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Research article

Hopf bifurcation in a CTL-inclusive HIV-1 infection model with two time delays

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Abstract: In this paper, we investigate a delayed HIV-1 infection model with immune response. Though a logistic growth is incorporated in the growth of the target cells, our focus is on the effect of delays on the infection dynamics. We first study the existence of steady states, which depends on the basic reproduction number R_0. When $R_0 \leq 1$, there is only the infection-free steady state, which is globally asymptotically stable if $R_0 < 1$. When $R_0 > 1$, besides the unstable infection-free steady state, there is a unique infected steady state. We then study the local stability of the infected steady state and local Hopf bifurcation at it. The theoretical analysis indicates that the dynamics scenario is complicated. For example, there can be three sequences of critical values, stability switches and double Hopf bifurcation can occur. Some of the theoretical results are also illustrated with numerical simulations.

Keywords: HIV-1 infection; Hopf bifurcation; time delay; CTL immune response; stability

1. Introduction

AIDS (acquired immunodeficiency syndrome) is a syndrome caused by HIV (human immunodeficiency virus). HIV is a lentivirus (a subgroup of retrovirus). It infects vital cells in the human immune system, such as helper T cells (specifically $CD4^+$ T cells), macrophages, and dendritic cells [1]. When the number of $CD4^+$ T cells declines below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections, leading to the development of AIDS. Mathematical modeling has contributed a lot to the understanding of HIV infection (see, for example, the review by Perelson and Ribeiro [2] for within-host models).

In the simplest and earliest models of HIV infection, only the key players were taken into account. These models include uninfected target cells (T), productively infected cells (T^*), and free viruses (V). One such model is described by the following system of ordinary differential equations,

$$\begin{aligned}\frac{dT}{dt} &= \lambda - dT - kVT,\\ \frac{dT^*}{dt} &= kVT - \delta T^*,\\ \frac{dV}{dt} &= pT^* - cV.\end{aligned}$$

For more detail, we refer the readers to Ribeiro and Perelson [3]. Inspired by this model, researchers have proposed many other HIV models by considering, for example, different uninfected target cell growth and incidence, latently infected CD4$^+$ T cells, treatment, drug resistance, and immune response (to name a few, see [4–16]).

Time delay is commonly observed in many biological processes. For HIV infection, on the one hand, it roughly takes about 1 day for a newly infected cell to become productive and then to be able to produce new virus particles [17]. On the other hand, during CTL response, effector CTLs need time to recognize infected cells and destroy them. Herz *et al.* [18] were the first to introduce an intracellular delay to describe the time between the initial viral entry into a target cell and subsequent viral production. They obtained the effect of the delay on viral load change. Since then, delayed HIV models have attracted the attention of many researchers. See, for example, [19–26] and the references therein.

In this paper, motivated by the studies in [7, 10, 27], we propose and study the following delayed HIV model,

$$\frac{dT(t)}{dt} = s - dT(t) + rT(t)\left(1 - \frac{T(t)}{T_{\max}}\right) - kV(t)T(t), \tag{1.1a}$$

$$\frac{dT^*(t)}{dt} = k_1 V(t-\tau_1)T(t-\tau_1) - \delta T^*(t) - d_x E(t)T^*(t), \tag{1.1b}$$

$$\frac{dV(t)}{dt} = N\delta T^*(t) - cV(t), \tag{1.1c}$$

$$\frac{dE(t)}{dt} = \lambda_E + pT^*(t-\tau_2) - d_E E(t). \tag{1.1d}$$

Here $T(t)$, $T^*(t)$, $V(t)$, and $E(t)$ represent the densities of uninfected CD4$^+$ T-cells, productively infected CD4$^+$ T-cells, free viruses, and immune effectors at time t, respectively. As in [7, 28], $k_1 = ke^{-\alpha\tau_1}$, where $\alpha \in [d, \delta]$ is the death rate of infected cells before becoming productive. τ_1 denotes the time delay between viral entry and viral production while τ_2 stands for the time needed for the CTLs immune response to emerge to control viral replication. The interpretations of the parameters are summarized in Table 1, where their units and ranges will be given in Section 4. The logistic growth in target cells and natural growth of immune effectors combined is a new feature of Model (1.1). Our main focus is on the effects of delays, especially τ_2, on the dynamics of (1.1).

Table 1. Descriptions of parameters in (1.1).

Parameter	Description
s	Production rate of uninfected CD_4^+ T-cells
d	Death rate of uninfected CD_4^+ T-cells
r	Proliferation rate of uninfected CD_4^+ T-cells
$T_{\max}$	CD_4^+ T-cells density where proliferation stops
k	Infection rate of CD_4^+ T-cells with virus particles
α	Death rate of infected CD_4^+ T-cells before becoming productive
δ	Death rate of infected CD_4^+ T-cells
d_x	CTL effectiveness
N	Bursting term for viral production after lysis
c	Clearance rate of virus
λ_E	Proliferation rate of CTL from natural resources
p	Production rate of CTL response
d_E	Death rate of CTL response

The rest of the paper is organized as follows. In Section 2, we present some preliminary results of (1.1), which include the positivity and boundedness of solution, the existence of steady states. Then we analyze the stability of steady states and possible Hopf bifurcation in Section 3. We conclude the paper with some numerical simulations to illustrate the main theoretical results.

2. Preliminaries

The suitable phase space for (1.1) is $C = C_1 \times C_2 \times C_1 \times R$, where $C_i = C([-\tau_i, 0], R)$ is the Banach space of all continuous functions from $[-\tau_i, 0]$ to R equipped with the supremum norm, $i = 1, 2$. The norm on C is the usual product norm. The nonnegative cone of C_i is $C_i^+ = C([-\tau_i, 0], R_+)$. To be biologically meaningful, in the sequel, the initial conditions of (1.1) will be always from $C_+ = C_1^+ \times C_2^+ \times C_1^+ \times R_+$.

For each $\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in C_+$, by the standard theory of functional differential equations [29], Model (1.1) has a unique and global solution through it. For such a solution, we first claim that $T(t) > 0$ for $t > 0$. In fact, it is clear that there exists $t_0 > 0$ such that $T(t) > 0$ for $t \in (0, t_0)$. Suppose to the contrary that there exists $t_1 > t_0$ such that $T(t) > 0$ for $t \in (0, t_1)$ and $T(t_1) = 0$. Then by (1.1a), $\frac{dT(t_1)}{dt} = s > 0$ and hence there exists $\varepsilon \in (0, t_1)$ such that $T(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$, a contradiction. This proves the claim. Next, with step-by-step method we show that $T^*(t) \geq 0$ and $V(t) \geq 0$ for $t \geq 0$. Note that, for $t \geq 0$, by (1.1b) and (1.1c), we have

$$T^*(t) = e^{-\int_0^t (\delta + d_x E(s))ds} T^*(0) + \int_0^t e^{-\int_u^t (\delta + d_x E(s))ds} k_1 V(u - \tau_1) T(u - \tau_1) du \tag{2.1}$$

and

$$V(t) = e^{-ct} V(0) + \int_0^t e^{c(u-t)} N\delta T^*(u) du, \tag{2.2}$$

respectively. It follows from (2.1) that $T^*(t) \geq 0$ for $t \in [0, \tau_1]$. This, combined with (2.2), gives $V(t) \geq 0$ for $t \in [0, \tau_1]$, which together with (2.1) yields $T^*(t) \geq 0$ for $t \in [0, 2\tau_1]$. In turn from (2.2)

we have $V(t) \geq 0$ for $t \in [0, 2\tau_1]$. Continuing this way gives the desired result. Finally, from (1.1d), we get

$$E(t) = e^{-d_E t}E(0) + \int_0^t e^{d_E(u-t)}(\lambda_E + pT^*(u-\tau_2))du$$

for $t \geq 0$ and hence $E(t) \geq 0$ for $t \geq 0$. Therefore, the solution of (1.1) with initial condition in C_+ is nonnegative.

Next, we consider the boundedness of solutions. Firstly, we obtain from (1.1a) that

$$\frac{dT(t)}{dt} \leq s - dT(t) + rT(t)\left(1 - \frac{T(t)}{T_{\max}}\right)$$

for $t \geq 0$. It follows that

$$\limsup_{t\to\infty} T(t) \leq T_0,$$

where

$$T_0 = \frac{T_{\max}}{2r}\left[r - d + \sqrt{(r-d)^2 + \frac{4rs}{T_{\max}}}\right]$$

is the unique positive zero of $s - dT + rT(1 - \frac{T}{T_{\max}})$. Moreover, if $T(0) \leq T_0$ then $T(t) \leq T_0$ for $t \geq 0$. Secondly, consider the Lyapunov functional

$$L_1(t) = T(t-\tau_1) + \frac{k}{k_1}T^*(t).$$

The derivative of L_1 along solutions of (1.1) is

$$\begin{aligned}
\frac{dL_1(t)}{dt} &= s - dT(t-\tau_1) + rT(t-\tau_1)\left(1 - \frac{T(t-\tau_1)}{T_{\max}}\right) - \frac{k\delta}{k_1}T^*(t) - \frac{kd_x}{k_1}E(t)T^*(t) \\
&\leq -dT(t-\tau_1) - \delta\frac{k}{k_1}T^*(t) + rT(t-\tau_1) - \frac{r}{T_{\max}}T^2(t-\tau_1) + s \\
&\leq -d_1L_1(t) + M_0,
\end{aligned}$$

where $d_1 = \min\{\delta, d\}$ and $M_0 = \frac{rT_{\max}+4s}{4}$ (> 0). Then $\limsup_{t\to\infty} L_1(t) \leq \frac{M_0}{d_1}$. In particular, $\limsup_{t\to\infty} T^*(t) \leq \frac{k_1M_0}{kd_1}$. Finally, this combined with (1.1c) and (1.1d) immediately gives

$$\limsup_{t\to\infty} V(t) \leq \frac{N\delta k_1 M_0}{ckd_1} \qquad \text{and} \qquad \limsup_{t\to\infty} E(t) \leq \frac{\lambda_E kd_1 + pk_1M_0}{d_E kd_1}, \qquad \text{respectively.}$$

Lastly, we study the lower boundedness of T. For any $\varepsilon > 0$, there exists $t_2 > 0$ such that $V(t) \leq \frac{N\delta k_1M_0}{ckd_1} + \varepsilon$ for $t \geq t_2$. This, together with (1.1a), gives us

$$\frac{dT(t)}{dt} \geq s - dT + rT\left(1 - \frac{T}{T_{\max}}\right) - kT\left(\frac{N\delta k_1M_0}{ckd_1} + \varepsilon\right) \qquad \text{for } t \geq t_2.$$

Hence, as ε is arbitrary, we get

$$\liminf_{t\to\infty} T(t) \geq \frac{T_{\max}}{2r}\left[r - d - \frac{N\delta k_1M_0}{cd_1} + \sqrt{\left(r - d - \frac{N\delta k_1M_0}{cd_1}\right)^2 + \frac{4rs}{T_{\max}}}\right].$$

To summarize, we have shown the following result.

Proposition 2.1. *The solutions of (1.1) with initial conditions in C_+ are nonnegative and bounded. Moreover, the region*

$$\Gamma = \left\{ \Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in C_+ \;\middle|\; \begin{array}{l} \text{the solution } (T(t), T^*(t), V(t), E(t)) \text{ of } (1.1) \\ \text{through } \Phi \text{ satisfies } \phi_1(0) \le T_0, \\ \phi_1(0) + \frac{k}{k_1} T^*(\tau_1) \le \frac{M_0}{d_1}, \phi_3(0) \le \frac{N\delta k_1 M_0}{ckd_1}, \\ \text{and } \phi_4 \le \frac{\lambda_E k d_1 + p k_1 M_0}{d_E k d_1} \end{array} \right\}$$

is a positively invariant and attracting subset of (1.1) in C_+.

