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## Methods for two-sample comparisons from censored time-to-event data

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## ABSTRACT

### METHODS FOR TWO-SAMPLE COMPARISONS FROM CENSORED TIME-TO-EVENT DATA

by  
**Nubyra Ahmed**

In the analysis of censored survival data, it is frequently of interest to determine the efficacy of a treatment or new method over a control or existing method. For this purpose, one may report estimates of the two survival functions or, more specifically, their difference, accompanied by simultaneous confidence bands (SCBs). Alternatively, or in addition, one may conduct hypothesis testing for the difference of the two survival functions.

The first project exploits two bootstrap methods to develop new Wald-type SCBs for the difference of survival functions. The censored data bootstrap is employed to obtain nonparametric SCBs for the difference of two survival curves. Furthermore, a recently developed two-stage bootstrap is exploited to obtain semiparametric SCBs for the difference. The two-stage bootstrap combines the classical bootstrap with a model-based regeneration of censoring indicators. Simulation studies are presented to show that the new SCBs are superior to a currently existing one, in the sense of producing empirical coverage closer to the nominal level. The model-based approach produces tighter and, hence, more informative SCBs. Specifically, for censoring rates between 10% and 40%, the semiparametric SCBs provide a relative reduction in enclosed area amounting to between 2% and 7% over their nonparametric counterparts, with the increase in reduction being directly proportional to the censoring rate. In particular, the reduction is expected to be even higher for high censoring rates. The methods are illustrated using real data sets from cancer and other biomedical studies.

The second project develops semiparametric SCBs for the difference using the method of empirical likelihood. Simulation studies are presented to show that the semiparametric approach is superior to the nonparametric counterpart, with the new SCBs producing empirical coverage closer to the nominal level. Further comparisons reveal that the semiparametric confidence bands are tighter and, hence, more informative. For censoring rates between 10% and 40%, the semiparametric confidence bands provide a relative reduction in enclosed area amounting to between 2% and 7% over their nonparametric bands, with increased reduction attained for higher censoring rates. The methods are illustrated using an University of Massachusetts AIDS data set.

Finally, the third project develops two test procedures for the null hypothesis of no difference between the survival functions. The test statistics are based on the group-specific nonparametric or semiparametric survival function estimators. The censored data and two-stage bootstrap procedures are again deployed to obtain critical values for the testing. Numerical simulations show that the new test procedures outperform an existing one, in terms of producing the correct empirical significance level. Furthermore, power studies reinforce the superiority of the proposed method. A real example illustration is given to demonstrate the proposed method.

**METHODS FOR TWO-SAMPLE COMPARISONS FROM CENSORED  
TIME-TO-EVENT DATA**

by  
**Nubyra Ahmed**

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**APPROVAL PAGE**

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*He who loves practice without theory is like the sailor who boards ship without a rudder and compass and never knows where he may be cast.*

Leonardo da Vinci

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## CHAPTER 1

### INTRODUCTION

In clinical trials, it is frequently of interest to determine whether or not a new treatment is as or more effective than a control. To address this goal, one approach would be to display areas around point estimates of the difference  $\alpha(t) = S_1(t) - S_2(t)$  of two survival functions using pointwise confidence intervals (PCIs). A plot of the PCIs over a region facilitates visual examination to determine the inclusion or exclusion of the zero line of no difference, which, in turn, may be used to conclude the presence or absence of treatment effect. However, although PCIs are simple to implement, they have the potential to lead to erroneous conclusions. Indeed, as shown by Parzen, Wei, and Ying (1997), henceforth **PWY**, decisions based on PCIs can lead to poor judgment regarding treatment efficacy. PWY provided a compelling example in which they evaluated the efficacy and safety of a reduced dose of AZT, through simultaneous confidence bands (SCBs) for the difference  $D$ . The PCIs showed positive difference in survival rates over the region  $[450, 700]$ , measured in days, leading one to incorrectly surmise the inefficacy of low dose of AZT in improving survival. PWY's two-sample SCBs, however, provided a persuasive argument that low dose was as effective as the standard one over the entire region of observation. More generally, it is common for PCIs to depict incorrect regions of positive or negative survival-rate difference, leading to potentially incorrect conclusions. SCBs are global, allow simultaneous conclusions at multitude time points that do not have to be prespecified, present correct estimate of treatment difference over a region, in turn promoting correct decision making. The goal is to develop SCBs for the difference of two survival functions, and to develop method for testing the null hypothesis of no difference between the two survival functions, when data are right censored.

Censoring occurs when we are unable to observe time to event of interest for all study participants. For instance, a clinical trial monitoring the remission of cancer in a group of patients, some patients may still be in remission at the end of the trial, or lost to follow-up. Therefore, all known is that their true remission is longer than could be observed. Such patients are right-censored, since their true lifetimes are to the right of their observed censor times.

For right censored data, several different types of two-sample and, more generally, subject-specific SCBs have been developed so far. Dabrowska, Doksum, and Song (1989) developed SCBs to check the proportionality of hazards of treatment and control groups. Dickson et al. (1989), in their analysis of the Mayo data base, make a strong case for computing subject-specific survival estimates accompanied by SCBs. Lin, Fleming, and Wei (1994) developed such subject-specific SCBs under the Cox proportional hazards (PH) model. Zhang and Klein (2001) proposed subject-specific SCBs based on a stratified Cox PH model. More recently, Wei and Schaubel (2008) proposed SCBs based on an estimator for treatment-specific baseline cumulative hazards under a stratified Cox nonproportional hazards model. Einmahl and McKeague (1999) developed confidence tubes for Q-Q plots. McKeague and Zhao (2002, 2006) derived two-sample SCBs for the ratio of two survival functions using Owen's (1988, 1990) empirical likelihood (EL). McKeague and Zhao (2005) on the other hand proposed SCBs, based on EL with plug-in, for the difference of two survival functions. Shen and He (2006) also proposed EL-based SCBs for the difference. Yang and Prentice (2011) developed SCBs for a time-dependent hazard ratio using Yang and Prentice's (2005) semiparametric model. Finally, well-known statistical packages such as R, SAS, SPSS, and Stata now provide the user with the ability to compute the Hall-Wellner and equal-precision one-sample SCBs, underlining their importance in practice. Indeed, judged by their utility, two-sample SCBs may be more useful and a case may be made for their implementation in SAS.

In the first project, new SCBs will be developed for  $\alpha(t)$ , in two settings: (i) the standard random censorship model (RCM henceforth) and (ii) its semiparametric extension (SRCMs henceforth) developed by Dikta (1998). In the one-sample RCM, there are  $n$  independent and identically distributed copies of  $(Z, \delta)$ , where  $Z = \min(X, C)$ ,  $X$  and  $C$  are independent failure and censoring times, respectively, and  $\delta = I(X \leq C)$  is the event indicator, sometimes also called the censoring indicator. On the other hand, in the one-sample SRCMs, the censoring indicator corresponding to the observed  $Z$  is replaced with a model-based estimate of its conditional expectation given  $Z$ . More specifically, introducing a model  $m(t, \theta)$  for  $m(t) = P(\delta = 1|Z = t)$ , where  $\theta \in \mathbb{R}^k$  is an unknown  $k$ -dimensional parameter, the censoring indicator is replaced with  $m(t, \hat{\theta})$ , where  $\hat{\theta}$  is the maximum likelihood estimate (MLE) of  $\theta$ . When the model for  $m(t)$  is correctly chosen, the resulting survival function estimator is semiparametric efficient (Dikta, 2014) and asymptotically as or more efficient than the Kaplan–Meier (KM henceforth) estimator (Dikta, 1998). This efficiency is reflected in improved SRCMs-based SCBs for  $S(t)$ , see Subramanian and Zhang (2013), as well as Section 3.1. Clearly, the effectiveness of the SRCMs in producing improved SCBs is predicated on the rationale that a good-fitting model can be supplied for  $m(t)$ . A suitable choice can usually be obtained from well-known models for binary responses, such as the logistic, Cauchy, probit, complementary log-log, generalized proportional hazards (Dikta, 1998), among others; see also Cox and Snell (1989) and Collett (2002). Furthermore, in the search for a good-fitting model, a recently proposed resampling-based diagnostic method can be applied to discard ill-fitting models (Dikta, Kvesic, and Schmidt, 2006). Two-sample SRCMs are extensions of the one sample scenario wherein model based estimates are specified for each group-specific conditional probability. Details regarding two-sample SRCMs are given in Chapter 2. Simulation studies presented in Section 3.1 indicate that, between the logistic and Cauchy models, the Cauchy link performs better, in

terms of providing SCBs that have approximately correct coverage and least average width.

To compute Wald-type SCBs for the difference  $\alpha(t)$ , critical values from the asymptotic distribution of a suitable estimator, say  $\hat{\alpha}(t) = \hat{S}_1(t) - \hat{S}_2(t)$ , are obtained. When the asymptotic distributions are intractable, however, resampling techniques may be employed. Under the framework of RCM, PWY employed the Gaussian multiplier bootstrap, henceforth GMB, to obtain the requisite critical values to construct their Wald-type SCBs for the difference. Lin, Fleming, and Wei (1994), among others, employed the GMB for constructing SCBs.

Our approach to compute the critical values is different. We exploit two bootstrap methods to produce the newly proposed SCBs for the difference of survival functions from censored data, and these relate to the RCM and SRCMs. Essentially, the methods rely on the bootstrapped KM and SRCMs-based survival function estimators for each group to calibrate the critical values from the (bootstrap) distributions of their difference. As is well known, for the RCM, resamples are obtained by drawing at random from the empirical distribution of  $(Z, \delta)$ , see Efron (1981). This bootstrap is equivalent to drawing samples from the KM estimators of the failure time and censoring distributions (Akritas, 1986; Lo and Singh, 1986). For the SRCMs, resamples are obtained in two stages, combining classical bootstrap (samples drawn from the empirical distribution of  $Z$ ) with model-based regeneration of the censoring indicators (Subramanian and Zhang, 2013). When the SRCMs holds, the two-stage bootstrap fully exploits the assumed model to generate resamples and is more efficient than Efron's censored data bootstrap. It will be shown that the proposed "linear" and variable-width SCBs would offer simple and enduring alternatives to the PWY approach.

There are good reasons why the bootstrap would be preferable to a simulated process approach. It is well known that the bootstrap uses the sample as a surrogate

for the population. Instead of drawing from an asymptotic distribution through a simulation process, the bootstrap draws with replacement from the sample. It therefore, takes the empirical distribution function as the true distribution function and, therefore, is often more accurate in finite samples than asymptotic approximations. It has been shown that for various estimators or test statistics the bootstrap yields approximation that are as accurate or better than the approximations based on asymptotic theory (Bickel and Freedman, 1981; Singh, 1981). This is supported by our simulation results where the proposed nonparametric and semiparametric bootstraps produce demonstrably superior SCBs than the ones developed by PWY.

In the second project, we develop SRCMs-based SCBs for  $\alpha(t)$  via the empirical likelihood (EL) approach (Thomas and Grunkemeier, 1975; Li (1995), Owen, 1988, 1990; McKeague and Zhao, 2005). The SCBs obtained by empirical likelihood ratio statistics possess several attractive features compared to the conventional Wald-type confidence intervals. There are several advantages that the EL method provides. It has range preserving property, that is, the bounds of the SCBs do not exceed the  $(0, 1)$  range. This is particularly an attractive feature since, survival probability ranges between  $(0, 1)$ . The EL method provides estimates that performed better than the normal-approximation-based approaches. Lastly, the SCBs based on the EL are not necessarily symmetric about  $\alpha(t)$ , being determined by the empirical likelihood function.

Our proposed method draws inspiration from that of McKeague and Zhao (2005). To describe their method, note from Eq. (2.6.10) of Andersen et al. (1993) that  $F_i(t) = 1 - S_i(t)$ ,  $i = 1, 2$ , can be represented as a cumulative hazard integral, over  $[0, t]$ , with integrand  $S_i(s-)$ . McKeague and Zhao (2005) utilized this representation to express  $\alpha(t)$  as the difference of two cumulative hazard integrals. When the respective integrals,  $S_i(s-)$ ,  $i = 1, 2$ , are regarded as nuisance parameters, a plug-in EL analysis entails replacing them with  $\tilde{S}_i(s-)$ , the corresponding KM estimators.

See also Qin and Tsao (2003) and Hjort et al. (2009) for more on plug-in EL. Shen and He (2006) instead formulated their EL in terms of  $\alpha(t)$ , with one of the survival functions playing the role of a nuisance parameter. Both EL statistics are not asymptotically distribution free, with the weak limits being proportional to a squared mixture of independent time-transformed Brownian motions but having different proportionality constants. Since Shen and He (2006) did not provide a procedure to invert their EL statistic, it appears difficult to implement their method. In contrast, the method of McKeague and Zhao (2005) utilizes the standard technique of computing two roots of the Lagrange multiplier (Thomas and Grunkemeier, 1975; Li, 1995; Hollander, McKeague and Yang, 1997), hence is less difficult to implement; see Section 4.3 for details.

McKeague and Zhao (2005) as well as Shen and He (2006), however, employed the nonparametric likelihood combined with the KM estimator. An alternative approach, pursued in the second project, is based on a semiparametric adjustment to the nonparametric likelihood combined with Dikta's (1998) SRCMs-based estimator of  $S_i(t)$ . Incorporating SRCMs has been shown to improve estimation and inference in a variety of settings, including more informative SCBs (Subramanian and Dikta, 2009; Subramanian, 2012; Subramanian and Zhang, 2013; Mondal and Subramanian, 2014, 2015; Bhattacharya and Subramanian, 2014).

We continue with the plug-in EL setting developed by McKeague and Zhao (2005) and implement SRCMs-based SCBs for the difference  $\alpha(t)$ . We show that the adjusted semiparametric plug-in EL approach offers considerable improvements over McKeague and Zhao's (2005) nonparametric plug-in EL, in terms of producing narrower and, hence, more informative SCBs. As can be seen from Section 4.2, in particular, our analysis is nontrivial and is not a direct extension of the nonparametric case. The proposed log likelihood ratio statistic is shown to be asymptotically equivalent to  $W^2$  up to a scale factor (theorem 1), where  $W$  is a mixture of

group-specific normalized SRCMs-based survival function processes. Consequently, the variance of the weak limit is smaller than its nonparametric counterpart, and provides a good reason why the proposed procedure gives improved performance.

In the third project, we develop two test procedures for the null hypothesis of no difference between two survival functions. These procedures are based on the weighted KM (WKM henceforth) statistic (Pepe and Fleming, 1989), further modified by Lee, Omolo, and Omolo (2008), and its SRCMs extension. The WKM statistic was based on the integrated weighted difference between the group-specific KM estimators. The difference is integrated over the length of the study period. The random weight function, which satisfies certain stability conditions, downweights the difference  $\alpha(t) = S_1(t) - S_2(t)$ , appearing as the integrand, over later time periods when there may be heavy censoring. Lee, Lee, Omolos (2008) consider a functional version of Pepe and Fleming's (1989) WKM, which they showed is more powerful. The distributions of the test statistics can be approximated by zero-mean Gaussian processes under the null hypothesis. The critical values, on which our p-values are based, are obtained through the censored data and two-stage bootstraps. Numerical simulations and real example studies show that our procedures outperform Lee, Omolo, and Omolo (2008).

The thesis is organized as follows. Chapter 2 contains a review of basic two-sample set-up in the RCM and SRCMs framework, a detailed explanation of the two-stage bootstrap, and an outline of the PWY method. Chapter 3 provides details for the proposed bootstrap based SCBs. Simulation results are reported in Section 3.1. The proposed SCBs are illustrated using data from medical studies in Section 3.2. Chapter 4 provides detailed outline of the proposed empirical likelihood based SCBs. Section 4.1 develops preliminary SRCMs-based large sample theory necessary for the proposed EL based SCBs. Section 4.2 develops the SRCMs-based EL approach. Section 4.3 describes the semiparametric EL-based SCBs. For the EL-based SCBs,

we report the simulation results in Section 4.4 and provide a real example illustration in Section 4.5. Chapter 5 provides detailed outline of the proposed integrated test statistics. Simulation results are provided in Section 5.2 and results of real example is provided in Section 5.3. An overall concluding discussion is given in Section 6. All proofs fare given in the Appendix.



## CHAPTER 2

### BACKGROUND

In this chapter, a review of the basic two-sample set-up in the RCM and SRCMs framework and a detailed explanation of the two-stage bootstrap is given. An outline of the PWY method for constructing SCBs is also presented.

#### 2.1 Random Censorship Model (RCM)

Let  $Z_{ij}$  denote the minimum of the failure and censoring times for the  $j$ th patient in the  $i$ th group,  $i = 1, 2, j = 1, \dots, n_i$ . Also let  $\delta_{ij} = 1$  if  $Z_{ij}$  is uncensored and 0 otherwise. The data are given by  $\{(Z_{ij}, \delta_{ij}), j = 1, \dots, n_i, i = 1, 2\}$ . The  $(Z_{ij}, \delta_{ij}), j = 1, \dots, n_i$  are mutually independent having the same distribution as, say  $(Z_i, \delta_i)$ . For the  $i$ th group,  $i = 1, 2$ , let  $F_i$  denote the distribution of the failure time and  $G_i$  denote the distribution of censoring time. The group-specific survival functions are given by  $S_i(t) = 1 - F_i(t)$ ,  $i = 1, 2$ . Let  $1 - H_i = S_i(1 - G_i)$ . Under the RCM the KM estimator is asymptotically efficient (Wellner, 1982) and the choice estimator for survival functions.

