

EMPIRICAL LIKELIHOOD ANALYSIS FOR THE HETEROSCEDASTIC ACCELERATED FAILURE TIME MODEL

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Abstract: We provide a general framework for the accelerated failure time (AFT) model that ties different data generating mechanisms, namely correlation and regression models, with different estimators that have been proposed for the AFT model. We develop empirical likelihood methods for inference that yield asymptotic chi-squared results by adequately reflecting the underlying data generating mechanisms in the construction of the likelihood. The results are also applicable to censored quantile regression, as illustrated in an example.

Key words and phrases: Censored quantile regression, correlation model, regression model, Wilks' theorem.

1. Introduction

The semi-parametric accelerated failure time (AFT) model is an extension of linear regression to the analysis of survival data such that for some survival times T_i ,

$$\log(T_i) = Y_i = X_i^\top \beta + e_i, \quad (1.1)$$

where the distribution of the error term e_i is unspecified. Due to censoring on the responses, we observe $Z_i = \min(Y_i, C_i)$ and $\delta_i = I_{[Y_i \leq C_i]}$ for some censoring time variables C_i instead of Y_i .

This model has emerged as a useful alternative to the popular Cox proportional hazards model for analysing censored data, as it provides a direct interpretation of the results in terms of quantification of survival times instead of the more abstract hazard rates. However, inference for this model has been challenging. Under random right censoring, inference methods that require a direct estimation of the covariance matrices of the estimators are difficult to implement because the covariance matrices involve nonparametric estimation of the underlying distribution. In particular, for median (or quantile) estimation, the asymptotic variance of $\hat{\beta}$ involves the density at the median (or the quantile of interest), of which a reliable estimation is problematic even without censoring. Resampling methods, as proposed by Jin et al. (2003), constitute an alternative,

but they are computationally complex. Here we propose a new empirical likelihood ratio approach that is computationally simple and which applies to least squares estimation and quantile estimation equally well.

Qin and Jing (2001) and Li and Wang (2003) considered an empirical likelihood approach, in which they kept the likelihood of Owen (1991) unchanged and replaced the constraint equations by $\sum_{i=1}^n p_i X_i (Y_i^* - X_i^\top b) = 0$. Here, Y^* is the ‘synthetic data’ of Koul, Susarla, and Van Ryzin (1981). This approach has two major drawbacks. First, the inference method is based on an estimator that does not perform well (see Simulation Study 3 below). Second, their methods did not yield the non-parametric version of Wilks’ Theorem since their likelihood construction did not appropriately reflect the data generating mechanism. Indeed, the limiting distribution of the $-2 \log$ empirical likelihood ratio is that of a linear combination of weighted independent χ_1^2 random variables with weights to be estimated. In practice, the limiting distribution needs to be calibrated via resampling. These drawbacks have motivated our work.

We first provide a general framework for the AFT model that ties together different data generating mechanisms with the estimators that have been proposed for the AFT model. We distinguish two types of data generating schemes under random right censoring: the accelerated failure time *regression* model and the accelerated failure time *correlation* model. We find that in the accelerated failure time model, the different data generation models require different estimators, unlike the uncensored case of Freedman (1981), and different assumptions on the censoring times C_i as well. We provide details in Section 2.

Going further, we develop empirical likelihood methods that yield asymptotic χ^2 results by adequately reflecting the underlying data generating mechanisms in the construction of the likelihood. With regard to the bootstrap, Freedman (1981) noted that the resampling scheme must reflect the relevant features of the stochastic model assumed to have generated the data. Owen (1991) recognized this with empirical likelihood for linear models. He suggested that the empirical likelihood be constructed based on the homoscedasticity of (X_i, Y_i) for the correlation model, and that the likelihood be based on the homoscedasticity of the errors e_i for the regression model. We extend this distinction to the accelerated failure time model under random right-censoring and call the first type of empirical likelihood formulation *case-wise*, the latter *residual-wise*. Without censoring, the two likelihood formulations yield the same likelihood function and hence produce identical p-values and confidence regions, although interpreted differently (see Owen (1991)). With censoring however, the *case-wise* empirical likelihood is no longer the *residual-wise* one, and estimates, p-values, and confidence regions differ.

The proposed likelihood has a complex form and is not explicit under the constraints. We show that, nevertheless, the resulting inference methods are

computationally simple and yield the standard asymptotic χ^2 results. Results are also applicable to censored quantile regression.

2. Correlation and Regression Model

In this section, we summarize the main characteristics of the two data generating models and corresponding estimators. Our main focus is on the correlation AFT model. For comparison, we include a brief discussion of the empirical likelihood results regarding the AFT regression model in Subsection 2.1.

2.1. Regression model

The regression model is appropriate if, for example, the measurement error of the response is the main source of uncertainty (Freedman (1981)). The true value of the p -dimensional parameter vector β solves $\int (y - x^\top \beta) x dF_e = 0$, where F_e denotes the error distribution. The main assumptions in the regression model are that the covariates, x_1, \dots, x_n , are row vectors of p -dimensional fixed constants that form a matrix of full rank, the errors, e_1, \dots, e_n , are independent with common distribution F_e having mean 0 and finite variance σ^2 (both F_e and σ^2 unknown), and the censoring time variables, C_1, \dots, C_n , are independent with common unknown distribution G and independent of Y_i conditionally on x_i .

Popular estimators of the parameter vector β in this model with censored data include rank-based estimators (see Chapter 7 of Kalbfleisch and Prentice (2002) and references therein; Jin et al. (2003)) and the Buckley–James estimator (Buckley and James (1979); Lai and Ying (1991)).

The following empirical likelihood approach was proposed by Zhou and Li (2008). Let $Z_i = \min(Y_i, C_i)$ and $\delta_i = I_{[Y_i \leq C_i]}$. Let b be a vector, and define the residuals with respect to b as $r_i(b) = z_i - x_i^\top b$. Zhou and Li (2008) proposed that empirical likelihood be formulated with respect to $(r_i(b), \delta_i)$ as follows: given b , the *residual-wise* empirical likelihood for some univariate distribution F is defined as

$$L_e(F) = \prod_{\delta_i=1} p_i \prod_{\delta_i=0} (1 - \sum_{r_j(b) \leq r_i(b)} p_j),$$

where $p_i = dF[r_i(b)]$ is the probability placed by F on the i th residual. The likelihood ratio is

$$R_e(b) = \frac{\sup\{L_e(F) | F \in \mathbb{F}^b\}}{\sup\{L_e(F) | F \in \mathfrak{F}^b\}}, \quad (2.1)$$

where \mathfrak{F}^b denotes the set of all univariate distributions that place positive probabilities on each uncensored $r_i(b)$, as $L_e(F) = 0$ for any F that places zero probability on any uncensored $r_i(b)$, and \mathbb{F}^b denotes a subset of \mathfrak{F}^b that satisfies the constraints $\sum_{i=1}^n p_i \delta_i r_i(b) \tilde{x}_i = 0$ for $\tilde{x}_i = x_i + \sum_{\delta_j=0, j < i} m[j, i] x_j$. Here,

$m[j, i]$ denotes the weights derived from the Buckley–James estimating equation. We refer to Zhou and Li (2008) for more details. As the term in the denominator of (2.1) is maximized by the Kaplan–Meier estimator (Kaplan and Meier (1958)) of the residuals $r_i(b)$ whose calculation is straightforward, maximization is only required for the numerator, analogously to the uncensored case. When \hat{b} is the Buckley–James estimator, $R_e(\hat{b}) = 1$ and confidence regions based on (2.1) are ‘centered’ at the Buckley–James estimate. By formulating similar constraints with respect to rank estimators, Zhou (2005a) proposed a *residual-wise* likelihood for log-rank or Gehan-type estimators. In each case, the resulting likelihood ratio admits chi-squared limiting distributions (Zhou (2005a); Zhou and Li (2008)).

