CHAPTER 4

STOCHASTIC ANALYSIS OF INFECTED T-4 CELLS

4.1 ON THE CHARACTERISTICS OF HIV INFECTION TO T-4 CELLS

4.1.1 Introduction

One of the consequences of infection by an HIV is the selective depletion of CD4$^+$ cells, known as helper T cells or T-4 cells. During the past decade, a number of stochastic and deterministic models have been developed to describe the immune system and its interaction with an HIV. The model of Nowak et al., (1991) deal with the effects of variability among viral strains. Further Alan Perelson et al., (1993) describe the decline of T-4 cell count using dynamic models and suggest an improvement by considering a time-dependent model. Munoz et al., (1988) employ an autoregressive model to study the decline of T-4 cell count. Anderson (1989) examines the changes in the mean number of cells. Logini et al., (1989) have used a continuous time Markov process to model the decline of T-4 cell in HIV infected person.

Hence to generate a realistic model of T-4 cells infected by an HIV, we first need to know about the T-4 cell population in the absence of HIV. T-4 cells like other lymphocytes are produced in the bone marrow. Immature cells migrate to thymus, where they undergo further differentiation and get matured into immunocompetent T-4 cells. Within the healthy individuals the number of T-4 cells in the blood is maintained relatively constant, comprising about 1000 cells/mm$^3$. These T-4 cells get
infected by an HIV and lysis takes place. A large number of free virions are instantaneously released which in turn infect new uninfected T-4 cells. Therefore it is worthwhile to consider in detail a point process with special reference to T-4 cell population. Even this analysis is rather cumbersome and hence a method of phases suggested by Srinivasan (1988) have been adopted. Also the decline in the number of T-4 cells in peripheral blood is used in a clinical laboratory as indicators of the disease stage (Taylor et al., (1989)).

The main aim of this section is as follows. In section 4.1.2, we describe the formulation of a three-phase model of the infected T-4 cell population. Section 4.1.3 deals with the generating functions of the infected T-4 cell population whereas in section 4.1.4, we obtain the moments of the process. Section 4.1.5 is dealt with a numerical example and interpretation of results are given.

4.1.2 Formulation of the Problem

To model the influence of an HIV on the growth of T-4 cells, we need to take into consideration the life history of the virus. As discussed in the previous chapters, when an HIV infects a cell, it makes a DNA copy of its RNA genome by the enzyme reverse transcriptase. This DNA copy is then integrated into the DNA of the infected cell. The viral DNA, called the provirus, is then duplicated within the cell's DNA. Thus once infected, a cell remains infected throughout its lifetime. Stimulation of T-4 cells by antigen or a mitogen can lead to the production of new virus particles that bud from the surface of infected cells. The budding can take place slowly, sparing host cells or it can take place very rapidly, possibly leading to lysis of T-4 cells (Figure 4.1.1).
Figure 4.1.1 Replication cycle of HIV

1. HIV
2. Uncoated virus
3. RNA
4. Reverse transcriptase
5. Unintegrated linear DNA
6. Unintegrated circular DNA
7. Integrated proviral DNA
8. Cellular DNA
9. Genomic mRNA
10. Budding virus particle
11. New mature HIV virion
12. Protein synthesis processing and assembly
13. Viral mRNA
14. CDA Molecule
As the disease progress, the patient moves through five stages. The first stage is pre-antibody period, in which a person is infected, but not antibody seropositive. The second stage includes persons who are infected and antibody seropositive, but are asymptomatic. The third stage (symptomatic) occurs when the person develops an abnormal hematologic indicator and prodromal illness such as persistent generalised lymphadenopathy or oral candidiasis. The fourth stage is clinical AIDS and fifth stage is death due to AIDS (Table 4.1). So the interest is centered around the depletion of the T-4 cell population which is a determining factor for the severe impairment of the immune system leading to the progress of AIDS. Hence we encounter the stochastic problem of the time-dependent T-4 cell population in terms of phases.

A T-4 cell can be thought of in any one of the following three phases.

(i) In the first phase, the uninfected T-4 cell may undergo normal differentiation

(ii) It is in the second phase when an HIV attaches to the receptors of an uninfected T-4 cell. Thus an uninfected T-4 cell becomes latently infected T-4 cell (i.e. it contains the provirus but are not producing it)

(iii) It is in the third phase where the latently infected T-4 cell is converted into an actively infected T-4 cell (i.e. that are producing virus). In such a case, lysis takes place.
TABLE 4.1

T-4 cell count in various stages

<table>
<thead>
<tr>
<th>STAGES</th>
<th>CLINICAL INDICATOR</th>
<th>T-4 CELL COUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-antibody</td>
<td>T-4 ≥ 900</td>
</tr>
<tr>
<td>2</td>
<td>Asymptomatic</td>
<td>899 ≥ T-4 ≥ 500</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic</td>
<td>499 ≥ T-4 ≥ 199</td>
</tr>
<tr>
<td>4</td>
<td>AIDS</td>
<td>AIDS</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
<td>Death</td>
</tr>
</tbody>
</table>
4.1.3 Governing Equations of the Problem

Let $X_i(t)$ represent the size of the T-4 cell population at any time $t$ in phase $i$, $i=1,2,3$ respectively. At time $t$

(i) an uninfected T-4 cell undergoes normal differentiation with probability $e^{-\mu t}$;
(ii) an uninfected cell becomes infected cell by the attachment of HIV and let $k_1(t)$ be the transition rate from phase 1 to phase 2 and
(iii) let $k_2(t)$ be the rate at which the latently infected T-4 cell be converted into an actively infected T-4 cell.

