Multi State Markov Model with no Classification Errors with Application to Vertical Transmission

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Abstract

Disease progression occur through a number of states making the use of transition models applicable in estimating the transition probabilities from different states. Transition probabilities are often expressed in terms of transition intensities(rates). Multi-state models based on Markov process are a well established method of estimating rates of transition between stages of the disease. One of the well known multi-state Markov models is the birth-death model. In this paper we obtain transition probabilities for a four-state model in a process of a vertical transmission of HIV. We have considered a case of no errors of classification. A system of Kolmogorov forward equations are formed from the Chapman Kolmogorov equation and used to obtain the expressions for the transition probabilities which are in form of transition intensities. Using estimates for the transition intensities we are able to estimate the transition probabilities over a period of 50 years. We apply our data to the four state Healthy, Infected, Aids and Death model. It is observed that the probability of remaining in a state or transiting from one state to another generally decreases with time.

Keywords: Multi-State Models, Transition probabilities, Transition intensities, Vertical Transmission, HIV
1 Introduction

Often the interest in many longitudinal studies is to investigate time to a certain event. In medical studies, clinical status of individuals are usually observed over time with information being collected at several occasions. When a disease is detected at an early stage it may be more responsive to treatment. The effect therefore that an intervention has on the risk of illness, mortality and the risk of any other unintended harmful outcomes is often of interest. The analysis in such studies where individuals may experience several events is often performed using multi-state models. A multi-state model (MSM) is a model for a continuous time stochastic process \( (X(t), t \in T) \) in which the subject of interest at any one time occupies one of a number of finite state space where \( X(t) \) represents the state occupied by the process at time \( t \geq 0 \) with there being possible transition from one state to another. A multi-state model is therefore desirable in the description of disease process that naturally move through increasing stages of severity \([11]\). In the study of HIV/AIDS the states may be based on the CD4 counts, the viral load or other clinical symptoms. A change of state is called a transition, or an event. States can be transient or absorbing if no transition can emerge from the state. The complexity of a MSM greatly depends on the number of states and also the possible transitions.

Graphically, these models are represented by diagrams with rectangular boxes indicating the possible states and arrows representing possible transitions from the states.

Survival analysis of clinical trials often combine several distinct outcomes for inference on a combined outcome, which may not be the true outcome of interest. Continuous time multi-state models therefore provide a framework to describe the progression of a disease through successive events, with each event time modelled as a separate outcome.

The simplest form of a MSM is the two state mortality model also referred to as the alive-death model and has only one possible transition and first proposed by Du Pasquier\((1913)\). Splitting the alive state into two transient states results into the simplest progressive three-state model. These two models are special cases of the \( k – \text{progressive models} \).

The illness-death-model, also known as disability model is MSM widely used in medical studies to describe the disease progression and can be used to study the incidence of the disease and the rate of death.

The competing risks model is another MSM which extends the mortality model by considering the different causes of death. An individual can enter state \( i \) at time \( s \) and transit to state \( j \) at time \( t \). For the simplest three state model,
the possible transitions are:

i) Transition Probabilities: $P_{ij}(s,t)$ is given as $P_{12}(s,t), P_{13}(s,t)$ and $P_{23}(t)$

ii) Transition Intensities: $\mu_{ij}$ is given as $\mu_{12}, \mu_{13}$ and $\mu_{23}$

Since transition probabilities are expressed in terms of transition intensities, we are able to determine the transition probabilities from the Kolmogorov forward differential equation

$$P'_{ij}(s,t) = \sum_{k \neq j} P_{ik}(s,t)\mu_{kj} + P_{ij}(s,t)\mu_{jj}$$

(1)

Many studies have been carried out on HIV using multi state models (see for example [7], [12], [13] and [14]). However is most of these studies less emphasis is put in the process of obtaining the transition probabilities. In [14] a reversible multi state model was used obtain expressions for the transition intensities which was then used to determine the basic Reproduction number $R_0$ in vertical transmission of HIV. In this paper we consider a one directional four state model with no possibility of going back to a previous state. We obtain the expression for the transition probabilities which are then used to estimate the probabilities of remaining in a state or transiting from one state to the next. It is assumed that all subjects are in state 1 at time $t = 0$ and they may either visit state 2 at some time point or go directly to state 4 (absorbing state). Similarly from state 2 they either visit state 3 or go to state 4 and from state 3, they can only proceed to state 4.

