University of Venda

Stochastic Modelling of HIV/AIDS Epidemiology with TB Co-infection and Drug Reaction in South Africa

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Declaration

I, Claris Shoko, declare that this thesis is the result of my own research except as cited in the references. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

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Dedication

A linear regression model was fitted to check if there is a significant linear relationship between state and time. The model is of the form $HIVprogression_i = \beta_{0i} + \beta_{1i} time + \varepsilon_i$, for every i^{th} individual in the study. I dedicate this research to my children, Zandile, Anenyasha and Matidashe.

Abstract

The study explores the stochastic approach to multi-state modeling of HIV dynamic evolution and identification of the model that best describes HIV progression on individuals under ART. The effects of TB co-infection, as well as the patients' development of adverse reaction to drugs to the transition rates are also examined. The study uses a cohort analysis of the surveillance data for HIV-infected patients under antiretroviral (ART) from the Wellness Clinic in Bela Bela, South Africa. The survey was conducted between 2005 and 2009 and a follow up was done after every 6 months. The method partitions the HIV infection period into five CD4-cell count intervals followed by the end points, that is, death and withdrawal from study. The analysis is based on transition probabilities, transition rates (hazards), mean sojourn times, and time to absorption. The effects of the covariates, namely sex, age, TB co-infection, drug reaction, body mass index (BMI), baseline viral load (VLBL) and the CD4+ cell count baseline on enrollment, on transition intensities for each model are also analysed. The likelihood ratio test is used to compare the fitted models, and the test shows that the time inhomogeneous model describes the data better than the time homogeneous models. The results show that the rates of immune recovery are generally higher than the rates of immune deterioration. The patients who developed TB during treatment have higher rates of immune deterioration than recovery. Having TB as the initial marker of AIDS has higher contributory effects to the deaths from all the stages except from the AIDS defining stage. Reaction to drugs was the leading cause of transition from a CD4+ cell count ≥ 750 to a CD4+ cell count between 500 and 750.

Keywords: Covariates; Homogeneous Markov models; Likelihood ratio test; Longitudinal data; Inhomogeneous Markov models.

List of Abbreviations

AIC	Akaike Information Criterion
AIDS	Acquired Immuno Deficiency Syndrome
ART	Anti-retro-viral therapy
BMI	Body mass index
CD4	Cluster Difference 4
CD4BL	Cluster Difference 4 Baseline
CTMC	Continuous time Markov chain
DTB	Develop TB
DTMC	Discrete time Markov chain
HIV	Human Immuno Virus
LRT	Log ratio test
MSM	Multi-state modeling
PWC	Piece-wise constant
SEIR	Susceptible Exposed Infective Recovered
SIR	Susceptible Infective Recovered
SI	Susceptible Infectious
TB	Tuberculosis
TBB4	Tuberculosis before enrollment
VLBL	Viral load baseline
WHO	World Health Organisation
WSBL	WHO stage baseline

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Chapter 1

Introduction

1.1 Background of the study

Epidemiology is the study of the distribution and determinants of health related states or events in specified populations, and the application of this study to the control of health problems (Last, 1995). Epidemiological modeling offers a personal perspective on the role of mathematical models in the study of the dynamics, evolution and control of infectious diseases (Castillo-Chavez and Lee, 2011). It seeks to answer questions of disease control such as: To what extent do preventive interventions reduce the incidence of diseases? To what extent does therapeutic intervention lead to cure or symptom relief? (Johnson, 2004). In this thesis, the effects of the intervention of anti-retro-viral therapy (ART) on the progression of HIV/AIDS on individuals is modeled using the multi-state modeling approach to epidemiology.

Currently, there are more than 30 million people, globally, who are infected with the human immunodeficiency virus (HIV), the cause of the acquired immunodeficiency syndrome (AIDS) (Wolbers *et al.*, 2010, Biase *et al.*, 2007). Out of all these infected people, about two thirds live in sub-Saharan Africa, although the region contains only about twenty percent of the world's population (AVERT, 2013a). Since the beginning of the epidemic, more than 15 million Africans have died from HIV-related illnesses (AVERT, 2013a). In 2010, about 1.2 million people (adults and children) died as a result of AIDS in sub-Saharan Africa. Statistics show that less than half of the people who need treatment in Africa are receiving it (AVERT, 2013a).

In the middle of 2006, about 5.4 million people in South Africa were HIV positive (Dorrington *et al.*, 2006). Out of the 5.4 million, about 11 percent were already sick with AIDS. Among the infected individuals, 1.3 million were under the age of 25 years, 3.5 million were pre-AIDS and 225 were receiving treatment (Dorrington, 2006).

The impact of the HIV/AIDS has certainly not been confined to the health sector. Households, schools, workplaces and economies have been badly affected (AVERT, 2013a). In African hospitals, most beds are occupied by patients with HIV-related illnesses, leading to shortages of beds, hence reducing the chances of survival. The financial burden on health care expenses and funeral costs push affected households into poverty. The epidemic has also impacted negatively on life expectancy as AIDS is erasing decades of progress in extending life expectancy (AVERT, 2013a). In the worst affected countries, average life expectancy has fallen by 20 percent. In Swaziland, which has the highest HIV prevalence in the world, life expectancy at birth is only 48.7 years (AVERT, 2013b). AIDS is hitting adults in their most economically productive years and removing the very people who could be responding to the crisis.

A WHO report on TB/HIV shows that 50 percent of HIV positive patients develop TB (WHO, 2011). TB infection usually happens at the early stages of HIV. As a result, TB has become one of the leading causes of death among HIV-infected patients. It accelerates the progression of HIV to AIDS. TB activates CD4+ cells and macrophages harboring latent HIV, resulting in an increase in HIV replication (Jantjie, 2009). HIV also results in the depletion of CD4+ cells and this reactivates latent TB.

1.2 HIV/AIDS disease and treatment

The HIV/AIDS disease is a continuum of progressive damage to the immune system from the time of infection to the manifestation of severe immunologic damage by opportunistic infections, neoplasm, wasting or low CD4+T cell count that define AIDS (Biase et al, 2007). Some clinical markers such as the CD4+T cell count and the RNA viral load help a lot in providing information on disease progress. A normal CD4+T cell count varies from individual to individual, and it is usually between 800 and 1500 cells per mm^3. CD4+ cell count values below 500 are usually an indication of immune suppression and vulnerability to opportunistic infections (Health 24, 2003). These opportunistic infections can include TB, pneumonia, diarrhoea and many others.

HIV infection gradually evolves into AIDS and AIDS leads to death if not properly handled. Anti-retro viral therapy (ART) has helped quite significantly in reducing morbidity and mortality. South Africa has recently had one of the largest increases in treatment access in the world, with a scale-up of treatment services of 75 percent between 2009 and 2011 (International HIV and AIDS, 2013). However, understanding the progression of HIV and factors that influence the disease's progression helps in understanding pathogenesis and the development of new treatment strategies. Figure 1.1 shows a typical progression of HIV for an individual who is not on treatment (www.hiv-monitoring.nl).

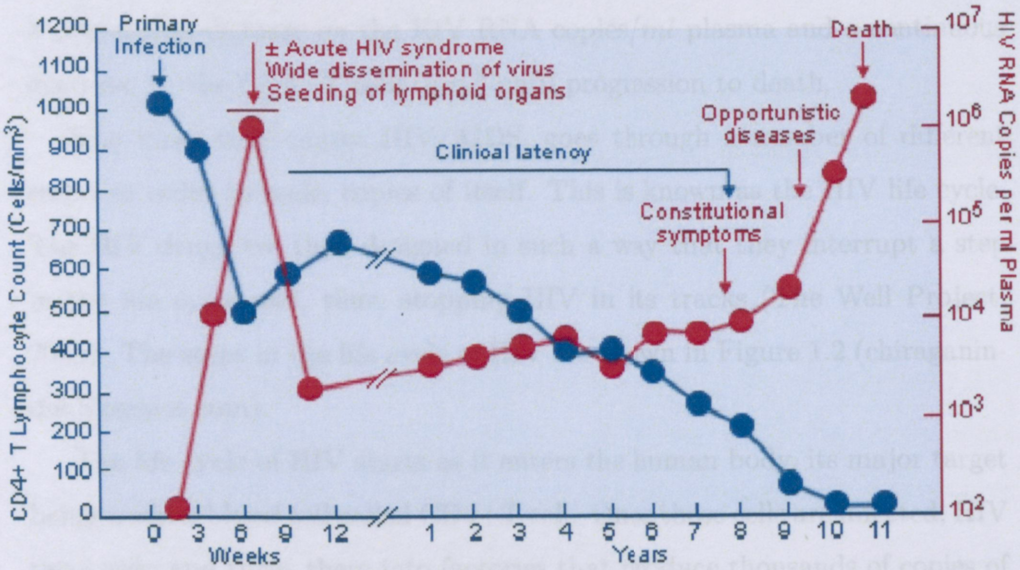


Figure 1.1: *Progression of HIV in a no-treatment scenario*

Figure 1.1 shows that from the time of primary infection, an individual can live for up to 10 years if no treatment is administered. This is supported by Yadavalli *et al.* (2010) who says that people who are infected with HIV can live for approximately 10 years on average before the onset of AIDS. This period is referred to as the incubation period or the clinical latency period. During this period, the individual appears to be very well, leading to a significant contribution to the spread of the epidemic. The graph also shows an inverse relationship between the CD4+T cells/mm^3 and the HIV RNA copies/ml plasma. However, around the 12^{th} week after infection, there is a sharp decrease on the HIV RNA copies/ml plasma and a slight increase on the CD4+T cells/mm^3. This is due to immune response. Thereafter, there is a continuous increase on the HIV RNA copies/ml plasma and a continuous decrease on the CD4+T cells/mm^3 until progression to death.

The virus that causes HIV/AIDS, goes through a number of different steps, in order to make copies of itself. This is known as the HIV life cycle. The HIV drugs are then designed in such a way that they interrupt a step in the life cycle and, thus, stopping HIV in its tracks (The Well Project, 2012). The steps in the life cycle of HIV are shown in Figure 1.2 (chiraganindia.blogspot.com).

The life cycle of HIV starts as it enters the human body, its major target being a white blood cell called CD4+T cell. Once these cells are infected, HIV takes over and turns them into factories that produce thousands of copies of the virus. The HIV makes use of the enzyme Reverse Transcriptase to change copies of its Ribonucleic Acid (RNA) into Deoxyribose nucleic Acid (DNA). The viral DNA then enters the nucleus of the host cell and combines with cell DNA and starts making copies of viral RNA. The enzyme protease helps in assembling the viral particles into thousands of new viruses, which will bud and destroy the host cell. These new viruses will then be ready to attack other CD4+T cells. Hence, the importance of CD4+T cell count in understanding the progression of HIV. Depreciation of the CD4+T cells in the human body

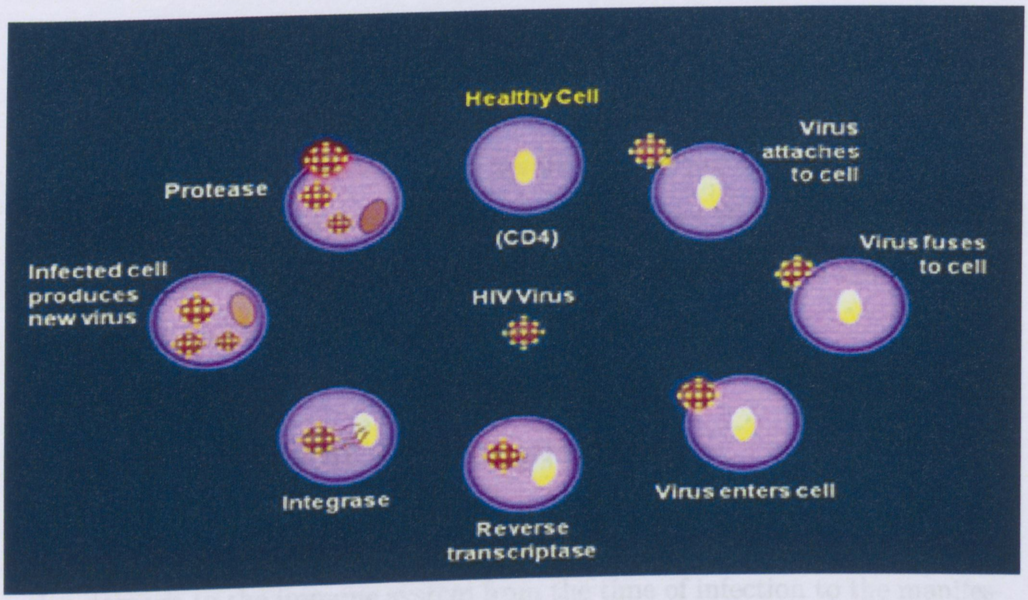


Figure 1.2: *HIV life cycle*

leads to the depreciation of the human immune system, which is why the virus is called the Human Immunodeficiency Virus (HIV). As the immune system depreciates, the individual is now prone to opportunistic infections like TB, diarrhoea, malaria, to mention a few.

There are basically four groups of antiretroviral drugs, those that target the reverse transcription of the viral RNA to DNA known as reverse transcriptase inhibitors and those that target viral protein production known as Protease inhibitors. The protease inhibitors prevent the infected CD4+T cell from producing infectious viruses. Drugs from different classes are often combined so that the virus is attacked at more than one step in the life cycle. This is so because when the virus reproduces, it mutates and certain mutations keep certain drugs from working, thereby causing HIV to be resistant to a particular HIV drug. The intake of a combination of drugs from different classes gives HIV a much harder time changing enough to develop drug resistance. Thus, combination therapy blocks HIV at different steps, preventing the production of new HIV. Thus, in turn, slows down disease progression and ensure a longer life for HIV+ people.

1.3 Statement of the problem

HIV/AIDS disease has been defined in Section 1.2 as a continuum of progressive damage to the immune system from the time of infection to the manifestation of severe immunologic damage by opportunistic infections, neoplasm, wasting or low CD4+T cell count that define AIDS. There is need to explore the HIV progression in an infected individual and assess whether it is time-homogeneous or not. Individuals on anti-retroviral drugs tend to develop some adverse reaction, so we need to know how these reactions affect the progression of HIV. During the early stages of HIV/AIDS, some individuals tend to develop TB prior and even after treatment. This begs for question: How does this affect the HIV progression?

1.3.1 Aim

The main aim of this research is to model the effects of having TB and reacting to drugs on the progression of HIV in patients under the ART follow-up programme using Markov processes.

1.3.2 Research questions

The developed models were then used to answer the following questions:

- What are the effects of developing TB or reacting to drugs on the HIV progression for any given individual?

- How do people who start treatment at low CD4+T cell count levels ($< 350mm^3$) compare to those who start at high CD4+T cell count levels ($\geq 350mm^3$) in terms of transition intensities?

- What are the transition rates 5 or more years post commencement of treatment?

- How do the variables gender and age affect the progression of HIV, that is, do males respond more positively to treatment than females? Do younger patients respond positively to treatment than older patients?

1.3.3 Definition of terms

• **Reaction to treatment**: Refers to adverse reactions to treatment.
• **HIV progression**: This is when a patient moves from one state of CD4+T cell count to a poor state of CD4+T cell count

1.4 Research methodology

Standard survival analysis techniques such as the Kaplan Meier survival curves and Cox regression are used to study the time to event data. However, these techniques fail to describe the sequence of events, and to utilise full information on longitudinal data involving multiple events. With the use of longitudinal data, Markov processes possess a potential solution to the modelling of the sequence of events. Examination of the conditions of the stochastic processes at various points in time, categorisation of the conditions, and examination of the external influences on the stochastic processes can be done using Markov models (Mullins, 1996). Markov processes are favourable to the modelling of diseases when the disease is grouped into a set of exhaustive and mutually exclusive health states, thereby forming a multi-state model (Foucher *et al.*, 2005).

Multi-state models are stochastic continuous time Markov models that allow computation of transition probabilities, transition rates (hazards), mean sojourn time (mean time spent in each state) and the modelling of the effects of covariates on transition rates. History is naturally generated as the multi-states evolve over time; it contains information on previous visits, time to entry into various states, and the length of stay in states, thereby forming multi-state models.

Markov chain models are increasingly used to model progression of chronic diseases, for example, cancer (Duffy *et al.*, 1995, Yen and Chen, 2007), stroke (Pan *et al.*, 2007) and diabetic retinopathy (Marshal and Jones, 1995). These models are quite useful for the study of both natural history and progressions of related diseases.

This dissertation proposes a Markov chain model defined by 7 states. The first five states are the CD4+ cell count intervals and the next two are the absorbing states, death and withdrawal from the hospital or treatment respectively. The five states based on CD4+ cell count intervals are: CD4

≥ 750, $[500, 750)$, $[350, 500)$, $[200, 350)$ and $[0, 200)$. The stage [0, 200) is normally defined as the AIDS defining stage. The good state, which is normally defined as $CD4 \geq 500$, was further split into two states, in order to observe if there are any possible backward transitions once an individual is in that state.

In this dissertation, stochastic modelling is applied on 318 HIV patients under ART follow up in Bela Bela Wellness clinic. Some of the patients were initiated on ART with TB being the initial marker of HIV, others were initiated based on their WHO stage baseline, while others were on the AIDS defining stage. All of the patients in the study were monitored after every 6 months. For every visit, the CD4+T cell count, body mass index (BMI), viral load, any adverse reaction to treatment and development of TB were noted. When the HIV infected patients were enrolled at the Wellness Clinic, they were given different antiretroviral combination therapy. Table 1.1 shows the different regimens that were administered to the 318 patients.

Table 1.1 shows that the majority of the patients were initially given a combination of d4T, 3TC and EFV (efavirenz). EFV is the most preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on TB treatment (WHO, 2009).

In this study, time homogeneous models and the time inhomogeneous models are built. These models are used to assess the effectiveness of the treatment by comparing the forward transition and the reverse transitions. This then leads to the building of models that allow transitions in both directions. The effects of having TB as an initial marker, developing TB during the course of treatment, reaction to treatment, gender, age, baseline

Table 1.1: Combination therapy on enrollment

Initial Combination Therapy	Frequency	Percentage
Missing	5	1.6
ABC-AZT-3TC	1	0.3
AZT-3TC	1	0.3
AZT-3TC-EFV	5	1.6
AZT-3TC-LPV/r	4	1.2
AZT-3TC-NVP	2	0.6
AZT-LPV/r	1	0.3
d4T-3TC-EFV	206	64.8
d4T-3TC-LPV/r	3	0.9
d4T-3TC-NVP	83	26.1
d4T-ddl	1	0.3
d4T-ddl-EFV	6	1.8
Total	318	100

viral load (VLBL), WHO stage baseline (WSBL) and CD4+ cell baseline (CD4BL) on the progression of HIV/AIDS were analysed. For these data, a time homogeneous model and a time inhomogeneous model were fitted and a likelihood ratio test was used to select the model that fits best.

However, before the Markov models were fitted, the linear relationship between progression of HIV and time was assessed and further analysis on the effects of the covariates on progression was done by fitting Aalen's additive regression model.

1.5 Limitations of the study

The data that were used for building the models was collected from 2005 to 2009 on six month intervals. This data were recorded at person-level, so it had to be converted to person-period for analysis purposes. Some individuals, in the study, were just enrolled, but no follow-up on their progression was done. Such individuals were not considered since there was no follow-up information. Individuals who were enrolled in 2004 and 2005 started treatment at almost the same time, hence these were the ones that were considered for analysis.

1.6 Structure of the thesis

Figure 1.3 is a mind map that shows a summary of the general structure of the thesis.

Chapter 2 explores the theory of disease modelling with particular emphasis on stochastic modelling. The differences between deterministic modelling and stochastic modelling approaches to disease modelling are discussed, as well as a justification to the use of stochastic Markov process in this thesis. Chapter 2 also gives a brief discussion of continuous time and discrete time stochastic processes. In Chapter 3, preliminary analysis of the data is done using linear regression analysis and Aalen's additive regression model. Chapter 4 builds a time homogeneous model for HIV data and, in Chapter 5, the inhomogeneous model is built. Comparison of the fitted homogeneous model and the fitted inhomogeneous models is done in Chapter 6. Finally, Chapter 7 gives a conclusion based on the findings from the analysis done

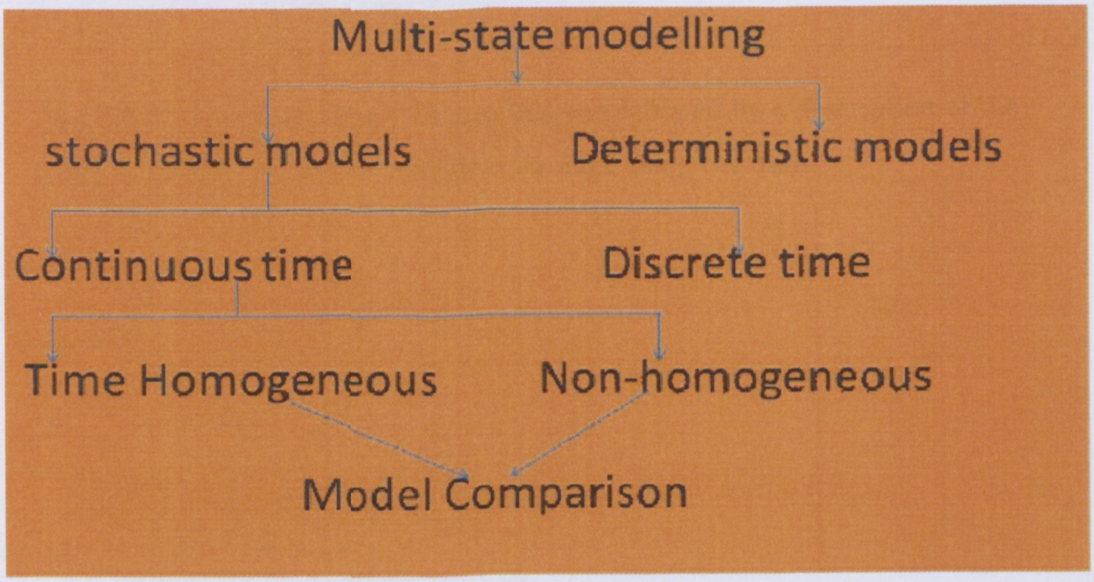


Figure 1.3: *Structure of the thesis*

from Chapter 3 to 6. It also gives directions for future studies emanating from this thesis.

1.7 Summary

In this chapter, the global view pertaining to HIV was discussed. This was followed by the African perspective, and then further narrowed down to South Africa, which is the study area for this thesis. The progression of HIV in an individual given a no-treatment scenario has been discussed and illustrated by use of diagrams. The life cycle of HIV in an individual has also been illustrated and the discussion as to how this relates to treatment was done. A justification as to why the study of HIV progression can best be described by Markov processes was given and this was followed by a description of the data and how the Markov models were built using the data.

Chapter 2

Literature Review

2.1 Introduction

This chapter reviews related literature on previous studies of HIV/AIDS disease progression using Markov chain modelling. Gaps to be filled are also identified. The modelling techniques used in the dissertation, as well as the theory of multi-state modelling in analysing the progression of diseases in an individual (stochastic) or within a population (deterministic) are discussed. State diagrams are used to illustrate various structures of disease progression which gives rise to the formulation of multi-state models in the context of stochastic modelling. The chapter also justifies why stochastic processes are an important tool for this research. Techniques for assessing model fit are discussed. These techniques include the likelihood ratio test for time homogeneous and the contingency table based method.

2.2 Previous stochastic modelling on HIV/AIDS

This section seeks to review the previous research work on the use of stochastic processes to model the progression of HIV. It starts by looking at research that has been done in South Africa and then moves on to look at the research that has been done in other countries. The similarities and differences of these researches and this dissertation are highlighted.

In 2011, Reddy carried out a research on the application of multistate Markov models to HIV disease progression of 451 patients from McCords hospital in South Africa. The progression of HIV was divided into 5 states, four of which were based on CD4 counts and the last one was based on anti-retro-viral (ARV) initiation. The research considered ARV initiation as the absorbing state. The effects of age, gender and baseline CD4 count on the transition intensities were analysed. The developed model allowed reversible transitions, and comparison of forward transitions with backward transitions was done. The results from the research showed that transitions to better states were lower than transitions to worst states.

This research is similar to Reddy's research in the sense that it also considers the progression of HIV as having forward and backward transitions. Gender and age are also considered as covariates in this research. However, the researches differ in that this research is carried out on patients who are already on treatment, whereas the one by Reddy was carried out on patients prior to treatment. Instead of using survival analysis to analyse the effects of TB co-infection, this research uses time homogeneous Markov models. It goes further to analyse the effects of developing adverse reaction to drugs on the progression of HIV. For Reddy, the main focus was natural immune deterioration, whereas the main focus of the current research is immune recovery through treatment since all the individuals in this study had already started treatment.

