Immune Cell Response to Negative Feedback Effect on HIV

Priti Kumar Roy[1*], Amar Nath Chatterjee[1], Sutapa Biswas Majee[2]

[1]Centre for Mathematical Biology and Ecology,
Department of Mathematics, Jadavpur University, Kolkata 700032, India
[2]NSHM College of Pharmaceutical Technology, Kolkata – 700053, India

[*]Corresponding Author:pritiju@gmail.com

Abstract- Alteration in host-virus interaction dynamics during long-term infection by HIV necessitates consideration of inverse relationship between high viral load and density of CTL response leading to dis-regulation of host immunity system. Mathematical modeling introducing negative feedback control mechanism helps in establishment of threshold condition for disease eradication as well as necessary conditions for existence of different equilibria depending on values of basic reproduction ratio. Moreover, IL-2 adjuvenated HAART therapy has been found to be highly cost-effective in recovery of the immunity status in the present mathematical model using negative feedback effect.

Keywords- HIV; CD4$^+$T Cells; CTL; Negative Feedback Control; HAART; IL-2

I. INTRODUCTION

The hallmark features of disease progression of HIV infection to full-blown AIDS include T-cell hyperactivation, impairment and dysregulation of the immune system manifested by depletion of CD4^+ T-cell and CTL exhaustion. Antigenic stimulation by HIV leads to high turnover rate of productively infected cells disturbing 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 delayed initiation of CTL activities until peak viremia is reached and its subsequent persistence leading to killing of infected cells. Loss of infected cells means lack of antigenic stimulation for CTL population resulting in a relative loss of CTL activity [1]. Thus, when viral load is considerably high, CTL-mediated killing and cytopathic effect of virus on CD4^+ T cells leads to exhaustion of HIV-specific immune response [2], emphasizing the existence of an indirect inverse relationship between high viral load and the density of CTL response [9]. A negative correlation may be assumed to exist between the viral load and rate of production of uninfected target cells [3]. When level of infection is low and also following therapeutic intervention through administration of HAART, where CD4^+ T cell depletion has not started or the count goes up respectively, specific CTL responses are found to decline slowly.

HIV infection can be finally eradicated through coordinated interplay between CD4^+ T cells and CTLs when infected CD4^+ T cells are killed by CTLs. Thus, if CTL population can always be maintained at a positive value, the HIV-infected individuals can remain healthy for a longer period of time due to slower disease progression. However, complete eradication of viral population from the system and total immune reconstitution is practically not feasible with HAART alone, even if continued for a long time, which may lead to precipitation of toxic effects. Viral relapse is known to occur as soon as the therapy is discontinued [1, 10, 13].

Evaluation of eradication threshold (T_0) for HIV infection constitutes a significant strategy in characterizing the stage of infection and guiding intervention strategies. Threshold condition for eradication does not quantify the transient dynamics, the time course of the infection or the prevalence of the disease. HIV can be eradicated under the condition that $T_0 < 1$, but it can not be eradicated under the condition that $T_0 > 1$ [6, 7].

The possibility of immunotherapy to correct individual HIV-driven immune alteration, by exploiting the specific effects of different immunomodulants like IL-2 on T cell dynamics is indeed a fascinating and novel perspective in the treatment of HIV infection. Increasing evidence favors co-administration of HAART and IL-2 following an optimal treatment schedule leading to selective expansion of immune system and near extinction of viral population from the system [6, 7]. 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 [12]. The present study has been designed with slight modifications of the above-mentioned model with introduction of two negative feedback functions 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.

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 three steady states with respect to feedback factor, the rate of infection and killing rate of virus producing cells. Till date, no studies incorporating mathematical modeling of effect of optimal treatment schedule corresponding to different combination of HAART and IL-2, on long-term host cell -HIV dynamics have been done although the effect of HAART has been previously studied using a similar approach [13]. The present study attempts to fill up this particular lacuna in optimal control of HIV with dual therapeutic agents and has satisfactorily designed the most cost-effective therapeutic intervention leading to restoration of uninfected $CD4^+$ T cell, infected cell population, and recovery of CTL population.

