

Viral dynamics of a delayed HIV-1 infection model with both virus-to-cell and cell-to-cell transmissions, and CTL immune response delay.

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1. Introduction

Over the recent years, great efforts have been paid in mathematical modeling of within-host virus dynamics. Mathematical models and their analysis are helpful in understanding the dynamical behavior of many human viruses such as HIV, HTLV-I and HBV (e.g., [2, 3, 4, 5, 6, 8]). Recently, it has been reported that the uninfected cells can also become infected because of direct contact with infected cells. The viral infection model with cell-to-cell transmission and distributed time delay have been proposed in [2, 3, 6, 7]. They observed that the basic reproduction number of their model might be underevaluated if either cell-to-cell spread or virus-to-cell infection is neglected.

Note that the immune response after viral infection is common and is necessary for eliminating or controlling the disease. In most virus infections, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking virus-infected cell. Many existing mathematical models for HIV infection with CTLs response are given by systems of ordinary differential equation (ODE) (see, e.g. [2, 4, 5, 6, 8]). However, time delays can not be ignored when modeling immune response, since antigenic stimulation generating CTLs may need a period of time, that is, the activation rate of CTL response at time t may depend on the population of antigen at a previous time [8]. Moreover, all the aforementioned works not take into account of the constant production rate of CTLs exported from thymus. This consideration of export rate of new CTLs from thymus is considered in [4, 5] and is ignored by many authors.

Motivated by the works in [4, 7], in the present paper, we are concerned by the effect of both virus-to-cell and cell-to-cell transmissions with intracellular delays, and immune response activation delay on the global dynamics of HIV-1 infection model. We consider a within-host viral infection model with both virus-to-cell and cell-to-cell transmissions, immune response and four distributed delays, in which the first, second and fourth delay respectively describes the intracellular latency for virus-to-cell infection, the intracellular latency for the cell-to-cell infection and the time period that viruses penetrated into cells and infected cells release new virions [7], and the third delay describes the activation delay of CTLs cells ([8]). The rest of the paper is organized as follows. In Section 2, the mathematical model is constructed, the preliminaries including the positivity and boundedness of solutions are introduced, the existence of an infection-free equilibrium and its global stability are obtained, the existence of a chronic infection equilibrium and the persistence of infection are also obtained. In section 3, numerical simulations for several cases of the main model are presented. Section 4 concludes the paper.

2. The model formulation

The compartmental model includes the concentrations of healthy target cells $T(t)$ which susceptible to infection, infected cells $T_i(t)$ that produces viruses, cytotoxic T lym-

phocytes (CTLs) cells $T_c(t)$ which are responsible of the destruction of infected cells and viruses $V(t)$. Let β_1 be the virus-to-cell infection rate, β_2 be the cell-to-cell infection rate, δ , μ_1 , α and c be death rates of healthy target cells, activated infected cells, cytotoxic CTLs cells and viruses, respectively. Let b be the production rate of healthy target cells, λ be the production rate of CTLs cells export from thymus, a be the proliferation rate of CTLs cells. Infected cells are eliminated by CTLs cells at a rate q , which represent the lytic activity of CTLs cells. $e^{-\mu_1 s_1}$ is the survival rate of cells that are infected by viruses at time t and become activated s_1 time later with a probability distribution $f_1(s_1)$. Then $\int_0^\infty \beta_1 T(t-s_1)V(t-s_1)f_1(s_1)e^{-\mu_1 s_1}ds_1$ describes the newly activated infected target cells which are infected by free viruses s_1 time ago [7]. Similarly, $\int_0^\infty \beta_2 T(t-s_2)T_i(t-s_2)f_2(s_2)e^{-\mu_1 s_2}ds_2$ represents the newly activated infected target cells which are infected by infected cells s_2 time ago [7]. $e^{-\mu_2 s_3}$ is the survival rate of CTLs cells that are activated at time t , and become cytotoxic s_3 time later with a probability distribution $f_3(s_3)$. Then, $\int_0^\infty aT_i(t-s_3)T_c(t-s_3)f_3(s_3)e^{-\mu_2 s_3}ds_3$ represents the newly CTLs cells proliferated at time t [8]. Let s_4 be the random variable that is the time between viral RNA transcript and viral release and maturation with a probability distribution $f_4(s_4)$. Then, $\int_0^\infty kT_i(t-s_4)f_4(s_4)e^{-\mu_3 s_4}ds_4$ describes the mature viral particles produced at time t [7]. k is the average number of viruses that bud out from an infected cell and $e^{-\mu_3 s_4}$ is the survival rates of cells that start budding from activated infected cells at time t and become free mature viruses s_4 time later. Note that s_1, s_2, s_3 and s_4 are all integration variables, without loss of generality, they all will be represented by s . The model is given as follows :

$$\left\{ \begin{array}{l} \frac{dT(t)}{dt} = b - \delta T - \beta_1 TV - \beta_2 TT_i \\ \frac{dT_i(t)}{dt} = \int_0^\infty \beta_1 T(t-s)V(t-s)f_1(s)e^{-\mu_1 s}ds \\ \quad + \int_0^\infty \beta_2 T(t-s)T_i(t-s)f_2(s)e^{-\mu_1 s}ds - \mu_1 T_i - qT_iT_c \\ \frac{dT_c(t)}{dt} = \lambda + a \int_0^\infty T_i(t-s)T_c(t-s)f_3(s)e^{-\mu_2 s}ds - \alpha T_c \\ \frac{dV(t)}{dt} = k \int_0^\infty T_i(t-s)f_4(s)e^{-\mu_3 s}ds - cV, \end{array} \right. \quad (1)$$

