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# Optimal Impulse Control of Systems with Control Constraints and Application to HIV Treatment

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***Abstract:*** In this paper, conditions for optimal impulse control of an impulsive system with constraints on control are derived. These hold for a system whose states can be changed instantaneously at discrete times with impulses while a continuous control is being applied between those times. The conditions derived are applied to the problem of optimal HIV treatment. Simulation results are presented to show the treatment procedure. The results obtained show that the intervention method developed leads to good results.

## 1. Introduction:

Control of many a practical problem requires that the control or inputs be given in impulses. Controlling a pest problem in a region by releasing predators, treatment of diseases by giving medicines, controlling the amount of money in a market by changing the interest rates are some examples of impulsive control applied to systems. Impulsive control has also been successfully used to get the optimal fuel consumption law in aerospace applications [4] and obtain an efficient method to control a biped [2]. Impulsive control applied to financial systems optimizes cash management [12]. Further details on impulse control of chaotic systems can be found in [13].

Treatments of most diseases involve consumption of medicines which can be modeled as an impulsive control process. In this paper, impulsive control is used to obtain an optimal treatment regime for Acquired Immune Deficiency Syndrome. The conditions for the optimal control of a system with control constraints are derived first and these conditions are applied to a model of Human Immunodeficiency Virus (HIV) to obtain a treatment regimen. Also unlike previous results on HIV control, this paper tried to incorporate the drug delivery mechanism by modeling it as exponential decay process.

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This paper is organized as follows. In section 2, an impulsive system is presented and a quadratic cost function is developed which is to be minimized to calculate optimal control.

The conditions for optimal impulse control are derived in section 3. Section 4 describes the model of HIV used in this study on which the proposed optimal control technique is applied. Simulation results are presented in section 5. The paper is summarized and its contributions are listed in section 6.

## 2. Impulsive System Model and Cost Function:

An impulsive system can be represented as,

$$\dot{x}_i = f(x_i, u_i) + h(x_i)v \qquad (2.1)$$

in the time interval $(t_{i-1}^+, t_i^-)$

where, $x_i$ is the state of the system $x_i \in R^n$, $u_i$ is the continuous control that is applied to the system, $t_i$ s are the instances at which impulse is applied and $v$ is the impulse control. 'f' and 'h' are continuous and differential functions (class $C^1$) for $x \in R^n, t \in [t_0, t_f]$. It is represented as

$$v = \sum_{t=t_0}^{t_f} c_i \delta(t - t_i) \qquad (2.2)$$

where $\delta(t - t_i)$ is the delta function. When the impulses are applied i.e. at $t_i$ (the control instants), one or more states of the system change according to the equation,

$$x_{i+1}(t_i^+) = x_i(t_i^-) + h(x_i(t_i^-))c_i \qquad (2.3)$$

where $c_i$ is the amount of impulsive control given and $u_i$ is the continuous control. Here $x_{i+1}(t_i^+)$ is the state vector after the impulse is applied and $x_i(t_i^-)$ is the state vector just before the impulse is applied. In most of the cases, the amount of control that can be administered is constrained.

The cost function is inspired from [8]. An additional control term is added to the cost function to account for the cost associated with giving the impulse. It is assumed that the cost associated with impulse control is a function of the magnitude of control only. This is true because all the states are penalized by the cost function.

$$J = \Phi(x_f) + \sum_{i=1}^{k} L_2(c_i) + \sum_{i=1}^{k+1} \int_{t_{i-1}^{+}}^{t_i^{-}} L(x_i, u_i)dt \qquad (2.4)$$

where $\Phi(x_f)$ is the cost on the final state, $i = 1, 2, \cdots, k$ are the instances when control applied. $\sum_{i=1}^{k} L_2(c_i)$ is the cost associated with the impulse control and $\sum_{i=1}^{k+1} \int_{t_{i-1}^{+}}^{t_i^{-}} L(x_i, u_i)dt$ is the cost on states and the continuous control being applied between the impulses.

It must be noted that since $L(x_i, u_i)$ is bounded,

$\int_{t_{i-1}}^{t_{i-1}^{+}} L(x_i, u_i)dt = 0$ and $\int_{t_i^{-}}^{t_i} L(x_i, u_i)dt = 0$.

