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INSIGHT OF T CELL PROLIFERATION IN THE ESTIMATION OF EXPECTED TIME TO EXTINCTION OF THE DISEASE HIV/AIDS

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Abstract: The expected time to extinction of the disease HIV/AIDS is a serious concern today. This expected time to extinction has a significant correlation with the increasing function of population size of $CD4^+$T cells. When HIV invades into the body, these healthy cells are stimulated by antigen or mitogen, multiply through mitosis which is being treated as proliferation of $CD4^+$T cells. On that outlook, we consider here the logistic growth of $CD4^+$T cells in our three component mathematical models in deterministic version but to find out the expected time to extinction of the disease HIV/AIDS, stochastic approach is needed. Thus, we introduce hypothesized transition rates for the stochastic model and the quasi stationary distribution of the infected $CD4^+$T cells. Our results reveal that proliferation of the $CD4^+$T cells contributes significantly for estimation of the expected time to extinction of the disease through stochastic

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1. Introduction

The infection of human cells by human immunodeficiency virus (HIV) is utmost concern today. Since 1981, HIV spreads through out the world and nowadays HIV becomes a major epidemic in the earth. The significant factors which may influence the rate and rigorousness of the HIV infection are the life cycle of virus, the host cellular environment and the number of virus particle in the infected individual. This process of infection could lengthen for many years. A recurrence of epidemic outbreaks is known to happen for HIV infection that confer immunity. Once HIV enters into the body, the human immune system tries to get rid of it. The invasion of HIV is reported to CD4$^+$T cells (a type of white blood cells and henceforth referred as T cells) which are produced from the precursors in the bone marrow and thymus. After invasion of HIV into the body, antigen or mitogen stimulates T cells. At the time of stimulation, these healthy cells multiply through mitosis which is the maximum level of CD4$^+$T cells concentration in the body [1], [2], [3]. Total population of T cells significantly contribute for estimation of expected time to extinction of the disease. T cells are also termed as helper T cells and considered as command centers of the immune system which is normally present in the peripheral blood at a level between 800 and 1200 mm^{-3}. Due to the HIV infection, when CD4$^+$T cells reach below 200 mm^{-3}, the HIV infected patients are treated as AIDS patients [4].

Over the last several years many researchers present their research articles to develop the conception of immune system [5], HIV infection and its time to extinction [6]. Both deterministic and stochastic models have been developed in this research arena. Stochastic models [7], [8] describe the early occurrence in the disease when there are smaller number of infected cells and viruses. A lot of works with deterministic approach have also been done to examine the mean cell number changes. Some of these works can be found in the research article [9]. Perelson and Nelson [1] proposed logistic growth for susceptible CD4$^+$T cells. Roy and Chatterjee [10] proposed a model with proliferation of existing CD4$^+$T cells in the body which shows the dynamical behavior of the human immune system through drug stimulation by generating CTL. Roy

and Chatterjee [4] also proposed a mathematical model to show the effect of HAART (Highly Active AntiRetroviral Therapy) on immune cells to an HIV infected individuals.

In another work, Roy et al. [6] introduced stochasticity in deterministic model of HIV proposed by Bonhoeffer et al. [11] and find the marginal distribution in quasi-stationarity and the expected time to extinction of the infected T-cell population. In this research article, we improve their early model [6] by considering introduction of T-cell proliferation from existing T-cells in the growth term of the uninfected T-cell which is more realistic from the biological point of view. Here we analyze the quasi-stationarity and the expected time to extinction of the infected T-cell population. We have also shown that the expected time to extinction is an increasing function of the cell population which arises from proliferation of existing T cells as well as by conventional creation. This paper deals specifically with the expected time to extinction of HIV infected cells considering that T-cells can be grown not only from precursors in the bone marrow and thymus but also from proliferation of infectible $CD4^+$T-cells.

In the present work, the deterministic model of HIV infection is described in Section 2. Section 3 is devoted for the stochastic model formulation. This section also includes the description of the transition states and Kolmogorov's forward equation. Time to extinction of the infected $CD4^+$T-cells is given in Section 4 and Section 5 is devoted for the distribution of the time to extinction. Diffusion approximation, the approximation of quasi-stationary distribution and the expected time to extinction are elaborately explained in Section 6. Section 7 includes results from numerical illustration from the model and finally discussions and conclusions are given in Section 8.