$f_i(\nu) : [0, \infty) \rightarrow [0, \infty)$ are probability distributions with compact support, $f_i(\nu) \geq 0$, and $\int_0^\infty f_i(\nu)d\nu = 1$, $i = 1, \dots, 4$.

From the modeling perspective, the model (1) extends the basic model developed in [4] by : (i) incorporating the cell-to-cell transmission, (ii) intracellular delays and (iii) immune activation delay. Together with this latter improvement (iii), the incorporation

of a constant production rate of CTLs export from thymus in our model also extend the works in [2, 6, 8]. It is also noticeable that, our model extends the models developed in [3, 7] by including CTL response immune delay.

2.1. Preliminaries

Define the Banach space of fading memory type (see [3, 7])
 $\mathcal{C} = \{ \phi \in C((-\infty, 0] | \phi(\theta) e^{\mu\theta} \text{ is continuous for } \theta \in (-\infty, 0] \text{ and } \|\phi\| < \infty \}$ where μ is positive constant and the norm $\|\phi\| = \sup_{\theta \leq 0} |\phi(\theta)| e^{\mu\theta}$. The nonnegative cone of \mathcal{C} is defined by $\mathcal{C}_+ = \mathcal{C}((-\infty, 0], \mathbb{R}_+)$. For $\phi \in \mathcal{C}$, Let $\phi_t(\theta) = \phi(t + \theta)$, $\theta \in (-\infty, 0]$. We consider solutions (T, T_i, T_c, V) of system (1) with initial conditions

$$(T(0), T_i(0), T_c(0), V(0)) \in X := \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+. \quad (2)$$

By the standard theory of functional differential equations, we can obtain the existence of solutions for $t > 0$. Let $\eta_i = \int_0^\infty e^{-\mu_1 s} f_i(s) ds$, $i = 1, 2$, $\eta_3 = \int_0^\infty f_3(s) e^{-\mu_3 s} ds$, $\eta_4 = \int_0^\infty f_4(s) e^{-\mu_4 s} ds$.

Theorem 2.1 *Solutions of system (1) with initial conditions (2) are positive and ultimately uniformly bounded for $t > 0$.*

Proof 2.1 *The proof of Theorem 2.1 is given in Appendix A.* □

Theorem 2.1 implies that omega limit sets of system(1) are contained in the following bounded feasible region :

$$\Omega = \left\{ (T, T_i, T_c, V) \in \mathcal{C}_+^4 : \|T_s\| \leq \frac{b}{\delta}, \|T_i\| \leq M_1, \frac{\lambda}{\alpha} \leq T_c \leq \frac{a}{q} M_3, \|V\| \leq M_2 \right\}.$$

It can be verified that the region Ω is positively invariant with respect (1) and the system is well posed.

2.2. The infection-free equilibrium and its stability

System (1) has an infection-free equilibrium $E_0 = (\frac{b}{\delta}, 0, \frac{\lambda}{\alpha}, 0)$. We defined the basic reproduction number as follows :

$$\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02} = \frac{k \beta_1 b \eta_1 \eta_4}{c \delta \left(\mu_1 + \frac{q\lambda}{\alpha} \right)} + \frac{\beta_2 b \eta_2}{\delta \left(\mu_1 + \frac{q\lambda}{\alpha} \right)},$$

which represents the average number of secondary infections. In fact, $\frac{k \beta_1 b \eta_1 \eta_4}{c \delta \left(\mu_1 + \frac{q\lambda}{\alpha} \right)}$ is the average number of secondary viruses caused by a virus, that is the basic reproduction number corresponding to virus-to-cell infection mode, while $\frac{\beta_2 b \eta_2}{\delta \left(\mu_1 + \frac{q\lambda}{\alpha} \right)}$ is the average number of secondary infected cells that caused by an infected cell, that is the basic reproduction number corresponding to cell-to-cell infection mode. The factors have the biological interpretations as follows :

- $\frac{b\beta_1\eta_1}{\delta}$ is the number of new infections caused by a virus in target susceptible cells ;
- $\frac{q\lambda}{\alpha}$ is the rate at which infected cells are eliminated by the CTLs response ;
- $\frac{1}{\mu_1 + \frac{q\lambda}{\alpha}}$ is the average time that an infectious cell survives ;
- $k\eta_4$ is the rate at which infected cells bud into viruses ;
- $\frac{1}{c}$ is gives the average life-span of a virus ;
- $\frac{b\beta_2\eta_2}{\mu_1 + \frac{q\lambda}{\alpha}}$ represents the number of new infections caused by an infected cell in target susceptible cells.

