Negative Feedback Effect in HIV Progression: An Optimal Control Theoretic Approach

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***Abstract*-Long-term infection by Human Immunodeficiency Virus produces a multitude of clinical symptoms resulting in total suppression of the immune system dominated by depletion in $CD4^+$ T cell count and reduction in density of Human Immunodeficiency Virus specific Cytotoxic T-Lymphocyte immune responses. Since the dynamics between viral infection and replication parameters and the host immunity system changes from short-term to long-term chronic infection, mathematical modeling of long-term dynamics necessitates incorporation of negative feedback control mechanism. By applying optimal control theory approach to the administration of combination therapy of reverse transcriptase inhibitor and interleukin 2 in the same model, the most cost-effective strategy has been established where maximum recovery of $CD4^+$ T cell population is attained.**

***Keywords*- Human Immunodeficiency Virus; Host Immune System; Negative Feedback Control; Optimal Control**

I. INTRODUCTION

Complete disruption of human immunity system by Human Immunodeficiency Virus (HIV) occurs over an extended period of approximately 15 years, culminating in development of full-blown AIDS characterized by appearance of several opportunistic infections. Monitoring of viral population through various stages of disease progression reveals rapid increase in viral load till it reaches a maximum, followed by a sharp decrease until set point or quasi-steady state is attained [1]. Sequential activities of two enzymes, reverse transcriptase and Human Immunodeficiency Virus (HIV) protease, transform uninfected $CD4^+$T cells into short-lived productively infected cells or long-lived latently infected cells through the creation of an infectious virion during each secondary infection. The viral antigen stimulates the generation of $CD4^+$T cell dependent Human Immunodeficiency Virus (HIV) specific immune responses mediated primarily by Cytotoxic T-Lymphocytes (CTLs) and non-cytotoxic $CD8^+$T immune cells during primary infection. Cytotoxic T-Lymphocyte (CTL) responses specific for *env* and gag genes of Human Immunodeficiency Virus (HIV) have been reported [2]. Interaction of host immune system with virus follows a complex dynamics. High turnover rate of productively infected cells alters circulating T cell homeostasis which is re-established by supply of fresh cells from the thymus and proliferation of existing cells. Constant recruitment of $CD4^+$T cells helps in persistence of Cytotoxic T-Lymphocyte (CTL) activities simultaneously allowing the virus to evolve and mutate fast [3]. In case of short-term infection by Human Immunodeficiency Virus (HIV), selection pressure exerted on viral population by the immune cells kills the infected cells as well as inhibits viral replication and the infection is kept in check without any impairment of the host immune system [4]. The above-mentioned compensatory feedback control may exert a short term beneficial effect but in long-term aggravates Human Immunodeficiency Virus (HIV) induced lymphopenia by providing fertile substrates for spread of the virus, infection and destruction of the progenitor cells [5]. Increase in the viral population with proportional increase in the number of virus-producing infected cells exerts a cytopathic effect on uninfected $CD4^+$T cells limiting their numbers. Thus, there exists a negative correlation between the viral load and rate of production of uninfected target cells [6]. When level of infection is low and also following therapeutic intervention, where $CD4^+$T cell depletion has not started or the count goes up respectively, specific Cytotoxic T-Lymphocyte (CTL) responses are found to decline slowly emphasizing the existence of an indirect inverse relationship between high viral load and the density of Cytotoxic T-Lymphocyte (CTL) response [7]. In a nutshell, high initial viral load in conjunction with low initial $CD4^+$T cell count suppresses $CD4^+$T supported proliferation, differentiation and clonal expansion of long-lived CTL_p into CTL_e under the influence of IL-2 [8] with subsequent inhibitory effect on the development of Human Immunodeficiency Virus (HIV) induced, T helper cell-dependent, persistent Cytotoxic T-Lymphocyte (CTL) response thereby sustaining the disease [5], [3] and progression of Human Immunodeficiency Virus (HIV) infection to AIDS. Strong Cytotoxic T-Lymphocyte (CTL) activity is responsible for better virus control and slower disease progression. Same Cytotoxic T-Lymphocytes (CTLs) may also recognize latently infected cells [2]. Rational introduction of Highly Active Anti Retroviral Therapy (HAART), consisting of a combination of reverse transcriptase inhibitor and protease inhibitor, at an optimum time in optimum dose and combination for optimum duration, can lead the viral population almost to the verge of extinction, but complete eradication seems to be an impossible task because of partial immune reconstitution, even if continued for a long time. Viral relapse is known to occur as soon as therapy is discontinued. Thus arises the need of addition of new therapeutic modalities in the form of administration of immunomodulatory agent, interleukin 2 (IL-2) in conjunction with Highly Active Anti Retroviral Therapy (HAART) to

promote complete immune reconstitution. Net outcome of IL-2 therapy is rejuvenation of peripheral naive T cell pool marked by decreases in T cell turnover, proliferation and activation [9]. In contrast, Highly Active Anti Retroviral Therapy (HAART) alone results in selective rescue of $CD4^+$T memory cells with no change in naive compartment [10].

In a previous mathematical model of viral dynamics, Bonhoeffer postulated that there is no significant difference in total virus load due to drug administration, primarily the reverse transcriptase inhibitor (RTI), as the reduction in the rate of infection actually helps in recovery and restoration of uninfected healthy T cell population [11]. In resent time a model [12] has been designed with slight modifications of the above mentioned model with introduction of two negative feedback functions both prior to treatment and after drug administration, justifying the inverse relationship between viral load and rate of production of uninfected cells on one hand and the decline in strength of immune response and viral load on the other hand. As the viral load increases in the later stages of HIV infection, host-virus interaction with respect to fresh cells decreases as the availability of uninfected $CD4^+$T cells decreases. This can be attributed to the existence of negative feedback factor between the viral load and rate of production of uninfected cells from the thymus. This effect of m on k was not observed in our previous model [12]. On that basis, in the current model, k^m is introduced, whereas in the previous model [12], only the host-virus interaction parameter, k was present in the denominator of the equation involving the rate of change of population of uninfected $CD4^+$ T cells. Modified mathematical model of long-term viral dynamics (Fig. 1) with subsequent analysis and numerical simulations has successfully established the necessary conditions for existence of two steady states with respect to feedback factor, the rate of infection and killing rate of virus producing cells. Results from analysis emphasize that if the feedback factor can be controlled and rate of infection can be minimized, the progression of Human Immunodeficiency Virus (HIV) infection can be restricted, i.e the system attains stability. The effect of Highly Active Anti Retroviral Therapy (HAART) on long-term host cell HIV dynamics has been previously studied [13, 14]. So far to our knowledge, a single study has been established incorporating mathematical modeling in effect to optimal treatment schedule corresponding to different combinations of Highly Active Anti Retroviral Therapy (HAART) and IL-2 on the outlook of immune response in Human Immunodeficiency Virus (HIV) infection [20]. In the present study we attempt to fill up this particular lacuna in optimal control of Human Immunodeficiency Virus (HIV) with dual therapeutic agents and have satisfactorily designed the most cost-effective therapeutic intervention leading to restoration of uninfected $CD4^+$T cell and decline in infected cell population.

