Estimation of Quality Adjusted Lifetime (QAL) Distribution

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To my parents, wife and son

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Contents

Chapter 1

Introduction

1.1 Quality Adjusted Lifetime (QAL)

Normally, overall survival time is considered as the end point for many clinical trials to study the effectiveness of different treatments. If the survival time passes through different health states, which differ in their quality of life, then other endpoints are also considered for treatment comparison, which incorporates both quality and duration of life. It is, therefore, necessary to provide a composite measure for comparison of different treatment choices, specially in the context of clinical trials, after taking into account both quality and duration of life. This issue has been first addressed by Gelber and coauthors in a series of papers (Gelber and Goldhirsch 1986; Gelber et al., 1987; Gelber et al., 1989) by introducing an endpoint called Time Without Symptoms of disease and Toxicity due to treatment (TWiST) in the context of breast cancer patients (Ludwig Breast Cancer Study Group, Trial III). Time with toxic side effects of treatment and time with unpleasant symptoms of disease are subtracted from overall survival time to calculate TWiST for each patient (Gelber et al., 1989). See also Gelber et al. (1991, 1992a, 1992b, 1995, 1996), Murray (2000) and Cole et al. (2004) for TWiST as a

composite measure for comparing treatments in the context of cancer patients.

The endpoint TWiST has been generalized by Goldhirsch et al. (1989) and Glasziou et al. (1990) to incorporate the concept of quality of life, termed as Q-TWiST which stands for 'Quality-Adjusted Time Without Symptoms of disease and Toxicity due to treatment'. The concept of quality adjusted lifetime (QAL), thus developed, has been made popular by many subsequent work and commonly used in the context where patients may experience several intermediate health states before ending in death. Quality of life associated with these states is measured by a utility coefficient ranging from zero to one. For each unit of time spent in the state, the utility coefficient reflects its value against perfect health (utility 1). Death has utility zero. This leads to a utility function over time which takes the value of the utility coefficient of the state occupied at that time. Then, QAL is formally defined as

$$Q = \int_0^T W(u)du,$$

where Q denotes the QAL, T the lifetime and $W(u)$ the utility function at time u. The number of health states is usually assumed finite. Then, the QAL reduces to a weighted sum of the time spent in each health state, where the weights are the utility coefficients. For example, as shown in Figure 1.1, if a patient experience k health states $1, \ldots, k$, which differ in their quality of life, before ending in death (D) with the corresponding sojourn times $T_1, \ldots, T_k$ and utility coefficients

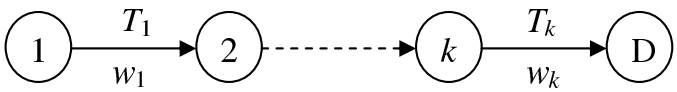

Figure 1.1: A model with k health states.

$w_1, \ldots, w_k$, then the QAL is given by

$$Q = \sum_{i=1}^{k} w_i T_i.$$

In HIV/AIDS research, for example, in a cohort of HIV positive patients, appearance of AIDS symptoms can be equated with intermediate health state before death (D). In this example, one would be interested in quality adjusted life of HIV patients. If T_{HIV} denotes the time till AIDS symptoms appear (since time of infection) and T_{AIDS} denotes the time till death (since onset of AIDS symptoms) with utility coefficients w_1 and w_2, respectively, then this QAL is defined as $w_1 T_{HIV} + w_2 T_{AIDS}$. In International Breast Cancer Study Group (IBCSG) Trial V data for cancer patients (Gelber et al. 1992a), the individuals, after going through the chemotherapy which induces a period of toxicity, start in the state of 'Toxicity' (state 1); at the end of this toxicity period they enter the state of 'No symptoms of disease and toxicity of treatment' (state 2), followed by 'Relapse of the disease' (state 3) and finally the death (absorbing state D). Here, the three periods (time spent in the health states) corresponding to the three health states are denoted by TOX, TWiST and REL. If w_1, w_2 and w_3 are the utility coefficients, then the QAL is defined as w_1TOX + w_2TWiST + w_3REL. A similar concept can be considered in the context of reliability. For example, in a parallel system with k components, the failure of successive components may be equated with successive illness states. The system fails when all the components fail. Also, while dealing with life or service times of items, the QAL may be interpreted as the quality adjusted service time as the items may be able to provide service, in its lifetime, with different levels of satisfaction or utility.

1.2 Objective and Salient Features of the Thesis

The main objective of this work is to estimate the distribution of QAL. Salient features of the thesis are as follows.

1. Develop a new method of estimating the QAL distribution, which explicitly uses the information on the interrelationship between the different health states.

2. Propose parametric, nonparametric and semi-parametric methods for different illness-death models.

3. Investigate the performance of the proposed estimator in terms of bias and precision through simulation experiments and compare with some existing estimator.

4. Analysis of real data set for illustrative purpose.

1.3 Review of Earlier Work

The aim of this work is to estimate the QAL distribution with censored data. While dealing with censored data, unfortunately, there is informative censoring when transformed into QAL scale (Gelber et al., 1989; Glasziou et al., 1990; Lin et al., 1997; Huang and Louis, 1999, Pradhan and Dewanji, 2009c). That is , even if the original lifetime T and the censoring time C are independent, the quality adjusted lifetime Q and the corresponding quality adjusted censoring time C^* do not remain independent. This, in the literature, is known as induced dependent censoring. Although it might seem natural to undertake a standard survival analysis with the observed QAL values (censored and uncensored), this approach leads to biased estimate due to this induced dependent censoring. In order to overcome this problem, Glasziou et al. (1990) have suggested partitioned survival analysis

for progressive state models restricted to a specific time, where an unbiased estimator of restricted mean QAL has been obtained by estimating the mean sojourn time in each health state separately using Kaplan-Meier (1958) estimate and then considering the weighted sum of the estimated mean sojourn times in different states. They termed this method as Q-TWiST, or Quality-Adjusted Time without Symptoms or Toxicity.

Note that the Q-TWiST method is a nonparametric method that restricts the mean survival estimate to the follow-up time of the study cohort, therefore, restricting the mean QAL as well. Having realised this, and also the fact that the estimate may be less efficient than the one based on an appropriate parametric model, Cole et al. (1994) have suggested a parametric Q-TWiST method to estimate the mean QAL. They have considered a multivariate competing risks model defined by the different health states and fit the data by modelling parametrically the different cause-specific hazard functions. The estimates of the model parameters are obtained by the maximum likelihood method, which are then used to estimate the mean QAL by simulation. Standard error and confidence interval are obtained using the bootstrap and delta method. In their simulation, they have assumed independent latent failure times and identified the minimum of them at each transition time. Other works on estimating the mean QAL are Hwang et al., (1996, 1999), Huang and Louis (1999), Zhao and Tsiatis (2000). These methods can also be used for lifetime medical cost (Bang and Tsiatis, 2000; Lin, 2003; Cook et al., 2003; Gardiner et al., 2006) and customer lifetime value (Pfeifer and Bang, 2005).

A number of different estimators have been proposed for estimating the QAL distribution. For example, Korn (1993) has proposed an improved estimator, although biased, over Kaplan-Meier estimator using the concept of inverse probability weighting. He assumed that observations on the quality of life are available only at certain discrete times. Zhao and Tsiatis (1997) have proposed a consistent

estimator for the distribution of QAL which is a member of the class of inverse probability of censoring weighted (IPCW) estimators (Robbins and Rotnitzky, 1992). Their estimator is preferable for point wise estimation, but the estimator may not be monotone (Huang and Louis, 1998) for finite sample. Huang and Louis have proposed a nonparametric estimator for the joint distribution of survival time and mark variable, where the mark variable may be quality adjusted lifetime. Zhao and Tsiatis (1999) have considered more efficient estimator than Zhao and Tsiatis (1997), but still lacks the requirement of monotonicity. Strawderman (2000) has developed a general framework from which most of the previous estimators of QAL come out as special cases. Almanassra et al. (2005) have proposed a monotonic estimator for the QAL distribution, but their method involves constrained optimization and, therefore, is computationally very intensive.

All the above estimators for the QAL distribution transform the observed data into QAL scale and then concentrate on adjusting for bias due to the induced dependence, while analyzing the data on observed QAL. It is clear that the above methods of estimating the QAL distributions are not applicable when observation on some sojourn times are missing. The times of different transitions to successive states are required to be observable in order to be able to estimate the distribution of QAL or mean QAL. This is a strong requirement while dealing with health history, specially when the patients suffer from cancer of inner organs (e.g., liver). Sometimes, the investigator has data collected at the time of death. Information on intermediate event times may be available in other secondary sources, some of which may not be accessible. For example, data on times of death from AIDS may be available to the investigator, whereas the information on times of diagnosis may be scattered over different sources, all of which may not be accessible. This loss of information results in non-observability of intermediate event times. In such situations, the methods based on the observed QAL values cannot be applied.

Regression analysis of QAL data to study any covariate effect on the QAL distribution, and also to estimate the QAL distribution for a given covariate, is an important aspect. Cole et al. (1993) have developed a method for estimating mean quality adjusted lifetime using Cox's proportional hazards model for the sojourn time in each health state. Bootstrap method has been suggested to estimate the variance of the estimator. Fine and Gelber (2001) have considered a semi-parametric bivariate linear regression model for some transformations of lifetime and QAL leading to accelerated life models for their marginal distributions. The regression coefficients are estimated based on some estimating equations which are then used to estimate the ratio of mean lifetimes, or mean QALs, corresponding to two different covariate values. Wang and Zhao (2007) have considered a regression model for the mean QAL and used the idea of inverse probability weighting to construct a simple weighted estimating equation for the regression parameters of the model. These parameter estimates are then used to estimate the mean QAL. Tunes-da-Silva et al. (2009) have considered estimation of mean QAL under semi-Markov multistate model for non-progressive processes with covariate effect. Jackknife resampling method has been used to estimate the variance of the estimator. See also Zhao and Wang (2008) for the regression analysis of mean QAL with censored data. However, estimation of QAL distribution for a given covariate has not been attempted in the literature.

1.4 Proposed Approach

In this work, a new approach for estimating the QAL distribution is proposed, in which the QAL distribution is first theoretically derived in terms of the joint distribution of sojourn times in the health states. When the sojourn times are independent, this theoretical expression for the QAL distribution involves only the marginal distributions of the different sojourn times. These sojourn time dis-

tributions are estimated from the observed lifetime data in each health state by standard survival analysis technique, which are then substituted in the theoretical expression for QAL distribution already derived to obtain its estimate. This method of estimation is possible even when some of the transition times are not observed (Kodell and Nelson, 1980; Borgan et al., 1984) as long as the sojourn time distributions are estimable by some missing data techniques. By construction, this method gives a monotonic estimate of the QAL distribution.

The multitude of possible paths of an individual's health history leads one to a compartment model, which can be modelled using transition rates, depending on past history. There is a weight or utility coefficient associated with each compartment or state. Given a model, the distribution of QAL, given by the weighted sum of sojourn times in different states, can be derived using the joint distribution of all the sojourn times. This expression can be in closed form in many situations, specially when the number of states is few. Utilizing this property, theoretical distribution of QAL has been derived for some illness-death models, before estimating the same by substituting the sojourn time distributions with the corresponding estimates. In this way, one can avoid the problem of bias due to induced dependence of censoring distribution in QAL scale, since estimation takes place in the original lifetime scale. Unlike other approaches, this method is easily amenable to incorporation of specific dependence structure between the sojourn times and any covariate effect.

Estimation of QAL distribution is considered using parametric, non-parametric and semi-parametric approaches. In parametric approach (Pradhan and Dewanji, 2009a; Pradhan et al., 2010), the theoretical distribution of QAL is derived by assuming particular parametric models for the sojourn time distributions. Model parameters are estimated by maximum likelihood method from the corresponding lifetime data. The QAL distribution is then estimated by substituting the parameters in its theoretical expression by the corresponding estimates. Standard error

of the estimator is obtained by the delta method. A parametric method in general has flexibility in the sense that it works for small sample sizes and the asymptotic properties are easier to establish using the delta method. In addition, a parametric model can also explicitly incorporate dependence between different sojourn times. Sometimes there may be evidence in favor of a particular parametric model with or without dependence. In such cases, a method based on an appropriate parametric model is more efficient than a nonparametric method. Note that some accounting for possible dependence between the different sojourn times is necessary for estimating the QAL distribution. Existing methods based on observed QAL data implicitly account for this dependence, but these methods cannot be applied when some transition times are not observable. The proposed method can handle the problem of non-observability, while accounting for dependence at the same time. Covariate effect can be easily incorporated in estimating the QAL distribution.

The nonparametric estimate of QAL distribution is obtained under the assumption that the sojourn times are independently distributed. In that case, as mentioned before, the theoretical expression for the QAL distribution involves only the marginal sojourn time distributions. The estimate of QAL distribution is obtained by substituting the sojourn time distributions by the corresponding Kaplan-Meier estimates obtained from the corresponding lifetime data. Asymptotic properties are also derived. In semi-parametric approach, hazard rate in each health state is modelled using Cox's proportional hazards regression. The estimate of QAL distribution for a given covariate is obtained by substituting the estimates of regression parameters and baseline sojourn time distributions in the expression of QAL distribution.

Note that the derivation of the theoretical distribution of QAL in general may be quite challenging and its closed form expression may not always exist. However, once the distribution of QAL is derived in a closed or in general form, it can

be estimated by substituting the model parameters with the corresponding estimates. Therefore, the expression for the QAL distribution needs to be evaluated only once.

1.5 Data Sets

In this work, two data sets, (1) Stanford Heart Transplant Data (Crowley and Hu, 1977) and (2) International Breast Cancer Study Group (IBCSG) Trial V Data (Gelber et al., 1992a), are analyzed to illustrate the proposed methodology. The two data sets are described in the following.

1.5.1 Stanford Heart Transplant Data

In Stanford Heart Transplant Program, patients have been admitted to the heart transplant program, from September 1967 to March 1974. The observations start from the admission of the patients with heart problem to the program. A donor heart, matched on blood type, has been sought, and if found available, heart transplantation has taken place. Some patients have died before a suitable heart has been found and some patients have been lost to follow-up before heart transplantation. When last seen, the state of a patient after transplantation has been given as dead (=1) or alive (=0). There have been 103 patients altogether. Of them, 69 patients have received heart transplantation, 30 have died before heart transplantation and 4 have been lost to follow up before transplantation. Out of the 69 patients with heart transplantation, 24 have been alive when last seen and the remaining 45 have been dead. For each patient, the date of acceptance into the the Stanford program and the date seen last are available along with the date of transplantation, if carried out. The covariates available are (a) previous history of any surgery, (b) age at acceptance and (c) mismatch score. Here, one

may be interested in quality adjusted life of the heart patients and whether this QAL depends on the covariate values.

1.5.2 IBCSG Trial V Data

In the IBCSG Trial V data set, 1229 patients have been randomized to receive either short duration chemotherapy (one month) or long duration chemotherapy (six or seven months). Out of the 1229 patients, 413 patients have been chosen for the short duration chemotherapy and 816 patients for the long duration chemotherapy. This randomized clinical trial compares two adjuvant chemotherapy schedules for node-positive breast cancer. For each patient, the observation consists of time till (1) the end of treatment toxicity (TOX), (2) relapse (disease-free survival time) (DFS), and (3) death from any cause (overall survival) (OS), along with censoring indicator and covariates. The three successive health states are: (1) toxic side effect of chemotherapy, (2) no symptoms of disease and toxicity of treatments and (3) disease relapsed. The sojourn times in these health states are denoted by TOX (Toxicity period), TWiST (Time without symptoms of disease and toxicity of treatment) =DFS-TOX and REL (Relapsed) = OS-DFS. Five covariates have been recorded from each patient upon enrollment in the clinical trial. The covariates are (a) treatment group, (b) tumor size, (c) age in years, (d) tumor grade and (e) number of nodes involved. One may be interested in the quality adjusted lifetime of the breast cancer patients and how it differs for different covariate values.

1.6 Summary of the Work

The summary of the whole work is presented chapterwise below.

[*Chapter 2*]: Models and Distribution of QAL

The main aim of this chapter is to describe different illness-death models those are considered for this study and derive the distribution of QAL. The proposed method of estimating the QAL distribution makes explicit use of the information on the structure of illness-death model while deriving the theoretical distribution of QAL. Other methods based on observed QAL data use this information only when transforming the data into QAL scale. As a result, these methods cannot distinguish between two illness-death models giving rise to same QAL values and, therefore, lead to less efficient estimates compared to the method which can distinguish between illness-death models. This motivates to consider the estimation of QAL distribution separately for different illness-death models. In this work, four illness-death models are considered, namely, (1) simple illness-death model, (2) progressive illness-death model, (3) competing illness-death model and (4) reversible illness-death model.

A typical simple illness-death model has three states. Starting from healthy state, an individual may enter an intermediate illness state before ending in death, or move directly to death. In progressive illness-death model, individuals may start from healthy state and then experience the different illness states $1, \ldots, k$, say, one after another in that fixed order, before moving to the absorbing state death. In a more general illness-death model , there is also the possibility of moving directly to absorbing state from any one of the k non-penultimate states $0, 1, \ldots, k-1$. In the Competing illness-death model, a healthy person transits to exactly one of the k distinct illness states $1, \ldots, k$, which presumably reduces the quality of life, and then to death without entering into any other illness states. One may also allow for a transition to death directly from the healthy state. Reversible illness-death model is a simple illness-death model, but an individual may recover from the illness state to transit back to the healthy state. That is, an individual in illness state can either recover and transit back to the healthy

state, or fail by moving to death state. Therefore, an individual may, in theory, visit the illness state an infinite number of times before moving to death.

The QAL distribution is derived in each of the above illness-death models. The theoretical distribution of QAL for the different models can be expressed analytically in general integral forms involving the joint distribution of all the sojourn times, or the individual marginal sojourn time distributions when the different sojourn times are independent. In particular, closed form expression of QAL distribution is obtained when the sojourn times are independent and exponentially distributed. In that case, for some illness-death models, the distribution of sum of independent and non-identical Gamma random variables with integer shape parameters is needed. This has been derived and discussed in Section 2.8.

[*Chapter 3*]: Induced Dependent Censoring

While dealing with censored data, unfortunately, there is induced dependent censoring when transformed into QAL scale. Due to this, as mentioned in Section 1.3, the standard survival analysis techniques can not be used with the observed QAL values. However, the issue of induced dependent censoring in the QAL scale still remains less-understood. Although there is some qualitative discussion, there is no formal proof of this dependence. There is one argument by Lin (2003) which can be described as follows. Noting that $Q = \int_0^T W(u)du$ and $C^* = \int_0^C W(u)du$, clearly, Q and C^* are positively correlated through the utility function $W(\cdot)$. Therefore, while a healthy person has high Q value and also high C^* value, a person getting sick early, but with same T and C, has low Q and C^*. The arguments presented by all other authors also speak of a positive correlations between Q and C^*.

In this work, a formal study is carried out on induced dependence in the context of a simple illness-death model. Suppose the sojourn times corresponding to the two health states (namely, healthy and illness), denoted by T_{01} and T_{12},

respectively, are independently distributed with constant hazards, λ_{01} and λ_{12}, respectively. It is assumed that the censoring variable C is also independent of both T_{01} and T_{12} and, C has constant hazard λ_c. The covariance between Q and C^* is worked out as

$$\text{cov}\,(Q, C^*) \;=\; E\,(QC^*) - E(Q)E(C^*) = \frac{w_0(w_0 - w_1)}{(\lambda_{01} + \lambda_c)^2}, \tag{1.1}$$

where w_0 and w_1 are the utility coefficients corresponding to healthy state and illness state, respectively. It is clear from the covariance expression (1.1) that the correlation between Q and C^* is not always positive, as argued by many authors. An approximate expression of bias of the Kaplan-Meier estimate based on observed (censored and uncensored) QAL data is obtained. The direction of bias of Kaplan-Meier estimate for the QAL distribution is investigated through a simulation study. The magnitude of bias seems to be increasing with the magnitude of correlation between Q and C^*. Although, it is difficult to comment on the direction of bias, the results of simulation study seems to indicate positive (negative) bias when $w_0 > (<) w_1$.

[*Chapter 4*]: Parametric Estimation of QAL Distribution

This chapter considers parametric estimation of QAL distribution in illness-death models discussed in Chapter 2 based on censored data. The QAL distribution is derived under some parametric models for the different sojourn time distributions. The model parameters are estimated by maximum likelihood method based on the survival data on each sojourn time. It may be pointed out that the transition time to some illness states may not always be observed. The method of parameter estimation in unobserved case is also considered. The distribution of QAL is then estimated by replacing the parameters in the theoretical expression of the QAL distribution by their estimates. Extensive simulation studies are carried out to investigate the bias and precision of the estimator of QAL distri-

bution. The performance of the parametric estimator is compared with that of the nonparametric estimator of Zhao and Tsiatis (1999). In another simulation study, the effect of model misspecification is investigated by generating data for each transition time from a Weibull distribution and estimating the parameters under the assumption of an exponential distribution. The Stanford Heart transplant data and the IBCSG Trial V breast cancer data are analyzed to illustrate the methodology.

[*Chapter 5*]: Nonparametric Estimation of QAL Distribution

The existing nonparametric methods for estimating the QAL distribution (Korn 1993, Zhao and Tsiatis 1997, 1999; Van der Laan and Hubbard 1999; Huang and Louis 1998; Strawderman, 2000) are applicable only when one can compute the QAL values for all the patients. If some transition times are not observable, QAL values are not available for all the individuals and hence these methods cannot be applied. The objective of this study is to present a simple alternative nonparametric method to estimate the QAL distribution, when information on the interrelationship between the different health states, giving the structure of the illness-death model, and the same between the corresponding sojourn times are available. This allows derivation of the QAL distribution in terms of the different sojourn time distributions. The nonparametric estimate of QAL distribution is obtained by substituting the sojourn time distributions by the corresponding Kaplan-Meier estimates obtained from the corresponding lifetime data. For example, the survival function of Q for simple illness-death Model 1 (see Section 2.2) is given by

$$S_Q(q) \;=\; 1 - F_{01}\left(\frac{q}{w_0}\right) + \int_0^{q/w_0} \bar{F}_{12}\left(\frac{q - w_0 x}{w_1}\right) dF_{01}(x), \qquad (1.2)$$

where $\bar{F}_{12}(\cdot) = 1 - F_{12}(\cdot)$. If $\hat{F}_{01}(\cdot)$ and $\hat{\bar{F}}_{12}(\cdot)$ are the Kaplan-Meier estimates of

$F_{01}(\cdot)$ and $\bar{F}_{12}(\cdot)$, respectively, then a nonparametric estimate of $S_Q(q)$ is given by

$$\hat{S}_Q(q) \;=\; 1 - \hat{F}_{01}\left(\frac{q}{w_0}\right) + \int_0^{q/w_0} \hat{\bar{F}}_{12}\left(\frac{q - w_0 x}{w_1}\right) d\hat{F}_{01}(x). \tag{1.3}$$

By construction, the above estimate is monotonic. Note that monotonicity is not guaranteed in the existing methods, except that of Almanassra et al. (2005). The proposed method can deal with some missingness of transition times, as long as the sojourn time distributions are estimable by some missing data techniques, whereas other methods based on observed QAL can not be applied with such missing data. Estimation in the presence of some missing data on the transition to illness state is also discussed in the context of simple illness-death model.

Consistency and asymptotic normality of the proposed nonparametric estimator are established. Nonparametric estimate for the QAL distribution in other illness-death models have also been obtained with asymptotic properties. Asymptotic variance for the estimator has also been obtained for the simple models. Expressions for the variance estimates in the case of general models are difficult to write. One can alternatively use some resampling technique to estimate the variance of survival estimates. Simulation studies are carried out to investigate the performance of the proposed estimator in terms of bias and precision. The performance of the estimator is compared with that of the ZT estimator. The two data sets are analyzed for illustrative purpose.

The estimation method for the QAL distribution is also outlined for different dependent scenarios. In particular, three dependent scenarios are considered, namely, (1) semi-parametric dependence, (2) Markov dependence and (3) arbitrary dependence. Although estimation method is discussed, asymptotic properties are not studied in this work. Derivation of asymptotic results is a challenging task. This will be considered in future work.

[*Chapter 6*]: Regression Analysis of QAL Data to Study Covariate Effect

The advantage of the proposed method of estimating the QAL distribution is that the theoretical expression for the QAL distribution helps one to incorporate covariate effect in a simple manner. Suppose one or more of the sojourn time distributions are possibly affected by some covariates, denoted by $Z = (Z^{(1)}, \ldots, Z^{(p)})'$, say, as in ordinary survival data. This dependence may be incorporated through usual regression modelling. For example, in the case of a hazard regression model, the theoretical expression for the QAL distribution remains the same except that the hazard rates are replaced by their regression forms in the expression. The estimates of the model parameters are obtained from the sojourn time data (some of which may be unobserved) with covariates, which can be subsequently substituted in the theoretical expression to obtain the estimate of QAL distribution for an individual with a particular covariate value. Both parametric and semi-parametric approaches are considered to estimate QAL distribution by incorporating covariate effect.

Consider the parametric approach in the context of simple illness-death model 1, where either or both of T_{01} and T_{12} may be affected by Z. For the sake of illustration, let us consider the independent case of simple illness-death model 1 with constant hazard rates and suppose that only the hazard rate λ_{01} of T_{01} is affected by Z via the proportional hazards model given by $\lambda_{01}(z) = \lambda_{01}e^{\theta z}$, for $Z = z$. Then, the expression for the survival function of Q, given $Z = z$, is

$$S_Q(q|z) = e^{-\frac{\lambda_{01}e^{\theta z}q}{w_0}} + \frac{\lambda_{01}e^{\theta z}e^{-\frac{\lambda_{12}q}{w_0}}}{\lambda_{01}e^{\theta z} - \lambda_{12}\frac{w_1}{w_0}}\left[1 - e^{-(\lambda_{01}e^{\theta z} - \frac{\lambda_{12}w_0}{w_1})\frac{q}{w_0}}\right]. \quad (1.4)$$

Therefore, given the estimate of the parameters λ_{01}, λ_{12} and θ, which can be easily obtained from the observation on T_{01}, T_{12} and Z, the QAL distribution can be

estimated for the given value of $Z = z$ using the expression (1.4).

Similarly, in the semi-parametric approach, either or both of T_{01} and T_{12} may be assumed to follow distribution(s) given by Cox's proportional hazards model. The regression parameters can be estimated by maximizing a suitable partial likelihood function whereas the baseline cumulative hazards can be estimated using the method of Breslow (1974). Asymptotic normality of the proposed semi-parametric estimator is established. Asymptotic variance is obtained for the simple model. For general models, it is difficult to write the expression for the variance estimates. Resampling technique can be used to estimate the variance. The two data sets are analyzed for illustration.

[*Chapter 7*]: Conclusions and Future Work

Limitations of the proposed method and scopes for future works are discussed in this chapter. An important issue for analyzing QAL data is selection of proper utility coefficients. Some remarks are made in this regard.

1.7 Estimator of Zhao and Tsiatis (1999)

In this thesis, the performance of the proposed estimator has been compared with a nonparametric estimate of QAL distribution by Zhao and Tsiatis (1999). Henceforth, the estimator of Zhao and Tsiatis (1999) for the survival function $S_Q(\cdot)$ of QAL will be denoted by ZT. The ZT estimator and its variance expression are given below.

As in Zhao and Tsiatis (1997), it is assumed that there are $k+1$ health states denoted by $S = \{1, \ldots, k, 0\}$ and the health states are transient except the state 0 representing death. The ith individual's health history is described by a discrete-state continuous-time stochastic process $\{V_i(t), t \geq 0\}$, where $V_i(t)$ maps to the state space S giving the state occupied at time t. Let Y_i^* be the the overall

survival time. Define $T_i^* = \min(Y_i^*, L)$, where L is an artificial endpoint before termination of the trial. The quality adjusted lifetime for the ith individual is given by

$$U_i = \int_0^{T_i^*} Q\{V_i(t)\}dt.$$

Define $s_i^*(q) = \inf\left[s : \int_0^s Q\{V_i(t)\}dt \geq q\right]$, $T_i(q) = \min\{T_i^*, s_i^*(q)\}$, $\Delta_i(q) = I\{C_i > T_i(q)\}$ and $B_i(q) = I(U_i > q)$. Let C be the censoring variable. The health status data for a sample of n individuals, for a given q, is of the form

$$\{X_i = \min(T_i(q), C_i), \Delta_i(q), V_i^H(X_i), i = 1, \ldots, n\},$$

where $V_i^H(X_i)$ denotes the history of the process $V_i(t)$ up to time X_i. Then, the ZT estimator is given by

$$ZT(q) = n^{-1}\sum_{i=1}^{n}\frac{\Delta_i(q)B_i(q)}{\hat{K}(T_i(q))} + n^{-1}\hat{C}\sum_{i=1}^{n}\int_0^{\infty}\frac{dN_i^c(u)}{\hat{K}(u)}\left[e\left\{V_i^H(u)\right\} - \hat{G}(e,u)\right],$$

where

$$\begin{aligned}\hat{C} &= \left\{\sum_{i=1}^{n}\frac{\Delta_i(q)B_i(q)}{\hat{K}(T_i(q))}\left[e\left\{V_i^H(u)\right\} - \hat{G}(e,u)\right] \times I(T_i(q) \geq u)\frac{dN_i^c(u)}{Y(u)\hat{K}(u)}\right\} \\ &\quad \div\left\{\left[e\left\{V_i^H(u)\right\} - \hat{G}(e,u)\right]^2 Y_i(u)\frac{dN_i^c(u)}{Y(u)\hat{K}(u)^2}\right\},\end{aligned}$$

$$\hat{G}(e,u) = \frac{\sum_{i=1}^{n} e\left\{V_i^H(u)\right\}Y_i(u)}{Y(u)},$$

$\hat{K}(u)$ is the Kaplan-Meier estimator of $K(u) = P[C > u]$ based on the observation $\{X_i, 1 - \Delta_i(q), i = 1, \ldots, n\}$, $N_i^c(u) = I(X_i \leq u, \Delta_i(q) = 0)$, $Y(u) = \sum Y_i(u) = \sum I(X_i \geq u)$ and $e\{V_i^H(u)\}$ is any functional of the health history $V_i^H(u)$. Here, the accumulated QAL $f_i(u) = \int_0^u Q_i\{V_i(t)\}dt$ is used as $e_i(\cdot)$.

Asymptotic variance of $\sqrt{n}\{ZT(q) - S_Q(q)\}$ can be estimated by

$$ZT(q)(1 - ZT(q)) + n^{-1}\int_0^{\infty}\frac{dN^c(u)}{\{\hat{K}(u)\}^2}\hat{G}(B,u)(1 - \hat{G}(B,u)\}$$

$$-n^{-1}\left\{\sum_{i=1}^{n}\frac{\Delta_i(x)B_i(q)}{\hat{K}(T_i(q))}\left[e\left\{V_i^H(u)\right\}-\hat{G}(e,u)\right]\times I(T_i(q)\geq u)\frac{dN_i^c(u)}{Y(u)\hat{K}(u)}\right\}^2$$
$$\div\left\{\left[e\left\{V_i^H(u)\right\}-\hat{G}(e,u)\right]^2 Y_i(u)\frac{dN_i^c(u)}{Y(u)\hat{K}(u)^2}\right\},$$

where $\hat{G}(B,u)=n^{-1}\frac{1}{\hat{S}_T(u)}\sum_{i=1}^{n}\frac{\Delta_i(q)B_i(q)I(T_i(q)\geq u)}{\hat{K}(T_i(q))}$ and $\hat{S}_T(u)$ is the Kaplan-Meier estimator for $S_T(u)=P(T>u)$ for the overall survival time T.

1.8 Publications from the work

The work of Chapters 2, 4 and a part of Chapter 6 are published in **Communications in Statistics-Theory and Methods (Pradhan et al., 2010)**, **Statistics in Medicine (Pradhan and Dewanji, 2009a)** and **Calcutta Statistical Association Bulletin (Pradhan and Dewanji, 2009b)**. Bias due to induced dependent censoring in Chapter 3 is published in **Statistics and Probability Letters** (Pradhan and Dewanji, 2009c). A part of Chapter 5 on nonparametric estimation of QAL distribution is published as Technical Report (Pradhan et al., 2009a; *submitted*) and another part is accepted for publication in **Journal of the Korean Statistical Society** (Pradhan and Dewanji, 2010). The semiparametric approach of estimating the QAL distribution is published as Technical Report (Pradhan and Dewanji, 2009d) and submitted.

Chapter 2

Models and Distribution of QAL

2.1 Introduction

Quality adjusted lifetime (QAL) is being increasingly used as a composite measure combining quality and duration of life in many clinical trials, where patient's health history may be described by different illness-death models. In illness-death models, patients experiences different health states, which differ in quality of life (QOL), before death. The illness-death model arises in many medical studies and animal experiments, examples of which have been studied for several decades with sustained interest. Applications can be found in animal carcinogenicity studies (Kodell and Nelson, 1980; Dewanji and Kalbfleisch, 1986; Biswas and Dewanji, 2004, among many others), medical studies involving human subjects, for example in HIV/AIDS research (Kalbfleisch and Lawless, 1989; Datta et al., 2000), and in industrial applications with machine faults (Dewanji and Dhar, 1993).

The objective of this chapter is to describe different illness-death models which are considered for our study and derive the theoretical distribution of QAL. In this work, four illness-death models are considered with the names (1) simple illness-death model, (2) progressive illness-death model, (3) competing illness-

death model and (4) reversible illness-death model. In principle, given a model, the QAL distribution can be derived in terms of the joint distribution of all the sojourn times. In particular, the closed form expression of the QAL distribution is obtained when the sojourn times are independent and exponentially distributed. Derivation of the theoretical distribution of QAL in general may be quite challenging and its closed form expression may not always exist. However, once the distribution of QAL is derived in a closed or in general form, it can be estimated by substituting the sojourn time distributions with the corresponding estimates. Therefore, the expression for the QAL distribution needs to be evaluated only once. The sojourn time distributions can be estimated from the corresponding life time data using the techniques of survival analysis.

This chapter is organised as follows. Different illness-death models are described along with the derivation of QAL distribution under different scenarios in Sections 2.2-2.5. The justification for considering different illness-death models is discussed in Section 2.6. Some conclusions are made in Section 2.7. Finally, in Section 2.8, some results on the distribution of sum of non-identical Gamma random variables are derived which are required for the derivation of QAL distribution.

2.2 Simple Illness-Death Model

A typical simple illness-death model has three states. Starting from the healthy state, an individual may enter an intermediate state before ending in death, or have transition directly to death. Two simple illness-death models are considered in this work. In simple illness-death model 1, as shown in Figure 2.1, one starts in a healthy state 0 from which the only possible transition is to the illness state 1, followed by transition to state 2, the absorbing state, death. The possibility of moving directly to absorbing state 2 is described in simple illness-death model 2

and shown in Figure 2.2. In HIV/AIDS research, for example, in a cohort of HIV positive patients, appearance of AIDS symptoms can be equated with illness. In this example, one would be interested in quality adjusted life of HIV patients.

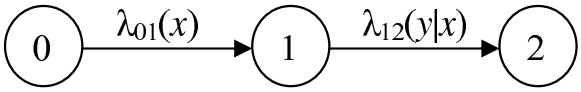

Figure 2.1: Simple Illness-Death Model 1.

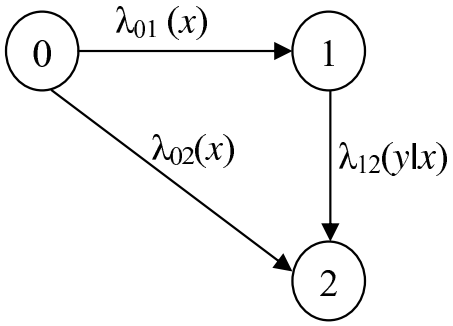

Figure 2.2: Simple Illness-Death Model 2.

2.2.1 QAL Distribution in Simple Illness-Death Model 1

Here, the distribution of QAL is derived in simple illness-death model 1 (See Figure 2.1). Let T_{01} be the sojourn time in state 0 and T_{12} denote the same in state 1 with utility coefficients w_0 and w_1, respectively. Usually, w_0 is taken to be 1 and w_1 is a suitably chosen fraction. Then, the QAL, as defined in Section 1.1, is given by $Q = w_0T_{01} + w_1T_{12}$. Suppose $\lambda_{01}(x)$ is the transition rate from state 0 to state 1 at sojourn time x. This is same as the hazard rate of T_{01} at time

x. Similarly, denote the conditional hazard rate of T_{12} at sojourn time y, given $T_{01} = x$, as $\lambda_{12}(y|x)$. It is also the transition rate from state 1 to state 2 at time y, given $T_{01} = x$. When $\lambda_{12}(y|x)$ does not involve x, that is, $\lambda_{12}(y|x) = \lambda_{12}(y)$, T_{12} is independent of T_{01}. Let $F_{T_{12}|T_{01}}(y|x)$ be the conditional distribution of T_{12} given T_{01}. The expression for the distribution of Q is given by

$$\begin{aligned} F_Q^{(S1)}(q) &= P(Q \leq q) \\ &= \int_0^{\frac{q}{w_0}} \left[\int_0^{\frac{q-w_0 x}{w_1}} \lambda_{12}(y|x) e^{-\Lambda_{12}(y|x)} dy \right] \lambda_{01}(x) e^{-\Lambda_{01}(x)} dx, \\ &= \int_0^{\frac{q}{w_0}} F_{T_{12}|T_{01}} \left(\frac{q - w_0 x}{w_1} | x \right) dF_{01}(x), \end{aligned} \tag{2.1}$$

where $\Lambda_{01}(x) = \int_0^x \lambda_{01}(u) du$, $F_{01}(\cdot)$ is the marginal distribution function of T_{01} and $\Lambda_{12}(y|x) = \int_0^y \lambda_{12}(u|x) du$.

The dependence between T_{01} and T_{12} is described by the conditional hazard $\lambda_{12}(y|x)$, which may be modelled, for example, by the proportional hazards assumption $\lambda_{12}(y|x) = \lambda_{12}(y) e^{\beta x}$ (Pradhan et al., 2010), or accelerated failure time assumption $\lambda_{12}(y|x) = \lambda_{12}(y e^{\beta x}) e^{\beta x}$. When T_{01} and T_{12} are independent, the expression (2.1) reduces to

$$\begin{aligned} F_Q^{(S1)}(q) &= \int_0^{\frac{q}{w_0}} \left[\int_0^{\frac{q-w_0 x}{w_1}} \lambda_{12}(y) e^{-\Lambda_{12}(y)} dy \right] \lambda_{01}(x) e^{-\Lambda_{01}(x)} dx, \\ &= \int_0^{\frac{q}{w_0}} F_{12} \left(\frac{q - w_0 x}{w_1} \right) dF_{01}(x), \end{aligned} \tag{2.2}$$

where $F_{12}(\cdot)$ is the distribution function of T_{12}. In particular, when T_{01} and T_{12} are independent exponential variates with $\lambda_{01}(x) = \lambda_{01}$ and $\lambda_{12}(y) = \lambda_{12}$, the expression (2.2) reduces to

$$F_Q^{(S1)}(q) = 1 - e^{-\frac{\lambda_{01} q}{w_0}} - \frac{\lambda_{01} e^{-\frac{\lambda_{12} q}{w_1}}}{\lambda_{01} - \lambda_{12} \frac{w_0}{w_1}} \left[1 - e^{-(\lambda_{01} - \frac{\lambda_{12} w_0}{w_1}) \frac{q}{w_0}} \right]. \tag{2.3}$$

2.2.2 QAL Distribution in Simple Illness-Death Model 2

Let T_0 be the sojourn time of the first event, that is the time to illness, or death without illness, whichever occurs first, and let δ be the corresponding indicator, which takes the values 1 and 2 for illness and death without illness, respectively. Also, let T_{12} denote the sojourn time in state 1 before moving to state 2. Then, the QAL is defined by

$$Q = \begin{cases} w_0 T_0 + w_1 T_{12} & \text{if } \delta = 1 \\ w_0 T_0 & \text{if } \delta = 2, \end{cases}$$

where w_0 and w_1 are the utility coefficients in state 0 and 1, respectively. The expression for the distribution function of Q is then given by

$$\begin{aligned} F_Q^{(S2)}(q) &= P(Q \leq q) \\ &= P(w_0 T_0 + w_1 T_{12} \leq q, \delta = 1) + P(w_0 T_0 \leq q, \delta = 2) \\ &= P_I + P_{II}, \text{ say.} \end{aligned} \tag{2.4}$$

Note that the first transition from state 0 to either state 1 or state 2 constitutes a competing risks framework with two failure types 1 and 2. Let $\lambda_{0j}(\cdot)$ be the cause-specific hazard rate for the failure type j and $F_{0j}(\cdot)$ be the corresponding cumulative incidence function given by

$$F_{0j}(t) = P(T_0 \leq t, \delta = j) = \int_0^t S_0(u) d\Lambda_{0j}(u), \quad \text{for } j = 1, 2,$$

where $S_0(t) = P[T_0 \geq t] = \exp\left[-\left(\Lambda_{01}(t) + \Lambda_{02}(t)\right)\right]$, the survival function of T_0 and $\Lambda_{0j}(t) = \int_0^t \lambda_{0j}(u) du$, for $j = 1, 2$. The conditional transition rate from state 1 to state 2 at sojourn time y, given the transition from state 0 to state 1 at sojourn time x, is denoted by $\lambda_{12}(y|x)$. Then,

$$P_I = \int_0^{\frac{q}{w_0}} \left[\left(\int_0^{\frac{q - w_0 x}{w_1}} \lambda_{12}(y \mid x) e^{-\Lambda_{12}(y|x)} dy \right) \lambda_{01}(x) e^{-(\Lambda_{01}(x) + \Lambda_{02}(x))} \right] dx$$

and

$$P_{II} = \int_0^{\frac{q}{w_0}} \lambda_{02}(u) e^{-(\Lambda_{01}(u)+\Lambda_{02}(u))} du = \int_0^{\frac{q}{w_0}} dF_{02}(u) = F_{02}\left(\frac{q}{w_0}\right).$$

Note that, $\lambda_{02}(u) = 0$, for all $u \geq 0$, leads to model 1. In this case, P_I reduces to (2.1) and $P_{II} = 0$. In general, the dependence between T_{12} and the sojourn time in healthy state 0 can be described in the same way as in the case of model 1 in the previous section. Under independence, that is when $\lambda_{12}(y|x) = \lambda_{12}(y)$ and with constant hazards, that is $\lambda_{01}(y) = \lambda_{01}$, $\lambda_{12}(y) = \lambda_{12}$ and $\lambda_{02}(y) = \lambda_{02}$, the expressions for P_I and P_{II} simplify to

$$P_I = \lambda_{01}\left[\frac{1 - e^{-(\lambda_{01}+\lambda_{02})\frac{q}{w_0}}}{\lambda_{01}+\lambda_{02}} - \frac{w_1\left(e^{-\frac{\lambda_{12}q}{w_1}} - e^{-(\lambda_{01}+\lambda_{02})\frac{q}{w_0}}\right)}{(\lambda_{01}+\lambda_{02})w_1 - \lambda_{12}w_0}\right] \text{ and}$$

$$P_{II} = \frac{\lambda_{02}}{\lambda_{01}+\lambda_{02}}\left(1 - e^{-(\lambda_{01}+\lambda_{02})\frac{q}{w_0}}\right),$$

respectively, leading to

$$F_Q^{(S2)}(q) = 1 + \frac{(\lambda_{12}w_0 - \lambda_{02}w_1)e^{-(\lambda_{01}+\lambda_{02})\frac{q}{w_0}}}{(\lambda_{01}+\lambda_{02})w_1 - \lambda_{12}w_0} - \frac{\lambda_{01}w_1 e^{-\frac{\lambda_{12}q}{w_1}}}{(\lambda_{01}+\lambda_{02})w_1 - \lambda_{12}w_0}. \quad (2.5)$$

2.3 Progressive Illness-Death Model

In a progressive illness-death model, individuals start from a healthy state 0 and then experience the different illness states $1, \ldots, k$, say, one after another in that fixed order, before moving to the absorbing state $k+1$ representing death. Individuals may be censored in any one of the $(k+1)$ states 0, $1, \ldots, k$, before failure or death occurs. Here k is the penultimate state before death. We refer to this as progressive illness-death model 1 and is shown in Figure 2.3. In a more general model, referred to as progressive illness-death model 2, there is also the possibility of moving directly to state $k+1$ from any of the k non-penultimate states 0, $1, \ldots, k-1$. The model is shown in Figure 2.4. These two models are the

multi-state versions of the two simple illness-death models considered in Figure 2.1 and Figure 2.2, respectively.

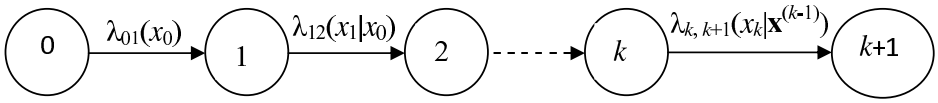

Figure 2.3: Progressive Illness-Death Model 1.

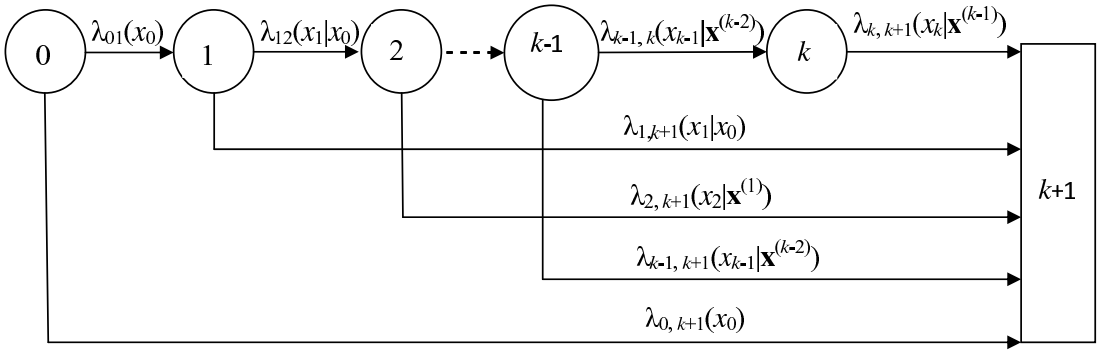

Figure 2.4: Progressive Illness-Death Model 2.

Examples of progressive illness-death model are common in medical studies. For example, in Trial V of IBCSG, patients enter the study as they start chemotherapy treatment resulting in a toxicity period. So, the individuals start in the state of 'Toxicity' (state 0), at the end of which they enter the state of 'No symptoms of disease and toxicity of treatment' (state 1), followed by 'Relapse of the disease' (state 2) and finally the death (absorbing state 3). Also, in HIV/AIDS studies, individuals may experience the different health states progressively as follows. Individuals start in healthy state (0) from which they acquire HIV infection (state 1), then onset of AIDS (state 2), followed by different health states depending upon the immunity level and the infection type, and finally death, the

absorbing state.

The theoretical distribution of QAL for progressive illness-death model is expressed analytically in integral forms for general sojourn time distributions, but derived for exponential distribution with constant hazards for simplicity, for both model 1 and model 2. Model 1 is usually appropriate with industrial products in the context of reliability. For example, in a parallel system with k components, the failure of successive components may be equated with the successive illness states. The system fails when all the components fail. Model 2 is usually appropriate with human subjects in medical studies, as in HIV/AIDS example. However, in some cases, when there are few or no direct deaths without experiencing all the illness states, model 1 is used instead.

2.3.1 QAL Distribution in Progressive Illness-Death Model 1

As shown in Figure 2.3, let $T_{j,j+1}$ be the sojourn time in state j before moving to state $j+1$, for $j = 0, 1, \ldots, k$, where $j = 0$ means healthy state and $j = k+1$ means death state. Let w_j be the utility coefficient corresponding to state j, for $j = 0, 1, \ldots, k$. Then, the QAL is given by

$$Q = \sum_{j=0}^{k} w_j T_{j,j+1}.$$

Suppose $\lambda_{01}(x_0)$ is the transition rate from state 0 to state 1 at corresponding sojourn time x_0. This is same as the hazard rate of T_{01} at time x_0. Similarly, denote the conditional hazard rate of $T_{j,j+1}$ at corresponding sojourn time x_j, given $T_{01} = x_0$, $T_{12} = x_1, \ldots, T_{j-1,j} = x_{j-1}$, by $\lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)})$, where $\mathbf{x}^{(j-1)} = (x_0, x_1, \ldots, x_{j-1})$, for $j = 1, \ldots, k$. When successive sojourn times are independent, $\lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)})$ does not depend on $\mathbf{x}^{(j-1)}$. That is, $\lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)}) = \lambda_{j,j+1}(x_j)$.

