Chapter 2

Semiparametric regression models for recurrent event data with multiple causes

2.1 Introduction

Proportional hazards model introduced by Cox (1972) is widely employed in survival studies to explain the relationship between lifetime and covariates. As mentioned in Chapter 1, when there are multiple causes, hazard based regression models can be extended through a consideration of intensity functions for various causes (see Larson and Dinse (1985), Fine and Gray (1999) and Lawless et al. (2001)). Larson and Dinse (1985) developed a mixture model for the regression analysis of competing risks data. The mixture model is derived with a multinomial distribution for failure types and piece-wise exponential distributions for failure times conditioned on failure type. Later, Fine and Gray (1999) introduced a proportional hazards model for the subdistribution of a competing risks model. Both models can be used for the analysis of univariate competing risks data. Thus the models developed by Larson and Dinse (1985) and Fine and Gray (1999) are less natural and less easily interpretable in the context of recurrent event data analysis. Lawless et al. (2001) discussed semiparametric methods for multiplicative hazard based models for the gap time distribution of recurrent event data when there is a single cause of recurrence. The development of semiparametric models for gap time distributions of recurrent event data with multiple causes is an area yet to be explored. Motivated by this, in this

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1 Some results in this chapter are published in the Journal of Kerala Statistical Association (see Anisha, 2010)
chapter, we introduce two semiparametric models for gap time distributions of recurrent event data with multiple causes.

The chapter is organized as follows. In Section 2.2, we introduce two semiparametric models for gap time data with multiple causes. In Section 2.3, estimation of the parameter vector and cumulative baseline cause specific hazard rate functions using counting process approach is discussed. Asymptotic properties of the estimators are established in Section 2.4. The proposed model is applied, in Section 2.5, to the bladder tumor data given in Kalbfleisch and Prentice (2002). In Section 2.6, a simulation study is carried to assess the performance of the estimates. Finally, Section 2.7 provides major conclusions of the study.

2.2 Models

Suppose that there are \( n \) individuals in a study. Assume that the sequence of events occur due to different causes in each individual. Let \( T_{ij} \) denote the time to occurrence of the \( j \)th event for the \( i \)th subject, \( j = 1, 2, \ldots, J < \infty, i = 1, 2, \ldots, n \). Here \( J \) is the number of recurrences which can take values \( 1, 2, 3, \ldots \). The events occur sequentially in real time; that is \( T_{ij} \) cannot be observed unless \( T_{ij-1} \) has already been observed \( (j = 2, 3, \ldots) \). Let \( D_i \) be the censoring time. Assume that \( D_i \) is independent of \( \{T_{i1}, T_{i2}, \ldots, T_{ij}\} \) conditional on the covariate pattern. Let \( \Delta_{ij} = I(T_{ij} < D_i) \) be the censoring indicator. The observation times are represented by \( X_{ij} = \min(T_{ij}, D_i) \). Gap times for the \( i \)th subject are denoted by \( T_{ij}^* = T_{ij} - T_{ij-1} \), where \( T_{i0} = 0 \). Then the observed gap times are denoted by \( X_{ij}^* = \min(T_{ij}^*, D_{ij}^*) \), where \( D_{ij}^* = D_i - X_{ij-1} \) are the gap censoring times. We define \( t^* = \sup\{t : \Pr(D_i \geq t) > 0\} \). If \( T_{ij-1} \) is independent of \( T_{ij}^* \), then the marginal distribution of \( T_{ij}^* \) is identifiable. However, in most biomedical studies, the independence assumption is not satisfied. To overcome the identifiability problem, we fix \( t_j \in [0, t^*] \) for \( j = 1, 2, \ldots, J - 1 \) and \( t_j^* = t^* - t_{j-1} \), with \( t_0 = 0 \). Then the conditional distribution of \( (T_{ij} | T_{ij-1} \leq t_{j-1}) \) is identifiable for \( T_{ij}^* \leq t_j^* \) (see Lin et al.
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(1999)). Note that the support of $T_{ij-1}$ is not contained in $[0, t^*]$ and for recurrent event, the gap times within subjects are not generally independent.

In addition, for each $T_{ij}^*$, one can observe causes of failure $C_{ij}$. Assume that an individual is exposed to two or more causes for recurrence (failure), but its eventual recurrence (failure) can be attributed to exactly one of the causes. When there are multiple causes or modes of failure, hazard based models can be extended by considering cause specific hazard rate functions. Assume that any covariates are fixed between events and let $Z_{ij}$ denote the covariate vector for individual $i$ and duration $j$. The cause specific hazard rate functions for gap time distributions are given by

$$
\lambda_{ijk}(t; t_{j-1}) = \lim_{\delta \to 0} \Pr[t < T_{ij}^* < t + \delta, C_{ij} = k | T_{ij}^* \geq t, Z_{ij}, t_{i,(j-1)}, C_i^{(j-1)}],
$$

(2.1)

for $t \in [0, t_j^*]$ and $k = 1, 2, \ldots, K$, where $C_{ij}$ is the cause for the $j$th failure of the $i$th individual $C_i^{(j-1)} = (C_{i1}, C_{i2}, \ldots, C_{i,j-1})$ and $t_{i,(j-1)} = (t_{i1}, t_{i2}, \ldots, t_{i,j-1})$, with $t_{i0} = 0$.

Now we consider a semiparametric model to analyze recurrent event data with multiple causes. The model is given by

$$
\lambda_{ijk}(t; \beta, t_{j-1}) = \lambda_{0jk}(t; t_{j-1}) \exp\{\beta'Z_{ij}\},
$$

(2.2)

where $\lambda_{0jk}(t)$ is an unknown and arbitrary function of $t$ depending on $j$ and $k$, representing the baseline cause specific hazard rate function for $j$th failure due to $k$th cause, $Z_{ij}$ is a covariate vector unaffected by the failure process and $\beta'Z_{ij}$ is a linear combination of the components of $Z_{ij}$ with $\beta = (\beta_1, \beta_2, \ldots, \beta_p)'$ being the vector of coefficient parameters (assumed to be the same for all $j$ and $k$). The vector $\beta$ measures the effect of the covariate vector on different cause specific hazard rate functions and this effect is assumed to be the same for all the failures due to different failure types. This may be a strong assumption, which is relaxed in the second model.
Alternatively, the second model, referred to as Model 2, is defined by
\[ \lambda_{ijk}(t; \beta_{jk}, t_{j-1}) = \lambda_{0jk}(t; t_{j-1}) \exp\{\beta'_{jk} Z_{ij}\}, \quad (2.3) \]
where \( \lambda_{0jk}(t; t_{j-1}) \) is an unknown and arbitrary function of \( t \) and \( t_{j-1} \). The vector \( \beta_{jk} = (\beta_{jk1}, \beta_{jk2}, \ldots, \beta_{jkp})' \) depends on both \( j \) and \( k \), thereby relaxing the assumption of same effect of the covariate vector on the different cause specific hazard rate functions, as in Model 1.

