MULTI-STATE TRANSITION MODELS WITH CENSORING IN VERTICAL TRANSMISSION OF HIV

Idah Atieno Orowe

A thesis subsmitted to the University of Nairobi
for the award of the degree of
Doctor of Philosophy in Mathematical Statistics

School of Mathematics
UNIVERSITY OF NAIROBI

November 18, 2016

DECLARATION

I declare that this thesis is a presentation of my original work and has not been submitted for an award of another degree in any other university or institution of learning. Wherever contributions of others are involved, every effort is made to indicate and acknowledge this with due reference to the literature.

Idah Atieno Orowe
Reg.No.I80/9260/2006
Signature.....Date.....

Approval

I/We declare that this work has been done under my/our supervision and has my/our approval for submission

Prof J.A.M. Ottieno
School of Mathematics
University of Nairobi
P.O.Box 30197, GPO−00100
NAIROBI
Signature.....Date.....

Prof P.G.O. Weke
School of Mathematics
University of Nairobi
P.O.Box 30197, GPO−00100
NAIROBI
Signature.....Date.....

DEDICATION

To my family.

ACKNOWLEDGMENT

I would like to most sincerely thank my supervisors Professor J.A.M.Ottieno and Professor P.G.O.Weke for their dedication and tireless contribution that has been instrumental to the completion of this thesis. Your time and patience with me in this journey is priceless.

I am grateful to the International Science Programme (ISP) in Mathematics, Sweden whose fellowship secured my stay in Uppsala, Sweden through a sandwich programme.

My special gratitude also goes to the staff and collegues at the School of Mathematics, University of Nairobi for their immense support throughout the duration of study.

Last but not least to my family, for their patience, love and encouragement throughout the period of study.

ABSTRACT

In this study we have developed multistate models with censoring for vertical transmission of HIV, also refered to as mother to child transmission of HIV. We then use the multistate models developed to derive the forward Kolmogorov differential equations. Depending on when transmission takes place, whether in-utero, intrapartum or postpartum we introduced the aspect of censoring when estimating the transition intensities from the transition probabilities. The study is in two parts, multi-state models for a child born infected where we consider two and three state models and multistate models for a child born healthy where we have three, four and five state models. In each part we have solved the respective forward Kolmogorov differential equations using the generator matrix approach to obtain the transition probabilities which are in form of transition intensities. Maximum likelihood estimation method is then used to estimate the transition intensities. From the results we observe that the transition probabilities are exponentialy distributed and that if the number of infected children are maintained at a constant number then the transition intensities will approach zero as time increases.

ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
DNA	Deoxyribonucleic acid
HT	Horizontal Transmission
HIV	Human Immunodeficiency Virus
KM	Kaplan-Meier
MCMC	Markov Chain Monte Carlo
MI	Multiple Imputation
MLE	Maximum Likelihood Estimation
MSM	Multi-State Model
MSMs	Multi-State Models
MTCT	Mother To Child Transmission
PCR	Polymerase chain reaction
PMTCT	Prevention of Mother To Child Transmission
PH	Proportional Hazards
RNA	Ribonucleic acid

KEYWORDS

Acquired Immune Deficiency Syndrome

Basic Reproduction Number

Eigen Values and Eigen Vectors

Event

Forward Kolmogorov-Differential Equations

Generator Matrix

Human Immunodeficiency Virus

Markov Model

Maximum Likelihood Estimation

Mother To Child Transmission

Multistate

Right, Left and Interval Censoring

Time Homogeneous

Transition Intensities

Transition Matrix

Transition Probabilities

Vertical Transmission

LIST OF SYMBOLS AND NOTATIONS

δ_i	censoring indicator
$P_{ij}(s,t)$	Probability of moving from state i at time s to state j at time t
$f(t)$	Probability distribution
$h(t)$	Hazard function
$S(t)$	Survival function
T	Survival time
t	Event time
μ_{ij}	Transition intensities
R_0	Basic Reproduction Number
$L(\Phi/t)$	Likelihood function
Q	Matrix of transition probabilities
I	Identity matrix
δ_{ij}	Kronecker delta
β_{ij}	Transition intensities in extended vertical transmission framework
S	Suscptibles
I	Infected
T	Recovered
A	Aids

LIST OF FIGURES

Contents

Chapter 1

GENERAL INTRODUCTION

1.1 Background Information

Diseases can either be infectious or noninfectious. Infectious diseases can be passed between individuals, whereas noninfectious develop over an individual's lifespan. The primary risk factor for catching an infectious disease is the presence of infectious cases in the local population. Infectous diseases are caused by pathogens such as viruses, bacteria, protozoa, flukes. HIV/AIDS is an infectious disease caused by a virus known as human immunodeficiency virus. It is a pandemic that has no cure and was first recognized by the United States Centre for Disease Control and Prevention in 1981. It is believed that HIV started to spread in Kenya between late 1970s and early 1980 with the first HIV case being reported in 1982. Men, women and children are all vulnerable to the disease. The progression of HIV infecton is shown in Figure 2.1 below.

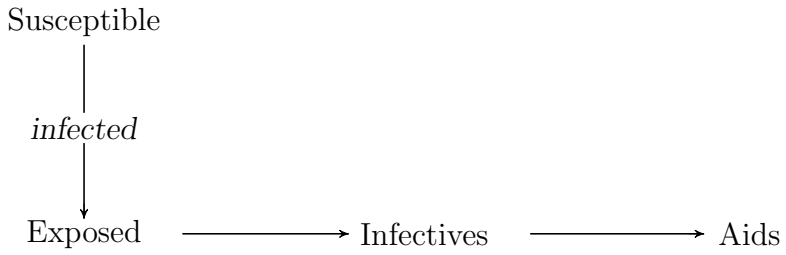

Figure 1.1: Progression of HIV infection

HIV model classifies the population into susceptibles (S) containing individuals who have not been infected with the virus, Exposed (E) individuals who are infected but in the latent stage, Infectives (I) containing individuals who are infected with the virus but have not yet developed AIDS symtoms and the AIDS cases (A) who are those individuals that have developed the disease. The boundaries between exposed and infectious (and infectious and Aids) are somewhat fuzzy because the ability to transmit does not simply switch on and off. This uncertainity is further complicated by the variability in response between different individuals and the variability in the virus levels over the infectious period. It is only with recent advances in molecular techniques that these within-host

individual-level details are beginning to emerge.

The two major modes of transmission of the virus is through unsafe sex (horizontal transmission) and from infected mother to her child $(0-5)$years (vertical transmission) Mother to child transmission of HIV (MTCT) occurs mainly during the perinatal period (from the 20^{th} to 28^{th} week of gestation and ends 1^{st} to 4^{th} week after birth) and postnatally during breastfeeding.

Since HIV pandemic first became visible, enormous mathematical models have been developed and they have proven to be valuable in umnderstanding the dynamics of the infection. The first mathematical models were of deterministic nature. Among the first deterministic models developed for MTCT was by Dunn et al., (1992). The stochastic models were then later developed. Some of the early stochastic models was by Rouzioux et.al (1995) who developed a Markov model for estimating timing of mother-to-child (HIV-1).

1.2 Notations, terminologies and definitions

i) Multi-state models MSM
A multi-state process is a process which can take a finite number of states $i.e$ for any t the variable $X(t)$ has values in $S = \{0, 1, \cdot k\}$

ii) Censoring
This occurs when an observation is incomplete. An event is known to occur but the actual time is not known. The most common yypes are right, left and interval censoring.

iii) Vertical transmission
It refers to the transmission of a disease from a parent to an offspring. The most common is from mother to her child.

iv) HIV
This stands for Human immunodeficiency syndrome and if left untreated can lead to the disease AIDS (acquired immunodificiency syndrome)

v) Probability Density function $f(t)$
This is the equation used to describe a continuous probability and is given as

$$f(t) = \lim_{\Delta t \to 0} \frac{\text{Prob}\,[t \leq T \leq t + \Delta t]}{\Delta t} \tag{1.1}$$

and satisfies the following conditions

- $f(t) \geq 0$ for all t

- $\int_{-\infty}^{\infty} f(t)dt = 1$

vi) Survival time (T)
The survival time is a variable which measures the time from a particular starting point to a certain end point of interest. T denotes the response variable
In most situations, survival data are collected over a finite period of time due to practical reasons. The observed time-to-event data are always non-negative, $T \geq 0$

vii) Survival Function ($S(t)$)
The survival functionis a basic quantity used to model the probability that a subject will survive beyond a specified time t. We denote by T the random variable representing survival time, which is the amount of time until the event of interest occurs.
The statistical expression of the survival function is shown in Equation given as:

$$S(t) = \text{Prob}\{T > t\} \tag{1.2}$$

As t ranges from 0 to ∞ the survival function has the following properties:

a) it is non-increasing

b) At $t = \infty$, $S(t) = S(\infty) = 0$ *i.e* as time goes to infinity, the survival curve goes to 0

Since T is a continuous random variable, the survival function can be represented as in Equation 1.3

$$\begin{aligned} S(t) &= \int_{\infty}^{t} f(x)dx \\ &= 1 - F(t) \end{aligned} \tag{1.3}$$

where $F(t)$ is the cumulative distribution function

viii) Hazard Function ($h(t)$)
The hazard function $h(t)$ is the instantaneous rate at which events occur, given no previous events.

$$h(t) = \lim_{\Delta t \to 0} \frac{\text{Prob}\{t \leq T \leq t + \Delta t | T > t\}}{\Delta t} \tag{1.4}$$

ix) Cumulative Hazard Function ($\Lambda(t)$)
The cumulative hazard describes the accumulated risk upto time t.

$$\Lambda(t) = \int_{0}^{t} h(u)du \tag{1.5}$$

It is a useful quantity in survival analysis because of it's relation with the hazard function and survival function.

$$S(t) = \exp(-\Lambda(t)) \tag{1.6}$$

$S(t), f(t)$ and $h(t)$ have the following relationships

$$\begin{aligned} S(t) &= \text{Prob}(T > t) \\ &= 1 - \text{Prob}(T \leq t) \\ &= 1 - F(t) \end{aligned} \tag{1.7}$$

where $F(t)$ is the cummulative function.

Therefore

$$\begin{aligned} \frac{dS(t)}{dt} &= -\frac{dF(t)}{dt} = -f(t) \\ f(t) &= -\frac{dS(t)}{dt} \end{aligned} \tag{1.8}$$

The quantity $f(t)dt$ might be considered an "approximate" probability that the event will occur at time t. Since the derivative of the survival function with respect to t is negative, then the function $f(t)$ in Equation 1.8 will be non negative. The survival curve $S(t)$ can be plotted to graphically represent the probability of an individual's survival at varying time points.

$$\begin{aligned} h(t) &= \lim_{\Delta t \to 0} \frac{\text{Prob}\left\{t \leq T \leq t + \Delta t | T > t\right\}}{\Delta t} \\ &= \lim_{\Delta t \to 0} \frac{\text{Prob}\left\{t \leq T \leq t + \Delta t, T > t\right\}}{\Delta t \text{Prob}(T > t)} \\ &= \lim_{\Delta t \to 0} \frac{\text{Prob}\left\{t \leq T \leq t + \Delta t, T > t\right\}}{\Delta t S(t)} \\ &= \frac{1}{S(t)} \lim_{\Delta t \to 0} \frac{\text{Prob}\left\{t \leq T \leq t + \Delta t\right\}}{\Delta t} \\ h(t) &= \frac{f(t)}{S(t)} \end{aligned} \tag{1.9}$$

From (1.8) and (1.9)

$$\begin{aligned} h(t) &= \frac{1}{S(t)} \frac{-dS(t)}{dt} \\ &= \frac{-d}{dt} \log S(t) \\ \int_0^x d\log S(t) &= -\int_0^x h(t)dt \\ \log S(x) - \log S(0) &= -\int_0^x h(t)dt \\ \log \frac{S(x)}{S(0)} &= -\int_0^x h(t)dt \\ \frac{S(x)}{S(0)} &= e^{-\int_0^x h(t)dt} \end{aligned} \tag{1.10}$$

That is

$$S(x) = e^{-\int_0^x h(t)dt} \tag{1.11}$$

Hence

$$S(t) = e^{-\int_0^t h(x)dx} \tag{1.12}$$

or

$$S(t) = e^{-\Lambda(t)} \tag{1.13}$$

From (1.9) the hazard function for an exponential function is

$$\begin{aligned} h(t) &= \frac{\lambda e^{-\lambda t}}{e^{-\lambda t}} \\ &= \lambda \end{aligned} \tag{1.14}$$

The study of Multi-state models often fit under a Markov or semi-Markov assumption. Given state-space E, states $i, j \in E$, and $s \leq t$, a Markov process assumes

$$P_{ij}(s,t) = \text{Prob}(X(t) = j / X(s) = i) \tag{1.15}$$

so that the transition probability depends on the current state i.
Under the semi-Markov assumption the transition probability depends on both the current state i and the time of entry to state i i.e $t + \Delta t$ so that

$$P_{ij}(s,t) = \text{Prob}(X(t) = j / X(s) = i, t + \Delta t). \tag{1.16}$$

Future events not only depend on the current state but also on the entry time to the state.
These approaches can either be defined in continous time and/or discrete time context.

- Transition rates are also refered to as transition intensities or forces of transition. All transition intensities are assumed to be constant as function of time.
  The explicit expression for transition probability functions are available when we assume that $\mu_{ij}(t) = \mu_{ij}$ for all t due to the assumption of time-homogeneous or stationary so that the transition probability $P_{ij}(s,t)$ depends only on $t - s$, i-e, $P_{ij}(s,t) = P_{ij}(0, t-s)$.
  To simplify notation, we may use only one argument in time $P_{ij}(t-s) = P_{ij}(0, t-s)$. Also, the functions $P_{ij}(s, s+t) = P_{ij}(0,t)$ are the same for all $s \geq 0$ and therefore can be written as $P_{ij}(t)$

- The assumption of constant forces of transition implies that the time spent in each state is exponentially distributed.

- For any short time interval of length h the probability of two or more transitions within that time period is $o(h)$

  A function $f(h)$ is said to be of $o(h)$ if

$$\lim_{h \to 0} \frac{f(h)}{h} = 0 \tag{1.17}$$

- For all states i and j, $P_{ij}(t)$ is a differentiable function of t

We can express transition probabilities in terms of transition rates

$$P_{ij}(t) = \mu_{ij}h + o(h)$$

Transition rates are also refered to as transition intensities or forces of transition.
Therefore for small values of h, we have the approximation

$$P_{ij}(t) \approx \mu_{ij}h$$

Suppose there are n states, denote the state space by S, then

$$S = \{1, 2, \cdots, n\} \tag{1.18}$$

Denote the set of direct transitions by Υ such that

$$\Upsilon \subseteq (i,j)|i \neq j \qquad i,j \in S \tag{1.19}$$

The pair (S, Υ) is called a multi-state model.
Define $X(t)$ as the state occupied by the subject under consideration at time t where $t \geq 0$. $\{X(t) : t \geq 0\}$ is said to be a time continuous Markov process if, for each finite set of times $0 \leq t_0 \leq t_1 \leq \cdots t_n$ and corresponding set of states $i_0, i_1, \cdots i_n, j \in S$
where

$$P\left[X(t_n) = i_n, X(t_{n-1}) = i_{n-1} \cdots, X(t_o) = i_o\right] > 0 \tag{1.20}$$

then the process satisfies the Markov property if

$$P\left[X(t_n) = i_n | X(t_{n-1}) = i_{n-1}, X(t_{n-2}) = i_{n-2} \cdots, X(t_o)\right] = P\left[X(t_n) = i_n | X(t_{n-1}) = i_{n-1}\right]$$

The Markov property shows that this probability does not depend on the history of the event but depends only on the immediate past. We say that $\{X(t) : t \geq 0\}$ is a time continuous Markov process since we are dealing with continuous time.
Transition probabilities of the Markov process are denoted by $p_{ij}(s,t)$ and defined by

$$\begin{aligned} P_{ij}(s,t) &= \text{conditional probability that an individual is in state } j \text{ at time } t \\ &\quad \text{given that they were in state } i \text{ at time } s \\ &= P\left[X(t) = j | X(s) = i\right] \\ &= \frac{P\left[X(t) = j, X(s) = i\right]}{P\left[X(s) = i\right]}; \qquad t \geq s \geq 0 \qquad i,j \in N \end{aligned} \tag{1.21}$$

if $P\left[X(s) = i\right] > 0$, otherwise $P_{ij}(s,t) = 0$

We also have

$$P_{ij}(s,s) = \delta_{ij} \qquad s \geq 0 \tag{1.22}$$

δ_{ij} is reffered to as the Kronecker delta and is equal to 0 for $i \neq j$ and 1 for $i = j$
The transition probabilities satisfy the following properties

$$\begin{aligned} 0 \leq P_{ij}(s,t) &\leq 1; \qquad i,j \in N; \\ \sum_{j \in N} P_{ij}(s,t) &= 1 \end{aligned}$$

We assume that transition probabilities for each fixed period of time is fixed and is therefore time homogeneous.

1.3 Research Problem

Alioum et al (2002) used data from four randomized trials carried out in Africa between 1995 and 2000 to evaluate the efficacy of interventions aimed at reducing mother to child transmission risk by first theoretically outlining prefered statistical methods for evaluating interventions aimed at reducing risk of transmission. The results from trials evaluating either peripartum antiretroviral therapy or refraining from breastfeeding showed an estimated long term efficacy at $15-24$ months of age between 25 and 50 percent. Differences in statistical methods, duration of follow-up, and age at weaning hindered direct comparison between the trials. These results suggested that for estimation of the cumulative proportion infected at age 6 weeks a standard Kaplan-Meier approach is likely to give valid results while those infected at age 18 months, more sophisticated methods such as the extension of the Kaplan-Meier procedure to interval-censored data and competing risks would be prefered. From the efficancy results the study shows that an appropriate time for intervention was not identified. Viera et al (2003) developed an operational model for the MTCT of HIV pregnancy by modelling the progress of infection over time. They defined suitable states that may be experienced by a particular HIV infected pregnant woman through time until she gives birth and the uncertainty in the model captured by probabilities of transitions through states. A semi-Markov process was considered as a better description of the biological process that follow pregnancy and HIV infection since the transitions from state to state were governed by probabilities and random duration of time on a given state before the transition to the next state.
Brown and Gard (2007) proposed a censored multinomial regression model for analyzing PMTCT of HIV. In the study in utero transmission rate was estimated by the fraction of infants testing positive shortly after birth, perinatal transmission rate estimated by the fraction of infants testing positive by 6 weeks which they extended to 8 weeks for analysis purposes and intrapartum transmission rate estimated by the fraction of infants testing positive by the end of the perinatal transmission window given they had a negative test result at birth. They studied the problem of estimating the effect of treatment on mother to child transmission of HIV when outcome data are incomplete and demonstrated through simulation that censored multinomial regression model outperforms standard logistic models.

HIV infection has become a persistant problem in the world with MTCT being a significant source of HIV infection in children below the age of 15 years. Due to improving intervention methods most of the infected children survive to adulthood.
MTCT can takes place before or after the child is born which results in left and right censoring. Intervel censoring can also occur particularly in children born negative but turn positive during followup visits. Most studies in multistate models for MTCT have all considered the multistate models and censoring separately.
Among the latest researchers on vertical transmission, Teeple (2013) came up with a good framework for studying MTCT which as shown below,

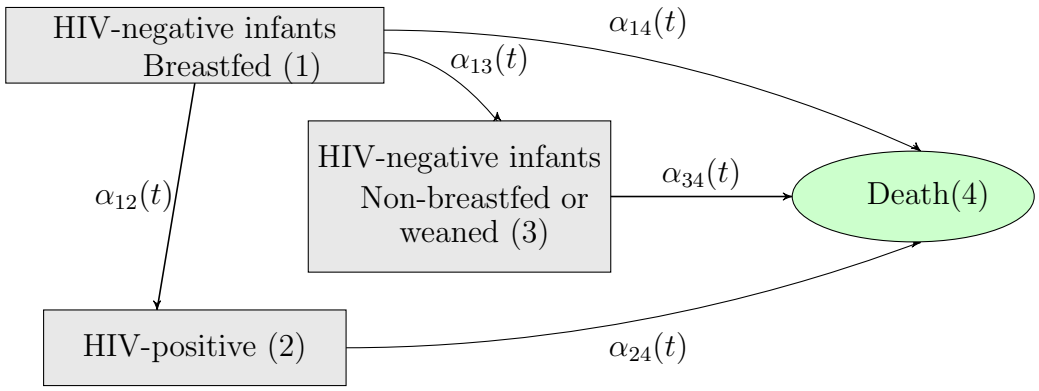

Figure 1.2: Teeple's Framework for the vertical transmission of HIV

This framework however can be extended to include other stages and types of censoring for the complete scenario.
We will therefore extend the framework to include before delivery and during birth and delivery.
Though Teeple (2013) considered the after birth situation, the Aids stage was not included.

The extended framework will therefore include all these situations implying various states and various types of censoring mainly left, right and interval censoring.

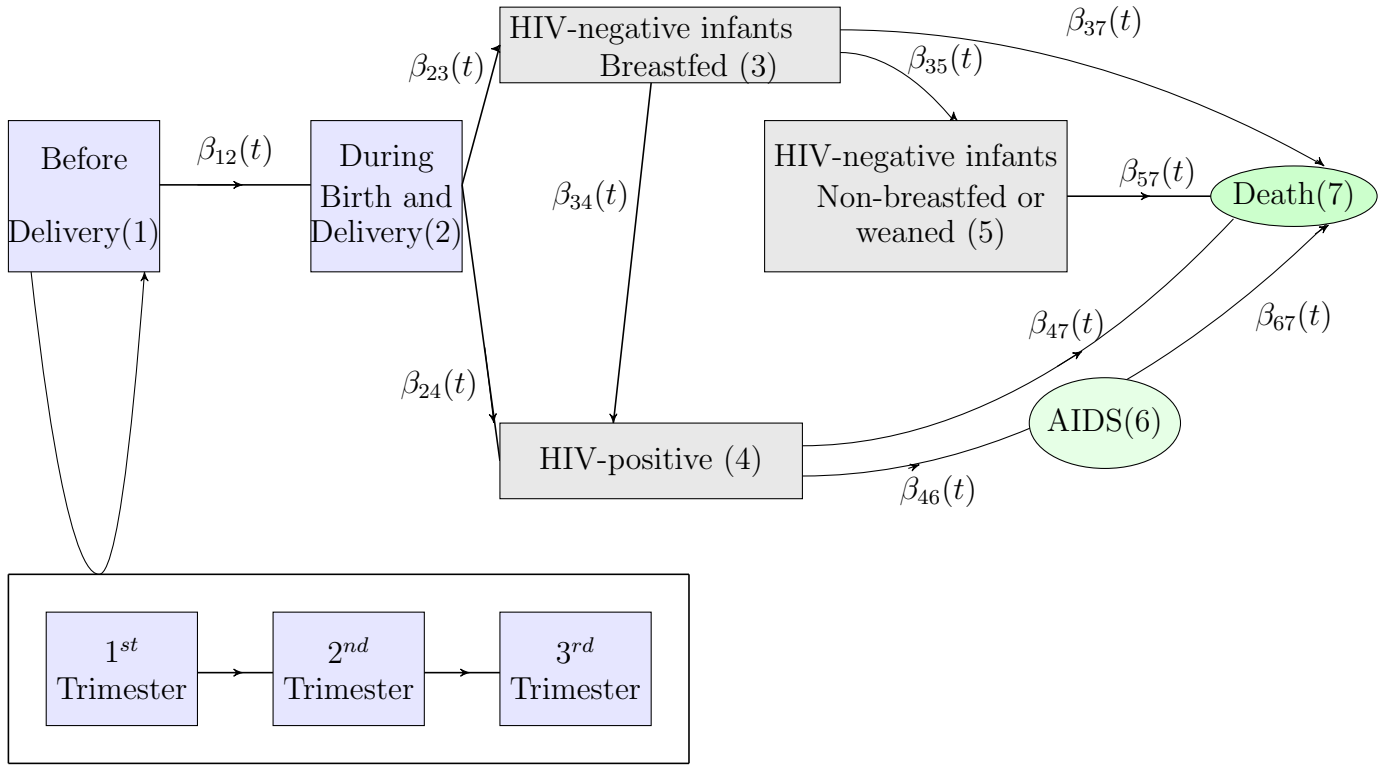

Figure 1.3: Modified Framework for the vertical transmission of HIV

Focus from researchers have not been in obtaining the transition probabilities or estimating the transition intensities. In this work we attempt to address this shortcoming in multistate models with censoring.

1.4 Objectives

1.4.1 General Objective

The main objective is to develop multi-state models transition with censoring for vertical transmission of HIV for a child born infected and a child born healthy

1.4.2 Specific Objectives

The specific objectives of the study are

(i) Formulate a deterministic model for MTCT and use it to obtain R_0

(ii) Develop multistate models for left censored and right censored vertical transmission of HIV

(iii) Obtain transition probabilities for the models by using generator matix approach

(iv) Use MLE to get the expressions for the estimators of transition intensities

1.5 Literature Review

1.5.1 Introduction

In this section we review the literature on multistate models in vertical transmission of HIV using both deterministic and stochastic models. All diseases are subject to stochasticity in terms of the chance nature of transmission and so, in principle, a stochastic model is always more realistic than a deterministic one. However, the relative magnitude of stochastic fluctuations reduces as the number of cases increases, therefore, in large populations with a hgh level of disease incdence, a deterministic model may be a good approximation. However, when the population is small or the disease is rare (for example, due to vaccination, other forms of interventions, or early during an epidemic) stochastcity can have a major role. We therefore start by reviewing some deterministic models and later stochastic models which are our main interest in this study.

1.5.2 Deterministic Studies in Vertical Transmission of HIV

Mugisha and Luboobi (2003) used a continuous age-structured model of Mckendric-von Foerster type to derive a two groups HIV/AIDS model in order to identify the most vulnerable age group to concentrate on when combating the spread. The two age groups were the children and infected mothers. They started from the continuous age distribution models and developed the ideas into the ordinary differential equations with interest being on how HIV/AIDS regulates the size of the population. Since AIDS cases have full-blown symptoms and are easily noticiable, they were assumed not to be sexually interacted with. It was also assumed that at the start of the epidemic, the population is at steady age distribution with exponential growth.
The results showed that the only possible way to ensure a disease free equilibrium is to bring the force of infection to zero, i.e, all the babies born by infected mothers are HIV free. This however does not guarantee safety in the adult group as it is only when the rate of infection in adults is zero that a disease free adult population is assured. The study showed a high possibility of having the basic reproduction number, $R_0 > 0$ or $R_0 = 0$ meaning that all infected mothers give birth to HIV-free babies. This means that we can have the epidemic die out if some effort is put on delivering of HIV free babies. Therefore in order to have a big fraction of HIV-free babies, measures to reduce risks associated with vertical transmission in the HIV-infected mothers must be intensified.
Waziri et al (2012) examined the dynamics of HIV/AIDS with treatment and vertical transmission using a nonlinear deterministic mathematical model and applying the stability theory of differential equations that models the dynamics of transmission in a varying population. They used the next generation matrix method to calculate R_0 and established the local stability of the disease free equilibrium. They did this by extending the model by Naresh et al (2006) who studied a mathematical model on the dynamics of HIV/AIDS epidemic with vertical transmission but without treatment and assumed that no infants born infected with HIV/AIDS lived long enough to reach the adolescent age.

This assumption was justified in 1991, since antiretroviral drugs capable of prolonging lives upto adulthood was unknown or not widely available. They noted that models of HIV/AIDS dynamic that ignore the impact of vertical transmission particularly during the current high usage of antiretroviral drugs may fail to capture the actual impact of HIV/AIDS in a population.
The results of both qualitative and numerical analysis showed that there exist a feasible region where the model is well posed in which a unique disease free equilibrium point exits. The disease free equilibrium is found to be locally asymtotically stable if the basic reproduction number $R_0 < 1$ and for $R_0 > 1$ it is unstable and the infection persists in the population. In this case the endemic equilibrium which exists only when $R_0 > 1$ is always locally asymptotically stable. It was found that an increase in the rate of vertical transmission leads to increase of the population of infectives which in turn increase the HIV infected and AIDS population. The numerical simulation showed that controlling the rate of vertical transmission significantly reduced the spread of HIV.

1.5.3 Stochastic Studies in Vertical Transmission of HIV

Rouzioux et al (1995) determined the frequencies of MTCT transmission during pregnancy and delivery in order to estimate the timing of MTCT of HIV and compared MTCT to HT by solving the Chapman-Kolmogorov differential equations for Birth-Illness-Death process using open population growth model. They carried out comperative analysis to investigate the rate of spread of HIV epidemic among these two modes and determine which mode of transmission had the highest rates and therefore enable policies formulated for government control of the epidemic. The time from infection to detectable antibody production was divided into three stages: Stage 1 in which the infant was infected, but was negative in viral culture or PCR and produced no HIV-1 specific antibodies, Stage 2 in which the infant was positive for viral culture or PCR and produced no specific antibodies and Stage 3 in which the infant was positive for viral load or PCR but produced detectable specific antibodies.
The statistical analysis had to deal with the fact that the different time points or periods of interest were either interval censored or right censored. The Markov modelling technique was found to be well suited to the analysis of the ordered clinical process subject to interval or right censoring.
MLE method was used to estimate the probability of transmission during delivery, the density of probability of the time of contamination in utero, and the probability of transmission from Stage 1 to Stage 2 and Stage 2 to Stage 3. The estimation of all parameters were obtained simultaneously by maximizing the likelihood using the Pseudo-Gauss-Newton algorithm in BMP(3R) statistical package and confidence interval obtained using the lielihood ratio statistics.
From this study we observe that further studies are required to determine whether maternal factors influence the course of HIV-1 infection through timing of transmission or it's mechanism.
Balasubramanian and Lagakos (2001) used time-dependent sensitivity of DNA and RNA PCR assays and HIV culture diagnostic tests to make nonparametric and semiparametric inferences about the distribution of the time of perinatal HIV transmission as well as the cumulative probability of perinatal transmission. They developed regression methods for the distribution of the timing of perinatal HIV transmission which they used to obtain expressions for the likelihood contributions for different types of observations that arise

in a perinatal transmission setting based on homogeneous subjects. The likelihood for special models for the sensitivity function were developed for identifiability and parameter estimations. Data from the AIDS Clinical Trials Group protocol 076 was used to illustrate these methods. These were then extended to incorporate covariates. It was observed that the extent to which the distribution of the timing of transmission is identifiable depended on the types of observations available. The estimates obtained suggested that the majority of perinatal infections occured at or shortly before birth, with very few occurring more than two weeks prior to birth. In addition to observing results of diagnostic tests, the database could also contain covariates that might affect the timing of perinatal transmission and therfore to incorporate covariates, proportional hazard models were used.