The expression for the distribution of QAL, denoted by Q, is given by

$$\begin{aligned} F_Q^{(P1)}(q) &= P(Q \leq q) \\ &= P\left(\sum_{j=0}^{k} w_j T_{j,j+1} \leq q\right) \\ &= \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{k-1} w_j x_j}{w_k}} \lambda_{k,k+1}(x_k|\mathbf{x}^{(k-1)}) e^{-\Lambda_{k,k+1}(x_k|\mathbf{x}^{(k-1)})} dx_k \\ &\quad \times \lambda_{k-1,k}(x_{k-1}|\mathbf{x}^{(k-2)}) e^{-\Lambda_{k-1,k}(x_{k-1}|\mathbf{x}^{(k-2)})} dx_{k-1} \\ &\quad \vdots \\ &\quad \times \lambda_{01}(x_0) e^{-\Lambda_{01}(x_0)} dx_0, \end{aligned} \tag{2.6}$$

where $\Lambda_{01}(x_0) = \int_0^{x_0} \lambda_{01}(u)du$ and $\Lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)}) = \int_0^{x_j} \lambda_{j,j+1}(u|\mathbf{x}^{(j-1)})du$, for $j = 1, \ldots, k$.

The expression (2.6) is very general including different sojourn time distributions and even arbitrary dependence between them. For $k = 1$, a dependence model has been considered in Pradhan et al. (2010). In general, one needs numerical techniques to calculate the QAL distribution. This, however, needs to be done only once with the parameter estimates. For simplicity, we consider the case when successive sojourn times $T_{j,j+1}$'s are independently distributed with constant hazards. That is, $\lambda_{01}(x_0) = \lambda_{01}$ and $\lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)}) = \lambda_{j,j+1}$, for $j = 1, 2, \ldots, k$.

Note that $Q = \sum_{j=0}^{k} w_j T_{j,j+1}$ can then be written as $\sum_{j=0}^{k} T'_{j,j+1}$, where $T'_{j,j+1}$'s are independent exponential random variables with respective hazard rates $\lambda'_j = \lambda_{j,j+1}/w_j$, for $j = 0, 1, \ldots, k$. So, Q is the convolution of non-identical independent exponential random variables. The distribution of Q is given by (Ross, 2000)

$$F_Q^{(P1)}(q) = 1 - \sum_{j=0}^{k} e^{-\lambda'_j q} \left(\prod_{i \neq j} \frac{\lambda'_i}{\lambda'_i - \lambda'_j}\right), \tag{2.7}$$

provided the λ'_j's are all distinct. The corresponding density function is given by

$$f_Q^{(P1)}(q) = \sum_{j=0}^{k} \lambda'_j e^{-\lambda'_j q} \left(\prod_{i \neq j} \frac{\lambda'_i}{\lambda'_i - \lambda'_j}\right)$$

and the mean QAL is $\sum_{j=0}^{k} \frac{1}{\lambda'_j}$.

2.3.2 QAL Distribution in Progressive Illness-Death Model 2

As shown in Figure 2.4, the model allows the possibility of moving directly to absorbing state $k+1$ from any of the k non-penultimate states $0, 1, \ldots, k-1$. Let $T_{j,j+1}$ denote the conceptual sojourn time in state j before moving to the illness state $j+1$ and $T_{j,k+1}$ denote the same before moving directly to the absorbing state $k+1$, for $j = 0, 1, \ldots, k-1$. Also let $T_{k,k+1}$ denote the sojourn time in the penultimate state k before moving to the next state $k+1$. Then, the QAL is given by $Q = \sum_{j=0}^{m-1} w_j T_{j,j+1} + w_m T_{m,k+1}$, when transition to death state $k+1$ occurs from the state m, for $m = 1, \ldots, k$. For m=0, $Q = w_0 T_{0,k+1}$. Note that with m fixed, we have $T_{j,j+1} < T_{j,k+1}$, for $j = 0, 1, \ldots, m-1$, and $T_{m,m+1} > T_{m,k+1}$ (except for $m = k$).

The distribution of Q is then given by

$$F_Q^{(P2)}(q) = P(Q \le q) = \sum_{m=0}^{k} P_m,$$

where $P_0 = P(w_0 T_{0,k+1} \le q, T_{0,k+1} < T_{01})$,

$$P_m = P\left(\sum_{j=0}^{m-1} w_j T_{j,j+1} + w_m T_{m,k+1} \le q, T_{j,k+1} > T_{j,j+1}, j = 0, 1, \ldots, m-1 \right.$$
$$\left. \text{and } \; T_{m,m+1} > T_{m,k+1} \right), \text{ for } m = 1, \ldots, k-1$$

and $P_k = P\left(\sum_{j=0}^{k-1} w_j T_{j,j+1} + w_k T_{k,k+1} \le q, T_{j,k+1} > T_{j,j+1}, \text{for } j = 0, 1, \ldots, k-1 \right)$,

for $k \ge 1$. For $k = 1$, the P_m's as given in the middle are not required.

It may be noted that the transition from state j to either state $j+1$ or to

state $k+1$, for $j = 0, 1, \ldots, k-1$, with 0 meaning the healthy state, constitutes a competing risks framework with $T_{j,j+1}$ and $T_{j,k+1}$ denoting the two corresponding conceptual sojourn times. Let $H^{(j)}$ denote the history up to the time just prior to entering state j. Note that $H^{(j)}$ consists of the event $\{T_{m,k+1} > T_{m,m+1} = x_m, \text{for } m = 0, 1, \ldots, j-1\}$. For progressive illness-death model 1 (See Figure 2.3), $H^{(j)}$ consists of only $x^{(j-1)}$=$(x_0, x_1 \ldots, x_{j-1})$. Let $\lambda_{j,j+1}(x_j|H^{(j)})$ and $\lambda_{j,k+1}(x_j|H^{(j)})$ be the cause specific hazards for the two possible transitions to state $j+1$ or $k+1$, respectively, at time x_j, given $H^{(j)}$, with $H^{(0)}$ being empty. Note that, for $j = k$, $T_{j,j+1}$ and $T_{j,k+1}$ are the same random variable representing the actual sojourn time in state k before death with ordinary hazard rate $\lambda_{k,k+1}(x_k|H^{(k)})$ at time x_k.

The expressions for P_0, P_m and P_k for general sojourn time distributions are as follows:

$$P_0 = \int_0^{\frac{q}{w_0}} \lambda_{0,k+1}(x) e^{-(\Lambda_{01}(x)+\Lambda_{0,k+1}(x))} dx,$$

$$\begin{aligned} P_m &= \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{m-1} w_j x_j}{w_m}} \lambda_{m,k+1}(x_m|H^{(m)}) \\ &\times e^{-(\Lambda_{m,k+1}(x_m|H^{(m)})+\Lambda_{m,m+1}(x_m|H^{(m)})} dx_m \\ &\times \lambda_{m-1,m}(x_{m-1}|H^{(m-1)}) e^{-\left(\Lambda_{m-1,m}(x_{m-1}|H^{(m-1)})+\Lambda_{m-1,k+1}(x_{m-1}|H^{(m-1)})\right)} dx_{m-1} \\ &\vdots \\ &\times \lambda_{01}(x_0) e^{-(\Lambda_{01}(x_0)+\Lambda_{0,k+1}(x_0))} dx_0, \end{aligned}$$

for $m = 1, \ldots, k-1$, and

$$\begin{aligned} P_k &= \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{k-1} w_j x_j}{w_k}} \lambda_{k,k+1}(x_k|H^{(k)}) e^{-\Lambda_{k,k+1}(x_k|H^{(k)})} dx_k \\ &\times \lambda_{k-1,k}(x_{k-1}|H^{(k-1)}) e^{-\left(\Lambda_{k-1,k}(x_{k-1}|H^{(k-1)})+\Lambda_{k-1,k+1}(x_{k-1}|H^{(k-1)})\right)} dx_{k-1} \\ &\vdots \\ &\times \lambda_{01}(x_0) e^{-(\Lambda_{01}(x_0)+\Lambda_{0,k+1}(x_0))} dx_0, \end{aligned}$$

where the Λ_{ij}'s are integrated λ_{ij}'s, as defined in the previous section, for different (i, j)'s.

One can find the distribution of Q for different choices of the conditional hazards including the models with dependence between different sojourn times. As remarked before, the derivation may be complicated, in general, requiring numerical integration technique. We, therefore, for simplicity, derive the distribution of Q with constant hazards under independent scenario. Then, the expressions for P_0, P_m and P_k are as follows.

First,

$$P_0 = \frac{\lambda_{0,k+1}}{\lambda_{01}+\lambda_{0,k+1}}\left[1-e^{-\left(\frac{\lambda_{01}+\lambda_{0,k+1}}{w_0}\right)q}\right].$$

Then, for $m = 1, \ldots, k-1$, and $k \geq 2$,

$$\begin{aligned} P_m &= \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{m-1} w_j x_j}{w_m}} \lambda_{m,k+1} e^{-(\lambda_{m,k+1}+\lambda_{m,m+1})x_m} dx_m \\ &\quad \times \lambda_{m-1,m} e^{-(\lambda_{m-1,m}+\lambda_{m-1,k+1})x_{m-1}} dx_{m-1} \\ &\quad \vdots \\ &\quad \times \lambda_{01} e^{-(\lambda_{01}+\lambda_{0,k+1})x_0} dx_0 \\ &= \lambda^{(m)} \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{m-1} w_j x_j}{w_m}} \prod_{j=0}^{m} f_j(x_j) dx_j, \end{aligned} \tag{2.8}$$

where $\lambda^{(m)} = \frac{\lambda_{m,k+1}}{\lambda_{m,m+1}+\lambda_{m,k+1}} \left[\prod_{j=0}^{m-1} \frac{\lambda_{j,j+1}}{\lambda_{j,j+1}+\lambda_{j,k+1}}\right]$ and $f_j(.)$ is the density of $X_{j,j+1} = \min(T_{j,j+1}, T_{j,k+1})$ having exponential distribution with constant hazard $(\lambda_{j,j+1}+\lambda_{j,k+1})$, for $j = 0, 1, \ldots, k-1$. Clearly, the expression (2.8) for P_m is equal to

$$\lambda^{(m)} P(w_0X_{01} + w_1X_{12} + \cdots + w_{m-1}X_{m-1,m} + w_mX_{m,m+1} \leq q),$$

which can be written as

$$\lambda^{(m)} P(X'_{01} + X'_{12} + \cdots + X'_{m-1,m} + X'_{m,m+1} \leq q),$$

where $X'_{j,j+1}$'s are independent exponential random variables with respective hazard rates $\lambda'_{j,j+1} = (\lambda_{j,j+1} + \lambda_{j,k+1})/w_j$. So, by the convolution of a number of non-identical independent exponential random variables, as in (2.7),

$$P_m = \lambda^{(m)} \left[1 - \sum_{j=0}^{m} e^{-\lambda'_{j,j+1} q} \prod_{i \neq j} \frac{\lambda'_{i,i+1}}{\lambda'_{i,i+1} - \lambda'_{j,j+1}} \right],$$

provided the $\lambda'_{j,j+1}$'s are distinct for different j's. Finally, as in the derivation of P_m, we have

$$\begin{aligned} P_k &= \lambda \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0 x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{k-1} w_j x_j}{w_k}} \lambda_{k,k+1} e^{-\lambda_{k,k+1} x_k} dx_k \\ &\quad \times \prod_{j=1}^{k-1} f_j(x_j) dx_j \\ &= \lambda \left[1 - \sum_{j=0}^{k} e^{-\lambda'_{j,j+1} q} \prod_{i \neq j} \frac{\lambda'_{i,i+1}}{\lambda'_{i,i+1} - \lambda'_{j,j+1}} \right], \end{aligned}$$

where $\lambda = \prod_{j=0}^{k-1} \left(\frac{\lambda_{j,j+1}}{\lambda_{j,j+1} + \lambda_{j,k+1}} \right)$ and $\lambda'_{k,k+1} = \frac{\lambda_{k,k+1}}{w_k}$.

If any two of the $\lambda'_{j,j+1}$'s, for $j = 0, 1, \ldots, k$, are equal, then the expressions for P_m and P_k will be different involving convolution of a number of non-identical exponential random variables and a Gamma random variable. See Result 2.8.2 of Section 2.8 for relevant expressions.

2.3.3 Extension to More General Progressive Illness-Death Model

One can think of more general type of illness-death models, but the analytical derivation of QAL distribution may not be an easy task. Consider a general illness-death model with, say, k states $1, \ldots, k$, in addition to the healthy state 0 and the absorbing state $k + 1$ representing death. Here, except state $k + 1$, transition is allowed from a state to any other state. In practice, for a particular

state i, for $i = 0, 1, \ldots, k$, there is a set, say, $S(i)$ of all possible health states (possibly including death $k+1$) which can be reached from state i. Assuming the different conceptual sojourn times to be independent with constant hazards, a general expression for the QAL distribution can be worked out as follows.

Let $\mathcal{P}$ be the set of all possible paths followed from state 0 to state $k+1$ including possibly multiple visits to some of the states. A typical path is represented by the vector $\underset{\sim}{p} = (0 = p_0, p_1, \ldots, p_{|\underset{\sim}{p}|} = k+1)$, where $(0, p_1, \ldots, p_{|\underset{\sim}{p}|} - 1, k+1)$ is the sequence of states followed in this path. Let $T_{p_i,p_{i+1}}$ be the conceptual sojourn time from state p_i to p_{i+1} with constant hazard $\lambda_{p_i,p_{i+1}}$. Then, QAL for a typical $\underset{\sim}{p}$ is given by

$$Q = \sum_{i=0}^{|\underset{\sim}{p}| - 1} w_{p_i} T_{p_i,p_{i+1}}.$$

The distribution of QAL is then given by

$$P[Q \leq q] = \sum_{\underset{\sim}{p} \in \mathcal{P}} P_{\underset{\sim}{p}}, \tag{2.9}$$

where

$$\begin{aligned} P_{\underset{\sim}{p}} &= P\left[\sum_{i=0}^{|\underset{\sim}{p}| - 1} w_{p_i} T_{p_i,p_{i+1}} \leq q, \quad \underset{\sim}{p}\right] \\ &= \lambda_{\sim}^{(p)} P\left[\sum_{i=0}^{k} X_i^{(p)}_{\sim} \leq q\right], \end{aligned}$$

with $\lambda_{\sim}^{(p)} = \prod_{i=0}^{|\underset{\sim}{p}| - 1} (\lambda_{p_i,p_{i+1}} / \sum_{j \in S(p_i)} \lambda_{p_i j})$. The random variables $X_i^{(p)}_{\sim}$'s are independent with $X_i^{(p)}_{\sim}$ following a Gamma$\left(\frac{\lambda_i}{w_i}, n_i^{(p)}_{\sim}\right)$ distribution, where $\lambda_i = \sum_{j \in S(i)} \lambda_{ij}$ and $n_i^{(p)}_{\sim}$ is the number of visits to state i in the path $\underset{\sim}{p}$. The distribution function for the sum of k non-identical Gamma variates can be obtained (See

Mathai, 1982; Ross, 2000). When the shape parameter is an integer (as is the case here), the distribution function has a simpler form, as given in Result 2.8.2 of Section 2.8. In practice, the set $\mathcal{P}$ of all possible paths from 0 to $k+1$ may not be very difficult to deal with in order to evaluate the distribution in (2.9). When $\mathcal{P}$ is very large, one can think of some sampling or simulation techniques to estimate (2.9).

2.4 Competing Illness-Death Model

In a competing illness-death model, individuals start from healthy state 0 and then experience any one of the k illness states $1, \ldots, k$, which presumably reduces the quality of life, and then move to the absorbing state $k+1$ representing death without entering into any other illness states. One may also allow for a transition to state $k+1$ directly from the healthy state 0; that is, one may die without experiencing any of the illness states $1, \ldots, k$. These two models are shown in Figures 2.5 and 2.6, and named as competing illness-death model 1 and competing illness-death model 2, respectively.

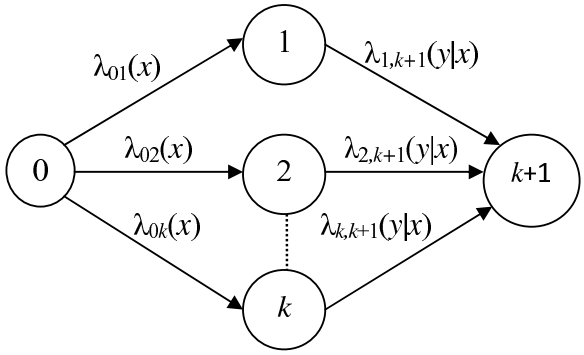

Figure 2.5: Competing Illness-Death Model 1.

For example, an AIDS patient may experience one of many types of infections

leading to death. Here, time starts from the onset of AIDS and the different types of infections correspond to the illness states. In industrial studies, one can think of different types of faults leading to break-down.

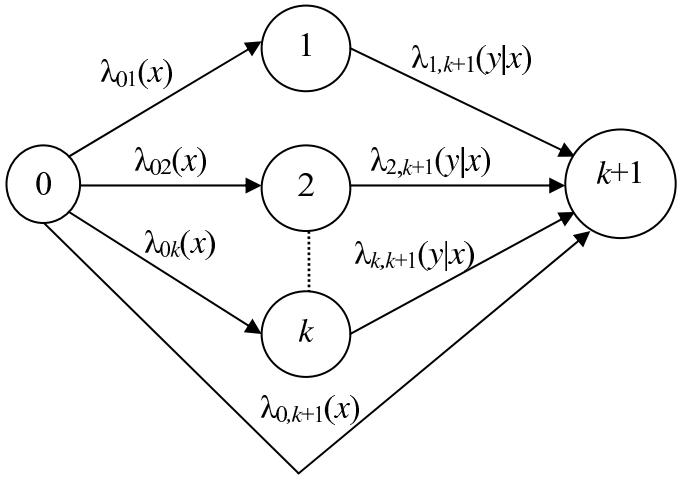

Figure 2.6: Competing Illness-Death Model 2.

2.4.1 QAL Distribution in Competing Illness-Death Model 1

As shown in Figure 2.5, the competing risks framework is apparent for the first transition. Let T_{0j} be the conceptual sojourn time in healthy state 0 before moving to the illness state j with cause-specific hazard rate $\lambda_{0j}(x)$, for $j = 1, \ldots, k$. Let $T_{j,k+1}$ be the sojourn time in the illness state j before moving to the absorbing state $k+1$ with $\lambda_{j,k+1}(y|x)$ being the conditional hazard rate of $T_{j,k+1}$ at y given $T_{0j} = x$, for $j = 1, \ldots, k$. Let w_0 be the utility coefficient corresponding to healthy state and w_j be the utility coefficient corresponding to jth illness state, for $j = 1, \ldots, k$. Then, the QAL is given by

$$Q = w_0 T_{0j} + w_j T_{j,k+1}, \text{if } T_{0j} = \min\{T_{01}, \ldots, T_{0k}\}, \text{for } j = 1, \ldots, k.$$

The distribution of QAL is given by

$$F_Q^{(C1)}(q) \;=\; P[Q \le q] = \sum_{j=1}^{k} P_j, \tag{2.10}$$

where

$$\begin{aligned} P_j &= P\left[w_0 T_{0j} + w_j T_{j,k+1} \le q, T_{0j} = \min\{T_{01}, \ldots, T_{0k}\}\right] \\ &= \int_0^{\frac{q}{w_0}} \left(\int_0^{\frac{q-w_0 x}{w_j}} \lambda_{j,k+1}(y|x) e^{-\Lambda_{j,k+1}(y|x)} dy \right) \lambda_{0j}(x) \exp\left[-\sum_{l=1}^{k} \Lambda_{0l}(x) \right] dx, \end{aligned}$$

with $\Lambda_{j,k+1}(y|x) = \int_0^y \lambda_{j,k+1}(u|x)du$ and $\Lambda_{0j}(x) = \int_0^x \lambda_{0j}(u)du$.

The dependence between T_{0j} and $T_{j,k+1}$ is described by the conditional hazard $\lambda_{j,k+1}(y|x)$. One can choose proportional hazard assumption $\lambda_{j,k+1}(y|x) = \lambda_{j,k+1}(y)e^{\beta x}$ for dependency, as in Section 2.2.1. When T_{0j} and $T_{j,k+1}$ are independent (that is, $\lambda_{j,k+1}(y|x)$ does not depend on x) and have constant hazards λ_{0j} and $\lambda_{j,k+1}$, respectively, then we have

$$P_j \;=\; \frac{\lambda_{0j}}{\lambda}\left(1 - e^{-\frac{\lambda}{w_0}q}\right) - \frac{\lambda_{0j}}{\lambda - \frac{\lambda_{j,k+1}w_0}{w_j}}\left[e^{-\frac{\lambda_{j,k+1}}{w_j}q} - e^{-\frac{\lambda}{w_0}q}\right],$$

where $\lambda = \sum_{j=1}^{k} \lambda_{0j}$. The distribution of QAL is, then, given by

$$\begin{aligned} F_Q^{(C1)}(q) &= \sum_{j=1}^{k} \frac{\lambda_{0j}}{\lambda}\left(1 - e^{-\frac{\lambda}{w_0}q}\right) - \sum_{j=1}^{k} \frac{\lambda_{0j}}{\lambda - \frac{\lambda_{j,k+1}w_0}{w_j}}\left[e^{-\frac{\lambda_{j,k+1}}{w_j}q} - e^{-\frac{\lambda}{w_0}q}\right] \\ &= 1 - e^{-\frac{\lambda}{w_0}q} - \sum_{j=1}^{k} \frac{\lambda_{0j}}{\lambda - \frac{\lambda_{j,k+1}w_0}{w_j}}\left[e^{-\frac{\lambda_{j,k+1}}{w_j}q} - e^{-\frac{\lambda}{w_0}q}\right]. \end{aligned} \tag{2.11}$$

The corresponding probability density function is given by

$$f_Q^{(C1)}(q) \;=\; \frac{\lambda}{w_0}e^{-\frac{\lambda}{w_0}q} - \sum_{j=1}^{k} \frac{\lambda_{0j}}{\lambda - \frac{\lambda_{j,k+1}w_0}{w_j}}\left[\frac{\lambda}{w_0}e^{-\frac{\lambda}{w_0}q} - \frac{\lambda_{j,k+1}}{w_j}e^{-\frac{\lambda_{j,k+1}}{w_j}q}\right].$$

and the mean QAL is $\dfrac{w_0}{\lambda} + \sum_{j=1}^{k}\left(\dfrac{\lambda_{0j}}{\lambda}\right)\left(\dfrac{w_j}{\lambda_{j,k+1}}\right)$.

2.4.2 QAL Distribution in Competing Illness-Death Model 2

Let $T_{0,k+1}$ be the conceptual sojourn time in healthy state before moving directly to the absorbing state $k+1$ with hazard rate $\lambda_{0,k+1}(x)$ at time x, as shown in Figure 2.6. Other sojourn times with corresponding hazard rates are as defined for model 1 in the previous section. The QAL is then defined by

$$Q = \begin{cases} w_0 T_{0j} + w_j T_{j,k+1} & \text{if } T_{0j} = \min\{T_{01}, \ldots, T_{0k}, T_{0,k+1}\}, \qquad \text{for } j = 1, \ldots, k, \\ w_0 T_{0,k+1} & \text{if } T_{0,k+1} = \min\{T_{01}, \ldots, T_{0k}, T_{0,k+1}\}. \end{cases}$$

The distribution of QAL is now given by

$$F_Q^{(C2)}(q) = \sum_{j=1}^{k} P_j + P_{k+1},$$

$$\begin{aligned} \text{where } P_j &= P\left[w_0 T_{0j} + w_j T_{j,k+1} \le q, T_{0j} = \min\{T_{01}, \ldots, T_{0k}, T_{0,k+1}\}\right] \\ &= \int_0^{\frac{q}{w_0}} \left(\int_0^{\frac{q - w_0 x}{w_j}} \lambda_{j,k+1}(y|x) e^{-\Lambda_{j,k+1}(y|x)} dy \right) \lambda_{0j}(x) \\ &\quad \times \exp\left[- \left(\sum_{l=1}^{k} \Lambda_{0l}(x) + \Lambda_{0,k+1}(x) \right) \right] dx \\ \text{and } P_{k+1} &= \int_0^{\frac{q}{w_0}} \lambda_{0,k+1}(x) \exp\left[- \left(\sum_{l=1}^{k} \Lambda_{0l}(x) + \Lambda_{0,k+1}(x) \right) \right] dx, \end{aligned}$$

with $\Lambda_{j,k+1}(y|x)$ and $\Lambda_{0j}(x)$ being the cumulative hazards as before and $\Lambda_{0,k+1}(x) = \int_0^x \lambda_{0,k+1}(u) du$.

One can obtain the expression for the distribution of QAL, as in model 1, for different choices of hazard rates and dependence structure. When the different sojourn times are independently distributed with constant hazards, the form of QAL distribution is given by

$$\begin{aligned} F_Q^{(C2)}(q) &= \sum_{j=1}^{k} \frac{\lambda_{0j}}{\lambda} \left(1 - e^{-\frac{\lambda'}{w_0} q} \right) - \sum_{j=1}^{k} \frac{\lambda_{0j}}{\lambda' - \frac{\lambda_{j,k+1} w_0}{w_j}} \left[e^{-\frac{\lambda_{j,k+1}}{w_j} q} - e^{-\frac{\lambda'}{w_0} q} \right] \\ &\quad + \frac{\lambda_{0,k+1}}{\lambda'} \left(1 - e^{-\frac{\lambda'}{w_0} q} \right) \end{aligned}$$

$$= \left(1+\frac{\lambda_{0,k+1}}{\lambda'}\right)\left(1-e^{-\frac{\lambda'}{w_0}q}\right)-\sum_{j=1}^{k}\frac{\lambda_{0j}}{\lambda'-\frac{\lambda_{j,k+1}w_0}{w_j}}\left[e^{-\frac{\lambda_{j,k+1}}{w_j}q}-e^{-\frac{\lambda'}{w_0}q}\right],$$

where $\lambda' = \sum_{j=1}^{k}\lambda_{0j}+\lambda_{0,k+1}$.

2.5 Reversible Simple Illness-Death Model

Here we consider the simple illness-death models of Section 2.2, but an individual may recover from the illness state to transit back to the healthy state 0. That is, an individual in state 1 can either recover and transit back to the the healthy state 0, or fail by moving to death state 2. Therefore, an individual may visit the illness state 1 an infinite number of times before moving to state 2. This is named as reversible simple illness-death model 1 and shown in Figure 2.7. As before, one may also allow, in addition, the possibility of moving to state 2 directly from state 0 (that is, death without illness). This is named as reversible simple illness-death model 2 and shown in Figure 2.8. In coronary heart disease (CHD) study, for example, individuals may experience CHD repeatedly. Once CHD is experienced, the individual may recover from it or die with the CHD. The repair model in industrial studies is a good example.

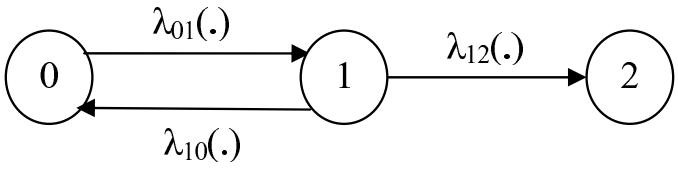

Figure 2.7: Reversible Simple Illness-Death Model 1.

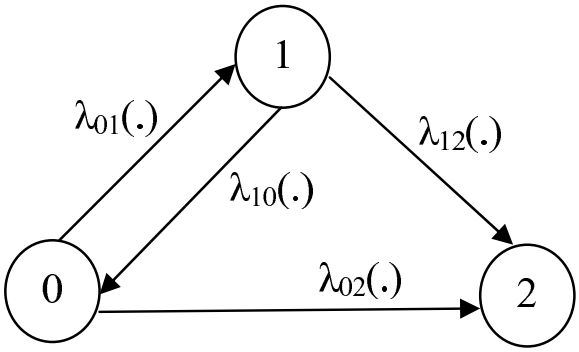

Figure 2.8: Reversible Simple Illness-Death Model 2.

2.5.1 QAL Distribution in Reversible Simple Illness-Death Model 1

As shown in Figure 2.7, an individual may recover from illness state 1 and transit back to the healthy state 0. Let V be the number of times an individual transits back from illness state 1 to healthy state 0. Note that V is a discrete random variable taking values $0, 1, 2, \ldots$, with probability mass function $p(v)$, say. Let $T_{01}^{(l)}$ be the sojourn time spent in healthy state 0 during the lth stay, $l = 1, 2, \ldots, V+1$. The competing risks structure for the transition from state 1 (to either 0 or 2) is to be noted. Accordingly, let $T_{10}^{(l)}$ be the conceptual sojourn time in state 1 before moving to state 0 and, similarly, $T_{12}^{(l)}$ be the same before moving to state 2, during the lth visit to state 1, for $l = 1, \ldots, V+1$. Let us write $X_1^{(l)} = \min(T_{10}^{(l)}, T_{12}^{(l)})$. The QAL is then given by

$$Q = w_0 \sum_{l=1}^{V+1} T_{01}^{(l)} + w_1 \sum_{l=1}^{V+1} X_1^{(l)},$$

where w_0 is the utility coefficient in the healthy state 0 and w_1 is the same in the illness state 1. The distribution of QAL is given by

$$F_Q^{(R1)}(q) \;=\; P\left[w_0 \sum_{l=1}^{V+1} T_{01}^{(l)} + w_1 \sum_{l=1}^{V+1} X_1^{(l)} \le q\right].$$

The form of $F_Q^{(R1)}(q)$, for general sojourn time distributions incorporating some dependence structure or not, would be too complicated. We, therefore, assume the different sojourn times $T_{01}^{(l)}$'s, $T_{10}^{(l)}$'s and $T_{12}^{(l)}$'s to be independent and identically distributed with constant hazards λ_{01}, λ_{10} and λ_{12}, respectively. Note that λ_{10} and λ_{12} may as well be interpreted as cause-specific hazard rates.

Note that, given $V = v$, we have $X_1^{(l)} = T_{10}^{(l)}$, for $l = 1, \ldots, v$, and $X_1^{(v+1)} = T_{12}^{(v+1)}$. Also, when $T_{10}^{(l)}$ and $T_{12}^{(l)}$ are independent exponential random variables, the conditional distribution of $X_1^{(l)}$ given that $X_1^{(l)} = T_{10}^{(l)}$, is same as the marginal distribution of $X_1^{(l)}$. This is true even when the conditioning event is $X_1^{(l)} = T_{12}^{(l)}$. Note also that the probability mass function $p(v)$ of V is given by the geometric distribution

$$P(V = v) = p(v) = \frac{\lambda_{12}}{\lambda_{10} + \lambda_{12}} \left(\frac{\lambda_{10}}{\lambda_{10} + \lambda_{12}} \right)^v, v = 0, 1, 2, ... \tag{2.12}$$

Therefore, the distribution function of $F_Q^{(R1)}(q)$ can be written as

$$\begin{aligned} F_Q^{(R1)}(q) &= \sum_{v=0}^{\infty} P\left[w_0 \sum_{l=1}^{v+1} T_{01}^{(l)} + w_1 \sum_{l=1}^{v+1} X_1^{(l)} \leq q \right] p(v) \\ &= \sum_{v=0}^{\infty} P\left[T'_{01(v+1)} + X'_{1(v+1)} \leq q \right] p(v), \end{aligned} \tag{2.13}$$

where $T'_{01(l)}$ and $X'_{1(l)}$ are independent Gamma random variables with shape parameter l and scale parameters $\lambda'_{01} = \lambda_{01}/w_0$ and $\lambda'_{10} = (\lambda_{10} + \lambda_{12})/w_1$, respectively. The distribution of a sum of two independent non-identical Gamma variates with integer shape parameters is given in Result 2.8.1 in Section 2.8. In practice, the S-Plus functions *dgamma* and *pgamma* can be used to evaluate this convoluted distribution.

In practice, regardless of the relative value of the recovery rate λ_{10} as compared to the death rate λ_{12}, the values of $p(v) = \lambda_{12}\lambda_{10}^v(\lambda_{12}+\lambda_{10})^{-(v+1)}$ decay with increasing values of v and, after some finite value, it contributes insignificantly and can be ignored. Therefore, using (2.12) and (2.13), the distribution $F_Q^{(R1)}(q)$ can be approximately obtained for given values of λ_{01}, λ_{10} and λ_{12}.

2.5.2 QAL Distribution in Reversible Simple Illness-Death Model 2

As before, let V denote the number of times an individual recovers from illness state 1. The competing risks structure for the transition from state 0 (to either 1 or 2), and also from state 1 (to either 0 or 2), is evident from Figure 2.8. Let $T_{01}^{(l)}$ be the conceptual sojourn time spent in state 0 before moving to state 1 and $T_{02}^{(l)}$ be the same before moving to state 2 during the lth stay in state 0, for $l = 1, ..., V+1$. Similarly, $T_{10}^{(l)}$ and $T_{12}^{(l)}$ are defined, as in the previous section, for the conceptual sojourn times during the lth visit to state 1, for $l = 1, ..., V + 1$. Let us write $X_0^{(l)} = \min\left(T_{01}^{(l)}, T_{02}^{(l)}\right)$ as the sojourn time in state 0 and $X_1^{(l)} = \min\left(T_{10}^{(l)}, T_{12}^{(l)}\right)$ as the sojourn time in state 1, during the lth stay in the corresponding states. The QAL is then given by

$$QAL = \begin{cases} w_0 \sum_{l=1}^{V+1} X_0^{(l)} + w_1 \sum_{l=1}^{V+1} X_1^{(l)}, & \text{if } X_0^{(V+1)} = T_{01}^{(V+1)} \\ w_0 \sum_{l=1}^{V+1} X_0^{(l)} + w_1 \sum_{l=1}^{V} X_1^{(l)}, & \text{if } X_0^{(V+1)} = T_{02}^{(V+1)}. \end{cases}$$

As before, for simplicity, we assume the different sojourn times $T_{01}^{(l)}$'s, $T_{10}^{(l)}$'s, $T_{02}^{(l)}$'s and $T_{12}^{(l)}$'s to be independent and, for different l, identically distributed with constant hazards λ_{01}, λ_{10}, λ_{02} and λ_{12}, respectively, which can be interpreted as cause-specific hazards as well.

Note that, given $V = v$, we have $X_0^{(l)} = T_{01}^{(l)}$ and $X_1^{(l)} = T_{10}^{(l)}$, for $l = 1, \ldots, v$; also, if $X_0^{(v+1)} = T_{01}^{(v+1)}$, then $X_1^{(v+1)} = T_{12}^{(v+1)}$; if $X_0^{(v+1)} = T_{02}^{(v+1)}$, then $X_1^{(v+1)}$ does not exist. Also note that the process starts in state 0 and restarts in state 0, after a recovery by going through the event of transition from state 0 to 1 and then from 1 to 0, with corresponding probability $p = \lambda_{01}\lambda_{10}(\lambda_{01} + \lambda_{02})^{-1}(\lambda_{10} + \lambda_{12})^{-1}$. The complement of this event is either direct transition from state 0 to 2 or transition from state 0 to 1 followed by transition to state 2 with probabilities $\lambda_{02}(\lambda_{01} + \lambda_{02})^{-1}$ and $\lambda_{01}\lambda_{12}(\lambda_{01} + \lambda_{02})^{-1}(\lambda_{10} + \lambda_{12})^{-1}$, respectively. Note that the

sum of these three probabilities is 1. Therefore, the probability distribution of V is given by

$$P[V = v] = p(v) = (1 - p)p^v, v = 0, 1, 2, \ldots$$

Following the same technique as that of the previous section, the distribution of QAL is then given by

$$\begin{aligned} F_Q^{(R2)}(q) &= \sum_{v=0}^{\infty} \Bigg\{ P\left[X'_{0(v+1)} + X'_{1(v+1)} \leq q\right] \frac{\lambda_{01}\lambda_{12}}{(\lambda_{01} + \lambda_{02})(\lambda_{10} + \lambda_{12})} \\ &\quad + P\left[X'_{0(v+1)} + X'_{1(v)} \leq q\right] \frac{\lambda_{0d}}{\lambda_{01} + \lambda_{02}} \Bigg\} p^v, \end{aligned} \tag{2.14}$$

where, as in the previous section $X'_{0(l)}$ and $X'_{1(l)}$ are independent Gamma random variables with shape parameter l and scale parameters $\lambda'_0 = (\lambda_{01} + \lambda_{02})/w_0$ and $\lambda'_1 = (\lambda_{10}+\lambda_{12})/w_1$, respectively. Using the distribution of sum of two independent non-identical Gamma variates with integer shape parameters, as in the previous section, the distribution function $F_Q^{(R2)}(\cdot)$ can be approximately evaluated for given values of λ_{01}, λ_{02}, λ_{10} and λ_{12}, after ignoring the insignificant terms for large v.

2.6 Justification for Using Different Illness-Death Models

As discussed in Introduction (See Section 1.4), the proposed method of estimating QAL distribution makes explicit use of the information on the structure of the illness-death model while deriving the theoretical distribution of QAL. Other methods based on observed QAL data use this information only when transforming the data into QAL scale. As a result, these methods cannot distinguish between two illness-death models giving rise to same QAL values and, therefore, lead to less efficient estimates compared to the method which can distinguish between different illness-death model.

In order to illustrate the above point, let us consider the following two illness-death models, given in Figures 2.9 and 2.10. The model in Figure 2.9 is the simple illness-death model of Section 2.2.1 in which a healthy person in state 0 becomes ill (state 1) with constant hazard λ_{01} followed by transition to death (state 2) with constant hazard λ_{12}. Suppose the utility coefficients in states 0 and 1 are w_0 and w_1, respectively. For the model in Figure 2.10, a healthy person moves either to state 1, or to state 2, with cause-specific hazard rates λ_{01} and λ_{02}, respectively, followed by transition to death (state 3) with hazard rates λ_{13} and λ_{23}, respectively. The weight is w_0 in state 0 and w_1 in state 1 or 2. This is the competing illness-death model 1 (See Figure 2.5) with k=2.

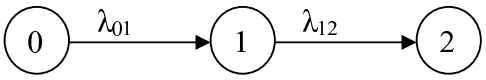

Figure 2.9: Illness-death Model 1.

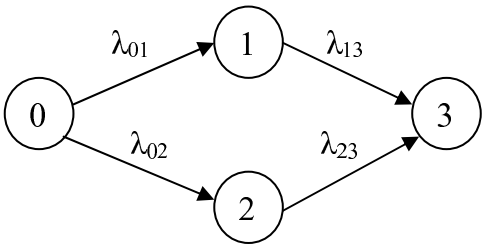

Figure 2.10: Illness-death Model 2.

Clearly, the QAL values (uncensored or censored) are the same regardless of the model (of those in Figure 2.9 or 2.10) which the ordinary lifetime data comes from. Therefore, the methods based on observed QAL are not able to distinguish between the two models. On the other hand, from Sections 2.2.1 and 2.4.1,

respectively, the QAL distributions for the two models can be seen to be

$$F_a(q) = 1 - e^{-\frac{\lambda_{01}}{w_0}q} - \frac{\lambda_{01}w_1}{\lambda_{01}w_1 - \lambda_{12}w_0}\left(e^{-\frac{\lambda_{12}}{w_1}q} - e^{-\frac{\lambda_{01}}{w_0}q}\right)$$

and

$$F_b(q) = 1 - e^{-\frac{\lambda_{01}+\lambda_{02}}{w_0}q} - \sum_{j=1}^{2}\frac{\lambda_{0j}w_1}{(\lambda_{01}+\lambda_{02})w_1 - \lambda_{j3}w_0}\left(e^{-\frac{\lambda_{j3}}{w_1}q} - e^{-\frac{\lambda_{01}+\lambda_{02}}{w_0}q}\right).$$

Note that these two distributions are different unless $\lambda_{13} = \lambda_{23}$. Therefore, a method that uses the theoretical distribution, thereby distinguishing between the two illness-death models, gives more efficient estimates. This has been verified through a small simulation study. In Chapter 5 (Section 5.2.1), the proposed nonparametric method using structure information gives more efficient estimates than another nonparametric method (Zhao and Tsiatis, 1999) based on observed QAL. In view of the above, it is important to develop methods for specific illness-death models using the information on their structures.

2.7 Concluding Remarks

Different illness-death models are considered for the derivation of QAL distribution. The main feature of this work is the analytical derivation of QAL distribution. The general form of the QAL distribution is obtained corresponding to each illness-death model. In most applications, when the number of states is not large, closed form expression for the QAL distribution is available. Otherwise, this expression involves multiple integration which needs to be evaluated by a suitable numerical method. However, this needs to be done only once using the estimates of the relevant sojourn time distributions. Closed form expression for the distribution of QAL is obtained under the assumption that the sojourn times are independent and exponentially distributed. The distribution of sum of independent non-identical exponential variates is required for both the progressive illness-death models. If some of the exponential distributions are identical then it

is nothing but sum of non-identical Gamma variates with integer shape parameters, the distribution of which is given in Result 2.8.2 of the next Section. One can find closed form expression for other distributions (Mathai, 1982; Moschopulos, 1985, Hitezenko, 1998; Gupta and Kundu, 1999) also.

2.8 Sum of Independent and Non-identical Gamma Variates

The distribution of sum of independent non-identical Gamma random variables with integer shape parameters is required for derivation of QAL distribution in progressive and reversible illness-death models. In this regard, we prove the following two results.

RESULT 2.8.1 *Suppose $T_i \sim$ Gamma(λ_i, n_i), for $i = 1, 2$, where T_i's are independently distributed and n_i's are integers and $\lambda_1 \neq \lambda_2$. Then, the distribution of $T = T_1 + T_2$ is given by*

$$\begin{aligned} G(t) = P(T < t) &= 1 - \sum_{k=0}^{n_1-1} e^{-\lambda_1 t} \frac{(\lambda_1 t)^k}{k!} \\ &\quad - \left[\frac{e^{-\lambda_2 t} \lambda_1^{n_1}}{\Gamma(n_1)} \sum_{i=0}^{n_2-1} \frac{\lambda_2^i}{i!} \sum_{j=0}^{i} (-1)^j \binom{i}{j} t^{i-j} \frac{\Gamma(n_1+j)}{(\lambda_1-\lambda_2)^{n_1+j}} \right. \\ &\quad \left. \times \left(1 - \sum_{k=0}^{n_1+j-1} \frac{(\lambda_1-\lambda_2)^k t^k}{k!} e^{-(\lambda_1-\lambda_2)t} \right) \right]. \end{aligned}$$

Proof of Result 2.8.1:

$$\begin{aligned} G(t) &= P(T_1 + T_2 < t) \\ &= \int_0^t F_2(t - t_1) f_1(t_1) dt_1 \\ &= \int_0^t \left[1 - \sum_{i=0}^{n_2-1} \frac{\lambda_2^i (t-t_1)^i}{i!} e^{-\lambda_2 (t-t_1)} \right] f_1(t_1) dt_1 \\ &= F_1(t) - A, \text{ say,} \end{aligned}$$

where $F_i(t)$ is the distribution function of T_i with density $f_i(t)$ and

$$\begin{aligned}
A &= e^{-\lambda_2 t}\sum_{i=0}^{n_2-1}\frac{\lambda_2^i}{i!}\int_0^t \frac{\lambda_1^{n_1}}{\Gamma(n_1)}e^{-(\lambda_1-\lambda_2)t_1}(t-t_1)^i t_1^{n_1-1}dt_1 \\
&= \frac{e^{-\lambda_2 t}\lambda_1^{n_1}}{\Gamma(n_1)}\sum_{i=0}^{n_2-1}\frac{\lambda_2^i}{i!}\int_0^t e^{-(\lambda_1-\lambda_2)t_1}\left(\sum_{j=0}^{i}(-1)^j\binom{i}{j}t^{i-j}t_1^j\right)t_1^{n_1-1}dt_1 \\
&= \frac{e^{-\lambda_2 t}\lambda_1^{n_1}}{\Gamma(n_1)}\sum_{i=0}^{n_2-1}\frac{\lambda_2^i}{i!}\sum_{j=0}^{i}(-1)^j\binom{i}{j}t^{i-j}\frac{\Gamma(n_1+j)}{(\lambda_1-\lambda_2)^{n_1+j}} \\
&\quad\times\left[\int_0^t\frac{(\lambda_1-\lambda_2)^{n_1+j}}{\Gamma(n_1+j)}e^{-(\lambda_1-\lambda_2)t_1}t_1^{n_1+j-1}dt_1\right] \\
&= \frac{e^{-\lambda_2 t}\lambda_1^{n_1}}{\Gamma(n_1)}\sum_{i=0}^{n_2-1}\frac{\lambda_2^i}{i!}\sum_{j=0}^{i}(-1)^j\binom{i}{j}t^{i-j}\frac{\Gamma(n_1+j)}{(\lambda_1-\lambda_2)^{n_1+j}} \\
&\quad\times\left(1-\sum_{k=0}^{n_1+j-1}\frac{(\lambda_1-\lambda_2)^k t^k}{k!}e^{-(\lambda_1-\lambda_2)t}\right).
\end{aligned}$$

Hence, the result is proved.

RESULT 2.8.2 *Suppose $T_i \sim$ Gamma(λ_i, n_i), for $i = 1,\ldots,k$, where T_i's are independently distributed and n_i's are integers. Then, the distribution of $T = \sum_{i=1}^{k} T_i$ is given by*

$$F_k\left(\lambda^{(k)}, n^{(k)}, t\right) = F_{k-1}\left(\lambda^{(k-1)}, n^{(k-1)}, t\right) - \sum_{m=0}^{n_k-1} e^{-\lambda_k t}\frac{\lambda_k^m}{m!}.A_m(t),$$

for $k \geq 2$, where

$$\begin{aligned}
A_m(t) &= \frac{\prod_{i=1}^{k-1}\lambda_i^{n_i}}{\prod_{i=1}^{k-1}\Gamma(n_i)}\sum\nolimits_*\left[\frac{m!(-1)^{m-r}}{r!r_1!\cdots r_{k-1}!}t^r\right. \\
&\quad\left.\times\frac{\prod_{i=1}^{k-1}\Gamma(n_i+r_i)}{\prod_{i=1}^{k-1}(\lambda_i-\lambda_k)^{n_i+r_i}}F_{k-1}\left(\lambda'^{(k-1)}, n'^{(k-1)}, t\right)\right],
\end{aligned}$$

$\lambda^{(k)} = (\lambda_1,\ldots,\lambda_k)$, $n^{(k)} = (n_1,\ldots,n_k)$, $\lambda'^{(k-1)} = (\lambda_1-\lambda_k,\ldots,\lambda_{k-1}-\lambda_k)$, $n'^{(k-1)} = (n_1+r_1,\ldots,n_{k-1}+r_{k-1})$ and the sum $\sum_*$ is over all possible $(r, r_1,\ldots,r_{k-1})$ such that $r + r_1 + \cdots + r_{k-1} = m$.