2. The Deterministic Model

To generate the deterministic model of HIV infection, we need to consider the population dynamics of $CD4^+$T cells when HIV enters into the body. T cells are produced from precursors in the bone marrow and thymus at a constant rate s and have a death rate μ. In presence of HIV virus, antigen or mitogen stimulates T cells. At the time of stimulation, T cells multiply through mitosis with a rate r i.e the growth or proliferation of T cells from existing T cells are governed by logistic fashion [1], [2], [3]. Here the model is discussed based on the HIV infection on $CD4^+$T cells. The growth rate of the uninfected T cell can be written as,

$$\frac{dx_1}{dt} = s + rx_1\left(1 - \frac{x_1}{T_m}\right) - \mu x_1$$

where r is the average growth rate of the T cells, the density of uninfected T cell in the blood is x_1. r depends on the degree of idiotypic network stimulation of the T cell proliferation. The total number of T cell is bounded, as T_m is the maximum number of T cell in the body [1], [10]. The dynamics of the HIV infection will be determined by the interactions between the uninfected T-cells, infected T-cells and the free virus. There are several research articles where elaborate description of the dynamics of the interactions of T-cells and HIV have been discussed.

The interaction of T-cells and HIV can be modeled as follows

$$\begin{aligned}
\frac{dx_1}{dt} &= s + rx_1\left(1 - \frac{x_1}{T_m}\right) - \mu x_1 - \beta x_1 v,\\
\frac{dx_2}{dt} &= \beta x_1 v - \alpha x_2,\\
\frac{dv}{dt} &= cx_2 - \gamma v.
\end{aligned} \tag{1}$$

Here the density of uninfected T-cells is $x_1(t)$, of infected such cells is $x_2(t)$ and free virus is $v(t)$. The infection rate of T-cells is 'β', per capita rate of disappearance of infected cells is 'α', rate of production of virus by an infected cells is 'c', and the death rate of the free virus particle is denoted by 'γ'.

We assumed that at the equilibrium state $\dot{v} = 0$, so v can be eliminated by putting $v = cx_2/\gamma$. So x_1, x_2 satisfy

$$\begin{aligned}
\frac{dx_1}{dt} &= s + rx_1\left(1 - \frac{x_1}{T_m}\right) - \mu x_1 - kx_1x_2,\\
\frac{dx_2}{dt} &= kx_1x_2 - \alpha x_2.
\end{aligned} \tag{2}$$

Here, $k = \beta c/\gamma$, all the parameters and variables are nonnegative.

3. The Stochastic Model Formulation

Here we consider two state variables, $x_1(t)$ is the number of uninfected T-cells and $x_2(t)$ is the number of infected such cells at time t. They jointly take values in the state space $S = \{(m, n) : m = 0, 1, 2, ...; n = 0, 1, 2, ...\}$. So,

Table 1: Hypothesized transition rates for the stochastic version

Event ($CD4^+$T-cells)	Transition	Transition rates
Birth of an uninfected	$(m,n) \to (m+1,n)$	$\lambda_1(m,n) = s + rx_1\left(1 - \frac{x_1}{T_m}\right)$
Death of an uninfected	$(m,n) \to (m-1,n)$	$\mu_1(m,n) = \mu m$
Infection of an uninfected	$(m,n) \to (m-1,n+1)$	$\lambda_2(m,n) = kmn$
Death of infected	$(m,n) \to (m,n-1)$	$\mu_2(m,n) = \alpha n$

$p_{m,n}(t) = P\{x_1(t) = m, x_2(t) = n\}$ is the joint distribution of $x_1(t)$, $x_2(t)$ 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, i.e. production of $CD4^+$T-cells from primary and secondary sources, infection of $CD4^+$T-cells, death of $CD4^+$T -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 (2).

