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Dynamics of a Fractional-Order Within-Host Virus Model with Adaptive Immune Responses and Two Routes of Infection

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Abstract

This paper introduces a novel fractional-order model using the Caputo derivative operator to investigate the virus dynamics of adaptive immune responses. Two infection routes, namely cell-to-cell and virus-to-cell transmissions, are incorporated into the dynamics. Our research establishes the existence and uniqueness of positive and bounded solutions through the application of the generalized mean-value theorem and Banach fixed-point theory methods. The fractional-order model is shown to be Ulam–Hyers stable, ensuring the model’s resilience to small errors. By employing the normalized forward sensitivity method, we identify critical parameters that profoundly influence the transmission dynamics of the fractional-order virus model. Additionally, the framework of optimal control theory is used to explore the characterization of optimal adaptive immune responses, encompassing antibodies and cytotoxic T lymphocytes (CTL). To assess the influence of memory effects, we utilize the generalized forward–backward sweep technique to simulate the fractional-order virus dynamics. This study contributes to the existing body of knowledge by providing insights into how the interaction between virus-to-cell and cell-to-cell dynamics within the host is affected by memory effects in the presence of optimal control, reinforcing the invaluable synergy between fractional calculus and optimal control theory in modeling within-host virus dynamics, and paving the way for potential control strategies rooted in adaptive immunity and fractional-order modeling.

Keywords: adaptive immune response; fractional-order model; Ulam–Hyers stability; sensitivity analysis; Pontryagin’s maximum principle; optimal control



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1. Introduction

Infectious diseases, particularly viral infections, continue to pose significant challenges to global public health. Understanding the dynamics of these infections, together with the responses of the immune system of the host, is crucial for the development of effective control strategies. Over the last decade, the field of biomathematics has witnessed the development of numerous epidemiological models to describe the dynamics of viral infections.

These models have been applied to gain insights into a variety of viral infections, like human immunodeficiency virus (HIV) [1], Chikungunya virus [2], and monkeypox virus [3]. These mathematical models have proven invaluable for comprehending the progression of disease outbreaks and assessing the effectiveness of control strategies. In the context of viral infections, two main types of immune responses come into play: the innate immune response, which is nonspecific in nature, and the adaptive immune response, which is specific and targeted. The innate immune system plays a key role in containing viral spread early in infection and sets the stage for the adaptive immune response to emerge. Notably, several days are required for the full maturity of the antigen-specific immune response, which is synonymous with the adaptive immune response [4]. The persistence or otherwise of a within-host virus infection largely depends on the makeup of the immune response adaptivity, underscoring its importance in the growth and elimination of pathogens [4].

A comprehensive understanding of the link between diseases and viruses necessitates a deep understanding of the adaptive immune response. The adaptive immune response is activated following antigen detection, leading to the accumulation of immune cells that specifically target the antigen. This adaptive immune response comprises two primary components: antibody immune responses and cytotoxic T lymphocyte (CTL) cells. The CTL cells perform the vital task of recognizing and eliminating compromised host cells, thereby curbing the spread of a virus. During the initial infection, the virus-infected cells become the primary target of the CTL immune response. This antibody immune response involves the production of proteins by B cells that are designed for virus neutralization. While the CTL immune activities emerge swiftly and dominantly during the primary infection, antibody responses come into play more significantly in protecting against viral reinfection. This is achieved through a rapid recall mechanism, enabling a swift and effective response upon re-exposure to the antigen [5].

Recent advances in the mathematical modeling of viral infections have involved the incorporation of the impact of humoral immunity and CTLs. However, only a few research works have been written on the incorporation of adaptive immune responses and virus-to-cell and cell-to-cell transmissions. In [6], the authors only considered virus–cell and cell–cell transmissions. The Holling type-II incidence rate of infection was employed. The system's global stability was proved using the basic reproduction number $\mathcal{R}_0$. The authors of [7] presented a model with two infection routes that incorporates immune impairment due to latent virus. Their work evaluated the impact of different modes of transmission and saturation effects and emphasized the importance of the model solutions being bounded and non-negative. Ghaleb et al. [8] gave insight into the behavior of cell-to-cell and virus-to-cell transmissions under adaptive immune responses in virus dynamics. The model's global behavior was rigorously analyzed, and the effects of key parameters were investigated. Incorporating both virus-to-cell and cell-to-cell transmission pathways in viral dynamics models is not only biologically realistic but also critical for capturing key features of viral spread, immune evasion, and treatment response. This dual-route framework is particularly relevant for viruses like HIV, HCV, HTLV-I, and potentially SARS-CoV-2 [9,10], making it a necessary assumption for robust and biologically grounded modeling. Readers may also see Ahmed et al. [11] for insights into how adaptive immune responses affect the within-host dynamics of malaria parasites.

It is important to note that the research studies mentioned earlier predominantly concentrated on formulating and analyzing virus models using classical differential equations. Although a related study exists (see [12]), the fractional modeling of adaptive immune responses incorporating both infection routes, as formulated in this work, has not been previously investigated to the best of our knowledge. Models employing fractional-order derivatives have demonstrated superior effectiveness in representing real-world systems

compared to those using classical or integer-order derivatives. This enhanced performance can be attributed to the fractional-order models' capacity to capture memory effects, a key feature found in many real-world phenomena (see, e.g., [13–17]).

Consequently, in this paper, we seek to advance and generalize the findings of Ghaleb et al. [8] by incorporating Caputo fractional-order derivatives to characterize adaptive immune responses with two time-dependent optimal control strategies, including a CTL booster and an antibody immune enhancer. This will give us more insights into how the interaction between virus-to-cell and cell-to-cell dynamics within the host is affected by memory effects in the presence of optimal control.

The remaining sections of this paper are structured as follows. Section 2 focuses on the development of the fractional-order virus dynamics model. In Section 3, we examine the properties of the model, including the boundedness and positivity of its solutions, the existence and uniqueness of these solutions, and the Ulam–Hyers stability of the model. Section 4 focuses on the sensitivity of the optimal control optimization of the fractional-order dynamics. The conclusions are drawn in Section 5.

2. Fractional Model Formulation

The classical model with an integer-order derivative operator studied in [8] is transformed into a non-integer derivative of Caputo type, yielding the following fractional model with virus–cell and cell–cell transmissions:

$${}^C D_t^\nu W(t) = \Pi - \delta W - a_1 W G - a_2 W A \quad (1)$$

$${}^C D_t^\nu L(t) = a_1 W G + a_2 W A - (\lambda_1 + \lambda_2) L \quad (2)$$

$${}^C D_t^\nu A(t) = \lambda_2 L - \epsilon A - kUA \quad (3)$$

$${}^C D_t^\nu G(t) = cA - \gamma G - qBG \quad (4)$$

$${}^C D_t^\nu B(t) = \nu BG - \mu B \quad (5)$$

$${}^C D_t^\nu U(t) = \rho UA - hU, \quad (6)$$

with initial conditions

$$W(0) = W_0, L(0) = L_0, A(0) = A_0, G(0) = G_0, B(0) = B_0, U(0) = U_0 \quad (7)$$

The variables $W(t)$, $L(t)$, $A(t)$, $G(t)$, $B(t)$, and $U(t)$ represent the concentrations of uninfected cells, latently infected cells, actively infected cells, free virus particles, B cells, and CTL cells, respectively. Π denotes the generation rate of uninfected cells, while the parameters a_1 and a_2 correspond to the contact rates of virus-to-cell and cell-to-cell transmissions, respectively. The bilinear incidence rate is chosen for its simplicity and analytical convenience, effectively capturing the interaction between target cells and virus particles, especially during early infection stages.