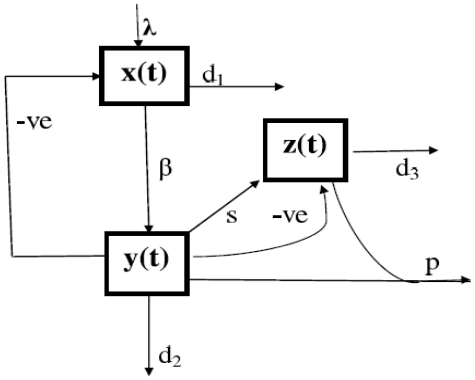


Fig. 1 Schematic explanation of Mathematical model (1)

II. GENERAL MATHEMATICAL MODEL

In view of above biological perspective, it becomes practically impossible to exert immunological restriction on the disease progression when the feedback factor is low. This happens because of rapid infection of available few uninfected cells and a substantial decline in the count of uninfected $CD4^+$T cells. This can be explained in the light of host-virus interaction factor.

As uninfected $CD4^+$T cells decrease, host-virus interaction decreases and CTL response fails to develop, resulting in disease progression. When the rate of infection is high and m attains a much higher value, it exerts a significant effect on host-virus interaction and k^m becomes negligibly small. However, this situation happens only if the viral load is sufficiently high when the infected cell population is considerably greater. Consequently, the final effect is lowering in the number of uninfected cell count. The above statements justify the introduction of k^m in the model in lieu of k [12] , for proper characterization of long-term HIV dynamics with respect to existence of negative feedback effect in the system. Thus, we reconstruct the mathematical model [12] considering x, y and z which represents the uninfected $CD4^+$T cell, infected $CD4^+$T cell and CTL response and hence the control equations are as follows:

$$\begin{aligned}\dot{x} &= \lambda + \frac{s_1}{k^m + y^m} - d_1 x - \beta xy \\ \dot{y} &= \beta xy - d_2 y - pyz \\ \dot{z} &= sy + \frac{s_2}{k^m + y^m} - d_3 z.\end{aligned} \tag{1}$$

The system needs to analyze with the following initial condition: $x(0) > 0$, $y(0) > 0$, $z(0) > 0$ and we denote

$$R_+^3 = \{(x, y, z) \in R^3, x \geq 0, y \geq 0, z \geq 0\}.$$

Here d_1, d_2 and d_3 are the natural death rate of uninfected CD4$^+$T cell, infected CD4$^+$T cell and CTL response respectively. We consider λ as the constant production rate of uninfected CD4$^+$T cell from thymus, where $\lambda > 0$ because thymus is always functioning. Here we also consider β is the rate of infection at which the uninfected cell become infected by the virus particle, and p is the killing rate of infected cell by CTL. We assume s as the rate of stimulation of CTL responses. Here s_1 and s_2 are growth terms and m is defined as feedback factor. We also assume k as host-virus interaction coefficient. Considering the dimensionless quantities

$$\begin{aligned}&X = xk^{-1}, Y = yk^{-1}, Z = zk^{-1}, T = tk\beta, l = \frac{\lambda}{\beta k^2}, \\ &A = \frac{s_1}{\beta k^{m+2}},\ B = \frac{s_2}{\beta k^{m+2}},\ \delta_1 = \frac{d_1}{\beta k},\ \delta_2 = \frac{d_2}{\beta k}, \\ &\delta_3 = \frac{d_3}{\beta k},\ \alpha_1 = \frac{p}{\beta},\ \alpha_2 = \frac{s}{\beta k}.\end{aligned} \tag{2}$$

The dimensionless form of the model becomes

$$\begin{aligned}\dot{X} &= l + \frac{A}{1 + Y^m} - \delta_1 X - XY \\ \dot{Y} &= XY - \delta_2 Y - \alpha_1 YZ \\ \dot{Z} &= \alpha_2 Y + \frac{B}{1 + Y^m} - \delta_3 Z.\end{aligned} \tag{3}$$

A. Theoretical Analysis

1) Steady State Analysis:

The system (3) has the following steady state. The first one is disease free equilibrium given by $E'(\frac{l}{\delta_1}, 0, 0)$ and another is infected equilibrium $E^*(X^*, Y^*, Z^*)$. The infected steady state E^* of the system (3) is obtained from

$$\begin{aligned}&X^* = \delta_2 + \frac{\alpha_1}{\delta_3}(\alpha_2 Y^* + \frac{B}{1 + Y^{*m}}), \\ &Z^* = \frac{1}{\delta_3}(\alpha_2 Y^* + \frac{B}{1 + Y^{*m}}) \\ &\text{and} \quad \alpha_1\alpha_2 Y^{*m+2} + (\alpha_1\alpha_2\delta_1 + \delta_2\delta_3)Y^{*m+1} + (\delta_1\delta_2\delta_3 - l\delta_3)Y^{*m} + \alpha_1\alpha_2 Y^{*2} + (\alpha_1\alpha_2\delta_1 + \\ &\quad \delta_2\delta_3 + \alpha_1 B)Y^* + (\alpha_1\delta_1 B - l\delta_3 - \delta_3 A) = 0.\end{aligned} \tag{4}$$

If the last Equation (4) has only one positive root then the steady state exists and uniqueness of the steady state is confirmed by Descartes rule of sign. Thus we get the condition (5) stated below, for which E^* always exists.

$$\frac{pd_1 s_2}{d_3(\lambda k^m + s_1)} < \beta < \frac{d_1 d_2}{\lambda} \tag{5}$$

From the above existence condition we can conclude that if the rates at which the uninfected T cell become infected by the

virus particle is restricted then only infected steady state exists. We can also state that the uninfected T cell population and CTL response are both affected by the feedback factor if and only if m increases reflected by decline in uninfected T cell and CTL response.