#### 2.2 Semiparametric Random Censorship Models (SRCMs)

Let  $\langle \cdot, \cdot \rangle$  denote the inner product in  $\mathbb{R}^k$ . Under two-sample SRCMs, we specify a model  $m_i(t, \boldsymbol{\theta}_i)$  for  $m_i(t) = P(\delta_{ij} = 1 | Z_{ij} = t)$ , where  $\boldsymbol{\theta}_i \in \mathbb{R}^k$  is an unknown  $k$ -dimensional parameter. Let  $\hat{\boldsymbol{\theta}}_i$  denote the maximum likelihood estimator (MLE) of  $\boldsymbol{\theta}_i$ . Write  $\hat{Q}_i(t) = \sum_{j=1}^{n_i} m_i(Z_{ij}, \hat{\boldsymbol{\theta}}_i) I(Z_{ij} \leq t) / n_i$  and  $Y_i(s) = \sum_{j=1}^{n_i} Y_{ij}(s) \equiv \sum_{j=1}^{n_i} I(Z_{ij} \geq s)$ . Also, let  $\bar{Y}_i(t) = Y_i(t) / n_i$ . By the strong law of large numbers,  $\bar{Y}_i(t) \xrightarrow{\text{a.s.}} y_i(t) \equiv P(Z_{i1} \geq t)$ . Note that  $y_i(t) = 1 - H_i(t-) = 1 - H_i(t)$ , under continuity of  $H_i(t)$ , the distribution function of  $Z_{i1}$ . The SRCMs-based survival

function estimator is given by

$$\hat{S}_i(t) = \prod_{0 \leq s \leq t} \left\{ 1 - d\hat{\Lambda}_i(s) \right\} = \prod_{0 \leq s \leq t} \left\{ 1 - \frac{n_i}{Y_i(s)} d\hat{Q}_i(s) \right\}, \quad i = 1, 2.$$

Let  $\text{Grad}_{\boldsymbol{\theta}}(m(t, \boldsymbol{\theta}))$  denote the vector of partial derivatives of  $m(t, \boldsymbol{\theta})$  with respect to  $\boldsymbol{\theta}$ , to be denoted by  $\text{Grad}_{\boldsymbol{\theta}}(m(t, \boldsymbol{\theta}_0))$  when evaluated at the true value  $\boldsymbol{\theta}_0$ . Let  $\boldsymbol{\theta}_{i0}$  denote the true value of  $\boldsymbol{\theta}_i$  and let

$$\alpha_i(u, v) = \langle \text{Grad}_{\boldsymbol{\theta}_i}(m_i(u, \boldsymbol{\theta}_{i0})), \mathbf{I}_{i0}^{-1} \text{Grad}_{\boldsymbol{\theta}_i}(m_i(v, \boldsymbol{\theta}_{i0})) \rangle,$$

where

$$\mathbf{I}_i(\boldsymbol{\theta}_{i0}) \equiv \mathbf{I}_{i0} = E \left[ \frac{\text{Grad}_{\boldsymbol{\theta}_i}(m_i(Z_{i1}, \boldsymbol{\theta}_{i0})) (\text{Grad}_{\boldsymbol{\theta}_i}(m_i(Z_{i1}, \boldsymbol{\theta}_{i0})))^T}{m_i(Z_{i1}, \boldsymbol{\theta}_{i0}) (1 - m_i(Z_{i1}, \boldsymbol{\theta}_{i0}))} \right], \quad i = 1, 2.$$

Let  $\tau_i$  satisfy  $y_i(\tau_i) > 0$ . From Dikta (1998),  $n_i^{1/2}(\hat{S}_i(\cdot) - S_i(\cdot))$  converges weakly in  $D[0, \tau_i]$  to  $U_i(\cdot)$ , a zero-mean Gaussian process with covariance function  $S_i(s)S_i(t)V_i(s, t)$ , where

$$V_i(s, t) = \int_0^s \frac{m_i^2(u)}{y_i^2(u)} dH_i(u) + \int_0^s \int_0^t \frac{\alpha_i(u, v)}{y_i(u)y_i(v)} dH_i(u)dH_i(v), \quad 0 \leq s \leq t \leq \tau_i. \quad (2.1)$$

For future reference  $V_i(t) \equiv V_i(t, t)$ , the limiting variance function, which is given by

$$V_i(t) = S_i^2(t) \left[ \int_0^t \frac{m_i(s)}{y_i(s)} d\Lambda_i(s) + \int_0^t \int_0^t \frac{\alpha_i(u, v)}{y_i(u)y_i(v)} dH_i(u)dH_i(v) \right]. \quad (2.2)$$

When the model for  $m_i(t)$  is correctly chosen,  $\hat{S}_i(t)$  attains semiparametric efficiency and is asymptotically as or more efficient than  $\tilde{S}_i(t)$  the KM estimator [Dikta, (2014), (1998)] given by

$$\tilde{V}_i(t) = \tilde{S}_i^2(t) \int_0^t \frac{1}{y_i(s)} d\Lambda_i(s). \quad (2.3)$$

### 2.3 The PWY Approach

Let  $\nu(t) \equiv \tilde{V}_1(t) + \tilde{V}_2(t)$ , where  $\tilde{V}_i(t), i = 1, 2$ , are given by Eq. (2.3). Note that each  $\tilde{V}_i(t), i = 1, 2$ , can be estimated from Eq. (2.3) using  $\tilde{S}_i(t)$ , the KM estimator, and the

Greenwood formula. Suppose that  $\hat{\nu}(t)$  converges in probability to  $\nu(t)$ , uniformly for  $t \in [t_1, t_2]$ . Here,  $[t_1, t_2]$  is the region over which the SCB for  $D = S_1 - S_2$  is desired. The PWY SCB for  $\alpha(t), t \in [t_1, t_2]$ , is based on the asymptotic representation for

$$\mathbb{V}(t) = \left( \frac{n}{\hat{\nu}(t)} \right)^{1/2} \left\{ \left( \tilde{S}_1(t) - S_1(t) \right) - \left( \tilde{S}_2(t) - S_2(t) \right) \right\},$$

where  $t \in [t_1, t_2]$  and  $n = n_1 + n_2$ . The martingale,  $\tilde{M}_{ij}(t)$ , associated with  $\tilde{N}_{ij}(t) = I(Z_{ij} \leq t, \delta_{ij} = 1)$  is given by

$$\tilde{M}_{ij}(t) = I(Z_{ij} \leq t, \delta_{ij} = 1) - \int_0^t Y_{ij}(s) d\Lambda_i(s), \quad (2.4)$$

where  $Y_{ij}(t) = I(Z_{ij} \geq t)$ . Writing  $\tilde{M}_i(t) = \sum_{j=1}^{n_i} \tilde{M}_{ij}(t)$ , it is well known [see, for example, Fleming and Harrington (2005)] that each group-specific KM process  $n^{1/2}(\tilde{S}_i(t) - S_i(t))$  is asymptotically equivalent to

$$U_i(t) = -n^{1/2} \tilde{S}_i(t) \sum_{j=1}^{n_i} \int_0^t Y_{i.}^{-1}(s) d\tilde{M}_i(s). \quad (2.5)$$

Now generate independent standard normal random deviates  $G_{ij}$ , and replace  $\tilde{S}_i, Z_{ij}$ , and  $\delta_{ij}$  in Eq. (2.5) with their respective observed values  $\tilde{s}_i, z_{ij}$  and  $d_{ij}$ , also replacing  $\tilde{M}_{ij}(s)$  in Eq. (2.5) with  $G_{ij}I(z_{ij} \leq s)\delta_{ij}$ , to obtain

$$\tilde{U}_i^{(l)}(t) = -n^{1/2} \tilde{s}_i(t) \sum_{j=1}^{n_i} \left[ \left\{ \sum_{k=1}^{n_i} I(z_{ik} \geq z_{ij}) \right\}^{-1} I(x_{ij} \leq t) d_{ij} G_{ij} \right], l = 1, \dots, B.$$

The distribution of  $\mathbb{V}(t)$  over  $[t_1, t_2]$  is approximated by the distribution of values

$$\tilde{\mathbb{V}}^{(l)}(t) = (\tilde{\nu}(t))^{-1/2} \{ \tilde{U}_1^{(l)}(t) - \tilde{U}_2^{(l)}(t) \}, \quad l = 1, \dots, B,$$

where  $\tilde{\nu}(t)$  is the observed value of  $\hat{\nu}(t)$ . Consequently, the distribution of  $\sup_{t \in [t_1, t_2]} |\mathbb{V}(t)|$  is approximated by the distribution of values  $\{W^{(l)}, l = 1, \dots, B\}$ , where  $W_l = \sup_{t \in [t_1, t_2]} |\tilde{\mathbb{V}}^{(l)}(t)|$ . The PWY 100(1 -  $\alpha$ )% SCB for  $\alpha(t)$  is then given by

$$\left\{ \tilde{s}_1(t) - \tilde{s}_2(t) \mp c(\alpha) \left( \frac{\tilde{\nu}(t)}{n} \right)^{1/2}, \quad t \in [t_1, t_2] \right\}, \quad (2.6)$$

where  $c(\alpha)$  is the  $100(1 - \alpha)B$ -th ordered value of the sequence  $\{W^{(l)}, l = 1, \dots, B\}$ . For example, when  $\alpha = 0.95$  and  $B = 1000$ , simply use the 950-th ordered  $W^{(l)}$  value for  $c(\alpha)$ .

## 2.4 The Censored Data and Two-Stage Bootstrap

The standard bootstrap KM estimator is computed using data obtained by drawing at random and with replacement from  $\{(Z_{ij}, \delta_{ij}), j = 1, \dots, n_i\}$  (Efron, 1981). Akritas (1986), Lo and Singh (1986) and Horváth and Yandell (1987) provided asymptotic justification for  $\tilde{S}_i^*(\cdot)$ , the bootstrapped KM estimator. Akritas proved that, for almost all sample sequences  $\{(Z_{ij}, \delta_{ij}), j = 1, \dots, n_i\}$ , the process  $n_i^{1/2}(\tilde{S}_i^*(\cdot) - \tilde{S}_i(\cdot))$  has a limit distribution that coincides with that of  $n_i^{1/2}(\tilde{S}_i(\cdot) - S_i(\cdot))$ . The bootstrap SRCMs-based survival function estimator, however, is obtained by the following two-stage resampling scheme, introduced by Subramanian and Zhang (2013):

1. Generate  $Z_{ij}^*$ ,  $j = 1, \dots, n_i$  from  $\hat{H}_i(t)$ , the empirical distribution function based on  $\{Z_{ij}, j = 1, \dots, n_i\}$ .
2. Generate the censoring indicator  $\delta_{ij}^*$ ,  $j = 1, \dots, n_i$  from a Bernoulli distribution having success probability  $m(Z_{ij}^*, \hat{\theta}_i)$ .

Subramanian and Zhang (2013) provided asymptotic justification for the bootstrap SRCMs estimator,  $\hat{S}_i^*(t)$ , computed using data generated from the two-stage bootstrap. It follows that the distribution of

$$\tilde{W}(\cdot) = n^{1/2}\{(\tilde{S}_1(\cdot) - \tilde{S}_2(\cdot)) - (S_1(\cdot) - S_2(\cdot))\}$$

and

$$\hat{W}(\cdot) = n^{1/2}\{(\hat{S}_1(\cdot) - \hat{S}_2(\cdot)) - (S_1(\cdot) - S_2(\cdot))\}$$

can be approximated by

$$\tilde{W}^*(\cdot) = n^{1/2}\{(\tilde{S}_1^*(\cdot) - \tilde{S}_2^*(\cdot)) - (\tilde{S}_1(\cdot) - \tilde{S}_2(\cdot))\}.$$

and

$$\hat{W}^*(\cdot) = n^{1/2}\{(\hat{S}_1^*(\cdot) - \hat{S}_2^*(\cdot)) - (\hat{S}_1(\cdot) - \hat{S}_2(\cdot))\},$$

respectively.

In the next chapter, we will develop the new SCBs that utilize the critical values obtained via the two bootstraps. We also present simulation studies and real example illustrations which showcase the efficiency of the new SCBs.

## CHAPTER 3

### PROPOSED BOOTSTRAP BASED APPROACHES

A  $100(1 - \alpha)\%$  “linear” SCB for  $\alpha(t) = S_1(t) - S_2(t)$  over  $[t_1, t_2] \subset [0, \tau]$  is given by

$$\left[ \tilde{\alpha}(t) - n^{-1/2}q_\alpha, \hat{\alpha}(t) + n^{-1/2}q_\alpha \right], \quad (3.1)$$

or

$$\left[ \hat{\alpha}(t) - n^{-1/2}q_\alpha, \hat{\alpha}(t) + n^{-1/2}q_\alpha \right], \quad (3.2)$$

where  $q_\alpha$  is the upper  $\alpha \in [0, 1]$  quantile of the distribution of  $\sup_{t \in [t_1, t_2]} |\tilde{W}^*(t)|$  or  $\sup_{t \in [t_1, t_2]} |\hat{W}^*(t)|$ . Alternatively, with  $\tilde{\nu}(t)$  or  $\hat{\nu}(t)$  denoting a consistent estimator of  $\nu(t) = \tilde{V}_1(t) + \tilde{V}_2(t)$  or  $\nu(t) = V_1(t) + V_2(t)$ , see Eqs. (2.3) and (2.2), respectively, a  $100(1 - \alpha)\%$  variable-width SCB for  $\alpha(t)$  is given by

$$\left[ \tilde{\alpha}(t) - q_\alpha (\tilde{\nu}(t)/n)^{1/2}, \hat{\alpha}(t) + q_\alpha (\tilde{\nu}(t)/n)^{1/2} \right], \quad (3.3)$$

or

$$\left[ \hat{\alpha}(t) - q_\alpha (\hat{\nu}(t)/n)^{1/2}, \hat{\alpha}(t) + q_\alpha (\hat{\nu}(t)/n)^{1/2} \right], \quad (3.4)$$

where now  $q_\alpha$  is the upper  $\alpha$ -quantile of the distribution of  $\sup_{t \in [t_1, t_2]} \left| \tilde{W}^*(t) / \sqrt{\tilde{\nu}(t)} \right|$  or  $\sup_{t \in [t_1, t_2]} \left| \hat{W}^*(t) / \sqrt{\hat{\nu}(t)} \right|$ . In our simulations, we have taken  $\tilde{\nu}(t)$  or  $\hat{\nu}(t)$  to be the estimated variance of  $\tilde{\alpha}(t) = \tilde{S}_1(t) - \tilde{S}_2(t)$  or  $\hat{\alpha}(t) = \hat{S}_1(t) - \hat{S}_2(t)$ . Thus, the “linear” and variable-width SCBs can be either nonparametric or semiparametric depending on whether  $S_i(t)$  is the KM or SRCMs estimator.

### 3.1 Simulation Studies

For each of the two simulation studies presented here, the survival curve was estimated 2,000 times for each group. Each replication was based on sample size 100 and the critical values, extracted as percentiles of the bootstrap distributions, were based on 1,000 bootstrap resamples. Thus, each method was examined for efficacy through 2,000 SCBs for the true difference  $\alpha(t) = S_2(t) - S_1(t)$ .

The empirical coverage probabilities (ECPs) of the competing SCBs were first evaluated to examine whether they were close to the nominal 95%. The ECP for a method is the proportion of the 2,000 SCBs that included, for that method,  $\alpha(t)$  for all  $t \in [t_1, t_2]$ . A method providing poor ECP was eliminated from further comparisons with other competing methods. The second stage of comparison between methods providing approximately correct ECPs was based on the estimated average enclosed area (EA EA), which is the average of the areas enclosed by the 2,000 SCBs; the area enclosed by an SCB is computed by summing the products of the width of the SCB at each point of jump of  $\hat{\alpha}(t) = \hat{S}_2(t) - \hat{S}_1(t)$  and the distance between points of jump. Comparisons were carried out between the two proposed methods and that of PWY.

#### 3.1.1 First Simulation Study

The  $i$ -th group failure time was Weibull, with  $F_i(x) = 1 - \exp(-(a_i x)^2)$ ,  $i = 1, 2$ . The censoring distribution was exponential with mean 1. Then

$$m_i(x, a_i) = 2a_i^2 x / (1 + 2a_i^2 x), \quad i = 1, 2. \quad (3.5)$$

Both the logistic and Cauchy models were fitted to the binary response data, given by

$$m_i^{\text{logistic}}(x, \boldsymbol{\theta}_i) = \frac{e^{\theta_{i0} + \theta_{i1}x}}{1 + e^{\theta_{i1} + \theta_{i2}x}}, \quad (3.6)$$

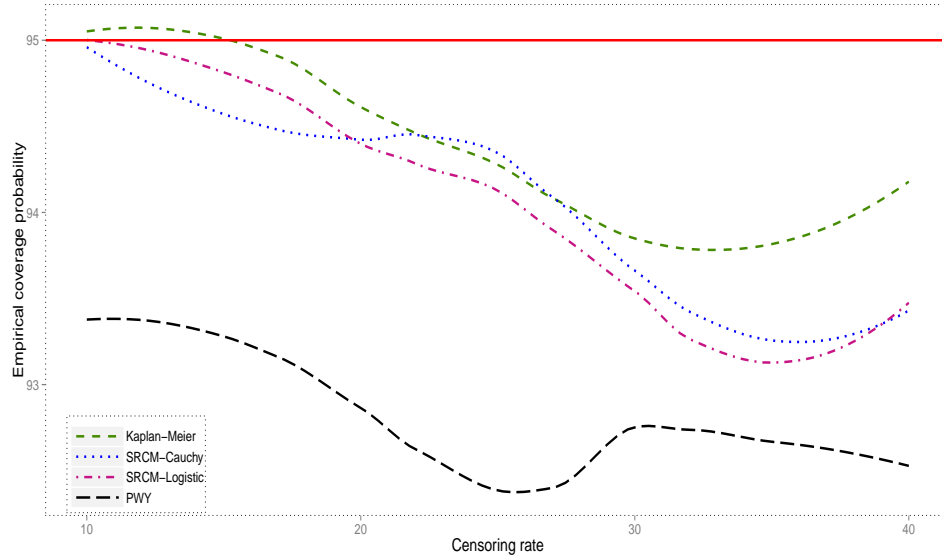
$$m_i^{\text{Cauchy}}(x, \boldsymbol{\theta}_i) = \frac{1}{\pi} \arctan(\theta_{i0} + \theta_{i1}x) + \frac{1}{2}. \quad (3.7)$$

The censoring rate (CR), expressed as a function of the parameter  $a_i$ , is given by

$$C_i(a_i) = \frac{\pi^{1/2}}{\alpha_i} \exp\left(\frac{1}{4a_i^2}\right) \left\{1 - \Phi\left(\frac{1}{2^{1/2}a_i}\right)\right\}, \quad i = 1, 2, \quad (3.8)$$

where  $\Phi(x)$  denotes the standard normal cumulative distribution function. The simulations were run for a number of values of the censoring rate (CR), ranging between 10% ( $a_i = 8.3$ ) and 40% ( $a_i = 1.6$ ). For each CR value, the ECPs of the competing SCBs and the percent relative reduction in EAEA of the proposed semiparametric SCBs over the proposed nonparametric counterpart were computed.

The ECPs of the “linear” SCBs, computed using proposed Eqs. (3.1) and (3.2) and Eq. (2.6) [PWY], are presented in Figure 3.1. The “linear” SCBs of PWY, shown in black dashed lines, give relatively poor ECPs for all the CRs investigated. The proposed nonparametric and semiparametric SCBs performed better, giving coverage closer to the nominal 95%.

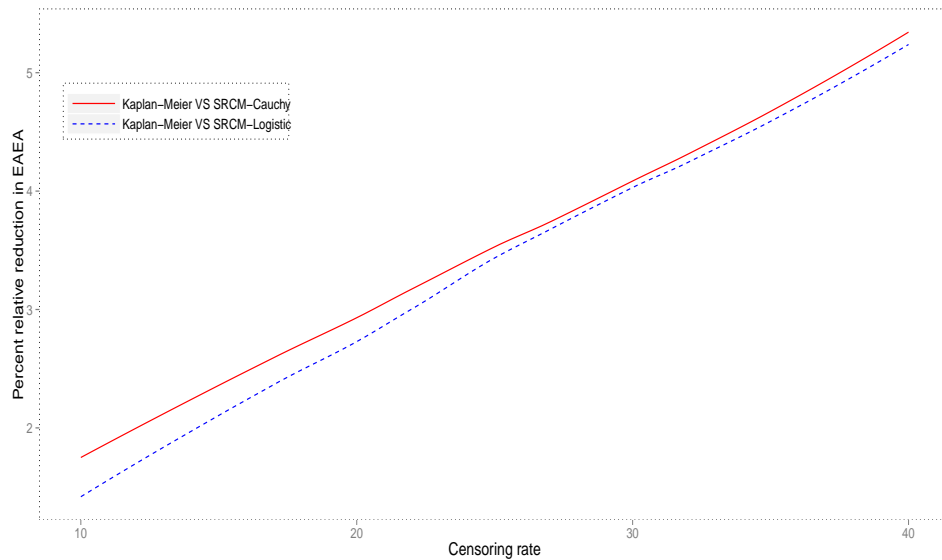


**Figure 3.1** Simulation 1 - Empirical Coverage Probabilities (ECPs) of the competing, 95% “linear” SCBs for various censoring rates (CRs)

Due to their relatively poor coverage, the SCBs of PWY were eliminated from further comparisons. The percent relative reduction in EAEA of the proposed



semiparametric SCBs over the proposed nonparametric ones are presented in Figure 3.2. The logistic and Cauchy based SCBs performed better than the KM based ones. The SCBs based on fitting a logistic model provided a relative reduction between 1.36% and 5.28% in EAEA. The SCBs based on fitting the Cauchy model gave a relative reduction between 1.69% and 5.38% in EAEA. The percent reduction increased with increasing CR.

