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Research article

Modelling and analysis of a delayed viral infection model with follicular dendritic cell

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Abstract: In this paper, we propose a new viral infection model by incorporating a new compartment for follicular dendritic cell (FDC), nonlinear incidence, CTL immune response, and two intracellular delays. The main purpose of the paper is to make an improvement and supplement to the global dynamics of the model proposed by Callaway and Perelson (2002), in which global stability has not been studied. The global stabilities of equilibria are established by constructing corresponding Lyapunov functionals in terms of two threshold parameters, $\Re_0$ and $\Re_1$. The obtained results imply that both nonlinear incidence and intracellular time delays have no impact on the stability of the model.

Keywords: follicular dendritic cell; intracellular time delays; nonlinear incidence; global stability; Lyapunov functionals

1. Introduction

Samples cannot always be taken frequently from patients, or detection techniques of the virus may not be accurate, and testing specific hypotheses based on clinical statistic data is a challengeable task, which justifies the key role played by mathematical models in this area. Mathematical models have been proposed to understand the in vivo infection dynamics of viruses. Particularly, theses within-host viral infection models were used to describe the viral infection process, estimate some key parameters, and provide support for research and development of antiviral drugs [1–4]. The classical viral dynamics can be described by the differential equations of three compartments: the uninfected target cells, the infected cells, and the free virus. Sometimes, a fourth compartment corresponding to the immune response was introduced into the model [5–8]. One of the main immune responses is the cytotoxic T-lymphocyte cells (CTLs), which play a crucial role in antiviral defense by attacking virus-infected cells in most virus infections. A basic and simple model with CTL immune response was proposed to explore the interaction between the CTLs and infected cells [5]. Then many kinds of models with im-

mune response were further developed to investigate the impact of immune response on the dynamics of virus infection [6–8] and references therein.

Though antiretroviral therapy can effectively suppress viral replication to a low level, it cannot eradicate the virus permanently. An reliable and possible explanation is that there exists a viral reservoir, which is a possible impediment to virus eradication. Currently, researchers have shown that follicular dendritic cells (FDC) reside in secondary lymphoid organs known as germinal centers and bind HIV-antibody complexes, thus creating an archive of infectious viruses that can perpetuate infection. As such, HIV trapped on FDC is thought to be a significant viral reservoir [9–13]. Even with antiretroviral therapy, the FDC can still provide a suitable microenvironment for ongoing infection and impair the B cell response [14–17]. It is thus important to consider this factor in viral infection models, and some earlier studies of FDC can be found in [9–11]. For example, Callaway and Perelson [11] proposed the following simple model with FDC to understand what the effect FDC could have on the steady state viral load:

$$\begin{cases} \dfrac{dT}{dt} = \lambda - dT - (1-\varepsilon)kTV, \\ \dfrac{dI}{dt} = (1-\varepsilon)kTV - \delta I, \\ \dfrac{dV}{dt} = N\delta I - (c_1+\mu)V + \alpha W, \\ \dfrac{dW}{dt} = \mu V - (\alpha + c_2)W, \end{cases} \tag{1.1}$$

where $T(t)$, $I(t)$, $V(t)$, and $W(t)$ are the concentrations of uninfected target cells, infected cells, free viruses, and virus particles bound to FDC at time t, respectively. λ is a constant production rate of uninfected cells that die at a rate d. The uninfected cells are infected by free virus at a rate of $(1-\varepsilon)kTV$, where ε represents the efficacy of RT inhibitors. The infected cells produce virions at a rate $N\delta I$ and die at a rate δ, where N is the number of virions produced by an infected cell during its life span (burst size). The virions are cleared at a rate of c_1. FDC binds free virus at rate μ, bound virus dissociates from FDC at rate α, and bound virus is cleared at rate c_2.

In addition, it needs to go through a period between initial viral entry into a cell and subsequent viral production, and a maturation time is necessary for the released virions before they become infectious. Moreover, as pointed out by Ciup et al. [18], allowing for time delays in the models better predicts viral load data when compared to models without delays. Thus taking time delays into account makes the models more realistic. Then motivated by [11], a general viral infection model with two intracellular time delays and CTL immune response takes as follows:

$$\begin{cases} \dfrac{dT}{dt} = \lambda - dT - (1-\varepsilon)kTf(V), \\ \dfrac{dI}{dt} = (1-\varepsilon)kT(t-\tau_1)f(V(t-\tau_1)) - \delta I - rIZ, \\ \dfrac{dV}{dt} = N\delta I(t-\tau_2) - (c_1+\mu)V + \alpha W, \\ \dfrac{dW}{dt} = \mu V - (\alpha + c_2)W, \\ \dfrac{dZ}{dt} = pIZ - qZ, \end{cases} \tag{1.2}$$