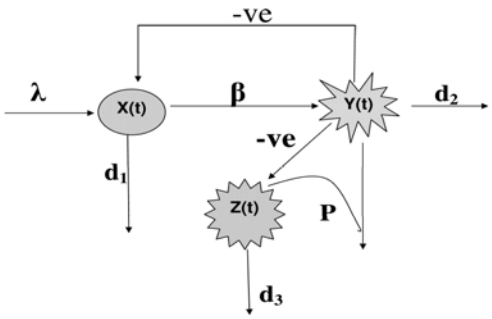


Fig. 1 Schematic explanation of Mathematical model

II. GENERAL MATHEMATICAL MODEL

In view of above biological perspective with slight modification [12], the infected $CD4^+$ T cells can be assumed to exert a negative feedback inhibition on the rate of formation of uninfected $CD4^+$ T cells and CTL stimulation [8]. Thus, we have reconstructed the mathematical model [12] considering x, y and z which represent the uninfected $CD4^+$ T cell, infected $CD4^+$ T cell and CTL response and hence the control equations are as follows:

$$\dot{x} = \lambda + \frac{s_1}{k + y^m} - d_1 x - \beta xy$$

$$\dot{y} = \beta xy - d_2 y - pyz$$

$$\dot{z} = sy + \frac{s_2}{k + y^m} - d_3 z. \tag{1}$$

The system will be analysed 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 rates of uninfected $CD4^+$ T cell, infected $CD4^+$ T cell and CTL response declination rate respectively. We have considered λ as the constant production rate of uninfected $CD4^+$ T cells from thymus, where $\lambda > 0$ as because thymus is always functioning. Here we have also considered β as the rate of infection at which the uninfected $CD4^+$ T cells become infected by the virus particle, and p is the killing rate of infected cell by CTL. We have assumed s as the rate of stimulation of CTL. 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.

III. THEORETICAL ANALYSIS

A. *Existence Condition*

In the present situation (1), three types of equilibria can exist:

(i) disease-free equilibrium $E_1(\frac{\lambda k + s_1}{k d_1}, 0, 0)$,

(ii) equilibrium $E_2(\frac{\lambda k + s_1}{kd_1}, 0, \frac{s_2}{kd_3})$, and last one

(iii) endemic equilibrium $E^*(x^*, y^*, z^*)$ where,

$$x^* = \frac{1}{\beta}[d_2 + \frac{p}{d_3}(sy^* + \frac{s_2}{k + y^{*m}})],$$

$$z^* = \frac{1}{d_3}(sy^* + \frac{s_2}{k + y^{*m}})$$

and

$$ps\beta y^{*m+2} + (psd_1 + d_2d_3\beta)y^{*m+1} + d_3(d_1d_2 - \lambda\beta)y^{*m} + psk\beta y^{*2} + (pskd_1 + \beta(d_2d_3k + ps_2)y^*) - \{\beta(\lambda d_3k + s_1d_3) - d_1(d_2d_3k + ps_1)\} = 0.$$

If the above last equation 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 (2) stated below, for which E^* always exists.

$$d_1d_2 > \lambda\beta, \qquad d_3\beta(\lambda k + s_1) > d_1(ps_1 + d_2d_3k). \tag{2}$$

B. Boundedness of the System

To verify the boundedness of the system, the following lemma is very much useful.

Lemma 1: For $x(t)$ satisfying $x'(t) < c - q(\phi)x(t)$ where c is a constant and $q(\phi)$ is independent of x and t.Then, $x(0) < \frac{c}{q(\phi)} \Rightarrow x(t) < \frac{c}{q(\phi)}$, for all t.

Proof: See Lemma 4.1 of [19] for the proof.

For the system (1),

$$\dot{x}(t) + \dot{y}(t) \le \lambda + \frac{s_1}{k} - d_1(x(t) + y(t))$$

$$\Rightarrow x(t) + y(t) \le \frac{\lambda k + s_1}{kd_1} \tag{3}$$

$$\Rightarrow x(t) \le \frac{\lambda k + s_1}{kd_1} \text{ and } y(t) \le \frac{\lambda k + s_1}{kd_1}. \tag{4}$$

Now,

$$\dot{z}(t) \le s(\frac{\lambda k + s_1}{kd_1}) + \frac{s_2}{k} - d_3z \Rightarrow z(t) \le \frac{s(\lambda k + s_1) + s_2d_1}{kd_1d_3}. \tag{5}$$