The result below follows is straightforward.

Theorem 2.2 *The infection-free equilibrium E_0 of system (1) is locally asymptotically stable in the feasible region Ω whenever $\mathcal{R}_0 < 1$ and unstable otherwise.*

Proof 2.2 *The characteristic equation of system (1) at the equilibrium E_0 is*

$$(\nu + \delta)(\nu + \alpha) \left[(\nu + c) \left(\nu + \mu_1 + \frac{q\lambda}{\alpha} - \frac{b\beta_2\bar{\eta}_2}{\delta} \right) - \frac{kb\beta_1}{\delta} \bar{\eta}_1 \bar{\eta}_4 \right] = 0, \quad (3)$$

where $\bar{\eta}_i = \int_0^\infty e^{-(\mu_1+\nu)s} f_i(s) ds$, $i = 1, 2$, $\bar{\eta}_3 = \int_0^\infty e^{-(\mu_2+\nu)s} f_3(s) ds$ and $\bar{\eta}_4 = \int_0^\infty e^{-(\mu_3+\nu)s} f_4(s) ds$. We see that (3) has eigenvalues $\nu_1 = -\delta$, $\nu_2 = -\alpha$ and other eigenvalues are determined by $(\nu + c) \left(\nu + \mu_1 + \frac{q\lambda}{\alpha} - \frac{b\beta_2\bar{\eta}_2}{\delta} \right) - \frac{kb\beta_1}{\delta} \bar{\eta}_1 \bar{\eta}_4 = 0$, which equivalent to

$$\Psi(\nu) := \left(\frac{\nu}{\mu_1 + \frac{q\lambda}{\alpha}} + 1 \right) (\nu + c) - \mathcal{R}_0 \left(\frac{\bar{\eta}_2 \mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} \nu + c \frac{\bar{\eta}_2 \mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} + c \frac{\bar{\eta}_1 \bar{\eta}_4 \mathcal{R}_{01}}{\eta_1 \eta_4 \mathcal{R}_0} \right) = 0. \quad (4)$$

Thus, $\Psi(0) = c(1 - \mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$. Note that $\bar{\eta}_1 \leq \int_0^\infty f_1(s) ds = 1$, $i = 1, 2, 3, 4$. Then, we have $\Psi(\nu) \geq \left(\frac{\nu}{\mu_1 + \frac{q\lambda}{\alpha}} + 1 \right) (\nu + c) - \mathcal{R}_0 \left(\frac{\mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} \nu + c \frac{\mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} + c \frac{\mathcal{R}_{01}}{\eta_1 \eta_4 \mathcal{R}_0} \right) \rightarrow +\infty$ as $\nu \rightarrow +\infty$. This yields that equation (4) has at least one positive root. Therefore, the infection-free equilibrium E_0 is unstable if $\mathcal{R}_0 > 1$. \square

Biologically speaking, Theorem 2.2 implies that infection can be eliminated if the initial sizes of cells are in the basin of attraction of the infection-free equilibrium. Thus, the infection can be effectively controlled if $\mathcal{R}_0 < 1$. One can remark that \mathcal{R}_0 depends on λ and is a decreasing function of this rate. Hence, the constant rate λ could be an important control parameter in order to reduce \mathcal{R}_0 to a value less than unity. To ensure that the effective control of the infection is independent of the initial size of the cells, a global stability result must be established for the infection-free equilibrium.

Theorem 2.3 *If $\mathcal{R}_0 \leq 1$, then the infection-free equilibrium E_0 of system (1) is globally asymptotically stable in Ω .*

Proof 2.3 *The proof of Theorem 2.3 is given in Appendix B.* \square

2.3. The chronic infection equilibrium and persistence of infection

In this section, we will show that there exists a chronic infection equilibrium and the model (1) is persistent when $\mathcal{R}_0 > 1$. The infection is endemic if the infected cells persist above a certain positive level.

Denote by $E^* = (T^*, T_i^*, T_c^*, V^*)$ the chronic infection equilibrium of system (1). Then

$$T^* = \frac{b}{\delta + \left(\beta_1 + \frac{\beta_2 c}{k\eta_4}\right) V^*}, T_i^* = \frac{cV^*}{k\eta_4}, T_c^* = \frac{kb\beta_1\eta_1\eta_4 + b\beta_2\eta_2c - c\mu_1\delta - c\mu_1\left(\beta_1 + \frac{\beta_2 c}{k\eta_4}\right) V^*}{qc\left(\delta + \beta_1 V^* + \frac{\beta_2 c}{k\eta_4} V^*\right)}, \quad (5)$$

where V^* is a positive root of $\lambda + a\eta_3 T_i^* T_c^* - \alpha T_c^* = 0$ (*). After expansion and substitution of T^*, T_i^*, T_c^* by their expressions, Eq. (*) is equivalent to polynomial $P(V) = a_2 V^2 + a_1 V + a_0 = 0$, with the coefficients a_2, a_1 and a_0 given by