Goshu and Dessie, in 2013, applied semi-Markov processes in modeling the progression of HIV disease stages using a cohort of 710 HIV patients on follow-up from June 2005 to August 2009 at Flege-Hiwot referral hospital in Ethiopia. The first four states of their study are similar to the ones in Reddy's study. The only difference is in the absorbing state, which, in their case, was death, while for Reddy the absorbing state was ART initiation. The five states which were used by Goshu and Dessie are also used in this research. However, there is an addition of another absorbing state, that is, withdrawal from the treatment, and a further splitting of the state CD4>500 into two states. Instead of using five states, as Goshu and Dessie did, this thesis has 7 states. This research focuses on application of time homogeneous and non-homogeneous Markov models and not the semi-Markov models, as proposed by Goshu and Dessie.

Yadavalli *et al.* (2009) proposed a stochastic model under combined therapeutic treatment by extending the model of the HIV pathogenesis under treatment by anti-viral drugs. Simulated data before and after treatment were compared. The results showed the importance of combined treatment and its overall effects. Using empirical data from Rakai studies in Uganda, Gray *et al.* (2009), also used stochastic simulation to model the effect of anti-retro-viral therapy and HIV vaccine on HIV transmission.

In 1998, Alioum carried out research on the effects of age and gender on HIV progression, using three categories, namely homosexual, heterosexual and individuals infected using injections. Alioum used a 3-state Markov model for his research. The research showed that AIDS was more rapid with older subjects than younger subjects regardless of the category. Alioum discovered that ART slows down disease progression, with females responding more positively to treatment than males.

However, Alioum could not carry out his research using the CD4+T count levels because of the unavailability of information. For this research, analysis is carried out on all individuals in the study regardless of their sexual behaviour or the mode of transmission of the HIV to individuals. In this research, the effects of gender and age on the progression is also analysed. This thesis goes further to analyse the effects of CD4+T cell baseline, TB co-infection, reaction to drugs WHO stage baseline, viral load baseline on the progression of HIV. CD4+T cell counts are used to define the different stages in the progression because the information was available.

In 2007, Biase carried out research on the stochastic modelling for the HIV/AIDS dynamic evolution using five states. The first four states were defined according to the CDC immunological classification as defined by WHO. The findings showed that having CD4+ T cell count $\leq$200 increases the probability of reaching the death state, and that there are less chances of being in a better state than being in a worst state. Two absorbing states are included, namely death and withdrawal. The effects of TB and the development of adverse reaction to treatment in all stages of HIV progression are addressed in this thesis.

In the next section the modelling framework for this thesis is discussed.

2.3 Disease Modelling Framework

In general multi-state models are typically used to describe various states that a sick individual can be in. Disease models provide planners with a direct measure of the demographic effect of a disease or an indication of the likely future evolution of the epidemic. They also simulate the likely effect of the prevention and treatment programmes. The most general two categories of disease models are the individual-based stochastic simulation models and deterministic models (Johnson and Dorrington, 2006). The stochastic models are probability models that describe the random movements of an individual through a finite number of states (Titman, 2007). The deterministic models are classified into two groups, that is, epidemic and immunologic models, whereas the stochastic are classified based on whether time and state are discrete or continuous. Figure 2.1 gives a schematic diagram of how disease models are formulated.

The individual-based stochastic models treat each individual as a discrete entity and characteristics are determined separately for each individual. Population averages assume that all individuals in a population have identical characteristics. For example, in modelling HIV/AIDS, the deterministic model will use factors such as age and sex as characteristics to define cohorts. The cohorts are further classified according to disease status, that is susceptible and infected individuals without looking at the different stages of infection within an individual. A good example is the SIR multi-state model illustrated in Figure 2.7 in subsection 2.5.3. Stochastic processes allow the event, HIV-infection, to be simulated by random processes. These random processes will be defined according to the different states of the infection.

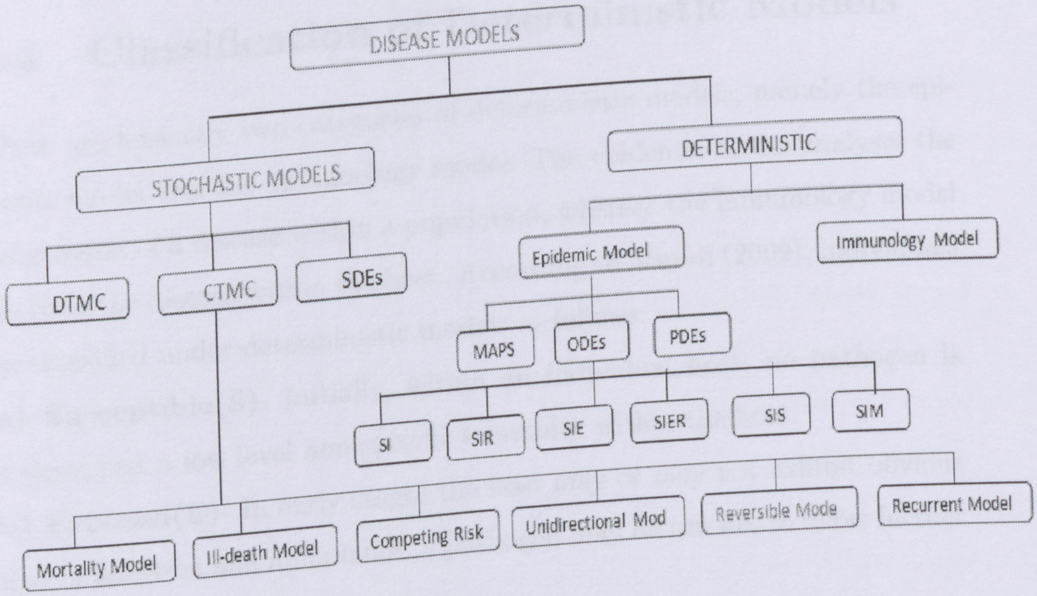


Figure 2.1: *Disease modelling*

The stochastic model generates different solutions each time it is run because the answers depend on the actual simulation of the random variable. As a result, the theory of stochastic modelling is based on the probability theory. The deterministic models, unlike the stochastic models, generate unique solutions since they are based on averages. Stochastic models provide the probability, taking into account the variability in the process due to deaths, transitions and the environmental variability that impacts on the biological process (Allen, 2010).

2.4 Classification of Deterministic Models

There are basically two categories of deterministic models, namely the epidemic model and the immunology model. The epidemic model analyses the progression of a disease within a population, whereas the immunology model analyses the disease within the host. According to Murali (2009), individuals are classified under deterministic models as follows:

(a) **Susceptible(S)**- Initially, within an individual/host, no pathogen is present; just a low level non-specific immunity within the host.

(b) **Exposed(E)**- In early stages the host may or may not exhibit obvious signs of infection and abundance of pathogen may be too low to allow further transmission.

(c) **Infectious(I)**- Host encounters infectious individual and becomes infected with a microparasite; abundance of the parasite grows with time.

(d) **Recovered(R)**- The host is either no longer infectious or is 'removed' (dead).

Classification of deterministic models depends solely on the ability of the host to transmit the pathogen. The health status of an individual is not relevant since an individual who is perfectly healthy can be excreting large amounts of pathogen. It is also important to note that, in reality, boundaries between exposed and infectious and infectious and recovered are fuzzy since the ability to transmit the pathogen is not binary (on-off).

2.4.1 Formulation of deterministic models

Deterministic models are formulated by combining different classifications of the disease within a population. It is also based on whether there is a possibility of recovering once individuals are infected by a particular pathogen.

Most deterministic models ignore the exposed class resulting in the SIR dynamics model. The SIR model divides the population into three classes that are, namely susceptible, $S(t)$, containing individuals who have the potential to develop the disease, infective $I(t)$, containing individuals who are capable of infecting the susceptible; and recovered $R(t)$, containing individuals that are no longer infectious. The SIR model is appropriate for disease, in particular, sexually transmitted infections like gonorrhoea because once recovered, the host is once again susceptible to infection. The Susceptible Infectious (SI) model is useful for some hosts that remain infectious until they die. For example with HIV infection, once an individual is in the infectious state he/she remains in that state until death.

Diseases like meningitis and chlamydia, require model specification with more classes of individuals, so they will not fit into SEIR classification. This is when stochastic processes come in because they are capable of classifying diseases into a finite number of states. Although the deterministic models can accommodate large data sets compared to the stochastic models, they fail to allow for changes over the course of the epidemic in the age profile of HIV cases and difficulties in establishing parameters of a cohort component projection model in a hypothetical 'no AIDS' scenario (Johnson and Dorrington, 2006).

2.5 Classification of Stochastic Models

Methods and techniques for formulating, analysing and numerically computing solutions of stochastic processes depend on whether the random variable $X(t)$, the state of a patient at any given time, or the index set (T_n) are discrete or continuous. Based on this, three types of stochastic models can be used, namely (1) A type where both time and the random variables are discrete-valued (discrete-time Markov chains (DTMC)), (2) A type where time is continuous and random variables are discrete (continuous-time Markov chains (CTMC)), and (3) Both time and random variables are continuous. This is referred to as diffusion processes, where the stochastic realisation $X(t)$ is a solution of a stochastic differential equation (SDE).

CTMC is particularly useful because it allows for interval censoring and unequally spaced observations, which are both common features of data in longitudinal studies of disease progression where subjects may be observed at discrete follow-up visits, which may occur at irregular times (Hubbard and Zhou, 2011).

Interval censoring occurs when the event of interest is known to have occurred between two time points. In monitoring the progression of HIV/AIDS in an individual, the exact time of occurrence of movements from one state to the other is not known, only the interval between which a transition has occurred is known. As a result, the data generated is known to be interval censored, hence the importance of CTMC models in this thesis.

The transition probabilities and the distribution functions associated with the times are the basic building blocks of the stochastic Markov processes (Halim, 1996). For a CTMC, transitions can occur at any (real-valued) time instant and these are modeled using exponential distributions. The exponential distributions are adequate for many real-life situations, for example, time until a radioactive particle decays (or time until death), and time it takes before your next telephone call (or waiting time before moving to another state). The exponential distributions are the only memoryless continuous distributions, hence their application in Markov processes.

The methods for studying CTMC include the forward and backward Kolmogorov differential equations and these are discussed in detail in chapter 4. The Kolmogorov differential equations are the ones that are used to calculate the forward and backward transitions between states.

2.5.1 Key aspects of continuous time Markov models

According to Mullins (1996), the charasterisation of continuous time Markov models is based on six basic attributes, namely states, stages, actions, rewards, transitions and constraints. These attributes are defined as follows:

(a) States

States refer to a complete set of mutually exclusive alternatives under which a system operates. In medical studies, these states represent various levels of disease progression. For mathematical simplification, these states are assumed to be finite because a complete set of the description of each state generally is provided. These states are either transient or absorbing. The transient states are the ones in which once entered they can be exited with certainty. The absorbing states are the ones in which once entered there is no escape. Examples of absorbing states are death, HIV+, early onset of cancer.

(b) Stages

For a Markov model, the stages are the points and times when the system is observed and data is collected. Markov models can accommodate either constant or random time intervals between stages.

(c) Actions/Decisions

At each stage of data collection, an action based on the state of the individual may be taken. In disease modelling, the actions may include a drug regiment, surgery, dietary modification, or no action at all. In the context of this thesis, when HIV+ individuals developed some adverse reactions to treatment, it resulted in the change of the combination therapy of the ARVs. If a patient developed TB during the course of treatment, the drug regimen was also changed. The effects of these treatment protocols can be analysed using Markov models.

(d) Rewards/Benefits

The major aim of the actions above is to achieve a certain goal, which could be recovery, extended years of life, or increased quality of life. As patients move from state to state, Markov process results in a sequence of rewards. The reward stream is a random variable, whose probability distribution is reflected by the nature of the Markov process itself and the sequences of actions taken.

(e) State transitions

The transitions for a Markov process describe the likelihood of being in a particular state at some future state given the current state. These transitions determine the probability distribution of the Markov random variable. For example, for three mutually-exclusive states denoted by X_j for $j = 1, 2, 3$; given state X_j, there are three associated probabilities, p_{ij}, that describe the probability of making transitions from state i to each of the three states over an interval of time equal to t, one of them being the probability of remaining in the same state.

2.5.2 Classification of states

The knowledge of the accessibility of a state is important in the study of Markov processes because it gives the basis for the classification of states. Markov chains are classified as follows: Communicating or not communicating, absorbing or transient, steady-state, and periodic of a state (Allen, 2010). The next subsection explores these classifications. For clarification, examples are used . Some properties for the various classifications are also mentioned.

(a) Communicating classes

State j can be reached from state i, written $i \longrightarrow j$, if there is a non-zero probability, $p_{ij}^{(n)} > 0$ for some $n \geq 0$ where n is the number of steps a process takes to transit from i to j. In addition, if $i \longrightarrow j$ and $j \longrightarrow i$, i and j are said to communicate, or to be in the same class, denoted $i \longleftrightarrow j$; that is, there exists n and n' : $p_{ji}^{(n)} > 0$ and $p_{ji}^{(n')} > 0$. The communicating classes satisfy the following properties:

1. Reflexivity: $i \longleftrightarrow i$, because $p_{ii}^{(0)} = 1$. Beginning in state i the system stays in state i if there is no time change.

2. Symmetry: $i \longleftrightarrow j$ implies $j \longleftrightarrow i$ following from the definition.

3. Transitivity: $i \longleftrightarrow j, j \longleftrightarrow k$ implies $i \longleftrightarrow k$. The first two properties imply that there exists non-negative integers n and m: $p_{ji}^{(n)} > 0$ and $p_{kj}^{(m)} > 0$. Thus,

$$
\begin{aligned}
p_{ki}^{n+m} &= Prob\{X_{n+m} = k | X_0 = i\}, && (2.1)\\
&\geq Prob\{X_{n+m} = k, X_n = j | X_0 = i\}, && (2.2)\\
&= Prob\{X_{n+m} = k | X_n = j\} Prob\{X_n = j | X_0 = i\}, && (2.3)\\
&= p_{kj}^{(m)} p_{ji}^{(n)}. && (2.4)\\
& && (2.5)
\end{aligned}
$$

Thus, $p^{(n+m)} > 0$ and $i \longrightarrow k$.

Similarly, it can be shown that $p_{ik}^{(n+m)} > 0 \Longrightarrow k \longrightarrow i$.

A set of states C is said to be closed if it is impossible to reach to any state outside of C by one-step transitions; $p_{ij} = 0$ if $i \in C$ and $j \in C'$.

If there is only one communicating class, then the Markov chain is said to be irreducible, but if there is more than one communicating class, then the Markov chain is said to be reducible.

(i) Irreducible/reducible

A Markov chain is said to be irreducible if there is only one communication class, that is, if it is possible to get to any state from any given state. Otherwise, it is said to be reducible. For a reducible stochastic matrix, the transition probability matrix P can be written as follows:

$$P = \begin{pmatrix} T_{11} & T_{12} \\ O & T_{22} \end{pmatrix} \tag{2.6}$$

where T_{11} is an r x r transition probability matrix (TPM) for the transitional states, T_{12} is an (r) x $(m-r)$ TPM representing movement from transient states to absorbing states, O is the $(m-r)$ x (r) with zero entries showing that transitions from the absorbing state are impossible and T_{22} is the $(m-r)$ x $(m-r)$ TPM matrix representing movement between absorbing states. The matrix P is said to be in canonical form. The canonical form of the reducible matrix helps us to answer the following question: How long does it take for a chain to end up in an ergodic class?

If we let λ_i represent the i^{th} transient class and let μ_j represent the j^{th} ergodic class, assuming the chain starts in a certain transient state. The question that we are interested in answering is: Which ergodic state is hit, and not, what happens when this class is entered? Hence, $P_{r+j,r+j}$ is now set to be I for every $j \geq 1$. The transition probability matrix is then changed to

$$P^* = \begin{pmatrix} T_{11} & T_{12} \\ O & I \end{pmatrix}. \tag{2.7}$$

For a reducible matrix, P assumes the standard form:

$$P = \begin{pmatrix} p_{11} & p_{12} & \cdots & p_{1r} & p_{1,r+1} & p_{1,r+2} & \cdots & p_{1,m} \\ 0 & p_{22} & \cdots & p_{2r} & p_{2,r+1} & p_{2,r+2} & \cdots & p_{2,m} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & p_{r,r} & p_{r,r+1} & p_{r,r+1} & \cdots & p_{rm} \\ 0 & 0 & \cdots & 0 & p_{r+1,r+2} & p_{r+1,r+1} & \cdots & 0 \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \cdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & p_{mm} \end{pmatrix} \tag{2.8}$$

The subsets corresponding to p_{kk} for $1 < k < r$ are called the k^{th} transient class, and once these states are left, they cannot be re-entered. The subsets of states that correspond to $p_{r+j,r+j}$ are called the j_{th} ergodic class.

If the limit exists, it is changed to

$$\lim_{t\to\infty} P^{*k} = \begin{pmatrix} O & (I - T_{11})^{-1}T_{12} \\ O & I \end{pmatrix} \tag{2.9}$$

$$= \begin{pmatrix} 0 & 0 & \cdots & 0 & L_{1,1} & L_{1,2} & \cdots & L_{1,s} \\ 0 & 0 & \cdots & 0 & L_{2,1} & L_{2,2} & \cdots & L_{2,s} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & L_{r,1} & L_{r,2} & \cdots & L_{r,s} \\ 0 & 0 & \cdots & 0 & I & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 & 0 & I & \cdots & 0 \\ \vdots & \vdots & \cdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & I \end{pmatrix} \tag{2.10}$$

L_{ij} corresponds to the probability of eventually hitting the q^{th} state in μ_i, which is our j^{th} ergodic class, given that we started in the p^{th} state in λ_i, which is the i^{th} transient class. $L_{i,j}$ are numbers that represent the probabilities of being absorbed into the j^{th} ergodic class, given that we started in the i^{th} transient class.

(ii) Ergodic Markov chain

A Markov chain is ergodic if:

$$\exists t : \forall r, s \in \Omega, P^t(r,s) > 0, \tag{2.11}$$

where Ω is the state space. If the Markov chain is finite, then the following pairs of conditions are equivalent to ergodicity:

- Irreducible: $\forall r, s \in \Omega, \exists t = t(r,s) : P^t(r,s) > 0$
- Aperiodic: $\forall r \in \Omega, gcd\{t : P^t(r,s) > 0\} = 1$

(b) Period of a state

The period of a state i, denoted as $d(i)$, is the greatest common divisor of all integers $n \geq 1$ for which $p_{ii}^{(n)} > 0$, that is,

$$d(i) = g.c.d\{n/p_{ii}^{(n)} > 0 \; and \; n \geq 1\}. \tag{2.12}$$

If state i has a period $d(i) > 1$, it is said to be periodic of period $d(i)$. If $p_{ii}^{(n)} = 0, \forall n \geq 1$, define $d(i) = 0$. If the period of a state equals one, it is said to be aperiodic.

(c) Absorbing state

Consider a state $i \in S$ and let τ_i be the number of steps it takes for the chain to visit state i. Thus:

$$\tau_i = min(n \geq 1 : X_n = i), \tag{2.13}$$

where $\tau_i = \infty$ if i is never visited. If $P_i(\tau_i < \infty) = 1$, state i is said to be recurrent, and if $P_i(\tau_i < \infty) < 1$, it is said to be transient. If in a recurrent state $p_{ii} = 1$ and $p_{ij} = 0$ for $i \neq j$, this is said to be an absorbing state. In other words, an absorbing state is a state in which once entered one cannot get out of it, for example, the state of being dead in disease modeling.

(i) Properties of absorbing states

1. A state s_i of a Markov chain is called absorbing if it is impossible to leave it (that is $p_{ii} = 1$). This means that the probability that you are in state i and that you will remain there is one. For example, in disease modeling, if a person is HIV+, that person is said to be in an absorbing state. Also, the death state is an absorbing state.

2. A Markov chain is absorbing if it has at least one absorbing state, and if from every state it is possible to go to an absorbing state (not necessarily in one step). For example, in a sample space, Healthy, Diseased, Dead, a person can reach the absorbing state, Dead, from being healthy or after having passed through the diseased state.

3. A state that is not absorbing is called transient. For example, with HIV-infected patients, the states $CD4 > 500, 350 < CD4 \leq 500, 200 <$

$CD4 \leq 350, CD4 \leq 200$ are transient states because it is possible to move from one state to another.

(ii) Time to absorption

To determine the expected number of steps necessary to first enter an ergodic state, or the mean sojourn times for the individual, given the initial state, we use the formula:

$$E\left[number\ of\ times\ in\ S_j | start\ in\ S_i\right] = \left[(I - T_{11})^{-1}\right]_{ij}. \qquad (2.14)$$

Summing this over all the transient states gives the expected number of times the chain is in some transient state, and this equals the expected number of times before hitting the first ergodic state given by

$$E\left[number\ of\ steps\ until\ absorption | start\ in\ i^{th}\ transient\ state\right] = \left[(I - T_{11})^{-1}e\right]_i$$

where e represents a column vector of ones. In disease modeling, if the absorbing state is $Death$ then the entries in the column matrix, $\left[(I - T_{11})^{-1}e\right]_i$, represents the expected time to death for each initial state of the individual. This will now be used as a basis for the calculation of the life expectancy for each initial state.

Theorem 2.1: *In an absorbing Markov chain, the probability that the process will be absorbing is one (that is, $T_{11}^n \longrightarrow 0$ as $n \longrightarrow \infty$).*

Theorem 2.2: *For an absorbing Markov chain, the matrix, $(I - T_{11})$, has an inverse N and $N = I + T_{11} + T_{11}^2 + \ldots$. The matrix N is called the fundamental matrix for the absorbing Markov process P.*

Proof:

The transition matrix P for any absorbing chain can be written in the *canonical* form:

$$P = \begin{pmatrix} T_{11} & T_{12} \\ O & I \end{pmatrix}. \tag{2.15}$$

Iterated multiplication of the matrix P yields:

$$P^2 = \begin{pmatrix} T_{11}^2 & T_{11}T_{12} + T_{12} \\ O & I \end{pmatrix}. \tag{2.16}$$

$$P^3 = \begin{pmatrix} T_{11}^3 & T_{11}^2 T_{12} + T_{11}T_{12} \\ O & I \end{pmatrix}. \tag{2.17}$$

Hence, by induction, we obtain:

$$P^t = \begin{pmatrix} T_{11}^t & (T_{11}^{t-1} + \ldots + T_{11}^2 + T_{11} + I)T_{12} \\ O & I \end{pmatrix}. \tag{2.18}$$

This illustrates the general results that $T_{11}^t \longrightarrow 0$ as $t \longrightarrow \infty$. Thus:

$$P^\infty = \begin{pmatrix} O & NT_{12} \\ O & I \end{pmatrix}, \tag{2.19}$$

where matrix

$$N = T_{11}^{t-1} + \ldots + T_{11}^2 + T_{11} + I = (I - T_{11})^{-1} \tag{2.20}$$

$$\Longrightarrow N(i,j) = T_{11}^0(i,j) + T_{11}^1(i,j) + T_{11}^2(i,j) + \ldots, \tag{2.21}$$

where $T_{11}^t(i,j)$ is the probability that the process which began in the i^{th} non-absorbing state will occupy the j^{th} non-absorbing state in period t. However, $T_{11}^t(i,j)$ can also be understood as the expected proportion of period t, spent in the j_{th} state.

(iii) Absorption probabilities

Let $b_{i,j}$ be the probability that an absorbing chain will be absorbed in the absorbing state s_j if it starts in the transient state s_i. Let B be the matrix with entries $b_{i,j}$. Then B is an $t-$by$-r$ matrix, and $B = NT_{12}$, where N is the fundamental matrix and T_{12} is as in the canonical form.

Proof

$$B_{i,j} = \sum n \sum k q_{ik}^{(n)} r_{kj} \tag{2.22}$$

$$= \sum k \sum n q_{ik}^{(n)} r_{kj} \tag{2.23}$$

$$= \sum k n_{ik} r_{kj} \tag{2.24}$$

$$= (NR)_{ij}. \tag{2.25}$$

(d) Steady-state probabilities or limiting state probabilities

After $n - step$ transition probabilities for a Markov chain have been calculated, the chain will display the characteristics of a steady-state. For this value of n, every row of the matrix will be the same, and, as such, the probability that the process is in each state does not depend on the initial state of the process. Therefore, the probability that the process will be in *state* k after a certain number of transitions, is a limiting probability that exists independent of the initial state.

Theorem 2.3:

If P is a transition probability matrix of a regular discrete Markov process, and P_k approaches a unique limiting matrix, then the process is said to have reached a steady state.

