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Dynamic behaviors of a class of HIV compartmental models

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ABSTRACT

Based on heterogeneities in drug efficacy (either spatial or phenotypic), two HIV compartmental models were proposed in Callaway and Perelson (2002) to study the HIV virus dynamics under drug treatment. In this paper, we provide a global analysis on the two models, including the positivity and boundedness of solutions and the global stability of equilibrium solutions. In particular, we show that when the basic reproduction number $R_0 \leqslant 1$ (for which the infection equilibrium does not exist), the infection-free equilibrium is globally asymptotically stable; while when $R_0 > 1$ (for which the infection equilibrium exists), the infection equilibrium is globally asymptotically stable.

1. Introduction

With considerable information obtained from the treatment of HIV-infected individuals using highly active antiretroviral therapy (HAART) [2,21,15,1,13], a large number of mathematical models have been proposed based on the decay characteristics of virus in the bodies of infected patients [9,22,8,4,14]. Some of these models were developed from the observations of Perelson et al. [13] that rapid decay of HIV in the first two weeks is mainly due to the fast elimination of free virus and the loss of productively infected cells, while the main contribution to the second phase is the loss of long-lived infected cells. Under the assumptions that combined drug efficacy being ϵ and a fraction α of infection events resulting in chronic infection, a standard and classic model developed on the basis of this decay characteristic is described by the following differential equations [2]:

$$
\begin{aligned}
\frac{dx}{dt} &= \lambda - dx - (1-\epsilon)kvx,\\
\frac{dy}{dt} &= (1-\alpha)(1-\epsilon)kvx - \delta y,\\
\frac{dz}{dt} &= \alpha(1-\epsilon)kvx - \mu z,\\
\frac{dv}{dt} &= N_T\delta y + N_m\mu z - cv,
\end{aligned}
\tag{1.1}
$$

where x, y, z and v denote, respectively, the densities of $CD4^+$ cells that are susceptible to infection, productively infected cells, long lived chronically infected cells and free virus; λ and k are the generation rates of $CD4^+$ cells and the infection rate

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constant, respectively; d, δ, μ and c are the death rates of $CD4^+$ cells, productively infected cells, long lived chronically infected cells and free virus, respectively; N_T and N_m represent the average numbers of virions produced in the lifetime of productively infected cells and chronically infected cells, respectively.

Although it has been shown that HAART is extremely effective in reducing the viral burden in HIV-infected individuals below the threshold of detectability, some evidence indicates that viral replication continuous in these individuals after an HAART treatment [19,23,5]. For example, Callaway and Perelson [2] have shown that most of existing models are extremely sensitive to minor changes in drug efficacy. More precisely, according to [2], there exists a critical drug efficacy at which the steady-state of virus becomes zero, implying that virus can be cleared in infected patients. Moreover, the virus vs. drug efficacy curve is concave down near the critical drug efficacy in most of existing models, showing that virus is sensitive to minor changes near the critical efficacy. That is to say, if these models describe the realistic situation, a lot of patients should have cleared the virus in their bodies, which has contrary to observations. To explore more realistic mechanisms responsible for sustained, yet undetectable viral load, two models were developed in [2]. These two models improve the previous existing ones by including heterogeneities in drug efficacy, with the use of either drug sanctuary sites created by physiological barrier or differential efficacy in cocirculating target cells.

There have been previous studies on drug sanctuary and differential efficacy in cocirculating target cells. Examination of changes in drug efficacy after a treatment with antiretroviral drugs has shown that drug efficiencies are reduced in certain physiologically distinct sites such as the tests [2,18] and the brain [18,6,12]. Researches in vitro [2,16,17,10] have indicated that drug efficacy may vary in different types of cells. For example, antiretroviral drugs have less effects in monocyte cell lines [16,17,10]. Based on the above mentioned facts and the observations in [13], Callawy and Perelson established two models [2], one including two cocirculating target cells with differential efficacy, and the other modeling two physiologically distinct compartments with one as drug sanctuary created by a physiological barrier.

1.1. Differential efficacy in cocirculating target cells

Making use of drug efficacy varying by target cell types, model (1.1) is generalized to a more sophisticated one under the following assumptions: (i) there are two types of target cells cocirculating in a single compartment, where in one population ($i = 1$) drug efficacy is $0 < \epsilon < 1$, while in the other one ($i = 2$) drug efficacy $f\epsilon$ is reduced by a factor $0 < f < 1$; and (ii) there is a fraction α of infection events which results in chronic infection ($0 < \alpha < 1$). Then, the generalized model can be written as

$$\begin{aligned}
\frac{dx_1}{dt} &= \lambda_1 - d_1x_1 - (1-\epsilon)k_1 v x_1, \\
\frac{dx_2}{dt} &= \lambda_2 - d_2x_2 - (1-f\epsilon)k_2 v x_2, \\
\frac{dy_1}{dt} &= (1-\alpha)(1-\epsilon)k_1 v x_1 - \delta y_1, \\
\frac{dy_2}{dt} &= (1-\alpha)(1-f\epsilon)k_2 v x_2 - \delta y_2, \\
\frac{dz_1}{dt} &= \alpha(1-\epsilon)k_1 v x_1 - \mu z_1, \\
\frac{dz_2}{dt} &= \alpha(1-f\epsilon)k_2 v x_2 - \mu z_2, \\
\frac{dv}{dt} &= N_T\delta(y_1+y_2) + N_m\mu(z_1+z_2) - cv,
\end{aligned} \tag{1.2}$$

where x_i, y_i, z_i ($i = 1, 2$) and v represent, respectively, the concentrations of HIV-1 target cells, short-lived infected cells, long lived chronically infected cells, and free virus. The constants, $\lambda_i,\ i = 1, 2$, denote the generation rates of target cells. $k_i,\ i = 1, 2$, are the infection rate constants. The parameters d_i ($i = 1, 2$), δ, μ and c represent the death rates of target cells, short-lived infected cells, long lived chronically infected cells and free HIV-1 RNA, respectively. N_T and N_m represent the average numbers of virions produced in the lifetime of short-lived and chronically infected cells, respectively.

1.2. Drug sanctuary created by a physiological barrier

Further, suppose in model (1.1) the HIV infection process occurs in two distinct compartments. The first compartment is the main compartment with larger volume and higher drug concentration, while the second one is the drug sanctuary with smaller volume and lower drug concentration. It is assumed that virus transporting between the two compartments is allowed, and moreover that the transport of virus between the main compartment and the sanctuary is governed by the rate constants, D_1 and D_2, and the difference in virus concentration between the two compartments. With the above additional assumptions, model (1.1) can be expanded to the new model,

$$\begin{aligned}
\frac{dx_1}{dt} &= \lambda - dx_1 - (1-\epsilon)kv_1x_1,\\
\frac{dx_2}{dt} &= \lambda - dx_2 - (1-f\epsilon)kv_2x_2,\\
\frac{dy_1}{dt} &= (1-\alpha)(1-\epsilon)kv_1x_1 - \delta y_1,\\
\frac{dy_2}{dt} &= (1-\alpha)(1-f\epsilon)kv_2x_2 - \delta y_2,\\
\frac{dz_1}{dt} &= \alpha(1-\epsilon)kv_1x_1 - \mu z_1,\\
\frac{dz_2}{dt} &= \alpha(1-f\epsilon)kv_2x_2 - \mu z_2,\\
\frac{dv_1}{dt} &= N_T\delta y_1 + N_m\mu z_1 - cv_1 + D_1(v_2 - v_1),\\
\frac{dv_2}{dt} &= N_T\delta y_2 + N_m\mu z_2 - cv_2 + D_2(v_1 - v_2),
\end{aligned} \tag{1.3}$$

where all the state variables and parameters are defined as the same as those in model (1.2). All the parameters in models (1.2) and (1.3) are positive constants.

In models (1.2) and (1.3), the steady state viral load vs. drug efficacy curve in main compartment is concave up near the point of critical efficacy, which means that the steady state viral load is not sensitive to small changes in drug efficacy [2]. This may explain why HIV-infected individuals carry sustained and low viral load. However, in [2], authors merely analyzed the equilibrium solutions and performed some numerical simulations for these two models. To explore the detailed dynamical behavior of the two models, we will study the global property of the models in Sections 2 and 3, including the positivity and boundedness of solutions, and the global stability of equilibrium solutions. The basic methodology used in this paper is a combination of fluctuation lemma, Lyapunov function and LaSalle's invariance principle. We will show that for models (1.2) and (1.3), if the basic reproduction number, $R_0 \leqslant 1$, for which the infection equilibrium does not exist, the infection-free equilibrium is globally asymptotically stable; if $R_0 > 1$, for which the infection equilibrium exists, the infection equilibrium is globally asymptotically stable. Simulations are presented in Section 4 to illustrate the theoretical results obtained in Sections 2 and 3. Finally, conclusion is drawn in Section 5.