The death rates of $W(t)$, $L(t)$, $A(t)$, $G(t)$, $B(t)$, and $U(t)$ are denoted as δ , λ_1 , ϵ , γ , μ , and h , respectively. The parameter λ_2 signifies the transition from latently infected cells to actively infected cells. The rate at which CTL cells attack actively infected cells is expressed as kUA , and the rates cA and qBG represent the production and neutralization of virus particles, respectively. The parameters ν and ρ denote the proliferation rate constants of B cells and CTL cells, respectively. To ensure consistency of the dimensions of the fractional-order model, it is expedient to state that the model parameters are measured per fractional-order time $t^{-\nu}$ [18–21]. The following definitions and concepts are necessary for the formulation and analysis of the fractional-order virus dynamics (see [18,22]).

Definition 1. The Riemann–Liouville fractional integral operator of order v for a function $g : \mathbb{R}_+ \rightarrow \mathbb{R}$ is denoted as $I_t^v g(t)$ and is defined as follows:

$$I_t^v g(t) = \frac{1}{\Gamma(v)} \int_0^t \frac{g(\eta)}{(t-\eta)^{1-v}} d\eta, \quad (8)$$

Here, v is a positive real number belonging to the interval $(0, 1)$, and t is a positive real number. The gamma function, denoted as $\Gamma(v)$, is defined by

$$\Gamma(v) = \int_0^\infty \zeta^{v-1} e^{-\zeta} d\zeta \quad (9)$$

Definition 2. The Caputo fractional v -order derivative of $g : \mathbb{R}_+ \rightarrow \mathbb{R}$, denoted by ${}^C D_t^v g(t)$, is defined as

$${}^C D_t^v g(t) = \frac{1}{\Gamma(1-v)} \int_0^t \frac{g'(\eta)}{(t-\eta)^v} d\eta, \quad (10)$$

where $0 < v \leq 1$ and $D_t^v = \frac{d^v}{dt^v}$.

Lemma 1 (Generalized Mean-Value Theorem). Let $p(t) \in C[0, t^+]$ and ${}^C D_t^v p(t) \in C[0, t^+]$ for $0 < v \leq 1$. Then,

$$p(t) = p(0) + \frac{{}^C D_t^v p(\phi) t^v}{\Gamma(v)}, \quad \phi \in [0, t], \text{ for all } t \in (0, t^+].$$

- (i) If ${}^C D_t^v p(t) \geq 0$ for all $t \in (0, t^+]$, then $p(t)$ is non-decreasing for each $t \in (0, t^+]$.
- (ii) If ${}^C D_t^v p(t) \leq 0$ for all $t \in (0, t^+]$, then $p(t)$ is non-increasing for each $t \in (0, t^+]$.

Lemma 2. Let $f(t) \in C([0, \infty))$ satisfy ${}^C D_t^v f(t) + n_1 f(t) \leq n_2$, $f(0) = f_0$, where $v \in (0, 1]$ and $n_1, n_2 \in \mathbb{R}$ with $n_1 \neq 0$. Then,

$$f(t) \leq \left(f_0 - \frac{n_2}{n_1} \right) E_{v,1}(-n_1 t^v) + \frac{n_2}{n_1},$$

where $E_{v,1}(\cdot)$ is a Mittag–Leffler operator given by

$$E_{v,1}(y) = \sum_{n=0}^{\infty} \frac{y^n}{\Gamma(vn+1)}.$$

It is pertinent to emphasize that we employ the Caputo derivative operator in formulating the cell-to-cell and virus-to-cell in-host transmission dynamics owing to the proven usefulness of the fractional derivative operator in describing physical problems with traditional initial conditions that are well-defined. Moreover, the Caputo derivative operator extends the concept of differentiation more favorably compared to some other fractional derivative operators, yielding the same result as the classical differentiation of a constant function [21,23].

2.1. Invariant Region

Theorem 1. The solutions $W(t)$, $L(t)$, $A(t)$, $G(t)$, $B(t)$, and $U(t)$ of the fractional-order virus model (1)–(6) are non-negative for all $t > 0$ if the initial conditions (7) are non-negative.

Proof. From systems (1)–(6), we have

$$\begin{aligned}
{}^C D_t^\nu W(t)|_{W=0} &= \Pi > 0, \\
{}^C D_t^\nu L(t)|_{L=0} &= a_1 W G + a_2 W A \geq 0 \text{ for all } W, G, A \geq 0, \\
{}^C D_t^\nu A(t)|_{A=0} &= \lambda_2 L \geq 0 \text{ for all } L \geq 0, \\
{}^C D_t^\nu G(t)|_{G=0} &= c A \geq 0, \text{ for all } A \geq 0, \\
{}^C D_t^\nu B(t)|_{B=0} &= 0, \\
{}^C D_t^\nu U(t)|_{U=0} &= 0.
\end{aligned} \tag{11}$$

Since the Caputo derivatives in (11) exhibit non-negativity over the boundary planes $\mathbb{R}_{\geq 0}^6$, the solutions $W(t), L(t), A(t), G(t), B(t)$, and $U(t)$ demonstrate non-decreasing behavior for all $t > 0$ when the initial conditions in (7) are non-negative, according to the generalized mean-value theorem. $\square$

Define a set Ω by

$$\Omega = \left\{ (W, L, A, G, B, U) \in \mathbb{R}_{\geq 0}^6 : W + L + A + \left(\frac{M_1}{M_2}\right)G + \left(\frac{M_1}{M_3}\right)B + \left(\frac{M_1}{M_4}\right)U \leq M_1 \right\} \tag{12}$$

where $M_1 = \frac{\Pi}{\sigma_1}$, $M_2 = \frac{2cM_1}{\epsilon}$, $M_3 = \frac{2cvM_1}{\epsilon q}$, and $M_4 = \frac{\rho M_1}{k}$, with $\sigma_1 = \min\{\delta, \lambda_1, \frac{\epsilon}{2}, \gamma, \mu, h\}$.

Theorem 2. The set Ω is positively invariant with respect to the fractional-order virus model (1)–(6).

Proof. Let

$$K(t) = W(t) + L(t) + A(t) + \frac{\epsilon}{2c}G(t) + \frac{\epsilon q}{2vc}B(t) + \frac{k}{\rho}U(t),$$

and then the Caputo derivative of $K(t)$ takes the form

$$\begin{aligned}
{}^C D_t^\nu K(t) &= {}^C D_t^\nu W(t) + {}^C D_t^\nu L(t) + {}^C D_t^\nu A(t) + \left(\frac{\epsilon}{2c}\right) {}^C D_t^\nu G(t) \\
&\quad + \left(\frac{\epsilon q}{2cv}\right) {}^C D_t^\nu B(t) + \left(\frac{k}{\rho}\right) {}^C D_t^\nu U(t).
\end{aligned} \tag{13}$$

It follows that

$${}^C D_t^\nu K(t) + \sigma_1 K(t) \leq \frac{\Pi}{\sigma_1} + \frac{2c\Pi}{\sigma_1 \epsilon} + \frac{2cv\Pi}{\sigma_1 \epsilon q} + \frac{\rho\Pi}{\sigma_1},$$

then,

$${}^C D_t^\nu K(t) + \sigma_1 K(t) \leq M_1 + \frac{2cM_1}{\epsilon} + \frac{2cvM_1}{\epsilon q} + \frac{\rho M_1}{k}. \tag{14}$$

Using Lemma 2, we have

$$K(t) \leq (K(0) - M_1)E_{\nu,1}(-\sigma_1 t^\nu) + M_1,$$

taking the $\lim_{t \rightarrow \infty} \sup K(t) \leq M_1$. Hence, the trajectories of the fractional-order system (1)–(6) originating in Ω remain bounded within this invariant set. $\square$

