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IMPULSIVE CONTROL PROBLEM GOVERNED BY FRACTIONAL DIFFERENTIAL EQUATIONS AND APPLICATIONS

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ABSTRACT. We consider an impulsive control problem governed by fractional differential equations for which we establish a set of necessary conditions. The results are applied to a model of an HIV-immune system with memory. The fact that fractional differential equations possess memory enhances their usefulness in the modeling effort. The objective of the control problem is to minimize the infectious viral load and count of infected CD4+T cells while using optimal level of dosage of anti-HIV drugs and optimal therapy. Simulation results are presented and discussed.

1. Introduction

There has been a continued effort in the mathematical modeling of the dynamics and control of human immunodeficiency virus (HIV) by various authors ([7], [9], [11], [14], [15], [24], [25], [33], [37], [39], [44], [48]). One of the earliest models dealing with HIV is due to Perelson, Kirschner and De Boer [33]. They consider the interaction of HIV with CD4+ T-cells where the CD4+ T-cells consist of four population groups: uninfected T-cells, latently infected T cells, actively infected T cells, and free virus. Much effort has been put toward the study of the global dynamics of the HIV differential equation models. There have also been a number of studies where optimal control techniques are employed [24], [6], [45], [15], [21]. Memory is an important feature in immune response ([14], [38]). To include memory in the model fractional differential equations have been used ([14], [15], [21]). Hou and Wong consider ([23]) an impulsive control problem with application to HIV treatment. The rational for impulsive formulations is that while treatment by medication can suppress the virus to a very low level, the cost of purchasing the drugs as well as the amount of damage done to the body due to the intake of drugs can greatly offset the benefit of suppressing the HIV virus. Thus, a treatment regime of taking medication and the amount of medication at optimal instants may be more beneficial. Thus, in the current paper an impulsive fractional models is considered. We have decision variables at the impulse

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times and between impulse times. We start with a general formulation useful for a wider application besides the HIV modeling.

Besides applications in HIV modeling fractional differential equations have proved to be valuable tools in the modeling of many phenomena in engineering, physics, and economics ([18], [19], [20], [28], [29], [34], [43]). Fractional differential equations have also been useful in biology, fluid mechanics, modeling of viscoelasticity. The most fundamental characteristics in these models is their nonlocal characteristics. That is, the future aspect of the model relates not only the present state, but also its historical states.

Impulsive control problems have also been useful in engineering and in finance, production control and inventory management. In production planning ([8], [16],[30], [32]), a decision maker may have to decide the proper quantity of products being produced at different times with the objective of maximizing profit over a planning horizon. The goals that a decision maker has to accomplish are generally complex and involve conflicting objectives. The decision maker must meet demands while adhering to industry requirement needs, capabilities, limitations, and restrictions. Depending on the particular application an appropriate model may be discrete or continuous time optimization problem.

In [30] a production-planning model conducive to optimization is developed and used with the preference-based optimization method: linear physical programming, multiobjective programming. In [16] a continuous-time aggregate production-planning is considered where the objective is to determine the total production-planning cost, which involves various sets of costs like production cost, subcontracting cost, overtime cost, hiring cost, firing cost, and inventory cost.

Mathematical aspects of impulsive hybrid control systems have been considered by engineers and mathematicians. In addition to the references in production planning above relevant references include [4], [5], [17], [35], [36], [42].

The organization of the paper is as follows. We first present preliminaries, then the problem statement. Then, we establish necessary conditions for the control problem, and finally present computational results.

2. **Preliminaries**

For information on fractional differential equation we recommend the reference [34]. Let $f : [0, \infty) \longrightarrow \mathcal{R}$. For $-\infty < a < b < \infty$ the fractional integral of order $\alpha > 0$ of f with lower limit zero is defined as

$$ {}_aI_t^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t \frac{f(s)}{(t-s)^{1-\alpha}}. $$

The left Riemann-Liouville fractional derivative of order α of f is given as

$$ {}_a^L D_t^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_0^t \frac{f(s)}{(t-s)^{\alpha+1-n}} ds, \quad t > 0,\ n-1 < \alpha < n. $$

The right Riemann-Liouville fractional derivative of order α of f is given as

$$ {}_t^L D_b^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \left(-\frac{d}{dt}\right)^n \int_t^b \frac{f(s)}{(s-t)^{\alpha+1-n}} ds, \quad t > 0,\ n-1 < \alpha < n. $$

The right Caputo derivative of f of order α with lower limit zero is given as

$$ {}_0^C D_t^\alpha f(t) = {}_0^L D_t^\alpha \left[f(t) - \sum_{k=0}^{n-1} \frac{t^k}{k!} f^k(0) \right], \quad t > 0,\ n-1 < \alpha < n. $$

The right and left Caputo derivatives, in integral form, are given as

$$ {}_a^C D_t^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t \frac{f(s)}{(t-s)^{\alpha+1-n}} ds, $$

$$ {}_a^C D_b^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_t^b \frac{f(s)}{(s-t)^{\alpha+1-n}} ds. $$

The initial value problem

$$ \begin{aligned} &{}_0^C D_t^\alpha f(t) = f(t, x(t)), \quad 0 < \alpha < 1 \\ &x(t_0) = x_0 \end{aligned} \tag{2.1} $$

is equivalent to the nonlinear Volterra integral equation ([34]):

$$ x(t) = x_0 + \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} f(s, x(s)) ds. $$

In this paper we take $\alpha = 0.9$.

3. **Problem Statement**

Let $0 = t_0 < t_1 < t_2 < \cdots < t_{n-1} < t_n = t_f$ and, for $i = 1, 2, \ldots, n$ the functions $f_i : [t_{i-1}, t_i] \times \mathcal{R}^n \times \mathcal{R}^m \longrightarrow \mathcal{R}$ be such that $f_i(\cdot, x, u)$ is measurable for fixed (x, u). For fixed t and u, the function f_i is continuously differentiable in x. For fixed t, $f_i(t, \cdot, \cdot)$ is continuous. We also assume that

$$ \begin{aligned} &\|\partial_x f_i(t, x_2, u_2) - \partial_x f_i(t, x_1, u_1)\| + \|f_i(t, x_2, u_2) - f_i(t, x_1, u_1)\| \\ &\qquad \le K\{\|x_2 - x_1\| + \|u_2 - u_1\|\}, \end{aligned} $$

where K is a fixed constant.

Next let h_i, $i = 1, 2, \ldots, n$ be an $n \times n$ matrix with continuously differentiable entries. That is, if the (k, j) entry of $h_i(\eta)$ is $a_{kj}^i(\eta)$, then a_{kj}^i is a continuously differentiable of η.

Now, we consider the following fractional differential equation

$$ {}_0^C D_t^q x_1(t) = f_1(t, x_1(t), u_1(t)), \quad 0 < q < 1, \quad 0 = t_0 < t < t_1 $$

$$x(t_0) = h_1 \cdot c_1 \tag{3.1}$$

and for $i = 2, \ldots, n$

$$\begin{aligned} {}_{t_{i-1}}^{\ \ C}D_t^q x_i(t) &= f_i(t, x_i(t), u_i(t)), \quad t_{i-1} < t < t_i \\ x_i(t_{i-1}) &= h_i(x_i(t_{i-1}^-))c_i + x_i(t_{i-1}^-) \end{aligned} \tag{3.2}$$

We consider the objective function

$$T_n(x_n(t_n)) + \sum_{i=1}^n \int_{t_{i-1}}^{t_i} \Phi_i(s, x_i(s), u_i(s))ds.$$

The impulsive control problem we consider is

$$(\mathcal{P}) \quad \min \left\{ J(x_1, u_1, \ldots, x_n, u_n) = T_n(x_n(t_n)) + \sum_{i=1}^n \int_{t_{i-1}}^{t_i} \Phi_i(s, x_i(s), u_i(s))ds \right\}$$

subject to

$$\begin{aligned} {}_0^C D_t^q f(t) &= f_1(t, x_1(t), u_1(t)), \quad 0 < q < 1, \quad 0 = t_0 < t < t_1, \\ x(t_0) &= h_1(c_1), \\ {}_{t_{i-1}}^{\ \ C}D_t^q x_i(t) &= f_i(t, x_i(t), u_i(t)), \quad t_{i-1} < t < t_i, \\ x_i(t_{i-1}) &= h_i(x_i(t_{i-1}^-))(c_i) + x_i(t_{i-1}^-). \end{aligned} \tag{3.3}$$

Assume that problem $(\mathcal{P})$ has a solution $(\bar{c}_1, \ldots \bar{c}_n)$, $(\bar{u}_1, \ldots \bar{u}_n)$. We denote the corresponding trajectories, $\bar{x}_i$, $i = 1, \ldots, n$. Let $\mathcal{U} = \mathcal{U}_1 \times \cdots \times \mathcal{U}_n$ be the control set containing the controls $\bar{u}_1, \ldots \bar{u}_n$. Assume that $\mathcal{U}$ is a convex set. We can put constraints on the decision variables $c_1, \ldots, c_n$.