2) Stability of the system:

Here we consider the basic reproduction ratio R_0, which means the average number of secondary infection caused by a single infected T cell in an entirely susceptible T cell. Here $R_0 = \frac{\lambda\beta}{d_1 d_2}$. For E' the Jacobian matrix becomes J' where the eigen values for J' are $-\delta_1, -(\frac{l}{\delta_1} + \delta_2)$ and $-\delta_3$.

Thus we get the proposition.

Proposition 1: For E', if $R_0 < 1$ then E' is local asymptotically stable. If $R_0 > 1$ then the system E' is unstable.

The Jacobian matrix for E^* is J^*. The characteristic equation for $J(E^*)$ is $\rho^3 + a_1\rho^2 + a_2\rho + a_3 = 0$.

where,

$$\begin{aligned} a_1 &= \delta_1 + \delta_3 + Y^* > 0, \\ a_2 &= \delta_1\delta_3 + \delta_3 Y^* + X^* Y^* + \alpha_1\alpha_2 Y^* + \delta^*(AY^* - B\alpha_1 Y^*) > 0, \\ a_3 &= Y^*[\{\delta_3 X^* + \alpha_1\alpha_2(\delta_1 + Y^*)\} + \delta^*\{A\delta_3 - \alpha_1 B(\delta_1 + Y^*)\}] > 0 \end{aligned} \tag{6}$$

and

$$\delta^* = \frac{mY^{*m-1}}{(1+Y^{*m})^2} > 0.$$

From Routh-Hurwitz condition, the necessary and sufficient condition for locally asymptotically stability of the steady state is $a_1 a_2 - a_3 > 0$

$$\Rightarrow \quad \delta_1\delta_3(\delta_2 + \delta_3 + 2Y^*) + \delta_3 Y^*(\delta_3 + \alpha_1\alpha_2 + Y^*) + X^* Y^*(Y^* + \delta_1) + \delta^* Y^*(A\delta_1 + AY^* - B\alpha_1\delta_3) > 0.$$

Proposition 2: The system E^* is stable if (i) $R_0 > 1$ and (ii) $a_1 a_2 - a_3 > 0$ are satisfied.

B. Numerical Analysis

We now numerically illustrate the change of the stability due to varying the time delay. We choose the initial condition of the parameters as given in Table 1. At t=0 the values of the model variables are considered as $x(0) = 1000$, $y(0) = 100$, $z(0) = 10$. It should be noted that the asymptotic time series solutions of the model equation do not depend on the choice of the initial values of the model variables. Variation of the parameter p is restricted by the condition $\frac{ps}{d_3} : 0.01 - 0.05$ [11]. The parameter s and d_3 are mentioned in the Table 1.

TABLE 1 LIST OF PARAMETERS FOR INFECTIVITY

Parameters	Definition	Range (day $^{-1}$)	Reference
λ	Constant rate of production of CD4 $^+$ T cells	1-10 (mm^{-3})	[17]
d_1	Death rate of uninfected CD4 $^+$ T cells	0.007-0.1 (mm^{-3})	[17]
β	Rate of infection of uninfected T cell	0.00025-0.5 (mm^{-3})	[11]
d_2	Death rate of virus producing cells	0.2-0.3 (mm^{-3})	[18], [19]
p	Killing rate of virus producing cells	0.002	[11]
s	Rate of stimulation of CTL	0.1-1	[11]
d_3	Death rate of CTL	0.1-0.15	[11]

Fig. 2 (left panel) shows the existence and stability condition for the system E'. Here we plot the basic reproduction ratio R_0 with respect to β and d_2. It is easily seen that for reducing value of β basic reproduction ratio R_0 reduces proportionately and if we restrict $\beta < 0.1$, then it shows that $R_0 < 1$, which reflects the stability of the system. But if d_2 increases $R_0 < 1$ regardless of large value of β.

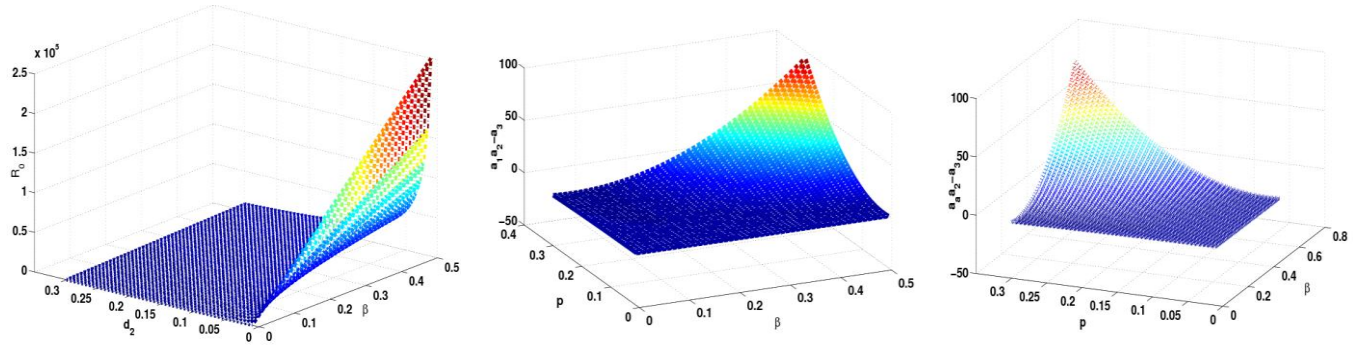


Fig. 2 Left panel:(A) Phase plane for the condition of existence of the stability of the uninfected steady state E'. Center panel: (B) Mesh diagram showing the existence condition of E^* for β, p and $m = 1$. Right panel: (C) Mesh diagram showing the existence condition of E^* for β, p and $m = 2$

From Fig. 3 (right panel) we observe that if $m \geq 4$, the stationary point becomes unstable which implies that infected steady-state is disturbed and the viral count starts increasing. It contradicts in vivo viral replication because high viral load is known to exert a negative feedback effect on the supply of fresh target cells and attains a quasi-steady state of viral population. In Fig. 3 (a), (b) we see that for $m = 1$, $a_1 > 0$ when $\beta < 0.004$. But if $\beta > 0.004$, $a_1 < 0$. Thus if the rate of infection is restricted then E^* remains stable. But when $m = 2$ (Fig. 3(c), (d)) the system E^* remains stable for $\beta > 0.004$.

