

Global Dynamics of Delayed HIV Model with Two Transmission Modes, Nonlinear Incidence Rate and CTL Immunity Impairment

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Abstract—This article study the dynamic characteristics of a delayed HIV model with impaired CTL responses and two transmission modes: virus-to-cell infection and cell-to-cell transmission. Moreover, generalized functions are adopted to characterize these two transmission modes. Two threshold values, as well as the conditions governing the global dynamic behavior of the model, are established. Additionally, local stability of E_0 and E_1 is analyzed. Furthermore, it is proved that the equilibria for E_0 , E_1 and E_2 is globally asymptotically stable. The study examines how the CTL response impairment and time delays impact the behavior of virus dynamics. Finally, by numerical simulations, the results obtained from relevant theoretical analysis are further illustrated.

Index Terms—Delayed viral infection model; CTL impairment; Cell-to-cell transmission; Global stability; Lyapunov functional.

I. INTRODUCTION

THE matter of AIDS infection has constantly been a top global concern. Typically, the humoral immune response gives rise to antibodies which counteract the virus. On the other hand, the CTL immune response attacks and destroys the cells invaded by the virus[1,2]. Multiple scholars have suggested several models, factoring in cellular immunity[1,3,4,12,15,17,20,23,26,27] as well as humoral immunity[9,13,16,24].

Nevertheless, these investigations are limited to virus-to-cell infection. Research in this area has indicated that highly efficient virus-to-cell infection might cause multiple virions to be passed on to cells that are not yet infected[3]. The process of cell-to-cell spread not only promotes the swift dissemination of the virus. It also diminishes the effectiveness of neutralizing antibodies and viral inhibitors as the virus evades the immune system[4]. So, numerous scholars have advanced AIDS infection models[5-8,14,21,22,24] that factored in virus-to-cell and cell-to-cell transmissions.

However, when there is an overwhelming load of pathogens, some pathogens not only restrain the immune response but can also lead to substantial destruction of the immune system[8,9]. Even though scholars have taken into account some models featuring CTL impairment[10,11,13,17,19,20,23], existing research has

overlooked the interactive effects of impaired CTL responses, virus-to-cell infection and cell-to-cell transmission.

Motivated by the work in [16,18,19,22], a general delayed HIV model with two transmission modes: virus-to-cell and cell-to-cell transmissions, nonlinear incidence rate and CTL immunity impairment is proposed in this paper:

$$\begin{aligned}\frac{d\Gamma(t)}{dt} &= N(\Gamma) - J_1(\Gamma, \Omega) - J_2(\Gamma, \Lambda), \\ \frac{d\Lambda(t)}{dt} &= e^{-\delta_1 \tau_1} J_1(\Gamma(t - \tau_1), \Omega(t - \tau_1)) \\ &\quad + e^{-\delta_1 \tau_1} J_2(\Gamma(t - \tau_1), \Lambda(t - \tau_1)) \\ &\quad - \mu_1 Q_1(\Lambda) - \omega Q_1(\Lambda) Q_3(\Psi), \\ \frac{d\Omega(t)}{dt} &= \kappa e^{-\delta_2 \tau_2} Q_1(\Lambda(t - \tau_2)) - \mu_2 Q_2(\Omega), \\ \frac{d\Psi(t)}{dt} &= \gamma Q_1(\Lambda) Q_3(\Psi) - \mu_3 Q_3(\Psi) \\ &\quad - \varphi Q_1(\Lambda) Q_3(\Psi),\end{aligned}\quad (1)$$

where Γ , Λ , Ω and Ψ represent the densities of uninfected target cells, infected cells, virus and CTL cells at time t , respectively. $N(\Gamma)$ denotes the intrinsic growth rate of uninfected target cells. The typical forms are $N(\Gamma) = \lambda - d\Gamma$ and $N(\Gamma) = \lambda - d\Gamma + \gamma\Gamma(1 - \frac{\Gamma}{K})$, where λ , d , γ , K are positive real numbers [5-7,10-21,24]. The general nonlinear functions $J_1(\Gamma, \Omega)$ and $J_2(\Gamma, \Lambda)$, which are satisfied the following conditions:

(H_1): $N(\Gamma)$ is continuously differentiable. There exists $\bar{\Gamma} > 0$ such that $N(\bar{\Gamma}) = 0$ and $N'(\bar{\Gamma}) < 0$.

(H_2): $J_i(\Gamma, \theta)$ is continuously differentiable; $J_i(\Gamma, \theta) > 0$ for $\Gamma \in (0, \infty)$, $\theta \in (0, \infty)$; $J_i(\Gamma, \theta) = 0$ if and only if $\Gamma = 0$ or $\theta = 0$; $J_i(\Gamma, \theta) < J_i(\bar{\Gamma}, \theta)$ for $\Gamma \in [0, \bar{x})$, $\theta > 0$; $J_i(\Gamma, \theta)$ is increasing with respect to θ for $\theta \in [0, \infty)$, $i = 1, 2$.

(H_3): $Q_i(\xi)$ ($i = 1, 2, 3$) is strictly increasing on $[0, \infty)$; $\lim_{\xi \rightarrow \infty} Q_i(\xi) = \infty$; $Q_i(0) = 0$; $Q'_i(0) = 1$ and there exists $k_i > 0$ such that $Q_i(\xi) \geq k_i \xi$ for any $\xi \geq 0$.

(H_4): $\frac{J_1(\Gamma, \Omega)}{Q_2(\Omega)}$ is non-increasing with respect to Ω for $\Omega \in (0, \infty)$ and $\frac{J_2(\Gamma, \Lambda)}{Q_1(\Lambda)}$ is non-increasing with respect to Λ for $\Lambda \in (0, \infty)$.

It is also assumed that the death rates of the infected cells, viruses and CTL responses depend on their concentrations. These rates are given by $\mu_1 Q_1(\Lambda)$, $\mu_2 Q_2(\Omega)$ and $\mu_3 Q_3(\Psi)$, respectively. Let $\omega Q_1(\Lambda) Q_3(\Psi)$ and $\gamma Q_1(\Lambda) Q_3(\Psi)$ be the removed rate of infected cells and activation rate of CTL cells. The typical forms can be seen as $\omega \Lambda \Psi$ and $\gamma \Lambda \Psi$

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[12,13,15,17,20,23,26].

For model (1), the probability of surviving the time period from $t - \tau_1$ to t is $e^{-\delta_1 \tau_1}$. $e^{-\delta_2 \tau_2}$ denotes the surviving rate of virus during the delay period. In this paper, the purpose is to explore the dynamical properties of model (1), including the local and global stability of equilibria.