In the interval (t_{n-1}, t_n) we have the fractional differential equation

$$\begin{aligned} {}_{t_{n-1}}^{\ \ C}D_t^q \bar{x}_n(t) &= f_n(t, \bar{x}_n(t), \bar{u}_n(t)), \quad t_{n-1} < t < t_n \\ \bar{x}_n(t_{n-1}) &= h_n(\bar{x}_n(t_{n-1}^-))(\bar{c}_n) + \bar{x}_{n-1}(t_{n-1}^-) \end{aligned} \tag{3.4}$$

Let $v \in \mathcal{U}_n$. Consider

$$\begin{aligned} {}_{t_{n-1}}^{\ \ C}D_t^q x_{\theta n}(t) &= f_n(t, x_{\theta n}(t), \bar{u}_n(t) + \theta v(t)), \quad t_{n-1} < t < t_n \\ x_{\theta n}(t_{n-1}) &= h_n(x_{\theta n}(t_{n-1}^-))(\bar{c}_n) + x_{n-1}(t_{n-1}^-) \end{aligned} \tag{3.5}$$

Then,

$$x_{\theta n}(t) = x_{\theta n}(t_{n-1}) + \frac{1}{\Gamma(q)} \int_{t_{n-1}}^t (t-s)^{q-1} f_n(s, x_{\theta n}(s), \bar{u}_n(s) + \theta v(s))ds \tag{3.6}$$

Set

$$\begin{aligned} \delta x_n(t) = \frac{1}{\Gamma(q)} \int_{t_{n-1}}^t & (t-s)^{q-1} \{\partial_x f_n(s, \bar{x}_n(s), \bar{u}_n(s)\delta x_n(s)) \\ &+ \partial_u f_n(s, \bar{x}_n(s), \bar{u}_n(s) v(s)\} ds \end{aligned} \tag{3.7}$$

Then

$$\|\frac{x_{\theta n}(t)-\bar{x}_n(t)}{\theta}-\delta x_n(t)\|_\infty \longrightarrow 0 \text{ as } \theta \longrightarrow 0^+.$$

Given $u \in \mathcal{U}_n$ let

$$z(t)=\frac{1}{\Gamma(q)}\int_{t_{n-1}}^{t}(t-s)^{q-1}\{\partial_x f_n(s,\bar{x}_n(s),\bar{u}_n(s))z(s) + \partial_u f_n(s,\bar{x}_n(s),\bar{u}_n(s)u(s)\}ds \tag{3.8}$$

Now, let $p_n \in L_2([t_{n-1},t_n])$ such that

$$\int_{t_{n-1}}^{t_n} p_n(s)u(s)ds=\int_{t_{n-1}}^{t_n}\partial_x\Phi(s,\bar{x}_n,\bar{u}_n(s)z(s)ds+\partial_x T_n(x_n(t_n))\cdot z(t_n) \tag{3.9}$$

Then,

$$\int_{t_{n-1}}^{t_n} p_n(s)\partial_u f_n(s,\bar{x}_n(s),\bar{u}_n(s))v(s)ds = \int_{t_{n-1}}^{t_n}\partial_x\Phi(s,\bar{x}_n,\bar{u}_n(s)\delta x_n(s)ds+\partial_x T_n(x_n(t_n))\cdot \delta x_n(t_n) \tag{3.10}$$

For ease of notation let us write

$$f_n(s) \text{ for } f_n(s,\bar{x}_n(s),\bar{u}_n(s)),$$
$$\partial_x f_n(s) \text{ for } \partial_x f_n(s,\bar{x}_n(s),\bar{u}_n(s)),$$
$$\partial_u f_n(s) \text{ for } \partial_u f_n(s,\bar{x}_n(s),\bar{u}_n(s)).$$

Then, using (3.7) and (3.10)

$$\int_{t_{n-1}}^{t_n} p_n(s)[\partial_x f_n(s)\delta x_n(s)+\partial_u f_n(s)v(s)]ds = \frac{1}{\Gamma(q)}\int_{t_{n-1}}^{t_n}\left[\int_s^{t_n} p_n(\xi)\partial_x f_n(\xi)+\partial_x\Phi(\xi)\right] \cdot(\xi-s)^{q-1}d\xi[\partial_x f_n(s)\delta x_n(s)+\partial_u f_n(s)v(s)]ds \tag{3.11}$$

We also have

$$\partial_x T_n(\bar{x}_n(t_n))\cdot\delta x_n(t_n)=\partial_x T_n(\bar{x}_n(t_n)) \cdot\frac{1}{\Gamma(q)}\int_{t_{n-1}}^{t_n}(t_n-s)^{q-1}[\partial_x f_n(s)\delta x_n(s)+\partial_u f_n(s)v(s)]ds \tag{3.12}$$

Thus,

$$p_n(s)=\frac{1}{\Gamma(q)}\int_s^{t_n}(\xi-s)^{q-1}[p_n(\xi)\partial_x f_n(\xi)+\partial_x\Phi_n(\xi)]d\xi + \frac{1}{\Gamma(q)}\partial_x T_n(\bar{x}_n(t_n-s))^{q-1}. \tag{3.13}$$

Let

$$\gamma_n=\partial_x T_n(\bar{x}_n(t_n)). \tag{3.14}$$

Next, we move to the interval $[t_{n-2}, t_{n-1}]$ and consider

$$
\begin{aligned}
{}_{t_{n-2}}{}^{C}D^{q}_{t_{n-1}}\bar{x}_{n-1}(t) &= f_{n-1}(t,\bar{x}_{n-1}(t),\bar{u}_{n-1}(t)), \quad t_{n-2} < t < t_{n-1} \\
\bar{x}_{n-1}(t_{n-2}) &= h_{n-1}(\bar{x}_{n-2}(t^{-}_{n-2}))c_{n-1} + \bar{x}_{n-2}(t^{-}_{n-2})
\end{aligned} \tag{3.15}
$$

We have

$$
\begin{aligned}
\bar{x}_{n-1}(t) &= h_{n-1}(\bar{x}_{n-2}(t^{-}_{n-2}))c_{n-1} + \bar{x}_{n-2}(t^{-}_{n-2}) \\
&\quad + \frac{1}{\Gamma(q)}\int_{t_{n-2}}^{t}(t-s)^{q-1}f_{n-1}(s,\bar{x}_{n-1}(s),\bar{u}_{n-1}(s))ds, \quad t_{n-2} < t < t_{n-1}.
\end{aligned} \tag{3.16}
$$

For $v \in \mathcal{U}_{n-1}$, $0 < \theta < 1$, let

$$
\begin{aligned}
x_{\theta,n-1}(t) &= h_{n-1}(\bar{x}_{n-2}(t_{n-2}) \cdot \bar{c}_{n-1} + \bar{x}_{n-2}(t_{n-2}) \\
&\quad + \frac{1}{\Gamma(q)}\int_{t_{n-2}}^{t}(t-s)^{q-1}f_{n-1}(s,x_{\theta,n-1}(s),\bar{u}_{n-1}(s)+\theta v(s))ds
\end{aligned}
$$

Proceeding as in (3.5–3.7) and taking limit as was done following (3.7) we arrive at the following two equations which are the changes in the states x_{n-1}, x_n due to the change in u_{n-1} from u_{n-1} to $\bar{u}_{n-1} - \theta v$ while $\bar{u}_n$ is unchanged.

$$
\begin{aligned}
\delta x_{n-1}(t) &= \frac{1}{\Gamma(q)}\int_{t_{n-2}}^{t}(t-s)^{q-1}\{\partial_x f_{n-1}(s,\bar{x}_{n-1}(s),\bar{u}_{n-1}(s)\delta x_{n-1}(s)) \\
&\quad + \partial_u f_{n-1}(s,\bar{x}_{n-1}(s),\bar{u}_{n-1}(s)v(s)\}ds,
\end{aligned} \tag{3.17}
$$

$$
\begin{aligned}
\delta x_{n}(t) &= ([h_n(\bar{x}_{n-1}(t_{n-1})) \cdot \bar{c}_n]_{,x})\delta x_{n-1}(t_{n-1}) \\
&\quad + \frac{1}{\Gamma(q)}\int_{t_{n-1}}^{t}(t-s)^{q-1}\partial_x f_n(s,\bar{x}_n(s),\bar{u}_n(s)\delta x_n(s))ds.
\end{aligned} \tag{3.18}
$$

For $k = 2, 3, \ldots, n$ let L_k be the solution of the fractional differential equation

$$
\begin{aligned}
{}_{t_{k-1}}{}^{C}D^{q}_{t}L_k(t) &= \partial_x f_k(t,\bar{x}_k(t),\bar{u}_k(t)), \quad t_{k-1} < t < t_k, \\
L_k(t_{k-1}) &= I.
\end{aligned} \tag{3.19}
$$

Next, for $k = 2, 3, \ldots, n$ set

$$
Q_k(\bar{x}_{k-1}(t_{k-1}),\bar{c}_k) = [h_k(\bar{x}_{k-1}(t_{k-1})) \cdot \bar{c}_k]_{,x}) + I. \tag{3.20}
$$

Using (3.19) and (3.20) the solution of (3.18) is given by

$$
\delta x_n(t) = L_n(t)Q_n(\bar{x}_{n-1}(t_{n-1}),\bar{c}_n)\delta x_{n-1}(t_{n-1}) \tag{3.21}
$$

Next, we note that

$$
\begin{aligned}
\int_{t_{n-1}}^{t_n}\partial_x\Phi_n(s,\bar{x}_n(s),\bar{u}_n(s)) \cdot \delta x_n(s)ds &= \left[\int_{t_{n-1}}^{t_n}\partial_x\Phi_n(s,\bar{x}_n(s),\bar{u}_n(s)) \cdot L_n(s)ds\right] \\
&\quad \cdot Q_n(\bar{x}_{n-1}(t_{n-1}),\bar{c}_n)\delta x_{n-1}(t_{n-1})
\end{aligned} \tag{3.22}
$$

The variation in the total cost due to the variation in $\bar{u}_{n-1} \in \mathcal{U}_{n-1}$ involves the costs in the intervals $[t_{n-2}, t_{n-1}]$ and $[t_{n-1}, t_n]$ and is given by

$$\int_{t_{n-2}}^{t_{n-1}} \partial_x \Phi_{n-1}(s, \bar{x}_{n-1}(s), \bar{u}_{n-1}(s)) \cdot \delta x_{n-1}(s) ds + \left[\int_{t_{n-1}}^{t_n} \partial_x \Phi(s, \bar{x}_n(s), \bar{u}_n(s)) \cdot L_n(s) ds\right] \cdot Q_n(\bar{x}_{n-1}(t_{n-1}), \bar{c}_n) \delta x_{n-1}(t_{n-1}) \tag{3.23}$$

Similarly, the variation in the total cost due to the variation in $\bar{u}_{n-2} \in \mathcal{U}_{n-2}$ involves the costs in the intervals $[t_{n-3}, t_{n-2}]$, $[t_{n-2}, t_{n-1}]$ and $[t_{n-1}, t_n]$. As in (3.8) given $u \in \mathcal{U}_{n-1}$ let

$$\begin{aligned} z(t) = \frac{1}{\Gamma(q)} \int_{t_{n-2}}^{t} &(t-s)^{q-1} \{\partial_x f_{n-1}(s, \bar{x}_{n-1}(s), \bar{u}_{n-1}(s)) z(s) \\ &+ \partial_u f_{n-1}(s, \bar{x}_{n-1}(s), \bar{u}_{n-1}(s) u(s)\} ds \end{aligned} \tag{3.24}$$

