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Research article

Note on a class of time-delay virus models with virus-to-cell infection, cell-to-cell transmission, CTL and antibody immune responses

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Abstract: This paper investigates the coexistence of equilibria and local and global asymptotic stability of a class of time-delay virus models involving virus-to-cell infection, cell-to-cell transmission, Cytotoxic T Lymphocytes (CTL), and antibody immune responses. These models typically exhibit five equilibria; however, the existing literature lacks comprehensive studies on the uniqueness and coexistence of these equilibria. Our study fills the gaps and rectifies the shortcomings or lack of rigor in certain prior research.

Keywords: virus-to-cell infection; cell-to-cell transmission; CTL and antibody immune responses; co-existence; stability analysis
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1. Introduction

Since the classic work on HIV dynamics was proposed by Perelson [1, 2], many scholars are investigating various pathways of viral infection, such as virus-to-cell infection [3, 4], and cell-to-cell transmission [5]. Additionally, some studies examine cytokine-enhanced viral infection [6–8]. As indicated by the above references, caspase-1-mediated pyroptosis is the primary pathway driving $CD4^+$ T cell death. Infected $CD4^+$ T cells that undergo death release inflammatory signals, attracting more uninfected $CD4^+$ T cells to die. Also, more and more work has focused on the two modes of viral infection (virus-to-cell infection and cell-to-cell transmission) and the two responses of human immunity (Cytotoxic T Lymphocyte (CTL) and antibody immunity) [9–11]. Wodarz [12] first considered two immune responses to establish a five-dimensional ODE model with bilinear

interaction. Subsequently, a large number of papers have developed models with rich dynamic behavior to study virus transmission and immune response, taking into account time delay [13, 14], saturation relationship [15–17], general functional relationship [18–20], or only considering virus-to-cell infection [21,22]. Lai and Zou [5] first proposed (possibly for the first time) two transmission modes of virus-cell and cell-to-cell infection and focused on the study of Hopf bifurcation. Subsequently, Wang et al. [23], Lin et al. [17], and Guo et al. [14] continued with a series of follow-up studies focusing on the global stability of equilibria. These models typically have five equilibria, and it is worth noting that accounting for time delay generally does not significantly change the dynamic behavior. Existing studies mainly focus on verifying the global asymptotic stability of equilibria; however, there are limitations in the following three key dimensions: (1) coexistence of the equilibria of the models is not discussed; (2) the models usually do not discuss the local asymptotic stability of each equilibrium; (3) the conditions for the global asymptotic stability of the equilibria are not rigorous.

To elucidate critical computational details, we conduct a re-examination of the time-delayed viral dynamics model originally formulated by Guo et al. [14], incorporating dual transmission pathways and two modes of immune responses for further investigation:

$$\begin{cases} \dfrac{dx(t)}{dt} = b - cx(t) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t), \\ \dfrac{dy(t)}{dt} = \beta_1 e^{-a_1\tau_1} x(t-\tau_1)v(t-\tau_1) + \beta_2 e^{-a_1\tau_1} x(t-\tau_1)y(t-\tau_1) - dy(t) - hy(t)w(t), \\ \dfrac{dv(t)}{dt} = ke^{-a_2\tau_2} y(t-\tau_2) - mv(t) - nv(t)z(t), \\ \dfrac{dw(t)}{dt} = ry(t)w(t) - sw(t), \\ \dfrac{dz(t)}{dt} = pv(t)z(t) - qz(t), \end{cases} \tag{1.1}$$

where $x(t)$, $y(t)$, $v(t)$, $w(t)$, and $z(t)$ denote concentrations of uninfected cells, infected cells, free virus particles, CTL, and B cells, respectively. Uninfected cells are produced at a constant rate b, and the rate of natural death is c. β_1 and β_2 denote the rate of infection transmission between uninfected cells and viral particles and cell-to-cell spread, respectively. d is the death rate of infected cells. m and q are the clearance rates of free virus and B cells. CTL expands at a rate of r and decays at s. The parameter h is the killing rate of CTL on productive infected cells. k and p represent the generation rate of virus and B cells, respectively. n determines the rate at which B cells neutralize free virus. The delay τ_1 denotes the duration of infection, while τ_2 represents the period of virus production. The terms $e^{-a_i\tau_i}(i = 1, 2)$ are the survival probabilities from time $t - \tau_i$ $(i = 1, 2)$ to t. All the parameters are positive constants. The five threshold conditions of model (1.1) are as follows:

$$\begin{aligned} \mathcal{R}_0 &= \frac{\beta_1 e^{-a_1\tau_1 - a_2\tau_2} bk}{cdm} + \frac{\beta_2 e^{-a_1\tau_1} b}{cd}, \ \mathcal{R}_1^w = \frac{r\left(b\beta_1 ke^{-a_1\tau_1 - a_2\tau_2} + b\beta_2 me^{-a_1\tau_1} - cdm\right)}{sd\left(\beta_1 ke^{-a_2\tau_2} + \beta_2 m\right)}, \\ \mathcal{R}_1^z &= \frac{pk\left(b\beta_1 ke^{-a_1\tau_1 - a_2\tau_2} + b\beta_2 me^{-a_1\tau_1} - cdm\right)}{mdq\left(\beta_1 k + \beta_2 me^{a_2\tau_2}\right)}, \ \mathcal{R}_2^z = \frac{ke^{-a_2\tau_2} sp}{qmr}, \\ \mathcal{R}_2^w &= \frac{re^{-a_1\tau_1}\left(bp\beta_2 - cdpe^{a_1\tau_1} - \beta_1 dqe^{a_1\tau_1} + L\right)}{2sdp\beta_2}, \end{aligned}$$

where $L = \sqrt{4b\beta_1\beta_2 de^{a_1\tau_1} pq + \left(-bp\beta_2 + cdpe^{a_1\tau_1} + \beta_1 dqe^{a_1\tau_1}\right)^2}$.

Obviously, the study results in [10, 16, 24] and others are similar to model (1.1). Moreover, for viral dynamic models that consider only one mode of transmission or one immune response, they are only special cases of the model (1.1). Our new main results and proofs will be presented in Section 2. The numerical simulations are presented in Section 3, while the conclusions are placed in Section 4.