$$\begin{aligned} a_2 &= \frac{a\eta_3 c^2 \mu_1}{k\eta_4} \left(\beta_1 + \frac{\beta_2 c}{k\eta_4}\right), \\ a_1 &= \frac{a\eta_3 c^2 \mu_1 \delta}{k\eta_4} - a\eta_3 bc \left(\beta_1 \eta_1 + \frac{\beta_2 \eta_2 c}{k\eta_4}\right) - \left(\beta_1 + \frac{\beta_2 c}{k\eta_4}\right) (\mu_1 c\alpha + q\lambda c), \\ a_0 &= c\delta\alpha \left(\mu_1 + \frac{q\lambda}{\alpha}\right) (\mathcal{R}_0 - 1). \end{aligned} \quad (6)$$

Using $T_c \geq 0$ one shows that $V \leq V_{max}$, where $V_{max} = \frac{kb\beta_1\eta_1\eta_4 + b\beta_2\eta_2c - c\mu_1\delta}{c\mu_1\left(\beta_1 + \frac{\beta_2 c}{k\eta_4}\right)} = \frac{c\mu_1\delta(\mathcal{R}_0 - 1) + \mathcal{R}_0 \frac{c\delta q\lambda}{\alpha}}{c\mu_1\left(\beta_1 + \frac{\beta_2 c}{k\eta_4}\right)} > 0$, since $\mathcal{R}_0 > 1$. Using $P(0)$ and $P(V_{max})$ one shows that $P(0)P(V_{max}) = -\frac{a_0 b \lambda q (k\beta_1\eta_1\eta_4 + \beta_2\eta_2c)}{\mu_1} < 0$. Since P is continuous and strictly decreasing on interval $]0; V_{max}[$, the intermediate value theorem implies that P vanishes on $]0; V_{max}[$, which proves the existence and uniqueness of a positive chronic infection equilibrium when $\mathcal{R}_0 > 1$.

In the following, we will show that the model (1) is persistent when $\mathcal{R}_0 > 1$. To achieve our goal, we will apply Theorem 4.2 in [1]. To this end, let $S(t), t > 0$, be the solution semiflow of model (1), we can prove the following persistence result for (1).

Theorem 2.4 *For system (1), if $\mathcal{R}_0 > 1$, then the solution semiflow $S(t)$ is uniformly persistent; that is, there exists a $\sigma > 0$ such that any solution of (1) satisfies*

$$\liminf_{t \rightarrow \infty} T(t) \geq \sigma, \quad \liminf_{t \rightarrow \infty} T_i(t) \geq \sigma, \quad \liminf_{t \rightarrow \infty} T_c(t) \geq \sigma, \quad \liminf_{t \rightarrow \infty} V(t) \geq \sigma.$$

Proof 2.4 *The proof of Theorem 2.4 is given in Appendix C.* \square

3. Numerical simulations

In this section, we perform numerical simulations for the model (1) with particular distribution functions $f_i(s)$, $i = 1, 2, 3, 4$ as : $f_1(s) = f_2(s) = \delta(s - s_1)$, $f_3(s) = \delta(s - s_3)$ and $f_4(s) = \delta(s - s_4)$, where $\delta(\cdot)$ is the dirac delta function, s_i , $i = 1, 2, 3, 4$ are positive constants. Then, we can see that $\eta_1 = \eta_2 = e^{-\mu_1 s_1}$, $\eta_3 = e^{-\mu_2 s_3}$ and $\eta_4 = e^{-\mu_3 s_4}$. We examine the behavior of the infected steady state E^* using data sets that are commonly used in the literature [4, 6, 7]. Values of parameters are defined as : $b = 10$, $\delta = 0.01$, $\beta_1 = 2e - 6$, $\beta_2 = 3e - 4$, $\mu_1 = 0.1$, $a = 3e - 2$, $q = 2e - 4$, $k = 100$, $\alpha = 0.02$, $c = 3.2$, $\lambda = 1$, $\mu_2 = 0.5$ and $\mu_3 = 0.1$. By simple computing, the persistence of the infection when $\mathcal{R}_0 > 1$ as demonstrated in Theorem 2.4 is numerically shown on Figure 1.

3.1. Effect of CTLs constant production rate

In order to investigate the effect of CTLs production rate, we carry out some numerical simulations to show the contribution of CTLs constant production rate during the whole infection. We set the production rate λ as 0.5, 1, 1.5, 2. We choose $s_1 = s_2 = 3$, $s_3 = 8$ and $s_4 = 2.5$. From the four figures of Figure 1, we can observe that uninfected and CTLs cells reach a higher peak level as λ increases. While, the peak level of infected cells and viruses decreases as λ increases. If we interpret the constant rate $\lambda > 0$ as an inflow of antiviral drugs, one can observe from Figure 1 that the entry of antiviral drugs into the host is important as a control parameter in order to reduce the viral load.