2. Global analysis of model (1.2)

In this section, we give a detailed analysis on model (1.2), including well-posedness of solutions, equilibrium solutions and their stability.

2.1. Well-posedness, equilibria and basic reproduction number

In order for model (1.2) to be biologically meaningful, we will show that all solutions of this model are non-negative for any given non-negative initial conditions. Moreover, we will show that all solutions of this model are bounded.

Theorem 2.1. *Any solution of model (1.2), $(x_1(t), x_2(t), y_1(t), y_2(t), z_1(t), z_2(t), v(t))$, is non-negative for all $t > 0$ provided that the initial conditions are non-negative, and is bounded.*

Proof. Using the first two equations of model (1.2), we can write the solutions of $x_1(t)$ and $x_2(t)$ as

$$x_1(t) = x_1(0)e^{-\int_0^t [d_1+(1-\epsilon)k_1v(s)]ds} + \lambda_1\int_0^t e^{-\int_s^t [d_1+(1-\epsilon)k_1v(\xi)]d\xi}ds$$

and

$$x_2(t) = x_2(0)e^{-\int_0^t [d_2+(1-f\epsilon)k_2v(s)]ds} + \lambda_2\int_0^t e^{-\int_s^t [d_2+(1-f\epsilon)k_2v(\xi)]d\xi}ds.$$

This clearly indicates that $x_1(t) > 0$ and $x_2(t) > 0$ for all $t > 0$ if $x_1(0) \geqslant 0$ and $x_2(0) \geqslant 0$. Next, we consider the last five equations of model (1.2) as an autonomous system for y_1, y_2, z_1, z_2 and v:

$$\begin{aligned}
\frac{dy_1}{dt} &= (1-\alpha)(1-\epsilon)k_1vx_1 - \delta y_1,\\
\frac{dy_2}{dt} &= (1-\alpha)(1-f\epsilon)k_2vx_2 - \delta y_2,\\
\frac{dz_1}{dt} &= \alpha(1-\epsilon)k_1vx_1 - \mu z_1,\\
\frac{dz_2}{dt} &= \alpha(1-f\epsilon)k_2vx_2 - \mu z_2,\\
\frac{dv}{dt} &= N_T\delta(y_1+y_2) + N_m\mu(z_1+z_2) - cv.
\end{aligned} \tag{2.1}$$

By Theorem 2.1 in [20], we know that any solution of system (2.1) with $y_1(0) \geqslant 0, y_2(0) \geqslant 0, z_1(0) \geqslant 0, z_2(0) \geqslant 0$ and $v(0) \geqslant 0$ is non-negative for all $t \geqslant 0$ in its maximal interval of existence.

It remains to prove that all non-negative solutions are bounded. Let $(x_1, x_2, y_1, y_2, z_1, z_2, v)$ be a non-negative solution of model (1.2) and $\widetilde{N} = \max\{N_T + 1, N_m + 1\}$. Consider

$$g(t) = \widetilde{N}(x_1 + x_2 + y_1 + y_2 + z_1 + z_2) + v.$$

Then, we have

$$\left.\frac{dg}{dt}\right|_{(1.2)} = \widetilde{N}(\lambda_1 + \lambda_2) - \widetilde{N}(d_1x_1 + d_2x_2) - (\widetilde{N} - N_T)\delta(y_1 + y_2) - (\widetilde{N} - N_m)\mu(z_1 + z_2) - cv,$$

which implies that

$$\left.\frac{dg}{dt}\right|_{(1.2)} \begin{cases} < 0 & \text{for } \widetilde{N}(d_1x_1 + d_2x_2) + (\widetilde{N} - N_T)\delta(y_1 + y_2) + (\widetilde{N} - N_m)\mu(z_1 + z_2) + cv > \widetilde{N}(\lambda_1 + \lambda_2), \\ > 0 & \text{for } \widetilde{N}(d_1x_1 + d_2x_2) + (\widetilde{N} - N_T)\delta(y_1 + y_2) + (\widetilde{N} - N_m)\mu(z_1 + z_2) + cv < \widetilde{N}(\lambda_1 + \lambda_2). \end{cases}$$

Thus, every component of $(x_1, x_2, y_1, y_2, z_1, z_2, v)$ must be bounded. By extension theory of ODE, the boundedness of the solution is proved.

The proof is complete. □

Let $R_0 = R_0^1 + R_0^2$, where

$$R_0^1 = [N_T(1-\alpha) + N_m\alpha]\frac{\lambda_1 k_1(1-\epsilon)}{cd_1} \quad \text{and} \quad R_0^2 = [N_T(1-\alpha) + N_m\alpha]\frac{\lambda_2 k_2(1-f\epsilon)}{cd_2}.$$

If we just consider one compartment i in model (1.2), then R_0^i is the basic reproduction number of subsystem i ($i = 1, 2$).

It is easy to obtain the equilibrium solutions of model (1.2) in the form of

$$\begin{aligned} x_1(v) &= \tfrac{\lambda_1}{d_1 + (1-\epsilon)k_1 v}, & x_2(v) &= \tfrac{\lambda_2}{d_2 + (1-f\epsilon)k_2 v}, \\ y_1(v) &= \tfrac{(1-\alpha)(1-\epsilon)k_1}{\delta} v x_1, & y_2(v) &= \tfrac{(1-\alpha)(1-f\epsilon)k_2}{\delta} v x_2, \\ z_1(v) &= \tfrac{\alpha(1-\epsilon)k_1}{\mu} v x_1, & z_2(v) &= \tfrac{\alpha(1-f\epsilon)k_2}{\mu} v x_2, \end{aligned}$$

where v is either zero or a non-zero solution which is determined by the following equation:

$$[N_T(1-\alpha) + N_m\alpha]\left[\frac{\lambda_1 k_1(1-\epsilon)}{d_1 + (1-\epsilon)k_1 v} + \frac{\lambda_2 k_2(1-f\epsilon)}{d_2 + (1-f\epsilon)k_2 v}\right] - c = 0. \tag{2.2}$$

Obviously, (2.2) is equivalent to the equation,

$$ck_1k_2(1-\epsilon)(1-f\epsilon)v^2 - bv + cd_1d_2(1-R_0) = 0, \tag{2.3}$$

where

$$b = [N_T(1-\alpha) + N_m\alpha]k_1k_2(1-\epsilon)(1-f\epsilon)(\lambda_1 + \lambda_2) - c[d_1(1-f\epsilon)k_2 + d_2(1-\epsilon)k_1].$$

Let v_1 and v_2 be the two roots of (2.3) with $v_1 \leqslant v_2$. Then,

$$v_1 v_2 = \frac{d_1 d_2(1-R_0)}{k_1k_2(1-\epsilon)(1-f\epsilon)}, \tag{2.4}$$

which, combined with (2.2), yields the following results:

(a) $v_1 \leqslant v_2 < 0$ if $R_0 < 1$;
(b) $v_1 < v_2 = 0$ if $R_0 = 1$;
(c) $v_1 < 0 < v_2$ if $R_0 > 1$.

Based on the above results, we find conditions for the existence of equilibrium solutions of model (1.2) as follows:

(1) model (1.2) has a unique equilibrium $E_0 = (\frac{\lambda_1}{d_1}, \frac{\lambda_2}{d_2}, 0, 0, 0, 0, 0)$, if $R_0 \leq 1$; or
(2) model (1.2) has two equilibria E_0 and $E_1 = (x_1(\hat{v}), x_2(\hat{v}), y_1(\hat{v}), y_2(\hat{v}), z_1(\hat{v}), z_2(\hat{v}), \hat{v})$ where $\hat{v} > 0$ is the root of (2.3) for $R_0 > 1$.

