Optimal Control Therapeutic Approach to Recovery of Infected Cells in HIV Model with Expected Time to Extinction of the Disease

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***Abstract*- Controlling disease like HIV/AIDS is a serious concern today. Mathematical modeling with control therapeutic approach for understanding the extinction of disease is quite significant. But under deterministic model this approach is not viable. With a view to obtain the feasibility, stochasticity might play an escalating role in estimating the expected time to extinction of the disease in epidemiological system. In this research article, we consider a deterministic model with therapeutic control approach to find out recovery of the disease after a certain period. Additionally, by incorporating stochasticity we also estimated the expected time to extinction of the disease.**

Keywords- HIV; CD4$^+$ T Cell; Transition Rates; Stochastic Version; Quasi-Stationary Distribution; Time to Extinction

I. INTRODUCTION

In the last few years, HIV/AIDS spreads among young adults dreadfully in most parts of the world, which ultimately causes morbidity and mortality. The number of people suffering due to HIV and AIDS are enormous and nowadays it has become a global problem. One of the main causes of HIV/AIDS is the declining nature of CD4$^+$ T cells by HIV and finally results failure of body immune system after a certain period of time. Researchers mainly clinicians and experimentalists are paying their attention enormously towards control of the disease using drug like HAART (Highly Active Antiretroviral Therapy). Different approaches have been developed for the drug treatment of HIV but most widely used drugs are inhibitors like Reverse Transcriptase Inhibitor (RTIs) and Protease Inhibitor (PIs), which are enzymes responsible for replication of HIV in human body. Mathematicians also made a significant contribution in this approach by formulating mathematical models to predict the way of control of the disease [1-4]. Roy and Chatterjee [5] also proposed a mathematical model to investigate the effect of HAART on immune cells to an HIV infected patients. Different control measures have also been adopted in different stages of the disease progression for remediation. Optimal control therapeutic approach on the used drugs has added a new dimension in this aspect. Chatterjee and Roy [6] studied a control based mathematical approach with immune activator IL-2, which showed that applying of RTIs for sufficient intervals are more effective than fixed intervals of IL-2 therapy by impulsive differential equations. However, researchers fail to achieve full immune reconstitution of the patient at the end of treatment and also fail to exert their action in case of rapidly mutating viruses.

Recently, a new class of molecules, chemokine analogs, has been designed to control the entry of viruses, even if they undergo spontaneous mutation [7]. On that outlook, Roy et al. [8] introduced a novel concept establishing the pivotal role of chemokine analogs and fixing optimum dosage regimen in AIDS prevention strategy.

So, recovery of the infected individuals by perfect drug adherence and ultimately expected time to extinction of the disease have become a challenge at this moment. In this research article, we enrich the mathematical model suggested by Zhou et al. [9] by the introduction of control parameters on the adherence of drug dose, which is more realistic from the biological point of view. In his deterministic version, Zhou showed that the recovery of the disease can be achieved by the immune system of our body, which is much more time dependent. Our research work explores that by applying control measures with perfect drug adherence using in implicit way, time of recovery is much lesser than advised by Zhou. But in this case, extinction of the disease is not possible.

It is well known to us that the deterministic version is nothing but an approximation of stochastic model and hence it is difficult

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to find the time to extinction through deterministic version. Nasell [10] was the pioneer to derive such approximation for expected time to extinction. The quasi-stationary distribution is exceptionally essential owing to epidemic context. Hence it has its curiosity in its own precise as an approximation of the allotment of states before extermination. The time to extinction from quasi-stationary is a frequent as well as natural measure of the perseverance of an infection, which has been going on for an elongated time usually. In this research article, we derive the quasi-stationary distribution of infected individuals and expected time to extinction is estimated by this approach. Analytical and Numerical results provide excellent approximation for the true density and time to extinction.

In the present work, the deterministic model of HIV infection is described in section 2. Section 3 is devoted for the necessity of optimal control in the deterministic model and section 4 explains about the optimal control problem. Stochastic version of the model formulation is described in section 5. This section also includes the description of the transition states and Kolmogorov's forward equation. Time to extinction of the infected $CD4^+T$ cells, distribution of the time to extinction and diffusion approximation are discussed in section 5. Discussion on estimation of expected time to extinction of infected cells and formation of theorem are elaborately explained in this section also. Section 6 includes results from numerical illustration from the model and finally discussions and conclusions are given in section 7.

II. THE DETERMINISTIC MODEL

To generate a mathematical model of T-cell infection by HIV, we first consider the deterministic model originally created by Zhou et al. [9]. They proposed a mathematical demonstration involving a set of differential equations, relating to uninfected $CD4^+T$ cells or target cells T, virus producing $CD4^+T$ cells or infected cells I and free virous V as

$$\begin{aligned} \frac{dT}{dt} &= s - d_1 T + aT(1 - \frac{T}{T_{max}}) - \beta TV + \rho I \\ \frac{dI}{dt} &= \beta TV - \delta I - \rho I \\ \frac{dV}{dt} &= qI - cV. \end{aligned} \tag{1}$$

Where s represents the constant growth rate of T-cells produced from bone marrow and mature in thymus. Death rate of uninfected $CD4^+T$-cells is denoted by d_1. It should be mentioned here that in presence of HIV virus, antigen or mitogen stimulates T cells. At the time of stimulation, T cells multiply through mitosis with a rate a, i.e the growth or proliferation of T cells from existing T cells are governed by logistic fashion. Thus a is denoted as the proliferation rate and T_{max} is the maximum density of the T-cell at which the proliferation shuts off [11]. Furthermore, 'β' is considered as the infection rate of uninfected $CD4^+T$ cells and 'δ' is the per capita rate of disappearance of infected cells I. Here, the recovery rate of infected cell is considered as 'ρ', whereas 'q', and'c' are denoted as the reproductive rate of the virus from infected cell and the clearance rate of the virus respectively.

III. WHY OPTIMAL CONTROL STRATEGY SHOULD BE IMPROVISED?

Various chemotherapies for patients with human immunodeficiency virus (HIV) are being examined to determine the optimal scheme for better treatment [12, 13]. The trickiest task is to decide when and how this treatment should be started so that we can get most cost effective results. In this section we present an optimal control problem in which the coefficient of the cellular infection rate is to be controlled. We seek to minimize the performance index, which is the benefit based on the suppression of infected $CD4^+T$ cell populations levels and reduces the systematic cost of chemotherapy. We characterize the optimal control using Pontryagin's Minimum Principle [14]. Also it is to be examined whether any qualitative differences in treatment outcomes among the model have a significant impact on optimal therapeutic value. This control represents the percentage of effect of the therapy on the interaction term when uninfected $CD4^+T$ cells interrelate with infected cell population, and this interaction specially implies that the uninfected $CD4^+T$ cells are maximally infected at a rate of β per day.