2.2. Existence and Uniqueness of Solutions

The fractional dynamics described by (1)–(6) can be expressed in condensed form as

$$\begin{aligned}
{}^C D_t^\nu (\Theta(t)) &= Y(t, \Theta(t)), 0 \leq t \leq \xi, \\
\Theta(0) &= \Theta_0,
\end{aligned} \tag{15}$$

where $\Theta(t) = (W(t), L(t), A(t), G(t), B(t), U(t))^T$, and $Y(t, \Theta(t)) : [0, \xi] \times \mathbb{R}_{\geq 0}^6 \rightarrow \mathbb{R}$ is defined by

$$Y_1(t, \Theta(t)) = (Y_i(t, W, L, A, G, B, U))^T, \quad i = 1, 2, \dots, 6,$$

so that

$$\begin{aligned} Y_1(t, W, L, A, G, B, U) &= \Pi - \delta W - a_1 WG - a_2 WA, \\ Y_2(t, W, L, A, G, B, U) &= a_1 WG + a_2 WA - (\lambda_1 + \lambda_2)L, \\ Y_3(t, W, L, A, G, B, U) &= \lambda_2 L - \epsilon A - kUA, \\ Y_4(t, W, L, A, G, B, U) &= cA - \gamma G - qBG, \\ Y_5(t, W, L, A, G, B, U) &= \nu BG - \mu B, \\ Y_6(t, W, L, A, G, B, U) &= \rho UA - hU. \end{aligned} \quad (16)$$

The fractional integration of the system (15), performed according to Definition 1, yields a Volterra integral equation of the form

$$\Theta(t) = \Theta_0 + \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \Theta(\omega)) d\omega. \quad (17)$$

Let $\mathcal{B} = (C[0, \xi], \|\cdot\|)$ be a Banach space for all continuous functions equipped with the supremum norm defined by

$$\|\Theta(t)\| = \sup\{|\Theta(t)| : t \in [0, \xi]\}.$$

To demonstrate the Lipschitz continuity of $Y(t, \Theta(t))$, we rely on the following result.

Theorem 3. *If there exists a constant $S > 0$ such that*

$$\|Y(t, \Theta(t)) - Y(t, \bar{\Theta}(t))\| \leq S \|\Theta(t) - \bar{\Theta}(t)\|, \quad (18)$$

then $Y(t, \Theta(t))$ is Lipschitz continuous for all $\Theta(t), \bar{\Theta}(t)$ in $(C[0, \xi] \times \mathbb{R}_{\geq 0}^6, \mathbb{R})$, and $t \in [0, \xi]$.

Proof. The boundedness within a positive invariant set Ω for the fractional-order virus model (1)–(6) has already been established. Now, for $W(t)$ and $\bar{W}(t)$, we have

$$\|Y_1(t, W, L, A, G, B, U) - Y_1(t, \bar{W}, L, A, G, B, U)\| \leq \|\delta + a_1 G + a_2 A\| \|W - \bar{W}\|. \quad (19)$$

Consequently, since $A \leq M_1$ and $G \leq M_2$ in Ω ,

$$\|Y_1(t, W, L, A, G, B, U) - Y_1(t, \bar{W}, L, A, G, B, U)\| \leq S_1 \|W - \bar{W}\|, \quad (20)$$

where $S_1 = \delta + a_1 M_2 + a_2 M_1 > 0$. Using a similar method, we obtain the following:

$$\|Y_2(t, W, L, A, G, B, U) - Y_2(t, W, \bar{L}, A, G, B, U)\| \leq S_2 \|L - \bar{L}\|, \quad (21)$$

where $S_2 = \lambda_1 + \lambda_2 > 0$.

$$\|Y_3(t, W, L, A, G, B, U) - Y_3(t, W, L, \bar{A}, G, B, U)\| \leq S_3 \|A - \bar{A}\|, \quad (22)$$

where $S_3 = \epsilon + \rho M_1 > 0$, since $U \leq \frac{\rho M_1}{k}$.

$$\|Y_4(t, W, L, A, G, B, U) - Y_4(t, W, L, A, \bar{G}, B, U)\| \leq S_4 \|G - \bar{G}\|, \quad (23)$$

where $S_4 = \gamma + \frac{2cvM_1}{\epsilon} > 0$, since $B \leq \frac{2cvM_1}{\epsilon q}$.

$$\|Y_5(t, W, L, A, G, B, U) - Y_5(t, W, L, A, G, \bar{B}, U)\| \leq S_5 \|B - \bar{B}\|, \quad (24)$$

where $S_5 = vM_2 - \mu > 0$, since $G \leq M_2$.

$$\|Y_6(t, W, L, A, G, B, U) - Y_6(t, W, L, A, G, B, \bar{U})\| \leq S_6 \|U - \bar{U}\|, \quad (25)$$

where $S_6 = \rho M_1 - h > 0$, since $U \leq \frac{\rho M_1}{k}$.

Therefore, condition (18) is satisfied, where $S = \max\{S_1, S_2, S_3, S_4, S_5, S_6\}$ is the Lipschitz constant. $\square$

Next, define the fixed point of an operator $F : \mathcal{B} \rightarrow \mathcal{B}$ by $F(\Theta(t)) = \Theta(t)$, so that

$$F(\Theta(t)) = \Theta_0 + \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \Theta(\omega)) d\omega. \quad (26)$$

Theorem 4. The fractional-order virus model (1)–(6) (equivalently, the system (15)) has a unique solution if $\xi^v S < \Gamma(v + 1)$.

Proof. It suffices to prove that F is a contraction. Since $Y(t, \Theta(t))$ is Lipschitz continuous, as shown in Theorem 3, for $\Theta(t), \bar{\Theta}(t) \in \mathcal{B}$ and $0 \leq t \leq \xi$,

$$\begin{aligned} \|F(\Theta(t)) - F(\bar{\Theta}(t))\| &= \left\| \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \Theta(\omega)) - Y(\omega, \bar{\Theta}(\omega)) d\omega \right\| \\ &\leq \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} \|Y(\omega, \Theta_1(\omega)) - Y(\omega, \bar{\Theta}(\omega))\| d\omega \\ &\leq \frac{S}{\Gamma(v)} \|\Theta(t) - \bar{\Theta}(t)\| \int_0^t (t - \omega)^{v-1} d\omega \\ &\leq \mathcal{L} \|\Theta(t) - \bar{\Theta}(t)\|, \end{aligned} \quad (27)$$

where $\mathcal{L} = \xi^v S / (v\Gamma(v))$. It follows that $\mathcal{L} < 1$ if $\xi^v S < (\Gamma(v + 1))$. Therefore, F is identified as a contraction, affirming the existence of a unique solution for the fractional-order virus model. $\square$

2.3. Ulam–Hyers Stability

The property of the fractional-order within-host virus model (1)–(6) that guarantees its resilience to small errors is determined by the Ulam–Hyers stability criterion, which ensures that small changes in the input parameters of the model do not generate major deviations from the predicted behavior of the model [19,24]. Simply put, Ulam–Hyers stability guarantees that there is an exact, unique solution close to any approximate function that satisfies the fractional-order differential equations.

Definition 3. The fractional-order system written in compact form (15) is said to be Ulam–Hyers stable if, for all $\beta > 0$ for which the following inequality holds:

$$\|{}^C D_t^v \Theta(t) - Y(t, \Theta(t))\| \leq \beta, \quad t \in [0, \xi], \quad \beta = \max\{\beta_i\}, i = 1, 2, \dots, 6, \quad (28)$$

there exists a constant $\varphi > 0$ and a unique solution $\bar{\Theta} \in \mathcal{B}$ satisfying

$$\|\Theta(t) - \bar{\Theta}(t)\| \leq \varphi \beta, \quad t \in [0, \xi], \quad \varphi = \max\{\varphi_i\}, i = 1, 2, \dots, 6. \quad (29)$$

Now, we provide a brief remark following Pandey et al. [19] about the inequality (28).