2.2. Stability of the infection-free equilibrium E_0

In this subsection, we study the stability of the infection-free equilibrium E_0. To analyze the local stability of E_0, we use the Jacobian matrix of model (1.2) evaluated at E_0 and consider its characteristic equation. By a simple calculation, we get the Jacobian matrix of model (1.2) evaluated at E_0 in the form of

$$J(E_0) = \begin{bmatrix} -d_1 & 0 & 0 & 0 & 0 & 0 & -(1-\epsilon)k_1\frac{\lambda_1}{d_1} \\ 0 & -d_2 & 0 & 0 & 0 & 0 & -(1-f\epsilon)k_2\frac{\lambda_2}{d_2} \\ 0 & 0 & -\delta & 0 & 0 & 0 & (1-\alpha)(1-\epsilon)k_1\frac{\lambda_1}{d_1} \\ 0 & 0 & 0 & -\delta & 0 & 0 & (1-\alpha)(1-f\epsilon)k_2\frac{\lambda_2}{d_2} \\ 0 & 0 & 0 & 0 & -\mu & 0 & \alpha(1-\epsilon)k_1\frac{\lambda_1}{d_1} \\ 0 & 0 & 0 & 0 & 0 & -\mu & \alpha(1-f\epsilon)k_2\frac{\lambda_2}{d_2} \\ 0 & 0 & N_T\delta & N_T\delta & N_m\mu & N_m\mu & -c \end{bmatrix}, \quad (2.5)$$

which, with help of Maple for a symbolic computation, gives the characteristic equation:

$$\det(\lambda I - J(E_0)) = (\lambda + d_1)(\lambda + d_2)(\lambda + \mu)(\lambda + \delta)(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0, \quad (2.6)$$

where

$$\begin{aligned} a_1 &= \mu + \delta + c, \\ a_2 &= \mu\delta + c(\mu + \delta) - \left[\tfrac{\lambda_1 k_1(1-\epsilon)}{d_1} + \tfrac{\lambda_2 k_2(1-f\epsilon)}{d_2}\right][N_T(1-\alpha)\delta + N_m\alpha\mu], \\ a_3 &= c\mu\delta(1 - R_0). \end{aligned}$$

We have the following result.

Theorem 2.2. *The infection-free equilibrium E_0 of model (1.2) is globally asymptotically stable for $R_0 < 1$.*

Proof. First, we show that E_0 is locally asymptotically stable. E_0 is asymptotically stable if and only if all roots of the characteristic polynomial (2.6) have negative real parts. By the Hurwitz criterion, all roots of (2.6) have negative real parts if and only if the following conditions hold:

$$\begin{aligned} \Delta_1 &= a_1 > 0, \\ \Delta_2 &= \det\begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix} = a_1a_2 - a_3 > 0, \\ \Delta_3 &= \det\begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{bmatrix} = a_3\Delta_2 > 0. \end{aligned}$$

Now we show that $\Delta_i > 0, i = 1, 2, 3$ for $R_0 < 1$. Obviously, $\Delta_1 > 0$ and $a_3 > 0$ for $R_0 < 1$. Recall that

$$R_0 = R_0^1 + R_0^2 = [N_T(1-\alpha) + N_m\alpha]\left[\frac{\lambda_1 k_1(1-\epsilon)}{cd_1} + \frac{\lambda_2 k_2(1-f\epsilon)}{cd_2}\right].$$

Thus, $R_0 < 1$ results in

$$c > [N_T(1-\alpha) + N_m\alpha]\left[\frac{\lambda_1 k_1(1-\epsilon)}{d_1} + \frac{\lambda_2 k_2(1-f\epsilon)}{d_2}\right],$$

which in turn yields that

$$\begin{aligned} c(\mu+\delta) &> [N_T(1-\alpha) + N_m\alpha](\mu+\delta)\left[\frac{\lambda_1 k_1(1-\epsilon)}{d_1} + \frac{\lambda_2 k_2(1-f\epsilon)}{d_2}\right] \\ &> [N_T(1-\alpha)\delta + N_m\alpha\mu]\left[\frac{\lambda_1 k_1(1-\epsilon)}{d_1} + \frac{\lambda_2 k_2(1-f\epsilon)}{d_2}\right]. \end{aligned} \quad (2.7)$$

With (2.7), it is easy to show that

$$\Delta_2 = a_1\left\{c(\mu+\delta) - [N_T(1-\alpha)\delta + N_m\alpha\mu]\left[\frac{\lambda_1 k_1(1-\epsilon)}{d_1} + \frac{\lambda_2 k_2(1-f\epsilon)}{d_2}\right]\right\} + \mu\delta(\mu+\delta) + c\mu\delta R_0 > 0.$$

Therefore, E_0 is locally asymptotically stable for $R_0 < 1$.

Next, we apply the fluctuation lemma [7] to prove that E_0 is globally attractive for $R_0 < 1$. To achieve this, we first define, for a continuous and bounded function $g : [0, \infty] \to \mathcal{R}$,

$$g_\infty = \lim_{t\to\infty}\inf g(t) \quad \text{and} \quad g^\infty = \lim_{t\to\infty}\sup g(t).$$

Then, by the fluctuation lemma, there exists a sequence t_n with $t_n \to \infty$ as $n \to \infty$ such that

$$\lim_{n\to\infty} x_1(t_n) = x_1^\infty, \quad \lim_{n\to\infty}\frac{dx_1}{dt}(t_n) = 0,$$
$$\lim_{n\to\infty} x_2(t_n) = x_2^\infty, \quad \lim_{n\to\infty}\frac{dx_2}{dt}(t_n) = 0.$$

Hence, the first two equations in (1.2) indicate that

$$\frac{dx_1}{dt}(t_n) + d_1x_1(t_n) + (1-\epsilon)k_1v(t_n)x_1(t_n) = \lambda_1$$

and

$$\frac{dx_2}{dt}(t_n) + d_2x_2(t_n) + (1-f\epsilon)k_2v(t_n)x_2(t_n) = \lambda_2,$$

which result in, as $n \to \infty$,

$$d_1x_1^\infty \leqslant [d_1 + (1-\epsilon)k_1v_\infty]x_1^\infty \leqslant \lambda_1, \quad \text{implying that} \quad x_1^\infty \leqslant \frac{\lambda_1}{d_1}, \tag{2.8}$$

and

$$d_2x_2^\infty \leqslant [d_2 + (1-f\epsilon)k_2v_\infty]x_2^\infty \leqslant \lambda_2, \quad \text{implying that} \quad x_2^\infty \leqslant \frac{\lambda_2}{d_2}. \tag{2.9}$$

Applying a similar procedure to the remaining equations in (1.2), we have

$$\begin{aligned}
&\delta y_1^\infty \leqslant (1-\alpha)(1-\epsilon)k_1v^\infty x_1^\infty,\\
&\delta y_2^\infty \leqslant (1-\alpha)(1-f\epsilon)k_2v^\infty x_2^\infty,\\
&\mu z_1^\infty \leqslant \alpha(1-\epsilon)k_1v^\infty x_1^\infty,\\
&\mu z_2^\infty \leqslant \alpha(1-f\epsilon)k_2v^\infty x_2^\infty,\\
&cv^\infty \leqslant N_T\delta(y_1^\infty + y_2^\infty) + N_m\mu(z_1^\infty + z_2^\infty).
\end{aligned} \tag{2.10}$$

Combining (2.8), (2.9) and (2.10) yields

$$cv^\infty \leqslant cR_0v^\infty \quad \text{i.e.} \quad c(1-R_0)v^\infty \leqslant 0,$$

which implies that $v^\infty = 0$ due to $R_0 < 1$ and the positivity of v. This, together with (2.10), results in $y_i^\infty = 0$ and $z_i^\infty = 0$ $(i = 1, 2)$. Thus, as $t \to \infty$,

$$y_i(t) \to 0, \quad z_i(t) \to 0 \quad \text{and} \quad v(t) \to 0 \quad (i = 1, 2).$$

Then, with $\lim_{t\to\infty} v(t) \to 0$, we obtain the asymptotic differential equations from the first two equations of model (1.2) as

$$\frac{dx_1}{dt} = \lambda_1 - d_1x_1 \quad \text{and} \quad \frac{dx_2}{dt} = \lambda_2 - d_2x_2.$$

By the theory for asymptotically autonomous systems [3], we obtain

$$\lim_{t\to\infty} x_1(t) = \frac{\lambda_1}{d_1} \quad \text{and} \quad \lim_{t\to\infty} x_2(t) = \frac{\lambda_2}{d_2}.$$

Finally, combining the local stability and global attractiveness of E_0, we conclude that E_0 is globally asymptotically stable.

The proof of Theorem 2.2 is finished. □

2.3. Stability of the infection equilibrium E_1

In this subsection, we assume $R_0 > 1$ and study the stability of the infection equilibrium E_1.

