CHAPTER FOUR

STOCHASTIC MODEL OF THE GROWTH OF HIV IN AN INFECTED INDIVIDUAL

4.1 INTRODUCTION

In the discussion about the progression of the human immunodeficiency virus (HIV) infection, it is often seen that there is a variation in the viral genome. Studies (Kaye et al. 1992 and Loveday 1996) have shown that HIV may make 1 to 40 base errors per replication cycle with no genetic mechanisms for correction resulting in the production of genetically diverse viral species or quasi species with 20 – 25% variability. Feinberg (1996) also observed that HIV has an inherent tendency to evolve at a rate (about 1 million times faster than the human DNA) which is believed to be responsible for the development of resistance to antiviral treatments within a matter of months thereby undermining the attempts to produce effective vaccines. Holmes (1998) observed that even in the course of a single infection, a multitude of different genomes are produced through mutation, recombination and natural selection, which allow the virus to continually evade immune responses and infect a variety of cell types. Further, Musey et al. (1997), Phillips et al. (1997) and Barker et al. (1998) observed that there is a correlation between the antigen receptors of T-cells and HIV replication. Consequently, the pathogenesis of the infection can be understood only when the genetic variation in HIV and the receptor-specific HIV infection are given their due importance in the formulation of any model of the dynamics of HIV in an infected individual.

Stilianakis et al. (1997) analysed a model for the pathogenesis of AIDS in which the effect of the ongoing generation and selection of HIV mutants are considered. However, the nature of evolution of the resistant forms in a virus that is continually mutating in response to environmental pressures, and the impact of the location of the antigen receptor through which the virus has entered the cell body on the variable nature of viral replication through mutation have not been analysed so far in the literature. Accordingly, in this chapter, we propose and analyse two stochastic models:

(i) Model I which describes the dynamics of the viral load in a HIV infected person taking into consideration the fact that genetically diverse viral species are produced even in the course of a single infection and that the infection is receptor-specific.

(ii) Model II which describes the multiplication process of the virons inside an infected T4 cell under the assumption that genetically diverse viral species are produced at every lysis that occurs in a T4 cell population.

The organization of this chapter is as follows. Section 4.2 describes model I as a multi-type branching process. In Section 4.2.1, an infinite system of inter-connected integral equations for the probability generating functions of the various viral type populations is obtained. Explicit expressions for the means and co-variances of the viral populations are derived in Section 4.2.2 for a particular case where the virus exist in two forms only. In Section 4.3, model II which describes the dynamics of the growth of HIV inside an infected cell is analysed by a binary splitting process. Also provided in this section is a numerical illustration that brings out the impact of the genetic diversity in viral production.

4.2 MODEL I: THE MUTATION MODEL

We assume that at time t = 0, one HIV of type 0 is introduced into the blood stream (medium of T4 cells). Since each of the T4 cells has an infinite number of CD4+ receptors on its cell wall, we assume that the virus bonds with probability $\pi(j|0)$, j = 1, 2, … to the j-th CD4+ receptor on the cell membrane of one of the T4 helper cells and injects its RNA into the cell medium. The virus arrests the growth of the infected cell but utilises the cell medium to multiply itself into random numbers z_0 and z_j of virons of type 0 and type j respectively after which the cell undergoes a lysis releasing the virons whose numbers are governed by the probability generating function

$$f^{(0j)}(u,v) = \mathrm{E}[u^{z_0} v^{z_j}] = \sum_{m,n=0}^{\infty} p_{mn}^{(0j)} u^m v^n,\ j = 1,2,...$$

These virons in turn go to infect other T4 cells and the process continues indefinitely. We assume that a virus of type i, $i \neq 0$ anchors to the j-th CD4+ receptor on the cell membrane of a T4 cell with probability $\pi(j|i)$, j = 1, 2, … but generates virons of type i only according to the probability generating function defined by

$$f^{(i)}(s) = \sum_{j=0}^{\infty} p_j^{(i)} s^j,\ i = 1, 2, ...$$

where $\pi(j \mid i) = p_j^i$.

We also assume that, for each of the virons of type $\ell, \ell = 0, 1, 2, ...,$ the time from its release to the time of lysis it generates is a random variable T_ℓ whose distribution function is given by

$$f_\ell^{(t)} = \Pr\{T_\ell \leq t\},\ t \geq 0.$$

Let $X_\ell(t)$ denote the number of virons of type ℓ, ℓ = 0, 1, 2, … at time t and

$$X(t) = (X_0(t), X_1(t), ..., X_\ell(t), X_{\ell+1}(t), ...).$$

Then the process X(t) is identified as a multi-type branching process with state-space Z_+^∞, where Z_+ is the set of all non-negative integers. To study the process X(t), we investigate its probability generating function in the next section.

4.2.1 The Probability Generating Functions

Denoting $s = (s_0, s_1, ...)$, we define the following probability generating functions:

$$G^{(i)}(t,s) = \mathrm{E}[s_0^{x_0(t)} s_1^{x_1(t)} ... \mid X(0) = (\delta_{i0}, \delta_{i1}, \delta_{i2}, ...)],\ i = 0, 1, 2, ...$$

Using probabilistic arguments, it is easily seen that

$$G^{(0)}(t,s)=[1-\mathrm{F}_0(t)]s_0+\sum_{\ell=1}^{\infty}\pi(\ell\mid 0)\int_0^t f^{(0\ell)}(G^{(0)}(t-u,s),G^{(\ell)}(t-u,s))dF_0(u) \qquad (4.2.1.1)$$

$$G^{(i)}(t,s)=[1-\mathrm{F}_i(t)]s_i+\int_0^t f^{(i)}(G^{(i)}(t-u,s))dF_i(u),\mathrm{i}=1,2,... \qquad (4.2.1.2)$$

The moments of $X_j(t)$, j = 0, 1, 2, … can be derived from the equations (4.2.1.1) and (4.2.1.2).

We define

$$M_j(t\mid i)=\mathrm{E}[\mathrm{X}_j(t)\mid \mathrm{X}(0)=(\delta_{i0},\delta_{i1},\delta_{i2},...)],\mathrm{i}=0,1,2,...$$

Differentiating (4.2.1.1) partially with respect to s_j and setting s_k =1, k = 0, 1, 2, …, we obtain

$$M_j(t\mid 0)=[1-\mathrm{F}_0(t)]\delta_{0j}+\sum_{\ell=1}^{\infty}\pi(\ell\mid 0)\int_0^t\{\mathrm{m}_1^{(0\ell)}M_j(t-u\mid 0)+\mathrm{m}_2^{(0\ell)}M_j(t-u\mid \ell)\}dF_0(u) \qquad (4.2.1.3)$$

where j = 0, 1, 2, … and

$$m_1^{(0i)}=\left\{\frac{\partial}{\partial \mathrm{u}}f^{(0i)}(u,v)\right\}_{u=1,v=1},\quad m_2^{(0i)}=\left\{\frac{\partial}{\partial v}f^{(0i)}(u,v)\right\}_{u=1,v=1}$$

Differentiating (4.2.1.2) partially with respect to s_j and setting s_k =1, k = 0, 1, 2, …, we obtain

$$M_j(t\mid i)=[1-\mathrm{F}_i(t)]\delta_{ij}+\mathrm{m}^{(i)}\int_0^t M_j(t-u\mid i)dF_i(u) \qquad (4.2.1.4)$$

where i = 1, 2, …, j = 0, 1, 2, … and

$$m_1^{(i)}=\left\{\frac{\partial}{\partial \mathrm{u}}f^{(i)}(u)\right\}_{u=1}$$

If we assume $F_j(u)=1-\mathrm{e}^{-\lambda_1 u}$, then taking Laplace transform on both sides of (4.2.1.3) and (4.2.1.4), we obtain

$$M_j^*(\theta\mid 0)=\frac{\delta_{0\mathrm{j}}}{(\theta+\lambda_0)}+\sum_{\ell=1}^{\infty}\pi(\ell\mid 0)\frac{\lambda_0}{(\theta+\lambda_0)}\{m_1^{(0\ell)}M_j^*(\theta\mid 0)+m_2^{(0\ell)}M_j^*(\theta\mid \ell)\} \qquad (4.2.1.5)$$

$$M_j^*(\theta\mid i)=\frac{\delta_{\mathrm{ij}}}{(\theta+\lambda_{\mathrm{i}})}+\frac{\lambda_{\mathrm{i}}}{(\theta+\lambda_{\mathrm{i}})}m_1^{(i)}M_j^*(\theta\mid i) \qquad (4.2.1.6)$$

where i = 1, 2, …, and j = 0, 1,2 , …. Solving the equation (4.2.1.6), we get

$$M_j^*(\theta \mid i) = \frac{\delta_{ij}}{\theta + \lambda_i(1 - m_1^{(i)})}, \; i, j = 1, 2, \ldots \qquad (4.2.1.7)$$

Substituting (4.2.1.7) in (4.2.1.5) and simplifying, we get

$$M_j^*(\theta \mid 0) = \frac{\delta_{0j}}{\theta + \lambda_0(1 - m_1^{(0)})} + \frac{\lambda_0}{(\theta + \lambda_0(1 - m_1^{(0)}))} \sum_{\ell=1}^{\infty} \pi(\ell \mid 0) \frac{\delta_{\ell j} m_2^{(0\ell)}}{\theta + \lambda_\ell(1 - m_1^{(\ell)})} \qquad (4.2.1.8)$$

where $m_1^{(0)} = \sum_{\ell=1}^{\infty} \pi(\ell \mid 0) m_1^{(0\ell)}$

Inverting the equations (4.2.1.7) and (4.2.1.8), we obtain

$$M_j(t \mid i) = \delta_{ij} e^{-\alpha_i t} \qquad (4.2.1.9)$$

$$M_j(t|0) = \delta_{0j} e^{-\alpha_0 t} + (1 - \delta_{0j}) \frac{\lambda_0 m_2^{(0j)} \pi(j|0)}{(\alpha_0 - \alpha_j)} (e^{-\alpha_j t} - e^{-\alpha_0 t}), \qquad (4.2.1.10)$$

$M_j(t \mid 0) = \delta_{ij} e^{-\alpha_i t}$

where $\alpha_0 = \lambda_0(1 - m_1^{(0)})$; $\alpha_i = \lambda_i(1 - m_1^{(i)})$; i = 1, 2, …; j = 0, 1,2 , ….

To obtain the covariance structure of $X_j(t)$ and $X_k(t)$ where j, k = 0, 1, 2, …, we define

$$M_{jk}(t|i) = E[X_j(t)X_k(t)|X(0) = (\delta_{i0}, \delta_{i1}, \delta_{i2}, \ldots)], \; i = 0, 1, 2, \ldots. \qquad (4.2.1.11)$$

Differentiating (4.2.1.1) with respect to s_j and s_k and setting $s_0 = 1$, $s_1 = 1$, $s_2 = 1$, …, we obtain

$$M_{jk}(t|0) = \sum_{\ell=1}^{\infty} \pi(\ell|0) \int_0^t [m_1^{(0\ell)} M_{jk}(t - u|0) + m_2^{(0\ell)} M_{jk}(t - u|\ell)$$

$$+ m_{11}^{(0\ell)} M_j(t - u|0) M_k(t - u|0) + m_{22}^{(0\ell)} M_j(t - u|\ell) M_k(t - u|\ell)$$

$$+ m_{12}^{(0\ell)} \{M_j(t - u|0) M_k(t - u|\ell) + M_j(t - u|\ell) M_k(t - u|0)\}] dF_0(u), \qquad (4.2.1.12)$$

where

$$m_{11}^{(0\ell)} = \left\{ \frac{\partial^2 f^{(0\ell)}(u, v)}{\partial u^2} \right\}_{u=1, v=1}$$

$$m_{12}^{(0\ell)} = \left\{\frac{\partial^2 f^{(0\ell)}(u, v)}{\partial u \partial v}\right\}_{u=1,v=1}$$

$$m_{22}^{(0\ell)} = \left\{\frac{\partial^2 f^{(0\ell)}(u, v)}{\partial v^2}\right\}_{u=1,v=1}$$

Differentiating (4.2.1.2) with respect to s_j and s_k and setting $s_0 = 1$, $s_1 = 1$, $s_2 = 1$, …, we obtain

$$M_{jk}(t|i) = \int_0^t \{m_1^{(i)} M_{jk}(t - u|i) + m_{11}^{(i)} M_j(t - u|i) M_k(t - u|i)\} dF_i(u), \qquad (4.2.1.13)$$

where

$$m_{11}^{(i)} = \left\{\frac{\partial^2 f^{(i)}(u)}{\partial u^2}\right\}_{u=1}, \quad i = 1, 2, \ldots.$$

Taking Laplace transform on both sides of (3.2.1.13), we get

$$M_{jk}^*(\theta|i) = \frac{\lambda_i}{\theta + \lambda_i}\left\{m_1^{(i)} M_{jk}^*(\theta|i) + \frac{m_{11}^{(i)} \delta_{ij} \delta_{ik}}{\theta + 2\alpha_i}\right\}.$$

Which on simplification gives

$$M_{jk}^*(\theta|i) = \frac{\lambda_i m_{11}^{(i)} \delta_{ij} \delta_{ik}}{(\theta + \alpha_i)(\theta + 2\alpha_i)}. \qquad (4.2.1.14)$$

Inverting (4.2.1.14), we get

$$M_{jk}(t|i) = \frac{\lambda_i m_{11}^{(i)} \delta_{ij} \delta_{ik}}{\alpha_i}(e^{-\alpha_i t} - e^{-2\alpha_i t}). \qquad (4.2.1.15)$$

Now, taking Laplace transform on both sides of (4.2.1.12), we get

$$M_{jk}^*(\theta|0) = \frac{\lambda_0}{\theta + \lambda_0} \sum_{\ell=1}^{\infty} \pi(\ell|0)[m_1^{(0\ell)} M_{jk}^*(\theta|0) + m_2^{(0\ell)} M_{jk}^*(\theta|\ell)$$

$$+ m_{11}^{(0\ell)} L\{M_j(t|0) M_k(t|0)\} + m_{22}^{(0\ell)} L(M_j(t|\ell) M_k(t|\ell))$$

$$+ m_{12}^{(0\ell)} L\{M_j(t|0) M_k(t|\ell) + M_j(t|\ell) M_k(t|0)\}]. \qquad (4.2.1.16)$$