2. Main result

The threshold values in literature [10, 14, 16] are not suitable for further discussion because their positivity cannot be guaranteed. We redefine the following four threshold conditions (the basic reproduction number $\mathcal{R}_1$, the CTL immune response reproduction number $\mathcal{R}_2$, the antibody immune response reproduction number $\mathcal{R}_3$, and two immune response reproduction numbers $\mathcal{R}_4$) to discuss the coexistence and local stability of the equilibria:

$$\begin{aligned} &\mathcal{R}_1 = \frac{\beta_1 bke^{-a_1\tau_1-a_2\tau_2} + \beta_2 bme^{-a_1\tau_1}}{cdm}, \qquad \mathcal{R}_2 = \frac{bre^{-a_1\tau_1}(\beta_1 ke^{-a_2\tau_2} + \beta_2 m)}{cdmr + \beta_2 dms + \beta_1 dske^{-a_2\tau_2}}, \\ &\mathcal{R}_3 = \frac{bpke^{-a_1\tau_1-a_2\tau_2}(\beta_1 ke^{-a_2\tau_2} + \beta_2 m)}{dm(\beta_2 qm + pcke^{-a_2\tau_2} + \beta_1 qke^{-a_2\tau_2})}, \ \ \mathcal{R}_4 = \min\{\mathcal{R}_4^z, \mathcal{R}_4^w\}, \end{aligned} \tag{2.1}$$

where $\mathcal{R}_4^z = \dfrac{spke^{-a_2\tau_2}}{qrm}$ and $\mathcal{R}_4^w = \dfrac{rbe^{-a_1\tau_1}(\beta_1 qr + \beta_2 sp)}{ds(\beta_1 qr + \beta_2 sp + cpr)}$. It is worth noting that $\mathcal{R}_2$, $\mathcal{R}_3$, and $\mathcal{R}_1$ have obvious relationships as below:

$$\mathcal{R}_2 = \frac{cmr}{cmr + \beta_2 ms + \beta_1 ske^{-a_2\tau_2}}\mathcal{R}_1 < \mathcal{R}_1, \ \ \mathcal{R}_3 = \frac{pcke^{-a_2\tau_2}}{\beta_2 mq + pcke^{-a_2\tau_2} + \beta_1 qke^{-a_2\tau_2}}\mathcal{R}_1 < \mathcal{R}_1.$$

2.1. Coexistence of equilibria

Referring to the results in [14] and doing further simplification, we have the following five equilibria of model (1.1):

(1) The infection-free equilibrium $E_0 = (x_0, y_0, v_0, w_0, z_0) = (\dfrac{b}{c}, 0, 0, 0, 0)$.

(2) The immunity-inactivated equilibrium $E_1 = (x_1, y_1, v_1, w_1, z_1)$, where $x_1 = \dfrac{dme^{a_1\tau_1}}{\beta_1 ke^{-a_2\tau_2} + \beta_2 m} = \dfrac{b}{c\mathcal{R}_1}$, $y_1 = \dfrac{cm(\mathcal{R}_1 - 1)}{\beta_1 ke^{-a_2\tau_2} + \beta_2 m}$, $v_1 = \dfrac{cke^{-a_2\tau_2}(\mathcal{R}_1 - 1)}{\beta_1 ke^{-a_2\tau_2} + \beta_2 m}$, $w_1 = 0$, $z_1 = 0$.

(3) The cell-mediated immunity-activated equilibrium $E_2 = (x_2, y_2, v_2, w_2, z_2)$, where $x_2 = \dfrac{brm}{\beta_1 ske^{-a_2\tau_2} + \beta_2 ms + cmr} = \dfrac{b\mathcal{R}_2}{c\mathcal{R}_1}$, $y_2 = \dfrac{s}{r}$, $v_2 = \dfrac{ske^{-a_2\tau_2}}{mr}$, $w_2 = \dfrac{d}{h}(\mathcal{R}_2 - 1)$, $z_2 = 0$.

(4) The humoral immunity-activated equilibrium $E_3 = (x_3, y_3, v_3, w_3, z_3)$, where $x_3 = \dfrac{bp}{cp + \beta_1 q + \beta_2 py_3}$, $y_3 = \dfrac{mq + nqz_3}{pke^{-a_2\tau_2}}$, $v_3 = \dfrac{q}{p}$, $w_3 = 0$ and z_3 is the positive real root of the following quadratic equation:

$$z_3^2 + \frac{(2\beta_2 qme^{a_2\tau_2} + pck + \beta_1 qk)\left(1 - \mathcal{R}_3^z\right)}{\beta_2 nqe^{a_2\tau_2}}z_3 + \frac{m(\beta_2 qme^{a_2\tau_2} + pck + \beta_1 qk)\,(1 - \mathcal{R}_3)}{\beta_2 n^2 qe^{a_2\tau_2}} = 0,$$

where

$$\mathcal{R}_3^z = \frac{\beta_2 bkpe^{-a_1\tau_1-a_2\tau_2}}{d(2\beta_2 qm + pcke^{-a_2\tau_2} + \beta_1 qke^{-a_2\tau_2})} = \frac{\beta_2 mbkpe^{-a_1\tau_1-a_2\tau_2}}{\beta_2 dqm^2 + dm(\beta_2 qm + pcke^{-a_2\tau_2} + \beta_1 qke^{-a_2\tau_2})} < \mathcal{R}_3.$$

Obviously, if $\mathcal{R}_3 > 1$, and the above quadratic equation has only one positive root. Otherwise, if $\mathcal{R}_3 \leq 1$, then $\mathcal{R}_3^z < 1$, and the equation has only negative roots or zero roots.

(5) The immunity-activated equilibrium $E_4 = (x_4, y_4, v_4, w_4, z_4)$, where $x_4 = \dfrac{bpr}{\beta_1 qr + \beta_2 ps + cpr}$, $y_4 = \dfrac{s}{r}$, $v_4 = \dfrac{q}{p}$, $w_4 = \dfrac{d}{h}(\mathcal{R}_4^w - 1)$, $z_4 = \dfrac{m}{n}(\mathcal{R}_4^z - 1)$.

Based on the above statements, we can directly conclude that the four thresholds $\mathcal{R}_1 > 1$, $\mathcal{R}_2 > 1$, $\mathcal{R}_3 > 1$, and $\mathcal{R}_4 > 1$ can determine the existence of the four equilibria E_1, E_2, E_3, and E_4 in model (1.1). Then, we give the complete results on the coexistence of the equilibria neglected by Guo et al. [14].