3.1. Description of the Transition States

Here we have introduced two forms of generation of uninfected T-cells. Primary source is from precursors in the bone marrow and thymus and secondary source is proliferation of infectible T-cells considering that total number of T cell proliferate to its maximum T_m, at which its proliferation shuts off.

We also consider here that natural birth of the uninfected T-cells or stimulation by antigen or mitogen is balanced by the natural death of uninfected T-cells as the programmed cell cycle that continuously operate the process at cellular level to maintain equilibrium state. This cycle continues until or unless it is hindered by any biological or environmental stress factor.

3.2. Kolmogorov's Forward Equation

Let us assume that in a infinitesimally small time interval Δt, the probability of exactly one birth (or, one death) is given by {birth rate(or, death rate)$\times(\Delta t) + O(\Delta t)$}, and that of more than one event (birth and/ or death) is $O(\Delta t)$.

Let us consider the probability $p_{m,n}(t + \Delta t)$ where $\Delta t \to 0$. So,

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

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.

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:

$$p'_{m,n}(t) = p_{m-1,n}(t)\lambda_1(m-1,n) + p_{m+1,n}(t)\mu_1(m+1,n) + p_{m+1,n-1}(t)$$
$$\lambda_2(m+1,n-1) + p_{m,n+1}(t)\mu_2(m,n+1) - p_{m,n}(t)K(m,n). \tag{3}$$

4. Time to Extinction of the Infected T-Cells

The time to extinction is an important measure which can be elucidated through the epidemiological perceptive. It was used to define thresholds for stochastic endemic models, see [12].

Here the time to extinction of the infected T-cells is denoted by the random variable τ, i.e., when we have $\{t \leq \tau\}$, infected T-cells will exist.

$$\therefore P(t \leq \tau) = P\{x_2(t) > 0\},$$

and

$$P(\tau \leq t) = P\{x_2(t) = 0\} = p_{.0}(t),$$

where

$$p_{.0}(t) = \sum_{m=0}^{N} p_{mn}(t).$$

Let the c.d.f and p.d.f of τ are denoted by F and f respectively.

$$\therefore F(t) = P\{x_2(t) > 0 = \sum_{m=0}^{N} P\{x_1(t) = m, x_2(t) = 0\}\} = \sum_{m=0}^{N} p_{m,0}(t)$$

$$\therefore f(t) = \sum_{m=0}^{N} p'_{m,0}(t) = p'_{.0}(t).$$

Putting $n = 0$ in eq. (3), we have

$$p'_{m,0}(t) = p_{m-1,0}(t)\lambda_1(m-1,0) + p_{m+1,0}(t)\mu_1(m+1,0) + p_{m+1,-1}(t)$$
$$\lambda_2(m+1,-1) + p_{m,1}(t)\mu_2(m,1) - p_{m,0}(t)K(m,0)$$
$$= (s + r(m-1)(1 - \frac{m-1}{T_m}))p_{m-1,0}(t) + \mu(m+1)p_{m+1,0}(t)$$
$$+\alpha p_{m,1}(t) - (s + rm(1 - \frac{m}{T_m}) + \mu m)p_{m,0}(t).$$

$$\therefore \sum_{m=0}^{\infty} p'_{m,0}(t) = s\sum_{m=0}^{\infty} p_{m-1,0}(t) + r\sum_{m=0}^{\infty} p_{m-1,0}(t)(m-1)(1-\frac{m-1}{T_m})$$

$$+\mu\sum_{m=0}^{\infty}(m+1)p_{m+1,0}(t) + \alpha\sum_{m=0}^{\infty} p_{m,1}(t) - s\sum_{m=0}^{\infty} p_{m,0}(t)$$

$$-r\sum_{m=0}^{\infty} p_{m,0}(t)m(1-\frac{m}{T_m}) - \mu\sum_{m=0}^{\infty} mp_{m,0}(t)$$

$$= \alpha\sum_{m=0}^{\infty} p_{m,1}(t) = \alpha\sum_{m=0}^{\infty} P(x_1(t)=m, x_2(t)=1).$$