Hence the system is bounded in the region Ω defined below:

$$\Omega = \{(x(t), y(t), z(t)) \in R_+^3, x(t) \le \frac{\lambda k + s_1}{kd_1},$$

$$y(t) \le \frac{\lambda k + s_1}{kd_1}, z(t) \le \frac{s(\lambda k + s_1) + s_2d_1}{kd_1d_3}\}$$

C. Stability of the System

For E_1, the Jacobian matrix becomes J_1 where the eigen values for J_1 are $-d_1, \frac{\beta(\lambda k + s_1)}{d_1 k} - d_2$ and $-d_3$ respectively. Thus we get the basic reproduction ratio $R_0 = \frac{\beta(\lambda k + s_1)}{d_1 d_2 k}$.

Proposition 1: The disease-free equilibrium E_1 corresponds to the maximum level of healthy uninfected CD4$^+$ T cells in absence of virus when the population of infected cells or CTL is nil. Here E_1 is attained when $R_0 < 1$. Also if $R_0 < 1$ then E_1 is local asymptotically stable. If $R_0 > 1$ then the system E_1 becomes unstable.

For E_2, the Jacobian matrix becomes J_2 where the eigen values are $-d_1, \frac{\beta(\lambda k + s_1)}{d_1 k} - d_2 - \frac{ps_2}{kd_3}$ and $-d_3$ respectively.

Proposition 2 : Equilibrium state E_2 exists when R_0 varies between 1 and $1 + \frac{ps_2}{kd_2 d_3}$, i.e if $1 < R_0 < 1 + \frac{ps_2}{kd_2 d_3} = 1 + R_1$, then E_2 is local asymptotically stable. If $R_0 > 1 + \frac{ps_2}{kd_2 d_3}$ then the system E_2 is unstable. In other words, condition for existence of E_2 holds when immune response is highly active in killing the infected cells i.e. the host system has a tendency to eliminate infection on its own and is yet to attain endemic equilibrium.

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,

$$a_1 = d_1 + d_3 + \beta y^* > 0, a_2 = d_3(d_1 + \beta y^*) + sp^2 y^{*2}$$
$$+ \beta^2 x^* y^* + \frac{ms_1 y^{*m}}{(k + y^{*m})^2} \quad \times (\beta y^* - p^2 y^{*2})$$

and

$$a_3 = p^2 y^{*2}(d_1 + \beta y^*)(s - \frac{ms_2 y^{*m-1}}{(k + y^{*m})^2}) + \beta d_3 y^*$$
$$\times (\beta x^* + \frac{ms_1 y^{*m-1}}{(k + y^{*m})^2}) > 0$$

From Routh-Hurwitz condition, the necessary and sufficient condition for local asymptotical stability |of the steady state is $a_1 > 0, a_3 > 0, a_1 a_2 - a_3 > 0$.

Proposition 3: The system E^* is stable if

(i) $1 + \frac{ps_1}{d_2 d_3 k} < R_0 < 1 + \frac{s_1}{\lambda k} = 1 + R_2$ and

(ii) $a_1 a_2 - a_3 > 0$ are satisfied. Thus we can conclude that the endemic equilibrium E^* exists when all the three components considered in host-virus dynamics possess positive values and the system attains infected equilibrium state. Moreover, it has been observed that E^* does not exist for very large values of k or host-virus interaction coefficient. High

viral load affects the source of T cells, kills uninfected and infected CD 4^+ T cells and results in immunological gap due to deficiency of CTL stimulation.

IV. THE OPTIMAL CONTROL PROBLEM

In this section our main aim is to minimize the cost as well as the infected CD 4^+ T cell count and maximize the uninfected CD 4^+ T cell. Thus we construct the optimal control problem where the state system is

$$\begin{aligned}\dot{x} &= \lambda + \frac{s_1}{k+y^m} - d_1 x - \beta(1-\eta_1 u_1(t))xy + \eta_2 u_2(t)x \\ \dot{y} &= \beta(1-\eta_1 u_1(t))xy - d_2 y - pyz \\ \dot{z} &= sy + \frac{s_2}{k+y^m} - d_3 z + \eta_3 u_2(t)z,\end{aligned} \tag{6}$$

and the control function is defined as

$$J(u_1,u_2) = \int_{t_i}^{t_f} [Pu_1^{\,2} + Qu_2^{\,2} - x^2 + y^2]dt. \tag{7}$$

The control functions $u_1(t)$ and $u_2(t)$ represent the percentage of effect RTIs and IL-2 have on interaction of T cell with virus. The Parameters P and Q are the weight on the benefit of the cost. These are the cost of per unit of RTI and IL-2 respectively.