![Figure 1: A Four-State Model with Irreversible Transitions](image-url)
There are nine different transition probabilities to estimate, \( P_{11}(s,t), P_{12}(s,t), P_{13}(s,t), P_{14}(s,t), P_{22}(s,t), P_{23}(s,t), P_{24}(s,t), P_{33}(s,t) \) and \( P_{34}(s,t) \). However only six of them need to be estimated since the other three transition probabilities can be obtained from the relationship

\[
P_{11}(s,t) + P_{12}(s,t) + P_{23}(s,t) + P_{24}(s,t) = 1
\]

\[
P_{22}(s,t) + P_{23}(s,t) + P_{34}(s,t) = 1
\]

\[
P_{33}(s,t) + P_{34}(s,t) = 1
\]

The Chapman-Kolmogorov equation is given as

\[
P_{ij}(s,t) = \sum_k P_{ik}(s,\tau)P_{kj}(\tau,t)
\] (2)

Using (2) we deduce that

\[
P_{ij}(s,t+h) = \sum_k P_{ik}(s,t)P_{kj}(t,t+h)
\]

\[
P_{ij}(s,t+h) = \sum_{k\neq j} P_{ik}(s,t)P_{kj}(t,t+h) + P_{ij}(s,t)P_{jj}(t,t+h)
\]

\[
\therefore P_{ij}(s,t+h) - P_{ij}(s,t) = \sum_{k\neq j} P_{ik}(s,t)P_{kj}(t,t+h) + P_{ij}(s,t)P_{jj}(t,t+h) - P_{ij}(s,t)
\]

\[
= \sum_{k\neq j} P_{ik}(s,t)P_{kj}(t,t+h) + P_{ij}(s,t)\{P_{jj}(t,t+h) - 1\}
\] (3)

Dividing equation (3) by \( h \) and taking the limit \( h \to 0 \), we have

\[
P'_{ij}(s,t) = \sum_{k\neq j} P_{ik}(s,t)\mu_{kj} + P_{ij}(s,t)\mu_{jj}
\]

which is the Kolmogorov forward differential equation.

2 Determining Transition Probabilities in a four-state model

In Markov models, the transition probabilities can be calculated from the transition intensities by solving the forward Kolmogorov differential equations. We
assume that the transition probabilities are time homogeneous i.e time independent. In a four-state model $i, j, k = 1, 2, 3$ and $4$. Therefore, the Kolmogorov forward differential equations have solutions given in a matrix form.

We determine a system of differential equations of transition probabilities as follows

\[
P_{11}(s, t+h) = P_{11}(s, t)P_{11}(t, t+h) + P_{12}(s, t)P_{21}(t, t+h) + P_{13}(s, t)P_{31}(t, t+h) + P_{14}(s, t)P_{41}(t, t+h)
\]

\[
P_{11}(s, t)(1 - (\mu_{12} + \mu_{14})h + o(h))
\]

\[
P_{11}'(s, t) = -P_{11}(s, t)(\mu_{12} + \mu_{14})
\] (4)

\[
P_{12}(s, t+h) = P_{11}(s, t)P_{12}(t, t+h) + P_{12}(s, t)P_{22}(t, t+h) + P_{13}(s, t)P_{32}(t, t+h) + P_{14}(s, t)P_{42}(t, t+h)
\]

\[
P_{12}(s, t)(\mu_{12}h + o(h)) + P_{12}(s, t)((1 - (\mu_{23} + \mu_{24})h) + o(h))
\]

\[
P_{12}'(s, t) = P_{11}(s, t)\mu_{12} - P_{12}(s, t)(\mu_{23} + \mu_{24})
\] (5)

\[
P_{13}(s, t+h) = P_{11}(s, t)P_{13}(t, t+h) + P_{12}(s, t)P_{23}(t, t+h) + P_{13}(s, t)P_{33}(t, t+h) + P_{14}(s, t)P_{43}(t, t+h)
\]

\[
P_{13}(s, t)(\mu_{23}h + o(h)) + P_{13}(s, t)(1 - \mu_{34}h) + o(h)
\]

\[
P_{13}'(s, t) = P_{12}(s, t)\mu_{23} + P_{13}(s, t)\mu_{34}
\] (6)

\[
P_{14}(s, t+h) = P_{11}(s, t)P_{14}(t, t+h) + P_{12}(s, t)P_{24}(t, t+h) + P_{13}(s, t)P_{34}(t, t+h) + P_{14}(s, t)P_{44}(t, t+h)
\]

\[
P_{14}(s, t)(\mu_{14}h + o(h)) + P_{12}(s, t)(\mu_{24}h + o(h)) + P_{13}(s, t)(\mu_{34}h + o(h)) + P_{14}(s, t)(1 + o(h))
\]

\[
P_{14}'(s, t) = P_{11}(s, t)\mu_{14} + P_{12}(s, t)\mu_{24} + P_{13}(s, t)\mu_{34}
\] (7)
Equations (4),(5),(6) and (7) are the respective Kolmogorov forward equations. Writing these equations in matrix form we obtain the compact form

\[ P'(s, t) = P(s, t)Q \]  