$$i.e., \quad p'_{.0}(t) = \alpha p_{.1}(t). \tag{4}$$

$$\therefore f(t) = p'_{.0}(t) = \alpha P\{x_2(t)=1\} = \alpha p_{.1}(t),$$

where

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

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

5. The Distribution of the Time to Extinction

To find the absorption of $x_2(t)$ at 0, the distribution of $(x_1(t),\ x_2(t)),\forall\ \ t \geq 0$, 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 $\{x_1(t), x_2(t)\}, t \geq 0$, has a unique conditional distribution (conditioned on being not absorbed) $q_{m,n}$, where, $q_{m,n} = \lim_{t\to\infty} P\{x_1(t)=m,\ \ x_2(t)=n|x_2(t)\neq 0\}$, whatever the distribution of initial state $(x_1(0), x_2(0))$ is.

Let

$$q_{m,n}(t) = P\{x_1(t)=m, x_2(t)=n|x_2(t)\neq 0\}$$

$$= \frac{p_{m,n}(t)}{1-p_{.0}(t)}, m = 0,1,2,.....; n = 1,2.....;$$

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

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

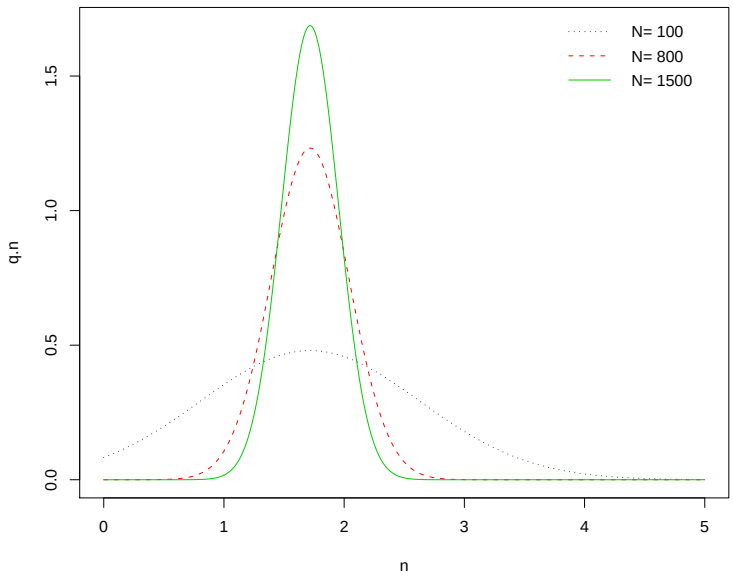

Figure 1: The quasi-stationary distribution $q_{.n}$ for different values of N of Eq.(2) for $s = 10$, $r = 0.04$, $T_m = 1500$, $\beta = 0.024$, $c = 50$ Virion/CD4, γ= 2.0, μ= 0.01, α= 0.24.

If the initial distribution is assumed to be the quasi-stationary distribution, i.e., $p_{m,n}(0) = q_{m,n}, \quad \forall m, n$, then the distribution of the time to extinction will be especially simple.

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

$$q'_{m,n}(t) = \frac{p'_{m,n}(t)}{1 - p_{.0}(t)} + \alpha p_{.1}(t) \frac{p_{m,n}(t)}{(1 - p_{.0}(t))}.$$

Also we can write:

$$q'_{m,n}(t) = \frac{p'_{m,n}(t)}{1 - p_{.0}(t)} + \alpha p_{.1}(t) \frac{q_{m,n}(t)}{(1 - p_{.0}(t))}.$$

Since the initial distribution is assumed to be quasi-stationary,
i.e. $p_{m,n}(0) = q_{m,n}$,

$$\therefore q'_{m,n}(t) = \frac{p'_{m,n}(t)}{1 - p_{.0}(t)} + \alpha q_{.1}(t) \frac{p_{m,n}(t)}{(1 - p_{.0}(t))}. \tag{5}$$

Putting $q'_{m,n}(t) = 0$, in the Eq.(5), we get $\quad p'_{m,n}(t) = -\alpha q_{.1} p_{m,n}(t)$.