**3. Derivation of conditions for impulse control:**

Optimal control law is derived for the system where the states of the system are changed by applying an impulse. We assume that there are constraints on state and control values. The constraints can be written as $C(x_i(t_i^{-}), c_i) \le 0$ where $x_i(t_i^{-})$ is the state vector just before the impulse at time $t_i$ and $c_i$ is the amount of the impulse given. The state vector before the control instant is chosen because the amount of control can be adjusted according to the state before the instant. The constraint can also be written as a function of states after the instant, but in that case, the computation of control will be difficult if the control instants are not known and are to be computed.

The problem is to achieve a desired state $x_f$ by using minimum amount of control $c_i$ with the constraint on the control given by $C(x_i(t_i^{-}), c_i)$. The constraint is introduced into the cost function by introducing a multiplier. The cost function equation is,

$$J = \Phi(x_f) + \sum_{i=1}^{k} L_2(c_i) + \sum_{i=1}^{k+1} \int_{t_{i-1}^{+}}^{t_i^{-}} L(x_i, u_i)dt + \sum_{i=1}^{k} \mu^T C(x_i(t_i^{-}), c_i) \quad (3.1)$$

where

$\mu = 0$ if $C < 0$

$\mu \ge 0$ if $C = 0$. The constraint can be violated only by increasing the value of the cost function.

The control has to minimize the cost function while satisfying the differential equations. Introducing the differential equations into the cost function by multipliers $\lambda_i$. The cost function becomes,

$$J = \Phi(x_f) + \sum_{i=1}^{k} L_2(c_i) + \sum_{i=1}^{k+1} \int_{t_{i-1}^{+}}^{t_i^{-}} L(x_i, u_i) + \lambda^T (f(x_i, u_i) - \dot{x}_i)dt + \sum_{i=1}^{k} \mu^T C(x_i(t_i^{-}), c_i) \qquad (3.2)$$

It must be noted that $\lambda_i$ is time varying and the index I is used to indicate that it belongs to $(t_{i-1}^{+}, t_i^{-})$.

Defining a scalar function $H(x_i, u_i)$ the Hamiltonian as $L(x_i, u_i) + \lambda_i^T f(x_i, u_i)$,

$$J = \Phi(x_f) + \sum_{i=1}^{k} L_2(c_i) + \sum_{i=1}^{k+1} \int_{t_{i-1}^{+}}^{t_i^{-}} (H(x_i, u_i) - \lambda_i^T \dot{x}_i)dt + \sum_{i=1}^{k} \mu^T C(x_i(t_i^{-}), c_i) \qquad (3.3)$$

Considering the variation in $J$ due to variations in $c_i$, $x_i$, $u_i$, $x_f$ and $t_i$ to obtain

$$\delta J = \frac{\partial \Phi(x_f)}{\partial x_f}\delta x_f + \sum_{i=1}^{k} \frac{\partial L_2(c_i)}{\partial c_i}\delta c_i + \sum_{i=1}^{k+1} \delta \int_{t_{i-1}^{+}}^{t_i^{-}} (H(x_i, u_i) - \lambda_i^T \dot{x}_i)dt$$
$$+ \sum_{i=1}^{k+1} (H(x_i, u_i) - \lambda_i^T \dot{x}_i)\delta t_i + \sum_{i=1}^{k+1} (H(x_i, u_i) - \lambda_i^T \dot{x}_i)\delta t_{i-1}$$
$$+ \sum_{i=1}^{k} \mu^T \left( \frac{\partial C}{\partial x_i}\delta x_i(t_i^{-}) + \frac{\partial C}{\partial c_i}\delta c_i \right) \qquad (3.4)$$