In the remaining of this section, we consider the steady states of (1.1). Note that a steady state is a solution of the following system of algebraic equations,

$$s - dT + rT\left(1 - \frac{T}{T_{\max}}\right) - kVT = 0, \tag{2.3a}$$

$$k_1 VT - \delta T^* - d_x E T^* = 0, \tag{2.3b}$$

$$N\delta T^* - cV = 0, \tag{2.3c}$$

$$\lambda_E + pT^* - d_E E = 0. \tag{2.3d}$$

It follows from (2.3c) that $V = \frac{N\delta T^*}{c}$. Sustituting it into (2.3b) gives

$$\frac{k_1 N\delta}{c} T^* T - \delta T^* - d_x E T^* = 0.$$

Then $T^* = 0$ or $T = \frac{c(\delta + d_x E)}{N\delta k_1}$. When $T^* = 0$, we get the infection-free steady state $P_0 = (T_0, 0, 0, E_0)$, where $E_0 = \frac{\lambda_E}{d_E}$. Now assume $T = \frac{c(\delta + d_x E)}{N\delta k_1}$. Combining it with $E = \frac{\lambda_E + pT^*}{d_E}$ obtained from (2.3d), we can get after a little computation that

$$T^* = \frac{[N\delta k_1 T - c(\delta + \frac{d_x \lambda_E}{d_E})] d_E}{c d_x p}. \tag{2.4}$$

Then

$$V = \frac{d_E N\delta}{c^2 d_x p}\left[N\delta k_1 T - c\left(\delta + \frac{d_x \lambda_E}{d_E}\right)\right].$$

Substituting it into (2.3a) yields

$$G(T) = 0,$$

where

$$G(T) = s + \left[r - d + \frac{k d_E N\delta}{c d_x p}\left(\delta + \frac{d_x \lambda_E}{d_E}\right)\right] T - \left[\frac{r}{T_{\max}} + \left(\frac{N\delta}{c}\right)^2 k k_1 \frac{d_E}{d_x p}\right] T^2.$$

Note that G always has a positive zero and it only has one positive zero. However, for infected steady states, we have $T > \frac{c(\delta + \frac{d_x \lambda_E}{d_E})}{N\delta k_1}$ from (2.4), or equivalently, $G(\frac{c(\delta + \frac{d_x \lambda_E}{d_E})}{N\delta k_1}) > 0$ or $\frac{c(\delta + \frac{d_x \lambda_E}{d_E})}{N\delta k_1} < T_0$. Thus there is an infected steady state if and only if $R_0 > 1$, where

$$R_0 = \frac{N\delta k_1 T_0}{c(\delta + d_x \frac{\lambda_E}{d_E})}.$$

In summary we have obtained the following result.

Theorem 2.1. *(i) If* $R_0 \le 1$ *then* (1.1) *only has the infection-free steady state* P_0.
(ii) If $R_0 > 1$ *then, besides* P_0, (1.1) *also has a unique infected steady state* $P_1 = (T_1, T_1^*, V_1, E_1)$, *where*

$$\begin{aligned} T_1 &= \frac{b + \sqrt{b^2 + 4as}}{2a}, \\ a &= \frac{r}{T_{\max}} + \left(\frac{N\delta}{c}\right)^2 \frac{kk_1 d_E}{d_x p}, \\ b &= r - d + (\delta d_E + d_x \lambda_E)\frac{N\delta k}{cpd_x}, \\ T_1^* &= \frac{d_E}{d_x p}\left(\frac{N\delta k_1 T_1}{c} - \delta - d_x \frac{\lambda_E}{d_E}\right), \\ V_1 &= \frac{N\delta}{c} T_1^*, \\ E_1 &= \frac{\lambda_E + pT_1^*}{d_E}. \end{aligned}$$

Note that, in epidemiology, R_0 is called the basic reproduction number, whose expression can also be derived by the procedure in [30].

3. Stability and bifurcation

3.1. Global stability of P_0

We start with the local stability of the infection-free steady state P_0.

Theorem 3.1. *(i) If* $R_0 < 1$, *then the infection-free steady state* P_0 *of* (1.1) *is locally asymptotically stable.*
(ii) If $R_0 > 1$, *then* P_0 *is unstable.*

Proof. The characteristic equation at P_0 is

$$(\lambda + d_E)\left(\lambda + d - r + \frac{2rT_0}{T_{\max}}\right)\left[\lambda^2 + (c + \delta + d_x E_0)\lambda + c(\delta + d_x E_0) - N\delta k_1 T_0 e^{-\lambda\tau_1}\right] = 0.$$

Clearly, $-d_E$ and $-(d - r + \frac{2rT_0}{T_{\max}}) = -\frac{s}{T_0} - \frac{rT_0}{T_{\max}}$ are eigenvalues and both are negative. The other eigenvalues are roots of the following transcendental equation,

$$\Delta_0(\lambda) = \lambda^2 + (c + \delta + d_x E_0)\lambda + c(\delta + d_x E_0) - N\delta k_1 T_0 e^{-\lambda\tau_1} = 0. \tag{3.1}$$

Noting

$$R_0 = \frac{N\delta k_1 T_0}{c(\delta + d_x E_0)},$$

we can rewrite (3.1) as

$$\Delta_0(\lambda) = \lambda^2 + (c + \delta + d_x E_0)\lambda + c(\delta + d_x E_0)(1 - R_0 e^{-\lambda\tau_1}) = 0 \tag{3.2}$$

or equivalently

$$R_0 = \left(\frac{\lambda}{c} + 1\right)\left(\frac{\lambda}{\delta + d_x E_0} + 1\right) e^{\lambda \tau_1}. \tag{3.3}$$

(i) Assume $R_0 < 1$. We claim that all roots of (3.3) have negative real parts. Otherwise, (3.3) has a root $\lambda = \sigma + \omega i$ with $\sigma \geq 0$ and $\sigma^2 + \omega^2 > 0$ since 0 is not a root by $R_0 > 1$. Taking moduli of both sides of (3.3) gives

$$R_0 = e^{\sigma \tau_1} \sqrt{\left[\left(\frac{\sigma}{c} + 1\right)^2 + \frac{\omega^2}{c^2}\right]\left[\left(\frac{\sigma}{\delta + d_x E_0} + 1\right)^2 + \left(\frac{\omega}{\delta + d_x E_0}\right)^2\right]}.$$

This is impossible as the right side of the above is > 1 and $R_0 < 1$. This proves the claim and hence P_0 is locally asymptotically stable if $R_0 < 1$.

(ii) Assume $R_0 > 1$. In this case, (3.2) has a positive root. In fact, this follows from the Intermediate Value Theorem and

$$\Delta_0(0) = c(\delta + d_x E_0)(1 - R_0) < 0 \qquad \text{and} \qquad \lim_{\lambda \to \infty} \Delta_0(\lambda) = \infty.$$

Therefore, P_0 is unstable if $R_0 > 1$. This completes the proof. □

In fact, the local stability of P_0 implies its global stability.

Theorem 3.2. *If $R_0 < 1$, then the infection-free steady state P_0 of (1.1) is globally asymptotically stable.*

Proof. Define the Lyapunov functional

$$W_0(t) = T^*(t) + \frac{k_1 T_0}{c} V(t) + k_1 \int_{t-\tau_1}^{t} V(\theta) T(\theta) d\theta.$$

Then the time derivative of W_0 along solutions of (1.1) is

$$\begin{aligned}
\frac{dW_0(t)}{dt} &= \frac{dT^*(t)}{dt} + \frac{k_1 T_0}{c}\frac{dV(t)}{dt} + k_1 V(t)T(t) - k_1 V(t-\tau_1)T(t-\tau_1) \\
&= k_1 V(t-\tau_1)T(t-\tau_1) - \delta T^*(t) - d_x E(t) T^*(t) \\
&\quad + \frac{N\delta k_1 T_0}{c} T^*(t) - k_1 T_0 V(t) \\
&\quad + k_1 V(t)T(t) - k_1 V(t-\tau_1)T(t-\tau_1) \\
&= \left(\frac{N\delta k_1 T_0}{c} - (\delta + d_x E(t))\right) T^*(t) + k_1 V(t)(T(t) - T_0) \\
&\leq \left(\frac{N\delta k_1 T_0}{c} - (\delta + d_x E_0)\right) T^*(t) \\
&= (\delta + d_x E_0)(R_0 - 1) T^*(t) \\
&\leq 0.
\end{aligned}$$

Moreover, $\frac{dW_0}{dt} = 0$ if and only if $T^*(t) = 0$ and $V(t)(T(t) - T_0) = 0$. Then one can see that the largest invariant subset of $\{\frac{dW_0}{dt} = 0\}$ is $\{P_0\}$. By the Lyapunov-LaSalle invariance principle (see [29, Theorem 5.3.1] or [31, Theorem 3.4.7]) and Theorem 3.1, we conclude that if $R_0 < 1$ then P_0 is globally asymptotically stable. □

3.2. Stability of P_1 and bifurcation analysis

Recall that P_1 exists only when $R_0 > 1$, which implies that necessarily $\frac{N\delta k_1 T_0}{c(\delta+d_x\frac{\lambda_E}{d_E})} > 1$ as $k_1 = ke^{-\alpha\tau_1}$. The purpose of this paper is to consider the effects of delays on the dynamics. As a result, in the sequel of this section, we always assume that $\frac{N\delta k_1 T_0}{c(\delta+d_x\frac{\lambda_E}{d_E})} > 1$ and denote

$$\hat{\tau}_1 = \frac{1}{\alpha}\ln\frac{N\delta k T_0}{c(\delta + d_x\frac{\lambda_E}{d_E})}.$$

Then $R_0 > 1$ is equivalent to $\tau_1 < \hat{\tau}_1$.

The characteristic equation at P_1 is

$$\begin{aligned}&\left(\lambda + d - r + \frac{2rT_1}{T_{\max}} + kV_1\right)(\lambda + c)[(\lambda + \delta + d_x E_1)(\lambda + d_E) + pd_x T_1^* e^{-\lambda\tau_2}]\\ =&\left(\lambda + d - r + \frac{2rT_1}{T_{\max}}\right)(\lambda + d_E)N\delta k_1 T_1 e^{-\lambda\tau_1}.\end{aligned} \tag{3.4}$$

In the following, we follow the arguments in [23] to first show that P_1 is locally stable for $\tau_1 \in [0, \hat{\tau}_1)$ and $\tau_2 = 0$. Then for given $\tau_1 \in [0, \hat{\tau}_1)$, we discuss the possible bifurcations.

Theorem 3.3. *Suppose $\tau_1 \in [0, \hat{\tau}_1)$, $\tau_2 = 0$, and $0 \le r < \frac{d}{1-\frac{T_1}{T_{\max}}}$. Then the infected steady state P_1 is locally asymptotically stable.*

Proof. When $\tau_2 = 0$, the characteristic equation (3.4) reduces to

$$\begin{aligned}&(\lambda + d - r + \tfrac{2rT_1}{T_{\max}} + kV_1)(\lambda + c)\left[(\lambda + \delta + d_x E_1)(\lambda + d_E) + pd_x T_1^*\right]\\ =\;&(\lambda + d - r + \tfrac{2rT_1}{T_{\max}})(\lambda + d_E)N\delta k_1 T_1 e^{-\lambda\tau_1}.\end{aligned} \tag{3.5}$$

We will prove that all roots of (3.5) have negative real parts in three steps.