Thus, we have $p_{m,n}(t) = e^{-\alpha q_{.1} t}$, constant.
At $t = 0$, we have $p_{m,n}(0) = q_{mn}$,

$$\therefore p_{mn}(t) = q_{mn} e^{-\alpha q_{.1} t} \quad and \quad p_{.1}(t) = q_{.1} e^{-\alpha q_{.1} t}.$$

Using the above form of $p_{.1}(t)$ in Eq. (4), we have

$$f(t) = p'_{.0}(t) = (\alpha q_{.1})\, e^{-}(\alpha q_{.1})t, \quad t > 0.$$

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

From the diffusion approximation, $q_{.1}$ can be estimated; the quasi-stationary distribution is approximated asymptotically by a bivariate normal distribution [13].

6. Diffusion Approximation and the Approximation of Quasi-Stationary Distribution

Let us consider the two-dimensional process (2):

$$\frac{dx_1}{dt} = s + rx_1 \left(1 - \frac{x_1}{T_m}\right) - \mu x_1 - kx_1 x_2,$$

$$\frac{dx_2}{dt} = kx_1 x_2 - \alpha x_2.$$

If the total population N is sufficiently large, the quasi-stationary distribution is approximated by a bivariate normal distribution.

The critical point of the deterministic model is given by $\widehat{x} = (\widehat{x_1}, \widehat{x_2})$, where $\widehat{x_1} = \frac{\alpha}{k}$ and $\widehat{x_2} = \frac{sk - \alpha\mu}{\alpha k}$.

Possible changes in the two-population system (2) with the probabilities

Changes	Probability
$\triangle x_1 = [1, 0]^T$	$p_1 = \left(s + rx_1 \left(1 - \frac{x_1}{T_m}\right)\right) \triangle t$
$\triangle x_2 = [-1, 0]^T$	$p_2 = (\mu x_1 + kx_1 x_2)\, \triangle t$
$\triangle x_3 = [0, -1]^T$	$p_3 = \alpha x_2 \triangle t$
$\triangle x_4 = [0, 1]^T$	$p_4 = kx_1 x_2 \triangle t$

Now we want to find the mean change $E(\triangle x)$ and the covariance matrix $E\left(\triangle x (\triangle x)^T\right)$ for the time interval $\triangle t$, neglecting terms of order $(\triangle t)^2$.

In the time interval t to $t + \triangle t$, the changes in the state variables x_1 and x_2 are denoted by $\triangle(x_1)$ and $\triangle(x_2)$. So,

$$E(\triangle x) = E\left(\ \triangle x_1 \triangle x_2\ \right) = \sum_{j=1}^{4} p_j \triangle x_j$$

$$= \left(s + rx_1\left(1 - \frac{x_1}{T_m}\right) - \mu x_1 - kx_1x_2 - \alpha x_2 + kx_1x_2\right)\triangle t + O(\triangle t)$$

$$= b(x)\triangle t + O(\triangle t).$$

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

$$B(x) = \frac{\partial b(x)}{\partial x} = \begin{pmatrix} r - \frac{2rx_1}{T_m} - \mu - kx_2 & -kx_1 \\ kx_2 & -\alpha + kx_1 \end{pmatrix}.$$

The approximated value of $B(x)$ at the critical point $\widehat{x} = (\widehat{x_1}, \widehat{x_2})$ is

$$B(\widehat{x}) = \begin{pmatrix} \frac{-sk}{\alpha} - \frac{r\alpha}{kT_m} & -\alpha \\ \frac{1}{\alpha}[sk + r\alpha\left(1 - \frac{\alpha}{kT_m}\right) - \alpha\mu] & 0 \end{pmatrix}.$$

Now,

$$E\left(\triangle x(\triangle x)^T\right) = \sum_{j=1}^{4} p_j \triangle x_j (\triangle x_j)^T = S(x)$$

$$= \begin{pmatrix} 2s + 2rx_1\left(1 - \frac{x_1}{T_m}\right) & 0 \\ 0 & 2\alpha x_2 \end{pmatrix}.$$