(8)

where

\[ P'(s, t) = \begin{bmatrix} P'_{11}(s, t) & P'_{12}(s, t) & P'_{13}(s, t) & P'_{14}(s, t) \\ P'_{21}(s, t) & P'_{22}(s, t) & P'_{23}(s, t) & P'_{24}(s, t) \\ P'_{31}(s, t) & P'_{32}(s, t) & P'_{33}(s, t) & P'_{34}(s, t) \\ P'_{41}(s, t) & P'_{42}(s, t) & P'_{43}(s, t) & P'_{44}(s, t) \end{bmatrix} \]

and

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

which describes transition of states and is therefore referred to as transition probability matrix.

The transition rate(intensity) matrix \( Q \) given as

\[ Q = \begin{bmatrix} -(\mu_{12} + \mu_{14}) & \mu_{12} & 0 & \mu_{14} \\ 0 & -(\mu_{23} + \mu_{24}) & \mu_{23} & \mu_{24} \\ 0 & 0 & -\mu_{34} & \mu_{34} \\ 0 & 0 & 0 & 0 \end{bmatrix} \]  

(9)

The eigen values of matrix \( Q \) are

\[ \lambda_1 = -\mu_{34} \]
\[ \lambda_2 = -(\mu_{12} + \mu_{14}) \]
\[ \lambda_3 = -(\mu_{23} + \mu_{24}) \]
\[ \lambda_4 = 0 \]
Since matrix $Q$ has distinct eigen values then $Q$ can be written as

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

where

- $U$ = the matrix of right eigen vectors of $Q$
- $D$ = the diagonal matrix whose elements are the eigen values of $Q$
- $U^{-1}$ = the inverse of $U$

Therefore

$$U = \begin{bmatrix}
\frac{\mu_{12}}{\mu_{23} + \mu_{24} - \mu_{34}} & \frac{\mu_{12}}{\mu_{12} + \mu_{14} - \mu_{34}} & 1 & \frac{\mu_{12}}{\mu_{12} + \mu_{14} - \mu_{23} - \mu_{24}} & 1 \\
\mu_{23} & 0 & 1 & 1 \\
\mu_{23} + \mu_{24} - \mu_{34} & 0 & 1 & 1 \\
1 & 0 & 0 & 1 \\
0 & 0 & 0 & 1
\end{bmatrix}$$

and

$$U^{-1} = \begin{bmatrix}
0 & 0 & 1 & -1 \\
1 - \frac{\mu_{12}}{\eta} & \frac{\mu_{12}}{\eta \Omega} & \mu_{12} \mu_{14} - \mu_{12} \mu_{24} - \mu_{14} \mu_{34} + \mu_{24} \mu_{34} \\
0 & 1 & -\mu_{23} & \mu_{24} - \mu_{34} \\
0 & 0 & 0 & 1
\end{bmatrix}$$

where

- $\eta = \mu_{12} + \mu_{14} - \mu_{23} - \mu_{24}$
- $\Omega = \mu_{12} + \mu_{14} - \mu_{34}$
- $\Psi = \mu_{23} + \mu_{24} - \mu_{34}$
Solving (8) we obtain

\[ P(s, t) = e^{tQ} = I + \frac{Qt}{1!} + \frac{(Qt)^2}{2!} + \frac{(Qt)^3}{3!} + \cdots \]

\[ = I + \sum_{k=1}^{\infty} \frac{(Qt)^k}{k!} \]

\[ = I + U \left( \sum_{k=1}^{\infty} \frac{(tD)^k}{k!} \right) U^{-1} \]

Also

\[ \sum_{k=1}^{\infty} \frac{(tD)^k}{k!} = \begin{bmatrix}
\sum_{k=1}^{\infty} \frac{(\lambda_1 t)^k}{k!} & 0 & 0 & 0 \\
0 & \sum_{k=1}^{\infty} \frac{(\lambda_2 t)^k}{k!} & 0 & 0 \\
0 & 0 & \sum_{k=1}^{\infty} \frac{(\lambda_3 t)^k}{k!} & 0 \\
0 & 0 & 0 & \sum_{k=1}^{\infty} \frac{(\lambda_4 t)^k}{k!}
\end{bmatrix} \]