Applying integration by parts to the third term and regrouping to get,

$$\delta J = \left( \frac{\partial \Phi(x_f)}{\partial x_f} - \lambda_f^T \right)\delta x_f + \sum_{i=1}^{k} \frac{\partial L_2(c_i)}{\partial c_i}\delta c_i + \sum_{i=1}^{k} \mu^T \left( \frac{\partial C}{\partial x_i}\delta x_i(t_i^{-}) + \frac{\partial C}{\partial c_i}\delta c_i \right)$$
$$+ \sum_{i=1}^{k} (H(x_i(t_i^{-}), u_i(t_i^{-})) - H(x_{i+1}(t_i^{+}), u_{i+1}(t_i^{+})))\delta t_i - \sum_{i=1}^{k} [\lambda_i^T \delta x_i(t_i^{-}) - \lambda_{i+1}^T \delta x_{i+1}(t_i^{+})]$$
$$+ H(x_f(t_f^{-}), u(t_f^{-}))\delta t_f + \sum_{i=1}^{k+1} \int_{t_{i-1}^{+}}^{t_i^{-}} \left( (\frac{\partial H(x_i, u_i)}{\partial x_i} + \dot{\lambda}_i^T)\delta x_i + \frac{\partial H(x_i, u_i)}{\partial u_i}\delta u_i \right) dt \qquad (3.5)$$

When the impulse is applied, the first variation relation is given as,

$$\delta x_{i+1}(t_i^{+}) = \delta x_i(t_i^{-}) + \frac{\partial h(x_i(t_i^{-}))}{\partial x_i} c_i \delta x_i(t_i^{-}) + h(x_i(t_i^{-}))\delta c_i \qquad (3.6)$$

Substituting (3.6) in (3.5),

$$\delta J = \left( \frac{\partial \Phi(x_f)}{\partial x_f} - \lambda_f^T \right)\delta x_f + \sum_{i=1}^{k} \frac{\partial L_2(c_i)}{\partial c_i}\delta c_i + \sum_{i=1}^{k} \mu^T \left( \frac{\partial C}{\partial x_i}\delta x_i(t_i^{-}) + \frac{\partial C}{\partial c_i}\delta c_i \right)$$
$$+ \sum_{i=1}^{k+1} (H(x_i(t_i^{-}), u_i(t_i^{-})) - H(x_{i+1}(t_i^{+}), u_{i+1}(t_i^{+})))\delta t_i + H(x_f(t_f^{-}))\delta t_f$$
$$- \sum_{i=1}^{k} \left[ \lambda_i^T \delta x_i(t_i^{-}) - \lambda_{i+1}^T \left( \delta x_i(t_i^{-}) + \frac{\partial h(x_i(t_i^{-}))}{\partial x_i} c_i \delta x_i(t_i^{-}) + h(x_i(t_i^{-}))\delta c_i \right) \right]$$
$$+ \sum_{i=1}^{k+1} \int_{t_{i-1}^{+}}^{t_i^{-}} \left( (\frac{\partial H(x_i, u_i)}{\partial x_i} + \dot{\lambda}_i^T)\delta x_i + \frac{\partial H(x_i, u_i)}{\partial u_i}\delta u_i \right) dt \qquad (3.7)$$

Regrouping the terms and knowing that the function $h(x_i(t_i)$ is differentiable and continuous,

$$\delta J=\left(\frac{\partial\Phi(x_f)}{\partial x_f}-\lambda_f^T\right)\delta x_f+\sum_{i=1}^{k}\frac{\partial L_2(c_i)}{\partial c_i}\delta c_i+\sum_{i=1}^{k}\mu^T\left(\frac{\partial C}{\partial x_i}\delta x_i(t_i^-)+\frac{\partial C}{\partial c_i}\delta c_i\right)$$
$$+\sum_{i=1}^{k+1}(H(x_i(t_i^-),u_i(t_i^-))-H(x_{i+1}(t_i^+),u_{i+1}(t_i^+)))\delta t_i \qquad (3.8)$$
$$+H(x_f(t_f^-))\delta t_f+\sum_{i=1}^{k+1}\int_{t_{i-1}^+}^{t_i^-}\left((\frac{\partial H(x_i,u_i)}{\partial x_i}+\dot{\lambda}_i^T)\delta x_i+\frac{\partial H(x_i,u_i)}{\partial u_i}\delta u_i\right)dt$$
$$-\sum_{i=1}^{k}\left[\lambda_i^T\delta x_i(t_i^-)-\lambda_{i+1}^T\left(\delta x_i(t_i^-)+\frac{\partial h(x_i(t_i^-))}{\partial x_i}c_i\delta x_i(t_i^-)+h(x_i(t_i^-))\delta c_i\right)\right]$$