It would however be useful to extend these methods to settings where there is a risk of HIV infection following birth due to breastfeeding. This would be especially useful for the assessment of research studies that aim to recruit uninfected infants shortly after birth based on negative diagnostic tests and then randomize these to different strategies for preventing transmission from breatfeeding

Frydman and Szarek (2009) derived a nonparametric maximum likelihood maximum likelihood estimate of the overall survival distribution in an illness -death model from interval censored observations with unknown status of HIV-1 infection that corrects both the overestimation of the cumulative probability of death prior to infection and underestimation of the cumulative probability of the infection. This was done by deriving an expression for the distribution of the survival time T as the sum of the pre- and post natal HIV infection survival subdistributions which allowed for one to explore HIV free survival as a surrogate for overall survival.

Data from a randomized clinical trial between November 1992 and July 1998 in Nairobi, Kenya of HIV positive pregnant women who were randomly assigned to breastfeeding (BF) or counselled for formula feeding (FF) of their infants and followed for 24 months for HIV positivity, HIV free survival and overall survival was used to obtain the nonparametric maximum likelihood estimators (NPMLEs) of the cumulative incidence function of infection, the cumulative probability of death before infection and the discrete intensity from infection to death.

The distribution or the cumulative intensity of interest was estimated for each subsample and the estimated variance determined from the collection of 100 estimates. The p values for each treatment groups were abtained and compared using the statistic based on the logarithmic transformation of the survival functions. This statistic showed that for right censored survival data, the tests based on transformed survival functions were superior (in terms of type 1 error) to the naive test based on the difference in the estimates of survival. Similarly the test statistics used for testing equality of the cumulative intensities of death after (or before) HIV-1positivity was obtained and the confidence intervals at specified timepoints constructed from the subsampling empirical percentilesfor each estimated distributions

It was noted that while the clinical diagnosis of HIV inspection is usually determined by a positive test, the sensitivity of the test can depend on the age of an infant and the time since infection. We also observe that these methods can be further developed to incoporate left and right censoring. We can also incorporate covariates and therefore involve semi-parametric or parametric modelling of transition intensities.

Brown and Chen (2012) developed an imputation method (MI) to analyze the censored MTCT timing in presence of auxiliary information. The interest was in the estimation of

late postnatal transmission rate at 12 months and the effects of covariates on the hazard of late postnatal infection. The Kaplan-Meier (KP) approach was used to estimate the cumulative infection rate among those uninfected at 6 weeks and the proportional hazards models used to estimate the association between timing of MTCT and covariates. MI performed better in terms of bias for both the KM and PH estimates which had twice the bias in most of the MI analyses. The goal was to find a flexible MI model that could easily be implemented in available software such as R and OpenBugs and allows the inclusion of those infants whose timing could not be previously categorized. Using MI the estimates of postnatal transmission was found to be 0.2. An approach to take into account the imperfect sensitivity in imputation step and censoring to account for weaning was also used. This was done by first presenting a mixture model that allows a proportion of infants born with detectable HIV infection from in utero and another significant proportion that never experience MTCT of HIV. In addition mixtures of Weibull models that allows for a flexible estimate in the distribution of time to detectable infection after birth was used. Interest now is in estimating the distribution of timing of MTCT among those infants who experience MTCT for use in planning HIV testing schedules. Also there could be need to assess how baseline covariates predict transmission during the three exposure periods and not only late postnatal transmission.

Teeple (2013) developed a model for estimating baseline risk and associated covariates of time to postnatal infection, time to death, and time to weaning. This they did by first jointly modelling time to postnatal infection and time to death as two outcomes of an illness-death model by using an exponential random variable to incorporate sensitivity. The illness-death model was then expanded to include time to weaning as an additional outcome of the model. Bayesian MCMC algorithm was then implemented to estimate the parameters and the likelihood of the model formulated to account for imperfect sensitivity and interval censoring in the measurement of the time to illness ,and right censoring in the measurement of time to death.

Numerical optimization algorithms led to non-positive definite estimated variance-covariance matrices in approximately 5% of the models fit whereby the negative variance estimates occurred primarily in the spline coefficients of the healthy-death intensity for a period where there were few events probably as a result of lack of information.

It was observed that the choice of sensitivity function did not affect the illness-mortality rate although adjusting for sensitivity increased the duration in the illness state prior to death. In infected infants mortality peaked at 4 months after infection followed by a steady decline.

The model also indicated that the antibiotics had a harmful effect on both HIV infection and risk of mortality in HIV-uninfected infants with point estimates of log proportional hazard coefficient of 0.2 and 0.5 respectively since infants who benefited from an in utero treatment became more susceptible to harmfull events after birth when the treatment was no longer given.

We have observed that this model can still be extended to include more states, in paticular the prenatal stage. Also, instead of the exponential distribution, the more flexible Weibull distribution can be used.

1.5.4 Multistate Modelling MTCT

Teeple (2013) introduced new methods that incorporate time-dependent sensitivity in MSMs by considering HIV infection and disease progression in infants who acquire HIV

from their mother by regarding the fact that most infants born to HIV-positive mothers will test positive using an antibody test because of maternal HIV antibodies that circulate in the infant for the first year resulting in high false positive rates (Wessman et al 2012). This was done by comparing a proportional harzards survival models of time to postnatal illness to that of the healthy illness transition model to address the possible source of bias while focusing on time to postnatal infection basing their approach on MSM framework. In addition a new random variable was included in the MSM to measure the delay in the detection that results from imperfect diagnostic testing which accounts for the downward bias that is caused by using an observed event time that is later than the true onset and the uncertainty of an infants true status prior to death.

1.6 Summary of the Literature Review

From the literature reviewed, the transition probabilities and transition intensities are approximated directly from the data available and also noted was the fact that the specific time at which an infected individual was infected, or the time an individual might get infected is rarely observed, is not used in obtaining these estimates. This has enabled us come up with the following guideline for our research

(i) Perform a decomposition of the transition intensities matrices to obtain matrices of transition probabilities.

(ii) Consider transmission taking place before and after birth resulting in different type of censoring

(iii) Use expanded and all stages in HIV transmission

(iv) Get estimate of transition intensities using MLEs

1.7 Methodology

In this study we will use the following tools to come up with the model

i) Chapmam-Kolmogorov equation

$$P_{ij} = \sum_{k} P_{ik}(s)P_{kj}(t) \tag{1.23}$$

(ii) Kolmogorov forward dfferential equations
We obtain the transition probabilities from these differential equations in terms of transition rates by use of the Generator matrix method

(iii) Use of Maximum likelihood method in parametric estimation and use of non parametric methods to obtain the transiton rates.

1.8 Significance of the study

In studies of vertical transmission of HIV, the main focus is either on the stages of HIV or in estimating the time transmission occurs. Several recent examples include adjusting for misclassified outcomes in a multistate model (Teeple, 2013), an imputation method for interval censored time-to-event with auxilliary information: analysis of the timing of mother-to-child transmission of HIV (Brown and Chen, 2012). However, none of the studies considered both multistate models and censoring together in estimating the time of transmission. In this work we obtain transition probabilities in terms of transition intensities and estimate the transition intensities which can then be used to determine the time of transmission or that of transition from one state to another and therefore enabling intervention to be introduced at the most appropriate time.

Chapter 2

DETERMINATION OF R_0 THROUGH DETERMINISTIC MODELLING OF HIV TRANSMISSION

2.1 Introduction

A deterministic model assumes that its outcome is fixed. No matter how many times one recalculates, one obtains exactly the same results. It assumes that the vital rates (such as birth, death) are constant and unchanging over time and every run of the model will yield the same (fixed) outcome.
Infectious diseases are categorized as either being acute or chronic. In acute infections the pathogen causes illness for a period of time which is then followed by immunity e.g influenza, rabies and chickenpox. This scenario is mathematically best described by the SIR models (Dietz 1967) in which

(i) S(t) which is the number of susceptibe individuals at time t and,

(ii) I(t) which is the number of infected individuals at time t,

(iii) R(t) the number of recovered individuals at time t.

(iv) N is the popuation size.

Chronic infections on the other hand, last for much longer periods (months or years) and examples include herpes, chlamydia and HIV/AIDS.
The simplest HIV model is the SI (Susceptible Infected) model. In this model there is no recovery class and once infection takes place are assumed to remain infectious for an average period of time after which they succumb to the infection.
There are a number of studies that have been done in modelling mother to child transmission of HIV/AIDS with emphasis being on the deterministic models.
Mugisha and Luboobi (2003) modelled the effect of vertical transmission by using a continuous age structured model of McKendrick-von-Foerster type to derive a two- age group HIV/AIDS epidemic model and concluded that the epidemic can die out if some effort is put on delivery of HIV-free babies. By using a deterministic dynamic transmission model,

Wang *et al.* (2010) determined the effect of key parameters on the likely long term trends of the HIV MTCT epidemic in China and concluded that prevention of MTCT should not only focus on the reduction of HIV transmission rates and incidences among women but also on the increase of HIV testing for pregnant women.

The SI model is used to compute the amount of susceptible and infected individuals in the population under the assumptions presented in the next section.

2.1.1 Assumptions and Notations:

Let

(i) deaths occur from all stages naturally at rate = μ;

(ii) death rate due to infection = λ;

(iii) birth rate into susceptible group be equal to natural death rate and be represented by b at equilibrium;

(iv) transmission occur only from infected mothers at rate β;

(v) population be fixed and consists of children born free of HIV virus and those who get infected by their mothers.

A central concept in the theory of infectious disease transmission is the mass action principle which states that the net rate at which new cases of infectives arise is proportional to the number of susceptible individuals (S), times the number of infective individuals (I) times the probability of transmission from infectious to susceptible individuals (β), that is βSI. The probability of transmission β is formed from two components, namely the likelihood of close contact between two individuals such that transmission can occur plus the probability that transmission will occur as a result of the contact. This principle is based on the assumption that susceptible and infectious individuals mix in a homogeneous (random) manner which in practice rarely occurs but can be modified to take account of age and space dependent mixing or other forms of heterogeneity that exist in host or parasites populations (Anderson, Grenfell and May, 1984).
The diagram below represents the transition from susceptible to infected.

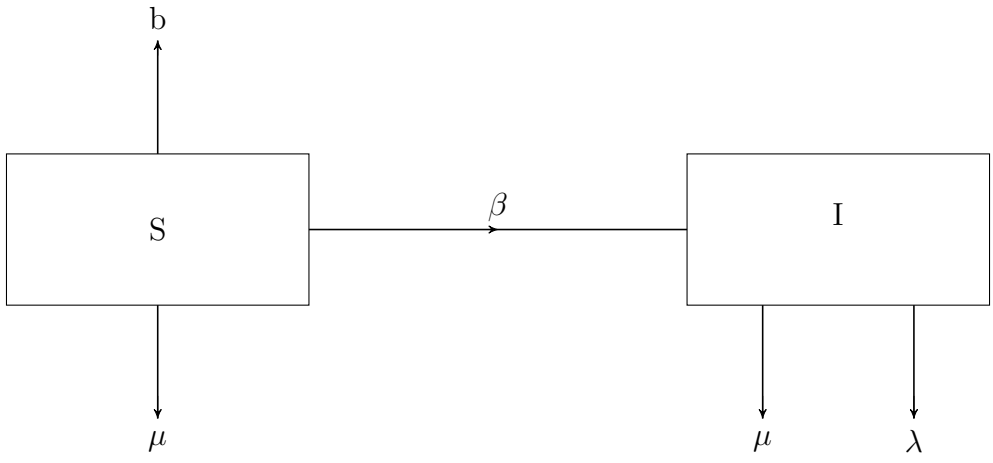

Figure 2.1: An illustration of a HIV SI model

Based on Figure 2.1 we derive the differential equations

$$\frac{dS}{dt} = b - \beta S(t)I(t) - \mu S(t), \tag{2.1}$$

$$\frac{dI}{dt} = \beta S(t)I(t) - \lambda I(t) - \mu I(t), \tag{2.2}$$

As $t \to \infty$ it is assumed that the system develops an equilibrium and we explore what happens by setting the system of equations to zero. The equilibrium states for the SI model is therefore given by

$$\frac{dS}{dt} = 0 \quad \text{with it's solution denoted by} \quad S^* \tag{2.3}$$

$$\frac{dI}{dt} = 0 \quad \text{and it's solution denoted by} \quad I^* \tag{2.4}$$

There are two equilibriun solutions

i) The case where none of the individuals are infectious (disease free equilibrium)
$S^* = N$ $I^* = 0$ and therefore $S^* = N$,
This equilibrium can also be due to the fact that the virus has suffered extinction, and therefore eventually everyone in the population is susceptible.

ii) The case where a fraction of the individuals are infected (endemic equilibrium)

Proposition 1. *Let there be a disease free equilibrium, then, the equilibrium solution S^* is given by*

$$S^* = \frac{\gamma + \mu}{\beta} \tag{2.5}$$

Proof.

$$\beta S(t)I(t) - \gamma I(t) \equiv \mu I(t) = 0,$$

which yields

$$S^* = \frac{\gamma + \mu}{\beta}. \tag{2.6}$$

□

If the initial fraction of susceptibles is less than $\frac{\gamma + \mu}{\beta}$ then $\frac{dI}{dt} < 0$ and the infection dies out which is attributed to Kermack and McKendrick (1927). The inverse $\frac{\beta}{\gamma + \mu}$ is the basic reproductive ratio R_0 which will be discussed later
Substituting equation (2.5) in the equation (2.1) and equating it to zero and using the assumption (iii) gives

$$\begin{aligned} 0 &= \mu - \beta(\frac{\gamma + \mu}{\beta})I - \mu(\frac{\gamma + \mu}{\beta}), \\ (\gamma + \mu)I &= \mu(I - \frac{\gamma - \mu}{\beta}). \end{aligned} \tag{2.7}$$

Proposition 2. *Let* $R_0 = \dfrac{\beta}{\gamma + \mu}$.
Then from equation (2.7)
$I = \dfrac{\mu}{\gamma + \mu}(I - \dfrac{1}{R_0})$,

Therefore,

$$\begin{aligned} I &= (\frac{\mu}{\gamma + \mu})(\frac{\gamma + \mu}{\beta})(R_0 - 1), \\ &= \frac{\mu}{\beta}(R_0 - 1). \end{aligned}$$

One universal condition on population variables is that they cannot be negative and hence endemic equlibrium is biologically feasible only if $R_0 > 1$.

2.1.2 Formulation of the MTCT Model

Here we modify Li *et al.* $(1999)'s$ Susceptibe Exposed Infectious Recovery (SEIR) model into a Suscptible Infected Treatment Aids (SITA) model. The modification involves taking the exposed and infectious stages as one state and calling it the Infected state and introducing a new state called the treatment stage. The Aids stage is assumed to be the removal stage. We consider a population size N with constant inflow of susceptible at rate bN and various categories of the population designated as $S(t), I(t), T(t)$ and $A(t)$. It is assumed that susceptible children get infected by their HIV positive mothers either in-utero, intrapartum or postpartum at the rate β. We also assumed that some of those infected move to the treatment class at a rate of ϕ and then proceed to the AIDS class at a rate α. Those in the AIDS class also join the treated class at the rate ω
The stages, rates and order of the process is shown in the diagram below

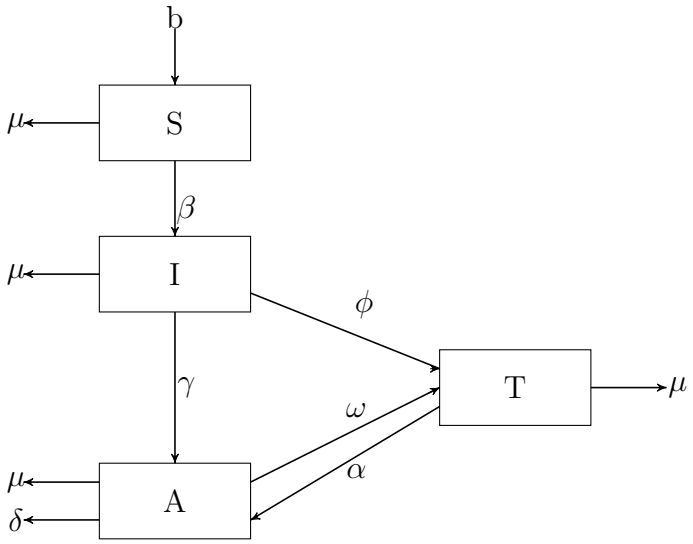

Figure 2.2: HIV Transition model 2.1

The various estimates of the parameter values are given in the Table 2.1 below

Table 2.1: Parameters of the SITA model

Symbol	Description	Estimate
b	Natural birth rate	0.03
μ	Natural mortality rate	0.09
β	Rate of newborns infected with HIV	0.15
ϕ	Fraction of infected who get treatment	0.31
γ	Rate of movement from infected to AIDS	0.015
ω	Rate at which AIDS group get treatment	0.105
α	Rate at which treated group develops full blown AIDS	0.07
δ	AIDS induced death	0.18
N	That total number of children exposed to HIV positive mothers	1000

A non-linear model is proposed and analyzed to study the dynamics of vertical transmission of HIV with and without treatment. In modelling the dynamics, the population of size $N(t)$ at time t with constant inflow of Susceptible $S(t)$, Infectives $I(t)$, Treated $T(t)$, and AIDS patients $A(t)$ with natural mortality rate μ in all classes and mortality due to AIDs as δ. The interaction between the classes is assumed to be that some of susceptible infants become infected from their HIV positive mothers at the rate of β with others dying at the natural mortality μ. It is also assumed that some of the infectives become treated at the rate of ϕ with the rest eventually developing AIDS at the rate of γ. Some of those who have developed AIDS are treated at the rate of ω. Within those who get treated not all respond to treatment and therefore develop full blown AIDS at the rate at α. It is assumed that those with full blown AIDS will all eventually die due to the condition at the rate of δ. The model as presented in Figure 2.2 is thus governed by the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= bN - \mu S - \frac{\beta SI}{N}, \\
\frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I - \mu I - \Phi I, \\
\frac{dT}{dt} &= \Phi I - \alpha T - \mu T + \omega A, \\
\frac{dA}{dt} &= \gamma I + \alpha T - \omega A - \mu A - \delta A.
\end{aligned} \tag{2.8}$$

We assume that mortality rate μ will be a function of the state variables.
The state variables can be normalized by setting:

$$s = \frac{S}{N}, \qquad i = \frac{I}{N}, \qquad e = \frac{T}{N}, \qquad a = \frac{A}{N} \tag{2.9}$$

This leads to the normalized system

$$\begin{aligned}
\frac{dS}{dt} &= b - \mu s - \beta si, \\
\frac{dI}{dt} &= \beta si - \gamma i - \mu i - \Phi i, \\
\frac{dT}{dt} &= \Phi i - \alpha e - \mu e + \omega a, \\
\frac{dA}{dt} &= \gamma i + \alpha e - \omega a - \mu a - \delta a.
\end{aligned} \tag{2.10}$$

where

$$s + i + e + a = 1 \tag{2.11}$$

and

$$s(t) > 0, \qquad i(t) \geq 0, \qquad e(t) \geq 0, \qquad a(t) \geq 0 \tag{2.12}$$

for all $t \geq 0$.

The three parameters γ, α and δ are determined by the lifespan of HIV positive children (from acquisition of HIV to AIDS.) and thus play an important role in their survival.

The total size N at any time t is given by

$$N(t) = S(t) + I(t) + T(t) + A(t). \tag{2.13}$$

From this relation we obtain

$$\begin{aligned}
\frac{dN}{dt} &= \frac{dS}{dt} + \frac{dI}{dt} + \frac{dT}{dt} + \frac{dA}{dt}, \\
&= b - \mu S - \mu I - \mu T - \mu A - \delta A, \\
&= b - \mu N - \delta A.
\end{aligned} \tag{2.14}$$

When the system is in equilibrium with

$$\begin{aligned}
\frac{dS}{dt} = \frac{dI}{dt} = \frac{dT}{dt} = \frac{dA}{dt} &= 0, \\
b - \mu N - \delta A &= 0.
\end{aligned}$$

At disease free equilibrium we assume A in (2.14) equals zero.
Therefore,

$$\frac{dN(t)}{dt} + \mu N(t) = b. \tag{2.15}$$

Solving

$$\begin{aligned}
N(t) &= e^{-\int \mu dt} \left\{ \int b e^{\int \mu dt} dt + C \right\}, \\
&= e^{\mu t} \left\{ b \int e^{\mu t} dt + C \right\}, \\
&= e^{\mu t} \left\{ \frac{b}{\mu} e^{\mu t} + C \right\}, \\
&= \frac{b}{\mu} + C e^{-\mu t},
\end{aligned} \tag{2.16}$$

where $C = N(0)$ (the initial condition)

$$N(t) = \frac{b}{\mu} + N(0)e^{-\mu t}. \tag{2.17}$$

As $t \to \infty$ (2.17) becomes

$$N(t) = \frac{b}{\mu} \tag{2.18}$$

Parameter estimates, including their uncertainty is important for the spread of infection To establish the endemic equilibrium for the SITA model we set the equation for the infectives in (2.10) to zero.

$$\beta si - (\gamma + \mu + \Phi)i = 0. \tag{2.19}$$

After factoring out i we have

$$i(\beta s - (\gamma + \mu + \Phi)) = 0 \tag{2.20}$$

which is satisfied whenever $i^* = 0$ or $s^* = \dfrac{(\gamma + \mu + \Phi)}{\beta}$. i^* is a disease free equlibrium (DFE) and is achieved when all infections are zero , i.e $i = 0, \quad e = 0, \quad a = 0$ and therefore from (2.8)

$$s^*(t) = \frac{b}{\mu} \tag{2.21}$$

This is true from (2.17) when $a = 0$ and if s, i, e and a are proportions of the population The system at DFE is $(\dfrac{b}{\mu}, 0, 0, 0)$.
We concentrate on s^* which is the endemic equilibrium as it determines whether infection persits or not.
The reciprical of s^* is the basic reproduction number i.e $s^* = \dfrac{1}{R_0}$ and is characterized by the fraction of susceptible in the population.
The parameter R_0 plays a crucial role in determining the probability of a major outbreak. Only major outbreaks are of interest since minor outbreaks would rarely be observed.

2.2 Basic Reproduction Number (R_0)

This is the average number of new cases of an infection caused by one typical infected individual during the early stages of the epidemic. It is arguably the most important quantity in infectious disease epidemiology and among the quantities most urgently estimated for emerging infectious diseases in outbreak situations and possible interventions procedures. It is conveniently defined as the expected number of infections generated by one infectious individual in a large susceptible population. It is a dimensionless number and predicts whether a disease will become endemic or die out. The case when $R_0 < 1$, implies that each individual produces on average less than one new infected individual and hence the disease dies out. If $R_0 > 1$ then each individual produces more than one new infected individual and hence the disease is able to invade the susceptible population and therefore persists. It's value provides insight when designing control interventions for established infections.

One method used in the calculation of R_0 is the Next Generation Matrix (NGM). This

is a square matrix in which the ij^{th} element is the expected number of secondary infections of type i caused by a single infected individual of type j. This method calculates R_0 by using many finitely many different categories of individuals or states of an individual. These categories are referred to as generations. Infection transmission which results to a new infection is regarded as a birth hence leading to the viewing of the infection process in terms of consecutive generations of infected individuals. Subsequent generations growing in size indicate a growing generation i.e an epidemic, and the growth factor per generation indicates the potential for growth. The growth factor is the mathematical characterization of R_0.
Diekman *et al.* (1990) introduced the NGM for deriving R_0 in such cases, encompassing any situation in which the population is divided into disjoint cases.
In order to compute R_0, it is important to distinguish new infections from all other changes in population.
At infection-free steady state we form matrix J of the different states of the infection described by a system of ordinary diferential equations (2.10) which is then partitioned into a nonnegative new infection sub-matrix $\mathcal{F}$ and another sub-matrix $\mathcal{V}$ of rates of death, improved status and other transitions, such that

$$J = \mathcal{F} - \mathcal{V}, \tag{2.22}$$

$$\mathcal{F} = \begin{pmatrix} \beta SI \\ 0 \\ 0 \end{pmatrix} \qquad \mathcal{V} = \begin{pmatrix} \gamma i + \mu i + \Phi i \\ -\Phi i \alpha e + \mu e - \omega a \\ -\gamma i - \alpha t + (\omega + \mu + \delta) a \end{pmatrix}$$

We then get the partial derivatives for both $\mathcal{F}$ and $\mathcal{V}$ with respect to I, T and A which are the states with infection resulting in 3×3 matrices F and V.
Hefferman *et al.* 2005 provided the formala for calculating NGM as

$$K = FV^{-1} \tag{2.23}$$

where

$$F = \left[\frac{\partial \mathcal{F}}{\partial x_j} \right] \tag{2.24}$$

and

$$V = \left[\frac{\partial \mathcal{V}}{\partial x_j} \right] \tag{2.25}$$

for $x_j = I, T, A$ The values of K gives the number of new infections in the next generation.
R_0 is the eigenvalue with the largest magnitude of the matrix K.

$$F = \begin{pmatrix} \beta s & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \qquad \text{and} \qquad V = \begin{pmatrix} \gamma + \mu + \Phi & 0 & 0 \\ -\Phi & \alpha + \mu & -\omega \\ -\gamma & -\alpha & (\omega + \mu + \delta) \end{pmatrix}$$

and therefore from equation (2.23)

$$FV^{-1} = \begin{pmatrix} \dfrac{\beta s}{(\gamma+\mu+\Phi)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Replacing s with (2.21) we have

$$K = \begin{pmatrix} \dfrac{\beta b}{\mu(\gamma+\mu+\Phi)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

The reproduction number R_0 is given as

$$R_0 = \frac{\beta b}{\mu(\gamma+\mu+\Phi)}. \tag{2.26}$$

The disease free equilibrium is locally asymtotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. To calculate the value of R_0 in (2.26) we use Table 2.2 which has the required parameters and is obtained from Table 2.1.

Table 2.2: Parameters estimates for R_0

	Symbol				
	b	μ	β	Φ	γ
Estimate	0.4	0.08	0.15	0.31	0.3

Using equation (2.26) we obtain the basic reproduction number given as $R_0 = 1.087$ i.e $R_0 > 1$ which implies the need for more emphasis on intervention and preventive mechanisms to control vertical transmission.
Since $R_0 > 1$ we can conclude that an infected mother will infect one child or more.

With higher values of b the reproduction number, R_0, increases faster than it does for β. Also the effect of γ and ϕ is the same and an increase on both results in a decrease in R_0 with the rate of decrease reducing as both increase.
The graph also shows that initial increase in μ results in a sharp decrease in R_0 which then stabilize when $R_0 = 0$

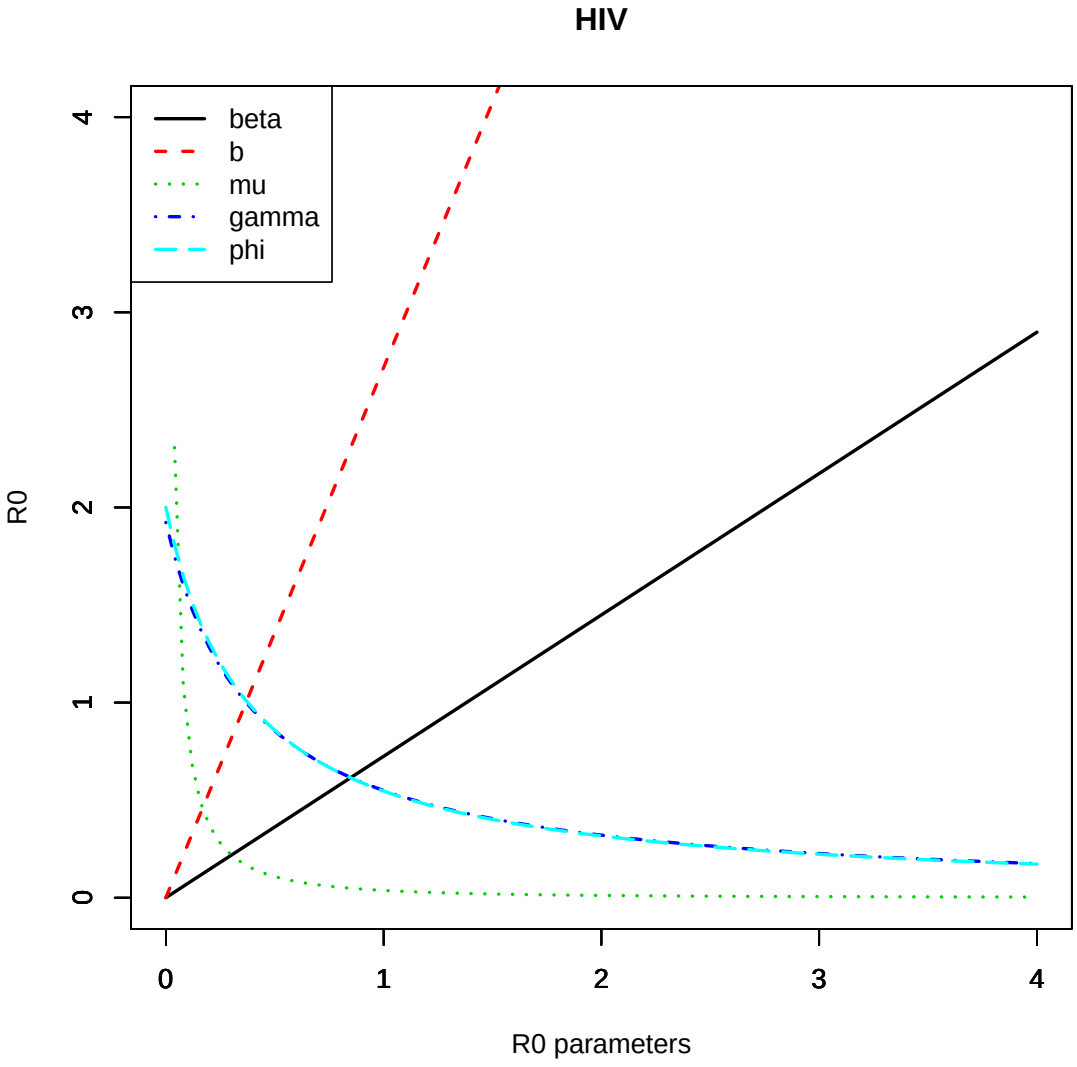

Figure 2.3: Effect of β, b, μ γ and ϕ on R_0.

Chapter 3

KOLMOGOROV DIFFERENTIAL EQUATIONS, CENSORING TECHNIQUES AND SOME PROBABILITY DISTRIBUTIONS

3.1 Introduction

In this chapter we describe the various mathematical tools used to achieve our objectives which include a description of the general setup of a Markov multi-state models from which we develop the Kolmogorov forward differential equations.
We introduce the aspect of censoring and give examples of some distribution commonly used.

