Modeling and analysis of recurrent autoimmune disease

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A R T I C L E   I N F O

A B S T R A C T

In this paper, we consider dynamics and bifurcations in two HIV models with cell-to-cell interaction. The difference between the two models lies in the inclusion or omission of the effect of involvement. Particular attention is focused on the effects due to the cell-to-cell transmission and the effect of the involvement. We investigate the local and global stability of equilibria of the two models and give a comparison. We derive the existence condition for Hopf bifurcation and prove no Bogdanov-Takens bifurcation in this system. In particular, we show that the system exhibits the recurrence phenomenon, yielding complex dynamical behavior. It is also shown that the effect of the involvement is the main cause of the periodic symptoms in HIV or malaria disease. Moreover, it is shown that the increase of cell-to-cell interaction may be the main factor causing Hopf bifurcation to disappear, and thus eliminating oscillation behavior. Finally, numerical simulations are present to demonstrate our theoretical results.

1. Introduction

Many mathematical models have been developed for modeling HIV diseases in order to find the method for efficient medical treatments. In general, there are two fundamental modes of viral infection and transmission, one is the classical virus-to-cell infection and the other is direct cell-to-cell transmission. In the classical mode, viral particles that are released from infected cells arbitrarily move around to discover a new target cell to infect. For the direct cell-to-cell transmission, on the other hand, HIV infection can occur through moving viruses with the direct contact between infected cells and uninfected cells via some structures, such as membrane nanotubes [1]. Recently, HIV infection models which involve different infection modes, such as the classical virus-to-cell infection [2–7], the direct cell-to-cell transmission [8–10], and both virus-to-cell infection and cell-to-cell transmission [9,11–19], have been extensively studied by many scholars. However, recent

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studies have also revealed that the cell-to-cell (infected source and a susceptible target cell) interaction is vital to the spread of virus, which is even more effective than that of the virus-to-cell mechanism. For example, the results in [20,21] show that the cell-to-cell spread is a much more important mode of infection than the virus-to-cell spread. The data reported in [22] indicate that the cell-to-cell spread of HIV is the predominant route of viral spread since viral replication in a system with rapid cell turnover kinetics depends on the cell-to-cell transfer of virus. In the process of cell-to-cell interaction, viral particles can be simultaneously transferred from infected $CD4^+T$ cells to uninfected ones by virological synapses. Thus, there is no doubt that the cell-to-cell infection affects the mechanism of HIV transmission. When pathogens get into blood, the B cells are activated and secrete antibody, and then the immune system removes pathogens from blood with the aid of antibody. Uninfected cells can be reduced when immune complexes are combined into the model, because uninfected cells can be involved in the immune response to pathogens. We call it the effect of involvement. For example, in malaria infection, the effect of the "involvement" is regarded as one of the causes of anaemia [23]. However, it has been noticed that most of the publications mainly focus on the virus-to-cell infection and the cell-to-cell transmission. To the best of our knowledge, only few papers have investigated the effect of the involvement in HIV models [23,24], especially the interaction between the cell-to-cell spread and the effect of the involvement.

In this paper, we will study both the cell-to-cell infection and the effect of the involvement in HIV models and find their relations, by investigating the dynamics and bifurcations of the equilibria or steady states in two mathematical systems which describe virus-immune dynamics of HIV models. One important object in the study of biological systems is to identify the conditions under which the solutions of the system eventually approach a steady state or a periodic oscillation. As we all know, if a positive equilibrium of the model is stable, then the disease will persist and approach a steady state. Alternatively, Hopf bifurcation may occur, leading to the disease oscillating periodically.

Let us start from a simple HIV model, which ignores the loss of pathogens due to absorption, described by the following ordinary differential equations [25]:

$$\begin{aligned} \dot{T} &= s - d_1 T - \beta_1 TV, \\ \dot{I} &= \beta_1 TV - \delta I, \\ \dot{V} &= kI - d_2 V, \end{aligned} \tag{1}$$

where T, I and V respectively represent the densities of the uninfected $CD4^+T$ cells, the infected $CD4^+T$ cells and the immunodeficiency virus (HIV) in blood. The $\beta_1 TV$ term measures the effect due to the virus-to-cell transmission. Uninfected cells are recruited at a constant rate s from the source within the body, just like bone marrow, with the natural life expectancy of $1/d_1$ (days). Cells are infected by contact with pathogens, and turned to become infected cells at rate $\beta_1 V$. Infected cells die at rate δ, resulting in the release of k/δ pathogens per infected cell, and these pathogens have a life-expectancy $1/d_2$ (days) in the blood. Pathogens will either die or affect healthy cells. The parameters s, d_1, β_1, δ, k and d_2 are all positive.

As we know, the humoral immunity is the aspect of immunity that is mediated by macromolecules found in extracellular fluids such as secreted antibodies, complement proteins, and certain antimicrobial peptides, which is often called antibody-mediated immunity. It plays an important role in adaptive immune response in HIV infection processes [1], especially it is more effective than cell-mediated immunity in malaria infection. Thus, the effect of humoral immunity was introduced into model (1), yielding the following model [24]:

$$\begin{aligned} \dot{T} &= s - d_1 T - \beta_1 TV, \\ \dot{I} &= \beta_1 TV - \delta I, \\ \dot{V} &= kI - d_2 V - pAV, \\ \dot{A} &= qAV - d_3 A, \end{aligned} \tag{2}$$

where A represents the density of pathogens-specific lymphocytes, p is the killing rate, and d_3 is the death rate of pathogens-specific lymphocytes. The term pAV is the loss rate of virus under the attack of pathogens-specific lymphocytes, and the pathogens are removed at rate pA by the immune system. The pathogens-specific lymphocytes proliferate at rate qV by contact with the pathogens and die at rate d_3. Note that this model considers the humoral immunity instead of cell-mediated immunity.

As discussed above, the effects of both the humoral immunity and the cell-to-cell interaction should be included in a model for a more realistic study, we consider the following model:

$$
\begin{aligned}
\dot{T} &= s - d_1 T - \beta_1 TV - \beta_2 TI, \\
\dot{I} &= \beta_1 TV + \beta_2 TI - \delta I, \\
\dot{V} &= kI - d_2 V - pAV, \\
\dot{A} &= qAV - d_3 A,
\end{aligned}
\tag{3}
$$

where the $\beta_2 TI$ term represents the effect due to the cell-to-cell interaction and $\beta_2 \geqslant 0$. The rest of parameters are the same as those in model (2). Local and global stability, bifurcation of its equilibria, including the role of the cell-to-cell interaction, will be investigated by using linearization, Lyapunov function and fluctuation lemma in this paper.

Suppose that the density of the immune complex is proportional to the product of the densities of the pathogens and the pathogens-specific lymphocytes [24]. Then, the uninfected cells are reduced at the rate proportional to the product of the densities of the uninfected cells and the immune complex. Murase et al. [24] have incorporated the effect of involvement into system (2), by introducing the $-\gamma TVA$ term in the first equation of (2), to obtain the following system:

$$
\begin{aligned}
\dot{T} &= s - d_1 T - \beta_1 TV - \gamma TVA, \\
\dot{I} &= \beta_1 TV - \delta I, \\
\dot{V} &= kI - d_2 V - pAV, \\
\dot{A} &= qAV - d_3 A,
\end{aligned}
\tag{4}
$$

and studied the stability of its equilibria and the existence of Hopf bifurcation.

From the above discussions we also know that both the cell-to-cell transmission and the effect of cells involving immune response are very important in establishing and analyzing HIV models. Thus, in this paper, we will further consider the combination of the interaction between the cell-to-cell transmission and the effect of involvement, yielding the following model:

$$
\begin{aligned}
\dot{T} &= s - d_1 T - \beta_1 TV - \beta_2 TI - \gamma TVA, \\
\dot{I} &= \beta_1 TV + \beta_2 TI - \delta I, \\
\dot{V} &= kI - d_2 V - pAV, \\
\dot{A} &= qAV - d_3 A.
\end{aligned}
\tag{5}
$$

Stability and bifurcations related to both the cell-to-cell transmission and the effect of the involvement will be studied in detail in this paper, including the occurrence of Hopf bifurcation and the feature of bifurcating limit cycles.

In order to have a comparison, in this paper, we will consider the role of the cell-to-cell transmission and the humoral immune response in the two HIV models (3) and (5), with the effect of involvement included. Stability and bifurcation analysis are carried out to study the two models with respect to the basic reproduction number R_0. It will be shown that model (3) can have only transcritical bifurcations between equilibria, while model (5) can exhibit not only transcritical bifurcations, but also Hopf and generalized Hopf bifurcations. In fact, it will be shown that both systems (3) and (5) have three equilibrium solutions

Table 1
Description of the parameters in models (3) and (5).

Parameter	Description	Value	Unit	Reference
s	Recruitment rate of uninfected CD4$^+$T cells	1	$\mu\mathrm{l}^{-1}\,\mathrm{day}^{-1}$	[24,26,27]
d_1	Natural death rate of CD4$^+$T cells	0.00833	day^{-1}	[24,26,27]
β_1	Infection coefficient	0.1	$\mu\mathrm{l}\,\mathrm{day}^{-1}$	[24,26]
β_2	The infection rate of productively infected CD4$^+$T cells	0.0064	$\mu\mathrm{l}\,\mathrm{day}^{-1}$	[17,24]
δ	Death rate of infected cells	0.5	day^{-1}	[24,26]
k	Product of the number of free virus particles and δ	8	day^{-1}	[24,26]
d_2	Clearance rate of virus particles	72	day^{-1}	[24,26]
p	Killing rate of pathogens	0.1	$\mu\mathrm{l}\,\mathrm{day}^{-1}$	[24,26]
q	Growth rate of humoral immune response ($\mu\mathrm{l}\,\mathrm{day}^{-1}$)	Bifurcation parameter		[24,26]
d_3	Death rate of lymphocytes	0.05	day^{-1}	[24,26]
γ	Proportional death rate of T, V and A	0.05	$\mu\mathrm{l}^2\,\mathrm{day}^{-1}$	[24]

E_k $(k = 1, 2, 3)$ and $\hat{E}_k$ $(k = 1, 2, 3)$ with $\hat{E}_k = E_k$, $k = 1, 2$. For system (3) there only exist transcritical bifurcations between E_1 and E_2, as well as between E_2 and E_3; while for system (5), besides these two transcritical bifurcations, there is also a Hopf bifurcation which occurs from the equilibrium $\hat{E}_3$ at a critical point. This shows that the cell involvement in immune system can cause complex dynamics, and shows how it affects the system's behavior as well as what is the implication of biological importance.

The typical parameter values used in the literature for models (3) and (5) are listed in Table 1. In our simulations, these parameter values will be used to demonstrate more realistic theoretical results obtained in this paper.

To simplify the analysis in the following sections, we introduce the changes of state variables and the time rescaling:

$$T = \frac{d_3^2}{k\beta_1}\,x_1, \quad I = \frac{d_3^2}{k\beta_1}\,x_2, \quad V = \frac{d_3}{\beta_1}\,x_3, \quad A = \frac{qd_3}{p\beta_1}\,x_4, \quad \tau = d_3\,t, \tag{6}$$

into models (3) and (5) to obtain the following dimensionless systems:

$$\begin{aligned}
\dot{x}_1 &= S - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3, \\
\dot{x}_2 &= D_2 x_1 x_2 + x_1 x_3 - D_4 x_2, \\
\dot{x}_3 &= x_2 - D_5 x_3 - D_6 x_3 x_4, \\
\dot{x}_4 &= D_6 x_3 x_4 - x_4.
\end{aligned} \tag{7}$$

and

$$\begin{aligned}
\dot{x}_1 &= S - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3 - D_3 x_1 x_3 x_4, \\
\dot{x}_2 &= D_2 x_1 x_2 + x_1 x_3 - D_4 x_2, \\
\dot{x}_3 &= x_2 - D_5 x_3 - D_6 x_3 x_4, \\
\dot{x}_4 &= D_6 x_3 x_4 - x_4.
\end{aligned} \tag{8}$$

respectively, where for convenience the dot is still used for differentiation with respect to the new scaled time τ, and the new parameters are defined as

$$S = \frac{sk\beta_1}{(d_3)^3}, \quad D_1 = \frac{d_1}{d_3}, \quad D_2 = \frac{\beta_2 d_3}{k\beta_1}, \quad D_3 = \frac{\gamma q d_3}{p(\beta_1)^2}, \quad D_4 = \frac{\delta}{d_3}, \quad D_5 = \frac{d_2}{d_3}, \quad D_6 = \frac{q}{\beta_1}. \tag{9}$$

According to Table 1, the typical values of the above new parameters are given by

$$\begin{aligned}
D_1 &= \tfrac{d_1}{d_3} = 0.1666, \quad D_2 = \tfrac{\beta_2 d_3}{\beta_1 k} = 0.0004, \quad D_3 = \tfrac{d_3 q\gamma}{p(\beta_1)^2} = 2.5q = 1.25, \\
D_4 &= \tfrac{\delta}{d_3} = 10, \qquad\quad D_5 = \tfrac{d_2}{d_3} = 1440, \qquad\quad S = \tfrac{\beta_1 ks}{(d_3)^3} = 6400, \qquad\qquad D_6 = \tfrac{q}{\beta_1} = 10,
\end{aligned} \tag{10}$$

where D_6 or q is treated as the primary bifurcation parameter.

It is seen from (7) and (8) that simply setting $D_3 = 0$ in system (8) results in system (7), showing the direct relation between these two models.

The rest of the paper is organized as follows. In Section 2, a complete bifurcation analysis is given for model (7) (or the original model (3)), and then bifurcation analysis on model (8) (or the original model (5)) is presented in Section 3. Detailed Hopf bifurcation on model (8) is given in Section 4. Moreover, it is shown that no Bogdanov-Takens bifurcation can exist for this model. Forward bifurcation is discussed in Section 5, and finally conclusion and discussion are drawn in Section 6.

2. The effect of cell-to-cell interaction in model (7)

In this section, we consider model (7) and pay attention to the immune response against pathogens, with only humoral immunity involved. First, we show the well-posedness of solutions of system (7), as stated in the following theorem.

Theorem 2.1. *All solutions of system* (7) *are non-negative if the initial conditions are non-negative. Moreover, they are bounded.*

Proving the positivity of solutions needs the following lemma.

Lemma 2.2 (*Proposition 1.1 in [28]*)**.** *The cone* R_n^+ *is invariant for the flow generated by the differential equation,* $\frac{dx}{dt} = f(x)$, *if and only if the function* $f(x)$ *is quasi-positive, i.e., for every* $i = 1, 2, \ldots, n$, *the function* $f_i(x_1, \ldots, 0, \ldots, x_n) \geqslant 0$, *where* 0 *stands at the ith position and* $x_j \geqslant 0$ *for* $j \neq i$.

Proof. It is straightforward to verify that system (7) satisfies the conditions given in Lemma 2.2 and thus the first statement in Theorem 2.1 is proved. To prove the boundness of the solutions, we construct a Lyapunov function $V_1(x) = x_1 + x_2 + \frac{D_4}{2}(x_3 + x_4)$, which satisfies $V_1 > 0$ for $x > 0$ and $V_1(0) = 0$. Here, $x = (x_1, x_2, x_3, x_4)^T$ and $x > 0$ means that $x_i > 0$, $i = 1, 2, 3, 4$. Note that $x_4 = 0$ is invariant. Then, differentiating V_1 with respect to τ, and using system (7), we obtain

$$\frac{dV_1}{d\tau}\bigg|_{(7)} = S - D_1 x_1 - \frac{D_4}{2} x_2 - \frac{D_4 D_5}{2} x_3 - \frac{D_4}{2} x_4.$$

Thus,

$$\frac{dV_1}{d\tau}\bigg|_{(7)} < 0, \quad \text{for} \quad \left\{ x \,\middle|\, D_1 x_1 + \frac{D_4}{2} x_2 + \frac{D_4 D_5}{2} x_3 + \frac{D_4}{2} x_4 - S \equiv \Pi_1 > 0 \right\};$$

and $\frac{dV_1}{d\tau}\big|_{(7)} = 0$ on the plane $\Pi_1 = 0$.