Proposition 1. *Firstly, the model (1.1) always has the equilibrium E_0, then,*
(1) If $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_4 \leq 1$, model (1.1) has only the equilibrium E_0;
(2) If $\mathcal{R}_1 \leq 1$ and $\mathcal{R}_4 > 1$, two equilibria, E_0 and E_4 coexist;
(3) If $\mathcal{R}_1 > 1$, $\mathcal{R}_2 \leq 1$, $\mathcal{R}_3 \leq 1$, and $\mathcal{R}_4 \leq 1$, two equilibria E_0 and E_1 coexist;
(4) If $\mathcal{R}_2 > 1$, $\mathcal{R}_3 \leq 1$, and $\mathcal{R}_4 \leq 1$, three equilibria E_0, E_1, and E_2 coexist;
(5) If $\mathcal{R}_2 \leq 1$, $\mathcal{R}_3 > 1$, and $\mathcal{R}_4 \leq 1$, three equilibria E_0, E_1, and E_3 coexist;
(6) If $\mathcal{R}_1 > 1$, $\mathcal{R}_2 \leq 1$, $\mathcal{R}_3 \leq 1$, and $\mathcal{R}_4 > 1$, three equilibria E_0, E_1, and E_4 coexist;
(7) If $\mathcal{R}_2 > 1$, $\mathcal{R}_3 > 1$, and $\mathcal{R}_4 \leq 1$, four equilibria E_0, E_1, E_2, and E_3 coexist;
(8) If $\mathcal{R}_2 > 1$, $\mathcal{R}_3 \leq 1$, and $\mathcal{R}_4 > 1$, four equilibria E_0, E_1, E_2, and E_4 coexist;
(9) If $\mathcal{R}_2 \leq 1$, $\mathcal{R}_3 > 1$, and $\mathcal{R}_4 > 1$, four equilibria E_0, E_1, E_3, and E_4 coexist;
(10) If $\mathcal{R}_2 > 1$, $\mathcal{R}_3 > 1$, and $\mathcal{R}_4 > 1$, all equilibria E_0, E_1, E_2, E_3, and E_4 coexist.

The newly proposed basic reproduction number of model (1.1) inherently ensures positivity. Through the analysis of equilibrium existence, we demonstrate that each threshold corresponds to distinct virological-immune implications: the viral infection reproduction number $\mathcal{R}_1$ (where the first term represents the average number of actively infected cells generated through virus-to-cell infection, and the second term represents the average number generated through cell-to-cell transmission), the CTL immune-response reproduction number $\mathcal{R}_2$ (representing the average number of CTL cells activated by infected cells when viral infection succeeds in the absence of antibody response), the humoral immunity reproduction number $\mathcal{R}_3$ (denoting the average number of antibodies activated by viruses when CTL response is absent), the competitive reproduction numbers for CTL-mediated ($\mathcal{R}_4^w$, the average number of CTLs activated by infected cells when antibody response is present) and humoral ($\mathcal{R}_4^z$, the average number of antibodies generated per viral infection under active CTL response) immune responses $\mathcal{R}_4$. The specific results can also be seen in the following Table 1.

Table 1. Coexistence of equilibrium states of model (1.1).

Condition		Coexist
$\mathcal{R}_1 \leq 1$	$\mathcal{R}_4 \leq 1$	E_0
	$\mathcal{R}_4 > 1$	E_0, E_4
$\mathcal{R}_1 > 1$	$\mathcal{R}_2 \leq 1, \mathcal{R}_3 \leq 1, \mathcal{R}_4 \leq 1$	E_0, E_1
	$\mathcal{R}_2 > 1, \mathcal{R}_3 \leq 1, \mathcal{R}_4 \leq 1$	E_0, E_1, E_2
	$\mathcal{R}_2 \leq 1, \mathcal{R}_3 > 1, \mathcal{R}_4 \leq 1$	E_0, E_1, E_3
	$\mathcal{R}_2 \leq 1, \mathcal{R}_3 \leq 1, \mathcal{R}_4 > 1$	E_0, E_1, E_4
	$\mathcal{R}_2 > 1, \mathcal{R}_3 > 1, \mathcal{R}_4 \leq 1$	E_0, E_1, E_2, E_3
	$\mathcal{R}_2 > 1, \mathcal{R}_3 \leq 1, \mathcal{R}_4 > 1$	E_0, E_1, E_2, E_4
	$\mathcal{R}_2 \leq 1, \mathcal{R}_3 > 1, \mathcal{R}_4 > 1$	E_0, E_1, E_3, E_4
	$\mathcal{R}_2 > 1, \mathcal{R}_3 > 1, \mathcal{R}_4 > 1$	E_0, E_1, E_2, E_3, E_4

2.2. Local asymptotic stability

The characteristic equation of model (1.1) at an arbitrary equilibrium $\overline{E} = (\overline{x}(t), \overline{y}(t), \overline{v}(t), \overline{w}(t), \overline{z}(t))$ can be calculated as

$$P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0, \tag{2.2}$$

where

$$\begin{aligned}
P_0(\lambda) &= (\lambda + \beta_1\bar{v} + \beta_2\bar{y} + c)\left((\lambda + s - r\bar{y})(\lambda + d + h\bar{w}) + r\overline{w}h\overline{y}\right)\\
&\quad \times \left((\lambda + q - p\bar{v})(\lambda + m + n\bar{z}) + n\bar{v}p\bar{z}\right),\\
P_1(\lambda) &= -\beta_2\bar{x}e^{-a_1\tau_1}(\lambda + s - r\bar{y})(\lambda + c)\left((\lambda + q - p\bar{v})(\lambda + m + n\bar{z}) + n\bar{v}p\bar{z}\right),\\
P_2(\lambda) &= -\beta_1 k\bar{x}e^{-a_1\tau_1}e^{-a_2\tau_2}(\lambda + s - r\bar{y})(\lambda + c)(\lambda + q - p\bar{v}).
\end{aligned}$$

Theorem 1. *If $\mathcal{R}_1 < 1$, the infection-free equilibrium E_0 of the model (1.1) is locally asymptotically stable; if $\mathcal{R}_1 > 1$, then E_0 is unstable.*

Proof. The characteristic equation of model (1.1) at E_0 is

$$(\lambda+c)(\lambda+s)(\lambda+q)\times\left((\lambda+d)(\lambda+m)-\beta_2 x_0 e^{-a_1\tau_1}(\lambda+m)e^{-\lambda\tau_1}-\beta_1 k x_0 e^{-a_1\tau_1}e^{-a_2\tau_2}e^{-\lambda\tau_1}e^{-\lambda\tau_2}\right) = 0. \tag{2.3}$$

It is clear that Eq (2.3) has three negative roots, $\lambda = -c$, $\lambda = -s$, and $\lambda = -q$ at E_0, and other roots are determined by the following equation:

$$(\lambda + d)(\lambda + m) - \beta_2 x_0 e^{-a_1\tau_1}(\lambda + m)e^{-\lambda\tau_1} - \beta_1 k x_0 e^{-a_1\tau_1}e^{-a_2\tau_2}e^{-\lambda\tau_1}e^{-\lambda\tau_2} = 0. \tag{2.4}$$

Denote $\mathcal{R}_1 = \mathcal{R}_{10} + \mathcal{R}_{11}$, where $\mathcal{R}_{10} = \dfrac{\beta_1 bke^{-a_1\tau_1-a_2\tau_2}}{cdm}$, $\mathcal{R}_{11} = \dfrac{\beta_2 be^{-a_1\tau_1}}{cd}$. Substituting $\mathcal{R}_{10}$ and $\mathcal{R}_{11}$ into Eq (2.4) yields

$$\left(\mathcal{R}_{10}e^{-\lambda\tau_2} + \mathcal{R}_{11}\left(\frac{\lambda}{m} + 1\right)\right)e^{-\lambda\tau_1} = \left(\frac{\lambda}{d} + 1\right)\left(\frac{\lambda}{m} + 1\right). \tag{2.5}$$

