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Research article

Stability analysis for a HIV model with cell-to-cell transmission, two immune responses and induced apoptosis

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Abstract: In this paper, a dynamic HIV model with cell-to-cell transmission, two immune responses, and induced apoptosis is proposed and studied. First, the non-negativity and boundedness of the solutions of the model are given, and then the exact expression of the basic reproduction number R_0 is obtained by using the next generation matrix method. Second, criteria are obtained for the local stability of the disease-free equilibrium, immune response-free equilibrium, and the infected equilibrium with both humoral and cellular immune responses. Furthermore, the threshold conditions are also derived for the global asymptotic stability of the disease-free equilibrium, immune response-free equilibrium, and the infected equilibrium with both humoral and cellular immune responses by constructing the suitable Lyapunov function. Finally, some numerical simulations are conducted to verify the theoretical results; the numerical simulation results show that the increase of apoptosis rate had a positive role in the control of viral infection.

Keywords: HIV model; cell-to-cell transmission; induced apoptosis; global asymptotic stability; Lyapunov function
Mathematics Subject Classification: 34D23, 92D20, 92D30

1. Introduction

Human immunodeficiency virus (HIV) is a virus that can invade the body's immune cells and multiply; when the virus enters the body, it weakens the immune system's defense against infection, resulting in a fatal human disease known as acquired immunodeficiency syndrome (AIDS). According to the data reported in [1], the year 2022 witnessed a staggering 39 million individuals living with HIV; among this, 37.5 million were adults and 1.5 million were children. The same year saw 1.3 million new infections and 630,000 AIDS-related deaths. HIV has become an important public health

problem that seriously threatens human health, attracting wide attention from the field of mathematics and epidemiology.

In 1996, Nowak and Bangham [2] proposed a basic HIV infection model, which describes the interaction between uninfected cells, infected cells, and free viruses, in the following form:

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - dx(t) - \beta x(t)v(t), \\ \dfrac{\mathrm{d}y(t)}{\mathrm{d}t} = \beta x(t)v(t) - ay(t), \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = Ky(t) - uv(t), \end{cases} \tag{1.1}$$

where $x(t)$, $y(t)$, and $v(t)$ represent the concentration of uninfected cells, infected cells, and free viruses at time t, respectively. Where λ is the rate at which new uninfected cells are produced, d and a are the death rates of uninfected and infected cells, respectively, infected cells produce virus particles at rate K, and the rate at which viruses are removed is u. β represents the infection rate of the virus-to-cell. The global dynamics of (1.1) is given in [2]. In recent years, researchers have found that after the virus enters the human body, in addition to the virus-to-cell infection [2], there is another transmission mode, namely cell-to-cell transmission [3, 4]. In virus-to-cell infection, the virus replicates within the cell, producing additional viral particles that are released into the external environment to infect other healthy cells nearby [5, 6]. In cell-to-cell transmission, HIV particles are transmitted between cells through virological synapses [7, 8]. Based on the above facts, researchers improved the model (1.1) by incorporating the transmission mode of cell-to-cell transmission [9–12]. In [11], the authors studied an age-structured HIV infection model that included two modes of cell-to-cell transmission and virus-to-cell infection, and discussed the effect of the basic reproduction number on the global stability of the equilibrium. Wang et al. [12] studied a general random HIV model with two modes of infection and found that, as the rate of cell-to-cell transmission increased, the number of healthy cells decreased, and the number of infected cells, virions, and CTLs(cytotoxic T lymphocyte) increased.

In addition, after the virus enters the human body, it triggers the immune system in addition to intercellular action. The immune system is divided into non-specific immunity and adaptive immunity (specific immunity), with adaptive immunity further divided into two types: humoral immunity and cellular immunity. During viral infection, immune responses play a crucial role in recognizing pathogens and killing them as well as infected cells [13, 14]. Therefore, many researchers have attempted to incorporate immune responses into HIV models to study the dynamic relationship between immune responses and invading pathogens [10, 15–18]. For example, Wang et al. [15] studied the dynamic behavior of a host-virus model with humoral immunity and intracellular delay. In [16], the authors considered models of reactive-diffuse viral infections with humoral immunity and nonlinear incidence in heterogeneous and homogeneous environments and analyzed the global stability of the models. In [17], the authors proposed an HIV model with saturated virus-target and infected-target incidences and cellular immunity and analyzed the existence and global stability of all equilibria in the model under two thresholds. Zhu et al. [18] studied HIV models with cellular immunity and cell-to-cell transmission and obtained the local and global stability of the equilibrium. Most of the models mentioned above only consider humoral or cellular immunity. In fact, after the virus enters the body, T cells and B cells jointly recognize the pathogen and activate adaptive immunity, that is, humoral immunity and cellular immunity.

In recent years, research [19] has revealed a new mode of cell death called apoptosis. Additionally, authors in [20] have discovered that viruses and cells can interact and produce signals to induce or inhibit apoptosis, thereby controlling cell fate. Based on the findings in [19,20], many researchers have incorporated apoptosis into mathematical models to investigate its influence on disease dynamics. For instance, Fan et al. [21] included the direct effect of activation-induced apoptosis on uninfected cells in their model and demonstrated through analysis that increased apoptosis had a positive impact on controlling viral infection. In [22], authors proposed a delayed viral dynamics model with apoptosis and both virus-to-cell and cell-to-cell infections and analyzed the global attractivity of the equilibrium. Furthermore, there is a discussion about HIV genome reverse transcription. After HIV infects resting cells, the viral genome is not completely reverse transcribed [23]. Later, Zack et al. [24] found that non-fully integrated viruses latent in resting cells may fail over time, and some unstable DNA transcripts degrade rapidly. Therefore, when the virus genome is not fully transcribed in resting cells, a portion of the infected cells can return to the uninfected state [25]. Based on this hypothesis, Srivastava et al. [26] studied a delayed HIV model, discussed the stability of the equilibrium, and analyzed the effects of delayed and infected cells returning to the uninfected state on HIV infection. In fact, in real life, HIV transmission is still affected by many other factors, which we will not detail here, such as impulse [27], noise [28], delay [29], and so on.

Although the aforementioned researchers have examined the influence of various factors (such as humoral immunity, cellular immunity, viral transmission mode, apoptosis, etc.) on HIV transmission in the host and achieved promising theoretical results, there are few models that consider the combined effects of all these factors simultaneously. Therefore, we propose and investigate an HIV model that incorporates cell-to-cell transmission, virus-to-cell infection, adaptive immunity, apoptosis, and the ability of infected cells to return to an uninfected state. The main objectives of this study are: (i) to explore the local and global asymptotic stability of the equilibrium of the general HIV infection model, and (ii) to investigate the impact of the apoptosis rate on the dynamics of HIV models under different parameter values.

We divide cells into the following categories: uninfected cells, infected cells, B cells, and T cells; in addition to cells, there are viruses. Considering factors such as adaptive immunity, cell-to-cell transmission, virus-to-cell infection, apoptosis, and a fraction of infected cells returned to the uninfected class, Figure 1 is used to illustrate the transmission dynamics between chambers.

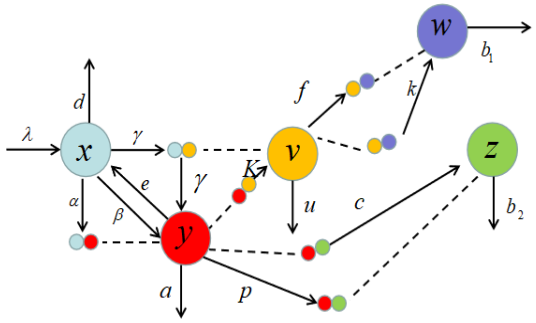

Figure 1. Schematic representation of the mathematical model (1.2).

The following is our model:

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - dx - \beta xy - \alpha xy - \gamma xv + ey, \\ \dfrac{\mathrm{d}y(t)}{\mathrm{d}t} = \beta xy + \gamma xv - pyz - ay - ey, \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = Ky - uv - fwv, \\ \dfrac{\mathrm{d}w(t)}{\mathrm{d}t} = kwv - b_1 w, \\ \dfrac{\mathrm{d}z(t)}{\mathrm{d}t} = cyz - b_2 z, \end{cases} \tag{1.2}$$

where $x(t)$, $y(t)$, $v(t)$ represent the concentration of uninfected cells, infected cells, and free viruses at time t, respectively. $w(t)$ is the concentration of antibodies in the body at time t, and $z(t)$ is the concentration of CTLs in the body at time t. For biological considerations, we assume that all the model parameters are positive. Accordingly, the initial conditions for the model (1.2) are taken as $(x(0), y(0), v(0), w(0), z(0)) \in R_+^5$. The meanings of all other parameters are shown in the following Table 1:

Table 1. The meanings of all parameters in model (1.2).