Obviously, the plane $\Pi_1 = 0$ intersects the x_i-axis $(i = 1, 2, 3, 4)$ at $\frac{S}{D_1}$, $\frac{2S}{D_4}$, $\frac{2S}{D_4 D_5}$ and $\frac{2S}{D_4}$, respectively. Similarly, the plane $V_1 = C$ intersects the x_i-axis $(i = 1, 2, 3, 4)$ at C, C, $\frac{2C}{D_4}$ and $\frac{2C}{D_4}$, respectively, where C is an arbitrary positive constant. In order to guarantee that the plane $\Pi_1 = 0$ is inside the plane $V_1 = C$ (which implies that the region bounded by the plane $V_1 = C$ and the three coordinate planes is attractive), we define the plane,

$$\Pi = \left\{ x \,\middle|\, x_1 + x_2 + \frac{D_4}{2}(x_3 + x_4) - \bar{C} = 0 \right\},$$

where $\bar{C} = S \max\{\frac{1}{D_1}, \frac{2}{D_4}, \frac{1}{D_5}, 1\}$, so that in the cone R_+^4, all solutions of system (7) are attracted into the trapping region Ω bounded by the four coordinate planes and the plane Π. $\square$

It is easy to show that system (7) has three equilibria:

Infection-free equilibrium　E_1 : 　$\left(\frac{S}{D_1}, 0, 0, 0\right)$,

Infectious equilibrium　　E_2 : 　$\left(\frac{D_4 D_5}{1+D_2 D_5}, \frac{1}{D_4}\left(S - \frac{D_1 D_4 D_5}{1+D_2 D_5}\right), \frac{1}{D_4 D_5}\left(S - \frac{D_1 D_4 D_5}{1+D_2 D_5}\right), 0\right),$ 　　(11)

Positive equilibrium　　　E_3 : 　$\left(\frac{S - D_4 \tilde{x}_2}{D_1}, \tilde{x}_2, \frac{1}{D_6}, \tilde{x}_2 - \frac{D_5}{D_6}\right),$

where $\tilde{x}_2$ is determined from the quadratic equation:

$$D_2 D_4 D_6 \tilde{x}_2^2 - \left[S D_2 D_6 - D_4(1 + D_1 D_6)\right]\tilde{x}_2 - S = 0, \tag{12}$$

and so

$$\tilde{x}_2 = \frac{1}{2 D_2 D_4 D_6}\left\{S D_2 D_6 - D_4(1 + D_1 D_6) + \sqrt{\left[S D_2 D_6 - D_4(1 + D_1 D_6)\right]^2 + 4 S D_2 D_4 D_6}\right\}. \tag{13}$$

Note in the above expression that only positive sign is taken for the square root, since the negative root yields $\tilde{x}_2 < 0$.

The equilibrium E_2 indicates that the pathogens are present while the lymphocytes are absent. It is easy to see that E_2 exists for $S \geqslant \frac{D_1 D_4 D_5}{1+D_2 D_5}$.

The third equilibrium E_3 is an interior positive solution, implying that both the pathogens and the lymphocytes are present. To find the existence condition of E_3, note that the solution $\tilde{x}_2$ given in (13) is positive, we only need to consider the condition $\tilde{x}_2 \geqslant \frac{D_5}{D_6}$ (see E_3 in (11)), which is equivalent to $S \geqslant \frac{D_1 D_4 D_5}{1+D_2 D_5} + \frac{D_4 D_5}{D_6}$, as shown below. First note that

$$\tilde{x}_2 \geqslant \frac{D_5}{D_6}$$
$$\Longleftrightarrow \quad \sqrt{\left[S D_2 D_6 - D_4(1 + D_1 D_6)\right]^2 + 4 S D_2 D_4 D_6} - \left[D_4(1 + D_1 D_6 + 2 D_2 D_5) - S D_2 D_6\right] > 0.$$

If $S \geqslant \frac{D_4(1+D_1 D_6 + 2 D_2 D_5)}{D_2 D_6}$, E_3 exists. If $S < \frac{D_4(1+D_1 D_6 + 2 D_2 D_5)}{D_2 D_6}$, then a direct calculation shows that the above inequality is equivalent to

$$S \geqslant \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}. \tag{14}$$

Noticing that $\frac{D_1 D_4 D_5}{1+D_2 D_5} + \frac{D_4 D_5}{D_6} < \frac{D_4(1+D_1 D_6 + 2 D_2 D_5)}{D_2 D_6}$, we know that E_3 exists if the condition (14) is satisfied.

Summarizing the above results shows that the equilibrium E_1 exists for any positive parameter values, E_2 exists for $S \geqslant \frac{D_1 D_4 D_5}{1+D_2 D_5}$ and E_3 exists for $S \geqslant \frac{D_1 D_4 D_5}{1+D_2 D_5} + \frac{D_4 D_5}{D_6}$. Next, we turn to consider stability of these equilibria, on the basis of the Jacobian matrix $J(E_k), k = 1, 2, 3$ of (7), given by

$$J(E_k) = \begin{bmatrix} -D_1 - D_2 x_2 - x_3 & -D_2 x_1 & -x_1 & 0 \\ D_2 x_2 + x_3 & D_2 x_1 - D_4 & x_1 & 0 \\ 0 & 1 & -D_5 - D_6 x_4 & -D_6 x_3 \\ 0 & 0 & D_6 x_4 & D_6 x_3 - 1 \end{bmatrix}. \tag{15}$$

Theorem 2.3. *The infection-free equilibrium* E_1 *of system* (7) *is asymptotically stable if* $S < \frac{D_1 D_4 D_5}{1+D_2 D_5}$; *when* $S > \frac{D_1 D_4 D_5}{1+D_2 D_5}$, E_1 *is unstable, implying that pathogens may persist.*

Proof. Evaluating the Jacobian matrix (15) at the infection-free equilibrium E_1 results in the characteristic polynomial,

$$P_1(\lambda) = \det\left[\lambda I - J(E_1)\right] = (\lambda + 1)(\lambda + D_1)\left[\lambda^2 + \left(D_4 + D_5 - \frac{D_2}{D_1}S\right)\lambda + D_4 D_5 - \frac{(1+D_2 D_5)S}{D_1}\right].$$

Hence, E_1 is asymptotically stable if $S < \frac{D_1}{D_2}(D_4 + D_5)$ and $S < \frac{D_1 D_4 D_5}{1+D_2 D_5}$. Note that the second inequality $S < \frac{D_1 D_4 D_5}{1+D_2 D_5}$ implies $S < \frac{D_1}{D_2}(D_4 + D_5)$. Thus, E_1 is asymptotically stable for $S < \frac{D_1 D_4 D_5}{1+D_2 D_5}$, and unstable for $S > \frac{D_1 D_4 D_5}{1+D_2 D_5}$. □

From the above stability condition of the infection-free equilibrium E_1, we can see that HIV becomes effective at $S = \frac{D_1 D_4 D_5}{1 + D_2 D_5}$ or $\frac{S(1 + D_2 D_5)}{D_1 D_4 D_5} = 1$. Thus, we may define the basic reproduction number [29] for system (7) as

$$\mathcal{R}_0 = \frac{S(1 + D_2 D_5)}{D_1 D_4 D_5}. \tag{16}$$

Thus,

$$\mathcal{R}_0 \lessgtr 1 \iff S \lessgtr \frac{D_1 D_4 D_5}{1 + D_2 D_5},$$

and we will alternatively use them in the following analysis for convenience.

In the following we prove that E_1 is also globally asymptotically stable if $\mathcal{R}_0 \leqslant 1$. It should be noted here that the global stability means that all trajectories converge to E_1 as long as the initial points are located in the cone R_+^4. This applies to all the global stability in the rest of the paper.

Theorem 2.4. *The infection-free equilibrium E_1 of system (7) is globally asymptotically stable if $\mathcal{R}_0 \leqslant 1$.*

Proof. Consider the following Lyapunov function,

$$V_2(x) = x_1 - \frac{S}{D_1} - \frac{S}{D_1} \ln\left(\frac{D_1}{S} x_1\right) + x_2 + \frac{S}{D_1 D_5}(x_3 + x_4),$$

which satisfies $V_2(E_1) = 0$. Differentiating V_2 with respect to τ and using system (7) yields

$$
\begin{aligned}
\frac{dV_2}{d\tau}\Big|_{(7)} &= \left(1 - \frac{S}{D_1 x_1}\right)\dot{x}_1 + \dot{x}_2 + \frac{S}{D_1 D_5}(\dot{x}_3 + \dot{x}_4) \\
&= \left(1 - \frac{S}{D_1 x_1}\right)(S - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3) + D_2 x_1 x_2 + x_1 x_3 - D_4 x_2 \\
&\quad + \frac{S}{D_1 D_5}(x_2 - D_5 x_3 - x_4) \\
&= -D_1 x_1\left(1 - \frac{S}{D_1 x_1}\right)^2 - \frac{S}{D_1 D_5} x_4 - \left[D_4 - \frac{(1 + D_2 D_5)S}{D_1 D_5}\right] x_2.
\end{aligned}
$$

Obviously, when $S < \frac{D_1 D_4 D_5}{1 + D_2 D_5}$, i.e., $\mathcal{R}_0 < 1$, we have $\frac{dV_2}{d\tau}\Big|_{(7)} < 0$ as long as $(x_1, x_2, x_4) \neq (\frac{S}{D_1}, 0, 0)$, and $\frac{dV_2}{d\tau}\Big|_{(7)} = 0$ if and only if $(x_1, x_2, x_4) = (\frac{S}{D_1}, 0, 0)$. However, when $(x_1, x_2, x_4) = (\frac{S}{D_1}, 0, 0)$, the third equation in (7) implies $x_3 \to 0$ as $\tau \to \infty$. Thus, by the LaSalle invariance principle, we have shown that E_1 is globally asymptotically stable for $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 = 1$, the last term in the square bracket in the above derivative $\frac{dV_2}{d\tau}\Big|_{(7)}$ becomes zero. Thus, $\frac{dV_2}{d\tau}\Big|_{(7)} < 0$ as long as $(x_1, x_4) \neq (\frac{S}{D_1}, 0)$, and $\frac{dV_2}{d\tau}\Big|_{(7)} = 0$ if and only if $(x_1, x_4) = (\frac{S}{D_1}, 0)$. However, when $(x_1, x_4) = (\frac{S}{D_1}, 0)$, the first equation in (7) becomes $\dot{x}_1 = -\frac{S}{D_1}(D_2 x_2 + x_3)$, which implies that $x_1 \to 0$ as $\tau \to \infty$, which is not possible. Hence, $x_2 \to 0$ and $x_3 \to 0$ as $\tau \to \infty$. Thus, by the LaSalle invariance principle, we can also conclude that E_1 is globally asymptotically stable for $R_0 = 1$. $\square$

Next, consider the stability of E_2. Note that E_2 does not biologically exist for $\mathcal{R}_0 < 1$ and emerges to exist for $\mathcal{R}_0 \geqslant 1$ when E_1 becomes unstable.

Theorem 2.5. *The infectious equilibrium E_2 of system (7) is asymptotically stable if $\frac{D_1 D_4 D_5}{1 + D_2 D_5} < S < \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}$, or equivalently, $1 < \mathcal{R}_0 < \mathcal{R}_1$, where $\mathcal{R}_1 := 1 + \frac{1 + D_2 D_5}{D_1 D_6}$.*

Proof. Similarly, evaluating the Jacobian matrix (15) at E_2 yields the characteristic polynomial, $P_2(\lambda) = \left[\lambda + 1 + \frac{D_1 D_6}{1 + D_2 D_5} - \frac{D_6 S}{D_4 D_5}\right](\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3)$, where

$$a_1 = \frac{(1 + D_2 D_5)S}{D_4 D_5} + D_5 + \frac{D_4}{1 + D_2 D_5},$$

$$a_2 = \left[\frac{(1 + D_2 D_5)S}{D_4 D_5} - D_1\right](D_4 + D_5) + D_1\left(D_5 + \frac{D_4}{1 + D_2 D_5}\right),$$

$$a_3 = S(1 + D_2 D_5) - D_1 D_4 D_5.$$

Thus, by the Hurwitz criterion, E_2 is asymptotically stable if

$$a_1 > 0, \quad a_3 > 0, \quad a_1 a_2 - a_3 > 0, \quad \text{and} \quad 1 + \frac{D_1 D_6}{1 + D_2 D_5} - \frac{D_6 S}{D_4 D_5} > 0, \quad \text{i.e.,} \quad S < \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}.$$

A direct computation shows that $a_1 a_2 - a_3 > 0$ is equivalent to (in the sense that the following expression and $a_1 a_2 - a_3$ differs only by a positive factor)

$$\begin{aligned} &\left[S(1 + D_2 D_5) - D_1 D_4 D_5\right]^2 (1 + D_2 D_5)^2 (D_4 + D_5) + D_4 D_5 \Big\{ \left[S(1 + D_2 D_5) - D_1 D_4 D_5\right] \\ &\times (1 + D_2 D_5)\left[(D_5 + 2D_1)\left(D_4 + D_5(1 + D_2 D_5)\right) + D_4(D_4 + D_1 D_2 D_5)\right] \\ &+ D_1 D_4 D_5 (D_4 + D_5 + D_2 D_5^2)\left[D_4 + (D_1 + D_5)(1 + D_2 D_5)\right] \Big\} > 0, \end{aligned}$$

which is true if $S(1 + D_2 D_5) - D_1 D_4 D_5 > 0$ (i.e. $\mathcal{R}_0 > 1$). Hence, E_2 is asymptotically stable if

$$\frac{D_1 D_2 D_5}{1 + D_2 D_5} < S < \frac{D_1 D_2 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6} \quad (\text{or} \quad 1 < \mathcal{R}_0 < \mathcal{R}_1). \tag{17}$$

The proof is complete. $\square$

Theorem 2.6. *The infectious equilibrium E_2 of system (7) is globally asymptotically stable if $1 < \mathcal{R}_0 \leqslant \mathcal{R}_1$ (namely, $\frac{D_1 D_2 D_5}{1 + D_2 D_5} < S \leqslant \frac{D_1 D_2 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}$).*

Proof. Again, by constructing a Lyapunov function and applying LaSalle invariance principle, we can show that E_2 is globally asymptotically stable. To achieve this, consider the following Lyapunov function ($E_2 = (x_1^*, x_2^*, x_3^*, x_4^*)$ is used for simplicity),

$$V_3(x) = x_1 - x_1^* - x_1^* \ln \frac{x_1}{x_1^*} + x_2 - x_2^* - x_2^* \ln \frac{x_2}{x_2^*} + \frac{x_1^* x_3^*}{x_2^*}\left(x_3 - x_3^* - x_3^* \ln \frac{x_3}{x_3^*}\right) + \frac{x_1^* x_3^*}{x_2^*} x_4. \tag{18}$$