Substituting (4.2.1.7), (4.2.1.8) and (4.2.1.14) in (4.2.1.16) and simplifying, we get

$$M^{*}_{jk}(\theta|0) = \lambda_0^2(1 - \delta_{0j})(1 - \delta_{0k})\delta_{jk}\frac{\pi(\mathrm{j}|0)\mathrm{m}_2^{(0\mathrm{j})}\mathrm{m}_{11}^{(j)}}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{j}})(\theta + 2\alpha_{\mathrm{j}})}$$

$$+ \lambda_0\mathrm{m}_{11}^{(0)}\Big\{\delta_{0j}\delta_{0k} + (1 - \delta_{0j})\delta_{0k}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(\mathrm{j}|0)}{\alpha_{\mathrm{j}} - \alpha_0} + \delta_{0j}(1 - \delta_{0k})\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(\mathrm{k}|0)}{\alpha_{\mathrm{k}} - \alpha_0}$$

$$+ (1 - \delta_{0j})(1 - \delta_{0k})\frac{\lambda_0^2(\mathrm{m}_2^{(0)})\pi(\mathrm{j}|0)\pi(\mathrm{k}|0)}{(\alpha_{\mathrm{j}} - \alpha_0)(\alpha_{\mathrm{k}} - \alpha_0)}\Big\}\frac{1}{(\theta + \alpha_0)(\theta + 2\alpha_0)}$$

$$- \lambda_0\mathrm{m}_{11}^{(0)}\{\delta_{0j}(1 - \delta_{0k})\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(\mathrm{k}|0)}{\alpha_{\mathrm{k}} - \alpha_0}$$

$$+ (1 - \delta_{0j})(1 - \delta_{0k})\frac{\lambda_0^2(\mathrm{m}_2^{(0)})^2\pi(\mathrm{j}|0)\pi(\mathrm{k}|0)}{(\alpha_{\mathrm{j}} - \alpha_0)(\alpha_{\mathrm{k}} - \alpha_0)}\}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_0 + \alpha_{\mathrm{k}})}$$

$$+ \lambda_0\mathrm{m}_{11}^{(0)}(1 - \delta_{0j})(1 - \delta_{0k})\frac{\lambda_0^2(\mathrm{m}_2^{(0)})^2\pi(\mathrm{j}|0)\pi(\mathrm{k}|0)}{(\alpha_{\mathrm{j}} - \alpha_0)(\alpha_{\mathrm{k}} - \alpha_0)}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{j}} + \alpha_{\mathrm{k}})}$$

$$+ \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{22}^{(0\ell)}\delta_{\ell j}\delta_{\ell k}\frac{1}{(\theta + \alpha_0)(\theta + 2\alpha_\ell)}$$

$$+ \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}\frac{(\delta_{0j}\delta_{\ell k} - \delta_{\ell j}\delta_{0k})}{(\theta + \alpha_0)(\theta + \alpha_0 + \alpha_\ell)}$$

$$+ \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}\{(1 - \delta_{0j})\delta_{\ell k}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(j|0)}{\alpha_{\mathrm{j}} - \alpha_0}$$

$$+ (1 - \delta_{0k})\delta_{\ell j}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(k|0)}{\alpha_{\mathrm{k}} - \alpha_0}\Big\}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_0 + \alpha_\ell)}$$

$$- \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}(1 - \delta_{0j})\delta_{\ell k}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(j|0)}{\alpha_{\mathrm{j}} - \alpha_0}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{j}} + \alpha_\ell)}$$

$$- \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}(1 - \delta_{0k})\delta_{\ell j}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(k|0)}{\alpha_{\mathrm{k}} - \alpha_0}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{k}} + \alpha_\ell)}. \quad (4.2.1.17)$$

Inverting (4.2.1.17), we get explicitly the covariance structure of the viral population.

4.2.2 A Particular Case

For simplicity, we assume that there are two genetically different virons only, called type 0 and type 1. Precisely, on bonding to a T4 cell, a type 0 HIV produces type 0 virons and type 1 virons, while type 1 HIV produces type 1 virons only. Following the same notation as in 4.2.1, we obtain the mean population sizes of the two types of virons as given below:

$$M_0(t|1) = 0, \quad M_1(t|1) = e^{-\alpha_1 t};$$

$$M_0(t|0) = e^{-\alpha_0 t}, \quad M_1(t|0) = \frac{\lambda_0 m_2^{(01)}}{\alpha_1 - \alpha_0}\{e^{-\alpha_0 t} - e^{-\alpha_1 t}\}.$$

The co-variances of the population sizes of the virons are obtained in the following form:

$$M_{00}(t|1) = 0, \quad M_{01}(t|1) = 0,$$

$$M_{11}(t|1) = \frac{\lambda_1 m_{11}^{(11)}}{\alpha_1}\{e^{-\alpha_1 t} - e^{-2\alpha_1 t}\};$$

$$M_{00}(t|0) = \frac{\lambda_0 m_{11}^{(01)}}{\alpha_0}\{e^{-\alpha_0 t} - e^{-2\alpha_0 t}\};$$

$$M_{01}(t|0) = \lambda_0\left[\frac{\lambda_0 m_{11}^{(01)} m_2^{(01)}}{\alpha_0(\alpha_1 - \alpha_0)}(e^{-\alpha_0 t} - e^{-2\alpha_0 t})\right.$$

$$\left. + \left\{\frac{m_{12}^{(01)}}{\alpha_1} - \frac{\lambda_0 m_{11}^{(01)} m_2^{(01)}}{\alpha_1(\alpha_1 - \alpha_0)}\right\}(e^{-\alpha_0 t} - e^{-(\alpha_0 + \alpha_1)t})\right]$$

$$M_{11}(t|0) = \lambda_0\left[\lambda_1 m_2^{(01)} m_{11}^{(1)}\left\{\frac{e^{-\alpha_0 t} - e^{-\alpha_1 t}}{\alpha_1(\alpha_1 - \alpha_0)} - \frac{e^{-\alpha_0 t} - e^{-2\alpha_1 t}}{\alpha_1(2\alpha_1 - \alpha_0)}\right\}\right.$$

$$\left. + \frac{C_{12}}{(\alpha_1 - \alpha_0)^2}\lambda_0^2 (m_2^{(01)})^2\left\{\frac{e^{-\alpha_0 t} - e^{-2\alpha_0 t}}{\alpha_0} - 2\frac{e^{-\alpha_0 t} - e^{-(\alpha_0+\alpha_1)t}}{\alpha_1} + \frac{e^{-\alpha_0 t} - e^{-2\alpha_1 t}}{(2\alpha_1 - \alpha_0)}\right\}\right]$$

where $C_{12} = m_{11}^{(01)} + 2m_{12}^{(01)} + m_{22}^{(01)}$.

If $\alpha_0 = \alpha_1 = \alpha \neq 0$, then

$$M_0(t|0) = M_1(t|1) = e^{-\alpha t}, \; M_0(t|1) = 0, \; M_1(t|0) = \lambda_0 m_2^{(01)} t e^{-\alpha t};$$

$$M_{00}(t|1) = M_{01}(t|1) = 0,\ M_{11}(t|1) = \frac{\lambda_1 m_{11}^{(1)}}{\alpha}\{e^{-\alpha t} - e^{-2\alpha t}\},$$

$$M_{00}(t|0) = \frac{\lambda_0 m_{11}^{(01)}}{\alpha}\{e^{-\alpha t} - e^{-2\alpha t}\},$$

$$M_{11}(t|0) = \{m_{11}^{(01)} + 2m_{12}^{(01)} + m_{22}^{(01)}\}(m_2^{(01)})^2 \frac{(\lambda_0 t)^3}{3},$$

$$M_{01}(t|0) = \left\{\frac{\lambda_0}{\alpha}\right\}^2 m_{11}^{(01)} m_2^{(01)} e^{-\alpha t}\{1 - (1 + \alpha t)e^{-\alpha t}\} + \left\{\frac{\lambda_0}{\alpha}\right\} m_{12}^{(01)} e^{-\alpha t}(1 - e^{-\alpha t}).$$

4.3 MODEL II: THE MULTIPLICATION PROCESS INSIDE A T4 CELL

Before describing model II, we briefly outline the life-cycle of HIV and the events that occur between the time of an infection of HIV with a T4 cell and the lysis of the host cell (for a more detailed account, see Fauci (1988), Shaw et al. (1988), Haseltine (1990) and Greene (1991)).

4.3.1 The Life Cycle of HIV

The HIV is a retrovirus and its RNA carries the genetic information. The HIV has a dense cylindrical core encasing two molecules of the viral genome. Virus-encoded enzymes required for efficient multiplication, such as reverse transcriptase and integrase, are also incorporated into the virus particle. After attaching itself to the cell wall of the host T4 cell, the virus injects its RNA together with the enzymes reverse transcriptase and integrase into the cytoplasm of the host cell. The viral reverse transcriptase enzyme first synthesises a single complementary, negative-sense DNA copy to the HIV RNA; next the RNA is denatured; and then a complementary positive-sense DNA copy is synthesised to create double-stranded proviral DNA.

The proviral DNA may either reside in episomal form or enter the cell nucleus and become integrated into host DNA under the action of the viral integrase enzyme. Within the cell, the proviral DNA (also called provirus) can remain latent, giving no sign of its presence for several months or years. In this stage, every time the infected cell divides, the provirus is duplicated with the cell's DNA. On the other hand, once the cell activation occurs due to antigen or mitogen, the proviral DNA transcribes viral genomic RNA and messenger RNA (mRNA). The messenger RNA translates the regulatory proteins tat and rev. Tat protein promotes transcription of more messenger RNA. Rev protein causes multiple spliced segments of messenger RNA to form singly spliced segments that are translated into structural proteins, envelope proteins and viral enzymes. The assembly of proteins and enzymes, together with the viral genomic RNA are assembled to form mature HIV virus which buds on the cell wall. The ongoing process of budding of mature virons on the cell wall takes place until the infected cell is unable to withstand the burden of the viral production when the cell undergoes the lysis releasing the mature virons ready to attack other T4 cells.

Loveday et al. (1995) observed that the replication process has limited efficiency as incomplete, RNA-deficient and damaged virons may be released from the host cell and viral proteins may be produced in excess during the life-cycle and can be detected while the host cell undergoes lysis. The population of defective virons may inhibit the production of fully mature virons. Accordingly, we proceed to formulate a stochastic model of viral production in a host cell by taking into consideration the fact that along with fully mature HIV virons, damaged virons are also produced at the time of lysis.

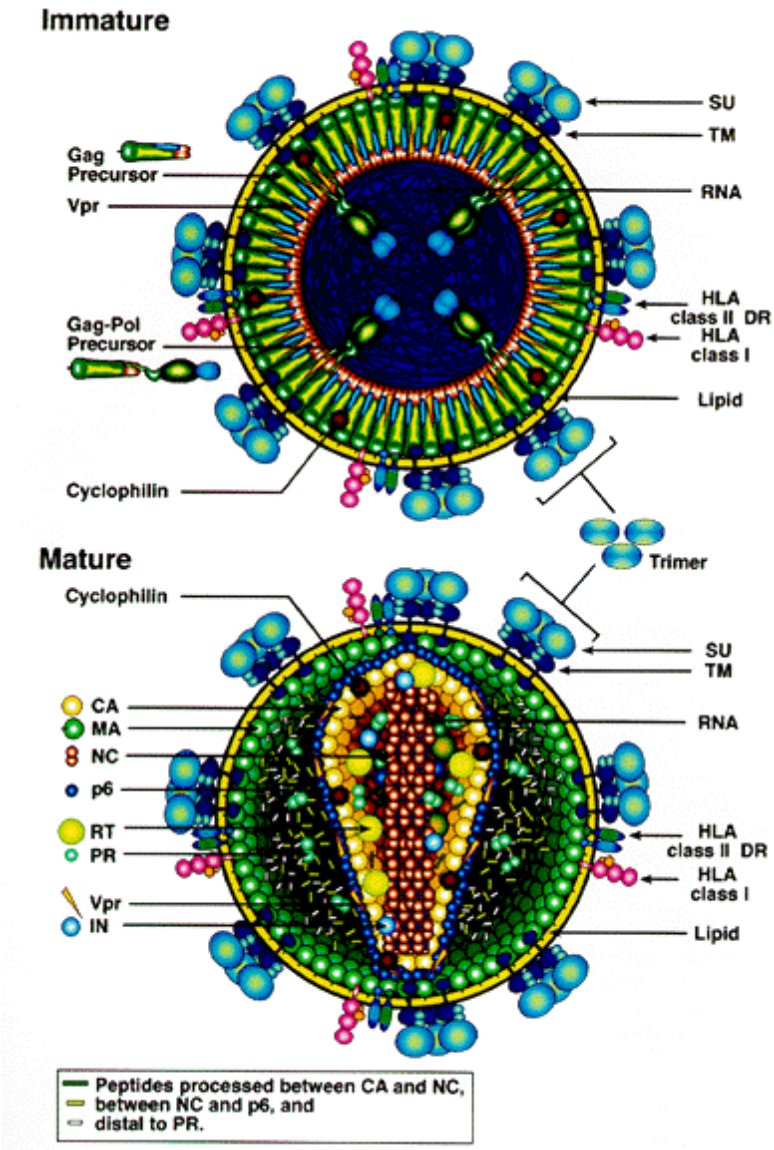

Figure 4.1 The immature and the mature HIV-1 viron
(Excerpt from http://msl.cs.uiuc.edu/~yershova/bcb495/bcbProjects-3.htm)

4.3.2 The Model Formulation

We assume that at time t = 0, a HIV attaches to the cell wall of a T4 cell and injects its RNA instantaneously into the cytoplasm of the host cell. Let T be the time at which the viral DNA gets integrated with the host DNA. Let the probability distribution function of T be given by

$$\Pr\{T \leq \tau\} = 1 - e^{-\alpha\tau},\ \alpha > 0,\ \tau > 0.$$

We assume that viral RNAs are replicated according to a Poisson process with rate λ, λ > 0. Let N(t) be the number of viral RNAs that are present inside the cell at time t. We assume that at any time t, the budding of HIV takes place with a rate proportional to N(t). Let X(t) be the number of HIV buds that are present on the cell wall at time t. Then the vector process (X(t), N(t)) is Markov and its structure is analysed in the following section. For brevity, we denote Z(t) = (X(t), N(t)).

