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INDEPENDENCE TEST FOR BIVARIATE CENSORED DATA UNDER UNIVARIATE CENSORSHIP†

JINHEUM KIM[1] AND JIANWEN CAI[2]

ABSTRACT

We propose a test for independence of bivariate censored data under univariate censorship. To do this, we first introduce a process defined by the difference between bivariate survival function estimator proposed by Lin and Ying (1993) and the product of the product-limit estimators (Kaplan and Meier, 1958) for the marginal survival functions, and derive its asymptotic properties under the null hypothesis of independence. We propose a Cramér-von Mises-type test procedure based on the process. We conduct simulation studies to investigate the finite-sample performance of the proposed test and illustrate the proposed test with a real example.

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1. INTRODUCTION

Bivariate censored failure time data arise frequently in biomedical research. For example, in eye studies, both eyes of the patients are followed for severe visual loss, and in breast cancer prevention trials, both breasts of the participants contribute data to the studies. Due to the natural pairing, the times from the eyes or the breasts from the same participant might be correlated. It is of interest to test whether failure times from the same patient are independent. Several procedures have been developed to test independence in bivariate survival data. Oakes (1982)

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[1]Department of Applied Statistics, University of Suwon, Suwon 445-743, Korea
[2]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7420. U.S.A.

proposed a test based on an extension of Kendall's coefficient of concordance to censored data. Cuzick (1982) suggested a test based on the generalized ranks with calculations of the loss of efficiencies arising from model misspecification in a particular class of models. Dabrowska (1986) studied linear rank statistics that generalize the Spearman rank correlation and the log-rank correlation in the presence of censoring. Pons (1986), Pons and de Turckheim (1991), and Pons *et al.* (1992) proposed tests based on the difference between an estimator of bivariate cumulative hazard function and the product of the marginal ones. Shih and Louis (1996) and Hsu and Prentice (1996) proposed tests based on the covariance process of the marginal martingale residuals. Under independent censorship applicable to case-control studies, Kim (1999) proposed a Kolmogorov-Smirnov-type test by comparing the bivariate survival function estimator of Wang and Wells (1997) to the product of the product-limit estimators for the marginal survival functions. In this article, we focus on testing independence of two failure times occurring in an individual under a single censoring time. This type of data is common in studies involving pairs of organs, for example, eyes and breasts. In such studies, the failure times of the organs from the same participant would be censored at the same time if the participant was lost to follow up and no event had happened to any of the organs. The rest is organized as following. In Section 2, we introduce a process defined by the difference between bivariate survival function estimator proposed by Lin and Ying (1993) and the product of the product-limit estimators for the marginal survival functions. We derive its asymptotic properties under the null hypothesis of independence and propose a Cramér-von Mises-type test statistic to test independence of bivariate failure time data under univariate censoring. Section 3 performs simulation studies to investigate the finite-sample performance of the proposed test. We illustrate the proposed test with a dataset from Diabetic Retinopathy Study (Diabetic Retinopathy Study Research Group, 1985) in Section 4. Final remarks are given in Section 5.

2. A Cramér-von Mises-type Test Statistic

Let $(X_1, Y_1), \ldots, (X_n, Y_n)$ be independent and identically distributed (*iid*) pairs of failure times with continuous bivariate survival function $S(x,y) = \Pr(X \geq x, Y \geq y)$ and marginal survival functions S_1, S_2 and let $C_1, \ldots, C_n$ be *iid* univariate censoring times with survival function $G(t) = \Pr(C \geq t)$. We assume that (X_i, Y_i) are independent of C_i. Under a right censorship, we observe $(T_i, U_i, \delta_i^x, \delta_i^y)$

$(i = 1, \ldots, n)$, where

$$T_i = X_i \wedge C_i,\ U_i = Y_i \wedge C_i,\ \delta_i^x = I(X_i \le C_i),\ \delta_i^y = I(Y_i \le C_i).$$

