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Modeling cell-to-cell spread of HIV-1 with logistic target cell growth ☆

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ABSTRACT

In this paper, we consider a model containing two modes for HIV-1 infection and spread, one is the diffusion-limited cell-free virus transmission and the other is the direct cell-to-cell transfer of viral particles. We show that the basic reproduction number is underestimated in the existing models that consider only the cell-free virus transmission, or the cell-to-cell infection, ignoring the other. Assuming logistic growth for target cells, we find that if the basic reproduction number is greater than one, the infection can persist and the Hopf bifurcation can occur from the positive equilibrium within certain parameter ranges.

1. Introduction

HIV-1 has two predominant infection modes, the classical cell-free infection and direct cell-to-cell transfer. In the classical mode, viral particles released from infected cells travel some distance to find a new target cell to infect. Recently, it was revealed that HIV-1 can be transferred from infected cells to uninfected cells through direct contact via some structures, for example membrane nanotubes or macromolecular adhesive contacts termed virological synapses [6–8]. During this cell-to-cell transfer, many viral particles can be simultaneously transferred from infected CD4$^+$ T cells to uninfected ones.

In the preceding paper [4], we incorporated the two modes of transmission into a classic model leading to the following model system

$$\frac{dT(t)}{dt} = H - d_T T(t) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t),$$
$$\frac{dT^*(t)}{dt} = \int_0^\infty \left[\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)\right] e^{-ms} f(s)ds - d_{T^*}T^*(t),$$

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$$\frac{dV(t)}{dt} = \gamma T^*(t) - d_V V(t). \tag{1.1}$$

Here $T(t)$, $T^*(t)$ and $V(t)$ represent the concentrations of susceptible CD4$^+$ T cells (target cells), productively infected T cells and free virus particles at time t respectively. A time delay, s, from the time of initial infection until the production of new virions, is considered, and s is assumed to be distributed according to a probability distribution $f(s)$. Target cells are infected by free viral particles and infectious cells (productively infected cells) at rates $\beta_1 T(t)V(t)$ and $\beta_2 T(t)T^*(t)$ respectively. e^{-ms} represents the survival rate of infected cells during the time delay s, from the time of the infection to the time when release of viral particles starts. Target cells are recruited at a constant rate H. Free viral particles are released by infected cells at a rate $\gamma T^*(t)$. The losing rate of target cells, productively infected cells and free viruses is $d_T T(t)$, $d_{T^*} T^*(t)$ and $d_V V(t)$ respectively. We found that the basic reproduction number was underestimated by some models where only one mode of virus spread was considered. In model (1.1), we assumed that target T cells have a constant source term and an exponential death rate. This is mainly for the purpose of reducing the difficulty level in analyzing the model, since introduction of delay into the model has already made the model an infinite dimensional system.

It is more realistic to assume that the population of the CD4$^+$ T cells has a logistic growth function. De Boer and Perelson [3] considered the cell-free virus infection with logistic cell growth by model

$$\begin{aligned}
\frac{dT(t)}{dt} &= \alpha_T T(t)\left(1 - \frac{T_{tot}}{T_{max}}\right) - (\beta+\gamma)T(t)V(t),\\
\frac{dI(t)}{dt} &= \beta T(t)V(t) - \delta_I I(t),\\
\frac{dV(t)}{dt} &= pI(t) - cV(t),
\end{aligned} \tag{1.2}$$

where $T(t)$, $I(t)$ and $V(t)$ represent target cell counts, productively infected T cell counts and free HIV-1 virus loads at time t respectively. Here, target cells grow at a rate α_T and this growth is limited by a carrying capacity, T_{max} cells. T_{tot} is the total number of T cells, $T_{tot} = T + I$. β is a true infection rate and γ combines all other virus-induced depletion of the CD4$^+$ T cells. δ_I represents the turnover rate of productively infected T cells. Virus particles are produced by productively infected cells at a rate p and cleared at a per capita rate c. In this model, we see that infected cells are produced only by the route that free viruses infect uninfected T cells. Mathematical analysis of this model can be found in [5] when $\gamma = 0$. Although the notation in [5] is different from that in (1.2) and the model is about HBV, the model in [5] has the same properties as model (1.2) mathematically when $\gamma = 0$. It was found that when the basic reproduction number is less than one, the infection cannot establish. When the basic reproduction number is greater than one, the infection can persist and the Hopf bifurcation may occur, that is, (1.2) has periodic solutions for some range of parameter values.

Culshaw et al. [2] studied the cell-to-cell spread of HIV-1 by model

$$\begin{aligned}
\frac{dC}{dt} &= r_C C(t)\left(1 - \frac{C(t)+I(t)}{C_M}\right) - k_I C(t)I(t),\\
\frac{dI}{dt} &= k_I' \int_{-\infty}^{t} C(u)I(u)F(t-u)du - \mu_I I(t),
\end{aligned} \tag{1.3}$$

where $C(t)$ and $I(t)$ represent the concentration of target cells and productively infected cells respectively. Target cells assume logistic growth rate. r_C indicates the effective reproductive rate of target cells. C_M denotes the effective carrying capacity of the system. Target cells are infected by productively infected cells at a rate $k_I C(t)I(t)$. k_I/k'_I represents the fraction of infected cells surviving the incubation period. It is assumed here that the cells productively infected at time t were infected u time units ago, where u is distributed according to a probability distribution $F(u)$. For the corresponding ODE models, the positive equilibrium is globally stable, while delay models exhibit Hopf bifurcations. We see that in this model, the infection is assumed to spread directly from infected cells to target cells, neglecting cell-free virus infection.

In this paper, we study the virus dynamics which combines diffusion-limited cell-free virus transmission and cell-to-cell transfer of HIV-1, and the effects of cell-to-cell transfer of HIV-1 on the virus dynamics with *logistic target cell growth*. We use the same notation as in model (1.1), and consider the following model

$$\begin{aligned}
\frac{dT(t)}{dt} &= rT(t)\left(1-\frac{T(t)+\alpha T^*(t)}{T_M}\right) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t),\\
\frac{dT^*(t)}{dt} &= \beta_1 T(t)V(t) + \beta_2 T(t)T^*(t) - d_{T^*}T^*(t),\\
\frac{dV(t)}{dt} &= \gamma T^*(t) - d_V V(t),
\end{aligned} \tag{1.4}$$

where r is a target cell growth rate, and this growth is limited by a carrying capacity of target cells, T_M. The constant α represents the limitation of infected cells imposed on the cell growth of target cells, generally $\alpha \geq 1$. In this model, we do not consider any delay effect.

For mathematical convenience, we rescale the model (1.4) by

$$\begin{gathered}
u(t) = \frac{T(t)}{T_M}, \qquad w(t) = \frac{T^*(t)}{T_M}, \qquad v(t) = \frac{d_{T^*}}{\gamma T_M}V(t), \qquad \tilde{t} = d_{T^*}t,\\
\rho_1 = \frac{\beta_1\gamma T_M}{d_{T^*}^2}, \qquad \rho_2 = \frac{\beta_2 T_M}{d_{T^*}}, \qquad \delta = \frac{r}{d_{T^*}}, \qquad \mu = \frac{d_V}{d_{T^*}},
\end{gathered}$$

then the rescaled model reads

$$\begin{aligned}
\frac{du(t)}{dt} &= \delta u(t)\big[1-u(t)-\alpha w(t)\big] - \rho_1 u(t)v(t) - \rho_2 u(t)w(t),\\
\frac{dw(t)}{dt} &= \rho_1 u(t)v(t) + \rho_2 u(t)w(t) - w(t),\\
\frac{dv(t)}{dt} &= w(t) - \mu v(t).
\end{aligned} \tag{1.5}$$

The rest of the paper is organized as follows. Nonnegativity and boundedness of solutions of system (1.5) are given in Section 2. Stability of the infection-free equilibrium is discussed in Section 3. Uniform persistence of the infection is shown in Section 4. Stability of the positive equilibrium and Hopf bifurcation are analyzed in Section 5. The Hopf bifurcation is illustrated numerically in Section 6. In Section 7, we give our conclusion and discussion.

2. Nonnegativity and boundedness of solutions

Assume initial conditions for system (1.5) are given as follows:

$$u(0) = u_0 > 0, \qquad w(0) = w_0 > 0, \qquad v(0) = v_0 > 0, \quad \text{and} \quad u_0 + w_0 \leq 1. \tag{2.1}$$

Since the right hand side functions of (1.5) satisfy the Lipschitz condition, there is a unique solution $(u(t), w(t), v(t)) \in C([0, +\infty), \mathbb{R}_+)$ to system (1.5) with the initial conditions (2.1).

Theorem 2.1. *Let $(u(t), w(t), v(t))$ be a solution of system (1.5) satisfying the initial conditions (2.1). Then the solution is positive and bounded: $0 < u(t) \leq 1$, $0 < w(t) \leq 1$, $0 < v(t) < v_0 + \frac{1}{\mu}$, for all $t \geq 0$. Moreover, $u(t) + w(t) \leq 1$, for all $t \geq 0$.*

Proof. To prove the positivity of solutions, we suppose by contradiction that t_i, $i = 1, 2, 3$, are the first times when $u(t)$, $w(t)$, $v(t)$ reach zero respectively, and $t_0 = \min\{t_1, t_2, t_3\}$.

First, if $t_0 = t_1$, we assume $t_1 \neq t_2$ and $t_1 \neq t_3$. Then $u(t_1) = 0$, $w(t_1) > 0$, $v(t_1) > 0$, and $u(t), w(t), v(t) > 0$ for all $t \in [0, t_1)$. From the first and second equations in (1.5), we observe that

$$\frac{d}{dt}\big[u(t) + w(t)\big] = \delta u(t)\big[1 - \big(u(t) + w(t)\big)\big] - \delta(\alpha - 1)u(t)w(t) - w(t), \quad \forall t \in [0, t_1]. \tag{2.2}$$

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

$$\frac{d}{dt}\big[u(t) + w(t)\big]\big|_{t=t^*} = -\delta(\alpha - 1)u\big(t^*\big)w\big(t^*\big) - w\big(t^*\big) \leq -w\big(t^*\big) < 0. \tag{2.3}$$

This means $u(t) + w(t) \leq 1$, for all $t \in [0, t_1]$. Thus we have $u(t) < 1$ and $w(t) < 1$, for $t \in [0, t_1]$. From the third equation in (1.5), we see that

$$\frac{dv(t)}{dt} \leq 1 - \mu v(t),$$

which means

$$v(t) \leq e^{-\mu t}\left[v(0) + \frac{1}{\mu}\big(e^{\mu t} - 1\big)\right] \leq v(0)e^{-\mu t} + \frac{1}{\mu}, \quad t \in [0, t_1]. \tag{2.4}$$

Again from the first equation in (1.5), we have

$$\frac{du(t)}{dt} \geq -\big[\rho_1 v(t) + (\rho_2 + \delta\alpha)w(t)\big]u(t), \quad t \in [0, t_1],$$

thus

$$u(t) \geq u(0)e^{-\int_0^t [\rho_1 v(s) + (\rho_2 + \delta\alpha)w(s)]ds}, \quad t \in [0, t_1]. \tag{2.5}$$

We know from (2.4) and (2.5) that

$$u(t_1) \geq u(0)e^{-\int_0^{t_1} [\rho_1 (v(0)e^{-\mu s} + \frac{1}{\mu}) + (\rho_2 + \delta\alpha)]ds} = u(0)e^{-[v(0)\rho_1(1 - e^{-\mu t_1}) + (\rho_1 \frac{1}{\mu} + \rho_2 + \delta\alpha)t_1]} > 0,$$

which contradicts $u(t_1) = 0$.

