THRESHOLD DYNAMICS OF A GENERAL DELAYED WITHIN-HOST VIRAL INFECTION MODEL WITH HUMORAL IMMUNITY AND TWO MODES OF VIRUS TRANSMISSION

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Abstract. In this paper, a general viral infection model with humoral immunity is investigated. The model describes the interaction of uninfected target cells, infected cells, free viruses and humoral immune response, incorporating two virus transmission modes and intracellular delay. Some reasonable hypotheses are made for the general incidence rates. Through stability analysis of equilibria under these hypotheses, the model exhibits threshold dynamics with respect to the immune-inactivated reproduction rate \( R_0 \) and the immune-activated reproduction rate \( R_1 \). The theoretical results and corresponding numerical simulations show that the intracellular latency, both of virus-to-cell infection and cell-to-cell infection have direct effects on the global dynamics of the general viral infection model. Our results improve and generalize some known results on within-host virus dynamics.

1. Introduction. The development of infectious diseases due to viruses is a complicated and multi-stage process. In the past decades, various mathematical models on this subject have been constructed to explore the within-host dynamics of viral infection process, such as human immunodeficiency virus (HIV) [1, 7, 8], hepatitis C virus (HCV) [11, 47], hepatitis B virus (HBV) [6, 29], and so on. Though the introduction of HBV vaccination for the newborn can reduce the prevalence of HBV infections [24], there exist no effective vaccinations for many other viruses, such as HIV and HCV. Understanding threshold dynamics of virus models can be significant to design preventive measures, intervention means and treatment strategies for the infectious disease control and help to take more effective drug therapies [4, 5, 18, 26].

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A basic within-host virus dynamics model consists of three compartments: uninfected target cells $T(t)$, infected cells $I(t)$ and free viruses $V(t)$, constituting the following model:

\[
\begin{align*}
\frac{dT}{dt} &= \Lambda - dT(t) - f(T(t), V(t)), \\
\frac{dI}{dt} &= f(T(t), V(t)) - aI(t), \\
\frac{dV}{dt} &= cI(t) - kV(t).
\end{align*}
\] (1)

In model (1), the target cells are produced at the constant rate $\Lambda$ and free virus particles are produced at the rate $cI$. $d, a$ and $k$ denote the corresponding death rate of uninfected target cells, infected cells and free viruses, respectively. The viral infection on the uninfected target cells is modeled by the generalized incidence function $f(T, V)$. Within-host virus model (1) with various specific infection functions has been proposed and studied recently. The most classical infection function in viral models is the mass-action infection rate, according to which the infection function $f(T, V)$ linearly depends on the concentrations of target cells $T$ and free viruses $V$. Based on this, Nowak et al. [30], Ho et al. [14] and Perelson et al. [32] proposed and analyzed model (1) with bilinear incidence function $hT(t)V(t)$. Further, Huang et al. [15] investigated (1) with Beddington-DeAngelis function $\frac{hTV}{\alpha + \beta T + \gamma V}$ and Regoes et al. [35] considered the epidemiological process (1) with the incidence function $\frac{T(V/D)^p}{1+T(V/D)^p}(D > 0, p > 1)$. The model (1) with two time delays has been investigated by Huang et al. in [16].

In model (1), uninfected healthy cells are considered to be infected only directly by free viruses, that is, through the virus-to-cell transmission in the bloodstream, in which virions are released from infected cells and then move randomly around to find a new uninfected target cell to infect. However, the cell-to-cell transmission also has a significant impact on the viral infection, in which virus particles can be transferred directly between infected cells and uninfected cells, passing through certain structures termed virological synapses [42]. The study of the cell-to-cell transmission of virus has attracted great attention recently [3, 9, 27, 28, 45, 51]. For instance, the infected cells can directly transfer HIV to uninfected cells through virological synapses [17] in lymph nodes and brains, and cell-to-cell transmission is the major mode for HIV infection [10, 12, 44]. Culshaw et al. [8] studied the direct cell-to-cell spread of HIV-1 by constructing a two-dimensional differential equation model and neglecting the effects of free virus. The infection of human T-cell lymphotrophic virus 1 (HTLV-1) is primarily achieved through the cell-to-cell spread [2]. Katri and Ruan [19] explored the dynamics of HTLV-1 infection of CD4+ T-cells, in which contagion is achieved through cell-to-cell. For the two modes of virus transmission, we here are concerned with the general interaction functions. That is, the contribution of the interaction between uninfected target cells $T$ and free viruses $V$ (infected cells $I$) to the growth rate of the infected cells is represented by a general functional response term $f(T, V) (g(T, I))$, no longer accounted for by a specific function, such as the linear type and the Holling types. Through this approach, we establish a unified theoretical framework to describe different virus propagation processes. In addition, it also provides deeper insight into the internal relationship among various kinds of transmission dynamics. This not only helps us to understand the mechanism of virus spreading, but also has potential applications in the control of epidemic diseases.
In addition, it is not instantaneous to produce new virus particles in the process of viral spread. It is delayed by the time for virions entering into cells and the replication of new virions, including the process of the transcription and integration of RNA and the production of the capsid proteins. Recently, researchers have constructed and analyzed delayed intra-host viral infection models incorporating both of virus-to-cell and cell-to-cell transmissions of virions \[43, 46\]. In Lai and Zou \[21\], an HIV infection model was demonstrated to perform global threshold dynamics, taking two distributed delays and two modes of virus propagation into consideration. Yang et al. \[50\] discussed the stability and bifurcation of a delayed vivo viral infection model with both virus-to-cell spread and cell-to-cell spread.

Besides, human immune system consists of the non-specific immune system and the specific immune system, which take effect at different stages after the attack of viruses. The non-specific immune system acts as the first defense line fighting against the invading pathogens. It is hard to completely eliminate pathogens only through the non-specific immune system. Then the specific immune system is the second defense line for eradicating the invading pathogens again. The specific immune system is composed of cellular immunity (in which T lymphocytes secrete proteins called cytokines to kill the invading pathogens and stimulate to produce the cytotoxic T-cells to lyse the infected cells) and humoral immunity (in which B lymphocytes are activated by the antigen in blood and then antibodies are secreted into blood circulation to remove the antigen from blood). Humoral immunity plays an important role in human immunity and plenty of research has been done based on human immunity \[23, 36, 48\].

Motivated by above works, in this paper, we focus on the following delayed viral infection model with general functions, incorporating humoral immunity, both of virus-to-cell transmission and cell-to-cell transmission

\[
\begin{align*}
\frac{dT}{dt} &= \Lambda - dT(t) - f(T(t), V(t)) - g(T(t), I(t)), \\
\frac{dI}{dt} &= e^{-m\tau} f(T(t-\tau), V(t-\tau)) + e^{-m\tau} g(T(t-\tau), I(t-\tau)) - aI(t), \\
\frac{dV}{dt} &= cI(t) - kV(t) - pV(t)Z(t), \\
\frac{dZ}{dt} &= sV(t)Z(t) - rZ(t),
\end{align*}
\]

(2)

where \(Z(t)\) denotes the concentration of B cells at time \(t\), which are cleared at per capita rate \(r\). Viruses are killed by B cells at rate \(pVZ\) and new B cells are produced by antigenic stimulation at rate \(sVZ\). The parameter \(\tau \geq 0\) represents the intracellular latency for the virus-to-cell infection and the cell-to-cell infection in which target cells are infected to become productive infected cells and \(m\) denotes the constant death rate of infected cells which have not produced viruses. Then \(e^{-m\tau}\) is the probability for infected cells to survive from time \(t - \tau\) to \(t\). The average life spans of the uninfected cells, infected cells, free viruses and B-cells are \(\frac{1}{d}\), \(\frac{1}{a}\), \(\frac{1}{k}\) and \(\frac{1}{r}\), respectively. In system (2), the virus-to-cell transmission and the cell-to-cell transmission are represented by the incidence functions \(f(T, V)\) and \(g(T, I)\), which are assumed to satisfy the following assumptions:

\((A1)\) : \(f, g \in C^1(\mathbb{R}_+^2, \mathbb{R}_+)\) are differentiable; \(f(T, 0) = f(0, V) = g(T, 0) = g(0, I) = 0\) for all \(T, I, V \geq 0\), \(f(T, V) > 0\) and \(g(T, I) > 0\) for all \(T, I, V > 0\). These hypotheses are reasonable for actual viral models.
(A2) \( \frac{\partial f(T,V)}{\partial T} > 0 \) and \( \frac{\partial g(T,I)}{\partial T} > 0 \) for all \( T \geq 0 \) and \( V,I > 0 \); \( \frac{\partial f(T,V)}{\partial V} \geq 0 \) and \( \frac{\partial g(T,I)}{\partial I} \geq 0 \) for all \( T,V,I \geq 0 \). These hypotheses follow the biological fact that if the total number of virions (infected cells) is constant, then the more the amount of target cells is, the more healthy cells will be infected by each virus (infected cell); if the total number of target cells is constant, then the more the amount of virus particles (infected cells) is, the more target cells will be infected.

(A3) \( \frac{\partial^2 f(T,V)}{\partial T^2} \geq 0 \), \( \frac{\partial^2 g(T,I)}{\partial T^2} \geq 0 \), \( \frac{\partial f(T,V)}{\partial V} \leq \frac{f(T,V)}{V} \) and \( \frac{\partial g(T,I)}{\partial I} \leq \frac{g(T,I)}{I} \) for all \( T,V,I \geq 0 \). This indicates that \( \frac{\partial}{\partial \theta} \left( \frac{f(T,V)}{V} \right) \leq 0 \) and \( \frac{\partial}{\partial \theta} \left( \frac{g(T,I)}{I} \right) \leq 0 \), with the biological interpretation that the per capita dependence of new infections on the number of virus particles (infected cells), is a non-increasing function with respect to virus particles (infected cells).

In this paper, we focus on the threshold dynamics of system (2). We start with the sufficient and necessary conditions for the existence of the infection-free equilibrium, the immunity-inactivated equilibrium and the immunity-activated equilibrium in terms of the immune-inactivated reproduction rate \( R_0 \) and the immune-activated reproduction rate \( R_1 \). For each equilibrium, we first explore the local asymptotical stability by analyzing the corresponding characteristic equations in different approaches. Then we discuss their global attractiveness by using the method in McCluskey [25] to construct corresponding Lyapunov functionals, arriving at the global asymptotical stability of these equilibria. Our results improve and generalize some known results for within-host virus dynamics, such as the models and their corresponding results in Li et al. [22], Lin et al. [23] and Xu [49].

The paper is organized as follows. In Section 2, we study the boundedness and positivity of solutions and the existence of equilibria for system (2). In Sections 3-5, we explore the corresponding local and global stability of infection-free equilibrium, immunity-inactivated equilibrium and immunity-activated equilibrium, respectively. In Section 6, some specific examples and applications are presented to support the theoretical results. Conclusions can be found in Section 7.

