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A generalized viral immunological model in presence of adaptive immunity with lytic and non-lytic effects

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Abstract

This article develops a new mathematical model that describes the dynamics of viral infections in presence of adaptive immunity. The developed model accounts for the presence of a non-cytolytic cure and considers both cell-to-cell and virus-to-cell transmission modes, along with the lytic and non-lytic effects of both cellular and humoral immune responses. Moreover, the well-posedness of the model is demonstrated through the non-negativity and boundedness of its solutions. Also, five equilibriums are established and five threshold parameters are derived to ensure the global stability of these equilibria. Finally, the dynamics of the model have been shown through numerical illustrations using specific parameters related to human immunodeficiency virus (HIV) infection.

Keywords: Immunology, viral infection, mode of transmission, mathematical modeling, global stability.

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1. Introduction

After the introduction of the virus into the body, its spread occurs through several modes of transmission [14]. In addition to the conventional virus-to-cell mode of transmission, cell-to-cell transmission also plays a crucial role in the spread of the virus. The propagation of the virus is facilitated by its three-dimensional diffusion, creating concentration gradients around infected cells. Moreover, surface retention and cell-cell adhesion as well as cell-cell adhesion and polarization contribute to this process [27]. Merwaiss et al. [15] have explored the phenomenon of cell-to-cell transmission in the context of the bovine viral diarrhea virus (BVDV), while Sattentau's work has shed light on its relevance to human immunodeficiency virus (HIV) transmission [20]. Additionally, Zeng's research has delved into cell-to-cell transmission with regard to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [26]. Notably, Xiao et al. [25] demonstrated that the inhibition of cell-to-cell transmission could lead to the clearance of the hepatitis C virus (HCV).

When faced with a viral infection, the body activates its immune system. There are two main categories of immune responses: innate immunity and the adaptive immune response, also known as the

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specific response. The latter has two branches: cellular immunity which involves cytotoxic T lymphocyte (CTL) cells, and humoral immunity which operates through antibodies. Adaptive immunity it also functions in countering viral infections through two mechanisms: lytic and non-lytic. The lytic immune response of CTL cells consists of killing infected cells, while the antibody immune response neutralizes the virus. The non-lytic immune response involves inhibiting viral replication through soluble factors secreted by immune cells [24]. The non-lytic impact of immunity was initially modelled by Wodarz, without making a distinction between the contribution of antibodies and CTL cells [24]. Subsequently, multiple models were developed that account for the non-lytic influence of antibodies [3, 11] and CTL cells [9] separately. Further, other recent immunological models described by delay differential equations (DDES) have been presented in [1, 18, 19].

A cure is characterized by a non-cytolytic recovery mechanism, facilitating the transformation of some infected cells into uninfected ones. Guidotti et al. [5] have observed cytokine-induced recovery in individuals afflicted with acute hepatitis B. This recovery is the result of the loss of covalently closed circular DNA (cccDNA) from their nucleus [5].

Motivated by both biological factors and mathematical models cited above, we develop a mathematical model for viral infection that takes into account the cure of infected cells, both cell-to-cell and virus-to-cell transmissions, as well as the adaptative immunity with lytic and non-lytic effects. The developed model is formulated by the following system of ordinary differential equations (ODEs):

$$\begin{cases} U'(t) = \lambda - d_U U - \dfrac{\beta_1 UV}{(1+q_1 C)(1+\overline{q_1}A)} - \dfrac{\beta_2 UI}{(1+q_2 C)(1+\overline{q_2}A)} + \epsilon I, \\ I'(t) = \dfrac{\beta_1 UV}{(1+q_1 C)(1+\overline{q_1}A)} + \dfrac{\beta_2 UI}{(1+q_2 C)(1+\overline{q_2}A)} - (d_I + \epsilon) I - pIC, \\ V'(t) = kI - d_V V - rVA, \\ C'(t) = \sigma IC - d_C C, \\ A'(t) = \rho VA - d_A A, \end{cases} \tag{1.1}$$

where $U(t)$, $I(t)$, $V(t)$, $C(t)$, and $A(t)$ denote the concentrations of the uninfected cells, infected cells, virus particles, CTL cells, and antibodies at time t, respectively. It is assumed that uninfected cells are produced at a constant rate λ, die at rate d_U, and become infected with either the virus-to-cell mode of transmission at rate $\beta_1 UV$ or the cell-to-cell mode of transmission at rate $\beta_2 UI$. Both modes of infection are inhibited by the non-lytic component of cellular immunity at rates $1 + q_1 C$ and $1 + q_2 C$, respectively and by the non-lytic component of humoral immunity at rate $1 + \overline{q_1}A$ and $1 + \overline{q_2}A$, respectively. Infected cells die at rate d_I and are killed by the lytic component of cellular immunity at rate pIC and return to the uninfected state at rate ϵI. The virus is produced at rate kI and cleared at rate $d_V V$. Antibodies occur at rate ρVA, die at rate $d_A A$, and neutralize the virus at rate rVA. CTL cells occur at rate σIC and die at rate $d_C C$. The flow diagram of our model is shown in Figure 1. In addition, Table 1 summarizes the biological meaning of each parameter of model (1.1).

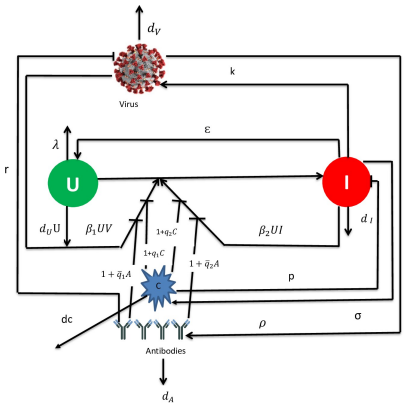

Figure 1: The flowchart representing the dynamics of model (1.1).

Table 1: Biological meanings of model's parameters.

Parameter	Biological meaning
λ	Production rate of uninfected cells
d_U	Death rate of uninfected cells
d_I	Death rate of infected cells
d_V	Clearance rate of virions
k	Viral production rate
p	Clearance rate of infection by CTL cells
r	Neutralization rate of virus by antibodies
d_A	Death rate of antibodies
d_C	Death rate of CTL cells
q_1	CTL non-lytic strength against virus-to-cell infection
$\overline{q}_1$	Antibodies non-lytic strength against virus-to-cell infection
q_2	CTL non-lytic strength against cell-to-cell infection
$\overline{q}_2$	Antibodies non-lytic strength against cell-to-cell infection
β_1	Virus-to-cell infection rate
β_2	Cell-to-cell infection rate
ρ	Activation rate of antibodies
σ	Activation rate of CTL cells
ϵ	Cure rate of infected cells

The importance of the present study is that our model formulated by system (1.1) covers and improves numerous mathematical models recently constructed to describe the dynamics of viral infections. For instance, in the absence of humoral immunity and the cure of infected cells, system (1.1) comes back to the model introduced by Hattaf and Yousfi in [9] for SARS-CoV-2 infection that includes the models proposed in [4, 13, 16]. In the absence of cellular immunity, system (1.1) is reduced to the immunological model presented by El Karimi et al. [11], which includes the recent viral models proposed in [2, 3, 10, 17]. Furthermore, the model of Wodarz [23] for HCV infection in presence of both humoral and cellular immunity is improved and generalized by considering cell-to-cell transmission, cure of infected cells, as well as lytic and non-lytic immune responses effects.

The rest of the paper is organized as follows. The next section establishes the basic results including the well-posedness of the model by establishing the global existence, uniqueness, non-negativity, and boundedness of solutions, as well as the threshold parameters and equilibria. Section 3 is dedicated to the study of the global stability for the equilibria using the Lyapunov functions. As for Section 4, it illustrates our analytical findings by numerical simulations based on biological parameters related to the case of HIV infection. The conclusion of our work on the results is the focus in the last section.

2. Basic results

By the standard results on differential equations, it is obvious that the model (1.1) admits a unique solution. In this section, we determine some basic results concerning the proprieties of such solution, equilibria and threshold parameters like the basic reproduction number and the reproduction numbers for adaptative immunity.

Theorem 2.1. *Any solution of system* (1.1) *with non-negative initial conditions, remains non-negative and bounded for all* $t \geqslant 0$.