Knowing that $\delta x_0=0$, and taking $H(x_f(t_f^-))$ and $H(x_0)$ out from the fourth term,

$$\delta J=\left(\frac{\partial\Phi(x_f)}{\partial x_f}-\lambda_f^T\right)\delta x_f+\sum_{i=1}^{k}\left(\frac{\partial L_2(c_i)}{\partial c_i}+\lambda_{i+1}^T h(x_i(t_i)+\mu^T\frac{\partial C}{\partial c_i}\right)\delta c_i$$
$$+\sum_{i=1}^{k+1}\int_{t_{i-1}^+}^{t_i^-}\left((\frac{\partial H(x_i)}{\partial x_i}+\dot{\lambda}_i^T)\delta x_i+\frac{\partial H(x_i,u_i)}{\partial u_i}\delta u_i\right)dt+H(x_f(t_f^-))\delta t_f$$
$$-\sum_{i=1}^{k}\left[\lambda_i^T-\lambda_{i+1}^T\left(I+\frac{\partial h(x_i(t_i^-))}{\partial x_i}c_i)\right)+\mu^T\frac{\partial C}{\partial x_i}\right]\delta x_i(t_i)$$
$$+\sum_{i=1}^{k+1}(H(x_i(t_i^-),u_i(t_i^-))-H(x_{i+1}(t_i^+),u_{i+1}(t_i^+)))\delta t_i \qquad (3.9)$$

Thus the conditions for optimal control obtained by setting the coefficients of each of the terms equal to zero.

Between the impulses $(t_{i-1}^+,t_i^-)$,

$$\left(\frac{\partial H(x_i,u_i)}{\partial x_i}+\dot{\lambda}_i^T\right)=0 \qquad (3.10)$$

$$\frac{\partial H(x_i,u_i)}{\partial u_i}=0 \qquad (3.11)$$

The final state constraint is,

$$\left(\frac{\partial\Phi(x_f)}{\partial x_f}-\lambda_f^T\right)=0 \qquad (3.12)$$

$H(x_f(t_f^-))=0$ if final time is not fixed.

At the time when impulse is applied,

$$\left(\frac{\partial L_2(c_i)}{\partial c_i}+\lambda_{i+1}^T h(x_i(t_i))+\mu^T\frac{\partial C}{\partial c_i}\right)=0, \qquad (3.13)$$

where $C<0,\mu=0$ and $C=0,\mu\geq 0$.

$H(x_i(t_i^-))-H(x_{i+1}(t_i^+))=0$

and $\lambda_i^T-\lambda_{i+1}^T\left(I+\frac{\partial h(x_i(t_i^-))}{\partial x_i}c_i)\right)+\mu^T\frac{\partial C}{\partial x_i}=0$, (3.14)

where $C<0,\mu=0$ and $C=0,\mu\geq 0$.

## 4. Application to HIV model:

To show an application of the optimal control method presented above, the problem of HIV treatment is considered. Different costs have been used and applied to develop optimal ways of HIV treatment [6],[7],[11]. All the studies so far have considered treatment processes with continuous control. Since the actual treatment procedure is impulsive in nature, application of the optimal impulse control formulation developed herein seems natural to obtain a better understanding of this problem

When a person is infected by HIV, the immune system of the body deteriorates. The HIV disables the T-helper cells (CD4+T). When a person is infected by the virus, these T-helper cells identify the infection and alert other defense mechanisms in the body of the infection. The CD4+T cell count keeps reducing in a person infected by HIV. When the cell count is not high enough to alert other immune mechanisms, the person develops symptoms of HIV. The CD4+T cells that are infected and carry virus are attacked by the CTLe (Cytotoxic T-Lymphocytes effectors). The CTLes are deployed by the CTLps (Cytotoxic T-Lymphocytes precursors). CTLps act as memory of the disease i.e. in an event of attack in future, the CTLps are converted to CTLes which go and kill the cells infected by the virus. More details on HIV can be found in [10]. This process of killing of virus and generation of the CTLps and CTLes, causes the number of healthy CD4+T cells, number of unhealthy CD4+T cells, number of CTLps and number of CTLes to reach a steady value.