Next, we show that Eq (2.5) has only the roots with negative real parts. Otherwise, one assumes that Eq (2.5) has a root of the form $\lambda_1 = \mathrm{Re}\lambda_1 + i\mathrm{Im}\lambda_1$ with $\mathrm{Re}\lambda_1 \geq 0$. In this case, if $\mathcal{R}_1 < 1$, then it is clear that $e^{-\lambda_1\tau_1} < \left|\dfrac{\lambda_1}{d} + 1\right|$ and

$$\left|\mathcal{R}_{10}e^{-\lambda_1\tau_2} + \mathcal{R}_{11}\left(\frac{\lambda_1}{m} + 1\right)\right| < \left|\mathcal{R}_1 + \mathcal{R}_{11}\frac{\lambda_1}{m}\right| < \left|\frac{\lambda_1}{m} + 1\right|.$$

It follows that,

$$\left|\frac{\lambda_1}{d} + 1\right|\left|\frac{\lambda_1}{m} + 1\right| > \left|\left(\mathcal{R}_{10}e^{-\lambda_1\tau_2} + \mathcal{R}_{11}\left(\frac{\lambda_1}{m} + 1\right)\right)e^{-\lambda_1\tau_1}\right|,$$

which contradicts Eq (2.5). Therefore, if $\mathcal{R}_1 < 1$, all roots of Eq (2.3) have negative real parts, and E_0 is locally asymptotically stable. If $\mathcal{R}_1 > 1$, we denote the left side of Eq (2.4) by $F(\lambda)$:

$$F(\lambda) = (\lambda + d)(\lambda + m) - \beta_2 x_0 e^{-a_1\tau_1}(\lambda + m)e^{-\lambda\tau_1} - \beta_1 k x_0 e^{-a_1\tau_1}e^{-a_2\tau_2}e^{-\lambda\tau_1}e^{-\lambda\tau_2},$$

where $F(0) = dm(1 - \mathcal{R}_1) < 0$ and $F(+\infty) = +\infty$. Noting that $F(\lambda)$ is a continuous function with respect to λ, if $\mathcal{R}_1 > 1$, Eq (2.3) has at least a positive real root, then E_0 is unstable. □

Theorem 2. *If $\mathcal{R}_1 > 1$, $\mathcal{R}_2 < 1$, and $\mathcal{R}_3 < 1$, the immunity-inactivated equilibrium E_1 of the model (1.1) is locally asymptotically stable; E_1 is unstable if $\mathcal{R}_2 > 1$ or $\mathcal{R}_3 > 1$.*

Proof. First, we give the characteristic equation of the model (1.1) at E_1 as

$$\begin{aligned}&(\lambda + s - ry_1)(\lambda + q - pv_1)\Big((\lambda + \beta_1 v_1 + \beta_2 y_1 + c)(\lambda + d)(\lambda + m) \\ &-\beta_2 x_1 e^{-a_1\tau_1}(\lambda + m)(\lambda + c)e^{-\lambda\tau_1} - \beta_1 k x_1 e^{-a_1\tau_1} e^{-a_2\tau_2} e^{-\lambda\tau_1} e^{-\lambda\tau_2}(\lambda + c)\Big) = 0.\end{aligned} \tag{2.6}$$

The following results can be converted from the expression of y_1 and v_1:

$$\begin{aligned}\mathcal{R}_2 - 1 &= (ry_1 - s)\frac{\beta_1 k e^{-a_2\tau_2} + \beta_2 m}{cmr + \beta_2 ms + \beta_1 sk e^{-a_2\tau_2}}, \\ \mathcal{R}_3 - 1 &= (pv_1 - q)\frac{\beta_1 k e^{-a_2\tau_2} + \beta_2 m}{\beta_2 qm + pcke^{-a_2\tau_2} + \beta_1 qke^{-a_2\tau_2}}.\end{aligned}$$

It is clear that if $\mathcal{R}_2 < 1$ and $\mathcal{R}_3 < 1$, Eq (2.6) has two negative real roots $\lambda = ry_1 - s$ and $\lambda = pv_1 - q$. Next, we continue to discuss the case of the remaining roots of Eq (2.6), and

$$\begin{aligned}&(\lambda + \beta_1 v_1 + \beta_2 y_1 + c)(\lambda + d)(\lambda + m) - \beta_2 x_1 e^{-a_1\tau_1}(\lambda + m)e^{-\lambda\tau_1}(\lambda + c) \\ &-\beta_1 k x_1 e^{-a_1\tau_1} e^{-a_2\tau_2} e^{-\lambda\tau_1} e^{-\lambda\tau_2}(\lambda + c) = 0.\end{aligned} \tag{2.7}$$

Note that, $\lambda + \beta_1 v_1 + \beta_2 y_1 + c = \lambda + c\mathcal{R}_1$, and we assume that Eq (2.7) has a root of the form $\lambda_2 = \mathrm{Re}\lambda_2 + i\mathrm{Im}\lambda_2$ with $\mathrm{Re}\lambda_2 \geq 0$. By modulo operation, we get

$$\left|\frac{\lambda_2}{c} + \mathcal{R}_1\right|\left|\frac{\lambda_2}{d} + 1\right|\left|\frac{\lambda_2}{m} + 1\right| = \left|e^{-\lambda_2\tau_1}\right|\left|\frac{\lambda_2}{c} + 1\right|\left|\frac{\mathcal{R}_{11}}{\mathcal{R}_1}\left(\frac{\lambda_2}{m} + 1\right) + \frac{\mathcal{R}_{10}}{\mathcal{R}_1}e^{-\lambda_2\tau_2}\right|.$$

But when $\mathcal{R}_1 > 1$, it's very easy to get $\left|\frac{\lambda_2}{c} + 1\right| < \left|\frac{\lambda_2}{c} + \mathcal{R}_1\right|$, $\left|e^{-\lambda_2\tau_1}\right| < \left|\frac{\lambda_2}{d} + 1\right|$ and

$$\left|\frac{\mathcal{R}_{11}}{\mathcal{R}_1}\left(\frac{\lambda_2}{m} + 1\right) + \frac{\mathcal{R}_{10}}{\mathcal{R}_1}e^{-\lambda_2\tau_2}\right| = \left|\frac{\mathcal{R}_{11}}{\mathcal{R}_1}\frac{\lambda_2}{m} + \frac{\mathcal{R}_{11}}{\mathcal{R}_1} + \frac{\mathcal{R}_{10}}{\mathcal{R}_1}e^{-\lambda_2\tau_2}\right| < \left|\frac{\lambda_2}{m} + 1\right|.$$