Theorem 2.3. *The infection equilibrium E_1 is globally asymptotically stable for $R_0 > 1$.*

Proof. Consider the Lyapunov function,

$$V = [N_T(1-\alpha) + N_m\alpha]\sum_{i=1}^{2}\left(x_i - \hat{x}_i - \hat{x}_i\ln\frac{x_i}{\hat{x}_i}\right) + N_T\sum_{i=1}^{2}\left(y_i - \hat{y}_i - \hat{y}_i\ln\frac{y_i}{\hat{y}_i}\right) + N_m\sum_{i=1}^{2}\left(z_i - \hat{z}_i - \hat{z}_i\ln\frac{z_i}{\hat{z}_i}\right) + \left(v - \hat{v} - \hat{v}\ln\frac{v}{\hat{v}}\right).$$

Differentiating V with respect to time t and evaluating it along the trajectory of system (1.2) gives

$$\begin{aligned}\frac{dV}{dt}\bigg|_{(1.2)} = {} & [N_T(1-\alpha)+N_m\alpha]\sum_{i=1}^{2}\left[\lambda_i - d_ix_i - (1-f_i\epsilon)k_i v x_i - \frac{\lambda_i\hat{x}_i}{x_i} + d_i\hat{x}_i + (1-f_i\epsilon)k_i v\hat{x}_i\right]\\ & + N_T\sum_{i=1}^{2}\left[(1-\alpha)(1-f_i\epsilon)k_i v x_i - \delta y_i - (1-\alpha)(1-f_i\epsilon)k_i v x_i\frac{\hat{y}_i}{y_i} + \delta\hat{y}_i\right]\\ & + N_m\sum_{i=1}^{2}\left[\alpha(1-f_i\epsilon)k_i v x_i - \mu z_i - \alpha(1-f_i\epsilon)k_i v x_i\frac{\hat{z}_i}{z_i} + \mu\hat{z}_i\right] + N_T\delta(y_1+y_2) + N_m\mu(z_1+z_2) - cv\\ & - \frac{N_T\delta(y_1+y_2)+N_m\mu(z_1+z_2)}{v}\,\hat{v} + c\hat{v},\end{aligned}$$

where $f_1 = 1$ and $f_2 = f$. Using the solution of E_1, we obtain the following equations:

$$\begin{aligned}& [N_T(1-\alpha)+N_m\alpha]\sum_{i=1}^{2}(1-f_i\epsilon)k_i v\hat{x}_i - cv = 0,\\ & \sum_{i=1}^{2}[N_T\delta\hat{y}_i + N_m\mu\hat{z}_i] = [N_T(1-\alpha)+N_m\alpha]\sum_{i=1}^{2}(1-f_i\epsilon)k_i\hat{v}\hat{x}_i,\\ & c\hat{v} = [N_T(1-\alpha)+N_m\alpha]\sum_{i=1}^{2}(1-f_i\epsilon)k_i\hat{v}\hat{x}_i,\end{aligned}$$

which are used to simplify $\frac{dV}{dt}|_{(1.2)}$, yielding

$$\begin{aligned}\frac{dV}{dt}\bigg|_{(1.2)} = {} & [N_T(1-\alpha)+N_m\alpha]\sum_{i=1}^{2}\left[\lambda_i - d_ix_i - \frac{\lambda_i\hat{x}_i}{x_i} + d_i\hat{x}_i + 2(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\right]\\ & - \sum_{i=1}^{2}\left[N_T(1-\alpha)(1-f_i\epsilon)k_i v x_i\frac{\hat{y}_i}{y_i} + N_m\alpha(1-f_i\epsilon)k_i v x_i\frac{\hat{z}_i}{z_i} + \frac{N_T\delta y_i\hat{v}}{v} + \frac{N_m\mu z_i\hat{v}}{v}\right].\end{aligned} \tag{2.11}$$

Noticing that

$$\begin{aligned}\lambda_i - d_ix_i - \frac{\lambda_i\hat{x}_i}{x_i} + d_i\hat{x}_i + 2(1-f_i\epsilon)k_i\hat{v}\hat{x}_i = {} & \lambda_i - d_ix_i - \frac{\lambda_i\hat{x}_i}{x_i} + d_i\hat{x}_i - (1-f_i\epsilon)k_i\hat{v}\hat{x}_i + (1-f_i\epsilon)k_i\hat{v}\hat{x}_i\frac{\hat{x}_i}{x_i} + 3(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\\ & - (1-f_i\epsilon)k_i\hat{v}\hat{x}_i\frac{\hat{x}_i}{x_i} = \left(1-\frac{\hat{x}_i}{x_i}\right)[\lambda_i - (1-f_i\epsilon)k_i\hat{v}\hat{x}_i - d_ix_i] + 3(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\\ & - (1-f_i\epsilon)k_i\hat{v}\hat{x}_i\frac{\hat{x}_i}{x_i} = -\frac{d_i}{x_i}(x_i-\hat{x}_i)^2 + 3(1-f_i\epsilon)k_i\hat{v}\hat{x}_i - (1-f_i\epsilon)k_i\hat{v}\hat{x}_i\frac{\hat{x}_i}{x_i},\end{aligned} \tag{2.12}$$

we then obtain

$$\begin{aligned}& [N_T(1-\alpha)+N_m\alpha]\left[3(1-f_i\epsilon)k_i\hat{v}\hat{x}_i - (1-f_i\epsilon)k_i\hat{v}\hat{x}_i\frac{\hat{x}_i}{x_i}\right] - N_T(1-\alpha)(1-f_i\epsilon)k_i v x_i\frac{\hat{y}_i}{y_i}\\ & \quad - N_m\alpha(1-f_i\epsilon)k_i v x_i\frac{\hat{z}_i}{z_i} - \frac{N_T\delta y_i\hat{v}}{v} - \frac{N_m\mu z_i\hat{v}}{v} = 3N_T(1-\alpha)(1-f_i\epsilon)k_i\hat{v}\hat{x}_i - N_T(1-\alpha)(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\frac{\hat{x}_i}{x_i}\\ & \quad - N_T(1-\alpha)(1-f_i\epsilon)k_i v x_i\frac{\hat{y}_i}{y_i} - \frac{N_T\delta y_i\hat{v}}{v} + 3N_m\alpha(1-f_i\epsilon)k_i\hat{v}\hat{x}_i - N_m\alpha(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\frac{\hat{x}_i}{x_i}\\ & \quad - N_m\alpha(1-f_i\epsilon)k_i v x_i\frac{\hat{y}_i}{y_i} - \frac{N_m\mu z_i\hat{v}}{v} = -N_T(1-\alpha)(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\left[-3 + \frac{\hat{x}_i}{x_i} + \frac{vx_i\hat{y}_i}{\hat{v}\hat{x}_iy_i} + \frac{\delta y_i}{(1-\alpha)(1-f_i\epsilon)k_i\hat{x}_iv}\right]\\ & \quad - N_m\alpha(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\left[-3 + \frac{\hat{x}_i}{x_i} + \frac{vx_i\hat{z}_i}{\hat{v}\hat{x}_iz_i} + \frac{\mu z_i}{\alpha(1-f_i\epsilon)k_i\hat{x}_iv}\right]\\ & \leqslant -3N_T(1-\alpha)(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\left\{\left[\frac{\delta\hat{y}_i}{(1-\alpha)(1-f_i\epsilon)k_i\hat{x}_i\hat{v}}\right]^{\frac{1}{3}} - 1\right\} - 3N_m\alpha(1-f_i\epsilon)k_i\hat{v}\hat{x}_i\left\{\left[\frac{\mu\hat{z}_i}{\alpha(1-f_i\epsilon)k_i\hat{x}_i\hat{v}}\right]^{\frac{1}{3}} - 1\right\} = 0.\end{aligned} \tag{2.13}$$

Hence, $\frac{dV}{dt}|_{(1.2)} \leqslant 0$. Let

$$S_0 = \left\{(x_1,x_2,y_1,y_2,z_1,z_2,v) \in (\mathbb{R}^+)^7 \,\middle|\, \frac{dV}{dt}\bigg|_{(1.2)} = 0\right\}.$$

Note in (2.13) that the equality holds if and only if

$$\frac{\hat{x}_i}{x_i} = \frac{v x_i \hat{y}_i}{\hat{v}\hat{x}_i y_i} = \frac{\delta y_i}{(1-\alpha)(1-f_i\epsilon)k_i\hat{x}_i v}, \quad \frac{\hat{x}_i}{x_i} = \frac{v x_i \hat{z}_i}{\hat{v}\hat{x}_i z_i} = \frac{\mu z_i}{\alpha(1-f_i\epsilon)k_i\hat{x}_i v}, \quad i = 1,2, \tag{2.14}$$

which, combined with (2.12), yields

$$S_0 = \left\{(x_1,x_2,y_1,y_2,z_1,z_2,v) \in (\mathbb{R}^+)^7 \,|\, x_i = \hat{x}_i, \frac{v}{z_i} = \frac{\hat{v}}{\hat{z}_i}, \frac{v}{y_i} = \frac{\hat{v}}{\hat{y}_i}, i = 1,2\right\}.$$

Next, we want to find the invariant set of S_0. Let $X(t) = (x_1(t), x_2(t), y_1(t), y_2(t), z_1(t), z_2(t), v(t))$ be an arbitrary solution of model (1.2) with its initial condition belonging to S_0. Then, $X(t) \in S_0$ for all $t \geqslant 0$ if and only if

$$x_i(t) \equiv \hat{x}_i, \quad t \geqslant 0, \quad i = 1,2,$$

which indicates that $v(t) \equiv \hat{v}$ for all $t \geqslant 0$. Correspondingly, $y_i(t) \equiv \hat{y}_i$ and $z_i(t) \equiv \hat{z}_i$ for all $t \geqslant 0$ $(i = 1,2)$. Thus, $X(t) = E_1$, i.e., $\{E_1\}$ is the maximal invariant set of S_0. Therefore, E_1 is globally asymptotically stable by the LaSalle's invariance principle [11].