As in (3.9) define $p_{n-1} \in L_2([t_{n-2}, t_{n-1}])$ by the equation

$$\begin{aligned} \int_{t_{n-2}}^{t_{n-1}} p_{n-1}(s) u(s) ds &= \int_{t_{n-2}}^{t_{n-1}} \partial_x \Phi_{n-1}(s, \bar{x}_{n-1}(s), \bar{u}_{n-1}(s)) \cdot z(s) ds \\ &+ \left[\int_{t_{n-1}}^{t_n} \partial_x \Phi(s, \bar{x}_n(s), \bar{u}_n(s)) \cdot L_n(s) ds\right] \cdot Q_n(\bar{x}_{n-1}(t_{n-1}), \bar{c}_n) z(t_{n-1}) \\ &+ \partial_x T_n(x_n(t_{n-1})) L_n(t_n) Q_n(\bar{x}_{n-1}(t_{n-1}), \bar{c}_n) z(t_{n-1}) \end{aligned} \tag{3.25}$$

Following the steps that we used to get (3.13) we obtain

$$\begin{aligned} p_{n-1}(s) &= \frac{1}{\Gamma(q)} \int_s^{t_{n-1}} (\xi - s)^{q-1} [p_{n-1}(\xi) \partial_x f_{n-1}(\xi, \bar{x}_{n-1}(\xi), \bar{u}_{n-1}(\xi) + \partial_x \Phi_{n-1}(\xi)] d\xi \\ &+ \frac{1}{\Gamma(q)} \left[\int_{t_{n-1}}^{t_n} \partial_x \Phi_n(\xi, \bar{x}_{n-1}(\xi), \bar{u}_{n-1}(\xi) L_n(\xi)) d\xi \; Q_n(\bar{x}_{n-1}(t_{n-1}), \bar{c}_n) \right. \\ &\left. + \partial_x T_n(x_n(t_{n-1})) L_n(t_n) Q_n(\bar{x}_{n-1}(t_{n-1}), \bar{c}_n) \right] (t_{n-1} - s)^{q-1} \end{aligned} \tag{3.26}$$

Set

$$\begin{aligned} \gamma_{n-1} &= \left(\int_{t_{n-1}}^{t_n} \partial_x \Phi_n(\xi, \bar{x}_n(\xi), \bar{u}_n(\xi)) L_n(\xi)\right) d\xi \; Q_n(\bar{x}_{n-1}(t_{n-1}), \bar{c}_n) \\ &+ \gamma_n L_n(t_n) Q_n(\bar{x}_{n-1}(t_{n-1}), \bar{c}_n) \end{aligned} \tag{3.27}$$

where γ_n is defined in (3.14). Then, we may rewrite (3.26) as

$$\begin{aligned} p_{n-1}(s) = \frac{1}{\Gamma(q)} \int_s^{t_{n-1}} &(\xi - s)^{q-1} [p_{n-1}(\xi) \partial_x f_{n-1}(\xi, \bar{x}_{n-1}(\xi), \bar{u}_{n-1}(\xi)) \\ &+ \partial_x \Phi_{n-1}(\xi, \bar{x}_{n-1}(\xi), \bar{u}_{n-1}(\xi)] d\xi \\ &+ \gamma_{n-1}(t_{n-1} - s)^{q-1}. \end{aligned} \tag{3.28}$$

Setting

$$\gamma_{n-2} = \left(\int_{t_{n-2}}^{t_{n-1}} \partial_x \Phi_{n-1}(\xi, \bar{x}_{n-1}(\xi), \bar{u}_{n-1})(\xi)\right) L_{n-1}(\xi) d\xi Q_{n-1}(\bar{x}_{n-1}(t_{n-1}), \bar{c}_{n-1})$$

$$+ \gamma_{n-1} L_{n-1}(t_{n-1}) Q_{n-1}(\bar{x}_{n-2}(t_{n-2}), \bar{c}_{n-1}), \tag{3.29}$$

the adjoint function in the interval $[t_{n-3}, t_{n-2}]$ is given by

$$p_{n-2}(s) = \frac{1}{\Gamma(q)} \int_s^{t_{n-2}} (\xi - s)^{q-1} [p_{n-2}(\xi) \partial_x f_{n-2}(\xi, \bar{x}_{n-2}(\xi), \bar{u}_{n-2}(\xi))$$

$$+ \partial_x \Phi_{n-2}((\xi, \bar{x}_{n-2}(\xi), \bar{u}_{n-2}(\xi))] d\xi$$

$$+ \gamma_{n-2}(t_{n-2} - s)^{q-1}. \tag{3.30}$$

Next we proceed to give a formula for the adjoint function in any interval $[t_{n-(i+2)}, t_{n-(i+1)}]$.

Let

$$\gamma_{n-(i+1)} = \left(\int_{t_{n-(i+1)}}^{t_{n-i}} \partial_x \Phi_{n-i}(\xi, \bar{x}_{n-i}(\xi), \bar{u}_{n-i})(\xi)\right) L_{n-i}(\xi) d\xi Q_{n-i}(\bar{x}_{n-i}(t_{n-i}), \bar{c}_{n-i})$$

$$+ \gamma_{n-i} L_{n-i}(t_{n-i}) Q_{n-i}(\bar{x}_{n-(i+1)}(t_{n-(i+1)}), \bar{c}_{n-i}), \tag{3.31}$$

Then,

$$p_{n-(i+1)}(s) = \frac{1}{\Gamma(q)} \int_s^{t_{n-(i+1)}} (\xi - s)^{q-1} [p_{n-(i+1)}(\xi) \partial_x f_{n-(i+1)}(\xi, \bar{x}_{n-(i+1)}(\xi), \bar{u}_{n-(i+1)}(\xi))$$

$$+ \partial_x \Phi_{n-(i+1)}((\xi, \bar{x}_{n-(i+1)}(\xi), \bar{u}_{n-(i+1)}(\xi))] d\xi$$

$$+ \gamma_{n-(i+1)}(t_{n-(i+1)} - s)^{q-1}. \tag{3.32}$$

We now define the Hamiltonian in the interval $[t_{(i-1)}, t_i]$, $i = 1, 2, \ldots, n$ by

$$H_i(t, x_i(t), q_i(t), u_i(t)) = q_i(t) \cdot f_i(t, x_i(t), q_i(t), u_i(t)) + \Phi(t, x_i(t), q_i(t), u_i(t)) \tag{3.33}$$

Then, for any $v \in \mathcal{U}_i$,

$$H_i(t, \bar{x}_i(t), q_i(t), v(t)) \geq H_i(t, \bar{x}_i(t), q_i(t), \bar{u}_i(t) \text{ a.e. } t, \ i = 1, 2, \ldots, n \tag{3.34}$$

To show the validity of (3.34) we will verify it in the last interval $[t_{(n-1)}, t_n]$. When we perturb the control $\bar{u}_n$ only the last term of the cost

$$J(x_1, u_1, \ldots, x_n, u_n) = T_n(x_n(t_n)) + \sum_{i=1}^{n} \int_{t_{i-1}}^{t_i} \Phi_i(s, x_i(s), u_i(s)) ds, \tag{3.35}$$

which is,

$$T_n(x_n(t_n)) + \int_{t_{n-1}}^{t_n} \Phi_i(s, x_n(s), u_n(s)) ds \tag{3.36}$$

is affected. Thus, if we perturb $\bar{u}_n$ by adding θv, $v \in \mathcal{U}_n$ to it, then

$$\frac{d}{d\theta} J(\bar{x}_1, u_1, \bar{x}_2, u_2, \ldots, \bar{x}_n, \bar{u}_n + \theta v)$$

$$(3.37) \qquad = \frac{d}{d\theta}\left\{T_n(\bar{x}_n(t_n)) + \int_{t_{n-1}}^{t_n} \Phi_i(s, \bar{x}_n(s), \bar{u}_n(s) + \theta v(s))ds\right\}$$

Thus,

$$\begin{aligned}\frac{d}{d\theta}J(\bar{x}_1, u_1, \bar{x}_2, u_2, \ldots, \bar{x}_n, \bar{u}_n + \theta v)|_{\theta=0^+} &= \partial_x T_n(\bar{x}_n(t_n))\delta x_n(t_n) \\ &+ \int_{t_{n-1}}^{t_n} \{\partial_x \Phi_i(s, \bar{x}_n(s), \bar{u}_n(s))\delta x_n(s) \\ &+ \partial_u \Phi_i(s, \bar{x}_n(s), \bar{u}_n(s))v(s)\}ds \qquad (3.38)\end{aligned}$$

Next, using (3.10), and writing

$$p_n(s)\partial_u f_n v(s) = p_n(s)\partial_u f_n(s, \bar{x}_n(s), \bar{u}_n(s))v(s),$$

$$\partial_u \Phi v = \partial_u \Phi_n(s, \bar{x}_n(s), \bar{u}_n(s))v(s),$$

$$\partial_x \Phi_n = \partial_x \Phi_n(s, \bar{x}_n(s), \bar{u}_n(s)),$$

$$J(\bar{u}_n + \theta v) = J(\bar{x}_1, u_1, \bar{x}_2, u_2, \ldots, \bar{x}_n, \bar{u}_n + \theta v),$$

we have

$$\begin{aligned}&\frac{d}{d\theta}\int_{t_{n-1}}^{t_n} H_n(s, \bar{x}_n(s), p_n(s), \bar{u}_n(s) + \theta v(s))ds|_{\theta=0^+}i \\ &= \int_{t_{n-1}}^{t_n} \{p_n(s)\partial_u f_n v(s) + \partial_u \Phi_n v(s))\}ds \\ &\quad + \partial_x T_n(\bar{x}_n(t_n))\delta x_n(t_n) + \int_{t_{n-1}}^{t_n} \{\partial_x \Phi_n \delta x_n(s) + \partial_u \Phi_n v(s)\}ds \\ &= \frac{d}{d\theta}J(\bar{u}_n + \theta v)|_{\theta=0^+} \\ &\geq 0 \qquad (3.39)\end{aligned}$$

Thus,

$$(3.40) \qquad \int_{t_{n-1}}^{t_n} H_n(t, \bar{x}_n(t), p_n(t), v(t))dt \geq \int_{t_{n-1}}^{t_n} H_n(t, \bar{x}_n(t), p_n(t), \bar{u}_n(t))dt.$$

