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DYNAMIC PROGRAMMING METHOD FOR IMPULSIVE CONTROL PROBLEMS

TESHOME BALKEW[1] AND N.G. MEDHIN[2]

[1,2]Department of Mathematics
North Carolina State University
Raleigh, North Carolina, 27695, USA

ABSTRACT: We consider a nonlinear impulsive control problem governed by a system of ordinary differential equations which we study using dynamic programming approach. We then present two HIV models which are particular instances of the problem. In the first HIV model the objective of the control problem is to find an optimal trajectory to guide the system to LTNP (Long term Non-Progressor) equilibrium point while the cost of treatment is minimal, the viral load is undetectable, and CD4+T cell-count is at an acceptable level. In the second model we look for a treatment regime in which the infectious viral load is minimized and the CD4+T cell-count increases while using optimal dosage of anti-HIV drug. Simulation results are presented and discussed for each model.

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1. INTRODUCTION

Many evolutionary processes are characterized by the fact that at certain moments of time they experience a change of state abruptly. These processes are subject to short-term perturbations whose durations are negligible in comparison with the duration of the process. Consequently, it is natural to assume that these perturbations act instantaneously, that is, in the form of impulses [2]. For such an idealization, it becomes necessary to study dynamical systems with discontinuous trajectories, and they might be called differential equations with impulses or impulsive differential equations [1].

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Impulsive control system is a control paradigm based on impulsive differential equations. In an impulsive control system, the underlying dynamic system should have at least one "impulsively " changeable state variable.

Theories involving impulsive control systems have been widely studied. In such systems the states are governed by systems of ordinary differential equations, and the states are continuous except at certain instances where jump discontinuities occur [22].

Impulsive control problems arise in many modeling problems such as treatment of diseases, production planning and inventory management, pest control, engineering, economics, financial management sciences, and the physical sciences [30], [31], [32], [33].

1.1. PROBLEM STATEMENT

We now present a mathematical formulation of a general impulsive control system which we will later specialize to HIV models. Let t_i, $i = 1, 2, 3, ..., n$ be the instances where the discontinuities in the system state occur. We may call such instances impulse times. The vector fields governing the system dynamics may change across impulse times. Thus, let

$$0 = t_0 < t_1 < t_2 < ... < t_{n-1} < t_n.$$

be the instances where the jump discontinuities occur. In the initial interval $[t_0, t_1]$ the state dynamics is given by

$$\begin{aligned} \dot{x}_1(t) &= f_1(x_1(t), u_1(t)),\ t_0 < t < t_1, \\ x_1(t_0) &= x_0. \end{aligned}$$

and for $i = 2, 3, ..., n$ the state dynamic system is given by

$$\begin{aligned} \dot{x}_i(t) &= f_i(x_i(t), u_i(t)),\ t_{i-1} < t < t_i, \\ x_i(t_{i-1}) &= h_i(x_{i-1}(t_{i-1}))c_i + x_{i-1}(t_{i-1}). \end{aligned}$$

We assume that,

$$\begin{aligned} f_i &: [t_{i-1}, t_i] \times R^n \times R^k \longrightarrow R, \\ \Phi_i &: [t_{i-1}, t_i] \times R^n \times R^k \longrightarrow R, \\ h_i &: R^n \longrightarrow R^n \times R^n, \\ \Theta &: R^n \longrightarrow R. \end{aligned} \tag{1.1}$$

We note that state changes as we move from one interval to another. Note that h_i above is an $n \times n$ matrix. For example, in the interval $[t_0, t_1]$, the state is given by x_1, and in the interval $[t_1, t_2]$ it is given by x_2. The functions f_i, Φ_i, h_i and Θ are continuously differentiable with respect to x_i and u_i for fixed time t.

The objective function is given by

$$\sum_{i=1}^{n} \int_{t_{i-1}}^{t_i} \Phi_i(x_i(t_i), u_i(t_i))dt + \Theta(x_n(t_n)). \tag{1.2}$$

The control problem is given by

$$min\ J(x_1, u_1, ..., x_n, u_n) = \sum_{i=1}^{n} \int_{t_{i-1}}^{t_i} \Phi_i(x_i(t_i), u_i(t_i)))dt + \Theta(x_f(t_f))$$

subject to

$$\begin{aligned} \dot{x}_i(t) &= f_i(x_i(t), u_i(t)), \quad t_{i-1} < t < t_i, \\ x_i(t_{i-1}) &= h_i(x_{i-1}(t_{i-1}))c_i + x_{i-1}(t_{i-1}), \\ i &= 1, 2, 3, ...n. \end{aligned} \tag{P1}$$

1.2. SOLUTION METHOD

In this section we apply dynamic programming approach to study the control problem $(P1)$. This approach has an advantage over considering the entire problem $(P1)$ at once. It reduces the number of variables dealt with at a given time significantly and avoids some mathematical difficulties of optimizing a non-continuous function over the entire interval.

We assume the control problem $(P1)$ has solution $(\bar{c}_1, \bar{c}_2, ..., \bar{c}_n, \bar{u}_1, \bar{u}_2, ..., \bar{u}_n)$. We denote the corresponding trajectories by $\bar{x}_k(t)$, $k = 1, 2, ..., n$. Let $U = U_1 \times U_2 \times ... \times U_n$ be the control set. Assume that U is a convex set.

We have two types of controls in our control system, the controls in between impulses u_i's and the impulsive controls c_i's. We study them separately.

1.2.1. CONTROLS BETWEEN IMPULSES u_i's

In this section we only consider controls in between impulses . We assume that the state equation in $[t_{i-1}, t_i]$, has one and only one solution when control $u_i(t)$ is given. We apply dynamic programming approach to deal with the control problem $(P1)$. We start analyzing the problem in the last interval $[t_{n-1}, t_n]$ and go backwards.

Above we assumed the control problem $(P1)$ has solution $(\bar{c}_1, \bar{c}_2, ..., \bar{c}_n, \bar{u}_1, \bar{u}_2, ..., \bar{u}_n)$ and denoted the corresponding trajectories by $\bar{x}_i(t), i = 1, 2, ..., n$. Now let us consider

the interval $[t_{n-(i+1)}, t_{n-i}]$. In this interval we perturb the control $\bar{u}_{n-i}$ leaving the remaining controls fixed. Perturbing this control has the consequence of perturbing the trajectories $x_k(t),\ k = n-i,\ n-i+1,\ \cdots,\ n$. Thus, we have the control problem

$$\min_{u_{n-i}} \{ \int_{t_{n-(i+1)}}^{t_{n-i}} \Phi_{n-i}(x_{n-i}(t), u_{n-i}(t))dt + \sum_{j=1}^{i} \int_{t_{n-(i+1)+j}}^{t_{n-i+j}} \Phi_{n-i+j}(x_{n-i+j}(t), \bar{u}_{n-i+j}(t))dt + \cdots + \Theta(x_f(t_f))\} \tag{1.3}$$

subject to

$$\begin{aligned} \dot{x}_{n-i}(t) &= f(x_{n-i}(t), u_{n-i}(t)), \quad t_{n-(i+1)} < t < t_{n-i}, \\ x_{n-i}(t_{n-(i+1)}) &= h_{n-i}(\bar{x}_{n-(i+1)}(t_{n-(i+1)}))\bar{c}_{n-i} + \bar{x}_{n-(i+1)}(t_{n-(i+1)}). \end{aligned} \tag{1.4}$$

In (1.3), when $i = 0$ the sum is not there, and we are in the last interval (t_{n-1}, t_n), with the last cost in (t_{n-1}, t_n)

$$\int_{t_{n-1}}^{t_n} \Phi_n(x_n(t), u_n(t)dt + \Theta(x_n(t_n)).$$

The variation of the state x_{n-i} corresponding to the perturbation of the optimal control $\bar{u}_{n-i}$, that is, $u_{n-i,\theta} = \bar{u}_{n-i} + \theta v_{n-i}$, is given by

$$d\delta x_{n-i} = (f_{n-i,x_{n-i}}(\bar{x}_{n-i}(t), \bar{u}_{n-i}(t))\delta x_{n-i}(t) + f_{n-i,u_{n-i}}(x_{n-i}(t), \bar{u}_{n-i}(t))v_{n-i}(t))dt. \tag{1.5}$$

We know that the perturbation of $\bar{u}_{n-i}$ affects the dynamics in the intervals $[t_{n-i}, t_{n-(i-1)}]$, $[t_{n-(i-1)}, t_{n-(i-2)}]$,..., $[t_{n-1}, t_n]$. The variations in the state in the interval $[t_{n-(i+1)+j}, t_{n-i+j}]$, $j = 1, 2, \cdots, i$ is given by

$$\begin{aligned} d\delta x_{n-i+j} &= f_{n-i+j,x_{n-i+j}}(\bar{x}_{n-i+j}(t), \bar{u}_{n-i+j}(t))\delta x_{n-i+j}(t)dt. \\ j &= 1, 2, ..., i. \end{aligned} \tag{1.6}$$

Consider the following equation.

$$\begin{aligned} dL_{n-i+j}(t, t_{n-(i+1)+j}) &= f_{n-i+j,x_{n-i+j}}(\bar{x}_{n-i+j}(t), \bar{u}_{n-i+j}(t))L_{n-i+j}(t, t_{n-i+j})dt, \\ L_{n-i+j}(t_{n-(i+1)+j}, t_{n-(i+1)+j}) &= Id, \\ j &= 1, 2, ..., i. \end{aligned}$$

Now, the change in the cost (1.3) is given by

$$\int_{t_{n-(i+1)}}^{t_{n-i}} (\Phi_{n-i,x_{n-i}}\delta x_{n-i}(t) + \Phi_{n-i,u_{n-i}}v_{n-i})dt + \gamma_{n-i}\delta x_{n-i}(t_{n-i}) \tag{1.7}$$

where,

$$\gamma_{n-i} = \int_{t_{n-i}}^{t_{n-(i-1)}} \Phi_{n-(i-1),x_{n-(i-1)}} L_{n-(i-1)}(t, t_{n-i}) Q_{n-(i-1)}(t_{n-i}) dt + \gamma_{n-(i-1)} L_{n-(i-1)}(t_{n-(i-1)}, t_{n-i}) Q_{n-(i-1)}(t_{n-i}), \tag{1.8}$$

$$\Phi_{n-(i-1),x_{n-(i-1)}} = \Phi_{n-(i-1),x_{n-(i-1)}}(\bar{x}_{n-(i-1)}, \bar{u}_{n-(i-1)}).$$

$$Q_{n-(i-1)}(t_{n-i}) = [h_{n-(i-1)}(\bar{x}_{n-i}(t_{n-i}))\bar{c}_{n-(i-1)}]_{,x_{n-(i-1)}} + I.$$

and

$$\gamma_n = \Theta_{x_n}(\bar{x}_n(t_n)).$$

We are now ready to characterize the adjoint variable $P_{n-i}(t)$ in the interval $(t_{n-(i+1)}, t_{n-i})$.