This is in contradiction to Eq (2.7). To sum up the above discussion, if $\mathcal{R}_1 > 1$, $\mathcal{R}_2 < 1$, and $\mathcal{R}_3 < 1$, all roots of Eq (2.6) have a negative real part, and E_1 is locally asymptotically stable. □

Theorem 3. *If $\mathcal{R}_2 > 1$ and $\mathcal{R}_4^z < 1$, then the cell-mediated immunity-activated equilibrium E_2 of model (1.1) is locally asymptotically stable; E_2 is unstable if $\mathcal{R}_4^z > 1$.*

Proof. Let us write the characteristic equation of model (1.1) at E_2 in terms of Eq (2.2), and

$$\begin{aligned}P_0(\lambda) &= (\lambda + \beta_1 v_2 + \beta_1 y_2 + c)\left((\lambda + s - ry_2)(\lambda + d + hw_2) + ry_2 hw_2\right)(\lambda + q - pv_2)(\lambda + m), \\ P_1(\lambda) &= -\beta_2 x_2 e^{-a_1\tau_1}(\lambda + s - ry_2)(\lambda + c)(\lambda + q - pv_2)(\lambda + m), \\ P_2(\lambda) &= -\beta_1 k x_2 e^{-a_1\tau_1} e^{-a_2\tau_2}(\lambda + s - ry_2)(\lambda + c)(\lambda + q - pv_2).\end{aligned}$$

It is easy to know $pv_2 - q = q(\mathcal{R}_4^z - 1)$ by the expression for v_2, so naturally, when $\mathcal{R}_4^z < 1$, model (1.1) has one negative real root $\lambda = pv_2 - q$. Note that $\lambda + \beta_1 v_2 + \beta_2 y_2 + c = \lambda + \frac{c\mathcal{R}_1}{\mathcal{R}_2}$, and according to the characteristic equation of (1.1) at E_2, we remove the common factor $\lambda + q - pv_2$, then

$$\begin{aligned}&\left(\lambda+\frac{c\mathcal{R}_1}{\mathcal{R}_2}\right)\left(\lambda^2+d\mathcal{R}_2\lambda+sd(\mathcal{R}_2-1)\right)(\lambda+m)-\beta_2x_2e^{-a_1\tau_1}\lambda\,(\lambda+m)\,(\lambda+c)\,e^{-\lambda\tau_1}\\&-\beta_1kx_2e^{-a_1\tau_1}e^{-a_2\tau_2}e^{-\lambda\tau_1}e^{-\lambda\tau_2}\lambda\,(\lambda+c)=0.\end{aligned}\tag{2.8}$$

Next, we assume that Eq (2.8) has a root of the form $\lambda_3 = \mathrm{Re}\lambda_3 + i\mathrm{Im}\lambda_3$ with $\mathrm{Re}\lambda_3 \geq 0$. Denote $\mathcal{R}_2 = \mathcal{R}_{20} + \mathcal{R}_{21}$, where $\mathcal{R}_{20} = \dfrac{br\beta_1ke^{-a_1\tau_1}e^{-a_2\tau_2}}{cdmr+\beta_2dms+\beta_1dske^{-a_2\tau_2}}$ and $\mathcal{R}_{21} = \dfrac{br\beta_2me^{-a_1\tau_1}}{cdmr+\beta_2dms+\beta_1dske^{-a_2\tau_2}}$. By modulo operation,

$$\left|\frac{\lambda_3}{c}+\frac{\mathcal{R}_1}{\mathcal{R}_2}\right|\left|{\lambda_3}^2+d\mathcal{R}_2\lambda_3+sd(\mathcal{R}_2-1)\right|\left|\frac{\lambda_3}{m}+1\right|=\left|\frac{\lambda_3}{c}+1\right|\left|\mathcal{R}_{21}\left(\frac{\lambda_3}{m}+1\right)+\mathcal{R}_{20}e^{-\lambda_3\tau_2}\right|\left|d\lambda_3e^{-\lambda_3\tau_1}\right|.$$

Obviously, when $\mathcal{R}_2 > 1$ (in this case, $\mathcal{R}_1 > \mathcal{R}_2 > 1$), $\left|\frac{\lambda_3}{c}+1\right| < \left|\frac{\lambda_3}{c}+\frac{\mathcal{R}_1}{\mathcal{R}_2}\right|$, $\left|d\mathcal{R}_2\lambda_3e^{-\lambda_3\tau_1}\right| < \left|{\lambda_3}^2+d\mathcal{R}_2\lambda_3+sd(\mathcal{R}_2-1)\right|$ and

$$\left|\frac{\mathcal{R}_{21}}{\mathcal{R}_2}\left(\frac{\lambda_3}{m}+1\right)+\frac{\mathcal{R}_{20}}{\mathcal{R}_2}e^{-\lambda_3\tau_2}\right|=\left|\frac{\mathcal{R}_{21}}{\mathcal{R}_2}\frac{\lambda_3}{m}+\frac{\mathcal{R}_{21}}{\mathcal{R}_2}+\frac{\mathcal{R}_{20}}{\mathcal{R}_2}e^{-\lambda_3\tau_2}\right|<\left|\frac{\lambda_3}{m}+1\right|.$$

As a result, the above equation is in contradiction to Eq (2.8). We can get that if $\mathcal{R}_2 > 1$ and $\mathcal{R}_4^z < 1$, all roots of the model (1.1) at E_2 have a negative real part and E_2 is locally asymptotically stable. □

Theorem 4. *If $\mathcal{R}_3 > 1$ and $\mathcal{R}_4^w < 1$, then the humoral immunity-activated equilibrium E_3 of the model (1.1) is locally asymptotically stable; E_3 is unstable if $\mathcal{R}_4^w > 1$.*

Proof. We can write the characteristic equation of the model (1.1) at E_3 in terms of Eq (2.2) and

$$\begin{aligned}P_0(\lambda)&=(\lambda+\beta_1v_3+\beta_2y_3+c)\,(\lambda+s-ry_3)\,(\lambda+d)\,(\lambda(\lambda+m+nz_3)+nv_3pz_3),\\P_1(\lambda)&=-\beta_2x_3e^{-a_1\tau_1}\,(\lambda+s-ry_3)\,(\lambda+c)\,(\lambda(\lambda+m+nz_3)+nv_3pz_3),\\P_2(\lambda)&=-\beta_1kx_3e^{-a_1\tau_1}e^{-a_2\tau_2}\lambda\,(\lambda+s-ry_3)\,(\lambda+c).\end{aligned}$$