2.2. Correlation model

The correlation model is appropriate if, for example, the goal is to estimate the regression plane for a certain population on the basis of a simple random sample (Freedman (1981)). The true value of the parameter β solves $\iint (y - x^\top \beta)x dF_{xy} = 0$, where F_{xy} denotes the joint $(p + 1)$ -variate distribution of x and y . Here, we assume that the vectors (X_i, Y_i) are independent, the $p \times p$ covariance matrix of the rows of X , $EX^\top X$ is positive definite, and $E\|(X, Y)\|^3$ exists. Some more technical conditions are listed in the appendix.

The estimation method we consider for this model is given through the (case-wise weighted) estimating equation below. Weighted least squares and M-estimation methods have been proposed by Koul, Susarla, and Van Ryzin (1982), Zhou (1992a), Stute (1996), and Gross and Lai (1996). The estimator b can be expressed as the solution of the estimating equation

$$\sum_{i=1}^n w_i (Z_i - X_i^\top b) X_i = 0. \quad (2.2)$$

In contrast to the ‘synthetic data’ approach of Koul, Susarla, and Van Ryzin (1981), Leurgans (1987), and various generalizations, the ‘case-wise weighted’ approach never creates any new response values (i.e. synthetic data). Instead, it tries to recoup the effect of censored responses by properly weighting the uncensored responses. On the other hand, it does not require iteration in the calculation of the estimator, as opposed to the Buckley–James estimator.

Two weighting schemes have been used to determine the weights w_i . Stute (1996) ordered the Z_i so $\delta_{(i)}$ is the censoring indicator δ corresponding to the i th order statistic $Z_{(i)}$, and rewrote the jumps of the Kaplan–Meier estimator of the marginal distribution of Y as

$$\Delta_1 = \delta_{(1)}/n \quad \text{and} \quad \Delta_i = \frac{\delta_{(1)}}{n - i + 1} \prod_{j=1}^{i-1} \left(\frac{n - j}{n - j + 1} \right)^{\delta_{(j)}}, \quad i = 2, \dots, n.$$

He used the Δ_i as weights in (2.2).

On the other hand, inverse censoring probability weights have been used in many different places, for example in van der Laan and Robins (2003) and Rotnitzky and Robins (2005). These weights are given by

$$w_i^* = \frac{\delta_i}{1 - \hat{G}(Z_i)},$$

with $\hat{G}(\cdot)$ being the Kaplan–Meier estimator of the censoring distribution G based on $(Z_i, 1 - \delta_i)$.

The two weighting schemes are in fact identical. Inverse censoring probability weighting is equivalent to weighting by the jumps of the Kaplan–Meier. Indeed, for all t ,

$$[1 - \hat{F}(t)][1 - \hat{G}(t)] = 1 - \hat{H}(t), \quad (2.3)$$

where $\hat{F}(t)$ and $\hat{G}(t)$ are the Kaplan–Meier estimators for Y_i based on (Z_i, δ_i) and the censoring variable C_i based on $(Z_i, 1 - \delta_i)$, respectively, and $\hat{H}(t)$ is the empirical distribution based on Z_i . From (2.3), we observe that when $t = Z_i$ with $\delta_i = 1$, then $\Delta_i[1 - \hat{G}(t)] = 1/n$, from which it follows that

$$\Delta_i = \frac{\delta_i}{n[1 - \hat{G}(Z_i)]} = \frac{w_i^*}{n}.$$

Stute (1996) also proposed

$$\hat{F}_{xy}(A) = \sum_{i=1}^n \Delta_i I_{\{(Z_i, X_i) \in A\}} \quad \text{for some set } A \text{ in } R^{(p+1)}$$

as a multivariate extension of the univariate Kaplan–Meier estimator. Based on these two observations, we call a solution to (2.2) with $w_i = \Delta_i$ *case-wise* weighted estimator.

3. Main Results

We define the *case-wise* empirical likelihood for the AFT correlation model. Reflecting the independent and identical distributions of the vectors (X_i, Y_i) , although the observations are censored, we propose formulating the empirical likelihood *case-wise* as follows. Consider the estimating equation $\int \int (y - x^\top \beta) x dF_{xy} = 0$. For any integrable function $\phi(x, y)$, equality holds for the two integrals $\int \phi(x, y) dF_{xy}$ and $\int \int \phi(x, y) dF_{x|y} dF_y$, where $F_{x|y}$ denotes the conditional distribution of X given Y . Based on the data (X_i, Z_i, δ_i) $i = 1, \dots, n$, a reasonable estimator of $F_{x|y}$ when $y = Z_i$ and $\delta_i = 1$ is a point mass at X_i . In fact, using this conditional distribution coupled with the marginal distribution estimator of

F_y , namely the Kaplan–Meier estimator, one obtains an estimator that is identical to Stute’s \hat{F}_{xy} mentioned above (see the appendix for more details of this equivalency).

Using this relationship, the *case-wise* empirical likelihood is

$$L_{xy}(F_y, F_{x|y}) = \prod_{\delta_i=1} 1 \prod_{\delta_i=0} p_i \prod (1 - \sum_{Z_j \leq Z_i} p_j),$$

where $p_i = dF_y[Z_i]$ is the probability that F_y places on the i th *case*. Since the conditional distribution $F_{x|y}$ remains as a point mass throughout (as discussed above) and does not change, we drop $F_{x|y}$ from L_{xy} and denote F_y simply as F . Similarly we drop the constant point mass from the likelihood

$$L_{xy}(F_y) = \prod_{\delta_i=1} p_i \prod_{\delta_i=0} (1 - \sum_{Z_j \leq Z_i} p_j).$$

The likelihood ratio is

$$R_{xy}(b) = \frac{\sup\{L_{xy}(F)|F \in \tilde{\mathbb{F}}^b\}}{\sup\{L_{xy}(F)|F \in \mathfrak{F}\}}, \quad (3.1)$$

where \mathfrak{F} is the set of univariate distributions that place positive probabilities on each uncensored case (as $L_{xy}(F) = 0$ for any F that places zero probability on some uncensored (Z_i, δ_i)), and $\tilde{\mathbb{F}}^b$ denotes the subset of \mathfrak{F} that satisfies the constraints

$$\sum_{i=1}^n p_i \delta_i (Z_i - X_i^\top b) X_i = 0.$$

This constraint can also be interpreted as

$$\sum_{Z_i} \sum_{X_j} p_i \delta_i (Z_i - X_j^\top b) X_j d_{ij} = 0 \quad \text{or} \quad \int \int (y - x^\top b) x d\hat{F}_{xy} = 0,$$

where $d_{ij} = 1$ if and only if $i = j$ and zero otherwise, and \hat{F}_{xy} is similar to Stute’s estimator except that we identify $p_i = \Delta_i$.