The proof is complete. □

3. Global analysis of model (1.3)

Now we turn to consider model (1.3) and mainly focus on the global stability of equilibrium solutions.

3.1. Well-posedness and equilibria of model (1.3)

For convenience in the following analysis, we first introduce the following rescalings into (1.3):

$$x_i \to \frac{\lambda}{d}x_i, \quad y_i \to \frac{d^2}{N_T\delta}y_i, \quad z_i \to \frac{d^2}{N_m\mu}z_i, \quad v_i \to d v_i, \quad t \to \frac{1}{d}t \quad (i = 1,2).$$

Then, model (1.3) is transformed to

$$\begin{aligned}
\frac{dx_1}{dt} &= 1 - x_1 - k_1 v_1 x_1,\\
\frac{dx_2}{dt} &= 1 - x_2 - k_2 v_2 x_2,\\
\frac{dy_1}{dt} &= M_1 k_1 \delta v_1 x_1 - \delta y_1,\\
\frac{dy_2}{dt} &= M_1 k_2 \delta v_2 x_2 - \delta y_2,\\
\frac{dz_1}{dt} &= M_2 k_1 \mu v_1 x_1 - \mu z_1,\\
\frac{dz_2}{dt} &= M_2 k_2 \mu v_2 x_2 - \mu z_2,\\
\frac{dv_1}{dt} &= y_1 + z_1 - c v_1 + D_1(v_2 - v_1),\\
\frac{dv_2}{dt} &= y_2 + z_2 - c v_2 + D_2(v_1 - v_2),
\end{aligned} \tag{3.1}$$

where

$$k_1 = (1-\epsilon)k, \quad k_2 = (1-f\epsilon)k, \quad M_1 = \frac{N_T(1-\alpha)\lambda}{d^2}, \quad M_2 = \frac{N_m\alpha\lambda}{d^2}$$

and in model (3.1), the new parameters,

$$\frac{\delta}{d}, \quad \frac{\mu}{d}, \quad \frac{c}{d}, \quad \frac{D_1}{d}, \quad \frac{D_2}{d}$$

are re-named as δ, μ, c, D_1, D_2, respectively, for simplicity.

Let

$$R_0^1 = \frac{k_1(M_1+M_2)}{D_1+c} \quad \text{and} \quad R_0^2 = \frac{k_2(M_1+M_2)}{D_2+c}.$$

It is easy to see that R_0^i is the basic reproduction number for each sub-population i $(i = 1,2)$.

The equilibrium solutions of model (3.1) are obtained in the form of

$$x_1(v_1)=\tfrac{1}{1+k_1v_1},\qquad x_2(v_2)=\tfrac{1}{1+k_2v_2},$$
$$y_1(v_1)=M_1k_1x_1v_1,\quad y_2(v_2)=M_1k_2x_2v_2,$$
$$z_1(v_1)=M_2k_1x_1v_1,\quad z_2(v_2)=M_2k_2x_2v_2,$$

where v_1 and v_2 satisfy the following two equations:

$$D_1v_2=(D_1+c)(1-R_0^1x_1)v_1 \quad \text{and} \quad D_2v_1=(D_2+c)(1-R_0^2x_2)v_2, \tag{3.2}$$

which yield solutions: $v_1=v_2=0$ or $v_1\neq 0,\, v_2\neq 0$.

Lemma 3.1. *Any solution of model (3.1), $(x_1(t),x_2(t),y_1(t),y_2(t),z_1(t),z_2(t),\, v_1(t),\, v_2(t))$, is non-negative for all $t>0$ provided that the initial conditions are non-negative, and is bounded.*

The proof of Lemma 3.1 is similar to that for Theorem 2.1, and thus omitted here for brevity.

Let

$$\mathbb{D}_1=\left\{(R_0^1,R_0^2)\in\mathbb{R}^+\times\mathbb{R}^+\,|\,0<R_0^1\leqslant 1-\frac{D_1D_2}{(D_1+c)(D_2+c)},\quad 0<R_0^2\leqslant 1-\frac{D_1D_2}{(D_1+c)(D_2+c)(1-R_0^1)}\right\}$$

and $\mathbb{D}_2=\mathbb{R}^+\times\mathbb{R}^+\setminus\mathbb{D}_1$, where $\mathbb{R}^+$ represents all positive real numbers.

Lemma 3.2. *If $(R_0^1,R_0^2)\in\mathbb{D}_1$, model (3.1) has a unique equilibrium $E_0=(1,1,0,0,0,0,0,0)$. If $(R_1^0,R_2^0)\in\mathbb{D}_2$, model (3.1) has two equilibria E_0 and $E_1=(x_1(v_1),x_2(v_2),y_1(v_1),y_2(v_2),z_1(v_1),z_2(v_2),\,v_1,\,v_2)$ with $v_1>0$ and $v_2>0$.*

Proof. Substituting the expressions of $x_1(v_1)$ and $x_2(v_2)$ into (3.2), we obtain two curves on the v_1-v_2 plane, described by

$$C_1:\quad v_2=\frac{D_1+c}{D_1}\left(1-\frac{R_0^1}{1+k_1v_1}\right)v_1,\quad v_1\geqslant 0 \tag{3.3}$$

and

$$C_2:\quad v_1=\frac{D_2+c}{D_2}\left(1-\frac{R_0^2}{1+k_2v_2}\right)v_2,\quad v_1\geqslant 0. \tag{3.4}$$

It follows from (3.3) that

$$\frac{dv_2}{dv_1}=\frac{D_1+c}{D_1}\left[1-\frac{R_0^1}{(1+k_1v_1)^2}\right] \quad \text{and} \quad \frac{d^2v_2}{dv_1^2}=\frac{D_1+c}{D_1}\frac{2k_1R_0^1}{(1+k_1v_1)^3}. \tag{3.5}$$

Thus,

$$\left.\frac{dv_2}{dv_1}\right|_{v_1=0}=\frac{D_1+c}{D_1}(1-R_0^1).$$

Since (3.4) has the same form as that of (3.3) if v_1 and v_2 are exchanged, we similarly have the following result for C_2,

$$\frac{dv_1}{dv_2}=\frac{D_2+c}{D_2}\left[1-\frac{R_0^2}{(1+k_2v_2)^2}\right] \quad \text{and} \quad \frac{d^2v_1}{dv_2^2}=\frac{D_2+c}{D_2}\frac{2k_2R_0^2}{(1+k_2v_2)^3}, \tag{3.6}$$

and so we obtain

$$\left.\frac{dv_1}{dv_2}\right|_{v_2=0}=\frac{D_2+c}{D_2}(1-R_0^2).$$

The above formulas indicate that, for $R_0^1<1$ ($R_0^2<1$), the function defining the curve C_1 (C_2) is monotonically increasing and the whole curve C_1 (C_2) is above (below) the line $L_1: v_2=l_1v_1,\, v_1\geqslant 0$ ($L_2: v_2=l_2v_1,\ v_1\geqslant 0$), where $l_1=\frac{(D_1+c)(1-R_0^1)}{D_1}$ $\left(l_2=\frac{D_2}{(D_2+c)(1-R_0^2)}\right)$.

For $(R_0^1,R_0^2)\in\mathbb{D}_1, 0<l_2\leqslant l_1$, which implies that the two curves C_1 and C_2 have no interior intersection point. Hence, model (3.1) has a unique equilibrium $E_0=(1,1,0,0,0,0,0,0)$.