Since the equilibrium of model (1.1) is easily obtained as follows: $be^{-a_1\tau_1} = dy_3 + cx_3e^{-a_1\tau_1}$ and $p\beta_2e^{-a_1\tau_1}x_3y_3 = pdy_3 - q\beta_1e^{-a_1\tau_1}x_3$, hence,

$$\begin{aligned}\mathcal{R}_4^w-1=&\frac{r\,(cx_3e^{-a_1\tau_1}+dy_3)\,(\beta_1qr+\beta_2sp)y_3-ds(\beta_1qr+\beta_2sp+cpr)y_3}{ds(\beta_1qr+\beta_2sp+cpr)y_3}\\=&(ry_3-s)\,\frac{\beta_1qrdy_3+\beta_2spdy_3+\beta_1qrcx_3e^{-a_1\tau_1}}{ds(\beta_1qr+\beta_2sp+cpr)y_3}.\end{aligned}$$

Evidently, if $\mathcal{R}_4^w < 1$, model (1.1) has a negative real root $\lambda = ry_3 - s$. Note that $m + nz_3 = \dfrac{pke^{-a_2\tau_2}y_3}{q}$, we discuss the remaining eigenvalues of the model (1.1) at E_3 as follows:

$$\begin{aligned}&(\lambda+\beta_1v_3+\beta_2y_3+c)\,(\lambda+d)\left(\lambda\left(\lambda+\frac{pke^{-a_2\tau_2}y_3}{q}\right)+pke^{-a_2\tau_2}y_3-qm\right)\\&-\beta_2x_3e^{-a_1\tau_1}\,(\lambda+c)\left(\lambda\left(\lambda+\frac{pke^{-a_2\tau_2}y_3}{q}\right)+pke^{-a_2\tau_2}y_3-qm\right)e^{-\lambda\tau_1}\\&-\beta_1kx_3e^{-a_1\tau_1}e^{-a_2\tau_2}\lambda\,(\lambda+c)\,e^{-\lambda\tau_1}e^{-\lambda\tau_2}.\end{aligned}\tag{2.9}$$

It's assumed that Eq (2.9) has a root of the form $\lambda_4 = \mathrm{Re}\lambda_4 + i\mathrm{Im}\lambda_4$ with $\mathrm{Re}\lambda_4 \geq 0$. By modulo operation, we have $|\lambda_4 + \beta_1 v_3 + \beta_2 y_3 + c| > |\lambda_4 + c|$, $\left|\frac{\lambda_4}{d} + 1\right| > \left|e^{-\lambda_4\tau_1}\right|$ and

$$\begin{aligned}
&\left|\lambda_4\left(\lambda_4 + \frac{pke^{-a_2\tau_2}y_3}{q}\right) + pke^{-a_2\tau_2}y_3 - qm\right| - \frac{\beta_2 x_3 e^{-a_1\tau_1}}{d}\left|\lambda_4\left(\lambda_4 + \frac{pke^{-a_2\tau_2}y_3}{q}\right) + pke^{-a_2\tau_2}y_3 - qm\right| \\
&\quad - \frac{\beta_1 k x_3 e^{-a_1\tau_1}e^{-a_2\tau_2}}{d}\left|\lambda_4 e^{-\lambda_4\tau_2}\right| \\
&> \left(1 - \frac{\beta_2 x_3 y_3 e^{-a_1\tau_1}}{dy_3}\right)\left|{\lambda_4}^2 + pke^{-a_2\tau_2}y_3 - qm\right| - \frac{\beta_1 e^{-a_1\tau_1}x_3 v_3}{dy_3}\left|{\lambda_4}^2 + pke^{-a_2\tau_2}y_3 - qm\right| > 0.
\end{aligned}$$

This contradicts Eq (2.9). In summary, we have that if $\mathcal{R}_3 > 1$ (ensure the existence of E_3) and $\mathcal{R}_4^w < 1$, all roots of the model (1.1) at E_3 have a negative real part, and E_3 is locally asymptotically stable. □

Theorem 5. *If $\mathcal{R}_4 > 1$, then the immunity-activated equilibrium E_4 of the model (1.1) is locally asymptotically stable.*

Proof. The characteristic equation of Eq (2.2) at E_4 of model (1.1) is

$$\begin{aligned}
P_0(\lambda) &= (\lambda + \beta_1 v_4 + \beta_2 y_4 + c)\left(\lambda\left(\lambda + d\mathcal{R}_4^w\right) + sd(\mathcal{R}_4^w - 1)\right)\left(\lambda\left(\lambda + m\mathcal{R}_4^z\right) + qm(\mathcal{R}_4^z - 1)\right), \\
P_1(\lambda) &= -\beta_2 x_4 e^{-a_1\tau_1}\lambda\left(\lambda + c\right)\left(\lambda\left(\lambda + m\mathcal{R}_4^z\right) + qm(\mathcal{R}_4^z - 1)\right), \\
P_2(\lambda) &= -\beta_1 k x_4 e^{-a_1\tau_1}e^{-a_2\tau_2}\lambda^2\left(\lambda + c\right).
\end{aligned}$$

We assume that model (1.1) at E_4 has a root of the form $\lambda_5 = \mathrm{Re}\lambda_5 + i\mathrm{Im}\lambda_5$ with $\mathrm{Re}\lambda_5 \geq 0$. Denote $\mathcal{R}_{41}^w = \dfrac{\beta_2 sprbe^{-a_1\tau_1}}{ds(\beta_1 qr + \beta_2 sp + cpr)}$, by modulo operation,

$$\begin{aligned}
&\left|P_0(\lambda) + P_1(\lambda)e^{-\lambda_5\tau_1} + P_2(\lambda)e^{-\lambda_5\tau_1}e^{-\lambda_5\tau_2}\right| \\
&> |\lambda + \beta_1 v_4 + \beta_2 y_4 + c|\left(|\lambda_5|^4 + (d\mathcal{R}_4^w + m\mathcal{R}_4^z - \beta_2 x_4 e^{-a_1\tau_1})|\lambda_5|^3\right. \\
&\quad + (sd(\mathcal{R}_4^w - 1) + qm(\mathcal{R}_4^z - 1) + dm\mathcal{R}_4^w\mathcal{R}_4^z - \beta_2 x_4 m\mathcal{R}_4^z e^{-a_1\tau_1} - \beta_1 k x_4 e^{-a_1\tau_1}e^{-a_2\tau_2})|\lambda_5|^2 \\
&\quad \left. + (sdm(\mathcal{R}_4^w - 1)\mathcal{R}_4^z + qmd(\mathcal{R}_4^z - 1)\mathcal{R}_4^w - \beta_2 x_4 qm(\mathcal{R}_4^z - 1)e^{-a_1\tau_1})|\lambda_5| + sdqm(\mathcal{R}_4^w - 1)(\mathcal{R}_4^z - 1)\right) \qquad (2.10) \\
&= |\lambda + \beta_1 v_4 + \beta_2 y_4 + c|\left(|\lambda_5|^4 + (m\mathcal{R}_4^z + \beta_1 e^{-a_1\tau_1}\tfrac{xv}{y})|\lambda_5|^3 + (sd(\mathcal{R}_4^w - 1) + qm(\mathcal{R}_4^z - 1))|\lambda_5|^2\right. \\
&\quad \left. + (sdm(\mathcal{R}_4^w - 1)\mathcal{R}_4^z + qmd(\mathcal{R}_4^z - 1)(\mathcal{R}_4^w - \mathcal{R}_{41}^w))|\lambda_5| + sdqm(\mathcal{R}_4^w - 1)(\mathcal{R}_4^z - 1)\right) > 0.
\end{aligned}$$

