ANALYZING LONGITUDINALLY CORRELATED FAILURE TIME DATA: A GENERALIZED ESTIMATING EQUATION APPROACH

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Analyzing Longitudinally Correlated Failure Time Data : A Generalized Estimating Equation Approach

by

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Abstract

Multivariate correlated failure time data can be classified into two different groups: structural failure time data and longitudinal failure time data. As compared to the analysis of the structural failure time data, the analysis of longitudinal failure time data has however proven to be difficult, perhaps because of the difficulty in the modeling the true longitudinal correlation structures. In the present thesis, following certain longitudinal correlation models, recently developed for discrete data, we develop three longitudinal correlation models for exponential failure times to deal with such multivariate longitudinal data. Under these three models, we construct the covariance structures of the martingales of the failure times for both uncensored and censored cases, and use them to develop a generalized estimating equation approach to estimate the parameters of main interest, namely, the hazard ratio parameters. The efficiency loss due to misspecification of the correlation structure is studied for both uncensored and censored cases. As the proposed generalized estimating equation approach use either the underlying true correlation structure for both uncensored and censored cases or a suitable robust correlation structure for the uncensored case, the methodology yields consistent as well as efficient estimators for the hazard ratio parameters. We apply the methodology to a numerical example.

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Chapter 1

Introduction

1.1 Motivation for Multivariate Failure Time Data Analysis

The regression models for univariate failure time data have been extensively studied in the literature. For example, we refer to Kalbfleisch and Prentice (1980), Lawless (1982), Cox and Oakes (1984) and the references therein. The univariate regression failure time problems mostly arise in medical and engineering studies. For example, Kardaun (1983) (see also Klein and Moeschberger, 1997) reports data on 90 males diagnosed with cancer of the larynx during the period 1970-1978 at a Dutch hospital. Times recorded are intervals (in years) between first treatment and either death or the end of the study (January 1, 1983). Also recorded are the patient's age at the time of diagnosis, the year of diagnosis (from 1970-1978) and the stage of the patient's cancer where stage of the disease was defined based on certain characteristics, namely, the primary tumor, nodal involvement and distant metastasis by the American Joint Committee for Cancer Staging (1972). Here the failure time of the individual male is the univariate response, and age and the cancer stage of the individual patient are the covariates. If any patient is not dead by the end of the study or somehow missing from the study without death then that patient has considered as censored. In the above example, it is of interest to find the regression effect of age and stage of cancer on the failure times of the patients.

There are however many situations in practice where the failure time data are collected from a large number of groups or clusters of size more than one. For example, in connection with the above larynx cancer study, the failure responses along with the corresponding covariates could be collected from 90 groups of siblings (related to the individual male) instead of 90 individual males. For analyzing this type of data, one has to take the correlation of the responses of the siblings of the group into account as the failure times arise from the related members of the same group. The analysis of such multi-dimensional failure time data is referred to as the structural or familial failure time data analysis. Over the last two decades, there has been a good number of initiatives to analyze such structural failure time data. For example, we refer to Clayton and Cuzick (1985), Prentice and Cai (1992), Cai and Prentice (1995), Prentice and Zhao (1991), Prentice and Hsu (1997), Cai, Wei and Wilcox (2000). The main thrust of these studies is to obtain consistent estimators for the regression effects after taking the correlation among the failure times into account. A limited number of studies, such as Cai and Prentice (1995) also studied the efficiency aspects of the regression estimators for independent versus certain dependent structures.

Similar to but different than the structural set up, it may also be the case that failure time data are collected repeatedly for a number of periods from each of a large number of individuals. For example, in Byar's (1980) bladder cancer study 86 patients had superficial bladder tumors when they entered the trial. These tumors were removed and patients were randomly assigned to one of three treatments. If tumors reoccured then the patient was supposed to visit the clinic. Thus, the patients were followed for a repeated number of times and their failure times and covariate information were repeatedly recorded. Here it is reasonable to assume that these repeated failure times are correlated as they arise from the same individual. To analyze this type of multivariate longitudinal or repeated failure time data one should however take the longitudinal correlations among the repeated failure times into account and compute the regression effects on the repeated failure times. Note that as opposed to the structural failure time data analysis the analysis of such longitudinal failure time data is not adequately addressed in the literature, although a limited number of attempts have been made towards such analysis. For example we refer to Wei, Lin and Weissfeld (1989) and Gao and Lin (1994). These authors have however used certain types of structural correlation to model the repeated data and examined the effects of correlations on the regression estimation. This naturally raises concerns to investigate the longitudinal correlation effects on the regression estimation by modeling the repeated data through suitable longitudinal correlations rather than structural correlations.

For the reasons discussed above, in this thesis, our motivation is to model the longitudinal correlation for repeated failure times using some flexible exponential models, which we believe will be the first attempt of this kind toward analyzing such regression data. We do this in the spirit of Liang and Zeger (1986), Sutradhar and Das (1999) and Jowaheer and Sutradhar (2001). Further, longitudinal correlations computed from the repeated failure time data will be utilized to obtain consistent as well as efficient estimates of the regression effects.

1.2 Objective of the Thesis

As the longitudinal failure time data (as opposed to the structural failure time data) are not analyzed adequately in the literature, in this thesis we model the longitudinal correlation for repeated failure times and find the consistent as well as efficient estimates of regression effects using this specific correlation structure. The specific plan of the thesis is as follows.

In Chapter 2, we provide some background for clustered models for failure times and review some methods used to analyze such correlated failure time data under the structural and longitudinal situations.

Chapter 3 concentrates on the derivation of the form of the bivariate survival function for certain general correlation structures, such as exponential AR(1), exponential MA(1) and exponential equi-correlation processes.

In Chapter 4 we will use the survival functions derived in Chapter 3, as well as some results of Cai and Prentice (1995), to derive the correlation matrix of the martingales for each of our exponential processes. This will be done for uncensored data. We will also present simulation results to compare the efficiencies of the hazard ratio parameter estimators under misspecification of the correlation structure. It will be shown that the efficiency loss can be quite dramatic if the incorrect correlation structure is used. Chapter 5 will extend the results of Chapter 4 to the case of censored data. Chapter 5 will also include an analysis of a data set consisting of the times of infection from the time of insertion of the catheter for 38 kidney patients using portable dialysis equipment.

We will give some conclusions in Chapter 6, including some results on using a robust correlation structure with longitudinal failure times, as well as areas of further research.

Chapter 2

Background of Clustered Models for Failure Time Data

Clustered failure times data arise in many situations, for example, in epidemiological cohort studies in which the ages of disease occurrence are recorded among members of a sample of families; in animal experiments where treatments are applied to samples of littermates; in clinical trials in which individual study subjects are followed for the occurance of repeated events.

Consider K independent failure time response vectors $\mathbf{T}_k^T=(T_{k1},T_{k2},\ldots,T_{kn})$ for $k = 1,2,\ldots,K$. For example $T_{k1}, T_{k2}, \ldots, T_{kn}$ may denote n disease occurance times for siblings in the kth family of a cohort study. In this problem, it will be of interest to find the effect of associated covariates on these failure times of the members of the families. To be specific, in a medical study involving heart diseases, the length of survival times after the first heart attack among the n siblings of the kth family form a multivariate life distribution. As the siblings of a family share a common family effect, it is reasonable to assume that the failure times of these siblings will be correlated. This type of correlation among the members of the families or cluster is referred to as structural correlation. Here it is of interest to find the effects of the treatments along with other covariates by taking these correlations into account.

As mentioned earlier, as opposed to the structural or familial correlation set up, there are situations where $T_{k1}, T_{k2}, \ldots, T_{kn}$ may denote the n repeated failure times for the kth patient in a clinical trial. Here the correlations among the repeated failure times are referred to as the longitudinal correlations. Note that while it may be sensible to think that the structural correlations may be caused by a certain common random effect shared by family members, it is however quite appropriate to assume that longitudinal correlations are usually observation driven, when observations are taken repeatedly from the same individual. In this problem, it will be of interest to find the effect of associated covariates on these repeated failure times of K individuals. An interesting example can be found in a bladder cancer study (Byar, 1980), which was conducted by the Veterans Administration Cooperative Urological Research Group. In this study all the patients had superficial bladder tumors when they entered the trial. These tumors were removed and patients were randomly assigned to one of three treatments. If the treatment was found to cease its actions, i.e. if tumors reoccured, the patient was supposed to visit the clinic. Here it is reasonable to assume that these repeated failure times are correlated. This type of correlation is referred to as longitudinal correlation.

Because of their importance in practice, structural and longitudinal failure time data, similar to the data discussed above, were analyzed by many authors over the last two decades. More specifically, many of these studies are found to deal with structural failure time data, while a limited number of studies concentrated on longitudinal failure time data analysis. We now describe some of the past research on structural and longitudinal failure time data analyses and their limitations in the following subsections.

2.1 Structural Models for Failure Time Data

Recall that $\mathbf{T}_k^T = (T_{k1}, T_{k2}, \ldots, T_{kn})$ for $k = 1, 2, \ldots, K$ are K independent failure time response vectors. Suppose that these n failure times are recorded for the n individuals of a cluster or family which are likely to be correlated. In general it is however very difficult to write a joint hazard function or joint probability density function for these n correlated failure times. As far as the marginal hazard function of a failure time is concerned, a marginal hazard function of the form (Cox 1972)

$$\lambda_{ki}(t) = Y_{ki}(t)\lambda_{0i}(t)\exp(\mathbf{Z}_{ki}^{T}(t)\boldsymbol{\beta}) \tag{2.1}$$

is widely used to model the failure time responses. In (2.1) $Y_{ki}(.)$ is an at risk indicator process for the *ith* member of the *kth* response vector. Therefore if C_{ki} is the corresponding censoring time of the failure time T_{ki} and X_{ki}=min(T_{ki},C_{ki}), then $Y_{ki} = I(X_{ki} \geq t)$, where $I(.)$ is an indicator function. We assume $\lambda_{0i}(.)$ is the unspecified baseline hazard function pertaining to the *ith* member of each response vector. Further $\mathbf{Z}_{ki}^{T}(.) = (Z_{ki1}(.), Z_{ki2}(.), ..., Z_{kip}(.))$ is a $1 \times p$ covariate vector corresponding to the *ith* member of the *kth* family, with failure times T_{ki}, where these covariate vectors $\mathbf{Z}_{ki}(.)$ may or may not be time dependent. In (2.1) $\boldsymbol{\beta}^{T}$=(β_1,β_2,...,β_p) is a hazard ratio, or relative risk parameter which is also referred to as the regression effects. Here our interest is to find the effects of the covariates $\boldsymbol{\beta}$ by taking the correlations of the failure times into account, as $T_{k1}, T_{k2}, \ldots, T_{kn}$ arise from the individuals of the same family.

In a bivariate set up Clayton and Cuzick (1985) have considered a marginal hazard model similar to (2.1) and modelled the correlations of the failure times by introducing a bivariate survival function for any two failure time responses. More specifically, they considered the bivariate survival function of two failure times T_1 and T_2 as

$$F(t_1, t_2; \gamma) = Pr(T_1 > t_1, T_2 > t_2; \gamma) = \left\{e^{\gamma t_1} + e^{\gamma t_2} - 1\right\}^{-1/\gamma} \tag{2.2}$$

where γ is the dependence parameter. This model gives independence between T_1 and T_2 when $\gamma = 0$ and maximal dependence as $\gamma \to \infty$. Note that the bivariate survival function in (2.2) yields the exponential marginal survival function which can be related to the marginal hazard function (2.1). Based on (2.1) and (2.2) these authors have exploited a maximum likelihood approach for joint estimation of $\boldsymbol{\beta}$ and γ.

Prentice and Cai (1992) have considered a similar bivariate correlation model to (2.2) and estimated the required survival function nonparametrically through the estimation of a covariance function of bivariate martingales. Here the martingale for the ith member of the kth family is defined as

$$M_{ki}(t) = N_{ki}(t) - \int_0^t \lambda_{ki}(s)ds, \tag{2.3}$$

where $N_{ki}(t) = I(X_{ki} \leq t, \Delta = 1)$, with $\Delta = \mathrm{I}(T_{ki}=X_{ki})$ and $I(.)$ denotes an indicator function. Note that the covariance function computed in Prentice and Cai (1992) is quite general which can be used to find the correlations for the martingales under the bivariate survival function $F(t_1, t_2)$ considered by Clayton and Cuzick (1985) as well as under other possible bivariate survival functions.

Cai and Prentice (1995) proposed a weighted partial likelihood estimating equation for estimating the marginal hazard ratio parameter $\boldsymbol{\beta}$ in (2.1) after taking the structural correlation of the failure times into account. More specifically , instead of using the unweighted estimating equation

$$\sum_{k=1}^{K} \int_0^\infty \mathbf{Z}_k^T(u)\mathbf{U}_k(du) = \mathbf{0} \tag{2.4}$$

they incorporated the correlation matrix of the martingales and constructed the weighted estimating equation given by

$$\sum_{k=1}^{K} \int_0^\infty \mathbf{Z}_k^T(u)\mathbf{W}_k(\boldsymbol{\beta}, u)\mathbf{U}_k(du) = 0 \tag{2.5}$$

for the estimation of $\boldsymbol{\beta}$. In (2.4) and (2.5)

$$\mathbf{Z}_k^T(u) = (\mathbf{Z}_{k1}(u), ..., \mathbf{Z}_{kn}(u)), \mathbf{U}_k^T(u) = (U_{k1}(u), ..., U_{kn}(u))$$

with

$$U_{ki}(t) = \hat{M}_{ki}(t) = N_{ki}(t) - \int_0^t Y_{ki}(s)\exp(\mathbf{Z}_{ki}^T(s)\boldsymbol{\beta})\hat{\Lambda}_{0i}(ds)$$

where

$$\hat{\Lambda}_{0i}(t) = \int_0^t [Y_{ki}(s)\exp(\mathbf{Z}_{ki}^T(s)\boldsymbol{\beta})]^{-1} \sum_{l=1}^{K} N_{li}(ds).$$

Further in (2.5) the weight matrix is

$$\mathbf{W}_k(\boldsymbol{\beta}, u) = (W_{kij}(\boldsymbol{\beta}, u))\,; \quad i, j = 1, 2, ...n$$

where $W_{kij}(\beta, u)$ is the $(i, j)th$ element of the inverse of the correlation matrix between the martingales, i.e.

$$\mathbf{W}_k(\boldsymbol{\beta}, u) = corr^{-1}(M_k(X_k)),$$

where $M_k(X_k) = [M_{k1}(X_{k1}), M_{k2}(X_{k2}), \ldots, M_{kn}(X_{kn})]$. Note that the efficient estimation of $\boldsymbol{\beta}$ in Cai and Prentice (1995) requires the consistent estimation of the correlation parameters, say γ, involved in $\mathbf{W}_k(\boldsymbol{\beta}, u)$. It is however not clear from Cai and Prentice (1995) how this γ parameter can be consistently estimated, although there is an indication for using an alternative nonparametric approach to estimate the $\mathbf{W}_k(\boldsymbol{\beta}, u)$ matrix in general.

Following Prentice and Zhao (1991), recently Prentice and Hsu (1997) utilized a joint estimating equation approach for simultaneous estimation of $\boldsymbol{\beta}$ and γ, where γ is the dependence parameter. More specifically, for the failure time response vectors these equations have the form:

$$\sum_{k=1}^{K} \mathbf{D}_{k1}^T \mathbf{V}_{k1}^{-1}(\mathbf{T}_k - \boldsymbol{\mu}_k) = \mathbf{0}, \quad \sum_{k=1}^{K} \mathbf{D}_{k2}^T \mathbf{V}_{k2}^{-1}(\mathbf{s}_k - \boldsymbol{\sigma}_k) = \mathbf{0}, \tag{2.6}$$

where for $k = 1, 2, \ldots, K$, $\mathbf{T}_k = (T_{k1} T_{k2} .... T_{kn_k})^T$ is the n_k dimensional response vector having mean vector $\boldsymbol{\mu}_k = \boldsymbol{\mu}_k(\boldsymbol{\beta})$, and covariance vector

$$\boldsymbol{\sigma}_k = \boldsymbol{\sigma}_k(\boldsymbol{\beta}, \boldsymbol{\gamma}) = (\sigma_{k11}, \sigma_{k12}, ..., \sigma_{k22}, \sigma_{k23}, ..., \sigma_{kn_kn_k})^T.$$

In (2.6) $\mathbf{s}_k = (s_{k11}, s_{k12}, ..., s_{kn_kn_k})^T$, with $s_{kij} = (T_{ki} - \mu_{ki})(T_{kj} - \mu_{kj})$, is an empirical covariance vector, $\mathbf{D}_{k1} = \partial \boldsymbol{\mu}_k / \partial \beta^T$, $\mathbf{D}_{k2} = \partial \boldsymbol{\sigma}_k / \partial \gamma^T$, while $\mathbf{V}_{k1}$ and $\mathbf{V}_{k2}$ are possibly working versions of the covariance matrices $\mathbf{T}_k$ and $\mathbf{s}_k$.

Cai, Wei and Wilcox (2000) used generalized estimating equations techniques to modify the Cox partial likelihood score function for the analysis of data which consist of a large number of independent small groups of correlated failure time observations.

They modeled each individual failure time with subject and cluster-specific time-dependent covariates using linear transformation models but no specific parametric correlation structure was imposed on the observations. To be specific, their regression approach accommodates the correlations nonparametrically which appears to be a similar idea as indicated by Cai and Prentice (1995). Nothing is however known about the efficiency loss of such semiparametric or nonparametric estimation which may be caused by high correlation in the data.

2.2 Longitudinal Models for Failure Time Data

As opposed to the structural models for failure time data, the correlation among the failure times may arise because of the repetition of the failure times of an individual. These failure times constitute a cluster, which is different than a cluster of responses of a group of members recorded at a time. The analysis of such longitudinal failure time data, however, is not adequately addressed in the literature. Wei, Lin and Weissfeld(1989) made an interesting attempt to analyze continuous multivariate failure time data of longitudinal nature but they used an independent working correlation assumption and constructed marginal models in fitting such failure time data. The covariance matrix of the marginal approach based regression estimator was estimated consistently (see A.2, p.1072, Wei, Lin and Weissfeld, 1989) by using a proper sample covariance structure for the actual but unknown covariance structure involved in the expression of the covariance of the regression estimator. However note that these marginal approach based estimates of the regression covariates may not be efficient. Gao and Lin (1994) studied a similar regression model as in Wei et al. (1989) by using marginal approach but unlike Wei et al. (1989) they considered discrete type or grouped failure time responses.

Since the seminal work of Liang and Zeger (1986), the marginal approach for multivariate data has gained considerable popularity in the literature. But Crowder (1995) and Sutradhar and Das (1999) suggested this marginal approach based on a so called working correlation structure may encounter difficulties, mainly in the sense of efficiencies. As there do not appear detail works available so far in estimation the regression effects on the longitudinal correlated failure times, in this thesis we will make an attempt to model longitudinal correlation for repeated failure times and this structure will be utilized to obtain consistent as well as efficient regression effects estimators under the multivariate failure time set up.

Chapter 3

Survival Functions for Exponential AR(1), MA(1) and Exchangeable Processes

As explained in Chapter 2, in analyzing a regression model for failure times, Cai and Prentice (1995) introduced a weighted estimating equation approach, where weights were constructed for the martingales of failure times in a structural set up. We recall the estimating equation (2.5) from Chapter 2 in this regard. Note however that in Cai and Prentice's (1995) approach one assumes the same dependency parameter for any two failure time variables under the multivariate set up. As for the repeated failure time data, there is no reason to assume that correlations can be constant among all time variables. One is therefore required to model the longitudinal correlation with special care such that the usual behavior of Gaussian types of auto-correlation are reflected in the present exponential set up. The purpose of this chapter is to discuss such correlation structures for positive exponential failure times and develop the survival functions under such correlation structures of exponential variables. Note that the survival functions developed in this chapter will be exploited in Chapter 4 to construct the correlation structures for the martingales for the uncensored failure times. Similar computation will be done in Chapter 5 for the censored case. Further note that the exponential AR(1), MA(1) and exchangeable(equi-correlation) processes to be discussed in this chapter are well studied by several authors in connection with binary and Poisson longitudinal variables. For example, we refer to the recent study of Jowaheer and Sutradhar (2001) for correlated count data analysis and the PhD thesis of Jowaheer (2001) for detailed analysis of multivariate longitudinal count data.

3.1 Survival Function for Exponential AR(1) Failure Time Data

3.1.1 Exponential AR(1) Process

Following Jowaheer and Sutradhar (2001), we recall from Gaver and Lewis (1980) that the first order autoregressive model for exponential failure times $T_1, \ldots, T_i, \ldots, T_n$ can be written as

$$T_i = \rho T_{i-1} + I_i \varepsilon_i \tag{3.1}$$

where

$$I_i = \begin{cases} 0 & \text{with probability } \rho \\ 1 & \text{with probability } 1-\rho \end{cases}$$

with ρ as the probability parameter $(0 \le \rho < 1)$, and ε_i is an i.i.d. sequence of exponential random variables with parameter λ. Note that the AR(1) process is based on an initial identity $T_0 = \varepsilon_0$. We will refer to (3.1) as an exponential AR(1) (EAR(1)) model.

3.1.2 Marginal Bivariate Distribution

To find the correlations among n repeated failure times, it is sufficient to consider a general bivariate density for any of the two failure times. For the EAR(1) model (3.1) the bivariate density function of T_{i+j} and T_i has the form (Gaver and Lewis, 1980 and Sim, 1990) given by

$$f_{T_{i+j},T_i}(t_{i+j},t_i) = \lambda\rho^j e^{-\lambda t_i}\delta(t_{i+j}-\rho^j t_i) + \lambda^2(1-\rho^j)e^{-\lambda t_i}e^{-\lambda(t_{i+j}-\rho^j t_i)} \tag{3.2}$$

Marginally, T_{i+j} and T_i follow exponential(λ) distributions and $\delta(x)$ is the discrete Dirac delta function, i.e. $\delta(x)$ is the distribution with atom of probability 1 at $x = 0$. From Gaver and Lewis (1980) we know that

$$corr(T_{i+j}, T_i) = \rho^j$$

3.1.3 Computation of Bivariate Survival Function

Lemma 3.1: Let

$$F_{T_1,T_2}(u_1,u_2) \quad = \quad P(T_1 \geq u_1, T_2 \geq u_2)$$

be the bivariate survival function of T_1 and T_2. For the exponential AR(1) model (3.1), this survival function is given by

$$F_{T_1,T_2}(u_1,u_2) = \begin{cases} e^{-\lambda u_1} & \text{for } u_2 \leq \rho u_1 \\ e^{-\lambda u_2}e^{-\lambda(1-\rho)u_1} & \text{for } u_2 > \rho u_1 \end{cases}$$

Proof: We know from (3.1) that T_1 and T_2 must satisfy the relationship $T_2 \geq \rho T_1$. However u_2 (a realized value of the r.v. T_2) can be either $u_2 > \rho t_1$ or $u_2 \leq \rho t_1$. Therefore the bivariate survival function of T_1 and T_2 may be computed as follows:

$$F_{T_1,T_2}(u_1,u_2) \quad = \quad \int_{u_1}^{\infty}\int_{u_2}^{\infty} f_{T_1,T_2}(t_1,t_2)dt_2dt_1.$$

The lower limit of the integration with respect to T_2 should be the maximum of u_2 and ρt_1, i.e. $\max(u_2, \rho t_1)$. It then follows that

$$\begin{aligned} F_{T_1,T_2}(u_1,u_2) &= \int_{u_1}^{\infty}\int_{\max(u_2,\rho t_1)}^{\infty} f_{T_1,T_2}(t_1,t_2)dt_2dt_1 \\ &= \int_{u_1}^{\infty} I(t_1)dt_1 \quad \text{(say)}. \end{aligned} \tag{3.3}$$

Note that there are two cases to consider to evaluate the integral $I(t_1)$ in (3.3). For the case when $u_2 > \rho t_1$, $I(t_1)$ is computed as

$$\begin{aligned} I(t_1) &= \int_{u_2}^{\infty} f_{T_1,T_2}(t_1,t_2)dt_2 \\ &= \int_{u_2}^{\infty} \left[\lambda\rho e^{-\lambda t_1}\delta(t_2-\rho t_1) + \lambda^2(1-\rho)e^{-\lambda t_1}e^{-\lambda(t_2-\rho t_1)}\right] dt_2 \\ &= \lambda(1-\rho)e^{-\lambda(1-\rho)t_1}e^{-\lambda u_2}, \end{aligned}$$

whereas for the case $u_2 \leq \rho t_1$, one needs to compute the integral $I(t_1)$ as

$$\begin{aligned} I(t_1) &= \int_{\rho t_1}^{\infty} f_{T_1,T_2}(t_1,t_2)dt_2 \\ &= \int_{\rho t_1}^{\infty} \lambda\rho e^{-\lambda t_1}\delta(t_2-\rho t_1)dt_2 + \int_{\rho t_1}^{\infty} \lambda^2(1-\rho)e^{-\lambda t_1}e^{-\lambda(t_2-\rho t_1)}dt_2 \\ &= \lambda e^{-\lambda t_1}, \end{aligned}$$

which yield

$$I(t_1) = \begin{cases} \lambda(1-\rho)e^{-\lambda t_1}e^{\lambda\rho t_1}e^{-\lambda u_2} & \text{for } u_2 > \rho t_1 \\ \lambda e^{-\lambda t_1} & \text{for } u_2 \leq \rho t_1. \end{cases}$$

Next by using the above formula for $I(t_1)$ we evaluate the remaining integral in (3.3) over u_1 as follows. For the case when $u_2 > \rho u_1$ the integral in (3.3) is evaluated as

$$\begin{aligned} F_{T_1,T_2}(u_1,u_2) &= \int_{u_1}^{u_2/\rho} \lambda(1-\rho)e^{-\lambda t_1}e^{\lambda\rho t_1}e^{-\lambda u_2}dt_1 + \int_{u_1}^{u_2/\rho} \lambda e^{-\lambda t_1}dt_1 \\ &= e^{-\lambda u_2}e^{-\lambda(1-\rho)u_1}, \end{aligned}$$

whereas for the case $u_2 \leq \rho u_1$ we evaluate the integral in (3.3) as

$$\begin{aligned} F_{T_1,T_2}(u_1,u_2) &= \int_{u_1}^{\infty} \lambda e^{-\lambda t_1}dt_1 \\ &= e^{-\lambda u_1}. \end{aligned}$$

It then follows that the bivariate survival function of T_1 and T_2 has the form given by

$$F_{T_1,T_2}(u_1,u_2) = \begin{cases} e^{-\lambda u_1} & \text{for } u_2 \leq \rho u_1 \\ e^{-\lambda u_2}e^{-\lambda(1-\rho)u_1} & \text{for } u_2 > \rho u_1 \end{cases} \tag{3.4}$$

This completes the proof. □

Note that for any two general elements of the vector of survival times $\mathbf{T}_k, k = 1, 2, \ldots, K$, the bivariate survival function of T_{k1} and T_{k2} can be written following (3.4) as

$$F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) = \begin{cases} e^{-\lambda u_{k1}} & \text{for } u_{k2} \leq \rho u_{k1} \\ e^{-\lambda u_{k2}} e^{-\lambda(1-\rho)u_{k1}} & \text{for } u_{k2} > \rho u_{k1} \end{cases} \tag{3.5}$$

Further note that the bivariate survival function (3.5) will be used in Chapter 4 and Chapter 5 to compute the correlation of the martingales of the failure times for uncensored and censored cases respectively, for the purpose of constructing estimating equations for the desired regression effects.

