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Parametric Five State Progression Model: Estimation and Application

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Abstract

Multi-state models (MSMs) are an extension of classical survival analysis, which allows adjustment to the prediction of survival duration of the patient in the course of time by incorporating new information regarding the progression of the medical history and to better understand how prognostic factors influence the different phases of the disease/recovery process. In recent years, a wide range of medical situations have been modelled using MSMs such as problems following lung transplantation, problems following heart transplantation, hepatic cancer, HIV infection and AIDS. Disease progression model is needed for understanding the progression of disease and important in retrospective cohort analyses. In this paper five states progression model is suggested. The suggested model is studied in the case of continuous time non-homogeneous multistate model based on non-homogeneous Markov processes. A parametric time-dependent multistate model are considered to fit a non-homogeneous Markov process where transitions are specified by the hazard of exponential and Weibull distribution. The parameters of the suggested models are estimated by ML method. An application using dataset containing histories of bronchiolitis obliterans syndrome (BOS) from lung transplant recipients is applied using the suggested models. The BOS data set is provided in the R package **msm**.

Keywords:

Markov processes, Non-Markov processes, Interval-censored, Staged progression model, Parametric multi-state models.

1. Introduction

In most longitudinal medical studies on progression of healthy individuals to chronic diseases, such as cancer, AIDS, and dementia, the nature of the development is often expressed in terms of distinct health stages, where patients are observed at certain time points.

MSMs are considered as generalizations of survival and competing risks models, are the most common models for describing longitudinal failure time data. These models have wide application in modeling the complex evolution of chronic diseases. In epidemiology, multi-state models are used to represent the trajectory of subjects through different discrete states, generally including clinical disease and death.

MSMs are increasingly being used to model complex diseases. By modeling transitions between disease states, accounting for competing events at each transition helps in understanding patient trajectories and how risk factors impact over the entire disease pathway.

Multi-state interval-censored data are usually handled by time homogenous Markov models. However, the assumption of time homogeneity would be inappropriate if the disease process is heavily dependent on the time scale considered in the model. In this case, a non-homogeneous Markov assumption is assumed to model the multi-state process.

For the analysis of time-homogeneous multi-state processes, Kalbfleisch and Lawless (1985) introduced the MSMs. They developed a general procedure for obtaining maximum likelihood estimates of the model parameters. Kay (1986) proposed a similar method that calculates the first and second order derivatives of some particular multi-state processes and provided methods for hypothesis testing and model diagnostics. Satten and Longini (1996) developed a method for fitting these models when states are subject to measurement errors. Commenge (1999) discussed some assumptions for multi-state models in epidemiology and considered different inference approaches. Lintu *et al.* (2022) estimated covariate effects on the bidirectional transition rates for a continuous time homogeneous multi-state Markov model with three transient states, and an absorbing state (death) for kidney disease progression.

For time-dependent multi-state processes, Kalbfleisch and Lawless (1985) suggested two methods to time-dependent processes. The first method uses piecewise-constant hazards; in this case the hazards are constant within specified intervals, but can change for different intervals. The second method focuses on a special case in which the non-homogeneity is due to a time-varying multiplicative change in the matrix of transition intensities. Omar *et al.* (1995) constructed three-state model with simple parametric forms for the transition rates. Maximum likelihood method was used to estimate the transition rates and different treatment groups are compared using likelihood ratio tests. Joly and Commenges (1999) considered the estimation of the intensity and survival functions for a continuous time progressive three-state semi-Markov model with intermittently observed data. Hsieh *et al.* (2002) discussed a three-state

progressive non-homogenous Markov model with two non-homogeneous models using the Weibull distribution and piecewise exponential model with covariate functions of the proportional hazard to accommodate non-constant transition rates. Van den Hout and Matthews (2008) provided a general method for estimating multi-state models for interval-censored data. They focused on time-dependent parametric models such as, Gompertz and Weibull distributions. A piecewise-constant approximation to the parametric hazards was considered, using a scoring algorithm for estimating the models. Machado and van den Hout (2021) presented a new and efficient method to estimate multi-state models with splines using automatic estimation of penalty parameters. They showed that using splines with penalty parameters can improve model fit. Jackson *et al.* (2022) compared two multi-state modelling frameworks that can be used to represent dates of events following hospital admission for people infected during an epidemic. One modelling framework was based on defining transition-specific hazard, the second was using a mixture model to estimate the probability that an individual will experience each event, and the distribution of the time to the event given that it occurs.

Most studies focused on modeling the true disease progression as a discrete time stationary Markov chain, and only a few studies have been carried out regarding non-homogenous multi-state models in the presence of interval-censored data. Most of the literature are limited to the three-state models.

In this paper staged disease progression model with four transient states and one absorbing state is proposed. The suggested model is studied

in the case of continuous time non -homogeneous multistate model based on non-homogeneous Markov processes. A parametric time-dependent multistate models are considered to fit a non-homogeneous Markov process where transitions are specified by the hazard of exponential and Weibull distribution. The parameters of the suggested models are estimated by ML method. The likelihood function is constructed using transition probabilities, therefore they are derived first.

This paper is organized as follows: Section (2) introduces multi-state models and discusses the framework of Markov processes. Section (3) discusses parametric multi-state models. Section (4) discusses some extractor quantities. Section (5) is devoted to the suggested models and the estimation of their parameters. In section (6) an application using BOS data set is applied to represent the performance of the suggested models. Section (7) contains conclusions.

2. Multi-state models

MSMs are the most commonly used models for describing the development for longitudinal data. MSMs are models for a stochastic process, which at any time point each individual occupies one of a set of discrete states. In medicine, the states can describe conditions like healthy, diseased, diseased with complications, and death. A change of state is called a transition. This corresponds to outbreak of disease, occurrence of complications and death.

MSMs can be illustrated using diagrams with boxes representing the states and with arrows between the states representing the possible transitions. A state is called an absorbing state if transitions cannot occur

from that state. A transient state meaning that at least one transition is possible from that state. The complexity of a MSM depends on the number of states and also on the possible transitions.

MSMs for interval-censored data are commonly formulated in a Markov processes framework [Kalbfleisch and Lawless (1985)]. The Markov property states that the future of the process only depends on the current state. There are two types of Markov process in the literature, the discrete-time Markov process, and the continuous-time Markov process. This paper is concerned with continuous-time multi-state processes.

Continuous-time Markov process expresses the condition that the state space, , is discrete and the time T is continuous. Given the time points $t_1, t_2, \dots, t_n$, it is of interest to examine the joint distribution of $Y_1, Y_2, \dots, Y_n$, where $Y_j = Y(t_j)$ for $j = 1,2, \dots, n$. Commonly, $(Y(t) | t \in T)$ is assumed to be a Markov process, which means that the future state of the process only depends on the current state. Thus, a continuous-time Markov process on the discrete states D is defined through a set of probabilities, $p_{rs}(t)$, such that,

$$\boldsymbol{p_{rs}(t,u) = p(Y(u+t) = s | Y(u) = r) \text{ for } u \geq 0 \ t \geq 0.} \qquad (\mathbf{2.1})$$

which represents probability of being in state s at a specified time $u + t$ in the future.

[Van den Hout (2017)].

In applications, models are specified through the transition intensities over a small time interval. The transition intensities from state r to state s are given by

$$q_{rs}(t) = q_{rs} = \lim_{\Delta t \to 0} \frac{p(Y(t+\Delta t) = s | Y(t) = r)}{\Delta t} \quad , r \neq s \quad , \qquad (2.2)$$

where $q_{rs}(t)$ is the instantaneous risk of moving from state *r* to state *s* [Andersen and Keiding (2002)].

Transition intensity matrix, $\boldsymbol{Q}(t)$, is given by:

$$\boldsymbol{Q}(t) = \begin{bmatrix} q_{11} = -\sum_{s \neq 1} q_{1s} & q_{12} & q_{13} & \cdots & q_{1n} \\ q_{21} & q_{22} = -\sum_{s \neq 2} q_{2s} & q_{23} & \cdots & q_{2n} \\ \vdots & & q_{32} & \ddots & \cdots & q_{3n} \end{bmatrix}, \qquad (2.3)$$

where $\boldsymbol{Q}(t)$, is a matrix with off-diagonal entries q_{rs} and diagonal entries $q_{rr} = -\sum_{s \neq r} q_{rs}$. If $q_{rr} = 0$ the state r is called absorbing.

the generator matrix satisfies:

- $q_{rs} \geq 0 \quad for \ r \neq s$
- $\sum_s q_{rs} = 0$

The Markov process $(Y(t) | \, t \in T)$ is time homogeneous if the probability (2.1) only depends on the initial state as follows:

$$p_{rs}(t) = p(Y(t) = s | Y(0) = r) \ , \qquad (2.4)$$

The probabilities in (2.4) satisfy:

- $0 \leq p_{rs}(t) \leq 1, \qquad (2.5)$
- $p_{rk}(t) = \sum_s p_{rs}(u) \, p_{rk}(t - u) , \qquad t > u \qquad (2.6)$
- $\sum_s p_{rs}(t) = 1, \qquad (2.7)$

Eq. (2.6) is the Chapman-Kolmogorov equation for a time homogeneous Markov process. Then, the matrix $\boldsymbol{P}(t)$ which contains these probabilities is called the *transition probability matrix*, $\boldsymbol{P}(t)$, and is defined as

$$\boldsymbol{P}(t) = \boldsymbol{P}(u)\boldsymbol{P}(t-u) \quad with\, \boldsymbol{p}(0) = \boldsymbol{I}\,, \tag{2.8}$$

For a given generator matrix, Q, a Markov process is defined. The link between a generator matrix and its probability matrix is established by the forward and backward equations as follows:

$$\grave{\boldsymbol{P}}(t) = \boldsymbol{P}(t)\,\boldsymbol{Q}\,, \tag{2.9}$$

$$\grave{\boldsymbol{P}}(t) = \boldsymbol{Q}\,\boldsymbol{P}(t), \tag{2.10}$$

Given the initial condition $\boldsymbol{P}(0) = \boldsymbol{I}$, the unique solution of both forward and backward equations in (2.9) and (2.10) is

$$\boldsymbol{P}(t) = exp(\boldsymbol{Q}t) = \sum_{k=0}^{\infty} \frac{t^k \boldsymbol{Q^k}}{k!}\,, \tag{2.11}$$

where exp is the matrix exponential.