Also let $l_1(t)$ and $l_2(t)$ be the probability of lysis to occur in phases 2 and 3 respectively. Hence it is convenient to introduce the following notation for the generating functions in phase $i$ ($i=1,2,3$) characterising the T-4 cell population as

$$g_i(z_1, z_2, z_3; t) = E \left[ \frac{3}{\prod_{i=1}^3 X_i(t)} \right] \left| \begin{array}{c} X_i(0) = 1, X_j(0) = 0 \\ i = j = 1,2,3; j \neq i. \end{array} \right. (4.1.1)$$

Now to obtain an equation for $g_1$ one may argue that the T-4 cell population which is in phase 1, in the interval $(0,\Delta)$

(i) undergoes normal differentiation with probability $\mu \Delta + o(\Delta)$;
(ii) can move to phase 2 with probability $k_1 \Delta + o(\Delta)$ and
(iii) can continue to be in phase 1 with the residual probability $(1 - \mu \Delta - k_1 \Delta) + o(\Delta)$. Thus
\begin{align*}
g_1(z_1, z_2, z_3; t) &= (1 - \mu \Delta - k_1 \Delta) g_1(z_1, z_2, z_3; t-\Delta) \\
&\quad + \mu \Delta g_1^2(z_1, z_2, z_3; t-\Delta) + k_1 \Delta g_2(z_1, z_2, z_3; t-\Delta). \quad (4.1.2)
\end{align*}

Now proceeding to the limit as \( \Delta \to 0 \) we obtain
\begin{align*}
\frac{\partial g_1(z_1, z_2, z_3; t)}{\partial t} &= -(\mu + k_1) g_1(z_1, z_2, z_3; t) + \mu g_1^2(z_1, z_2, z_3; t) \\
&\quad + k_1 g_2(z_1, z_2, z_3; t). \quad (4.1.3)
\end{align*}

Similarly in phase 2
\begin{enumerate}
\item the latently infected cell undergoes lysis with probability \( \ell_1 \Delta + o(\Delta) \);
\item can move to phase 3 (converted as actively infected T-4 cell) with probability \( k_2 \Delta + o(\Delta) \) and
\item can continue to be in phase 2 with the residual probability \( (1-k_2 \Delta - \ell_1 \Delta) + o(\Delta) \).
\end{enumerate}

Again as limit \( \Delta \to 0 \) we have
\begin{align*}
\frac{\partial g_2(z_1, z_2, z_3; t)}{\partial t} &= -(k_2 + \ell_1) g_2(z_1, z_2, z_3; t) + \ell_1 + k_2 g_3(z_1, z_2, z_3; t). \quad (4.1.4)
\end{align*}

Similarly one has
\begin{align*}
\frac{\partial g_3(z_1, z_2, z_3; t)}{\partial t} &= -\ell_2 g_3(z_1, z_2, z_3; t) + \ell_2 \quad (4.1.5)
\end{align*}

with initial conditions being \( g_i(z_1, z_2, z_3; 0) = z_i, \ i=1,2,3. \)
4.1.4 Moments of the T-4 Cell Population

Let us introduce the first order moments as

\[ a_{ij}(t) = \frac{\partial g_i(z_1, z_2, z_3; t)}{\partial z_j} \bigg|_{z_1=z_2=z_3=1}, \quad i=j=1,2,3. \]

Differentiating equations (4.1.3-4.1.5.) with respect to \( z_j \) and using the above notation we have

\[
\frac{d a_{ij}(t)}{dt} = -(k_{1}+\mu) a_{ij}(t) + k_1 a_{2j}(t) \quad (4.1.6)
\]

\[
\frac{d a_{2j}(t)}{dt} = -(k_2+i_j) a_{2j}(t) + k_2 a_{3j}(t) \quad (4.1.7)
\]

\[
\frac{d a_{3j}(t)}{dt} = \mu a_{3j}(t), \quad j=1,2,3 \quad (4.1.8)
\]

with

\[
a_{ij}(0) = \begin{cases} 1, & \text{for } i=j \\ 0, & \text{otherwise} \end{cases}
\]

where \( a_{ij}(t) \)'s are the expected number of T-4 cells in phase j initiated by a T-4 cell in phase i. The solutions of the above system of differential equations (4.1.6-4.1.8) are given by

\[
a_{33}(t) = e^{at}, \quad a_{22}(t) = e^{bt}
\]

\[
a_{23}(t) = k_2 \left[ \frac{e^{bt} - e^{-at}}{d} \right]
\]
\[
\begin{align*}
    a_{13}(t) &= k_1 k_2 \left[ \frac{e^{ct}}{gf} - \frac{e^{-bt}}{dg} + \frac{e^{-at}}{df} \right] \\
    a_{12}(t) &= k_1 \left[ \frac{e^{ct} - e^{-bt}}{g} \right] \\
    a_{11}(t) &= e^{ct} \\
    a_{21}(t) &= a_{31}(t) = a_{32}(t) = 0
\end{align*}
\]

where
\[
\begin{align*}
    a &= \ell_2 \\
    b &= k_2 + \ell_1 \\
    c &= k_1 - \mu \\
    d &= \ell_2 - k_2 - \ell_1 \\
    f &= \ell_2 - k_1 + \mu \\
    g &= k_2 + \ell_1 - k_1 + \mu
\end{align*}
\]

The above model is dealt with a numerical example and graphs are also drawn.

