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Global stability of a class of fractional partial differential equations describing the dynamics of viral infection with therapy and adaptive immunity

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Abstract In this article, we formulate a mathematical model based on fractional partial differential equations (FPDEs) to describe the spatiotemporal progression of viral infections, incorporating the effects of adaptive immunity and antiviral treatment. The model includes a regional fractional Laplace operator to account for the anomalous diffusion observed within the infected medium. We investigate the existence and uniqueness of equilibria and establish their global stability using Lyapunov functions tailored to the associated reaction systems. Moreover, numerical simulations are presented to illustrate the analytical results.

Keywords Viral infection, fractional partial differential equations, anomalous diffusion, Lyapunov functions, global stability

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1. Introduction

Since the dawn of humankind, viral infections have posed one of the most significant challenges to public health. These infections involve complex interactions between pathogens, host cells and the immune system. This intricate biological conflict requires a deep understanding and accurate modeling to design effective treatment strategies and appropriate control measures. Mathematical modeling plays a fundamental role in this context, offering tools to describe the spatial and temporal dynamics of viral spread and the associated immune responses.

Among these tools, fractional partial differential equations (FPDEs) stand out for their ability to incorporate anomalous diffusion and memory effects, which are frequently observed in biological tissues but are only partially captured by classical models based on integer-order derivatives. Fractional derivatives offer a flexible and powerful framework for representing nonlocal interactions and heterogeneous transport processes, both of which are essential for accurately describing viral dissemination within biological systems.

Stability analysis is crucial for assessing the reliability and robustness of mathematical models under various conditions. It helps detect and prevent unexpected or unstable behavior in simulations, ensuring

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biologically consistent and meaningful predictions. Several studies have addressed the global dynamics of viral infection models by applying stability criteria. For instance, Xu and Ma [1] investigated the global behavior of a time-delayed model for hepatitis B virus (HBV) infection, incorporating spatial diffusion, saturation effects in the infection rate and a delay associated with intracellular incubation. In a related study, Shaoli et al. [2] proposed a spatially diffusive HBV model that integrates the role of cellular immune response alongside a nonlinear infection process. They demonstrated that free virus diffusion does not alter global stability under homogeneous Neumann boundary conditions. In addition, Hattaf and Yousfi [3] were among the first to introduce a systematic approach for constructing Lyapunov functions specifically tailored to reaction-diffusion systems, both with and without time delays. Their method has found broad application in recent studies [4, 5, 6, 7, 8, 9] for the global stability analysis of classical models. More recently, this approach has been extended to fractional differential equations (FDEs) with classical diffusion [10], and further applied in [11]. It has also been extended to PDEs involving a fractional Laplacian operator [12], as well as to diffusion-reaction systems with and without time delays governed by the p-Laplacian operator [13]. In another application, the method was employed to analyze the global dynamics of SARS-CoV-2 infection model incorporating both antiviral treatment and diffusion, using the regional fractional Laplacian operator [14].

In the present study, we propose a class of FPDEs to model the progression of viral infection, accounting for both adaptive immunity and antiviral treatment. To describe the anomalous diffusion confined within the infected tissue, we employ the regional fractional Laplacian operator. Accordingly, the article is organized as follows: SectionÂ 2 formulates the viral infection model by means of FPDEs and investigates the existence and uniqueness of equilibria. SectionÂ 3 is dedicated to the global stability analysis. Section 4 is devoted to parameters estimation and sensitivity analysis. SectionÂ 5 presents numerical simulations that illustrate and support the theoretical results. Finally, SectionÂ 6 summarizes the main findings of this research.

2. Formulation of the viral infection model and equilibria

This section presents a fresh approach to modeling viral infections using fractional spatial diffusion, non-lytic and lytic immune responses, adaptive immunity, and two modes of transmission. The model is constructed as the following nonlinear system of FPDEs:

$$\begin{cases} \dfrac{\partial U}{\partial t} = -d_U(-\Delta)^s_\Omega U(y,t) + A - m_U U(y,t) - \dfrac{\beta_1 U(y,t)V(y,t)}{(1+q_1Z(y,t))(1+\overline{q_1}W(y,t))} - \dfrac{\beta_2 U(y,t)I(y,t)}{(1+q_2Z(y,t))(1+\overline{q_2}W(y,t))} + \theta I(y,t), \\ \dfrac{\partial I}{\partial t} = -d_I(-\Delta)^s_\Omega I(y,t) + \dfrac{\beta_1 U(y,t)V(y,t)}{(1+q_1Z(y,t))(1+\overline{q_1}W(y,t))} + \dfrac{\beta_2 U(y,t)I(y,t)}{(1+q_2Z(y,t))(1+\overline{q_2}W(y,t))} - (m_I+\theta)I(y,t) - pI(y,t)Z(y,t), \\ \dfrac{\partial V}{\partial t} = -d_V(-\Delta)^s_\Omega V(y,t) + k(1-\varepsilon)I(y,t) - m_V V(y,t) - rV(y,t)W(y,t), \\ \dfrac{\partial W}{\partial t} = -d_W(-\Delta)^s_\Omega W(y,t) + \rho V(y,t)W(y,t) - m_W W(y,t), \\ \dfrac{\partial Z}{\partial t} = -d_Z(-\Delta)^s_\Omega Z(y,t) + \sigma I(y,t)Z(y,t) - m_Z Z(y,t). \end{cases} \tag{1}$$

Here, the functions $Z(y,t)$, $W(y,t)$, $V(y,t)$, $I(y,t)$ and $U(y,t)$ denote, respectively, the spatial and temporal concentrations of cytotoxic T lymphocyte (CTL) cells, antibodies, free virus particles, infected cells, and uninfected cells. The production of uninfected cells occurs at a constant rate A, undergo natural death at a rate m_U. These cells can become infected through two primary mechanisms: virus-mediated transmission, occurring at rate $\beta_1 UV$, and cell-to-cell contact at rate $\beta_2 UI$. Both of these infection pathways are modulated by immune responses: cellular immunity reduces the infection rates through the non-lytic effects represented by the factors $1+q_1Z$ and $1+q_2Z$, while humoral immunity adds inhibitory effects via $1+\overline{q_1}W$ and $1+\overline{q_2}W$. Infected cells are lost due to natural death at rate $m_I I$, targeted elimination by CTL at rate pIZ, or recovery back to the uninfected state at rate θI. The virus is produced by infected

cells at rate k, and is removed from the system at rate $m_V V$. Antibodies are generated as a result of interactions between virus and antibodies at rate ρVW, degrade naturally at rate $m_W W$, and neutralize free virus at a rate rVW. CTL populations grow in response to the presence of infected cells, expanding at rate σIZ, and decay at rate $m_Z Z$. Furthermore, the parameter $\varepsilon \in [0,1]$ quantifies the efficacy of antiviral therapy in suppressing viral production, where higher values of ε reflect more effective treatment. Lastly, d_U, d_I, d_V, d_W and d_Z denote the diffusion coefficients for the respective biological components, capturing their spatial spread within the domain, and are assumed to be non-negative. In model (1), the diffusion of particules is described using the regional fractional Laplacian operator $(-\Delta)^s_\Omega$ as defined in [15], by the following formula:

$$(-\Delta)^s_\Omega u(y) \quad = C(n,s) \lim_{\varepsilon \to 0^+} \int_{\{z \in \Omega, ||y-z|| > \varepsilon\}} \frac{u(y)-u(z)}{||y-z||^{\frac{n}{2}+s}} dz, \tag{2}$$

where $\|\cdot\|$ is the Euclidean norm on $\mathbb{R}^n$, n is the dimension of the space and $C(n,s)$ denotes a normalization constant, given in the same reference [15] by:

$$C(n,s) = \left(\int_{\mathbb{R}^n} \frac{1-\cos(\xi_1)}{||\xi||^{\frac{n}{2}+s}} d\xi \right)^{-1} = \frac{s4^s}{\pi^{\frac{n}{2}}} \frac{\Gamma(s+\frac{n}{2})}{\Gamma(1-s)}, \tag{3}$$

with $s \in (0,1)$ the fractional parameter, $\xi = (\xi_1, \xi')$, $\xi' \in \mathbb{R}^{n-1}$ and $\Gamma(z) = \int_0^{+\infty} t^{z-1} e^{-t}\, dt, \quad z \in \mathbb{R}^*_+$.

Since the infected organ occupies a well-defined and bounded region within the human body, we represent it in our model by a domain $\Omega \subset \mathbb{R}^n$ with a smooth boundary $\partial\Omega$. The operator $(-\Delta)^s_\Omega$ is used to describe the random motion of particles within this domain, where a particle may move from one location $y_1 \in \Omega$ to another $y_2 \in \Omega$, with a likelihood of transition governed by the kernel $||y_1 - y_2||^{-\frac{n}{2}-s}$. The fractional order s is defined as a parameter characterizing anomalous diffusion in biological tissues. Biologically, it reflects the heterogeneity of the tissue microenvironment and the irregular movement of viral particles and immune cells. Lower values of s correspond to more heterogeneous tissue structure and subdiffusive behavior, whereas values approaching 1 indicate nearly classical and homogeneous diffusion. On the other hand, it is important to note that particles are not allowed to exit the domain Ω. When they reach the boundary $\partial\Omega$, they are either redirected back into the interior or removed from the system. Taking this spatial restriction into account, we now examine problem (1) under the framework of generalized Neumann-type boundary conditions involving fractional normal derivatives. Following the definition proposed in [15], the boundary conditions take the form:

$$\mathcal{ND}^{(-2s+2)} U = \mathcal{ND}^{(-2s+2)} I = \mathcal{ND}^{(-2s+2)} V = \mathcal{ND}^{(-2s+2)} W = \mathcal{ND}^{(-2s+2)} Z = 0,$$

on $\partial\Omega \times (0, +\infty)$, where the operator $\mathcal{ND}^{(-2s+2)} u$ denotes the fractional normal derivative of the function u in the direction of the outward unit normal vector. It is defined as:

$$\mathcal{ND}^{(-2s+2)} u(y) = -\lim_{t \to 0^+} \frac{du(y + \boldsymbol{n}(y)t)}{dt} t^{-2s+2},$$

with $\boldsymbol{n}(y)$ represents the interior normal vector at the boundary point $y \in \partial\Omega$, as introduced in [15]. To finalize the model initialization, we assume that

$$U(y,0) \geqslant 0, \quad I(y,0) \geqslant 0, \quad V(y,0) \geqslant 0, \quad W(y,0) \geqslant 0, \quad Z(y,0) \geqslant 0, \quad \text{for all} \quad y \in \overline{\Omega}.$$

It is worth highlighting that model (1) enhances and extends the ODE model introduced in [16] by incorporating both spatial diffusion and antiviral treatment. Furthermore, the model proposed by El Hassani et al. [14] can be regarded as a special case of the model presented in this work.