The derivative of V_3 with respect to τ along the trajectory of system (7) is given by

$$\begin{aligned} \frac{dV_3}{d\tau}\Big|_{(7)} &= \left(1 - \frac{x_1^*}{x_1}\right)\dot{x}_1 + \left(1 - \frac{x_2^*}{x_2}\right)\dot{x}_2 + \frac{x_1^* x_3^*}{x_2^*}\left(1 - \frac{x_3^*}{x_3}\right)\dot{x}_3 + \frac{x_1^* x_3^*}{x_2^*}\dot{x}_4 \\ &= \left(1 - \frac{x_1^*}{x_1}\right)\left(D_1 x_1^* + D_2 x_1^* x_2^* + x_1^* x_3^* - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3\right) \\ &\quad + \left(1 - \frac{x_2^*}{x_2}\right)\left[D_2 x_1 x_2 + x_1 x_3 - \frac{x_2}{x_2^*}(D_2 x_1^* x_2^* + x_1^* x_3^*)\right] \\ &\quad + \frac{x_1^* x_3^*}{x_2^*}\left(1 - \frac{x_3^*}{x_3}\right)(x_2 - D_5 x_3 - D_6 x_3 x_4) + \frac{x_1^* x_3^*}{x_2^*}(D_6 x_3 x_4 - x_4), \end{aligned}$$

where

$$S = D_1 x_1^* + D_2 x_1^* x_2^* + x_1^* x_3^*, \quad \text{and} \quad D_4 = \frac{D_2 x_1^* x_2^* + x_1^* x_3^*}{x_2^*},$$

have been used. Noticing $x_2^* = D_5 x_3^*$, we obtain

$$
\begin{aligned}
\frac{dV_3}{d\tau}\Big|_{(7)} &= D_1 x_1^* + D_2 x_1^* x_2^* + x_1^* x_3^* - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3 - D_1 \frac{x_1^{*2}}{x_1} - D_2 \frac{x_1^{*2} x_2^*}{x_1} - \frac{x_1^{*2} x_3^*}{x_1} + D_1 x_1^* \\
&\quad + D_2 x_1^* x_2 + x_1^* x_3 + D_2 x_1 x_2 + x_1 x_3 - D_1 x_1^* x_2 - \frac{x_1^* x_3^*}{x_2^*} x_2 - D_2 x_2^* x_1 - \frac{x_2^* x_1 x_3}{x_2} + D_2 x_1^* x_2^* \\
&\quad + x_1^* x_3^* + \frac{x_1^* x_3^*}{x_2^*}(D_6 x_3 x_4 - x_4) + \frac{x_1^* x_3^*}{x_2^*}\Big[x_2 - D_5 x_3 - D_6 x_3 x_4 - \frac{x_3^* x_2}{x_3} + D_5 x_3^* + D_6 x_3^* x_4\Big] \\
&= 2 D_1 x_1^* - D_1 x_1 - D_1 \frac{x_1^{*2}}{x_1} + 2 D_2 x_1^* x_2^* - D_2 x_2^* x_1 - D_2 \frac{x_1^{*2} x_2^*}{x_1} \\
&\quad + 2 x_1^* x_3^* + D_5 \frac{x_1^* x_3^{*2}}{x_2^*} - \frac{x_1^{*2} x_3^*}{x_1} - \frac{x_2^* x_1 x_3}{x_2} - \frac{x_1^* x_3^{*2} x_2}{x_2^* x_3} \\
&= x_1^*(D_1 + D_2 x_2^*)\Big(2 - \frac{x_1}{x_1^*} - \frac{x_1^*}{x_1}\Big) + \frac{x_1^* x_3^*}{x_2^*}(D_6 x_3^* - 1) x_4 + x_1^* x_3^*\Big(3 - \frac{x_1^*}{x_1} - \frac{x_2^* x_1 x_3}{x_1^* x_3^* x_2} - \frac{x_3^* x_2}{x_2^* x_3}\Big) \\
&\leqslant 0,
\end{aligned}
$$

because that $2 - \frac{x_1^*}{x_1} - \frac{x_1}{x_1^*} \leqslant 0$ for $x_1, x_1^* > 0$, and it equals 0 if and only if $x_1 = x_1^*$. Similarly, $3 - \frac{x_1^*}{x_1} - \frac{x_2^* x_1 x_3}{x_1^* x_3^* I x_2} - \frac{x_3^* x_2}{x_2^* x_3} \leqslant 0$ for all $x_1, x_1^*, x_2, x_2^*, x_3, x_3^* > 0$, and it equals 0 if and only if $x_1 = x_1^*$, $x_2 = x_2^*$, $x_3 = x_3^*$. Moreover, one can show that $D_6 x_3^* - 1 \leqslant 0$, which is equivalent to $\mathcal{R}_0 \leqslant \mathcal{R}_1$. Therefore, when $\mathcal{R}_0 \in (1, \mathcal{R}_1)$, $\frac{dV_3}{d\tau}\big|_{(7)} < 0$ and $\frac{dV_3}{d\tau}\big|_{(7)} = 0$ if and only if $(x_1, x_2, x_3, x_4) = E_2$. This shows that E_2 is globally asymptotically stable for $\mathcal{R}_0 \in (1, \mathcal{R}_1)$. For $\mathcal{R}_0 = \mathcal{R}_1$, we can similarly follow the proof for Theorem 2.4 and apply the LaSalle invariance principle to conclude that E_2 is also globally asymptotically stable. $\quad\square$

Now suppose $\mathcal{R}_0 > \mathcal{R}_1$, i.e., $S > \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}$, for which the infectious equilibrium E_2 becomes unstable, and the interior equilibrium E_3 emerges to exist. To find stability of E_3, we calculate the Jacobian matrix (15) at E_3 to obtain the characteristic polynomial: $P_3(\lambda) = \lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4$, where

$$
\begin{aligned}
a_1 = &\ \frac{1}{D_6(1 + D_2 D_6 \tilde{x}_2)} \Big\{ \big[D_2(D_6 \tilde{x}_2 - D_5) + 1 + D_2 D_5\big]^2 + D_2 D_6 (D_6 \tilde{x}_2)^2 \\
&\ + (D_6 \tilde{x}_2 - D_5) D_6(1 + D_1 D_2) + D_6\big[D_1(1 + D_2 D_5) + D_4 + D_5\big] \Big\}, \\
a_2 = &\ \frac{1}{D_6(1 + D_2 D_6 \tilde{x}_2)} \Big\{ (D_6 \tilde{x}_2 - D_5)\big[(D_2 \tilde{x}_2 - D_5) + 1 + D_2 D_5\big]^2 \\
&\ + (D_4 + D_5)(1 + D_2 D_6 \tilde{x}_2)^2 + D_1 D_2 D_6 (D_6 \tilde{x}_2)^2 + D_2 D_6 (D_2 \tilde{x}_2 - D_5)^2 \\
&\ + D_6 (D_6 \tilde{x}_2)(D_1 + 1 + D_2 D_5) + D_1 D_6(D_4 + D_5) \Big\}, \\
a_3 = &\ \frac{1}{D_6(1 + D_2 D_6 \tilde{x}_2)} \Big\{ \big[(1 + D_4)(D_6 \tilde{x}_2 - D_5) + D_4 D_5\big]\big[D_2(D_6 \tilde{x}_2 - D_5) + 1 + D_2 D_5\big]^2 \\
&\ + D_2 D_2 D_6 (D_6 \tilde{x}_2 - D_5)^2 + D_6\big[D_4 + D_1(1 + D_2 D_5)\big](D_6 \tilde{x}_2 - D_5) \Big\}, \\
a_4 = &\ \frac{D_4}{D_6(1 + D_2 D_6 \tilde{x}_2)}(D_6 \tilde{x}_2 - D_5)\Big\{ D_1 D_6 + \big[D_2(D_6 \tilde{x}_2 - D_5) + 1 + D_2 D_5\big]^2 \Big\}.
\end{aligned}
$$

Since $D_6 \tilde{x}_2 - D_5 \geqslant 0$, we have $a_i > 0$, $i = 1, 2, 3, 4$. This shows that at the critical point determined by $D_6 \tilde{x}_2 - D_5 = 0$, i.e. $S = \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}$, or $\mathcal{R}_0 = \mathcal{R}_1$, there exists a transcritical bifurcation between E_2 and E_3. The equilibrium E_3 is asymptotically stable if

$$
a_i > 0, \ i = 1, 2, 3, 4, \quad \Delta_2 = a_1 a_2 - a_3 > 0 \quad \text{and} \quad \Delta_3 = a_3 \Delta_2 - a_1^2 a_4 > 0.
$$

It can be shown by a direct computation that $\Delta_2 > 0$ and $\Delta_3 > 0$ for $\mathcal{R}_0 > \mathcal{R}_1$. Thus, the only bifurcation arising from the equilibrium E_3 is the transcritical bifurcation between E_2 and E_3. In particular, there is no Hopf bifurcation or Bogdanov-Takens bifurcation which may arise from E_3. Next, we prove that E_3 is also globally asymptotically stable for $\mathcal{R}_0 > \mathcal{R}_1$.

Theorem 2.7. *The positive equilibrium* E_3 *of system* (7) *is globally asymptotically stable for* $\mathcal{R}_0 > \mathcal{R}_1$, *or* $S > \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}$.

Proof. As usual, for simplicity let $E_3 = (\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4)$. Then we construct the following Lyapunov function:

$$
V_4(x) = x_1 - \hat{x}_1 - \hat{x}_1 \ln \frac{x_1}{\hat{x}_1} + x_2 - \hat{x}_2 - \hat{x}_2 \ln \frac{x_2}{\hat{x}_2} + \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}\left(x_3 - \hat{x}_3 - \hat{x}_3 \ln \frac{x_3}{\hat{x}_3}\right)
$$
$$
+ \frac{\hat{x}_2 \hat{x}_3}{\hat{x}_2}\left(x_4 - \hat{x}_4 - \hat{x}_4 \ln \frac{x_4}{\hat{x}_4}\right).
$$

Differentiating V_4 with respect to τ and evaluating it along the trajectory of system (7) yields

$$
\left.\frac{dV_4}{d\tau}\right|_{(7)} = \left(1 - \frac{\hat{x}_1}{x_1}\right)\dot{x}_1 + \left(1 - \frac{\hat{x}_2}{x_2}\right)\dot{x}_2 + \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}\left(1 - \frac{\hat{x}_3}{x_3}\right)\dot{x}_3 + \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}\left(1 - \frac{\hat{x}_4}{x_4}\right)\dot{x}_4
$$
$$
= \left(1 - \frac{\hat{x}_1}{x_1}\right)\left(S - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3\right) + \left(1 - \hat{x}_2 x_2\right)\left(D_2 x_1 x_2 + x_1 x_3 - D_4 x_2\right)
$$
$$
+ \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}\left(1 - \frac{\hat{x}_3}{x_3}\right)\left(x_2 - D_5 x_3 - D_6 x_3 x_4\right) + \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}\left(1 - \frac{\hat{x}_4}{x_4}\right)\left(D_6 x_3 x_4 - x_4\right).
$$

In view of the expression of the equilibrium E_3 we use the following expressions,

$$
S = D_1 \hat{x}_1 + D_2 \hat{x}_1 \hat{x}_2 + \hat{x}_1 \hat{x}_3, \quad D_4 = \frac{D_2 \hat{x}_1 \hat{x}_2 + \hat{x}_1 \hat{x}_3}{\hat{x}_2}, \quad \text{and} \quad \hat{x}_3 = \frac{1}{D_6}.
$$

and follow the same procedure in the proof for Theorem 2.6 to obtain

$$
\left.\frac{dV_4}{d\tau}\right|_{(7)} = \left(1 - \frac{\hat{x}_1}{x_1}\right)\left[D_1 \hat{x}_1 + D_2 \hat{x}_1 \hat{x}_2 + \hat{x}_1 \hat{x}_3 - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3\right]
$$
$$
+ \left(1 - \frac{\hat{x}_2}{x_2}\right)\left[D_2 \hat{x}_1 \hat{x}_2 + \hat{x}_1 \hat{x}_3 - \frac{x_2}{\hat{x}_2}(D_2 \hat{x}_1 \hat{x}_2 + \hat{x}_1 \hat{x}_3)\right]
$$
$$
+ \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}\left[\left(1 - \frac{\hat{x}_3}{x_3}\right)(x_2 - D_5 x_3 - D_6 x_3 x_4)\left(1 - \frac{\hat{x}_4}{x_4}\right)(D_6 x_3 x_4 - x_4)\right]
$$
$$
= 2D_1 \hat{x}_1 - D_1 x_1 - D_1 \frac{\hat{x}_1^2}{x_1} + 2D_2 \hat{x}_1 \hat{x}_2 - D_2 \hat{x}_2 x_1 - D_2 \frac{\hat{x}_1^2 \hat{x}_2}{x_1} + 2\hat{x}_1 \hat{x}_3 + \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}(D_5 \hat{x}_3 + \hat{x}_4)
$$
$$
- \frac{\hat{x}_1^2 \hat{x}_3}{x_1} - \frac{\hat{x}_2 x_1 x_3}{x_2} - \frac{\hat{x}_1 \hat{x}_3^2 x_2}{\hat{x}_2 x_3} + \frac{\hat{x}_1}{\hat{x}_2}\left[\hat{x}_2 + \hat{x}_3(-D_5 - D_6 \hat{x}_4)\right] x_3 + \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}(D_6 \hat{x}_3 - 1)x_4.
$$

Since

$$
\frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}(D_5 \hat{x}_3 + \hat{x}_4) = \frac{\hat{x}_1 \hat{x}_3}{\hat{x}_2}\left(\frac{D_5}{D_6} + \hat{x}_2 - \frac{D_5}{D_6}\right) = \hat{x}_1 \hat{x}_3,
$$
$$
\hat{x}_2 + \hat{x}_3(-D_5 - D_6 \hat{x}_4) = \hat{x}_2 - \frac{D_5}{D_6} - \hat{x}_2 + \frac{D_5}{D_6} = 0,
$$
$$
D_6 \hat{x}_3 - 1 = 0,
$$

the above derivative $\frac{dV_4}{d\tau} | |_{(7)}$ can be rewritten as

$$
\left.\frac{dV_4}{d\tau}\right|_{(7)} = \hat{x}_1(D_1 + D_2 \hat{x}_2)\left(2 - \frac{x_1}{\hat{x}_1} - \frac{\hat{x}_1}{x_1}\right) + \hat{x}_1 \hat{x}_3\left(3 - \frac{\hat{x}_1}{x_1} - \frac{\hat{x}_2 x_1 x_3}{\hat{x}_1 \hat{x}_3 x_2} - \frac{\hat{x}_3 x_2}{\hat{x}_2 x_3}\right) < 0,
$$

for $(x_1, x_2, x_3) \neq (\hat{x}_1, \hat{x}_2, \hat{x}_3)$, and $\frac{dV_4}{d\tau}|_{(7)} = 0$ if and only if $(x_1, x_2, x_3) = (\hat{x}_1, \hat{x}_2, \hat{x}_3)$. When $(x_1, x_2, x_3) = (\hat{x}_1, \hat{x}_2, \hat{x}_3)$, the third equation in (7) yields $x_4 = \hat{x}_4$. Hence, by the LaSalle invariance principle, we have shown that the positive equilibrium E_3 of system (7) is globally asymptotically stable for $\mathcal{R}_0 > \mathcal{R}_1$. $\square$

Summarizing the results obtained in this section, we have shown that the disease-free equilibrium E_1 exists for $\mathcal{R}_0 > 0$ and is globally asymptotically stable for $0 < \mathcal{R}_0 \leqslant 1$ and becomes unstable for $\mathcal{R}_0 > 1$; the equilibrium E_2 exists for $\mathcal{R}_0 \geqslant 1$, and is GAS (globally asymptotically stable) for $1 < \mathcal{R}_0 \leqslant \mathcal{R}_1$, and becomes unstable for $\mathcal{R}_0 > \mathcal{R}_1$; the equilibrium E_3 exists for $\mathcal{R}_0 \geqslant \mathcal{R}_1$ and is GAS. Note that $E_2 = E_1$ at $\mathcal{R}_0 = 1$, and $E_3 = E_2$ at $\mathcal{R}_0 = \mathcal{R}_1$. Moreover, at $\mathcal{R}_0 = 1$, E_1 loses its stability and E_2 emerges to
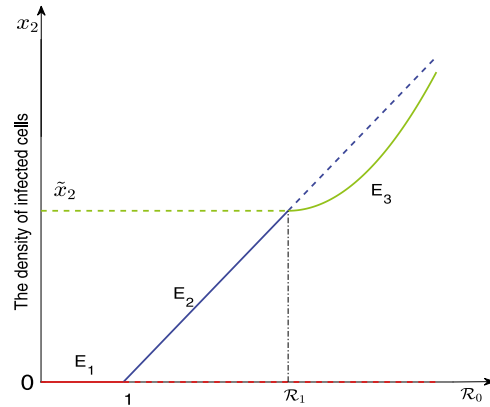
Fig. 1. Bifurcation diagram for system (7) showing the equilibrium solutions E_1, E_2 and E_3, where solid and dotted lines/curves represent stable and unstable equilibrium solutions, respectively.

be a stable equilibrium. Thus a transcritical bifurcation occurs between E_1 and E_2 at the critical point $\mathcal{R}_0 = 1$. Similarly, a transcritical bifurcation happens between E_2 and E_3 at the critical point $\mathcal{R}_0 = \mathcal{R}_1$. The bifurcation diagram for the dynamics of three equilibria of system (7) with $\mathcal{R}_0$ as the bifurcation parameter is shown in Fig. 1.