3.2 Multi-state Models

In the study of diseases the ultimate outcome of interest is recovery or death. In addition a number of intermediate (transient) states exists. For these reasons, multi-state models (MSM) are extremely useful in understanding this process by taking into consideration the health condition and causes of death as criteria for defining states.
A multi-state model is defined as a model for a (continuous time) stochastic process (X(t), t$\in$ T) in which the subject of interest at any time occupies one of a number of finite state space S= $\{1, 2 \cdots N\}$ and describe random movements of a subject among various states. In multistate process T=$[0, \tau], \tau < \infty$ is a time interval and the value of the process at time t is the state occupied at that time.
Multi-state models are often fit under a Markov or semi-Markov assumption.
Given state-space E, states $i, j \in E$, and $s \leq t$, a Markov process assumes

$$P_{ij}(s,t) = \text{Prob}(X(t) = j | X(s) = i) \tag{3.1}$$

so that the transition probability depends on the current state i.
Under the semi-Markov assumption the transition probability depends on both the current state i and the time of entry to state i i.e $t + \Delta t$ so that

$$P_{ij}(s,t) = \text{Prob}(X(t) = j | X(s) = i, t + \Delta t). \tag{3.2}$$

Future events not only depend on the current state but also on the entry time to the state.
Both these approaches can either be defined in continous time and — or discrete time context.
Suppose there are n states, then we denote the state space by E where E is a countable finite set such that

$$E = \{1, 2, \cdots n\} \tag{3.3}$$

Graphically, multi-state models may be illustrated using diagrams such as boxes or circles to represent the states and by the arrows between the states representing the possible transitions which are the the non zero transition intensities.
Transition intensities are also refered to as transition rates or forces of transition.

The transition intensity denoted by $\mu_{ij}(t)$ is defined as the transition intensity between two states i and j and is the rate of change of the probability $P_{ij}(s,t)$ in a very small time interval h.

$$\mu_{ij}(t) = \lim_{h\to 0} \frac{P_{ij}(t, t+h)}{h} \tag{3.4}$$

for any given time $\{t : 0 < t < T\}$ and interval length $h > 0$

3.2.1 Assumptions

i) Multi-state models are often fit under the Markov assumption.
The Markov property holds if $P\left[X(s+t) = j | X(s) = i, X(\tau) = k, 0 \leq \tau < s\right]$

$$= P\left[X(s+t) = j | X(s) = i\right]$$

ii) All transition intensities are assumed to be constant over time in that $\mu_{ij}(t) = \mu_{ij}$ for all t. Such a Markov process is referred to as time-homogeneous or stationary. Some transition intensities may be 0 for all t.
This can be shown using the Chapman-Kolmogorov formula given in equation (3.11)

from where we deduce that

$$\begin{aligned}
P_{ij}(s,t+h) &= \sum_k P_{ik}(s,t)P_{kj}(t,t+h) + P_{ij}(s,t)P_{jj}(t,t+h) \\
P_{ij}(s,t+h) - P_{ij}(s,t) &= \sum_k P_{ik}(s,t)P_{kj}(t,t+h) + P_{ij}(s,t)P_{jj}(t,t+h) - P_{ij}(s,t) \\
&= \sum_k P_{ik}(s,t)P_{kj}(t,t+h) - [1 - P_{jj}(t.t+h)]\, P_{ij}(s,t) \\
\lim_{h\to 0}\frac{P_{ij}(s,t+h) - P_{ij}(s,t)}{h} &= \lim_{h\to 0}\frac{\sum_k P_{ik}(s,t)P_{kj}(t,t+h) - [1 - P_{jj}(t,t+h)]\, P_{ij}(s,t)}{h} \\
\frac{\partial}{\partial t}P_{ij}(s,t) &= \sum_k P_{ik}(s,t)\lim_{h\to 0}\frac{P_{kj}(t,t+h)}{h} \\
&\quad -P_{ij}(s,t)\lim_{h\to 0}\frac{1 - P_{jj}(t,t+h)}{h} \\
&= \sum_k P_{ik}(s,t)\mu_{kj} - P_{ij}(s,t)\mu_{jj} \qquad (3.5)
\end{aligned}$$

where

$$\lim_{h\to 0}\frac{P_{kj}(t,t+h)}{h} = \mu_{kj} \qquad (3.6)$$

and

$$\lim_{h\to 0}\frac{1 - P_{jj}(t,t+h)}{h} = \mu_{jj} \qquad (3.7)$$

for $k \neq j$
Moreover a process is time homogeneous if for any $s \leq t$ and any state $i, j \in E$

$$P(X(t) = j | X(s) = i) = P(X(t-s) = j | X(0) = i) \qquad (3.8)$$

The dependence on time is only through the length of time elapsed between events. The time homogeneous property means that whenever state i is entered at time s, the way the process evolves is equivalent to having started in state i at time 0.
Each transition probability $P_{ij}(s,t)$ therefore depends only on $t-s$, i.e, $P_{ij}(s,t) = P_{ij}(0,t-s)$.
We may use only one argument in time $P_{ij}(0,t-s) = P_{ij}(t-s)$ to simplify notation. Also, the functions $P_{ij}(s,s+t) = P_{ij}(0,t)$ are the same for all $s \geq 0$ and therefore can be written as $P_{ij}(t)$.

iii) For all states i and j, $P_{ij}(t)$ is a differentiable function of t

We can then express transition probabilities in terms of transition rates as

$$P_{ij}(t) = \mu_{ij}h + o(h)$$

iv) For any short time interval of length h the probability of two or more transitions within that time period is $o(h)$

A function $f(h)$ is said to be of $o(h)$ if

$$\lim_{h\to 0}\frac{f(h)}{h} = 0 \tag{3.9}$$

and so

$$P_{ij}(t) \approx \mu_{ij}h$$

v) The assumption of constant forces of transition implies that the time spent in each state is exponentially distributed. This can be expressed as

Theorem 1. *For a time homogeneous continuous time Markov process, T_i (the sojourn time in state i) is exponentially distributed*

Proof. The proof is based on the memoryless property which is unique for the exponential distribution. By time homogeneity we assume that the process starts in time i

$$\begin{aligned} P(T_i > s+t | T_i > s) &= P(X(\tau) = i \quad \text{for} \quad 0 \le \tau \le s+t | X(\tau) = i, \quad 0 \le \tau \le s) \\ &= P(X(\tau) = i \quad \text{for} \quad s < \tau \le s+t | X(\tau) = i, \quad 0 \le \tau \le s) \\ &= P(X(\tau) = i \quad \text{for} \quad 0 < \tau \le t | X(0) = i) \\ &= P(T_i > t) \end{aligned} \tag{3.10}$$

This indicates the memoryless property which is unique to an exponentially distributed random variable, therefore T_i must be exponentially distributed. □

In addition, the transition probabilities are solutions of the Chapman-Kolmogorov equation.
Chapman-Kolmogorov equation has a strong interpretation that can be split according to intermediate times and states, i.e

$$P_{ij}(s, t+h) = \sum_k P_{ik}(s,t)P_{kj}(t, t+h) \tag{3.11}$$

The probability that there is a transition from state i to some other state in the time interval $[0, t]$ equals one and hence the matrix of transition probabilities $P(s, t)$ is a stochastic matrix for all $s, t \ge 0$.
Transition probability of the Markov process are denoted by $P_{ij}(s, t)$ and defined by

$$\begin{aligned} P_{ij}(s,t) &= \text{Conditional probability that an individual is in state } j \text{ at time } t \text{ given that they} \\ &\quad \text{were in state } i \text{ at time } s \\ &= \text{Prob}\left[X(t) = j | X(s) = i\right] \qquad (3.12) \\ &= \frac{\text{Prob}\left[X(t) = j, X(s) = i\right]}{\text{Prob}\left[X(s) = i\right]}, \qquad 0 \le s \le t, \qquad i, j \in N \qquad (3.13) \end{aligned}$$

on condition that Prob $[X(s) = i] > 0$, otherwise $P_{ij}(s,t) = 0$

$$P_{ij}(s,s) = \begin{cases} 0 \text{ for } i \neq j \\ 1 \text{ for } i = j \end{cases}$$

The transition probabilities satisfy the following properties

i) $0 \leq P_{ij}(s,t) \leq 1; \qquad i,j \in N$

ii) $\sum_{j \in N} P_{ij} = 1; \qquad 0 \leq s \leq t$

The transition intensity denoted by $\mu_{ij}(t)$ is defined as the transition between two states i and j and is the rate of change of the probability $P_{ij}(s,t)$ in a very small time interval h.

$$\mu_{ij}(t) = \lim_{h \to 0} \frac{P_{ij}(t, t+h)}{h} \tag{3.14}$$

for any given time $\{t : 0 < t < T\}$ and interval length $h > 0$ and with $\mu_{ij}(t) = \mu_{ij}$ i.e constant over time for all t as the process is time-homogeneous. Some transition intensities may be 0 for all t.
In our study we will use the definition of the transition probabilities and transition intensities interchangably as
$P_{ij}(s,t) = P_{ij}(t)$ to be the transition probability of an individual from a medical state i at time s to state j at time t

and $\mu_{ij}(t) = \mu_{ij}$ to be the transition intensity rate from state i to state j at time t.

3.3 Kolmogorov Differential Equations

The Chapman-Kolmogorov equations provide a method for computing $n-$step transition probabilities. These equations are of the form

$$P_{ij}^{n+m} = \sum_{k=0}^{\infty} P_{ik}^{n} P_{kj}^{m} \tag{3.15}$$

and are most easily understood by noting that $P_{ik}^{n} P_{kj}^{m}$ represent the probability that starting in state i, the process will go to state j in $n+m$ transition through a path which takes it into state k at the n^{th} transition.
For time $s < t$, where s is the time it takes to be in state E_k and t, the time it takes to be in state E_j and therefore $s + t$, the time it takes to be in state E_j and for one step transition, we have

$$P_{ij}(s,t) = \sum_{k} P_{ik} P_{kj} \tag{3.16}$$

as shown in Figure 3.1 below

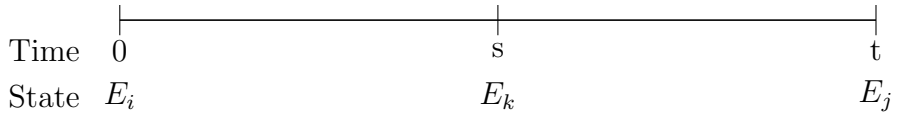

Figure 3.1: A time dependent derivation of forward Kolmogorov equations

where the states E_i, E_j and E_k are experienced at time s, t and $t + h$ respectively.
For any continuous time Markov process, the Kolmogorov differential equation is given by

$$\frac{dP_{ij}(s,t)}{dt} = \sum_{k \in S} P_{ik}(s,t) P_{kj} \tag{3.17}$$

We want therefore to develop a differential equation based on Chapman-Kolmogorov equations of which the difference-differential equation is a special case and for time $s < t$ where the primary application is to calculate the transition probabilities $P_{ij}(s,t)$ based on the transition intensities $\mu_{ij}(s,t)$.

We have
Lemma 1**:**

$$P_{ij}(s,t) = \sum_{k} P_{ik}(s) P_{kj}(t) \tag{3.18}$$

where

- $P_{ij}(s,t)$ is the probability of moving from state i at time s to j at time t

  and

- $P_{ik}(s)P_{kj}(t)$ the probability of moving from state i to state j through state k

Proof
Consider Figure 3.1
$P_{ij}(s,t)$=the probability of moving from state E_i at time zero to state E_j at time $s+t$, passing via some state E_k at time s

$$\begin{aligned}
P_{ij}(s,t) &= \sum_k \text{Prob}\{X(s,t)=j, X(s)=k/X(0)=i\} \\
&= \sum_k \frac{\text{Prob}\{X(s+t)=j, X(s)=k, X(0)=i\}}{\text{Prob}\{X(0)=i\}} \\
&= \sum_k \frac{\text{Prob}\{X(s+t)=j/X(s)=k, X(0)=i\}\,\text{Prob}\{X(s)=k, X(0)=i\}}{\text{Prob}\{X(0)=i\}} \\
&= \sum_k \frac{\text{Prob}\{X(s+t)=j/X(s)=k, X(0)=i\}\,\text{Prob}\{X(s)=k/X(0)=i\}\,\text{Prob}\{X(0)=i\}}{\text{Prob}\{X(0)=i\}} \\
&= \sum_k \text{Prob}\{X(s+t)=j/X(s)=k, X(0)=i\}\,\text{Prob}\{X(s)=k/X(0)=i\}
\end{aligned}$$

Therefore,

$$P_{ij}(s,t) = \sum_k \text{Prob}\{X(s+t)=j/X(s)=k\}\,\text{Prob}\{X(s)=k/X(0)=i\}$$

(because of Markov property)

$$\begin{aligned}
&= \sum_k P_{kj}(t)P_{ki}(s) \\
&= \sum_k P_{ik}(s)P_{kj}(t) \qquad (3.19)
\end{aligned}$$

Using the Chapman-Kolmogorov formula given in (3.18) we deduce that

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

Thus,

$$\begin{aligned} P_{ij}(s,t+h) - P_{ij}(s,t) &= \sum_{k\neq j} P_{ik}(s,t)P_{kj}(t,t+h) + P_{ij}(s,t)P_{jj}(t+t+h) - P_{ij}(s,t) \\ &= \sum_{k\neq j} P_{ik}(s,t)P_{kj}(t,t+h) - [1 - P_{jj}(t,t+h)]\, P_{ij}(s,t) \\ \lim_{h\to 0}\frac{P_{ij}(s,t+h) - P_{ij}(s,t)}{h} &= \lim_{h\to 0}\frac{\sum_{i\neq j} P_{kj}(t,t+h) - [1 - P_{jj}(t,t+h)]\, P_{ij}(s,t)}{h} \\ \frac{\partial}{\partial t}P_{ij}(s,t) &= \sum_{k\neq j} P_{ik}(s,t)\lim_{h\to 0}P_{kj}\frac{(t,t+h)}{h} - P_{ij}(s,t)\lim_{h\to 0}\frac{[1 - P_{jj}(t,t+h)]}{h} \\ &= \sum_{k\neq j} P_{ik}(s,t)\mu_{kj} - P_{ij}(s,t)\mu_j \end{aligned} \tag{3.20}$$

where

$$\begin{aligned} \lim_{h\to 0}\frac{P_{kj}(t,t+h)}{h} &= \mu_{kj} \\ \lim_{h\to 0}\frac{[1 - P_{jj}(t,t+h)]}{h} &= \mu_j \qquad , k \neq j \end{aligned}$$

The Kolmogorov Forward equation is thus

$$\frac{\partial}{\partial t}P_{ij}(s,t) = \sum_{k\neq j} P_{ik}(s,t)\mu_{kj} - P_{ij}(s,t)\mu_j \tag{3.21}$$

where $\mu_{ij}(t)$ is defined as the transition intensity between two states i and j i.e $\mu_{ij}(t)$ is the rate of change of the probability p_{ij} in a very small time interval h

$$\mu_{ij}(t) = \lim_{h\to 0}\frac{P_{ij}(t,t+h)}{h}, \qquad i \neq j \tag{3.22}$$

for any given time $\{t : 0 < t < T\}$ and interval length $h > 0$
In our study therefore

$$\begin{aligned} P_{ij}(s,t) &= \text{The probability that a child in state } j \text{ at time } t \\ &\quad \text{was in state } i \text{ at time } s \\ \mu_{ij}(s,t) &= \text{The transition intensity/rate from state } i \text{ at time } s \text{ to state } j \text{ at time } t \end{aligned}$$

Assuming the homogeneous property

$$\mu_{ij}(s,t) = \mu_{ij}(t) \tag{3.23}$$

3.4 The Maximum Likelihood Estimation

Maximum likelihood estimation is a method of estimating unknown parameters of a statistical model whereby the parameters are obtained by maximizing the likelihood function

of the model. The likelihood function is the probability density function of the joint distribution of the data of a sample or a continuous/disrete random variable and contains the parameters of a statistical model.
The likelihood of a set of parameter values θ, given some observed outcomes t, is equal to the probability of those observed outcomes given the parameter values;

$$L\left(\theta|t\right) = \prod_{i=1}^{n} f(t_i, \theta) \tag{3.24}$$

The logarithm is taken of the likelihood function, which is practical as the logarithm is a monotonically increasing function.
Studying the logarithm of the likelihood function has the advantage of giving a linear model. To obtain the expressions for the parameters, the partial derivatives of the log likelihood with respect to the parameters are set equal to zero.
To obtain the Maximum likelihood (ML) estimators we use log L and solve the equation

$$\frac{\partial \ln L}{\partial \theta} = 0 \tag{3.25}$$

Let the probability density function of the time T to an event be $f(t), \quad t \geq 0$ and T_i be the time when an i^{th} individual is censored i.e the last time an i^{th} individual is observed then censored.
Also let t_i be the time an i^{th} individual experiences the event of interest,
then

$$0 \leq T_i \leq t_i$$

3.5 Censoring

Survival analysis is a branch of statistics that deals with time to event e.g time to infection, time to recovery or time to death. In cases where we have complete information about an individual/patient then we have uncensored information. However if the information is incomplete we have censored information.
If a study comes to an end after a certain period of time we have Type I censoring and if the study stops when a certain number of events has been achieved we have Type II censoring.
Our interest in this study is on Type I censored information.

3.5.1 Left Censoring

For a model with parameter θ, the probability for a left censored observation is given as

$$P(T_i < t_i) = F(t_i; \theta) \tag{3.26}$$

where the cumulative distribution function is

$$F(t_i; \theta) = 1 - S(t_i; \theta). \tag{3.27}$$

When n individuals are considered, and among them r have not experienced the event at the censoring limit C_l while $n - r$ have, then the lifetime and censoring times can be

expressed as

$$Y_i = \begin{cases} T_i & \delta_i = 1, \text{ for uncensored data} \\ \max(T_i, C_l) & \delta_i = 0, \text{ for left censored data} \end{cases}$$

where C_l is the left censoring time.
The contribution to the maximum likelihood with left censored data is the product of those who experienced the event and those who failed to. If an individual is observed to experienced the event at y_i, the contribution to the likelihood function is the cumulative distribution of that time interval, $L_i = F(y_i; \theta)$. If the event is experienced by y_i meaning that the event is observed, then the contribution is the density of the time interval $L_i = f(y_i)$.
The likelihood can then be written as

$$\begin{aligned} L(\theta) &= \prod_{i=1}^{n} L_i(\theta) = \prod_{\delta_i=1} f(t_i;\theta) \prod_{\delta_i=0} F(t_i;\theta) \\ &= \prod_{i=1}^{n} f(t_i;\theta)^{\delta_i} F(t_i;\theta)^{1-\delta_i} \end{aligned} \tag{3.28}$$

3.5.2 Right Censoring

Let the density function be $f(t_i; \theta)$, the distribution function be $F(t_i; \theta)$ and the survival function be $S(t_i; \theta)$. The probability of a child being born healthy at a specific time t_i is defined by

$$\begin{aligned} S(t_i;\theta) &= P(T > t_i) = \int_{t_i}^{\infty} f(u;\theta) = F(\infty;\theta) - F(t_i;\theta) \\ &= 1 - F(t_i;\theta) \end{aligned} \tag{3.29}$$

Suppose we have n individuals, where r individuals are infected and $n - r$ are negative at the time of birth, C_r.
Then the lifetime and censoring can be expressed as

$$Y_i = \begin{cases} T_i & \delta_i = 1, \text{ for uncensored data} \\ \min(T_i, C_r) & \delta_i = 0, \text{ for right censored data} \end{cases}$$

where C_r is the time limit, the right censoring time. The contribution to the likelihood with right censoring observations is the product of the individuals who are negative and those who are born already infected. The contribution of an individual infected at y_i is the density of that time interval, $L_i = f(y_i; \theta)$. Similarly for an individual still not infected at y_i, it means the lifetime of the individual exceeds y_i and therefore the contribution to the likelihood is $L_i = S(y_i)$.
Thus, the likelihood for a child born healthy can be expressed as

$$\begin{aligned} L(\theta) &= \prod_{i=1}^{n} L_i(\theta) = \prod_{\delta_i=1} f(t_i;\theta) \prod_{\delta_i=0} S(t_i;\theta) \\ &= \prod_{i=1}^{n} \left(f(t_i;\theta)\right)^{\delta_i} \left(S(t_i;\theta)\right)^{1-\delta_i} \end{aligned} \tag{3.30}$$

3.5.3 Interval Censoring

The likelihood function is given by

$$L(\theta) = \prod_{i=1}^{n} \left[f(t_i;\theta)^{\delta_i} \left(F(t_{i1};\theta) - F(t_{io};\theta) \right)^{1-\delta_i} \right] \tag{3.31}$$

Then the lifetime and censoring can be expressed as

$$Y_i = \begin{cases} T_i & \delta_i = 1, \text{ for uncensored data} \\ (t_{0i} < T_i < t_{1i}) & \delta_i = 0, \text{ for interval censored data} \end{cases}$$

where T_i is the event time and t_{0i} and t_{1i} are the observed times.

3.5.4 Combined Censoring

Let the time an individual is observed be x_i and the censoring time be t_i.
Also let

$$\begin{aligned} t_{L_i} &= \text{Left censoring time} \\ t_{R_i} &= \text{Right censoring time} \end{aligned}$$

Further let

$$\begin{aligned} \delta E_i &= 1 \quad \text{if event is observed at exactly}(t_i = x_i), 0 \quad \text{otherwise} \\ \delta R_i &= 1 \quad \text{if right censoring has occured}(x_i < t_i), 0 \quad \text{otherwise} \\ \delta L_i &= 1 \quad \text{if left censoring has occured } (x_i > t_i), 0 \quad \text{otherwise} \\ \delta I_i &= 1 \quad \text{if interval censoring has occured}(t_{L_i} < x_i < t_{R_i}), 0 \quad \text{otherwise} \end{aligned}$$

We have four possibilities of occurrences with the following probabilities

i) $\text{Prob}(T = t_i) = f(t_i)$

ii) $\text{Prob}(T \leq t_{L_i}) = F(t_{L_i})$

iii) $\text{Prob}(T > t_{R_i}) = 1 - F(t_{R_i})$

iv) $\text{Prob}(t_{L_i} < T < t_{R_i}) = F(t_{R_i}) - F(t_{L_i})$

Therefore under the assumption of independent censoring, the likelihood function for a sample of n indepedent observations is

$$L = \prod_{i=1}^{n} \left[f(t_i) \right]^{\delta E_i} \left[F(t_{L_i}) \right]^{\delta L_i} \left[1 - F(t_{R_i}) \right]^{\delta R_i} \left[\left(F(t_{R_i}) - F(t_{L_i}) \right) \right]^{\delta I_i} \tag{3.32}$$

3.6 Distributions

3.6.1 Exponential Distribution

A continuous random variable X is said to have an Exponential (λ) distribution if it has the probability density function

$$f(x) = \begin{cases} \lambda e^{-\lambda x}, & \text{for } x > 0 \\ 0, & \text{for } x \leq 0 \end{cases}$$

where $\lambda > 0$ is called the rate of the distribution. The exponential distribution is one of the widely used continuous distribution. It is often used to model the time that has elapsed between events and is the only continuous distribution with the memoryless property in that $P(X > a + b|X > a) = P(X > b)$

Theorem 2. *For a time homogeneous continuous time Markov process, T_i (the sojourn time in state i) is exponentially distributed*

Proof. The proof is based on the memoryless property which is unique for the exponential distribution. By time homogeneity we assume that the process starts in time i

$$\begin{aligned} P(T_i > s + t|T_i > s) &= P(X(\tau) = i \quad \text{for} \quad 0 \leq \tau \leq s + t|X(\tau) = i, \quad 0 \leq \tau \leq s) \\ &= P(X(\tau) = i \quad \text{for} \quad s < \tau \leq s + t|X(\tau) = i, \quad 0 \leq \tau \leq s) \\ &= P(X(\tau) = i \quad \text{for} \quad s < \tau \leq s + t|X(\tau) = i), \\ &= P(X(\tau) = i \quad \text{for} \quad 0 < \tau \leq t|X(0) = i) \\ &= P(T_i > t) \end{aligned} \tag{3.33}$$

This indicates the memoryless property which is unique to an exponentially distributed random variable, therefore T_i must be exponentially distributed. □

In the study of continuous-time stochastic process, the exponential distribution is usually used to model the time until something happens in the process.
The mean and the standard deviation are equal, i.e

$$E(X) = \frac{1}{\lambda} \tag{3.34}$$

and

$$\sqrt{\text{Var}(X)} = \frac{1}{\lambda} \tag{3.35}$$

3.6.2 Gamma Distribution

In probability theory and statistics, the gamma distribution is a two parameter family of continuous probability distributions.
Let us take two parameters $\alpha > 0$ and $\beta > 0$. Gamma function $\Gamma(\alpha)$ is defined by

$$\Gamma(\alpha) = \int_0^{\alpha} x^{\alpha-1} e^{-x} dx \tag{3.36}$$

If we devide both sides by $\Gamma(\alpha)$ we get

$$\begin{aligned} 1 &= \int_0^\infty \frac{1}{\Gamma(\alpha)} x^{\alpha-1} e^{-x} dx \\ &= \int_0^\infty \frac{\beta^\alpha}{\Gamma(\alpha)} y^{\alpha-1} e^{-\beta y} dy \end{aligned} \tag{3.37}$$

where we made a change of variable $x = \beta y$
Therefore, if we define

$$f(x|\alpha,\beta) = \begin{cases} \dfrac{\beta^\alpha}{\Gamma(\alpha)} x^{\alpha-1} e^{-\beta x}, & \text{for } x \geq 0 \\ 0, & \text{for } x < 0 \end{cases}$$

then $f(x|\alpha,\beta)$ will be the probability density since it is nonnegative and it integrates to one.
The distribution with probability density function $f(x|\alpha,\beta)$ is called Gamma distribution with parameters α and β and it is denoted as $\Gamma(\alpha,\beta)$
The mean is given by

$$E(X) = \frac{\alpha}{\beta} \tag{3.38}$$

and the variance

$$Var(X) = \frac{\alpha}{\beta^2} \tag{3.39}$$

One major disadvantage of the gamma distribution is that the distribution function or survival function cannot be expressed in a closed form if the shape parameter is not an integer. Also, since it is in terms of an incomplete gamma function, one needs to obtain the distribution function, survival function or the failure rate by numerical integration. This makes gamma distribution less popular compared to the Weibull distribution.

3.6.3 Lognormal Distribution

The lognormal distribution is widely used in many areas of application, including engineering, medicine and finance.
The probability density function is given as

$$f(t;\mu,\delta) = \frac{1}{\delta t} \varphi_{\text{nor}} \left[\frac{\log(t) - \mu}{\sigma} \right], \qquad t > 0 \tag{3.40}$$

and the corresponding cumulative density function is

$$F(t;\mu,\delta) = \Phi \left[\frac{\log(t) - \mu}{\sigma} \right], \qquad t > 0 \tag{3.41}$$

where

$$\begin{aligned} \varphi_{\text{nor}}(z) &= \left(\frac{1}{\sqrt{2\pi}} \right) \exp\left(\frac{-z^2}{2} \right) \\ \Phi_{\text{nor}}(z) &= \int_\infty^z \varphi_{\text{nor}}(w) dw \end{aligned}$$

for a standardized normal ($\mu = 0, \sigma = 1$).
The natural logarithms of a lognormal random variable follows the well known normal distribution with mean and standard deviation μ and σ respectively.
Following from the central limit theorem, the lognormal distribution can be motivated as the distribution of the product of a large number of similarly distributed positive quantities.

3.6.4 Weibull Distribution

The Weibull distribution is a continuous probability distribution widely applicable in probability theory and statistics. It was first identified by Frechet in 1927, and first applied by Rosin and Rammler in 1933 but Waloddi Weibull was the first to study and describe the distribution in detail in 1951
The Weibull distribution has many applications because of it's flexibility and is widely used in problems of reliability and survival analysis. It is in many ways (including the general shape of cdf and pdf) similar to the lognormal distribution. It is very popular in analysing lifetime data mainly because in the presence of censoring it is much easier to handle, at least numerically, compared to gamma distribution. Also the domain of a Weibull distributed variable ranges from 0 to ∞ making it the most used distribution in survival analysis.
The Weibull distribution also has increasing and decreasing failure rates depending on the shape parameter. The probability density function of a Weibull random variable, X, is defined as

$$f(x:\theta,\alpha) = \begin{cases} \frac{\alpha}{\theta}^{\alpha-1} e^{(-\frac{x}{\theta})^{\alpha}}, & \text{for } x \geq 0 \\ 0, & \text{for } x < 0 \end{cases}$$

where $\alpha > 0$ is the shape parameter and $\theta > 0$ is the scale parameter of the distribution.
When $\alpha = 1$, the Weibull distribution becomes an exponential distribution
If the quatity, X, is the time to the event of interest, then the Weibull distribution gives a distribution for which the event rate is proportional to the power of time interpreted as follows:

$\alpha < 1$: The rate of the event of interest decreases over time

$\alpha = 1$: The rate of the event is constant over time

$\alpha > 1$: The event rate increases over time

The cumulative distribution function for the Weibull distribution is

$$F(x:\theta,\alpha) = \begin{cases} 1 - e^{-(\frac{x}{\theta})^{\alpha}}, & \text{for } x \geq 0 \\ 0, & \text{for } x < 0 \end{cases}$$

The mean and the variance of the Weibull distribution are expressed as

$$E(X) = \theta\Gamma\left(1 + \frac{1}{\alpha}\right) \tag{3.42}$$

and

$$\text{Var}(X) = \theta^2 \left[\Gamma\left(1 + \frac{2}{\alpha}\right) - \left(\Gamma(1 + \frac{1}{\alpha})\right)^2 \right] \tag{3.43}$$

where $\Gamma(\cdot)$ is a gamma function.

3.6.5 Exponentiated Exponential Distribution

The probability density function of the exponentiated exponential (EE) distribution is defined by

$$f(x, \alpha, \lambda) = \alpha\lambda(1 - e^{-\lambda x})^{\alpha-1} e^{-\lambda x} \qquad \alpha, \lambda, x > 0 \tag{3.44}$$

with a distribution function

$$F(x, \alpha, \lambda) = (1 - e^{-\lambda x})^{\alpha}$$

a survival function

$$S(x, \alpha, \lambda) = 1 - (1 - e^{-\lambda x})^{\alpha}$$

and a hazard function

$$h(x, \alpha, \lambda) = \frac{\alpha\lambda \left(1 - e^{-\lambda x}\right)^{\alpha-1} e^{-\lambda x}}{1 - (1 - e^{-\lambda x})^{\alpha}}$$

The two parameters of an exponentiated exponential distribution are α which is the shape parameter and λ which is the scale parameter. It also has the increasing or decreasing failure rate depending on the shape parameter. The density function varies significantly depending on the shape parameter.
The EE distribution has a lot of properties which are quite similar to those of a gamma distribution but with an explicit expression of the distribution function or the survival function like a Weibull distribution.
Gupta and Kundu (2001) observed that EE family of distribution are quite similar in nature to the other two parameter family like Weibull family and gamma family. They observed that most of the properties are similar to those of a gamma distribution but computationally it is quite similar to a Weibull distribution and can therefore be used as an alternative to a Weibull or gamma distribution.