In Model 1, the baseline cause specific hazard rate functions \( \lambda_{0jk}(t; t_{j-1}) \) are assumed to be distinct for \( j = 1, 2, \ldots, J \) and \( k = 1, 2, \ldots, K \), while gap time specific regression coefficients can be accommodated upon appropriate expansion of the covariate vector. Model 2 is a very general model and it reduces to Model 1 if all \( \beta_{jk} \)'s are identical.

### 2.3 Inference on Parameters

To estimate baseline cause specific hazard rate functions and regression parameters for Model 1, define, for \( j = 1, 2, \ldots, J \), \( k = 1, 2, \ldots, K \), and \( i = 1, 2, \ldots, n \)

\[ N_{ijk}(t; t_{j-1}) = I(X_{ij}^* \leq t, T_{ij-1} \leq t_{j-1}, \Delta_{ij} = 1, C_{ij} = k) \]

and

\[ Y_{ijk}(t; t_{j-1}) = 1 - N_{ijk}(t; t_{j-1}), \]

which denote the counting process and the risk set process respectively. The history of the entire process up to time \( t \) is represented by \( F_t \) which is the \( \sigma \)-field generated by the process \( \{N_{ijk}(t; t_{j-1}), j = 1, 2, \ldots, J, k = 1, 2, \ldots, K, i = 1, 2, \ldots, n, \} \). The martingale process with respect to the increasing family of \( \sigma \)-fields \( \{F_t, t \geq 0\} \) is defined by

\[ M_{ijk}(t; \beta, t_{j-1}) = N_{ijk}(t; t_{j-1}) - \int_0^t Y_{ijk}(s; t_{j-1}) \exp\{\beta'_{jk} Z_{ij}\} \Lambda_{0jk}(ds; t_{j-1}), \]
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for $j = 1, 2, \ldots, J$, $k = 1, 2, \ldots, K$ and $i = 1, 2, \ldots, n$, where $\Lambda_{0jk}(t; t_{j-1}) = \int_0^t \lambda_{0jk}(s; t_{j-1}) ds$.

If the $T_{ij}^*$’s were independent, the score function $U_n(\beta; t)$ is given by

$$U_n(\beta; t) = \sum_{i=1}^n \sum_{j=1}^J \sum_{k=1}^K \int_0^{t_j^*} [Z_{ij} - \sum_{l=1}^n Y_{ijk}(s; t_{j-1}) Z_{lj} \exp\{\beta'_j Z_{lj}\} \sum_{l=1}^n Y_{ijk}(s; t_{j-1}) \exp\{\beta'_j Z_{lj}\}] N_{ijk}(ds; t_{j-1}),$$

(2.4)

(See Schaubel and Cai (2004)).

If independence assumption fails, $U_n(\beta; t)$ may be biased. Following the arguments given in Schaubel and Cai (2004), one can show that

$$E[M_{ijk}(ds; \beta; t_{j-1}) | T_{ij-1} \leq t_{j-1}] = 0,$$

which gives the following estimating equation for $\beta$ as

$$\sum_{i=1}^n \sum_{j=1}^J \sum_{k=1}^K \int_0^{t_j^*} Z_{ij} W_{ijk}(s) M_{ijk}(ds; \beta; t_{j-1}) = 0$$

(2.5)

and that for $\Lambda_{0jk}(t; t_{j-1})$ as

$$\sum_{i=1}^n \int_0^t W_{ijk}(s) M_{ijk}(ds; \beta; t_{j-1}) = 0,$$

(2.6)

where

$$W_{ijk}(s) = Y_{ijk}(s; t_{j-1}) \Pr(D_i \geq s + T_{ij-1} | T_{ij-1} - t_{j-1}, j \geq 2).$$

On similar lines, for Model 2, if the $T_{ij}^*$’s were independent, the score function $U_n(\beta_{jk}; t)$ is obtained as

$$U_n^*(\beta_{jk}; t) = \sum_{i=1}^n \int_0^{t_j^*} [Z_{ij} - \sum_{l=1}^n Y_{ijk}(s; t_{j-1}) Z_{lj} \exp\{\beta'_j Z_{lj}\} \sum_{l=1}^n Y_{ijk}(s; t_{j-1}) \exp\{\beta'_j Z_{lj}\}] N_{ijk}(ds; t_{j-1}).$$

(2.7)
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Defining

\[ M_{ijk}^*(t; \beta_{jk}, t_{j-1}) = N_{ijk}(t; t_{j-1}) - \int_0^t Y_{ijk}(s; t_{j-1}) \exp\{\beta'_{jk} Z_{ij}\} \Lambda_{0jk}(ds; t_{j-1}), \]

a martingale process with respect to \( \{\mathbb{F}_t, t \geq 0\} \), we obtain the estimating equation for \( \beta_{jk} \) as

\[
\sum_{i=1}^n \int_0^{t_j^*} Z_{ij} W_{ijk}(s) M_{ijk}^*(ds; \beta_{jk}, t_{j-1}) = 0 \quad (2.8)
\]

and that for \( \Lambda_{0jk}(t; t_{j-1}) \) as

\[
\sum_{i=1}^n \int_0^t W_{ijk}(s) M_{ijk}^*(ds; \beta_{jk}, t_{j-1}) = 0. \quad (2.9)
\]

In practice, the censoring distribution is unknown and hence \( W_{ijk} \) is to be estimated. To estimate the censoring distribution, allow \( D_i \) depending on \( Z_{i}^C \), a \( p_C \times 1 \) covariate vector. Under the assumption of the proportional hazards model \( \lambda_i^C(t; \gamma) = \lambda_0^C(t) \exp\{\gamma' Z_i^C\} \) for the data \( \{X_i, 1 - \Delta_i, Z_i^C\}, i = 1, 2, \ldots, n \), with \( \gamma \) as the vector of regression parameters, the quantity \( \Pr\{D_i \geq t|Z_i^C\} \) can be estimated as \( \exp\{-\hat{\Lambda}_i^C(t; \gamma)\} \), where

\[
\hat{\Lambda}_i^C(t; \gamma) = \int_0^t \exp\{\gamma' Z_i^C\} d\hat{\Lambda}_0^C(s; \gamma),
\]

with \( \hat{\gamma} \) represents the likelihood estimator of \( \gamma \), (see Schaubel and Cai (2004)).