Symbol	Meaning
β	the cell-to-cell transmission rate
α	the rate of apoptosis at which infected cells induce uninfected cells
γ	the virus-to-cell infection rate
e	rate of infected cells in the latent stage reverting to the uninfected cells
p	the rate at which infected cells are cleared by immune cells
f	the rate at which virus particles are neutralized by antibodies
k	the rate at which B cells produce antibodies
b_1	the natural death rate of B cells
c	the rate of CTLs production stimulated by infected cells
b_2	the natural death rate of CTLs

The aim of this paper is to study the dynamics of model (1.2) and the effect of apoptosis. The organization of this paper is as follows. In Section 2, we discuss the non-negativity and boundedness of the solution. The basic reproduction number R_0 is defined in Section 3. In Section 4, we obtain the local and global asymptotic stability of the disease-free equilibrium, the immune response-free equilibrium and the infected equilibrium with both humoral and cellular immune responses. In Section 5, a simple numerical example is given to illustrate our results. In Section 6, a brief conclusion is given.

2. Non-negativity and boundedness of solutions

In this section, we show that the solutions to the model (1.2) are unique, non-negative, and bounded. The right-hand side of this model (1.2) being completely continuous and Lipschitz on $[0, a]$, $a > 0$, the model (1.2) with the non-negative initial condition has the unique solution $(x(0), y(0), v(0), w(0), z(0))$. The non-negative and bounded solutions of model (1.2) are proved below.

Theorem 1. *The solutions to the model* (1.2) *with the initial condition in* R^5_+ *are non-negative and bounded.*

Proof. From the first three equations of the model (1.2), we have

$$\frac{\mathrm{d}x}{\mathrm{d}t}\mid_{x=0}= \lambda + ey,\ \frac{\mathrm{d}y}{\mathrm{d}t}\mid_{y=0}= \gamma xv,\ \frac{\mathrm{d}v}{\mathrm{d}t}\mid_{v=0}= Ky.$$

Assume that the condition $\frac{\mathrm{d}v}{\mathrm{d}t}\mid_{v=0}\geq 0$ does not hold for some $t > 0$, that is, there exists a t_v such that

$$t_v = \inf\left\{t \mid v(t) = 0,\ \frac{\mathrm{d}v}{\mathrm{d}t} < 0,\ t > 0\right\}.$$

Therefore, $\frac{\mathrm{d}v}{\mathrm{d}t}\mid_{v(t_v)=0}= Ky(t_v) < 0,\ K > 0,\ y(t_v) < 0$. We now define

$$t_y = \inf\left\{t \mid y(t) = 0,\ \frac{\mathrm{d}y}{\mathrm{d}t} < 0,\ t > 0\right\},$$

then, we get $t_y < t_v$. Since $v(t_y) > 0$ and $\frac{\mathrm{d}y(t_y)}{\mathrm{d}t} = \gamma x(t_y)v(t_y) < 0$, we can easily obtain that $x(t_y) < 0$. We further define

$$t_x = \inf\left\{t \mid x(t) = 0,\ \frac{\mathrm{d}x}{\mathrm{d}t} < 0,\ t > 0\right\}.$$

Obviously, $t_x < t_y < t_v$. We observe that $\frac{\mathrm{d}x(t_x)}{\mathrm{d}t} = \lambda + ey(t_x) > 0$, since $y(t_x) > 0$, which is a contradiction to the definition of t_x itself. Therefore, $\frac{\mathrm{d}v}{\mathrm{d}t}\mid_{v=0}\geq 0$ and hence, $v(t) > 0$ for all $t > 0$. Consequently, $x(t) \geq 0$ as well as $y(t) \geq 0$ for all $t > 0$.

Finally, from the fourth equation of the model (1.2), we have

$$w(t) = w(0)\exp\left\{\int_0^t [kv(s) - b_1]ds\right\} \geq 0,\ \text{for all } t > 0.$$

From the last equation of the model (1.2), we have

$$z(t) = z(0)\exp\left\{\int_0^t [cy(s) - b_2]ds\right\} \geq 0,\ \text{for all } t > 0.$$

Hence, the non-negativity of the solution $(x(t), y(t), v(t), w(t), z(t))$ with the initial condition in R^5_+ is guaranteed.

In order to prove the boundedness of the solutions to the model (1.2), we define two new variables $T(t) = x(t) + y(t) + \frac{p}{c}z(t)$ and $I(t) = v(t) + \frac{f}{k}w(t)$. From the first, second, and fifth equations of (1.2), we obtain:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \lambda - dx - \alpha xy - ay - \frac{pb_2}{c}z \leq \lambda - mT,$$

where $m = \min\{a,\ d,\ b_2\}$. Therefore,

$$\limsup_{t\to\infty} T(t) \leq \frac{\lambda}{m},\ 0 \leq x(t) \leq \frac{\lambda}{m},\ 0 \leq y(t) \leq \frac{\lambda}{m},\ 0 \leq z(t) \leq \frac{c\lambda}{pm}.$$

Further, from the third and fourth equations of (1.2), we obtain:

$$\frac{\mathrm{d}I}{\mathrm{d}t} = Ky - uv - \frac{fb_1}{k}w \leq K\frac{\lambda}{m} - nI,$$

where $n = \min\{u,\ b_1\}$. Therefore,

$$\limsup_{t\to\infty} I(t) \leq \frac{K\lambda}{mn},\ 0 \leq v(t) \leq \frac{K\lambda}{mn},\ 0 \leq w(t) \leq \frac{kK\lambda}{fmn}.$$

Hence, the solutions of model (1.2) with non-negative initial conditions are bounded with the closed and bounded positively invariant set

$$\Omega = \Big\{(x(t), y(t), v(t), w(t), z(t)) \in R_+^5;\ 0 \leq x(t) \leq \frac{\lambda}{m},\ 0 \leq y(t) \leq \frac{\lambda}{m},$$
$$0 \leq v(t) \leq \frac{K\lambda}{mn},\ 0 \leq w(t) \leq \frac{Kk\lambda}{mnf},\ 0 \leq z(t) \leq \frac{c\lambda}{mp}\Big\}.$$

3. Basic reproduction number

By simple calculation, that there are three equilibriums for model (1.2):

(i) The disease-free equilibrium $E_0 = (x_0, y_0, v_0, w_0, z_0) = (\frac{\lambda}{d}, 0, 0, 0, 0)$.

The basic reproduction number of model (1.2) is calculated using the next generation matrix method [30]:

$$R_0 = \frac{K\gamma x_0}{u(a+e)} + \frac{\beta x_0}{a+e} = R_{01} + R_{02},$$

where $R_{01} = \frac{K\gamma x_0}{u(a+e)}$, $R_{02} = \frac{\beta x_0}{a+e}$. Biologically, R_{01} and R_{02} are the basic reproduction number corresponding to the virus-to-cell and cell-to-cell infections, respectively [31].

(ii) The immune response-free equilibrium $E_1 = (x_1, y_1, v_1, 0, 0)$, where

$$x_1 = \frac{u(a+e)}{\beta u + \gamma K},\ y_1 = \frac{1}{[\alpha u(a+e) + a(\beta u + \gamma K)]du(a+e)}(R_0 - 1),\ v_1 = \frac{K}{u}y_1.$$

(iii) The infected equilibrium with both humoral and cellular immune responses $E^* = (x^*, y^*, v^*, w^*, z^*)$, where

$$x^* = \frac{\lambda + ey^*}{d + (\alpha+\beta)y^* + \gamma v^*},\ y^* = \frac{b_2}{c},\ v^* = \frac{b_1}{k},\ w^* = \frac{u}{f}(R_a - 1),\ z^* = \frac{(a+e)}{p}(R_b - 1),$$

with $R_a = \frac{Ky^*}{uv^*}$, $R_b = \frac{(\beta y^* + \gamma v^*)x^*}{(a+e)y^*}$.