As the system reaches a steady state, the k^{th} and the $(k+1)^{th}$ states are the same:

$$p(0) \cdot P^{k+1} = p(k+1) = p(k). \tag{2.26}$$

The steady state vector can be obtained using the equation $\pi = \pi P$ where π is the steady state vector for m states under the constraint that $\sum \pi_i = 1$. If the limiting probabilities exist then the process is said to be egordic (Kapodistria and Resing, 2012).

2.5.3 Further classification of stochastic models based on type of movement between states

Based on the classification of states discussed above, various state structures for continuous time Markov models are illustrated. A state structure determines the states in the model, showing clearly which ones are transient and which ones are absorbing. The arrows show possible movements within the model (Gibson, 2008). The next state to which the individual moves, and the time of change, are governed by a set of transition intensities $q_{hi}(t)$ for each pair of states h and i (Jackson, 2007). The intensities represent the instantaneous risk of moving from state h to state i.

In the context of disease modelling, there are basically the following state structures: bidirectional (alternating), bivariate, competing risk, mortality (illness-death), disability and recurrent (uni-directional). These structures are illustrated in the diagrams that follow.

(a) Mortality model

The simplest multi-state model is the mortality model, which has only two states, namely Alive and Dead. This type of model is basically known as the survival analysis model. The structure of the model is shown in Figure 2.2.

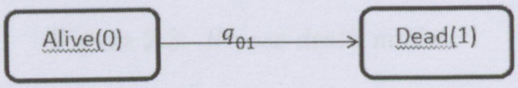


Figure 2.2: *Mortality model*

The arrow between the states is one directional, meaning that there is only one possible transition since an individual cannot move back to the state of being alive once the death state is reached. The label, q_{01}, on the arrow, represents the hazard rate or the transition intensity rate for the movement from state 0 to state 1.

(b) Ill-death model

The state of being alive in the mortality model can be split into two, that is, health and ill, to form a three state progressive model as shown in Figure 2.3. In this model, an individual can progress from a state of being healthy to a state of being ill, before moving to the absorbing state. From either state 0 or state 1 the death state can be reached.

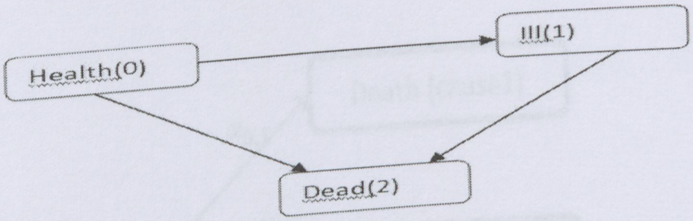


Figure 2.3: *Illness-death model*

(c) Competing risk model

We can also have a competing risk model, whereby two or more causes of death compete for the life of an individual. Competing risks can be modeled with one transient state corresponding with Alive and say k absorbing states corresponding to the dead by cause h, where $h = 1, 2, ..., k$. With this model, only the state that the event occurs in can be described. The notation, $\alpha_{0,k}$, represents the instantaneous risk of dying from cause k. The structure of the competing risk model is illustrated in Figure 2.4.

The structure of the multi-state models can also be categorised in terms of the direction of the arrows between states. As a result, we can have uni-directional models, bi-directional and recurrent models.

(d) Unidirectional model

A uni-directional model is when subjects move through a chain of states, starting from state 1 and progressing sequentially through the states until the absorbing state R is reached. With uni-directional models, once a subject leaves a state, there is a zero chance of visiting the state again. The structure of the model is shown in Figure 2.5.

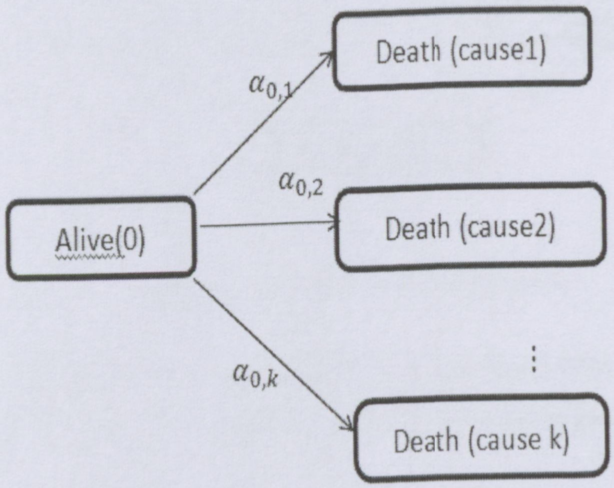


Figure 2.4: *Competing risk model*

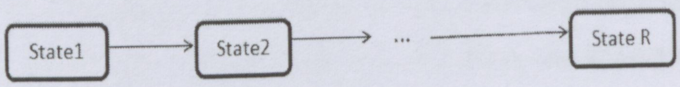


Figure 2.5: *Uni-directional model*

(e) Reversible or bi-directional model

Reversible or bi-directional models allow transitions in either direction between some of the transient states. With bi-directional models, an individual can return to a state provided that he/she does not go to an absorbing state. Absorbing states are also contained in these models. The structure of the bi-directional model is shown in Figure 2.6.

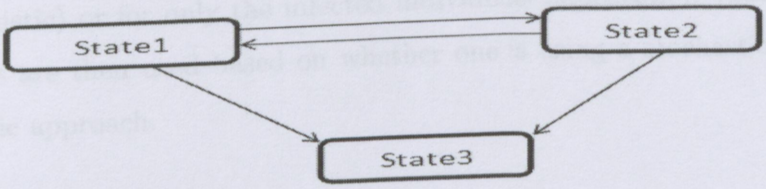


Figure 2.6: *Bi-directional model*

An example of bi-directional models is the three state disease model in which the probability of recovering from the disease is greater than zero.

(f) Recurrent model

Recurrent models are those models which do not have an absorbing state. With this structure, the transitions are uni-directional. An example of such models is the SIR model where susceptible (S) individuals become ill (I) and after some time, the individuals recover (R) from the illness as shown in Figure 2.7.

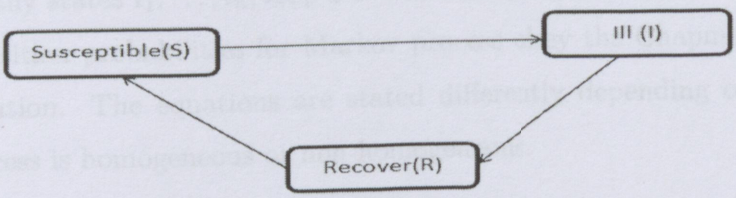


Figure 2.7: *Recurrent model*

These structures depend on whether one is modeling the epidemic of a particular disease for the whole population within that particular area (deterministic) or for only the infected individuals (stochastic). Mathematical models are then used based on whether one is using a stochastic or deterministic approach.

2.6 Markov Processes

Markov processes are the commonly used mathematical models for describing stochastic processes with dependence (Johansen, 2006). The assumption of Markov processes is that, once a patient is healthy, for example, the waiting time in that state is independent of the past history of the patient and only depends on the state the patient is in. A finite Markov chain is then a model for a stochastic process $X(t),\ t \geq 0$ with values in the finite state space S. the probability measure P, which describes the probabilistic properties of X, satisfies the Markov property:

$$P(X(t_{n+1}) = i_{n+1}|X(t_1) = i, \ldots, X(t_n) = i_n) = P(X(t_{n+1}) = i_{n+1}|X(t_n) = i_n) \quad (2.27)$$

for any states $i_1, \ldots, i_n, i_{n+1} \in S$ and time points $t_1 < \ldots < t_n < t_{n+1}$. The transition probabilities for Markov process obey the Chapman-Kolmogorov equation. The equations are stated differently depending on whether the process is homogeneous or non-homogeneous.

(a) Discrete-time Markov chain with homogeneous transition probabilities

Given an initial distribution $\mu = (\mu(x) : x \in S)$, where $\mu(x) = P(X_0 = x)$, the goal is to compute $\mu_n = (\mu_n(x) : x \in S)$, where $\mu_n(x) = P(X_n = x)$.

The sequence $(\mu_n : n \geq 0)$ satisfies the recursion;

$$\mu_n = \mu_{n-1}P, \tag{2.28}$$

such that $\mu_0 = \mu$. Or;

$$\mu_n - \mu_{n-1} = \mu_{n-1}(P - I) \tag{2.29}$$

(b) Discrete-time Markov chain with non-homogeneous transition probabilities

To compute μ_n for the sequence $(\mu_n : n \geq 0)$ we use the recursion;

$$\mu_n = \mu_{n-1}P(t), \tag{2.30}$$

such that $\mu_0 = \mu$. Or equivalently;

$$\mu_n - \mu_{n-1} = \mu_{n-1}(P(t) - I) \tag{2.31}$$

The equations that satisfy the steady state distribution are derived by setting the time-derivative in the forward equation to zero. That is, the mass function $\pi = (\pi(x) : x \in S)$ should satisfy;

$$\pi(P - I) = 0, \tag{2.32}$$

that is,

$$\pi = \pi P. \tag{2.33}$$

The transition probability matrix $P(t)$ with elements $(p_{ij}(t))$ has the following properties:

1. $p_{ij}(t) \geq 0$, for all $i, j \in S$ and $t \geq 0$
2. $\sum_{j \in S} P_{ij}(t) = 1, \forall i \in S$ and $t \geq 0$
3. $p_{ij}(t+s) = \sum_{k \in S} p_{ik}(t)p_{kj}(s), \forall t, s \geq 0, i, j \in S$

Proof of property 3 can be done as follows:

The transition probability matrix can be obtained from the Markov property,

$$
\begin{aligned}
P_{ij}(t+s) &= P\{X_{t+s} = j | X_0 = i\} && (2.34)\\
&= \sum_k P\{X_{t+s} = j, X_t = k | X_0 = i\} P\{X_t = k | X_0 = i\} && (2.35)\\
&= \sum_k P\{X_{t+s} = j | X_t = k\} P\{X_t = k | X_0 = i\} && (2.36)\\
&= \sum_k P_{kj}(s) P_{ik}(t) && (2.37)
\end{aligned}
$$

Thus:

$$P(t+s) = P(t)P(s) \tag{2.38}$$

2.6.1 Transition probability matrix for a continuous-time Markov process

A continuous time Markov model can be defined in terms of its matrix of transition intensities $Q(t, X_t)$ with (r, s) entries;

$$q_{rs} = \lim_{\delta t \to 0} \frac{P(X(t+\delta t) = s | X(t) = r, X_t)}{\delta t} \tag{2.39}$$

where X_t is a σ -algebra representing a history generated by the multi-state process $X(\cdot)$.

Computation of parameters for a continuous-time Markov process include calculation of mean sojourn time (time of stay in a state), jump chain (movement from state to state), time to absorption, which gives rise to calculation of transition probabilities. Kolmogorov's forward and backward equations are used for all these calculations.

(a) Sojourn times

For multi-state models, the subjects involved in the processes spend a random amount of time in each state known as the holding time or sojourn time. The amount of time spent in each state has an exponential distribution because the Markov process is memoryless. Markov property and time-homogeneity imply that, if at time t the process is in state j, the time remaining in state j is independent of the time already spent in state j, thus, the Markov property. Given a state, say $x \in S, X(0) = x$ and let T_x denote the time of the subject's transition away from state x. To find the distribution of T_x, we let $s, t \geq 0$ and consider

$$\begin{aligned}
P(T_x > s+t|T_x > s) &= P(X(r) = x \; for \; r \in [0, s+t] \,|X(r) = x \; for \; r \in [0, s]) \\
&= P(X(r) = x \; for \; r \in [s, s+t] \,|X(r) = x \; for \; r \in [0, s]) \\
&= P(X(r) = x \; for \; r \in [0, s+t] \,|X(r) = x), (Markov \; property) \\
&= P(X(r) = x \; for \; r \in [0, t] \,|X(0) = x), (time \; homogeneity) \\
&= P(T_x > t)
\end{aligned}$$

Thus, T_x satisfies the loss of memory property, meaning that the time spent in state x is exponentially distributed. The parameter of the exponential holding time in state x is denoted by $\lambda(x)$.

When analysing the data for HIV-infected individuals on treatment, the sojourn times can be used to assess the effectiveness of the drugs. If the time spent, particularly in the worst states, is shorter than the time spent in good states, it means that the drugs are effective.

(b) Jump chain

This is when a Markov process is observed at the times it makes transitions to a new state. In other words, a jump chain is a stochastic matrix R, a matrix where each row sums to one, on the state space X, which describes the next state an individual goes to after leaving state i. If $\lambda(i) > 0$, then one never stays in state i, one makes a jump out, resulting in having $R_{ii} = 0$; and if $\lambda(i) = 0$, then one never leaves state i, meaning that $R_{ii} = 1$.

Lemma 2.1: Chapman-Kolmogorov's equations

The transition probabilities of a Markov jump process obey the Chapman-Kolmogorov equation:

$$P_{ij}(s,t) = \textstyle\sum_{\forall k \in S} P_{ik}(u,t)$$

for all states i, j in state space S and all times $s < u < t$.

The transition rate matrix also known as transition intensity at time t between any two points i and j of a Markov jump process is defined as follows:

$$\alpha_{ij}(t) = \frac{\partial}{\partial s} p_{ij}(s,t)|_{s=t} = \lim_{h \to 0} \frac{p_{ij}(t,t+h) - p_{ij}(t,t)}{h} \tag{2.40}$$

Bearing in mind that:

$$p_{ij}(t,t) = \delta_{ij} = \begin{cases} 0, & i \neq j, \\ 1, & i = j \end{cases}, \tag{2.41}$$

where δ_{ij} is the Kronecker delta,

$$\alpha_{ij} = \lim_{h\to 0}\frac{p_{ij}(t,t+h)-p_{ij}(t,t)}{h} \tag{2.42}$$

$$= \begin{cases} \lim\limits_{h\to 0}\frac{p_{ij}(t,t+h)}{h}, & j\neq i, \\ \lim\limits_{h\to 0}\frac{p_{ij}(t,t+h)-1}{h}, & i=j. \end{cases} \tag{2.43}$$

By cross multiplication we get

$$p_{ij}(t,t+h) = \begin{cases} h\alpha_{ij}(t)+O(h), & i\neq j \\ 1+h\alpha_{ij}(t)+O(h) & i=j \end{cases} \tag{2.44}$$

where $f(h)=O(h)$ means $\lim\limits_{h\to 0}\frac{f(h)}{h}=0$.

For $j\neq i, p_{ij}(t,t)$ is equal to zero since the probability to move between two states is zero when no time has elapsed and $p_{ij}(t,t)$ for $i=j$ is equal to one since the probability of remaining in the same state when no time elapsed is one. Transition rates behave differently from probabilities in that:

- It is possible to have a negative rate; and
- The rows of the transition matrix sum to zero.

Lemma 2.2: *Let $P_{ij}(s,t)$ denote the transition probabilities of a Markov jump process with associated transition rates $\alpha_{ij}(t)$. Then $\sum_{\forall j}\alpha_{ij}(t)=0$, for all i and all $s\geq 0$.*

Proof: For all $s\geq 0$, we have $\sum_{\forall j}P_{ij}(t,s)=1$

$$\Rightarrow \quad \frac{\partial}{\partial s}\sum_{\forall j} P_{ij}(t,s)|_{s=t} = \frac{\partial}{\partial s}(1) \tag{2.45}$$

$$\Rightarrow \quad \sum_{\forall j} \frac{\partial}{\partial s} P_{ij}(t,s)|_{s=t} = 0 \tag{2.46}$$

$$\Rightarrow \quad \sum_{\forall j} \alpha_{ij}(t) = 0 \tag{2.47}$$

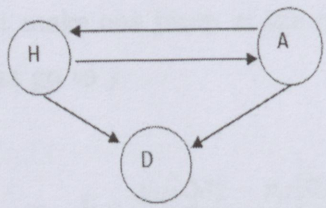
From the definition, if $t \neq j$, then:

$$\alpha_{ij}(t) = \lim_{h \to 0} \frac{p_{ij}(t, t+h)}{h} \geq 0. \tag{2.48}$$

So

$$\alpha_{ij}(t) \leq 0 \Rightarrow \alpha_{ij}(t) = -\sum_{\forall j, j \neq i} \alpha_{ij}(t) \tag{2.49}$$

As an example, suppose we have an HIV progression model with three states, namely HIV+ (H), AIDS (A) and DEAD (D), connected as shown below:



The transition rate matrix is given as

$$Q(t) = \begin{pmatrix} -(\rho(t)+\sigma(t)) & \rho(t) & \sigma(t) \\ \mu(t) & -(\mu(t)+\alpha(t)) & \alpha(t) \\ 0 & 0 & 0 \end{pmatrix} \tag{2.50}$$

The transition rates form a matrix known as the infinitesimal generator matrix Q. The transition rate matrix can be directly obtained from the holding times and the jump times. Consider the case where the holding time of a given state $\lambda_i \neq 0$. We make an approximation that in a small time Δ_t, the chain will make only, at most, one jump, that is as $\Delta_t \longrightarrow 0$. First, consider the state $j \neq i$. We have:

$$
\begin{aligned}
Q_{ij} &= \lim_{\Delta t \to 0} \frac{p_{ij}(\Delta t) - p_{ij}(0)}{\Delta t} && (2.51)\\
&= \lim_{\Delta t \to 0} \frac{p_{ij}(\Delta t)}{\Delta t} && (2.52)\\
&= \lim_{\Delta t \to 0} \frac{(1-\exp(-\lambda_i \Delta t))R_{ij}}{\Delta t} && (2.53)\\
&= \lambda_i R_{ij} && (2.54)
\end{aligned}
$$

where R is the stochastic matrix that gives the transition probabilities of the jump chain.

The assumption that was used is that, if the chain goes from i to j in time Δt, then the chain must make one jump in the interval $[0, \Delta t]$, and when it makes this jump, it must go to j.

Computing Q_{ii}:

$$
\begin{aligned}
Q_{ii} &= \lim_{\Delta t \to 0} \frac{p_{ii}(\Delta t) - p_{ii}(0)}{\Delta t} && (2.55)\\
&= \lim_{\Delta t \to 0} \frac{p_{ii}(\Delta t) - 1}{\Delta t} && (2.56)\\
&= \lim_{\Delta t \to 0} \frac{(1-\exp(-\lambda_i \Delta t)) - 1}{\Delta t} && (2.57)\\
&= -\lambda_i && (2.58)
\end{aligned}
$$

This proof uses the fact that being in state i and remaining in the same state in time $t = 0$ has probability of 1 since there is no time that has elapsed. The probability of being in the same state after a small change in time Δt is exponentially distributed with parameter Δt.

Definition 2.1 : *The matrix of transition rates $Q = (q_{ij})$ is known as infinitesimal generator matrix,*

$$Q(t) = \begin{pmatrix} q_{1,1} & q_{1,2} & q_{1,3} & \cdots \\ q_{2,1} & q_{2,2} & q_{2,3} & \cdots \\ q_{3,1} & q_{3,2} & q_{3,3} & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \tag{2.59}$$

$$= \begin{pmatrix} -\sum_{i=2}^{\infty} q_{i,1} & q1,2 & q_{1,3} & \cdots \\ q_{2,1} & -\sum_{i=1,i\neq 2}^{\infty} & q_{2,3} & \cdots \\ q_{3,1} & q_{3,2} & -\sum_{i=1,i\neq 3}^{\infty} & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \tag{2.60}$$

Matrix Q has a property that each column sum is zero and each diagonal element is the negative of the sum of off diagonal element in that column.

2.6.2 Kolmogorov's forward and backward equations for continuous-time Markov models

The Kolmogorov backward equation is useful when the question is: Given that the system at a future time s has a particular behaviour, what can we say about the distribution at time $t < s$? This means predicting the past events using the present phenomenon. Likewise Kolmogorov's forward equation can be used to predict future events.

Lemma 2.3: Kolmogorov's forward equation

Let $P_{ij}(s,t)$ denote the transition probabilities of a Markov jump process with associated transition rate $\alpha_{ij}(t)$. Then:

$$\frac{\partial P_{ij}(s,t)}{\partial t} = \sum_{\forall k} P_{ik}(s,t)\alpha_{kj}(t) \tag{2.61}$$

Or in matrix form

$$\frac{\partial P_{ij}(s,t)}{\partial t} = P(s,t)A(t) \tag{2.62}$$

where A is the transition rate matrix $(A(t))_{ij} = \alpha_{ij}(t)$.

Proof

Consider $P_{ij}(s,t+h)$.

$$\begin{aligned} P_{ij}(s,t+h) &= \sum_{\forall k} P_{ik}(s,t)P_{kj}(t,t+h), && (2.63)\\ &= P_{ij}(s,t)P_{jj}(t,t+h) + \sum_{\forall k, k\neq j} P_{ik}(s,t)P_{kj}(t,t+h) && (2.64)\end{aligned}$$

But:

$$p_{ij}(t,t+h) = \begin{cases} h\alpha_{ij}(t) + O(h) & ,k \neq j, \\ 1 + h\alpha_{ij}(t) + O(h) & ,k = j. \end{cases} \tag{2.65}$$

Substituting in our equations gives:

$$P_{ij}(s,t+h) = P_{ij}(s,t)\left[1 + h\alpha_{ij}(t)\right] + \sum_{\forall k, k\neq j} P_{ik}(s,t)\left[h\alpha_{ij}(t) + O(h)\right] \tag{2.66}$$

$$P_{ij}(s,t+h) = P_{ij}(s,t) + \sum_{\forall k} P_{ik}(s,t)\left[h\alpha_{ij}(t) + O(h)\right] \tag{2.67}$$

$$P_{ij}(s,t+h) - P_{ij}(s,t) = \sum_{\forall k} P_{ik}(s,t)\left[h\alpha_{ij}(t) + O(h)\right]. \tag{2.68}$$

Dividing by h and taking limits as $h \longrightarrow 0$ yields:

$$\frac{\partial P_{ij}(s,t)}{\partial t} = \sum_{\forall k} P_{ik}(t)\alpha_{kj}(t). \tag{2.69}$$

Lemma 2.4: Kolmogorov's backward equation

Let $P_{ij}(s,t)$ denote the transition probabilities of a Markov jump process with associated transition rates $\alpha_{ij}(t)$. Then

$$\frac{\partial P_{ij}(s,t)}{\partial t} = -\sum_{\forall k} \alpha_{ik}(t) P_{kj}(s,t). \tag{2.70}$$

Or in matrix notation,

$$\frac{\partial P(s,t)}{\partial s} = A(s)P(s,t), \tag{2.71}$$

where $A(s)$ is the transition rate matrix $(A(s))_{ij} = \alpha_{ij}(s)$.