IV. THE OPTIMAL CONTROL PROBLEM

Here our main object is to minimize the level of infected $CD4^+$ T cell population and maximize the level of healthy $CD4^+$ T cells. From this understanding we wish to make relation where the immune response is also to be increased with the simultaneous occurrence of uninfected T cell population and depletion of infected cell population. Also, it is our object to keep in mind that,

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cost- as measured in terms of chemotherapy strength which is a combination of time and efficacy - as low as possible. To reach our intention for cost effective better treatment of a HIV patient, we thus formulate an optimal control problem, and hence in the model Eq. (1) which was considered by Zhou et al. [9], we use a control variable $u(t)$, which represents the drug dose at a time t satisfying $0 \le u(t) \le 1$. Here $u(t)$ represents control input with values normalised to be between 0 and 1 [15]. Also $u(t) = 1$ represents the maximal use of chemotherapy and $u(t) = 0$, which signifies no treatment. Since the control reduces viral replication rate, so after using control the infection rate becomes $\beta(1-u(t))$. It should be noted here that both cellular infection rate and viral production rate are represented by the same term, β, so that the drug RTI may be introduced for better treatment [11].

On the above assumption our optimal control problem corresponding to the Eq. (1) [9] would be:

$$\begin{aligned} \frac{dT}{dt} &= s - d_1 T + aT(1-\frac{T}{T_{max}}) - (1-u(t))\beta TV + \rho I, \\ \frac{dI}{dt} &= (1-u(t))\beta TV - \delta I - \rho I, \\ \frac{dV}{dt} &= qI - cV. \end{aligned} \tag{2}$$

satisfying the initial condition $T(0) = T_0, I(0) = I_0$ and $V(0) = V_0$.

The objective function is defined as,

$$J(u) = \int_{t_i}^{t_f} [I(t) - T(t) + Ru^2(t)]dt. \tag{3}$$

The parameter R ($R > 0$) is the weight constants, on the benefit of the cost. The benefit is based on the minimization of cost and infected cell count together with maximisation of uninfected T cell count. Now, we want to find the optimal control u^* such that

$J(u^*) = min\{J(u) : u \in U\}$ subject to the system of ODE's (2) where U is the admissible control set defined by

$U = \{u(t) : u(t)\ \ is\ measurable, 0 \le u(t) \le 1, t \in [t_i, t_f]\}$, is the control set.

To determine the optimal control, we use the "Pontryagin Minimum Principle" [14].

Let us consider the Hamiltonian given by

$$\begin{aligned} H &= I(t) - T(t) + Ru^2(t) + \xi_1\{s - d_1 T + aT(1-\frac{T}{T_{max}}) \\ &-(1-u(t))\beta TV + \rho I\} + \xi_2\{(1-u(t))\beta TV - \delta I - \rho I\} \\ &+\xi_3(qI - cV), \end{aligned} \tag{4}$$

where ξ_1, ξ_2 and ξ_3 are the adjoint variables.

Theorem 1: If the given optimal control u^* and the solutions T^*, I^*, V^* of the corresponding state system (2) minimize $J(u)$ over U, then there exists the adjoint variables ξ_1, ξ_2, ξ_3 which satisfy the following equations

$$\begin{aligned} \frac{d\xi_1}{dt} &= -\left[-1 + \xi_1\{-d_1 + a(1-\frac{2T}{T_{max}}) - \beta V(1-u(t))\} + \xi_2 \beta V(1-u(t))\right] \\ \frac{d\xi_2}{dt} &= -\left[1 + \xi_1 \rho - \xi_2(\delta + \rho) + \xi_3 q\right] \\ \frac{d\xi_3}{dt} &= -\left[-\xi_1 \beta T(1-u(t)) + \xi_2 \beta T(1-u(t)) - \xi_3 c\right] \end{aligned}$$

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along with the transversality condition $\xi_i(t_f) = 0 \quad for\ i = 1,2,3$. Moreover, u^* is represented by $u^* = \max\{0, \min\{\frac{\beta TV\left(\xi_2 - \xi_1\right)}{2R}, 1\}\}$.

Proof: The Hamiltonian (4) can be written as

$$H = Ru^2(t) + \xi_1 u(t)\beta TV - \xi_2 u(t)\beta TV + other\ term\ without\ u(t) \tag{5}$$

According to the Pontryagin Minimum Principal [14], the unconstrained optimal control variable u^* satisfies

$$\frac{\partial H}{\partial u^*} = 0, \tag{6}$$

$$\text{i.e}\ \frac{\partial H}{\partial u^*} = 2Ru^*(t) + \beta TV\left(\xi_1 - \xi_2\right) = 0.$$

Hence, we obtain from the above expression [16]

$$u^* = \frac{\beta TV\left(\xi_2 - \xi_1\right)}{2R}. \tag{7}$$

By applying the standard control arguments involving the bounds on the control [17, 18], we conclude for u :

$$u^* = \begin{cases} 0, & \frac{\beta TV\left(\xi_2 - \xi_1\right)}{2R} \le 0; \\ \frac{\beta TV\left(\xi_2 - \xi_1\right)}{2R}, & 0 < \frac{\beta TV\left(\xi_2 - \xi_1\right)}{2R} < 1; \\ 1, & \frac{\beta TV\left(\xi_2 - \xi_1\right)}{2R} \ge 1. \end{cases} \tag{8}$$

To ensure the positivity of u^*, we use the following notation $u^+ = \max(s, 0)$ [13, 16].

Therefore, in compact notation,

$$u^* = \min\{\frac{\beta TV\left(\xi_2 - \xi_1\right)^+}{2R}, 1\}. \tag{8a}$$

Now, according to the Pontryagin Minimum Principal [14], we can write

$$\frac{d\xi_i}{dt} = -\frac{\partial H}{\partial x}, i = 1,2,3 \tag{9}$$

where, $x \equiv \left(T, I, V\right)$ and the necessary condition satisfying the optimal control $u(t)$ are

$$H\left(x(t), u^*(t), \xi_i(t), t\right) = \min_{u \in U} H\left(x(t), u(t), \xi_i(t), t\right), i = 1,2,3. \tag{10}$$

So, the adjoint equation corresponding to the system (5) are

$$\frac{d\xi_1}{dt} = -\frac{\partial H}{\partial T}, \frac{d\xi_2}{dt} = -\frac{\partial H}{\partial I}, \frac{d\xi_3}{dt} = -\frac{\partial H}{\partial V}.$$

Therefore,

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$$\begin{aligned}
\frac{d\xi_1}{dt} &= -\left[-1+\xi_1\left(-d_1+a(1-\frac{2T}{T_{max}})-\beta V(1-u(t))\right)+\xi_2\beta V\left(1-u(t)\right)\right] \\
\frac{d\xi_2}{dt} &= -\left[1+\xi_1\rho-\xi_2(\delta+\rho)+\xi_3 q\right] \\
\frac{d\xi_3}{dt} &= -\left[-\xi_1\beta T(1-u(t))+\xi_2\beta T(1-u(t))-\xi_3 c\right].
\end{aligned} \tag{11}$$

Where, $\xi_i(t_f)=0, i=1,2,3$ are transversality conditions and $T(0)=T_0$, $I(0)=I_0$, $V(0)=V_0$ are initial conditions.