The denominator of (3.1) is provided when F is the Kaplan–Meier estimator and the maximization is required for the numerator only, which can be obtained using the method of Zhou (2005b), among others. When b is the *case-wise* weighted estimator (the solution to estimating equation (2.2)), then $R_{xy}(b) = 1$ and confidence regions based on (3.1) are ‘centered’ at this estimator.

Consider the AFT correlation model equation (1.1) and the testing of the null hypothesis $H_0 : \beta = \beta_0$ vs. $H_1 : \beta \neq \beta_0$. The following theorem contains the main result for the proposed *case-wise* empirical likelihood ratio statistic for least squares regression. A proof can be found in the Appendix.

Theorem 1. For the correlation model under $H_0 : \beta = \beta_0$, conditions (C1)–(C3) and (C6) from the Appendix and assumptions of Theorem 3.1 in Zhou (1992b), imply that $-2 \log R_{xy}(\beta_0) \rightarrow \chi_p^2$ in distribution as $n \rightarrow \infty$.

In many applications, inference is only sought for a part of the β vector. A usual approach is to “profile” out the components that are not under consideration. Profiling has been proposed for empirical likelihood in uncensored cases (e.g., Qin and Lawless (2001)). Under censoring, Lin and Wei (1992) proposed profiling with Buckley-James estimators. We similarly consider a profile empirical likelihood ratio: let $\beta = (\beta_1, \beta_2)$ where $\beta_1 \in R^q$, $q < p$, is the part of the parameter under testing. Similarly, let $\beta_0 = (\beta_{10}, \beta_{20})$. A profile empirical likelihood ratio for β_1 is given by $\sup_{\beta_2} R_{xy}(\beta = (\beta_1, \beta_2))$.

Theorem 2. Consider the correlation model and assume conditions of Theorem 1 above. Under $H_0 : \beta_1 = \beta_{10}$, we have $-2 \log \sup_{\beta_2} R_{xy}(\beta = (\beta_{10}, \beta_2)) \rightarrow \chi_q^2$ in distribution as $n \rightarrow \infty$.

Similar results hold for censored quantile models when the τ th conditional quantile of Y_i is modelled by

$$Q_\tau(\log T_i | X_i) = Q_\tau(Y_i | X_i) = X_i^\top \beta_\tau,$$

and, instead of Y_i , we observe $Z_i = \min(Y_i, C_i)$ and $\delta_i = I_{[Y_i \leq C_i]}$ for some censoring time variables C_i . This model may also be written as $Y_i = X_i^\top \beta_\tau + e_i$, with the error terms e_i independent random variables with zero τ th quantiles. When $\tau = 0.5$, this is censored median regression, and Huang, Ma, and Xie (2007) proposed a *case-wise* weighted estimator that is a special case of our *case-wise* weighted estimator. Here, we propose a *case-wise* empirical likelihood inference for the general censored quantile regression using

$$\mathbb{R}_{xy}(b) = \frac{\sup\{L_{xy}(F) | F \in \tilde{\mathfrak{F}}^b\}}{\sup\{L_{xy}(F) | F \in \mathfrak{F}\}},$$

where $\tilde{\mathfrak{F}}^b$ is the subset of \mathfrak{F} that satisfies the constraints

$$\sum_{i=1}^n p_i \delta_i \psi_\tau(Z_i - X_i^\top b) X_i = 0,$$

and $\psi_\tau(u)$ is the derivative of the so-called check function $\rho_\tau(u) = u(\tau - I_{[u < 0]})$ of Koenker and Bassett (1978). Similar to the censored accelerated failure time model, the denominator of $\mathbb{R}_{xy}(b)$ is maximized by the Kaplan–Meier estimator, and thus when calculating $\mathbb{R}_{xy}(b)$, maximization is only needed for the numerator.

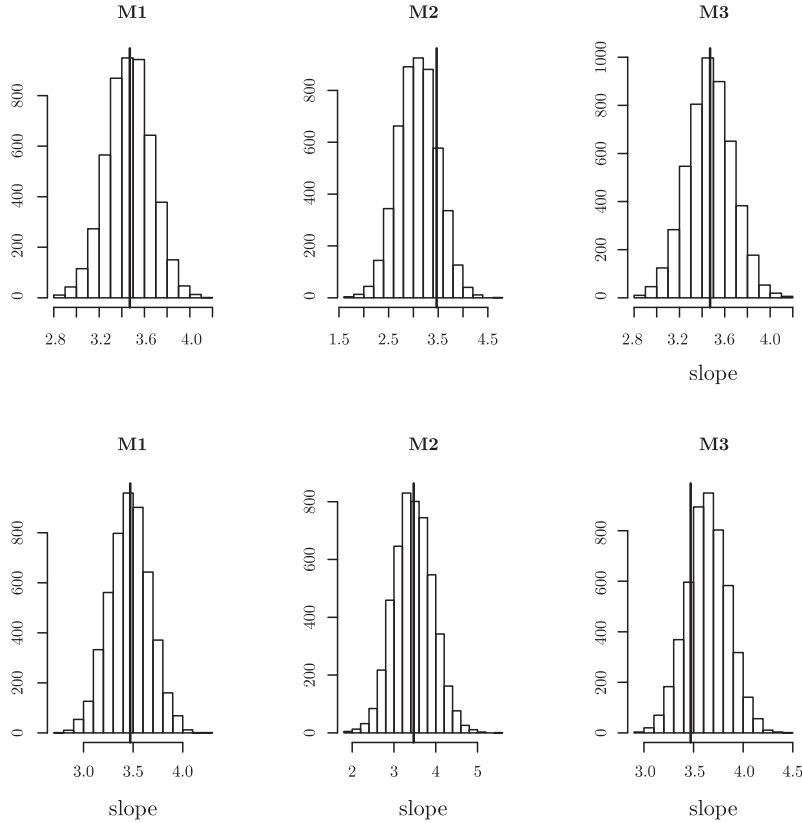


Figure 1. Histogram plots of slope estimates by the Buckley–James estimator and *case-wise* weighted estimator based on 5,000 simulations with $n = 400$ with 28.5% censoring in each case. Vertical lines indicate the true value of the slope parameter. First row is Buckley–James estimator.

Theorem 3. Under $H_0 : \beta_\tau = \beta_0$ and assuming conditions (C1)–(C6) of the Appendix, for given τ , $-2 \log \mathbb{R}_{xy}(\beta_0) \rightarrow \chi_p^2$ in distribution as $n \rightarrow \infty$. If $\beta_\tau = (\beta_1, \beta_2)$ with $\beta_1 \in \mathbb{R}^q$, $q < p$, under $H_0 : \beta_1 = \beta_{10}$ we have $-2 \log \sup_{\beta_2} \mathbb{R}_{xy}(\beta_\tau = (\beta_{10}, \beta_2)) \rightarrow \chi_q^2$ in distribution as $n \rightarrow \infty$.