Here we have considered that RTI reduces the infection rate by $(1-\eta_1 u_1)$ where η_1 is the drug effectiveness and u_1 is the control input doses of RTI. We have also considered the enhancement of uninfected CD 4^+ T cells and CTL responses through IL-2 treatment, defined by $\eta_2 u_2$, and $\eta_3 u_2$ respectively. Here u_2 denotes control input of IL-2 treatment and η_2, η_3 are the drug effectiveness of IL-2 for uninfected CD4$^+$ T cells and CTL population respectively.

Here the control functions $u_1(t)$ and $u_2(t)$ are bounded, Lebesgue integrable function [20].

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

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

To determine the optimal control $u_1^{\,*}$ and $u_2^{\,*}$, we use the "Pontryagin Minimum Principle" [14]. To solve the problem we use the Hamiltonian given by

$$\begin{aligned}H = Pu_1^{\,2} + Qu_2^{\,2} - x^2 + y^2 + \xi_1\{\lambda + \frac{s_1}{k+y^m} \\ - d_1 x - \beta(1-\eta_1 u_1(t))xy + \eta_2 u_2(t)x\} + \\ \xi_2\{\beta(1-\eta_1 u_1(t))xy - d_2 y - pyz\} + \xi_3\{sy + \\ \frac{s_2}{k+y^m} - d_3 z + \eta_3 u_2(t)z\}.\end{aligned} \tag{8}$$

By using the "Pontryagin Minimum Principle" and the existence condition for the optimal control theory [14] we obtain the following theorem.

Theorem: 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 functions ξ_1, ξ_2, ξ_3 satisfying the equation.

Proof: By using Pontryagin Minimum principle [14] the unconstrained optimal control variable u_1^* and u_2^* satisfy

$$\frac{\partial H}{\partial u_1^*} = \frac{\partial H}{\partial u_2^*} = 0, \tag{9}$$

since

$$H = [Pu_1^2 - \xi_1(1-\eta_1 u_1(t))\beta xy + \xi_2(1-\eta_1 u_1(t))\beta xy] + [Qu_2^2 + \xi_1 u_2 x + \xi_3 \eta_3 u_2 z]$$
$$+ other\ terms\ without\ u_1\ and\ u_2. \tag{10}$$

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

$$\frac{\partial H}{\partial u_1^*} = 2Pu_1^* + \beta xy\,\eta_1(\xi_1 - \xi_2) = 0,$$

$$\frac{\partial H}{\partial u_2^*} = 2Qu_2^* + \xi_1\eta_2 x + \xi_3\eta_3 z = 0.$$

Then we obtain

$$u_1^* = \frac{\beta xy\eta_1(\xi_2 - \xi_1)}{2P},\ u_2^* = -\frac{(\xi_1\eta_2 x + \xi_3\eta_3 z)}{2Q}. \tag{11}$$

Since the standard control is bounded, thus we conclude for the control u_1:

$$u_1^* = \begin{cases} 0, & \frac{\beta xy\,\eta_1(\xi_2 - \xi_1)}{2P} \le 0; \\ \frac{\beta xy\,\eta_1(\xi_2 - \xi_1)}{2P}, & 0 < \frac{\beta xy\,\eta_1(\xi_2 - \xi_1)}{2P} < 1; \\ 1 & \frac{\beta xy\,\eta_1(\xi_2 - \xi_1)}{2P} \ge 1. \end{cases}$$

Hence the compact form of u_1^* is

$$u_1^* = \min\{1, \frac{\beta xy\eta_1(\xi_2 - \xi_1)}{2P}\}. \tag{12}$$

In similar way we get the compact form of u_2^* in the form of $u_2^* = \min\{1, \frac{-(\xi_1\eta_2 x + \xi_3\eta_3 z)}{2Q}\}$. (13)

According to "Pontryagin Minimum Principle"[14]

$$\frac{d\xi}{dt} = -\frac{\partial H}{\partial x}, \quad and \tag{14}$$

$$H(x(t), u^*(t), \xi(t), t) = \min_{u \in U} H(x(t), u(t), \xi(t), t). \tag{15}$$

The above equations are the necessary condition satisfying the optimal control $u_1(t), u_2(t)$ and the variables $x(t), y(t), z(t)$.