2. Preliminaries. Now define the following Banach space
\[ C_+ = \{ \phi \in C([-\tau,0], \mathbb{R}_+) \mid \phi(\theta) \text{ is uniformly continuous for } \theta \in [-\tau,0], ||\phi|| < \infty \}, \]
where the norm \( || \cdot || \) in the space \( C_+ \) is \( ||\phi|| = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)| \). Then, we consider system (2) with the following initial conditions
\[ T(\theta) = \phi_1(\theta) \geq 0, \quad I(\theta) = \phi_2(\theta) \geq 0, \]
\[ V(\theta) = \phi_3(\theta) \geq 0, \quad Z(0) = Z_0 > 0, \quad \theta \in [-\tau,0], \] \( (3) \)
where \( (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), Z_0) \in C_+^3 \times \mathbb{R}_+ := C_+ \times C_+ \times C_+ \times \mathbb{R}_+ \) satisfies \( \phi_i(0) > 0 \) (i = 1, 2, 3).

Through the fundamental theory on functional differential equations [13, 20], system (2) with initial condition (3) admits a unique solution. In this section, we firstly explore the positivity and boundedness of solutions.

**Theorem 2.1.** For system (2) with initial condition (3), solutions are positive and ultimately uniformly bounded for all \( t > 0 \).

**Proof.** For \( T(t) \), suppose that there exists \( t_1 > 0 \) such that \( T(t_1) = 0 \). Then the first equation of (2) implies that \( T'(t_1) = \Lambda > 0 \). Thus, there exists sufficiently small
\( \epsilon_1 > 0 \), such that \( T(t) < 0 \) for \( t \in (t_1 - \epsilon_1, t_1) \), which contradicts with \( T(t) \geq 0 \). Thus, \( T(t) > 0 \) for \( t > 0 \).

For \( I(t) \), let \( t_2 > 0 \) be the first time such that \( I(t_2) = 0 \). Then the second equation of (2) yields \( I'(t_2) \geq e^{-rt_4}g(T(t_2 - \tau), I(t_2 - \tau)) > 0 \). Thus, there exists sufficiently small \( \epsilon_2 > 0 \), such that \( I(t) < 0 \) for \( t \in (t_2 - \epsilon_2, t_2) \), which contradicts with \( I(t) \geq 0 \). Thus, \( I(t) > 0 \) for \( t > 0 \).

Similarly, suppose that there exist \( t_3 > 0 \) and \( t_4 > 0 \) such that \( V(t_3) = 0 \) and \( Z(t_4) = 0 \). Then the third equation of (2) indicates \( V'(t_3) = cI(t_3) > 0 \). So we conclude that \( V(t) > 0 \) for all \( t > 0 \) as proved before. The last equation of (2) indicates \( Z'(t) \geq -rZ(t) \). This implies that \( Z(t_4) \geq Z(0)e^{-rt_4} > 0 \) due to comparison principle, which is also a contradiction. Thus, \( Z(t) > 0 \) for \( t > 0 \).

From the first equation of (2), we obtain
\[
\frac{dW_1}{d\tau} \leq \Lambda - dT.
\]
This implies that \( \limsup_{\tau \to +\infty} W_1(\tau) \leq \frac{\Lambda}{d} \). Let \( W_1(t) = T(t - \tau) + e^{rt}I(t) \). Then \( \frac{dW_1}{dt} \leq \Lambda - \min\{a, d\}W_1 \).

This implies that \( \limsup_{\tau \to +\infty} W_1(\tau) \leq \frac{\Lambda}{d} \). Thus, we have \( \limsup_{\tau \to +\infty} I(\tau) \leq \frac{\Lambda}{\min\{a, d\}} \).

Let \( W_2(t) = V(t) + \frac{c}{r}Z(t) \). Then \( \frac{dW_2}{d\tau} \leq \frac{c\Lambda}{\min\{a, d\}} - \min\{k, r\}W_2 \). This implies that
\[
\limsup_{\tau \to +\infty} W_2(\tau) \leq c\frac{\Lambda}{\min\{a, d\}}
\]
and \( \limsup_{\tau \to +\infty} Z(\tau) \leq \frac{sc\Lambda}{p\min\{a, d\}} \min\{k, r\} \).

Hence, solutions of system (2) with initial condition (3) are positive and ultimately uniformly bounded for all \( t > 0 \).

Define the following bounded feasible region
\[
\Omega = \left\{ (T, I, V, Z) \in C^4_+ \mid \|T\| \leq \frac{\Lambda}{d}, \|I\| \leq \Upsilon_1, \|V\| \leq \Upsilon_2, \|Z\| \leq \Upsilon_3 \right\},
\]
where \( \Upsilon_1 = \frac{\Lambda}{\min\{a, d\}} \), \( \Upsilon_2 = \frac{c\Lambda}{\min\{a, d\}} \min\{k, r\} \), and \( \Upsilon_3 = \frac{sc\Lambda}{p\min\{a, d\}} \min\{k, r\} \).

Then from Theorem 2.1, \( \Omega \) is a positively invariant set for system (2) with initial condition (3).

Secondly, we explore the existence of equilibria for system (2). For this purpose, we need to define the following immunity-inactivated reproduction rate, whose first and second parts represent the average number of secondary infected cells arising from a single virus particle and a single infected cell, respectively, in their life spans in absence of immunity response,
\[
\mathcal{R}_0 := \frac{c}{ake_{\tau}} \frac{\partial f}{\partial V} \left( \frac{\Lambda}{d}, 0 \right) + \frac{1}{aek_{\tau}} \frac{\partial g}{\partial I} \left( \frac{\Lambda}{d}, 0 \right),
\]
and the following immunity-activated reproduction rate, whose first and second parts represent the average number of secondary infected cells caused by a single virus particle and a single infected cell, respectively, in their life spans when the immunity response is activated,
\[
\mathcal{R}_1 := \frac{cs}{akre_{\tau}} f \left( \frac{\Lambda}{d}, \frac{akr}{csd}e_{\tau}r \right) + \frac{cs}{akre_{\tau}} g \left( \frac{\Lambda}{d}, \frac{akr}{csd}e_{\tau}, \frac{kr}{cs} \right).
\]

**Lemma 2.2.** The immunity-activated reproduction rate is smaller than the immunity-inactivated reproduction rate, that is, \( \mathcal{R}_1 < \mathcal{R}_0 \).

**Proof.** Define \( \bar{V} = \frac{x}{\xi} \) and \( \bar{I} = \frac{kr}{cs} \). Since \( \frac{\partial f(T, V)}{\partial T} > 0 \) and \( \frac{\partial g(T, V)}{\partial I} > 0 \) from Assumption (A2), we have
\[
\mathcal{R}_1 < \frac{cs}{akre_{\tau}} f \left( \frac{\Lambda}{d}, \frac{r}{s} \right) + \frac{cs}{akre_{\tau}} g \left( \frac{\Lambda}{d}, \frac{kr}{cs} \right) = \frac{c}{ake_{\tau}} \int \frac{1}{\bar{V}} \frac{\partial f}{\partial \bar{V}} \left( \frac{\Lambda}{d}, \bar{V} \right) + \frac{1}{aek_{\tau}} \int \frac{1}{\bar{I}} \frac{\partial g}{\partial \bar{I}} \left( \frac{\Lambda}{d}, \bar{I} \right).
\]
Further, since Assumption (A3) implies \( \frac{\partial}{\partial V} f(T,V) \leq 0 \) and \( \frac{\partial}{\partial I} g(T,I) \leq 0 \), there holds
\[
R_1 < \frac{c}{ake^\tau m} \lim_{V \to +} \frac{1}{V} f\left(\frac{\Lambda}{d},V\right) + \frac{1}{ake^\tau m} \lim_{I \to +} \frac{1}{I} g\left(\frac{\Lambda}{d},I\right)
\leq \frac{c}{ake^\tau m} \frac{\partial f\left(\frac{\Lambda}{d},0\right)}{\partial V} + \frac{1}{ake^\tau m} \frac{\partial g\left(\frac{\Lambda}{d},0\right)}{\partial I} = R_0.
\]
This completes the proof. \( \square \)

In the following, we prove that the existence of equilibria of system (2) with initial condition (3) is determined by the sign of \( R_i - 1 \) for \( i = 0, 1 \).

**Theorem 2.3.** If \( R_0 < 1 \), then system (2) with initial condition (3) only has an infection-free equilibrium \( E_0 \); if \( R_1 < 1 < R_0 \), then there exist \( E_0 \) and an immunity-inactivated equilibrium \( E_1 \); if \( R_1 > 1 \), then there exist \( E_0, E_1 \) and an immunity-activated equilibrium \( E_2 \).

**Proof.** Note that the infection-free equilibrium \( E_0 = (\frac{\Lambda}{d}, 0, 0, 0) \) always exists. In order to explore the existence of immunity-inactivated equilibrium \( E_1 = (T_1, I_1, V_1, 0) \), we discuss the following equations
\[
\begin{cases}
\Lambda - dT - f(T, V) - g(T, I) = 0, \\
f(T, V) + g(T, I) - ae^\tau I = 0, \\
cI - kV = 0.
\end{cases}
\]
From the first and second equations of (4), we obtain \( T = \frac{\Lambda - ae^\tau I}{d} \). The third equation yields \( V = \frac{c}{k} I \). By substituting them into the left-hand side of the second equation of (4), we define the following auxiliary mapping:
\[
\Phi(I) = f\left(\frac{\Lambda - ae^\tau I}{d}, \frac{c}{k} I\right) + g\left(\frac{\Lambda - ae^\tau I}{d}, I\right) - ae^\tau I.
\]
Clearly, \( \Phi(0) = f\left(\frac{\Lambda}{d}, 0\right) + g\left(\frac{\Lambda}{d}, 0\right) = 0 \) and \( \Phi\left(\frac{\Lambda}{d}, \frac{c}{k} \right) + g\left(\frac{\Lambda}{d}, \frac{\Lambda}{d}\right) - \Lambda = -\Lambda < 0 \). Besides, we have
\[
\Phi'(0) = \frac{ae^\tau}{d} \left( \frac{\partial f\left(\frac{\Lambda}{d}, 0\right)}{\partial T} + \frac{\partial g\left(\frac{\Lambda}{d}, 0\right)}{\partial T} \right) + \frac{c}{k} \frac{\partial f\left(\frac{\Lambda}{d}, 0\right)}{\partial V} + \frac{\partial g\left(\frac{\Lambda}{d}, 0\right)}{\partial I} - ae^\tau
= ae^\tau (R_0 - 1).
\]
When \( R_0 > 1 \), \( \Phi'(0) > 0 \). Then, there exists an \( I_1 \in (0, \frac{\Lambda}{ae^\tau m}) \), such that \( E_1 = (\frac{\Lambda - ae^\tau I_1}{d}, I_1, \frac{c}{k} I_1, 0) \) exists. Moreover, on \( E_1 \), due to \( ae^\tau I_1 = f(T_1, V_1) + g(T_1, I_1) \) and \( I_1 = \frac{c}{k} V_1 \), there holds
\[
\Phi'(I_1) = -\frac{ae^\tau}{d} \left( \frac{\partial f\left(\frac{\Lambda - ae^\tau I_1}{d}, \frac{c}{k} I_1\right)}{\partial T} + \frac{\partial g\left(\frac{\Lambda - ae^\tau I_1}{d}, I_1\right)}{\partial T} \right) + \frac{c}{k} \left( \frac{\partial f\left(\frac{\Lambda - ae^\tau I_1}{d}, \frac{c}{k} I_1\right)}{\partial V} - \frac{f\left(\frac{\Lambda - ae^\tau I_1}{d}, \frac{c}{k} I_1\right)}{V_1} \right)
+ \left( \frac{\partial g\left(\frac{\Lambda - ae^\tau I_1}{d}, I_1\right)}{\partial I} - g\left(\frac{\Lambda - ae^\tau I_1}{d}, I_1\right) \right).
\]
Under Assumptions (A2) and (A3), \( \Phi'(I_1) < 0 \). Thus, when \( R_0 > 1 \), there exists a unique immunity-inactivated equilibrium \( E_1 = (\frac{\Lambda - ae^\tau I_1}{d}, I_1, \frac{c}{k} I_1, 0) \) with \( I_1 \in (0, \frac{\Lambda}{ae^\tau m}) \). When \( R_0 < 1 \), \( \Phi'(0) < 0 \) and thus there exists no immunity-inactivated equilibrium. Whereas, when \( R_0 = 1 \), \( \Phi'(0) = 0 \) and \( \Phi'(I_1) \leq 0 \). If \( \Phi'(0) < 0 \),
then there exists no immunity-inactivated equilibrium. If \( \Phi''(0) = 0 \), then \( \Phi^{(i)}(0) = 0 \), \( i = 3, 4, \ldots \), and due to Assumptions (A1) and (A3), for any \( I \in (0, \frac{\Lambda}{ae^\mu}] \),