Now, from (3.40), making needle-like variation, we obtain

$$(3.41) \qquad H_n(t, \bar{x}_n(t), p_n(t), v(t)) \geq H_n(t, \bar{x}_n(t), p_n(t), \bar{u}_n(t)), \text{ a.e. } t$$

So far we have perturbed only the controls between impulse times. That is, we have assumed that problem $(\mathcal{P})$ has a solution $(\bar{c}_1, \ldots \bar{c}_n)$, $(\bar{u}_1, \ldots \bar{u}_n)$, and perturbed only the controls $(\bar{u}_1, \ldots \bar{u}_n)$ between the impulse times and obtained the minimum principle (3.41) where the adjoint variables are as presented in (3.13), (3.26), and in general, in the interval $[t_{n-(i+2)}, t_{n-(i+1)}]$, by (3.32). Next we perturb the decision variables $(\bar{c}_1, \dots \bar{c}_n)$. First we perturb only the decision variable $\bar{c}_n$, while holding the other decision variables $(\bar{c}_1, \dots \bar{c}_{n-2}, \bar{c}_{n-1})$, $(\bar{u}_1, \dots \bar{u}_n)$ fixed. Only the last component

$$T_n(\bar{x}_n(t_n)) + \int_{t_{n-1}}^{t_i} \Phi_n(s, \bar{x}_n(s), \bar{u}_n(s))ds$$

of the total cost

$$J(\bar{x}_1, u_1, \dots, \bar{x}_n, \bar{u}_n) = T_n(\bar{x}_n(t_n)) + \sum_{i=1}^{n} \int_{t_{i-1}}^{t_i} \Phi_i(s, \bar{x}_i(s), \bar{u}_i(s))ds$$

is affected. Next, we perturb only $\bar{c}_{n-1}$ while holding the remaining decision variables $(\bar{c}_1, \dots \bar{c}_{n-2}, \bar{c}_n)$, $(\bar{u}_1, \dots \bar{u}_n)$ fixed. Only,

$$T_n(\bar{x}_n(t_n)) + \sum_{i=n-1}^{n} \int_{t_{i-1}}^{t_i} \Phi_i(s, \bar{x}_i(s), \bar{u}_i(s))ds$$

of the total cost $J(\bar{x}_1, \bar{u}_1, \dots, \bar{x}_n, \bar{u}_n)$ is affected. Next we perturb $\bar{c}_{n-2}$ and continue in this manner backwards. We obtain the following necessary conditions.

$$\begin{aligned} \gamma_n L_n(t_n) h_n(\bar{x}_{n-1}(t_{n-1})) &= 0, \\ \gamma_{n-1} L_{n-1}(t_{n-1}) h_{n-1}(\bar{x}_{n-2}(t_{n-2})) &= 0, \\ \gamma_{n-i} L_{n-i}(t_{n-i}) h_{n-i}(\bar{x}_{n-(i+1)}(t_{n-(i+1)})) &= 0, \quad i = 0, \dots, \ n-1 \end{aligned} \tag{3.42}$$

4. **Application**

The following model of HIV-immune system with memory was considered in [21]. Here we extend this model to one where we consider impulsive model with added constraints at the impulse times. This extension is appropriate as stated in the introduction [23]. The model considered in [21] is given by the system

$$\begin{aligned} {}_0^C D_t^q x_1(t) &= -a_1 x_1 + a_2 x_1 x_2 (1 - u_2) + a_3 a_4 x_4 (1 - u_1), \\ {}_0^C D_t^q x_2(t) &= \frac{a_5}{1 + x_1} - a_2 x_1 x_2 (1 - u_2)(1 - u_4) - a_6 x_2 \\ &\quad + a_7 \left(1 - \frac{1}{a_8}(x_2 + x_3 + x_4)\right) x_2 (1 + u_) \\ {}_0^C D_t^q x_3(t) &= a_2 x_1 x_2 (1 - u_2)(1 - u_4) - a_9 x_3 - a_6 x_3, \\ {}_0^C D_t^q x_4(t) &= a_9 x_3 - a_4 x_4, , \\ x(0) &= (x_1(0), x_2(0), x_3(0), x_4(0))^T, \end{aligned} \tag{4.1}$$

where x_1 represents free virus, x_2 uninfected CD4+ T cells, x_3 lately infected CD4+ T cells, x_4 actively infected CD4+ T cells. The control u_1 is the concentration of protease inhibitor, u_2 fusion inhibitor, u_3 CD4+ T cell enhancer, u_4 reverse transcription inhibitor. The parameters s_i, q_i, $i = 1, 2, 3, 4$ and r are weight constants in the objective functional below.

Further,

$a_1 =$ death rate of free virus,
$a_2 =$ rate CD4+ T cells become infected with virus.
$a_3 =$ number of free virus produced by actively infected CD4+ T cells.
$a_4 =$ death rate of actively infected CD4+ T cell population.
$a_5 =$ source term of uninfected CD4+ T cells.
$a_6 =$ death rate of infected (latently infected) CD4+ T cell population.
$a_7 =$ growth rate of CD4+ T cell population.
$a_8 =$ maximum population level of CD4+ T cells.
$a_9 =$ rate of latently infected cells becoming active.

Rational for this model has been presented [14], [15], [21]. In [21] necessary conditions for optimality were presented for a control problem with the dynamics given by the above model where the cost

$$J(u) = \frac{1}{2}[s_1 x_1^2(t_f) + s_3 x_3^2(t_f) + s_4 x_4^2(t_f)] + \frac{1}{2}\int_0^{t_f} [q_1 x_1^2(t) + q_3 x_3^2(t) + q_4 x_4^2(t) + r u_1^2(t)]dt \tag{4.2}$$

is to be minimized.

The objective in this paper is to deal with the impulsive control version of this control problem. We consider $t_0 < t_1, \dots, t_n = t_f$ where $t_1, t_2, \dots, t_{n-1}$ are the impulse times, and constraints are imposed on the trajectories at these impulse times. We can add constraints at the initial and final times t_0 and t_f. The material presented in the previous sections applies to more general models than we are considering in this section.

We now proceed to formulate the impulsion version of the above problem. First we divide the interval $[t_0, t_f]$ into n intervals: $[t_{i-1}, t_i],\ i = 1, 2, \dots, n$. In the interval $[t_{i-1}, t_i]$, we consider

$$\begin{aligned}
{}_0^C D_t^q x_{i1}(t) &= -a_1 x_{i1} + a_2 x_{i1} x_{i2}(1 - u_{i2}) + a_3 a_4 x_{i4}(1 - u_{i1}),\\
{}_0^C D_t^q x_{i2}(t) &= \frac{a_5}{1 + x_{i1}} - a_2 x_{i1} x_2 (1 - u_{i2})(1 - u_{i4}) - a_6 x_{i2}\\
&\quad + a_7 \left(1 - \frac{1}{a_8}(x_{i2} + x_{i3} + x_{i4})\right) x_2 (1 + u_{i3}),\\
{}_0^C D_t^q x_{i3}(t) &= a_2 x_{i1} x_{i2}(1 - u_{i2})(1 - u_{i4}) - a_9 x_{i3} - a_6 x_{i3},\\
{}_0^C D_t^q x_{i4}(t) &= a_9 x_{i3} - a_4 x_{i4},\\
x_i(t_{i-1}) &= h_i(x_{i-1}(t_{i-1}))c_i + x_{i-1}(t_{i-1}),
\end{aligned} \tag{4.3}$$

At the impulse times $t_1, t_2, \dots, t_{n-1}$ we have

$$x_i(t_{i-1}) = h_i(x_{i-1}(t_{i-1}))c_i + x_{i-1}(t_{i-1}). \tag{4.4}$$

At $t = t_0$

$$x_1(t_0) = h_1(c_1). \tag{4.5}$$

We remark that the h_i, $i = 1, 2, \ldots, n$ are 4×4 matrices and $c_i = (c_{i1}, c_{i2}, c_{i3}, c_{i4})^T$. The cost is given by

$$\begin{aligned} J(u_1, u_2, \ldots, u_n)) &= \frac{1}{2}[s_1 x_{n1}^2(t_n) + s_3 x_{n3}^2(t_n) + s_4 x_{n4}^2(t_n)] \\ &+ \frac{1}{2}\sum_{i=1}^{n}\int_{t_{i-1}}^{t_i} [q_1 x_{i1}^2(t) + q_3 x_{i3}^2(t) + q_4 x_{i4}^2(t) + r u_{i1}^2(t)]dt \end{aligned} \tag{4.6}$$

We now proceed to write the adjoint system. In the time interval $[t_{i-1}, t_i]$

$$\begin{aligned} {}_t^C D_{t_i}^q p_{i1}(t) &= -(a_1 + a_2 x_{i2}(1 - u_{i2}))p_{i1} \\ &+ \left[\frac{a_5}{(1 + x_{i1})^2} + a_2 x_{i2}(1 - u_{i2})(1 - u_{i4})\right] p_{i2} \\ &- a_2 x_{i2}(1 - u_{i2})(1 - u_{i4})p_{i3} + q_1 x_{i1}, \\ {}_t^C D_{t_i}^q p_{i2}(t) &= -a_2 x_{i1}(1 - u_{i2})p_{i1} - [a_2 x_{i1}(1 - u_{i2})(1 - u_{i4}) + a_6]p_{i2} \\ &+ a_7\left(1 - \frac{1}{a_8}x_{i2}(1 + u_{i3})\right) p_{i2} \\ &+ a_7\left(1 - \frac{x_{i2} + x_{i3} + x_{i4}}{8}\right)(1 + u_{i3})p_{i2} + a_2 x_{i1}(1 - u_{i2})(1 - u_{i4})p_{i3}, \\ {}_t^C D_{t_i}^q p_{i3}(t) &= \frac{a_7}{a_8}x_{i2}(1 + u_{i3})p_{i2} - a_9 p_{i3} - a_6 p_{i3} - a_9 p_{i4} - q_3 x_{i3}, \\ {}_t^C D_{t_i}^q p_{i4}(t) &= a_3 a_4(1 - u_{i4})p_{i1} - \frac{a_7}{a_8}x_{i2}(1 + u_{i3})p_{i2} \\ &- a_9 p_{i3} - a_4 p_{i4} + q_4 x_{i4}, \end{aligned} \tag{4.7}$$