Proof

$$P_{ij} \;=\; \sum_{\forall k} P_{ik}(s,s+h)P_{s+h,t}P_{ii}(s,s+h)P_{ij}(s+h,t) + \sum_{\forall k, k\neq j} P_{ik}(s,s+h)P_{kj}(s+h,t)$$

But:

$$p_{ij}(s,s+h) = \begin{cases} h\alpha_{ij}(s) + O(h) & ,k \neq j, \\ 1 + h\alpha_{ij}(s) + O(h) & ,k = j. \end{cases} \tag{2.72}$$

So we have:

$$P_{ij}(s,t) = [1 + h\alpha_{ij}(s) + O(h)]\, P_{ij}(s+h,t) + \sum_{\forall k, k\neq i} [h\alpha_{ij}(s) + O(h)]\, P_{kj}(s+h,t)$$

$$P_{ij}(s,t) = P_{ij}(s+h,t) + \sum_{\forall k} [h\alpha_{ij}(s) + O(h)]\, P_{kj}(s+h,t)$$

$$P_{ij}(s,t) - P_{ij}(s+h,t) = \sum_{\forall k} [h\alpha_{ij}(s) + O(h)]\, P_{kj}(s+h,t)$$

$$\frac{P_{ij}(s,t) - P_{ij}(s+h,t)}{h} = \sum_{\forall k} \left[\alpha_{ij}(s) + \frac{O(h)}{h})\right] P_{kj}(s+h,t)$$

$$-\left(\frac{P_{ij}(s+h,t) - P_{ij}(s,t)}{h}\right) = \sum_{\forall k} \left[\alpha_{ij}(s) + \frac{O(h)}{h})\right] P_{kj}(s+h,t).$$

Taking limits as $h \longrightarrow 0$ yields

$$-\frac{\partial P_{ij}(s,t)}{\partial t} = \sum_{\forall k} \alpha_{ik}(t) P_{kj}(s,t). \tag{2.73}$$

Or

$$\frac{\partial P_{ij}(s,t)}{\partial t} = -\sum_{\forall k} \alpha_{ik}(t) P_{kj}(s,t). \tag{2.74}$$

For example, if we have a model for HIV+ patients who are not on treatment, the model can have three states, namely HIV (H), AIDS (A) and Dead (D). With no treatment, the assumption is that these states are not recurrent, such that the time homogeneous model looks like the one shown in Figure 2.8

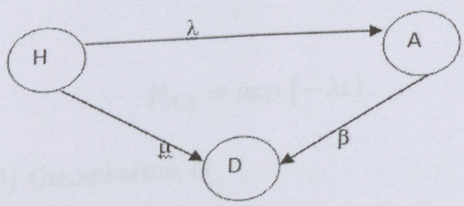


Figure 2.8: *Illness-death model for HIV*

By using Kolmogorov's forward equations, the differential equations for the various movements between states are:

$$\frac{\partial P_{HH}(s,t)}{\partial t} = -[\lambda+\mu]\, P_{HH}, \tag{2.75}$$

$$\frac{\partial P_{HA}(s,t)}{\partial t} = -[\lambda+\mu] P_{HA} + \lambda P_{AA}, \tag{2.76}$$

$$\frac{\partial P_{HD}(s,t)}{\partial t} = -[\lambda+\mu] P_{HD} + \lambda P_{AD} + \mu P_{DD}, \tag{2.77}$$

$$\frac{\partial P_{AA}(s,t)}{\partial t} = -\beta P_{AA}, \tag{2.78}$$

$$\frac{\partial P_{AD}(s,t)}{\partial t} = -\beta(P_{AD}-1), \tag{2.79}$$

$$\frac{\partial P_{DD}(s,t)}{\partial t} = 0. \tag{2.80}$$

Solving equation (2.75) by integrating from s to t yields

$$P_{HH} = \exp\{-(\lambda+\mu)t\}.$$

From (2.78)

$$P_{AA} = \exp\{-\lambda t\}.$$

For equation (2.80) the solution is

$$P_{DD}(s,t) = 1.$$

Equation (2.76) becomes:

$$\frac{\partial P_{HA}(t)}{\partial t} = -[\lambda+\mu]\, P_{HA} + \lambda \exp\{-\lambda t\}.$$

Equation (2.77) becomes:

$$\frac{\partial P_{HD}(t)}{\partial t} = -[\lambda+\mu]\, P_{HD} + \mu P_{AD} + \mu.$$

Explicit solutions for equations (2.79), (2.76) and (2.77) can be found by using R software or Matlab.

2.6.3 The time-homogeneous continuous Markov model

The assumption of time homogeneity simplifies the Markov model and is often a convenient baseline for analysis. All the other models can be obtained by examining departure from this model. This section explores the theory of time-homogeneous Markov model and illustrations as to how important parameters are calculated when building the model is done using examples.

Multi-state homogeneous Markov models are time-continuous, that is, the transition probability only depends on the difference between the two times one is considering. In medical research, the state of the patient at observation time is the only thing known. The researcher may know the time interval in which a transition has occurred, but not the exact time. Thus, homogeneous Markov models are interval censored (Gibson, 2008). That is, if for all $t \geq 0$, the probability of moving from state i to state j is given by:

$$P_{ij}(t,s) = P(X_s = j|X_t = i) = P(X_{s-t} = j|X_0 = i), \forall s \geq 0 \ for \ s > t \quad (2.81)$$

Time-homogeneous models are based on the assumption that the intensities are constant functions of time. Assuming that we have n patients moving independently within the states $X = \{1, 2, \dots, x\}$, the following property holds for a time homogeneous model:

$$Q(t) = Q, \ \forall t.$$

Once the value of Q has been obtained, the transition probability matrix can be obtained using the Chapman-Kolmogorov's forward or backward equations:

$$\frac{dP(t)}{dt} = P(t)Q.$$

Solving the differential equation with boundary initial condition $P(0) = I$ yields;

$$\begin{aligned} P(t) &= e^{Qt} = \sum_{n=0}^{\infty} \frac{(tQ)^n}{n!} \\ &= I + Qt + \frac{Q^2t^2}{2!} + \frac{Q^3t^3}{3!} + \dots . \end{aligned}$$

Matrix Q is then diagonalised into the form BDB^{-1} provided the eigenvalues of Q are distinct. Matrix D represents the diagonal matrix with diagonal entries representing the eigenvalues of Q and B is matrix whose column representing the respective eigen-vectors.

$$\begin{aligned} P(t) = BIB^{-1} + Bdiag(d_1, \dots, d_s)B^{-1}t/1! + Bdiag(d_1, \dots, d_s)B^{-1}t^2/2! + \\ Bdiag(d_1, \dots, d_s)B^{-1}t^3/3! + \dots, \end{aligned}$$

Now we have:

$$\begin{aligned} P(t) &= B\left[\sum_{i=0}^{\infty} diag\left(\frac{d_1^i t^i}{i!}, \dots, \frac{d_s^i t^i}{i!}\right)\right] B^{-1}, \\ &= B\left[diag\left(\sum_{i=0}^{\infty}\frac{d_1^i t^i}{i!}, \dots, \sum_{i=0}^{\infty}\frac{d_s^i t^i}{i!}\right)\right] B^{-1}, \\ &= B\left[diag\sum_{i=0}^{\infty}\left(e^{d^1 t}, \dots, e^{d^s t}\right)\right] B^{-1}, \\ &= Bexp(tD)B^{-1}. \end{aligned}$$

As a result, the transition probability matrix will be computed as follows:

$$P(t) = Bexp(tD)B^{-1}.$$

This reduces the problem of finding the transition probability matrix to a problem of simply determining the eigenvalues and eigen-vectors of the transition intensity matrix, Q. The softwares for computing these are readily available.
For example, suppose we have a two state model with state 0, *Alive*, and state 1, *Dead*. If α_{01} represents the rate of moving from state 0 to state 1 then $-\alpha_{01}$ represents the force of being in state 0. Then:

$$Q = \begin{pmatrix} -\alpha_{01} & \alpha_{01} \\ 0 & 0 \end{pmatrix}.$$

Then $d_1 = -\alpha_{01}$ and $d_2 = 0$ and the corresponding eigen-vectors are $(1,0)'$ and $(1,1)'$. Thus:

$$B = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}, B^{-1} = \begin{pmatrix} 1 & -1 \\ 0 & 1 \end{pmatrix}$$

We then have

$$\begin{aligned} P(t) &= B\exp(tD)B^{-1} \\ &= \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}\begin{pmatrix} e^{-\alpha_{01}t} & 0 \\ 0 & 1 \end{pmatrix}\begin{pmatrix} 1 & -1 \\ 0 & 1 \end{pmatrix} \\ &= \begin{pmatrix} e^{-\alpha_{01}t} & 1-e^{-\alpha_{01}t} \\ 0 & 1 \end{pmatrix} \end{aligned}$$

as desired.
A two-state continuous-time Markov chain, according to Privault (2013) is illustrated as follows: Consider a continuous-time Markov process with state space $S = \{0, 1\}$, with the infinitesimal generator Q of $(X_t), t > 0$, is of the form

$$B^{-1} = \begin{pmatrix} -\alpha & \alpha \\ \beta & -\beta \end{pmatrix},$$

with $\alpha, \beta \geq 0$. The forward Kolmogorov equation for this is:

$$P'(t) = P(t)\begin{pmatrix} -\alpha & \alpha \\ \beta & -\beta \end{pmatrix}, t > 0,$$

that is:

$$\begin{pmatrix} P'_{0,0}(t) & P'_{0,1}(t) \\ P'_{1,0}(t) & P'_{1,1}(t) \end{pmatrix} = \begin{pmatrix} P_{0,0}(t) & P_{0,1}(t) \\ P_{1,0}(t) & P_{1,1}(t) \end{pmatrix}\begin{pmatrix} -\alpha & \alpha \\ \beta & -\beta \end{pmatrix}, t > 0,$$

which is a system of differential equations:

$$P(0) = \begin{pmatrix} P_{0,0}(t) & P_{0,1}(t) \\ P_{1,0}(t) & P_{1,1}(t) \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} = I_d.$$

The solution of the forward Kolmogorov equation is given by the matrix exponential

$$P(t) = P(0)e^{tQ} = e^{tQ} = \exp\left[t\begin{pmatrix} -\alpha & \alpha \\ \beta & -\beta \end{pmatrix}\right].$$

Proposition 2.1:
The solution $P(t)$ of the forward Kolmogorov equation is

$$P(t) = \begin{bmatrix} \frac{\beta}{\alpha+\beta} + \frac{\alpha}{\alpha+\beta}e^{-t(\alpha+\beta)} & \frac{\alpha}{\alpha+\beta} - \frac{\alpha}{\alpha+\beta}e^{-t(\alpha+\beta)} \\ \frac{\beta}{\alpha+\beta} - \frac{\beta}{\alpha+\beta}e^{-t(\alpha+\beta)} & \frac{\alpha}{\alpha+\beta} + \frac{\beta}{\alpha+\beta}e^{-t(\alpha+\beta)} \end{bmatrix}, t > 0.$$

Proof:
Matrix Q has two eigen-vectors $(1,1)'$ and $(-\alpha,\beta)'$, with respective eigen-values, $\lambda_1 = 0$ and $\lambda_2 = -\alpha - \beta$. Hence Q can be expressed in the diagonal form:

$$Q = MDM^{-1}.$$

$$\Rightarrow Q = \begin{bmatrix} 1 & -\alpha \\ 1 & \beta \end{bmatrix} \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix} \begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ \frac{-1}{\alpha+\beta} & \frac{1}{\alpha+\beta} \end{bmatrix}.$$

Consequently, we have:

$$\begin{aligned} P(t) &= e^{tQ} = \sum_{n=0}^{\infty} \frac{t^n}{n!} Q^n = \sum_{n=0}^{\infty} \frac{t^n}{n!} (MDM^{-1})^n \\ &= \sum_{n=0}^{\infty} \frac{t^n}{n!} MD^n M^{-1} = M \left(\sum_{n=0}^{\infty} \frac{t^n}{n!} D^n \right) M^{-1} = M \exp(tD) M^{-1}, \\ &= \begin{bmatrix} 1 & -\alpha \\ 1 & \beta \end{bmatrix} \begin{bmatrix} e^{-t\lambda_1} & 0 \\ 0 & e^{-t\lambda_2} \end{bmatrix} \begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ \frac{-1}{\alpha+\beta} & \frac{1}{\alpha+\beta} \end{bmatrix}, \\ &= \begin{bmatrix} 1 & -\alpha \\ 1 & \beta \end{bmatrix} \begin{bmatrix} 1 & 0 \\ 0 & e^{-t(\alpha+\beta)} \end{bmatrix} \begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ \frac{-1}{\alpha+\beta} & \frac{1}{\alpha+\beta} \end{bmatrix}, \\ &= \begin{bmatrix} 1 & \alpha e^{-t(\alpha+\beta)} \\ 0 & \beta e^{-t(\alpha+\beta)} \end{bmatrix} \begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ \frac{-1}{\alpha+\beta} & \frac{1}{\alpha+\beta} \end{bmatrix}, \\ &= \begin{bmatrix} \frac{\beta}{\alpha+\beta} + \frac{\alpha}{\alpha+\beta} e^{-t(\alpha+\beta)} & \frac{\alpha}{\alpha+\beta} - \frac{\alpha}{\alpha+\beta} e^{-t(\alpha+\beta)} \\ \frac{\beta}{\alpha+\beta} - \frac{\beta}{\alpha+\beta} e^{-t(\alpha+\beta)} & \frac{\alpha}{\alpha+\beta} + \frac{\beta}{\alpha+\beta} e^{-t(\alpha+\beta)} \end{bmatrix}. \end{aligned}$$

2.6.4 Time homogeneous Markov models and covariates

When analysing disease progression in any given subject, so many covariates are responsible for causing the process to be non-homogeneous over time. For example, if we consider age as a covariate, time-homogeneity is violated in that, with chronic disease, ageing has a significant influence on mortality rates (Hosgood, 2002). To ensure homogeneity, infected individuals are put in different age groups and separate matrices are created for each age group.

These matrices are then compared to see the effects of age on the progression of the disease. This strategy can also be used with fixed covariates such as gender.

Let $x_{j1}, x_{j2}, \ldots, x_{jn}$ be the states that individual j occupies at times $t_{j1}, t_{j2}, ..., t_{jn}$, then the likelihood over all k processes or patients is:

$$\prod_{j=1}^{k} \prod_{i=2}^{n} P_{x_{j,i-1},x_{ji}}(t_{j,i} - t_{j,i-1}).$$

As the longitudinal data is collected, a lot of covariates are considered. For this project, the covariates include gender, age, baseline CD4 cell count, clinical stages of the disease, to mention a few. There is need to study the relationship between these covariates and the transition intensities, q_{ij}, in the Markov model. Kalbfleisch and Lawless (1985) defined the likelihood as follows:

Suppose that each individual has an associated vector of s covariates, $\vec{z}' = (z_1, z_2, \ldots, z_s)$, where $z_1 = 1$. For any given $\vec{z}$, we suppose that the process is homogeneous Markov, with transition intensity matrix:

$Q(\vec{z}) = (q_{ij}(\vec{z}))$ where $q_{ij}(\vec{z}) = q_{ij0}\exp(\vec{z}'\beta_{ij})$, for $i \neq j$, where $\beta_{ij} = (\beta_{1ij}, \ldots, \beta_{xij})'$ is a vector of s regression parameters relating the instantaneous rate of transitions from state i to state j to the covariates $\vec{z}$. For this model, $q_{ii} = \sum_{i \neq j} q_{ij}(\vec{z})$.

2.6.5 Approaches to fitting inhomogeneous models

When dealing with medical data, quite often, it does not make sense to assume homogeneity on underlying intensities. Non-homogeneous models are required because transition rates change as subjects age (Hubbard and

Zhou, 2011). Therefore, there is need to employ methods that can account for intensities that are functions of time. There are various approaches that can be employed for fitting the inhomogeneous models. These approaches include:

- Allowing transition intensities to be piece-wise constant (PWC). This is the most commonly used method;
- Allowing transitions to have smooth parameters form, for example the Weibull hazard functions. For Markov models, this requires solving the Kolmogorov forward equations which are set to be non-linear ordinary differential equations for time homogeneous models; and
- Non-parametric or semi-parametric techniques

This study is going to focus on the PWC model. Define Θ as a non-homogeneous vector of intensities, $\Theta = \Theta(t)|0 < t < T$, to be estimated, where T is the maximum observed time. By using the HIV states defined for this study:

$$\Theta(t) = [q_{12}(t), q_{16}(t), q_{17}(t), q_{21}(t), q_{23}(t), q_{26}(t), q_{27}(t), \ldots, q_{57}(t)], \quad (2.82)$$

with each entry a function of time. Aalen and Johansen (1978), employ the product integral, denoted by π, to relate transition probability matrix to the cumulative intensities, defined as:

$$\mathbf{Z}(t) = \pi_{s\epsilon[t]}(\mathbf{I} + \mathbf{X}(ds)) = lim_{max|t-t_{i-1}|\to 0}\Pi(\mathbf{I} + \mathbf{X}(t_i) - \mathbf{X}(t_{i-1}), \quad (2.83)$$

where $\mathbf{X}(t)$ is a $K \times K$ matrix valued function of time t and $\mathbf{I}$ is the identity matrix. In the MSM context, let $\mathbf{A}$ be a $K \times K$ matrix where the entries

$A_{uv}, u \neq v$, are integrated intensity functions for transitions from state u to state v. Then the relationship between P and A is defined as follows:

$$P(s,t) = \pi_{(s,t]}(\mathbf{I} + d\mathbf{A}(u)). \tag{2.84}$$

The method seems difficult to implement easily in the context of the MSM models. A more commonly implemented method to estimate $\Theta(t)$ is to use a piece-wise constant (PWC) model. Models involving constant intensities between states allow the assumption of time homogeneity to be relaxed, while, at the same time, retaining closed form algebraic expressions for the transition probabilities (Titman, 2007).

The PWC model partitions the entire time interval into R continuous, disjoint intervals, $\tau_1, \ldots, \tau_R$ where τ_r is the interval from time t_{r-1} to t_r and $\tau_r < \tau_{r'}$. Each time interval is treated as a distinct time homogeneous process. This method is an extension of a time homogeneous case. If we have two time dependent segments $\mathbf{Q}$ and Θ, defined as follows:

$$\mathbf{Q}(t) = \mathbf{Q}_r, \ t\epsilon\tau_r, \tag{2.85}$$

$$\Theta(t) = \Theta_r, \ t\epsilon\tau_r. \tag{2.86}$$

Computing $P(0, t_i$ for a t_i in segment τ_r, entails multiplying all the transition matrices across the various intervals as seen below:

$$P(0,t_i) = [\Pi_{b=1}^{r-1} P^{(b)}(\tau_b)] P^{(r)}(t_{(r-1)}, t_j), \tag{2.87}$$

where $P^{(b)}$ is the transition matrix using $\mathbf{Q}_b$ for the b^{th} segment, τ_b. If subjects are observed on an equal spaced grid and segments are divided up along these time points, then $P_{uv}(0, t_i)$ would simply be the $(u, v)^{th}$ element of the matrix in the above equation. When data are not equally spaced, then observations would be considered missing at the breakpoints. To resolve this, a model that accounts for all possible pathways between the last observed state in the segment b_{i-1} and the first observation in segment b was suggested. For example, if a breakpoint t' is created between two points t_j and t_k, then the likelihood contribution from interval t_j, t_k for individual i can be found as:

$$L_i = \sum_{l=1}^{k} P_{ul}^{(1)}(t_j, t') P_{lv}^{(2)}(t', t_k), \tag{2.88}$$

for states u, v. A likelihood ratio test can then be used to determine whether a PWC model is a better fit than the constant model. The next section explores the techniques used for assessing model fit with the likelihood ratio test included.

2.7 Techniques for assessing model fit

Titman (2007) suggested a number of methods that can be used as diagnostic tools for the fitted Markov models. He classified the methods into two groups, the formal methods and the informal methods. The formal methods included the use of the log-likelihood ratio tests (LRT) and the Pearson's chi-squared test. The log-likelihood ratio test is used to compare two different fitted models, for example, a Markov model without covariates with a Markov model with covariates. Pearson's chi-squared test is used to compare prevalence counts using observed and expected frequencies.

The informal methods use graphs to compare the fitted model with the observed data and they do not involve a calculation of likelihood ratios. The informal methods are preferred because they give a clear picture of how the fitted model compares with expected model.

2.7.1 Testing the Markov assumption

The Markov assumption is that a future state of a process only depends on the current state and is independent of the past. The method by Kay (cited by Titman 2007) involves creating data for the exact transition times between states, using interpolation when the data is completed and a test is performed. For example, given an illness-death model with two communicating states, 1 and 2, and death being the absorbing state and letting x be the time spent in state 2 during the last sojourn in state 1, we can fit the model for intensity, $q_{12} = \lambda_0 exp(\beta x)$ and test the hypothesis, $H_0 : \beta = 0$. This hypothesis will assess the assumption that the transition rate to death from state 1 is unaffected by the previous sojourn time.

2.7.2 Testing the homogeneous assumption

The homogeneous assumption is that the transition intensities are constant throughout time, that is $q_{ij}(t) = q_{ij}$. This assumption is tested using piecewise constant transition intensities which use a formal likelihood ratio test for the independence of the two models. The fitted parametric time-dependent models will be of the form $q_{rs}(t) = q_{rs} exp(-\lambda t)$ and perform a likelihood ratio test on the null hypothesis $H_0 : \lambda = 0$.

The purpose of the likelihood ratio test, in this study, is to determine whether transition history can be modelled adequately by a homogeneous Markov model and transition probabilities, thus, exhibiting the invariant behaviour. The null hypothesis for time-homogeneity is then stated as follows: $H_0 : \forall h, j \in X : \exists q_{hj} \in \mathbf{R}^t : q_{hj}(t) \equiv q_{hji} \forall t \in [0, T)$, and the alternative hypothesis is that transition probabilities are time-dependent, which can be approximated by structural breaks in the transition intensities. The likelihood ratio test is then computed as follows:

$$LRT = -2log_e\left(\frac{L_s(\hat{\theta})}{L_g(\hat{\theta})}\right), \tag{2.89}$$

for a simpler model (s) with fewer parameters and the general model (g). The test statistic is asymptotically distributed as a chi-squared random variable, with degrees of freedom equal to the difference between the number of parameters of the two models. The likelihood ratio test can be done provided the simpler model is a special case of the complex model.

The LRT can also be presented in terms of deviance, that is:

$$\begin{aligned} LRT &= -2(log_e(L_s) - log_e(L_g)) && (2.90)\\ &= -2log_e(L_s) + 2log_e(L_g) && (2.91)\\ &= deviance_s - deviance_g. && (2.92) \end{aligned}$$

Thus, LRT can be computed as a difference between the deviance for the two fitted models. For this research, the LRT is also going to be used to compare the homogeneous model with covariates and the homogeneous model without covariates.

2.7.3 Kaplan-Meier survival curves

Kaplan-Meier product limit estimates of the survival function can be compared to survival estimates from the fitted Markov models. This can be done in cases where a model has an absorbing state for which time of entry is precisely known. Kaplan-Meier estimates are only valid for the assumption of homogeneous subjects.

2.7.4 Contingency table-based methods

This method provides an assessment of the overall fit of the assumed model. Kalbfleisch and Lawless (1985) dealt with balanced observation with categorical covariates. They fitted the model by considering observed and expected transition frequencies either through a likelihood ratio test or an asymptotically equivalent Pearson chi-squared statistic. However, Chen and Sen argue that Pearson chi-square has low power, particularly when the degrees of freedom are very large, and that the asymptotic null distribution cannot be applied when counts in table are small. A Fisher's exact test could be used in case of small counts.

2.8 Summary

The following chapters build the models and fit the models for the HIV data used in the study. The time homogeneous and time inhomogeneous models are fitted, after which a likelihood ratio test is computed to decide which model fits the data best. Comparison of the fitted models and the observed is done using the Kaplan-Meier curves and survival probability curves. Since the data used for this study is made up of patients on treatment, the main focus of this research is the rate of immune recovery, which is defined as the movement from a lower CD4+T cell count to a higher CD4+T cell count.

These models are built in Chapter 4 and Chapter 5, and comparison of fitted models is done in Chapter 6. However, before fitting the models, some preliminary data analysis is done in Chapter 3.

Chapter 3

Preliminary Data Analysis

3.1 Introduction

This chapter describes the data that was used in the study. The trend of the HIV progression, based on CD4+ T-cell count, in patients is also examined by means of line graphs, and a model that explains the relationship is fitted. The Aalen additive regression model is also used in order to have a general view of the covariates effects on the progression of HIV with time.

3.2 Variable coding

For the purpose of analysis, the variables were coded as follows: Gender: 1 - Male , 0 - Female; TB before enrolment (TBB4): 1 - yes, 0 - no; Developed TB on ART (DTB): 1 - yes , 0 - no; Reacted to ART: 1 - yes, 0 - no; The BMI are as follows: $Underweight - < 18.5$, $Normalweight - [18.5; 24.9]$, $Overweight - [25; 25.9]$, $Obese - \geq 30$;

The body mass index (BMI) was measured in kg/m^2 and was calculated using the formula; $BMI = \frac{Weight}{(Height)^2}$ where weight is measured in kilogrammes and height is measured in metres.

The CD4BL are as follows: $1 - CD4 \geq 750,\ 2 - 500 \leq CD4 < 750,\ 3 - 350 \leq CD4 < 500,\ 4 - 200 \leq CD4 < 350,\ 5 - 0 \leq CD4 < 200$;

The WSBL are as follows: 1 - WSBL=4 , 0 - Otherwise; Ages are as follows: $1 - age \leq 40,\ 0 - age > 40$; The VLBL are as follows: $1 - VL \geq 10,000\ 0 - VL < 10,000$.

3.3 Summary statistics

The analysis is done on patients who were enrolled at the clinic in 2004 and 2005. Commencement of treatment for these patients was in 2005 and follow up was done after every 6 months. The size of the population was 318. Table 3.1 shows the frequency distribution for males and females for each given baseline variable.

Table 3.1: Distribution of covariates by gender

		TBB4		DTB		WSBL				CD4BL			
		0	1	0	1	1	2	3	4	2	3	4	5
Female	0	154	73	192	35	1	11	38	107	6	16	37	118
Male	1	55	36	74	17	0	2	12	45	1	1	12	56

Of this population, 227 were females and 91 males. Seventy-three of the females and 36 males had TB before they were enrolled for ART. The WHO stage baseline of the individuals ranged from one to four before commencement of treatment. However, of these individuals, only one had a WHO stage baseline of one, 13 had a WHO stage baseline of two, 50 had a WHO stage baseline of three and 152 had a WHO stage baseline of four. This shows that the majority of the HIV-infected individuals in the study, had a baseline of four. The CD4+T baseline of the selected patients enrollment ranged from 2 to 5, with the majority, $\frac{174}{318}$, having a CD4+T baseline of 5. Out of the 318 HIV-infected individuals, 52 developed TB while they were on treatment. Table 3.2 shows the summary statistics for the variables used in the study.