Proof. From system (1.1), we have

$$\frac{dU}{dt}|_{U=0} = \lambda + \epsilon I \geqslant 0, \text{ for all } I \geqslant 0,$$

$$\begin{aligned}
&\frac{dI}{dt}|_{I=0} = \frac{\beta_1 UV}{(1+q_1C)(1+\overline{q_1}A)} \geqslant 0, \text{ for all } U, V, A, C \geqslant 0,\\
&\frac{dV}{dt}|_{V=0} = kI \geqslant 0, \text{ for all } I \geqslant 0,\\
&\frac{dC}{dt}|_{C=0} = 0,\\
&\frac{dA}{dt}|_{A=0} = 0.
\end{aligned}$$

Hence, it follows from [21, Proposition B.7] that U, I, V, C, and A are non-negative. Next, let consider

$$N(t) = U(t) + I(t) + \frac{d_I}{2k}V(t) + \frac{p}{\sigma}C(t) + \frac{rd_I}{2k\rho}A.$$

Then

$$N'(t) = \lambda - d_U U - \frac{d_I}{2}I(t) - \frac{d_I d_V}{2k}V - \frac{pd_C}{r}C(t) - \frac{rd_I d_A}{2k\rho}A \leqslant \lambda - dN(t),$$

where $d = \min\{d_U, \frac{d_I}{2}, d_V, d_C, d_A\}$. Hence, $\limsup_{t\to+\infty} N(t) \leqslant \frac{\lambda}{d}$. Therefore, U, I, V, C, and A are bounded. This completes the proof. □

Now, we determine all possible equilibria of the system (1.1). Obviously, the point $N_0 = (U_0, 0, 0, 0, 0)$ with $U_0 = \frac{\lambda}{d_U}$ is an equilibrium corresponding to the state without infection called the infection-free equilibrium. As a result, the basic reproduction number R_0 given by

$$R_0 = \frac{\lambda(k\beta_1 + d_V\beta_2)}{d_U(d_I+\epsilon)d_V} = R_{01} + R_{02},$$

where $R_{01} = \frac{\lambda k\beta_1}{d_U(d_I+\epsilon)d_V}$ and $R_{02} = \frac{\lambda k\beta_2}{d_U(d_I+\epsilon)}$ are the basic reproduction numbers related to virus-to-cell and cell-to-cell transmission, respectively. Biologically, R_0 represents the average number of secondary infections produced by one infected cell at the beginning of infection. When $R_0 > 1$, model (1.1) has a second equilibrium point $N_1 = (U_1, I_1, V_1, 0, 0)$, where

$$U_1 = \frac{\lambda}{d_U R_0}, \quad I_1 = \frac{\lambda(R_0-1)}{d_I R_0}, \quad \text{and} \quad V_1 = \frac{k\lambda(R_0-1)}{d_I d_V R_0}.$$

This case corresponds to the presence of infection and the absence of immunity. In the presence of cellular immunity and the absence of humoral immunity, any equilibrium for the model (1.1) satisfies the following system

$$\begin{cases}
\lambda - d_U U - d_I I - pIC = 0,\\
\dfrac{\beta_1 UV}{1+q_1C} + \dfrac{\beta_2 UI}{1+q_2C} - (d_I+\epsilon)I - pIC = 0,\\
kI - d_V V = 0,\\
\sigma IC - d_C C = 0.
\end{cases}$$

Since $C > 0$, we have $I = \frac{d_C}{\sigma}$, $V = \frac{kd_C}{\sigma d_V}$, $C = \frac{\sigma(\lambda - d_U U) - d_I d_C}{pd_C}$, and $U\left[\frac{\beta_1 k}{d_V(1+q_1C)} + \frac{\beta_2}{1+q_2C}\right] - (d_I+\epsilon) - pC = 0$. Let $u_1^* = \frac{\lambda}{d_U} - \frac{d_I d_C}{\sigma d_U}$. Then $0 < U < u_1^*$. If the humoral immunity is not started (not established), then $\sigma I_1 - d_C \leqslant 0$. So, we define the reproduction number for cellular immunity as follows

$$R_1^C = \frac{\sigma I_1}{d_C} = \frac{\sigma\lambda(R_0-1)}{d_C d_I R_0},$$

which represents the average number of the CTL cells activated by infected cells when viral infection is successful and antibody immune response has failed [6]. Let us define the functions g_1 and f_1 on the closed interval $[0, u_1^*]$ as follows

$$g_1(U) = \frac{\sigma(\lambda - d_U U) - d_I d_C}{p d_C} \quad \text{and} \quad f_1(U) = U\left[\frac{\beta_1 k}{d_V(1+q_1 g_1(U))} + \frac{\beta_2}{1+q_2 g_1(U)}\right] - d_I - \epsilon - p g_1(U).$$

We have $f_1(0) = -d_I - \epsilon - p g_1(0) < 0$, $f_1(u_1^*) = u_1^*[\frac{\beta_1 k}{d_V} + \beta_2] - d_I - \epsilon$, and

$$f_1'(U) = \left[\frac{k\beta_1}{d_V(1+q_1 g_1(U))} + \frac{\beta_2}{1+q_2 g_1(U)}\right] - U\left[\frac{k\beta_1 q_1 g_1'(U)}{d_V(1+q_1 g_1(U))^2} + \frac{\beta_2 q_2 g_2'(U)}{(1+q_2 g_1(U))^2}\right] - p g_1'(U).$$

Since $g_1'(U) < 0$, we have $f_1'(U) > 0$. If $R_1^C < 1$, then $I_1 < \frac{d_C}{\sigma}$. Thus $U_1 > u_1^*$ and we have

$$f_1(u_1^*) = u_1^*[\frac{k}{d_V}\beta_1 + \beta_2] - d_I - \epsilon < U_1[\frac{k}{d_V}\beta_1 + \beta_2] - d_I - \epsilon.$$

Moreover, $U_1[\frac{k}{d_V}\beta_1 + \beta_2] - d_I - \epsilon = \frac{(d_I+\epsilon)d_V}{k\beta_1 + d_V\beta_2}[\frac{k}{d_V}\beta_1 + \beta_2] - d_I - \epsilon = 0$. So $f_1(u_1^*) < 0$. As f_1 is an increasing function, then $f_1(u) = 0$ has no solution and the model (1.1) has no equilibrium. If $R_1^C > 1$, then $U_1 < u_1^*$ and $f_1(u_1^*) > 0$. Thus, there is a unique point $U_2 \in (0, u_1^*)$ such that $f_1(U_2) = 0$, this establishes the existence and uniqueness of an equilibrium point of the model (1.1), when $C \neq 0$, $A = 0$, and $R_1^C > 1$.

In the presence of humoral immunity and the absence of CTL immunity, any equilibrium must satisfy the following system

$$\begin{cases} \lambda - d_U U - d_I I = 0, \\ \dfrac{\beta_1 U V}{1+\overline{q_1}A} + \dfrac{\beta_2 U I}{1+\overline{q_2}A} - (d_I+\epsilon)I = 0, \\ kI - d_V V - rVA = 0, \\ \rho VA - d_A A = 0. \end{cases} \tag{2.1}$$

By system (2.1) we deduce that $V = \frac{d_A}{\rho}$, $I = \frac{1}{d_I}(\lambda - d_U U)$, and A and U satisfy the following equations

$$A = \frac{k\rho}{r d_A d_I}(\lambda - d_U U) - \frac{d_V}{r} \quad \text{and} \quad U\left[\frac{\beta_1 d_A}{\rho(1+\overline{q_1}A)} + \frac{\beta_2(\lambda - d_U U)}{d_I(1+\overline{q_2}A)}\right] - \frac{d_I+\epsilon}{d_I}(\lambda - d_U U) = 0.$$

By the last equation of the system (1.1), if the humoral immunity has not started, then $\rho V - d_A \leqslant 0$, so we define the reproduction number for humoral immunity by

$$R_1^A = \frac{\rho}{d_A} V_1 = \frac{\rho k \lambda}{d_A d_I d_V R_0}(R_0 - 1),$$

which represents the average number of the antibodies activated by virus when viral infection is successful and CTL immune response has failed [6]. Since $A > 0$, then $0 < U < u_2^*$, where $u_2^* = \frac{\lambda}{d_U} - \frac{d_V d_A d_I}{k\rho d_U}$. Now, consider the functions g_2 and f_2 defined on the closed interval $[0, u_2^*]$ by

$$g_2(U) = \frac{k\rho}{r d_A d_I}(\lambda - d_U U) - \frac{d_V}{r} \quad \text{and} \quad f_2(U) = U\left[\frac{\beta_1 d_A}{\rho(1+\overline{q_1}g_2(U))} + \frac{\beta_2(\lambda - d_U U)}{d_I(1+\overline{q_2}g_2(U))}\right] - \frac{d_I+\epsilon}{d_I}(\lambda - d_U U).$$