\[
\Phi'(I) = -\frac{ae^\mu}{d} \left( \frac{\partial f(\frac{\Lambda - ae^\mu I}{d}, \frac{\dot{I}}{k})}{\partial I} + \frac{\partial g(\frac{\Lambda - ae^\mu I}{d}, I)}{\partial I} \right) + \frac{c}{k} \frac{\partial f(\frac{\Lambda - ae^\mu I}{d}, \frac{\dot{I}}{k})}{\partial V} + \frac{\partial g(\frac{\Lambda - ae^\mu I}{d}, I)}{\partial I} - ae^\mu
\]

\[
< \frac{c}{k} \frac{\partial f(\frac{\Lambda - ae^\mu I}{d}, 0)}{\partial V} + \frac{\partial g(\frac{\Lambda - ae^\mu I}{d}, I)}{\partial I} - ae^\mu
\]

\[
\approx ae^\mu (\Re_0 - 1) = 0.
\]

Thus, in this case, there exists no immunity-inactivated equilibrium.

To consider the existence of immunity-activated equilibrium \( E_2 = (T_2, I_2, V_2, Z_2) \), we analyze the following equations

\[
\begin{cases}
\Lambda - dT - f(T, V) - g(T, I) = 0, \\
\frac{f(T, V)}{T} + g(T, I) - ae^\mu I = 0, \\
cI - kV - pVZ = 0, \\
sVZ - rZ = 0.
\end{cases}
\tag{5}
\]

From the first and second equations of (5), we obtain \( T = \frac{\Lambda - ae^\mu I}{d} \). The third and last equations yield \( Z = \frac{ae^\mu I}{s} - \frac{k}{p} \) and \( V = \frac{r}{s} \). Then we again define the following auxiliary mapping:

\[
\Psi(I) = f\left(\frac{\Lambda - ae^\mu I}{d}, \frac{\dot{I}}{s}\right) + g\left(\frac{\Lambda - ae^\mu I}{d}, I\right) - ae^\mu I.
\]

Clearly, \( \Psi\left(\frac{\Lambda}{ae^\mu}\right) = f(0, \frac{\dot{I}}{s}) + g(0, \frac{\Lambda}{ae^\mu}) - \Lambda = -\Lambda < 0 \). Since \( \dot{I} = \frac{kr}{es} \), we have

\[
\Psi(\dot{I}) = f\left(\frac{\Lambda - ae^\mu \dot{I}}{d}, \frac{\dot{I}}{s}\right) + g\left(\frac{\Lambda - ae^\mu \dot{I}}{d}, \dot{I}\right) - ae^\mu \dot{I} = ae^\mu \dot{I} (\Re_1 - 1).
\]

If \( \Re_1 > 1 \), then \( \Psi(\dot{I}) > 0 \). Thus, there exists an \( I_2 \in (\dot{I}, \frac{\Lambda}{ae^\mu}] \) such that \( E_2 = (\frac{\Lambda - ae^\mu I_2}{d}, I_2, \frac{ae^\mu I_2}{s} - \frac{k}{p} I_2 - \frac{s}{p}) \) exists. Moreover, due to \( ae^\mu I_2 = f(T_2, V_2) + g(T_2, I_2) \), there holds

\[
\Psi'(I_2) = -\frac{ae^\mu}{d} \left( \frac{\partial f(\frac{\Lambda - ae^\mu I_2}{d}, \frac{\dot{I}}{s})}{\partial I} + \frac{\partial g(\frac{\Lambda - ae^\mu I_2}{d}, I_2)}{\partial I} \right) + \frac{c}{k} \frac{\partial f(\frac{\Lambda - ae^\mu I_2}{d}, \frac{\dot{I}}{s})}{\partial V} + \frac{\partial g(\frac{\Lambda - ae^\mu I_2}{d}, I_2)}{\partial I} - ae^\mu
\]

\[
< \frac{c}{k} \frac{\partial f(\frac{\Lambda - ae^\mu I_2}{d}, 0)}{\partial V} + \frac{\partial g(\frac{\Lambda - ae^\mu I_2}{d}, I_2)}{\partial I} - ae^\mu
\]

\[
\approx ae^\mu (\Re_1 - 1) = 0.
\]

Under Assumptions (A2) and (A3), \( \Psi'(I_2) < 0 \). Thus, when \( \Re_1 > 1 \), there exists a unique immunity-activated equilibrium \( E_2 = (\frac{\Lambda - ae^\mu I_2}{d}, I_2, \frac{ae^\mu I_2}{s} - \frac{k}{p} I_2 - \frac{s}{p}) \) with \( I_2 \in (\dot{I}, \frac{\Lambda}{ae^\mu}] \). When \( \Re_1 < 1 \), there exists no immunity-activated equilibrium \( E_2 \). Whereas, when \( \Re_1 = 1 \), \( \Psi(\dot{I}) = 0 \) and \( \Psi'(\dot{I}) < 0 \). In this case, if there exists an
has no non-negative real root. Then the characteristic equation is

$$R_{\text{immunity-activated equilibrium}} \text{ when } \tau > 3.$$  

3. Stability analysis of the infection-free equilibrium. In this section, we investigate the stability of the infection-free equilibrium $E_0$. We first focus on the local asymptotical stability of $E_0$ by discussing the distribution of the corresponding characteristic values. The linearization of system (2) at $E_0$ can be expressed by

$$\frac{dX}{dt} = L_0X + M_0X, \text{ where } X = (T(t), I(t), V(t), Z(t)), X_{\tau} = (T(t-\tau), I(t-\tau), V(t-\tau), Z(t-\tau)).$$

The characteristic equation is

$$\det(\lambda I - L_0 - M_0 e^{-\lambda \tau}) = (\lambda + d)(\lambda + r)G_0(\lambda) = 0,$$

where

$$G_0(\lambda) = \lambda^2 + R_1\lambda + R_0 + S_1 \lambda e^{-\lambda \tau} + S_0 e^{-\lambda \tau},$$

with $R_1 = a + k$, $R_0 = ak$, $S_1 = -\frac{\partial g(\frac{\lambda}{a}, 0)}{\partial I} e^{-m \tau}$, $S_0 = -\left(k \frac{\partial g(\frac{\lambda}{a}, 0)}{\partial I} + e \frac{\partial f(\frac{\lambda}{a}, 0)}{\partial V}\right) e^{-m \tau}$. It is critical to analyze the roots of $G_0(\lambda) = 0$. Ruan [39] discussed the distributions of the roots of the second degree transcendental polynomial equation $G_0(\lambda) = 0$, by first analyzing the non-existence of non-negative roots as $\tau = 0$ and then verifying the non-existence of roots with zero real parts or zero root as $\tau > 0$. Here we take a different approach to analyze the local stability. We first verify that there exist no non-negative real roots and then prove that $G_0(\lambda) = 0$ has no complex roots with non-negative real parts, arriving at the following theorem.

**Theorem 3.1.** If $R_0 < 1$, then the infection-free equilibrium $E_0$ is locally asymptotically stable; if $R_0 = 1$, then $E_0$ is linearly neutrally stable; if $R_0 > 1$, then $E_0$ is unstable.

**Proof.** When $R_0 < 1$, there holds

$$G_0(0) = R_0 + S_0 = ak \left( k \frac{\partial g(\frac{\lambda}{a}, 0)}{\partial I} + e \frac{\partial f(\frac{\lambda}{a}, 0)}{\partial V}\right) e^{-m \tau} = ak(1 - R_0) > 0. (8)$$

Since $R_0 < 1$ implies $\frac{1}{ae^{m \tau}} \frac{\partial g(\frac{\lambda}{a}, 0)}{\partial I} < 1$, for any real $\lambda \geq 0$, we have

$$\frac{dG_0(\lambda)}{d\lambda} = 2\lambda + R_1 + S_1 e^{-\lambda \tau} - S_0 e^{-\lambda \tau} - S_1 \tau e^{-\lambda \tau} \geq R_1 + S_1 = k + a \left(1 - \frac{1}{ae^{m \tau}} \frac{\partial g(\frac{\lambda}{a}, 0)}{\partial I}\right) > 0. (9)$$