From (2.5) and (2.6), we estimate \( \beta \) by \( \hat{\beta}^\gamma \) which is obtained by solving \( U_n^\gamma(\beta, t) = 0 \) and \( \Lambda_{0jk}(t; t_{j-1}) \) by \( \hat{\Lambda}_{0jk}^\gamma(t; \hat{\beta}^\gamma, \hat{\gamma}, t_{j-1}) \), where

\[
U_n^\gamma(\beta, t) = \sum_{i=1}^n \sum_{j=1}^J \sum_{k=1}^K \int_0^{t_j^*} [Z_{ij} - E_{ijk}^\gamma(s; \beta, \hat{\gamma})] W_{ijk}^\gamma(s; \beta, \hat{\gamma}) N_{ijk}(ds; t_{j-1}) \]
and
\[ \hat{\Lambda}_{ijk}^*(t; \beta, \gamma, t_{j-1}) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{t} \frac{\hat{W}_{ijk}^*(s; \gamma)}{S_{jk}^{(0)}(s; \beta, \gamma)} N_{ijk}(ds; t_{j-1}). \]

Here
\[ \hat{W}_{ijk}^*(s; \gamma) = Y_{ijk}(s; t_{j-1}) \exp\{\hat{\Lambda}_{i}^{C}(s + T_{ij-1}; \gamma)\}, \quad i \geq j \geq 2, \]
\[ S_{jk}^{(d)}(s; \beta, \gamma) = \frac{1}{n} \sum_{i=1}^{n} \hat{W}_{ijk}^*(s; \gamma) Z_{ij}^{d} \exp\{\beta' Z_{ij}\}, \quad d = 0, 1, 2 \]

and
\[ E_{jk}^*(s; \beta, \gamma) = \frac{S_{jk}^{(1)}(s; \beta, \gamma)}{S_{jk}^{(0)}(s; \beta, \gamma)}, \]

with \( Z^{\otimes 0} = 1, Z^{\otimes 1} = Z \) and \( Z^{\otimes 2} = ZZ^T \) for a vector \( Z \).

For Model 2, from (2.8), the estimate of \( \beta_{jk} \), denoted by \( \hat{\beta}_{jk}^* \), is the solution of the equation
\[ \hat{U}_{jk}^*(\beta_{jk}, t) = 0, \]
where
\[ \hat{U}_{jk}^*(\beta_{jk}, t) = \sum_{i=1}^{n} \int_{0}^{t_{j}} \{Z_{ij} - E_{jk}^*(s; \beta_{jk}, \hat{\gamma})\} \hat{W}_{ijk}^*(s; \hat{\gamma}) N_{ijk}(ds; t_{j-1}) \]
\[ (2.10) \]

with
\[ E_{jk}^*(s; \beta_{jk}, \gamma) = \frac{S_{jk}^{(1)*}(s; \beta_{jk}, \gamma)}{S_{jk}^{(0)*}(s; \beta_{jk}, \gamma)}, \]

where
\[ S_{jk}^{(d)*}(s; \beta_{jk}, \gamma) = \frac{1}{n} \sum_{i=1}^{n} \hat{W}_{ijk}^*(s; \gamma) Z_{ij}^{d} \exp\{\beta_{jk}' Z_{ij}\}, \quad d = 0, 1, 2. \]

From (2.9), the estimator of \( \Lambda_{0jk}(t; t_{j-1}) \), represented by \( \hat{\Lambda}_{ijk}^*(t; \beta_{jk}, \gamma, t_{j-1}) \), is given by,
\[ \hat{\Lambda}_{ijk}^*(t; \beta_{jk}, \gamma, t_{j-1}) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{t} \frac{\hat{W}_{ijk}^*(s; \gamma)}{S_{jk}^{(0)*}(s; \beta_{jk}, \gamma)} N_{ijk}(ds; t_{j-1}). \]
\[ (2.11) \]
To check the proportionality assumption of Model 1, we plot $\Delta U^l_n(\hat{\beta},t)$ versus time $t$, where $\Delta U^l_n(\hat{\beta},t)$ is the increment in $U^l_n(\hat{\beta},t)$, the $l$th component of $U_n(\hat{\beta},t)$. Similarly to check the proportionality assumption of Model 2, we plot $\Delta U^*_l(\hat{\beta}_{jk},t)$ versus time $t$, where $\Delta U^*_l(\hat{\beta}_{jk},t)$ is the increment in $U^*_l(\hat{\beta}_{jk},t)$, the $l$th component of $U^*_n(\hat{\beta}_{jk},t)$. If the plot is centered around zero for all $t$, then the assumption of proportionality is deemed reasonable.

2.4 Asymptotic Properties

We only discuss asymptotic properties of $\hat{\beta}_{jk}$ and $\hat{\Lambda}_{0jk}(t; t_{j-1})$. The asymptotic properties of $\hat{\beta}$ can be established in a similar manner.