4. Simulation Studies

4.1. Simulation study 1

We compared the *case-wise* and *residual-wise* (Zhou and Li (2008)) empirical likelihoods using three models: homoscedastic errors with independent censoring (M1), heteroscedastic errors with independent censoring (M2), and homoscedas-

tic errors with censoring dependent on x (M3).

$$\begin{aligned} \text{M1} : Y_i &= X_i^\top \beta + e_i, & C_i &= \epsilon_i, \\ \text{M2} : Y_i &= X_i^\top \beta + e_i \exp(X_i^\top \gamma), & C_i &= \epsilon_i, \\ \text{M3} : Y_i &= X_i^\top \beta + e_i, & C_i &= X_i^\top \eta + \epsilon_i, \end{aligned}$$

where $X_i = (1, X_{1i})$ with $X_{1i} \sim U(0, 1)$, $e_i \sim N(0, 1)$, and ϵ_i is from a mixture of $N(3, 3^2)$ and $U(-2, 18)$. Here, β , γ , and η were chosen such that the censoring in each model was 28.5% and the error heteroscedasticity in (M2) and the conditional dependency of C_i on X_i in (M3) was non-negligible. Due to the heteroscedastic errors, the R^2 of the least squares regression analysis of (M2) (without censoring) was on average reduced to 0.25 from 0.5 of an equivalent analysis of (M1), and an average R^2 of 0.28 was yielded for the least squares regression analysis of C_i on X_i for (M3).

We first examine the slope estimate by the *case-wise* weighted and the Buckley–James estimator. Figure 1 shows that the Buckley–James estimator is biased for the heteroscedastic errors model (M2), while the *case-wise* weighted estimator is not. When the censoring variables are dependent on X_i (M3), however, the *case-wise* weighted estimator is biased.

We confirmed that the differences in the data generating models require the empirical likelihood to be formulated differently. Q-Q plots in Figure 2 show that only the *case-wise* empirical likelihood is valid for the heteroscedastic errors model (M2), and only the *residual-wise* likelihood is valid for covariate-dependent censoring (M3). Deviation from the limiting chi-squared distribution in the likelihood ratio statistic corresponds to bias in the estimates. Both empirical likelihoods were appropriate for (M1), as they are equivalent to the first order with the same limiting chi-squared distribution.

4.2. Simulation study 2

We examined the performance of the *case-wise* empirical likelihood for censored quantile regression using three models that are similar to those used in Simulation Study 1.

$$\begin{aligned} \text{M1} : Y_i &= X_i^\top \beta + e_i, & C_i &= \epsilon_i, \\ \text{M2} : Y_i &= X_i^\top \beta + e_i(X_i + 1), & C_i &= \epsilon_i, \\ \text{M3} : Y_i &= X_i^\top \beta + e_i, & C_i &= X_{1i} + \epsilon_i, \end{aligned}$$

where $X_i = (1, X_{1i})$ with $X_{1i} \sim U(0, 1)$. The error $e_i \sim N(0, 0.75^2)$ in (M1) and (M3), $e_i \sim N(0, 0.5^2)$ in (M2). The parameter $\beta = (0.5, 1.5)$; for the censoring $\epsilon_i \sim 0.5 + \exp(0.5)$ in (M1) and (M2), and $\epsilon_i \sim \exp(0.5)$ in (M3). The

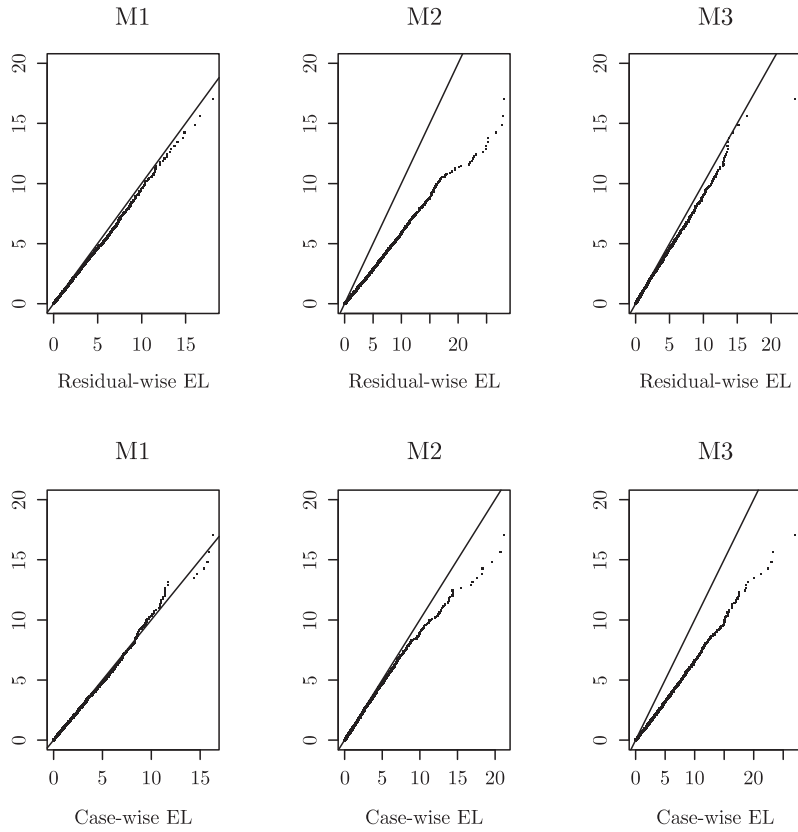


Figure 2. Q-Q plots of quantiles of χ^2_2 versus $-2 \log R_e(\beta)$ (*residual-wise*) and $-2 \log R_{xy}(\beta)$ (*case-wise*), respectively, based on 5,000 simulations with $n = 400$ and 28.5% censoring in each case.

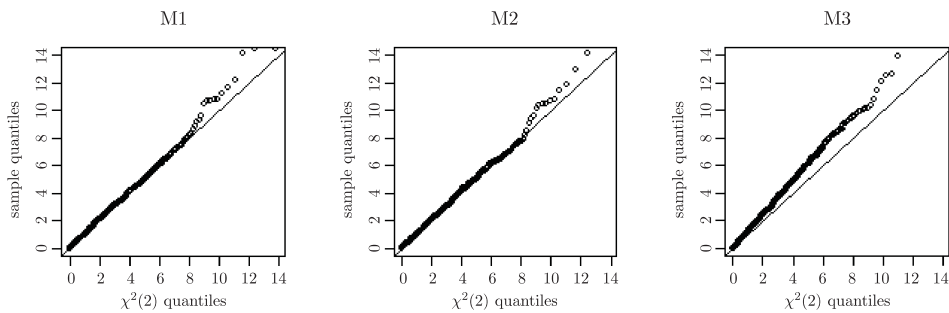


Figure 3. Q-Q plots of the quantiles χ^2_2 versus $-2 \log R_{xy}(\beta_0)$ (*case-wise*) based on 1,000 simulations with sample size $n = 200$ and about 30% censoring in each case.