Thus, for any non-negative real $\lambda$, $G_0(\lambda) > 0$. Hence characteristic equation (6) has no non-negative real root.
Moreover, for any $\lambda = \alpha + i\beta$ ($\alpha \geq 0$), we have
\[
G(\alpha + i\beta) = (\alpha + i\beta)^2 + R_1(\alpha + i\beta) + R_0 + S_1(\alpha + i\beta)e^{-(\alpha + i\beta)\tau} + S_0e^{-(\alpha + i\beta)\tau}.
\]
\[
= (\alpha^2 - \beta^2 + R_1\alpha + R_0 + \alpha S_1 e^{-\alpha\tau} \cos \beta \tau + \beta S_1 e^{-\alpha\tau} \sin \beta \tau + S_0 e^{-\alpha\tau} \cos \beta \tau) + i(R_1\beta + 2\alpha\beta + \beta S_1 e^{-\alpha\tau} \cos \beta \tau - \alpha S_1 e^{-\alpha\tau} \sin \beta \tau - S_0 e^{-\alpha\tau} \sin \beta \tau).
\]
Then, by applying Euler’s formula and separating the real and imaginary parts of $G(\alpha + i\beta) = 0$, we yield
\[
\begin{cases}
\beta^2 - \alpha^2 - R_0 - R_1\alpha = S_1 e^{-\alpha\tau}(\alpha \cos \beta \tau + \beta \sin \beta \tau) + S_0 e^{-\alpha\tau} \cos \beta \tau, \\
(2\alpha + R_1)\beta = S_1 e^{-\alpha\tau}(\alpha \sin \beta \tau - \cos \beta \tau) + S_0 e^{-\alpha\tau} \sin \beta \tau.
\end{cases}
\]
Squaring and adding the two equations together gives
\[
\beta^4 + A_2\beta^2 + A_0 = 0,
\]
where
\[
A_2 = 2\alpha^2 + 2\alpha R_1 + R_1^2 - 2R_0 - S_1^2 e^{-2\alpha\tau}, \\
A_0 = (\alpha^2 + R_0 + \alpha R_1)^2 - (\alpha S_1 + S_0)^2 e^{-2\alpha\tau}.
\]
Clearly, $\frac{\partial A_2}{\partial \alpha} > 0$. Due to $R_0 < 1$, we obtain
\[
A_2|_{\alpha=0} = R_1^2 - 2R_0 - S_1^2 = a^2 + k^2 - \left(\frac{\partial g}{\partial I}(0, 0) e^{-m\tau}\right)^2 > 0.
\]
Further, from the verification process in (8) and (9), we have $R_i > -S_i > 0$ ($i = 0, 1$). This yields $R_0R_1 - S_0S_1 > 0$ and $R_1^2 - S_1^2 > 0$. Then, there holds that $A_0|_{\alpha=0} = R_0^2 - S_0^2 = (R_0 - S_0)(R_0 + S_0) > 0$
and
\[
\frac{\partial A_0}{\partial \alpha} = 4\alpha^3 + 6R_1\alpha^2 + (4R_0 + 2R_1)\alpha + 2R_0R_1 + 2\tau\alpha^2 S_1^2 e^{-2\alpha\tau}
- 2\alpha S_1^2 e^{-2\alpha\tau} + 2\tau S_0 S_1 e^{-2\alpha\tau} - 2S_0S_1 e^{-2\alpha\tau} + 4\tau\alpha S_0 S_1 e^{-2\alpha\tau}
> 2\alpha(R_1^2 - S_1^2) + 2(R_0R_1 - S_0S_1) > 0.
\]
Above all, $A_2 > 0$ and $A_0 > 0$ for any $\alpha \geq 0$. This contradicts with (10). Thus, there exists no $\alpha + i\beta$ ($\alpha \geq 0$), such that $G(\alpha + i\beta) = 0$.

Hence, if $R_0 < 1$, then all roots of characteristic equation (6) possess negative real parts and thus $E_0$ is locally asymptotically stable. Further, due to similar analysis, when $R_0 = 1$, any root of characteristic equation (6) has negative real part except a simple zero root $\lambda = 0$ and thus $E_0$ is linearly neutrally stable. Besides, if $R_0 > 1$, then $G(0) = ak(1-R_0) < 0$ and $G(\lambda) = \lambda^2 + R_1\lambda + R_0 + S_1\lambda e^{-\lambda\tau} + S_0 e^{-\lambda\tau} \to +\infty$ as $\lambda \to +\infty$. Thus, there exists at least one $\lambda_0 > 0$ such that $G(\lambda_0) = 0$. Hence, $E_0$ is unstable when $R_0 > 1$.

Based on the local asymptotical stability analysis, we construct a Lyapunov functional to verify the global asymptotical stability of $E_0$. Similar to the local asymptotical stability of $E_0$, the following theorem shows that the immune-inactivated reproduction rate $\mathcal{R}_0$ plays a vital role on the global property of $E_0$.

**Theorem 3.2.** If $R_0 < 1$, then the infection-free equilibrium $E_0$ is globally asymptotically stable; if $R_0 = 1$, then $E_0$ is globally attractive.
Proof. Define the following Lyapunov functional
\[
V_0(t) = e^{mr}I(t) + \frac{a}{c}e^{mr}V(t) + \int_{t-\tau}^{t} f(T(\delta), V(\delta))d\delta + \int_{t-\tau}^{\infty} g(T(\delta), I(\delta))d\delta.
\]
Let $T_\tau = T(t-\tau), V_\tau = V(t-\tau)$ and $I_\tau = I(t-\tau)$. Calculating the time derivative of $V_0(t)$ along (2), we yield
\[
\frac{dV_0}{dt} = e^{mr}\frac{\partial I}{\partial t} + \frac{a}{c}e^{mr}\frac{\partial V}{\partial t} + f(T, V) - f(T_\tau, V_\tau) - g(T_\tau, I_\tau)
\]
\[
= -\frac{ak}{c}e^{mr}V - \frac{ap}{c}e^{mr}VZ + f(T, V)
\]
\[
\leq \frac{ak}{c}e^{mr}V \left( \frac{c}{ake^{mr}} \frac{f(\frac{A}{c}, V)}{V} - 1 \right) - \frac{ap}{c}e^{mr}VZ.
\]
From Assumption (A3), $\frac{f(\frac{A}{c}, V)}{V}$ is decreasing with respect to $V$. Thus, when $R_0 \leq 1$,
\[
\frac{dV_0}{dt} \leq \frac{ak}{c}e^{mr}V \left( \frac{c}{ake^{mr}} \lim_{V \to 0} \frac{f(\frac{A}{c}, V)}{V} - 1 \right)
\]
\[
= \frac{ak}{c}e^{mr}V \left( \frac{c}{ake^{mr}} \frac{\partial f(\frac{A}{c}, 0)}{\partial V} - 1 \right)
\]
\[
\leq \frac{ak}{c}e^{mr}V (R_0 - 1) \leq 0.
\]
Let $\Theta_0 = \{(T, I, V, Z) : \frac{dV_0}{dt} = 0\}$ and the largest invariant subset of $\Theta_0$ just consists of $E_0$. Thus, due to the LaSalle’s invariance principle [20], when $R_0 \leq 1$, $E_0$ is a global attractor. Further, combining the local asymptotical stability of $E_0$ under the condition $R_0 < 1$, $E_0$ is globally asymptotically stable. \[\square\]

4. Stability analysis of the immunity-inactivated equilibrium. In this section, we focus on the stability of the immunity-inactivated equilibrium $E_1$. For the local asymptotical stability, we need to analyze the characteristic equation of system (2) on $E_1$. The linearization of system (2) at $E_1$ can be expressed by $\frac{dX}{dt} = L_1X + M_1X_\tau$, where
\[
L_1 = \begin{pmatrix}
-d - \frac{\partial g(T_1, I_1)}{\partial T} - \frac{\partial f(T_1, V_1)}{\partial T} & -\frac{\partial g(T_1, I_1)}{\partial I} & -\frac{\partial f(T_1, V_1)}{\partial V} & 0 \\
0 & 0 & c & -k & -pV_1 \\
0 & 0 & 0 & sV_1 - r \\
\end{pmatrix}
\]
and
\[
M_1 = \begin{pmatrix}
e^{-mr} \frac{\partial g(T_1, I_1)}{\partial T} & e^{-mr} \frac{\partial f(T_1, V_1)}{\partial T} & 0 & 0 \\
e^{-mr} \frac{\partial g(T_1, I_1)}{\partial I} & e^{-mr} \frac{\partial f(T_1, V_1)}{\partial I} & 0 & 0 \\
e^{-mr} \frac{\partial g(T_1, I_1)}{\partial V} & e^{-mr} \frac{\partial f(T_1, V_1)}{\partial V} & 0 & 0 \\
0 & 0 & 0 & 0 \\
\end{pmatrix}
\]
Then the characteristic equation is
\[
det(\lambda \mathcal{I} - L_1 - M_1e^{-\lambda \tau}) = (\lambda + r - sV_1)G_1(\lambda) = 0,
\]
where
\[
G_1(\lambda) = \lambda^3 + P_2\lambda^2 + P_1\lambda + P_0 + Q_2\lambda^2e^{-\lambda \tau} + Q_1\lambda e^{-\lambda \tau} + Q_0e^{-\lambda \tau},
\]
Thus, it is crucial to judge \( \text{sgn}(V_1 - \frac{c}{k}) \), that is, \( \text{sgn}(V_1 - \bar{V}) \). To this end, we first make the following hypothesis on \( f(T, V) \) and \( g(T, I) \):

\[
(A4) : \left( \frac{f(T, V)}{f(T, V_1)} - 1 \right) \left( \frac{V}{V_1} - \frac{f(T, V)}{f(T, V_1)} \right) \geq 0, \\
\left( \frac{g(T, I)}{g(T, I_1)} - 1 \right) \left( \frac{I}{I_1} - \frac{g(T, I)}{g(T, I_1)} \right) \geq 0.
\]

Then, based on Assumption (A4), we have the following lemma.

**Lemma 4.1.** Under Assumption (A4), \( \text{sgn}(\mathcal{R}_1 - 1) = \text{sgn}(V_1 - \bar{V}) \).

**Proof.** Due to

\[
\begin{align*}
T_1 &= \frac{\Lambda - ae^{m\tau}I_1}{d} \\
\bar{T} &= \frac{\Lambda - ae^{m\tau}\bar{I}}{d}
\end{align*}
\]

and

\[
\begin{align*}
V_1 &= \frac{c}{k} I_1 \\
\bar{V} &= \frac{c}{k} \bar{I}
\end{align*}
\]

there holds

\( \text{sgn}(\bar{T} - T_1) = \text{sgn}(I_1 - \bar{I}) = \text{sgn}(V_1 - \bar{V}) \). \hspace{1cm} (11)

Moreover, \( f(T_1, V_1) + g(T_1, I_1) = ae^{m\tau}I_1 \) and \( I_1 = \frac{c}{k} V_1 \) imply that

\[\frac{f(T_1, V_1)}{ae^{m\tau}I_1} + \frac{g(T_1, I_1)}{ae^{m\tau}I_1} = 1.\] \hspace{1cm} (12)