where $Z(t)$ be the concentrations of CTLs at time t. The uninfected cells are infected by free virus at a rate of $(1-\varepsilon)kTf(V)$. The infected cells are cleared by CTLs at a rate of rIZ. The CTLs are proliferated at a rate pIZ and decay at a rate q. τ_1 represents the time period from being infected to becoming productive infected cells, and τ_2 represents the time necessary for the newly produced virions to become mature. Throughout this paper, we assume that the incidence function $f(V)$ satisfies the following conditions:

$$f(0) = 0, \quad f'(V) > 0, \quad f''(V) \leq 0. \tag{1.3}$$

Based on condition (1.3), it follows that

$$f'(V)V \leq f(V) \leq f'(0)V, \quad \text{for} \quad V \geq 0. \tag{1.4}$$

The initial conditions for model (1.2) are

$$T(\theta) = \varphi_1(\theta), I(\theta) = \varphi_2(\theta), V(\theta) = \varphi_3(\theta), W(\theta) = \varphi_4(\theta), Z(\theta) = \varphi_5(\theta), \tag{1.5}$$

where $\tau = \max\{\tau_1, \tau_2\}$ and $(\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta), \varphi_4(\theta), \varphi_5(\theta)) \in C([-\tau, 0], \mathbb{R}^5_+)$. It is obviously that the model (1.2) includes the model [11] as an special case, in which the global dynamics that has not been investigated will be solved in this paper.

The rest of the paper is organized as follows: In Section 2, we derive the basic reproduction number for the viral infection, the basic reproduction number for the immune response, and the existence of equilibria. In Section 3, we prove that the global dynamics of the model are determined by the two threshold parameters. Simulations are carried out to validate the obtained results in Section 4. A summary and a discussion are presented in Section 5.

2. Preliminary results and thresholds

Some preliminary results will be presented in this part before analyzing the dynamics of model (1.2). According to literature [19], it is easy to show that the solutions of model (1.2) are non-negative. Moreover, let $P_1(t) = T + I(t+\tau_1) + \frac{r}{p}Z(t+\tau_1)$, then we have

$$P_1' = \lambda - dT - \delta I(t+\tau_1) - \frac{r}{p}qZ(t+\tau_1) \leq \lambda - m_1 P_1(t),$$

which implies that $\limsup_{t\to+\infty} P_1(t) \leq \frac{\lambda}{m_1}$, where $m_1 = \min\{d, \delta, q\}$. Then, let $P_2(t) = V(t) + W(t)$, it follows that $P_2'(t) \leq \frac{N\delta\lambda}{m_1} - m_2 P_2(t)$, which leads to that $\limsup_{t\to+\infty} P_2(t) \leq \frac{N\delta\lambda}{m_1 m_2}$ with $m_2 = \min\{c_1, c_2\}$. Therefore, the above analysis leads to the following result.

Lemma 2.1. *The solutions* $(T(t), I(t), V(t), W(t), Z(t))$ *of model* (1.2) *with initial conditions* (1.5) *are non-negative and ultimately bounded.*

It is easily seen that the model (1.2) possesses an infection-free equilibrium $E_0 = (T_0, 0, 0, 0, 0)$ with $T_0 = \frac{\lambda}{d}$. Define the basic reproduction number for viral infection $\Re_0$ of model (1.2) as

$$\Re_0 = \frac{\lambda(1-\varepsilon)kf'(0)N(\alpha + c_2)}{d(c_1\alpha + c_1c_2 + c_2\mu)}.$$

When $Z = 0$, an immune-inactivated equilibrium $E_1 = (T_1, I_1, V_1, W_1, 0)$ exists if $T_1, I_1, V_1, W_1 > 0$ satisfy

$$\lambda - dT_1 = (1-\varepsilon)kT_1 f(V_1) = \delta I_1 = \frac{c_1\alpha + c_1c_2 + c_2\mu}{N(c_2+\alpha)}V_1 = \frac{c_1\alpha + c_1c_2 + c_2\mu}{N\mu}W_1. \tag{2.1}$$

Since $T_1, V_1 > 0$, it then follows from (2.1) that $V_1 \le \frac{\lambda N(c_2+\alpha)}{c_1\alpha+c_1c_2+c_2\mu} =: \tilde{V}$. In order to show the existence of E_1, we define

$$F(V) = \frac{d(c_1\alpha + c_1c_2 + c_2\mu)V}{kN(1-\varepsilon)(c_2+\alpha)f(V)} + \frac{c_1c_2 + c_1\alpha + c_2\mu}{N(c_2+\alpha)}V - \lambda.$$

Together with (1.3) and (1.4), it follows that $F'(V) > 0$. Moreover, for $\Re_0 > 1$ a simple calculation gives

$$\lim_{V\to 0^+} F(V) = \frac{\lambda(1-\Re_0)}{\Re_0} > 0, \quad F(\tilde{V}) = \frac{d\lambda}{(1-\varepsilon)kf(\tilde{V})} > 0.$$

Thus, if $\Re_0 > 1$, there exists $V_1 \in (0, \tilde{V})$ such that $F(V_1) = 0$. This proves the existence of E_1 when $\Re_0 > 1$.