4.3.3 The Probability Generating Function for (X(t), N(t))

The probability generating function of the vector process (X(t), N(t)) defined by $G(u, v; t) = E[u^{X(t)}u^{N(t)}]$. We proceed to obtain a differential equation for $G(u, v; t)$. First, we define the probability function

$$p(n, m; t) = \Pr\{Z(t) = (n, m)\}. \qquad (4.3.3.1)$$

Then, we see that

$$p(0, 0; t) = e^{-\alpha t} + \alpha e^{-\alpha t} \otimes e^{-\lambda t}$$

$$= \frac{\lambda e^{-\alpha t} - \alpha e^{-\lambda t}}{(\lambda - \alpha)}; \qquad (4.3.3.2)$$

$$p(0, 1; t) = \alpha e^{-\alpha t} \otimes \lambda e^{-\lambda t} \otimes e^{-(\lambda+\mu)t}$$

$$= \frac{\lambda\alpha}{\mu(\lambda - \alpha)(\lambda + \mu - \alpha)}\{\mu e^{-\alpha t} - (\lambda + \mu - \alpha)e^{-\lambda t} + (\lambda - \alpha)e^{-(\lambda+\mu)t}\}. \qquad (4.3.3.3)$$

The infinitesimal transition probabilities are given by

$$\Pr\{Z(t + \Delta) = (n, m+1) | Z(t) = (n, m)\} = \lambda\Delta, \; n \geq 0, \; m \geq 1;$$

$$\Pr\{Z(t + \Delta) = (n + 1, m-1) | Z(t) = (n, m)\} = \mu m\Delta, \; n \geq 0, \; m \geq 1;$$

Then, by using probabilistic laws, we obtain

$$\frac{\partial p(n, m; t)}{\partial t} = -(\lambda + m\mu)p(n, m; t) + \lambda p(n, m - 1; t) + \mu(m + 1)p(n - 1, m + 1; t), \; n \geq 1, \; m \geq 1, \tag{4.3.3.4}$$

$$\frac{\partial p(0, m; t)}{\partial t} = -(\lambda + m\mu)p(0, m; t) + \lambda p(0, m - 1; t), \; m \geq 2, \tag{4.3.3.5}$$

$$\frac{\partial p(n, 0; t)}{\partial t} = -\lambda p(n, 0; t) + \mu p(n - 1, 1; t), \; n \geq 1. \tag{4.3.3.6}$$

Equations (4.3.3.4) to (4.3.3.6) can be recursively solved starting with (4.3.3.2) and (4.3.3.3) to give the state probabilities $p(n, m; t)$, $n \geq 0$, $m \geq 0$. However, the expressions are quite unwieldy and hence, we proceed to obtain the differential equation satisfied by probability generating function $G(u, v; t)$.

We note that

$$G(u, v; t) = \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} p(n, m; t)u^n v^m$$

and hence, by using the equations (4.3.3.2) to (4.3.3.6), we obtain the following partial differential equation:

$$\frac{\partial G}{\partial t} + \mu(v - u)\frac{\partial G}{\partial v} = \lambda(v - 1)(G - e^{-\alpha t}), \tag{4.3.3.7}$$

with the initial condition $G(u, v; 0) = 1$. When $\alpha \to \infty$, equation (4.3.3.7) becomes

$$\frac{\partial G}{\partial t} + \mu(v - u)\frac{\partial G}{\partial v} = \lambda(v - 1)G. \tag{4.3.3.8}$$

Equation (4.3.3.8) is readily solved to yield

$$G(u, v; t) = e^{\frac{\lambda}{\mu}\{(v - u)(1 - e^{-\mu t}) + (\mu - 1)\mu t\}}$$

from which all the moments of X(t) and N(t) can be easily obtained. However, for the nontrivial case $\alpha < \infty$, equation (4.3.3.7) appears to be intractable and as such, we content ourselves in obtaining the moments of X(t) and N(t) in the next section.

4.3.4 The Moment of (X(t), N(t))

Differentiating (4.3.3.7) with respect to u at u = 1, v = 1, we get the differential equation

$$\frac{\partial E[X(t)]}{\partial t} - \mu E[N(t)] = 0. \qquad (4.3.4.1)$$

Differentiating (4.3.3.7) with respect to v at u = 1, v = 1, we get the differential equation

$$\frac{\partial E[N(t)]}{\partial t} + \mu E[N(t)] = \lambda(1 - e^{-\alpha t}). \qquad (4.3.4.2)$$

Differentiating (4.3.3.7) twice with respect to u at u = 1, v = 1, we get

$$\frac{\partial E[X(t)\{X(t) - 1\}]}{\partial t} = 2\mu E[X(t)N(t)]. \qquad (4.3.4.3)$$

Differentiating (4.3.3.7) twice with respect to v at u = 1, v = 1, we get

$$\frac{\partial E[N(t)\{N(t) - 1\}]}{\partial t} + 2\mu E[N(t)\{N(t) - 1\}] = \lambda E[N(t)]. \qquad (4.3.4.4)$$

Differentiating (4.3.3.7) with respect to u and v at u = 1, v = 1, we get

$$\frac{\partial E[X(t)N(t)]}{\partial t} + \mu E[X(t)N(t)] = \mu E[N(t)\{N(t) - 1\}] + \lambda E[X(t)]. \qquad (4.3.4.5)$$

Using Laplace transform method, the system of equations (4.3.4.1) to (4.3.4.5) yields the Laplace transforms:

$$L\{E[N(t)]\} = \frac{\lambda\alpha}{\theta(\theta + \alpha)(\theta + \mu)}; \qquad (4.3.4.6)$$

$$L\{E[X(t)]\} = \frac{\lambda\mu\alpha}{\theta^2(\theta + \alpha)(\theta + \mu)}; \qquad (4.3.4.7)$$

$$L\{E[X(t)N(t)]\} = \frac{2\lambda^2\mu\alpha}{\theta^2(\theta + \alpha)(\theta + \mu)(\theta + 2\mu)}; \qquad (4.3.4.8)$$

$$L\{E[N(t)\{N(t)\ -1\}]\} = \frac{\lambda^2\alpha}{\theta(\theta + \alpha)(\theta + \mu)(\theta + 2\mu)}; \qquad (4.3.4.9)$$

$$L\{E[X(t)\{X(t)\ -1\}]\} = \frac{4\lambda^2\mu^2\alpha}{\theta^3(\theta + \alpha)(\theta + \mu)(\theta + 2\mu)}. \qquad (4.3.4.10)$$

Inverting equations (4.3.4.6) to (4.3.4.10), we get

$$E[N(t)] = \frac{\lambda}{\mu}\left\{1 - \frac{\mu e^{-\alpha t} - \alpha e^{-\mu t}}{\mu - \alpha}\right\}; \qquad (4.3.4.11)$$

$$E[X(t)] = \lambda t - \frac{\lambda}{\mu - \alpha}\left\{\frac{\mu}{\alpha}(1 - e^{-\alpha t}) - \frac{\alpha}{\mu}(1 - e^{-\mu t})\right\}; \qquad (4.3.4.12)$$

$$E[X(t)N(t)] = \frac{\lambda^2}{\mu}t - \frac{2\lambda^2\mu}{\alpha(\mu - \alpha)(2\mu - \alpha)}(1 - e^{-\alpha t})$$

$$+ \frac{2\lambda^2\alpha}{\mu^2(\mu - \alpha)}(1 - e^{-\mu t}) - \frac{\lambda^2\alpha}{2\mu^2(2\mu - \alpha)}(1 - e^{-2\mu t}); \qquad (4.3.4.13)$$

$$E[N(t)\{N(t) - 1\}] = \frac{\lambda^2}{2\mu^2}\left\{1 - \frac{2\mu^2}{(\mu - \alpha)(2\mu - \alpha)}e^{-\alpha t} + \frac{2\alpha}{\mu - \alpha}e^{-\mu t} - \frac{\alpha}{2\mu - \alpha}e^{2\mu t}\right\}$$

(4.3.4.14)

$$E[X(t)\{X(t) - 1\}] = \lambda^2t^2 - \frac{4\lambda^2\mu^2}{\alpha(\mu - \alpha)(2\mu - \alpha)}t + \frac{4\lambda^2\alpha}{\mu(\mu - \alpha)}t - \frac{\lambda^2\alpha}{\mu(2\mu - \alpha)}t$$

$$+ \frac{4\lambda^2\mu^2}{\alpha^2(\mu - \alpha)(2\mu - \alpha)}(1 - e^{-\alpha t}) - \frac{4\lambda^2\alpha}{\mu^2(\mu - \alpha)}(1 - e^{-\mu t}) + \frac{\lambda^2\alpha}{2\mu(2\mu - \alpha)}(1 - e^{-2\mu t})$$

(4.3.4.15)

Using the expressions (4.3.4.11) to (4.3.4.15), we can obtain explicitly the correlation coefficient ρ between X(t) and N(t). However, we present in the following section a numerical illustration to highlight the impact of the parameters α, λ and μ on ρ.

4.3.5 A Numerical Illustration

For the purpose of illustration we assume $\alpha = 100.0$, $\lambda = 200.0$, $\mu = 300.0$ and obtain the first two moments of X(t) and N(t), the ratio between their means and the correlation coefficient (ρ) between them. The results are highlighted in Tables 4.1 to 4.3.

Since $\alpha = 100$, the mean time for the viral RNA to get integrated and start releasing the HIV buds is 0.01. Hence for increasing values of $t > 0.01$ both E[X(t)] and E[N(t)] can be expected to increase. Table 4.1 shows this trend. We also observe that the released viral RNAs rapidly become buds since the ratio E[X(t)]/E[N(t)] is increasing (Table 4.1). As the viral RNAs become buds, the number of buds will increase and the number of viral RNAs will increase which is indicated as negative correlation between X(t) and N(t) in Table 4.1.

As μ increases E[X(t)] increases but E[N(t)] decreases and hence the ratio between E[X(t)] and E[N(t)] increases (Table 4.2) and the correlation between X(t) and N(t) remains negative (Table 4.2). As the rate of releasing viral RNAs increases, both the mean number of buds and the viral RNAs should increase. However, since the rate of buds is a constant, we find that the ratio remains a constant even though the value of λ increases (Table 4.3). In this case also the correlation between X(t) and N(t) remains negative (Table 4.3).

4.4 CONCLUSION

In this chapter, the mean of X(t) i.e. the number of HIV buds that are present on the cell wall at time t and N(t) i.e. the number of viral RNAs that are present inside the cell at time t have been obtained. Contribution of the stochastic models to statistical work is the ability to obtain the covariance structure of which is very difficult to obtain.

Table 4.1 $\mathbf{E}[X(t)]$, $\mathbf{E}(N(t)]$, $\mathbf{E}[X(t)]/\ \mathbf{E}(N(t)]$, ρ **versus** t

for $\alpha = 100.0$, $\lambda = 200.0$, $\mu = 300.0$

t	$\mathbf{E}[X(t)]$	$\mathbf{E}(N(t)]$	$\mathbf{E}[X(t)]/\ \mathbf{E}(N(t)]$	ρ
0.0500	7.3535	0.6599	11.1429	-0.5067
0.0600	9.3408	0.6642	14.0634	-0.5406
0.0700	11.3361	0.6658	17.0274	-0.5366
0.0800	13.3343	0.6663	20.0116	-0.5184
0.0900	15.3337	0.6665	23.0048	-0.4963
0.1000	17.3335	0.6666	26.0020	-0.4746
0.1100	19.3334	0.6666	29.0008	-0.4545
0.1200	21.3334	0.6667	32.0003	-0.4364
0.1300	23.3333	0.6667	35.0001	-0.4202
0.1400	25.3333	0.6667	38.0000	-0.4055
0.1500	27.3333	0.6667	41.0000	-0.3923

Table 4.2 E[X(t)], **E**(N(t)], **E**[X(t)]/ **E**(N(t)], ρ **versus** μ

for α = 100.0, λ = 200.0, t = 0.05

μ	**E**[X(t)]	**E**(N(t)]	**E**[X(t)]/ **E**(N(t)]	ρ
300.00	7.3535	0.6599	11.1429	-0.5067
310.00	7.3747	0.6387	11.5457	-0.4631
320.00	7.3946	0.6189	11.9485	-0.4241
330.00	7.4133	0.6002	12.3513	-0.3890
340.00	7.4309	0.5826	12.7542	-0.3575
350.00	7.4474	0.5660	13.1571	-0.3291
360.00	7.4631	0.5504	13.5601	-0.3034
370.00	7.4779	0.5355	13.9631	-0.2802
380.00	7.4920	0.5215	14.3661	-0.2592
390.00	7.5053	0.5082	14.7692	-0.2400
400.00	7.5180	0.4955	15.1722	-0.2260
410.00	7.5300	0.4835	15.5753	-0.2067
420.00	7.5415	0.4720	15.9784	-0.1922
430.00	7.5524	0.4610	16.3816	-0.1790
440.00	7.5629	0.4506	16.7847	-0.1668
450.00	7.5729	0.4406	17.1879	-0.1557
460.00	7.5824	0.4310	17.5911	-0.1454
470.00	7.5916	0.4219	17.9942	-0.1360
480.00	7.6004	0.4131	18.3974	-0.1273
490.00	7.6088	0.4047	18.8006	-0.1193
500.00	7.6168	0.3966	19.2039	-0.1119