Proof of Result 2.8.2:

$$\begin{aligned}
F_k\left(\lambda^{(k)}, n^{(k)}, t\right) &= P(T \le t) = \int_0^t \int_0^{t-t_1} \cdots \int_0^{t-\sum_{i=1}^{k-1} t_i} \prod_{i=1}^{k} f_i(t_i) dt_i \\
&= F_{k-1}\left(\lambda^{(k-1)}, n^{(k-1)}, t\right) \\
&\quad - \int_0^t \int_0^{t-t_1} \cdots \int_0^{t-\sum_{i=1}^{k-2} t_i} \sum_{m=0}^{n_k-1} \left[\frac{e^{-\lambda_k\left(t-\sum_{i=1}^{k-1} t_i\right)}}{m!} \right. \\
&\quad \left. \times \lambda_k^m \left(t - \sum_{i=1}^{k-1} t_i\right)^m \prod_{i=1}^{k-1} f_i(t_i) dt_i \right] \\
&= F_{k-1}\left(\lambda^{(k-1)}, n^{(k-1)}, t\right) - \sum_{m=0}^{n_k-1} e^{-\lambda_k t} \frac{\lambda_k^m}{m!} . A_m(t),
\end{aligned}$$

where $f_i(t)$ is the density of T_i and

$$\begin{aligned}
A_m(t) &= \int_0^t \int_0^{t-t_1} \cdots \int_0^{t-\sum_{i=1}^{k-2} t_i} e^{\lambda_k\left(\sum_{i=1}^{k-1} t_i\right)} \left(t - \sum_{i=1}^{k-1} t_i\right)^m \prod_{i=1}^{k-1} f_i(t_i) dt_i \\
&= \int_0^t \int_0^{t-t_1} \cdots \int_0^{t-\sum_{i=1}^{k-2} t_i} e^{\lambda_k\left(\sum_{i=1}^{k-1} t_i\right)} \\
&\quad \times \left(\sum_* \frac{m!(-1)^{m-r}}{r! r_1! \ldots r_{k-1}!} t^r \prod_{i=1}^{k-1} t_i^{r_i}\right) \prod_{i=1}^{k-1} \frac{\lambda_i^{n_i}}{\Gamma(n_i)} e^{-\lambda_i t_i} t_i^{n_i-1} dt_i \\
&= \frac{\prod_{i=1}^{k-1} \lambda_i^{n_i}}{\prod_{i=1}^{k-1} \Gamma n_i} \sum_* \left[\frac{m!(-1)^{m-r}}{r! r_1! \ldots r_{k-1}!} t^r \right. \\
&\quad \times \int_0^t \int_0^{t-t_1} \cdots \int_0^{t-\sum_{i=1}^{k-2} t_i} \frac{\prod_{i=1}^{k-1} \Gamma(n_i + r_i)}{\prod_{i=1}^{k-1} (\lambda_i - \lambda_k)^{n_i + r_i}} \\
&\quad \left. \times \prod_{i=1}^{k-1} \frac{(\lambda_i - \lambda_k)^{n_i + r_i}}{\Gamma(n_i + r_i)} e^{-(\lambda_i - \lambda_k) t_i} t_i^{n_i + r_i - 1} dt_i \right] \\
&= \frac{\prod_{i=1}^{k-1} \lambda_i^{n_i}}{\prod_{i=1}^{k-1} \Gamma(n_i)} \sum_* \left[\frac{m!(-1)^{m-r}}{r! r_1! \ldots r_{k-1}!} t^r \right. \\
&\quad \left. \times \frac{\prod_{i=1}^{k-1} \Gamma(n_i + r_i)}{\prod_{i=1}^{k-1} (\lambda_i - \lambda_k)^{n_i + r_i}} F_{k-1}\left(\lambda'^{(k-1)}, n'^{(k-1)}, t\right) \right].
\end{aligned}$$

Hence the result is proved.

Chapter 3

Induced Dependent Censoring

3.1 Introduction

While dealing with censored data for estimation of QAL distribution, there is informative censoring when the data is transformed into the QAL scale, as reported by many authors (Gelber et al., 1989; Glasziou et al., 1990; Lin et al., 1997; Huang and Louis, 1999, among many others). That is, even if the original lifetime T and the censoring time C are independent, the quality adjusted lifetime Q and the corresponding quality adjusted censoring time C^* do not remain independent. This, in the literature, is known as induced dependent censoring.

Although it might seem natural to undertake a standard survival analysis with the observed QAL values (censored and uncensored), this approach leads to bias due to this induced dependent censoring. Most of the work done so far, on the analysis of QAL data, concentrates on adjusting for this bias while estimating the mean QAL (Huang and Louis, 1999; Zhao and Tsiatis, 2000) or QAL distribution (Korn, 1993; Zhao and Tsiatis, 1997, 1999; Huang and Louis, 1998; Van der Laan and Hubbard, 1999; Strawderman, 2000; Almanassra et al., 2005). Despite all this work, the issue of induced dependent censoring in the QAL scale still remains

less-understood. Although there is some qualitative discussion, there is no formal proof of this dependence. There is one argument by Lin (2003) which can be described as follows. Noting that $Q = \int_0^T W(u)du$ and $C^* = \int_0^C W(u)du$, clearly, Q and C^* are positively correlated through the utility function $W(\cdot)$. Therefore, while a healthy person has high Q value and also high C^* value, a person getting sick early, but with same T and C, has low Q and C^*. The arguments presented by all other authors also speak of a positive correlations between Q and C^*. In this work, we formally study the nature of this induced dependence in the context of a simple illness-death model and show that there can be situations when Q and C^* are negatively correlated. The direction of bias of the Kaplan-Meier estimate of the QAL distribution is investigated.

The issue of induced dependent censoring is investigated in Section 3.2 in the context of simple illness-death model. In particular, we work out the covariance between Q and C^*. Section 3.3 studies the bias in the Nelson-Aalen and Kaplan-Meier estimators of the QAL distribution due to this dependent censoring. Section 3.4 ends with some concluding remarks.

3.2 Induced Dependent Censoring

We consider the simple illness-death model 1 of Section 2.2 as shown in Figure 2.1 and assume that T_{01} and T_{12} are independent. The distribution function of Q is given by

$$\begin{aligned} F_Q(q) &= \int_0^{\frac{q}{w_0}} \left[\int_0^{\frac{q-w_0x}{w_1}} \lambda_{12}(y) e^{-\Lambda_{12}(y)} dy \right] \lambda_{01}(x) e^{-\Lambda_{01}(x)} dx \\ &= \int_0^{q/w_0} F_{12}\left(\frac{q - w_0 x}{w_1} \right) dF_{01}(x), \end{aligned}$$

where $F_{01}(\cdot)$ are $F_{12}(\cdot)$ are distribution functions of T_{01} and T_{12}, respectively. The survival function of Q is given by

$$S_Q(q) = P[Q > q] = \int_0^\infty \bar{F}_{12}\left(\frac{q - w_0 x}{w_1}\right) dF_{01}(x), \tag{3.1}$$

where $\bar{F}_{12}(\cdot) = 1 - F_{12}(\cdot)$ is the survival function of T_{12}.

Note that

$$C^* = w_0 C I(C < T_{01}) + \{w_0 T_{01} + w_1(C - T_{01})\} I(C \geq T_{01}). \tag{3.2}$$

For the investigation, it is assumed that censoring variable C is independent of T_{01} and T_{12}. Let $\bar{F}_c(\cdot)$ be the survival function of C. Then, the survival function of C^* is given by

$$\begin{aligned} P[C^* > c^*] &= P\left[w_0 C > c^*, C < T_{01}\right] + P\left[w_0 T_{01} + w_1(C - T_{01}) > c^*, C \geq T_{01}\right] \\ &= P_1 + P_2, \text{say}, \end{aligned}$$

$$\begin{aligned} \text{where } P_1 &= \int_{\frac{c^*}{w_0}}^\infty \left[\bar{F}_c\left(\frac{c^*}{w_0}\right) - \bar{F}_c(t_{01})\right] dF_{01}(t_{01}) \text{ and} \\ P_2 &= \int_0^\infty P\left[C > \max\left(\frac{c^* - (w_0 - w_1)t_{01}}{w_1}, t_{01}\right)\right] dF_{01}(t_{01}) \\ &= \int_0^\infty \bar{F}_c\left(\max\left\{\frac{c^* - (w_0 - w_1)t_{01}}{w_1}, t_{01}\right\}\right) dF_{01}(t_{01}) \\ &= \int_0^{\frac{c^*}{w_0}} \bar{F}_c\left(\frac{c^* - (w_0 - w_1)t_{01}}{w_1}\right) dF_{01}(t_{01}) + \int_{\frac{c^*}{w_0}}^\infty \bar{F}_c(t_{01}) dF_{01}(t_{01}). \end{aligned}$$

After some simplification, we have

$$P[C^* > c^*] = \bar{F}_c\left(\frac{c^*}{w_0}\right) \bar{F}_{01}\left(\frac{c^*}{w_0}\right) + \int_0^{\frac{c^*}{w_0}} \bar{F}_c\left(\frac{c^* - (w_0 - w_1)t_{01}}{w_1}\right) dF_{01}(t_{01}). \tag{3.3}$$

The joint survival function of Q and C^* is given by

$$\begin{aligned} P\left[Q > q, C^* > c^*\right] &= P\left[C > \frac{c^*}{w_0}, w_0 T_{01} + w_1 T_{12} > q, C < T_{01}\right] \\ &+ P\left[C > \frac{c^* - (w_0 - w_1)T_{01}}{w_1}, w_0 T_{01} + w_1 T_{12} > q, C > T_{01}\right] \\ &= P_1' + P_2', \text{ say}, \end{aligned}$$

where

$$P_1' = \int_{\frac{c^*}{w_0}}^{\infty} \left[\bar{F}_c\left(\frac{c^*}{w_0}\right) - \bar{F}_c(t_{01})\right] \bar{F}_{12}\left(\frac{q - w_0 t_{01}}{w_1}\right) dF_{01}(t_{01}) \text{ and}$$

$$P_2' = \int_0^{\infty} \bar{F}_c\left(\max\left\{\frac{c^* - (w_0 - w_1)t_{01}}{w_1}, t_{01}\right\}\right) \bar{F}_{12}\left(\frac{q - w_0 t_{01}}{w_1}\right) dF_{01}(t_{01}).$$

After simplification, we get

$$\begin{aligned} P\left[Q > q, C^* > c^*\right] &= \bar{F}_c\left(\frac{c^*}{w_0}\right) \int_{\frac{c^*}{w_0}}^{\infty} \bar{F}_{12}\left(\frac{q - w_0 t_{01}}{w_1}\right) dF_{01}(t_{01}) \\ &\quad + \int_0^{\frac{c^*}{w_0}} \bar{F}_c\left(\frac{c^* - (w_0 - w_1)t_{01}}{w_1}\right) \bar{F}_{12}\left(\frac{q - w_0 t_{01}}{w_1}\right) dF_{01}(t_{01}). \end{aligned} \tag{3.4}$$

Note that the above joint survival function (3.4) reduces to $S_Q(q)$ given by (3.1), by putting $c^* = 0$. Similarly, by putting $q = 0$, the equation (3.4) reduces to $P[C^* > c^*]$, given by (3.3). Under the assumption that $T_{i,i+1}$ follows $\exp(\lambda_{i,i+1})$, for $i = 0, 1$, and C follows $\exp(\lambda_c)$, we have

$$P[C^* > c^*] = \frac{\lambda_c(w_1 - w_0)}{(\lambda_{01} + \lambda_c)w_1 - \lambda_c w_0} e^{-\frac{c^*}{w_0}(\lambda_{01} + \lambda_c)} + \frac{\lambda_{01} w_1}{(\lambda_{01} + \lambda_c)w_1 - \lambda_c w_0} e^{-\frac{c^*}{w_1}\lambda_c}.$$

This implies

$$E(C^*) = \int_0^{\infty} P[C^* > c^*] dc^* = \frac{\lambda_{01} w_1 + \lambda_c w_0}{\lambda_c(\lambda_{01} + \lambda_c)}.$$

We also have, from the definition of Q,

$$E(Q) = \frac{w_0}{\lambda_{01}} + \frac{w_1}{\lambda_{12}}.$$

Note that, from Barlow and Proschan (1975, p. 135),

$$\begin{aligned} E(QC^*) &= \int_0^{\infty} \int_0^{\infty} P[Q > q, C^* > c^*] dc^* dq \\ &= \int_0^{\infty} \left[\int_0^{q} P[Q > q, C^* > c^*] dc^* + \int_q^{\infty} P[Q > q, C^* > c^*] dc^*\right] dq. \end{aligned} \tag{3.5}$$

For $c^* < q$, we have $P[Q > q, C^* > c^*]$

$$\begin{aligned} &= \bar{F}_c\left(\frac{c^*}{w_0}\right)\left[\int_{\frac{c^*}{w_0}}^{\frac{q}{w_0}} \bar{F}_{12}\left(\frac{q-w_0t_{01}}{w_1}\right) dF_{01}(t_{01}) + \bar{F}_{01}\left(\frac{q}{w_0}\right)\right] \\ &\quad + \int_0^{\frac{c^*}{w_0}} \bar{F}_c\left(\frac{c^*-(w_0-w_1)t_{01}}{w_1}\right)\bar{F}_{12}\left(\frac{q-w_{01}t_{01}}{w_1}\right) dF_{01}(t_{01}), \end{aligned}$$

which, under the exponential models as before, reduces to

$$\begin{aligned} &\frac{\lambda_{01}w_1 e^{-\frac{\lambda_c c^*+\lambda_{12}q}{w_1}}}{\lambda_{01}w_1-\lambda_{12}w_0}\left[e^{-\left(\frac{\lambda_{01}}{w_0}-\frac{\lambda_{12}}{w_1}\right)c^*} - e^{-\left(\frac{\lambda_{01}}{w_0}-\frac{\lambda_{12}}{w_1}\right)q}\right] \\ &+e^{-\frac{(\lambda_{01}q+\lambda_c c^*)}{w_0}} + \frac{\lambda_{01}w_1\left[e^{-\frac{\lambda_c c^*+\lambda_{12}q}{w_1}} - e^{-\frac{c^*}{w_0}(\lambda_{01}+\lambda_c)-\frac{\lambda_{12}}{w_1}(q-c^*)}\right]}{\lambda_{01}w_1-\lambda_c(w_0-w_1)-\lambda_{12}w_0}. \end{aligned} \tag{3.6}$$

For $c^* > q$, we have $P[Q > q, C^* > c^*]$

$$\begin{aligned} &= \bar{F}_c\left(\frac{c^*}{w_0}\right)\bar{F}_{01}\left(\frac{c^*}{w_0}\right) + \int_0^{\frac{q}{w_0}} \bar{F}_c\left(\frac{c^*-(w_0-w_1)t_{01}}{w_1}\right)\bar{F}_{12}\left(\frac{q-w_0t_{01}}{w_1}\right) dF_{01}(t_{01}) \\ &\quad + \int_{\frac{q}{w_0}}^{\frac{c^*}{w_0}} \bar{F}_c\left(\frac{c^*-(w_0-w_1)t_{01}}{w_1}\right) dF_{01}(t_{01}), \end{aligned}$$

which reduces to

$$\begin{aligned} &e^{-(\lambda_{01}+\lambda_c)\frac{c^*}{w_0}} + \frac{\lambda_{01}w_1 e^{-\frac{\lambda_c c^*+\lambda_{12}q}{w_1}}}{(\lambda_{01}+\lambda_c)w_1-(\lambda_{12}+\lambda_c)w_0}\left[1-e^{-\frac{q}{w_0}\left(\frac{\lambda_{01}+\lambda_c)w_1-(\lambda_{12}+\lambda_c)w_0}{w_1}\right)}\right] \\ &+\frac{\lambda_{01}w_1}{(\lambda_{01}+\lambda_c)w_1-\lambda_c w_0}\left[e^{-\frac{q}{w_0}\left(\frac{\lambda_{01}+\lambda_c)w_1-\lambda_c w_0}{w_1}\right)}e^{-\lambda_c\frac{c^*}{w_1}} - e^{-\frac{c^*}{w_0}(\lambda_{01}+\lambda_c)}\right], \end{aligned} \tag{3.7}$$

under the exponential models. Then, using (3.5)-(3.7), we have, under the exponential models,

$$\begin{aligned} E\left(QC^*\right) &= \frac{w_0w_1}{\lambda_{12}(\lambda_{01}+\lambda_c)} + \frac{w_0^2}{\lambda_{01}(\lambda_{01}+\lambda_c)} + \frac{\lambda_{01}w_1^2}{\lambda_{12}(\lambda_{01}+\lambda_c)(\lambda_{12}+\lambda_c)} \\ &\quad + \frac{w_0^2}{(\lambda_{01}+\lambda_c)^2} + \frac{\lambda_{01}w_1^2}{\lambda_c(\lambda_{01}+\lambda_c)(\lambda_{12}+\lambda_c)} + \frac{\lambda_{01}w_0w_1}{\lambda_c(\lambda_{01}+\lambda_c)^2} \\ &= \frac{w_0w_1}{\lambda_{12}(\lambda_{01}+\lambda_c)} + \frac{w_0^2}{\lambda_{01}(\lambda_{01}+\lambda_c)} + \frac{\lambda_{01}w_1^2}{\lambda_{12}\lambda_c(\lambda_{01}+\lambda_c)} \\ &\quad + \frac{w_0^2}{(\lambda_{01}+\lambda_c)^2} + \frac{\lambda_{01}w_0w_1}{\lambda_c(\lambda_{01}+\lambda_c)^2}. \end{aligned}$$

Hence, after simplification, we have

$$\text{cov}[Q, C^*] \;=\; E[QC^*] - E(Q)E(C^*) = \frac{w_0(w_0 - w_1)}{(\lambda_{01} + \lambda_c)^2}. \tag{3.8}$$

It is clear from the covariance expression (3.8) that the correlation between Q and C^* is not always positive, as argued by many authors. These arguments favoring positive correlation between Q and C^* implicitly assume, in the framework of the simple illness-death model, that $w_0 > w_1$, in which case the covariance given by (3.8) is positive. As is clear from the expression (3.2), the sojourn time T_{01} in healthy state 0 is a source of dependence affecting both Q and C^* in a complicated way. If T_{01} increases, then Q increases, but C^* increases (or decreases) if $w_0 > w_1$ (or, $w_0 < w_1$). The case of $w_0 = w_1$ trivially gives independence. Note that this nature of dependence between Q and C^* holds in general for any choice of distributions for the sojourn times T_{01} and T_{12} and censoring time C. Therefore, as is evident from (3.8), when $w_0 < w_1$, there is negative correlation between Q and C^*. Also, note that, from (3.2) and (3.8), the sojourn time T_{12} in illness state 1 does not play any role in this induced dependence (See also the second panel in Table 3.4 with w_0 =0 and w_1=0.8 leading to independence between Q and C^*).

3.3 Bias due to Induced Dependence

Due to the induced dependent censoring, estimates obtained by standard survival analysis of observed QAL data are biased as discussed in Section 3.1. In this section, the direction of bias in estimating the QAL distribution is investigated, while using survival analysis techniques with the observed QAL values. We first consider the Nelson-Aalen estimator of $\Lambda_Q(q) = \int_0^q \lambda_Q(u)du$, the integrated hazard of Q, as given by

$$\hat{\Lambda}_Q(q) = \int_0^q \frac{J_Q(u)dN_Q(u)}{Y_Q(u)}, \tag{3.9}$$

where $N_Q(u)$ is the counting process giving the number of uncensored Q values less than or equal to u, $Y_Q(u)$ is the number at risk (that is, the number of $Q \wedge C^*$-values greater than or equal to u) and $J_Q(u) = I(Y_Q(u) > 0)$. Note that this estimator depends on the assumption that $N_Q(q) - \int_0^q Y_Q(u)\lambda_Q(u)du$ is a square-integrable martingale, which is true if Q and C^* are independent. Note that $N_Q(q) - \int_0^q P\left[dN_Q(u) = 1|Q \geq u, C^* \geq u\right]$ is always a square-integrable martingale and $P\left[dN_Q(u) = 1|Q \geq u, C^* \geq u\right]$=$Y_Q(u)\lambda_Q(u)du$, if Q and C^* are independent. Since Q and C^* are not independent and

$$P\left[dN_Q(u) = 1|Q \geq u, C^* \geq u\right] = Y_Q(u)P\left[Q \in I_{du}|Q \geq u, C^* \geq u\right],$$

where I_{du} is the infinitesimal interval $[u, u + du)$, the expected value of $\hat{\Lambda}_Q(q)$ is given approximately by $\int_0^q P\left[Q \in I_{du}|Q \geq u, C^* \geq u\right]$. Hence, the approximate bias in $\hat{\Lambda}_Q(q)$ is given by

$$B\left(\hat{\Lambda}_Q(q)\right) = \int_0^q \left\{P\left[Q \in I_{du}|Q \geq u, C^* \geq u\right] - \lambda_Q(u)du\right\}. \tag{3.10}$$

For the simple illness-death model 1 of Section 2.2, using (2.2) and from the joint survival function of Q and C^* in (3.4), we get, after some calculations,

$$\lambda_Q(u) = \frac{\frac{1}{w_1}\int_0^{\frac{u}{w_0}} f_{12}\left(\frac{u-w_0t_{01}}{w_1}\right) dF_{01}(t_{01})}{\bar{F}_{01}\left(\frac{u}{w_0}\right) + \int_0^{\frac{u}{w_0}} \bar{F}_{12}\left(\frac{u-w_0t_{01}}{w_1}\right) dF_{01}(t_{01})}, \tag{3.11}$$

where $f_{12}(\cdot)$ is the density of T_{12}, and
$P\left[Q \in I_{du}|Q \geq u, C^* \geq u\right] =$

$$\frac{\frac{1}{w_1}\int_0^{\frac{u}{w_0}} \bar{F}_c\left(\frac{u-(w_0-w_1)t_{01}}{w_1}\right) f_{12}\left(\frac{u-w_0t_{01}}{w_1}\right) dF_{01}(t_{01})du}{\bar{F}_C\left(\frac{u}{w_0}\right)\bar{F}_{01}\left(\frac{u}{w_0}\right) + \int_0^{\frac{u}{w_0}} \bar{F}_c\left(\frac{u-(w_0-w_1)t_1}{w_1}\right)\bar{F}_{12}\left(\frac{u-w_0t_{01}}{w_1}\right) dF_{01}(t_{01})}, \tag{3.12}$$

respectively. Under the exponential models, (3.11) and (3.12) reduces to

$$\lambda_Q(u) \;=\; \frac{\lambda_{01}\lambda_{12}\left[e^{-\frac{\lambda_{12}u}{w_1}} - e^{-\frac{\lambda_{01}u}{w_0}}\right]}{\lambda_{01}w_1e^{-\frac{\lambda_{12}u}{w_1}} - \lambda_{12}w_0e^{-\frac{\lambda_{01}u}{w_0}}}. \tag{3.13}$$

and

$$P\left[Q \in I_{du} | Q \geq u, C^* \geq u\right] = \frac{\lambda_{01}\lambda_{12}\left[e^{-\frac{(\lambda_{12}+\lambda_c)u}{w_1}} - e^{-\frac{(\lambda_{01}+\lambda_c)u}{w_0}}\right]du}{\lambda_{01}w_1 e^{-\frac{(\lambda_{12}+\lambda_c)u}{w_1}} + \left[\lambda_c w_1 - (\lambda_{12}+\lambda_c)w_0\right]e^{-\frac{(\lambda_{01}+\lambda_c)u}{w_0}}}, \tag{3.14}$$

respectively. Hence, using (3.13) and (3.14), the approximate bias $B\left(\hat{\Lambda}_Q(q)\right)$ in (3.10) can be calculated for the exponential models.

Instead of reporting the bias $B\left(\hat{\Lambda}_Q(q)\right)$ of the Nelson-Aalen estimator, we estimate the bias in more commonly used Kaplan-Meier estimator $\hat{S}_Q(q)$ of $S_Q(q)$. Noting that $S_Q(q)$ is equal to $\exp[-\Lambda_q(q)]$ and using Taylor series expansion upto second order, the bias $B\left(\hat{S}_Q(q)\right)$ in the Kaplan-Meier estimator $\hat{S}_Q(q)$ is given approximately by

$$B\left(\hat{S}_Q(q)\right) \approx -B\left(\hat{\Lambda}_Q(q)\right)S_Q(q) + \frac{\left[B\left(\hat{\Lambda}_Q(q)\right)\right]^2}{2}S_Q(q). \tag{3.15}$$

The value of this bias is given in Tables 3.1-3.4 for several set of parameters $(\lambda_{01}, \lambda_{12}, \lambda_c)$ and utility coefficients (w_0, w_1), and for different values of q. This bias is also estimated by means of simulation (See Section 4.2.3 for details) with sample size n=200 and based on 1000 simulated data sets. These values are also reported in Tables 3.1-3.4 under 'K-M bias'. From the simulation study, we see that the estimated bias in the Kaplan-Meier estimate is close to the true bias computed by using (3.15) except in the tail area. Although, from (3.10) and (3.15), it is difficult to comment on the direction of bias, the results of Table 3.1-3.4 seem to indicate positive (negative) bias when $w_0 > (<)\ w_1$. The magnitude of bias seems to be increasing with the magnitude of correlation between Q and C^* (reported in Table 3.1-3.4), as expected. In the particular case when the correlation is zero (Second panel of Table 3.4), there is no bias.

Table 3.1: Bias of Kaplan-Meier Estimates

Set of parameters: $(\lambda_{01}, \lambda_{12}, \lambda_c) = (0.02, 0.04, 0.03)$					
$(w_0, w_1) = (1, 0.1)$ $\text{corr}(Q, C^*) = 0.356$			$(w_0, w_1) = (0.1, 1)$ $\text{corr}(Q, C^*) = -0.053$		
q	bias	K-M bias	q	bias	K-M bias
5	0.013	0.013	4	-0.011	-0.010
15	0.072	0.072	11	-0.043	-0.044
25	0.116	0.118	16	-0.047	-0.048
40	0.157	0.157	24	-0.039	-0.040
70	0.174	0.180	40	-0.022	-0.023
110	0.142	0.166	60	-0.010	0.011

Table 3.2: Bias of Kaplan-Meier Estimates

Set of parameters: $(\lambda_{01}, \lambda_{12}, \lambda_c) = (0.02, 0.04, 0.03)$					
$(w_0, w_1) = (1, 0.3)$ $\text{corr}(Q, C^*) = 0.257$			$(w_0, w_1) = (0.3, 1)$ $\text{corr}(Q, C^*) = -0.105$		
q	bias	K-M bias	q	bias	K-M bias
7	0.005	0.006	7	-0.006	-0.006
20	0.046	0.047	17	-0.040	-0.041
30	0.079	0.080	25	-0.063	-0.065
45	0.114	0.114	35	-0.074	-0.077
75	0.134	0.135	53	-0.059	-0.065
115	0.111	0.133	75	-0.032	-0.027

Table 3.3: Bias of Kaplan-Meier Estimates

Set of parameters: $(\lambda_{01}, \lambda_{12}, \lambda_c) = (0.01, 0.002, 0.003)$					
$(w_0, w_1) = (0.8, 0.3)$ $\text{corr}(Q, C^*) = 0.121$			$(w_0, w_1) = (0.3, 0.8)$ $\text{corr}(Q, C^*) = -0.008$		
q	bias	K-M bias	q	bias	K-M bias
40	0.003	0.002	44	-0.002	-0.002
100	0.020	0.020	135	-0.005	-0.005
140	0.033	0.034	205	-0.004	-0.003
200	0.046	0.047	335	-0.003	-0.002
305	0.051	0.052	580	-0.002	0.003
430	0.039	0.049	900	-0.001	0.014

Table 3.4: Bias of Kaplan-Meier Estimates

Set of parameters: $(\lambda_{01}, \lambda_{12}, \lambda_c) = (0.01, 0.002, 0.003)$					
$(w_0, w_1) = (0.8, 0)$ $\text{corr}(Q, C^*) = 0.769$			$(w_0, w_1) = (0, 0.8)$ $\text{corr}(Q, C^*) = 0$		
q	bias	K-M bias	q	bias	K-M bias
4	0.029	0.029	20	0	0
20	0.126	0.127	100	0	0
35	0.191	0.194	175	0	0
60	0.260	0.269	300	0	0.002
110	0.294	0.324	550	0	0.004
170	0.249	0.304	850	0	0.011

3.4 Concluding Remarks

The main purpose of this chapter has been to study the induced dependent censoring and the resulting bias in the Kaplan-Meier estimator based on the QAL data. We carry out this study in the context of a simple illness-death model for the sake of illustration. In principle, this can be done with any general illness-death model, but the derivation of results becomes more complicated. As can be seen from the bias expression (3.15) that, although the bias can be calculated for a given model, its estimation is difficult. Hence, the straightforward method for bias correction cannot be used. As discussed in Section 3.1, method of adjustment for bias exist in the literature. In this work, a simple alternative is proposed, as discussed in the following chapters.

In addition to the bias calculation of $\hat{\Lambda}_Q(q)$ in Section 3.3, one can also calculate the asymptotic variance of $\hat{\Lambda}_Q(q)$, from (3.9), as given by

$$\int_0^q \frac{J_Q(u)}{Y_Q(u)} P\left[Q \in I_{du} | Q \geq u, C^* \geq u\right],$$

using the same argument as those used for bias calculation. Therefore, not only the expectation of $\hat{\Lambda}_Q(q)$ is different from $\Lambda_Q(q)$, its asymptotic variance is also different from what it would be with QAL survival data.

The problem of induced dependent censoring leads to bias not only in the Kaplan-Meier estimate, it leads to bias in any estimate obtained by using standard survival techniques which assume independent censoring. In particular, a parametric method to fit the observed QAL data will also give biased estimates of the parameters. We have verified this through simulation from the exponential models and then fitting the parametric model for the QAL distribution in (2.3), derived theoretically from the exponential models for T_{01} and T_{12}. The corresponding parameter estimates turn out to be biased.

Chapter 4

Parametric Estimation of QAL Distribution

4.1 Introduction

In this chapter, the parametric estimation of QAL distribution is considered for all the illness-death models discussed in Chapter 2. Though there have been number of works developing nonparametric methods for estimating QAL distribution, the parametric approach has not received much attention (except Cole, 1994) in spite of some advantages over nonparametric method. Cole et al. (1994) suggested a parametric Q-TWiST method to estimate the mean QAL. A parametric method in general has flexibility in the sense that it works for small sample sizes and the asymptotic properties are easier to establish using the delta method. In addition, a parametric model can also explicitly incorporate dependence between different sojourn times. Sometimes there may be evidence in favor of a particular parametric model with or without dependence. In such cases, a method based on an appropriate parametric model is more efficient than a nonparametric method. Note that some accounting for possible dependence between the different sojourn

times is necessary for estimating the QAL distribution. Existing methods based on observed QAL's implicitly account for the dependence, but these methods cannot be applied when some transition times are not observable. The proposed method can handle the problem of non-observability, while accounting for dependence at the same time.

The model parameters are estimated by maximum likelihood method from the corresponding lifetime data that may be censored. In the following sections, the observation with corresponding likelihood function is described for each illness-death model. In particular, simple analytic expressions for the maximum likelihood estimators of the model parameters are obtained when sojourn times are independent and exponentially distributed. The QAL distribution in each case is estimated by substituting the model parameters in the theoretical expression derived in Chapter 2 by the corresponding estimates. Model parameters can be estimated even when the transition times are unobserved. A simulation study investigates bias and precision of the estimate of QAL distribution and compares it with an existing nonparametric estimate. Application of the proposed methodology has been illustrated using the Stanford heart transplant data and IBCSG Trial V data.

This chapter is organized as follows. Estimation in simple illness-death model is discussed in Section 4.2 with a simulation study and analysis of heart transplant data. Estimation in progressive illness-death model is discussed in Section 4.3 with a simulation study and analysis of IBCSG Trial V data. Estimation in competing illness-death model and reversible illness-death model are discussed with simulation study in Sections 4.4 and 4.5, respectively.

4.2 Estimation in Simple Illness-Death Model

The maximum likelihood estimates of the unknown parameters are obtained for the two simple illness-death models (Figures 2.1 and 2.2) discussed in Section 2.2. It may be pointed out that the transition time from healthy state to illness state may not always be observed. The method of estimation of the parameters in both the models and both for observed and unobserved cases are discussed. Random censored data are considered and let C be the censoring random variable.

4.2.1 Estimation in Simple Illness-Death Model 1

First, the model parameters are estimated when T_{01}, the time from healthy state (0) to illness state (1), is observed. The possible observations are given below.
i) $X_0 = \min(T_{01}, C)$, $\delta_0 = I(T_{01} \leq C)$, observed in all cases;
ii) $X_1 = \min(T_{12}, C - T_{01})$ and $\delta_1 = I(T_{01} + T_{12} \leq C)$, observed when $\delta_0 = 1$.
Suppose we have n individuals with the observed data $\{(x_{0i}, \delta_{0i}),\ i = 1, \ldots, n\}$ and $\{(x_{1i}, \delta_{1i}), i : \delta_{0i} = 1\}$. For convenience, let us write $x_{1i} = \delta_{1i} = -1$, whenever $\delta_{0i} = 0$. The likelihood function can be written as

$$\begin{aligned} L \ \propto \ & \prod_{i=1}^{n} \left\{ \lambda_{01}^{\delta_{0i}}(x_{0i}) \left[\lambda_{12}(x_{1i}|x_{0i})\right]^{\delta_{0i}\delta_{1i}} \exp\left[-\int_0^{x_{0i}} \lambda_{01}(u)du\right] \right. \\ & \left. \times \exp\left[-\delta_{0i}\int_0^{x_{1i}} \lambda_{12}(u|x_{0i})du\right] \right\}. \end{aligned} \tag{4.1}$$

With $\lambda_{12}(y|x) = \lambda_{12}e^{\beta x}$ and $\lambda_{01}(x) = \lambda_{01}$, the likelihood function (4.1) simplifies to

$$L_d \propto \prod_{i=1}^{n} \left\{ \lambda_{01}^{\delta_{0i}} \left[\lambda_{12}e^{\beta x_{0i}}\right]^{\delta_{0i}\delta_{1i}} \exp\left[-\lambda_{01}x_{0i}\right] \times \exp\left[-\lambda_{12}\delta_{0i}x_{1i}e^{\beta x_{0i}}\right] \right\}. \tag{4.2}$$

In this case, some numerical techniques, for example, Newton-Raphson method, can be used to obtain the estimates. Under independence (β=0), the likelihood function (4.2) reduces further to

$$L_{ind} \propto \lambda_{01}^{d_{01}} \lambda_{12}^{d_{12}} \exp\left[-\left(\lambda_{01}\sum_{i=1}^{n} x_{0i} + \lambda_{12}\sum_{i=1}^{n} \delta_{0i}x_{1i}\right)\right], \tag{4.3}$$

where $d_{01} = \sum_{i=1}^{n} \delta_{0i}$ is the number of individuals who experience illness and $d_{12} = \sum_{i=1}^{n} \delta_{0i}\delta_{1i}$ is the number of individuals who die with illness. In this case, the maximum likelihood estimates have simple analytic forms and are given by

$$\hat{\lambda}_{01} = d_{01} / \sum_{i=1}^{n} x_{0i} \quad \text{and } \hat{\lambda}_{12} = d_{12} / \sum_{i=1}^{n} \delta_{0i} x_{1i}.$$

The maximum likelihood estimate of QAL distribution is obtained by replacing the parameters in (2.2) by the above estimates and standard error is obtained by delta method.

Next, the maximum likelihood estimate of the parameters are obtained when T_{01} is unobserved. The different types of observations and the corresponding likelihood contributions are given in Table 4.1 with δ indicating the type of observation. Here t is the censoring time when $\delta = 1$ and 2, and t is the failure time when $\delta = 3$. It is assumed that this missingness (of information on T_{01}), for $\delta = 2$ and 3, is at random in the sense that the conditional probability of missingness, given $\{T_{01} = t_1 < C = t < T_{01} + T_{12}\}$, and the conditional probability of missingness, given $\{T_{01} = t_1 < T_{01} + T_{12} = t < C\}$ are both independent of $\{T_{01} = t_1\}$ (Little and Rubin, 1987, p 90).

Table 4.1: Types of observation and likelihood contributions for simple illness-death model 1 in unobserved case

Types of observation	δ	Likelihood contribution
$C = t < T_{01}$	1	$e^{-\Lambda_{01}(t)}$
$T_{01} < C = t < T_{01} + T_{12}$	2	$\int_0^t e^{-\Lambda_{12}(t-x\|x)} \lambda_{01}(x) e^{-\Lambda_{01}(x)} dx$
$T_{01} + T_{12} = t < C$	3	$\int_0^t \lambda_{12}(t-x\|x) e^{-\Lambda_{12}(t-x\|x)} \lambda_{01}(x) e^{-\Lambda_{01}(x)} dx$

In particular, for constant hazards, the likelihood contributions for dependent (with $\lambda_{12}(y|x) = \lambda_{12} e^{\beta x}$) and independent cases are given in Table 4.2.

Table 4.2: Types of observation and likelihood contributions with constant hazards for simple illness-death model 1 in unobserved case

	Likelihood contribution	
δ	Dependent	Independent
1	$e^{-\lambda_{01}t}$	$e^{-\lambda_{01}t}$
2	$\int_0^t e^{-\lambda_{12}e^{\beta x}(t-x)}\lambda_{01}e^{-\lambda_{01}x}dx$	$\frac{\lambda_{01}}{\lambda_{12}-\lambda_{01}}[e^{-\lambda_{01}t}-e^{-\lambda_{12}t}]$
3	$\int_0^t \lambda_{12}e^{\beta x}e^{-\lambda_{12}e^{\beta x}(t-x)}\lambda_{01}e^{-\lambda_{01}x}dx$	$\frac{\lambda_{01}\lambda_{12}}{\lambda_{12}-\lambda_{01}}[e^{-\lambda_{01}t}-e^{-\lambda_{12}t}]$

Write $X_1' = ((T_{01}+T_{12}) \wedge C)I_{(\delta_0=1)} - I_{(\delta_0=0)}$. Note that, when $\delta = 1$, then observation on $X_1^{'}$ is not available and its value is set as -1 in its definition. When $\delta = 2$ or 3, X_1' is observed, but X_0 is not observed, but is known to be less than X_1'. The observation, therefore, consists of $\{(x_{0i}, x_{1i}', \delta_i), i = 1, \ldots, n\}$. To obtain the maximum likelihood estimate, we have to take the product over all likelihood contributions from all the observations and then maximize it with respect to the parameters. It is clear that the likelihood function is a complicated function of the parameters, which needs computer intensive numerical maximization. One can use EM algorithm (Dempster et al., 1977) to obtain the maximum likelihood estimates, wherein the complete data version has T_{01} as observed. For the independent model, the E-step needs to calculate the conditional expectation of T_{01} given the incomplete data corresponding to $\delta = 2$ and $\delta = 3$. Let $D_2(t)$ and $D_3(t)$ be these conditional expectations corresponding to $\delta = 2$ and $\delta = 3$, respectively, given the observation time $C = t$ and $T_{01} + T_{12} = t$. Then, for the independent model, $D_2(t)$ and $D_3(t)$ are given by

$$D_2(t) = E[T_{01}|T_{01} < C = t < T_{01} + T_{12}] = \frac{e^{-\lambda_{12}t} - \{1 + (\lambda_{01} - \lambda_{12})t\}e^{-\lambda_{01}t}}{(\lambda_{12} - \lambda_{01})(e^{-\lambda_{01}t} - e^{-\lambda_{12}t})}$$

and

$$D_3(t) = E[T_{01}|T_{01} + T_{12} = t < C] = \frac{e^{-\lambda_{12}t} - \{1 + (\lambda_{01} - \lambda_{12})t\}e^{-\lambda_{01}t}}{(\lambda_{12} - \lambda_{01})(e^{-\lambda_{01}t} - e^{-\lambda_{12}t})},$$

respectively.

Given the current estimates $\hat{\lambda}_{01}^{(0)}$ and $\hat{\lambda}_{12}^{(0)}$, E-step calculates $D_2(t)$ for all censored times t with $\delta = 2$ and $D_3(t)$ for all death times t with $\delta = 3$, at these parameter values, which are denoted by $D_2^{(0)}(t)$ and $D_3^{(0)}(t)$, respectively. The M-step involves maximizing the complete data log likelihood function given by

$$\begin{aligned} &-\lambda_{01} \sum_{i:\delta_i=1} x_{0i} + (n_2 + n_3) \log \lambda_{01} + n_3 \log \lambda_{12} - \lambda_{12} \sum_{i:\delta_i=2,3} x'_{1i} \\ &-(\lambda_{01} - \lambda_{12}) \sum_{k=2,3} \sum_{i:\delta_i=k} D_k^{(0)}(x'_{1i}) \end{aligned} \tag{4.4}$$

where n_2 and n_3 are the number of observations with δ =2 and 3, respectively. Clearly, (4.4) has closed form solution. The information matrix in the independent case can be obtained directly from the log likelihood function corresponding to the incomplete data and is given by

$$I(\lambda_{01}, \lambda_{12}) = \begin{pmatrix} \dfrac{n_2 + n_3}{\lambda_{01}^2} - a & a \\ a & \dfrac{n_3}{\lambda_{12}^2} - a \end{pmatrix}$$

where $a = \dfrac{n_2 + n_3}{(\lambda_{12} - \lambda_{01})^2} - \sum_{i:\delta_i=2,} \dfrac{x_{1i}'^2 e^{-(\lambda_{01}+\lambda_{12})x'_{1i}}}{(e^{-\lambda_{01}x'_{1i}} - e^{-\lambda_{12}x'_{1i}})^2} - \sum_{i:\delta_i=3} \dfrac{x_{1i}'^2 e^{-(\lambda_{01}+\lambda_{12})x'_{1i}}}{(e^{-\lambda_{01}x'_{1i}} - e^{-\lambda_{12}x'_{1i}})^2}.$

A similar EM algorithm can be developed for the estimators of the parameters in the dependent model. When T_{01} is observed for some individuals and unobserved for rest of the individuals, the likelihood can be easily obtained by considering individual likelihood contributions (See (4.1) and Table 4.1) and taking their product.

4.2.2 Estimation in Simple Illness-Death Model 2

As for model 1, let us first consider the case when the time to illness is observed. Recall that T_0 is the time of first event (time to illness or death without illness whichever is earlier). The observations consist of the following.

1. $X_0 = \min(T_0, C)$, $\delta_0 = I(T_0 \leq C)$, observed in all cases.

2. When $\delta_0 = 1$, write

$$\delta_{01} = \begin{cases} 1 & \text{if } T_0 \text{ is the time to illness state} \\ 0 & \text{if } T_0 \text{ is the time to death without illness} \end{cases}$$

3. $X_1 = \min(T_{12}, C - T_0)$ and $\delta_1 = I(T_0 + T_{12} \leq C)$, observed when $\delta_{01} = 1$.

For the n individuals, the data set is given by $\{(x_{0i}, \delta_{0i}),\ i = 1, \ldots, n\}$, $\{\delta_{01i}, i : \delta_{0i} = 1\}$ and $\{(x_{1i}, \delta_{1i}), i : \delta_{01i} = 1\}$. As before, let us write $\delta_{01i} = x_{1i} = \delta_{1i} = -1$, whenever $\delta_{0i} = 0$ and $x_{1i} = \delta_{1i} = -1$, whenever $\delta_{01i} = 0$. The likelihood function can be written as

$$\begin{aligned} L \ \propto \ & \prod_{i=1}^{n} \Big\{ [\lambda_{01}(x_{0i})]^{\delta_{0i}\delta_{01i}} \, [\lambda_{02}(x_{0i})]^{\delta_{0i}(1-\delta_{01i})} \, [\lambda_{12}(x_{1i}|x_{0i})]^{\delta_{0i}\delta_{01i}\delta_{1i}} \\ & \times \exp\left(- \int_0^{x_{0i}} (\lambda_{01}(u) + \lambda_{02}(u)) du \right) \times \exp\left(-\delta_{0i}\delta_{01i} \int_0^{x_{1i}} \lambda_{12}(u|x_{0i}) du \right) \Big\}. \end{aligned} \tag{4.5}$$

With $\lambda_{12}(y|x) = \lambda_{12} e^{\beta x}$, $\lambda_1(x) = \lambda_{01}$ and $\lambda_{02}(x) = \lambda_{02}$, the likelihood function (4.5) simplifies to

$$\begin{aligned} L_d \ \propto \ & \prod_{i=1}^{n} \Big\{ \lambda_{01}^{\delta_{0i}\delta_{01i}} \lambda_{02}^{\delta_{0i}(1-\delta_{01i})} (\lambda_{12} e^{\beta x_{0i}})^{\delta_{0i}\delta_{01i}\delta_{1i}} \\ & \times \exp\left[-(\lambda_{01} + \lambda_{02}) x_{0i} - \lambda_{12} \delta_{0i}\delta_{01i} x_{1i} e^{\beta x_{0i}} \right] \Big\}. \end{aligned} \tag{4.6}$$

Numerical techniques can be used to solve the likelihood equations. When T_0 and T_{12} are independent (β=0), the likelihood function (4.6) reduces further to

$$L_{ind} \ \propto \ \lambda_{01}^{d_{01}} \lambda_{12}^{d_{12}} \lambda_{02}^{d_{02}} \exp\left[-(\lambda_{01} + \lambda_{02}) \sum_{i=1}^{n} x_{0i} - \lambda_{12} \sum_{i=1}^{n} \delta_{0i}\delta_{01i} x_{1i} \right], \tag{4.7}$$

where d_{01} and d_{12} are as in (4.3) and d_{02} is the number of deaths without illness. Expression (4.7) gives the maximum likelihood estimates in simple analytic forms.

Next, the parameters are estimated when T_0 is unobserved. Different types of observations and the corresponding likelihood contributions are given in Table 4.3, with δ being the indicator for type of observation. Here, t is failure time when $\delta = 3$ and 4, and t is censoring time when $\delta = 1$ and 2. As before, either the Newton-Raphson method or the EM algorithm can be used to obtain the maximum likelihood estimates. The estimates can be obtained when T_0 is observed for some individuals and unobserved for the rest.

Table 4.3: Types of observation and likelihood contributions for simple illness-death model 2 in unobserved case.

Types of observation	δ	Likelihood contribution
$C = t < T_0$	1	$e^{-(\Lambda_{01}(t)+\Lambda_{02}(t))}$
$T_0 < C = t < T_0 + T_{12}$, $\delta_{01} = 1$	2	$\int_0^t e^{-\Lambda_{12}(t-x\|x)}\lambda_{01}(x)e^{-(\Lambda_{01}(x)+\Lambda_{02}(x))}dx$
$T_0 + T_{12} = t, \delta_{01} = 1$	3	$\int_0^t \lambda_{12}(t-x)e^{-\Lambda_{12}(t-x\|x)}\lambda_{01}(x)e^{-(\Lambda_{01}(x)+\Lambda_{02}(x))}dx$
$T_0 = t < C, \delta_{01} = 0$	4	$\lambda_{02}(t)e^{-(\Lambda_{01}(t)+\Lambda_{02}(t))}$

4.2.3 Simulation Study

In this section, the bias and precision of the estimator of QAL distribution are investigated through a simulation study. In particular, the survival probabilities are estimated for a number of values for $Q = q$ and performance is compared with that of the nonparametric estimator (ZT) of Zhao and Tsiatis (1999). The simulation is carried out with data from both independent and dependent models. When data are generated from the dependent model, the effect of assuming an independent model is investigated. The performance of the estimator is also

investigated when all the transition times to the illness state are unobserved. In another simulation study, the effect of model misspecification is investigated by generating data for each transition time from a Weibull distribution and estimating the parameters under the assumption of an exponential distribution.

In each scenario, simulation is repeated 1000 times for sample sizes n =50 and 200. For one set of simulated data, n observations of the form $\{(x_{0i}, \delta_{0i}, \delta_{01i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$ are generated from model 2, as described in Section 4.2.2. Based on 1000 such simulated data sets, 1000 estimates of the survival probability $S_Q(q)$ are obtained using both parametric and nonparametric methods, which are then averaged. The sample standard errors (SSE) are also obtained based on the 1000 estimated survival probabilities. The standard errors for the estimated survival probabilities, obtained by using delta method for the parametric estimators and the formula given in Zhao and Tsiatis (1999) for the ZT estimator, are averaged over the 1000 simulations. These are similar to the corresponding SSE values and, hence, not reported. The average bias (AB) and SSE are presented for each simulation study. The results of simulation study are presented for simple illness-death model 2 only. The results for model 1 (not presented here) are qualitatively similar.

Simulation from Independent Model: Simulation is carried out from the model 2 of Section 2.2 with $\lambda_{01} = 0.02$, λ_{12}=0.04 and λ_{02}=0.005. The censoring variable C is assumed to have an exponential distribution, independent of T_0 and T_{12}, with hazard rate λ_c=0.03. Simulation with many different sets of values for the parameters (not reported here) led to similar findings. The probability of a censored observation is given by $P[C < X_0]$+ $P[\delta_0 = \delta_{01} = 1, C < X_0 + X_1]$. For the given parameter values, this leads to 70% censored observations. For each simulated data set, the parameters λ_{01}, λ_{12} and λ_{02} are estimated by the maximum likelihood method (while the parameter λ_c factors out), which are then substituted

in the theoretical expression for the survival function of QAL (see (2.5) in Section 2.2.2) with $w_0 = 1$ and $w_1 = 0.3$, for different values of q. Let us call this as the parametric (observed) estimate. The parameters are also estimated by assuming that all the transition times to the illness state are unobserved and then estimated survival probabilities are obtained; this is termed as the parametric (unobserved) estimate. The Q values of the n observations are also computed which are used to obtain the nonparametric estimate ZT for finite sample comparison with the proposed parametric estimates. The results are presented in Table 4.4.