3.2. Effect of intracellular delays and immune response delay on the stability of steady states

In this case, we choose $s_4 = 2.5$ and without loss of generality, we let $S = s_1 = s_2$. Figure 2 plots the chronic infection equilibrium E^* when S varies and $s_3 = 5$ is fixed (left column), and when s_3 is varied and $S = 3$ is fixed (right column). This figure demonstrates that the chronic equilibrium destabilizes as S and s_3 decreases. Therefore, an increase in the intracellular delay S or the immune response delay can stabilize the infected steady state E^* . In the instabilities cases, one observe oscillation patterns where a larger viral peak is generated before the viral load and the infected cells dynamics are "trapped" by the invariant plan $T_i = V = 0$. These transient viral peaks strongly resemble viral load blips clinically observed in HIV-infected patients, and they provide an alternative interpretation of these phenomena. This result is consistent with the study in [4].

4. Conclusion

In this paper, we have investigated the dynamical properties of a delayed HIV-1 infection model with both virus-to-cell and cell-to-cell transmissions, and CTL immune response delay. This model extends some previous models and also take into account of a rate of CTLs cells exported from thymus. We have derived the basic reproductive number, \mathcal{R}_0 , which depends on $\frac{\beta\lambda}{\alpha}$ (it is the rate at which infected cells with virus are eliminated by the CTLs response), that can contribute to the control of viral infection. When the basic reproductive number \mathcal{R}_0 is less than unity, we have proved the global asymptotic stability of the disease free equilibrium E_0 . When the basic reproductive number \mathcal{R}_0 is greater than unity, the persistence of the chronic infection equilibrium E^* has been obtained. It is challenging to analyze model (1) for the joint effect of four delays theoretically. So, numerical simulations were used to further investigate the infected steady state and the existence of the Hopf bifurcation when $s_i > 0$, $i = 1, 2, 3, 4$. Notice that the existence of the Hopf bifurcation contributes at the emergence of viral load blips which is clinically observed in HIV-infected patients. It was found that the intracellular delays and immune response delay can stabilize and/or destabilize the chronic infection equilibrium (see Figure 2).

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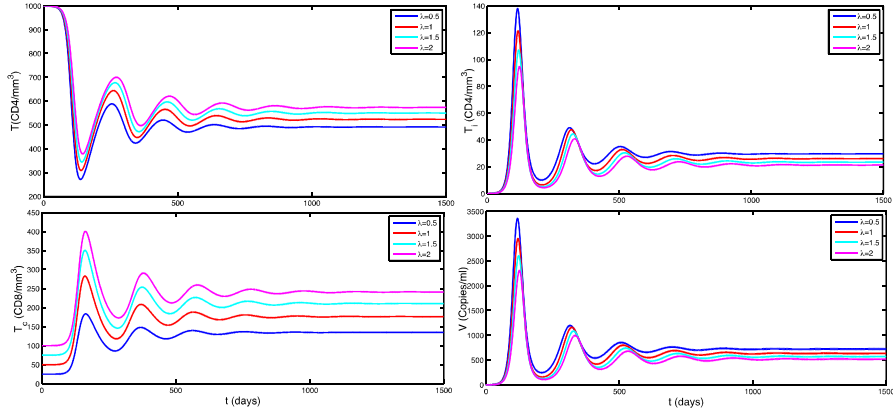


Figure 1 – Simulation results showing the effect of λ on the dynamics of the model with $s_1 = s_2 = 3$, $s_3 = 8$ and $s_4 = 2.5$.

Appendix A : Proof of Theorem 2.1

Let $m(t) = \delta + \beta_1 V(t) + \beta_2 T_i(t)$ and $d(t) = \mu_1 + qT_c(t)$. Let $r(t)$ be the sum of the two integral terms in the second equation of system (1) and $n(t)$ be the integral term in the fourth equation of system (1). From the first equation in (1), we then have $T(t) = T(0)e^{-\int_0^t m(\xi)d\xi} + \int_0^t e^{-\int_\xi^t m(\theta)d\theta} b d\xi > 0$ for $t \geq 0$. From the third equation in (1), it follows that $\liminf_{t \rightarrow \infty} T_c(t) \geq \frac{\lambda}{\alpha} > 0$. From the second and fourth equation in (1), we then have $T_i(t) = T_i(0)e^{-\int_0^t d(\xi)d\xi} + \int_0^t r(\xi)e^{-\int_\xi^t d(\theta)d\theta} d\xi$ and $V(t) = \left[V(0) + \int_0^t n(\xi)e^{c\xi} d\xi \right] e^{-ct}$, which yield that $T_i(t) > 0$, $V(t) > 0$ for small $t > 0$. Now we prove that $T_i(t) > 0$ and $V(t) > 0$ for all $t > 0$. Otherwise, there exists $t_1 > 0$ such that $\min\{T_i(t_1), V(t_1)\} = 0$. If $T_i(t_1) = 0$, $T_i(t) > 0$ for $0 \leq t < t_1$, and $V(t) > 0$ for $0 \leq t < t_1$, then we have $\frac{dT_i(t_1)}{dt} > 0$. This contradicts $T_i(t_1) = 0$ and $T_i(t) > 0$ for $0 \leq t < t_1$. If $V(t_1) = 0$, $V(t) > 0$ for $0 \leq t < t_1$, and $T_i(t) > 0$ for $0 \leq t < t_1$, then we obtain $\frac{dV(t_1)}{dt} > 0$, which is also a contradiction. Hence, $T_i(t) > 0$ and $V(t) > 0$ for all $t > 0$.