V. STOCHASTIC VERSION OF THE MODEL

In this we introduce stochasticity in deterministic model of HIV considered by Zhou et al. [9] and find the marginal distribution in quasi-stationary and the expected time to extinction keeping in mind that the infected class is to be extinct. We have performed the numerical simulation to confirm our analysis.

Now we reduce the dimension of the system (1), by assuming a rapid time scale for the free virus dynamics, $V \approx qI/c$ [19, 20]. Thus the reduced ODE model can be written in the form of

$$\begin{aligned}
\frac{dT}{dt} &= s-d_1T+aT(1-\frac{T}{T_{max}})-kTI+\rho I, \\
\frac{dI}{dt} &= kTI-\delta I-\rho I.
\end{aligned}$$

Where, $k=\beta q/c$, all the parameters and variables are non negative.

Before describing the stochastic formulation, the logistic term can be written as $A(T)-B(T)=aT(1-\frac{T}{T_{max}})$, where $A(T)$ is the birth rate and $B(T)$ is the death rate and $A(T)$, $B(T)$ can be written as $A(T)=a_1T-a_2T^2$ and $B(T)=b_1T+b_2T^2$ respectively, where a_i and b_i (i=1,2) are constants. So from the above relations we can state that $a=(a_1-b_1)$ and $T_{max}=\frac{a_1-b_1}{a_2+b_2}$.

Therefore the above system of two equations can be written as

$$\begin{aligned}
\frac{dT}{dt} &= s-d_1T+(a_1-b_1)T(1-\frac{T}{\frac{a_1-b_1}{a_2+b_2}})-kTI+\rho I, \\
\frac{dI}{dt} &= kTI-\delta I-\rho I.
\end{aligned} \tag{12}$$

A. The Stochastic Model Formulation

There are two state variables, namely the number of uninfected CD4$^+$ T cells $T(t)$ and the number of infected such cells $I(t)$ at time t. They jointly take values in the state space $S=\{(m,n): m=0,1,2,.....; n=0,1,2,.....\}$. So, $p_{m,n}(t)=P\{T(t)=m, I(t)=n\}$ is the joint distribution of $T(t), I(t)$ at time t. If m and/or n are negative, $p_{m,n}(t)$ is then equal to 0. The model is based on the following four basic events, which are production of CD4$^+$T cells primarily from bone marrow and secondarily antigen or mitogen stimulates T cells in presence of HIV virus, infection of CD4$^+$ T cells, death of CD4$^+$ T

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cells and death of infected of such cells. Here we assume that the total population is N. Table 1 represents the hypothesized transition rates of the model 12.

TABLE 1 HYPOTHESIZED TRANSITION RATES FOR THE STOCHASTIC VERSION

Event ($CD4^+$ T-cells)	Transition	Transition rates
Birth of an uninfected	$(m,n) \to (m+1,n)$	$\lambda_1(m,n) = s + m(a_1 - a_2 m) + \rho m$
Death of an uninfected	$(m,n) \to (m-1,n)$	$\mu_1(m,n) = m(b_1 + b_2 m + d_1)$
Infection of an uninfected	$(m,n) \to (m-1,n+1)$	$\lambda_2(m,n) = kmn$
Recovery or Death of infected	$(m,n) \to (m,n-1)$	$\mu_2(m,n) = (\rho + \delta)n$

B. Description of the Transition States

The total number of population N is increased by unity. We can assume that in a infinitesimally small time interval Δt, the probability of the production of uninfected $CD4^+$T cells from precursors in the bone marrow and thymus are zero, but within the due time the constant rate of production of uninfected $C4^+$ T cells is s. However, to make the population to be same, we should assume that there must be a natural death of uninfected $CD4^+$ T cells. This phenomena is captured through the first two rows of the transition matrix. On the other hand if there is an infection in the uninfected $CD4^+$ T cells it can be balanced by an increase of an infected $CD4^+$ T cells. The infectible class is infected by direct infection with replication of virus generated within the infected population. This occurs one at a time and so the increases of the infected class are reflected by the rise of unity in the transition state. If there is an infected $CD4^+$ T cells, the natural death should be reflected through a natural birth of uninfected $CD4^+$ T cells. At the end, naturally the recovery of infected host must be reinstate to the uninfected $CD4^+$T cells.

C. Kolmogorov's Forward Equation

The Kolmogorov's forward equation for the model can be written as

$$\begin{aligned} p_{m,n}(t+\Delta t) &= p_{m-1,n}(t)\lambda_1(m-1,n)\Delta t + p_{m+1,n}(t)\mu_1(m+1,n)\Delta t \\ &+ p_{m+1,n-1}(t)\lambda_2(m+1,n-1)\Delta t + p_{m,n+1}(t)\mu_2(m,n+1)\Delta t \\ &+ p_{m,n}(t)(1-K(m,n)\Delta t) + o(\Delta t), \end{aligned}$$

where, $K(m,n) = \lambda_1(m,n) + \mu_1(m,n) + \lambda_2(m,n) + \mu_2(m,n)$. It is considered here that events consisting of more than one birth or more than one death are included in the $o(\Delta t)$ term. Thus,

$$\begin{aligned} \frac{p_{m,n}(t+\Delta t) - p_{m,n}(t)}{\Delta t} &= p_{m-1,n}(t)\lambda_1(m-1,n) + p_{m+1,n}(t)\mu_1(m+1,n) \\ &+ p_{m+1,n-1}(t)\lambda_2(m+1,n-1) + p_{m,n+1}(t)\mu_2(m,n+1) - p_{m,n}(t)K(m,n) + \frac{o(\Delta t)}{\Delta t}. \end{aligned}$$

$$Now,\ p_{m,n}'(t) = \lim_{\Delta t \to 0} \frac{p_{m,n}(t+\Delta t) - p_{m,n}(t)}{\Delta t}.$$

Therefore the Kolmogorov's Forward Equation for the model can be written as :

$$\begin{aligned} p_{m,n}'(t) &= p_{m-1,n}(t)\lambda_1(m-1,n) + p_{m+1,n}(t)\mu_1(m+1,n) \\ &+ p_{m+1,n-1}(t)\lambda_2(m+1,n-1) + p_{m,n+1}(t)\mu_2(m,n+1) - p_{m,n}(t)K(m,n). \end{aligned} \tag{13}$$

D. Time to Extinction of the Infected T-Cells

The distribution of the time to extinction is an important measure in epidemiological perceptive which can be determined from the solution of the Kolmogorov's Forward Eq. (13).

Here time to extinction of the infected T-cells representing as τ is less than or equal to t, when the number of infected individuals equals to zero, i.e., when we have $\{t \le \tau\}$, infected T-cells will exist. So we can write $P(t \le \tau) = P\{I(t) > 0\}$ and

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$P(\tau \le t) = P\{I(t) = 0\} = p_{.0}(t)$, where, $p_{.0}(t) = \sum_{m=0}^{N} p_{m,n}(t)$.

Thus the marginal probability of infected T-cells equals to zero at time t equals to the cumulative distribution function of the time to extinction at time t. Let the c.d.f and p.d.f of τ be denoted by F and f respectively.