Second, if $t_0 = t_2$, $w(t_2) = 0$, $u(t_2) \geq 0$, $v(t_2) \geq 0$, and $u(t), w(t), v(t) > 0$ for $t \in [0, t_2)$, then from the second equation in (1.5), we have

$$\frac{dw(t)}{dt} \geq -w(t), \quad t \in [0, t_2],$$

thus

$$w(t_2) \geq w(0)e^{-t_2} > 0,$$

which is in contradiction to $w(t_2) = 0$. Notice that this case includes all the cases of $t_2 \neq t_1$ or $t_2 \neq t_3$ or $t_1 = t_2 \neq t_3$ or $t_2 = t_3 \neq t_1$ or $t_1 = t_2 = t_3$.

Third, if $t_0 = t_3$, $v(t_3) = 0$, $u(t_3) \geq 0$, $w(t_3) \geq 0$, and $u(t), w(t), v(t) > 0$ for $t \in [0, t_3)$, then from the third equation in (1.5), we have

$$\frac{dv(t)}{dt} \geq -\mu v(t), \quad t \in [0, t_3],$$

thus

$$v(t_3) \geq v(0)e^{-\mu t_3} > 0,$$

which is in contradiction to $v(t_3) = 0$. This case includes the cases of $t_3 \neq t_1$ or $t_3 \neq t_2$ or $t_3 = t_1 \neq t_2$. So far we have considered all the cases and found a contradiction for each case. Therefore, there is no such t_i, $i = 1, 2, 3$. This means $u(t), w(t), v(t) > 0$, for $t \geq 0$.

With the positivity of the solution $(u(t), w(t), v(t))$, we know that (2.2), (2.3) and (2.4) hold for all $t \geq 0$. Therefore,

$$u(t) + w(t) \leq 1, \qquad v(t) \leq v(0) + \frac{1}{\mu}, \quad \forall t \geq 0.$$

This completes the proof. □

Furthermore, from (2.4), we see that

$$v(t) \leq e^{-\mu t}\left(v(0) - \frac{1}{\mu}\right) + \frac{1}{\mu}.$$

Therefore, if $v(0) \leq \frac{1}{\mu}$, then $v(t) \leq \frac{1}{\mu}$ for all $t \geq 0$.

In fact, we can see from Lemma 4.1 and Lemma 4.2 appearing later, that the set

$$\mathbb{Y} := \left\{(u, w, v) \in \mathbb{R}^3 \;\middle|\; u \geq 0,\ w \geq 0,\ v \geq 0,\ u + w \leq 1,\ v \leq \frac{1}{\mu}\right\},$$

is invariant for the solution semiflow of (1.5).

3. Stability of the infection-free equilibrium

For model (1.5), the basic reproduction number is given by

$$\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}, \qquad \mathcal{R}_{01} = \frac{\rho_1}{\mu}, \qquad \mathcal{R}_{02} = \rho_2.$$

System (1.5) has three equilibria: the trivial equilibrium $E_0 = (0, 0, 0)$, the infection-free equilibrium $E_1 = (1, 0, 0)$ and the positive equilibrium $\bar{E} = (\bar{u}, \bar{w}, \bar{v})$, where

$$\bar{u} = \frac{\mu}{\rho_1 + \mu\rho_2} = \frac{1}{\mathcal{R}_0}, \qquad \bar{w} = \frac{\delta}{\mathcal{R}_0 + \delta\alpha}\left(1 - \frac{1}{\mathcal{R}_0}\right), \qquad \bar{v} = \frac{1}{\mu}\bar{w}.$$

We can easily see that for model (1.4), the basic reproduction number is $\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}$, where

$$\mathcal{R}_{01} = \frac{T_M \beta_1 \gamma}{d_{T^*} d_V}, \qquad \mathcal{R}_{02} = \frac{T_M \beta_2}{d_{T^*}}.$$

In the following, we consider stability of equilibria for model (1.5).

Theorem 3.1. *For system (1.5),*

(i) The trivial equilibrium E_0 is always unstable;
(ii) If $\mathcal{R}_0 < 1$, the infection-free equilibrium E_1 is locally asymptotically stable. If $\mathcal{R}_0 > 1$, E_1 is unstable.

Proof. To discuss local stability, we consider linearized system of (1.5). The Jacobian matrix of (1.5) at E_0 is given by

$$J_0 = \begin{pmatrix} \delta & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 1 & -\mu \end{pmatrix},$$

which has a positive eigenvalue $\lambda = \delta$. Therefore, E_0 is always unstable.

The Jacobian matrix of (1.5) at E_1 is given by

$$J_1 = \begin{pmatrix} -\delta & -(\delta\alpha + \rho_2) & -\rho_1 \\ 0 & \rho_2 - 1 & \rho_1 \\ 0 & 1 & -\mu \end{pmatrix}.$$

We see that it has an eigenvalue $\lambda_1 = -\delta < 0$, and other eigenvalues are given by eigenvalues of the matrix

$$J_{10} = \begin{pmatrix} \rho_2 - 1 & \rho_1 \\ 1 & -\mu \end{pmatrix},$$

that is, the roots of characteristic equation

$$\lambda^2 + a_1\lambda + a_2 = 0, \tag{3.1}$$

where

$$a_1 = \mu + 1 - \rho_2,$$
$$a_2 = \mu(1 - \rho_2) - \rho_1 = \mu(1 - \mathcal{R}_0).$$

We see that if $\mathcal{R}_0 < 1$, then $a_1 > 0$, $a_2 > 0$, and all eigenvalues have negative real parts. If $\mathcal{R}_0 > 1$, then $a_2 < 0$, and J_{10} has at least one positive eigenvalue. Therefore, E_1 is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$. □

Theorem 3.2. *If $\mathcal{R}_0 < 1$, the infection-free equilibrium E_1 is globally asymptotically stable.*

Proof. We have to prove that $\lim_{t\to+\infty}(u, w, v) = (1, 0, 0)$. Since $u(t) \le 1$ for all $t \ge 0$, we have

$$\frac{dw(t)}{dt} \le \rho_1 v(t) + \rho_2 w(t) - w(t),$$
$$\frac{dv(t)}{dt} \le w(t) - \mu v(t).$$

For the linear cooperative system

$$\begin{aligned}\frac{d\tilde{w}(t)}{dt} &= \rho_1\tilde{v}(t) + \rho_2\tilde{w}(t) - \tilde{w}(t),\\ \frac{d\tilde{v}(t)}{dt} &= \tilde{w}(t) - \mu\tilde{v}(t),\end{aligned} \tag{3.2}$$

there exists a principal eigenvalue λ_0 associated with strictly positive eigenvector ξ_0 [9]. Given $M > 0$, it follows that the linear system (3.2) admits a solution $(\tilde{w}(t), \tilde{v}(t)) = Me^{\lambda_0 t}\xi_0$. Choosing $M > 0$ such that $(w(0), v(0)) \le (\tilde{w}(0), \tilde{v}(0))$, by the comparison principle, it follows that

$$\big(w(t), v(t)\big) \le Me^{\lambda_0 t}\xi_0, \quad \forall t \ge 0.$$

From (3.1), we see that $\lambda_0 < 0$ if $\mathcal{R}_0 < 1$. Therefore, if $\mathcal{R}_0 < 1$, we have

$$\lim_{t\to+\infty} w(t) = 0, \qquad \lim_{t\to+\infty} v(t) = 0.$$

Then the first equation in (1.5) is asymptotic to the following equation

$$\frac{d\tilde{u}(t)}{dt} = \delta\tilde{u}(t)\big[1 - \tilde{u}(t)\big],$$

which is the logistic equation. Since $\delta > 0$, it is easy to see that $\lim_{t\to+\infty}\tilde{u}(t) = 1$. By the asymptotic autonomous semiflow theory (see Corollary 4.3 in [12]), we have

$$\lim_{t\to+\infty} u(t) = 1.$$

Thus, if $\mathcal{R}_0 < 1$, then

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

This completes the proof of the theorem. □

4. Uniform persistence of infection

Notice that when $u_0 = 0$, the unique solution of (1.5)–(2.1) is given by

$$u(t) = 0, \qquad w(t) = w_0e^{-t}, \qquad v(t) = e^{-\mu t}\left[v_0 + w_0\int_0^t e^{(\mu-1)s}ds\right], \quad \forall t > 0. \tag{4.1}$$

We see that $w(t) \to 0$ and $v(t) \to 0$ as $t \to +\infty$. Therefore, if $u_0 = 0$, the system cannot be persistent. To discuss the persistence of system (1.5), we consider the following solution space:

$$\mathbb{X} := \left\{(u, w, v) \in \mathbb{R}^3 \;\middle|\; u > 0,\ w \ge 0,\ v \ge 0,\ u + w \le 1,\ v \le \frac{1}{\mu}\right\},$$

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

$$\mathbb{X}_0 := \big\{(u, w, v) \in \mathbb{X} \;\big|\; w > 0 \text{ and } v > 0\big\},$$

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

$$\partial\mathbb{X}_0 := \mathbb{X}\backslash\mathbb{X}_0 = \big\{(u, w, v) \in \mathbb{X} \;\big|\; w = 0 \text{ or } v = 0\big\},$$

and

$$M_\partial := \{(u_0, w_0, v_0) \in \partial\mathbb{X}_0 \mid \Phi_t(u_0, w_0, v_0) \in \partial\mathbb{X}_0,\ t \geq 0\},$$

where Φ_t is the solution semiflow defined by (1.5).

Lemma 4.1. *The sets* $\mathbb{X}$ *and* $\mathbb{X}_0$ *are positively invariant for the solution semiflow* Φ_t *defined by (1.5). Moreover,*

$$M_\partial = \{(\hat{u}, 0, 0) \mid 0 < \hat{u} \leq 1\}. \tag{4.2}$$

Proof. Given $(u_0, w_0, v_0) \in \mathbb{X}$, we consider the different cases of w_0 and v_0:

(i) If $w_0 = 0$ and $v_0 = 0$, then

$$u(t) = \frac{u_0}{u_0 + [1 - u_0]e^{-\delta t}} > 0, \qquad w(t) = 0, \qquad v(t) = 0, \quad \forall t \geq 0. \tag{4.3}$$

(ii) If $w_0 = 0$ and $v_0 > 0$, then

$$\frac{d}{dt} w(0) = \rho_1 u(0)v(0) = \rho_1 u_0 v_0 > 0.$$

Thus, for small $\varepsilon > 0$, $w(t) > 0$ for $t \in (0, \varepsilon)$. We assume t_2 to be the first time when $w(t)$ reaches zero other than $t = 0$. By the same argument as in the proof of Theorem 2.1, we obtain that $u(t) > 0$, $w(t) > 0$ and $v(t) > 0$.