[cox and Miller (2017)].

For many applications, the risks of moving across states depend on the current state and on time. In this case, a non-homogeneous Markov assumption is assumed to model the multi-state process. The generator matrix is then a function of time, which means that the matrix $\boldsymbol{Q}(t)$ can vary over time. In these models *transition intensities*,q_{rs}, are assumed to depend on time and the individual characteristics through a covariate vector. Time-dependent models can be defined by using proportional hazards model for transition from r to $s, r \neq s$, as follows:

$$q_{rs}(t) = q_{rs.0}(t)\exp\left(\hat{\boldsymbol{\beta}}_{rs}\boldsymbol{X}\right), \tag{2.12}$$

where

- $q_{rs.0}(t)$ represent the hazard function for an individual for whom the values of all the explanatory variables that make up the vector **x** is zero.
- $\boldsymbol{X} = (x_1, x_2, \dots, x_p)^T$ is the vector of values of the explanatory variables which may be recorded at the time origin of the study or changing over time.
- $\boldsymbol{\beta}_{rs} = (\beta_{rs.1}, \dots, \beta_{rs.p})^T$ is the vector of coefficients of the p explanatory variables acting on transition from state r to state s.

3. Parametric Time-Dependent Multi-State Models

Several time-dependent models can be fitted with parametric specifications for transition hazards. In time-dependent hazard regression multi-state models in E. (2.12) transition-specific time dependency introduced with parametric baseline hazards. Examples of parametric baseline hazards are

- exponential: $q_{rs.0}(t) = \lambda_{rs}$, $\lambda_{rs} > 0$
- Weibull: $q_{rs,0}(t) = \lambda_{rs}\alpha_{rs}\, t^{\alpha_{rs}-1}$. $\lambda_{rs}.\tau_{rs} > 0$
- Gompertz: : $q_{rs.0}(t) = \lambda_{rs}\, e^{-(\xi_{rs}t)}$, $\lambda_{rs} > 0$
- log-logistic: $q_{rs,0}(t) = \frac{\lambda_{rs}\,\rho_{rs}(\lambda_{rs}t)^{\rho_{rs}-1}}{1+(\lambda_{rs}t)^{\rho_{rs}}}$ $\lambda_{rs}\ \rho_{rs} > 0$

The exponential model is the simplest parametric hazard specification, which does not allow for time-dependent modelling.The Weibull, Gompertz and log-logistic specifications are useful to model monotonic upward or downward over time.

Fully parametric multi-state models are appealing in a number of situations such scientific background may suggest specific forms for certain

intensities. Data sparsity in certain time regions lead to imprecise nonparametric estimates, in such settings a more precise parametric estimate that agrees with observed data may be preferable. When data are incomplete, nonparametric estimation may be difficult or the corresponding estimator may be undefined.

[Cook and Lawless (2018)].

In this study fully-parametric models are considered where transitions can be specified by a variety of parametric models with no explanatory variables effects, thus transitions intensities are depending on time only.

Let t denotes time in a progressive continuous-time multi-state survival model. At $t \geq 0$, the true state of an individual is $Y_t \in \{1,2,\dots,D\}$. Transitions intensities of multi-state model, $q_{rs}(t)$, are specified by the hazard function of a certain distribution.

Given time interval $[t_1, t_2]$, the transition probability from state r to state s is obtained by

$$p_{rs}(t_1,t_2) = p\big(Y_{t_2}(t) = s \big| Y_{t_1}(t) = r\big) =$$
$$\int_{t_1}^{t_2} \exp\left[-Hr(t_1,u)\right]\ q_{rs}(u) \exp\left[-Hs(u,t_2)\right] du, \qquad (3.1)$$

And the transition probability for staying in state $r$is given by:

$$p_{rr}(t_1,t_2) = p\big(Y_{t_2}(t) = r \big| Y_{t_1}(t) = r\big) = Hr(t_1,t_2) \quad for\ r = 1,2,3,\dots \qquad (3.2)$$

where

$$Hr(t_1,t_2) = \int_{t_1}^{t_2} h_r(u)\ \ du \qquad (3.3)$$

[Van den Hout and Matthews (2008)].

3.1 Inference of Parametric Multi-State Models:

Maximum likelihood method can be used to estimate the model parameters in case of parametric time-dependent multi-state models. Estimation of model parameters is undertaken by maximising the log-likelihood. Because of the interval censoring, the likelihood is constructed using transition probabilities.

3.1.1 Likelihood function of multi-state models:

Let the state space be $S = \{1,2,..,D\}$, with D is the dead state. Consider a series of states $Y_1, Y_2, \dots, Y_n$ observed at times $t_1, t_2, \dots, t_J$, respectively. Using the Markov assumption, the contribution of the individual to the likelihood conditional on the first state is given by:

$$L_i(\boldsymbol{\theta}\,|y) = P\left(Y_J = y_J, \dots, y_2 = y_2 \middle| Y_1 = y_1, \boldsymbol{\theta}\right)$$

$$= \prod_{j=2}^{J-2} P\left(Y_j = y_j \middle| Y_{j-1} = y_{j-1}, \boldsymbol{\theta}\right) \; C\left(y_J / y_{J-1}\right) \tag{3.4}$$

where $\boldsymbol{\theta} = \left(\theta_1, \dots, \theta_q\right)^T = (q_{12}, q_{15}, q_{23}, q_{25}, q_{34}, q_{35}, q_{45})^T$ is the vector with the model parameters,

If a living state at t_J is observed, then

$$C\left(y_J / y_{J-1}\right) = P\left(Y_J = y_J \middle| Y_{J-1} = y_{J-1}\right), \tag{3.5}$$

If the state is right censored at t_J, then

$$C\left(y_J / y_{J-1}\right) = \sum_{s=1}^{D-1} P\left(Y_J = s \middle| Y_{J-1} = y_{J-1}\right), \tag{3.6}$$

If death is observed at t_J, then

$$C\left(y_n / y_{n-1}\right) = \sum_{s=1}^{D-1} P\left(Y_J = s \middle| Y_{J-1} = y_{J-1}\right) q_{sD}(t_J), \tag{3.7}$$

Thus, the likelihood contribution for an individual is

$$L_i(\theta\,|y) = \prod_{j=2}^{J} L_{ij}, \tag{3.8}$$

where

$$L_{ij} = \begin{cases} P(Y_j = y_j | Y_{j-1} = y_{j-1}, \boldsymbol{\theta}, t_{j-1}) & for\ j = 2, \dots, J-1 \\ C(y_J / y_{J-1}) & for\ j = J \end{cases}, \tag{3.9}$$

Given N individuals, the likelihood function is given by

$$L = \sum_{i=1}^{N} L_i(\theta\,|y) = \sum_{i=1}^{N} \prod_{j=2}^{J} L_{ij}, \tag{3.10}$$

The natural logarithm of the likelihood function is:

$$\ell(\boldsymbol{\theta}) = \sum_{i=1}^{N} \sum_{j=1}^{J} \log L_{ij} \tag{3.11}$$

The maximum likelihood equations are:

$$U_k(\theta) = \frac{\partial \ell(\boldsymbol{\theta})}{\partial \boldsymbol{\theta_k}} = \sum_{i=1}^{N} \sum_{j=1}^{J} \frac{\partial}{\partial \boldsymbol{\theta_k}} \log L_{ij} = 0, \qquad k = 1,2, \dots, q \tag{3.12}$$

The maximum likelihood estimates of $U_k(\theta)$ are derived using numerical methods.

[Machado (2018)].

3.1.2 Confidence Intervals for the Parameters

The ML estimators of the parameters are asymptotically normal, asymptotically unbiased and have asymptotic variance–covariance matrix given by the inverse of the Fisher information matrix. The elements of the fisher information matrix are obtained by taking the negative expectation of the second derivatives of the natural logarithm of the likelihood function, $L(\boldsymbol{\theta})$, with respect to $\boldsymbol{\theta}$ as follows:

$$I(\boldsymbol{\theta}) = -E\left(\frac{\partial^2 \ell(\boldsymbol{\theta})}{\partial \boldsymbol{\theta_k} \partial \boldsymbol{\theta_v}}\right), \tag{3.13}$$

Then the second derivatives of the natural logarithm of the likelihood function is given by:

$$\frac{\partial^2 \ell(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}_k \partial \boldsymbol{\theta}_v} = \sum_{i=1}^{N} \sum_{j=1}^{J} \frac{\partial}{\partial \boldsymbol{\theta_k} \partial \boldsymbol{\theta_v}} \log L_{ij} \ , \tag{3.14}$$

Unfortunately, the exact mathematical expressions for the above expectations are very difficult to obtain.

Therefore, the asymptotic Fisher information matrix is

$$\hat{I}_{ij}(\boldsymbol{\theta}) = -\left(\frac{\partial^2 \ell(\boldsymbol{\theta})}{\partial \theta_k \partial \theta_v}\right) = -\sum_{i=1}^{N} \sum_{j=1}^{J} \frac{\partial}{\partial \boldsymbol{\theta_k} \partial \boldsymbol{\theta_v}} \log L_{ij} \quad , \tag{3.15}$$

which is obtained by dropping the expectation operator E .

The approximate asymptotic variance –covariance matrix for the ML estimators is the inverse

of asymptotic Fisher information matrix. It is useful for computing the standard error of

ML estimation.

$$I(\boldsymbol{\theta})^{-1} = \frac{1}{|I(\boldsymbol{\theta})|} adj \ I(\boldsymbol{\theta}) \tag{3.16}$$

where $adj \ I(\boldsymbol{\theta})$ is the ad joint of $I(\boldsymbol{\theta})$.