Here and in the sequel $I(\cdot)$ denotes the indicator function, $a \wedge b = \min(a, b)$, and $a \vee b = \max(a, b)$. As in Lin and Ying (1993), Wang and Wells (1997), and Tsai and Crowley (1998), we note that $S(x, y)$ can be decomposed as

$$S(x,y) = \frac{H(x,y)}{G(x \vee y)},$$

where $H(x, y) = \Pr(T \ge x, U \ge y)$. Based on this decomposition, Lin and Ying (1993) proposed a bivariate survival function estimator of S given by

$$\hat{S}(x,y) = \frac{\hat{H}(x,y)}{\hat{G}(x \vee y)},$$

where $H(x,y) = n^{-1}\sum_i I(T_i \ge x, U_i \ge y)$ and $\hat{G}$ is the product-limit estimator of G based on $\{(T_i \vee U_i, 1 - \delta_i^x\delta_i^y),\ i = 1, \ldots, n\}$, *i.e.*,

$$\hat{G}(t) = \prod_{i: T_i \vee U_i < t} \left(1 - \frac{1 - \delta_i^x \delta_i^y}{n_i}\right),$$

where $n_i = \sum_j I(T_j \vee U_j \ge T_i \vee U_i)$. Lin and Ying (1993), following Shorack and Wellner (1986, p. 295), showed $\hat{S}(x,0) = \hat{S}_1(x)$ and $\hat{S}(0,y) = \hat{S}_2(y)$, where $\hat{S}_j$ $(j = 1, 2)$ are the product-limit estimators of S_j based on $\{(T_i, \delta_i^x),\ i = 1, \ldots, n\}$ and $\{(U_i, \delta_i^y),\ i = 1, \ldots, n\}$, respectively. It is desirable to test the hypothesis of independence, *i.e.*,

$$H_0 : S(x,y) = S_1(x)S_2(y) \quad \text{for all } (x,y).$$

To test independence between X and Y, we compare the bivariate estimator $\hat{S}$ of S with its estimator $\hat{S}_1\hat{S}_2$ under the hypothesis of independence. Define a process Z on $[0, \tau_1] \times [0, \tau_2]$ as

$$Z(x,y) = n^{1/2}\{\hat{S}(x,y) - \hat{S}_1(x)\hat{S}_2(y)\},$$

where $(\tau_1, \tau_2) \in \mathcal{R}^+ \times \mathcal{R}^+$ satisfies $H(\tau_1, \tau_2) > 0$. Define the following martingales:

$$M_i^{\vee}(t) = I(T_i \vee U_i \le t, \delta_i^x\delta_i^y = 0) - \int_0^t I(T_i \vee U_i \ge s)\,d\Lambda_c(s),$$

$$M_i^x(t) = I(T_i \le t, \delta_i^x = 0) - \int_0^t I(T_i \ge s) d\Lambda_c(s),$$

$$M_i^y(t) = I(U_i \le t, \delta_i^y = 0) - \int_0^t I(U_i \ge s) d\Lambda_c(s),$$

where $\Lambda_c(\cdot)$ is the cumulative hazard function of censoring time C. Let $H_1(t) = \Pr(T \ge t)$, $H_2(t) = \Pr(U \ge t)$ and $\phi_\vee(t) = \Pr(X \vee Y \ge t)$.

THEOREM 2.1. *Under H_0, the process $Z(x,y)$ on $[0,\tau_1] \times [0,\tau_2]$ converges weakly to a zero-mean Gaussian process with variance function given by*

$$\begin{aligned}
&\sigma^2(x,y)\\
&= S_1^2(x)S_2^2(y) \times \Bigg[\frac{1}{H(x,y)} - \frac{1}{H_1(x)} - \frac{1}{H_2(y)} + 4\frac{H(x,y)}{H_1(x)H_2(y)} - 3\\
&+ \int_0^{x\vee y} \frac{dG(s)}{G^2(s)\phi_\vee(s)} + 2\int_0^x \frac{dG(s)}{G^2(s)\phi_\vee(s)} + 2\int_0^y \frac{dG(s)}{G^2(s)\phi_\vee(s)} - \int_0^x \frac{dG(s)}{G(s)H_1(s)}\\
&- \int_0^y \frac{dG(s)}{G(s)H_2(s)} + 2\frac{1}{H_1(x)}E\left\{I(T \ge x)\int_0^y \frac{dM^y(s)}{H_2(s)}\right\}\\
&+2\frac{1}{H_2(y)}E\left\{I(U \ge y)\int_0^x \frac{dM^x(s)}{H_1(s)}\right\} - 2\frac{1}{H_1(x)}E\left\{I(T \ge x)\int_0^{x\vee y} \frac{dM^\vee(s)}{G(s)\phi_\vee(s)}\right\}\\
&- 2\frac{1}{H_2(x)}E\left\{I(U \ge y)\int_0^{x\vee y} \frac{dM^\vee(s)}{G(s)\phi_\vee(s)}\right\}\Bigg].
\end{aligned}$$

The proof is provided in Appendix.