Proposition 1.1. *$P_{n-i}(t)$ is adjoint variable if and only if it satisfies the costate equation*

$$\begin{aligned} dP_{n-i} &= -H_{n-i,x_{n-i}}(\bar{x}_{n-i}, \bar{u}_{n-i}, P_{n-i})dt \\ &= -\{\Phi_{n-i,x_{n-i}}(\bar{x}_{n-i}, \bar{u}_{n-i}) + f^t_{n-i,x_{n-i}}(\bar{x}_{n-i}, \bar{u}_{n-i})P_{n-i}\}dt, \\ P_{n-i}(t_{n-i}) &= \gamma_{n-i}. \end{aligned}$$

Proof. Considering the last objective function in the last interval (t_{n-1}, t_n) the fact that the corresponding adjoint or costate variable is P_{n-i} where $i = 0$ is well known ([26]). Now, considering (1.3), and using the steps shown above leading to the definition of γ_{n-i} in (1.8), the fact that the corresponding adjoint variable to (1.3) is given by the equations in the proposition follows.

We remind the reader that the Hamiltonian has the form

$$H_{n-i}(t_{n-i}, x_{n-i}, u_{n-i}, P_{n-i}) = \Phi_{n-i} + f_{n-i} \cdot P_{n-i}. \tag{1.9}$$

1.3. THE DECISION VARIABLES ($c_i's$)

In this section we consider only the decision variables $c_i's$. We keep the control's between impulse instances to remain unchanged. That is, we keep $\bar{u}_i, i = 1, ..., n$ unchanged and perturb the $c_i's$, $i = 1, ..., n$.

We start analyzing the problems from the last interval $[t_{n-1}, t_n]$ and go backwards.

As above let us consider the interval $[t_{n-(i+1)}, t_{n-i}]$. We consider the problem

$$\min_{c_{n-i}} \{ \int_{t_{n-(i+1)}}^{t_{n-i}} \Phi_{n-i}(x_{n-i}(t), \bar{u}_{n-i}(t)))dt +$$

$$\sum_{j=1}^{i}\int_{t_{n-(i+1)+j}}^{t_{n-i+j}} \Phi_{n-i+j}(x_{n-i+j}(t),\bar{u}_{n-i+j}(t)))dt+\cdots+\Theta(x_f(t_f))\}$$

(1.10)

subject to

$$\begin{aligned}\dot{x}_{n-i}(t) &= f(x_{n-i}(t),\bar{u}_{n-i}(t)),\ \ t_{n-(i+1)}<t<t_{n-i},\\ x_{n-i}(t_{n-(i+1)}) &= h_{n-i}(\bar{x}_{n-(i+1)}(t_{n-(i+1)}))c_{n-i}+\bar{x}_{n-(i+1)}(t_{n-(i+1)}).\end{aligned}$$

(1.11)

The variation of the state with respect to variation of $\bar{c}_{n-i}$ is

$$\begin{aligned}\frac{d}{dt}\delta x_{n-i}(t) &= f_{n-i,x_{n-i}}(\bar{x}_{n-i}(t),\bar{u}_{n-i}(t))\delta x_{n-i}(t),\\ \delta x_{n-i}(t_{n-(i+1)}) &= h_{n-i}(\bar{x}_{n-(i+1)}(t_{n-(i+1)}))\delta c_{n-i}\\ &= \tilde{Q}_{n-i}(\bar{x}_{n-(i+1)}(t_{n-(i+1)}))\delta c_{n-i}\end{aligned}$$

(1.12)

The perturbation of $\bar{c}_{n-i}$ affects the states in the succeeding intervals $[t_{n-i},t_{n-i+1}],\ldots,$ $[t_{n-1},t_n]$.

The change in the cost (1.10) is given by

$$[\int_{t_{n-(i+1)}}^{t_{n-i}} \Phi_{n-i,x_{n-i}}L_{n-i}(t,t_{n-i})h_{n-i}(\bar{x}_{n-(i+1)}(t_{n-(i+1)}))dt+\tilde{\gamma}_{n-i}]\delta c_{n-i)} \tag{1.13}$$

where,

$$\begin{aligned}\tilde{\gamma}_{n-i} =& \int_{t_{n-i}}^{t_{n-(i-1)}} \Phi_{n-(i-1),x_{n-(i-1)}}L_{n-(i-1)}(t,t_{n-i})\tilde{Q}_{n-(i-1),x_{n-i}}(t_{n-i})L_{n-i}(t_{n-i})\\ &\times\tilde{Q}_{n-i}(t_{n-i})dt\\ &+\tilde{\gamma}_{n-(i-1)}L_{n-(i-1)}(t_{n-(i-1)},t_{n-i})\tilde{Q}_{n-(i-1),x_{n-i}}(t_{n-i})L_{n-i}(t_{n-i})\\ &\times\tilde{Q}_{n-i}(t_{n-i}),\\ \tilde{\gamma}_n =&\Theta_{\bar{x}_n}(\bar{x}_n(t_n))L_n(t_n,t_{n-1})\tilde{Q}_{n,x_{n-1}}(t_{n-1}).\end{aligned}$$

(1.14)

We remark that, with respect to the decision variables c_i's, using (1.13) and (1.14), we can now avail ourselves of techniques from nonlinear programming where we can use the method of descent to minimize the cost. If there are constraints with respect to these variables we can avail ourselves of methods of feasible directions and/or penalty techniques. We get a direction of descent using (1.13) and (1.14) which we do in dealing with the applications problems we are considering below.

2. APPLICATIONS

In this section we give two applications involving two different types of HIV models. The first model involves jumps in the state at different instances of time we call impulse times and the sizes of the jumps involve our decision variables of our optimization problem. The decision variables constitute medical interventions. A rational for this model is given in ([22]). In this model whether or not medication intervention takes place is included. In the current paper we consider a general framework that includes ([22]). The second application involves decision variables governing the jumps at the impulse times, and control variables between the impulses. That is, we have decision variables reflecting medical interventions at scheduled times, and between scheduled medical interventions. We will refer to both types of decision variables as controls.

2.1. APPLICATION 1

In our first application problem we use stability analysis to get additional insight into the controlled HIV model problem as well as design appropriate controls for minimal cost. We now proceed to provide details of the problem under consideration. There are two immune responses in the human body: the humoral immune response and the cellular immune response [6]. The humoral immune response employs antibodies produced by B cells to attack antigens in body fluids, while the cellular immune response employs CD4+T cells to destroy body cells that have been infected with virus [7]. When an alien enters our system T-helper cells (CD4 +T) identify it and alert our body's defense system so that the system forms some kind of defense mechanism. Unlike many other common diseases HIV virus attacks CD4+T cells. By killing and converting the T-cells to hosts of the virus the disease weakens our immune mechanism. Eventually when the defense cell count is not high enough the patient shows symptoms of AIDS.

We use a mathematical model by [**?**] and [9]. They both used cell counts of uninfected, infected, CTLP and CTLe cells to study "Long Term Non-Progressor" (LTNP). Although it is usual for HIV infected patients to progress to AIDS after a certain latent period, less than 1% of them still have a sufficient amount of T-helper cells and never develop AIDS. Thus, their immune system is able to fight off other diseases in spite of the HIV infection. They are called long-term non-progressors (LTNP) and may provide clues to the control of HIV without continued drugs [7].

The model we study has four equilibrium points. Three of them have biological meaning but not the fourth one. Without medication it is common phenomenon for

the system to end up in the basin of attraction of AIDS stage equilibrium. Hence we rely on drug treatment. The drug treatment helps to guide the system to enter the basin of attraction of LTNP and once it is there we terminate the medication [7].

In [**?**] and [9] such a possibility has been suggested by the use of the structured treatment interruption, which is basically a switching scheme between zero and maximum medication. Since then, this problem has been dealt with by various methodologies such as model predictive control [10], [11], [12], optimal control [13], [14], and an approximation method [15]. On the other hand, a control theoretic approach has been used to determine when to initiate HIV therapy [16], and to estimate the parameter of HIV models [17], [18].

Consider the following HIV treatment model

$$\begin{aligned} \dot{x} &= \lambda - dx - (1-\eta u)\beta xy, \\ \dot{y} &= (1-\eta u)\beta xy - ay - pyz, \\ \dot{w} &= cxyw - cqyw - bw, \\ \dot{z} &= cqyw - hz, \\ \dot{u} &= -u, \end{aligned} \tag{2.1}$$

where,
x is number of healthy CD4+T cells,
y number of unhealthy CD4+T cells,
w number of CTLP cells (memory cells),
z number of CTLe cells,
u amount of medication delivered to the patient.

