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Mathematical Modeling of IL-2 Based Immune Therapy on T Cell Homeostasis in HIV

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1. Introduction

The past few years there have been witnessed the initiation of new or more effective therapies for the treatment of HIV disease. But it is the established reality for the treatment procedure of HIV disease; mathematical modeling is very essential and supportive, in accepting the dynamics of HIV infection and also for the purpose of specific antiviral treatment strategies. Mathematical models have been constructed to explore the co- relation between disease progression, generation of HIV specific immune response in primary stage, depletion of CD4$^+$ T cell population, leading to severe impairment and dysregulation of host immune system and emergence of numerous opportunistic infection. Mathematical model accompanied with definite biological interpretation and relevance can provide a clear representation of host-pathogen interaction dynamics. Human Immunodeficiency Virus (HIV) targets the immune cells mainly CD4 positive T lymphocytes (CD4$^+$T, a type of white blood cells), which is the main component of immune system. CD4$^+$T cells or " helper" T cells also send signals to the second group of immune response cells (CD8$^+$T cell or CTL) in the body, the precursor Cytotoxic T Lymphocytes (CTL_p) to induce HIV-specific CTL response through the generation of functionally active effector CTL (CTL_e). HIV infection can be finally eradicated through co-ordinated interplay between CD4$^+$T cells and CTLs when infected CD4$^+$T cells are killed by CTLs. Thus, if CTL population can be maintained at a high level, the HIV-infected individuals can remain healthy for a longer period of time due to slower disease progression. The safest and cheapest therapeutic intervention aims to keep the CD4$^+$T cell population together with CTL count at a positive value, both of which will bring down the viremia to very low levels.

From an immunological standpoint, progression of HIV can be characterized by continual reduction of CD4$^+$T lymphocyte subset levels in peripheral compartment and lymphoid tissue as well, with greater reduction being observed in the former. Dysfunctional lymphocytes with high propensity for apoptosis and loss of proper cell cycle control account

for deviation from T cell homeostasis in an HIV-infected individual. HIV antigen activates immune system, increases cell turnover and induces apoptosis of uninfected $CD4^+T$ and $CD8^+T$ cells leading to complete impairment of immune system (Sereti et al., 2004).

Immune activation and subsequent sensitivity to apoptotic stimuli can be reverted back by introduction of potent antiretroviral agents. Successful therapy with Highly Active Anti Retroviral Therapy (HAART) efficiently suppresses viral replication but with only partial immune reconstitution. Moreover, complete eradication of viral population from the system is practically not feasible with HAART alone, even if continued for a long time. Viral relapse is known to occur as soon as the therapy is discontinued (Roy & Chatterjee, 2011). Thus arises the need of addition of new therapeutic modalities in the form of administration of immunomodulatory agent, IL-2, to the armamentarium of antiretroviral agents promoting complete immune reconstitution.

IL-2 is a very well characterized T-cell growth factor determining proliferation and differentiation of whole T cell compartment. Following antigen-activation, IL-2 is produced by both $CD4^+$ and $CD8^+T$ (in comparatively lesser quantities) cell subsets, in the peripheral lymphoid tissues of spleen and lymph nodes, in an autocrine and paracrine fashion respectively (Smith, 2001), (Banerjee, 2008).

Infection by HIV affects $CD4^+T$ and $CD8^+T$ cells in a differential manner with selective depletion of the $CD4^+T$ cells whereas expansion of $CD8^+T$ cells is maintained till late stages of infection (Marchettia et al., 2004). Though IL-2 is produced by $CD4^+$ and $CD8^+T$ cells, it exerts differential effects on $CD4^+T$ cells, with preferential expansion and prolonged survival of peripheral naïve and recall subsets, but not effector and memory phenotype (Sereti et al., 2004), (Marchettia et al., 2004). IL-2 does not target progenitor cells of the bone marrow or thymus (Smith, 2001), (De, 2001). Net outcome of IL-2 therapy is rejuvenation of T cell pool marked by decreases in T cell turnover, proliferation and activation. IL-2 therapy also increases T cell responsiveness to suboptimal levels of endogenous IL-2 by increasing expression of its receptor, CD25, on $CD4^+$ T cells (Sklar et al., 2007). $CD8^+$ cells seem to follow different homeostatic dynamics, more or less independent of immunoregulatory activity of IL-2. Apart from its regulatory activity on specific cellular populations, IL-2 can also augment the production of IL-2 itself (Bortolin et al., 2001). In contrast, HAART alone results in selective rescue of $CD4^+$ memory cells, with no change in naïve compartment (Franzetti et al., 2005). Thus, IL-2 immunotherapy broadens HAART-induced immune recovery.

The degree of $CD4^+T$ cell recuperation after IL-2 administration depends on the nadir $CD4^+$ T cell count and the dose and duration of IL-2 therapy (Paredes et al., 2002). IL-2 can be given either intravenously or subcutaneously at a low dose intermittently but it is recommended that it should never be given alone. It should always be administered as an adjuvant to HAART for maximum biological and clinical benefits. It may be stopped as soon as $CD4^+T$ cell count is "normalized" to pre-infection levels and immune activation is reduced (De, 2001). Improvement in immunological parameters of the host such as expansion of $CD4^+T$ cells may continue for several months even after IL-2 administration has been interrupted (Bortolin et al., 2001). The potential of IL-2 to reverse the HIV-mediated T cell homeostasis imbalances by altering the in vivo dynamics of T-lymphocytes and regulatory cytokines, with transient or almost no change in HIV viral load, offers the appealing prospect of obtaining major immune reconstitution in the treatment of HIV disease.

Several mathematical models have been developed to describe the behavior of the HIV, when it interacts with the human immune system and causes a decline in the $CD4^+T$ cells count (Bonhoeffer et al., 1997), (Perelson & Nelson, 1999), (Wodarz et al., 2000), (Gumel et al., 2002), (Roy & Chatterjee, 2010). In their research they expand a innovative thinking, impact of drag in a HIV individual integrating with their model dynamics. Perelson et al. utilized clinical data from HIV infected patients and fitted them to their mathematical model and subsequent numerical simulations to prove the clinical manifestations of AIDS such as long latency period, depletion of $CD4^+T$ cells and low level of free virus in the whole body.

Now a days most of the authors developed their work by including various aspects of HIV specific antiviral immune response dominated by CTLs because of its significant role in controlling virus replication and disease progression. A simple mathematical model was developed by Wodarz et al. (Wodarz et al., 1999) to study the co-relation between HIV and immune system during the natural course of infection and in the background of different antiviral treatment regimes. They have suggested the need for an efficient CTL memory response for effective containment of viral replication. CTL memory is adversely affected during long-term infection due to depletion of $CD4^+T$ cell pool in the system. From analytical and numerical analysis in their mathematical model, (Roy & Chatterjee, 2011) has been shown that when the immune response are high, less medication is needed to control and regulate infection. Their mathematical model also reflect that optimal treatment is reduces the period of time while the immune response of the uninfected T cell takes over.

Discrete and continuous time delay or time lag is assumed to exist in the various stages of HIV progression (Herz et al., 1996), (Calshaw et al., 2000), (Roy & Chatterjee, 2011), and (Roy & Chatterjee, 2010) which have been incorporated into the mathematical model with firm biological explanations. It is well known that, delay differential equations cause a stable steady state to lose its stability and cause oscillations. For avoiding the side effects due to chemotherapy, various mathematical models have been formulated in control therapeutic approach (Fleming et al., 1975), (Gumel et al., 2002).

In the present paper, the reconstitution dynamics of $CD4^+T$ cells and effect on CTLs in HIV-infected individuals has been studied in presence of HAART and IL-2, where the basic model as proposed by Wodarz and Nowak has been modified (Wodarz and Nowak). They have suggested the need for an efficient CTL memory response for effective containment of viral replication. CTL memory is adversely affected during long-term infection due to depletion of $CD4^+T$ cell pool in the system. Mathematical modeling of such dynamics will help in delineating the interplay between T lymphocyte subsets in the course of HIV infection and thereby establishing optimum conditions for effective immune -based therapy associated with HAART. In this research article delay induced system in the same mathematical model of HIV has been investigated to understand the effect of combination therapy of HAART and IL-2. Attempts have also been made to apply the principles of optimal control theory to the proposed mathematical model for rational administration of IL-2 adjuvanated HAART in an effort to successfully eradicate the virus from the host system and cure the patient completely.