Therefore, $F(t) = P\{I(t) = 0\} = \sum_{m=0}^{N} P\{T(t) = m, I(t) = 0\} = \sum_{m=0}^{N} p_{m,0}(t)$

So, $f(t) = \sum_{m=0}^{N} p_{m,0}'(t) = p_{.0}'(t)$.

Putting $n = 0$ in the Eq. 13, we have,

$$\begin{aligned}
&p_{m,0}'(t) = p_{m-1,0}(t)\lambda_1(m-1,0) + p_{m+1,0}(t)\mu_1(m+1,0)\\
&+p_{m+1,-1}(t)\lambda_2(m+1,-1) + p_{m,1}(t)\mu_2(m,1) - p_{m,0}(t)K(m,0).\\
&= (s + (m-1)(a_1 - a_2(m-1)))p_{m-1,0}(t) + ((m+1)(b_1 + b_2(m+1)) + d_1)\\
&p_{m+1,0}(t) + (\rho+\delta)p_{m,1}(t) - p_{m,0}(t)(s + m(a_1 - a_2 m) + m((b_1 + b_2 m) + d_1).
\end{aligned}$$

Taking summation on the both side from $m = 0 \to \infty$, we get

$$\begin{aligned}
&\sum_{m=0}^{\infty} p_{m,0}'(t) = s\sum_{m=0}^{\infty} p_{m-1,0}(t) + \sum_{m=0}^{\infty}(m-1)(a_1 - a_2(m-1))\\
&p_{m-1,0}(t) + \sum_{m=0}^{\infty}(m+1)(b_1 + b_2(m+1))p_{m+1,0} + d_1\sum_{m=0}^{\infty}(m+1)p_{m+1,0}(t)\\
&+\delta\sum_{m=0}^{\infty} p_{m,1}(t) + \rho\sum_{m=0}^{\infty} p_{m,1}(t) - s\sum_{m=0}^{\infty} p_{m,0}(t)\\
&-\sum_{m=0}^{\infty} m(a_1 - a_2 m)p_{m,0}(t) - \sum_{m=0}^{\infty} m(b_1 + b_2 m)p_{m,0}(t) - d_1\sum_{m=0}^{\infty} m p_{m,0}(t).\\
&= \delta\sum_{m=0}^{\infty} p_{m,1}(t) + \rho\sum_{m=0}^{\infty} p_{m,1}(t). = (\delta+\rho)\sum_{m=0}^{\infty} P(T(t) = m, I(t) = 1).
\end{aligned}$$

$$i.e.,\ p'_{.0}(t) = (\delta + \rho)p_{.1}(t). \tag{14}$$

So we can write, $f(t) = p'_{.0}(t) = (\delta+\rho)P\{I(t) = 1\} = (\delta+\rho)p_{.1}(t)$,

where, $p_{.1}(t) = \sum_{m=0}^{\infty} p_{m,1}(t)$.

To find the expected time to extinction, we need to compute $p_{.1}(t)$.

E. The Distribution of the Time to Extinction

To find the absorption of $I(t)$ at 0, the distribution of $(T(t), I(t)), \forall .1int \ge 0$ is necessary but is not possible. So, we look for the process that will give more detailed information regarding eventual absorption in the class $\{(m,0): m = 1,2,.....\}$, which is assured in this perspective. Thus, we try to find out the quasi-limiting distribution. The process $\{T(t), I(t)\}, t \ge 0$ has a unique conditional distribution (conditioned on being not absorbed) $q_{m,n}$, where,

$$q_{m,n}(t) = P\{T(t) = m, I(t) = n \mid I(t) \ne 0\} = \frac{p_{m,n}(t)}{1 - p_{.0}(t)},$$

$$m = 0,1,2,.....; n = 1,2.....$$

Now we derive a system of differential equation for $q_{m,n}(t)$. Differentiating the expression for $q_{m,n}(t)$ and using the relation (14), we obtain

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$$q_{m,n}'(t) = \frac{p_{m,n}'(t)}{1-\sum_{m=0}^{\infty} p_{m,0}(t)} + (-1)\frac{-\sum_{m=0}^{\infty} p_{m,0}'(t)}{(1-p_{.0}(t))^2} p_{m,n}(t)$$

$$= \frac{p_{m,n}'(t)}{1-p_{.0}(t)} + \frac{p_{m,n}(t)}{(1-p_{.0}(t))^2}(\delta+\rho)p_{.1}(t).$$

The distribution of the random variable τ depends upon the initial distribution of the infected T-cell population. If at time t, the infection exists and if it exists for a long time, then it can be assured that the distribution of the number of infected T-cell population $I(t)$ can be described by the quasi-stationary distribution. On this standpoint we are assuming that the initial distribution is quasi-stationary.

Let us consider τ_Q be the time to extinction of infected T-cells. We can write $q_{m,n}'(t)$ as:

$$q_{m,n}'(t) = \frac{p_{m,n}'(t)}{1-p_{.0}(t)} + (\delta+\rho)p_{.1}(t)\frac{p_{m,n}(t)}{(1-p_{.0}(t))^2}.$$

Also we can write

$$q_{m,n}'(t) = \frac{p_{m,n}'(t)}{1-p_{.0}(t)} + (\delta+\rho)p_{.1}(t)\frac{q_{m,n}(t)}{(1-p_{.0}(t))}.$$

Since the initial distribution is assumed to be quasi-stationary

i.e. $p_{m,n}(0) = q_{m,n}$, So we can write,

$$q_{m,n}'(t) = \frac{p_{m,n}'(t)}{1-p_{.0}(t)} + (\delta+\rho)q_{.1}(t)\frac{p_{m,n}(t)}{(1-p_{.0}(t))}. \tag{15}$$

Putting $q_{m,n}'(t) = 0$, in the Eq. 15, we get

$$p_{m,n}'(t) = -(\delta+\rho)q_{.1}p_{m,n}(t) \tag{16}$$

i.e., $p_{m,n}(t) = q_{m,n}e^{-(\delta+\rho)q_{.1}t}$.

So, $p_{.1}(t) = q_{.1}e^{-(\delta+\rho)q_{.1}t}$.

Using the above form of $p_{.1}(t)$ in Eq. 14, we have,

$$f(t) = p_{.0}'(t) = \left((\delta+\rho)q_{.1}\right)e^{-}((\delta+\rho)q_{.1})t, t > 0.$$

Thus the expected time to extinction of the infected T-cells has an exponential distribution and is equal to $E(\tau_Q) = \frac{1}{(\delta+\rho)q_{.1}}$.

Therefore, we can say that the expected time to extinction from quasi-stationary distribution is inversely proportional to the probability $q_{.1}$, It is also proportional to the sum of the recovery rate ρ and the disappearance rate δ of the infected T-cell population. From the above expression we say that for fixed parameter values ρ and δ, τ_Q is determinable and quasi-stationary probability $q_{.1}$, is the marginal distribution for one infected individual at time t conditioned on not being absorb.