There are three such steady points or equilibrium points. One equilibrium point is of a healthy person where the number of unhealthy CD4+T cells, number of CTLps and number of CTLes is zero. The other two equilibrium points correspond to a person affected by the virus. One of these equilibrium points has high unhealthy CD4+T count and low healthy CD4+T and low CTLp count. The other unhealthy equilibrium point has low virus count low and the healthy cell count and high CTLp count. Treatment is given to take the body to the last equilibrium point. The stability analysis of the equilibrium points can be found in [5]. An analysis on controllability of the HIV infection can be found in [9].

## 5. Model:

In this study, the model from [14] is used for analysis and treatment. This model is selected to show that the impulsive control concepts developed in the paper can be applied to control a system with impulsive inputs. The model though simple, serves the purpose of demonstrating the effectiveness of the scheme developed here. It is important to note that the control method can be applied to a more complex model in a similar manner. Many other models have been suggested. In [7], a ten state model was presented. The additional six states represent the mutation of the HIV virus as the treatment is given. The thrust here

is the nature of control and not direct transfer to the clinical treatment (at least at this point).

The equations governing the growth of HIV are

$$\begin{aligned}\dot{x} &= \lambda - dx - \eta\ \beta xy \\ \dot{y} &= \eta\ \beta xy - ay - pyz \\ \dot{w} &= cxyw - cqyw - bw \\ \dot{z} &= cqyw - hz\end{aligned} \tag{5.1}$$

where,

x = number of healthy CD4+T cells
y = number of unhealthy CD4+T cells
w = number of CTLp (memory cells)
z = number of CTLe

The value of $\eta$ represents the efficiency of the drug. This value can be chosen by using an appropriate combination of drugs and by choosing the appropriate quantity of the drug. It is assumed that all possible drug efficiencies can be achieved. Note that $0 \le \eta \le 1$. A combination of different drugs in different quantities is used to obtain different drug efficiencies.

The drug efficiency term $\eta$ can be written as $(1-\eta^* u)$ [5] where u is related to the amount of medicine that is delivered to the patient. Different value of drug efficiency can be obtained by using different combinations of medicines. From now onwards, treatment of HIV will be referred as control of HIV. Note that in the model considered eq (5.1) only the amount of medicine can be changed instantaneously. The medicine changes the efficiency of the drug. The change in efficiency of the drug changes the dynamics of the reaction governing the generation of unhealthy cells and death of healthy cells.

Impulse control is achieved by changing one or more states of the system at an instant. Different examples of the use of impulse control to control a system can be found in [2],[4],[12]. As the control of HIV (treatment) involves instantaneous change in 'u', 'u' is introduced into the control equation as a state of the system. The consumption rate of the medicine by the body is taken to be proportional to the amount of the medicine remaining in the body. An exponential decay is considered because of the simplicity of the equations (although by no means confining). A more elaborate description on the drug delivery can be obtained in [3].

Thus the additional equation introduced in the system equation eq (5.1) becomes,

$$\dot{u} = -u \tag{5.2}$$

The decay constant is chosen as 1. The efficiency of the drug can be described as $\eta = (1-\eta^* u)$. Another term 'v' is introduced into the equations. 'v' is the impulse control term. It gives the amount of drug delivered. 'v' can be written as (from 2.2),

$$v = \sum_{t=t_0}^{t_f} c_i \delta(t - t_i) \tag{5.3}$$

where $c_i$ is the amount of medicine given and $t_i$ is the instant at which the medicine is given.

Rewriting the equations by including 'v' and $\eta$ terms for the dynamics of the healthy cells with the impulse control term it can be seen that,

$$\begin{aligned}\dot{x}_i &= f(x_i) \\ x_{i+1} &= x_i + h(x_i) v_i\end{aligned} \tag{5.4}$$

where,

$$f(x) = \begin{bmatrix} \lambda - dx - (1-\eta^* u)\beta xy \\ (1-\eta^* u)\beta xy - ay - pyz \\ cxyw - cqyw - bw \\ cqyw - hz \\ -u \end{bmatrix}; \tag{5.5}$$

$$h(x) = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 \end{bmatrix}^T; \tag{5.6}$$

Note that the f(x) term has 'u' (the medicine) as a state and since there is no continuous control being applied to the system, f is only function of states.