II. PRELIMINARIES

Let $\tau = \max\{\tau_1, \tau_2\}$ and $R_+^4 = \{(\Gamma_1, \Gamma_2, \Gamma_3, \Gamma_4) : \Gamma_i \geq 0, i = 1, 2, \dots, 4\}$. $C([- \tau, 0], R_+^4)$ denotes the space of continuous functions mapping interval $[- \tau, 0]$ into R_+^4 with norm $\|\phi\| = \sup_{-\tau \leq t \leq 0} \{|\phi(t)|\}$ for any $\phi \in C([- \tau, 0], R_+^4)$.

The initial conditions of model (1) are:

$$\begin{aligned} &(\Gamma(\theta), \Lambda(\theta), \Omega(\theta), \Psi(\theta)) \\ &= (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)), \\ &\phi_i(\theta) \geq 0, \theta \in [- \tau, 0], \phi_i(0) > 0, i = 1, 2, 3, 4, \end{aligned} \quad (2)$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C([- \tau, 0], R_+^4)$. By the fundamental theory of functional differential equation [25], model (1) admits a unique solution $(\Gamma(t), \Lambda(t), \Omega(t), \Psi(t))$ satisfying initial conditions (2).

Using an argument similar to [24], there is the following result.

Theorem 2.1 Assume that assumptions (H_1) – (H_4) hold. Let $(\Gamma(t), \Lambda(t), \Omega(t), \Psi(t))$ be the solution of model (1) with initial conditions (2), then $(\Gamma(t), \Lambda(t), \Omega(t), \Psi(t))$ is positive and ultimately bounded.

Next, The existence and uniqueness of equilibria of model (1) are discussed. Also, any equilibrium $E = (\Gamma, \Lambda, \Omega, \Psi)$ of model (1) is satisfied:

$$\begin{cases} N(\Gamma) - J_1(\Gamma, \Omega) - J_2(\Gamma, \Lambda) = 0, \\ e^{-\delta_1 \tau_1} J_1(\Gamma, \Omega) + e^{-\delta_1 \tau_1} J_2(\Gamma, \Lambda) \\ - \mu_1 Q_1(\Lambda) - \omega Q_1(\Lambda) Q_3(\Psi) = 0, \\ \kappa e^{-\delta_2 \tau_2} Q_1(\Lambda) - \mu_2 Q_2(\Omega) = 0, \\ \gamma Q_2(\Lambda) Q_3(\Psi) - \mu_2 Q_3(\Psi) - \varphi Q_1(\Lambda) Q_3(\Psi) = 0. \end{cases} \quad (3)$$

It is clear from (3) that model (1) has a unique infection-free equilibrium $E_0 = (\bar{\Gamma}, 0, 0, 0)$. From (3), there is $N(\Gamma) = J_2(\Gamma, \Lambda)$, $e^{-\delta_1 \tau_1} J_2(\Gamma, \Lambda) = \mu_1 Q_1(\Lambda) + \omega Q_1(\Lambda) Q_3(\Psi)$, $Q_1(\Lambda) = 0$ and $(\gamma - \varphi) Q_1(\Lambda) Q_3(\Psi) - \mu_3 Q_3(\Psi) = 0$ when $\Omega = 0$. Solving these equations, there is $\Gamma = \bar{\Gamma}$, $\Omega = 0$ and $\Psi = 0$. From (3), there is $s(\Gamma) = J_1(\Gamma, \Omega)$, $e^{-\delta_1 \tau_1} J_1(\Gamma, \Omega) = 0$, $Q_2(\Omega) = 0$ and $Q_3(\Psi) = 0$ when $\Lambda = 0$.

Therefore, besides equilibrium E_0 , model (1) only has the following two possible equilibria: $E_1 = (\Gamma_1, \Lambda_1, \Omega_1, 0)$ and $E_2 = (\Gamma_2, \Lambda_2, \Omega_2, \Psi_2)$.

Define the basic reproduction number for viral infection

$$R_0 = \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2} \frac{\partial J_1(\bar{\Gamma}, 0)}{\partial \Omega}}{\mu_1 \mu_2} + \frac{e^{-\delta_1 \tau_1} \frac{\partial J_2(\bar{\Gamma}, 0)}{\partial \Lambda}}{\mu_1}.$$

The existence of immune-free equilibrium $E_1 = (\Gamma_1, \Lambda_1, \Omega_1, 0)$ is equivalent to the existence of positive solution $(\Gamma_1, \Lambda_1, \Omega_1)$ of the following equations:

$$\begin{aligned} N(\Gamma) &= J_1(\Gamma, \Omega) + J_2(\Gamma, \Lambda) = \mu_1 e^{\delta_1 \tau_1} Q_1(\Lambda) \\ &= \frac{\mu_1 \mu_2 e^{\delta_1 \tau_1 + \delta_2 \tau_2}}{\kappa} Q_2(\Omega). \end{aligned}$$

By (H_3) , the inverse functions $Q_1^{-1}(\Lambda)$ and $Q_2^{-1}(\Omega)$ exist. Solving the above equilibrium equations for Λ and Ω yields

$$\Lambda = \chi(\Gamma) = Q_1^{-1}\left(\frac{e^{-\delta_1 \tau_1} N(\Gamma)}{\mu_1}\right)$$

and

$$\Omega = \psi(\Gamma) = Q_2^{-1}\left(\frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2} N(\Gamma)}{\mu_1 \mu_2}\right) \quad (4)$$

with $\chi(\bar{\Gamma}) = \psi(\bar{\Gamma}) = 0$. Define

$$J(x) = J_1(\Gamma, \Omega) + J_2(\Gamma, \Lambda) - N(\Gamma).$$

Then it follows from (H_2) that $J(0) = -N(0) < 0$ and $J(\bar{\Gamma}) = 0$. Moreover, from (H_2) , it is observed that $J_i(\Gamma, 0) \equiv 0$ and thus $\frac{\partial J_i(\Gamma, 0)}{\partial \Gamma} \equiv 0$ for $i = 1, 2$. Since

$$Q'_i(0) = 1 \text{ for } i = 1, 2, \text{ there are } \chi'(\bar{\Gamma}) = \frac{e^{-\delta_1 \tau_1} N'(\bar{\Gamma})}{\mu_1} \text{ and}$$

$$\psi'(\bar{\Gamma}) = \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2} N'(\bar{\Gamma})}{\mu_1 \mu_2}.$$

Together with the expression of R_0 , yields $J'(\bar{\Gamma}) = N'(\bar{\Gamma})(R_0 - 1)$. Note that $N'(\bar{\Gamma}) < 0$ by (H_1) . Then $J'(\bar{\Gamma}) < 0$ if $R_0 > 1$, which implies that there exists $\Gamma_1 \in (0, \bar{\Gamma})$ such that $J(\Gamma_1) = 0$. Therefore, there exists a immune-free equilibrium $E_1 = (\Gamma_1, \Lambda_1, \Omega_1, 0)$ with $\Lambda_1 = \chi(\Gamma_1)$, $\Omega_1 = \psi(\Gamma_1)$ if $R_0 > 1$.

