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A SIMPLE ESTIMATOR OF THE BIVARIATE DISTRIBUTION FUNCTION FOR CENSORED GAP TIMES

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Abstract

Let (T_1, T_2) be gap times corresponding to two consecutive events, which are observed subject to random right-censoring. In this paper a simple estimator of the bivariate distribution function of (T_1, T_2) is proposed. We investigate the conditions under which the introduced estimator is consistent. Applications to the estimation of the marginal distributions of the gap times and to correlation analysis are included. We explore the behaviour of the proposed methods through simulations.

Key Words and Phrases: bivariate censoring, Kaplan-Meier, nonparametric estimation, recurrent events

1 Introduction

Let (T_1, T_2) be a pair of gap times of successive events, which are observed subject to random right-censoring. Let C be the right-censoring variable, assumed to be independent of (T_1, T_2) , and let $Y = T_1 + T_2$ be the total time. Due to censoring, rather than (T_1, T_2) we observe $(\tilde{T}_1, \tilde{T}_2, \Delta_1, \Delta_2)$, where $\tilde{T}_1 = T_1 \wedge C$, $\Delta_1 = I(T_1 \leq C)$ and $\tilde{T}_2 = T_2 \wedge C_2$, $\Delta_2 = I(T_2 \leq C_2)$, where $C_2 = (C - T_1)I(T_1 \leq C)$ is the censoring variable for the second gap time. Note that $\Delta_2 = 1$ implies $\Delta_1 = 1$. Hence, $\Delta_2 = \Delta_1 \Delta_2 = I(Y \leq C)$ is the censoring indicator pertaining to the total time. Let $(\tilde{T}_{1i}, \tilde{T}_{2i}, \Delta_{1i}, \Delta_{2i})$, $1 \leq i \leq n$, be iid data with the same distribution as $(\tilde{T}_1, \tilde{T}_2, \Delta_1, \Delta_2)$. Due to the independence assumption, the marginal distribution of the first gap time T_1 may be consistently estimated by the Kaplan-Meier estimator based on the $(\tilde{T}_{1i}, \Delta_{1i})$'s. Similarly, the distribution of the total time may be consistently estimated by the Kaplan-Meier estimator based on the $(\tilde{T}_{1i} + \tilde{T}_{2i}, \Delta_{2i})$'s.

However, since T_2 and C_2 will be in general dependent, the estimation of the marginal distribution of the second gap time is not such a simple issue. By the same reason, it is not clear in principle how the bivariate distribution function $F_{12}(x, y) = P(T_1 \leq x, T_2 \leq y)$ can be efficiently estimated. This issue was investigated, among others, by Wang and Wells (1998), Lin *et al.* (1999), Wang and Chang (1999), Peña *et al.* (2001), van der Laan *et al.* (2002), Schaubel and Cai (2004) or van Keilegom (2004).

In this paper we propose a simple estimator for the bivariate distribution function of the gap times, $F_{12}(x, y)$. The idea behind the estimator (and the reason for its simplicity) is using the Kaplan-Meier estimator pertaining to the distribution of the total time (the Y) to weight the bivariate data. We will show that this procedure is consistent whenever $x + y$ is smaller than the upper bound of the support of the censoring time. The proposed estimator is a proper distribution function; this is interesting, since previous proposals (as those investigated by Wang and Wells (1998) and Lin *et al.* (1999)) do not guarantee a nonnegative weighting of the data. Of course, given an estimator $\hat{F}_{12}(x, y)$ for $F_{12}(x, y)$, one immediately gets an estimator of the marginal distribution of the second gap time by taking $\hat{F}_{12}(\infty, y)$.

The paper is organized as follows. In Section 2 we introduce the estimator for the joint distribution function of (T_1, T_2) and we establish its consistency. We will see that the proposed estimator is somehow connected (but it is not equal) to that in Lin *et al.* (1999). Some related problems as estimation of the marginal distribution of T_2 and correlation analysis will be discussed. In Section 3 we investigate the performance of the proposed methods in a simulated scenario. Main conclusions and some final remarks are reported in Section 4.