To test the hypothesis H_0, we propose a Cramér-von Mises type statistic based on the process Z as

$$T_P = \int_0^{\tau_1}\int_0^{\tau_2} Z^2(s,t) d\hat{S}_1(s) d\hat{S}_2(t).$$

We reject H_0 for large values of T_P. Note that $S(x,y) - S_1(x)S_2(y)$ in the last term of (A.1) in Appendix is not zero any longer under the alternative of non-independence, and thereby $Z(x,y)$ goes to infinity under non-independence as n does. Thus, the test T_P is consistent in the sense that the power of T_p goes to 1 as the sample size goes to infinity. As shown in $\sigma^2(x,y)$, since the process Z does not have an independent increment structure, it is difficult to evaluate analytically the null distribution of the test T_P. To overcome this difficulty, we introduce a bootstrap approach proposed by Beran (1986).

Let $d(\alpha)$ be an upper α-quantile of the null distribution of T_P. The $d(\alpha)$ can be approximated by generating the bootstrap distribution of T_P. To do this, we first obtain B bootstrap samples of size n each of which consists of

$$\{(Z_1^*, C_1^*), \ldots, (Z_n^*, C_n^*)\},$$

where $Z_i^* = (X_i^*, Y_i^*)$ has the distribution $\hat{S}_1 \otimes \hat{S}_2$ under H_0 and C_i^* has the distribution $\hat{G}$. To be specific, let $\tilde{x}_1 \leq \cdots \leq \tilde{x}_{l_1}$ ($l_1 \leq n$) be the ordered sequence of uncensored distinct times among the observed values of T_i, *i.e.*, $\{t_1, \ldots, t_n\}$, and $\tilde{y}_1 \leq \cdots \leq \tilde{y}_{l_2}$ ($l_2 \leq n$) be the ordered sequence of uncensored distinct times among the observed values of U_i, *i.e.*, $\{u_1, \ldots, u_n\}$. Also, let $\tilde{c}_1 \leq \cdots \leq \tilde{c}_m$ ($m \leq n$) be the ordered sequence of uncensored distinct times among $\{t_1 \vee u_1, \ldots, t_n \vee u_n\}$. The Z_i^* are generated from the distribution with mass of size $[\{\hat{S}_1(\tilde{x}_i) - \hat{S}_1(\tilde{x}_i+)\}] \times [\{\hat{S}_1(\tilde{y}_j) - \hat{S}_1(\tilde{y}_j+)\}]$ at point $(\tilde{x}_i, \tilde{y}_j)$ ($i = 1, \ldots, l_1; j = 1, \ldots, l_2$) on the grid $\{(\tilde{x}_1, \tilde{y}_1), \ldots, (\tilde{x}_{l_1}, \tilde{y}_{l_2})\}$. The C_i^* are generated from the distribution with mass of $\{\hat{G}(\tilde{c}_k) - \hat{G}(\tilde{c}_k+)\}$ at point $\tilde{c}_k$ ($k = 1, \ldots, m$). Then, for each bootstrap sample we compute the bootstrap values of the test statistic T_P, say T_P^*, based on

$$\{(\tilde{T}_1^*, \tilde{U}_1^*, \delta_1^{*x}, \delta_1^{*y}), \ldots, (\tilde{T}_n^*, \tilde{U}_n^*, \delta_n^{*x}, \delta_n^{*y})\},$$

where

$$\tilde{T}_i^* = X_i^* \wedge C_i^*, \ \tilde{U}_i^* = Y_i^* \wedge C_i^*, \ \delta_i^{*x} = I(X_i^* \leq C_i^*), \ \delta_i^{*y} = I(Y_i^* \leq C_i^*).$$

Let $T_P^{*1}, \ldots, T_P^{*B}$ be the bootstrap values of T_P. The estimated value $\hat{d}(\alpha)$ of $d(\alpha)$ is given as the empirical upper α-quantile based on $T_P^{*1}, \ldots, T_P^{*B}$. Thus, we reject H_0 when the observed value of T_P exceeds $\hat{d}(\alpha)$ at level α.