3.7 Non Paramatric Estimation Methods for Censored Data

3.7.1 Kaplan-Meier Method

Let

i) N be the sample size under investigation

ii) m be the total number that experienced the event

iii) $t_{(1)} < t_{(2)} < t_{(3)} \cdots < t_{(k)}$ be the ordered times of events

iv) d_j be the number of events experienced at time t_j
therefore $d_1 + d_2 + \cdots + d_k = m$

v) c_j be the number of individuals censored between time t_j and t_{j+1}

vi) n_j be the number of persons at risk (susceptibles) just before time t_j

Then the Kaplan-Meier estimator, also called Product Limit estimator is given by

$$\hat{S(t)} = \prod_{t_j \leq t} \left(\frac{n_j - d_j}{n_j} \right) \tag{3.45}$$

and the variance as

$$\text{Var}\hat{S(t)} \approx \left[\hat{S(t)}\right]^2 \sum_{t_j < t} \frac{d_j}{n_j(n_j - d_j)} \tag{3.46}$$

Therefore
$(1-\alpha)\%$ confidence interval for $\hat{S(t)}$ is given by

$$\text{CI} = \hat{S(t)} \pm Z_{\frac{\alpha}{2}} \sqrt{\text{Var}\hat{S(t)}} \tag{3.47}$$

3.7.2 Aalen-Nelson Estimator

From (3.45)

$$\begin{aligned} \hat{S(t)} &= \prod_{t_j \leq t} \left(1 - \frac{d_j}{n_j}\right) \\ \log\hat{S(t)} &= \sum_{t_j \leq t} \log\left(1 - \frac{d_j}{n_j}\right) \\ &\approx -\sum_{t_j \leq} \frac{d_j}{n_j} \\ \text{Let} \qquad \hat{H(t)} &= \sum_{t_j \leq} \frac{d_j}{n_j} \\ \hat{S(t)} &\approx e^{-\hat{H(t)}} \end{aligned} \tag{3.48}$$

is the Aalen-Nelson estimator

3.7.3 The Delta Method

If $\hat{\theta}$ follows $N(\theta, \sigma_\theta^2)$

then

$$f(\hat{\theta})\text{follows}N\left[f(\hat{\theta}), \sigma_f^2\right] \tag{3.49}$$

where

$$\sigma_\theta^2 = \left|\frac{df}{d\theta}\right|^2 \sigma_f^2 \tag{3.50}$$

Let X be a random variable with a bernoulli property then

$$X = \begin{cases} 1 \text{ with probability } p \\ 0 \text{ with probability } 1-p \end{cases}$$

Therefore

$$P_x = \text{Prob}(X = x) = p^x(1-p)^{1-x} \qquad ; x = 0, 1 \tag{3.51}$$

likelihood function is

$$\begin{aligned} L &= \prod_{i=1}^{n} f(x_i) \\ &= \prod_{i=1}^{n} p^{x_i}(1-p)^{1-x_i} \\ &= p^{\sum x_i}(1-p)^{n-\sum x_i} \end{aligned} \tag{3.52}$$

Taking the logarithm and derivative

$$\begin{aligned} \log L &= \sum x_i \log p + (n - \sum x_i)\log(1-p) \\ \frac{\partial}{\partial p}\text{Log}L &= \frac{\sum x_i}{p} - \frac{(n - \sum x_i)}{1-p} \end{aligned} \tag{3.53}$$

Getting the maximum

$$\begin{aligned} \frac{\sum x_i}{p} - \frac{n - \sum x_i}{(1-p)} &= 0 \\ \frac{\sum x_i}{p} &= \frac{n - \sum x_i}{1-p} \\ \hat{p} &= \frac{\sum x_i}{n} = \overline{X} \end{aligned} \tag{3.54}$$

Also

$$\begin{aligned} E(\hat{p}) &= E\left[\frac{\sum X_i}{n}\right] \\ &= \sum_{i=1}^{n} \frac{E(X_i)}{n} \\ &= \sum_{i=1}^{n} \frac{1}{n}\left[1 \times p + 0(1-p)\right] \\ &= \sum_{i=1}^{n} \frac{p}{n} \\ &= \frac{np}{n} \\ \therefore E(\hat{p}) &= p \end{aligned} \tag{3.55}$$

and

$$\begin{aligned} \mathrm{Var}(\hat{p}) &= \mathrm{Var} \sum_{i=1}^{n} \frac{X_i}{n} \\ &= \sum_{i=1}^{n} \mathrm{Var}\left(\frac{X_i}{n}\right) \\ &= \sum_{i=1}^{n} \frac{1}{n^2} \mathrm{Var} X_i \\ &= \sum_{i=1}^{n} \frac{1}{n^2}\left[E(X_i^2) - [E(X_i)]^2\right] \\ &= \sum_{i=1}^{n} \frac{1}{n^2}\left\{E(X_i) - p^2\right\} \\ &= \sum_{i=1}^{n} \frac{1}{n^2}\left[p - p^2\right] \\ &= \frac{n}{n^2} p(1-p) \\ &= \frac{p(1-p)}{n} \end{aligned} \tag{3.56}$$

3.7.4 Interval Censoring

Peto (1973) was the first to propose a non-parametric method for estimating the survival distribution based on interval censored data. Later Turnbull (1976) derived the same estimator using a different approach in estimation. He considered survival times $T_i (i = 1 \cdots n)$ for n patients that were not directly observed but were known to lie in the interval

$[L_i, R_i]$ then the likelihood for the n observations is

$$L = \prod_{i}^{n} \left\{ S(L_i) - S(R_i^+) \right\} \tag{3.57}$$

where
By $S(t^+)$ means $\lim_{\Delta \to 0^+} S(t + \Delta)$ Some authors, among them Rucher and Messerer (1988), Odel et al. (1992) and Dorey et al. (1993) state that assuming interval times as exact times can lead to biased estimates as well as results and conclusions that are not fully reliable.
A non parametric estimate of the survival function in such interval censored situations can be found by the iterative procedure proposed by Turnbull (1976). He proposed that since the event of interest is not observed for all individuals, an indicator variable for censoring should be defined. For each individual the upper and lower limits of the intervals within which the event of interest has occurred together with the censoring indicator has to be known.
To construct the estimator, let $0 = \tau_1 < \tau_2 < \cdots < \tau_m$ be a grid of time which includes all the points L_i and U_i for $i = 1, 2, \cdots n$.
For the i^{th} observation, define an event ϕ_{ij} to be 1 if the interval (τ_{j-1}, τ_j) is contained in the interval $(L_i, U_i]$ and 0 otherwise.
Whether the event ϕ_{ij} which occurs in the interval $(L_i, U_i]$ could have occured at τ_j is determined with an initial guess at $S(\tau_j)$ using the Turnbull's algorithm as follows:

1) Compute the probability of an event occuring at time τ_j by

$$P_j = S(\tau_{j-1}) - S(\tau_j) \qquad\qquad j = 1, \cdots, m \tag{3.58}$$

2) Estimate the number of events which occurred at τ_j by

$$d_j = \sum_{i=1}^{n} \frac{\phi_{ij} p_j}{\sum_{k=1}^{m} \phi_{ij} p_k} \qquad\qquad j = 1, \cdots, m \tag{3.59}$$

3) Compute the expected number at risk at time τ_j by

$$Y_j = \sum_{k=j}^{m} d_k \tag{3.60}$$

4) Compute the updated Product Limit estimator using the values found in steps 2 and 3. If the updated estimate of S is close to the old version of S for all $\tau_j's$ stop the iterative process, otherwise repeat steps 1 to 3 using the updated estimate of S.

The initial $S(\tau_j)$ estimates can be obtained from Kaplan-Meir estimator, Nelson Aalen or the delta method

Chapter 4

A TWO STATE MODEL FOR A CHILD BORN INFECTED

4.1 Introduction

A two state model is the simplest multistate model and forms an essential building block for other models. Observation for any given event will here be in the most simple form. In this chapter we shall apply a two state model to a child born infected and derive the forward Kolmogorov-differential equation which we will then solve using the Generator Matrix method to obtain the transition probabilities. We then solve the transition probabilities which are in form of transition intensities using maximum likelihood estimation approach

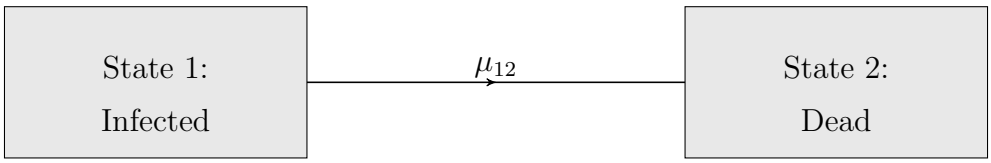

Figure 4.1: Infected-Death two-state model

Figure 4.1 shows a two states consisting of the infected and dead states with only transition intensity given as μ_{12}. Since it is unidirectional, there is no possibility of reversibility and therefore $\mu_{21} = 0$.
Once an individual leaves a state they can not return to it.

4.2 Derivation of Forward Kolmogorov-Differential Equations

By the Chapman-Kolmogorov equation the probability function for the model in Figure 4.1 is given as

$$P_{ij}(s, t+h) = \sum_{k=1}^{2} P_{ik}(s,t) P_{kj}(t, t+h), \qquad i, j = 1, 2 \tag{4.1}$$

The probabilities are given by a set of differential equations. These probabilities satisfy equation (4.1) whenever $s \leq t \leq t+h$.
The differential equations for $P_{ij}(s,t)$ are obtained by considering two continuous time intervals (s,t) and $(t,t+h)$ and the probabilities $P_{ij}(s,t+h)$.
We obtatin the probability of being in state 1 and remaining there from time s to time $t+h$ as follows:

$$\begin{aligned} P_{11}(s,t+h) &= \sum_{k=1}^{2} P_{1k}(s,t)P_{k1}(t,t+h) \\ &= P_{11}(s,t)P_{11}(t,t+h) + P_{12}(s,t)P_{21}(t,t+h) \\ &= P_{11}(s,t)((1-(\mu_{12}h+o(h)) + P_{12}(s,t)\cdot 0 \\ P_{11}(s,t+h) - P_{11}(s,t) &= (-\mu_{12}h+o(h))P_{11}(s,t) + P_{12}(s,t)\cdot 0 \end{aligned} \tag{4.2}$$

Dividing (4.2) by h expresses it as a probability of transition in unit time.
Taking limits as $h \to 0$ leads to the concept of transition rates.

$$\begin{aligned} \frac{\partial}{\partial t}P_{11}(s,t) &= \lim_{h\to 0}\frac{P_{11}(s,t+h)-P_{11}(s,t)}{h} = -\mu_{12}P_{11}(s,t) + 0\cdot P_{12}(s,t) \\ P_{11}^{'}(s,t) &= -\mu_{12}P_{11}(s,t) + 0\cdot P_{12}(s,t) \end{aligned} \tag{4.3}$$

This can be solved by separating variables to give

$$P_{11}(s,t) = e^{-\mu_{12}t} \tag{4.4}$$

The equation (4.3) represents the transition rate of being in the infected state and remaining infected and equation (4.4) represents the corresponding transition probability. Transition rates are also refered to as transition intensities or forces of transition.
Similarly the transition probability of moving from state 1 at time s to state 2 at time $t+h$ is given as follows:

$$\begin{aligned} P_{12}(s,t+h) &= \sum_{k=1}^{2} P_{1k}(s,t)P_{k2}(t,t+h) \\ &= P_{11}(s,t)P_{12}(t,t+h) + P_{12}(s,t)P_{22}(t,t+h) \\ &= P_{11}(s,t)(\mu_{12}h+o(h)) + P_{12}(s,t)((1-(\mu_{21}h+o(h)) \\ \frac{\partial}{\partial t}P_{12}(s,t) &= \lim_{h\to 0}\frac{P_{11}(s,t+h)-P_{12}(s,t)}{h} = -\mu_{12}P_{11}(s,t) + 0\cdot P_{12}(s,t) \\ &= \mu_{12}P_{11}(s,t) + 0\cdot P_{12}(s,t) \\ P_{12}^{'}(s,t) &= \mu_{12}P_{11}(s,t) + 0\cdot P_{12}(s,t) \end{aligned} \tag{4.5}$$

The solution to (4.5) gives the transition probability

$$P_{12}(s,t) = 1 - e^{-\mu_{12}t} \tag{4.6}$$

Equation (4.5) gives the transition probability from alive state to dead state.
The Kolmogorov forward differential equations for the two state model are therefore given by

$$P_{11}^{'}(s,t) = -\mu_{12}P_{11}(s,t) + 0\cdot P_{12}(s,t) \tag{4.7}$$

$$P_{12}^{'}(s,t) = \mu_{12}P_{11}(s,t) + 0\cdot P_{12}(s,t) \tag{4.8}$$

4.3 Solution of Forward Kolmogorov Differential Equations by Generator Matrix Approach

The Kolmogorov differential equations has an explicit solution using the decomposition of the intensity matrix into eigen vectors (see for example Cox and Miller(1965)).
It is therefore convenient to express the forces of transition and transition probability in (4.8) in matrix form.
We have

$$\left[\begin{array}{cc} P_{11}^{'}(s,t) & P_{12}^{'}(s,t) \end{array}\right]^{'} = \left[\begin{array}{cc} P_{11}(s,t) & P_{12}(s,t) \end{array}\right] \left[\begin{array}{cc} -\mu_{12} & \mu_{12} \\ 0 & 0 \end{array}\right]$$

Let Q be the 2×2 matrix with (i,j) entry μ_{ij} and $P(s,t)$ be the 2×2 matrix with (ij) entry $P_{ij}(s,t)$
Then in compact form we have

$$P^{'}(s,t) = P(s,t)Q, \tag{4.9}$$

Our interest is to solve the above matrix equation (4.9) using the generator matrix approach

$$\begin{aligned} \frac{P^{'}(s,t)}{P(s,t)} &= Q & (4.10)\\ \ln P(s,t) &= Qt + c, & (4.11)\\ P(s,t) &= e^{Qt+c} = ke^{tQ} & (4.12) \end{aligned}$$

To calculate k we use the boundary condition which is obtained by letting $t = s$ as s is the initial time.
Therefore,

$$P(s,s) = I(\text{identity matrix}) \tag{4.13}$$

and together with equation (4.12)

$$P(s,s) = ke^{tQ} \tag{4.14}$$

This implies that

$$\begin{aligned} I &= ke^{tQ} \\ &= k\left[I + \sum_{k=1}^{\infty} t^k \frac{Q^k}{k!}\right] \\ &= kI + k\sum_{k=1}^{\infty} t^k \frac{Q^k}{k!} & (4.15) \end{aligned}$$

Comparing we have

$$\begin{aligned} I &= kI \Rightarrow I = k \\ 0 &= k\sum_{k=1}^{\infty} t^k \frac{Q^k}{k!} \end{aligned}$$

With initial conditions $P_{11}(s,s) = 1$ and $P_{12}(s,s) = 0$ Therefore

$$\begin{aligned} P(s,t) &= e^{tQ} && (4.16)\\ &= I + \frac{Qt}{1!} + \frac{(Qt)^2}{2!} + \frac{(Qt)^3}{3!} + \cdots \\ &= I + \sum_{k=1}^{\infty} \frac{(Qt)^k}{k!} && (4.17) \end{aligned}$$

As noted by Cox and Miller (1965), if Q has distinct eigen values, then $Q = ADC$ where

$$\begin{aligned} A &= \text{the matrix of right eigen vectors of} \quad Q \\ D &= \text{the diagonal matrix whose elements are the eigen values of} \quad Q \\ C &= A^{-1}\text{exist} \end{aligned}$$

Therefore, the problem of finding the transition probability functions is reduced to a problem of determining the eigen values and eigen vectors.
Futhermore

$Q = ADA^{-1}$

Thus

$$\begin{aligned} Q^k &= (ADA^{-1})^k \\ &= (ADA^{-1})(ADA^{-1})(ADA^{-1})\cdots(ADA^{-1})(ADA^{-1}) \\ &= ADA^{-1}ADA^{-1}ADA^{-1}\cdots ADA^{-1}ADA^{-1} \\ &= ADIDID\cdots DIDA^{-1} \\ &= ADDD\cdots DDDA^{-1} \\ Q^k &= AD^kA^{-1} && (4.18) \end{aligned}$$

Substituting (4.18) in (4.17)

$$\begin{aligned} P(s,t) &= I + \sum_{k=1}^{\infty} \frac{t^k}{k!} AD^kA^{-1} \\ &= I + A\left(\sum_{k=1}^{\infty} \frac{t^kD^k}{k!}\right) A^{-1} \\ &= I + A\left(\sum_{k=1}^{\infty} \frac{(tD)^k}{k!}\right) A^{-1} && (4.19) \end{aligned}$$

We now wish to determine D and A i.e to determine the eigen values and eigen vectors for the matrix Q which will then simplifies the process of solving Q^k.
To find the eigen values we solve the equation

$$|Q - \lambda I| = 0 \qquad (4.20)$$

Substituting the value of Q and solving gives

$$\begin{vmatrix} -\mu_{12} - \lambda & \mu_{12} \\ 0 & -\lambda \end{vmatrix} = 0$$

$$\lambda_1 = -\mu_{12} \quad \text{and} \quad \lambda_2 = 0 \tag{4.21}$$

The corresponding eigen vectors are obtained as follows:

$$\begin{pmatrix} -\mu_{12} & \mu_{12} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \lambda_1 \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

$$-\mu_{12}x_1 + \mu_{12}x_2 = \lambda_1 x_1$$

Substituting λ_1 gives

$$\begin{aligned} -\mu_{12}x_1 + \mu_{12}x_2 &= -\mu_{12}x_1 \\ x_2 &= 0 \cdot x_1 \end{aligned}$$

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} x_1 \\ 0 \cdot x_1 \end{pmatrix} = x_1 \begin{pmatrix} 1 \\ 0 \end{pmatrix}$$

For $\lambda_2 = 0$ we have

$$\begin{pmatrix} -\mu_{12} & \mu_{12} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \lambda_2 \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}$$

$$\begin{aligned} -\mu_{12}x_1 + \mu_{12}x_2 &= 0 \\ x_1 &= x_2 \end{aligned}$$

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} x_2 \\ x_2 \end{pmatrix} = x_2 \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

Therefore the eigen vectors for $\lambda_1 = \mu_{12}$ and $\lambda_2 = 0$ are

$$\lambda_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix} \quad \text{and} \quad \lambda_2 = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

Since we have distinct eigen values $Q = ADA^{-1}$
where

$$A = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix} \quad \text{and} \quad D = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}$$

Also

$$\sum_{k=1}^{\infty}\frac{(tD)^k}{k!} = \sum_{k=1}^{\infty}\frac{t^k}{k!}\begin{pmatrix}\lambda_1 & 0\\ 0 & \lambda_2\end{pmatrix}^k \tag{4.22}$$

$$= \sum_{k=1}^{\infty}\frac{t^k}{k!}\begin{pmatrix}{\lambda_1}^k & 0\\ 0 & {\lambda_2}^k\end{pmatrix} \tag{4.23}$$

Equation (4.23) becomes

$$\begin{pmatrix}\sum_{k=1}^{\infty}\frac{(\lambda_1 t)^k}{k!} & 0\\ 0 & \sum_{k=1}^{\infty}\frac{(\lambda_2 t)^k}{k!}\end{pmatrix}$$

The diagonals are exponentially distributed without the first term and therefore we have

$$\begin{pmatrix}e^{\lambda_1 t}-1 & 0\\ 0 & e^{\lambda_2 t}-1\end{pmatrix}$$

From (4.19)

$$P(s,t) = I+\begin{pmatrix}1 & 1\\ 0 & 1\end{pmatrix}\begin{pmatrix}\sum_{k=1}^{\infty}\frac{(\lambda_1 t)^k}{k!} & 0\\ 0 & \sum_{k=1}^{\infty}\frac{(\lambda_2 t)^k}{k!}\end{pmatrix}\begin{pmatrix}1 & -1\\ 0 & 1\end{pmatrix}$$

$$= I+\begin{pmatrix}e^{\lambda_1 t}-1 & e^{\lambda_2 t}-1\\ 0 & e^{\lambda_2 t}-1\end{pmatrix}\begin{pmatrix}1 & -1\\ 0 & 1\end{pmatrix}$$

$$= I+\begin{pmatrix}e^{\lambda_1 t}-1 & 1-e^{\lambda_1 t}+e^{\lambda_2 t}-1\\ 0 & e^{\lambda_2 t}-1\end{pmatrix}$$

$$= I+\begin{pmatrix}e^{\lambda_1 t}-1 & e^{\lambda_2 t}-e^{\lambda_1 t}\\ 0 & e^{\lambda_2 t}-1\end{pmatrix} \tag{4.24}$$

Subtituting $\lambda_1 = \mu_{12}$ and $\lambda_2 = 0$ then equation 4.24 becomes

$$P(s,t) = I+\begin{pmatrix}e^{-\mu_{12}t}-1 & e^0-e^{-\mu_{12}t}\\ 0 & 0\end{pmatrix}$$

$$= \begin{pmatrix}1 & 0\\ 0 & 1\end{pmatrix}+\begin{pmatrix}e^{-\mu_{12}t}-1 & e^0-e^{-\mu_{12}t}\\ 0 & 0\end{pmatrix}$$

$$\begin{pmatrix}P_{11}(s,t) & P_{12}(s,t)\\ P_{21}(s,t) & P_{22}(s,t)\end{pmatrix} = \begin{pmatrix}e^{-\mu_{12}t} & 1-e^{-\mu_{12}t}\\ 0 & 1\end{pmatrix} = Q \tag{4.25}$$

It follows that:

The probability of being infected and remaining infected is $P_{11}(s,t) = e^{-\mu_{12}t}$

The probability from infected to dead is$P_{12}(s,t) = 1-e^{-\mu_{12}t}$

The probability from dead to infected is $P_{21}(s,t) = 0$

The probability of being dead and remaining dead is $P_{22}(s,t) = 1$

4.4 Estimation for Left Censoring

Using multistate models for a child born infected we have using (4.25) that

$$P_{12}(s,t) = 1 - e^{-\mu_{12}t} \tag{4.26}$$

and

$$F_{12}(s,t) = t + \frac{e^{-\mu_{12}t}}{\mu_{12}} \tag{4.27}$$

Therefore

$$\begin{aligned} L &= \prod_{i=1}^{n} \left(P_{12}(s,t)\right)^{\delta_i} \left(F_{12}(s,t)\right)^{1-\delta_i} \\ &= \prod_{i=1}^{n} \left(1 - e^{-\mu_{12}t_i}\right)^{\delta_i} \left(t_i + \frac{e^{-\mu_{12}t_i}}{\mu_{12}}\right)^{1-\delta_i} \end{aligned}$$

Getting the natural logarithm of (4.28) results in

$$l = \sum_{i=1}^{n} \delta_i \ln\left(1 - e^{-\mu_{12}t_i}\right) + \sum_{i=1}^{n} (1-\delta_i) \ln\left(t_i + \frac{e^{-\mu_{12}t_i}}{\mu_{12}}\right) \tag{4.28}$$

Since censored, then $\delta_i = 0$ and therefore

$$l = \sum_{i=1}^{n} \ln\left(t_i + \frac{e^{-\mu_{12}t_i}}{\mu_{12}}\right) \tag{4.29}$$

Differentiating (4.29) with respect to μ_{12} we get

$$\begin{aligned} \frac{\partial l}{\partial \mu_{12}} &= \sum_{i=1}^{n} \frac{\dfrac{-t_i e^{-\mu_{12}t_i}}{\mu_{12}} - \dfrac{e^{-\mu_{12}t_i}}{\mu_{12}^2}}{t_i + \dfrac{e^{-\mu_{12}t_i}}{\mu_{12}}} \\ &= \sum_{i=1}^{n} \frac{\dfrac{e^{-\mu_{12}t_i}}{\mu_{12}} \left(-t_i - \dfrac{1}{\mu_{12}}\right)}{t_i + \dfrac{e^{\mu_{12}t_i}}{\mu_{12}}} \end{aligned} \tag{4.30}$$

Equating (4.30) to zero

$$\begin{aligned} -\sum_{i=1}^{n} t_i - \frac{1}{\mu_{12}} &= 0 \\ \hat{\mu_{12}} = -\frac{1}{\sum_{i=1}^{n} t_i} \end{aligned} \tag{4.31}$$

Chapter 5

A THREE STATE MODEL FOR A CHILD BORN INFECTED

5.1 Introduction

This three state model is a unidirectional model without the possibility of returning back to the previous condition. It is an extention of model in Figure 4.1. Here the first state is the infected state, the second state is the Aids state and the third is the Death state. Our interest is to obtain the transition intensities from the states of Infected to Aids, Infected to Death and Aids to Death.

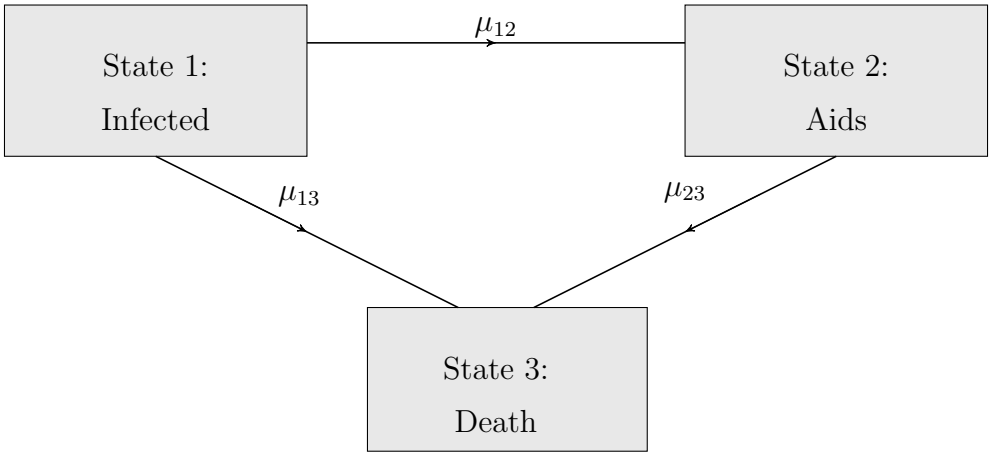

Figure 5.1: Infected-Aids-Death Model

5.2 Derivation of Forward Kolmogorov Differential Equations

Now by the Chapman-Kolmogorov equation

$$P_{ij}(s, t+h) = \sum_{k=1}^{3} P_{ik}(s,t) P_{kj}(t, t+h), \qquad i, j = 1, 2, 3 \tag{5.1}$$

$$
\begin{aligned}
P_{11}(s,t+h) &= \sum_{k=1}^{3} P_{1k}(s,t)P_{k1}(t,t+h) \\
&= P_{11}(s,t)P_{11}(t,t+h) + P_{12}(s,t)P_{21}(t,t+h) + P_{13}(s,t)P_{31}(t,t+h) \\
&= P_{11}(s,t)((1-(\mu_{12}+\mu_{13}))h + o(h)) + P_{12}(s,t)(\mu_{21}h + o(h)) + P_{13}(s,t)\cdot 0 \\
P'_{11}(s,t) &= -P_{11}(s,t)(\mu_{12}+\mu_{13}) + P_{12}(s,t)\mu_{21} \qquad (5.2)
\end{aligned}
$$

$$
\begin{aligned}
P_{12}(s,t+h) &= \sum_{k=1}^{3} P_{1k}(s,t)P_{k2}(t,t+h) \\
&= P_{11}(s,t)P_{12}(t,t+h) + P_{12}(s,t)P_{22}(t,t+h) + P_{13}(s,t)P_{32}(t,t+h) \\
&= P_{11}(s,t)((\mu_{12}h + o(h)) + P_{12}(s,t)(1-(\mu_{21}+\mu_{23})h + o(h)) + P_{13}(s,t)\cdot 0 \\
P'_{12}(s,t) &= P_{11}(s,t)\mu_{12} - P_{12}(s,t)(\mu_{21}+\mu_{23}) \qquad (5.3)
\end{aligned}
$$

$$
\begin{aligned}
P_{13}(s,t+h) &= \sum_{k=1}^{3} P_{1k}(s,t)P_{k3}(t,t+h) \\
&= P_{11}(s,t)P_{13}(t,t+h) + P_{12}(s,t)P_{23}(t,t+h) + P_{13}(s,t)P_{33}(t,t+h) \\
&= P_{11}(s,t)(\mu_{13}h + o(h)) + P_{12}(s,t)(\mu_{23}h + o(h)) + P_{13}(s,t)(1+o(h)) \\
P'_{13}(s,t) &= P_{11}(s,t)\mu_{13} + P_{12}(s,t)\mu_{23} \qquad (5.4)
\end{aligned}
$$

Equations (5.2),(5.3) and (5.4) are the respective Kolmogorov Forward equations.