For large sample size, the ML estimators under regularity conditions are consistent and asymptotically unbiased as well as asymptotically normally distributed; hence the asymptotic two sided confidence intervals of the parameters for the ML estimators are obtained by:

$$p\left[-z < \frac{\hat{\theta}_{iML} - \theta_i}{\sigma_{\hat{\theta}_{iML}}} < z\right] = 1 - \alpha, \tag{3.17}$$

where z is the $100(1-\frac{\tau}{2})\ th$ standard normal percentile. The two sided approximate $100(1-\frac{\tau}{2})100\%$ confidence intervals are given by:

$$L_\theta = \hat{\theta}_{iML} - Z_{\frac{\tau}{2}}\,\hat{\sigma}_{\hat{\theta}_{iML}},\quad and\quad U_\theta = \hat{\theta}_{iML} + Z_{\frac{\tau}{2}}\,\hat{\sigma}_{\hat{\theta}_{iML}}\ , i = 1,2,\dots,b \tag{3.18}$$

where $\hat{\sigma}_{\hat{\theta}_{iML}}$ is the standard deviation of the parameters $\widehat{\theta}_i$ and $\hat{\theta}_{iML}$ is [Tanner (1996)].

4. Some extractor quantities

A set of quantities can be used to extract interesting features of the fitted multi-state model including expected duration in each state and the population size of states.

4.1 Expected duration time in each state:

It represents the average duration that an individual is expected to stay in each state with a time period of length t depending on the initial state. The expected duration of stay in state s between times t_0 and t for an individual in state r at time t_0, is defined by the integral from t_0 to t of the r,s entry of the transition probability matrix, $\boldsymbol{P}(t)$.

For person in state r at current time t_0, let

$e_{rs}(t)$ is the expected duration of stay in state s in the interval (t_0,t), $s = 1,2,\dots,D$.

Let an individual be in state r at time t_0 and, for each u, $t_0 \le u \le t$, the indicator function $I_{rs}(u)$ is defined as:

$$I_{rs}(u) = \begin{cases} 1 & if\ the\ individual\ is\ in\ state\ r\ at\ time\ t \\ 0 & otherwise \end{cases}, \tag{4.1}$$

With the expectation

$$E[I_{rs}(u)] = p_{rs}(u) \qquad (4.2)$$

Then,

$$e_{rs}(t) = E\int_{t_0}^{t} I_{rs}(u)\ du, \qquad (4.3)$$

Interchanging the expectation and the integral sign gives

$$e_{rs}(t) = \int_{t_0}^{t} p_{rs}(u)\ du, \quad t_0 \le u \le t\ , \qquad r,s = 1,2,\dots,D \qquad (4.4)$$

The sum of the expected durations of stay over all states is equal to the entire length of the interval,

$$e_{r1}(t) + e_{rs}(t) + \cdots + e_{rs}(t) = t, \qquad r = 1,2,\dots,D \qquad (4.5)$$

[Chiang (1968)].

4.2 The population size of states:

It provides a description of population size in all states over a period of time. An individual in state S_r at time 0 must be either in the same state or move to another state at time t.

At time t = 0, let there be $x_1(0)$ individuals in state S_1 and $x_2(0)$ individuals in state S_2 , and so on $x_r(0)$ individuals in states S_r , where $r = 1,2,\dots,D$. Thus the sum $x(0) = x_1(0) + x_2(0) + \cdots + x_D\ (0)$ be the initial size of the population.

Suppose that the $x(0)$ individuals travel independently from one state to another, and at the end of the interval $(0,t)$ individuals are in states $S_1, S_2, \dots, S_D$,Then

$$x(0) = X_1(t) + X_2(t) + \cdots + X_D(t) \qquad (4.6)$$

Each r of the random variables on the right side of (4.6) has a multinomial distribution with probability generating function given by:

$$E\left[z_1^{X_{r1}(t)} z_2^{X_{r2}(t)} \dots z_D^{X_{rs}(t)} \mid x_r(0)\right] = [p_{r1}(t)\, z_1 + p_{r2}(t)\, z_2 + \cdots + p_{rD}(t)\, z_D]^{x_r(0)} \qquad (4.7)$$

Therefore, the probability generating function of the joint probability distribution for the population sizes of all the states at time t is

$$E\left[z_1^{X_{r1}(t)} z_2^{X_{r2}(t)} \dots z_D^{X_{rs}(t)} \mid x_1(0), x_2(0), \dots, x_r(0)\right] = \prod_r [p_{r1}(t)\, z_1 + p_{r2}(t)\, z_2 + \cdots + p_{rD}(t)\, z_D]^{x_r(0)} \qquad (4.8)$$

and the joint probabilities are

$$p\left(X_1(t) = x_1, X_2(t) = x_2, \dots, X_s(t) = x_s \mid x_1(0), x_2(0), \dots, x_r(0)\right) = \sum_{rs} \prod_{r=1}^{D} \frac{x_r(0)!}{x_{r1}!\, x_{r2}! \dots x_{rD}!} p_{r1}(t)^{x_{r1}}\, p_{r2}(t)^{x_{r2}} \dots\, p_{rD}(t)^{x_{rD}} \quad r, s = 1,2, \dots, D \qquad (4.9)$$

The expected number of individuals in state S_β at time t is given by:

$$E\left[X_\beta(t) \mid x_1(0), x_2(0), \dots, x_r(0)\right] = x_1(0)\, p_{1\beta}(t) + x_2(0)\, p_{2\beta}(t) + \cdots + x_r(0)\, p_{r\beta}(t) \qquad (4.10)$$

[Chiang (1968)].

5. The Suggested Model

The model contains four transient states and one absorbing state. The four transient states are healthy state S_1, mild disease state S_2, moderate disease state S_3 and the severe disease state S_4. An absorbing state is the death state S_5 .

5.1 Model Assumption

Transitions are permitted from:

- healthy state to mild state $(S_1 \rightarrow S_2)$.
- healthy state to death state $(S_1 \rightarrow S_5)$.
- mild state to moderate state $(S_2 \rightarrow S_3)$.
- mild state to death state $(S_2 \rightarrow S_5)$.
- moderate state to severe state $(S_3 \rightarrow S_4)$.
- moderate state to death state $(S_3 \rightarrow S_5)$.
- severe state to death state $(S_4 \rightarrow S_5)$.
- The considered disease is so dangerous that recovery from it is not allowed i.e. no transition from mild, moderate state and severe disease state to healthy state.

The possible transitions are shown in the following figure:

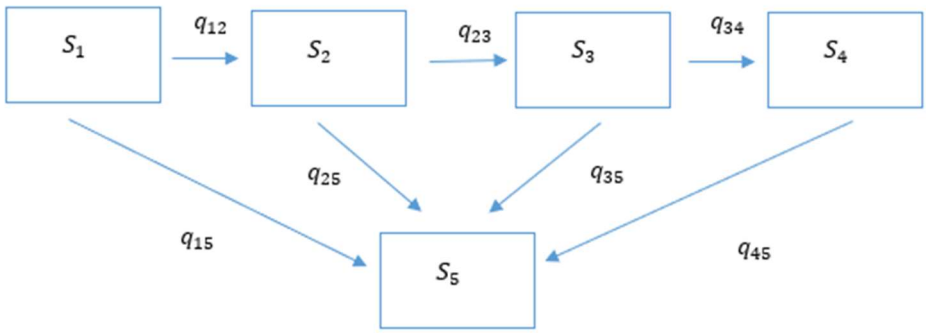

Figure 5.1: The proposed 5-state model.

It is assumed that the transitions between states described by an irreversible continuous-time five-state model. The transition intensities are allowed to depend on time where transitions are specified by parametric models including exponential, Weibull. Let t denotes time from state r entry to state s. At $t \geq 0$, the true state of an individual is $Y_t \in \{1,2,3,4,5\}$. The death state is state 5. Given time interval $[t_1, t_2]$, the cumulative hazard functions for leaving state 1,2,3 and 4 are given by

$$H1(t_1, t_2) = \int_{t_1}^{t_2} [q_{12}(u) + q_{15}(u)]du, \quad (5.1)$$

$$H2(t_1, t_2) = \int_{t_1}^{t_2} [q_{23}(u) + q_{25}(u)]du, \quad (5.2)$$

$$H3(t_1, t_2) = \int_{t_1}^{t_2} [q_{34}(u) + q_{35}(u)]du, \quad (5.3)$$

$$H4(t_1, t_2) = \int_{t_1}^{t_2} q_{45}(u)\, du, \quad (5.4)$$

respectively, where $q_{rs}(t)$ is called the intensity of a transition from state r to state s, for $r \neq s$.