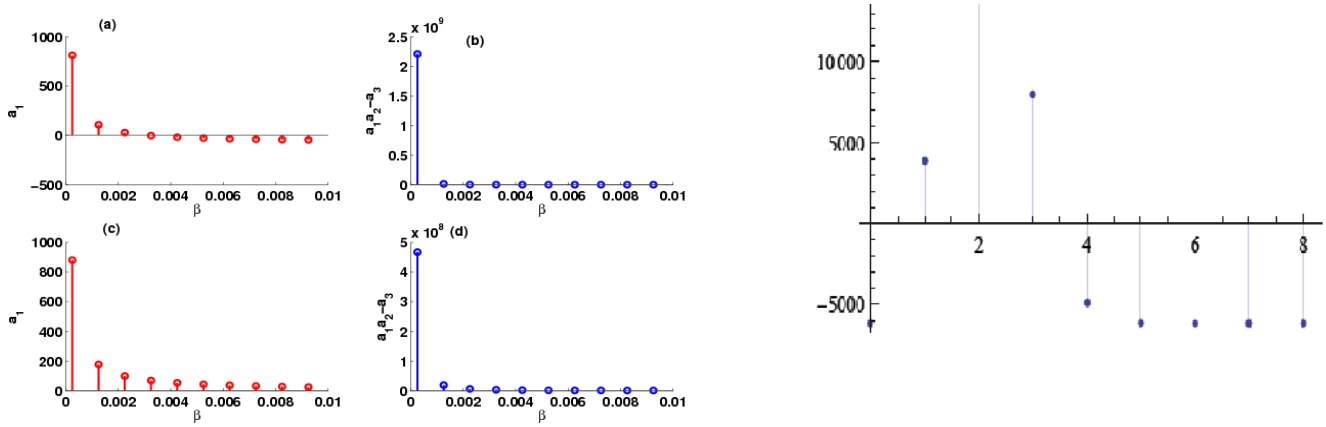


Fig. 3 Left Panel: Phase plane for the condition of existence of the stability of the infected steady state E^*. Right panel: Figure shows that when $m \geq 4$ the system becomes unstable. Whereas when $m < 4$ the system remain stable. That means for large compatibility the system become unstable

If β lies above a threshold value $(i.e. 0.004)$ and feedback factor is of lower magnitude $(m = 1)$, it becomes practically impossible to exert immunological restriction on the disease progression because of rapid infection of available few uninfected cells, failure of establishment of effective, sustained CTL response in presence of viral antigen and a substantial decline in the count of uninfected T cells in comparison to the number of infected cells. The system is yet to attain persistent infection equilibrium.

However, if β lies below the threshold value, it will take longer time to infect uninfected cells. Immune system is strong enough to control the infection because of the development of effective CTL response. Viral load and the number of infected cells are on a decline leading to the generation of disease free equilibrium. Infected steady state can be attained if the feedback factor increases $(m = 2)$ when $\beta > 0.004$, since, now the immune system is totally impaired due to weakening of HIV-specific CTL-mediated responses and further viral replication is inhibited due to depletion of uninfected $CD4^+$ T cells and death and destruction of T cell progenitors.

III. THE OPTIMAL CONTROL PROBLEM

In this section our main aim is to minimize the cost as well as minimize the infected $CD4^+$T cell and maximize the

uninfected CD4$^+$T cell. In this section we study the optimal control problem for the stable system, keeping m below 4. Thus we construct the optimal control problem where the state system is

$$\begin{aligned}\dot{x} &= \lambda + \frac{s_1}{k^m + y^m} - d_1 x - \beta(1-u_1(t))xy + u_2(t)x \\ \dot{y} &= \beta(1-u_1(t))xy - d_2 y - pyz \\ \dot{z} &= sy + \frac{s_2}{k^m + y^m} - d_3 z + u_2(t)z,\end{aligned} \tag{7}$$

and the control function is defined as

$$J(u_1,u_2) = \int_{t_i}^{t_f} [Pu_1^{\,2} + Qu_2^{\,2} - x^2 + y^2]dt. \tag{8}$$

Here the control functions $u_1(t)$ and $u_2(t)$ represent the percentage of effect RTI and IL-2 on interaction of T cell with virus and the parameters P and Q represent respectively the weight factor on the benefit of the cost of RTI and IL-2 therapy. Here the control function $u_1(t)$ and $u_2(t)$ are bounded [15]. The control $u_1(t)$ represents the efficacy of the drug therapy in inhibiting the reverse transcription i.e., blocking new infection. The control $u_2(t)$ represents the efficacy of IL-2 therapy. In this problem we are seeking the optimal control pair $(u_1^{\,*}, u_2^{\,*})$ such that

$J(u_1^{\,*}, u_2^{\,*}) = \min\{J(u_1,u_2) : (u_1,u_2) \in U\}$. Where U is the control set defined by,

$U = \{u = (u_1,u_2) : u_1, u_2 \text{ are the measurable}, \ 0 \le u_1(t) \le 1, \ 0 \le u_2(t) \le 1, \ t \in [t_i, t_f]\}$.

To determine the optimal control $u_1^{\,*}$ and $u_2^{\,*}$, we use the "Pontryagin Minimum Principle"[16]. To solve the problem we use the Hamiltonian given by

$$\begin{aligned}H = Pu_1^{\,2} + Qu_2^{\,2} - x^2 + y^2 + \xi_1\{\lambda + \frac{s_1}{k^m + y^m} - d_1 x - \beta(1-u_1(t))xy + u_2(t)x\} + \\ \xi_2\{\beta(1-u_1(t))xy - d_2 y - pyz\} + \xi_3\{sy + \frac{s_2}{k^m + y^m} - d_3 z + u_2(t)z\}.\end{aligned} \tag{9}$$

By using the "Pontryagin Minimum Principle" and the existence condition for the optimal control theory [16] we obtain the theorem.