Table 3.2: Summary statistics

	Age BL (Years)	BMIBL	WHO stage BL	CD4 BL	Viral load BL
Minimum	2	0	1	2	56
1st Quartile	30	16.66	3	4	19719
Median	36	19.38	4	5	58523
Mean	36.47	19.17	-	-	105573
3rd Quartile	44	22.03	4	5	148520
Maximum	77	46.2	4	5	818600

Table 3.2 shows that at enrollment, the ages of the HIV-infected individuals, under study, ranged from 2 years to 77 years, with a mean age of 36.47 years and a median age of 36 years. The viral load baseline ranged from 56 to 818600 viral particles in each millilitre of blood, with a mean of 105573 and a median of 58523. Figure 3.3 shows the frequency distribution of CD4 baseline for each category.

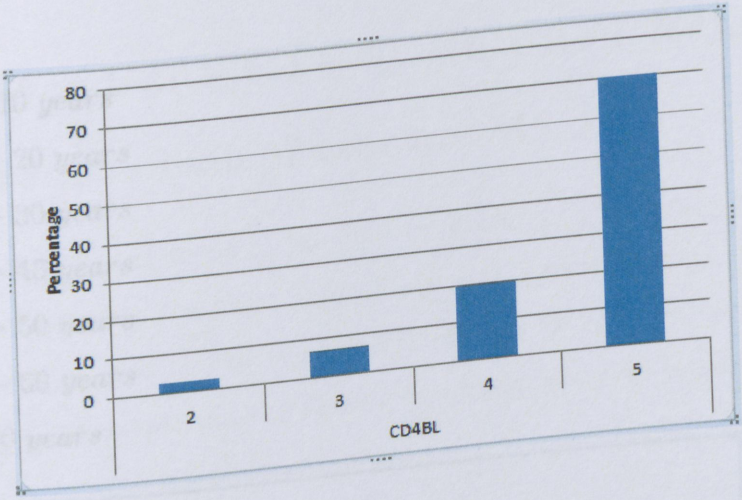


Figure 3.1: *Distribution of CD4 baseline*

Figure 3.1 shows the percentage number of patients in each CD4 baseline level. The results show that there were no patient with CD4BL> 750; the bulk of the patients had $CD4 \leq 200$ (70%) and 30% had $200 \leq CD4BL <$ 750. The interval, $CD4 \leq 200$, is normally referred to as the AIDS defining stage. This means that the majority of the patients started medication when they were already sick from AIDS. There were no subjects with a CD4 baseline level of 1 before initiation of treatment.

Figure 3.2 gives a distribution of CD4 baseline levels by age group. In Figure 3.2 the age groups for the subjects were defined as follows:

$1: \ 0 - 10 \ years$

$2: \ 11 - 20 \ years$

$3: \ 21 - 30 \ years$

$4: \ 31 - 40 \ years$

$5: \ 41 - 50 \ years$

$6: \ 51 - 60 \ years$

$7: \ > 60 \ years$

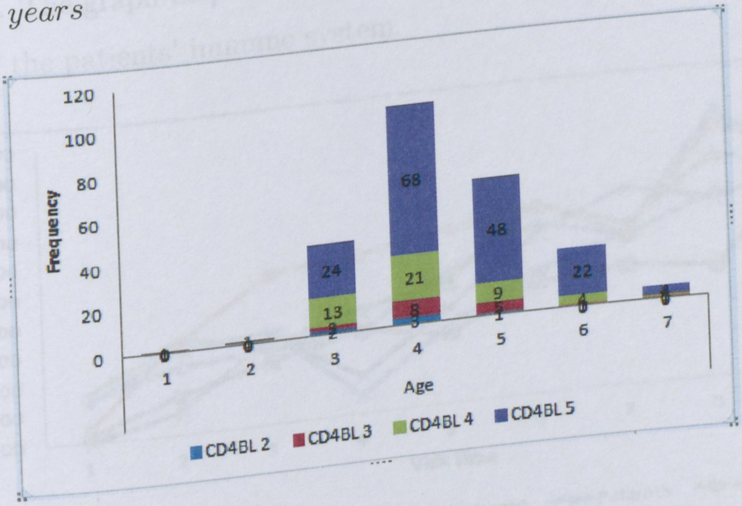


Figure 3.2: *Comparison of CD4 baseline by age*

Figure 3.2 shows that the distribution of the age groups is negatively skewed. It shows that there were very few participants in the age groups 1 (0-10 years) and 2 (11-20 years). The highest number of participants were in the age group 4 (31-40 years) followed by age group 3 (21-30 years).

3.4 Trend of CD4+ T cell count from commencement of treatment

Figure 3.3 shows the trend of the HIV progression of six randomly selected patients. Focus was on the CD4+ T cell count before classification. The purpose of this was to see the general pattern of HIV progression in an individual. The graph helps to show if treatment plays an important role in improving the patients' immune system.

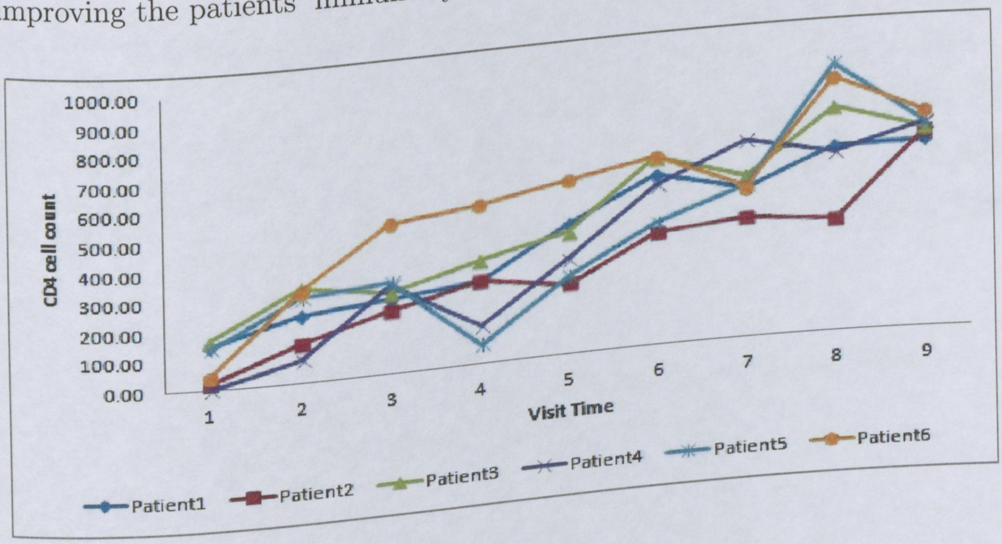


Figure 3.3: *Progression of HIV in individuals under ART based on CD4+T cell count*

Figure 3.3 shows a generally increasing trend on the CD4+T cells at every visit. The trend is characterised by a sharp decrease at one particular point for each individual. For patients 1, 3 and 6, the decrease was noticed on the 7th visit. For patients 5 and 4, the decrease was noticed on the 4th visit, and for patient 2, the decrease was on the 8th visit.

3.5 Analysing the linear relationship between time and CD4+ T-cell count

In this section a linear regression analysis for the response variable CD4+ T-cell count of infected individuals and the independent variable, Time in years, was done. A linear regression model was fitted to check if there is a significant linear relationship between CD4+ T-cell count and time. The model is of the form $CD4 + T - cellcount_i = \beta_{0i} + \beta_{1i}time + \varepsilon_i$, for every i^{th} individual in the study. The results from the analysis are shown in Table 3.3.

Table 3.3: Fitted model for the progression of HIV over time

	Estimate	Std.error	t-value	$Pr(>\lvert t \rvert)$
Intercept	110.4	15.71	7.003	5.41e-12
time	94.61	5.73	16.513	<2e-16

Res. std. error	df	Multiple R-sq	Adj. R-sq	F-statistic	p-value
230.9	780	0.259	0.2581	272.7	<2.20e-16

The results of the linear relationship between CD4+ T-cell count and time shown in Table 3.3 show a positive linear relationship between the two variables. The linear model that best describes the linear relationship between state and time is:

$$CD4 + T - cellcount = 110.04 + 94.61 * time \tag{3.1}$$

This shows that during the period of study, the CD4+ T-cell count of an individual i increased with time. This is an indication of effectiveness of ART that was being administered to the patients. The p-values of $5.41e-2$ and $< 2e-16$ show that both the intercept and time contribute significantly to change in CD4+ T-cell count. The overall fit with a $p < 2.20e-16$ also confirms this. The fitted regression model accounts for about 26 percent of the variation in CD4+ T-cell count by knowing an individual's time of entry into a particular CD4+ T-cell count.

3.6 Aalen model for HIV progression

Torner (2004) described Aalen's additive regression model as follows: Assume that one observes the possibly censored life time of a number of individuals. Let λ_i be the hazard rate of individual i, n be the number of individuals and r the number of covariates in the analysis. By considering the column vector $\lambda(t)$of hazard rates $\lambda_i(t), i = 1, 2, \ldots n$, the additive model is given by:

$$\lambda(t) = Y(t)\alpha(t) \tag{3.2}$$

where the $n \times (r+1)$ matrix, $Y(t)$ is constructed as follows: If the individual is a member of the risk set at time t, then the ith row of the $Y(t)$ is the vector:

$$Z^i(t) = (1, z_1^i(t), z_2^i(t), \ldots, z_r^i(t))' \tag{3.3}$$

where $z_j^i(t), j = 1, \ldots, r$ are possibly time-dependent, covariate values. If at time t, the individual i is at risk, then the corresponding row of $Y(t)$ contains only zeros.

The vector $\alpha(t) = (\alpha_0(t), \alpha_1(t), \ldots \alpha_r(t))'$, contains the regression information. The first element α_0 is a baseline function, while the remaining elements are called regression functions that measure the influence of the respective covariates. These functions are allowed to vary freely over time.

3.6.1 Hypothesis testing

One primary question may be, "does a specific covariate have any influence on the distribution of lifetimes?" This corresponds with the hypothesis:

$$H_j : \alpha_j(t) = 0 \tag{3.4}$$

where j corresponds to the j^{th} covariate in the analysis. A test statistic for H_j is given by the j^{th} element U_j of the vector:

$$U = \sum_{T_i} K(T_i) X(T_i) I_i \tag{3.5}$$

where $K(t)$ is an $(r+1)\times(r+1)$ diagonal matrix of weight function. $X(T_k)I_k$ is the cumulative regression function estimator and the test statistic is, therefore, simply a weighted summation of the cumulative regression function estimator for all events.

3.6.2 Aalen's additive regression model for HIV data

For the HIV data used in this study, $n = 318$ and the number of covariates is $j = 9$. The covariates are: CD4 baseline ($CD4BL$), Age, Gender ($Male$), TB before enrollment ($TBB4$), Developed TB during the course of treatment (DTB), adverse reaction to treatment ($Reaction$), the WHO stage baseline ($WSBL$), BMI progression (BMI) and viral load baseline ($VLBL$). The effects of these covariates on the progression of HIV was analysed using the package "survival" in R and the results are discussed next.

To identify the model that fits the data best, I considered a full model in which all the covariates were included. The full model resulted in a $p-value = 0.16$, which is not significant. The next step was to remove the variable $VLBL$ which was highly insignificant ($p-value = 0.6170$). The resulting model had a $p-value = 0.066$, which although marginally significant, is quite an improvement compared to the full model . In the next step, the variable $WSBL$ was removed since it had a $p-value = 0.399$ and this resulted in a fitted model with $p-value = 0.03$, which is significant. A further attempt to reduce the model was done by removing the variable $TBB4$, which had a $p-value = 0.15$, resulting in the $p-value$ of the fitted model rising to 0.046. Table 3.4 shows the Aalen model that best describes HIV progression.

The fitted model in Table 3.4 suggests that the variables CD4, DTB and gender are significant contributors to the cumulative hazard of HIV progression in any given subject. The regression parameters $\hat{\beta}(DTB) = -0.011$, SE=0.00394 and p-value=0.00512 show that the patients who developed TB have lower incidence rates. $\hat{\beta}(Gender) = 0.0103$, SE=0.00516 and p-value=0.0452 show that males have higher incidence rates than females. This could be due to the fact that females are more sensitive to health issues com-

Table 3.4: Aalen's model for HIV progression

	Slope ($\alpha_j(t)$)	Coef.	SE(coef.)	z-value	p-value
Intercept	0.61300	0.0461	0.0137	3.37	0.000741
Age	-0.00511	-0.000396	0.000211	-1.87	0.0609
Gender	0.11600	0.010300	0.005160	2.00	0.0452
TBB4	0.04480	0.00431	0.002990	1.44	0.15000
DTB	-0.13900	-0.011000	0.003940	-2.80	0.00512
CD4	-0.08470	-0.00601	0.00214	-2.81	0.00494
BMI	0.00540	0.000437	0.000235	1.86	0.0624

pared to men. Although not significant contributors, the patients who had TB before treatment had higher incidence rates than those who did not have TB as the initial marker. Younger patients (below 40 years) had lower incidence rates than older ones (above 40 years).

3.7 Summary

In this chapter, the linear relationship between CD4+ T-cell count and time was assessed. The Aalen regression model was then used to analyse the effects of the covariates on HIV progression with time. However, the Aalen model had some shortfalls in the sense that it failed to give the covariates effect in each stage of progression. The next chapter seeks to address this issue by fitting time homogeneous Markov models on HIV data.

Chapter 4

Fitting a Time-Homogeneous Markov Models

4.1 Introduction

In this chapter, time homogeneous models are fitted using the methods discussed in Chapter 2. In this chapter observed and expected prevalences are used to diagnose the goodness of fit of the models: the model with covariates and the model without covariates. However, a test for homogeneity is done in Chapter 6 after fitting the inhomogeneous model in Chapter 5.

4.2 Time homogeneous model for HIV data

In this model, a 7-state structure is proposed for the HIV data. The first five states are constructed based on HIV/AIDS progression and the last two states are absorbing states, namely death and withdrawal from the study.

Based on this structure, a two-way transition intensity matrix is developed. The plot of residuals was used to clearly identify the outliers before fitting the models. The time homogeneous model is fitted and the effects of the covariates on transition intensities is assessed. The *msm* package for *R* developed by Jackson (2013) is used for all the analysis in this study.

The first stage of Markov modeling involved the computation of transition counts between the seven states: $CD4 > 750$ (SI), $500 \leq CD4 < 750$ (SII), $350 \leq CD4 < 500$ (SIII), $200 \leq CD4 < 350$ (SSIV), $CD4 < 200$ (SV), Death and Withdrawal. The progression of HIV within an individual is modeled as shown in the state diagram on Figure 4.1. The arrows in the diagram show possible transitions from one state to the other. The diagram shows

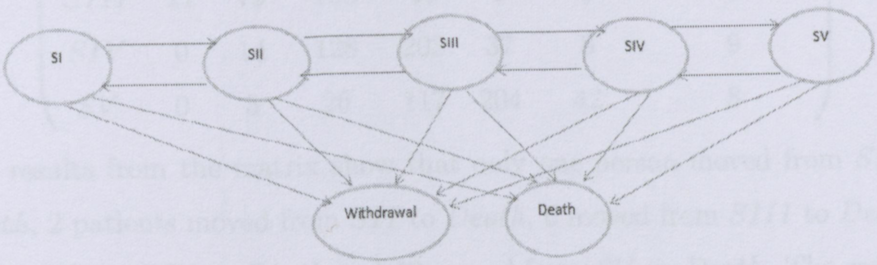


Figure 4.1: *The state diagram for HIV progression in the human body*

that state *Death* and state *Withdrawal* represent the absorbing states. As HIV progresses in an individual's body, there is a possibility of an individual being in the same state in consecutive visit times. The Markov models were built based on the states shown in the state diagram in Figure 4.1.

The transition count for all the individuals, in the study, were computed before computation of all the other parameters. The transition counts were calculated by counting the transitions from state h to state j from the beginning of the study until time t and these are denoted by:

$$N_{hj\cdot}(t) = \sum_{i=1}^{n} N_{hji}(t), t \in [0, T], h \neq j. \tag{4.1}$$

The matrix below shows the transition counts from each state for the individuals in the study:

	To						
From	SI	SII	$SIII$	SIV	SV	$Death$	$Withdrawal$
SI	69	34	5	1	1	1	1
SII	47	80	37	4	0	2	4
$SIII$	21	79	193	46	9	6	5
SIV	0	14	128	203	37	8	9
SV	0	3	26	117	204	42	8

The results from the matrix show that only one person moved from SI to $Death$, 2 patients moved from SII to $Death$, 6 moved from $SIII$ to $Death$, 8 moved from SIV to $Death$ and 42 moved from SV to $Death$. The results show that the number of transitions to the death state for HIV-infected individuals increases as the CD4 cell count per mm^3 of blood decreases. The patients in SV have the lowest number of CD4 cells, hence the highest number moving from that state to the death state. The results also show that there is no movement from the first five states to the absorbing states, $Death$ and $Withdrawal$.

Transition counts for patients who remain in the same state are higher compared to the movement to different states. The upper part of the matrix has got lower values compared to the lower part. This means that more people are moving to a better state, which might be an indication that treatment is effectiveness.

4.2.1 Computing the Transition intensity matrix without covariates

The transition intensity matrix was constructed based on the assumption that movement from state to state is two-way (forward or backward). This means that if a process is in state i, the next movement is to state $i+1$, $i-1$ or to either of the absorbing states, *Death* or *Withdrawal*, provided that state i is not absorbing. The transition intensity matrix used was of the form:

$$\begin{pmatrix} q_{11} & q_{12} & 0 & 0 & 0 & q_{16} & q_{17} \\ q_{21} & q_{22} & q_{23} & 0 & 0 & q_{26} & q_{27} \\ 0 & q_{32} & q_{33} & q_{34} & 0 & q_{36} & q_{37} \\ 0 & 0 & q_{43} & q_{44} & q_{45} & q_{46} & q_{47} \\ 0 & 0 & 0 & q_{54} & q_{55} & q_{56} & q_{57} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

where

$$
\begin{aligned}
q_{11} &= -(q_{12} + q_{16} + q_{17}), \\
q_{22} &= -(q_{21} + q_{23} + q_{26} + q_{27}), \\
q_{33} &= -(q_{32} + q_{34} + q_{36} + q_{37}), \\
q_{44} &= -(q_{43} + q_{45} + q_{46} + q_{47}) and \\
q_{21} &= -(q_{54} + q_{56} + q_{57}).
\end{aligned}
$$

The expressions for the q_{ii}s are based on the assumption that $\sum_{j=1}^{k} q_{ij} = 0$. The transition rate matrix defined above is the basis for building the intensity matrix for the HIV data. Computation of the approximate transition intensity matrix is done as follows:

$$\hat{q}_{hj}^{n} = \frac{N_{hj.}(t)}{\int_0^T Y_{h.}(s)ds}, h \neq j, \tag{4.2}$$

for $\int_0^T Y_{h.}(s) > 0$, $Y_{h.}(t) = \sum_{i=1}^{n} Y_{hj}(t) \leq n$, with $Y_{hj}(t) = I_{(X_{t\_}^{i}=h)}$, gives the number of HIV infected individuals in state h just before time t. $N_{hj.}(t)$ is defined in (4.2). The resulting transition intensity matrix was as follows;

$$
\begin{array}{l}
\begin{array}{cccccccc}
 & SI & SII & SIII & SIV & SV & Death & Withdrawal
\end{array} \\
\begin{array}{c|ccccccc}
SI & -1.215 & 0.982 & 0 & 0 & 0 & 0.1176 & 0.1153 \\
SII & 0.6871 & -1.211 & 0.4256 & 0 & 0 & 0.07264 & 0.02606 \\
SIII & 0 & 0.4373 & -0.8327 & 0.3382 & 0 & 0.0273 & 0.02983 \\
SIV & 0 & 0 & 0.5524 & -0.8509 & 0.2242 & 0.0364 & 0.03818 \\
SV & 0 & 0 & 0 & 0.5482 & -0.6744 & 0.09044 & 0.03574 \\
Death & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
Withdrawal & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{array}
\end{array}
$$

$-2 * LL : 3969.72$.

The best state in the HIV progression, according to this model, is SI with $CD4 \geq 750$ and the worst state is SV with CD4 cells in the range $[0, 200)$. The results from the transition rate matrix show a higher rate of moving to a better state compared to the rate of moving to a worst state of HIV progression. For example, the rate of moving from SII to SI is 0.6871, which is higher than the rate of movement from SII to $SIII$ at 0.4256. However, the rate of withdrawal from SI is the highest compared to withdrawal from all the other states. There is a higher rate of dying from SV than from SII, $SIII$ and SIV. From $SIII$ to SV, the rates of reaching death are increasing with decreasing CD4 cell counts.

Before proceeding with the building up of the model, there is need to check whether there are any outlying subjects in the data since these may have effects on the calculated parameters. This is done by computing score residuals and then plotting the graph to identify the outlying subjects as shown in the next subsection.

4.2.2 Score Residuals Plot

The residuals plot displays the residuals for each subject in the order labeled by subject identifiers. For a single subject, the score residual is given by:

$$U(\theta)^T I(\theta)^{-1} U(\theta)$$

where $U(\theta)$ is the vector of first derivatives of the log-likelihood for that subject at maximum likelihood estimates θ, and $I(\theta)$ is the observed Fisher information matrix, that is, the matrix of second derivatives of minus the log-likelihood for that subject at theta. Subjects with a higher influence on the maximum likelihood estimates will have higher score residuals (Jackson, 2013). The plot of residuals for each of the individuals, in the study, was drawn using the *msm* command *scoreresid.msm* to identify the outliers (subjects with higher influence) in the data. Figure 4.2 shows the plot of residuals.

Figure 4.2 shows that patients with ID numbers 81 and 82 are outliers. The corresponding residuals for these values are 1.58315799 and 1.58315999, respectively. Patient number 81 was enrolled whilst in SI and maintained the state throughout the study period. Patient number 82 was enrolled whilst in state SIV and, during the third visit, was already in state SI and maintained it throughout the study period. The next section compares transition intensities from a model with outliers and the one without outliers.

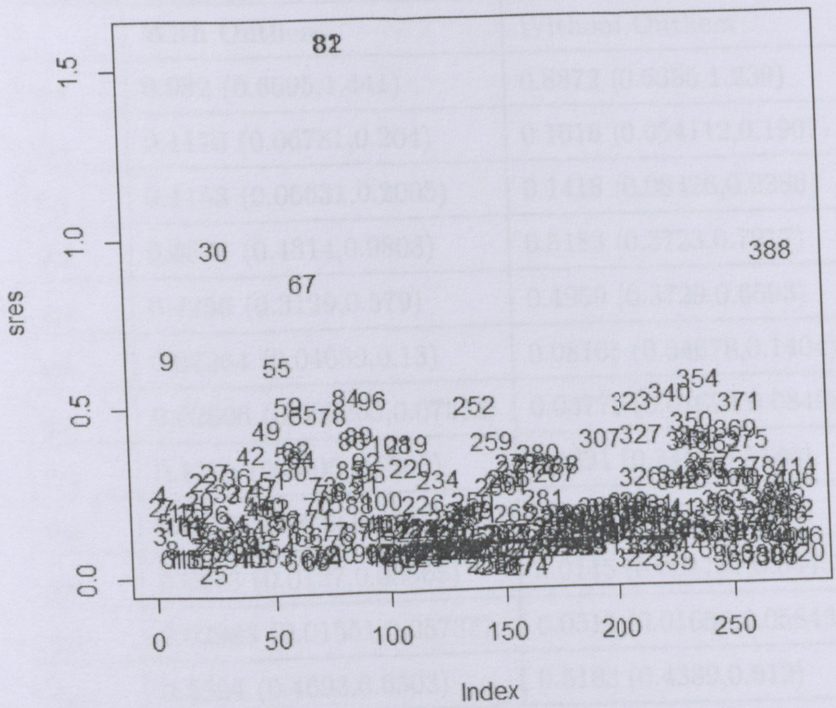


Figure 4.2: *The score residuals plot*

4.2.3 Comparison of the homogeneous model with outliers and the homogeneous model without outliers

To check whether the outliers have any effect on the transition intensities, the transition intensities recomputed after the outliers were removed. Table 4.1 is a comparison of the the two models.