Table 4.3 E[X(t)], **E**(N(t)], **E**[X(t)]/ **E**(N(t)], ρ **versus** λ

for α = 100.0, μ = 300.0, t = 0.05

λ	**E**[X(t)]	**E**(N(t)]	**E**[X(t)]/ **E**(N(t)]	ρ
200.00	7.3535	0.6599	11.1429	-0.5067
210.00	7.7212	0.6929	11.1429	-0.5027
220.00	8.0889	0.7259	11.1429	-0.4995
230.00	8.4566	0.7589	11.1429	-0.4967
240.00	8.8243	0.7919	11.1429	-0.4944
250.00	9.1919	0.8249	11.1429	-0.4924
260.00	9.5596	0.8579	11.1429	-0.4907
270.00	9.9273	0.8909	11.1429	-0.4892
280.00	10.2950	0.9239	11.1429	-0.4879
290.00	10.6626	0.9569	11.1429	-0.4868
300.00	11.0303	0.9899	11.1429	-0.4858
310.00	11.3980	1.0229	11.1429	-0.4849
320.00	11.7657	1.0559	11.1429	-0.4841
330.00	12.1334	1.0889	11.1429	-0.4834
340.00	12.5010	1.1219	11.1429	-0.4828
350.00	12.8687	1.1549	11.1429	-0.4823
360.00	13.2364	1.1879	11.1429	-0.4818
370.00	13.6041	1.2209	11.1429	-0.4813
380.00	13.9717	1.2539	11.1429	-0.4810
390.00	14.3394	1.2869	11.1429	-0.4806
400.00	14.7071	1.3299	11.1429	-0.4803

CHAPTER FIVE

THE T4 CELL COUNT AS A MARKER OF HIV PROGRESSION IN THE ABSENCE OF ANY DEFENSE MECHANISM

5.1 INTRODUCTION

T4 cells which originate in the bone marrow and mature in the thymus gland play a dominant role in the immune system of the human body. Infact, these cells amplify immune responses through the release of various cytokine mediators. It has been observed in HIV infected individuals that as a consequence of HIV infection, selective depletion of T4 cells occurs. When the T4 cell count in such an individual drops, these cells are unable to mount an effective immune response and consequently, the individual becomes susceptible to opportunistic infections and lymphomas. Accordingly, the T4 cell count can be considered a marker of disease progression in an infected individual and the loss of T4 cells accounts for a major part of the immunosuppressive effect of HIV (Stein et al. 1992, Phillips et al. 1992, Feinberg 1996 and Sabin et al.1998).

In the recent past, several researchers have developed various stochastic and deterministic models to describe the temporal progression of the T4 cell count in a HIV infected individual and its relationship to the survival time of the individual (Longini et al. 1991, Perelson et al.1993, De Gruttola and Tu 1994, Philips et al. 1994, Cozzi-Lepri et al. 1997 and Wick 1999). Longini et al. (1991) modelled the decline of T4 cells in HIV infected individuals with a continuous-time Markov process in which the state space consists of seven states. These states are the end points of six progression T4 cell count intervals and the beginning of the first interval corresponds to the time of HIV infection and the end of the last interval synchronizes with the time of AIDS diagnosis. Perelson et al. (1993) developed a model for the interaction of HIV with T4 cells by considering four populations namely, uninfected T4 cells, latently infected T4 cells, actively infected T4 cells, and free HIV; and using the model, they examined several features of HIV infection and in particular the process of T4 cell depletion.

De Gruttola and Tu (1994) proposed a model to study the progression of the T4 cell count and the relationship between different features of this progression and survival time. In their model, they observed the T4 cell count only at certain fixed time points and using random effects estimated the T4 trajectory.

Philips et al. (1994) developed an extrapolation model based upon T4 cell counts measured at discrete points, and using the model estimated the probability of remaining free of AIDS for up to 25 years after infection with HIV. Cozzi Lepri et al. (1997) used multilevel modelling techniques to asses the rate of T4 cell decline in HIV infected individuals and predicted that the rate of T4 cell decline is actually slower at the later stage of the disease.

In the work of Wick (1999), the T4 cell loss in a HIV infected individual has been analysed by proposing a model in which the rates of proliferation and programmed cell death (apoptosis) control the rise and fall of the T4 cell count. In all these works, the stochastic mechanism of HIV production has not been given its due importance in understanding the decline of the T4 cell count and the status of HIV progression in infected individuals. Further, no work appears to be available in literature incorporating the correlation structure between uninfected and infected T4 cell populations.

Also, in HIV related models, there appears to be no work which quantifies the amount of toxins produced during the progression of HIV in infected individuals and its correlation with the loss of T4 cells. In this chapter, an attempt is made to fill the gap by building a more realistic stochastic model of HIV production/progression leading to the decline of the T4 cell count in an infected individual.

The organization of this chapter is as follows: In Section 5.2, we develop a catastrophe model of HIV production. The probability generating function for X(t), the number of uninfected cells, Y(t), the number of infected cells at any time t and Z(t), the number of lysed cells up to time t is obtained in Section 5.3. The means and variances of X(t), Y(t), and Z(t) are explicitly found in Section 5.4. We also obtain explicit expressions for the co-variances between X(t) and Y(t), Y(t) and Z(t), and Z(t) and X(t) in section 5.4. The total amount of toxins produced up to time t since the time of HIV infection is quantified and analysed in Section 5.5. In Section 5.6, a numerical illustration is provided to drive home a satisfactory picture of what happens during the progression of HIV in an infected individual up to the onset of AIDS.

5.2 THE CATASTROPHE MODEL

At time t = 0, one HIV infects a cell population of size N of uninfected T4 cells. The infected cell either splits into two infected cells or undergoes a lysis releasing a random number K of HIV's which instantaneously infect an equal number of uninfected T4 cells; and the process continues. Further, there is an independent Poisson arrival of uninfected T4 cells with rate α into the population of T4 cells. The process of splitting of an infected cell into two infected cells can be viewed as a birth of an infected cell with the parent survival; and the event of a lysis of an infected cell can be considered as the death of an infected cell. The death of an infected cell is a disaster to the population of uninfected cells. This observation enables us to make the assumption that the population of infected cells undergoes a linear birth and death process, with λ and μ as the birth and death rates respectively; and the population of uninfected cells is subject to disasters occurring at the event of the death of an infected cell. Let X(t) and Y(t) denote respectively the number of uninfected and infected cells at time t.

Then, by the initial condition, we have X(0) = N – 1 and Y(0) = 1, where N is sufficiently large and fixed. Let Z(t) represents the number of cells that have undergone lysis up to time t. Then, it is easy to note that

$$X(t) + Y(t) + Z(t) \geq N.$$

We assume that K has a discrete distribution defined by

$$\Pr(K = r) = \pi_r, \quad r = 0, 1, 2, \ldots$$

The vector process (X(t), Y(t), Z(t)) is clearly Markov and we proceed to obtain its probability generating function in the next section.

5.3 THE PROBABILITY GENERATING FUNCTION

We define the probability generating function of (X(t), Y(t), Z(t)).

$$G(u, v, w; t) = E[u^{X(t)}v^{Y(t)}w^{Z(t)}].$$

Then it is easy to note that $G(u, v, w; 0) = u^{N-1}v$. To derive an expression for $G(u, v, w; t)$, we first define the probability function

$$p(i, j, k; t) = \Pr\{X(t) = i, Y(t) = j, Z(t) = k\}$$

Then, using probabilistic laws, we obtain

$$\frac{\partial p(i, j, k: t)}{\partial t} = -\{j(\lambda + \mu) + \alpha\}p(i, j, k; t) + \alpha p(i - 1, j, k; t)$$

$$+ (j - 1)\lambda p(i, j - 1, k; t) + \sum_{r=0}^{j+1}(j + 1 - r)\mu p(i + r, j + 1 - r, k - 1; t)\pi_r \qquad (5.3.1)$$

From (5.3.1), following the lines of Bailey (1975), it can be shown that the probability generating function $G(u, v, w; t)$ satisfies the partial differential equation

$$\frac{\partial G}{\partial t} = -(\lambda + \mu)v\frac{\partial G}{\partial v} - \alpha(1 - u)G + \lambda v^2\frac{\partial G}{\partial v} + \mu w\sum_{r=0}^{\infty}\pi_r u^{-r}v^r\frac{\partial G}{\partial v}, \qquad (5.3.2)$$

with the initial condition $G(u, v, w; 0) = u^{N-1}v$.

On simplification, the equation (5.3.2) becomes

$$\frac{\partial G}{\partial t} = -\alpha(1 - u)G + \{-(\lambda + \mu)v + \lambda v^2 + \mu w h(\frac{v}{u})\}\frac{\partial G}{\partial v}, \tag{5.3.3}$$

with the initial condition $G(u, v, w; 0) = u^{N-1}v$.

The equation (5.3.3) is not easily solvable even for any simple form of the generating function h(.). However, we can obtain from the equation (5.3.3) the various moments of X(t), Y(t) and Z(t). Accordingly, in the next section, we study the moment structure of the process (X(t), Y(t), Z(t)). We also study the covariance structure of X(t), Y(t) and Z(t).

5.4 THE MOMENT STRUCTURE (X(t), Y(t), Z(t))

We have the following notations:

$M_X(t) = E[X(t)]$, $M_Y(t) = E[Y(t)]$, $M_Z(t) = E[Z(t)]$,
$M_X^{(2)}(t) = E[X(t)\{X(t) - 1\}]$, $M_Y^{(2)}(t) = E[Y(t)\{Y(t) - 1\}]$, $M_Z^{(2)}(t) = E[Z(t)\{Z(t) - 1\}]$,
$M_{XY}(t) = E[X(t)Y(t)]$, $M_{YZ}(t) = E[Y(t)Z(t)]$, $M_{ZX}(t) = E[Z(t)X(t)]$.

Then, from the equation (5.3.3), we obtain the following system of equations:

$$\frac{\partial M_X(t)}{\partial t} = \alpha - \mu h'(1) M_Y(t) \tag{5.4.1}$$

$$\frac{\partial M_Y(t)}{\partial t} = a M_Y(t) \tag{5.4.2}$$

$$\frac{\partial M_z(t)}{\partial t} = \mu M_Y(t) \tag{5.4.3}$$

$$\frac{\partial M_X^{(2)}(t)}{\partial t} = -2\mu h'(1) M_{XY}(t) + 2\alpha M_X(t) + d M_Y(t) \tag{5.4.4}$$

$$\frac{\partial M_Y^{(2)}(t)}{\partial t} = 2a M_Y^{(2)}(t) + c M_Y(t) \tag{5.4.5}$$

$$\frac{\partial M_Z^{(2)}(t)}{\partial t} = 2\mu M_{YZ}(t) \tag{5.4.6}$$

$$\frac{\partial M_{XY}(t)}{\partial t} = aM_{XY}(t) + bM_Y(t) - \mu h'(1) M_Y^{(2)}(t) \tag{5.4.7}$$

$$\frac{\partial M_{YZ}(t)}{\partial t} = aM_{YZ}(t) + \mu M_Y^{(2)}(t) + \mu h'(1) M_Y(t) \tag{5.4.8}$$

$$\frac{\partial M_{ZX}(t)}{\partial t} = \alpha M_Z(t) + \mu M_{XY}(t) - \mu h'(1) M_Y(t) - \mu h'(1) M_{YZ}(t) \tag{5.4.9}$$

where

$a = \lambda - \mu + \mu h'(1)$, $b = \alpha - \mu h'(1) - \mu h''(1)$, $c = 2\lambda + \mu h''(1)$, $d = 2\mu h'(1) + \mu h''(1)$.

Noting the fact that

$$M_X(0) = N - 1,\ M_Y(0) = 1,\ M_Z(0) = 0,$$
$$M_X^{(2)}(0) = (N - 1)(N - 2),\ M_Y^{(2)}(0) = 0,\ M_Z^{(2)}(0) = 0,$$
$$M_{XY}(0) = N - 1,\ M_{YZ}(0) = 0,\ M_{ZX}(0) = 0$$

And using Laplace transformation, the equations (5.4.1) to (5.4.9) yield

$$M_X^*(s) = \frac{N - 1}{s} + \frac{\alpha}{s^2} - \frac{\mu h'(1)}{s(s - a)} \tag{5.4.10}$$

$$M_Y^*(s) = \frac{1}{s - a} \tag{5.4.11}$$

$$M_Z^*(s) = \frac{\mu}{s(s - a)} \tag{5.4.12}$$

$$M_X^{(2)*}(s) = \frac{(N - 1)(N - 2)}{s} + \frac{d}{s(s - a)} - 2\mu h'(1)\left\{\frac{N - 1}{s(s - a)} + \frac{b(s - 2a) - \mu h'(1)c}{s(s - a)^2(s - 2a)}\right\}$$
$$+ 2\alpha\left\{\frac{N - 1}{s^2} + \frac{\alpha}{s^3} - \frac{\mu h'(1)}{s^2(s - a)}\right\} \tag{5.4.13}$$

$$M_Y^{(2)*}(s) = \frac{c}{(s - a)(s - 2a)} \tag{5.4.14}$$

$$M_Z^{(2)}(s) = 2\mu^2\left\{\frac{c + h'(1)(s - 2a)}{s(s - a)^2(s - 2a)}\right\} \tag{5.4.15}$$

$$M^{*}_{XY}(s) = \frac{N - 1}{s - a} + \frac{b(s - 2a) - \mu h'(1)c}{(s - a)^2(s - 2a)} \tag{5.4.16}$$

$$M^{*}_{YZ}(s) = \mu\left\{\frac{c + h'(1)(s - 2a)}{(s - a)^2(s - 2a)}\right\} \tag{5.4.17}$$

$$M^{*}_{ZX}(s) = \mu\left\{\frac{N - 1}{s(s - a)}\frac{h'(1)}{s(s - a)} + \frac{(b - \mu\{h'(1)\}^2)(s - 2a) - 2\mu h'(1)c}{s(s - a)^2(s - 2a)} + \frac{\alpha}{s^2(s - a)}\right\} \tag{5.4.18}$$