Proposition 3: The objective cost function $J(u_1,u_2)$ over U is minimum for the optimal control $u^* = (u_1^{\,*}, u_2^{\,*})$ corresponding to the interior equilibrium (x^*, y^*, z^*). Also there exist adjoint function ξ_1, ξ_2, ξ_3 satisfying the Equation (14).

Proof: By using Pontryagin Minimum Principle [16] the unconstrained optimal control variable $u_1^{\,*}$ and $u_2^{\,*}$ satisfy

$$\frac{\partial H}{\partial u_1^{\,*}} = \frac{\partial H}{\partial u_2^{\,*}} = 0, \tag{10}$$

since

$$\begin{aligned}H = [Pu_1^{\,2} - \xi_1(1-u_1(t))\beta xy + \xi_2(1-u_1(t))\beta xy] + [Qu_2^{\,2} + \xi_1 u_2 x + \xi_3 4u_2 z] \\ + \text{other terms without } u_1 \text{ and } u_2.\end{aligned} \tag{11}$$

Then we obtain $\frac{\partial H}{\partial u_i^{\,*}}$ for $u_i^{\,*}$, $(i = 1,2)$ and equation with zero, we get

$$\frac{\partial H}{\partial u_1^{\,*}} = 2Pu_1^{\,*} + \beta xy(\xi_1 - \xi_2) = 0$$

$$\frac{\partial H}{\partial u_2^*} = 2Qu_2^* + \xi_1 x + \xi_3 z = 0.$$

Then we obtain

$$u_1^* = \frac{\beta_1 xy(\xi_2 - \xi_1)}{2P},\ u_2^* = -\frac{(\xi_1 x + \xi_3 z)}{2Q}. \tag{12}$$

Then according to the standard control arguments, we can conclude for u_1^*:

$$u_1^* = \begin{cases} 0, & \frac{\beta_1 xy(\xi_2 - \xi_1)}{2P} \le 0; \\ \frac{\beta_1 xy(\xi_2 - \xi_1)}{2P}, & 0 < \frac{\beta_1 xy(\xi_2 - \xi_1)}{2P} < 1; \\ 1 & \frac{\beta_1 xy(\xi_2 - \xi_1)}{2P} \ge 1. \end{cases}$$

In compact form we can rewrite $u_1^*(t) = \min\{1, \frac{\beta xy(\xi_2 - \xi_1)}{2P}\}$. Similarly, for $u_2^*(t)$ we have the compact form $u_2^* = \min\{1, -\frac{\xi_1 x + \xi_3 z}{2Q}\}$.

According to Pontryagin Minimum Principle [16]

$$\frac{d\xi}{dt} = -\frac{\partial H}{\partial x}, \quad and \ \ H(x(t), u^*(t), \xi(t), t) = \min_{u \in U} H(x(t), u(t), \xi(t), t). \tag{13}$$

The above equation are the necessary condition satisfying the optimal control $u(t)$ and the variable. The system (4) is the adjoint system and in our problem it becomes

$\frac{d\xi_1}{dt} = -\frac{\partial H}{\partial x}$, $\frac{d\xi_2}{dt} = -\frac{\partial H}{\partial y}$, $\frac{d\xi_3}{dt} = -\frac{\partial H}{\partial z}$. Taking the partial derivative of H in (9) we get,

$$\begin{aligned} \frac{d\xi_1}{dt} &= 2x + \xi_1\{d_1 + (1 - u_1(t))\beta y - u_2(t)\} - \xi_2(1 - u_1(t))\beta y \\ \frac{d\xi_2}{dt} &= -2y + \xi_1\{(1 - u_1(t))\beta x + \frac{s_1 m y^{m-1}}{(k^m + y^m)^2}\} - \xi_2(1 - u_1(t))\beta x - \xi_3\{s - \frac{s_2 m y^{m-1}}{(k^m + y^m)^2}\} \\ \frac{d\xi_3}{dt} &= -\xi_2 py + \xi_3(d_3 - u_2(t)). \end{aligned} \tag{14}$$

We have analyzed the optimality of the system which consists of the state system, the adjoint system together with the initial condition and the transversality conditions. The transversability condition is given at final time t_f by $\xi_i(t_f) = 0,\ i = 1,2,3.$

Using the state system (7), and the adjoint system (14), we can conclude that the objective function (8) will be minimized, for u_1^*, and u_2^* (12), if the initial conditions are $x(0) = x_0, y(0) = y_0, z(0) = z_0$, and the transversality condition $\xi_i(t_f) = 0,\ i = 1,2,3$ does hold.

A. Numerical Analysis

For the numerical illustration of the optimal control problem (7) and (8) we assume $t_f = 100$, which can be used as an initial guess. We solve the optimality system by making the changes of the variable $\tau = t/t_f$ and transferring the interval $[0,1]$. Here τ represents the step size which is used for better strategy with a line search method which will maximize the reduction of performance measure. We choose $t_f = 1 + \Delta t_f$ and initially $t_f = 1$. We also assume that $\Delta t_f = 0.1$ and our desired value of $t_f = 100$. This process is continued until the desire problem is solved. Thus we have got the successive values which are chosen as a homotopy path. Here we choose the initial condition for the state variable as

$x_0 = 5,\ y_0 = 1,\ z_0 = 2$ [14] and we have also used the parameters given in Table 1.

The solutions are displayed in Fig. 4 (Table 2), Fig. 5 (Table 3), Fig. 6 (Table 4), Fig. 7 (Table 5). Here we have plotted the trajectories of the state variables and the optimal control variables for different values of the cost in the form of weight factor. From the numerical study we have observed that if the weight factor of IL-2 increases then the treatment control u_2 will remain at upper bound for short period of time in comparison with respect to the earlier case. Also it is observed that the treatment control u_1 takes more time to reach at its maximum value (which is comparatively lower to previous one). We have also observed that the weight factor of HAART does not make any significant impact on the system due to the negative feedback effect. Thus the combination of drug therapeutic treatment (HAART and IL-2) is more effective in presence of negative feedback effect.