The system (10) is the adjoint system

$$\frac{d\xi_1}{dt} = -\frac{\partial H}{\partial x}, \frac{d\xi_2}{dt} = -\frac{\partial H}{\partial y}, \frac{d\xi_3}{dt} = -\frac{\partial H}{\partial z}.$$

Taking the partial derivative of H we get,

$$\frac{d\xi_1}{dt} = 2x + \xi_1\{d_1 + (1-\eta_1 u_1(t))\beta y - \eta_2 u_2(t)\} - \xi_2(1-\eta_1 u_1(t))\beta y,$$

$$\frac{d\xi_2}{dt} = -2y + \xi_1\{(1-\eta_1 u_1(t))\beta x + \frac{s_1 m y^{m-1}}{(k+y^m)^2}\} - \xi_2\{(1-\eta_1 u_1(t))\beta x - d_2 - pz\} - \xi_3\{s - \frac{s_2 m y^{m-1}}{(k+y^m)^2}\},$$

$$\frac{d\xi_3}{dt} = \xi_2 py + \xi_3(d_3 - \eta_3 u_2(t)). \quad (16)$$

The optimality of the system consists of the state system with the adjoint system together with the initial condition and the transversality conditions satisfying $\xi_i(t_f) = 0, (i = 1,2,3)$ and $x(0) = x_0,\ y(0) = y_0,\ z(0) = z_0$.

V. NUMERICAL ANALYSIS

We now numerically illustrate the change of the stability due to the negative feedback factor. We have chosen the initial condition of the parameters given as in Table 1. The initial values of the model variables are considered as $x(0) = 1000$, $y(0) = 100$, $z(0) = 10$ [15] and the cell population is expressed as per mm^3. 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 which implies that CTL activity is limited upto a certain value because of the negative feedback effect exerted by high viral load on the stimulation and persistence of HIV-specific immune response after which immune system can no longer trigger off to fight against foreign antigen. The parameters s and d_3 are as mentioned in the Table1. Fig. 2 shows the existence and stability conditions for the systems E_1, E_2 and E^*. Here we plot the basic reproduction ratio R_0 with respect to k. The zone above the red line indicates the zone where there is no possibility of existence of equilibrium of any type because of total break down of the host immunity system due to large value of k.

TABLE I LIST OF PARAMETERS

Para meters	Definition	Range (day $^{-1}$)	Ref.
λ	Constant rate of production rate of CD 4^+ T cells	1-10 mm^{-3}	[16]
d_1	Death rate of uninfected CD 4^+ T cells	0.007-0.1 mm^{-3}	[16]
β	Rate of infection of uninfected T cell	0.00025-0.5 mm^{-3}	[12]
d_2	Death rate of virus producing cells	0.2-0.3 mm^{-3}	[17], [18]
p	Killing rate of virus producing cells by CTL	0.002	[12]
s	Rate of stimulation of CTL	0.1-1	[12]
d_3	Decay rate of CTL	0.1-0.15	[12]

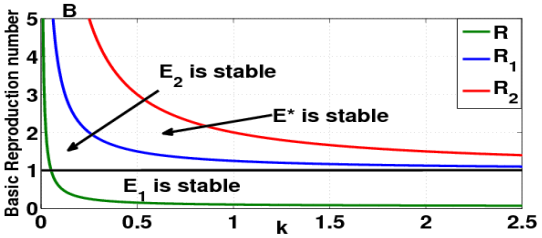


Fig. 2 Phase diagram showing the basic reproduction ratio for the system (1) as a function of k

Thus the infection persists throughout with out any chance of remission. Fig. 3 reflects that numerical value of eradication threshold remains above 1 and possesses similar magnitude if rate of production of $CD4^+$ T cells is increased keeping host-virus interaction coefficient constant at low values and rate of infection considerably high. Thus disease outbreak occurs because of the availability of target uninfected cells susceptible to infection, high infectivity of virus as well as less than the required CTL population for containment of infection.