First define the quantities

$$V_{jk}(s; \hat{\beta}_{jk}, \hat{\gamma}) = \frac{S_{jk}^{(2)}(s; \hat{\beta}_{jk}, \hat{\gamma})}{S_{jk}^{(0)}(s; \hat{\beta}_{jk}, \hat{\gamma})} - E_{jk}(s; \hat{\beta}_{jk}, \hat{\gamma})^{\otimes 2};$$  \hspace{1cm} (2.12)

$$s_{jk}^{(d)}(s; \hat{\beta}_{jk}) = E[W_{1jk}(s)Z_{1j}^{\otimes d} \exp{\{\hat{\beta}_{jk}Z_{1j}\}}];$$  \hspace{1cm} (2.13)

$$e_{jk}(s; \hat{\beta}_{jk}) = \frac{s_{jk}^{(1)}(s; \hat{\beta}_{jk})}{s_{jk}^{(0)}(s; \hat{\beta}_{jk})};$$  \hspace{1cm} (2.14)

and

$$v_{jk}(s; \hat{\beta}_{jk}) = \frac{s_{jk}^{(2)}(s; \hat{\beta}_{jk})}{s_{jk}^{(0)}(s; \hat{\beta}_{jk})} - e_{jk}(s; \hat{\beta}_{jk})^{\otimes 2};$$  \hspace{1cm} (2.15)

where $s_{jk}^{(d)}(s; \hat{\beta}_{jk})$, $e_{jk}(s; \hat{\beta}_{jk})$ and $v_{jk}(s; \hat{\beta}_{jk})$ are the limiting values of $S_{jk}^{(d)}(s; \hat{\beta}_{jk}, \hat{\gamma})$, $E_{jk}(s; \hat{\beta}_{jk}, \hat{\gamma})$ and $V_{jk}(s; \hat{\beta}_{jk}, \hat{\gamma})$ respectively. The counting process for censoring situation is given by

$$N^C_i(t) = I(X_{iJ} \leq t, \Delta_{iJ} = 0), \hspace{1cm} Y^*_i(t) = I(X_{iJ} \geq t).$$
and
\[ M_i^\gamma(t; \gamma) = N_i^C(t) - \int_0^t Y_i(s) \exp\{\gamma Z_i^C\} d\Lambda_0^C(s), \]
where \( M_i^\gamma(t; \gamma) \) is a martingale with respect to the filtration \( \mathbb{F}_t = \sigma\{Y_i(s), Z_i^C, N_i^C(s-); s \in [0, t]\} \).

Assume that the following conditions hold for \( i = 1, 2, \ldots, n \).

1. \( \{N_{ijk}(.; t_{j-1}), Y_{ij}(.; t_{j-1}), Z_{ij}\}, j = 1, 2, \ldots, J \) and \( k = 1, 2, \ldots, K \) are independent and identically distributed.

2. \( \Pr(D_i \geq t^*) > 0 \) and \( \Pr(X_{ij}^* \geq t_j^* \geq 0) > 0 \) for \( j = 1, 2, \ldots, J \).

3. The matrix \( A(\beta_{jk}) = \int_{t_j^*}^{t^*} v_{jk}(s; \beta_{jk}) s_{jk}^{(0)}(s; \beta_{jk}) \Lambda_0 ds; t_{j-1} \) is positive definite.

Also assume boundedness of \( Z_{im}^C \) for \( m = 1, 2, \ldots, p_C \) in the same sense as positive definiteness of the matrix,

\[ A^C(\gamma) = \int_{t_j^*}^{t^*} v(s; \gamma) s_{i}^{(0)}(s; \gamma) d\Lambda_0^C(s), \]

where define
\[ S_{d}^{(d)}(s; \gamma) = \frac{1}{n} \sum_{i=1}^{n} Y_i(s) Z_{i}^{C^{\otimes d}} \exp\{\gamma Z_i^C\}, \quad d = 0, 1, 2, \]
\[ E_C(s; \gamma) = \frac{S_{d}^{(1)}(s; \gamma)}{S_{d}^{(0)}(s; \gamma)} \]
and
\[ V_C(s; \gamma) = \frac{S_{d}^{(2)}(s; \gamma)}{S_{d}^{(0)}(s; \gamma)} - E_C(s; \gamma)^{\otimes 2}, \]
with their respective limiting values \( s_{d}^{(d)}(s; \gamma), e_C(s; \gamma) \) and \( v_C(s; \gamma) \).
2.4. ASYMPTOTIC PROPERTIES

To prove the asymptotic normality of \( \hat{\beta}_{jk} \), define the following quantities.

\[
q_{jk:n}(s; \beta_{jk}, \gamma) = \frac{1}{n} \sum_{i=1}^{n} \exp\{\gamma Z_{ij}^c\} \int_{0}^{t_j^*} \{Z_{ij} - E_{jk}(r; \beta_{jk})\} I(r + T_{ij-1} \geq s)W_{ijk}(r)M_{ijk}(dr; \beta_{jk}, t_{j-1}),
\]

\[
b_{ij}(t; \gamma) = \int_{0}^{t} \exp\{\gamma' Z_{i}^{c}\}\{Z_{i}^{c} - e_{C}(s; \gamma)\}d\Lambda_{C}^{c}(s),
\]

\[
Q_{jk:n}(\beta_{jk}; \gamma) = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{t_j^*} \{Z_{ij} - E_{jk}^{*}(s; \beta_{jk}, \gamma)\} b_{ij}(s + T_{ij-1}; \gamma)^{\prime}W_{ijk}(s)M_{ijk}(ds; \beta_{jk}, t_{j-1}),
\]

\[
U_{i,c}^{C}(\gamma, t) = \int_{0}^{t^*} \{Z_{i}^{c} - e_{C}(s; \gamma)\}dM_{i}^{C}(s; \gamma)
\]

and

\[
U_{i,jk}^{C}(\beta_{jk}; t) = \int_{0}^{t_j^*} \{Z_{ij} - e_{jk}(s; \beta_{jk})\}W_{ijk}(s)M_{ijk}(ds; \beta_{jk}, t_{j-1}) + I(j \geq 2) \int_{0}^{t^*} q_{jk}^{C}(s; \beta_{jk}, \gamma)s_{C}^{(0)}(s; \gamma)^{-1}dM_{i}^{C}(s; \gamma)
\]

\[
+ I(j \geq 2)Q_{jk}(\beta_{jk}; \gamma)A_{C}(\gamma)^{-1}U_{i,c}^{C}(\gamma, t),
\]

where \( q_{jk}^{C}(s; \beta_{jk}, \gamma) \) and \( Q_{jk}(\beta_{jk}; \gamma) \) are the limiting values of \( q_{jk:n}(s; \beta_{jk}, \gamma) \) and \( Q_{jk:n}(\beta_{jk}, \gamma) \) respectively.