Firstly, we show that (3.5) has no roots on the imaginary axis with contradictory arguments. Let $\lambda = i\omega_0$ with $\omega_0 \ge 0$ be a root of (3.5). Then

$$\begin{aligned}&(i\omega_0 + d - r + \tfrac{2rT_1}{T_{\max}} + kV_1)(i\omega_0 + c)\left[(i\omega_0 + \delta + d_x E_1)(i\omega_0 + d_E) + pd_x T_1^*\right]\\ =\;&(i\omega_0 + d - r + \tfrac{2rT_1}{T_{\max}})(i\omega_0 + d_E)N\delta k_1 T_1 e^{-i\omega_0\tau_1}.\end{aligned} \tag{3.6}$$

Note that the modulus of the right hand side of (3.6) is

$$N\delta k_1 T_1|i\omega_0 + d_E|\cdot\left|i\omega_0 + d - r + \frac{2rT_1}{T_{\max}}\right| = c(\delta + d_x E_1)|i\omega_0 + d_E|\cdot\left|i\omega_0 + d - r + \frac{2rT_1}{T_{\max}}\right|.$$

However, since

$$\begin{aligned}&|(i\omega_0 + \delta + d_x E_1)(i\omega_0 + d_E) + pd_x T_1^*|^2 - (\delta + d_x E_1)^2|i\omega_0 + d_E|^2\\ =\;&\omega_0^2 d_E^2 + 2pd_E d_x T_1^*(\delta + d_x E_1) + (\omega_0^2 - pd_x T_1^*)^2\\ >\;&0\end{aligned}$$

and

$$\begin{aligned}
&\left|\left(i\omega_0 + d - r + \frac{2rT_1}{T_{\max}} + kV_1\right)(i\omega_0 + c)\right|^2 - \left|\left(i\omega_0 + d - r + \frac{2rT_1}{T_{\max}}\right)\right|^2 c^2 \\
> &\left|\left(i\omega_0 + d - r + \frac{2rT_1}{T_{\max}}\right)\right|^2 c^2 - \left|\left(i\omega_0 + d - r + \frac{2rT_1}{T_{\max}}\right)\right|^2 c^2 \\
= &\ 0,
\end{aligned}$$

it follows that the modulus of the left hand side of (3.6) is strictly larger than that of its right hand side, a contradiction. Thus we have verified that (3.5) has no roots on the imaginary axis.

Secondly, we show that (3.5) has no nonnegative real roots. Again, by contradiction, assume that (3.5) has a root $\lambda_0 \geq 0$ and we know that $e^{-\lambda_0\tau_1} \in (e^{-\lambda_0\hat{\tau}_1}, 1]$. Noting

$$\left(\lambda_0 + d - r + \frac{2rT_1}{T_{\max}}\right)(\lambda_0 + d_E)N\delta k_1 T_1 e^{-\lambda_0\tau_1} \leq \left(\lambda_0 + d - r + \frac{2rT_1}{T_{\max}}\right)(\lambda_0 + d_E)N\delta k_1 T_1,$$

we get from (3.5) that

$$\begin{aligned}
&(\lambda_0 + d - r + \tfrac{2rT_1}{T_{\max}} + kV_1)(\lambda_0 + c)\left[(\lambda_0 + \delta + d_x E_1)(\lambda_0 + d_E) + pd_x T_1^*\right] \\
\leq &\ N\delta k_1 T_1(\lambda_0 + d - r + \tfrac{2rT_1}{T_{\max}})(\lambda_0 + d_E).
\end{aligned} \tag{3.7}$$

But

$$\begin{aligned}
&\left(\lambda_0 + d - r + \frac{2rT_1}{T_{\max}} + kV_1\right)(\lambda_0 + c)\left[(\lambda_0 + \delta + d_x E_1)(\lambda_0 + d_E) + pd_x T_1^*\right] \\
> &\left(\lambda_0 + d - r + \frac{2rT_1}{T_{\max}}\right)(\lambda_0 + c)(\lambda_0 + \delta + d_x E_1)(\lambda_0 + d_E) \\
\geq &\ c(\delta + d_x E_1)\left(\lambda_0 + d - r + \frac{2rT_1}{T_{\max}}\right)(\lambda_0 + d_E) \\
= &\ N\delta k_1 T_1\left(\lambda_0 + d - r + \frac{2rT_1}{T_{\max}}\right)(\lambda_0 + d_E)
\end{aligned}$$

as $N\delta k_1 T_1 = c(\delta + d_x E_1)$, which contradicts with (3.7). This proved that (3.5) has no nonnegative real root.

Finally, we claim that there exists $\eta_0 > 0$ such that all roots of (3.5) have negative real parts when $1 < R_0 < 1 + \eta_0$. If this is not true, then there exists a sequence of values for the parameters where R_0 (> 1) $\to 1$ such that for each set of values for the parameters there exists a pair of conjugate roots for (3.5) with positive real parts (which follows from the results just proved above). Note that roots of (3.5) having nonnegative real parts are uniformly bounded. Without loss of generality, we suppose that the sequence of the conjugate roots converges to $\alpha_0 \pm i\beta_0$, otherwise just consider a subsequence. Then $\alpha_0 \geq 0$ and $\alpha_0 \pm i\beta_0$ are roots of the characteristic equation of the infection-free steady state P_0 when $R_0 = 1$. However, when $R_0 = 1$, this characteristic equation has no roots with nonnegative real parts except the simple root 0. Then $\alpha_0 = \beta_0 = 0$, which implies that 0 is a root of at least multiplicity 2 of this characteristic equation, a contradiction. This proves the claim.

Now the proof is done by noting the fact that the roots of (3.5) depend continuously on the parameters. □

Theorem 3.4. *If $\tau_1 = \tau_2 = 0$ and $0 \le r < \frac{d}{1-\frac{T_1}{T_{\max}}}$ holds, then the infected steady state P_1 is global asymptotically stable.*

Proof. We define a Lyapunov functional

$$\begin{aligned} W_1(t) &= T_1\left(\frac{T}{T_1} - 1 - \ln\frac{T}{T_1}\right) + \frac{k}{k_1}T_1^*\left(\frac{T^*}{T_1^*} - 1 - \ln\frac{T^*}{T_1^*}\right) \\ &\quad + \frac{kT_1}{c}V_1\left(\frac{V}{V_1} - 1 - \ln\frac{V}{V_1}\right) + \frac{kd_xE_1}{k_1p}E_1\left(\frac{E}{E_1} - 1 - \ln\frac{E}{E_1}\right). \end{aligned}$$

Then the time derivative of $W_1(t)$ along solutions of system (1.1) is

$$\begin{aligned} \frac{dW_1}{dt} &= \left(1-\frac{T_1}{T}\right)\frac{dT}{dt} + \frac{k}{k_1}\left(1-\frac{T_1^*}{T^*}\right)\frac{dT^*}{dt} + \frac{kT_1}{c}\left(1-\frac{V_1}{V}\right)\frac{dV}{dt} + \frac{kd_xE_1}{k_1p}\left(1-\frac{E_1}{E}\right)\frac{dE}{dt} \\ &= \left(1-\frac{T_1}{T}\right)\left(s - dT + rT - \frac{rT^2}{T_{\max}} - kVT\right) + \frac{k}{k_1}\left(1-\frac{T_1^*}{T^*}\right)(k_1VT - \delta T^* - d_xET^*) \\ &\quad + \frac{kT_1}{c}\left(1-\frac{V_1}{V}\right)(N\delta T^* - cV) + \frac{kd_xE_1}{k_1p}\left(1-\frac{E_1}{E}\right)(\lambda_E + pT^* - d_EE) \\ &= 2dT_1 - 2rT_1 + \frac{rT_1^2}{T_{\max}} - dT + rT - \frac{rT^2}{T_{\max}} - \frac{dT_1^2}{T} + \frac{rT_1^2}{T} - \frac{rT_1^3}{TT_{\max}} + \frac{rTT_1}{T_{\max}} \\ &\quad + kV_1T_1 - \frac{kV_1T_1^2}{T} - \frac{k}{k_1}\delta T^* - \frac{k}{k_1}d_xET^* - kVT\frac{T_1^*}{T^*} + \frac{k}{k_1}\delta T_1^* + \frac{k}{k_1}d_xET_1^* \\ &\quad + \frac{kN\delta T_1T^*}{c} - \frac{kN\delta V_1T_1T^*}{cV} + kT_1V_1 + \frac{kd_xE_1}{k_1p}d_EE_1 - \frac{k}{k_1}d_xE_1T_1^* + \frac{k}{k_1}d_xE_1T^* \\ &\quad - \frac{kd_xE_1}{k_1p}d_EE - \frac{kd_xE_1E_1}{k_1pE}d_EE_1 + \frac{kE_1}{k_1E}d_xE_1T_1^* - \frac{kE_1}{k_1E}d_xE_1T^* + \frac{kd_xE_1}{k_1p}d_EE_1 \\ &= \left(r - d - \frac{rT_1}{T_{\max}} - \frac{rT}{T_{\max}}\right)\frac{(T-T_1)^2}{T} + kV_1T_1\left(3 - \frac{T_1}{T} - \frac{T_1^*VT}{T^*V_1T_1} - \frac{V_1T^*}{VT_1^*}\right) \\ &\quad + \frac{kd_xE_1}{k_1p}d_EE_1\left(2 - \frac{E}{E_1} - \frac{E_1}{E}\right) - \frac{k}{k_1}d_xE_1T_1^*\left(2 - \frac{E}{E_1} - \frac{E_1}{E}\right) \\ &\quad + \frac{k}{k_1}d_xE_1T^*\left(2 - \frac{E}{E_1} - \frac{E_1}{E}\right) \\ &= \left(r - d - \frac{rT_1}{T_{\max}} - \frac{rT}{T_{\max}}\right)\frac{(T-T_1)^2}{T} + kV_1T_1\left(3 - \frac{T_1}{T} - \frac{T_1^*VT}{T^*V_1T_1} - \frac{V_1T^*}{VT_1^*}\right) \\ &\quad + \frac{k}{k_1}d_xE_1\left(\frac{\lambda_E}{p} + T^*\right)\left(2 - \frac{E}{E_1} - \frac{E_1}{E}\right) \\ &\le 0. \end{aligned}$$

It is clear that $\frac{dW_1}{dt} = 0$ if and only if $(T, T^*, V, E) = P_1$. By the Laypunov asymptotic stability theorem, we conclude that P_1 of system (1.1) is globally asymptotically stable. □

In the following, we study the effects of delays by fixing $\tau_1 = \tau_1^0 \in [0, \hat{\tau}_1)$ and changing τ_2. Then the characteristic equation (3.4) can be rewritten as

$$P(\lambda, \tau_1^0) + Q(\lambda, \tau_1^0)e^{-\lambda\tau_1^0} + R(\lambda, \tau_1^0)e^{-\lambda\tau_2} = 0, \tag{3.8}$$

where

$$
\begin{aligned}
P(\lambda,\tau_1^0) &= \lambda^4 + A_3\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0,\\
Q(\lambda,\tau_1^0) &= B_2\lambda^2 + B_1\lambda + B_0,\\
R(\lambda,\tau_1^0) &= C_2\lambda^2 + C_1\lambda + C_0,\\
A_3 &= c+\delta+d_xE_1+d_E+\frac{S}{T_1}+\frac{rT_1}{T_{\max}},\\
A_2 &= c(\delta+d_xE_1)+(c+\delta+d_xE_1)\left(d_E+\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right)+d_E\left(\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right),\\
A_1 &= d_E(c+\delta+d_xE_1)\left(\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right)+c(\delta+d_xE_1)\left(d_E+\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right),\\
A_0 &= cd_E(\delta+d_xE_1)\left(\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right),\\
B_2 &= -N\delta k_1T_1 = -c(\delta+d_xE_1),\\
B_1 &= -c(\delta+d_xE_1)\left(d_E+d-r+\frac{2rT_1}{T_{\max}}\right),\\
B_0 &= -cd_E(\delta+d_xE_1)\left(d-r+\frac{2rT_1}{T_{\max}}\right),\\
C_2 &= pd_xT_1^*,\\
C_1 &= pd_xT_1^*\left(c+\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right),\\
C_0 &= cpd_xT_1^*\left(\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right).
\end{aligned}
$$