We have $f_2(0) < 0$ and by computation $f_2(u_2^*) = \frac{d_I d_V d_A^2}{k^2\rho^2 d_U}(k\beta_1 + d_V\beta_2)(R_1^A - 1)$. If $R_1^A > 1$, then $f_2(u_2^*) > 0$. Thus, there is a point $U_3 \in (0, u_2^*)$ such that $f_2(U_3) = 0$. Furthermore, using the equality $d_I + \epsilon =$

$\frac{\beta_1 U_3 V}{I(1+\overline{q_1}A)} + \frac{\beta_2 U_3}{1+\overline{q_2}A}$, we deduce that

$$f_2'(U_3) = \beta_1 V \frac{1+\overline{q_1}g_2(U_3) - \overline{q_1}U_3 g_2'(U_3)}{(1+\overline{q_1}g_2(U_3))^2} - \frac{\beta_2 U_3 \overline{q_2} g_2'(U_3) h(U_3)}{(1+\overline{q_2}g_2(U_3))^2} - h'(U_3)\frac{\beta_1 U_3 V}{h(U_3)(1+\overline{q_1}g_2(U_3))},$$

where $h(U) = \frac{1}{d_U}(\lambda - d_U U)$. Since $h' < 0$ and $g_2' < 0$, then $f_2'(U_3) > 0$, this establishes the uniqueness of U_3 and therefore that of the equilibrium point $N_3 = (U_3, I_3, V_3, 0, A_3)$, where $I_3 = h(U_3)$, $V_3 = \dfrac{d_A}{\rho}$, and $A_3 = g_2(U_3)$.

Now, we consider the ultimate case, which corresponds to $A \neq 0$ and $C \neq 0$. Any equilibrium point must satisfy the following system

$$\begin{cases} \lambda - d_U U - d_I I - pIC = 0, \\ \dfrac{\beta_1 UV}{(1+q_1 C)(1+\overline{q_1}A)} + \dfrac{\beta_2 UI}{(1+q_1 C)(1+\overline{q_2}A)} - (d_I+\epsilon)I - pIC = 0, \\ kI - d_V V - rVA = 0, \\ \sigma IC - d_C C = 0, \\ \rho VA - d_A A = 0. \end{cases}$$

So, $V = \dfrac{d_A}{\rho}$, $I = \dfrac{d_C}{\sigma}$, $A = \dfrac{k\rho d_C}{r\sigma d_A} - \dfrac{d_V}{r}$, and $C = \dfrac{\sigma}{p d_C}(\lambda - d_U U) - \dfrac{d_I}{p}$. In addition, we have the following equation

$$U\left[\frac{\beta_1 V}{(1+q_1 C)(1+\overline{q_1}A)} + \frac{\beta_2 I}{(1+q_1 C)(1+\overline{q_2}A)}\right] - (d_I+\epsilon)I - pIC = 0.$$

Since $C > 0$, $0 < U < u_3^*$, where $u_3^* = \dfrac{1}{\sigma d_U}(\lambda\sigma - d_I d_C)$. So, we define the functions g_3 and f_3 on the interval $[0, u_3^*]$ by

$$\begin{aligned} g_3(U) &= \frac{\sigma}{p d_C}(\lambda - d_U U) - \frac{d_I}{p}, \\ f_3(U) &= U\left[\frac{\beta_1 V}{(1+q_1 g_3(U))(1+\overline{q_1}A)} + \frac{\beta_2 I}{(1+q_1 g_3(U))(1+\overline{q_2}A)}\right] - (d_I+\epsilon)I - pIg_3(U). \end{aligned}$$

Thus, in the presence of both humoral and cellular immunity, the model (1.1) admits an equilibrium point if and only if there is $U_4 \in (0, u_3^*)$ such that $f_3(U_4) = 0$, in this case, the equilibrium point is given by

$$N_4 = \left(U_4, \frac{d_C}{\sigma}, \frac{d_A}{\rho}, g_3(U_4), \frac{k\rho d_C}{r\sigma d_A} - \frac{d_V}{r}\right).$$

Now, we define the reproduction number for humoral immunity in competition as

$$R_2^A = \frac{\rho}{d_A} V_2 = \frac{\rho k d_C}{\sigma d_V d_A},$$

where $V_2 = \dfrac{k d_C}{d_V d_A}$, as well as the reproduction number for cellular immunity in competition as

$$R_2^C = \frac{\sigma}{d_C} I_3 = \frac{I_3}{I_4} = \frac{\sigma}{d_I d_C}(\lambda - d_U U_3).$$

From the biological perspective, R_2^C provides a measure for the average number of CTL cells activated by infected cells when the antibody immune response is already triggered, and R_2^A describes the same for antibody immune cells activated by virions when the CTL immune response is already triggered

[6, 22]. Note that $A_4 = \frac{d_V}{r}(R_2^A - 1)$, so $R_2^A > 1$. We have $f_3(0) = -(d_I + \epsilon)I_4 - pI_4g_3(0) < 0$ and $f_3' > 0$. Furthermore,

$$f_3(u_3^*) = \frac{I_4}{I_3}\left[u_3^*\left(\frac{I_3}{I_4}\frac{\beta_1 V_3}{1+\overline{q_1}A_4} + \frac{\beta_2 I_3}{1+\overline{q_2}A_4}\right) - (d_I+\epsilon)I_3\right],$$

thus, if $R_2^C \leqslant 1$, then $I_3 \leqslant I_4$, $u_3^* \leqslant U_3$, and $A_3 \leqslant A_4$, so, we deduce

$$f_3(u_3^*) \leqslant \frac{I_4}{I_3}\left[U_3\left(\frac{\beta_1 V_3}{1+\overline{q_1}A_3} + \frac{\beta_2 I_3}{1+\overline{q_2}A_3}\right) - (d_I+\epsilon)I_3\right] = \frac{I_4}{I_3}f_2(U_3) = 0.$$

It follows that $f_3 < 0$ on the interval $(0, u_3^*)$ and the model (1.1) has no equilibrium when $R_2^C \leqslant 1$. On the other hand, if $R_2^C > 1$, then $I_3 > I_4$, $u_3^* > U_3$, $A_3 > A_4$, and

$$f_3(u_3^*) > \frac{I_4}{I_3}\left[U_3\left(\frac{\beta_1 V_3}{1+\overline{q_1}A_3} + \frac{\beta_2 I_3}{1+\overline{q_2}A_3}\right) - d_I I_3\right] = \frac{I_4}{I_3}f_2(U_3) = 0.$$

It follows that there is a unique point $U_4 \in (0, u_2^*)$ such that $f_3(U_4) = 0$. Thus if $R_2^C > 1$, then the model (1.1) admits a unique equilibrium.

We summarize the discussions above to the following theorem.

Theorem 2.2.

1. *If* $R_0 \leqslant 1$, *then model* (1.1) *admits one infection-free equilibrium* $N_0 = (U_0, 0, 0, 0, 0)$, *where* $U_0 = \frac{\lambda}{d_U}$.
2. *If* $R_0 > 1$, *then model* (1.1) *has an infection equilibrium without immunity,* $N_1 = (U_1, I_1, V_1, 0, 0)$, *where*
$$U_1 = \frac{\lambda}{d_U R_0}, \quad I_1 = \frac{\lambda(R_0-1)}{d_I R_0}, \quad \textit{and} \quad V_1 = \frac{k\lambda(R_0-1)}{d_I d_V R_0}.$$
3. *If* $R_1^C > 1$, *then the model* (1.1) *has an infection equilibrium with only cellular immunity* $N_2 = (U_2, I_2, V_2, C_2, 0)$, *where*
$$U_2 \in (0, \frac{\lambda}{d_U} - \frac{d_I d_C}{\sigma d_U}), \quad I_2 = \frac{d_C}{\rho}, \quad V_2 = \frac{k d_C}{\rho d_V}, \quad \textit{and} \quad C_2 = \frac{\sigma(\lambda - d_U U_2) - d_I d_C}{p d_C}.$$
4. *If* $R_1^A > 1$, *then model* (1.1) *has an equilibrium with only humoral immunity* $N_3 = (U_3, I_3, V_3, 0, A_3)$, *where*
$$U_3 \in (0, \frac{\lambda}{d_U} - \frac{d_I d_V d_A}{k\rho d_U}), \quad I_3 = \frac{1}{d_I}(\lambda - d_U U_3), \quad V_3 = \frac{d_A}{\rho}, \quad \textit{and} \quad A_3 = \frac{k\rho(\lambda - d_U U_3)}{r d_A d_I} - \frac{d_V}{r}.$$
5. *If* $R_2^A > 1$ *and* $R_2^C > 1$, *then model* (1.1) *has an infection equilibrium with both cellular and humoral immune responses* $N_4 = (U_4, I_4, V_4, C_4, A_4)$, *where*
$$U_4 \in (0, \frac{(\lambda\sigma - d_I d_C)}{\sigma d_U}), \quad I_4 = \frac{d_C}{\sigma}, \quad V_4 = \frac{d_A}{\rho}, \quad C_4 = \frac{(\sigma(\lambda - d_U U) - d_I d_C)}{p d_C}, \quad \textit{and} \quad A_4 = \frac{k\rho d_C}{r\sigma d_A} - \frac{d_V}{r}.$$

3. Stability analysis

In this section, we study the stability of model's equilibria. In the next, we use the function ϕ given by $\phi(x) = x - 1 - \ln x$. Note that ϕ is defined and nonnegative on the interval $(0, +\infty)$. Moreover, $\phi(x) = 0$ if and only if $x = 1$.

