac{3\rho_1\rho_9}{R_0} + \frac{2\rho_1 d}{R_0} + a + \frac{\rho_1\rho_9 a}{R_0} + \frac{2\rho_1\rho_9 d}{R_0} + \rho_1\rho_9 S(a-1) + \frac{2a\rho_1 d}{R_0} + \frac{\rho_1^2 aS}{R_0} + \frac{\rho_1}{R_0}\\
&+ d + \rho_9 + 2\rho_9 a + 2\rho_9 d + 2ad + \frac{\rho_1^2}{R_0^2} + \rho_9^2 a + \rho_9^2 d + \rho_9^2 + \rho_9(a^2 + d^2) + a^2 d\\
&+ a^2 + ad^2 + d^2 + \frac{\rho_1^2 d}{R_0^2} + \frac{\rho_1 d^2}{R_0} + \rho_1 a^2 S + \frac{\rho_1^2\rho_9}{R_0^2} + \frac{\rho_1\rho_9^2}{R_0} + 2\rho_9 ad + \frac{2a\rho_1}{R_0} + \frac{\rho_5\rho}{R_0}.
\end{aligned}$$

We denote

$$F(p) = \Delta_3(p) = \Delta_{30}(p) + b_1(p)b_5(p),$$

where $p = (\rho_1,\ \rho,\ a,\ \rho_5,\ \rho_6,\ \rho_7,\ d,\ \rho_9)$.

Under hypothesis (H1), if $R_0 > 1$ and $a > 1$, we see that $b_i > 0 (i = 1,\ 2,\ 3,\ 4,\ 5)$, $\Delta_1 > 0$ and $\Delta_2 > 0$. If we further assume that $F(p) > 0$ and $\Delta_4 > 0$, then E^* is locally asymptotically stable by the Routh-Hurwitz criterion. If $F(p) < 0$, then E^* is unstable. If there is a $(\overline{\rho_1},\ \overline{\rho},\ \overline{a},\ \overline{\rho_5},\ \overline{\rho_6},\ \overline{\rho_7},\ \overline{d},\ \overline{\rho_9})$ such that $F(\overline{p}) = 0$, then there is a Hopf bifurcation at E^* by [33, Theorem 2]. Further, we find that the term $F(p) = 0$ has a positive root (see Figure 1(a)). In fact, the term $\Delta_4 = 0$ can also have a positive solution(see Figure 1(b)). For the sake of simplicity, we only discuss the sign of Δ_3 to study the Hopf bifurcation at E^*.

For convenience, we choose ρ_5 as the bifurcation parameter to discuss Hopf bifurcation of the positive equilibrium E^*. We fix the parameters $(\overline{\rho_1}, \overline{\rho}, \overline{a}, \overline{\rho_6}, \overline{\rho_7}, \overline{d}, \overline{\rho_9})$. The sign of function $F(p)$ regarding as a function of ρ_5 changes near $\overline{\rho_5}$, it can be expressed by $F(\rho_5) = \Delta_3 = A\rho_5 + B$ (we omit the bar of $(\overline{\rho_1}, \overline{\rho}, \overline{a}, \overline{\rho_6}, \overline{\rho_7}, \overline{d}, \overline{\rho_9})$ for notational convenience), where

$$\begin{aligned} A =& - a\rho U - \frac{2a\rho U\rho_1\rho_9}{R_0} - 2a^2\rho U - 2a^2\rho U\rho_9 - 2a^2\rho U d - \frac{2a\rho U\rho_1}{R_0} - a\rho U d \\ & - 2a\rho U\rho_9 - a\rho U\rho_9^2 - a^3\rho U - \frac{a\rho U\rho_1^2}{R_0^2} - \frac{2a^2\rho U\rho_1}{R_0} - \rho\rho_9 adU + d^2\rho U - ad^2\rho U \\ & + \frac{\rho\rho_1 dU}{R_0} - \frac{2\rho\rho_1 adU}{R_0} + \rho dU - \rho adU, \end{aligned}$$