To prove boundedness, first by the positivity of solutions we have $\frac{dT(t)}{dt} < b - \delta T(t)$. It follows that $\lim_{t \rightarrow \infty} \sup T(t) \leq \frac{b}{\delta}$, implying $T_s(t)$ is bounded. Let $G_1(t) = \int_0^\infty f_1(s)e^{-\mu_1 s} T(t-s)ds + \int_0^\infty f_2(s)e^{-\mu_1 s} T(t-s)ds + T_i(t)$. Since $T(t)$ is bounded and $\int_0^\infty f(u)du$ is convergent, the integral in $G(t)$ is well defined and differentiable

with respect to t . Moreover, when taking the time derivative of $G(t)$, the order of the differentiation and integration can be switched. Thus, we have

$$\begin{aligned}\dot{G}_1(t) &= b(\eta_1 + \eta_2) - \delta \int_0^\infty f_1(s)e^{-\mu_1 s}T(t-s)ds - \delta \int_0^\infty f_2(s)e^{-\mu_1 s}T(t-s)ds \\ &\quad - \mu_1 T_i - qT_i T_c, \\ &\leq b(\eta_1 + \eta_2) - \delta \int_0^\infty f_1(s)e^{-\mu_1 s}T(t-s)ds - \delta \int_0^\infty f_2(s)e^{-\mu_1 s}T(t-s)ds \\ &\quad - \left(\mu_1 + \frac{q\lambda}{\alpha}\right)T_i(t) \leq b(\eta_1 + \eta_2) - d_1 G_1(t),\end{aligned}$$

where $d_1 = \min\left\{\delta, \mu_1 + \frac{q\lambda}{\alpha}\right\}$. Therefore, $\lim_{t \rightarrow \infty} \sup G_1(t) \leq \frac{b(\eta_1 + \eta_2)}{d_1} := M_1$, implying that $\lim_{t \rightarrow \infty} \sup T_i(t) \leq M_1$. Then, from the fourth equation of system (1), we have

$$\dot{V}(t) = k \int_0^\infty e^{-\mu_4 s} f_4(s)T_i(t-s)ds - cV \leq kM_1\eta_4 - cV.$$

Thus, $\lim_{t \rightarrow \infty} \sup V(t) \leq \frac{kM_1\eta_4}{c} := M_2$. Now determine the upper bound of $T_c(t)$. Let $G_2(t) = \int_0^\infty f_3(s)e^{-\mu_3 s}T_i(t-s)ds + \frac{q}{a}T_c(t)$. Thus, we have

$$\begin{aligned}\dot{G}_2(t) &= \int_0^\infty f_3(s)e^{-\mu_3 s}r(t-s)ds - \mu_1 \int_0^\infty f_3(s)e^{-\mu_3 s}T_i(t-s)ds + \frac{q\lambda}{a} - \alpha \frac{q}{a}T_c(t), \\ &\leq \frac{b\eta_3}{\delta}(\beta_1\eta_1 M_2 + \beta_2\eta_2 M_1) + \frac{q\lambda}{a} - \mu_1 \int_0^\infty f_3(s)e^{-\mu_3 s}T_i(t-s)ds - \alpha \frac{q}{a}T_c(t), \\ &\leq d_2 - d_3 G_2(t),\end{aligned}$$

where $d_2 = \frac{b\eta_3}{\delta}(\beta_1\eta_1 M_2 + \beta_2\eta_2 M_1) + \frac{q\lambda}{a}$ and $d_3 = \{\alpha, \mu_1\}$. Hence, $\lim_{t \rightarrow \infty} \sup G_2(t) \leq \frac{d_2}{d_3} := M_3$, implying that $\lim_{t \rightarrow \infty} \sup T_c(t) \leq \frac{a}{q}M_3$. Thus, $T(t)$, $T_i(t)$, $T_c(t)$ and $V(t)$ are uniformly bounded. \square

Appendix B : Proof of Theorem 2.3

We define a Lyapunov function as follows :

$$\begin{aligned}L(t) &= T_i + \frac{b\beta_1\eta_1}{c\delta}V + \int_0^\infty f_1(s)e^{-\mu_1 s} \int_{t-s}^t \beta_1 T(\tau)V(\tau)d\tau ds + \int_0^\infty f_2(s)e^{-\mu_1 s} \\ &\quad \int_{t-s}^t \beta_2 T(\tau)T_i(\tau)d\tau ds + \frac{b\beta_1\eta_1}{c\delta} \int_0^\infty f_4(s)e^{-\mu_3 s} \int_{t-s}^t kT_i(\tau)d\tau ds.\end{aligned}$$