Inverting the equations (5.4.10) and (5.4.11), we obtain

$$M_X(t) = N - 1 + \alpha t - \frac{\mu h'(t)}{a}(e^{at} - 1) \tag{5.4.19}$$

$$M_Y(t) = e^{at} \tag{5.4.20}$$

$$M_Z(t) = \frac{\mu}{a}(e^{at} - 1) \tag{5.4.21}$$

$$M^{(2)}_X(t) = (N - 1)(N - 2)\frac{d}{a}(e^{at} - 1) + \frac{\alpha}{a^2}\{2(N - 1)a^2t + \alpha(at)^2 - 2\mu h'(1)(e^{at} - at - 1)\}$$

$$- 2\mu h'(1)\left\{\frac{N - 1}{a}(e^{at} - 1) - \frac{\mu h'(1)c}{2a^2(e^{2at} - 2ate^{at} - 1)} - \frac{b}{a^2}(e^{at} - ate^{at} - 1)\right\} \tag{5.4.22}$$

$$M^{(2)}_Y(t) = \frac{c}{a}(e^{2at} - e^{at}) \tag{5.4.23}$$

$$M^{(2)}_Z(t) = \frac{\mu^2}{a^2}\left\{\frac{c}{a}(e^{2at} - 2ate^{at} - 1) - 2h'(1)(e^{at} - ate^{at} - 1)\right\} \tag{5.4.24}$$

$$M_{XY}(t) = (N - 1 + bt)e^{at} - \frac{\mu h'(1)c}{a^2}(e^{2at} - ate^{at} - e^{at}) \tag{5.4.25}$$

$$M_{YZ}(t) = \mu\left\{\frac{c}{a^2}(e^{2at} - ate^{at} - e^{at}) + h'(1)te^{at}\right\} \tag{5.4.26}$$

$$M_{ZX}(t) = \frac{\mu}{a}\left\{(N - 1 - h'(1))(e^{at} - 1) - \frac{(b - \mu)\{h'(1)\}^2)}{a}(e^{at} - ate^{at} - 1)\right.$$

$$+ \frac{\alpha}{a}(e^{at} - at - 1) - \frac{\mu h'(1)c}{a^2}(e^{2at} - 2ate^{at} - 1)\Big\} \qquad (5.4.27)$$

5.5 THE AMOUNT OF TOXIN PRODUCED

Whenever an infected cell appears, a quantity of toxic substance is produced in the blood. The estimation of the total amount of toxins produced by the infected cells since the beginning of the HIV infection up to any time is useful in knowing the level of HIV infection. In this section, we quantify the total amount of the toxins and obtain its mean and variance. Since the amount of toxins produced at time t is proportional to the number of infected cells present at time t, it is evident that the total amount of toxins produced up to time t since the beginning of the HIV infection is given by the stochastic integral

$$W(t) = \int_0^t Y(u)du \qquad (5.5.1)$$

The stochastic integral in (5.5.1) exists almost surely and has been studied very extensively in several biological applications by several researchers (Puri 1966, Jagers 1967, Pakes 1975 and Udayabaskaran and Sudalaiyandi 1986).

We proceed to obtain the joint moment generating function of Y(t) and W(t) defined by

$$H(u, v; t) = E[u^{Y(t)}e^{-vW(t)}|Y(0) = 1] \qquad (5.5.2)$$

Fixing the occurrence of the first event since time t = 0 and using probabilistic arguments, we obtain the following integral equation:

$$H(u, v; t) = ue^{-(\lambda+\mu+\varepsilon)t} + \lambda\int_0^t e^{-(\lambda+\mu+\varepsilon)\tau}\{H(u, v; t - \tau)\}^2 d\tau$$

$$+ \mu\int_0^t e^{-(\lambda+\mu+\varepsilon)\tau}h(H(u, v; t - \tau))d\tau \qquad (5.5.3)$$

where $h(s) = \sum_{0}^{\infty} P_r^{s^r}$ is the generating function of the number of HIV's produced at the time of a lysis. From the equation (5.5.3), we can obtain the mean and variance of W(t) and the correlation structure of W(t) with Y(t).

Differentiating (5.5.3) with respect to v at (u = 1, v = 0), we get

$$M_W(t) = te^{-(\lambda+\mu)t} + \lambda\int_0^t e^{-(\lambda+\mu)\tau}[2M_W(t-\tau) + \tau]d\tau$$

$$+ \mu\int_0^t e^{-(\lambda+\mu)\tau}[h'(1)M_W(t-\tau) + \tau]d\tau \qquad (5.5.4)$$

Differentiating (5.5.3) twice with respect to v at (u = 1, v = 0), we get

$$M_{WW}(t) = t^2e^{-(\lambda+\mu)t} + (\lambda+\mu)\int_0^t e^{-(\lambda+\mu)\tau}\tau^2 d\tau$$

$$+ [2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}M_{WW}(t-\tau)d\tau$$

$$+ [2\lambda + \mu h''(1)]\int_0^t e^{-(\lambda+\mu)\tau}\{M_W(t-\tau)\}^2 d\tau$$

$$+ 2[2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}\tau M_W(t-\tau)d\tau \qquad (5.5.5)$$

Differentiating (5.5.3) with respect to u and v at (u = 1, v = 0), we get

$$M_{YW}(t) = te^{-(\lambda+\mu)t} + [2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}M_{YW}(t-\tau)d\tau$$

$$+ [2\lambda + \mu h''(1)]\int_0^t e^{-(\lambda+\mu)\tau}M_Y(t-\tau)M_W(t-\tau)d\tau$$

$$+ [2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}\tau M_Y(t-\tau)d\tau \qquad (5.5.6)$$

On applying Laplace transform to equations (5.5.4), (5.5.5) and (5.5.6) we get

$$M_W^*(s) = \frac{1}{s(s-a)} \qquad (5.5.7)$$

$$M_{WW}^*(s) = \frac{2}{s(s-a)(s+\lambda+\mu)} + \frac{2\lambda+\mu h''(1)}{a^2}\left\{\frac{1}{s-2a} - \frac{2a}{(s-a)^2} - \frac{1}{s}\right\}$$

$$+ \frac{2[2\lambda + \mu h'(1)]}{a^2}\left\{\frac{a}{(s - a)^2} - \frac{1}{s - a} + \frac{1}{s}\right\} \qquad (5.5.8)$$

$$M^*_{YW}(s) = \frac{1}{(s - a)^2} + \frac{2\lambda + \mu h''(1)}{a^2}\frac{1}{(s - 2a)} - \frac{a}{(s - a)^2} + \frac{1}{s - a} \qquad (5.5.9)$$

On inversion, the equations (5.5.7), (5.5.8) and (5.5.9) yield

$$M_W(t) = \frac{1}{a}(e^{at} - 1) \qquad (5.5.10)$$

$$M_{WW}(t) = 2\left\{\frac{1}{a(\lambda + \mu + a)}e^{at} + \frac{1}{(\lambda + \mu)(\lambda + \mu + a)}e^{-(\lambda+\mu)t} - \frac{1}{a(\lambda + \mu)}\right\}$$

$$+ \frac{2\lambda + \mu h''(1)}{a^3}\{e^{2at} - 2ate^{at} - 1\} - \frac{2[2\lambda + \mu h'(1)]}{a^2}(e^{at} - ate^{at} - 1) \qquad (5.5.11)$$

$$M_{YW}(t) = te^{at} + \frac{2\lambda + \mu h''(1)}{a^2}(e^{2at} - ate^{at} - e^{at}) \qquad (5.5.12)$$

5.6 NUMERICAL ILLUSTRATION

The behaviour of the means of X(t), Y(t) and Z(t) and the correlation coefficient (ρ) between X(t) and Y(t) (R_{XY}) and that between Y(t) and Z(t) (R_{YZ}) with respect to time is studied. For this, we assume α = 100.0, λ = 0.20, μ = 0.10, and vary t from 0.5 to 0.8 in steps of 0.5. The results are highlighted in Tables 5.1 to 5.4.

The number of uninfected T4 cells present at any instant of time decreases (Table 5.1) and that of the infected cells (Table 5.2) increases with time as can be expected. This implies that the mean of the cumulative quantity of toxin produced should also increase with time and Table 5.1 confirms this result. Also we observe that the correlation between X(t) and Y(t) remains negative (Table 5.2) whereas correlation between Y(t) and Z(t) is positive throughout the period under consideration (Table 5.2).

As the rate of arrival of uninfected T4 cells increases (α = 100), the mean number of uninfected T4 cells present at the time of instant 0.5 increases. However, the means of the number of infected cells and that of the cumulative quantity of toxin produced remain the same irrespective of the values of α (Table 5.3). Also, there is a negative correlation between X(t) and Y(t) (Table 5.4). Correlation between Y(t) and Z(t) exists but nothing can be said about the nature of its variation (Table 5.4) with respect to α.

5.6 CONCLUSION

In this chapter, we have obtained the mean number of uninfected, infected and lysed T cells in a HIV infected individual. Unlike other models proposed by some mathematical scientist (see Longini et al. 1991, Perelson et al.1993, De Gruttola and Tu 1994, Philips et al. 1994, Cozzi-Lepri et al. 1997 and Wick 1999), our model not only gave moment structure of our variables, but also the co-variance relationship between them. Hence we have been able to build on previous models establish in the line of the T4 cell count as marker of the disease progression. Also we were able to model the quantity of toxin produced at time t in a HIV infected individual.

Table 5.1 E[X(t)], E[Y(t)], E[Z(t)] versus t

for α = 100.0, λ = 0.20, μ = 0.10

t	E[X(t)]	E[Y(t)]	E[Z(t)]
0.50	10.0483	0.0017	0.0007
1.00	10.0972	0.0030	0.0018
1.50	10.1452	0.0052	0.0038
2.00	10.1917	0.0090	0.0073
2.50	10.2357	0.0156	0.0133
3.00	10.2753	0.0156	0.0133
3.50	10.2753	0.0271	0.0237
4.00	10.3259	0.0815	0.0731
4.50	10.3216	0.1412	0.1274
5.00	10.2775	0.2447	0.2215
5.50	10.1644	0.4241	0.3846
6.00	9.9316	1.2741	1.1574
6.50	9.4916	0.7351	0.6674
7.00	8.6923	2.2083	2.0067
7.50	7.2702	3.8276	3.4788
8.00	4.7688	6.6342	6.0302

Table 5.2 R_{XY} , R_{YZ} versus t

for α = 100.0, λ = 0.20, μ = 0.10

t	R_{XY}	R_{YZ}
0.50	-0.8770	0.8406
1.00	-0.9226	0.9130
1.50	-0.9616	0.9446
2.00	-0.9829	0.9641
2.50	-0.9934	0.9769
3.00	-0.9970	0.9854
3.50	-0.9989	0.9909
4.00	-0.9995	0.9944
4.50	-0.9998	0.9966
5.00	-0.9999	0.9980
5.50	-1.0000	0.9988
6.00	-1.0000	0.9993
6.50	-1.0000	0.9996
7.00	-1.0000	0.9998
7.50	-1.0000	0.9999
8.00	-1.0000	0.9999

Table 5.3 E[X(t)], E[Y(t)], E[Z(t)] versus α

for t = 0.50, λ = 0.20, μ = 0.01

α	E[X(t)]	E[Y(t)]	E[Z(t)]
100.00	10.0483	0.0017	0.0007
200.00	10.0983	0.0017	0.0007
300.00	10.1483	0.0017	0.0007
400.00	10.1983	0.0017	0.0007
500.00	10.2483	0.0017	0.0007
600.00	10.2983	0.0017	0.0007
700.00	10.3483	0.0017	0.0007
800.00	10.3983	0.0017	0.0007
900.00	10.4483	0.0017	0.0007
1000.00	10.4983	0.0017	0.0007

Table 5.4 R_{XY} , R_{YZ} versus α for

t = 0.50, λ = 0.20, μ = 0.01

α	R_{XY}	R_{YZ}
100.00	-0.8770	0.8406
200.00	-0.7595	0.8406
300.00	-0.6578	0.8406
400.00	-0.6036	0.8406
500.00	-0.5674	0.8406
600.00	-0.5262	0.8406
700.00	-0.4929	0.8406
800.00	-0.4688	0.8406
900.00	-0.4479	0.8406
1000.00	-0.4297	0.8406

CHAPTER SIX

A STOCHASTIC MODEL OF THE DYNAMICS OF HIV UNDER A COMBINATION THERAPEUTIC INTERVENTION

6.1 INTRODUCTION

In HIV infected individuals, the infection exhibits a long asymptomatic phase (after the initial high infectious phase), on average about 10 years before the onset of AIDS. During this incubation period which some call the clinical latency period, the individuals appear to be well and may contribute significantly to the spread of the epidemic in a community. Some clinical markers such as the CD4 cell count and the RNA viral load (viraemia) provide information about the progression of the disease in infected individuals. Also, the clinical latency period of the disease may provide a sufficiently long period to try for an effective suppressive therapeutic intervention in HIV infections.

The knowledge of principal mechanisms of viral pathogenesis, namely the binding of the retrovirus to the gp120 protein on the CD4 cell, the entry of the viral RNA into the target cell, the reverse transaction of viral RNA to viral DNA, the integration of the viral DNA with that of the host, the viral regulatory processes mediated through regulatory proteins such as tat and rev and the action of viral protease in cleaving viral proteins into mature products, led to the design of drugs (chemotherapeutic agents) to control the production of HIV. Two principal directions along which drugs (such as AZT and Ritonavir (Shafer et al. 2001) are attempted are inhibition of the reverse transcriptase of HIV and inhibition of the protease of HIV. The inhibition of the function of either the reverse transcriptase or the protease of HIV reduces the production of infectious free HIV thereby the onset of AIDS can be delayed in HIV-infected individuals (Brookmeyer and Gail 1994).

A cure for HIV is yet to be discovered but progress is being made in obtaining effective vaccine and/or eradicating the virus from the human body. For example, in recent months result from a bone marrow transplant of a then HIV infected individual to be saved from leukaemia showed no known virus in his system (neither in the blood nor the reservoirs); is

this not a cure at hand? It was stated that this is not a recommended way of tackling HIV infection as it is very expensive and it takes time for the individual to have immunity because at the stage of transplant the individual has no immunity due to the new stem cells that are yet to grow and replicate (http://www.welt.de/english-news/article2715739/HIV-patient-cured-by-marrow-transplant.html). With the widespread of the epidemic and also in the absence of an "effective" vaccine or cure, therapeutic interventions still have to be heavily relied on. Several research studies have been made in the recent past both theoretically and experimentally to analyse the impact of therapy on the viral load in HIV infected persons to test the effectiveness of the treatment (Nelson and Perelson 1995, Wei et al. 1995, Perelson et al. 1996, Mellors et al. 1997, Nijhuis et al. 1998, Tan and Xiang 1999 and Bangsberg et al. 2004).