Writing $f_i = (f_{i1}, f_{i2}, f_{i3}, f_{i4})^T$ for the right hand side of (4.3) and $p_i = (p_{i1}, p_{i2}, p_{i3}, p_{i4})^T$ the in $[t_{i-1}, t_i]$ is given by

$$H_i(t, x_i(t), p_i(t), u_i(t)) = p_i \cdot f_i + \frac{1}{2}\left[q_1 x_{i1}^2(t) + q_3 x_{i3}^2(t) + q_4 x_{i4}^2(t) + r u_{i1}^2(t)\right] \tag{4.8}$$

If $u_i = (u_{i1}, u_{i2}, u_{i3}, u_{i4})^T$ were an interior point of the control constraint $\mathcal{U}_i$ then, using (3.34) we have

$$\partial_{u_i} H_i(t, x_i(t), p_i(t), u_i(t)) = 0. \tag{4.9}$$

From (4.9) we get

$$\begin{aligned} \partial_{u_{i1}} H_i &= -a_3 a_4 x_{i4} + r u_{i1} = 0; \\ \partial_{u_{i2}} H_i &= a_2 x_{i1} x_{i2} p_{i1} - a_2 x_{i1} x_{i2}(1 - u_{i4})p_{i3} = 0 \\ \partial_{u_{i3}} H_i &= a_7\left(1 - \frac{x_{i2} + x_{i3} + x_{i4}}{8}\right) x_{i2} p_{i2} = 0 \\ \partial_{u_{i4}} H_i &= a_2 x_{i1} x_{i2}(1 - u_{i2})p_{i2} - a_2 x_{i1} x_{i2}(1 - u_{i2})p_{i3} = 0 \end{aligned} \tag{4.10}$$

We remark that the optimal control may not be an interior point of $\mathcal{U}_i$. In the next section we take three intervals and carry out a numerical computation. Our numerical procedure is going to based on the method of steepest descent.

5. Numerical Computation and Simulation

In this section we take three intervals $[t_0, t_1]$, $[t_1, t_2]$, $[t_2, t_3]$, $t_3 = t_f$ and carry out a numerical simulation of the following impulsive control problem. For simplicity of notation we use different symbols for the states and controls in different intervals. All parameters will be given specific values later.

In the interval $[t_0, t_1]$, we consider

$$\begin{aligned}
{}_0^C D_t^q x_1(t) &= -a_1 x_1 + a_2 x_1 x_2 (1-u_2) + a_3 a_4 x_4 (1-u_{i1}),\\
{}_0^C D_t^q x_2(t) &= \frac{a_5}{1+x_1} - a_2 x_1 x_2 (1-u_{i2})(1-u_{i4}) - a_6 x_2\\
&\quad + a_7 \left(1 - \frac{1}{a_8}(x_{i2} + x_3 + x_{i4})\right) x_2 (1+u_3),\\
{}_0^C D_t^q x_3(t) &= a_2 x_1 x_2 (1-u_2)(1-u_4) - a_9 x_3 - a_6 x_3,\\
{}_0^C D_t^q x_4(t) &= a_9 x_3 - a_4 x_4,\\
x_1(t_0) &= c_{01},\\
x_2(t_0) &= c_{02},\\
x_3(t_0) &= c_{03},\\
x_4(t_0) &= c_{04}.
\end{aligned} \tag{5.1}$$

In the interval $[t_1, t_2]$, we consider

$$\begin{aligned}
{}_0^C D_t^q y_1(t) &= -a_1 y_1 + a_2 y_1 y_2 (1-v_2) + a_3 a_4 y_4 (1-v_1),\\
{}_0^C D_t^q y_2(t) &= \frac{a_5}{1+y_1} - a_2 y_1 y_2 (1-v_2)(1-v_{i4}) - a_6 y_2\\
&\quad + a_7 \left(1 - \frac{1}{a_8}(y_{i2} + y_3 + y_{i4})\right) y_2 (1+v_3),\\
{}_0^C D_t^q y_3(t) &= a_2 y_1 y_2 (1-v_2)(1-v_4) - a_9 y_3 - a_6 y_3,\\
{}_0^C D_t^q y_4(t) &= a_9 y_3 - a_4 y_4,\\
y_1(t) &= dd1 + cc1 \cdot x1(t_1) + x1(t_1),\\
y_2(t) &= dd1 + cc1 \cdot x2(t_1) + x2(t_1),\\
y_3(t) &= dd1 + cc1 \cdot x3(t_1) + x3(t_1),\\
y_4(t) &= dd1 + cc1 \cdot x4(t_1) + x4(t_1).
\end{aligned} \tag{5.2}$$

In the interval $[t_2, t_3]$, we consider

$$ {}_0^C D_t^q z_1(t) = -a_1 z_1 + a_2 z_1 z_2 (1-w_2) + a_3 a_4 z_4 (1-w_1), $$

$$
\begin{aligned}
{}_0^C D_t^q z_2(t) &= \frac{a_5}{1+z_1} - a_2 z_1 z_2 (1-w_{i2})(1-w_4) - a_6 z_2 \\
&\quad + a_7 \left(1 - \frac{1}{a_8}(z_{i2} + z_3 + z_{i4})\right) z_2 (1+w_3), \\
{}_0^C D_t^q z_3(t) &= a_2 z_1 z_2 (1-w_2)(1-w_4) - a_9 z_3 - a_6 z_3, \\
{}_0^C D_t^q z_4(t) &= a_9 z_3 - a_4 z_4, \\
z_1(t) &= DD1 + CC1 \cdot y1(t_2) + y1(t_2), \\
z_2(t) &= DD1 + CC1 \cdot y2(t_2) + y2(t_2), \\
z_3(t) &= DD1 + CC1 \cdot y3(t_2) + y3(t_2), \\
z_4(t) &= DD1 + CC1 \cdot y4(t_2) + y4(t_2). \qquad (5.3)
\end{aligned}
$$

The cost is given by

$$
\begin{aligned}
J(u,v,w) &= \frac{1}{2}[s_1 z_1^2(t_3) + s_3 z_3^2(t_3) + s_4 z_4^2(t_3)] \\
&\quad + \frac{1}{2}\int_{t_0}^{t_1} [q_1 x_1^2(t) + q_3 x_3^2(t) + q_4 x_4^2(t) + r u_1^2(t)] dt \\
&\quad + \frac{1}{2}\int_{t_1}^{t_2} [q_1 y_1^2(t) + q_3 y_3^2(t) + q_4 y_4^2(t) + r v_1^2(t)] dt \\
&\quad + \frac{1}{2}\int_{t_2}^{t_3} [q_1 z_1^2(t) + q_3 z_3^2(t) + q_4 z_4^2(t) + r w_1^2(t)] dt \qquad (5.4)
\end{aligned}
$$

Let $f^{(3)}(z,w) = (f_1^{(3)}(z,w), f_2^{(3)}(z,w), f_3^{(3)}(z,w), f_4^{(3)}(z,w))$ where

$$
\begin{aligned}
f_1^{(3)}(z,w) &= -a_1 z_1 + a_2 z_1 z_2 (1-w_2) + a_3 a_4 z_4 (1-w_1), \\
f_2^{(3)}(z,w) &= \frac{a_5}{1+z_1} - a_2 z_1 z_2 (1-w_{i2})(1-w_4) - a_6 z_2 \\
&\quad + a_7 \left(1 - \frac{1}{a_8}(z_{i2} + z_3 + z_{i4})\right) z_2 (1+w_3) \\
f_3^{(3)}(z,w) &= a_2 z_1 z_2 (1-w_2)(1-w_4) - a_9 z_3 - a_6 z_3, \\
f_4^{(3)}(z,w) &= a_9 z_3 - a_4 z_4, \qquad (5.5)
\end{aligned}
$$

Let $f^{(2)}(y,v) = (f_1^{(2)}(y,v), f_2^{(2)}(y,v), f_3^{(2)}(y,v), f_4^{(2)}(y,v))$ where

$$
\begin{aligned}
f_1^{(2)}(y,v) &= -a_1 y_1 + a_2 y_1 y_2 (1-v_2) + a_3 a_4 y_4 (1-v_1), \\
f_2^{(2)}(y,v) &= \frac{a_5}{1+y_1} - a_2 y_1 y_2 (1-v_{i2})(1-v_4) - a_6 y_2 \\
&\quad + a_7 \left(1 - \frac{1}{a_8}(y_{i2} + y_3 + y_{i4})\right) y_2 (1+v_3) \\
f_3^{(2)}(y,v) &= a_2 y_1 y_2 (1-v_2)(1-v_4) - a_9 y_3 - a_6 y_3, \\
f_4^{(2)}(y,v) &= a_9 y_3 - a_4 y_4, \qquad (5.6)
\end{aligned}
$$

Let $f^{(1)}(x,u) = (f_1^{(1)}(x,u), f_2^{(1)}(x,u), f_3^{(1)}(x,u), f_4^{(1)}(x,u))$ where

$$\begin{aligned}
f_1^{(1)}(x,u) &= -a_1x_1 + a_2x_1x_2(1-u_2) + a_3a_4x_4(1-u_1),\\
f_2^{(1)}(x,u) &= \frac{a_5}{1+x_1} - a_2x_1x_2(1-u_{i2})(1-u_4) - a_6x_2\\
&\quad + a_7\left(1 - \frac{1}{a_8}(x_{i2}+x_3+x_{i4})\right)x_2(1+u_3),\\
f_3^{(1)}(x,u) &= a_2x_1x_2(1-u_2)(1-u_4) - a_9x_3 - a_6x_3,\\
f_4^{(1)}(x,u) &= a_9x_3 - a_4x_4, \qquad (5.7)
\end{aligned}$$

Let $L^{(3)}$ be defined by the equation

$$\begin{aligned}
{}_{t_2}^{\;C}D_t^q L^{(3)}(t) &= \partial_z f^{(3)}(z(t), w(t)), \quad t_2 < t < t_3,\\
L^{(3)}(t_2) &= I. \qquad (5.8)
\end{aligned}$$

Let $L^{(2)}$ be defined by the equation

$$\begin{aligned}
{}_{t_1}^{\;C}D_t^q L^{(2)}(t) &= \partial_y f^{(2)}(y(t), v(t)), \quad t_1 < t < t_2,\\
L^{(2)}(t_1) &= I. \qquad (5.9)
\end{aligned}$$