The term $1-\eta u,\ 0 \le 1-\eta u \le 1$ represents the efficacy of the drug. The drug is 100% effective if $1-\eta u = 0$ and ineffective if $1-\eta u = 1$. The cost of interest is

$$\begin{aligned} J(c_1, c_2, ..., c_n) = &\sum_{i=1}^{n} R\frac{c_i^2}{2} + S_x\frac{(x_n(t_n)-x_f)^2}{2} + S_y\frac{(y_n(t_n)-y_f)^2}{2} \\ &+ S_w\frac{(w_n(t_n)-w_f)^2}{2} + S_z\frac{(z_n(t_n)-z_f)^2}{2}. \end{aligned} \tag{2.2}$$

Here R is the cost associated with the intake of the drug, which includes the cost of the drug as well as the amount of damage to the health due to the drug taken. Here, x_f, y_f, w_f, z_f are chosen so that if the system is left without further medication after this point, it converges to the desired equilibrium point which is high healthy cell count and low unhealthy cell count. The $c_i's$ are decision variables where c_i is the amount of medicine given at time t_i. In what follows we sometimes refer to the $c_i's$ as impulsive controls. Let us assume, in what follows, that $(\bar{c}_1, \bar{c}_2, ..., \bar{c}_n)$ minimizes the above cost.

2.2. STABILITY OF EQUILIBRIUM POINTS OF THE MODEL

In this section we determine the equilibrium points of the HIV treatment model

$$\begin{aligned}\dot{x} &= \lambda - dx - (1-\eta u)\beta xy,\\ \dot{y} &= (1-\eta u)\beta xy - ay - pyz,\\ \dot{w} &= cxyw - cqyw - bw,\\ \dot{z} &= cqyw - hz.\end{aligned} \tag{2.3}$$

as a function of $\eta^* = (1-\eta u)$. The stability analysis helps us to get additional insight into the controlled model problem as well as design appropriate controls and formulate our conclusions. The objective of the control problem is to find an optimal control to guide the system to the basin of attraction of LTNP (Long term Non-Progressor) equilibrium point while the cost of treatment is minimal and the viral load is undetectable and CD4+T cell count is at an acceptable level. Supporting simulation results are presented below. We set $\dot{x} = \dot{y} = \dot{w} = \dot{z} = 0$ to have the equilibrium points. We do have four equilibrium points as a function of η^* where three of them have biological meaning but not the fourth one.

1. HIV free equilibrium point $X_A(\eta^*) = (x_A, y_A, w_A, z_A)$.

$$x_A = \frac{\lambda}{d}, \quad y_A = w_A = z_A = 0. \tag{2.4}$$

2. AIDS stage $X_B(\eta^*) = (x_B, y_B, w_B, z_B)$.

$$x_B = \frac{a}{\eta^*\beta}, \quad y_B = \frac{\lambda\beta - da}{a\eta^*\beta}, \quad w_B = z_B = 0. \tag{2.5}$$

3. Long term non-progressor $X_C(\eta^*) = (x_C, y_C, w_C, z_C)$.

   Let $K := [c(\lambda + dq) - b\eta^*\beta]^2 - 4c^2\lambda qd$.

$$\begin{aligned}x_C &= \frac{[c(\lambda+dq) - b\eta^*\beta] + \sqrt{K}}{2cd}, \quad y_C = \frac{b}{c(x_C - q)}, \quad w_C = \frac{hz_C}{cqy_C},\\ z_C &= \frac{\eta^*\beta x_C - a}{p}.\end{aligned} \tag{2.6}$$

4. The fourth equilibrium point $X_D(\eta^*) = (x_D, y_D, w_D, z_D)$.

$$\begin{aligned}x_D &= \frac{[c(\lambda+dq) - b\eta^*\beta] - \sqrt{K}}{2cd}, \quad y_D = \frac{b}{c(x_D - q)}, \quad w_D = \frac{hz_D}{cqy_D},\\ z_D &= \frac{\eta^*\beta x_D - a}{p}.\end{aligned} \tag{2.7}$$

We consider the following two sets of assumptions for the purpose of our analysis.

1. ***Assumption 1:***

$$d < a. \tag{2.8}$$

$$b < h. \tag{2.9}$$

$$q < \frac{\lambda}{d}. \tag{2.10}$$

$$c > \frac{4abd}{(\lambda - dq)^2}. \tag{2.11}$$

$$\beta < \frac{c(\sqrt{\lambda} - \sqrt{dq})^2}{b}. \tag{2.12}$$

$$\beta > \frac{ac(\lambda + dq) - \sqrt{a^2c^2(\lambda + dq)^2 - 4a^2cd(ad + cq\lambda)}}{2(ab + cq\lambda)}. \tag{2.13}$$

2. ***Assumption 2:***

   The basic reproductive ratio [23] is less than unity by the application of drug, i.e., $\eta^* \frac{\lambda\beta}{ad} < 1$.

We need the following values for stability analysis

$$\eta_1^* := \frac{ad}{\beta\lambda}. \tag{2.14}$$

$$\eta_2^* := \frac{ac(\lambda + dq) - \sqrt{a^2c^2(\lambda + dq)^2 - 4a^2cd(ad + cq\lambda)}}{(2(ab + cq\lambda)\beta)}. \tag{2.15}$$

$$\eta_3^* := \frac{ac(\lambda + dq) + \sqrt{a^2c^2(\lambda + dq)^2 - 4a^2cd(ad + cq\lambda)}}{2(ab + cq\lambda)\beta}. \tag{2.16}$$

Theorem 2.1. *Under **Assumption 1** we have the following.*

1. *$X_A(\eta^*)$ is locally exponentially stable if $\eta \in [0, \eta_1^*)$ and unstable if $\eta \in (\eta_1^*, 1]$.*
2. *$X_B(\eta^*)$ is locally exponentially stable if $\eta \in (\eta_1^*, \eta_2^*) \cup (\eta_3^*, 1]$ and unstable if $\eta^* \in (0, \eta_1^*) \cup (\eta_2^*, \eta_3^*)$.*
3. *$X_C(\eta^*)$ is locally exponentially stable if $\eta^* \in (\eta_2^*, 1]$ and unstable if $\eta \in (0, \eta_2^*)$.*

Corollary: Transcritical bifurcation occurs at η_1^*, η_2^* and η_3^*.

1. We now proceed the following optimization problem in the last interval $[t_{n-1}, t_n]$. First, let us recall that our cost functional, which is minimized by $(\bar{c}_1, \bar{c}_2, ..., \bar{c}_n)$,

is given by

$$J(c_1, c_2, ..., c_n) = \sum_{i=1}^{n} R\frac{c_i^2}{2} + S_x\frac{(x_n(t_n) - x_f)^2}{2} + S_y\frac{(y_n(t_n) - y_f)^2}{2} + S_w\frac{(w_n(t_n) - w_f)^2}{2} + S_z\frac{(z_n(t_n) - z_f)^2}{2}. \quad (2.17)$$

Let $J_n(c_n) = J(\bar{c}_1, \bar{c}_2, ..., \bar{c}_{n-1}, c_n)$. The control/optimization problem in the interval $[t_{n-1}, t_n]$ is given by

$$\begin{aligned} \min_{c_n} \quad & J_n(c_n) \\ & Subject\ to \\ & \dot{X}_n(t) = f_n(X_n(t)), t_{n-1} < t < t_n \\ & X_n(t_{n-1}) = \bar{X}_{n-1}(t_{n-1}) + h_n(\bar{X}_{n-1}(t_{n-1}))(0, 0, 0, 0, c_n)^t, \\ & h_n(\bar{X}_{n-1}(t_{n-1})) = diag(0\ 0\ 0\ 0\ 1). \end{aligned} \quad (2.18)$$

The variation of the dynamics with respect to variation of the optimal impulsive control $\bar{c}_n$ is

$$\begin{aligned} \frac{d}{dt}\delta X_n &= f_{n,X_n}(X_n(t))\delta X_n, \\ \delta X_n(t_{n-1}^+) &= h_n(\bar{X}_{n-1}(t_{n-1}^-)(0, 0, 0, 0, \delta c_n)^t. \end{aligned}$$

Let $L_n(t, t_{n-1})$ be fundamental matrix solution of the following linear ODE

$$\begin{aligned} \frac{d}{dt}L_n(t, t_{n-1}) &= f_{n,X_n}(X_n)L_n(t, t_{n-1}), \\ L_n(t_{n-1}, t_{n-1}) &= I. \end{aligned}$$

Then,

$$\delta X_n(t) = L_n(t, t_{n-1})Q_n(t_{n-1})(0, 0, 0, 0, \delta c_n)^t, \quad (2.19)$$

where,

$$Q_n(t_{n-1}) = h_n(\bar{X}_{n-1}(t_{n-1}^-).$$

Variation of the cost J_n with respect to variation of the optimal control $\bar{c}_n$ is

$$\delta J_n = \Theta_{X_n}(X_n(t))\delta X_n(t). \quad (2.20)$$

Using (3.5) the variation of the cost is

$$\delta J_n = \Theta_{X_n}(X_n(t_n))L_n(t_n, t_{n-1})Q_n(t_{n-1})(0, 0, 0, 0, \delta c_n)^t. \quad (2.21)$$

Then the variation of the cost is

$$\delta J_n = \Theta_{x_n}(t_n)L_n(t_n, t_{n-1})Q_n(t_{n-1})(0, 0, 0, 0, \delta c_n)^t. \quad (2.22)$$

Moving one step backward to interval $[t_{n-2}, t_{n-1}]$. The cost is

$$J_{n-1}(c_{n-1}) = J(\bar{c}_1, \bar{c}_2, ..., \bar{c}_{n-1}, c_{n-1}, \bar{c}_n)$$

We minimize this cost subject to

$$\begin{aligned}
\dot{X}_{n-1}(t) &= f_{n-1}(X_{n-1}(t)), t_{n-2} < t < t_{n-1}, \\
X_{n-1}(t_{n-1}) &= \bar{X}_{n-2}(t_{n-2}) + h_{n-1}(\bar{X}_{n-2}(t_{n-2}))(0,0,0,0,c_{n-1})^t, \\
h_{n-1}(\bar{X}_{n-1}(t)) &= diag(0\ 0\ 0\ 0\ 1).
\end{aligned}$$