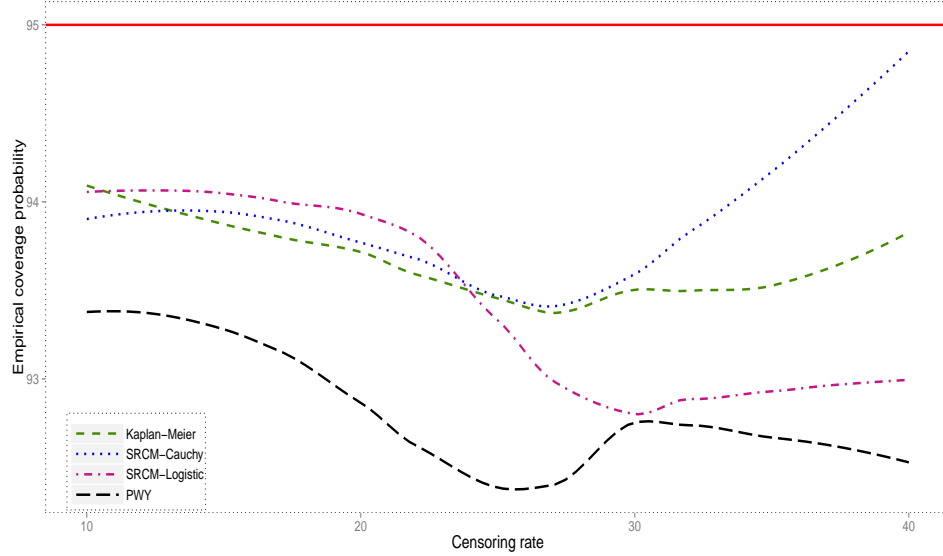


**Figure 3.2** Simulation 1 - Percent relative reduction in EAEA of the proposed 95% “linear” semiparametric over nonparametric SCBs for various censoring rates (CRs)

Next, the competing variable-width SCBs were computed using proposed Eqs. (3.3) and (3.4) and Eq. (2.6) of PWY. The ECPs presented in Figure 3.3 again show that the proposed SCBs provide better coverage than PWY, with the SCBs based on fitting the Cauchy model giving overall best coverage.

As in the “linear” case, the logistic and Cauchy fitted variable-width SCBs performed better than the KM based ones. The percent relative reduction in EAEAs of the proposed semiparametric over the KM based variable-width SCBs are shown in Figure 3.4. Note that for CRs above 25% the logistic fitted SCBs produced poorer coverage, so their EAEA values for higher CRs are not indicative of better

performance. Factoring this into the assessment one may conclude that the proposed variable-width semiparametric SCBs provide a relative reduction in EAEA amounting to about as high as 3% over the proposed nonparametric KM based counterpart.



**Figure 3.3** Simulation 1 - Empirical Coverage Probabilities (ECPs) of the competing, 95% variable-width, SCBs for various censoring rates (CRs)

### 3.1.2 Second Simulation Study

For the  $i$ -th group,  $i = 1, 2$ , the distribution of  $X_i = \min(T_i, C_i)$  was taken to be uniform over  $(0, 1)$ . The conditional expectation of  $\delta_i$  given  $X_i = x$  was taken as

$$m_i(x, \boldsymbol{\theta}_i) = \frac{\exp(\theta_{i1} + \theta_{i2}x)}{(c_i + \exp(\theta_{i1} + \theta_{i2}x))}, \quad i = 1, 2.$$

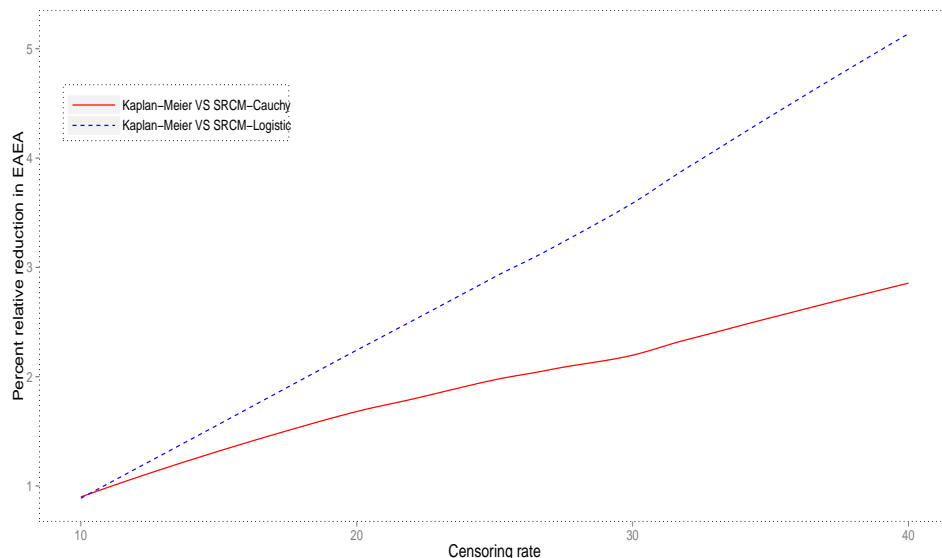
The  $i$ -th group failure time distribution, useful for computing the ECP, is then given by the equation  $1 - F_i(t) = e^{-\Lambda_i(t)}$ , where the group-specific cumulative hazard is given by

$$\Lambda_i(t) = \int_0^t \frac{e^{\theta_{i1} + \theta_{i2}x}}{(c_i + e^{\theta_{i1} + \theta_{i2}x})(1 - x)} dx, \quad i = 1, 2.$$

For the  $i$ -th group, the CR, expressed as a function of the parameter  $c_i$ , is given by

$$\text{CR}_i = \int_0^1 \frac{c_i}{c_i + \exp(\theta_{i1} + \theta_{i2}x)} dx, \quad i = 1, 2.$$

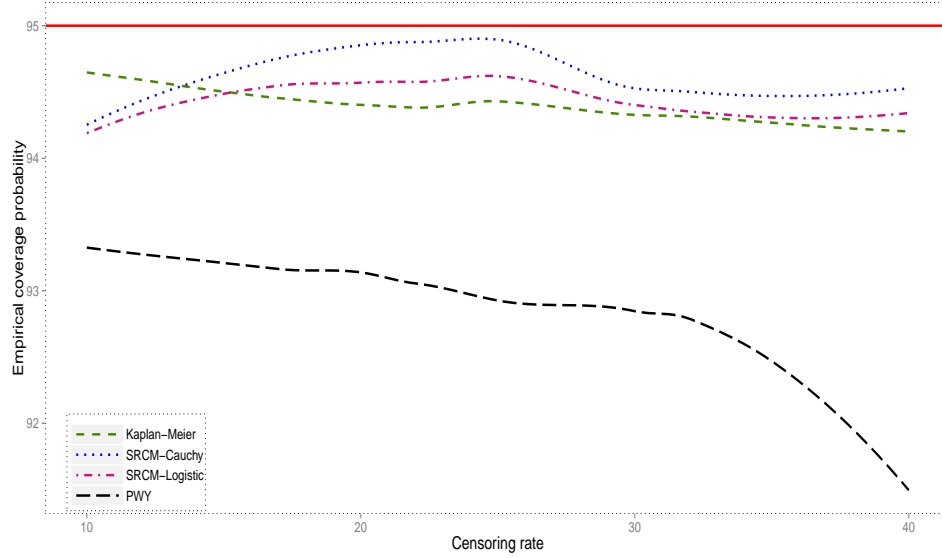
The group-specific model parameters  $\theta_{i1}$  and  $\theta_{i2}$  were each set to 1 and 2, respectively. The simulations were run for various CRs between 10% ( $c_i = 0.72$ ) and 40% ( $c_i = 4.8$ ). As before, both the logistic and the Cauchy models were fitted to the binary response data. For each CR, the ECPs of the competing SCBs and the percent relative reduction in EAEA of the proposed semiparametric SCBs over the proposed nonparametric counterparts were computed.



**Figure 3.4** Simulation 1 - Percent relative reduction in EAEA of the proposed 95% variable-width semiparametric over nonparametric SCBs for various censoring rates (CRs)

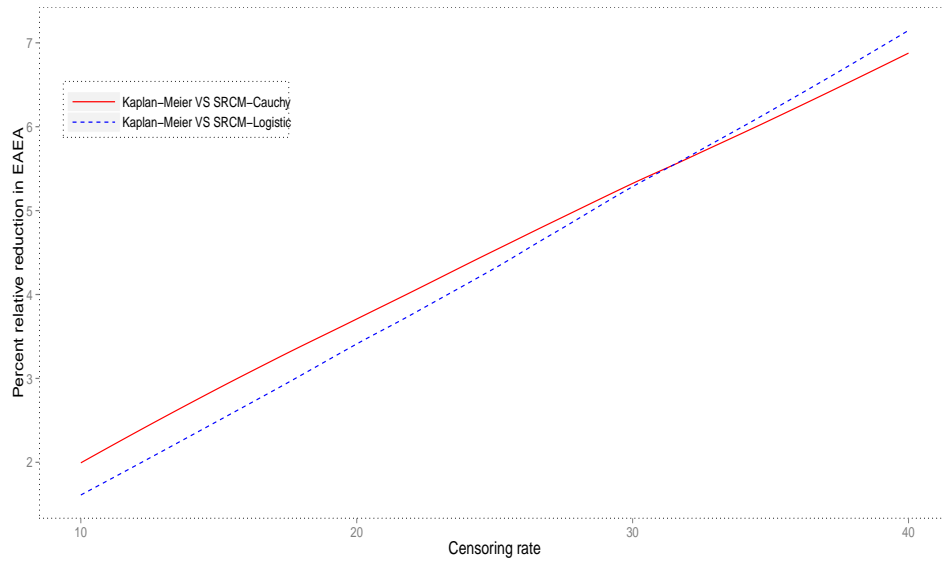
Figure 3.5 shows the ECPs of the proposed “linear” SCBs computed using Eqs. (3.1) and (3.2) and the SCBs of PWY computed using Eq. (2.6). For all CRs, the proposed “linear” SCBs provided superior ECPs than the SCBs of PWY (which are shown in purple dashed-dotted lines). The empirical coverages for the SCBs of PWY are below 94% for all CRs and drop to as low as 92.5% when CRs approach 40%. The

proposed nonparametric and semiparametric SCBs performed better, giving coverage closer to the nominal 95%.



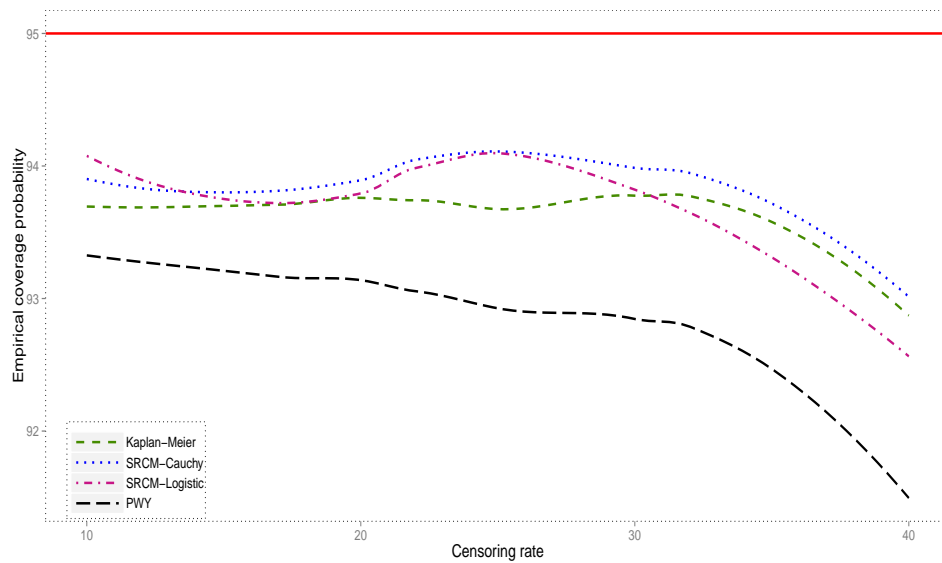
**Figure 3.5** Simulation 2 - Empirical Coverage Probabilities (ECPs) of the competing, 95% “linear”, SCBs for various censoring rates (CRs)

Further comparisons with the SCBs of PWY are eliminated since their empirical coverage were poorer than the proposed. The percent relative reduction in EAEA of the proposed semiparametric SCBs over the proposed nonparametric ones are presented in Figure 3.6. For CRs between 10% and 40%, the SCBs based on fitting the logistic model provided a relative reduction between 1.62% and 7.18% in EAEA over the nonparametric SCBs, while the SCBs based on fitting the Cauchy model provided a relative reduction between 1.96% and 6.90% in EAEA over the nonparametric SCBs.



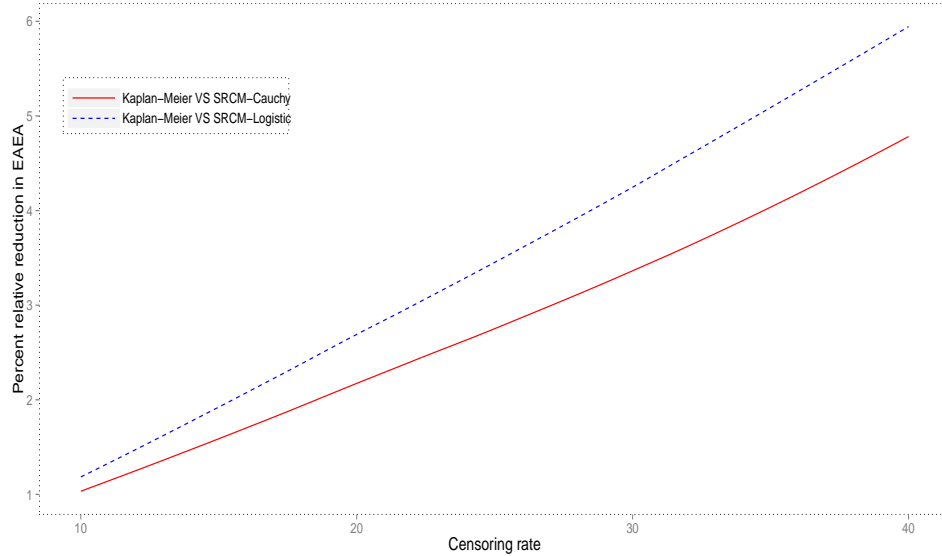
**Figure 3.6** Simulation 2 - Percent relative reduction in EAEA of the proposed 95% “linear” semiparametric over nonparametric SCBs for various censoring rates (CRs)

Next, in Figure 3.7, the ECPs of the proposed variable-width SCBs using Eqs. (3.3) and (3.4) and PWY’s Eq. (2.6) are presented. These figures show that the proposed SCBs provide better coverage than the ones developed by PWY.



**Figure 3.7** Simulation 2 - Empirical Coverage Probabilities (ECPs) of the competing, 95% variable-width, SCBs for various censoring rates (CRs)

Figure 3.8 presents the percent relative reduction in EAEA of the proposed semiparametric SCBs over the proposed nonparametric ones. The SCBs based on fitting the logistic model provided a relative reduction between 1.20% and 5.90% in EAEA. The SCBs based on fitting the Cauchy model provided a relative reduction between 1.10% and 4.75% in EAEA.



**Figure 3.8** Simulation 2 - Percent relative reduction in EAEA of the proposed 95% variable-width semiparametric over nonparametric SCBs for various censoring rates (CRs)

In summary, the proposed “linear” and variable-width SCBs provided superior empirical coverage compared to the SCBs of PWY. In terms of EAEAs, for both “linear” and variable-width SCBs, the proposed SRCMs-based SCBs performed better than the RCM, that is KM-based, SCBs. Compared to the proposed KM-based SCBs, there was up to 7% relative reduction in EAEA for SRCMs-based SCBs.

### 3.2 Real Data Analysis

In this Section, the new SCBs are constructed for two real data sets and compared with the SCBs of PWY. Through the real data examples, it is demonstrated that the proposed methods produce SCBs that are, at the very least, as informative as

the Wald-Type bands of PWY. When the sample size is small and the CR is high, however, the proposed SCBs are shown to be clearly superior than that of PWY. The first two publicly available real data sets were obtained from Klein and Moeschberger (2005). The first data set is from a HIV infection study, the second data set is from a bone marrow transplantation study.

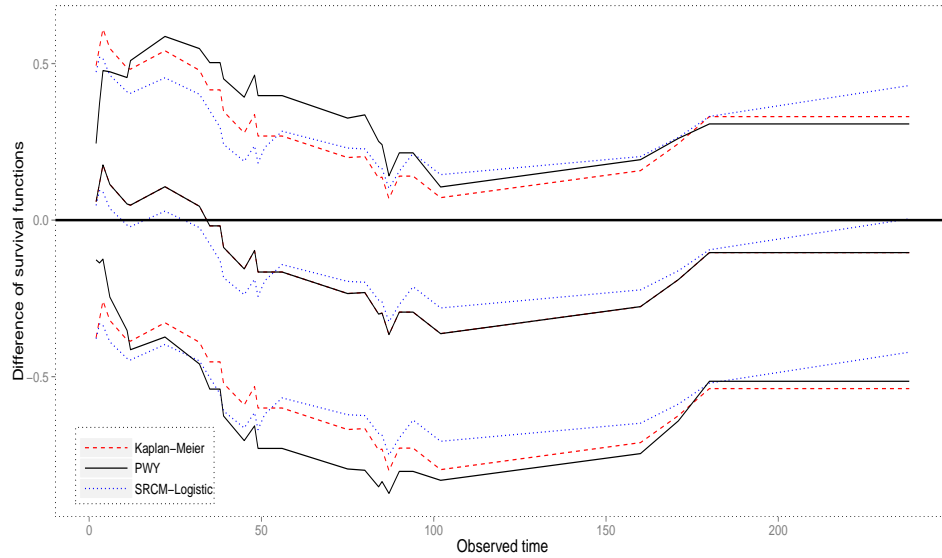
### 3.2.1 Analysis of HIV Infection Data

**Table 3.1** HIV Infection Data: Testing Adequacy of the Logistic and Cauchy Models

Model	Parameter estimates		KS statistic		CvM statistic	
	$\theta_0$	$\theta_1$	Estimate	p-value	Estimate	p-value
Treatment						
Logistic	2.168	-0.010	0.276	0.175	0.023	0.085
Cauchy	4.378	-0.029	0.344	0.058	0.044	0.024
Control						
Logistic	1.367	-0.002	0.303	0.127	0.017	0.231
Cauchy	1.255	-0.002	0.316	0.106	0.018	0.225

The dataset consisted information on 34 HIV-infected patients, with 17 patients receiving AZT zalcitabine and the 17 remaining patients receiving AZT zalcitabine saquinavir. An overall 22% censoring rate was present in the data. One goal of this study was to explore the efficacy of triple-drug combinations of antiretroviral therapy for treatment of HIV-infected patients. The SCBs were calculated over the interval [2, 238] days, representing time from administration of treatment until the CD4 count. We formally tested the adequacy of our parametric specifications [logistic given by Eq. (3.6) and Cauchy given by Eq. (3.7)] via a model-based resampling procedure (Dikta et al., 2006). We computed the Kolmogorov–Smirnov (KS) and Cramér von Mises (CvM) statistics from the observed data and then computed their bootstrap versions 3,000 times. The test rejects the null hypothesis of no model misspecification

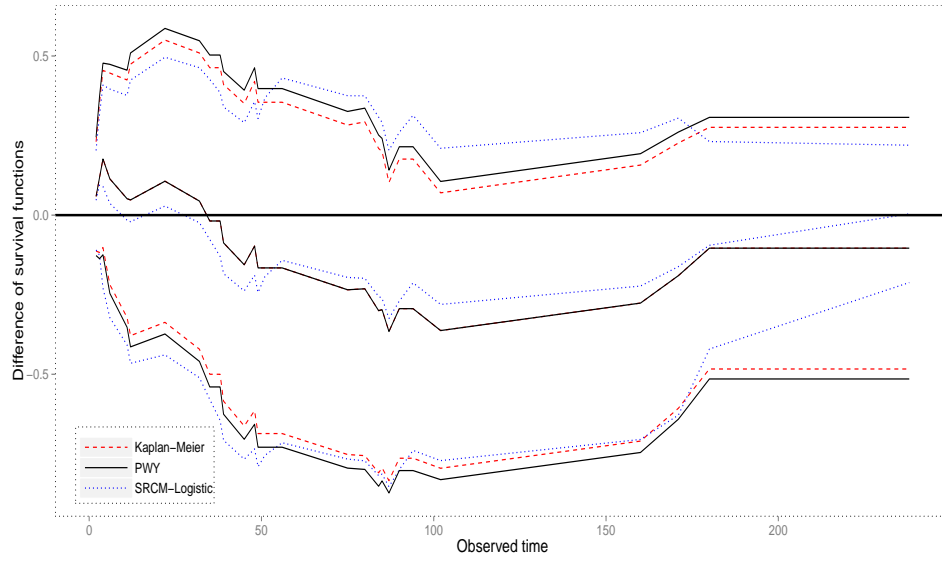
when the proportion of 3,000 bootstrap values exceeding the test statistics fell below the 5% threshold. We present the results of our analysis in Table 3.1. There is indication that the logistic model may be a better fit over the Cauchy model.