Theorem 3.1. *The infection-free equilibrium* N_0 *is globally asymptotically stable if* $R_0 \leqslant 1$, *and becomes unstable when* $R_0 > 1$.

Proof. Let $N = (U, I, V, C, A)$ and consider the Lyapunov function T_0 defined by

$$T_0(N) = U_0\phi\left(\frac{U}{U_0}\right) + I + \frac{U_0\beta_1}{d_V}V + \frac{p}{\sigma}C + \frac{rU_0\beta_1 d_A}{\rho d_V}A.$$

We have $T_0(N) \geqslant 0$, for all $N \in \mathbb{R}_+^* \times (\mathbb{R}_+)^4$ and $T_0(N) = 0$ iff $N = N_0$. Furthermore, for any solution $N(t)$ of model (1.1), we have

$$\begin{aligned}
\frac{dT_0}{dt} &= -\frac{d_U}{U}(U-U_0)^2 + U_0\left[\frac{\beta_1 V}{(1+\overline{q_1}A)(1+q_1C)} + \frac{\beta_2 I}{(1+\overline{q_2}A)(1+q_2C)}\right] - d_I I - pIC \\
&\quad + \frac{U_0\beta_1}{d_V}V' + \frac{p}{\sigma}C' + \frac{rU_0\beta_1 d_A}{\rho d_V}A' \\
&\leqslant -\frac{d_U}{U}(U-U_0)^2 + U_0(\beta_1 V + \beta_2 I) - d_I I - pIC + \frac{U_0\beta_1}{d_V}V' + \frac{p}{\sigma}C' + \frac{rU_0\beta_1 d_A}{\rho d_V}A' \\
&\leqslant -\frac{d_U}{U}(U-U_0)^2 + d_I I(R_0 - 1) - \frac{P}{\sigma}d_C C - \frac{rU_0\beta_1 d_A}{\rho d_V}A.
\end{aligned}$$

Thus if $R_0 \leqslant 1$, then $\frac{dT_0}{dt} \leqslant 0$ and $\frac{dT_0}{dt} = 0$ iff $N = N_0$. By LaSalle's ivariance principle [12], we deduce that N_0 is globally asymptotically stable when $R_0 \leqslant 1$. If $R_0 > 1$, then the characteristic equation of model (1.1) at N_0 is given by

$$(x + d_U)(x + d_V)(x + d_A)w(x) = 0, \tag{3.1}$$

where $w(x) = (x^2 + d_V - \frac{\lambda\beta_2}{d_U} + d_I)x + d_V d_I(1 - R_0)$. We have $w(0) = d_V d_I(1 - R_0) < 0$ and $\lim\limits_{x\to+\infty} w(x) = +\infty$. Then the characteristic equation (3.1) has at least one positive eigenvalue, thus N_0 is unstable when $R_0 > 1$, which proves the theorem. □

To study the global stability of the remaining equilibria, we need the following condition

$$\begin{cases}
\left(\dfrac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_i)(1+\overline{q_1}A_i)} - 1\right)\left(\dfrac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_i)(1+\overline{q_1}A_i)} - \dfrac{V}{V_i}\right) \leqslant 0, \\
\left(\dfrac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_i)(1+\overline{q_1}A_i)} - 1\right)\left(\dfrac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_i)(1+\overline{q_1}A_i)} - \dfrac{I}{I_i}\right) \leqslant 0.
\end{cases} \tag{H}$$

Theorem 3.2. *If the condition* (H) *holds for* N_1, $R_1^A \leqslant 1$, *and* $R_1^C \leqslant 1$, *then the infection free-immunity equilibrium* N_1 *is globally asymptotically stable, and it becomes unstable if* $R_1^C > 1$ *or* $R_1^A > 1$.

Proof. We define the Lyapunov function as follows

$$T_1(N) = U_1\phi\left(\frac{U}{U_1}\right) + I_1\phi\left(\frac{I}{I_1}\right) + \frac{\beta_1 U_1 V_1}{kI_1}V_1\phi\left(\frac{V}{V_1}\right) + \frac{p}{\sigma}C + \frac{\beta_1 rU_1 V_1}{k\rho I_1}A.$$

Clearly, $T_1(N) \geqslant 0$, for all $N \in (\mathbb{R}_+^*)^3 \times \mathbb{R}_+^2$, and $T_1(N) = 0$ iff $N = N_1$. In addition along a solution $N(t)$, for model (1.1), we have

$$\begin{aligned}
\frac{dT_1}{dt} &= \left(1 - \frac{U_1}{U}\right)U' + \left(1 - \frac{I_1}{I}\right)I' + \left(1 - \frac{V_1}{V}\right)V' + \frac{p}{\sigma}C' + \frac{\beta_1 rU_1 V_1}{k\rho I_1}A' \\
&= \left(1 - \frac{U_1}{U}\right)\left(\lambda - d_U U - \frac{\beta_1 UV}{(1+q_1C)(1+\overline{q_1}A)} - \frac{\beta_2 UI}{(1+q_2C)(1+\overline{q_2}A)}\right) \\
&\quad + \left(1 - \frac{I_1}{I}\right)\left(\frac{\beta_1 UV}{(1+q_1C)(1+\overline{q_1}A)} + \frac{\beta_2 UI}{(1+q_2C)(1+\overline{q_2}A)} - d_I I - pIC\right) \\
&\quad + \left(1 - \frac{V_1}{V}\right)(kI - d_V V - rVA) + \frac{p}{\sigma}(\sigma IC - d_C C) + \frac{\beta_1 rU_1 V_1}{k\rho I_1}(\rho VA - d_A A).
\end{aligned}$$

Since $\lambda = d_U U_1 + \beta_1 U_1 V_1 + \beta_2 U_1 I_1$, $d_I = \dfrac{\beta_1 U_1 V_1}{I_1} + \beta_2 U_1$ and $d_V V_1 = kI_1$, we deduce that

$$\begin{aligned}
\frac{dT_1}{dt} &= \left(1-\frac{U_1}{U}\right)\left(d_U(U_1-U)+\beta_1 U_1 V_1 - \frac{\beta_1 UV}{(1+q_1C)(1+\overline{q_1}A)} + \beta_2 U_1 I_1 - \frac{\beta_2 UI}{(1+q_2C)(1+\overline{q_2}A)}\right)\\
&+\left(1-\frac{I_1}{I}\right)\left(\frac{\beta_1 UV}{(1+q_1C)(1+\overline{q_1}A)} + \frac{\beta_2 UI}{(1+q_2C)(1+\overline{q_2}A)} - (\frac{\beta_1 U_1 V_1}{I_1} + \beta_2 U_1)I - pIC\right)\\
&+\left(1-\frac{V_1}{V}\right)(kI - \frac{kI_1}{V_1}V - rVA) + \frac{p}{\sigma}(\sigma IC - d_C C) + \frac{\beta_1 r U_1 V_1}{k\rho I_1}(\rho VA - d_A A)\\
&= -\frac{d_U}{U}(U-U_1)^2 + \beta_2 U_1 I_1\left(3 - \frac{U_1}{U} - \frac{U}{U_1(1+q_2C)(1+\overline{q_2}A)} - (1+q_2C)(1+\overline{q_2}A)\right)\\
&+\beta_1 U_1 V_1\left(4 - \frac{U_1}{U} - \frac{V_1 I}{VI_1} - \frac{UVI_1}{U_1 V_1 I(1+q_1C)(1+\overline{q_1}A)} - (1+q_1C)(1+\overline{q_1}A)\right)\\
&+\beta_1 U_1 V_1\left(-1+(1+q_1C)(1+\overline{q_1}A) - \frac{V}{V_1} + \frac{V}{V_1(1+q_1C)(1+\overline{q_1}A)}\right)\\
&+\beta_2 U_1 I_1\left(-1+(1+q_2C)(1+\overline{q_2}A) - \frac{I}{I_1} + \frac{I}{I_1(1+q_2C)(1+\overline{q_2}A)}\right)\\
&+\frac{pd_C}{\sigma}C(R_1^C-1) + \frac{\beta_1 U_1 V_1^2 r}{kI_1 R_1^A}A(R_1^A-1).
\end{aligned}$$