**Theorem 2.1.** Under conditions 1 - 3, \( \hat{\beta}_{jk}^{\gamma} \) is a strongly consistent estimator of \( \beta_{jk} \) and \( \sqrt{n}(\hat{\beta}_{jk}^{\gamma} - \beta_{jk}) \) converges to a p-variate normal distribution with mean 0_{p \times 1} and covariance matrix \( \sum^{\gamma}(\beta_{jk}) \).
where \( \sum_{j,k} \gamma (\beta_{jk}) = A(\beta_{jk})^{-1} B^\gamma (\beta_{jk}) A(\beta_{jk})^{-1}' \) with \( A(\beta_{jk}) \) as defined in condition 3 and

\[
B^\gamma (\beta_{jk}) = E[\{ \sum_{j=1}^J \sum_{k=1}^K U_{i,jk}(\beta_{jk}, t) \} \otimes 2],
\]

where \( U_{i,jk}(\beta_{jk}, t) \) as given in (2.19).

Proof. The strong consistency of \( \hat{\beta}_{jk}^\gamma \) is established by considering the properties of the function

\[
\frac{1}{n} \left\{ l_n^\gamma (\beta_{jk}) - l^\gamma (\beta_{jk}) \right\},
\]

where

\[
l_n^\gamma (\beta_{jk}) = \sum_{i=1}^n \int_0^{t_j} \left[ \beta_{jk} Z_{ij} - \log \left\{ n S_{jk}(0) \right\} \right] \hat{W}_{ijk}(s; \hat{\gamma}) N_{ijk}(ds; t_{j-1})
\]

and

\[
\frac{\partial l_n^\gamma (\beta_{jk})}{\partial \beta_{jk}} = U_n^\gamma (\beta_{jk}, t).
\]

The asymptotic normality can be proved through the expression \( n^{1/2}(\hat{\beta}_{jk}^\gamma - \beta_{jk}) \) as a normalized sum of independent and identically distributed random vectors. The rest of the proof is similar to that of Theorem 1 in Schaubel and Cai (2004). \qed

Next we discuss the limiting behavior of the estimators of the cumulative baseline cause specific hazard rate functions.

Define the quantities

\[
m_{jk;n}(s, t; \beta_{jk}, \gamma) = \frac{1}{nk} \sum_{i=1}^n \exp\left\{ \gamma' Z_i' \right\} \int_0^t I(s \leq r + T_{ij-1}) W_{ijk}(r) M_{ijk}(dr; \beta_{jk}, t_{j-1}),
\]

\[
x_{jk;n}(t; \beta_{jk}, \gamma) = \frac{1}{nk} \sum_{i=1}^n \int_0^t \hat{W}_{ijk}(s; \gamma) \hat{b}_{ij}(s + T_{ij-1}; \gamma) M_{ijk}(ds; \beta_{jk}, t_{j-1})
\]

(2.20)
and

\[
y_{j;k;n}(t; \beta_{jk}; \gamma) = \frac{1}{nk} \sum_{i=1}^{n} \int_0^t \frac{\hat{W}_{ijk}(s; \gamma)}{\{S_{jk}^{(0)}(s; \beta_{jk}, \gamma)\}^2} f_{j;k;n}(s + T_{ij-1}; \beta_{jk}, \gamma)^{\prime} M_{ijk}(ds; \beta_{jk} t_{j-1}),
\]

(2.22)

where

\[
f_{j;k;n}(s + T_{ij-1}; \beta_{jk}, \gamma) = -\frac{1}{nk} \sum_{i=1}^{n} \hat{W}_{ijk}(s; \gamma) \exp\{\beta_{ijk} Z_{ij}\} \hat{b}_{ij}(s + T_{ij-1}; \gamma).
\]

(2.23)

The limiting values of above quantities are denoted by \(m_{jk}(s, t; \beta_{jk}, \gamma), x_{jk}(t; \beta_{jk}, \gamma), y_{jk}(t; \beta_{jk}, \gamma)\) and \(f_{jk}(s + T_{ij-1}; \beta_{jk}, \gamma)\) respectively.

Let

\[
\rho_{i,j,k}(t; \beta_{jk}, \gamma) = \int_0^t \frac{W_{ijk}(s)}{S_{jk}^{(0)}(s; \beta_{jk})} M_{ijk}(ds; \beta_{jk}, t_{j-1}) + g_{ijk}(t; \beta_{jk}) A(\beta_{jk})^{-1} \sum_{j=1}^{J} \sum_{k=1}^{K} U_{i,j,k}(\beta_{jk}, t) \\
+ I(j \geq 2) \int_0^t m_{jk}(s, t; \beta_{jk}, \gamma) S_{C}^{(0)}(s; \gamma)^{-1} dM_{i}^{C}(s; \gamma) \\
+ I(j \geq 2) \{x_{jk}(t; \beta_{jk}, \gamma) + y_{jk}(t; \beta_{jk}, \gamma)\} A^{C}(\gamma)^{-1} U_{i,c}^{C}(\gamma, t),
\]

(2.24)

with \(g_{ijk}(t; \beta_{jk}) = -\int_0^t e_{jk}(s; \beta_{jk}) \Lambda_{0,jk}(ds, t_{j-1}), U_{i,c}^{C}(\gamma, t)\) and \(U_{i,j,k}(\beta_{jk}, t)\) as defined in (2.18) and (2.19) respectively.

**Theorem 2.2.** Under conditions 1 - 3, \(\hat{\Lambda}_{0,jk}(t; \beta_{jk}, \gamma, t_{j-1})\) converges almost surely to \(\Lambda_{0,jk}(t; t_{j-1})\), uniformly in \(t \in [0, t^*]\) and \(n^{1/2}(\hat{\Lambda}_{0,jk}(t; \beta_{jk}, \gamma, t_{j-1}) - \Lambda_{0,jk}(t; t_{j-1}))\) converges weakly to a Gaussian process with mean 0 and covariance function

\[
\sigma_{jk}(s, t; t_{j-1}) = E\{\rho_{i,j,k}(s; \beta_{jk}, \gamma) \rho_{i,j,k}(t; \beta_{jk}, \gamma)\},
\]

where \(\rho_{i,j,k}(t; \beta_{jk}, \gamma)\) as given in (2.24).
2.5. DATA ANALYSIS

\textbf{Proof.} The proof for uniform consistency of \( \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}) \) follows from the fact that \( \hat{\gamma} \) and \( \hat{\Lambda}^\gamma_0(t; \hat{\gamma}, t_{j-1}) \) are strong consistent estimators of \( \gamma \) and \( \Lambda^\gamma_0(t; \gamma, t_{j-1}) \).