**Figure 3.9** Proposed and PWY “linear” SCBs in HIV infection study

Figures 3.9 and 3.10 show the proposed and PWY’s SCBs’s, consisting of both the “linear” and variable-width types. Note that the SCBs contain the zero horizontal line, indicating that there is no difference between the two treatments over time. As seen in Table 3.3, there are differences between the proposed and PWY SCBs in terms of the enclosed area of the bands. Compared to PWY, for “linear” SCBs, relative reduction in enclosed area was about 8% to 12%. Similarly, for variable-width SCBs, relative reduction in enclosed area was approximately 4% to 11%. This suggests that the proposed SCBs are at least as or more informative than the SCBs of PWY.





**Figure 3.10** Proposed and PWY variable-width SCBs in HIV infection study

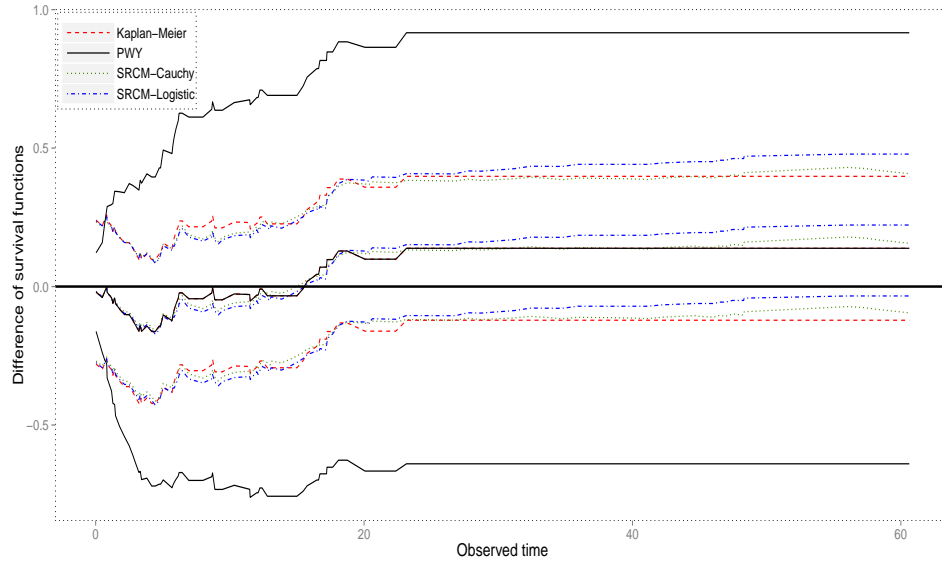
### 3.2.2 Analysis of Bone Marrow Transplantation Data

**Table 3.2** Bone Marrow Transplantation Data: Testing Adequacy of the Logistic and Cauchy Models

Model	Parameter estimates		KS statistic		CvM statistic	
	$\theta_0$	$\theta_1$	Estimate	p-value	Estimate	p-value
Allogeneic Bone Marrow Transplant						
Logistic	2.581	-0.235	0.221	0.243	0.006	0.287
Cauchy	2.809	-0.265	0.265	0.067	0.010	0.491
Autogeneic Bone Marrow Transplant						
Logistic	1.719	-0.096	0.331	0.229	0.025	0.121
Cauchy	2.234	-0.144	0.232	0.578	0.012	0.438

This study provided data on 101 patients with advanced acute myelogenous leukemia. Out of the 101 patients, 51 received an autologous bone marrow transplant and the remaining 50 patients received allogeneic bone marrow transplant. The overall censoring rate was 50%. An important objective in bone marrow transplantation

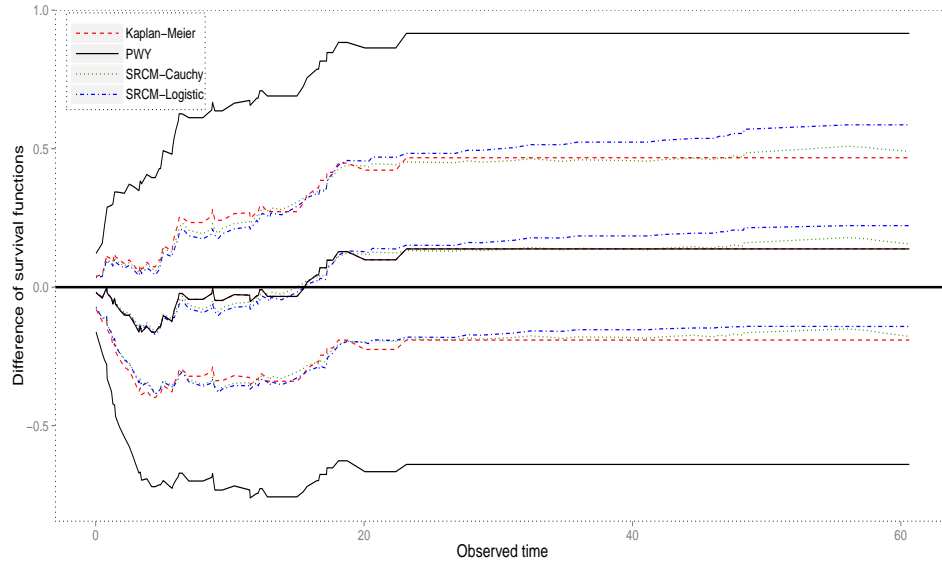
is to compare the effectiveness of the treatment methods. We formally tested the adequacy of our parametric specifications [logistic given by Eq. (3.6) and Cauchy given by Eq. (3.7)]. We computed the Kolmogorov–Smirnov (KS) and Cramér von Mises (CvM) statistics from the observed data and then computed their bootstrap versions 3,000 times. We present the results of our analysis in Table 3.2. There is strong indication that both the logistic and Cauchy models are adequate.



**Figure 3.11** Proposed and PWY “linear” SCBs in bone marrow transplants study

The SCBs were calculated over the interval  $[0.030, 60.625]$  months. Figures 3.11 and 3.12 show the proposed and PWY’s SCBs, consisting of both “linear” and variable-width types. The SRCMs-based estimator for the difference of two survival functions shows good agreement with KM-based estimator of the difference. Note that the SCBs contain the 0 horizontal line, indicating difference being 0, that there is no difference between the two treatments. The SCBs of PWY, shown in black solid line, are substantially wider than the proposed nonparametric and semiparametric SCBs. As seen in Table 3.3, compared to PWY, for “linear” SCBs, relative reduction in enclosed area was about 43% to 45%. Similarly, for variable-width SCBs, relative reduction in enclosed area was approximately 58% to 62%. Thus, it may be deduced

that the proposed SCBs are more informative over the time interval. In comparison to the data on HIV infection study (CR = 22%), the censoring rate was more than double for the bone marrow transplantation study (CR = 50%). This suggests that the proposed SCBs may be better indicators of treatment effect for data with small sample size and high censoring rate.



**Figure 3.12** Proposed and PWY variable-width SCBs in bone marrow transplants study

**Table 3.3** Percent Relative Reduction in Enclosed Area

SCB Type	PWY vs. KM	PWY vs. SRCM-Cauchy	PWY vs. SRCM-Logistic
HIV Infection Data			
Linear	8.2633	—	12.1720
Variable-width	11.4190	—	4.1528
Bone Marrow Transplantation Data			
Linear	42.8435	44.7315	43.6532
Variable-width	57.6979	61.1874	61.9301

## CHAPTER 4

### PROPOSED EMPIRICAL LIKELIHOOD BASED SCBS

As stated before in Chapter 2, we shall consider the standard two-sample setting with independent right censoring. Specifically, there are two samples of independent and identically distributed observations

$$\{(Z_{ij}, \delta_{ij}), j = 1, \dots, n_i, i = 1, 2\},$$

where  $Z_{ij} = \min(X_{ij}, C_{ij})$ ,  $\delta_{ij} = I(X_{ij} \leq C_{ij})$ . The distribution functions of  $X_{ij}$  and  $C_{ij}$ , the failure and censoring times, are  $F_i = 1 - S_i$  and  $G_i$ , respectively,  $j = 1, \dots, n_i, i = 1, 2$ .

#### 4.1 Asymptotic Representation of $\hat{\mathbb{H}}_i(t)$

For facilitating the bootstrap that we will employ in Section 4.3, we develop here an asymptotic representation of  $\hat{\mathbb{H}}_i(t) = n_i^{1/2}(\hat{\Lambda}_i(t) - \Lambda_i(t))$  using martingale theory, not available in Dikta (1998). Let  $N_{ij}(t) = I(Z_{ij} \leq t)$ . Note from Mondal and Subramanian (2014) that

$$M_{ij}(t) = N_{ij}(t) - \int_0^t \frac{Y_{ij}(u)}{m_i(u, \boldsymbol{\theta}_{i0})} d\Lambda_i(u) \quad (4.1)$$

is a martingale. The predictable covariation process is given by

$$\langle M_{ij}, M_{ij} \rangle (t) = \int_0^t \frac{Y_{ij}(u)}{m_i(u, \boldsymbol{\theta}_{i0})} d\Lambda_i(u). \quad (4.2)$$

We show that  $\hat{\mathbb{H}}_i(t) = L_{n_i,1}(t) + L_{n_i,2}(t) + o_p(1)$ , uniformly for  $t \in [0, \tau_i]$ , where

$$L_{n_i,1}(t) = n_i^{-1/2} \sum_{j=1}^{n_i} \int_0^t \frac{m_i(s, \boldsymbol{\theta}_{i0})}{y_i(s)} dM_{ij}(s), \quad (4.3)$$

$$L_{n_i,2}(t) = n_i^{-1/2} \sum_{j=1}^{n_i} \frac{\delta_{ij} - m_i(Z_{ij}, \boldsymbol{\theta}_{i0})}{m_i(Z_{ij}, \boldsymbol{\theta}_{i0})(1 - m_i(Z_{ij}, \boldsymbol{\theta}_{i0}))} \int_0^t \frac{\alpha_i(u, Z_{ij})}{y_i(u)} dH_i(u). \quad (4.4)$$

Write  $\hat{\Lambda}_i(t) = \hat{\Lambda}_i(t, \hat{\boldsymbol{\theta}}_i)$ . Taylor's expansion of  $\hat{\Lambda}_i(t)$  about  $\boldsymbol{\theta}_{i0}$  yields

$$\hat{\Lambda}_i(t) - \Lambda_i(t) = (\hat{\Lambda}_i(t, \boldsymbol{\theta}_{i0}) - \Lambda_i(t)) + \left\langle \text{Grad}_{\boldsymbol{\theta}_i}(\hat{\Lambda}_i(t, \boldsymbol{\theta}_i^*)), (\hat{\boldsymbol{\theta}}_i - \boldsymbol{\theta}_{i0}) \right\rangle, \quad (4.5)$$

where  $\boldsymbol{\theta}_i^*$  denotes a value on the line segment joining  $\hat{\boldsymbol{\theta}}_i$  and  $\boldsymbol{\theta}_{i0}$ . Let

$$\Lambda_i^*(t) = \int_0^t I(Y_{i\cdot}(s) > 0) d\Lambda_i(s), \quad i = 1, 2. \quad (4.6)$$

Using Eq. (4.1), the first term on the right hand side of Eq. (4.5) can be expressed as

$$\hat{\Lambda}_i(t, \boldsymbol{\theta}_{i0}) - \Lambda_i(t) = \sum_{j=1}^{n_i} \int_0^t \frac{I(Y_{i\cdot}(s) > 0) m_i(s, \boldsymbol{\theta}_{i0})}{Y_{i\cdot}(s)} dM_{ij}(s) + \Lambda_i^*(t) - \Lambda_i(t).$$

We show that  $\|\Lambda_i^* - \Lambda_i\|_0^{\tau_i} = o(n_i^{-1/2})$  almost surely, where  $\|\cdot\|_0^{\tau_i}$  is the sup-norm over  $[0, \tau_i]$ . By the Glivenko–Cantelli lemma, given  $\epsilon = y_i(\tau_i)/2 > 0$ , we can find  $n_{i0}(\epsilon)$  such that  $\bar{Y}_i(\tau_i) > \epsilon$  for all  $n_i \geq n_{i0}$  and all  $\omega \in \Omega \setminus \mathcal{N}$ , where  $P(\mathcal{N}) = 0$ . Since the indicator on the right hand side of Eq. (4.6) is nonincreasing, it equals one, uniformly over  $[0, \tau_i]$ , for  $n_i \geq n_{i0}$  and  $\omega \in \Omega \setminus \mathcal{N}$ .

Applying Lenglar's inequality (Fleming and Harrington, 2005) and then Eq. (4.2), it follows that  $n^{1/2}$  times the first term on the right hand side of Eq. (4.5) equals  $L_{n_i,1}(t) + o_p(1)$  uniformly for  $t \in [0, \tau_i]$ . From Dikta (1998),  $n^{1/2}$  times the second term on the right hand side of Eq. (4.5) equals  $L_{n_i,2}(t) + o_p(1)$  uniformly for  $t \in [0, \tau_i]$ . The first term of Eq. (2.1) is the covariance function of  $L_{n_i,1}(t)$ , as can be readily verified using Eq. (4.2). The second term of Eq. (2.1) is the covariance function of  $L_{n_i,2}(t)$ , see Dikta (1998). The covariance between  $L_{n_i,1}(s)$  and  $L_{n_i,2}(t)$  is zero.

## 4.2 Semiparametric Likelihood Ratio Estimation

Let  $\Delta$  denote the space of all survival functions on  $[0, \infty)$  supported by the uncensored survival times. For  $K_1 \in \Delta$  and  $K_2 \in \Delta$ , the nonparametric likelihood for the

two-sample censored data problem (McKeague and Zhao, 2005) is given by

$$L_{\text{NP}}(K_1, K_2) = \prod_{i=1}^2 \prod_{j=1}^{n_i} [K_i(Z_{ij-}) - K_i(Z_{ij})]^{\delta_{ij}} [K_i(Z_{ij})]^{1-\delta_{ij}}. \quad (4.7)$$

The group-specific KM estimators,  $\tilde{S}_1$  and  $\tilde{S}_2$ , are the nonparametric maximum likelihood estimators, see p.15 and p.16 of Kalbfleisch and Prentice (2002). Since the two samples are independent, it follows that  $L_{\text{NP}}(\tilde{S}_1, \tilde{S}_2)$  is the maximum.

To derive the semiparametric EL ratio statistic, let  $\Gamma$  denote the space of survival functions on  $[0, \infty)$ , with corresponding cumulative hazards  $d\Lambda_i(t) = m(t, \boldsymbol{\theta}_{i0})dH_i(t)/y_i(t)$ , and supported by all the observed times. Write  $\bar{m}(\cdot, \boldsymbol{\theta}) = 1 - m(\cdot, \boldsymbol{\theta})$  and define, for,  $K_1 \in \Gamma, K_2 \in \Gamma$ ,

$$L_{\text{SP}}(K_1, K_2) = \prod_{i=1}^2 \prod_{j=1}^{n_i} [K_i(Z_{ij-}) - K_i(Z_{ij})]^{m_i(Z_{ij}, \hat{\boldsymbol{\theta}}_i)} [K_i(Z_{ij})]^{\bar{m}_i(Z_{ij}, \hat{\boldsymbol{\theta}}_i)} \quad (4.8)$$

which is a semiparametric adjustment of Eq. (4.7). Then,  $L_{\text{SP}}(\hat{S}_1, \hat{S}_2)$  is the maximum. To prove this assertion, let  $0 \leq T_{i1} < \dots < T_{i\kappa_i} < \infty$  denote the  $\kappa_i \leq n_i$  observed distinct uncensored or censored lifetimes and let  $d_{ij}$  denote the number of ‘‘outcomes’’ at  $T_{ij}, j = 1, \dots, \kappa_i$ , so that  $\sum_{j=1}^{\kappa_i} d_{ij} = n_i$ . Also, let  $r_{ij} = \sum_{k=j}^{\kappa_i} d_{ik}$  denote the number ‘‘at risk’’ just before  $T_{ij}$ . Finally, write  $m_{ij} = m(T_{ij}, \boldsymbol{\theta}_i)$ ,  $\hat{m}_{ij} = m(T_{ij}, \hat{\boldsymbol{\theta}}_i)$ , and  $\hat{\bar{m}}_{ij} = 1 - \hat{m}_{ij}$ . Then

$$L_{\text{SP}}(K_1, K_2) = \prod_{i=1}^2 \prod_{j=1}^{\kappa_i} [K_i(T_{ij-}) - K_i(T_{ij})]^{d_{ij}\hat{m}_{ij}} [K_i(T_{ij})]^{d_{ij}\hat{\bar{m}}_{ij}}.$$

Let  $P_{ij} = K_i(T_{ij})$  and write  $p_{ij} = P_{ij}/P_{i,j-1}$ . Note that  $P_{i0} = 1$ . We follow Subramanian (2012) to obtain in terms of the parameters  $\{p_{ij}, j = 1, \dots, \kappa_i, i = 1, 2\}$  that

$$L_{\text{SP}}(K_1, K_2) = \prod_{i=1}^2 \prod_{j=1}^{\kappa_i} (1 - p_{ij})^{d_{ij}\hat{m}_{ij}} p_{ij}^{r_{ij} - d_{ij}\hat{m}_{ij}}, \quad (4.9)$$

which, in turn, is maximized at

$$\hat{p}_{ij} = 1 - \frac{d_{ij}\hat{m}_{ij}}{r_{ij}}, \quad j = 1, \dots, \kappa_i, \quad i = 1, 2.$$

Since  $K_i(T_{ij}) \equiv P_{ij} = \prod_{l=1}^j (P_{il}/P_{i,l-1}) = \prod_{l=1}^j p_{il}$ , the assertion follows readily.

We next maximize Eq. (4.9) subject to  $\alpha(t) = \int_0^t \hat{S}_1(s) \log K_1(ds) - \int_0^t \hat{S}_2(s) \log K_2(ds)$ .