(iii) If $w_0 > 0$ and $v_0 = 0$, then

$$\frac{d}{dt} v(0) = w(0) = w_0 > 0.$$

Like in case (ii), it follows that $u(t) > 0$, $w(t) > 0$ and $v(t) > 0$.

(iv) If $w_0 > 0$ and $v_0 > 0$, from Theorem 2.1, we have $u(t) > 0$, $w(t) > 0$ and $v(t) > 0$.

In summary, sets $\mathbb{X}$ and $\mathbb{X}_0$ are positively invariant for the solution semiflow Φ_t defined by (1.5). Next, we assume that $(u_0, w_0, v_0) \in M_\partial$. This implies that $\Phi_t(u_0, w_0, v_0) \in \partial\mathbb{X}_0$. Hence, cases (ii), (iii) and (iv) cannot occur. That is, $w_0 = 0$ and $v_0 = 0$. This proves (4.2). We complete the proof of the lemma. □

We see that J_{10} is a quasi-positive matrix. By Corollary 4.3.2 in [9], $\lambda_0(u_1) = \max\{Re\,\lambda | \lambda \in \sigma(J_{10})\}$ is an eigenvalue of J_{10}, called the principal eigenvalue, where $\sigma(J_{10})$ is the set of eigenvalues of matrix J_{10}. From Theorem 3.1, we know that if $\mathcal{R}_0 > 1$, then $\lambda_0(u_1) > 0$. By continuity of the principal eigenvalue, we have $\lambda_0(u_1 - \eta_0) > 0$, for some $\eta_0 > 0$.

Lemma 4.2. *If* $\mathcal{R}_0 > 1$*, the solution* $(u(t), w(t), v(t))$ *of (1.5) with initial value* $(u_0, w_0, v_0) \in \mathbb{X}_0$ *satisfies*

$$\limsup_{t\to\infty} \|(u(t), w(t), v(t)) - (u_1, 0, 0)\| \geq \eta_0,$$

where $u_1 = 1$.

Proof. To prove the lemma, we suppose by contradiction that

$$\limsup_{t\to\infty} \|(u(t), w(t), v(t)) - (u_1, 0, 0)\| < \eta_0,$$

for a solution with some initial value $(u_0, w_0, v_0) \in \mathbb{X}_0$. Then for this solution, there exists a $t_0 > 0$ such that $u(t) > u_1 - \eta_0$, $w(t) < \eta_0$, $v(t) < \eta_0$, for $t \geq t_0$. Thus, from the second equation in (1.5), we have

$$\frac{dw(t)}{dt} \geq \rho_1(u_1 - \eta_0)v(t) + \rho_2(u_1 - \eta_0)w(t) - w(t), \quad t \geq t_0.$$

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

$$\begin{aligned} \frac{d\tilde{w}(t)}{dt} &= \rho_1(u_1 - \eta_0)\tilde{v}(t) + \rho_2(u_1 - \eta_0)\tilde{w}(t) - \tilde{w}(t), \\ \frac{d\tilde{w}(t)}{dt} &= \tilde{w}(t) - \mu\tilde{v}(t). \end{aligned} \tag{4.4}$$

Let $(\xi_1, \xi_2)^T$ be the strictly positive eigenvector associated with $\lambda_0(u_1 - \eta_0)$, then $(\tilde{w}, \tilde{v})^T = e^{\lambda_0(u_1 - \eta_0)t}(\xi_1, \xi_2)^T$ is a solution of (4.4). Since $w(t_0) > 0$, $v(t_0) > 0$, there exists a $\zeta > 0$, such that $(w(t_0), v(t_0))^T \geq \zeta(\tilde{w}(t_0), \tilde{v}(t_0))^T$. By the comparison principle, we have

$$\big(w(t), v(t)\big)^T \geq \zeta e^{\lambda_0(u_1 - \eta_0)t}(\xi_1, \xi_2)^T, \quad \forall t \geq t_0. \tag{4.5}$$

Since $\lambda_0(u_1 - \eta_0) > 0$, it follows from (4.5) that $w(t)$ and $v(t)$ are unbounded. Thus we obtain the contradiction and prove the lemma. □

Theorem 4.1. *For system (1.5), if $\mathcal{R}_0 > 1$, the infection is uniformly persistent with respect to $(\mathbb{X}_0, \partial\mathbb{X}_0)$, in the sense that there exists an $\eta > 0$ such that*

$$\liminf_{t\to\infty} w(t) \geq \eta, \qquad \liminf_{t\to\infty} v(t) \geq \eta. \tag{4.6}$$

Proof. By Lemma 4.1, $\mathbb{X}_0$ is positively invariant for the solution semiflow Φ_t defined by (1.5). Furthermore, Φ_t is compact and point dissipative. By Theorem 1.1.3 in [16], there is a global attractor A for Φ_t.

Let $M = (1, 0, 0)$. From the proof of Lemma 4.1, we know that M_∂ is the maximal compact invariant set in $\partial\mathbb{X}_0$. From (4.3), 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 $W^s(M) \cap \mathbb{X}_0 = \emptyset$, where $W^s(M)$ is the stable set of M. Furthermore, there is no cycle in M_∂ from M to M.

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

$$p(x) = \min\{w_0, v_0\}, \quad \forall x = (u_0, w_0, v_0) \in \mathbb{X}.$$

Then from Lemma 4.1, we see that $p^{-1}(0, \max\{1, 1/\mu\}) \subset \mathbb{X}_0$, and that $p(x) > 0$ for $x \in \mathbb{X}_0$. Moreover, if $p(x) > 0$, then $x \in \mathbb{X}_0$. Thus, p is a generalized distance function for the semiflow $\Phi_t : \mathbb{X} \to \mathbb{X}$. It follows from Theorem 3 in [10] that there exists an $\eta > 0$ such that

$$\min_{x \in \omega(y)} p(x) > \eta, \quad \forall y \in \mathbb{X}_0.$$

Therefore,

$$\liminf_{t\to\infty} w(t) \geq \eta, \qquad \liminf_{t\to\infty} v(t) \geq \eta,$$

which completes the proof of the theorem. □

Remark 4.1. If $\mathcal{R}_0 > 1$, the target cell population $u(t)$ is uniformly weakly persistent in the sense that there exists some $\eta > 0$ such that

$$\limsup_{t\to\infty} u(t) \geq \eta. \tag{4.7}$$

In fact, if (4.7) is not true, then by the definition $\limsup_{t\to\infty} u(t) = \lim_{t\to\infty} \sup_{\tau\geq t} u(\tau)$, for any $\varepsilon > 0$ there exists a $t_1 > 0$ such that $\sup_{\tau\geq t_1} u(\tau) < \varepsilon$, thus $u(t) < \varepsilon$ for $t \geq t_1$. This means $\lim_{t\to\infty} u(t) = 0$. In this case, the second equation in (1.5) is asymptotic to the following equation

$$\frac{d\tilde{w}(t)}{dt} = -\tilde{w}(t),$$

which has only one equilibrium $\tilde{w} = 0$. By the asymptotic autonomous semiflow theory (Corollary 4.3 in [12]), $w(t) \to 0$ as $t \to \infty$. Similarly, from the third equation in (1.5), $v(t) \to 0$ as $t \to \infty$. These contradict (4.6), that is, the uniform persistence of $w(t)$ and $v(t)$.

5. Stability of the positive equilibrium $\bar{E}$ and Hopf bifurcation

In this section we consider stability of the positive equilibrium $\bar{E}$. Noticing that

$$\begin{aligned}
\delta(1-2\bar{u}-\alpha\bar{w}) - \rho_1\bar{v} - \rho_2\bar{w} &= -\delta\bar{u} = -\frac{\delta}{\mathcal{R}_0}, \\
\rho_1\bar{v} + \rho_2\bar{w} &= \left(\frac{\rho_1}{\mu} + \rho_2\right)\bar{w} = \frac{\delta(\mathcal{R}_0 - 1)}{\mathcal{R}_0 + \delta\alpha}, \\
\mu(1-\rho_2\bar{u}) - \rho_1\bar{u} &= \mu - (\rho_2\mu + \rho_1)\frac{1}{\mathcal{R}_0} = 0,
\end{aligned}$$

the Jacobian matrix of (1.5) at $\bar{E}$ is given by

$$\bar{J} = \begin{pmatrix} -\frac{\delta}{\mathcal{R}_0} & -(\frac{\delta\alpha}{\mathcal{R}_0} + \rho_2\bar{u}) & -\rho_1\bar{u} \\ \rho_1\bar{v} + \rho_2\bar{w} & \rho_2\bar{u} - 1 & \rho_1\bar{u} \\ 0 & 1 & -\mu \end{pmatrix}.$$

The corresponding characteristic equation is

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0, \tag{5.1}$$

where

$$\begin{aligned}
b_1 &= \frac{\delta}{\mathcal{R}_0} + \mu + 1 - \frac{\rho_2}{\mathcal{R}_0} = \frac{\delta}{\mathcal{R}_0} + \mu + \frac{\mathcal{R}_{01}}{\mathcal{R}_0} > 0, \\
b_2 &= \frac{\delta}{\mathcal{R}_0}(1 - \rho_2\bar{u} + \mu) + \mu(1-\rho_2\bar{u}) - \rho_1\bar{u} + (\rho_1\bar{v} + \rho_2\bar{w})\left(\frac{\delta\alpha}{\mathcal{R}_0} + \rho_2\bar{u}\right) \\
&= \frac{\delta}{\mathcal{R}_0}\left(1 + \mu - \frac{\rho_2}{\mathcal{R}_0}\right) + \frac{\delta(\mathcal{R}_0 - 1)}{\mathcal{R}_0 + \delta\alpha}\left(\frac{\delta\alpha}{\mathcal{R}_0} + \frac{\rho_2}{\mathcal{R}_0}\right) \\
&= \frac{\delta}{\mathcal{R}_0}\left(\mu + \frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right) + \frac{\delta}{\mathcal{R}_0}\frac{\mathcal{R}_{02} + \delta\alpha}{\mathcal{R}_0 + \delta\alpha}(\mathcal{R}_0 - 1) > 0,
\end{aligned}$$