Remark 1. The results obtained in this section clearly indicate that the model (7) does not exhibit any complex dynamical behavior such as oscillation for any combination of the positive parameter values, but all the system solutions eventually converge to one of the three equilibria, depending on the value of $\mathcal{R}_0 = \frac{S(1+D_2 D_5)}{D_1 D_4 D_5} = \frac{sd_3(k\beta_1+d_2\beta_2)}{d_1 d_2 \delta}$. Let us consider the situation as the parameter S (a similar discussion can be carried out using the original parameter s) is varied, with other parameters fixed, and study how the parameter S plays an important role in the infection process. Based on $\mathcal{R}_0 = 1$ and $\mathcal{R}_0 = \mathcal{R}_1$ we have two critical values for S: called $S_1 = \frac{D_1 D_4 D_5}{1+D_2 D_5}$ and $S_2 = S_1 + \frac{D_4 D_5}{D_6}$ such that when $S < S_1$ the virus-infected cells produce on average less infected cells and so the virus cannot survive and eventually die out, leading to infected cells to recover and the virus is cleaned up. This is a health stage. When S is increased to cross the critical value S_1, health cells get more infected and virus can survive via contact of the infected cells. Moreover, if S is not too large, satisfying $S_1 < S < S_2$, then the immune system is not activated and lymphocytes are not released to kill the virus. During this stage, health cells, infected cells and virus are in a constant balance and none of the infected cells and virus can be eliminated. When S is further increased to cross the critical value S_2 ($S > S_2$), then the immune system is activated and lymphocytes are released to kill the virus. Nevertheless, the immune system cannot clean up the virus, and thus the health cells, infected cells, virus and lymphocytes are in a constant balance. We can similarly discuss the effect of other parameters. For example, considering D_1 shows an opposite direction in the variation since it appears on the denominator of $\mathcal{R}_0$. But it should be noted that the parameters are implicitly related, so realistically more parameters should be considered in variation. Thus, the basic reproduction number $\mathcal{R}_0$ represents a hypersurface in the 5-dimensional parameter space (or in the 8-dimensional parameter space if the original parameters are used). Then $\mathcal{R}_0 = 1$ and $\mathcal{R}_0 = \mathcal{R}_1$ denote two critical planes in the parameter space, which is more realistically describing the combined effect of the parameters.

The model (7) shows the existence of only equilibrium solutions might miss certain realistic situation such as oscillations. This may be because we only consider cell-to-cell interaction in model (7). In reality, it is quite possible to have the components of the equilibrium E_3 not a constant but a stable periodic oscillation. In the next section, we will explore such dynamical behaviors by adding the effect of the involvement to model (7), leading to the unified model (8).

3. The effect of the involvement in model (8)

In this section, besides the effect of cell-to-cell interaction, we also consider the effect of the involvement in the unified model (8). It will be shown that the effect of the involvement will change the stability of equilibria, yielding Hopf bifurcation and oscillating behavior.

Note that the basic reproduction number $\mathcal{R}_0$ for system (8) is the same as that for system (7), i.e.,

$$\mathcal{R}_0 = \frac{S(1 + D_2 D_5)}{D_1 D_4 D_5},$$

since the infection-free equilibrium of system (8) is the same as that of system (7) and their stability is also identical. System (8) also has three equilibria, $\bar{\mathrm{E}}_1$, $\bar{\mathrm{E}}_2$ and $\bar{\mathrm{E}}_3$, among which $\bar{\mathrm{E}}_1$ and $\bar{\mathrm{E}}_2$ are boundary equilibria, while $\bar{\mathrm{E}}_3$ is a positive (interior) equilibrium. When the component x_4 in their equilibria of systems (7) and (8) is zero, implying that the pathogens-specific lymphocytes are absent, the two boundary equilibria are exactly the same since $x_4 = 0$, i.e.,

$$\bar{\mathrm{E}}_1 = \mathrm{E}_1, \quad \bar{\mathrm{E}}_2 = \mathrm{E}_2.$$

This indicates that the perturbation term $-D_3 x_1 x_3 x_4$ (or $-\gamma TVA$ in the original model (5)) has no effect on these two equilibria.

The third equilibrium is given by

$$\bar{\mathrm{E}}_3 = (\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4) = \left(\frac{D_4 D_6 \hat{x}_2}{1 + D_2 D_6 \hat{x}_2}, \ \hat{x}_2, \ \frac{1}{D_6}, \ \hat{x}_2 - \frac{D_5}{D_6} \right).$$

Note here that we use the same notation $(\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4)$ to denote the equilibrium E_3 of system (7) and $\bar{\mathrm{E}}_3$ of system (8), but now for system (8),

$$
\hat{x}_2 = \frac{1}{2D_4 D_6 (D_3 + D_2 D_6)} \left\{ SD_2 D_6^2 + D_4 \left[D_3 D_5 - D_6 (1 + D_1 D_6) \right] \right. \\
\left. + \sqrt{\left[SD_2 D_6^2 + D_4 \left(D_3 D_5 - D_6 (1 + D_1 D_6) \right) \right]^2 + 4SD_4 D_6^2 (D_3 + D_2 D_6)} \right\},
\tag{19}
$$

where only positive sign is taken for the square root, since the negative root yields $\hat{x}_2 < 0$. The existence condition of $\bar{\mathrm{E}}_3$ requires $\hat{x}_2 \geqslant \frac{D_5}{D_6}$, or $D_6 \hat{x}_2 - D_5 \geqslant 0$. Similar to the discussion for the existence of E_3 for model (7), we can show that $\bar{\mathrm{E}}_3$ exists for

$$S \geqslant \frac{D_1 D_2 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}, \quad \text{i.e., } \quad \mathcal{R}_0 \geqslant \mathcal{R}_1,$$

which is exactly the same as that for the existence condition for the equilibrium E_3 of model (7). This shows that although the perturbation term $-D_3 x_1 x_3 x_4$ changes the solution of the equilibrium $\bar{\mathrm{E}}_3$, it does not change its existence condition. However, we will see in the following that this term does change the stability of $\bar{\mathrm{E}}_3$.

Similar to Theorems 2.1 and 2.3, we have the following two theorems for system (8).

Theorem 3.1. *All solutions of system (8) are non-negative if the initial conditions are non-negative. Moreover, they are ultimately bounded.*

Proof. The proof follows that for proving Theorem 2.1. First note that system (8) satisfies the conditions in Lemma 2.2, and so all solutions of system (8) are non-negative provided that the initial conditions are chosen non-negative. Secondly, to prove the boundness of the solutions, we can still use the function $V_1(x) = x_1 + x_2 + \frac{D_4}{2}(x_3 + x_4)$, which yields

$$\left. \frac{dV_1}{d\tau} \right|_{(8)} = S - D_1 x_1 - \frac{D_4}{2}(x_2 + x_4) - \frac{D_4 D_5}{2} x_3 - D_3 x_1 x_3 x_4 \equiv -\Pi_1 - D_3 x_1 x_3 x_4,$$

which implies that in the cone R^4_+, the surface defined by $-\Pi_1 - D_3\,x_1x_3x_4 = 0$ is inside the place $\Pi_1 = 0$. Hence, we can still use the planes $\Pi_1 = 0$ and $V_1 = C$, and the same argument applied for system (7) to prove the boundedness of the solutions of system (8). □

Theorem 3.2. *The infection-free equilibrium $\bar{E}_1$ of system (8) is asymptotically stable if $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$.*

Proof. The proof is simply based on the Jacobian matrix of (8), given by

$$J(\bar{E}_k) = \begin{bmatrix} -D_1 - D_2x_2 - x_3 - D_3x_3x_4 & -D_2x_1 & -x_1 - D_3x_1x_4 & -D_3x_1x_3 \\ D_1x_2 + x_3 & D_2x_1 - D_4 & x_1 & 0 \\ 0 & 1 & -D_5 - D_6x_4 & -D_6x_3 \\ 0 & 0 & D_6x_4 & D_6x_3 - 1 \end{bmatrix},$$

which obviously yields $J(\bar{E}_1) = J(E_1)$ since $x_2 = x_3 = x_4 = 0$ in E_1, implying that the characteristic polynomial of $J(\bar{E}_1)$ is exactly the same as the $P_1(\lambda)$ of system (7), and so the conclusion in Theorem 3.2 is true. □

However, proving the global stability of $\bar{E}_1$ and $\bar{E}_2$ now becomes difficult due to the involvement of the third order term $-D_3x_1x_3x_4$. We shall, instead of using Lyapunov function method, apply a different approach to prove their global stability. We will use the fluctuation lemma [30] to prove the global stability of $\bar{E}_1$ when $\mathcal{R}_0 < 1$.

First, we introduce some basic notations. For a continuous and bounded function $f : [0, +\infty) \to R$, let

$$f_\infty = \lim_{\tau \to \infty} \inf f(\tau), \quad f^\infty = \lim_{\tau \to \infty} \sup f(\tau).$$

By Theorem 3.1, we know that $\lim_{\tau \to \infty} \inf$ and $\lim_{\tau \to \infty} \sup$ exist for all the functions on the right-hand side of (8). According to the fluctuation lemma [30], there is a sequence τ_n with $\tau_n \to \infty$ as $n \to \infty$ satisfying

$$\lim_{n \to \infty} x_k(\tau_n) = x_k^\infty \quad \text{and} \quad \lim_{n \to \infty} \dot{x}_k(\tau_n) = 0, \quad k = 1, 2, 3, 4, \quad \text{as} \quad n \to \infty.$$

Thus, it follows from the first equation in (8) that

$$\dot{x}_1(\tau_n) + D_1x_1(\tau_n) + D_2x_1(\tau_n)x_2(\tau_n) + x_1(\tau_n)x_3(\tau_n) + D_3x_1(\tau_n)x_3(\tau_n)x_4(\tau_n) = S.$$

Taking $n \to \infty$ in the above equation, and noticing that all variables x_i are non-negative, yields the following inequality,

$$D_1x_1^\infty \leqslant \left(D_1 + D_2x_{2\infty} + x_{3\infty} + D_3x_{3\infty}x_{4\infty}\right)x_1^\infty \leqslant S, \quad \text{i.e.,} \quad x_1^\infty \leqslant \frac{S}{D_1}.$$

By a similar argument, the second and third equations in (8) yield

$$D_4x_2^\infty \leqslant x_1^\infty\left(D_2x_2^\infty + x_3^\infty\right) \leqslant \frac{S}{D_1}\left(D_2x_2^\infty + x_3^\infty\right) \quad \text{and} \quad D_5x_3^\infty \leq x_3^\infty\left(D_5 + D_6x_{4\infty}\right) \leqslant x_2^\infty,$$

respectively, where $x_1^\infty \leqslant \frac{S}{D_1}$ has been used. Combining the above two inequalities, we obtain

$$D_4x_2^\infty \leqslant \frac{S}{D_1}\left(D_2 + \frac{1}{D_5}\right)x_2^\infty, \quad \text{i.e.,} \quad x_2^\infty\left[1 - \frac{S(1 + D_2D_5)}{D_1D_4D_5}\right] \leqslant 0 \quad \text{or} \quad x_2^\infty(1 - \mathcal{R}_0) \leqslant 0,$$

implying that $x_2^\infty = 0$ due to $x_2^\infty \geqslant 0$ and $\mathcal{R}_0 < 1$, which in turn yields $x_3^\infty = 0$ and $x_4^\infty = 0$. Since $0 \leqslant x_{2\infty} \leqslant x_2^\infty$, we have $x_{2\infty} = x_2^\infty = 0$, yielding $x_2(\tau) \to 0$ as $\tau \to \infty$. Similarly, we can conclude that $x_3(\tau) \to 0$ and $x_4(\tau) \to 0$ as $\tau \to \infty$. Thus, the first equation in system (8) becomes an asymptotically autonomous equation with the limiting equation, $\dot{x}_1 = S - D_1x_1$, which has the solution,

$$x_1(\tau) = \frac{c}{D_1}e^{-D_1\tau} + \frac{S}{D_1} \quad \Longrightarrow \quad \lim_{\tau \to +\infty} x_1(\tau) = \frac{S}{D_1}.$$

Hence, we have the following theorem.

Theorem 3.3.   *The infection-free equilibrium* $\bar{\mathrm{E}}_1$ *of system* (8) *is globally asymptotically stable* (GAS) *for* $\mathcal{R}_0 < 1$.

Similarly, we can prove the following result.

Theorem 3.4.   *The infectious equilibrium* $\bar{\mathrm{E}}_2$ *of system* (8) *is asymptotically stable for* $1 < \mathcal{R}_0 < \mathcal{R}_1$ *and GAS if* $1 < \mathcal{R}_0 < \mathcal{R}_1$, *where* $\mathcal{R}_1$ *is the same as that for system* (7): $\mathcal{R}_1 = 1 + \frac{1 + D_2 D_5}{D_1 D_6}$.

Proof. The local asymptotic stability of $\bar{\mathrm{E}}_2$ can be obtained from the Jacobian matrix of (8), and the proof is almost exactly the same as that for proving Theorem 2.6. So the proof is omitted here for brevity.

For the global stability of $\bar{\mathrm{E}}_2$, we have found that it is difficult to apply a Lyapunov function due to the existence of the third order term $-D_3 x_1 x_2 x_3$ in the first equation of (8). Since $\bar{\mathrm{E}}_2$ is locally asymptotically stable for $1 < \mathcal{R}_0 < \mathcal{R}_1$, it suffices to prove that $\bar{\mathrm{E}}_2$ is globally attractive when $\mathcal{R}_0 \in (1, \mathcal{R}_1)$, i.e., for any non-negative solutions $(x_1(\tau), x_2(\tau), x_3(\tau), x_4(\tau))$ of system (8), we need to show that $\lim_{\tau \to \infty} (x_1(\tau), x_2(\tau), x_3(\tau), x_4(\tau)) = (x_1^*, x_2^*, x_3^*, 0)$ under the condition $1 < \mathcal{R}_0 < \mathcal{R}_1$. First, we again apply the fluctuation lemma [30] to show that $\lim_{\tau \to \infty} x_4(\tau) = 0$, and then consider the limiting system.

By the fluctuation lemma we have the following inequalities derived from (8),

$$
\begin{aligned}
D_1 x_1^\infty + D_2 x_1^\infty x_2^\infty + x_1^\infty x_3^\infty + D_3 x_1^\infty x_3^\infty x_{4\infty} &\leqslant S, \\
D_4 x_2^\infty &\leqslant (D_2 x_2^\infty + x_3^\infty) x_1^\infty, \\
D_5 x_3^\infty + D_6 x_3^\infty x_{4\infty} &\leqslant x_2^\infty, \\
x_4^\infty &\leqslant D_6 x_3^\infty x_4^\infty.
\end{aligned}
\tag{20}
$$

We prove $x_4^\infty = 0$ by contradiction. Since $x_4^\infty \geqslant 0$, suppose $x_4^\infty > 0$. Then, the fourth inequality in (20) gives

$$
x_3^\infty \geqslant \frac{1}{D_6} > 0.
\tag{21}
$$

It follows from the first inequality in (20) that

$$
D_1 x_1^\infty + D_2 x_1^\infty x_2^\infty + x_1^\infty \frac{1}{D_6} \leq D_1 x_1^\infty + D_2 x_1^\infty x_2^\infty + x_1^\infty x_3^\infty + D_3 x_1^\infty x_3^\infty x_{4\infty} \leqslant S,
$$

which leads to

$$
x_1^\infty \left[D_1 + \frac{1}{D_6} + D_2 x_2^\infty \right] \leqslant S.
\tag{22}
$$

The third inequality in (20) gives

$$
x_2^\infty \geqslant D_5 x_3^\infty \geqslant \frac{D_5}{D_6}, \quad \text{due to } x_{4\infty} \geqslant 0 \quad \text{and} \quad x_3^\infty \geqslant \frac{1}{D_6}.
\tag{23}
$$

Now it follows from (22) into (23) that

$$
x_1^\infty D_1 \left[1 + \frac{1 + D_2 D_5}{D_1 D_6} \right] = x_1^\infty \left(D_1 + \frac{1}{D_6} + \frac{D_2 D_5}{D_6} \right) \leqslant x_1^\infty \left(D_1 + \frac{1}{D_6} + D_2 x_2^\infty \right) \leqslant S,
$$

that is,

$$
x_1^\infty D_1 \mathcal{R}_1 \leqslant S = \mathcal{R}_0 \frac{D_1 D_4 D_5}{1 + D_2 D_5}, \quad \text{or} \quad x_1^\infty \frac{1 + D_2 D_5}{D_4 D_5} \mathcal{R}_1 \leqslant \mathcal{R}_0.
$$

If $x_1^\infty \frac{1 + D_2 D_5}{D_4 D_5} \geqslant 1$, then we have $\mathcal{R}_0 \gg \mathcal{R}_1$, a contradiction with the given condition $1 < \mathcal{R}_0 < \mathcal{R}_1$.