4.1.5 Interpretation of Results

We note the following observations from Figures 4.1.2 and 4.1.3. We observe that as time t (in years) increases, the expected number of T-4 cells decreases. We also note that from Figure 4.1.2, for fixed values of \( k_2 = 0.2, \ell_1 = 0.04, \ell_2 = 0.84, \mu = 0.02 \) and for different values of \( k_1 = 0.025, 0.03, 0.05 \) and 0.1, as the infection rate increases the expected number of T-4 cells decreases rapidly. Moreover from Figure 4.1.3, for the same values of \( k_1, \ell_1, \ell_2, \mu \) and increased value of \( k_2 = 0.4 \), we note that the expected number of T-4 cells decline much faster than that of in Figure 4.1.2.
Figure 4.1.2 Expected number of T-4 cells vs. time $t$ (in years) when $k_2=0.2$. 
Figure 4.1.3 Expected number of T-4 cells vs. time t (in years) when $k_2=0.4$
4.2 A POPULATION MODEL OF INFECTED T-4 CELLS IN AIDS

4.2.1 Introduction

The discussion in section 4.1, regarding the characteristics of HIV infection to T-4 cells was explained in detail. However in this section, the purpose is to study a population model of infected T-4 cells in AIDS and obtain the various measures of interest. Stochastic models of T-4 cell growth are interesting and have acquired paramount importance in view of their close connection to the rapid decline of the immunizing efficiency of an HIV infected individual. Jones and Soloman (1988) discussed the importance of the seronegative period for infections induced by needle-stick injury. Nagarjuna and Iyer (1994) have analysed the seronegative period for a very low initial viral load with some interesting numerical results.

The main object of this section is as follows. Sections 4.2.2 deals with the formulation and assumptions of an n-phase model of infected T-4 cells. In section 4.2.3, we introduce the method of moments. This section is further subdivided into four subsections. Section 4.2.3.1 and 4.2.3.2 respectively deal with the notation and moments of infected T-4 cells and graphs are drawn for the same whereas in section 4.2.3.3, the emigration process is introduced and for different parametric values the stationarity distribution are tabulated. Section 4.2.3.4 considers a special case for n=2 of the above problem. In section 4.2.4, we deal the same problem by product density approach. Again this section is further subdivided into two subsections. In section 4.2.4.1, we present the n-phase model whereas in section 4.2.4.2, we illustrate the problem for n=2. We observe that the results agree with both the combinatorial method (method of moments) as well as the product density approach. In section 4.2.5, interpretation of results are given.
4.2.2 Description of the Model

We recall from section 4.1 that the new viral RNA and viral proteins of an HIV are produced which combine to form new virus particles of infected T-4 cells. So at this stage, the interest is concerned around the depletion of the T-4 cell population which is the determining factor for the severe impairment of the immune system leading to the progress of AIDS.

Hence we encounter the stochastic problem of time-dependent infected T-4 cell population and assume that the infected T-4 cells undergo n-phases before the cell is lysed. We give below the following assumptions associated with the model.

(i) Let X be the total number of infected T-4 cells (conditional upon its survival from death (lysis) and emigration) given by the sum of n independent and exponentially distributed random variables $X_1, X_2, \ldots, X_n$ and each $X_i$ is the number of infected T-4 cells in phase $i$ with parameter $\alpha_i$, $i=1,2,\ldots,n$.

(ii) Each infected T-4 cell has a constant probability $\mu$ per unit time of death which is independent of other infected T-4 cells of the population. Further death (lysis) can take place only in the $n^{th}$ phase of its life.

(iii) In the $i^{th}$ phase the normal differentiation of infected T-4 cell can happen with rate $\lambda_i$, $i = 1,2,\ldots,n-1$ (before the lysis).

(iv) Immigrations into the system takes place at random at a constant rate $\upsilon$ and the infected T-4 cell entering the population by this process are assumed to be in phase 1.

(v) The infected T-4 cell can emigrate at a constant rate $\eta$ and this can happen in any phase.
4.2.3 Method of Moments

4.2.3.1 Notation

It is convenient to introduce the following notation

\[ X_i(t) \] number of infected T-4 cells in phase i at time t, i=1,2,...,n

\[ X(t) \] the total number of infected T-4 cells at time t

\[ g_i(z_1, z_2, ..., z_n, z; t) \] the joint probability generating function of \( X_i(t) \) and \( X(t) \) in the absence of immigration. Symbolically, we have

\[
\begin{align*}
g_i(z_1, z_2, ..., z_n, z; t) &= \mathbb{E} \left( \prod_{j=1}^{n} z_j^{X_j(t)} \bigg| X_i(0) = X(0) = 1, u=0 \right), \quad i=1,2,...,n \\
g(z_1, z_2, ..., z_n, z; t) &= \mathbb{E} \left( \prod_{j=1}^{n} z_j^{X_j(t)} \bigg| X_i(0) = X(0) = 0, u\neq0 \right), \quad i=1,2,...,n
\end{align*}
\]
Now to find the connecting relation between \( g \) and \( g_1 \) we note that in view of the conditioning on the right hand side of equation (4.2.2) that somewhere in the interval \((\tau, \tau + d\tau)\) contained in \((0, t)\), the first immigration occurs with probability \( v e^{\nu t} d\tau \) and that the infected T-4 cell is in phase 1 and it generates a population independent of further immigration over the interval \((\tau, t)\). Hence we have

\[
g(z_1, z_2, \ldots, z_n, z; t) = v \int_0^t (\exp (-\nu \tau) g_1(z_1, z_2, \ldots, z_n, z; t - \tau) g(z_1, z_2, \ldots, z_n, z; t - \tau) d\tau + e^{\nu t}
\]

where the second term arises from the possibility that there is no immigration in \((0, t)\). The above integral equation can be converted into a differential equation for \( g(z_1, z_2, \ldots, z_n, z; t) \) whose solution is given by

\[
g(z_1, z_2, \ldots, z_n, z; t) = \exp \left\{ -\nu \int_0^t (1 - g_1(z_1, z_2, \ldots, z_n, z; \tau) d\tau) \right\}
\]