Table 4.4: Average bias (AB) and sample standard error (SSE) of the parametric and ZT estimators for model 2 in independent case with constant hazard rates.

q	$S_Q(q)$	n	Parametric (observed)		Parametric (unobserved)		ZT	
			AB	SSE	AB	SSE	AB	SSE
8	0.906	50	-0.002	0.024	-0.002	0.024	-0.006	0.047
		200	-0.001	0.012	-0.001	0.012	-0.002	0.024
20	0.706	50	-0.001	0.057	-0.002	0.058	-0.018	0.081
		200	0.000	0.029	0.001	0.030	-0.004	0.042
35	0.492	50	0.003	0.076	0.004	0.077	-0.023	0.110
		200	0.001	0.039	0.002	0.040	-0.009	0.053
55	0.299	50	0.006	0.078	0.008	0.078	-0.033	0.130
		200	0.002	0.039	0.002	0.039	-0.013	0.060
70	0.206	50	0.007	0.068	0.009	0.070	-0.051	0.137
		200	0.002	0.034	0.003	0.036	-0.017	0.069
90	0.125	50	0.008	0.055	0.010	0.057	-0.062	0.107
		200	0.001	0.028	0.003	0.028	-0.025	0.074

As expected, the parametric (observed) estimator has the smallest bias and standard errors, which are only marginally better than those of the parametric (unobserved) estimator. The bias and standard errors of these two estimators are

substantially less than those of the ZT estimator for small sample size (n=50). As expected, the performance of all the three estimators improves with increasing sample size. These results demonstrate the capability of the parametric method to perform well even when the transition time to the illness state is completely unobserved, while nonparametric estimator such as the ZT estimator cannot handle such incompleteness of data.

Robustness Study: In another simulation study, data are generated from Weibull hazards and the QAL distribution is estimated under the assumption of exponential hazards. In particular, we take $\lambda_{ij}(x) = p_{ij}\lambda_{ij}(\lambda_{ij}x)^{p_{ij}-1}$, for $2 \geq j > i = 0, 1$. As before, C is assumed to follow the exponential distribution with parameter λ_c independent of T_0 and T_{12}. The two sets of parameters are considered with different values of the shape parameters. In both cases, the scale parameter values are $\lambda_{01} = 0.04$, $\lambda_{12} = 0.08$, $\lambda_{02} = 0.03$ and $\lambda_c = 0.04$. The shape parameters are taken as follows. In the first set, $p_{01} = 1.1$, $p_{12} = 1.0$ and $p_{02} = 1.0$ and, in the second set, $p_{01} = 1.3$, $p_{12} = 1.5$ and $p_{02} = 1.8$. These two choices reflect different extents of deviation from the exponential assumption. The censoring percentages under the first and the second sets are 49 and 56, respectively. As before, $w_0 = 1$ and $w_1 = 0.3$. The results for the observed case are reported in Table 4.5. In this table, the entries under parametric (Weibull) and parametric (exponential) give the estimates under the rightly assumed Weibull hazards and wrongly assumed exponential hazards, respectively. As expected, the parametric (exponential) estimator is biased, but the bias is less when the shape parameters are not very different from 1 (the first set). The parametric estimator seems to be robust against slight deviation from the assumption of exponential distribution. This robustness makes the parametric estimator an attractive choice. The ZT estimator, as expected, performs well for large sample size (n=200), but not as well for small sample size (n=50). This estimator is also more robust, as expected.

Table 4.5: Average bias (AB) and sample standard error (SSE) of the parametric and ZT estimators in the independent and observed case for the Weibull model with two sets of parameters.

Parameter	q	$S_Q(q)$	n	Parametric (Weibull)		Parametric (exponential)		ZT	
				AB	SSE	AB	SSE	AB	SSE
p_{01}=1.1	2	0.931	50	0.001	0.039	-0.006	0.017	0.008	0.045
λ_{01}=0.04			200	0.000	0.014	-0.004	0.008	0.002	0.028
p_{12}=1.0	5	0.806	50	0.002	0.059	-0.014	0.039	-0.009	0.072
λ_{12}=0.08			200	0.001	0.023	-0.009	0.018	0.002	0.035
p_{02}=1.0	10	0.599	50	0.002	0.077	-0.014	0.061	-0.010	0.086
λ_{02}=0.03			200	0.001	0.032	-0.010	0.029	0.001	0.039
λ_c=0.04	13	0.493	50	-0.001	0.081	-0.011	0.066	-0.011	0.090
			200	0.000	0.034	-0.006	0.032	0.001	0.044
	25	0.212	50	-0.004	0.076	0.007	0.059	-0.015	0.088
			200	-0.001	0.032	0.007	0.029	-0.003	0.044
	35	0.101	50	-0.003	0.062	0.013	0.043	-0.016	0.079
			200	0.000	0.025	0.011	0.021	-0.004	0.040
p_{01}=1.3	6	0.898	50	0.001	0.034	-0.084	0.029	-0.004	0.050
λ_{01}=0.04			200	0.001	0.018	-0.075	0.017	0.000	0.028
p_{12}=1.5	11	0.708	50	0.005	0.060	-0.065	0.045	-0.006	0.077
λ_{12}=0.08			200	0.002	0.031	-0.064	0.029	-0.004	0.039
p_{02}=1.8	16	0.514	50	0.002	0.071	-0.014	0.054	-0.009	0.091
λ_{02}=0.03			200	0.000	0.036	-0.014	0.037	-0.002	0.041
λ_c=0.04	19	0.410	50	0.002	0.074	0.010	0.056	-0.008	0.094
			200	0.000	0.036	0.008	0.035	-0.002	0.045
	24	0.270	50	-0.005	0.072	0.061	0.056	-0.016	0.092
			200	-0.002	0.036	0.060	0.035	-0.004	0.046
	30	0.152	50	-0.007	0.061	0.091	0.053	-0.013	0.084
			200	-0.002	0.031	0.099	0.032	-0.004	0.043

Simulation from Dependent Model: Now the simulation study is carried out with a slightly modified model where the distribution of T_{12} depends on the observed value of T_0. The dependence is modeled through the conditional hazard rate, given $T_0 = x$, which is taken as $\lambda_{12}(y|x) = \lambda_{12}e^{\beta x}$ (See Section 2.2). Other features of the simulation remain the same. The simulation is carried out by choosing $\lambda_{01} = 0.02$, $\lambda_{12}= 0.04$, $\lambda_{02}= 0.005$ and $\lambda_c =0.03$, together with $\beta = 0.1$. Under this set up, the censoring percentage is 61. The results for other β values ranging from 0.005 to 0.2 are qualitatively similar.

For each simulated data set, QAL distribution is estimated in the observed case using the likelihood (4.6) and expression (2.4) with $w_0 = 1$ and $w_1 = 0.5$, for different values of q. This is termed as the parametric (dependent) estimate. In order to investigate the effect of assuming independence between T_0 and T_{12}, estimated survival probabilities are also obtained by fitting the independent model, referred to as the parametric (independent) estimate. The ZT estimate is calculated as before. The average bias (AB) and the SSE are presented in Table 4.6 for different q values.

As expected, the parametric (dependent) estimate, under the correctly assumed dependent model, performs very well. The nonparametric ZT estimate performs better than the parametric (independent) estimate, under the wrongly assumed independent model, even for small sample size n=50, except in the tail area, which is not surprising. With the increasing values of β, the parametric (independent) estimate becomes worse. The standard errors of the parametric (independent) estimates are, however, smaller than those of the ZT estimates, which also result in smaller mean squared errors.

Table 4.6: Average bias and sample standard error (SSE) of the parametric and ZT estimators for model 2 in the dependent and observed case with constant hazard rates.

q	$S_Q(q)$	n	Parametric (dependent)		Parametric (independent)		ZT	
			AB	SSE	AB	SSE	AB	SSE
8	0.914	50	-0.004	0.025	-0.040	0.027	-0.007	0.045
		200	-0.001	0.012	-0.037	0.014	-0.001	0.022
18	0.711	50	-0.003	0.057	-0.023	0.053	-0.011	0.081
		200	0.000	0.029	-0.020	0.027	-0.001	0.038
28	0.518	50	0.000	0.070	0.019	0.067	-0.016	0.093
		200	0.000	0.037	0.021	0.035	-0.002	0.045
37	0.403	50	0.002	0.074	0.026	0.072	-0.013	0.101
		200	0.001	0.039	0.028	0.038	-0.003	0.048
65	0.197	50	0.003	0.065	0.019	0.066	-0.032	0.129
		200	0.001	0.033	0.018	0.035	0.003	0.054
90	0.105	50	0.005	0.049	0.014	0.051	-0.041	0.102
		200	0.001	0.026	0.011	0.027	-0.005	0.066

4.2.4 Analysis of Heart Transplant Data

In this section, the data set of the Stanford Heart Transplant Program is analyzed for illustration. The details about the program has been discussed in Chapter 1 (Section 1.5.1). This can be viewed as an illness-death model by equating the event of heart transplantation with the incidence of illness. Both the simple illness-death models (model 1 and model 2) are fitted for this data. While fitting model 1, observations corresponding to deaths and lost to follow-up before transplantation (a total of 30+4 = 34 cases) are considered as censored. For model 2, only the cases lost to follow-up (only 4) are regarded as censored. Observations on those alive, when last seen after transplantation (a total of 24 cases), are con-

sidered as censored for both models 1 and 2. It is to be noted that there is a subtle difference in the notion of QAL under the two models. While QAL under model 2 represents the time to death with quality adjustment, that under model 1 represents the time to death from post-transplantation only, with quality adjustment, as direct deaths before transplantation are treated as censoring. Since some deaths in model 2 are treated as censoring in model 1, the latter will give higher survival for QAL (see Table 4.8).

The model 1 is fitted by letting T_{01} to be the sojourn time (in days) since acceptance till the heart transplantation (waiting time) and T_{12} to be the survival time after heart transplantation. The uncensored and censored observations on T_{01} and T_{12} can be calculated easily from the date of acceptance into the Stanford Program, date of heart transplantation (if carried out) and date of last observation or death before or after transplantation. Although the length of T_{01} is observed here, we also estimate the parameters by assuming T_{01} to be unobserved only to illustrate the method for the unobserved case. The model 2 is fitted by considering the time since acceptance till death without heart transplantation. As in the case of model 1, both the observed and unobserved cases are analyzed. The Newton-Raphson method is used to maximize the likelihood function.

The first step in the parametric approach is to make an assessment of the possible models for the hazards in both model 1 and model 2. This involves testing for the hazards $\lambda_{01}(x)$ and $\lambda_{12}(y|x)$ in model 1; the same is required for the cause specific hazards $\lambda_{01}(x)$ and $\lambda_{02}(x)$, and for the hazard $\lambda_{12}(y|x)$, in model 2. In order to make an assessment for the possible models of $\lambda_{12}(y|x)$, some graphical and correlation check are carried out based on uncensored data, for possible dependence between T_{01} and T_{12}, which gives evidence in favor of independence. $\lambda_{12}(y|x)$ is also modeled by $\lambda_{12}(y|x) = \lambda_{12}(y)e^{\beta x}$ with $\lambda_{12}(y) = p_{12}\lambda_{12}(\lambda_{12}y)^{p_{12}-1}$ and β being the dependence parameter, to carry out an analytical test for $\beta = 0$. The estimate of β is -0.00605 with standard error 0.00621 for both model 1 and

Table 4.7: Estimated parameters and standard errors (in parentheses) for the Stanford Heart Transplant Data.

Parameter	Model 1		Model 2	
	Observed	Unobserved	Observed	Unobserved
p_{01}	0.663(0.056)	0.765(0.101)	0.663(0.056)	0.528(0.139)
λ_{01}	0.014(0.003)	0.006(0.001)	0.014(0.003)	0.013(0.06)
p_{12}	0.557(0.070)	0.278(0.081)	0.557(0.070)	0.475(0.108)
λ_{12}	0.002(0.001)	0.003(0.002)	0.002(0.001)	0.002(0.001)
p_{02}	-	-	0.607(0.082)	0.550(0.085)
λ_{02}	-	-	0.004(0.001)	0.003(0.002)

model 2. This implies that β is not significant, giving evidence in favor of an independent model against the model-specified dependence. Thereafter, assuming independent model, it is found by graphical methods (Lawless, 2003) that Weibull hazards give reasonably good fit for the observations, rather than the commonly assumed exponential hazards, in both the models. Also it is evident from the estimates of the shape parameters and the corresponding standard errors in Table 4.7 that the null hypothesis of exponential hazard is rejected in favor of the alternative hypothesis of Weibull hazard for each of the three sojourn time variables. Hence, Weibull hazards are assumed with $\lambda_{ij}(x) = p_{ij}\lambda_{ij}(\lambda_{ij}x)^{p_{ij}-1}$, for $2 \geq j > i = 0, 1$. Maximum likelihood estimates of the parameters, namely, p_{01}, λ_{01}, p_{12}, λ_{12}, p_{02} and λ_{02}, along with the standard errors (in parentheses) for both observed and unobserved cases are given in Table 4.7. As expected, the standard error of an estimate in an unobserved case is more than that in the corresponding observed case except in respect of λ_{01} in model 1. The coefficient of variation is always more in the unobserved case than in the observed case.

Next, the estimation of survival function for QAL distribution is considered for a heart patient starting from the time of acceptance into the Stanford

Program. The utility coefficient w_0 for the sojourn time till the transplant is taken as 0.3 and, assuming that the heart transplantation improves the quality of life to some extent, the coefficient w_1 for the sojourn time till death since heart transplantation is taken as 0.8. The estimated survival probabilities, using the expressions (2.1) and (2.4) of Section 2.2 with $\lambda_{01}(x) = p_{01}\lambda_{01}(\lambda_{01}x)^{p_{01}-1}$, $\lambda_{12}(y|x) = p_{12}\lambda_{12}(\lambda_{12}y)^{p_{12}-1}$ and $\lambda_{02}(x) = p_{02}\lambda_{02}(\lambda_{02}x)^{p_{02}-1}$, and the estimated parameters of Table 4.7, are presented in Table 4.8 for both models 1 and 2.

Table 4.8: Estimated survival probabilities and standard errors (in parentheses) for the Stanford heart transplant data.

q	Model 1			Model 2		
	Parametric		Nonparametric	Parametric		Nonparametric
	Observed	Unobserved	ZT	Observed	Unobserved	ZT
10	0.961	0.933	0.989	0.779	0.769	0.815
	(0.012)	(0.021)	(0.016)	(0.034)	(0.036)	(0.039)
80	0.752	0.664	0.656	0.516	0.503	0.451
	(0.041)	(0.055)	(0.056)	(0.044)	(0.051)	(0.049)
150	0.632	0.537	0.592	0.429	0.414	0.385
	(0.048)	(0.066)	(0.066)	(0.044)	(0.052)	(0.050)
300	0.481	0.411	0.473	0.328	0.319	0.326
	(0.053)	(0.062)	(0.061)	(0.043)	(0.049)	(0.048)
400	0.417	0.369	0.451	0.285	0.281	0.309
	(0.055)	(0.060)	(0.062)	(0.043)	(0.046)	(0.048)
600	0.328	0.316	0.350	0.225	0.228	0.243
	0.057)	(0.059)	(0.065)	(0.043)	(0.044)	0.048)
800	0.267	0.283	0.260	0.184	0.193	0.179
	(0.057)	(0.061)	(0.069)	(0.042)	(0.043)	(0.048)

The interesting point to note is the difference in survival estimates under model 1 and model 2 in each situation. Higher value of estimated survival probability in

model 1 is because of the difference in the notion of QAL under the two models, as pointed out at the beginning of this section. As for the parameter estimates in Table 4.7, the standard errors for the survival estimates in the observed case are smaller than those in the corresponding unobserved case. Table 4.8 also presents the ZT estimates. As expected, the ZT estimates have somewhat larger standard errors than the parametric estimates in the observed case. Note that the three sets of survival estimates for a particular model are not very different from each other, possibly because of the large sample size. The usefulness of the parametric model for small sample size is seen in an analysis of data from a set of 50 randomly selected patients out of 103 (results not reported here). While the parametric estimates remains stable, the ZT estimates seem to differ over the sample size. This lends some support for the assumed parametric model.

4.3 Estimation in Progressive Illness-Death Model

In this section, maximum likelihood estimation of the model parameters are obtained for the progressive illness-death models (see Figures 2.3 and 2.4) discussed in Section 2.3. The distribution of QAL is then estimated by substituting the model parameters by their estimates. In practice, for some individuals, all the transition times may not be observed. The model parameters can still be estimated by maximum likelihood method.

4.3.1 Estimation in Progressive Illness-Death Model 1

First, consider the case when all the transition times are observed for all the individuals. An observation terminates due to either death (in which case all the sojourn times $T_{01},\ldots,T_{k,k+1}$ are observed as uncensored) or censoring (in which

case the first few sojourn times are uncensored and the next one is censored with subsequent ones not being observed at all). Therefore, the observations on an individual consists of the censoring indicator variable δ and the corresponding (uncensored or censored) sojourn times. The observations are given below.

1. For $j = 0, 1, \ldots, k$, write

$$\delta_j = \begin{cases} 0, & \text{if censoring takes place in state } j \\ j+1, & \text{if transition takes place from state } j \text{ to state } j+1 \\ & \text{(that is, } T_{j,j+1} < C - \sum_{l=0}^{j-1} T_{l,l+1}\text{)}. \end{cases}$$

   Note that for $j = 0$, $\sum_{l=0}^{j-1} T_{l,l+1}$ is treated to be 0.

2. Write $X_0 = \min(T_{01}, C)$.

3. For $j = 1, \ldots, k$, if $\delta_{j-1} = j$, write $X_j = \min\left(T_{j,j+1}, C - \sum_{l=0}^{j-1} T_{l,l+1}\right)$.

For $j = 1, \ldots, k$, whenever $\delta_{j-1} = 0$, the state j and the subsequent states $j+1$ $, \ldots, k$ are not attained. Then we write $X_l = \delta_l = -1$, for $l = j, j+1, \ldots, k$. For n individuals, the data set is then given by $\{(x_{ji}, \delta_{ji}), j = 0, 1, \ldots, k, i = 1, \ldots, n\}$, where (x_{ji}, δ_{ji}) denotes the observed value of (X_j, δ_j) for the ith individual. The likelihood contribution for such observation can, therefore, be written as

$$L_1 = \begin{cases} e^{-\Lambda_{01}(x_0)}, & \text{if } \delta_0 = 0 \\ \prod_{m=0}^{j-1} \left[\lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)}) e^{-\Lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)})}\right] & \\ \quad \times e^{-\Lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)})}, \text{ for } j = 1, \ldots, k & \text{if } \delta_j = 0. \\ \prod_{m=0}^{k} \left[\lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)}) e^{-\Lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)})}\right], & \text{if } \delta_k = k+1 \end{cases}$$

The total likelihood L is the product of contributions of the form L_1, over the individuals under study. In the independent case, the likelihood is simply the product of likelihood contributions from individual health states and the estimation becomes simple.

When some of the transitions (that is, the corresponding sojourn times) are not observed for an individual, the likelihood contribution can be obtained by integrating an expression of the form L_1 over the unobserved sojourn times with ranges determined by the available observations. For example, suppose we observe $\delta_k = k+1$ and all the sojourn times, except T_{m_0-1,m_0} and T_{m_0,m_0+1}; instead, we observe $T_{m_0-1,m_0}+T_{m_0,m_0+1}=t_{m_0}$, say, so that the m_0th transition time is unobserved. Then, the corresponding likelihood contribution is given by

$$\int_0^{t_{m_0}} \prod_{m=0}^{k} \left[\lambda_{m,m+1}(x_m|x^{(m-1)})e^{-\Lambda_{m,m+1}(x_m|x^{(m-1)})}\right] dx_{m_0-1},$$

where $x_{m_0} = t_{m_0}-x_{m_0-1}$. The first (m_0-2) terms in the product inside the integral do not depend on x_{m_0-1} and, hence, can be taken outside the integral. Each of the remaining terms, however, depends on x_{m_0-1}, except in the independent model. The likelihood contribution can be, in principle, obtained even when there are more than one unobserved transitions, but the notation becomes increasingly difficult. One can now directly maximize the observed likelihood using some numerical technique or employ the EM algorithm suitably.

4.3.2 Estimation in Progressive Illness-Death Model 2

The observations, as in Section 4.3.1, for progressive illness-death model 2 are described below.

1. For $j = 0, 1, \ldots, k$, write

$$\delta_j = \begin{cases} 0, & \text{if censoring takes place in state } j \\ j+1, & \text{if transition takes place from state } j \text{ to state } j+1 \\ & \text{(that is, } T_{j,j+1} < T_{j,k+1}, C - \sum_{l=0}^{j-1} T_{l,l+1}) \\ k+1, & \text{if transition takes place from state } j \text{ to state } k+1 \\ & \text{(that is, } T_{j,k+1} < T_{j,j+1}, C - \sum_{l=0}^{j-1} T_{l,l+1}). \end{cases}$$

Note that for $j = 0$, $\sum_{l=0}^{j-1} T_{l,l+1}$ is treated to be 0.

2. Write $X_0 = \min(T_{01}, T_{0,k+1}, C)$.

3. For $j = 1, \ldots, k-1$, if $\delta_{j-1} = j$, write $X_j = \min\left(T_{j,j+1}, T_{j,k+1}, C - \sum_{l=0}^{j-1} T_{l,l+1}\right)$, and if $\delta_{k-1} = k$, $X_k = \min\left(T_{k,k+1}, C - \sum_{l=0}^{k-1} T_{l,l+1}\right)$.

4. For $j = 1, \ldots, k$, whenever $\delta_{j-1} = 0$ or $k+1$, the state j and the subsequent states $j+1, \ldots, k$ are not attained. Then, we write $X_l = \delta_l = -1$ for $l = j, j+1, \ldots, k$.

For n individuals, the data set is then given by $\{(x_{ji}, \delta_{ji}), j = 0, 1, \ldots, k, i = 1, \ldots, n\}$, where (x_{ji}, δ_{ji}) denotes the observed value of (X_j, δ_j) for the ith individual. The likelihood contribution for such observation can, therefore, be written as

$$
L_2 = \begin{cases}
e^{-(\Lambda_{01}(x_0)+\Lambda_{0,k+1}(x_0))}, & \text{if } \delta_0 = 0 \\
\prod_{m=0}^{j-1} \left[\lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)}) e^{-(\Lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)})+\Lambda_{m,k+1}(x_m|\mathbf{x}^{(m-1)}))}\right] & \\
\quad \times e^{-(\Lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)})+\Lambda_{j,k+1}(x_j|\mathbf{x}^{(j-1)}))}, \text{ for } j = 1, \ldots, k-1, & \text{if } \delta_j = 0, \\
\prod_{m=0}^{k-1} \left[\lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)}) e^{-(\Lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)})+\Lambda_{m,k+1}(x_m|\mathbf{x}^{(m-1)}))}\right] & \\
\quad \times e^{-\Lambda_{k,k+1}(x_k|\mathbf{x}^{(k-1)})}, & \text{if } \delta_k = 0. \\
\lambda_{0,k+1}(x_0) e^{-(\Lambda_{0,1}(x_0)+\Lambda_{0,k+1}(x_0))}, & \text{if } \delta_0 = k+1, \\
\prod_{m=0}^{j-1} \left[\lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)}) e^{-(\Lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)})+\Lambda_{m,k+1}(x_m|\mathbf{x}^{(m-1)}))}\right] & \\
\quad \times \lambda_{j,k+1}(x_j|\mathbf{x}^{(j-1)}) e^{-(\Lambda_{j,j+1}(x_j|\mathbf{x}^{(j-1)})+\Lambda_{j,k+1}(x_j|\mathbf{x}^{(j-1)}))}, & \\
\quad \text{for } j = 1, \ldots, k-1, & \text{if } \delta_j = k+1, \\
\prod_{m=0}^{k-1} \left[\lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)}) e^{-(\Lambda_{m,m+1}(x_m|\mathbf{x}^{(m-1)})+\Lambda_{m,k+1}(x_m|\mathbf{x}^{(m-1)}))}\right] & \\
\quad \times \lambda_{k,k+1}(x_j|\mathbf{x}^{(j-1)}) e^{-\Lambda_{k,k+1}(x_k|\mathbf{x}^{(k-1)})}, & \text{if } \delta_k = k+1.
\end{cases}
$$

The total likelihood L is the product of contributions of the form L_2, over the individuals under study. In the independent case, the likelihood is simply the product of likelihood contributions from individual health states and the estimation becomes simple. When some transition times are not observed, the corresponding likelihood can, in theory, be obtained using the same technique as that of the previous section.

4.3.3 Simulation Study

The bias and precision of the estimator of QAL distribution are investigated through a simulation study as in simple illness-death models. The simulation is carried out for progressive illness-death model 1 with k=2. It is assumed that the sojourn times T_{01}, T_{12} and T_{23} are independent and follow exponential distributions with parameters $\lambda_{01} = 0.03$, $\lambda_{12} = 0.02$ and $\lambda_{23} = 0.04$. The censoring variable C is assumed to follow another exponential distribution with parameter $\lambda_c = 0.0125$ and independent of T_{01}, T_{12} and T_{23}. For each simulated data set, the QAL survival probabilities are estimated using (2.7) and the nonparametric method (ZT) of Zhao and Tsiatis (1999) with $w_0 = 0.5$, $w_1 = 1$ and $w_2 = 0.5$. This simulation is repeated 1000 times with $n = 100$. Based on 1000 estimates of survival probabilities $S_Q(q)$, average bias (AB) and sample standard error (SSE) are computed and reported in the left panel of Table 4.9. As expected, the parametric method gives more efficient estimates with less bias in the tail area.

In order to study robustness, the simulation model now assumes Weibull distribution for T_{01} with $\lambda_{01}(x) = \alpha_{01}\lambda_{01}\left(\lambda_{01}x\right)^{\alpha_{01}-1} = 2(0.03)^2x$ (that is the shape parameter is equal to 2 and scale parameter is equal to 0.03). Also, T_{12}, T_{23} and C follow exponential distributions with $\lambda_{12} = 0.02$, $\lambda_{23} = 0.04$ and $\lambda_c = 0.0125$, as before. However, the estimation is carried out using (2.7) and the nonparametric method (ZT). The results are reported in the right panel of Table 4.9. As

expected, the nonparametric method gives more robust estimates.

Table 4.9: The average bias (AB), sample standard error (SSE) of parametric and nonparametric (ZT estimates) estimates for a three-state progressive illness-death model.

q	Exponential					Weibull				
	$S_Q(q)$	Parametric		ZT		$S_Q(q)$	Parametric		ZT	
		AB	SSE	AB	SSE		AB	SSE	AB	SSE
25	0.902	-0.002	0.018	-0.002	0.037	0.923	-0.021	0.017	-0.004	0.033
35	0.809	-0.003	0.031	-0.002	0.051	0.818	-0.009	0.029	-0.003	0.051
50	0.655	-0.003	0.046	-0.007	0.070	0.642	0.013	0.043	-0.007	0.066
65	0.510	-0.001	0.053	-0.012	0.081	0.487	0.025	0.051	-0.009	0.077
85	0.354	0.001	0.054	-0.021	0.087	0.330	0.028	0.053	-0.008	0.082
105	0.241	0.003	0.050	-0.027	0.089	0.222	0.024	0.050	-0.009	0.081
130	0.148	0.003	0.041	-0.024	0.083	0.135	0.018	0.042	-0.012	0.080

4.3.4 Analysis of IBCSG Trial V Data

The proposed methodology is illustrated using data from the IBCSG Trial V (See Section 1.5.2, Chapter 1). In this data, there is no direct death from the first two states and, therefore, the progressive illness-death model 1 is used for the analysis. Other work using this example also consider the same illness-death model. Using the notation of Section 2.3.1, write T_{01}=TOX, T_{12}=TWiST and T_{23}=REL, and they are measured in months. Let w_0, w_1 and w_2 are the utility coefficients corresponding to three health states. Then, QAL is given by

$$Q = w_0 \times T_{01} + w_1 \times T_{12} + w_2 \times T_{23},$$

The objective is to estimate the QAL distribution for the patients by parametric method with suitably chosen distributions for the sojourn times T_{01}, T_{12} and T_{23}.

Both short duration chemotherapy (Treatment Group 0, say) and the long duration chemotherapy (Treatment Group 1, say) are considered for this analysis. First, we make an assessment of the possible models for the distribution of T_{01}, T_{12} and T_{23}. Since the number of distinct observations on T_{01} are rather few, the distribution of T_{01} is modeled by a discrete distribution in both the groups. Let $p_j = P(T_{01} = t_j)$, for $j = 1, \ldots, m$, with $\sum_{j=1}^{m} p_j = 1$. Here t_j, $j = 1, \ldots, m$, denote the m distinct mass points. Note that m and the t_j's and p_j's vary over the two treatment groups. The observations on T_{01} are 0, 1 and 3 in Group 0 and 0, 1,. . .,9 in Group 1. For T_{12} and T_{23}, the possible models are assessed by graphical methods. It is observed that exponential distribution gives reasonably good fit for the observations on both T_{12} and T_{23} in treatment Group 0, whereas Weibull distribution seems to fit well for both T_{12} and T_{23} in Treatment Group 1. Possible dependence between any two successive sojourn time variables is checked by scatter plot of the corresponding uncensored observations. It is seen that there is no indication of dependence among the successive sojourn times. So independent model is considered in both the groups. We take exponential model for $T_{i,i+1}$ with $\lambda_{i,i+1}(x) = \lambda_{i,i+1}$, for $i = 1, 2$, in Group 0. In Group 1, we take Weibull model for $T_{i,i+1}$ with $\lambda_{i,i+1}(x) = \alpha_{i,i+1}\lambda_{i,i+1}(\lambda_{i,i+1}x)^{(\alpha_{i,i+1}-1)}$, for i= 1, 2. The model parameters are estimated by maximum likelihood method (See Section 4.3.1). Estimated model parameters along with their standard errors (in parentheses) are given in Table 4.10.

Next, estimated survival probabilities of QAL are obtained by using (2.6) and utility coefficients w_0=0.5, w_1=1 and w_2=0.5, as in Zhao and Tsiatis (1999). Estimated survival probabilities for several q values along with their standard errors in parentheses are reported in Table 4.11 under Method 1. The entries under Method 2 are obtained by using (2.7), based on the assumption that the sojourn time distribution in each health state follows exponential distribution. For the sake of comparison with a nonparametric method, the ZT estimate is also ob-

Table 4.10: Estimated parameters and standard errors (in parentheses) for the IBCSG Trial V dataset.

Treatment Group 0	Treatment Group 1
$\hat{p_1}$= 0.287 (0.022)	$\hat{p}_1$= 0.077 (0.009), $\hat{p}_2$= 0.054 (0.008)
$\hat{p_2}$= 0.647 (0.024)	$\hat{p}_3$= 0.034 (0.006), $\hat{p}_4$=0.047 (0.008)
	$\hat{p}_5$= 0.067 (0.009), $\hat{p}_6$= 0.077 (0.009)
$\hat{\lambda}_{12}$= 0.014 (0.001)	$\hat{p}_7$= 0.138 (0.012), $\hat{p}_8$= 0.133 (0.012)
$\hat{\lambda}_{23}$= 0.030 (0.002)	$\hat{p}_9$= 0.254 (0.015)
	$\hat{\alpha}_{12}$= 0.842 (0.039), $\hat{\lambda}_{12}$= 0.008 (0.001)
	$\hat{\alpha}_{23}$= 0.904 (0.044), $\hat{\lambda}_{23}$= 0.042 (0.003)

tained. The survival probabilities are also estimated by treating all the transition times from TWiST to Relapsed as unobserved and with the same distributional assumptions as those in Method 1. These estimates are reported under Unobserved. There is little difference in the estimated survival probabilities between Method 1 and Method 2 in both treatment groups. Even the estimates in the Unobserved case are not very different from those of Method 1 and Method 2 in both the groups. The estimates in the Unobserved case have higher standard errors, as expected. One can also observe that the parametric estimates are similar to the nonparametric ZT estimates (possibly because the sample size is very large) and with lower standard errors, as expected.

Table 4.11: Estimated survival probabilities and standard errors (in parentheses) for the IBCSG Trial V dataset.

q	Treatment Group 0				Treatment Group 1			
	Method 1	Method 2	ZT	Unobserved	Method 1	Method 2	ZT	Unobserved
5	0.992	0.992	0.998	0.991	0.996	0.997	0.994	0.991
	(0.001)	(0.001)	(0.002)	(0.001)	(0.001)	(0.000)	0.003	(0.006)
10	0.970	0.970	0.968	0.967	0.975	0.983	0.975	0.957
	(0.003)	(0.003)	(0.009)	(0.003)	(0.003)	(0.001)	(0.005)	(0.014)
20	0.899	0.899	0.895	0.892	0.912	0.932	0.885	0.878
	(0.007)	(0.007)	(0.015)	(0.008)	(0.007)	(0.004)	(0.011)	(0.023)
30	0.812	0.812	0.754	0.803	0.843	0.867	0.815	0.805
	(0.012)	(0.012)	(0.021)	(0.013)	(0.010)	(0.007)	(0.014)	(0.028)
40	0.723	0.723	0.661	0.715	0.777	0.800	0.765	0.742
	(0.016)	(0.016)	(0.023)	(0.017)	(0.012)	(0.010)	(0.015)	(0.029)
50	0.638	0.638	0.598	0.632	0.716	0.734	0.712	0.688
	(0.019)	(0.019)	(0.025)	(0.019)	(0.013)	(0.012)	(0.016)	(0.028)
70	0.491	0.490	0.447	0.489	0.612	0.616	0.636	0.603
	(0.022)	(0.022)	(0.027)	(0.022)	(0.015)	(0.015)	(0.017)	(0.021)
90	0.373	0.373	0.361	0.376	0.526	0.516	0.515	0.538
	(0.023)	(0.023)	(0.040)	(0.023)	(0.017)	(0.018)	(0.022)	(0.018)
100	0.325	0.325	0.291	0.330	0.489	0.472	0.485	0.511
	(0.022)	(0.023)	(0.040)	(0.023)	(0.018)	(0.018)	(0.025)	(0.019)

4.4 Estimation in Competing Illness-Death Model

In this Section, estimation of model parameters are considered for both the competing illness-death models (See Figures 2.5 and 2.6) of Section 2.4 when transi-

tion time to illness states are observed for all the individuals. In principle, the model parameters can be estimated even when transition time to illness states are unobserved. The observations and likelihood functions are given below.

4.4.1 Estimation in Competing Illness-Death Model 1

The observations are described as follows.

1. $X_0 = \min\{T_{01}, \ldots, T_{0k}, C\}$, $\delta_0 = \sum_{j=1}^{k} jI(T_{0j} = \min\{C, T_{01}, \ldots, T_{0k}\})$.
2. If $\delta_0 = j$, then $X_1 = \min(T_{j,k+1}, C - T_{0j})$ and $\delta_1 = I(T_{0j} + T_{j,k+1} \leq C)$.

Note that $\delta_0 = j$, if $T_{0j} = \min\{T_{01}, \ldots, T_{0k}, C\}$, for $j = 1, \ldots, k$, and $\delta_0 = 0$ if $C < \min\{T_{01}, \ldots, T_{0k}\}$. For n individuals, we have the data set $\{(x_{0i}, \delta_{0i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$. For convenience, let us write $x_{1i} = \delta_{1i} = -1$ whenever $\delta_{0i} = 0$. The likelihood function can then be written as

$$L_{C1} \propto \prod_{i=1}^{n} S_0(x_{0i})^{1-\delta_{0i}} \prod_{j=1}^{k} \left\{ \lambda_{0j}(x_{0i}) S_0(x_{0i}) \left[\lambda_{j,k+1}(x_{1i}|x_{0i})\right]^{\delta_{1i}} S_{j,k+1}(x_{1i}|x_{0i}) \right\}^{I_{(\delta_{0i}=j)}}, \tag{4.8}$$

where $S_0(y) = \exp\left[-\sum_{j=1}^{k} \Lambda_{0j}(y)\right]$ and $S_{j,k+1}(y|x) = \exp\left[-\Lambda_{j,k+1}(y|x)\right]$, for $j = 1, \ldots, k$. We consider the special case when T_{0j} and $T_{j,k+1}$ are independent exponential variates with $\lambda_{0j}(y) = \lambda_{0j}$ and $\lambda_{j,k+1}(y|x) = \lambda_{j,k+1}$, for $j = 1, \ldots, k$. Then the likelihood (4.8) simplifies to

$$L_{C1} \propto \prod_{i=1}^{n} \exp\left[-\lambda(1-\delta_{0i})x_{0i}\right] \prod_{j=1}^{k} \left\{ \lambda_{0j} \exp\left[-\lambda x_{0i}\right] \lambda_{j,k+1}^{\delta_{1i}} \exp\left[-\lambda_{j,k+1} x_{1i}\right] \right\}^{I_{(\delta_{0i}=j)}},$$

where $\lambda = \sum_{j=1}^{k} \lambda_{0j}$. The maximum likelihood estimates of the parameters are obtained as

$$\hat{\lambda}_{0j} = \frac{\sum_{i=1}^{n} I_{(\delta_{0i}=j)}}{\sum_{i=1}^{n}(1-\delta_{0i})x_{0i} + \sum_{i=1}^{n} x_{0i} \sum_{j=1}^{k} I_{(\delta_{0i}=j)}} = \frac{n_{0j}}{\sum_{i=1}^{n} x_{0i}}, \text{ for } j = 1, \ldots, k,$$

$$\text{and} \qquad \hat{\lambda}_{j,k+1} = \frac{\sum_{i=1}^{n} \delta_{1i} I_{(\delta_{0i}=j)}}{\sum_{i=1}^{n} I_{(\delta_{0i}=j)} x_{1i}} = \frac{n_{j,k+1}}{\sum_{i=1}^{n} I_{(\delta_{0i}=j)} x_{1i}}, \text{ for } j = 1, \ldots, k,$$

where $n_{0j} = \sum_{i=1}^{n} I_{(\delta_{0i}=j)}$ is the number of transition to state j from state 0 and $n_{j,k+1} = \sum_{i=1}^{n} \delta_{1i} I_{(\delta_{0i}=j)}$ is the same from state j to state $k+1$.

4.4.2 Estimation in Competing Illness-Death Model 2

The observations are described as follows.

1. $X_0 = \min\{T_{01}, \ldots, T_{0k}, , T_{0,k+1}, C\}$, $\delta_0 = I(\min\{T_{01}, \ldots, T_{0k}, T_{0,k+1}\} \leq C)$.
2. If $\delta_0 = 1$, then $\delta_{01} = \sum_{j=1}^{k} jI\left(T_{0j} = \min\{T_{0,k+1}, T_{01}, \ldots, T_{0k}\}\right)$.
3. If $\delta_{01} = j$, then $X_1 = (T_{j,k+1}, C - T_{0j})$ and $\delta_1 = I(T_{0j} + T_{j,k+1} \leq C)$.

Note that $\delta_0 = 0$, if $C < \min\{T_{01}, \ldots, T_{0k}, T_{0,k+1}\}$ and $\delta_0 = 1$ otherwise; when $\delta_0 = 1$, we have $\delta_{01} = 0$, if death occurs directly from 0, that is $T_{0,k+1} < \min\{T_{01}, \ldots, T_{0k}\}$, and $\delta_{01} = j$ if the transition from 0 is to state j, that is $T_{0j} = \min\{T_{01}, \ldots, T_{0k}, T_{0,k+1}\}$. For n individuals, the data set is given by $\{(x_{0i}, \delta_{0i}, \delta_{01i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$. As before, whenever any of $\{(\delta_{01i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$ does not exist, we write them as -1. The likelihood function can be written as

$$L_{C2} \propto \prod_{i=1}^{n} S_0(x_{0i})^{1-\delta_{0i}} \{\lambda_{0,k+1}(x_{0i}) S_0(x_{0i})\}^{\delta_{0i}(1-\delta_{01i})} \times \left\{ \prod_{j=1}^{k} \left(\lambda_{0j}(x_{0i}) S_0(x_{0i}) \left[\lambda_{j,k+1}(x_{1i}|x_{0i})\right]^{\delta_{1i}} S_{j,k+1}(x_{1i}|x_{0i}) \right)^{I_{(\delta_{01i}=j)}} \right\}^{\delta_{0i}}, \quad (4.9)$$

where $S_0(y) = \exp\left[-\sum_{j=1}^{k} \Lambda_{0j}(y) - \lambda_{0,k+1}(y) \right]$ and $S_{j,k+1}(y|x) = \exp\left[-\Lambda_{j,k+1}(y|x)\right]$.

Under the special case, when T_{0j}, $T_{j,k+1}$ and $T_{0,k+1}$ are independent exponential variates with $\lambda_{0j}(y) = \lambda_{0j}$, $\lambda_{j,k+1}(y|x) = \lambda_{j,k+1}$, for $j = 1, \ldots, k$ and

$\lambda_{0,k+1}(y) = \lambda_{0,k+1}$, the likelihood function (4.9) becomes

$$L_{C2} \propto \prod_{i=1}^{n} \exp\left[-\lambda'(1-\delta_{0i})x_{0i}\right] \lambda_{0,k+1}^{\delta_{0i}(1-\delta_{01i})} \exp\left[-\lambda'\delta_{0i}(1-\delta_{01i})x_{0i}\right] \times \left\{ \prod_{j=1}^{k} \left(\lambda_{0j} \exp\left(-\lambda' x_{0i}\right) \times \lambda_{j,k+1}^{\delta_{1i}} \exp\left[-\lambda_{j,k+1} x_{1i}\right]\right)^{I_{(\delta_{01i}=j)}} \right\}^{\delta_{0i}},$$

where $\lambda' = \sum_{j=1}^{k} \lambda_{0j} + \lambda_{0,k+1}$. The maximum likelihood estimates of the parameters are obtained as

$$\hat{\lambda}_{0j} = \frac{\sum_{i=1}^{n} \delta_{0i} I_{(\delta_{01i}=j)}}{\sum_{i=1}^{n} x_{0i} - \sum_{i=1}^{n} \delta_{0i}\delta_{01i}x_{0i} + \sum_{i=1}^{n} \delta_{0i}x_{0i} \sum_{j=1}^{k} I_{(\delta_{01i}=j)}} = \frac{n_{0j}}{\sum_{i=1}^{n} x_{0i}}, \quad \text{for } j = 1, \ldots, k.$$

$$\hat{\lambda}_{j,k+1} = \frac{\sum_{i=1}^{n} \delta_{0i}\delta_{1i} I_{(\delta_{01i}=j)}}{\sum_{i=1}^{n} \delta_{0i} I_{(\delta_{01i}=j)} x_{1i}} = \frac{n_{j,k+1}}{\sum_{i=1}^{n} I_{(\delta_{01i}=j)} x_{1i}}, \quad \text{for } j = 1, \ldots, k$$

and

$$\hat{\lambda}_{0,k+1} = \frac{\sum_{i=1}^{n} \delta_{0i}(1-\delta_{01i})}{\sum_{i=1}^{n} x_{0i} - \sum_{i=1}^{n} \delta_{0i}\delta_{01i}x_{0i} + \sum_{i=1}^{n} \delta_{0i}x_{0i} \sum_{j=1}^{k} I_{(\delta_{01i}=j)}} = \frac{n_{0,k+1}}{\sum_{i=1}^{n} x_{0i}},$$

where $n_{0j} = \sum_{i=1}^{n} \delta_{0i} I_{(\delta_{01i}=j)}$ and $n_{j,k+1} = \sum_{i=1}^{n} \delta_{0i}\delta_{1i} I_{(\delta_{01i}=j)}$ are, as before, the number of transitions to state j from state 0 and the same to state $k+1$ from state j, respectively, and $n_{0,k+1} = \sum_{i=1}^{n} \delta_{0i}(1-\delta_{01i})$ is the number of direct transitions from state 0 to state $k+1$.

4.4.3 Simulation Study

In this section, the finite sample properties of the estimator of QAL distribution are investigated through a simulation study. As before, the performance of the estimator is compared with that of the ZT estimator. The simulation study is carried out for competing illness-death model 1 by choosing $k = 3$, $\lambda_{01} = 0.04$,

$\lambda_{02} = 0.05$, $\lambda_{03} = 0.06$, $\lambda_{14} = 0.08$, $\lambda_{24} = 0.15$ and $\lambda_{34} = 0.10$. The censoring variable C is assumed to have an exponential distribution, independent of all the sojourn time variables, with hazard rate λ_c=0.035. The simulation is repeated 1000 times for sample sizes $n = 10$, 30 and 100.

For each set of simulated data, n observations of the form $\{(x_{0i}, \delta_{0i}, \delta_{01i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$, as described in Section 4.4.1, are generated and the six parameters are estimated. The survival probabilities are estimated with $w_0 = 1$, $w_1 = 0.6$, $w_2 = 0.5$, $w_3 = 0.4$ and using (2.11). Based on 1000 such simulated data sets, the average bias (AB) and sample standard error (SSE) of parametric and nonparametric (ZT) estimators are presented in Table 4.12.

As expected, the estimates of bias for both parametric and nonparametric methods are small for large sample size (n=100). For n=30, the bias is still fairly small, except that the nonparametric methods tends to be biased in the tail, as expected. Also, for small sample size (n=10), as expected, both the parametric and nonparametric estimates are biased and more so in the tail. The bias of the nonparametric estimate is always higher in the tail area. As expected, the parametric method gives more efficient estimates than the nonparametric method in all cases. The medians of both parametric and nonparametric estimates are also calculated, but not reported here, to study the symmetricity of the sampling distribution of the proposed estimate. There is evidence that the sampling distribution of the estimate may be symmetric for large sample size.

4.5 Estimation in Reversible Illness-Death Model

Estimation of parameters are considered for the two reversible illness-death models (See Figures 2.7 and 2.8) discussed in Section 2.5. We consider only the case when transition times to illness state are observed for all the individuals. As in Sections 2.5.1 and 2.5.2, the different transition times are assumed independent and the

Table 4.12: The average estimate (AB) and sample standard error (SSE) in parentheses of parametric and nonparametric (ZT) estimators for the competing illness-death model 1 for n= 10, 30 and 100.

q	$S_Q(q)$	Parametric			ZT		
		n=10	n=30	n=100	n=10	n=30	n=100
2	0.946	-0.018	-0.005	-0.001	0.010	-0.003	-0.001
		(0.034)	(0.017)	(0.009)	(0.075)	(0.045)	(0.024)
4	0.831	-0.030	-0.009	-0.003	-0.005	-0.005	0.000
		(0.076)	(0.044)	(0.023)	(0.144)	(0.076)	(0.042)
6	0.700	-0.025	-0.010	-0.002	-0.020	-0.006	-0.003
		(0.104)	(0.064)	(0.035)	(0.182)	(0.097)	(0.053)
9	0.516	-0.008	-0.003	0.000	-0.025	-0.008	-0.003
		(0.126)	(0.081)	(0.044)	(0.212)	(0.110)	(0.060)
12	0.368	0.015	0.006	0.002	-0.037	-0.010	-0.005
		(0.134)	(0.083)	(0.045)	(0.211)	(0.118)	(0.061)
15	0.258	0.033	0.011	0.003	-0.055	-0.019	-0.004
		(0.129)	(0.078)	(0.043)	(0.189)	(0.115)	(0.058)
22	0.108	0.056	0.018	0.004	-0.052	-0.027	-0.008
		(0.114)	(0.058)	(0.029)	(0.118)	(0.086)	(0.051)

sojourn times $T_{jk}^{(l)}$, for $l = 1, \ldots,$ are identically distributed for $jk = 01, 02, 10$ and 12.