The non-zero elements in the matrix represents sum of Poisson distribution without the first term and can therefore be presented as

\[ = \begin{bmatrix}
e^{\lambda_1 t} - 1 & 0 & 0 & 0 \\
0 & e^{\lambda_2 t} - 1 & 0 & 0 \\
0 & 0 & e^{\lambda_3 t} - 1 & 0 \\
0 & 0 & 0 & e^{\lambda_4 t} - 1
\end{bmatrix} \]

Now

\[ P(s, t) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} + U \left( \sum_{k=1}^{\infty} \frac{(tD)^k}{k!} \right) U^{-1} \]
which equals

\[
\begin{bmatrix}
\frac{e^{\lambda_2 t}}{\Phi} & \frac{\zeta(e^{\lambda_1 t} + e^{\lambda_3 t} - \Omega)}{(\Phi)(\omega)} & (e^{\lambda_4 t} - 1) - \frac{\zeta\Psi - \Theta(\mu_{12}\eta(\tau) - \psi)(\Omega)}{(\Phi)\omega} \\
0 & e^{\lambda_3 t} & \frac{\mu_{23}(e^{\lambda_3 t} - e^{\lambda_4 t})}{\omega} \\
0 & 0 & e^{\lambda_1 t} - e^{\lambda_2 t} \\
0 & 0 & e^{\lambda_3 t}
\end{bmatrix}
\]

where

\[
\begin{align*}
\Psi &= e^{\lambda_1 t} - 1 \\
\Omega &= e^{\lambda_3 t} - 1 \\
\Theta &= e^{\lambda_2 t} - 1 \\
\psi &= \mu_{12}(\mu_{24} - \mu_{34}) \\
\tau &= (\mu_{23} + \mu_{24}) - \mu_{14}(\mu_{34} - 1) \\
\eta &= \mu_{12}(\mu_{14} - \mu_{24}) \\
\zeta &= \mu_{12}\mu_{13} \\
\omega &= \mu_{23} + \mu_{24} - \mu_{34} \\
\Phi &= \mu_{12} + \mu_{14} - \mu_{23} - \mu_{24}
\end{align*}
\]

3 Application to Vertical Transmission of HIV

One of the modes of HIV transmission is Mother to child transmission of HIV in which an infected mother can transmit the virus to her unborn child in utero or during birth and delivery (intrapartum) or after birth throughout the duration of breastfeeding i.e during the post-partum period.

A child can enter state \( i \) at time \( s \) and transit to state \( j \) at time \( t \).

Consider a Healthy-Infected-Aids-death model for vertical transmission of HIV as given in Figure 2 below. This is a four state model with no possibility of recovery. An individual can only enter a state once and cannot go back to a state that he/she had visited before; i.e irreversible transitions.

The possible transitions are:

i) Transition Probabilities: \( P_{ij}(s,t) \) given as \( P_{12}(s,t), P_{14}(s,t), P_{23}(t), P_{24}(s,t) \)
and $P_{34}(s, t)$

ii) Transition Intensities: $\mu_{ij}$ given as $\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}$ and $\mu_{34}$

Transition probabilities are expressed in terms of transition intensities.

Figure 2: A Four-State Model for Vertical Transmission of HIV with Irreversible Transitions

Considering the below relation

\[
\begin{align*}
P_{11}(st) + P_{12}(st) + P_{13} + P_{14} &= 1 \\
P_{22}(s, t) + P_{23}(s, t) + P_{24}(s, t) &= 1 \\
P_{33}(s, t) + P_{34}(s, t) &= 1 \\
P_{44}(s, t) &= 1
\end{align*}
\]

we determine $P_{11}(s, t), P_{12}(s, t), P_{14}(s, t), P_{22}(s, t), P_{23}(s, t), P_{24}(s, t), P_{33}(s, t)$ which are transition probabilities of remaining negative, being infected, remaining infected and developing AIDS with life is preserved.
By solving the transition matrix we derive the following transition probabilities

\[ P_{11}(s,t) = e^{\lambda_{2}t} = e^{-(\mu_{12}+\mu_{14})t} \]

\[ P_{12}(s,t) = \frac{\mu_{12}(e^{\lambda_{3}t} - e^{\lambda_{2}t})}{\mu_{14} + \mu_{12} - \mu_{23} - \mu_{24}} \]

\[ = \frac{\mu_{12}(e^{-(\mu_{23}+\mu_{24})t} - e^{-(\mu_{12}+\mu_{14})t})}{\mu_{12} + \mu_{14} - \mu_{23} - \mu_{24}} \]