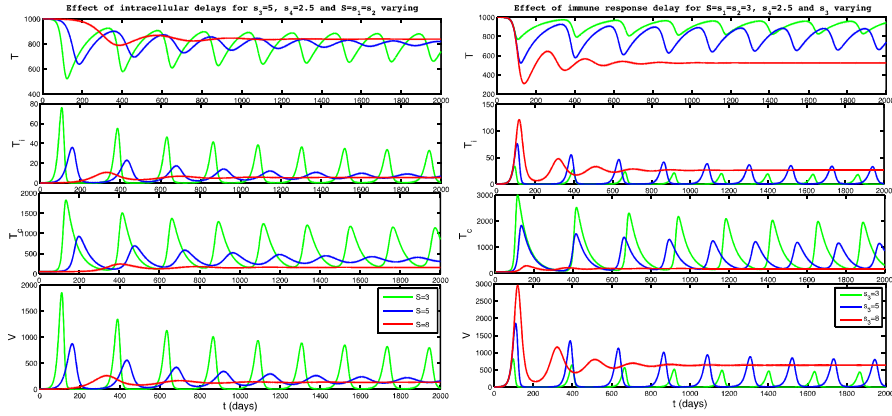


Figure 2 – Simulation results showing the effect of S and s_3 on the dynamics of the model. Then the time derivative of $L(t)$ along solutions of system (1) satisfies

$$\frac{dL(t)}{dt} = \beta_1 \eta_1 T V + \beta_2 \eta_2 T T_i + \frac{k b \beta_1 \eta_1 \eta_4}{c \delta} T_i - \mu_1 T_i - q T_i T_c - \frac{b \beta_1 \eta_1}{\delta} V.$$

Since $T \leq \frac{b}{\delta}$ and $T_c \geq \frac{\lambda}{\alpha}$, we have

$$\frac{dL(t)}{dt} \leq \left[\frac{b \beta_2 \eta_2}{\delta} + \frac{k b \beta_1 \eta_1 \eta_4}{c \delta} - \left(\mu_1 + \frac{q \lambda}{\alpha} \right) \right] T_i = \left(\mu_1 + \frac{q \lambda}{\alpha} \right) (\mathcal{R}_0 - 1) T_i.$$

$\frac{dL(t)}{dt} \leq 0$ whenever $\mathcal{R}_0 \leq 1$. Moreover, $\frac{dL(t)}{dt} = 0 \Leftrightarrow T_i = V = 0$ or $T = \frac{b}{\delta}, T_c = \frac{\lambda}{\alpha}$ and $\mathcal{R}_0 = 1$. Thus, the largest invariant set \mathcal{H} such as $\mathcal{H} \subset \left\{ (T, T_i, T_c, V) \in \mathbb{R}_+^4 / \frac{dL(t)}{dt} = 0 \right\}$ is the singleton $\{E_0\}$. By LaSalle's Principle, E_0 is globally asymptotically stable in Ω , completing the proof.

Appendix C : Proof of Theorem 2.4

Let $\mathcal{D}^0 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X : \phi_2(\theta) > 0 \text{ or } \phi_4(\theta) > 0, \text{ for all } \theta \in (-\infty, \theta]\}$ and $\mathcal{D}_0 = X \setminus \mathcal{D}^0$. We just need to verify the conditions (i) – (vii) of Theorem 4.2 in [1]. It is easy to verify that $X = \mathcal{D}^0 \cup \mathcal{D}_0$, $\mathcal{D}^0 \cap \mathcal{D}_0 = \emptyset$, and $S(t)\mathcal{D}^0 \subset \mathcal{D}^0$, $S(t)\mathcal{D}_0 \subset \mathcal{D}_0$ for all $t > 0$. Furthermore, from Theorem 2.1, we know that $S(t)$ is point dissipative in X . Notice that the boundedness of each component does not depend on the initial condition (2). Thus, for any bounded set Y in X , the positive orbit $\gamma^+(Y) = \bigcup_{t>0} S(t)(Y)$ through $Y \subset X$ is bounded in X . In view of this property, $S(t)$ is asymptotically smooth, that is, for any nonempty bounded set $Y \subset X$ with $S(t)Y \subset Y$, there is a compact set $Y_0 \subset Y$

such that Y_0 attracts Y . Let A_0 be the global attractor of $S(t)$ restricted to \mathcal{D}_0 . We have $\mathcal{A} = \bigcup_{x \in A_0} w(x) = E_0$. $\{E_0\}$ is a compact and isolated invariant set. Thus, the covering is simply $\{E_0\}$, which is acyclic because no orbit connects E_0 to itself in \mathcal{D}_0 .