2. Presentation of the mathematical model

In this research article we develop a viral dynamical model of Wodarz et. al (Wodarz et al., 1999) by introducing IL-2 therapy in presence of HAART.

The model is given below,

$$\dot{x}(t) = \lambda - \beta(1 - \eta_1 u_1)x(t)y(t) - dx(t) + \gamma x(t)$$
$$\dot{y}(t) = \beta(1 - \eta_1 u_1)x(t)y(t) - ay(t) - py(t)z(t)$$
$$\dot{w}(t) = cx(t)y(t)w(t) - cq_1 y(t)w(t) - bw(t) + \gamma_1 w(t)$$
$$\dot{z}(t) = cq_2 y(t)w(t) - hz(t), \tag{1}$$

with initial conditions: $x(0) > 0, y(0) > 0, w(0) > 0, z(0) > 0$.

Here x represents uninfected CD4$^+$T cells, and y, w, z are infected CD4$^+$T cells, Cytotoxic T lymphocyte precursors (CTL_p), CTL effector cells respectively. Here λ represents the rate of production of CD4$^+$T cells from bone marrow and these immature cells migrate to thymus and they are matured to immunocompetent T cells. The natural death rate of uninfected CD4$^+$T cell is d and β is the rate at which uninfected CD4$^+$T cell become infected. Natural death rate of infected cell is a. The clearance rate of infected cells by CTL effector is p. CTL_p are assumed to proliferate in response to antigenic stimulation and then differentiate into CTL memory. The rate of proliferation of CTL_p population is c and they decay at a rate b. Since the differentiation rate of precursor CTL (CTL_p) not at all same as the proliferation rate of effector CTL (CTL_e), thus we consider q_1 and q_2 as multiplicative capacity of differentiated precursor CTL and proliferated effector CTL respectively. We also assume that the removal rate of effector CTL is h.

Here we introduce IL-2 therapy in presence of HAART. We also consider that the RTI reduces the infection rate β by $(1 - \eta_1 u_1)$ where η_1 represents the drug efficacy parameter and u_1 is the control input doses of the drug RTI. By introducing interleukin protein it enhances the growth of uninfected T cell and also in a smaller quantity, increases growth of CTL_p. Here γ and γ_1 are the activation rates of uninfected T cell and CTL_p population respectively.

3. General analysis of the mathematical model

Figure 1 shows that, due to introducing of cocktail drug therapy (HAART and IL-2), uninfected CD4$^+$ T cell moves to its stable position. Further infected CD4$^+$ T cell population moves to a very lower levels, and ultimately goes towards extinction. Thus effector CTL population attains a lower steady state, where as CTL precursor enhanced due to effect of IL-2.
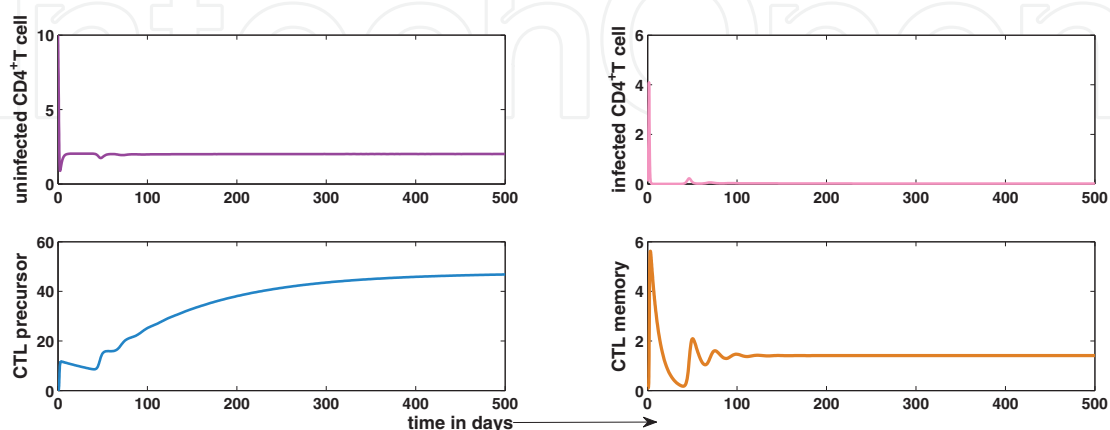

Fig. 1. Solution trajectory of the non-delayed system. All parameter values are taken from Table 1.

3.1 Equilibria and their existence

The system (1) with the initial condition possesses the following positive equilibrium $E_1(x_1, 0, 0, 0)$, $E_2(x_2, y_2, 0, 0)$ and $E^*(x^*, y^*, w^*, z^*)$.

Where, $x_1 = \frac{\lambda}{d-\gamma}$, $x_2 = \frac{a}{\beta(1-\eta_1 u_1)}$, $y_2 = \frac{\beta(1-\eta_1 u_1)\lambda + a(\gamma-d)}{a\beta(1-\eta_1 u_1)}$ and $x^* = \frac{\lambda}{d+\beta(1-\eta_1 u_1)y^* - \gamma}$,

$y^* = \frac{-\{(d-\gamma)cq_1 + \beta(1-\eta_1 u_1)(b-\gamma_1) - c\lambda\} + \sqrt{\{(d-\gamma)cq_1 + \beta(1-\eta_1 u_1)(b-\gamma_1) - c\lambda\}^2 - 4acq_1\beta(1-\eta_1 u_1)(b-\gamma_1)(d-\gamma)}}{2cq_1\beta(1-\eta_1 u_1)}$,

$w^* = \frac{h\beta(1-\eta_1 u_1)x^* - ha}{cpq_2 y^*}$, $z^* = \frac{\beta(1-\eta_1 u_1)x^* - a}{p}$.

During initial stages of infection when the virus enter in the system but not yet attack any CD4$^+$T cell, then infection free steady state E_1 exists, if $d > \gamma$, entail that death rate of uninfected CD4$^+$T cells is greater than the rate of production of uninfected cells under the influence of IL-2.

E_2 exists if $x_1 > x_2$, i.e at early stages of infection when T cells have become infected but CTL response is yet to develop and it indicates a very crucial situation. It exists when uninfected cell population at initial stage of infection is greater than steady state value of uninfected T cell population in presence of infection but without any immune response.

E^* exists if the following conditions holds, (i)$\frac{\gamma-d}{\beta(1-\eta_1 u_1)} < y^* < y_2$, (ii)$(b-\gamma_1)(d-\gamma) < 0$.

From the above two conditions we can say that (i) if infected cell population (y^*) at coexistence equilibrium point lies between these two threshold values and (ii) product of two terms $(b - \gamma_1)(d - \gamma)$, i.e. difference between death rate and production rate of CTL_p in presence of IL-2 $(b - \gamma_1)$ and difference between death rate and production rate of uninfected CD4$^+$T cell in presence of IL-2, $(d - \gamma)$ is negative.

3.2 Stability analysis of the system:

Here we study the nature of stability of the system (1) around different equilibrium points. From our mathematical study we have the following three propositions.

Proposition 1 : The system (1) is locally asymptotically stable around E_1 if the following condition holds,

$$(i)\gamma < d$$
$$(ii)\gamma_1 < b$$
$$(iii)\frac{\beta(1-\eta_1 u_1)\lambda + a(\gamma-d)}{a\beta(1-\eta_1 u_1)} < 0.$$

Proof :
The s/eigenvalues of the above upper triangular jacobian matrix are

$$\xi_1 = \gamma - d$$
$$\xi_2 = \frac{\beta(1-\eta_1 u_1)\lambda}{d-\gamma} - a$$
$$\xi_3 = \gamma_1 - b$$
$$\xi_4 = -h.$$

All the characteristic roots corresponding to E_1 will be negative if above proposed conditions are satisfied. Hence the system is locally asymptotically stable around E_1. Whenever E_1 is locally asymptotically stable E_2 does not exists.