Set
\[
H^\gamma_{jk:n}(t) = \{ \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}) - \Lambda^\gamma_0(t; t_{j-1}) \} = \sum_{l=1}^3 H^\gamma_{jk:l:n}(t),
\]
where
\[
H^\gamma_{jk1:n}(t) = \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}) - \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}), \tag{2.25}
\]
\[
H^\gamma_{jk2:n}(t) = \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}) - \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}) \tag{2.26}
\]
and
\[
H^\gamma_{jk3:n}(t) = \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}) - \Lambda^\gamma_0(t; t_{j-1}). \tag{2.27}
\]

The identities (2.25) and (2.26) converge to 0 almost surely and \( \hat{\Lambda}^\gamma_{0jk}(t; \hat{\beta}^\gamma_{jk}, \hat{\gamma}, t_{j-1}) - \Lambda^\gamma_0(t; t_{j-1}) \) can be asymptotically expressed as a sum of independent and identically distributed zero mean random variates. Then the proof for asymptotic normality follows from the proof of Theorem 2 given in Schaubel and Cai (2004). \( \square \)

2.5 Data Analysis

The proposed method is applied to the bladder tumor data given in Kalbfleisch and Prentice (2002). The data set includes 48 patients assigned to placebo in which there were a total of 87 observed recurrence times and 38 patients assigned to thiotepa in whom there were 45 recurrence times during trial follow up, which averaged about 31 months. Tumors present at baseline were removed transurethrally prior to randomization. The possible dependence of the recurrence rate on the number and sizes of pre-randomization tumors is also of interest. Number and sizes of initial tumors are considered as two covariates. Treatment groups, placebo and thiotepa are treated as two different causes.
The primary objective is to determine the effect of number and sizes of initial tumors for different causes on the hazard rate functions corresponding to the recurrence times. For Model 1, the vector of regression parameters are assumed to be the same for all $j$ and $k$. The estimate of $\beta$ and its mean square error (MSE) are computed which are presented in Table 2.1. The bootstrap procedure is employed to compute the mean square error of $\hat{\beta}$. The covariate, number of initial tumors has negative effect and sizes have positive effect on the cumulative baseline cause specific hazard rate functions.

Table 2.1: Estimates and MSE of the parameter vector for Model 1.

<table>
<thead>
<tr>
<th></th>
<th>Estimates</th>
<th>MSE of $\hat{\beta}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1$</td>
<td>-0.24846</td>
<td>0.58123</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.30457</td>
<td>0.41175</td>
</tr>
</tbody>
</table>

To check the proportionality assumption, we plot $\Delta U_n^l(\hat{\beta}, t)$ versus the follow up time, $l = 1, 2$. Since the plots given in Figure 2.1 are centered around zero for all time $t$ the assumption of proportionality is valid.

The estimates of the cumulative baseline cause specific hazard rate functions are also computed. The plots of the estimates of $\Lambda_{0jk}(t)$ for $j = 1, 2$ and $k = 1, 2$, are given in Figure 2.2. In Figure 2.2, the darkened line corresponds to first recurrence time and the dotted line corresponds to second recurrence time. Figure 2.2 suggests that the causes have less effect on recurrences.

For Model 2, the parameter vector depends on all the recurrences and all the failure types. The estimates of $\beta_{jk}$ and MSE of $\hat{\beta}_{jk}$ are computed, for $j = 1, 2$ and $k = 1, 2$. The mean square errors are computed using the bootstrap method, which are given in Table 2.2. From Table 2.2, it follows that, the covariate, number of tumors has negative effect on the first recurrence times and the second recurrence times of the individuals with first cause. However, the covariate, size has negative effect on the first and the second recurrence times of the individual with second cause and positive effect on the first and the second recurrence times with first cause.
2.5. DATA ANALYSIS

Figure 2.1: (a) Plot of the residuals $\Delta U^1_n(\hat{\beta}, t)$, (b) Plot of the residuals $\Delta U^2_n(\hat{\beta}, t)$, for Model 1.
Figure 2.2: Plots of cumulative baseline cause specific hazard rate functions for Model 1.

(a) - cause 1

(b) - cause 2
Table 2.2: Estimates and MSE of the parameter vectors for Model 2.

<table>
<thead>
<tr>
<th>Gap time</th>
<th>Covariates</th>
<th>Causes</th>
<th>$\hat{\beta}_{jk}$</th>
<th>MSE of $\hat{\beta}_{jk}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J = 1$</td>
<td>Number of tumors</td>
<td>Placebo Group</td>
<td>-1.9958</td>
<td>0.25403</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiotepa Group</td>
<td>1.2192</td>
<td>0.14261</td>
</tr>
<tr>
<td></td>
<td>Size</td>
<td>Placebo Group</td>
<td>0.0754</td>
<td>0.19919</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiotepa Group</td>
<td>-0.0074</td>
<td>0.00095</td>
</tr>
<tr>
<td>$J = 2$</td>
<td>Number of tumors</td>
<td>Placebo Group</td>
<td>-1.5681</td>
<td>0.05178</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiotepa Group</td>
<td>-0.0896</td>
<td>0.03303</td>
</tr>
<tr>
<td></td>
<td>Size</td>
<td>Placebo Group</td>
<td>0.4021</td>
<td>0.05402</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiotepa Group</td>
<td>-0.6764</td>
<td>0.02629</td>
</tr>
</tbody>
</table>

Similarly for the second model, the plots $\Delta U_{jk}(\hat{\beta}_{jk}, t)$ versus follow up time, $l = 1, 2$ and $k = 1, 2$ are given in Figure 2.3. This plot is also centered around zero for all time $t$. In Figure 2.3, the darkened line corresponds to the covariate 1 (number of tumors) and the dotted line corresponds to the covariate 2 (sizes). From Figure 2.3, it is shown that the proportionality assumption is valid for Model 2.