Table 1. Simulation results comparing $\hat{\beta}_{KSV}$ with $\hat{\beta}_{ZS}$

	With intercept				Without intercept	
	$\hat{\beta}_{KSV}$		$\hat{\beta}_{ZS}$		$\hat{\beta}_{KSV}$	$\hat{\beta}_{ZS}$
	intercept	slope	intercept	slope	slope	slope
Mean	-0.00088	0.99964	-0.00122	1.00002	0.99899	0.99907
Variance	0.02061	0.02002	0.01395	0.01133	0.00312	0.00230

censoring percentage was about 30%. We fit $Q_\tau(Y_i|X_i)$ at $\tau = 0.25$. The quantile regression Q-Q plots in Figure 3 exhibit similar properties as the mean regression in Simulation Study 1. Specifically, the *case-wise* empirical likelihood approach for censored quantile regression is not adversely affected by heteroscedastic errors, but it is biased in the presence of covariate-dependent censoring.

4.3. Simulation study 3

In order to compare the proposed method with the empirical likelihood method proposed by Qin and Jing (2001) and Li and Wang (2003), it is instructive to compare the estimators that form the basis of the proposed inferential methods. Their estimator is based on the ‘synthetic data’ approach of Koul, Susarla, and Van Ryzin (1981), we refer to it as $\hat{\beta}_{KSV}$. The estimator considered here is based on Zhou (1992a) and Stute (1996), denoted $\hat{\beta}_{ZS}$.

For the direct comparison, we assumed the simplest model from the previous section, namely (M1), and used the setting $X_i = (1, X_{1i})$, $X_{1i} \sim U(1, 0.5^2)$, $e_i \sim N(0, 0.5^2)$, $\beta = (0, 1)$, and $\epsilon_i \sim N(6 \cdot 1, 4^2)$. Table 1 provides results based on 10,000 simulations for sample size $n = 100$. Both estimators appear to be unbiased, but the variance of the components of $\hat{\beta}_{ZS}$ was at least 30% and 40% smaller for the model including the intercept, and at least 25% smaller for the without-intercept model. The simulation indicates that the estimator $\hat{\beta}_{KSV}$ is far from efficient, any inference method based on this estimator cannot be expected to perform as well as inferential procedures based on $\hat{\beta}_{ZS}$.

4.4 Simulation study 4

Here we compared confidence intervals based on the proposed empirical likelihood method with those based on Huang, Ma, and Xie (2007), comparing average length and coverage probability. The methods provide the same parameter estimates, but the method of Huang, Ma, and Xie (2007) requires a bootstrap resampling technique for the calculation of confidence intervals.

The assumed model was $Y_i = X_i\beta + \epsilon_i$, where $\beta = 1$, $X_i \sim N(1, 0.25)$, $\epsilon_i \sim N(0, 0.25)$. The censoring distribution was chosen as $C_i \sim N(3.1, 0.25)$ to generate about 30% censoring. Sample sizes were $n = 40, 60, \text{ and } 120$. We

Table 2. Simulation results comparing proposed empirical likelihood based (EL) confidence intervals with Huang, Ma, and Xie (2007) (HMX). Nominal level 95%.

		$n = 40$		$n = 60$		$n = 120$	
		EL	HMX	EL	HMX	EL	HMX
Interval	Mean	0.3213	0.3259	0.2698	0.2713	0.1917	0.1909
Length	Std. Dev.	0.0648	0.0681	0.0443	0.0463	0.0230	0.0233
Coverage	Probability	0.925	0.928	0.928	0.923	0.944	0.939

used 1,000 bootstrap replications for the application of the method proposed by Huang, Ma, and Xie (2007). Simulation size was 1,000.

Results are displayed in Table 2. The methods show very similar performance in terms of confidence interval length and coverage probability. An advantage of the proposed empirical likelihood procedure is that it does not require a bootstrap, which makes it less computationally demanding and free of possible bootstrap sampling error.

5. Small-Cell Lung Cancer Data

We consider a lung cancer data set (Maksymiuk et al. (1994)) that has been analysed by Ying, Jung, and Wei (1995) using median regression, and by Huang, Ma, and Xie (2007) using a least absolute deviations method in the accelerated failure time (AFT) model. In this study, 121 patients with limited-stage small-cell lung cancer were randomly assigned to one of two different treatment sequences, A and B , with 62 patients assigned to A and 59 patients to B . Each death time was either observed or administratively censored, and the censoring variable did not depend on the covariates *treatment* and *age*.

Denote the treatment indicator variable by X_{1i} , and the entry age for the i th patient by X_{2i} , where $X_{1i} = 1$ if the patient is in group B . Let Y_i be the base 10 logarithm of the i th patient's failure time. We assume the AFT model

$$Y_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \sigma(X_{1i}, X_{2i}) \epsilon_i .$$

The estimated parameter values obtained using the approach described in this paper need to be equal to the ones from Huang, Ma, and Xie (2007), provided weighting has been done in the same way. The major difference is in inference about the parameters, where empirical likelihood has the advantage that it is not necessary to estimate the asymptotic variance of the estimator in order to perform hypothesis tests and to construct confidence regions. An empirical likelihood confidence region for this data set is displayed in Figure 4.

Median regression estimates were obtained by Ying, Jung, and Wei (1995) and Huang, Ma, and Xie (2007) as

$$\hat{\beta}_0 = 3.028, \hat{\beta}_1 = -0.163, \text{ and } \hat{\beta}_2 = -0.004 \quad (\text{Ying, Jung, and Wei (1995)})$$

$$\hat{\beta}_0 = 2.693, \hat{\beta}_1 = -0.146, \text{ and } \hat{\beta}_2 = 0.001 \quad (\text{Huang, Ma, and Xie (2007)}).$$

Huang, Ma, and Xie (2007) did not always treat the largest Y observation as uncensored. This resulted in weights that sum to less than one (the sum of the weights without the last observation is 0.85). We recommend treating the largest Y observation as uncensored so that the weights sum to one lest the estimation be biased since the information from the largest Y observation is ignored. Treating the largest Y as uncensored, the median regression estimates are

$$\hat{\beta}_0 = 2.603, \hat{\beta}_1 = -0.263, \text{ and } \hat{\beta}_2 = 0.0038 \quad (\text{with last weight}).$$

While the different approaches lead to the same conclusions with regard to the treatment (predictor X_1), the data analysis suggests possibly conflicting interpretations regarding the role of the predictor X_2 (entry age). Ying, Jung, and Wei (1995) calculate a negative coefficient (-0.004), while Huang, Ma, and Xie (2007) and the approach proposed here find 0.001 and 0.003837, respectively, depending on whether or not the largest observation is treated as uncensored. However, the confidence interval for β_2 in Ying, Jung, and Wei (1995) includes zero (-0.0162, 0.003), and so does the empirical likelihood confidence interval based on the newly proposed inference method, (-0.0024, 0.0151). Thus, the methods agree that the predictor “entry age” is not significant. The empirical likelihood based confidence interval is about 10% shorter than the interval provided by Ying, Jung, and Wei (1995). This is not surprising when considering that the latter is not based on the likelihood and may therefore not be efficient, and the former does not have to rely on inverting the estimated variance-covariance matrix of an estimating function, which could lead to unstable estimates. Perhaps this explains the differences in the estimated intercept that lead to rather different estimated median survival times between $10^{2.6} = 398$ and $10^3 = 1,000$ days.