3. Simulation Studies

Simulation studies were carried out to investigate the finite sample performance of the proposed test T_P in terms of sizes and powers. For examining the sizes of T_P, pairs of failure times were generated from two independent exponential distributions, while for studying the powers of T_P, pairs of failure times were generated from the Clayton (1978) bivariate exponential model

$$S(x, y) = (e^{\frac{x}{\theta}} + e^{\frac{y}{\theta}} - 1)^{-\theta}$$

using the algorithm of Prentice and Cai (1992). Here the parameter $\theta(> 0)$ characterizes the degree of dependence between two failure times. For example, θ=1.5

TABLE 3.1 *Empirical sizes and powers of test T_p based on 1,000 simulations and 500 bootstrap samples*

		Model								
		Independence			Clayton (θ=1.5)			Clayton (θ=0.8)		
		% censoring			% censoring			% censoring		
n	α	0	25	50	0	25	50	0	25	50
30	.01	.011	.006	.014	.259	.111	.033	.673	.299	.074
	.05	.054	.046	.064	.479	.266	.132	.848	.587	.243
	.10	.112	.101	.148	.599	.373	.249	.908	.695	.389
50	.01	.016	.011	.014	.488	.222	.047	.916	.591	.145
	.05	.044	.056	.075	.710	.478	.198	.983	.811	.379
	.10	.093	.111	.145	.807	.624	.314	.990	.880	.525
100	.01	.013	.007	.010	.853	.527	.157	.999	.941	.402
	.05	.049	.058	.066	.955	.770	.370	1.00	.984	.653
	.10	.095	.113	.128	.975	.846	.487	1.00	.994	.784
200	.01	.009	.010	.015	.994	.882	.414	1.00	.999	.827
	.05	.048	.049	.060	.999	.966	.645	1.00	1.00	.949
	.10	.093	.112	.108	1.00	.978	.764	1.00	1.00	.981

and 0.8 correspond to correlation coefficients of 0.51 and 0.71, respectively, while $\theta \to 0$ gives the maximal positive dependence and $\theta \to \infty$ gives independence. The censoring times were generated from exponential distribution Exp(λ) with mean of $\lambda(> 0)$, where λ can be suitably chosen to satisfy the desired censoring fraction. We considered 36 different configurations according to the combination of the following parameters: n = 30, 50, 100 or 200; independent failure times from Exp(1) or bivariate survival times following Clayton model with $\theta = 1.5$ or 0.8, which correspond to a moderate or a strong dependency, respectively; and censoring fractions are 0%, 25% ($\lambda = 3$) or 50% ($\lambda = 1$). For each configuration, we generated 1,000 data realizations, and for each realization, we approximated $d(\alpha)$ based on $B = 500$ bootstrap samples.

Table 3.1 presents the simulation results for the empirical sizes and powers of T_p under univariate censoring. We note from entries in the column for independent model that the sizes of T_p are well controlled regardless of censoring fraction except for n = 30 or 50 with 50% censoring. For Clayton model with $\theta = 0.8$, the test T_p is fairly powerful. The power increases as the sample size increases. As expected, the power of T_p for Clayton model with $\theta = 1.5$ is not as much as that with $\theta = 0.8$. The powers of proposed test decrease as the censoring fraction increases.

4. A Real Example

We illustrate the proposed test with a dataset from Diabetic Retinopathy Study (DRS) (Diabetic Retinopathy Study Research Group, 1985). Diabetic retinopathy is a common complication of diabetes affecting the blood vessels in the retina. The DRS study primarily focused on assessing the effectiveness of laser photocoagulation treatment in delaying the onset of blindness. Four hundred and fifty one patients were involved in this study. The laser treatment was randomly assigned to one eye of each patient and the other eye was left untreated. The failure time is defined as time to the occurrence of visual acuity less than 5/200. Censoring proportions of each group are high: 71% for controlled eyes and 83% for laser-treated eyes. Figure 4.1 displays the Kaplan-Meier survival curves for each treatment group. It implies that the laser photocoagulation treatment is effective in prolonging time to blindness. For this analysis, we are interested in testing whether survival times for the laser-treated and controlled eyes of a patient are independent. The test statistic T_P equals 5.85×10^{-5} and p-value corresponding to the observed value, based on 5,000 bootstrap samples, is approximately 0.0002. This provides strong evidence against independence of survival times for laser-treated and controlled eyes. This result is expected with data paired in such a natural way.