Nelson and Perelson (1995) proposed a mathematical model of therapeutic intervention to delay the onset of AIDS by the stimulated production of genetically engineered defective interfering virus (DIVs) that interferes with the HIV replication process. A DIV is a deletion mutant and it is incapable of replicating by itself in a host cell (CD4 cell), but may replicate if the host cell is co-infected with HIV. Assuming that DIV depends on HIV to multiply, Nelson and Perelson (1995) constructed a mathematical model describing the interaction among HIV, DIV and uninfected CD4 cells and they analysed the co-evolution of DIV and HIV in a single compartment. Their model is essentially given by a system of ordinary differential equations involving eight variables and several parameters representing the activities of DIV and HIV. By considering a higher level of DIV activity in the production of co-infected CD4 cells, they investigated the possibility of blocking the production of HIV so that the burden of HIV on the population of CD4 cells is reduced.

In the paper of Wei et al. (1995), based upon the results of several experimental studies of the dynamics of HIV replication in the presence of antiretroviral agents, it was reported that HIV had enormous potential in showing resistance to drugs and undergoing several mutations and a rapid and virtually complete replacement of wild-type HIV by drug resistant virus occurred when anti-viral drugs were administered. Nijhuis et al. (1998) noticed high drug resistance and unique combination of mutation in individuals when they proposed a stochastic model to test the resistance to protease inhibitors, although there was reduced effective free HIV population (500 – 15000).

Perelson et al. (1996) presented a mathematical model which was used to analyse the kinetic picture of HIV pathogenesis subject to the administration of a drug called Ritonavir to inhibit potently the protease of HIV. In their paper, they represented the dynamics of cell infection and viral production after treatment with ritonavir, by a set of ordinary differential equations using deterministic model and, assumed that the viral inhibition of ritonavir was 100% so that all newly produced virons after the treatment with ritonavir were non-infectious. Hence by using the mathematical model and non-linear least squares fitting of the viral load data of five HIV-1 infected patients, they were able to obtain estimates of the rate of viral clearance, the infected cell life-span and the average viral generation time.

Tan and Xiang (1999) had a state-space model of HIV pathogenesis in HIV infected individuals undergoing a combination-treatment (i.e. a treatment with a combination of anti-viral drugs such as AZT and Ritonavir which can inhibit either the reverse transcriptase or the protease of HIV). Their model gave way for the production of infectious free HIV and non-infectious free HIV, by extending the model of Perelson et al. (1996) and developing procedures for estimating and predicting the number of uninfected CD4 cells, infectious free

HIV, non-infectious free HIV and HIV infected CD4 cells. They not only extended Perelson et al. (1996) model into a stochastic model, but they also applied their model to data of some patients given by Perelson et al. (1996). Their model was discrete in time and was described by a system of stochastic difference equations which were derived based on the biological specifications of the HIV-replication cycle. However, the nature of the HIV-replication cycle indicated that a stochastic model approach of point events that are distributed over continuous infinity of states is very much appropriate to analyse the basic underlying process of generation of HIV and the interaction of defective HIV on the kinetics of HIV, so that an efficient therapeutic intervention may be devised to combat the production of HIV.

Since Perelson et al. (1996) had considered the deterministic model and Tan and Xiang (1999) had a state-space model, we considered a stochastic model of the growth of HIV population which carries over the principle of the virology of HIV and the life-cycle of HIV and allows the production of non-infectious (defective) free HIV to reduce the severity of HIV in a HIV-infected individual undergoing a combination-therapeutic treatment. Our aim in this paper is to use stochastic model obtained by extending the model of Perelson et al. (1996) to determine number of uninfected T4 cells, infected T4 cells and free HIV in an infected individual by examining the combined antiviral treatment of HIV. This is important because it helps in determining the efficacy of methods used in the research areas of pathogenesis, progression and combined treatment of HIV. By obtaining the variance and co-variance structures of the variables X(t), V(t) and D(t), we have contributed to the work afore done by Perelson et al. (1996) and Tan and Xiang (1999). Based upon the model, we obtain the expected numbers of HIV infected cells, infectious free HIV and non-infectious free HIV at any time t, and derive conclusions for the reduction or elimination of HIV in HIV-infected individuals.

The organisation of this chapter is as follows: In Section 6.2, we formulate a stochastic model to describe the production and the clearance of virus producing cells, infectious free HIV and non-infectious free HIV in a therapeutic environment. In Section 6.3, we derive a system of differential difference equations for the probability function associated with the process and also obtain a partial differential equation for the probability generating function of the numbers of HIV-infected CD4 cells, infectious free HIV and non-infectious free HIV at time t. The population measures are derived in Section 6.4. In Section 6.5, we provide a numerical illustration to show the impact of the usage of combination-therapy in controlling the progression of HIV and also obtained variance and co-variance structures of the variables. We have also compared equations we obtained with those obtained by Perelson et al. (1996) as our model is an extension of their model.

6.2 THE FORMULATION OF THE MODEL

Assume that at time t = 0, a combination-therapy treatment is initiated in an HIV-infected individual. We assume that the therapeutic intervention inhibits either the enzyme action of reverse transcriptase or that of the protease of an HIV in a HIV-infected cell. A HIV-infected cell with the inhibited HIV-transcriptase can be considered as a dead cell as it cannot participate in the production of the copies of any type of HIV. On the other, a HIV-infected cell in which the reverse transcription has already taken place and the viral DNA is fused with the DNA of the host but the enzyme activity of HIV-protease is inhibited, undergoes a lysis releasing infectious free HIV and non-infectious free HIV. A non-infectious free HIV cannot successfully infect a CD4 cell. Accordingly, at any time t, the blood of the infected person contains virus-producing HIV-infected cells, infectious free HIV and non-infectious free HIV.

A virus producing cell existing at time t in the therapeutic environment undergoes one of the following possibly in the interval $(t, t+\Delta)$:

(i) it splits into two HIV-infected cells with probability $\lambda_1\Delta + o(\Delta)$;

(ii) it undergoes a lysis with probability $\upsilon\Delta + o(\Delta)$, producing a random number K_1 of infectious free HIV and a random number K_2 of non-infectious free HIV;

(iii) it dies with probability $\mu\Delta + o(\Delta)$;

(iv) it remains as it is with probability $1 - (\lambda_1 + \upsilon + \mu)\Delta + o(\Delta)$;

We assume that K_1 and K_2 have the joint probability generating function $h(s_1, s_2)$ defined by

$$h(s_1, s_2) = \sum_{l=0}^{\infty} \sum_{m=0}^{\infty} \pi_{lm} s_1^l s_2^m$$

where π_{lm} represents the probability that l infections free HIV and m non-infectious free HIV are released at the lysis occurring at any time. An infectious free HIV existing at time t in the blood of the individual may undergo one of the following possibilities in the interval $(t, t+\Delta)$:

(i) it infects a T4 cell with probability $\lambda_2\Delta + o(\Delta)$ making the cell into a viruses producing cell;

(ii) it dies with probability $c\Delta + o(\Delta)$;

(iii) it remains as it is with probability $1 - (\lambda_2 + c)\Delta + o(\Delta)$;

The population of non-infectious free HIV does not grow by replication of its members but grows by admitting bulk immigrations which occur at the lysis of HIV-infected cells. A non-infectious HIV existing at time t dies in the interval $(t, t+\Delta)$ with probability $c\Delta + o(\Delta)$.

Let X(t) be the number of virus producing cells (these are cells that produce more virus to infect other cells) at time t. Let V(t) and D(t) be respectively the number of infectious free HIV (these are HIV in the body that infect cells in the body) and the number of non-

infectious free HIV (these are HIV in the body that do not infect cells in the body) at time t. For simplicity, we assume that X(0) = N, V(0) = n, D(0) = 0. We proceed to discuss the probability generating function of the vector process (X(t), V(t), D(t)) in the next section.

6.3 PROBABILITY GENERATING FUNCTION

The probability generating function of (X(t), V(t), D(t)) is defined by

$$G(u_1, u_2, u_3; t) = E[u_1^{X(t)} u_2^{V(t)} u_3^{D(t)}]$$

From the initial condition, it is easy to note that:

$$G(u_1, u_2, u_3; 0) = E[u_1^N u_2^n u_3^0] = E[u_1^N u_2^n]$$

To derive an equation for $G(u_1,u_2,u_3;t)$, we need the probability function which is defined for any time t by

$$p(i,j,k;t) = \Pr\{X(t) = i, V(t) = j, D(t) = k\},$$

where i, j, k = 0, 1, 2 …

Now, we proceed to derive a system of differential-difference equations for the function p(i, j, k; t). For this, we list below the exhaustive and mutually exclusive events that occur in (t, t+Δ) given that X (t) = i > 0, V (t) = j > 0 and D (t) = k > 0:

(i) one HIV infected cell splits into two HIV-infected cells in (t, t+Δ). The probability for this event to occur is $i\lambda_1\Delta + o(\Delta)$;

(ii) one HIV-infected cell undergoes a lysis in (t, t+Δ). The probability for this event to occur is $i\upsilon\Delta + o(\Delta)$;

(iii) one HIV-infected cell dies in (t, t+Δ). The probability for this event to occur is $i\mu\Delta + o(\Delta)$;

(iv) one infectious free HIV virus infects one CD4 cell making the CD4 cell an HIV-infected cell in (t, t+Δ). The probability for this event to occur is

$j\lambda_2\Delta + o(\Delta)$;

(v) one infectious free HIV virus dies in $(t, t+\Delta)$. The probability for this event to occur is $jc\Delta + o(\Delta)$;

(vi) one non-infectious free HIV virus dies in $(t, t+\Delta)$. The probability for this event to occur is $kc\Delta + o(\Delta)$;

(vii) none of the above occurs in $(t, t+\Delta)$.

Using probabilistic arguments, we obtain

$$p(i,j,k;t+\Delta) = p(i,j,k;t)\left[1-\{i(\lambda_1+\nu+\mu)+j(\lambda_2+c)+kc\}\Delta\right]+ p(i-1,j,k;t)(i-1)\lambda_1\Delta$$

$$+\sum_{l=0}^{j}\sum_{m=0}^{k}\pi_{lm}\,p(i+1,j-l,k-m;t)(i+1)\nu\Delta + p(i+1,j,k;t)(i+1)\mu\Delta + p(i-1,j+1,k;t)(j+1)\lambda_2\Delta$$

$$+ p(i,j+1,k;t)(j+1)c\Delta + p(i,j,k+1;t)(k+1)c\Delta \qquad (6.3.1)$$

From equation 6.3.1, we readily obtain the following equations:

$$p'(i,j,k;t) = -\{i(\lambda_1+\nu+\mu)+j(\lambda_2+c)+kc\}\,p(i,j,k;t) + (i-1)\lambda_1 p(i-1,j,k;t)$$

$$+(i+1)\nu\sum_{l=0}^{j}\sum_{m=0}^{k}\pi_{lm}\,p(i+1,j-l,k-m;t) + (i+1)\mu p(i+1,j,k;t) + (j+1)\lambda_2 p(i-1,j+1,k;t)$$

$$+(j+1)cp(i,j+1,k;t) + (k+1)cp(i,j,k+1;t),\ i>0 \qquad (6.3.2)$$

$$p'(0,j,k;t) = -\{j(\lambda_2+c)+kc\}\,p(0,j,k;t) + \nu\sum_{l=0}^{j}\sum_{m=0}^{k}\pi_{lm}\,p(1,j-l,k-m;t)$$

$$+\mu p(1,j,k;t) + (j+1)cp(0,j+1,k;t) + (k+1)cp(0,j,k+1;t) \qquad (6.3.3)$$

Now, we have

$$G(u_1,u_2,u_3;t)=\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}\sum_{k=0}^{\infty}p(i,j,k;t)u_1^i u_2^j u_3^k,$$

And so, by using equations 6.3.2 and 6.3.3, we obtain

$$\frac{\partial G}{\partial t}=[(\mu-\lambda_1 u_1)(1-u_1)+\nu\{h(u_2,u_3;t)-u_1\}]\frac{\partial G}{\partial u_1}+[\lambda_2(u_1-u_2)+c(1-u_2)]\frac{\partial G}{\partial u_2}+c(1-u_3)\frac{\partial G}{\partial u_3} \quad (6.3.4)$$

Equation 6.3.4 is not solvable even for any simple form of $h(u_2,u_3;t)$. However, we can obtain the moment-structure of (X(t), V(t), D(t)). We do this in the next section.