4.5.1 Estimation in Reversible Illness-Death Model 1

Observation on an individual terminates either by censoring or by death. Let U denote the number of observed recoveries from state 1 to state 0. Note that U takes values 0, 1, ... Given $U = u$, let us write, for $l = 1, \ldots, u$,

1. $X_{01}^{(l)} = \min\left\{T_{01}^{(l)}, C - \sum_{j=1}^{l-1}\left(T_{01}^{(j)} + T_{10}^{(j)}\right)\right\} = T_{01}^{(l)}$,

2. $X_{10}^{(l)} = \min\left\{T_{10}^{(l)}, T_{12}^{(l)}, C - \sum_{j=1}^{l} T_{01}^{(j)} - \sum_{j=1}^{l-1} T_{10}^{(j)}\right\} = T_{10}^{(l)}$,

3. $X_{01}^{(u+1)} = \min\left\{T_{01}^{(u+1)}, C - \sum_{j=1}^{u}\left(T_{01}^{(j)} + T_{10}^{(j)}\right)\right\}$ and
   $\delta_0 = I\left(T_{01}^{(u+1)} < C - \sum_{j=1}^{u}\left(T_{01}^{(j)} + T_{10}^{(j)}\right)\right)$,

4. If $\delta_0 = 1$, then we also observe,
   $$X_{10}^{(u+1)} = \min\left\{T_{10}^{(u+1)}, T_{12}^{(u+1)}, C - \sum_{j=1}^{u+1} T_{01}^{(j)} - \sum_{j=1}^{u} T_{10}^{(j)}\right\}$$
   $$= \min\left\{T_{12}^{(u+1)}, C - \sum_{j=1}^{u+1} T_{01}^{(j)} - \sum_{j=1}^{u} T_{10}^{(j)}\right\}$$
   and $\delta_1 = I\left(T_{12}^{(u+1)} < C - \sum_{j=1}^{u+1} T_{01}^{(j)} - \sum_{j=1}^{u} T_{10}^{(j)}\right)$.

For n individuals, we have the data set

$$\left\{(u_i, (x_{01i}^{(l)}, x_{10i}^{(l)}, l = 1, \ldots, u_i), x_{01i}^{(u_i+1)}, \delta_{0i}, x_{10i}^{(u_i+1)}, \delta_{1i}), i = 1, \ldots, n\right\}.$$

As before, if any of these observations does not exist, we write that as -1. The likelihood function can be written as

$$L_{R1} \propto \prod_{i=1}^{n}\prod_{l=1}^{u_i}\left\{\lambda_{01}(x_{01i}^{(l)})\exp\left[-\Lambda_{01}(x_{01i}^{(l)})\right]\lambda_{10}(x_{10i}^{(l)})S_{R1}\left(x_{10i}^{(l)}\right)\right\} \times \left(\lambda_{01}(x_{01i}^{(u_i+1)})\right)^{\delta_{0i}} \times \exp\left[-\Lambda_{01}(x_{01i}^{(u_i+1)})\right]\left(\lambda_{12}(x_{10i}^{(u_i+1)})\right)^{\delta_{0i}\delta_{1i}}\left(S_{R1}(x_{10i}^{(u_i+1)})\right)^{\delta_{0i}}, \quad (4.10)$$

where $S_{R1}(x) = \exp\left[-(\Lambda_{10}(x) + \Lambda_{12}(x))\right]$. Under the special case, when T_{01}, T_{10} and T_{12} are exponential variates with $\lambda_{01}(y) = \lambda_{01}$, $\lambda_{10}(y) = \lambda_{10}$ and $\lambda_{12}(y) = \lambda_{12}$, the likelihood function (4.10) simplifies to

$$L_{R1} \propto \prod_{i=1}^{n}\prod_{l=1}^{u_i}\left\{\lambda_{01}\exp[-\lambda_{01}x_{01i}^{(l)}]\lambda_{10}\exp[-(\lambda_{10}+\lambda_{12})x_{10i}^{(l)}]\right\} \times\lambda_{01}^{\delta_{0i}}\exp[-\lambda_{01}x_{01i}^{(u_i+1)}]\lambda_{12}^{\delta_{0i}\delta_{1i}}\exp[-\delta_{0i}(\lambda_{10}+\lambda_{12})(x_{10i}^{(u_i+1)})].$$

The maximum likelihood estimates of the parameters are obtained as

$$\hat{\lambda}_{01} = \frac{\sum_{i=1}^{n} u_i + \sum_{i=1}^{n} \delta_{0i}}{\sum_{i=1}^{n} \sum_{l=1}^{u_i+1} x_{01i}^{(l)}}, \quad \hat{\lambda}_{10} = \frac{\sum_{i=1}^{n} u_i}{\sum_{i=1}^{n} \sum_{l=1}^{v_i} x_{10i}^{(l)} + \sum_{i=1}^{n} \delta_{0i} x_{10i}^{(u_i+1)}} \quad \text{and}$$

$$\hat{\lambda}_{12} = \frac{\sum_{i=1}^{n} \delta_{0i}\delta_{1i}}{\sum_{i=1}^{n} \sum_{l=1}^{u_i} x_{10i}^{(l)} + \sum_{i=1}^{n} \delta_{0i} x_{10i}^{(u_i+1)}}.$$

4.5.2 Estimation in Reversible Illness-Death Model 2

As before, given $U = u$, we have, for $l = 1, \ldots, u$, the following observations.

1. $X_{01}^{(l)} = \min\left\{T_{01}^{(l)}, T_{02}^{(l)}, C - \sum_{j=1}^{l-1}\left(T_{01}^{(j)} + T_{10}^{(j)}\right)\right\} = T_{01}^{(l)}$,

2. $X_{10}^{(l)} = \min\left\{T_{10}^{(l)}, T_{12}^{(l)}, C - \sum_{j=1}^{l} T_{01}^{(j)} - \sum_{j=1}^{l-1} T_{10}^{(j)}\right\} = T_{10}^{(l)}$,

3. $X_{01}^{(u+1)} = \min\left\{T_{01}^{(u+1)}, T_{02}^{(u+1)}, C - \sum_{j=1}^{u}\left(T_{01}^{(j)} + T_{10}^{(j)}\right)\right\}$ and
   $\delta_0 = I\left(T_{01}^{(u+1)} \wedge T_{02}^{(u+1)} < C - \sum_{j=1}^{u}\left(T_{01}^{(j)} + T_{10}^{(j)}\right)\right)$,

4. If $\delta_0 = 1$, then $\delta_{01} = I\left(T_{01}^{(u+1)} < T_{02}^{(u+1)}\right)$.

5. If $\delta_{01} = 1$, then we observe,
   $$X_{10}^{(u+1)} = \min\left\{T_{10}^{(u+1)}, T_{12}^{(u+1)}, C - \sum_{j=1}^{u+1} T_{01}^{(j)} - \sum_{j=1}^{u} T_{10}^{(j)}\right\}$$
   $$= \min\left\{T_{12}^{(u+1)}, C - \sum_{j=1}^{u+1} T_{01}^{(j)} - \sum_{j=1}^{u} T_{10}^{(j)}\right\}$$
   and $\delta_1 = I\left(T_{12}^{(u+1)} < C - \sum_{j=1}^{u+1} T_{01}^{(j)} - \sum_{j=1}^{u} T_{10}^{(j)}\right)$.

For n individuals, we have the data set

$$\left\{\left(u_i,(x_{01i}^{(l)},x_{10i}^{(l)},l=1,\ldots,u_i),x_{01i}^{(u_i+1)},\delta_{0i},\delta_{01i},x_{10i}^{(u_i+1)},\delta_{1i}\right),i=1,\ldots,n\right\}.$$

The likelihood function can be written as

$$\begin{aligned}L_{R2} \;\propto\; & \prod_{i=1}^{n}\prod_{l=1}^{u_i}\left\{\lambda_{01}(x_{01i}^{(l)})S_{R0}(x_{01i}^{(l)})\lambda_{10}(x_{10i}^{(l)})S_{R1}\left(x_{10i}^{(l)}\right)\right\}\\ & \times\left(\lambda_{01}(x_{01i}^{(u_i+1)})\right)^{\delta_{0i}\delta_{01i}}\left(\lambda_{02}(x_{01i}^{(u_i+1)})\right)^{\delta_{0i}(1-\delta_{01i})}S_{R0}(x_{01i}^{(u_i+1)})\\ & \times\left(\lambda_{12}(x_{10i}^{(u_i+1)})\right)^{\delta_{0i}\delta_{01i}\delta_{1i}}\left(S_{R1}(x_{10i}^{(u_i+1)})\right)^{\delta_{0i}\delta_{01i}},\end{aligned}\tag{4.11}$$

where $S_{R0}(x)=\exp\left[-(\Lambda_{01}(x)+\Lambda_{02}(x))\right]$ and $S_{R1}(x)=\exp\left[-(\Lambda_{10}(x)+\Lambda_{12}(x))\right]$. With constant hazards, that is $\lambda_{01}(y)=\lambda_{01}$, $\lambda_{10}(y)=\lambda_{10}$, $\lambda_{02}(y)=\lambda_{02}$ and $\lambda_{12}(y)=\lambda_{12}$, the likelihood function (4.11) becomes

$$\begin{aligned}L_{R2} \;\propto\; & \prod_{i=1}^{n}\prod_{l=1}^{u_i}\left\{\lambda_{01}\exp[-(\lambda_{01}+\lambda_{02})x_{01i}^{(l)}]\lambda_{10}\exp[-(\lambda_{10}+\lambda_{12})x_{10i}^{(l)}]\right\}\\ & \times\lambda_{01}^{\delta_{0i}\delta_{01i}}\lambda_{02}^{\delta_{0i}(1-\delta_{01i})}\exp[-(\lambda_{01}+\lambda_{02})x_{01i}^{(u_i+1)}]\\ & \times\lambda_{12}^{\delta_{0i}\delta_{01i}\delta_{1i}}\exp[-\delta_{0i}\delta_{01i}(\lambda_{10}+\lambda_{12})(x_{10i}^{(u_i+1)})].\end{aligned}$$

The maximum likelihood estimate of the parameters are obtained as

$$\hat{\lambda}_{01}=\frac{\sum_{i=1}^{n}u_i+\sum_{i=1}^{n}\delta_{0i}\delta_{01i}}{\sum_{i=1}^{n}\sum_{l=1}^{u_i+1}x_{01i}^{(l)}},\quad \hat{\lambda}_{10}=\frac{\sum_{i=1}^{n}u_i}{\sum_{i=1}^{n}\sum_{l=1}^{u_i}x_{10i}^{(l)}+\sum_{i=1}^{n}\delta_{0i}\delta_{01i}x_{10i}^{(u_i+1)}},$$

$$\hat{\lambda}_{02}=\frac{\sum_{i=1}^{n}\delta_{0i}(1-\delta_{01i})}{\sum_{i=1}^{n}\sum_{l=1}^{u_i+1}x_{01i}^{(l)}}\quad\text{and}\quad \hat{\lambda}_{12}=\frac{\sum_{i=1}^{n}\delta_{0i}\delta_{01i}\delta_{1i}}{\sum_{i=1}^{n}\sum_{l=1}^{u_i}x_{10i}^{(l)}+\sum_{i=1}^{n}\delta_{0i}\delta_{01i}x_{10i}^{(u_i+1)}}.$$

4.5.3 Simulation Study

In this section, the finite sample properties of the estimator of QAL distribution are investigated through simulation. The performance of the estimator is

compared with that of the nonparametric estimator ZT. The simulation study is carried out for reversible illness-death model 1 with $\lambda_{01} = 0.02$, $\lambda_{10} = 0.03$, $\lambda_{12} = 0.04$ and $\lambda_c = 0.01$. As before, simulation is repeated 1000 times for sample sizes $n = 10$, 30 and 100. For each set of simulated data set, n observations, as described in Section 4.5.1, are generated and the three parameters λ_{01}, λ_{10} and λ_{12} are estimated. The survival probabilities are estimated with $w_0 = 1$, $w_1 = 0.5$ and using (2.13). Based on 1000 such simulated data sets, average bias (AB) and SSE (in parentheses) are reported in Table 4.13.

As expected, the estimates of bias for both parametric and nonparametric methods are small for large sample size (n=100). For n=30, the bias is still fairly small, except that the nonparametric methods tends to be biased in the tail, as expected. Also, for small sample size (n=10), as expected, both the parametric and nonparametric estimates are biased and more so in the tail. The bias of the nonparametric estimate is always higher in the tail area. As expected, the parametric method gives more efficient estimates than the nonparametric method in all cases. The medians of both parametric and nonparametric estimates are also calculated, but not reported here, to study the symmetricity of the sampling distribution of the proposed estimate. There is evidence that the sampling distribution of the estimate may be symmetric for large sample size.

Table 4.13: The average bias(AB) and sample standard error (SSE) in parentheses of parametric and nonparametric (ZT) estimators for the Reversible illness-death model 1 for n=10, 30 and 100.

q	$S_Q(q)$	Parametric			ZT		
		n=10	n=30	n=100	n=10	n=30	n=100
10	0.950	-0.006	-0.002	0.000	0.008	-0.002	-0.002
		(0.030)	(0.016)	(0.008)	(0.072)	(0.043)	(0.020)
25	0.822	-0.013	-0.006	-0.002	-0.016	-0.012	-0.008
		(0.085)	(0.048)	(0.020)	(0.141)	(0.076)	(0.042)
40	0.702	-0.014	-0.009	-0.003	-0.037	-0.017	-0.014
		(0.123)	(0.071)	(0.037)	(0.175)	(0.094)	(0.054)
60	0.566	-0.009	-0.008	-0.002	-0.051	-0.029	-0.011
		(0.152)	(0.089)	(0.047)	(0.208)	(0.111)	(0.061)
90	0.411	0.002	-0.005	-0.002	-0.070	-0.042	-0.031
		(0.169)	(0.098)	(0.053)	(0.231)	(0.123)	(0.066)
130	0.267	0.019	0.001	0.000	-0.102	-0.052	-0.039
		(0.167)	(0.093)	(0.051)	(0.182)	(0.133)	(0.070)
200	0.126	0.035	0.008	0.002	-0.086	-0.063	-0.042
		(0.144)	(0.071)	(0.039)	(0.161)	(0.106)	(0.069)

Chapter 5

Nonparametric Estimation of QAL Distribution

5.1 Introduction

This chapter considers the nonparametric estimation of quality adjusted lifetime distribution in illness-death models. There have been a number of work developing nonparametric methods for estimating the distribution of QAL (Korn 1993, Zhao and Tsiatis 1997, 1999; Van der Laan and Hubbard 1999; Huang and Louis 1998). These methods are applicable only when one can compute the QAL values for all the patients. If some transition times are not observable, QAL values are not available for all the individuals and hence these methods cannot be applied. It may also be noted that some of the above estimators are not monotonic. For example, the estimator proposed by Zhao and Tsiatis (1997, 1999) is not monotonic. The objective of this work is to present a simple alternative nonparametric method to estimate the QAL distribution (See Pradhan et al., 2009), when information on the interrelationship between the different health states, giving the structure of the illness-death model, and the same between the corresponding sojourn times

are available. The method is first described for the two simple illness-death models with independent sojourn times and, then, generalized to progressive models. In principle, given a model, the QAL distribution is first derived in terms of the joint distribution of all the sojourn times. The sojourn time distributions are then substituted by their estimates obtained by survival analysis techniques. When the different sojourn times are independent, the theoretical expression for the QAL distribution involves only the individual marginal sojourn time distribution, which can be substituted by the corresponding Kaplan-Meier estimates. See Pradhan et al. (2010) and Pradhan and Dewanji (2009a,b) for parametric estimation using this approach.

In addition to being simple in nature, this method has several advantages. First the structure of the illness-death model involving different health states and the relationship between the different sojourn times are explicitly used in the derivation of QAL distribution, making the estimate more efficient when such information is available (See Sections 2.6 and 5.2.1). As a result, this estimate is naturally less robust against misspecification of such information. Second, by construction, this method gives a monotonic estimate of the QAL distribution, whereas this monotonicity is not guaranteed in the existing methods, except Almanassra et al. (2005); however, their method involves constrained optimization and, therefore, is computationally very intensive. Third, this method can deal with the issue of some missing transition times, as long as the sojourn time distributions are estimable by some missing data techniques, whereas other methods based on observed QAL cannot be applied with such missing data.

This chapter is organised as follows. Estimation of QAL distribution for the case of independent sojourn times in simple illness-death model 1 is discussed in Section 5.2. The asymptotic properties are also derived. A simulation is carried out to investigate the performance of the proposed estimator. Estimation of QAL distribution when transition time to illness state is missing for some individuals

is also considered. A data set of the Stanford Heart Transplant Program is analyzed for illustration. Extension to progressive illness-death model 1 with an example of IBCSG Trial V data is discussed. Estimation of QAL distribution in simple illness-death model 2 along with asymptotic properties, simulation study and analysis of heart transplant data is considered in Section 5.3. As an extension of simple illness-death model 2, estimation in competing illness-death model 2 and progressive illness-death model 2 is also discussed. Estimation in reversible simple illness-death model 2 is considered in Section 5.4. In this chapter, the different sojourn times have been mostly assumed to be independent. In Section 5.5, we discuss estimation for some models with dependence. The Appendix in Section 5.6 gives proofs of the theorems and details of some of the results/methods stated in this chapter.

5.2 Estimation in Simple Illness-death Model 1

In this section, the simple illness-death model 1 of Figure 2.1 in Section 2.2 is considered for nonparametric estimation of QAL distribution. It is assumed that T_{01} and T_{12} are independent. Let $F_{01}(\cdot)$ and $F_{12}(\cdot)$ be the distribution functions of T_{01} and T_{12}, respectively. The survival function of QAL is then given by (See Section 2.2.1)

$$S_Q(q) \;=\; 1 - F_{01}\left(\frac{q}{w_0}\right) + \int_0^{q/w_0} \bar{F}_{12}\left(\frac{q - w_0 x}{w_1}\right) dF_{01}(x). \tag{5.1}$$

where $\bar{F}_{12}(\cdot) = 1 - F_{12}(\cdot)$. The distribution functions $F_{01}(\cdot)$ and $F_{12}(\cdot)$ are assumed to be arbitrary but non-degenerate. Consider $(X_0,\ \delta_0,\ X_1,\ \delta_1)$ and the observed data set for n individuals $\{(x_{0i}, \delta_{0i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$ as in Section 4.2.1. Since T_{01} and T_{12} are independent, T_{12} is also independent of $C - T_{01}$ so that the problem of induced dependent censoring does not arise when we estimate $\bar{F}_{12}$ (See Lin et al., 1999). Let $\hat{F}_{01}(\cdot)$ and $\hat{\bar{F}}_{12}(\cdot)$ be the Kaplan-Meier estimates of $F_{01}(\cdot)$ and

$\bar{F}_{12}(\cdot)$, based on observations $\{(x_{0i}, \delta_{0i}), i = 1, \ldots, n\}$ and $\{(x_{1i}, \delta_{1i}), i : \delta_{0i} = 1\}$, respectively. Then, using (5.1), a nonparametric estimate of $S_Q(q)$ is given by

$$\hat{S}_Q(q) \;=\; 1 - \hat{F}_{01}\left(\frac{q}{w_0}\right) + \int_0^{q/w_0} \hat{\bar{F}}_{12}\left(\frac{q - w_0 x}{w_1}\right) d\hat{F}_{01}(x). \tag{5.2}$$

Let H_0 be the distribution function of X_0 and H_1 be the conditional distribution function of X_1, given $C > T_{01}$ (or, $\delta_0 = 1$). Write $\tau_i = H_i^{-1}(1)$, for $i = 0, 1$, and $\tau = w_0\tau_0 \wedge w_1\tau_1$. Then, we have the following theorems on the asymptotic properties of the proposed estimator.

THEOREM 5.2.1 *$\hat{S}_Q(q)$, as defined in (5.2), is uniformly consistent for $S_Q(q)$ in $[0, \tau)$. That is, $\sup_{0 \le q < \tau} |\hat{S}_Q(q) - S_Q(q)| \xrightarrow{a.s.} 0$, as $n \to \infty$.*

THEOREM 5.2.2 *$\sqrt{n}\left[\hat{S}_Q(q) - S_Q(q)\right]$ converges weakly to a mean zero Gaussian process in $[0, \theta]$, where $\theta < \tau$ is a constant, with a variance given by (5.27) which is estimated by (5.28).*

The proofs of Theorems 5.2.1 and 5.2.2 are given in Section 5.6.1. Although the proofs are given for the interval $[0, \tau)$, one can show by considering different cases that this interval can be extended to one which is specified by the range of estimability of $S_Q(\cdot)$ and can be as large as 0 to $w_0\tau_0 + w_1\tau_1$.

5.2.1 Simulation Study

In this section, the finite sample properties of the proposed nonparametric estimate of QAL distribution are investigated by simulation. In particular, the bias and precision of the proposed nonparametric (NP) estimator, given by (5.2), are studied for a number of QAL values. The performance of the proposed estimator is compared with that of the nonparametric estimator ZT. In this simulation study, it is assumed that the sojourn times T_{01} and T_{12} are independent and follow exponential distributions with parameters $\lambda_{01} = 0.02$ and $\lambda_{12} = 0.04$, respectively.

The censoring variable C is assumed to be independent of T_{01} and T_{12} and follow exponential distribution with parameter λ_c=0.03. The proposed NP estimate and the ZT estimate are computed with $w_0 = 1$ and $w_1 = 0.3$ for each set of simulated data of the form $\{(x_{0i}, \delta_{0i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$. The simulation is repeated 1000 times for sample size n=50 and 200. Based on 1000 estimates of $S_Q(q)$, the average bias and sample standard error (SSE) are computed. The standard errors for the estimated survival probabilities, obtained by using (5.28) for the proposed nonparametric estimators and the formula given in Zhao and Tsiatis (1999) for the ZT estimator, are averaged over the 1000 simulations. These are similar to the corresponding SSE values and, hence, not reported. The results on the average bias with corresponding SSE in parentheses are presented in Table 5.1.

Table 5.1: Average bias and sample standard error (in parentheses) of the proposed NP and ZT estimators for the simple illness-death model 1 for sample size n=50 and 200.

q	$S_Q(q)$	n	NP	ZT
10	0.916	50	-0.003 (0.034)	-0.008 (0.048)
		200	-0.001 (0.018)	-0.002 (0.023)
20	0.776	50	-0.001 (0.057)	-0.014 (0.079)
		200	0.000 (0.032)	-0.003 (0.038)
35	0.592	50	-0.009 (0.091)	-0.018 (0.110)
		200	0.003 (0.043)	-0.011 (0.055)
50	0.433	50	-0.015 (0.115)	-0.033 (0.143)
		200	0.008 (0.053)	-0.013 (0.064)
70	0.290	50	-0.034 (0.145)	-0.040 (0.177)
		200	0.013 (0.064)	-0.018 (0.078)
90	0.194	50	0.058 (0.158)	-0.046 (0.183)
		200	0.015 (0.082)	-0.030 (0.104)

As expected, both bias and standard error decrease with sample size. The proposed nonparametric estimator NP seems to perform better than the ZT estimator in terms of both bias and precision. However, as expected, for large sample size, the ZT estimator seems to work equally well compared to the proposed NP estimator. It is to be noted that, with increasing sample size, the possibility of missingness also increases, in which case the ZT estimator cannot even be applied, whereas the proposed method can still be used. The quantiles of the 1000 standardized NP estimates are compared with those of the standard normal distribution. Although the convergence seems to be slow, specially in the tail area, the comparison result is found to be satisfactory.

5.2.2 Estimation in Unobserved Case:

Let us now suppose that the time of transition to illness state (1) from healthy state (0) (see Figure 2.1) is missing or unobserved for some patients. Then, the different types of observations (denoted by δ) are as given in Table 5.2, with $\delta = 1$, 2 and 3 representing the observed case and $\delta = 4$ and 5 representing the unobserved case. Here t denotes the time of observation. It is assumed that this missingness (of information on T_{01}), for $\delta = 4$ and 5, is at random (See Section 4.2.1). The likelihood contributions for the different types of observations, under this missing-at-random assumption, are given in Table 5.2, where $f_{01}(\cdot)$ and $f_{12}(\cdot)$ are the densities of T_{01} and T_{12}, respectively.

Write $X_1' = ((T_{01} + T_{12}) \wedge C)I_{(\delta_0=1)} - I_{(\delta_0=0)}$. Note that, when $\delta = 1$, then observation on $X_1^{'}$ is not available and its value is set as -1 in its definition. When $\delta = 2$ or 3, both X_0 and X_1' are observed. For $\delta = 4$ or 5, X_1' is observed, but X_0 is not observed, but is known to be less than X_1'. The observation, therefore, consists of $\{(x_{0i}, x'_{1i}, \delta_i), i = 1, \ldots, n\}$. It is clear, from the likelihood contributions in Table 5.2, that the nonparametric maximum likelihood estimate of F_{01} will have

Table 5.2: Types of observations and likelihood contribution in unobserved case.

Type (δ)	Observation	Likelihood Contribution
1	$T_{01} > C = t$	$\bar{F}_{01}(t+)$
2	$T_{01} = t_1, T_{01} + T_{12} > C = t$	$f_{01}(t_1)\bar{F}_{12}(t - t_1)$
3	$T_{01} = t_1, T_{01} + T_{12} = t < C$	$f_{01}(t_1)f_{12}(t - t_1)$
4	$T_{01} < C = t < T_{01} + T_{12}$	$\int_0^t f_{01}(t_1)\bar{F}_{12}(t - t_1)dt_1$
5	$T_{01} + T_{12} = t < C$	$\int_0^t f_{01}(t_1)f_{12}(t - t_1)dt_1$

mass at the distinct values of x_{0i}'s with $\delta_i = 2$ or 3. Let these distinct values be denoted by $t_{0(1)} < \ldots < t_{0(k_1)}$. Note that, if $\min_{i:\delta_i=4,5}\{x'_{1i}\} \leq t_{0(1)}$, there has to be another mass point $t_{0(0)}$, say, which is less than or equal to $\min_{i:\delta_i=4,5}\{x'_{1i}\}$. Let the discrete hazards of F_{01} at these distinct mass points be denoted by the vector $\underset{\sim}{\lambda}_0 = \{\lambda_{0j}, j = 0, 1, \ldots, k_1\}$. It is also clear that the nonparametric maximum likelihood estimate of F_{12} will have mass at the distinct points from the set

$$\{x'_{1i} - x_{0i}, i : \delta_i = 3\} \cup \{x'_{1i} - t_{0(j)}, j = 0, 1, \ldots, k_1, i : \delta_i = 5 \text{ and } x'_{1i} > t_{0(j)}\}.$$

Let these distinct values be denoted by $t_{1(1)} < \ldots < t_{1(k_2)}$ and the discrete hazards of F_{12} at these points be denoted by the vector $\underset{\sim}{\lambda}_1 = \{\lambda_{1j}, j = 1, \ldots, k_2\}$.

For those i with $\delta_i = 5$ and j with $x'_{1i} > t_{0(j)}$, let $j_{(i)}$ be such that $t_{1(j_{(i)})} = x'_{1i} - t_{0(j)}$. Also, based on the observation with $\delta_i = 1, 2$ and 3, and, for $j = 1, \ldots, k_1$, let d_{0j} be the number of uncensored observations on T_{01} at time $t_{0(j)}$ and n_{0j} the number at risk strictly prior to time $t_{0(j)}$; that is, the number of individuals with $T_{01} \geq t_{0(j)}$. Similarly, based on those i with $\delta_i = 1, 2$ and 3, let d_{1j} be the number of uncensored observations on T_{12} at time $t_{1(j)}$ and n_{1j} the number of individuals with $T_{12} \geq t_{1(j)}$, for $j = 1, \ldots, k_2$. Then, the likelihood L, as a function of $\underset{\sim}{\lambda}_0$ and $\underset{\sim}{\lambda}_1$, can be written as product of three likelihood terms L_1, L_2 and L_3, which are contributions from those i with $\delta_i = 1, 2$ and 3, those with $\delta_i = 4$ and those with

$\delta_i = 5$, respectively. It can be easily checked that

$$L_1(\underset{\sim}{\lambda}_0, \underset{\sim}{\lambda}_1) = \prod_{j=1}^{k_1} \left[\lambda_{0j}^{d_{0j}} (1-\lambda_{0j})^{n_{0j}-d_{0j}}\right] \prod_{j=1}^{k_2} \left[\lambda_{1j}^{d_{1j}} (1-\lambda_{1j})^{n_{1j}-d_{1j}}\right],$$

$$L_2(\underset{\sim}{\lambda}_0, \underset{\sim}{\lambda}_1) = \prod_{i:\delta_i=4} \left[\sum_{l:t_{0(l)}<x'_{1i}} \lambda_{0l} \left(\prod_{j<l}(1-\lambda_{0j})\right) \left(\prod_{j:t_{1(j)}\le x'_{1i}-t_{0(l)}} (1-\lambda_{1j})\right)\right] \text{ and}$$

$$L_3(\underset{\sim}{\lambda}_0, \underset{\sim}{\lambda}_1) = \prod_{i:\delta_i=5} \left[\sum_{l:t_{0(l)}<x'_{1i}} \lambda_{0l} \left(\prod_{j<l}(1-\lambda_{0j})\right) \lambda_{1l_{(i)}} \left(\prod_{j<l_{(i)}} (1-\lambda_{1j})\right)\right].$$

This likelihood $L(\underset{\sim}{\lambda}_0, \underset{\sim}{\lambda}_1)$ can be maximized with respect to $\underset{\sim}{\lambda}_0$ and $\underset{\sim}{\lambda}_1$ to obtain their maximum likelihood estimates. This requires numerical method. The EM algorithm is used here (Dempster et al., 1977) with the complete data version having information on T_{01} (that is, x_{0i}), whenever $\delta_i = 4$ and 5. The steps of EM algorithm are described in Section 5.6.3. Nevertheless, with the estimates of $\hat{\underset{\sim}{\lambda}}_0$ and $\hat{\underset{\sim}{\lambda}}_1$ of $\underset{\sim}{\lambda}_0$ and $\underset{\sim}{\lambda}_1$, respectively, the nonparametric maximum likelihood estimate of survival function S_{01} corresponding to F_{01} is given by

$$\hat{S}_{01}(t) = \prod_{j:t_{0(j)}<t} \left(1-\hat{\lambda}_{0j}\right),$$

and that of S_{12} corresponding to F_{12} is given by

$$\hat{S}_{12}(t) = \prod_{j:t_{1(j)}<t} \left(1-\hat{\lambda}_{1j}\right).$$

Variance estimates of $\hat{S}_{01}(t)$, $\hat{S}_{12}(t)$, and then of $\hat{S}_Q(q)$, can be obtained from those of $\hat{\underset{\sim}{\lambda}}_0$ and $\hat{\underset{\sim}{\lambda}}_1$, using delta method. This may be numerically challenging because of the large dimension of $(\hat{\underset{\sim}{\lambda}}_0, \hat{\underset{\sim}{\lambda}}_1)$. Alternatively, one can use a bootstrap method to estimate the variance of $\hat{S}_Q(q)$, as has been done in the next section.

5.2.3 Analysis of Heart Transplant Data

The data set of Stanford Heart Transplant Program (Section 1.5.1 and also Section 4.2.4) is analyzed to illustrate the proposed nonparametric estimate. The

estimated survival probabilities using the expression (5.2), with $w_0 = 0.3$ and $w_1 = 0.8$, and standard errors of the estimates using expression (5.28) are presented in Table 5.3 under NP. Although the length of T_{01} is observed here, the survival probabilities are estimated by assuming T_{01} to be unobserved for randomly selected 10% (≈ 7) of 69 patients, who have received heart transplantation, using the method of Section 5.2.2. The estimates are presented under Unobserved in Table 5.3. The standard errors of the estimates are obtained by using bootstrap method with 200 bootstrap samples, each of size 103 drawn with replacement from the incomplete data. The ZT estimate is also computed for the sake of comparison. The two estimates NP and ZT are similar, except at the tail area, with the ZT estimate having marginally higher standard error than that of NP. The estimates in unobserved case are also similar to the estimates in observed case (NP), except at the tail area, with higher standard error, as expected.

Table 5.3: Estimated QAL survival probabilities for the heart transplant data with standard errors in parentheses.

q	NP	ZT	Unobserved
10	0.978(0.012)	0.989(0.016)	0.979(0.011)
20	0.938(0.023)	0.928(0.033)	0.931(0.026)
40	0.865(0.036)	0.865(0.040)	0.813(0.054)
50	0.794(0.042)	0.788(0.049)	0.745(0.064)
80	0.657(0.054)	0.656(0.056)	0.582(0.094)
150	0.578(0.059)	0.592(0.066)	0.520(0.104)
300	0.498(0.061)	0.473(0.061)	0.486(0.105)
400	0.479(0.062)	0.451(0.062)	0.479(0.108)
600	0.420(0.064)	0.350(0.065)	0.460(0.111)
800	0.351(0.067)	0.260(0.065)	0.442(0.120)

5.2.4 Extension to Progressive Illness-Death Model 1

This section consider progressive illness-death model 1 (See Figure 2.3) of Section 2.3 as an extension to multistate illness-death model for the estimation of QAL distribution. The extension is straightforward. Let $T_{j,j+1}$ be the sojourn time in state j having distribution function $F_{j,j+1}(\cdot)$, assumed arbitrary but non-degenerate, for $j = 0, 1, \ldots, k$. Let w_j be the utility coefficient corresponding to state j, for $j = 0, 1, \ldots, k$. Then, the QAL is given by $Q = \sum_{j=0}^{k} w_j T_{j,j+1}$. The distribution of Q, under the assumption that the sojourn times are independently distributed, is given by (See Section 2.3.1)

$$F_Q^{(k)}(q) = \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0 t_1}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{k-1} w_j t_j}{w_k}} F_{k,k+1}\left(\frac{q-\sum_{j=0}^{k-1} w_j t_j}{w_k}\right) \prod_{j=0}^{k-1} dF_{j,j+1}(t_j). \tag{5.3}$$

As in Section 4.3.1, consider (X_j, δ_j), for $j = 0, 1, \ldots, k$ and the data set for n individuals given by $\{(x_{ji}, \delta_{ji}),\ j = 0, 1, \ldots, k,\ i = 1, \ldots, n\}$. Let $\hat{F}_{j,j+1}(\cdot)$ be the Kaplan-Meier estimate of the distribution function $F_{j,j+1}(\cdot)$ based on the data corresponding to the jth health state, for $j = 0, 1, \ldots, k$. Since $T_{j,j+1}$'s are independent, the problem of induced dependent censoring does not arise here. Note that $\hat{F}_{j,j+1}(\cdot)$ is based on n_j observations, where n_j is the number of observations for which $T_{01} + \cdots + T_{j-1,j} < C$, for $j = 1, \ldots, k$, and $\hat{F}_{01}(\cdot)$ is based on all the n observations. Then, using (5.3), a natural estimate of $F_Q^{(k)}(q)$ is given by

$$\hat{F}_Q^{(k)}(q) = \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0 t_1}{w_1}} \cdots \int_0^{\frac{q-\sum_{j=0}^{k-1} w_j t_j}{w_k}} \hat{F}_{k,k+1}\left(\frac{q-\sum_{j=0}^{k-1} w_j t_j}{w_k}\right) \prod_{j=0}^{k-1} d\hat{F}_{j,j+1}(t_j). \tag{5.4}$$

THEOREM 5.2.3 *$\sqrt{n}\left[\hat{F}_Q^{(k)}(q) - F_Q^{(k)}(q)\right]$ converges weakly to a mean zero Gaussian process in $[0, \theta]$, where $\theta < \tau$ is a constant with $\tau = \min\{w_j \tau_j, j = 0, 1, \ldots, k\}$.*

As before, τ can be as large as $\sum_{j=0}^{k} w_j \tau_j$ depending on the range of estimability of $F_Q^{(k)}(\cdot)$. The proof of Theorem 5.2.3 is briefly sketched in Section 5.6.2. It may be noted that the asymptotic variance of $\hat{F}_Q^{(k)}(q)$ cannot be obtained in closed form in general, but can be derived with few states. The variance expression for $k = 1$ is given in (5.27). The variance expression for k=2 is given in (5.30) for the analysis of the IBCSG Trial V data. In general, one can use some resampling method like bootstrap.

Analysis of IBCSG Trial V Data: The proposed method for estimating QAL distribution in progressive illness-death model is illustrated using data from both groups of the IBCSG Trial V (See Section 1.5.2 and also Section 4.3.4). The QAL distribution for the patients is estimated by the proposed nonparametric (NP) method using (5.4). The ZT estimate is also computed for comparison purpose. The estimated survival probabilities with $w_0 = 0.5$, $w_1 = 1$ and $w_2 = 0.5$, as considered by Zhao and Tsiatis (1999) and Pradhan and Dewanji (2009a), for different values of q are presented in Table 5.4 with standard errors (in parentheses) obtained by using (5.31). Note that both the estimates give similar results possibly because of the large sample size.

5.3 Estimation in Simple Illness-Death Model 2

In this section, the nonparametric estimate of QAL distribution is obtained for the simple illness-death model 2 (See Figure 2.2) of Section 2.2. It is assumed that T_0 and T_{12} are independent. The survival function of Q is then given by

$$\begin{aligned} S_Q(q) &= 1 - F_{02}\left(\frac{q}{w_0}\right) - \int_0^{\frac{q}{w_0}} F_{12}\left(\frac{q - w_0 x}{w_1}\right) dF_{01}(x) \\ &= 1 - F_{02}\left(\frac{q}{w_0}\right) - F_{01}\left(\frac{q}{w_0}\right) + \int_0^{\frac{q}{w_0}} S_{12}\left(\frac{q - w_0 x}{w_1}\right) dF_{01}(x) \\ &= S_0\left(\frac{q}{w_0}\right) + P_{12}\left(\frac{q}{w_0}\right), \text{ say,} \end{aligned} \tag{5.5}$$

Table 5.4: Estimated QAL survival probabilities for the IBCSG Trial V data with standard errors in parentheses.

	Group 0		Group 1	
q	NP	ZT	NP	ZT
5	0.996(0.002)	0.998(0.002)	0.997(0.001)	0.994(0.003)
10	0.978(0.005)	0.960(0.009)	0.979(0.003)	0.975(0.005)
20	0.893(0.015)	0.895(0.015)	0.910(0.009)	0.885(0.011)
30	0.781(0.022)	0.754(0.021)	0.837(0.013)	0.815(0.014)
40	0.675(0.026)	0.661(0.023)	0.771(0.015)	0.765(0.015)
50	0.591(0.027)	0.598(0.025)	0.702(0.016)	0.712(0.016)
70	0.495(0.027)	0.447(0.027)	0.594(0.018)	0.636(0.017)
90	0.426(0.028)	0.361(0.040)	0.519(0.019)	0.515(0.022)
100	0.399(0.029)	0.291(0.040)	0.495(0.020)	0.485(0.025)

where

$$S_0(u) = P[T_0 \geq u] = 1 - F_{01}(u) - F_{02}(u) = \exp\left[-\left(\Lambda_{01}(u) + \Lambda_{02}(u)\right)\right],$$

$$S_{12}(u) = P[T_{12} \geq u] = 1 - F_{12}(u) \text{ and}$$

$$P_{12}\left(\frac{q}{w_0}\right) = \int_0^{\frac{q}{w_0}} S_{12}\left(\frac{q - w_0 x}{w_1}\right) dF_{01}(x) = \int_0^{\frac{q}{w_0}} S_{12}\left(\frac{q - w_0 x}{w_1}\right) S_0(x) d\Lambda_{01}(x).$$

Consider $(X_0,\ \delta_0,\ \delta_{01},\ X_1,\ \delta_1)$ and the data set for n individuals given by $\{(x_{0i}, \delta_{0i}, \delta_{01i}, x_{1i}, \delta_{1i}),\ i{=}1, \ldots, n\}$, as in Section 4.2.2. First, the Kaplan-Meier estimate of $S_0(u)$ is obtained based on the observations $\{(x_{0i}, \delta_{0i}), i = 1, \ldots, n\}$ and denote it by $\hat{S}_0(u)$. Next, the estimation of $S_{12}(u)$ is considered. Since T_0 and T_{12} are independent, T_{12} is also independent of $C - T_0$ so that the problem of induced dependent censoring does not arise when $S_{12}(u)$ is estimated (See Lin et al., 1999) based on observations $\{(x_{1i}, \delta_{1i}), i : \delta_{01i} = 1\}$. Let $\hat{S}_{12}(u)$ denote the Kaplan-Meier estimate of $S_{12}(u)$. Note that the assumption of independence between T_0 and T_{12} leads to the semi-Markov model (See Voelkel and Crowley,

1984, and Shu et al., 2007). It may be noted that the semi-Markov model does not fit readily into the multiplicative intensity framework (Andersen et al., 1993) because of its renewal nature. This difficulty is tackled by introducing time-shifted multivariate counting process over a fixed interval, say $[0, \tau]$, given by

$$\mathbf{N}(x) = \{N_{hji}(x), hj = 01, 02, 12;\ i = 1, \ldots, n, x \in [0, \tau]\},$$

where $N_{hji}(x)$ counts the number of $h \rightarrow j$ transitions for individual i with corresponding transition time less than or equal to x, for hj =01, 02, 12 and $\tau = \sup\{u : \int_0^u \lambda_{hj}(x)dx < \infty, hj = 01, 02, 12\}$. Note that such formulated counting process $N_{hji}(x)$ have the intensity processes $\alpha_{hji}(x)$ in the form of a multiplicative intensity model given by

$$\alpha_{hji}(x) = Y_{hi}(x)\lambda_{hj}(x),$$

where $Y_{hi}(x)$ is the indicator for individual i being at risk in the state h just before time $x-$, for $h = 0, 1$. Under independent censoring, $N_{hji}(x)$ can be uniquely decomposed as

$$N_{hji}(x) = \int_0^x Y_{hi}(u)\lambda_{hj}(u)du + M_{hji}(x),$$

where $M_{hji}(x)$'s are orthogonal local square integrable martingales with predictable variation process given by $\langle M_{hji}(x)\rangle = \int_0^x Y_{hi}(u)\lambda_{hj}(u)du$. Writing $N_{hj}(x) = \sum_{i=1}^n N_{hji}(x)$ and $Y_h(x) = \sum_{i=1}^n Y_{hi}(x)$, the Nelson-Aalen estimator for $\Lambda_{hj}(t)$ is given by

$$\hat{\Lambda}_{hj}(t) = \int_0^t \frac{J_h(u)}{Y_h(u)} dN_{hj}(u), \text{for } hj = 01, 02 \text{ and } 12,$$

where $J_h(u) = I(Y_h(u) > 0)$, for $h = 0, 1$. Then, using (5.5), a nonparametric estimate of $S_Q(q)$ is given by

$$\begin{aligned} \hat{S}_Q(q) &= \hat{S}_0\left(\frac{q}{w_0}\right) + \hat{P}_{12}\left(\frac{q}{w_0}\right) \\ &= \hat{S}_0\left(\frac{q}{w_0}\right) + \int_0^{\frac{q}{w_0}} \hat{S}_{12}\left(\frac{q - w_0 x}{w_1}\right) \hat{S}_0(x) d\hat{\Lambda}_{01}(x). \end{aligned} \tag{5.6}$$

Note that the two Kaplan-Meier estimators $\hat{S}_0(u)$ and $\hat{S}_{12}(u)$ are approximately equal to the estimates of the corresponding survival functions derived from the Nelson-Aalen estimators, given by $\exp\left[-\hat{\Lambda}_{01}(u) - \hat{\Lambda}_{02}(u)\right]$ and $\exp\left[-\hat{\Lambda}_{12}(u)\right]$, respectively. For the derivation of asymptotic results in the Appendix (Section 5.6.4), the latter estimators of $S_0(u)$ and $S_{12}(u)$ are considered.

5.3.1 Asymptotic Results

Let $\tau_0 = H_0^{-1}(1)$, where H_0 is the distribution function of X_0. Also, let $\tau_1 = H_1^{-1}(1)$, where H_1 is the conditional distribution function of $X_1 = T_{12} \wedge (C - T_0)$, given $C > T_0$ and $\delta_{01} = 1$. Note that the counting processes $N_{01}(x)$ and $N_{02}(x)$ are actually defined on $[0, \tau_0]$ and the counting process $N_{12}(x)$ is actually defined on $[0, \tau_1]$, where τ_0 and τ_1 are greater than or equal to τ. Let $\tau_w = w_0\tau_0 \wedge w_1\tau_1$. Then, we have the following theorems with the proofs given in Section 5.6.4.

THEOREM 5.3.1 *The process* $\sqrt{n}\left[\hat{S}_0(\cdot) - S_0(\cdot)\right]$ *converges weakly on* $[0, \theta]$*, for* $\theta < \tau$*, to a zero-mean Gaussian process whose variance at* q/w_0 *can be estimated uniformly consistently by*

$$\hat{\psi}^{(0)}\left(\frac{q}{w_0}, \frac{q}{w_0}\right) = n\hat{S}_0^2\left(\frac{q}{w_0}\right)\int_0^{\frac{q}{w_0}} J_0(u)\frac{dN_{01}(u) + dN_{02}(u)}{Y_0^2(u)}. \tag{5.7}$$

THEOREM 5.3.2 *The process* $\sqrt{n}\left[\hat{P}_{12}(\cdot) - P_{12}(\cdot)\right]$ *converges weakly on* $[0, \theta]$*, for* $\theta < \tau$*, to a zero-mean Gaussian process whose variance at* q/w_0 *can be estimated uniformly consistently by* $\hat{\psi}^{(12)}\left(\frac{q}{w_0}, \frac{q}{w_0}\right)$

$$\begin{aligned} = \; & n\int_0^{\frac{q}{w_0}} \left\{\hat{S}_0(u)\hat{S}_{12}\left(\frac{q - w_0u}{w_1}\right) - \int_u^{\frac{q}{w_0}} \hat{S}_0(x)\hat{S}_{12}\left(\frac{q - w_0x}{w_1}\right) d\hat{\Lambda}_{01}(x)\right\}^2 \\ & \times J_0(u)\frac{d\hat{\Lambda}_{01}(u)}{Y_0(u)} \end{aligned}$$

$$+n\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}}\hat{S}_0(x)\hat{S}_{12}\left(\frac{q-w_0x}{w_1}\right)d\hat{\Lambda}_{01}(x)\right\}^2 J_0(u)\frac{d\hat{\Lambda}_{02}(u)}{Y_0(u)}$$
$$+n\int_0^{\frac{q}{w_1}}\left\{\int_0^{\frac{q-w_1u}{w_0}}\hat{S}_0(x)\hat{S}_{12}\left(\frac{q-w_0x}{w_1}\right)d\hat{\Lambda}_{01}(x)\right\}^2 J_1(u)\frac{d\hat{\Lambda}_{12}(u)}{Y_1(u)} \qquad (5.8)$$

THEOREM 5.3.3 *$\sqrt{n}\left[\hat{S}_Q(q)-S_Q(q)\right]$ converges weakly to a mean zero Gaussian process in $[0,\theta_w]$, where $\theta_w<\tau_w$ is a constant, with the estimated variance given by*

$$\widehat{\text{var}}\left\{\hat{S}_Q(q)\right\} = \widehat{\text{var}}\left\{\hat{S}_0\left(\frac{q}{w_0}\right)\right\}+\widehat{\text{var}}\left\{\hat{P}_{12}\left(\frac{q}{w_0}\right)\right\}+2\widehat{\text{cov}}\left\{\hat{S}_0\left(\frac{q}{w_0}\right),\hat{P}_{12}\left(\frac{q}{w_0}\right)\right\}, \qquad (5.9)$$

where $\widehat{\text{var}}\left\{\hat{S}_0\left(\frac{q}{w_0}\right)\right\}=\hat{\psi}^{(0)}\left(\frac{q}{w_0},\frac{q}{w_0}\right)/n$, $\widehat{\text{var}}\left\{\hat{P}_{12}(q)\right\}=\hat{\psi}^{(12)}\left(\frac{q}{w_0},\frac{q}{w_0}\right)/n$
and $\widehat{\text{cov}}\left\{\hat{S}_0\left(\frac{q}{w_0}\right),\hat{P}_{12}\left(\frac{q}{w_0}\right)\right\}$

$$= -\hat{S}_0\left(\frac{q}{w_0}\right)\int_0^{\frac{q}{w_0}}\left\{\hat{S}_0(u)\hat{S}_{12}\left(\frac{q-w_0u}{w_1}\right)-\int_u^{\frac{q}{w_0}}\hat{S}_0(x)\hat{S}_{12}\left(\frac{q-w_0x}{w_1}\right)d\hat{\Lambda}_{01}(x)\right\}$$
$$\times J_0(u)\frac{d\hat{\Lambda}_{01}(u)}{Y_0(u)}$$
$$+\hat{S}_0\left(\frac{q}{w_0}\right)\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}}\hat{S}_0(x)\hat{S}_{12}\left(\frac{q-w_0x}{w_1}\right)d\hat{\Lambda}_{01}(x)\right\}J_0(u)\frac{d\hat{\Lambda}_{02}(u)}{Y_0(u)}. \qquad (5.10)$$

5.3.2 Simulation Study

The performance of the proposed nonparametric estimate (NP) of QAL distribution is investigated in terms of bias and precision through a simulation study. As before, the performance of the estimator is compared with that of the nonparametric estimator ZT. The simulation is carried out with $\lambda_{01}(x)=0.02$, $\lambda_{12}(x)$=0.04 and $\lambda_{02}(x)$=0.005 for sample size n=50 and 200, and repeated 1000 times. The censoring variable C is assumed to have an exponential distribution, independent of T_0 and T_{12}, with hazard rate λ_c=0.03. For each set of simulated data set $\{(x_{0i},\delta_{0i},\delta_{01i},x_{1i},\delta_{1i}),i=1,\ldots,n\}$, the survival probability $S_Q(q)$ is estimated

using both (5.6) and ZT estimator along with the corresponding variance estimates with $w_0 = 1$ and $w_1 = 0.3$. The average bias, average standard error and sample standard error (SSE) are obtained based on 1000 estimates of $S_Q(q)$ for several values of q. The average standard error and the SSE give similar values. Therefore, the results on only average bias and SSE are reported in Table 5.5.