5. Remarks

We have proposed a test procedure for testing independence with correlated survival data. The T_p is a rank-based statistic and its distribution is distribution-free under H_0. To obtain the null distribution of the proposed test, we introduced bootstrap approach proposed by Beran (1986). The simulation results show that the proposed method works well except for small samples ($n = 30$ or 50) with heavy censoring, where the test sizes were over-estimated. As the associate editor pointed out, we can adapt another resampling method as an alternative to Beran (1986). This is an extension of drawing a sample of size n with replacement from the original data to the bivariate case. To be specific, first, generate $\{(\tilde{T}_i^*, \delta_i^{*x})$:

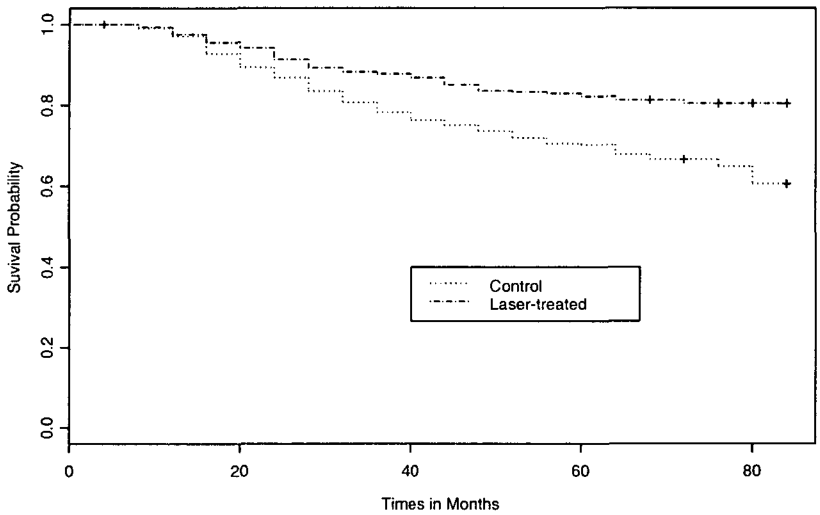

FIGURE 4.1 *Kaplan-Meier survival curves by treatment groups*

$i = 1, \ldots, n\}$ from $\{(T_i, \delta_i^x) : i = 1, \ldots, n\}$ with probability $1/n$ of each element and with replacement, and also generate $\{(\tilde{U}_i^*, \delta_i^{*y}) : i = 1, \ldots, n\}$ from $\{(U_i, \delta_i^y) : i = 1, \ldots, n\}$ in the same manner. Then, combining these sample results in bootstrap sample $\{(\tilde{T}_i^*, \tilde{U}_i^*, \delta_i^{*x}, \delta_i^{*y}) : i = 1, \ldots, n\}$. As in the univariate case, these two resampling methods are asymptotically equivalent. A detailed analysis of the simulation results shows that when a bootstrap sample has less censored values than the original one, the value of T_p^* is smaller than that of T_p and thereby the critical value is under-estimated by $\hat{d}(\alpha)$ and the test rejects H_0 too often. Consequently, the size of the test is over-estimated. This often happens under small sample size and heavy censoring. Moreover, based on the simulation results not reported here, in general, the sizes of the proposed Cramér-von Mises-type test are better controlled than that of a Kolmogorov-Smirnov-type test using the maximum of process $Z(\cdot, \cdot)$.