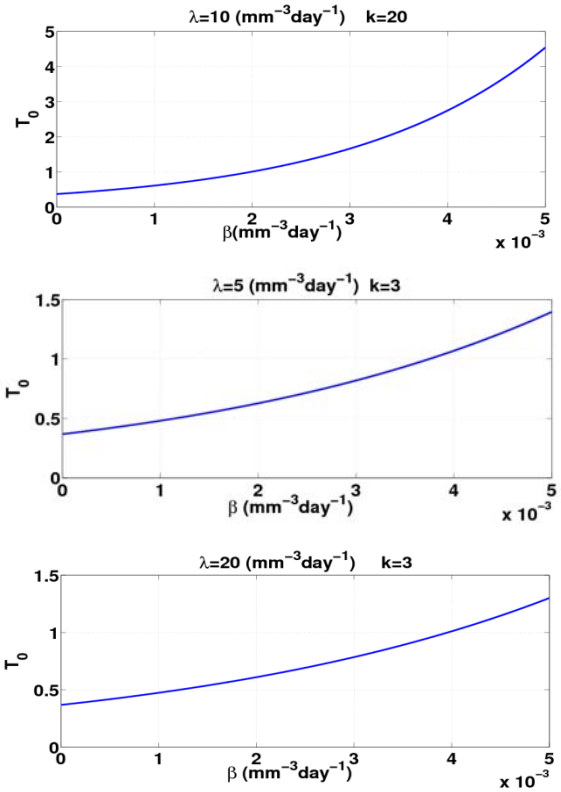
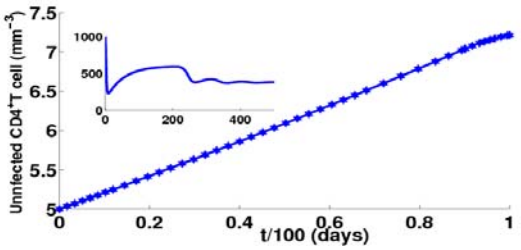


Fig.3 Phase diagram showing the outbreak condition of the system (1) as a function of β

Eradication is possible ($T_0 < 1$) for low values of β even if k and λ are increased because CTL response is effective at this stage.

Thus it can be concluded that k acts as a determinant in deciding the conditions for existence of eradication threshold or disease outbreak and CTL stimulation depends on β. Therapeutic intervention which will interfere with interaction between host cell and virus can theoretically lead to disease-free condition when eradication threshold T will be less than one. But with continuous increase of β, a point will come when eradication is no longer possible because of collapse of immune system.

For the numerical illustration of the optimal control problem (5) and (6) 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 $[0,0.8]$. 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 $t_f = 100$. The solution are displayed in Fig. 4.



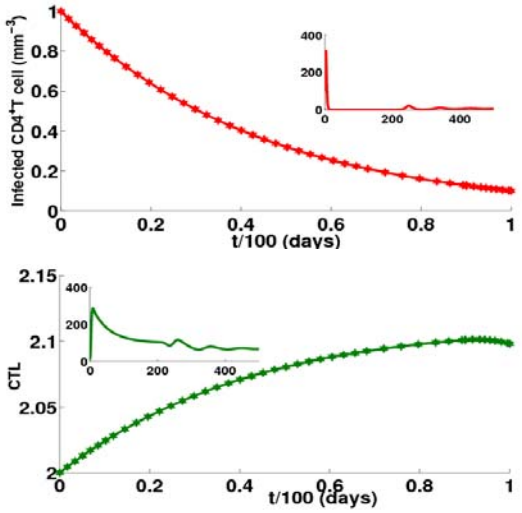


Fig. 4 The system behavior for the optimal treatment schedule of the control variable $u_1(t)$ and $u_2(t)$

Inset: The system behavior in absence of treatment.

If insets of Fig. 4 are considered, the negative feedback effect of virus load on intensity of CTL response is very clear. During primary stage of infection when viral load is low, CTL population is quite high which declines when viral count starts increasing.