Since

$$
\begin{aligned}
P(0,\tau_1^0)+Q(0,\tau_1^0)+R(0,\tau_1^0) &= A_0+B_0+C_0\\
&= cd_E(\delta+d_xE_1)kV_1+cpd_xT_1^*\left(\frac{S}{T_1}+\frac{rT_1}{T_{\max}}\right)\\
&> 0,
\end{aligned}
$$

we know that $\lambda = 0$ is not a root of (3.8). Therefore, for stability changes of P_1 to occur, we first look for τ_2 where (3.8) has a pair of conjugate roots $\lambda = \pm i\omega(\tau_1^0,\tau_2)$ with $\omega(\tau_1^0,\tau_2) > 0$. Substitute $\lambda = i\omega(\tau_1^0,\tau_2)$ into (3.8) and then separate the real and imaginary parts to obtain

$$
\begin{aligned}
(-C_2\omega^2+C_0)\cos\omega\tau_2 + C_1\omega\sin\omega\tau_2 &= M_1,\\
C_1\omega\cos\omega\tau_2 - (-C_2\omega^2+C_0)\sin\omega\tau_2 &= M_2,
\end{aligned}
\tag{3.9}
$$

where

$$
\begin{aligned}
M_1 &= (-\omega^4+A_2\omega^2-A_0)-(-B_2\omega^2+B_0)\cos\omega\tau_1^0 - B_1\omega\sin\omega\tau_1^0,\\
M_2 &= (A_3\omega^3-A_1\omega)-B_1\omega\cos\omega\tau_1^0+(-B_2\omega^2+B_0)\sin\omega\tau_1^0.
\end{aligned}
$$

It follows that

$$\begin{aligned}\sin\omega\tau_2 &= \frac{M_1C_1\omega - (-C_2\omega^2 + C_0)M_2}{(-C_2\omega^2 + C_0)^2 + C_1^2\omega^2},\\ \cos\omega\tau_2 &= \frac{(-C_2\omega^2 + C_0)M_1 + C_1\omega M_2}{(-C_2\omega^2 + C_0)^2 + C_1^2\omega^2}.\end{aligned}$$

Using $\sin^2\omega\tau_2 + \cos^2\omega\tau_2 = 1$, we see that $\omega(\tau_1^0, \tau_2)$ satisfies $F(\omega, \tau_1^0) = 0$, where

$$F(\omega, \tau_1^0) = \omega^8 + a_6\omega^6 + a_5\omega^5 + a_4\omega^4 + a_3\omega^3 + a_2\omega^2 + a_1\omega + a_0 \tag{3.10}$$

with

$$\begin{aligned}a_6 &= A_3^2 - 2A_2 - 2B_2\cos\omega\tau_1^0,\\ a_5 &= 2(B_1 - A_3B_2)\sin\omega\tau_1^0,\\ a_4 &= 2A_0 + A_2^2 - 2A_1A_3 + B_2^2 + 2(B_0 - A_3B_1 + A_2B_2)\cos\omega\tau_1^0 - C_2^2,\\ a_3 &= 2(A_3B_0 - A_2B_1 + A_1B_2)\sin\omega\tau_1^0,\\ a_2 &= A_1^2 - 2A_0A_2 + B_1^2 - 2B_0B_2 - 2(A_2B_0 - A_1B_1 + A_0B_2)\cos\omega\tau_1^0 - C_1^2 + 2C_0C_2,\\ a_1 &= 2(-A_1B_0 + A_0B_1)\sin\omega\tau_1^0,\\ a_0 &= A_0^2 + B_0^2 + 2A_0B_0\cos\omega\tau_1^0 - C_0^2.\end{aligned}$$

Therefore, $\omega(\tau_1^0, \tau_2)$ is independent of τ_2. Denote

$$I_{\tau_1^0} = \{\omega : F(\omega, \tau_1^0) = 0\},$$

which is a finite set. If $I_{\tau_1^0} = \emptyset$ then P_1 is stable for $\tau_1 = \tau_1^0$ and $\tau_2 \geq 0$. Now, suppose $I_{\tau_1^0} \neq \emptyset$. For example, this is true if $A_0 + B_0 < C_0$ since

$$F(0, \tau_1^0) = (A_0 + B_0)^2 - C_0^2, \qquad \lim_{\omega\to\infty} F(\omega, \tau_1^0) = \infty,$$

and $A_0 + B_0 + C_0 > 0$.

Assume $I_{\tau_1^0} = \{\omega_1(\tau_1^0), \ldots, \omega_{j(\tau_1^0)}(\tau_1^0)\}$. For $j \in \mathbb{N}(\tau_1^0) = \{1, \ldots, j(\tau_1^0)\}$, choose the unique angle $\theta_j(\tau_1^0) \in [0, 2\pi)$ such that

$$\begin{aligned}\sin\theta_j(\tau_1^0) &= \frac{C_1\omega_j(\tau_1^0)M_1 - (-C_2\omega_j^2(\tau_1^0) + C_0)M_2}{(-C_2\omega_j^2(\tau_1^0) + C_0)^2 + C_1^2\omega_j^2(\tau_1^0)},\\ \cos\theta_j(\tau_j^0) &= \frac{(-C_2\omega_j^2(\tau_1^0) + C_0)M_1 + C_1\omega_j(\tau_1^0)M_2}{(-C_2\omega_j^2(\tau_1^0) + C_0)^2 + C_1^2\omega_j^2(\tau_1^0)}.\end{aligned} \tag{3.11}$$

Now, define

$$\tau_{2j}^n(\tau_1^0) = \frac{\theta_j(\tau_1^0) + 2n\pi}{\omega} \qquad \text{for } n \in \mathbb{N} = \{0, 1, 2, \ldots\}.$$

Then the characteristic equation (3.8) at $\tau_2 = \tau_{2j}^n$ has a pair of conjugate eigenvalues $\lambda = \pm i\omega_j(\tau_1^0)$ for $j \in \mathbb{N}(\tau_1^0)$ and $n \in \mathbb{N}$. The following result comes from [32, Theorem 2.2].

Theorem 3.5. *Let $\tau_1^0 \in [0, \hat{\tau}_1)$. Then the following two statements are true.*

(i) *If $I_{\tau_1^0} = \emptyset$, then P_1 is locallay asymptotically stable for $\tau_1 = \tau_1^0$ and $\tau_2 \geq 0$.*

(ii) *If $I_{\tau_1^0} \neq \emptyset$, then a pair of simple conjugate pure imaginary roots $\lambda(\tau_{2j}^n(\tau_1^0)) = \pm i\omega_j(\tau_1^0)$ of (3.8) exists at $\tau_2 = \tau_{2j}^n(\tau_1^0)$ for $j \in \mathbb{N}(\tau_1^0)$ and $n \in \mathbb{N}$, which crosses the imaginary axis from left to right if $\delta(\tau_{2j}^n(\tau_1^0)) > 0$ and crosses the imaginary axis from right to left if $\delta(\tau_{2j}^n(\tau_1^0)) < 0$, where*

$$\delta(\tau_{2j}^n(\tau_1^0)) = \text{sign}\left\{\frac{d\text{Re}\,\lambda}{d\tau_2}\Big|_{\tau_2=\tau_{2j}^n(\tau_1^0)}\right\} = \text{sign}\{F'_\omega(\omega_j(\tau_1^0), \tau_1^0)\}.$$

By Theorem 3.5, for any $\tau_1 \in [0, \hat{\tau_1})$, there exists a $\tau_2^*(\tau_1) \in (0, \infty]$ such that P_1 is locally asymptotically stable for $\tau < \tau_2^*(\tau_1)$.

In general, it is hard to determine whether I_{τ_1} is empty or not. Moreover, if $I_{\tau_1} \neq \emptyset$ and has more than one element, then Theorem 3.5 indicates that there may be stability switches for P_1. To get a clear picture of it, we consider the case where $\tau_1^0 = 0$. Moreover, $F(\omega, 0)$ in (3.10) reduces to $h(\omega^2)$, where

$$h(z) = z^4 + b_3z^3 + b_2z^2 + b_1z + b_0 \tag{3.12}$$

with

$$\begin{aligned}
b_3 &= A_3^2 - 2(A_2 + B_2),\\
b_2 &= 2A_0 + A_2^2 - 2A_1A_3 + B_2^2 + 2(B_0 - A_3B_1 + A_2B_2) - C_2^2,\\
b_1 &= A_1^2 - 2A_0A_2 + B_1^2 - 2B_0B_2 - 2(A_2B_0 - A_1B_1 + A_0B_2) - C_1^2 + 2C_0C_2,\\
b_0 &= (A_0 + B_0)^2 - C_0^2.
\end{aligned}$$

In this case, $\delta(\tau_{2j}^n(0))$ in Theorem 3.5 is $\text{sign}(h'(\omega_j^2(0)))$. As a result, for Hopf bifurcation to occur, we only focus on the situations where $h(z)$ defined by (3.12) has simple positive real zeros.

Though a simple calculation gives $b_3 = d_E^2 + (c + \delta + d_xE_1)^2 + (\frac{s}{T_1} + \frac{rT_1}{T_{\max}})^2 > 0$, we cannot easily get the signs of the other coefficients. By Descartes' rule of sign, the polynomial $h(z)$ has at most three positive real zeros. In fact, Yan and Li [33] have obtained the conditions on the existence of at least one positive real zero for $h(z)$. To cite the result, let

$$\begin{aligned}
p &= \frac{8b_2 - 3b_3^2}{16},\\
q &= \frac{b_3^3 - 4b_3b_2 + 8b_1}{32},\\
\Delta &= \frac{q^2}{4} + \frac{p^3}{27},\\
z_1^* &= -\frac{b_3}{4} + \sqrt[3]{-\frac{q}{2} + \sqrt{\Delta}} + \sqrt[3]{-\frac{q}{2} - \sqrt{\Delta}} \qquad \text{if } \Delta > 0,\\
z_2^* &= \max\left\{-\frac{b_3}{4} - 2\sqrt[3]{\frac{q}{2}}, -\frac{b_3}{4} + \sqrt[3]{\frac{q}{2}}\right\} \qquad \text{if } \Delta = 0,\\
z_3^* &= \max\left\{-\frac{b_3}{4} + 2\text{Re}\{\rho\}, -\frac{b_3}{4} + 2\text{Re}\{\rho\epsilon\}, -\frac{b_3}{4} + 2\text{Re}\{\rho\bar{\epsilon}\}\right\} \qquad \text{if } \Delta < 0,
\end{aligned}$$

where ρ is one of the cubic roots of the complex number $-\frac{q}{2}+\sqrt{\Delta}$ and $\epsilon=\frac{-1+\sqrt{3}i}{2}$. Note that when $\Delta>0$, z_1^* is the only real zero of $h'(z)$; when $\Delta=0$, $z_1=-\frac{b_3}{4}-2\sqrt[3]{\frac{q}{2}}$, $z_2=z_3=-\frac{b_3}{4}+\sqrt[3]{\frac{q}{2}}$ are the three real zeros of $h'(z)$; when $\Delta<0$, $-\frac{b_3}{4}+2\mathrm{Re}\{\rho\}$, $-\frac{b_3}{4}+2\mathrm{Re}\{\rho\epsilon\}$, and $-\frac{b_3}{4}+2\mathrm{Re}\{\rho\bar{\epsilon}\}$ are the three real zeros of $h'(z)$ and we arrange them as $\hat{z}_1<\hat{z}_2<z_3^*$.