By employing the same approach outlined in [16], we can conclude that the system (1) has five steady states. To determine all possible equilibria of the system, we consider homogeneous solutions, i.e., solutions

that are constant in time and space. Thus, we assume that time derivatives and fractional diffusion terms disappear. System (1) thus reduces to:

$$\begin{cases} A - m_U U - \dfrac{\beta_1 UV}{(1+q_1 Z)(1+\overline{q_1}W)} - \dfrac{\beta_2 UI}{(1+q_2 Z)(1+\overline{q_2}W)} + \theta I = 0, \\ \dfrac{\beta_1 UV}{(1+q_1 Z)(1+\overline{q_1}W)} + \dfrac{\beta_2 UI}{(1+q_2 Z)(1+\overline{q_2}W)} - (m_I+\theta)I - pIZ = 0, \\ k(1-\varepsilon)I - m_V V - rVW = 0, \\ \rho VW - m_W W = 0, \\ \sigma IZ - m_Z Z = 0. \end{cases} \tag{4}$$

First, we assume the absence of infection, i.e., $I = V = W = Z = 0$. In this case, system (4) simplifies to the equation: $0 = A - m_U U_0$, which gives $U_0 = \dfrac{A}{m_U}$. So, it is clear that the point $\mathcal{E}_0 = (U_0, 0, 0, 0, 0)$ represents an equilibrium state in the absence of infection, called the infection-free equilibrium. Consequently, the basic reproduction number of our model can be readily determined as follows:

$$\mathcal{R}_0 = \underbrace{\frac{\beta_1 U_0 k(1-\varepsilon)}{m_V(m_I+\theta)}}_{\mathcal{R}_{01}} + \underbrace{\frac{\beta_2 U_0}{m_I+\theta}}_{\mathcal{R}_{02}} = \mathcal{R}_{01} + \mathcal{R}_{02}. \tag{5}$$

Considering biological perspectives, and in accordance with references [17, 18], the basic reproduction number $\mathcal{R}_0$ can be decomposed into two distinct components $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$. The first component $\mathcal{R}_{01}$, corresponds to the virus-to-cell infection pathway and is given by the expression $\mathcal{R}_{01} = \frac{\beta_1 U_0 k(1-\varepsilon)}{m_V(m_I+\theta)}$. While the second component, $\mathcal{R}_{02}$, represents the direct cell-to-cell transmission mode and is calculated as $\mathcal{R}_{02} = \frac{\beta_2 U_0}{m_I+\theta}$.

When $\mathcal{R}_0 > 1$, model (1) admits a second equilibrium point, denoted by $\mathcal{E}_1 = (U_1, I_1, V_1, 0, 0)$, which represents infection occurring without any immune response. For $Z = W = 0$, the system reduces to:

$$\begin{cases} 0 &= A - m_U U\_\beta_1 UV - \beta_2 UI + \theta I, \\ 0 &= \beta_1 UV + \beta_2 UI - (m_I+\theta)I, \\ 0 &= k(1-\varepsilon)I - m_V V. \end{cases}$$

From the third equation, we have $V = \frac{k(1-\varepsilon)}{m_V} I$. Substituting this expression for V into the second equation, we obtain $\beta_1 U\left(\frac{k(1-\varepsilon)}{m_V} I\right) + \beta_2 UI = (m_I+\theta)I$. Factoring I from both sides and rearranging the equation, we get $U\left(\frac{\beta_1 k(1-\varepsilon)}{m_V} + \beta_2\right) = m_I + \theta$. We find the following expression:

$$U_1 = \frac{m_I+\theta}{\dfrac{\beta_1 k(1-\varepsilon)}{m_V} + \beta_2} = \frac{U_0}{\mathcal{R}_0}.$$

We now substitute $U_1 = \dfrac{U_0}{\mathcal{R}_0} = \dfrac{A}{m_U \mathcal{R}_0}$ into the first equation in order to determine the value of I. Since $V = \dfrac{k(1-\varepsilon)}{m_V} I$, we obtain from the first equation $A - m_U U_1 - \left(\beta_1 U_1 \frac{k(1-\varepsilon)}{m_V} + \beta_2 U_1 - \theta\right) I = 0$. Using the relation $\beta_1 U_1 \frac{k(1-\varepsilon)}{m_V} + \beta_2 U_1 = m_I + \theta$, the equation simplifies to $A - m_U U_1 - m_I I = 0$. We find $I_1 = \frac{A - m_U U_1}{m_I} = \frac{A - \frac{A}{\mathcal{R}_0}}{m_I} = \frac{A(\mathcal{R}_0 - 1)}{m_I \mathcal{R}_0}$ and $V_1 = \frac{k(1-\varepsilon)}{m_V} I_1 = \frac{Ak(1-\varepsilon)(\mathcal{R}_0-1)}{m_I m_V \mathcal{R}_0}$.

In the context where humoral immunity is active while CTL immunity remains absent, any equilibrium configuration must fulfill the following system of equations:

$$\begin{cases} A - m_U U - m_I I = 0, \\ \dfrac{\beta_1 UV}{1+\overline{q_1}W} + \dfrac{\beta_2 UI}{1+\overline{q_2}W} - (m_I+\theta)I = 0, \\ k(1-\varepsilon)I - m_V V - rVW = 0, \\ \rho VW - m_W W = 0. \end{cases} \tag{6}$$

In situation where the humoral immune system has not yet been activated, the inequality $\rho V - m_W \leq 0$ holds. Under this condition, the reproduction number associated with the humoral response can be characterized by:

$$\mathcal{R}_1^W = \frac{\rho}{m_W} V_1 = \frac{\rho k(1-\varepsilon)A}{m_W m_I m_V \mathcal{R}_0}(\mathcal{R}_0 - 1),$$

which quantifies the average number of antibodies generated by the immune system in response to viral infection, in the absence of CTL activity [19].

Assuming that $W > 0$, one obtains $V = \frac{m_U}{\rho}$, $\quad I = \frac{1}{m_I}(A - m_U U)$. Consequently, the variables W and U must satisfy the relations $W = \frac{k(1-\varepsilon)\rho}{r m_W m_I}(A - m_U U) - \frac{m_V}{r}$, $\quad$ and $\quad U\left[\frac{\beta_1 m_W}{\rho(1+\overline{q_1}W)} + \frac{\beta_2(A-m_U U)}{m_I(1+\overline{q_2}W)}\right] - \frac{m_I+\theta}{m_I}(A - m_U U) = 0$.

Let us introduce the threshold parameter: $a = \dfrac{A}{m_U} - \dfrac{m_V m_W m_I}{k(1-\varepsilon)\rho m_U}$, and restrict our analysis to the interval $U \in (0, a)$. Within this domain, define the auxiliary functions:

$$g_1(U) = \frac{k(1-\varepsilon)\rho}{r m_W m_I}(A - m_U U) - \frac{m_V}{r}, \quad f_1(U) = U\left[\frac{\beta_1 m_W}{\rho(1+\overline{q_1}g_1(U))} + \frac{\beta_2(A-m_U U)}{m_I(1+\overline{q_2}g_1(U))}\right] - \frac{d_I+\theta}{d_I}(A - m_U U).$$

By direct computation, one observes $f_1(0) < 0$, and further:

$$f_1(a) = \frac{m_I m_V m_W^2}{(k(1-\varepsilon))^2 \rho^2 m_U}(k(1-\varepsilon)\beta_1 + m_V\beta_2)(\mathcal{R}_1^W - 1).$$

Thus, if $\mathcal{R}_1^W > 1$, then $f_1(a) > 0$, ensuring the existence of a solution $U_2 \in (0, a)$ such that $f_1(U_2) = 0$. Using the relation $m_I + \theta = \dfrac{\beta_1 U_2 V}{I(1+\overline{q_1}W)} + \dfrac{\beta_2 U_2}{1+\overline{q_2}W}$, we compute the derivative of f_1 at U_2:

$$f_1'(U_2) = \beta_1 V \frac{1 + \overline{q_1}g_1(U_2) - \overline{q_1}U_2 g_1'(U_2)}{(1+\overline{q_1}g_1(U_2))^2} - \frac{\beta_2 U_2 \overline{q_2} g_1'(U_2)h(U_2)}{(1+\overline{q_2}g_2(U_2))^2} - h'(U_2)\frac{\beta_1 U_2 V}{h(U_2)(1+\overline{q_1}g_1(U_2))},$$

where $h(U) = \frac{1}{m_U}(A - m_U U)$. Since both $h'(U) < 0$ and $g_1'(U) < 0$, it follows that $f_1'(U_2) > 0$, confirming the uniqueness of the solution U_2 and thereby the uniqueness of the associated equilibrium: $\mathcal{E}_2 = (U_2, I_2, V_2, W_2, 0)$, with $I_2 = h(U_2)$, $V_2 = \frac{m_W}{\rho}$ and $\quad W_2 = g_1(U_2)$.

In situations where cellular immunity is present and the humoral response is absent, the equilibrium of the system (1) is governed by:

$$\begin{cases} A - m_U U - \dfrac{\beta_1 UV}{1+q_1 Z} - \dfrac{\beta_2 UI}{1+q_2 Z} + \theta I = 0, \\ \dfrac{\beta_1 UV}{1+q_1 Z} + \dfrac{\beta_2 UI}{1+q_2 Z} - (m_I+\theta)I - pIZ = 0, \\ k(1-\varepsilon)I - m_V V = 0, \\ \sigma IZ - m_Z Z = 0. \end{cases} \tag{7}$$

In the absence of cellular activation, the inequality $\sigma I_1 - m_Z \leq 0$ must be satisfied. Accordingly, the reproduction number for CTL-mediated immunity is defined as:

$$\mathcal{R}_1^Z = \frac{\sigma I_1}{m_Z} = \frac{\sigma A(\mathcal{R}_0 - 1)}{m_Z m_I \mathcal{R}_0},$$

is reflecting the mean number of CTL produced per infected individual in the absence of humoral neutralization [19].

Given $Z > 0$, we derive the expressions: $I = \frac{m_Z}{\sigma}$, $V = \frac{km_Z}{\sigma m_V}$, $Z = \frac{\sigma(A - m_U U) - m_I m_Z}{pm_Z}$, and the equation: $U\left[\frac{\beta_1 k(1-\varepsilon)}{m_V(1+q_1 Z)} + \frac{\beta_2}{1+q_2 Z}\right] - (m_I + \theta) - pZ = 0$. Introducing the threshold: $b = \frac{A}{m_U} - \frac{m_I m_Z}{\sigma m_U}$, with $0 < U < b$, we define the functions:

$$g_2(U) = \frac{\sigma(A - m_U U) - m_I m_Z}{pm_Z}, \quad f_2(U) = U\left[\frac{\beta_1 k(1-\varepsilon)}{m_V(1 + q_1 g_2(U))} + \frac{\beta_2}{1 + q_2 g_2(U)}\right] - (m_I + \theta) - pg_2(U).$$

We observe $f_2(0) = -(m_I + \theta) - pg_2(0) < 0$, and $f_2(b) = b\left[\frac{\beta_1 k(1-\varepsilon)}{m_V} + \beta_2\right] - (m_I + \theta)$. The derivative $f_2'(U)$ is given by:

$$f_2'(U) = \left[\frac{\beta_1 k(1-\varepsilon)}{m_V(1 + q_1 g_2(U))} + \frac{\beta_2}{1 + q_2 g_2(U)}\right] - U\left[\frac{\beta_1 k(1-\varepsilon) q_1 g_2'(U)}{m_V(1 + q_1 g_2(U))^2} + \frac{\beta_2 q_2 g_2'(U)}{(1 + q_2 g_2(U))^2}\right] - pg_2'(U).$$

Since $g_2'(U) < 0$, we conclude that $f_2'(U) > 0$.

If $\mathcal{R}_1^Z < 1$, then $I_1 < \frac{m_C}{\sigma}$, so $U_1 > b$, leading to:

$$f_2(b) < f_2(U_1) = 0 \Rightarrow f_2(b) < 0.$$

This indicates that no equilibrium solution exists in this case. On the contrary, if $\mathcal{R}_1^Z > 1$, then $f_2(b) > 0$, implying the existence of a unique solution $U_3 \in (0, b)$ such that $f_2(U_3) = 0$. Thus, a unique equilibrium point when $\mathcal{R}_1^Z > 1$, which is given by $\mathcal{E}_3 = (U_3, I_3, V_3, 0, Z_3)$, with $I_3 = \frac{m_Z}{\sigma}$, $V_3 = \frac{km_Z}{\sigma m_V}$ and $Z_3 = \frac{\sigma(A - m_U U_3) - m_I m_Z}{pm_Z}$.