Transition probabilities $p_{rs}(t_1, t_2) = p(Y_{t_2}(t) = s | Y_{t_1}(t) = r)$ are given by

$$p_{11}(t_1, t_2) = \exp[-H1(t_1, t_2)], \quad (5.5)$$

$$p_{12}(t_1, t_2) = \int_{t_1}^{t_2} \exp[-H1(t_1, u)]\ q_{12}(u) \exp[-H2(u, t_2)]\, du, \quad (5.6)$$

$$p_{13}(t_1, t_2) = \int_{t_1}^{t_2} \int_{u}^{t_2} \exp[-H1(t_1, u)]\ q_{12}(u) \exp[-H2(u, v)]\ q_{23}(v) \exp[-H3(v, t_2)]\, dv\, du, \quad (5.7)$$

$$p_{14}(t_1,t_2) = \int_{t_1}^{t_2}\int_{u}^{t_2}\int_{v}^{t_2} \exp[-H1(t_1,u)]\; q_{12}(u)\exp[-H2(u,v)]\; q_{23}(v)\exp[-H3(v,k)]\, q_{34}(k)\exp[-H4(k,t_2)]\, dk\, dv\, du, \quad (5.8)$$

$$p_{15}(t_1,t_2) = 1 - p_{11}(t_1,t_2) - p_{12}(t_1,t_2) - p_{13}(t_1,t_2) - p_{14}(t_1,t_2), \quad (5.9)$$

$$p_{22}(t_1,t_2) = \exp[-H2(t_1,t_2)], \quad (5.10)$$

$$p_{23}(t_1,t_2) = \int_{t_1}^{t_2} \exp[-H2(t_1,u)]\; q_{12}(u)\exp[-H3(u,t_2)]\, du, \quad (5.11)$$

$$\boldsymbol{p_{24}(t_1,t_2) = \int_{t_1}^{t_2}\int_{u}^{t_2} \exp[-H2(t_1,u)]\; q_{23}(u)\exp[-H3(u,v)]\; q_{34}(v)\exp[-H4(v,t_2)]\, dv\, du,} \quad \mathbf{(5.12)}$$

$$p_{25}(t_1,t_2) = 1 - p_{22}(t_1,t_2) - p_{23}(t_1,t_2) - p_{24}(t_1,t_2), \quad (5.13)$$

$$p_{33}(t_1,t_2) = \exp[-H3(t_1,t_2)], \quad (5.14)$$

$$p_{34}(t_1,t_2) = \int_{t_1}^{t_2} \exp[-H3(t_1,u)]\; q_{34}(u)\exp[-H4(u,t_2)]\, du, \quad (5.15)$$

$$p_{35}(t_1,t_2) = 1 - p_{33}(t_1,t_2) - p_{34}(t_1,t_2), \quad (5.16)$$

$$p_{44}(t_1,t_2) = \exp[-H4(t_1,t_2)], \quad (5.17)$$

$$p_{45}(t_1,t_2) = 1 - p_{44}(t_1,t_2), \quad (5.18)$$

$$p_{55}(t_1,t_2) = 1, \quad (5.19)$$

5.2 The exponential model

The exponential model is the simplest parametric hazard specification, which does not allow for time-dependent modelling. In the exponential model, transition-specific hazards are specified by constants. For the current five-state model. Let

$$q_{rs}(t) = q_{rs}\ ,\ for\ (r,s) \in \{(1,2),(1,5),\ (2,3),(2,5),\ (3,4),(3,5),(4,5)\}, \qquad (5.20)$$

Then, the transition probabilities are as follows:

$$p_{11}(t_1,t_2) = \exp[-(t_2-t_1)(q_{12}+q_{15})], \qquad (5.21)$$

$$p_{12}(t_1,t_2) = \frac{q_{12}}{q_{12}+q_{15}-q_{23}-q_{25}}[\exp(-(q_{23}+q_{25})(t_2-t_1) - \exp[-(q_{12}+q_{15})(t_2-t_1)]], \qquad (5.22)$$

$$p_{13}(t_1,t_2) = \frac{q_{12}\,q_{23}\left[(q_{22}-q_{33})e^{q_{11}(t_2-t_1)} - (q_{11}-q_{33})e^{q_{22}(t_2-t_1)} + (q_{11}-q_{22})e^{q_{33}(t_2-t_1)}\right]}{(q_{11}-q_{33})(q_{22}-q_{33})(q_{11}-q_{22})}, \qquad (5.23)$$

$$p_{14}(t_1,t_2) = \frac{q_{12}\,q_{23}\,q_{34}}{(q_{33}-q_{44})}\left[\frac{z\ e^{q_{11}(t_2-t_1)}}{(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})(q_{11}-q_{33})(q_{11}-q_{44})} - \frac{(q_{33}-q_{44})\ e^{q_{22}(t_2-t_1)}}{(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})} + \frac{e^{q_{33}(t_2-t_1)}}{(q_{22}-q_{33})(q_{11}-q_{33})} - \frac{e^{q_{44}(t_2-t_1)}}{(q_{22}-q_{44})(q_{11}-q_{44})}\right], \qquad (5.24)$$

where

$$z = (q_{22}-q_{44})(q_{11}-q_{33})(q_{11}-q_{44}) - (q_{22}-q_{33})(q_{11}-q_{33})(q_{11}-q_{44}) - (q_{22}-q_{44})(q_{11}-q_{22})(q_{11}-q_{44}) + (q_{22}-q_{33})(q_{11}-q_{33})(q_{11}-q_{22})$$

$$p_{15}(t_1,t_2) = 1 - \exp[-(t_2-t_1)(q_{12}+q_{15})] - \frac{q_{12}}{q_{12}+q_{15}-q_{23}-q_{25}}[\exp(-(q_{23}+q_{25})(t_2-t_1) - \exp[-(q_{12}+q_{15})(t_2-t_1)]] - \frac{q_{12}\,q_{23}\,q_{34}}{(q_{33}-q_{44})}\left[\frac{z\ e^{q_{11}(t_2-t_1)}}{(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})(q_{11}-q_{33})(q_{11}-q_{44})} - \frac{(q_{33}-q_{44})\ e^{q_{22}(t_2-t_1)}}{(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})} + \frac{e^{q_{33}(t_2-t_1)}}{(q_{22}-q_{33})(q_{11}-q_{33})} - \frac{e^{q_{44}(t_2-t_1)}}{(q_{22}-q_{44})(q_{11}-q_{44})}\right], \quad (5.25)$$

$$p_{22}(t_1,t_2) = \exp[-(t_2-t_1)(q_{23}+q_{25})], \quad (5.26)$$

$$p_{23}(t_1,t_2) = \frac{q_{23}}{q_{23}+q_{25}-q_{34}-q_{35}}[\exp(-(q_{34}+q_{35})(t_2-t_1) - \exp[-(q_{23}+q_{25})(t_2-t_1)]], \quad (5.27)$$

$$p_{24}(t_1,t_2) = q_{23}q_{34}\left[\frac{e^{q_{22}(t_2-t_1)}}{(q_{22}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{33}(t_2-t_1)}}{(q_{33}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{44}(t_2-t_1)}}{(q_{33}-q_{44})(q_{22}-q_{44})}\right], \quad (5.28)$$

$$p_{25}(t_1,t_2) = 1 - \exp[-(t_2-t_1)(q_{23}+q_{25})] - \frac{q_{23}}{q_{23}+q_{25}-q_{34}-q_{35}}[\exp(-(q_{34}+q_{35})(t_2-t_1) - \exp[-(q_{23}+q_{25})(t_2-t_1)] - q_{23}q_{34}\left[\frac{e^{q_{22}(t_2-t_1)}}{(q_{22}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{33}(t_2-t_1)}}{(q_{33}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{44}(t_2-t_1)}}{(q_{33}-q_{44})(q_{22}-q_{44})}\right], \quad (5.29)$$

$$p_{33}(t_1,t_2) = \exp[-(t_2-t_1)(q_{34}+q_{35})], \quad (5.30)$$

$$p_{34}(t_1,t_2) = \frac{q_{34}}{q_{34}+q_{35}-q_{45}}[\exp(-q_{45}(t_2-t_1) - \exp[-(q_{34}+q_{35})(t_2-t_1)]], \quad (5.31)$$

$$p_{35}(t_1,t_2) = 1 - \exp\left[-(t_2-t_1)(q_{34}+q_{35})\right] - \frac{q_{34}}{q_{34}+q_{35}-q_{45}}\left[\exp(-q_{45}(t_2-t_1) - \exp[-(q_{34}+q_{35})(t_2-t_1)]\right], \quad (5.32)$$

$$p_{44}(t_1,t_2) = \exp[-q_{45}(t_2-t_1)], \quad (5.33)$$

$$p_{45}(t_1,t_2) = 1 - \exp[-q_{45}(t_2-t_1)], \quad (5.34)$$

For an individual, the likelihood function is given by (3.1)

If the state is right censored at t_{J}, then

$$C(y_{\mathrm{J}}/y_{\mathrm{J}-1}) = \sum_{s=1}^{4} P(Y_{\mathrm{J}} = \mathrm{s} | Y_{\mathrm{J}-1} = y_{\mathrm{J}-1}), \quad (5.35)$$

If death is observed at t_{J}, then

$$C(y_{\mathrm{n}}/y_{\mathrm{n}-1}) = \sum_{s=1}^{4} P(Y_{\mathrm{J}} = \mathrm{s} | Y_{\mathrm{J}-1} = y_{\mathrm{J}-1})\, q_{s5}(t_{\mathrm{J}}), \quad (5.36)$$

Substituting with probabilities in (3.1) , differentiating with respect to $\boldsymbol{\theta}$ and equating to zero yields the score equations. These equations don't have closed form solution. They can be solved numerically to obtain the estimator of the elements of the transition intensities matrix $\hat{q}_{11}, \hat{q}_{12}, \hat{q}_{15}, \hat{q}_{22}, \hat{q}_{23}, \hat{q}_{25}, \hat{q}_{33}, \hat{q}_{34}, \hat{q}_{35}$, $\hat{q}_{44}$ *and* $\hat{q}_{45}$.