$$
\begin{aligned}
b_3 &= \frac{\delta}{\mathcal{R}_0}(1-\rho_2\bar{u})\mu + \rho_1\bar{u}(\rho_1\bar{v}+\rho_2\bar{w}) - \rho_1\bar{u}\frac{\delta}{\mathcal{R}_0} + \mu(\rho_1\bar{v}+\rho_2\bar{w})\left(\frac{\delta\alpha}{\mathcal{R}_0}+\rho_2\bar{u}\right)\\
&= (\rho_1\bar{v}+\rho_2\bar{w})\left[\rho_1\bar{u}+\mu\left(\frac{\delta\alpha}{\mathcal{R}_0}+\rho_2\bar{u}\right)\right]\\
&= \frac{\delta(\mathcal{R}_0-1)}{\mathcal{R}_0+\delta\alpha}\left(\frac{\delta\alpha}{\mathcal{R}_0}+1\right)\mu\\
&= \frac{\delta\mu}{\mathcal{R}_0}(\mathcal{R}_0-1) > 0,\\
b_1b_2 - b_3 &= \frac{\delta}{\mathcal{R}_0}\left\{\left(\frac{\delta}{\mathcal{R}_0}+\mu+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)\left[\left(\mu+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)+\frac{\mathcal{R}_{02}+\delta\alpha}{\mathcal{R}_0+\delta\alpha}(\mathcal{R}_0-1)\right]-\mu(\mathcal{R}_0-1)\right\}\\
&= \frac{\delta}{\mathcal{R}_0}\left\{\left(\frac{\delta}{\mathcal{R}_0}+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)\left[\left(\mu+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)+\frac{\mathcal{R}_{02}+\delta\alpha}{\mathcal{R}_0+\delta\alpha}(\mathcal{R}_0-1)\right]+\mu\left(\mu+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)-\mu\frac{\mathcal{R}_{01}}{\mathcal{R}_0+\delta\alpha}(\mathcal{R}_0-1)\right\}\\
&= \frac{\delta}{\mathcal{R}_0}\left\{\left(\frac{\delta}{\mathcal{R}_0}+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)\frac{\mathcal{R}_{02}+\delta\alpha}{\mathcal{R}_0+\delta\alpha}(\mathcal{R}_0-1)+\frac{\delta}{\mathcal{R}_0}\left(\mu+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)+\left(\mu+\frac{\mathcal{R}_{01}}{\mathcal{R}_0}\right)^2-\mu\frac{\mathcal{R}_{01}}{\mathcal{R}_0+\delta\alpha}(\mathcal{R}_0-1)\right\}\\
&= \frac{\delta\mu}{\rho_1+\mu\rho_2}\left\{\left(\frac{\delta\mu}{\rho_1+\mu\rho_2}+\frac{\rho_1}{\rho_1+\mu\rho_2}\right)\frac{\rho_2+\delta\alpha}{\rho_1+\mu\rho_2+\mu\delta\alpha}(\rho_1+\mu\rho_2-\mu)\right.\\
&\quad\left.+\frac{\delta\mu}{\rho_1+\mu\rho_2}\left(\mu+\frac{\rho_1}{\rho_1+\mu\rho_2}\right)+\left(\mu+\frac{\rho_1}{\rho_1+\mu\rho_2}\right)^2-\frac{\rho_1}{\rho_1+\mu\rho_2+\mu\delta\alpha}(\rho_1+\mu\rho_2-\mu)\right\}.
\end{aligned}
$$

We denote

$$
b_1(p)b_2(p) - b_3(p) = G(p)F(p),
$$

where

$$
\begin{aligned}
p &= (\rho_1,\rho_2,\mu,\delta,\alpha),\\
G(p) &= \frac{\delta\mu}{(\rho_1+\mu\rho_2)^3(\rho_1+\mu\rho_2+\mu\delta\alpha)},\\
F(p) &= (\delta\mu+\rho_1)(\rho_1+\mu\rho_2)(\rho_2+\delta\alpha)(\rho_1+\mu\rho_2-\mu)+\delta\mu\big[\mu(\rho_1+\mu\rho_2)+\rho_1\big]\big[(\rho_1+\mu\rho_2)+\mu\delta\alpha\big]\\
&\quad+\big[\mu(\rho_1+\mu\rho_2)+\rho_1\big]^2\big[(\rho_1+\mu\rho_2)+\mu\delta\alpha\big]-\rho_1(\rho_1+\mu\rho_2)^2(\rho_1+\mu\rho_2-\mu).
\end{aligned}
$$

We see that if $\mathcal{R}_0 > 1$, then $b_i > 0$, $i = 1,2,3$. Thus, if $b_1b_2 - b_3 > 0$ then $\bar{E}$ is locally asymptotically stable by the Routh–Hurwitz criterion, and if $b_1b_2 - b_3 < 0$, $\bar{E}$ is unstable. Since $G(p) > 0$, the sign of $b_1(p)b_2(p) - b_3(p)$ is determined by the sign of $F(p)$. If there is a $\bar{p} = (\bar{\rho}_1,\bar{\rho}_2,\bar{\mu},\bar{\delta},\bar{\alpha})$ such that $F(\bar{p}) = 0$, then there is a Hopf bifurcation at $\bar{E}$, by Theorem 2 in [14]. In fact, when $p = \bar{p}$, we have $b_3(\bar{p}) = b_1(\bar{p})b_2(\bar{p})$, and further the characteristic equation (5.1) has a negative root $\bar{\lambda}_1 = -b_1(\bar{p})$ and a pair of pure imaginary roots $\bar{\lambda}_{2,3} = \pm i\sqrt{b_2(\bar{p})}$.

First, we consider the Hopf bifurcation at $\bar{E}$ choosing ρ_1 as the bifurcation parameter, that is, the parameters $(\rho_2,\mu,\delta,\alpha)$ are fixed at $(\bar{\rho}_2,\bar{\mu},\bar{\delta},\bar{\alpha})$ while ρ_1 changes near $\bar{\rho}_1$. Then $F(p)$ is a function of ρ_1, which can be expressed in the following form

$$
\begin{aligned}
F(\rho_1) &= -\rho_1^4 + \big(\delta\alpha+\rho_2+1-3\mu\rho_2+\mu^2+3\mu\big)\rho_1^3\\
&\quad+\big(3\mu^3\rho_2+\mu^3\delta\alpha+\delta\mu\rho_2+\delta\mu^2+2\rho_2^2\mu+2\delta\alpha\mu\rho_2+\delta\mu+\delta^2\mu\alpha+6\mu^2\rho_2+2\mu^2\delta\alpha-3\rho_2^2\mu^2\big)\rho_1^2\\
&\quad+\big(\delta\alpha\mu^2\rho_2^2+2\delta\mu^2\rho_2^2+\delta^2\mu^3\alpha+2\delta^2\mu^2\alpha\rho_2-\rho_2^2\mu^2+2\delta\mu^3\rho_2-\delta\alpha\mu^2\rho_2+2\mu^4\rho_2\delta\alpha
\end{aligned}
$$

$$+ 3\mu^4\rho_2^2 + \rho_2^3\mu^2 + 3\mu^3\rho_2^2 - \mu^3\rho_2^3 + 2\mu^3\rho_2\delta\alpha\big)\rho_1$$
$$- \delta^2\mu^3\alpha\rho_2 + \mu^5\rho_2^3 + \delta\mu^3\rho_2^3 + b^2\mu^3\alpha\rho_2^2 - \delta\mu^3\rho_2^2 + \delta\mu^4\rho_2^2 + \mu^5\rho_2^2\delta\alpha + \delta^2\mu^4\rho_2\alpha,$$

where we omit the bar of $(\bar{\rho}_2, \bar{\mu}, \bar{\delta}, \bar{\alpha})$ for notational convenience. We see that if $\rho_1 = 0$, then $\mathcal{R}_0 = \rho_2 > 1$, and

$$F(0) = \mu^3\rho_2(\rho_2 + \delta\alpha)\big[\delta(\rho_2 - 1) + \mu^2\rho_2 + \delta\mu\big] > 0.$$

On the other hand, $\lim_{\rho_1\to+\infty} F(\rho_1) = -\infty$. Therefore, $F(\rho_1) = 0$ has at least one positive root.

Proposition 5.1. *Assume that parameters $(\rho_2, \mu, \delta, \alpha)$ are fixed. If $\mathcal{R}_0 > 1$ and $F(\rho_1) > 0$, then $\bar{E}$ is locally asymptotically stable. If there exists a critical value $\bar{\rho}_1 > 0$ such that $\mathcal{R}_0 > 1$ and $F(\bar{\rho}_1) = 0$, then a Hopf bifurcation occurs at $\bar{E}$ when ρ_1 passes through the critical value $\bar{\rho}_1$.*

By the similar arguments, we can obtain the following results about different bifurcation parameters.

Proposition 5.2. *Assume that parameters $(\rho_1, \mu, \delta, \alpha)$ are fixed. If $\mathcal{R}_0 > 1$ and $F(\rho_2) > 0$, then $\bar{E}$ is locally asymptotically stable. If there exists a critical value $\bar{\rho}_2 > 0$ such that $\mathcal{R}_0 > 1$ and $F(\bar{\rho}_2) = 0$, then a Hopf bifurcation occurs at $\bar{E}$ when ρ_2 passes through the critical value $\bar{\rho}_2$. Here, $F(p)$ is a function of ρ_2:*

$$\begin{aligned} F(\rho_2) = {} & \big(\rho_1\mu^2 + \mu^5 + \mu^3\delta - \mu^3\rho_1\big)\rho_2^3 \\ & + \big(\mu^2\delta\alpha\rho_1 + \delta^2\mu^3\alpha - \rho_1\mu^2 + 3\mu^3\rho_1 + 2\rho_1^2\mu - \mu^3\delta + \delta\mu^4 + 2\delta\mu^2\rho_1 + \mu^5\delta\alpha + 3\mu^4\rho_1 - 3\mu^2\rho_1^2\big)\rho_2^2 \\ & + \big(2\mu^3\rho_1\delta\alpha + \delta\mu\rho_1^2 + 2\rho_1\delta^2\mu^2\alpha + 2\rho_1^2\mu\delta\alpha + 2\mu^4\rho_1\delta\alpha + \delta^2\mu^4\alpha - \delta^2\mu^3\alpha - \mu^2\delta\alpha\rho_1 + \rho_1^3 \\ & + 3\mu^3\rho_1^2 + 6\mu^2\rho_1^2 - 3\mu\rho_1^3 + 2\delta\mu^3\rho_1\big)\rho_2 \\ & + \rho_1^3 + \delta\mu\rho_1^2 + \delta^2\mu\alpha\rho_1^2 + \mu^2\rho_1^3 + \mu^3\rho_1^2\delta\alpha - \rho_1^4 + \delta^2\mu^3\rho_1\alpha + 2\mu^2\rho_1^2\delta\alpha + \delta\mu^2\rho_1^2 + 3\mu\rho_1^3 + \rho_1^3\delta\alpha, \end{aligned}$$

where we also omit the bar of $(\bar{\rho}_2, \bar{\mu}, \bar{\delta}, \bar{\alpha})$ for notational convenience.