4. Local and global asymptotic stability

4.1. Local asymptotic stability analysis

In order to analyze the local asymptotic stability of the equilibrium, we apply the Routh-Hurwitz criteria [32]. Linearize the model (1.2) at any equilibrium E_i, we get the following Jacobian matrix:

$$J(E_i) = \begin{bmatrix} -d-\beta y_i-\alpha y_i-\gamma v_i & -\beta x_i-\alpha x_i+e & -\gamma x_i & 0 & 0 \\ \beta y_i+\gamma v_i & \beta x_i-pz_i-a-e & \gamma x_i & 0 & -py_i \\ 0 & K & -u-fw_i & -fv_i & 0 \\ 0 & 0 & kw_i & kv_i-b_1 & 0 \\ 0 & cz_i & 0 & 0 & cy_i-b_2 \end{bmatrix}. \tag{4.1}$$

Theorem 2. *The disease-free equilibrium E_0 is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.*

Proof. Substituting E_0 into (4.1), a simple calculation yields the characteristic equation at E_0 as

$$(d+r)(b_1+r)(b_2+r)(r^2+A_1r+A_2) = 0, \tag{4.2}$$

where

$$\begin{aligned} A_1 &= u+(a+e)(1-R_0+R_{01}), \\ A_2 &= u(a+e)(1-R_0). \end{aligned}$$

Clearly, three of the eigenvalues for system (4.2) are $r_1 = -d$, $r_2 = -b_1$, $r_3 = -b_2$. All three eigenvalues are negative, while the other two eigenvalues are given by the solution to the quadratic equation $r^2 + A_1r+A_2 = 0$. Observing that $A_1 > 0, A_2 > 0$ when $R_0 < 1$. Therefore, by the Routh-Hurwitz criteria, the disease-free equilibrium E_0 is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.

Theorem 3. *The immune response-free equilibrium E_1 is locally asymptotically stable when $R_1 < 1 < R_0$ and unstable when $R_1 > 1$ with $R_1 = \max\{R_H, R_C\}$, where*

$$\begin{aligned} R_H &= \frac{Kk\lambda(\beta u+\gamma K)}{[Kk+ub_1du(a+e)[\alpha u(a+e)+a(\beta u+\gamma K)]]du(a+e)}, \\ R_C &= \frac{c\lambda(\beta u+\gamma K)}{[c+b_1du(a+e)[\alpha u(a+e)+a(\beta u+\gamma K)]]du(a+e)}. \end{aligned}$$

Proof. Substituting E_1 into (4.1), a simple calculation yields the characteristic equation at E_1 as

$$(cy_1-b_2-r)(kv_1-b_1-r)(r^3+B_1r^2+B_2r+B_3) = 0, \tag{4.3}$$

where

$$\begin{aligned} B_1 &= (u+d)+(a+e)(1-\frac{R_{02}}{R_0})+\frac{\beta u+\gamma k}{u[\alpha u(a+e)+a(\beta u+\gamma k)]}(R_0-1)+\alpha y_1, \\ B_2 &= du+(\beta u+\alpha u+\alpha\beta+ea+a\alpha+K\gamma+\frac{aK\gamma}{u}+\frac{\alpha\gamma K(a+e)}{\alpha u(a+e)+a(\beta u+\gamma K)})(R_0-1) \\ &\quad +d(a+e)(1-\frac{R_{02}}{R_0}), \\ B_3 &= \left[\alpha u(a+e)(1-\frac{R_{01}}{R_0})+\alpha\beta u+\gamma Ka+\frac{\alpha\gamma Ku(a+e)}{\gamma K+\beta u}\right]\frac{du(a+e)}{\alpha u(a+e)+a(\beta u+\gamma K)}(R_0-1). \end{aligned}$$

Clearly, two of the eigenvalues for (4.3) are

$$r_1 = cy_1-b_2 = \frac{\lambda c(K\gamma+\beta u)}{d^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_C}(R_C-1),$$

$$r_2 = kv_1 - b_1 = \frac{\lambda Kk(K\gamma + \beta u)}{ud^2u^2(a+e)^2[\alpha u(a+e) + a(K\gamma + \beta u)]R_H}(R_H - 1),$$

which is negative when $R_1 < 1$. The other three eigenvalues are given by the solution to the quadratic equation $r^3 + B_1r^2 + B_2r + B_3 = 0$. It is easily seen that $B_1, B_2, B_3 > 0$ when $R_0 > 1$. Further,

$$\begin{aligned} B_1B_2 - B_3 = &\left[(a+e)\left(1 - \frac{R_{02}}{R_0}\right)d + a(\gamma v_1 + \beta y_1) + (a+e)\alpha y_1\right]\left[d + (\alpha+\beta)y_1 + \gamma v_1\right. \\ &\left. + (a+e)(1 - \frac{R_{02}}{R_0})\right] + \left[du + uy_1(\alpha+\beta) + \gamma v_1 u + \alpha\gamma v_1 x_1\right]\left[u + d\right. \\ &\left. + y_1(\alpha+\beta) + \gamma v_1 + (a+e)(1 - \frac{R_{02}}{R_0})\right] + Kd\gamma x_1 + K\alpha\gamma x_1 y_1. \end{aligned}$$

Hence, $B_1B_2 - B_3 > 0$ when $R_0 > 1$. Therefore, by the Routh-Hurwitz criteria, the immune response-free equilibrium E_1 is locally asymptotically stable when $R_1 < 1 < R_0$, and unstable when $R_1 > 1$.

Theorem 4. *The infected equilibrium with both humoral and cellular immune responses E^* is locally asymptotically stable when $R_a > 1$ and $R_b > 1$.*

Proof. Substituting E^* into (4.1), a simple calculation yields the characteristic equation at E^* as

$$r^5 + C_1r^4 + C_2r^3 + C_3r^2 + C_4r + C_5 = 0, \tag{4.4}$$

where

$$\begin{aligned} C_1 &= d + (\alpha+\beta)y^* + \gamma v^* + \frac{\gamma x^* v^*}{y^*} + u + fw^*, \\ C_2 &= \frac{Ky^*}{v^*}[d + (\alpha+\beta)y^* + \gamma v^*] + \frac{d\gamma x^* v^*}{y^*} + pz^* + a + \alpha\beta x^* y^* \\ &\quad + 2\alpha\gamma x^* v^* + \beta c y^* z^* + fkw^* v^*, \\ C_3 &= fkw^* v^*[d + (\alpha+\beta)y^* + \gamma v^* + \frac{\gamma x^* v^*}{y^*}] + K\alpha\gamma x^* y^* + \frac{Ky^*}{v^*}(a + pz^* \\ &\quad + \alpha\beta x^* y^*) + pcy^* z^*[d + (\alpha+\beta)y^* + \gamma v^* + u + fw^*], \\ C_4 &= pcy^* z^*[fkw^* v^* + (d + (\alpha+\beta)y^* + \gamma v^*)(u + fw^*)] + fkw^* v^*(\frac{d\gamma x^* v^*}{y^*} \\ &\quad + pz^* + a + \alpha\beta x^* y^* + 2\alpha\gamma x^* v^*), \\ C_5 &= pcy^* z^* fkw^* v^*(d + (\alpha+\beta)y^* + \gamma v^*). \end{aligned}$$

In order to verify that all the eigenvalues of the polynomial (4.4) are all negative, we remark that x^*, y^*, v^*, w^*, and z^* are all positive, which is true whenever $R_a > 1$ and $R_b > 1$. In addition, for the quintic characteristic (4.4), $C_1C_2 - C_3 > 0$, $C_1C_2C_3 - C_1C_4^2 - C_3C_2^2 + 2C_1C_3C_4 > 0$, $C_1C_2C_3C_4 - C_1C_4^3 - C_3C_2C_4^2 + C_3^2C_5 + C_1C_3C_4^2 - C_2C_5C_1^2 > 0$, if $R_a > 1$ and $R_b > 1$. According to the Routh-Huriwitz criteria, the infected equilibrium with both humoral and cellular immune responses E^* is locally asymptotically stable whenever $R_a > 1$ and $R_b > 1$.

4.2. Global asymptotic stability analysis

In order to discuss the global asymptotic stability of model (1.2), for all the equilibrium, we construct appropriate Lyapunov functional and adopt the Lyapunov-LaSalle invariance principle [33].