The variation of the state is

$$\begin{aligned}
\frac{d}{dt}\delta X_{n-1} &= f_{n-1,X_{n-1}}(\bar{X}_{n-1}(t))\delta X_{n-1}(t), \\
\delta X_{n-1}(t^+_{n-2}) &= h_{n-1}(\bar{X}_{n-2}(t^-_{n-1}))(0,0,0,0,\delta c_n)^t.
\end{aligned}$$

Let $L_{n-1}(t, t_{n-2})$ be the solution of the equation

$$\begin{aligned}
\frac{d}{dt}L_{n-1}(t, t_{n-2}) &= f_{n,X_n}L_{n-1}(t, t_{n-2}), \\
L_{n-1}(t_{n-1}, t_{n-2}) &= I.
\end{aligned}$$

We know that the state in interval $[t_{n-1}, t_n]$ is affected by the perturbation of $\bar{c}_{n-1}$. Consider the following equation in the interval $[t_{n-1}, t_n]$

$$\begin{aligned}
\frac{d}{dt}L_n(t, t_{n-1}) &= f_{n,X_n}(X_n)L_n(t, t_{n-1}), \\
L_n(t_{n-1}, t_{n-1}) &= I.
\end{aligned} \tag{2.23}$$

Then, the perturbation $\delta X_n(t)$ of the state X_n due to the perturbation of $\bar{c}_{n-1}$ is given by

$$\delta X_n(t) = L_n(t, t_{n-1})\delta X_{n-1}(t_{n-1}), \tag{2.24}$$

where

$$\delta X_{n-1}(t_{n-2}) = Q_{n-1}(t_{n-2})(0,0,0,0,\delta c_n)^t. \tag{2.25}$$

and

$$Q_{n-1}(t_{n-2}) = h_{n-1}(\bar{X}_{n-2}(t^-_{n-1}))(0,0,0,0,\delta c_n)^t. \tag{2.26}$$

Then the variation of the cost is

$$\delta J_{n-1} = \Theta_{X_n}(t_n)L_n(t_n, t_{n-1})IL_{n-1}(t_{n-1}, t_{n-2})Q_{n-1}(t_{n-2})(0,0,0,0,\delta c_n)^t. \tag{2.27}$$

2. Continuing the same way, in the ith interval $[t_{n-(i+1)}, t_{n-i}]$. The control problem is

$$\begin{aligned}
\min_{c_{n-i}} \quad & J_{n-i}(c_{n-i}) \\
& \textit{Subject to} \\
& \dot{X}_{n-i}(t) = f_{n-i}(X_{n-i}(t)), t_{n-(i+1)} < t < t_{n-i}, \\
& X_{n-i}(t_{n-(i+1)}) = h_{n-i}(\bar{X}_{n-(i+1)}(t_{n-(i+1)}))c_{n-i} + \bar{X}_{n-(i+1)}(t_{n-(i+1)}), \\
& h_{n-i}(X_{n-i}(t)) = diag(0\ 0\ 0\ 0\ 1).
\end{aligned} \tag{2.28}$$

where,

$$J_{n-i}(c_{n-i}) = J(\bar{c}_1, \bar{c}_2, ..., \bar{c}_{n-(i+1)}), c_{n-i}, \bar{c}_{n-(i-1}, ..., \bar{c}_n).$$

The variation of the state due to the variation in $\bar{c}_n$ is given by

$$\begin{aligned}
\frac{d}{dt}\delta X_{n-i}(t) &= f_{n-i,X_{n-i}}(X_{n-i}(t))\delta X_{n-i}(t), \\
\delta X_{n-i}(t_{n-(i+1)}) &= h_{n-i}(\bar{X}_{n-(i+1)}(t_{n-(i+1)}))(0,0,0,0,\delta c_{n-i})^t.
\end{aligned} \tag{2.29}$$

The perturbation of $\bar{c}_{n-i}$ affects the dynamics in the succeeding intervals. The variation in the cost $J_{n-i}(\bar{c}_{n-i})$ due to variation in $\bar{c}_{n-i}$ is given by

$$\begin{aligned}
\delta J_{n-i}(\bar{c}_{n-i}) = \Theta_{X_n}(t_n)L_n(t_n, t_{n-1})L_{n-1}(t_{n-1}, t_{n-2}) \cdots Q_{n-i}(t_{n-(i+1)}) \\
L_{n-i}(t, t_{n-(i+1)})(0,0,0,0,\delta c_{n-i})^t.
\end{aligned} \tag{2.30}$$

2.3. NUMERICAL COMPUTATION AND SIMULATION

We use four intervals $[t_0, t_1], [t_1, t_2]$, $[t_2, t_3], [t_3, t_4]$ where $t_4 = t_f$ for the simulation. With apply controls c_1 at t_1, and c_2 at t_2. The fourth interval is included to give the system enough time to come closer to the intended cell count. The dynamics in each interval is given by

1. In interval $[t_0, t_1]$ we consider

$$\begin{aligned}
\dot{x_1} &= \lambda - dx_1 - (1 - \eta u_1)\beta x_1 y_1, \\
\dot{y_1} &= (1 - \eta u_1)\beta x_1 y_1 - a y_1 - p y_1 z_1, \\
\dot{w_1} &= c x_1 y_1 w_1 - cq y_1 w_1 - b w_1, \\
\dot{z_1} &= cq y_1 w_1 - h z_1, \\
\dot{u_1} &= -u_1, \\
X_1(t_0) &= (x_1(t_0), y_1(t_0), w_1(t_0), z_1(t_0), u_1(t_0))^t = (2, 0.4, 0.22, 0.1, 0)^t.
\end{aligned} \tag{2.31}$$

2. In interval $[t_1, t_2]$ we consider

$$\begin{aligned}
\dot{x_2} &= \lambda - dx_2 - (1-\eta u_2)\beta x_2 y_2,\\
\dot{y_2} &= (1-\eta u_2)\beta x_2 y_2 - a y_2 - p y_2 z_2,\\
\dot{w_2} &= c x_2 y_2 w_2 - cq y_2 w_2 - b w_2,\\
\dot{z_2} &= cq y_2 w_2 - h z_2,\\
\dot{u_2} &= -u_2,\\
X_2(t_1) &= \bar{X}_1(t_1) + h(\bar{X}_1(t_1))(0,0,0,0,c_1)^t,\ h(\cdot) = diag(0\ 0\ 0\ 0\ 1).
\end{aligned} \tag{2.32}$$

3. In interval $[t_2, t_3]$ we consider

$$\begin{aligned}
\dot{x_3} &= \lambda - dx_3 - (1-\eta u_3)\beta x_3 y_3,\\
\dot{y_3} &= (1-\eta u_3)\beta x_3 y_3 - a y_3 - p y_3 z_3,\\
\dot{w_3} &= c x_3 y_3 w_3 - cq y_3 w_3 - b w_3,\\
\dot{z_3} &= cq y_3 w_3 - h z_3,\\
\dot{u_3} &= -u_3\\
X_3(t_2) &= \bar{X}_2(t_2) + h(\bar{X}_2(t_2))(0,0,0,0,c_2)^t,\ h(\cdot) = diag(0\ 0\ 0\ 0\ 1).
\end{aligned} \tag{2.33}$$

4. In interval $[t_3, t_4]$ we consider

$$\begin{aligned}
\dot{x_4} &= \lambda - dx_4 - (1-\eta u_4)\beta x_4 y_4,\\
\dot{y_4} &= (1-\eta u_4)\beta x_4 y_4 - a y_4 - p y_4 z_4,\\
\dot{w_4} &= c x_4 y_4 w_4 - cq y_4 w_4 - b w_4,\\
\dot{z_4} &= cq y_4 w_4 - h z_4,\\
\dot{u_4} &= -u_4\\
X_4(t_3) &= (2, 2, 0.4, 0.25, 0)^t.
\end{aligned}$$

The cost is

$$\begin{aligned}
J(\bar{c}_1, \bar{c}_2) = \frac{R}{2}((\bar{c}_1)^2 + (\bar{c}_2)^2) + S_x\frac{(x_4(4)-2)^2}{2}\\
+ S_y\frac{(y_4(4)-2)^2}{2} + S_w\frac{(w_4(4)-0.4)^2}{2} + S_z\frac{(z_4(4)-0.25)^2}{2}.
\end{aligned}$$

The next step is to determine the fundamental matrix solutions, L_1, L_2, L_3, and L_4.

1. L_4 is determined from the following equation

$$\frac{dL_4}{dt} = f_{4,X_4}(\bar{X}_4(t))L_4(t),$$

$$L_4(t_3) = I.$$
$$t_3 < t < t_4$$

2. L_3 is determined from the following equation

$$\frac{dL_3}{dt} = f_{3,X_3}(\bar{X}_3(t))L_3(t),$$
$$L_3(t_2) = I,$$
$$t_2 < t < t_3.$$

3. L_2 is determined from the following equation

$$\frac{dL_2}{dt} = f_{2,X_2}(\bar{X}_2(t))L_2(t),$$
$$L_2(t_1) = I,$$
$$t_1 < t < t_2.$$

4. L_1 is determined from the following equation

$$\frac{dL_1}{dt} = f_{1,X_1}(\bar{X}_1(t))L_1(t),$$
$$L_1(t_0) = I,$$
$$t_0 < t < t_1.$$

Also,

1. in the interval $[t_3, t_4]$ Q_4 is given by $Q_4 = diag(0, 0, 0, 0, 1)$.

2. in the interval $[t_2, t_3], [t_1, t_2], [t_0, t_1]$ Q_3, Q_2, Q_1 are defined by $Q_3 = Q_2 = Q_1 = I$.