Remark 1. The inequality (28) holds true on the premise that there is another function, say $f(t) \in \mathcal{B} \forall t \in [0, \xi]$, with the following conditions:

- (i.) $\|f(t)\| \leq \beta$;
- (ii.) ${}^C D_t^v \Theta(t) = Y(t, \Theta(t)) + f(t)$.

Lemma 3. Given that $\Theta(t)$ solves the inequality (28), then

$$\left\| \Theta(t) - \Theta_0 - \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \Theta(\omega)) d\omega \right\| \leq \frac{\beta \xi^v}{v \Gamma(v)}. \quad (30)$$

Proof. Since $\Theta(t)$ solves the inequality (28), from item (ii) of Remark 1, we have that

$${}^C D_t^v \Theta(t) = Y(t, \Theta(t)) + f(t), \text{ with } \Theta(0) = \Theta_0,$$

which, on integration using Definition 1, yields

$$\Theta(t) = \Theta_0 + \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} [Y(\omega, \Theta(\omega)) + f(\omega)] d\omega,$$

implying that

$$\begin{aligned} \left\| \Theta(t) - \Theta_0 - \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \Theta(\omega)) d\omega \right\| &= \left\| \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} f(\omega) d\omega \right\| \\ &\leq \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} \|f(\omega)\| d\omega. \end{aligned}$$

Applying item (i) of Remark 1 and simplifying further yields

$$\left\| \Theta(t) - \Theta_0 - \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \Theta(\omega)) d\omega \right\| \leq \frac{\beta \xi^v}{v \Gamma(v)}.$$

□

We proceed to show that the fractional-order system written in compact form (15) is Ulam–Hyers stable.

Theorem 5. Given a Lipschitz continuous function $Y(t, \Theta(t)) \in (C[0, \xi] \times \mathbb{R}_{\geq 0}^6, \|\cdot\|)$ with a Lipschitz constant $S = \max\{S_i\} > 0, i = 1, 2, \dots, 6$, the fractional-order within-host virus dynamics written in compact form (15) is Ulam–Hyers stable.

Proof. For any solution $\Theta(t) \in \mathcal{B}$ and unique solution $\bar{\Theta}(t) \in \mathcal{B}$, we have

$$\begin{aligned} \|\Theta(t) - \bar{\Theta}(t)\| &= \left\| \Theta(t) - \Theta_0 - \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \bar{\Theta}(\omega)) d\omega \right\| \\ &\leq \left\| \Theta(t) - \Theta_0 - \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} Y(\omega, \Theta(\omega)) d\omega \right\| \\ &\quad + \frac{1}{\Gamma(v)} \int_0^t (t - \omega)^{v-1} \|Y(\omega, \Theta(\omega)) - Y(\omega, \bar{\Theta}(\omega))\| d\omega \end{aligned} \quad (31)$$

By Lemma 3 and the Lipschitz continuity condition (18), we obtain

$$\begin{aligned}\|\Theta(t) - \bar{\Theta}(t)\| &\leq \frac{\beta \xi^v}{v\Gamma(v)} + \frac{S}{\Gamma(v)} \|\Theta(t) - \bar{\Theta}(t)\| \int_0^t (t - \omega)^{v-1} d\omega \\ &\leq \frac{\beta \xi^v}{v\Gamma(v)} + \frac{\xi^v S}{v\Gamma(v)} \|\Theta(t) - \bar{\Theta}(t)\|,\end{aligned}\quad (32)$$

implying that

$$\|\Theta(t) - \bar{\Theta}(t)\| \leq \varphi \beta, \quad (33)$$

where $\varphi = \xi^v / [v\Gamma(v)(1 - \mathcal{L})]$, with $\mathcal{L} = \xi^v S / v\Gamma(v)$. Noting that $\mathcal{L} < 1$, it follows that $\varphi > 0$. Hence, inequality (29) is satisfied, and the fractional-order system (15) is Ulam–Hyers stable. $\square$

3. Sensitivity and Fractional Optimal Control Model

Here, we examine how the fractional-order virus model (1)–(6) responds to changes in the model parameters. This enables us to design optimal control strategies capable of hindering the destructive tendencies of virus particles and infected cells within the host.

3.1. Sensitivity Indices

We make use of the normalized forward sensitivity index defined in [25,26] to compute the sensitivity indices of the basic reproduction number of the model (1)–(6) relative to each of its parameters. As obtained for the classical model studied in [8], the basic reproduction number of the virus dynamics fractional model (1)–(6) is given by

$$R_0 = \frac{\Pi \lambda_2 (c a_1 + \gamma a_2)}{\delta \epsilon \gamma (\lambda_1 + \lambda_2)}. \quad (34)$$

The normalized forward sensitivity index of R_0 relative to any parameter, say w , is given by

$$\Upsilon_w^{R_0} = \frac{\partial R_0}{\partial w} \frac{w}{R_0}. \quad (35)$$

As a consequence of (35), the sensitivity indices for the associated parameters are depicted in Figure 1, where the positive and negative sensitivity indices are, respectively, shown as

$$\Upsilon_{(\Pi, \lambda_2, c, a_1, a_2)}^{R_0} = (1.0000, 0.8333, 0.6250, 0.6250, 0.3750)$$

and

$$\Upsilon_{(\delta, \epsilon, \lambda_1, \gamma)}^{R_0} = (-1.0000, -1.0000, -0.8333, -0.6250).$$

Parameters such as the generation rate Π of uninfected cells and the death rates δ and ϵ of the concentrations of uninfected and actively infected cells, respectively, are found to be the most influential due to their calculated sensitivity indices. Other sensitivity parameters of interest include the transition rate λ_2 , the virus production rate c , and the virus-to-cell contact rate a_1 . Parameters with positive sensitivity indices are directly related to the basic reproduction number R_0 , while those with negative indices are indirectly related to R_0 . For example, a 100% increase in the value of c (production of virus particles) results in a 62.5% increase in R_0 , while a 100% increase in the value of ϵ (death rate of actively infected cells) results in a 100% decrease in R_0 . These results are clearly illustrated in Figure 2, suggesting the need for effective strategies to combat virus particles and actively infected cells through adaptive immune responses. We made use of some of the parameter values provided in Table 1 to perform the sensitivity analysis.

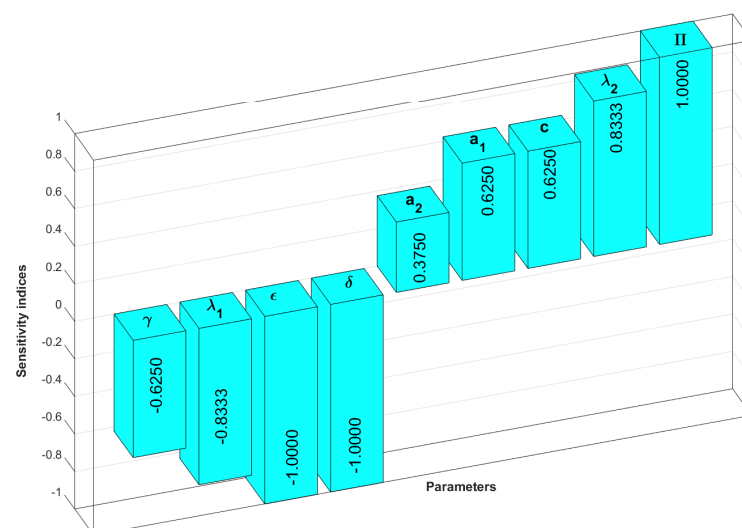


Figure 1. Sensitivity parameters of the within-host virus dynamics with respect to the basic reproduction number R_0 .