Next we set up the differential equations satisfied by the generating function \( g_i(z_1, z_2, \ldots, z_n, z; t) \). To do this, we note that since the duration of the phase in which any particular infected T-4 cell is found to be exponentially distributed, it enjoys a constant rate \( \alpha_i \), \( i = 1, 2, \ldots, n-1 \) of transition to the next phase. We use this property to determine the equation satisfied by the function \( g_i(z_1, z_2, \ldots, z_n, z; t) \). In particular, use of backward differential equation gives

\[
\frac{\partial g_i}{\partial t} = - (\alpha_i + \lambda_i + \eta) g_i + \alpha_i g_{i+1} + \mu g_i^2 + \eta, \quad i = 1, 2, \ldots, n-1
\]

\[
\frac{\partial g_n}{\partial t} = - (\alpha_n + \mu + \eta) g_n + \mu + \eta + \alpha_n.
\]
where for simplicity of notation, we denote \( g_i(z_1, z_2, ..., z_n, z; t) \) by \( g_i \), \( i=1,2,\ldots,n \). The \( g_i \)'s are subject to initial conditions

\[ g_i(z_1, z_2, ..., z_n, z; 0) = z_i z, \quad i=1,2,\ldots,n. \]

The death-rate in the last phase is taken as \( \mu + \alpha_n \). Hence our object is to obtain the steady-state or limiting distribution of infected T-4 cells and this is best done by taking the limit as \( t \to \infty \) in \( g(z_1, z_2, ..., z_n, z; t) \).

### 4.2.3.2 Moments of Infected T-4 cells

We define the moments \( a_i(t), a_i'(t), a(t), b_j(t), b_k^{ij}(t) \) and \( b(t) \) by

\[
\begin{align*}
    a_i'(t) &= \frac{\partial g_i}{\partial z_i} \bigg|_{z_1 = z_2 = \ldots = z_n = 1} \\
    a_i(t) &= \frac{\partial g_i}{\partial z} \bigg|_{z_1 = z_2 = \ldots = z_n = 1} \\
    a(t) &= \frac{\partial g}{\partial z} \bigg|_{z_1 = z_2 = \ldots = z_n = 1} \\
    b_k^{ij}(t) &= \frac{\partial^2 g_k}{\partial z_i \partial z_j} \bigg|_{z_1 = z_2 = \ldots = z_n = 1} \\
    b_j(t) &= \frac{\partial^2 g_j}{\partial z^2} \bigg|_{z_1 = z_2 = \ldots = z_n = 1} \\
    b(t) &= \frac{\partial^2 g}{\partial z^2} \bigg|_{z_1 = z_2 = \ldots = z_n = 1}, \quad (i=j=k=1,2,\ldots,n) \quad (4.2.6)
\end{align*}
\]
From equations (4.2.4) and (4.2.5) we obtain

\[
\frac{d}{dt} a_i^j(t) = - (\lambda_i - \lambda_j + \eta) a_i^j(t) + \alpha_i a_{i+1}^j(t), \quad i=1,2,...,n-1
\]

\[
\frac{d}{dt} a_n^j(t) = - (\alpha_n + \mu + \eta) a_n^j(t)
\]

\[
\frac{d}{dt} a_i(t) = - (\alpha_i - \lambda_i + \eta) a_i(t) + \alpha_i a_{i+1}(t), \quad i=1,2,...,n-1
\]

\[
\frac{d}{dt} a_n(t) = - (\alpha_n + \mu + \eta) a_n(t)
\]

\[
\frac{d}{dt} b_i^j(t) = - (\alpha_k - \lambda_k + \eta) b_i^j(t) + \alpha_k b_{k+1}^j(t) + 2\lambda_k (a_i^k(t) a_k^j(t)), \quad i=j=1,2,...,n, \quad k=1,2,...,n-1.
\]

\[
\frac{d}{dt} b_n^j(t) = - (\alpha_n - \lambda_n + \eta) b_n^j(t)
\]

\[
\frac{d}{dt} b_i(t) = - (\alpha_i - \lambda_i + \eta) b_i(t) + \alpha_i b_{i+1}(t) + 2\lambda_i [a_i(t)]^2, \quad i=1,2,...,n-1
\]

\[
\frac{d}{dt} b_n(t) = - (\alpha_n + \mu + \eta) b_n(t)
\]

with initial conditions

\[
a_i^j(0) = \begin{cases} 
1, & i=j \\
0, & \text{otherwise}
\end{cases}
\]

\(a_i(0)=1, \ b_i^j(0) = b_i(0) = 0, \quad i=j=k=1,2,...,n. \) (4.2.8)
From equation (4.2.3), it follows that

\[ a(t) = v \int_0^t a_1(\tau) \, d\tau \quad \text{and} \]

\[ b(t) = u \int_0^t b_1(\tau) \, d\tau + [a(t)]^2. \]

The above set of equations for \( a_i(t) \), \( a^{(i)}_i(t) \), \( b^{(i)}_i(t) \) and \( b^{(i)}_i(t) \) (\( i=j=k=1,2,\ldots, n \)) can be solved for any given \( n \) and the limit of \( a(t) \) and \( b(t) \) gives the first two factorial moments of infected T-4 cells. We shall illustrate this in section 4.2.3.4. We now proceed to analyse the emigration process.