Using equation (4.4) and $q_{11} = -(q_{12}+q_{15})$, $q_{22} = -(q_{23}+q_{25})$, $q_{33} = -(q_{34}+q_{35})$, $q_{44} = -q_{45}$, the expected duration of stay in S_1 , S_2 , S_3, S_4 and S_5 in the interval $(0,t)$ can be derived respectively as follows:

- For an individual in state S_1 at time 0 :

$$e_{11}(t) = \frac{e^{q_{11}t} - 1}{q_{11}}, \quad (5.37)$$

$$e_{12}(t) = \frac{q_{12}[\frac{(e^{q_{11}t}-1)}{q_{11}} - \frac{(e^{q_{22}t}-1)}{q_{22}}]}{q_{11}-q_{22}}, \quad (5.38)$$

$$e_{13}(t) = \frac{q_{12}\, q_{23}\left[(q_{22}-q_{33})\frac{(e^{q_{11}t}-1)}{q_{11}} - (q_{11}-q_{33})\frac{(e^{q_{22}t}-1)}{q_{22}} + (q_{11}-q_{22})\frac{(e^{q_{33}t}-1)}{q_{33}}\right]}{(q_{11}-q_{33})(q_{22}-q_{33})(q_{11}-q_{22})}, \quad (5.39)$$

$$e_{14}(t) = \frac{q_{12}\, q_{23}\, q_{34}}{(q_{33}-q_{44})}\left[\frac{z\,(e^{q_{11}t}-1)}{q_{11}(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})(q_{11}-q_{33})(q_{11}-q_{44})} - \frac{(q_{33}-q_{44})\ (e^{q_{22}t}-1)}{q_{22}(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})} + \frac{(e^{q_{33}t}-1)}{q_{33}(q_{22}-q_{33})(q_{11}-q_{33})} - \frac{(e^{q_{44}t}-1)}{q_{44}\,(q_{22}-q_{44})(q_{11}-q_{44})}\right], \quad (5.40)$$

$$\begin{aligned} e_{15}(t) = t &- \frac{(e^{q_{11}t}-1)}{q_{11}} - \frac{q_{12}\left[\frac{(e^{q_{11}t}-1)}{q_{11}} - \frac{(e^{q_{22}t}-1)}{q_{22}}\right]}{q_{11}-q_{22}} \\ &- \frac{q_{12}\, q_{23}\left[(q_{22}-q_{33})\frac{(e^{q_{11}t}-1)}{q_{11}} - (q_{11}-q_{33})\frac{(e^{q_{22}t}-1)}{q_{22}} + (q_{11}-q_{22})\frac{(e^{q_{33}t}-1)}{q_{33}}\right]}{(q_{11}-q_{33})(q_{22}-q_{33})(q_{11}-q_{22})} \\ &- \frac{q_{12}\, q_{23}\, q_{34}}{(q_{33}-q_{44})}\left[\frac{z\,(e^{q_{11}t}-1)}{q_{11}(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})(q_{11}-q_{33})(q_{11}-q_{44})}\right. \\ &- \frac{(q_{33}-q_{44})\ (e^{q_{22}t}-1)}{q_{22}(q_{22}-q_{33})(q_{11}-q_{22})(q_{22}-q_{44})} + \frac{(e^{q_{33}t}-1)}{q_{33}(q_{22}-q_{33})(q_{11}-q_{33})} \\ &\left. - \frac{(e^{q_{44}t}-1)}{q_{44}\,(q_{22}-q_{44})(q_{11}-q_{44})}\right], \end{aligned} \quad (5.41)$$

- For an individual in state S_2 at time 0 :

$$e_{22}(t) = \frac{e^{q_{22}t}-1}{q_{22}}, \quad (5.42)$$

$$e_{23}(t) = \frac{q_{23}}{(q_{22}-q_{33})}\left[\frac{(e^{q_{22}t}-1)}{q_{22}} - \frac{(e^{q_{33}t}-1)}{q_{33}}\right], \quad (5.43)$$

$$e_{24}(t) = q_{23}q_{34}\left[\frac{e^{q_{22}t}-1}{q_{22}(q_{22}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{33}t}-1}{q_{33}(q_{33}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{44}t}-1}{q_{44}(q_{33}-q_{44})(q_{22}-q_{44})}\right], \quad (5.44)$$

$$e_{25}(t) = t - \frac{e^{q_{22}t}-1}{q_{22}} - \frac{q_{23}}{(q_{22}-q_{33})}\left[\frac{(e^{q_{22}t}-1)}{q_{22}} - \frac{(e^{q_{33}t}-1)}{q_{33}}\right] - q_{23}q_{34}\left[\frac{e^{q_{22}t}-1}{q_{22}(q_{22}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{33}t}-1}{q_{33}(q_{33}-q_{44})(q_{22}-q_{33})} - \frac{e^{q_{44}t}-1}{q_{44}(q_{33}-q_{44})(q_{22}-q_{44})}\right], \quad (5.45)$$

- For an individual in state S_3 at time 0:

$$e_{33}(t) = \frac{e^{q_{33}t}-1}{q_{33}}, \quad (5.46)$$

$$e_{34}(t) = \frac{q_{34}}{(q_{33}-q_{44})}\left[\frac{e^{q_{33}t}-1}{q_{33}} - \frac{e^{q_{44}t}-1}{q_{44}}\right], \quad (5.47)$$

$$e_{35}(t) = t - \frac{e^{q_{33}t}-1}{q_{33}} - \frac{q_{34}}{(q_{33}-q_{44})}\left[\frac{e^{q_{33}t}-1}{q_{33}} - \frac{e^{q_{44}t}-1}{q_{44}}\right], \quad (5.48)$$

For an individual in state S_4 at time 0 :

$$e_{44}(t) = \frac{e^{q_{44}t}-1}{q_{44}}, \quad (5.49)$$

$$e_{45}(t) = t + \frac{1-e^{q_{44}t}}{q_{44}}, \quad (5.50)$$

5.3 The Weibull model

In the Weibull model, transition-specific hazards are time-dependent. For the current five-state model. Let

$$q_{rs}(t) = \alpha\lambda_{rs}t^{\alpha-1} \quad for\ (r,s) \in \{(1,2),(1,5),\ (2,3),(2,5),\ (3,4),(3,5),(4,5)\}, \qquad (5.51)$$

where for each pair (r,s), the scale parameter is $\alpha > 0$ and the shape parameter is $\lambda_{rs} > 0$.

Then, the transition probabilities are as follows:

$$p_{11}(t_1,t_2) = \exp[-(t_2^{\alpha} - t_1^{\alpha})(\lambda_{12} + \lambda_{15})], \qquad (5.52)$$

$$p_{12}(t_1,t_2) = \frac{\lambda_{12}}{\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15}}[\exp(-(\lambda_{12} + \lambda_{15})(t_2^{\alpha} - t_1^{\alpha}) - \exp[-(\lambda_{23} + \lambda_{25})(t_2^{\alpha} - t_1^{\alpha})]], \qquad (5.53)$$

$$p_{13}(t_1,t_2) = \frac{\lambda_{12}\,\lambda_{23}[(\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})e^{-(\lambda_{12}+\lambda_{15})(t_2^{\alpha}-t_1^{\alpha})} - (\lambda_{34} + \lambda_{35} - \lambda_{12} - \lambda_{15})e^{-(\lambda_{23}+\lambda_{25})(t_2^{\alpha}-t_1^{\alpha})} + (\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15})e^{-(\lambda_{34}+\lambda_{35})(t_2^{\alpha}-t_1^{\alpha})}]}{(\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15})\,(\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})(\lambda_{34} + \lambda_{35} - \lambda_{12} - \lambda_{15})}, \qquad (5,54)$$

$$\boldsymbol{p_{14}(t_1,t_2)} = \frac{\lambda_{12}\,\lambda_{23}\,\lambda_{34}}{(\lambda_{45}-\lambda_{34}-\lambda_{35})}\left[\frac{z^{*}\,\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{12}+\lambda_{15})]}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{12}-\lambda_{15})} - \frac{(\lambda_{45}-\lambda_{34}-\lambda_{35})\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{12}+\lambda_{15})]}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})} + \frac{\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{34}+\lambda_{35})]}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})} - \frac{e^{-\lambda_{45}(t_2^{\alpha}-t_1^{\alpha})}}{(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{45}-\lambda_{12}-\lambda_{15})}\right], \qquad (5.55)$$

where

$$\begin{aligned} z^{*} = {} & (\lambda_{45} - \lambda_{23} - \lambda_{25})(\lambda_{34} + \lambda_{35} - \lambda_{12} - \lambda_{15})(\lambda_{45} - \lambda_{12} - \lambda_{15}) \\ & - (\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})(\lambda_{34} + \lambda_{35} - \lambda_{12} - \lambda_{15})(\lambda_{45} - \lambda_{12} - \lambda_{15}) \\ & - (\lambda_{45} - \lambda_{23} - \lambda_{25})(\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15})(\lambda_{45} - \lambda_{12} - \lambda_{15}) \\ & + (\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})(\lambda_{34} + \lambda_{35} - \lambda_{12} - \lambda_{15})(\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15}), \boldsymbol{(5.56)} \end{aligned}$$

$$p_{15}(t_1,t_2)$$
$$= 1-\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{12}+\lambda_{15})]-\frac{\lambda_{12}}{\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15}}[\exp(-(\lambda_{12}+\lambda_{15})(t_2^{\alpha}-t_1^{\alpha})-\exp[-(\lambda_{23}+\lambda_{25})(t_2^{\alpha}-t_1^{\alpha})]]$$
$$-\frac{\lambda_{12}\,\lambda_{23}[(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})e^{(\lambda_{12}+\lambda_{15})(t_2^{\alpha}-t_1^{\alpha})}-(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})e^{(\lambda_{23}+\lambda_{25})(t_2^{\alpha}-t_1^{\alpha})}+(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})e^{(\lambda_{34}+\lambda_{35})(t_2^{\alpha}-t_1^{\alpha})}]}{(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})\,(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})}$$
$$-\frac{\lambda_{12}\,\lambda_{23}\,\lambda_{34}}{(\lambda_{45}-\lambda_{34}-\lambda_{35})}\Big[\frac{z^{*}\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{12}+\lambda_{15})]}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{12}-\lambda_{15})}$$
$$-\frac{(\lambda_{45}-\lambda_{34}-\lambda_{35})\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{12}+\lambda_{15})]}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})}+\frac{\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{34}+\lambda_{35})]}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})}$$
$$-\frac{e^{-\lambda_{45}(t_2^{\alpha}-t_1^{\alpha})}}{(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{45}-\lambda_{12}-\lambda_{15})}\Big], \qquad (5.57)$$