Combining (12) and \( \bar{I} = \frac{c}{k} \bar{V} \), we have

\[
\mathcal{R}_1 - 1 = \left( \frac{f(\bar{T}, \bar{V})}{ae^{m\tau}\bar{V}_1} + \frac{g(\bar{T}, \bar{I})}{ae^{m\tau}\bar{I}_1} \right) - \left( \frac{f(T_1, V_1)}{ae^{m\tau}V_1} + \frac{g(T_1, I_1)}{ae^{m\tau}I_1} \right)
\]

\[= \frac{c}{ae^{m\tau}V_1} \left( f(\bar{T}, \bar{V}) - f(T_1, \bar{V}) \right) + \frac{1}{ae^{m\tau}I} \left( g(\bar{T}, \bar{I}) - g(T_1, \bar{I}) \right) \]

\[+ \frac{c}{ae^{m\tau}V_1} \left( V_1 f(T_1, \bar{V}) - \bar{V} f(T_1, V_1) \right) \]

\[+ \frac{1}{ae^{m\tau}I_1} \left( I_1 g(T_1, \bar{I}) - \bar{I} g(T_1, I_1) \right). \] \hspace{1cm} (13)
From Assumption (A2), we have
\[
\begin{align*}
(f(T_1, V) - f(T_1, V_1)) (\bar{V} - V_1) &> 0, \\
(g(T_1, I) - g(T_1, I_1)) (\bar{I} - I_1) &> 0.
\end{align*}
\]

Further, substituting $T = T_1$ and $V = \bar{V}$ into the equations of Assumption (A4) yields
\[
\begin{align*}
(f(T_1, \bar{V}) - f(T_1, V_1)) (\bar{V} f(T_1, V_1) - V_1 f(T_1, \bar{V})) &> 0, \\
(g(T_1, \bar{I}) - g(T_1, I_1)) (\bar{I} g(T_1, I_1) - I_1 g(T_1, \bar{I})) &> 0.
\end{align*}
\]

It follows from (14) and (15) that
\[
\begin{align*}
(\bar{V} - V_1) (\bar{V} f(T_1, V_1) - V_1 f(T_1, \bar{V})) &> 0, \\
(\bar{I} - I_1) (\bar{I} g(T_1, I_1) - I_1 g(T_1, \bar{I})) &> 0.
\end{align*}
\]

Then, from (11), (13) and (16), we obtain $\text{sgn}(R_{11} - 1) = \text{sgn}(V_1 - \bar{V})$.

Based on Lemma 4.1, we yield the following theorem on local asymptotical stability of $E_1$.

**Theorem 4.2.** Suppose that Assumption (A4) holds. If $R_{11} < 1 < R_0$, then the immunity-inactivated equilibrium $E_1$ is locally asymptotically stable; if $R_{11} = 1$, then $E_1$ is linearly neutrally stable; if $R_{11} > 1$, then $E_1$ is unstable.

**Proof.** From Lemma 4.1, when $R_{11} > 1$, we have $V_1 > \bar{V} = \frac{\bar{x}}{\bar{y}}$ and thus $E_1$ is unstable; when $R_{11} \leq 1$, we have $V_1 \leq \bar{V} = \frac{\bar{x}}{\bar{y}}$. Thus, to explore the stability of $E_1$ under $R_{11} \leq 1$, we need to analyze the distribution of roots of $G_1(\lambda) = 0$. For this, we first verify that without time delay $\tau$, the roots of $G_1(\lambda) = 0$ possess negative real parts, and then show that $G_1(\lambda) = 0$ with $\tau$ has no pure imaginary roots.

When $\tau = 0$, we have
\[
G_1(\lambda)|_{\tau=0} = \lambda^3 + (P_2 + Q_2)\lambda^2 + (P_1 + Q_1)\lambda + (P_0 + Q_0).
\]

Due to Assumption (A3) and $f(T_1, V_1) + g(T_1, I_1) = a e^{-\tau} I_1$, we obtain
\[
\frac{\partial g(T_1, I_1)}{\partial I} e^{-\tau} \leq \frac{g(T_1, I_1)}{I_1} e^{-\tau} \leq a.
\]

Then, there holds
\[
P_2 + Q_2 > a - \frac{\partial g(T_1, I_1)}{\partial I} e^{-\tau} \geq 0.
\]

Further, $f(T_1, V_1) + g(T_1, I_1) = a e^{-\tau} I_1$ implies that $\frac{f(T_1, V_1)}{I_1} e^{-\tau} = a - \frac{g(T_1, I_1)}{I_1} e^{-\tau}$.

Due to Assumption (A3) and $V_1 = \frac{\bar{x}}{\bar{y}} I_1$, we have
\[
\begin{align*}
\frac{\partial f(T_1, V_1)}{\partial V} e^{-\tau} &\leq \frac{f(T_1, V_1)}{V_1} e^{-\tau} \\
&= k \left( a - \frac{g(T_1, I_1)}{I_1} e^{-\tau} \right) \leq k \left( a - \frac{\partial g(T_1, I_1)}{\partial I} e^{-\tau} \right).
\end{align*}
\]

It follows from (17) that
\[
P_0 + Q_0 > d \left( ak - k \frac{\partial g(T_1, V_1)}{\partial I} e^{-\tau} - c \frac{\partial f(T_1, V_1)}{\partial V} e^{-\tau} \right) \geq 0.
\]
Moreover,

\[ (P_2 + Q_2)(P_1 + Q_1) - (P_0 + Q_0) > d \left( a + k - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \left( a - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \]

\[ + \left( a + k - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \left( \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ - ak \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) + dk \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau}. \]

Then, due to inequalities (17) and \( a \geq \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \), there holds

\[ (P_2 + Q_2)(P_1 + Q_1) - (P_0 + Q_0) \]

\[ > a \left( a + k - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \left( \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ + k \left( a + k - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ - ak \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ + k \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ - k \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \left( \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ \geq ak \left( \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ + k \left( a - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ - k \left( a - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ - k \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \left( \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \]

\[ = k \left( a - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \left( \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right) \geq 0. \]

Thus, for \( \tau = 0 \), when \( R_1 < 1 < R_0 \), \( G_1(\lambda)|_{\tau=0} = 0 \) only have roots with negative real parts by the Routh-Hurwitz criterion \([7, 20]\). Now, in order to obtain the theorem, we just need to verify that no real part of any root increases to reach zero as \( \tau \) varies, that is, for \( \tau > 0 \), \( G_1(\lambda) = 0 \) has no pure imaginary roots or zero root \([40, 41]\).
Assume that there exists a pair of simple imaginary roots or zero root $\lambda = i\omega$, $\omega \in \mathbb{R}$, such that $G_1(\lambda) = 0$, that is, $G_1(i\omega) = 0$, where

$$
G_1(i\omega) = (-P_2\omega^2 + P_0 - Q_2\omega^2 \cos \omega \tau + Q_1\omega \sin \omega \tau + Q_0 \cos \omega \tau) + i(-\omega^3 + P_1\omega + Q_2\omega^2 \sin \omega \tau + Q_1\omega \cos \omega \tau - Q_0 \sin \omega \tau).
$$

Moreover, from (17), we obtain

$$
\omega^2 = \frac{-P_1}{2P_2} = \frac{(Q_2\omega^2 - Q_0) \cos \omega \tau - Q_1 \omega \sin \omega \tau}{Q_2 \omega^2 + (P_0 - Q_2) \omega^4 + (P_0 - 2P_0P_2 + 2Q_0Q_2 - Q_1^2) \omega^2 + (P_0^2 - Q_0^2)}.
$$

In Ruan et al. [41], the sufficient and necessary condition for the existence of $\omega^2$ for (19) was obtained. In the following, we apply the result to verify the non-existence of $\omega^2$, $\omega \in \mathbb{R}$.

Here $P_0^2 - Q_0^2 > 0$ has been verified in (18). Due to $a \geq \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau}$, we have

$$
P_0^2 - 2P_1 - Q_0^2
= \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right)^2 + a^2 + k^2 - \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right)^2 > 0.
$$

Moreover, from (17), we obtain

$$
d^2 k^2 - 2ck \frac{\partial g(T_1, I_1)}{\partial I} \frac{\partial f(T_1, V_1)}{\partial T} e^{-2m\tau} - c^2 \left( \frac{\partial f(T_1, V_1)}{\partial V} \right)^2 e^{-2m\tau}
\geq d^2 k^2 - 2k^2 \left( a + \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right) \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau}
-k^2 \left( a - \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right)^2
+ k^2 \left[ d^2 - a^2 + \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m\tau} \right)^2 \right].
$$

Due to

$$
P_1^2 - 2P_0P_2 + 2Q_0Q_2 - Q_1^2
=a^2 k^2 + (a^2 + k^2) \left( d + \frac{\partial f(T_1, V_1)}{\partial T} + \frac{\partial g(T_1, I_1)}{\partial T} \right)^2
- \left[ d^2 \left( \frac{\partial g(T_1, I_1)}{\partial I} \right)^2 + k^2 \left( \frac{\partial g(T_1, I_1)}{\partial I} \right)^2 \right] e^{-2m\tau}
- \left[ c^2 \left( \frac{\partial f(T_1, V_1)}{\partial V} \right)^2 + 2ck \frac{\partial g(T_1, I_1)}{\partial I} \frac{\partial f(T_1, V_1)}{\partial I} \right] e^{-2m\tau},
$$
combining Assumption (A3) and (20), we have
\[
P_1^2 - 2P_0P_2 + 2Q_0Q_2 - Q_1^2 > k^2 \left[ a^2 - \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m^\tau} \right)^2 \right] + d^2 \left[ a^2 - \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m^\tau} \right)^2 \right] \\
+ \left[ d^2k^2 - 2ck \frac{\partial g(T_1, I_1)}{\partial I} \frac{\partial f(T_1, V_1)}{\partial V} e^{-2m^\tau} - c^2 \left( \frac{\partial f(T_1, V_1)}{\partial V} e^{-m^\tau} \right)^2 \right]
\]
\[
> k^2 \left[ a^2 - \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m^\tau} \right)^2 \right] + d^2 \left[ a^2 - \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m^\tau} \right)^2 \right] \\
+ k^2 \left[ d^2 - a^2 + \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m^\tau} \right)^2 \right]
\]
\[
= k^2d^2 + d^2 \left[ a^2 - \left( \frac{\partial g(T_1, I_1)}{\partial I} e^{-m^\tau} \right)^2 \right] > 0.
\]

Above all, due to Proposition 1 (iii) of [41], there exists no \( \omega, \omega \in \mathbb{R} \), such that (19) holds. Thus, there exists no \( i\omega, \omega \in \mathbb{R} \), such that \( G_1(i\omega) = 0 \). Hence, all roots of \( G_1(\lambda) = 0 \) possess negative real parts when \( \mathfrak{R}_1 < 1 < \mathfrak{R}_0 \). Similar result can be obtained for the case when \( \mathfrak{R}_1 = 1 \).

Consequently, under Assumption (A4), when \( \mathfrak{R}_1 < 1 < \mathfrak{R}_0 \), \( E_1 \) is locally asymptotically stable; when \( \mathfrak{R}_1 = 1 \), any root of characteristic equation has negative real part except a simple zero root \( \lambda = 0 \) and thus \( E_1 \) is linearly neutrally stable; when \( \mathfrak{R}_1 > 1 \), \( E_1 \) is unstable.