Next, it is show that $E_1 = (\Gamma_1, \Lambda_1, \Omega_1, 0)$ is a unique immune-free equilibrium. Otherwise, there exists another $E_1^* = (\Gamma_1^*, \Lambda_1^*, \Omega_1^*, 0)$. Without of loss of generality, it is assumed that $\Gamma_1^* < \Gamma_1$, then $N(\Gamma_1^*) > N(\Gamma_1)$. Meanwhile, together with (4), yields $\Lambda_1 < \Lambda_1^*$ and $\Omega_1 < \Omega_1^*$. By (H_3) and (H_4) , we get

$$\begin{aligned} 1 &= \frac{e^{-\delta_1 \tau_1} J_2(\Gamma_1^*, \Lambda_1^*)}{\mu_1 Q_1(\Lambda_1^*)} + \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2} J_1(\Gamma_1^*, \Omega_1^*)}{\mu_1 \mu_2 Q_2(\Omega_1^*)} \\ &\leq \frac{e^{-\delta_1 \tau_1} J_2(\Gamma_1^*, \Lambda_1)}{\mu_1 Q_1(\Lambda_1)} + \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2} J_1(\Gamma_1^*, \Omega_1)}{\mu_1 \mu_2 Q_2(\Omega_1)} \\ &< \frac{e^{-\delta_1 \tau_1} J_2(\Gamma_1, \Lambda_1)}{\mu_1 Q_1(\Lambda_1)} + \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2} J_1(\Gamma_1, \Omega_1)}{\mu_1 \mu_2 Q_2(\Omega_1)} = 1. \end{aligned}$$

This is a contradiction. Thus E_1 is a unique immune-free equilibrium.

Further, considering the existence of infection equilibrium $E_2 = (\Gamma_2, \Lambda_2, \Omega_2, \Psi_2)$ with antibody response. It is clear that $\Lambda_2 = Q_2^{-1}\left(\frac{\mu_3}{\gamma - \varphi}\right)$ and $\Omega_2 = Q_2^{-1}\left(\frac{\kappa \mu_3 e^{-\delta_2 \tau_2}}{\mu_2(\gamma - \varphi)}\right)$. Define $J(\Gamma) = N(\Gamma) - J_1(\Gamma, \Omega_2) - J_2(\Gamma, \Lambda_2)$. By (H_1) and (H_2) , there is $J'(\Gamma) < 0$. Since $J(0) = N(0) > 0$ and $J(\bar{\Gamma}) = N(\bar{\Gamma}) - J_1(\bar{\Gamma}, \Omega_2) - J_2(\bar{\Gamma}, \Lambda_2) < 0$, there exists a unique $\Gamma_2 \in (0, \bar{\Gamma})$ such that $J(\Gamma_2) = 0$.

Define the constant

$$R_1 = \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2} J_1(\Gamma_2, \Omega_2) + J_2(\Gamma_2, \Lambda_2)}{\mu_1 \mu_2 Q_2(\Omega_2)},$$

which is called the CTL response reproductive number of model (1). If $R_1 > 1$, solving z_2 from (3), there is:

$$\begin{aligned} z_2 &= Q_3^{-1}\left(\frac{e^{-\delta_1 \tau_1} J_1(\Gamma_2, \Omega_2) + e^{-\delta_1 \tau_1} J_2(\Gamma_2, \Lambda_2)}{\omega Q_1(\Lambda_2)}\right) \\ &\quad - \frac{\mu_1 Q_1(\Lambda_2)}{\omega Q_1(\Lambda_2)} \\ &= Q_3^{-1}\left(\frac{\mu_1(R_1 - 1)}{\omega}\right) > 0. \end{aligned}$$

Therefore, E_2 exists and is unique if $R_1 > 1$.

III. STABILITY ANALYSIS

To state the global stability on E_0 , an additional assumption is needed:

(H_5): The supremum of $\lim_{\Lambda \rightarrow 0} \frac{J_2(\Gamma, \Lambda)}{Q_1(\Lambda)} / \lim_{\Omega \rightarrow 0} \frac{J_1(\Gamma, \Omega)}{Q_2(\Omega)}$ on $(0, \bar{\Gamma}]$ is achieved at $\Gamma = \bar{\Gamma}$. Define

$$J_{11}(\Gamma) = \lim_{\Omega \rightarrow 0} \frac{J_1(\Gamma, \Omega)}{Q_2(\Omega)}, \quad J_{21}(\Gamma) = \lim_{\Lambda \rightarrow 0} \frac{J_2(\Gamma, \Lambda)}{Q_1(\Lambda)}$$

Assumptions (H_2)-(H_3) imply that

$$J_{11}(\Gamma) = \frac{\partial J_1(\Gamma, 0)}{\partial \Omega} > 0,$$

and

$$J_{21}(\Gamma) = \frac{\partial J_2(\Gamma, 0)}{\partial \Lambda} > 0 \text{ for any } \Gamma > 0.$$

Theorem 3.1 (a) If $R_0 \leq 1$, infection-free equilibrium E_0 is globally asymptotically stable.

(b) If $R_0 > 1$, E_0 is unstable.

Proof: Consider conclusion (a). Define a Lyapunov functional $V_1(t)$ as follows:

$$\begin{aligned} V_1(t) = & \Gamma(t) - \int_{\bar{\Gamma}}^{\Gamma(t)} \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{J_1(\theta, \Omega)} d\theta + e^{\delta_1 \tau_1} \Lambda(t) \\ & + \frac{1}{\mu_2} \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{Q_2(\Omega)} \Omega(t) + \frac{\omega e^{\delta_1 \tau_1}}{\gamma - \varphi} \Psi(t) \\ & + \int_{-\tau_1}^0 (J_1(\Gamma(t+s), \Omega(t+s))) ds \\ & + \int_{-\tau_1}^0 (J_2(\Gamma(t+s), \Lambda(t+s))) ds \\ & + \frac{\kappa e^{-\delta_2 \tau_2}}{\mu_2} \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{Q_2(\Omega)} \int_{-\tau_2}^0 Q_1(\Lambda(t+s)) ds. \end{aligned}$$