We now consider the most comprehensive case, in which both humoral and cellular immune mechanisms are simultaneously active. In this setting, i.e., when $Z \neq 0$ and $W \neq 0$, any equilibrium configuration must satisfy the system (4). In this competitive environment, the reproduction number of humoral immunity in competition, denoted by $\mathcal{R}_2^W$, is defined as:

$$\mathcal{R}_2^W = \frac{\rho}{m_W} V_3 = \frac{\rho k(1-\varepsilon) m_Z}{\sigma m_V m_W},$$

where $V_3 = \dfrac{k(1-\varepsilon)m_Z}{\sigma m_V}$ represents the equilibrium viral load under the influence of both immune responses. Analogously, the reproduction number of cellular immunity in competition is given by:

$$\mathcal{R}_2^Z = \frac{\sigma}{m_Z} I_2 = \frac{\sigma}{m_I m_Z}(A - m_U U_2),$$

which reflects the rate of CTL proliferation driven by infected cells, modulated by the availability of uninfected target cells U_2.

From a biological perspective, the quantity $\mathcal{R}_2^Z$ represents the expected proliferation rate of CTL induced by infected cells, under the premise that the humoral immune response is already active. In contrast, $\mathcal{R}_2^W$ measures the average number of antibody-secreting immune cells triggered by viral particles, assuming that CTL-mediated immunity is concurrently operational [19, 20].

Since $Z>0$, $W>0$, then $V=\frac{m_W}{\rho}$, $I=\frac{m_Z}{\sigma}$, $W=\frac{k(1-\varepsilon)\rho m_Z}{r\sigma m_W}-\frac{m_V}{r}$, $Z=\frac{\sigma}{pm_Z}(A-m_UU)-\frac{m_I}{p}$. In addition, we have the following equation:

$$U\left[\frac{\beta_1 V}{(1+q_1Z)(1+\overline{q_1}W)}+\frac{\beta_2 I}{(1+q_1Z)(1+\overline{q_2}W)}\right]-(m_I+\theta)I-pIZ=0.$$

Let $c=\frac{1}{\sigma m_U}(A\sigma-m_Im_Z)$. Then $0<U<c$. The functions g_3 and f_3 are defined on the interval $[0,c]$ as follows:

$$g_3(U)=\frac{\sigma}{pm_Z}(A-m_UU)-\frac{m_I}{p},$$

$$f_3(U)=U\left[\frac{\beta_1 V}{(1+q_1g_3(U))(1+\overline{q_1}W)}+\frac{\beta_2 I}{(1+q_1g_3(U))(1+\overline{q_2}W)}\right]-(m_I+\theta)I-pIg_3(U).$$

Therefore, the model (1) admits an equilibrium point with both humoral and cellular immune responses if and only if there exists a value $U_4\in(0,c)$ satisfying $f_3(U_4)=0$. Under this condition, the associated equilibrium is expressed as $\mathcal{E}_4=(U_4,I_4,V_4,W_4,Z_4)$, with $I_4=\frac{m_Z}{\sigma}, V_4=\frac{m_W}{\rho}, W_4=\frac{k(1-\varepsilon)pm_Z}{r\sigma m_W}-\frac{m_V}{r}$ and $Z_4=g_3(U_4)$. Observe that $W_4=\frac{m_V}{r}(R_2^W-1)$, which implies $R_2^W>1$. Moreover, we compute $f_3(0)=(-m_I-\theta-pg_3(0))I_4<0$, and $f_3'(0)>0$. In addition, we have

$$f_3(c)=\frac{I_4}{I_2}\left[c\left(\frac{\beta_1V_2}{1+\overline{q_1}W_4}+\frac{\beta_2I_2}{1+\overline{q_2}W_4}\right)-(m_I+\theta)I_2\right].$$

Hence, if $R_2^Z\le 1$, then $I_2\le I_4$, $c\le U_3$, and $W_2\le W_4$, which leads to

$$f_3(c)\le\frac{I_4}{I_2}\left[U_2\left(\frac{\beta_1V_2}{1+\overline{q_1}W_2}+\frac{\beta_2I_2}{1+\overline{q_2}W_2}\right)-(m_I+\theta)I_2\right]=\frac{I_4}{I_2}f_1(U_2)=0.$$

It follows that $f_3(U)<0$ for all $U\in(0,c)$, thus the system (1) does not admit an equilibrium in this range when $R_2^Z\le 1$. Conversely, if $R_2^Z>1$, we find $I_2>I_4$, $c>U_3$, and $W_2>W_4$, so that

$$f_3(c)>\frac{I_4}{I_2}\left[U_2\left(\frac{\beta_1V_2}{1+\overline{q_1}W_2}+\frac{\beta_2I_2}{1+\overline{q_2}W_2}\right)-m_II_2\right]=\frac{I_4}{I_2}f_1(U_2)=0.$$

Therefore, exactly one value $U_4\in(0,c)$ can be identified such that $f_3(U_4)=0$. We conclude that if $R_2^Z>1$, the system (1) possesses a unique steady state.

Based on the above reasoning, we formulate the following theorem.

Theorem 2.1

1. Suppose that $\mathcal{R}_0\leqslant 1$. In this case, the system (1) admits a unique infection-free equilibrium denoted by $\mathcal{E}_0=(U_0,0,0,0,0)$, where $U_0=\frac{A}{m_U}$.
2. Assume that $\mathcal{R}_0>1$. Under this condition, system (1) exhibits an infection equilibrium in the absence of immune responses. This equilibrium is given by $\mathcal{E}_1=(U_1,I_1,V_1,0,0)$, where $U_1=\frac{A}{m_U\mathcal{R}_0}$, $I_1=\frac{A(\mathcal{R}_0-1)}{m_I\mathcal{R}_0}$ and $V_1=\frac{k(1-\varepsilon)A(\mathcal{R}_0-1)}{m_Im_V\mathcal{R}_0}$.
3. Suppose that the condition $\mathcal{R}_1^W>1$ holds. Then system (1) admits an infection equilibrium in the presence of humoral immunity only, denoted by $\mathcal{E}_2=(U_2,I_2,V_2,W_2,0)$, where $U_2\in\left(0,\frac{A}{m_U}-\frac{m_Im_Vm_W}{k(1-\varepsilon)\rho m_U}\right)$, $I_2=\frac{1}{m_I}(A-m_UU_2)$, $V_2=\frac{m_W}{\rho}$ and $W_2=\frac{k(1-\varepsilon)\rho(A-m_UU_2)}{rm_Wm_I}-\frac{m_V}{r}$.

4. Assume that $\mathcal{R}_1^Z > 1$. In this scenario, the model (1) possesses an equilibrium involving cellular immunity only, expressed as $\mathcal{E}_3 = (U_3, I_3, V_3, 0, Z_3)$, where $U_3 \in \left(0, \frac{A}{m_U} - \frac{m_I m_Z}{\sigma m_U}\right)$, $I_3 = \frac{m_Z}{\sigma}$, $V_3 = \frac{k(1-\varepsilon)m_Z}{\sigma m_V}$ and $Z_3 = \frac{\sigma(A - m_U U_3) - m_I m_Z}{p m_Z}$.
5. Suppose further that both reproduction numbers satisfy $\mathcal{R}_2^W > 1$ and $\mathcal{R}_2^Z > 1$. In this case, system (1) admits an infection equilibrium involving both humoral and cellular immune responses. This equilibrium is denoted by $\mathcal{E}_4 = (U_4, I_4, V_4, W_4, Z_4)$, where $U_4 \in \left(0, \frac{A\rho - m_I m_Z}{\rho m_U}\right)$, $I_4 = \frac{m_Z}{\sigma}$, $V_4 = \frac{m_W}{\rho}$, $W_4 = \frac{k(1-\varepsilon)\rho m_Z}{r\sigma m_W} - \frac{m_V}{r}$ and $Z_4 = \frac{\sigma(A - m_U U_4) - m_I m_Z}{p m_Z}$.

3. Global stability

In this part, we focus on analyzing the global stability of the equilibria associated with system (1). This will be achieved using the approach outlined in [14]. In the following analysis, we employ the function $\phi(y) = y - 1 - \ln y$, which is known to be well-defined and strictly positive on the interval $(0, +\infty)$. Moreover, the function attains zero if and only if $y = 1$.

Let us denote by u the vector of the relative components of system (1) and by F the reaction function:

$$u = \begin{pmatrix} U \\ I \\ V \\ W \\ Z \end{pmatrix} \quad \text{and} \quad F(u) = \begin{pmatrix} A - m_U U - \dfrac{\beta_1 UV}{(1+q_1 Z)(1+\overline{q_1}W)} - \dfrac{\beta_2 UI}{(1+q_2 Z)(1+\overline{q_2}W)} + \theta I \\ \dfrac{\beta_1 UV}{(1+q_1 Z)(1+\overline{q_1}W)} + \dfrac{\beta_2 UI}{(1+q_2 Z)(1+\overline{q_2}W)} - (m_I + \theta)I - pIZ \\ k(1-\varepsilon)I - m_V V - rVW \\ \rho VW - m_W W \\ \sigma IZ - m_Z Z \end{pmatrix}. \tag{8}$$

Theorem 3.1
Assume that $\mathcal{R}_0 \leq 1$. Then the infection-free state $\mathcal{E}_0 = (U_0, 0, 0, 0, 0)$ of system (1) is globally asymptotically stable.

Proof
Define the following functional:

$$L_0(u) = U_0\, \phi\left(\frac{U}{U_0}\right) + I + \frac{U_0 \beta_1}{m_V} V + \frac{p}{\sigma} Z + \frac{r U_0 \beta_1 m_W}{\rho m_V} W,$$

and define

$$\mathcal{L}_0(u) = \int_\Omega L_0(u(y,t))\, dy.$$

For all $u \in \mathbb{R}_+^{*5}$, the functional $L_0(u)$ satisfies $L_0(u) > 0$, with equality $L_0(u) = 0$ occurring only when $u = \mathcal{E}_0$. By applying the method described in [14], we obtain

$$\frac{d\mathcal{L}_0(u)}{dt} = -\frac{C(n,s)}{2} \sum_{i=1}^{5} d_i\, \mathcal{E}\left(u_i, \frac{\partial L_0}{\partial u_i}(u)\right) + \int_\Omega \nabla L_0(u) \cdot F(u)\, dy,$$

with u_i are the components of u and d_i are diffusion coefficients. Our analysis reveals the negativity of $\nabla L_0(u)\cdot F(u)$ from [16] as follows

$$\begin{aligned}\nabla L_0(u)\cdot F(u) = \frac{dL_0}{dt} &= -\frac{m_U}{U}(U-U_0)^2 + U_0\left[\frac{\beta_1 V}{(1+\overline{q_1}W)(1+q_1Z)} + \frac{\beta_2 I}{(1+\overline{q_2}W)(1+q_2Z)}\right]\\ &\quad - m_I I - pIZ + \frac{U_0\beta_1}{m_V}V' + \frac{p}{\sigma}Z' + \frac{rU_0\beta_1 m_W}{\rho m_V}W',\\ &\leq -\frac{m_U}{U}(U-U_0)^2 + U_0(\beta_1 V + \beta_2 I) - m_I I - pIZ + \frac{U_0\beta_1}{m_V}V' + \frac{p}{\sigma}Z' + \frac{rU_0\beta_1 m_W}{\rho m_V}W',\\ &\leq -\frac{m_U}{U}(U-U_0)^2 + m_I I(\mathcal{R}_0 - 1) - \frac{p}{\sigma}m_Z Z - \frac{rU_0\beta_1 m_W}{\rho \text{fl} m_V}\text{fl}W.\end{aligned}$$