Proposition 2: System (1) is locally asymptotically stable around E_2 if $y_2 < \frac{\beta(1-\eta_1 u_1)(b-\gamma_1)}{c(a-q_1\beta(1-\eta_1 u_1))}$ holds.

Proof :
By the same way we can prove this proposition.

Proposition 3: The system is locally asymptotically stable around E^* under R-H criterion for the following parameter values in Table 1.

Parameters	Definition	Values assigned
λ	Constant rate of production of $CD4^+T$ Cells	10.0 cells/ day
d	Death rate of Uninfected $CD4^+T$ cells	0.01 cells/ day
β	Rate of infection	0.001 cells/ day
a	Death rate of infected cells	0.24 cells/ day
p	Clearance rate of infected cells by CTL_e	0.002 / day
c	Rate of proliferation of CTL_p	0.6 /day
b	Decay rate of CTL_p	0.01 /day
h	Decay rate of CTL_e	0.02/day
γ	activation rate of uninfected CD4$^+$T cell by IL-2	0.5/day
γ_1	activation rate of CTL_p by IL-2	0.1/day
q_1	multiplication capacity of differentiated precursor CTL	0.5
q_2	multiplication capacity of proliferated effector CTL	0.3

Table 1. Variables and parameters used in the models (1), (2), (16, 17). All parameter values are taken from (Wodarz et al., 1999), (Calshaw et al., 2000), (Roy & Chatterjee, 2010), (Bonhoeffer et al., 1997), (Nowak and Bangham, 1996).

4. Delay induced system

In this section we proposed and analyzed the mathematical model (1), incorporating delay in activation of uninfected CD4$^+$T cell populations through IL-2 therapy. It should be mentioned here that delay-differential equations demonstrate in a complex dynamics rather than ordinary-differential equations in view of the fact that a time lag could cause a stable equilibrium to become unstable and hence the population may be fluctuated. For better understanding and also for realistic emulation of the delay induced system, we thus introduced a time delay in the production of CTL in our model (1). We also initiated another discrete time delay due to the account of the time lag in CTL_p activation. Thus we have the following delay differential equation model in the form of:

$$\dot{x}(t) = \lambda - \beta(1-\eta_1 u_1)x(t)y(t) - dx(t) + \gamma x(t-\tau_1)$$
$$\dot{y}(t) = \beta(1-\eta_1 u_1)x(t)y(t) - ay(t) - py(t)z(t)$$
$$\dot{w}(t) = cx(t)y(t)w(t) - cq_1 y(t)w(t) - bw(t) + \gamma_1 w(t-\tau_2)$$
$$\dot{z}(t) = cq_2 y(t)w(t) - hz(t), \tag{2}$$

with initial conditions $x(\theta) = x_0 > 0, y(\theta) = 0, w(\theta) = 0, z(\theta) = 0$ for $\theta \in [-max\{\tau_1, \tau_2\}, 0]$.

4.1 Stability analysis of the delay induced system

We further paying our attention to investigate the local asymptomatic stability of the infected steady state E^* for the delay induced system (Equation 2). Now linearizing the system (2)
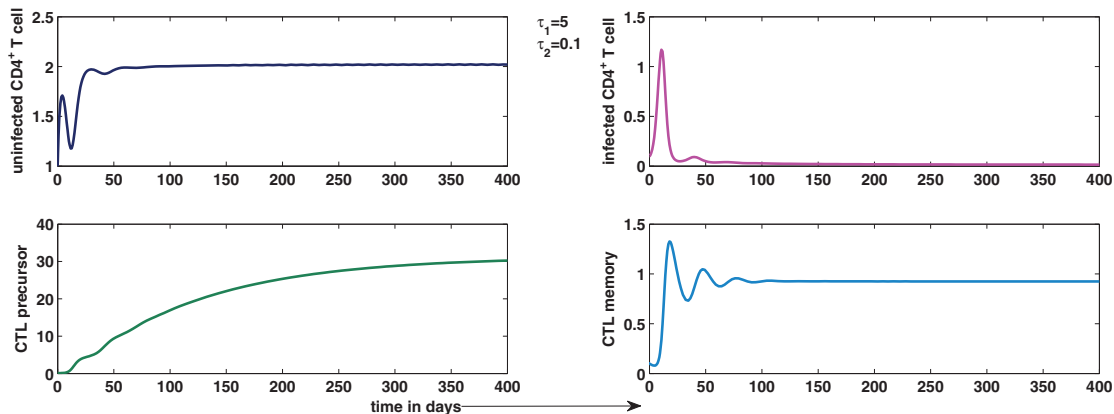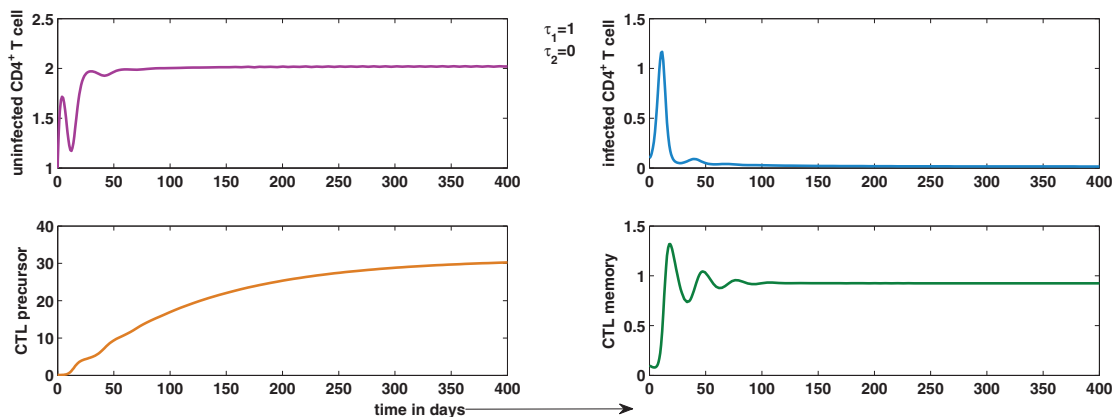
Fig. 2. Solution trajectory of the delayed system. Here $\tau_1 = 5$, $\tau_2 = 0.1$, and all other parameter values are same as Table 1.

about E^* we get,

$$\frac{dT}{dt} = FT(t) + GT(t - \tau_1) + HT(t - \tau_2). \tag{3}$$

Here F, G, H are 4x4 matrices given below,

$$F = \begin{pmatrix} -d - \beta(1 - \eta_1 u_1)y^* & -\beta(1 - \eta_1 u_1)x^* & 0 & 0 \\ \beta(1 - \eta_1 u_1)y^* & \beta(1 - \eta_1 u_1)x^* - a - pz^* & 0 & -py^* \\ cy^*w^* & cx^*w^* - cq_1w^* & cx^*y^* - cq_1y^* - b & 0 \\ 0 & cq_2w^* & cq_2y^* & -h \end{pmatrix}$$

Fig. 3. Solution trajectory of the delayed system. Here $\tau_1 = 1$, $\tau_2 = 0$, and all other parameter values are same as Table 1.

$$G = \begin{pmatrix} \gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$H = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_1 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

The characteristic equation of system (2) is given by,

$$\triangle(\xi) = \mid \xi I - F - e^{-\xi \tau_1} G - e^{-\xi \tau_2} H \mid = 0.$$