$$\begin{aligned} B =& - (\rho_9 + a + d + \frac{\rho_1}{R_0} + 1)^2\Big(\rho_1\rho_9 adS + \rho_1\rho_9 aS + \rho_1 adS + \frac{\rho_1\rho_9 d}{R_0}\Big)\Big((\rho_9 + a + d \\ & + \frac{\rho_1}{R_0} + 1)(\rho_1 aS + \rho_9 a + \rho_9 d + ad + \frac{\rho_1\rho_9}{R_0} + \frac{\rho_1 d}{R_0} + \rho_9 + a + d + \frac{\rho_1}{R_0}) - \rho_1\rho_9 S \\ & - \rho_1 adS - \rho_1 aS - G - \frac{\rho_1\rho_9 a}{R_0} - \frac{\rho_1\rho_9}{R_0} - \rho_9 a - \rho_9 d - ad - \frac{\rho_1 d}{R_0}\Big)(\rho_1\rho_9 S \\ & + \rho_1 adS + \rho_1 aS + G + \frac{\rho_1\rho_9 a}{R_0} + \frac{\rho_1\rho_9 d}{R_0}\rho_9 a + \rho_9 d + ad + \frac{\rho_1 d}{R_0}) \\ & + \Big(\rho_9 + a + d + \frac{\rho_1}{R_0} + 1\Big)\Big(\rho_1\rho_9 Sad + \rho_6\rho_7 U\rho\Big). \end{aligned}$$

Further, we have $B = ES^2 + HS + I$,where

$$\begin{aligned} E =& \rho_1^2\rho_9 a^2 d - \rho_1^2\rho_9 ad + \rho_1^2\rho_9^2 a - \rho_1^2\rho_9^2 + \rho_1^2\rho_9 a^2 - \rho_1^2\rho_9 a + \frac{\rho_1^3 a^2 d}{R_0} + \rho_1^2 a^3 + \rho_1^2 a^3 d \\ & + \frac{\rho_1^3 a\rho_9}{R_0} + \frac{\rho_1^3 a^2}{R_0} + \rho_1^2\rho_9 a^2, \end{aligned}$$

$$\begin{aligned} H =& \rho_1\rho_9 aG - 2\rho_1\rho_9 G + \rho_1 a^2 G - \rho_1 aG - \rho_1 adG + \frac{\rho_1^2\rho_9^2 a^2}{R_0} - \frac{\rho_1^2\rho_9^2 a}{R_0} + \rho_1\rho_9^2 ad \\ & - \rho_1\rho_9^2 ad^2 + \rho_1\rho_9^2 a^2 - \rho_1\rho_9^2 a^2 d + \rho_1\rho_9 a^2 d^2 - \rho_1\rho_9 ad^2 + \rho_1\rho_9 a^2 d - \rho_9^3\rho_1 ad \\ & + \rho_1\rho_9 a^2 d - \rho_1\rho_9 ad + a^2 d^2\rho_1 + \rho_1\rho_9 d + \rho_9^2 d^2\rho_1 + \rho_1 a^2 + a^3\rho_1 + \rho_1\rho_9 a^2 \\ & + d^2\rho_1\rho_9 + \rho_1\rho_9 a + \frac{3\rho_1^2\rho_9^2}{R_0} + \frac{\rho_1^3\rho_9^2}{R_0^2} + \rho_1\rho_9^2 + \rho_9^3\rho_1 + \rho_1\rho_9^2 d + \frac{2a^2\rho_1^2}{R_0} + \frac{\rho_1^2\rho_9^3}{R_0} \\ & + 2a^3\rho_1 d + \frac{\rho_1^2 a}{R_0} + \frac{3a\rho_1^2\rho_9 d}{R_0} + \frac{\rho_1^3\rho_9 ad}{R_0^2} + \frac{\rho_1^3 d\rho_9}{R_0^2} + \frac{\rho_1^3 d^2 a}{R_0^2} + \frac{\rho_1^2\rho_9^2 d}{R_0} + \frac{2a^2\rho_1^2 d^2}{R_0} \\ & + \frac{\rho_1^2 aG}{R_0} + \frac{\rho_1^3 a^2\rho_9}{R_0^2} + \frac{\rho_1^2 d\rho_9}{R_0} + \frac{\rho_1^2 a^3\rho_9}{R_0} + \frac{\rho_1^2 d^2\rho_9}{R_0} + \frac{\rho_1^2 d^3 a}{R_0} + \frac{\rho_1^2 d^2 a}{R_0} + \frac{4a^2\rho_1^2 d}{R_0} \\ & + \frac{\rho_1^3\rho_9}{R_0^2} + \frac{\rho_1^3 a}{R_0^2} + \rho_9^3 d\rho_1 + a^3 d^2\rho_1 + a^2 d^3\rho_1 + \frac{\rho_1^2\rho_9}{R_0} + \rho_1 a^2 d + a^3\rho_1\rho_9 + \frac{2\rho_1^3 ad}{R_0^2} \\ & + \frac{3a\rho_1^2\rho_9}{R_0} + \frac{\rho_1^2 ad}{R_0} + \Big(\rho_9 + a + d + \frac{\rho_1}{R_0} + 1\Big)\rho_1\rho_9 ad, \end{aligned}$$