Therefore, if $\mathcal{R}_0 \leq 1$, we have $\nabla L_0(u)\cdot F(u) \leq 0$, and the equality $\nabla L_0(u)\cdot F(u) = 0$ occurs exclusively when u equals $\mathcal{E}_0$. Furthermore, L_0 complies with the requirements specified in Theorem 1 in [14],

$$\begin{aligned}\mathcal{E}\left(U, \frac{\partial L_0}{\partial U}(u)\right) &= U_0\int_\Omega\int_\Omega \frac{(U(y_1,t)-U(y_2,t))^2}{U(y_1,t)\,U(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\ \mathcal{E}\left(I, \frac{\partial L_0}{\partial I}(u)\right) &= \mathcal{E}\left(V, \frac{\partial L_0}{\partial V}(u)\right) = \mathcal{E}\left(W, \frac{\partial L_0}{\partial W}(u)\right) = \mathcal{E}\left(Z, \frac{\partial L_0}{\partial Z}(u)\right) = 0.\end{aligned}$$

If $\mathcal{R}_0 \leq 1$, then it follows that $\frac{d\mathcal{L}_0}{dt} \leq 0$. This derivative equals zero only when $u = \mathcal{E}_0$ Thus, the global asymptotic stability holds for the equilibrium point $\mathcal{E}_0$. □

We now proceed to analyze the asymptotic stability of the four infection equilibria $\mathcal{E}_1$, $\mathcal{E}_2$, $\mathcal{E}_3$, and $\mathcal{E}_4$. For this analysis, we will assume the following additional hypothesis:

$$\begin{cases}\left(\dfrac{(1+q_1Z)(1+\overline{q_1}W)}{(1+q_1Z_i)(1+\overline{q_1}W_i)} - 1\right)\left(\dfrac{(1+q_1Z)(1+\overline{q_1}W)}{(1+q_1Z_i)(1+\overline{q_1}W_i)} - \dfrac{V}{V_i}\right) \leq 0,\\ \left(\dfrac{(1+q_2Z)(1+\overline{q_2}W)}{(1+q_2Z_i)(1+\overline{q_2}W_i)} - 1\right)\left(\dfrac{(1+q_2Z)(1+\overline{q_2}W)}{(1+q_2Z_i)(1+\overline{q_2}W_i)} - \dfrac{I}{I_i}\right) \leq 0,\end{cases} \tag{H}$$

where Z_i, W_i, V_i, I_i, and U_i denote, respectively, the components of CTL cells, antibodies, viral particles, infected cells, and uninfected cells at the equilibrium states $\mathcal{E}_i$ corresponding to $i = 1, 2, 3, 4$.

Remark *3.2*
It obvious that the assumption (H) is always satisfied when the non-lytic effects of humoral and cellular immune responses are ignored, i.e., $q_1 = q_2 = \overline{q_1} = \overline{q_2} = 0$.

Theorem 3.3
Suppose that the hypothesis (H) is satisfied for the infection equilibria $\mathcal{E}_i$, with $i = 1, 2, 3, 4$.

(i) The equilibrium $\mathcal{E}_1$ is globally asymptotically stable if the conditions $\mathcal{R}_1^{\mathrm{W}} \leq 1$ and $\mathcal{R}_1^{\mathrm{Z}} \leq 1$ hold.
(ii) If $\mathcal{R}_2^{\mathrm{Z}} \leq 1 < \mathcal{R}_1^{\mathrm{W}}$, then the infection equilibrium $\mathcal{E}_2$ is globally asymptotically stable.
(iii) When $\mathcal{R}_2^{\mathrm{W}} \leq 1 < \mathcal{R}_1^{\mathrm{Z}}$, the infection equilibrium $\mathcal{E}_3$, characterized by absence of humoral immunity, is globally asymptotically stable.
(iv) If both $\mathcal{R}_2^{\mathrm{W}} > 1$ and $\mathcal{R}_2^{\mathrm{Z}} > 1$, then the infection equilibrium $\mathcal{E}_4$, which includes both humoral and cellular immune responses, is globally asymptotically stable.

Proof

- For the case (i), let us introduce the Lyapunov functional $\mathcal{L}_1$ given by:

$$\mathcal{L}_1(u) = \int_\Omega L_1(u(y,t))\,dy,$$

where

$$L_1(u) = U_1\phi\left(\frac{U}{U_1}\right) + I_1\phi\left(\frac{I}{I_1}\right) + \frac{\beta_1 U_1 V_1}{k(1-\varepsilon)I_1} V_1\phi\left(\frac{V}{V_1}\right) + \frac{p}{\sigma}Z + \frac{\beta_1 r U_1 V_1}{k(1-\varepsilon)\rho I_1} W.$$

According to [16], we have $\nabla L_1(u)\cdot F(u) \leq 0$ provided that condition (H) holds for $\mathcal{E}_1$, and that both $\mathcal{R}_1^W \leq 1$ and $\mathcal{R}_1^Z \leq 1$ are satisfied. Moreover, equality holds, i.e., $\nabla L_1(u)\cdot F(u) = 0$, if and only if $u = \mathcal{E}_1$.

Additionally, L_1 takes the form of equation (11) in [14], thus

$$\begin{aligned}
\mathcal{E}\left(U, \frac{\partial L_1}{\partial U}(u)\right) &= U_1 \int_\Omega\int_\Omega \frac{(U(y_1,t)-U(y_2,t))^2}{U(y_1,t)\,U(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\
\mathcal{E}\left(I, \frac{\partial L_1}{\partial I}(u)\right) &= I_1 \int_\Omega\int_\Omega \frac{(I(y_1,t)-I(y_2,t))^2}{I(y_1,t)\,I(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\
\mathcal{E}\left(V, \frac{\partial L_1}{\partial V}(u)\right) &= \frac{\beta_1 U_1 V_1}{k(1-\varepsilon)I_1} V_1 \int_\Omega\int_\Omega \frac{(V(y_1,t)-V(y_2,t))^2}{V(y_1,t)\,V(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\
\mathcal{E}\left(W, \frac{\partial L_1}{\partial W}(u)\right) &= \mathcal{E}\left(Z, \frac{\partial L_1}{\partial Z}(u)\right) = 0.
\end{aligned}$$

Consequently, we have

$$\frac{d\mathcal{L}_1}{dt} = \int_\Omega \nabla L_1(u)\cdot F(u)\,dy - \frac{C(n,s)}{2}\sum_{i=1}^{5} d_i\,\mathcal{E}\left(u_i, \frac{\partial L_1}{\partial u_i}(u)\right) \leq 0.$$

Therefore, the equilibrium point $\mathcal{E}_1$ is globally asymptotically stable under the conditions that (H) holds, $\mathcal{R}_1^W \leq 1$ and $\mathcal{R}_1^Z \leq 1$.

- In case (ii), let us consider the Lyapunov function $\mathcal{L}_2$ defined as follows:

$$\mathcal{L}_2(u) = \int_\Omega L_2(u(y,t))\,dy,$$

with

$$\begin{aligned}
L_2(u) = U_2\,\phi\left(\frac{U}{U_2}\right) + I_2\,\phi\left(\frac{I}{I_2}\right) + \frac{\beta_1 U_2 V_2}{k(1-\varepsilon)(1+\overline{q_1}W_2)I_2} V_2\,\phi\left(\frac{V}{V_2}\right) + \frac{p}{\sigma}Z\\
+ \frac{r\,\beta_1\,U_2\,V_2}{\rho\,k(1-\varepsilon)(1+\overline{q_1}W_2)I_2} W_2\,\phi\left(\frac{W}{W_2}\right).
\end{aligned}$$

From [16], it follows that $\nabla L_2(u)\cdot F(u) \leq 0$ when H applies to $\mathcal{E}_2$, $\mathcal{R}_1^W > 1$ and $\mathcal{R}_2^Z \leq 1$. Furthermore, we have $\nabla L_2(u)\cdot F(u) = 0$ precisely when $u = \mathcal{E}_2$. Moreover, the function L_2 corresponds to the general form given in equation (11) of [14]. Accordingly, the following relations hold:

$$\begin{aligned}
\mathcal{E}\left(U, \frac{\partial L_2}{\partial U}(u)\right) &= U_2 \int_\Omega\int_\Omega \frac{\big(U(y_1,t)-U(y_2,t)\big)^2}{U(y_1,t)\,U(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\
\mathcal{E}\left(I, \frac{\partial L_2}{\partial I}(u)\right) &= I_2 \int_\Omega\int_\Omega \frac{\big(I(y_1,t)-I(y_2,t)\big)^2}{I(y_1,t)\,I(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\
\mathcal{E}\left(V, \frac{\partial L_2}{\partial V}(u)\right) &= \frac{\beta_1 U_2 V_2}{k(1-\varepsilon)(1+\overline{q_1}W_2)\,I_2} V_2 \int_\Omega\int_\Omega \frac{\big(V(y_1,t)-V(y_2,t)\big)^2}{V(y_1,t)\,V(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\
\mathcal{E}\left(W, \frac{\partial L_2}{\partial W}(u)\right) &= \frac{r\,\beta_1\,U_2\,V_2}{\rho\,k(1-\varepsilon)(1+\overline{q_1}W_2)\,I_2} W_2 \int_\Omega\int_\Omega \frac{\big(W(y_1,t)-W(y_2,t)\big)^2}{W(y_1,t)\,W(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\,dy_1\,dy_2 \geq 0,\\
\mathcal{E}\left(Z, \frac{\partial L_2}{\partial Z}(u)\right) &= 0.
\end{aligned}$$

As a result, by applying point (ii) of Theorem 1 in [14], we obtain $\frac{d\mathcal{L}_2}{dt} \leq 0$. Therefore, the equilibrium point $\mathcal{E}_2$ is globally asymptotically stable, provided that condition (H) holds and the reproduction numbers satisfy $\mathcal{R}_1^W > 1$ and $\mathcal{R}_2^Z \leq 1$.