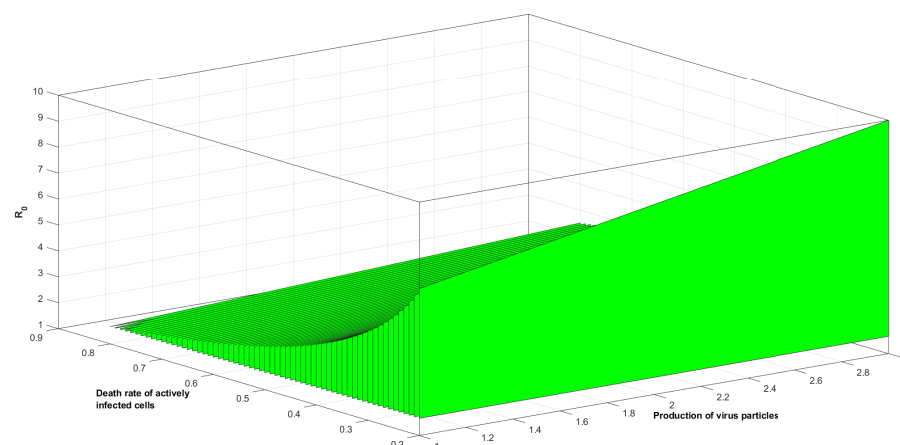


Figure 2. Three-dimensional plot illustrating how the rate of production of virus particles, denoted by c , and the death rate, ϵ , of actively infected cells affect the basic reproduction number R_0 .

Table 1. Virus dynamics parameters, descriptions, and their values, as given in [8].

Parameter	Description	Value
Π	Generation rate of uninfected or healthy cells	10
δ	Death rate of uninfected or healthy cells	0.01
a_1	Contact rate of virus-to-cell transmission	0.006
a_2	Contact rate of cell-to-cell transmission	0.006
λ_1	Death rate of latently infected cells	0.5
λ_2	Transition rate of latently to actively infected cells	0.1
ϵ	Death rate of actively infected cells	0.4
k	Response rate of CTL cells to actively infected cells	0.1
c	Production rate of virus particles	5.0
q	Response rate of B cells to virus particles	0.2
ν	Proliferation rate of B cells	0.1
ρ	Proliferation rate of CTL cells	0.1
h	Death rate of CTL cells	0.1

3.2. Fractional Virus Dynamics with Optimal Control

Given the need for adaptive immune responses against virus particles and within-host infected cells, as indicated by the sensitivity results, we design a fractional optimal control

model for virus dynamics, incorporating two time-dependent control variables: a cytotoxic T lymphocyte booster, denoted by $u_1(t)$, and a B cell (antibody immune response) enhancer, denoted by $u_2(t)$. The resulting non-autonomous model is given as follows:

$$\begin{aligned}
 {}^C D_t^\nu W(t) &= \Pi - \delta W - a_1 W G - a_2 W A \\
 {}^C D_t^\nu L(t) &= a_1 W G + a_2 W A - (\lambda_1 + \lambda_2) L \\
 {}^C D_t^\nu A(t) &= \lambda_2 L - \epsilon A - k(1 + u_1(t)) U A \\
 {}^C D_t^\nu G(t) &= c A - \gamma G - q(1 + u_2(t)) B G \\
 {}^C D_t^\nu B(t) &= \nu(1 + u_2(t)) B G - \mu B \\
 {}^C D_t^\nu U(t) &= \rho(1 + u_1(t)) U A - h U.
 \end{aligned} \tag{36}$$

We should mention that the control variables $u_i(t) \in [0, 1]$, $i = 1, 2$, represent the extent of immune response activation. When $u_i(t) = 0$, the fractional non-autonomous system (36) reduces to the autonomous model (1)–(6), reflecting no control. When $u_i(t) = 1$, the control represents full activation of the respective immune response. Therefore, the fractional optimal control problem in this study involves finding the optimal controls u_1^* and u_2^* that minimize the performance index

$$\mathbb{P}(u_1(t), u_2(t)) = \min_{\mathbb{U}} \int_0^{T_f} \left(\beta_1 L(t) + \beta_2 A(t) + \beta_3 G(t) + \frac{1}{2} \sum_{i=1}^2 \sigma_i u_i^2(t) \right) dt, \tag{37}$$

subject to the system (36), where T_f is the final time required in the performance index to minimize the concentrations of latently infected cells, actively infected cells, and virus particles with their respective weight constants β_j , $j = 1, 2, 3$ for balancing the performance index (37). The quadratic term $1/2 \sigma_i u_i^2(t)$ represents the implementation costs of the controls [27–29], where σ_i , $i = 1, 2$, are their respective cost weights. Readers may refer to [30] for a special case involving a terminal cost in the objective functional.

The non-empty control set $\mathbb{U}$ is a Lebesgue measurable set defined by

$$\mathbb{U} = \{(u_1(t), u_2(t)) : 0 \leq u_1(t), u_2(t) \leq 1, t \in [0, T_f]\}.$$

Hence, the optimal controls u_1^* and u_2^* solve the following minimization problem:

$$\mathbb{P}(u_1^*(t), u_2^*(t)) = \min\{\mathbb{P}(u_1(t), u_2(t)) : (u_1(t), u_2(t)) \in \mathbb{U}\}, \tag{38}$$

subject to the fractional state system (36). We make use of Pontryagin's maximum principle [31,32] to convert the minimization problem (38) into an auxiliary problem of minimizing the Hamiltonian $\mathbb{H}$, given by

$$\begin{aligned}
 \mathbb{H}(t, \mathbf{x}(t), u_i(t), \mathcal{A}_{\mathbf{x}}(t)) &= \beta_1 L(t) + \beta_2 A(t) + \beta_3 G(t) + \frac{1}{2} \sum_{i=1}^2 \sigma_i u_i^2(t) \\
 &\quad + \mathcal{A}_W({}^C D_t^\nu W(t)) + \mathcal{A}_L({}^C D_t^\nu L(t)) + \mathcal{A}_A({}^C D_t^\nu A(t)) \\
 &\quad + \mathcal{A}_G({}^C D_t^\nu G(t)) + \mathcal{A}_B({}^C D_t^\nu B(t)) + \mathcal{A}_U({}^C D_t^\nu U(t)),
 \end{aligned} \tag{39}$$

where $\mathbf{x} = (W, L, A, G, B, U)$ is the vector of state variables, and the co-state variables corresponding to each state variable of the fractional non-autonomous system (36) are $\mathcal{A}_W$, $\mathcal{A}_L$, $\mathcal{A}_A$, $\mathcal{A}_G$, $\mathcal{A}_B$, and $\mathcal{A}_U$. We now present and prove the existence of the co-state variables required for this formulation.

Theorem 6. For the optimal controls u_1^* and u_2^* that satisfy the minimization problem (38), there exist co-state variables $\mathcal{A}_x$ satisfying the fractional co-state system

$$\begin{aligned} {}^c D_t^\nu \mathcal{A}_W &= (a_1 G + a_2 A)(\mathcal{A}_W - \mathcal{A}_L) + \delta \mathcal{A}_W, \\ {}^c D_t^\nu \mathcal{A}_L &= \lambda_2(\mathcal{A}_L - \mathcal{A}_A) + \lambda_1 \mathcal{A}_L - \beta_1, \\ {}^c D_t^\nu \mathcal{A}_A &= a_2 W(\mathcal{A}_W - \mathcal{A}_L) + (1 + u_1(t))U(k\mathcal{A}_A - \rho\mathcal{A}_U) + \epsilon \mathcal{A}_A - c\mathcal{A}_G - \beta_2, \\ {}^c D_t^\nu \mathcal{A}_G &= a_1 W(\mathcal{A}_W - \mathcal{A}_L) + (1 + u_2(t))B(q\mathcal{A}_G - \nu\mathcal{A}_B) + \gamma \mathcal{A}_G - \beta_3, \\ {}^c D_t^\nu \mathcal{A}_B &= (1 + u_2(t))G(q\mathcal{A}_G - \nu\mathcal{A}_B) + \mu \mathcal{A}_B, \\ {}^c D_t^\nu \mathcal{A}_U &= (1 + u_1(t))A(k\mathcal{A}_A - \rho\mathcal{A}_U) + h \mathcal{A}_U, \end{aligned} \quad (40)$$

with terminal conditions

$$\mathcal{A}_x(T_f) = 0, \quad \mathbf{x} = (W, L, A, G, B, U) \quad (41)$$

and optimal control characterizations

$$\begin{aligned} u_1^* &= \min \left\{ \max \left\{ 0, \frac{UA(k\mathcal{A}_A - \rho\mathcal{A}_U)}{\sigma_1} \right\}, 1 \right\}, \\ u_2^* &= \min \left\{ \max \left\{ 0, \frac{GB(q\mathcal{A}_G - \nu\mathcal{A}_B)}{\sigma_2} \right\}, 1 \right\}. \end{aligned} \quad (42)$$