6. Numerical simulation

We choose the baseline parameters in model (1.4) as $r = 0.1$, $T_M = 1000$, $d_{T^*} = 0.4$, $\gamma = 850$ and $d_V = 3$ [1,11]. Then for model (1.5), we have $\delta = 0.25$, $\mu = 7.5$. We set $\alpha = 1.2$ and use ρ_1 and ρ_2 as bifurcation parameters.

Notice that if $\rho_1 = 0$, then $\mathcal{R}_0 = \rho_2$ and

$$b_1b_2 - b_3 = \frac{\delta}{\rho_2^2}\big[\delta(\rho_2 - 1) + \delta\mu + \mu^2\rho_2\big].$$

Thus, if $\mathcal{R}_0 = \rho_2 > 1$, $b_1b_2 - b_3 > 0$. Therefore, $\bar{E}$ is locally asymptotically stable for all $\delta, \alpha, \mu > 0$, $\rho_2 > 1$ and $\rho_1 = 0$. This is the case when there is only cell-to-cell transmission, which is considered by Culshaw et al. [2] for $\alpha = 1$.

When $\rho_1 > 0$, the surface $F(\rho_1, \rho_2)$ is shown in Fig. 1. We see that $\bar{E}$ is also locally asymptotically stable, when ρ_1 and ρ_2 satisfy $\mathcal{R}_0 > 1$, $\rho_1 < \bar{\rho}_1$ and $\rho_2 < \bar{\rho}_2$, where $(\bar{\rho}_1, \bar{\rho}_2)$ is at the intersection curve of the two surfaces in Fig. 1, $F(\bar{\rho}_1, \bar{\rho}_2) = 0$.

First, we consider ρ_1 as a bifurcation parameter. Assume $\beta_2 = 0.65 \times 10^{-3}$, then $\rho_2 = 1.625$. When the parameters are fixed at $\delta = 0.25$, $\alpha = 1.2$, $\mu = 7.5$ and $\rho_2 = 1.625$, $F(\rho_1) = 0$ has a positive root $\rho_1 = 79.98204093$, a negative root $\rho_1 = -13.50810411$ and a pair of conjugate complex roots $\rho_1 = -10.68071841\pm$

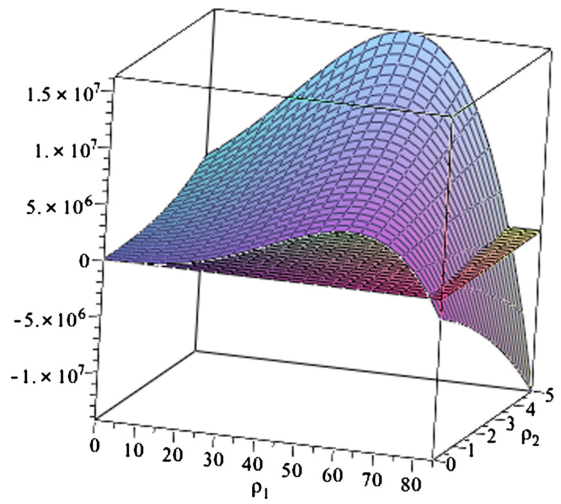


Fig. 1. The surface of $F(\rho_1, \rho_2)$, when $\delta = 0.2$, $\alpha = 1.2$, $\mu = 10$.

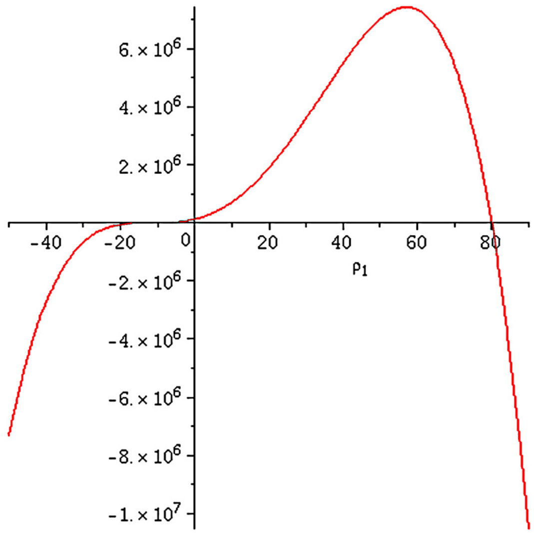


Fig. 2. The function $F(\rho_1)$ has only a positive root $\bar{\rho}_1 = 79.98204093$.

$0.2299679133i$ (see Fig. 2). Thus $\bar{\rho}_1 = 79.98204093$ is a critical value for bifurcation. Since $\mathcal{R}_0 \geq \rho_2 > 1$, we see that if $0 \leq \rho_1 < \bar{\rho}_1$, $\bar{E}$ is locally asymptotically stable, while it is unstable if $\rho_1 \geq \bar{\rho}_1$ (see Fig. 3 and Fig. 4). When $\rho_1 = \bar{\rho}_1$, there is a Hopf bifurcation, and a family of periodic solutions bifurcates from $\bar{E}$ (see Fig. 5).

When $\rho_1 = \bar{\rho}_1$, $\bar{J}$ has a pair of pure imaginary eigenvalues $\lambda = \pm 0.4531462285i$ and a negative real eigenvalue $\lambda = -8.3881137969$. In the following, we determine the bifurcation direction and stability, magnitudes and periods of the bifurcated periodic solutions by applying the normal form theory and Maple program developed by Yu [13] using computer algebra system. First we transform the fixed point to the origin and let $\rho_1 = \bar{\rho}_1 + \varepsilon$, and then transform the Jacobian matrix of system (1.5) evaluated at the trivial equilibrium solution to Jordan canonical form. By the linear transformation

$$\begin{pmatrix} u \\ w \\ v \end{pmatrix} = \begin{pmatrix} \bar{u} \\ \bar{w} \\ \bar{v} \end{pmatrix} + P \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix}, \tag{6.1}$$

where

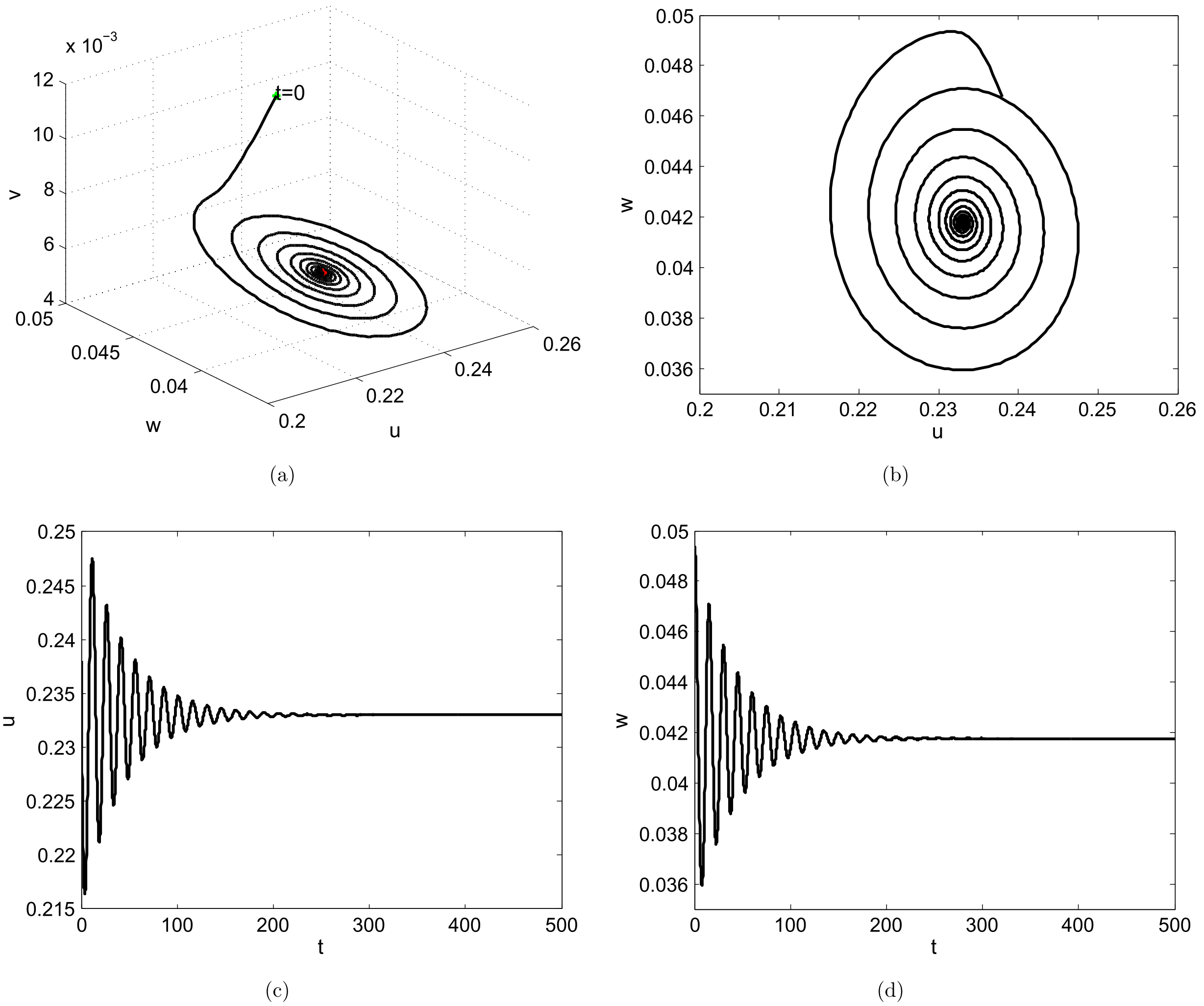


Fig. 3. Trajectories of system (1.5), when $\rho_1 = 20$. We have $\mathcal{R}_0 = 4.291666666$, and $\bar{E}$ is locally asymptotically stable, where $\bar{E} = (0.233009709, 0.041759907, 0.005567988)$.