The numerical simulation we are going to carry out is based on the state equations and the impulsive controls. We use steepest descent method for optimization purpose. We follow the following procedure for numerical simulation

1. We solve the ODEs in each interval starting from the one in the first interval forward.

2. Determine Q_4 and L_4 in interval 4.

3. In the third interval calculate Q_3, L_3 and gradient of the objective function. Use the information to update c_2. After updating c_2 use the improved information to update the state variables both in the third and forth interval.

4. Calculate Q_2 and L_2. Using the information improve c_1. After improving c_1 use the improved information to update the state variables both in the second, third and fourth interval.

5. Finally go to first interval. Solve the ODE in the interval. Changes in the state variable in this interval affects the values of the state variables in the second, third, and fourth interval.

The following is a pseudo code for our numerical simulation

```
BEGIN psuedocode
Solve ODE's in all intervals.
Fourth interval:
Calculate Q4, L4 and gradJ4.

Third interval:
Calculate Q3  L3 and gradJ3.
Use steepest decent method to improve c2.
Solve ODE's in third and fourth interval using the improved c2.

Second interval:
Calculate Q2 L2 and gradJ2.
Using steepest decent method improve c1.
Solve ODE's in second, third and fourth interval using the improved c1.

First interval:
Calculate Q1 L1 gradJ1.
Update states variables in all intervals.
END psuedocode
```

The parameter values we use are [9] $\lambda = 1, e = 0.1, d = 0.1, a = 0.2, \eta = 0.5, \beta = 0.42, p = 1, b = 0.1, h = 0.1, q = 0.5$, and the initial amount of medicine in the body chosen to be $u(0) = 0$.

The numbers S_x, S_y, S_w, S_z are measures of importance attached to the difference between the final cell numbers and desired cell counts. These values are all chosen to be 2.

2.3.1. CONCLUSION

Taking $R = 0.1$, we have the following cost and optimal impulsive values: $Cost = 0.042833315801935$, $c1 = 0.523975314189902$, $c2 = 0.349153540962085$.

The following table gives us the cell counts for the first three iterations and last three iterations of our simulation. We remark that a maximum population level of CD+T cells is $1500/mm^3$ and a lower level is $500/mm^3$. We may take the lower as a unit in the following table.

Table 1

$Healthycells$	$Unhealthycells$	$Memorycells$	$Effectors$	$Control$
3.411988	0.9208089	0.3096524	0.1031824	0.1120595
3.063783	1.203528	0.3222986	0.1078693	0.9651733
2.799905	1.417936	0.3290286	0.1113703	0.8556089
2.024841	2.038927	0.3335831	0.1216719	0.5363530
2.024838	2.038922	0.3335830	0.1216724	0.5363640
2.024835	2.038917	0.3335829	0.1216729	0.5363750

What we showed here is that by applying the optimal amount of medication, we guided our system to go from the given cell count $(2, 0.4, 0.22, 0.1)$ to a cell count $(2.024835, 2.038917, 0.3335829, 0.1216729)$ which is closer to the target cell count $(2, 2, 0.4, 0.25)$. Our conclusion is that if the patient's cell count is not below thresh hold cell count, then it is possible to guide the system to basin of attraction of LTNP equilibrium point starting from the existing cell count by giving optimal amount of medication in a finite time horizon with minimum cost and minimum side effect.

2.4. APPLICATION 2

The HIV-immune system model we study here is based on [29]. Here we consider a hybrid model leading to an impulsive control problem (see (2.36), (2.37) below) and arrive at our conclusions. The rational for our hybrid/impulsive model is motivated by [22]. The model is

$$\dot{x_1}(t) = -a_1x_1 - a_2x_1x_2(1 - u_2) + a_3a_4x_4(1 - u_1),$$

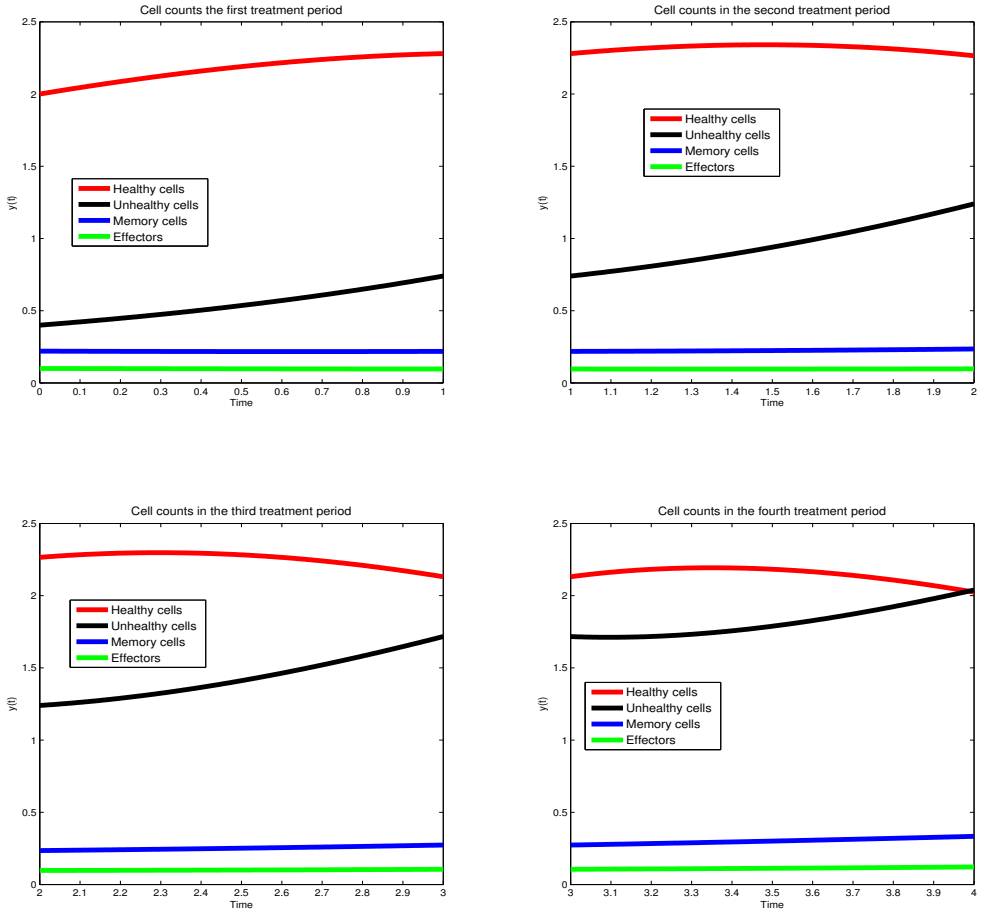

Figure 1: Cell count of the simulation.

$$\dot{x_2}(t) = \frac{a_5}{1+x_1} - a_2x_2(1-u_2)(1-u_4) - a_6x_2 + a_7(1 - \frac{1}{a_8}(x_2+x_3+x_4))x_2(1+u_3),$$
$$\dot{x_3}(t) = a_2x_1x_2(1-u_2)(1-u_4) - a_9x_3 - a_6x_3,$$
$$\dot{x_4}(t) = a_9x_3 - a_4x_4,$$
$$X(0) = (x_1(0), x_2(0), x_3(0), x_4(0))^t.$$

where,

1. x_1 represents free virus.
2. x_2 uninfected $CD4+T$ cells.
3. x_3 latently infected $CD4+T$ cells.
4. x_4 actively infected $CD4+T$ cells.

The controls:

5. u_1 is the concentration of protease inhibitors.
6. u_2 fusion inhibitors.
7. u_3 $CD4+T$ cell enhancer.
8. u_4 reverse transcription inhibitor.

Parameters:

9. a_1 death rate of free virus.
10. a_2 rate $CD4+T$ cells become infected with virus.
11. a_3 number of free virus produced by actively infected $CD4+T$ cells.
12. a_4 death rate of actively infected $CD4+T$ cell population.
13. a_5 source term of uninfected $CD4+T$ cells.
14. a_6 death rate of infected (latently infected) $CD4+T$ cell population.
15. a_7 growth rate of $CD4+T$ cell population.
16. a_8 maximum population level of $CD4+T$ cells.
17. a_9 rate of latently infected cells becoming active.

The cost to be minimized is given by

$$\begin{aligned} J(u) =& \frac{1}{2}[s_1x_1^2(t_f) + s_3x_3^2(t_f) + s_4x_4^2(t_f)] \\ &+ \frac{1}{2}\int_0^{t_f}[q_1x_1^2(t) + q_3x_3^2(t) + q_4x_4^2(t) + ru_1^2(t)]dt. \end{aligned} \tag{2.34}$$

Let $t_1 < t_2 < ... < t_{n-1}$ be the instances at which the impulses are applied. Let us consider $[t_{i-1}, t_i], i = 1, 2, 3, ..., n$

$$\begin{aligned} \dot{x_{i1}}(t) =& -a_1x_{i1} - a_2x_{i1}x_{i2}(1-u_{i2}) + a_3a_4x_{i4}(1-u_{i1}) \\ \dot{x_{i2}}(t) =& \frac{a_5}{1+x_{i1}} - a_2x_{i2}(1-u_{i2})(1-u_{i4}) \\ & - a_6x_{i2} + a_7(1 - \frac{1}{a_8}(x_{i2}+x_{i3}+x_{i4}))x_i2(1+u_{i3}), \\ \dot{x_{i3}}(t) =& a_2x_{i1}x_{i2}(1-u_{i2})(1-u_{i4}) - a_9x_{i3} - a_6x_{i3}, \\ \dot{x_{i4}}(t) =& a_9x_{i3} - a_4x_{i4}, \\ X_i(t_{i-1}) =& h_i(\bar{X}_{i-1}(t_{i-1}))c_i + \bar{X}_{i-1}(t_{i-1}). \end{aligned}$$