Next, we will verify that $W^s(E_0) \cap \mathcal{D}^0 = \emptyset$. To this end, we suppose the opposite, that is, there exists a solution $u_t \in \mathcal{D}^0$ such that $\lim_{t \rightarrow \infty} T(t) = \frac{b}{\delta}$, $\lim_{t \rightarrow \infty} T_i(t) = 0$, $\lim_{t \rightarrow \infty} T_c(t) = \frac{\lambda}{\alpha}$, $\lim_{t \rightarrow \infty} V(t) = 0$. Note that $\mathcal{R}_0 > 1$ is equivalent to $\frac{b}{\delta} \left[\frac{k\beta_1\eta_1\eta_4}{c} + \beta_2\eta_2 \right] > \mu_1 + \frac{q\lambda}{\alpha}$. For a small enough $\epsilon > 0$, we have $\left(\frac{b}{\delta} - \epsilon \right) \left[\frac{k\beta_1\eta_1\eta_4}{c} + \beta_2\eta_2 \right] > \mu_1 + \frac{q\lambda}{\alpha}$ ($\star\star$). For this ϵ , there exists a $\tau_0 > 0$ such that $T(t) > \frac{b}{\delta} - \epsilon$ for all $t > \tau_0$. Truncating the integral of η_1 , η_2 and η_4 in ($\star\star$), there is another $\tau_1 > 0$ such that

$$\left(\frac{b}{\delta} - \epsilon \right) \left[\frac{k\beta_1\tilde{\eta}_1\tilde{\eta}_4}{c} + \beta_2\tilde{\eta}_2 \right] > \mu_1 + \frac{q\lambda}{\alpha}, \quad (7)$$

where $\tilde{\eta}_i = \int_0^{\tau_1} e^{-\mu_1 s} f_i(s) ds$, $i = 1, 2$, and $\tilde{\eta}_4 = \int_0^{\tau_1} f_4(s) e^{-\mu_3 s} ds$. Let $\tau_2 = \tau_0 + \tau_1$. Then, for $t \geq \tau_2$, we have

$$\begin{aligned} \frac{dT_i}{dt} &\geq \int_0^{\tau_1} \beta_1 T(t-s) V(t-s) f_1(s) e^{-\mu_1 s} ds + \int_0^{\tau_1} \beta_2 T(t-s) T_i(t-s) f_2(s) e^{-\mu_1 s} ds \\ &\quad - \left(\mu_1 + \frac{q\lambda}{\alpha} \right) T_i \\ &\geq \left(\frac{b}{\delta} - \epsilon \right) \left[\int_0^{\tau_1} \beta_1 V(t-s) f_1(s) e^{-\mu_1 s} ds + \int_0^{\tau_1} \beta_2 T_i(t-s) f_2(s) e^{-\mu_1 s} ds \right] - \left(\mu_1 + \frac{q\lambda}{\alpha} \right) T_i. \end{aligned}$$

This suggests the following comparison system for $(T_i(t), V(t))$:

$$\begin{cases} \dot{u}_1(t) = \left(\frac{b}{\delta} - \epsilon \right) \left[\int_0^{\tau_1} \beta_1 u_2(t-s) f_1(s) e^{-\mu_1 s} ds + \int_0^{\tau_1} \beta_2 u_1(t-s) f_2(s) e^{-\mu_1 s} ds \right] \\ \quad - \left(\mu_1 + \frac{q\lambda}{\alpha} \right) u_1(t), \\ \dot{u}_2(t) = k \int_0^{\tau_1} u_1(t-s) f_4(s) e^{-\mu_3 s} ds - c u_2(t), \quad \text{for } t \geq \tau_2. \end{cases} \quad (8)$$

Notice that this is a monotone system, and by the comparison theorem and the equations $\lim_{t \rightarrow \infty} T_i(t) = 0$ and $\lim_{t \rightarrow \infty} V(t) = 0$, one should have $\lim_{t \rightarrow \infty} (u_1(t), u_2(t)) = (0, 0)$. On the other hand, the two equations for $u_1(t)$ and $u_2(t)$ are in the same forms of the second and fourth equations in system (1). Repeating the same argument for proving the instability of E_0 in Theorem 2.2 and replacing the condition $\mathcal{R}_0 > 1$ by (7), we conclude that the characteristic equation of system (8) has a positive real eigenvalue, which is a contradiction to $\lim_{t \rightarrow \infty} (u_1(t), u_2(t)) = (0, 0)$. Thus, we have $W^s(E_0) \cap \mathcal{D}^0 = \emptyset$. By Theorem 4.2 in [1], we know that there exists a value $\sigma > 0$ such that $\lim_{t \rightarrow \infty} \inf d(S(t)\phi, \mathcal{D}_0) \geq \sigma$, $\forall \phi \in \mathcal{D}_0$, which means that each component of the solution with the initial condition (2) satisfies

$$\lim_{t \rightarrow \infty} \inf T(t) \geq \sigma, \quad \lim_{t \rightarrow \infty} \inf T_i(t) \geq \sigma, \quad \lim_{t \rightarrow \infty} \inf T_c(t) \geq \sigma, \quad \lim_{t \rightarrow \infty} \inf V(t) \geq \sigma.$$