An immune-activated equilibrium $E_2 = (T_2, I_2, V_2, W_2, Z_2)$ exists if $T_2, I_2, V_2, W_2, Z_2 > 0$ satisfy the following equilibrium equations:

$$\begin{aligned} T_2 =& \frac{\lambda}{d + (1-\varepsilon)kf(V_2)}, \quad I_2 = \frac{q}{p}, V_2 = \frac{N\delta I_2(c_2+\alpha)}{c_1\alpha + c_1c_2 + c_2\mu}, \quad W_2 = \frac{\mu V_2}{c_2+\alpha}, \\ Z_2 =& \frac{1}{rI_2}\left[\frac{\lambda(1-\varepsilon)kf(V_2)}{\delta I_2(d+(1-\varepsilon)kf(V_2))} - 1\right] = \frac{1}{rI_2}(\Re_1 - 1). \end{aligned} \tag{2.2}$$

Thus, an immune-activated equilibrium E_2 exists if and only if $\Re_1 > 1$, where

$$\Re_1 = \frac{\lambda(1-\varepsilon)kf(V_2)}{\delta I_2(d+(1-\varepsilon)kf(V_2))} < \frac{\lambda(1-\varepsilon)kf'(0)N(c_2+\alpha)}{d(c_1\alpha + c_1c_2 + c_2\mu)} = \Re_0.$$

Lemma 2.2. $Sign\{T_2 - T_1\} = Sign\{I_1 - I_2\} = Sign\{V_1 - V_2\} = Sign\{W_1 - W_2\} = Sign\{\Re_1 - 1\}$.

Proof. It follows from (2.1) and (2.2) that

$$d(T_1 - T_2) = (1-\varepsilon)k(T_2 - T_1)f(V_2) + (1-\varepsilon)kT_1(f(V_2) - f(V_1)).$$

Then we have $(d+(1-\varepsilon)kf(V_2))(T_1-T_2) = (1-\varepsilon)kT_1(f(V_2)-f(V_1))$, which implies that $Sign\{T_2-T_1\} = Sign\{V_1 - V_2\}$.

Moreover, it follows from (2.1) and (2.2) that $Sign\{V_1 - V_2\} = Sign\{W_1 - W_2\}$ and

$$N\delta(I_1 - I_2) = (c_1+\mu)(V_1 - V_2) - \alpha(W_1 - W_2) = \left(\frac{(c_1+\mu)(c_2+\alpha)}{\mu} - \alpha\right)(W_1 - W_2),$$

we then have $Sign\{I_1 - I_2\} = Sign\{V_1 - V_2\} = Sign\{W_1 - W_2\}$.

Then

$$\begin{aligned} \Re_1 - 1 =& \frac{(1-\varepsilon)kT_2f(V_2)}{\delta I_2} - 1 = \frac{(1-\varepsilon)kT_2f(V_2)}{(c_1+\mu)V_2 - \alpha W_2} - \frac{(1-\varepsilon)kT_1f(V_1)}{(c_1+\mu)V_1 - \alpha W_1} \\ =& \frac{(1-\varepsilon)kN}{(c_1+\mu)(c_2+\alpha) - \alpha\mu}\left\{\frac{(T_2-T_1)f(V_2)}{V_2} + T_1\left(\frac{f(V_2)}{V_2} - \frac{f(V_1)}{V_1}\right)\right\}. \end{aligned}$$

It follows from (1.4) that $Sign\{V_1 - V_2\} = Sign\{\frac{f(V_2)}{V_2} - \frac{f(V_1)}{V_1}\}$, then we have $Sign\{\Re_1 - 1\} = Sign\{V_1 - V_2\} = Sign\{I_1 - I_2\}$. This completes the proof. □

3. Global stability analysis

In this part, the global stability of the equilibria E_0, E_1, and E_2 will be established by constructing Lyapunov functionals, which are motivated by [20–23]. Here, we will use the function $\varphi(x) = 1 + \ln x - x$, which satisfies $\varphi(x) \leq 0$ for $x > 0$ and $\varphi(x) = 0$ if and only if $x = 1$.