2 The estimator: consistency

Let $\tilde{Y}_i = \tilde{T}_{1i} + \tilde{T}_{2i}$ be the i th recorded total time, and let W_i be the Kaplan-Meier weight attached to \tilde{Y}_i when estimating the marginal distribution of Y from the $(\tilde{Y}_i, \Delta_{2i})$'s. That is,

$$W_i = \frac{\Delta_{2i}}{n - R_i + 1} \prod_{j=1}^{i-1} \left[1 - \frac{\Delta_{2j}}{n - R_j + 1} \right] \quad \text{where } R_i = \text{Rank}(\tilde{Y}_i),$$

and where the ranks of the censored \tilde{Y}_i 's are higher than those for uncensored values in the case of ties. In the uncensored case we have $W_i = n^{-1}$ for each i . Introduce

$$\hat{F}_{12}(x, y) = \sum_{i=1}^n W_i I(\tilde{T}_{1i} \leq x, \tilde{T}_{2i} \leq y). \quad (1)$$

Below we show that this estimator is consistent whenever $x + y$ is smaller than the upper bound of the support of the censoring time. From (1) we can obtain an estimator for the marginal distribution of the second gap time, $F_2(y) = P(T_2 \leq y)$, namely

$$\hat{F}_2(y) = \hat{F}_{12}(\infty, y) = \sum_{i=1}^n W_i I(\tilde{T}_{2i} \leq y). \quad (2)$$

Note that \hat{F}_2 is not the Kaplan-Meier estimator based on the $(\tilde{T}_{2i}, \Delta_{2i})$'s. This is because the weights W_i are based on the \tilde{Y}_i -ranks rather than on the \tilde{T}_{2i} -ranks. Indeed, since T_2 and C_2 are expected to be dependent, the ordinary Kaplan-Meier estimator of F_2 will be in general inconsistent.

Define $\tilde{Y} = Y \wedge C$. Let F , G and H denote the distribution functions of Y , C and \tilde{Y} , respectively. Let τ_F be the upper bound of the support of F , and similarly define τ_G and τ_H . Since Y and C are assumed to be independent, we have $\tau_H = \tau_F \wedge \tau_G$. Let A be the (possibly empty) set of atoms of \tilde{Y} . We have the following result.

Theorem 1 *If F and G have no jumps in common, we have with probability 1 and in the mean*

$$\lim_{n \rightarrow \infty} \hat{F}_{12}(x, y) = P(T_1 \leq x, T_2 \leq y, T_1 + T_2 < \tau_H) +$$

$$I(\tau_H \in A)P(T_1 \leq x, T_2 \leq y, T_1 + T_2 = \tau_H),$$

and

$$\lim_{n \rightarrow \infty} \hat{F}_2(y) = P(T_2 \leq y, T_1 + T_2 < \tau_H) + I(\tau_H \in A)P(T_2 \leq y, T_1 + T_2 = \tau_H)$$

Proof. First note that, under the censoring scheme described in Section 1, the variable T_2 is censored whenever T_1 is. Hence, W_i is zero whenever the pertaining \tilde{T}_{1i} is a right-censored value of T_{1i} . This enables us to write

$$\hat{F}_{12}(x, y) = \sum_{i=1}^n W_i I(T_{1i} \leq x, \tilde{T}_{2i} \leq y) = \sum_{i=1}^n W_i \varphi_{x,y}(T_{1i}, \tilde{Y}_i)$$

where $\varphi_{x,y}(u, v) = I(u \leq x, v - u \leq y)$. Since (T_1, T_2) and C are independent, conditions (i) and (ii) in Stute (1993) hold. Apply his Theorem to conclude. \square

Note that if any of the following conditions hold:

- (a) $\tau_H \in A$, or

$$(b) P(T_1 \leq x, T_2 \leq y, T_1 + T_2 = \tau_H) = 0$$

((b) is valid in particular if Y is continuous), we have from Theorem 1 that

$$\lim_{n \rightarrow \infty} \hat{F}_{12}(x, y) = P(T_1 \leq x, T_2 \leq y, T_1 + T_2 \leq \tau_H).$$