Let us define a function $g(x) = x - 1 - \ln(x)$, $x > 0$. Note that $g(x) \geq 0$, for all $x > 0$ and $g(x) = 0 \Leftrightarrow x = 1$.

Theorem 5. *The disease-free equilibrium E_0 is globally asymptotically stable when $R_0 < 1$.*

Proof. According to Theorem 1, we can obtain:

$$\limsup_{t\to\infty} T(t) \leq \frac{\lambda}{m},$$

and denote $x_n = \frac{\lambda}{m}$. We assume that $x(t) \leq x_n$ for all $t \geq 0$. Clearly, the second and third equations of model (1.2) satisfy

$$\begin{cases} \dfrac{\mathrm{d}y}{\mathrm{d}t} \leq \beta x_n y + \gamma x_n v - ay - ey, \\ \dfrac{\mathrm{d}v}{\mathrm{d}t} \leq Ky - uv. \end{cases} \tag{4.5}$$

The corresponding comparison system is

$$\begin{cases} \dfrac{\mathrm{d}Y}{\mathrm{d}t} = \beta x_n Y + \gamma x_n V_1 - aY - eY, \\ \dfrac{\mathrm{d}V_1}{\mathrm{d}t} = KY - uV_1. \end{cases} \tag{4.6}$$

Furthermore, the matrix is obtained as follows:

$$A = \begin{pmatrix} \beta x_n - (a+e) & \gamma x_n \\ K & -u \end{pmatrix}.$$

Where the characteristic equation is

$$|rE - A| = 0. \tag{4.7}$$

Therefore, the eigenvalue r of the characteristic Eq (4.7) is

$$r = \frac{-(u + a + e - \beta x_n) \pm \sqrt{(u + a + e - \beta x_n)^2 + 4u(a+e)(R_n - 1)}}{2},$$

where

$$R_n = \frac{\gamma K x_n}{u(a+e)} + \frac{\beta x_n}{a+e},$$

if $R_n < 1$, then $r < 0$. Thus, from the principle of comparison, when $t \to \infty$, we can get $(y(t), v(t) \to (0, 0))$. Furthermore, from the first, fourth, and fifth equations of the model (1.2), the following limit equations are obtained:

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx, \\ \dfrac{\mathrm{d}w}{\mathrm{d}t} = -b_1 w, \\ \dfrac{\mathrm{d}z}{\mathrm{d}t} = -b_2 z. \end{cases}$$

It is clear from the theory of asymptotically autonomous semiflows [34], we further obtain that $z(t) \to 0$, $w(t) \to 0$ and $x(t) \to x_0$ as $t \to \infty$. Thus, the disease-free equilibrium E_0 is globally asymptotically stable.

Remark 1. *(1) If $a \neq d$, then $R_0 < R_n < 1$, and E_0 is globally asymptotically stable.*
(2) If $a = d$, then $R_0 = R_n < 1$, and E_0 is globally asymptotically stable.

Before proving the global asymptotic stability of the immune response-free equilibrium and the infected equilibrium with both humoral and cellular immune responses, we define B and J are the real symmetric matrices:

$$B = \begin{pmatrix} B_{11} & -B_{12} & -B_{13} \\ -B_{12} & B_{22} & -B_{23} \\ -B_{13} & -B_{23} & B_{33} \end{pmatrix}, J = \begin{pmatrix} J_{11} & -J_{12} & -J_{13} \\ -J_{12} & J_{22} & -J_{23} \\ -J_{13} & -J_{23} & J_{33} \end{pmatrix},$$

where

$$\begin{aligned} B_{11} &= \frac{1}{x_n x_1}(dx_1 - ey_1 + \alpha x_1 y_1) + \frac{de}{(a+d)x_1},\ B_{22} = \frac{e(a+\alpha x_1)}{(a+d)x_1}, \\ B_{12} &= \frac{1}{2}[\alpha + \frac{\alpha e x_1}{(a+d)x_1} + \frac{\alpha e y_n}{(a+d)x_1} + \frac{epz_n}{(a+d)x_1}],\ B_{23} = \frac{1}{2}\left[\frac{epy_1}{(a+d)x_1} + cz_n\right], \\ B_{13} &= \frac{1}{2}\frac{epy_1}{(a+d)x_1},\ B_{33} = \frac{\lambda c(K\gamma + \beta u)}{d^2u^2(a+e)^2[\alpha u(a+e) + a(K\gamma + \beta u)]R_C}(1 - R_C), \end{aligned}$$

and

$$\begin{aligned} J_{11} &= \frac{1}{x_n x^*}(dx^* - ey^* + \alpha x^* y^*),\ J_{22} = \frac{e(a+\alpha x^*)}{(a+d)x^*}, \\ J_{12} &= \frac{1}{2}\left[\alpha + \frac{\alpha e}{a+d} + \frac{\alpha e y_n}{(a+d)x^*}\right],\ J_{23} = \frac{1}{2}\frac{ep}{c(a+d)x^*}(a + cy^* + \alpha x^*), \\ J_{13} &= \frac{1}{2}\frac{ep}{c(a+d)x^*}(d + cy^* + \alpha y_n),\ J_{33} = \frac{p^2 ey^*}{c(a+d)x^*}. \end{aligned}$$

with $x_n = \frac{\lambda}{m}$, $y_n = \frac{\lambda}{m}$ and $z_n = \frac{c\lambda}{mp}$.

Theorem 6. *The immune response-free equilibrium E_1 is globally asymptotically stable when $R_1 \leq 1 < R_0 \leq 1 + \frac{a}{e}$ and matrix B is positive definite.*

Proof. We define a Lyapunov function $L_1(x, y, v, w, z)$ as

$$L_1(x, y, v, w, z) = x_1 g(\frac{x}{x_1}) + y_1 g(\frac{y}{y_1}) + \frac{\gamma x_1 v_1}{K y_1} g(\frac{v}{v_1}) + \frac{f\gamma x_1 v_1}{K k y_1} w + \frac{p}{c} z.$$

Taking the time derivative of $L_1(x, y, v, w, z)$ along the solution of (1.2), we have

$$\begin{aligned} \frac{dL_1}{dt} &= (1 - \frac{x_1}{x})(\lambda - dx - \beta xy - \alpha xy - \gamma xv + ey) + (1 - \frac{y_1}{y})(\beta xy + \gamma xv - pyz - ay - ey) \\ &\quad + \frac{\gamma x_1 v_1}{K y_1}(1 - \frac{v_1}{v})(Ky - uv - fwv) + \frac{f\gamma x_1 v_1}{K k y_1}(kwv - b_1 w) + \frac{p}{c}(cyz - b_2 z). \end{aligned}$$

We observe that

$$\frac{e}{x}(x - x_1)(y - y_1) = -e(y - y_1)\frac{(x - x_1)^2}{x x_1} + \frac{e}{x_1}(x - x_1)(y - y_1).$$

Thus,

$$\begin{aligned}\frac{dL_1}{dt} =& -\frac{1}{x}(d+\alpha y_1)(x-x_1)^2+\frac{e}{x}(x-x_1)(y-y_1)-\alpha(x-x_1)(y-y_1)\\ &-\gamma x_1 v_1(\frac{x_1}{x}+\frac{yv_1}{y_1v}+\frac{xy_1v}{x_1yv_1}-3)-\beta x_1y_1(\frac{x}{x_1}+\frac{x_1}{x}-2)\\ &+\frac{f\gamma x_1v_1^2w\lambda(K\gamma+\beta u)}{y_1ud^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_H}(R_H-1)\\ &+\frac{pz\lambda(K\gamma+\beta u)}{y_1ud^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_C}(R_C-1).\end{aligned}$$

We define a Lyapunov function $L_2(x,y,v,w,z)$ as

$$L_2(x,y,v,w,z)=\frac{1}{2}\frac{e}{(a+d)x_1}[(x-x_1)+(y-y_1)]^2,$$

and then,

$$\begin{aligned}\frac{dL_2}{dt} =& -\frac{e(d+\alpha y)}{(a+d)x_1}(x-x_1)^2-\frac{e(a+\alpha x_1+pz)}{(a+d)x_1}(y-y_1)^2\\ &-\frac{e(a+d+\alpha x_1+\alpha y+pz)}{(a+d)x_1}(x-x_1)(y-y_1)\\ &-\frac{epy_1}{(a+d)x_1}(x-x_1)(z-z_1)\\ &-\frac{epy_1}{(a+d)x_1}(y-y_1)(z-z_1).\end{aligned}$$