Theorem 3.1. *If $\Re_0 \leq 1$, then the infection-free equilibrium of E_0 is globally asymptotically stable.*

Proof. Let $T(t), I(t), V(t), W(t), Z(t)$ be any arbitrary positive solution of model (1.2) and recall that $T_0 = \dfrac{\lambda}{d}$. Define a Lyapunov functional $G_1(t)$ as

$$G_1(t) = \varphi\left(\frac{T}{T_0}\right) + I(t) + \frac{V(t)}{N} + \frac{\alpha W}{N(c_2+\alpha)} + \frac{r}{p}Z + \int_{t-\tau_1}^{t}(1-\varepsilon)kT(\theta)f(V(\theta))d\theta + \int_{t-\tau_2}^{t}\delta I(\theta)d\theta.$$

Computing the time derivative of $G_1(t)$ along the solution of model (1.2), which leads to

$$\begin{aligned}\frac{dG_1}{dt} =& dT_0\left(1-\frac{T_0}{T}\right)\left(1-\frac{T}{T_0}\right) + (1-\varepsilon)kT_0f(V) + \left(\frac{\alpha\mu}{N(c_2+\alpha)} - \frac{c_1+\mu}{N}\right)V - \frac{qr}{p}Z\\ \leq& dT_0\left(1-\frac{T_0}{T}\right)\left(1-\frac{T}{T_0}\right) + \frac{c_1\alpha + c_1c_2 + c_2\mu}{N(c_2+\alpha)}(\Re_0 - 1)V - \frac{qr}{p}Z.\end{aligned}$$

Clearly, if $\Re_0 \leq 1$, then $\dfrac{dG_1}{dt} \leq 0$, for all $T, I, V, W, Z \leq 0$ and $\dfrac{dG_1}{dt} = 0$ is satisfied if and only if $T = T_0, I = V = W = Z = 0$. Thus, the maximal compact invariant set in $\{G_1'(t) = 0\}$ is the singleton $\{E_0\}$. This proves the global stability of E_0 by applying the LaSalle invariance principle [24]. □

Theorem 3.2. *If $\Re_1 < 1 < \Re_0$, then the immune-inactivated equilibrium E_1 is globally asymptotically stable.*

Proof. Define

$$\begin{aligned}G_2(t) =& \varphi\left(\frac{T}{T_1}\right) + \varphi\left(\frac{I}{I_1}\right) + \frac{1}{N}\varphi\left(\frac{V}{V_1}\right) + \frac{\alpha}{N(c_2+\alpha)}\varphi\left(\frac{W}{W_1}\right) + \frac{r}{p}Z\\ &+ \int_{t-\tau_2}^{t}\delta I_1\varphi\left(\frac{I(\theta)}{I_1}\right)d\theta + \int_{t-\tau_1}^{t}(1-\varepsilon)kT_1f(V_1)\varphi\left(\frac{T(\theta)f(V(\theta))}{T_1f(V_1)}\right)d\theta.\end{aligned}$$

For convenience, let $u_\tau = u(t-\tau)$. Taking the time derivative of $G_1(t)$ along the solution of model (1.2) and using the equilibrium conditions (2.1) for E_1, we have

$$\begin{aligned}\frac{dG_2}{dt} =& dT_1\left(1-\frac{T}{T_1}\right)\left(1-\frac{T_1}{T}\right) + (1-\varepsilon)kT_1f(V_1)\left\{3 - \frac{T_1}{T} - \frac{V}{V_1} - \frac{V_1I_{\tau_2}}{VI_1}\right.\\ &\left. - \frac{T_{\tau_1}I_1f(V_{\tau_1})}{T_1If(V_1)} + \frac{f(V)}{f(V_1)} + \ln\frac{T_{\tau_1}f(V_{\tau_1})I_{\tau_2}}{Tf(V)I}\right\} + rZ(I_1 - I_2) + \frac{\alpha W_1}{N}\left(2 - \frac{V_1W}{VW_1} - \frac{VW_1}{V_1W}\right)\\ =& dT_1\left(1-\frac{T}{T_1}\right)\left(1-\frac{T_1}{T}\right) + (1-\varepsilon)kT_1f(V_1)\left\{\varphi\left(\frac{T_1}{T}\right) + \varphi\left(\frac{T_{\tau_1}I_1f(V_{\tau_1})}{T_1If(V_1)}\right)\right.\\ &\left. + \varphi\left(\frac{V_1I_{\tau_2}}{VI_1}\right) + \varphi\left(\frac{f(V_1)V}{f(V)V_1}\right) + \left(\frac{f(V)}{f(V_1)} - \frac{V}{V_1}\right)\left(1 - \frac{f(V_1)}{f(V)}\right)\right\}\end{aligned}$$

$$+ rZ(I_1 - I_2) + \frac{\alpha W_1}{N}\left(2 - \frac{V_1 W}{V W_1} - \frac{V W_1}{V_1 W}\right).$$

From Lemma 2.2, we have $I_1 - I_2 < 0$. Moreover, $\left(\frac{f(V)}{f(V_1)} - \frac{V}{V_1}\right)\left(1 - \frac{f(V_1)}{f(V)}\right) \leq 0$ follows from (1.3) and (1.4). Then, we have $\frac{dG_2}{dt} \leq 0$ and $\frac{dG_2}{dt} = 0$ if and only if $T = T_1, I = I_1, V = V_1, W = W_1, Z = Z_1$. Thus, the largest compact invariant set of $\{G_2' = 0\}$ is the singleton $\{E_1\}$. Therefore, the global stability of E_1 follows from the LaSalle invariance principle [24]. □