(2.35)

where, $h_i, i = 1, 2, 3, ...n$ are 4×4 matrices and $c_i = (c_{i1}, c_{i2}, c_{i3}, c_{i4})^T$. At impulsive times $t_1, ...t_{n-1}$ we have

$$X_i(t_{i-1}) = h_i(\bar{X}_{i-1}(t_{i-1}))c_i + \bar{X}_{i-1}(t_{i-1}),$$

The cost is given by

$$\begin{aligned} J(u_1, u_2, ..., u_n) =& \frac{1}{2}[s_1 x_{n1}^2(t_n) + s_3 x_{n3}^2(t_n) + s_4 x_{n4}^2(t_n)] \\ &+ \frac{1}{2}\sum_{i=1}^{n}\int_{t_{i-1}}^{t_i}[q_1 x_{i1}^2(t) + q_3 x_{i3}^2(t) + q_4 x_{i4}^2(t) + r u_{i1}^2(t)]dt \end{aligned} \tag{2.36}$$

The adjoint system in the interval $[t_{i-1}, t_i]$ is given by

$$\dot{p_i} = p_i.f_{i,n,x_n} + \Phi_{i,x_n}$$

componentwise

$$\begin{aligned} \dot{p_{i1}}(t) =& -(a_1 - a_2 x_{i2}(1-u_{i2})p_{i1} + [\frac{a_5}{(1+x_{i1})^2}, \\ &+ a_2 x_{i2}(1-u_{i2})(1-u_{i4})]p_{i2} - a_2 x_{i2}(1-u_{i2})(1-u_{i4})p_{i3} + q_1 x_{i1}, \\ \dot{p_{i2}}(t) =& -a_2 x_{i1}(1-u_{i2})p_{i1} - [a_2 x_{i1}(1-u_{i2})(1-u_{i4}) + a_6]p_{i2}, \\ &+ a_7(1 - \frac{1}{a_8}x_{i2}(1+u_{i3}))p_{i3} + a_7(1 - \frac{x_{i2}+x_{i3}+x_{i4}}{a_8})(1+u_{i2})(1-u_{i4})p_{i4}, \\ \dot{p_{i3}}(t) =& \frac{a_7}{a_8}x_{i2}(1+u_{i3})p_{i1} - a_9 p_{i2} - a_6 p_{i3} - a_9 p_{i4} - q_3 x_{i3}, \\ \dot{p_{i4}}(t) =& a_3 a_4(1-u_{i4})p_{i1} - \frac{a_7}{a_8}x_{i2}(1+u_{i3})p_{i2} - a_9 p_{i3} - a_4 p_{i4} + q_4 x_{i4}. \end{aligned} \tag{2.37}$$

Taking $F_i = (f_{i1}, f_{i2}, f_{i3}, f_{i4})^T$ and $p_i = (p_{i1}, p_{i2}, p_{i3}, p_{i4})$ the Hamiltonian in the interval $[t_{i-1}, t_i]$ is given by

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

If $u_i = (u_{i1}, u_{i2}, u_{i3}, u_{i4})^T$is an interior point of the control u_i, then we have

$$\partial_{u_i} H_i(t, x_i(t), p_i(t), u_i(t)) = 0, \tag{2.38}$$

componentwise we have

$$\begin{aligned} \partial_{u_{i1}} H_i &= -a_3 a_4 x_{i4} + r u_{i1} = 0, \\ \partial_{u_{i2}} H_i &= a_2 x_{i1} x_{i2} p_{i1} - a_2 x_{i1} x_{i2}(1-u_{i4})p_{i3} = 0, \\ \partial_{u_{i3}} H_i &= a_7(1 - \frac{x_{i2}+x_{i3}+x_{i4}}{a_8})x_{i2} p_{i2} = 0, \\ \partial_{u_{i4}} H_i &= a_2 x_{i1} x_{i2}(1-u_{i2})p_{i2} - a_2 x_{i1} x_{i2}(1-u_{i2})p_{i3} = 0. \end{aligned}$$

2.5. NUMERICAL COMPUTATION AND SIMULATION

Let t_1 and t_2 be the time instances where the impulsive controls are applied. That is, jumps in the state occur due to these decision variables at these instances. We also have controls between between the time instances t_i and $t_{i+1},\ i = 0, 1, 2$. To facilitate computation we use different symbols for states and controls in the intervals between impulse times. Then, we have the following

1. In interval $[t_0, t_1]$, the dynamics is given by

$$\begin{aligned}
\dot{x_1}(t) &= -a_1x_1 - a_2x_1x_2(1-u_2) + a_3a_4x_4(1-u_1),\\
\dot{x_2}(t) &= \frac{a_5}{1+x_1} - a_2x_2(1-u_2)(1-u_4) - a_6x_2\\
&\quad + a_7(1-\frac{1}{a_8}(x_2+x_3+x_4))x_2(1+u_3),\\
\dot{x_3}(t) &= a_2x_1x_2(1-u_2)(1-u_4) - a_9x_3 - a_6x_3,\\
\dot{x_4}(t) &= a_9x_3 - a_4x_4,\\
x_1(t_0) &= c_{01},\\
x_2(t_0) &= c_{02},\\
x_3(t_0) &= c_{03},\\
x_4(t_0) &= c_{04}.
\end{aligned}$$

2. In the interval $[t_1, t_2]$, the dynamics is given by

$$\begin{aligned}
\dot{y_1}(t) &= -a_1y_1 - a_2y_1y_2(1-v_2) + a_3a_4y_4(1-v_1),\\
\dot{y_2}(t) &= \frac{a_5}{1+y_2} - a_2y_2(1-v_2)(1-v_4) - a_6y_2\\
&\quad + a_7(1-\frac{1}{a_8}(y_2+y_3+y_4))y_2(1+v_3),\\
\dot{y_3}(t) &= a_2y_1y_2(1-v_2)(1-v_4) - a_9y_3 - a_6y_3,\\
\dot{y_4}(t) &= a_9y_3 - a_4y_4,\\
y_1(t_1) &= b_{21} + c_{21}.x_1(t_1) + x_1(t_1),\\
y_2(t_1) &= b_{22} + c_{22}.x_2(t_1) + x_2(t_1),\\
y_3(t_1) &= b_{23} + c_{23}.x_3(t_1) + x_3(t_1),\\
y_4(t_1) &= b_{24} + c_{24}.x_4(t_1) + x_4(t_1).
\end{aligned}$$

3. In the interval $[t_2, t_3]$. The dynamics is

$$\dot{z_1}(t) = -a_1z_1 - a_2z_1z_2(1-w_2) + a_3a_4z_4(1-w_1),$$

$$
\begin{aligned}
\dot{z_2}(t) &= \frac{a_5}{1+z_1} - a_2 z_2(1-w_2)(1-w_4) - a_6 z_2 \\
&\quad + a_7(1 - \frac{1}{a_8}(z_2+z_3+z_4))z_2(1+w_3), \\
\dot{z_3}(t) &= a_2 z_1 z_2(1-w_2)(1-w_4) - a_9 z_3 - a_6 z_3, \\
\dot{z_4}(t) &= a_9 z_3 - a - 4z_4, \\
z_1(t_1) &= b_{31} + c_{31}.y_1(t_2) + y_1(t_2), \\
z_2(t_1) &= b_{32} + c_{32}.y_2(t_2) + y_2(t_2), \\
z_3(t_1) &= b_{33} + c_{33}.y_3(t_2) + y_3(t_2), \\
z_4(t_1) &= b_{34} + c_{34}.y_4(t_2) + y_4(t_2).
\end{aligned}
$$

The cost is given by

$$
\begin{aligned}
J(u_1,u_2,...,u_n) =& \frac{1}{2}[s_1 x_{n1}^2(t_n) + s_3 x_{n3}^2(t_n) + s_4 x_{n4}^2(t_n)] \\
&+ \frac{1}{2}\int_{t_0}^{t_1}[q_1 x_1^2(t) + q_3 x_3^2(t) + q_4 x_4^2(t) + r u_1^2(t)]dt \\
&+ \frac{1}{2}\int_{t_1}^{t_2}[q_1 y_1^2(t) + q_3 y_3^2(t) + q_4 y_4^2(t) + r v_1^2(t)]dt \\
&+ \frac{1}{2}\int_{t_2}^{t_3}[q_1 z_1^2(t) + q_3 z_3^2(t) + q_4 z_4^2(t) + r w_1^2(t)]dt.
\end{aligned}
$$

Let $F_3(z,w) = (f_1(z,w), f_2(z,w), f_3(z,w), f_4(z,w))^t$. The dynamics in interval $[t_2, t_3]$ is given by

$$
\begin{aligned}
f_1(z,w) &= -a_1 z_1 - a_2 z_1 z_2(1-w_2) + a_3 a_4 z_4(1-w_1), \\
f_2(z,w) &= \frac{a_5}{1+z_1} - a_2 z_2(1-w_2)(1-w_4) - a_6 z_2 \\
&\quad + a_7(1 - \frac{1}{a_8}(z_2+z_3+z_4))z_2(1+w_3), \\
f_3(z,w) &= a_2 z_1 z_2(1-w_2)(1-w_4) - a_9 z_3 - a_6 z_3, \\
f_4(z,w) &= a_9 z_3 - a_4 z_4.
\end{aligned}
$$

Let $F_2(y,v) = (f_1(y,v), f_2(y,v), f_3(y,v), f_4(y,v))^t$. The dynamics in interval $[t_1, t_2]$ is given by

$$
\begin{aligned}
f_1(y,v) &= -a_1 y_1 - a_2 y_1 y_2(1-v_2) + a_3 a_4 y_4(1-v_1), \\
f_2(y,v) &= \frac{a_5}{1+y_1} - a_2 y_2(1-v_2)(1-v_4) - a_6 y_2 \\
&\quad + a_7(1 - \frac{1}{a_8}(y_2+y_3+y_4))y_2(1+v_3),
\end{aligned}
$$

$$f_3(y,v) = a_2y_1y_2(1-v_2)(1-v_4) - a_9y_3 - a_6y_3,$$
$$f_4(y,v) = a_9y_3 - a_4y_4.$$