- In case (iii), consider the Lyapunov function $\mathcal{L}_3$ defined by:

$$\mathcal{L}_3(u) = \int_\Omega L_3(u(y,t))\, dy$$

where

$$L_3(u) = U_3\,\phi\left(\frac{U}{U_3}\right) + I_3\,\phi\left(\frac{I}{I_3}\right) + \frac{\beta_1 U_3 V_3}{k(1-\varepsilon)(1+q_1 Z_3)\, I_3} V_3\,\phi\left(\frac{V}{V_3}\right) + \frac{p}{\sigma} Z_3\,\phi\left(\frac{Z}{Z_3}\right) + \frac{r\,\beta_1\, U_3\, V_3}{\rho\, k(1-\varepsilon)(1+q_1 Z_3)\, I_3} W.$$

According to the results in [16], we have $\nabla L_3(u)\cdot F(u) \leq 0$, whenever condition (H) is satisfied, $\mathcal{R}_2^W \leq 1$, and $\mathcal{R}_1^Z > 1$. The equality $\nabla L_2(u)\cdot F(u) = 0$ holds only when $u = \mathcal{E}_3$. Moreover, the function L_3 corresponds to the general form (11) presented in [14]. As a result, the following expressions are satisfied:

$$\begin{aligned}
\mathcal{E}\left(U, \frac{\partial L_3}{\partial U}(u)\right) &= U_3 \int_\Omega\int_\Omega \frac{(U(y_1,t)-U(y_2,t))^2}{U(y_1,t)\,U(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0,\\
\mathcal{E}\left(I, \frac{\partial L_3}{\partial I}(u)\right) &= I_3 \int_\Omega\int_\Omega \frac{(I(y_1,t)-I(y_2,t))^2}{I(y_1,t)\,I(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0,\\
\mathcal{E}\left(V, \frac{\partial L_3}{\partial V}(u)\right) &= \frac{\beta_1 U_3 V_3}{k(1-\varepsilon)(1+q_1 Z_3)\, I_3} V_3 \int_\Omega\int_\Omega \frac{(V(y_1,t)-V(y_2,t))^2}{V(y_1,t)\,V(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0,\\
\mathcal{E}\left(W, \frac{\partial L_3}{\partial W}(u)\right) &= 0,\\
\mathcal{E}\left(Z, \frac{\partial L_3}{\partial Z}(u)\right) &= \frac{p}{\sigma} Z_3 \int_\Omega\int_\Omega \frac{(Z(y_1,t)-Z(y_2,t))^2}{Z(y_1,t)\,Z(y_2,t)\,|y_1-y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0.
\end{aligned}$$

Therefore, by applying point (ii) of Theorem 1 in [14], it follows that $\frac{d\mathcal{L}_2}{dt} \leq 0$. This implies that the equilibrium point $\mathcal{E}_3$ is globally asymptotically stable, provided that the hypothesis (H) holds, $\mathcal{R}_2^W \leq 1$ and $\mathcal{R}_1^Z > 1$.

- In case (iv), the Lyapunov function $\mathcal{L}_4$ is given by:

$$\mathcal{L}_4(u) = \int_\Omega L_4(u(y,t))\, dy$$

with

$$L_4(u) = U_4\,\phi\left(\frac{U}{U_4}\right) + I_4\,\phi\left(\frac{I}{I_4}\right) + \frac{\beta_1 U_4 V_4}{k(1-\varepsilon)(1+q_1 Z_4)(1+\overline{q_1} W_4)\, I_4} V_4\,\phi\left(\frac{V}{V_4}\right) + \frac{p}{\sigma} Z_4\,\phi\left(\frac{Z}{Z_4}\right) + \frac{r\,\beta_1\, U_4\, V_4}{\rho\, k(1-\varepsilon)(1+q_1 Z_4)(1+\overline{q_1} W_4)\, I_4} W_4\,\phi\left(\frac{W}{W_4}\right).$$

Then, according to the results in [16], provided that condition (H) holds, $\mathcal{R}_2^W > 1$, and $\mathcal{R}_2^Z > 1$, it follows that $\nabla L_4(u)\cdot F(u) \leq 0$. Moreover, the equality $\nabla L_4(u)\cdot F(u) = 0$ holds if and only if $u = \mathcal{E}_3$. In addition, the function L_4 corresponds to the general form (11) presented in [14]. Consequently,

the following expressions hold:

$$\mathcal{E}\left(U, \frac{\partial L_4}{\partial U}(u)\right) = U_4 \int_\Omega \int_\Omega \frac{(U(y_1,t) - U(y_2,t))^2}{U(y_1,t)\, U(y_2,t)\, |y_1 - y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0,$$

$$\mathcal{E}\left(I, \frac{\partial L_4}{\partial I}(u)\right) = I_4 \int_\Omega \int_\Omega \frac{(I(y_1,t) - I(y_2,t))^2}{I(y_1,t)\, I(y_2,t)\, |y_1 - y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0,$$

$$\mathcal{E}\left(V, \frac{\partial L_4}{\partial V}(u)\right) = \frac{\beta_1 U_4 V_4}{k(1-\varepsilon)(1+q_1 Z_4)(1+\overline{q_1} W_4)\, I_4} V_4 \int_\Omega \int_\Omega \frac{(V(y_1,t) - V(y_2,t))^2}{V(y_1,t)\, V(y_2,t)\, |y_1 - y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0,$$

$$\mathcal{E}\left(W, \frac{\partial L_4}{\partial W}(u)\right) = \frac{r\, \beta_1\, U_4\, V_4}{\rho\, k(1-\varepsilon)(1+q_1 Z_4)(1+\overline{q_1} W_4)\, I_4} W_4 \int_\Omega \int_\Omega \frac{(W(y_1,t) - W(y_2,t))^2}{W(y_1,t)\, W(y_2,t)\, |y_1 - y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0,$$

$$\mathcal{E}\left(Z, \frac{\partial L_4}{\partial Z}(u)\right) = \frac{p}{\sigma} Z_3 \int_\Omega \int_\Omega \frac{(Z(y_1,t) - Z(y_2,t))^2}{Z(y_1,t)\, Z(y_2,t)\, |y_1 - y_2|^{\frac{n}{2}+s}}\, dy_1\, dy_2 \geq 0.$$

Hence, by applying point (ii) of Theorem 1 in [14], it follows that $\frac{d\mathcal{L}_2}{dt} \leq 0$. As a result, the equilibrium point $\mathcal{E}_4$ is globally asymptotically stable, provided that hypothesis (H) holds and that $\mathcal{R}_2^W > 1$ as well as $\mathcal{R}_2^Z > 1$.

□

4. Parameters estimation and sensitivity analysis

This section presents a detailed analysis of parameter estimation and sensitivity. It quantifies the main biological parameters of our model, examines the experimental and theoretical data sources on which these estimates rely, and evaluates how variations in these parameters influence the overall dynamics of the system.

From the above mathematical analysis of our FPDE model, the infection-free equilibrium $\mathcal{E}_0\left(\frac{A}{m_U}, 0, 0, 0, 0\right)$ represents a state in which no infection is present. In the case of HIV infection, the quantity $\frac{A}{m_U}$ corresponds the total number of healthy CD4$^+$ T cells when the system is in a stable state, without any viral infection or immune response. It follows from the references [21, 22] that the average half-life of naive CD4 cells is approximately 22 to 50 days, which implies that $\frac{\ln 2}{50} \leq m_U \leq \frac{\ln 2}{22}$, giving m_U between 0.0139 and 0.0315 day^{-1}. In healthy adults, the CD4$^+$ T cells typically range between 500 and 1500 $cells/\mu$L [23]. Hence, the parameter A can be range between 6.95 and 47.25 cells μL^{-1}day^{-1}.

For the virion infection rate of CD4$^+$ T cells β_1, we selected a range from 2.4×10^{-5} to 4.8×10^{-3} μL virion^{-1} day^{-1}. This range is based on the standard estimates provided by Perelson et al. [24], as well as the extended values reported by Stafford et al. [25]. The second infection pathway, mediated by cell-to-cell transmission and represented by the parameter β_2, has not been directly quantified experimentally. Nonetheless, the study in [26] showed that this mode of transmission contributes to roughly 60% of viral infections.

The death rate of productively infected CD4$^+$ T cells is commonly estimated to be $m_I = 0.29 \pm 0.02$ day^{-1}[27]. This value reflects the rapid turnover characteristic of HIV infection, corresponding to an average infected cell lifespan of roughly 3 to 4 days. The estimations of the other parameters are given in Table 1.

Table 1. The 19 parameters of the FPDE model (1) with their values.

Parameter	Meaning	Value	Source
A	Production rate of uninfected cells	6.95 - 47.25 cells μL^{-1}day^{-1}.	Calculated
m_U	Death rate of uninfected cells	0.0139 - 0.0315 day^{-1}	Estimated
β_1	Virus-to-cell infection rate	$2.4\times10^{-5}-4.8\times10^{-3}$ μL virion^{-1}day^{-1}	[24, 25]
β_2	Cell-to-cell infection rate	$0-1$ μL cell^{-1}day^{-1}	Assumed
m_I	Death rate of infected cells	$0.27-0.31$ day^{-1}	[27]
θ	Cure rate of infected cells	0.01 day^{-1}	[28]
m_V	Clearance rate of virus	$2.06-3.81$ day^{-1}	[24]
k	Viral production rate	27-7073 virion cell^{-1}day^{-1}	[5]
p	Clearance rate by CTL cells	$0.001-1$ cell$^{-1}\mu$L day^{-1}	[18]
r	Neutralization rate by antibodies	0.5 molecule$^{-1}\mu$L day^{-1}	Assumed
m_W	Death rate of antibodies	0.35 day^{-1}	Assumed
m_Z	Death rate of CTL cells	$0.05-0.15$ day^{-1}	[29, 30]
q_1	CTL non-lytic strength virus-to-cell	0.01 μL cell^{-1}	Assumed
$\bar{q}_1$	Antibody non-lytic strength virus-to-cell	0.001 μL cell^{-1}	Assumed
q_2	CTL non-lytic strength cell-to-cell	0.02 μL cell^{-1}	Assumed
$\bar{q}_2$	Antibody non-lytic strength cell-to-cell	0.002 μL cell^{-1}	Assumed
ρ	Activation rate of antibodies	$6.7\times10^{-6}-6.7\times10^{-3}$ μL virion^{-1} day^{-1}	Assumed
σ	Activation rate of CTL cells	$0.002-0.025$ μL cell^{-1} day^{-1}	Assumed
ϵ	Effectiveness of antiviral treatment	$0-1$	Assumed

Sensitivity analysis enables quantification of how changes in model parameters affect the progression of viral infection infection. The basic reproduction number, $\mathcal{R}_0=\frac{A\left(\beta_1 k(1-\varepsilon)+\beta_2 m_V\right)}{m_U m_V(m_I+\theta)}$, serves as a critical threshold, indicating whether the infection will be cleared or persist within the host. To evaluate the relative influence of each parameter, we use the normalized sensitivity index defined for any parameter α as

$$\Gamma^{\alpha}_{\mathcal{R}_0}=\frac{\alpha}{\mathcal{R}_0}\frac{\partial\mathcal{R}_0}{\partial\alpha}. \tag{9}$$

By applying Equation (9) and analyzing the data presented in Table 1, we find that the parameters exerting the most significant influence on $\mathcal{R}_0$ in the viral infection model are A, β_1, β_2, and k. An increase in any of these parameters results in a higher basic reproduction number, whereas increasing m_U, m_I, m_V, θ, or ε tends to decrease $\mathcal{R}_0$. These findings are summarized in Table 2 and illustrated in Figures 1 and 2.

Table 2. Sensitivity of $\mathcal{R}_0$ to model parameters.

Parameter	Value	Sensitivity index
A	10	1
m_U	0.0139	-1
β_1	2.4×10^{-5}	0.166667
β_2	1.8×10^{-3}	0.83333
k	50	0.166667
ε	0.1	-0.0185185
m_V	3	-0.166667
m_I	0.29	-0.9666667
θ	0.01	-0.0333333

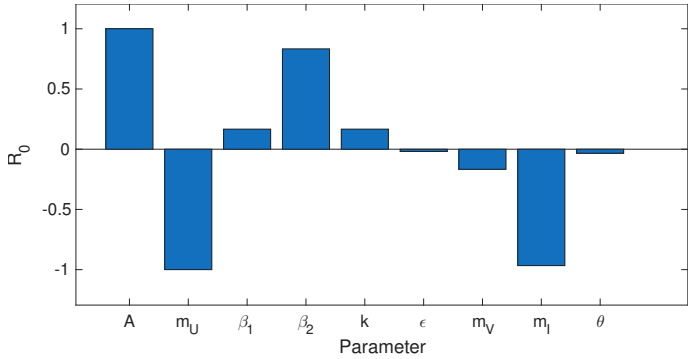

Figure 1. Sensitivity indices of $\mathcal{R}_0$.