Let

$$\begin{aligned}\mathbb{D}_{21} &= \{(R_0^1, R_0^2) \in \mathbb{D}_2 | 0 < R_0^1 < 1, 0 < R_0^2 < 1\},\\ \mathbb{D}_{22} &= \{(R_0^1, R_0^2) \in \mathbb{D}_2 | 0 < R_0^1 \leq 1, R_0^2 \geqslant 1\},\\ \mathbb{D}_{23} &= \{(R_0^1, R_0^2) \in \mathbb{D}_2 | R_0^1 \geqslant 1, 0 < R_0^2 < 1\},\\ \mathbb{D}_{24} &= \{(R_0^1, R_0^2) \in \mathbb{D}_2 | R_0^1 \geqslant 1, R_0^2 \geqslant 1\}.\end{aligned}$$

Further, we will prove that for $(R_0^1, R_0^2) \in \mathbb{D}_{2j}$ $(j = 1, 2, 3, 4)$, the two curves C_1 and C_2 have a unique interior intersection point in the first quadrant of the v_1–v_2 plane. To achieve this, we first show that there exists a line $L_3 : v_2 = kv_1, v_1 \geqslant 0$, such that the line L_3 and the curve C_i $(i = 1, 2)$ have a unique interior intersection point, where

(1) $k \in \left(l_1, \frac{D_1+c}{D_1}\right) \bigcap \left(\frac{D_2}{D_2+c}, l_2\right)$ for $(R_0^1, R_0^2) \in \mathbb{D}_{21}$;
(2) $k \in \left(l_1, \frac{D_1+c}{D_1}\right) \bigcap \left(\frac{D_2}{D_2+c}, +\infty\right)$ for $(R_0^1, R_0^2) \in \mathbb{D}_{22}$;
(3) $k \in \left(0, \frac{D_1+c}{D_1}\right) \bigcap \left(\frac{D_2}{D_2+c}, l_2\right)$ for $(R_0^1, R_0^2) \in \mathbb{D}_{23}$;
(4) $k \in \left(\frac{D_2}{D_2+c}, \frac{D_1+c}{D_1}\right)$ for $(R_0^1, R_0^2) \in \mathbb{D}_{24}$.

That is to say, there exist $v_{ij} > 0$ $(i,j = 1, 2)$ such that

$$L_3 \bigcap C_i = \{(0, 0), (v_{1i}, v_{2i})\}, \quad i = 1, 2,$$

i.e.,

$$1 + k_1 v_{11} = \frac{R_0^1}{1 - \frac{D_1 k}{D_1 + c}} \quad \text{and} \quad 1 + k_2 v_{22} = \frac{R_0^2}{1 - \frac{D_2}{k(D_2 + c)}}.$$

Obviously, v_{11} and v_{22} are well-defined if and only if

$$\frac{R_0^1}{1 - \frac{D_1 k}{D_1 + c}} > 1 \quad \text{and} \quad \frac{R_0^2}{1 - \frac{D_2}{k(D_2 + c)}} > 1. \tag{3.7}$$

A simple calculation shows that (3.7) holds for $(R_0^1, R_0^2) \in \mathbb{D}_{21}$ if and only if

$$k \in \left(l_1, \frac{D_1 + c}{D_1}\right) \bigcap \left(\frac{D_2}{D_2 + c}, l_2\right).$$

By noticing that $0 < l_1 < l_2$ for $(R_0^1, R_0^2) \in \mathbb{D}_{21}$, we have

$$\left(l_1, \frac{D_1 + c}{D_1}\right) \bigcap \left(\frac{D_2}{D_2 + c}, l_2\right) \neq \emptyset.$$

Similarly, for $(R_0^1, R_0^2) \in \mathbb{D}_{2i}$ $(i = 2, 3, 4)$, we can show that (by a similar argument as that used for $\mathbb{D}_{21}$)

$$\begin{aligned} k &\in \left(l_1, \tfrac{D_1+c}{D_1}\right) \bigcap \left(\tfrac{D_2}{D_2+c}, +\infty\right) \quad \text{for} \quad (R_0^1, R_0^2) \in \mathbb{D}_{22},\\ k &\in \left(0, \tfrac{D_1+c}{D_1}\right) \bigcap \left(\tfrac{D_2}{D_2+c}, l_2\right) \quad \text{for} \quad (R_0^1, R_0^2) \in \mathbb{D}_{23},\\ k &\in \left(\tfrac{D_2}{D_2+c}, \tfrac{D_1+c}{D_1}\right) \quad \text{for} \quad (R_0^1, R_0^2) \in \mathbb{D}_{24}.\end{aligned}$$

The uniqueness of interior intersection points between the line L_3 and the curve C_i $(i = 1, 2)$ is obvious. The above results, together with (3.5) and (3.6), imply that the curve C_1 (C_2) is below (above) the line L_3 for $0 < v_1 < v_{11}$ $(0 < v_1 < v_{12})$ and the curve C_1 (C_2) is above (below) the line L_3 for $v_1 > v_{11}$ $(v_1 > v_{12})$. Moreover, on the curve C_i, $v_j \to +\infty$ as $v_i \to +\infty, i,j = 1, 2,\ i \neq j$. Hence, we conclude that the two curves C_1 and C_2 have a unique interior intersection point with the first component $v_1 \in [\min\{v_{11}, v_{12}\}, \max\{v_{11}, v_{12}\}]$.

Summarizing the above results gives that for $(R_0^1, R_0^2) \in \mathbb{D}_2$, model (3.1) has two equilibria E_0 and $E_1 = (x_1(v_1), x_2(v_2), y_1(v_1), y_2(v_2), z_1(v_1), z_2(v_2), v_1, v_2)$ with $v_1 > 0$ and $v_2 > 0$.

The proof of Lemma 3.2 is complete. □

3.2. Global stability of equilibria E_0 and E_1

In this subsection, we will study the global stability of the equilibrium solutions E_0 and E_1. First, we consider E_0 and have the following result.

Theorem 3.1. *The infection-free equilibrium E_0 is globally asymptotically stable for $(R_0^1, R_0^2) \in \mathbb{D}_1$.*

Proof. For $(R_0^1, R_0^2) \in \mathbb{D}_1$, we have $R_0^1 < 1$ and $R_0^2 \leqslant 1 - \frac{D_1 D_2}{(D_1+c)(D_2+c)(1-R_0^1)} < 1$, which implies that

$$D_1 > k_1(M_1 + M_2) - c, \quad D_2 > k_2(M_1 + M_2) - c \tag{3.8}$$

and

$$D_1[c - k_2(M_1 + M_2)] + D_2[c - k_1(M_1 + M_2)] + [c - k_1(M_1 + M_2)][c - k_2(M_1 + M_2)] \geqslant 0. \tag{3.9}$$

Recall that $k_2 > k_1$. Then by a simple calculation, we can show that the valid region of (D_1, D_2) is nonempty and lies in the first quadrant if and only if one of the following conditions holds:

(i) $k_1(M_1 + M_2) - c \leqslant 0, k_2(M_1 + M_2) - c \leqslant 0$;
(ii) $k_1(M_1 + M_2) - c \le 0, k_2(M_1 + M_2) - c \geqslant 0$.

Now we study the stability of E_0 for the two cases (i) and (ii). Consider the Lyapunov function

$$V_1 = \sum_{i=1}^{2} m_i \left[(M_1 + M_2)(x_i - 1 - \ln x_i) + \frac{y_i}{\delta} + \frac{z_i}{\mu} + v_i\right],$$

where $m_i, i = 1, 2$ are positive constants to be determined. Differentiating V_1 with respect to time along the trajectory of model (3.1) gives

$$\begin{aligned}\left.\frac{dV_1}{dt}\right|_{(3.1)} &= \sum_{i,j=1, i\neq j}^{2} m_i \left\{(M_1+M_2)(1 - x_i - k_i v_i x_i - \frac{1}{x_i} + 1 + k_i v_i) + [(M_1+M_2)k_i v_i x_i - y_i - z_i] + [y_i + z_i - (c+D_i)v_i + D_i v_j]\right\} \\ &= -\sum_{i=1}^{2}(M_1+M_2)m_i\frac{(1-x_i)^2}{x_i} + \sum_{i,j=1, i\neq j}^{2}\{[k_i(M_1+M_2) - (c+D_i)]m_i + m_j D_j\} v_i.\end{aligned}$$