Proposition 3.1 ([33, Lemma 2.1])**.** (i) *If $b_0<0$, then $h(z)$ has at least one positive real zero.*

(ii) *If $b_0\geq 0$, then $h(z)$ has no positive real zero if one of the following conditions holds.*

(ii-1) $\Delta>0$ *and* $z_1^*<0$*;*
(ii-2) $\Delta=0$ *and* $z_2^*<0$*;*
(ii-3) $\Delta<0$ *and* $z_3^*<0$.

(iii) *If $b_0\geq 0$, then $h(z)$ has at least one positive real zero if one of the following conditions holds.*

(iii-1) $\Delta>0$, $z_1^*>0$ *and* $h(z_1^*)<0$*;*
(iii-2) $\Delta=0$, $z_2^*>0$ *and* $h(z_2^*)<0$*;*
(iii-3) $\Delta<0$, $z_3^*>0$ *and* $h(z_3^*)<0$.

When $\tau_1=0$, by Proposition 3.1 we can have the following result.

Theorem 3.6. *Assume $\tau_1=0$ and one of the conditions in statement (ii) of Proposition 3.1 holds. Then the infected steady state P_1 is locally asymptotically stable for all $\tau_2\geq 0$.*

In the following result, we characterize the situations where $h(z)$ has simple positive real zeros, which is not difficult to see by considering the possible graphs of $h(z)$ and $h'(z)$. Recall that $h(z)$ can have at most three positive real zeros.

Proposition 3.2. *For the polynomial $h(z)$ defined by* (3.12)*, the following results hold.*

(i) *$h(z)$ has one simple positive zero and no other positive zeros if and only if* **($\mathbf{H_1}$)***: one of the following conditions hold.*

(i-1) $\Delta\geq 0$ *and* $b_0<0$.
(i-2) $\Delta>0$, $b_0=0$, *and* $z_1^*>0$.
(i-3) $\Delta=0$, $b_0=0$ *and* ($z_2^*=z_1>0$ *or* $z_2^*=z_2>z_1>0$).
(i-4) $\Delta<0$, $b_0<0$ *and* $\hat{z}_2\leq 0$.
(i-5) $\Delta<0$, $b_0<0$, $\hat{z}_2>0$ *and* $h(\hat{z}_2)<0$.
(i-6) $\Delta<0$, $b_0<0$, $\hat{z}_2>0$, $h(\hat{z}_2)>0$ *and* $h(z_3^*)>0$.
(i-7) $\Delta<0$, $b_0=0$ *and* $\hat{z}_2<0<z_3^*$.
(i-8) $\Delta<0$, $b_0=0$, $\hat{z}_1>0$, $h(\hat{z}_2)>0$ *and* $h(z_3^*)>0$.
(i-9) $\Delta<0$, $b_0=0$, $\hat{z}_1>0$ *and* $h(\hat{z}_2)<0$.

(ii) *$h(z)$ has two simple positive zeros and no other positive zeros if and only if* **($\mathbf{H_2}$)***: one of the following conditions holds.*

(ii-1) $\Delta>0$, $b_0>0$, $z_1^*>0$ *and* $h(z_1^*)<0$.
(ii-2) $\Delta=0$, $b_0>0$, $z_2^*=z_1>0$ *and* $h(z_2^*)<0$.
(ii-3) $\Delta=0$, $b_0>0$, $z_2^*=z_2>z_1>0$ *and* $h(z_1)<0$.
(ii-4) $\Delta<0$, $b_0=0$, $\hat{z}_1\leq 0<\hat{z}_2$ *and* $h(z_3^*)<0$.
(ii-5) $\Delta<0$, $b_0>0$, $\hat{z}_2\leq 0<z_3^*$ *and* $h(z_3^*)<0$.

(ii-6) $\Delta < 0$, $b_0 > 0$, $\hat{z}_1 \le 0 < \hat{z}_2$ *and* $h(z_3^*) < 0$.
(ii-7) $\Delta < 0$, $b_0 > 0$, $\hat{z}_1 > 0$, $h(\hat{z}_1) > 0$ *and* $h(z_3^*) < 0$.
(ii-8) $\Delta < 0$, $b_0 > 0$, $\hat{z}_1 > 0$, $h(\hat{z}_1) < 0$ *and* $h(\hat{z}_2) < 0$.
(ii-9) $\Delta < 0$, $b_0 > 0$, $\hat{z}_1 > 0$, $h(\hat{z}_1) < 0$, $h(\hat{z}_2) > 0$ *and* $h(z_3^*) > 0$.

(iii) $h(z)$ *has three simple positive zeros and no other positive zeros if and only if* **($\mathbf{H_3}$)***: one of the following conditions holds.*

(iii-1) $\Delta < 0$, $b_0 < 0$, $\hat{z}_2 > 0$, $h(\hat{z}_2) > 0$, *and* $h(z_3^*) < 0$.
(iii-2) $\Delta < 0$, $b_0 = 0$, $\hat{z}_1 > 0$, $h(\hat{z}_2) > 0$ *and* $h(z_3^*) < 0$.

If **($\mathbf{H_1}$)** holds, let $\tilde{z} > 0$ be the unique simple positive zero of $h(z)$ and denote $\tilde{\omega} = \sqrt{\tilde{z}}$. Solving (3.11) to obtain the unique $\tilde{\theta} \in [0, 2\pi)$. Define

$$\tau_2^n = \frac{2n\pi + \tilde{\theta}}{\tilde{\omega}} \qquad \text{for } n \in \mathbb{N}.$$

As $h'(\tilde{z}) > 0$, we have $\delta(\tau_2^n) = 1$ and hence the following result holds.

Theorem 3.7. *Assume that* $\tau_1 = 0$ *and assumption* **($\mathbf{H_1}$)** *holds. Then there exists a sequence* $0 < \tau_2^0 < \tau_2^1 < \tau_2^2 < \cdots$ *such that* P_1 *is locally asymptotically stable for* $\tau_2 \in [0, \tau_2^0)$ *and unstable for* $\tau > \tau_2^0$*, and system* (1.1) *undergoes a Hopf bifurcation at* P_1 *when* $\tau_2 = \tau_2^n$ *for* $n \in \mathbb{N}$.

Now, assume **($\mathbf{H_2}$)** holds. Let $\tilde{z}_2 < \tilde{z}_1$ be the only positive real zeros of $h(z)$, which are also simple. Similarly as for the case of **($\mathbf{H_1}$)**, we can get two increasing positive sequences $\{\tau_{21}^n\}$ and $\{\tau_{22}^n\}$, associated with $\tilde{z}_1$ and $\tilde{z}_2$, respectively. Since $h'(\tilde{z}_1) > 0 > h'(\tilde{z}_2)$, we easily see that $\tau_{21}^0 < \tau_{22}^0$. Since $\tilde{\omega}_1 = \sqrt{\tilde{z}_1} > \sqrt{\tilde{z}_2} = \tilde{\omega}_2$, we have $\frac{2\pi}{\tilde{\omega}_1} < \frac{2\pi}{\tilde{\omega}_2}$. Thus we define

$$k = \min\left\{ l \in \mathbb{N} : \tau_{21}^{l+1} = \tau_{21}^0 + \frac{2\pi(l+1)}{\tilde{\omega}_1} \le \tau_{22}^0 + \frac{2\pi l}{\tilde{\omega}_2} = \tau_{22}^l \right\}.$$

Such k exists due to $\tau_{21}^{l+1} - \tau_{22}^l \to -\infty$ as $l \to \infty$. Then the first few Hopf bifurcation values can be ordered as

$$\tau_{21}^0 < \tau_{22}^0 < \tau_{21}^1 < \tau_{22}^1 < \cdots < \tau_{21}^{k-1} < \tau_{22}^{k-1} < \tau_{21}^k < \tau_{21}^{k+1} \le \tau_{22}^k < \cdots .$$

Theorem 3.8. *Assume* $\tau_1 = 0$ *and* **($\mathbf{H_2}$)** *holds. Given* $n \in \mathbb{N}$ *and* $j \in \{1, 2\}$*, system* (1.1) *undergoes Hopf bifurcation at* $\tau_2 = \tau_{2j}^n$ *if* $\tau_{2j}^n \ne \tau_{2(3-j)}^l$ *for all* $l \in \mathbb{N}$*. Furthermore, the stability of* P_1 *switches off (namely, it becomes unstable) when* τ_2 *crosses* $\tau_{21}^0, \ldots, \tau_{21}^k$ *and switches on (namely, it becomes stable) when* τ_2 *crosses* $\tau_{22}^0, \ldots, \tau_{22}^{k-1}$*. In other words,* P_1 *is stable when* $\tau_2 \in [0, \tau_{21}^0) \cup (\tau_{22}^0, \tau_{21}^1) \cup \cdots \cup (\tau_{22}^{k-1}, \tau_{21}^k)$ *and unstable when* $\tau_2 \in (\tau_{21}^0, \tau_{22}^0) \cup \cdots \cup (\tau_{21}^{k-1}, \tau_{22}^{k-1}) \cup (\tau_{21}^k, \infty)$.

We mention that we can study the global continuation of Hopf bifurcation in Theorem 3.8 as in Li and Shu [34]. We believe that the Hopf bifurcation branches are bounded and each joins a pair of τ_{21}^n and τ_{22}^n for $n \in \mathbb{N}$. As a result, for $\tau_2 \in (\tau_{21}^{k+1}, \tau_{22}^k)$, there will be two stable periodic orbits.

Also in Theorem 3.8, we exclude the situation where $\tau_{21}^n = \tau_{22}^l$ for some $n, l \in \mathbb{N}$. If this happens, then $n > l$ since $\tau_{21}^0 < \tau_{22}^0$ and $\frac{2\pi}{\tilde{\omega}_1} < \frac{2\pi}{\tilde{\omega}_2}$. In this critical situation, as τ_2 crosses this common critical value, two pairs of purely imaginary eigenvalues $\pm i\tilde{\omega}_1$ and $\pm i\tilde{\omega}_2$ appear and all other eigenvalues have nonzero real parts. Therefore, a double Hopf bifurcation occurs.

Theorem 3.9. *Assume* $\tau_1 = 0$ *and* **($\mathbf{H_2}$)** *holds. If there exist integers* $n > l \geq 0$ *such that* $\tau_{21}^n = \tau_{22}^l = \tau_{20}$, *then* (1.1) *undergoes a double Hopf bifurcation at* P_1 *when* $\tau_2 = \tau_{20}$.

When **($\mathbf{H_3}$)** holds, we can similarly get three sequences of critical values for τ_2. Similar results as those in Theorem 3.8 and Theorem 3.9 can be obtained. Moreover, the global Hopf bifurcation associated with the third sequence is unbounded (one can refer to Li *et al.* [35] for a similar discussion).

4. Numerical simulations

In this paper, we rigorously analyzed an HIV-infection model with CTL-immune response and two time delays. The model incorporates a logistic growth term for the target cell growth and a natural resource for the immune effectors. The basic reproduction number R_0 played an important in the infection dynamics. If $R_0 < 1$ then the infection-free steady state is globally asymptotically stable. Note that R_0 explicitly depends on τ_1. It follows that if τ_1 is large enough then the virus will be cleared. We emphasize that this has not been noted in most existing study. Of course, in the real situation, this delay between viral entry and subsequent viral production usually is not very big. This leads to the complicated dynamics when $R_0 > 1$. In this case, the unique infected steady state could be stable or unstable, depending on the parameter values. In particular, we focused on the effects of time delays. Theoretical results indicate that there can be Hopf bifurcation, double Hopf bifurcation and stability switches.

We conclude this paper with some numerical simulations to illustrate the above mentioned main results. The ranges of the parameters except the delays are summarized in Table 2.

Table 2. Parameter values for simulation.