Let  $\tilde{\kappa}_i(t) = \sum_{j=1}^{n_i} I(Z_{ij} \leq t)$ . Following Thomas and Grunkemeier (1975), we find  $\tilde{p}_{ij}$ , the  $p_{ij}$  that maximize  $D = \log[L_{\text{SP}}(K_1, K_2)] + \lambda(t)\alpha(t)$ , where  $\lambda(t)$  is the Lagrange multiplier and

$$\alpha(t) = \sum_{j=1}^{\tilde{\kappa}_1(t)} \hat{S}_1(s) \log(p_{1j}) - \sum_{j=1}^{\tilde{\kappa}_2(t)} \hat{S}_2(s) \log(p_{2j}). \quad (4.10)$$

Using Eq. (4.9) and Eq. (4.10), we have

$$\begin{aligned} D &= \sum_{j=1}^{\tilde{\kappa}_1(t)} d_{1j}\hat{m}_{1j} \log(1 - p_{1j}) + (r_{1j} + \lambda\hat{S}_1(T_{1j}) - d_{1j}\hat{m}_{1j}) \log(p_{1j}) \\ &\quad + \sum_{j=1}^{\tilde{\kappa}_2(t)} d_{2j}\hat{m}_{2j} \log(1 - p_{2j}) + (r_{2j} - \lambda\hat{S}_2(T_{2j}) - d_{2j}\hat{m}_{2j}) \log(p_{2j}) \\ &\quad + \sum_{j=\tilde{\kappa}_1(t)+1}^{\kappa_1} d_{1j}\hat{m}_{1j} \log(1 - p_{1j}) + (r_{1j} - d_{1j}\hat{m}_{1j}) \log(p_{1j}) \\ &\quad + \sum_{j=\tilde{\kappa}_2(t)+1}^{\kappa_2} d_{2j}\hat{m}_{2j} \log(1 - p_{2j}) + (r_{2j} - d_{2j}\hat{m}_{2j}) \log(p_{2j}). \end{aligned}$$

Maximizing  $D$ , the constrained estimates  $\tilde{p}_{ij}$  and  $\hat{\lambda}(t) \equiv \hat{\lambda}$  satisfy the equations

$$\begin{aligned} \tilde{p}_{ij} &= 1 - \frac{d_{ij}\hat{m}_{ij}}{r_{ij} + (-1)^{i+1}\hat{\lambda}\hat{S}_i(T_{ij})}, \quad j = 1, \dots, \tilde{\kappa}_i(t), \quad i = 1, 2; \\ \tilde{p}_{ij} &= 1 - \frac{d_{ij}\hat{m}_{ij}}{r_{ij}}, \quad j = \tilde{\kappa}_i(t) + 1, \dots, \kappa_i, \quad i = 1, 2, \\ \alpha(t) &= \sum_{j=1}^{\tilde{\kappa}_1(t)} \log\left(1 - \frac{d_{1j}\hat{m}_{1j}}{r_{1j} + \hat{\lambda}\hat{S}_1(T_{1j})}\right) \hat{S}_1(T_{1j}) - \sum_{j=1}^{\tilde{\kappa}_2(t)} \log\left(1 - \frac{d_{2j}\hat{m}_{2j}}{r_{2j} - \hat{\lambda}\hat{S}_2(T_{2j})}\right) \hat{S}_2(T_{2j}). \quad (4.11) \end{aligned}$$

Plugging in the unconstrained and constrained estimates of  $p_{ij}$  into Eq. (4.9), we obtain

$$L_{\text{SP}}(\hat{S}_1, \hat{S}_2) = \prod_{i=1}^2 \prod_{j=1}^{\kappa_i} \left( \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right)^{d_{ij} \hat{m}_{ij}} \left( 1 - \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right)^{r_{ij} - d_{ij} \hat{m}_{ij}},$$

$$\begin{aligned} L_{\text{SP}}(\hat{S}_{1,C}, \hat{S}_{2,C}) &= \prod_{i=1}^2 \prod_{j=1}^{\tilde{\kappa}_i(t)} \left( \frac{d_{ij} \hat{m}_{ij}}{r_{ij} + (-1)^{i+1} \hat{\lambda} \hat{S}_1(T_{ij})} \right)^{d_{ij} \hat{m}_{ij}} \\ &\quad \left( 1 - \frac{d_{ij} \hat{m}_{ij}}{r_{ij} + (-1)^{i+1} \hat{\lambda} \hat{S}_1(T_{ij})} \right)^{r_{ij} - d_{ij} \hat{m}_{ij}} \\ &\quad \times \prod_{i=1}^2 \prod_{j=\tilde{\kappa}_i(t)+1}^{\kappa_i} \left( \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right)^{d_{ij} \hat{m}_{ij}} \left( 1 - \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right)^{r_{ij} - d_{ij} \hat{m}_{ij}}. \end{aligned}$$

The modified EL test statistic is given by  $R(t) := \log(L_{\text{SP}}(\hat{S}_{1,C}, \hat{S}_{2,C})) - \log(L_{\text{SP}}(\hat{S}_1, \hat{S}_2))$ . Then, suppressing the dependence on  $t$ , we can write  $R = \tilde{R}_1 + \tilde{R}_2 + \tilde{R}_3 + \tilde{R}_4$ , where

$$\begin{aligned} \tilde{R}_1 &= \sum_{j=1}^{\tilde{\kappa}_1(t)} d_{1j} \hat{m}_{1j} \log \left( \frac{d_{1j} \hat{m}_{1j}}{r_{1j} + \hat{\lambda} \hat{S}_1(T_{1j})} \right) - \sum_{j=1}^{\tilde{\kappa}_1(t)} d_{1j} \hat{m}_{1j} \log \left( \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right), \\ \tilde{R}_2 &= \sum_{j=1}^{\tilde{\kappa}_1(t)} (r_{1j} - d_{1j} \hat{m}_{1j}) \log \left( 1 - \frac{d_{1j} \hat{m}_{1j}}{r_{1j} + \hat{\lambda} \hat{S}_1(T_{1j})} \right) \\ &\quad - \sum_{j=1}^{\tilde{\kappa}_1(t)} (r_{1j} - d_{1j} \hat{m}_{1j}) \log \left( 1 - \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right), \\ \tilde{R}_3 &= \sum_{j=1}^{\tilde{\kappa}_2(t)} d_{2j} \hat{m}_{2j} \log \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j} - \hat{\lambda} \hat{S}_2(T_{2j})} \right) - \sum_{j=1}^{\tilde{\kappa}_2(t)} d_{2j} \hat{m}_{2j} \log \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right), \\ \tilde{R}_4 &= \sum_{j=1}^{\tilde{\kappa}_2(t)} (r_{2j} - d_{2j} \hat{m}_{2j}) \log \left( 1 - \frac{d_{2j} \hat{m}_{2j}}{r_{2j} - \hat{\lambda} \hat{S}_2(T_{2j})} \right) \\ &\quad - \sum_{j=1}^{\tilde{\kappa}_2(t)} (r_{2j} - d_{2j} \hat{m}_{2j}) \log \left( 1 - \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right). \end{aligned}$$



However, writing  $\tilde{R}_1 = R_1 - \check{R}_1$ , where

$$\check{R}_1 = \sum_{j=1}^{\tilde{\kappa}_1(t)} (r_{1j} - d_{1j}\hat{m}_{1j}) \log \left( \frac{d_{1j}\hat{m}_{1j}}{r_{1j} + \hat{\lambda}\hat{S}_1(T_{1j})} \right) - \sum_{j=1}^{\tilde{\kappa}_1(t)} (r_{1j} - d_{1j}\hat{m}_{1j}) \log \left( \frac{d_{1j}\hat{m}_{1j}}{r_{1j}} \right),$$

we see that

$$\begin{aligned} R_1 &\equiv \sum_{j=1}^{\tilde{\kappa}_1(t)} r_{1j} \log \left( \frac{d_{1j}\hat{m}_{1j}}{r_{1j} + \hat{\lambda}\hat{S}_1(T_{1j})} \right) - \sum_{j=1}^{\tilde{\kappa}_1(t)} r_{1j} \log \left( \frac{d_{1j}\hat{m}_{1j}}{r_{1j}} \right) \\ &= - \sum_{j=1}^{\tilde{\kappa}_1(t)} r_{1j} \log \left( 1 + \frac{\hat{\lambda}\hat{S}_1(T_{1j})}{r_{1j}} \right). \end{aligned}$$

Next we write  $\tilde{R}_1 + \tilde{R}_2 \equiv R_1 + R_2$ , where  $R_2 = \tilde{R}_2 - \check{R}_1$ . Then, after some algebra, we obtain

$$R_2 = \sum_{j=1}^{\tilde{\kappa}_1(t)} (r_{1j} - d_{1j}\hat{m}_{1j}) \log \left( 1 + \frac{\hat{\lambda}\hat{S}_1(T_{1j})}{r_{1j} - d_{1j}\hat{m}_{1j}} \right).$$

Applying exactly the same technique, we have that  $\tilde{R}_3 + \tilde{R}_4 \equiv R_3 + R_4$ , where

$$\begin{aligned} R_3 &= - \sum_{j=1}^{\tilde{\kappa}_2(t)} r_{2j} \log \left( 1 - \frac{\hat{\lambda}\hat{S}_2(T_{2j})}{r_{2j}} \right), \\ R_4 &= \sum_{j=1}^{\tilde{\kappa}_2(t)} (r_{2j} - d_{2j}\hat{m}_{2j}) \log \left( 1 - \frac{\hat{\lambda}\hat{S}_2(T_{2j})}{r_{2j} - d_{2j}\hat{m}_{2j}} \right). \end{aligned}$$

Therefore, we have shown that  $R(t) = R_1 + R_2 + R_3 + R_4$ . It now follows that

$$\begin{aligned} R(t) &= \sum_{j=1}^{\tilde{\kappa}_1(t)} \left[ (r_{1j} - d_{1j}\hat{m}_{1j}) \log \left( 1 + \frac{\hat{\lambda}\hat{S}_1(T_{1j})}{r_{1j} - d_{1j}\hat{m}_{1j}} \right) - r_{1j} \log \left( 1 + \frac{\hat{\lambda}\hat{S}_1(T_{1j})}{r_{1j}} \right) \right] \\ &\quad + \sum_{j=1}^{\tilde{\kappa}_2(t)} \left[ (r_{2j} - d_{2j}\hat{m}_{2j}) \log \left( 1 - \frac{\hat{\lambda}\hat{S}_2(T_{2j})}{r_{2j} - d_{2j}\hat{m}_{2j}} \right) - r_{2j} \log \left( 1 - \frac{\hat{\lambda}\hat{S}_2(T_{2j})}{r_{2j}} \right) \right]. \end{aligned} \quad (4.12)$$

The Lagrange multiplier  $\hat{\lambda}$  is such that  $D_1 < \hat{\lambda} < -D_2$ , where

$$D_i = \max_{j:T_{ij} \leq t} \left[ \frac{d_{ij}\hat{m}_{ij} - r_{ij}}{\hat{S}_i(T_{ij})} \right] \quad \text{and} \quad \hat{S}_i(T_{ij}) > 0, \quad i = 1, 2. \quad (4.13)$$

As in McKeague and Zhao (2005), we now define some quantities more precisely. Let  $\tau_1$  be such that  $S_i(\tau_1) < 1$  and  $\tau_2 \geq \tau_1$  be such that  $y_i(\tau_2) > 0$ ,  $i = 1, 2$ . Let  $n_i/n \rightarrow p_i > 0$  as  $n \rightarrow \infty$ . From theorem 2.4 of Dikta (1998),  $\hat{F}_i(t)$  and  $\hat{G}_i(t)$ , the SRCMs-based estimators of  $F_i(t) = 1 - S_i(t)$  and  $G_i(t)$ , respectively, are strongly uniformly consistent over  $[0, \tau_2]$ . Define

$$\gamma_i(t) = \int_0^t \frac{dF_i(s)}{1 - G_i(s-)}, \quad i = 1, 2, \quad (4.14)$$

and let  $\hat{\gamma}_i(t)$  denote its strongly uniformly consistent estimator over  $[0, \tau_2]$ , obtained by plugging in  $\hat{F}_i(t)$  and  $\hat{G}_i(t)$  into the right hand side of Eq. (4.14). Let

$$\sigma_d^2(t) = \frac{\gamma_1(t)}{p_1} + \frac{\gamma_2(t)}{p_2}. \quad (4.15)$$

Then  $\hat{\sigma}_d^2(t) = \hat{\gamma}_1(t)/p_1 + \hat{\gamma}_2(t)/p_2$  is a strongly uniformly consistent estimator of  $\sigma_d^2(t)$  over  $[\tau_1, \tau_2]$ . We have the following theorem the proof of which is given in the Appendix.

**Theorem 1** *Let  $V_i(s, t)$  be given by Eq. (2.1). The process  $-2R(\cdot)$  converges weakly in  $D[\tau_1, \tau_2]$  to  $W^2(\cdot)/\sigma_d^2(\cdot)$ , where  $W$  is a mean zero Gaussian process with covariance function*

$$\text{Cov}(W(s), W(t)) = \frac{S_1(s)S_1(t)V_1(s, t)}{p_1} + \frac{S_2(s)S_2(t)V_2(s, t)}{p_2}. \quad (4.16)$$

**Remark 1** For the KM based plug-in EL scenario (McKeague and Zhao, 2005), the respective Nelson–Aalen limiting covariance functions Figure in place of  $V_1$  and  $V_2$  in Eq. (4.16). From Dikta (1998), then, one may deduce that  $-2R(\cdot)$ , the SRCMs-based EL statistic, is asymptotically as or more efficient than its nonparametric counterpart.

**Remark 2** From the proof of lemma 5 and Section 4.1,  $W(t)$  is the weak limit of

$$\left[ \frac{S_1(t)}{\sqrt{p_1}} (L_{n_1,1}(t) + L_{n_1,2}(t)) + \frac{S_2(t)}{\sqrt{p_2}} (L_{n_2,1}(t) + L_{n_2,2}(t)) \right].$$

### 4.3 Simultaneous Confidence Bands for $\alpha(\cdot)$

From theorem 1 and the continuous mapping theorem,  $\| -2R \|_{\tau_1}^{\tau_2} \xrightarrow{D} \| W^2 / \sigma_d^2 \|_{\tau_1}^{\tau_2}$ , where  $\| \cdot \|$  is the sup-norm over  $[\tau_1, \tau_2]$ . An asymptotic  $100(1 - \alpha)\%$  SCB for  $\alpha(t)$  over  $[\tau_1, \tau_2]$  is given by

$$B_d = \{(t, \alpha(t)) : -2R(t) \leq c_\alpha[\tau_1, \tau_2], t \in [\tau_1, \tau_2]\}, \quad (4.17)$$

where  $c_\alpha[\tau_1, \tau_2]$  denotes the upper  $\alpha$ -quantile of the distribution of  $\| W^2 / \sigma_d^2 \|_{\tau_1}^{\tau_2}$ . The inversion of  $-2R(t)$ , implicit in Eq.(4.17), is achieved by following McKeague and Zhao (2005). For fixed  $t$ , consider  $-2R(t)$  as a function of  $\lambda$ , say  $\varphi(\lambda)$ . Then there exist exactly two roots  $\hat{\lambda}_L < 0 < \hat{\lambda}_U$  for  $\varphi(\hat{\lambda}_L) = \varphi(\hat{\lambda}_U) = c_\alpha[\tau_1, \tau_2]$ . Furthermore,  $\{\lambda : \varphi(\lambda) \leq c_\alpha[\tau_1, \tau_2]\} = [\hat{\lambda}_L, \hat{\lambda}_U]$ . The confidence set for  $\alpha(t)$  is a closed interval  $[\alpha_L, \alpha_U]$  (Thomas and Grunkemeier, 1975). From Eq.(4.11), the lower and upper limits of the confidence band are given, for  $I = L, U$ , by

$$\alpha_I(t) = \sum_{j=1}^{\tilde{\kappa}_1(t)} \log \left( 1 - \frac{d_{1j} \hat{m}_{1j}}{r_{1j} + \hat{\lambda}_I \hat{S}_1(T_{1j})} \right) \hat{S}_1(T_{1j}) - \sum_{j=1}^{\tilde{\kappa}_2(t)} \log \left( 1 - \frac{d_{2j} \hat{m}_{2j}}{r_{2j} - \hat{\lambda}_I \hat{S}_2(T_{2j})} \right) \hat{S}_2(T_{2j}).$$

To compute  $c_\alpha[\tau_1, \tau_2]$ , we apply the Gaussian multiplier bootstrap (Lin, Wei, and Ying, 1993). Let  $\{G_{11}, \dots, G_{1n_i}, i = 1, 2\}$  be independent standard normal variables, independent of the data. A version of the process  $W(t)/\sigma_d(t)$  that can be simulated is

$$\mathbb{W}^*(t) = \frac{1}{\hat{\sigma}_d(t)} \left[ \frac{\hat{S}_1(t)}{\sqrt{p_1}} (L_{n_{1,1}}^*(t) + L_{n_{1,2}}^*(t)) + \frac{\hat{S}_2(t)}{\sqrt{p_2}} (L_{n_{2,1}}^*(t) + L_{n_{2,2}}^*(t)) \right] \quad (4.18)$$

where, for  $i = 1, 2$ ,

$$L_{n_{i,1}}^*(t) = n_i^{1/2} \sum_{j=1}^{n_i} \frac{\hat{m}_{ij}}{Y_{i \cdot}(Z_{ij})} I(Z_{ij} \leq t) G_{ij}, \quad (4.19)$$

$$L_{n_{i,2}}^*(t) = n_i^{-1/2} \sum_{j=1}^{n_i} \frac{\delta_{ij} - \hat{m}_{ij}}{\hat{m}_{ij} \hat{m}_{ij}} \int_0^t \frac{\hat{\alpha}(u, Z_{ij})}{1 - \hat{H}_i(u-)} d\hat{H}_i(u) G_{ij}. \quad (4.20)$$

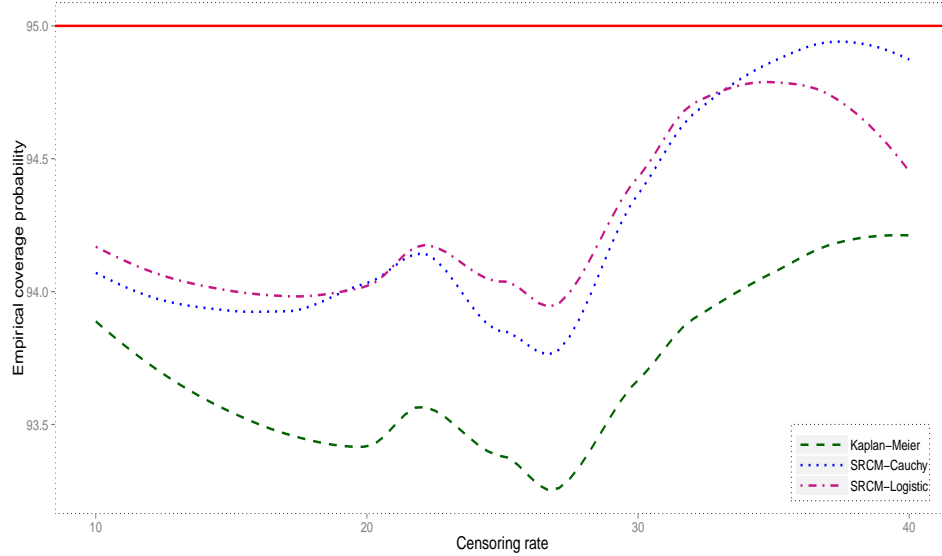
Conditional on the data, we show in the Appendix that for almost all sample sequences  $\{Z_{ij}, \delta_{ij}, 1 \leq j \leq n_i, 1 \leq i \leq 2\}$ , the weak limit of  $\mathbb{W}^*$  coincides with the distribution of  $W/\sigma_d$ . The bootstrap resampling method is then used to generate the critical value. For given integer  $M$ , such as, say 1000, independent  $\mathbb{W}_1^*, \dots, \mathbb{W}_M^*$  are generated and the upper  $\alpha$ -quantile of  $\sup_{[\tau_1, \tau_2]} [\mathbb{W}_1^{*2}, \dots, \mathbb{W}_M^{*2}]$  is taken to obtain the critical value  $c_\alpha[\tau_1, \tau_2]$ .