Representing these equations in matrix form we have

$$
\begin{bmatrix} P'_{11}(s,t) & P'_{12}(s,t) & P'_{13}(s,t) \\ P'_{21}(s,t) & P'_{22}(s,t) & P'_{23}(s,t) \\ P'_{31}(s,t) & P'_{32}(s,t) & P'_{33}(s,t) \end{bmatrix} = \begin{bmatrix} P_{11}(s,t) & P_{12}(s,t) & P_{13}(s,t) \\ P_{21}(s,t) & P_{22}(s,t) & P_{23}(s,t) \\ P_{31}(s,t) & P_{32}(s,t) & P_{33}(s,t) \end{bmatrix} \begin{bmatrix} -(\mu_{12}+\mu_{13}) & \mu_{12} & \mu_{13} \\ \mu_{21} & -\mu_{23} & \mu_{23} \\ 0 & 0 & 0 \end{bmatrix}
$$

where the transition rates matrix is given by

$$
Q = \begin{pmatrix} -(\mu_{12}+\mu_{13}) & \mu_{12} & \mu_{13} \\ \mu_{21} & -\mu_{23} & \mu_{23} \\ 0 & 0 & 0 \end{pmatrix} \qquad (5.5)
$$

The eigen values for matrix in (5.5) are

$$
\begin{aligned}
\lambda_1 &= -(\mu_{12}+\mu_{13}), \\
\lambda_2 &= -\mu_{23}, \\
\lambda_3 &= 0.
\end{aligned}
$$

We then obtain the corresponding eigen vectors as follows:
For $\lambda = \lambda_3 = 0$

$$\begin{pmatrix} -(\mu_{12}+\mu_{13}) & \mu_{12} & \mu_{13} \\ 0 & -\mu_{23} & \mu_{23} \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix},$$

where x_3 can be any number.
Taking $x_3 = 1$ (as we are interested in any non zero vector)

$$\begin{aligned} -\mu_{23}x_2 + \mu_{23}x_3 &= 0, \\ x_2 &= \frac{\mu_{23}}{\mu_{23}} = 1. \end{aligned}$$

Similarly

$$\begin{aligned} -\mu_{12}x_1 - \mu_{13}x_1 + \mu_{12}x_2 + \mu_{13}x_3 &= 0, \\ -\mu_{12}x_1 - \mu_{13}x_1 + \mu_{12} + \mu_{13} &= 0, \\ x_1 &= \frac{\mu_{12}+\mu_{13}}{\mu_{12}+\mu_{13}} = 1., \end{aligned}$$

The eigen vector for $\lambda = 0$ is

$$\begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix}$$

For$\lambda = \lambda_2 = -\mu_{23}$

$$\begin{pmatrix} -\mu_{12}-\mu_{13}+\mu_{23} & \mu_{12} & \mu_{13} \\ 0 & 0 & \mu_{23} \\ 0 & 0 & \mu_{23} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

This leads to

$$\begin{pmatrix} -\mu_{12}-\mu_{13}+\mu_{23} & \mu_{12} & \mu_{13} \\ 0 & 0 & \mu_{23} \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

x_3 can take any value, we take $x_2 = 1$
$\mu_{23}x_3 = 0$ and since $\mu_{23} \neq 0$ as this is the probability of death once infected
$\Rightarrow x_3 = 0$

$$\begin{aligned} -\mu_{12}x_1 - \mu_{13}x_1 + \mu_{23}x_1 + \mu_{12}x_2 + \mu_{13}x_3 &= 0 \\ x_1 &= \frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} \end{aligned}$$

The eigen vector for $\lambda = -\mu_{23}$ is

$$\begin{pmatrix} \dfrac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} \\ 1 \\ 0 \end{pmatrix}$$

For $\lambda = \lambda_1 = -\mu_{12} - \mu_{13}$

$$\begin{pmatrix} 0 & \mu_{12} & \mu_{13} \\ 0 & \mu_{12}+\mu_{13}-\mu_{23} & \mu_{23} \\ 0 & 0 & \mu_{12}+\mu_{13} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

$$\begin{aligned} \mu_{12}x_3 + \mu_{13}x_3 &= 0 \\ (\mu_{12}+\mu_{13})x_3 &= 0 \\ \text{but} \quad (\mu_{12}+\mu_{13}) &\neq 0 \\ \Rightarrow x_3 &= 0 \end{aligned}$$

Similarly

$$\begin{aligned} (\mu_{12}+\mu_{13}-\mu_{23})x_2 + \mu_{23}x_3 &= 0 \\ (\mu_{12}+\mu_{13}-\mu_{23})x_2 &= 0 \\ \Rightarrow x_2 &= 0 \quad (\text{since} \quad \mu_{12}+\mu_{13}-\mu_{23} \neq 0) \end{aligned}$$

$0x_1 = 0 \Rightarrow x_1$ can take any value and therefore we take $x_1 = 1$
The eigen vector corresponding to $\lambda = \lambda_1$ is therefore given as

$$\begin{pmatrix} 1 & 0 & 0 \end{pmatrix}'$$

The matrix based on the eigen vectors is

$$U = \begin{pmatrix} 1 & \dfrac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} & 1 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{pmatrix}$$

Since the eigen values are distinct, we have

$$Q = UDU^{-1}$$

where

$$U^{-1} = \begin{pmatrix} 1 & \dfrac{-\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} & \dfrac{\mu_{23}-\mu_{13}}{\mu_{12}+\mu_{13}-\mu_{23}} \\ 0 & 1 & -1 \\ 0 & 0 & 1 \end{pmatrix}$$

From (4.17)

$$\begin{aligned} P(s,t) &= e^{tQ} = 1 + \frac{tQ}{1!} + \frac{(tQ)^2}{2!} + \cdots \\ &= \sum_{k=0}^{\infty} Q^k \frac{t^k}{k!} \\ &= 1 + \sum_{k=1}^{\infty} \frac{t^k}{k!} U D^k U^{-1} \\ &= 1 + U \left[\sum_{k=1}^{\infty} \frac{(tD)^k}{k!} \right] U^{-1} \end{aligned}$$

where

$$D = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

which implies that

$$(tD)^k = \begin{pmatrix} (\lambda_1 t)^k & 0 & 0 \\ 0 & (\lambda_2 t)^k & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{5.6}$$

Summing up elements (5.6) and dividing by $k!$ we get

$$\sum_{k=1}^{\infty} \frac{(tD)^k}{k!} = \begin{pmatrix} \sum_{k=1}^{\infty} \dfrac{(\lambda_1 t)^k}{k!} & 0 & 0 \\ 0 & \sum_{k=1}^{\infty} \dfrac{(\lambda_2 t)^k}{k!} & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{5.7}$$

The non zero elements in matrix (5.7) represents exponential distribution without the first term and can therefore be presented as

$$= \begin{pmatrix} e^{\lambda_1 t} - 1 & 0 & 0 \\ 0 & e^{\lambda_2 t} - 1 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{5.8}$$

We deduce that

$$U\sum_{k=1}^{\infty}\frac{(tD)^k}{k!}U^{-1}=\begin{pmatrix} e^{\lambda_1 t}-1 & \dfrac{\mu_{12}(e^{\lambda_2 t}-e^{\lambda_1 t})}{\mu_{12}+\mu_{13}-\mu_{23}} & \dfrac{(\mu_{23}-\mu_{13})(e^{\lambda_1 t}-1)-\mu_{12}(e^{\lambda_2 t}-1)}{\mu_{12}+\mu_{13}-\mu_{23}} \\ 0 & e^{\lambda_2 t}-1 & 1-e^{\lambda_2 t} \\ 0 & 0 & 0 \end{pmatrix}$$

Now

$$P(s,t)=\begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}+\begin{pmatrix} e^{\lambda_1 t}-1 & \dfrac{\mu_{12}(e^{\lambda_2 t}-e^{\lambda_1 t})}{\mu_{12}+\mu_{13}-\mu_{23}} & \dfrac{(\mu_{23}-\mu_{13})(e^{\lambda_1 t}-1)-\mu_{12}(e^{\lambda_2 t}-1)}{\mu_{12}+\mu_{13}-\mu_{23}} \\ 0 & e^{\lambda_2 t}-1 & 1-e^{\lambda_2 t} \\ 0 & 0 & 0 \end{pmatrix}$$

$$=\begin{pmatrix} e^{\lambda_1 t} & \dfrac{\mu_{12}(e^{\lambda_2 t}-e^{\lambda_1 t})}{\mu_{12}+\mu_{13}-\mu_{23}} & \dfrac{(\mu_{23}-\mu_{13})(e^{\lambda_1 t}-1)-\mu_{12}(e^{\lambda_2 t}-1)}{\mu_{12}+\mu_{13}-\mu_{23}} \\ 0 & e^{\lambda_2 t} & 1-e^{\lambda_2 t} \\ 0 & 0 & 1 \end{pmatrix} \tag{5.9}$$

It therefore follows that

The probability of being infected and remaining infected is $e^{\lambda_1 t}$

The probability of developing Aids after being infected $\dfrac{\mu_{12}(e^{\lambda_2 t}-e^{\lambda_1 t})}{\mu_{12}+\mu_{13}-\mu_{23}}$

The probability of dying after being infected $\dfrac{(\mu_{23}-\mu_{13})(e^{\lambda_1 t}-1)-\mu_{12}(e^{\lambda_2 t}-1)}{\mu_{12}+\mu_{13}-\mu_{23}}$

The probability condition improving after developing Aids is zero

The probability of remaining in the Aids state $e^{\lambda_2 t}$

The probability of dying from Aids is $1-e^{\lambda_2 t}$

Since death is an absorbing state once reached it can not be reversed.

5.3 Estimation for Left Censoring

Using probability of remaining in the infected state given in (5.9) it follows that

$$P_{11}(s,t) = e^{-t(\mu_{12}+\mu_{13})} \tag{5.10}$$

$$F_{11}(s,t) = -\frac{e^{-t(\mu_{12}+\mu_{13})}}{\mu_{12}+\mu_{13}} \tag{5.11}$$

Therefore likelihood function is given as

$$L = -\prod_{i=1}^{n} \left(e^{-(\mu_{12}+\mu_{13})t_i}\right)^{\delta_i} \left(\frac{e^{-t_i(\mu_{12}+\mu_{13})}}{\mu_{12}+\mu_{13}}\right)^{1-\delta_i}$$

and the log likelihood is

$$l = -\sum_{i=1}^{n} \delta_i \ln\left(e^{-(\mu_{12}+\mu_{13})t_i}\right) - \sum_{i=1}^{n}(1-\delta_i)\ln\left(\frac{e^{-t_i(\mu_{12}+\mu_{13})}}{\mu_{12}+\mu_{13}}\right) \tag{5.12}$$

To obtain estimate for μ_{12} we differentiate (5.12) with respect to μ_{12} and get

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{12}} &= -\sum_{i=1}^{n} \delta_i \ln e^{-(\mu_{12}+\mu_{13})t_i} + \frac{n\mu_{12}}{(\mu_{12}+\mu_{13})^2} + \frac{n\mu_{13}}{(\mu_{12}+\mu_{13})^2} \\
&\quad - \left(\sum_{i=1}^{n}\left(\frac{\delta_i t_i \mu_{13}}{\mu_{12}+\mu_{13}}\right)\right) \qquad (5.13) \\
&\quad + \left(\sum_{i=1}^{n}\left(\frac{\delta_i t_i \mu_{12}}{\mu_{12}+\mu_{13}} + \frac{\delta_i \mu_{13}}{(\mu_{12}+\mu 13)^2} + \frac{\delta_i \mu_{12}}{(\mu_{12}+\mu_{13})^2} - \frac{t\mu_{13}}{\mu_{12}+\mu_{13}} - \frac{t_i\mu_{12}}{\mu_{12}+\mu_{13}}\right)\right) \qquad (5.14)
\end{aligned}$$

Simplifying results in (5.14) gives

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{12}} &= -\frac{1}{\mu_{12}+\mu_{13}}\left(\ln \sum_{i=1}^{n} \delta_i t_i e^{-(\mu_{12}+\mu_{13})t_i}\right)\mu_{12} + \ln\left(\sum_{i=1}^{n} \delta_i t_i e^{-(\mu_{12}+\mu_{13})t_i}\right)\mu_{13} \\
&\quad -n + \left(\sum_{i=1}^{n}(-t_i\mu_{12} + t_i\mu_{12}\delta_i + t_i\mu_{13}\delta_i + \delta_i - t_i\mu_{13})\right) \qquad (5.15)
\end{aligned}$$

Since censoring has occured $\delta_i = 0$ and (5.15) becomes

$$\frac{\partial l}{\partial \mu_{12}} = -\frac{1}{\mu_{12}+\mu_{13}}\left(-n + \left(\sum_{i=1}^{n}(-t_i\mu_{12} - t_i\mu_{13})\right)\right) \tag{5.16}$$

Equating (5.16) to zero

$$\begin{aligned}
0 &= n + \sum_{i=1}^{n} t_i\mu_{12} + \sum_{i=1}^{n} t_i\mu_{13} \\
-\sum_{i=1}^{n} t_i\mu_{12} - \sum_{i=1}^{n} t_i\mu_{13} &= n \\
-\mu_{12}\sum_{i=1}^{n} t_i &= n + \mu_{13}\sum_{i=1}^{n} t_i \\
\hat{\mu_{12}} &= -\left(\frac{n + \mu_{13}\sum_{i=1}^{n} t_i}{\sum_{i=1}^{n} t_i}\right) \qquad (5.17)
\end{aligned}$$

If we assume that all are born infected and that there are no deaths then $\mu_{13} = 0$ and therefore

$$\hat{\mu_{12}} = -\frac{n}{\sum_{i=1}^{n} t_i} \tag{5.18}$$

Similarly differentiating (5.12) with respect to μ_{13} results in

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{13}} &= -\sum_{i=1}^{n} \delta_i \ln t_i e^{-(\mu_{12}+\mu_{13})t_i} + \frac{n\mu_{12}}{(\mu_{12}+\mu_{13})^2} + \frac{n\mu_{13}}{(\mu_{12}+\mu_{13})^2} \\
&\quad -\sum_{i=1}^{n} \left(\frac{\delta_i t_i \mu_{13}}{\mu_{12}+\mu_{13}} + \frac{\delta_i t_i \mu_{12}}{\mu_{12}+\mu_{13}} + \frac{\delta_i \mu_{13}}{(\mu_{12}+\mu_{13})^2} + \frac{\delta_i \mu_{12}}{(\mu_{12}+\mu_{13})^2} - \frac{t_i \mu_{13}}{\mu_{12}+\mu_{13}} - \frac{t_i \mu_{12}}{\mu_{12}+\mu_{13}} \right) \\
&= -\frac{1}{\mu_{12}+\mu_{13}} \left(\left(\ln \sum_{i=1}^{n} \delta_i t_i e^{-(\mu_{12}+\mu_{13})t_i} \right) \mu_{12} + \ln \left(\sum_{i=1}^{n} \delta_i t_i e^{-(\mu_{12}+\mu_{13})t_i} \right) \mu_{13} \right) \\
&\quad -n + \sum_{i=1}^{n} \left(t_i \mu_{12} \delta_i - t_i \mu_{12} + t_i \mu_{13} \delta_i + \delta_i - t_i \mu_{13} \right)
\end{aligned}$$

Since censored $\delta_i = 0$ and

$$\frac{\partial l}{\partial \mu_{13}} = -\frac{1}{\mu_{12}+\mu_{13}} \left(-n - \sum_{i=1}^{n} t_i \mu_{12} + \sum_{i=1}^{n} t_i \mu_{13} \right) \tag{5.19}$$

Equating (5.19) to zero

$$\begin{aligned}
-\sum_{i=1}^{n} t_i \mu_{13} - \sum_{i=1}^{n} t_i \mu_{12} &= n \\
-\mu_{13} \sum_{i=1}^{n} t_i &= n + \mu_{12} \sum_{i=1}^{n} t_i \\
\hat{\mu_{13}} &= -\left(\frac{n + \mu_{12} \sum_{i=1}^{n} t_i}{\sum_{i=1}^{n} t_i} \right)
\end{aligned} \tag{5.20}$$

Assuming that no individual survived after infection then $\mu_{12} = 0$ and we have

$$\hat{\mu_{13}} = -\frac{n}{\sum_{i=1}^{n} t_i} \tag{5.21}$$

To estimate μ_{23} we use

$$\begin{aligned}
P_{22}(s,t) &= e^{\lambda_2 t} = e^{-\mu_{23} t} \\
F_{22}(s,t) &= \frac{-e^{-\mu_{23}} t}{\mu_{23}}
\end{aligned}$$

Therefore

$$\begin{aligned} L &= -\prod_{i=1}^{n}(e^{-\mu_{23}t_i})^{\delta_i}\left(\frac{e^{-\mu_{23}t_i}}{\mu_{23}}\right)^{1-\delta_i} \\ l &= \sum_{i=1}^{n}\delta_i \ln(e^{-\mu_{23}t_i}) - \sum_{i=1}^{n}(1-\delta_i)\ln(\frac{e^{-\mu_{23}t_i}}{\mu_{23}}) \\ \frac{\partial l}{\partial \mu_{23}} &= -\left(\sum_{i=1}^{n}(\delta_i t_i)\right) + \frac{n}{\mu_{23}} - \sum_{i=1}^{n}(\delta_i t_i - t_i + \frac{\delta_i}{\mu_{23}}) \\ &= -(\sum_{i=1}^{n}\delta_i t_i)\mu_{23} - n + \sum_{i=1}^{n}(\delta_i \mu_{23} t_i - \mu_{23} t_i + \delta_i) \\ &= -n - \mu_{23}\sum_{i=1}^{n} t_i + \sum_{i=1}^{n}\delta_i \end{aligned} \tag{5.22}$$

Equating (5.22) to zero and making μ_{23} the subject

$$\mu_{23} = \frac{\sum_{i=1}^{n}\delta_i - n}{\sum_{i=1}^{n} t_i}$$

Since there is censoring then

$$\hat{\mu_{23}} = -\frac{n}{\sum_{i=1}^{n} t_i} \tag{5.23}$$

5.3.1 Situations when Born Infected

We use transition probability matrix (5.9) to obtain all the possibilities which we then use to estimate the transition intensities

$$\begin{aligned} P_{12}(s,t) &= P_{11}P_{12} + P_{12}P_{22} \\ P_{13}(s,t) &= P_{12}P_{23} + P_{13}P_{33} \\ P_{23}(s,t) &= P_{22}P_{23} + P_{23}P_{33} \end{aligned}$$

Using the matrix of transition probabilities we have

$$\begin{aligned} P_{12} &= e^{\lambda_1 t}\frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12} + \mu_{12} - \mu_{23}} + \frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})e^{\lambda_2 t}}{\mu_{12} + \mu_{13} - \mu_{23}}e^{\lambda_2 t} \\ &= \frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12} + \mu_{13} - \mu_{23}}\left(e^{\lambda_1 t} + e^{\lambda_2 t}\right) \\ &= \frac{\mu_{12}}{\mu_{12} + \mu_{13} - \mu_{23}}(e^{\lambda_2 t} - e^{\lambda_1 t})(e^{\lambda_2 t} + e^{\lambda_1 t}) \\ &= \frac{\mu_{12}}{\mu_{12} + \mu_{13} - \mu_{23}}\left(e^{2\lambda_2 t} - e^{2\lambda_1 t}\right) \end{aligned} \tag{5.24}$$

but

$$\begin{aligned} \lambda_1 &= -\mu_{12} - \mu_{13} \\ \lambda_2 &= -\mu_{23} \end{aligned}$$

Therefore

$$P_{12}(s,t) = \frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}}\left(e^{-2\mu_{23}t}-e^{-2(\mu_{12}+\mu_{13})t}\right) \tag{5.25}$$

$$F_{12}(s,t) = -\frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}}\left(\frac{e^{-2t\mu_{23}}}{2\mu_{23}}+\frac{e^{-2(\mu_{12}+\mu_{23})t}}{-2\mu_{12}-2\mu_{13}}\right) \tag{5.26}$$

The likeihood is therefore given as

$$L=\prod_{i=1}^{n}(\Phi)^{\delta_i}(\Omega)^{1-\delta_i} \tag{5.27}$$

where

$$\Phi = \frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}}(e^{-2\mu_{23}t_i}-e^{-2(\mu_{12}+\mu_{13})t_i})$$

$$\Omega = \frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}}\left(\frac{-e^{-2\mu_{23}t_i}}{2\mu_{23}}-\frac{e^{-2(\mu_{12}+\mu_{23})t_i}}{-2\mu_{12}-2\mu_{13}}\right)$$

and the log likelihood as

$$l=\sum_{i=1}^{n}\frac{\delta_i \ln\mu_{12}(e^{-2\mu_{23}t_i}-e^{-2(\mu_{12}+\mu_{13})t_i})}{\mu_{12}+\mu_{13}-\mu_{23}}+\sum_{i=1}^{n}\frac{(1-\delta_i)\ln\mu_{12}\left(\frac{-e^{-2\mu_{23}t_i}}{\mu_{23}}-\frac{e^{-2(\mu_{12}+\mu_{13})t_i}}{-2\mu_{12}-2\mu_{13}}\right)}{\mu_{12}+\mu_{13}-\mu_{23}} \tag{5.28}$$

Differentiating (5.28) with respect to μ_{12} we obtain

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{12}} &= \sum_{i=1}^{n}\left(\frac{\delta_i \ln(e^{-2\mu_{23}t_i}-e^{-2(\mu_{12}+\mu_{13})t_i})}{\mu_{12}+\mu_{13}-\mu_{23}}\right) \\
&+\sum_{i=1}^{n}\left(\frac{2\delta_i \ln\mu_{12}t_i e^{-2(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}-\mu_{23}}-\frac{\delta_i \ln\mu_{12}(e^{-2\mu_{23}t_i}-e^{-2(\mu_{12}+\mu_{13})t_i})}{(\mu_{12}+\mu_{13}-\mu_{23})^2}\right) \\
&+\sum_{i=1}^{n}\left(\frac{(1-\delta_i)\ln\left(\frac{-e^{-2\mu_{23}t_i}}{2\mu_{23}}-\frac{e^{-2(\mu_{12}+\mu_{13})t_i}}{-2\mu_{12}-2\mu_{13}}\right)}{\mu_{12}+\mu_{13}-\mu_{23}}\right) \\
&+\sum_{i=1}^{n}\left(\frac{(1-\delta_i)\ln\mu_{12}\left(\frac{2t_i e^{-2(\mu_{12}+\mu_{13})t_i}}{-2\mu_{12}-2\mu_{13}}-\frac{-2e^{-2(\mu_{12}+\mu_{13})t_i}}{(-2\mu_{12}-2\mu_{13})^2}\right)}{\mu_{12}+\mu_{13}-\mu_{23}}\right) \\
&-\sum_{i=1}^{n}\left(\frac{(1-\delta_i)\ln\mu_{12}\left(\frac{-e^{-2\mu_{23}t_i}}{2\mu_{23}}-\frac{e^{-2(\mu_{12}+\mu_{13})t_i}}{-2\mu_{12}-2\mu_{13}}\right)}{(\mu_{12}+\mu_{13}-\mu_{23})^2}\right)
\end{aligned}$$

Since censoring has occured then $\delta_i = 0$ and therefore

$$\begin{aligned}\frac{\partial l}{\partial \mu_{12}} &= \frac{\ln \sum_{i=1}^{n}\left(-\frac{e^{-2\mu_{23}t_i}}{2\mu_{23}} - \frac{e^{-2(\mu_{12}+\mu_{13})t_i}}{-2\mu_{12}-2\mu_{13}}\right)}{\mu_{12}+\mu_{13}-\mu_{23}} \\ &+\ln\mu_{12}\frac{\sum_{i=1}^{n}\left(\frac{2t_i e^{-2(\mu_{12}+\mu_{13})t_i}}{-2\mu_{12}-2\mu_{13}} - \frac{2e^{-2(\mu_{12}+\mu_{13})t_i}}{(-2\mu_{12}-2\mu_{13})^2}\right)}{\mu_{12}+\mu_{13}-\mu_{23}} \\ &-\ln\mu_{12}\frac{\sum_{i=1}^{n}\left(\frac{-e^{-2\mu_{23}t_i}}{2\mu_{23}} - \frac{e^{-2(\mu_{12}+\mu_{13})t_i}}{-2\mu_{12}-2\mu_{13}}\right)}{(\mu_{12}+\mu_{13}-\mu_{23})^2} \qquad (5.29)\end{aligned}$$

If we assume that there are no deaths then μ_{13} and μ_{23} equals zero and (5.29) simplifies to

$$\begin{aligned}\frac{\partial l}{\partial \mu_{12}} &= \frac{\sum_{i=1}^{n}\ln e^{-2\mu_{12}t_i}}{2\mu_{12}} - \sum_{i=1}^{n}\ln\mu_{12}\left(\frac{t_i e^{-2\mu_{12}t_i}}{\mu_{12}} - \frac{e^{-2\mu_{12}t_i}}{2\mu_{12}^2}\right) \\ &-\sum_{i=1}^{n}\ln\mu_{12}\frac{\frac{e^{-2\mu_{12}t_i}}{2\mu_{12}}}{\mu_{12}} \qquad (5.30)\end{aligned}$$

simplifying (5.30) we get

$$\frac{\partial l}{\partial \mu_{12}} = \sum_{i=1}^{n}\ln\left(-\frac{t_i e^{-2t_i\mu_{12}}}{\mu_{12}} - \frac{e^{-2t_i\mu_{12}}}{\mu_{12}^2}\right) \qquad (5.31)$$

Equating (5.31) to zero

$$\begin{aligned}\ln\sum_{i-1}^{n}\frac{t_i e^{-2t_i\mu_{12}}}{\mu_{12}} &= \ln\frac{1}{2}\sum_{i=1}^{n}\frac{e^{-2t_i\mu_{12}}}{\mu_{12}^2} \\ \sum_{i=1}^{n}\frac{t_i e^{-2t_i\mu_{12}}}{\mu_{12}} &= \frac{1}{2}\sum_{i=1}^{n}\frac{e^{-2t_i\mu_{12}}}{\mu_{12}^2} \\ \hat{\mu_{12}} &= -\frac{\sum_{i=1}^{n}e^{-2t_i\mu_{12}}}{\sum_{i=1}^{n}t_i e^{-2t_i\mu_{12}}} \qquad (5.32)\end{aligned}$$

Let $e^{-2t\mu_{12}} = f(t)$
then

$$\begin{aligned}\hat{\mu_{12}} &= -\frac{\sum_{i=1}^{n}f(t_i)}{E(T)} \\ &= -\frac{1}{E(T)} \qquad (5.33)\end{aligned}$$

Therefore from (5.33) as $t \to \infty$, $\mu_{12=0}$ implying that in the long run those infected will not develop AIDS.

To estimate μ_{13} we use

$$P_{12}(s,t) = P_{11}P_{12} + P_{12}P_{22} \tag{5.34}$$

Substituting from the transition matrix we get

$$\begin{aligned} f(t) = P_{12}(s,t) &= e^{\lambda_1 t}\frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12}+\mu_{13}-\mu_{23}} + \frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12}+\mu_{13}-\mu_{23}}(1 - e^{\lambda_2 t}) \\ &= \left(\frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12}\mu_{13}-\mu_{23}}\right)(e^{\lambda_1 t} + 1 - e^{\lambda_2 t}) \\ &= \frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}}\left(e^{(\lambda_1+\lambda_2)t} + e^{\lambda_2 t} - e^{2\lambda_2 t} - e^{2\lambda_1 t} - e^{\lambda_1 t} + e^{(\lambda_1+\lambda_2)t}\right) \end{aligned}$$

Differentiating we get

$$F(t) = F_{12}(s,t) = \frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}}\left(\frac{e^{(\lambda_1+\lambda_2)t}}{\lambda_1+\lambda_2}\frac{e^{\lambda_2 t}}{\lambda_2} - \frac{e^{2\lambda_2 t}}{2\lambda_2} - \frac{e^{2\lambda_1 t}}{2\lambda_1} - \frac{e^{\lambda_1 t}}{\lambda_1} + \frac{e^{\lambda_1+\lambda_2 t}}{\lambda_1+\lambda_2}\right)$$

Assuming that there are no deaths due to AIDS then $\mu_{23} = 0$ and therefore

$$\begin{aligned} f(t) &= -\frac{\mu_{12}}{\mu_{12}+\mu_{13}}\left(e^{2\lambda_1 t} + e^{\lambda_1 t}\right) \\ F(t) &= -\frac{\mu_{12}}{\mu_{12}+\mu_{13}}\left(\frac{e^{\lambda_1 t}}{\lambda_1} + \frac{e^{2\lambda_1 t}}{2\lambda_1}\right) \end{aligned} \tag{5.35}$$

The likelihood function is given as

$$L = \left(\frac{\mu_{12}}{\mu_{12}+\mu_{13}}(e^{2\lambda_1 t} + e^{\lambda_1 t})\right)^{\delta_i}\left(\frac{\mu_{12}}{\mu_{12}+\mu_{13}}(\frac{e^{\lambda_1 t}}{\lambda_1} + \frac{e^{2\lambda_1} t}{2\lambda_1})\right)^{1-\delta_i} \tag{5.36}$$

Substituting the values of λ_1 in (5.36) and taking the logs results in

$$\begin{aligned} l &= \sum_{i=1}^{n}\delta_i \ln\frac{\mu_{12}}{\mu_{12}+\mu 13}\left(e^{-2(\mu_{12}+\mu_{13})t_i} + e^{-(\mu_{12}+\mu_{13})t_i}\right) \\ &\quad + \sum_{i=1}^{n}(1-\delta_i)\ln\frac{\mu_{12}}{\mu_{12}+\mu_{13}}\left(\frac{e^{-(\mu_{12}+\mu_{13})t_i}}{-(\mu_{12}+\mu_{13})} - \frac{e^{-2(\mu_{12}+\mu_{13})}}{2(\mu_{12}+\mu_{13})}\right) \end{aligned} \tag{5.37}$$

Since censored $\delta_i = 0$ and therefore (5.37) simplifies to

$$l = -\frac{\sum_{i=1}^{n}\ln\mu_{12}}{\left(\frac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}} + \frac{e^{-2(\mu_{12}+\mu_{13})t_i}}{2(\mu_{12}+\mu_{13})}\right)}\mu_{12} + \mu_{13} \tag{5.38}$$

Equating (5.38) to zero results in

$$\begin{aligned}
\sum_{i=1}^{n} \frac{e^{-2(\mu_{12}+\mu_{13})t_i}}{2(\mu_{12}+\mu_{13})} &= -\sum_{i=1}^{n} \frac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}} \\
\frac{\sum_{i=1}^{n} e^{-2(\mu_{12}\mu_{13})t_i}}{\sum_{i=1}^{n} e^{-(\mu_{12}+\mu_{13})t_i}} &= \frac{2(\mu_{12}+\mu_{13})}{\mu_{12}+\mu_{13}} \\
\frac{\sum_{i=1}^{n} e^{(\mu_{12}\mu_{13})t_i}}{\sum_{i=1}^{n} e^{2(\mu_{12}+\mu_{13})t_i}} &= \frac{\mu_{12}+\mu_{13}}{2(\mu_{12}+\mu_{13})} \\
\frac{1}{\sum_{i=1}^{n} e^{(\mu_{12}+\mu_{13})t_i}} &= \frac{1}{2} \\
\frac{1}{e^{(\mu_{12}+\mu_{13})\sum_{i=1}^{n} t_i}} &= \frac{1}{2} \\
e^{(\mu_{12}+\mu_{13})\sum_{i=1}^{n} t_i} &= 2 \\
(\mu_{12}+\mu_{13})\sum_{i=1}^{n} t_i &= \ln 2 \\
\mu_{12}+\mu_{13} &= \frac{\ln 2}{\sum_{i=1}^{n} t_i} \\
\hat{\mu_{12}} &= \frac{\ln 2}{\sum_{i=1}^{n} t_i} - \mu_{13} \qquad (5.39)
\end{aligned}$$

Substituting (5.33) for μ_{12} gives

$$\hat{\mu_{13}} = \frac{\ln 2}{\sum_{i=1}^{n} t_i} - \frac{1}{E(T)} \qquad (5.40)$$

To estimate μ_{23} we use

$$P_{23}(s,t) = P_{22}(s,t)P_{23}(s,t) + P_{23}(s,t)P_{33}(s,t) \qquad (5.41)$$

Substituting gives

$$\begin{aligned}
P_{23}(s,t) &= e^{\lambda_2 t}(1-e^{\lambda_2 t}) + 1 - e^{\lambda_2 t} \\
&= 1 - e^{2\lambda_2 t}
\end{aligned}$$

Therefore

$$\begin{aligned}
f(t) &= 1 - e^{2\lambda_2 t} \\
F(t) &= t - \frac{e^{2\lambda_2 t}}{2\lambda_2}
\end{aligned}$$

Substituting the values gives

$$\prod_{i=1}^{n}\left(1-e^{-2\mu_{23}t_i}\right)^{\delta_i}\left(t+\frac{e^{-2\mu_{23}t_i}}{2\mu_{23}}\right)^{1-\delta_i} \tag{5.42}$$

Taking the logs of (5.42) we get

$$l=\sum_{i=1}^{n}\delta_i \ln\left(1-e^{-2\mu_{23}t_i}\right)+\sum_{i=1}^{n}(1-\delta_i)\ln\left(t+\frac{e^{-2\mu_{23}}}{2\mu_{23}}\right) \tag{5.43}$$

Since censored then $\delta_i=0$ and (5.43) becomes

$$l=\sum_{i=1}^{n}\ln\left(t_i+\frac{e^{-2\mu_{23}t_i}}{2\mu_{23}}\right) \tag{5.44}$$

Differentiating (5.44) with respect to μ_{23}

$$\frac{\partial l}{\mu_{23}}=-\sum_{i=1}^{n}\frac{\left(\frac{t_i e^{-2\mu_{23}t_i}}{\mu_{23}}+\frac{e^{-2\mu_{23}t_i}}{2\mu_{23}^2}\right)}{t_i+\frac{e^{-2\mu_{23}t_i}}{\mu_{23}}} \tag{5.45}$$

Equating (5.45) to zero

$$\sum_{i=1}^{n}\frac{t_i e^{-2\mu_{23}t_i}}{\mu_{23}} = -\frac{\sum_{i=1}^{n}e^{-2\mu_{23}t_i}}{\sum_{i=1}^{n}t_i e^{-2\mu_{23}t_i}}$$

If we let

$$e^{-2\mu_{23}t_i}=f(t) \tag{5.46}$$

then

$$\sum_{i=1}^{n}t_i e^{-2\mu_{23}t_i}=E(T) \tag{5.47}$$

Therefore

$$\begin{aligned}\hat{\mu_{23}} &= -\frac{\sum_{i=1}^{\infty}f(t)}{E\left[(T)\right]}\\ &= -\frac{1}{E^2(T)}\end{aligned} \tag{5.48}$$

Therefore we observe that the maximum likelihood estimators of μ_{12},μ_{13} and μ_{23} exits and are all in terms of $E(T)$.