Then, three essentially different situations are possible. (A) If $\tau_F < \tau_G$ (or if $\tau_F = \tau_G = \infty$), then we get that (1) is consistent for any (x, y) . (B) If $\tau_G < \tau_F$, then $\tau_H < \tau_F$ and consistency is only ensured for $x + y < \tau_H$ (or for $x + y \leq \tau_H$ provided that (a) or (b) above hold). This is not surprising, since in this case relevant information on F is missing on the whole interval $(\tau_G, \tau_F]$. The bivariate estimators proposed in Wang and Wells (1998) and Lin *et al.* (1999) suffer from the same problem, in addition to the issue of not being proper distribution functions. Finally, (C) if $\tau_F = \tau_G < \infty$, then consistency follows if (a) or (b) are fulfilled.

Similar comments hold for (2). However, note that in this latter case, to get consistency of $\hat{F}_2(y)$ in situation (B) one should require $P(T_1 \leq \tau_H - y) = 1$, a condition that will fail for y at the right tail of F_2 . Specifically, if τ_1 stands for the upper bound of the support of T_1 , we have $\hat{F}_2(y) \rightarrow F_2(y)$ w.p. 1 for $y \leq \tau_H - \tau_1$ (assumed that any of the conditions (a) or (b) above hold).

The idea of weighting the bivariate data $(\tilde{T}_{1i}, \tilde{T}_{2i})$ through the W_i 's can be used to introduce consistent estimation of the correlation between the gap times. Certainly, define the empirical covariance

$$\hat{\sigma}_{12} = \sum_{i=1}^n W_i (\tilde{T}_{1i} - \hat{\mu}_1) (\tilde{T}_{2i} - \hat{\mu}_2)$$

where

$$\hat{\mu}_1 = \sum_{i=1}^n W_i \tilde{T}_{1i} \quad \text{and} \quad \hat{\mu}_2 = \sum_{i=1}^n W_i \tilde{T}_{2i}.$$

The marginal variances of T_1 and T_2 (assumed to exist) are consistently estimated through

$$\hat{\sigma}_1^2 = \sum_{i=1}^n W_i (\tilde{T}_{1i} - \hat{\mu}_1)^2 \quad \text{and} \quad \hat{\sigma}_2^2 = \sum_{i=1}^n W_i (\tilde{T}_{2i} - \hat{\mu}_2)^2.$$

Introduce the correlation coefficient

$$\hat{\rho}_{12} = \frac{\hat{\sigma}_{12}}{\sqrt{\hat{\sigma}_1^2 \hat{\sigma}_2^2}}.$$

In the uncensored case, $\hat{\rho}_{12}$ reduces to the Pearson correlation coefficient. Let ρ_{12} be the true correlation between both gap times. Then we have the following result.

Theorem 2 Assume for simplicity $\tau_F < \tau_G$. If F and G have no jumps in common, we have with probability 1

$$\lim_{n \rightarrow \infty} \hat{\rho}_{12} = \rho_{12}.$$

Proof. This result is a consequence of the Theorem in Stute (1993) when applied to the special φ -functions $\varphi_1(u, v) = u$, $\varphi_2(u, v) = v - u$, $\varphi_3(u, v) = u^2$, $\varphi_4(u, v) = (v - u)^2$, and $\varphi_5(u, v) = u(v - u)$. Condition $\tau_F < \tau_G$ ensures that the empirical quantities involved in the definition of $\hat{\rho}_{12}$ converge to their "right" respective limits. \square

The estimator (1) is somehow related (although not equal) to that proposed in Lin *et al.* (1999). These authors suggested the estimator

$$\tilde{F}_{12}(x, y) = \tilde{H}(x, 0) - \tilde{H}(x, y) \quad (3)$$

where

$$\tilde{H}(x, y) = \frac{1}{n} \sum_{i=1}^n \frac{I(\tilde{T}_{1i} \leq x, \tilde{T}_{2i} > y) \Delta_{2i}}{1 - \hat{G}((\tilde{T}_{1i} + y)^-)}$$

and where \hat{G} stands for the Kaplan-Meier estimator (of the censoring distribution) based on the $(\tilde{Y}_i, 1 - \Delta_{2i})$'s. On its turn, (1) is also written as $\hat{F}_{12}(x, y) = \hat{H}(x, 0) - \hat{H}(x, y)$ where

$$\hat{H}(x, y) = \frac{1}{n} \sum_{i=1}^n \frac{I(\tilde{T}_{1i} \leq x, \tilde{T}_{2i} > y) \Delta_{2i}}{1 - \hat{G}((\tilde{T}_{1i} + \tilde{T}_{2i})^-)}.$$