3.2 Survival Function for Exponential MA(1) Failure Time Data

3.2.1 Exponential MA(1) Process

In this section our main objective is to define the exponential MA(1) process of order 1 (EMA(1)) for failure times and to find the bivariate survival function for this MA(1) process. Although there are different ways to define an MA(1) process for exponential random variables, we follow Lawrance and Lewis (1977) to model EMA(1), as their approach is quite complementary to the exponential AR(1) approach of Gaver and Lewis (1980).

To be specific, following Lawrance and Lewis (1977), an EMA(1) is a stationary sequence of random variables T_i, given as

$$T_i = \begin{cases} \rho\varepsilon_i & \text{with probability } \rho \\ \rho\varepsilon_i + \varepsilon_{i+1} & \text{with probability } 1-\rho \end{cases} \tag{3.6}$$

with ρ as the probability parameter $(0 \leq \rho \leq 1)$ and ε_i are i.i.d. exponential with parameter λ, for $i = 0, \pm1, \pm2, \ldots$.

3.2.2 Marginal Bivariate Distribution

Following Lawrance and Lewis (1977) one may write the joint probability density function of T_i and T_{i+1} for all possible values of i. For convenience, we write the joint probability density function of T_1 and T_2 as

$$\begin{aligned} f_{T_1,T_2}(t_1,t_2) &= k_1(\rho)(\lambda/\rho)e^{-\lambda t_1/\rho}\lambda e^{-\lambda t_2} \\ &\quad +k_2(\rho)(\lambda/\rho)^2 e^{-\lambda(\rho t_1-t_2)/\rho^2} e^{-\lambda t_2/\rho} \quad (\text{for} \quad \rho t_1 > t_2) \\ &\quad +k_3(\rho)\lambda^2 e^{-\lambda t_1} e^{-\lambda(t_2-\rho t_1)} \qquad (\text{for} \quad \rho t_1 < t_2), \end{aligned} \tag{3.7}$$

where $k_1(\rho) = \frac{\rho^2}{1-\rho+\rho^2}$, $k_2(\rho) = \frac{\rho(1-\rho)}{1-\rho+\rho^2}$ and $k_3(\rho) = \frac{(1-\rho)^2}{1-\rho+\rho^2}$.

It is also shown by the same authors that the correlation between T_1 and T_2 is given by

$$corr(T_1,T_2) = \rho(1-\rho)$$

Note that as in EAR(1) case, the above density (3.7) will be exploited to derive the bivariate survival function under the EMA(1) process.

3.2.3 Computation of Bivariate Survival Function

Lemma 3.2: Recall that $F_{T_1,T_2}(u_1,u_2)$ denotes the bivariate survival function of T_1 and T_2 in general. For the exponential MA(1) model (3.6), this bivariate survival function has the form given by

$$F_{T_1,T_2}(u_1,u_2) = \begin{cases} k_1(\rho)e^{-\lambda u_1/\rho}e^{-\lambda u_2} + (k_2(\rho)/\rho)e^{-\lambda(1-\rho)u_1}e^{-\lambda u_2} & \text{for } \rho u_1 \le u_2 \\ k_1(\rho)e^{-\lambda u_1/\rho}e^{-\lambda u_2} + e^{-\lambda u_1} - k_1(\rho)e^{-\lambda u_1/\rho}e^{-\lambda((1-\rho)/\rho^2)u_2} & \text{for } \rho u_1 > u_2 \end{cases}$$

where $k_1(\rho)$ and $k_2(\rho)$ are defined in Section 3.2.2.

Proof: By using (3.7), the bivariate survival function of T_1 and T_2, $F_{T_1,T_2}(u_1,u_2)$, under the EMA(1) model can be computed as

$$\begin{aligned} F_{T_1,T_2}(u_1,u_2) &= P(T_1 \ge u_1, T_2 \ge u_2) \\ &= \int_{u_1}^{\infty}\int_{u_2}^{\infty} f_{T_1,T_2}(t_1,t_2)dt_2dt_1 \end{aligned}$$

$$
\begin{aligned}
&= \int_{u_1}^{\infty}\int_{u_2}^{\infty}\Big[k_1(\rho)(\lambda/\rho)e^{-\lambda t_1/\rho}\lambda e^{-\lambda t_2} \\
&\qquad +k_2(\rho)(\lambda/\rho)^2 e^{-\lambda(\rho t_1-t_2)/\rho^2}e^{-\lambda t_2/\rho}I(\rho t_1>t_2) \\
&\qquad +k_3(\rho)\lambda^2 e^{-\lambda t_1}e^{-\lambda(t_2-\rho t_1)}I(\rho t_1<t_2)\Big]\,dt_2dt_1 \\
&= I_1+I_2+I_3, \quad \text{(say)}
\end{aligned}
\tag{3.8}
$$

where $I(.)$ is an indicator function.

Now, the integral I_1 in (3.8) can be evaluated as

$$
\begin{aligned}
I_1 &= k_1(\rho)\int_{u_1}^{\infty}\int_{u_2}^{\infty}(\lambda/\rho)e^{-\lambda t_1/\rho}\lambda e^{-\lambda t_2}dt_2dt_1 \\
&= k_1(\rho)e^{-\lambda u_1/\rho}e^{-\lambda u_2}.
\end{aligned}
$$

In (3.8) the integral I_2 can be evaluated as

$$
\begin{aligned}
I_2 &= k_2(\rho)\int_{u_1}^{\infty}\int_{u_2}^{\infty}(\lambda/\rho)^2 e^{-\lambda t_2/\rho}e^{-\lambda(\rho t_1-t_2)/\rho^2}I(\rho t_1>t_2)dt_2dt_1 \\
&= k_2(\rho)\int_{u_1}^{\infty}(\lambda/\rho)e^{-\lambda t_1/\rho}\left[\int_{u_2}^{\rho t_1}(\lambda/\rho)e^{-\lambda((\rho-1)/\rho^2)t_2}dt_2\right]I(\rho t_1>t_2)dt_1 \\
&= k_2(\rho)\frac{\rho}{\rho-1}\int_{u_1}^{\infty}\left[(\lambda/\rho)e^{-\lambda t_1/\rho}e^{-\lambda((\rho-1)/\rho^2)u_2}-(\lambda/\rho)e^{-\lambda t_1}\right]I(\rho t_1>t_2)dt_1 \\
&= k_2(\rho)\frac{\rho}{\rho-1}\int_{\max(u_1,u_2/\rho)}^{\infty}\left[e^{-\lambda((\rho-1)/\rho^2)u_2}(\lambda/\rho)e^{-\lambda t_1/\rho}-(\lambda/\rho)e^{-\lambda t_1}\right]dt_1 \\
&= k_2(\rho)\frac{\rho}{\rho-1}\left[e^{-\lambda((\rho-1)/\rho^2)u_2}e^{-(\lambda/\rho)\max(u_1,u_2/\rho)}-\frac{1}{\rho}e^{-\lambda\max(u_1,u_2/\rho)}\right]
\end{aligned}
$$

For evaluating I_2 in (3.8) we need to consider two different cases: (a) $\rho u_1 > u_2$ and (b) $\rho u_1 \le u_2$. For case (a) when $\rho u_1 > u_2$, one obtains

$$
I_2 = k_2(\rho)\frac{\rho}{\rho-1}\left[e^{-\lambda((\rho-1)/\rho^2)u_2}e^{-(\lambda/\rho)u_1}-\rho^{-1}e^{-\lambda u_1}\right],
$$

whereas for case (b) $\rho u_1 \le u_2$, we have

$$
\begin{aligned}
I_2 &= k_2(\rho)\frac{\rho}{\rho-1}\left[e^{-\lambda u_2/\rho}-\rho^{-1}e^{-\lambda u_2/\rho}\right] \\
&= k_2(\rho)e^{-\lambda u_2/\rho},
\end{aligned}
$$

yielding I_2 in (3.8) as

$$
I_2 = \begin{cases} k_2(\rho)\frac{\rho}{\rho-1}\left[e^{-\lambda((\rho-1)/\rho^2)u_2}e^{-(\lambda/\rho)u_1}-\rho^{-1}e^{-\lambda u_1}\right] & \text{for } \rho u_1 > u_2 \\ k_2(\rho)e^{-\lambda u_2/\rho} & \text{for } \rho u_1 \le u_2. \end{cases}
$$

Now I_3 in (3.8) can be evaluated as

$$\begin{aligned} I_3 &= k_3(\rho)\int_{u_1}^{\infty}\int_{u_2}^{\infty}\lambda^2 e^{-\lambda t_1}e^{-\lambda(t_2-\rho t_1)}I(\rho t_1 < t_2)dt_2dt_1 \\ &= k_3(\rho)\int_{u_1}^{\infty}\int_{\max(u_2,\rho t_1)}^{\infty}\lambda^2 e^{-\lambda t_1}e^{-\lambda(t_2-\rho t_1)}dt_2dt_1 \end{aligned}$$

For evaluating I_3 we again need to consider two different cases: (a) $\rho u_1 > u_2$ and (b) $\rho u_1 \le u_2$ as in the computation of I_2. For case (a) when $\rho u_1 > u_2$, one computes

$$\begin{aligned} I_3 &= k_3(\rho)\int_{u_1}^{\infty}\int_{\rho t_1}^{\infty}\lambda^2 e^{-\lambda t_1}e^{\lambda\rho t_1}e^{-\lambda t_2}dt_2dt_1 \\ &= k_3(\rho)\lambda e^{-\lambda u_1}, \end{aligned}$$

whereas for case (b) $\rho u_1 \le u_2$, one obtains

$$\begin{aligned} I_3 &= k_3(\rho)\int_{u_1}^{u_2/\rho}\int_{u_2}^{\infty}\lambda e^{-\lambda(1-\rho)t_1}\lambda e^{-\lambda t_2}dt_2dt_1 \\ &\quad +k_3(\rho)\int_{u_2/\rho}^{\infty}\int_{\rho t_1}^{\infty}\lambda e^{-\lambda(1-\rho)t_1}\lambda e^{-\lambda t_2}dt_2dt_1 \\ &= k_3(\rho)\left[\int_{u_1}^{u_2/\rho}\lambda e^{-\lambda(1-\rho)t_1}e^{-\lambda u_2}dt_1 + \int_{u_2/\rho}^{\infty}\lambda e^{-\lambda t_1}dt_1\right] \\ &= k_3(\rho)\left[\frac{e^{-\lambda u_2}}{1-\rho}\left(e^{-\lambda(1-\rho)u_1} - e^{-\lambda(1-\rho)u_2/\rho}\right)\right] \\ &= \frac{k_3(\rho)}{(1-\rho)}\left[e^{-\lambda u_2}e^{-\lambda(1-\rho)u_1} - \rho e^{-\lambda u_2/\rho}\right] \end{aligned}$$

yielding I_3 in (3.8) as

$$I_3 = \begin{cases} k_3(\rho)\lambda e^{-\lambda u_1} & \text{for } \rho u_1 > u_2 \\ \frac{k_3(\rho)}{(1-\rho)}\left[e^{-\lambda u_2}e^{-\lambda(1-\rho)u_1} - \rho e^{-\lambda u_2/\rho}\right] & \text{for } \rho u_1 \le u_2 \end{cases}$$

By combining the values of I_1, I_2 and I_3 we may obtain the bivariate survival function under two different cases : (a) $\rho u_1 > u_2$ and (b) $\rho u_1 \le u_2$ for (3.8) which has the form

$$F_{T_1,T_2}(u_1,u_2) = \begin{cases} k_1(\rho)e^{-\lambda u_1/\rho}e^{-\lambda u_2} + \frac{k_2(\rho)}{\rho}e^{-\lambda(1-\rho)u_1}e^{-\lambda u_2} & \text{for } \rho u_1 \le u_2 \\ k_1(\rho)e^{-\lambda u_1/\rho}e^{-\lambda u_2} + e^{-\lambda u_1} - k_1(\rho)e^{-\lambda u_1/\rho}e^{-\lambda((1-\rho)/\rho^2)u_2} & \text{for } \rho u_1 > u_2 \end{cases} \tag{3.9}$$

This completes the proof. □

Note that for any two general elements of the vector of survival times $\mathbf{T}_k, k = 1, 2, \ldots, K$, the bivariate survival function of T_{k1} and T_{k2} can be written following (3.9) as

$$F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) = \begin{cases} k_1(\rho)e^{-\lambda u_{k1}/\rho}e^{-\lambda u_{k2}} + \frac{k_2(\rho)}{\rho}e^{-\lambda(1-\rho)u_{k1}}e^{-\lambda u_{k2}} \\ \qquad\qquad \text{(for } \rho u_{k1} \leq u_{k2}) \\ k_1(\rho)e^{-\lambda u_{k1}/\rho}e^{-\lambda u_{k2}} - k_1(\rho)e^{-\lambda u_{k1}/\rho}e^{-\lambda((1-\rho)/\rho^2)u_{k2}} + e^{-\lambda u_{k1}} \\ \qquad\qquad \text{(for } \rho u_{k1} > u_{k2}). \end{cases} \tag{3.10}$$

Further note that this bivariate survival function in (3.10) will be used in Chapter 4 and Chapter 5 to compute the correlation of the martingales of the failure times for uncensored and censored cases respectively, for the EMA(1) process.

3.3 Survival Function for Exponential Equi-Correlation Failure Time Data

3.3.1 Exponential Equi-correlation (EEQ) Process

In the exponential equi-correlation(EEQ) structure, our goal is to construct a process such that $corr(T_i, T_j) = c$ for $i \neq j$ $(i, j = 1, 2, \ldots, n)$, where T_i and T_j are failure times. We can construct this stationary sequence of random variables as follows:

$$T_i = \begin{cases} \rho T_0 & \text{with probability } \rho \\ \rho T_0 + \varepsilon_i & \text{with probability } 1 - \rho \end{cases}$$

with ρ as the probability parameter $(0 \leq \rho \leq 1)$, for $i = 1, 2, \ldots$ and ε_i are i.i.d. exponential with parameter λ. For convenience one can write the above relationship as

$$T_i = \rho T_0 + I_i \varepsilon_i, \tag{3.11}$$

where

$$I_i = \begin{cases} 0 & \text{w.p. } \rho \\ 1 & \text{w.p. } 1-\rho \end{cases}$$

we assume $T_0 = \varepsilon_0$, where ε_0 again is exponential with parameter λ.

Note that unlike the EAR(1) and EMA(1) processes, the expression for the correlation between any two exponential equi-correlation variables is not available in the literature. We may however compute this correlation easily by using the moment generating function which is discussed in the next subsection.

3.3.2 Moment Generating Function and Correlation for EEQ Process

For $i = 1, 2, \ldots, n$ the moment generating function of T_i can be written as

$$\begin{aligned}
\Phi_{T_i}(s) &= E(e^{-sT_i}) \\
&= E_{T_i} E_{I_i}(e^{-sT_i} \mid I_i) \\
&= E_{T_i}\left[E_{I_i}(e^{-s\rho T_0 - sI_i\varepsilon_i} \mid I_i)\right] \\
&= E_{T_i}\left[\rho e^{-s\rho T_0} + (1-\rho)e^{-s\rho T_0 - s\varepsilon_i}\right] \\
&= \rho\frac{\lambda}{\lambda+\rho s} + (1-\rho)\left[E(e^{-s\rho T_0})E(e^{-s\varepsilon_i})\right] \\
&= \frac{\rho\lambda}{\lambda+\rho s} + (1-\rho)\frac{\lambda}{\lambda+\rho s}\frac{\lambda}{\lambda+s} \\
&= \frac{\lambda}{\lambda+s}
\end{aligned}$$

By using the relationship between T_i and T_0 for all i, we write

$$\begin{aligned}
E(T_iT_{i+j}) &= \rho^2 E(\rho^2 T_0^2) + \rho(1-\rho)E(\rho^2T_0^2 + \rho T_0\varepsilon_{i+j}) \\
&\quad +\rho(1-\rho)E(\rho^2T_0^2 + \rho T_0 \varepsilon_i) + E(\rho^2T_0^2 + \rho T_0\varepsilon_{i+j} + \rho T_0\varepsilon_i + \varepsilon_i\varepsilon_{i+j}) \\
&= \frac{2\rho^4}{\lambda^2} + \frac{4\rho^3(1-\rho)}{\lambda^2} + \frac{2\rho^2(1-\rho)}{\lambda^2} + \frac{2\rho(1-\rho)^2}{\lambda^2} \\
&\quad + \frac{2\rho^2(1-\rho)^2}{\lambda^2} + \frac{(1-\rho)^2}{\lambda^2} \\
&= \frac{\rho^2+1}{\lambda^2},
\end{aligned}$$

yielding the covariance between T_i and T_{i+j} as

$$cov(T_i, T_{i+j}) = E(T_i, T_{i+j}) - E(T_i)E(T_{i+j}) \quad = \quad \frac{\rho^2}{\lambda^2},$$

because $E(T_i) = 1/\lambda$ and $var(T_i) = 1/\lambda^2$. Thus, the correlation between T_i and T_{i+j} is given by

$$corr(T_i, T_{i+j}) \quad = \quad \rho^2.$$

Recall that although the correlation function for the EAR(1) process appears to be same as for the Gaussian AR(1) process, the correlation functions however are different for the MA(1) and equi-correlation cases under the exponential and Gaussian models.

3.3.3 Computation of Bivariate Survival Function

Lemma 3.3: For the EEQ model in (3.11), the bivariate survival function $F_{T_1,T_2}(u_1, u_2)$ has the form given by,

$$F_{T_1,T_2}(u_1, u_2) \quad = \quad \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_1+u_2)} - \frac{\rho^2}{1-2\rho} e^{-\lambda \max(u_1,u_2)} e^{-\lambda((1-\rho)/\rho)\min(u_1,u_2)}.$$

Proof: In this case the joint survival function of T_1 and T_2 is

$$\begin{aligned}
F_{T_1,T_2}(u_1, u_2) &= P(T_1 \geq u_1, T_2 \geq u_2) \\
&= P(\rho T_0 + I_1\varepsilon_1 \geq u_1, \rho T_0 + I_2\varepsilon_2 \geq u_2) \\
&= P[\rho T_0 \geq u_1, \rho T_0 \geq u_2, I_1 = I_2 = 0] \\
&\quad + P[\rho T_0 \geq u_1, \rho T_0 + \varepsilon_2 \geq u_2, I_1 = 0, I_2 = 1] \\
&\quad + P[\rho T_0 + \varepsilon_1 \geq u_1, \rho T_0 \geq u_2, I_1 = 1, I_2 = 0] \\
&\quad + P[\rho T_0 + \varepsilon_1 \geq u_1, \rho T_0 + \varepsilon_2 \geq u_2, I_1 = 1, I_2 = 1] \\
&= \rho^2 P[\rho T_0 \geq \max(u_1, u_2)] + \rho(1-\rho)P[\rho T_0 \geq u_1, \varepsilon_2 \geq u_2 - \rho T_0] \\
&\quad + \rho(1-\rho)P[\rho T_0 \geq u_2, \varepsilon_1 \geq u_1 - \rho T_0] \\
&\quad + (1-\rho)^2 P[\varepsilon_1 \geq u_1 - \rho T_0, \varepsilon_2 \geq u_2 - \rho T_0] \\
&= I_1 + I_2 + I_3 + I_4 \qquad (3.12)
\end{aligned}$$

In (3.12) I_1 can be computed as

$$\begin{aligned} I_1 &= \rho^2 P[\rho T_0 \geq \max(u_1, u_2)] \\ &= \rho^2 P[T_0 \geq \max(u_1, u_2)/\rho] \\ &= \rho^2 \int_{\max(u_1,u_2)/\rho}^{\infty} \lambda e^{-\lambda t_0} dt_0 \\ &= \rho^2 e^{-\lambda \max(u_1,u_2)/\rho} \end{aligned}$$

Therefore I_1 has the form

$$I_1 = \begin{cases} \rho^2 e^{-\lambda u_2/\rho} & \text{for } u_1 \leq u_2 \\ \rho^2 e^{-\lambda u_1/\rho} & \text{for } u_1 > u_2 \end{cases}$$