**4.2.3.3 Emigration Process**

We are interested in the number of infected T-4 cells emigrated over an arbitrary interval \((t_0, t_0+t)\) (Shepherd (1981)). The model we are dealing with yields a stationary emigration process and hence we proceed in a manner analogous to that of section 4.2.3.1 and obtain the differential equations satisfied by the appropriate generating functions. We then differentiate the resulting equations to obtain the moment-structure of the number of infected T-4 cells emigrated over the interval \((t_0, t_0+t)\) or \((0,t)\). There is a second line of approach in which we can deal with the point process generated by the epochs of emigration. In this case, the point process of emigration can be characterised in terms of the sequence of coincidence functions (Kelley and Kleiner (1964)) known as product densities in the literature of point processes. These product densities are defined by

\[
f_1(t) = \lim_{\Delta \to 0} \Pr \left\{ \frac{N(t+\Delta)-N(t)}{\Delta} = 1 \mid \text{population in equilibrium initially} \right\} / \Delta
\]

\[ (4.2.11) \]
where $N(t)$ represents the number of infected T-4 cells emigrated over the interval $(0,t)$. Higher order product densities can be introduced in a similar manner. Also due to the stationarity of the process and the construction of the model we have

\[ f_1(t) = \text{a constant} \quad \text{and} \]

\[ f_2(t_1, t_2) = h_{sty}(t_2 - t_1). \tag{4.2.14} \]

To characterise the emigration process up to the second order, it is necessary to identify the constant on the right hand side of equation (4.2.13) and then determine the function $h_{sty}(\cdot)$. In the definition of product densities given above, the origin corresponds to the epoch at which the population is maintained in equilibrium and consequently direct determination of these product densities are not appropriate. Therefore to make further progress we introduce the conditional product densities by choosing convenient conditioning and then revert back to the equilibrium condition. Hence we define

\[ h_1(t) = \lim_{\Delta \to 0} \Pr \left\{ \frac{N(t+\Delta)-N(t)=1}{X_1(0) = X(0) = 1, \Delta=0} \right\} / \Delta \]

\[ h_1(t) = \lim_{\Delta \to 0} \Pr \left\{ \frac{N(t+\Delta)-N(t)=1}{X_1(0) = X(0) = 0, \Delta \neq 0} \right\} / \Delta \tag{4.2.15} \]

Next we observe that the function $h_1(\cdot)$ and $f_1(\cdot)$ are connected by the relation
\( f_{1}(\cdot) = \lim_{t \to \infty} h_{1}(t). \) (4.2.16)

To obtain \( h_{1}(t) \) we use the conditioning on the right hand side of equation (4.2.15) and observe that an infected T-4 cell may be emigrated at the epoch \( t \), it should happen by the process of immigration between 0 and \( t \) and that the infected T-4 cell which is emigrated at time \( t \), may be generated by the first immigration or subsequent one. Hence we have

\[
\begin{align*}
    h_{1}(t) &= u \int_{0}^{t} \exp(-v\tau) [h_{1}(t-\tau) + h_{1}^{1}(t-\tau)] \, d\tau \\
    &= u \int_{0}^{t} \exp(-v\tau) h_{1}(t-\tau) \, d\tau + u \int_{0}^{t} \exp(-v\tau) h_{1}^{1}(t-\tau) \, d\tau
    
\end{align*}
\] (4.2.17)

The above equation is solved to yield

\[
\begin{align*}
    h_{1}(t) &= u \int_{0}^{t} \exp(-v\tau) h_{1}(t-\tau) \, d\tau \\
    &= u \int_{0}^{t} h_{1}(t-\tau) \, d\tau
    
\end{align*}
\] (4.2.18)

Further to obtain \( h_{1}^{1}(t) \), we use the definition (4.2.15) directly and relate it to the moment \( a_{1}(t) \) as

\[
\begin{align*}
    h_{1}^{1}(t) &= \eta \int_{0}^{t} a_{1}(t) \, dt \\
    f(\cdot) &= \int_{0}^{\infty} \eta a_{1}(\tau) \, d\tau
    
\end{align*}
\]

To obtain \( h_{st}(t) \) (for \( t > 0 \)), we note that the two emigrations separated by \( t \) can arise from the same population tree or from two different trees, in which case, the infected T-4 cell that is emigrated at time \( t \) is generated by an immigrated T-4 cell that entered between 0 and \( t \). Thus the contribution from the latter case can be seen to be \( f_{1}(\cdot) h_{1}(t) \). In the former case, we have the infected T-4 cell population maintained in equilibrium at the origin from which point of time one of the infected T-4 cell has emigrated. Taking into account that the emigrated T-4 cell could be in any one of the phases and
any one of the members of the remaining population can generate a population tree between 0 and t we obtain

\[
h_{sty}(t) = f(\cdot)h_1(t) + \eta \sum_{i=j=1}^{n} b_{ij} h_i(t).
\]

In the next section, we illustrate the problem with a special case.

4.2.3.4 Special Case

Now the generating functions for a two-phase model satisfy the following differential equations given by

\[
\frac{dg_1}{dt} (z_1, z_2, z; t) = - (\alpha_1 + \lambda_1 + \eta) g_1 + \alpha_1 g_2 + \lambda_1 g_1^2 + \eta 
\]

\[
(4.2.19)
\]

\[
\frac{dg_2}{dt} (z_1, z_2, z; t) = - (\alpha_2 + \mu + \eta) g_2 + \mu + \eta + \alpha_2 
\]

\[
(4.2.20)
\]

The first order moment-structure of the above equations yield

\[
\frac{d}{dt} a_j(t) = - (\alpha_j - \lambda_j + \eta) a_j(t) + \alpha_j a_j(t) 
\]

\[
(4.2.19')
\]

\[
\frac{d}{dt} a_j(t) = - (\alpha_j + \mu + \eta) a_j(t), \quad j=1,2
\]

\[
(4.2.20')
\]

with initial conditions given by

\[
a_1(0) = a_2(0) = 1, \quad a_1(0) = a_2(1) = 0.
\]

Solving equations (4.2.19) and (4.2.20) we get

\[
a_j(t) = e^{(\alpha_j - \lambda_j + \eta)t}
\]
\[ a_{12}^2(t) = \frac{\alpha_1}{c} \left[ e^{-at} - e^{-dt} \right] \]

where \( a = \alpha_1 \lambda_1 + \eta, \quad c = \alpha_2 - \alpha_1 + \lambda_1 + \mu, \quad d = \alpha_2 + \mu + \eta. \)