For Case (i), taking $m_1 = D_2$ and $m_2 = D_1$, we have

$$\left.\frac{dV_1}{dt}\right|_{(3.1)} = -(M_1+M_2)\left[\frac{D_2(1-x_1)^2}{x_1} + \frac{D_1(1-x_2)^2}{x_2}\right] - D_2[c - k_1(M_1+M_2)]v_1 - D_1[c - k_2(M_1+M_2)]v_2 \leqslant 0. \tag{3.10}$$

For Case (ii), we choose m_1 and m_2 as the roots of the following equations:

$$\begin{cases} m_1[k_1(M_1+M_2) - (c+D_1)] + D_2 m_2 = [k_1(M_1+M_2) - c][k_2(M_1+M_2) - c], \\ m_1 D_1 + [k_2(M_1+M_2) - (c+D_2)]m_2 = [k_1(M_1+M_2) - c][k_2(M_1+M_2) - c], \end{cases}$$

i.e.,

$$m_i = \frac{[k_1(M_1+M_2) - c][k_2(M_1+M_2) - c][k_j(M_1+M_2) - c - 2D_j]}{[k_1(M_1+M_2) - c - D_1][k_2(M_1+M_2) - c - D_2] - D_1 D_2} > 0, \quad i,j = 1,2, \quad i \neq j,$$

which implies

$$\left.\frac{dV_1}{dt}\right|_{(3.1)} = -\sum_{i=1}^{2}(M_1+M_2)m_i\frac{(1-x_i)^2}{x_i} - [c - k_1(M_1+M_2)][k_2(M_1+M_2) - c](v_1 + v_2) \leqslant 0. \tag{3.11}$$

Set

$$S_1 = \left\{(x_1, x_2, y_1, y_2, z_1, z_2, v_1, v_2) \in (\mathbb{R}^+)^8 \middle| \left.\frac{dV_1}{dt}\right|_{(3.1)} = 0\right\}.$$

According to (3.10), we have for Case (i),

$$S_1 = \left\{(x_1, x_2, y_1, y_2, z_1, z_2, v_1, v_2) \in (\mathbb{R}^+)^8 | x_1 = x_2 = 1, \quad D_2[c - k_1(M_1+M_2)]v_1 + D_1[c - k_2(M_1+M_2)]v_2 = 0\right\}.$$

We now want to verify that the invariant set of S_1 is $\{E_0\}$. Let $X(t) = (x_1(t), x_2(t), y_1(t), y_2(t), z_1(t), z_2(t), v_1(t), v_2(t))$ be an arbitrary solution of model (3.1) initiating from S_1. Then, we have $X(t) \in S_1$ for all $t \geqslant 0$ if and only if

$$x_i(t) \equiv 1, \quad i = 1, 2,$$

which indicates that $v_i(t) \equiv 0$ for all $t \geqslant 0$ $(i = 1, 2)$. According to (3.1), we have $y_i(t) = z_i(t) \equiv 0$ for all $t \geqslant 0$ $(i = 1, 2)$. Thus, the maximal invariant set of S_1 is $\{E_0\}$ for Case (i). Similarly, we can show that the maximal invariant set of S_1 is $\{E_0\}$ for Case (ii). Hence, the global asymptotic stability of E_0 follows from the LaSalle's invariance principle [11].

The proof is complete. □

Theorem 3.2. *If the infection equilibrium E_1 of model (3.1) exists, then it is globally asymptotically stable.*

Proof. Consider the Lyapunov function,

$$V_2 = \sum_{i=1}^{2} m_i \left[(M_1 + M_2)\left(x_i - \hat{x}_i - \hat{x}_i \ln \frac{x_i}{\hat{x}_i} \right) + \frac{1}{\delta}\left(y_i - \hat{y}_i - \hat{y}_i \ln \frac{y_i}{\hat{y}_i} \right) + \frac{1}{\mu}\left(z_i - \hat{z}_i - \hat{z}_i \ln \frac{z_i}{\hat{z}_i} \right) + \left(v_i - \hat{v}_i - \hat{v}_i \ln \frac{v_i}{\hat{v}_i} \right) \right],$$

where $m_1 = D_2 \hat{v}_1$ and $m_2 = D_1 \hat{v}_2$. Then, the time derivative of V_2 along the trajectory of model (3.1) is given by

$$\left.\frac{dV_2}{dt}\right|_{(3.1)} = \sum_{i,j=1,i\neq j}^{2} m_i \left[(M_1 + M_2)\left(1 - x_i - \frac{\hat{x}_i}{x_i} + \hat{x}_i + k_i v_i \hat{x}_i \right) - \frac{M_1 k_i v_i x_i \hat{y}_i}{y_i} + \hat{y}_i - \frac{M_2 k_i v_i x_i \hat{z}_i}{z_i} + \hat{z}_i - (c + D_i) v_i + D_i v_j - \frac{\hat{v}_i (y_i + z_i)}{v_i} + (c + D_i)\hat{v}_i - \frac{D_i v_j \hat{v}_i}{v_i} \right].$$

Recall that

$$\sum_{i=1}^{2} (\hat{y}_i + \hat{z}_i) = (M_1 + M_2)(k_1 \hat{v}_1 \hat{x}_1 + k_2 \hat{v}_2 \hat{x}_2),$$
$$(M_1 + M_2) k_i v_i \hat{x}_i - (c + D_i) v_i = -\tfrac{D_i v_i \hat{v}_j}{\hat{v}_i}, \quad i,j = 1,2, \quad i \neq j,$$
$$(c + D_i)\hat{v}_i = (M_1 + M_2) k_i \hat{v}_i \hat{x}_i + D_i \hat{v}_j, \quad i,j = 1,2, \quad i \neq j.$$

Hence,

$$\left.\frac{dV_2}{dt}\right|_{(3.1)} = \sum_{i=1}^{2} m_i \left[(M_1 + M_2)(1 - x_i - \frac{\hat{x}_i}{x_i} + \hat{x}_i + 2k_i \hat{v}_i \hat{x}_i) - \frac{M_1 k_i v_i x_i \hat{y}_i}{y_i} - \frac{M_2 k_i v_i x_i \hat{z}_i}{z_i} - \frac{\hat{v}_i (y_i + z_i)}{v_i} \right] + g(v_1, v_2),$$

where

$$g(v_1, v_2) = \sum_{i,j=1,i\neq j}^{2} m_i D_i \left(v_j + \hat{v}_j - \frac{\hat{v}_i}{v_i} v_j - \frac{v_i}{\hat{v}_i}\hat{v}_j \right) = D_1 D_2 \hat{v}_1 \hat{v}_2 \left[2 - \frac{\hat{v}_1 v_2}{v_1 \hat{v}_2} - \frac{\hat{v}_2 v_1}{v_2 \hat{v}_1} \right].$$

Then, by a similar procedure used in proving Theorem 3.1, we obtain

$$\begin{aligned} \left.\frac{dV_2}{dt}\right|_{(3.1)} &= -(M_1 + M_2)\sum_{i=1}^{2} \frac{m_i (x_i - \hat{x}_i)^2}{x_i} - \sum_{i=1}^{2} M_1 m_i k_i \hat{v}_i \hat{x}_i \left(-3 + \frac{\hat{x}_i}{x_i} + \frac{v_i x_i \hat{y}_i}{y_i \hat{v}_i \hat{x}_i} + \frac{y_i}{M_1 k_i \hat{x}_i v_i} \right) \\ &\quad - \sum_{i=1}^{2} M_2 m_i k_i \hat{v}_i \hat{x}_i \left(-3 + \frac{\hat{x}_i}{x_i} + \frac{v_i x_i \hat{z}_i}{z_i \hat{v}_i \hat{x}_i} + \frac{z_i}{M_2 k_i \hat{x}_i v_i} \right) + g(v_1, v_2) \leqslant -(M_1 + M_2)\sum_{i=1}^{2} \frac{m_i (x_i - \hat{x}_i)^2}{x_i} \\ &\quad - \sum_{i=1}^{2} M_1 m_i k_i \hat{v}_i \hat{x}_i \left(-3 + \frac{3\hat{y}_i}{M_1 k_i \hat{v}_i \hat{x}_i} \right) - \sum_{i=1}^{2} M_2 m_i k_i \hat{v}_i \hat{x}_i \left(-3 + \frac{3\hat{z}_i}{M_2 k_i \hat{v}_i \hat{x}_i} \right) + g(v_1, v_2). \end{aligned} \tag{3.12}$$

Obviously, $g(v_1, v_2) \leqslant 0$. Thus, we conclude that

$$\left.\frac{dV_2}{dt}\right|_{(3.1)} \leqslant -(M_1 + M_2)\sum_{i=1}^{2} \frac{m_i (x_i - \hat{x}_i)^2}{x_i} \leq 0.$$