In (3.12) for computing I_2 we require to consider two cases: (a) $u_1 \leq u_2$ and (b) $u_1 > u_2$. For case (a) when $u_1 \leq u_2$, we compute I_2 as

$$\begin{aligned} I_2 &= \rho(1-\rho)P[\rho T_0 \geq u_1, \varepsilon_2 \geq u_2 - \rho t_0] \\ &= \rho(1-\rho)P[\rho T_0 \geq u_1]P[\varepsilon_2 \geq u_2 - \rho t_0] \\ &= \rho(1-\rho)P[T_0 \geq u_1/\rho]P[\varepsilon_2 \geq \max(u_2 - \rho t_0, 0)] \\ &= \rho(1-\rho)\int_{u_1/\rho}^{\infty} \lambda e^{-\lambda t_0} dt_0 \int_{\max(u_2-\rho t_0,0)}^{\infty} \lambda e^{-\lambda \varepsilon_2} d\varepsilon_2 \\ &= \rho(1-\rho)\int_{u_1/\rho}^{u_2/\rho} \lambda e^{-\lambda t_0} \left[e^{-\lambda(u_2-\rho t_0)} I(u_2 > \rho t_0) + I(u_2 \leq \rho t_0)\right] dt_0 \\ &= \rho(1-\rho)e^{-\lambda u_2}\lambda \int_{u_1/\rho}^{u_2/\rho} e^{-\lambda(1-\rho)t_0} dt_0 + \rho(1-\rho)\lambda \int_{u_2/\rho}^{\infty} \lambda e^{-\lambda t_0} dt_0 \\ &= \rho e^{-\lambda u_2} e^{-\lambda((1-\rho)/\rho)u_1} - \rho^2 e^{-\lambda u_2/\rho}, \end{aligned}$$

where as for the case $u_1 > u_2$ we compute I_2 as

$$\begin{aligned} I_2 &= \rho(1-\rho)P[\rho T_0 \geq u_1, \varepsilon_2 \geq u_2 - \rho t_0] \\ &= \rho(1-\rho)P[T_0 \geq u_1/\rho]P[\varepsilon_2 \geq \max(u_2 - \rho t_0, 0)] \\ &= \rho(1-\rho)P[T_0 \geq u_1/\rho]P[\varepsilon_2 \geq 0] \\ &= \rho(1-\rho)P\left[T_0 \geq u_1/\rho\right] \\ &= \rho(1-\rho)\int_{u_1/\rho}^{\infty} \lambda e^{-\lambda t_0} dt_0 \\ &= \rho(1-\rho)e^{-\lambda u_1/\rho}, \end{aligned}$$

which yield I_2 in the form

$$I_2 = \begin{cases} \rho e^{-\lambda u_2} e^{-\lambda((1-\rho)/\rho)u_1} - \rho^2 e^{-\lambda u_2/\rho} & \text{for } u_1 \le u_2 \\ \rho(1-\rho)e^{-\lambda u_1/\rho} & \text{for } u_1 > u_2. \end{cases}$$

Similarly, following I_2 and by interchanging u_1 by u_2 and vice versa, we can write I_3 in (3.12) as

$$I_3 = \begin{cases} \rho(1-\rho)e^{-\lambda u_2/\rho} & \text{for } u_1 \le u_2 \\ \rho e^{-\lambda u_1} e^{-\lambda((1-\rho)/\rho)u_2} - \rho^2 e^{-\lambda u_1/\rho} & \text{for } u_1 > u_2. \end{cases}$$

Next I_4 in (3.12) can be computed as

$$\begin{aligned} I_4 &= (1-\rho)^2 P[\varepsilon_1 \ge u_1 - \rho T_0, \varepsilon_2 \ge u_2 - \rho T_0] \\ &= (1-\rho)^2 \int_0^\infty P[\rho T_0 = u] P[\varepsilon_1 \ge u_1 - \rho T_0, \varepsilon_2 \ge u_2 - \rho T_0 \mid \rho T_0 = u] du \\ &= (1-\rho)^2 \int_0^\infty P\left[T_0 = u/\rho\right] P[\varepsilon_1 \ge u_1 - u, \varepsilon_2 \ge u_2 - u] du \\ &= (1-\rho)^2 \int_0^\infty \lambda/\rho e^{-\lambda u/\rho} \left[e^{-\lambda(u_1-u)} I(u_1 > u) + I(u_1 \le u)\right] \\ &\qquad\qquad \times \left[e^{-\lambda(u_2-u)} I(u_2 > u) + I(u_2 \le u)\right] du \\ &= (1-\rho)^2 \int_0^{\min(u_1,u_2)} (\lambda/\rho) e^{-\lambda u/\rho} e^{-\lambda(u_1-u)} e^{-\lambda(u_2-u)} du \\ &\quad + (1-\rho)^2 \int_{\min(u_1,u_2)}^{\max(u_1,u_2)} (\lambda/\rho) e^{-\lambda u/\rho} e^{-\lambda(\max(u_1,u_2)-u)} du \\ &\quad + (1-\rho)^2 \int_{\max(u_1,u_2)}^{\infty} (\lambda/\rho) e^{-\lambda u/\rho} du \\ &= (1-\rho)^2 \int_0^{\min(u_1,u_2)} e^{-\lambda(u_1+u_2)} (\lambda/\rho) e^{-\lambda((1-2\rho)/\rho)u} du \\ &\quad + (1-\rho)^2 \int_{\min(u_1,u_2)}^{\max(u_1,u_2)} e^{-\lambda(\max(u_1,u_2)} (\lambda/\rho) e^{-\lambda((1-\rho)/\rho)u} du \\ &\quad + (1-\rho)^2 \int_{\max(u_1,u_2)}^{\infty} (\lambda/\rho) e^{-\lambda u/\rho} du \\ &= \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_1+u_2)} \left[1 - e^{-\lambda((1-2\rho)/\rho)\min(u_1,u_2)}\right] \\ &\quad + \frac{(1-\rho)^2}{1-\rho} e^{-\lambda \max(u_1,u_2)} \left[e^{-\lambda((1-\rho)/\rho)\min(u_1,u_2)} - e^{-\lambda((1-\rho)/\rho)\max(u_1,u_2)}\right] \\ &\quad + (1-\rho)^2 e^{-\lambda \max(u_1,u_2)/\rho} \end{aligned}$$

$$\begin{aligned}
&= \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)} - \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)}e^{-\lambda((1-2\rho)/\rho)\min(u_1,u_2)} \\
&\quad +(1-\rho)^2 e^{-\lambda \max(u_1,u_2)/\rho} + (1-\rho)e^{-\lambda \max(u_1,u_2)}e^{-\lambda((1-\rho)/\rho)\min(u_1,u_2)} \\
&\quad -(1-\rho)e^{-\lambda \max(u_1,u_2)}e^{-\lambda((1-\rho)/\rho)\max(u_1,u_2)}
\end{aligned}$$

To be specific, for case $u_1 \leq u_2$, I_4 has the form

$$\begin{aligned}
I_4 &= \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)} - \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)}e^{-\lambda((1-2\rho)/\rho)u_1} + (1-\rho)^2 e^{-\lambda u_2/\rho} \\
&\quad +(1-\rho)e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_1} - (1-\rho)e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_2},
\end{aligned}$$

whereas for case (b) $u_1 > u_2$, I_4 has the form given by

$$\begin{aligned}
I_4 &= \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)} - \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)}e^{-\lambda((1-2\rho)/\rho)u_2} + (1-\rho)^2 e^{-\lambda u_1/\rho} \\
&\quad +(1-\rho)e^{-\lambda u_1}e^{-\lambda((1-\rho)/\rho)u_2} - (1-\rho)e^{-\lambda u_1}e^{-\lambda((1-\rho)/\rho)u_1}
\end{aligned}$$

Consequently, for $u_1 \leq u_2$ the survival function can be written as

$$\begin{aligned}
F_{T_1,T_2}(u_1,u_2) &= P(T_1 \geq u_1, T_2 \geq u_2) \\
&= \rho^2 e^{-\lambda u_2/\rho} + \rho e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_1} - \rho^2 e^{-\lambda u_2/\rho} + \rho(1-\rho)e^{-\lambda u_2/\rho} \\
&\quad +\frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)} - \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)}e^{-\lambda((1-2\rho)/\rho)u_1} \\
&\quad +(1-\rho)^2 e^{-\lambda u_2/\rho} + (1-\rho)e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_1} \\
&\quad -(1-\rho)e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_2} \\
&= e^{-\lambda u_2/\rho}\left[\rho^2 + \rho - 2\rho^2 + (1-\rho)^2 - (1-\rho)\right] + \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)} \\
&\quad -\frac{(1-\rho)^2}{1-2\rho}e^{-\lambda u_2}e^{-\lambda u_1((1-\rho)/\rho)} + (1-\rho)e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_1} \\
&\quad +\rho e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_1} \\
&= \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)} - \frac{\rho^2}{1-2\rho}e^{-\lambda u_2}e^{-\lambda((1-\rho)/\rho)u_1}.
\end{aligned}$$

Similarly, for $u_1 > u_2$ the survival function has the form

$$\begin{aligned}
F_{T_1,T_2}(u_1,u_2) &= P(T_1 \geq u_1, T_2 \geq u_2) \\
&= \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda(u_1+u_2)} - \frac{\rho^2}{1-2\rho}e^{-\lambda u_1}e^{-\lambda((1-\rho)/\rho)u_2}.
\end{aligned}$$

By considering the above two cases, the survival function may be computed as

$$F_{T_1,T_2}(u_1,u_2) = \begin{cases} \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_1+u_2)} - \frac{\rho^2}{1-2\rho} e^{-\lambda u_2} e^{-\lambda((1-\rho)/\rho)u_1} & \text{for } u_1 \leq u_2 \\ \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_1+u_2)} - \frac{\rho^2}{1-2\rho} e^{-\lambda u_1} e^{-\lambda((1-\rho)/\rho)u_2} & \text{for } u_1 > u_2 \end{cases}$$

or in a more compact form the function is given by:

$$F_{T_1,T_2}(u_1,u_2) = \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_1+u_2)} - \frac{\rho^2}{1-2\rho} e^{-\lambda \max(u_1,u_2)} e^{-\lambda((1-\rho)/\rho)\min(u_1,u_2)}. \quad (3.13)$$

This completes the proof. □

Note that for any two elements of the vector of survival times $\mathbf{T}_k$, $k = 1, 2, \ldots, K$, the bivariate survival function of T_{k1} and T_{k2} can be written following (3.13) as

$$\begin{aligned} F_{T_{k1},T_{k2}}(u_{k1},u_{k2}) &= \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_{k1}+u_{k2})} \\ &\quad - \frac{\rho^2}{1-2\rho} e^{-\lambda \max(u_{k1},u_{k2})} e^{-\lambda((1-\rho)/\rho)\min(u_{k1},u_{k2})} \end{aligned} \quad (3.14)$$

The survival functions described in Sections 3.1, 3.2 and 3.3 will be used in Chapters 4 and 5 to compute the correlations between the martingales of the failure times for uncensored and censored cases respectively, for the purpose of evaluating the estimating equations for the regression effects.

Chapter 4

Regression Model for Longitudinal Uncensored Failure Time Data

As discussed in Chapter 2, in analyzing regression models for failure times, Cai and Prentice (1995) introduced a weighted estimating equation approach, where the required weights were constructed from the correlations of the martingales for the bivariate failure times in a structural set up. In Chapter 3, we introduced longitudinal models for exponential failure times and derived the survival functions under such longitudinal models. To be specific, similar to the well known Gaussian set-up, we have discussed three widely used, namely, AR(1), MA(1) and equi-correlation models. As mentioned earlier, we use these survival functions in this chapter for calculating the correlations between the martingales for the failure times. Then these martingale correlations are used in constructing the estimating equations for regression effects under appropriate longitudinal models.

4.1 Martingale Correlation Structure for Exponential Uncensored Failure Times

Uncensored failure times generally arise if we have information on failure times for every individual. For the uncensored case the martingales $M_{ki}(X_{ki})$ defined in (2.3) for $(i = 1, 2, \ldots, n)$ reduce to

$$M_{ki}(X_{ki}) = 1 - \Lambda_{ki}(T_{ki}), \tag{4.1}$$

where $\Lambda_{ki}(T_{ki}) = \int_0^t \lambda_{ki}(s)ds$, with the variance of martingale as unity, i.e. $var(M_{ki}(X_{ki}))$ = 1 (Cai and Prentice,1995, p. 157-8). In the following subsections we will derive the correlation structures for the martingales in (4.1) where $X_{ki} = T_{ki}$ (for the uncensored cases), following the exponential AR(1), MA(1) and equi-correlation models.

4.1.1 Martingale Correlations Under Exponential AR(1) Process

Theorem 4.1: Let $X_{ki}, (i - 1, \ldots, n)$ satisfy the EAR(1) model (3.1). In the absence of censorship, the martingales $M_{ki}(X_{ki})$ $(i = 1, 2, \ldots, n)$ defined in (4.1) have the pairwise correlation given by

$$corr(M_{ki}(X_{ki}), M_{k(i+j)}(X_{k(i+j)})) = \rho^j$$

which is interestingly the same as the correlation between T_{ki} and $T_{k(i+j)}$, the original exponential variables.

Proof: From (3.5) of Chapter 3 we can write the bivariate survival function of T_{k1} and T_{k2} as

$$F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) = \begin{cases} e^{-\lambda u_{k1}} & \text{for } u_{k2} \leq \rho u_{k1} \\ e^{-\lambda u_{k2}} e^{-\lambda(1-\rho)u_{k1}} & \text{for } u_{k2} > \rho u_{k1} \end{cases} \tag{4.2}$$

Since $var(M_{ki}(X_{ki})) = 1$ for $i = 1, 2, \ldots, n$ by exploiting the survival function (4.2), the correlation between the first and second martingales (martingales separated by 1 time lag) can be computed as

$$\begin{aligned}
corr(M_{k1}(X_{k1}), M_{k2}(X_{k2})) &= cov(M_{k1}(X_{k1}), M_{k2}(X_{k2})) \\
&= cov(\Lambda_{k1}(T_{k1}), \Lambda_{k2}(T_{k2})) \\
&= \int_0^\infty \int_0^\infty \lambda^2 F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) du_{k2} du_{k1} - 1 \\
&= \int_0^\infty \int_0^{\rho u_{k1}} \lambda^2 e^{-\lambda u_{k1}} du_{k2} du_{k1} \\
&\quad + \int_0^\infty \int_{\rho u_{k1}}^\infty \lambda^2 e^{-\lambda u_{k2}} e^{-\lambda(1-\rho)u_{k1}} du_{k2} du_{k1} - 1 \\
&= \int_0^\infty \rho\lambda^2 u_{k1} e^{-\lambda u_{k1}} du_{k1} \\
&\quad + \int_0^\infty \lambda e^{-\lambda(1-\rho)u_{k1}} e^{-\lambda\rho u_{k1}} du_{k1} - 1 \\
&= \rho + 1 - 1 \\
&= \rho,
\end{aligned}$$

which is same as the correlation between T_{k1} and T_{k2}.

To find the lag 2 correlation between martingales we note that the bivariate survival function of T_{k1} and T_{k3}, for example, can be written as

$$F_{T_{k1},T_{k3}}(u_{k1}, u_{k3}) = \begin{cases} e^{-\lambda u_{k1}} & \text{for } u_{k3} \le \rho^2 u_{k1} \\ e^{-\lambda u_{k3}} e^{-\lambda(1-\rho^2)u_{k1}} & \text{for } u_{k3} > \rho^2 u_{k1}. \end{cases} \tag{4.3}$$

It then follows that the correlation between the martingales of T_{k1} and T_{k3}, by exploiting the survival function (4.3), can be computed as

$$\begin{aligned}
corr(M_{k1}(X_{k1}), M_{k3}(X_{k3})) &= cov(\Lambda_{k1}(T_{k1}), \Lambda_{k3}(T_{k3})) \\
&= \int_0^\infty \int_0^\infty \lambda^2 F_{T_{k1},T_{k3}}(u_{k1}, u_{k3}) du_{k3} du_{k1} - 1 \\
&= \int_0^\infty \left[\int_0^{\rho^2 u_{k1}} \lambda^2 e^{-\lambda u_{k1}} du_{k3} \right. \\
&\quad \left. + \int_{\rho^2 u_{k1}}^\infty \lambda^2 e^{-\lambda u_{k3}} e^{-\lambda(1-\rho^2)u_{k1}} du_{k3} \right] du_{k1} - 1 \\
&= \rho^2,
\end{aligned}$$

which is same as the correlation between T_{k1} and T_{k3}.

By similar argument as in (4.2) and (4.3), the bivariate survival function of T_{k1} and $T_{k(j+1)}$ can be written as

$$F_{T_{k1},T_{k(j+1)}}(u_{k1},u_{k(j+1)}) = \begin{cases} e^{-\lambda u_{k1}} & \text{for } u_{k(j+1)} \leq \rho^j u_{k1} \\ e^{-\lambda u_{k(j+1)}} e^{-\lambda(1-\rho^j)u_{k1}} & \text{for } u_{k(j+1)} > \rho^j u_{k1} \end{cases}$$

which yields the correlation between the martingales $M_{k1}(X_{k1})$ and $M_{k(j+1)}(X_{k(j+1)})$ as

$$\begin{aligned} corr(M_{k1}(X_{k1}), M_{k(j+1)}(X_{k(j+1)})) &= \int_0^\infty \int_0^\infty \lambda^2 F_{T_{k1},T_{k(1+j)}}(u_{k1},u_{k(1+j)}) du_{k(1+j)} du_{k1} \\ &\quad -1 \\ &= \rho^j, \end{aligned} \tag{4.4}$$

which is the correlation between the martingales of T_{ki} and $T_{k(i+j)}$ as well as the correlation between the failure times T_{ki} and $T_{k(i+j)}$. □

Note that it now follows from Theorem 4.1 that under the EAR(1) process, the variance-covariance matrix **V**, say, of the martingales $M_{ki}(X_{ki})$, $i = 1, 2, \ldots, n$ can be written as

$$V = \begin{bmatrix} 1 & \rho & \rho^2 & \ldots & \rho^{n-1} \\ \rho & 1 & \rho & \ldots & \rho^{n-2} \\ \rho^2 & \rho & 1 & \ldots & \rho^{n-3} \\ \vdots & \vdots & \vdots & \ldots & \vdots \\ \rho^{n-1} & \rho^{n-2} & \rho^{n-3} & \ldots & 1 \end{bmatrix}, \tag{4.5}$$

which is naturally the correlation matrix of the martingales for the uncensored case.

4.1.2 Martingale Correlations Under Exponential MA(1) Process

Theorem 4.2: Under the EMA(1) process, in the absence of censorship, the martingales $M_{ki}(X_{ki})$ defined in (4.1) for $(i = 1, 2, \ldots, n)$ have the pairwise correlation given by

$$corr(M_{ki}(X_{ki}), M_{k(i+1)}(X_{k(i+1)})) = \rho(1-\rho)$$

and

$$corr(M_{ki}(X_{ki}), M_{k(i+j)}(X_{k(i+j)})) = 0 \quad (\text{for} \quad j > 1)$$

which is interestingly the same as the correlation between T_{ki} and $T_{k(i+j)}$, the original exponential failure times.

Proof: The derivation of the martingale correlations under the EMA(1) process is quite similar to that of the EAR(1) process, discussed in the previous section. The difference lies only in the form of the survival functions. We now use the appropriate survival function (3.10) for the EMA(1) process and compute the martingale correlation as

$$\begin{aligned} corr(M_{k1}(X_{k1}), M_{k2}(X_{k2})) &= cov(\Lambda_{k1}(T_{k1}), \Lambda_{k2}(T_{k2})) \\ &= \int_0^\infty \int_0^\infty \lambda^2 F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) du_{k2} du_{k1} - 1 \\ &= \int_0^\infty I(u_{k1}) du_{k1} - 1, \end{aligned} \tag{4.6}$$

where

$$\begin{aligned} I(u_{k1}) &= \int_0^\infty \lambda^2 F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) du_{k2} \\ &= \int_0^{\rho u_{k1}} k_1(\rho)\lambda^2 e^{-\lambda u_{k1}/\rho} e^{-\lambda u_{k2}} du_{k2} + \int_0^{\rho u_{k1}} \lambda^2 e^{-\lambda u_{k1}} du_{k2} \\ &\quad - \int_0^{\rho u_{k1}} \lambda^2 k_1(\rho) e^{-\lambda u_{k1}/\rho} e^{-\lambda((1-\rho)/\rho^2) u_{k2}} \\ &\quad + \int_{\rho u_{k1}}^\infty \lambda^2 k_1(\rho) e^{-\lambda u_{k1}/\rho} e^{-\lambda u_{k2}} du_{k2} \\ &\quad + \int_{\rho u_{k1}}^\infty \lambda^2 \frac{k_2(\rho)}{\rho} e^{-\lambda(1-\rho)u_{k1}} e^{-\lambda u_{k2}} du_{k2}, \end{aligned}$$

with $k_1(\rho)$ and $k_2(\rho)$ as given in Section 3.2.2. The above integration is straightforward, which after some algebra, yields

$$I(u_{k1}) = \lambda^2 \rho u_{k1} e^{-\lambda u_{k1}} + \frac{\lambda\rho^2}{1-\rho} e^{-\lambda u_{k1}/\rho} + \frac{\lambda(1-\rho+\rho^2)}{1-\rho} e^{-\lambda u_{k1}}$$

Now by using the value of $I(u_{k1})$ in (4.6) we evaluate the correlation between two martingales as

$$corr(M_{k1}(X_{k1}), M_{k2}(X_{k2})) = \int_0^\infty I(u_{k1}) du_{k1} - 1$$

$$\begin{aligned}
&= \int_0^\infty \lambda^2 \rho u_{k1} e^{-\lambda u_{k1}} du_{k1} + \int_0^\infty \frac{\lambda\rho^2}{1-\rho} e^{-\lambda u_{k1}/\rho} du_{k1} \\
&\quad + \int_0^\infty \frac{\lambda(1-\rho+\rho^2)}{1-\rho} e^{-\lambda u_{k1}} du_{k1} - 1 \\
&= \rho + \frac{\rho^3}{1-\rho} + \frac{(1-\rho+\rho^2)}{1-\rho} - 1 \\
&= \rho + 1 - \rho^2 - 1 \\
&= \rho(1-\rho)
\end{aligned}$$

Next for all lags more than 1, we note from Lawrance and Lewis (1977) that $corr(T_i, T_{i+2}) = 0$, for all $i = 1, 2, 3, \ldots$. So it is easy to show that

$$corr(M_{ki}(X_{ki}), M_{k(i+2)}(X_{k(i+2)})) = 0$$

and

$$corr(M_{ki}(X_{ki}), M_{k(i+j)}(X_{k(i+j)})) = 0 \quad (\text{for} \quad j > 1)$$

for $i = 1, 2, 3, \ldots$. This completes the proof. □

Note that it now follows from Theorem 4.2 that under the EMA(1) process, the variance-covariance matrix **V**, say, of the martingales $M_{ki}(X_{ki})$, for $i = 1, 2, \ldots, n$ can be written as

$$V = \begin{bmatrix} 1 & \rho(1-\rho) & 0 & \ldots & 0 \\ \rho(1-\rho) & 1 & \rho(1-\rho) & \ldots & 0 \\ 0 & \rho(1-\rho) & 1 & \ldots & 0 \\ \vdots & \vdots & \vdots & \ldots & \vdots \\ 0 & 0 & 0 & \ldots & 1 \end{bmatrix} \qquad (4.7)$$

which is naturally the correlation matrix of the martingales for the uncensored case.

4.1.3 Martingale Correlations Under Exponential Equi-correlation Process

Theorem 4.3: For uncensored failure times under the EEQ process, the martingales

$M_{ki}(X_{ki})$ defined in (4.1) for $i = 1, 2, \ldots, n$ have the pairwise correlation given by

$$corr(M_{ki}(X_{ki}), M_{kj}(X_{kj})) = \rho^2$$

which is interestingly the same as the correlation between T_{ki} and T_{kj} $(i \neq j; i, j = 1, 2, \ldots, n)$, the original failure times.