Differentiating twice the equations (4.2.19) and (4.2.20) successively we obtain

\[
\frac{d}{dt} b_{ij}^{(2)}(t) = -(\alpha_1 - \lambda_1 + \eta) b_{ij}^{(1)}(t) + \alpha_1 b_{ij}^{(2)}(t) + 2\lambda_1 (a_1(t) a_{ij}^{(1)}(t))
\]

\[
\frac{d}{dt} b_{ij}^{(2)}(t) = -(\alpha_2 + \mu + \eta) b_{ij}^{(2)}(t), \quad i=j=1,2.
\]

The above system of equations can be solved to arrive at an explicit expression for \( b_k^{(\nu)}(s) \) as

\[
b_{11}^{11}(t) = b_{12}^{12}(t) = b_{21}^{21}(t) = b_{22}^{22}(t) = 0
\]

\[
b_{12}^{12}(s) = b_{12}^{21}(s) = \frac{2\lambda_1 \alpha_1}{c(s+a)} \left[ \frac{1}{s+2a} - \frac{1}{s+f} \right]
\]

\[
b_{11}^{22}(s) = \frac{2\lambda_1 \alpha_1^2}{c^2(s+a)} \left[ \frac{1}{s+2a} + \frac{1}{s+2d} - \frac{2}{s+f} \right]
\]

\[
b_{11}^{11}(s) = \frac{2\lambda_1}{(s+2a)(s+a)}
\]

where \( f = \alpha_1 + \alpha_2 - \lambda_1 + \mu + 2\eta. \)
The moments and cross correlations of the equilibrium distribution can be obtained from (4.2.9) and (4.2.10) by taking the limit as $t \to \infty$ and are given by

$$a^{1}(\infty) = \frac{\nu}{a}, \quad a^{2}(\infty) = \frac{\nu \alpha_1}{ad}$$

$$b^{11}(\infty) = \frac{\lambda_1 \nu}{a^2} + \frac{\nu^2}{a^2}$$

$$\beta^{2}(\infty) = \beta^{1}(\infty) = \frac{2\lambda_1 \alpha_1 \nu}{ca} \left[ \frac{1}{2a} - \frac{1}{f} \right] + \frac{\nu^2 \alpha_1}{a^2 d}$$

$$\beta^{2}(\infty) = \frac{2\lambda_1 \alpha_1^2 \nu}{c^2 a} \left[ \frac{1}{2a} + \frac{1}{2d} - \frac{2}{f} \right].$$

Hence from section 4.2.3.3, we have

$$h_{st}(t) = \eta^2 \nu^2 \left\{ \frac{b}{ca} - \frac{\alpha_1}{cd} \right\}^2 + \eta^2 \nu \left\{ \frac{\lambda_1 b^2}{c^2 a^2} - \frac{2\lambda_1 \alpha_1 b}{fc^2 a} \right\} e^{-at}$$

$$+ \eta^2 \nu \left\{ \frac{\lambda_1 \alpha_1^2}{c^2 a d} - \frac{2\lambda_1 \alpha_1 b}{fc^2 a} \right\} e^{dt} \quad (4.2.21)$$

where $b = \alpha_2 + \lambda_1 + \mu$.

The above model is also dealt with the differential equations satisfied by the product densities of order one and two respectively in the following section.
4.2.4 Product Density Approach

4.2.4.1 n-Phase Model

For the n-phase model discussed in section 4.2.2, we once again recall that

\( X_j(t) \) \text{ number of infected T-4 cells in phase } i \text{ at time } t, \ i = 1,2,\ldots,n \n
\( X(t) \) \text{ total number of infected T-4 cells at time } t \n
\( N(t) \) \text{ number of infected T-4 cells emigrated in } (0,t) \n
\( h_j^*(t) \) \text{ the first order product density of the process } N(t) \text{ in the absence of immigration defined by} \n
\[ \lim_{\Delta \to 0} \frac{1}{\Delta} \Pr \left\{ \frac{N(t+\Delta) - N(t)}{\Delta} \right\} = 1 \quad X_j(0) = X(0) = 1, \forall i = 0,1,2,\ldots,n \n
\n
\( h_j(t) \) \text{ the first order product density of the process } N(t) \text{ in the presence of immigration defined by} \n
\[ \lim_{\Delta \to 0} \frac{1}{\Delta} \Pr \left\{ \frac{N(t+\Delta) - N(t)}{\Delta} \right\} = 1 \quad X_j(0) = X(0) = 0, \forall i = 1,2,\ldots,n \n
\n
\( h_{ij}(t_1,t_2) \) \text{ the second order product density of the process } N(t) \text{ in the absence of immigration given by} \n
\[ \lim_{\Delta_1 \Delta_2 \to 0} \frac{1}{\Delta_1 \Delta_2} \Pr \left\{ \frac{N(t_1+\Delta_1) - N(t_1)}{\Delta_1} \cdot \frac{N(t_2+\Delta_2) - N(t_2)}{\Delta_2} = 1 \right\} \quad X_j(0) = X(0) = 1, \forall i = 0,1,2,\ldots,n \n
\]
h_2(t_1,t_2) \quad \text{the second order product density of the process } N(t) \text{ in the presence of immigration given 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)}{N(t_2+\Delta_2) - N(t_2)} = 1 \right\} \quad X_2(0) = X(0) = 0, \nu \neq 0

To obtain the equation for h_i(t) (i=1,2,...,n-1), we note that the following mutually exclusive and exhaustive events of an infected T-4 cell which is in phase i, in the interval (0, \Delta)

i) can move to phase (i+1) with probability \(\alpha_i \Delta + o(\Delta)\);
ii) can undergo normal differentiation and emigrate with probability \((\lambda_i + \eta) \Delta + o(\Delta)\) and
iii) can continue to be in phase i with the residual probability \(1 - (\alpha_i + \lambda_i + \eta) \Delta + o(\Delta)\).