APPENDIX

PROOF OF THEOREM 2.1. We first write $Z(x, y)$ as

$$Z(x,y) = n^{1/2}\{\hat{S}(x,y) - S(x,y)\} - n^{1/2}\{\hat{S}_1(x) - S_1(x)\}\{\hat{S}_2(y) - S_2(y)\}$$

$$-S_2(y)n^{1/2}\{\hat{S}_1(x) - S_1(x)\} - S_1(x)n^{1/2}\{\hat{S}_2(y) - S_2(y)\} \quad \text{(A.1)}$$
$$+n^{1/2}\{S(x,y) - S_1(x)S_2(y)\}.$$

From Lin and Ying (1993), the first term in (A.1) converges to a zero-mean Gaussian process $W(x,y)$. By the consistency and weak convergence of product-limit estimators $\hat{S}_1, \hat{S}_2$, the second term converges in probability to zero and the third and fourth terms converge weakly to zero-mean Gaussian processes $-S_2(y)W_1(x), -S_1(x)W_2(y)$, respectively, where $W_1(\cdot)$ and $W_2(\cdot)$ are zero-mean Gaussian processes. The last term becomes zero under the null hypothesis. Thus, $Z(x,y)$ converges weakly to zero-mean Gaussian process $W(x,y) - S_2(y)W_1(x) - S_1(x)W_2(y)$. At first, define some processes:

$$A(x,y) = \frac{1}{G(x \vee y)} n^{1/2}\{\hat{H}(x,y) - H(x,y)\},$$

$$B(x,y) = S(x,y)n^{-1/2}\sum_{i=1}^{n}\int_0^{x\vee y}\frac{dM_i^{\vee}(s)}{G(s)\phi_{\vee}(s)},$$

$$C(z) = \frac{1}{G(z)}n^{1/2}\{\hat{H}_1(z) - H_1(z)\}, \quad D(z) = S_1(z)n^{-1/2}\sum_{i=1}^{n}\int_0^{z}\frac{dM_i^{x}(s)}{H_1(s)},$$

$$E(z) = \frac{1}{G(z)}n^{1/2}\{\hat{H}_2(z) - H_2(z)\}, \quad F(z) = S_2(z)n^{-1/2}\sum_{i=1}^{n}\int_0^{z}\frac{dM_i^{y}(s)}{H_2(s)},$$

where $\hat{H}_1(t) = n^{-1}\sum_i I(T_i \geq t)$, $\hat{H}_2(t) = n^{-1}\sum_i I(U_i \geq t)$. To obtain asymptotic variance of $Z(x,y)$, we introduce the following expressions based on the same arguments as in Lin and Ying (1993):

$$n^{1/2}\{\hat{S}(x,y) - S(x,y)\} = A(x,y) + B(x,y) + o_p(1) = U(x,y) + o_p(1), \quad \text{(A.2)}$$
$$n^{1/2}\{\hat{S}_1(x) - S_1(x)\} = C(x) + D(x) + o_p(1) = U_1(x) + o_p(1), \quad \text{(A.3)}$$
$$n^{1/2}\{\hat{S}_2(y) - S_2(y)\} = E(y) + F(y) + o_p(1) = U_2(y) + o_p(1), \quad \text{(A.4)}$$

where $U(x,y) = A(x,y) + B(x,y)$, $U_1(z) = C(z) + D(z)$ and $U_2(z) = E(z) + F(z)$. By the elementary probability arguments, it can be shown that

$$E\{A(x_1,y_1)C(x_2)\} = S(x_1,y_1)S_1(x_2)\left\{\frac{H(x_1 \vee x_2, y_1)}{H(x_1,y_1)H_1(x_2)} - 1\right\}, \quad \text{(A.5)}$$

$$E\{A(x_1,y_1)E(y_2)\} = S(x_1,y_1)S_2(y_2)\left\{\frac{H(x_1, y_1 \vee y_2)}{H(x_1,y_1)H_2(y_2)} - 1\right\}, \quad \text{(A.6)}$$

$$E\{A(x_1,y_1)D(x_2)\} = S_1(x_2)S(x_1,y_1)\int_0^{(x_1\vee y_1)\wedge x_2}\frac{dG(s)}{G(s)H_1(s)}, \quad \text{(A.7)}$$

$$E\{A(x_1,y_1)F(y_2)\} = S_2(y_2)S(x_1,y_1)\int_0^{(x_1\vee y_1)\wedge y_2}\frac{dG(s)}{G(s)H_2(s)}, \quad (A.8)$$

$$E\{B(x_1,y_1)C(x_2)\} = \frac{S(x_1,y_1)S_1(x_2)}{H_1(x_2)}E\left\{I(T\geq x_2)\int_0^{x_1\vee y_1}\frac{dM^{\vee}(s)}{G(s)\phi_{\vee}(s)}\right\}, \quad (A.9)$$