Of course, under $\tilde{T}_{2i} > y$ we have $\hat{G}((\tilde{T}_{1i} + \tilde{T}_{2i})^-) \geq \hat{G}((\tilde{T}_{1i} + y)^-)$ and hence $\hat{H}(x, y) \geq \tilde{H}(x, y)$. Both $\hat{H}(x, y)$ and $\tilde{H}(x, y)$ are estimators for $H(x, y) = P(T_1 \leq x, T_2 > y)$. In the next Section we report a simulation study which indicates that $\hat{F}_{12}(x, y)$ may behave more efficiently than $\tilde{F}_{12}(x, y)$ (the relative efficiency of Lin *et al.* (1999)'s estimator may be as poor as 64%)

3 Simulation study

In this Section we investigate the performance of the proposed estimation methods through simulations. The simulated scenario is the same as that described in Lin *et al.* (1999), see their Section 3. To be precise, the gap times (T_1, T_2) were generated according to the bivariate distribution

$$F_{12}(x, y) = F_1(x)F_2(y) [1 + \theta \{1 - F_1(x)\} \{1 - F_2(y)\}]$$

where the marginal distribution functions F_1 and F_2 are exponential with rate parameter 1. The parameter θ was set to 0 for simulating independent gap

times, and also to 1, corresponding to 0.25 correlation between T_1 and T_2 . An independent uniform censoring time C was generated, according to models $U[0, 4]$ and $U[0, 3]$. The first model resulted in 25% of censoring on the first gap time, and in 46% of censoring on the second gap time. The second model increased these censoring levels to 32% and about 60%, respectively. Sample sizes $n = 50$ and $n = 100$ were considered. In each simulation, 10,000 samples were generated.

We computed the mean and standard deviation along the simulated samples for the estimator $\hat{F}_{12}(x, y)$ introduced in (1), for x and y values 0.2231, 0.5108, 0.9163, and 1.6094, corresponding to marginal survival probabilities of 0.8, 0.6, 0.4 and 0.2. The true values of $F_{12}(x, y)$ in all the cases are reported in Table 1.

[Put Table 1 about here]

Table 2 reports the mean values of $\hat{F}_{12}(x, y)$ along the simulated samples, in both the independent ($\theta = 0$) and dependent ($\theta = 1$) cases, for each censoring level and for each sample size. It is seen that the bias of the bivariate distribution estimator achieved reasonable levels. Similarly, Table 3 reports the standard deviation of this estimate. In this case it is clearly seen that the variance increases at the right tail of the bivariate distribution, where the censoring effects are stronger. We also observe that an increasing sample size results in smaller variance. Besides, by increasing the censoring percentage, the standard deviation achieves larger values. All these facts were expected.

[Put Tables 2 and 3 about here]

Due to the existing connection between the proposed estimator and that considered in Lin *et al.* (1999), see (3), we also computed the bias and the standard deviation of the latter estimate along the simulated samples. The bias turned out to be of the same order as that of (1), and hence results are not displayed here. Then, the efficiency of $\tilde{F}_{12}(x, y)$ relative to $\hat{F}_{12}(x, y)$ was measured through the squared quotient of standard deviations. The results for $n = 50$ are displayed in Table 4 (results for $n = 100$ were quite similar so they are omitted). We see that $\hat{F}_{12}(x, y)$ was always more efficient than $\tilde{F}_{12}(x, y)$ except for a few cases corresponding to small x and large y . In these cases, the bivariate distribution is relatively close to the marginal distribution of the first gap time, and the estimator of Lin *et al.* (1999) seems to be more convenient (for small x). This effect is stronger when increasing the censoring level. In most of the support of $F_{12}(x, y)$ the proposed estimator behaved better than $\tilde{F}_{12}(x, y)$ (more clearly seen for an increasing censoring level); indeed, the relative efficiency of $\tilde{F}_{12}(x, y)$ decreased when moving the pair (x, y) to the right tail of the distribution. For example, for $x = 1.6094$ and $C \sim U[0, 3]$, the relative efficiency of Lin *et al.* (1999)'s estimator was never above 70%.