We claim that $x_1^\infty \frac{1 + D_2 D_5}{D_4 D_5} \geqslant 1$ is true under the assumption $x_4^\infty > 0$. The inequality $x_1^\infty \frac{1 + D_2 D_5}{D_4 D_5} \geqslant 1$ is equivalent to $x_1^\infty \geqslant \frac{D_4 D_5}{1 + D_2 D_5}$. On the other hand, it follows from the second inequality in (20) that

$$
D_4 x_2^\infty \leqslant (D_2 x_2^\infty + x_3^\infty) x_1^\infty \quad \Longleftrightarrow \quad x_1^\infty \geqslant \frac{D_4 x_2^\infty}{D_2 x_2^\infty + x_3^\infty} > 0 \quad (\text{since } x_2^\infty > 0, x_3^\infty > 0).
$$

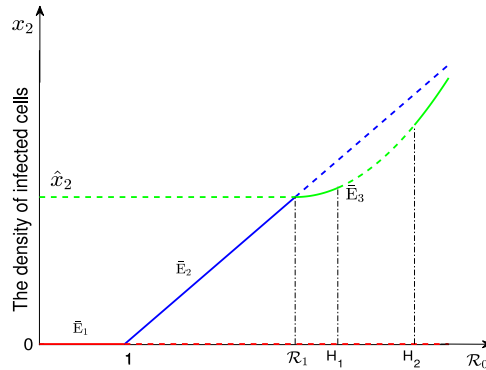**Fig. 2.** Bifurcation diagram for system (8) showing the equilibrium solutions $\bar{\mathrm{E}}_1$, $\bar{\mathrm{E}}_2$ and $\bar{\mathrm{E}}_3$, where H_1 and H_2 denote the Hopf bifurcation points, solid and dotted lines/curves represent stable and unstable equilibrium solutions, respectively.

Further, it follows from the inequality $x_2^\infty \geqslant D_5 x_3^\infty$ that

$$x_2^\infty \geqslant D_5 x_3^\infty \iff x_2^\infty + D_2 D_5 x_2^\infty \geqslant D_5 D_2 x_2^\infty + D_5 x_3^\infty \iff \frac{D_4 x_2^\infty}{D_2 x_2^\infty + x_3^\infty} \geqslant \frac{D_4 D_5}{1 + D_2 D_5},$$

and so combining the above two inequalities we obtain $x_1^\infty \geqslant \frac{D_4 D_5}{1 + D_2 D_5}$, yielding $\mathcal{R}_0 \geqslant \mathcal{R}_1$. This contradiction implies that assuming $x_4^\infty > 0$ is not true. Hence, $x_4^\infty = 0$ for $1 < \mathcal{R}_0 < \mathcal{R}_1$. Since $0 \leqslant x_{4\infty} \leqslant x_4^\infty$, we also have $x_{4\infty} = 0$. Thus, $\lim_{\tau \to \infty} x_4(\tau) = 0$.

Finally, having proved $\lim_{\tau \to \infty} x_4(\tau) = 0$, we consider the following limiting system,

$$\dot{x}_1 = S - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3,$$
$$\dot{x}_2 = D_2 x_1 x_2 + x_1 x_3 - D_4 x_2,$$
$$\dot{x}_3 = x_2 - D_5 x_3.$$

This system has an equilibrium (x_1^*, x_2^*, x_3^*) and it is easy to use a Lyapunov function to prove that it is globally asymptotically stable if $\mathcal{R}_0 \in (1, \mathcal{R}_1)$ [15]. That is to say, $\lim_{\tau \to \infty}(x_1(\tau), x_2(\tau), x_3(\tau), x_4(\tau)) = (x_1^*, x_2^*, x_3^*, 0)$ if $\mathcal{R}_0 \in (1, \mathcal{R}_1)$. $\quad\square$

It should be noted that the fluctuation lemma can also be used to prove the global stability of the equilibria E_i, $i = 1, 2, 3$ of system (7). We present both methods to show different approaches in proving global stability of equilibria.

Summarizing the results obtained in this section, we can conclude that the disease-free equilibrium $\bar{\mathrm{E}}_1$ is GAS for $\mathcal{R}_0 < 1$, and becomes unstable for $\mathcal{R}_0 > 1$, for which the equilibrium $\bar{\mathrm{E}}_2$ exists and is GAS for $1 < \mathcal{R}_0 < \mathcal{R}_1$. For $\mathcal{R}_0 > \mathcal{R}_1$, the equilibrium $\bar{\mathrm{E}}_3$ exists, however it may lose its stability at a critical point $\mathcal{R}_0 = \mathcal{R}_\mathrm{H} > \mathcal{R}_1$ at which Hopf bifurcation occurs. The bifurcation diagram for system (8) with $\mathcal{R}_0$ as the bifurcation parameter is depicted in Fig. 2. But as the strength of the cell-to-cell interaction increases, the Hopf bifurcation may disappear, and the positive equilibrium becomes stable. Further, the interaction of the effect of the involvement and the humoral immune response also plays an important role, and may generate Hopf bifurcation if the humoral immune response reaches certain critical values. To demonstrate the effect of the cell-to-cell interaction in terms of D_2 (i.e., with respect to the original parameter β_2), we show a 2-parameter bifurcation $(D_2, \mathcal{R}_0)$ diagram for Hopf bifurcation, as depicted in Fig. 3, where for definite, instead of the general $\mathcal{R}_0$, we use S. It is seen from this figure that the model (8) always has two Hopf bifurcation points for $D_2 \geqslant 0$ (i.e., $\beta_2 \geqslant 0$), with the smaller one being almost a constant with respect to S when D_2 is increasing, while the larger one being decreasing with respect to S when D_2 is increasing. In other words, as D_2 (or β_2) increases, the interval $S \in (\mathrm{H}_1, \mathrm{H}_2)$ is decreasing, implying that the equilibrium $\hat{\mathrm{E}}_3$ becomes more stable.
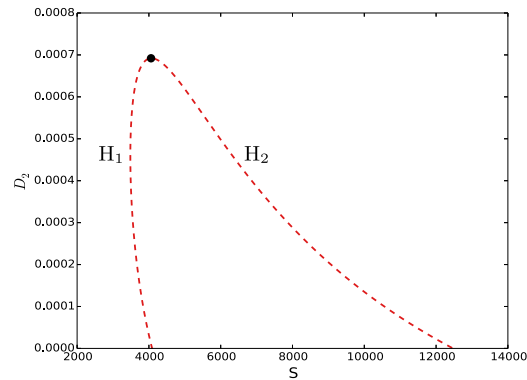
Fig. 3. Two-parameter (D_2, S) Hopf bifurcation diagram for system (8) for $D_6 = 12$, with the vertex of the curve at $(S, D_2) = (4070.22, 6.920 \times 10^{-4})$.

Remark 2. Since the models (7) and (8) have the same basic reproduction number $\mathcal{R}_0$ (which does not involve D_3 or γ) and the same equilibria E_1 and E_2, the stability and bifurcations of E_1 and E_2 for these two models are identical, regardless the value of D_3 or γ, implying that the effect of involvement has no impact at all on these two equilibrium solutions and their stability. In other words, the involvement becomes effective only if $\mathcal{R}_0$ reaches the critical value $\mathcal{R}_1$ for which the immune system is activated and the lymphocytes are released to kill the virus. In the next section, we will show that when the "involvement" term $-\gamma TVA$ is added, the positive equilibrium $\bar{E}_3$ may become unstable, leading to Hopf bifurcation. This indicates that the effect of the involvement can yield oscillating dynamical behavior, which may be more appropriate to describe the real situation. However, it is noted that when $D_3 = 0$ (or $\gamma = 0$), the systems (7) and (8) (or (3) and (5)) are identical and thus $\bar{E}_3 = E_3$ is GAS. This implies that the model (8) is essentially the same as the model (7) if the effect of the involvement (measured by the parameter D_3 or γ) is small. Moreover, when oscillations occur due to Hopf bifurcation, with the increase, for example, of D_2 or β_2 (indicating the strength of cell-to-cell interaction), increasing the effect of involvement can suppress the oscillations. From the viewpoint of biology, this means that releasing more lymphocytes will kill more virus and suppress the oscillating behavior, but not completely clean virus. In order to further illustrate the relation between the parameters D_2 and D_3, we plot another 2-parameter (D_2, D_3) bifurcation diagram, as shown in Fig. 4. It is seen from this figure that there does not exist Hopf bifurcation for $D_3 = 0$, as expected. It is also seen that for small values of D_3 (e.g., $D_3 < 2$), the Hopf bifurcation curve monotonically increases very rapidly as D_2 increases; but for non-small values of D_3 (e.g., $D_3 > 2$), the Hopf bifurcation cure is almost saturated with respect to D_2. This implies that the model (8) always has oscillations with the increase of D_3 when $D_2 \leqslant 5 \times 10^{-4}$, but no oscillation at all for $D_2 > 5 \times 10^{-4}$.

4. Hopf bifurcation in system (8)

Now we turn to consider Hopf bifurcation in system (8) from the positive equilibrium $\bar{E}_3$. First, we need the following lemma to determine the critical point for Hopf bifurcation.

Lemma 4.1 (*Theorem 2 in [31]*)**.** *The necessary and sufficient condition for a general nonlinear differential system to have a Hopf bifurcation at a fixed point of the system: $\dot{x} = f(x, \mu)$, $x \in R^n$, $\mu \in R$, is $\Delta_{n-1} = 0$, with other Hurwitz conditions to be held, i.e., $\Delta_i > 0$ for $i = 1, 2, \ldots, n-2$ and $b_n > 0$, leading to that all the remaining eigenvalues of the Jacobian have negative real parts.*
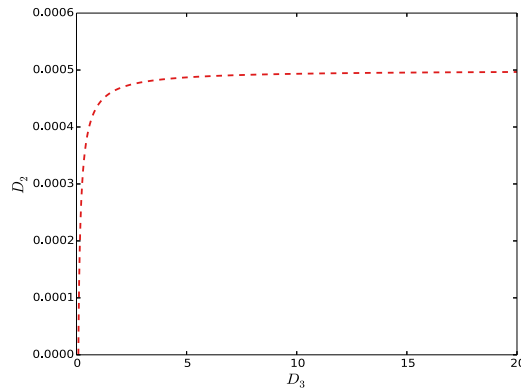
Fig. 4. Two-parameter (D_2, D_3) Hopf bifurcation diagram for system (8) for $D_6 = 12$.

Thus, we suppose the characteristic polynomial for the equilibrium $\bar{\mathrm{E}}_3$ is $P_3(\lambda) = \lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4$, then

$$\Delta_1 = b_1, \quad \Delta_2 = b_1 b_2 - b_3, \quad \Delta_3 = b_3\Delta_2 - b_1^2 b_4, \quad \Delta_4 = b_4\Delta_3. \tag{24}$$

It is well known from the Hurwitz criterion that $\bar{\mathrm{E}}_3$ is asymptotically stable if $\Delta_i > 0$, $i = 1, 2, 3, 4$. When $b_4 = 0$, $(b_1 > 0, b_3 > 0, \Delta_2 > 0)$, there exists a transcritical bifurcation between $\bar{\mathrm{E}}_2$ and $\bar{\mathrm{E}}_3$. When $b_4 = 0$, there are several possibilities that $\bar{\mathrm{E}}_3$ may lose its stability. If $\Delta_3 = 0$, $(b_1 > 0, b_4 > 0, \Delta_2 > 0)$, then by Lemma 4.1, we know that system (8) has a Hopf bifurcation from $\bar{\mathrm{E}}_3$. If $b_4 = b_3 = 0$, $(b_1 > 0, b_2 > 0)$, then Bogdanov-Takens bifurcation associated with a double-zero eigenvalue occurs. When $b_4 = b_3 = b_2 = 0$, $(b_1 > 0)$, even more complex bifurcation associated with a triple-zero eigenvalue happens. In practical problems, Hopf and Bogdanov–Takens bifurcations are the two most popular bifurcations to generate complex dynamics such as bifurcation of limit cycles and homoclinic loops. However, in the following, we will show that from the equilibrium $\bar{\mathrm{E}}_3$ of system (8) the only possible bifurcation is Hopf bifurcation.

Theorem 4.2. *For system (8) with positive parameter values, there exists a transcritical bifurcation between $\bar{\mathrm{E}}_2$ and $\bar{\mathrm{E}}_3$, at which $\bar{\mathrm{E}}_2$ loses its stability and $\bar{\mathrm{E}}_3$ emerges to exist. Then the only possible bifurcation which may occur from $\bar{\mathrm{E}}_3$ is Hopf bifurcation, and Bogdanov-Takens bifurcation is not possible.*

Proof. We first summarize the results obtained in previous section as follows. Here, instead of $\mathcal{R}_0$, we use S as the bifurcation parameter for convenience.

$$
\begin{array}{lll}
\bar{\mathrm{E}}_1 & \text{exists for any positive parameter values,} & \text{GAS for } S \in \left(0, \frac{D_1 D_4 D_5}{1 + D_2 D_5}\right) \\
\bar{\mathrm{E}}_2 & \text{exists for } S \geqslant \frac{D_1 D_4 D_5}{1 + D_2 D_5}, & \text{GAS for } S \in \left(\frac{D_1 D_4 D_5}{1 + D_2 D_5}, \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}\right) \\
\bar{\mathrm{E}}_3 & \text{exists for } S \geqslant \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}.
\end{array}
\tag{25}
$$

It is easy to see that a transcritical bifurcation occurs between $\bar{\mathrm{E}}_1$ and $\bar{\mathrm{E}}_2$ when $S = \frac{D_1 D_4 D_5}{1 + D_2 D_5}$ at which $\bar{\mathrm{E}}_2 = \bar{\mathrm{E}}_1 = \left(\frac{D_4 D_5}{1 + D_2 D_5}, 0, 0, 0\right)$. In the following we will show that another transcritical bifurcation occurs between $\bar{\mathrm{E}}_2$ and $\bar{\mathrm{E}}_3$ when $S = \frac{D_1 D_4 D_5}{1 + D_2 D_5} + \frac{D_4 D_5}{D_6}$ at $\hat{x}_2 = \frac{D_5}{D_6}$ and $\bar{\mathrm{E}}_3 = \bar{\mathrm{E}}_2 = \left(\frac{D_4 D_5}{1 + D_2 D_5}, \frac{D_5}{D_6}, \frac{1}{D_6}, 0\right)$. Therefore, there are no Hopf bifurcation or any other kind of bifurcations which can occur from the boundary equilibria $\bar{\mathrm{E}}_1$ and $\bar{\mathrm{E}}_2$.