6. Concluding Remarks

We note some differences and similarities of the *case-wise* and *residual-wise* empirical likelihood. A trade-off exists between assumptions on the error terms and the censoring time variables: the homoscedastic errors assumption of the regression model is relaxed for the correlation model, while the conditional independence assumption on C_i is strengthened such that the C_i need to be independent of the random vector (X_i, Y_i) (or at least satisfy assumption (C1) in the Appendix). This is confirmed by the simulation study: the *case-wise* empirical

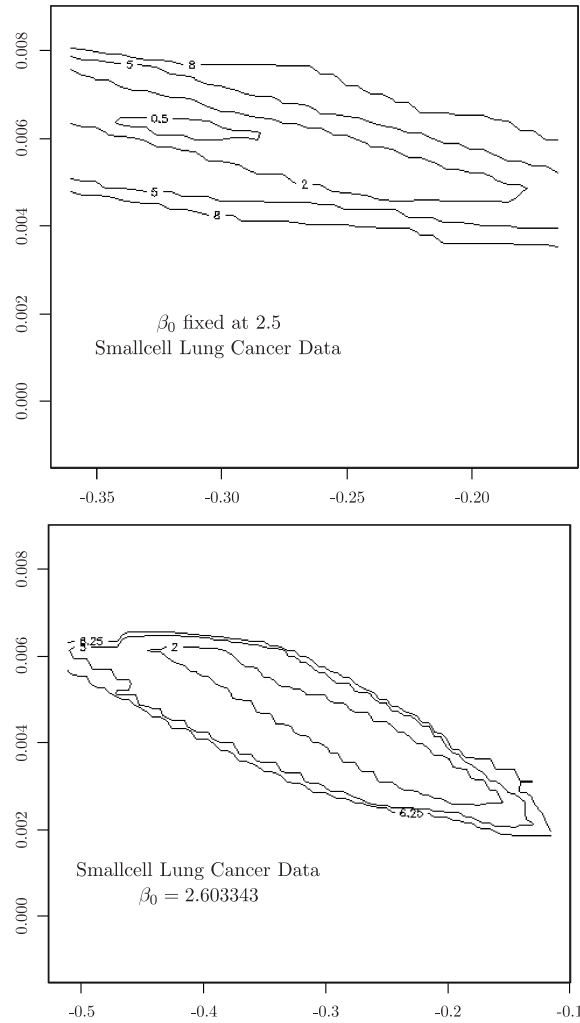


Figure 4. Confidence regions for (β_1, β_2) in the small-cell lung cancer data. The original parameter space is 3-dimensional, therefore only two two-dimensional cuts at $\beta_0 = 2 \cdot 5$ and $\beta_0 = 2 \cdot 603$ are displayed. The contour lines correspond to different critical values.

likelihood is biased when C_i are only conditionally independent of Y_i , while the *residual-wise* one is biased in the presence of heteroscedastic errors. Hence, the *case-wise* empirical likelihood is more appropriate when error heteroscedasticity is more a concern than independent censoring. The computation of (3.1) does not involve X_i with $\delta_i = 0$, so the *case-wise* empirical likelihood allows missingness in X_i with $\delta_i = 0$, while the *residual-wise* empirical likelihood does not.

Both methods provide a computationally simple inference method, and soft-

ware is readily available in R . This contrasts with other methods that require a direct estimation of the covariance matrices of the estimators. For example, the median regression approach proposed by Ying, Jung, and Wei (1995) requires for inference the inversion of an estimated variance-covariance matrix which may be unstable, in particular at the tails of the survival functions. Also, this approach is expected to lack efficiency because it is not based on the likelihood.

Portnoy (2003) investigated the censored quantile regression process using a recursive algorithm that fits the entire quantile regression process successively from below. The model accommodates both heteroscedastic errors and conditionally independent censoring. His method, however, requires the strong assumption that the entire quantile process is linear in x_i . This implies that the validity of quantile estimates at, for example, the median depends on the linearity of the entire conditional functionals at all lower quantiles, as non-linear relations at any of the lower quantiles bias the median estimates. The Peng and Huang (2008) method is similarly restricted by the global linearity assumption. Wang and Wang (2009) relaxed the global linearity assumption by a local Kaplan-Meier method. However, their method is subject to the so-called “curse-of-dimensionality”. For inference, all these methods rely on resampling. The proposed *case-weighted* estimator and accompanying *case-wise* empirical likelihood method provide simple and practical alternatives with only slightly more restrictive conditions.

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Appendix

Let $(X_1, Y_1), \dots, (X_n, Y_n)$ be a random sample of vectors from a joint distribution $F(x, y)$, where the Y_i are subject to right censoring, and take $\phi(x, y) = (y - x^\top \beta)x$ for the AFT model, $\phi(x, y) = \psi_\tau(y - x^\top \beta)x$ for the quantile regression model.

A.1. Assumptions

- (C1) The (transformed) survival times Y_i and the censoring times C_i are independent. Furthermore, $\text{pr}(Y_i \leq C_i | X_i, Y_i) = \text{pr}(Y_i \leq C_i | Y_i)$.
- (C2) The survival functions $\text{pr}(Y_i \geq t)$ and $\text{pr}(C_i \geq t)$ are continuous and either $\xi_Y < \xi_C$, or $\forall t < \infty, \text{pr}(Z_i \geq t) > 0$. Here, for any random variable U , ξ_U denotes the right end point of the support of U .
- (C3) The X_i are independent, identically distributed according to some distribution with finite, nonzero variance, and they are independent of Y_i and of C_i .

- (C4) Let $F_e(\cdot|x)$ be the conditional distribution of the e_i given $X = x$, with $f_e(\cdot|x)$ as the corresponding conditional density function. For the given τ , $F_e(0|x) = \tau$, and $f_e(u|x)$ is continuous in u in a neighborhood of 0 for almost all x .
- (C5) $E(XX^\top f_e(0|X))$ is finite and nonsingular.
- (C6) $\sigma_{KM}^2(\phi) < \infty$, where $\sigma_{KM}^2(\phi)$ is the asymptotic variance of $\sqrt{n} \sum_i \phi(x_i, t_i) \Delta \hat{F}_{KM}(t_i)$.

Some of these assumptions have been formulated in related works (Zhou (1992b); Stute (1996); Huang, Ma, and Xie (2007)).

A.2. Equivalency Between Two Kaplan–Meier Estimators

We show that in the correlation model, the Kaplan–Meier estimator of the marginal distribution F_y is identical to Stute’s \hat{F}_{xy} , multivariate extension of the univariate Kaplan–Meier estimator. Recall that Z_i are the censored values of Y_i , $Z_i = \min(Y_i, C_i)$, with the censoring indicator δ_i .