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F. Diffusion Approximation:

Let us consider the two-dimensional process (12):

$$\frac{dT}{dt} = s - d_1 T + T(a_1 - b_1)\left(1 - \frac{T}{\frac{a_1 - b_1}{a_2 + b_2}}\right) - kTI + \rho I,$$

$$\frac{dI}{dt} = kTI - \delta I - \rho I.$$

If the total population N is sufficiently large, the quasi-stationary distribution is approximated by a bivariate normal distribution. Here we consider $y_1 = T$, $y_2 = I$ and the process $y(t) = (y_1(t), y_2(t))$.

The critical point of the deterministic model (1) is given by $\hat{y} = \left(\hat{y}_1, \hat{y}_2\right)$ where, $\hat{y}_1 = \frac{\delta + \rho}{k}$, and $\hat{y}_2 = \frac{1}{\delta}[s + a\frac{\delta + \rho}{k}(1 - \frac{\delta + \rho}{kT_{max}}) - \frac{d(\delta + \rho)}{k}]$.

Now we want to find the mean change $E(\Delta y)$ and the covariance matrix $E\left(\Delta y(\Delta y)^T\right)$ for the time interval Δt (neglecting the terms of order $(\Delta t)^2$). In the time interval t to $t + \Delta t$, there are four possibilities of population change Δy neglecting multiple births and deaths in the time interval t to $t + \Delta t$ which are of order $(\Delta t)^2$. The possibilities of population change are given in Table 2 along with their corresponding probabilities.

TABLE 2 POSSIBLE CHANGES IN THE TWO-POPULATION SYSTEM (12) WITH THE PROBABILITIES

Changes	Probability
$\Delta y_1 = [1, 0]^T$	$p_1 = (s + y_1(a_1 - a_2 y_1) + \rho y_2)\Delta t$
$\Delta y_2 = [-1, 0]^T$	$p_2 = y_1(b_1 + b_2 y_1 + d_1)\Delta t$
$\Delta y_3 = [-1, 1]^T$	$p_3 = k y_1 y_2 \Delta t$
$\Delta y_4 = [0, -1]^T$	$p_4 = (\rho + \delta) y_2 \Delta t$

Here, $E(\Delta y) = \sum_{j=1}^{4} p_j \Delta y_j$

$$= \begin{pmatrix} s + a_1 y_1 - a_2 y_1^2 + \rho y_2 - b_1 y_1 - b_2 y_1^2 - d_1 y_1 - k y_1 y_2 \\ k y_1 y_2 - (\rho + \delta) y_2 \end{pmatrix} \Delta t + o(\Delta t)$$

$$= b(y)\Delta t + o(\Delta t).$$

The Jacobian matrix of the vector $b(y)$ with respect to y is denoted by $B(y)$, and it is defined by,

$$B(y) = \frac{\partial b(y)}{\partial y} = \begin{pmatrix} (a_1 - b_1) - 2y_1(a_2 + b_2) - d_1 - k y_2 & \rho - k y_1 \\ k y_2 & k y_1 - \delta - \rho \end{pmatrix}.$$

The approximated value of $B(y)$ at the critical point $\hat{y} = \left(\hat{y}_1, \hat{y}_2\right)$ is

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$$\hat{B}(y) = \begin{pmatrix} B_1 & B_2 \\ B_3 & B_4 \end{pmatrix}.$$

Where $B_1 = \frac{-s-\rho \hat{y}_2}{\hat{y}_1} - \frac{\hat{y}_1 a}{T_{max}}$, $B_2 = -\delta$, $B_3 = k\hat{y}_2$, $B_4 = 0.$

Now, $.1inEE\left(\Delta y(\Delta y)^T\right) = \sum_{j=1}^{4} p_j \Delta y_j (\Delta y_j)^T = S(y)$

$$= \begin{pmatrix} S_1 & S_2 \\ S_2 & S_3 \end{pmatrix}.$$

Where, $S_1 = s + y_1(a_1 - a_2 y_1) + \rho y_2 + y_1(b_1 + b_2 y_1 + d_1) + k y_1 y_2$, $S_2 = -k y_1 y_2$, and $S_3 = 2(\delta + \rho) y_2$.

At the critical point $\hat{y}$, the value of $S(y)$ is given by,

$$\hat{S}(y) = \begin{pmatrix} 2(s + \hat{y}_1(a_1 - a_2 \hat{y}_1) + \rho \hat{y}_2) & -k \hat{y}_1 \hat{y}_2 \\ -k \hat{y}_1 \hat{y}_2 & 2(\delta + \rho)\hat{y}_2 \end{pmatrix}.$$

For large N, the process $N^{1/2}\{y(t) - \hat{y}\}$ is approximated by a bivariate Ornstein-Uhlenbeck process, with local drift matrix $\hat{B}(y)$ and local covariance matrix $\hat{S}(y)$. Thus its stationary distribution approximates the quasi-stationary distribution. The process $N^{1/2}\{y(t) - \hat{y}\}$ is approximately bivariate normal with mean 0 and covariance matrix C, where the matrix C can be determined with the help of the local drift matrix $\hat{B}(y)$ and local covariance matrix $\hat{S}(y)$, through the relationship

$\hat{B}(y)C + CB^T(\hat{y}) = -\hat{S}(y)$, where B^T is the transpose of B. After solving the above equation we get, $C = \begin{pmatrix} C_1 & C_2 \\ C_2 & C_3 \end{pmatrix}$.

The above result leads to the conclusion that in quasi-stationarity the marginal distribution of the number of uninfected T-cells and infected T-cells are approximately $N(\mu_{y_1}, \sigma_{y_1})$ and $N(\mu_{y_2}, \sigma_{y_2})$ respectively, where

$$\mu_{y_1} = \hat{y}_1, \sigma_{y_1} = \sqrt{(C_1 / N)}$$

$$\mu_{y_2} = \hat{y}_2, \sigma_{y_2} = \sqrt{(C_3 / N)}.$$

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Further, the covariance is approximated by $\sigma_{y_1 y_2} = C_2 = \frac{-(\delta+\rho)}{k}$.

Where,

$$C_1 = \frac{A}{B}, C_3 = \frac{B_1 C_2 + B_3 C_1 - k\hat{y}_1\hat{y}_2}{\delta} \quad and,$$

$$A = s + \hat{y}_1(a_1 - a_2\hat{y}_1) + \rho\hat{y}_2 + \frac{\delta(\delta+\rho)}{k}, \qquad B = \frac{s+\rho\hat{y}_2}{\hat{y}_1} + \hat{y}_1(a_2 + b_2).$$

Note that the parameters should also satisfy $C_1 > 0$, $C_3 > 0$.

G. Discussion on Estimation of Expected Time to Extinction of the Infected CD4$^+$T Cells and Formation of Theorem

In the deterministic version of the model, it is not possible to find out expected time to extinction of the disease by this approach recovery of the disease can be achieved by the immune system. Here, it is not sufficient to mention that recovery of the infected cells and extinction of the disease are both equally important. Stochastic approach is the only method by which expected time to extinction of the disease can be imagined, which is obviously related to the total number of cell populations.