This equation can be written as,

$$\psi(\xi, \tau_1, \tau_2) = \xi^4 + A_1 \xi^3 + A_2 \xi^2 + A_3 \xi + A_4 \xi + e^{-\xi \tau_1}[B_1 \xi^3 + B_2 \xi^2 + B_3 \xi + B_4]$$
$$e^{-\xi \tau_2}[C_1 \xi^3 + C_2 \xi^2 + C_3 \xi + C_4] + e^{-\xi(\tau_1 + \tau_2)}[D_1 \xi^2 + D_2 \xi + D_3] = 0. \quad (4)$$

The coefficients are given below,

$$m_{11} = -d - \beta(1 - \eta_1 u_1)y^*, \quad m_{12} = -\beta(1 - \eta_1 u_1)x^*, \quad m_{21} = \beta(1 - \eta_1 u_1)y^*,$$
$$m_{22} = \beta(1 - \eta_1 u_1)x^* - a - pz^*, \quad m_{24} = py^*, \quad m_{31} = cy^*w^*, \quad m_{32} = cx^*w^* - cq_1 w^*,$$
$$m_{33} = cx^*y^* - cq_1 y^* - b, \quad m_{42} = cq_2 w^*, m_{43} = cq_2 y^*, m_{44} = -h,$$

where,

$$A_1 = m_{44} - m_{33} - m_{22} - m_{11},$$

$$A_2 = m_{33}m_{44} + m_{11}m_{44} + m_{22}m_{44} + m_{22}m_{33} + m_{11}m_{33} + m_{22}m_{11} - m_{12}m_{21} - m_{24}m_{42},$$

$$A_3 = -m_{11}m_{33}m_{44} - m_{22}m_{33}m_{44} - m_{11}m_{22}m_{44} + m_{12}m_{21}m_{44} - m_{24}m_{32}m_{43},$$
$$+ m_{24}m_{33}m_{42} + m_{11}m_{24}m_{42} + m_{11}m_{24}m_{42} - m_{11}m_{22}m_{33} + m_{12}m_{21}m_{33},$$

$$A_4 = m_{11}m_{22}m_{33}m_{44} - m_{12}m_{21}m_{33}m_{44} + m_{11}m_{24}m_{32}m_{43} - m_{12}m_{24}m_{31}m_{43}$$
$$- m_{11}m_{24}m_{33}m_{42},$$

$$B_1 = -\gamma,$$

$$B_2 = \gamma(m_{44} + m_{33}m_{22}),$$

$$B_3 = \gamma(-m_{33}m_{44} - m_{22}m_{44} - m_{22}m_{33} + m_{24}m_{42}),$$

$$B_4 = \gamma(m_{22}m_{33}m_{44} + m_{24}m_{32}m_{43} - m_{24}m_{33}m_{42}),$$

$$C_1 = -\gamma_1,$$

$$C_2 = \gamma_1(m_{44} + m_{22}m_{11}),$$

$$C_3 = \gamma_1(-m_{22}m_{44} - m_{11}m_{44} - m_{22}m_{11} + m_{24}m_{42}),$$

$$C_4 = \gamma_1(m_{11}m_{22}m_{44} - m_{12}m_{21}m_{44} - m_{11}m_{24}m_{42}),$$

$$D_1 = \gamma\gamma_1,$$

$$D_2 = \gamma\gamma_1(-m_{22}m_{44}),$$

$$D_3 = \gamma\gamma_1(m_{22}m_{44}).$$

The characteristic equation (4) is a transcendental equation in ξ. It is known that E^* is locally asymptotically stable if all the roots of the corresponding characteristic equation have negative real parts and unstable if purely imaginary roots are appears. As we know that the transcendental equation has infinitely many complex roots (Calshaw et al., 2000), so in presence of τ_1, τ_2, analysis of the sign of roots is very complicated. Thus, we begin our analysis by setting one delay which is equal to zero and then deduce the conditions for stability, when both time delays are non zero.

Case I :- When $\tau_1 = \tau_2 = 0$:

In absence of both the delays the characteristics equation (4) becomes,

$$\xi^4 + \xi^3(A_1 + B_1 + C_1) + \xi^2(A_2 + B_2 + C_2 + D_1) + \xi(A_3 + B_3 + C_3 + D_2)$$
$$+ (A_4 + B_4 + C_4 + D_3) = 0. \qquad (5)$$

Employing Routh Hurwitz criteria for sign of roots we have the same results as in non delayed system analysis.
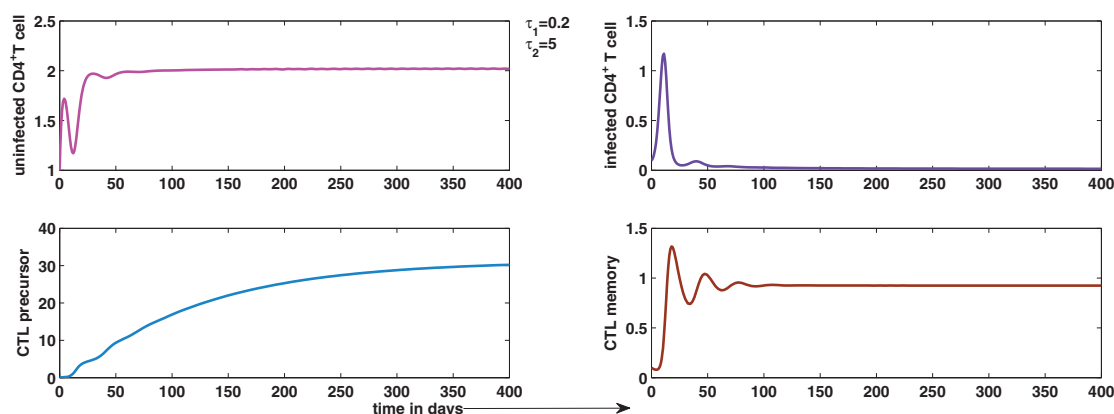

Fig. 4. Solution trajectory of the delayed system. Here $\tau_1 = 0.2, \tau_2 = 5$, and all other parameter values are same as Table 1.

Case II :- When $\tau_1 > 0, \tau_2 = 0$:

In this case we consider no delay in CTL precursor immune response i.e $\tau_2 = 0$, then the characteristic equation becomes,

$$\xi^4 + \xi^3(A_1 + C_1) + \xi^2(A_2 + C_2) + \xi(A_3 + C_3) + (A_4 + C_4)$$
$$+ e^{-\xi\tau_1}[B_1\xi^3 + \xi^2(B_2 + D_1) + \xi(B_3 + D_2) + (B_4 + D_3)] = 0. \qquad (6)$$

For $\tau_1 > 0$, (6) has infinitely many roots. Using Rouche's theorem and continuity of τ_1, the transcedental equation has roots with positive real parts if and only if it has purely imaginary roots. Let $i\theta$ be a root of equation (6) and hence we get,

$$\theta^4 - \theta^2(A_2 + C_2) + (A_4 + C_4) = \cos\theta\tau_1[\theta^2(B_2 + D_1) - (B_4 + D_3)]$$
$$+ \sin\theta\tau_1[\theta^3 D_1 - \theta(B_3 + D_2)]$$
$$\theta(A_3 + C_3) - \theta^3(A_1 + C_1) = \cos\theta\tau_1[\theta^3 D_1 - \theta(B_3 + D_2)]$$
$$- \sin\theta\tau_1[\theta^2(B_2 + D_1) - (B_4 + D_3)]. \qquad (7)$$