$$p_{22}(t_1,t_2)=\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{23}+\lambda_{25})], \qquad (5.58)$$

$$p_{23}(t_1,t_2)=\frac{\lambda_{23}}{\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25}}[\exp(-(\lambda_{23}+\lambda_{25})(t_2^{\alpha}-t_1^{\alpha})$$
$$-\exp[-(\lambda_{34}+\lambda_{35})(t_2^{\alpha}-t_1^{\alpha})]], \qquad (5.59)$$

$$p_{24}(t_1,t_2)=\frac{\lambda_{23}\,\lambda_{34}}{(\lambda_{45}-\lambda_{34}-\lambda_{35})(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{45}-\lambda_{23}-\lambda_{25})}[\,(\lambda_{45}-\lambda_{34}-\lambda_{35})\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{23}+\lambda_{25})]$$
$$-(\lambda_{45}-\lambda_{23}-\lambda_{25})\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{34}+\lambda_{35})]$$
$$-(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})\exp[-\lambda_{45}(t_2^{\alpha}-t_1^{\alpha})]], \qquad (5.60)$$

$$p_{25}(t_1,t_2)$$
$$=1-\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{23}+\lambda_{25})]$$
$$-\frac{\lambda_{23}}{\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25}}[\exp(-(\lambda_{23}+\lambda_{25})(t_2^{\alpha}-t_1^{\alpha})-\exp[-(\lambda_{34}+\lambda_{35})(t_2^{\alpha}-t_1^{\alpha})]]$$
$$-\frac{\lambda_{23}\,\lambda_{34}}{(\lambda_{45}-\lambda_{34}-\lambda_{35})(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{45}-\lambda_{23}-\lambda_{25})}[\,(\lambda_{45}-\lambda_{34}-\lambda_{35})\exp[-(t_2^{\alpha}$$
$$-t_1^{\alpha})(\lambda_{23}+\lambda_{25})]-(\lambda_{45}-\lambda_{23}-\lambda_{25})\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{34}+\lambda_{35})]$$
$$-(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})\exp[-\lambda_{45}(t_2^{\alpha}-t_1^{\alpha})]], \qquad (5.61)$$

$$p_{33}(t_1,t_2)=\exp[-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{34}+\lambda_{35})], \qquad (5.62)$$

$$p_{34}(t_1,t_2)=\frac{\lambda_{34}}{\lambda_{45}-\lambda_{34}-\lambda_{35}}[\exp(-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{34}+\lambda_{35})-\exp[-\lambda_{45}(t_2^{\alpha}-t_1^{\alpha})]], \qquad (5.63)$$

$$p_{35}(t_1,t_2)=1-\frac{\lambda_{34}}{\lambda_{45}-\lambda_{34}-\lambda_{35}}[\exp(-(t_2^{\alpha}-t_1^{\alpha})(\lambda_{34}+\lambda_{35})-\exp[-\lambda_{45}(t_2^{\alpha}-t_1^{\alpha})]], \qquad (5.64)$$

$$p_{44}(t_1,t_2)=\exp[-\lambda_{45}(t_2^{\alpha}-t_1^{\alpha})], \qquad (5.65)$$

$$p_{45}(t_1, t_2) = 1 - \exp[-\lambda_{45}(t_2^{\alpha} - t_1^{\alpha})], \quad (5.66)$$

For an individual, the likelihood function is given by (3.1) and substituting with probabilities in (3.1) , differentiating with respect to $\boldsymbol{\theta}$ and equating to zero yields the score equations. These equations don't have closed form solution. They can be solved numerically to obtain $\alpha, \hat{\lambda}_{12}, \hat{\lambda}_{15}, \hat{\lambda}_{23}, \hat{\lambda}_{25}, \hat{\lambda}_{34}, \hat{\lambda}_{35}$ *and* $\hat{\lambda}_{45}$.

Using Equation (4.4) the expected duration of stay in S_1 , S_2 , S_3, S_4 and S_5 in the interval $(0, t)$ can be derived respectively as follows:

- For an individual in state S_1 at time 0 :

$$e_{11}(t) = \frac{1 - e^{-(\lambda_{12}+\lambda_{15})t}}{(\lambda_{12} + \lambda_{15})}, \quad (5.67)$$

$$e_{12}(t) = \frac{\lambda_{12}}{\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15}} \left[\frac{1 - e^{-(\lambda_{12}+\lambda_{15})t}}{(\lambda_{12} + \lambda_{15})} - \frac{1 - e^{-(\lambda_{23}+\lambda_{25})t}}{(\lambda_{23} + \lambda_{25})}\right], \quad (5.68)$$

$$e_{13}(t) = \frac{\lambda_{12}\lambda_{23}\left[(\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})\frac{(1 + e^{-(\lambda_{12}+\lambda_{15})t})}{(\lambda_{12} + \lambda_{15})} - (\lambda_{34} + \lambda_{35} - \lambda_{12} - \lambda_{15})\frac{(1 + e^{-(\lambda_{23}+\lambda_{25})t})}{(\lambda_{23} + \lambda_{25})} + (\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15})\frac{(1 + e^{-(\lambda_{34}+\lambda_{35})t})}{(\lambda_{34} + \lambda_{35})}\right]}{(\lambda_{23} + \lambda_{25} - \lambda_{12} - \lambda_{15})(\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})(\lambda_{34} + \lambda_{35} - \lambda_{12} - \lambda_{15})}, \quad (5.69)$$

$$e_{14}(t) = \frac{\lambda_{12}\lambda_{23}\lambda_{34}}{(\lambda_{45} - \lambda_{34} - \lambda_{35})}\left[\frac{z\left(\frac{(1+e^{-(\lambda_{12}+\lambda_{15})t})}{(\lambda_{12}+\lambda_{15})}\right)}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{12}-\lambda_{15})} - \frac{(\lambda_{45}-\lambda_{34}-\lambda_{35})\frac{(1+e^{-(\lambda_{23}+\lambda_{25})t})}{(\lambda_{23}+\lambda_{25})}}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})} + \frac{\frac{(1+e^{-(\lambda_{34}+\lambda_{35})t})}{(\lambda_{34}+\lambda_{35})}}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})} - \frac{\frac{(1+e^{-\lambda_{45}t})}{(\lambda_{45})}}{(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{45}-\lambda_{12}-\lambda_{15})}\right], \quad (5.70)$$

$$e_{15}(t) = t - \frac{1-e^{-(\lambda_{12}+\lambda_{15})t}}{(\lambda_{12}+\lambda_{15})} - \frac{\lambda_{12}}{\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15}}\left[\frac{1-e^{-(\lambda_{12}+\lambda_{15})t}}{(\lambda_{12}+\lambda_{15})} - \frac{1-e^{-(\lambda_{23}+\lambda_{25})t}}{(\lambda_{23}+\lambda_{25})}\right],$$
$$- \frac{\lambda_{12}\lambda_{23}\left[(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})\frac{(1+e^{-(\lambda_{12}+\lambda_{15})t})}{(\lambda_{12}+\lambda_{15})} - (\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})\frac{(1+e^{-(\lambda_{23}+\lambda_{25})t})}{(\lambda_{23}+\lambda_{25})} + (\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})\frac{(1+e^{-(\lambda_{34}+\lambda_{35})t})}{(\lambda_{34}+\lambda_{35})}\right]}{(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})}$$
$$- \frac{\lambda_{12}\lambda_{23}\lambda_{34}}{(\lambda_{45}-\lambda_{34}-\lambda_{35})}\left[\frac{z\left(\frac{(1+e^{-(\lambda_{12}+\lambda_{15})t})}{(\lambda_{12}+\lambda_{15})}\right)}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{12}-\lambda_{15})}\right.$$
$$- \frac{(\lambda_{45}-\lambda_{34}-\lambda_{35})\frac{(1+e^{-(\lambda_{23}+\lambda_{25})t})}{(\lambda_{23}+\lambda_{25})}}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{23}+\lambda_{25}-\lambda_{12}-\lambda_{15})(\lambda_{45}-\lambda_{23}-\lambda_{25})} + \frac{\frac{(1+e^{-(\lambda_{34}+\lambda_{35})t})}{(\lambda_{34}+\lambda_{35})}}{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{34}+\lambda_{35}-\lambda_{12}-\lambda_{15})}$$
$$\left. - \frac{\frac{(1+e^{-\lambda_{45}t})}{(\lambda_{45})}}{(\lambda_{45}-\lambda_{23}-\lambda_{25})(\lambda_{45}-\lambda_{12}-\lambda_{15})}\right], \tag{5.71}$$