Further, set

$$S_2 = \left\{ (x_1, x_2, y_1, y_2, z_1, z_2, v_1, v_2) \in (\mathbb{R}^+)^8 \,\middle|\, \frac{dV_2}{dt}|_{(3.1)} = 0 \right\}.$$

According to (3.12), $\frac{dV_2}{dt}|_{(3.1)} = 0$ if and only if

$$x_i = \hat{x}_i, \quad \frac{\hat{x}_i}{x_i} = \frac{v_i x_i \hat{y}_i}{y_i \hat{v}_i \hat{x}_i} = \frac{y_i}{M_1 k_i \hat{x}_i v_i}, \quad \frac{\hat{x}_i}{x_i} = \frac{v_i x_i \hat{z}_i}{z_i \hat{v}_i \hat{x}_i} = \frac{z_i}{M_2 k_i \hat{x}_i v_i}, \quad i = 1,2,$$

and $\frac{\hat{v}_1 v_2}{v_1 \hat{v}_2} = \frac{\hat{v}_2 v_1}{v_2 \hat{v}_1}$. This implies that the maximal invariant set of S_2 is $\{E_1\}$. Therefore, E_1 is globally asymptotically stable by the LaSalle's invariance principle [11].

The proof is finished. □

4. Numerical simulations

To illustrate the theoretical results obtained in Sections 2 and 3, we present simulations with the parameter values used in [2]. More precisely, for model (1.2), $\lambda_1 = 10^4$ cells/ml/day, $\lambda_2 = 31.98$ cells/ml/day, $d_1 = d_2 = 0.01$/day, $k_1 = 8 \times 10^{-7}$ ml/copy, $k_2 = 10^{-4}$ ml/copy, $\delta = 0.7$/day, $\mu = 0.07$/day, $N_T = 100, N_m = 4.11, \alpha = 0.195, c = 13$/day; and for model (1.3),

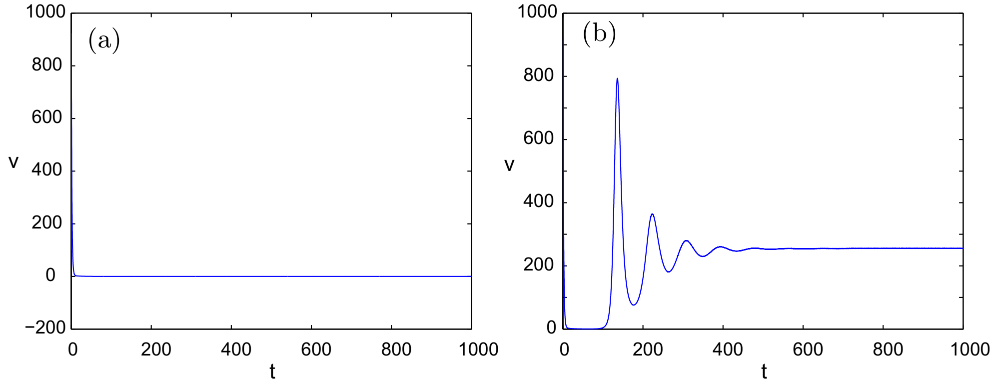

Fig. 1. Simulated trajectories of v for model (1.2): (a) $\epsilon = 0.9$ and $f = 0.85$; and (b) $\epsilon = 0.9$ and $f = 0.34$.

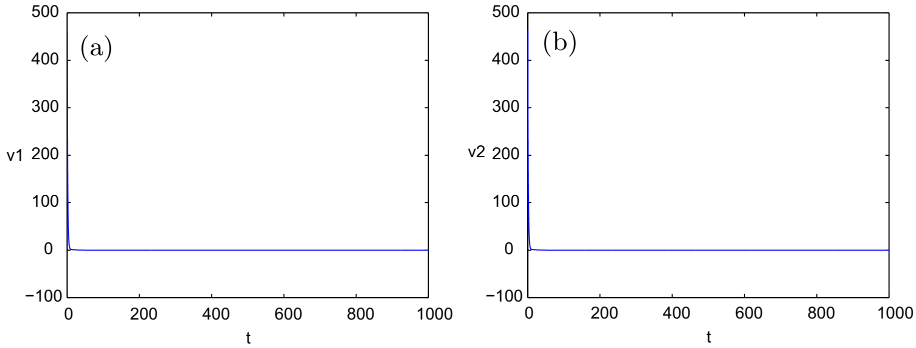

Fig. 2. Simulated trajectories of virus for model (1.3) with $\epsilon = 0.9$ and $f = 0.85$: (a) the virus v_1; and (b) the virus v_2.

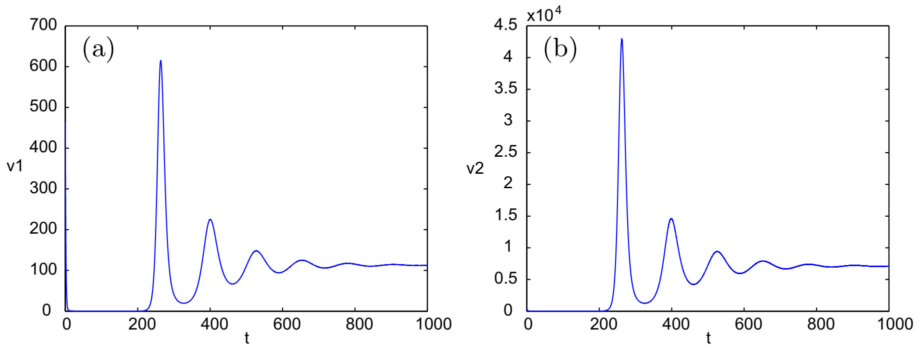

Fig. 3. Simulated trajectories of virus for model (1.3) with $\epsilon = 0.9$ and $f = 0.34$: (a) the virus v_1; and (b) the virus v_2.

$\lambda = 10^4$ cells/ml/day, $d = 0.01$/day, $k = 8 \times 10^{-7}$ ml/copy, $\delta = 0.7$/day, $\mu = 0.07$/day, $N_T = 100$, $N_m = 4.11$, $\alpha = 0.195$, $c = 13$/day, $D_1 = 0.1048$/day, $D_2 = 19.66$/day. We use these parameter values to perform simulations with f and ϵ chosen as perturbation parameters.

For model (1.2), taking $\epsilon = 0.9$ and $f = 0.85$ gives $R_0 = 0.97 < 1$. Hence, the infection-free equilibrium is globally asymptotically stable by Theorem 2.2, as shown in Fig. 1(a). Fig. 1(b) shows that the virus persists for $\epsilon = 0.9$ and $f = 0.34$ (for which $R_0 = 1.888$), which agrees with the theoretical result given in Theorem 2.3 that the infection equilibrium is globally asymptotically stable for $R_0 > 1$.

For model (3.1), choosing $\epsilon = 0.9$ and $f = 0.85$ yields $R_0^1 = 0.496$ and $R_0^2 = 0.468$. Thus, $(R_0^1, R_0^2) \in \mathbb{D}_1$ which implies that the infection-free equilibrium is globally asymptotically stable by Theorem 3.1, see Fig. 2(a) and (b). If we choose $\epsilon = 0.9$ and $f = 0.34$, then $R_0^1 = 0.496$ and $R_0^2 = 1.382 > 1$ and so $(R_0^1, R_0^2) \in \mathbb{D}_2$, which means that the infection equilibrium is globally asymptotically stable by Theorem 3.2, as depicted in Fig. 3(a) and (b). Fig. 3 indicates that the concentration of virus in the main compartment is lower than that in the drug sanctuary due to the less efficacy in the latter. This may explain why there is less effect of treatment on some physiological sites such as the brain [6,12].

5. Conclusion

In this paper, we have reinvestigated two HIV compartmental models that make use of heterogeneities in drug efficacy [2]. In particular, we have studied the qualitative behavior of the two models to show that any solution of these models is non-negative for non-negative initial conditions, and bounded. Moreover, it has been shown that the dynamics of these models are simple, i.e., the infection-free equilibrium is globally asymptotically stable when the basic reproduction number $R_0 \leqslant 1$; and the infection equilibrium exists and is globally asymptotically stable when $R_0 > 1$. It has indicated that it is necessary to measure the drugs and virus levels in multiple compartments and to identify subcompartments where drugs are ineffective. Future study is therefore needed to develop multiple compartments HIV models and investigate dynamical behaviors which maybe more complex.

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