CHAPTER 3

A NON-MARKOVIAN EVOLUTION MODEL OF HIV POPULATION WITH BUNCHING BEHAVIOUR

3.1 INTRODUCTION

The discussion in chapter 2, regarding a model of HIV population to seropositivity is very exhaustive and a good number of statistical conclusions can be obtained from the results available there. However the objective is to study the stochastic problem of time-dependent viral population with non-Markovian evolution of immigration. The organization of this chapter is as follows. In the next section, we briefly describe the model under consideration whereas section 3.3 deals with the notation of the model. In section 3.4, we give the governing equations while in section 3.5, we obtain the moments and cross correlations. In the final section, we examine the emigration process of the model and obtain $h_{\text{sty}}(t)$.

3.2 DESCRIPTION OF THE MODEL

We recall from chapter 2, that each of the HIV population conditional upon its survival and emigration is assumed to evolve through two phases. In the first phase, the HIV is in the blood stream only (no attachment) and it is incorporated into the T-4 cell. The second phase is characterised by the replication of HIV inside the T-4 cell. An HIV, at any time, is in
(i) phase 1 with probability $e^{\beta t}$, where $\beta$ represents the probability of an HIV incorporated into a T-4 cell and
(ii) phase 2 with probability $\beta e^{\lambda t}$ where $\lambda$ is the probability of replication.

Also the HIV population immigrate into the system in a non-Markovian manner. Further we assume that the point process associated with immigration, taken in isolation, forms an ordinary renewal process. The discrete-state Markov chain undergoes transitions from state 1 to state 2 with rate $\alpha_1$. When the Markov chain is in state 2, the next transition occurs at a rate $\alpha_2$, results in the materialization of immigration and the state of immigration makes a transition to the state 2 itself (Figure 3.1). In matrix form, we have

$$
\begin{pmatrix}
0 & \alpha_1 \\
0 & \alpha_2
\end{pmatrix}
$$

Hence for the two-phase model, we proceed to analyse the immigration process.

### 3.3 NOTATION

- $X(t)$: total size of HIV population at time $t$
- $N(t)$: number of emigrations in $(0,t)$
- $Y(t)$: state of immigration process at time $t$
- $\tau_{ji}(t)$: $P[Y(t) = i \mid Y(0) = j]$, $i = j = 1,2$
- $g_i(z,t)$: probability generating function of the process $X(t)$ when there is no immigration defined by $E[z^{X(t)} \mid X(0) = 1, \alpha_1 = 0]$, $i = 1,2$
- $G_i(z,t)$: probability generating function of the process $X(t)$ in the presence of immigration defined by $E[z^{X(t)} \mid X(0) = 0, Y(0) = 1]$, $i = 1,2$.
- $f'_i(t)$: first order product density of the process $N(t)$ defined by
Figure 3.1 Possible transitions for the immigration processes with rates $\alpha_1$ and $\alpha_2$
\[ \lim_{\Delta \to 0} \frac{1}{\Delta} \Pr \left\{ \frac{N(t+\Delta) - N(t)}{\Delta} = 1 \mid \text{population is in equilibrium initially} \right\} \]

\[ f_2(t_1,t_2) \text{ the second order product density of the process } N(t) \text{ defined by} \]

\[ \lim_{\Delta_1,\Delta_2 \to 0} \frac{1}{\Delta_1 \Delta_2} \Pr \left\{ \frac{N(t_1+\Delta_1)-N(t_1)=1, N(t_2+\Delta_2)-N(t_2)=1}{\Delta_1 \Delta_2} \mid \text{population is in equilibrium initially} \right\} \]

### 3.4 GOVERNING EQUATIONS

To obtain the equations satisfied by the functions \( g_i(z,t), i=1,2 \) we follow the same type of arguments discussed in Sridharan et al. (1998) and obtain the following differential equations as

\[ \frac{\partial g_1(z,t)}{\partial t} = -\beta g_1(z,t) + \beta g_2(z,t) \quad (3.1) \]

\[ \frac{\partial g_2(z,t)}{\partial t} = - (\lambda + \eta) g_2(z,t) + \lambda g_2^2(z,t) + \eta \quad (3.2) \]

with initial conditions

\[ g_i(z,0) = z_i, \quad i = 1,2. \quad (3.3) \]

To obtain the equations satisfied by \( G_i(z,t), i=1,2 \) we fix our attention in the time interval \((0,\Delta)\). If the process of immigration is in phase 1, it