Chapter 6

A THREE STATE MODEL FOR A CHILD BORN HEALTHY

6.1 Introduction

This is a three state model with no possibility of recovery. An individual can only enter a state once with there being no ability to go back to a state that they had visited before. The three states are Healthy, Infected and Death and are represented by $S = 1, 2, 3$ where 1 is HIV-negative, 2 is HIV positive and 3 is Death as given in Figure 6.1
For state-space S, the probability of being in state j by time t given an initial state i at time s is the transition probability defined as $P_{ij}(s,t) = \text{Prob}(X(t) = j/X(s) = i)$
The instantaneous risk or hazard of transitioning from state i to state j is the transition intensity

$$\mu_{ij}(t) = \lim_{h \to 0} \frac{P_{ij}(t, t+h)}{h} \tag{6.1}$$

We denote the cumulative intensity as

$$A_{ij}(t) = \int_0^t \mu_{ij}(s)ds \tag{6.2}$$

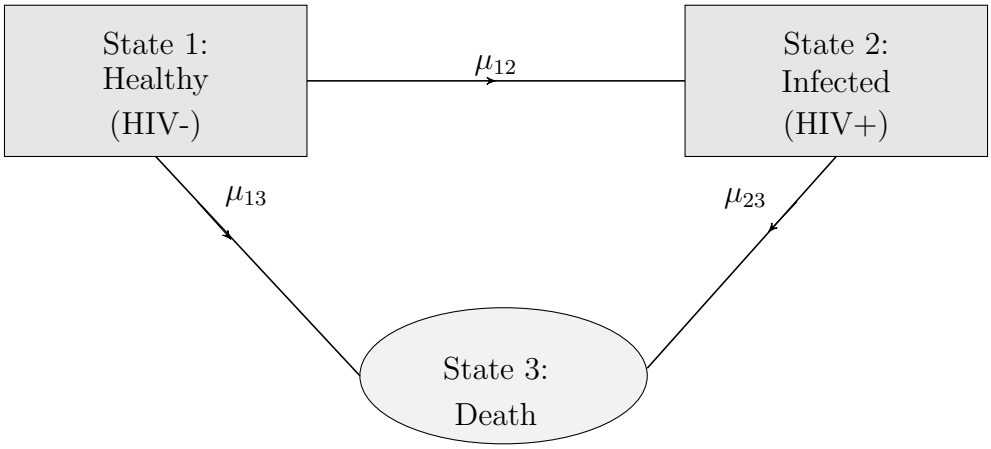

Figure 6.1: Illness-Death model for MTCT of HIV

6.2 Derivation of Forward Kolmogorov Differential Equations

From the model in Figure 6.1 we use the Chapman- Kolmogorov equations to derive the following differential equations for transition probabilities

$$\begin{aligned}
P_{11}(s,t+h) &= \sum_{k=1}^{3} P_{1k}(s,t)P_{k1}(t,t+h) \\
&= P_{11}(s,t)P_{11}(t,t+h) + P_{12}(s,t)P_{21}(t,t+h) + P_{13}(s,t)P_{31}(t,t+h) \\
&= P_{11}(s,t)((1-(\mu_{12}+\mu_{13}))h + o(h)) + P_{12}(s,t)\cdot 0 + P_{13}(s,t)\cdot 0 \\
P_{11}^{'}(s,t) &= -P_{11}(s,t)(\mu_{12}+\mu_{13}) \qquad (6.3)
\end{aligned}$$

$$\begin{aligned}
P_{12}(s,t+h) &= \sum_{k=1}^{3} P_{1k}(s,t)P_{k2}(t,t+h) \\
&= P_{11}(s,t)P_{12}(t,t+h) + P_{12}(s,t)P_{22}(t,t+h) + P_{13}(s,t)P_{32}(t,t+h) \\
&= P_{11}(s,t)((\mu_{12}h + o(h)) + P_{12}(s,t)(1-(\mu_{23})h + o(h)) + P_{13}(s,t)\cdot 0 \\
P_{12}^{'}(s,t) &= P_{11}(s,t)\mu_{12} - P_{12}(s,t)\mu_{23} \qquad (6.4)
\end{aligned}$$

$$\begin{aligned}
P_{13}(s,t+h) &= \sum_{k=1}^{3} P_{1k}(s,t)P_{k3}(t,t+h) \\
&= P_{11}(s,t)P_{13}(t,t+h) + P_{12}(s,t)P_{23}(t,t+h) + P_{13}(s,t)P_{33}(t,t+h) \\
&= P_{11}(s,t)(\mu_{13}h + o(h)) + P_{12}(s,t)(\mu_{23}h + o(h)) + P_{13}(s,t)(1+o(h)) \\
P_{13}^{'}(s,t) &= P_{11}(s,t)\mu_{13} + P_{12}(s,t)\mu_{23} \qquad (6.5)
\end{aligned}$$

Equations (6.3),(6.4) and (6.5) are the respective Kolmogorov Forward equations.

$$\begin{bmatrix} P_{11}^{'}(s,t) & P_{12}^{'}(s,t) & P_{13}^{'}(s,t) \\ P_{21}^{'}(s,t) & P_{22}^{'}(s,t) & P_{23}^{'}(s,t) \\ P_{31}^{'}(s,t) & P_{32}^{'}(s,t) & P_{33}^{'}(s,t) \end{bmatrix} = \begin{bmatrix} P_{11}(s,t) & P_{12}(s,t) & P_{13}(s,t) \\ P_{21}(s,t) & P_{22}(s,t) & P_{23}(s,t) \\ P_{31}(s,t) & P_{32}(s,t) & P_{33}(s,t) \end{bmatrix} \begin{bmatrix} -(\mu_{12}+\mu_{13}) & \mu_{12} & \mu_{13} \\ 0 & -\mu_{23} & \mu_{23} \\ 0 & 0 & 0 \end{bmatrix}$$

where the transition rates matrix is given by

$$Q = \begin{pmatrix} -(\mu_{12}+\mu_{13}) & \mu_{12} & \mu_{13} \\ 0 & -\mu_{23} & \mu_{23} \\ 0 & 0 & 0 \end{pmatrix} \qquad (6.6)$$

The Kolmogorov differential equations in (6.3), (6.4) and (6.5) results in the transition matrix (6.6) whose eigen values are

$$\begin{aligned}\lambda_1 &= -(\mu_{12}+\mu_{13}),\\ \lambda_2 &= -\mu_{23},\\ \lambda_3 &= 0.\end{aligned}$$

We then obtain the corresponding eigen vectors as follows:
For $\lambda = \lambda_3 = 0$

$$\begin{pmatrix} -(\mu_{12}+\mu_{13}) & \mu_{12} & \mu_{13} \\ 0 & -\mu_{23} & \mu_{23} \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix},$$

where x_3 can be any number.
Taking $x_3 = 1$ (as we are interested in any non zero vector)

$$\begin{aligned}-\mu_{23}x_2 + \mu_{23}x_3 &= 0,\\ x_2 &= \frac{\mu_{23}}{\mu_{23}} = 1.\end{aligned}$$

Similarly

$$\begin{aligned}-\mu_{12}x_1 - \mu_{13}x_1 + \mu_{12}x_2 + \mu_{13}x_3 &= 0,\\ -\mu_{12}x_1 - \mu_{13}x_1 + \mu_{12} + \mu_{13} &= 0,\\ x_1 &= \frac{\mu_{12}+\mu_{13}}{\mu_{12}+\mu_{13}} = 1.,\end{aligned}$$

The eigen vector for $\lambda = 0$ is

$$\begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix}$$

For$\lambda = \lambda_2 = -\mu_{23}$

$$\begin{pmatrix} -\mu_{12}-\mu_{13}+\mu_{23} & \mu_{12} & \mu_{13} \\ 0 & 0 & \mu_{23} \\ 0 & 0 & \mu_{23} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

This leads to

$$\begin{pmatrix} -\mu_{12}-\mu_{13}+\mu_{23} & \mu_{12} & \mu_{13} \\ 0 & 0 & \mu_{23} \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

x_3 can take any value, we take $x_2 = 1$
$\mu_{23}x_3 = 0$ and since $\mu_{23} \neq 0$ as this is the probability of death once infected
$\Rightarrow x_3 = 0$

$$\begin{aligned} -\mu_{12}x_1 - \mu_{13}x_1 + \mu_{23}x_1 + \mu_{12}x_2 + \mu_{13}x_3 &= 0 \\ x_1 &= \frac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} \end{aligned}$$

The eigen vector for $\lambda = -\mu_{23}$ is

$$\begin{pmatrix} \dfrac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} \\ 1 \\ 0 \end{pmatrix}$$

For $\lambda = \lambda_1 = -\mu_{12} - \mu_{13}$

$$\begin{pmatrix} 0 & \mu_{12} & \mu_{13} \\ 0 & \mu_{12}+\mu_{13}-\mu_{23} & \mu_{23} \\ 0 & 0 & \mu_{12}+\mu_{13} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

$$\begin{aligned} \mu_{12}x_3 + \mu_{13}x_3 &= 0 \\ (\mu_{12}+\mu_{13})x_3 &= 0 \\ \text{but} \quad (\mu_{12}+\mu_{13}) &\neq 0 \\ \Rightarrow x_3 &= 0 \end{aligned}$$

Similarly

$$\begin{aligned} (\mu_{12}+\mu_{13}-\mu_{23})x_2 + \mu_{23}x_3 &= 0 \\ (\mu_{12}+\mu_{13}-\mu_{23})x_2 &= 0 \\ \Rightarrow x_2 &= 0 \quad (\text{since} \quad \mu_{12}+\mu_{13}-\mu_{23} \neq 0) \end{aligned}$$

$0x_1 = 0 \Rightarrow x_1$ can take any value and therefore we take $x_1 = 1$
The eigen vector corresponding to $\lambda = \lambda_1$ is therefore given as

$$\begin{pmatrix} 1 & 0 & 0 \end{pmatrix}'$$

The matrix based on the eigen vectors is

$$U = \begin{pmatrix} 1 & \dfrac{\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} & 1 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{pmatrix}$$

Since the eigen values are distinct, we have

$$Q = UDU^{-1}$$

where

$$U^{-1} = \begin{pmatrix} 1 & \dfrac{-\mu_{12}}{\mu_{12}+\mu_{13}-\mu_{23}} & \dfrac{\mu_{23}-\mu_{13}}{\mu_{12}+\mu_{13}-\mu_{23}} \\ 0 & 1 & -1 \\ 0 & 0 & 1 \end{pmatrix}$$

Using the relation

$$\begin{aligned} P(s,t) &= e^{tQ} = 1 + \frac{tQ}{1!} + \frac{(tQ)^2}{2!} + \cdots \\ &= \sum_{k=0}^{\infty} Q^k \frac{t^k}{k!} \\ &= 1 + \sum_{k=1}^{\infty} \frac{t^k}{k!} UD^k U^{-1} \\ &= 1 + U\left[\sum_{k=1}^{\infty} \frac{(tD)^k}{k!}\right] U^{-1} \end{aligned}$$

where

$$D = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

which implies that

$$(tD)^k = \begin{pmatrix} (\lambda_1 t)^k & 0 & 0 \\ 0 & (\lambda_2 t)^k & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{6.7}$$

Summing up elements (6.7) and dividing by $k!$ we get

$$\sum_{k=1}^{\infty} \frac{(tD)^k}{k!} = \begin{pmatrix} \sum_{k=1}^{\infty} \frac{(\lambda_1 t)^k}{k!} & 0 & 0 \\ 0 & \sum_{k=1}^{\infty} \frac{(\lambda_2 t)^k}{k!} & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{6.8}$$

The non zero elements in matrix (6.8) represents exponential distribution without the first term and can therefore be presented as

$$= \begin{pmatrix} e^{\lambda_1 t} - 1 & 0 & 0 \\ 0 & e^{\lambda_2 t} - 1 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{6.9}$$

We deduce that

$$U \sum_{k=1}^{\infty} \frac{(tD)^k}{k!} U^{-1} = \begin{pmatrix} e^{\lambda_1 t} - 1 & \frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12} + \mu_{13} - \mu_{23}} & \frac{(\mu_{23} - \mu_{13})(e^{\lambda_1 t} - 1) - \mu_{12}(e^{\lambda_2 t} - 1)}{\mu_{12} + \mu_{13} - \mu_{23}} \\ 0 & e^{\lambda_2 t} - 1 & 1 - e^{\lambda_2 t} \\ 0 & 0 & 0 \end{pmatrix}$$

Now

$$P(s,t) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} + \begin{pmatrix} e^{\lambda_1 t} - 1 & \frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12} + \mu_{13} - \mu_{23}} & \frac{(\mu_{23} - \mu_{13})(e^{\lambda_1 t} - 1) - \mu_{12}(e^{\lambda_2 t} - 1)}{\mu_{12} + \mu_{13} - \mu_{23}} \\ 0 & e^{\lambda_2 t} - 1 & 1 - e^{\lambda_2 t} \\ 0 & 0 & 0 \end{pmatrix}$$

$$= \begin{pmatrix} e^{\lambda_1 t} & \frac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12} + \mu_{13} - \mu_{23}} & \frac{(\mu_{23} - \mu_{13})(e^{\lambda_1 t} - 1) - \mu_{12}(e^{\lambda_2 t} - 1)}{\mu_{12} + \mu_{13} - \mu_{23}} \\ 0 & e^{\lambda_2 t} & 1 - e^{\lambda_2 t} \\ 0 & 0 & 1 \end{pmatrix}$$

It therefore follows that

The probability of being healthy and remaining healthy is $e^{\lambda_1 t}$

The probability of being infected is $\dfrac{\mu_{12}(e^{\lambda_2 t} - e^{\lambda_1 t})}{\mu_{12} + \mu_{13} - \mu_{23}}$

The probability of being healthy and dying is $\dfrac{(\mu_{23} - \mu_{13})(e^{\lambda_1 t} - 1) - \mu_{12}(e^{\lambda_2 t} - 1)}{\mu_{12} + \mu_{13} - \mu_{23}}$

The probability of being healthy once infected is zero

The probability of remaining infected once infected is given by $e^{\lambda_2 t}$

The probability of dying from infection is $1 - e^{\lambda_2 t}$

Death being an absorbing state nothing can be reversed from this state once reached.

6.3 Estimation for Right Censoring

Using

$$\begin{aligned} P_{11}(s,t) &= e^{-(\mu_{12}+\mu_{13})t_i} \\ S_{11}(s,t) &= 1 + \frac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}} \end{aligned}$$

The likelihood function is

$$L = \prod_{i=1}^{n} \left(e^{-(\mu_{12}+\mu_{13})t_i}\right)^{\delta_i} \left(1 + \frac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}}\right)^{1-\delta_i} \tag{6.10}$$

Taking the log of (6.10) we get

$$l = \sum_{i=1}^{n} \delta_i \ln\left(e^{-(\mu_{12}+\mu_{13})t_i}\right) + \sum_{i=1}^{n} (1-\delta_i) \ln\left(1 + \frac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}}\right) \tag{6.11}$$

Differentiating (6.11) with respect to μ_{12}

$$\frac{\partial l}{\partial \mu_{12}} = -\sum_{i=1}^{n} \left(\delta_i \ln t_i e^{-(\mu_{12}+\mu_{13})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}} - \dfrac{e^{-(\mu_{12}+\mu_{13})t_i}}{(\mu_{12}+\mu_{13})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}}} \tag{6.12}$$

Since censored $\delta_i = 0$ and therefore (6.12) becomes

$$\begin{aligned} \frac{\partial l}{\partial \mu_{12}} &= \sum_{i=1}^{n} \frac{\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}} - \dfrac{e^{(\mu_{12}+\mu_{13})t_i}}{(\mu_{12}+\mu_{13})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}}} \\ &= \sum_{i=1}^{n} \frac{-t_i e^{(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}+e^{-(\mu_{12}+\mu_{13})t_i}} - \sum_{i=1} \frac{e^{(\mu_{12}+\mu_{13})t_i}}{(\mu_{12}+\mu_{13})\left(\mu_{12}+\mu_{13}+e^{-(\mu_{12}+\mu_{13})t_i}\right)} \\ &= \sum_{i=1}^{n} \frac{-e^{(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}+e^{-(\mu_{12}+\mu_{13})t_i}} \left(\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{13}}\right) \end{aligned} \tag{6.13}$$

Equating (6.13) to zero then

$$\begin{aligned}\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{13}} &= 0 \\ \frac{1}{\sum_{i=1}^{n} t_i} &= -(\mu_{12}+\mu_{13}) \\ \mu_{12} &= \mu_{13} - \frac{1}{\sum_{i=1}^{n} t_i} \end{aligned} \tag{6.14}$$

If we assume that all get infected and therefore there are no deaths from healthy individuals then $\mu_{13} = 0$ resulting in

$$\hat{\mu_{12}} = -\frac{1}{\sum_{i=1}^{n} t_i} \tag{6.15}$$

Similarly in order to estimate μ_{13} we differentiate(6.11) with respect to μ_{13}

$$\frac{\partial l}{\partial \mu_{13}} = -\sum_{i=1}^{n} \left(\delta_i \ln t_i e^{-(\mu_{12}+\mu_{13})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}} - \dfrac{e^{-(\mu_{12}+\mu_{13})t_i}}{(\mu_{12}+\mu_{13})^2}\right)}{1+\dfrac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}}} \tag{6.16}$$

With censoring $\delta_i = 0$ and therefore

$$\begin{aligned}\frac{\partial l}{\partial \mu_{13}} &= \sum_{i=1}^{n} \frac{\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}} - \dfrac{e^{-(\mu_{12}+\mu_{13})t_i}}{(\mu_{12}+\mu_{13})^2}\right)}{1+\dfrac{e^{-(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}}} \\ &= \sum_{i=1}^{n} \frac{-t_i e^{(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}+e^{-(\mu_{12}+\mu_{13})t_i}} + \sum_{i=1}^{n} \frac{-e^{(\mu_{12}+\mu_{13})t_i}}{(\mu_{12}+\mu_{13})\left(\mu_{12}+\mu_{13}+e^{-(\mu_{12}+\mu_{13})t_i}\right)} \\ &= \sum_{i=1}^{n} \frac{-e^{(\mu_{12}+\mu_{13})t_i}}{\mu_{12}+\mu_{13}+e^{-(\mu_{12}+\mu_{13})t_i}} \left(\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{13}}\right) \end{aligned} \tag{6.17}$$

Equating (6.17) to zero then

$$\begin{aligned}\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{13}} &= 0 \\ \frac{1}{\sum_{i=1}^{n} t_i} &= -(\mu_{12}+\mu_{13}) \\ \mu_{13} &= \mu_{12} - \frac{1}{\sum_{i=1}^{n} t_i} \end{aligned} \tag{6.18}$$

Assuming everyone dies before being infected then $\mu_{12} = 0$
and therefore (6.18) becomes

$$\hat{\mu_{13}} = -\frac{1}{\sum_{i=1}^{n} t_i} \tag{6.19}$$

To estimate μ_{23} we use

$$P_{22}(s,t) = e^{-\mu_{23}t}$$

$$S_{22}(s,t) = 1 + \frac{e^{-\mu_{23}t}}{\mu_{23}}$$

Therefore

$$L = \prod_{i=1}^{n} \left(e^{-\mu_{23}t_i}\right)^{\delta_i} \left(1 + \frac{e^{-\mu_{23}t_i}}{\mu_{23}}\right)^{1-\delta_i}$$

and therefore

$$l = \sum_{i=1}^{n} \delta_i \ln e^{-\mu_{23}t_i} + \sum_{i=1}^{n} (1-\delta_i) \ln \left(1 + \frac{e^{-\mu_{23}t_i}}{\mu_{23}}\right) \tag{6.20}$$

Differentiating (6.20) with respect to μ_{23}

$$\frac{\partial l}{\partial \mu_{23}} = -\sum_{i=1}^{n} t_i \delta_i + \sum_{i=1}^{n} \left(\frac{(1-\delta_i)\dfrac{-t_i e^{-\mu_{23}t_i}}{\mu_{23}} - \dfrac{e^{-\mu_{23}t_i}}{\mu_{23}^2}}{1 + \dfrac{e^{-\mu_{23}t_i}}{\mu_{23}}} \right) \tag{6.21}$$

If censored then $\delta_i = 0$

$$\therefore \frac{\partial l}{\partial \mu_{23}} = -\sum_{i=1}^{n} \left(\frac{\dfrac{-t_i e^{-\mu_{23}t_i}}{\mu_{23}} - \dfrac{e^{-\mu_{23}t_i}}{\mu_{23}^2}}{1 + \dfrac{e^{-\mu_{23}t_i}}{\mu_{23}}} \right) \tag{6.22}$$

Equating (6.22) to zero

$$\begin{aligned} -\sum_{i=1}^{n} \frac{t_i e^{-\mu_{23}t_i}}{\mu_{23}} &= \sum_{i=1}^{n} \frac{e^{-\mu_{23}t_i}}{\mu_{23}^2} \\ \hat{\mu_{23}} &= -\frac{1}{\sum_{i=1}^{n} t_i} \end{aligned} \tag{6.23}$$

From the expressions obtained for the transition intensities for the three state model for a child born healthy the estimates are the recipricals of the total infection time.

Chapter 7

A FOUR STATE MODEL FOR A CHILD BORN HEALTHY

7.1 Introduction

We now consider the process of HIV infection as a four state model by extending the three state model in Figure 6.1 to consist of the following state space:
State 1=Healthy

State 2=Infected

State 3=AIDS

State 4=Death

Figure 7.1 shows the model with the combined effect of intervention. Individuals may

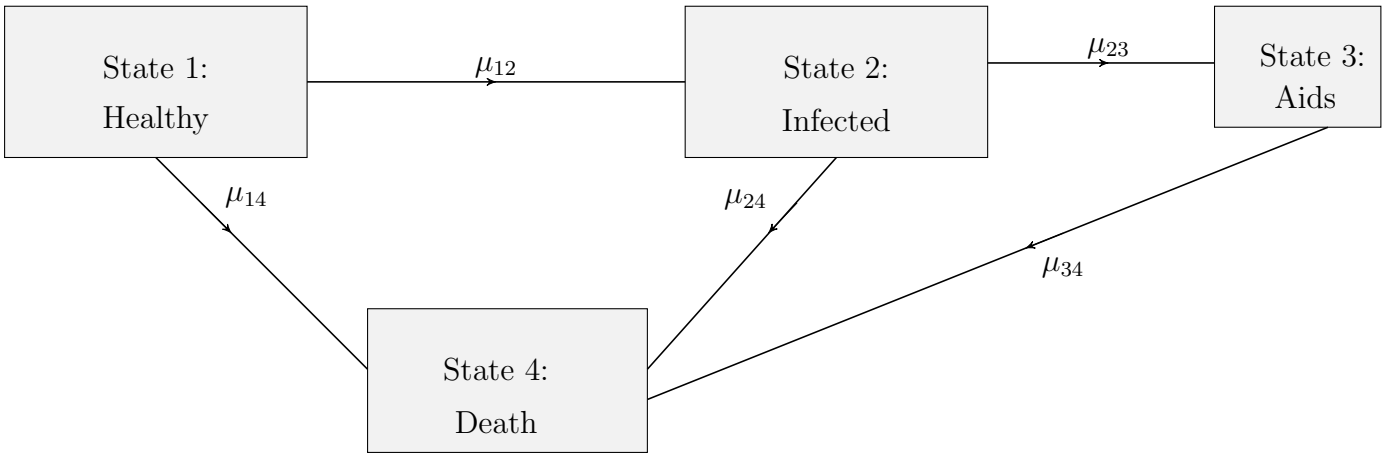

Figure 7.1: Healthy-Infected-Aids-Death Model

pass from the initial state (Healthy) to the Infected state with a proportion proceeding to the AIDS state and then to the absorbing state (Death). Individuals are at risk of death in each transient state (State $1, 2$ and 3)

7.2 Derivation of Forward Kolmogorov Differential Equations

This four state model forms the Chapman-Kolmogorov equations;

$$P_{ij}(s,t+h) = \sum_{k=1}^{4} P_{ik}(s,t)P_{kj}(t,t+h)$$

Thus we may derive the following transition probabilities

$$\begin{aligned}
P_{11}(s,t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k1}(t,t+h) \\
&= P_{11}(s,t)P_{11}(t,t+h) + P_{12}(s,t)P_{21}(t,t+h) + P_{13}(s,t)P_{31}(t,t+h) \\
&\quad + P_{14}(s,t)P_{41}(t,t+h) \\
&= P_{11}(s,t)((1-(\mu_{12}+\mu_{14}))h + 0(h)) + P_{12}(s,t)\cdot 0 + P_{13}(s,t)\cdot 0 + P_{14}(s,t)\cdot 0 \\
P_{11}^{'}(s,t) &= -P_{11}(s,t)(\mu_{12}+\mu_{14}) \qquad (7.1)
\end{aligned}$$

$$\begin{aligned}
P_{12}(s,t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k2}(t,t+h) \\
&= P_{11}(s,t)P_{12}(t,t+h) + P_{12}(s,t)P_{22}(t,t+h) + P_{13}(s,t)P_{32}(t,t+h) \\
&\quad + P_{14}(s,t)P_{42}(t,t+h) \\
&= P_{11}(s,t)((\mu_{12}h + 0(h)) + P_{12}(s,t)(1-(\mu_{23}+\mu_{24})h + 0(h)) + P_{13}(s,t)\cdot 0 \\
&\quad + P_{14}(s,t)\cdot 0 \\
P_{12}^{'}(s,t) &= P_{11}(s,t)\mu_{12} - P_{12}(s,t)(\mu_{23}+\mu_{24}) \qquad (7.2)
\end{aligned}$$

$$\begin{aligned}
P_{13}(s,t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k3}(t,t+h) \\
&= P_{11}(s,t)P_{13}(t,t+h) + P_{12}(s,t)P_{23}(t,t+h) + P_{13}(s,t)P_{33}(t,t+h) \\
&\quad + P_{14}(s,t)P_{43}(t,t+h) \\
&= P_{11}(s,t)\cdot 0 + P_{12}(s,t)(\mu_{23}h + 0(h)) + P_{13}(s,t)(1-\mu_{34}h + 0(h)) + P_{14}(s,t)\cdot 0 \\
P_{13}^{'}(s,t) &= P_{12}(s,t)\mu_{23} - P_{13}(s,t) + \mu_{34} \qquad (7.3)
\end{aligned}$$

$$
\begin{aligned}
P_{14}(s,t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k3}(t,t+h) \\
&= P_{11}(s,t)P_{14}(t,t+h) + P_{12}(s,t)P_{24}(t,t+h) + P_{13}(s,t)P_{34}(t,t+h) \\
&\quad + P_{14}(s,t)P_{44}(t,t+h) \\
&= P_{11}(s,t)(\mu_{14}h + 0(h)) + P_{12}(s,t)(\mu_{24}h + 0(h)) + P_{13}(s,t)(\mu_{34})h + 0(h)) \\
&\quad + P_{14}(s,t)(1 + 0(h)) \\
P_{14}^{'}(s,t) &= P_{11}(s,t)\mu_{14} + P_{12}(s,t)\mu_{24} + P_{13}(s,t)\mu_{34} \qquad (7.4)
\end{aligned}
$$

From equations given in (7.1), (7.2), (7.3) and (7.4) we get the transition matrix

$$
Q = \begin{pmatrix}
-(\mu_{12}+\mu_{14}) & \mu_{12} & 0 & \mu_{14} \\
0 & -(\mu_{23}+\mu_{24}) & \mu_{23} & \mu_{24} \\
0 & 0 & -\mu_{34} & \mu_{34} \\
0 & 0 & 0 & 0
\end{pmatrix}. \qquad (7.5)
$$

The eigen values for matrix in (7.5) are

$$
\begin{aligned}
\lambda_1 &= -\mu_{34} \\
\lambda_2 &= -\mu_{12} - \mu_{14} \\
\lambda_3 &= -\mu_{23} - \mu_{24} \\
\lambda_4 &= 0
\end{aligned}
$$

The matrix based on the eigen vectors is

$$
P = \begin{pmatrix}
\frac{\mu_{12}\mu_{23}}{(-\mu_{34}+\mu_{23}+\mu_{24})(-\mu_{34}+\mu_{12}+\mu_{14})} & 1 & \frac{\mu_{12}}{-\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14}} & 1 \\
\frac{\mu_{23}}{-\mu_{34}+\mu_{23}+\mu_{24}} & 0 & 1 & 1 \\
1 & 0 & 0 & 1 \\
0 & 0 & 0 & 1
\end{pmatrix}
$$

The inverse of P given as matrix S is

$$S = \begin{pmatrix} 0 & 0 & 1 & -1 \\ 1 & \frac{-\mu_{12}}{\vartheta} & \frac{\mu_{23}\mu_{12}}{\vartheta\Psi} & -\frac{-\mu_{24}\mu_{12}+\mu_{14}\mu_{12}+\mu_{34}\mu_{24}+\mu_{14}^2-\mu_{34}\mu_{14}+\mu_{34}\mu_{23}-\mu_{23}\mu_{14}-\mu_{24}\mu_{14}}{\vartheta\Psi} \\ 0 & 1 & \frac{-\mu_{23}}{\Omega} & -\frac{-\mu_{34}+\mu_{24}}{\Omega} \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

where

$$\begin{aligned} \vartheta &= -\mu_{23} - \mu_{24} + \mu_{12} + \mu_{14} \\ \Psi &= -\mu_{34} + \mu_{12} + \mu_{14} \\ \Omega &= -\mu_{34} + \mu_{23} + \mu_{24} \end{aligned}$$