Proof: The calculation of this correlation between the martingles of the failure times under the EEQ process are similar to the calculation under the EAR(1) and EMA(1) processes, except that the survival functions are different under different processes. To derive the correlation between the martingales $M_{ki}(X_{ki})$ and $M_{kj}(X_{kj})$, for convenience, we compute the correlation between the first and second martingales (martingales with lag 1) for the EEQ process by using the bivariate survival function (3.14) as

$$\begin{aligned}
corr(M_{k1}(X_{k1}), M_{k2}(X_{k2})) &= cov(M_{k1}(X_{k1}), M_{k2}(X_{k2})) \\
&= cov(\Lambda_{k1}(T_{k1}), \Lambda_{k2}(T_{k2})) \\
&= -1 + \int_0^\infty \int_0^\infty \lambda^2 F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) du_{k2} du_{k1} \\
&= -1 + \int_0^\infty \int_0^\infty \lambda^2 \left[\frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_{k1}+u_{k2})} \right. \\
&\quad \left. - \frac{\rho^2}{1-2\rho} e^{-\lambda \max(u_{k1},u_{k2})} e^{-\lambda((1-\rho)/\rho)\min(u_{k1},u_{k2})} \right] du_{k2} du_{k1} \\
&= -1 + \frac{(1-\rho)^2}{1-2\rho} \\
&\quad - \int_0^\infty \int_0^\infty \lambda^2 \frac{\rho^2}{1-2\rho} \left[e^{-\lambda \max(u_{k1},u_{k2})} \right. \\
&\qquad \left. \times e^{-\lambda((1-\rho)/\rho)\min(u_{k1},u_{k2})} \right] du_{k2} du_{k1} \\
&= -1 + \frac{(1-\rho)^2}{1-2\rho} - \frac{\rho^2}{1-2\rho} \int_0^\infty I(u_{k1}) du_{k1}, \qquad (4.8)
\end{aligned}$$

where in (4.8)

$$\begin{aligned}
I(u_{k1}) &= \int_0^\infty \lambda^2 e^{-\lambda \max(u_{k1},u_{k2})} e^{-\lambda((1-\rho)/\rho)\min(u_{k1},u_{k2})} du_{k2} \\
&= \int_0^{u_{k1}} \lambda^2 e^{-\lambda u_{k1}} e^{-\lambda((1-\rho)/\rho)u_{k2}} du_{k2} + \int_{u_{k1}}^\infty \lambda^2 e^{-\lambda u_{k2}} e^{-\lambda((1-\rho)/\rho)u_{k1}} du_{k2}
\end{aligned}$$

$$
\begin{aligned}
&= \lambda e^{-\lambda u_{k1}} \frac{\rho}{1-\rho}\left[1 - e^{-\lambda((1-\rho)/\rho)u_{k1}}\right] + \lambda e^{-\lambda u_{k1}/\rho} \\
&= \lambda \frac{\rho}{1-\rho} e^{-\lambda u_{k1}} + \lambda \frac{1-2\rho}{1-\rho} e^{-\lambda u_{k1}/\rho}.
\end{aligned}
$$

Therefore using the value of $I(u_{k1})$ in (4.8) we get

$$
\begin{aligned}
corr(M_{k1}(X_{k1}), M_{k2}(X_{k2})) &= -1 + \frac{(1-\rho)^2}{1-2\rho} \\
&\quad - \frac{\rho^2}{1-2\rho} \int_0^\infty \lambda \frac{\rho}{1-\rho} e^{-\lambda u_{k1}} du_{k1} \\
&\quad + \int_0^\infty \lambda \frac{1-2\rho}{1-\rho} e^{-\lambda u_{k1}/\rho} du_{k1} \\
&= -1 + \frac{(1-\rho)^2}{1-2\rho} - \frac{2\rho^3}{1-2\rho} \\
&= \rho^2
\end{aligned}
$$

Similarly, it is easy to show that the correlation between $M_{k1}(X_{k1})$ and $M_{k3}(X_{k3})$ is

$$
corr(M_{k1}(X_{k1}), M_{k2}(X_{k2})) = \rho^2.
$$

Also, in general, for any $i \neq j; i, j = 1, 2, \ldots, n$ we can write the correlation between $M_{ki}(X_{ki})$ and $M_{kj}(X_{kj})$ as

$$
corr(M_{ki}(X_{ki}), M_{kj}(X_{kj})) = \rho^2.
$$

This completes the proof. □

Note that it now follows from Theorem 4.3 that under the EEQ process, the variance-covariance matrix $\mathbf{V}$, say, of the martingales $M_{ki}(X_{ki})$, $i = 1, 2, \ldots, n$ can be written as

$$
V = \begin{bmatrix}
1 & \rho^2 & \rho^2 & \ldots & \rho^2 \\
\rho^2 & 1 & \rho^2 & \ldots & \rho^2 \\
\rho^2 & \rho^2 & 1 & \ldots & \rho^2 \\
\vdots & \vdots & \vdots & \ldots & \vdots \\
\rho^2 & \rho^2 & \rho^2 & \ldots & 1
\end{bmatrix} \tag{4.9}
$$

which is naturally the correlation matrix of the martingales for the uncensored case.

Further, note that the martingale correlation structures (4.5), (4.7) and (4.9) respectively, for the EAR(1), EMA(1) and EEQ processes will be utilized in the next section to construct the estimating equations to obtain efficient as well as consistent regression estimates. To be specific, this will be done following Cai and Prentice (1995) by using the inverse of the martingale covariance matrix as the weight matrix in the estimating equation.

4.2 Estimating Equations for Hazard Ratio Parameters

Recall from Section 2.1 that $\lambda_{ki}(t)$ is the instantaneous rate of failure at time t of the kth member at occasion i, which has the form

$$\lambda_{ki}(t) = Y_{ki}(t)\lambda_{0i}(t)\exp(\mathbf{Z}_{ki}^T(t)\boldsymbol{\beta}). \tag{4.10}$$

In (4.10) $Y_{ki}(t) = I(T_{ki} \geq t)$ is an at risk indicator process for the kth member at occasion i, $\mathbf{Z}_{ki}^T(.) = (Z_{ki1}(.), Z_{ki2}(.), \ldots, Z_{kip}(.))$ is a $1 \times p$ covariate vector for the kth member at occasion i with failure times T_{ki}, $\lambda_{0i}(.)$ is the unspecified baseline hazard function and $\boldsymbol{\beta}^T$=(β_1,β_2,...,β_p) is a hazard ratio vector, or relative risk parameter which is also referred to as the regression effects.

Now to motivate the estimating equation for $\boldsymbol{\beta}$, we write the partial likelihood function (Cox and Oakes, 1984) under the independence assumption for the repeated failure times, as

$$L(\boldsymbol{\beta}) = \prod_{k=1}^{K}\prod_{i=1}^{n}\left[exp\{\mathbf{Z}_{ki}^T(T_{ki})\boldsymbol{\beta}\}/\sum_{l=1}^{K} Y_{li}(T_{ki})exp\{\mathbf{Z}_{li}^T(T_{ki})\boldsymbol{\beta}\}\right],$$

which yields the estimating equation for estimating $\boldsymbol{\beta}$ after some algebraic manipulation (Fleming and Harrington, 1991, p .26) as

$$\sum_{k=1}^{K}\sum_{i=1}^{n}\int_0^{\infty} \mathbf{Z}_{ki}^T(u)U_{ki}(du) = \mathbf{0}, \tag{4.11}$$

where $U_{ki}(t) = \hat{M}_{ki}(t) = 1 - \Lambda_{ki}(t)$. In matrix notation the above independent estimating equation for $\boldsymbol{\beta}$ may be expressed as

$$\sum_{k=1}^{K} \int_0^\infty \mathbf{Z}_k^T(u)\mathbf{U}_k(du) = \mathbf{0}, \tag{4.12}$$

where

$$\mathbf{Z}_k^T(u) = (\mathbf{Z}_{k1}(u), ..., \mathbf{Z}_{kn}(u)) \quad \text{and} \quad \mathbf{U}_k^T(u) = (U_{k1}(u), ..., U_{kn}(u)).$$

Next, to accommodate the longitudinal correlation of the failure times of the kth individual, following Cai and Prentice (1995) we propose to use the generalized estimating equation

$$\sum_{k=1}^{K} \int_0^\infty \mathbf{Z}_k^T(u)\mathbf{W}_k(\boldsymbol{\beta}, u)\mathbf{U}_k(du) = \mathbf{0} \tag{4.13}$$

instead of (4.12), to estimate $\boldsymbol{\beta}$ under our longitudinal set-up. Note that in (4.13), $\mathbf{W}_k(\boldsymbol{\beta}, u)$ is the inverse of the longitudinal covariance matrix of the martingales under the appropriate exponential AR(1), MA(1) or equi-correlation process. Further note that, as compared to $\mathbf{W}_k(\boldsymbol{\beta}, u)$ in (4.13), $\mathbf{W}_k(\boldsymbol{\beta}, u)$ in Cai and Prentice (1995, eq. 3) is the inverse of the correlation matrix of martingales under a structural set-up.

Let $\hat{\boldsymbol{\beta}}_T$ be the estimate of $\boldsymbol{\beta}$ when the true covariance structure is used in (4.13) to estimate $\boldsymbol{\beta}$. This estimate may be obtained by solving the estimating equation (4.13) by using the well-known Gauss-Newton iteration procedure

$$\hat{\boldsymbol{\beta}}_T(t+1) = \hat{\boldsymbol{\beta}}_T(t) + \left[\frac{\partial}{\partial \boldsymbol{\beta}} g(\boldsymbol{\beta})\right]_{(t)}^{-1} [g(\boldsymbol{\beta})]_{(t)} \tag{4.14}$$

where $g(\beta) = \sum_{k=1}^{K} \int_0^\infty \mathbf{Z}_k^T(u)\mathbf{W}_k(\beta, u)\mathbf{U}_k(du) = \mathbf{0}$ and $[\ \ ]_{(t)}$ denotes that the expression within the square brackets is evaluated at $\hat{\boldsymbol{\beta}}_T(t)$, the values of $\hat{\boldsymbol{\beta}}_T$ at the tth iteration. For the purpose of numerical computation the iterative equation (4.14) may further be expressed as (Cai and Prentice, 1995)

$$\hat{\boldsymbol{\beta}}_T(t+1) = \hat{\boldsymbol{\beta}}_T(t) + \left[\frac{1}{K}\sum_{k=1}^{K}\sum_{j=1}^{n} \hat{A}_{w,kj}\right]^{-1} \frac{1}{K}\sum_{k=1}^{K}\sum_{j=1}^{n} \hat{G}_{w,kj}(\boldsymbol{\beta}), \tag{4.15}$$

where $\hat{A}_{w,kj}$ is given by

$$\hat{A}_{w,kj} = -\left[\sum_{i=1}^{n} \mathbf{Z}_{ki}(T_{kj})\frac{\partial \hat{w}_{kij}(\boldsymbol{\beta}, T_{kj})}{\partial \boldsymbol{\beta}^T} + \frac{\hat{S}_j^{(2)}(\boldsymbol{\beta}, T_{kj})\hat{S}_j^{(1)}(\boldsymbol{\beta}, T_{kj})^T}{\hat{S}_j^{(0)}(\boldsymbol{\beta}, T_{kj})^2} - \frac{\hat{S}_j^{(3)}(\boldsymbol{\beta}, T_{kj})}{\hat{S}_j^{(0)}(\boldsymbol{\beta}, T_{kj})} - \frac{\hat{S}_j^{(4)}(\boldsymbol{\beta}, T_{kj})}{\hat{S}_j^{(0)}(\boldsymbol{\beta}, T_{kj})}\right] \tag{4.16}$$

and $\hat{G}_{kj}(\boldsymbol{\beta})$ can be written as

$$\begin{aligned}\hat{G}_{w,kj}(\boldsymbol{\beta}) &= \sum_{i=1}^{n} \mathbf{Z}_{ki}(T_{kj})\hat{w}_{kij}(\boldsymbol{\beta}, T_{kj}) - \frac{\hat{S}_j^{(2)}(\boldsymbol{\beta}, T_{kj})}{\hat{S}_j^{(0)}(\boldsymbol{\beta}, T_{kj})} \\ &\quad - \frac{1}{K}\sum_{m=1}^{K} Y_{kj}(T_{mj}) exp\{\mathbf{Z}_{kj}^T(T_{mj})\boldsymbol{\beta}\}\hat{S}_j^{(0)}(\boldsymbol{\beta}, T_{mj})^{-1} \\ &\quad \times \left[\sum_{i=1}^{n} \mathbf{z}_{ki}(T_{mj})\hat{w}_{kij}(\boldsymbol{\beta}, T_{mj}) - \frac{\hat{S}_j^{(2)}(\boldsymbol{\beta}, T_{mj})}{\hat{S}_j^{(0)}(\boldsymbol{\beta}, T_{mj})}\right].\end{aligned} \tag{4.17}$$

In (4.16) and (4.17) $\hat{S}_j^{(d)}(d = 0, \ldots, 4)$ are the sample estimates of $S_j^{(d)}(d = 0, \ldots, 4)$, where

$$S_j^{(d)}(\boldsymbol{\beta}, t) = K^{-1}\sum_{k=1}^{K} Y_{kj}(t)\mathbf{Z}_{kj}(t)^d exp\{\mathbf{Z}_{kj}^T(t)\boldsymbol{\beta}\} \quad (d = 0, 1),$$

$$S_j^{(d)}(\boldsymbol{\beta}, t) = K^{-1}\sum_{k=1}^{K} Y_{kj}(t)\mathbf{Z}_{kj}(t)w_{kij}(\boldsymbol{\beta}, t)\{\mathbf{Z}_{kj}^T(t)\}^{d-2} exp\{\mathbf{Z}_{kj}^T(t)\boldsymbol{\beta}\} \quad (d = 2, 3)$$

and

$$S_j^{(4)}(\boldsymbol{\beta}, t) = K^{-1}\sum_{k=1}^{K} Y_{kj}(t)\mathbf{Z}_{kj}(t)\{\partial w_{kij}(\boldsymbol{\beta}, t)/\partial \boldsymbol{\beta}^T\} exp\{\mathbf{Z}_{kj}^T(t)\boldsymbol{\beta}\}$$

4.2.1 Estimation of Martingales Covariance Matrix

Note that the weight matrix $\mathbf{W}_k(\boldsymbol{\beta}, u)$ in (4.13) or (4.15) is the inverse of the $\mathbf{V}$ matrix, $\mathbf{V}$ is the covariance matrix of the martingales for longitudinal failure times. As the elements of $\mathbf{V}$ are functions of the dependence (or probability) parameter ρ, we need to estimate this parameter in order to solve the estimating equation (4.13). Further note that the covariance matrix $\mathbf{V}$ was constructed under the condition that the failure times T_{ki} have stationary exponential distributions with mean $1/\lambda$ and variance $1/\lambda^2$. In practice, however, one would expect that T_{ki} has mean $1/\lambda_{ki}$ and variance $1/\lambda_{ki}^2$, i.e. the mean and variance may be functions of the covariates at occasion i for the kth individual. These failure time variables with such non i.i.d. exponential distributions may be related to a set of stationary variables T_{ki}^* as $T_{ki}^* = T_{ki}\lambda_{ki}/\lambda$, where T_{ki}^* may be considered as the exponential failure times of Chapter 3 with $E(T_{ki}^*) = 1/\lambda$ and $var(T_{ki}^*) = 1/\lambda^2$. This stationary variables T_{ki}^* was based on the assumption that the parameters involved ($\boldsymbol{\beta}$) is Known. This transformation remains valid approximately even if $\boldsymbol{\beta}$ is replaced by its consistent estimator. As the correlation between two non i.i.d. exponential variables T_{ki} and T_{kj} is given by

$$\begin{aligned} corr(T_{ki}, T_{kj}) &= \frac{cov(T_{ki}, T_{kj})}{[var(T_{ki})var(T_{kj})]^{1/2}} \\ &= \frac{E[\{T_{ki} - 1/\lambda_{ki}\}\{T_{kj} - 1/\lambda_{kj}\}]}{1/(\lambda_{ki}\lambda_{kj})}, \end{aligned}$$

and using the relationship $T_{ki}^* = T_{ki}\lambda_{ki}/\lambda$, this correlation reduces to

$$corr(T_{ki}, T_{kj}) = corr(T_{ki}^*, T_{kj}^*) = \rho_{|i-j|}^*, \tag{4.18}$$

where $\rho_{|i-j|}^*$ is the lag $\mid i - j \mid$ correlation between T_{ki}^* and T_{kj}^*.

Note that for the EAR(1) process

$$\rho_{|i-j|}^* = \rho^{|i-j|},$$

for the EMA(1) process

$$\rho_{|i-j|}^* = \begin{cases} \rho(1-\rho) & \text{for } j = i+1 \\ 0 & \text{otherwise} \end{cases}$$

and similarly for the EEQ process

$$\rho_{|i-j|}^* = \rho^2.$$

Further note that this ρ parameter which defines all lag correlations can be estimated by using the estimate of ρ_1^* under the EAR(1) and EMA(1) processes.

To be specific, under the EAR(1) process $\hat{\rho} = \hat{\rho}_1^*$ and under the EMA(1) process $\hat{\rho}(1-\hat{\rho}) = \hat{\rho}_1^*$. To estimate ρ under the EEQ process one needs to compute all lag correlation estimates such that

$$\hat{\rho}^2 = \frac{(n-1)\hat{\rho}_1 + (n-2)\hat{\rho}_2 + \ldots + \hat{\rho}_{n-1}}{n(n-1)/2}$$

Now in general, ρ_l^* ($l = \mid i - j \mid$) can be estimated by using method of moments as

$$\hat{\rho}_l^* = \frac{\sum_{k=1}^{K} \sum_{i=1}^{n-l} \left[\frac{(T_{ki} - \hat{E}(T_{ki}))(T_{k(i+l)} - \hat{E}(T_{k(i+l)}))}{[\hat{var}(T_{ki}) \hat{var}(T_{k(i+l)})]^{1/2}} \right] / K(n-l)}{\sum_{k=1}^{K} \sum_{i=1}^{n} \left[\frac{(T_{ki} - \hat{E}(T_{ki}))(T_{ki} - \hat{E}(T_{ki}))}{\hat{var}(T_{ki})} \right] / Kn}. \tag{4.19}$$

4.3 Efficiency Comparison Under Correlation Structure Misspecification Through A Simulation Study

The hazard ratio estimate obtained from (4.13) is consistent and efficient, provided the underlying correlation structure for the exponential failure times such as EAR(1), EMA(1) or EEQ is known. To be specific, if it is known that the failure times $T_{k1}, \ldots, T_{ki}, \ldots, T_{kn}$ follow the EAR(1) process (3.1) and we compute the $\mathbf{W}_k(\boldsymbol{\beta}, u)$ matrix based on this underlying EAR(1) process as in Theorem 4.1, then the $\boldsymbol{\beta}$ estimate using (4.13) is consistent and efficient. Note however that in practice the underlying correlation process may not be known. The purpose of this section is to examine the loss of efficiencies in $\boldsymbol{\beta}$ estimation if one uses a "working" correlation structure different than the true longitudinal correlation structure in the estimating equation for $\boldsymbol{\beta}$. We do this through a simulation study.

4.3.1 Simulation Design and Generation of the Exponential Failure time Data

For our simulation study we consider $K = 100$ individuals each with $n = 4$ repeated failure times. We also consider a two dimensional ($p = 2$) covariate vector $\mathbf{Z}_{ki} =$

$(Z_{ki1}, Z_{ki2})^T$ at occasion i for each of the K individuals. To be specific, we choose 2-dimensional covariates under two different designs, say D_1 and D_2. Under D_1, we consider both Z_{ki1} and Z_{ki2} as binary with 50-50 probabilities. Under D_2 we consider Z_{ki1} as binary with 50-50 probability but Z_{ki2} is chosen as from a Poisson distribution with mean 0.5.

Generation Under EAR(1) Process

To generate T_{ki} for a fixed k and all $i = 1, \ldots, 4$ we first generate initial values T^*_{k0} and ε_{ki} from a standard exponential distribution with mean 1 and variance 1. Using T^*_{k0} and ε_{ki} and following (3.1) of Chapter 3 we generate T^*_{ki} for $i = 1, \ldots, 4$ for a given value of the dependence parameter ρ. We do this for various choices of the dependence parameter (ρ=0.10, 0.25, 0.49, 0.64 and 0.81). Since in our regression set up, the exponential variable T_{ki} depends on the covariates, we now generate T_{ki} with mean $1/\lambda_{ki}$ and variance $1/\lambda^2_{ki}$, where λ_{ki} is a function of covariates given by

$$\lambda_{ki} = \exp(Z_{ki1}\beta_1 + Z_{ki2}\beta_2); \quad i = 1, \ldots, 4 \tag{4.20}$$

by using the transformation $T_{ki} = T^*_{ki}/\lambda_{ki}$. This we do for all $k = 1, 2, \ldots, 100$.

Generation Under EMA(1) Process

To generate T_{ki} under EMA(1) process we first generate ε_{ki} for a fixed k and all $i = 1, \ldots, 5$ from a standard exponential distribution with mean 1 and variance 1. Note that unlike the EAR(1) case, the generation of T_{ki} depends only on ε_{ki}. Next for a given value of the dependence parameter ρ we generate T^*_{ki} for $i = 1, \ldots, 4$ following (3.6) of Chapter 3. Although $0 < \rho < 1$, for the EMA(1) process we choose ρ=0.10, 0.25 and 0.49 only. This is because the lag 1 correlation , $\rho(1-\rho)$, is maximized when $\rho = 0.50$. To clarify this point further, if $\rho = 0.70$, for example, the lag 1 correlation will be $\rho(1-\rho) = 0.21$. Now by using the transformation $T_{ki} = T^*_{ki}/\lambda_{ki}$, where λ_{ki} is defined as in (4.20), we get T_{ki} with mean $1/\lambda_{ki}$ and variance $1/\lambda^2_{ki}$ for the EMA(1) process. We again do this for $k = 1, 2, \ldots, 100$.

Generation Under EEQ Process

Similarly, to generate T_{ki} for the EEQ process we first generate initial values T^*_{k0} and ε_{ki} $(i = 1, \dots, 4)$ for a fixed value of k from a standard exponential distribution. For fixed dependence parameter ρ we generate T^*_{ki} for $i = 1, \dots, 4$ following (3.11) of Chapter 3. Then for generating the values of T_{ki} we simply use the transformation $T_{ki} = T^*_{ki}/\lambda_{ki}$ as it was done for EAR(1) and EMA(1) process, where λ_{ki} is defined as in (4.20) and we repeat this generation for $k = 1, 2, \dots, 100$.

4.3.2 Empirical Efficiency Comparison Due to Misspecification of Correlation Structure

We now use the exponential responses (discussed in the previous section) generated under a given correlation structure and compute the estimate of $\boldsymbol{\beta}$ by using this known correlation structure in the estimating equation for $\boldsymbol{\beta}$ in (4.13). As this estimate is computed using the true known correlation structure, we refer this as the true $\boldsymbol{\beta}$ estimate which was denoted by $\hat{\boldsymbol{\beta}}_T$ in Section 4.2. We compute such $\boldsymbol{\beta}$ estimates for 2000 simulations and obtain the average and calculate the mean square error (MSE). This MSE is referred to as $MSE(True)$. Next we generate the exponential data following a given correlation structure but use a different "working" correlation structure in (4.13) to obtain an estimate of $\boldsymbol{\beta}$. This estimate is called the "working" $\boldsymbol{\beta}$ estimate, which we denote for convenience by $\hat{\boldsymbol{\beta}}_{W|T}$. After computing this estimate for 2000 simulations we calculate the mean and MSE using this "working" structure. This MSE under "working" structure is referred to as $MSE(Working)$. To be specific, suppose that we generate the failure times from EAR(1) process. Now if we use the EAR(1) correlation structure for estimating $\boldsymbol{\beta}$ by using (4.13) and calculate mean and MSE, then this MSE is referred to as $MSE(True)$. However if we generate failure times from an EAR(1) process but we use an incorrect correlation structure, such as EMA(1), EEQ or Independence(ID) to find $\hat{\boldsymbol{\beta}}$, its mean and MSE, we refer to this MSE as $MSE(Working)$. It then follows that one may compute the relative efficiency as

$$R.E.(\hat{\beta}_{W|T}) = \frac{MSE(Working)}{MSE(True)} \times 100, \tag{4.21}$$

where $R.E.(\hat{\boldsymbol{\beta}}_{T|T})$ is 100 as $\hat{\boldsymbol{\beta}}_{T|T}$ is nothing but $\hat{\boldsymbol{\beta}}_T$. Note that by using (4.21) we calculate the percentage loss of efficiencies due to misspecification of the correlation structure and we report these results in the tables of Appendix A.

Table A.1 contains results when our $\mathbf{T}_k$ values are generated from an EAR(1) process, for various choices of ρ under design D_1. From Table A.1 we can see that our estimates are unbiased, whether we use the correct correlation structure (EAR(1) in this case) or an incorrect correlation structure such as EMA(1), EEQ or Independence(ID). We can see that we are losing a lot of efficiency if we do not use the true correlation structure, especially for correlation larger than 0.25. One very important point is the poor performance of the working independence structure when the correlation is high. This suggests we could have problems if we incorrectly assume that our failure times are independent. Note that we do not have results for the working EMA(1) structure for $\rho > 0.25$ because the maximum correlation from the EMA(1) model is 0.25. We know that under an EAR(1) process, ρ is the lag 1 correlation and if we generate failure times under an EAR(1) process with $\rho = 0.49$, our lag 1 correlation will be the estimate of ρ which cannot be the lag 1 correlation for EMA(1), because under $\rho = 0.49$ the estimate of ρ will be greater than 0.25. Table A.2 is similar to Table A.1, except Z_{ki} are generated under design D_2. From Table A.2 we can see that the estimates are unbiased and the efficiency losses are very similar to those in Table A.1.