Calculating the time derivative of $V_1(t)$, there is:

$$\begin{aligned} \frac{dV_1(t)}{dt} = & N(\Gamma)(1 - \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{J_1(\Gamma, \Omega)}) \\ & + \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{J_1(\Gamma, \Omega)} (J_1(\Gamma, \Omega) \\ & - \lim_{\Omega \rightarrow 0} \frac{J_1(\Gamma, \Omega)}{Q_2(\Omega)} \cdot Q_2(\Omega)) \\ & + \mu_1 e^{\delta_1 \tau_1} Q_1(\Lambda) \left(\frac{e^{-\delta_1 \tau_1}}{\mu_1} \right. \\ & \times \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{J_1(\Gamma, \Omega)} \cdot \lim_{\Lambda \rightarrow 0} \frac{J_2(\Gamma, \Lambda)}{Q_1(\Lambda)} \\ & + \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2}}{\mu_1 \mu_2} \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{Q_2(\Omega)} - 1 \Big) \\ & - \frac{\omega \mu_3 e^{\delta_1 \tau_1}}{\gamma - \varphi} Q_3(z). \end{aligned}$$

Assumption (H_4) implies that

$$J_1(\Gamma, \Omega) \leq \lim_{\Omega \rightarrow 0} \frac{J_1(\Gamma, \Omega)}{Q_2(\Omega)} \cdot Q_2(\Omega),$$

$$J_2(\Gamma, \Lambda) \leq \lim_{\Lambda \rightarrow 0} \frac{J_2(\Gamma, \Lambda)}{Q_1(\Lambda)} \cdot Q_1(\Lambda).$$

From assumption (H_5) yields

$$\frac{J_1(\bar{\Gamma}, \Omega)}{J_1(\Gamma, \Omega)} \cdot \frac{J_2(\Gamma, \Lambda)}{Q_1(\Lambda)} \leq \frac{J_{21}(\Gamma)/J_{11}(\Gamma)}{J_{21}(\bar{\Gamma})/J_{11}(\bar{\Gamma})} \cdot J_{21}(\bar{\Gamma}) \leq J_{21}(\bar{\Gamma})$$

for $\Gamma \leq \bar{\Gamma}$. Assumptions (H_1)-(H_2) imply that $N(\Gamma)(1 - \lim_{\Omega \rightarrow 0} \frac{J_1(\bar{\Gamma}, \Omega)}{J_1(\Gamma, \Omega)}) \leq 0$. It follows that

$$\frac{dV_1(t)}{dt} \leq \mu_1 e^{\delta_1 \tau_1} Q_1(\Lambda)(R_0 - 1).$$

Note that $\frac{dV_1(t)}{dt} = 0$ if and only if $\Gamma(t) = \bar{\Gamma}$, $\Omega(t) = 0$, $\Psi(t) = 0$ and $\Lambda(t) = 0$. So, the maximal compact invariant set in $\{(\Gamma, \Lambda, \Omega, \Psi) \in R_+^4 : \frac{dV_1(t)}{dt} = 0\}$ is singleton $\{E_0\}$. By the LaSalle's invariance principle [25], E_0 is globally asymptotically stable.

Next, considering conclusion (b). the characteristic equation of the linearization system of model (1) at E_0 is

$$(\lambda + \mu_3)(\lambda - N'(\bar{\Gamma}))\varphi_1(\lambda) = 0,$$

where

$$\begin{aligned} \varphi_1(\lambda) = & \lambda^2 + \left(\mu_1 + \mu_2 - e^{-(\delta_1 + \lambda)\tau_1} \frac{\partial J_2(\bar{\Gamma}, 0)}{\partial \Lambda} \right) \lambda \\ & + \mu_2 \left(-e^{-(\delta_1 + \lambda)\tau_1} \frac{\partial J_2(\bar{\Gamma}, 0)}{\partial \Lambda} + \mu_1 \right) \\ & - \kappa e^{-(\delta_1 + \lambda)\tau_1} e^{-(\delta_2 + \lambda)\tau_2} \frac{\partial J_1(\bar{\Gamma}, 0)}{\partial \Omega}. \end{aligned}$$

When $R_0 > 1$, $\varphi_1(0) = \mu_1 \mu_2 (1 - R_0) < 0$ and $\lim_{\lambda \rightarrow +\infty} \varphi_1(\lambda) = +\infty$ are obtained. Hence, there is a $\lambda^* > 0$ such that $\varphi_1(\lambda^*) = 0$. Therefore, when $R_0 > 1$, E_0 is unstable.

IV. STABILITY OF EQUILIBRIUM E_1

Firstly, one lemma which will be used in the proof of theorem.

Lemma 3.1. Suppose that (H_1)-(H_4) hold and $R_0 > 1$. Let Γ_2 and Ω_2 satisfy $Q_1(\Lambda_2) = \frac{\mu_3}{\gamma - \varphi}$, $Q_2(\Omega_2) = \frac{\kappa \mu_3 e^{-\delta_2 \tau_2}}{\mu_2 (\gamma - \varphi)}$ and $S(\Gamma_2) = J_1(\Gamma_2, \Omega_2) + J_2(\Gamma_2, \Lambda_2)$. Then for equilibrium $E_1 = (\Gamma_1, \Lambda_1, \Omega_1, 0)$, $\text{sign}(\Gamma_2 - \Gamma_1) = \text{sign}(\Lambda_1 - \Lambda_2) = \text{sign}(\Omega_1 - \Omega_2) = \text{sign}(R_1 - 1)$.

Proof: Since $S(\Gamma_1) = J_1(\Gamma_1, \Omega_1) + J_2(\Gamma_1, \Lambda_1)$, there is:

$$\begin{aligned} S(\Gamma_2) - S(\Gamma_1) = & (J_1(\Gamma_2, \Omega_2) - J_1(\Gamma_1, \Omega_2)) \\ & + (J_1(\Gamma_1, \Omega_2) - J_1(\Gamma_1, \Omega_1)) \\ & + (J_2(\Gamma_2, \Lambda_2) - J_2(\Gamma_1, \Lambda_2)) \\ & + (J_2(\Gamma_1, \Lambda_2) - J_2(\Gamma_1, \Lambda_1)). \end{aligned}$$

By (H_1) and (H_2), there is $\text{sign}(\Gamma_2 - \Gamma_1) = \text{sign}(\Omega_1 - \Omega_2)$. Using

$$\frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2}}{\mu_1 \mu_2} \frac{J_1(\Gamma_1, \Omega_1) + J_2(\Gamma_1, \Lambda_1)}{Q_2(\Omega_1)} = 1,$$

there is:

$$\begin{aligned} R_1 - 1 = & \frac{\kappa e^{-\delta_1 \tau_1 - \delta_2 \tau_2}}{\mu_1 \mu_2} \left(\frac{J_1(\Gamma_2, \Omega_1) - J_1(\Gamma_1, \Omega_1)}{Q_2(\Omega_1)} \right. \\ & \left. + \frac{J_1(\Gamma_2, \Omega_2)}{Q_2(\Omega_2)} - \frac{J_1(\Gamma_2, \Omega_1)}{Q_2(\Omega_1)} \right) \end{aligned}$$

$$+ \frac{e^{-\delta_1 \tau_1}}{\mu_1} \left(\frac{J_2(\Gamma_2, \Lambda_1) - J_2(\Gamma_1, \Lambda_1)}{Q_1(\Lambda_1)} \right. \\ \left. + \frac{J_2(\Gamma_2, \Lambda_2)}{Q_1(\Lambda_2)} - \frac{J_2(\Gamma_2, \Lambda_1)}{Q_1(\Lambda_1)} \right).$$