Parameter	Unit	Range	References
s	cells $\text{ml}^{-1}\text{day}^{-1}$	$0 \sim 10$	[28]
d	day^{-1}	$0.0001 \sim 0.2$	[23]
r	day^{-1}	$0.03 \sim 3$	[36]
$T_{\max}$	cells ml^{-1}	$600 \sim 1600$	[36]
k	$\text{ml}^{-1}\text{day}^{-1}$	$4.6 \times 10^{-8} \sim 0.5$	[7]
α	day^{-1}	$\alpha \in [d, \delta]$	[7]
δ	day^{-1}	$0.00019 \sim 1.4$	[23]
d_x	$\text{ml}^{-1}\text{day}^{-1}$	$0.0001 \sim 4.048$	[7, 23]
N	viron cells^{-1}	$6.25 \sim 23599.9$	[23]
c	day^{-1}	$2 \sim 36$	[23, 36]
λ_E	cells $\text{ml}^{-1}\text{day}^{-1}$	$0 \sim \infty$	[37]
p	day^{-1}	$0.0051 \sim 3.912$	[23]
d_E	day^{-1}	$0.004 \sim 8.087$	[23, 37]
τ_1	days	$0 \sim 1.5$	[7]
τ_2	days	$0 \sim 35$	[7]

For simplicity, we use the same initial condition $(T_0, T_0^*, V_0, E_0) = (100, 0, 10^{-2}, 0.6)$ in all simulations.

First, we take $s = 10$, $d = 0.01$, $r = 0.03$, $T_{\max} = 1500$, $\alpha = 0.02$, $\delta = 0.3$, $d_x = 0.01$, $N = 21$, $c = 3$, $\lambda_E = 1$, $p = 0.3$, $d_E = 0.1$, $\tau_1 = 1.2$ and $k = 2.4 \times 10^{-5}$. Then $R_0 = 0.1680 < 1$. By Theorem 3.2, the infection-free steady state $P_0 = (1366, 0, 0, 10)$ is globally asymptotically stable (see Figure 1 with $\tau_2 = 4$).

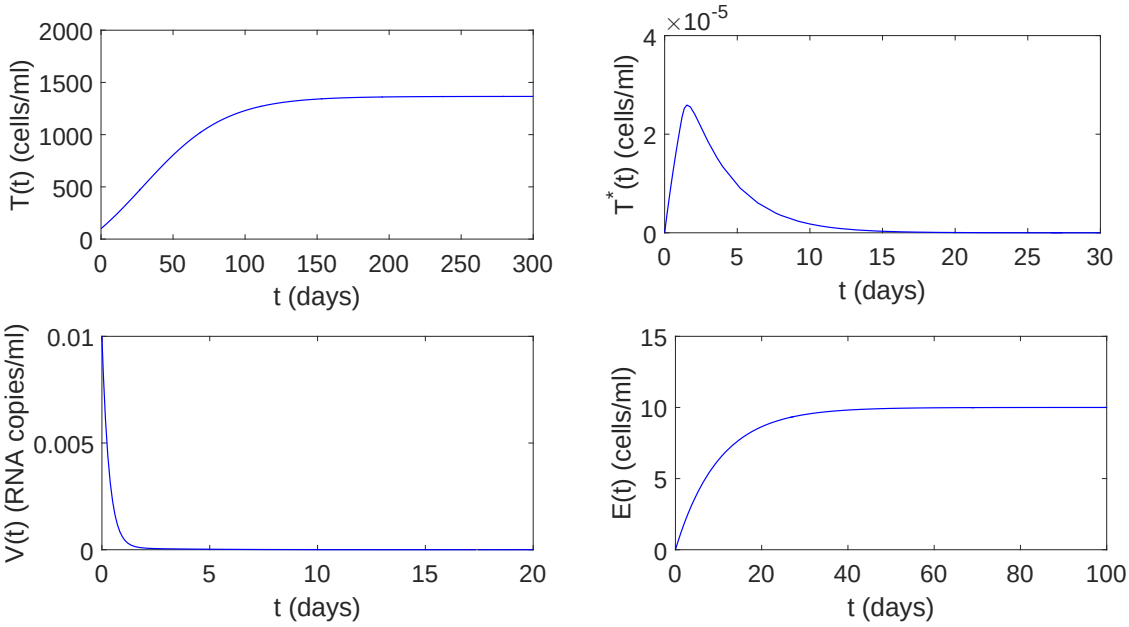

Figure 1. When $R_0 < 1$ the infection-free steady state P_0 is globally asymptotically stable. See the text for the parameter values.

Next, we only change k to $k = 2.4 \times 10^{-3}$ and keep the others as above. In this case, we have $\hat{\tau}_1 = 142.2801$. Take $\tau_1 = 1.2 \in [0, \hat{\tau}_1)$. Then $R_0 = 16.8038 > 1$. Through numerical calculations, we get the first few critical values $\tau_{21}^0 = 2.9940$ and $\tau_{21}^1 = 32.9360$ associated with $\omega_1 = 0.2098$ and $\tau_{22}^0 = 28.8271$ associated with $\omega_2 = 0.1066$. By Theorem 3.5, the infected steady state $P_1 = (171.7615, 14.8383, 31.1604, 54.5149)$ is locally asymptotically stable for $\tau_2 < \tau_{21}^0$ (see Figure 2 with $\tau_2 = 2$).

In fact, numerical simulations indicates that there is Hopf bifurcation for $\tau_2 \in (\tau_{21}^0, \tau_{22}^0)$ (see Figure 3 with $\tau_2 = 5$) and there is a stability switch at $\tau_2 = \tau_{22}^0$, that is, P_1 is locally asymptotically stable for $\tau_2 \in (\tau_{22}^0, \tau_{21}^1)$ (see Figure 4 with $\tau_2 = 32$).

In the following we illustrate this more clearly with the special case where $\tau_1 = 0$. We distinguish three cases.

Case 1: (ii) of Proposition 3.1 holds. We take $s = 5$, $d = 0.2$, $r = 0.03$, $T_{\max} = 1500$, $\alpha = 0.2$, $\delta = 0.3$, $d_x = 0.01$, $N = 2800$, $c = 15$, $\lambda_E = 1$, $p = 0.3$, $d_E = 0.1$, $\tau_1 = 0$ and $k = 2.4 \times 10^{-3}$. Then $R_0 = 9.8484 > 1$ and system (1.1) has the unique infected steady state $P_1 = (4.5277, 6.9510, 389.2547, 30.8529)$. In this case, $\Delta = 4.1507 \times 10^6 > 0$, $b_0 = 0.6078 > 0$, and $z_1^* = -1.9553 \times 10^{-2} < 0$. This means that (ii-1) of Proposition 3.1 holds. It follows from Theorem 3.6 that the infected steady state P_1 is locally asymptotically stable for all $\tau_2 \geq 0$ (see Figure 5 with $\tau_2 = 1$).

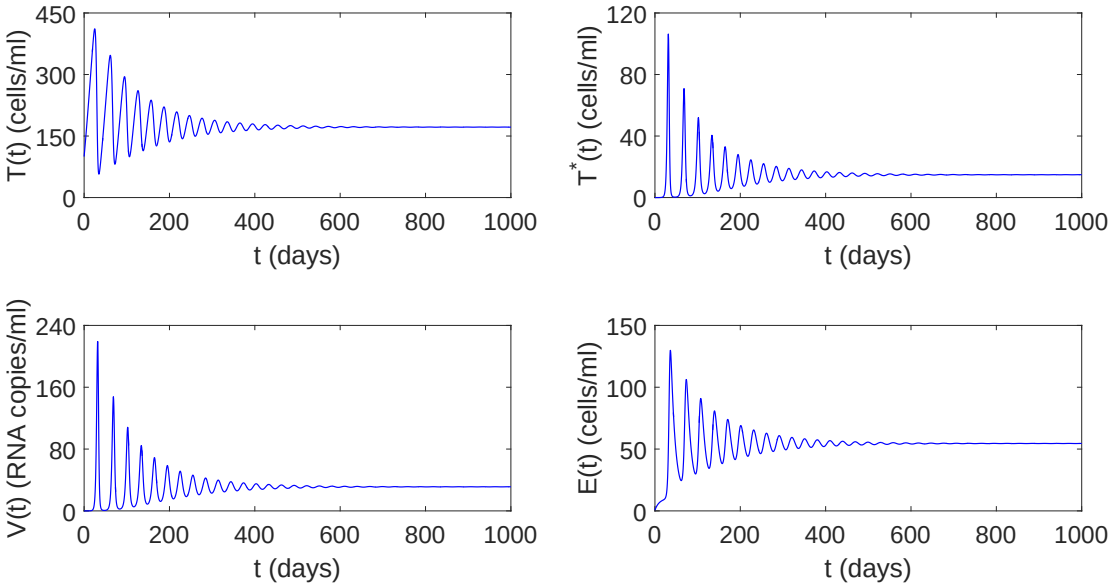

Figure 2. The infected steady state P_1 is locally stable. We refer to the text for the parameter values.

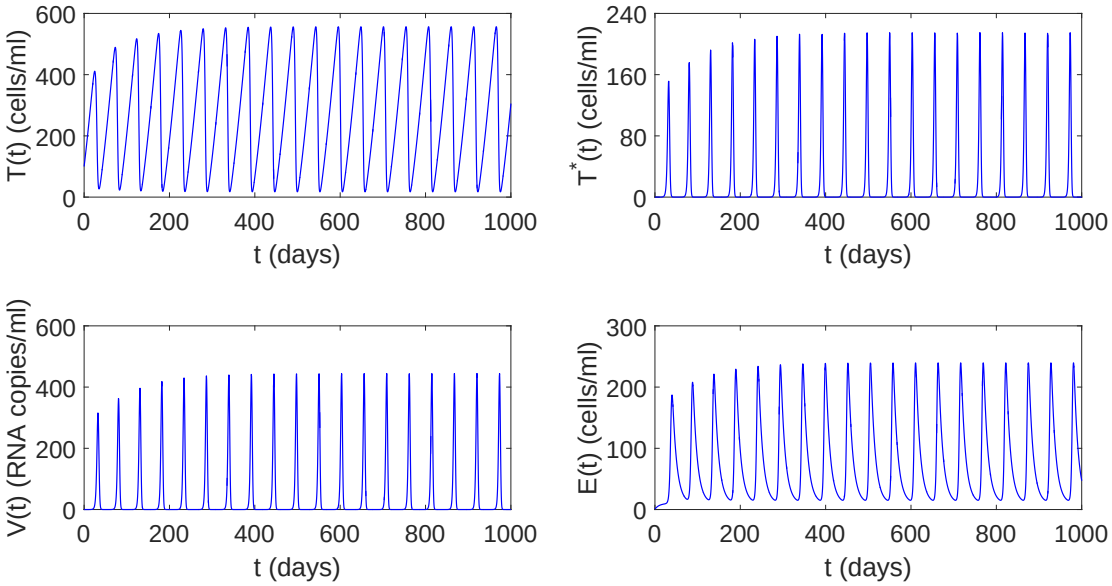

Figure 3. There is a periodic solution bifurcated from the infected steady state P_1 through Hopf bifurcation. Parameter values are given in the text.