Tables A.3 and A.4 contain results when our $\mathbf{T}_k$ values are generated using an EEQ process, for various choices of ρ under the design D_1 and D_2 respectively. Like Tables A.1 and A.2, we can conclude from A.3 and A.4 that the estimates of β_1 and β_2 are unbiased, whether we use the correct correlation structure or an incorrect working structure. Note that the estimates under a working independent structure are quite inefficient when the correlation is high. Although any working correlation except the true structure do poorly, the independent working approach does the worst. We do see that using a working EAR(1) structure does reasonably well when the correlation is high. As discussed before we cannot use the working EMA(1) structure if the correlation exceeds 0.25. So under the EEQ model we can consider our dependence parameter up to 0.5.

Tables A.5 and A.6 contain results when the $\mathbf{T}_k$ values are generated under an EMA(1) process, with $\rho = 0.10, 0.25$ and 0.49 under design D_1 and D_2 respectively. As mentioned previously, we cannot consider lag 1 correlation $\rho(1-\rho) > 0.25$ for the EMA(1) process. We see in Tables A.5 and A.6 that we have unbiased estimates and efficiency losses are small using the incorrect working correlation structures.

From the above discussion of simulation studies we can conclude that we get unbiased estimates of the regression parameter $\boldsymbol{\beta}$ no matter whether we are using the true or incorrect correlation structure. For small correlation ($\rho \leq 0.25$) there is not a large efficiency gain in using the true correlation structure in the estimation of $\boldsymbol{\beta}$. But if we have high correlation ($\rho > 0.25$) then we should use the true correlation structure for estimating $\boldsymbol{\beta}$, otherwise we lose a lot of efficiency. Note that one will lose efficiency to a greater extent if the working correlation structure is used in estimating $\boldsymbol{\beta}$, the independent working approach being the worst.

Chapter 5

Regression Model for Longitudinal Censored Failure Time Data

In Chapter 4, it was shown how to solve the estimating equation (4.13) for the hazard ratio parameters when longitudinal failure times were not subject to any censorship. However, in practice there are situations where repeated failure times can be censored. An interesting example can be found in Wei, Lin and Weissfeld (1989) (see also Makuch and Parks, 1988). From their study, in a randomized clinical trial to evaluate the effectiveness of the drug rivavirin, patients with acquired immune deficiency syndrome (AIDS) were randomly assigned to one of three groups: placebo, low-dose rivavirin and high-dose rivavirin. One of the main interests of the study was to investigate the antiretroviral capability of rivavirin over time. Blood samples for each patient were collected at weeks 4, 8 and 12. For each serum sample, measurements of p24 antigen levels, which are important markers of HIV-1 infection, were repeatedly taken for a period of four weeks. Therefore, potentially each patient in the study should have three such event times. Some observations were missing, however, because patients did not make the scheduled visits or because serum specimens were inadequate for laboratory analysis. In addition, censored observations occurred when the culture required a longer period of time to register as virus positive than was achievable in the laboratory, or when the serum sample was contaminated before positivity was detected. The accommodation of such censorship information and the construction of estimating equations for longitudinal failure time data appears to be a challenging task, which we address in this chapter.

5.1 Martingale Correlation Structure for Exponential Censored Failure Time Data

As in the previous chapter, let T_{ki} denote the failure time, where $k = 1, 2, \ldots, K$ and $i = 1, 2, \ldots, n$. We define C_{ki} as the corresponding censoring time for T_{ki} and $X_{ki} = \min(T_{ki}, C_{ki})$. So $X_{ki} = T_{ki}$ if the failure time of the kth individual is uncensored at occasion i and $X_{ki} = C_{ki}$ if the failure time of kth individual is censored at occasion i. For the censored case the martingales $M_{ki}(X_{ki})$ defined in (2.3) reduce to

$$M_{ki}(X_{ki}) = \begin{cases} 1 - \Lambda_{ki}(T_{ki}) & \text{if } X_{ki} = T_{ki} \\ -\Lambda_{ki}(C_{ki}) & \text{if } X_{ki} = C_{ki} \end{cases} \tag{5.1}$$

According to the discussion of the previous chapter we need to calculate the variances and covariances between the martingales (5.1) of the failure times and our weight matrix will be the inverse of the variance-covariance matrix as discussed earlier. From Cai and Prentice (1995, p. 158), we write the variance of $M_{ki}(X_{ki})$ as

$$Var\left[M_{ki}(X_{ki})\right] = 1 - e^{-c_{ki} exp(Z_{ki1}\beta_1 + Z_{ki2}\beta_2)}$$

and the covariance between $M_{ki}(X_{ki})$ and $M_{kj}(X_{kj})$ as

$$\begin{aligned} Cov\left[M_{ki}(X_{ki}), M_{kj}(X_{kj})\right] &= F_k(c_{ki}, c_{kj}; \rho) + \int_0^{c_{ki}} \lambda F_k(u_{ki}, c_{kj}; \rho) du_{ki} \\ &\quad + \int_0^{c_{kj}} \lambda F_k(c_{ki}, u_{kj}; \rho) du_{kj} \\ &\quad + \int_0^{c_{ki}} \int_0^{c_{kj}} \lambda^2 F_k(u_{ki}, u_{kj}; \rho) du_{kj} du_{ki} - 1 \\ &= I_1 + I_2 + I_3 + I_4 - 1 \end{aligned} \tag{5.2}$$

We will now discuss evaluating I_1 through I_4 in (5.2) for each of the three models EAR(1), EMA(1) and EEQ.

5.1.1 Martingale Correlation Under Censored Exponential AR(1) Process

Theorem 5.1: In the presence of censorship the martingales $M_{ki}(X_{ki})$ defined in (5.1) have the pairwise covariance given by

$$Cov\left[M_{ki}(X_{ki}), M_{k(i+j)}(X_{k(i+j)})\right] = \rho^j - \rho^j e^{-\lambda \min(c_{ki}, c_{k(i+j)}/\rho^j)}$$

for $i, j = 1, 2, \ldots, n$.

Proof: From (3.5) (Chapter 3) we get the bivariate survival function of T_{k1} and T_{k2} as

$$F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) = \begin{cases} e^{-\lambda u_{k1}} & \text{for } u_{k2} \leq \rho u_{k1} \\ e^{-\lambda u_{k2}} e^{-\lambda(1-\rho)u_{k1}} & \text{for } u_{k2} > \rho u_{k1} \end{cases} \tag{5.3}$$

We will use the bivariate survival function in (5.3) for evaluating the integrals I_1, I_2, I_3 and I_4 in (5.2), which will give us the covariance of martingales of the failure times, i.e. $Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right]$. For evaluating these integrals we get two different cases: (a) $c_{k2} > \rho c_{k1}$ and (b)$c_{k2} \leq \rho c_{k1}$.

Under case (a) when $c_{k2} > \rho c_{k1}$ we can evaluate I_1 as

$$\begin{aligned} I_1 &= F_k(c_{k1}, c_{k2}; \rho) \\ &= e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}} \end{aligned}$$

and we can calculate I_2 as

$$\begin{aligned} I_2 &= \int_0^{c_{k1}} \lambda F_k(u_{k1}, c_{k2}; \rho) du_{k1} \\ &= \int_0^{c_{k1}} \lambda e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)u_{k1}} du_{k1} \\ &= \frac{e^{-\lambda c_{k2}}}{1-\rho} - \frac{e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}}}{1-\rho}. \end{aligned}$$

Similarly, I_3 can be evaluated as

$$\begin{aligned} I_3 &= \int_0^{c_{k2}} \lambda F_k(c_{k1}, u_{k2}; \rho) du_{k2} \\ &= \int_0^{\rho c_{k1}} \lambda e^{-\lambda c_{k1}} du_{k2} + \int_{\rho c_{k1}}^{c_{k2}} \lambda e^{-\lambda(1-\rho)c_{k1}} e^{-\lambda u_{k2}} du_{k2} \\ &= \lambda \rho c_{k1} e^{-\lambda c_{k1}} + e^{-\lambda c_{k1}} - e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}}, \end{aligned}$$

and again I_4 can be evaluated as

$$\begin{aligned}
I_4 &= \int_0^{c_{k1}}\int_0^{c_{k2}} \lambda^2 F_k(u_{k1},u_{k2};\rho)du_{k2}du_{k1} \\
&= \int_0^{c_{k1}}\int_0^{\rho u_{k1}} \lambda^2 e^{-\lambda u_{k1}} du_{k2}du_{k1} + \int_0^{c_{k1}}\int_{\rho u_{k1}}^{c_{k2}} \lambda^2 e^{-\lambda u_{k2}} e^{-\lambda(1-\rho)u_{k1}} du_{k2}du_{k1} \\
&= \int_0^{c_{k1}} \lambda^2 \rho u_{k1} du_{k1} + \int_0^{c_{k1}} \lambda e^{-\lambda(1-\rho)u_{k1}} \left[e^{-\lambda\rho u_{k1}} - e^{-\lambda c_{k2}}\right] du_{k1} \\
&= -\rho\lambda c_{k1} e^{-\lambda c_{k1}} + \rho - \rho e^{-\lambda c_{k1}} + 1 - e^{-\lambda c_{k1}} + \int_0^{c_{k1}} \lambda e^{-\lambda(1-\rho)u_{k1}} e^{-\lambda c_{k2}} du_{k1} \\
&= -\rho\lambda c_{k1} e^{-\lambda c_{k1}} + \rho - \rho e^{-\lambda c_{k1}} + 1 - e^{-\lambda c_{k1}} - \frac{e^{-\lambda c_{k2}}}{1-\rho} + \frac{e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}}}{1-\rho}.
\end{aligned}$$

Therefore, by combining I_1, I_2, I_3 and I_4 in (5.2) under case (a) when $c_{k2} > \rho c_{k1}$, we get the covariance between $M_{k1}(X_{k1})$ and $M_{k2}(X_{k2})$ as

$$\begin{aligned}
Cov[M_{k1}(X_{k1}), M_{k2}(X_{k2})] &= e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}} + \frac{e^{-\lambda c_{k2}}}{1-\rho} - \frac{e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}}}{1-\rho} \\
&\quad + \lambda\rho c_{k1} e^{-\lambda c_{k1}} + e^{-\lambda c_{k1}} - e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}} \\
&\quad - \rho\lambda c_{k1} e^{-\lambda c_{k1}} + \rho - \rho e^{-\lambda c_{k1}} + 1 - e^{-\lambda c_{k1}} - \frac{e^{-\lambda c_{k2}}}{1-\rho} \\
&\quad + \frac{e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)c_{k1}}}{1-\rho} - 1 \\
&= \rho - \rho e^{-\lambda c_{k1}}. \qquad (5.4)
\end{aligned}$$

Under case (b) $c_{k2} \le \rho c_{k1}$ we can evaluate I_1 as

$$I_1 = F_k(c_{k1}, c_{k2}; \rho) = e^{-\lambda c_{k1}}$$

and we can evaluate I_2 as

$$\begin{aligned}
I_2 &= \int_0^{c_{k1}} \lambda F_k(u_{k1}, c_{k2}; \rho) du_{k1} \\
&= \int_0^{c_{k2}/\rho} \lambda e^{-\lambda c_{k2}} e^{-\lambda(1-\rho)u_{k1}} du_{k1} + \int_{c_{k2}/\rho}^{c_{k1}} \lambda e^{-\lambda u_{k1}} du_{k1} \\
&= \frac{e^{-\lambda c_{k2}}}{1-\rho} - \frac{e^{-\lambda(1-\rho)c_{k2}/\rho}}{1-\rho} + e^{-\lambda c_{k2}/\rho} - e^{-\lambda c_{k1}}.
\end{aligned}$$

Similarly, we can calculate I_3 as

$$\begin{aligned}
I_3 &= \int_0^{c_{k2}} \lambda F_k(c_{k1}, u_{k2}; \rho) du_{k2} = \int_0^{c_{k2}} \lambda e^{-\lambda c_{k1}} du_{k2} \\
&= \lambda c_{k2} e^{-\lambda c_{k1}}.
\end{aligned}$$

Now I_4 can be evaluated as

$$\begin{aligned} I_4 &= \int_0^{c_{k1}} \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho) du_{k2} du_{k1} \\ &= \int_0^{c_{k1}} I(u_{k1}) du_{k1} \quad \text{(say).} \end{aligned}$$

For evaluating the integral $I(u_{k1})$ we will again get two different cases: (i) $\rho u_{k1} > c_{k2}$ and (ii) $\rho u_{k1} < c_{k2}$. Under (i) $\rho u_{k1} > c_{k2}$, $I(u_{k1})$ is evaluated as

$$\begin{aligned} I(u_{k1}) &= \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho) du_{k2} \\ &= \int_0^{c_{k2}} \lambda^2 e^{-\lambda u_{k1}} du_{k2} \\ &= \lambda^2 c_{k2} e^{-\lambda u_{k1}}, \end{aligned}$$

then I_4 can be denoted as $I_{4(i)}$ under case (i) $\rho u_{k1} > c_{k2}$ and calculated as

$$\begin{aligned} I_{4(i)} &= \int_0^{c_{k1}} I(u_{k1}) du_{k1} \\ &= \int_{c_{k2}/p}^{c_{k1}} \lambda^2 c_{k2} e^{-\lambda u_{k1}} du_{k1} \\ &= \lambda c_{k2} e^{-\lambda c_{k2}/p} - \lambda c_{k2} e^{-\lambda c_{k1}} \end{aligned}$$

and under (ii) $\rho u_{k1} < c_{k2}$, $I(u_{k1})$ is

$$\begin{aligned} I(u_{k1}) &= \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho) du_{k2} \\ &= \int_0^{\rho u_{k1}} \lambda^2 e^{-\lambda u_{k1}} du_{k2} + \int_{\rho u_{k1}}^{c_{k2}} \lambda^2 e^{-\lambda u_{k2}} e^{-\lambda(1-\rho)u_{k1}} du_{k2} \\ &= \rho u_{k1} \lambda^2 e^{-\lambda u_{k1}} + \lambda e^{-\lambda u_{k1}} - \lambda e^{-\lambda(1-\rho)u_{k1}} e^{-\lambda c_{k2}} \end{aligned}$$

then again I_4 can be denoted as $I_{4(ii)}$ under case (ii) $\rho u_{k1} \leq c_{k2}$ and calculated as

$$\begin{aligned} I_{4(ii)} &= \int_0^{c_{k1}} I(u_{k1}) du_{k1} \\ &= \int_0^{c_{k2}/\rho} I(u_{k1}) du_{k1} \\ &= \rho \lambda^2 \int_0^{c_{k2}/\rho} u_{k1} e^{-\lambda u_{k1}} du_{k1} + \lambda \int_0^{c_{k2}/\rho} e^{-\lambda u_{k1}} du_{k1} \\ &\quad -\lambda \int_0^{c_{k2}/\rho} e^{-\lambda(1-\rho)u_{k1}} e^{\lambda c_{k2}} du_{k1} \\ &= -\rho c_{k2} e^{-\lambda c_{k2}/\rho} + \rho - \rho e^{-\lambda c_{k1}/\rho} + 1 - e^{-\lambda c_{k1}/\rho} - \frac{e^{-\lambda c_{k2}}}{1-\rho} + \frac{e^{-\lambda c_{k2}/\rho}}{1-\rho}. \end{aligned}$$

Therefore, I_4 is the sum of $I_{4(i)}$ and $I_{4(ii)}$ and can be evaluated as

$$I_4 = \rho - \rho e^{-\lambda c_{k1}/\rho} + 1 - e^{-\lambda c_{k1}/\rho} - \frac{e^{-\lambda c_{k2}}}{1-\rho} + \frac{e^{-\lambda c_{k2}/\rho}}{1-\rho} - \lambda c_{k2} e^{-\lambda c_{k1}}.$$

Similarly, under case (b) $c_{k2} \le \rho c_{k1}$, after combining I_1, I_2, I_3 and I_4 in (5.2) we can calculate $Cov\,[M_{k1}(X_{k1}), M_{k2}(X_{k2})]$ as

$$\begin{aligned} Cov\,[M_{k1}(X_{k1}), M_{k2}(X_{k2})] &= e^{-\lambda c_{k1}} + \frac{e^{-\lambda c_{k2}}}{1-\rho} - \frac{e^{-\lambda c_{k2}/\rho}}{1-\rho} + e^{-\lambda c_{k2}/\rho} \\ &\quad - e^{-\lambda c_{k1}} + \lambda c_{k2} e^{-\lambda c_{k1}} + \rho - \rho e^{-\lambda c_{k1}/\rho} + 1 - e^{-\lambda c_{k2}/\rho} \\ &\quad - \frac{e^{-\lambda c_{k2}}}{1-\rho} + \frac{e^{-\lambda c_{k2}/\rho}}{1-\rho} - \lambda c_{k2} e^{-\lambda c_{k1}} - 1 \\ &= \rho - \rho e^{-\lambda c_{k2}/\rho} \end{aligned} \tag{5.5}$$

From (5.4) and (5.5) we can express $Cov\,[M_{k1}(X_{k1}), M_{k2}(X_{k2})]$ as

$$Cov\,[M_{k1}(X_{k1}), M_{k2}(X_{k2})] = \begin{cases} \rho - \rho e^{-\lambda c_{k1}} & \text{if } \rho c_{k1} \le c_{k2} \\ \rho - \rho e^{-\lambda c_{k2}/\rho} & \text{if } c_{k2} > \rho c_{k1}, \end{cases}$$

which can be written in a more compact form

$$Cov\,[M_{k1}(X_{k1}), M_{k2}(X_{k2})] = \rho - \rho e^{-\lambda \min(c_{k1}, c_{k2}/\rho)} \tag{5.6}$$

which is the martingale covariance at lag 1 for the censored case.

To find the lag 2 correlation between the martingales of the failure times T_{k1} and T_{k3} we can write the bivariate survival function from (4.3) of Chapter 4 in the following form

$$F_{T_{k1},T_{k3}}(u_{k1}, u_{k3}) = \begin{cases} e^{-\lambda u_{k1}} & \text{for } u_{k3} \le \rho^2 u_{k1} \\ e^{-\lambda u_{k3}} e^{-\lambda(1-\rho^2)u_{k1}} & \text{for } u_{k3} > \rho^2 u_{k1}, \end{cases} \tag{5.7}$$

and after doing some algebra it is easy to write $Cov\,[M_{k1}(X_{k1}), M_{k3}(X_{k3})]$ as

$$Cov\,[M_{k1}(X_{k1}), M_{k2}(X_{k2})] = \rho^2 - \rho^2 e^{-\lambda \min(c_{k1}, c_{k3}/\rho^2)} \tag{5.8}$$

which is the martingale covariance at lag 2 for the censored case.

By a similar argument from (5.6) and (5.8) we can write the martingale covariance between X_{k1} and $X_{k(j+1)}$ of lag j is

$$Cov\left[M_{k1}(X_{k1}), M_{k(j+1)}(X_{k(j+1)})\right] \;=\; \rho^j - \rho^j e^{-\lambda \min(c_{k1}, c_{k(j+1)}/\rho^j)} \qquad (5.9)$$

This completes the proof. □

Note that the martingale covariance in the censored case is quite different than in the uncensored case. Specifically, these covariances are no longer the same as the covariances for the original failure time variables. Recall that C_{ki} is the corresponding censoring time for the correlated failure time T_{ki}. If we consider $C_{ki} \to \infty$ (so T_{ki} is uncensored) then

$$Cov\left[M_{k1}(X_{k1}), M_{k(j+1)}(X_{k(j+1)})\right] \;=\; \rho^j$$

which is the covariance of martingales for the uncensored case as discussed in Chapter 4.

5.1.2 Martingale Correlation Under Censored Exponential MA1 Process

Theorem 5.2: Under an EMA(1) process, in the presence of censorship the martingales $M_{ki}(X_{ki})$ defined in (5.1) have the pairwise covariance given by

$$\begin{aligned} Cov\left[M_{ki}(X_{ki}), M_{k(i+1)}(X_{k(i+1)})\right] \;&=\; \rho(1-\rho) + \rho^2 e^{-\lambda c_{ki}/\rho} - \rho e^{-\lambda \min(c_{ki}, c_{k(i+1)}/\rho)} \\ &\quad \times \left[1 - \rho + \rho e^{-\lambda c_{ki}/\rho} e^{\frac{\lambda}{\rho}\min(c_{ki}, c_{k(i+1)}/\rho)}\right] \end{aligned}$$

and

$$Cov\left[M_{ki}(X_{ki}), M_{k(i+j)}(X_{k(i+j)})\right] = 0 \quad (\text{for} \quad j > 1)$$

for $i, j = 1, 2, \ldots, n$.

Proof: The derivation of the correlation of the martingales for the censored case for EMA(1) is quite similar to EAR(1). The only difference is in the form of the survival function. To prove this theorem we are considering the failure times T_{k1} and T_{k2} for convenience. From (3.10) we get the bivariate survival function for T_{k1} and T_{k2} as

$$F_{T_{k1},T_{k2}}(u_{k1},u_{k2}) = \begin{cases} k_1(\rho)e^{-\lambda u_{k1}/\rho}e^{-\lambda u_{k2}} + k_2(\rho)/\rho e^{-\lambda(1-\rho)u_{k1}}e^{-\lambda u_{k2}} \\ \qquad\qquad \text{for } \rho u_{k1} \le u_{k2} \\ k_1(\rho)\left[e^{-\lambda u_{k1}/\rho}e^{-\lambda u_{k2}} - e^{-\lambda u_{k1}/\rho}e^{-\lambda((\rho-1)/\rho^2)u_{k2}}\right] + e^{-\lambda u_{k1}} \\ \qquad\qquad \text{for } \rho u_{k1} > u_{k2} \end{cases} \tag{5.10}$$

where $k_1(\rho) = \frac{\rho^2}{1-\rho+\rho^2}$ and $k_2(\rho) = \frac{\rho(1-\rho)}{1-\rho+\rho^2}$. As in the previous section, we use (5.2) to find the covariance between $M_{k1}(X_{k1})$ and $M_{k2}(X_{k2})$ and we get two different cases: (a) $\rho c_{k1} \le c_{k2}$ and (b) $\rho c_{k1} > c_{k2}$.