Table 5.5: The average bias and standard error SSE (in parenteses) of NP and ZT estimates for the simple illness-death model 2.

q	$S_Q(q)$	n	NP	ZT
8	0.906	50	0.000 (0.040)	-0.006 (0.047)
		200	0.000 (0.019)	-0.002 (0.024)
20	0.706	50	0.001 (0.076)	-0.018 (0.081)
		200	-0.001(0.037)	-0.004 (0.042)
35	0.492	50	0.013 (0.099)	-0.023 (0.110)
		200	0.003 (0.047)	-0.009 (0.053)
55	0.299	50	0.024 (0.121)	-0.033 (0.130)
		200	0.012(0.058)	-0.013 (0.060)
70	0.206	50	0.032 (0.134)	-0.051 (0.137)
		200	0.013 (0.063)	-0.017 (0.069)
90	0.125	50	0.059 (0.120)	-0.062 (0.107)
		200	0.015(0.071)	-0.025 (0.074)

As expected, both bias and standard error decrease with sample size. The proposed estimate (NP) seems to perform better than the ZT estimate, with respect to both bias and precision, specially for small sample size (n=50), except in the tail area. The quantiles of the 1000 standardized NP estimates are compared with those of the standard normal distribution. Although the convergence seems to be slow, specially in the tail area, the comparison result is found to be satisfactory (results not reported here).

5.3.3 Data Analysis

The proposed nonparametric estimate is illustrated using the Stanford Heart Transplant data (See Section 1.5.1 and also Section 4.2.4). The NP estimates for the survival probabilities using the expression (5.6), with $w_0 = 0.3$ and $w_1 = 0.8$, and standard errors of the estimates using expression (5.9) are presented in Table 5.6. The ZT estimate is also computed for the sake of comparison. The two estimates NP and ZT are similar, except in the tail area, with the ZT estimate having marginally higher standard error than that of the NP estimate.

Table 5.6: Estimated QAL survival probabilities for the heart transplant data with standard errors (in parentheses).

q	Estimate	
	NP	ZT
5	0.855 (0.034)	0.854 (0.035)
20	0.712 (0.043)	0.704 (0.046)
30	0.661 (0.045)	0.654 (0.047)
50	0.556 (0.047)	0.553 (0.050)
80	0.448 (0.048)	0.451 (0.049)
150	0.386 (0.048)	0.385 (0.050)
400	0.314 (0.047)	0.309 (0.048)
600	0.268 (0.046)	0.243 (0.048)
800	0.216 (0.046)	0.179 (0.048)

5.3.4 Extension to Competing Illness-Death Model 2

In this section, the competing illness-death model 2 (See Figure 2.6) of Section 2.4 is considered for the estimation of QAL distribution as an extension to simple illness-death model 2. Note that the simple illness-death model 2 is a special

case of competing illness-death model 2 with k=1. The nonparametric estimate of QAL distribution is obtained under the assumption that the different sojourn times are independently distributed. The survival function of QAL is given by

$$S_Q^C(q) \;=\; S_0\left(\frac{q}{w_0}\right) + P_{ID}\left(\frac{q}{w_0}\right), \tag{5.11}$$

where

$$S_0\left(\frac{q}{w_0}\right) = P\left(T_0 \geq \frac{q}{w_0}\right) = \exp\left[-\left(\sum_{l=1}^{k}\Lambda_{0l}\left(\frac{q}{w_0}\right) + \Lambda_{0,k+1}\left(\frac{q}{w_0}\right)\right)\right],$$

$$P_{ID}\left(\frac{q}{w_0}\right) = \sum_{j=1}^{k} P_j, \text{with } P_j = \int_0^{\frac{q}{w_0}} S_{j,k+1}\left(\frac{q-w_0x}{w_j}\right) S_0(x)d\Lambda_{0j}(x),$$

for $j = 1, \ldots, k$, and the Λ's denoting the corresponding cumulative hazards.

As in Section 4.4.2, consider (X_0, δ_0, δ_{01}, X_1, δ_1) and the data set for n individuals $\{(x_{0i}, \delta_{0i}, \delta_{01i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$. Let $\hat{S}_0(u)$ be the Kaplan-Meier estimate of $S_0(u)$ based on observations $\{(x_{0i}, \delta_{0i}), i = 1, \ldots, n\}$ and $\hat{S}_{j,k+1}(u)$ be the Kaplan-Meier estimate of $S_{j,k+1}(u)$ based on observations $\{(x_{1i}, \delta_{1i}),\ i = 1, \ldots, n$ and $\delta_{01i} = j\}$. Also, the Nelson-Aalen estimator for $\Lambda_{0j}(t)$ is

$$\hat{\Lambda}_{0j}(t) = \int_0^t \frac{J_0(u)}{Y_0(u)} dN_{0j}(u), \text{ for } j = 1, \ldots, k+1,$$

where $N_{0j}(t) = \sum_{i=1}^{n} I\{X_{0i} \leq t, \delta_{01i} = j\}$, for $j = 1, \ldots, k$, $N_{0,k+1}(t) = \sum_{i=1}^{n} I\{X_{0i} \leq t, \delta_{01i} = 0\}$, $Y_0(t) = \sum_{i=1}^{n} I\{X_{0i} \geq t\}$ and $J_0(t) = I(Y_0(t) > 0)$. Then, a nonparametric estimate of $S_Q^C(q)$ is obtained by putting the estimates of $S_0(\cdot)$, $S_{j,k+1}(\cdot)$ and $\Lambda_{0j}(\cdot)$ in (5.11) and is given by

$$\hat{S}_Q^C(q) \;=\; \hat{S}_0\left(\frac{q}{w_0}\right) + \sum_{j=1}^{k} \hat{P}_j,$$

where $\hat{P}_j = \int_0^{\frac{q}{w_0}} \hat{S}_{j,k+1}\left(\frac{q-w_0x}{w_j}\right) \hat{S}_0(x)d\hat{\Lambda}_{0j}(x)$, for $j = 1, \ldots, k$.

Following the same techniques as those used for the simple illness-death model 2 in the Appendix (Section 5.6.4), one can establish asymptotic normality for $\hat{S}_0(\cdot)$

and each of the $\hat{P}_j$'s. Hence, one can prove that $\sqrt{n}\left[\hat{S}_Q^C(q) - S_Q^C(q)\right]$ converges weakly to a mean zero Gaussian process with a variance that can be estimated.

5.3.5 Extension to Progressive Illness-Death Model 2

In this section, the progressive illness-death model 2 (See Figure 2.4) is considered for the estimation of QAL distribution as another extension to simple illness-death model 2. The estimate of QAL distribution is obtained under the assumption that the different sojourn time distributions are independent. The distribution of Q is then given by

$$F_Q^{(k)}(q) = P(Q \leq q) = \sum_{m=0}^{k} P_m, \tag{5.12}$$

where the superscript (k) represents the k intermediate states and the expressions for P_0, P_m and P_k are as in Section 2.3.2. Let us write $S_j(u) = \exp[-\Lambda_{j,j+1}(u)$-$\Lambda_{j,k+1}(u)]$ as the overall survival function for the sojourn time in state j, for $j = 0, 1, \ldots, k-1$. As in Section 4.3.2, consider $(X_j,\ \delta_j)$, for $j = 0, 1 \ldots, k$, and the data set for n individuals given by $\{(x_{ji}, \delta_{ji}), j = 0, 1, \ldots, k, i = 1, \ldots, n\}$. Define $\eta_j = I(\delta_j = j+1 \text{ or } k+1)$, for $j = 0, 1, \ldots, k$. For $j = 0, 1, \ldots, k-1$, let $\hat{S}_j(u)$ be the Kaplan-Meier estimate of $S_j(u)$ based on observations $\{(x_{ji}, \eta_{ji}), i = 1, \ldots, n, \text{ and } \delta_{ji} \neq -1\}$, where η_{ji} denotes the observed value of η_j for the ith individual. Also, let $\hat{F}_{k,k+1}(u)$ be the Kaplan-Meier estimate of $F_{k,k+1}(u)$ based on observations $\{(x_{ki}, \eta_{ki}), i = 1, \ldots, n, \text{ and } \delta_{ki} \neq -1\}$. For $j = 0, 1, \ldots, k-1$, the Nelson-Aalen estimators for $\Lambda_{j,j+1}(t)$ and $\Lambda_{j,k+1}(t)$ are given by

$$\hat{\Lambda}_{j,j+1}(t) = \int_0^t \frac{J_j(u)}{Y_j(u)} dN_{j,j+1}(u) \quad \text{and } \hat{\Lambda}_{j,k+1}(t) = \int_0^t \frac{J_j(u)}{Y_j(u)} dN_{j,k+1}(u),$$

respectively, where $N_{j,j+1}(t) = \sum_{i=1}^n I(X_{ji} \leq t, \delta_{ji} = j+1)$, $N_{j,k+1}(t) = \sum_{i=1}^n I(X_{ji} \leq t, \delta_{ji} = k+1)$, $Y_j(t) = \sum_{i=1}^n I(X_{ji} \geq t)$ and $J_j(t) = I(Y_j(t) > 0)$. A nonparametric estimate of the QAL distribution $F_Q^{(k)}(q)$ is then obtained by substituting $S_j(\cdot)$'s,

$\Lambda_{j,j+1}(\cdot)$'s, $\Lambda_{j,k+1}(\cdot)$'s and $F_{k,k+1}(\cdot)$ in (5.12) by the corresponding estimates.

Note that $F_Q^{(k)}(q)$ can be written as

$$F_Q^{(k)}(q) = \int_0^{\frac{q}{w_0}} S_0(x) d\Lambda_{0,k+1}(x) + \int_0^{\frac{q}{w_0}} F_{Q^*}^{(k-1)}(q - w_0 x_0) S_0(x) d\Lambda_{01}(x),$$

where Q^* is defined in the same way as Q in Section 2.3.2, but starting from state 1 instead of state 0. The corresponding survival function given by

$$S^{(k)}(q) = S_0\left(\frac{q}{w_0}\right) + \int_0^{\frac{q}{w_0}} S_{Q^*}^{(k-1)}(q - w_0 x) dF_{01}(x),$$

having the similar form as in (5.5) with $S_{Q^*}^{(k-1)}(\cdot)$ in place of $S_{12}(\cdot)$. Hence, following the proofs of Theorems 5.3.1-5.3.3 and using method of induction, one can prove weak convergence of $\sqrt{n}\left[\hat{S}_Q^{(k)}(q) - S_Q^{(k)}(q)\right]$ to a mean zero Gaussian process with a variance that can be estimated, where $\hat{S}_Q^{(k)}(q)$ denotes the nonparametric estimate of $S_Q^{(k)}(q)$ as described above. The asymptotic variance of $\hat{S}_Q^{(k)}(q)$ in general is difficult to obtain in closed form. One can use resampling technique to obtain variance estimate of $\hat{S}_Q^{(k)}(q)$.

5.4 Estimation in Reversible Illness-death Model

In this section, the reversible illness-death model (See Figures 2.7 and 2.8) is considered for the estimation of QAL distribution. The different sojourn times for model 1 and model 2 are described in Sections 4.5.1 and 4.5.2, respectively, along with the forms of corresponding data on n individuals. For simplicity, the different sojourn times are assumed to be independent. Also, the sojourn times (and the conceptual times for model 2) in the same state are assumed to be identically distributed. Formally, in model 1, the $T_{jk}^{(l)}$'s for $l = 1, 2, \ldots,$ are assumed to independent and identically distributed with unknown and arbitrary distributions, for $jk = 01, 10$ and 12; the $T_{jk}^{(l)}$'s for different jk's are also independent. The conceptual sojourn times $T_{10}^{(l)}$ and $T_{12}^{(l)}$ form a competing risks framework with

unknown and arbitrary cumulative cause specific hazards $\Lambda_{10}(\cdot)$ and $\Lambda_{12}(\cdot)$, respectively. The likelihood function can be written, using (4.10), in terms of $\Lambda_{10}(\cdot)$, $\Lambda_{12}(\cdot)$ and $S_{R0}(\cdot)$, which can be factored into two terms involving $S_{R0}(\cdot)$ and the two cumulative hazards $\Lambda_{10}(\cdot)$ and $\Lambda_{12}(\cdot)$, respectively. While the Kaplan-Meier estimate of $S_{R0}(\cdot)$ can be easily obtained based on the corresponding sojourn time observations in state 0, the Nelson-Aalen estimates of $\Lambda_{10}(\cdot)$ and $\Lambda_{12}(\cdot)$ can be obtained from the sojourn times observations in state 1. Similarly, in model 2, the $T_{01}^{(l)}$ and $T_{12}^{(l)}$, defining another competing risks framework, are assumed to be independent and identically distributed, for $l = 1, 2, \ldots$, with common cumulative cause specific hazards $\Lambda_{01}(\cdot)$ and $\Lambda_{02}(\cdot)$, respectively. The likelihood function can be written, using (4.11), in terms of the arbitrary cumulative hazards $\Lambda_{01}(\cdot)$ and $\Lambda_{02}(\cdot)$. The Nelson-Aalen estimates for $\Lambda_{01}(\cdot)$ and $\Lambda_{02}(\cdot)$ can now be obtained, which can be used to estimate $S_{R0}(\cdot)$ and $S_{R1}(\cdot)$.

The theoretical expression for QAL distribution is, however, complicated involving multiple integration. Hence, it would be difficult to estimate it by substituting the different sojourn time distributions in its expression by the corresponding estimates. One can instead estimate the QAL distribution via simulation using the estimated sojourn time distributions. The standard errors can be computed by some resampling method.

5.5 Estimation in Dependent Models

In the previous sections of this chapter, estimation is considered under the assumption that the successive sojourn times are independently distributed. This section considers three dependent scenarios and, for each of them, outlines a method of estimation for the QAL distribution in the simple illness-death model (See Section 2.2.1) of Figure 2.1. For other models, similar methods may be followed. The

distribution of Q for this model is given by the survival function

$$S_Q(q) \;= 1 - \int_0^{\frac{q}{w_0}} \left[\int_0^{\frac{q-w_0 x}{w_1}} \lambda_{12}(y \mid x) e^{-\Lambda_{12}(y|x)} dy \right] \lambda_{01}(x) e^{-\Lambda_{01}(x)} dx, \qquad (5.13)$$

where $\lambda_{01}(x)$ the hazard rate of T_{01} at time x and $\lambda_{12}(y|x)$ is the conditional hazard rate of T_{12} at corresponding sojourn time y, given $T_{01} = x$. The dependence between T_{01} and T_{12} is described by the conditional hazard $\lambda_{12}(y|x)$. Three dependent structures are considered here to describe the dependence between T_{01} and T_{12}: (1) the conditional hazard $\lambda_{12}(y|x)$ is modelled by the proportional hazards assumption $\lambda_{12}(y|x) = \lambda_{120}(y)e^{\beta x}$, (2) dependence between T_{01} and T_{12} is described by Markov assumption for the hazard rates of T_{01} and $T_{01} + T_{12}$, and (3) arbitrary dependence between T_{01} and T_{12}. As in Section 4.2.1, the observed data set for n individuals is of the form $\{(x_{0i}, \delta_{0i}, x_{1i}, \delta_{1i}), i = 1, \ldots, n\}$.

In this section, we give only some outline of the estimation procedure without studying the properties, etc., in detail. These are to be taken as some extension of the main work of this thesis to be carried out in future.

5.5.1 Semi-parametric Dependence

The dependence between T_{01} and T_{12} is modelled by the semi-parametric proportional hazards assumption $\lambda_{12}(y|x) = \lambda_{120}(y)e^{\beta x}$, where $\lambda_{120}(y)$ denotes the baseline hazard rate for T_{12} and β is the dependence parameter. The survival function (5.13) of Q is then given by

$$\begin{aligned} S_Q(q) &= 1 - \int_0^{\frac{q}{w_0}} \left[1 - \bar{F}_{12}\left(\frac{q - w_0 x}{w_1} | x \right) \right] dF_{01}(x) \\ &= 1 - F_{01}\left(\frac{q}{w_0} \right) + \int_0^{\frac{q}{w_0}} \left\{ \bar{F}_{120}\left(\frac{q - w_0 x}{w_1} \right) \right\}^{e^{\beta x}} dF_{01}(x), \qquad (5.14) \end{aligned}$$

where $\bar{F}_{12}\left(\frac{q - w_0 x}{w_1} | x \right) = \left\{ \bar{F}_{120}\left(\frac{q - w_0 x}{w_1} \right) \right\}^{e^{\beta x}}$ is the conditional survival function for T_{12}, given $T_{01} = x$, with $\bar{F}_{120}(\cdot)$ denoting the corresponding baseline survival function, given by $\exp[-\Lambda_{120}(\cdot)]$ with $\Lambda_{120}(y) = \int_0^y \lambda_{120}(u)du$, and $F_{01}(\cdot)$

denotes the distribution function of T_{01}.

Let $\hat{F}_{01}(\cdot)$ denote the Kaplan-Meier estimate of $F_{01}(\cdot)$ based on the observations $(x_{0i},\ \delta_{0i};\ i = 1, \ldots, n)$. Then, β is estimated by maximizing the partial likelihood based on the observations $(x_{1i}, \delta_{1i}, x_{0i}, \delta_{0i}; i = 1, \ldots, n)$, where x_{0i} values are treated as covariate values, as given by

$$L(\beta) = \prod_{i=1}^{n} \left(\frac{\exp(\beta x_{0i})}{\sum_{l=1}^{n} Y_l(x_{1i}) \exp(\beta x_{0l})} \right)^{\delta_{0i}\delta_{1i}},$$

where $Y_i(x)$ is the indicator for individual i being at risk in the illness state just before time x; that is, $Y_i(x) = 1$ if, the sojourn time for the ith individual in the illness state is greater than or equal to x, and 0 otherwise. Then, estimate of $\Lambda_{120}(t)$ is given by (Breslow, 1974)

$$\hat{\Lambda}_{120}(t, \hat{\beta}) = \int_0^t \frac{J(x)}{\sum_{l=1}^{n} Y_l(x) \exp(\hat{\beta} x_{0l})} dN_{12}(x),$$

where $N_{12}(x)$ is the counting process corresponding to the observations on T_{12}, $Y(x) = \sum_{i=1}^{n} Y_i(x)$ and $J(x) = I(Y(x) > 0)$. The conditional survival function of T_{12}, for given $T_{01} = x$, is then estimated by

$$\hat{\bar{F}}_{12}(t|x) = \left(\prod_{u<t} \left\{ 1 - d\hat{\Lambda}_{120}(u, \hat{\beta}) \right\} \right)^{e^{\hat{\beta} x}}. \tag{5.15}$$

Then, a nonparametric estimate of $S_Q(q)$ is given by

$$\hat{S}_Q(q) \;=\; 1 - \hat{F}_{01}\left(\frac{q}{w_0}\right) + \int_0^{\frac{q}{w_0}} \hat{\bar{F}}_{12}\left(\frac{q - w_0 x}{w_1} | x\right) d\hat{F}_{01}(x). \tag{5.16}$$

5.5.2 Markov Dependence

Here, the dependence between T_{01} and T_{12} is described through a Markov model in which different transition rates depend on the time since the beginning instead of the time spent in the current state. That is, $\lambda_{12}(y|x) = \lambda_{12}(y + x)$. Then, survival function (5.13) of Q can be written as

$$S_Q(q) \;=\; 1 - \int_0^{\frac{q}{w_0}} P\left(T_{12} \leq \frac{q - w_0 x}{w_1} | T_{01} = x\right) dF_{01}(x)$$

$$
\begin{aligned}
&= 1 - \int_0^{\frac{q}{w_0}} \left(1 - \exp\left[-\int_0^{\frac{q-w_0x}{w_1}} \lambda_{12}(x+u)du\right]\right) dF_{01}(x) \\
&= 1 - \int_0^{\frac{q}{w_0}} \left(1 - \exp\left[-\Lambda_{12}\left(\frac{q-w_0x+w_1x}{w_1}\right) + \Lambda_{12}(x)\right]\right) dF_{01}(x),
\end{aligned} \tag{5.17}
$$

where $\Lambda_{12}(t) = \int_0^t \lambda_{12}(u)$. The estimate of $\Lambda_{12}(t)$ can be obtained (Andersen et al., 1993, p 238) as

$$\hat{\Lambda}_{12}(t) = \int_0^t \frac{J^*(u)}{Y^*(u)} dN_{12}^*(u),$$

where $N_{12}^*(t)$ is the process counting the number of transition from state 1 to state 2 over the calender time t (that is, $N_{12}^*(t)$=number of i with δ_{1i}=1 and $x_{0i} + x_{1i} \leq t$), $Y^*(t) = \sum_{i=1}^{n} Y_i^*(t)$ with $Y_i^*(t) = 1$ whenever the ith individual is at risk of a transition from state 1 at calender time t, and 0 otherwise, and $J^*(t) = I(Y^*(t) > 0)$.

Then, a nonparametric estimate of the survival function $S_Q(q)$ is obtained as

$$
\hat{S}_Q(q) = 1 - \int_0^{\frac{q}{w_0}} \left(1 - \exp\left[-\hat{\Lambda}_{12}\left(\frac{q-w_0x+w_1x}{w_1}\right) + \hat{\Lambda}_{12}(x)\right]\right) d\hat{F}_{01}(x), \tag{5.18}
$$

where $\hat{F}_{01}(\cdot)$ denotes the Kaplan-Meier estimate of F_{01}, as in Section 5.5.1.

5.5.3 Arbitrary Dependence

The survival function of Q can be written as

$$
\begin{aligned}
S_Q(q) &= 1 - \int_0^{\frac{q}{w_0}} P\left(T_{12} \leq \frac{q-w_0x}{w_1} | T_{01} = x\right) dF_{01}(x) \\
&= 1 - \int_0^{\frac{q}{w_0}} \left[F\left(x + dx, \frac{q-w_0x}{w_1}\right) - F\left(x, \frac{q-w_0x}{w_1}\right)\right],
\end{aligned} \tag{5.19}
$$

where $F(x,y) = P[T_{01} \leq x, T_{12} \leq y]$ is the joint distribution function of T_{01} and T_{12}. Now $F(x,y)$ can be written as $F(x,y) = H(x,0) - H(x,y)$, where $H(x,y) = P(T_{01} \leq x, T_{12} > y)$. An estimate of $S_Q(q)$ can now be obtained by

estimating $H(x,y)$. Let G be the survival function of the censoring variable C and $\hat{G}$ be the corresponding Kaplan-Meier estimator based on the data $\{(x_{0i},\, 1-\delta_{0i}),\, i=1,\ldots,n\}$ or $\{(x_{0i}+x_{1i},\, 1-\delta_{1i}),\, i=1,\ldots,n\ \}$. An estimate of $H(x,y)$ is given by (Lin et al., 1999)

$$\hat{H}(x,y) = n^{-1}\sum_{i=1}^{n}\frac{I(x_{0i}\le x, x_{1i}>y)}{\hat{G}(x_{0i}+y)}.$$

The corresponding estimate of $F(x,y)$ is given by

$$\hat{F}(x,y) = \hat{H}(x,0) - \hat{H}(x,y). \tag{5.20}$$

Hence, an estimate of $S_Q(q)$ is obtained by substituting (5.20) in (5.19) and is given by

$$\hat{S}_Q(q) \;=\; 1 - \sum_{i:x_{0i}\le\frac{q}{w_0}}\left[\hat{F}\left(x_{0i}+,\frac{q-w_0x_{0i}}{w_1}\right) - \hat{F}\left(x_{0i},\frac{q-w_0x_{0i}}{w_1}\right)\right]. \tag{5.21}$$

The joint distribution of T_{01} and T_{12} can also be estimated by the method of Wang and Wells (1998). Let $\bar{F}(x,y) = P[T_{01}>x, T_{12}>y]$ be the joint survival function of T_{01} and T_{12}. Then $\bar{F}(x,y)$ can be written as

$$\bar{F}(x,y) = P[T_{12}>y|T_{01}>x]P[T_{01}>x] = \prod_{v\le y}\{1-\Lambda_{T_{12}|T_{01}>x}(dv)\}\bar{F}_{01}(x),$$

where $\Lambda_{T_{12}|T_{01}>x}(y)$ is the conditional cumulative hazard of T_{12}, given $T_{01}>x$. Let $\hat{G}(\cdot)$ be the Kaplan-Meier estimate of of $G(\cdot)$ based on the data $\{(x_{0i}+x_{1i},$ $1-\delta_{0i}\delta_{1i}),\, i=1,\ldots,n\}$. An estimator of $\Lambda_{T_{12}|T_{01}>x}(dv)$ is given by (Wang and Wells, 1998)

$$\hat{\Lambda}_{T_{12}|T_{01}>x}(dv) = \frac{\sum_{i=1}^{n} I(x_{0i}>x, \delta_{0i}=1, x_{1i}=v, \delta_{1i}=1)/\hat{G}(x_{0i}+v)}{\sum_{i=1}^{n} I(x_{0i}>x, \delta_{0i}=1, x_{1i}\ge v)/\hat{G}(x_{0i}+v)},$$

Then, $\bar{F}(x,y)$ is estimated by

$$\hat{\bar{F}}(x,y) = \prod_{v\le y}\{1-\hat{\Lambda}_{T_{12}|T_{01}>x}(dv)\}\hat{\bar{F}}_{01}(x), \tag{5.22}$$

where $\hat{F}_{01}(\cdot)$ denotes the Kaplan-Meier estimate of F_{01}, as in Section 5.5.1. Hence, a nonparametric estimate of $S_Q(q)$ is given by

$$\begin{aligned}\hat{S}_Q(q) &= 1 - \sum_{i:x_{0i} \le \frac{q}{w_0}} \left[\left\{ \hat{\bar{F}}\left(x_{0i}+, \frac{q - w_0 x_{0i}}{w_1}\right) - \hat{\bar{F}}\left(x_{0i}, \frac{q - w_0 x_{0i}}{w_1}\right) \right\} \right. \\ &\qquad \left. - \left\{ \hat{\bar{F}}_{01}(x_{0i}+) - \hat{\bar{F}}_{01}(x_{0i}) \right\} \right]. \qquad (5.23)\end{aligned}$$

5.5.4 Analysis of Heart Transplant Data

The proposed nonparametric methods for estimating the QAL distribution in different dependent models are illustrated using the Stanford Heart Transplant data (See Section 1.5.1 and also Section 4.2.4). The estimates for the survival probabilities under the three dependent models are obtained using the expressions (5.16), (5.18), (5.21) and (5.23), with $w_0 = 0.3$ and $w_1 = 0.8$, and presented in Table 5.7. The estimates under semi-parametric dependence and Markov dependence are labeled as SD and MD, respectively. The estimates under arbitrary dependence obtained by using the methods of Lin et al. (1999) and Wang and Wells (1998) are labeled as LSY and WW, respectively. The nonparametric estimate (NP) under independent model and ZT estimate are also presented for the sake of comparison. Note that the estimates of Lin et al. (1999) and Wang and Wells (1998) for the joint distribution of T_{01} and T_{12} may lack the monotonicity property for finite samples. This may lead to non-monotonicity in the corresponding estimate of $S_Q(\cdot)$. For our data set, this non-monotonicity has been observed for the estimate WW, using the method of Wang and Wells (See Table 5.7).

Table 5.7: Estimated QAL survival probabilities for the heart transplant data in dependent models.

q	SD	MD	AD		NP	ZT
			LSY	WW		
10	0.960	0.992	0.925	0.996	0.978	0.989
20	0.904	0.968	0.795	0.945	0.938	0.928
40	0.826	0.878	0.710	0.877	0.865	0.865
50	0.750	0.830	0.629	0.748	0.794	0.788
80	0.627	0.761	0.539	0.599	0.657	0.656
150	0.559	0.682	0.437	0.467	0.578	0.592
300	0.488	0.583	0.422	0.537	0.498	0.473
400	0.472	0.559	0.413	0.520	0.479	0.451
600	0.418	0.483	0.366	0.457	0.420	0.350
800	0.355	0.385	0.302	0.479	0.351	0.260

5.6 Appendix

5.6.1 Proofs of the Theorems for Simple Illness-Death Model 1

Note that, from Shorack and Wellner (1986, p 304-308), the following results hold.

RESULT 5.6.1 *As* $n \to \infty$, $\sup_{u\in[0,\tau_0)} |\hat{F}_{01}(u) - F_{01}(u)| \xrightarrow{a.s.} 0$ *and* $\sup_{u\in[0,\tau_1)} |\hat{\bar{F}}_{12}(u) - \bar{F}_{12}(u)| \xrightarrow{a.s.} 0$.

RESULT 5.6.2 *As* $n \to \infty$, $Z_{1n}(u)=\sqrt{n}\left[\hat{F}_{01}(u) - F_{01}(u)\right]$ *converges to a mean zero Gaussian process* $Z_{F_{01}}(u)$*, say, in* $[0, \theta_0]$ *for* $\theta_0 < \tau_0$*, with covariance given by*

$$\text{cov}[Z_{F_{01}}(s), Z_{F_{01}}(t)] = \bar{F}_{01}(s)\bar{F}_{01}(t) \int_0^{s\wedge t} \frac{dF_{01u}(x)}{[1 - H_0(x)]^2},$$

where $F_{01u}(x) = P(X_0 \le x, \delta_0 = 1)$. This implies $\sup_{0\le u\le\theta_1} |Z_{1n}(u) - Z_{F_{01}}(u)| \to 0$ with probability 1, as $n \to \infty$.

RESULT 5.6.3 *As* $n \to \infty$, $Z_{2n}(u)=\sqrt{n_1}\left[\hat{\bar{F}}_{12}(u) - \bar{F}_{12}(u)\right]$ *converges to a mean zero Gaussian process* $Z_{\bar{F}_{12}}(u)$, *say, in* $[0, \theta_1]$ *for* $\theta_1 < \tau_1$, *with covariance function given by*

$$\text{cov}[Z_{\bar{F}_{12}}(s), Z_{\bar{F}_{12}}(t)] = \bar{F}_{12}(s)\bar{F}_{12}(t)\int_0^{s\wedge t} \frac{dF_{12u}(x)}{[1-H_1(x)]^2},$$

where $n_1 = \#\{i : \delta_{0i} = 1\}$ and $F_{12u}(x) = P[X_1 < x, \delta_1 = 1 | \delta_0 = 1]$. Note that, since $n_1/n \overset{a.s.}{\to} P[\delta_0 = 1] = P[T_{01} < C] > 0$, then $n_1 \to \infty$ as $n \to \infty$. This implies, as $n \to \infty$, $\sup_{0\le u\le\theta_1} |Z_{2n}(u) - Z_{\bar{F}_{12}}(u)| \to 0$ with probability 1.

Proof of Theorem 5.2.1:

$$\hat{S}_Q(q) - S_Q(q) \;=\; F_{01}\left(\frac{q}{w_0}\right) - \hat{F}_{01}\left(\frac{q}{w_0}\right) + A_{1n}(q) + A_{2n}(q), \text{say},$$

where

$$A_{1n}(q) = \int_0^{\frac{q}{w_0}} \left[\hat{\bar{F}}_{12}\left(\frac{q-w_0x}{w_1}\right) - \bar{F}_{12}\left(\frac{q-w_0x}{w_1}\right)\right] d\hat{F}_{01}(x), \text{ and}$$
$$A_{2n}(q) = \int_0^{\frac{q}{w_0}} \bar{F}_{12}\left(\frac{q-w_0x}{w_1}\right) d\left(\hat{F}_{01}(x) - F_{01}(x)\right).$$

Integration by parts gives

$$A_{2n}(q) = \hat{F}_{01}\left(\frac{q}{w_0}\right) - F_{01}\left(\frac{q}{w_0}\right) - \int_0^{\frac{q}{w_1}} \left[\hat{F}_{01}\left(\frac{q-w_1x}{w_0}\right) - F_{01}\left(\frac{q-w_1x}{w_0}\right)\right] dF_{12}(x)$$

so that

$$\begin{aligned}\hat{S}_Q(q) - S_Q(q) \;&=\; \int_0^{\frac{q}{w_0}} \left[\hat{\bar{F}}_{12}\left(\frac{q-w_0x}{w_1}\right) - \bar{F}_{12}\left(\frac{q-w_0x}{w_1}\right)\right] d\hat{F}_{01}(x) \\ &-\; \int_0^{\frac{q}{w_1}} \left[\hat{F}_{01}\left(\frac{q-w_1x}{w_0}\right) - F_{01}\left(\frac{q-w_1x}{w_0}\right)\right] dF_{12}(x). \quad (5.24)\end{aligned}$$

Then, for $0 \le q < \tau$,

$$|\hat{S}_Q(q) - S_Q(q)| \;\le\; \int_0^{\frac{q}{w_0}} \left|\hat{\bar{F}}_{12}\left(\frac{q-w_0x}{w_1}\right) - \bar{F}_{12}\left(\frac{q-w_0x}{w_1}\right)\right| d\hat{F}_{01}(x)$$

$$
\begin{aligned}
& + \int_0^{\frac{q}{w_1}} \left| \hat{F}_{01}\left(\frac{q-w_1x}{w_0}\right) - F_{01}\left(\frac{q-w_1x}{w_0}\right) \right| dF_{12}(x) \\
\leq & \sup_{0\leq x\leq \frac{q}{w_0}} \left| \hat{\bar{F}}_{12}\left(\frac{q-w_0x}{w_1}\right) - \bar{F}_{12}\left(\frac{q-w_0x}{w_1}\right) \right| \\
& + \sup_{0\leq x\leq \frac{q}{w_1}} \left| \hat{F}_{01}\left(\frac{q-w_1x}{w_0}\right) - F_{01}\left(\frac{q-w_1x}{w_0}\right) \right|. \\
= & \sup_{0\leq y\leq \frac{q}{w_1}} \left| \hat{\bar{F}}_{12}(y) - \bar{F}_{12}(y) \right| + \sup_{0\leq y\leq \frac{q}{w_0}} \left| \hat{F}_{01}(y) - F_{01}(y) \right|.
\end{aligned}
$$

Therefore,

$$
\sup_{0\leq q\leq \tau} |\hat{S}_Q(q) - S_Q(q)| \leq \sup_{0\leq y< \frac{\tau}{w_1}} \left| \hat{\bar{F}}_{12}(y) - \bar{F}_{12}(y) \right| + \sup_{0\leq y< \frac{\tau}{w_0}} \left| \hat{F}_{01}(y) - F_{01}(y) \right|.
$$

Then, the proof of Theorem 5.2.1 follows using Result 5.6.1.

Now in order to investigate the validity of this result over an extended interval, consider the following different cases.

1. $\tau_0 = \tau_1 = \infty$. This implies $w_0\tau_0 \wedge w_1\tau_1 = w_0\tau_0 + w_1\tau_1$.

2. $\tau_0 = \infty$, $\tau_1 < \infty \Rightarrow$ Support of C is $(0, \infty)$ and support of T_{12} is $(0, \tau_1]$. Then, for $t > \tau_1$ $\bar{F}_{12}(t) = 0$ and $\hat{\bar{F}}_{12}(t) = o_p(1)$. If $\frac{q}{w_1} > \tau_1$, or $q > w_1\tau_1 = w_0\tau_0 \wedge w_1\tau_1$, then also $\sup_{0\leq y\leq \frac{q}{w_1}} \left| \hat{\bar{F}}_{12}(y) - \bar{F}_{12}(y) \right| = o_p(1)$ so that the upper limit of the interval can be $w_0\tau_0 + w_1\tau_1$.

3. $\tau_0 < \infty$, $\tau_1 = \infty \Rightarrow$ only support of T_{01} is finite. By similar argument as in case 2, the upper limit can be $w_0\tau_0 + w_1\tau_1$.

4. $\tau_0 < \infty$, $\tau_1 < \infty \Rightarrow$ Support of T_{01}, T_{12} and C are finite. If τ_0 and τ_1 corresponds to support of T_{01} and T_{12}, respectively, then also, by the same argument, as in cases 2 and 3, the upper limit can be $w_0\tau_0 + w_1\tau_1$. When C corresponds to τ_0, then $F_{01}(\cdot)$ is not estimable beyond τ_0, and there is problem with estimability of $S_Q(q)$ beyond $w_0\tau_0 \wedge w_1\tau_1$.

Proof of Theorem 5.2.2: Using (5.24), it is easy to write

$$\sqrt{n}\left[\hat{S}_Q(q) - S_Q(q)\right] \;=\; C_{1n}(q) + C_{2n}(q) - C_{3n}(q), \tag{5.25}$$

where

$$C_{1n}(q) = \sqrt{\frac{n}{n_1}} \int_0^{\frac{q}{w_0}} \sqrt{n_1}\left[\hat{\bar{F}}_{12}\left(\frac{q - w_0 x}{w_1}\right) - \bar{F}_{12}\left(\frac{q - w_0 x}{w_1}\right)\right] d\left(\hat{F}_{01}(x) - F_{01}(x)\right),$$

$$C_{2n}(q) = \sqrt{\frac{n}{n_1}} \int_0^{\frac{q}{w_0}} \sqrt{n_1}\left[\hat{\bar{F}}_{12}\left(\frac{q - w_0 x}{w_1}\right) - \bar{F}_{12}\left(\frac{q - w_0 x}{w_1}\right)\right] dF_{01}(x), \text{ and}$$

$$C_{3n}(q) = \int_0^{\frac{q}{w_1}} \sqrt{n}\left[\hat{F}_{01}\left(\frac{q - w_1 x}{w_0}\right) - F_{01}\left(\frac{q - w_1 x}{w_0}\right)\right] dF_{12}(x).$$

Note that for $0 \le q \le \theta$,

$$|C_{1n}(q)| \le \sqrt{\frac{n}{n_1}} \left\{|D_{1n}(q)| + |D_{2n}(q)|\right\}, \tag{5.26}$$

where $D_{1n}(q) = \displaystyle\int_0^{\frac{q}{w_0}} \left[Z_{2n}\left(\frac{q - w_0 x}{w_1}\right) - Z_{\bar{F}_{12}}\left(\frac{q - w_0 x}{w_1}\right)\right] d\left(\hat{F}_{01}(x) - F_{01}(x)\right)$
and $D_{2n}(q) = \displaystyle\int_0^{\frac{q}{w_0}} Z_{\bar{F}_{12}}\left(\frac{q - w_0 x}{w_1}\right) d\left(\hat{F}_{01}(x) - F_{01}(x)\right)$.

Now, using the result in Apostol (1989, p. 177),

$$\begin{aligned} |D_{1n}(q)| \;&\le\; 2 \sup_{0 \le x \le \frac{q}{w_0}} \left| Z_{2n}\left(\frac{q - w_0 x}{w_1}\right) - Z_{\bar{F}_{12}}\left(\frac{q - w_0 x}{w_1}\right)\right| \\ &=\; 2 \sup_{0 \le y \le \frac{q}{w_1}} \left|Z_{2n}(y) - Z_{\bar{F}_{12}}(y)\right|, \end{aligned}$$

so that $\sup_{0 \le q \le \theta} |D_{1n}(q)| \le 2 \sup_{0 \le y \le \frac{\theta}{w_1}} |Z_{2n}(y) - Z_{\bar{F}_{12}}(y)|$. Then, using Result 5.6.3, $\sup_{0 \le q \le \theta} |D_{1n}(q)| \to 0$ with probability 1, as $n \to \infty$. Next, for any given $\epsilon > 0$ and $M > 0$, $P\left[\sup_{0 \le q \le \theta} |D_{2n}(q)| > \epsilon\right]$

$$\begin{aligned} =\; P\Bigg[&\sup_{0 \le q \le \theta} \left| \int_0^{\frac{q}{w_0}} Z_{\bar{F}_{12}}\left(\frac{q - w_0 x}{w_1}\right) d\left(\hat{F}_{01}(x) - F_{01}(x)\right)\right| > \epsilon, \\ &\sup_{0 \le y \le \frac{\theta}{w_1}} |Z_{\bar{F}_{12}}(y)| \le M \Bigg] \end{aligned}$$

$$
\begin{aligned}
+ \quad & P\left[\sup_{0\le q\le\theta}\left|\int_0^{\frac{q}{w_0}} Z_{\bar{F}_{12}}\left(\frac{q-w_0x}{w_1}\right)d\left(\hat{F}_{01}(x)-F_{01}(x)\right)\right|>\epsilon,\right. \\
& \left.\sup_{0\le y\le\frac{\theta}{w_1}}|Z_{\bar{F}_{12}}(y)|>M\right] \\
\le \quad & P\left[\sup_{0\le q\le\theta}|\int_0^{\frac{q}{w_0}} d(\hat{F}_{01}(x)-F_{01}(x))|>\epsilon/M\right]+P\left[\sup_{0\le y\le\frac{\theta}{w_1}}|Z_{\bar{F}_{12}}(y)|>M\right].
\end{aligned}
$$

Now, given any $\delta>0$, M can be chosen large enough to satisfy

$$
P\left[\sup_{0\le y\le\frac{\theta}{w_1}}|Z_{\bar{F}_{12}}(y)|>M\right]<\delta/2.
$$

Also, using Result 5.6.1,

$$
\begin{aligned}
& P\left[\sup_{0\le q\le\theta}|\int_0^{\frac{q}{w_0}} d(\hat{F}_{01}(x)-F_{01}(x))|>\epsilon/M\right] \\
& \qquad = \quad P\left[\sup_{0\le q\le\theta}|\hat{F}_{01}\left(\frac{q}{w_0}\right)-F_{01}\left(\frac{q}{w_0}\right)|>\epsilon/M\right] \\
& \qquad = \quad P\left[\sup_{0\le y\le\frac{\theta}{w_0}}|\hat{F}_{01}(y)-F_{01}(y)|>\epsilon/M\right]
\end{aligned}
$$

can be made $<\delta/2$. Hence, $P\left[\sup_{0\le q\le\theta}|D_{2n}(q)|>\epsilon\right]\to 0$ as $n\to\infty$. Hence, from (5.26), $C_{1n}(q)$ converges to 0 in probability as $n\to\infty$. Let p_1=$(P[T_{01}<C])^{-1/2}$, which is consistently estimated by $(n_1/n)^{-1/2}$. Then, by Results 5.6.2 and 5.6.3, for $0\le q\le\theta$, $C_{2n}(q)$ and $C_{3n}(q)$ converges to $p_1\int_0^{\frac{q}{w_0}} Z_{\bar{F}_{12}}\left(\frac{q-w_0x}{w_1}\right)dF_{01}(x)$ and $\int_0^{\frac{q}{w_1}} Z_{F_{01}}\left(\frac{q-w_1x}{w_0}\right)dF_{12}(x)$, respectively, which themselves are mean zero Gaussian processes (Parzen, 1962, p 90).

It now follows, from (5.25), that $\sqrt{n}\left[\hat{S}_Q(q)-S_Q(q)\right]$ converges to a mean zero Gaussian process $Z_Q(q)$ given by

$$
Z_Q(q)=p_1\int_0^{\frac{q}{w_0}} Z_{\bar{F}_{12}}\left(\frac{q-w_0x}{w_1}\right)dF_{01}(x)-\int_0^{\frac{q}{w_1}} Z_{F_{01}}\left(\frac{q-w_1x}{w_0}\right)dF_{12}(x).
$$

Derivation of Variance of $Z_Q(q)$:

Following Parzen (1962, p 79), $\text{cov}[Z_Q(q), Z_Q(q')]$

$$
\begin{aligned}
&= p_1^2 \text{cov}\left[\int_0^{\frac{q}{w_0}} Z_{\bar{F}_{12}}\left(\frac{q-w_0x}{w_1}\right) dF_{01}(x), \int_0^{\frac{q'}{w_0}} Z_{\bar{F}_{12}}\left(\frac{q'-w_0x}{w_1}\right) dF_{01}(x)\right] \\
&\quad + \text{cov}\left[\int_0^{\frac{q}{w_1}} Z_{F_{01}}\left(\frac{q-w_1x}{w_0}\right) dF_{12}(x), \int_0^{\frac{q'}{w_1}} Z_{F_{01}}\left(\frac{q'-w_1x}{w_0}\right) dF_{12}(x)\right] \\
&= p_1^2 \int_0^{\frac{q}{w_0}} dF_{01}(r_1) \int_0^{\frac{q'}{w_0}} \text{cov}\left[Z_{\bar{F}_{12}}\left(\frac{q-w_0r_1}{w_1}\right), Z_{\bar{F}_{12}}\left(\frac{q'-w_0u_1}{w_1}\right)\right] dF_{01}(u_1) \\
&\quad + \int_0^{\frac{q}{w_1}} dF_{12}(r_2) \int_0^{\frac{q'}{w_1}} \text{cov}\left[Z_{F_{01}}\left(\frac{q-w_1r_2}{w_0}\right), Z_{F_{01}}\left(\frac{q'-w_1u_2}{w_0}\right)\right] dF_{12}(u_2).
\end{aligned}
$$

Now, $\text{cov}\left[Z_{\bar{F}_{12}}\left(\frac{q-w_0r_1}{w_1}\right), Z_{\bar{F}_{12}}\left(\frac{q'-w_0u_1}{w_1}\right)\right]$

$$= \bar{F}_{12}\left(\frac{q-w_0r_1}{w_1}\right)\bar{F}_{12}\left(\frac{q'-w_0u_1}{w_1}\right)\int_0^{\alpha_1}\frac{dF_{12u}(x)}{(1-H_1(x))^2}$$

and $\text{cov}\left[Z_{F_{01}}\left(\frac{q-w_1r_2}{w_0}\right), Z_{F_{01}}\left(\frac{q'-w_1u_2}{w_0}\right)\right]$

$$= \bar{F}_{01}\left(\frac{q-w_1r_2}{w_2}\right)\bar{F}_{01}\left(\frac{q'-w_1u_2}{w_0}\right)\int_0^{\alpha_2}\frac{dF_{01u}(x)}{(1-H_0(x))^2},$$

where $\alpha_1 = \min\left(\frac{q-w_0r_1}{w_1}, \frac{q'-w_0u_1}{w_1}\right)$ and $\alpha_2 = \min\left(\frac{q-w_1r_2}{w_0}, \frac{q'-w_1u_2}{w_0}\right)$.