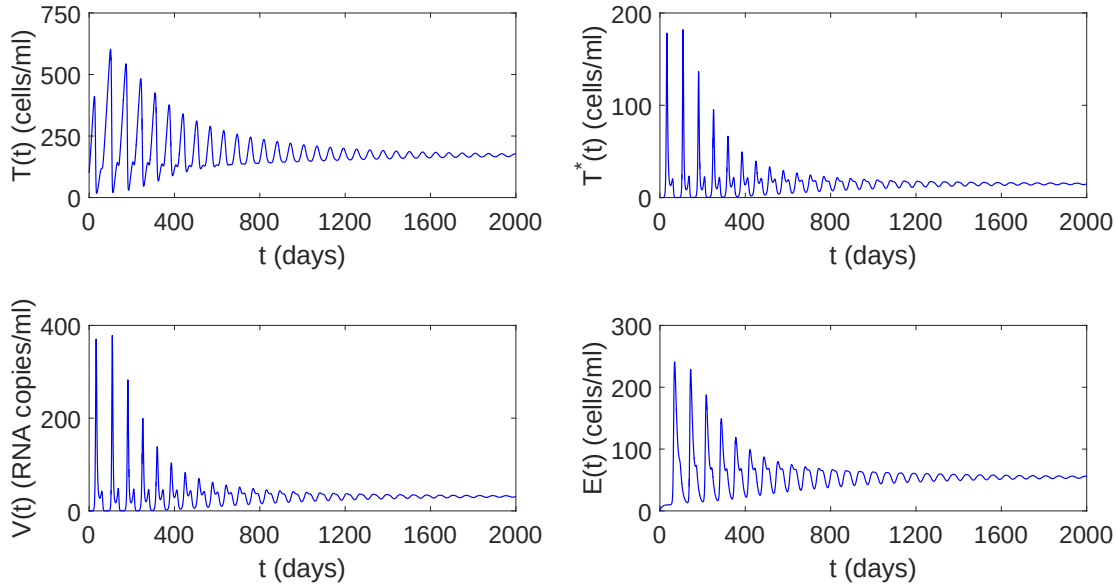

Figure 4. The infected steady state P_1 gains stability and this indicates a stability switch. See the text for the parameter values.

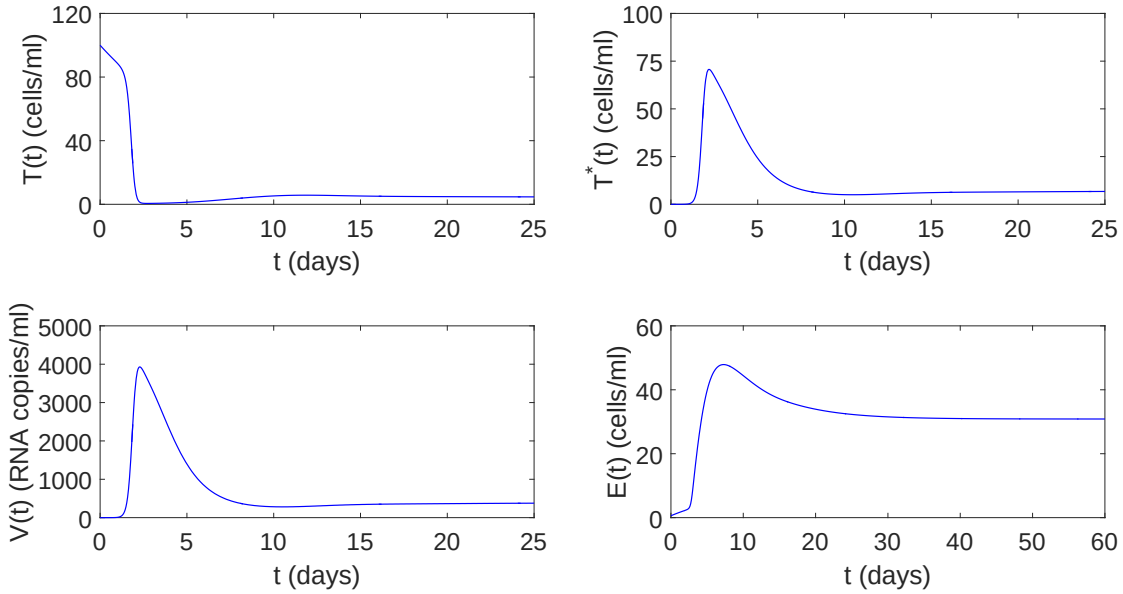

Figure 5. The infected steady state P_1 is locally asymptotically stable. For parameter values, see the text.

Case 2: Assumption **($\mathbf{H_1}$)** holds. We choose the parameter values $s = 10$, $d = 0.01$, $r = 0.25$, $T_{\max} = 1500$, $\alpha = 0.02$, $\delta = 0.3$, $d_x = 0.01$, $N = 21$, $c = 3$, $\lambda_E = 1$, $p = 0.3$, $d_E = 0.1$ and $k = 2.4 \times 10^{-4}$. Then $R_0 = 1.8655 > 1$ and system (1.1) has the unique infected steady state $P_1 = (1448.2000, 10.9961, 23.0918, 42.9882)$. Note that $\Delta = -0.2247 < 0$, $b_0 = -6.0220 \times 10^{-4} < 0$, and $\hat{z}_2 = -0.0442 < 0$, namely, assumption **($\mathbf{H_1}$)** (i-4) holds. We can get $\omega = 0.1519$ and $\tau_2^j = 4.3175 + \frac{2j\pi}{\omega}$ for $j \in \mathbb{N}$. It follows from Theorem 3.7 that the infected steady state P_1 is locally asymptotically stable for $\tau_2 \in [0, \tau_2^0)$ (see Figure 6 with $\tau_2 = 4 < \tau_2^0$) and unstable for $\tau > \tau_2^0$. Moreover, system (1.1) undergoes Hopf bifurcation at $\tau_2 = \tau_2^j$ for $j \in \mathbb{N}$. Figure 7 supports this with $\tau_2 = 5 > \tau_2^0$. Figure 8 provides the bifurcation diagram.

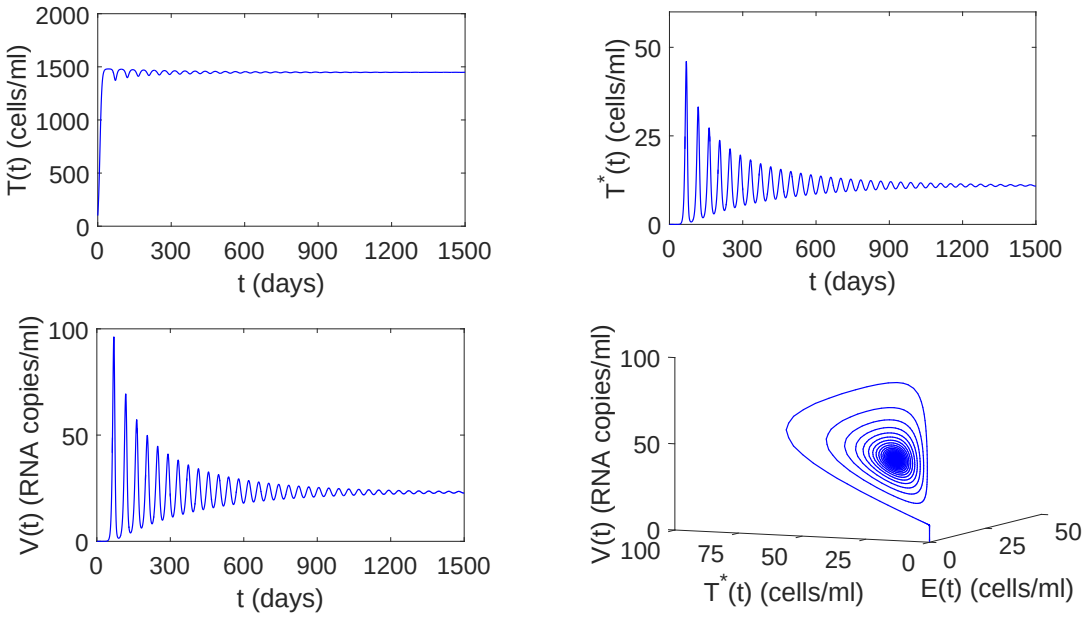

Figure 6. The infected steady state P_1 is locally asymptotically stable. For parameter values, we refer to the text.

Case 3: Assumption **($\mathbf{H_2}$)** holds. This time we replace k with $k = 2.4 \times 10^{-3}$, and r with $r = 0.03$, and keep the other parameter values as in Case 2. It follows that $R_0 = 17.2119 > 1$ and system (1.1) has the unique infected steady state $P_1 = (168.9145, 15.0443, 31.5930, 55.1329)$. Moreover, $\Delta = -0.4441 < 0$, $b_0 = 3.0321 \times 10^{-4} > 0$, $\hat{z}_1 = -11.1936 < 0 < \hat{z}_2 = 0.0018 > 0$, and $h(z_3^*) = -9.3650 \times 10^{-4} < 0$. Therefore, assumption **($\mathbf{H_2}$)** (ii-6) holds. In this case, we have $\tilde{\omega}_1 = 0.2845$, $\tilde{\omega}_2 = 0.1401$, $\tau_{21}^j = 2.0033 + \frac{2j\pi}{\tilde{\omega}_1}$, and $\tau_{22}^j = 22.3237 + \frac{2j\pi}{\tilde{\omega}_2}$ for $j \in \mathbb{N}$. Then the first few Hopf bifurcation values are ordered as $\tau_{21}^0 < \tau_{22}^0 < \tau_{21}^1 < \tau_{21}^2 < \tau_{22}^1 < \cdots$. By Theorem 3.8, the infected steady state P_1 is locally asymptotically stable for $\tau_2 \in [0, \tau_{21}^0) \cup (\tau_{22}^0, \tau_{21}^1)$ (see Figure 9 and Figure 10 with $\tau_2 = 1.5 < \tau_{22}^0$ and $\tau_2 = 24 \in (\tau_{22}^0, \tau_{21}^1)$, respectively) and is unstable for $\tau_2 \in (\tau_{21}^0, \tau_{22}^0) \cup (\tau_{21}^1, \infty)$. Thus there are stability switches for P_1. Moreover, there are supercritical Hopf bifurcation at $\tau_2 = \tau_{21}^j$ and subcritical Hopf bifurcation at $\tau_2 = \tau_{22}^j$ (see Figures 11 and 12). The numerical simulations also strongly indicate that the global Hopf bifurcation branches are bounded and each branch connects a pair τ_{21}^j and τ_{22}^j, which we will confirm in a future work.

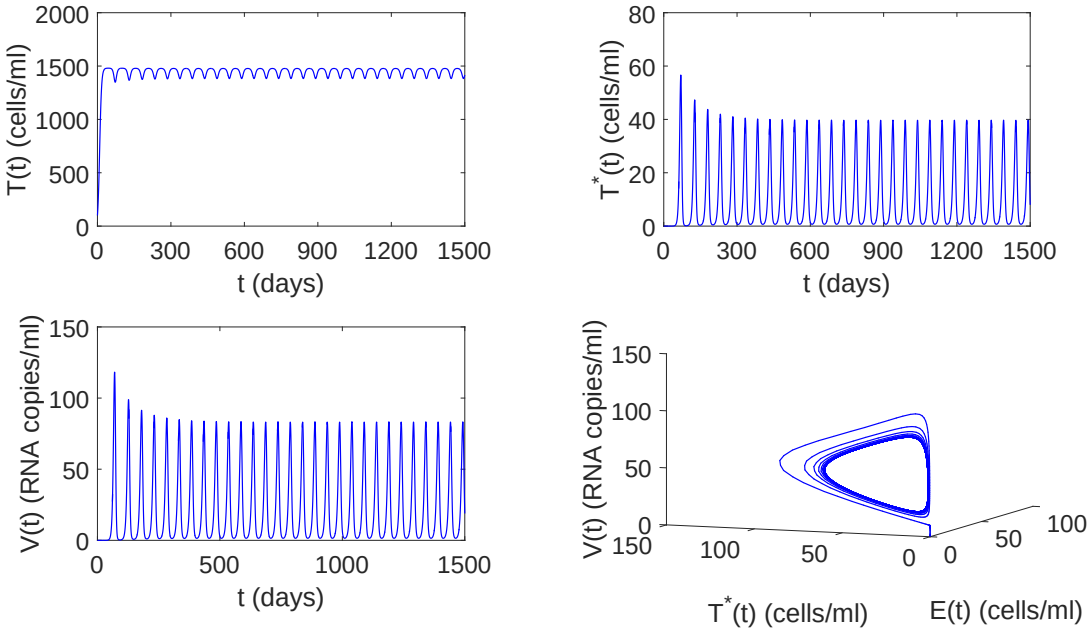

Figure 7. There is a periodic orbit bifurcated through Hopf bifurcation at the infected steady state P_1 when $\tau_2 = 5 > \tau_2^0$. See the text for parameter values.