Let $L^{(1)}$ be defined by the equation

$$\begin{aligned}
{}_{t_0}^{\;C}D_t^q L^{(1)}(t) &= \partial_x f^{(1)}(x(t), u(t)), \quad t_0 < t < t_1,\\
L^{(1)}(t_0) &= I. \qquad (5.10)
\end{aligned}$$

Let $Q^{(3)}$ be be the matrix defined by

$$Q^{(3)} = diag(CC1+1, CC2+1, CC3+1, CC4+1) \qquad (5.11)$$

In (5.11) the notation "*diag*" means that matrix has all entries zero except the diagonal elements. Let $Q^{(2)}$ be be the matrix defined by

$$Q^{(2)} = diag(cc1+1, cc2+1, cc3+1, CC4+1)$$

From the objective function in problem $(\mathcal{P})$, (4.6), and (3.3)

$$\begin{aligned}
\gamma_3 &= (s_1z_1(t_3), 0, s_3z_3(t_3), s_4z_4(t_3))\\
\gamma_2 &= \left[\int_{t_2}^{t_1} (q_1y_1, 0, q_3y_3, q_4y_4)L^{(3)}(s)ds\right]Q^{(3)} + \gamma_3L^{(3)}(t_3)Q^{(3)}\\
\gamma_1 &= \left[\int_{t_1}^{t_2} (q_1x_1, 0, q_3x_3, q_4x_4)L^{(2)}(s)ds\right]Q^{(2)} + \gamma_2L^{(2)}(t_2)Q^{(2)} \qquad (5.12)
\end{aligned}$$

We now proceed to write the adjoint equations. We denote the adjoint variable by $p^{(3)}$ in the third interval, by $p^{(2)}$ in the second interval, and by $p^{(3)}$ in the first interval. In the third interval $p^{(3)}$ is the solution of the fractional differential equation

$${}_{t}^{C}D_{t_3}^q p_1^{(3)}(t) = -(a_1 + a_2z_2(1-w_2))p_1^{(3)}$$

$$+\left[\frac{a_5}{(1+z_1)^2}+a_2z_2(1-w_2)(1-w_4)\right]p_2^{(3)}$$
$$-a_2z_2(1-w_2)(1-w_4)p_3^{(3)}+q_1z_1$$
$${}_t^CD_{t_3}^q p_2^{(3)}(t)=-a_2z_1(1-w_2)p_1^{(3)}-[a_2z_1(1-w_2)(1-w_4)+a_6]p_2^{(3)}$$
$$+a_7\left(1-\frac{1}{a_8}z_2(1+w_3)\right)p_2^{(3)}$$
$$a_7\left(1-\frac{z_2+z_3+z_4}{8}\right)(1+w_3)p_2^{(3)}+a_2z_1(1-w_2)(1-w_4)p_3^{(3)}$$
$${}_t^CD_{t_3}^q p_3^{(3)}(t)=\frac{a_7}{a_8}z_2(1+w_3)p_2^{(3)}-a_9p_3^{(3)}-a_6p_3^{(3)}-a_9p_4^{(3)}-q_3z_3,$$
$${}_t^CD_{t_3}^q p_4^{(3)}(t)=a_3a_4(1-w_4)p_1^{(3)}-\frac{a_7}{a_8}z_2(1+w_3)p_2^{(3)}-a_9p_3^{(3)}-a_4p_4^{(3)}+q_4z_4,$$
$$(5.13)\quad {}_t^CD_{t_3}^q p^{(3)}(t_3)=\gamma_3$$

In the interval $[t_1,t_2]$ the adjoint is the solution of the fractional differential equation

$${}_t^CD_{t_2}^q p_1^{(2)}(t)=-(a_1+a_2y_2(1-v_2))p_1^{(2)}$$
$$+\left[\frac{a_5}{(1+y_1)^2}+a_2y_2(1-v_2)(1-v_4)\right]p_2^{(2)}$$
$$-a_2y_2(1-v_2)(1-v_4)p_2^{(2)}+q_1y_1$$
$${}_t^CD_{t_2}^q p_2^{(2)}(t)=-a_2y_1(1-v_2)p_1^{(2)}-[a_2y_1(1-v_2)(1-v_4)+a_6]p_2^{(2)}$$
$$+a_7\left(1-\frac{1}{a_8}y_2(1+v_2)\right)p_2^{(2)}$$
$$+a_7\left(1-\frac{y_2+y_2+y_4}{8}\right)(1+v_2)p_2^{(2)}$$
$$+a_2y_1(1-v_2)(1-v_4)p_2^{(2)}$$
$${}_t^CD_{t_2}^q p_2^{(2)}(t)=\frac{a_7}{a_8}y_2(1+v_3)p_2^{(2)}-a_9p_2^{(2)}-a_6p_2^{(2)}-a_9p_4^{(2)}-q_3y_3,$$
$${}_t^CD_{t_2}^q p_4^{(2)}(t)=a_3a_4(1-v_4)p_1^{(2)}-\frac{a_7}{a_8}y_2(1+v_2)p_2^{(2)}-a_9p_2^{(2)}-a_4p_4^{(2)}+q_4y_4,$$
$$(5.14)\quad {}_t^CD_{t_2}^q p^{(2)}(t_2)=\gamma_2$$

In the interval $[t_0,t_1]$ the adjoint is the solution of the fractional differential equation

$${}_t^CD_{t_1}^q p_1^{(1)}(t)=-(a_1+a_2x_2(1-u_2))p_1^{(1)}$$
$$+\left[\frac{a_5}{(1+x_1)^2}+a_2x_2(1-u_2)(1-u_4)\right]p_2^{(1)}$$
$$-a_2x_2(1-u_2)(1-u_4)p_2^{(1)}+q_1x_1$$
$${}_t^CD_{t_1}^q p_2^{(1)}(t)=-a_2x_1(1-u_2)p_1^{(1)}-[a_2x_1(1-u_2)(1-u_4)+a_6]p_2^{(1)}$$
$$+a_7\left(1-\frac{1}{a_8}x_2(1+u_2)\right)p_2^{(1)}$$

$$a_7\left(1-\frac{x_2+x_2+x_4}{8}\right)(1+u_2)p_2^{(1)}+a_2x_1(1-u_2)(1-u_4)p_2^{(1)}$$

$${}_t^CD_{t_1}^q p_2^{(1)}(t)=\frac{a_7}{a_8}x_2(1+u_3)p_2^{(1)}-a_9p_2^{(1)}-a_6p_2^{(1)}-a_9p_4^{(1)}-q_3x_3,$$

$${}_t^CD_{t_1}^q p_4^{(1)}(t)=a_3a_4(1-u_4)p_1^{(1)}-\frac{a_7}{a_8}x_2(1+u_2)p_2^{(1)}-a_9p_2^{(1)}-a_4p_4^{(1)}+q_4x_4,$$

$$(5.15)\quad {}_t^CD_{t_1}^q p^{(1)}(t_1)=\gamma_1$$

Next we write the Hamiltonians in each of the intervals. In the interval $[t_2,t_3]$ we have

$$H_3(t,z_3(t),p^{(3)}(t),\nu)\geq H_3(t,z_3(t),p^{(3)}(t),w(t)),\ \text{a.e. } t\ \forall\ \nu\in\mathcal{U}_3 \tag{5.16}$$

The Hamiltonian in the interval $[t_1,t_2]$ we have

$$H_2(t,y_2(t),p^{(2)}(t),\nu)\geq H_2(t,y_2(t),p^{(2)}(t),v(t)),\ \text{a.e. } t\ \forall\ \nu\in\mathcal{U}_2 \tag{5.17}$$

The Hamiltonian in the interval $[t_0,t_1]$ we have

$$H_1(t,y_1(t),p^{(1)}(t),\nu)\geq H_1(t,y_1(t),p^{(1)}(t),u(t)),\ \text{a.e. } t\ \forall\ \nu\in\mathcal{U}_1 \tag{5.18}$$

To carry out the numerical simulation we use the state equations (5.1), (5.2), (5.3), the adjoint equations (5.13), (5.14), (5.15) and the Hamiltonians (5.16), (5.17), (5.18). Specific values for the parameters in the state equations, and the cost are given below. The numerical procedure goes as follows. We start with the third interval, use the Hamiltonian to improve on the control. Using the improved control we update the state and the adjoint variables in the third interval. Then move to the second interval and use the Hamiltonian in the second interval to improve the control in the second interval. Then we use the improved control and update the states in the second interval and the third interval. The states in the third interval get updated because of the change in the state variables at t_2. Finally move to the first interval and use the Hamiltonian there to improve on the control. Using the improved control update the states in the first interval. Due to the change in the states of the first interval at t_1 the states in the second interval, hence the states in the third interval are updated.

```
BEGIN pseudocode
Third interval:
Use Hamiltonian to improve control.
Using improved control update state, adjoint variables in
third interval.

Second interval:
Improve control in the second interval.
Update states in second and third interval.
```

```
First interval:  Improve control.
Update states in all intervals.
END pseudocode
```

This procedure is essentially dynamic programming procedure.

The values of the parameters in (4.1) are given in the following table.

Parameters	Values
a_1 = Death rate of free virus	$2.5d^{-1}$
a_2 = Rate CD4+ T cells become infected with virus	$2.4 \times 10^{-5}mm^3d^{-1}$
a_3 = Number of free virus produced by actively infected CD4+ T cells	1200
a_4 = Death rate of actively infected CD4+ T cells population	$0.24d^{-1}$
a_5 = Source term for uninfected CD4+ T cells	$10d^{-1}mm^{-3}$
a_6 = Death rate of uninfected (latently infected) CD4+ T cells population	$0.02d^{-1}$
a_7 = Growth rate of CD4+ T cells population	$0.02d^{-1}$
a_8 = Maximal population level of CD4+ T cells	$1500mm^{-3}$
a_9 = Rate latently infected cells become active	$3 \times 10^{-3}d^{-1}$

In (5.4) the parameters in the cost are give the values

$$s_1 = s_3 = s_4 = q_1 = q_3 = q_4 = 10^3 \tag{5.19}$$

In (5.1) the parameters in the cost are give the values

$$\begin{aligned} x_1(t_0) &= c_{01} = 0.049, \\ x_2(t_0) &= c_{02} = 904, \\ x_3(t_0) &= c_{03} = 0.034, \\ x_4(t_0) &= c_{04} = 0.042, \end{aligned} \tag{5.20}$$

Next, we give particular values to the parameters in (5.2) and (5.3)

$$\begin{gathered} dd1 = dd2 = dd3 = dd4 = 0.002, \\ DDD1 = .0002, DDD2 = 0.002, DDD3 = DDD4 = 0.002 \\ cc1 = -0.99, cc2 = -0.95, cc3 = cc4 = -0.99, \\ CCC1 = -.995, CCC2 = -0.35, CCC3 = CCC4 = -0.995. \end{gathered} \tag{5.21}$$

The control variables take the values in the following table (Table 1).