(i) can move to phase 2 with probability \( \alpha_1 \Delta + o(\Delta) \)

(ii) can continue to be in phase 1 with the residual probability \( 1-\alpha_1 \Delta + o(\Delta) \).
Thus

\[ G_1(z,t) = 1 - \alpha_1 \Delta G_1(z,t-\Delta) + \alpha_1 \Delta G_2(z,t-\Delta) + o(\Delta). \]

On the other hand, if the immigration process is in phase 2, immigration materializes at a rate \( \alpha_2 \) (Figure 3.1). Taking into consideration the fact that the immigrant is in phase 2 and will generate a population independent of the state of immigration, we get

\[ G_2(z,t) = 1 - \alpha_2 \Delta G_2(z,t-\Delta) + \alpha_2 \Delta G_2(z,t-\Delta) g_2(z,\Delta) + o(\Delta). \]

Proceeding to the limit as \( \Delta \to 0 \), we have

\[
\frac{\partial G_1(z,t)}{\partial t} = - \alpha_1 G_1(z,t) + \alpha_1 G_2(z,t) \quad (3.4)
\]

\[
\frac{\partial G_2(z,t)}{\partial t} = - \alpha_2 G_2(z,t) + \alpha_2 G_2(z,t) g_2(z,t) \quad (3.5)
\]

the initial condition being \( G_i(z,0) = 1, i = 1,2 \). From the above differential equations, we calculate the moments of the population as follows.

### 3.5 MOMENTS OF THE POPULATION

Next we proceed to obtain the first and second order moments of the population at time \( t \) in phases 1 and 2 respectively. Consider \( \partial g_i(z,t) / \partial z \mid z=1 \) which is defined as \( E [X(t) \mid X(0) = 1, \alpha_i = 0] \) and is denoted by \( a_i(t), i = 1,2 \). Let \( \partial^2 g_i(z,t) / \partial z^2 \) at \( z=1 \) be \( E [X(t) (X(t)-1) \mid X(0)=1, \alpha_i = 0] \) which is the second factorial moment of \( X(t) \) and is given by \( b_i(t), i=1,2 \). Next, consider \( \partial G_i(z,t) / \partial z \) at \( z=1 \); this is seen to be \( E [X(t) \mid X(0) = 0, Y_i(0) = 1] \) and is labelled as \( A_i(t), i=1,2 \). Finally, \( \partial^2 G_i(z,t) / \partial z^2 \mid z=1 \) defined as \( E [X(t) (X(t)-1) \mid X(0) = 0, Y_i(0) = 1] \) and is denoted by \( B_i(t), i=1,2 \).
On differentiating (3.1) and (3.2) we get

\[
\frac{da_1(t)}{dt} = -\beta a_1(t) + \beta a_2(t)
\] (3.6)

\[
\frac{da_2(t)}{dt} = - (\eta - \lambda) a_2(t)
\] (3.7)

with \( a_i(0) = 1, \ i = 1,2. \)

Again differentiating equations (3.1) and (3.2) we obtain

\[
\frac{db_1(t)}{dt} = -\beta b_1(t) + \beta b_2(t)
\] (3.8)

\[
\frac{db_2(t)}{dt} = - (\lambda + \eta) b_2(t) + 2\lambda b_2(t) + 2\lambda [a_2(t)]^2
\] (3.9)

with initial conditions being \( b_i(0) = 0, \ i = 1,2. \)

Further differentiation of (3.4) and (3.5) lead to

\[
\frac{dA_1(t)}{dt} = -\alpha_1 A_1(t) + \alpha_1 A_2(t)
\] (3.10)

\[
\frac{dA_2(t)}{dt} = \alpha_2 a_2(t).
\] (3.11)

Similarly once again differentiating equations (3.4) and (3.5) yield

\[
\frac{dB_1(t)}{dt} = -\alpha_1 B_1(t) + \alpha_1 B_2(t)
\] (3.12)

\[
\frac{dB_2(t)}{dt} = \alpha_2 b_2(t) + 2\alpha_2 A_2(t) a_2(t)
\] (3.13)
with initial conditions given by
\[ A_i(0) = B_i(0) = 0, \ i = 1,2. \]