Let $F_1(x,u) = (f_1(x,u), f_2(x,u), f_3(x,u), f_4(x,u))^t$. The dynamics in interval $[t_1,t_2]$ is given by

$$\begin{aligned}
f_1(x,u) &= -a_1x_1 - a_2x_1x_2(1-u_2) + a_3a_4x_4(1-u_1),\\
f_2(x,u) &= \frac{a_5}{1+x_1} - a_2x_2(1-u_2)(1-u_4) - a_6x_2\\
&\quad + a_7(1 - \frac{1}{a_8}(x_2+x_3+x_4))x_2(1+u_3),\\
f_3(x,u) &= a_2x_1x_2(1-u_2)(1-u_4) - a_9x_3 - a_6x_3,\\
f_4(x,u) &= a_9x_3 - a_4x_4,
\end{aligned}$$

We now calculate the fundamental matrix solution in each interval

1. In the third interval, L_3 is determined from the following ODE.

$$\begin{aligned}
\frac{dL_3}{dt} &= F_{3,z}(z(t),w(t))L_3(t),\\
L_3(t_2) &= I,\\
t_2 &< t < t_3.
\end{aligned} \tag{2.39}$$

2. In the second interval, L_2 is determined from the following initial value problem.

$$\begin{aligned}
\frac{dL_2}{dt} &= F_{2,y}(y(t),v(t))L_2(t),\\
L_2(t_1) &= I,\\
t_1 &< t < t_2.
\end{aligned}$$

3. In the first interval L_1 is determined from the following equation.

$$\begin{aligned}
\frac{dL_1}{dt} &= F_{1,x}(x(t),u(t))L_1(t),\\
L_1(t_0) &= I,\\
t_0 &< t < t_1.
\end{aligned} \tag{2.40}$$

1. In interval $[t_2,t_3]$ let Q_3 be defined by

$$Q_3 = diag(c_{31}+1, c_{32}+1, c_{33}+1, c_{34}+1).$$

2. In interval $[t_1,t_2]$ let Q_2 be defined by

$$Q_2 = diag(c_{21}+1, c_{22}+1, c_{23}+1, c_{24}+1).$$

The γ's we defined for the terminal values of the costates/adjoints are given by

1. $\gamma_3 = (s_1 z_1(t_3), 0, s_3 z_3(t_3), s_4 z_4(t_3))$,
2. $\gamma_2 = \int_{t_1}^{t_2} (q_1 y_1(s), 0, q_3 y_3(s), q_4 y_4(s)) L_3(s) Q_3 ds + \gamma_3 L_3(t_3) Q_3$,
3. $\gamma_1 = \int_{t_1}^{t_2} (q_1 x_1(s), 0, q_3 x_3(s), q_4 x_4(s)) L_2(s) Q_2 ds + \gamma_2 L_2(t_2) Q_2$.

We now are in a position to write the adjoint equation in each interval. Then, we will formulate the Hamiltonian.

The adjoint variable $p_3 = (p_{31}, p_{32}, p_{33}, p_{34})$ in the interval $[t_2, t_3]$ is governed by the system of equations

$$\begin{aligned}
\dot{p}_{31}(t) =& -(a_1 + a_2 z_2(1-w_2))p_{31} + [\frac{a_5}{(1+z_1)^2} \\
&+ a_2 z_2(1-w_2)(1-w_4)]p_{32} - a_2 z_2(1-w_2)(1-w_4)p_{33} + q_1 z_1, \\
\dot{p}_{32}(t) =& -a_2 z_1(1-w_2)p_{31} - [a_2 z_1(1-w_2)(1-w_4) \\
&+ a_6]p_{32} + a_7(1 - \frac{1}{a_8} z_2(1+w_3))p_{33}(t) \\
&+ a_7(1 - \frac{z_2+z_3+z_4}{a_8})(1+w_2)(1-w_4) + p_{34}, \\
\dot{p}_{33}(t) =& \frac{a_7}{a_8} z_2(1+w_3)p_{31} - a_9 p_{32} - a_6 p_{33} - a_9 p_{34} - q_3 z_3, \\
\dot{p}_{34}(t) =& a_3 a_4(1-w_4)p_{31} - \frac{a_7}{a_8} z_2(1+w_3)p_{32} - a_9 p_{33} - a_4 p_{34} + q_4 z_4, \\
p_3(t_3) =& \gamma_3.
\end{aligned}$$

In the interval $[t_1, t_2]$ the adjoint $p_2 = (p_{21}, p_{22}, p_{23}, p_{24})$ is governed by

$$\begin{aligned}
\dot{p}_{21}(t) =& -(a_1 + a_2 y_2(1-v_2))p_{21} + [\frac{a_5}{(1+y_1)^2} \\
&+ a_2 y_2(1-v_2)(1-v_4)]p_{22} - a_2 y_2(1-v_2)(1-v_4)p_{23} + q_1 y_1, \\
\dot{p}_{22}(t) =& -a_2 y_1(1-v_2)p_{21} - [a_2 y_1(1-v_2)(1-v_4) + a_6]p_{22} \\
&+ a_7(1 - \frac{1}{a_8} y_2(1+v_3))p_{23}(t) + a_7(1 - \frac{y_2+y_3+y_4}{a_8})(1+v_2)(1-v_4)p_{24}, \\
\dot{p}_{23}(t) =& \frac{a_7}{a_8} y_2(1+v_3)p_{21} - a_9 p_{22} - a_6 p_{23} - a_9 p_{24} - q_3 y_3, \\
\dot{p}_{24}(t) =& a_3 a_4(1-v_4)p_{21} - \frac{a_7}{a_8} y_2(1+v_3)p_{22} - a_9 p_{23} - a_4 p_{24} + q_4 y_4, \\
p_2(t_3) =& \gamma_2.
\end{aligned}$$

In the interval $[t_0, t_1]$ the adjoint $p_1 = (p_{11}, p_{12}, p_{13}, p_{14})$ is governed by

$$\begin{aligned}
\dot{p}_{11}(t) =& -(a_1 + a_2 x_2(1-u_2))p_{11} + [\frac{a_5}{(1+x_1)^2} \\
&+ a_2 x_2(1-u_2)(1-u_4)]p_{12} - a_2 x_2(1-u_2)(1-u_4)p_{13} + q_1 x_1,
\end{aligned}$$

$$\begin{aligned}
\dot{p}_{12}(t) =& - a_2x_1(1-u_2)p_{11} - [a_2x_1(1-u_2)(1-u_4) \\
&+ a_6]p_{12} + a_7(1 - \frac{1}{a_8}x_2(1+u_3))p_{13}(t) \\
&+ a_7(1 - \frac{x_2+x_3+x_4}{a_8})(1+u_2)(1-u_4)p_{14}, \\
\dot{p}_{13}(t) =& \frac{a_7}{a_8}x_2(1+u_3)p_{11} - a_9p_{12} - a_6p_{13} - a_9p_{14} - q_3x_3, \\
\dot{p}_{14}(t) =& a_3a_4(1-u_4)p_{11} - \frac{a_7}{a_8}x_2(1+u_3)p_{12} - a_9p_{13} - a_4p_{14} + q_4x_4, \\
p_1(t_3) =& \gamma_1.
\end{aligned}$$

Let H_3, H_2, and H_1 be the Hamiltonian in the interval 3, 2, and 1.

1. In the interval $[t_2, t_3]$

$$H_3(t, z(t), p_3, w) \geq H_3(t, z(t), p_3(t), \bar{w}), \quad a.e, \quad \forall w \in U_3.$$

2. In the interval $[t_1, t_2]$

$$H_2(t, y(t), p_2, v) \geq H_2(t, y(t), p_2(t), \bar{v}), a.e, \ \forall v \in U_2.$$

3. In the interval $[t_0, t_1]$

$$H_1(t, x(t), p_1, u) \geq H_1(t, x(t), p_1(t), \bar{u}), \quad a.e, \ \forall u \in U_1.$$

The numerical simulation we are going to do is based on the state equations, the adjoint equations, and the Hamiltonians. We use steepest descent method to optimize.

We follow the following procedure for numerical simulation. We start in the third interval.

1. Use H_3, the Hamiltonian in the third interval, to update the control w in third interval.

2. Using the improved control we update the state and adjoint variable $p^{(3)}$ in the interval.

   Second interval

3. Use H_2, the Hamiltonian in the second interval, to update the control v in second interval.

4. We use the improved control in the second interval to update the states in the second and third interval.

   First interval

5. Use Hamiltonian H_1 to update the control u in the first interval.
6. Using the improved control we update the states in the first second and third intervals.