In [6], the control affected the dynamics of the cells involved in the HIV problem by changing the parameter $\beta$ and the relation between $\beta$ and the control was exponential. A quadratic cost function was set up and optimal control was obtained. Different models were suggested for HIV problem. It was assumed that a continuous control was being applied during the time of treatment. To reduce the complexity of the math involved and to make the solution process numerically less demanding, a quadratic cost function is considered in this study.

The cost function chosen in this work is,

$$J = \sum_{i=1}^{k} \frac{Rc_i^2}{2} + S_x \frac{(x-x_f)^2}{2} + S_y \frac{(y-y_f)^2}{2} + S_w \frac{(w-w_f)^2}{2} + S_z \frac{(z-z_f)^2}{2} \tag{5.7}$$

The term R represents the cost associated with the intake of the drug. Concerns regarding the cost of the drug and the dosage can be expressed through R.

Final state values in the final state constraints are chosen as the values of the states at which if the system is left without further medication will go to the desired equilibrium point. The desired equilibrium point has high healthy cell count and low unhealthy cell count.

As stated earlier, the amount of dosage that can be given is a constraint. And it can be stated as

$$\begin{bmatrix} u + c_i - 1 \\ -c_i \end{bmatrix} < 0; \tag{5.8}$$

The first constraint states that effectiveness of the administered drug cannot be greater than 1 i.e. the sum of the efficiency of the drug already present in the body and the drug given to the body cannot exceed 1. Also the efficiency of the drug cannot be made negative.

We introduce the constraint term in the cost function by means of a multiplier $\mu$ the cost function thus becomes,

$$J=\sum_{i=1}^{k}\frac{Rc_i^2}{2}+S_x\frac{(x-x_f)^2}{2}+S_y\frac{(y-y_f)^2}{2}+S_w\frac{(w-w_f)^2}{2}+S_z\frac{(z-z_f)^2}{2} \quad (5.9)$$
$$+\mu_1(-c_i)+\mu_2(u+c_i-1)$$

After applying the optimal laws derived earlier (3.10 to 3.14),

If $c_i \geq 0$ and $u_i(t_i^-)+c_i \leq 1$,

we have $\mu_1 = 0; \mu_2 = 0$;

The control is obtained as follows,

$c_i = -R^{-1}h(x_i(t_i^-))\lambda_{i+1}^T$

i.e.

$$c_i = -R^{-1}\lambda_{5,i+1}(t_i^+) \quad (5.10)$$

The co-state changes at these jumps are given by

$$\lambda_{i+1}=\left(I+\frac{\partial h(x_i(t_i^-))}{\partial x_i}c_i\right)^{-T}\lambda_i$$

i.e.

$$\lambda_{1,i+1}=\lambda_{1,i}\ \ \lambda_{2,i+1}=\lambda_{2,i}\ \lambda_{3,i+1}=\lambda_{3,i}\ \lambda_{4,i+1}=\lambda_{4,i}$$
$$\lambda_{5,i+1}=\lambda_{5,i} \quad (5.11)$$

If $c_i \leq 0$ ,the control is obtained as,

$$\left(\frac{\partial L_2(c_i)}{\partial c_i}+\lambda_{i+1}^T h(x_i(t_i)+\mu^T\frac{\partial C}{\partial c_i}\right)=0 \text{ with } C=0;$$

we thus get,

$c_i = 0$

$$\mu_1 = -\lambda_{5,i+1}(t_i^+) \quad (5.12)$$

and the equations for co-state are

$$\lambda_i^T-\lambda_{i+1}^T\left(I+\frac{\partial h(x_i(t_i^-))}{\partial x_i}c_i)\right)+\mu^T\frac{\partial C}{\partial x_i}=0;$$

i.e.

$$\lambda_{1,i+1}=\lambda_{1,i}\ \ \lambda_{2,i+1}=\lambda_{2,i}\ \lambda_{3,i+1}=\lambda_{3,i}\ \lambda_{4,i+1}=\lambda_{4,i}$$
$$\lambda_{5,i+1}=\lambda_{5,i} \quad (5.13)$$