Squaring and adding above two equations,

$$\theta^8 + \theta^6[(A_1 + C_1)^2 - 2(A_2 + C_2) - D_1^2]$$
$$+ \theta^4[(A_2 + C_2)^2 + 2(A_4 + C_4) - 2(A_3 + C_3)(A_1 + C_1) - (B_2 + D_1)^2$$
$$+ 2D_1(B_3 + D_2)] + \theta^2[(A_3 + C_3)^2$$
$$- 2(A_2 + C_2)(A_4 + C_4) + 2(B_2 + D_1)(B_4 + D_3) - (B_3 + D_2)^2]$$
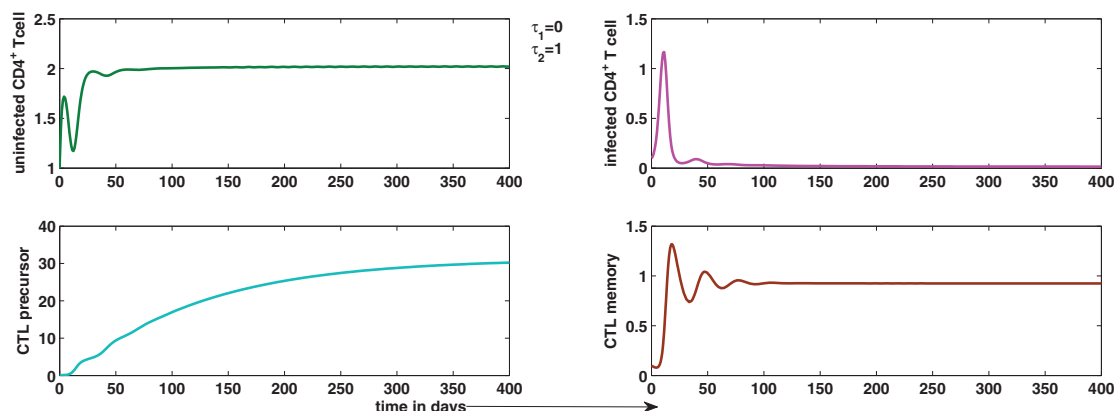$$+ [(A_4 + C_4)^2 - (B_4 + D_3)^2] = 0. \qquad (8)$$

Fig. 5. Solution trajectory of the delayed system. Here $\tau_1 = 0$, $\tau_2 = 1$, and all other parameter values are same as Table 1.

Simplifying and substituting $\theta^2 = l$ in equation (8) we get the following equation,

$$l^4 + \alpha_1 l^3 + \alpha_2 l^2 + \alpha_3 l + \alpha_4 = 0. \tag{9}$$

Where,

$$\alpha_1 = (A_1 + C_1)^2 - 2(A_2 + C_2) - D_1^2,$$
$$\alpha_2 = (A_2 + C_2)^2 + 2(A_4 + C_4) - 2(A_3 + C_3)(A_1 + C_1) - (B_2 + D_1)^2 + 2D_1(B_3 + D_2),$$
$$\alpha_3 = (A_3 + C_3)^2 - 2(A_2 + C_2)(A_4 + C_4) + 2(B_2 + D_1)(B_4 + D_3) - (B_3 + D_2)^2,$$
$$\alpha_4 = (A_4 + C_4)^2 - (B_4 + D_3)^2.$$

It may be noted that the equation (9) will have negative real part if and only if Routh-Hurwitz criterion is satisfied and hence equation (6) will have no purely imaginary root. From the above analysis we have the following proposition.

Proposition 4 : In the delay induced system (2), the infected steady state E^* will be locally asymptotically stable for all $\tau_1 > 0$ if the following conditions are satisfied:
$\alpha_1 > 0$, $\alpha_4 > 0$, $\psi = \alpha_1 \alpha_2 - \alpha_3 > 0$, $\psi \alpha_3 - \alpha_1^2 \alpha_4 > 0$.

Case III :- When $\tau_1 = 0, \tau_2 > 0$:
In absence of τ_1, the characteristic equation (4) have the following form,

$$\xi^4 + \xi^3(A_1 + B_1) + \xi^2(A_2 + B_2) + \xi(A_3 + B_3) + (A_4 + B_4)$$
$$+ e^{-\xi\tau_2}[C_1\xi^3 + \xi^2(C_2 + D_1) + \xi(C_3 + D_2) + (C_4 + D_3)] = 0. \tag{10}$$

Similarly as in case II we substitute $\xi = i\theta$ and we get,

$$\theta^4 - \theta^2(A_2 + B_2) + (A_4 + B_4) = \cos\theta\tau_2[\theta^2(C_2 + D_1) - (C_4 + D_3)]$$
$$+ \sin\theta\tau_2[\theta^3 C_1 - \theta(C_3 + D_2)]. \tag{11}$$

$$\theta(A_3 + B_3) - \theta^3(A_1 + B_1) = \cos\theta\tau_2[\theta^3 C_1 - \theta(C_3 + D_2)]$$
$$- \sin\theta\tau_1[\theta^2(C_2 + D_1) - (C_4 + D_3)]. \tag{12}$$

Squaring and adding, and then substituting $\theta^2 = s$ we have,

$$s^4 + \delta_1 s^3 + \delta_2 s^2 + \delta_3 s + \delta_4 = 0. \tag{13}$$

Where,

$$
\begin{aligned}
\delta_1 &= (A_1 + B_1)^2 - 2(A_2 + B_2) - C_1^2 \\
\delta_2 &= (A_2 + B_2)^2 + 2(A_4 + B_4) - 2(A_3 + B_3)(A_1 + B_1) - (C_2 + D_1)^2 + 2C_1(C_3 + D_2) \\
\delta_3 &= (A_3 + B_3)^2 - 2(A_2 + B_2)(A_4 + B_4) + 2(C_2 + D_1)(C_4 + D_3) - (C_3 + D_2)^2 \\
\delta_4 &= (A_4 + B_4)^2 - (C_4 + D_3)^2.
\end{aligned}
$$

From the above analysis we have the following proposition.

Proposition 5 : In the delay induced system (2), the infected steady state E^* will be locally asymptotically stable for all $\tau_2 > 0$ if the following conditions are satisfied
$\delta_1 > 0$, $\delta_4 > 0$, $\varphi = \delta_1 \delta_2 - \delta_3 > 0$, $\varphi \delta_3 - \delta_1^2 \delta_4 > 0$. If $\delta_4 < 0$ then we have the following proposition,

Proposition 6 : Equation (13) admits at least one positive root if $\delta_4 < 0$ is satisfied.

If θ_0 be a positive root of (13), then equation (10) will have a purely imaginary root $\pm i\theta_0$ corresponding to τ_2. Now we evaluate the critical value of τ_2 for which the deley induced system (2) remain stable. From equation (11,12),

$$\tau_2^* = \frac{acos\phi(\theta_0)}{\theta_0}. \tag{14}$$

Where,

$$
\begin{aligned}
\phi(\theta_0) = &[\{\theta^2(C_2 + D_1) - (C_4 + D_3)\}\{\theta^4 - \theta^2(A_2 + B_2) + (A_4 + B_4)\} \\
&+ \{\theta^3 C_1 - \theta(C_3 + D_2)\}\{\theta(A_3 + B_3) - \theta^3(A_1 + B_1)\}] \\
&\div [\{\theta^2(C_2 + D_1) - (C_4 + D_3)\}^2 + \{\theta^3 C_1 - \theta(C_3 + D_2)\}^2]. \tag{15}
\end{aligned}
$$

From the above analysis we construct the following theorem.

Theorem 1 :

If $\delta_4 < 0$ is satisfied, then the steady state E^* is locally asymptotically stable for $\tau_2 < \tau_2^*$ and becomes unstable for $\tau_2 > \tau_2^*$. When $\tau_2 = \tau_2^*$ a Hopf bifurcation occurs.

Case IV :- $\tau_1 > 0, \tau_2 > 0$

In this case we studied the stability of the steady state E^* in presence of both delays. If all the roots of equation (10) have negative real parts for $\tau > 0$ i.e when the system is locally asymptotically stable then there exists a τ_1^* depending upon τ_2 such that all roots of equation (4) have negative real parts whenever $\tau_1 < \tau_1^*$. Considering all the cases we have the following theorem .

Theorem 2 : Whenever $\delta_4 < 0$ holds then for $\tau_2 < \tau_2^*$, there exists a τ_1^* depending upon τ_2 the steady state E^* is locally asymptotically stable for $\tau_1 < \tau_1^*$ and $\tau_2 < \tau_2^*$.