By the arithmetic-geometric mean inequality, we have

$$\begin{aligned}
3 - \frac{U_1}{U} - \frac{U}{U_1(1+q_2C)(1+\overline{q_2}A)} - (1+q_2C)(1+\overline{q_2}A) &\leqslant 0,\\
4 - \frac{U_1}{U} - \frac{V_1 I}{VI_1} - \frac{UVI_1}{U_1 V_1 I(1+q_1C)(1+\overline{q_1}A)} - (1+q_1C)(1+\overline{q_1}A) &\leqslant 0.
\end{aligned}$$

In addition, we have from the condtion (H) that

$$\begin{aligned}
&-1+(1+q_1C)(1+\overline{q_1}A) - \frac{V}{V_1} + \frac{V}{V_1(1+q_1C)(1+\overline{q_1}A)}\\
&= \frac{(1+q_1C_1)(1+\overline{q_1}A_1)}{(1+q_1C)(1+\overline{q_1}A)}\left[\frac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_1)(1+\overline{q_1}A_1)} - 1\right]\left[\frac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_1)(1+\overline{q_1}A_1)} - \frac{V}{V_1}\right] \leqslant 0,
\end{aligned}$$

and

$$\begin{aligned}
&-1+(1+q_2C)(1+\overline{q_2}A) - \frac{I}{I_1} + \frac{I}{I_1(1+q_2C)(1+\overline{q_2}A)}\\
&= \frac{(1+q_2C_1)(1+\overline{q_2}A_1)}{(1+q_2C)(1+\overline{q_2}A)}\left[\frac{(1+q_2C)(1+\overline{q_2}A)}{(1+q_2C_1)(1+\overline{q_2}A_1)} - 1\right]\left[\frac{(1+q_2C)(1+\overline{q_2}A)}{(1+q_2C_1)(1+\overline{q_2}A_1)} - \frac{I}{I_1}\right] \leqslant 0.
\end{aligned}$$

Hence, $\dfrac{dT_1}{dt} \leqslant 0$, when $R_1^A \leqslant 1$ and $R_1^C \leqslant 1$. It is clear that $\dfrac{dT_1}{dt} = 0$ iff $U = U_1$, $I = 1$, $V = V_1$, $C = C_1$, and $A = 0$. Then by LaSalle's invariance principle, N_1 is globally asymptotically stable. The characteristic equation of model (1.1) at the equilibrium N_1 is given by

$$(\rho V_1 - d_A - x)(\sigma I_1 - d_C - x)\begin{vmatrix} -d_V - x & -d_I & 0\\ \beta_1 V_1 + \beta_2 I_1 & \beta_2 U_1 - d_I - x & \beta_1 U_1\\ 0 & k & -d_V - x\end{vmatrix} = 0, \tag{3.2}$$

we have $\rho V_1 - d_A = d_A(R_1^A - 1)$ and $\sigma I_1 - d_C = d_C(R_1^C - 1)$ are a roots of the equation (3.2). Thus, if $R_1^A > 1$ or $R_1^C > 1$, then the equation (3.2) has at least one positive root. This implies that the equilibrium N_1 is unstable, when $R_1^A > 1$ or $R_1^C > 1$. □

Theorem 3.3. *If* $R_2^A \leqslant 1 < R_1^C$ *and the condition* (H) *holds for* N_2*, then the infection equilibrium with only cellular immunty* N_2 *is globally asymptotically stable.*

Proof. We consider the Lyapunov function defined as follows

$$T_2(N) = U_2\phi\left(\frac{U}{U_2}\right) + I_2\phi\left(\frac{I}{I_2}\right) + \frac{\beta_1 U_2 V_2}{(1+q_1C)kI_2}V_2\phi\left(\frac{V}{V_2}\right) + \frac{p}{\sigma}C_2\phi\left(\frac{C}{C_2}\right) + \frac{\beta_1 r U_2 V_2}{(1+q_1C_2)\rho k I_2}A.$$

It is obvious that $T_2(N) \geqslant 0$, for any point $N \in (\mathbb{R}_+^*)^4 \times \mathbb{R}_+$, with equality iff $N = N_2$. Moreover, along a solution $N(t)$ of the model (1.1), we have

$$\begin{aligned}\frac{dT_2}{dt} &= \left(1-\frac{U_2}{U}\right)\left(\lambda - d_U U - \frac{\beta_1 U_2 V_2}{(1+q_1C)(1+\overline{q_1}A)} - \frac{\beta_2 U_2 I_2}{(1+q_2C)(1+\overline{q_2}A)}\right)\\ &+ \left(1-\frac{I-2}{I}\right)\left(\frac{\beta_1 U_2 V_2}{(1+q_1C)(1+\overline{q_1}A)} + \frac{\beta_2 U_2 I_2}{(1+q_2C)(1+\overline{q_2}A)} - d_I I - pIC\right)\\ &+ \frac{p}{\sigma}\left(1-\frac{C_2}{C}\right)(\sigma IC - d_C C) + \frac{\beta_1 r U_2 V_2}{(1+q_1C_2)\rho k I_2}(\rho AV - d_A A).\end{aligned}$$

Using the following equalities

$$\begin{cases}\lambda = d_U U_2 + \dfrac{\beta_1 U_2 V_2}{(1+q_1C_2)} + \dfrac{\beta_2 U_2 I_2}{(1+q_2C_2)},\\ d_I I_2 = \dfrac{\beta_1 U_2 V_2}{(1+q_1C_2)} + \dfrac{\beta_2 U_2 I_2}{(1+q_2C_2)},\\ d_V V_2 = kI_2,\\ I_2 = \dfrac{d_C}{\sigma},\end{cases}$$

and after simple computations, we obtain

$$\begin{aligned}\frac{dT_2}{dt} &= -\frac{d_U}{U}(U-U_2)^2 + \frac{\beta_2 U_2 I_2}{1+q_2C_2}\left(3 - \frac{U_2}{U} - \frac{U(1+q_2C_2)}{U_2(1+q_2C)(1+\overline{q_2}A)} - \frac{(1+q_2C)(1+\overline{q_2}A)}{1+q_2C_2}\right)\\ &+ \frac{\beta_1 U_2 V_2}{1+q_1C_2}\left(4 - \frac{U_2}{U} - \frac{IV_2}{I_2V} - \frac{UVI_2(1+q_1C_2)}{U_2V_2I(1+q_1C)(1+\overline{q_1}A)} - \frac{(1+q_1C)(1+\overline{q_1}A)}{1+q_1C_2}\right)\\ &+ \frac{\beta_1 U_2 V_2}{1+q_1C_2}\left(-1 + \frac{(1+q_1C)(1+\overline{q_1}A)}{1+q_1C_2} - \frac{V}{V_2} + \frac{V(1+q_1C_2)}{V_2(1+q_1C)(1+\overline{q_1}A)}\right)\\ &+ \frac{\beta_2 U_2 I_2}{1+q_2C_2}\left(-1 + \frac{(1+q_2C)(1+\overline{q_2}A)}{1+q_2C_2} - \frac{I}{I_2} + \frac{I(1+q_2C_2)}{I_2(1+q_2C)(1+\overline{q_2}A)}\right) + \frac{\beta_1 r U_2 V_2 d_A}{\rho k(1+q_1C_2)I_2}A(R_2^A - 1).\end{aligned}$$

According to the arithmetic-geometric mean inequality, we have

$$\begin{aligned}3 - \frac{U_2}{U} - \frac{U(1+q_2C_2)}{U_2(1+q_2C)(1+\overline{q_2}A)} - \frac{(1+q_2C)(1+\overline{q_2}A)}{1+q_2C_2} &\leqslant 0,\\ 4 - \frac{U_2}{U} - \frac{IV_2}{I_2V} - \frac{UVI_2(1+q_1C_2)}{U_2V_2I(1+q_1C)(1+\overline{q_1}A)} - \frac{(1+q_1C)(1+\overline{q_1}A)}{1+q_1C_2} &\leqslant 0.\end{aligned}$$