From Fig. 5 it is evident that IL-2 needs to be continued for a longer duration and given at a higher initial value compared to HAART.

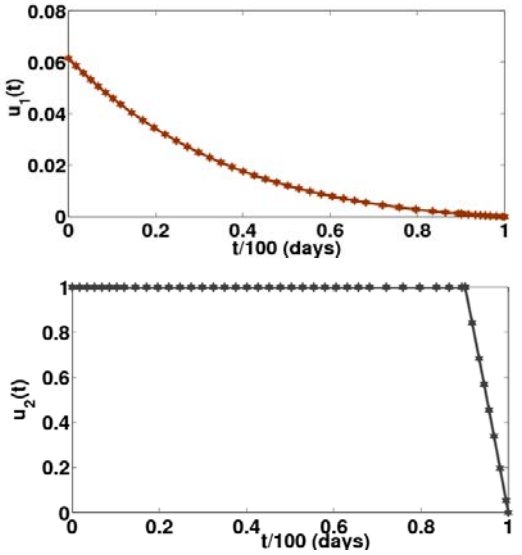


Fig. 5 The optimal control schedule for the system (1)

If the observations from Fig. 4 and Fig. 5 are combined together, it can be concluded that keeping IL-2 dose constant through time interval of treatment reduces the dose requirement of HAART with time with successful enhancement of CTL and CD 4^+ T cell population, and consequent decline in count of infected cells. This maximizes treatment benefit with respect to incidence of side effects and cost. Thus if a sufficient immune response can be maintained through administration of immunomodulants such as IL-2, low drug treatment schedule with HAART can be achieved.

VI. DISCUSSION AND CONCLUSIONS

In the present study, the concept of host-virus interaction coefficient, k, has been introduced in delineating the complexities of host-virus interaction dynamics. For proper characterization of long-term dynamics it becomes essential to incorporate negative feedback control effect induced by high viral load on stimulation of HIV-specific CTL-mediated immune response. During primary stage of infection, when viral load is substantially low and CTL response is yet to develop in a full-fledged manner, negative feedback effect is negligible.The present paper focuses on the existence and conditions of stability of

three equilibria depending on different values of basic reproduction ratio, R_0.

Effect of negative feedback control by high viral load on CTL stimulation is observed in the relationship between β and T when threshold condition for eradication (or infection persistence) is established.

Previous studies postulated that IL-2 acts as a potential adjuvant with HAART in effective containment of viral infection and rejuvenation of completely impaired host immune system. Our model shows that even if negative feedback effect is considered, the combination therapy of reverse transcriptase inhibitor and IL-2 is highly effective in immune reconstitution and simultaneous control of infected cell population by reduced doses of HAART in a cost-effective fashion.

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Priti Kumar Roy (Associate Professor): Awarded Ph.D. degree from Jadavpur University in 2007. Scientific publication in international level commenced before this and now the number of publication stands near about 50. Most of the publications have been cited by others many times. Edited two books, among one of this is on Infectious Disease published by Intech Open Access Publisher. 8 Ph.D. students doing their research works under his supervision and one student already submitted his thesis. Selected as reviewer in many International and National Journals. Engaged teaching in Jadavpur University since 2008 and before that involved in Govt. colleges. Invited to deliver lectures in various Indian Universities, Institutes and abroad also. Member in different National and International Societies like Bio mathematical Society of India and IAENG. Handles research projects sponsored by various Indian Government agencies. Received Best Paper Award in World Congress on Engineering 2010 which was held in London, UK. Selected as an Indian Scientist for nomination under International Collaboration/Exchange programme 2011-2012 by INSA.

Amar Nath Chatterjee (Research Student): He studied his BSc and MSc from the Jadavpur University. Submitted his thesis in Mathematical Biology at Jadavpur University under the guidance of Dr. Priti Kumar Roy. He has more than fifteen publications in different national and international journals, and also in book chapter.

Sutapa Biswas Majee (Asst. Professor): She has been working in the field of microbiology, parasitology and mathematical modeling of diseases for the last 10 years. She has completed her M. Pharm. and Ph.D in Pharmacy from Jadavpur University. She has five publications in different international journals.