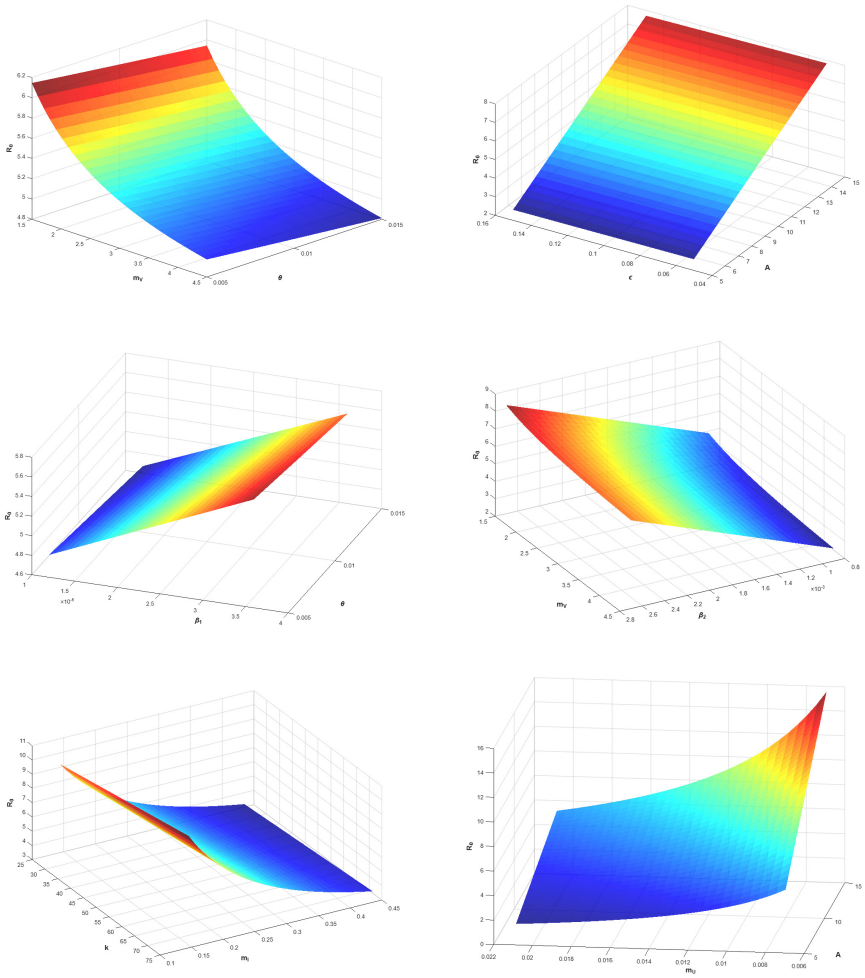

Figure 2. The dependence of $\mathcal{R}_0$ on specific parameters.

5. Numerical simulations

Initially, we introduce a computational method for approximating solutions to the FPDE model (1). Applying the explicit Euler scheme, the temporal discretization reads as follows:

$$\frac{u_l^{n+1} - u_l^n}{\Delta t} = D\,(-\Delta_h)^s u_l^n + F(u_l^n).$$

Here, $(-\Delta_h)^s$ corresponds to the discrete version employing the regional fractional Laplacian operator, which can be approximated in one dimension as in [31] by the following discrete operator:

$$(-\Delta_h)^s u_l = \sum_{k=-\infty}^{+\infty} (u_l - u_{l-k}) w_k = \sum_{k=1}^{+\infty} (-u_{l-k} + 2u_l - u_{l+k}) w_k, \tag{10}$$

for a function $u = \{u_l\}_{l\in\mathbb{Z}}$ defined on the discrete spatial domain $\Omega_h = \{lh \mid l \in \mathbb{Z}\} \cap \Omega$, with mesh size $h > 0$. The weights $\{w_k\}_{k\in\mathbb{Z}}$ are positive correction coefficients satisfying the normalization condition $\sum_{k\in\mathbb{Z}} w_k = 1$. Following [32], the weights are chosen as

$$w_k = \frac{C(1,s)}{|k|^{1+2s}}, \quad k \neq 0.$$

Given that the fractional Laplacian inherently possesses symmetry, it is appropriate to enforce symmetry on the weights, that is, $w_k = w_{-k}$. The normalization constant $C(1,s)$, as defined in equation (3), ensures consistency in the operator's definition. Thus, we can write the scheme in the form

$$\begin{aligned} u_l^{n+1} &= \big(1 + \Delta t\, w_0\big) u_l^n + D \sum_{k\neq 0} \Delta t\, (u_l^n - u_{l-k}^n) w_k + \Delta t\, F(u_l^n), \\ &= \big(1 + \Delta t\, w_0\big) u_l^n + D \sum_{k=1}^{+\infty} \Delta t\, (-u_{l+k}^n + 2u_l^n - u_{l-k}^n) w_k + \Delta t\, F(u_l^n), \end{aligned}$$

where $u_l = (U_l, I_l, V_l, W_l, Z_l)$ and $F = (F_1, F_2, F_3, F_4, F_5)$ denotes the reaction term as defined in (8). The weight coefficient w_0 can be chosen arbitrarily, as it does not appear explicitly in equation (10).
So, to numerically approximate model (1), we employ the following recursive formulas:

$$\begin{aligned} U_l^{n+1} &= (1 + \Delta t\, w_0) U_l^n + d_U \sum_{k=1}^{N} \Delta t\, (-U_{l+k}^n + 2U_l^n - U_{l-k}^n) w_k + \Delta t\, F_1(u_l^n), \\ I_l^{n+1} &= (1 + \Delta t\, w_0) I_l^n + d_I \sum_{k=1}^{N} \Delta t\, (-I_{l+k}^n + 2I_l^n - I_{l-k}^n) w_k + \Delta t\, F_2(u_l^n), \\ V_l^{n+1} &= (1 + \Delta t\, w_0) V_l^n + d_V \sum_{k=1}^{N} \Delta t\, (-V_{l+k}^n + 2V_l^n - V_{l-k}^n) w_k + \Delta t\, F_3(u_l^n), \\ W_l^{n+1} &= (1 + \Delta t\, w_0) W_l^n + d_W \sum_{k=1}^{N} \Delta t\, (-W_{l+k}^n + 2W_l^n - W_{l-k}^n) w_k + \Delta t\, F_4(u_l^n), \\ Z_l^{n+1} &= (1 + \Delta t\, w_0) Z_l^n + d_Z \sum_{k=1}^{N} \Delta t\, (-Z_{l+k}^n + 2Z_l^n - Z_{l-k}^n) w_k + \Delta t\, F_5(u_l^n). \end{aligned}$$

Based on Table 1, the numerical values of the model parameters are chosen as follows: $\varepsilon = 0.1$, $\theta = 0.01$, $\beta_1 = 2.4 \times 10^{-5}$, $m_U = 0.0139$, $m_I = 0.29$, $m_V = 3$ and $m_W = 0.35$.

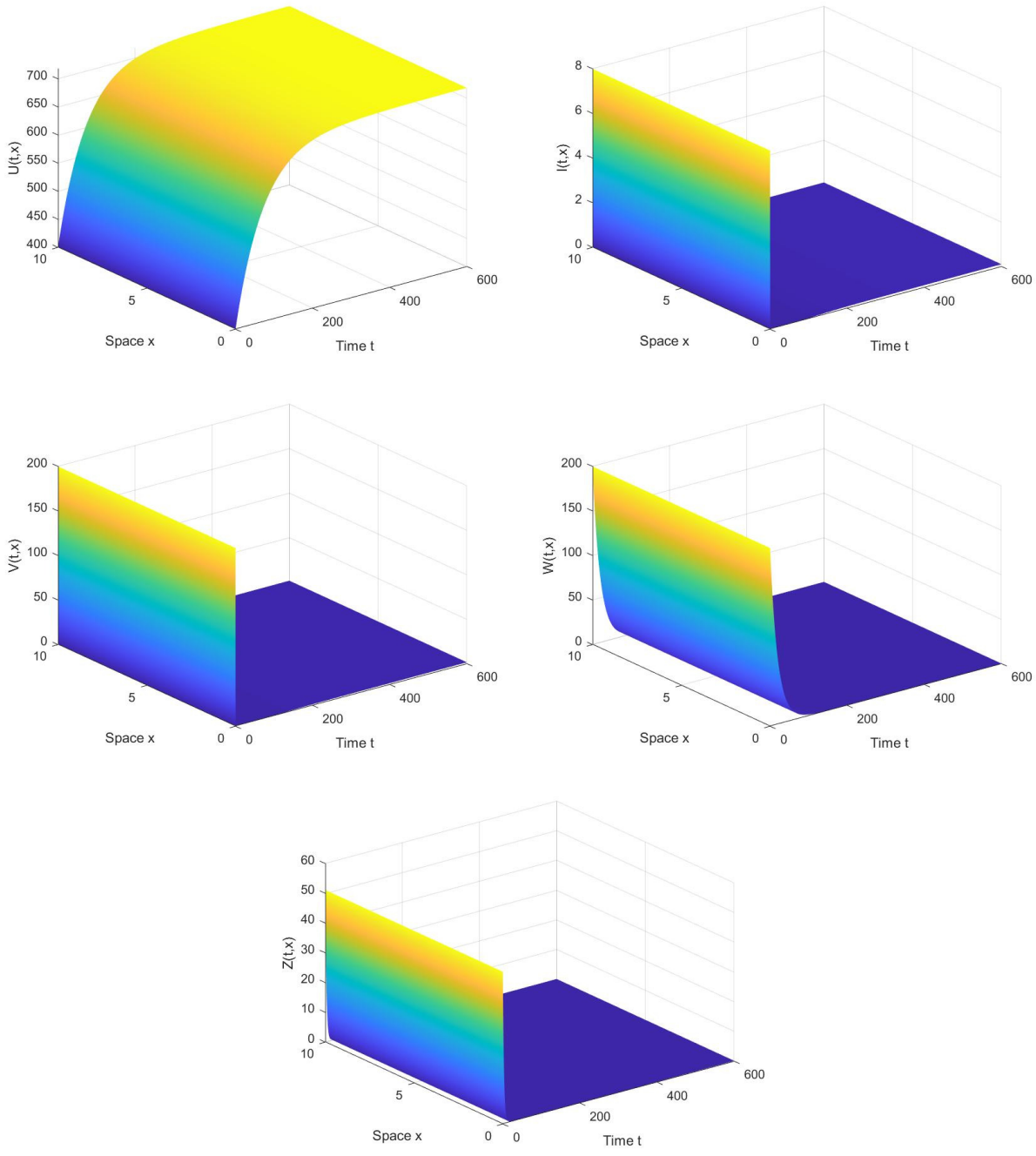

Figure 3. Dynamics of the system (1) at $\mathcal{E}_0$ when $\mathcal{R}_0 = 0.8975 < 1$.