Hence we have

\[ h_i(t) = (1 - (\alpha_i + \lambda_i + \eta) \Delta) h_i(t-\Delta) + 2\lambda_i h_i(t-\Delta) + \alpha_i h_{i+1}(t-\Delta) + o(\Delta), \quad i = 1,2,...,n-1 \]

which leads to

\[ \frac{d}{dt} h_i(t) = - (\alpha_i - \lambda_i + \eta) h_i(t) + \alpha_i h_{i+1}(t), \quad i = 1,2,...,n-1. \]

(4.2.22)
On the other hand, if the infected T-4 cell is in phase $n$ initially, then in $(0,\Delta)$,

1) lysis or emigration can take place with probability $(\mu + \eta) \Delta + o(\Delta)$ and

2) can continue to be in the $n^{th}$ phase with the residual probability $1 - (\alpha_n + \mu + \eta) \Delta + o(\Delta)$.

Therefore

$$h_n(t) = ((\alpha_n + \mu + \eta) \Delta + o(\Delta)) h(t - \Delta) + o(\Delta)$$

which leads to

$$\frac{d}{dt} h_n(t) = -((\alpha_n + \mu + \eta) \Delta + o(\Delta)) h_n(t). \quad (4.2.23)$$

with initial conditions given by

$$h_i^1(0) = \eta_i, \quad i = 1, 2, ..., n.$$

The ultimate aim of this section is to obtain $h_1(t)$. Since the limit of $h_i(t)$ as $t \to \infty$ yields the stationarity product density of order one of the point process of emigration, one can note that in $(0,\Delta)$, the following mutually exclusive and exhaustive events are possible:

1) an infected T-4 cell can enter the system by immigration with probability $\nu \Delta + o(\Delta)$ and

2) no infected T-4 cell enters the system by immigration with probability $1 - \nu \Delta + o(\Delta)$. 
In case (i) the contribution to the first order product density arising from a single infected T-4 cell present at time \( \Delta \) is \( h_1^1(t-\Delta) \); in addition, there is a contribution due to immigration in \((\Delta,t)\) and this is given by \( h_1(t-\Delta) \). Therefore one has

\[
 h_1(t) = v \Delta \left[ h_1^1(t-\Delta) + h_1(t-\Delta) \right] + (1-v\Delta) h_1(t-\Delta) + o(\Delta)
\]

Proceeding to the limit as \( \Delta \to 0 \) one obtains

\[
 \frac{d}{dt} h_1(t) = v h_1^1(t) \tag{4.2.24}
\]

with the initial condition \( h_1(0) = 0 \).

Similarly the equations satisfied by \( h_i^j(t_1,t_2) \) (\( i=1,2,\ldots,n \)) are given by

\[
 \left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_i^j(t_1,t_2) = -(\alpha_i - \lambda_i + \eta) h_i^j(t_1,t_2) + 2\lambda_i h_i^1(t_1) h_i^1(t_2) + \alpha_i h_i^{j+1}(t), \quad i = 1,2,\ldots,n-1 \tag{4.2.25}
\]

\[
 \left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_i^n(t_1,t_2) = -(\alpha_i + \mu + \eta) h_i^n(t_1,t_2) \tag{4.2.26}
\]

with initial conditions

\[
 h_i^j(0,t_2) = 0, \quad i = 1,2,\ldots,n.
\]

Using similar arguments one has

\[
 \left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_2(t_1,t_2) = v h_2^1(t_1,t_2) + v [h_1(t_1) h_1^1(t_2) + h_1(t_2) h_1^1(t_1)] \tag{4.2.27}
\]
To solve the above equations (4.2.25) and (4.2.26) we use the well-known method of characteristics. Hence we have $t_2 - t_1 = \text{a constant}$. Now rewriting equations (4.2.25) and (4.2.26) using the transformation $t_1 = t_1$, $t = t_2 - t_1$ and indicating the transformed functions $h_2^1(t_1,t+\tau)$ by $h_2^1(t_1,t)$ (for convenience, $i = 1,2,...,n$), we have $h_2^* (s,t)$ to denote the Laplace transforms of the function $h_2(t_1,t)$ with reference to $t_1$. Hence the limiting solution of equation (4.2.27) as $s \to 0$ gives the stationarity distribution and this is given by

$$\lim_{t_1,t_2 \to \infty} h_2^1(t_1,t_2) = \lim_{s \to 0} s h_2^* (s,t) = h_{sy}(t). \quad (4.2.28)$$

In the following section, we deal the problem for $n=2$.

**4.2.4.2 Two-Phase Model**

Using the same notation as in the previous section for $i = 1,2$ we argue as follows. To obtain an equation for $h_1^1(t)$ one observes that in $(0,\Delta)$, the infected T-4 cell

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

ii) can undergo normal differentiation or emigrate with probability $(\lambda_1 + \eta) \Delta + o(\Delta)$ and

iii) can continue to be in phase 1 with the residual probability $1-(\alpha_1 + \lambda_1 + \eta) \Delta + \omega(\Delta)$.