To find possible Hopf bifurcation arising from $\bar{E}_3$, we compute the characteristic polynomial for $\bar{E}_3$ to obtain $P_3(\lambda) = \lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4$, where

$$
\begin{aligned}
b_1 = {} & \frac{1}{D_6^2(1+D_2D_6\hat{x}_2)} \Big\{ D_2(D_6\hat{x}_2 - D_5)^2(D_6^2 + D_2D_6 + D_3) + (D_6\hat{x}_2 - D_5)\big[(D_3 + 2D_2D_6)(1 + D_2D_5) \\
& + D_6^2(1 + D_1D_2 + 2D_2D_5) \big] + D_6\big[(1 + D_2D_5)^2 + D_6(D_1 + D_5)(1 + D_2D_5) + D_4D_6\big] \Big\}, \\
b_2 = {} & \frac{1}{D_6^2(1+D_2D_6\hat{x}_2)} \Big\{ D_2(D_6\hat{x}_2 - D_5)^3(D_2D_6 + D_3) \\
& + (D_6\hat{x}_2 - D_5)^2\big[(D_3 + 2D_2D_6)(1 + D_2D_5) + D_2D_6\big(D_6(1 + D_1) + D_2(D_4 + D_5)\big) + D_2D_3D_5\big] \\
& + (D_6\hat{x}_2 - D_5)\big[\big(D_6(D_6D_1 + 1 + D_6 + 2D_2D_4 + 3D_2D_5) + D_3D_5\big)(1 + D_2D_5) \\
& + D_3D_4 + D_1D_2D_5D_6^2 \big] + D_6\big[D_1D_6(D_4 + D_5 + D_2D_5^2) + (1 + D_2D_5)^2(D_4 + D_5)\big] \Big\}, \\
b_3 = {} & \frac{1}{D_6^2(1+D_2D_6\hat{x}_2)} \Big\{ D_2(D_6\hat{x}_2 - D_5)^3(1 + D_4)(D_3 + D_2D_6) \\
& + (D_6\hat{x}_2 - D_5)^2\big[(1 + D_4)(1 + D_2D_5)(D_3 + 2D_2D_6) + D_2\big(D_4D_5(D_3 + D_2D_6) + D_1D_6^2\big)\big] \\
& + (D_6\hat{x}_2 - D_5)\big[D_6^2\big(D_4 + D_1(1 + D_2D_5)\big) + (1 + D_2D_5)\big(D_6(1 + D_2D_5 \\
& + 3D_2D_4D_5 + D_4) + D_3D_4D_5 \big)\big] + D_4D_5D_6(1 + D_2D_5)^2 \Big\}, \\
b_4 = {} & \frac{D_4(D_6\hat{x}_2 - D_5)}{D_6^2(1+D_2D_6\hat{x}_2)} \Big\{ D_2(D_6\hat{x}_2 - D_5)^2(D_3 + D_2D_6) \\
& + 2(D_6\hat{x}_2 - D_5)(1 + D_2D_5)(D_3 + D_2D_6) + \big[D_6(1 + D_2D_5) + D_3D_5\big](1 + D_2D_5) + D_1D_6^2 \Big\},
\end{aligned}
$$

where $\hat{x}_2$ is determined from (19). Since the equilibrium $\bar{E}_3$ exists for $D_6\hat{x}_2 - D_5 \geqslant 0$, we have $b_i > 0$, $i = 1, 2, 3$, and $b_4 \geqslant 0$.

The equilibrium $\bar{E}_3$ is asymptotically stable if the following conditions hold: $\Delta_i > 0$, $i = 1, 2, 3, 4$. At the critical point defined by $b_4 = 0$, i.e., $S = \frac{D_1D_2D_5}{1+D_2D_5} + \frac{D_4D_5}{D_6}$, $\bar{E}_2$ loses its stability at $\hat{x}_2 = \frac{D_5}{D_6}$, and $\bar{E}_3$ emerges to exist in the cone R_+^4, showing that a transcritical bifurcation may occur between the equilibria $\bar{E}_2$ and $\bar{E}_3$. We need to verify if other stability conditions still hold at $b_4 = 0$. It is easy to see that $b_1 > 0, b_3 > 0$ at $b_4 = 0$. Since $\Delta_3 = b_3\Delta_2$ at $b_4 = 0$, we only need to verify $\Delta_2 > 0$. A simple calculation shows that at $b_4 = 0$, i.e., $\hat{x}_2 = \frac{D_5}{D_6}$, we have

$$
\begin{aligned}
& \Delta_2|_{b_4=0} \\
= {} & \frac{1}{D_6^2(1+D_2D_5)^2} \Big\{ D_6\big[(1 + D_2D_5)^2 + D_1D_6\big]D_4^2 \\
& + (1 + D_2D_5)\big[(1 + D_2D_5)^3 + D_6(1 + D_2D_5)\big(2D_1 + D_5(1 + D_1D_2)\big) + D_1D_6^2(D_1 + 2D_5)\big]D_4 \\
& + D_5(1 + D_2D_5)^2(D_1D_6 + 1 + D_2D_5)\big[1 + D_2D_5 + D_6(D_1 + D_5)\big] \Big\} > 0.
\end{aligned}
$$

The above results indeed show that a transcritical bifurcation occurs between $\bar{E}_2$ and $\bar{E}_3$ at the critical point $S = \frac{D_1D_2D_5}{1+D_2D_5} + \frac{D_4D_5}{D_6}$.

Next, we want to investigate what kind of bifurcations can occur from the equilibrium $\bar{E}_3$ for $S > \frac{D_1D_2D_5}{1+D_2D_5} + \frac{D_4D_5}{D_6}$, under which $b_4 > 0$. Now all $b_i > 0$, $i = 1, 2, 3, 4$, we only need to consider Δ_2 and Δ_3. It is easy to obtain from $\Delta_3 = b_3\Delta_2 - b_1^2b_4$ that $\frac{\Delta_3}{b_3} = \Delta_2 - \frac{b_1^2b_4}{b_3} < \Delta_2$, which implies that when S is increasing from the critical point $S = \frac{D_1D_2D_5}{1+D_2D_5} + \frac{D_4D_5}{D_6}$, Δ_3 will cross zero before Δ_2 does. This means that the only possible condition under which $\bar{E}_3$ loses its stability is $\Delta_3 = 0$ at which Hopf bifurcation occurs. Moreover, a simple computation shows that

$$
b_3|_{b_4=0} = \frac{D_4D_5(1 + D_2D_5)}{D_6} > 0,
$$

which implies that no feasible parameter values exist for the model (8) to have Bogdanov-Takens bifurcation from the equilibrium $\bar{E}_3$.

In order to find the parameter values under which Hopf bifurcation does occur from the equilibrium $\bar{\mathrm{E}}_3$ of system (8). So substituting b_i's into $\Delta_3 = b_3(b_1 b_2 - b_3) - b_1^2 b_4$ and using the quadratic equation (19) to eliminate higher order powers of $\hat{x}_2$ yields an equation, $B_1 \hat{x}_2 + B_0 = 0$, where B_1 and B_0 are polynomials in system parameters, which in turn gives

$$\begin{aligned}
&\left\{ 2D_4 D_6 (D_3 + D_2 D_5) B_0 + \left[SD_2 D_6^2 + D_4 \left[D_3 D_5 - D_6 (1 + D_1 D_6) \right] \right] B_1 \right\}^2 \\
&- \; B_1^2 \left\{ \left[SD_2 D_6^2 + D_4 \left(D_3 D_5 - D_6 (1 + D_1 D_6) \right) \right]^2 + 4SD_4 D_6^2 (D_3 + D_2 D_6) \right\} = 0,
\end{aligned}$$

from which we can obtain a very lengthy multivariate polynomial $F(S, D_i) = 0$. This multivariate polynomial can be used to determine the Hopf critical point.

Even with the explicit function $F(S, D_i)$, in general it is still very difficult to prove the existence of the Hopf critical point due to the very complex expression of the function and multiple parameters involved. However, when some parameters are fixed (as shown in the following examples), it is possible to use the function $F(S, D_i)$ to obtain the critical parameter values in terms of other remaining parameters. Thus, the Hopf bifurcation indeed exists for various feasible parameter values. □

Now we consider the stability of the equilibrium $\bar{\mathrm{E}}_3$ of model (8), compared with the original model (5). Note that if we take $\beta_2 = 0$ in system (5) (or $D_2 = 0$ in system (8)), i.e., the cell-to-cell interaction is not considered (which changes the basic reproduction number $\mathcal{R}_0$), then the reduced system has been studied in [24], where the parameter values given in Table 1 are used, showing the existence of Hopf bifurcations at the critical parameter values: $q_1 = 0.6493$ and $q_2 = 74.2520$.

Next, consider $\beta_2 > 0$. Since system (8) exhibits Hopf bifurcation for $\beta_2 = 0$, it is expected that the system also undergoes Hopf bifurcation for small values of β_2. For example, choosing $\beta_2 = 0.0107$, we can show that system (5) has Hopf bifurcations at the critical values: $q_1 = 2.8738$ and $q_2 = 8.3010$. As the value of β_2 is increasing, the gap between the two critical values q_1 and q_2 becomes smaller and smaller, until q_1 and q_2 coincide at a critical point at which Hopf bifurcation disappears. Then, all the equilibria become asymptotically stable for corresponding parameter values.

To demonstrate the dynamical behavior of system (8) (or system (5)) with respect to parameters, in the following, we present bifurcation diagrams for several combinations of parameters. We use the parameter values used in [16,17,32], as given in Table 1 and the above function $F(S, D_i)$ to consider Hopf bifurcation. The used parameter values in decimal point format are transformed to rational numbers for the convenience in symbolic computation, as given below:

$$s = 1, \quad \beta_1 = p = \tfrac{1}{10}, \quad \beta_2 = \tfrac{4}{625}, \quad d_1 = \tfrac{833}{100000}, \quad \delta = \tfrac{1}{2}, \quad d_2 = 72, \quad \gamma = d_3 = \tfrac{1}{20}, \quad k = 8.$$

We choose D_6 (originally q) as the primary bifurcation parameter with the second bifurcation parameter D_2 (originally β_2), or D_3 (originally γ), or S (originally s) to present two-parameter bifurcation diagrams.

First, consider the (D_6, D_2)-bifurcation diagram, which can be obtained from plotting the polynomial equation $F(D_6, D_2) = 0$ on the D_2-D_6 plane, which has also been verified by AUTO07P [33], as shown in Fig. 5(a). Moreover, besides the blue curve representing the Hopf bifurcation, four Hopf critical points are shown at $D_2 = 0$ and $D_2 = 0.0004$ (see the red dotted line), marked by the black circles. Note that according to the typical parameter values given in Table 1, the dimensionless parameter D_2 has a typical value $D_2 = \frac{\beta_2 d_3}{k \beta_1} = \frac{0.0064 \times 0.05}{8 \times 0.1} = 0.0004$. Therefore, taking small values for D_2 is biologically meaningful. These four critical Hopf critical points are solved from the equation $F(S, D_i) = F(6400, D_6) = 0$, given by

$$\begin{aligned}
D_2 &= 0: & D_{6H_1}^1 &= 6.5055, & D_{6H_2}^1 &= 58.9276; \\
D_2 &= 0.0004: & D_{6H_1}^2 &= 10.4228, & D_{6H_2}^2 &= 35.4659.
\end{aligned} \tag{26}$$

When D_6 is increased from $D_{6H_1}^1$, the two complex eigenvalues of Jacobian matrix of system (8), evaluated at the stationary point, move into the right half of the complex plane. So the solutions along the stationary
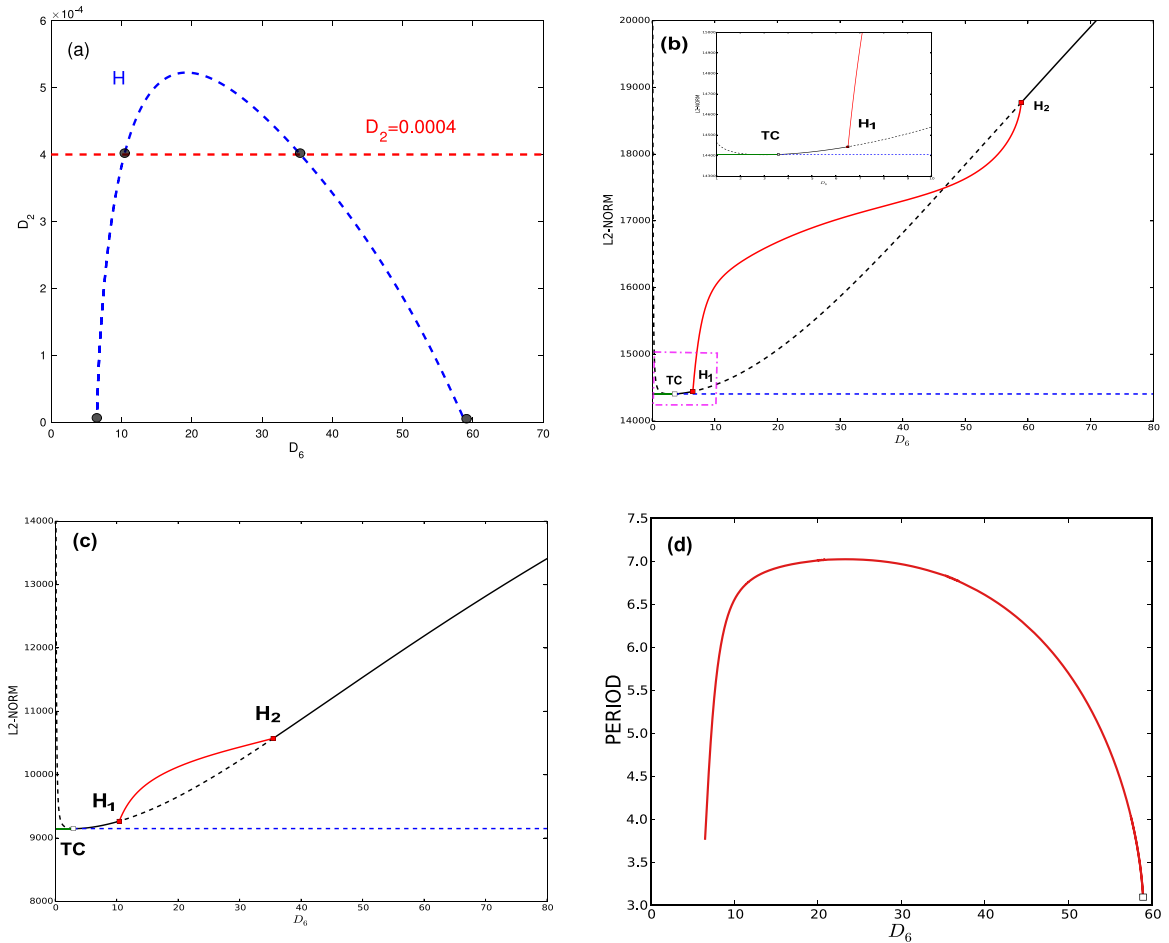
Fig. 5. (a) Two-parameter (D_2, D_6) Hopf bifurcation diagram of system (8), where the horizontal red line is $D_2 = 0.0004$; (b) Bifurcation diagram of system (8) for $D_2 = 0$ with a zoomed area at the lower left corner, where H_1 and H_2 denote Hopf bifurcation points, and TC denotes a transcritical bifurcation point, with the solid and dotted curves to denote stable and unstable solutions, respectively; (c) Bifurcation diagram of system (8) for $D_2 = 0.0004$, where H_1 and H_2 denote Hopf bifurcation points, and TC denotes a transcritical bifurcation point, with the solid and dotted curves to denote stable and unstable solutions, respectively; and (d) The period of bifurcating limit cycles of system (8) vs. D_6 when $D_2 = 0$. The red curves in (b) and (c) indicate the periodic solutions, while the black curves denote the equilibrium solution. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