$$
\begin{aligned}
I =&\rho_9 aG - G^2 + \frac{3\rho_1\rho_9 a^2}{R_0} + \frac{2\rho_1^2\rho_9^2 d^2}{R_0^2} + \frac{\rho_1^2\rho_9^2 a^2}{R_0^2} + \frac{3\rho_9^2 a^2\rho_1}{R_0} + \frac{3a^2d^2\rho_1}{R_0} + \frac{3a\rho_1^2 d^2}{R_0^2}\\
&+ \frac{3\rho_1\rho_9 G}{R_0} + \frac{4\rho_1^2\rho_9^2 a}{R_0^2} + \frac{4\rho_1\rho_9^2 a}{R_0} + \frac{\rho_1 d^2 G}{R_0} + \frac{\rho_1^2 d^3\rho_9}{R_0^2} + \frac{2\rho_1 d^3 a}{R_0} + \frac{\rho_1^2 dG}{R_0^2} + \frac{\rho_1^3 d^2\rho_9}{R_0^3}\\
&+ 3\rho_9 adG + \frac{\rho_1^2\rho_9 G}{R_0^2} + \frac{\rho_1^3\rho_9^2 a}{R_0^3} + \frac{\rho_1^3\rho_9^2 d}{R_0^3} + \frac{2G\rho_1 a}{R_0} + \frac{2\rho_1^2\rho_9 a^2}{R_0^2} + \frac{3\rho_1 a^2 d}{R_0} + \frac{3a\rho_1^2 d}{R_0^2}\\
&+ \frac{a^3\rho_1\rho_9}{R_0} + \frac{\rho_1\rho_9^2 G}{R_0} + \frac{\rho_1^2\rho_9^3 a}{R_0^2} + \frac{\rho_1^2\rho_9^3 d}{R_0^2} + \frac{2\rho_1\rho_9^3 a}{R_0} + \frac{\rho_1^3\rho_9 a}{R_0^3} + \frac{2a\rho_1^2\rho_9}{R_0^2} + \frac{\rho_1\rho_9 d}{R_0}\\
&+ \frac{\rho_9^3 a^2\rho_1}{R_0} + \frac{\rho_1\rho_9 a}{R_0} + \frac{\rho_9^3 d^2\rho_1}{R_0} + \frac{\rho_9^2 a^3\rho_1}{R_0} + \frac{\rho_9^2 d^3\rho_1}{R_0} + \frac{3\rho_1^2 d^2\rho_9}{R_0^2} + \frac{3\rho_1^2\rho_9^2 d}{R_0^2} + \frac{\rho_9^3 d\rho_1}{R_0}\\
&+ dG + aG + \rho_9^2 G + \rho_9^3 a + \rho_9^3 d + a^2 G + a^3\rho_9 + a^3 d + d^2 G + d^3\rho_9 + d^3 a + \rho_9^3 a^2\\
&+ \rho_9^3 d^2 + \rho_9^2 a^3 + a^3 d^2 + \rho_9^2 d^3 + a^2 d^3 + \rho_9 G + 2\rho_9^2 a^2 + 2\rho_9^2 d^2 + 2a^2 d^2 + \frac{\rho_1 dG}{R_0}\\