Special Remarks of the Delay Induced System in view of Numerical Analysis:
Though it is eventually true from our analytical results that for a longer value of delay the
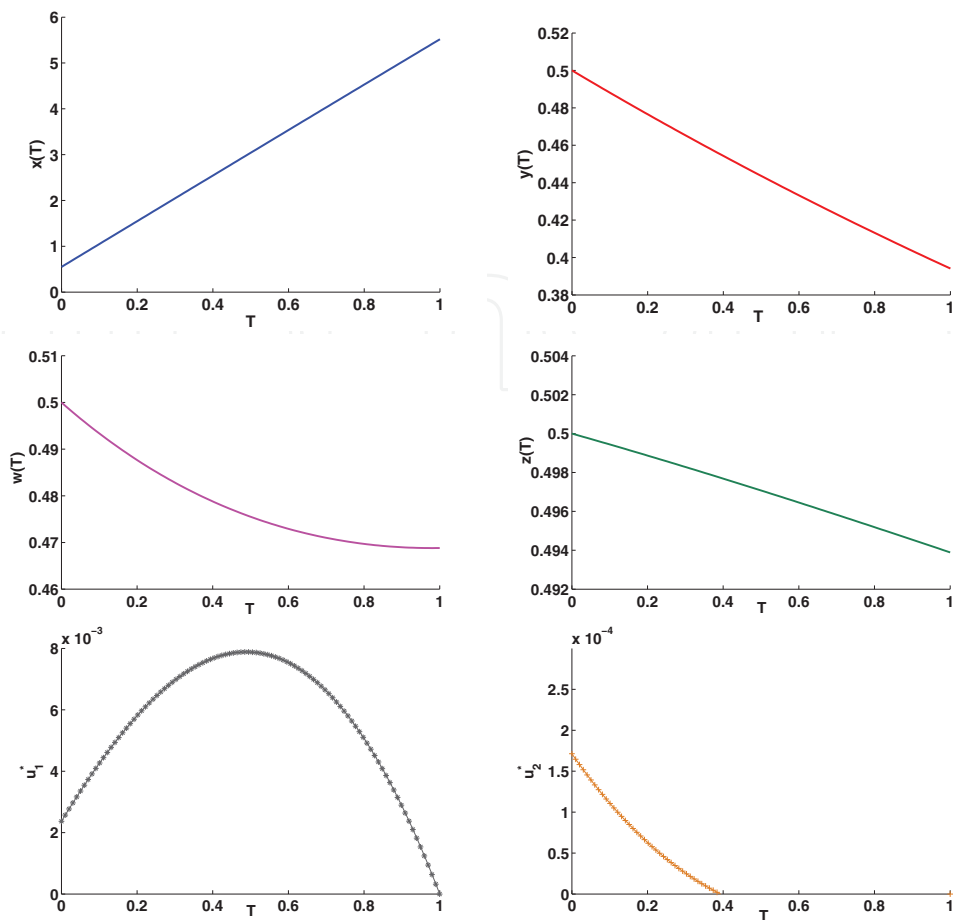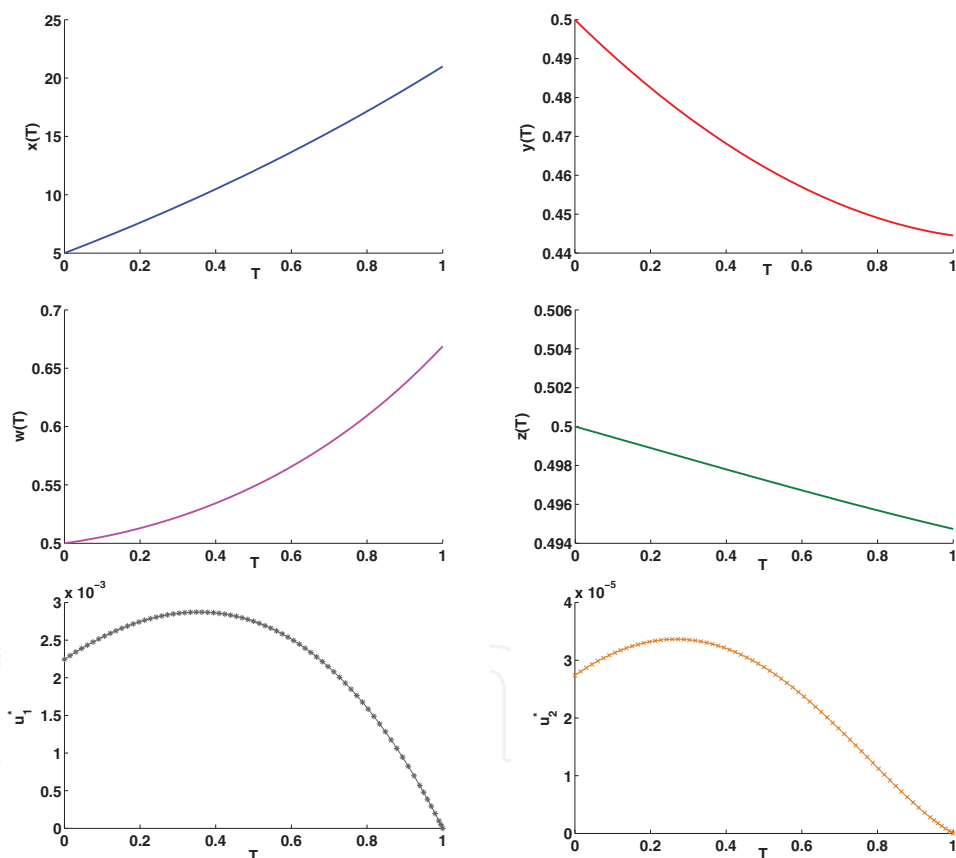
Fig. 6. This figure shows the system behavior for the Optimal treatment schedule of the control variable $u_1(t)$ and $u_2(t)$ for $R = 0.1$, $P = 0.5$, and $\eta_1 = 0.5$, $\eta_2 = 0.1$, $\eta_3 = 0.01$. All other parameter values are same as Table 1.

system become unstable (Theorem 1 and Theorem 2), however it is essential to mention here that in our delay induced system, numerical analysis reveal, when $\tau_1 = 0$ and $\tau_2 = 1$, its reflect from solution trajectory, there are no such oscillations in Figure, which may conclude that delay does affect the stability of the system.

Further we change the values of both delays τ_1, and τ_2, and varied them from 1 to 20, we also observe that no significant changes does arise in each case for which we can express that delay affect the stability of the system. Thus, in a nutshell we can say that incorporation of time delay into the existing model to account for time lag in activation of CTL_p did not exhibit any biologically significant interpretation.

5. The optimal control problem

In this section our main object is to minimize the infected CD4$^+$T cells population as well as minimize the systemic cost of drug treatment. Here we formulate an optimal control problem. We also want to maximize the level of healthy CD4$^+$T cells. So in our basic model (1), we use control variables $u_1(t), u_2(t)$ represents the drug dose satisfying $0 \leq u_1(t) \leq 1$ and $0 \leq u_2(t) \leq 1$. Here $u_1(t) = 1$, $u_2(t) = 1$ events are represents the maximal use of chemotherapy and $u_1(t) = 0$, $u_2(t) = 0$ represents no treatment.

Here we consider that the RTI reduces the infection rate by $(1 - \eta_1 u_1)$, where η_1 represents the drug efficacy and u_1 is the control input doses of the drug RTI. We also consider the enrichment of uninfected T cell and CTL responses through IL-2 treatment is given by $\eta_2 u_2$, and $\eta_3 u_2$, where u_2 as a control input of IL-2 treatment and η_2, η_3 are the drug efficacy of IL-2 for uninfected T cell and precursor CTL responses.