branch become unstable. At the right Hopf bifurcation point $D^1_{6H_2}$ the eigenvalues move back into the left half of the complex plane if D_6 is further increased from $D^1_{6H_2}$, and the solutions along the branch of stationary solutions regain stability. So, according to Hopf bifurcation theorem, a family of small-amplitude periodic solutions emanates from the bifurcation point $D^1_{6H_1}$ or $D^1_{6H_2}$. To see the bifurcation property more clearly, we plot the one-parameter (D_6) bifurcation diagrams for $D_2 = 0$ and $D_6 = 0.0004$, which are given in Fig. 5(b) and (c), respectively, where the L_2-norm is the Euclidean norm defined as $\sqrt{x_1^2 + x_2^2 + x_3^2 + x_4^2}$. The bifurcation diagrams include one transcritical bifurcation point TC and two Hopf bifurcation points H_1 and H_2. It is seen from Fig. 5(a) that two stable limit cycles are born from the two Hopf critical points and a family of periodic solutions occurs, showing that the periodic bifurcation branches are connected when D_6 is varied. Here, the stability of the limit cycles is determined numerically. Theoretically, we may apply normal form theory to calculate the first Lyapunov constant (or the first-order focus value) to determine the stability of bifurcating limit cycles. Since for our system, determining the Hopf critical point is already very complex, computing the normal form for the 4-dimensional system will become extremely difficult (even
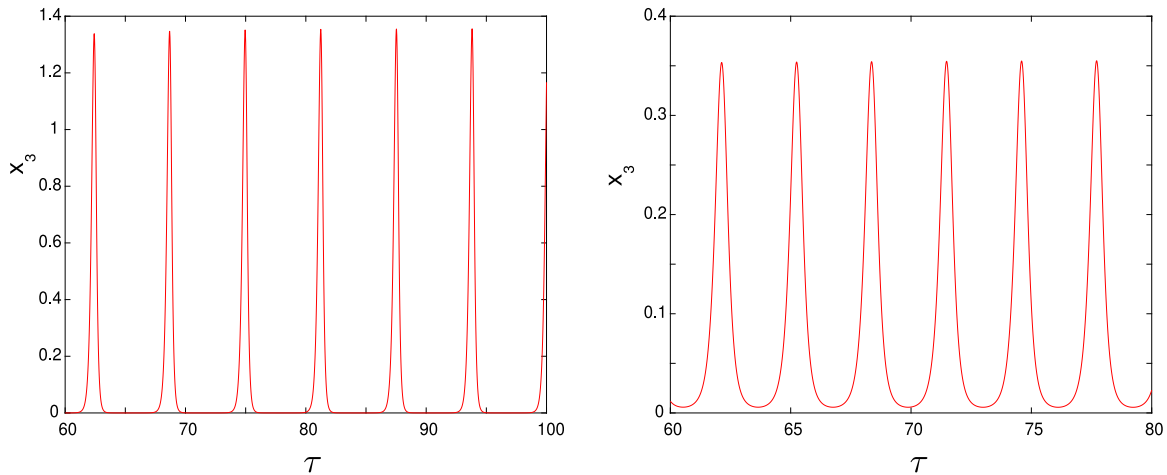
Fig. 6. Simulated time history of x_3 of system (8), with the initial point $(x_1, x_2, x_3, x_4) = (14\,400, 160, 0, 40)$, showing the recurrence phenomenon for $S = 6400$, $D_1 = 0.1666$, $D_4 = 10$, $D_5 = 1440$: (a) when $D_2 = 0$, $D_3 = 1.25$, $D_6 = 9$; and (b) when $D_2 = 0.0004$, $D_3 = 6$, $D_6 = 12$.

combining symbolic and numerical approaches), and so we do not pursue further on the analytic stability of limit cycles. However, it should be noted that the branch of periodic orbits born from two different Hopf bifurcation points may not be always connected as unstable limit cycles can occur from Hopf bifurcation, see, for example, [34]. Here, it is seen from Fig. 5(b) and (c) that oscillating motion emanating from the left Hopf bifurcation point H_1 persists until the right Hopf bifurcation point H_2 is reached. The period of the oscillations for $D_2 = 0$ along the branch of periodic solutions is given in Fig. 5(d). When $D_2 \neq 0$ (i.e., $\beta_2 \neq 0$), system (8) undergoes Hopf bifurcation when D_2 increases from 0 to 5.2242×10^{-4}, and the two Hopf bifurcations coincide at $D_2 = 5.2242 \times 10^{-4}$, and then disappear for $D_2 > 5.2242 \times 10^{-4}$. In other words, as shown in Fig. 5(c), the distance between the two Hopf bifurcation points becomes smaller and smaller when D_2 is increasing, and reaches zero at $D_2 = 5.2242 \times 10^{-4}$.

Further, it is seen from Fig. 5(b) that there exists a window between the two Hopf critical points for which all equilibria are unstable, and the amplitude of the oscillation grows very fast when the Hopf critical point is crossed. The simulated time history for $D_2 = 0$, $D_3 = 1.25$ and $D_6 = 9$ (and other parameter values are given in (10)) is given in Fig. 6(a), showing a special oscillation behavior, called recurrence. This interesting phenomenon, characterized by short episodes of high viral reproduction, separated by long periods of relative quiescence, is often observed in many persistent infections, including the "viral blips" observed during chronic infection with the human immunodeficiency virus (HIV). This special oscillation appears for most of the interval $D_6 \in (D_{6H_1}, D_{6H_2})$ (see Fig. 5(b) and (c)). Note that the phenomenon disappears as D_2 reaches $D_2 = 5.2242 \times 10^{-4}$ since the two Hopf critical points coincide and Hopf bifurcation vanishes. It is easy to see from Fig. 6(a) that the time history of x_3 (which is the density of the dimensionless virus) has a very "flat" bottom, implying that the HIV level keeps almost zero for a period of about $\tau = 6$ unit. Transforming it back to the original time $t_{\text{period}} = \frac{\tau}{d_3} = \frac{6}{0.05} = 120$ days, which indeed clearly indicates a recurrence behavior. Although these blips have been the focus of much recent research, their etiology is still not well-understood. Recently, Zhang et al. [35,36] applied dynamical system theory to study the recurrence phenomenon using simple ODE models, and developed an efficient approach to identify this phenomenon.

Next, consider (D_6, D_3)-bifurcation diagram, which can be similarly obtained, as shown in Fig. 7(a), where D_2 is taken as $D_2 = 0.0004$. As we have seen that when $D_3 = 0$ (i.e., $\gamma = 0$), model (8) is reduced to model (7) which does not have Hopf bifurcation. However, increasing D_3 from zero would bring the Hopf bifurcation back at a critical value. It is seen from Fig. 5(a) that no Hopf bifurcation exists for $D_2 = 0.0004$ and $D_6 < 10.4228$. We choose $D_6 = 12$ and then increase D_3 (i.e., γ) from zero. It can be seen from
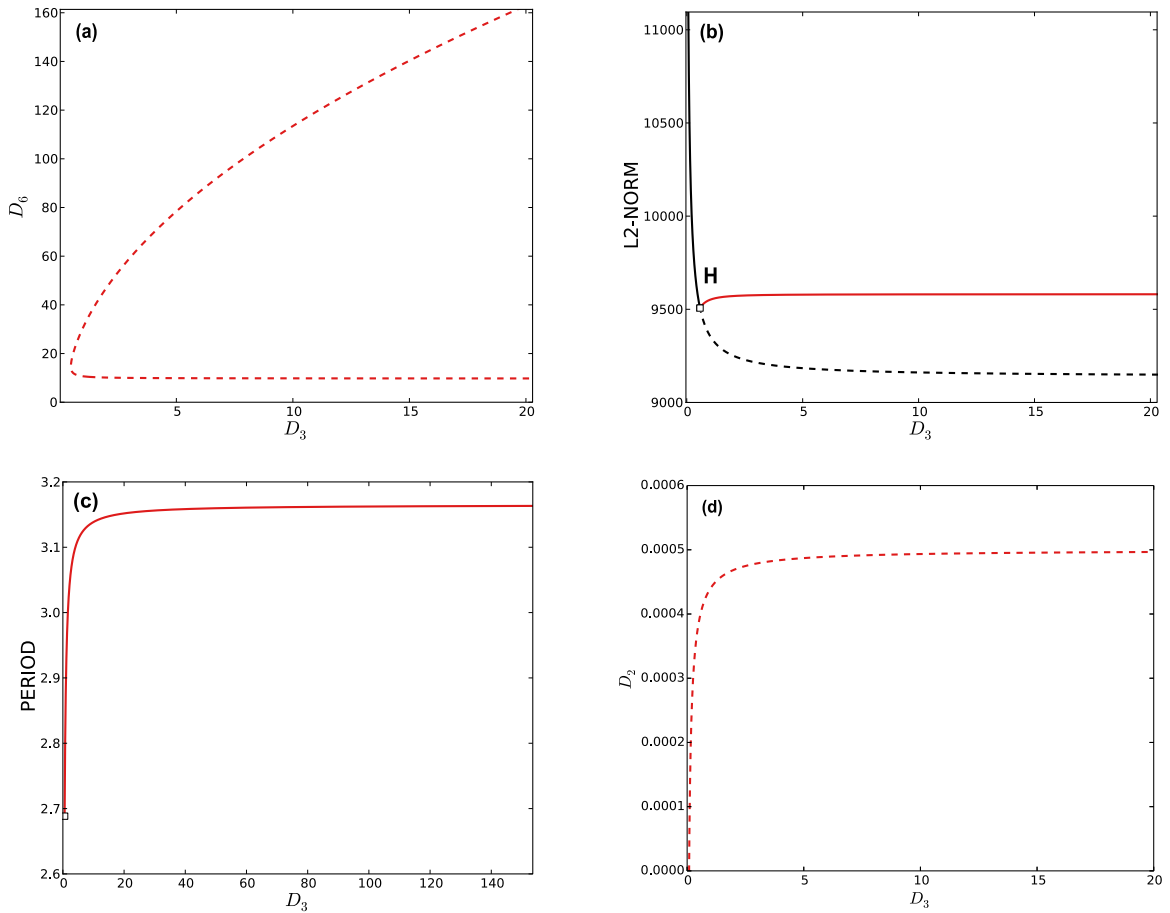
Fig. 7. (a) Two parameter (D_6, D_3) Hopf bifurcation diagram of system (8) for $D_2 = 0.0004$; with the dotted curve representing the unstable equilibrium solution; (b) one-parameter bifurcation diagram for system (8) with $D_6 = 12$, where H denotes the Hopf bifurcation point, and the red curve denotes the amplitude of periodic orbits, with the solid and dotted curves representing the stable and unstable equilibrium solutions, respectively; (c) the period of bifurcating limit cycles of system (8) vs. D_3 when $D_6 = 12$; and (d) two parameter (D_2, D_3) Hopf bifurcation diagram of system (8) when $D_6 = 12$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figs. 7(b) and 8 that the components x_1, x_2 and x_4 have a similar trend – decrease monotonically, while $x_3 \approx 0.0551$ – a constant until a supercritical Hopf bifurcation occurs, yielding stable limit cycles. It is interesting to note that the period of the bifurcating limit cycles, as shown in Fig. 7(c), almost becomes a constant for large values of D_3. This implies that even if the density of the HIV in blood (in terms of V) keeps unchanged, the oscillation behavior can be induced by the effect of the involvement. Biologically speaking, once a patient is infected by the HIV, although the density of the HIV in blood is kept at a constant level, the patient may go through a sudden occurrence of HIV, and then continue to keep the density of the HIV in blood a constant, yielding the recurrence phenomenon [35,36]. An example for $D_2 = 0.0004$, $D_3 = 6$ and $D_6 = 12$ (and other parameter values are given in (10)) is shown in Fig. 6(b). It should be noted that unlike the case $D_2 = 0$, for this case $(D_2 \neq 0)$ the system can always have blips as D_3 increases from $D_3 = 0.4745$, though the relaxation does not have so "flat" bottom like that shown in Fig. 6(a) when $D_2 = 0$. Similarly, the period is about $t_{\text{period}} = \frac{\tau}{d_3} = \frac{3}{0.05} = 60$ days. Further, it is seen from Fig. 7(a) that Hopf bifurcation starts at the critical point $D_3 = 0.4745$, and no Hopf bifurcation can happen if D_3 is below this critical value. Moreover, there exists only one Hopf bifurcation point for every fixed value of the parameter D_6. If we take the parameter D_6 as the primary bifurcation parameter and fix $D_2 = 0.0004$, then we obtain
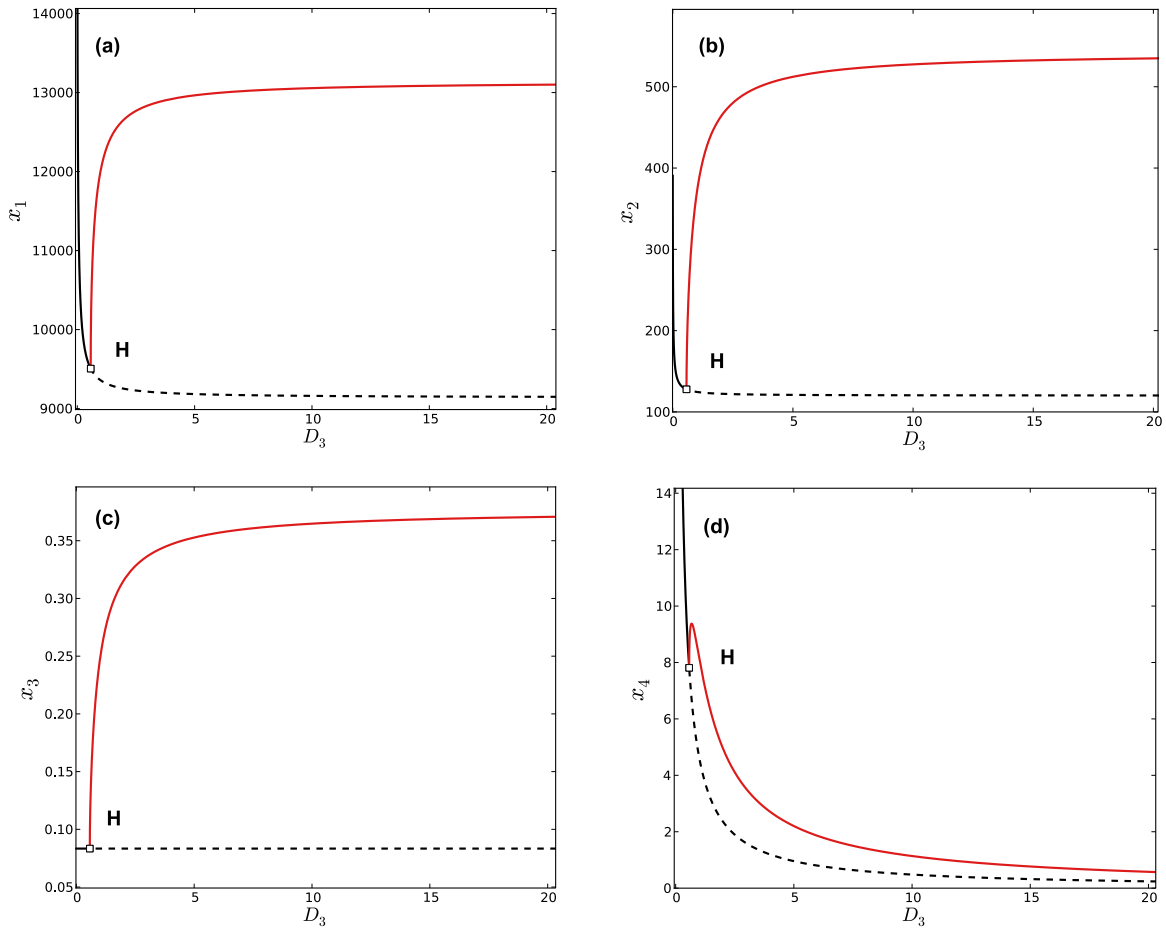
Fig. 8. One-parameter bifurcation (D_3) diagrams for system (8) with $D_6 = 12$, projected on (a) the D_3-x_1 plane, (b) the D_3-x_2 plane, (c) the D_3-x_3 plane, and (d) the D_3-x_4 plane, where H denotes the Hopf bifurcation point, the red curve denotes the periodic orbit branch. The solid/dotted lines/curves represent, respectively, stable and unstable equilibrium solutions.

the one-parameter bifurcation diagrams, shown in Fig. 9(a)–(d) for different projections with respect to the variables x_1, x_2, x_3 and x_4, corresponding to the dimensionless densities of the uninfected CD4+T cells, the infected CD4+T cells, the immunodeficiency virus (HIV), and pathogens-specific lymphocytes, respectively. It is seen from these bifurcation diagrams that the densities of the uninfected cells and the pathogens-specific lymphocytes have a similar trend in changes, and that of the infected cells and the pathogens in blood also have a similar trend in changes. It should be pointed out here that the bifurcation comparison (with D_6 as the bifurcation parameter and fixed $D_2 = 0.0004$) is between the four components x_k, showing the similarity of dynamics between the different components, is different from that as shown in Fig. 5 where the bifurcation comparison is considered for two different values $D_2 = 0$ and $D_2 = 0.0004$ (with D_6 as the bifurcation parameter), but for general L_2-norm (which denotes the average amplitude of motions).