Theorem 3.3. *If $\Re_1 > 1$, then the immune-activated equilibrium E_2 is globally asymptotically stable.*

Proof. Define

$$\begin{aligned} G_3(t) =& \varphi\left(\frac{T}{T_2}\right) + \varphi\left(\frac{I}{I_2}\right) + \frac{\delta + rZ_2}{N\delta}\varphi\left(\frac{V}{V_2}\right) + \frac{(\delta + rZ_2)\alpha}{N\delta(c_2 + \alpha)}\varphi\left(\frac{W}{W_2}\right) + \frac{r}{p}\varphi\left(\frac{Z}{Z_2}\right) \\ &+ \int_{t-\tau_1}^{t} (1-\varepsilon)kT_2 f(V_2)\varphi\left(\frac{T(\theta)f(V(\theta))}{T_2 f(V_2)}\right)d\theta + \int_{t-\tau_2}^{t} (\delta + rZ_2)I_2\varphi\left(\frac{I(\theta)}{I_2}\right)d\theta. \end{aligned}$$

Taking the time derivative of $G_3(t)$ along the solution of model (1.2) and using the equilibrium conditions (2.1) for E_2, we have

$$\begin{aligned} \frac{dG_3}{dt} =& dT_2\left(1 - \frac{T}{T_2}\right)\left(1 - \frac{T_2}{T}\right) + (1-\varepsilon)kT_2 f(V_2)\left\{3 - \frac{T_2}{T} - \frac{V}{V_2} - \frac{V_2 I_{\tau_2}}{V I_2}\right. \\ &\left. - \frac{T_{\tau_1} I_2 f(V_{\tau_1})}{T_2 I f(V_2)} + \frac{f(V)}{f(V_2)} + \ln\frac{T_{\tau_1} f(V_{\tau_1}) I_{\tau_2}}{T f(V) I}\right\} + \frac{\alpha W_2(\delta + rZ_2)}{N\delta}\left(2 - \frac{V_2 W}{V W_2} - \frac{V W_2}{V_2 W}\right) \\ =& dT_2\left(1 - \frac{T}{T_2}\right)\left(1 - \frac{T_2}{T}\right) + (1-\varepsilon)kT_2 f(V_2)\left\{\varphi\left(\frac{T_2}{T}\right) + \varphi\left(\frac{T_{\tau_1} I_2 f(V_{\tau_1})}{T_2 I f(V_2)}\right)\right. \\ &\left. + \varphi\left(\frac{V_2 I_{\tau_2}}{V I_2}\right) + \varphi\left(\frac{f(V_2)V}{f(V)V_2}\right) + \left(\frac{f(V)}{f(V_2)} - \frac{V}{V_2}\right)\left(1 - \frac{f(V_2)}{f(V)}\right)\right\} \\ &+ \frac{\alpha W_2(\delta + rZ_2)}{N\delta}\left(2 - \frac{V_2 W}{V W_2} - \frac{V W_2}{V_2 W}\right). \end{aligned}$$

Similar to the proof of Theorem 3.2, we have $\frac{dG_3}{dt} \leq 0$ and $\frac{dG_3}{dt} = 0$ if and only if $T = T_2, I = I_2, V = V_2, W = W_2, Z = Z_2$. Thus, the largest compact invariant set of $\{G_2' = 0\}$ is the singleton $\{E_2\}$. Therefore, the global stability of E_2 follows from the LaSalle invariance principle [24]. □

4. Numerical simulations

In this part, numerical simulations are carried out to validate the obtained results. Here, we select the function $f(V) = \frac{V}{1+mV}$. Choosing a certain parameter value of the model (1.2), and a simple calculation show that $\Re_0 = 0.016 < 1$, which implies that the infection-free equilibrium E_0 is globally asymptotically stable and the infection dies out (see Figure 1). When choosing parameter values, we have $\Re_1 = 0.1894 < 1 < \Re_0 = 15.9999$, then the immune-inactivated equilibrium E_1 is globally asymptotically stable, which means the immune response is not enough to inhibit the infection and the

virus dominates the infection process, as shown in Figure 2. Moreover, choosing parameter values such that $\Re_1 = 1.8936 > 1$, which implies that the immune-activated equilibrium E_2 is globally asymptotically stable, and then immune cells can coexist with viruses within the host, as shown in Figure 3.