Hence we have

$$h_1^1(t) = (1-(\alpha_1 + \lambda_1 + \eta) \Delta) h_1^1(t-\Delta) + \alpha_1 \Delta h_1^2(t-\Delta) + o(\Delta)$$

which leads to

$$\frac{d}{dt} h_1^1(t) = -(\alpha_1 + \lambda_1 + \eta) h_1^1(t) + \alpha_1 h_1^2(t) \quad (4.2.29)$$
Similarly one can obtain $h^2_1(t)$ as

$$\frac{d}{dt} h^2_1(t) = -(\alpha_2 + \mu + \eta) h^2_1(t)$$  \hspace{1cm} (4.2.30)$$

with initial conditions $h^1_i(0) = \eta$, \hspace{0.5cm} $i = 1,2$.

Solving the above system of equations (4.2.29) and (4.2.30) we get

$$h^1_i(t) = \frac{\eta}{c} \left[ b e^{-at} - \alpha_1 e^{\gamma dt} \right]$$ \hspace{0.5cm} and \hspace{0.5cm} (4.2.31)

$$h^2_i(t) = \eta e^{\gamma dt}$$

where

$$a = \alpha_1 - \lambda_1 + \eta, \hspace{0.5cm} b = \alpha_2 + \lambda_1 + \mu, \hspace{0.5cm} c = \alpha_2 - \alpha_1 + \lambda_1 + \mu \hspace{0.5cm} \text{and} \hspace{0.5cm} d = \alpha_2 + \mu + \eta.$$ 

Using equation (4.2.24) we obtain

$$h_1(t) = \eta u \left[ \frac{\alpha_2 + \lambda_1 + \mu}{ca} \frac{\alpha_1}{cd} - \frac{\alpha_2 + \lambda_1 + \mu}{ca} e^{\gamma at} + \frac{\alpha_1}{cd} e^{\gamma dt} \right]$$  \hspace{1cm} (4.2.32)$$

with

$$h_1(\infty) = \eta u \left[ \frac{\alpha_2 + \lambda_1 + \mu}{ca} \frac{\alpha_1}{cd} \right].$$  \hspace{1cm} (4.2.33)$$

Similarly the equations satisfied by $h^i_2(t_1,t_2)$, \hspace{0.5cm} $i = 1,2$ are given by

$$\left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h^1_2(t_1,t_2) = -(\alpha_1 - \lambda_1 + \eta) h^1_2(t_1,t_2)$$

$$+ 2\lambda_1 h^1_1(t_1) h^1_1(t_2) + \alpha_1 h^2_2(t_1,t_2)$$  \hspace{1cm} (4.2.34)$$
\[
\left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_2^2(t_1,t_2) = -(\alpha_2 + \mu + \eta) h_2^2(t_1,t_2)
\]

(4.2.35)

with initial conditions being

\[ h_2^1(0,t_2) = 0, \quad i = 1,2,...,n. \]

The equation for \( h_2(t_1,t_2) \) is given by

\[
\left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_2(t_1,t_2) = v h_2^2(t_1,t_2) + v \left[ h_1(t_1) h_2^1(t_2) + h_1(t_2) h_2^1(t_1) \right]
\]

(4.2.36)

with the initial condition \( h_2(0,t_2) = 0 \).

To solve equations (4.2.34) and (4.2.35) one can use the method of characteristics as discussed in section 4.2.4.1 and obtain \( h_2^*(s,t) \) as

\[
h_2^*(s,t) = \frac{2\lambda_1^2}{(s+a)^2} \left\{ \frac{(\alpha_2 + \lambda_1 + \mu)^2}{(s+2a) c^2} - \frac{\alpha_1(\alpha_2 + \lambda_1 + \mu)}{(s+f) c^2} \right\} e^{-at}
\]

\[
+ \left\{ \frac{\alpha_1^2}{c^2 (s+2d)} - \frac{\alpha_1(\alpha_2 + \lambda_1 + \mu)}{(s+f) c^2} \right\} e^{-dt}
\]

and the Laplace transforms solution of equation (4.2.36) is given by

\[
s h_2^*(s,t) = v h_2^1*(s,t) + \eta^2 v^2 \left[ \frac{\alpha_2 + \lambda_1 + \mu}{ac} - \frac{\alpha_1}{cd} \right]^2.
\]
As $s \to 0$ we have

$$h_{st}(t) = \eta^2 v^2 \left[ \frac{\alpha_2 + \lambda_1 + \mu}{ac} - \frac{\alpha_1}{cd} \right]^2 + 2\lambda_1 \eta^2 v$$

$$+ \left\{ \left[ \frac{(\alpha_2 + \lambda_1 + \mu)^2}{2a^2c^2} - \frac{\alpha_1 (\alpha_2 + \lambda_1 + \mu)}{f^2a} \right] e^{-at} ight.$$  

$$\left. + \left[ \frac{\alpha_1^2}{2c^2ad} - \frac{\alpha_1 (\alpha_2 + \lambda_1 + \mu)}{c^2fa} \right] e^{-dt} \right\}$$

(4.2.37)

which is in agreement with (4.2.21).

4.2.5 Interpretation of Results

For some specific parametric values namely $\alpha_1 = 0.2$, $\alpha_2 = 0.4$, $\mu = 0.2$, $\eta = 0.4$, $v = 0.5$ and for different values of $\lambda_1 = 0.025$, 0.05, 0.1 and 0.15, the expected number of infected T-4 cells are calculated and shown graphically. It is observed that from Figure 4.2.1 as time $t$ (in years) increases for different infection rates, the expected number of infected T-4 cells increases. It is also observed from Figure 4.2.2, for an increased value of $\alpha_2 = 0.6$, the expected number of infected T-4 cells increases. For the above parameteric values the stationarity distribution are tabulated for different values of time $t$ and emigration rate $\eta$ in Table 4.2.
Figure 4.2.1 Expected number of infected T-4 cells vs. time $t$ (in years) when $a_2 = 0.4$
Figure 4.2.2 Expected number of infected T-4 cells vs. time $t$ (in years) when $a_2=0.6$
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