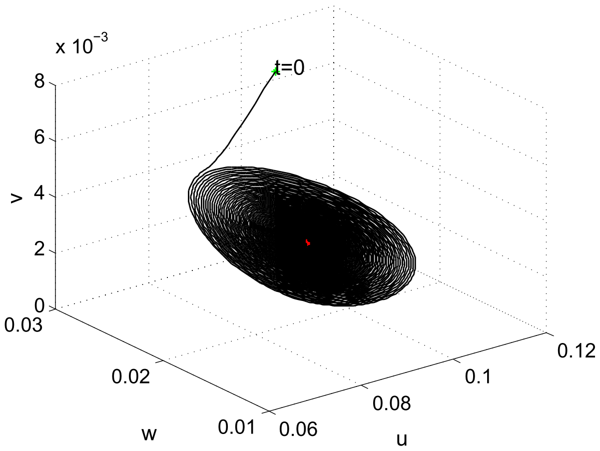
$$\begin{pmatrix} \bar{u} \\ \bar{w} \\ \bar{v} \end{pmatrix} = \begin{pmatrix} 0.08137178429 \\ 0.01824228214 \\ 0.002432304285 \end{pmatrix}, \qquad P = \begin{pmatrix} 0.9127757680 & 0.0000000000 & 0.4946210560 \\ 0.0025286175 & -0.4048829165 & -0.5771230032 \\ -0.0029139233 & -0.0538083311 & 0.6498300164 \end{pmatrix},$$

system (1.5) is transformed to

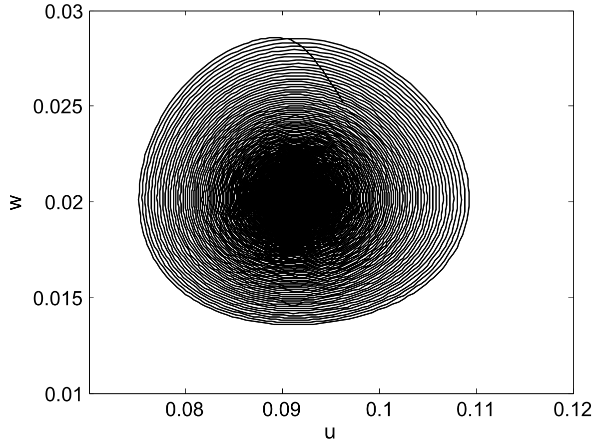
$$\frac{dx_i}{d\tau} = F_i(x_1, x_2, x_3; \varepsilon), \quad i = 1, 2, 3, \tag{6.2}$$

where

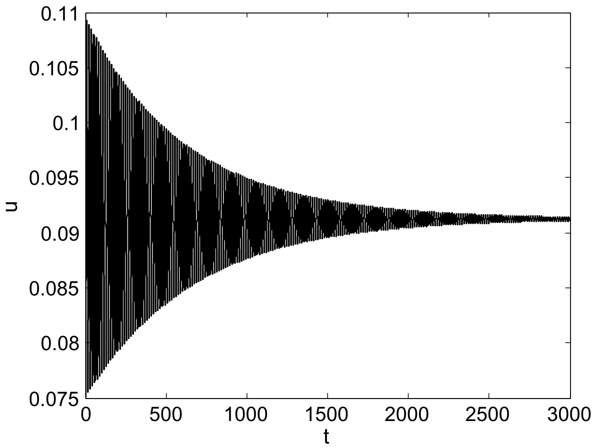
$$\begin{aligned} F_1 = {} & 0.4531462284x_2 + \varepsilon(-0.0001967387 - 0.0019711916x_1 + 0.0043523250x_2 \\ & - 0.053757844x_3) + \varepsilon\big(0.0488215521x_1x_2 - 0.5881732311x_1x_3 + 0.0264557501x_3x_2 \\ & + 0.0026438705x_1^2 - 0.3194996052x_3^2\big) + O(\varepsilon) \\ & - 0.0206649222x_1^2 - 46.2688096803x_1x_3 + 4.6229780433x_1x_2 \\ & - 25.0663848848x_3^2 + 2.5051303527x_3x_2, \end{aligned}$$



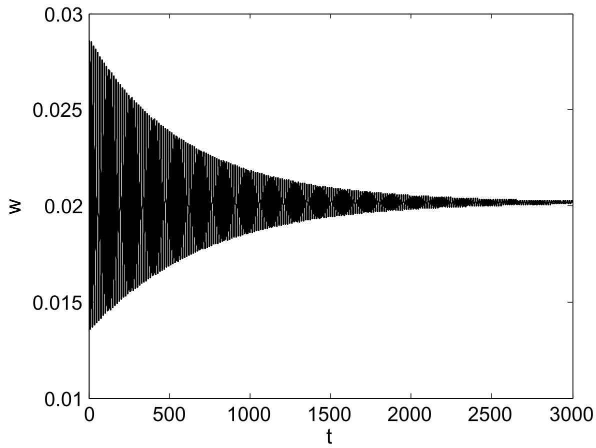
(a)



(b)



(c)



(d)

Fig. 4. Trajectories of system (1.5), when $\rho_1 = 70$. We have $\mathcal{R}_0 = 10.958333333$, and $\bar{E}$ is locally asymptotically stable, where $\bar{E} = (0.091254753, 0.020179391, 0.002690585)$.

$$
\begin{aligned}
F_2 = {} & -0.4531462284x_1 + \varepsilon(-0.0004372035 - 0.0043804908x_1 + 0.0096719770x_2 \\
& - 0.1194636492x_3) + \varepsilon\big(0.1084939488x_1x_2 - 1.3070710312x_1x_3 + 0.0587914287x_3x_2 \\
& + 0.0058753550x_1^2 - 0.7100096645x_3^2\big) + O(\varepsilon) \\
& + 0.4616677914x_1^2 - 102.6557485267x_1x_3 + 10.0041479776x_1x_2 \\
& - 55.7633503054x_3^2 + 5.4211148132x_3x_2, \\
F_3 = {} & -8.3881137969x_3 + \varepsilon(-0.0000370843 - 0.0003715599x_1 + 0.0008203919x_2 \\
& - 0.0101330897x_3) + \varepsilon\big(0.0092026229x_1x_2 - 0.1108677664x_1x_3 + 0.0049867790x_3x_2 \\
& + 0.0004983566x_1^2 - 0.0602241070x_3^2\big) + O(\varepsilon) \\
& + 0.0381351380x_1^2 - 8.7077514501x_1x_3 + 0.8491105307x_1x_2 \\
& - 4.7298128146x_3^2 + 0.4601217101x_3x_2.
\end{aligned}
$$

It is easy to see that the Jacobian matrix of system (6.2) at $x = (0, 0, 0)$ is in the Jordan canonical form

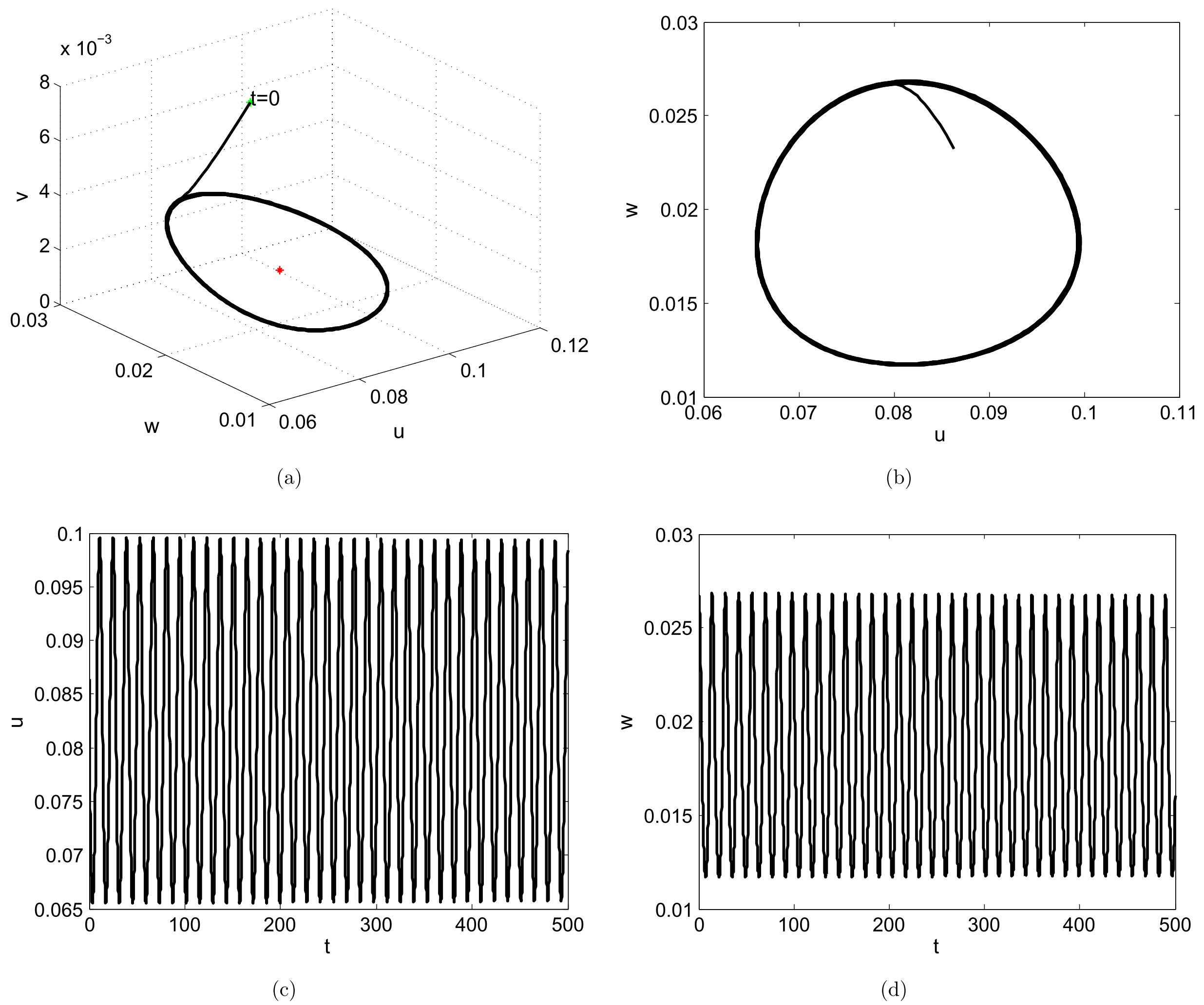


Fig. 5. Trajectories of system (1.5), when $\rho_1 = 80$. We have $\mathcal{R}_0 = 12.291666667$, and the Hopf bifurcation occurs at $\bar{E}$, and there is a stable limit cycle. Here $\bar{E} = (0.081355932, 0.018239128, 0.002431884)$.

$$J = \begin{pmatrix} 0 & 0.4531462284 & 0 \\ -0.4531462284 & 0 & 0 \\ 0 & 0 & -8.3881137969 \end{pmatrix}. \tag{6.3}$$

The general normal form can be written in polar coordinates as

$$\frac{dr}{d\tau} = r\big(\nu_0\varepsilon + \nu_1 r^2\big) + O\big(\varepsilon^2 r, \varepsilon r^3, r^5\big),$$
$$\frac{d\theta}{d\tau} = \omega_0 + \tau_0\varepsilon + \tau_1 r^2 + O\big(\varepsilon^2, \varepsilon r^2, r^4\big).$$

For system (6.2), $\omega_0 = 0.4531462284$ corresponds to the pair of the pure imaginary eigenvalues. ν_0 and τ_0 can be found from linear analysis. By the theory in [15], we have

$$\begin{aligned}\nu_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_1 \partial\varepsilon} + \frac{\partial^2 F_2}{\partial x_2 \partial\varepsilon}\right)\Bigg|_{\varepsilon=0,\, x_i=0} \\ &= (0.0048359885 + 0.0542469744x_1 + 0.0293957144x_3)|_{x_i=0} \\ &= 0.0048359885,\end{aligned}$$