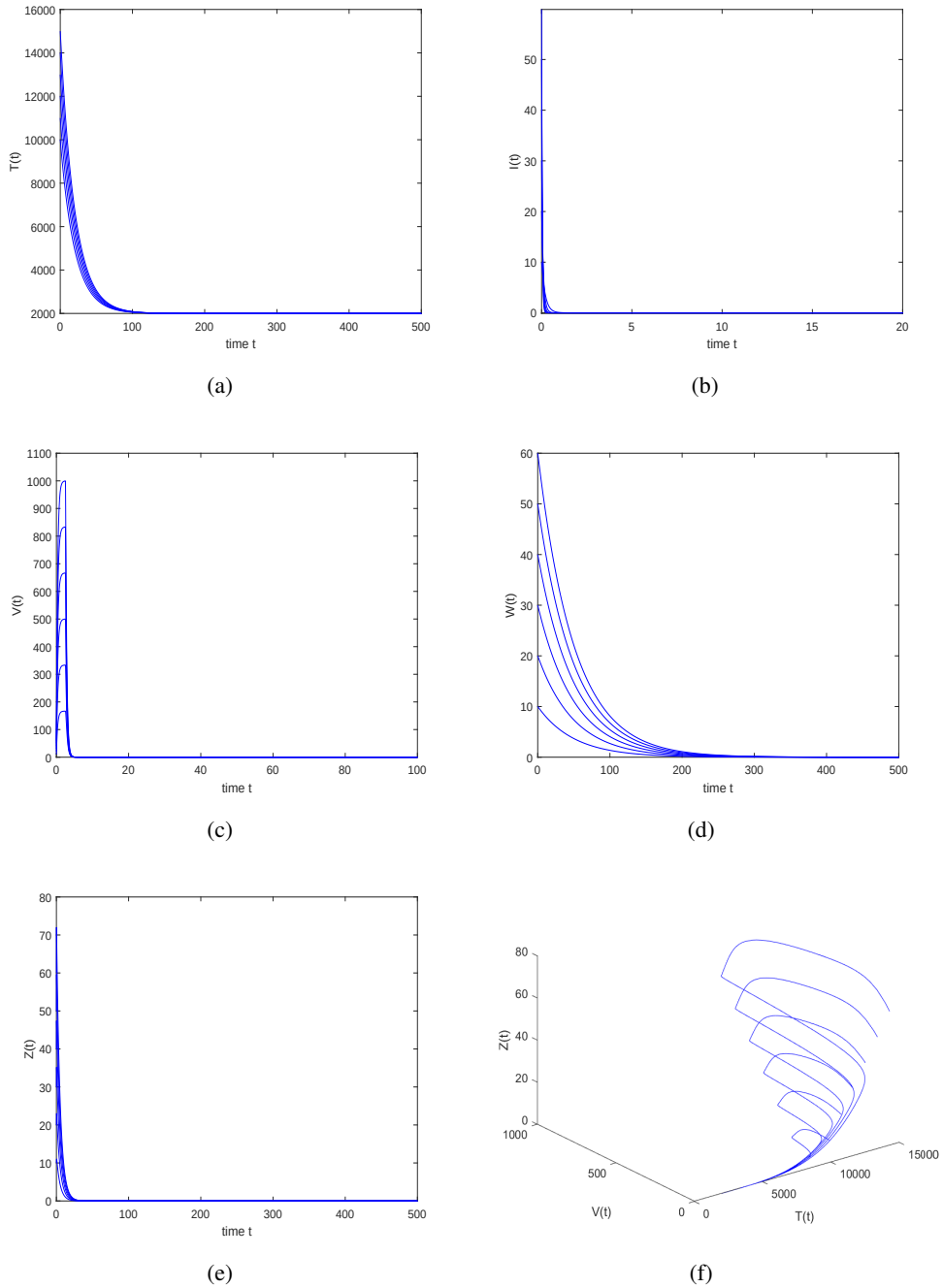

Figure 1. Let $\lambda = 100$, $d = 0.05$, $k = 8 \times 10^{-7}$,$\varepsilon = 0.7$, $N = 100$, $\delta = 0.5$, $c_1 = 3$, $c_2 = 0.01$, $\mu = 3.6 \times 10^{-5}$, $\alpha = 0.01$, $p = 0.1$, $q = 0.2$, $r = 0.42$, $m = 0.25$, then $\Re_0 = 0.016 < 1$, which implies that the infection-free equilibrium E_0 is globally asymptotically stable.