If $u_i(t_i^-)+c_i \geq 1$, we have $\mu_1 = 0;$(note that this constraint can hold only if $c_i \geq 0$ )

The optimal control is given by

$c_i = 1-u_i(t_i^-)$;

$$\mu_2 = -R(1-u_i(t_i^-))-\lambda_{5,i+1}(t_i^+) \quad (5.14)$$

The co-state equations are given by,

$$\lambda_i^T-\lambda_{i+1}^T\left(I+\frac{\partial h(x_i(t_i^-))}{\partial x_i}c_i)\right)+\mu^T\frac{\partial C}{\partial x_i}\delta(t-t_i)=0$$

i.e.

$$\lambda_{1,i+1}=\lambda_{1,i}\ \ \lambda_{2,i+1}=\lambda_{2,i}\ \lambda_{3,i+1}=\lambda_{3,i}\ \lambda_{4,i+1}=\lambda_{4,i}$$
$$\lambda_{5,i+1}=\lambda_{5,i}+\mu_2 \quad (5.15)$$

The numerical results obtained after applying the above conditions and computing the optimal control are presented in the next section.

## 6. Simulation results:

A code in MATLAB was written to simulate the growth of the number of cells in the body. The values of the number of cells taken are normalized values. The parameters take the values $\lambda=1$, $d=.1$, $a=.2$, $\beta=.5$, $p=1$, $b=.01$, $h=.1$, $c=.1$ and $q=.5$ similar to [14]. The initial conditions are also taken from [14]. The value of R is chosen to be 100,000. The time instances at which the impulses (medicine) are given are fixed to reflect practicality. A lot of medical regimens dictate treatment a few times a day. A treatment with dosages thrice a day is considered in this study. The treatment is given for 20 days. After 20 days, the states to be achieved are those at which if the system is left, will go to a stable equilibrium point. The points at which the system is desired to be taken are, $x_f=3; y_f=3; w_f=.15; z_f=.25;$. These values were chosen so that the memory cell count increases to a high value soon. The costs associated with the deviation from these states are $S_x=S_y=S_w=S_z=10000$. The two point boundary value problem (TPBVP) was solved by first assuming a value of co-states at initial time and correcting them every time after integrating. The TPBVP was solved to get the deviation of the final states from the desired states within 15% deviation. A numerical method to solve the TPBVP will be presented in future work.

The simulation results are shown in (6.1 to 6.3).

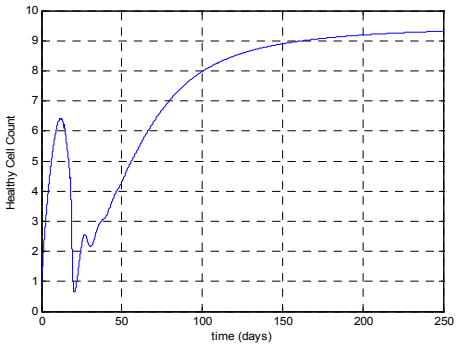


Fig 6.1. Healthy cell count

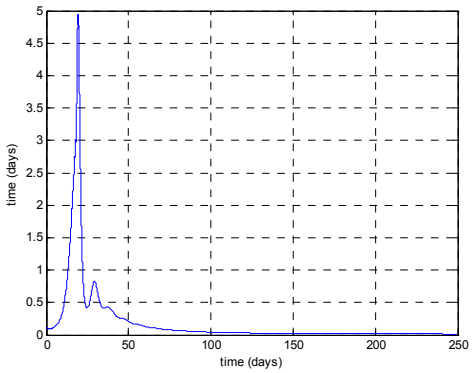


Fig 6.2. Healthy cell count

Note from figure 6.1 that the healthy cell count increases and reaches the healthy equilibrium point value. Figure 6.2 shows the unhealthy cell count. It can be seen that the unhealthy cell count decreases. Also high CTLp count is established.