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. Thus we construct the optimal control problem where the state system is

$$\dot{x} = \lambda - dx - \beta(1 - \eta_1 u_1(t))xy + (1 - \eta_2 u_2(t))\gamma x$$
$$\dot{y} = \beta(1 - \eta_1 u_1(t))xy - ay - pyz$$
$$\dot{w} = cxyw - cq_1 yw - bw + (1 - \eta_3 u_2(t))\gamma_1 w$$
$$\dot{z} = cq_2 yw - hz, \tag{16}$$

and the control function is defined as

Fig. 7. This figure shows the system behavior for the Optimal treatment schedule of the control variable $u_1(t)$ and $u_2(t)$ for $R = 10$, $P = 50$, and $\eta_1 = 0.1$, $\eta_2 = 0.1$, $\eta_3 = 0.01$. All other parameter values are same as Table 1.

$$J(u_1, u_2) = \int_{t_0}^{t_f} [y(t) - x(t) - w(t) + Ru_1^2 + Pu_2^2]dt. \tag{17}$$

Where the parameter R and P respectively the weight on the benefit of the cost.

Here the control function $u_1(t)$ and $u_2(t)$ are bounded, Lebesgue integrable function (Swan, 1984).

In this problem we are seeking the optimal control pair $(u_1{}^*, u_2{}^*)$ such that
$J(u_1{}^*, u_2{}^*) = \min\{J(u_1, u_2) : (u_1, u_2) \in U\}$.

Here U is the control set defined by
$U = \{u = (u_1, u_2) : u_1, u_2 \text{ are the measurable}, 0 \leq u_1(t) \leq 1, 0 \leq u_2(t) \leq 1, t \in [t_0, t_f]\}$.

To determine the optimal control $u_1{}^*$ and $u_2{}^*$, we use the "Pontryagin Minimum Principle" (Pontryagin et al., 1986). To solve the problem we use the Hamiltonian given by

$$H = y(t) - x(t) - w(t) + Ru_1^2 + Pu_2^2 + \xi_1\{\lambda - dx - \beta(1 - \eta_1 u_1(t))xy + (1 - \eta_2 u_2(t))\gamma x\}$$
$$+ \xi_2\{\beta(1 - \eta_1 u_1(t))xy - ay - pyz\} + \xi_3\{cxyw - cq_1yw - bw + (1 - \eta_3 u_2(t))\gamma_1 w\}$$
$$+ \xi_4\{cq_2yw - hz\}. \tag{18}$$

By using the "Pontryagin Minimum Principle" and the existence condition for the optimal control theory (Fleming et al., 1975) we obtain the theorem.
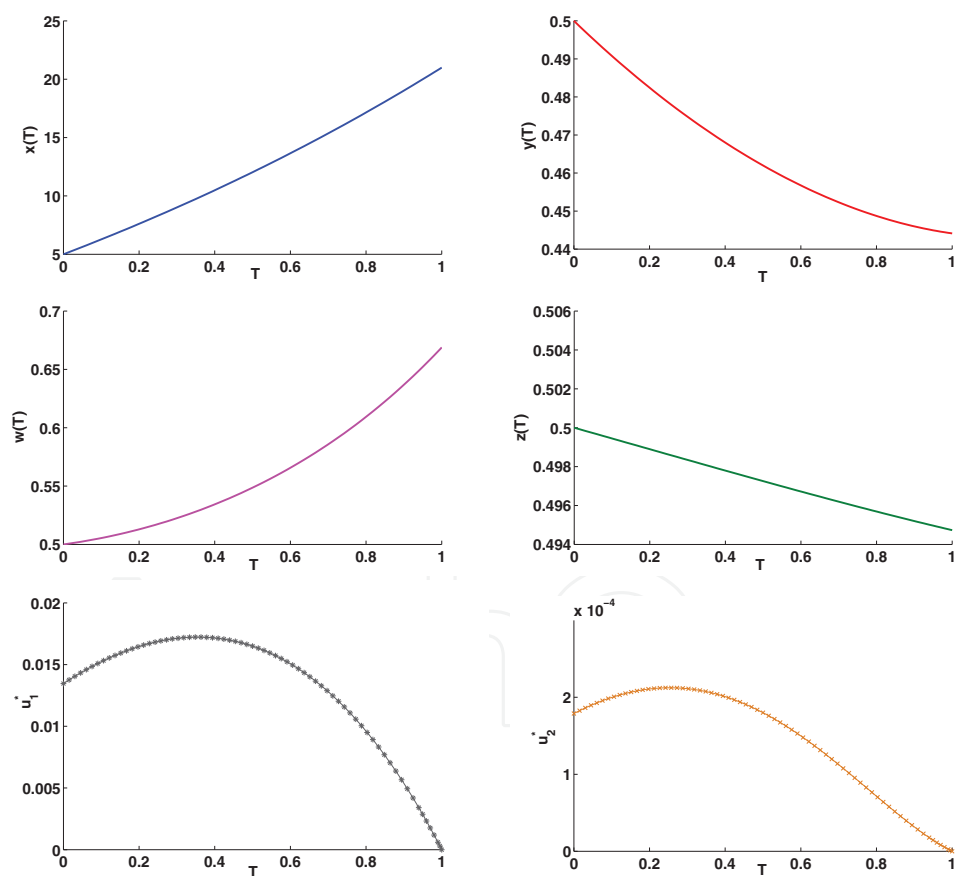

Fig. 8. This figure shows the system behavior for the Optimal treatment schedule of the control variable $u_1(t)$ and $u_2(t)$ for $R = 10$, $P = 50$, and $\eta_1 = 0.6$, $\eta_2 = 0.1$, $\eta_3 = 0.01$. All other parameter values are same as Table 1.

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^*, w^*, z^*). Also there exist adjoint function ξ_1, ξ_2, ξ_3, ξ_4 satisfying the equation (18) and (19).

Proof: By using Pontryagin Minimum principle (Fleming et al., 1975) the unconstrained optimal control variable u_1^* and u_2^* satisfy

$$\frac{\partial H}{\partial u_1^*} = \frac{\partial H}{\partial u_2^*} = 0. \tag{19}$$

Since

$$
\begin{aligned}
H = [Ru_1^2 - \xi_1(1 - \eta_1 u_1(t))\beta xy + \xi_2(1 - \eta_1 u_1(t))\beta xy] + [Pu_2^2 + \xi_1(1 - \eta_2 u_2)\gamma x \\
+ \xi_3(1 - \eta_3 u_2)\gamma_1 w] + \text{other terms without } u_1 \text{ and } u_2,
\end{aligned}
\tag{20}
$$

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

$$\frac{\partial H}{\partial u_1^*} = 2Ru_1^* + \eta_1 \beta x^* y^* (\xi_1 - \xi_2) = 0$$

$$\frac{\partial H}{\partial u_2^*} = 2Pu_2^* - \xi_1 \eta_2 \gamma x^* - \xi_3 \eta_3 \gamma_1 z^* = 0.$$

Thus we obtain the optimal control u_1^* and u_2^* corresponding to the interior equilibrium (x^*, y^*, w^*, z^*) as,

$$u_1^* = \frac{\beta \eta_1 x^* y^* (\xi_2 - \xi_1)}{2R}$$

$$u_2^* = \frac{(\xi_1 \eta_2 \gamma x^* + \xi_3 \eta_3 \gamma_1 z^*)}{2P}. \tag{21}$$

According to Pontryagin minimum Principle (Pontryagin et al., 1986) we know that,

$$\frac{d\xi}{dt} = -\frac{\partial H}{\partial x}, \tag{22}$$

and

$$H(x(t), u^*(t), \xi(t), t) = \min_{u \in U} H(x(t), u(t), \xi(t), t). \tag{23}$$

The above equations are the necessary conditions satisfying the optimal control $u(t)$ and again for the system (16, 17) the adjoint equations are

$$\frac{d\xi_1}{dt} = -\frac{\partial H}{\partial x}, \quad \frac{d\xi_2}{dt} = -\frac{\partial H}{\partial y}, \quad \frac{d\xi_3}{dt} = -\frac{\partial H}{\partial w}, \quad \frac{d\xi_4}{dt} = -\frac{\partial H}{\partial z}.$$