From the condition (H), we have

$$\begin{aligned}-1 + \frac{(1+q_2C)(1+\overline{q_2}A)}{1+q_2C_2} - \frac{I}{I_2} + \frac{I(1+q_2C_2)}{I_2(1+q_2C)(1+\overline{q_2}A)} &\leqslant 0,\\ -1 + \frac{(1+q_1C)(1+\overline{q_1}A)}{1+q_1C_2} - \frac{V}{V_2} + \frac{V(1+q_1C_2)}{V_2(1+q_1C)(1+\overline{q_1}A)} &\leqslant 0.\end{aligned}$$

Thus, if $R_2^A \leqslant 1$, then $\dfrac{dT_2}{dt} \leqslant 0$ for any solution of the system (1.1) with equality iff $N = N_1$. So, according the LaSalle's invariance principle, if (H) applies to N_2 and $R_2^1 \leqslant 1 < R_1^C$, then N_2 is globally asymptotically stable. □

Theorem 3.4. *If* $R_2^C \leqslant 1 < R_1^A$ *and the condition* (H) *holds for* N_3*, then the infection equilibrium with only humoral immunity* N_3 *is globally asymptotically stable.*

Proof. To prove this theorem, we define the Lyapunov function as follows

$$T_3(N) = U_3\phi\left(\frac{U}{U_3}\right) + I_3\phi\left(\frac{I}{I_4}\right) + \frac{\beta_1 U_3 V_3}{(1+\overline{q_1}A_3)kI_3}V_3\phi\left(\frac{V}{V_3}\right) + \frac{p}{\sigma}C + \frac{r\beta_1 U_3 V_3}{\rho k I_3(1+\overline{q_1}A_3)}A_3\phi\left(\frac{A}{A_3}\right),$$

for any $N = (U, I, V, C, A) \in (\mathbb{R}_+^*)^3 \times \mathbb{R}_+ \times \mathbb{R}_+^*$. Obviously, $T_3(N) \geqslant 0$ and with equality iff $N = N_3$. For any solution $N(t)$ of the system (1.1), we have

$$\begin{aligned}
\frac{dT_3}{dt} &= \left(1-\frac{U_3}{U}\right)U' + \left(1-\frac{I_3}{I}\right)I' + \left(1-\frac{V_3}{V}\right)V' + \frac{p}{\sigma}C' + \frac{r\beta_1 U_3 V_3}{\rho k I_3(1+\overline{q_1}A_3)}\left(1-\frac{A_3}{A}\right)A' \\
&= -\frac{d_U}{U}(U-U_3)^2 + \left(1-\frac{U_3}{U}\right)\left(\lambda - d_U U - \frac{\beta_1 UV}{(1+q_1C)(1+\overline{q_1}A)} - \frac{\beta_2 UI}{(1+q_2C)(1+\overline{q_2}A)}\right) \\
&\quad + \left(1-\frac{I_3}{I}\right)\left(\frac{\beta_1 UV}{(1+q_1C)(1+\overline{q_1}A)} + \frac{\beta_2 UI}{(1+q_2C)(1+\overline{q_2}A)} - d_I I - pIC\right) \\
&\quad + \frac{p}{\sigma}(\sigma IC - d_C C) + \frac{r\beta_1 U_3 V_3}{\rho k I_3(1+\overline{q_1}A_3)}\left(1-\frac{A_3}{A}\right)(\rho VA - d_A A).
\end{aligned}$$

By using the following inequalities

$$\begin{cases}
\lambda = d_U U_3 + \dfrac{\beta_1 U_3 V_3}{1+\overline{q_1}A_3} + \dfrac{\beta_2 U_3 I_3}{1+\overline{q_2}A_3}, \\
d_I = \dfrac{\beta_1 U_3 V_3}{I_3(1+\overline{q_1}A_3)} + \dfrac{\beta_2 U_3}{1+\overline{q_2}A_3}, \\
d_V = \dfrac{kI_3}{V_3} - rA_3, \\
V_3 = \dfrac{d_A}{\rho},
\end{cases}$$

we deduce that

$$\begin{aligned}
\frac{dT_3}{dt} &= -\frac{d_U}{U}(U-U_3)^2 + \frac{\beta_1 U_3 V_3}{1+\overline{q_1}A_3}\left[-1 + \frac{(1+q_1C)(1+\overline{q_1}A)}{1+\overline{q_1}A_3} + \frac{V(1+\overline{q_1}A_3)}{V_3(1+q_1C)(1+\overline{q_1}A)} - \frac{V}{V_3}\right] \\
&\quad + \frac{\beta_2 U_3 I_3}{1+\overline{q_2}A_3}\left[-1 + \frac{(1+q_2C)(1+\overline{q_2}A)}{1+\overline{q_2}A_3} + \frac{I(1+\overline{q_2}A_3)}{I_3(1+q_2C)(1+\overline{q_2}A)} - \frac{I}{I_3}\right] \\
&\quad + \frac{\beta_1 U_3 V_3}{1+\overline{q_1}A_3}\left[4 - \frac{U_3}{U} - \frac{UVI_3(1+\overline{q_1}A)}{U_3V_3I(1+q_1C)(1+\overline{q_1}A)} - \frac{IV_3}{I_3V} - \frac{(1+q_1C)(1+\overline{q_1}A)}{1+\overline{q_1}A_3}\right] \\
&\quad + \frac{\beta_2 U_3 I_3}{1+\overline{q_2}A_3}\left[3 - \frac{U_3}{U} - \frac{U(1+\overline{q_2}A_3)}{U_3(1+q_2C)(1+\overline{q_2}A)} - \frac{(1+q_2C)(1+\overline{q_2}A)}{1+\overline{q_2}A_3}\right] + \frac{pd_C C}{\sigma}(R_2^C - 1).
\end{aligned}$$

From the condition (H), we have

$$\begin{aligned}
-1 + \frac{(1+q_1C)(1+\overline{q_1}A)}{1+\overline{q_1}A_3} + \frac{V(1+\overline{q_1}A_3)}{V_3(1+q_1C)(1+\overline{q_1}A)} - \frac{V}{V_3} &\leqslant 0, \\
-1 + \frac{(1+q_2C)(1+\overline{q_2}A)}{1+\overline{q_2}A_3} + \frac{I(1+\overline{q_2}A_3)}{I_3(1+q_2C)(1+\overline{q_2}A)} - \frac{I}{I_3} &\leqslant 0,
\end{aligned}$$

and by the arithmetic-geometric inequality, we have

$$4 - \frac{U_3}{U} - \frac{UVI_3(1+\overline{q_1}A)}{U_3V_3I(1+q_1C)(1+\overline{q_1}A)} - \frac{IV_3}{I_3V} - \frac{(1+q_1C)(1+\overline{q_1}A)}{1+\overline{q_1}A_3} \leqslant 0,$$

$$3-\frac{U_3}{U}-\frac{U(1+\overline{q_2}A_3)}{U_3(1+q_2C)(1+\overline{q_2}A)}-\frac{(1+q_2C)(1+\overline{q_2}A)}{1+\overline{q_2}A_3}\leqslant 0.$$

Thus, we deduce that $\frac{dT_3}{dt}\leqslant 0$ and with equality iff $N=N_3$, as N_3 exists, when $R_1^A>2$. This completes the proof of the theorem. □

Theorem 3.5. *If $R_2^A>1$, $R_2^C>1$ and the condition (H) holds for N_4, then the infection equilibrium with both humoral and cellular immunity N_4 is globally asymptotically stable.*

Proof. We define the Lyapunov function as follows

$$T_4(N)=U_4\phi\left(\frac{U}{U_4}\right)+I_4\phi\left(\frac{I}{I_4}\right)+\frac{\beta_1U_4V_4}{kI_4(1+q_1C_4)(1+\overline{q_1}A_4)}V_4\phi\left(\frac{V}{V_4}\right)+\frac{p}{\sigma}C_4\phi\left(\frac{C}{C_4}\right)$$
$$+\frac{r\beta_1U_4V_4}{\rho kI_4(1+q_1C_4)(1+\overline{q_1}A_4)}A_4\phi\left(\frac{C}{C_4}\right).$$