By (H_2) and (H_4) , it follows $\text{sign}(R_1 - 1) = \text{sign}(\Gamma_2 - \Gamma_1)$. The following condition is needed to guarantee the global stability of the immune-free equilibrium E_1 .

$$(H_6) : \left(\frac{Q_1(\Lambda)}{Q_1(\Lambda_i)} - \frac{J_1(\Gamma_i, \Omega_i) J_2(\Gamma, \Lambda)}{J_1(\Gamma, \Omega_i) J_2(\Gamma_i, \Lambda_i)} \right) \\ \times \left(\frac{J_1(\Gamma, \Omega_i) J_2(\Gamma_i, \Lambda_i)}{J_1(\Gamma_i, \Omega_i) J_2(\Gamma, \Lambda)} - 1 \right) \leq 0$$

for $\Gamma \in [0, \bar{\Gamma}]$, $\Lambda > 0$, $i = 1, 2$.

Theorem 3.2 Assume that the condition (H_6) is satisfied.

(a) If $R_1 \leq 1 < R_0$, then immune-free equilibrium E_1 is globally asymptotically stable.

(b) If $R_1 > 1$, then E_1 is unstable.

Proof: Consider conclusion (a). Denote $H(\xi) = \xi - 1 - \ln \xi$ with $\xi \in R_+$. Define a Lyapunov functional $V_2(t)$ as follows

$$V_2(t) = \Gamma(t) - \int_{\Gamma_1}^{\Gamma(t)} \frac{J_1(\Gamma_1, \Omega_1)}{J_1(\theta, \Omega_1)} d\theta \\ + e^{\delta_1 \tau_1} \left(\Lambda(t) - \int_{\Lambda_1}^{\Lambda(t)} \frac{Q_1(\Lambda_1)}{Q_1(\theta)} d\theta \right) \\ + \frac{\omega e^{\delta_1 \tau_1}}{\gamma - \varphi} \Psi(t) + \frac{J_1(\Gamma_1, \Omega_1)}{\mu_2 Q_2(\Omega_1)} \\ \times \left(\Omega(t) - \int_{\Omega_1}^{\Omega(t)} \frac{Q_2(\Omega_1)}{Q_2(\theta)} d\theta \right) \\ + J_1(\Gamma_1, \Omega_1) \int_{-\tau_2}^0 H \left(\frac{Q_1(\Lambda(t + \theta))}{Q_1(\Lambda_1)} \right) d\theta \\ + J_1(\Gamma_1, \Omega_1) \int_{-\tau_1}^0 H \left(\frac{J_1(\Gamma(t + \theta), \Omega(t + \theta))}{J_1(\Gamma_1, \Omega_1)} \right) d\theta \\ + J_2(\Gamma_1, \Lambda_1) \int_{-\tau_1}^0 H \left(\frac{J_2(\Gamma(t + \theta), \Lambda(t + \theta))}{J_2(\Gamma_1, \Lambda_1)} \right) d\theta.$$

Calculating the derivative of $V_2(t)$ along solutions of model (1), there is:

$$\frac{dV_2(t)}{dt} \\ = (N(\Gamma) - N(\Gamma_1)) \left(1 - \frac{J_1(\Gamma_1, \Omega_1)}{J_1(\Gamma, \Omega_1)} \right) \\ - J_1(\Gamma_1, \Omega_1) \left(H \left(\frac{Q_2(\Omega_1) Q_1(\Lambda(t - \tau_2))}{Q_1(\Lambda_1) Q_2(\Omega)} \right) \right. \\ + H \left(\frac{J_1(\Gamma_1, \Omega_1)}{J_1(\Gamma, \Omega_1)} \right) + H \left(\frac{Q_2(\Omega) J_1(\Gamma, \Omega_1)}{Q_2(\Omega_1) J_1(\Gamma, \Omega)} \right) \\ \left. + H \left(\frac{Q_1(\Lambda_1) J_1(\Gamma(t - \tau_1), \Omega(t - \tau_1))}{Q_1(y) J_1(\Gamma_1, \Omega_1)} \right) \right) \\ - J_2(\Gamma_1, \Lambda_1) \left(H \left(\frac{J_1(\Gamma_1, \Omega_1)}{J_1(\Gamma, \Omega_1)} \right) \right. \\ \left. + H \left(\frac{J_1(\Gamma, \Omega_1) J_2(\Gamma_1, \Lambda_1) Q_1(\Lambda)}{J_1(\Gamma_1, \Omega_1) J_2(\Gamma, \Lambda) Q_1(\Lambda_1)} \right) \right)$$

$$+ H \left(\frac{Q_1(\Lambda_1) J_2(\Gamma(t - \tau_1), \Lambda(t - \tau_1))}{Q_1(\Lambda) J_2(\Gamma_1, \Lambda_1)} \right) \\ + \omega e^{\delta_1 \tau_1} (Q_1(\Lambda_1) - Q_1(\Lambda_2)) Q_3(\Psi) \\ + J_1(\Gamma_1, \Omega_1) \frac{Q_2(\Omega)}{Q_2(\Omega_1)} \left(\frac{J_1(\Gamma, \Omega)}{J_1(\Gamma, \Omega_1)} - 1 \right) \\ \times \left(\frac{Q_2(\Omega_1)}{Q_2(\Omega)} - \frac{J_1(\Gamma, \Omega_1)}{J_1(\Gamma, \Omega)} \right) \\ + J_2(\Gamma_1, \Lambda_1) \left(\frac{Q_1(\Lambda)}{Q_1(\Lambda_1)} - \frac{J_1(\Gamma_1, \Omega_1) J_2(\Gamma, \Lambda)}{J_1(\Gamma, \Omega_1) J_2(\Gamma_1, \Lambda_1)} \right) \\ \times \left(\frac{J_1(\Gamma, \Omega_1) J_2(\Gamma_1, \Lambda_1)}{J_1(\Gamma_1, \Omega_1) J_2(\Gamma, \Lambda)} - 1 \right).$$