Under case (a) $\rho c_{k1} \le c_{k2}$, we can evaluate I_1 as

$$\begin{aligned} I_1 &= F_k(c_{k1}, c_{k2}; \rho) \\ &= \frac{\rho^2}{1-\rho+\rho^2}e^{-\lambda c_{k1}/\rho}e^{-\lambda c_{k2}} + \frac{1-\rho}{1-\rho+\rho^2}e^{-\lambda(1-\rho)c_{k1}}e^{-\lambda c_{k2}} \end{aligned}$$

and we can calculate I_2 as

$$\begin{aligned} I_2 &= \int_0^{c_{k1}} \lambda F_k(u_{k1}, c_{k2}; \rho)du_{k1} \\ &= \int_0^{c_{k1}} \lambda \left[\frac{\rho^2}{1-\rho+\rho^2}e^{-\lambda u_{k1}/\rho}e^{-\lambda c_{k2}} + \frac{1-\rho}{1-\rho+\rho^2}e^{-\lambda(1-\rho)u_{k1}}e^{-\lambda c_{k2}}\right] du_{k1} \\ &= \frac{\rho^3 e^{-\lambda c_{k2}}}{1-\rho+\rho^2} - \frac{\rho^3 e^{-\lambda c_{k2}}e^{-\lambda c_{k1}/\rho}}{1-\rho+\rho^2} + \frac{e^{-\lambda c_{k2}}}{1-\rho+\rho^2} - \frac{e^{-\lambda c_{k2}}e^{-\lambda(1-\rho)c_{k1}}}{1-\rho+\rho^2}. \end{aligned}$$

Similarly, I_3 can be evaluated as

$$\begin{aligned} I_3 &= \int_0^{c_{k2}} \lambda F_k(c_{k1}, u_{k2}; \rho)du_{k2} \\ &= \int_0^{\rho c_{k1}} \frac{\rho^2\lambda}{1-\rho+\rho^2}e^{-\lambda c_{k1}/\rho}e^{-\lambda u_{k2}}du_{k2} + \int_0^{\rho c_{k1}} \lambda e^{-\lambda c_{k1}}du_{k2} \\ &\quad - \int_0^{\rho c_{k1}} \frac{\rho^2}{1-\rho+\rho^2}\lambda e^{-\lambda c_{k1}/\rho}e^{-\lambda((\rho-1)/\rho^2)u_{k2}}du_{k2} \\ &\quad + \int_{\rho c_{k1}}^{c_{k2}} \frac{\rho^2}{1-\rho+\rho^2}\lambda e^{-\lambda c_{k1}/\rho}e^{-\lambda u_{k2}}du_{k2} \end{aligned}$$

$$
\begin{aligned}
& + \int_{\rho c_{k1}}^{c_{k2}} \frac{(1-\rho)\lambda}{1-\rho+\rho^2} e^{-\lambda(1-\rho)c_{k1}} e^{-\lambda u_{k2}} du_{k2} \\
= \; & \frac{\rho^2 e^{-\lambda c_{k1}/\rho}}{1-\rho+\rho^2}\left[1-e^{-\lambda\rho c_{k1}}\right] + \lambda\rho c_{k1} e^{-\lambda c_{k1}} \\
& - \frac{\rho^4 e^{-\lambda c_{k1}/\rho}}{(1-\rho+\rho^2)(\rho-1)}\left[1-e^{-\lambda((\rho-1)/\rho^2)c_{k2}}\right] \\
& + \frac{\rho^2 e^{-\lambda c_{k1}/\rho}}{1-\rho+\rho^2}\left[e^{-\lambda\rho c_{k1}} - e^{-\lambda c_{k2}}\right] + \frac{(1-\rho)e^{-\lambda(1-\rho)c_{k1}}}{1-\rho+\rho^2}\left[e^{-\lambda\rho c_{k1}} - e^{-\lambda c_{k2}}\right] \\
= \; & \lambda\rho c_{k1} e^{-\lambda c_{k1}} + \frac{\rho^2}{1-\rho} e^{-\lambda c_{k1}/\rho} - \frac{\rho^2 e^{-\lambda c_{k1}/\rho} e^{-\lambda c_{k2}}}{1-\rho+\rho^2} - \frac{(1-\rho)e^{-\lambda(1-\rho)c_{k1}} e^{-\lambda c_{k2}}}{1-\rho+\rho^2} \\
& + \frac{1-\rho+\rho^2}{1-\rho} e^{-\lambda c_{k1}},
\end{aligned}
$$

and we can evaluate I_4 as

$$
\begin{aligned}
I_4 &= \int_0^{c_{k1}} \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho) du_{k2} du_{k1} \\
&= \int_0^{c_{k1}} I(u_{k1}) du_{k1}, \quad \text{(say)}. \qquad (5.11)
\end{aligned}
$$

For evaluating I_4 in (5.11) we can calculate $I(u_{k1})$ as

$$
\begin{aligned}
I(u_{k1}) &= \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho) du_{k2} \\
&= \int_0^{\rho u_{k1}} \frac{\rho^2\lambda^2}{1-\rho+\rho^2} e^{-\lambda u_{k1}/\rho} e^{-\lambda u_{k2}} du_{k2} + \int_0^{\rho u_{k1}} \lambda^2 e^{-\lambda u_{k1}} du_{k2} \\
&\quad - \int_0^{\rho u_{k1}} \frac{\rho^2\lambda^2}{1-\rho+\rho^2} e^{-\lambda u_{k1}/\rho} e^{-\lambda((\rho-1)/\rho^2)u_{k2}} du_{k2} \\
&\quad + \int_{\rho u_{k1}}^{c_{k2}} \frac{\rho^2\lambda^2}{1-\rho+\rho^2} e^{-\lambda u_{k1}/\rho} e^{-\lambda u_{k2}} du_{k2} \\
&\quad + \int_{\rho u_{k1}}^{c_{k2}} \frac{(1-\rho)\lambda^2}{1-\rho+\rho^2} e^{-\lambda(1-\rho)u_{k1}} e^{-\lambda u_{k2}} du_{k2} \\
&= \frac{\rho^2\lambda e^{-\lambda u_{k1}/\rho}}{1-\rho+\rho^2}\left[1-e^{-\lambda\rho u_{k1}}\right] + \lambda^2\rho u_{k1} e^{-\lambda u_{k1}} \\
&\quad - \frac{\rho^4\lambda e^{-\lambda u_{k1}/\rho}}{(1-\rho+\rho^2)(\rho-1)}\left[1-e^{-\lambda((\rho-1)/\rho)u_{k1}}\right] \\
&\quad + \frac{\rho^2\lambda e^{-\lambda u_{k1}/\rho}}{1-\rho+\rho^2}\left[e^{-\lambda\rho u_{k1}} - e^{-\lambda c_{k2}}\right] + \frac{(1-\rho)\lambda e^{-\lambda(1-\rho)u_{k1}}}{1-\rho+\rho^2}\left[e^{-\lambda\rho u_{k1}} - e^{-\lambda c_{k2}}\right] \\
&= \lambda^2\rho u_{k1} e^{-\lambda u_{k1}} - \frac{\rho^2\lambda e^{-\lambda u_{k1}/\rho} e^{-\lambda c_{k2}}}{1-\rho+\rho^2} - \frac{(1-\rho)\lambda e^{-\lambda(1-\rho)u_{k1}} e^{-\lambda c_{k2}}}{1-\rho+\rho^2}
\end{aligned}
$$

$$-\frac{\rho^2\lambda e^{-\lambda u_{k1}/\rho}}{1-\rho}+\frac{\lambda(1-\rho+\rho^2)e^{-\lambda u_{k1}}}{1-\rho}.$$

By using the value of $I(u_{k1})$ in (5.11) we can evaluate I_4 as

$$\begin{aligned} I_4 &= \int_0^{c_{k1}} I(u_{k1})du_{k1} \\ &= -\rho\lambda c_{k1}e^{-\lambda c_{k1}}+\rho-\rho e^{-\lambda c_{k1}}-\frac{\rho^3 e^{-\lambda c_{k2}}}{1-\rho+\rho^2}+\frac{\rho^3 e^{-\lambda c_{k2}}e^{-\lambda c_{k1}/\rho}}{1-\rho+\rho^2}-\frac{e^{-\lambda c_{k2}}}{1-\rho+\rho^2} \\ &\quad +\frac{e^{-\lambda c_{k2}}e^{-\lambda(1-\rho)c_{k1}}}{1-\rho+\rho^2}+\frac{\rho^3}{1-\rho}-\frac{\rho^3 e^{-\lambda c_{k1}/\rho}}{1-\rho}+\frac{1-\rho+\rho^2}{1-\rho}-\frac{(1-\rho+\rho^2)e^{-\lambda c_{k1}}}{1-\rho}. \end{aligned}$$

Then after substituting I_1, I_2, I_3 and I_4 in (5.2) and simplifying the expression we find for $\rho c_{k1}\le c_{k2}$, the expression $Cov\,[M_{k1}(X_{k1}),M_{k2}(X_{k2})]$ is

$$\begin{aligned} Cov\,[M_{k1}(X_{k1}),M_{k2}(X_{k2})] &= \rho+\frac{1-\rho+\rho^2}{1-\rho}+\frac{\rho^3}{1-\rho}-1-\rho e^{-\lambda c_{k1}}+\rho^2 e^{-\lambda c_{k1}/\rho} \\ &= \rho(1-\rho)-\rho e^{-\lambda c_{k1}}+\rho^2 e^{-\lambda c_{k1}/\rho}. \end{aligned} \tag{5.12}$$

Under case (b) $\rho c_{k1} > c_{k2}$ we can evaluate I_1 as

$$\begin{aligned} I_1 &= F_k(c_{k1},c_{k2};\rho) \\ &= \frac{\rho^2}{1-\rho+\rho^2}e^{-\lambda c_{k1}/\rho}e^{-\lambda c_{k2}}+e^{-\lambda c_{k1}}-\frac{\rho^2}{1-\rho+\rho^2}e^{-\lambda c_{k1}/\rho}e^{-\lambda((\rho-1)/\rho^2)c_{k2}}, \end{aligned}$$

we can evaluate I_2 as

$$\begin{aligned} I_2 &= \int_0^{c_{k1}} \lambda F_k(u_{k1},c_{k2};\rho)du_{k1} \\ &= \int_0^{c_{k2}/\rho}\frac{\rho^2\lambda}{1-\rho+\rho^2}e^{-\lambda u_{k1}/\rho}e^{-\lambda c_{k2}}du_{k1}+\int_0^{c_{k2}/\rho}\frac{(1-\rho)\lambda}{1-\rho+\rho^2}e^{-\lambda(1-\rho)u_{k1}}e^{-\lambda c_{k2}}du_{k1} \\ &\quad +\int_{c_{k2}/\rho}^{c_{k1}}\frac{\rho^2\lambda}{1-\rho+\rho^2}e^{-\lambda u_{k1}/\rho}e^{-\lambda c_{k2}}du_{k1}+\int_{c_{k2}/\rho}^{c_{k1}}\lambda e^{-\lambda u_{k1}}du_{k1} \\ &\quad -\int_{c_{k2}/\rho}^{c_{k1}}\frac{\rho^2\lambda}{1-\rho+\rho^2}e^{-\lambda u_{k1}\rho}e^{-\lambda((\rho-1)/\rho^2)c_{k2}}du_{k1} \\ &= \frac{\rho^3 e^{-\lambda c_{k2}}}{1-\rho+\rho^2}+\frac{e^{-\lambda c_{k2}}}{1-\rho+\rho^2}-\frac{e^{-\lambda c_{k2}/\rho}}{1-\rho+\rho^2}-\frac{\rho^3 e^{-\lambda c_{k2}}e^{-\lambda c_{k1}/\rho}}{1-\rho+\rho^2}+e^{-\lambda c_{k2}/\rho} \\ &\quad -e^{-\lambda c_{k1}}-\frac{\rho^3 e^{-\lambda c_{k2}/\rho}}{1-\rho+\rho^2}+\frac{\rho^3 e^{-\lambda c_{k1}/\rho}e^{-\lambda((\rho-1)/\rho^2)c_{k2}}}{1-\rho+\rho^2}. \end{aligned}$$

Similarly, we can calculate I_3 as

$$\begin{aligned} I_3 &= \int_0^{c_{k2}} \lambda F_k(c_{k1}, u_{k2}; \rho) du_{k2} \\ &= \int_0^{c_{k2}} \frac{\rho^2 \lambda e^{-\lambda c_{k1}/\rho} e^{-\lambda u_{k2}}}{1-\rho+\rho^2} du_{k2} + \int_0^{c_{k2}} \lambda e^{-\lambda c_{k1}} du_{k2} \\ &\quad - \int_0^{c_{k2}} \frac{\rho^2 \lambda e^{-\lambda c_{k1} \rho} e^{-\lambda((\rho-1)/\rho^2) u_{k2}}}{1-\rho+\rho^2} du_{k2} \\ &= \frac{\rho^2 e^{-\lambda c_{k1}/\rho}}{1-\rho+\rho^2} - \frac{\rho^2 e^{-\lambda c_{k1}/\rho} e^{-\lambda c_{k2}}}{1-\rho+\rho^2} + \lambda c_{k2} e^{-\lambda c_{k1}} - \frac{\rho^4 e^{-\lambda c_{k1}/\rho}}{(\rho-1)(1-\rho+\rho^2)} \\ &\quad + \frac{\rho^4 e^{-\lambda c_{k1}/\rho} e^{-\lambda((\rho-1)/\rho^2) u_{k2}}}{(\rho-1)(1-\rho+\rho^2)}, \end{aligned}$$

and we can evaluate I_4 as

$$\begin{aligned} I_4 &= \int_0^{c_{k1}} \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}; u_{k2}; \rho) du_{k2} du_{k1} \\ &= \int_0^{c_{k2}} I(u_{k2}) du_{k2} \quad \text{(say)}. \end{aligned} \tag{5.13}$$

We can evaluate $I(u_{k2})$ in (5.13) as

$$\begin{aligned} I(u_{k2}) &= \int_0^{c_{k1}} \lambda^2 F_k(u_{k1}; u_{k2}; \rho) du_{k1} \\ &= \int_0^{u_{k2}/\rho} \frac{\rho^2 \lambda^2}{1-\rho+\rho^2} e^{-\lambda u_{k1}/\rho} e^{-\lambda u_{k2}} du_{k1} \\ &\quad + \int_0^{u_{k2}/\rho} \frac{(1-\rho)\lambda^2}{1-\rho+\rho^2} e^{-\lambda(1-\rho) u_{k1}} e^{-\lambda u_{k2}} du_{k1} \\ &\quad + \int_{u_{k2}/\rho}^{c_{k1}} \frac{\rho^2 \lambda^2}{1-\rho+\rho^2} e^{-\lambda u_{k1}/\rho} e^{-\lambda u_{k2}} du_{k1} + \int_{u_{k2}/\rho}^{c_{k1}} \lambda^2 e^{-\lambda u_{k1}} du_{k1} \\ &\quad - \int_{u_{k2}/\rho}^{c_{k1}} \frac{\rho^2 \lambda^2}{1-\rho+\rho^2} e^{-\lambda u_{k1}/\rho} e^{-\lambda((\rho-1)/\rho^2) u_{k2}} du_{k1}. \end{aligned}$$

After extensive calculation it can be shown that

$$\begin{aligned} I(u_{k2}) &= (1+\rho)\lambda e^{-\lambda u_{k2}} - \lambda \rho e^{-\lambda u_{k2}/\rho} - \frac{\rho^3 \lambda}{1-\rho+\rho^2} e^{-\lambda u_{k2}} e^{-\lambda c_{k1}/\rho} - \lambda e^{-\lambda c_{k1}} \\ &\quad + \frac{\rho^3 \lambda}{1-\rho+\rho^2} e^{-\lambda c_{k1}/\rho} e^{-\lambda((\rho-1)/\rho^2) u_{k2}}. \end{aligned}$$

Therefore, substituting the value of $I(u_{k2})$ in (5.13) we get I_4 as

$$I_4 = \int_0^{c_{k2}} I(u_{k2}) du_{k2}$$

$$= 1+\rho - e^{-\lambda c_{k2}} - \rho e^{-\lambda c_{k2}} - \rho^2 + \rho^2 e^{-\lambda c_{k2}/\rho} - \frac{\rho^3 e^{-\lambda c_{k1}/\rho}}{1-\rho+\rho^2} + \frac{\rho^3 e^{-\lambda c_{k1}/\rho} e^{-\lambda c_{k2}}}{1-\rho+\rho^2}$$
$$-\lambda c_{k2} e^{-\lambda c_{k1}} + \frac{\rho^5 e^{-\lambda c_{k1}/\rho}}{(\rho-1)(1-\rho+\rho^2)} - \frac{\rho^5 e^{-\lambda c_{k1}/\rho} e^{-\lambda((\rho-1)/\rho^2)c_{k2}}}{(\rho-1)(1-\rho+\rho^2)}$$

Therefore, using (5.2) after extensive simplification, we get the covariance of the martingales of the failure times i.e. $Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right]$ for $\rho c_{k1} > c_{k2}$ as

$$\begin{aligned} Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right] &= \rho(1-\rho) + \rho^2 e^{-\lambda c_{k1}/\rho} - \rho e^{-\lambda c_{k2}/\rho} \\ &\quad \times \left[1 - \rho + \rho e^{-\lambda c_{k1}/\rho} e^{\lambda c_{k2}/\rho^2}\right] \end{aligned} \tag{5.14}$$

By using (5.12) and (5.14) we can write $Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right]$ as

$$\begin{aligned} & Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right] \\ &= \begin{cases} \rho(1-\rho) - \rho e^{-\lambda c_{k1}} + \rho^2 e^{-\lambda c_{k1}/\rho} & \text{if } \rho c_{k1} \leq c_{k2} \\ \rho(1-\rho) + \rho^2 e^{-\lambda c_{k1}/\rho} - \rho e^{-\lambda c_{k2}/\rho}\left[1-\rho+\rho e^{-\lambda c_{k1}/\rho} e^{\lambda c_{k2}/\rho^2}\right] & \text{if } \rho c_{k1} > c_{k2} \end{cases} \\ &= \rho(1-\rho) + \rho^2 e^{-\lambda c_{k1}/\rho} - \rho e^{-\lambda \min(c_{k1}, c_{k2}/\rho)} \\ &\qquad \times \left[1 - \rho + \rho e^{-\lambda c_{k1}/\rho} e^{\frac{\lambda}{\rho}\min(c_{k1}, c_{k2}/\rho)}\right] \end{aligned} \tag{5.15}$$

Next, for all lags more than 1, we note from Lawrence and Lewis (1977) that $corr(T_i, T_{i+2}) = 0$, for all $i = 1, 2, 3, \ldots$. So it is easy to show that

$$Cov(M_{ki}(X_{ki}), M_{k(i+2)}(X_{k(i+2)})) = 0$$

for $i = 1, 2, 3, \ldots$. This completes the proof. □

Like the EAR(1) model for the censored case, this covariance expression between the martingales of the failure times for lag 1 under an EMA(1) process for censored case is quite different than that for the uncensored case. Recall that C_{ki} are the corresponding censoring times for the correlated failure times T_{ki}. If we consider $C_{ki} \to \infty$ (all T_{ki} observations are uncensored) then

$$Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right] = \rho(1-\rho)$$

which is the covariance of the martingales of the failure times for the uncensored case.

5.1.3 Martingale Correlation Under Censored Exponential Equi-correlation Process

Theorem 5.3: Under censorship for the EEQ process the martingales $M_{ki}(X_{ki})$ defined in (5.1) have the pairwise covariance given by

$$Cov\left[M_{ki}(X_{ki}), M_{kj}(X_{kj})\right] = \rho^2 - \rho^2 e^{-\lambda \min(c_{ki}, c_{kj})/\rho}$$

For $i \neq j; i,j = 1,2,\ldots,n$.

Proof: The calculation of this correlation between the martingales of the failure times under an EEQ process for the censored case is similar to the calculation under EAR(1) and EMA(1) processes discussed in the previous two sections. To derive the covariance between the martingales $M_{ki}(X_{ki})$ and $M_{kj}(X_{kj})$, we compute the correlation between the first and second martingales (martingales with lag 1) for convenience. Recall from (3.14) that we can write the survival function as

$$F_{T_{k1},T_{k2}}(u_{k1}, u_{k2}) = \begin{cases} \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_{k1}+u_{k2})} - \frac{\rho^2}{1-2\rho} e^{-\lambda u_{k2}} e^{-\lambda((1-\rho)/\rho)u_{k1}} & \text{if } u_{k1} \leq u_{k2} \\ \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(u_{k1}+u_{k2})} - \frac{\rho^2}{1-2\rho} e^{-\lambda u_{k1}} e^{-\lambda((1-\rho)/\rho)u_{k2}} & \text{if } u_{k1} > u_{k2} \end{cases} \tag{5.16}$$

For solving (5.2), we use the survival function (5.16) and get two different cases: (a) $c_{k1} > c_{k2}$ and (b) $c_{k1} \leq c_{k2}$

Under case (a) $c_{k1} > c_{k2}$ then for evaluating (5.2) we get I_1 as

$$\begin{aligned} I_1 &= F_k(c_{k1}, c_{k2}; \rho) \\ &= \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda(c_{k1}+c_{k2})} - \frac{\rho^2}{1-2\rho} e^{-\lambda c_{k1}} e^{-\lambda((1-\rho)/\rho)c_{k2}}, \end{aligned}$$

we can evaluate I_2 as

$$\begin{aligned} I_2 &= \int_0^{c_{k1}} \lambda F_k(u_{k1}, c_{k2}; \rho) du_{k1} \\ &= \int_0^{c_{k1}} \frac{\lambda(1-\rho)^2}{1-2\rho} e^{-\lambda u_{k1}} e^{-\lambda c_{k2}} du_{k1} - \int_0^{c_{k2}} \frac{\lambda\rho^2}{1-2\rho} e^{-\lambda c_{k2}} e^{-\lambda((1-\rho)/\rho)u_{k1}} du_{k1} \\ &\quad - \int_{c_{k2}}^{c_{k1}} \frac{\lambda\rho^2}{1-2\rho} e^{-\lambda u_{k1}} e^{-\lambda((1-\rho)/\rho)c_{k2}} du_{k1} \end{aligned}$$

$$
\begin{aligned}
&= \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda c_{k2}} - \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda c_{k2}}e^{-\lambda c_{k1}} - \frac{\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k2}} \\
&\quad + \frac{\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k2}}e^{-\lambda((1-\rho)/\rho)c_{k2}} - \frac{\rho^2}{1-2\rho}e^{-\lambda c_{k2}/\rho} \\
&\quad + \frac{\rho^2}{1-2\rho}e^{-\lambda c_{k1}}e^{-\lambda((1-\rho)/\rho)c_{k2}}.
\end{aligned}
$$

Similarly, I_3 can be evaluated as

$$
\begin{aligned}
I_3 &= \int_0^{c_{k2}} \lambda F_k(c_{k1}, u_{k2}; \rho)du_{k2} \\
&= \int_0^{c_{k2}} \frac{\lambda(1-\rho)^2}{1-2\rho}e^{-\lambda c_{k1}}e^{-\lambda u_{k2}}du_{k2} - \int_0^{c_{k2}} \frac{\lambda\rho^2}{1-2\rho}e^{-\lambda c_{k1}}e^{-\lambda((1-\rho)/\rho)u_{k2}}du_{k2} \\
&= \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda c_{k1}} - \frac{(1-\rho)^2}{1-2\rho}e^{-\lambda c_{k1}}e^{-\lambda c_{k2}} - \frac{\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k1}} \\
&\quad + \frac{\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k1}}e^{-\lambda((1-\rho)/\rho)c_{k2}},
\end{aligned}
$$

and finally I_4 can be calculated as

$$
\begin{aligned}
I_4 &= \int_0^{c_{k1}}\int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho)du_{k2}du_{k1} \\
&= \int_0^{c_{k1}} I(u_{k1})du_{k1} \quad \text{(say)}. \qquad (5.17)
\end{aligned}
$$

To evaluate $I(u_{k1})$ in (5.17) we again get two different cases: (i) $u_{k1} \le c_{k2}$ and (ii) $u_{k1} > c_{k2}$. Under case (i) $u_{k1} \le c_{k2}$ we calculate $I(u_{k1})$ as

$$
\begin{aligned}
I(u_{k1}) &= \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho)du_{k2} \\
&= \int_0^{c_{k2}} \frac{\lambda^2(1-\rho)^2}{1-2\rho}e^{-\lambda u_{k1}}e^{-\lambda u_{k2}}du_{k2} - \int_0^{u_{k1}} \frac{\lambda^2\rho^2}{1-2\rho}e^{-\lambda u_{k1}}e^{-\lambda((1-\rho)/\rho)u_{k2}}du_{k2} \\
&\quad - \int_{u_{k1}}^{c_{k2}} \frac{\lambda^2\rho^2}{1-2\rho}e^{-\lambda u_{k2}}e^{-\lambda((1-\rho)/\rho)u_{k1}}du_{k2} \\
&= \frac{\lambda(1-\rho)^2}{1-2\rho}e^{-\lambda u_{k1}} - \frac{\lambda(1-\rho)^2}{1-2\rho}e^{-\lambda u_{k1}}e^{-\lambda c_{k2}} - \frac{\lambda\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda u_{k1}} \\
&\quad + \frac{\lambda\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda u_{k1}/\rho} - \frac{\lambda\rho^2}{1-2\rho}e^{-\lambda u_{k1}/\rho} + \frac{\lambda\rho^2}{1-2\rho}e^{-\lambda c_{k2}}e^{-\lambda((1-\rho/\rho)u_{k1}}
\end{aligned}
$$

and under case (ii) $u_{k1} > c_{k2}$ we can calculate $I(u_{k1})$ as

$$
I(u_{k1}) = \int_0^{c_{k2}} \lambda^2 F_k(u_{k1}, u_{k2}; \rho)du_{k2}
$$

$$
\begin{aligned}
&= \int_0^{c_{k2}} \frac{\lambda^2(1-\rho)^2}{1-2\rho} e^{-\lambda u_{k1}} e^{-\lambda u_{k2}} du_{k2} - \int_0^{c_{k2}} \frac{\lambda^2\rho^2}{1-2\rho} e^{-\lambda u_{k1}} e^{-\lambda((1-\rho)/\rho)u_{k2}} du_{k2} \\
&= \frac{\lambda(1-\rho)^2}{1-2\rho} e^{-\lambda u_{k1}} - \frac{\lambda(1-\rho)^2}{1-2\rho} e^{-\lambda u_{k1}} e^{-\lambda c_{k2}} - \frac{\lambda\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda u_{k1}} \\
&\quad + \frac{\lambda\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda u_{k1}} e^{-\lambda((1-\rho)/\rho)c_{k2}}.
\end{aligned}
$$