Table 4.1: Comparison of transition intensities for the model with outliers and the model without

	With Outliers	Without Outliers
q_{12}	0.982 (0.6695,1.441)	0.8872 (0.6355,1.239)
q_{16}	0.1176 (0.06781,0.204)	0.1016 (0.054112,0.1907)
q_{17}	0.1153 (0.06631,0.2005)	0.1418 (0.08426,0.2386)
q_{21}	0.6871 (0.4814,0.9808)	0.5183 (0.3723,0.7217)
q_{23}	0.4256 (0.3129,0.579)	0.4959 (0.3729,0.6593)
q_{26}	0.07264 (0.04059,0.13)	0.08105 (0.04678,0.1404)
q_{27}	0.02606 (0.009253,0.07338)	0.03772 (0.01674,0.08498)
q_{32}	0.4373 (0.3605,0.5305)	0.4231 (0.3451,0.5186)
q_{34}	0.3382 (0.2639,0.4335)	0.3324 (0.2605,0.4241)
q_{36}	0.0273 (0.0127,0.05865)	0.0145 (0.004737,0.04439)
q_{37}	0.02983 (0.01551,0.05737)	0.0311 (0.01656,0.05843)
q_{43}	0.5524 (0.4693,0.6503)	0.5183 (0.4389,0.612)
q_{45}	0.2242 (0.1686,0.298)	0.2523 (0.1936,0.3287)
q_{46}	0.03614 (0.01712,0.07629)	0.003325 (0.0149,0.07419)
q_{47}	0.03818 (0.02253,0.0647)	0.05414 (0.03518,0.08333)
q_{54}	0.5482 (0.4651,0.6463)	0.5164 (0.4356,0.6123)
q_{56}	0.09044 (0.06217,0.1316)	0.09058 (0.06249,0.1313)
q_{57}	0.03574 (0.02112,0.06048)	0.0288 (0.01582,0.0524)
-2xLL	3969.72	3941.971

Table 4.1 shows that the removal of outliers from the data had a significant effect on the likelihood, as well as on the transition intensity estimates for

the fitted model. The removal of the outliers resulted in a change by 27.749 of the $-2LL$, which shows that the removal of outliers has a significant effect on the model. Generally, the model without outliers has lower transition intensities compared to the one with outliers.

4.2.4 Mean sojourn times for homogeneous Markov model

The mean sojourn time in a transient state r is estimated by $\frac{-1}{q_{rr}}$, where q_{rr} is the rth entry on the diagonal of the estimated transition intensity matrix. The mean sojourn times were computed to see the average time of stay in each state by the process. The results are shown in the Table 4.2;

Table 4.2: Mean sojourn times

	Estimates	SE	Confidence interval
SI	0.8844741	0.12602569	(0.6689603; 1.169418)
SII	0.8826571	0.09158707	(0.7202261; 1.081721)
SIII	1.2482706	0.09636263	(1.0729973; 1.452175)
SIV	1.1655588	0.07925375	(1.020130301; 1.331720)
SV	1.5728163	0.11539878	(1.3621492; 1.816065)

Just like the transition probability matrix, the mean sojourn time results confirm that the process spends more time in state SV, followed by state $SIII$ compared to the time spent in the other states. The results from the matrix show that death from SV, which is the class with the lowest number of CD4 cell counts, is rapid, with a mean of 1.5728.

4.2.5 Computing the probability of each state being next

This subsection seeks to answer the question: "Suppose an HIV+ individual is in state r, what is the probability of that individual being in the next state, either $r+1$, $r-1$, *death* or *withdrawal*". The computed matrix of probabilities of each state being next, together with the mean sojourn times in each state, fully define a continuous-time Markov model. This is a more intuitively meaningful description of a model than the transition intensity matrix. The matrix for the probability of each state being next is shown below:

$$
\left(\begin{array}{lccccccc}
 & To & & & & & & \\
From & SI & SII & SIII & SIV & SV & Death & Withdraw \\
SI & 0 & 0.7847 & 0 & 0 & 0 & 0.08986 & 0.1254 \\
SII & 0.5281 & 0 & 0.4377 & 0 & 0 & 0.07154 & 0.03329 \\
SIII & 0 & 0.5281 & 0 & 0.4149 & 0 & 0.0181 & 0.03883 \\
SIV & 0 & 0 & 0.6041 & 0 & 0.294 & 0.03875 & 0.06311 \\
SV & 0 & 0 & 0 & 0.8123 & 0 & 0.1425 & 0.04529 \\
Death & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
Withdraw & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{array}\right)
$$

The results from the fitted matrix show that, from any given state, the probability of a state of immune recovery being next is higher than the probability of moving to a state of immune deterioration. This is an indication of the effectiveness of treatment. Probability of the death state being next is higher for those patients with CD4 counts less than 500. These probabilities increase with the decreasing number of CD4 counts.

4.2.6 Computation of the probability matrix

The fitted transition probability matrix $P(t)$ over an interval $t = \frac{1}{2}$ year was constructed to compare the probabilities of immune recovery with probabilities immune maintenance and the probability of immune deterioration. The results are shown in the matrix below.

$$
\begin{array}{c|ccccccc}
 & \multicolumn{7}{l}{To} \\
From & SI & SII & SIII & SIV & SV & Death & Withdraw \\
\hline
SI & 0.2912 & 0.3131 & 0.1256 & 0.02115 & 0.002141 & 0.1148 & 0.132 \\
SII & 0.1829 & 0.3503 & 0.234 & 0.05481 & 0.007209 & 0.09679 & 0.07403 \\
SIII & 0.06261 & 0.1996 & 0.4329 & 0.1726 & 0.03287 & 0.04426 & 0.05511 \\
SIV & 0.01644 & 0.07291 & 0.2692 & 0.3847 & 0.1382 & 0.05277 & 0.06584 \\
SV & 0.003407 & 0.01963 & 0.1049 & 0.2829 & 0.4388 & 0.1026 & 0.04775 \\
Death & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
Withdraw & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{array}
$$

The fitted probabilities suggest that in half a year, 31%, 12.5%, 2%, 0.2%, 11% and 13% of the patients in SI will be in SII, $SIII$, SIV, SV, dead and withdrawn, respectively. The results from the probability matrix show that there is a higher probability of transition from any given state to a better HIV state than that of moving to a worst HIV state. For example, given that the process is in state SIV, the probability of moving to $SIII$ is 0.2692, which is greater than the probability of moving to SV. The probabilities get smaller and smaller for every step in the movement to a worst HIV state. If the process is in state SI, the probabilities get smaller for every step transition to state SV. The probabilities of being in a state and remaining in that state are higher than the probabilities of moving to the next state. The probability of remaining in state SV is the highest, with a probability of 0.4388, compared to the probability of remaining in the other four states. This is an indication that HIV-infected individuals on treatment take more time in SV, which is the AIDS defining state.

4.2.7 Prevalence for the model without covariate

Using the fitted time-homogeneous Markov model, the percentage prevalence plots were done to compare the fitted model with the observed. The percentage prevalence plots were fit for each state. The results are shown in Figure 4.3.

The results show a sharp decrease on SV percentage prevalence with the fitted model, underestimating the model for observed data up to $time = 7$. The percentage prevalence for the $death$ state is increasing at a slow rate with some form of stationarity $time = 2$ to $time = 8$. For all the other states, the model seems to be fitting very well except for the $withdrawal$ state where the fitted model over estimates the observed by a very high margin.

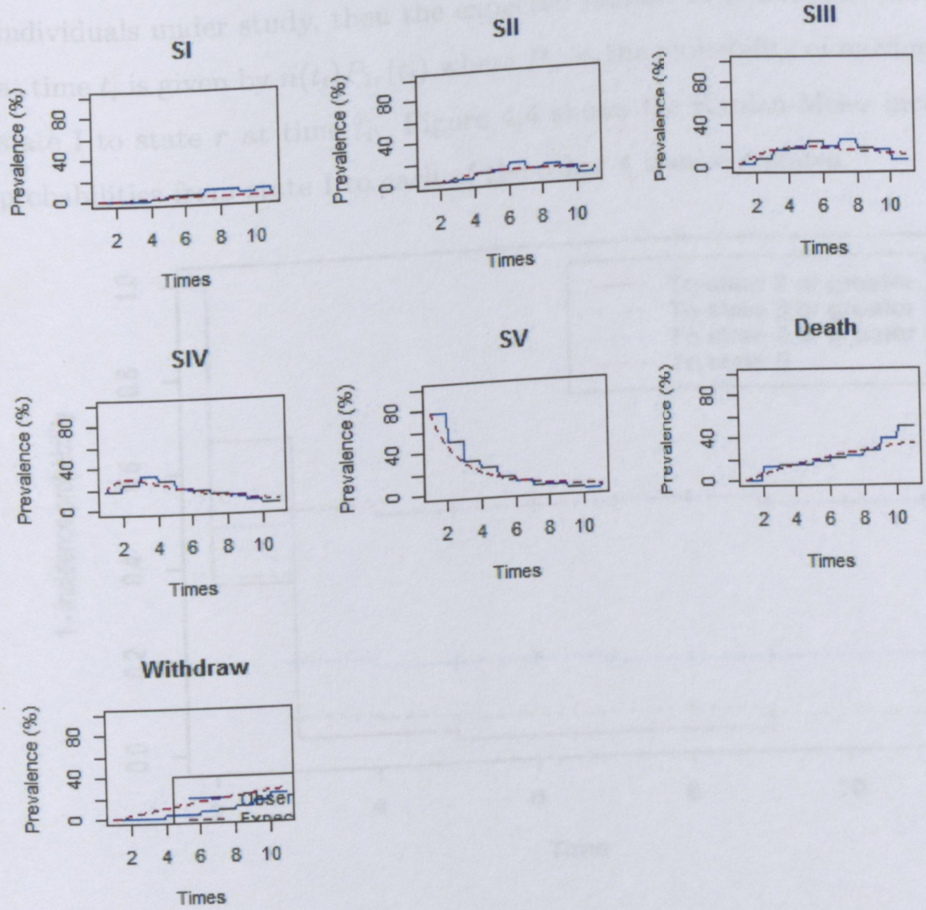


Figure 4.3: *Comparison of observed and expected prevalence from the time-homogeneous model without covariates*

4.2.8 Kaplan-Meier Incidence

The Kaplan-Meier incidence was developed by assuming that an individual's state at time t was the same as the state at their previous observation time for all individuals. For any given time, t_i, suppose we have $n(t_i)$ HIV-infected individuals under study, then the expected number of individuals in state r at time t_i is given by $n(t_i)P_{1r}(t_i)$ where P_{1r} is the probability of moving from state I to state r at time t_i. Figure 4.4 shows the Kaplan-Meier incidence probabilities from state I to each of the other 4 transient states.

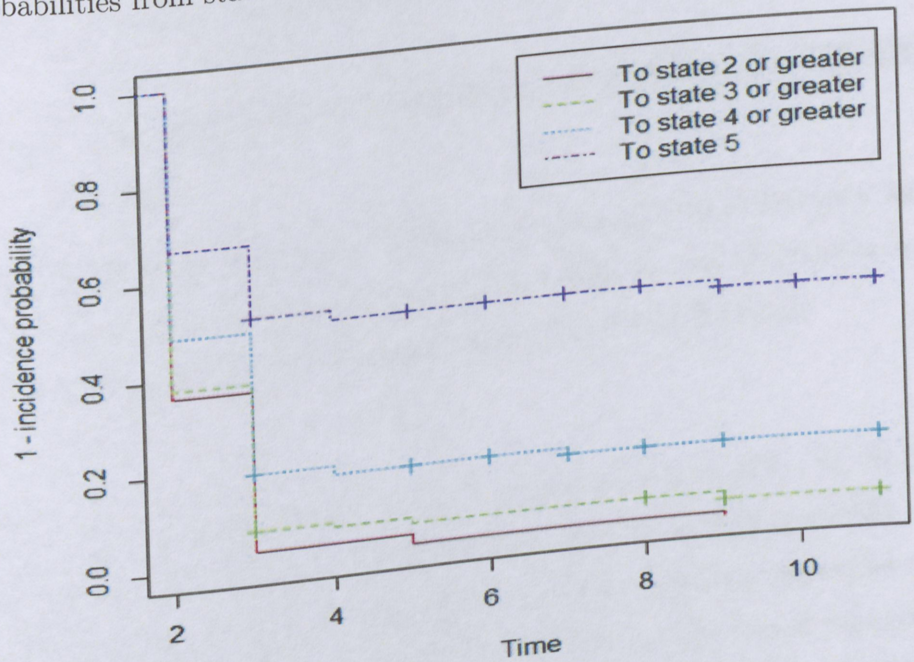


Figure 4.4: *Kaplan-Meier incidence for CD4 states*

Figure 4.4 shows that the incidence probabilities to all the states are decreasing with time. However, the incidence probabilities to state 2 (SII), $CD4 = [500, 750)$, or greater are decreasing at the fastest rate compared to the other four states and state 5 (SV). $CD4 = [0, 200)$, had the highest incidence probabilities throughout the whole study period. The incidence probabilities are decreasing as the CD4 count increases, thus, the higher the

CD4 count, the lower the incidence probabilities. This means that, by the end of the study, we will be having the highest number of individuals in state 2 (SII) and lowest in state 5 (SV).

4.2.9 Comparison of transition intensities by CD4BL levels

The CD4BL levels range from 2 to 5 since at the beginning of the study there were no individuals with $CD4 \geq 750$. The results for the effects of each of the levels to the transition intensities are shown in the Table 4.3.

The results from Table 4.3 show that transition rates from $SII-SI$, $SIII-SII$, $SIV-SIII$ and $SV-SIV$ increase with the increasing CD4BL. Individuals with a $CD4BL = [500, 750)$ had highest transition intensities to a better state, and those with $CD4BL = [0, 200)$ had the lowest transitions to a better state. The transitions intensities $SI-Death$, $SII-Death$ and $SIII-Death$ are the lowest for the individuals who had a CD4BL in the range $[500, 750)$ and the intensities decrease as the CD4BL decreases. The transition rates $SI-SII$ and $SII-SIII$ are the highest for those individuals who had a CD4BL below 200, and these rates decrease with increasing CD4BL.

Table 4.3: Transition intensities for each CD4 baseline

	CD4 Baseline (CD4BL)			
	[500;750)	[350;500)	[200;350)	[0;200)
SI-SII	3.128	6.318	12.76	25.78
SI-Death	0.01249	0.02031	0.03302	0.05369
SI-Withdraw	0.03888	0.05601	0.0807	0.1163
SII-SI	0.6644	0.5991	0.5407	0.487
SII-SIII	0.2842	0.4054	0.5783	0.8249
SII-Death	0.01763	0.01848	0.01936	0.02029
SII-Withdraw	0.02269	0.0278	0.03406	0.04172
SIII-SII	0.245	0.1658	0.1123	0.076
SIII-SIV	0.2749	0.1781	0.1153	0.0747
SIII-Death	0.007937	0.008799	0.009755	0.01081
SIII-Withdraw	0.03473	0.03324	0.03182	0.03045
SIV-SIII	1.399	0.8116	0.4708	0.2731
SIV-SV	0.8935	0.6913	0.5348	0.4138
SIV-Death	0.01097	001062	0.01027	0.009937
SIV-Withdraw	0.04956	0.05095	0.05239	0.05387
SV-SIV	13.14	5.33	2.162	0.8774
SV-Death	0.01921	0.01667	0.01448	0.01257
SV-Withdraw	0.3747	0.2259	0.1362	0.08209

4.2.10 Comparison of transition intensities by WSBL levels

The WSBL for the individuals in the study ranged from 1-4. These stages were developed by WHO in 1990 and were further revised in 2007 based on clinical findings that guide the diagnosis, evaluation and management of HIV/AIDS (WHO,2007). Stage 1 represents the asymptomatic stage and it corresponds with the primary infection stage discussed in Figure 1.1 of chapter 1. Stage 2 is associated with moderate unexplained weight ($< 10\%$). Stage 3 is associated with unexplained weight loss ($> 10\%$). Stage 4 is the symptomatic stage. Table 4.4 shows a comparison of the transition intensities for each of the WSBL levels.

The results from Table 4.4 show that transition intensities to the Death state, from all the states except from SI, are the highest for those individuals who were severely asymptomatic ($WSBL = 4$) and these intensities decrease with the decreasing WSBL.

4.2.11 Hazard ratios of covariates on transition intensities

In this section the function *hazard.msm* was used to display the hazard ratios, $exp(\beta_{ij})$, for each of the predictor variables; Reaction, DTB, TBB4 and Gender. The results are shown the Table 4.5.

The $-2 * Log - likelihood = 3699.259$. The results from Table 4.5 show that the strongest predictor of progression from state $SI - SII$ is reaction to treatment, which has a hazard ratio of 4.715. This means that patients who developed some form of reaction were over 4 times more likely to transit

Table 4.4: Transition for the WSBL

	WHO Stage Baseline (WSBL)			
	1	2	3	4
SI-SII	0.3143	0.1289	0.05286	0.02168
SI-Death	0.004379	0.004059	0.003763	0.003488
SI-Withdraw	0.01389	0.0103	0.007634	0.00566
SII-SI	0.846	0.8758	0.9066	0.9384
SII-SIII	0.125	0.1119	0.1001	0.08961
SII-Death	0.01711	0.01824	0.01944	0.02073
SII-Withdraw	0.01394	0.1286	0.01185	0.01093
SIII-SII	0.8116	1.232	1.87	2.839
SIII-SIV	0.8856	1.197	1.617	2.185
SIII-Death	0.007244	0.008124	0.009111	0.01022
SIII-Withdraw	0.0305	0.02453	0.01973	0.01587
SIV-SIII	4.593	5.075	5.607	6.195
SIV-SV	1.236	1.024	0.8484	0.7028
SIV-Death	0.0139	0.01647	0.01953	0.02315
SIV-Withdraw	0.03253	0.02258	0.01567	0.01088
SV-SIV	67.22	56.63	47.71	40.19
SV-Death	0.03897	0.05961	0.09117	0.1394
SV-Withdraw	0.5792	0.3253	0.1827	0.1026

from a level of $CD4 \geq 750$ to a level of $500 \leq CD4 < 750$ than patients who did not react to treatment.

Table 4.5: Hazard ratios for the covariates on intensities

	Hazard ratios							
	VLBL	DTB	TBB4	Gender	Reac	CD4BL	WSBL	Age
q_{12}	0.69	2.29	0.31	2.04	4.72	1.17	0.55	1.45
q_{16}	1.57	0.87	1.11	1.55	0.60	1.30	1.11	0.83
q_{17}	1.01	0.96	1.00	1.26	0.68	0.92	0.56	0.40
q_{21}	0.48	1.14	0.76	1.33	1.46	1.17	0.74	2.63
q_{23}	0.92	1.98	0.67	6.46	0.67	1.37	0.26	0.40
q_{26}	1.12	0.96	1.69	1.45	0.54	0.997	1.16	1.10
q_{27}	1.30	1.19	1.92	0.93	0.73	1.33	0.79	0.70
q_{32}	0.68	1.58	1.10	2.35	2.08	0.69	0.75	0.83
q_{34}	0.42	2.55	0.53	1.04	0.55	1.57	1.06	0.89
q_{36}	0.92	1.17	2.03	1.20	0.59	1.05	1.32	1.77
q_{37}	1.34	0.86	2.34	0.72	0.20	1.20	0.54	2.06
q_{43}	1.52	1.72	0.86	0.61	1.02	0.27	0.84	1.08
q_{45}	0.74	2.25	1.65	1.36	0.65	1.05	0.46	0.89
q_{46}	1.31	1.09	1.09	1.59	0.22	1.01	1.40	1.96
q_{47}	1.56	1.17	1.88	0.58	0.36	1.02	0.52	2.18
q_{54}	0.51	1.86	1.02	0.81	1.32	0.61	0.40	0.63
q_{56}	0.92	0.65	0.41	2.10	0.06	1.003	2.09	2.60
q_{57}	0.97	1.20	0.88	1.19	0.66	0.87	0.40	2.31

Developing TB during treatment was a second strong predictor of the transition between these states, with a hazard ratio which is over 2 times more than that of those who did not develop TB. Having TB before enrollment was the strongest predictor for the transition from $SIII - Death$. These patients are over 2 times more likely to die from state $SIII$ than those who were enrolled without having TB. Having TB before enrollment is, generally, the major cause of movement of patients to other hospitals.

A hazard ratio of 6.46 for the predictor variable male shows that males were over 6 times more likely to move from $SII - SIII$. The hazard ratios of males from a bad state to a better state are less than 1, which is an indication that males are less likely to respond to treatment compared to females.

The strongest predictor of immune deterioration from a CD4+ cell level between 350 and 500 to a CD4+ cell level between 200 and 350 ($SIII - SIV$) is developing TB during treatment, with a hazard ratio of over 2. Developing TB is also the strongest predictor of immune deterioration from $SIV - SIV$, with a hazard ratio also greater than 2. This means that TB is the major cause of further immune deterioration when the immune system is too weak. This supports the idea that TB is most likely to infect an individual, especially when the immune system is weak.

The hazard ratios for the patients who reacted to treatment are higher for immune deterioration than for immune recovery, which is an indication that reaction plays an important role in HIV progression and reduction in CD4+ cell count levels. The hazard ratios for the transitions to a better state for patients who were enrolled with CD4+ cell counts less than 350 are less than one, but those to a worst state are greater than one, an indication that starting treatment when the CD4+ cell levels are below 350 reduces the rate of immune recovery. The transitions to the death state for individuals who started treatment when they were on the WHO stage of 4 are all more than one, meaning that starting treatment with a WHO stage of 4 is a leading cause of being absorbed in the death state.

4.2.12 Linear effects of covariates on transition intensities

The object project.cov.msm was assigned to the Markov model to analyse the effects of the covariates; Age, CD4BL, VLBL, WSBL, Reaction, DTB, TBB4 and Gender on transition intensities. The function coef(project.cov.msm) was then used to assess the linear effects of each of the covariates on the baseline transition intensities. The results are shown in two separate Tables 4.6 and 4.7;

The fitted time homogeneous model with covariates has -2xLL=3699.259, which represents an improvement of 242.712 compared to the model without covariates. The results from the table show that the rates of recovery of the immune system for both models are higher than the rates of immune deterioration. The transition intensities for the model with covariates are generally lower than the transition intensities for the model without covariates.

The next table shows the linear effect of each of the covariates on the baseline transition intensities (BL intensities) computed above. The model was fit with an assumption of patient homogeneity including covariates on the transition intensities q_{ij}, such that the transition intensity for patient k is given by:

$$q_{ij} = q_{ij}^{(0)} exp\left[\beta_{ij}^{(Reaction)} Reaction_k + \ldots + \beta_{ij}^{(DTB)} DTB_k + \beta_{ij}^{(TBB4)} TBB4_k\right],$$

Table 4.6: Baseline intensities for the covariates effects

	Intensities (q_{ij})	BL Intensities($q_{ij}^{(0)}$)
SI-SII	0.8872	0.503
SI-Death	0.1016	0.020
SI-Withdraw	0.1418	0.0175
SII-SI	0.5183	0.390
SII-SIII	0.4959	0.444
SII-Death	0.08105	0.0111
SII-Withdraw	0.03772	0.0116
SIII-SII	0.4231	0.376
SIII-SIV	0.3324	0.2333
SIII-Death	0.0145	0.0.00630
SIII-Withdraw	0.0311	0.00946
SIV-SIII	0.5183	0.560
SIV-SV	0.2523	0.230
SIV-Death	0.003325	0.00704
SIV-Withdraw	0.05414	0.0084
SV-SIV	0.5164	0.502
SV-Death	0.09058	0.0198
SV-Withdraw	0.288	0.00547
-2xLog-likelihood	3941.971	3699.259

where $q_{ij}^{(0)}$ is the baseline intensity and β_{ij} is the contributing effect of covariate k to the transition intensities. The baseline transition rates presented in Table 4.6 refers to patients who did not react to treatment; patient who did not develop TB during the course of treatment; those who did not have TB before enrollment; and those who had gender 0 indicating that they are females.