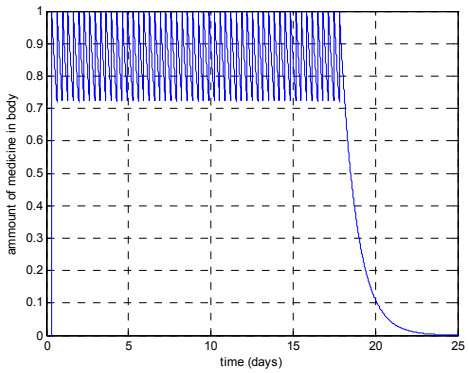


Fig 6.3. Control

It can be seen from figure 6.3 that the medication is given for first 20 days and the system is left on its own. The desired equilibrium point is achieved from this state without any external interference.

Also, the amount of medicine required earlier is less. The control asked for at the beginning of the treatment is less because the cost on the impulse control term penalizes the control magnitude. This can be interpreted as follows. Initially when the body is not used to the new medication, the amount of dosage must be kept low.

## 7. Conclusion:

In this paper, the necessary conditions for optimal impulse control with control constraints were derived. The scheme developed proposes a method to handle impulse control problems with control constraints. The conditions derived were then applied to the problem of HIV treatment by taking a quadratic cost function which penalizes the amount of virus in the body and the amount of control to be given to the person. Drug delivery in the body was modeled as an exponential decay process. Simulation studies performed based on the model chosen show the potential of the impulse control scheme.

## References


[1] Arthur E. Bryson, Jr. and Yu-Chi Ho, *Applied optimal control; optimization, estimation, and control*, Waltham, Mass., Ginn, [c1969].

[2] Chevallereau, C.; Formal'sky, A.; Perrin, B.;*Low energy cost reference trajectories for a biped robot, Robotics and Automation*. Proceedings. 1998 IEEE International Conference on, Volume:2, 16-20May1998 Pages:1398 - 1404 vol.2

[3] David R. Friend, Gregory E. Parry, T.Francis, Gary Kupper, Suggy S. Chrai, Gerald Slack, *Mathematical Modeling of a Novel Controlled-Release Dosage Form*. http://www.drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=7

[4] Elmer G. Gilbert, Gerald A Harsty*, A class of fixed-time fuel optimal impulsive control problems and an efficient algorithm for their solution*, IEEE Transaction on Automatic Control. Vol AC-16, February 1971

[5] H.J.Chang, H.Shim and J.H.Seo, *Control of immune response of HIV Infection Model by Gradual Reduction of Drug Dose*. 43th IEEE Conference on Decision and Control, December 2004. Pages:1048-1054

[6] J.A.M Felippe de Souza, Marco Antonio Leonel Caetano, Takashi Yoneyama. *Optimal Control Theory Applied to the Anti-Viral treatment of HIV*, Proceedings 39th IEEE Conference on Decision and Control, December 2000 Pages: 4839-4844

[7] Jason J Kultch, Pini Gurfil, *Optimal control of HIV infection with a continuously mutating viral population*,Proceedings of American Control Conference, May (2002), Pages: 4033-4039

[8] Luo J.C and Lee. E.B, *Time-Optimal Control of the Swing using Impulse Control Actions*, Proceedings of the American Control Conference Philadelphia, Pennsylvania June 1998 Pages: 200-204

[9] M. Jeffrey, X. Xia, and I. K. Craig*, Controllability analysis of the chemotherapy of HIV/HIV*. in Proceedings. 15th IFAC Triennial World Congress Automatic Control, vol. Q, July 2002, pp. 127–132.

[10] National Institute of Allergy and Infectious Disease (NIAID) *How HIV causes AIDS*, http://www.niaid.nih.gov/factsheets/howhiv.htm

[11] Rebecca V. Culsaw, Shingui Ruan, Raymond J. Spiteri, *Optimal HIV treatment by maximizing immune response*. Journal of Mathematical Biology (2004) 48.Pages: 545-562

[12] Stefano Baccarin, *Optimal Impulse Control for Cash Management with Quadratic Holding Penalty Costs*.

[13] Tao Yang, *Impulsive Control Theory,* Berlin: Spinger-Verlag, Aug. 2001, Lecture Notes in Control and Information Sciences, vol. 272, ISBN: 354042296X

[14] Wodarz D., Nowak M., *Specific therapies could lead to long term immunological control of AIDS*. Proceedings National Academy of Sciences. 96, 14464-14469 (1999).