Proof. The existence of the optimal controls u_1^* and u_2^* follows from the convexity of both the non-empty control set $\mathbb{U}$ and the Lagrangian of the performance index $\mathbb{P}$. The existence also follows from the boundedness of the fractional-order system (36) and the Lagrangian of the performance index $\mathbb{P}$ (see [33] and the references therein for details). Following Pontryagin's maximum principle, the optimality conditions below help establish the existence of the co-state variables $\mathcal{A}_x$ and characterize the optimal controls, as shown in [34].

$${}^c D_t^\nu \mathbf{x} = \frac{\partial \mathbb{H}(t, \mathbf{x}(t), u_i(t), \mathcal{A}_x(t))}{\partial \mathcal{A}_x}. \quad (43)$$

$${}^c D_t^\nu \mathcal{A}_x = - \frac{\partial \mathbb{H}(t, \mathbf{x}(t), u_i(t), \mathcal{A}_x(t))}{\partial \mathbf{x}} \quad (44)$$

$$0 = \frac{\partial \mathbb{H}(t, \mathbf{x}(t), u_i(t), \mathcal{A}_x(t))}{\partial u_i}, \quad i = 1, 2. \quad (45)$$

In particular, the fractional-order co-state system (40) follows from the condition (44), while the control characterizations (42) follow from the optimality condition (45). $\square$

4. Simulations and Discussion

4.1. Simulations of the Fractional Model Without Optimal Control

The virus dynamics fractional model (1)–(6), in the absence of control, is first resolved numerically by utilizing the fractional Euler method, which generalizes the classical Euler method [35–37]. Several other successful numerical solution schemes for general fractional systems also exist in the literature (see, for example, Yi et al. [38] and the references therein). We use the parameter values in Table 1, for which the basic reproduction number $R_0 = 6.6667$, with the initial conditions $W(0) = 400$, $L(0) = 10$, $A(0) = 1$, $G(0) = 2$, $B(0) = 2$, and $U(0) = 1$. The effects of memory on the dynamics of uninfected cells and

latently infected cells are shown in Figure 3. We can observe that the concentrations of uninfected cells and latently infected cells stabilize faster with time as memory increases (equivalently, as the fractional order ν decreases). It can also be observed that the absence of memory at the fractional order $\nu = 1$ leads to slower convergence over time compared with the presence of memory at other fractional-order values. Thus, it suffices to say that the smaller the fractional-order value ν , the faster the concentrations of the within-host cells become stable due to a high degree of memory effect. We can observe similar dynamic behaviors for the virus particle and actively infected cell concentrations, as shown in Figure 4, as well as for the CTL and B cell responses depicted in Figure 5. This dynamic behavior is in agreement with the results obtained in [27,39] for different values of the fractional order. It is equally interesting to note that the simulation at the fractional-order value $\nu = 1$ is in harmony with the trajectories obtained in the classical model studied in [8].

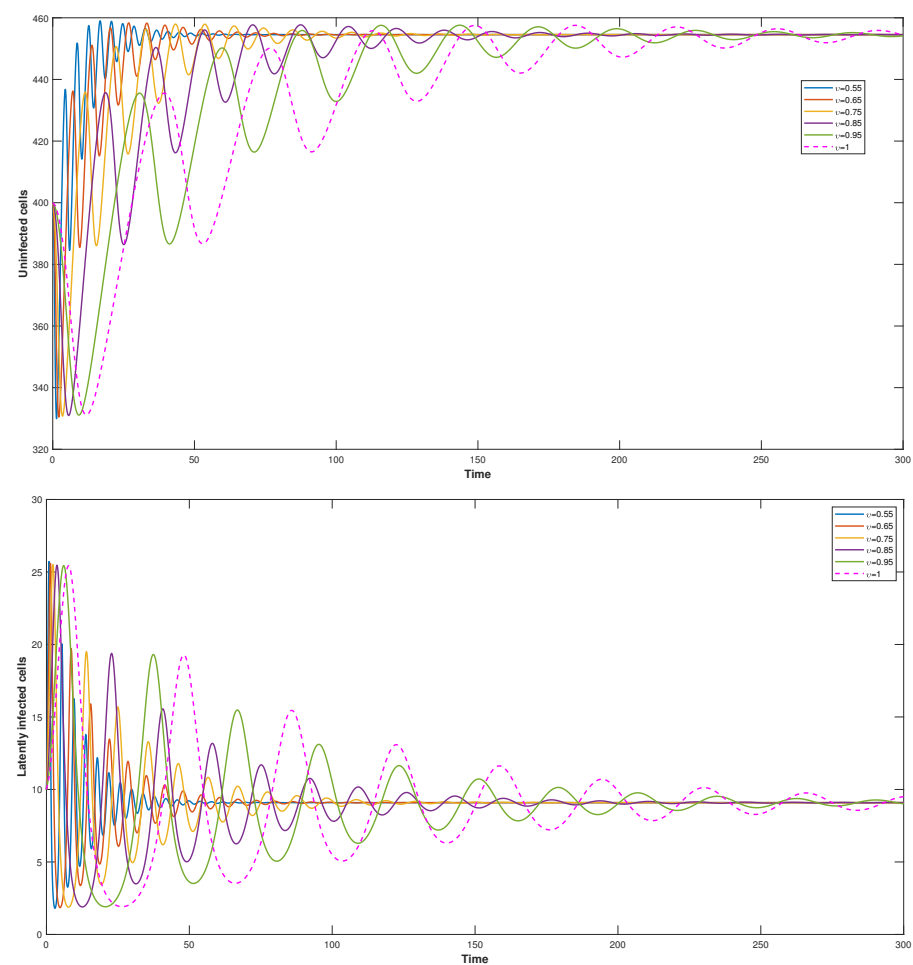


Figure 3. Memory effects on the trajectories of the concentrations of uninfected cells and latently infected cells at varying fractional orders $\nu = (0.55, 0.65, 0.75, 0.85, 0.95, 1.00)$.