Finally, we consider (D_6, S)-bifurcation diagram of system (8), which is shown in Fig. 10, displaying two saddle–node bifurcation (SN) points at $(D_6, S) = (1.2805 \times 10^2, 1.7627 \times 10^3)$ and $(D_6, S) = (9.2899, 5.2411 \times 10^3)$, and a Generalized Hopf bifurcation (GH) or Bautin bifurcation at the point $(D_6, S) = (1.1027 \times 10^2, 2.0077 \times 10^3)$ at which the first Lyapunov coefficient vanishes and the second Lyapunov coefficient is obtained as -2.2130×10^{-9}. This implies that two limit cycles exist via appropriate perturbations on D_6 and S, with outer limit cycle stable and inner one unstable.
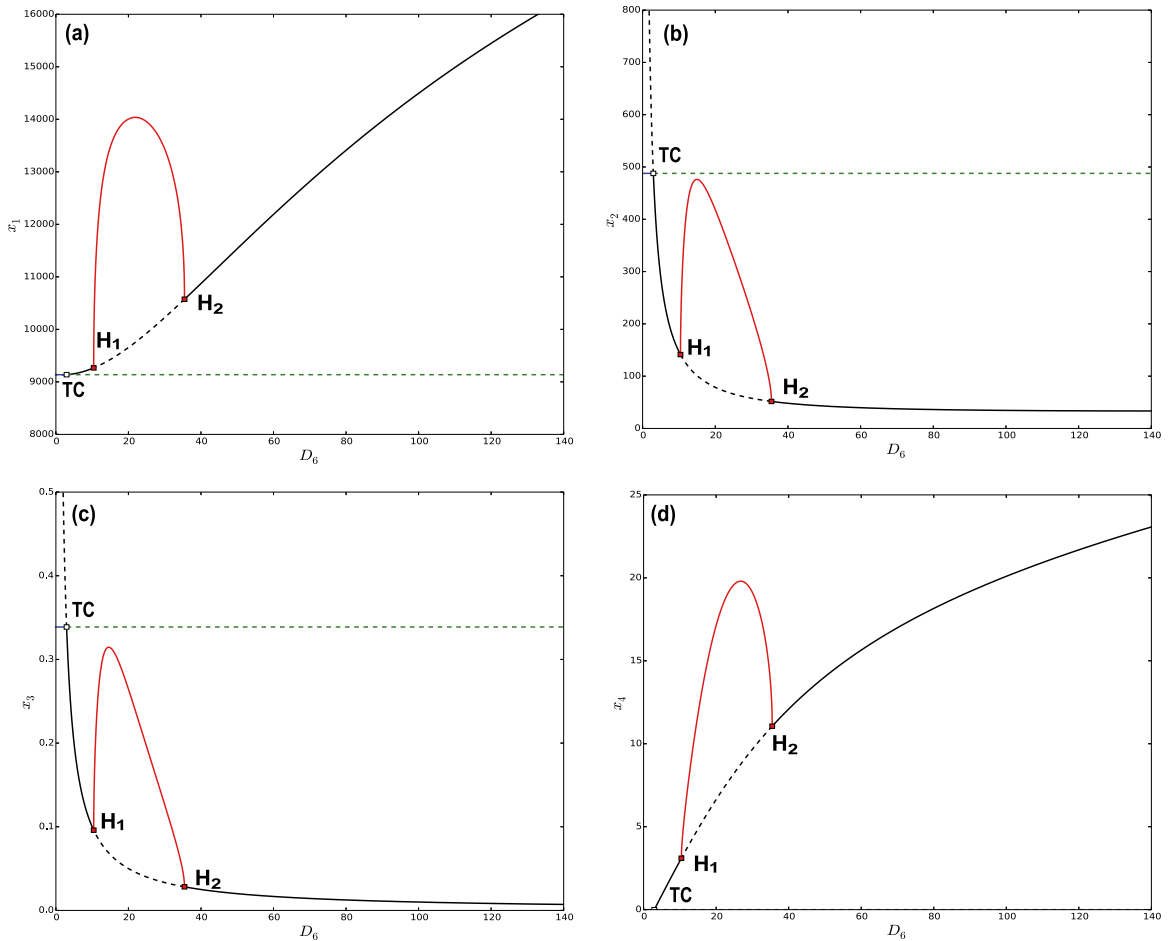
Fig. 9. One-parameter bifurcation (D_6) diagrams for system (8), projected on (a) the D_6-x_1 plane, (b) the D_6-x_2 plane, (c) the D_6-x_3 plane, and (d) the D_6-x_4 plane.
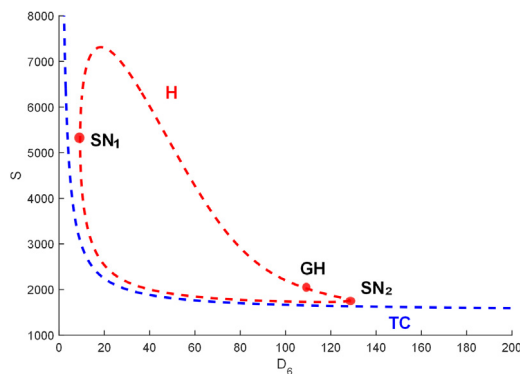

Fig. 10. Two-parameter (S, D_6) bifurcation diagram of system (8) with $D_2 = 0.0004$, where H denotes Hopf bifurcation branch (a closed cycle), TC denotes the transcritical bifurcation branch, SN and GH denote the saddle–node bifurcation point and generalized Hopf bifurcation point, respectively, with $(D_6, S)_{SN_1} = (9.2899, 5.2411 \times 10^3)$, $(D_6, S)_{SN_2} = (1.2805 \times 10^2, 1.7627 \times 10^3)$ and $(D_6, S)_{GH} = (1.1027 \times 10^2, 2.0077 \times 10^3)$.

Remark 3. Multiple Hopf bifurcations occurring from a same equilibrium is a quite common phenomenon in disease systems (or more generally in biological systems), e.g. see the HIV model in [36]. This implies that

disease oscillation only happens for certain average parameter values. For model (8), for example, choosing D_6 (or q) as the bifurcation parameter and fix other parameter values, the oscillating behavior only occurs for $D_6 \in (D_{6H_1}, D_{6H_2})$, and the oscillations become equilibrium $\bar{E}_3$ for $D_6 < D_{6H_1}$ or $D_6 > D_{6H_2}$. Biologically, this shows that when the immune system starts to activate to release the lymphocytes (whose strength is measured by the parameter q) to kill the virus, the system stays at the equilibrium $\bar{E}_3$ at the beginning; when the lymphocytes are increasing to reach certain critical value, oscillations are trigged which continue till the lymphocytes reach another larger critical value at which the oscillations are suppressed and the equilibrium $\bar{E}_3$ is resumed. This suggests that a good control strategy should not let the immune system over activated, but keep at a suitable level such that the system can stay at the equilibrium $\bar{E}_3$ rather than oscillations.

5. Existence of forward transcritical bifurcation

In this section, we analyze forward bifurcations which occur at the transcritical bifurcation points by applying center manifold theory [36]. Since the analysis for system (7) is similar to system (8), we will only give a detailed analysis for system (8).

Suppose $\mathcal{R}_0 = 1$, then the stability condition of $\bar{E}_1$ for system (8) becomes $D_1 D_4 D_5 - S(1 + D_2 D_5) = 0$, showing that the characteristic equation has one simple zero eigenvalue and three negative eigenvalues: $-1, -D_1$ and $-\frac{S + D_1 D_5^2}{D_1 D_5}$.

There is a right eigenvector associated with the zero eigenvalue, given by $w = (w_1, w_2, w_3, w_4)^T = (-\frac{(1+D_2 D_5)S}{D_1^2} x_3, D_5 x_3, x_3, 0)^T$. The left eigenvector is $v = (v_1, v_2, v_3, v_4) = (0, \frac{D_1 D_5}{S} y_3, y_3, 0)$. Upon using the orthogonal condition $\langle v, w \rangle = 1$, we obtain

$$x_3 y_3 = \frac{S}{D_1 D_5^2 + S}.$$

It follows from $\mathcal{R}_0 = 1$ that $D_2 = D_2^* = \frac{S - D_1 D_4 D_5}{D_5 S}$. Thus, model (8) can be rewritten as $\frac{dx}{dt} = f$, with $x = (x_1, x_2, x_3, x_4)^T$ and $f = (f_1, f_2, f_3, f_4)^T$, where

$$\begin{aligned}
f_1 &= S - D_1 x_1 - D_2 x_1 x_2 - x_1 x_3 - D_3 x_1 x_3 x_4, \\
f_2 &= D_2 x_1 x_2 + x_1 x_3 - D_4 x_2, \\
f_3 &= x_2 - D_5 x_3 - D_6 x_3 x_4, \\
f_4 &= D_6 x_3 x_4 - x_4.
\end{aligned} \tag{27}$$

The bifurcation coefficients in this compartmental model at $\bar{E}_1$ are given as follows:

$$a = \sum_{i,j,k=1}^{4} v_i w_j w_k \frac{\partial^2 f_i}{\partial x_j \partial x_k}(\bar{E}_1, D_2^*), \quad b = \sum_{i,j=1}^{4} v_i w_j \frac{\partial^2 f_i}{\partial x_j \partial D_2}(\bar{E}_1, D_2^*).$$

Since $v_1 = v_4 = 0$, we only need to consider the cross derivatives of f_2 and f_3 in system (27) at the equilibrium $\bar{E}_1$, yielding the following non-zero terms:

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = D_2, \qquad \frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = 1, \\
\frac{\partial^2 f_3}{\partial x_3 \partial x_4} &= \frac{\partial^2 f_3}{\partial x_4 \partial x_3} = -D_6, \qquad \frac{\partial^2 f_2}{\partial D_2 \partial x_2} = \frac{\partial^2 f_2}{\partial x_2 \partial D_2} = x_1^* = \frac{S}{D_1}.
\end{aligned}$$

In order to determine whether the transcritical bifurcation is forward or backward, we consider the direction of the transcritical bifurcation by computing the following values (e.g., using the formulas in [36]):

$$a = v_2 \sum_{i,j=1}^{4} w_j w_k \frac{\partial^2 f_2}{\partial x_j \partial x_k}(\bar{E}_1, D_2^*) + v_3 \sum_{i,j=1}^{4} w_j w_k \frac{\partial^2 f_3}{\partial x_j \partial x_k}(\bar{E}_1, D_2^*) = -2D_5 \frac{(1 + D_2^* D_5)^2}{D_1} x_3^2 y_3,$$

and

$$b = v_2 \sum_{j=1}^{4} w_j \frac{\partial^2 f_2}{\partial x_j \partial D_2}(\bar{E}_1, D_2^*) + v_3 \sum_{j=1}^{4} w_j \frac{\partial^2 f_3}{\partial x_j \partial D_2}(\bar{E}_1, D_2^*) = 2D_5^2 x_3 y_3.$$

Without loss of generality, we take $x_3 > 0$ and $y_3 > 0$, which gives $b > 0$. According to [36], the local dynamics of the system near the equilibrium $\bar{E}_1$ depends upon the signs of a and b. Since all the parameters in system (8) are positive, we obtain $a < 0$ and $b > 0$. This indicates that the transcritical bifurcation from the equilibrium $\bar{E}_1$ is a forward bifurcation.

Remark 4. It has been shown that the parameter D_3 in the term $D_3 x_1 x_3 x_4$ of system (8) has no effect on the bifurcation between the equilibria $\bar{E}_1$ and $\bar{E}_2$, and the infection-free equilibrium $\bar{E}_1$ is exactly the same as E_1 of system (7), we know that the transcritical bifurcation in system (7) from the equilibrium E_1 is also a forward bifurcation.

6. Conclusion and discussion

In this paper, we have studied the effect of cell-to-cell interaction in two HIV models. The difference between the two models lies in the inclusion or omission of the effect of the involvement. Both the two models have three equilibria: the infection-free equilibrium, the infectious equilibrium with specific immune cells absent, and the positive equilibrium which includes immune cells. Their local and global stability are fully analyzed to show that

(1) When the basic reproduction number $\mathcal{R}_0 \leqslant 1$, the disease-free equilibrium is GAS (globally asymptotically stable).
(2) When $\mathcal{R}_0 > 1$, the disease-free equilibrium becomes unstable and the infectious equilibrium exists, which is GAS for $1 < \mathcal{R}_0 \leqslant \mathcal{R}_1$.
(3) When $\mathcal{R}_0 > \mathcal{R}_1$, the infectious equilibrium becomes unstable and the positive equilibrium appears, which is GAS for system (7) or the original model (3).
(4) For system (8) or the original model (5), when $\mathcal{R}_0 > \mathcal{R}_1$, the positive equilibrium loses its stability and two Hopf bifurcations occur. However, with the increasing of cell-to-cell interaction, the gap between the two Hopf bifurcation points decreases to zero at which the two Hopf bifurcation points coincide.
(5) Forward bifurcation appears in the two models at the transcritical bifurcation points.
(6) The cell-to-cell interaction considered in model (3), which is ignored in model (2), does not affect the stability of equilibria in model (3). However, the effect of the involvement in model (5), which is ignored in model (3), generates the recurrence phenomenon.

Moreover, we have presented a detailed analysis to identify Hopf critical points and performed various parameter studies related to Hopf bifurcations. For stability analysis, instead of the Lyapunov function which is not easy to be found due to the cubic term γTVA, we have applied fluctuation lemma to prove the global stability of the infection-free equilibrium and the infectious equilibrium. One-parameter and two-parameter bifurcation diagrams are used to display two families of limit cycles bifurcating from the two Hopf bifurcation points. It has been shown that even for small effect of involvement, the stability of the equilibria is significantly affected, which is usually destabilized. However, with the increasing of cell-to-cell interaction, the instability caused by the effect of the involvement can be balanced. Furthermore, if the coefficient of the cell-to-cell interaction is fixed, then the effect of the involvement will always lead to the occurrence of Hopf bifurcation when the humoral immune response reaches a critical value. From the viewpoint of biology, our study has indicated that although the disease considered in our models is recrudescent, the situation of patients may be improved by taking some medicine to increase the level of humoral immunity, and then the densities of infected cells and pathogens of patients would decrease until a critical value is reached at which

Hopf bifurcation occurs. It has been known that the effect of the involvement can also affect the stability of the positive equilibrium in the model of malaria infection [23], which even incorporated cell-mediated immunity. Thus, we may speculate that the sustained oscillations generated from Hopf bifurcation may disappear if the intensity of humoral immune response is increased. It is well known that many infectious diseases exhibit periodic symptoms, which may be explained by the oscillation due to Hopf bifurcation. Therefore, based on the study of the models (7) and (8), we may conclude that the effect of the involvement could be one of the main causes to generate the periodic behavior in HIV and malaria diseases. In particular, we find that the HIV carriers may go through a sudden occurrence (or recurrence) of HIV even the density of human immunodeficiency virus keep unchanged. In addition, we have shown the existence of generalized Hopf bifurcation (Bautin bifurcation), which may explain more complex behavior in disease models or other biological systems. This is out of the scope of this paper and will be investigated in future study.

Acknowledgments

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