Clearly, $T(N)\geqslant 0$ for all $N\in(\mathbb{R}_+^*)^5$, and with equality iff $N=N_4$. The differential function of T_4 along a solution $N(t)$ of the system (1.1) is given by

$$\begin{aligned}\frac{dT_4}{dt}=&-\frac{d_U}{U}(U-U_4)^2+\frac{\beta_1U_4V_4}{(1+q_1C_4)(1+\overline{q_1}A_4)}\left[4-\frac{U_4}{U}\right.\\
&\left.-\frac{UVI_4(1+q_1C_4)(1+\overline{q_1}A_4)}{U_4V_4I(1+q_1C)(1+\overline{q_1}A)}-\frac{IV_4}{I_4V}-\frac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_4)(1+\overline{q_1}A_4)}\right]\\
&+\frac{\beta_1U_4V_4}{(1+q_1C_4)(1+\overline{q_1}A_4)}\left[-1+\frac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_4)(1+\overline{q_1}A_4)}+\frac{V(1+q_1C_4)(1+\overline{q_1}A_4)}{V_4(1+q_1C)(1+\overline{q_1}A)}-\frac{V}{V_4}\right]\\
&+\frac{\beta_2U_4I_4}{(1+q_1C_4)(1+\overline{q_1}A_4)}\left[3-\frac{U_4}{U}-\frac{U(1+q_2C_4)(1+\overline{q_2}A_4)}{U_4(1+q_2C)(1+\overline{q_2}A)}-\frac{(1+q_2C)(1+\overline{q_2}A)}{(1+q_2C_4)(1+\overline{q_1}A_4)}\right]\\
&+\frac{\beta_2U_4I_4}{(1+q_2C_4)(1+\overline{q_2}A_4)}\left[-1+\frac{(1+q_2C)(1+\overline{q_2}A)}{(1+q_2C_4)(1+\overline{q_2}A_4)}+\frac{I(1+q_2C_4)(1+\overline{q_2}A_4)}{I_4(1+q_2C)(1+\overline{q_2}A)}-\frac{I}{I_4}\right]\\
&+\frac{r\beta_1U_4V_4}{kI_4(1+q_1C_4)(1+\overline{q_1}A_4)}\left[-A_4V_4+AV_4-\frac{d_A}{\rho}A+\frac{d_A}{\rho}A_4\right]+pI_4C-pC_4I_4-\frac{pd_C}{\sigma}C+\frac{pd_C}{\sigma}C_4.\end{aligned}$$

Since $I_4=\frac{d_C}{\sigma}$ and $V_4=\frac{d_A}{\rho}$, we have $pI_4C-pC_4I_4-\frac{pd_C}{\sigma}C+\frac{pd_C}{\sigma}C_4=-A_4V_4+AV_4-\frac{d_A}{\rho}A+\frac{d_A}{\rho}A_4=0$. By arithmetic-geometric inequality, we have

$$4-\frac{U_4}{U}-\frac{UVI_4(1+q_1C_4)(1+\overline{q_1}A_4)}{U_4V_4I(1+q_1C)(1+\overline{q_1}A)}-\frac{IV_4}{I_4V}-\frac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_4)(1+\overline{q_1}A_4)}\leqslant 0,$$
$$3-\frac{U_4}{U}-\frac{U(1+q_2C_4)(1+\overline{q_2}A_4)}{U_4(1+q_2C)(1+\overline{q_2}A)}-\frac{(1+q_2C)(1+\overline{q_2}A)}{(1+q_2C_4)(1+\overline{q_1}A_4)}\leqslant 0.$$

Form the condition (H), we have

$$-1+\frac{(1+q_1C)(1+\overline{q_1}A)}{(1+q_1C_4)(1+\overline{q_1}A_4)}+\frac{V(1+q_1C_4)(1+\overline{q_1}A_4)}{V_4(1+q_1C)(1+\overline{q_1}A)}-\frac{V}{V_4}\leqslant 0,$$
$$-1+\frac{(1+q_2C)(1+\overline{q_2}A)}{(1+q_2C_4)(1+\overline{q_2}A_4)}+\frac{I(1+q_2C_4)(1+\overline{q_2}A_4)}{I_4(1+q_2C)(1+\overline{q_2}A)}-\frac{I}{I_4}\leqslant 0.$$

Then, $\frac{dT_4}{dt}\leqslant 0$ and $\frac{dT_4}{dt}=0$ iff $N=N_4$. Thus, by the LaSalle invariance principle N_4 is globally asymptotically stable. The conditions $R_2^A>1$ and $R_2^C>1$ are necessary for the existence of the equilibrium N_4, so this completes the proof of theorem. □

4. Numerical simulations

In this section, we conduct numerical simulations to assess the stability of the equilibria established earlier. Such numerical simulations are based on the mixed Euler method presented in [7], which preserves the qualitative properties of model (1.1). Our attention centers on the HIV virus, characterized by the parameter set detailed in Table 2. The objective is to simulate five distinct global stability scenarios by employing the parameter values specified in Table 2, while adjusting the values of the parameters λ, β_2, σ, k, d_C, and ρ.

Table 2: Estimation of model parameters.

Parameter	Unit	Value	Range	Source
λ	cells $\mu L^{-1} day^{-1}$	10	$5.9770 - 24.1860$	[8]
d_U	day^{-1}	0.0139	-	[8]
β_1	μL virion^{-1} day^{-1}	2.4×10^{-5}	$2.4 \times 10^{-5} - 4.8 \times 10^{-3}$	[8]
d_I	day^{-1}	0.29	$0.2666 - 0.7073$	[8]
d_V	day^{-1}	3	$2.06 - 3.81$	[8]
k	virion cell^{-1} day^{-1}	-	$27 - 7073$	[8]
p	cell^{-1} μL day^{-1}	0.01	$0.001 - 1$	[8]
r	molecule^{-1} μL day^{-1}	0.5	-	[8]
d_A	day^{-1}	0.35	-	Assumed
d_C	day^{-1}	-	$0.05 - 0.15$	[8]
q_1	μL cell^{-1}	0.01	-	Assumed
$\overline{q}_1$	μL cell^{-1}	0.001	-	Assumed
q_2	μL cell^{-1}	0.02	-	Assumed
$\overline{q}_2$	μL cell^{-1}	0.002	-	Assumed
ϵ	day^{-1}	0.01	-	Assumed

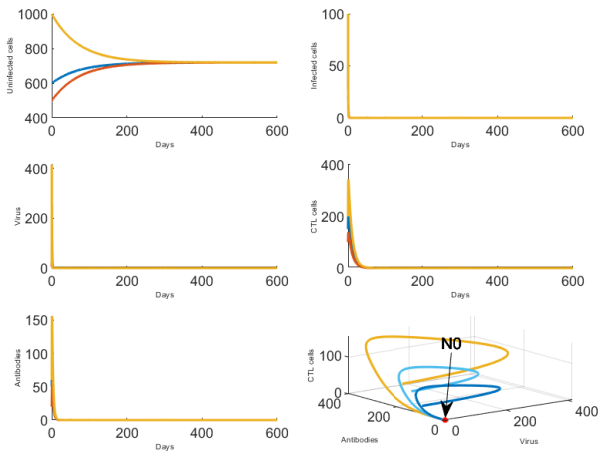

Figure 2: Dynamics of model (1.1) for $R_0 = 0.9968 \leqslant 1$.

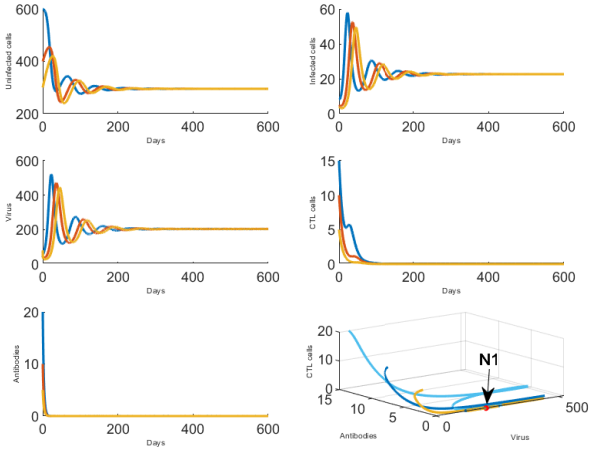

Figure 3: Dynamics of model (1.1) for $R_0 = 3.6199 > 1$, $R_1^C = 0.5990 \leqslant 1$, and $R_1^A = 0.0052 \leqslant 1$.

When $\lambda = 10$, $k = 50$, $d_C = 0.1$, $\beta_2 = 1.8 \times 10^{-6}$, $\rho = 6.7 \times 10^{-3}$ and $\sigma = 0.02$, we obtained $R_0 = 0.9968$. According to Theorem 2.2, system (1.1) possesses one infection-free equilibrium $N_0 = (719.4244, 0, 0, 0, 0)$. From Figure 2, the concentration of uninfected cells approaching the value $U_0 = 719.4245$, while the concentrations of infected cells, free HIV particles, antibodies, and CTL cells show a declining pattern, ultimately converging towards zero. This aligns with the results asserted in Theorem 3.1.