Solving equations (3.6) and (3.7) we obtain
\[
\begin{align*}
a_1(t) &= \frac{1}{\eta \lambda} \left[ (\eta - \lambda) e^{\beta t} + \beta e^{(\eta - \lambda) t} \right] \\
\alpha_2(t) &= e^{(\eta - \lambda) t}.
\end{align*}
\]

Also the Laplace transforms solution of \( b_i \)'s, \( i = 1,2 \) are given by
\[
b_1^*(s) = \frac{2\lambda \beta}{(s+\beta)(s+\eta - \lambda)(s+2\eta - 2\lambda)}; \quad b_2^*(s) = \frac{2\lambda}{(s+\eta - \lambda)(s+2\eta - 2\lambda)} 
\tag{3.15}
\]

Similarly from equations (3.10) and (3.11) one has
\[
\begin{align*}
A_1^*(s) &= \frac{\alpha_1 \alpha_2}{s(s+\alpha_1)(s+\eta - \lambda)}; \\
A_2^*(s) &= \frac{\alpha_2}{s(s+\eta - \lambda)} 
\end{align*}
\tag{3.16}
\]

and from equations (3.12) and (3.13) we get
\[
\begin{align*}
B_1^*(s) &= \frac{2\alpha_1 \alpha_2 (\lambda + \alpha_2)}{s(s+\alpha_1)(s+\eta - \lambda)(s+2\eta - 2\lambda)}; \\
B_2^*(s) &= \frac{2\alpha_2 (\lambda + \alpha_2)}{s(s+\eta - \lambda)(s+2\eta - 2\lambda)} 
\end{align*}
\tag{3.17}
\]

Inverting equation (3.16) leads to
\[
\begin{align*}
A_1(t) &= \frac{\alpha_2}{(\eta - \lambda)} - \frac{\alpha_2 e^{-\alpha_1 t}}{(\lambda + \alpha_1 - \eta)} + \frac{\alpha_1 \alpha_2 e^{(\eta - \lambda) t}}{(\eta - \lambda)(\eta - \lambda - \alpha_1)} \\
A_2(t) &= \frac{\alpha_2}{(\eta - \lambda)} [1 - e^{(\eta - \lambda) t}] 
\end{align*}
\tag{3.18-19}
\]
The factorial moments of the equilibrium distribution of the population size are obtained by using the Tauberian theorem as

\[ B_1(\infty) = B_2(\infty) = \frac{\alpha_2 [\lambda + \alpha_2]}{(\eta - \lambda)^2} \]  

(2.20)

and

\[ A_1(\infty) = A_2(\infty) = \frac{\alpha_2}{\eta - \lambda} \]  

(3.21)

### 3.6 EMIGRATION PROCESS

We are interested in the statistical properties of the number of HIV emigrated in an arbitrary interval \((t_0, t)\). Since the differential equations satisfied by the appropriate generating function is exactly the same as obtained in the previous section, we use an alternative approach (Kendall (1949)). This method is simpler particularly in view of the results already available. Here we deal with the point process generated by the epochs of emigrations. From the construction of the model it is clear that this point process is stationary and hence its statistical characteristics are independent of the time \(t_0\). Thus we can denote it by \(N(t)\) and hence the emigration point process \(N(t)\) can be characterised in terms of the product densities. To make further progress, we introduce the following additional conditional product densities by choosing some initial conditions and revert back to the equilibrium condition. Let

\[ h^i_1(t) = \lim_{\Delta \to 0} \frac{1}{\Delta} \Pr [N(t+\Delta) - N(t) = 1 \mid X(0) = 1, \alpha_i = 0], \quad i = 1, 2 \]  

(3.22)

\[ h_1(t) = \lim_{\Delta \to 0} \frac{1}{\Delta} \Pr [N(t+\Delta) - N(t) = 1 \mid X(0) = 0, \alpha_i \neq 0]. \quad i = 1, 2 \]  

(3.23)
Further the functions $f_1(t)$ and $h_1(t)$ are related by

$$f_1(t) = \lim_{t \to \infty} h_1(t) = \eta \ A_1(\infty).$$

Hence $f_1(t) = \text{a constant} = \eta \alpha_2 / (\eta - \lambda).$ (3.24)

To obtain $h_1^1(t)$ we use the definition in (3.22) directly and relate it to the moment $a_1(t)$ as

$$h_1^1(t) = \eta \ a_1(t).$$

Hence we have

$$h_1^1(t) = \frac{\eta}{\eta - \lambda - \beta} \left[ (\eta - \lambda) e^{-\beta t} - \beta e^{-(\eta - \lambda)t} \right]$$