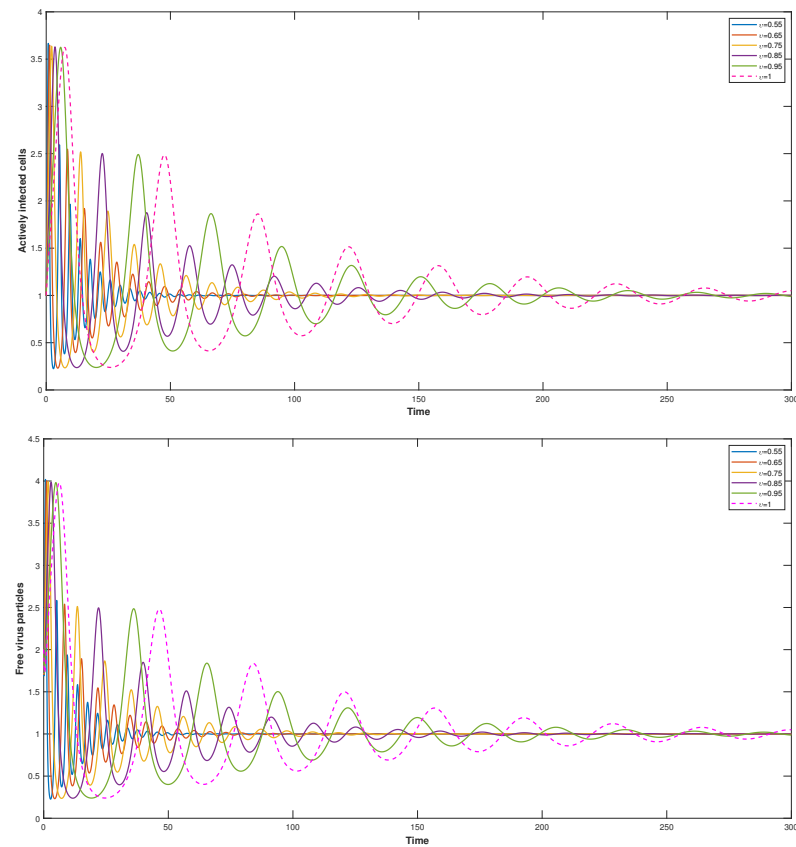


Figure 4. Memory effects on the trajectories of the concentrations of actively infected cells and virus particles at varying fractional orders $v = (0.55, 0.65, 0.75, 0.85, 0.95, 1.00)$.

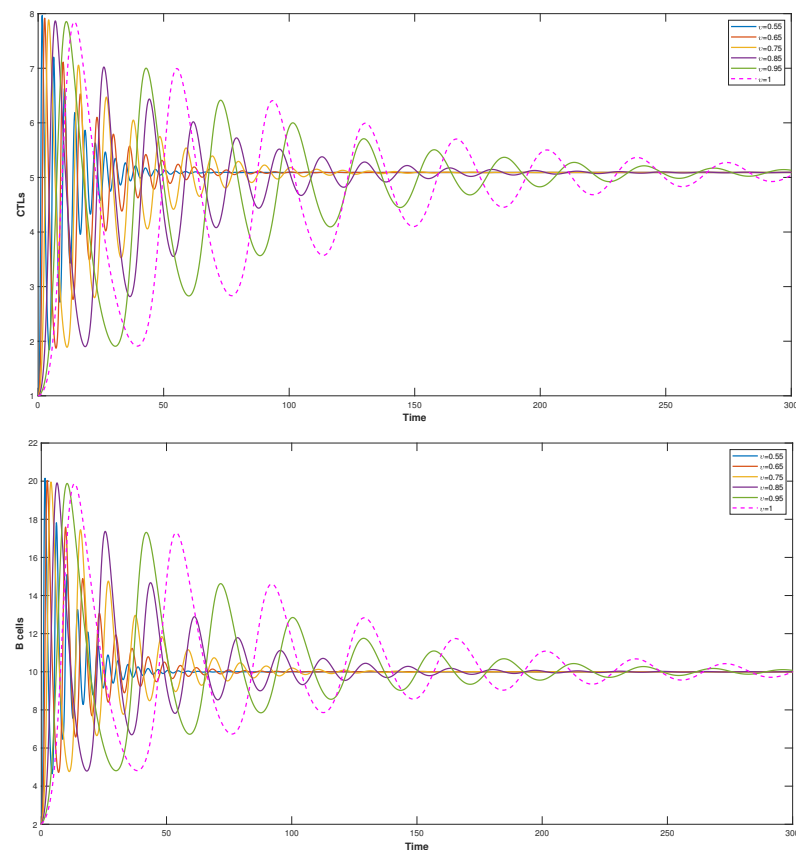


Figure 5. Memory effects on the trajectories of the concentrations of CTL and B cells at varying fractional orders $v = (0.55, 0.65, 0.75, 0.85, 0.95, 1.00)$.

4.2. Simulations of the Fractional Optimal Control Model

Here, we investigate the effect of the two adaptive immune responses boosters—the optimal controls $u_1(t)$ and $u_2(t)$ —on the non-autonomous fractional-order virus dynamics model (36). We make use of the same parameters from Table 1, where $R_0 = 6.6667 > 1$, and the weight constants $\beta_1 = 0.01$, $\beta_2 = 0.1$, $\beta_3 = 1$, and $\sigma_1 = \sigma_2 = 10$ are chosen to balance the performance index (37) with the final time $T_f = 200$. The non-autonomous fractional-order virus dynamics model (36) with its initial conditions $W(0) = 400$, $L(0) = 10$, $A(0) = 1$, $G(0) = 2$, $B(0) = 2$, and $U(0) = 1$ is coupled with the co-state system (40) with its associated terminal conditions $\mathcal{A}_x(200) = 0$, and the numerical resolution of the derived optimality system is achieved through the implementation of the generalized forward–backward Euler technique [39,40].

In Figure 6, the different trajectories of the concentrations of latently infected cells are shown with and without the optimal controls, as well as in the absence or presence of memory. We can observe higher concentrations of latently infected cells in the absence of memory ($v = 1.00$) and both controls ($u_1(t) = 0$, $u_2(t) = 0$) compared with the concentrations of latently infected cells in the presence of memory ($v = 0.75$), either without controls or with one or both controls applied. It is clear that the presence of the CTL control $u_2(t)$ with memory yields a greater reduction in the concentration of latently infected cells than when the antibody control $u_1(t)$ with memory is applied. This result, which is also similar to the observations in Figure 7 for actively infected cells, emphasizes the importance of cytotoxic T lymphocyte cells over antibodies (B cells) in combating within-host infected cells. However, the latently infected cells show a pronounced decline in concentration when both the cytotoxic T lymphocyte and antibody controls are simultaneously activated. Similarly, in Figure 8, the concentration of free virus particles is minimized when the production of both the CTL and B cell controls is stimulated in the presence of memory. This result is consistent with that obtained by Olaniyi et al. [41] concerning the study of a fractional-order model for within-host Chikungunya virus dynamics with adaptive responses.

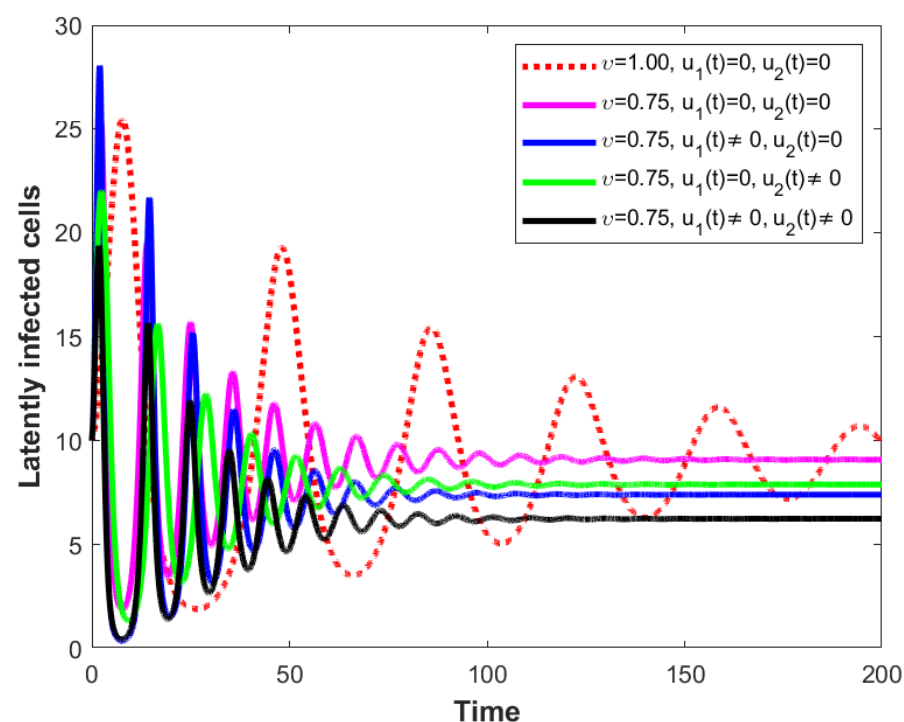


Figure 6. Dynamics of latently infected cells with and without the optimal controls $u_1(t)$ and $u_2(t)$ at fractional orders $v = 1.00$ and $v = 0.75$.