Therefore, using Parzen (1962, p. 80),

$$
\begin{aligned}
\text{var}(Z_Q(q)) &= 2p_1^2 \int_0^{\frac{q}{w_0}} dF_{01}(r_1)\left[\int_0^{r_1}\bar{F}_{12}\left(\frac{q-w_0r_1}{w_1}\right)\bar{F}_{12}\left(\frac{q-w_0u_1}{w_1}\right)\right. \\
&\qquad \left.\times\int_0^{q_1}\frac{dF_{12u}(x)}{(1-H_1(x))^2}dF_{01}(u_1)\right] \\
&\quad +2\int_0^{\frac{q}{w_1}} dF_{12}(r_2)\left[\int_0^{r_2}\bar{F}_{01}\left(\frac{q-w_1r_2}{w_0}\right)\bar{F}_{01}\left(\frac{q-w_1u_2}{w_0}\right)\right. \\
&\qquad \left.\times\int_0^{q_2}\frac{dF_{01u}(x)}{(1-H_0(x))^2}dF_{12}(u_2)\right], \qquad (5.27)
\end{aligned}
$$

where $0 \leq u_1 \leq r_1 \leq \frac{q}{w_0}$, $q_1 = \frac{q - r_1 w_0}{w_1}$ and $0 \leq u_2 \leq r_2 \leq \frac{q}{w_1}$, $q_2 = \frac{q - r_2 w_1}{w_0}$. The variance of $\hat{S}_Q(q)$ can be consistently estimated by

$$\begin{aligned}
\widehat{\text{var}}(\hat{S}_Q(q)) &= \frac{2}{n_1} \int_0^{\frac{q}{w_0}} d\hat{F}_{01}(r_1) \left[\int_0^{r_1} \hat{\bar{F}}_{12}\left(\frac{q - w_0 r_1}{w_1}\right) \hat{\bar{F}}_{12}\left(\frac{q - w_0 u_1}{w_1}\right) \right. \\
&\quad \left. \times \int_0^{q_1} \frac{d\hat{F}_{12u}(x)}{(1 - \hat{H}_1(x))^2} d\hat{F}_{01}(u_1) \right] \\
&\quad + \frac{2}{n} . \int_0^{\frac{q}{w_1}} d\hat{F}_{12}(r_1) \left[\int_0^{r_1} \hat{\bar{F}}_{01}\left(\frac{q - w_1 r_1}{w_0}\right) \hat{\bar{F}}_{01}\left(\frac{q - w_1 u_2}{w_0}\right) \right. \\
&\quad \left. \times \int_0^{q_2} \frac{d\hat{F}_{01u}(x)}{(1 - \hat{H}_0(x))^2} d\hat{F}_{12}(u_2) \right], \qquad (5.28)
\end{aligned}$$

where $0 \leq u_1 \leq r_1 \leq \frac{q}{w_0}$, $q_1 = \frac{q - r_1 w_0}{w_1}$ and $0 \leq u_2 \leq r_2 \leq \frac{q}{w_1}$, $q_2 = \frac{q - r_2 w_1}{w_0}$; also, $\hat{F}_{01u}(\cdot)$, $\hat{F}_{12u}(\cdot)$, $\hat{H}_0(\cdot)$ and $\hat{H}_1(\cdot)$ are empirical estimates of $F_{01u}(\cdot)$, $F_{12u}(\cdot)$, $H_0(\cdot)$ and $H_1(\cdot)$, respectively, as given by $\hat{F}_{01u}(\cdot) = n^{-1} \sum_{i=1}^{n} I(x_{0i} \leq x, \delta_{0i} = 1)$, $\hat{F}_{12u}(\cdot) = n_1^{-1} \sum_{i:\delta_{0i}=1}^{n} I(x_{1i} \leq x, \delta_{1i} = 1)$, $\hat{H}_0(\cdot) = n^{-1} \sum_{i=1}^{n} I(x_{0i} \leq x)$ and $\hat{H}_1(\cdot) = n_1^{-1} \sum_{i:\delta_{0i}=1} I(x_{1i} \leq x)$.

5.6.2 Proof of the Theorem for Progressive Illness-Death Model 1

Proof of Theorem 5.2.3: Note that, for $j = 1, \ldots, k$, $n_j/n \xrightarrow{a.s} P[T_{01} + \cdots + T_{j-1,j} < C] > 0$. So, $n_j \to \infty$ as $n \to \infty$. Write $p_j = [P(T_{01} + \cdots + T_{j-1,j} < C)]^{-1/2}$, which is consistently estimated by $(n_j/n)^{-1/2}$, for $j = 1, \ldots, k$. As in Result 5.6.3, $\sqrt{n_j} \left[\hat{F}_{j,j+1}(u) - F_{j,j+1}(u) \right]$ converges to a mean zero Gaussian process, say $Z_{F_{j,j+1}}(u)$, in $[0, \theta_j]$ for $\theta_j < \tau_j$, where $\tau_j = H_j^{-1}(1)$ with H_j being the conditional distribution function of $T_{j,j+1}$, given $C > T_{01} + \cdots + T_{j-1,j}$, for $j = 1, \ldots, k$. The theorem is proved by the method of induction as follows. Suppose that the theorem holds for $k = m$, i.e. $\sqrt{n} \left[\hat{F}_Q^{(m)}(q) - F_Q^{(m)}(q) \right]$ converges to mean-zero gaussian process, $Z_m(q)$, say. Now it is proved that the theorem is true for $k = m + 1$.

Note that

$$\begin{aligned}
&\sqrt{n}\left[\hat{F}_Q^{(m+1)}(q) - F_Q^{(m+1)}(q)\right] \\
&= \sqrt{n}\int_0^{\frac{q}{w_0}}\int_0^{\frac{q-w_0t_1}{w_1}}\cdots\int_0^{\frac{q-\sum_{j=0}^m w_jt_j}{w_{m+1}}} \hat{F}_{m+1,m+2}\left(\frac{q-\sum_{j=0}^m w_jt_j}{w_{m+1}}\right)\prod_{j=0}^m d\hat{F}_{j,j+1}(t_j) \\
&\quad -\sqrt{n}\int_0^{\frac{q}{w_1}}\int_0^{\frac{q-w_1t_1}{w_2}}\cdots\int_0^{\frac{q-\sum_{j=0}^m w_jt_j}{w_{m+1}}} F_{m+1,m+2}\left(\frac{q-\sum_{j=0}^m w_jt_j}{w_{m+1}}\right)\prod_{j=0}^m dF_{j,j+1}(t_j).
\end{aligned} \tag{5.29}$$

Define $Q^* = w_1T_{12} + \cdots + w_{m+1}T_{m+1,m+2}$ and let $F_{Q^*}^{(m)}(\cdot)$ be the distribution function of Q^*. Then

$$\begin{aligned}
F_{Q^*}^{(m)}(q - w_0t_1) &= P(Q^* \le q - w_0t_1) \\
&= \int_0^{\frac{q-w_0t_1}{w_1}}\cdots\int_0^{\frac{q-\sum_{j=0}^m w_jt_j}{w_{m+1}}} F_{m+1,m+2}\left(\frac{q-\sum_{j=0}^m w_jt_j}{w_{m+1}}\right) \\
&\qquad \times\prod_{j=1}^m dF_{j,j+1}(t_j)
\end{aligned}$$

and (5.29) can be written as

$$\begin{aligned}
&\sqrt{n}\left[\hat{F}_Q^{(m+1)}(q) - F_Q^{(m+1)}(q)\right] = \\
&\qquad \sqrt{n}\left[\int_0^{\frac{q}{w_0}} \hat{F}_{Q^*}^{(m)}(q - w_0t_1)d\hat{F}_{01}(t_1) - \int_0^{\frac{q}{w_0}} F_{Q^*}^{(m)}(q - w_0t_1)dF_{01}(t_1)\right] \\
&\qquad = B_{1n}^*(q) + B_{2n}^*(q) + B_{3n}^*(q), \text{ say,}
\end{aligned}$$

where

$$\begin{aligned}
B_{1n}^*(q) &= \int_0^{\frac{q}{w_0}} \sqrt{n}\left[\hat{F}_{Q^*}^{(m)}(q - w_0t_1) - F_{Q^*}^{(m)}(q - w_0t_1)\right] d\left(\hat{F}_{01}(t_1) - F_{01}(t_1)\right), \\
B_{2n}^*(q) &= \int_0^{\frac{q}{w_0}} \sqrt{n}\left[\hat{F}_{Q^*}^{(m)}(q - w_0t_1) - F_{Q^*}^{(m)}(q - w_0t_1)\right] dF_{01}(t_1) \text{ and} \\
B_{3n}^*(q) &= \int_0^{\frac{q}{w_0}} \sqrt{n}F_{Q^*}^{(m)}(q - w_0t_1)d\left(\hat{F}_{01}(t_1) - F_{01}(t_1)\right).
\end{aligned}$$

Integration by parts, as before, leads to

$$B_{3n}^*(q) = \int_0^q \sqrt{n}\left[\hat{F}_{01}\left(\frac{q-u}{w_0}\right) - F_{01}\left(\frac{q-u}{w_0}\right)\right] dF_{Q^*}^{(m)}(u).$$

This implies, using Result 5.6.2, that $B^*_{3n}(q) \xrightarrow{w} \int_0^q Z_{F_{01}}\left(\frac{q-u}{w_0}\right) dF^{(m)}_{Q^*}(u)$, a mean zero Gaussian process. By our assumption, $\sqrt{n}\left[\hat{F}^{(m)}_{Q^*}(\cdot) - F^{(m)}_{Q^*}(\cdot)\right]$ converges to a mean-zero Gaussian process, $Z^{(m)}_{Q^*}(\cdot)$, say. As in the proof of Theorem 5.2.2, $B^*_{1n}(q) \xrightarrow{P} 0$. Using the result for $k = m$, $B^*_{2n}(q) \xrightarrow{w} \int_0^{\frac{q}{w_0}} Z^{(m)}_{Q^*}(q - w_0 t_1) dF_{01}(t_1)$ another mean zero Gaussian process. Therefore, $\sqrt{n}\left[\hat{F}^{(m+1)}_{Q}(q) - F^{(m+1)}_{Q}(q)\right]$ converges to the mean-zero Gaussian process, $Z^{(m+1)}_{Q}(q)$, say,

$$\text{where } Z^{(m+1)}_{Q}(q) = \int_0^{\frac{q}{w_1}} Z_{Q^*}(q - w_0 t_1) dF_{01}(t_1) + \int_0^q Z_{F_{01}}\left(\frac{q-u}{w_0}\right) dF^{(m)}_{Q^*}(u).$$

Hence, the theorem is true for any k.

Variance expression for three state Model: Here the variance expression is derived for three state model, that is, for $k = 2$.

$$\begin{aligned} Z^{(3)}_{Q}(q) &= p_2 \int_0^{\frac{q}{w_0}} \left\{ \int_0^{\frac{q-w_0 t_1}{w_1}} Z_{F_{23}}\left(\frac{q - w_0 t_1 - w_1 t_2}{w_2}\right) dF_{12}(t_2) \right\} dF_{01}(t_1) \\ &\quad + p_1 \int_0^{\frac{q}{w_0}} \left\{ \int_0^{\frac{q-w_0 t_1}{w_2}} Z_{F_{12}}\left(\frac{q - w_0 t_1 - w_2 t_2}{w_1}\right) dF_{23}(t_2) \right\} dF_{01}(t_1) \\ &\quad + \int_0^q Z_{F_{01}}\left(\frac{q-u}{w_0}\right) dF^{(2)}_{Q^*}(u) \end{aligned}$$

Let $Z^*_{F_3}(s) = \int_0^{\frac{s}{w_1}} Z_{F_{23}}\left(\frac{s - w_1 t_2}{w_2}\right) dF_{12}(t_2)$
and $Z^*_{F_{12}}(s) = \int_0^{\frac{s}{w_2}} Z_{F_{12}}\left(\frac{s - w_2 t_2}{w_1}\right) dF_{23}(t_2)$.
It is clear that $Z^*_{F_3}(s)$ and $Z^*_{F_2}(s)$ are mean zero Gaussian processes. Now

$$\begin{aligned} Z^{(3)}_{Q}(q) &= p_2 \int_0^{\frac{q}{w_0}} Z^*_{F_{23}}(q - w_0 t_1) dF_{01}(t_1) + p_1 \int_0^{\frac{q}{w_0}} Z^*_{F_{12}}(q - w_0 t_1) dF_{01}(t_1) \\ &\quad + \int_0^q Z_{F_{01}}\left(\frac{q-u}{w_0}\right) dF^{(2)}_{Q^*}(u). \end{aligned}$$

$$\operatorname{cov}\Big[Z_Q^{(3)}(s), Z_Q^{(3)}(t)\Big]$$

$$\begin{aligned}
&= p_2^2 \int_0^{\frac{s}{w_0}} dF_{01}(r) \int_0^{\frac{t}{w_0}} \operatorname{cov}\left[Z^*_{F_{23}}(s-w_0r), Z^*_{F_{23}}(t-w_0u)\right] dF_{01}(u) \\
&\quad + p_1^2 \int_0^{\frac{s}{w_0}} dF_{01}(r) \int_0^{\frac{t}{w_0}} \operatorname{cov}\left[Z^*_{F_{12}}(s-w_0r), Z^*_{F_{12}}(t-w_0u)\right] dF_{01}(u) \\
&\quad + \int_0^{s} dF^{(2)}_{Q^*}(r) \int_0^{t} \operatorname{cov}\left[Z_{F_{01}}\left(\frac{s-r}{w_0}\right), Z_{F_{01}}\left(\frac{t-u}{w_0}\right)\right] dF^{(2)}_{Q^*}(u).
\end{aligned}$$

Now $\operatorname{cov}\left[Z^*_{F_{23}}(s-w_0r), Z^*_{F_{23}}(t-w_0u)\right]$

$$\begin{aligned}
&= \operatorname{cov}\left[\int_0^{\frac{s-w_0r}{w_1}} Z_{F_{23}}\left(\frac{s-w_0r-w_1t_2}{w_2}\right) dF_{12}(t_2), \right. \\
&\qquad \left. \int_0^{\frac{t-w_0u}{w_1}} Z_{F_{23}}\left(\frac{t-w_0u-w_1t_2}{w_2}\right) dF_{12}(t_2)\right] \\
&= \int_0^{\frac{s-w_0r}{w_1}} dF_{12}(y) \left\{ \int_0^{\frac{t-w_0u}{w_1}} \bar{F}_{23}\left(\frac{s-w_0r-w_1y}{w_2}\right) \bar{F}_{23}\left(\frac{t-w_0u-w_1z}{w_2}\right) \right. \\
&\quad \left. \times \int_0^{\min\left(\frac{s-w_0r-w_1y}{w_2}, \frac{t-w_0u-w_1z}{w_2}\right)} \frac{dF_{23u}(x)}{(1-H_2(x))^2} \right\} dF_{12}(z)
\end{aligned}$$

and $\operatorname{cov}\left[Z^*_{F_{12}}(s-w_0r), Z^*_{F_{12}}(t-w_0u)\right]$

$$\begin{aligned}
&= \int_0^{\frac{s-w_0r}{w_2}} dF_{23}(y) \left\{ \int_0^{\frac{t-w_0u}{w_1}} \bar{F}_{12}\left(\frac{s-w_0r-w_2y}{w_1}\right) \bar{F}_{12}\left(\frac{t-w_0u-w_2z}{w_1}\right) \right. \\
&\quad \left. \times \int_0^{\min\left(\frac{s-w_0r-w_1y}{w_2}, \frac{t-w_0u-w_1z}{w_2}\right)} \frac{dF_{12u}(x)}{(1-H_1(x))^2} \right\} dF_{23}(z).
\end{aligned}$$

Hence, $\operatorname{cov}\left[Z_Q^{(3)}(s), Z_Q^{(3)}(t)\right]$

$$\begin{aligned}
&= p_2^2 \int_0^{\frac{s}{w_0}} dF_{01}(r) \int_0^{\frac{t}{w_0}} \left[\int_0^{\frac{s-w_0r}{w_1}} dF_{12}(y) \int_0^{\frac{t-w_0u}{w_1}} \bar{F}_{23}(h_1)\bar{F}_{23}(h_2) \right. \\
&\qquad \left. \times \int_0^{\min(h_1,h_2)} \frac{dF_{23u}(x)}{(1-H_2(x))^2} dF_{12}(z) \right] dF_{01}(u) \\
&\quad + p_1^2 \int_0^{\frac{s}{w_0}} dF_{01}(r) \int_0^{\frac{t}{w_0}} \left[\int_0^{\frac{s-w_0r}{w_2}} dF_{23}(y) \int_0^{\frac{t-w_0u}{w_2}} \bar{F}_{12}(h_3)\bar{F}_{12}(h_4) \right. \\
&\qquad \left. \times \int_0^{\min(h_3,h_4)} \frac{dF_{12u}(x)}{(1-H_1(x))^2} dF_{23}(z) \right] dF_{01}(u)
\end{aligned}$$

$$+\int_0^s dF_{Q^*}^{(2)}(r)\left[\int_0^t \bar{F}_{01}\left(\frac{s-r}{w_0}\right)\bar{F}_{01}\left(\frac{t-u}{w_0}\right)\right.$$
$$\left.\times\left(\int_0^{\frac{s-r}{w_0}\wedge\frac{t-u}{w_0}}\frac{dF_{01u}(x)}{(1-H_0(x))^2}\right)dF_{Q^*}^{(2)}(u)\right], \tag{5.30}$$

where $h_1=(s-w_0r-w_1y)/w_2$, $h_2=(t-w_0u-w_1z)/w_2$, $h_3=(s-w_0r-w_2y)/w_1$ and $h_4=(t-w_0u-w_2z)/w_1$.

The variance of $\hat{F}_Q^{(2)}(q)$ can be consistently estimated by

$$\frac{n}{n_2}\int_0^{\frac{q}{w_0}} d\hat{F}_{01}(r)\int_0^{\frac{q}{w_0}}\left[\int_0^{\frac{q-w_0r}{w_1}} d\hat{F}_{12}(y)\int_0^{\frac{q-w_0u}{w_1}}\hat{\bar{F}}_{23}(h_1)\hat{\bar{F}}_{23}(h_2)\right.$$
$$\left.\times\int_0^{\min(h_1,h_2)}\frac{d\hat{F}_{23u}(x)}{(1-\hat{H}_2(x))^2}d\hat{F}_{12}(z)\right]d\hat{F}_{01}(u)$$
$$+\frac{n}{n_1}\int_0^{\frac{q}{w_0}} d\hat{F}_{01}(r)\int_0^{\frac{q}{w_0}}\left[\int_0^{\frac{q-w_0r}{w_2}} d\hat{F}_{23}(y)\int_0^{\frac{q-w_0u}{w_2}}\hat{\bar{F}}_{12}(h_3)\hat{\bar{F}}_{12}(h_4)\right.$$
$$\left.\times\int_0^{\min(h_3,h_4)}\frac{d\hat{F}_{12u}(x)}{(1-\hat{H}_1(x))^2}d\hat{F}_{23}(z)\right]d\hat{F}_{01}(u)$$
$$+\int_0^q d\hat{F}_{Q^*}^{(2)}(r)\left[\int_0^q \hat{\bar{F}}_{01}\left(\frac{q-r}{w_0}\right)\hat{\bar{F}}_{01}\left(\frac{q-u}{w_0}\right)\right.$$
$$\left.\times\left(\int_0^{\frac{q-r}{w_0}\wedge\frac{q-u}{w_0}}\frac{d\hat{F}_{01u}(x)}{(1-\hat{H}_0(x))^2}\right)d\hat{F}_{Q^*}^{(2)}(u)\right], \tag{5.31}$$

where $\hat{F}_{01u}(\cdot)$, $\hat{F}_{12u}(\cdot)$, $\hat{H}_0(\cdot)$ and $\hat{H}_1(\cdot)$ are empirical estimates of $F_{01u}(\cdot)$, $F_{12u}(\cdot)$, $H_0(\cdot)$ and $H_1(\cdot)$, respectively, as defined in the context of two-state model; $\hat{F}_{23u}(\cdot)$ and $\hat{H}_2(\cdot)$ are empirical estimates of $F_{23u}(\cdot)$ and $H_2(\cdot)$, respectively, similarly defined corresponding to the sojourn time in health state 3; $\hat{F}_{Q^*}^{(2)}(\cdot)$ is the non-parametric estimate of $F_{Q^*}^{(2)}(\cdot)$, the distribution function of $Q^*=w_1T_{12}+w_2T_{23}$ as obtained by using the method of Section 5.2 and is given by

$$\hat{F}_{Q^*}^{(2)}(r)=\int_0^{\frac{r}{w_1}}\hat{F}_{23}\left(\frac{r-w_1x}{w_2}\right)d\hat{F}_{12}(x).$$

5.6.3 EM Algorithm in the Unobserved Case

The steps of the EM algorithm for estimating QAL distribution in unobserved case (Section 5.2.2) is discussed below. Note that the complete data likelihood is

$$\begin{aligned} L_c(\underset{\sim}{\lambda_0}, \underset{\sim}{\lambda_1}) &= \prod_{j=1}^{k_1} \left[\lambda_{0j}^{d_{0j}} (1-\lambda_{0j})^{n_{0j}-d_{0j}}\right] \prod_{j=1}^{k_2} \left[\lambda_{1j}^{d_{1}j} (1-\lambda_{1j})^{n_{1j}-d_{1j}}\right] \\ &\quad \times \prod_{i:\delta_i=4} \prod_{l:t_{0(l)}<x'_{1i}} \left[\lambda_{0l} \left(\prod_{j<l}(1-\lambda_{0j})\right) \left(\prod_{j:t_{1(j)}\le x'_{1i}-t_{0(l)}} (1-\lambda_{1j})\right)\right]^{I_{4li}} \\ &\quad \times \prod_{i:\delta_i=5} \prod_{l:t_{0(l)}<x'_{1i}} \left[\lambda_{0l} \left(\prod_{j<l}(1-\lambda_{0j})\right) \lambda_{1l_{(i)}} \left(\prod_{j<l_{(i)}} (1-\lambda_{1j})\right)\right]^{I_{5li}}, \end{aligned}$$

where $I_{4li} = 1$ if $x_{0i} = t_{0(l)}$ and 0 otherwise, for i with $\delta_i = 4$, and $I_{5li} = 1$ if $x_{0i} = t_{0(l)}$ and 0 otherwise, for i with $\delta_i = 5$. After some rearrangements of terms, we have

$$L_c(\underset{\sim}{\lambda_0}, \underset{\sim}{\lambda_1}) = \left[\prod_{j=0}^{k_1} \lambda_{0j}^{d^*_{0j}} (1-\lambda_{0j})^{n^*_{0j}-d^*_{0j}}\right] \left[\prod_{j=0}^{k_2} \lambda_{1j}^{d^*_{1j}} (1-\lambda_{1j})^{n^*_{1j}-d^*_{1j}}\right],$$

where $d^*_{0j} = d_{0j} + \sum_{i:\delta_i=4, x'_{1i}>t_{0(j)}} I_{4ji} + \sum_{i:\delta_i=5, x'_{1i}>t_{0(j)}} I_{5ji}$,

$$n^*_{0j} = n_{0j} + \sum_{l\ge j} \left[\sum_{i:\delta_i=4, x'_{1i}\ge t_{0(j)}} I_{4li} + \sum_{i:\delta_i=5, x'_{1i}>t_{0(j)}} I_{5li}\right],$$

$$d^*_{1j} = d_{1j} + \sum_{i:\delta_i=5, x'_{1i}>t_{1(j)}} I_{5j^{(i)}i}, \text{ and}$$

$$n^*_{1j} = n_{1j} + \sum_{i:\delta_i=4} \sum_{l:x'_{1i}-t_{0(l)}\ge t_{1(j)}} I_{4li} + \sum_{i:\delta_i=5} \sum_{l:x'_{1i}-t_{0(l)}>t_{1(j)}} I_{5li}.$$

Here, for those i with $\delta_i = 5$ and j with $x'_{1i} > t_{1(j)}$, $j^{(i)}$ is such that $t_{1(j)} = x'_{1i} - t_{0(j^{(i)})}$.

In the application of EM algorithm, we consider, in the E-step,

$$E\left[\log L_c\left(\underset{\sim}{\lambda_0}, \underset{\sim}{\lambda_1}\right) | \text{Observed data }, \underset{\sim}{\lambda_0} = \overset{0}{\underset{\sim}{\lambda_0}}, \underset{\sim}{\lambda_1} = \overset{0}{\underset{\sim}{\lambda_1}}\right]$$

the conditional expectation of logarithm of complete data likelihood, given observed data and an initial estimate $\{\underset{\sim}{\lambda}_0 = \overset{0}{\underset{\sim}{\lambda}}_0, \underset{\sim}{\lambda}_1 = \overset{0}{\underset{\sim}{\lambda}}_1\}$. This reduces to finding

$$\begin{aligned} I^0_{4li} &= E\left[I_{4li}|\delta_i = 4, x'_{1i}, \underset{\sim}{\lambda}_0 = \overset{0}{\underset{\sim}{\lambda}}_0, \underset{\sim}{\lambda}_1 = \overset{0}{\underset{\sim}{\lambda}}_1\right] \\ &= \frac{\lambda^0_{0l}\left[\prod_{j<l}(1-\lambda^0_{0j})\right]\left[\prod_{j:t_{1(j)}\le x'_{1i}-t_{0(l)}}(1-\lambda^0_{1j})\right]}{\sum_{l':t_{0(l')}<x'_{1i}}\lambda^0_{0l'}\left[\prod_{j<l'}(1-\lambda^0_{0j})\right]\left[\prod_{j:t_{1(j)}\le x'_{1i}-t_{0(l')}}(1-\lambda^0_{1j})\right]} \end{aligned}$$

and

$$\begin{aligned} I^0_{5li} &= E\left[I_{5li}|\delta_i = 5, x'_{1i}, \underset{\sim}{\lambda}_0 = \overset{0}{\underset{\sim}{\lambda}}_0, \underset{\sim}{\lambda}_1 = \overset{0}{\underset{\sim}{\lambda}}_1\right] \\ &= \frac{\lambda^0_{0l}\left[\prod_{j<l}(1-\lambda^0_{0j})\right]\left[\lambda^0_{1l_{(i)}}\prod_{j<l_{(i)}}(1-\lambda^0_{1j})\right]}{\sum_{l':t_{0(l')}<x'_{1i}}\lambda^0_{0l'}\left[\prod_{j<l'}(1-\lambda^0_{0j})\right]\left[\lambda^0_{1l_{(i)}}\prod_{j<l_{(i)}}(1-\lambda^0_{1j})\right]}. \end{aligned}$$

When d^*_{ij} and n^*_{ij}, for $i = 0, 1$, are computed with I_{4li} and I_{5li} replaced by I^0_{4li} and I^0_{5li}, respectively, suppose they are denoted by d^{*0}_{ij} and n^{*0}_{ij}, respectively. The M-step is now simple giving improved estimates of λ_{0j} and λ_{1j} as $\lambda^1_{0j} = \dfrac{d^{*0}_{0j}}{n^{*0}_{0j}}$ and $\lambda^1_{1j} = \dfrac{d^{*0}_{1j}}{n^{*0}_{1j}}$, respectively.

5.6.4 Proofs of the Theorems for Simple Illness-Death Model 2

Define $\Lambda^*_{hj}(t) = \int_0^t J_h(u)\lambda_{hj}(u)du$ and $M_{hj} = \sum_{i=1}^n M_{hji}$, for $hj = 01, 02, 12$. Then, using Theorem IV.1.1 and IV.1.2 of Andersen et al. (1993, p 190-191) and under the conditions therein, the following results hold.

RESULT 5.6.4

(i) $\sup_{u\in[0,\tau)} |\hat{\Lambda}_{hj}(u) - \Lambda_{hj}(u)| \xrightarrow{P} 0.$

(ii) $$\sqrt{n}\left\{\hat{\Lambda}_{hj}(t) - \Lambda_{hj}(t)\right\} = \sqrt{n}\left\{\hat{\Lambda}_{hj}(t) - \Lambda^{*}_{hj}(t)\right\} + o_p(1)$$
$$= \sqrt{n}\int_0^t \frac{J_h(u)dM_{hj}(u)}{Y_h(u)} + o_p(1) \quad \textit{for } t \in [0,\tau).$$

(iii) *The process* $\sqrt{n}[\hat{\Lambda}_{hj}(\cdot) - \Lambda_{hj}(\cdot)]$ *converges weakly on* $[0,\theta]$, *with* $\theta < \tau$, *to a zero-mean Gaussian process with finite variance function.*

Note that the above results (i)-(iii) hold when τ is replaced by τ_0, for $hj = 01, 02$, and τ_1, for $hj = 12$.

RESULT 5.6.5 *Using Result 5.6.4, the following results (See Shu et al., 2007) hold.*

(i) $$\sqrt{n}[\hat{S}_0(u) - S_0(u)] = -S_0(u)\left[\sqrt{n}\{\hat{\Lambda}_{01}(u) - \Lambda_{01}(u)\} + \sqrt{n}\{\hat{\Lambda}_{02}(u) - \Lambda_{02}(u)\}\right]$$
$$+o_p(1), u \in [0,\tau_0)$$
$$\sqrt{n}[\hat{S}_{12}(u) - S_{12}(u)] = -S_{12}(u)\sqrt{n}\{\hat{\Lambda}_{12}(u) - \Lambda_{12}(u)\} + o_p(1), u \in [0,\tau_1).$$

(ii) $\sup_{u\in[0,\tau_0)} |\hat{S}_0(u) - S_0(u)| \xrightarrow{P} 0.$

$\sup_{u\in[0,\tau_1)} |\hat{S}_{12}(u) - S_{12}(u)| \xrightarrow{P} 0.$

Proof of Theorem 5.3.1: Using Results 5.6.4 and 5.6.5,

$$\sqrt{n}\left[\hat{S}_0\left(\frac{q}{w_0}\right) - S_0\left(\frac{q}{w_0}\right)\right] = n^{-1/2}\sum_{i=1}^{n}\left\{W^{(0)}_{1i}(q) + W^{(0)}_{2i}(q)\right\} + o_p(1), \quad (5.32)$$

where $W^{(0)}_{1i}(q) = -nS_0\left(\frac{q}{w_0}\right)\int_0^{\frac{q}{w_0}} \frac{J_0(u)dM_{01i}(u)}{Y_0(u)}$

and $W^{(0)}_{2i}(q) = -nS_0\left(\frac{q}{w_0}\right)\int_0^{\frac{q}{w_0}} \frac{J_0(u)dM_{02i}(u)}{Y_0(u)}$.

Note that, for each q, the right hand side of (5.32) is essentially a sum of n independent and identically distributed zero-mean random variables. Using the arguments of Shu et al. (2007), it can be concluded that $\sqrt{n}\left[\hat{S}_0(\cdot) - S_0(\cdot)\right]$ converges weakly to a zero-mean Gaussian process with covariance function at $\left(\frac{q}{w_0}, \frac{q'}{w_0}\right)$ given by

$$\begin{aligned}
\psi^{(0)}\left(\frac{q}{w_0}, \frac{q'}{w_0}\right) &= \frac{1}{n}\sum_{i=1}^{n} \operatorname{cov}\left\{W_{1i}^{(0)}(q) + W_{2i}^{(0)}(q), W_{1i}^{(0)}(q') + W_{2i}^{(0)}(q')\right\} \\
&= nS_0\left(\frac{q}{w_0}\right) S_0\left(\frac{q'}{w_0}\right) E\left\{\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}} \frac{J_0(u)d\Lambda_{01}(u)}{Y_0(u)}\right\} \\
&\quad + nS_0\left(\frac{q}{w_0}\right) S_0\left(\frac{q'}{w_0}\right) E\left\{\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}} \frac{J_0(u)d\Lambda_{02}(u)}{Y_0(u)}\right\},
\end{aligned}$$

which, for $q = q'$, can be consistently estimated by (5.7) in Section 5.3.

Proof of Theorem 5.3.2: Following the similar decomposition technique as that used in Voelkel and Crowley (1984) and Shu et al. (2007), it can be shown that

$$\begin{aligned}
\sqrt{n}\left[\hat{P}_{12}\left(\frac{q}{w_0}\right) - P_{12}\left(\frac{q}{w_0}\right)\right] &= n^{-1/2}\sum_{i=1}^{n}\left\{W_{1i}^{(12)}(q) + W_{2i}^{(12)}(q)\right. \\
&\quad \left. + W_{3i}^{(12)}(q)\right\} + o_p(1), \qquad (5.33)
\end{aligned}$$

where

$$\begin{aligned}
W_{1i}^{(12)}(q) &= n\int_0^{\frac{q}{w_0}} \left\{S_0(u)S_{12}\left(\frac{q - w_0u}{w_1}\right) - \int_u^{\frac{q}{w_0}} S_0(x)S_{12}\left(\frac{q - w_0x}{w_1}\right) d\Lambda_{01}(x)\right\} \\
&\quad \times \frac{J_0(u)dM_{01i}(u)}{Y_0(u)}, \\
W_{2i}^{(12)}(q) &= -n\int_0^{\frac{q}{w_0}} \left\{\int_u^{\frac{q}{w_0}} S_0(x)S_{12}\left(\frac{q - w_0x}{w_1}\right) d\Lambda_{01}(x)\right\} \frac{J_0(u)dM_{02i}(u)}{Y_0(u)}
\end{aligned}$$

and

$$W_{3i}^{(12)}(q) = -n\int_0^{\frac{q}{w_1}} \left\{\int_0^{\frac{q-w_1u}{w_0}} S_0(x)S_{12}\left(\frac{q - w_0x}{w_1}\right) d\Lambda_{12}(x)\right\} \frac{J_1(u)dM_{12i}(u)}{Y_1(u)}.$$

Note that, for each q, the right hand side of (5.33) is essentially a sum of n independent and identically distributed zero-mean random variables. Using the arguments of Shu et al. (2007), it follows that $\sqrt{n}\left[\hat{P}_{12}(\cdot) - P_{12}(\cdot)\right]$ converges weakly to a zero-mean Gaussian process with covariance function at $\left(\frac{q}{w_0}, \frac{q'}{w_0}\right)$ given by $\psi^{(12)}\left(\frac{q}{w_0}, \frac{q'}{w_0}\right)$

$$
\begin{aligned}
= \quad & \frac{1}{n}\sum_{i=1}^{n} \operatorname{cov}\Big\{W_{1i}^{(12)}(q) + W_{2i}^{(12)}(q) + W_{3i}^{(12)}(q), \\
& \qquad W_{1i}^{(12)}(q') + W_{2i}^{(12)}(q') + W_{3i}^{(12)}(q')\Big\} \\
= \quad & E\left[\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}} \left\{S_0(u)S_{12}\left(\frac{q-w_0u}{w_1}\right) - \int_u^{\frac{q}{w_0}} S_0(x)S_{12}\left(\frac{q-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\}\right. \\
& \times\left\{S_0(u)S_{12}\left(\frac{q'-w_0u}{w_1}\right) - \int_u^{\frac{q'}{w_0}} S_0(x)S_{12}\left(\frac{q'-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\} \\
& \qquad \left.\times nJ_0(u)\frac{d\Lambda_{01}(u)}{Y_0(u)}\right] \\
& + E\left[\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}} \left\{\int_u^{\frac{q}{w_0}} S_0(x)S_{12}\left(\frac{q-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\}\right. \\
& \quad \left.\times\left\{\int_u^{\frac{q'}{w_0}} S_0(x)S_{12}\left(\frac{q'-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\} nJ_0(u)\frac{d\Lambda_{02}(u)}{Y_0(u)}\right] \\
& + E\left[\int_0^{\frac{q}{w_1}\wedge\frac{q'}{w_1}} \left\{\int_0^{\frac{q-w_1u}{w_0}} S_0(x)S_{12}\left(\frac{q-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\}\right. \\
& \quad \left.\times\left\{\int_0^{\frac{q'-w_1u}{w_0}} S_0(x)S_{12}\left(\frac{q'-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\} nJ_1(u)\frac{d\Lambda_{12}(u)}{Y_1(u)}\right],
\end{aligned}
$$

which, for $q = q'$, can be consistently estimated by (5.8) in Section 5.3.

Proof of Theorem 5.3.3: Note that

$$
\begin{aligned}
\sqrt{n}\left[\hat{S}_Q(q) - S_Q(q)\right] \quad = \quad & \sqrt{n}\left[\hat{S}_0\left(\frac{q}{w_0}\right) - S_0\left(\frac{q}{w_0}\right)\right] \\
& + \sqrt{n}\left[\hat{P}_{12}\left(\frac{q}{w_0}\right) - P_{12}\left(\frac{q}{w_0}\right)\right].
\end{aligned}
$$

Hence, by some rearrangement of terms following the techniques used in the proofs of Theorems 5.3.1 and 5.3.2, $\sqrt{n}\left[\hat{S}_Q(q) - S_Q(q)\right]$ can be written as a sum of n independent and identically distributed zero mean random variables. The weak convergence result follows by using the same arguments. The covariance term in Theorem 5.3.3 is given by

$$
\begin{aligned}
&\operatorname{cov}\left[\sqrt{n}\left\{\hat{S}_0\left(\tfrac{q}{w_0}\right) - S_0\left(\tfrac{q}{w_0}\right)\right\}, \sqrt{n}\left\{\hat{P}_{12}\left(\tfrac{q}{w_0}\right) - P_{12}\left(\tfrac{q}{w_0}\right)\right\}\right] \\
&= \frac{1}{n}\sum_{i=1}^{n} \operatorname{cov}\left\{W_{1i}^{(0)}(q) + W_{2i}^{(0)}(q), W_{1i}^{(12)}(q) + W_{2i}^{(12)}(q) + W_3^{(12)}(q)\right\} \\
&= -nS_0\left(\frac{q}{w_0}\right) E\left[\int_0^{\frac{q}{w_0}} \left\{S_0(u) S_{12}\left(\frac{q - w_0 u}{w_1}\right)\right.\right. \\
&\qquad \left.\left. - \int_u^{\frac{q}{w_0}} S_0(x) S_{12}\left(\frac{q - w_0 x}{w_1}\right) d\Lambda_{01}(x)\right\}\right. \\
&\qquad \left. \times J_0(u) \frac{d\Lambda_{01}(u)}{Y_0(u)}\right] \\
&\quad + nS_0\left(\frac{q}{w_0}\right) E\left[\int_0^{\frac{q}{w_0}} \left\{\int_u^{\frac{q}{w_0}} S_0(x) S_{12}\left(\frac{q - w_0 x}{w_1}\right) d\Lambda_{01}(x)\right\} J_0(u) \frac{d\Lambda_{02}(u)}{Y_0(u)}\right],
\end{aligned}
$$

which can be consistently estimated by n times the expression (5.10) in Section 5.3.

Chapter 6

Regression Analysis of QAL Data to Study Covariate Effect

6.1 Introduction

This chapter considers estimation of QAL distribution with covariate effect assuming some suitable regression model. Regression analysis of QAL data has received less attention than the problem of estimating the QAL distribution. Cole et al. (1993) have considered a Cox-type parametric regression model to estimate mean QAL using bootstrap method to obtain the variance estimate. Fine and Gelber (2001) have considered a semi-parametric bivariate linear regression model to estimate the ratio of mean lifetimes, or mean QALs, corresponding to two different covariate values. Wang and Zhao (2007) have considered the problem of estimating the mean QAL in the presence of covariates. They have considered a regression model for the mean QAL and used the idea of inverse probability weighting to construct a simple weighted estimating equation for the regression parameters of the model. These parameter estimates are then used to estimate the mean QAL. See also Tunes-da-Silva et al. (2009) for a regression analysis to

estimate mean QAL for semi-Markov multistate non-progressive processes.

In the proposed method of estimating the QAL distribution either by parametric or nonparametric method in Chapters 4 and 5, respectively, the theoretical expression for the QAL distribution is first derived and then the sojourn time distributions are substituted by their estimates obtained by standard survival analysis techniques. This helps one to estimate the covariate effect, in addition to the sojourn time distributions, in a simple manner. Suppose one or more of the sojourn time distributions are possibly affected by some covariates, denoted by $\mathbf{Z}= (Z^{(1)}, \ldots, Z^{(p)})$(say), as in ordinary survival data. This dependence may be incorporated through usual regression modeling. For example, in the case of a hazard regression model, the theoretical expression for the QAL distribution remains the same except that the hazard rates are replaced by their regression forms in the expression. The estimates of the model parameters are obtained from the sojourn time data (some of which may be unobserved) with covariates, which can be similarly substituted in the theoretical expression to obtain the estimate of QAL distribution for an individual with a particular covariate value. In this work, both parametric and semi-parametric approaches are considered to estimate the QAL distribution with covariate effect. In addition to estimating the QAL distributions, an additional objective is to assess the covariate effects.

This chapter is organised as follows. The distribution of QAL with covariate effect is considered in Section 6.2. Parametric and semi-parametric methods of estimating QAL distribution are discussed in Sections 6.3 and 6.4, respectively. Some conclusions are made in Section 6.5. The Appendix in Section 6.6 gives proofs of the theorems stated in this chapter.

6.2 Distribution of QAL with Covariate Effect

In this section, the expression of the QAL distribution is derived for a given covariate value. The progressive illness-death model 2 (See Figure 2.4) is considered to study the covariate effect on QAL data, since the models in Figures 2.1, 2.2 and 2.3 are special cases of this model. The QAL distribution is estimated under the assumption that the different sojourn times are independently distributed. As mentioned in Section 2.3.2, the transition from state h to either state $h+1$ or to state $k+1$, for $h = 0, 1, \ldots, k-1$, constitutes a competing risks framework with $T_{h,h+1}$ and $T_{h,k+1}$ (see Figure 2.4) denoting the two corresponding conceptual sojourn times. Let $\lambda_{h,h+1}(x_h; \mathbf{Z})$ and $\lambda_{h,k+1}(x_h; \mathbf{Z})$ be the cause specific hazards for the two possible transitions to state $h+1$ or $k+1$, respectively, at time x_h, for an individual with covariate vector $\mathbf{Z}$. Note that, for $h = k$, $T_{h,h+1}$ and $T_{h,k+1}$ are the same random variable representing the actual sojourn time in state k before death with ordinary hazard rate $\lambda_{k,k+1}(x_k; \mathbf{Z})$ at time x_k.

In general, let $\lambda_{hj}(\cdot;\cdot)$ be the rate of the $h \to j$ transition. It is assumed that the transition rates depend only on the sojourn time in the current state and this leads to a semi-Markov model in which successive sojourn times are independent. The dependence of the transition rates on the covariates are specified via proportional hazards regression model, as given by

$$\lambda_{hj}(t; \mathbf{Z}_i) = \lambda_{hj0}(t) \exp\left(\beta^T \mathbf{Z}_{hji}\right), \tag{6.1}$$

where $\lambda_{hj0}(t)$ is the baseline rate for the $h \to j$ transition, β is the vector of regression coefficients, $\mathbf{Z}_{hji}$ is the vector of state-specific covariates for individual i obtained from the basic covariates $\mathbf{Z}_i$ (see Andersen et. al. 1993, p. 478) and

$$hj = \begin{cases} (h, h+1), (h, k+1) & \text{for } h = 0, 1, \ldots, k-1 \\ (h, h+1) & \text{for } h = k. \end{cases}$$

For example, in the context of simple illness-death model 2 (see Figure 2.2) for heart transplant data (Section 4.2.4), let $\mathbf{Z}_i = (Z_i^{(1)}, Z_i^{(2)}, Z_i^{(3)})^T$, where $Z_i^{(1)}$= an indicator for previous history of surgery, $Z_i^{(2)}$= age at acceptance into the program and $Z_i^{(3)}$ = mismatch score. Note that the mismatch score is available after heart transplantation. Hence, it affects T_{12} only. The state-specific covariate vector $\mathbf{Z}_{hji}$ is formed to be a 7-variate vector by including the extra components equal to zero, where hj= 01, 02, and 12. The state-specific covariate vectors are $\mathbf{Z}_{01i} = (Z_i^{(1)}, Z_i^{(2)}, 0, 0, 0, 0, 0)$, $\mathbf{Z}_{02i} = (0, 0, Z_i^{(1)}, Z_i^{(2)}, 0, 0, 0)$ and $\mathbf{Z}_{12i} = (0, 0, 0, 0, Z_i^{(1)}, Z_i^{(2)}, Z_i^{(3)})$. In parametric approach, the baseline hazard $\lambda_{hj0}(t)$ has a particular parametric form. For example, with constant hazard rates, that is for $\lambda_{hj0}(t)$= λ_{hj}, the state-specific hazard rate becomes $\lambda_{hj}(t; \mathbf{Z})$= λ_{hj} $\exp\left(\beta^T \mathbf{Z}_{hj}\right)$. In semi-parametric approach, the baseline hazard $\lambda_{hj0}(t)$ is taken as arbitrary, that is Cox's (1972) proportional hazard regression model is considered.

The distribution function of Q in progressive illness-death model 2 for the given covariate $\mathbf{Z}_0$, and state-specific covariate $\mathbf{Z}_{hj0}$, is given by (see Section 2.3.2)

$$F_Q^{(k)}(q; \mathbf{Z}_0) = P(Q \leq q) = \sum_{m=0}^{k} P_m, \tag{6.2}$$

where the expressions for P_0, P_m and P_k are as follows.

$$P_0 = \int_0^{\frac{q}{w_0}} \lambda_{0,k+1}(x; \mathbf{Z}_0) e^{-(\Lambda_{01}(x;\mathbf{Z}_0)+\Lambda_{0,k+1}(x;\mathbf{Z}_0))} dx = \int_0^{\frac{q}{w_0}} S_0(x; \mathbf{Z}_0) d\Lambda_{0,k+1}(x; \mathbf{Z}_0),$$

$$\begin{aligned} P_m = & \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{i=0}^{m-1} w_i x_i}{w_m}} S_m(x_m; \mathbf{Z}_0) d\Lambda_{m,k+1}(x_m; \mathbf{Z}_0) \\ & \times S_{m-1}(x_{m-1}; \mathbf{Z}_0) d\Lambda_{m-1,m}(x_{m-1}; \mathbf{Z}_0) \\ & \vdots \\ & \times S_0(x_0; \mathbf{Z}_0) d\Lambda_{01}(x_0; \mathbf{Z}_0), \end{aligned}$$

for $m = 1, \ldots, k-1$, and

$$\begin{aligned} P_k &= \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{i=0}^{k-2} w_i x_i}{w_{k-1}}} F_{k,k+1}\left(\frac{q-\sum_{i=0}^{k-1} w_i x_i}{w_k}; \mathbf{Z}_0\right) \\ &\quad \times S_{k-1}(x_{k-1}; \mathbf{Z}_0) d\Lambda_{k-1,k}(x_{k-1}; \mathbf{Z}_0) \\ &\quad \vdots \\ &\quad \times S_0(x_0; \mathbf{Z}_0) d\Lambda_{01}(x_0; \mathbf{Z}_0), \end{aligned}$$

where $S_h(x; \mathbf{Z}_0) = \exp\left[-\Lambda_{h,h+1}(x; \mathbf{Z}_0) - \Lambda_{h,k+1}(x; \mathbf{Z}_0)\right]$, for $h = 0, 1, \ldots, k-1$, $\Lambda_{i,j}(x) = \int_0^x \lambda_{i,j}(u)du$ and $F_{k,k+1}(\cdot)$ is the distribution function of $T_{k,k+1}$.

6.3 Parametric Estimation of QAL Distribution with Covariate Effect

In this section, the parametric estimation of QAL distribution with covariate effect is considered. The theoretical expression for the QAL distribution remains the same except that the hazard rates are replaced by their regression forms in the expression. Following the notation in Section 4.3.2, the data set for n individuals is given by $\{(x_{hi},\ \delta_{hi},\ \mathbf{Z}_i),\ h = 0, 1, \ldots, k, i = 1, \ldots, n\}$. The model parameters are estimated by maximum likelihood method based on sojourn time data (some of which may be unobserved). The likelihood function can be easily written using the likelihood function of Section 4.3.2, where state-specific hazard rates are raplecd by those in (6.1) for some specific parametric form of baseline hazard. The estimate of QAL distribution for a given covariate value is obtained by substituting the parameters by their estimates. The standard error of the estimate is obtained by delta method. The proposed method of parametric estimation of QAL distribution is illustrated by two examples.

Example 1: The data set of Stanford Heart Transplant Program (See Section 1.5.1) is used to illustrate the proposed methodology. In this example, the

survival function for QAL distribution is estimated for the heart patients by incorporating covariate effect. The set-up of simple illness-death model 2 is considered and, for the sake of illustration, only the effect of mismatch score (Z, say) is considered. Mismatch scores are available for 65 patients out of the 69, who went through heart transplantation. The covariate analysis is based on the data of 65 patients. The effect of mismatch score is considered on post transplant survival time, that is, on T_{12} only. The hazard rate for T_{12} given $Z = z$ is taken as $\lambda_{12}(y|x, z) = p_{12}\lambda_{12}(\lambda_{12}y)^{p_{12}-1}e^{\theta z}$. The model parameters are estimated by maximum likelihood method. The parameters are estimated in both observed and unobserved cases (See Section 4.2.4).