6.4 THE MOMENT STRUCTURE OF (X(t), V(t), D(t))

We have the following notation:

$$M_{\xi}(t)=E[\xi(t)]$$

$$M_{\xi}^{(2)}(t)=E[\xi(t)(\xi(t)-1)]$$

$$M_{\xi\eta}(t)=E[\xi(t)\eta(t)]$$

$$Var(\xi(t))=E[\xi(t)^2]-(E[\xi(t)])^2$$

$$Cov(\xi(t),\eta(t))=E[\xi(t)\eta(t)]-E[\xi(t)]E[\eta(t)]$$

$$m_1=\left[\frac{\partial h(s_1,s_2)}{\partial s_1}\right]s_1=1,s_2=1,$$

$$m_2=\left[\frac{\partial h(s_1,s_2)}{\partial s_2}\right]s_1=1,s_2=1,$$

$$m_{11}=\left[\frac{\partial^2 h(s_1,s_2)}{\partial s_1^2}\right]s_1=1,s_2=1,$$

$$m_{22} = \left[\frac{\partial^2 h(s_1, s_2)}{\partial s_2^2}\right] s_1 = 1, s_2 = 1,$$

$$m_{12} = \left[\frac{\partial^2 h(s_1, s_2)}{\partial s_1 s_2}\right] s_1 = 1, s_2 = 1,$$

$$A = (u_1 = 1, u_2 = 1, u_3 = 1), \alpha = \mu - \lambda_1 + \nu, \beta = \lambda_2 + c.$$

Differentiating equation 6.3.4 with respect to u_1 at A, we obtain

$$\frac{\partial M_X(t)}{\partial t} + \alpha M_X(t) = \lambda_2 M_V(t) \tag{6.4.1}$$

Differentiating (6.3.4) with respect to u_2 at A, we obtain

$$\frac{\partial M_V(t)}{\partial t} + \beta M_V(t) = \nu m_1 M_X(t) \tag{6.4.2}$$

Differentiating (6.3.4) with respect to u_3 at A, we obtain

$$\frac{\partial M_D(t)}{\partial t} + c M_D(t) = \nu m_2 M_X(t) \tag{6.4.3}$$

Differentiating (6.3.4) with respect to u_1 twice at A, we get

$$\frac{\partial M_X^{(2)}(t)}{\partial t} + 2\alpha M_X^{(2)}(t) = 2\left[\lambda_1 M_X(t) + \lambda_2 M_{XV}(t)\right] \tag{6.4.4}$$

Differentiating (6.3.4) with respect to u_2 twice at A, we get

$$\frac{\partial M_V^{(2)}(t)}{\partial t} + 2\beta M_V^{(2)}(t) = \nu\left[m_{11} M_X(t) + m_1 M_{XV}(t)\right] \tag{6.4.5}$$

Differentiating (6.3.4) with respect to u_3 twice at A, we get

$$\frac{\partial M_D^{(2)}(t)}{\partial t} + 2c M_D^{(2)}(t) = \nu\left[2m_2 M_{XD}(t) + m_{22} M_X(t)\right] \tag{6.4.6}$$

Differentiating (6.3.4) with respect to u_1 and u_2 at A, we get

$$\frac{\partial M_{XV}(t)}{\partial t} + (\alpha+\beta)M_{XV}(t) = \nu m_1 M_X^{(2)}(t) + \lambda_2 M_V^{(2)}(t) \qquad (6.4.7)$$

Differentiating (6.3.4) with respect to u_2 and u_3 at A, we get

$$\frac{\partial M_{VD}(t)}{\partial t} + (\beta+c)M_{XD}(t) = \nu\left[m_1 M_{XD}(t) + m_{12} M_X(t) + m_2 M_{XV}(t)\right] \qquad (6.4.8)$$

Differentiating (6.3.4) with respect to u_1 and u_3 at A, we get

$$\frac{\partial M_{XD}(t)}{\partial t} + (\alpha+c)M_{XD}(t) = \nu m_2 M_X^{(2)}(t) + \lambda_2 M_{VD}(t) \qquad (6.4.9)$$

Although the differential equations 6.4.2 and 6.4.3 are similar to the equations in Perelson et al. (1996), equation 6.4.1 differs from the corresponding equation in Perelson et al. (1996). Equations 6.4.2 and 6.4.3 in Perelson et al. (1996) were given as $\frac{dV}{dt} = \mathrm{N}\delta\Gamma^* - \mathrm{cV}$ and $\frac{dV_{NI}}{dt} = \mathrm{N}\delta\Gamma^* - \mathrm{cV_{NI}}$ respectively and equation 6.4.1 as $\frac{dT^*}{dt} = \mathrm{kVT} - \delta\Gamma^*$ (where T is target cells, T^* is productively infected cells, V is the concentration of viral particles in plasma, δ is the rate of loss of virus producing cells, N is the number of new virons produced per infected cell during its lifetime, c is the rate constant for viron clearance and V_{NI} is the concentration of virons in the non-infectious pool).We proceed to solve the above equations to obtain the moments $M_X(t)$, $M_V(t)$ and $M_D(t)$ explicitly. Writing these equations in the matrix form, we obtain the following matrix differential equation:

$$\frac{\partial}{\partial t}\begin{pmatrix} M_X(t) \\ M_V(t) \\ M_D(t) \end{pmatrix} = R\begin{pmatrix} M_X(t) \\ M_V(t) \\ M_D(t) \end{pmatrix} \qquad (6.4.10)$$

Where R is the matrix given by

$$R = \begin{pmatrix} -\alpha & \lambda_2 & 0 \\ \nu m_1 & -\beta & 0 \\ \nu m_2 & 0 & -c \end{pmatrix}$$

The characteristic equation of the matrix R is given by

$$(c+\lambda)\left[(\alpha+\lambda)(\beta+\lambda) - \nu m_1 \lambda_2\right] = 0 \qquad (6.4.11)$$

Solving equation 6.4.11, we obtain the characteristic values of R which are real and distinct, and are given as

$$-c, \frac{-(\alpha+\beta) \pm \sqrt{(\alpha-\beta)^2 + 4\nu m_1 \lambda_2}}{2}$$

The corresponding characteristic vectors are respectively,

$$R_1 = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}, R_2 = \begin{pmatrix} \lambda_2 (c+\theta_1) \\ (c+\theta_1)(\alpha+\theta_1) \\ \nu m_2 \lambda_2 \end{pmatrix}, R_3 = \begin{pmatrix} \lambda_2 (c+\theta_2) \\ (\alpha+\theta_2)(c+\theta_2) \\ \nu m_2 \lambda_2 \end{pmatrix}$$

Where

$$\theta_1 = \frac{-(\alpha+\beta) + \sqrt{(\alpha-\beta)^2 + 4\nu m_1 \lambda_2}}{2}$$

and

$$\theta_2 = \frac{-(\alpha+\beta) - \sqrt{(\alpha-\beta)^2 + 4\nu m_1 \lambda_2}}{2}$$

Accordingly, the general solution of 6.4.10 is

$$\begin{pmatrix} M_X(t) \\ M_V(t) \\ M_D(t) \end{pmatrix} = C_1 R_1 e^{-ct} + C_2 R_2 e^{\theta_1 t} + C_3 R_3 e^{\theta_2 t},$$

where C_1, C_2 and C_3 are constants. In our model, we have assumed that X(0) = N, V(0) = n, D(0) = 0 and so we have the following initial conditions:

$M_X(0) = N$, $M_V(0) = n$, $M_D(0) = 0$.

Consequently, the constants C_1, C_2 and C_3 satisfy the following system of linear equations:

$$\begin{aligned} \lambda_2(c+\theta_1)C_2 + \lambda_2(c+\theta_2)C_3 &= N \\ (c+\theta_1)(\alpha+\theta_1)C_2 + (c+\theta_2)(\alpha+\theta_2)C_3 &= n \\ C_1 + \nu m_2 \lambda_2 C_2 + \nu m_2 \lambda_2 C_3 &= 0 \end{aligned} \qquad (6.4.12)$$

Solving the system (6.4.12), we obtain

$$C_1 = \frac{-\nu m_2 \{N(c+\alpha+\theta_1+\theta_2) - n\lambda_2\}}{(c+\theta_1)(c+\theta_2)}$$

$$C_2 = \frac{N(\alpha+\theta_2) - n\lambda_2}{\lambda_2(c+\theta_1)(\theta_2-\theta_1)}$$

$$C_3 = \frac{-N(\alpha+\theta_1) + n\lambda_2}{\lambda_2(c+\theta_2)(\theta_2-\theta_1)}$$

Hence, we obtain

$$\begin{aligned} M_X(t) = & \frac{N(c+\theta_2)(\alpha+\theta_2) - n\lambda_2(c+\theta_2)}{(c+\theta_2)(\theta_2-\theta_1)} e^{-\theta_1 t} \\ & + \frac{-N(c+\theta_1)(\alpha+\theta_1) + n\lambda_2(c+\theta_1)}{(c+\theta_1)(\theta_2-\theta_1)} e^{-\theta_2 t} \end{aligned} \qquad (6.4.13)$$

$$M_V(t) = \begin{aligned} &\frac{N(c+\theta_2)(\alpha+\theta_2)-n\lambda_2(c+\theta_2)}{\lambda_2(c+\theta_2)(\theta_2-\theta_1)}(\alpha+\theta_1)e^{\theta_1 t} \\ &+\frac{-N(c+\theta_1)(\alpha+\theta_1)+n\lambda_2(c+\theta_1)}{\lambda_2(c+\theta_1)(\theta_2-\theta_1)}(\alpha+\theta_2)e^{\theta_2 t} \end{aligned} \qquad (6.4.14)$$

$$M_D(t) = \begin{aligned} &\frac{vm_2\{n\lambda_2 - N(c+\alpha+\theta_1+\theta_2)\}}{(c+\theta_1)(c+\theta_2)}e^{-ct} \\ &+\frac{vm_2\{N(c+\theta_2)(\alpha+\theta_2)-n\lambda_2(c+\theta_2)\}}{(c+\theta_1)(c+\theta_2)(\theta_2-\theta_1)}e^{\theta_1 t} \\ &+\frac{vm_2\{n\lambda_2(c+\theta_1)-N(\alpha+\theta_1)(c+\theta_1)\}}{(c+\theta_1)(c+\theta_2)(\theta_2-\theta_1)}e^{\theta_2 t} \end{aligned} \qquad (6.4.15)$$

We have not obtained explict results for $M_X^{(2)}(t), M_D^{(2)}(t), M_{XV}(t), M_{VD}(t)$ and $M_{XD}(t)$.

However, we are able to solve completely the equations (6.4.1) to (6.4.9) in a special case where no infectious free virus is released at the lysis of every HIV-infected cell treated with combination therapy. We have for this special case, $m_1 = 0$, $m_{11} = 0$, $m_{12} = 0$.

Consequently, equations 6.4.1 to 6.4.9 yield

$$M_X(t) = Ne^{-\alpha t} - n\lambda_2\left(\frac{e^{-\alpha t} - e^{-\beta t}}{\alpha-\beta}\right) \qquad (6.4.16)$$

$$M_V(t) = ne^{-\beta t} \qquad (6.4.17)$$

$$M_D(t) = vm_2\left[\frac{n\lambda_2 - N(c-\beta)}{(c-\alpha)(c-\beta)}e^{-ct} - \frac{n\lambda_2 - N(\alpha-\beta)}{(c-\alpha)(\alpha-\beta)}e^{-\alpha t} + \frac{n\lambda_2}{(c-\beta)(\alpha-\beta)}e^{-\beta t}\right] \qquad (6.4.18)$$

$$M_V^{(2)}(t) = n(n-1)e^{-2\beta t} \qquad (6.4.19)$$

$$M_{XV}(t) = Nne^{-(\alpha+\beta)t} + \frac{\lambda_2 n(n-1)}{\alpha-\beta}\{e^{-2\beta t} - e^{-(\alpha+\beta)t}\} \tag{6.4.20}$$

$$M_{VD}(t) = \begin{aligned} &\frac{Nn\nu m_2}{c-\alpha}\{e^{-(\alpha+\beta)t} - e^{-(\beta+c)t} \\ &-\frac{\nu m_2 \lambda_2 n(n-1)}{(\alpha-\beta)(\beta-c)(c-\alpha)}\{(c-\alpha)e^{-2\beta t} \\ &+(\beta-c)e^{-(\alpha+\beta)t} + (\alpha-\beta)e^{-(\beta+c)t}\} \end{aligned} \tag{6.4.21}$$

$$M_X^{(2)}(t) = \begin{aligned} &\frac{2\lambda_1\{(\alpha-\beta)N-n\lambda_2\}}{\alpha(\alpha-\beta)}e^{-\alpha t} + \frac{2\lambda_1\lambda_2 n}{(\alpha-\beta)(2\alpha-\beta)}e^{-\beta t} \\ &+\frac{2\lambda_2\{Nn(\alpha-\beta)-\lambda_2 n(n-1)\}}{(\alpha-\beta)^2}e^{-(\alpha+\beta)t} \\ &+\left[\frac{N(N-1)\alpha(2\alpha-\beta)-2\lambda_1\{(2\alpha-\beta)N-n\lambda_2\}}{\alpha(2\alpha-\beta)} + \frac{\lambda_2\{\lambda_2 n(n-1)-2Nn(\alpha-\beta)\}}{(\alpha-\beta)^2}\right]e^{-2\alpha t} \\ &+\frac{\lambda_2^2 n(n-1)}{(\alpha-\beta)^2}e^{-2\beta t} \end{aligned} \tag{6.4.22}$$

$$M_{XD}(t) = A_1e^{-\alpha t} + A_2e^{-\beta t} + A_3e^{-2\alpha t} + A_4e^{-2\beta t} + A_5e^{-(\alpha+c)t} + A_6e^{-(\beta+c)t} + A_7e^{-(\alpha+\beta)t} \tag{6.4.23}$$

$$M_D^{(2)}(t) = 2\nu m_2 [\ A_1\left\{\frac{e^{-2ct}-e^{-\alpha t}}{\alpha-2c}\right\}+A_2\left\{\frac{e^{-2ct}-e^{-\beta t}}{\beta-2c}\right\}$$

$$+A_3\left\{\frac{e^{-2ct}-e^{-2\alpha t}}{2(\alpha-c)}\right\}+A_4\left\{\frac{e^{-2ct}-e^{-2\beta t}}{2(\beta-c)}\right\}$$

$$+A_5\left\{\frac{e^{-2ct}-e^{-(\alpha+c)t}}{\alpha-c}\right\}+A_6\left\{\frac{e^{-2ct}-e^{-(\beta+c)t}}{\beta-c}\right\}+A_7\left\{\frac{e^{-2ct}-e^{-(\alpha+\beta)t}}{\alpha+\beta-2c}\right\}\ ]$$

$$+\nu m_{22}\left[\left\{N-\frac{n\lambda_2}{\alpha-\beta}\right\}\left\{\frac{e^{-2ct}-e^{-\alpha t}}{\alpha-2c}\right\}+\frac{n\lambda_2}{\alpha-\beta}\left\{\frac{e^{-2ct}-e^{-\beta t}}{\beta-2c}\right\}\right] \quad (6.4.24)$$

where $A_1=\dfrac{2\lambda_1\{N(\alpha-\beta)-\lambda_2 n\}}{\alpha c(\alpha-\beta)}$

$$A_2=\frac{2\lambda_1\lambda_2 n}{(\alpha-\beta)(2\alpha-\beta)(\alpha-\beta+c)}$$

$$A_3=\frac{N(2\alpha-\beta)\{\nu m_2(N-1)\alpha-2\lambda_1\}+2\lambda_1\lambda_2 n}{\alpha(2\alpha-\beta)(c-\alpha)}+\frac{\nu m_2\lambda_2 n\{\lambda_2(n-1)-2N(\alpha-\beta)\}}{(\alpha-\beta)^2(c-\alpha)}$$

$$A_4=\frac{\nu m_2\lambda_2^2 n(n-1)}{(\alpha-\beta)^2(c-\beta)}$$

$$A_5=\frac{\nu m_2\lambda_2 n\{N(\alpha-2\beta-c)-\lambda_2(n-1)\}}{(c-\beta)(\alpha-\beta)(\alpha-2\beta-c)}+\frac{2\nu m_2\lambda_2 n\{N(\alpha-2\beta-c)-\lambda_2(n-1)\}}{(c-\beta)(c-\alpha)(\alpha-2\beta+c)}$$

$$+\frac{\{2\lambda_1-\nu m_2(N-1)c\}N(\alpha-\beta+c)-2\lambda_1\lambda_2 n}{c(c-\alpha)(\alpha-\beta)(\alpha-\beta+c)}$$

$$A_6=\frac{\nu m_2\lambda_2 n\{\lambda_2(n-1)-N(c-\beta)\}}{(c-\alpha)(c-\beta)(\alpha-\beta)}$$

$$A_7=\frac{2\nu m_2\lambda_2 n\{N(\alpha-\beta)-\lambda_2(n-1)\}}{(\alpha-\beta)^2(c-\beta)}+\frac{\nu m_2\lambda_2 n\{N(\alpha-\beta)-\lambda_2(n-1)\}}{(c-\alpha)(c-\beta)(\alpha-\beta)}$$