Therefore from (5.18) we can evaluate I_4 as

$$
\begin{aligned}
I_4 &= \int_0^{c_{k1}} I(u_{k1}) du_{k1} \\
&= \int_0^{c_{k2}} I(u_{k1}) \left[I(u_{k1} \le c_{k2})\right] du_{k1} + \int_{c_{k2}}^{c_{k1}} I(u_{k1}) \left[I(u_{k1} > c_{k2})\right] du_{k1} \\
&= II_1 + II_2 \quad \text{(say).} \qquad (5.18)
\end{aligned}
$$

In (5.18) we can calculate II_1 as

$$
\begin{aligned}
II_1 &= \int_0^{c_{k2}} I(u_{k1}) \left[I(u_{k1} \le c_{k2})\right] du_{k1} \\
&= \frac{(1-\rho)^2}{1-2\rho} - \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k2}} - \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k2}} + \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k2}} e^{-\lambda c_{k2}} \\
&\quad - \frac{\rho^3}{(1-2\rho)(1-\rho)} + \frac{\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k2}} + \frac{\rho^4}{(1-2\rho)(1-\rho)} \\
&\quad - \frac{\rho^4}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k2}/\rho} - \frac{\rho^3}{1-2\rho} + \frac{\rho^3}{1-2\rho} e^{-\lambda c_{k2}/\rho} + \frac{\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k2}} \\
&\quad - \frac{\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k2}/\rho},
\end{aligned}
$$

and II_2 can be calculated as

$$
\begin{aligned}
II_2 &= \int_{c_{k2}}^{c_{k1}} I(u_{k1}) \left[I(u_{k1} > c_{k2})\right] du_{k1} \\
&= \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k2}} - \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k1}} - \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k2}} e^{-\lambda c_{k2}} \\
&\quad + \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k2}} e^{-\lambda c_{k1}} - \frac{\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k2}} + \frac{\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k1}} \\
&\quad + \frac{\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k2}/\rho} - \frac{\rho^3}{(1-2\rho)(1-\rho)} e^{-\lambda c_{k1}} e^{-\lambda((1-\rho)\rho)c_{k2}}.
\end{aligned}
$$

By using the values of II_1 and II_2 in (5.18) we can evaluate I_4 as

$$
I_4 = \frac{(1-\rho)^2}{1-2\rho} - \frac{(1-\rho)^2}{1-2\rho} e^{-\lambda c_{k2}} - \frac{\rho^3}{(1-2\rho)(1-\rho)} + \frac{\rho^4}{(1-2\rho)(1-\rho)}
$$

$$-\frac{\rho^4}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k2}/\rho}-\frac{\rho^3}{1-2\rho}+\frac{\rho^3}{1-2\rho}e^{-\lambda c_{k2}/\rho}$$
$$+\frac{\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k2}}-\frac{(1-\rho)^2}{1-2\rho}e^{-\lambda c_{k1}}+\frac{(1-\rho)^2}{1-2\rho}e^{-\lambda c_{k2}}e^{-\lambda c_{k1}}$$
$$+\frac{\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k1}}-\frac{\rho^3}{(1-2\rho)(1-\rho)}e^{-\lambda c_{k1}}e^{-\lambda((1-\rho)/\rho)c_{k2}}.$$

Therefore, substituting I_1, I_2, I_3 and I_4 into (5.2), it can eventually be shown that if $c_{k1} > c_{k2}$ then

$$Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right] = \rho^2-\rho^2 e^{-\lambda c_{k2}/\rho}.$$

By similar arguments as shown above, we can evaluate (5.2) for the case (ii) $c_{k1} \leq c_{k2}$ as,

$$Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right] = \rho^2-\rho^2 e^{-\lambda c_{k1}/\rho}.$$

Therefore, we can write $Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right]$ in a more compact form:

$$Cov\left[M_{k1}(X_{k1}), M_{k2}(X_{k2})\right] = \rho^2-\rho^2 e^{-\lambda \min(c_{k1},c_{k2})/\rho}. \tag{5.19}$$

Under an EEQ model we know that the covariance is the same for all lags. So, from (5.19) we can write $Cov\left[M_{ki}(X_{ki}), M_{kj}(X_{kj})\right]$ as

$$Cov\left[M_{ki}(X_{ki}), M_{kj}(X_{kj})\right] = \rho^2-\rho^2 e^{-\lambda \min(c_{ki},c_{kj})/\rho}, \tag{5.20}$$

for $i \neq j; i,j = 1,2,\ldots,n$. This completes the proof. □

Like the EAR(1) and EMA(1) processes under censorship, this covariance expression between the martingales of the failure times under the EEQ process under censorship is quite different than that for the uncensored case. Recall that C_{ki} and C_{kj} are the corresponding censoring times for the correlated failure times T_{ki} and T_{kj}. If we consider $C_{ki}, C_{kj} \to \infty$ then

$$Cov\left[M_{ki}(X_{ki}), M_{kj}(X_{kj})\right] = \rho^2$$

which is the covariance of the martingales of the failure times for the uncensored case under an EEQ process.

Note that the martingale covariances expressions (5.9), (5.15) and (5.20) respectively, for the EAR(1), EMA(1) and EEQ processes will be utilized in the next section to construct the estimating equations to obtain consistent and efficient estimates of the regression parameter $\boldsymbol{\beta}$ for the censored case. Specifically, this will be done following Cai and Prentice (1995) by using the inverse of the martingale covariance matrix as the weight of the estimating equation.

5.2 Estimating Equations for Hazard Ratio Parameters Under Censored Case

In Section 4.2 of Chapter 4 we discussed the estimating equations for the hazard ratio parameters in the uncensored case. We now wish to extend these equations so that they can be used in the case of censored observations.

First the partial likelihood function of Section 4.2 will become:

$$L(\boldsymbol{\beta}) = \prod_{k=1}^{K}\prod_{i=1}^{n}\left[exp\{\mathbf{Z}_{ki}^{T}(X_{ki})\boldsymbol{\beta}\}/\sum_{l=1}^{K}Y_{li}(X_{ki})exp\{\mathbf{Z}_{li}^{T}(X_{ki})\boldsymbol{\beta}\}\right]^{\Delta_{ki}}, \qquad (5.21)$$

where $X_{ki} = \min(T_{ki}, C_{ki})$ and Δ_{ki} is an indicator function $I(.)$ which means $\Delta_{ki} = 1$ if $X_{ki} = T_{ki}$ and $\Delta_{ki} = 0$ if $X_{ki} = C_{ki}$. As explained in Section 4.2 of Chapter 4, this partial likelihood function (5.21) eventually leads us to the generalized estimating equations

$$\sum_{k=1}^{K}\int_{0}^{\infty}\mathbf{Z}_{k}^{T}(u)\mathbf{W}_{k}(\boldsymbol{\beta},u)\mathbf{U}_{k}(du) = \mathbf{0}. \qquad (5.22)$$

However, we now have $U_{ki}(t) = \hat{M}_{ki}(t)$, where $M_{ki}(t)$ is defined in (5.1) and $\mathbf{W}_k(\boldsymbol{\beta}, u)$ is the inverse of the longitudinal covariance matrix of the martingales under the appropriate exponential AR(1), MA(1) or equi-correlation process discussed in Theorems 5.1, 5.2 and 5.3.

For solving the estimating equation (5.22), we use the same Gauss-Newton iteration procedure (4.15) discussed in Section 4.2 of Chapter 4. As in the uncensored case, let $\hat{\boldsymbol{\beta}}_T$ be the estimate of $\boldsymbol{\beta}$ when the true covariance structure is used in (5.22) to estimate $\boldsymbol{\beta}$. To be specific, we use the Gauss-Newton iteration procedure (4.15), but we replace $\hat{A}_{w,kj}$ in (4.15) with $\Delta_{kj}\hat{A}_{w,kj}$, where Δ_{kj} is defined previously in this section. Also we modify $\hat{A}_{w,kj}$ in (4.16) by replacing T_{kj} and T_{mj} with X_{kj} and X_{mj} and $\hat{G}_{w,kj}(\boldsymbol{\beta})$ is calculated following Cai and Prentice (1995, p. 156).

5.2.1 Estimation of Martingales Covariance Matrix for Censored Case

Note that the weight matrix $\mathbf{W}_k(\boldsymbol{\beta}, u)$ in (5.22) is the inverse of the covariance matrix for the censored case which has been discussed in Theorems 5.1, 5.2 and 5.3. As the elements of the covariance matrix are functions of the dependence parameter ρ, we need to estimate this parameter in order to construct the weight matrix as well as to solve the estimating equation (5.22). We already discussed in Section 4.2.1 how we can generate failure times T_{ki} with mean $1/\lambda_{ki}$ and variance $1/\lambda_{ki}^2$. Similarly, we can also generate censoring times C_{ki} with mean $1/\lambda_{ki}$ and variance $1/\lambda_{ki}^2$, where $X_{ki} = \min(T_{ki}, C_{ki})$. As discussed in Section 4.2.1, by using the relationship $X_{ki}^* = X_{ki}\lambda_{ki}/\lambda$, this correlation reduces to

$$corr(X_{ki}, X_{kj}) = corr(X_{ki}^*, X_{kj}^*) = \rho_{|i-j|}^*, \tag{5.23}$$

where $\rho_{|i-j|}^*$ is the lag $\mid i-j \mid$ correlation between X_{ki}^* and X_{kj}^*.

Note that the parameter ρ which is involved in all lag covariance expressions in Theorems 5.1, 5.2 and 5.3 can be estimated by using the estimate of ρ_1^* under the EAR(1) and EMA(1) processes. To estimate ρ under the EEQ process one requires to compute all lag correlation estimates such that

$$\hat{\rho}^2 = \frac{(n-1)\hat{\rho}_1 + (n-2)\hat{\rho}_2 + \ldots + \hat{\rho}_{n-1}}{n(n-1)/2}.$$

We simply use the expression for $\hat{\rho}_l$ in (4.19), but we replace T_{ki} by X_{ki} to account for the censoring.

After getting the estimates of $\hat{\rho}$, we need to substitute the values of $\hat{\rho}$ in the covariance expressions in Theorems 5.1, 5.2 and 5.3 to calculate the covariance between the martingales of the failure times for the censored cases under the EAR(1), EMA(1) and EEQ processes respectively, to solve the estimating equation (5.22) and to estimate the regression parameter $\boldsymbol{\beta}$ consistently and efficiently.

5.3 Efficiency Comparison for Censored Data Under Correlation Structure Misspecification Through a Simulation Study

As discussed in Chapter 4 the hazard ratio estimate $\boldsymbol{\beta}$ in the censored case from (5.22) will be consistent and efficient if the underlying correlation structure for the failure times is known. Specifically, if it is known that the failure times $T_{k1}, \ldots, T_{ki}, \ldots, T_{kn}$ with censoring times $C_{k1}, \ldots, C_{ki}, \ldots, C_{kn}$ follow the EAR(1) process (3.1) of Chapter 3 and we compute the $\mathbf{W}_k(\boldsymbol{\beta}, u)$ matrix based on this underlying EAR(1) process as in Theorem 5.1, then the estimate of $\boldsymbol{\beta}$ solving (5.22) will be consistent and efficient. Note that in practice the underlying correlation structure is generally not known. In this section our purpose is to examine the loss of efficiencies if one uses a working correlation structure different than the true correlation structure in (5.22) for estimating $\boldsymbol{\beta}$. We do this examination here through a simulation study under the presence of censored observations.

5.3.1 Simulation Design and Generation of Exponential Failure and Censored Time Data

As in Chapter 4, for our simulation study we consider $K = 100$ individuals each with $n = 4$ repeated failure and censoring times. We also consider a two dimensional ($p = 2$) covariate vector $\mathbf{Z}_{ki} = (Z_{ki1}, Z_{ki2})^T$ at occasion i for each of the K individuals. For choosing 2-dimensional covariates we use the design matrix D_1 of Chapter 4. The censoring times are generated by using the covariates for different censoring probabilities. To be specific, we consider censoring probabilities $P = 0.10$ and $P = 0.20$, where censoring probability $P = 0.10$ means that there is a 10% chance that an observation will be censored in the generated failure times.

Generation of Failure and Censoring Times Under EAR(1) Process

To generate the failure times T_{ki} values for an EAR(1) process, we follow the same procedure discussed in Section 4.3 of Chapter 4. For generating censoring times for a fixed k and all $i = 1, \dots, 4$ under censoring probability $P = 0.10$ we generate initial values C^*_{k0} and ε_{ki} from an exponential distribution with rate 1/9. Then using C^*_{k0} and ε_{ki} and following (3.1), replacing T_{ki} by C_{ki}, we generate censoring times C^*_{ki} for various choices of the dependence parameter. Then making the same transformation for the failure times, ($C_{ki} = C^*_{ki}/\lambda_{ki}$, where λ_{ki} is defined in (4.20)) we can generate our censoring times C_{ki}. We do this for all $k = 1, 2, \dots, 100$. It can be easily shown that

$$P\left[T_{ki} > c_{ki}\right] = \frac{1}{10},$$

which means that there is a 10% chance of finding a censored observation. For 20% censorship, i.e. $P = 0.20$, we follow the same procedure, except the initial values C^*_{k0} and ε_{ki}, where these initial values C^*_{k0} and ε_{ki} should follow an exponential distribution with rate 1/4.

Generation of Failure and Censoring Times Under EMA(1) Process

To generate the failure times T_{ki} under an EMA(1) process, we follow the same procedure discussed in Section 4.3. Note that unlike the EAR(1) case, the generation of C_{ki} depends only on ε_{ki}. As in the EAR(1) model, we generate the ε_{ki} values from an exponential distribution with rates 1/9 and 1/4 to obtain $P = 0.10$ and $P = 0.20$ respectively. Then we generate censoring times C^*_{ki} for various choices of the dependence parameter using (3.6) with T_{ki} replaced by C^*_{ki} and do the same transformation as in the EAR(1) case to obtain the censoring times C_{ki}.

Generation of Failure and Censoring Times Under EEQ Process

Similarly, to generate T_{ki} from the EEQ process we follow the same procedure discussed in Section 4.3. Then for generating censoring times, we first generate initial values C^*_{k0} and ε_{ki} from exponential distributions with rate 1/9 and 1/4 to obtain $P = 0.10$ and $P = 0.20$ respectively. Following (3.11) of Chapter 3 and replacing T_{ki} by C^*_{ki} and using C^*_{k0} and ε_{ki}, we generate C^*_{ki} for various choices of the dependence parameter. Then using same transformation as in the EAR(1) and EMA(1) cases we obtain the censoring times C_{ki}.

5.3.2 Empirical Efficiency Comparison due to Misspecification of Correlation Structure

We now use the exponential failure and censoring times generated under a given correlation structure and compute the estimate of $\boldsymbol{\beta}$ by using this known correlation structure in the estimating equation for $\boldsymbol{\beta}$ in (5.22). This estimate is computed using the true known correlation structure and denoted by $\hat{\boldsymbol{\beta}}_T$ in Section 5.2. As in Chapter 4, we compute such $\boldsymbol{\beta}$ estimates for 2000 simulations and calculate the mean and MSE and refer to this MSE to as $MSE(True)$. Next we generate the exponential data following a given correlation structure but using a different "working" correlation structure in (5.22) to obtain an estimate of $\boldsymbol{\beta}$. This estimate is called the "working" $\boldsymbol{\beta}$ estimate, which we denote by $\hat{\boldsymbol{\beta}}_{W|T}$. After computing this estimate over 2000 simulations we calculate the mean and MSE using this "working" structure and refer to this MSE as $MSE(Working)$. As in Chapter 4, one may calculate the relative efficiency using (4.21). The results of this simulation study are given in the tables of Appendix B only for true EAR(1) process.

Table B.1 contains results when our failure times were generated following an EAR(1) process under 10% censorship for various choices of ρ under design matrix D_1. From Table B.1 we can see that our estimates of $\boldsymbol{\beta}$ are biased, whether we use the correct or incorrect correlation structures. The amount of bias is decreasing if the correlation increases. We can see that we are losing a lot of efficiency if we do not use the true correlation structure, especially for correlation larger than 0.25. The efficiency loss is higher for 10% censorship than that for uncensorship. One very important point is the poor performance of the working independence structure when the correlation is high. As in the uncensored case, this suggests we could have problems if we incorrectly assume that our failure times are independent. We do not have results for the working EMA(1) structure for $\rho > 0.25$ for the reasons given in Chapter 4. Similarly, Table B.2 contains results when the failure times follow an exponential distribution under 20% censorship. The estimates of $\boldsymbol{\beta}$ are biased and similar with Table B.1 for any working correlation and efficiency loss is high if we do not use the true correlation structure, especially for correlation larger than 0.25. The percentage of efficiency loss is higher for 20% censorship than that for 10% censorship as well as for uncensorship. For the working EMA(1) process, we have some convergence problems which require further study.

From the above discussion we can conclude that we get biased estimates of the regression parameter $\boldsymbol{\beta}$ no matter whether we are using the true or incorrect working correlation structure for both 10% and 20% censorship. For small correlation ($\rho \leq 0.25$), the efficiency gain is not large for using true correlation structure in the estimation of $\boldsymbol{\beta}$. But if we have high correlation ($\rho > 0.25$) then we should use the true correlation structure for estimating $\boldsymbol{\beta}$, otherwise we loss a lot of efficiency. Note that the percentage efficiency loss is higher for 20% censorship than that for 10% censorship as well as for uncensorship. This implies that the higher the rate of censorship, the more important it is to specify the appropriate correlation structure.

5.4 An Illustration: Kidney Infection Data

So far we have discussed the modeling of failure times and estimation procedures of the hazard ratio parameters for longitudinal correlated failure times after taking the longitudinal correlations into account for uncensored and censored cases respectively.

To be specific, the estimation for the uncensored case was discussed in details in Chapter 4 and the censored case was dealt in this chapter through Sections 5.1-5.3. In this section, we will illustrate the methodology developed for both uncensored and censored failure time data through a numerical example. These data were reported by McGilchrist and Aisbett (1991) and then studied by Aslanidou, Dey and Sinha (1998). The data are given in Table C.1, which consist of the times of infection from the time of insertion of the catheter for 38 kidney patients using portable dialysis equipment. The first column shows the patient number. For each patient the second column contains the time to the first and second infection respectively. The third column contains sex, which is the only covariate in this data set, which was coded 1 for male and 2 for female. Note that McGilchrist and Aisbett (1991) originally dealt with two other covariates, the age and disease types of patients, but these covariates were found to be insignificant as indicated by Aslanidou et al. (1998). This motivated us to analyze the kidney infection data with only one covariate. The last column shows the binary variables representing the censoring indicators for the first and second infection respectively. In this column occurrence of infection is indicated by 1 and right censoring by 0. Further note that the kidney infection data considered here are longitudinal by nature as the infections were reported at two consecutive occasions.

It is therefore clear that the two recurrence times of kidney infection for any patient are longitudinally correlated and it is important to take this correlation into account to obtain the hazard ratio parameter estimate. This correlation issue was however not addressed in the above mentioned paper for the estimation of the regression parameter. As it is likely that the correlation among recurrence times will decay as the lag between the recurrence times increases, we assume an EAR(1) longitudinal correlation structure for the repeated kidney infection and use this assumption for the estimation of the hazard ratio parameter. We do this in the following subsections for both uncensored and censored cases.

5.4.1 Hazard Ratio Parameter Estimation Based on Uncensored Data

For analyzing the uncensored data set we removed all censored observations from the data set. We have only 23 patients for whom both failure times are available. As discussed earlier we use the EAR(1) "working" correlation structure (4.5) for the uncensored case to estimate the regression effects of the covariate sex. We use the estimating equation (4.13) and solve that estimating equation by using Gauss-Newton iteration procedure (4.15). We start with an initial value of $\beta = 0.0$, and estimate the dependence parameter ρ and hazard ratio parameter β. After 18 iterations the Newton-Raphson method converged and we obtained the estimate of the dependence parameter $\hat{\rho} = 0.4356$. Our estimate of β is $\hat{\beta} = -2.9814$ with standard error 0.0653, computed by the square root of $\hat{A}_w^{-1}(\beta)\hat{\Sigma}_w(\beta)\hat{A}_w^{-1}(\beta)$ with $\hat{A}_w(\beta) = K^{-1}\sum_{k=1}^{K}\sum_{j=1}^{n}\hat{A}_{w,kj}$ and $\hat{\Sigma}_w(\beta) = \sum_{k=1}^{K}\sum_{i=1}^{n}\sum_{j=1}^{n}\hat{G}_{w,ki}(\beta)\hat{G}_{w,kj}^{T}(\beta)$, where $\hat{A}_{w,kj}(\beta)$ and $\hat{G}_{w,kj}(\beta)$ are in (4.16) and (4.17) respectively. The negative effect of this covariate is indicating that the infection rate for female patients is lower as compared to the infection rate for male patients. Although we considered the true longitudinal correlation structure is EAR(1), for repeated failure times, any other correlation structure such as EMA(1) or EEQ will give the same results as there are only two recurrence times.

5.4.2 Hazard Ratio Parameter Estimation Based on Complete (Uncensored and Censored) Data

For the censoring case, we consider the whole data set of 38 patients and true correlation structure as EAR(1) for analyzing the data. We use the EAR(1) "working" correlation structure (5.9) for solving the estimating equation (5.22) and use the Gauss-Newton iteration procedure to estimate the hazard ratio parameter β. From the EAR(1) correlation structure (5.9) we see that the martingale correlation structure is a function of the dependence parameter ρ and the censoring times. For uncensored observations we consider the censoring times as infinity. For the complete data we use the correlation estimate $\hat{\rho} = 0.4356$ from the uncensored case under the assumption that the correlation parameter ρ is the same for both uncensored and censored data. Then $\hat{\rho}$ was used in (5.9) to compute the covariance of two martingales for each of the 38 patients and use the estimating equation (5.22) to find the hazard ratio parameter. Our process has converged after 10 iterations and we get the estimate of β as $\hat{\beta} = -1.8613$ with standard error 0.0197, computed by the square root of $\hat{A}_w^{-1}(\beta)\hat{\Sigma}_w(\beta)\hat{A}_w^{-1}(\beta)$, where $\hat{A}_w(\beta)$ and $\hat{G}_w(\beta)$ are calculated following Cai and Prentice (1995, p. 156). Like the uncensored case, the covariate sex has a significant effect as the standard error of sex is very small. The negative effect of sex is indicating that the infection rate for female patients is lower as compared to the infection rate for male patients. Note that $\hat{\beta} = -1.8613$ is similar to the result found by McGilchrist and Aisbett (1991), but our estimate has a much smaller standard error.

Chapter 6

Concluding Remarks

6.1 General Remarks

Longitudinal correlated failure times data analysis is an important problem in practice. The statistical inference under such models, however, was not adequately addressed in the literature, perhaps because of the difficulty in modeling longitudinal correlation structure for repeated failure times. As mentioned earlier, some authors such as Wei, Lin and Weissfeld (1989) and Gao and Lin (1994) discussed the regression estimation problem under this longitudinal setup, but they have used structural correlations rather than longitudinal correlations in modeling the correlations for the repeated failure times. In Chapters 3, 4 and 5 we have shown how to model the correlations for particular types of longitudinal data. These include exponential AR(1), MA(1) and equi-correlation structures. The proposed correlation structures were then used to compute estimating equations for the hazard ratio or regression parameters. Thus if the longitudinal correlation structures are known, then by following the results of Chapter 4 and 5 one may obtain efficient estimators for the regression parameters.

Note that for the cases when it is not possible to specify the correlation structure, it is difficult to construct a robust correlation structure for the estimating equations to model the censored data. As it is clear from Chapter 4 that for the uncensored data the correlation between any two martingales of the failure times is the same as the correlation between the corresponding original failure times, one may therefore attempt to use a robust correlation structure to model the unknown longitudinal true correlation structure and use it for estimation of regression effects. This we show in brief in Section 6.2.