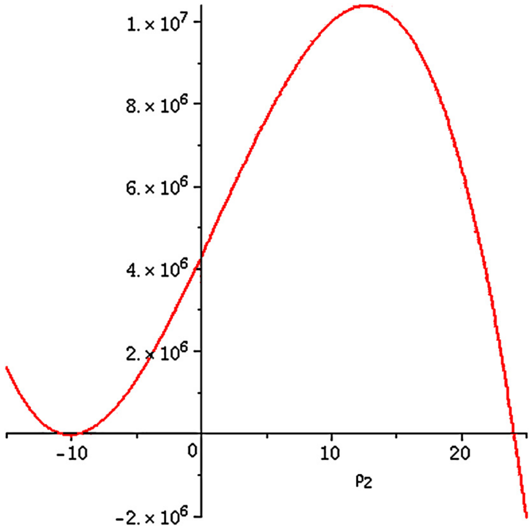


Fig. 6. The function $F(\rho_2)$ has only one positive root $\bar{\rho}_1 = 24.06639452$.

$$\begin{aligned}\tau_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_2 \partial \varepsilon} - \frac{\partial^2 F_2}{\partial x_1 \partial \varepsilon}\right)\bigg|_{\varepsilon=0,\, x_i=0} \\ &= (0.0021902454 - 0.0542469744x_2 + 0.6535355156x_3 - 0.0058753550x_1)|_{x_i=0} \\ &= 0.0021902454.\end{aligned}$$

On the other hand, ν_1 and τ_1 are determined by nonlinear analysis. Applying the Maple program developed in [13] to system (6.2), setting $\varepsilon = 0$, we obtain

$$\nu_1 = -0.09674296998, \qquad \tau_1 = -2.380920393.$$

Therefore, the normal form of the system (6.2) up to the third order is given by

$$\begin{aligned}\frac{dr}{d\tau} &= r\big(0.0048359885\varepsilon - 0.09674296998r^2\big), \\ \frac{d\theta}{d\tau} &= 0.4531462284 + 0.0021902454\varepsilon - 2.380920393r^2.\end{aligned} \tag{6.4}$$

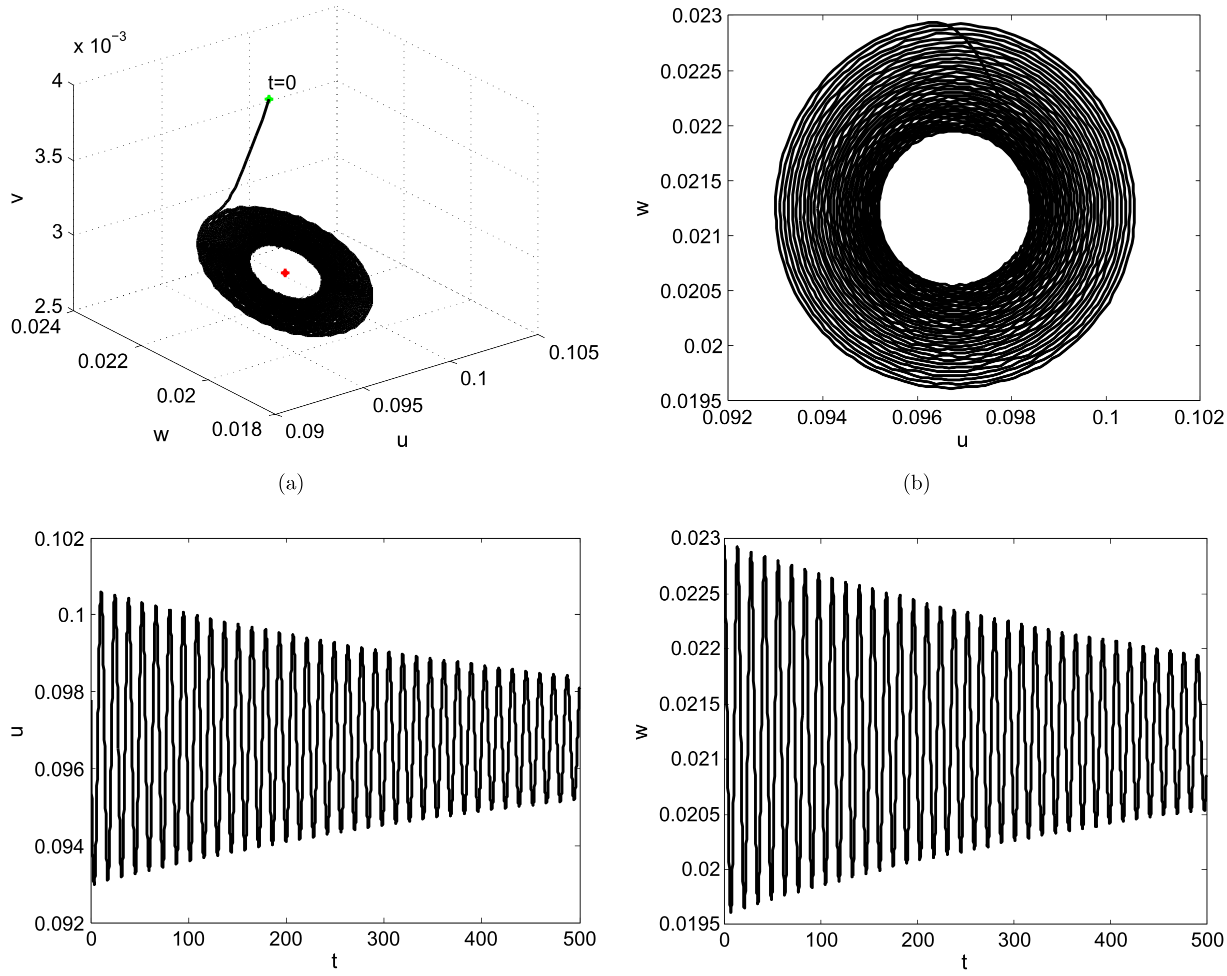
System (6.4) has equilibrium solutions $\bar{r} = 0$ and $\bar{r}^2 = 0.0499880095\varepsilon$. The solution $\bar{r} = 0$ corresponds to the equilibrium solution $\bar{E}$ of the original system (1.5). Linearization of the equation $dr/d\tau$ indicates that $\bar{r} = 0$ ($\bar{E}$) is stable for $\varepsilon < 0$, that is $\rho_1 < \bar{\rho}_1$. When ε increases from negative values and crosses zero, a Hopf bifurcation occurs and the amplitude of the periodic solution is given by

$$\bar{r} = 0.2235799845\sqrt{\varepsilon}, \quad \varepsilon > 0.$$

Since $\nu_1 < 0$, the Hopf bifurcation is supercritical and the bifurcation limit cycle is stable. The amplitude of the bifurcating limit cycle is $\bar{r} = 0.2235799845\sqrt{\varepsilon}$, and the frequency is

$$\omega = 0.4531462284 - 0.1168272258\varepsilon.$$

Similarly, if we fix $\delta = 0.25$, $\alpha = 1.2$, $\mu = 7.5$ and $\rho_1 = 70$, $F(\rho_2) = 0$ has only one positive root $\bar{\rho}_2 = 24.06639452$ (see Fig. 6) and two negative roots $\rho_2 = -9.466977953$ and $\rho_2 = -10.77608331$. Thus $\bar{\rho}_2 = 24.06639452$ is a critical value of bifurcation. When $0 \le \rho_2 < \bar{\rho}_2$, $\bar{E}$ is locally asymptotically stable



(a) (b) (c) (d)

Fig. 7. Trajectories of system (1.5), when $\rho_2 = 1$. We have $\mathcal{R}_0 = 10.333333333$, and $\bar{E}$ is locally asymptotically stable, where $\bar{E} = (0.096774194, 0.021235716, 0.002831429)$.

(see Fig. 7), while it is unstable if $\rho_2 \geq \bar{\rho}_2$. When $\rho_2 = \bar{\rho}_2$, there is a Hopf bifurcation, and a family of periodic solutions bifurcates from $\bar{E}$ (see Fig. 8).

Let $\rho_2 = \bar{\rho}_2 + \varepsilon$ and the linear transformation (6.1) with

$$\begin{pmatrix} \bar{u} \\ \bar{w} \\ \bar{v} \end{pmatrix} = \begin{pmatrix} 0.0299403637 \\ 0.0071963462 \\ 0.0009595128 \end{pmatrix}, \qquad P = \begin{pmatrix} -0.0074850909 & -0.7295387145 & -2.0958254600 \\ 0.2403560052 & -0.2794433946 & 2.0958254600 \\ 0 & 1 & -7.5000000000 \end{pmatrix},$$

then system (1.5) is transformed to

$$\frac{dx_i}{d\tau} = F_i(x_1, x_2, x_3; \varepsilon), \quad i = 1, 2, 3, \tag{6.5}$$

where

$$\begin{aligned} F_1 = {} & 0.4832999609x_2 + \varepsilon(-0.0002317009 - 0.0069984666x_1 + 0.0138985043x_2 \\ & + 0.0068913568x_3) + \varepsilon\big(0.2597749886x_1x_3 + 0.1053782781x_3x_2 - 0.0009634203x_1^2 \\ & + 0.0655698598x_3^2 + 0.4178786217x_1x_2\big) + O(\varepsilon) \end{aligned}$$