Under (C1), a reasonable estimate for the marginal distribution of Y is the Kaplan–Meier estimate \hat{F}_{KM} based on Z_i and δ_i . A reasonable estimate of the conditional distribution $F(x|y)$ is

$$\hat{F}(x|y = z_i) = \text{point mass at } x_i, \text{ if } \delta_i = 1; \quad (\text{A.1})$$

otherwise $\hat{F}(x|y = z_i)$ is left undefined. This gives rise to an estimator of the joint distribution, identical to the one proposed by Stute (1996).

For the function of the random vector $\phi(x, y)$, the expectation

$$E\phi(x, y) = \int \phi(x, y) dF(x, y) = \int \int \phi(x, y) dF(x|y) dF(y)$$

can be estimated using the joint distribution estimator, that is, the Kaplan–Meier estimator for the marginal distribution, and the conditional distribution defined in (A.1):

$$\sum_i \left[\sum_j \phi(x_j, t_j) I_{[j=i]} \delta_i \right] \Delta \hat{F}_{KM}(t_i) = \sum_i \phi(x_i, t_i) \Delta \hat{F}_{KM}(t_i).$$

If we take the function ϕ to be $I[s \leq x; t \leq y]$, this also defines an estimator of the joint distribution $F(x, y)$.

By the Law of Large Numbers and Central Limit Theorem for this estimator (see Stute (1996)) and the assumption $\int \phi(x, t) dF(x, t) = 0$, we have, as $n \rightarrow \infty$,

$$\sqrt{n} \left(\sum_{i=1}^n \phi(x_i, t_i) \Delta \hat{F}_{KM}(t_i) \right) \rightarrow N(0, \sigma_{KM}^2(\phi))$$

in distribution, where $\sigma_{KM}^2(\phi) < \infty$ by (C6). The variance $\sigma_{KM}^2(\phi)$ can be written in several different but equivalent ways. Akritas (2000) gave a form of $\sigma_{KM}^2(\phi)$ on which the following variance estimator is based. The variance $\sigma_{KM}^2(\phi)$ can be consistently estimated by

$$\hat{\sigma}^2 = \sum_i [\phi(x_i, t_i) - \bar{\phi}(t_i)]^2 \frac{\Delta \hat{F}_{KM}(t_i)}{1 - \hat{G}_{KM}(t_i)}, \quad (\text{A.2})$$

where $\bar{\phi}(s) = \sum_{j:t_j > s} \phi(x_j, t_j) \Delta \hat{F}_{KM}(t_j) / [1 - \hat{F}_{KM}(s)]$ is the so called advanced-time transformation of Efron and Johnstone (1990). See also Akritas (2000) for details.

A.3 Outline of the Proofs for Theorems 1 and 3

Recall that when computing the numerator in the likelihood ratio (3.1), we need to compute the supremum of the empirical likelihood over all F , dominated by the Kaplan–Meier estimator, that satisfy the constraint equations. We first construct these distributions indexed by an $h(\cdot)$ function. Later we take the supremum over h .

Notice that any distribution that is dominated by the Kaplan–Meier estimator can be written as (by its jumps)

$$\Delta F(t_i) = \Delta \hat{F}_{KM}(t_i) \frac{1}{1 + h(t_i)}$$

for some h , but may not satisfy the constraint equations. We thus write an F that is dominated by the Kaplan–Meier *and* satisfies the constraint equation (A.4) as

$$\Delta F_\lambda(t_i) = \Delta \hat{F}_{KM}(t_i) \times \frac{1}{1 + \lambda h(x_i, t_i)} \times \frac{1}{C(\lambda)}, \quad i = 1, 2, \dots, n, \quad (\text{A.3})$$

where $C(\lambda)$ is the normalizing constant

$$C(\lambda) = \sum_{i=1}^n \frac{\Delta \hat{F}_{KM}(t_i)}{1 + \lambda h(x_i, t_i)}.$$

This parameter λ is chosen so that the resulting F satisfies the constraint equations, i.e., λ is the solution of

$$\int \phi(x, t) dF_\lambda(x, t) = \frac{1}{C(\lambda)} \sum_{i=1}^n \Delta \hat{F}_{KM}(t_i) \frac{\phi(x_i, t_i)}{1 + \lambda h(x_i, t_i)} = 0. \quad (\text{A.4})$$

We suppose the function $h = h(x, y)$ satisfies $\|h(x, y)\| = 1$ and $|\int \phi(x, y) h(x, y) dF(x, y)| \geq \epsilon > 0$.

Lemma A below gives an asymptotic representation of λ , and we denote this parameter value as λ_0 . With λ_0 , the distribution F_{λ_0} satisfies the conditions $F_{\lambda_0} \ll \hat{F}_{KM}$ and $\int \phi(x, t) dF_{\lambda_0}(x, t) = 0$.

When restricted to these distributions (indexed by h), we define a (profile) empirical likelihood ratio function as

$$\mathcal{R}_h = \left\{ \frac{L_{xy}(F_{\lambda_0})}{L_{xy}(\hat{F}_{KM})} \mid h \text{ satisfies (i), (ii) above} \right\},$$

where L_{xy} is defined in Section 3. By Theorem A below we have

$$-2 \log R_{xy} = -2 \log(\sup_h \mathcal{R}_h) = \chi_{(p)}^2 + o_p(1),$$

and the proof is complete.

Lemma A. Under (C1)–(C6) and the conditions on h ,

- (1) with probability tending to one as $n \rightarrow \infty$, λ_0 is well defined,
- (2) $\lambda_0 = O_p(n^{-1/2})$ as $n \rightarrow \infty$,
- (3) λ_0 has the representation given at (A.5) for $n \rightarrow \infty$.

Proof. Expanding (A.4), we have

$$\begin{aligned} 0 &= \sum_{i=1}^n \Delta \hat{F}_{KM}(t_i) \frac{\phi(x_i, t_i)}{1 + \lambda_0 h(x_i, t_i)} \\ &= \sum_{i=1}^n \phi(x_i, t_i) \Delta \hat{F}_{KM}(t_i) - \lambda_0 \sum_{i=1}^n \phi(x_i, t_i) h(x_i, t_i) \Delta \hat{F}_{KM}(t_i) \\ &\quad + \lambda_0^2 \sum_{i=1}^n \frac{\phi(x_i, t_i) h^2(x_i, t_i)}{1 + \lambda_0 h(x_i, t_i)} \Delta \hat{F}_{KM}(t_i). \end{aligned}$$

It follows that

$$\lambda_0 = \frac{\sum_{i=1}^n \phi(x_i, t_i) \Delta \hat{F}_{KM}(t_i)}{\sum_{i=1}^n \phi(x_i, t_i) h(x_i, t_i) \Delta \hat{F}_{KM}(t_i)} + o_p(n^{-1/2}). \quad (\text{A.5})$$

The uniqueness of λ_0 follows from observing that in (A.4), $C(\lambda)$ is positive, and the remaining term is strictly monotone in λ . Existence requires feasibility of the parameter under the hypothesis (for a detailed discussion of feasibility in censored empirical likelihood see Pan and Zhou (2002)). However, for $n \rightarrow \infty$, the probability that the true parameter is feasible approaches one.