Next, we give particular values to the parameters in (5.2) and (5.3) when there is no memory, that is the model is no more fractional differential equation. Thus, in (4.1), the left hand sides are ordinary derivatives of the states. The control variables in (5.2) and (5.3) are given in the following table (Table 1).

$$dd1 = dd2 = dd3 = dd4 = 0.002,$$

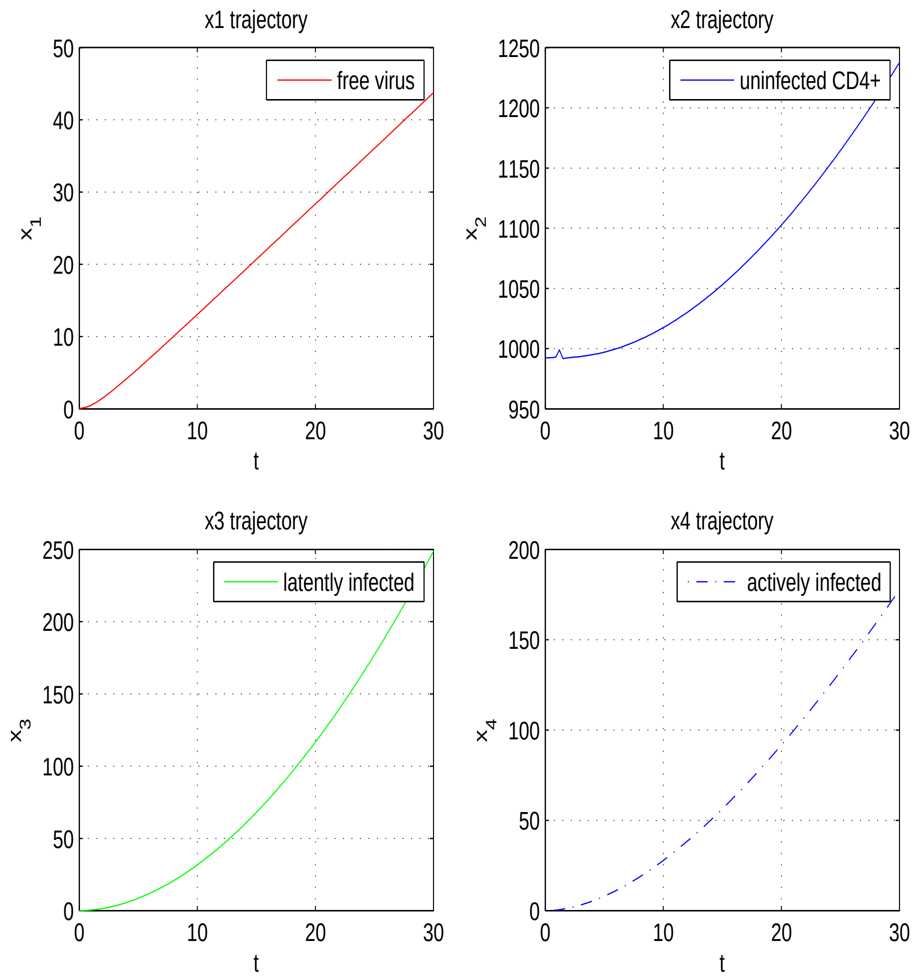

FIGURE 1. States in Time Interval 1.

TABLE 1

Interval 1	Interval 2	Interval 3
$u1 = 1.0$	$v1 = 1$	$w1 = 1$
$u2 = .95$	$v2 = 0$	$w2 = 1$
$u3 = 0.0$	$v3 = 1$	$w3 = 0.9$
$u4 = .95$	$v4 = 1$	$w4 = 1$

$$DDD1 = .0002, DDD2 = 0.002, DDD3 = DDD4 = 0.002$$
$$cc1 = -0.95, cc2 = -0.95, cc3 = cc4 = -0.95,$$
$$CCC1 = -.95, CCC2 = -0.95, CCC3 = CCC4 = -0.95. \tag{5.22}$$

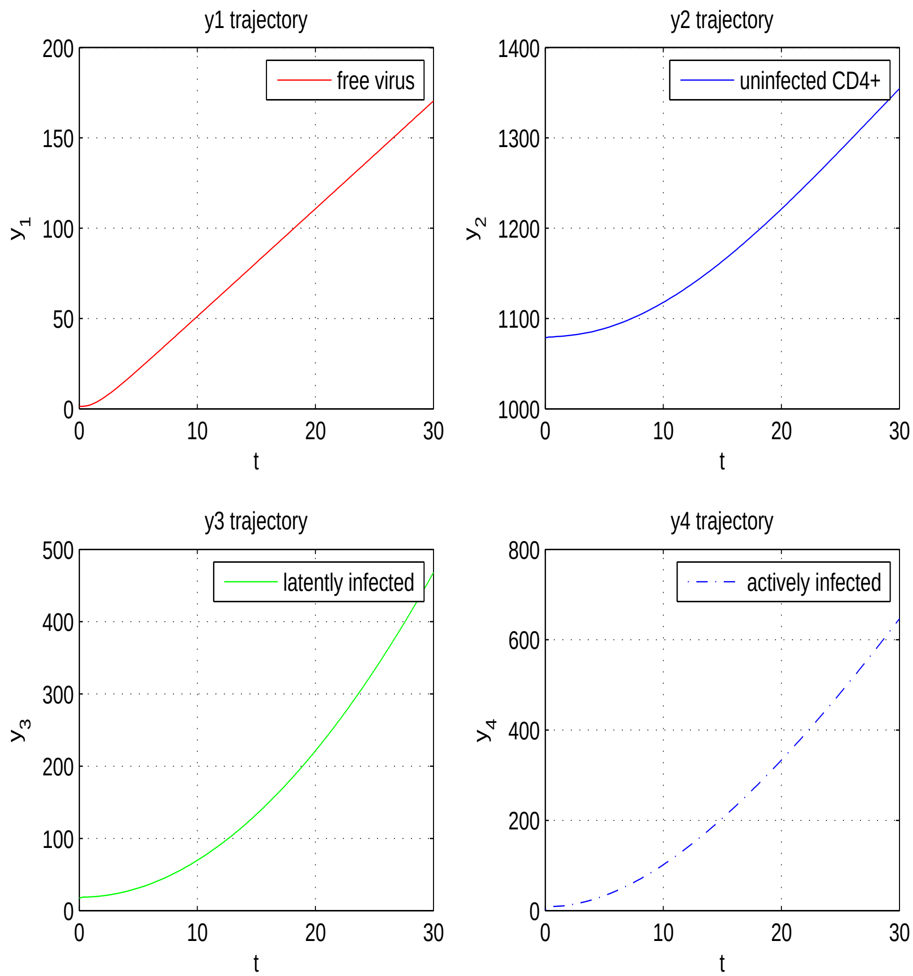

FIGURE 2. States in Time Interval 2.

TABLE 2

Interval 1	Interval 2	Interval 3
$u1 = 0$	$v1 = 0$	$w1 = 0.0418538$
$u2 = 1$	$v2 = 1$	$w2 = 1$
$u3 = 0.0009521$	$v3 = 0.0009401$	$w3 = 0.0008798$
$u4 = 1.026987$	$v4 = 1.010854$	$w4 = 1$

Then, we get the following graphs (Figure 4–Figure 6).

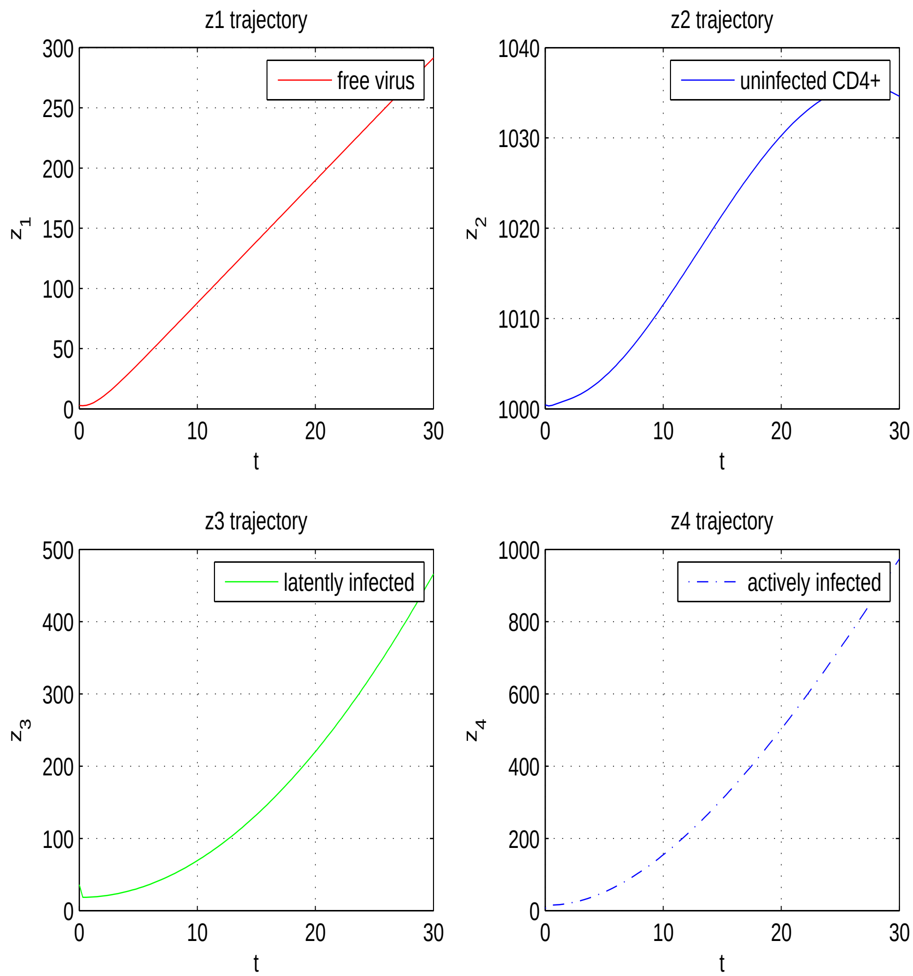

Figure 3. States in Time Interval 3.