The estimates of cumulative baseline cause specific hazard rate functions are computed and these are plotted in Figure 2.4. In Figure 2.4, the darkened line corresponds to first recurrence time and the dotted line corresponds to second recurrence time. From Figure 2.4, it is clear that the cause placebo has more effect on second recurrence time than cause thiotepa. The cause placebo has less effect on the first recurrence time than cause thiotepa.
Figure 2.3: (a) Plot of the residuals $\Delta U_n^{I_j}(\hat{\beta}_{j1}, t)$, (b) Plot of the residuals $\Delta U_n^{I_j}(\hat{\beta}_{j2}, t)$, for Model 2.
2.5. DATA ANALYSIS

Figure 2.4: Plots of cumulative baseline cause specific hazard rate functions for Model 2.

(a) – cause 1

(b) – cause 2

Figure 2.4: Plots of cumulative baseline cause specific hazard rate functions for Model 2.
2.6 Simulation Studies

In this section, we carry out a simulation study to evaluate the performance of the aforementioned inference procedures. The results for Model 2 are presented here. We consider a Gumbel’s (1960) bivariate exponential distribution with survival function

\[ S(t_1, t_2) = \exp(-t_1 - t_2 - \theta t_1 t_2), \quad 0 \leq \theta \leq 1. \]  

(2.28)

We consider two causes of failure with \( J = 2 \). A single covariate \( Z \) is generated from uniform \([0, 1]\) distribution. For \( k = 1, 2 \), the gap times are generated from Gumbel’s bivariate exponential distribution such that

\[ P(T_{i1k} > t_1 | Z) = \exp\{-t_1 e^{\beta_{1k} Z}\} \quad \text{and} \quad P(T_{i2k} > t_2 | T_{i1k} > t_1, Z) = \exp\{-(1 + \theta t_1) t_2 e^{\beta_{2k} Z}\} \]

for various combinations of \( \theta \) and \( \beta_{jk} \). Censoring times are generated as \( D_i = D_i^* \wedge t^* \), where \( D_i^* \sim \text{Exp}(\lambda_0^C \exp(\gamma_0 Z_i)) \) with \( \gamma_0 = \log(1.25) \). Approximately 30% of the observations are censored.

The estimates of \( \beta_1 = (\beta_{11}, \beta_{12})' \) and \( \beta_2 = (\beta_{21}, \beta_{22})' \) are computed based on one thousand simulations for different combinations of \( \theta \) and \( n \). The average empirical bias and mean squared error (MSE) of the estimates \( \hat{\beta}_{11}^\gamma, \hat{\beta}_{12}^\gamma, \hat{\beta}_{21}^\gamma \) and \( \hat{\beta}_{22}^\gamma \) are presented in Table 2.3 to Table 2.6. The average empirical bias and MSE of the estimates of cumulative baseline cause specific hazard rate functions are given in Table 2.7 to Table 2.10. As \( n \) increases, both bias and MSE of the estimates decrease. From Tables 2.3 and 2.5, one can observe that the biases of \( \hat{\beta}_{11}^\gamma \) and \( \hat{\beta}_{21}^\gamma \) are all negative except for one combination of parameter values. From Table 2.7 and Table 2.8, it is obvious that the biases of \( \hat{\Lambda}_{011}^\gamma \) and \( \hat{\Lambda}_{012}^\gamma \) are negative for all combinations of parameter values. From Table 2.9 and Table 2.10, it follows that the biases of \( \hat{\Lambda}_{021}^\gamma \) and \( \hat{\Lambda}_{022}^\gamma \) are positive for all combinations of parameter values. Wald 95% confidence interval empirical coverage probability for the proposed estimates of \( \beta_{jk} \) and \( \Lambda_{0jk} \) are calculated. The censoring distribution was estimated using the Breslow-Aalen estimator based on a proportional hazards model fitted to
\{X_{i,2}; 1 - \Delta_{i2}, Z_i\}, i = 1, 2, \ldots, n.

From the tables, one can observe that the coverage probabilities are closely approximate the nominal 95\% confidence level.

Table 2.3: Bias and MSE of \( \hat{\beta}_{11}^{\gamma} \).

<table>
<thead>
<tr>
<th>( \beta_{11} )</th>
<th>( \beta_{12} )</th>
<th>( \beta_{21} )</th>
<th>( \beta_{22} )</th>
<th>( \theta )</th>
<th>( n )</th>
<th>Bias of ( \hat{\beta}_{11}^{\gamma} )</th>
<th>MSE of ( \hat{\beta}_{11}^{\gamma} )</th>
<th>Coverage probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.65</td>
<td>0.5</td>
<td>100 \hspace{1em} 200</td>
<td>-0.0099 \hspace{1em} -0.0082</td>
<td>0.0322 \hspace{1em} 0.0119</td>
<td>0.935 \hspace{1em} 0.942</td>
</tr>
<tr>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.65</td>
<td>0.6</td>
<td>100 \hspace{1em} 200</td>
<td>-0.0398 \hspace{1em} -0.0393</td>
<td>0.0223 \hspace{1em} 0.0120</td>
<td>0.945 \hspace{1em} 0.954</td>
</tr>
<tr>
<td>0.4</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>100 \hspace{1em} 200</td>
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<td>0.0202 \hspace{1em} 0.0118</td>
<td>0.969 \hspace{1em} 0.970</td>
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<td>0.4</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
<td>0.9</td>
<td>100 \hspace{1em} 200</td>
<td>0.0102 \hspace{1em} -0.0040</td>
<td>0.0338 \hspace{1em} 0.0123</td>
<td>0.964 \hspace{1em} 0.965</td>
</tr>
</tbody>
</table>

Table 2.4: Bias and MSE of \( \hat{\beta}_{12}^{\gamma} \).