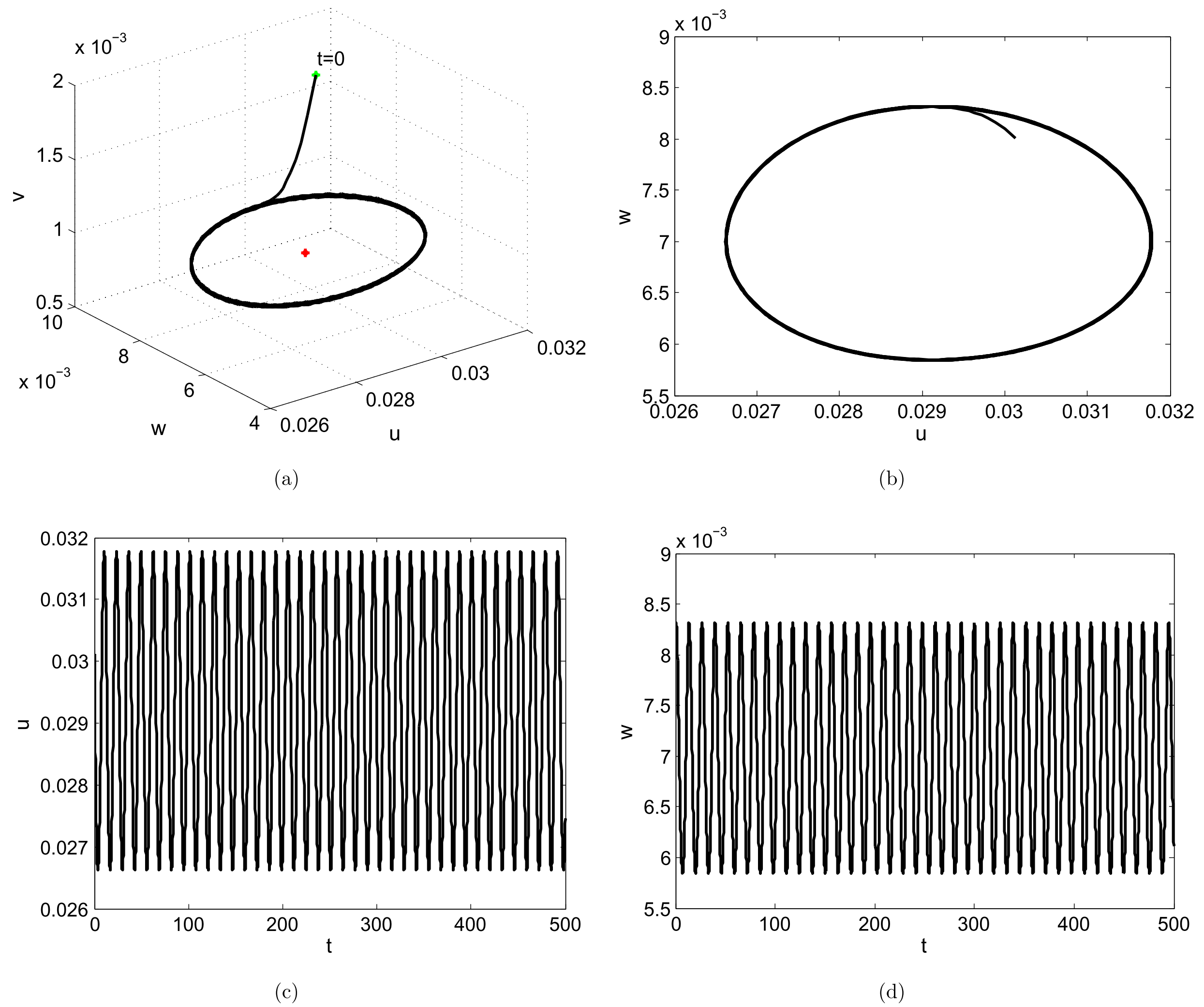


Fig. 8. Trajectories of system (1.5), when $\rho_2 = 25$. We have $\mathcal{R}_0 = 34.333333333$, and the Hopf bifurcation occurs at $\bar{E}$, and there is a stable limit cycle. Here $\bar{E} = (0.029126214, 0.007008232, 0, 0009344309783)$.

$$
\begin{aligned}
&- 0.0069840861x_1^2 - 57.1550777084x_1x_3 + 14.0708577570x_1x_2\\
&- 14.4126015770x_3^2 + 3.5483096890x_3x_2,\\
F_2 = {} & -0.4832999610x_1 + \varepsilon(-0.0004807986 - 0.0145223983x_1 + 0.0288405483x_2\\
&+ 0.0143001366x_3) + \varepsilon\big(0.5390546324x_1x_3 + 0.2186686613x_3x_2 - 0.0019991770x_1^2\\
&+ 0.1360628938x_3^2 + 0.8671327754x_1x_2\big) + O(\varepsilon)\\
&+ 0.4526901833x_1^2 - 118.5331112012x_1x_3 + 28.9297201243x_1x_2\\
&- 29.9198000655x_3^2 + 7.2953339441x_3x_2,\\
F_3 = {} & -7.7869284856x_3 + \varepsilon(-0.0000303249 - 0.0009159543x_1 + 0.0018190263x_2\\
&+ 0.0009019358x_3) + \varepsilon\big(0.0339991640x_1x_3 + 0.0137918334x_3x_2 - 0.0001260918x_1^2\\
&+ 0.0085817362x_3^2 + 0.0546916540x_1x_2\big) + O(\varepsilon)\\
&+ 0.0276954677x_1^2 - 7.4762260736x_1x_3 + 1.8251427125x_1x_2\\
&- 1.8870738072x_3^2 + 0.4602542135x_3x_2.
\end{aligned}
$$

It is easy to see that the Jacobian matrix of system (6.5) at $x = (0, 0, 0)$ is in the Jordan canonical form

$$J = \begin{pmatrix} 0 & 0.4832999610 & 0 \\ -0.4832999610 & 0 & 0 \\ 0 & 0 & -7.7869284856 \end{pmatrix}. \tag{6.6}$$

For system (6.5), $\omega_0 = 0.4832999610$ corresponds to the pair of the pure imaginary eigenvalues. ν_0 and τ_0 can be derived from linear analysis similarly to the previous case, then we have

$$\begin{aligned}
\nu_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_1 \partial \varepsilon} + \frac{\partial^2 F_2}{\partial x_2 \partial \varepsilon}\right)\bigg|_{\varepsilon=0,\, x_i=0} \\
&= (0.0144202741 + 0.1093343306 x_3 + 0.4335663877 x_1)|_{x_i=0} \\
&= 0.0144202741, \\
\tau_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_2 \partial \varepsilon} - \frac{\partial^2 F_2}{\partial x_1 \partial \varepsilon}\right)\bigg|_{\varepsilon=0,\, x_i=0} \\
&= (0.0072611992 - 0.2695273162 x_3 + 0.0019991770 x_1 - 0.4335663877 x_2)|_{x_i=0} \\
&= 0.0072611992.
\end{aligned}$$

On the other hand, ν_1 and τ_1 are determined by nonlinear analysis. Applying the Maple program developed in [13] to system (6.2) again, setting $\varepsilon = 0$, we obtain

$$\nu_1 = -0.2039007979, \qquad \tau_1 = -21.07423997.$$

Therefore, the normal form of the system up to the third order is given by

$$\begin{aligned}
\frac{dr}{d\tau} &= r\big(0.0144202741\varepsilon - 0.2039007979 r^2\big), \\
\frac{d\theta}{d\tau} &= 0.4832999610 + 0.0072611992\varepsilon - 21.07423997 r^2.
\end{aligned} \tag{6.7}$$

System (6.7) has equilibrium solutions $\bar{r} = 0$ and $\bar{r}^2 = 0.2039007979\varepsilon$. The solution $\bar{r} = 0$ corresponds to the equilibrium solution $\bar{E}$ of the original system (1.5). Linearization of the equation $dr/d\tau$ indicates that $\bar{r} = 0$ ($\bar{E}$) is stable for $\varepsilon < 0$, that is $\rho_2 < \bar{\rho}_2$. When ε increases from negative to cross zero, a Hopf bifurcation occurs and the amplitude of the periodic solution is

$$\bar{r} = 0.2659360998\sqrt{\varepsilon}, \quad \varepsilon > 0.$$

Since $\nu_1 < 0$, the Hopf bifurcation is supercritical and the bifurcation limit cycle is stable. The amplitude of the bifurcating limit cycle is $\bar{r} = 0.2235799845\sqrt{\varepsilon}$, and the frequency is

$$\omega = 0.4832999610 - 1.4831513940\varepsilon.$$

7. Conclusion and discussion

In this paper, we considered the direct cell-to-cell transfer of HIV-1 in addition to cell-free virus transmission by mathematical modeling. We found that the basic reproduction number $\mathcal{R}_0$ is larger than that of previous models which just considered cell-free virus spread mode. In fact, $\mathcal{R}_0$ is the sum of the basic reproduction number determined by cell-free virus infection, $\mathcal{R}_{01}$, and that determined by cell-to-cell infection, $\mathcal{R}_{02}$. When applying models considering only cell-to-cell transmission or infection by cell-free viruses to experimental data, parameters are always estimated to be an average of the effect of both modes of transmission. Thus, the estimate of $\mathcal{R}_0$ based on a model neglecting cell-to-cell transmission is not the exact basic reproductive number of the model with infection by cell-free mode, but an average of both modes of infections.

When only cell-free spread of HIV-1 is considered, we have $\beta_2 = 0$ in (1.4), and the model (1.4) becomes the model (1.2) with $\gamma = 0$ or the model considered in [5]. We see from the analysis in [5] that the basic reproduction number is $\mathcal{R}_{01} = \frac{T_M \beta_1 \gamma}{d_{T^*} d_V}$. When $\mathcal{R}_{01} < 1$, the infection cannot establish. When $\mathcal{R}_{01} > 1$, the infection can persist, and for some large β_1 the Hopf bifurcation occurs, that is a family of periodic solutions bifurcates from the positive equilibrium $\bar{E}$. This property is very similar to the case when cell-to-cell transfer is considered simultaneously. However, the basic reproduction number $\mathcal{R}_{01}$ is only a part of $\mathcal{R}_0$, the basic reproduction number of (1.4), that is, the case when both transmission modes exist. On the other hand, we see from Fig. 1 that the bifurcation critical point $\bar{\rho}_1$ decreases as $\bar{\rho}_2$ increases. Therefore, the bifurcation critical point $\bar{\beta}_1$ decreases as $\bar{\beta}_2$ increases. That means the periodic solution occurs for smaller infection rate of cell-free mode β_1, when cell-to-cell transfer establishes compared with the case when only cell-free mode is considered.

In contrast, when only cell-to-cell transfer is considered, $\beta_1 = 0$ in (1.4). We know from the analysis in [2] that the basic reproduction number is $\mathcal{R}_{02} = \frac{T_M \beta_2}{d_{T^*}}$. The infection cannot establish if $\mathcal{R}_{02} < 1$, while it persists if $\mathcal{R}_{02} > 1$. Furthermore, the positive equilibrium $\bar{E}$ is stable if $\mathcal{R}_{02} > 1$, and there are no Hopf bifurcation and periodic solutions. Since $\mathcal{R}_{02}$ is only a part of $\mathcal{R}_0$, the basic reproduction number is also underestimated when only the cell-to-cell mode is considered. The dynamical behavior of the system is very different from the case when both infection modes are considered where the Hopf bifurcation and periodic solutions occur for some values of infection rates β_1 and β_2, that is, for some ρ_1 and ρ_2.

The nonlinear term, say the logistic growth of target cells, leads to the Hopf bifurcation and periodic solutions of the system for some range of parameter values. With stable periodic solutions, the concentration of infected cells and virus load cannot stabilize at a constant level, but show oscillations. This is important for experimental or clinic estimation of virus load. Due to the periodic oscillation, lower (or higher) virus load detected at a moment does not indicate the same lower (or higher) load for a long time. The oscillations of viral load levels in the plasma are also plausible under the effects of immune responses or delays in the virus infection dynamics [1].

In the model (1.5), we do not consider any delay effects, such as the delay from the time of initial infection until the production of new virions. Culshaw et al. [2] considered this delay for the cell-to-cell infection model and found that there is a Hopf bifurcation for some critical values of the delay time. For the model (1.5), if we consider delay effects, there may be Hopf bifurcations for some delay time. This needs further study.

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