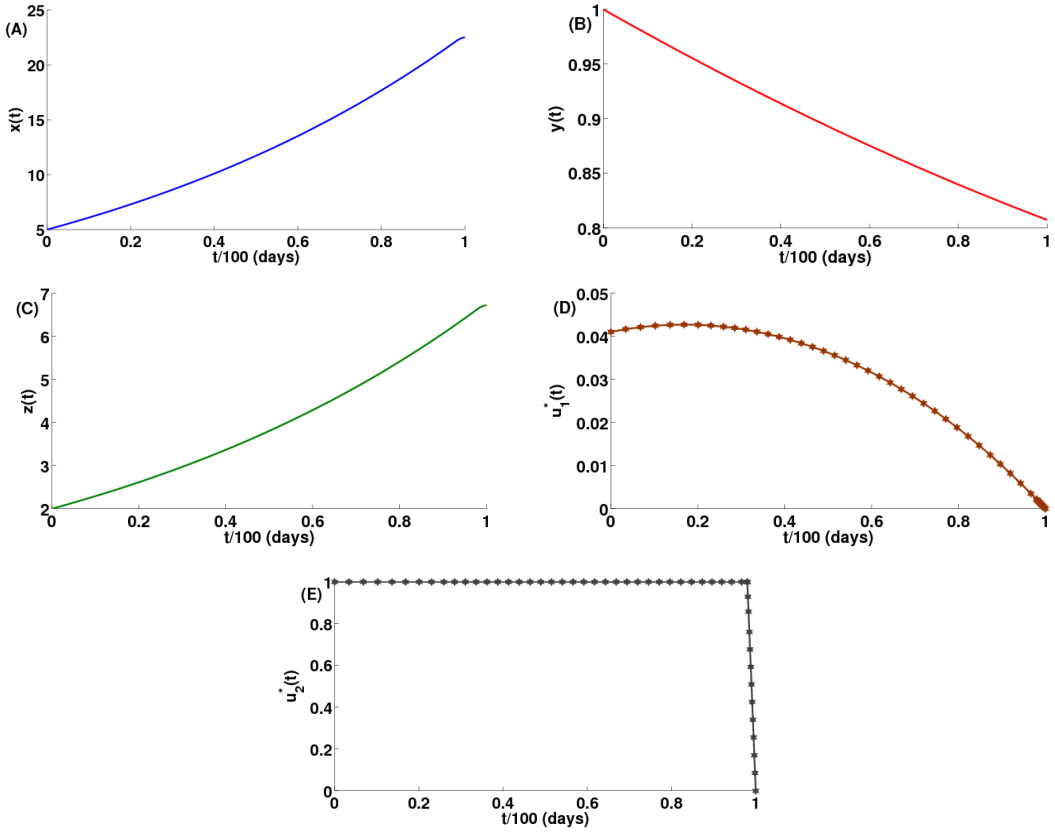
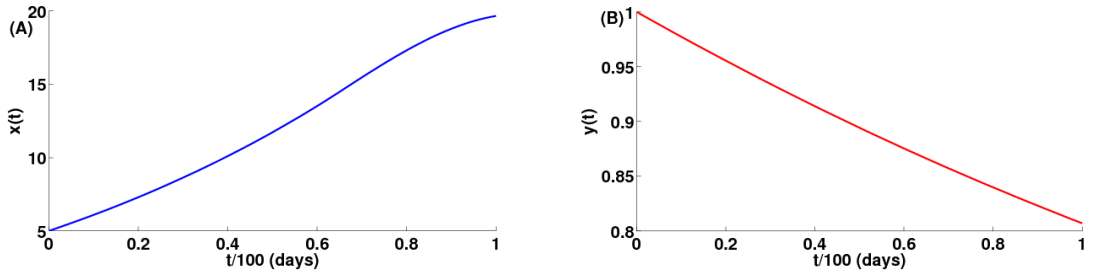


Fig. 4 Optimal trajectories of the state variables and control variables for $P = 10$ and $Q = 10$

TABLE 2 VARIABLE VALUES AT THE FINAL TIME OF TREATMENT FOR THE OPTIMAL CONTROL INPUT WITH DIFFERENT SET OF COST

P	Q	x_f	y_f	z_f	u_1^*	u_2^*
10	10	22.52	0.8076	6.724	0.04251 at 0.1023	1 up to 0.9798



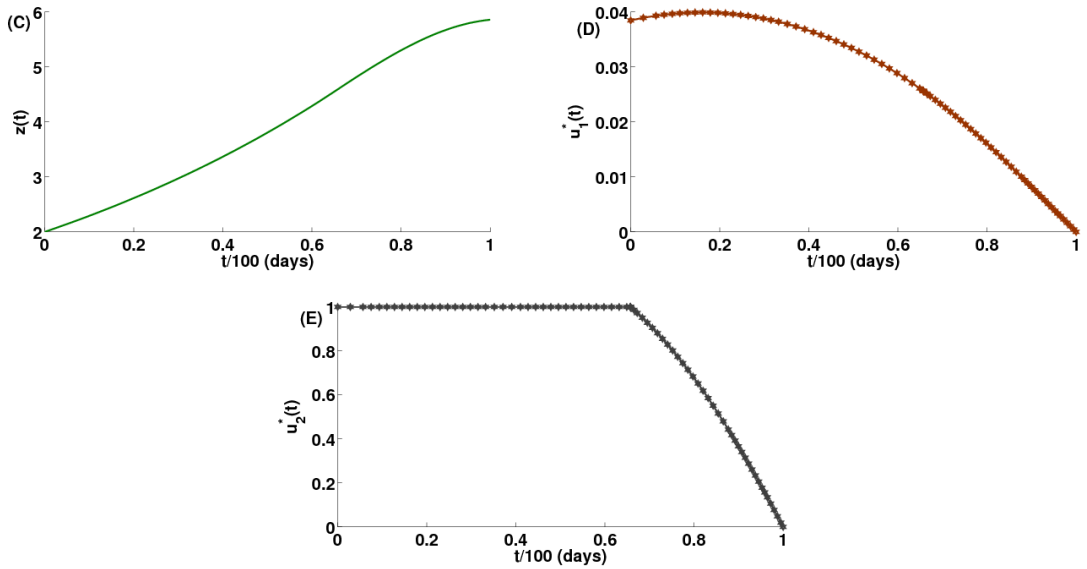


Fig. 5 Optimal trajectories of the state variables and control variables for $P = 10$ and $Q = 100$