We derive a contradiction with Eq (2.10). To summarize the above discussion, if $\mathcal{R}_4 > 1$, all roots of the model (1.1) at E_4 have a negative real part, and E_4 is locally asymptotically stable. □

Therefore, combining the coexistence and the local asymptotic stability of the equilibria, we correct the results of the global stability of the equilibria, and the specific proof can refer to the results of [10, 14, 16, 17, 21].

Theorem 6. *(1) If $\mathcal{R}_1 < 1$ and $\mathcal{R}_4 \leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable;*
(2) If $\mathcal{R}_1 > 1$, $\mathcal{R}_2 \leq 1$, $\mathcal{R}_3 \leq 1$, and $\mathcal{R}_4 \leq 1$, the immunity-inactivated equilibrium E_1 is globally

asymptotically stable;
(3) If $\mathcal{R}_2 > 1$, $\mathcal{R}_3 \leq 1$, *and* $\mathcal{R}_4 \leq 1$, *the cell-mediated immunity-activated equilibrium* E_2 *is globally asymptotically stable;*
(4) If $\mathcal{R}_2 \leq 1$, $\mathcal{R}_3 > 1$, *and* $\mathcal{R}_4 \leq 1$, *the antibody immunity-activated equilibrium* E_3 *is globally asymptotically stable;*
(5) If $\mathcal{R}_1 > 1$, $\mathcal{R}_4 > 1$ *and the immunity-activated equilibrium* E_4 *is globally asymptotically stable.*

Through straightforward calculations, it can be verified that our basic reproduction number is equivalent to Guo et al.'s [14]. Therefore, we omit the proof of global asymptotic stability for the equilibria. Clearly, the basic reproduction numbers we propose exhibits stronger positivity and better interpretability. Compared to Theorem 6 in this paper with Guo's Theorems 3.1–3.5 (as well as Yan and Wang [10], Jiang and Wang [16], Lin et al. [17], and so on), our results differ due to the consideration of coexistence and local asymptotic stability of equilibria. Under the premise of unique local stability, the conditions for global stability are distinct.

Remark 1. *The equilibria* E_0 *(when* $\mathcal{R}_1 = 1$*),* E_1 *(when* $\mathcal{R}_1 = 1$ *or* $\mathcal{R}_2 = 1$ *or* $\mathcal{R}_3 = 1$*),* E_2 *(when* $\mathcal{R}_2 = 1$ *or* $\mathcal{R}_4^z = 1$*),* E_3 *(when* $\mathcal{R}_3 = 1$ *or* $\mathcal{R}_4^w = 1$*), and* E_4 *(when* $\mathcal{R}_4^w = 1$ *or* $\mathcal{R}_4^z = 1$*) all have saddle-node bifurcations.*

3. Numerical simulation

In this section, we refer to the results obtained by Li et al. [9] using a time-delay age-structured model for fitting HIV data, and we take Patient ID 1092 as an example. We will demonstrate the global stability of the five equilibria through some numerical simulations. We have selected the following initial parameter values for system (1.1): $c = 0.0076$, $\beta_1 = \beta_2 = 0.0133$, $a_1 = 0.5014$, $a_2 = 0.0014$, $h = 0.0500$, $k = 2.9787$, $m = 2.0602$, $n = 0.0002$, $r = 0.2056$, $s = 0.0911$, $p = 0.0830$, $q = 0.0500$, $\tau_1 = \tau_2 = 8.8609$, $x(\theta) = 482$, $y(\theta) = 2$, $v(\theta) = 16$, $w(0) = 3$, and $z(0) = 5$, while the other three variable parameters are displayed in the captions of Figures 1–5. As can be seen from Figures 1–5, the numerical results are consistent with the theoretical analysis.

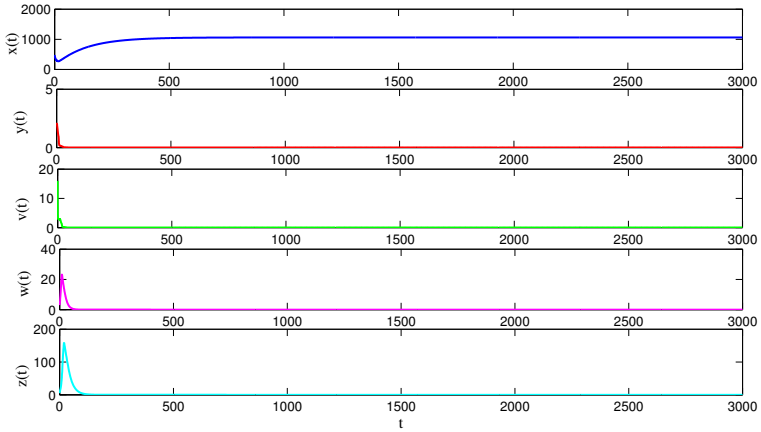

Figure 1. The global stability diagram of the infection-free equilibrium $E_0 = (1061.55, 0, 0, 0, 0)$ of system (1.1), where $\mathcal{R}_1 = 0.8748$, $\mathcal{R}_2 = 0.3031$, $\mathcal{R}_3 = 0.3129$, $\mathcal{R}_4 = 0.3000$. The three variable parameters are $b = 8.0678$, $d = 0.4619$, $r = 0.2056$.

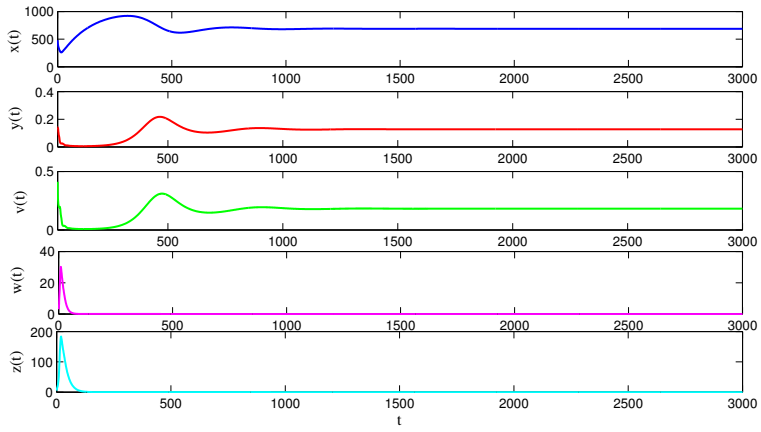

Figure 2. The global stability diagram of the immunity-inactivated equilibrium $E_1 = (688.01, 0.13, 0.18, 0, 0)$ of system (1.1), where $\mathcal{R}_1 = 1.5429$, $\mathcal{R}_2 = 0.5345$, $\mathcal{R}_3 = 0.5518$, $\mathcal{R}_4 = 0.5292$. The three variable parameters are $b = 8.0678$, $d = 0.2619$, $r = 0.2056$.