&+ \frac{\rho_1^3\rho_9 d}{R_0^3} + \frac{2d^3\rho_1\rho_9}{R_0} + \frac{3\rho_1^2\rho_9 d}{R_0^2} + \frac{3\rho_9^2 d^2\rho_1}{R_0} + \frac{3\rho_1\rho_9^2 d}{R_0} + \frac{3d^2\rho_1\rho_9}{R_0} + \frac{ad^3\rho_1\rho_9}{R_0}\\
&+ \frac{\rho_1^3 d\rho_9 a}{R_0^3} + \frac{4\rho_9^2 a^2\rho_1 d}{R_0} + \frac{4\rho_9^2 d^2\rho_1 a}{R_0} + \frac{2\rho_9^3\rho_1 ad}{R_0} + \frac{a^3 d\rho_1\rho_9}{R_0} + \frac{2a^2 d^2\rho_1\rho_9}{R_0} + \frac{2a\rho_1 d}{R_0}\\
&+ \frac{\rho_1\rho_9 dG}{R_0} + \frac{3\rho_1^2\rho_9^2 da}{R_0^2} + \frac{2a\rho_1 dG}{R_0} + \frac{2a^2\rho_1^2 d\rho_9}{R_0^2} + \frac{3a\rho_1^2 d^2\rho_9}{R_0^2} + \frac{\rho_1 G}{R_0} + \frac{4\rho_1 d^2 a}{R_0}\\
&+ \frac{2\rho_1^2 d^2}{R_0^2} + \frac{\rho_1^2 d^3}{R_0^2} + \frac{\rho_1^3 d^2}{R_0^3} + 5\rho_9^2 ad + 2\rho_9 a^3 d + 3\rho_9 ad + 2\rho_9 d^3 a + 2\rho_9^3 ad + 5\rho_9^2 ad^2\\
&+ 5\rho_9 a^2 d^2 + 5a^2\rho_9 d + 5\rho_9^2 a^2 d + 5d^2\rho_9 a + \rho_9^2 a + \rho_9^2 d + \rho_9 a^2 + a^2 d + \rho_9 d^2 + ad^2\\
&+ \frac{d^3\rho_1}{R_0} + \frac{\rho_1^2 G}{R_0^2} + \frac{\rho_1^3 d}{R_0^3} + \rho_9^2 aG + \rho_9^2 dG + \rho_9 a^2 G + a^2 dG + \rho_9 d^2 G + ad^2 G + \frac{\rho_1 d^2}{R_0}\\
&+ \frac{\rho_1^2 d}{R_0^2} + \frac{9a\rho_1\rho_9 d}{R_0} + \frac{5a\rho_1^2\rho_9 d}{R_0^2} + \frac{6\rho_1\rho_9 a^2 d}{R_0} + \frac{7\rho_9^2\rho_1 ad}{R_0} + \frac{9d^2\rho_1\rho_9}{R_0} + \rho_9 dG + adG\\
&+ \Big(\rho_9 + a + d + \frac{\rho_1}{R_0} + 1\Big)\rho_6\rho_7 U\rho.
\end{aligned}
$$