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

$$S(\widehat{x}) = 2\begin{pmatrix} s + \frac{r\alpha}{k}\left(1 - \frac{\alpha}{kT_m}\right) & 0 \\ 0 & s + \frac{r\alpha}{k}\left(1 - \frac{\alpha}{kT_m}\right) - \frac{\alpha\mu}{k} \end{pmatrix}.$$

The process $N^{1/2}\{x(t) - \widehat{x}\}$ is approximated by a bivariate Ornstein - Uhlenbeck process for large N, with local drift matrix $B(\widehat{x})$ and local covariance matrix $S(\widehat{x})$. Then the stationary distribution of the Ornstein - Uhlenbeck process approximates the quasi-stationary distribution which is approximately bivariate normal with mean 0 and covariance matrix $\sum$, where the matrix $\sum$ can be determined with the help of the local drift matrix $B(\widehat{x})$ and local covariance matrix $S(\widehat{x})$, through the relationship $B(\widehat{x})\sum + \sum B^T(\widehat{x}) = -S(\widehat{x})$, where the superscript T is used to denote the transpose. After solving the above equation we get,

$$\sum = \begin{pmatrix} \sigma_1 & \sigma_2 \\ \sigma_2 & \sigma_3 \end{pmatrix}.$$

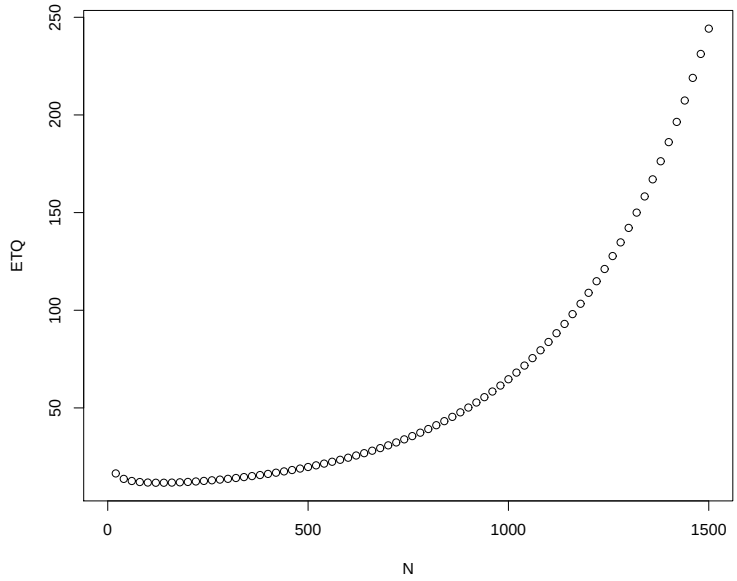

Figure 2: The expected time to extinction in transition region are shown as a function of N, all other parameters are same as in Figure 1.

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 $N(\mu_{x_1}, \sigma_{x_1})$ and $N(\mu_{x_2}, \sigma_{x_2})$ respectively, where

$$\mu_{x_1} = \widehat{x_1}, \quad \sigma_{x_1} = \sqrt{(}\sigma_1/N), \quad \mu_{x_2} = \widehat{x_2}, \quad \sigma_{x_2} = \sqrt{(}\sigma_3/N)$$

Further, the covariance is approximated by $\sigma_{x_1x_2} = \frac{-\alpha}{k}$, where, $\sigma_1 = \frac{A}{B}$, $\sigma_2 = \frac{-\alpha}{k}$, $\sigma_3 = \frac{1}{\alpha^2}\frac{AC}{B} + \frac{B}{k}$, and $A = s + \frac{r\alpha}{k}\left(1 - \frac{\alpha}{kT_m}\right) + \frac{\alpha^2}{k}$, $B = \frac{sk}{\alpha} + \frac{r\alpha}{kT_m}$, $C = sk + r\alpha\left(1 - \frac{\alpha}{kT_m}\right) - \mu\alpha$. Note that the parameters should also satisfy $\sigma_1 > 0$, $\sigma_3 > 0$.