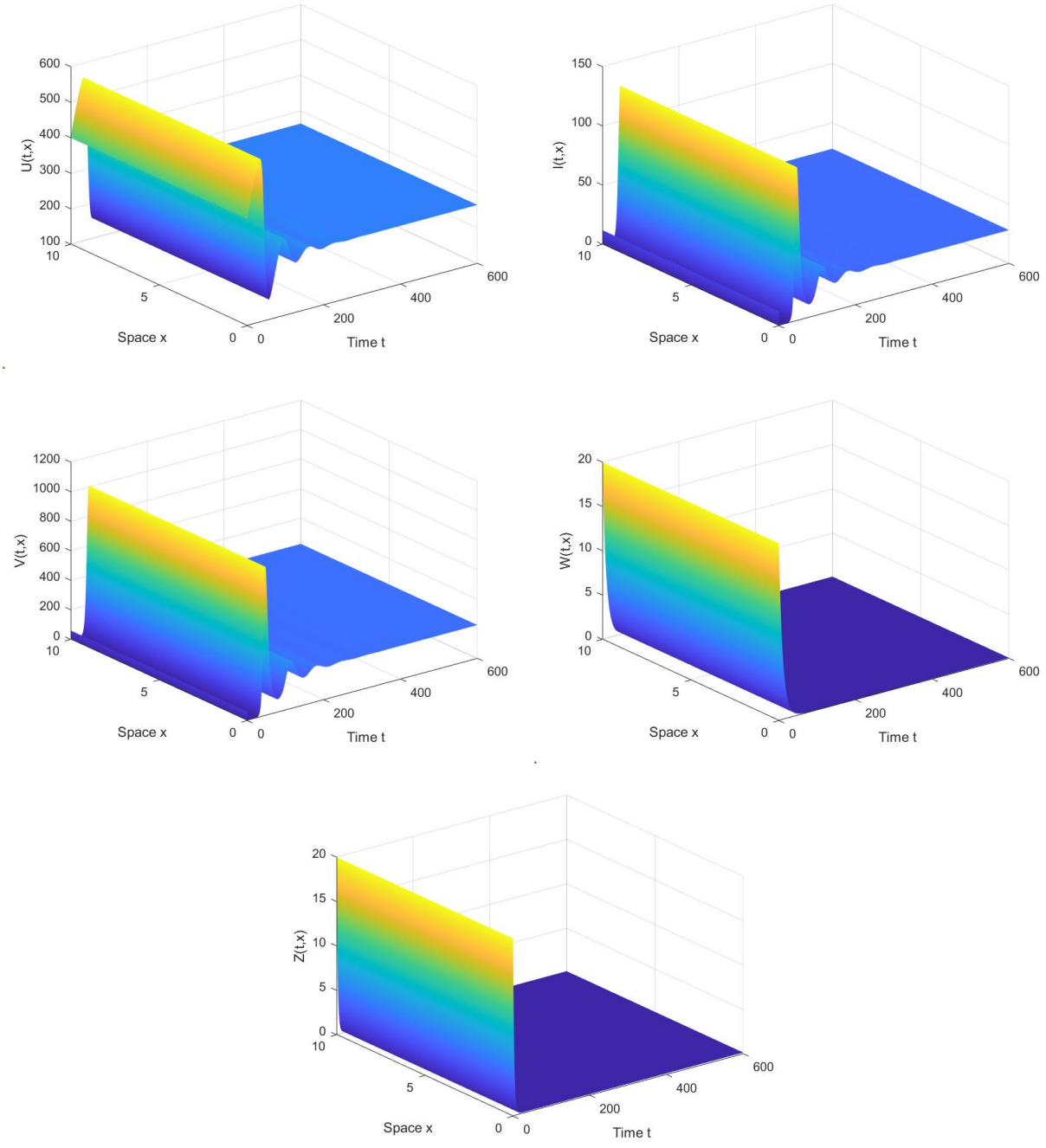

Figure 4. Dynamics of system (1) at $\mathcal{E}_1$ when $\mathcal{R}_0 = 3.437 > 1$, $\mathcal{R}_1^W = 4.55 \times 10^{-3} \leq 1$ and $\mathcal{R}_1^Z = 0.5868 \leq 1$.

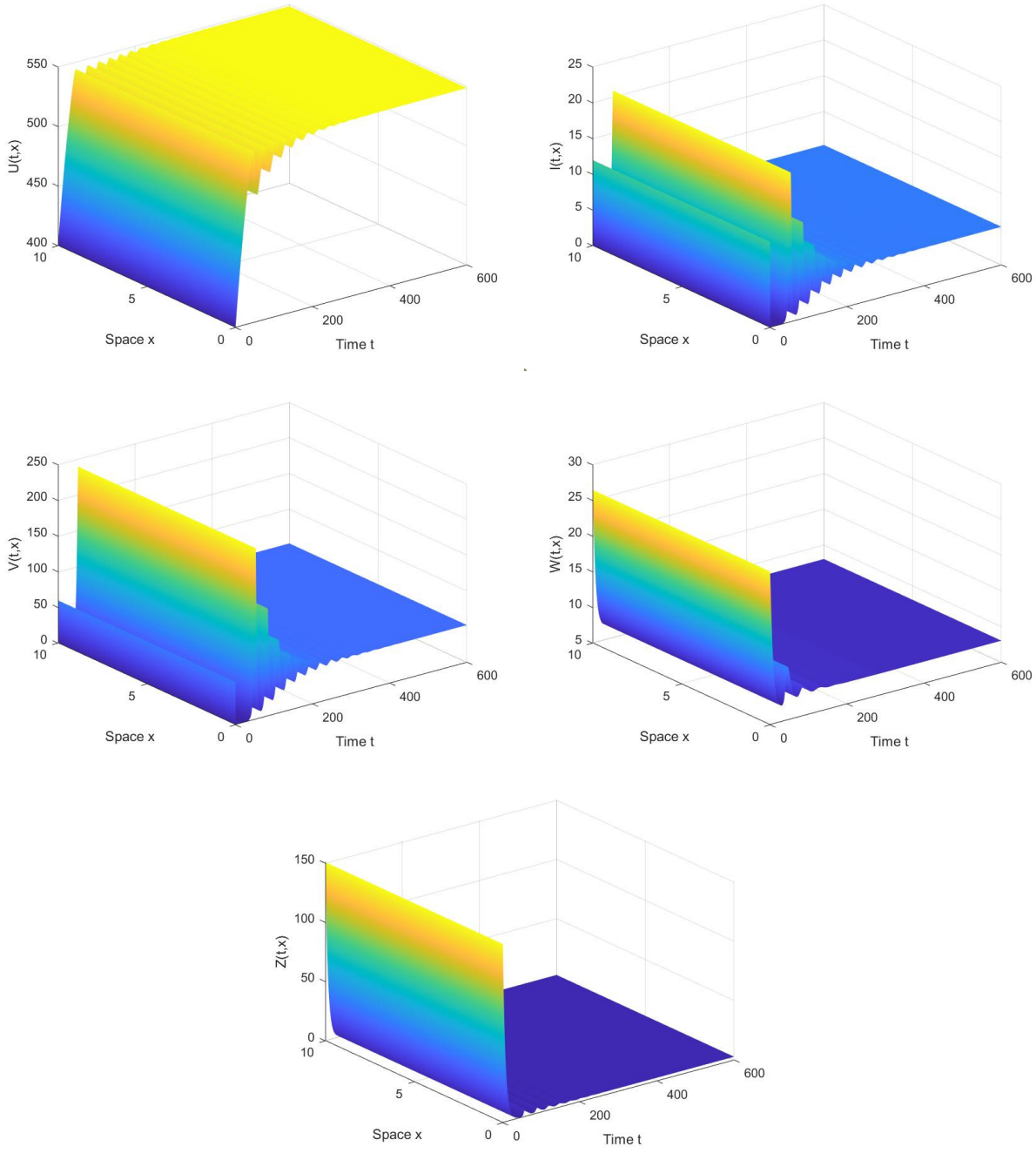

Figure 5. Dynamics of system (1) at $\mathcal{E}_2$ when $\mathcal{R}_0 = 5.18 > 1$, $\mathcal{R}_1^W = 4.549 > 1$ and $\mathcal{R}_2^Z = 0.3796 \leq 1$.

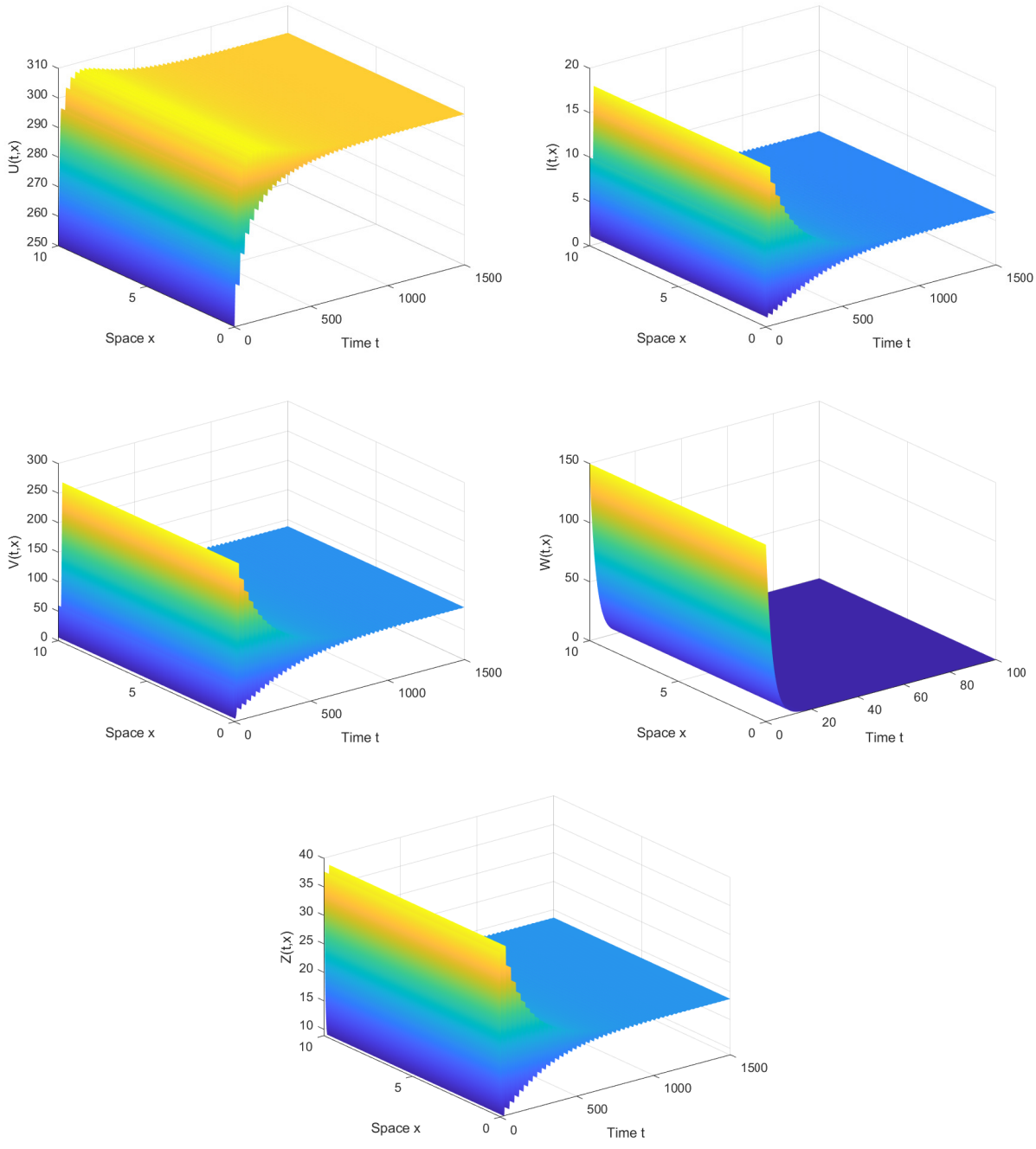

Figure 6. Dynamics of system (1) at $\mathcal{E}_3$ when $\mathcal{R}_0 = 3.1079 > 1$, $\mathcal{R}_1^Z = 3.425 > 1$ and $\mathcal{R}_2^W = 0.0257 \leq 1$.