6.2 Robust Correlation Structure Based Regression Estimation for Uncensored Failure Time Data

As indicated above, in the uncensored case the correlation between the martingales of the failure times is nothing but the correlation of the failure times. Consequently one may follow Sutradhar and Das (1999) and write a robust autocorrelation structure for the martingales of the failure times under the uncensored case as

$$V = \begin{bmatrix} 1 & \rho_1^* & \rho_2^* & \cdots & \rho_{n-1}^* \\ \rho_1^* & 1 & \rho_1^* & \cdots & \rho_{n-2}^* \\ \rho_2^* & \rho_1^* & 1 & \cdots & \rho_{n-3}^* \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ \rho_{n-1}^* & \rho_{n-2}^* & \rho_{n-3}^* & \cdots & 1 \end{bmatrix}, \tag{6.1}$$

where $corr(M_{ki}(T_{ki}), M_{k(i+l)}(T_{k(i+l)})) = \rho_l^*$. We can estimate ρ_l^* by r_l^*, where r_l^* can be expressed as

$$r_l^* = \sum_{k=1}^{K}\sum_{i=1}^{n-l} \tilde{T}_{ki}\tilde{T}_{k(i+l)}/K(n-l)$$

for $l = 1, 2, \ldots, (n-1)$ and $\tilde{T}_{ki}$ is

$$\tilde{T}_{ki} = \frac{T_{ki} - E(T_{ki})}{var(T_{ki})}.$$

This correlation structure **V** in (6.1) can be used in the estimating equation (4.13) of Chapter 4 to estimate the regression effects.

6.3 Efficiency Aspects for Uncensored Data Based on Robust Correlation Structure

Here we conduct a simulation study under the "working" robust correlation structure to estimate the hazard ratio parameter by using estimating equation (4.13) of Chapter 4. For this simulation study we generate correlated failure times as in Section 4.3 of Chapter 4 using the two design matrices D_1 and D_2 . We then compute $\boldsymbol{\beta}$ using the robust correlation structure (6.1). We refer to this as the robust $\boldsymbol{\beta}$ estimate and denote it for convenience by $\hat{\boldsymbol{\beta}}_R$. We compute these $\boldsymbol{\beta}$ estimates for 2000 simulations, and obtain the average and the mean square error (MSE). This MSE is referred to as the $MSE(Robust)$. It then follows that one may compute the relative efficiency as

$$R.E.(\hat{\beta}_{R|T}) = \frac{MSE(Robust)}{MSE(True)} \times 100, \qquad (6.2)$$

where $R.E.(\hat{\beta}_{T|T})$ is 100 as $\hat{\beta}_{T|T}$ is nothing but $\hat{\beta}_T$. From (6.2) we can calculate the loss of efficiencies for using the robust correlation structure. We report these results in the tables of Appendix D.

Tables D.1 and D.2 contain the results of generated correlated failure times under the EAR(1) process and estimates using the true correlation structure and "working" robust structure (6.1) for designs D_1 and D_2 respectively. From these two tables we can conclude that if we generate data from an EAR(1) process and by using the "working" robust structure the loss of efficiencies is quite small. Tables D.3 and D.4 contain similar results under the designs D_1 and D_2 respectively when we generate failure times under the EEQ process. Under design matrix D_1 we get 94% efficiency for using the "working" robust correlation structure and for design matrix D_2 we get 90% efficiency for using the "working" robust correlation structure. Although for a true EEQ process the efficiency loss is 10%, it is still better than the other "working" correlation structure such as EAR(1), EMA(1) and independence. Tables D.5 and D.6 contain similar results under the designs D_1 and D_2 respectively when we generate failure times under an EMA(1) process. At that time we get 100% efficiencies for using the "working" robust correlation structure (6.1). All throughout IMSL based Fortran 90 was used as software to carry out the simulation as well as data analysis.

From the above discussion we see that the efficiency loss is not great for using the "working" robust correlation structure (6.1) as compared to other "working" correlation structures discussed in Chapter 4, regardless of the true correlation structure. Therefore, this method seems to have a strong potential to give consistent and efficient estimates when analyzing a real data set where the true correlation structure is not known for the uncensored case.

6.4 Proposal for Further Research

From Chapter 5, as the martingale correlations of the failure times are not the same as the correlations between the original failure times, it appears difficult to write a robust correlation structure for the censored data. This issue requires further investigation for the construction of a possible robust correlation structure, which is beyond the scope of this thesis. Moreover, if multivariate structural data are repeatedly collected over a period of time, this will require us to combine the structural and longitudinal correlations to estimate the regression parameters. This appears to be a challenging work which is also beyond the scope of this thesis.

Appendix A

Tables for Uncensored Case

		Working Correlation Structure							
		EAR(1)		ID		EEQ		EMA(1)	
ρ	Statistic	$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$
0.10	Mean	1.0064	0.9970	1.0071	0.9970	1.0065	0.9970	1.0062	0.9969
	MSE	0.0068	0.0062	0.0069	0.0062	0.0068	0.0063	0.0068	0.0062
	R.E.	100.00	100.00	99.000	100.00	100.00	98.000	100.00	100.00
0.25	Mean	1.0011	1.0003	1.0031	0.9997	1.0014	0.9998	1.0007	0.9998
	MSE	0.0064	0.0057	0.0068	0.0061	0.0066	0.0059	0.0064	0.0058
	R.E.	100.00	100.00	94.000	93.000	97.000	97.000	100.00	98.000
0.49	Mean	0.9996	1.0052	1.0020	1.0047	1.0011	1.0047		
	MSE	0.0050	0.0052	0.0070	0.0071	0.0056	0.0057		
	R.E.	100.00	100.00	71.000	73.000	89.000	91.000		
0.64	Mean	1.0014	1.0048	1.0027	1.0062	1.0024	1.0049		
	MSE	0.0044	0.0040	0.0076	0.0068	0.0051	0.0046		
	R.E.	100.00	100.00	58.000	59.000	86.000	87.000		
0.81	Mean	1.0056	1.0072	1.0080	1.0083	1.0058	1.0076		
	MSE	0.0038	0.0032	0.0091	0.0079	0.0044	0.0038		
	R.E.	100.00	100.00	42.000	41.000	86.000	84.000		

Table A.1: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EAR(1) process, under design D_1. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure							
		EAR(1)		ID		EEQ		EMA(1)	
		$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$
0.10	Mean	1.0109	0.9897	1.0118	0.9903	1.0105	0.9901	1.0105	0.9893
	MSE	0.0062	0.0035	0.0062	0.0035	0.0062	0.0035	0.0063	0.0035
	R.E.	100.00	100.00	100.00	100.00	100.00	100.00	98.000	100.00
0.25	Mean	1.0056	0.9919	1.0082	0.9925	1.0054	0.9920	1.0043	0.9908
	MSE	0.0058	0.0028	0.0061	0.0031	0.0061	0.0030	0.0064	0.0029
	R.E.	100.00	100.00	95.000	90.000	95.000	93.000	91.000	97.000
0.49	Mean	1.0043	0.9951	1.0079	0.9964	1.0050	0.9954		
	MSE	0.0051	0.0024	0.0070	0.0036	0.0055	0.0026		
	R.E.	100.00	100.00	73.000	67.000	93.000	92.000		
0.64	Mean	1.0065	0.9954	1.0090	0.9974	1.0066	0.9959		
	MSE	0.0048	0.0020	0.0078	0.0036	0.0052	0.0022		
	R.E.	100.00	100.00	62.000	56.000	92.000	91.000		
0.81	Mean	1.0113	0.9949	1.0158	0.9963	1.0104	0.9956		
	MSE	0.0044	0.0015	0.0101	0.0042	0.0052	0.0017		
	R.E.	100.00	100.00	44.000	36.000	85.000	88.000		

Table A.2: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EAR(1) process, under design D_2. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure: EAR(1) $\hat\beta_{W\|T(1)}$	EAR(1) $\hat\beta_{W\|T(2)}$	ID $\hat\beta_{W\|T(1)}$	ID $\hat\beta_{W\|T(2)}$	EEQ $\hat\beta_{T\|T(1)}$	EEQ $\hat\beta_{T\|T(2)}$	EMA(1) $\hat\beta_{W\|T(1)}$	EMA(1) $\hat\beta_{W\|T(2)}$
0.10	Mean	0.9996	1.0030	1.0003	1.0037	1.0000	1.0032	0.9994	1.0029
	MSE	0.0060	0.0063	0.0060	0.0062	0.0060	0.0062	0.0060	0.0063
	R.E.	100.00	98.000	100.00	100.00	100.00	100.00	100.00	98.000
0.25	Mean	1.0016	1.0018	1.0021	1.0030	1.0017	1.0022	1.0016	1.0017
	MSE	0.0064	0.0063	0.0063	0.0062	0.0063	0.0062	0.0064	0.0064
	R.E.	98.000	98.000	100.00	100.00	100.00	100.00	98.000	97.000
0.49	Mean	0.9998	1.0012	1.0013	1.0028	1.0005	1.0012	1.0014	1.0022
	MSE	0.0058	0.0065	0.0063	0.0068	0.0056	0.0062	0.0060	0.0065
	R.E.	96.000	95.000	89.000	91.000	100.00	100.00	93.000	95.000
0.64	Mean	0.9992	1.0002	1.0015	1.0022	1.0005	1.0003		
	MSE	0.0058	0.0058	0.0069	0.0071	0.0054	0.0056		
	R.E.	93.000	96.000	78.000	79.000	100.00	100.00		
0.81	Mean	0.9989	1.0005	1.0016	1.0022	1.0002	1.0003		
	MSE	0.0049	0.0045	0.0073	0.0073	0.0042	0.0041		
	R.E.	85.000	91.000	58.000	56.000	100.00	100.00		

Table A.3: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EEQ process, under design D_1. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure							
		EAR(1)		ID		EEQ		EMA(1)	
		$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$
0.10	Mean	1.0053	0.9930	1.0067	0.9941	1.0054	0.9935	0.9994	1.0029
	MSE	0.0054	0.0034	0.0054	0.0034	0.0054	0.0034	0.0054	0.0035
	R.E.	100.00	100.00	100.00	100.00	100.00	100.00	100.00	98.000
0.25	Mean	1.0068	0.9934	1.0079	0.9946	1.0066	0.9939	1.0007	0.9937
	MSE	0.0056	0.0034	0.0056	0.0034	0.0056	0.0034	0.0056	0.0034
	R.E.	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.49	Mean	1.0046	0.9935	1.0069	0.9953	1.0050	0.9940	1.0064	0.9948
	MSE	0.0054	0.0033	0.0059	0.0036	0.0052	0.0031	0.0055	0.0033
	R.E.	96.000	94.000	88.000	86.000	100.00	100.00	95.000	94.000
0.64	Mean	1.0041	0.9924	1.0069	0.9947	1.0045	0.9925		
	MSE	0.0057	0.0028	0.0070	0.0037	0.0053	0.0026		
	R.E.	93.000	93.000	76.000	70.000	100.00	100.00		
0.81	Mean	0.9989	1.0005	1.0067	0.9956	1.0035	0.9936		
	MSE	0.0050	0.0023	0.0079	0.0040	0.0044	0.0019		
	R.E.	88.000	83.000	55.000	47.000	100.00	100.00		

Table A.4: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EEQ process, under design D_2. ρ= Correlation Parameter, MSE =Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure							
		EAR(1)		ID		EEQ		EMA(1)	
		$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$
0.10	Mean	0.9998	1.0028	1.0007	1.0036	1.0003	1.0030	0.9995	1.0027
	MSE	0.0060	0.0062	0.0060	0.0062	0.0061	0.0062	0.0060	0.0062
	R.E.	100.00	100.00	100.00	100.00	98.000	100.00	100.00	100.00
0.25	Mean	1.0026	1.0012	1.0030	1.0024	1.0027	1.0018	1.0023	1.0011
	MSE	0.0063	0.0058	0.0064	0.0060	0.0064	0.0060	0.0063	0.0058
	R.E.	100.00	100.00	98.000	96.000	98.000	96.000	100.00	100.00
0.49	Mean	1.0057	0.9996	1.0048	0.9998	1.0054	0.9998	1.0057	0.9994
	MSE	0.0059	0.0058	0.0063	0.0063	0.0062	0.0062	0.0059	0.0058
	R.E.	100.00	100.00	94.000	92.000	95.000	94.000	100.00	100.00

Table A.5: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EMA(1) process, under design D_1. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure							
		EAR(1)		ID		EEQ		EMA(1)	
		$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$
0.10	Mean	1.0056	0.9929	1.0071	0.9939	1.0058	0.9933	1.0050	0.9926
	MSE	0.0054	0.0033	0.0054	0.0033	0.0055	0.0033	0.0054	0.0033
	R.E.	100.00	100.00	100.00	100.00	98.000	100.00	100.00	100.00
0.25	Mean	1.0077	0.9931	1.0088	0.9941	1.0075	0.9934	1.0069	0.9928
	MSE	0.0056	0.0033	0.0056	0.0033	0.0058	0.0033	0.0056	0.0033
	R.E.	100.00	100.00	100.00	100.00	97.000	100.00	100.00	100.00
0.49	Mean	1.0088	0.9936	1.0081	0.9941	1.0082	0.9936	1.0088	0.9937
	MSE	0.0051	0.0031	0.0055	0.0034	0.0054	0.0032	0.0051	0.0031
	R.E.	100.00	100.00	93.000	91.000	94.000	97.000	100.00	100.00

Table A.6: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EMA(1) process, under design D_2. ρ= Correlation Parameter, MSE =Mean Square Error, R.E. = Relative Efficiency.

Appendix B

Tables for Censored Case

		Working Correlation Structure							
		EAR(1)		ID		EEQ		EMA(1)	
ρ	Statistic	$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$
	Mean	0.6479	0.6493	0.6255	0.6175	0.6939	0.7087	-	-
0.10	MSE	0.2530	0.2570	0.2613	0.2785	0.2500	0.2550	-	-
	R.E.	100.00	100.00	97.000	93.000	100.00	100.00	-	-
	Mean	0.7073	0.7075	0.6200	0.6175	0.7203	0.7378	-	-
0.25	MSE	0.1881	0.1844	0.2450	0.2546	0.2060	0.1939	-	-
	R.E.	100.00	100.00	77.000	73.000	91.000	95.000	-	-
	Mean	0.7901	0.7075	0.6200	0.6029	0.7202	0.7378		
0.49	MSE	0.0846	0.0817	0.2618	0.2546	0.2060	0.1939		
	R.E.	100.00	100.00	33.000	30.000	60.000	61.000		
	Mean	0.8751	0.8849	0.5941	0.5871	0.8343	0.8406		
0.64	MSE	0.0343	0.0313	0.2581	0.2655	0.0900	0.0833		
	R.E.	100.00	100.00	14.000	12.000	38.000	38.000		
	Mean	0.9823	0.9853	0.5995	0.5795	0.9342	0.9478		
0.81	MSE	0.0132	0.0099	0.2532	0.2751	0.0453	0.0386		
	R.E.	100.00	100.00	6.0000	4.0000	30.000	26.000		

Table B.1: Summary of estimates for censored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EAR(1) process with 10% censorship. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure							
		EAR(1)		ID		EEQ		EMA(1)	
		$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$	$\hat{\beta}_{W\|T(1)}$	$\hat{\beta}_{W\|T(2)}$
0.10	Mean	0.7434	0.7479	0.6894	0.6789	0.7928	0.7955	-	-
	MSE	0.1483	0.1548	0.1922	0.1977	0.1480	0.1540	-	-
	R.E.	100.00	100.00	78.000	78.000	100.00	100.00	-	-
0.25	Mean	0.7948	0.8041	0.6936	0.6849	0.8203	0.8310	-	-
	MSE	0.1033	0.1010	0.1860	0.2015	0.1514	0.1447	-	-
	R.E.	100.00	100.00	56.000	50.000	68.000	70.000	-	-
0.49	Mean	0.8676	0.8756	0.6822	0.6676	0.8353	0.8542		
	MSE	0.0460	0.0467	0.1953	0.2053	0.0862	0.0774		
	R.E.	100.00	100.00	24.000	23.000	53.000	60.000		
0.64	Mean	0.9282	0.9359	0.6774	0.6664	0.8941	0.9050		
	MSE	0.0156	0.0155	0.1914	0.2041	0.0603	0.0571		
	R.E.	100.00	100.00	8.0000	8.0000	26.000	27.000		
0.81	Mean	1.0060	1.0076	0.6725	0.6595	0.9685	0.9813		
	MSE	0.0067	0.0072	0.1855	0.1962	0.0342	0.0358		
	R.E.	100.00	100.00	3.0000	3.0000	20.000	20.000		

Table B.2: Summary of estimates for censored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EAR(1) process with 20% censorship. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

Appendix C

Kidney Infection Data

Patient number	Recurrence times	Sex	Event types
1	8, 16	1	1, 1
2	33, 13	2	1, 0
3	22, 28	1	1, 1
4	447,318	2	1, 1
5	30, 12	1	1, 1
6	24,245	2	1, 1
7	7, 9	1	1, 1
8	511, 30	2	1, 1
9	53,196	2	1, 1
10	15,154	1	1, 1
11	7,333	2	1, 1
12	141, 8	2	1, 0
13	96, 38	2	1, 1
14	149, 70	2	0, 0
15	536, 25	2	1, 0
16	17, 4	1	1, 0
17	185,117	2	1, 1
18	292,114	2	1, 1
19	22,159	2	0, 0
20	15,108	2	1, 0
21	152,562	1	1, 1
22	402, 24	2	1, 0
23	13, 66	2	1, 1
24	39, 46	1	1, 0
25	12, 40	1	1, 1
26	113,201	2	0, 1
27	132,156	2	1, 1
28	34, 30	2	1, 1
29	2, 25	1	1, 1
30	130, 26	2	1, 1
31	27, 58	2	1, 1
32	5, 43	2	0, 1
33	152, 30	2	1, 1
34	190, 5	2	1, 0
35	119, 8	2	1, 1
36	54, 16	2	0, 0
37	6, 78	2	0, 1
38	63, 8	1	1, 0

Table C.1: Recurrence times of infections in 38 kidney patients.

Appendix D

Tables Under Robust Structure for Uncensored Case

		Working Correlation Structure			
		EAR(1)		Robust	
ρ	Statistic	$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	$\hat{\beta}_{R\|T(1)}$	$\hat{\beta}_{R\|T(2)}$
	Mean	1.0064	0.9970	1.0052	0.9959
0.10	MSE	0.0068	0.0062	0.0068	0.0063
	R.E.	100.00	100.00	100.00	98.000
	Mean	1.0011	1.0003	0.9994	0.9990
0.25	MSE	0.0064	0.0057	0.0065	0.0058
	R.E.	100.00	100.00	98.000	98.000
	Mean	0.9996	1.0052	0.9984	1.0033
0.49	MSE	0.0050	0.0052	0.0051	0.0053
	R.E.	100.00	100.00	98.000	98.000
	Mean	1.0014	1.0048	0.9998	1.0030
0.64	MSE	0.0044	0.0040	0.0045	0.0040
	R.E.	100.00	100.00	98.000	100.00
	Mean	1.0056	1.0072	1.0035	1.0051
0.81	MSE	0.0038	0.0032	0.0039	0.0032
	R.E.	100.00	100.00	97.000	100.00

Table D.1: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EAR(1) process, under design D_1. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

		Working Correlation Structure			
		EAR(1)		Robust	
ρ	Statistic	$\beta_{T\|T(1)}$	$\beta_{T\|T(2)}$	$\beta_{R\|T(1)}$	$\beta_{R\|T(2)}$
	Mean	1.0109	0.9897	1.0097	0.9880
0.10	MSE	0.0062	0.0035	0.0066	0.0037
	R.E.	100.00	100.00	94.000	95.000
	Mean	1.0056	0.9919	0.9994	0.9990
0.25	MSE	0.0058	0.0028	0.0062	0.0030
	R.E.	100.00	100.00	94.000	94.000
	Mean	1.0043	0.9951	0.9984	1.0033
0.49	MSE	0.0051	0.0024	0.0054	0.0025
	R.E.	100.00	100.00	95.000	96.000
	Mean	1.0065	0.9954	0.9998	1.0030
0.64	MSE	0.0048	0.0020	0.0048	0.0020
	R.E.	100.00	100.00	100.00	100.00
	Mean	1.0113	0.9949	1.0035	1.0051
0.81	MSE	0.0044	0.0015	0.0044	0.0015
	R.E.	100.00	100.00	100.00	100.00

Table D.2: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EAR(1) process, under design D_2. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure EEQ $\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	Robust $\hat{\beta}_{R\|T(1)}$	$\hat{\beta}_{R\|T(2)}$
0.10	Mean	1.0000	1.0032	0.9988	1.0019
	MSE	0.0060	0.0062	0.0061	0.0063
	R.E.	100.00	100.00	98.000	98.000
0.25	Mean	1.0017	1.0022	0.9994	0.9990
	MSE	0.0063	0.0062	0.0065	0.0064
	R.E.	100.00	100.00	97.000	97.000
0.49	Mean	1.0005	1.0012	0.9987	0.9995
	MSE	0.0056	0.0062	0.0058	0.0064
	R.E.	100.00	100.00	97.000	97.000
0.64	Mean	1.0005	1.0003	0.9990	0.9974
	MSE	0.0054	0.0056	0.0056	0.0057
	R.E.	100.00	100.00	97.000	98.000
0.81	Mean	1.0002	1.0003	0.9988	0.9980
	MSE	0.0042	0.0041	0.0045	0.0043
	R.E.	100.00	100.00	94.000	94.000

Table D.3: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EEQ process, under design D_1. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure			
		EEQ		Robust	
		$\hat{\beta}_{T\mid T(1)}$	$\hat{\beta}_{T\mid T(2)}$	$\hat{\beta}_{R\mid T(1)}$	$\hat{\beta}_{R\mid T(2)}$
0.10	Mean	1.0054	0.9935	1.0045	0.9906
	MSE	0.0054	0.0034	0.0058	0.0036
	R.E.	100.00	100.00	95.000	95.000
0.25	Mean	1.0066	0.9939	1.0056	0.9913
	MSE	0.0056	0.0034	0.0060	0.0036
	R.E.	100.00	100.00	94.000	95.000
0.49	Mean	1.0050	0.9940	1.0041	0.9912
	MSE	0.0052	0.0031	0.0056	0.0034
	R.E.	100.00	100.00	93.000	91.000
0.64	Mean	1.0045	0.9925	0.9990	0.9974
	MSE	0.0053	0.0026	0.0057	0.0028
	R.E.	100.00	100.00	93.000	93.000
0.81	Mean	1.0035	0.9936	1.0037	0.9909
	MSE	0.0044	0.0019	0.0048	0.0022
	R.E.	100.00	100.00	91.000	87.000

Table D.4: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EEQ process, under design D_2. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

ρ	Statistic	Working Correlation Structure			
		EMA(1)		Robust	
		$\hat{\beta}_{T\mid T(1)}$	$\hat{\beta}_{T\mid T(2)}$	$\hat{\beta}_{R\mid T(1)}$	$\hat{\beta}_{R\mid T(2)}$
0.10	Mean	0.9995	1.0027	0.9990	1.0016
	MSE	0.0060	0.0062	0.0061	0.0062
	R.E.	100.00	100.00	98.000	100.00
0.25	Mean	1.0023	1.0011	1.0019	1.0000
	MSE	0.0063	0.0058	0.0064	0.0060
	R.E.	100.00	100.00	98.000	97.000
0.49	Mean	1.0057	0.9994	1.0059	0.9993
	MSE	0.0059	0.0058	0.0059	0.0058
	R.E.	100.00	100.00	100.00	100.00

Table D.5: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EMA(1) process, under design D_1. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

		Working Correlation Structure			
		EMA(1)		Robust	
ρ	Statistic	$\hat{\beta}_{T\|T(1)}$	$\hat{\beta}_{T\|T(2)}$	$\hat{\beta}_{R\|T(1)}$	$\hat{\beta}_{R\|T(2)}$
	Mean	1.0050	0.9926	1.0048	0.9905
0.10	MSE	0.0054	0.0033	0.0057	0.0034
	R.E.	100.00	100.00	95.000	97.000
	Mean	1.0069	0.9928	1.0068	0.9911
0.25	MSE	0.0056	0.0033	0.0059	0.0034
	R.E.	100.00	100.00	95.000	97.000
	Mean	1.0088	0.9937	1.0089	0.9934
0.49	MSE	0.0051	0.0031	0.0052	0.0031
	R.E.	100.00	100.00	98.000	100.00

Table D.6: Summary of estimates for uncensored case with $K = 100$, true $\beta_1 = \beta_2 = 1$ for true EMA(1) process, under design D_2. ρ= Correlation Parameter, MSE = Mean Square Error, R.E. = Relative Efficiency.

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