6. Discussion of the results of the numerical computation

The numerical computation shows that in the fractional differential equation model that the virus at the intervention/impulse times should be killed 99%. The same is true in latently and actively infected CD4+ cells. Although there is damage to uninfected CD4+ cells the number rises to what is regarded as normal. The virus level and the infected and latently infected CD4+ cells also increase. However their number does not reach the number for uninfected CD4+ cells. In the differential equation model if 95% of the virus and the CD4+ cells are killed at the time of the intervention the number of uninfected CD4+ cells rises quickly to the normal number while the virus level and the infected CD4+ cells remain low. What one observes in these models is the importance of planned strong interventions .

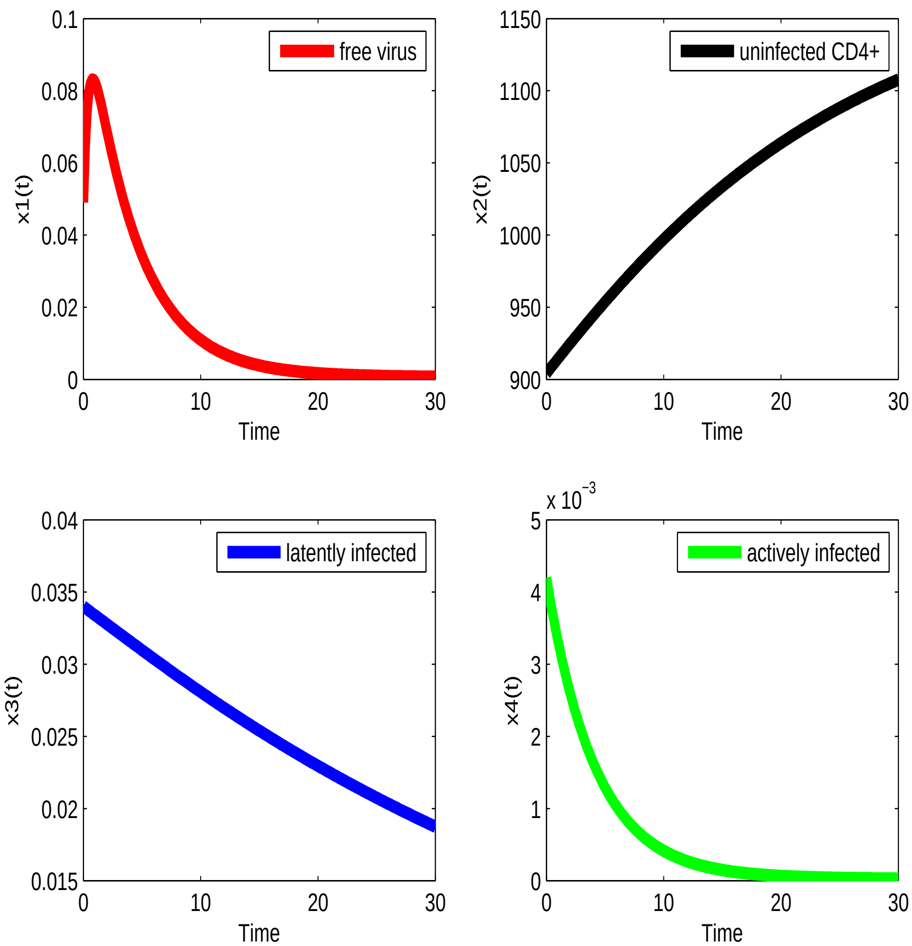

FIGURE 4. States in Time Interval 1.

7. Conclusion

We have considered an optimal control problem governed by fractional order differential equations modeling an HIV-immune system. The rational for using fractional differential equations is to account for the fact that the immune response involves memory. The impulse system formulation is to account for the fact a treatment regime of taking medication and the amount at optimal instants may be less damaging to the body and also less expensive. Some medications may still have to be taken regularly. Thus we have decision variables at impulse time and between impulse times. We have constructed necessary conditions for optimality and carried out numerical computation. Our results demonstrate that regardless of what we do between impulse times strong interventions are needed at impulse times, and the controls in between impulse times help increase the length of time between impulse times.

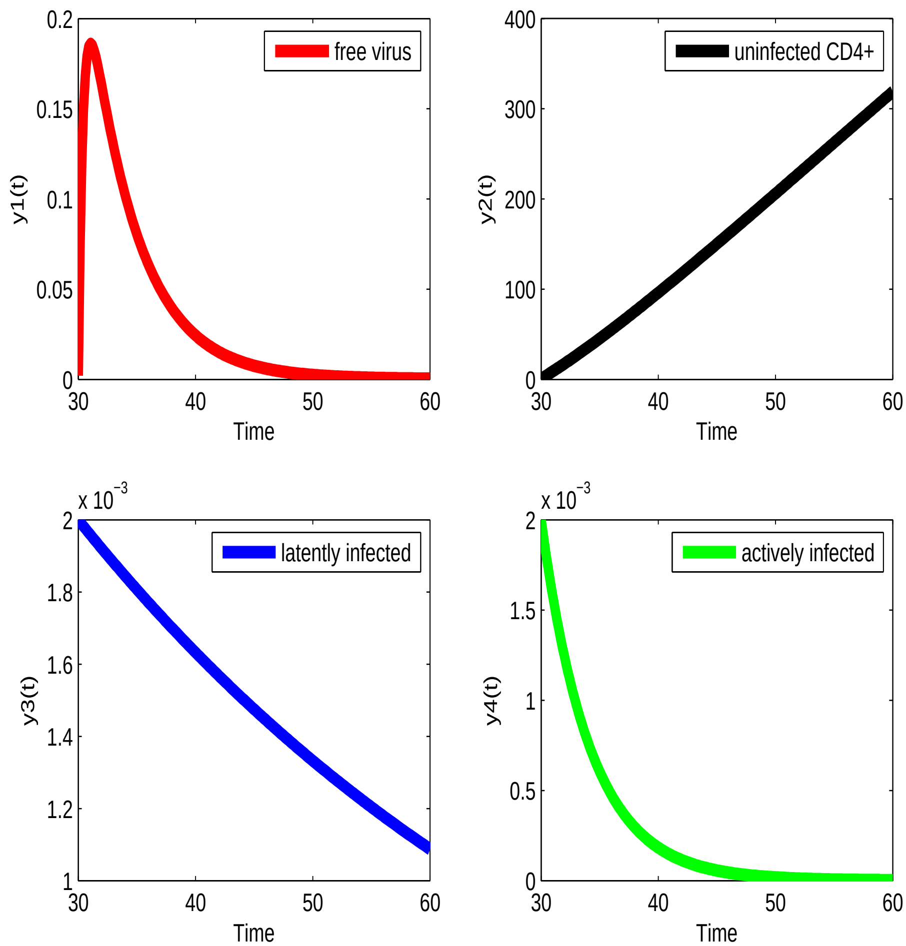

FIGURE 5. States in Time Interval 2.

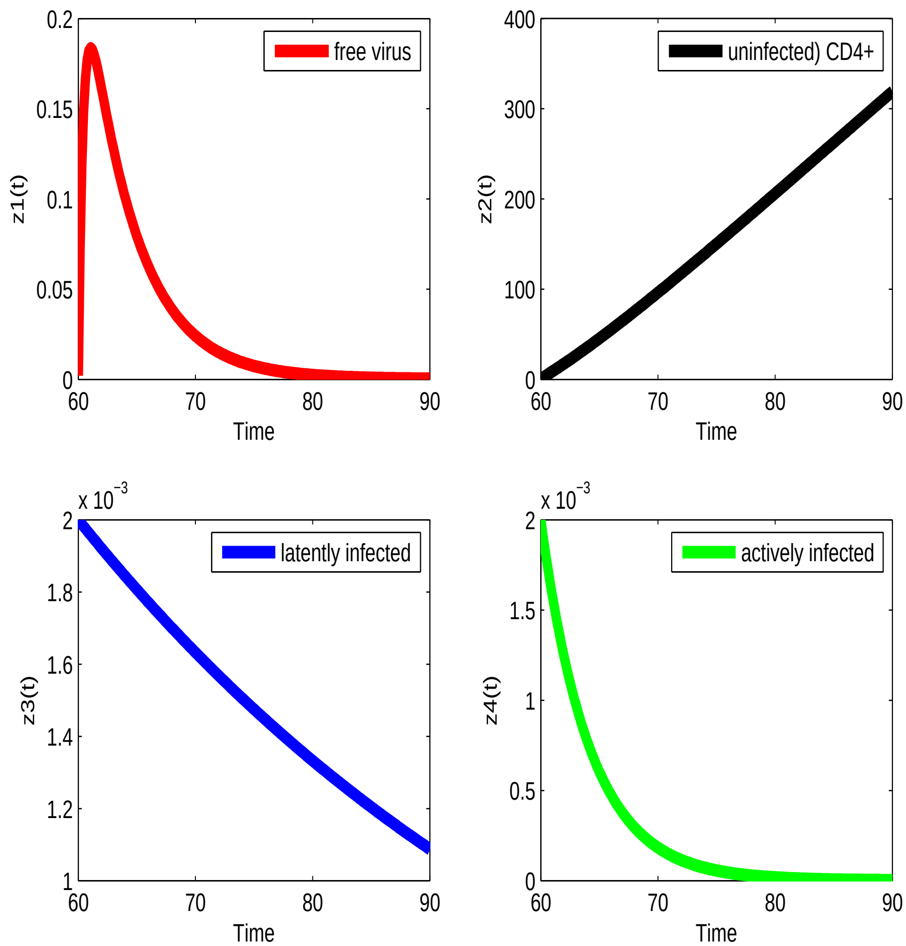

FIGURE 6. States in Time Interval 3.

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