To study the global asymptotical stability of the immunity-inactivated equilibrium \( E_1 \), we also need to make the following hypothesis on \( f(T, V) \) and \( g(T, I) \):

(A5) \[
\left( \frac{T_1 f(T, V)}{T f(T_1, V_1)} - 1 \right) \left( \frac{V}{V_1} - \frac{T_1 f(T, V)}{T f(T_1, V_1)} \right) \geq 0,
\]
\[
\left( \frac{T_1 g(T, I)}{T g(T_1, I_1)} - 1 \right) \left( \frac{I}{I_1} - \frac{T_1 g(T, I)}{T g(T_1, I_1)} \right) \geq 0.
\]

Then, by virtue of the Volterra type function \( h(\xi) = \xi - 1 - \ln \xi, \xi > 0 \) [25], we construct a Lyapunov functional to ensure \( E_1 \) to be globally attractive with respect to all the solutions with non-negative initial values, arriving at the following result.

**Theorem 4.3.** Suppose that Assumptions (A4) and (A5) hold. If \( \mathfrak{R}_1 < 1 < \mathfrak{R}_0 \), then immunity-inactivated equilibrium \( E_1 \) is globally asymptotically stable; if \( \mathfrak{R}_1 = 1 \), then \( E_1 \) is globally attractive.

**Proof.** Define the following Lyapunov functional
\[
V_1(t) = T_1 h \left( \frac{T(t)}{T_1} \right) + e^{m^\tau} I_1 h \left( \frac{I(t)}{I_1} \right) + \int_0^t f(T_1, V_1) h \left( \frac{V(t)}{V_1} \right) + \frac{p}{k_8 V_1} f(T_1, V_1) Z(t) + f(T_1, V_1) \int_{t-\tau}^t s h \left( \frac{f(T(s), V(s))}{f(T_1, V_1)} \right) ds + g(T_1, I_1) \int_{t-\tau}^t h \left( \frac{g(T(s), I(s))}{g(T_1, I_1)} \right) ds.
\]

\[
= \int_{t-\tau}^t h \left( \frac{f(T(s), V(s))}{f(T_1, V_1)} \right) ds + g(T_1, I_1) \int_{t-\tau}^t h \left( \frac{g(T(s), I(s))}{g(T_1, I_1)} \right) ds.
\]
Since \( f(T_1, V_1) + g(T_1, I_1) = ae^{mT_1}I_1 \) and \( cI_1 - kV_1 = 0 \) imply that \( \frac{f(T_1, V_1)}{ae^{mT_1}I_1} + \frac{g(T_1, I_1)}{ae^{mT_1}I_1} = 1 \) and \( c = k \frac{V_1}{I_1} \), calculating the time derivative of \( \mathcal{V}_1(t) \) along (2) yields

\[
\frac{d\mathcal{V}_1}{dt} = \left( 1 - \frac{T_1}{T} \right) (\Lambda - dT - f(T, V) - g(T, I))
\]

\[
+ \left( 1 - \frac{I_1}{I} \right) \left[ f(T, V) + g(T, I) - ae^{mT}I \right]
\]

\[
+ \frac{1}{kV_1} f(T_1, V_1) \left( 1 - \frac{V_1}{V} \right) (cI - kV - pVZ) + \frac{p}{ksV_1} f(T_1, V_1)(sVZ - rZ)
\]

\[
f(T_1, V_1)h\left( \frac{f(T, V)}{f(T_1, V_1)} \right) - f(T_1, V_1)h\left( \frac{f(T, V)}{f(T_1, V_1)} \right)
\]

\[
+ g(T_1, I_1)h\left( \frac{g(T, I)}{g(T_1, I_1)} \right) - g(T_1, I_1)h\left( \frac{g(T, I)}{g(T_1, I_1)} \right)
\]

\[
= J_1 + J_2,
\]

where

\[
J_1 := -d(T - T_1) \left( 1 - \frac{T_1}{T} \right) - \frac{1}{kV_1} f(T_1, V_1) \left( 1 - \frac{V_1}{V} \right) pVZ
\]

\[
+ \frac{p}{ksV_1} f(T_1, V_1)(sVZ - rZ)
\]

\[
= -d(T - T_1) \left( 1 - \frac{T_1}{T} \right) + \frac{p}{kV_1} f(T_1, V_1) \left( V_1 - \frac{r}{s} \right) Z
\]

and

\[
J_2 := \left( 1 - \frac{T_1}{T} \right) [-f(T, V) - f(T_1, V_1)]
\]

\[
+ \left( 1 - \frac{I_1}{I} \right) \left[ f(T, V) + g(T, I) - f(T_1, V_1) + g(T_1, I_1) \right]
\]

\[
f(T_1, V_1)h\left( \frac{f(T, V)}{f(T_1, V_1)} \right) - f(T_1, V_1)h\left( \frac{f(T, V)}{f(T_1, V_1)} \right)
\]

\[
+ g(T_1, I_1)h\left( \frac{g(T, I)}{g(T_1, I_1)} \right) - g(T_1, I_1)h\left( \frac{g(T, I)}{g(T_1, I_1)} \right).
\]
Clearly, under the condition $R_1 < 1$ and Assumptions (A2) and (A4), $J_1 \leq 0$. Moreover, in order to deal with $J_2$, we apply Lemma 2.3 in Mccluskey [25]. Through minor tweaking, we can reorganize $J_2$ as the combination of Vaterra type functions. For simplification, let

$$f := f(T, V), \ f_1 := f(T_1, V_1), \ f_T := f(T, V_T),$$

$$g := g(T, I), \ g_1 := g(T_1, I_1), \ g_T := g(T, I_T).$$

Then, $J_2$ can be converted to

$$J_2 = f_1 \left[ \left( 1 - \frac{I_1}{T} \right) \left( 1 - \frac{T_1}{T} \right) + \left( \frac{T_1}{T} - I_1 \right) \left( \frac{T_1}{T} - \frac{T_1}{T} \right) \right]$$

$$+ f_1 \left[ \left( 1 - \frac{V_1}{V} \right) \left( \frac{V}{V_1} - V \right) + h(\frac{T}{T_1}) - h(\frac{f_T}{f_1}) \right]$$

$$+ g_1 \left[ \left( 1 - \frac{I_1}{T} \right) \left( 1 - \frac{g}{I_1} \right) + \left( 1 - \frac{I_1}{T} \right) \left( \frac{g_T}{I_1} - \frac{I}{I_1} \right) + h(\frac{g}{I_1}) - h(\frac{g_T}{I_1}) \right]$$

Due to Assumption (A5), $\frac{T_1}{T}$ lies between 1 and $\frac{V_1}{V}$, $\frac{g_T}{g_1}$ lies between 1 and $\frac{f_T}{f_1}$. Then, there holds that $h(\frac{T_1}{T}) - h(\frac{V_1}{V}) \leq 0$ and $h(\frac{g_T}{g_1}) - h(\frac{f_T}{f_1}) \leq 0$. Thus, $J_2 \leq 0$.

Above all, when $R_1 < 1 < R_0$ and Assumptions (A4) and (A5) hold, $\frac{dV}{dt} \leq 0$. Let $\Theta_1 = \{(T, I, V, Z) : \frac{dV}{dt} = 0 \}$. Then the largest invariant subset of $\Theta_1$ just consists of $E_1$. Thus, due to the LaSalle’s invariance principle [20], $E_1$ is a global attractor. Further, combining the local asymptotical stability of $E_1$ under condition $R_1 < 1 < R_0$, $E_1$ is globally asymptotically stable.

5. Stability analysis of the immunity-activated equilibrium. In this section, we study the global asymptotical stability of the immunity-activated equilibrium $E_2$. We first explore the local asymptotical stability of $E_2$. The linearization of system (2) at $E_2$ can be expressed by $\frac{dx}{dt} = L_2 x + M_2 x_T$, where

$$L_2 = \begin{pmatrix}
-d - \frac{\partial f(T_2, J_2)}{\partial T} + \frac{\partial f(T_2, V_2)}{\partial T} & \frac{\partial f(T_2, J_2)}{\partial T} & -\frac{\partial f(T_2, V_2)}{\partial T} & -\frac{\partial f(T_2, V_2)}{\partial T} \\
0 & 0 & 0 & 0 \\
0 & -a & c & -k - p Z_2 \\
0 & 0 & s Z_2 & -p V_2
\end{pmatrix}$$
and
\[
\mathcal{M}_2 = \begin{pmatrix}
0 & e^{-m\tau} \frac{\partial g(T_2, I_2)}{\partial T} + e^{-m\tau} \frac{\partial f(T_2, V_2)}{\partial T} & 0 & e^{-m\tau} \frac{\partial g(T_2, I_2)}{\partial V} & 0

\end{pmatrix}.
\]

Then the characteristic equation is \( G_2(\lambda) = 0 \), where
\[
G_2(\lambda) = \text{det}(\lambda I - L_2 - M_2 e^{-\lambda \tau})
= \left( \lambda + d + \frac{\partial f(T_2, V_2)}{\partial I} + \frac{\partial g(T_2, I_2)}{\partial I} \right) (\lambda + a) \left[ \lambda^2 + (k + pZ_2) \lambda + spV_2Z_2 \right]
- \frac{\partial g(T_2, I_2)}{\partial I}(\lambda + d)[\lambda^2 + (k + pZ_2) \lambda + spV_2Z_2] e^{-(m + \lambda)\tau}
- c \frac{\partial f(T_2, V_2)}{\partial V} \lambda (\lambda + d) e^{-(m + \lambda)\tau}.
\]

In Theorem 4.2, Routh-Hurwitz criterion [20] is applied to help determine the local asymptotical stability of equilibria \( E_1 \). In the following, we will explore the local stability of equilibrium \( E_2 \) by directly comparing the modulus of the corresponding characteristic equation.