- For an individual in state S_2 at time 0 :

$$e_{22}(t) = \frac{1+\exp[-(\lambda_{23}+\lambda_{25})t]}{(\lambda_{23}+\lambda_{25})}, \tag{5.72}$$

$$e_{23}(t) = \frac{\lambda_{23}}{\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25}}\left[\frac{(1+\exp[-(\lambda_{23}+\lambda_{25})t])}{(\lambda_{23}+\lambda_{25})} - \frac{(1+\exp[-(\lambda_{34}+\lambda_{35})t])}{(\lambda_{34}+\lambda_{35})}\right], \tag{5.73}$$

$$\boldsymbol{e_{24}(t) = \frac{\lambda_{23}\lambda_{34}}{(\lambda_{45}-\lambda_{34}-\lambda_{35})(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})(\lambda_{45}-\lambda_{23}-\lambda_{25})}\left[(\lambda_{45}-\lambda_{34}\right.}$$
$$\boldsymbol{- \lambda_{35})\frac{(1+\exp[-(\lambda_{23}+\lambda_{25})t])}{(\lambda_{23}+\lambda_{25})} - (\lambda_{45}-\lambda_{23}-\lambda_{25})\frac{(1+\exp[-(\lambda_{34}+\lambda_{35})t])}{(\lambda_{34}+\lambda_{35})}}$$
$$\boldsymbol{\left. - \frac{(\lambda_{34}+\lambda_{35}-\lambda_{23}-\lambda_{25})\frac{(1+\exp[-\lambda_{45}t])}{-\lambda_{45}}}{q_{44}(q_{33}-q_{44})(q_{22}-q_{44})}\right],} \tag{5.74}$$

$$e_{25}(t) = t - \frac{1 + \exp[-(\lambda_{23} + \lambda_{25})t]}{(\lambda_{23} + \lambda_{25})} - \frac{\lambda_{23}}{\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25}}\left[\frac{(1 + \exp[-(\lambda_{23} + \lambda_{25})t])}{(\lambda_{23} + \lambda_{25})} - \frac{(1 + \exp[-(\lambda_{34} + \lambda_{35})t])}{(\lambda_{34} + \lambda_{35})}\right] - \frac{\lambda_{23}\,\lambda_{34}}{(\lambda_{45} - \lambda_{34} - \lambda_{35})(\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})(\lambda_{45} - \lambda_{23} - \lambda_{25})}\left[(\lambda_{45} - \lambda_{34} - \lambda_{35})\frac{(1 + \exp[-(\lambda_{23} + \lambda_{25})t])}{(\lambda_{23} + \lambda_{25})} - (\lambda_{45} - \lambda_{23} - \lambda_{25})\frac{(1 + \exp[-(\lambda_{34} + \lambda_{35})t])}{(\lambda_{34} + \lambda_{35})} - (\lambda_{34} + \lambda_{35} - \lambda_{23} - \lambda_{25})\frac{(1 + \exp[-\lambda_{45}t])}{-\lambda_{45}}\right]}{q_{44}(q_{33} - q_{44})(q_{22} - q_{44})}, \quad (5.75)$$

- For an individual in state S_3 at time 0 :

$$e_{33}(t) = \frac{(1 + \exp[-(\lambda_{34} + \lambda_{35})t])}{(\lambda_{34} + \lambda_{35})} \quad (5.76)$$

$$e_{34}(t) = \frac{\lambda_{34}}{\lambda_{45} - \lambda_{34} - \lambda_{35}}\left[\frac{(1 + \exp[-(\lambda_{34} + \lambda_{35})t])}{(\lambda_{34} + \lambda_{35})} - \frac{1 + \exp[-\lambda_{45}t]}{\lambda_{45}}\right], \quad (5.77)$$

$$e_{35}(t) = t - \frac{\lambda_{34}}{\lambda_{45} - \lambda_{34} - \lambda_{35}}\left[\frac{(1 + \exp[-(\lambda_{34} + \lambda_{35})t])}{(\lambda_{34} + \lambda_{35})} - \frac{1 + \exp[-\lambda_{45}t]}{\lambda_{45}}\right], \quad (5.78)$$

-For an individual in state S_4 at time 0 :

$$e_{44}(t) = \frac{1 + \exp[-\lambda_{45}t]}{\lambda_{45}}, \quad (5.79)$$

$$e_{45}(t) = t - \frac{1 + \exp[-\lambda_{45}t]}{\lambda_{45}}, \quad (5.80)$$

6. Application

The suggested model is illustrated using an application of BOS data set. The dataset containing histories of bronchiolitis obliterans syndrome (BOS) from lung transplant recipients. BOS is a chronic decline in lung function, often observed after lung transplantation. The data come from Papworth Hospital U.K and are available in the **msm package**. Applying parametric multistate model requires completely observed processes. By Converting BOS data set for a multi-state model fit, where observations represent the exact transition times of the process. To obtain complete observed processes the following steps are obtained:

- specifying **T start** which representing time at the start of the interval, **T stop** representing time at the end of the interval.
- The experimental time is calculated as the difference between **T start** and **T stop**.
- The status of each individual takes 1 if the transition to **state to** was observed, or 0 if the transition to **state to** was censored.

This enables flexible parametric multi-state models to be fitted with the **flexsurv package**. The obtained data is called NEW BOS data.

6.1 Data description

NEW BOS data representing data for a five-state model. It contains a sequence of observed transitions to the next stage 2, 3, 4, representing mild, moderate and severe BOS respectively, and stage 5, representing death. It contains 818 rows, representing transitions of patient, including histories of 204 patients. All patients start in state 1 (no BOS) at six months after transplant, and may subsequently develop BOS or die. It includes patient identification number (Ptnum), the observed starting state of the transition (From), the observed or potential ending state of the transition (To), **T start** representing time at the start of the interval, **T stop** representing time at the end of the interval, Time representing The experimental time and Status takes 1 if the transition to state to was observed, or 0 if the transition to state to was censored.

6.2 Results

Sample data layout for the NEW BOS data are illustrated in Table (6.1).

Table 6.1: Sample data layout for the NEW BOS data.

No. row	Ptnum	From	To	T start	T stop	Time (months)	Status
1	200001	1	2	6.0000	58.2666	52.2666	1
2	200001	1	5	6.0000	58.2666	52.2666	0
3	200001	2	3	58.2666	78.9000	20.6334	1
4	200001	2	5	58.2666	78.9000	20.6334	0
5	200001	3	4	78.9000	118.0667	39.7670	1
6	200001	3	5	78.9000	118.0667	39.7670	0
7	200001	4	5	118.0667	126.2000	8.1333	1
8	200002	1	2	6.000000	39.6333	33.6333	1
9	200002	1	5	6.000000	39.6333	33.6333	0
10	200002	2	3	39.6333	54.6333	15.0000	1
11	200002	2	5	39.6333	54.6333	15.000	0
12	200002	3	4	54.6333	65.2666	10.6333	1
13	200002	3	5	54.6333	65.2666	10.6333	0
14	200002	4	5	65.2666	71.2000	5.9334	1

The state table for NEW BOS data is summarised by the frequencies in Table (6.2).

Table 6.2: The state table for BOS data.

To state / From state	1	2	3	4	5
1	72	103	0	0	29
2	0	15	77	0	11
3	0	0	9	52	16
4	0	0	0	9	41

Table 6.2 shows that there were 29 deaths from state 1, 11 deaths from state 2, 16 deaths from state 3 and 41 deaths from state 4. The number of transitions from stage 4 to stage 5 is highest in comparison to transition from other stages to stage 5. There are no observations of mild, moderate and severe BOS followed by an observation of no BOS (state 1).

6.2.1 The exponential model

The estimated transition probability matrix of the Exponential model at $t = 30$ months is given in Table (6.3).

Table 6.3 : The estimated transition probability matrix of the Exponential model at $t = 30$ months.

To state / From state	1	2	3	4	5
1	0.5460	0.1155	0.0894	0.0693	0.1797
2	0	0.0804	0.1793	0.3069	0.4334
3	0	0	0.0794	0.3747	0.5460
4	0	0	0	0.3850	0.6150

Table 6.3shows that

- A person in state 1, has a probability of 0.1797 of being dead after thirty months, a probability of 0.5460 being still in state 1, a probability of 0.1155 of being alive with mild BOS and probabilities of 0.0894, 0.0693 of being alive with moderate/ or severe BOS, respectively.
- A person in state 2, has a probability of 0.4334 of being dead after thirty months, a probability of 0.0804 being still in state 2 and probabilities of $0.1793, 0.3069$ of being alive with moderate/ or severe BOS, respectively.

- A person in state 3, has a probability of 0.5460 of being dead after thirty months, a probability of 0.0794 being still in state 3 and a probability of 0.3747 of being alive with severe BOS.
- A person in state 4, has a probability of 0.6150 of being dead after thirty months and a probability of 0.3850 being still in state 4 .

The likelihood estimates of the transition intensities (estimated hazards) between various stages, standard error and 95% confidence intervals of the Exponential model are shown in Table (6.4).

Table 6.4: The likelihood estimates of transition intensities (estimated hazards) between various stages, standard error and 95% confidence intervals of the Exponential model.

Transition	Transition intensities (estimates)	SE	Confidence intervals		Length
			L	U	
q_{12}	0.0155	0.0015	0.0128	0.0189	0.0061
q_{15}	0.0043	0.0008	0.0030	0.0063	0.0033
q_{23}	0.0732	0.0083	0.0586	0.0916	0.033
q_{25}	0.0104	0.0031	0.0058	0.0189	0.0131
q_{34}	0.0644	0.0089	0.0491	0.0845	0.0354
q_{35}	0.0198	0.0049	0.0121	0.0323	0.0202
q_{45}	0.0320	0.0050	0.0236	0.0435	0.0199

Table 6.4 shows that transition intensity rate of moving from one state to the next is greater than the transition intensity rate of moving to death state. It is noticed that the SE of the transition intensities are small, the estimated

transition intensities lie in 95% confidence intervals and the lengths of the confidence intervals are small.

A plot of estimated transition intensities of the Exponential model is given in Figure (6.1).

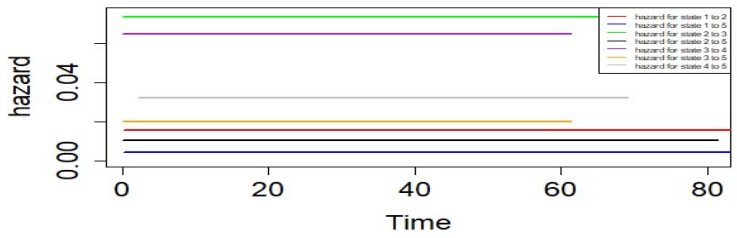

Figure 6.1 A plot of estimated transition intensities of the Exponential model.

Figure (6.1) shows that transition intensity rate of moving from one state to the next is greater than the transition intensity rate of moving to death state.

A plot of estimated cumulative hazard of transitions of Exponential model is given in Figure (6.2).