Table 4.7: Linear effects of covariates on intensities

Param.	VLBL	CD4BL	WSBL	Reac	DTB	TBB4	Gender	Age
β_{12}	-0.37	0.15	-0.59	1.55	0.83	-1.17	0.7118	0.37
β_{16}	0.45	0.27	0.101	-0.52	-0.14	0.11	0.4379	-0.18
β_{17}	0.0071	-0.088	-0.58	-0.39	-0.039	0.00086	0.23	-0.90
β_{21}	-0.73	0.156	-0.31	0.38	0.13	-0.28	0.29	0.97
β_{23}	-0.84	0.31	-1.35	-0.40	0.68	-0.39	1.87	-0.92
β_{26}	0.112	-0.0028	0.150	-0.63	-0.044	0.53	0.37	0.100
β_{27}	0.26	0.29	-0.24	-0.32	0.17	0.65	-0.077	-0.36
β_{32}	-0.39	-0.37	-0.28	0.73	0.46	0.096	0.86	-0.18
β_{34}	-0.86	0.45	0.057	-0.59	0.94	-0.63	0.036	-0.116
β_{36}	-0.085	0.047	0.28	-0.53	0.16	0.71	0.18	0.57
β_{37}	0.29	0.181	-0.24	-1.63	-0.15	0.85	-0.33	0.72
β_{43}	0.42	-1.32	-0.17	0.020	0.54	-0.15	-0.49	0.080
β_{45}	-0.305	0.049	-0.77	-0.43	0.81	0.50	0.31	-0.12
β_{46}	0.27	0.0079	0.34	-1.50	0.087	0.089	0.46	0.67
β_{47}	0.45	0.020	-0.66	-1.01	0.16	0.63	-0.55	0.78
β_{54}	-0.66	-0.501	-0.91	0.27	0.62	0.022	-0.22	-0.46
β_{56}	-0.079	0.0030	0.74	-2.83	-0.43	-0.89	0.74	0.95
β_{56}	-0.028	-0.141	-0.92	-0.41	0.19	-0.13	0.18	0.84

The results from Table 4.7 show a higher positive linear relationship between developing TB during the course of the treatment and HIV progression than that of recovery. This is an indication that developing TB affects the rate of immune recovery for HIV patients. There is a positive linear effect for patients who developed TB on the transition from a CD4 level below 500 to *Death*, with the highest effect being from a CD4 count between 350 and 200. This supports the results from hazard ratios which show that transition intensities from a CD4 count between 350 and 500 (SIII) to *Death* are the highest for patients who developed TB while on ART.

Having TB before enrollment has the highest effects on the progression from a CD4 count between 350 and 500 (SIII) to *Death* compared to the other covariates. It is also the highest contributor to the rate of withdrawal for patients with the CD4 counts between 350 and 750.

Reaction to treatment contributes highly to the progression from a CD4 count ≥ 750 (SI) to a CD4 count between 500 and 750 (SII).

Being male, generally, has negative effects in the progression of HIV to a better state and a positive effective effect to the progression to a worst state except for the transition from SIII. This means that the response of males to treatment is lower compared to the response of females. A better explanation for the effects of the covariates on HIV progression has been illustrated by the use of hazard ratios.

4.2.13 Prevalence for the model with covariates

The prevalences for the model with covariates were plotted to examine areas of poor fit of the time-homogeneous model with covariates. The plots are shown in Figure 4.5.

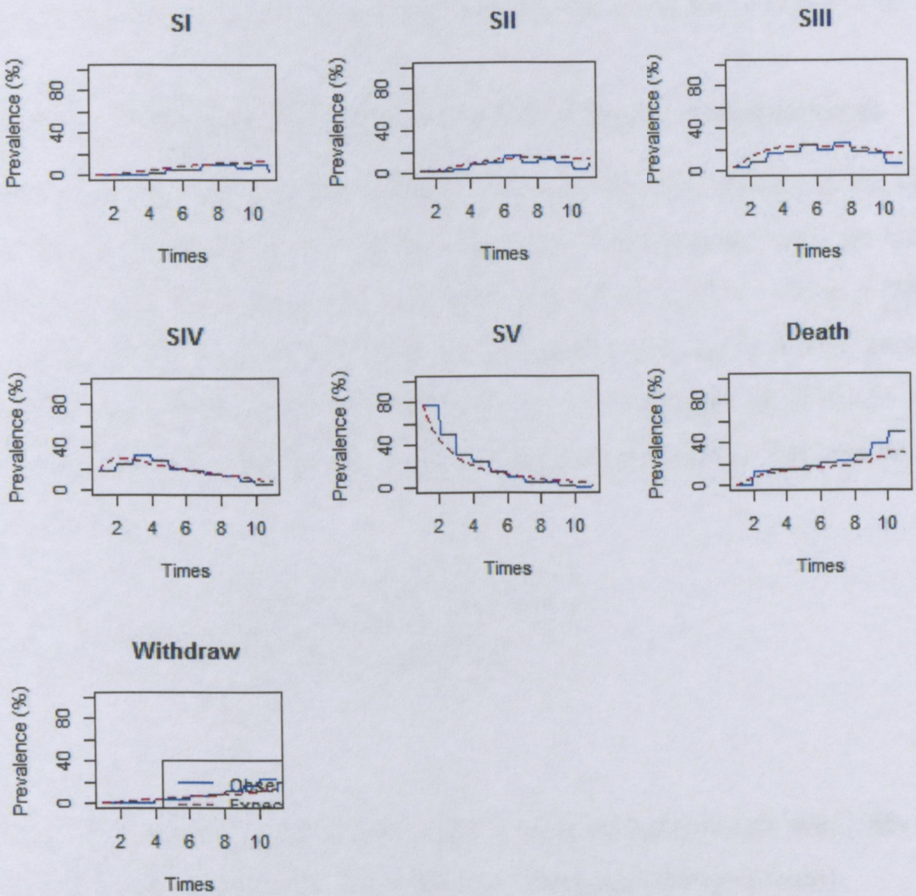


Figure 4.5: *Comparison of observed and expected prevalence from the time-homogeneous model with covarates*

Figure 4.5 shows that the expected counts are relatively close to the observed counts for all states. The model is quite an improvement since the expected and the fitted models for the withdrawal state are quite close.

However, the model still shows a poor fit for the death state from $t = 9$.

4.2.14 Likelihood ratio test for Model comparison

Likelihood ratio test was performed to compare the two nested models that were fit in **msm**, the one without covariates (project.msm) and the other with covariates (project.cov.msm). The value of the $LRT = -2log_e\left(\frac{L_s(\hat{\theta})}{L_g(\hat{\theta})}\right)$ where $L_s(\hat{\theta})$ is the simple model (project.msm) and $L_g(\hat{\theta})$ is the general model (project.cov.msm). A likelihood ratio test statistic of 1770.618 was compared to a χ^2 distribution with 144 degrees of freedom. The results are shown below:

	-2logLR	df	p-value
project.cov.msm	1770.186	144	0.00

The results show that the model with covariates (project.cov.msm) fits significantly better than the model without covariates (project.msm)

Another model with covariates effect constrained equal between different intensities was fit and this was assigned the variable *project.cov1.msm*. Constraints were assigned to each of the covariates based on the nature of transition intensities for that particular covariate. The effects on all deaths were constrained to be equal. A comparison of the likelihood ratio of 822 with a χ^2 distribution with 88 degrees of freedom was performed. The results are shown below:

	-2logLR	df	p-value
project.cov.msm	822.2177	88	0.00

The results still show that the bigger model project.cov.msm without constraints fits the data significantly better.

4.3 Summary

This chapter demonstrated how a time homogeneous Markov model can be fitted from a cohort of HIV-infected individuals. Identification of outliers helped a lot in improving the Markov model fitted for the data. A time homogeneous model was also fitted for the effect of covariates on transition intensities. The likelihood ratio test showed that the model with covariates fits better than the model without covariates. In the next chapter a time inhomogeneity model is fitted.

Chapter 5

Fitting a time Inhomogeneous Markov models

5.1 Introduction

In this chapter, the time-inhomogeneous Markov model for the HIV data from a Wellness clinic in Bela Bela is fitted using the piece-wise homogeneous models defined in chapter 2. The states that are defined in chapter 4 are used in developing the model.

5.2 Time-inhomogeneous model on HIV data

In this section, a piece-wise constant model is fitted for the HIV data to examine the possibility of intensities to change over time. The 5 and 8 cut points are used, implying that 3 segments are used. Since the data was collected after every 6 months, it means that the cut-off point of 5 corresponds with $2\frac{1}{2}$ years, and that of 8 corresponds with 4 years. Selection of the the 5 and 8 cut point was based on the fact that the prevalence rate graphs for homogeneous models showed some changes in their behaviour around these time periods. The use of three segments necessitates the computation of all possible pathways from the last observation time in segment 1 to the first observed time in segment 2, and from the last observed time in segment 2 to the first observed time in segment 3. The estimates of $\mathbf{Q}(t)$ are broken into three segments as shown below:

$$\mathbf{Q}(t) = \begin{cases} Q_1 & 0 \leq t < 5 \\ Q_2 & 5 \leq t < 8 \\ Q_3 & 8 \leq t < 11 \end{cases} \tag{5.1}$$

Applying msm to the defined intervals gives the following estimated intensities:

$$Q_1 = \left(\begin{array}{cccccccc} & SI & SII & SIII & SIV & SV & Death & Withdrawal \\ SI & -0.6668 & 0.6668 & 0 & 0 & 0 & 1.115e-04 & 9.945e-07 \\ SII & 0.494 & -0.878 & 0.358 & 0 & 0 & 1.517e-03 & 2.467e-02 \\ SIII & 0 & 0.379 & -0.659 & 0.277 & 0 & 1.189e-03 & 1.131e-03 \\ SIV & 0 & 0 & 0.535 & -0.778 & 0.224 & 3.111e-06 & 1.891e-02 \\ SV & 0 & 0 & 0 & 0.640 & -0.741 & 8.023e-02 & 2.142e-02 \\ D & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ W & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{array}\right)$$

Matrix Q_1 is the baseline intensity matrix for the interval $[0,\ 2\frac{1}{2}years)$. The matrix shows higher rates of immune recovery compared to immune deterioration. That is, for all the transition intensities $q_{r,r-1} > q_{r,r+1}$.

The intensities for period 1 (0-2.5 years) are given by $q_{ij}^{(1)}$ and for the periods $r = 2, 3$ the intensities are given by:

$$q_{ij}^{(r)} = q_{ij}^{(1)} exp(\beta_{ij}^{(r)}), \tag{5.2}$$

where β_{ij}^{r} represents the effects for the time in the r^{th} period for the $i \longrightarrow j$ transition intensities. A model allowing different effects for each of the transition intensity for the time points 5 and 8 was fitted. Table 5.1 below shows the effects of the two time periods, [2.5, 4) and [4, inf), on the baseline transition intensities represented by Q_1.

The results from Table 5.1 show an estimated reduction in transition rates to death, from most of the states except state $SIII$ for the time period 2.5 and 4 years post commencement of treatment. The rates of reduction of transitions to the death state SIV are tremendously high compared to the other states. The rate of progression from state $SIII$ to state SII is expected to increase after 2.5 years, but after 4 years, it is expected to decline. However, from state $SIII$ to state SIV its the opposite. For the same interval, the transition rate from state SIV to the AIDS defining state, SV, it is higher than transition to a better state. The same period contributed positively to transition to withdrawal from most of the states. For the time interval represented by Q_3, there is generally an estimated reduction on the rate of withdrawal from most of the states. The interval also has lower transitions to death compared to the time interval [2.5, 4).

Table 5.2 shows the hazard rates for the two time periods, [2.5, 4) and [4, inf), relative to the time interval [0, 2.5).

Table 5.1: Linear effects of different time periods on intensities

	Linear effects	
Parameter	Q_2: [2.5, 4)	Q_3: [4, inf)
β_{12}	-0.006	0.316
β_{16}	-13.56	1.197
β_{17}	12.46	-6.419
β_{21}	0.258	0.618
β_{23}	0.491	0.364
β_{26}	-0.864	-13.969
β_{27}	-0.163	-0.251
β_{32}	0.149	-0.197
β_{34}	-0.204	0.258
β_{36}	5.24	6.674
β_{37}	2.112	-7.854
β_{43}	0.0134	0.159
β_{45}	0.141	0.568
β_{46}	-17.06	-19.978
β_{47}	-0.041	-0.733
β_{54}	0.240	0.877
β_{56}	-0.186	-0.169
β_{57}	2.0218	2.930

For the time period $2.5 \leq t < 4$ the rates of immune deterioration are higher than the rates of immune recovery, and are more pronounced for the

Table 5.2: Hazard ratios for the time periods on intensities

	Hazard ratio	
Parameters	[2.5, 4)	[4, inf)
q_{12}	9.939e-01	1.372
q_{16}	1.297e-06	3.311
q_{17}	2.577	1.63e-03
q_{21}	1.294	1.856
q_{23}	1.634	1.439
q_{26}	4.21e-01	8.578e-07
q_{27}	8.493e-01	7.783e-01
q_{32}	1.160	8.212e-01
q_{34}	8.155e-01	1.295
q_{36}	13.94	58.46
q_{37}	8.266	3.881e-04
q_{43}	1.0135	1.172
q_{45}	1.151	1.764
q_{46}	3.89e-08	2.108e-09
q_{47}	9.599e-01	4.801e-01
q_{54}	1.2711	2.404
q_{56}	8.301	8.444e-01
q_{57}	7.552	1.874e+01

transition from state $SIII$ to state SIV, which has a hazard rate of more than 3. This interval also has very high risks of withdrawal from all states.

For the time period $[4, inf)$, the rates of immune recovery are much higher than the rates of immune deterioration, with the highest rate being recorded for the transition from state $SIII$ to state SII, which is more than 3. The period has the highest risks of transition to death. The risk transition from state $SIII$ to death is quite alarming, with a hazard ratio of 58.46 higher compared to the time period of 0-2.5 years. This calls for further analysis in the future to assess the likely cause of this.

The probability matrix for the fitted piece-wise constant model was fitted and the results are shown in the matrix below:

$$\begin{array}{c} \\ From \\ SI \\ SII \\ SIII \\ SIV \\ SV \\ D \\ W \end{array} \begin{pmatrix} To & & & & & & \\ SI & SII & SIII & SIV & SV & D & W \\ 0.593 & 0.339 & 0.049 & 0.0045 & 0.00022 & 0.0097 & 0.00571 \\ 0.220 & 0.569 & 0.156 & 0.0212 & 0.00140 & 0.0122 & 0.0204 \\ 0.041 & 0.2003 & 0.584 & 0.150 & 0.0148 & 0.00394 & 0.00662 \\ 0.0068 & 0.0496 & 0.273 & 0.533 & 0.1036 & 0.0173 & 0.0167 \\ 0.000897 & 0.0087 & 0.0711 & 0.274 & 0.567 & 0.0689 & 0.00921 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

The matrix shows that the probabilities of moving from a lower CD4 count level to a higher CD4 count level are higher than the probability of immune deterioration. The probabilities of maintaining the same state are almost the same, all between 0.5 and 0.6, with the highest probability of maintaining state SI, followed by state $SIII$. Patients who are in the AIDS defining state, SV, have the highest probability of dying compared to those in other states.

5.2.1 Sojourn times for the inhomogeneous model

For the fitted inhomogeneous model, the time spent in each state (sojourn time) before moving to any other states was computed. These sojourn times show how effective the antiretroviral (ARV) therapy is on the progression of HIV. Table 5.3 shows the computed sojourn times in each state for an inhomogeneous Markov model.

Table 5.3: Sojourn times for a time inhomogeneous Markov model

	SI	SII	SIII	SIV	SV
sojourn time	1.499782	1.138920	1.518583	1.286050	1.348762

The sojourn times for the homogeneous Markov model in Table 5.3 show that the HIV-infected patients in the study spent more time in the worst states than in the good states. Table 5.3 shows that, for the inhomogeneous models, HIV infected patients on ARVs spent more time in good states than in bad states. This is an indication that ARVs are playing an important role in reversing the progression of HIV to a better state.

5.2.2 Probability of each state being next

Together with the sojourn times, the probabilities of each state being next in the progression of a system gives a good description of the CTMC. Table 5.4 shows the computed probabilities of each state being next for all the transient states.

Table 5.4: Probability of each state being next

	SI	SII	SIII	SIV	SV	Death	Withdraw
SI	0	0.9998	0	0	0	0.0001673	1.492e-06
SII	0.5621	0	0.4081	0	0	0.001728	0.0281
SIII	0	0.5759	0	0.4205	0	0.001806	0.001718
SIV	0	0	0.6877	0	0.288	4.001e-06	0.02432
SV	0	0	0	0.8628	0	0.1082	0.02897
Death	0	0	0	0	0	0	0
Withdraw	0	0	0	0	0	0	0

Table 5.4 shows that probabilities of the death state being next, given that the process was in either SI, SII, SIII, SIV or SV, are much lower compared to the one for the homogeneous model. The results from the table also show that the probabilities of moving to better states are higher than the probabilities of moving to worst states. These probabilities of better states being next are even higher than the ones obtained for homogeneous Markov models.

5.2.3 Inhomogeneous models and covariates effects

The hazard ratios and the linear effects of covariates on baseline intensities were computed using the same covariates used for homogeneous models. However, the computed values were the same for both the homogeneous and the inhomogeneous models. The reason could be that there is not much difference between the homogeneous and the inhomogeneous model, although the baseline intensities are different.

5.3 Summary

This chapter explored the time inhomogeneous models and their importance in modelling the progression of diseases. Illustration of how the models work was done using the HIV cohort from Bela Bela. The effects of time change on the baseline transition intensities were analysed using three time periods; [0; 2.5), [2.5; 4) and [4, Inf). The baseline transitional intensities for the time period [0; 2.5) were computed. The hazard rates to the baseline intensities were also computed for the time periods [2.5; 4) and [4, Inf). The results from this chapter showed a general reduction on transitions to death as time increases. The transition probability matrix also showed that rates of immune recovery are higher than the rates of immune deterioration as revealed by the homogeneous model. In the next chapter, the fitted homogeneous and inhomogeneous models are compared to see which model fits the data best.

Chapter 6

Comparison of the fitted Time Homogeneous and Inhomogeneous models

6.1 Introduction

In Chapter 4 and Chapter 5, the time homogeneous and the time inhomogeneous models, respectively, were fitted for a cohort of HIV patients under treatment in Bela Bela. This chapter applies the diagnostic techniques discussed in Chapter 2 to find the model that best describes the HIV data.

6.2 Likelihoood ratio test for time homogeneity

We now focus on the question whether a time-homogeneous Markov model is suitable for rating the transition history for HIV/AIDS progression for the 318 individuals under study. Our interest is to test the null hypothesis of time homogeneity at a significance level $\alpha = 0.05$ against the alternative of transition intensities with structural breaks. Different partitions $0 = t_0 \leq t_1 \leq \ldots \leq t_{11}$ of time interval $[0; 11]$ containing all time since ART initiation. The maximum number of breaks is set to 2, yielding 3 intervals where transition intensities could vary. Data for eleven 6-month intervals was colected.

Under the null hypothesis, we have 18 parameters to estimate that is; the transition intensities (q_{ij}), and for the alternative we have $18 \times 3 intervals =$ 54 parameters to estimate, implying that we have 36 degrees of freedom. From the fitted homogeneous and non-homogeneous models we have:

$$-2L_s = 3941.971 \; and \; -2L_g = 3804.12, \tag{6.1}$$

respectively. This leads to:

$$X^2 = -2(L_s - L_g) = 137.8506 \tag{6.2}$$

which has a chi-square distribution on 36 degrees of freedom.

The outcome from the computation done in R is shown below:

	-2LogLR	Df	p-value
proj.pci1.msm	110.102	36	1.9466e-09

From the results, proj.pci1.msm represents the fitted inhomogeneous model. Therefore, we reject $H_0(p = 1.9466e-09)$ at the $\alpha = 0.05$ level and conclude that there is an improvement in using the piece-wise constant model.

6.3 Survival probability

By defining survival as "not dying from HIV/AIDS", the estimated survival functions were plotted for each of the 5 transient stages of infection. For each of the states, the probability of survival was initially set to be 1. The following formula was used to compute the survival probabilities:

$$S_{T_i}(t) = 1 - \hat{p}_{i6}(t), \tag{6.3}$$

where $i = 1, 2, 3, 4, 5$.

The graphs in Figure 6.1 show that probabilities of survival decrease with time, but not at an alarming rate. By the end of the period of study, the prevalences from each of the five transient states were all above 0.8. The probability of survival within time t is lowest for those individuals with previous CD4 count < 200 since they have the highest prevalence, and this increases as the previous CD4 count increases. Individuals with a previous CD4 count ≥ 750 have the highest chances of survival. The graph shows an improvement on the survival function from state SI compared to the one for the model without covariates. The fitted time-inhomogeneous model shows that five or more years after commencement of treatment, the probabilities

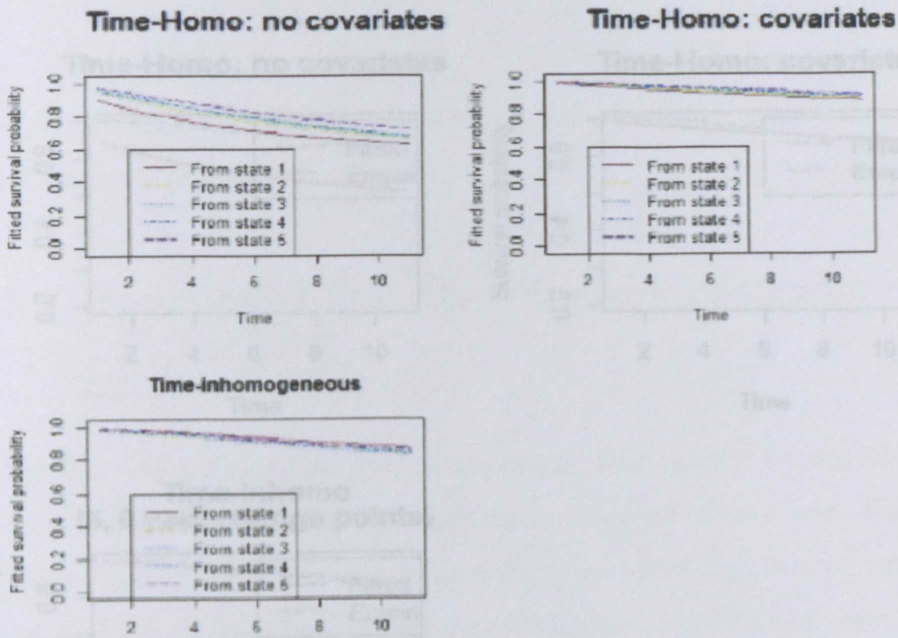


Figure 6.1: *Comparison of survival functions from each of the fitted models*

of survival for each state are greater than 0.8, and the probabilities from each have approximately the same function.

6.4 Diagnostic plots

Diagnostic plots were used to compare model predictions of the entry time into a particular state with non-parametric estimates like the Kaplan-Meier curves.

The results from the diagnostic plots shown in Figure 6.2 reveal that for

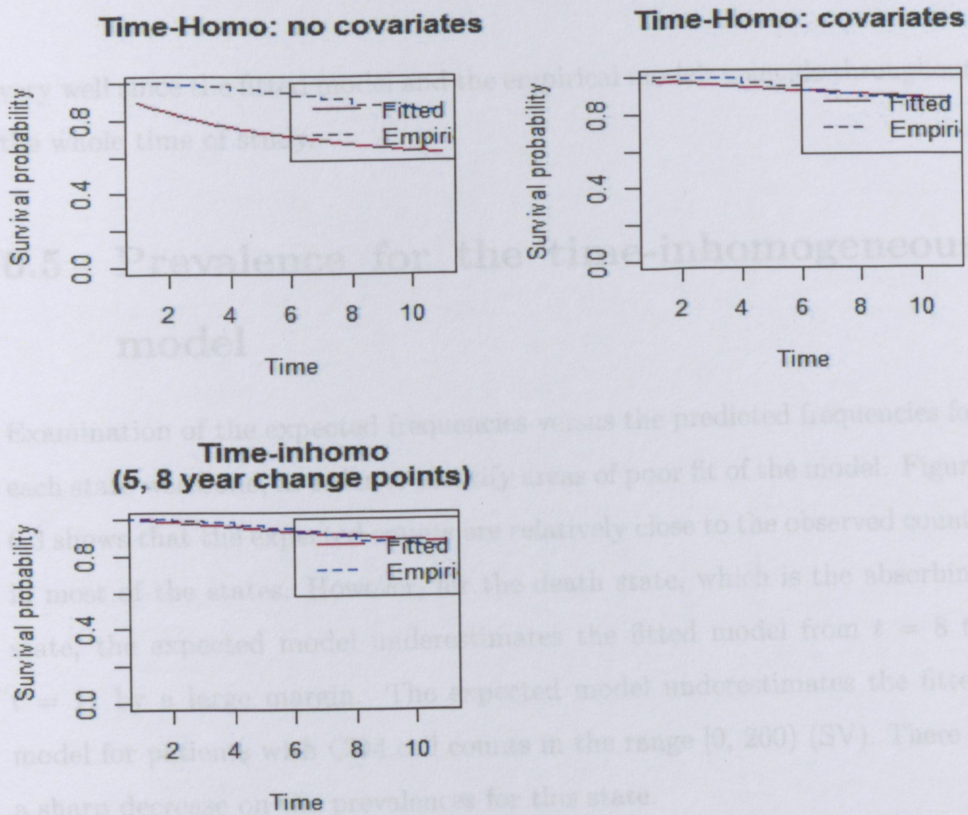


Figure 6.2: *Comparison of observed and fitted survival for four multi-state models*

the model with no covariates, the fitted model underestimates the empirical model by far. For the model with covariates, although the fitted model also underestimates the empirical model, the fitted line is closer to the empirical model compared to the model fitted with no covariates. The time-inhomogeneous model with 5 and 8 change point in intensities fits the data very well since the fitted model and the empirical models coincide throughout the whole time of study.