**Theorem 5.1.** If \( R_1 > 1 \), then the immunity-activated equilibrium \( E_2 \) is locally asymptotically stable.

**Proof.** Let
\[
X_1(\lambda) = \left( \frac{f(T_2, V_2)}{I_2} + \frac{g(T_2, I_2)}{I_2} \right) \left[ \lambda^2 + (k + pZ_2) \lambda + spV_2Z_2 \right],
\]
\[
X_2(\lambda) = \frac{\partial g(T_2, I_2)}{\partial I} \left[ \lambda^2 + (k + pZ_2) \lambda + spV_2Z_2 \right] + c \frac{\partial f(T_2, V_2)}{\partial V} \lambda.
\]

Since \( f(T_2, V_2) + g(T_2, I_2) = ae^{m\tau}I_2 \), we have
\[
G_2(\lambda) = \frac{1}{a} e^{-m\tau} \left( \lambda + d + \frac{\partial f(T_2, V_2)}{\partial I} + \frac{\partial g(T_2, I_2)}{\partial I} \right) (\lambda + a)X_1(\lambda)
- \frac{1}{a} e^{-m\tau} (\lambda + d) ae^{-\lambda \tau} X_2(\lambda).
\]

For any \( \lambda = \alpha + i\beta \) (\( \alpha \geq 0 \)), we have \( |\lambda + d + \frac{\partial f(T_2, V_2)}{\partial I} + \frac{\partial g(T_2, I_2)}{\partial I}| > |\lambda + d| \) and \( |\lambda + a| > ae^{-\lambda \tau} \). Moreover, due to \( \frac{k + pZ_2}{I_2} = \frac{f(T_2, V_2)}{I_2} \) and Assumption (A3), there holds
\[
X_1(\lambda) - X_2(\lambda)
\geq \left( \frac{g(T_2, I_2)}{I_2} - \frac{\partial g(T_2, I_2)}{\partial I} \right) \left[ \lambda^2 + (k + pZ_2) \lambda + spV_2Z_2 \right]
+ \left[ \frac{f(T_2, V_2)}{I_2} (k + pZ_2) - c \frac{\partial f(T_2, V_2)}{\partial V} \right] \lambda
\geq \left( \frac{cf(T_2, V_2)}{V_2} - c \frac{\partial f(T_2, V_2)}{\partial V} \right) \lambda \geq 0.
\]

Thus, for any \( \lambda = \alpha + i\beta \) (\( \alpha \geq 0 \)), \( G_2(\lambda) \neq 0 \). This implies that all roots of characteristic equation \( G_2(\lambda) = 0 \) possess negative real parts. Hence, if \( R_1 > 1 \), then \( E_2 \) is locally asymptotically stable. \( \square \)
Moreover, for the global asymptotical stability of the immunity-activated equilibrium \( E_2 \), we also need to make the following hypothesis on \( f(T, V) \) and \( g(T, I) \):

\[
(A6) : \left( \frac{T_2 f(T, V)}{T f(T_2, V_2)} - 1 \right) \left( \frac{V}{V_2} - \frac{T_2 f(T, V)}{T f(T_2, V_2)} \right) \geq 0,
\]

\[
\left( \frac{T_2 g(T, I)}{T g(T_2, I_2)} - 1 \right) \left( \frac{I}{I_2} - \frac{T_2 g(T, I)}{T g(T_2, I_2)} \right) \geq 0.
\]

Then, we obtain the following theorem on the global asymptotical stability of \( E_2 \) with respect to the immune-activated reproduction rate \( \mathcal{R}_1 \).

**Theorem 5.2.** Suppose that Assumption (A6) holds. If \( \mathcal{R}_1 > 1 \), then the immunity-activated equilibrium \( E_2 \) is globally asymptotically stable.

**Proof.** Define the following Lyapunov functional

\[
V_2(t) = T_2 h\left( \frac{T(t)}{T_2} \right) + e^{m_T} I_2 h\left( \frac{I(t)}{I_2} \right) + \frac{V_2}{c I_2} f(T_2, V_2) h\left( \frac{V(t)}{V_2} \right) + \frac{p Z_2}{s c I_2} f(T_2, V_2) h\left( \frac{Z(t)}{Z_2} \right) + f(T_2, V_2) \int_{t-\tau}^{t} h\left( \frac{f(T(\delta), V(\delta))}{f(T_2, V_2)} \right) d\delta + g(T_2, I_2) \int_{t-\tau}^{t} h\left( \frac{g(T(\delta), I(\delta))}{g(T_2, I_2)} \right) d\delta.
\]

Then, by calculating the time derivative of \( V_2(t) \) along (2), we have

\[
\frac{dV_2}{dt} = \left( 1 - \frac{T_2}{T} \right) (\Lambda - dT - f(T, V) - g(T, I))
\]

\[
+ \left( 1 - \frac{I_2}{I} \right) (f(T_2, V_2) - f(T, V)) + \frac{c I_2}{c I} f(T_2, V_2) \left( 1 - \frac{V_2}{V} \right) (c I - k V - p V Z)
\]

\[
+ \frac{p Z_2}{s c I_2 f(T_2, V_2)} \left( 1 - \frac{Z_2}{Z} \right) (s V Z - r Z)
\]

\[
+ f(T_2, V_2) h\left( \frac{f(T, V)}{f(T_2, V_2)} \right) - f(T_2, V_2) h\left( \frac{f(T_2, V_2)}{f(T_2, V_2)} \right)
\]

\[
+ g(T_2, I_2) h\left( \frac{g(T, I)}{g(T_2, I_2)} \right) - g(T_2, I_2) h\left( \frac{g(T_2, I_2)}{g(T_2, I_2)} \right).
\]

Since \( f(T_2, V_2) + g(T_2, I_2) = a e^{m_T} I_2 \) and \( c I_2 - k V_2 - p V_2 Z_2 = 0 \) imply

\[
\frac{f(T_2, V_2)}{a e^{m_T} I_2} + \frac{g(T_2, I_2)}{a e^{m_T} I_2} = 1 \text{ and } k = \frac{c I_2}{V_2} - p Z_2,
\]

we further obtain...
\[
\frac{dV_2}{dr} = \left(1 - \frac{T_2}{T}\right) \left[-d(T - T_2) - (f(T, V) - f(T_2, V_2)) - (g(T, I) - g(T_2, I_2))\right]
+ \left(1 - \frac{I_2}{T}\right) \left[f(T_\tau, V_\tau) + g(T_\tau, I_\tau) - (f(T_2, V_2) + g(T_2, I_2)) \frac{I}{I_2}\right]
+ \frac{1}{cI_2} f(T_2, V_2) \left(1 - \frac{V_2}{V}\right) \left[cI - \left(\frac{cI_2}{V_2} - pZ_2\right) V - pVZ\right]
+ \frac{p}{scI_2} f(T_2, V_2) \left(1 - \frac{Z_2}{Z}\right) (sVZ - rZ)
+ f(T_2, V_2) h_2 \left(\frac{f(T, V)}{f(T_2, V_2)} - f(T_2, V_2)\right) + g(T_2, I_2) h_2 \left(\frac{g(T, I)}{g(T_2, I_2)} - g(T_2, I_2)\right)
= K_1 + K_2,
\]

where

\[
K_1 := -\frac{d}{T} (T - T_2)^2 + \frac{1}{cI_2} f(T_2, V_2) (pVZ_2 - pVZ) \left(1 - \frac{V_2}{V}\right)
+ \frac{p}{scI_2} f(T_2, V_2) \left(1 - \frac{Z_2}{Z}\right) (sVZ - rZ)
= -\frac{d}{T} (T - T_2)^2 + \frac{p}{cI_2} f(T_2, V_2) (Z_2 - Z) (V - V_2)
+ \frac{p}{cI_2} f(T_2, V_2) (Z - Z_2) \left(V - \frac{r}{s}\right)
= -\frac{d}{T} (T - T_2)^2
\]

and

\[
K_2 := \left(1 - \frac{T_2}{T}\right) \left[-(f(T, V) - f(T_2, V_2)) - (g(T, I) - g(T_2, I_2))\right]
+ \left(1 - \frac{I_2}{T}\right) \left[f(T_\tau, V_\tau) + g(T_\tau, I_\tau) - (f(T_2, V_2) + g(T_2, I_2)) \frac{I}{I_2}\right]
+ f(T_2, V_2) \left(1 - \frac{V_2}{V}\right) \left(\frac{I}{I_2} - \frac{V}{V_2}\right)
+ f(T_2, V_2) h_2 \left(\frac{f(T, V)}{f(T_2, V_2)} - f(T_2, V_2)\right) + g(T_2, I_2) h_2 \left(\frac{g(T, I)}{g(T_2, I_2)} - g(T_2, I_2)\right).
\]

Clearly, \(K_1 \leq 0\). Further, similar to Theorem 4.3, we rewrite \(K_2\) with respect to the combination of Volterra type functions. For this, let

\[
f_2 := f(T_2, V_2), \quad g_2 := g(T_2, I_2).
\]
Then, \( K_2 \) can be simplified as

\[
K_2 = f_2 \left[ \left(1 - \frac{T_2}{T}\right) \left(1 - \frac{f}{f_2}\right) + \left(1 - \frac{I_2}{T}\right) \left(\frac{f_T}{f_2} - \frac{I}{I_2}\right) \right] \\
+ f_2 \left[ \left(1 - \frac{V_2}{V}\right) \left(\frac{I}{I_2} - \frac{V}{V_2}\right) + h\left(\frac{f}{f_2}\right) - h\left(\frac{f_T}{f_2}\right) \right] \\
+ g_2 \left[ \left(1 - \frac{T_2}{T}\right) \left(1 - \frac{g}{g_2}\right) + \left(1 - \frac{I_2}{T}\right) \left(\frac{g_T}{g_2} - \frac{I}{I_2}\right) + h\left(\frac{g}{g_2}\right) - h\left(\frac{g_T}{g_2}\right) \right]
\]

\[
= f_2 \left( h\left(\frac{f_T}{f_2} - h\left(\frac{f}{f_2}\right) - h\left(\frac{f_T}{f_2}\right) \right) \\
+ f_2 \left( -h\left(\frac{IV_2}{f_2 V}\right) - h\left(\frac{V}{V_2}\right) + h\left(\frac{f}{f_2}\right) - h\left(\frac{f_T}{f_2}\right) \right) \\
+ g_2 \left( h\left(\frac{g_T}{g_2}\right) - h\left(\frac{g}{g_2}\right) - h\left(\frac{f_T}{f_2}\right) \right) + h\left(\frac{f_T}{f_2}\right) \right)
\]

From Assumption (A6), \( \frac{f_T}{f_2} \) lies between 1 and \( \frac{V}{V_2} \), \( \frac{g_T}{g_2} \) lies between 1 and \( \frac{I}{I_2} \).

Then, \( h\left(\frac{f_T}{f_2}\right) - h\left(\frac{f}{f_2}\right) \leq 0 \) and \( h\left(\frac{g_T}{g_2}\right) - h\left(\frac{g}{g_2}\right) \leq 0 \). Thus, \( K_2 \leq 0 \).

Above all, when \( \mathcal{R}_1 > 1 \) and Assumption (A6) hold, \( \frac{dV_2}{dt} \leq 0 \). Let \( \Theta_2 = \{ (T, I, V, Z) : \frac{dV_2}{dt} = 0 \} \). Then the largest invariant subset of \( \Theta_2 \) just consists of \( E_2 \). Thus, due to the LaSalle’s invariance principle [20], \( E_2 \) is a global attractor. Further, combining the local asymptotical stability of \( E_2 \) under the condition \( \mathcal{R}_1 > 1 \), \( E_2 \) is globally asymptotically stable.

\[ \square \]

6. Applications and numerical simulations. Note that the general incidence rates \( f(T, V) \) and \( g(T, I) \) are assumed to satisfy Assumptions (A1)-(A6), and thus our results improve and generalize some known results of within-host virus dynamics. In this section, we perform some specific examples to support our main results, verifying the effects of \( \mathcal{R}_0 \) and \( \mathcal{R}_1 \) on system (2).