\[ P_{13}(s,t) = \frac{\mu_{12}\mu_{23}(e^{\lambda_{1}t} + e^{\lambda_{2}t} - e^{\lambda_{3}t} - 1)}{(\lambda_{3} - \lambda_{1})(-\mu_{23} - \lambda_{2})} \]

\[ = \frac{\mu_{12}\mu_{23}(e^{-\mu_{34}t} + e^{-(\mu_{12}+\mu_{14})t} - e^{-(\mu_{23}+\mu_{24})t} - 1)}{(\mu_{34} - \mu_{23} - \mu_{24})(\mu_{12} + \mu_{14} - \mu_{23})} \]

\[ P_{22}(s,t) = e^{\lambda_{3}t} = e^{-(\mu_{23}+\mu_{24})t} \]

\[ P_{23}(s,t) = \frac{\mu_{23}(e^{\lambda_{2}t} - e^{\lambda_{3}t})}{\mu_{23} + \mu_{24} - \mu_{34}} \]

\[ = \frac{\mu_{23}(e^{-(\mu_{12}+\mu_{14})t} - e^{-(\mu_{23}+\mu_{24})t})}{\mu_{23} + \mu_{24} - \mu_{34}} \]

\[ P_{33}(s,t) = e^{\lambda_{1}t} = e^{-\mu_{34}t} \]

4 Results and Discussion

We used available data in Kenya to obtain the below given estimates for the transition intensities

Using the transition intensities and applying them to (9) we obtained the transition matrix given as
Symbol: \[ \mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{34} \]

Estimate: \[ 0.15, 0.074, 0.49, 0.09, 0.18 \]

\[
Q = \begin{bmatrix}
-0.224 & 0.15 & 0 & 0.074 \\
0 & -0.58 & 0.49 & 0.09 \\
0 & 0 & -0.747 & 0.747 \\
0 & 0 & 0 & 0
\end{bmatrix}
\]

In order to see the effect of time on the transition probabilities we use the transition probability matrix (10) to obtained the transition probability matrices evaluated for years \( t = 1 \), \( t = 5 \) and \( t = 10 \) resulting in

\[
P(1) = \begin{bmatrix}
0.799 & 0.0763 & 0 & 0.125 \\
0 & 0.56 & 0.293 & 0.147 \\
0 & 0 & 0.835 & 0.165 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

\[
P(5) = \begin{bmatrix}
0.326 & 0.107 & 0 & 0.568 \\
0 & 0.055 & 0.332 & 0.613 \\
0 & 0 & 0.407 & 0.593 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

\[
P(10) = \begin{bmatrix}
0.114 & 0.046 & 0 & 0.84 \\
0 & 0.003 & 0.127 & 0.87 \\
0 & 0 & 0.165 & 0.835 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

Comparing the probabilities it is clear that transition probabilities from state 1, 2, 3 into state 4 (absorbing state) increases as time increases while transition from state 1 to 2 first increases and then decreases with time. This could be
attributed to the use of therapeutic and non-therapeutic interventions. 

Probabilities of remaining in state 3, the Aids state also decreases with time due due to reduced immunity as the diseases progresses or/aid patients developing resistant to medication. The outputs for the transition probabilities could be useful in further understanding the HIV infection stage over time. The transition probabilities are further illustrated with the graphs given in Figure 3 and Figure 4

Figure 3: Probabilities over time of remaining in State 1,2 or 3
Figure 4: Approximate Transition Probabilities from state 1 to 2 and from state 2 to 3

Figure 3 plots the probabilities of remaining in the different states while Figure 4 plots the transition probabilities from one state to another. In both these graphs suggests that time has a great influence on the transition probabilities.
5 Conclusion

The results reveal that the transition probabilities depend on the state an individual is in and is higher from state 2 to state 3 compared with from state 1 to state 2. This can be attributed to immunity being lower in state 2 than in state 1. The $P_{12}$ graph shows an initial increase to a maximum, then a decrease as the initial number of infected individual increases and then decreases. Therefore as time progresses, the probability of being in state 2 decreases and the probability of progressing to state 3 increases as a result of increase in opportunistic diseases in the infected state as the CD4 counts decreases leading to acquired immunodeficiency syndrome (AIDS). Both Figure 3 and Figure 4 show that it will take approximately 30 years for the transition probability to be Zero.

It is therefore important to discover what is at play that is not leading to the immediate zero transmission from mother to child inspite of the availability of interventions that have been proven to be completely effective in preventing this mode of transmission.

It is also important to find better ways of communicating in order to reach the unreached who are in need of information about appropriate ways that are available that can reduce probability of being infected and transmitting the virus.

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