6.5 Prevalence for the time-inhomogeneous model

Examination of the expected frequencies versus the predicted frequencies for each state was done, in order to identify areas of poor fit of the model. Figure 6.3 shows that the expected counts are relatively close to the observed counts in most of the states. However, for the death state, which is the absorbing state, the expected model underestimates the fitted model from $t = 8$ to $t = 11$ by a large margin. The expected model underestimates the fitted model for patients with CD4 cell counts in the range [0, 200) (SV). There is a sharp decrease on the prevalences for this state.

6.6 Summary

In terms of the likelihood ratio test, this chapter has shown that the inhomogeneous Markov model is preferred. The diagnostic plots and the survival plots were fitted and they were all in favour of the time inhomogeneous Markov model.

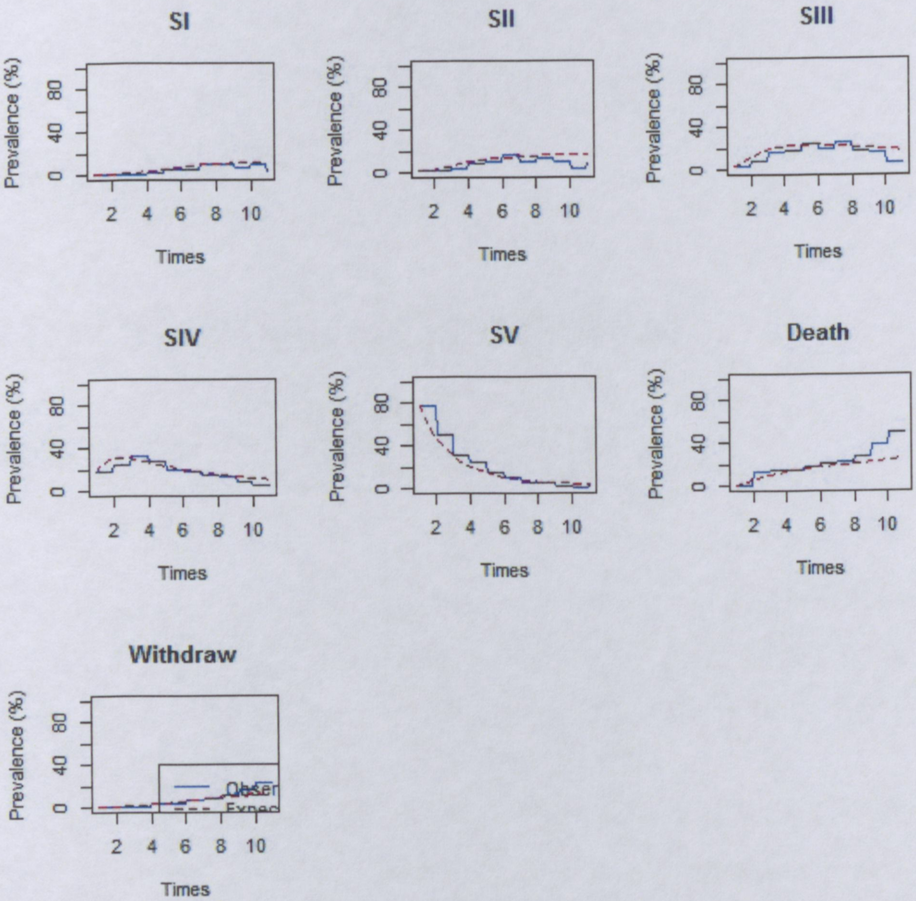


Figure 6.3: *Comparison of observed and expected prevalence from the time-inhomogeneous model 5 and 8-year change points*

Chapter 7

Conclusion and Future Research Directions

The main objective of this research was to model the progression of HIV/AIDS on individuals under ART monitoring and to understand the factors that influence HIV progression. The findings from the study confirms that TB is the leading cause of death in HIV-infected patients.

Chapter 2 explored the importance of stochastic processes in disease modeling. It went further to explain the concept of multi-state models, the structures of various multi-state models with reference to HIV, and briefly discussed various assumptions of multi-state modeling. This chapter also explained how covariates effects can be incorporated in the models.

Chapter 3 looked at the data description, as well as explored regression analysis on the covariates to the reaction to treatment and development of TB during the treatment. This was done using multiple regression analysis. The chapter also examined the linear relationship between time and CD4+

T-cell count, which showed that, as time increases, there is a increase on the CD4+ T-cell count. This shows that ART helps a lot in improving the immune system of HIV/AIDS patients. The Aalen model was also fit for the effects of covariates on the progression of HIV. The model showed that the covariates gender, DTB and CD4 are significant determinants of HIV progression with time.

Chapter 4 explored further, the theory of time-homogeneous Markov models and demonstrated how the parameters of interest can be estimated. These parameters include transition intensities, mean sojourn times, transition probability matrix, probability of each state being next and so on.

A time homogeneous model was fitted for the Bela Bela data. The model was used to analyse the effects of the covariates on the transition intensities. The likelihood ratio test was used to compare the model with covariates to the model without covariates. The results from the fitted model showed that the rates of immune recovery were much higher than the rates of immune deterioration.

Patients who started treatment whilst their CD4 baseline was ≥ 350 had higher rates of immune recovery than those who had a lower CD4 baseline. The probability of dying increases with decreasing CD4 count of the individual at enrollment. This is supported by the findings of Goshu and Dessie, (2013), Biadgilign *et al.* (2012) and Lifson *et al.* (2012), who also discovered that being in the AIDS defining stage leads to the highest probability of reaching the death state. The mean sojourn time revealed that patients take a longer time in the AIDS defining state, compared to the other state, before they move to the other state .

The patients who developed TB during treatment had higher rates of immune deterioration than recovery. Having TB as the initial marker of AIDS, had higher contributory effects to the deaths from all the states except from the AIDS defining stage.

Reaction to drugs is the leading cause of transition from a CD4 ≥ 750 to a CD4 count between 500 and 750. Reaction to drugs had lower contributory effects to death than those who did not react to drugs.

The younger people below the age of 40 had higher chances of immune recovery than the older ones. This finding is supported by Alioum (1998) who further argued that this can be caused by the fact that older subjects may have a reduced capacity to generate CD4 cells in response to the viral killing.

The rates of transition to death are higher for males than females. Alioum (1998) also discovered that females tend to respond to ART compared to males. The patients who started treatment with a $WSBL = 4$ had higher chances of transition to death compared to those in the lower levels of WSBL.

Chapter 5 explained the theory of inhomogeneous Markov models with particular reference to the piece-wise constant model. It also discussed the methods that can be used in model diagnostics. The methods include the formal likelihood ratio test, the Pearson test and the informal diagnostic plots for model comparison. The 3-segment piece-wise constant model to the HIV data was fitted. The fitted model was compared with the time homogeneous model using the likelihood ratio test in Chapter 6. The test showed that the inhomogeneous Markov model has the best fit. Diagnostic plots were also used to compare the models and the results still confirm that the inhomogeneous model is the best model for the data.

The major focus of this study was to explore the rates of immune recovery on HIV patients on antiretroviral therapy. There is need to further explore the costs incurred as individuals move from one state of immune recovery to the other and to come up with a model that best describes the costs.

The results obtained in this study form the basis for future research as follows:

1. A similar study can be done comparing the impact of different drugs on HIV progression.

2. The time spent in each state can be used to calculate the costs of the drugs that are administered to a patient until the CD4+T cell count is well above 500.

3. The study focused on CD4+T cell as a marker of immune recovery. There is also need to check on the infectiousness of those under treatment. The study may then focus on viral load as a marker of infectiousness of individuals under treatment.

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Appendices

Appendix A

A1. Manual computation of transition counts

$n_{54}(0,1)=2$	$n_5(0,1)=4$	$n_{54}=5$
$n_{44}(1,2)=2$	$n_5(1,2)=2$	$n_{55}=2$
$n_{44}(2,3)=2$	$n_5(3,4)=1$	$n_{44}=5$
$n_{43}(3,4)=1$	$n_4(1,2)=2$	$n_{43}=3$
$n_{32}(4,5)=2$	$n_4(2,3)=4$	$n_{45}=1$
$n_{23}(5,6)=1$	$n_4(3,4)=2$	$n_{42}=1$
$n_{32}(6,7)=1$	$n_4(4,5)=2$	$n_{33}=3$
$n_{22}(7,8)=2$	$n_3(3,4)=1$	$n_{32}=4$
$n_{55}(0,1)=2$	$n_3(4,5)=2$	$n_{23}=1$
$n_{54}(1,2)=2$	$n_3(6,7)=2$	$n_{22}=5$
$n_{44}(3,4)=1$	$n_3(5,6)=1$	$n_{21}=1$
$n_{43}(4,5)=1$	$n_3(7,8)=1$	$n_{12}=1$
$n_{33}(5,6)=1$	$n_2(5,6)=3$	
$n_{33}(6,7)=1$	$n_2(6,7)=2$	
$n_{32}(7,8)=1$	$n_2(7,8)=2$	
$n_{43}(2,3)=1$	$n_1(7,8)=1$	
$n_{33}(3,4)=1$		
$n_{22}(5,6)=2$		
$n_{21}(6,7)=1$		
$n_{12}(7,8)=1$		
$n_{45}(2,3)=1$		
$n_{54}(3,4)=1$		
$n_{42}(4,5)=1$		
$n_{22}(6,7)=1$		

Appendix B: R Commands and outputs

B1. R output of Score residuals

```
> scoreresid.msm(project.msm, plot=T)
         2          3          4          5          6          7          8          9         10         11 
0.22140473 0.13116442 0.25737643 0.17464319 0.06675404 0.21269317 0.09088715 0.65468604 0.15817886 0.06675404 
        12         13         14         15         16         17         18         19         20         21 
0.20070814 0.06628476 0.16884577 0.06675404 0.20352050 0.16062566 0.15311757 0.06675404 0.23946624 0.09978133 
        22         23         24         25         26         27         28         29         30         31 
0.29274378 0.13755718 0.10474977 0.02101791 0.19811581 0.31712449 0.12585630 0.06675404 0.97543869 0.08202976 
        32         33         34         35         36         37         38         39         40         41 
0.26071899 0.10366848 0.16804860 0.15776444 0.30414525 0.25409372 0.12807214 0.10430778 0.06675404 0.06675404 
        42         43         44         45         46         47         48         49         50         51 
0.36928165 0.06628476 0.21900610 0.10530518 0.20592545 0.27013173 0.15162415 0.44301554 0.21569223 0.29126121 
        52         53         54         55         56         57         58         59         60         61 
0.20854808 0.06675404 0.09232482 0.62733538 0.17552026 0.16386687 0.36557773 0.50933193 0.31446748 0.04935855 
        62         63         64         65         66         67         68         69         70         71 
0.37878986 0.13086535 0.34911632 0.48308944 0.12080539 0.87241259 0.05588578 0.04799032 0.21061248 0.17287296 
        72         73         74         75         76         77         78         79         80         81 
0.06675404 0.26782220 0.05409615 0.21318123 0.24637303 0.13266638 0.47038945 0.09853061 0.06448192 1.58315799 
        82         83         84         85         86         87         88         89         90         91 
1.58315799 0.24996013 0.52704844 0.31313890 0.40035794 0.12656017 0.20808080 0.41259164 0.06482688 0.26982135 
        92         94         95         96         97         99        100        101        103        106 
0.33624366 0.14959401 0.30269342 0.51787850 0.06179748 0.10895094 0.21691473 0.05776481 0.15045477 0.05044257 
       107        108        109        214        215        216        217        218        219        220 
0.15321745 0.38462524 0.03134775 0.06675404 0.13956161 0.06675404 0.06074001 0.06675404 0.38674713 0.31616328 
       221        222        224        225        226        228        229        230        231        232 
0.13241771 0.12335417 0.13259860 0.04630555 0.20592545 0.06675404 0.07630857 0.10462736 0.05482700 0.06675404 
       233        234        235        236        237        238        239        240        242        243 
0.06675404 0.27855127 0.06675404 0.13246418 0.10022935 0.15662181 0.06675404 0.12159308 0.05172884 0.16054662 
       244        245        246        247        248        249        250        251        252        253 
0.07658950 0.10240652 0.07317128 0.18061551 0.06675404 0.18111194 0.20797888 0.16844018 0.49566538 0.10421780 
       254        255        256        257        258        259        260        261        262        263 
0.06675404 0.02618744 0.06835223 0.06721678 0.01913285 0.38640387 0.24937044 0.01617801 0.11074358 0.10448986 
       264        265        266        267        268        270        271        272        273        274 
0.26013778 0.11278289 0.27530070 0.01449253 0.16844018 0.31845592 0.30095857 0.06675404 0.12376257 0.01017770 
       275        276        277        278        279        280        281        282        283        284 
0.06675404 0.03974197 0.06675404 0.31636648 0.10426570 0.34767395 0.20954009 0.09232482 0.16054662 0.07305149 
       285        286        287        288        289        290        291        292        293        294 
0.06518839 0.12842186 0.28484916 0.30933644 0.14932526 0.15268762 0.09318815 0.16597729 0.06527355 0.06675404 
       295        296        297        298        299        300        301        302        303        304 
0.11561943 0.08929606 0.16097374 0.06675404 0.06675404 0.14354197 0.13308053 0.13011743 0.15989713 0.10828686 
```

```
       305        306        307        308        309        311        312        313        314        315 
0.09756426 0.18432442 0.38692149 0.10273366 0.17817344 0.11025554 0.11417216 0.06675404 0.09678201 0.16750682 
       316        317        318        319        320        321        322        323        324        325 
0.15641371 0.12915777 0.11480103 0.18951412 0.19792817 0.15683516 0.02882891 0.49566538 0.14815085 0.16899140 
       326        327        328        329        330        331        332        333        334        335 
0.26796618 0.39347504 0.06721678 0.15795950 0.06675404 0.18696905 0.12569661 0.06675404 0.15393740 0.10828686 
       336        337        338        339        340        341        342        343        344        345 
0.12232250 0.06955679 0.10925452 0.01617801 0.51580778 0.17297472 0.25425804 0.27535674 0.06675404 0.10974149 
       346        348        349        350        351        352        353        354        355        356 
0.25878261 0.37263230 0.10817917 0.43287992 0.37640884 0.13959056 0.39300207 0.56086383 0.29125929 0.28339354 
       357        358        359        360        361        362        363        364        365        366 
0.31130188 0.17193252 0.09853061 0.10659903 0.05014792 0.36544890 0.19631563 0.09853061 0.18524796 0.03182753 
       367        368        369        370        371        372        374        375        376        377 
0.01297174 0.25847933 0.40251904 0.25969144 0.48407842 0.14881918 0.12240169 0.37154086 0.09815004 0.10178168 
       378        379        380        381        382        383        384        385        386        387 
0.29258367 0.23592640 0.02912171 0.16044439 0.08633610 0.20214364 0.12501852 0.19217215 0.01838415 0.01838415 
       388        389        395        396        399        401        402        406        414        416 
0.93642039 0.17701390 0.21369502 0.14366689 0.07638729 0.08111360 0.15852932 0.25238714 0.28832924 0.07697239 
       420 
0.02762763 
```

B2. R output of Q-matrix and P-matrix

```
>  qmatrix.msm

Call:
msm(formula = CD4 ~ t, subject = PTNUM, data = proj, qmatrix = twoway7.q,     death = 6)

Maximum likelihood estimates:
Transition intensity matrix
         SI                         SII                        SIII                        SIV
SI       -1.131 (-1.495,-0.8551)    0.8872 (0.6355,1.239)      0                           0
SII      0.5183 (0.3723,0.7217)     -1.133 (-1.388,-0.9245)    0.4959 (0.3729,0.6593)      0
SIII     0                          0.4231 (0.3451,0.5186)     -0.8011 (-0.932,-0.6886)    0.3324 (0.2605,0.4241)
SIV      0                          0                          0.5183 (0.4389,0.612)       -0.858 (-0.9803,-0.7509)
SV       0                          0                          0                           0.5164 (0.4356,0.6123)
Death    0                          0                          0                           0
Withdraw 0                          0                          0                           0
         SV                         Death                        Withdraw
SI       0                          0.1016 (0.05412,0.1907)      0.1418 (0.08426,0.2387)
SII      0                          0.08105 (0.04678,0.1404)     0.03772 (0.01674,0.08498)
SIII     0                          0.0145 (0.004737,0.04439)    0.0311 (0.01656,0.05843)
SIV      0.2523 (0.1936,0.3287)     0.03325 (0.0149,0.07419)     0.05414 (0.03518,0.08333)
SV       -0.6358 (-0.7341,-0.5506)  0.09058 (0.06249,0.1313)     0.0288 (0.01582,0.0524)
Death    0                          0                            0
Withdraw 0                          0                            0

-2 * log-likelihood:  3941.971

> pmatrix.msm(proj.msm,t=1.5,ci="normal")
         SI                          SII                          SIII                         SIV
SI       0.2912 (0.2192,0.3629)      0.3131 (0.2542,0.3669)       0.1256 (0.09376,0.1624)      0.02115 (0.01468,0.02998)
SII      0.1829 (0.1385,0.2222)      0.3503 (0.29,0.4043)         0.234 (0.1882,0.2798)        0.05481 (0.04005,0.07205)
SIII     0.06261 (0.04741,0.07963)   0.1996 (0.1654,0.2323)       0.4329 (0.3839,0.478)        0.1726 (0.1406,0.2053)
SIV      0.01644 (0.01176,0.02217)   0.07291 (0.05871,0.08784)    0.2692 (0.234,0.3025)        0.3847 (0.3405,0.4243)
SV       0.003407 (0.002381,0.004838) 0.01963 (0.01483,0.02483)   0.1049 (0.08677,0.1227)      0.2829 (0.2447,0.3159)
Death    0                           0                            0                            0
Withdraw 0                           0                            0                            0
         SV                          Death                        Withdraw
SI       0.002141 (0.001363,0.0033)  0.1148 (0.07779,0.1777)      0.132 (0.08841,0.1982)
SII      0.007209 (0.004959,0.01052) 0.09679 (0.06734,0.144)      0.07403 (0.05257,0.1161)
SIII     0.03287 (0.02387,0.04458)   0.04426 (0.03192,0.07331)    0.05511 (0.03991,0.08371)
SIV      0.1382 (0.1083,0.1693)      0.05277 (0.03832,0.08535)    0.06584 (0.04838,0.09029)
SV       0.4388 (0.3875,0.4833)      0.1026 (0.07884,0.1384)      0.04775 (0.03367,0.07047)
Death    0                           1 (1,1)                      0
Withdraw 0                           0                            1 (1,1)
```

B3. R output of sojourn time and probabilities of each state being next

```
> sojourn.msm(proj.msm)
     estimates         SE         L        U
SI   0.8844741 0.12602569 0.6689603 1.169418
SII  0.8826571 0.09158707 0.7202261 1.081721
SIII 1.2482706 0.09636263 1.0729973 1.452175
SIV  1.1655588 0.07925375 1.0201301 1.331720
SV   1.5728163 0.11539878 1.3621492 1.816065

> pnext.msm(proj.msm, covariates = "mean",
+ ci=c("delta","normal","bootstrap","none"), cl = 0.95,
+ B=1000)
         SI                       SII                      SIII                     SIV                      SV
SI       0                        0.7847 (0.7028,0.8762)   0                        0                        0
SII      0.4575 (0.3659,0.572)    0                        0.4377 (0.3505,0.5466)   0                        0
SIII     0                        0.5281 (0.4581,0.6088)   0                        0.4149 (0.3467,0.4966)   0
SIV      0                        0                        0.6041 (0.5418,0.6736)   0                        0.294 (0.2373,0.3644)
SV       0                        0                        0                        0.8123 (0.7568,0.8718)   0
Death    0                        0                        0                        0                        0
Withdraw 0                        0                        0                        0                        0
         Death                       Withdraw
SI       0.08986 (0.04791,0.1685)    0.1254 (0.07458,0.211)
SII      0.07154 (0.04144,0.1235)    0.03329 (0.01474,0.07516)
SIII     0.0181 (0.005934,0.05521)   0.03883 (0.02078,0.07255)
SIV      0.03875 (0.01757,0.08546)   0.06311 (0.04133,0.09636)
SV       0.1425 (0.09906,0.2049)     0.04529 (0.02506,0.08185)
Death    0                           0
Withdraw 0                           0
```

B4. Computated observed and expected Prevalences

```
> prevalence.msm(proj.msm)
$Observed
   State 1 State 2 State 3 State 4 State 5 State 6 State 7 Total
1        1       4       8      47     203       0       0   263
2        1       8      24      66     131      33       2   265
3        1      12      45      87      82      38       3   268
4        5      23      49      75      62      40       8   262
5       14      28      66      51      39      47      11   256
6       15      42      51      47      26      53      16   250
7       26      23      67      38      14      54      19   241
8       23      35      46      31      13      55      24   227
9       18      23      41      23       7      58      25   195
10      18      14      16      13       3      60      27   151
11       5      11       9       6       2      60      27   120

$Expected
          SI       SII     SIII      SIV         SV    Death  Withdraw Total
1   1.000000  4.000000  8.00000 47.00000 203.000000  0.00000  0.000000   263
2   2.062335  7.528428 30.18410 77.46473 121.165044 17.39482  9.200536   265
3   4.266697 14.359378 45.32436 75.31068  79.412938 30.89576 18.430178   268
4   6.809211 19.803980 50.16923 63.83856  53.869623 40.98947 26.519927   262
5   8.889360 23.073183 49.65423 52.80416  38.509660 49.28778 33.781626   256
6  10.179694 24.395012 46.59906 43.64809  28.698261 56.25443 40.225444   250
7  10.585686 24.004973 42.02592 35.88846  21.844487 61.35352 45.296958   241
8  10.183862 22.223879 36.50205 29.10910  16.705418 63.91206 48.363641   227
9   8.613707 18.297724 28.68023 21.73236  11.918724 59.69868 46.058580   195
10  6.404595 13.347836 20.21616 14.74382   7.807400 49.60947 38.870719   151
11  4.802276  9.872918 14.58127 10.33384   5.326246 41.86660 33.216856   120
```

$`Observed percentages`

	State 1	State 2	State 3	State 4	State 5	State 6	State 7
1	0.3802281	1.520913	3.041825	17.870722	77.186312	0.00000	0.000000
2	0.3773585	3.018868	9.056604	24.905660	49.433962	12.45283	0.754717
3	0.3731343	4.477612	16.791045	32.462687	30.597015	14.17910	1.119403
4	1.9083969	8.778626	18.702290	28.625954	23.664122	15.26718	3.053435
5	5.4687500	10.937500	25.781250	19.921875	15.234375	18.35938	4.296875
6	6.0000000	16.800000	20.400000	18.800000	10.400000	21.20000	6.400000
7	10.7883817	9.543568	27.800830	15.767635	5.809129	22.40664	7.883817
8	10.1321586	15.418502	20.264317	13.656388	5.726872	24.22907	10.572687
9	9.2307692	11.794872	21.025641	11.794872	3.589744	29.74359	12.820513
10	11.9205298	9.271523	10.596026	8.609272	1.986755	39.73510	17.880795
11	4.1666667	9.166667	7.500000	5.000000	1.666667	50.00000	22.500000

$`Expected percentages`

	SI	SII	SIII	SIV	SV	Death	Withdraw
1	0.3802281	1.520913	3.041825	17.870722	77.186312	0.000000	0.000000
2	0.7782398	2.840916	11.390227	29.231975	45.722658	6.564084	3.471900
3	1.5920511	5.357977	16.912075	28.101001	29.631693	11.528270	6.876932
4	2.5989355	7.558771	19.148560	24.365862	20.560925	15.644837	10.122110
5	3.4724064	9.012962	19.396184	20.626624	15.042836	19.253040	13.195948
6	4.0718776	9.758005	18.639626	17.459237	11.479304	22.501772	16.090178
7	4.3924007	9.960570	17.438141	14.891477	9.064102	25.457890	18.795418
8	4.4862829	9.790255	16.080197	12.823390	7.359215	28.155092	21.305569
9	4.4172858	9.383448	14.707809	11.144798	6.112166	30.614708	23.619785
10	4.2414537	8.839626	13.388187	9.764119	5.170463	32.853952	25.742198
11	4.0018966	8.227431	12.151056	8.611531	4.438538	34.888833	27.680713