Similarity, define a Lyapunov function $L_3(x,y,v,w,z)$ as

$$L_3(x,y,v,w,z)=\frac{1}{2}(z-z_1)^2,$$

then,

$$\frac{dL_3}{dt}=cz(y-y_1)(z-z_1)+\frac{\lambda c(K\gamma+\beta u)}{d^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_C}(R_C-1)(z-z_1)^2.$$

Finally, we define $L=L_1+L_2+L_3$, then,

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t} =& \frac{\mathrm{d}L_1}{\mathrm{d}t}+\frac{\mathrm{d}L_2}{\mathrm{d}t}+\frac{\mathrm{d}L_3}{\mathrm{d}t}\\ \le& -ey\frac{(x-x_1)^2}{xx_1}-\gamma x_1v_1(\frac{x_1}{x}+\frac{yv_1}{y_1v}+\frac{xy_1v}{x_1yv_1}-3)-\beta x_1y_1(\frac{x}{x_1}+\frac{x_1}{x}-2)\\ &+\frac{f\gamma x_1v_1^2w\lambda(K\gamma+\beta u)}{y_1ud^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_H}(R_H-1)\\ &+\frac{pz\lambda(K\gamma+\beta u)}{y_1ud^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_C}(R_C-1)\\ &-\frac{e\alpha y}{(a+d)x_1}(x-x_1)^2-\frac{epz}{(a+d)x_1}(y-y_1)^2-\frac{1}{x_nx_1}(dx_1+\alpha x_1y_1-ey_1)(x-x_1)^2\end{aligned}$$

$$
\begin{aligned}
&- \frac{de}{(a+d)x_1}(x-x_1)^2 - \frac{1}{(a+d)x_1}(ea+e\alpha x_1)(y-y_1)^2 \\
&+ \frac{\lambda c(K\gamma+\beta u)}{d^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_C}(R_C-1)(z-z_1)^2 \\
&+ (\alpha + \frac{\alpha e x_1}{(a+d)x_1} + \frac{\alpha e y_n}{(a+d)x_1} + \frac{epz_n}{(a+d)x_1})\,|(x-x_1)(y-y_1)| + \frac{epy_1}{(a+d)x_1}\,|(x-x_1)(z-z_1)| \\
&+ (\frac{epy_1}{(a+d)x_1} + cz_n)\,|(y-y_1)(z-z_1)| \\
&= -ey\frac{(x-x_1)^2}{xx_1} - \gamma x_1 v_1(\frac{x_1}{x} + \frac{yv_1}{y_1v} + \frac{xy_1v}{x_1yv_1} - 3) - \beta x_1 y_1(\frac{x}{x_1} + \frac{x_1}{x} - 2) \\
&+ \frac{f\gamma x_1 v_1^2 w\lambda(K\gamma+\beta u)}{y_1ud^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_H}(R_H-1) \\
&+ \frac{pz\lambda(K\gamma+\beta u)}{y_1ud^2u^2(a+e)^2[\alpha u(a+e)+a(K\gamma+\beta u)]R_C}(R_C-1) \\
&- \frac{e\alpha y}{(a+d)x_1}(x-x_1)^2 - \frac{epz}{(a+d)x_1}(y-y_1)^2 \\
&- (|x-x_1|, |y-y_1|, |z-z_1|)B(|x-x_1|, |y-y_1|, |z-z_1|)^T.
\end{aligned}
$$

Using the AM-GM inequality, it follows that

$$\frac{x}{x_1} + \frac{x_1}{x} - 2 \geq 0,\ \frac{x_1}{x} + \frac{yv_1}{y_1v} + \frac{xy_1v}{x_1yv_1} - 3 \geq 0.$$

We also note that

$$dx_1 - ey_1 = \frac{\lambda(\beta u+\gamma K)}{[du(a+e)+a(\beta u+\gamma K)]R_0}(a+e-eR_0+\frac{\lambda}{R_0}).$$

Since matrix B is positive definite, we have

$$\lim_{t\to\infty}|x(t)-x_1| = \lim_{t\to\infty}|y(t)-y_1| = \lim_{t\to\infty}|z(t)-z_1| = 0.$$

Hence, $\frac{dL}{dt} \leq 0$ when $R_1 \leq 1$ and $R_0 \leq 1 + \frac{a}{e}$, matrix B is positive definite. We note that $\frac{dL}{dt} = 0$ if and only if $x = x_1$, $y = y_1$, $v = v_1$, $w = w_1$, $z = z_1$. Again, since E_1 exists whenever $R_0 > 1$, therefore, it follows from Lyapunov-LaSalle invariance principle that E_1 is globally asymptotically stable when $R_1 \leq 1 < R_0 \leq 1 + \frac{a}{e}$ and matrix B is positive definite.

Theorem 7. *The infected equilibrium with both humoral and cellular immune responses E^* is globally asymptotically stable when $R_a > 1$, $R_b > 1$, $dx^* - ey^* \geq 0$ and matrix J is positive definite.*

Proof. We define a Lyapunov function $U_1(x, y, v, w, z)$ as

$$U_1(x,y,v,w,z) = x^*g(\frac{x}{x^*}) + y^*g(\frac{y}{y^*}) + \frac{\gamma x^*v^*}{Ky^*}g(\frac{v}{v^*}) + \frac{f\gamma x^*v^*}{Kky^*}g(\frac{w}{w^*}) + \frac{p}{c}g(\frac{z}{z^*}).$$

Taking the time derivative of $U_1(x, y, v, w, z)$ along the solution of (1.2), we have

$$\frac{dU_1}{dt} = (1-\frac{x^*}{x})(\lambda - dx - \beta xy - \alpha xy - \gamma xv + ey) + (1-\frac{y^*}{y})(\beta xy + \gamma xv - pyz - ay - ey)$$

$$+\frac{\gamma x^* v^*}{Ky^*}(1-\frac{v^*}{v})(Ky-uv-fwv)+\frac{f\gamma x^* v^*}{Kky^*}(1-\frac{w^*}{w})(kwv-b_1w)$$
$$+\frac{p}{c}(1-\frac{z^*}{z})(cyz-b_2z).$$

We observe that

$$\frac{e}{x}(x-x^*)(y-y^*)=-e(y-y^*)\frac{(x-x^*)^2}{xx^*}+\frac{e}{x^*}(x-x^*)(y-y^*).$$

Thus,

$$\frac{dU_1}{dt}=-\frac{1}{x}d(x-x^*)^2-e(y-y^*)\frac{(x-x^*)^2}{xx^*}+\frac{e}{x^*}(x-x^*)(y-y^*)-\frac{\alpha y^*}{x}(x-x^*)$$
$$-\alpha(x-x^*)(y-y^*)-\gamma x^* v^*(\frac{x^*}{x}+\frac{yv^*}{y^*v}+\frac{xy^*v}{x^*yv^*}-3)-\beta x^* y^*(\frac{x}{x^*}+\frac{x^*}{x}-2).$$

We define a Lyapunov function $U_2(x,y,v,w,z)$ as

$$U_2(x,y,v,w,z)=\frac{1}{2}\frac{e}{(a+d)x^*}[(x-x^*)+(y-y^*)+(z-z^*)]^2.$$

Taking the time derivative of $U_2(x,y,v,w,z)$ along the solution of (1.2), we have

$$\frac{\mathrm{d}U_2}{\mathrm{d}t}=-\frac{e(d+\alpha y)}{(a+d)x^*}(x-x^*)^2-\frac{e(a+\alpha x^*)}{(a+d)x^*}(y-y^*)^2$$
$$-\frac{p^2ey^*}{c(a+d)x^*}(z-z^*)^2-\frac{e(a+d+\alpha x^*+\alpha y)}{(a+d)x^*}(x-x^*)(y-y^*)$$
$$-\frac{ep(a+cy^*+\alpha x^*)}{c(a+d)x^*}(y-y^*)(z-z^*)$$
$$-\frac{pe(d+cy^*+\alpha y)}{(a+d)x^*}(x-x^*)(z-z^*).$$