Taking the partial derivative of H we get,

$$\frac{d\xi_1}{dt} = 1 + \xi_1\{d_1 + (1 - \eta_1 u_1(t))\beta y - (1 - \eta_2 u_2(t))\gamma\} - \xi_2(1 - \eta_1 u_1(t))\beta y - \xi_3 cyw$$

$$\frac{d\xi_2}{dt} = -1 + \xi_1(1 - \eta_1 u_1(t))\beta x - \xi_2\{(1 - \eta_1 u_1(t))\beta x - a - pz\} - \xi_3\{cxw - cq_1 w\} - \xi_4 cq_2 w$$

$$\frac{d\xi_3}{dt} = 1 - \xi_3\{cxy - cq_1 y - b + (1 - \eta_3 u_2(t))\gamma_1\} - \xi_4 cq_2 y$$

$$\frac{d\xi_4}{dt} = \xi_2 py + \xi_4 h. \tag{24}$$

Hence the optimality of the system consists of the state system along with the adjoint system. Also it depends on the initial conditions and the transversality condition which satisfy $\xi_i(t_f) = 0$ and $x(0) = x_0$, $y(0) = y_0$, $w(0) = w_0$, $z(0) = z_0$.
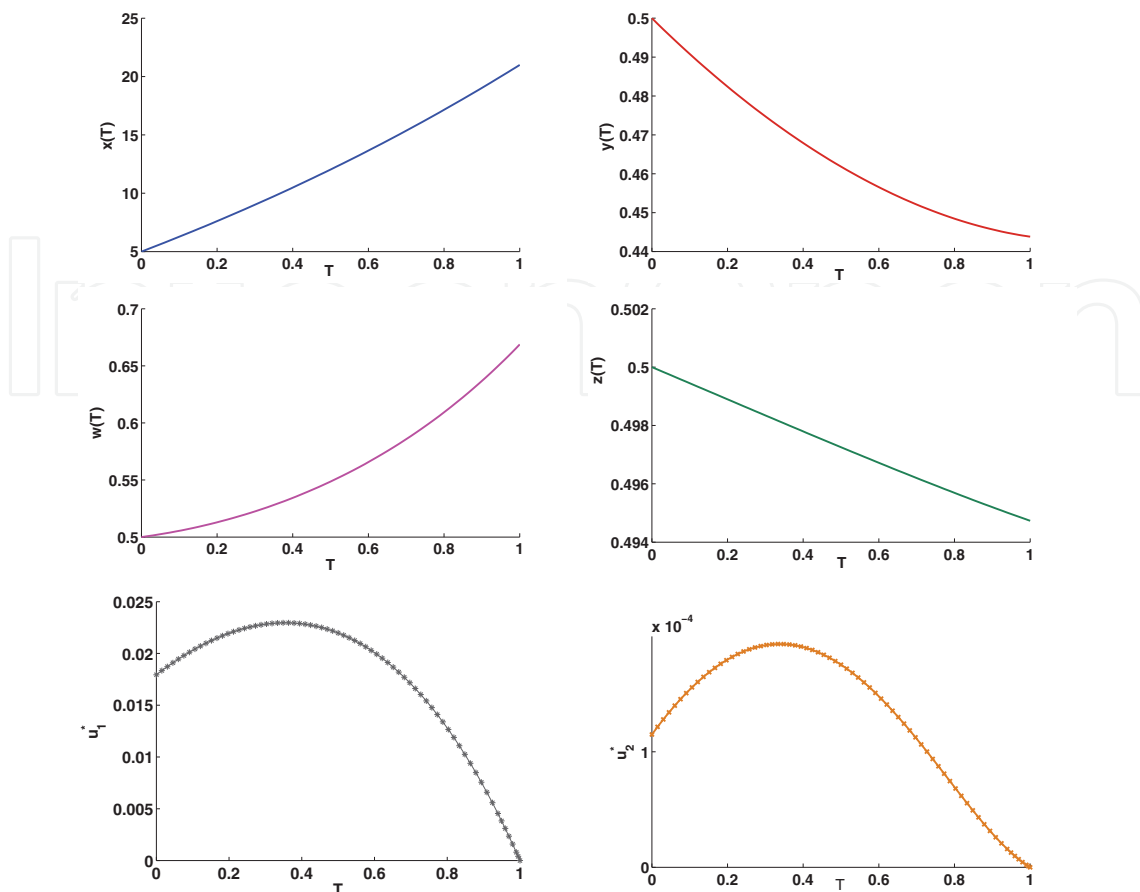
Fig. 9. This figure shows the system behavior for the Optimal treatment schedule of the control variable $u_1(t)$ and $u_2(t)$ for $R = 10$, $P = 50$, and $\eta_1 = 0.8$, $\eta_2 = 0.4$, $\eta_3 = 0.1$. All other parameter values are same as Table 1.

6. Conclusion

In this research article we have considered a mathematical model of immune system representing the response of a HIV infected individual in presence of HAART and IL-2. We have studied how the immune system recovers by applying IL-2 as an immune activator along with HAART. We have also observed the effect of delay in activation of uninfected CD4$^+$T populations through IL-2 therapy. We have noticed the control therapy, which is more effective with respect to cost and also less side effect. Here analytical as well as numerical approaches have been observed. We have also noticed that, the rational behind concomitant administration of IL-2 with HAART is to augment host immune responses through prevention of destruction of the immunity system without stimulation of HIV replication. In the beginning of our research article, our mathematical model of HIV dynamics in presence of HAART and IL-2 suggest the existence of three equilibrium conditions : $E_1(x_1, 0, 0, 0)$, $E_2(x_2, y_2, 0, 0)$ and $E^*(x^*, y^*, w^*, z^*)$. Our analytical studies first indicates the infection free steady state or uninfected equilibrium, where CD4$^+$T cells are healthy and no infected cell population exists and there is no HIV-specific CTL immune response. The second equilibrium condition is not a very desirable one since there is no immune response even in presence of HIV antigen. The third equilibrium state or infected steady state is said to be exist at certain limiting values of infected cell population in presence of HAART and IL-2. We also studied the stability of the system for different equilibrium points. Further a time

delay has been introduced into the existing model to account for the activation of immune response through infected CD4$^+$T cells. In that study, we noticed that delay induced system has no useful delay effect which changes its stability. From optimal control studies, several interesting results have been obtained. As weight factors (R and P) increase from 0.1 to 10 and 0.5 to 50 respectively, there is a significant increase in the uninfected cell population with very little effect on the count of infected cells. The increase in the weight factors does not produce proportionate increase in the precursor CTL population and increase in effectiveness of HAART or IL-2 as denoted by η, is not manifested by remarkable change in precursor CTL number. The CTL effector population is found to decrease in all the cases. Thus, optimal control approach will help in designing an innovative cost-effective safe therapeutic regimen of HAART and IL-2 where the uninfected cell population will be enhanced with simultaneous decrease in the infected cell population. Moreover, successful immune reconstitution can also be achieved with increase in precursor CTL population. Mathematical modeling of viral dynamics thus enables maximization of therapeutic outcome even in case of multiple therapies with specific goal of reversal of immunity impairment.

From our above discussion of the results, it is clear that, though incorporation of time delay into the existing model (1) to account for time lag in activation of CTL_p did not exhibit any biologically significant interpretation, however, adoption of optimal control strategy in optimization of therapeutic regime of combination therapy of HAART and IL-2 was found to be really satisfactory in terms of enhancing the life expectancy of HIV-afflicted patients by improving the uninfected T cell count.

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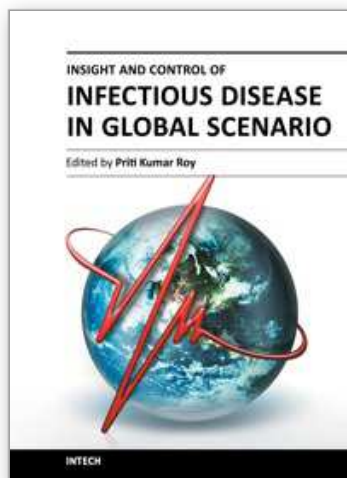
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