Although the above expressions for $M_{XD}(t)$ and $M_D^{(2)}(t)$ are quite laborious, we have presented them here for the sake of completeness. However, for the purpose of numerical illustration considered in the next section, we prefer the following integral expressions which are obtained from equations 6.4.18 to 6.4.24.

$$M_D(t) = \nu m_2 \int_0^t e^{-cu} M_X(t-u)du \tag{6.4.25}$$

$$M_{XV}(t) = Nn + \lambda_2 \int_0^t e^{-(\alpha+\beta)u} M_V^{(2)}(t-u)du \tag{6.4.26}$$

$$M_{VD}(t) = \nu m_2 \int_0^t e^{-(\beta+c)u} M_{XV}(t-u)du \tag{6.4.27}$$

$$M_X^{(2)}(t) = N(N-1) + 2\lambda_2 \int_0^t e^{-2\alpha u} M_{XV}(t-u)du + 2\lambda_1 \int_0^t e^{-2\alpha u} M_X(t-u)du \tag{6.4.28}$$

$$M_{XD}(t) = \nu m_2 \int_0^t e^{-(\alpha+c)u} M_X^{(2)}(t-u)du + \lambda_2 \int_0^t e^{-(\alpha+c)u} M_{VD}(t-u)du \tag{6.4.29}$$

$$M_D^{(2)}(t) = 2\nu m_2 \int_0^t e^{-2cu} M_{XD}(t-u)du + \nu m_{22} \int_0^t e^{-2cu} M_X(t-u)du \tag{6.4.30}$$

Where the expressions for $M_X(t)$, $M_V(t)$, $M_D(t)$ and $M_V^{(2)}(t)$ are given by equations 6.4.16, 6.4.17, 6.4.18 and 6.4.19 respectively.

6.5 NUMERICAL ILLUSTRATION OF MODEL

For the purpose of numerical illustration, we have extrapolated estimates from Perelson et al. (1996) and Tan and Xiang (1999) and considered three cases (we adopt Simpson's one-third rule for the computation of integrals (equations) 6.4.25 to 6.4.30).

Case (i): Both the mean numbers of the infectious free HIV m_1 and non-infectious free HIV m_2 produced by a virus producing cell at the time of its lysis are greater than zero.

Case (ii): $m_1 = 0$ and $m_2 \neq 0$ and obtain values of the means $M_X(t)$, $M_V(t)$, and $M_D(t)$ for the values of t ranging from 0.0 to 2.5 in steps of 0.5 for all the cases and the results are highlighted in Figure 6.1.

Case (iii): The second moments are evaluated by adopting Simpson's one-third rule for the evaluation of integrals. The assumed values of the parameters are given below in table 6.1 and the results are highlighted in Table 6.2 to 6.5 and figure 6.1. For simulated results, we take 1 hour as 0.5 time unit.

Table 6.1: Assumed values of parameters used in data simulation

Parameters Notation	Parameters	Assumed values
C	Rate of dying of a free HIV	3/day
N	Number of virus producing cells at time t = 0	412copies/ ml
n	Number of infectious free HIV at time t = 0	98000/mm^3
λ_1	Rate of splitting of a virus producing cell	5/day/mm^3 and 10/day/mm^3
λ_2	Rate with which a free HIV infects a CD4 cell	1/day/mm^3
ν	Rate of occurrence of lysis of virus producing cell	0.02/day
μ	Rate of death of virus producing cell	0.4/day
m_1	Expected number of infectious free HIV produced at the time of lysis of an infected cell	200/mm^3
m_2	Expected number of non-infectious free HIV produced at the time of lysis of an infected cell	100/mm^3
m_{22}	Second factorial moments of the number of non-infectious free HIV produced at the time of lysis of an infected cell	9900/mm^6

Case (i): From Figure 6.1 and table 6.2, it was easily noted that as t increases the values of $M_X(t), M_V(t), M_D(t)$ also increases for $\lambda_1 = 5.0$. When $\lambda_2 = 10.0$ (the rate at which HIV infected cell splits into two), the values of $M_X(t)$, $M_V(t), M_D(t)$ also increased with

increasing value of t (table 6.2). This shows that as the value of λ_1 increases, the values of $M_X(t)$, $M_V(t)$, $M_D(t)$ increases significantly with time before treatment.

Case (ii): Assume $m_1 = 0$, $m_2 = 100.0$, $m_{22} = 9900.0$. From Figure 6.1 that has the fitted curves for $M_X(t)$, $M_V(t)$, $M_D(t)$ before and after treatment, it is observed that there is a remarkable difference in the values obtained before and after treatment especially after t = 1.5. This shows the effectiveness of the treatment using the stochastic model. As such the expected number of virus producing cells and expected number of non-infectious free HIV decreased significantly after treatment (effect of reverse transcriptase drugs). And the expected numbers of infectious free HIV was reduced to almost nil at t = 2.5 which is the effect of protease inhibitor drugs as they reduce the generation of infectious free HIV at the death of actively infected T4 cells.

Case (iii): Assume $m_1 = 0$, $m_2 = 100.0$, $m_{22} = 9900.0$. The values of the second order moments namely: $M_X^{(2)}(t)$, $M_D^{(2)}(t)$, $M_V^{(2)}(t)$, $M_{XD}(t)$, $M_{XV}(t)$, and $M_{VD}(t)$ are provided in Table 6.4 and Table 6.5. The variances of virus producing cells and non-infectious free HIV are so large in comparison to those of infectious free HIV and their values increased significantly with t increasing. Unlike those of infectious free HIV that decreased significantly after treatment. The co-variance results shows that there is a positive relationship between virus producing cells and infectious free HIV.

Table 6.2 : $M_X(t)$, $M_V(t)$, $M_D(t)$ versus t (before treatment) with C = 3.0, N = 412.0, n = 98000.0, υ = 0.02, μ = 0.49, m_1 = 200.0, m_2 = 100.0, m_{22} = 9900.0, λ_2 = 1.0

	λ_1 = 5.0		
t	$M_X(t)*10^{-5}$	$M_V(t)*10^{5}$	$M_D(t)*10^{-4}$
0.50	1	1	3
1.00	15	7	38
1.50	178	80	449
2.00	2106	943	5307
2.50	24870	11131	62665

	λ_1 = 10.0		
t	$M_X(t)*10^{-5}$	$M_V(t)*10^{5}$	$M_D(t)*10^{-5}$
0.50	1	2	2
1.00	130	378	204
1.50	17324	50286	27111
2.00	2303609	6686681	3604945
2.50	306314300	889138100	479355000

Table 6.3: $M_X(t), M_V(t), M_D(t)$ versus t (after treatment) with C = 3.0, N = 412.0, n = 98000.0, $\upsilon = 0.02$, $\mu = 0.49$, $\lambda_2 = 1.0$, $m_2 = 100.0$, $m_{22} = 9900.0$

	$\lambda_1 = 5.0$		
t	$M_X(t) * 10^{-5}$	$M_V(t)$	$M_D(t) * 10^{-4}$
0.50	1	13263	3
1.00	11	1795	28
1.50	101	243	269
2.00	950	33	2535
2.50	8964	4	23936

Table 6.4: $M_X^{(2)}(t), M_D^{(2)}(t), M_V^{(2)}(t)$ versus t with C = 3.0, N = 412.0, n = 98000.0, $\upsilon = 0.02$, $\mu = 0.49$, $m_2 = 100.0$, $m_{22} = 9900.0$, $\lambda_1 = 2.5$, $\lambda_2 = 1.0$

t	$M_X^{(2)}(t) * 10^{-6}$	$M_D^{(2)}(t) * 10^{-6}$	$M_V^{(2)}(t)$
0.50	1893	195	175901600
1.00	15054	2349	3221750
1.50	105300	18217	59008
2.00	702573	134013	1081
2.50	4510266	969590	20

Table 6.5: $M_{XV}(t), M_{XD}(t), M_{VD}(t)$ versus t with C = 3.0, N = 412.0, n = 98000.0, $\upsilon = 0.02$, $\mu = 0.49$, $m_2 = 100.0$, $m_{22} = 9900.0$, $\lambda_1 = 2.5$, $\lambda_2 = 1.0$

t	$M_{XV}(t) * 10^{-6}$	$M_{XD}(t) * 10^{-6}$	$M_{VD}(t) * 10^{-6}$
0.50	598	605	186
1.00	255	5925	95
1.50	120	43175	43
2.00	70	295546	24
2.50	51	1948272	17

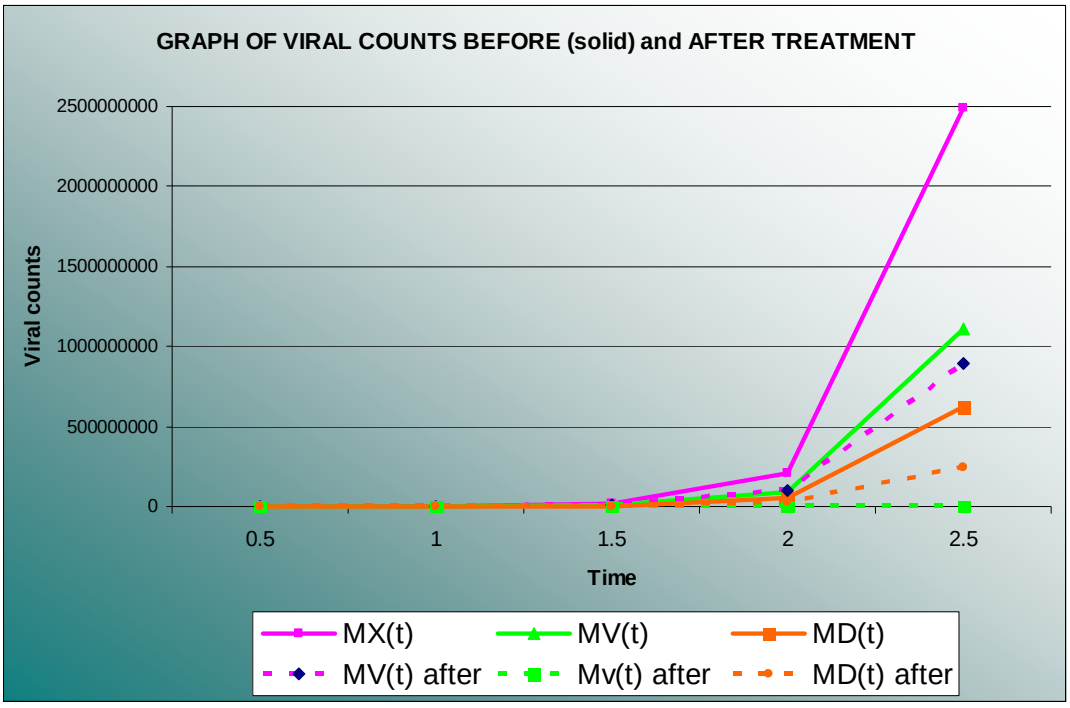

Figure 6.1: Graph of simulated mean number of free HIV, infectious free HIV and non-infectious free HIV before and after combined therapeutic treatment. (Units: on x-axis 0.5 is 1hour and viral counts on y-axis is copies/ml of blood)

6.6 CONCLUSION

In this chapter, we have shown the necessity of our stochastic model under combined treatment by obtaining the variance and co-variance structure of the number of virus producing cells at time t, the number of infectious free HIV and the number of non-infectious free HIV at time t. Compared with the models obtained by Perelson et al. (1996) and Tan and Xiang (1999), the variance and co-variance structures were not obtained, rather only the expected numbers of the variables and their estimates were obtained. Numerical simulation of results obtained in section 6.5 above has shown the efficacy of our model. We have not included t = 0 (after treatment) for the data simulation which is the time of pharmacokinetic delay which vary from person to person, and this is the time required for drug absorption, drug distribution and penetration into target cells (Perelson et al. 1996).

We have used estimates extrapolated from clinical data in Perelson et al. (1996) and Tan and Xiang (1999) to simulate our results. However a real life data for each time point are yet to be used because of limited resources to obtain RNA viral load of patients every 30 minutes to one hour interval. In a follow-up work, we intend to obtain such data as in Perelson et al. (1996) to test the efficacy of our model as we have done with simulated data.