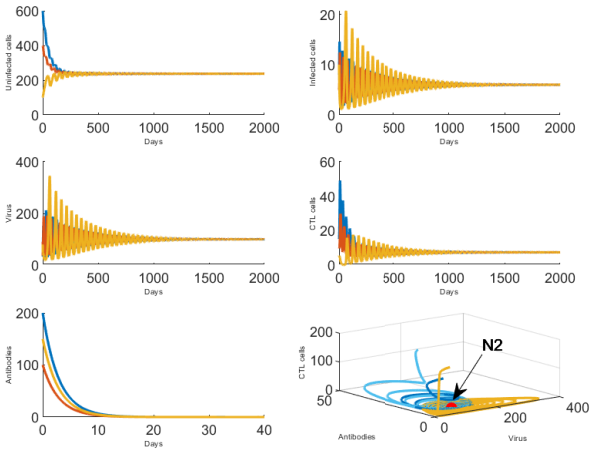

Figure 4: Dynamics of model (1.1) for $R_0 = 3.2746 > 1$, $R_1^C = 2.3952 > 1$, and $R_2^A = 0.0286 \leqslant 1$.

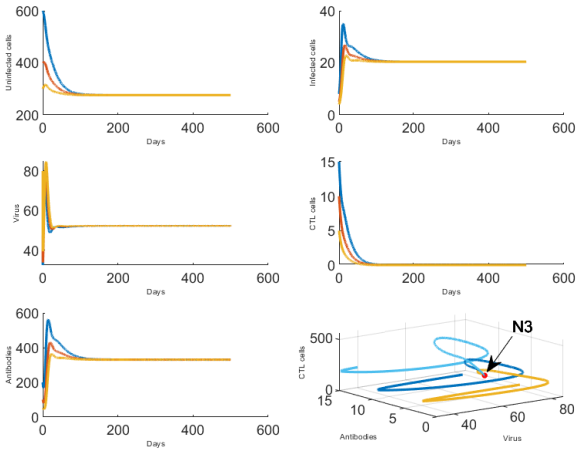

Figure 5: Dynamics of model (1.1) for $R_0 = 5.4577 > 1$, $R_1^A = 8.9858 > 1$, and $R_2^C = 0.4250 \leqslant 1$.

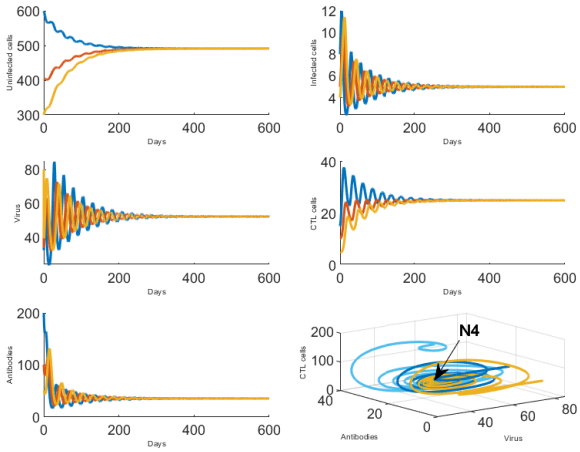

Figure 6: Dynamics of model (1.1) for $R_0 = 5.4577 > 1$, $R_2^C = 4.2891 > 1$, and $R_2^A = 1.5952 > 1$.

When $\lambda = 12$, $\beta_2 = 10^{-3}$, $\sigma = 0.002$, $k = 27$, $\rho = 6.7 \times 10^{-6}$, and $d_C = 0.1$, we obtain $R_0 = 3.6199 > 1$. According to Theorem 2.2, system (1.1) has one infection free-immunity equilibrium $N_1 = (238.4868, 29.9484, 269.5355, 0, 0)$. From Figure 3, the model (1.1) with different initial values converges towards N_1 as $R_1^A = 0.0052 \leqslant 1$ and $R_1^C = 0.3085 \leqslant 1$. This validates the outcome stated in Theorem 3.2.

When $\lambda = 6$, $\beta_2 = 1.8 \times 10^{-3}$, $\sigma = 0.025$, $k = 50$, $\rho = 10^{-4}$, $k = 50$, and $d_C = 0.15$, we obtain $R_0 = 3.2746 > 1$, $R_1^C = 2.3952 > 1$, and $R_2^A = 0.0286 \leqslant 1$. According Theorem 2.2, model (1.1) admits one infection equilibrium with only cellular immunity $N_2 = (237.3471, 6, 100, 7.3924, 0)$ and by Theorem 3.3, model (1.1) converges towards N_2. Figure 4 illustrates this finding.

When $\lambda = 10$, $d_U = 0.0139$, $\beta_2 = 1.8 \times 10^{-3}$, $\sigma = 0.002$, $k = 50$, $\rho = 6.7 \times 10^{-3}$, and $d_C = 0.1$, we obtain $R_0 = 5.4577 > 1$, $R_1^A = 8.9858 > 1$, and $R_2^C = 0.4250 \leqslant 1$. According Theorem 2.2, model (1.1) possesses one infection equilibrium with only humoral immunity $N_3 = (276.0895, 20.4190, 52.2388, 0, 330.8773)$. Figure 5 demonstrates that model (1.1) converges towards N_3, in accordance with Theorem 3.4.

When $\lambda = 10$, $\beta_2 = 1.8 \times 10^{-3}$, $\sigma = 0.02$, $k = 50$, $\rho = 6.7 \times 10^{-3}$, and $d_C = 0.1$, we obtain $R_0 = 5.4577 > 1$, $R_2^A = 1.5952 > 1$, and $R_2^C = 4.2891 > 11$. According to Theorem 2.2, model (1.1) possesses one infection equilibrium with cellular and humoral immunity $N_4 = (491.1226, 5, 52.2388, 25.0568, 35.7143)$. Figure 6

demonstrates that model (1.1) converges towards N_4, in accordance with Theorem 3.5.

5. Conclusion

In this work, we have developed a new mathematical model that captures the intricate dynamics of viral infection, considering both cell-to-cell and virus-to-cell transmission modes, adaptive immunity and non-cytolytic cure mechanisms. Furthermore, the developed model considered both lytic and non-lytic effects of adaptive immunity. Initially, we have established the well-posed nature of the model, demonstrating that the differential system possesses positive and bounded solutions. Subsequently, we have introduced five pivotal threshold parameters associated with our model. The initial threshold parameter denoted by R_0 representing the basic reproduction number, followed by R_1^A denoting the reproduction number of humoral immunity, and R_1^C representing the reproduction number of cellular immunity. Additionally, R_2^A and R_2^C correspond to the reproduction numbers of humoral immunity in competition and cellular immunity in competition, respectively. Our findings show that when $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable. This indicates that the virus will be completely eradicated from the human body. However when $R_0 > 1$, the infection-free equilibrium becomes unstable and the model has four infection equilibria. The stability of such infection equilibria depends on the values of the threshold parameters R_1^A, R_1^C, R_2^A, and R_2^C. More precisely, (i) the infection free-immunity equilibrium is globally asymptotically stable if $R_1^A \leqslant 1$ and $R_1^C \leqslant 1$, while it becomes unstable if either $R_1^A > 1$ or $R_1^C > 1$; (ii) if $R_1^C > 1$ and $R_2^A \leqslant 1$, then the infection equilibrium with only cellular immunity is globally asymptotically stable; (iii) if $R_2^C \leqslant 1 < R_1^A$, then the infection equilibrium with only humoral immunity is globally asymptotically stable; as well as (iv) if $R_2^A > 1$ and $R_2^C > 1$, then the infection equilibrium with both humoral and cellular immunity is globally asymptotically stable. From a biological point of view, the last results imply that when the basic reproduction number is greater than 1, the virus persists and the infection becomes chronic. In addition, the activation of one or both immune responses is unable to eliminate the virus in the human body. According to these findings, when $R_2^A \leqslant 1 < R_1^C$, cellular immunity dominates over humoral immunity, causing the model to converge towards the infection equilibrium with only cellular immunity. Conversely, if $R_2^C \leqslant 1 < R_1^A$, humoral immunity dominates over cellular immunity, leading the model to converge to the infection equilibrium with only humoral immunity. The former case is referred to as the over-domination of the cellular immunity, while the latter is denoted as the over-domination of the humoral immunity in [8].

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