Theorem 2: The expected time to extinction of the infected cell is approximately

$$E\left(\tau_Q\right) = \frac{1}{(\delta+\rho)q_{.1}} = \frac{\sigma_{y_2}}{(\delta+\rho)} \frac{\varphi\left(\frac{\mu_{y_2} - 1/2}{\sigma_{y_2}}\right)}{\phi\left(\frac{1-\mu_{y_2}}{\sigma_{y_2}}\right)}.$$

Proof. From (16), the time to extinction (τ_Q) in quasi-stationarity follows an exponential distribution with parameter $(\delta+\rho)q_{.1}$, where $q_{.1}$ is the marginal quasi-stationary distribution of the number of infected cells, conditioned on not being absorbed (i.e, $y_2 > 0$).

By using the diffusion approximation, the marginal distribution of the infected cells in quasi-stationarity will be univariate normal with mean μ_{y_2} and standard deviation σ_{y_2}, (see Section 5.6). To achieve consistency with the fact that $y_2 > 0$, the approximating normal distribution is modified by truncation at 0.5. Hence we have the following approximation of $q_{.n}$,

$$q_{.n} \approx \frac{1}{\varphi(\infty) - \varphi\left(\frac{1/2-\mu_{y_2}}{\sigma_{y_2}}\right)} \frac{1}{\sqrt{2\pi}} \cdot \frac{1}{\sigma_{y_2}} e^{-\frac{\left(n-\mu_{y_2}\right)^2}{2\sigma_{y_2}^2}}, \left(1/2 < n < \infty\right) = \frac{1}{1-\varphi\left(\frac{0.5-\mu_{y_2}}{\sigma_{y_2}}\right)} \frac{1}{\sigma_{y_2}} \phi\left(\frac{n-\mu_{y_2}}{\sigma_{y_2}}\right)$$

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$$\text{i.e} \quad q_{.n} \approx \frac{1}{\sigma_{y_2}} \frac{\phi\left(\dfrac{n-\mu_{y_2}}{\sigma_{y_2}}\right)}{\varphi\left(\dfrac{\mu_{y_2}-0.5}{\sigma_{y_2}}\right)}. \tag{17}$$

where ϕ and φ are the standard normal c.d.f. and the standard normal p.d.f. respectively.

Using approximation of (17), the expected time to extinction can be written as,

$$E\left(\tau_Q\right) = \frac{1}{(\delta+\rho)q_{.1}} = \frac{\sigma_{y_2}}{(\delta+\rho)} \frac{\varphi\left(\dfrac{\mu_{y_2}-1/2}{\sigma_{y_2}}\right)}{\phi\left(\dfrac{1-\mu_{y_2}}{\sigma_{y_2}}\right)}.$$

VI. NUMERICAL SIMULATION

The dynamics of the disease progression of HIV/AIDS along with control measures were analyzed using numerical methods. Here we build a computer simulation technique with a particular choices of parameter values that are reasonably realistic. The parameter values, considered here, are shown in Table 3. We find the quasi-stationary distribution and the expected time to extinction of the infected CD4$^+$T cells. Here we also consider the initial conditions for the state variables T, I and V along with the transversality condition for the adjoint variables ξ_i, $i = 1,2,3$, where $\xi_i(t_f) = 0$, $i = 1,2,3$. Here we analyze the effect of change of recovery rate of the infected individuals in presence of the control theoretic approach and find the expected time to extinction of the infected CD4$^+$T cells.

TABLE 3 A HYPOTHETICAL SET OF PARAMETER VALUES FOR THE MODEL SYSTEM (2)

Parameters	Values
s	5 $day^{-1}mm^{-3}$ .1in [9]
d_1	0.01 day^{-1} .3in [9]
a	0.5 day^{-1} .4in [9]
a_1	0.30 .4in [21]
b_1	0.015 .3in [21]
a_2	0.02 .4in [21]
b_2	0.001 .3in [21]
β	0.0002 mm^{-3} .1in [9]
k	$\beta q / c$ .7in [9]
ρ	0.01 day^{-1} .3in [9]
δ	1 day^{-1} .5in [9]
q	800 $day^{-1}mm^{-3}$ [9]
c	5 day^{-1} .5in [9]

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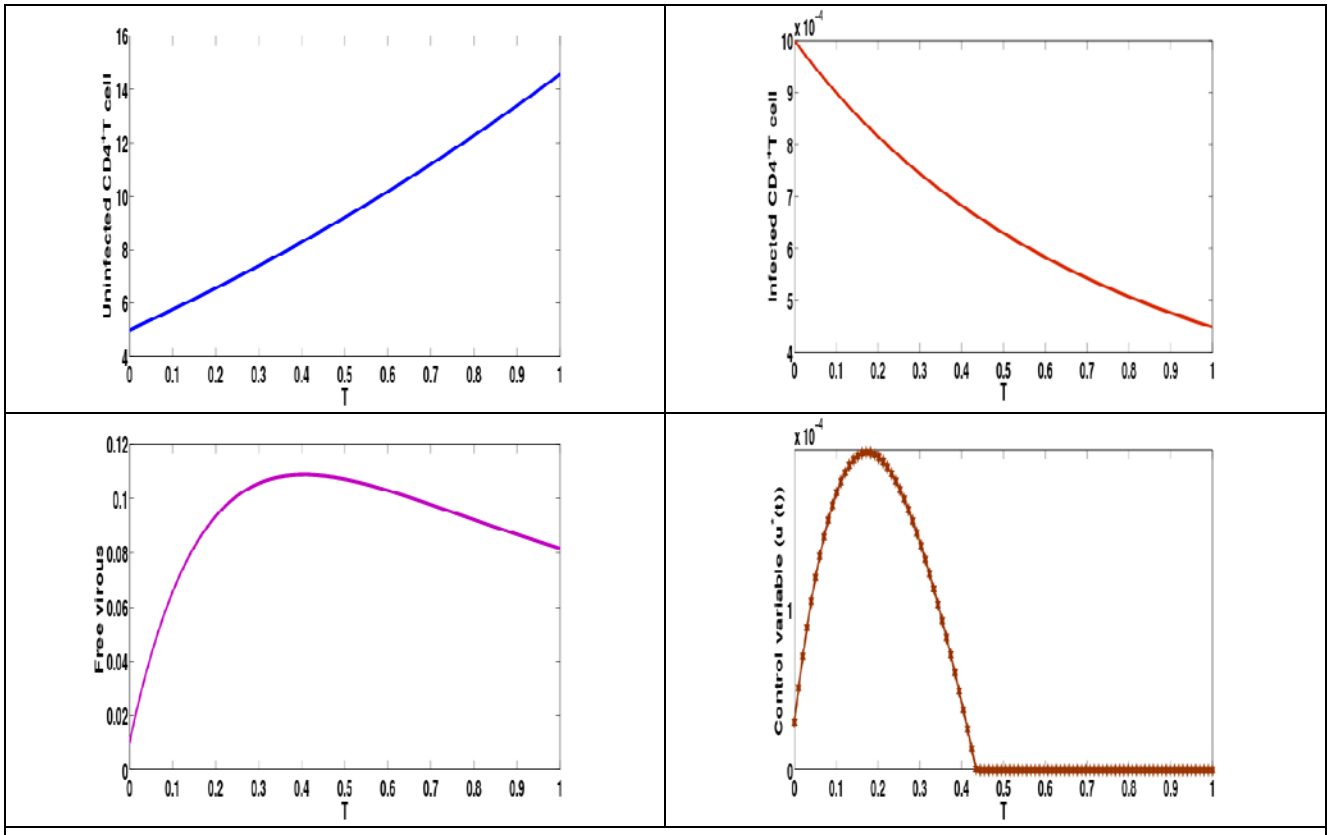
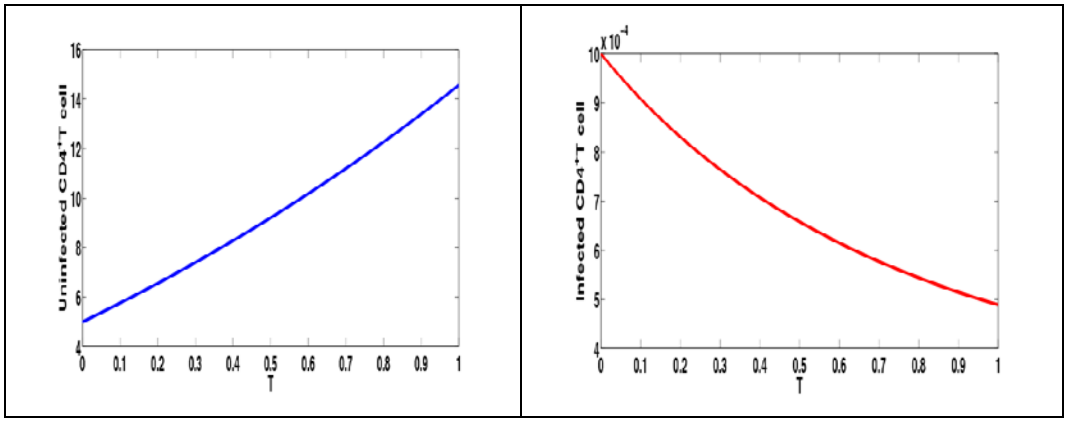