Finally, we define

$$U=U_1+U_2.$$

Thus,

$$\frac{\mathrm{d}U}{\mathrm{d}t}=\frac{\mathrm{d}U_1}{\mathrm{d}t}+\frac{\mathrm{d}U_2}{\mathrm{d}t}$$
$$\leq-\frac{ey}{xx^*}(x-x^*)^2-\gamma x^* v^*(\frac{x^*}{x}+\frac{yv^*}{y^*v}+\frac{xy^*v}{x^*yv^*}-3)-\beta x^* y^*(\frac{x}{x^*}+\frac{x^*}{x}-2)$$
$$-\frac{de}{(a+d)x^*}(x-x^*)^2-\frac{\alpha ey}{(a+d)x^*}(x-x^*)^2-\frac{1}{x_nx^*}(dx^*-ey^*+\alpha x^*y^*)(x-x^*)^2$$
$$-\frac{e(a+\alpha x^*)}{(a+d)x^*}(y-y^*)^2-\frac{p^2ey^*}{c(a+d)x^*}(z-z^*)^2+(\alpha+\frac{\alpha e(x^*+y_n)}{(a+d)x^*})\,|(x-x^*)(y-y^*)|$$
$$+\frac{ep}{c(a+d)x^*}(d+cy^*+\alpha y_n)\,|(x-x^*)(z-z^*)|+\frac{ep}{c(a+d)x^*}(a+cy^*+\alpha x^*)\,|(y-y^*)(z-z^*)|$$

$$
\begin{aligned}
&= -\frac{ey}{xx^*}(x-x^*)^2 - \gamma x^* v^*\left(\frac{x^*}{x} + \frac{yv^*}{y^*v} + \frac{xy^*v}{x^*yv^*} - 3\right) - \beta x^* y^*\left(\frac{x}{x^*} + \frac{x^*}{x} - 2\right)\\
&- \frac{de}{(a+d)x^*}(x-x^*)^2 - \frac{\alpha ey}{(a+d)x^*}(x-x^*)^2 - J_{11}(x-x^*)^2 - J_{22}(y-y^*)^2\\
&- J_{33}(z-z^*)^2 + 2J_{12}\left|(x-x^*)(y-y^*)\right| + 2J_{13}\left|(x-x^*)(z-z^*)\right| + 2J_{23}\left|(y-y^*)(z-z^*)\right|\\
&= -\left(|x-x^*|, |y-y^*|, |z-z^*|\right)J\left(|x-x^*|, |y-y^*|, |z-z^*|\right)^T\\
&- \frac{ey}{xx^*}(x-x^*)^2 - \gamma x^* v^*\left(\frac{x^*}{x} + \frac{yv^*}{y^*v} + \frac{xy^*v}{x^*yv^*} - 3\right) - \beta x^* y^*\left(\frac{x}{x^*} + \frac{x^*}{x} - 2\right)\\
&- \frac{de}{(a+d)x^*}(x-x^*)^2 - \frac{\alpha ey}{(a+d)x^*}(x-x^*)^2.
\end{aligned}
$$

Using the AM-GM inequality, it follows that

$$\frac{x}{x^*} + \frac{x^*}{x} - 2 \geq 0,\ \frac{x^*}{x} + \frac{yv^*}{y^*v} + \frac{xy^*v}{x^*yv^*} - 3 \geq 0.$$

Since matrix J is positive definite, we have

$$\lim_{t\to\infty}|x(t)-x^*| = \lim_{t\to\infty}|y(t)-y^*| = \lim_{t\to\infty}|z(t)-z^*| = 0.$$

Hence, $\frac{\mathrm{d}L}{\mathrm{d}t} \leq 0$ when $dx^* - ey^* \geq 0$, matrix J is positive definite. We note that $\frac{\mathrm{d}L}{\mathrm{d}t} = 0$ if and only if $x = x^*$, $y = y^*$, $v = v^*$, $w = w^*$, $z = z^*$. Again, since E^* exists whenever $R_a > 1$ and $R_b > 1$, therefore, it follows from Lyapunov-LaSalle invariance principle that E^* is globally asymptotically stable when $R_a > 1$, $R_b > 1$, $dx^* - ey^* \geq 0$ and matrix J is positive definite.

Remark 2. *The additional condition imposed in Theorem 6, namely $R_0 \leq 1 + \frac{a}{e}$, is equivalent to $dx_1 - ey_1 \geq 0$, which implies $\lambda - \beta x_1 y_1 - \alpha x_1 y_1 - \beta x_1 v_1 \geq 0$. Also, the additional condition imposed in Theorem 7, namely $dx^* - ey^* \geq 0$, which implies $\lambda - \beta x^* y^* - \alpha x^* y^* - \beta x^* v^* \geq 0$. These two additional conditions that the production rate of uninfected is greater than the infection rate at equilibrium, which is reasonable from the biological point of view.*

5. Numerical simulations

In this section, we choose three different initial conditions, namely, $ic_1 = (30, 0.5, 0.3, 50, 40)$, $ic_2 = (25, 0.8, 0.1, 60, 50)$, and $ic_3 = (20, 1.2, 0.5, 70, 60)$, to show the evolution solutions for model (1.2); see Figures 2–4.

5.1. The stability of the disease-free equilibrium E_0

Let $\lambda = 0.75$, $d = 0.01$, $\beta = 0.001$, $\alpha = 0.05$, $\gamma = 0.01$, $e = 0.01$, $p = 0.01$, $a = 1$, $K = 2.9$, $u = 6$, $f = 0.006$, $k = 0.1$, $c = 0.01$, $b_1 = 0.1$, $b_2 = 0.1$. With simple calculation, we get $R_0 = 0.4332 < 1$. The dynamics of the model (1.2), in this case, is presented in Figure 2 (a)–(e), which indicates that uninfected cells continuously increase over time and then, remarkably, stabilize at the level $\frac{\lambda}{d} = 75$. The simulation indicates that the disease-free equilibrium E_0 is globally asymptotically stable; see Figure 2 (f) affirming the theoretical result announced in Theorem 5.