$$E\{B(x_1,y_1)E(y_2)\} = \frac{S(x_1,y_1)S_2(y_2)}{H_2(y_2)}E\left\{I(U\geq y_2)\int_0^{x_1\vee y_1}\frac{dM^{\vee}(s)}{G(s)\phi_{\vee}(s)}\right\}, \quad (A.10)$$

$$E\{B(x_1,y_1)D(x_2)\} = -S_1(x_2)S(x_1,y_1)\int_0^{(x_1\vee y_1)\wedge x_2}\frac{dG(s)}{G^2(s)\phi_{\vee}(s)}, \quad (A.11)$$

$$E\{B(x_1,y_1)F(y_2)\} = -S_2(y_2)S(x_1,y_1)\int_0^{(x_1\vee y_1)\wedge y_2}\frac{dG(s)}{G^2(s)\phi_{\vee}(s)}, \quad (A.12)$$

$$E\{C(x_1)E(y_2)\} = S_1(x_1)S_2(y_2)\left\{\frac{H(x_1,y_2)}{H_1(x_1)H_2(y_2)}-1\right\}, \quad (A.13)$$

$$E\{C(x_1)F(y_2)\} = \frac{S_1(x_1)S_2(y_2)}{H_1(x_1)}E\left\{I(T\geq x_1)\int_0^{y_2}\frac{dM^y(s)}{H_2(s)}\right\}, \quad (A.14)$$

$$E\{D(x_1)E(y_2)\} = \frac{S_1(x_1)S_2(y_2)}{H_2(y_2)}E\left\{I(U\geq y_2)\int_0^{x_1}\frac{dM^x(s)}{H_1(s)}\right\}, \quad (A.15)$$

$$E\{D(x_1)F(y_2)\} = -S_1(x_1)S_2(y_2)\int_0^{x_1\wedge y_2}\frac{S(s,s)dG(s)}{H_1(s)H_2(s)}, \quad (A.16)$$

$$E\{C(x_1)C(x_2)\} = S_1(x_1)S_1(x_2)\left\{\frac{H_1(x_1\vee x_2)}{H_1(x_1)H_1(x_2)}-1\right\}, \quad (A.17)$$

$$E\{E(y_1)E(y_2)\} = S_2(y_1)S_2(y_2)\left\{\frac{H_2(y_1\vee y_2)}{H_2(y_1)H_2(y_2)}-1\right\}, \quad (A.18)$$

$$E\{C(x_1)D(x_2)\} = -E\{D(x_1)D(x_2)\} = S_1(x_1)S_1(x_2)\int_0^{x_1\wedge x_2}\frac{dG(s)}{G(s)H_1(s)}, \quad (A.19)$$

$$E\{E(y_1)F(y_2)\} = -E\{F(y_1)F(y_2)\} = S_2(y_1)S_2(y_2)\int_0^{y_1\wedge y_2}\frac{dG(s)}{G(s)H_2(s)}. \quad (A.20)$$

Using the expressions (A.2)–(A.4) and combining (A.5)–(A.20), we can easily obtain asymptotic covariances aCov$\{U(x_1,y_1),U_1(x_2)\}$, aCov$\{U(x_1,y_1),U_2(y_2)\}$, aCov$\{U_1(x_1),U_1(x_2)\}$, aCov$\{U_2(y_1), U_2(y_2)\}$, and aCov$\{U_1(x_1),U_2(y_2)\}$. Replacing x_1,x_2,y_1, and y_2 by x_2,x_1,y_2, and y_1, respectively, in (A.5)–(A.20), we can get the versions corresponding to (A.5)–(A.20) and also obtain asymptotic covariances aCov$\{U(x_2,y_2),U_1(x_1)\}$, aCov$\{U(x_2,y_2),U_2(y_1)\}$, and aCov$\{U_1(x_2), U_2(y_1)\}$, and thereby along with (2.4) in Lin and Ying (1993) for aCov$\{U(x_1,y_1), U(x_2,y_2)\}$ obtain the covariance function, aCov$\{Z(x_1,y_1),Z(x_2,y_2)\}$, of the process $Z(x, y)$. As expected, it is too lengthy to express explicitly the covariance function. Instead, to be specific, the asymptotic variance of the process $Z(x, y)$ is given by $\sigma^2(x, y)$ in Theorem 2.1. □

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