Fig. 1 The behavior of the state system and the control variable $u(t)$ of the optimality system (2) and (3) for $\rho = 0.01$, R=0.1, all other parameter values are the same as in Table 3



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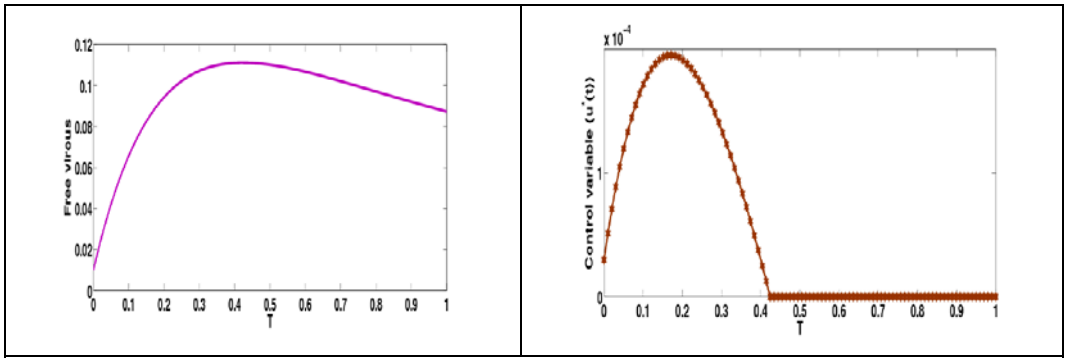

Fig. 2 The behavior of the state system and the control variable $u(t)$ of the optimality system (2) and (3) for $\rho = 0.1$, R=0.1, all other parameter values are same as in Table 3

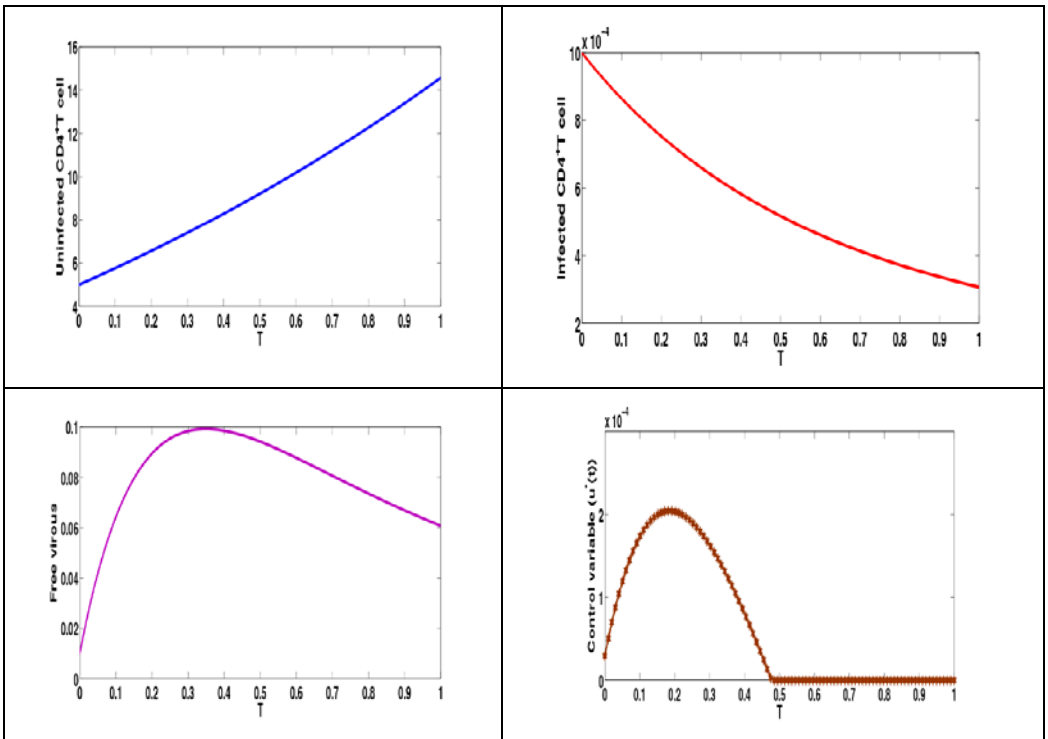

Fig. 3 The behavior of the state system and the control variable $u(t)$ of the optimality system (2) and (3) for $\rho = 0.5$, R=0.1, all other parameter values are same as in Table 3

Figs. 1-3 represent the behavior of the disease dynamics for control theoretic approach using control variable $u(t)$ for different values of recovery rate ($\rho = 0.01$, $\rho = 0.1$ and $\rho = 0.5$). From these figures, it can be inferred that if we increase the recovery rate from $\rho = 0.01$ to $\rho = 0.1$ and then $\rho = 0.5$ with the control approach of the drug adherence, then the number of infected $CD4^+$T cell decreases remarkably. This is due to the fact that with increasing recovery, antigen in the infected cells is being exhausted. Through this way, after reaching a certain level, number of virus also decreases. In the above figures, it has also been observed that by increasing the recovery rate of the infected cells, the infected $CD4^+$T cell decreases but it does not extinct. With this idea, we performed the numerical simulation for finding out the marginal distribution of the number of infected $CD4^+$T cells and its time to extinction.