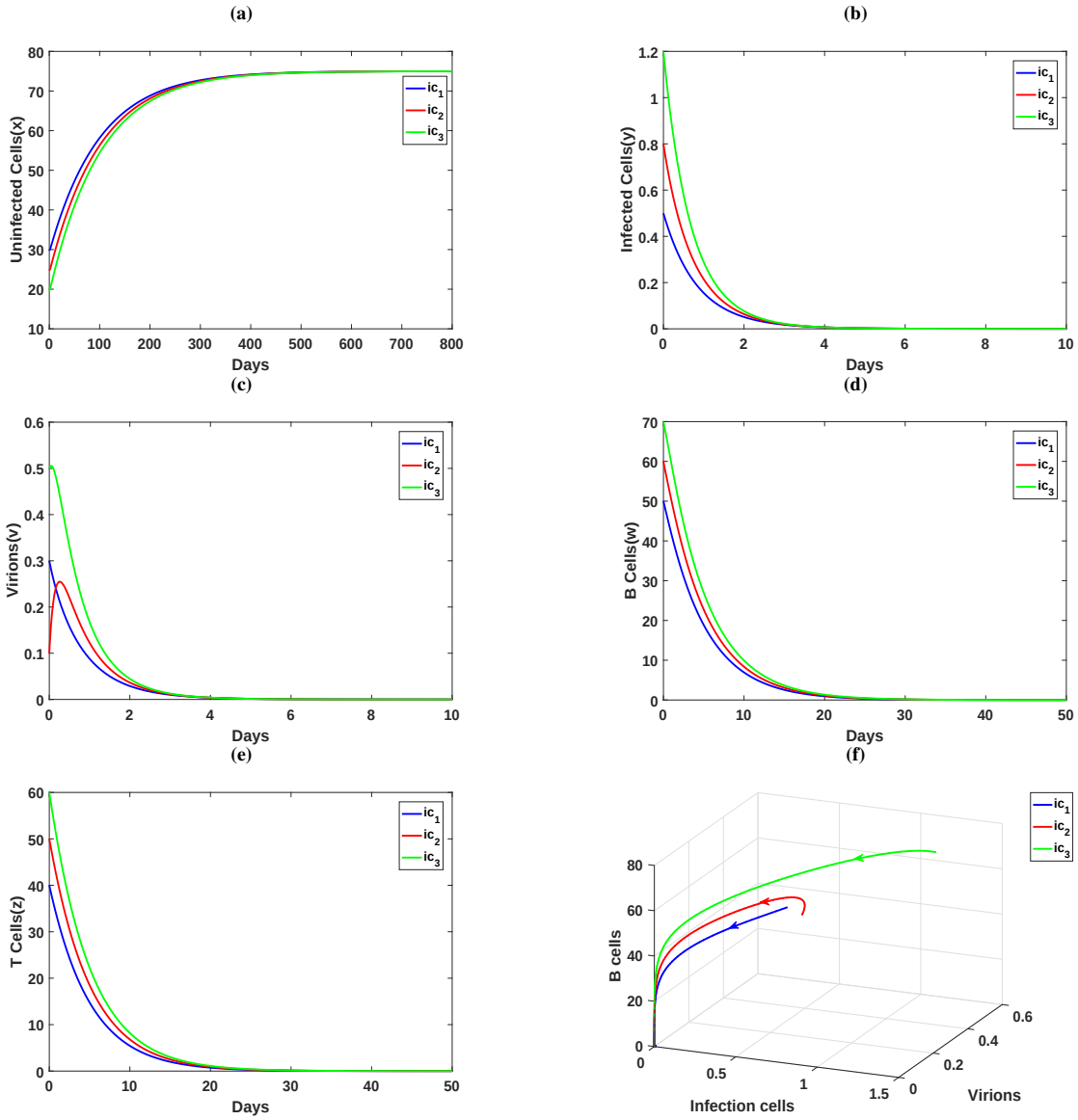

Figure 2. The evolution solution and phase diagram for model (1.2) with three different initial conditions ic_1, ic_2, and ic_3 in case of $R_0 < 1$.

5.2. *The stability of the immune response-free equilibrium* E_1

We choose $\lambda = 1$, $d = 1$, $\beta = 1$, $\alpha = 1$, $\gamma = 1.06$, $e = 0.1$, $p = 1$, $a = 1$, $K = 1$, $u = 1$, $f = 0.01$, $k = 1$, $c = 1$, $b_1 = 1$, $b_2 = 1$. By simple calculation, we get $R_1 = 0.571 < 1$ and $1 < R_0 = 1.873 < 1 + \frac{a}{e} = 11$. It is seen from Figure 3 (a)–(e) that the concentration levels of uninfected cells, infected cells, and free viral particles show oscillatory behaviour, eventually converging to their respective immune-free steady states after some time, while B-cells and T-cells level gradually decreases and eventually approaches zero. The observed immune-free steady state E_1 is globally asymptotically stable; see Figure 3 (f) confirming the theoretical results of Theorem 6.

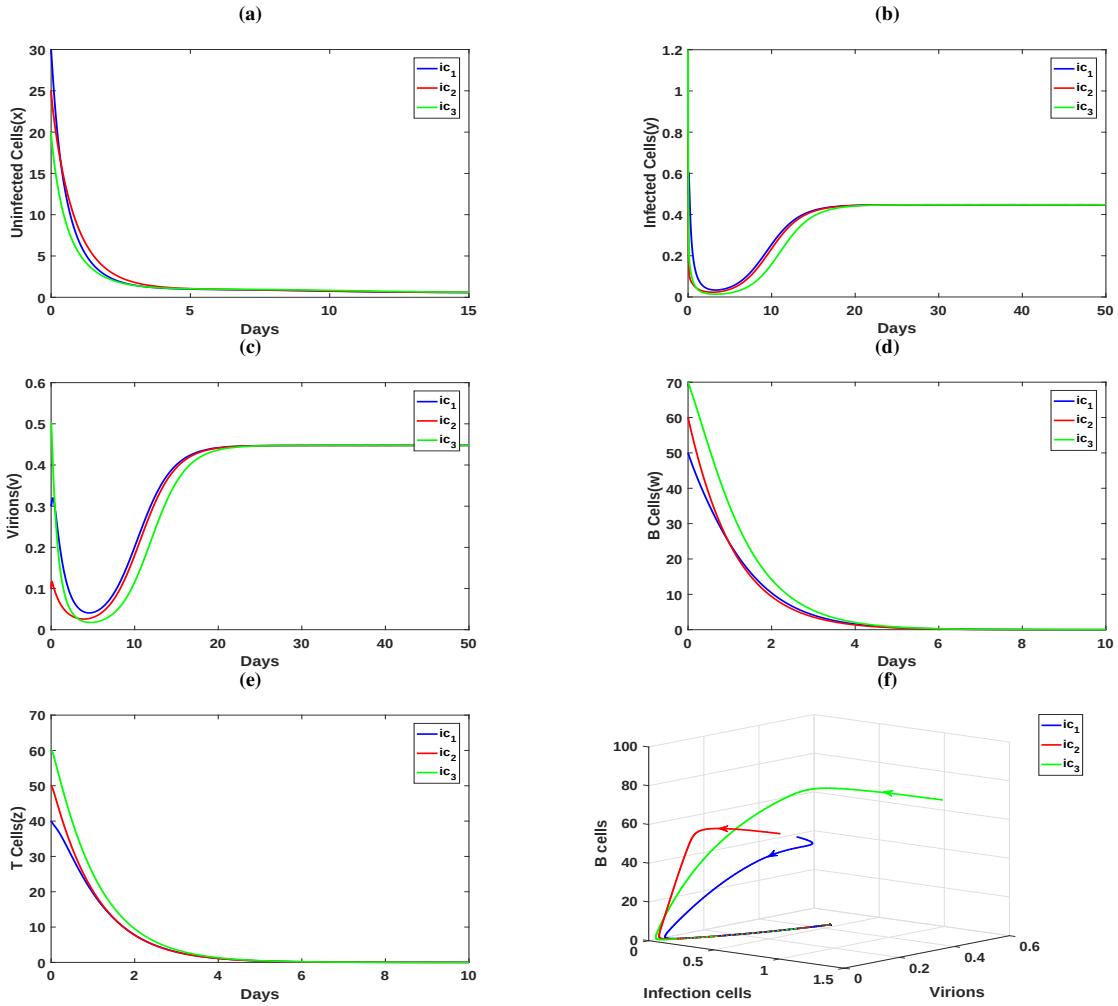

Figure 3. The evolution solution and phase diagram for model (1.2) with three different initial conditions ic_1, ic_2, and ic_3 in case of $R_1 < 1 < R_0$.

5.3. The stability of the infected equilibrium with both humoral and cellular immune responses E^*

Choose $\lambda = 10$, $d = 0.1$, $\beta = 0.1$, $\alpha = 0.0001$, $\gamma = 0.01$, $e = 0.1$, $p = 0.1$, $a = 0.1$, $K = 2.9$, $u = 0.006$, $f = 0.006$, $k = 0.1$, $c = 0.1$, $b_1 = 0.1$, $b_2 = 0.1$. As a result, we get $R_a = 2.9 > 1$, $R_b = 26.4385 > 1$ and $dx^* - ey^* > 0$. It is seen from Figure 4 that the curves for all the five functions x, y, v, w, and z oscillate for some time before approaching approximately towards the infected equilibrium with both humoral and cellular immune responses E^*. The observed steady state E_1 being globally asymptotically stable is in agreement with the theoretical result in Theorem 7. Therefore, during the infection phase, humoral and cellular immunity will be activated if sufficient levels of infected cells and free virions are produced.