From the discussions above, we obtain the following result.

Theorem 5.1. *Assume that (H1) holds and $a > 1$ and $\Delta_4 > 0$, the parameters $(\overline{\rho_1},\ \overline{\rho},\ \overline{a},\ \overline{\rho_6},\ \overline{\rho_7},\ \overline{d},\ \overline{\rho_9})$ are fixed. If $R_0 > 1$ and $F(\rho_5) > 0$, then E^* is locally asymptotically stable. If there exists a critical value $\overline{\rho_5} > 0$ such that $R_0 > 1$ and $F(\overline{\rho_5}) = 0$, then the Hopf bifurcation occurs at E^* when ρ_5 passes through the critical value $\overline{\rho_5}$.*

Remark 5.1. If $a > \max\{2,\ \rho_9^2\}$ and $d < 1$ hold, then we have

$$
\begin{aligned}
&d^2\rho U - ad^2\rho U = d^2\rho U(1-a) < 0,\\
&\frac{\rho\rho_1 dU}{R_0} - \frac{2\rho\rho_1 adU}{R_0} = \frac{\rho\rho_1 dU(1-2a)}{R_0} < 0,\\
&\rho dU - \rho adU = \rho dU(1-a) < 0,\\
&a^2\rho_1^2\rho_9 d - a\rho_1^2\rho_9 d = a\rho_1^2\rho_9 d(a-1) > 0,\\
&\rho_1^2\rho_9^2 a - \rho_1^2\rho_9^2 = \rho_1^2\rho_9^2(a-1) > 0,
\end{aligned}
$$

$$\begin{aligned}
&\rho_1^2\rho_9 a^2 - \rho_1^2\rho_9 a = a\rho_1^2\rho_9(a-1) > 0,\\
&\rho_1\rho_9 aG - 2\rho_1\rho_9 G = \rho_1\rho_9 G(a-2) > 0,\\
&\rho_1 a^2 G - \rho_1 aG - \rho_1 adG = \rho_1 aG(a-1-d) > 0,\\
&\frac{\rho_1^2\rho_9^2 a^2}{R_0} - \frac{\rho_1^2\rho_9^2 a}{R_0} = \frac{\rho_1^2\rho_9^2 a(a-1)}{R_0} > 0,\\
&\rho_1\rho_9^2 ad - \rho_1\rho_9^2 ad^2 = \rho_1\rho_9^2 ad(1-d) > 0,\\
&\rho_1\rho_9^2 a^2 - \rho_1\rho_9^2 a^2 d = \rho_1\rho_9^2 a^2(1-d) > 0,\\
&\rho_1\rho_9 a^2 d^2 - \rho_1\rho_9 ad^2 = \rho_1\rho_9 ad^2(a-1) > 0,\\
&\rho_1\rho_9 a^2 d - \rho_1\rho_9^3 ad = \rho_1\rho_9 ad(a-\rho_9^2) > 0,\\
&\rho_1\rho_9 a^2 d - \rho_1\rho_9 ad = \rho_1\rho_9 ad(a-1) > 0,\\
&\rho_9 aG - G^2 = G\left(\rho_9 a(1-d) + \frac{\rho_5\rho}{R_0}\right) > 0.
\end{aligned}$$

that is, $E > 0$, $H > 0$. Then one gets $B > 0$. We see that if $\rho_5 = 0$, then $F(0) = B > 0$. Moreover, since $A < 0$, one gets $\lim_{\rho_5\to+\infty} F(\rho_5) = -\infty$. Thus $F(\rho_5) = 0$ exists one positive root.

6. Numerical simulations

We choose ρ_5 as the bifurcation parameter. When the parameters are chosen as

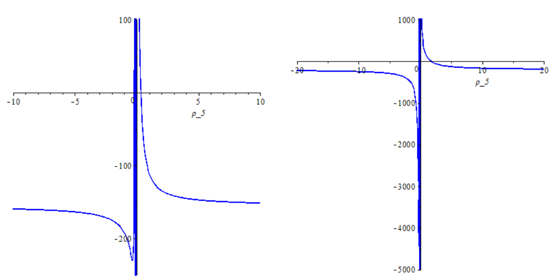
$$\begin{aligned}
&\rho = 15.34,\ \rho_1 = 2.6,\ \rho_2 = 0.6,\ \rho_3 = 0.8,\ \rho_4 = 0.8,\\
&\rho_6 = 0.1,\ \rho_7 = 0.12,\ \rho_8 = 0.67,\ \rho_9 = 0.6,
\end{aligned}$$