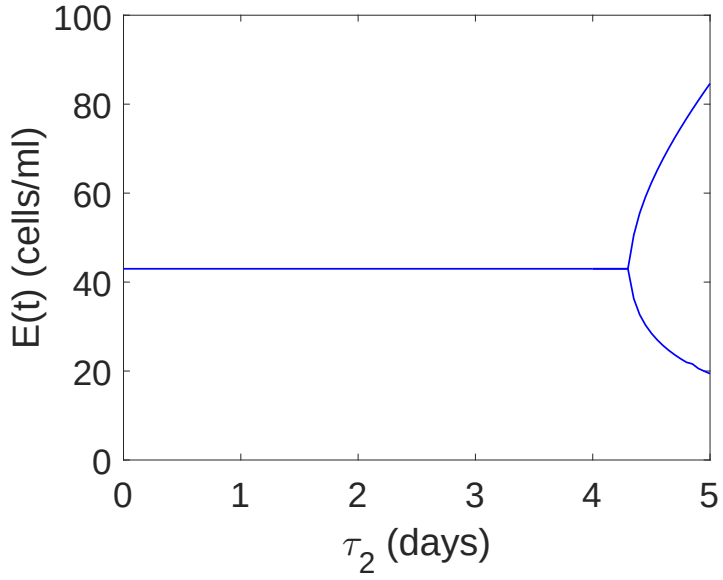

Figure 8. The bifurcation diagram at P_1 with τ_2 as the bifurcation parameter. See the text for the other parameter values.

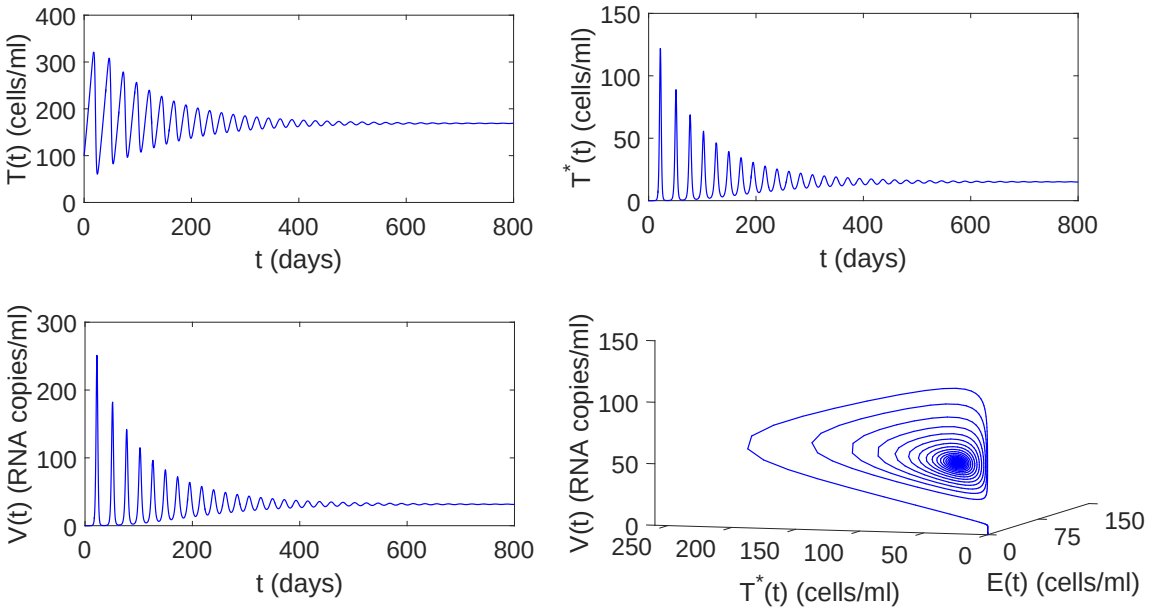

Figure 9. The infected steady state P_1 is locally asymptotically stable for $\tau_2 = 1.5 < \tau_{21}^0 = 2.0033$. See the text for the values of the other parameters.

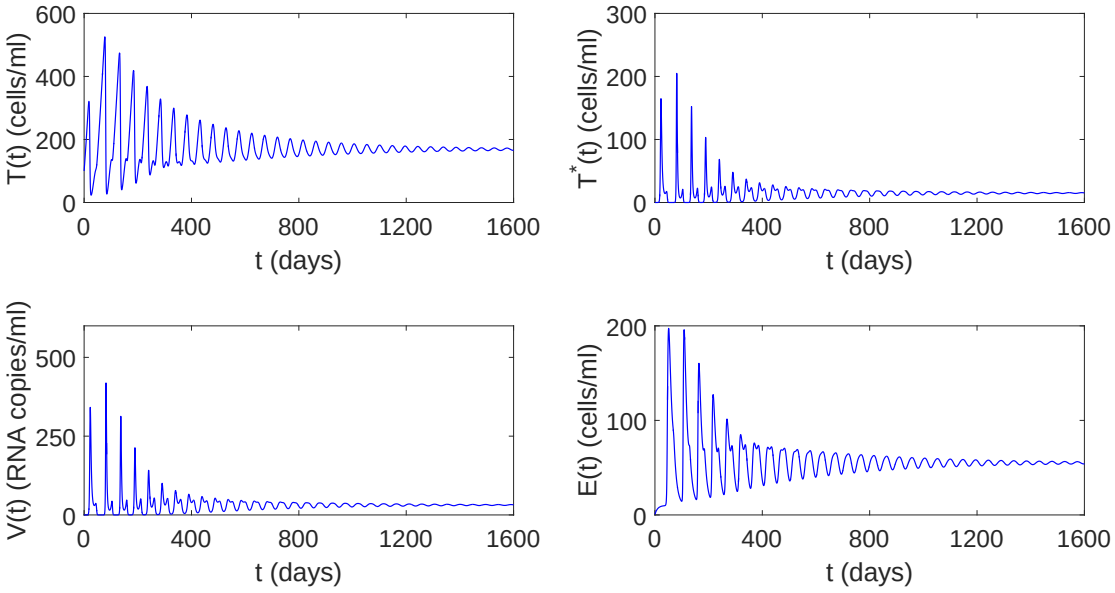

Figure 10. The infected steady state P_1 is asymptotically stable for $\tau_{22}^0 < \tau_2 = 24 < \tau_{21}^1$. We refer to the text for values of the other parameters.

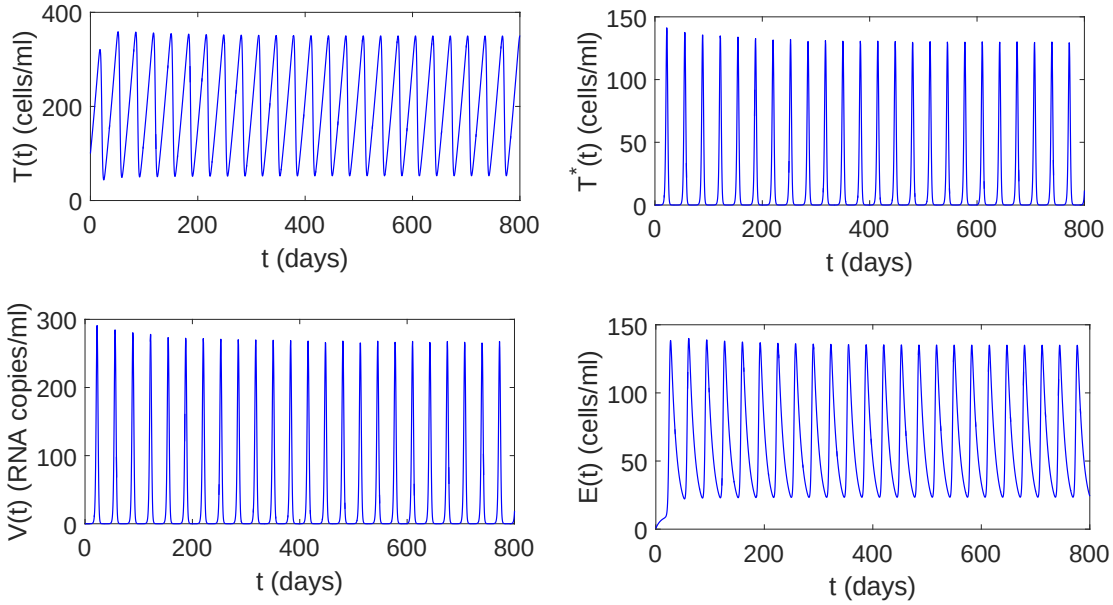

Figure 11. There is a periodic orbit bifurcated from the infected steady state P_1 through supercritical Hopf bifurcation when $\tau_{21}^0 < \tau_2 = 2.5 < \tau_{22}^0$. See the text for the values of the other parameters.

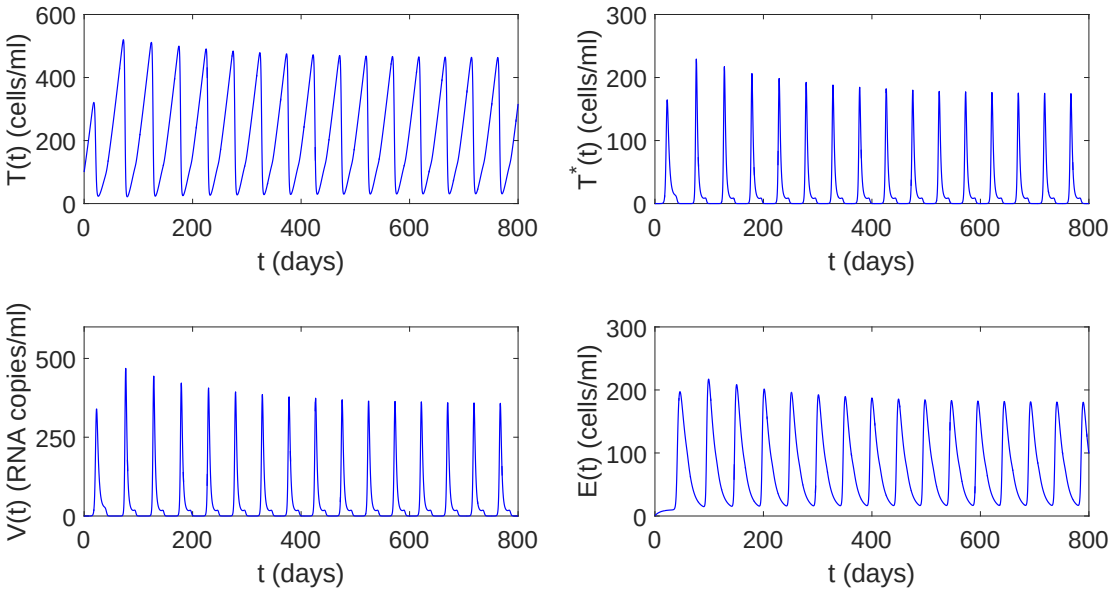

Figure 12. There is a periodic orbit bifurcated from the infected steady state P_1 through subcritical Hopf bifurcation when $\tau_{21}^0 < \tau_2 = 19 < \tau_{22}^0$. See the text for the values of the other parameters.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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