Using matrix R where

$$R = \begin{pmatrix} e^{\lambda_1 t} - 1 & 0 & 0 & 0 \\ 0 & e^{\lambda_2 t} - 1 & 0 & 0 \\ 0 & 0 & e^{\lambda_3 t} - 1 & 0 \\ 0 & 0 & 0 & e^{\lambda_4 t} - 1 \end{pmatrix}$$

together with matrix P and S and multiplying them in the form PRS we get the matrix of transition probabilities. The matrix of transition probabilities is given by

$$P(s,t) = I + PRS \tag{7.6}$$

where I is the identity matrix such that

$$P(s,t) = \begin{pmatrix} P_{11}(s,t) & P_{12}(s,t) & P_{13}(s,t) & P_{14}(s,t) \\ P_{21}(s,t) & P_{22}(s,t) & P_{23}(s,t) & P_{24}(s,t) \\ P_{31}(s,t) & P_{32}(s,t) & P_{33}(s,t) & P_{34}(s,t) \\ P_{41}(s,t) & P_{42}(s,t) & P_{43}(s,t) & P_{44}(st) \end{pmatrix}$$

and

$$
\begin{aligned}
P_{11}(s,t) &= e^{\lambda_2 t} \\
P_{12}(s,t) &= \frac{-(e^{\lambda_2 t}-1)\mu_{12}}{-\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14}} + \frac{\mu_{12}(e^{\lambda_3 t}-1)}{\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14}} \\
P_{13}(s,t) &= \frac{\mu_{12}\mu_{23}(e^{\lambda_1 t}-1)}{(-\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14})(-\mu_{34}+\mu_{12}+\mu_{14})} \\
&\quad + \frac{(e^{\lambda_2 t}-1)\mu_{23}\mu_{12}}{(-\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14})(-\mu_{34}+\mu_{12}+\mu_{14})} \\
&\quad - \frac{\mu_{12}(e^{\lambda_3 t}-1)\mu_{23}}{(-\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14})(-\mu_{34}+\mu_{12}+\mu_{14})} \\
P_{14}(s,t) &= -\frac{\mu_{12}\mu_{13})(e^{\lambda_1 t}-1)}{(-\mu_{34}+\mu_{23}+\mu_{24})(-\mu_{34}+\mu_{12}+\mu_{14})} \\
&\quad - \frac{-(e^{\lambda_2 t}-1)(-\mu_{24}\mu_{12}+\mu_{23}\mu_{34}+\mu_{34}\mu_{24}-\mu_{14}\mu_{34}\mu_{14}-\mu_{23}\mu_{14}-\mu_{24}\mu_{14}+\mu_{14}\mu_{12}+\mu_{14}^2)}{(-\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14})(-\mu_{34}+\mu_{12}+\mu_{14})} \\
&\quad - \frac{\mu_{12}(e^{\lambda_3 t}-1)(-\mu_{34}+\mu_{24})}{(-\mu_{23}-\mu_{24}+\mu_{12}+\mu_{14})(-\mu_{34}+\mu_{23}+\mu_{24})} + (e^{\lambda_4 t}-1) \\
P_{21}(s,t) &= 0 \\
P_{22}(s,t) &= e^{\lambda_3 t} \\
P_{23}(s,t) &= \frac{\mu_{23}(e^{\lambda_2 t}-1)}{(-\mu_{34}+\mu_{23}+\mu_{24})} - \frac{(e^{\lambda_3 t}-1)\mu_{23}}{-\mu_{34}+\mu_{23}+\mu_{24}} \\
P_{24}(s,t) &= -\frac{-\mu_{23}(e^{\lambda_1 t}-1)}{-\mu_{34}+\mu_{23}+\mu_{24}} - 1 - \frac{(e^{\lambda_3 t}-1)(-\mu_{34}+\mu_{24})}{-\mu_{34}+\mu_{23}+\mu_{24}} \\
P_{31}(s,t) &= 0 \\
P_{32}(s,t) &= 0 \\
P_{33}(s,t) &= e^{\lambda_1 t} \\
P_{34}(s,t) &= -e^{-\lambda_1 t} + e^{\lambda_4 t}
\end{aligned}
$$

$$
\begin{aligned}
P_{41}(s,t) &= 0 \\
P_{42}(s,t) &= 0 \\
P_{43}(s,t) &= 0 \\
P_{44}(s,t) &= e^{\lambda_4 t}
\end{aligned}
$$

Simplifying and adding we note that

$$
\begin{aligned}
P_{11}(s,t) + P_{12}(s,t) + P_{13}(s,t) + P_{14}(s,t) &= e^{\lambda_4 t} = 1 \\
P_{21}(s,t) + P_{22}(s,t) + P_{23}(s,t) + P_{24}(s,t) &= e^{\lambda_4 t} = 1 \\
P_{31}(s,t) + P_{32}(s,t) + P_{33}(s,t) + P_{34}(s,t) &= e^{\lambda_4 t} = 1 \\
P_{41}(s,t) + P_{42}(s,t) + P_{43}(s,t) + P_{44}(s,t) &= e^{\lambda_4 t} = 1
\end{aligned}
$$

7.3 Estimation for Right Censoring

From Figure 7.1, we estimate $\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{34}$
To estimate μ_{12} and μ_{12} we use

$$
\begin{aligned}
P_{11}(s,t) &= e^{-(\mu_{12}+\mu_{14})t} \\
\therefore S_{11}(s,t) &= 1 + \frac{e^{-(\mu_{12}+\mu_{14})t}}{\mu_{12}+\mu_{14}}
\end{aligned}
$$

The likelihood function is

$$
L = \prod_{i=1}^{n} \left(e^{-(\mu_{12}+\mu_{14})t_i}\right)^{\delta_i} \left(1 + \frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right)^{1-\delta_i} \tag{7.7}
$$

Taking the log of (7.7) we get

$$
\begin{aligned}
l &= \sum_{i=1}^{n} \delta_i \ln\left(e^{-(\mu_{12}+\mu_{14})t_i}\right) + \sum_{i=1}^{n} (1-\delta_i) \ln\left(1 + \frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right) \\
&= -\sum_{i=1}^{n} \delta_i (\mu_{12}+\mu_{14}) t_i + \sum_{i=1}^{n} (1-\delta_i) \ln\left(1 + \frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right) \qquad (7.8)
\end{aligned}
$$

Since censored $\delta_i = 0$ and (7.8) simplifies to

$$
l = \sum_{i=1}^{n} \ln\left(1 + \frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right) \tag{7.9}
$$

Differentiating (7.9) with respect to μ_{12}

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{12}} &= \sum_{i=1}^{n} \frac{\left(\frac{-t_i e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}} - \frac{e^{-(\mu_{12}+\mu_{14})t_i}}{(\mu_{12}+\mu_{14})^2}\right)}{1+\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}} \\
&= \sum_{i=1}^{n} \left(\left(\frac{-t_i e^{-(\mu_{12}+\mu_{14})t_i}}{\left(1+\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right)(\mu_{12}+\mu_{14})} \right) - \left(\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\left(1+\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right)(\mu_{12}+\mu_{14})} \right) \right) \\
&= -\sum_{i=1}^{n} \left(\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\left(1+\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right)(\mu_{12}+\mu_{14})} \right) \left(t_i + \frac{1}{\mu_{12}+\mu_{14}} \right) \qquad (7.10)
\end{aligned}$$

If $\left(\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{14}}\right) = 0$, then

$$\sum_{i=1}^{n} t_i = -\frac{1}{\mu_{12}+\mu_{14}} \qquad (7.11)$$

Assuming everyone gets infected and therefore no deaths occur then $\mu_{14} = 0$ resulting in

$$\hat{\mu_{12}} = -\frac{1}{\sum_{i=1}^{n} t_i} \qquad (7.12)$$

Similarly in order to estimate μ_{14} we differentiate (7.8) with respect to μ_{14}

$$\frac{\partial l}{\partial \mu_{14}} = -\sum_{i=1}^{n} \left(\delta_i \ln t_i e^{-(\mu_{12}+\mu_{14})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\frac{-t_i e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}} - \frac{e^{-(\mu_{12}+\mu_{14})t_i}}{(\mu_{12}+\mu_{14})^2}\right)}{1+\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}} \qquad (7.13)$$

Due to censoring $\delta_i = 0$ and therefore

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{14}} &= \sum_{i=1}^{n} \frac{\left(\frac{-t_i e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}} - \frac{e^{-(\mu_{12}+\mu_{14})t_i}}{(\mu_{12}+\mu_{14})^2}\right)}{1+\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}} \\
&= -\sum_{i=1}^{n} \left(\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\left(1+\frac{e^{-(\mu_{12}+\mu_{14})t_i}}{\mu_{12}+\mu_{14}}\right)(\mu_{12}+\mu_{14})} \right) \left(t_i + \frac{1}{\mu_{12}+\mu_{14}} \right) \qquad (7.14)
\end{aligned}$$

Since

$$\left(\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{14}}\right) = 0 \tag{7.15}$$

then

$$\sum_{i=1}^{n} t_i = -\frac{1}{\mu_{12}+\mu_{14}} \tag{7.16}$$

Assuming everyone dies before being infected then $\mu_{12} = 0$
and therefore

$$\hat{\mu_{14}} = -\frac{1}{\sum_{i=1}^{n} t_i} \tag{7.17}$$

Further, to estimate μ_{23} and μ_{24} we use

$$\begin{aligned} P_{11}(s,t) &= e^{-(\mu_{23}+\mu_{24})t} \\ \therefore S_{11}(s,t) &= 1 + \frac{e^{-(\mu_{23}+\mu_{24})t}}{\mu_{23}+\mu_{24}} \end{aligned}$$

The likelihood function is

$$L = \prod_{i=1}^{n} \left(e^{-(\mu_{23}+\mu_{24})t_i}\right)^{\delta_i} \left(1 + \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}}\right)^{1-\delta_i} \tag{7.18}$$

Taking the log of (7.18) we get

$$l = \sum_{i=1}^{n} \delta_i \ln\left(e^{-(\mu_{23}+\mu_{24})t_i}\right) + \sum_{i=1}^{n} (1-\delta_i) \ln\left(1 + \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}}\right) \tag{7.19}$$

Differentiating (7.19) with respect to μ_{23}

$$\frac{\partial l}{\partial \mu_{23}} = -\sum_{i=1}^{n} \left(\delta_i \ln t_i e^{-(\mu_{23}+\mu_{24})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\frac{-t_i e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}} - \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{(\mu_{23}+\mu_{24})^2}\right)}{1 + \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}}} \tag{7.20}$$

Since censoring has occured (7.24) becomes

$$\begin{aligned} \frac{\partial l}{\partial \mu_{23}} &= \sum_{i=1}^{n} \frac{\left(\frac{-t_i e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}} - \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{(\mu_{23}+\mu_{24})^2}\right)}{1 + \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}}} \\ &= -\sum_{i=1}^{n} \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}+e^{-(\mu_{23}+\mu_{23})t_i}} \left(\sum_{i=1}^{n} t_i + \frac{1}{\mu_{23}+\mu_{24}}\right) \end{aligned} \tag{7.21}$$

Equating to zero

$$\begin{aligned}\sum_{i=1}^{n} t_i + \frac{1}{\mu_{23}+\mu_{24}} &= 0\\ \frac{1}{\sum_{i=1}^{n} t_i} &= -(\mu_{23}+\mu_{24})\\ \mu_{23} &= -\mu_{24} - \frac{1}{\sum_{i=1}^{n} t_i} \qquad (7.22)\end{aligned}$$

Assuming everyone who gets infected proceeds to the Aids state and no deaths occur then $\mu_{24} = 0$ and therefore

$$\hat{\mu_{23}} = -\frac{1}{\sum_{i=1}^{n} t_i} \qquad (7.23)$$

Similarly in order to estimate μ_{24} we differentiate(7.19) with respect to μ_{24}

$$\frac{\partial l}{\partial \mu_{23}} = -\sum_{i=1}^{n}\left(\delta_i \ln t_i e^{-(\mu_{23}+\mu_{24})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}} - \dfrac{e^{-(\mu_{23}+\mu_{24})t_i}}{(\mu_{23}+\mu_{24})^2}\right)}{1+\dfrac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}}} \qquad (7.24)$$

Since censoring has occured (7.24) becomes

$$\begin{aligned}\frac{\partial l}{\partial \mu_{23}} &= \sum_{i=1}^{n} \frac{\left(\dfrac{-t_i e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}} - \dfrac{e^{-(\mu_{23}+\mu_{24})t_i}}{(\mu_{23}+\mu_{24})^2}\right)}{1+\dfrac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}}}\\ &= -\sum_{i=1}^{n} \frac{e^{-(\mu_{23}+\mu_{24})t_i}}{\mu_{23}+\mu_{24}+e^{-(\mu_{23}+\mu_{23})t_i}}\left(\sum_{i=1}^{n} t_i + \frac{1}{\mu_{23}+\mu_{24}}\right) \qquad (7.25)\end{aligned}$$

Equating to zero

$$\begin{aligned}\sum_{i=1}^{n} t_i + \frac{1}{\mu_{23}+\mu_{24}} &= 0\\ \frac{1}{\sum_{i=1}^{n} t_i} &= -(\mu_{23}+\mu_{24})\\ \mu_{24} &= -\mu_{23} - \frac{1}{\sum_{i=1}^{n} t_i} \qquad (7.26)\end{aligned}$$

Assuming everyone who gets infected dies before proceeding to the Aids state then $\mu_{23} = 0$ and therefore

$$\hat{\mu_{24}} = -\frac{1}{\sum_{i=1}^{n} t_i} \qquad (7.27)$$

In order to estimate μ_{34} we use

$$\begin{aligned}P_{22}(s,t) &= e^{-\mu_{34}t}\\ S_{22}(s,t) &= 1+\frac{e^{-\mu_{34}t}}{\mu_{34}}\end{aligned}$$

Therefore

$$L = \prod_{i=1}^{n} \left(e^{-\mu_{34} t_i}\right)^{\delta_i} \left(1 + \frac{e^{-\mu_{34} t_i}}{\mu_{34}}\right)^{1-\delta_i}$$

and therefore

$$l = \sum_{i=1}^{n} \delta_i \ln e^{-\mu_{34} t_i} + \sum_{i=1}^{n} (1-\delta_i) \ln \left(1 + \frac{e^{-\mu_{34} t_i}}{\mu_{34}}\right) \tag{7.28}$$

Differentiating (7.28) with respect to μ_{34}

$$\frac{\partial l}{\partial \mu_{34}} = -\sum_{i=1}^{n} t_i \delta_i + \sum_{i=1}^{n} \left(\frac{(1-\delta_i)\dfrac{-t_i e^{-\mu_{34} t_i}}{\mu_{34}} - \dfrac{e^{-\mu_{34} t_i}}{\mu_{34}^2}}{1 + \dfrac{e^{-\mu_{34} t_i}}{\mu_{34}}} \right) \tag{7.29}$$

If censored then $\delta_i = 0$

$$\begin{aligned} \therefore \frac{\partial l}{\partial \mu_{34}} &= -\sum_{i=1}^{n} \left(\frac{\dfrac{-t_i e^{-\mu_{34} t_i}}{\mu_{34}} - \dfrac{e^{-\mu_{34} t_i}}{\mu_{34}^2}}{1 + \dfrac{e^{-\mu_{34} t_i}}{\mu_{34}}} \right) \\ &= \sum_{i=1}^{n} \frac{e^{-\mu_{34} t_i}(\mu_{34} t_i + 1)}{\mu_{34}(\mu_{34} + e^{-\mu_{34} t_i})} \\ &= \sum_{i=1}^{n} \frac{(\mu_{34} t_i + 1)}{\mu_{34}} \left(\frac{e^{-\mu_{34} t_i}}{\mu_{34} + e^{-\mu_{34} t_i}} \right) \end{aligned} \tag{7.30}$$

Equating $\sum_{i=1}^{n} \dfrac{\mu_{34} t_i + 1}{\mu_{34}}$ to zero then

$$\begin{aligned} \sum_{i=1}^{n} t_i + \frac{1}{\mu_{34}} &= 0 \\ \hat{\mu_{34}} &= -\frac{1}{\sum_{i=1}^{n} t_i} \end{aligned} \tag{7.31}$$

The expressions of the transition intensities for the n individuals are expressed in the form of the total time of the individuals observed.

Chapter 8

A FIVE STATE MODEL FOR A CHILD BORN HEALTHY

8.1 Introduction

In the mother-to-child transmission (MTCT) of HIV an infant can experience one of these events: (i) HIV infection, (ii) weaning prior to HIV infection, (iii) death prior to HIV infection, or (iv) death after HIV infection.

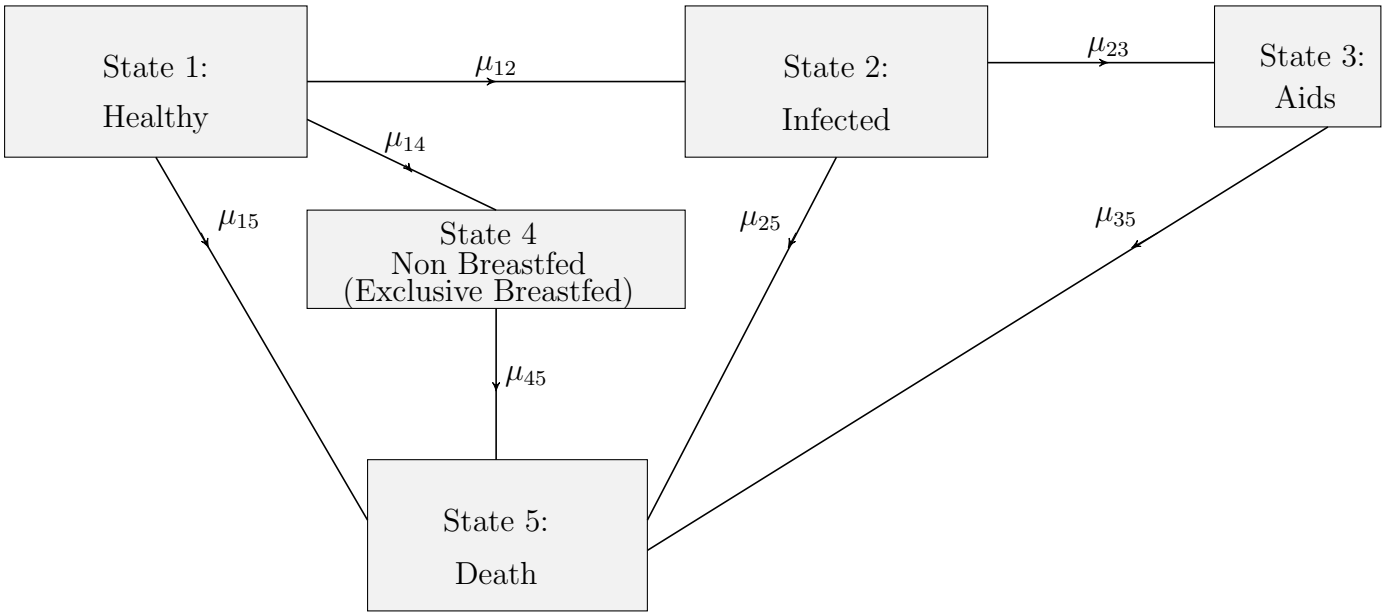

Figure 8.1: Healthy-Breastfeeding/Nonbreastfeeding-Infected-Aids-Death Model

Derivation of Forward Kolmogorov Differential Equations

We obtain the following differential equations for Figure 8.1

$$\begin{aligned}
P_{11}(s,t+h) &= \sum_{k=1}^{5} P_{1k}(s,t)P_{k1}(t,t+h) \\
&= P_{11}(s,t)P_{11}(t,t+h) + P_{12}(s,t)P_{21}(t,t+h) + P_{13}(s,t)P_{31}(t,t+h) \\
&\quad + P_{14}(s,t)P_{41}(t,t+h) + P_{15}(s,t)P_{51} \\
&= P_{11}(s,t)(1-(\mu_{12}+\mu_{14}+\mu_{15})h+o(h)) + P_{12}(s,t)\cdot 0 + P_{13}(s,t)\cdot 0 + P_{14}(s,t)\cdot 0 \\
&\quad + P_{15}(s,t)\cdot 0 \\
P_{11}'(s,t) &= -P_{11}(s,t)(\mu_{12}+\mu_{14}+\mu_{15}) \qquad (8.1)
\end{aligned}$$

$$\begin{aligned}
P_{12}(s,t+h) &= \sum_{k=1}^{5} P_{1k}(s,t)P_{k2}(t,t+h) \\
&= P_{11}(s,t)P_{12}(t,t+h) + P_{12}(s,t)P_{22}(t,t+h) + P_{13}(s,t)P_{32}(t,t+h) \\
&\quad + P_{14}(s,t)P_{42}(t,t+h) + P_{15}(s,t)P_{52}(t,t+h) \\
&= P_{11}(s,t)((\mu_{12}h+o(h)) + P_{12}(s,t)(1-(\mu_{23}+\mu_{25})h+o(h)) + P_{13}(s,t)\cdot 0 \\
&\quad + P_{14}(s,t)\cdot 0 + P_{15}(s,t)\cdot 0 \\
P_{12}'(s,t) &= P_{11}(s,t)\mu_{12} - P_{12}(s,t)(\mu_{23}+\mu_{25}) \qquad (8.2)
\end{aligned}$$

$$\begin{aligned}
P_{13}(s,t+h) &= \sum_{k=1}^{5} P_{1k}(s,t)P_{k3}(t,t+h) \\
&= P_{11}(s,t)P_{13}(t,t+h) + P_{12}(s,t)P_{23}(t,t+h) + P_{13}(s,t)P_{33}(t,t+h) \\
&\quad + P_{14}(s,t)P_{43}(t,t+h) + P_{15}(s,t)P_{53} \\
&= P_{11}(s,t)\cdot 0 + P_{12}(s,t)(\mu_{23}h+o(h)) + P_{13}(s,t)(1-\mu_{35})h+o(h)) + P_{14}(s,t)\cdot 0 \\
&\quad + P_{15}(s,t)\cdot 0 \\
P_{13}'(s,t) &= P_{12}(s,t)\mu_{23} - P_{13}(s,t)\mu_{35} \qquad (8.3)
\end{aligned}$$

$$
\begin{aligned}
P_{14}(s,t+h) &= \sum_{k=1}^{5} P_{1k}(s,t)P_{k4}(t,t+h) \\
&= P_{11}(s,t)P_{14}(t,t+h) + P_{12}(s,t)P_{24}(t,t+h) + P_{13}(s,t)P_{34}(t,t+h) \\
&\quad + P_{14}(s,t)P_{44}(t,t+h) + P_{15}(s,t)P_{54}(t,t+h) \\
&= P_{11}(s,t)(\mu_{14}h + o(h)) + P_{12}(s,t)\cdot 0 + P_{13}\cdot 0 \\
&\quad + P_{14}(s,t)(1-\mu_{45}h + o(h)) + P_{15}(s,t)\cdot 0 \\
P_{14}^{'}(s,t) &= P_{11}(s,t)\mu_{14} - P_{14}(s,t)\mu_{45} \qquad (8.4)
\end{aligned}
$$

$$
\begin{aligned}
P_{15}(s,t+h) &= \sum_{k=1}^{5} P_{1k}(s,t)P_{k5}(t,t+h) \\
&= P_{11}(s,t)P_{15}(t,t+h) + P_{12}(s,t)P_{25}(t,t+h) + P_{13}(s,t)P_{35}(t,t+h) \\
&\quad + P_{14}(s,t)P_{45}(t,t+h) + P_{15}(s,t)P_{55}(t,t+h) \\
&= P_{11}(s,t)(\mu_{15}h + o(h)) + P_{12}(s,t)(\mu_{25}h + o(h)) + P_{13}(\mu_{35}h + o(h)) \\
&\quad + P_{14}(s,t)(\mu_{45}h + o(h)) + P_{15}(s,t)(1 + o(h)) \\
P_{15}^{'}(s,t) &= P_{11}(s,t)\mu_{15} + P_{12}(s,t)\mu_{25} + P_{13}(s,t)\mu_{35} + P_{14}(s,t)\mu_{45} \qquad (8.5)
\end{aligned}
$$

From these differential equations we obtain the transition matrix for the five state

$$
Q = \begin{pmatrix}
-(\mu_{12}+\mu_{14}+\mu_{15}) & \mu_{12} & 0 & \mu_{14} & \mu_{15} \\
0 & -(\mu_{23}+\mu_{25}) & \mu_{23} & 0 & \mu_{25} \\
0 & 0 & -\mu_{35} & 0 & \mu_{35} \\
0 & 0 & 0 & -\mu_{45} & \mu_{45} \\
0 & 0 & 0 & 0 & 0
\end{pmatrix}. \qquad (8.6)
$$

which has eigen values

$$
\begin{aligned}
\lambda_1 &= -\mu_{35} \\
\lambda_2 &= -\mu_{12} - \mu_{14} - \mu_{15} \\
\lambda_3 &= -\mu_{23} - \mu_{25} \\
\lambda_4 &= -\mu_{45} \\
\lambda_5 &= 0
\end{aligned}
$$

and the matrix of eigen vectors

$$P = \begin{pmatrix} \frac{\mu_{12}\mu_{23}}{(-\mu_{35}+\mu_{23}+\mu_{25})(-\mu_{35}+\mu_{12}+\mu_{14}+\mu_{15})} & 1 & \frac{\mu_{12}}{\mu_{12}+\mu_{14}+\mu_{15}-\mu_{23}-\mu_{25}} & \frac{\mu_{14}}{\mu_{12}+\mu_{14}+\mu_{15}-\mu_{45}} & 1 \\ \frac{\mu_{23}}{-\mu_{35}+\mu_{23}+\mu_{25}} & 0 & 1 & 0 & 1 \\ 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

and .

$$S = \begin{pmatrix} 0 & 0 & 1 & 0 & -1 \\ 1 & \frac{\mu_{12}}{\phi} & \frac{\mu_{23}\mu_{12}}{\eta\phi} & \frac{-\mu_{14}}{\mu_{12}+\mu_{14}+\mu_{15}-\mu_{45}} & -\frac{-\mu_{45}\mu_{35\rho}+\mu_{45}\tau+\mu_{35}\kappa+\mu_{12}\mu_{14}\varphi+\mu_{15}\Psi-\mu_{25}\mu_{12}^2+\mu_{15}\mu_{14}^2+2\mu_{14}\mu_{15}^2-\mu_{45}\mu_{14}^2+\mu_{15}\varsigma}{\phi(\mu_{12}+\mu_{14}+\mu_{15}-\mu_{45})\eta} \\ 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

where

$$\begin{aligned}
\phi &= \mu_{12}+\mu_{14}+\mu_{15}-\mu_{23}-\mu_{25}\\
\eta &= -\mu_{35}+\mu_{12}+\mu_{14}+\mu_{15}\\
\rho &= \mu_{23}+\mu_{25}+\mu_{14}+\mu_{15}\\
\tau &= \mu_{23}\mu_{14}+\mu_{23}\mu_{15}+\mu_{25}\mu_{13}+\mu_{25}\mu_{14}+\mu_{25}\mu_{15}\\
\kappa &= \mu_{12}\mu_{23}+\mu_{23}\mu_{15}+\mu_{25}\mu_{12}+\mu_{25}\mu_{15}\\
\varphi &= 2\mu_{14}-\mu_{45}-\mu_{25}\\
\Psi &= -2\mu_{25}\mu_{12}-2\mu_{45}\mu_{14}+\mu_{15}^2+\mu_{12}^2+2\mu_{12}\mu_{15}\\
\varsigma &= -\mu_{35}\mu_{15}-\mu_{23}\mu_{15}-\mu_{25}\mu_{15}-\mu_{35}\mu_{12}-\mu_{35}\mu_{14}-\mu_{12}\mu_{13}-\mu_{14}\mu_{23}-\mu_{14}\mu_{25}-\mu_{45}\mu_{15}-\mu_{45}\mu_{12}
\end{aligned}$$

We multiply the matrices PRS and summing the result obained to the 5 by 5 identity matrix to obtain the matix of transition probabilities given as

$$P(s,t)=\begin{pmatrix}
e^{\lambda_2 t} & \frac{\varpi\mu_{12}}{\phi}+\frac{\mu_{12}(e^{\lambda_3 t}-1)}{\phi} & \frac{\nu\Xi}{\Omega\eta}+\frac{\varpi\nu}{\phi\eta}-\frac{\nu(e^{\lambda_3 t}-1)}{\phi\Omega} & -\frac{\varpi\mu_{14}}{\phi}+\frac{\mu_{14}(e^{\lambda_4 t}-1)}{\phi} & \frac{-(e^{\lambda_1 t}-1)\mu_{12}\mu_{13}}{(\mu_{23}+\mu_{25}-\mu_{35})(\mu_{12}+\mu_{14}+\mu_{15}-\mu_{35})}+\Theta\\
0 & e^{\lambda_3 t} & \frac{\mu_{23}\Xi}{\Omega}-\frac{(e^{\lambda_3 t}-1)\mu_{23}}{\Omega} & 0 & \frac{-\mu_{23}\Xi}{\Omega}-1-\frac{(e^{\lambda_3 t}-1)(-\mu_{35}+\mu_{25})}{\Omega}+e^{\lambda_5 t}\\
0 & 0 & e^{\lambda_1 t} & 0 & -e^{\lambda_1 t}+e^{\lambda_5 t}\\
0 & 0 & 0 & e^{\lambda_4 t} & -e^{\lambda_4 t}+e^{\lambda_5 t}\\
0 & 0 & 0 & 0 & e^{\lambda_5 t}
\end{pmatrix}$$

where

$$
\begin{aligned}
\Xi &= e^{\lambda_1 t-1} \\
\varpi &= e^{\lambda_2 t}-1 \\
\nu &= \mu_{12}\mu_{23} \\
\Omega &= -\mu_{35}+\mu_{23}+\mu_{25} \\
\phi &= \mu_{12}+\mu_{14}+\mu_{15}-\mu_{23}-\mu_{25} \\
\eta &= -\mu_{35}+\mu_{12}+\mu_{14}+\mu_{15} \\
\rho &= \mu_{23}+\mu_{25}+\mu_{14}+\mu_{15} \\
\tau &= \mu_{23}\mu_{14}+\mu_{23}\mu_{15}+\mu_{25}\mu_{13}+\mu_{25}\mu_{14}+\mu_{25}\mu_{15} \\
\kappa &= \mu_{12}\mu_{23}+\mu_{23}\mu_{15}+\mu_{25}\mu_{12}+\mu_{25}\mu_{15} \\
\varphi &= 2\mu_{14}-\mu_{45}-\mu_{25} \\
\Psi &= -2\mu_{25}\mu_{12}-2\mu_{45}\mu_{14}+\mu_{15}^2+\mu_{12}^2+2\mu_{12}\mu_{15} \\
\varsigma &= -\mu_{35}\mu_{15}-\mu_{23}\mu_{15}-\mu_{25}\mu_{15}-\mu_{35}\mu_{12}-\mu_{35}\mu_{14}-\mu_{12}\mu_{13}-\mu_{14}\mu_{23}-\mu_{14}\mu_{25}-\mu_{45}\mu_{15}-\mu_{45}\mu_{12}
\end{aligned}
$$