From diffusion approximation we have concluded that the marginal distribution of the infected T-cell population size in quasi-stationarity is approximately normal. Now again we modify the approximating normal distribution by truncation at 1/2 to achieve consistency with the fact that $x_2 \geq 0$. Hence we find that the distribution can be enunciated by the following approximation:

$$q_{.n} \approx \frac{1}{\sigma_{x_2}} \quad \frac{\varphi\left(\frac{n-\mu_{x_2}}{\sigma_{x_2}}\right)}{\phi\left(\frac{\mu_{x_2}-1/2}{\sigma_{x_2}}\right)}, \tag{6}$$

Table 2: A hypothetical set of parameter values for the model system (2)

Parameters	Default Values assigned (day^{-1})
s	10 mm^{-3} [10]
r	0.04 [1], [10]
T_m	1500 mm^{-3} [1]
k	$\beta * c/\gamma$
β	$0.002 \leq \beta \leq 0.5$ mm^{-3} [10],[14]
c	50 Virion/CD4 [6]
γ	2.0 [6]
μ	0.01 mm^{-3} [15]
α	0.24 mm^{-3}[10]

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

6.1. The Expected Time to Extinction

We find the expected time to extinction($E(\tau_Q)$) from quasi-stationary distribution. The Expected time to extinction is given by

$$E(\tau_Q) = \frac{1}{\alpha q_{.1}} = \frac{\sigma_{x_2}}{\alpha} \quad \frac{\phi\left(\frac{\mu_{x_2}-1/2}{\sigma_{x_2}}\right)}{\varphi\left(\frac{1-\mu_{x_2}}{\sigma_{x_2}}\right)}. \tag{7}$$

We see that the expected time to extinction is a function of population size N, which is a function when the population size is increasing (Figure 1).

7. Numerical Illustration

The entire simulation are done by using $MATLAB^R$ for approximating quasi-stationary distribution and the expected time to extinction. Here we have adopted Monte Carlo simulations techniques. The hypothesized parameter values are given in Table 2, though we consider different population size.

From Figure 1, we can say that when the population size $N = 100$, the quasi-stationary distribution is truncated and positively skewed i.e definitely non-normal. But if we increase the population size, the distribution becomes symmetric, i.e the quasi-stationary distribution is approximately normal in its body (Figure 1).

The expected time to extinction from quasi-stationarity for various population size is given in Figure 2. Here we notice that the expected time to extinction grows slowly with N up to 1000 after that it grows faster with N. When population size N is small it is natural that the number of infected T-cells are also expected to be small and at that time the human immune system can decelerate the rapid growth of infected cells resulting little time of extinction of the disease. But when population size is high, unsurprisingly the number of infected cells expected to be elevated and immune system cannot control the rapid growth of infected host cells and ultimately leads to high extinction time of disease.

Thus it is evident from our numerical analysis that accumulation of infected cell is enhanced when large number of susceptible cells is generated from both primary and secondary sources. In such a scenario, we find that instantaneous rate of contact is severely high and contributes higher kurtosis which implies that the instant infection recurring probability is much higher in the population. High contact rate boosts the immunity for larger signal implication which counters balance the negative effect of such alarming contact of infection. Contrastingly when we consider a low susceptible population, the contact process gets diluted to a large extent and thereby the skewness of the population expands (i.e positively skewed) while the kurtosis gets a little damped implicating a lower contact rate of the infection (Figure 2).

8. Discussion and Conclusions

In this paper we have presented a basic mathematical model of HIV infection in $CD4^+T$ cells considering generation of T cells from bone marrow and thymus. But after invasion of HIV into the body, antigen or mitogen stimulates T cells and these healthy cells multiply through mitosis. Based on the concept of quasi-stationarity, the diffusion approximation, the result can be used to study the transition region.

Introduction of the stochasticity of the existing deterministic model of HIV for finding out time to extinction of HIV infection gives a positive result in this research article. Approximation of the marginal distribution through quasi-stationarity added a new dimension in the epidemiological study. Our numerical simulation shows that our approximation of the expected time to extinction is quite satisfactory.

Thus, it can be concluded that the expected time to extinction of the HIV infection from quasi-stationarity is an increasing function of the population size. By this way, proliferation of T cells through mitosis when HIV invades, contributed significantly for expected time to extinction which reveals proper justification by our analytical and numerical results.

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