TABLE 3 VARIABLE VALUES AT THE FINAL TIME OF TREATMENT FOR THE OPTIMAL CONTROL INPUT WITH DIFFERENT SET OF COST

P	Q	x_f	y_f	z_f	u_1^*	u_2^*
10	100	19.66	0.8071	5.859	0.0399 at 0.1446	1 up to 0.6566

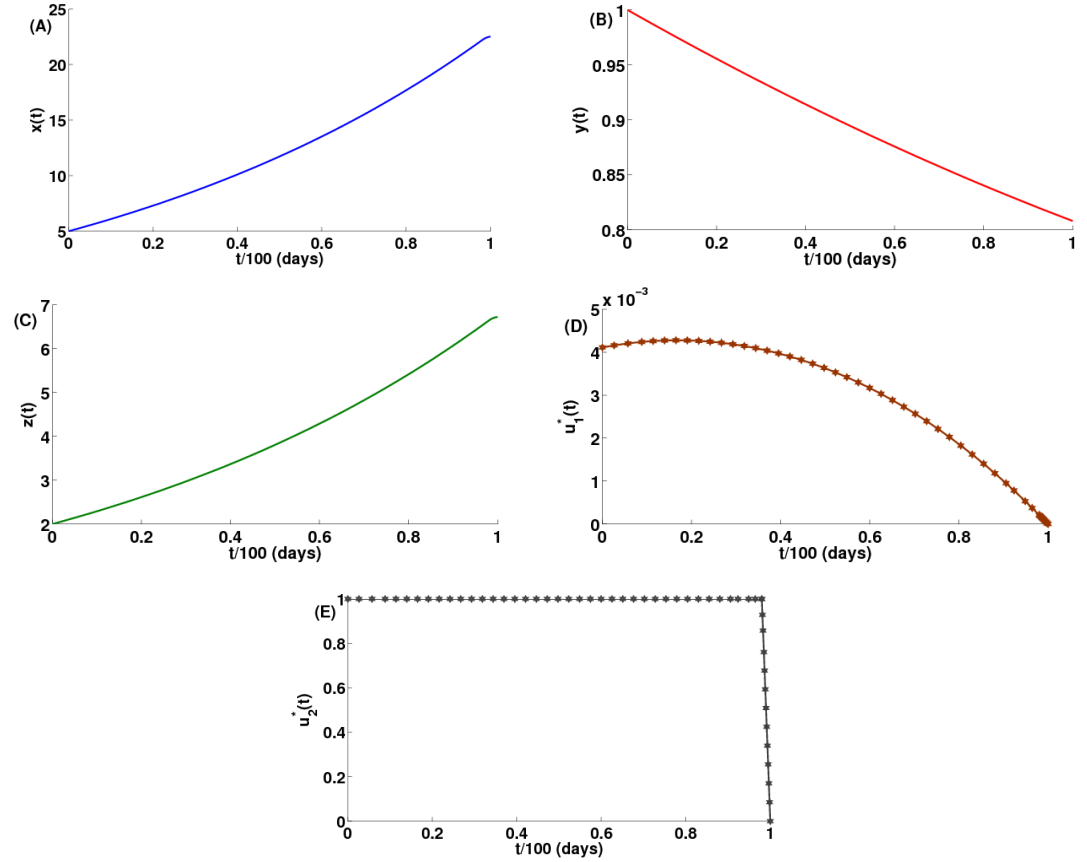


Fig. 6 Optimal trajectories for the state variables and control variables for $P = 100$ and $Q = 10$

TABLE 4 VARIABLE VALUES AT THE FINAL TIME OF TREATMENT FOR THE OPTIMAL CONTROL INPUT WITH DIFFERENT SET OF COST

P	Q	x_f	y_f	z_f	u_1^*	u_2^*
100	10	22.51	0.8082	6.723	0.004278 at 0.1651	1 up to 0.98