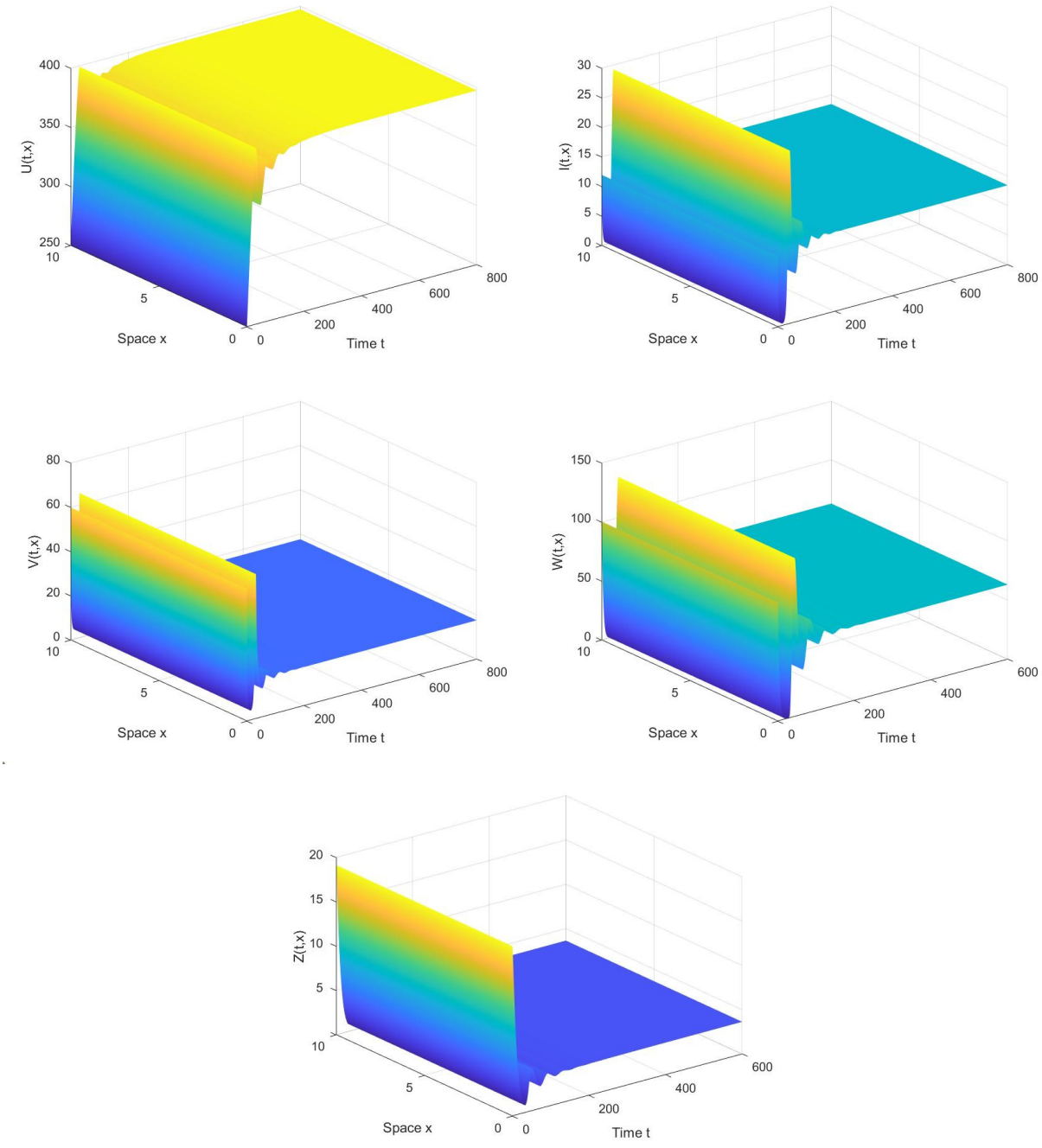

Figure 7. Dynamics of system (1) at $\mathcal{E}_4$ when $\mathcal{R}_0 = 5.179 > 1$, $\mathcal{R}_2^W = 1.4357 > 1$ and $\mathcal{R}_2^Z = 3.89 > 1$.

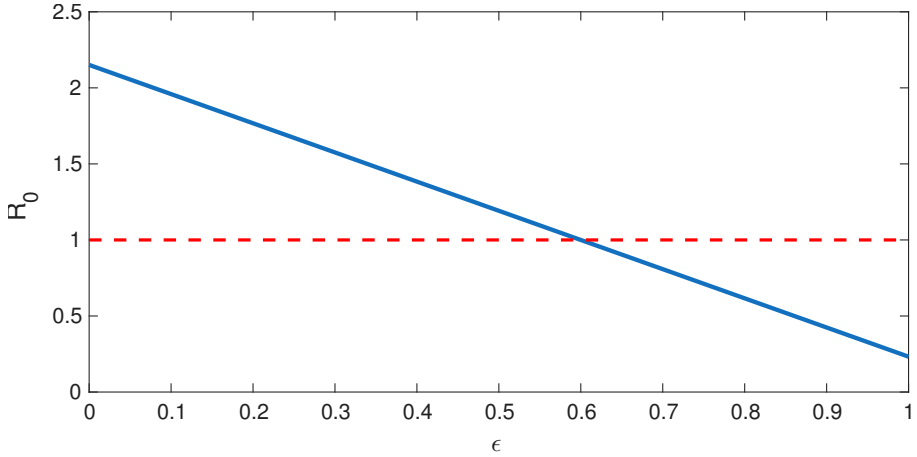

Figure 8. Effect of treatment on viral infection dynamics.

Infection-free steady state $\mathcal{E}_0$: For the dynamics of $\mathcal{E}_0$, we study the case where $\mathcal{R}_0 < 1$. If $A = 10$, $\beta_2 = 1.8 \times 10^{-6}$, $\sigma = 2 \times 10^{-3}$, $m_Z = 0.05$, $k = 50$ and $\rho = 6.7 \times 10^{-3}$, then $\mathcal{R}_0 = 0.8975 < 1$. Accordingly, the equilibrium $\mathcal{E}_0 = (719.4244, 0, 0, 0, 0)$ exhibits global asymptotic stability. This finding is supported by the numerical simulation shown in Figure 3, where the trajectories of model (1) converge to $\mathcal{E}_0$.

Infection equilibrium in the absence of immune responses $\mathcal{E}_1$: Let us consider the following parameter values: $k = 27$, $\rho = 6.7 \times 10^{-6}$, $A = 12$, $m_Z = 0.1$, $\beta_2 = 10^{-3}$ and $\sigma = 0.002$. For this configuration, we obtain the basic reproduction number $\mathcal{R}_0 = 3.437 > 1$, while the reproduction numbers related to immune responses are $\mathcal{R}_1^W = 4.55 \times 10^{-3} \leq 1$ and $\mathcal{R}_1^Z = 0.5868 \leq 1$. As illustrated in Figure 4, the system trajectories associated with model (1) converge to the infection equilibrium point $\mathcal{E}_1 = (251.181, 29.34, 237.65, 0, 0)$. This behavior supports the global asymptotic stability of $\mathcal{E}_1$ and corroborates the theoretical findings stated in point (i) of Theorem 3.3.

Infection equilibrium in the absence of cellular immunity $\mathcal{E}_2$: Consider the parameter values: $k = 50$, $\rho = 6.7 \times 10^{-3}$, $\beta_2 = 1.8 \times 10^{-3}$, $A = 10$, $m_Z = 0.1$ and $\sigma = 0.002$. Under these conditions, the basic reproduction number is $\mathcal{R}_0 = 5.18 > 1$, while the reproduction number for humoral immunity is $\mathcal{R}_1^W = 4.5493 > 1$, and that of cellular immunity is $\mathcal{R}_2^Z = 0.3796 \leq 1$. As illustrated in Figure 5, the trajectories of system (1) evolve toward the infection equilibrium without cellular immune response, denoted by $\mathcal{E}_2 = (550, 8.12, 52.238, 8, 0)$. This behavior confirms the global asymptotic stability of $\mathcal{E}_2$, in agreement with the analytical findings stated in item (ii) of Theorem 3.3.

Infection equilibrium without humoral immunity $\mathcal{E}_3$: For $k = 50$, $\beta_2 = 1.8 \times 10^{-3}$, $A = 7$, $\sigma = 0.025$, $m_Z = 0.15$ and $\rho = 10^{-4}$, we have $\mathcal{R}_0 = 3.6510 > 1$, $\mathcal{R}_1^Z = 2.9211 > 1$ and $\mathcal{R}_2^W = 0.0257 \leq 1$. As shown in Figure 6, the trajectories of the system (1) approach the infection equilibrium point $\mathcal{E}_3 = (298.9338, 6, 90, 0, 18.4137)$, which represents a configuration where the humoral immune response is inactive. This behavior supports the asymptotic stability of equilibrium $\mathcal{E}_3$, in accordance with item (iii) of Theorem 3.3.

Steady state $\mathcal{E}_4$ with both immune branches (humoral and cellular) are involved: Consider the parameter set: $k = 50$, $\rho = 6.7 \times 10^{-3}$, $A = 10$, $\sigma = 0.02$, $m_Z = 0.1$ and $\beta_2 = 1.8 \times 10^{-3}$. Under these conditions, the model yields $\mathcal{R}_0 = 5.179 > 1$, $\mathcal{R}_2^W = 1.4357 > 1$ and $\mathcal{R}_2^Z = 3.89 > 1$. As illustrated in Figure 7, the trajectories of system (1) evolve toward the infection equilibrium involving both humoral and cellular immunity, denoted by $\mathcal{E}_4 = (397.29, 14.9, 17.5, 60.55, 2.61)$. This numerical observation supports the theoretical conclusion regarding the global asymptotic stability of $\mathcal{E}_4$, as established in item (iv) of Theorem 3.3.

On the other hand, we examine the impact of antiretroviral therapy on the progression of viral infection. The analysis of the basic reproduction number, $\mathcal{R}_0$, indicates that it decreases with increasing treatment efficacy ε, demonstrating the effectiveness of antiretroviral therapy in controlling viral spread. As illustrated in Figure 8, $\mathcal{R}_0$ falls below 1 when treatment efficacy exceeds 60%, which biologically means that the infection will eventually disappear.

6. Conclusion

This work was devoted to formulate a mathematical model of viral infection that incorporates spatial fractional diffusion, represented through the regional fractional Laplacian operator, as well as the adaptive immune response. The model also accounts for two distinct transmission mechanisms and includes both lytic and non-lytic immune responses. We first identified the equilibrium states of the system, along with the threshold parameters governing its dynamics. Furthermore, the global stability of these equilibria was analyzed using an innovative approach based on the construction of Lyapunov functionals, tailored to a category of partial differential equations, both delayed and non-delayed, incorporating the regional fractional Laplacian operator.

During viral infection, immunologic memory enables the immune system to recognize and respond more rapidly and effectively to previously encountered pathogens, providing long-term protection and reducing the severity of subsequent infections. Therefore, it is of great interest to investigate the effect of this immunologic memory on the dynamical behavior of viral infection using the generalized Hattaf mixed fractional derivative [33, 34], instead of the classical time derivative used in (1). This will represent a potential direction for our future research.

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