#### 4.4 Simulation Studies

For the simulation study, we computed 2,000 SCBs for  $\alpha(t) = S_2(t) - S_1(t)$ , based on sample size 100 for each replication. The critical values, extracted as percentiles of the bootstrap distributions, were based on 1,000 bootstrap resamples. The empirical coverage probabilities (ECPs) of the competing SCBs were first evaluated to examine whether they were close to the nominal 95%. The ECP is the proportion of the 2,000 SCBs that included the true value of  $\alpha(t)$  for all  $t \in [\tau_1, \tau_2]$ . The second stage of comparison was based on the estimated average enclosed area (EAEA), which is the average of the areas enclosed by the 2,000 SCBs. The area enclosed by an SCB is computed by summing the products of the width of the SCB at each point of a fine partition over  $[\tau_1, \tau_2]$  and the (common) width of each subinterval.

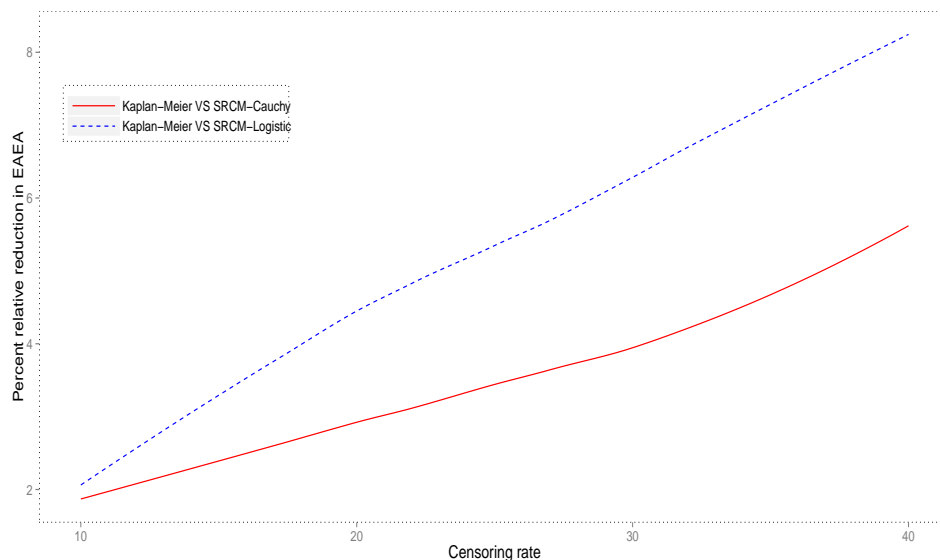
The failure time was Weibull, with  $F_i(x) = 1 - \exp(-(a_i x)^2)$ ,  $i = 1, 2$ . The censoring distribution was exponential with mean 1. Then  $m_i(x, a_i) = 2a_i^2 x / (1 + 2a_i^2 x)$ ,  $i = 1, 2$ . Both the logistic and Cauchy models were fitted to the binary response data, and are given by Eq. (3.6) and Eq. (3.7), respectively. The censoring rate (CR), expressed as a function of the parameter  $a_i$ , is given by Eq. (3.8). The simulations were run for several CRs, from 10% ( $a_i = 8.3$ ) to 40% ( $a_i = 1.6$ ). For each CR, we computed the ECPs and the percent relative reduction in EAEA of the proposed semiparametric SCBs over the ones developed by McKeague and Zhao (2005). The

ECP and EAEA were based on SCBs computed at 100 equally spaced time points  $t \in [\tau_1, \tau_2] = [F_1^{-1}(0.2), F_1^{-1}(0.8)]$ .



**Figure 4.1** Empirical Coverage Probabilities (ECPs) of the competing 95% confidence bands for various censoring rates (CRs)

The ECPs of the proposed SRCMs-based SCBs, computed using Eq. (4.17), and the KM based SCBs of McKeague and Zhao (2005) are presented in Figure 4.1. The proposed SRCMs-based SCBs gave ECPs closer to the nominal 95% than those of McKeague and Zhao (2005). The percent relative reduction in EAEA of the proposed over the KM based SCBs of McKeague and Zhao (2005) are presented in Figure 4.2. The proposed SCBs based on Cauchy fits provided a relative reduction between 1.91% and 5.61% in EAEA; while the ones based on logistic fits gave a relative reduction between 2.13% and 8.26% in EAEA.



**Figure 4.2** Percent relative reduction in EAEA of the proposed 95% SRCMs-based over KM-based confidence bands for various censoring rates (CRs)

#### 4.5 UMass AIDS Research Unit IMPACT Study

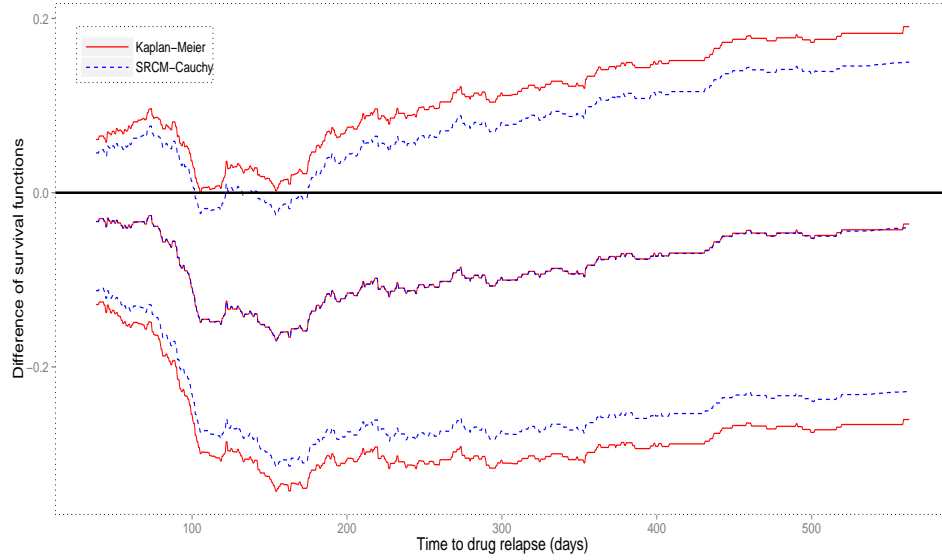
The purpose of the UMass AIDS study was to compare the effectiveness of a short-term and a long-term residential treatment program designed to reduce drug abuse and to prevent high-risk HIV behavior that triggers drug relapse. The study consisted of 628 subjects, where 320 subjects were randomly assigned to a short-term program and 308 subjects were assigned to a long-term treatment program. We formally tested the adequacy of our parametric specifications [logistic given by Eq. (3.6) and Cauchy given by Eq. (3.7)] via a model-based resampling procedure (Dikta et al., 2006). We computed the Kolmogorov–Smirnov (KS) and Cramér von Mises (CvM) statistics from the observed data and then computed their bootstrap versions 3,000 times. The test rejects the null hypothesis of no model misspecification when the proportion of 3,000 bootstrap values exceeding the test statistics fell below the 5% threshold. We present the results of our analysis in Table 4.1. There is strong indication that the Cauchy model may be adequate, although the evidence is not very strong.

**Table 4.1** UMASS Data: Testing Adequacy of the Logistic and Cauchy Models

Model	Parameter estimates		KS statistic		CvM statistic	
	$\theta_0$	$\theta_1$	Estimate	p-value	Estimate	p-value
Short Term Treatment						
Logistic	36.0398	-0.0727	0.0961	0.0167	0.0003	0.0267
Cauchy	732.1179	-1.4643	0.0507	0.368	0.0001	0.4620
Long Term Treatment						
Logistic	27.4365	-0.0542	0.1434	0.0353	0.0007	0.0627
Cauchy	296.3220	-0.5648	0.0769	0.300	0.0003	0.6363

Which plan was successful in reducing the probability of drug relapse after a certain number of months? To answer this question, Figure 4.3 gives the proposed and McKeague and Zhao's (2005) SCBs for  $\alpha(t) = S_1(t) - S_2(t)$ , computed over the time interval  $[38, 563]$ . The chosen end points represented the 10th and 90th percentiles, respectively of the ordered pooled data. Here  $S_1(t)$  and  $S_2(t)$  are the survival functions for the long-term and short-term treatment plans, respectively. The proposed semiparametric SCBs were obtained using a logistic fit for the parametric part. The nonparametric SCBs are seen to include the zero line of no difference over almost the whole region considered for analysis, implying that the approach is unable to detect any difference in the probability of drug relapse between the two treatment plans. Clearly, any conclusion of difference in probability of drug relapse is, at best, marginal. The semiparametric SCB, on the other hand, is seen to be uniformly narrower, providing a relative reduction amounting to about 13.75% over the nonparametric SCB. More significantly, the proposed semiparametric approach allows one to conclude that the difference is positive over the intervals  $[100, 135]$  and  $[140, 175]$ , which is clearly more definitive than the marginal decision given by the nonparametric approach in these regions. In particular, the proposed approach allows us to conclude that the probability of drug relapse is greater under the long-term

treatment plan than under the short-term plan over the aforementioned subintervals. Compared to the KM approach, proposed method had a 15.03% relative reduction in enclosed area.



**Figure 4.3** Proposed SRCMs-logistic and KM-based SCBs of McKeague and Zhao (2005) in UMASS AIDS research unit IMPACT study



## CHAPTER 5

### PROPOSED BOOTSTRAP BASED TEST STATISTICS

Again, we consider the standard two-sample setting with independent right censoring. Specifically, there are two samples of independent and identically distributed observations

$$\{(Z_{ij}, \delta_{ij}), j = 1, \dots, n_i, i = 1, 2\},$$

where  $Z_{ij} = \min(X_{ij}, C_{ij})$ ,  $\delta_{ij} = I(X_{ij} \leq C_{ij})$ . The distribution functions of  $X_{ij}$  and  $C_{ij}$ , the failure and censoring times, are  $F_i = 1 - S_i$  and  $G_i$ , respectively,  $j = 1, \dots, n_i, i = 1, 2$ .

The hypothesis of interest is that  $S_1(t)$  and  $S_2(t)$ , the two survival functions, are equal. In this project, we employ the censored data and two-stage bootstraps to approximate the distributions of certain weighted KM statistics. Through this mechanism, then, we are able to obtain the critical values for testing  $H_0 : S_1 = S_2$  against  $H_1 : S_1 \neq S_2$ .

The weighted KM test statistic was introduced by Pepe and Fleming (1989), and is defined as

$$W_{\text{KM}} = \sqrt{\frac{n_1 n_2}{n}} \int_0^T \tilde{w}(t) (\tilde{S}_1(t) - \tilde{S}_2(t)) dt, \quad (5.1)$$

where  $T = \sup\{t : G_1(t) \wedge G_2(t) > 0\}$ . In the presence of heavy censoring, the KM estimator is unstable for  $t$  close to the end of the study period. To address this tail problem, Pepe and Fleming (1989) introduced the random weight function given by

$$\tilde{w}(t) = \frac{\tilde{G}_1(t-) \tilde{G}_2(t-)}{p_1 \tilde{G}_1(t-) + p_2 \tilde{G}_2(t-)}, \quad (5.2)$$

where  $p_i = n_i/n$ , for  $i = 1, 2$ . The weight function  $\tilde{w}(t)$  downweights the contribution of the difference  $\tilde{S}_1(t) - \tilde{S}_2(t)$  appearing on the right hand side of Eq. (5.1). The weighted KM statistic converges in distribution to  $N(0, \sigma^2)$ , where

$$\sigma^2 = - \int_0^T \frac{\int_t^T [\tilde{w}(t)\tilde{S}(u)du]^2}{\tilde{S}(t)\tilde{S}(t-)} \frac{p_1\tilde{G}_1(t-) + p_2\tilde{G}_2(t-)}{\tilde{G}_1(t-)\tilde{G}_2(t-)} d\tilde{S}(t).$$

Lee, Lee, and Omolo (2008) proposed a modified version of the weighted KM statistic that utilizes the entire range of the data. Their modified weighted KM is given by

$$\varphi_{\text{KM}}(x) = \sqrt{\frac{n_1 n_2}{n}} \int_0^x \tilde{w}(t)(\tilde{S}_1(t) - \tilde{S}_2(t))dt. \quad (5.3)$$

By considering a range of values,  $x \in (0, T]$ , more information may be extracted than when only  $x = T$ . Under the martingale counting process approach, each group-specific KM process,  $n^{1/2}(\tilde{S}_i(t) - S_i(t))$ , is asymptotically equivalent to  $U_i(t)$ , see Eq. (2.5). Lee, Lee, and Omolo (2008), approximated  $\varphi_{\text{KM}}(x)$  using

$$\tilde{\varphi}_{\text{WKM}}(x) = \sqrt{\frac{n_1 n_2}{n}} \sum_{i=1}^2 (-1)^{i+1} \int_0^x \int_t^\infty \tilde{w}(s)\tilde{S}_i(s)Y_i^{-1}(t)dsd\tilde{M}_i(t). \quad (5.4)$$

According to them, under  $H_0$ , the process  $\varphi_{\text{KM}}(x)$  is asymptotically equivalent to  $\tilde{\varphi}_{\text{WKM}}(x)$ . Let  $D = \sup_{x \in (0, T]} |\tilde{\varphi}_{\text{WKM}}(x)|$ . Then, the p-value is obtained by evaluating  $P(D \geq d)$ , where  $d$  is the observed value of  $D$ .

The corresponding SRCMs version that we will analyze is given by

$$\varphi_{\text{SRCMs}}(x) = \sqrt{\frac{n_1 n_2}{n}} \int_0^x \hat{w}(t)(\hat{S}_1(t) - \hat{S}_2(t))dt. \quad (5.5)$$

We employ the censored data and two-stage bootstraps to approximate the distribution of  $\varphi_{\text{KM}}$  and  $\varphi_{\text{SRCMs}}$ , respectively. This provides us with the critical values for testing  $H_0$ . Numerical simulations and real example studies show that our procedures perform better than the approach of Lee, Lee, and Omolo (2008).

## 5.1 Proposed Integrated Weighted Test Statistics

Note that

$$\begin{aligned}
\varphi_{\text{KM}}(x) &= \sqrt{\frac{n_1 n_2}{n}} \int_0^x \tilde{w}(t) (\tilde{S}_1(t) - \tilde{S}_2(t)) dt \\
&= \sqrt{\frac{n_1 n_2}{n}} \int_0^x \tilde{w}(t) (\tilde{S}_1(t) - S_1(t)) - (\tilde{S}_2(t) - S_2(t)) + (S_1(t) - S_2(t)) dt \\
&= \sqrt{\frac{n_1 n_2}{n}} \int_0^x \tilde{w}(t) (\tilde{S}_1(t) - S_1(t)) - (\tilde{S}_2(t) - S_2(t)) dt \quad (H_0 : S_1 = S_2).
\end{aligned}$$

Likewise, we can write

$$\varphi_{\text{SRCMs}}(x) = \sqrt{\frac{n_1 n_2}{n}} \int_0^x \tilde{w}(t) (\hat{S}_1(t) - S_1(t)) - (\hat{S}_2(t) - S_2(t)) dt$$

It follows that, for testing  $H_0$ , the process  $\varphi_{\text{KM}}$  and  $\varphi_{\text{SRCMs}}$  can be approximated by

$$\varphi_{\text{KM}}^*(x) = \sqrt{\frac{n_1 n_2}{n}} \int_0^x \tilde{w}(t) [(\tilde{S}_1^*(t) - \tilde{S}_1(t)) - (\tilde{S}_2^*(t) - \tilde{S}_2(t))] dt$$

and

$$\varphi_{\text{SRCMs}}^*(x) = \sqrt{\frac{n_1 n_2}{n}} \int_0^x \hat{w}(t) [(\hat{S}_1^*(t) - \hat{S}_1(t)) - (\hat{S}_2^*(t) - \hat{S}_2(t))] dt,$$

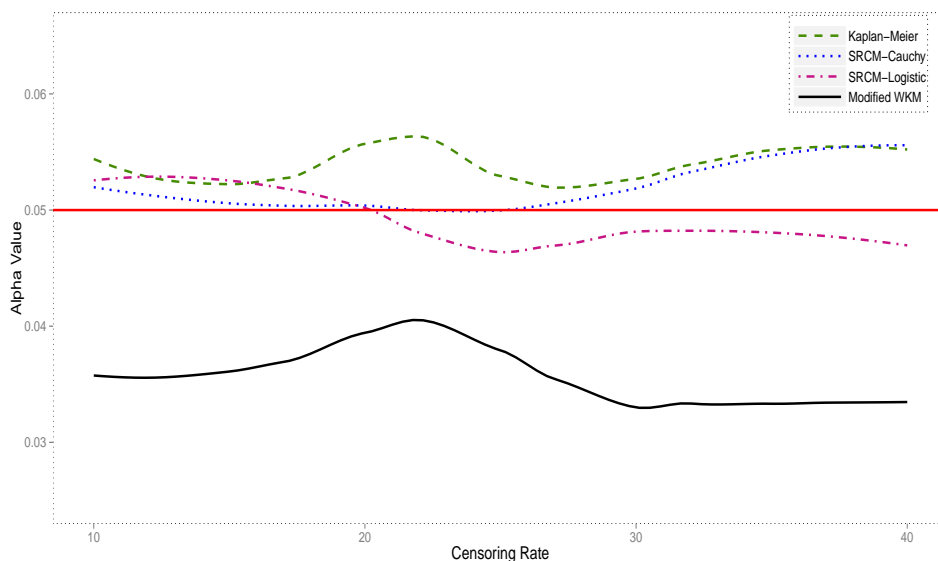
respectively. The weight function  $\tilde{w}(t)$  was defined by Eq. (5.2). Replace  $\tilde{G}_1$  and  $\tilde{G}_2$  in Eq. (5.2) with  $\hat{G}_1$  and  $\hat{G}_2$  to obtain  $\hat{w}(t)$ .

Let  $\tilde{D} = \sup_{x \in (0, T]} |\varphi_{\text{KM}}(x)|$  and  $\hat{D} = \sup_{x \in (0, T]} |\varphi_{\text{SRCMs}}(x)|$ . If we fail to reject  $H_0$ , a noticeable deviation of  $\varphi_{\text{diff}}(x)$  or  $\varphi_{\text{diff}}(x)$  from zero will be detected for some time interval. The distribution of  $\tilde{D}$  or  $\hat{D}$  can be approximated by a number of realizations, say 1000, from  $\tilde{D}^* = \sup_{x \in (0, T]} |\varphi_{\text{KM}}^*(x)|$  or  $\hat{D}^* = \sup_{x \in (0, T]} |\varphi_{\text{SRCMs}}^*(x)|$ , given the data. An unusually large value of  $\tilde{D}$  or  $\hat{D}$ , compared to 1000 values of  $\tilde{D}^*$  or  $\hat{D}^*$ , will suggest that the two survival functions may not be equal. Let  $\tilde{d}$  or  $\hat{d}$  denote the computed values of  $\tilde{D}$  or  $\hat{D}$ . Then, the p-value, represented by  $P(\tilde{D} \geq \tilde{d})$  or  $P(\hat{D} \geq \hat{d})$ , can be approximated by  $P(\tilde{D}^* \geq \tilde{d})$  or  $P(\hat{D}^* \geq \hat{d})$ .

## 5.2 Simulation Studies

Simulations were conducted for assessing the performance of the proposed methods. The failure time was Weibull, with  $F_i(x) = 1 - \exp(-(a_i x)^2)$ ,  $i = 1, 2$ . The censoring distribution was exponential with mean 1. Then  $m_i(x, a_i) = 2a_i^2 x / (1 + 2a_i^2 x)$ ,  $i = 1, 2$ . Both the logistic and Cauchy models were fitted to the binary response data, and are defined by Eq. (3.6) and Eq. (3.7), respectively. The CR, expressed as a function of the parameter  $a_i$  was given in Eq. (3.8).