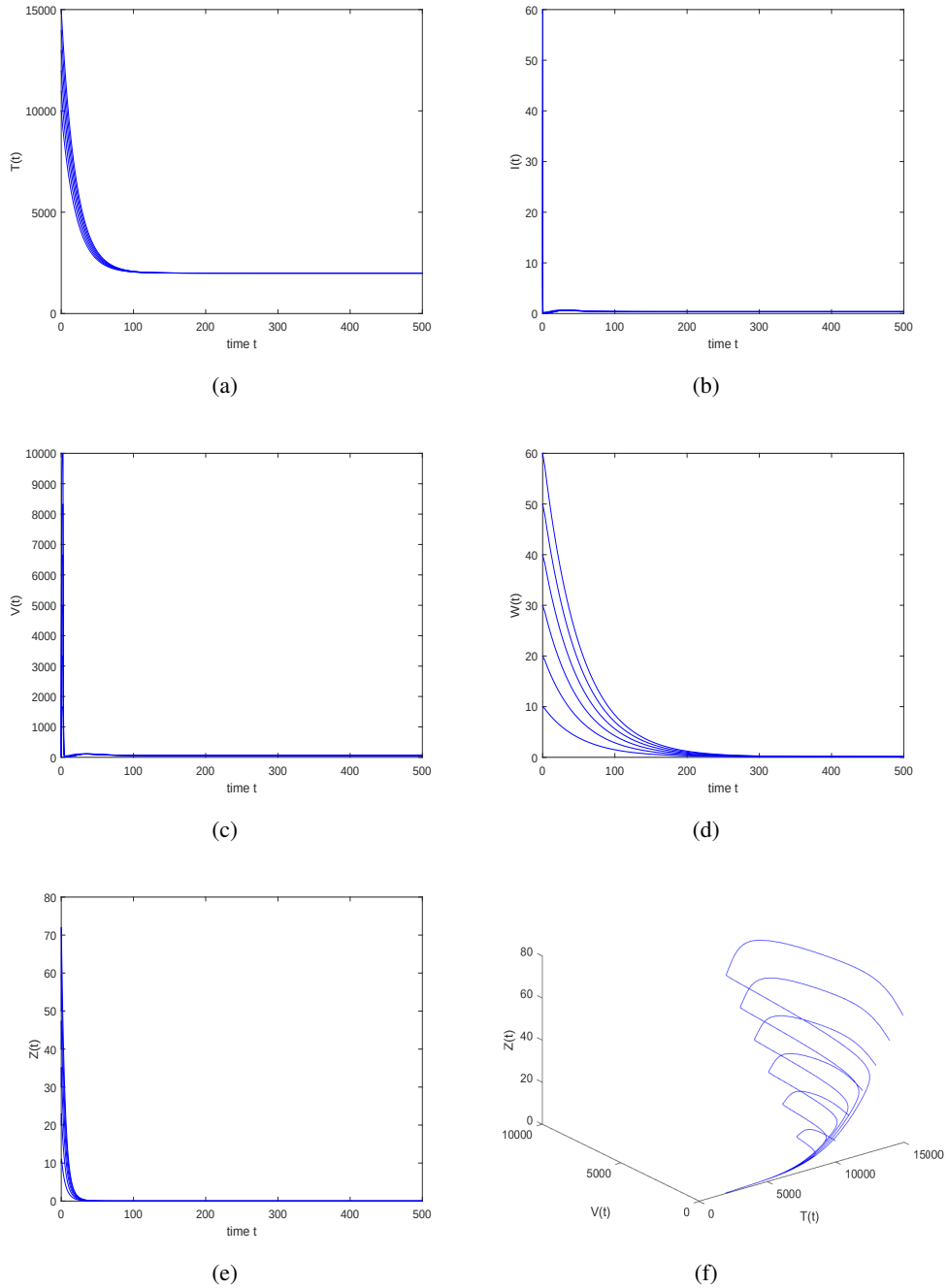

Figure 2. Let $\lambda = 100$, $d = 0.05$, $k = 8 \times 10^{-5}$,$\varepsilon = 0.7$, $N = 1000$, $\delta = 0.5$, $c_1 = 3$, $c_2 = 0.01$, $\mu = 3.6 \times 10^{-5}$, $\alpha = 0.01$, $p = 0.1$, $q = 0.2$, $r = 0.42$, $m = 0.25$, then $\Re_1 = 0.1894 < 1 < \Re_0 = 15.9999$, which implies that E_1 is globally asymptotically stable.