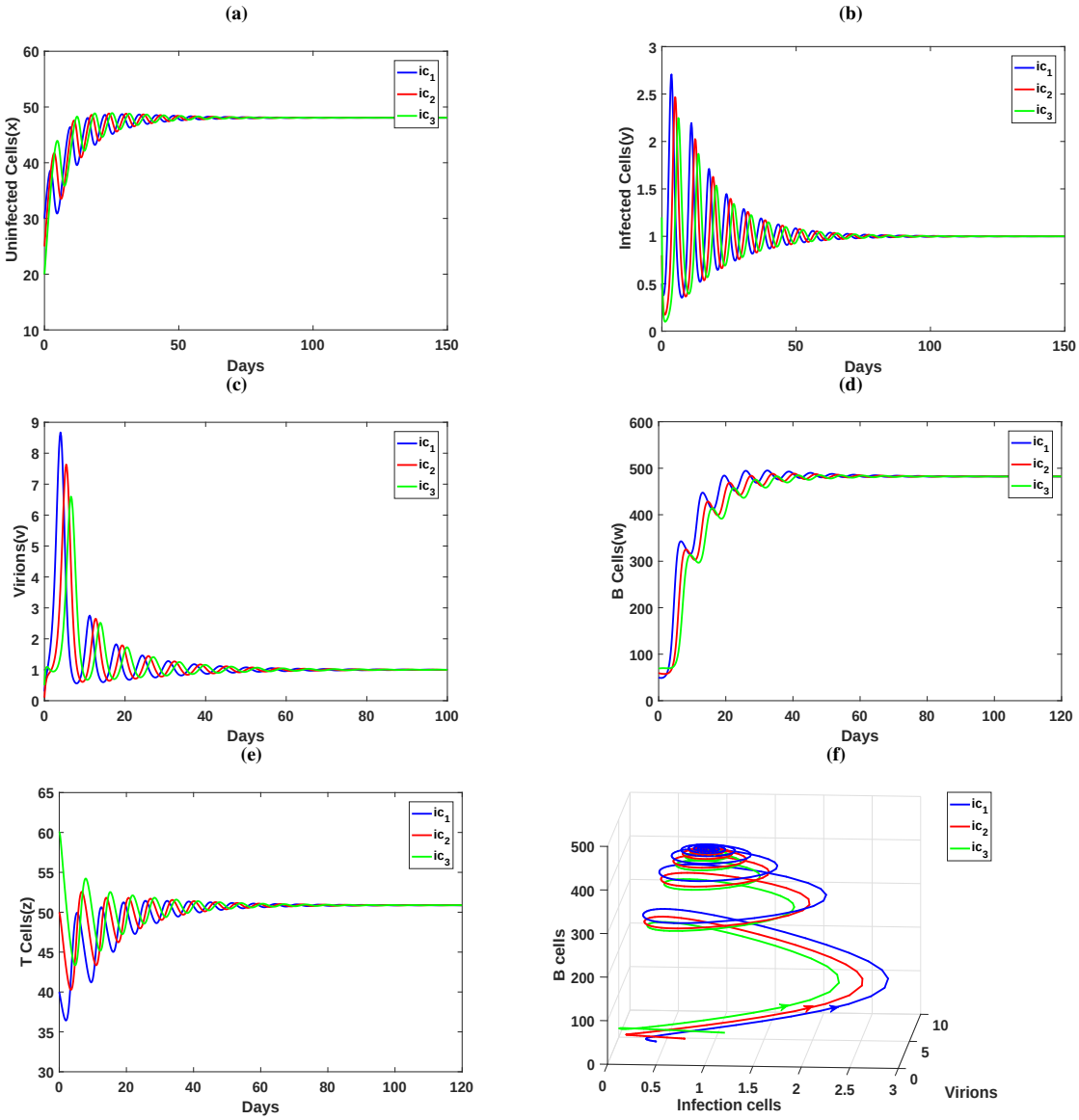

Figure 4. The evolution solution and phase diagram for model (1.2) with three different initial conditions ic_1, ic_2, and ic_3 in case of $1 < R_a$ and $1 < R_b$.

5.4. Sensitive analysis

Based on the above theoretical analysis, we found that R_b and R_0 are the main thresholds for controlling disease dynamics. In addition, we are interested in how cell apoptosis rate α, virus infection rate on cells γ, and intercellular transmission rate β affect disease dynamics. We choose $d = 0.01$, $\beta = 0.1$, $\gamma = 0.1$, $e = 0.1$, $p = 0.1$, $a = 0.01$, $k = 1$, $c = 1$, $b_1 = 1$, $b_2 = 1$. Based on the expression $R_b = \frac{(\beta b_2 k + b_1 \gamma c)(\lambda c + e b_2)}{(a+e)[dkc + (\alpha+\beta)kb_2 + b_1\gamma c]b_2}$, we give Figure 5 (a), which shows that R_b decreases the increase of apoptosis rate α, and R_b increases with the increase of recruitment rate λ. Therefore, we can improve the apoptosis rate and the recruitment rate to control the spread of HIV. In addition, we select the parameters $\lambda = 0.75$, $u = 6$, $K = 2.9$, $d = 0.01$, $a = 1$, $e = 0.01$ and combine the expression of $R_0 = \frac{(K\gamma + \beta u)\lambda}{du(a+e)}$ to obtain a three-dimensional graph of R_0 and γ, β; see Figure 5 (b), which indicates that decreasing the transmission virus infection rate on cells γ and intercellular transmission rate β can

effectively control the spread of HIV.

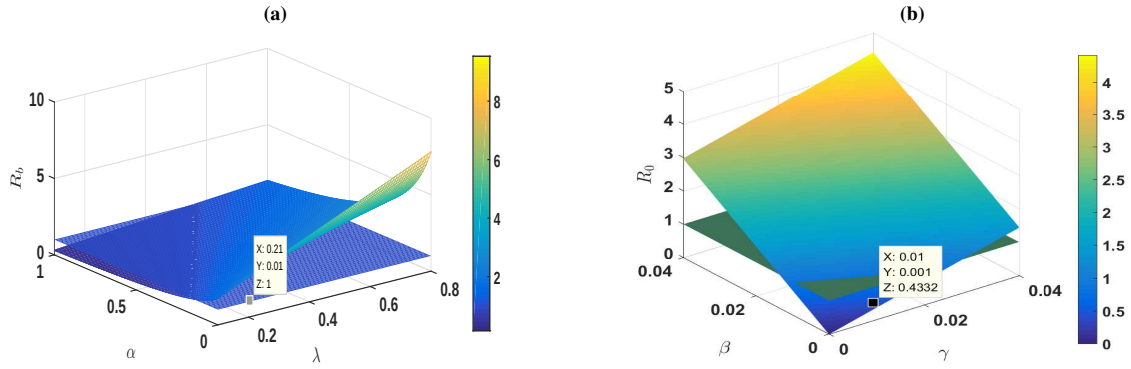

Figure 5. (a) Effect of apoptosis rate α and recruitment rate λ on R_b. (b) Effect of virus-to-cell infection rate γ and cell-to-cell infection rate β on R_0.

6. Conclusions

In this study, we model two modes of HIV transmission: cell-to-cell transmission and virus-to-cell infection. The model also incorporates two adaptive immunity types, that is, humoral and cellular immunity. Furthermore, the model accounts for apoptosis and the reversion of a fraction of infected cells to the uninfected class. Initially, we establish the positivity and boundedness of the solution and determine the basic reproduction number using the next-generation matrix approach. It follows from the expression of R_0 that ignoring cell-to-cell transmission or virus-to-cell infection may underestimate the value of R_0, and the apoptosis rate α does not affect the basic reproduction number R_0. However, even though the apoptosis rate α does not affect the basic regeneration number, it can determine the stability of the infected equilibrium with both humoral and cellular immune responses E^* (see Theorem 7). Moreover, due to the incorporation of two transmission modes (cell-to-cell transmission and virus-to-cell infection), two adaptive immunity types (humoral and cellular immunity), and the reversion of a fraction of infected cells to the uninfected class, the coupling degree of the model has increased, which has brought great difficulties to the stability analysis of the equilibrium point, especially for the immune response-free equilibrium E_1 and the infected equilibrium with both humoral and cellular immune responses E^*, (see Theorems 6 and 7). Finally, numerical simulations reveal that decreasing the transmission virus infection rate on cells γ and intercellular transmission rate β can effectively control the control the spread of HIV; moreover, proper regulation of apoptosis helps to eliminate viruses, control viral infections, and reduce viral damage to the host. Therefore, we can take some measures to reduce the transmission rate to control HIV transmission. For example, exhibiting safe sexual behaviours, receiving antiviral therapy (ART), and using pre-exposure drugs (PrEP).

Indeed, in addition to the factors considered above that affect viral dynamics, there are many others that can have an impact, such as impulse [27], noise [28], age structure [35], and so on [36–39]. In addition, cellular infection is closely related to the time of infection, due to the fact that healthy cells are in a latent infection state for some time after infection. Future studies may focus on modeling age structures that incorporate latent infection and further exploring the effects of latent infection and age structure on viral dynamics.

Use of AI tools declaration

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

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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