For the numerical simulation of the marginal distribution in quasi-stationarity, we use Monte Carlo simulations techniques. For this purpose, we consider different population size (N) and different recovery rate of the infected $CD4^+$T cells. In the analytical

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derivation as well as in numerical simulation, we consider $a = (a_1 - b_1)$ and $T_{max} = \dfrac{a_1 - b_1}{a_2 + b_2}$ where a_i and b_i, $i = 1, 2$, are constants.

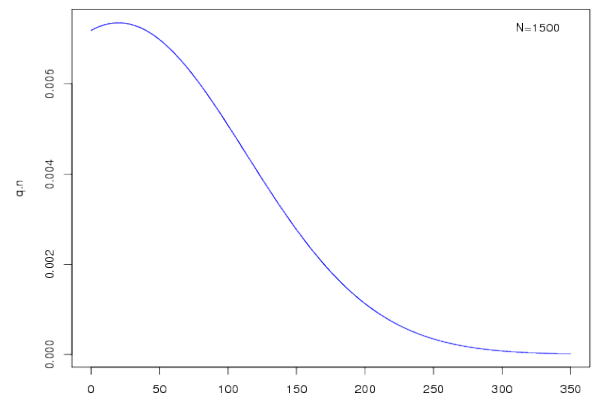

Fig. 4 The marginal distribution in quasi-stationarity of the number of infected CD4$^+$ T cell, which is truncated and positively skewed i.e non-normal for N=1500 of Eq. (12)

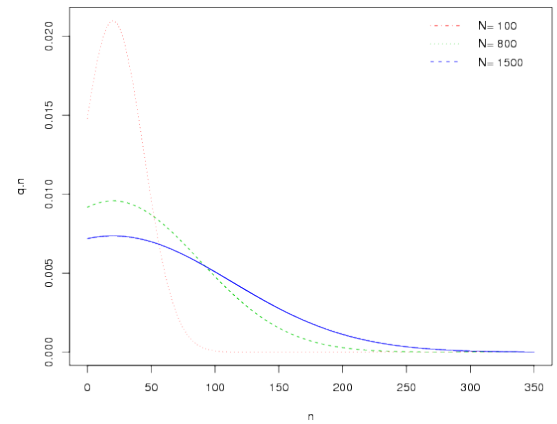

Fig. 5 The marginal distribution in quasi-stationarity of the number of infected CD4$^+$T cells for different values of N of Eq. (12)

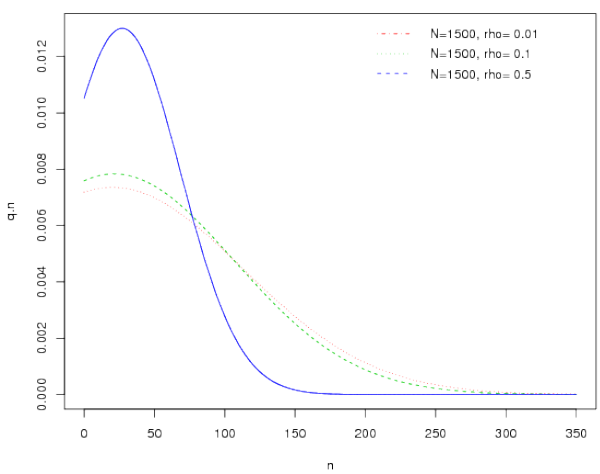

Fig. 6 The marginal distribution in quasi-stationarity of the number of infected CD4$^+$ T cells for different values of ρ of Eq. (12)

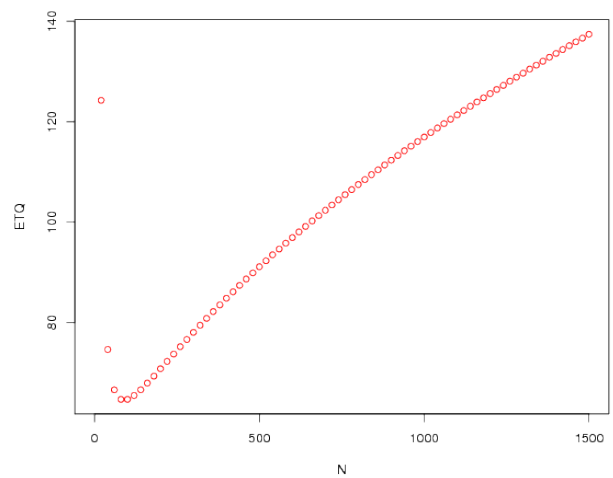

Fig. 7 The expected time to extinction $E(\tau_Q)$ in transition region are shown as a function of N of Eq. (12), all other parameter are the same as in Figs. 1 and 2.

Fig. 4 shows the marginal distribution in quasi-stationarity for the number of infected CD4$^+$T cells, which is truncated and positively skewed i.e non normal at $N = 1500$. Figs. 5 and 6 represent the marginal distribution of infected CD4$^+$T cells for different values of the total population N and recovery rate ρ. From Fig. 5, we can see that with increasing population size N, the number of infected CD4$^+$T cell also increases and the density of the infected CD4$^+$ T cell is also enhanced. Fig. 6 reflects the distribution of infected individuals for different values of ρ which shows that when we increase the recovery rate of the infected individual, the number of infected cell are also decreasing. So the skewness of the population decreases whereas the kurtosis gets higher value.

Fig. 7 represents the expected time to extinction from marginal distribution of the infected population in quasi-stationarity for various population size. Here we observed that when the population size N is very small, the expected time to extinction is very short but when N grows, the expected time to extinction increases rapidly. This type of phenomenon occurs because when the total population N is very small, it is expected that the number of infected cell is also very small. Furthermore, some of the infected cell become recovered, so the expected time to extinction becomes very short, but when the total population N is high

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then the number of infected cell grows rapidly which leads to the fact that the expected time to extinction is very long. Lastly our numerical analysis shows that the dynamics of disease progression can be reduced by applying control measures in the drug adherence with increasing recovery rate of the infected $CD4^+T$ cells. With this, it has also been concluded that expected time to extinction of the disease is a function of the total number of population size.

VII. DISCUSSION AND CONCLUSION

In this research article, we have enriched the mathematical model of Zhou et al. [9] by introducing optimal control therapeutic approach for successful recovery of the disease. Our analytical and numerical results reveal that, the number of infected $CD4^+T$ cell decreases remarkably by using systematic drug dose. By this, we get a better recovery of the infected class as it moves towards healthy class within a certain period of time. But for the estimation of expected time to extinction of the disease, it is not possible to analyze through deterministic version. For that purpose, we have studied the stochastic counterpart of the existing deterministic model of HIV. We also derived the quasi-stationary distribution of infected individuals as well as expected time to extinction of the disease. In this regard, our research findings may add a new dimension in epidemiological study through estimated approximation of marginal density of the infected individuals and its time to extinction. In conclusion, it can be stated that stochastic modeling provides a more accurate prediction in finding out the expected time to extinction of infected population for the disease HIV/AIDS.

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