<table>
<thead>
<tr>
<th>( \beta_{11} )</th>
<th>( \beta_{12} )</th>
<th>( \beta_{21} )</th>
<th>( \beta_{22} )</th>
<th>( \theta )</th>
<th>( n )</th>
<th>Bias of ( \hat{\beta}_{12}^{\gamma} )</th>
<th>MSE of ( \hat{\beta}_{12}^{\gamma} )</th>
<th>Coverage probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.65</td>
<td>0.5</td>
<td>100 \hspace{1em} 200</td>
<td>0.0050 \hspace{1em} -0.0334</td>
<td>0.0278 \hspace{1em} 0.0107</td>
<td>0.945 \hspace{1em} 0.956</td>
</tr>
<tr>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.65</td>
<td>0.6</td>
<td>100 \hspace{1em} 200</td>
<td>-0.0281 \hspace{1em} -0.0243</td>
<td>0.0318 \hspace{1em} 0.0115</td>
<td>0.935 \hspace{1em} 0.951</td>
</tr>
<tr>
<td>0.4</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>100 \hspace{1em} 200</td>
<td>0.0327 \hspace{1em} -0.0294</td>
<td>0.0331 \hspace{1em} 0.0104</td>
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</tr>
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<td>0.4</td>
<td>0.6</td>
<td>0.9</td>
<td>100 \hspace{1em} 200</td>
<td>0.0056 \hspace{1em} -0.0492</td>
<td>0.0255 \hspace{1em} 0.0179</td>
<td>0.946 \hspace{1em} 0.953</td>
</tr>
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</table>
### 2.6. SIMULATION STUDIES

Table 2.5: Bias and MSE of $\hat{\beta}_{21}$.

<table>
<thead>
<tr>
<th>$\beta_{11}$</th>
<th>$\beta_{12}$</th>
<th>$\beta_{21}$</th>
<th>$\beta_{22}$</th>
<th>$\theta$</th>
<th>$n$</th>
<th>Bias of $\hat{\beta}_{21}$</th>
<th>MSE of $\hat{\beta}_{21}$</th>
<th>Coverage probability</th>
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<td>0.935</td>
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</tr>
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<td>0.8</td>
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<td>0.6</td>
<td>100</td>
<td>-0.0583</td>
<td>0.0430</td>
<td>0.945</td>
</tr>
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<td>0.0214</td>
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</table>

Table 2.6: Bias and MSE of $\hat{\beta}_{22}$.

<table>
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<tr>
<th>$\beta_{11}$</th>
<th>$\beta_{12}$</th>
<th>$\beta_{21}$</th>
<th>$\beta_{22}$</th>
<th>$\theta$</th>
<th>$n$</th>
<th>Bias of $\hat{\beta}_{22}$</th>
<th>MSE of $\hat{\beta}_{22}$</th>
<th>Coverage probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.65</td>
<td>0.5</td>
<td>100</td>
<td>-0.0323</td>
<td>0.0451</td>
<td>0.945</td>
</tr>
<tr>
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<td>0.8</td>
<td>0.65</td>
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<td>100</td>
<td>0.0321</td>
<td>0.0449</td>
<td>0.951</td>
</tr>
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<td>-0.0005</td>
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</tbody>
</table>
Table 2.7: Bias and MSE of $\hat{\Lambda}_{011}^\gamma$.

<table>
<thead>
<tr>
<th>$(t_1, t_2)$</th>
<th>$\theta$</th>
<th>$n$</th>
<th>Bias of $\hat{\Lambda}_{011}^\gamma$</th>
<th>MSE of $\hat{\Lambda}_{011}^\gamma$</th>
<th>Coverage probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.05,0.06)</td>
<td>0.5</td>
<td>100</td>
<td>-0.0101</td>
<td>0.00020</td>
<td>0.945</td>
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<tr>
<td></td>
<td></td>
<td>200</td>
<td>-0.0097</td>
<td>0.00008</td>
<td>0.962</td>
</tr>
<tr>
<td>(0.05,0.06)</td>
<td>0.6</td>
<td>100</td>
<td>-0.0144</td>
<td>0.00016</td>
<td>0.950</td>
</tr>
<tr>
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<td>200</td>
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<td>0.952</td>
</tr>
<tr>
<td>(0.09,0.07)</td>
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<td>100</td>
<td>-0.0167</td>
<td>0.00035</td>
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<td>-0.0229</td>
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</tbody>
</table>

Table 2.8: Bias and MSE of $\hat{\Lambda}_{012}^\gamma$.

<table>
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<tr>
<th>$(t_1, t_2)$</th>
<th>$\theta$</th>
<th>$n$</th>
<th>Bias of $\hat{\Lambda}_{012}^\gamma$</th>
<th>MSE of $\hat{\Lambda}_{012}^\gamma$</th>
<th>Coverage probability</th>
</tr>
</thead>
<tbody>
<tr>
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<td>100</td>
<td>-0.0284</td>
<td>0.00023</td>
<td>0.956</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200</td>
<td>-0.0272</td>
<td>0.00012</td>
<td>0.962</td>
</tr>
<tr>
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<td>-0.0249</td>
<td>0.00022</td>
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</table>
Table 2.9: Bias and MSE of $\hat{\Lambda}_{021}^{\gamma*}$.

<table>
<thead>
<tr>
<th>$(t_1, t_2)$</th>
<th>$\theta$</th>
<th>$n$</th>
<th>Bias of $\hat{\Lambda}_{021}^{\gamma*}$</th>
<th>MSE of $\hat{\Lambda}_{021}^{\gamma*}$</th>
<th>Coverage probability</th>
</tr>
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<td>0.0612</td>
<td>0.03279</td>
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<td>0.02755</td>
<td>0.959</td>
</tr>
<tr>
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<td>0.0452</td>
<td>0.01987</td>
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<tr>
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<td>0.0459</td>
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Table 2.10: Bias and MSE of $\hat{\Lambda}_{022}^{\gamma*}$.

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<th>MSE of $\hat{\Lambda}_{022}^{\gamma*}$</th>
<th>Coverage probability</th>
</tr>
</thead>
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<td>0.00959</td>
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</tbody>
</table>
2.7 Conclusion

Two semiparametric models for gap time distributions of recurrent event data with multiple causes have been discussed in this chapter. To overcome the issue of non-identifiability, the conditional distribution discussed by Lin et al. (1999) is considered. The induced dependent censoring discussed in Schaubel and Cai (2004) for the analysis of gap time distributions of recurrent event is extended to multiple causes setup. Counting process approach is used for estimating the parameter vector and cumulative baseline cause specific hazard rate functions. The method is illustrated with the bladder tumor data given in Kalbfleisch and Prentice (2002).

In the present work, we employed the method of plotting $\Delta U_n^t(\hat{\beta}_{jk}, t)$ versus time $t$ to verify the proportionality assumption. Other regression diagnostic techniques such as martingale residual method, Cox-Snell residual technique and Andersen plot can be also used to check the proportional hazards assumption.