8.2 Estimation for Right Censoring

From Figure 8.1, we estimate $\mu_{12}, \mu_{14}, \mu_{15}, \mu_{23}, \mu_{25}, \mu_{35}, \mu_{45}$
To estimate μ_{12}, μ_{14} and μ_{15} we use

$$\begin{aligned} P_{11}(s,t) &= e^{-(\mu_{12}+\mu_{14}+\mu_{15})t} \\ \therefore S_{11}(s,t) &= 1 + \frac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t}}{\mu_{12}+\mu_{14}+\mu_{15}} \end{aligned}$$

The likelihood function is

$$L = \prod_{i=1}^{n} \left(e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}\right)^{\delta_i} \left(1 + \frac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}\right)^{1-\delta_i} \tag{8.7}$$

Taking the log of (8.7) we get

$$l = \sum_{i=1}^{n} \delta_i \ln\left(e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}\right) + \sum_{i=1}^{n} (1-\delta_i) \ln\left(1 + \frac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}\right) \tag{8.8}$$

Differentiating (8.8) with respect to μ_{12}

$$\frac{\partial l}{\partial \mu_{12}} = -\sum_{i=1}^{n} \left(\delta_i \ln t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}} - \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{(\mu_{12}+\mu_{14}+\mu_{15})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}} \tag{8.9}$$

Since censored $\delta_i = 0$ and therefore

$$\begin{aligned} \frac{\partial l}{\partial \mu_{12}} &= \sum_{i=1}^{n} \frac{\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}} - \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{(\mu_{12}+\mu_{14}+\mu_{15})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}} \\ &= -\sum_{i=1}^{n} \left(\frac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\left(1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}\right)(\mu_{12}+\mu_{14}+\mu_{15})}\right)\left(t_i + \frac{1}{\mu_{12}+\mu_{14}+\mu_{15}}\right) \end{aligned} \tag{8.10}$$

Equating (8.10) to zero and since $e^x > 0$ therefore

$$\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{14}+\mu_{15}} = 0 \tag{8.11}$$

$$\mu_{12}+\mu_{14}+\mu_{15} = -\frac{1}{\sum_{i=1}^{n} t_i} \tag{8.12}$$

$$\hat{\mu_{12}} = -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{14} + \mu_{15}\right) \tag{8.13}$$

Assuming no deaths then $\mu_{14} = 0$ and

$$\hat{\mu_{12}} = -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{15}\right) \tag{8.14}$$

Assuming HIV positive mothers mix feed after giving birth then $\mu_{15} = 0$ and therefore

$$\hat{\mu_{12}} = -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{14}\right) \tag{8.15}$$

Assuming no deaths occur and infected mothers mix feed leading to postnatal transmission then μ_{14} and $\mu_{15} = 0$ and so

$$\hat{\mu_{12}} = -\frac{1}{\sum_{i=1}^{n} t_i} \tag{8.16}$$

Differentiating (8.8) with respect to μ_{14}

$$\frac{\partial l}{\partial \mu_{14}} = -\sum_{i=1}^{n} \left(\delta_i \ln t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}} - \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{(\mu_{12}+\mu_{14}+\mu_{15})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}}$$

Since censoring occurs $\delta_i = 0$ and therefore

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{14}} &= \sum_{i=1}^{n} \frac{\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}} - \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{(\mu_{12}+\mu_{14}+\mu_{15})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}} \\
&= -\sum_{i=1}^{n} \left(\frac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\left(1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}\right)(\mu_{12}+\mu_{14}+\mu_{15})}\right)\left(t_i + \frac{1}{\mu_{12}+\mu_{14}+\mu_{15}}\right)
\end{aligned} \tag{8.17}$$

Equating (8.17) to zero then

$$\begin{aligned}
\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{14}+\mu_{15}} &= 0 \\
\mu_{12}+\mu_{14}+\mu_{15} &= -\frac{1}{\sum_{i=1}^{n} t_i} \qquad (8.18) \\
\hat{\mu_{14}} &= -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{12} + \mu_{15}\right) \qquad (8.19)
\end{aligned}$$

Assuming no transmission takes place then $\mu_{12} = 0$ and

$$\hat{\mu_{14}} = -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{15}\right) \tag{8.20}$$

Assuming HIV positive mothers breastfeed after giving birth then $\mu_{15} = 0$ and therefore

$$\hat{\mu_{14}} = -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{12}\right) \tag{8.21}$$

Assuming no deaths occur and infected mothers do not breastfeed or exclusively breastfeed their infants resulting in no postnatal transmission then μ_{12} and $\mu_{15} = 0$ and so

$$\hat{\mu_{14}} = -\frac{1}{\sum_{i=1}^{n} t_i} \tag{8.22}$$

Differentiating (8.8) with respect to μ_{15}

$$\frac{\partial l}{\partial \mu_{15}} = -\sum_{i=1}^{n} \left(\delta_i \ln t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}\right) + \sum_{i=1}^{n} \frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}} - \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{(\mu_{12}+\mu_{14}+\mu_{15})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}}$$

Since censoring occurs $\delta_i = 0$ and therefore

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{15}} &= \sum_{i=1}^{n} \frac{\left(\dfrac{-t_i e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}} - \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{(\mu_{12}+\mu_{14}+\mu_{15})^2}\right)}{1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}} \\
&= -\sum_{i=1}^{n} \left(\frac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\left(1 + \dfrac{e^{-(\mu_{12}+\mu_{14}+\mu_{15})t_i}}{\mu_{12}+\mu_{14}+\mu_{15}}\right)(\mu_{12}+\mu_{14}+\mu_{15})} \right) \left(t_i + \frac{1}{\mu_{12}+\mu_{14}+\mu_{15}} \right)
\end{aligned} \tag{8.23}$$

Equating (8.23) to zero then

$$\sum_{i=1}^{n} t_i + \frac{1}{\mu_{12}+\mu_{14}+\mu_{15}}$$

$$\begin{aligned}
\mu_{12}+\mu_{14}+\mu_{15} &= -\frac{1}{\sum_{i=1}^{n} t_i} \\
\hat{\mu_{15}} &= -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{12} + \mu_{14}\right)
\end{aligned} \tag{8.24}$$

Assuming no deaths occur and infected mothers breastfeed their infants resulting in no postnatal transmission then μ_{12} and $\mu_{14} = 0$ and so

$$\hat{\mu_{15}} = -\frac{1}{\sum_{i=1}^{n} t_i} \tag{8.25}$$

To estimate μ_{23} and μ_{25} we use

$$\begin{aligned}
P_{22}(s,t) &= e^{-(\mu_{23}+\mu_{25})t} \\
\therefore S_{22}(s,t) &= 1 + \frac{e^{-(\mu_{23}+\mu_{25})t}}{\mu_{23}+\mu_{25}}
\end{aligned}$$

The likelihood function is

$$L = \prod_{i=1}^{n} \left(e^{-(\mu_{23}+\mu_{25})t_i}\right)^{\delta_i} \left(1 + \frac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}\right)^{1-\delta_i} \tag{8.26}$$

Taking the log of (8.26) we get

$$l = \sum_{i=1}^{n} \delta_i \ln\left(e^{-(\mu_{23}+\mu_{25})t_i}\right) + \sum_{i=1}^{n}(1-\delta_i)\ln\left(1+\frac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}\right) \tag{8.27}$$

Differentiating (8.27) with respect to μ_{23}

$$\frac{\partial l}{\partial \mu_{23}} = -\sum_{i=1}^{n}\left(\delta_i \ln t_i e^{-(\mu_{23}+\mu_{25})t_i}\right) + \sum_{i=1}^{n}\frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}} - \dfrac{e^{-(\mu_{23}+\mu_{25})t_i}}{(\mu_{23}+\mu_{25})^2}\right)}{1+\dfrac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}} \tag{8.28}$$

Due to censoring $\delta_i = 0$ and (8.29) becomes

$$\begin{aligned}
\frac{\partial l}{\partial \mu_{23}} &= \sum_{i=1}^{n}\frac{\left(\dfrac{-t_i e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}} - \dfrac{e^{-(\mu_{23}+\mu_{25})t_i}}{(\mu_{23}+\mu_{25})^2}\right)}{1+\dfrac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}} \\
&= -\sum_{i=1}^{n}\left(\frac{e^{-(\mu_{23}+\mu_{25})t_i}}{\left(1+\dfrac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}\right)(\mu_{23}+\mu_{25})}\right)\left(t_i+\frac{1}{\mu_{23}+\mu_{25}}\right) \qquad (8.29)
\end{aligned}$$

Equating (8.29) to zero

$$\begin{aligned}
\sum_{i=1}^{n} t_i + \frac{1}{\mu_{23}+\mu_{25}} &= 0 \\
\mu_{23}+\mu_{25} &= \frac{-1}{\sum_{i=1}^{n} t_i} \\
\hat{\mu_{23}} &= -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{25}\right) \qquad (8.30)
\end{aligned}$$

Assuming that none of the infected proceed children proceed to the Aids state then $\mu_{25} = 0$
and therefore

$$\hat{\mu_{23}} = \frac{-1}{\sum_{i=1}^{n} t_i} \tag{8.31}$$

Similarly in order to estimate μ_{25} we differentiate(8.27) with respect to μ_{25}

$$\frac{\partial l}{\partial \mu_{25}} = -\sum_{i=1}^{n}\left(\delta_i \ln t_i e^{-(\mu_{23}+\mu_{25})t_i}\right) + \sum_{i=1}^{n}\frac{(1-\delta_i)\left(\dfrac{-t_i e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}} - \dfrac{e^{-(\mu_{23}+\mu_{25})t_i}}{(\mu_{23}+\mu_{25})^2}\right)}{1+\dfrac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}} \tag{8.32}$$

Due to censoring $\delta_i = 0$ and (8.32) becomes

$$\begin{aligned}\frac{\partial l}{\partial \mu_{23}} &= \sum_{i=1}^{n} \frac{\left(\frac{-t_i e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}} - \frac{e^{-(\mu_{23}+\mu_{25})t_i}}{(\mu_{23}+\mu_{25})^2}\right)}{1+\frac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}} \\ &= -\sum_{i=1}^{n}\left(\frac{e^{-(\mu_{23}+\mu_{25})t_i}}{\left(1+\frac{e^{-(\mu_{23}+\mu_{25})t_i}}{\mu_{23}+\mu_{25}}\right)(\mu_{23}+\mu_{25})}\right)\left(t_i+\frac{1}{\mu_{23}+\mu_{25}}\right) \qquad (8.33)\end{aligned}$$

Equating (8.33) to zero

$$\sum_{i}^{n} t_i + \frac{1}{\mu_{23}+\mu_{25}}$$

$$\begin{aligned}\mu_{23}+\mu_{25} &= \frac{-1}{\sum_{i=1}^{n} t_i} \\ \hat{\mu_{25}} &= -\left(\frac{1}{\sum_{i=1}^{n} t_i} + \mu_{23}\right) \qquad (8.34)\end{aligned}$$

Assuming all infected proceed to the Aids state then $\mu_{23} = 0$
and therefore

$$\hat{\mu_{25}} = \frac{-1}{\sum_{i=1}^{n} t_i} \qquad (8.35)$$

To estimate μ_{35}

$$\begin{aligned}P_{33}(s,t) &= e^{-\mu_{35}t} \\ S_{33}(s,t) &= 1+\frac{e^{-\mu_{35}t}}{\mu_{35}}\end{aligned}$$

Therefore

$$L = \prod_{i=1}^{n}\left(e^{-\mu_{35}t_i}\right)^{\delta_i}\left(1+\frac{e^{-\mu_{35}t_i}}{\mu_{35}}\right)^{1-\delta_i}$$

and therefore

$$l = \sum_{i=1}^{n}\delta_i \ln e^{-\mu_{35}t_i} + \sum_{i=1}^{n}(1-\delta_i)\ln\left(1+\frac{e^{-\mu_{35}t_i}}{\mu_{35}}\right) \qquad (8.36)$$

Differentiating (8.36) with respect to μ_{35}

$$\frac{\partial l}{\partial \mu_{35}} = -\sum_{i=1}^{n} t_i\delta_i + \sum_{i=1}^{n}\left(\frac{(1-\delta_i)\frac{-t_i e^{-\mu_{35}t_i}}{\mu_{35}} - \frac{e^{-\mu_{35}t_i}}{\mu_{35}^2}}{1+\frac{e^{-\mu_{35}t_i}}{\mu_{35}}}\right) \qquad (8.37)$$

Since censored $\delta_i = 0$

$$\therefore \frac{\partial l}{\partial \mu_{35}} = -\sum_{i=1}^{n} \left(\frac{\frac{-t_i e^{-\mu_{35} t_i}}{\mu_{35}} - \frac{e^{-\mu_{35} t_i}}{\mu_{35}^2}}{1 + \frac{e^{-\mu_{35} t_i}}{\mu_{35}}} \right) \tag{8.38}$$

Equating (8.38) to zero

$$\begin{aligned} -\sum_{i=1}^{n} \frac{t_i e^{-\mu_{35} t_i}}{\mu_{35}} &= \sum_{i=1}^{n} \frac{e^{-\mu_{35} t_i}}{\mu_{35}^2} \\ \hat{\mu_{35}} &= -\sum_{i=1}^{n} \frac{1}{\sum_{i=1}^{n} t_i} \end{aligned} \tag{8.39}$$

To estimate μ_{45}

$$\begin{aligned} P_{44}(s,t) &= e^{-\mu_{45} t} + 1 \\ S_{44}(s,t) &= 1 + \frac{e^{-\mu_{45} t}}{\mu_{45}} + t \end{aligned}$$

Therefore

$$L = \prod_{i=1}^{n} \left(1 + e^{-\mu_{45} t_i}\right)^{\delta_i} \left(1 + \frac{e^{-\mu_{45} t_i}}{\mu_{45}} - t\right)^{1-\delta_i}$$

and therefore

$$l = \sum_{i=1}^{n} \delta_i \ln\left(1 + e^{-\mu_{45} t_i}\right) + \sum_{i=1}^{n} (1 - \delta_i) \ln\left(1 + \frac{e^{-\mu_{45} t_i}}{\mu_{45}} - t\right) \tag{8.40}$$

Differentiating (8.40) with respect to μ_{45}

$$\frac{\partial l}{\partial \mu_{45}} = -\sum_{i=1}^{n} \frac{-t_i \delta_i e^{-\mu_{45} t_i}}{1 + e^{-\mu_{45} t_i}} + \sum_{i=1}^{n} \left(\frac{(1 - \delta_i) \frac{-t_i e^{-\mu_{45} t_i}}{\mu_{45}} - \frac{e^{-\mu_{45} t_i}}{\mu_{45}^2}}{1 + \frac{e^{-\mu_{45} t_i}}{\mu_{45}} - t} \right) \tag{8.41}$$

If censored then $\delta_i = 0$

$$\begin{aligned} \frac{\partial l}{\partial \mu_{45}} &= \sum_{i=1}^{n} \left(\frac{\frac{-t_i e^{-\mu_{45} t_i}}{\mu_{45}} - \frac{e^{-\mu_{45} t_i}}{\mu_{45}^2}}{1 + \frac{e^{-\mu_{45} t_i}}{\mu_{45}} - t} \right) \\ &= -\frac{\sum_{i=1}^{n} \frac{e^{-\mu_{45} t_i} (\mu_{45} t_i + 1)}{\mu_{45} + e^{-\mu_{45} t_i} - \mu_{45} t_i}}{\mu_{45}} \\ &= \frac{1}{\mu_{45}} \sum_{i=1}^{n} \frac{e^{-\mu_{45} t_i} (\mu_{45} t_i + 1)}{\mu_{45} + e^{-\mu_{45} t_i} - \mu_{45} t_i} \end{aligned} \tag{8.42}$$

Equating (8.42) to zero

$$0 = -\sum_{i=1}^{n} \left(\frac{e^{-\mu_{45} t_i}}{\mu_{45} + e^{-\mu_{45} t_i} - \mu_{45} t_i} \right) (\mu_{45} t_i + 1) \tag{8.43}$$

Therefore

$$\begin{aligned} -\mu_{45} \sum_{i}^{n} t_i + 1 &= 0 \\ \hat{\mu_{45}} &= -\frac{1}{\sum_{i=1}^{n} t_i} \end{aligned} \tag{8.44}$$

Chapter 9

CONCLUSIONS AND RECOMMENDATIONS

Introduction

This chapter has a summary of accomplishments of the thesis, conclusions from the findings of the study and recommendations on areas for future research.

Summary

First we used deterministic approach to obtain the basic reproduction number (R_0) for the Susceptible-Infected-Treated-Aids model. We then developed multistate models with censoring for mother to child transmission of HIV which we then used to obtain the transition probabilities and estimate transition intensities for a child born infected and a child born healthy. For a child born infected we have the two state Infected-death model and three state infected-aids-death model. For a child born healthy we have the three state healthy-infected-death model, four state healthy-infected-aids-death model and the five state healthy-non-breastfeed-infected-aids-death model. The transition probabilities were obtained using the generator matix approach and the transition intensities estimated using maximum likelihood estimaton.

Conclusion

The R_0 obtained showed that an infected mother will infect approximately one child emphasising the need to apply and monitor the intervention and control measures in use in order to further reduce and ulimately prevent this mode of transmission
From censored multistate models, the estimates obtained for the transition intensities were observed to be time dependent.
The time that infection occurs in a child born infected can be estimated by use of left censoring and the possible time of infection for a child born healthy can be estimated by applying right censoring in situations when infection occured after the followup period or by interval censoring if infection occurred between two time intervals.
The expressions for the transition intensities indicates that if the number of HIV infected children is maintained at a constant number n, then as time increases, the transition intensities will tend to zero.

The transition probabilities are all exponentially distributed and this proves the fact that the transition rates are constant over time, i.e, time homogeneous.

Recomendations

Since we assumed that the transition probabilities and intensities are time homogeneous further studies it would be interesting to see how estimates are affected if the assumption is that of non homogeneity.
In this study we used type 1 censoring and there is therefore need to consider also type 2 censoring in the study.
More states such as the treatment stage should also be included in the model.
Use the transition probabilities to obtain quantities such as the expected time spent in a given state or the expected current condition while in a given state by performing integration analytically.

References

[1] Abdulkarim U. M and Ndakwo H. S. Mathematical Model for Vertical Transmission of HIV/AIDs in a Homogeneous Mixing Population. *Research Journal for Applied Sciences* 2(4) : 267 − 371, 2007.

[2] Allen L. *An Introduction to Stochastic Processes with Application to Biology.*Taylor and Francis Group.Texas,USA, 2010.

[3] Anderson P. K and Keiding N. Multi-state models for event hisory analysis.*Stats Methods Med Res* 11(1) : 91 − 115, 2002.

[4] Anderson R. M., Grenfell B. T., and May R. M. Oscillatory fluctuations in the incidence of infectious diseases and impact of vaccination: time series analysis. *The Journal of Hygiene*93(3) : 587 − 608

[5] Balakrishnan N. and Kateri M. On the Maximum likelihood estimation of parameters of Weibull distribution based on complete and censored data. *Statistics and Probability Letters* 78 : 2971 − 2975, 2008.

[6] Balasubramanian R. and Lagakos S. W. Estimation of the Timing of Perinatal Transmission of HIV.*Biometrics* 57(1) : 1048 − 1058, 2001.

[7] Brown E. R. and Chen Y. Q. An imputation method for interval censored time-to-event with auxiliary information: analysis of the timing of mother-to-child transmission of HIV, *Stat Commun Infect Dis* 2(1)10 : 2202/1948−4690, 1018, 2012.

[8] Bruce L. J. Modelling Multi-state process using a markov assumption. *Actuarial Research Clearing House* 1(1) : 239 − 248, 1993.

[9] Busenberg S., Cooke K.L. and Pozio M. A. Analysis of a model of a vertically transmitted disease. *Journal of Mathematical Biology* 17(1) : 305 − 329, 1983.

[10] Cavender J. A. Quasi- Stationary Distribution for Birth-and-Death Processes.*Advances in Applied Probability* 10(3) : 570 − 589, 1978.

[11] Cox D. R. and Miller H. D.*The Theory of Stochastic Processes.* Chapman and Hall, London, 1965.

[12] Commenges D. *Multi-State Models in Epidemiology.* Kluwer Academic Publishers, Boston, 1999.

[13] Daniel W. J. *Multi-state transition models with actuarial applications.*Casualty Actuarial Society and the Society of Actuaries. 2004.

[14] Datta S. and Satten G. A. Validity of the Aalen-Johansen estimators of stage occupation probabilities and Nelson-Aalen estimators of integrated transition hazards for non-Markov models. *Statistics and Probability letters* $55 : 403 - 411, 2001$.

[16] Diekmann O., Heesterbeek J. A. and Metz J. A. On the definition and computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology* $28(4) : 265-282, 1990$.

[16] Diekmann O., Heesterbeek A. P. and Roberts M. G. The construction of next-generation matrices for compartmental epidemic models. *Journal of Royal Society Interface* $7 : 873 - 885, 2009$.

[17] Dunn D. T, Newell M. L, Ades A. E and Peckham C. Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet* $340 : 585-588, 1992$.

[18] Durret R. *Essentials of Stochastic Processes (2nd ed.).* Springer New York, 2012.

[19] Frydman H. and Szarek M. Estimation of overall survival in an 'illness-death' model with application to the vertical transmission of HIV−1. *Statistics in Medicine* $29 : 2045 - 2054, 2010$.

[20] Gard C. C. and Brown E. R. A coarsened multinomial regression model with application to perinatal mother to child transmission of HIV. *BMC Medical Research Methodology* $8 : 46, 2008$

[21] Gupta R. D and Kundu D. Exponentiated Exponential Family: An Alternative to Gamma and Weibull Distributions. *Biometrical Journal* $43(1) : 117 - 130, 2001$.

[22] Hefferman J. M, Smith R. J. and Wahl L. M. Perspectives on the basic reproductive ratio. *Journal of Royal Society Interface* $2(4) : 281 - 293, 2005$.

[23] Hamers R. L, Sigaloff K. C, Kityo C., Mugyenyi P. and Rinke de Wit T. F. Emerging HIV-1 drug resistance after roll out of antiretroviral therapy in Sub-Saharan Africa. *Waters Kluwer Health* $8 : 19 - 26, 2013$.

[24] Hougaard P. *Multi-State Models: A Review*. Kluwer Academic Publishers, Boston, 1999.

[25] Homsy J., Moore D. and Barasa A. Breastfeeding mother-to-child HIV transmission, and mortality among infants born to HIV-infected women on highly active antiretroviral therapy in rural Uganda. *Journal of Aquired Immune Deficiency Syndrome* $53 : 28 - 35, 2010$.

[27] Hudgens M. G, Li C.and Fine J. P. Parametric likelihood inference for interval censored competing risk data. *Biometrics* $70(1) : 1 - 9, 2014$.

[27] M. G. Hudgens M. G, Satter G. A and Longini Jr I. M. Non Parametric Maximum Likelihood Estimation for Competing Risk Survival Data Subject to Interval Censoring and Truncation. *Biometrics* $57 : 74 - 80, 2001$.

[28] *Flowgraph Modes for Multistate Time-to-Event Data*. John Wiley and Sons, Inc, New Jersey, 2005.

[29] Isham V. Mathematical Modelling of the Transmission Dynamics of HIV Infection and AIDs: a Review *Journal of the Royal Statistical Society. Series A* $151(1) : 5 - 30, 1988$.

[30] Islam M. and Ataharu l. A Birth-Death Process Approach to Constructing Multistate Life Tables.*Bullentin of the Malaysian Mathematical Science Society* $26(2) : 101 - 108, 2003$.

[31] Jackson C.*Multi state modelling with R*: the msm package, 2007.

[32] Karlin S. and Megregor J. Linear Growth, Birth and Death Process, *Journal of Mathematics and Mechanics* $7(4) : 1958$.

[33] Keeling M. J and Rohani P. *Modeling Infectious Diseases in Human and Animals*. Princeton University Press, New Jersey, 2008.

[34] Keiding N., Klein J. P and Horowitz M. M. Multi-state models and outcome in bone marrow transplantation. *Statistics in Medicine* $20(12) : 1871 - 85, 2001$

[35] Kitewo C., Karlsson K. andNgarina M. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania-the Mitra PLUS study.*JAIDS* $52(3) : 406 - 416, 2009$.

[36] Lemon G. H. Maximum Likelihood Estimation for the Three Parameter Weibull Distribution Based on Censored Samples. *Technometrics* $17(3) : 247 - 254, 1975$.

[37] Li M. Y, Graef J. R, Wang L.and J. Karsai J. Global dynamics of a SEIR model with varying total population size.*Mathematical Biosciences*$160 : 191 - 213, 1999$.

[38] Longini I. M and Clark W. S. Statistical Analysis of The Stages of HIV Infection using a Markov Model. *Statistics in Medicine* $8(1) : 831 - 843, 1989$.

[39] Azwaga-Lorenzo A., Ferreya C., Alvarez A., Palma P.P, Velilla E. and del Amo J. Effectiveness of a PMTCT programme in rural Western Kenya. *AIDS Care* $23(3) : 274 - 280, 2011$.

[40] Meier-Hirmer C. and Schumacher M. Multistate model for studying an intermediate event using time-dependent covariates:application to breast cancer.*BMC Medical Research Methodology* $201313 : 80$.

[41] Meira-Machado. Inference for Non-Markov Multi-state Model: An Overview. *Statistical Journal* $9(1) : 83 - 98, 2011$.

[42] Medhi J. *Stochastic Process*. New Age International Limited, 2009.

[43] Meira-Machano L., de Una-Alvarez J., Cadarso-Saurez C. and Anderson P. K. Multi-state models for the analysis of time-to-event data *Statistical Methods in Medical Research* $18(2) : 195 - 222, 2009$.

[44] Mitra S. and Kundu D. Analysis of left censored data from a Generalized Exponential Distribution. *Journal of Statistical Computation and Similation* $00(00) : 1 - 11, 2007$.

[45] Morgan B. J. Four Approaches to Solving Linear Birth-and-Death (and similar) Processes. *International Journal of Mathematics Education in Science and Technology* $10(1) : 51 - 64, 2005$.

[46] Mugisha J. Y. T and Luboobi L.S. Modelling the effect of vertical transmission in the dynamics of HIV /AIDS in an age structured population. *S.Pac. J. Nat Sci* $21 : 82 - 90, 2003$

[47] Myung I. J. Tutorial on Maximum Likelihood Estimation. *Journal of Mathematical Psychology* $47 : 90 - 100, 2003$.

[48] Naresh R., Tripathi A., Omar S. Modelling the spread of AIDS epidemic with vertical transmission. *Applied Mathematics and Computations* $178(1) : 262 - 272, 2006$

[49] Odell P. M, Anderson K. M, and D'Agostino R. B. Maximum likelihood Estimation of Interval Censored Data using a Weibull-Based Accelerated Future time Model.*Biometrics* $48(3) : 951 - 959, 1992$.

[50] Peltur C. A, Ndayisaba G. F, Lepage P. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother to child infection in Rwanda. *AIDS* $23 : 2416 - 2423, 2009$.

[51] Peto R. Experimental Survival Curves for Interval-censored Data. *Journal of Royal Statistical Society. Series C (Applied Statistics)* $22(1) : 86 - 91, 1973$.

[52] Putter S., Van der Hage J., de Bock G. H, Elgalta R., and Van de Velde C. J. H. Estimation and Prediction in a Multi- State Model for Breast Cancer. *Biometrical Journal* $48(3) : 366 - 380, 2006$.

[53] Rouzioux C. ,Costagliola D., Bergard M., Blanche S., Mayaux M. J., Groscelli C., Velleron A. J., and the HIV infection in Newborn French Collaborative Study Group. Estimating Timing of Mother-to-Child Human Immunodeficiency Virus Type 1 (HIV-1) Transmission by Use of Markov Model.*American Journal of Epidemiology* $142(12) : 1330 - 1337, 1995$.

[54] Redner A. R and Walker H. F. Mixture Densities, Maximum Likelihood and the EM Algorithm. *Society for Industrial and Applied Mathematics* $26(2) : 195 - 239, 1984$.

[55] Ross S. M.*Stochastic Processes*. John Wiley and Sons, New York, 1983.

[56] Singh R. S and Totawattage D. P. The Statistical Analysis of Interval-Censored Failure Time Data with Applications. *Journal of Statistics* $3 : 155 - 166, 2013$.

[57] Sparling Y. H, Younes N. and Lachin J. M. Parametric survival models for interval censored data with time dependent covariates. *Biostatistics Oxford Journal* $7(4) : 599 - 614, 2006$.

[58] Teeple E. A.*Adjusting for Misclassified Outcomes in a Multistate Model* PhD thesis, University of Washington, 2013.

[59] Thomas T., Masaba R. and Ndwo R. Prevention of mother-to-child transmission of HIV−1 among breastfeeding mothers using HAART: the Kisumu Breastfeeding Study, Kisumu, Kenya. In: Program and abstracts, $2003 - 2007$.

[60] Turnbull B. W. The Empirical Distribution Function with Arbitrarily Grouped, Censored and Truncated Data. *Journal of the Royal Statistical Society* $38(3) : 290 - 295, 1976$.

[61] Wang J. J, Reilly K. H, Peng H. Z and Wang N. Dynamic Characteristics Analysis of HIV Mother to Child Transmission in China. *Biomedical and Enviromental Sciences* $23(1) : 402 - 408, 2010$.

[62] Waters H. R. An Approach to the study of Multiple State Models. *Journal of the Institute of Actuaries* $111(11) : 363 - 374, 1984$.

[63] Waziri A. S, Massawe E. S and Oluwole D. M. Mathematical Modelling of HIV/AIDS Dynamics with Treatment and Vertical Transmission. *Applied Mathematics* $2(3) : 77 - 89, 2012$.

[64] Wessman M. J, Theilgaard Z. and Katzenstein T. L. Determination of HIV status of infants born to HIV-infected mothers: A review of the diagnostic methods with special focus on the application of p24 antigen testing in developing countries. *Scandinavian Journal of Infection* $44(3) : 1 - 7, 2012$.

List of Publications

1) Orowe I., Weke P., Ottieno J., Onyango N. Multistate Modelling Vertical Transmission and Determination of R_0 Using Transition Intensities. *Applied Mathematical Sciences* $9(79) : 3941 - 3956, 2015$

2) Omony J. and Orowe I. Recent Progress and Challenges in Combating the HIV/Aids Epidemic: A Review. *International STA Research and Reviews* $2(1) : 12 - 20, 2014$

3) Orowe I., Weke P. Transition Intensities for Left Censored Three State Mother-to-Child Transmission Model. *Journal of Applied Mathematical Sciences* (in press)