it satisfies (H1), $a > \max\{2,\ \rho_9^2\}$ and $d < 1$. Moreover, $F(\rho_5) = 0$ has a positive root $\rho_5 = 0.3529183723$ (see Figure 1).

The calculations show that $R_0 = 8.306916800000000 > 1$, then model (1.3) admits a positive equilibrium

$$\begin{aligned}
E^* = (&0.178943840915672,\ 0.143325796718976,\ 9.178584021883246,\\
&3.439819121255432,\ 9.178584021883246).
\end{aligned}$$

Thus $\overline{\rho_5} = 0.8944922006$ is the critical value for the occurence of the Hopf bifurcation. When $\rho_5 = \overline{\rho_5}$, there is a Hopf bifurcation, and a family of periodic solutions can bifurcate from E^* (see Figure 2).



(a) (b)

Figure 1. The function $F(\rho_5) = 0$ has a positive root.

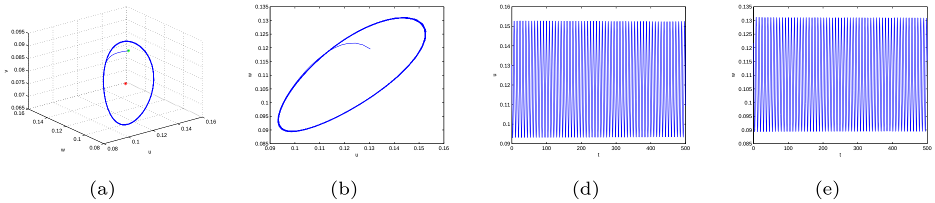


Figure 2. Trajectories of model (1.3) with $R_0 > 1$.

We choose the following values

$$\rho = 14, \quad \rho_1 = 2.5, \quad \rho_2 = 0.6, \quad \rho_3 = 0.8, \quad \rho_4 = 0.8,$$
$$\rho_5 = 0.7, \quad \rho_6 = 0.1, \quad \rho_7 = 0.12, \quad \rho_8 = 0.67, \quad \rho_9 = 0.6.$$

The calculations show that $R_0 = 7.581280000000000 > 1$, then model (1.3) has a positive equilibrium

$$E^* = (0.131903847371420,\ 0.113158204425729,\ 0.080974247582567,\\ 0.017635044845568,\ 0.134957079304279).$$

Moreover, it shows that E^* is globally asymptotically stable as shown in Figure 3.

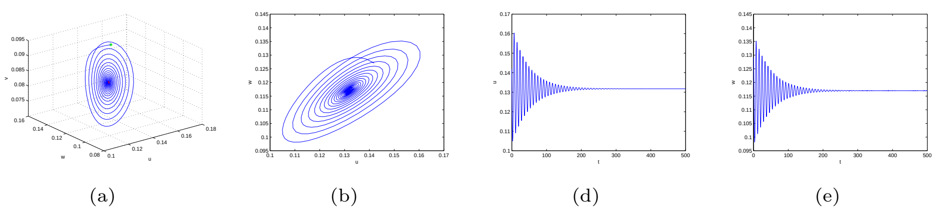


Figure 3. Trajectories of model (1.3) with $R_0 > 1$.

7. Discussions and conclusions

In this paper, we develop an ordinary differential equation model with logistic target cell growth to describe influence of raltegravir intensification on viral dynamics. We have shown that the IFE E_0 is globally attractive if $R_0 < 1$, while virus is uniformly persistent if $R_0 > 1$. We observe that Hopf bifurcation can occur at around the IE E^* under some suitable parameters.

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