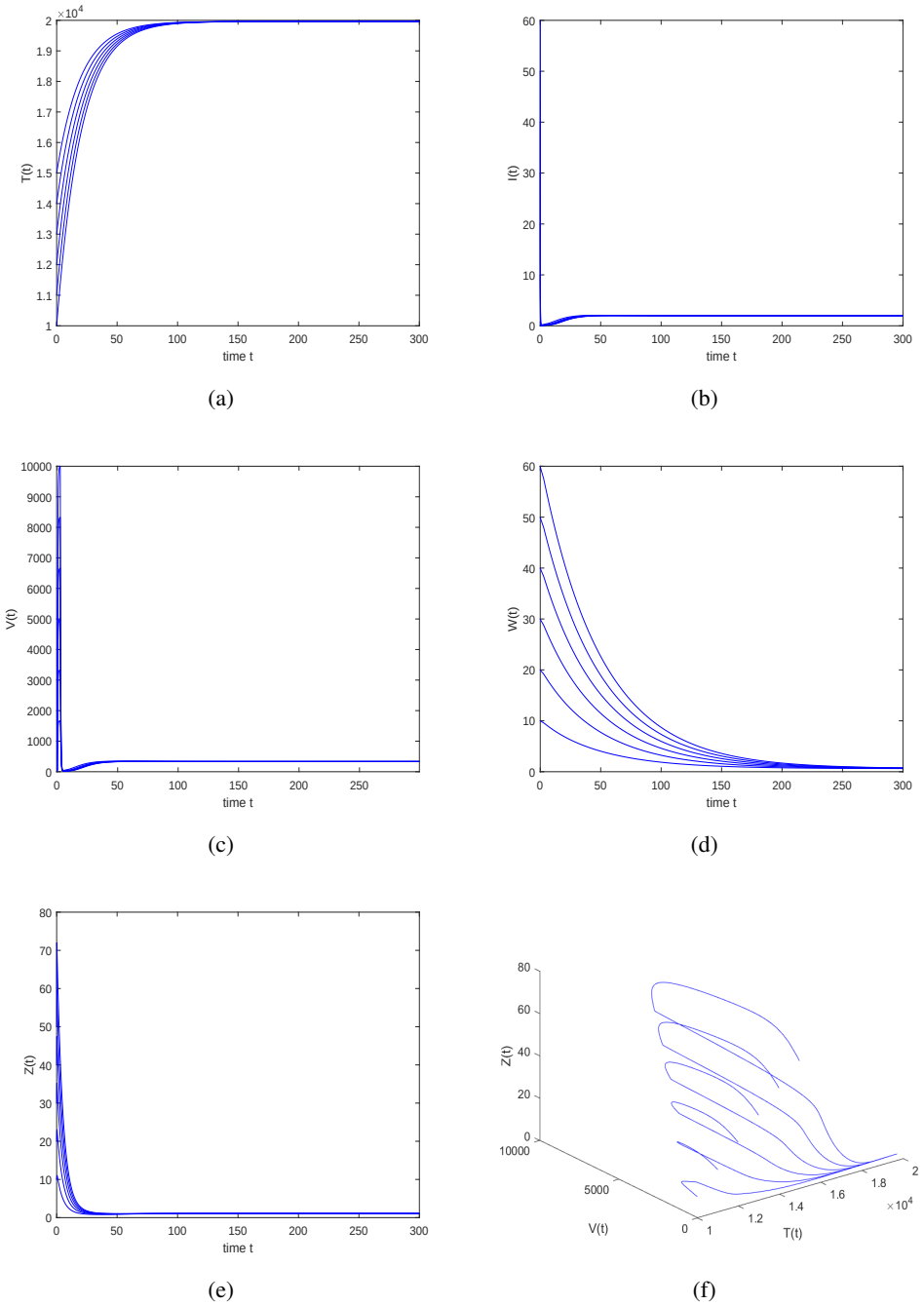

Figure 3. Let $\lambda = 1000$, $d = 0.05$, $k = 8\times10^{-5}$,$\varepsilon = 0.7$, $N = 1000$, $\delta = 0.5$, $c_1 = 3$, $c_2 = 0.01$, $\mu = 3.6\times10^{-5}$, $\alpha = 0.01$, $p = 0.1$, $q = 0.2$, $r = 0.42$, $m = 0.25$, then $\Re_1 = 1.8936 > 1$, which implies that E_2 is globally asymptotically stable.

5. Conclusions

In this paper, we studied an improved delayed viral infection model by incorporating nonlinear incidence and CTL immune response into the proposed model [11]. Thus, the model investigated here is including some existing literatures. We have shown that the model admits three equilibria E_0, E_1, and E_2. Moreover, two threshold parameters, $\Re_0$ and $\Re_1$ are defined. By constructing corresponding Lyapunov functionals, we have demonstrated that the infection can be inhibited when $\Re_0 \leq 1$. The infection will persist and the immune response can not be activated when $\Re_1 < 1 < \Re_0$. Both the viruses and immune cells can coexist and reach a steady state provided that $\Re_1 > 1$. The obtained results reveal that both nonlinear incidence and intracellular delay cannot change the stability of the model. Besides, the obtained global dynamics of the model are a theoretical supplement to [11], which has not been considered.

Literatures reveals that cell-to-cell transmission is vital to the spread of viruses in vivo [25–27], and only virus-to-cell infection is taken into consideration in this paper, and whether the cell-to-cell infection can retain the stability or not is an interesting question. Besides, the time for activating the immune response is not included in the model, i.e., the immune time delay. How immune time delays impact the dynamical behavior of the model is also worth studying. We leave these for future work.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there is no conflicts of interest.

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