(3.25)

Now to obtain $h_{sty}(t)$, we note that the HIV population is maintained in equilibrium at the origin, from which point of time, the emigration process takes place. Taking into consideration that the infected T-4 cell could be in any one of the phases and any one of the members of the HIV population can generate a population tree between $(0, t)$, we have the following contribution for $h_{sty}(t)$ as

$$h_{sty}(t) \bigg|_{\text{first term}} = \eta^2 \ B_1(\infty) \ e^{-(\eta - \lambda)t}$$

The second term corresponds to the following situation. We concentrate our attention at the point from which the immigration takes place and if $x$ is the time coordinate at the epoch from which it starts, the state of immigration is described by a two-state semi-Markov process discussed in section 3.2. Hence the contribution in this case is given by

$$h_{sty}(t) \bigg|_{\text{second term}} = \eta^2 \alpha_2 \sum_{i,j=1}^{2} \int_{-\infty}^{0} \pi_{ji}(-x) \ A_i(t) \ a_2(x) \ dx.$$
On simplification we have

\[ h_{sty}(t) = \eta^2 B_1(\infty) e^{-\eta \lambda t} + \eta^2 \alpha_2 \sum_{i,j=1}^{2} \pi_{ji}^* (\eta - \lambda) A_i(t). \] (3.26)

The expression for \( h_{sty}(t) \) is explicit once we determine \( \pi_{ji}^* \). Making use of the semi-Markov nature of the process \( N(t) \) and observing that the sojourn time distribution are exponential we obtain

\[ \frac{d}{dt} \pi_{i1}(t) = -\alpha_1 \pi_{i1}(t) + \alpha_1 \pi_{i2}(t), \quad i = 1, 2 \] (3.27)

\[ \pi_{21}(t) = 0 \text{ and } \pi_{22}(t) = 1. \]

The initial conditions being

\[ \pi_{ji}(0) = \begin{cases} 1, & \text{if } i = j \\ 0, & \text{otherwise.} \end{cases} \]

Solving equation (3.27) using Laplace transforms we have

\[ \pi_{11}(s) = \frac{1}{s + \alpha_1}, \quad \pi_{12}(s) = \frac{\alpha_1}{s(s + \alpha_1)} \text{ and } \pi_{22}(s) = \frac{1}{s}. \]

Further substituting for \( \pi_{ji}^*(s) \) in equation (3.26) we obtain

\[ h_{sty}(t) = \frac{2\eta^2 \alpha_2^2}{(\eta - \lambda)^2} + \frac{\eta^2 \alpha_2^2 e^{-\alpha_1 t}}{(\lambda + \alpha_1 - \eta)(\eta - \lambda + \alpha_1)} + \frac{(\alpha_1^2 \alpha_2 + \eta^2 \lambda + \lambda^3 - 2\eta \lambda^2 - \lambda \alpha_1^2) \eta^2 \alpha_2 e^{(\eta - \lambda)t}}{(\eta - \lambda)^2 (\eta - \lambda - \alpha_1)(\eta - \lambda + \alpha_1)}. \] (3.28)

A measure of bunching \( B \) (Srinivasan (1988)) is defined by

\[ B = \frac{h_{sty}(0)}{h_{sty}(\infty)}. \] (3.29)

In particular, substituting for \( \alpha_1 = 2\lambda, \alpha_2 = \lambda/2 \) and \( \eta = 2\lambda \), (with \( \alpha_2 < \lambda \), \( 0 < (\eta - \lambda) < \alpha_1 \)) in equations (3.28) and (3.29) we have respectively
\[ h_{\text{st}}(t) = 2\lambda^2 + \frac{\lambda^2}{3} e^{-2\lambda t} + \frac{2}{3} \lambda^2 e^{-\lambda t} \] and

\[ B = 3/2 > 1. \]

which behaves like a super-Poissonian or bunched manner.

For another choice of parameters, namely \( \alpha_1 = \lambda, \alpha_2 = \lambda/4, \eta = \lambda/2 \) (with \( \alpha_2 < \lambda, 0 < (\eta - \lambda) < \alpha_1 \)) we have the measure of bunching \( B \) also greater than unity and therefore it once again behaves like a super-Poissonian or bunched manner.