Theorem A If the conditions in Lemma A hold, then, as $n \rightarrow \infty$,

$$-2 \log \mathcal{R}_h = -\lambda_0 f''(0) \lambda_0 + o_p(1),$$

where $f(\cdot)$ is defined at (A.6). Furthermore,

$$-2 \log R_{xy} = -2 \log(\sup_h \mathcal{R}_h) = \chi_{(p)}^2 + o_p(1).$$

Proof. We assume $p = 1$ for simplicity. The same arguments work when $p \geq 1$. Define the marginal empirical likelihood as a function of λ by

$$f(\lambda) = \log \prod_{i=1}^n (\Delta F_\lambda(T_i))^{\delta_i} (1 - F_\lambda(T_i))^{1-\delta_i}, \quad (\text{A.6})$$

where $|\lambda| \leq C|\lambda_0|$. Then

$$f(0) = \log \prod_{i=1}^n (\Delta \hat{F}_{KM}(T_i))^{\delta_i} (1 - \hat{F}_{KM}(T_i))^{1-\delta_i} = L_{xy}(\hat{F}_{KM}).$$

By Lemma A, $\lambda_0 = O_p(n^{-1/2})$, so we can apply Taylor's expansion for $f(\lambda_0)$:

$$f(\lambda_0) = f(0) + \lambda_0 f'(0) + \frac{\lambda_0^2}{2} f''(0) + \frac{\lambda_0^3}{3!} f'''(\xi), \quad |\xi| \leq |\lambda_0|. \quad (\text{A.7})$$

Substituting (A.3) in (A.6),

$$\begin{aligned} f(\lambda) &= \sum_{i=1}^n \delta_i \log \Delta \hat{F}_{KM}(T_i) - \sum_{i=1}^n \delta_i \log(1 + \lambda h(x_i, T_i)) - n \log \left(\sum_{i=1}^n \frac{\Delta \hat{F}_{KM}(T_i)}{1 + \lambda h(x_i, T_i)} \right) \\ &\quad + \sum_{i=1}^n (1 - \delta_i) \log \left(\sum_{j:T_j > T_i} \frac{\Delta \hat{F}_{KM}(T_j)}{1 + \lambda h(x_j, T_j)} \right). \end{aligned}$$

Some tedious but straightforward calculation shows that $f'(0) = 0$ and that the second derivative of f with respect to λ , evaluated at $\lambda = 0$, is

$$\begin{aligned} f''(0) &= n \left(\sum_{i=1}^n h(x_i, T_i) \Delta \hat{F}_{KM}(T_i) \right)^2 - n \sum_{i=1}^n h^2(x_i, T_i) \Delta \hat{F}_{KM}(T_i) \\ &\quad + \sum_{i=1}^n (1 - \delta_i) \frac{\sum_{j:T_j > T_i} h^2(x_j, T_j) \Delta \hat{F}_{KM}(T_j)}{1 - \hat{F}_{KM}(T_i)} \\ &\quad - \sum_{i=1}^n (1 - \delta_i) \frac{\left(\sum_{j:T_j > T_i} h(x_j, T_j) \Delta \hat{F}_{KM}(T_j) \right)^2}{(1 - \hat{F}_{KM}(T_i))^2}. \end{aligned}$$

Similar calculations show that the third derivative of f evaluated at ξ is $f'''(\xi) = o_p(n^{2/3})$. Now as $f'(0) = 0$ and $f'''(\xi) = o_p(n^{2/3})$, it follows from (A.7) that

$$\begin{aligned} -2 \log \mathcal{R}_h &= 2[f(0) - f(\lambda_0)] \\ &= 2 \left(f(0) - f(0) - \lambda_0 f'(0) - \frac{\lambda_0^2}{2} f''(0) - \frac{\lambda_0^3}{3!} f'''(\xi) \right) \\ &= -\lambda_0^2 f''(0) - \frac{\lambda_0^3}{3} f'''(\xi) \\ &= n\lambda_0^2 \frac{-f''(0)}{n} + o_p(1). \end{aligned}$$

This proves the first assertion. Rewriting the last line of the above equalities using Lemma A, we obtain

$$-2 \log \mathcal{R}_h = \frac{[\sqrt{n} \sum \phi(x_i, t_i) \Delta F_{KM}(t_i)]^2}{\hat{\sigma}^2} \times r_h + o_p(1),$$

where

$$r_h = \frac{\hat{\sigma}^2}{[\sum \phi(x_i, t_i) h(x_i, t_i) \Delta F(t_i)]^2} \frac{-f''(0)}{n},$$

and $\hat{\sigma}^2$ is given in (A.2). Finally

$$\begin{aligned} -2 \log \mathcal{R}_{xy} &= -2 \log(\sup_h \mathcal{R}_h) = \inf_h -2 \log \mathcal{R}_h \\ &= \frac{[\sqrt{n} \sum \phi(x_i, t_i) \Delta F_{KM}(t_i)]^2}{\hat{\sigma}^2} \inf_h r_h + o_p(1). \end{aligned}$$

It can be shown (outlined below) by a Cauchy-Schwarz inequality that for any sample size n , the infimum of r_h over h is 1. Thus by Stute's Central Limit Theorem and the Slutsky Lemma we have

$$-2 \log \mathcal{R}_{xy} = \frac{[\sqrt{n} \sum \phi(x_i, t_i) \Delta F_{KM}(t_i)]^2}{\hat{\sigma}^2} + o_p(1) = \chi_{(1)}^2 + o_p(1). \quad (\text{A.8})$$

Finally we show $r_h \geq 1$. With $f''(0)$, after several tedious simplifications and using the self-consistency identity of the Kaplan–Meier estimator and the advanced time identity of Efron and Johnstone (1990), find

$$-\frac{f''(0)}{n} = \sum_{i=1}^n (h(x_i, t_i) - \bar{h}(t_i))^2 [1 - \hat{G}_{KM}(t_i)] \Delta \hat{F}_{KM}(t_i),$$

where \bar{h} denotes the advanced time transformation of h . From here, a straightforward application of the Cauchy-Schwarz inequality shows that $r_h \geq 1$, and the lower bound 1 is achieved when

$$h(x_i, t_i) - \bar{h}(t_i) = \frac{\phi(x_i, t_i) - \bar{\phi}(t_i)}{1 - \hat{G}_{KM}(t_i)}.$$

A.4. Proof of Theorem 2

Note that the first equality in (A.8) in a multivariate version is simply

$$-2 \log \mathcal{R}_{xy} = \hat{\tau} \hat{\theta} \hat{\Sigma}^{-1} \hat{\theta} + o_p(1),$$

where $\hat{\Sigma}$ denotes a multivariate version of $\hat{\sigma}$ defined in (A.2), and $\hat{\theta} = \sqrt{n}(\sum \phi(x_i, t_i) \Delta \hat{F}_{KM}(t_i))$. Standard results on the profiling of the quadratic form then lead to the conclusion of Theorem 2 (see e.g., Basawa and Koul (1980)).

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