### 5.2.1 Significance Level

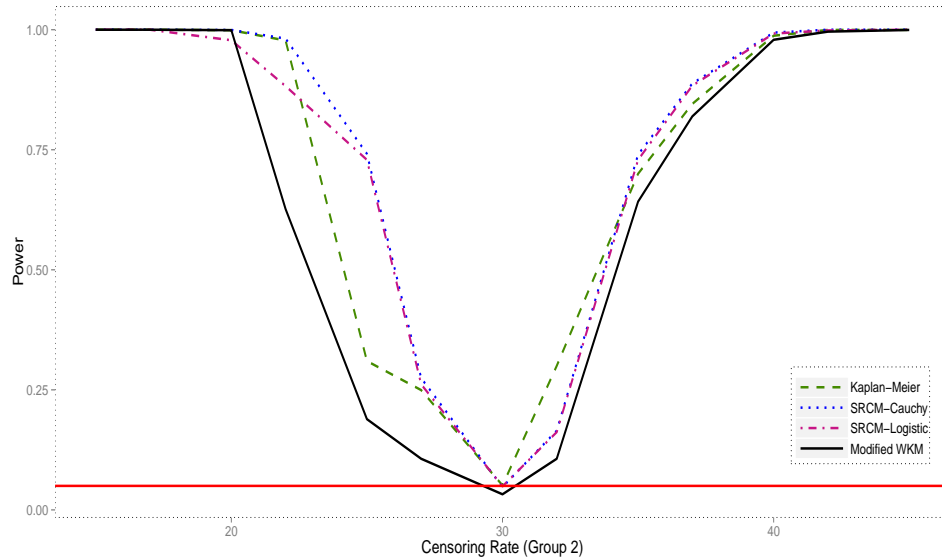


**Figure 5.1** Two-sided, at  $\alpha = .05$ , empirical significance level study for proposed weighted test statistics versus modified WKM

We tested the null hypothesis,  $H_0 : S_1 = S_2$ , against  $H_1 : S_1 \neq S_2$ , at  $\alpha = .05$ . The constant  $a_i$  was chosen to obtain CRs between 10% to 40%. For sample sizes  $n_1 = n_2 = 100$ , results were based on 2000 replications for various censoring rates between 10% ( $a_i = 8.3$ ) and 40% ( $a_i = 1.6$ ). For each replication, we computed 1000 values of  $\tilde{D}^*$  and  $\hat{D}^*$  and obtained the proportion of those values that exceeded  $\tilde{d}$  and  $\hat{d}$ , respectively. These are the p-values of the proposed test statistics. We then

determined the proportion of the 2000 p-values that fell below 5%. The latter quantity gives the empirical significance level, which, under the  $H_0$ , should be approximately 5%. Figure 5.1 below shows the plot of the empirical significance levels for CR 10% to 40% for the proposed tests. Our proposed tests, outperformed that of Lee, Lee, Omolo's (2008) for all CR, maintaining the correct significance level at  $\alpha = .05$ . The modified weighted KM yielded empirical significance levels that were always below 0.04.

### 5.2.2 Power Study

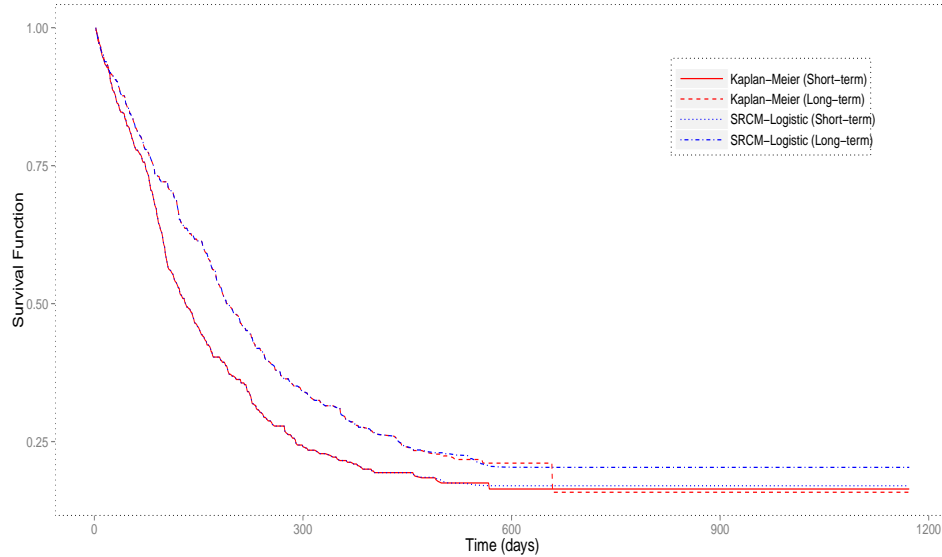


**Figure 5.2** Two-sided, at  $\alpha = .05$ , empirical power study for proposed weighted test statistics versus modified WKM

The results were based on 2000 replications, where, for the first group, the CR was always set to 30% ( $a_1 = 2.4$ ) and for the second group the CR varied from 15% ( $a_2 = 5.3$ ) to 45% ( $a_2 = 1.4$ ). Therefore, when the second group CR was 30%,  $H_0$  is true and we expect the power curve to reach its minimum there. Figure 5.2 below shows the empirical power values for the proposed tests and that of Lee, Lee, Omolo (2008). Each of the power plots are shown as a function of the second sample CR.

From the figure it can be seen that, the proposed tests were uniformly better than that of Lee, Lee, and Omolo (2008) in terms of having greater power to reject an incorrect  $H_0$ .

### 5.3 UMass AIDS IMPACT Study



**Figure 5.3** Estimated KM and SRCMs-Logistic model based survival functions for the short-term and long-term treatment plans in UMass AIDS study

As described in Section 5.3, the purpose of the UMass AIDS study was to compare the effectiveness of a short-term and a long-term residential treatment program designed to reduce drug abuse and to prevent high-risk HIV behavior that triggers drug relapse. The study consisted of 628 subjects, where 320 subjects were randomly assigned to a short-term program and 308 subjects were assigned to a long-term treatment program. As indicated in Chapter 4, there is some evidence that the logistic model may be adequate, although the evidence is not strong. Figure 5.3 below shows the estimated KM and SRCMs-logistic model based survival functions for the two treatment groups. We formally tested the null hypothesis of no difference in survival functions between the short-term and long-term treatment plan. The empirical p-value for the proposed

test statistics based on KM and SRCMs-Cauchy model was 0.001. The p-value for the Lee, Lee, and Omolo (2008) was 0.032. The empirical p-values for the proposed test statistics are much smaller than that of Lee, Lee, and Omolo (2008). This suggests that our proposed methods provide stronger support that there is a difference between the two treatment plans.

## CHAPTER 6

### CONCLUDING REMARKS AND FUTURE WORK

The focus of this dissertation is two-sample comparisons from censored time-to-event data. New simultaneous confidence bands for the difference of two survival functions were developed using asymptotic distribution theory as well as empirical likelihood. Furthermore, methods for testing the equality of the survival functions were also developed. The new methods are useful in biomedical studies and in randomized clinical trials for comparing two treatment groups or for comparing a treatment and a control.

The power of the censored data bootstrap and the two-stage bootstrap was exploited in the first and third projects. The proposed methods produced improved performance over existing methods. A challenging problem, but one that would be a worthwhile direction for future research, would be to investigate the feasibility of these two bootstrap procedures for improved empirical likelihood based SCBs. Another direction for future research would be to develop empirical likelihood based SCBs for the difference without using plug-ins.



## APPENDIX

### ASYMPTOTIC PROPERTIES AND JUSTIFICATION OF GMB

We prove a number of lemmas. Recall that  $\tilde{\kappa}_i(t) = \sum_{j=1}^{n_i} I(Z_{ij} \leq t)$ ,  $i = 1, 2$ . Define

$$\hat{\zeta}_i(t) = \sum_{j=1}^{\tilde{\kappa}_i(t)} \left( \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right) \hat{S}_i(T_{ij}) \equiv \int_0^t \hat{S}_i(s) d\hat{\Lambda}_i(s), \quad i = 1, 2. \quad (\text{A.1})$$

**Lemma 1** *The process  $n_i^{1/2}(\hat{\zeta}_i - F_i)$  is asymptotically equivalent to  $S_i \cdot n_i^{1/2}(\hat{\Lambda}_i - \Lambda_i)$ .*

**Proof** Add and subtract  $\int_0^t S_i(s) d\hat{\Lambda}_i(s)$  and apply the Duhamel equation to get

$$\begin{aligned} n_i^{1/2} \left( \hat{\zeta}_i(t) - F_i(t) \right) &= n_i^{1/2} \left( \int_0^t \hat{S}_i(s) d\hat{\Lambda}_i(s) - \int_0^t S_i(s) d\Lambda_i(s) \right) \\ &= -n_i^{1/2} \int_0^t S_i(s) \left( \int_0^s \frac{\hat{S}_i(u-)}{S_i(u)} d \left( \hat{\Lambda}_i(u) - \Lambda_i(u) \right) \right) d\Lambda_i(s) \\ &\quad + n_i^{1/2} \int_0^t S_i(s) d \left( \hat{\Lambda}_i(s) - \Lambda_i(s) \right) := I_1(t) + I_2(t). \end{aligned}$$

Interchanging the order of integration, we get, uniformly for  $t \in [0, t_i]$  such that  $y_i(t_i) > 0$ ,

$$I_1(t) = -n_i^{1/2} \int_0^t \left( \int_u^t S_i(s) d\Lambda_i(s) \right) \frac{\hat{S}_i(u-)}{S_i(u)} d \left( \hat{\Lambda}_i(u) - \Lambda_i(u) \right).$$

Applying Lengart's inequality, it follows that

$$\begin{aligned} I_1(t) &= -n_i^{1/2} \int_0^t (S_i(u) - S_i(t)) d \left( \hat{\Lambda}_i(u) - \Lambda_i(u) \right) + o_p(1) \\ &= -I_2(t) + S_i(t) n_i^{1/2} \left( \hat{\Lambda}_i(t) - \Lambda_i(t) \right) + o_p(1). \quad \square \end{aligned}$$

Noting that  $\int_0^t S_i^2(s) d\Lambda_i(s) = (1 - S_i^2(t))/2$ , next define

$$\hat{\zeta}_i^{(2)}(t) = \sum_{j=1}^{\tilde{\kappa}_i(t)} \left( \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right) \hat{S}_i^2(T_{ij}) \equiv \int_0^t \hat{S}_i^2(s) d\hat{\Lambda}_i(s), \quad i = 1, 2. \quad (\text{A.2})$$

**Lemma 2** *The process  $n_i^{1/2} \left( \hat{\zeta}_i^{(2)} - \frac{1-S_i^2}{2} \right)$  is asymptotically equivalent to  $S_i^2 n_i^{1/2} (\hat{\Lambda}_i - \Lambda_i)$ .*

**Proof** Add and subtract  $\int_0^t S_i^2(s) d\hat{\Lambda}_i(s)$  and apply the Duhamel equation to get

$$\begin{aligned} n_i^{1/2} \left( \hat{\zeta}_i^{(2)}(t) - \int_0^t S_i^2(s) d\Lambda_i(s) \right) &= -n_i^{1/2} \int_0^t 2S_i^2(s) \left( \int_0^s \frac{\hat{S}_i(u-)}{S_i(u)} d(\hat{\Lambda}_i(u) - \Lambda_i(u)) \right) d\Lambda_i(s) \\ &\quad + n_i^{1/2} \int_0^t S_i^2(s) d(\hat{\Lambda}_i(s) - \Lambda_i(s)) \\ &:= I_3(t) + I_4(t). \end{aligned}$$

Interchanging the order of integration, we get, uniformly for  $t \in [0, t_i]$  such that  $y_i(t_i) > 0$ ,

$$I_3(t) = -n_i^{1/2} \int_0^t \left( \int_u^t 2S_i^2(s) d\Lambda_i(s) \right) d(\hat{\Lambda}_i(u) - \Lambda_i(u)) + o_p(1).$$

Note that the integrand above equals  $S_i^2(u) - S_i^2(t)$ . It follows that

$$I_3(t) = S_i^2(t) n_i^{1/2} (\hat{\Lambda}_i(t) - \Lambda_i(t)) - I_4(t) + o_p(1). \quad \square$$

Recall that  $\|h\|_{\tau_1}^{\tau_2} = \sup_{t \in [\tau_1, \tau_2]} |h(t)|$ . For our next result, define

$$\tilde{\zeta}_i(t) = - \sum_{j=1}^{\tilde{\kappa}_i(t)} \log \left( 1 - \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right) \hat{S}_i(T_{ij}), \quad i = 1, 2. \quad (\text{A.3})$$

**Lemma 3** *For  $i = 1, 2$ , we have  $\|\hat{\zeta}_i - \tilde{\zeta}_i\|_{\tau_1}^{\tau_2} = o_p(n^{-1/2})$ .*

**Proof** Following McKeague and Zhao (2005), see their Eq. (A.6), we can show that

$$n_i^{1/2} |\hat{\zeta}_i(t) - \tilde{\zeta}_i(t)| \leq \left\{ \max_{j \leq \tilde{\kappa}_i(t)} \left( \frac{n_i^{1/2} d_{ij} \hat{m}_{ij}}{r_{ij}} \right) \right\} \times \left\{ \sum_{j=1}^{\tilde{\kappa}_i(t)} \left( \frac{d_{ij} \hat{m}_{ij}}{r_{ij}} \right) \hat{S}_i(T_{ij}) \right\} \quad (\text{A.4})$$

Under continuity of  $H_i$ , the first quantity on the right side of Eq. (A.4) is bounded above by

$$\max_{j \leq \tilde{\kappa}_i(t)} \left( n_i^{1/2} / r_{ij} \right) \leq n_i^{-1/2} \|1/\bar{Y}_i\|_0^{\tau_2} = O(n_i^{-1/2}) O_p(1) = o_p(1). \quad (\text{A.5})$$

From Eq. (A.1), the second quantity on the right side of Eq. (A.4) is bounded above by  $\hat{\zeta}_i(\tau_2) \xrightarrow{\text{a.s.}} F_i(\tau_2)$ , see also theorem 2.4 of Dikta (1998) and lemma 1. Thus,  $\hat{\zeta}_i(\tau_2) = O_p(1)$  which, combined with Eqs. (A.4) and (A.5), completes the proof.  $\square$

**Lemma 4** *The Lagrange multiplier,  $\hat{\lambda}(t) \equiv \hat{\lambda}$ , solving Eq. (4.11), satisfies*

$$|\hat{\lambda}| \leq \frac{n_2(\alpha(t) + \tilde{\zeta}_1(t) - \hat{\zeta}_2(t))}{\sum_{j=1}^{\tilde{\kappa}_2(t)} d_{2j} \hat{m}_{2j} \hat{S}_2^2(T_{2j})/r_{2j}}, \text{ when } \hat{\lambda} > 0; \quad (\text{A.6})$$

$$|\hat{\lambda}| \leq \frac{n_1(-\alpha(t) + \tilde{\zeta}_2(t) - \hat{\zeta}_1(t))}{\sum_{j=1}^{\tilde{\kappa}_1(t)} d_{1j} \hat{m}_{1j} \hat{S}_1^2(T_{1j})/r_{1j}}, \text{ when } \hat{\lambda} < 0. \quad (\text{A.7})$$

**Proof** For our semiparametric setting, we adapt the approach of McKeague and Zhao (2005), who follow Li (1995). From Eq. (4.11), write  $\alpha(t) = I_1(t) + I_2(t)$ , where

$$I_i(t) = (-1)^{i+1} \sum_{j=1}^{\tilde{\kappa}_i(t)} \log \left( 1 - \frac{d_{ij} \hat{m}_{ij}}{r_{ij} + (-1)^{i+1} \hat{\lambda} \hat{S}_i(T_{ij})} \right) \hat{S}_i(T_{ij}), \quad i = 1, 2.$$

First assume that  $\hat{\lambda} > 0$ . Since  $\log(1 - x) + x$  is decreasing for  $x \in (0, 1)$ , we have that

$$\log \left( 1 - \frac{d_{1j} \hat{m}_{1j}}{r_{1j} + \hat{\lambda} \hat{S}_1(T_{1j})} \right) + \frac{d_{1j} \hat{m}_{1j}}{r_{1j} + \hat{\lambda} \hat{S}_1(T_{1j})} \geq \log \left( 1 - \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right) + \frac{d_{1j} \hat{m}_{1j}}{r_{1j}}.$$

It follows that

$$I_1(t) \geq \sum_{j=1}^{\tilde{\kappa}_1(t)} \left[ -\frac{d_{1j} \hat{m}_{1j}}{r_{1j} + \hat{\lambda} \hat{S}_1(T_{1j})} + \log \left( 1 - \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right) + \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right] \hat{S}_1(T_{1j}). \quad (\text{A.8})$$

Since, for  $x > 0$ , the inequality  $n_1/(n_1 + x) \leq n_2/(n_2 + x)$  holds whenever  $n_1 \leq n_2$ , we have the following lower bound for the first term on the right hand side of Eq. (A.8):

$$\begin{aligned} -\sum_{j=1}^{\tilde{\kappa}_1(t)} \frac{d_{1j} \hat{m}_{1j}}{r_{1j} + \hat{\lambda} \hat{S}_1(T_{1j})} \hat{S}_1(T_{1j}) &= -\sum_{j=1}^{\tilde{\kappa}_1(t)} \left( \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right) \left( \frac{r_{1j}}{r_{1j} + \hat{\lambda} \hat{S}_1(T_{1j})} \right) \hat{S}_1(T_{1j}) \\ &\geq -\sum_{j=1}^{\tilde{\kappa}_1(t)} \left( \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right) \left( \frac{n_1}{n_1 + |\hat{\lambda}| \hat{S}_1(T_{1j})} \right) \hat{S}_1(T_{1j}). \quad (\text{A.9}) \end{aligned}$$

Note that the second term on the right hand side of Eq. (A.8) equals  $-\tilde{\zeta}_1(t)$ , see Eq. (A.3). Using the fact that  $-\log(1-x) \geq x$  when  $0 \leq x < 1$ , we obtain

$$I_2(t) \geq \sum_{j=1}^{\tilde{\kappa}_2(t)} \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j} - \hat{\lambda} \hat{S}_2(T_{2j})} \right) \hat{S}_2(T_{2j}) = \sum_{j=1}^{\tilde{\kappa}_2(t)} \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right) \left( \frac{r_{2j}}{r_{2j} - |\hat{\lambda}| \hat{S}_2(T_{2j})} \right) \hat{S}_2(T_{2j}).$$

Since  $n_1/(n_1-x) \geq n_2/(n_2-x)$ , when  $x > 0$  and  $n_1 \leq n_2$ , we obtain the lower bound

$$I_2(t) \geq \sum_{j=1}^{\tilde{\kappa}_2(t)} \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right) \left( \frac{n_2}{n_2 - |\hat{\lambda}| \hat{S}_2(T_{2j})} \right) \hat{S}_2(T_{2j}). \quad (\text{A.10})$$

From Eqs. (A.8)–(A.10), we obtain

$$\begin{aligned} \alpha(t) \geq & - \sum_{j=1}^{\tilde{\kappa}_1(t)} \left( \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right) \left( \frac{n_1}{n_1 + |\hat{\lambda}| \hat{S}_1(T_{1j})} \right) \hat{S}_1(T_{1j}) - \tilde{\zeta}_1(t) + \sum_{j=1}^{\tilde{\kappa}_1(t)} \left( \frac{d_{1j} \hat{m}_{1j}}{r_{1j}} \right) \hat{S}_1(T_{1j}) \\ & + \sum_{j=1}^{\tilde{\kappa}_2(t)} \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right) \left( \frac{n_2}{n_2 - |\hat{\lambda}| \hat{S}_2(T_{2j})} \right) \hat{S}_2(T_{2j}). \end{aligned} \quad (\text{A.11})$$