By (H_1) and (H_6) , there are:

$$(N(\Gamma) - N(\Gamma_1)) \left(1 - \frac{J_1(\Gamma_1, \Omega_1)}{J_1(\Gamma, \Omega_1)} \right) \leq 0,$$

$$\left(\frac{J_1(\Gamma, \Omega)}{J_1(\Gamma, \Omega_1)} - 1 \right) \left(\frac{Q_2(\Omega_1)}{Q_2(\Omega)} - \frac{J_1(\Gamma, \Omega_1)}{J_1(\Gamma, \Omega)} \right) \leq 0,$$

and

$$\left(\frac{Q_1(\Lambda)}{Q_1(\Lambda_1)} - \frac{J_1(\Gamma_1, \Omega_1) J_2(\Gamma, \Lambda)}{J_1(\Gamma, \Omega_1) J_2(\Gamma_1, \Lambda_1)} \right) \\ \times \left(\frac{J_1(\Gamma, \Omega_1) J_2(\Gamma_1, \Lambda_1)}{J_1(\Gamma_1, \Omega_1) J_2(\Gamma, \Lambda)} - 1 \right) \\ \leq 0.$$

Lemma 3.1 implies that $\Omega_1 \leq \Omega_2$ if $R_1 \leq 1$. There is $\frac{dV_2(t)}{dt} \leq 0$, and $\frac{dV_2(t)}{dt} = 0$ if and only if $\Gamma(t) = \Gamma_1$, $\Lambda(t) = \Lambda_1$, $\Omega(t) = \Omega_1$ and $\Psi(t) = 0$. From LaSalle's invariance principle [25], equilibrium E_1 is globally asymptotically stable when $R_1 \leq 1 < R_0$.

Next, considering conclusion (b).

By computing, the characteristic equation of the linearization system of model (1) at E_1 is

$$\varphi_1(\lambda) \varphi_2(\lambda) = 0,$$

where $\varphi_1(\lambda) = \lambda + \mu_3 - (\gamma - \varphi) Q_1(\Lambda_1)$ and

$$\varphi_2(\lambda) = \begin{vmatrix} a_{11} & \frac{\partial J_2(\Gamma_1, \Lambda_1)}{\partial \Lambda} & \frac{\partial J_1(\Gamma_1, \Omega_1)}{\partial \Omega} \\ a_{21} & a_{22} & a_{23} \\ 0 & -\kappa e^{-(\delta_2 + \lambda) \tau_2} Q_1'(\Lambda_1) & \lambda + u Q_2'(\Omega_1) \end{vmatrix},$$

where

$$a_{11} = \lambda - N'(\Gamma_1) + \frac{\partial J_1(\Gamma_1, \Omega_1)}{\partial \Gamma} \\ + \frac{\partial J_2(\Gamma_1, \Lambda_1)}{\partial \Gamma}, \\ a_{21} = -e^{-(\delta_1 + \lambda) \tau_1} \frac{\partial J_1(\Gamma_1, \Omega_1)}{\partial \Gamma} \\ - e^{-(\delta_1 + \lambda) \tau_1} \frac{\partial J_2(\Gamma_1, \Lambda_1)}{\partial \Gamma}, \\ a_{22} = \lambda + \mu_1 Q_1'(\Lambda_1) - e^{-(\delta_1 + \lambda) \tau_1} \frac{\partial J_2(\Gamma_1, \Lambda_1)}{\partial \Lambda}, \\ a_{23} = -e^{-(\delta_1 + \lambda) \tau_1} \frac{\partial J_1(\Gamma_1, \Omega_1)}{\partial \Omega}.$$

When $R_1 > 1$, we have $\varphi_1(0) = \mu_3(Q_1(\Lambda_2) - Q_1(\Lambda_1)) < 0$ and $\lim_{\lambda \rightarrow +\infty} \varphi_1(\lambda) = +\infty$. Hence, there is also a positive root λ^* such that $h_1(\lambda^*) = 0$. Therefore, when $R_1 > 1$, E_1 is unstable.

V. STABILITY OF EQUILIBRIUM E_2

Theorem 3.3 Assume that the condition (H_6) is satisfied. If $R_1 > 1$, then CTL immune response equilibrium E_2 is globally asymptotically stable.

Proof: Define a Lyapunov functional $V_3(t)$ as follows

$$\begin{aligned} V_3(t) = & \Gamma(t) - \int_{\Gamma_2}^{\Gamma(t)} \frac{J_1(\Gamma_2, \Omega_2)}{J_1(\theta, \Omega_2)} d\theta \\ & + e^{\delta_1 \tau_1} \left(\Lambda(t) - \int_{\Lambda_2}^{\Lambda(t)} \frac{Q_1(\Lambda_2)}{Q_1(\theta)} d\theta \right) \\ & + \frac{J_1(\Gamma_2, \Omega_2)}{\mu_2 Q_2(\Omega_2)} \left(\Omega(t) - \int_{\Omega_2}^{\Omega(t)} \frac{Q_2(\Omega_1)}{Q_2(\theta)} d\theta \right) \\ & + \frac{\omega e^{\delta_1 \tau_1}}{\gamma - \varphi} \left(\Psi(t) - \int_{\Psi_2}^{\Psi(t)} \frac{Q_3(\Psi_2)}{Q_3(\theta)} d\theta \right) \\ & + J_1(\Gamma_2, \Omega_2) \int_{-\tau_1}^0 H \left(\frac{J_1(\Gamma(t+\theta), \Omega(t+\theta))}{J_1(\Gamma_2, \Omega_2)} \right) d\theta \\ & + J_2(\Gamma_2, \Lambda_2) \int_{-\tau_1}^0 H \left(\frac{J_2(\Gamma(t+\theta), \Lambda(t+\theta))}{J_2(\Gamma_2, \Lambda_2)} \right) d\theta \\ & + J_1(\Gamma_2, \Omega_2) \int_{-\tau_2}^0 H \left(\frac{Q_1(\Lambda(t+\theta))}{Q_1(\Lambda_2)} \right) d\theta. \end{aligned}$$

Calculating the derivative of $V_3(t)$ along solutions of model (1), there is:

$$\begin{aligned} \frac{dV_3(t)}{dt} = & (N(\Gamma) - N(\Gamma_2)) \left(1 - \frac{J_1(\Gamma_2, \Omega_2)}{J_1(\Gamma, \Omega_2)} \right) \\ & - J_1(\Gamma_2, \Omega_2) \left(H \left(\frac{Q_2(\Omega_2) Q_1(\Lambda(t - \tau_2))}{Q_1(\Lambda_2) Q_2(\Omega)} \right) \right. \\ & + H \left(\frac{J_1(\Gamma_2, \Omega_2)}{J_1(\Gamma, \Omega_2)} \right) + H \left(\frac{Q_2(\Omega) J_1(\Gamma, \Omega_2)}{Q_2(\Omega_2) J_1(\Gamma, \Omega)} \right) \\ & + H \left(\frac{Q_1(\Lambda_2) J_1(\Gamma(t - \tau_1), \Omega(t - \tau_1))}{Q_1(\Lambda) J_1(\Gamma_2, \Omega_2)} \right) \\ & - J_2(\Gamma_2, \Lambda_2) \left(H \left(\frac{J_1(\Gamma_2, \Omega_2)}{J_1(\Gamma, \Omega_2)} \right) \right. \\ & + H \left(\frac{J_1(\Gamma, \Omega_2) J_2(\Gamma_2, \Lambda_2) Q_1(\Lambda)}{J_1(\Gamma_2, \Omega_2) J_2(\Gamma, \Lambda) Q_1(\Lambda_2)} \right) \\ & + H \left(\frac{Q_1(\Lambda_2) J_2(\Gamma(t - \tau_1), \Lambda(t - \tau_1))}{Q_1(\Lambda) J_2(\Gamma_2, \Lambda_2)} \right) \\ & + J_1(\Gamma_2, \Omega_2) \frac{Q_2(\Omega)}{Q_2(\Omega_2)} \left(\frac{J_1(\Gamma, \Omega)}{J_1(\Gamma, \Omega_2)} - 1 \right) \\ & \times \left(\frac{Q_2(\Omega_2)}{Q_2(\Omega)} - \frac{J_1(\Gamma, \Omega_2)}{J_1(\Gamma, \Omega)} \right) \\ & + J_2(\Gamma_2, \Lambda_2) \left(\frac{Q_1(\Lambda)}{Q_1(\Lambda_2)} - \frac{J_1(\Gamma_2, \Omega_2) J_2(\Gamma, \Lambda)}{J_1(\Gamma, \Omega_2) J_2(\Gamma_2, \Lambda_2)} \right) \\ & \times \left(\frac{J_1(\Gamma, \Omega_2) J_2(\Gamma_2, \Lambda_2)}{J_1(\Gamma_2, \Omega_2) J_2(\Gamma, \Lambda)} - 1 \right). \end{aligned}$$

Noting that

$$\begin{aligned} (N(\Gamma) - N(\Gamma_2)) \left(1 - \frac{J_1(\Gamma_2, \Omega_2)}{J_1(\Gamma, \Omega_2)} \right) & \leq 0, \\ \left(\frac{J_1(\Gamma, \Omega)}{J_1(\Gamma, \Omega_2)} - 1 \right) \left(\frac{Q_2(\Omega_2)}{Q_2(\Omega)} - \frac{J_1(\Gamma, \Omega_2)}{J_1(\Gamma, \Omega)} \right) & \leq 0 \end{aligned}$$

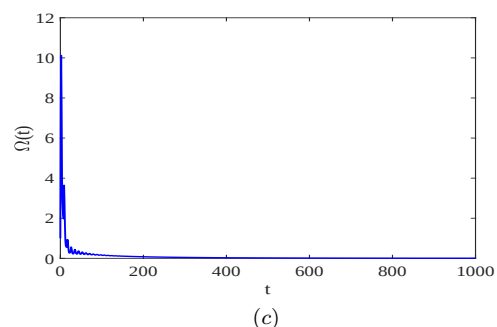
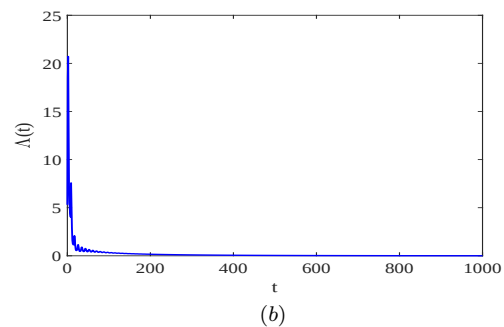
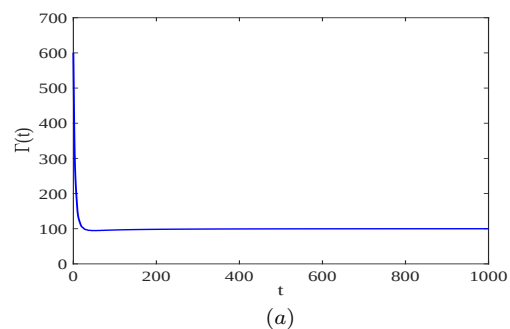
and

$$\begin{aligned} \left(\frac{Q_1(\Lambda)}{Q_1(\Lambda_2)} - \frac{J_1(\Gamma_2, \Omega_2) J_2(\Gamma, \Lambda)}{J_1(\Gamma, \Omega_2) J_2(\Gamma_2, \Lambda_2)} \right) & \times \left(\frac{J_1(\Gamma, \Omega_2) J_2(\Gamma_2, \Lambda_2)}{J_1(\Gamma_2, \Omega_2) J_2(\Gamma, \Lambda)} - 1 \right) \\ & \leq 0. \end{aligned}$$

Therefore, $\frac{dV_3(t)}{dt} \leq 0$, and $\frac{dV_3(t)}{dt} = 0$ if and only if $\Gamma(t) = \Gamma_2$, $\Lambda(t) = \Lambda_2$, $\Omega(t) = \Omega_2$ and $\Psi(t) = \Psi_2$. From LaSalle's invariance principle [25], E_2 is globally asymptotically stable when $R_1 > 1$.

VI. NUMERICAL SIMULATIONS

In model (1), $N(\Gamma) = \lambda - d\Gamma(t)$, $J_1(\Gamma, \Omega) = \frac{\beta_1 \Gamma(t) \Omega(t)}{1 + \alpha_1 \Omega(t)}$, $J_2(\Gamma, \Lambda) = \frac{\beta_2 \Gamma(t) \Lambda(t)}{1 + \alpha_2 \Lambda(t)}$ and $Q_i(\xi) = \xi$ ($i = 1, 2, 3$). It can easily verify that (H_1) – (H_6) hold. Taking $\lambda = 10$, $d = 0.1$, $\alpha_1 = \alpha_2 = 0.02$, $\delta_1 = \delta_2 = 0.01$, $\mu_1 = 0.5$, $\omega = 0.04$, $\mu_2 = 6$ and $\kappa = 2.9$, choose $\beta_1, \beta_2, \mu_3, \gamma, \varphi$ as free parameter.



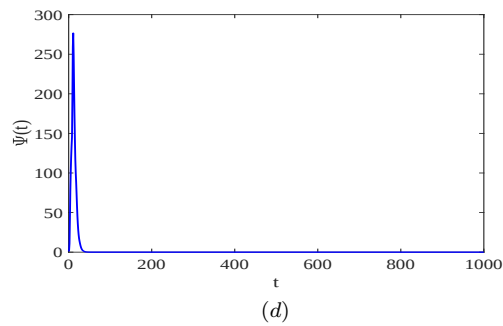


Fig.1. Taking $\beta_1 = 0.001$, $\beta_2 = 0.01$, $\mu_3 = 0.3$, $\gamma = 0.1$, $\varphi = 0.01$, $\tau_1 = 8$ and $\tau_2 = 0.1$. $R_0 = 0.9677 < 1$ and $E_0 = (10, 0, 0, 0)$ is globally asymptotically stable.