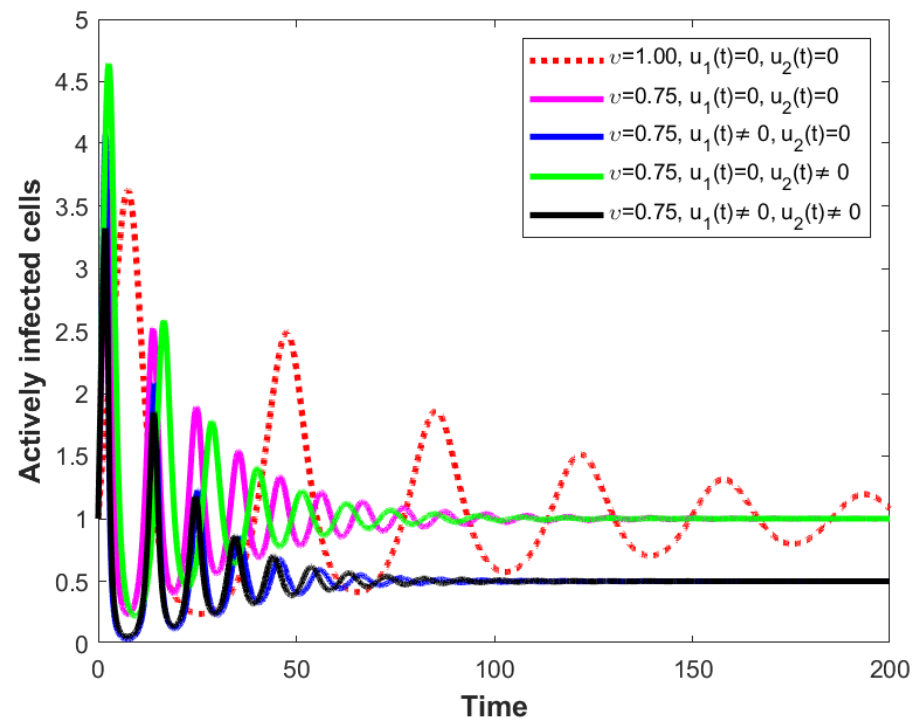


Figure 7. Dynamics of actively infected cells with and without the optimal controls $u_1(t)$ and $u_2(t)$ at fractional orders $v = 1.00$ and $v = 0.75$.

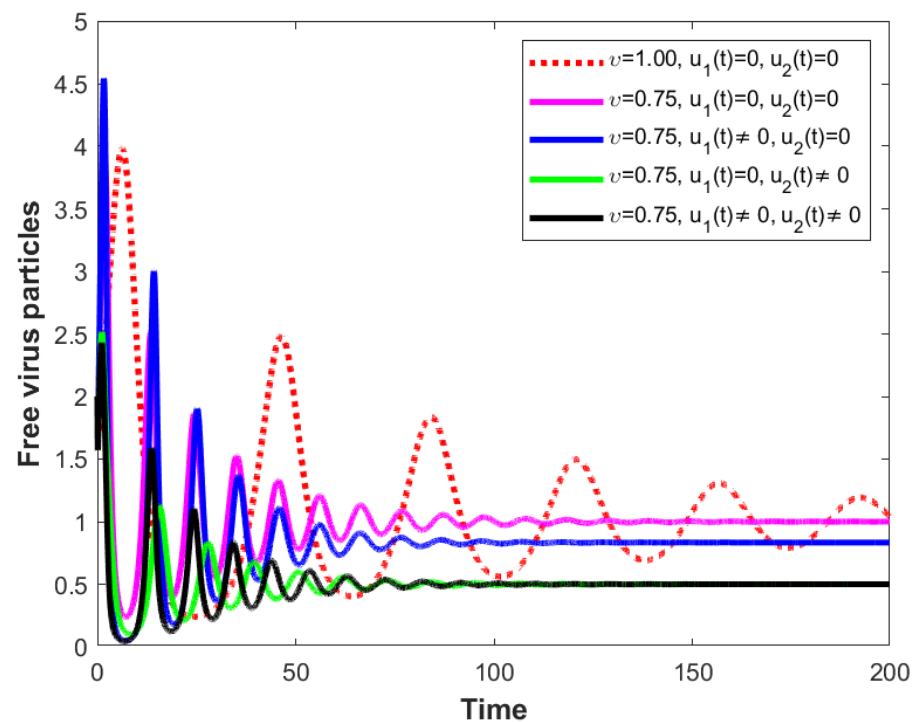


Figure 8. Dynamics of virus particles with and without the optimal controls $u_1(t)$ and $u_2(t)$ at fractional orders $v = 1.00$ and $v = 0.75$.

5. Conclusions

This work provides a generalization of a classical model of within-host dynamics for a virus transmitted through two routes: free virus particles and actively infected cells. This generalization is achieved through the use of the Caputo derivative operator, which enables the formulation of a fractional-order model, allowing for an investigation into the importance of the memory effect on the transmission dynamics of the within-host virus. The

generalized fractional-order model is shown to possess a unique positive solution using the Banach contraction approach from fixed-point theory. An explicit proof of the Ulam–Hyers stability of the fractional-order model is also established. Through sensitivity analysis, we examine how changes in the model parameters affect the basic reproduction number of the fractional-order model, enabling the design of a suitable fractional optimal control model for optimizing adaptive immune responses. In particular, two time-dependent optimal controls, $u_1(t)$ (a cytotoxic T lymphocyte (CTL) cell booster) and $u_2(t)$ (an antibody immune enhancer), are considered to, respectively, trigger the activity of CTL cells against infected host cells and stimulate the antibody immune response by promoting protein production by B cells against within-host viruses.

Consequently, using control theory, we apply Pontryagin’s maximum principle to analyze the fractional optimal control problem with an objective functional targeting the minimization of the concentrations of free virus particles, latently infected cells, and actively infected cells, together with the implementation costs. The generalized Euler forward–backward iterative scheme is used to solve the fractional-order optimality system. Simulations of the model show that the fractional derivative operator at fractional order $\nu < 1$ captures memory effects that help stabilize the concentrations of infected cells and viruses more rapidly than memoryless dynamics at fractional order $\nu = 1$. Further, the performance of memory with fractional order $\nu < 1$ is enhanced through the combined effect of the optimal controls $u_1(t)$ and $u_2(t)$, thereby decreasing the viral and infected cell concentrations most significantly at minimal implementation cost. This study, therefore, reveals the importance of the synergy between fractional calculus and optimal control theory in modeling within-host virus dynamics.

It must be noted that the bilinear incidence rate was selected to model the fractional within-host virus dynamics due to its simplicity and analytical convenience. Nonetheless, we acknowledge that alternative incidence forms could capture more nuanced biological behaviors, and we intend to explore such extensions in future work. It is also worth acknowledging that the fractional optimal control problem was formulated without constraints, as handling constraints is often challenging when applying Pontryagin’s maximum principle in this context. Nevertheless, various approaches have been developed to address optimal control problems with constraints, which may offer insights for extending the current work, as demonstrated in [42] and the references therein.

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