From the right hand side of Eq. (A.11), combining the first and third terms gives a nonnegative number. Since  $1/(1-x) \geq 1+x$  when  $x < 1$ , the fourth term is bounded below by

$$\sum_{j=1}^{\tilde{\kappa}_2(t)} \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right) \hat{S}_2(T_{2j}) \left( 1 + |\hat{\lambda}| \hat{S}_2(T_{2j})/n_2 \right) = \hat{\zeta}_2(t) + \frac{1}{n_2} \sum_{j=1}^{\tilde{\kappa}_2(t)} \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right) \hat{S}_2^2(T_{2j}) |\hat{\lambda}|,$$

provided that  $|\hat{\lambda}| \hat{S}_2(T_{2j})/n_2 < 1$  almost surely. To show this, assume no ties and note from Eq. (4.13) that  $0 < \hat{\lambda} < \min_{j: T_{2j} \leq t} \{(r_{2j} - d_{2j} \hat{m}_{2j})/\hat{S}_2(T_{2j})\}$ . Also,  $\bar{Y}_2(t)/\hat{S}_2(t) \xrightarrow{\text{a.s.}} 1 - G_2(t) < 1$  uniformly over  $[\tau_1, \tau_2]$ . For large enough  $n_2$ ,  $\epsilon$  sufficiently small, and some  $T_{2l} \neq 0$ , we have

$$\frac{\hat{\lambda}}{n_2} < \min_{j: T_{2j} \leq t} \frac{r_{2j}/n_2}{\hat{S}_2(T_{2j})} \leq \frac{\bar{Y}_2(T_{2l})}{\hat{S}_2(T_{2l})} < 1 - G_2(T_{2l}) + \epsilon < 1$$

almost surely. We therefore obtain a lower bound for  $\alpha(t)$  given by

$$\alpha(t) \geq -\tilde{\zeta}_1(t) + \hat{\zeta}_2(t) + \frac{1}{n_2} \sum_{j=1}^{\tilde{\kappa}_2(t)} \left( \frac{d_{2j} \hat{m}_{2j}}{r_{2j}} \right) \hat{S}_2^2(T_{2j}) |\hat{\lambda}|,$$

from which Eq.(A.6) follows. Proof of Eq.(A.7) can be shown by analogous techniques.  $\square$

**Lemma 5** *The Lagrange multiplier,  $\hat{\lambda}(t) \equiv \hat{\lambda}$ , solving Eq. (4.11), satisfies  $\|\hat{\lambda}\|_{\tau_1}^2 = O_p(n^{1/2})$ .*

**Proof** That the denominators of Eqs. (A.6) and (A.7) are each  $O_p(1)$ , uniformly for  $t \in [\tau_1, \tau_2]$ , follows from  $\|\hat{\Lambda}_i - \Lambda_i\|_0^2 = o(1)$  almost surely (cf. theorem 2.4 of Dikta, 1998) and lemma 2. It remains to show that the numerators of Eqs. (A.6) and (A.7) are each  $O_p(n^{-1/2})$ , uniformly for  $t \in [\tau_1, \tau_2]$ . By applying lemma 3, it suffices to show that  $\alpha(t) + \hat{\zeta}_1(t) - \hat{\zeta}_2(t) = O_p(n^{-1/2})$ . Let  $n_i/n \rightarrow p_i$  as  $n \rightarrow \infty$ . We then have by lemma 1 and results from subsection 4.1 that

$$\begin{aligned} n^{1/2} \left( \alpha(t) + \hat{\zeta}_1(t) - \hat{\zeta}_2(t) \right) &= \sum_{i=1}^2 S_i(t) \frac{n_i^{1/2} (\hat{\Lambda}_i(t) - \Lambda_i(t))}{(n_i/n)^{1/2}} + o_p(1) \\ &\xrightarrow{\mathcal{D}} \sum_{i=1}^2 \frac{S_i(t) U_i(t)}{\sqrt{p_i}} \equiv W(t), \end{aligned} \quad (\text{A.12})$$

where  $W$  is the zero-mean Gaussian process with covariance function given by Eq. (4.16).  $\square$

### A.1 Proof of Theorem 1

From Eq. (4.11), we can write  $\alpha(t) = f_1(\hat{\lambda}) - f_2(-\hat{\lambda})$ , where

$$f_i(\lambda) = \sum_{j=1}^{\tilde{\kappa}_i(t)} \log \left( 1 - \frac{d_{ij} \hat{m}_{ij}}{r_{ij} + \lambda \hat{S}_i(T_{ij})} \right) \hat{S}_i(T_{ij}). \quad (\text{A.13})$$

Note that  $f_i(0) = -\tilde{\zeta}_i(t)$  [cf. Eq. (A.3)]. Before applying a Taylor's expansion, we note that

$$\begin{aligned} f_i'(\lambda) &= \sum_{j=1}^{\tilde{\kappa}_i(t)} \frac{d_{ij} \hat{m}_{ij}}{(r_{ij} + \lambda \hat{S}_i(T_{ij}))(r_{ij} + \lambda \hat{S}_i(T_{ij}) - d_{ij} \hat{m}_{ij})} \hat{S}_i^2(T_{ij}), \\ f_i''(\lambda) &= \sum_{j=1}^{\tilde{\kappa}_i(t)} \frac{d_{ij} \hat{m}_{ij} (2(r_{ij} + \lambda \hat{S}_i(T_{ij})) - d_{ij} \hat{m}_{ij})}{(r_{ij} + \lambda \hat{S}_i(T_{ij}))^2 (r_{ij} + \lambda \hat{S}_i(T_{ij}) - d_{ij} \hat{m}_{ij})^2} \hat{S}_i^3(T_{ij}). \end{aligned}$$

Recall that  $\gamma_i(t)$  is defined by Eq. (4.14). Write  $n_i f'_i(0) = \tilde{\gamma}_i(t)$ , so that

$$\tilde{\gamma}_i(t) = n_i \sum_{j: T_{ij} \leq t} \frac{d_{ij} \hat{m}_{ij}}{r_{ij} (r_{ij} - d_{ij} \hat{m}_{ij})} \hat{S}_i^2(T_{ij}).$$

For  $i = 1, 2$ , let  $|\hat{\xi}_i| \leq |\hat{\lambda}|$ . Taylor's expansion about 0 yields

$$f_i \left( (-1)^{i-1} \hat{\lambda} \right) = -\tilde{\zeta}_i(t) + (-1)^{i-1} \frac{\tilde{\gamma}_i(t) \hat{\lambda}}{n_i} + \frac{1}{2} f_i''(\hat{\xi}_i) \hat{\lambda}^2. \quad (\text{A.14})$$

Applying the Glivenko–Cantelli lemma to  $r_{ij}$  and lemma 5, we have  $\|f_i''(\hat{\xi}_i)\|_{\tau_1}^{\tau_2} = O_p(n_i^{-2})$ . Therefore, by lemma 5, it follows that  $\|f_i''(\hat{\xi}_i) \hat{\lambda}^2\|_{\tau_1}^{\tau_2} = O_p(n_i^{-1}) = O_p(n^{-1})$ .

Furthermore,  $\tilde{\gamma}_i(t)$  is uniformly consistent for  $\gamma_i(t)$  over  $[0, \tau_2]$ . It follows from Eq. (A.14) and Eq. (4.15) that

$$\begin{aligned} \alpha(t) &= -\tilde{\zeta}_1(t) + \tilde{\zeta}_2(t) + \hat{\lambda} \left( \frac{\tilde{\gamma}_1(t)}{n_1} + \frac{\tilde{\gamma}_2(t)}{n_2} \right) + O_p \left( \frac{1}{n} \right) \\ &= -\tilde{\zeta}_1(t) + \tilde{\zeta}_2(t) + \hat{\lambda} n^{-1} \sigma_d^2(t) + O_p(n^{-1}). \end{aligned}$$

Solving for  $\hat{\lambda}$ , we obtain

$$\hat{\lambda} = n \sigma_d^{-2}(t) \left( \alpha(t) + \tilde{\zeta}_1(t) - \tilde{\zeta}_2(t) + O_p(n^{-1}) \right). \quad (\text{A.15})$$

To complete the proof of theorem 1, consider Eq. (4.12). Using Taylor expansions of  $\log(1+x)$  and  $\log(1-x)$  about 0, the leading term of  $-2R(t)$  is a product of  $\hat{\lambda}^2$  and a random scaling factor expressed as a double sum, and equals

$$\hat{\lambda}^2 \sum_{i=1}^2 \sum_{j=1}^{\tilde{\kappa}_i(t)} \frac{d_{ij} \hat{m}_{ij} \hat{S}_i^2(T_{ij})}{r_{ij} (r_{ij} - d_{ij} \hat{m}_{ij})}.$$

Each single sum can be expressed as an integral as in the proof of lemma 1. Applying Eq. (2.6.10) of Andersen et al. (1993), it follows that the double sum equals  $\sigma_d^2(t)/n + o_p(1)$ , uniformly over  $[0, \tau_2]$ . Therefore, applying Eq. (A.15), the leading term of  $-2R(t)$  equals

$$n \hat{\sigma}_d^{-2}(t) \left( \alpha(t) + \tilde{\zeta}_1(t) - \tilde{\zeta}_2(t) + O_p(n^{-1}) \right)^2 + o_p(1) = \left( \frac{W(t)}{\sigma_d(t)} \right)^2 + o_p(1). \quad (\text{A.16})$$

The other terms of  $-2R(t)$  are proportional to

$$\hat{\lambda}^l \left[ \sum_{i=1}^2 \sum_{j=1}^{\tilde{\kappa}_1(t)} \hat{S}_i^l(T_{ij}) \left( \frac{1}{(r_{ij} - d_{ij}\hat{m}_{ij})^{l-1}} - \frac{1}{r_{ij}^{l-1}} \right) \right], \quad l = 3, 4, \dots,$$

each of which is  $o_p(1)$ , uniformly for  $t \in [0, \tau_2]$ . For example, when  $l = 3$ , we have

$$\frac{2}{3} \hat{\lambda}^3 \sum_{j=1}^{\tilde{\kappa}_i(t)} \hat{S}_i^3(T_{1j}) \left( \frac{1}{r_{ij} - d_{ij}\hat{m}_{ij}} - \frac{1}{r_{ij}} \right) \left( \frac{1}{r_{ij} - d_{ij}\hat{m}_{ij}} + \frac{1}{r_{ij}} \right), \quad i = 1, 2,$$

which, uniformly for  $t \in [0, \tau_2]$ , equals

$$\frac{2}{3} O_p(n^{3/2}) O_p(n_i^{-1}) \sum_{j=1}^{\tilde{\kappa}_i(t)} \hat{S}_i^2(T_{ij}) \left( \frac{1}{r_{ij} - d_{ij}\hat{m}_{ij}} - \frac{1}{r_{ij}} \right) = O_p(n^{1/2}) \tilde{\gamma}_i(t) / n_i = o_p(1).$$

Now apply lemma 3 and Eq. (A.12) to complete the proof of theorem 1.  $\square$

## A.2 Large Sample Justification of the Multiplier Bootstrap

Write  $\hat{\mathbb{H}}_i^*(t) = L_{n_i,1}^*(t) + L_{n_i,2}^*(t)$ , where  $L_{n_i,1}^*(t)$  and  $L_{n_i,2}^*(t)$  are defined by Eqs. (4.19)–(4.20). To show that  $\mathbb{W}^*$  defined by Eq. (4.18) has the limit distribution as that of  $W/\sigma_d$ , it suffices to show that  $\hat{\mathbb{H}}_i^*(\cdot)$  has the same weak limit as  $\hat{\mathbb{H}}_i(t) = L_{n_i,1}(t) + L_{n_i,2}(t) + o_p(1)$ . Let  $\mathbb{P}_{n_i}$ ,  $\mathbb{E}_{n_i}$ ,  $\text{Cov}_{n_i}$ , and  $\text{Var}_{n_i}$  be the probability measure, expectation, covariance, and variance with respect to the bootstrap, that is, conditioned on the sample  $\{(Z_{ij}, \delta_{ij}), j = 1, \dots, n_i\}$ .

To show that  $\hat{\mathbb{H}}_i^*(t)$  has the limiting covariance structure given by Eq. (2.1), note that

$$\begin{aligned} \text{Cov}_{n_i}(\hat{\mathbb{H}}_i^*(s), \hat{\mathbb{H}}_i^*(t)) &= \mathbb{E}_{n_i}(L_{n_i,1}^*(s)L_{n_i,1}^*(t)) + \mathbb{E}_{n_i}(L_{n_i,2}^*(s)L_{n_i,2}^*(t)) \\ &\quad + \mathbb{E}_{n_i}(L_{n_i,1}^*(s)L_{n_i,2}^*(t)) + \mathbb{E}_{n_i}(L_{n_i,1}^*(t)L_{n_i,2}^*(s)). \end{aligned} \quad (\text{A.17})$$

Strong consistency of  $\hat{\boldsymbol{\theta}}_i$ , assumption  $A_6$  of Dikta (1998) and the arguments in the proof of theorem 2.4 of Dikta (1998) imply that  $\|m_i(\cdot, \hat{\boldsymbol{\theta}}_i) - m_i(\cdot, \boldsymbol{\theta}_i)\|_0^{\tau_2} = o(1)$  almost surely. Likewise,  $\hat{\alpha}(\cdot, \cdot)$  is strongly uniformly consistent over  $[0, \tau_2] \times [0, \tau_2]$ . Finally,

$\|\bar{Y}_i - y_i\|_0^{r_2} = o(1)$  almost surely. The first quantity on the right hand side of Eq. (A.17) can be computed to yield

$$\begin{aligned}\mathbb{E}_{n_i}(L_{n_i,1}^*(s), L_{n_i,2}^*(t)) &= \frac{1}{n_i} \sum_{j=1}^{n_i} \frac{\hat{m}_{ij}^2}{\bar{Y}_i^2(Z_{ij})} I(Z_{ij} < s \wedge t) \\ &= \frac{1}{n_i} \sum_{j=1}^{n_i} \frac{m_{ij}^2}{y_i^2(Z_{ij})} I(Z_{ij} < s \wedge t) + o(1).\end{aligned}$$

By the strong law of large numbers, for almost all sample sequences  $\{Z_{ij}, \delta_{ij}, 1 \leq j \leq n_i\}$ ,  $\mathbb{E}_{n_i}(L_{n_i,1}^*(s), L_{n_i,2}^*(t))$  converges to the first term on the right hand side of Eq. (2.1). The second quantity on the right hand side of Eq. (A.17) can be computed to yield

$$\begin{aligned}\mathbb{E}_{n_i}(L_{n_i,2}^*(s), L_{n_i,2}^*(t)) &= \frac{1}{n_i} \sum_{j=1}^{n_i} \left( \frac{\delta_{ij} - \hat{m}_{ij}}{\hat{m}_{ij} \hat{m}_{ij}} \right)^2 \int_0^s \int_0^t \frac{\hat{\alpha}(u, Z_{ij})}{\bar{Y}_i(u)} \frac{\hat{\alpha}(v, Z_{ij})}{\bar{Y}_i(v)} d\hat{H}_i(u) d\hat{H}_i(v) \\ &= \frac{1}{n_i} \sum_{j=1}^{n_i} \left( \frac{\delta_{ij} - m_{ij}}{m_{ij} \bar{m}_{ij}} \right)^2 \int_0^s \int_0^t \frac{\alpha(u, Z_{ij})}{y_i(u)} \frac{\alpha(v, Z_{ij})}{y_i(v)} dH_i(u) dH_i(v) \\ &\quad + o(1).\end{aligned}$$

By the strong law of large numbers, for almost all sample sequences  $\{Z_{ij}, \delta_{ij}, 1 \leq j \leq n_i\}$ ,  $\mathbb{E}_{n_i}(L_{n_i,2}^*(s), L_{n_i,2}^*(t))$  converges to the second term on the right hand side of Eq. (2.1). One of the cross-product moment terms on the right hand side of Eq. (A.17) is given by

$$E_{n_i}(L_{n_i,1}^*(t_1), L_{n_i,2}^*(t_2)) = \frac{1}{n_i} \sum_{j=1}^{n_i} \frac{(\delta_{ij} - \hat{m}_{ij}) \hat{m}_{ij}}{\hat{m}_{ij} \hat{m}_{ij}} \frac{I(Z_{ij} < t_1)}{\bar{Y}_i(Z_{ij})} \int_0^{t_2} \frac{\hat{\alpha}(u, Z_{ij})}{\bar{Y}_i(u)} d\hat{H}_i(u), \quad (\text{A.18})$$

with the other term given in an analogous way. The aforementioned arguments, followed by applying iterated conditional expectation with conditioning by  $Z_{i1}$ , implies that the two cross-moment terms in Eq. (A.17) are each zero.

To show that  $\hat{\mathbb{H}}_i^*(\cdot)$  converges weakly to a zero-mean Gaussian process we verify Lindeberg's condition and tightness. We can write  $\hat{\mathbb{H}}_i^*(t) = L_{n_i,1}^*(t) + L_{n_i,2}^*(t) =$



$\sum_{j=1}^{n_i} B_{ij}(t)G_{ij}$ , where

$$B_{ij}(t) = n_i^{-1/2} \left[ \frac{\hat{m}_{ij}}{\bar{Y}_i(Z_{ij})} I(Z_{ij} \leq t) + \frac{\delta_{ij} - \hat{m}_{ij}}{\hat{m}_{ij}\hat{m}_{ij}} \int_0^t \frac{\hat{\alpha}(u, Z_{ij})}{\bar{Y}_i(u)} d\hat{H}_i(u) \right].$$

Let  $s_i^2 = \sum_{j=1}^{n_i} \text{Var}_{n_i}[B_{ij}(t)G_{ij}] = \sum_{j=1}^{n_i} B_{ij}^2(t)$ . As in Mondal and Subramanian (2014), it can be shown that for almost all sample sequences  $\{Z_{ij}, \delta_{ij}, 1 \leq j \leq n_i\}$ , for any  $\eta_i > 0$ ,

$$\frac{1}{s_i^2} \sum_{j=1}^{n_i} \mathbb{E}_{n_1}[B_{ij}^2(t)G_{ij}^2 I(|B_{ij}(t)G_{ij}| > s_i\eta_i)] \rightarrow 0 \text{ as } n \rightarrow \infty.$$

Let  $K \geq 3$ . To verify tightness, we follow Mondal and Subramanian (2014) to show that

$$\overline{\lim}_{n \rightarrow \infty} [\hat{\mathbb{H}}_i^*(t) - \hat{\mathbb{H}}_i^*(s)]^4 \leq K \overline{\lim}_{n \rightarrow \infty} \left[ \sum_{j=1}^{n_i} (B_{ij}(t) - B_{ij}(s))^2 \right]^2, \quad s < t. \quad (\text{A.19})$$

The sum on the right hand side of inequality (A.19) is given by

$$\sum_{j=1}^{n_i} (B_{ij}(t) - B_{ij}(s))^2 = \frac{1}{n_i} \sum_{j=1}^{n_i} \left[ \frac{\hat{m}_{ij}}{\bar{Y}_i(Z_{ij})} I(s < Z_{ij} \leq t) + \frac{\delta_{ij} - \hat{m}_{ij}}{\hat{m}_{ij}\hat{m}_{ij}} \int_s^t \frac{\hat{\alpha}(u, Z_{ij})}{\bar{Y}_i(u)} d\hat{H}_i(u) \right]^2,$$

which can be shown equal to

$$\int_s^t \frac{m_i^2(u)}{y_i^2(u)} dH_i(u) + \int_s^t \int_s^t \frac{\alpha_i(u, v)}{y_i(u)y_i(v)} dH_i(u)dH_i(v) + o_p(1).$$

Therefore, the left hand side of inequality (A.19) is finite and tightness is verified.

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