For the observed case, the estimate of parameters in $\lambda_{01}(\cdot)$ and $\lambda_{02}(\cdot)$ do not change, since these are not affected by Z. These estimates are available in Table 4.7 of Section 4.2.4. Based on observations on T_{12} only, the maximum likelihood estimates are $\hat{p}_{12}$=0.5746, $\hat{\lambda}_{12}$=0.0005 and $\hat{\theta}$=0.6148 with standard errors 0.0754, 0.0003 and 0.2920, respectively. So, the dependence on Z given by the parameter θ, is significant. One can now estimate survival probabilities for QAL using the above estimates for a particular value of Z. The standard error can be calculated by the delta method. For example, given $z = 0.46$, the survival probability $S(q)$ at $q = 40$ is estimated as 0.6551 with standard error 0.0428.

For the unobserved case, the estimated value of the parameter θ is 0.6310 with standard error 0.2930 (indicating significance of θ). Further, for $z = 0.46$, the estimated survival probability at $q = 40$ is 0.6494 with standard error 0.0455.

Example 2: The data set of IBCSG Trial V (See Section 1.5.2) is used to illustrate the proposed method for progressive illness-death model. In this example, the survival function of QAL for the cancer patients of IBCSG Trial V (See Section 4.3.4) with covariate effect is estimated. For illustration, only two covariates, namely, age (Z_1, say) and tumor size (Z_2, say), are considered. Further, it is assumed that Z_1 and Z_2 have effect on TWiST, that is on T_{12}, only, for

the sake of illustration. The hazard rate for T_{12} given (Z_1, Z_2)=(z_1, z_2) is modeled as $\lambda_{12}(y|x) = \lambda_{12}\exp(\theta_1 z_1 + \theta_2 z_2)$ in Treatment Group 0, and $\lambda_{12}(y|x) = \alpha_{12}\lambda_{12}(\lambda_{12}y)^{\alpha_{12}-1}\exp(\theta_1 z_1 + \theta_2 z_2)$ in Treatment Group 1. In Group 0, the maximum likelihood estimates of the parameters are $\hat{\lambda}_{12} = 0.0233$, $\hat{\theta}_1 = -0.0199$ and $\hat{\theta}_2 = 0.0138$ with standard errors 0.0082, 0.0066 and 0.0035, respectively, while the same in Treatment Group 1 are $\hat{\alpha}_{12} = 0.8491$, $\hat{\lambda}_{12} = 0.0056$, $\hat{\theta}_1 = -0.0022$ and $\hat{\theta}_2 = 0.0119$ with standard errors 0.0388, 0.0007, 0.0028 and 0.0029, respectively. Therefore, in Treatment Group 0, both age and tumor size have significant effect on the hazard rate of TWiST; age has decreasing effect while tumor size has increasing effect. In Treatment Group 1, however, age does not seem to have significant effect, whereas tumor size has significant increasing effect on the hazard rate of TWiST. The QAL survival probabilities can be easily estimated using the above estimates and for particular values of Z_1 and Z_2. For example, given $Z_1 = 49$ and $Z_2 = 50$, the estimated survival probability at $q = 20$, is 0.8754 with standard error 0.0236 in Treatment Group 0 and 0.8949 with standard error 0.0094 in Treatment Group 1.

6.4 Semi-Parametric estimation of QAL Distribution

The semi-parametric method of estimating the QAL distribution is considered first for the simple illness-death model 2 (Figure 2.2) and then it is extended to progressive illness-death model 2. It is assumed that the transition rates depend on the sojourn time in the current state (a semi-Markov model) in which T_0 and T_{12} are independent. The dependence of the transition rates on the covariates are specified via Cox's (1972) proportional hazards regression model as given by (6.1). The survival function for the given covariate $\mathbf{Z}_0$, and state-specific covariate $\mathbf{Z}_{hj0}$,

is given by (See Section 2.2.2)

$$S_Q(q;\mathbf{Z}_0) = S_0\left(\frac{q}{w_0};\mathbf{Z}_0\right) + P_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right), \text{say} \tag{6.3}$$

$$\text{where } S_0(\frac{q}{w_0};\mathbf{Z}_0) = \exp\left[-\int_0^{q/w_0}\{\lambda_{01}(u;\mathbf{Z}_0)+\lambda_{02}(u;\mathbf{Z}_0)\}\,du\right]$$

$$\text{and } P_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right) = \int_0^{q/w_0} S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right) S_0(x;\mathbf{Z}_0)d\Lambda_{01}(x;\mathbf{Z}_0),$$

where $\Lambda_{hj}(x) = \int_0^x \lambda_{hj}(u;\mathbf{Z}_0)du$, for hj=01 and 02, and $S_{12}(\cdot,\mathbf{Z}_0)$ is the survival function of T_{12} for given $\mathbf{Z}_0$.

It may be noted that the semi-Markov model does not fit readily into the multiplicative intensity framework because of its renewal nature (See Voelkel and Crowley, 1984, and Shu et al. 2007). This can be dealt with by introducing time-shifted multivariate counting process over a fixed interval, say $[0,\tau]$, given by

$$\mathbf{N}(x) = \{N_{hji}(x), hj = 01, 02, 12;\ i = 1,\ldots,n, x \in [0,\tau]\},$$

where $N_{hji}(x)$ counts the number of $h \to j$ transitions for individual i whose transition time from state h to state j is less than or equal to x, for hj =01, 02 and 12. Note that such formulated counting process $N_{hji}(x)$ have the intensity processes $\alpha_{hji}(x;\mathbf{Z}_i)$ in the form of a multiplicative intensity model given by

$$\alpha_{hji}(x;\mathbf{Z}_i) = Y_{hi}(x)\lambda_{hj}(x;\mathbf{Z}_i),$$

with

$$\lambda_{hj}(x;\mathbf{Z}_i) = \lambda_{hj0}(x)\exp\left(\beta^T\mathbf{Z}_{hji}\right), \tag{6.4}$$

where $Y_{hi}(x)$ is the indicator for individual i being at risk just before sojourn time x in the state h, for $h = 0, 1$. That is, $Y_{hi}(x) = 1$ if the sojourn time of the ith individual in state h is larger than or equal to x, and 0 otherwise. Under independent censoring, $N_{hji}(x)$ can be uniquely decomposed as

$$N_{hji}(x) = \int_0^x Y_{hi}(u)\exp\left(\beta^T\mathbf{Z}_{hji}\right)\lambda_{hj0}(u)du + M_{hji}(x),$$

where $M_{hji}(x)$ are orthogonal local square integrable martingales with predictable variation process given by $\langle M_{hji}(x)\rangle = \int_0^x Y_{hi}(u)\exp\left(\beta^T \mathbf{Z}_{hji}\right)\lambda_{hj0}(u)du$. For convenience, we use the following notation (Shu et al., 2007):

$$S_{hj}^{(m)}(\beta, x) = \sum_{i=1}^{n} Y_{hi}(x)\mathbf{Z}_{hji}^{\otimes m}\exp(\beta^T \mathbf{Z}_{hji}), \quad m = 0, 1, 2,$$

$$\text{and} \quad E_{hj}(\beta, x) = \frac{S_{hj}^{(1)}(\beta, x)}{S_{hj}^{(0)}(\beta, x)}, \text{ for } hj = 01, 02, 12,$$

where for a column vector $\mathbf{a}$, $\mathbf{a}^{\otimes 0} = 1$, $\mathbf{a}^{\otimes 1} = \mathbf{a}$ and $\mathbf{a}^{\otimes 2} = \mathbf{a}\mathbf{a}^T$.

6.4.1 Estimation and Asymptotic Theory

This section considers estimation of β, the cumulative baseline hazards and the QAL survival function for a given covariate value along with their asymptotic properties. As in Section 4.2.2, the data set for n individuals is of the form $\{(x_{0i}, \delta_{0i}, \delta_{01i}, x_{1i}, \delta_{1i}, \mathbf{Z}_{01i}, \mathbf{Z}_{02i}, \mathbf{Z}_{12i});\ i = 1, \ldots, n\}$. Then, the Breslow (1974) estimator for $\Lambda_{hj0}(t) = \int_0^t \lambda_{hj0}(u)$ is given by

$$\hat{\Lambda}_{hj0}(t, \hat{\beta}) = \int_0^t \frac{J_h(x)}{S_{hj}^{(0)}(\hat{\beta}, x)} dN_{hj}(x), \text{ for } hj = 01, 02, 12,$$

where $J_h(x) = I(Y_h(x) > 0)$, for $h = 0, 1$ and $\hat{\beta}$ is obtained by maximizing the partial likelihood (See Andersen, 1993, p 481-482)

$$L(\beta) = \prod_{hj}\prod_{i}\left(\frac{\exp(\beta^T Z_{hji})}{S_{hj}^{(0)}(\beta, x_{hi})}\right)^{\eta_{hji}},$$

or by maximizing

$$\ln L(\beta) \;=\; \sum_{hj}\sum_{i=1}^{n}\eta_{hji}\left[\beta^T Z_{hji} - \log\left(\sum_{l=1}^{n} Y_{hl}(x_{hi})\exp(\beta^T Z_{hjl})\right)\right],$$

where $\eta_{01i} = I(\delta_{01i} = 1)$, $\eta_{02i} = I(\delta_{01i} = 0)$ and $\eta_{12i} = I(\delta_{1i} = 1)$.

The score vector and information matrix are given by

$$\begin{aligned} U(\beta) &= \sum_{hj}\sum_{i=1}^{n} \eta_{hji}\left[Z_{hji} - E_{hj}(\beta, x_{hi})\right], \text{and} \\ \mathcal{I}(\beta) &= \sum_{hj}\int_0^\infty \left\{ \frac{S_{hj}^{(2)}(\beta, x)}{S_{hj}^{(0)}(\beta, x)} - E_{hj}(\beta, x)^{\otimes 2} \right\} dN_{hj}(x), \end{aligned}$$

The cumulative hazards $\Lambda_{hj}(t, \mathbf{Z}_0) = \int_0^t \lambda_{hj}(u, \mathbf{Z}_0)du$ are estimated as $\hat{\Lambda}_{hj}(t, \mathbf{Z}_0)$ $= \hat{\Lambda}_{hj0}(t, \hat{\beta}) \exp(\hat{\beta}^T \mathbf{Z}_{hj0})$, for $hj = 01, 02$ and 12. Also, the survival functions for given $\mathbf{Z}_0$, $S_0(t; \mathbf{Z}_0)$ and $S_{12}(t; \mathbf{Z}_0)$ for T_0 and T_{12}, respectively, are estimated by

$$\hat{S}_0(t; \mathbf{Z}_0) = \prod_{u<t} \left\{1 - d\hat{\Lambda}_{01}(u; \mathbf{Z}_0) - d\hat{\Lambda}_{02}(u; \mathbf{Z}_0)\right\}, \text{ and} \tag{6.5}$$

$$\hat{S}_{12}(t; \mathbf{Z}_0) = \prod_{u<t} \left\{1 - d\hat{\Lambda}_{12}(u; \mathbf{Z}_0)\right\}. \tag{6.6}$$

Then, using (6.3), an estimate of $S_Q(q; \mathbf{Z}_0)$ is given by

$$\begin{aligned} \hat{S}_Q(q; \mathbf{Z}_0) &= \hat{S}_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right) + \hat{P}_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right) \\ &= \hat{S}_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right) + \int_0^{\frac{q}{w_0}} \hat{S}_{12}\left(\frac{q - w_0 x}{w_1}; \mathbf{Z}_0\right) \hat{S}_0(x; \mathbf{Z}_0) d\hat{\Lambda}_{01}(x; \mathbf{Z}_0). \end{aligned} \tag{6.7}$$

Note that the two product-limit estimators $\hat{S}_0(u; \mathbf{Z}_0)$ and $\hat{S}_{12}(u; \mathbf{Z}_0)$ are approximately equal to the corresponding ones derived from the Breslow estimators, given by $\exp\left[-\hat{\Lambda}_{01}(u; \mathbf{Z}_0) - \hat{\Lambda}_{02}(u; \mathbf{Z}_0)\right]$ and $\exp\left[-\hat{\Lambda}_{12}(u; \mathbf{Z}_0)\right]$, respectively. For the derivation of asymptotic results in the Appendix (Section 6.6), the latter estimators of $S_0(u; \mathbf{Z}_0)$ and $S_{12}(u; \mathbf{Z}_0)$ are considered for some algebraic convenience. Let $\theta \in [0, \tau)$. Following Shu et al. (2007) and under the regularity conditions 1-3 therein, we have the following Theorems on the asymptotic properties. The proof follows similar arguments as those in Shu et al. and are briefly sketched in the Appendix (Section 6.6).

THEOREM 6.4.1 *The random vector $\sqrt{n}(\hat{\beta} - \beta)$ converges weakly to a multivariate normal with mean zero and a covariance matrix Ω^{-1} which can be consistently estimated by $n\mathcal{I}(\hat{\beta})^{-1}$.*

THEOREM 6.4.2 *The process* $\sqrt{n}\left[\hat{S}_0(\cdot,\mathbf{Z}_0) - S_0(\cdot,\mathbf{Z}_0)\right]$ *converges weakly on* $[0,\theta]$ *to a zero-mean Gaussian process whose variance at* q/w_0 *can be estimated uniformly consistently by*

$$\begin{aligned}\hat{\psi}^{(0)}\left(\frac{q}{w_0};\mathbf{Z}_0\right) &= \widehat{Q}^{(0)}\left(\frac{q}{w_0},\hat{\beta}\right)^T n\mathcal{I}(\hat{\beta})^{-1}\widehat{Q}^{(0)}\left(\frac{q}{w_0},\hat{\beta}\right)\\ &+ n\left\{\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right\}^2\{\exp(\hat{\beta}^T\mathbf{Z}_{010})\}^2\int_0^{\frac{q}{w_0}}\frac{d\hat{\Lambda}_{010}(u,\hat{\beta})}{S_{01}^{(0)}(\hat{\beta},u)}\\ &+ n\left\{\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right\}^2\{\exp(\hat{\beta}^T\mathbf{Z}_{020})\}^2\int_0^{\frac{q}{w_0}}\frac{d\hat{\Lambda}_{020}(u,\hat{\beta})}{S_{02}^{(0)}(\hat{\beta},u)}, \quad (6.8)\end{aligned}$$

where

$$\begin{aligned}\widehat{Q}^{(0)}\left(\frac{q}{w_0},\hat{\beta}\right) &= -\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\left[\int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{010}-E_{01}(\hat{\beta},u)\}\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(u,\hat{\beta})\right.\\ &\left.+\int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{020}-E_{02}(\hat{\beta},u)\}\exp(\hat{\beta}^T\mathbf{Z}_{020})d\hat{\Lambda}_{020}(u,\hat{\beta})\right].\end{aligned}$$

THEOREM 6.4.3 *The process* $\sqrt{n}\left[\hat{P}_{12}(\cdot,\mathbf{Z}_0) - P_{12}(\cdot,\mathbf{Z}_0)\right]$ *converges weakly on* $[0,\theta]$ *to a zero-mean Gaussian process whose variance at* q/w_0 *can be estimated uniformly consistently by* $\hat{\psi}^{(12)}\left(\frac{q}{w_0};\mathbf{Z}_0\right)$

$$\begin{aligned}&= \widehat{Q}^{(12)}\left(\frac{q}{w_0},\hat{\beta}\right)^T n\mathcal{I}(\hat{\beta})^{-1}\widehat{Q}^{(12)}\left(\frac{q}{w_0},\hat{\beta}\right)\\ &+n\int_0^{\frac{q}{w_0}}\left[\hat{S}_0(u;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)-\int_u^{\frac{q}{w_0}}\left\{\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\right.\right.\\ &\left.\left.\times\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}\right]^2\times\{\exp(\hat{\beta}^T\mathbf{Z}_{010})\}^2\frac{d\hat{\Lambda}_{010}(u,\hat{\beta})}{S_{01}^{(0)}(\hat{\beta},u)}\\ &+n\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}}\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}^2\\ &\times\{\exp(\hat{\beta}^T\mathbf{Z}_{020})\}^2\frac{d\hat{\Lambda}_{020}(u,\hat{\beta})}{S_{02}^{(0)}(\hat{\beta},u)}\\ &+n\int_0^{\frac{q}{w_1}}\left\{\int_0^{\frac{q-w_1u}{w_0}}\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}^2\\ &\times\{\exp(\hat{\beta}^T\mathbf{Z}_{120})\}^2\frac{d\hat{\Lambda}_{120}(u,\hat{\beta})}{S_{12}^{(0)}(\hat{\beta},u)}, \quad (6.9)\end{aligned}$$

where

$$\begin{aligned}\widehat{Q}^{(12)}\left(\frac{q}{w_0},\hat{\beta}\right) &= \int_0^{\frac{q}{w_0}} \hat{S}_0(u;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)\Big[\{\mathbf{Z}_{010}-E_{01}(\hat{\beta},u)\}\\ &\quad -\int_0^u\{\mathbf{Z}_{010}-E_{01}(\hat{\beta},x)\}\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\\ &\quad -\int_0^u\{\mathbf{Z}_{020}-E_{02}(\hat{\beta},x)\}\exp(\hat{\beta}^T\mathbf{Z}_{020})d\hat{\Lambda}_{020}(x,\hat{\beta})\\ &\quad -\int_0^{\frac{q-w_0u}{w_1}}\left\{\mathbf{Z}_{120}-E_{12}(\hat{\beta},x)\right\}\exp(\hat{\beta}^T\mathbf{Z}_{120})d\hat{\Lambda}_{120}(x,\hat{\beta})\Big]\\ &\quad \times\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(u,\hat{\beta}).\end{aligned}$$

THEOREM 6.4.4 $\sqrt{n}\left[\hat{S}_Q(q;\mathbf{Z}_0)-S_Q(q;\mathbf{Z}_0)\right]$ *converges weakly to a mean zero Gaussian process in* $[0,\theta_w]$*, where* $\theta_w<\tau/w_0$ *is a constant, with a variance at* q *which can be estimated uniformly consistently by* $\hat{\psi}(q,\mathbf{Z}_0)$

$$=\hat{\psi}^{(0)}\left(\frac{q}{w_0};\mathbf{Z}_0\right)+\hat{\psi}^{(12)}\left(\frac{q}{w_0};\mathbf{Z}_0\right)+2\widehat{\text{cov}}\left\{\sqrt{n}\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right),\sqrt{n}\hat{P}_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right\}, \tag{6.10}$$

where $\widehat{\text{cov}}\left\{\sqrt{n}\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right),\sqrt{n}\hat{P}_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right\}$

$$\begin{aligned}&= \widehat{Q}^{(0)}\left(\frac{q}{w_0},\hat{\beta}\right)^T n\mathcal{I}(\hat{\beta})^{-1}\widehat{Q}^{(12)}\left(\frac{q}{w_0},\hat{\beta}\right)\\ &\quad -n\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\{\exp(\hat{\beta}^T\mathbf{Z}_{010})\}^2\int_0^{\frac{q}{w_0}}\left\{\hat{S}_0(u;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0u}{w_1}|\mathbf{Z}_0\right)\right.\\ &\quad \left.-\int_u^{\frac{q}{w_0}}\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}\frac{d\hat{\Lambda}_{010}(u,\hat{\beta})}{S_{01}^{(0)}(\hat{\beta},u)}\\ &\quad +n\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\{\exp(\hat{\beta}^T\mathbf{Z}_{020})\}^2\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}}\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\right.\\ &\quad \left.\times\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}\frac{d\hat{\Lambda}_{020}(u,\hat{\beta})}{S_{02}^{(0)}(\hat{\beta},u)}.\end{aligned} \tag{6.11}$$

Example 1: The Stanford Heart Transplant data (Section 1.5.1) is used to illustrate the proposed estimate of QAL distribution with covariate effect. Here T_0 is the time, since acceptance into the program, of heart transplantation or

death before transplantation, whichever is earlier, and T_{12} is the time till death since heart transplantation. The covariates we consider are indicator for previous history of surgery ($Z^{(1)}$), age at acceptance ($Z^{(2)}$) and mismatch score ($Z^{(3)}$). The mismatch score is available after heart transplantation. So $Z^{(3)}$ will have effect on T_{12} only. Let $\beta = (\beta_{011}, \beta_{012}, \beta_{021}, \beta_{022}, \beta_{121}, \beta_{122}, \beta_{123})'$ be the vector of regression coefficients. The estimates of the regression coefficients along with standard errors and p-values are presented in Table 6.1. From Table 6.1, it is clear that only age at acceptance ($Z^{(2)}$) has significant effect on the hazards of 01 and 12 transitions.

Table 6.1: Estimates of the regression coefficients for the heart transplant data

Transition	Parameters	Estimate	Standard error	p-value
01	β_{011}	0.1333	0.3224	0.680
	β_{012}	0.0313	0.0142	0.028
02	β_{021}	-0.4784	0.6137	0.440
	β_{022}	0.0149	0.0183	0.410
12	β_{121}	-0.7620	0.4858	0.120
	β_{122}	0.0520	0.0225	0.021
	β_{123}	0.5163	0.2957	0.081

One can easily estimate the survival probabilities for QAL using (6.7) and the estimates given in Table 6.1 for a particular value of $\mathbf{Z}$. The standard error is calculated by using (6.10). As in Section 4.2.4, we take $w_0 = 0.3$ and $w_1 = 0.8$. With $Z^{(1)} = 0$, $Z^{(2)} = 45$ and $Z^{(3)} = 1.5$, for example, the survival probability $S_Q(q)$ at $q = 10$ is estimated as 0.7819 with standard error 0.0333.

6.4.2 Extension to Progressive Illness-Death Model 2

In this section, the estimation of QAL distribution with covariate effect for the progressive illness-death model 2, as described in Figure 2.4, is considered. Considered the data $\{(x_{hi}, \delta_{hi}, \mathbf{Z}_i);\ h = 0, 1 \ldots, k,\ i = 1, \ldots, n\}$, as in Section 4.3.2. Define $\eta_{hj} = I(\delta_h = j)$ if $j = h+1$ or $k+1$, for $h = 0, 1, \ldots, k-1$ and $\eta_{k,k+1} = I(\delta_k = k+1)$. Also, η_{hji} denotes the value of η_{hj} for the ith individual. The estimate of the regression parameters β is obtained by maximizing the partial likelihood (Andersen, 1993, p 481-482)

$$L(\beta) = \prod_{hj} \prod_{i} \left(\frac{\exp(\beta^T Z_{hji})}{S_{hj}^{(0)}(\beta, x_{hi})} \right)^{\eta_{hji}}.$$

Then, the Breslow (1974) estimator for $\Lambda_{hj0}(t) = \int_0^t \lambda_{hj0}(u)$ is given by

$$\hat{\Lambda}_{hj0}(t, \hat{\beta}) = \int_0^t \frac{J_h(x)}{S_{hj}^{(0)}(\hat{\beta}, x)} dN_{hj}(x),$$

where $N_{hj}(t) = \sum_{i=1}^n I(X_{hi} \leq t, \delta_{hi} = j)$, for $j = h+1$ or $k+1$, $Y_h(t) = \sum_{i=1}^n I(X_{hi} \geq t)$ and $J_h(t) = I(Y_h(t) > 0)$, for $h = 0, 1, \ldots, k$. Then, $S_h(t; \mathbf{Z}_0)$ and $F_{k,k+1}(t; \mathbf{Z}_0)$ are estimated by

$$\hat{S}_h(t; \mathbf{Z}_0) = \prod_{u<t} \left\{ 1 - d\hat{\Lambda}_{h,h+1}(u; \mathbf{Z}_0) - d\hat{\Lambda}_{h,k+1}(x; \mathbf{Z}_0) \right\}, \tag{6.12}$$

for $h = 0, 1, \ldots, k-1$, and

$$\hat{F}_{k,k+1}(t; \mathbf{Z}_0) = 1 - \prod_{u \leq t} \left\{ 1 - d\hat{\Lambda}_{k,k+1}(u; \mathbf{Z}_0) \right\}, \tag{6.13}$$

respectively. Then, using (6.2), an estimate of $F_Q^{(k)}(q; \mathbf{Z}_0)$ is obtained by substituting $S_h(\cdot)$'s, $\Lambda_{h,h+1}(\cdot)$'s, $\Lambda_{h,k+1}(\cdot)$'s and $F_{k,k+1}(\cdot)$ by the corresponding estimates.

Note that $F_Q^{(k)}(q; \mathbf{Z}_0)$ can be written as

$$\begin{aligned} F_Q^{(k)}(q; \mathbf{Z}_0) &= \int_0^{\frac{q}{w_0}} S_0(x; \mathbf{Z}_0) d\Lambda_{0,k+1}(x; \mathbf{Z}_0) \\ &\quad + \int_0^{\frac{q}{w_0}} F_{Q^*}^{(k-1)}(q - w_0 x_0; \mathbf{Z}_0) S_0(x) d\Lambda_{01}(x; \mathbf{Z}_0), \end{aligned}$$

where Q^* is defined in the same way as Q in Section 2.3.2, but starting from state 1 instead of state 0 (See also Section 5.3.5). The corresponding survival function, given by

$$S_Q^{(k)}(q;\mathbf{Z}_0) = S_0\left(\frac{q}{w_0};\mathbf{Z}_0\right) + \int_0^{\frac{q}{w_0}} S_{Q^*}^{(k-1)}(q-w_0x;\mathbf{Z}_0)S_0(x;\mathbf{Z}_0)d\Lambda_{01}(x;\mathbf{Z}_0),$$

has the similar form as in (6.3) with $S_{Q^*}^{(k-1)}(\cdot)$ in place of $S_{12}(\cdot)$. Hence, following the proofs of Theorems 6.4.2-6.4.4 and using method of induction, one can prove weak convergence of $\sqrt{n}\left[\hat{S}_Q^{(k)}(q;\mathbf{Z}_0) - S_Q^{(k)}(q;\mathbf{Z}_0)\right]$ to a mean zero Gaussian process with a variance that can be estimated, where $\hat{S}_Q^{(k)}(q;\mathbf{Z}_0)$ denotes the estimate of $S_Q^{(k)}(q;\mathbf{Z}_0)$ as described above.

Example 2: The proposed method is illustrated using data from IBCSG Trial V (See Section 1.5.2). Note that there is no direct death from health states 0 and 1; therefore, the appropriate model for IBCSG data is a special case (See Figure 2.3) of the progressive illness-death model 2, in which there is no direct death from the states 0 and 1. Also as illustrated in Section 4.3.4, there is evidence of independence between the three different sojourn times.

Five covariates recorded from each patient upon enrollment in the clinical trial are considered for illustration as given below.

$Z^{(1)}$=treatment group (0: short duration and 1: long duration).

$Z^{(2)}$= age in years at the time enrollment.

$Z^{(3)}$= menopausal status (0: pre- and 1: post-).

$Z^{(4)}$ = tumor size, and

$Z^{(5)}$= nodal group (0: 1 to 3 nodes and 1: 4 or more nodes).

The state-specific covariate vectors are

$\mathbf{Z}_{01}$= $(Z^{(1)}, Z^{(2)}, Z^{(3)}, Z^{(4)}, Z^{(5)}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)'$.

$\mathbf{Z}_{12}$= $(0, 0, 0, 0, 0, Z^{(1)}, Z^{(2)}, Z^{(3)}, Z^{(4)}, Z^{(5)}, 0, 0, 0, 0, 0)'$.

$\mathbf{Z}_{23}$= $(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, Z^{(1)}, Z^{(2)}, Z^{(3)}, Z^{(4)}, Z^{(5)})'$.

The state-specific hazard rate is denoted by

$$\lambda_{hj}(t;\mathbf{Z}) = \lambda_{hj0}(t)\exp\left(\beta^T\mathbf{Z}_{hj}\right), \text{for } hj = 01, 12, 23,$$

where $\beta = (\beta_{011},\ \beta_{012},\ \beta_{013},\ \beta_{014},\ \beta_{015},\ \beta_{121},\ \beta_{122},\ \beta_{123},\ \beta_{124},\ \beta_{125},\ \beta_{231},\ \beta_{232},\ \beta_{233},\ \beta_{234}\ ,\ \beta_{235})'$ is the vector of regression coefficients. Then, from (6.2), the distribution function of Q for given covariate $\mathbf{Z}_0$ is given by (See also Section 2.3.1)

$$\begin{aligned} F_Q(q;\mathbf{Z}_0)) &= \int_0^{\frac{q}{w_0}}\int_0^{\frac{q-w_0x_0}{w_1}} F_{23}\left(\frac{q-w_0x_0-w_1x_1}{w_2};\mathbf{Z}_0\right) S_1(x_1;\mathbf{Z}_0)d\Lambda_{12}(x_1;\mathbf{Z}_0) \\ &\quad \times S_0(x_0;\mathbf{Z}_0)d\Lambda_{01}(x_0;\mathbf{Z}_0), \end{aligned} \tag{6.14}$$

where $S_0(t;\mathbf{Z}_0) = \exp\{-\Lambda_{01}(t;\mathbf{Z}_0)\}$, $S_1(t;\mathbf{Z}_0) = \exp\{-\Lambda_{12}(t;\mathbf{Z}_0)\}$ and $F_{23}(\cdot;\mathbf{Z}_0)$ is the distribution function of T_{23}.

Out of 1229 patients, all the covariate values are available for 1215 patients. So this analysis is based on 1215 patients. The estimates of the regression coefficients along with standard errors and p-values are presented in Table 6.2. From the p-values in Table 6.2, it is clear that duration of chemotherapy ($Z^{(1)}$) has significant decreasing effect on the hazards of TOX and TWiST and, increasing effect on the hazard of REL. Age ($Z^{(2)}$), menopausal status ($Z^{(3)}$) and tumor size ($Z^{(4)}$) have significant effect only on the hazard of TWiST. Nodal group ($Z^{(5)}$) has significant effect on both TWiST and REL.

Next, we estimate survival probabilities for QAL using (6.14) and the estimates in Table 6.2 for a given value of $\mathbf{Z}_0$. Since the algebraic expression for the standard error of this estimate is very complicated and difficult to obtain, it is computed by using a bootstrap method with 500 bootstrap samples, each of size 1215 drawn with replacement. The utility coefficients are taken as $w_0 = 0.5$, $w_1 = 1$ and $w_2 = 0.5$. The survival probability for $\mathbf{Z}_0$=(1, 50, 0, 35, 1)$'$ at $q = 10$ is estimated as 0.9836 with standard error 0.0030.

Table 6.2: Estimates of the regression coefficients for the IBCSG data

Transition	Parameters	Estimate	Standard error	p-value
01	β_{011}	-2.7599	0.1043	0.000
	β_{012}	-0.0039	0.0049	0.440
	β_{013}	0.0371	0.0937	0.690
	β_{014}	-0.0009	0.0018	0.620
	β_{015}	0.0739	0.0601	0.220
12	β_{121}	-0.4776	0.0797	0.000
	β_{122}	-0.0281	0.0069	0.000
	β_{123}	0.4281	0.1297	0.001
	β_{124}	0.0066	0.0022	0.003
	β_{125}	0.8523	0.0810	0.000
23	β_{231}	0.3071	0.0929	0.001
	β_{232}	-0.0005	0.0079	0.950
	β_{233}	-0.1725	0.1535	0.260
	β_{234}	0.0040	0.0026	0.130
	β_{235}	0.2099	0.0942	0.026

6.5 Concluding Remarks

In this work, regression analysis of QAL data has been proposed in progress illness-death model 2, which can be extended to some general models. For example, one can extend this method to the competing illness-death models of Section 2.4 in similar manner.

One can, in principle, use a Markov model in which the different baseline transition rates depend on the time since the beginning instead of the time spent in the current state. This represents a complicated structure of dependence between

the different sojourn times. This, however, readily fits into the multiplicative intensity framework. Therefore, the results of Andersen et al. (1993, p 481-482) are readily applicable for the estimation of the regression parameters, the baseline cumulative hazards, and, eventually, the QAL distribution. The asymptotic results also follow from those of Andersen et al. (1993, Section VII.2) following similar techniques. In a particular dependence structure, a transition rate may depend on the previous sojourn times(s), say, through a proportional hazards type modelling. The estimation through partial likelihood can be carried out in a similar manner.

6.6 Appendix

Let us assume the regularity conditions 1-3 of Shu et al. (2007). Theorem 6.4.1 is Lemma (ii) of their work.

Proof of Theorem 6.4.2: Using Lemmas 1 and 2 of Shu et al. (2007), ,

$$\sqrt{n}\left[\hat{S}_0\left(\tfrac{q}{w_0}, \mathbf{Z}_0\right) - S_0\left(\tfrac{q}{w_0}, \mathbf{Z}_0\right)\right]$$
$$= n^{-1/2}\sum_{i=1}^{n}\left\{W_{1i}^{(0)}(q) + W_{2i}^{(0)}(q) + W_{3i}^{(0)}(q)\right\} + o_p(1), \tag{6.15}$$

where

$$W_{1i}^{(0)}(q) = Q^{(0)}\left(\frac{q}{w_0}, \beta\right)^T \Omega^{-1}\sum_{hj}\int_0^\infty \{\mathbf{Z}_{hji} - E_{hji}(\beta, u)\}dM_{hji}(u),$$
$$Q^{(0)}\left(\frac{q}{w_0}, \beta\right) = -S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\left[\int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{010} - e_{01}(\beta, u)\}d\Lambda_{01}(u; \mathbf{Z}_0)\right.$$
$$\left. + \int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{020} - e_{02}(\beta, u)\}d\Lambda_{02}(u; \mathbf{Z}_0)\right],$$
$$W_{2i}^{(0)}(q) = -nS_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\exp\left(\beta^T\mathbf{Z}_{010}\right)\int_0^{\frac{q}{w_0}}\frac{J_0(u)dM_{01i}(u)}{S_{01}^{(0)}(\beta, u)},$$

$$W_{3i}^{(0)}(q) = -nS_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\exp\left(\beta^T\mathbf{Z}_{020}\right)\int_0^{\frac{q}{w_0}}\frac{J_0(u)dM_{02i}(u)}{S_{02}^{(0)}(\beta,u)}.$$

Note that, for each q, the right hand side of (6.15) is essentially a sum of n independent and identically distributed zero-mean random variables. Using the arguments of Shu et al. (2007), we conclude that $\sqrt{n}\left[\hat{S}_0(\cdot;\mathbf{Z}_0) - S_0(\cdot;\mathbf{Z}_0)\right]$ converges weakly to a zero-mean Gaussian process with covariance function at $\left(\frac{q}{w_0},\frac{q'}{w_0}\right)$ given by

$$\begin{aligned}
&\psi^{(0)}\left(\tfrac{q}{w_0},\tfrac{q'}{w_0}\right)\\
&= \frac{1}{n}\sum_{i=1}^{n}\mathrm{cov}\left\{W_{1i}^{(0)}(q)+W_{2i}^{(0)}(q)+W_{3i}^{(0)}(q), W_{1i}^{(0)}(q')+W_{2i}^{(0)}(q')+W_{3i}^{(0)}(q')\right\}\\
&= Q^{(0)}\left(\frac{q}{w_0},\beta\right)^T\Omega^{-1}\frac{1}{n}E\left[\sum_{hj}\int_0^{\infty}\left\{\frac{S_{hj}^{(2)}(\beta,u)}{S_{hj}^{(0)}(\beta,u)}-E_{hj}(\beta,u)^{\otimes 2}\right\}\right.\\
&\qquad\left.\times S_{hj}^{(0)}(\beta,u)d\Lambda_{hj0}(u)\right]\Omega^{-1}Q^{(0)}\left(\frac{q'}{w_0},\beta\right)\\
&\qquad +nS_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)S_0\left(\frac{q'}{w_0};\mathbf{Z}_0\right)\left\{\exp\left(\beta^T\mathbf{Z}_{010}\right)\right\}^2E\left\{\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}}\frac{J_0(u)d\Lambda_{02}(u)}{Y_0(u)}\right\}\\
&\qquad +nS_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)S_0\left(\frac{q'}{w_0};\mathbf{Z}_0\right)\left\{\exp\left(\beta^T\mathbf{Z}_{020}\right)\right\}^2E\left\{\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}}\frac{J_0(u)d\Lambda_{02}(u)}{Y_0(u)}\right\}
\end{aligned}$$

which, for $q = q'$, can be uniformly consistently estimated by (6.8) in Section 6.4.1.

Proof of Theorem 6.4.3: Following the similar decomposition technique as that used in Voelkel and Crowley (1984) and Shu et al. (2007), we have

$$\begin{aligned}
&\sqrt{n}\left[\hat{P}_{12}\left(\tfrac{q}{w_0};\mathbf{Z}_0\right)-P_{12}\left(\tfrac{q}{w_0};\mathbf{Z}_0\right)\right]\\
&\quad = n^{-1/2}\sum_{i=1}^{n}\left\{W_{1i}^{(12)}(q)+W_{2i}^{(12)}(q)+W_{3i}^{(12)}(q)+W_{4i}^{(12)}(q)\right\}+o_p(1), \qquad (6.16)
\end{aligned}$$

where

$$W_{1i}^{(12)} = Q^{(12)}\left(\frac{q}{w_0},\beta\right)^T\Omega^{-1}\sum_{hj}\int_0^{\infty}\{\mathbf{Z}_{hji}-E_{hji}(\beta,u)\}dM_{hji}(u),$$

$$
\begin{aligned}
W_{2i}^{(12)}(q) &= n\int_0^{\frac{q}{w_0}} \left\{ S_0(u;\mathbf{Z}_0) S_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right) \right. \\
&\quad \left. - \int_u^{\frac{q}{w_0}} S_0(x;\mathbf{Z}_0) S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right) d\Lambda_{01}(x) \right\}, \\
&\quad \times \exp(\beta^T \mathbf{Z}_{010}) \frac{J_0(u) dM_{01i}(u)}{S_{01}^{(0)}(\beta,u)}, \\
W_{3i}^{(12)}(q) &= -n\int_0^{\frac{q}{w_0}} \left\{ \int_u^{\frac{q}{w_0}} S_0(x;\mathbf{Z}_0) S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right) d\Lambda_{01}(x) \right\} \\
&\quad \times \exp(\beta^T \mathbf{Z}_{020}) \frac{J_0(u) dM_{02i}(u)}{S_{02}^{(0)}(\beta,u)}, \\
W_{4i}^{(12)}(q) &= -n\int_0^{\frac{q}{w_1}} \left\{ \int_0^{\frac{q-w_1u}{w_0}} S_0(x;\mathbf{Z}_0) S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right) d\Lambda_{12}(x) \right\} \\
&\quad \times \exp(\beta^T \mathbf{Z}_{120}) \frac{J_1(u) dM_{12i}(u)}{S_{12}^{(0)}(\beta,u)}, \\
Q^{(12)}\left(\frac{q}{w_0},\beta\right) &= \int_0^{\frac{q}{w_0}} S_0(u;\mathbf{Z}_0) S_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right) \left[\{\mathbf{Z}_{010} - e_{01}(\beta,u)\} \right. \\
&\quad - \int_0^u \{\mathbf{Z}_{010} - e_{01}(\beta,x)\} d\Lambda_{01}(x;\mathbf{Z}_0) \\
&\quad - \int_0^u \{\mathbf{Z}_{020} - e_{02}(\beta,x)\} d\Lambda_{02}(x;\mathbf{Z}_0) \\
&\quad \left. - \int_0^u \{\mathbf{Z}_{120} - e_{12}(\beta,x)\} d\Lambda_{12}(x;\mathbf{Z}_0) \right] d\Lambda_{01}(u;\mathbf{Z}_0).
\end{aligned}
$$

Note that, for each q, the right hand side of (6.16) is essentially a sum of n independent and identically distributed zero-mean random variables. Using the arguments of Shu et al. (2007), we conclude that $\sqrt{n}\left[\hat{P}_{12}(\cdot) - P_{12}(\cdot)\right]$ converges weakly to a zero-mean Gaussian process with covariance function at $\left(\frac{q}{w_0}, \frac{q'}{w_0}\right)$ given by

$$
\begin{aligned}
&\psi^{(12)}\left(\tfrac{q}{w_0}, \tfrac{q'}{w_0}\right) \\
&= \frac{1}{n}\sum_{i=1}^n \mathrm{cov}\left\{ W_{1i}^{(12)}(q) + W_{2i}^{(12)}(q) + W_{3i}^{(12)}(q) + W_{4i}^{(12)}(q), \right. \\
&\qquad \left. W_{1i}^{(12)}(q') + W_{2i}^{(12)}(q') + W_3^{(12)}(q') + W_{4i}^{(12)}(q') \right\} \\
&= Q^{(12)}\left(\frac{q}{w_0},\beta\right)^T \Omega^{-1} \frac{1}{n} E\left[\sum_{hj} \int_0^\infty \left\{ \frac{S_{hj}^{(2)}(\beta,u)}{S_{hj}^{(0)}(\beta,u)} - E_{hj}(\beta,u)^{\otimes 2} \right\} \right.
\end{aligned}
$$

$$
\begin{aligned}
&\times S_{hj}^{(0)}(\beta,u)d\Lambda_{hj0}(u)\Big]\,\Omega^{-1}Q^{(12)}\left(\frac{q'}{w_0},\beta\right)\\
&+nE\left[\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}}\left\{S_0(u;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)\right.\right.\\
&\quad\left.-\int_u^{\frac{q}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\right\}\\
&\quad\times\left\{S_0(u;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0u}{w_1};\mathbf{Z}_0\right)\right.\\
&\quad\left.-\int_u^{\frac{q'}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\right\}\\
&\quad\times\{\exp(\beta^T\mathbf{Z}_{010})\}^2J_0(u)\frac{d\Lambda_{01}(u)}{S_{01}^{(0)}(\beta,u)}\Big]\\
&+nE\left[\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}}\left\{\int_u^{\frac{q}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\right\}\right.\\
&\quad\times\left\{\int_u^{\frac{q'}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\right\}\\
&\quad\times\{\exp(\beta^T\mathbf{Z}_{020})\}^2J_0(u)\frac{d\Lambda_{02}(u)}{S_{02}^{(0)}(\beta,u)}\Big]\\
&+nE\left[\int_0^{\frac{q}{w_1}\wedge\frac{q'}{w_1}}\left\{\int_0^{\frac{q-w_1u}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\right\}\right.\\
&\quad\times\left\{\int_0^{\frac{q'-w_1u}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x)\right\}\\
&\quad\times\{\exp(\beta^T\mathbf{Z}_{120})\}^2J_1(u)\frac{d\Lambda_{12}(u)}{S_{12}^{(0)}(\beta,u)}\Big]
\end{aligned}
$$

which, for $q=q'$, can be uniformly consistently estimated by (6.9) in Section 6.4.1.

Proof of Theorem 6.4.4: Note that

$$
\begin{aligned}
\sqrt{n}\left[\hat{S}_Q\left(q;\mathbf{Z}_0\right)-S_Q\left(q;\mathbf{Z}_0\right)\right] &= \sqrt{n}\left[\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)-S_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right]\\
&\quad+\sqrt{n}\left[\hat{P}_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)-P_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right].
\end{aligned}
$$

Hence, by some rearrangement of terms and following the techniques used in the

proofs of Theorems 6.4.2 and 6.4.3, $\sqrt{n}\left[\hat{S}_Q\left(q;\mathbf{Z}_0\right)-S_Q\left(q;\mathbf{Z}_0\right)\right]$ can be written as a sum of n independent and identically distributed zero mean random variables. The weak convergence result follows by using similar arguments. The covariance term in Theorem 6.4.4 is given by

$$
\begin{aligned}
&\operatorname{cov}\left[\sqrt{n}\left\{\hat{S}_0\left(\tfrac{q}{w_0};\mathbf{Z}_0\right)-S_0\left(\tfrac{q}{w_0};\mathbf{Z}_0\right)\right\},\sqrt{n}\left\{\hat{P}_{12}\left(\tfrac{q}{w_0};\mathbf{Z}_0\right)-P_{12}\left(\tfrac{q}{w_0};\mathbf{Z}_0\right)\right\}\right] \\
&= \frac{1}{n}\sum_{i=1}^{n}\operatorname{cov}\Big\{W_{1i}^{(0)}(q)+W_{2i}^{(0)}(q)+W_{3i}^{(0)}(q), \\
&\qquad W_{1i}^{(12)}(q)+W_{2i}^{(12)}(q)+W_{3i}^{(12)}(q)+W_{4i}^{(12)}(q)\Big\}+o_p(1) \\
&= Q^{(0)}\left(\frac{q}{w_0},\beta\right)^{T}\Omega^{-1}\frac{1}{n}E\left[\sum_{hj}\int_0^{\infty}\left\{\frac{S_{hj}^{(2)}(\beta,u)}{S_{hj}^{(0)}(\beta,u)}-E_{hj}(\beta,u)^{\otimes 2}\right\}\right. \\
&\qquad \left.\times\, S_{hj}^{(0)}(\beta,u)d\Lambda_{hj0}(u)\right]\Omega^{-1}Q^{(12)}\left(\frac{q'}{w_0},\beta\right) \\
&\quad -nS_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\left\{\exp(\beta^T\mathbf{Z}_{010})\right\}^2E\left[\int_0^{\frac{q}{w_0}}\left\{S_0(u;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)\right.\right. \\
&\qquad \left.\left.-\int_u^{\frac{q}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x)\right\}J_0(u)\frac{d\Lambda_{01}(u)}{S_{01}^{(0)}(\beta,u)}\right] \\
&\quad +nS_0\left(\frac{q}{w_0}\right)\{\exp(\beta^T\mathbf{Z}_{020})\}^2E\left[\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}}S_0(x)S_{12}\left(\frac{q-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\}\right. \\
&\qquad \left.\times J_0(u)\frac{d\Lambda_{02}(u)}{S_{02}^{(0)}(\beta,u)}\right]+o_p(1),
\end{aligned}
$$

which can be uniformly consistently estimated by (6.11) in Section 6.4.1.

Chapter 7

Conclusions and Future Work

In this work, a new method is proposed to estimate the QAL distribution. The advantages of the proposed method over the existing methods are discussed in Introduction. Estimation of QAL distribution is considered using parametric, nonparametric and semi-parametric methods in the context of different illness-death models. In the proposed approach, one needs to derive the theoretical distribution of QAL in terms of the joint distribution of the sojourn times in the health states. This required joint modelling of the sojourn times in all states. This joint modelling may not be simple unless additional assumptions are made (e.g., independence).

Although there are several advantages of the proposed method over the existing methods, the proposed method has some limitations. It may be noted that the proposed method explicitly use the information on the interrelationship between the different health states and the same between the corresponding sojourn times. Hence the proposed method may be less robust to departures from model misspecification (See Section 4.2.3). The estimation, in general, becomes difficult as the number of health states increases.

In parametric approach, estimation of QAL distribution is considered when

sojourn times are both independent and dependent. Under the assumption of independence, nonparametric estimation is carried out using nonparametric estimates of the marginal distributions of the sojourn times (Satten and Datta, 2002). Estimation of the joint distribution of all the sojourn times, in general, is a difficult/impossible task. The nonparametric estimation of QAL distribution under some specific dependent models with the simple illness-death model 1 is considered (See Section 5.5), but the asymptotic properties are not studied. The semi-parametric estimation is also considered under independence (semi-Markov model). One can use Markov model to represent the dependence structure between the different sojourn times. The study of asymptotic properties is a challenging task for the dependent models both in nonparametric and semi-parametric methods. We keep these tasks for future work. Though parametric estimation is considered for the reversible model, nonparametric and semi-parametric methods are not considered in this work. These tasks will also be considered in future work. Bayes estimation of QAL distribution has not received much attention in literature. Bayes estimation will be a major area for work in future.

The choice of the utility coefficients (w_i's) remains a difficult issue in the study of QAL. In the context of estimating lifetime medical cost, the coefficients are essentially the different cost components, but this choice is largely subjective while studying QAL. One usually has to depend on the different opinions of the health experts. The utility coefficients may be formally elicited by means of some health questionnaire. It may be more realistic to let the coefficients also be affected by certain covariates, that is $w_i = w_i(z)$. This can also be easily dealt with using the proposed method. One needs to replace w_i by $w_i(z)$ in the theoretical expression for the QAL distribution. There is also suggestions that w_i's may be time dependent (Cook et al., 2003). For some simple functions (for example, linear), such time dependent w_i's may be, at least in theory, dealt with through the proposed method.

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