The following is a pseudo code for our numerical simulation.

```
BEGIN psuedocode
Third interval:

Use Hamiltonian to improve control.
Using improved control update state and adjoint variables
 in the third interval.


Second interval:

Improve control in the second interval.
Update adjoint variable in the second interval
and state variables both in the second and third intervals.


First interval:

Improve control in the interval.
update adjoint in the interval, and state in all intervals.

END psuedocode
```

The parameters in the cost are given to be

$$s_1 = s_3 = s_4 = q_1 = q_3 = q_4 = 10^3, r = 0.01.$$

The initial cell counts are

$$\begin{aligned} x_1(t_0) &= 0.049, \\ x_2(t_0) &= 904, \\ x_3(t_0) &= 0.034, \\ x_4(t_0) &= 0.042. \end{aligned}$$

Table 2

Parameter	Values
a_1 death rate of free virus.	$2.5d^{-1}$
a_2 rate CD4+T cells become infected with virus.	$2.4 \times 10^{-5} mm^3 d^{-1}$
a_3 number of free virus produced by actively infected CD4+T cells.	1200
a_4 death rate of actively infected CD4+T cell population.	$0.24d^{-1}$
a_5 source term of uninfected CD4+T cells.	$10d^{-1}mm^{-}3$
a_6 death rate of infected (latently infected) CD4+T cell population.	$0.02d^{-1}$
a_7 growth rate of CD4+T cell population.	$0.02d^{-1}$
a_8 maximum population level of CD4+T cells.	$1500mm^{-3}$
a_9 rate of latently infected cells becoming active.	$3x10^{-3}d^{-1}$

Values of parameters are given to be

$$
\begin{aligned}
b_{21} = b_{22} = b_{23} = b_{24} = 0.002,\\
b_{31} = b_{32} = b_{33} = b_{34} = 0.02,\\
c_{21} = c_{22} = c_{32} = c_{42} = -0.95,\\
c_{31} = c_{32} = c_{33} = c_{34} = -0.95.
\end{aligned}
$$

Table 3

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

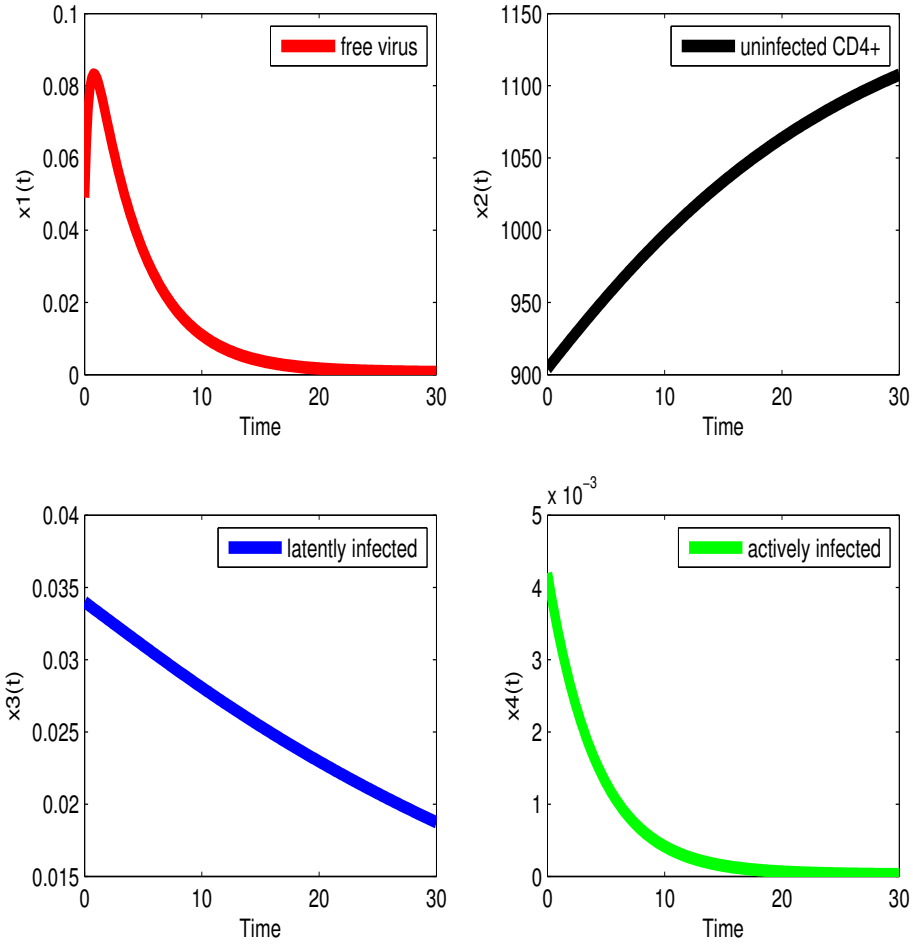

Figure 2: Cell count for the first interval

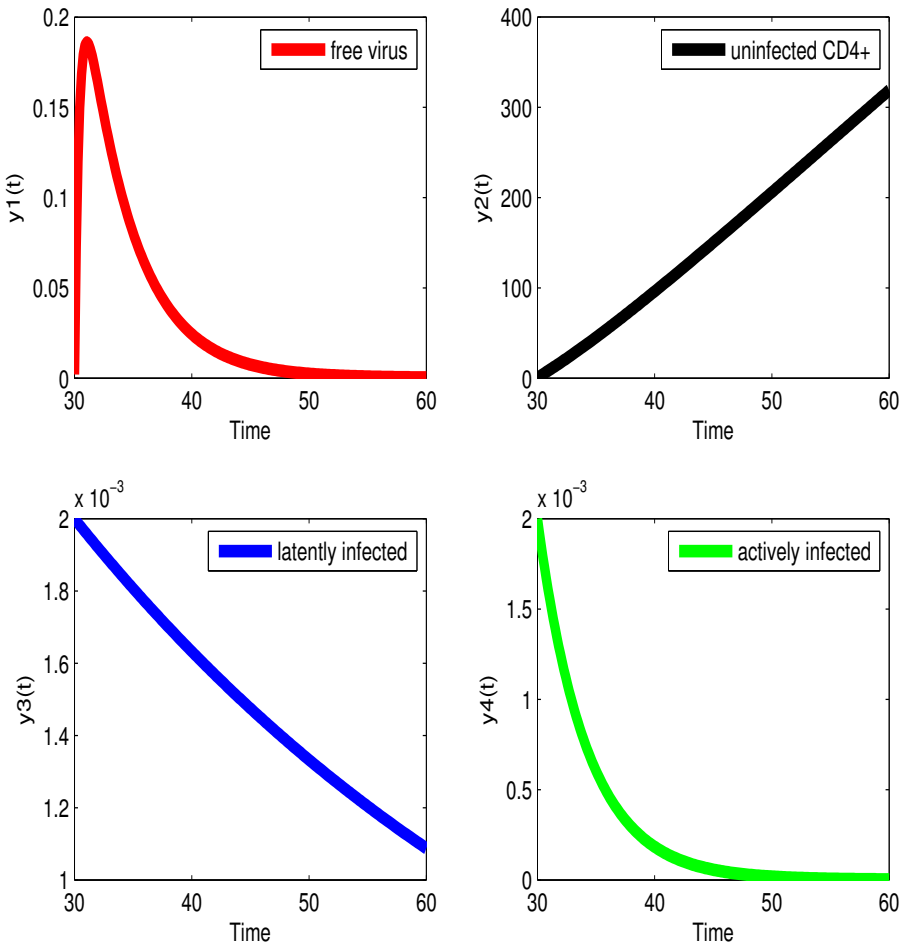

Figure 3: Cell count for the second interval

2.5.1. CONCLUSIONS

1. We need no protease inhibitor in the first two intervals and small amount in the last. Because we started medication early there are no much viruses ready to attack.

2. We need the maximum amount of fusion inhibitor in each interval. The first thing a virus does after entering a human body is look for (CD4 +T) cell and fuse itself. To stop that we need to medicate the patient by fusion inhibitor as soon as we can.

3. Since there are good number of healthy cells and the natural production of healthy cells is more at the the early stage of infection we only need a small

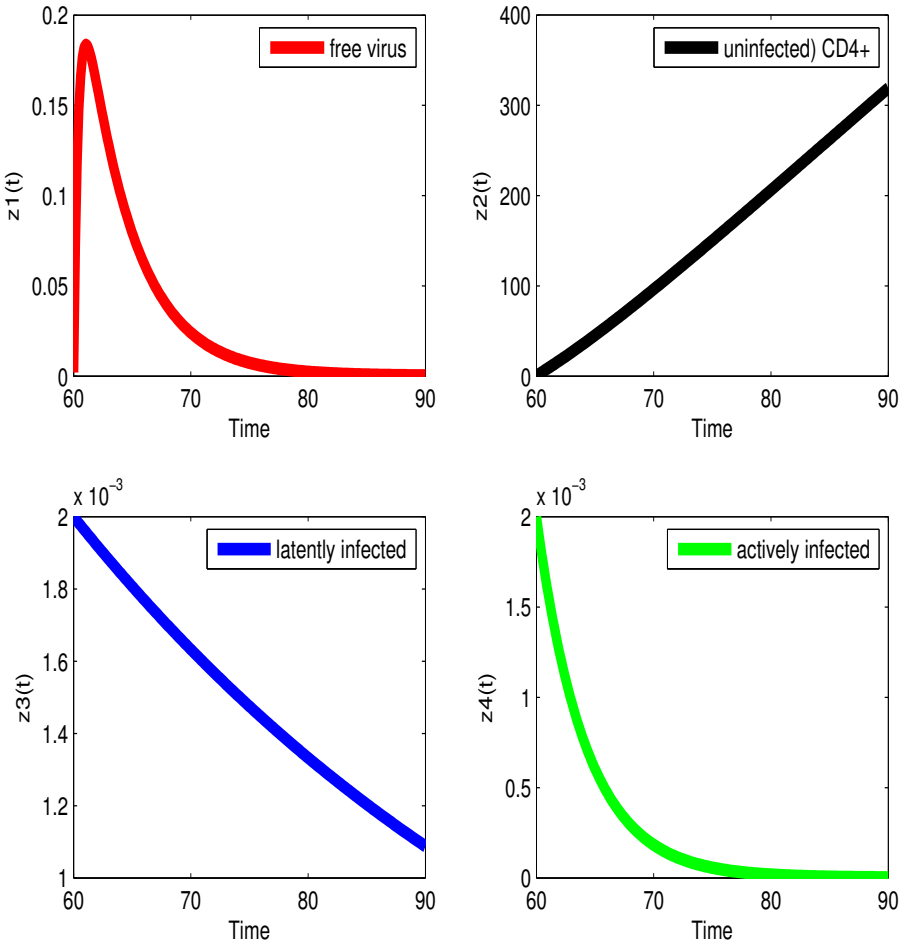

Figure 4: Cell count for the third interval

amount of medication to help generation of the healthy cells. Once we have acceptable number we can decrease the medication.

4. It is very important that we should apply reverse transcription inhibitor at the early stage of infection. Because if one virus is successful to clone itself to the CTLes cell, then the virus makes the CTLes cell to duplicate about a thousand viruses before the CTLes cell dies.

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