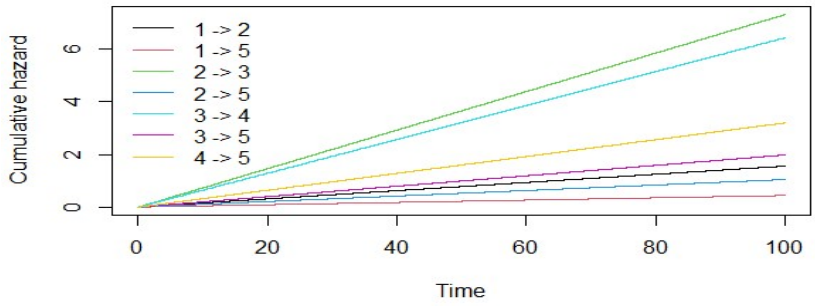

Figure 6.2 A plot of estimated cumulative hazard of transitions of Exponential model.

Figure (6.2) shows that cumulative hazard of transitions for all states are increasing over time. Transition cumulative hazards of moving from one state to the next is greater than the transition intensity rate of moving to death state.

The expected duration of stay in each state in the exponential model is given in Table (6.5).

Table 6.5: The expected duration of stay in each state in the exponential model.

Transient state / Initial state	State 1	State 2	State 3	State 4
State 1	50	9	8	16
State 2	-	12	10	21
State 3	-	-	12	24
State 4	-	-	-	31

Table 6.5 shows that

- a person in state 1 is forecasted to spend 50 months in state 1, 9 months in state 2, 8 months in state 3 and finally 16 months in state 4. These results show that a person is expected to spend more time in state 1 and state 4 compared to the time spent in other states.
- a person in state 2 is forecasted to spend 12 months in state 2,10 months in state 3, and finally 21 months in state 4. These results

show that a person is expected to spend more time in state 4 compared to the time spent in other states.

- a person in state 3 is forecasted to spend 12 months in state 3, 24 months in state 4.
- a person in state 4 is forecasted to spend 31 months in state 4.

The distribution of individuals in all states in the exponential model at time $t = 30$ months according to initial state at time $t = 6$ months is given in Table (6.6).

Table 6.6 : The distribution of individuals in all states in the exponential model at time $t = 30$ months according to initial state at time $t = 6$ months.

State at Time $t = 6$	State at Time $t = 30$					Initial population sizes
	S_1	S_2	S_3	S_4	S_5	
S_1	111	24	18	14	37	204

Table 6.6 shows the distribution of individuals in all states at time $t = 30$ months according to initial state at time $t = 6$ months. It is noticed that State 1 has the highest number of individuals. Since BOS is assumed to occur beyond six months after transplant, all individuals start from state 1 at time $t = 6$ months.

6.2.2 The Weibull model

The estimated parameters of the Weibull model are given in Table (6.7).

Table 6.7: The estimated parameters of the Weibull model

Parameters	ML estimate
α	0.6368
λ_{12}	0.0473
λ_{15}	0.0557
λ_{23}	0.0654
λ_{25}	0.0770
λ_{34}	0.0905
λ_{35}	0.1064
λ_{45}	0.1252

The estimated transition probability matrix of the Weibull model at $t = 30$ months is given in Table (6.8).

Table 6.8 : The estimated transition probability matrix of Weibull model at $t = 30$ months.

To state / From state	1	2	3	4	5
1	0.4090	0.1100	0.0270	0.0115	0.4426
2	0	0.2866	0.0920	0.0553	0.5661
3	0	0	0.1774	0.1608	0.6619
4	0	0	0	0.3370	0.6631

Table 6.8 shows that

- A person in state 1, has a probability of 0.4426 of being dead after thirty months, a probability of 0.4090 being still in state 1, a probability of 0.1100 of being alive with mild BOS and probabilities of 0.0270, 0.0115 of being alive with moderate/ or severe BOS, respectively.
- A person in state 2, has a probability of 0.5661 of being dead after thirty months, a probability of 0.2866 being still in state 2 and probabilities of $0.0920, 0.0553$ of being alive with moderate/ or severe BOS, respectively.
- A person in state 3, has a probability of 0.6619 of being dead after thirty months, a probability of 0.1774 being still in state 3 and a probability of 0.1608 of being alive with severe BOS.
- A person in state 4, has a probability of 0.6631 of being dead after thirty months and a probability of 0.3370 being still in state 4.

A plot of estimated transition intensities of Weibull model is given in Figure (6.3).

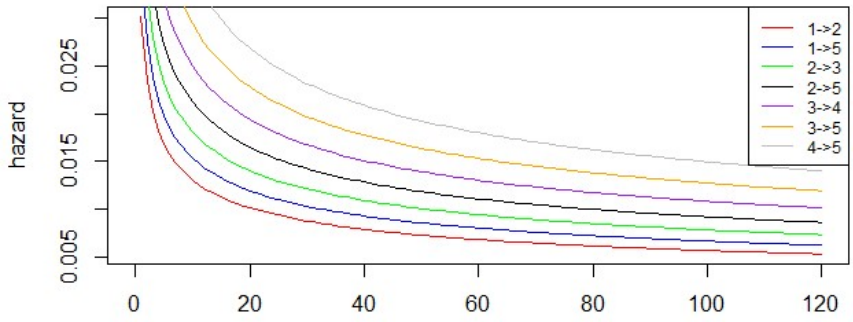

Figure 6.3 A plot of estimated transition intensities of Weibull model.

Figure (6.3) shows that transition intensities for all states are decreasing over time. Transition intensity of moving from state 4 to state 5 is the greatest.

A plot of estimated cumulative hazard of transitions of Weibull model is given in Figure (6.4).

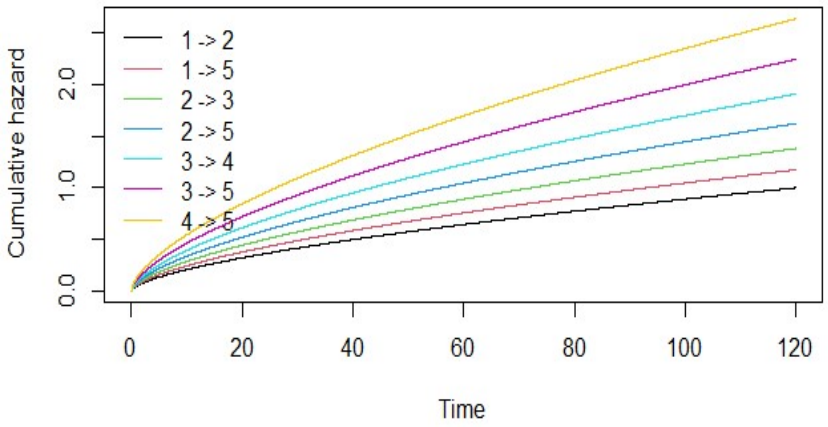

Figure 6.4 A plot of estimated cumulative hazard of transitions of Weibull model.

Figure 6.4 shows cumulative hazard of transitions for all states are increasing over time. Transition cumulative hazards of moving from state 4 to state 5 is the greatest.

The expected duration of stay in each state in the Weibull model is given in Table (6.9).

Table 6.9: The expected duration of stay in each state in the Weibull model.

Transient state / Initial state	State 1	State 2	State 3	State 4
State 1	50	14	4	4
State 2	-	30	8	8
State 3	-	-	18	17
State 4	-	-	-	37

Table 6.9 shows that

- a person in state 1 is forecasted to spend 50 months in state 1, 14 months in state 2, 4 months in state 3 and finally 4 months in state 4. These results show that a person is expected to spend more time in state 1 and state 2 compared to the time spent in other states.
- a person in state 2 is forecasted to spend 30 months in state 2, 8 months in state 3, and finally 8 months in state 4. These results show that a person is expected to spend more time in state 2 compared to the time spent in other states.
- a person in state 3 is forecasted to spend 18 months in state 3, 17 months in state 4.
- a person in state 4 is forecasted to spend 37 months in state 4.

The distribution of individuals in all states in the Weibull model at time $t = 30$ months according to initial state at time $t = 6$ months is given in Table (6.10).

Table 6.10 : The distribution of individuals in all states in the Weibull model at time $t = 30$ months according to initial state at time $t = 6$ months.

State at Time $t = 6$	State at Time $t = 30$					Initial population sizes
	S_1	S_2	S_3	S_4	S_5	
S_1	83	23	6	2	90	204

Table 6.10 shows the distribution of individuals in all states at time $t = 30$ months according to initial state at time $t = 6$ months. It is noticed that state 4 has the highest number of individuals. Since BOS is assumed to occur beyond six months after transplant, all individual start from state 1 at time $t = 6$ months.

7. Conclusions

The multi-state model is used to understand the progression of several chronic diseases involving transitions across different intermediate states indicating the severity of the disease in continuous time. The model provides more insight into the complex event pattern and thus it can be used as an effective tool to study the effectiveness of treatments. Parametric multi-state models have a particular importance in chronic diseases modelling. By direct modelling transitions intensities parametrically, one can understand how complex disease processes evolve over time. Incorporating time-dependent effects and extrapolation are much more convenient within a fully specified parametric model.

In this paper five states progression model is suggested. The suggested model is studied in the case of continuous time non - homogeneous multistate model based on non-homogeneous Markov processes. A parametric time-dependent multistate models are considered to fit a non-homogeneous Markov process where transitions are specified by the hazard of exponential and Weibull distributions. The parameters of the suggested model are estimated by maximum likelihood method. The transition probabilities are derived. Some extractor quantities of the model are derived. The estimated hazard and cumulative hazard of transitions are obtained.

The analysis in the current paper used the BOS data set provided in the R package msm. It is found that transition intensity rate of moving from one state to the next is greater than the transition intensity rate of moving to death state in the exponential model, but transition intensity of moving from state 4 to state 5 is the greatest in Weibull model. The probabilities of transition from state 3 to state 5 and from state 4 to state 5 are high in both models. The expected duration of stay in state 1 is the highest compared to the expected duration of stay in other states in both models. In both models cumulative hazard of transitions for all states are increasing over time

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