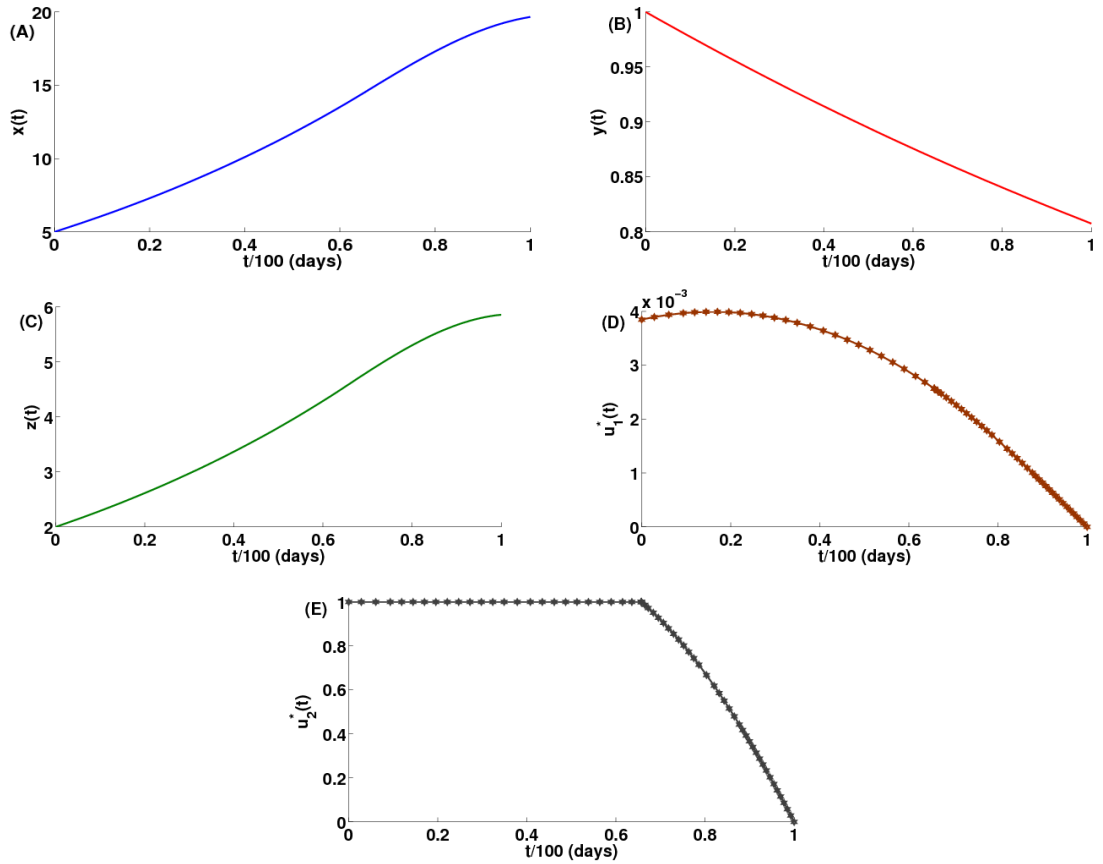


Fig. 7 Optimal trajectories for the state variables and control variables for $P = 100$ and $Q = 100$

TABLE 5 VARIABLE VALUES AT THE FINAL TIME OF TREATMENT FOR THE OPTIMAL CONTROL INPUT WITH DIFFERENT SET OF COST

P	Q	x_f	y_f	z_f	u_1^*	u_2^*
100	100	19.66	0.8076	5.859	0.00399 at 0.1701	1 up to 0.6566

IV. DISCUSSION

In this research article we consider the effect of negative feedback control on host-virus interaction parameter, infected T cell, uninfected T cell and CTL differentiation. Our analytical study reveals that the system has two steady states - disease free equilibrium and the infected equilibrium. Here we see that if the basic reproduction ratio $R_0 < 1$ then the system E' is locally asymptotically stable, but if $R_0 > 1$ then E' is unstable. We also find out E^* exist if $\beta < \frac{d_1 d_2}{\lambda}$ and $p < \frac{d_1(\lambda k^m + s_1)}{d_1 s_2}$. Further the disease free equilibrium E' is asymptotically stable in the Ω region if $R_0 < 1$, and the system E' does not exist if $R_0 > 1$. Also the infected equilibrium exists if $R_0 > 1$ and β is restricted by the restriction $\frac{p\delta_1 s_2}{d_3(\lambda k^m + s_1)} < \beta < \frac{d_1 d_2}{\lambda}$. If feedback factor, m increases, infected steady state continues to exist even for lower values of β, provided the condition R_0 is satisfied. Thus in a nut shell we can conclude that if $R_0 < 1$, number of secondary infected cells approaches zero as time proceeds to infinity because less than one new cell will be infected by a primary infected cell for which the system attains disease free equilibrium or E' becomes locally asymptotically stable and if $R_0 > 1$, stability of E' is lost.

In our numerical analysis Fig. 3(right panel) shows that when $m \le 3$, $a_1 a_2 - a_3 > 0$, but for large value of $m(\ge 4)$, $a_1 a_2 - a_3 < 0$. Thus negative feedback effects of infected cells always mess up the immune system which can no longer act against viral replication. When the infection rate β is small, CTL may control the disease (Fig. 3, left panel). Also when β lies below its threshold value the immune system acts properly against the infected cells but if m increases, the immune system totally collapses to act against viral replication (Fig. 3 (a), (b)).

The aim of any successful therapeutic intervention is to use minimum strength/dose of drug/drugs for a minimum time to obtain the maximum effect i.e. increased CD 4^+ T cell count. In Figs. 4-7, alterations in uninfected and infected T cell population in response to optimal treatment schedule of control variable, IL-2 when both HAART and IL-2 are administered, are depicted. Comparison of results of variations in numerical values of weight factors associated with control variables, $u_1(t)$ and $u_2(t)$, indicates that maximum increase in uninfected $CD4^+$ T cell count is observed at a comparatively low dose of HAART when combined with a high dose of IL-2. No extra beneficial effect is obtained if HAART is given at a weight factor either in 10 or 100. Another interesting revelation is that the infected cell population declines to similar level whatever may be the combination of weight factors associated with two control variables of treatment schedule. It has also been observed that time at which chemotherapy exerts, maximum effect does not depend on weight factors. Thus, the best possible cost-effective therapeutic outcome can be achieved at an optimal treatment schedule consisting of two control variables where the weight factors associated with HAART and IL-2 are 10 and 10 respectively. Also it is clearly observed that higher weight factor means drug is more toxic and that drugs are used less. Here both drugs are given within same time interval. But we have observed that time of giving maximal drug is different for different drug schedules. From our analytical as well as numerical observation we can conclude that the percentage of drug therapy is inversely proportional to the weight factor P and Q. Thus in a nutshell, we can conclude that the effect of optimal treatment schedule corresponding to different combination of HAART and IL-2 on the basis of immune response in HIV infection in presence of negative feedback effects provides a better improvement of an infected individual rather than using only HAART.

V. CONCLUSIONS

It should be mentioned here that the uninfected T cell and also the CTL response concurrently decrease for increasing value of the feedback factor m. Moreover, in the present paper, it has been shown that as m attains a much higher value, it exerts a significant effect on host-virus interaction and km becomes negligibly small. This effect of m on k was not observed in our previous model [12]. Furthermore, it has been proved that when $m \geq 4$, the host immune system totally collapses to act against viral replication. Thus, we have established the effect of negative feedback control on immunological restriction of the disease, when the disease can no longer be controlled, which remained unexplored in our previous work.

The virus producing cell inhibits the production of uninfected T cell and weakens CTL responses which cause destabilization and impairment of immune system inspite of drug dose. If $R_0 < 1$, number of secondary infected cells approaches zero as time proceeds to infinity because less than one new cell will be infected by a primary infected cell for which the system attains disease free equilibrium or E' becomes locally asymptotically stable and if $R_0 > 1$, stability of E' is lost. If rate of infection and feedback factor are high, CTL cannot act properly against the disease and simultaneously immune system is impaired as time progresses. When the negative feedback control factor is equal to or less than 3, best possible cost-effective therapeutic outcome can thus be achieved at an optimal treatment schedule consisting of combination of two control variables of HAART and IL-2.

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