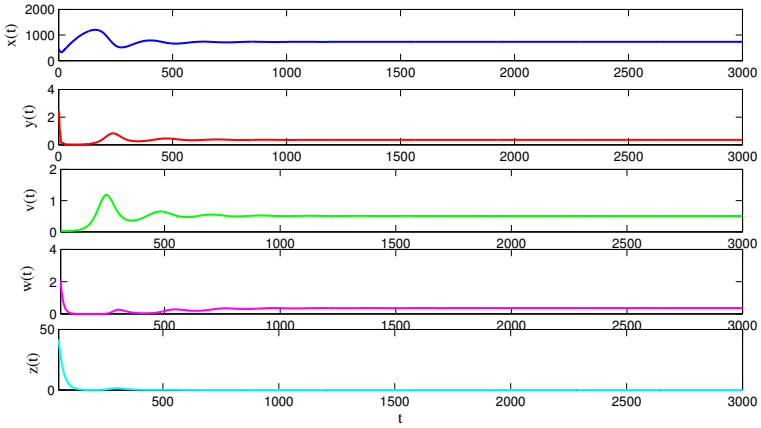

Figure 3. The global stability diagram of the cell-mediated immunity-activated equilibrium $E_2 = (735.20, 0.36, 0.51, 0.36, 0)$ of system (1.1), where $\mathcal{R}_1 = 2.6904$, $\mathcal{R}_2 = 1.0686$, $\mathcal{R}_3 = 0.9621$, $\mathcal{R}_4 = 0.8449$. The three variable parameters are $b = 14.0678$, $d = 0.4619$, $r = 0.2556$.

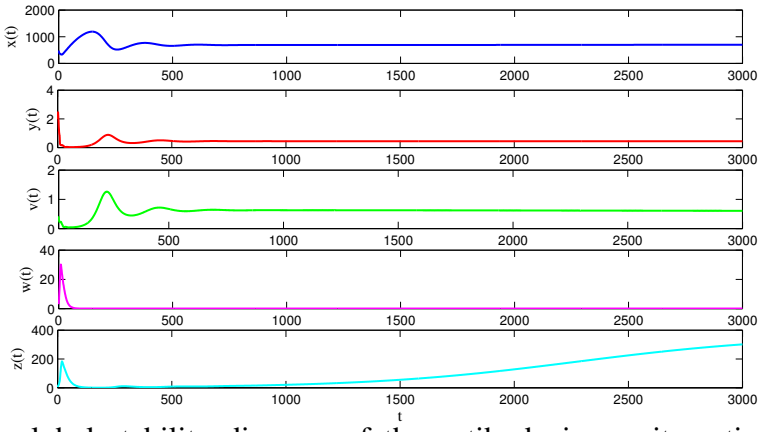

Figure 4. The global stability diagram of the antibody immunity-activated equilibrium $E_3 = (699.93, 0.44, 0.61, 0, 301.28)$ of system (1.1), where $\mathcal{R}_1 = 2.8816$, $\mathcal{R}_2 = 0.9982$, $\mathcal{R}_3 = 1.0305$, $\mathcal{R}_4 = 0.9883$. The three variable parameters are $b = 15.0678$, $d = 0.2619$, $r = 0.2056$.

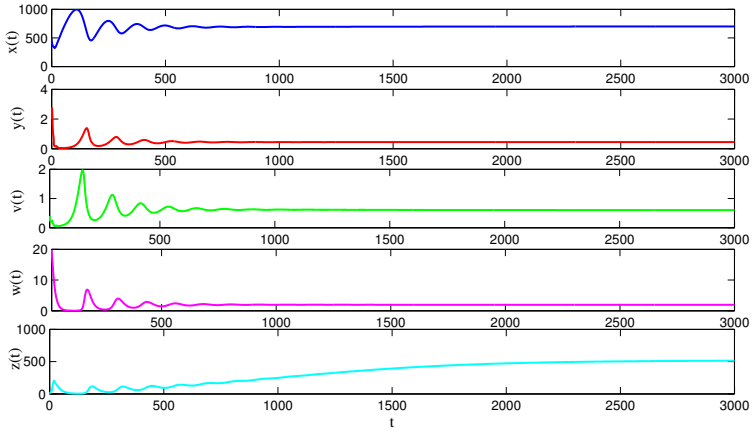

Figure 5. The global stability diagram of the immunity-activated equilibrium $E_4 = (699.55, 0.44, 0.60, 1.94, 514.00)$ of system (1.1), where $\mathcal{R}_1 = 4.6615$, $\mathcal{R}_2 = 1.6148$, $\mathcal{R}_3 = 1.6670$, $\mathcal{R}_4 = 1.0503$. The three variable parameters are $b = 15.0678$, $d = 0.1619$, $r = 0.2056$.

4. Conclusions

Based on the research findings of the existing model incorporating virus-to-cell infection, cell-to-cell transmission, CTL, and antibody immune responses, we redefined the basic reproduction number and established the necessary and sufficient conditions for the uniqueness of each equilibrium (where one class of equilibria is unique) and the coexistence among equilibria (five classes of equilibria). This aspect has not been investigated in existing dynamic analyses of such models.

Using the contraction and expansion method, we have obtained sufficient conditions (but not necessary ones) for the local stability and instability of these five equilibrium points. It is highly challenging to directly solve the characteristic equation to obtain the necessary and sufficient conditions for the local stability of each equilibrium state. Based on the coexistence of equilibrium states and their local asymptotic stability, we have revised the global stability conditions in the existing model. The revised global stability conditions for E_0 to E_4 remain slightly more stringent in our current work. This study can inspire future research to further refine these findings.

However, this class of models does not exhibit pure imaginary roots but may have zero eigenvalues, including multiple zero eigenvalues. Therefore, further research on these models remains meaningful.

Author contributions

Conceptualization and methodology, Xianshan Yang and Yong Li; writing-original draft, Yan Li and Rui Zhu; writing-review and editing, Xiaoqun Li and Ruixia Yuan; funding acquisition, Ruixia Yuan. All authors have read and agreed to the published version of the manuscript.

Use of Generative-AI tools declaration

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

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Conflict of interest

The authors declare that they have no competing interests.

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