Example 1. In [22], Li and Ma considered model (2) with \( m = 0 \) and \( f(T, V) = \frac{\beta TV}{1 + V} \), regardless of cell-to-cell transmission and humoral immunity, that is,

\[
\begin{align*}
\frac{dT}{dt} &= \Lambda - dT(t) - \frac{\beta T(t)V(t)}{1 + V(t)}, \\
\frac{dI}{dt} &= \frac{\beta T(t)}{1 + V(t)} - aI(t), \\
\frac{dV}{dt} &= cI(t) - kV(t). 
\end{align*}
\]

Based on the above analysis, we obtain \( \mathcal{R}_0 = \frac{\beta A}{\alpha_0 k} \). If \( \mathcal{R}_0 < 1 \), then model (21) only has an infection-free equilibrium \( E_0 \), which is globally asymptotically stable. This has been obtained in Theorem 3 of [22]. If \( \mathcal{R}_0 > 1 \), then there exist \( E_0 \) and a globally asymptotically stable infected equilibrium \( E_1 \). The time delay has no
effects on the global asymptotical stability of model (21) for \(m = 0\). Our analysis generalized the conclusions in [22].

**Example 2.** Suppose the virus-to-cell transmission and the cell-to-cell transmission functions as the mass-action infection rates, that is, \(f(t, V) = \beta_1TV\) and \(g(T, I) = \beta_2TI\) for \(\beta_1, \beta_2 > 0\). Then system (2) becomes

\[
\begin{align*}
\frac{dT}{dt} &= \Lambda - dT(t) - \beta_1 T(t) V(t) - \beta_2 T(t) I(t), \\
\frac{dI}{dt} &= \beta_1 e^{-\tau T} (t - \tau) V(t - \tau) + \beta_2 e^{-\tau T} (t - \tau) I(t - \tau) - aI(t), \\
\frac{dV}{dt} &= cI(t) - kV(t) - pV(t) Z(t), \\
\frac{dZ}{dt} &= sV(t) Z(t) - rZ(t).
\end{align*}
\]

(22)

From our analysis, we have

\[
\mathcal{R}_0 = \frac{\Lambda}{akde^{\tau}} (c \beta_1 + k \beta_2),
\]

\[
\mathcal{R}_1 = \frac{1}{akde^{\tau}} \left( \frac{\Lambda}{d} - \frac{akr}{csde^{\tau}} (c \beta_1 + k \beta_2) \right) = \frac{c \beta_1 + k \beta_2}{cs} (sV_1 - r) + 1.
\]

The model (22) presents threshold dynamics with respect to \(\mathcal{R}_0\) and \(\mathcal{R}_1\). The results are the same as those in [23], in which Lin et al. analyzed the global dynamics of the HIV-1 virus model (22).

**Example 3.** Let \(f(T, V) = \frac{\beta_1 T(t) V(t)}{1 + \alpha V(t)}\) and \(g(T, I) = \beta_2 T(t) I(t)\) for \(\beta_1, \beta_2, \alpha > 0\). We consider the following system

\[
\begin{align*}
\frac{dT}{dt} &= \Lambda - dT(t) - \beta_1 T(t) V(t) - \beta_2 T(t) I(t), \\
\frac{dI}{dt} &= \frac{\beta_1 e^{-\tau T} (t - \tau) V(t - \tau)}{1 + \alpha V(t - \tau)} + \frac{\beta_2 e^{-\tau T} (t - \tau) I(t - \tau) - aI(t)}, \\
\frac{dV}{dt} &= cI(t) - kV(t) - pV(t) Z(t), \\
\frac{dZ}{dt} &= sV(t) Z(t) - rZ(t).
\end{align*}
\]

(23)

Through our analysis, for system (23),

\[
\mathcal{R}_0 = \frac{\Lambda}{akde^{\tau}} (c \beta_1 + k \beta_2),
\]

\[
\mathcal{R}_1 = \frac{1}{akde^{\tau}} \left( \frac{\Lambda}{d} - \frac{akr}{csde^{\tau}} \right) \left( \frac{cs \beta_1}{s + \alpha r} + k \beta_2 \right)
\]

\[
= 1 + \frac{1}{cd} \left( \frac{cs \beta_1}{s + \alpha r} + k \beta_1 \right) \left( V_1 - \frac{r}{s} \right)
\]

\[
+ \frac{acs \beta_1}{akde^{\tau} (s + \alpha r)(1 + \alpha V_1)} \left( \frac{\Lambda}{d} - \frac{ak}{csde^{\tau} V_1} \right) \left( V_1 - \frac{r}{s} \right).
\]

The model (23) presents threshold dynamics with respect to \(\mathcal{R}_0\) and \(\mathcal{R}_1\) as shown in Theorem 3.2, Theorem 4.3 and Theorem 5.2.

For system (23) with parameters \(\Lambda = 10000\) cells·mL\(^{-1}\)·day\(^{-1}\) [1], \(d = 0.01\) day\(^{-1}\) [31], \(\beta_1 = 0.000000024\) mL·day\(^{-1}\) [37], \(\beta_2 = 0.000001\) mL·day\(^{-1}\) [33], \(a = 0.01\) day\(^{-1}\) [38], \(k = 23\) day\(^{-1}\) [34], we assume \(m_1 = m_2 = 1\) day\(^{-1}\), \(c = 100\) cell\(^{-1}\), and
\( \alpha = 0.01 \text{cells} \cdot \text{ml}^{-1} \). Then we perform the numerical simulations with respect to different values of time delay \( \tau \). Through our analysis, \( R_0 \) and \( R_1 \) are decreasing with respect to \( \tau \). Thus, extending the time delay with the aid of drug treatment can help to reduce viruses. When \( \tau = 4 \text{ days} \), \( R_0 = 1.3558 \) and \( R_1 = 1.2030 \), from Theorem 3.2, the infection-free equilibrium \( E_0 \) is globally asymptotically stable. When \( \tau = 4.5 \text{ days} \), \( R_0 = 1.1101 \) and \( R_1 = 0.9790 \), due to Theorem 4.3, the immunity-inactivated equilibrium \( E_1 \) is globally asymptotically stable. When \( \tau = 6 \text{ days} \), \( R_0 = 0.7441 \) and \( R_1 = 0.6453 \), by Theorem 5.2, the immunity-activated equilibrium \( E_2 \) is globally asymptotically stable. The graph trajectories of system (23) with respect to different values of \( \tau \) can be seen in Figure 1.

![Figure 1](image1)

**Figure 1.** Graph trajectories of system (23) with respect to different values of \( \Lambda \). The time delay \( \tau \) is increased from \( \tau = 4 \text{ days} \) (\( R_0 = 1.3558 \), \( R_1 = 1.2030 \)) to \( \tau = 4.5 \text{ days} \) (\( R_0 = 1.1101 \), \( R_1 = 0.9790 \)) and finally to \( \tau = 6 \text{ days} \) (\( R_0 = 0.7441 \), \( R_1 = 0.6453 \)).

Further, different values of \( \beta_i \) \( (i = 1, 2) \) also have effects on \( R_0 \) and \( R_1 \) and thus influence the dynamics of the virus model. Under certain medicine treatment, we can decrease the transmission rate of virions through the two spread modes to reduce viruses. In the following, we take numerical simulations to show the effects of transmission rates \( \beta_i \) \( (i = 1, 2) \). For this, based on above parameters, we assume \( \tau = 4.7 \text{ days} \) and choose \( \beta_1 = 0.000001 \text{ml} \cdot \text{day}^{-1} \) [33], the graph trajectories of system (23) with respect to different values of \( \beta_2 \) are depicted in Figure 2. Choose \( \beta_1 = 0.000000024 \text{ml} \cdot \text{day}^{-1} \) [37], the graph trajectories of system (23) with respect to different values of \( \beta_2 \) are depicted in Figure 3.

7. **Conclusions.** In this paper, the analysis of threshold dynamics of a general within-host viral infection model (2) with initial condition (3) with humoral immunity and intracellular delay was carried out. To understand the within-host virus infection dynamics more completely and deeply, we considered both of virus-to-cell infection and cell-to-cell infection by incorporating general incidence functions.
Figure 2. Graph trajectories of system (23) with respect to different values of $\beta_1$. $\beta_1$ is decreased from $\beta_1 = 0.0000004 \text{ ml} \cdot \text{day}^{-1}$ ($R_0 = 2.4913$, $R_1 = 1.0639$) to $\beta_1 = 0.00000015 \text{ ml} \cdot \text{day}^{-1}$ ($R_0 = 1.5027$, $R_1 = 0.9469$) and finally to $\beta_1 = 0.0000001 \text{ ml} \cdot \text{day}^{-1}$ ($R_0 = 0.9491$, $R_1 = 0.8814$).

$f(T,V)$ and $g(T,I)$, which were assumed to satisfy several reasonable biological assumptions. For model (2) with initial condition (3), we established the basic reproductive numbers $R_0$ and $R_1$ as threshold values to determine the existence and stability of equilibria. The conclusion generalizes some existing results on the dynamical properties of viral infection models.

We started with the boundedness and positivity of the solutions of system (2) with initial condition (3). Then the immune-inactivated reproduction rate $R_0$ and immune-activated reproduction rate $R_1$ were expressed with the relationship $R_1 < R_0$, which are composed of two parts separately: one is the contribution from the virus-to-cell infection and the other is the contribution from the cell-to-cell transmission. The basic reproduction rates could be underestimated if either of the two virus transmission modes is neglected. Then sufficient and necessary conditions for the existence of infection-free equilibrium $E_0$, immunity-inactivated equilibrium $E_1$ and immunity-activated equilibrium $E_2$ were given with respect to $R_0$ and $R_1$. Afterwards, through local and global analysis, we verified that the model exhibits threshold dynamics with respect to $R_0$ and $R_1$. That is, when $R_0 < 1$, there exists a unique infection-free equilibrium $E_0$, which is globally asymptotically stable; when $R_0 = 1$, there exists a unique $E_0$, which is linearly neutrally stable and globally attractive; when $R_1 < 1 < R_0$, there exist an unstable $E_0$ and a globally asymptotically stable immunity-inactivated equilibrium $E_1$; when $R_1 = 1$, there exists an unstable $E_0$ and a linearly neutrally stable and globally attractive $E_1$; when $R_1 > 1$, there exist an unstable $E_0$, an unstable $E_1$ and a globally asymptotically stable immunity-activated equilibrium $E_2$. The results showed that the intracellular time lags, both of virus-to-cell infection and cell-to-cell infection, have direct effects.
on the global asymptotical stability of the model. For the critical case when $R_i = 1$, $E_i$ is an linearly neutrally stable non-hyperbolic equilibrium, $i = 1, 2$. Center manifold theory should be applied to further explore the stability and bifurcation around $E_0$ for $R_0 = 1$ and $E_1$ for $R_1 = 1$ in our future work.

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