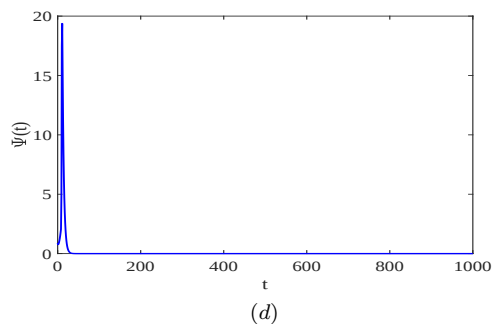
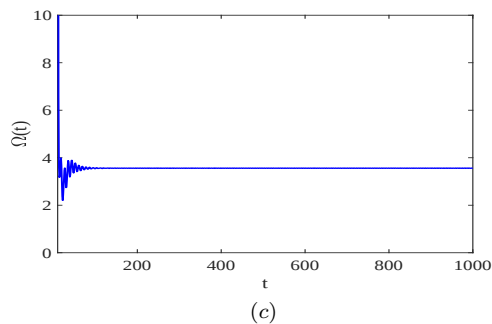
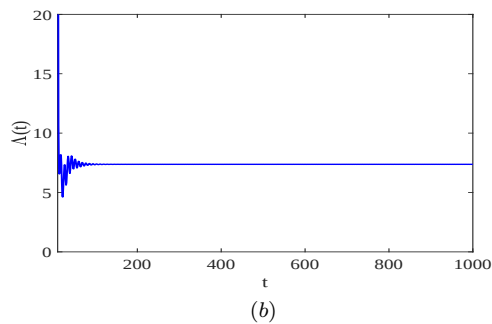
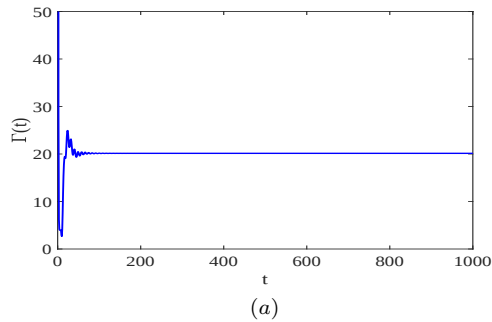


Fig.2. Taking $\beta_1 = 0.1$, $\beta_2 = 0.01$, $\mu_3 = 0.3$, $\gamma = 0.01$, $\varphi = 0.001$, $\tau_1 = 8$ and $\tau_2 = 0.1$. $R_0 = 5.3804 > 1$, $R_1 = 0.2212 < 1$ and $E_1 = (20.1388, 7.3721, 3.5596, 0)$ is globally asymptotically stable.

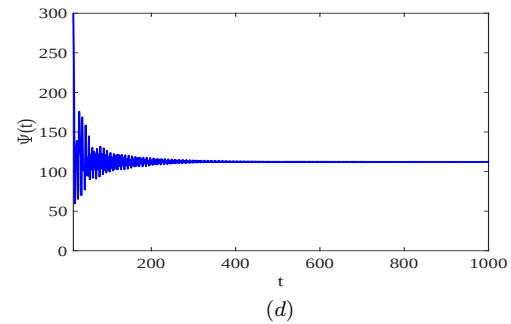
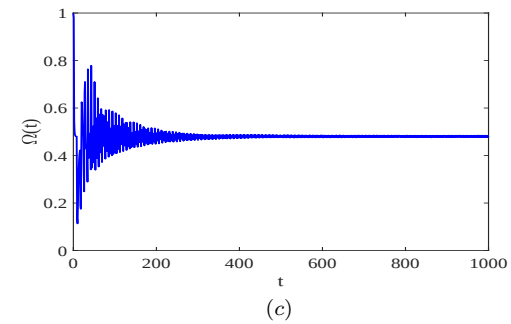
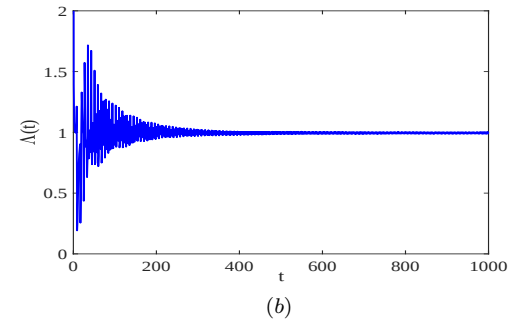
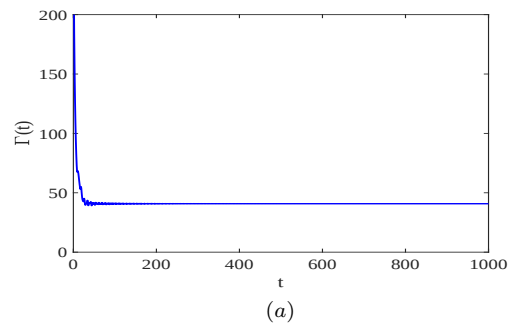


Fig.3. Taking $\beta_1 = 0.1$, $\beta_2 = 0.1$, $\mu_3 = 1.2$, $\gamma = 1.5$, $\varphi = 0.3$, $\tau_1 = 8$ and $\tau_2 = 0.1$. $R_0 = 13.6884 > 1$, $R_1 = 5.4766 > 1$ and $E_2 = (40.6732, 1, 0.4829, 111.9140)$ is globally asymptotically stable.

VII. DISCUSSION

This study explored the global dynamics of delayed HIV model incorporating CTL impairment, intracellular delay τ_1 , virus replication delay τ_2 and two transmission mechanisms are involved, namely virus-to-cell infection and cell-to-cell transmission. Under conditions (H_1) - (H_6) , this model allows for general target-cell dynamics $N(\Gamma)$ which containing $J_1(\Gamma, \Omega)$ and $J_2(\Gamma, \Lambda)$, discrete delays and state-dependent removal functions $Q_i (i = 1, 2, 3)$.

By the analysis, it is obtained that when $R_0 \leq 1$, E_0 is globally asymptotically stable. When $R_1 \leq 1 < R_0$, E_1 is globally asymptotically stable. As respect to the analysis of E_2 , when $R_1 > 1$, E_2 is globally asymptotically

stable, which implies susceptible cells, infected cells, free virus and CTL immune response coexist in vivo. The global stability of the three equilibria has been proved by constructing suitable Lyapunov functions and applying LaSalle's invariance principle. Our findings indicate that during viral infection, CTL dysfunction triggers a cascade of immunological events, a reduction in CTL cell count directly correlates with an elevation in viral load, establishing a critical immunological threshold for disease progression.

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