[Put Table 4 about here]

4 Conclusions and final remarks

In this paper a new, simple nonparametric estimator of the bivariate distribution of gap times was introduced. Conditions under which the proposed estimator is consistent were investigated. Consistency results for the marginal distribution pertaining to the second gap time have been derived. Since the second gap time is dependently censored, the proposed estimator can be regarded as a natural substitute for the ordinary Kaplan-Meier estimator, which will not work in general. Application of the proposed estimation method to correlation analysis has also been discussed.

Unlike other existing methods, the introduced estimator is a proper bivariate distribution, in the sense that it attaches positive mass to each pair of recorded gap times. Besides, simulations showed that the new estimator is virtually unbiased and that it may achieve efficiency levels clearly above those corresponding to previous proposals. However, more (theoretical) investigation is needed in order to get general conclusions to this regard.

One can easily derived further asymptotic results for $\hat{F}_{12}(x, y)$ and related quantities from the existing theory for multivariate Kaplan-Meier integrals. Central limit theorems and mathematical derivation of the asymptotic variance follow from the available representations of these integrals as sums of iid random variables (plus negligible remainders), see Stute (1996a) and references therein. Formal description of these results would require a much more extended manuscript and this is certainly out of the scope of the present note. On the other hand, an issue of much practical importance is that of the estimation of the standard error of (1). For this purpose, Stute (1996b) investigated the (modified) jackknife, establishing its consistency for a general Kaplan-Meier integral. Similar ideas could be applied here.

The proposed method can be easily extended to cope with a vector of k gap times, (T_1, \dots, T_k) . In such a case, the weights W_i in (1) must be defined as those of the Kaplan-Meier estimator of the marginal distribution of the total time $Y = T_1 + \dots + T_k$. This procedure will be consistent whenever the censoring time is independent of (T_1, \dots, T_k) , at least for those values (x_1, \dots, x_k) satisfying $x_1 + \dots + x_k < \tau_G$ (the upper bound of the support of the censoring distribution). The proof is similar to that in Theorem 1.

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$x \setminus y$	$\theta = 0$				$\theta = 1$			
	0.2231	0.5108	0.9163	1.6094	0.2231	0.5108	0.9163	1.6094
0.2231	.0400	.0800	.1200	.1600	.0656	.1184	.1584	.1856
0.5108	.0800	.1600	.2400	.3200	.1184	.2176	.2976	.3584
0.9163	.1200	.2400	.3600	.4800	.1584	.2976	.4176	.5184
1.6094	.1600	.3200	.4800	.6400	.1856	.3584	.5184	.6656

Table 1. True values of the bivariate distribution of the gap times under the simulated model.

$x \setminus y$	$\theta = 0$				$\theta = 1$			
	.2231	.5108	.9163	1.6094	.2231	.5108	.9163	1.6094
0.2231	.0398	.0802	.1201	.1604	.0660	.1181	.1576	.1856
0.5108	.0798	.1607	.2392	.3197	.1185	.2176	.2973	.3577
0.9163	.1193	.2396	.3605	.4795	.1582	.2980	.4172	.5184
1.6094	.1612	.3184	.4807	.6384	.1852	.3595	.5171	.6656

$n = 50, C \sim U[0, 4]$

0.2231	.0399	.0798	.1199	.1604	.0654	.1187	.1584	.1857
0.5108	.0798	.1594	.2399	.3206	.1188	.2179	.2980	.3580
0.9163	.1202	.2395	.3605	.4800	.1583	.2980	.4180	.5181
1.6094	.1605	.3206	.4804	.6406	.1854	.3580	.5180	.6645

$n = 100, C \sim U[0, 4]$

0.2231	.0404	.0798	.1193	.1593	.0657	.1189	.1588	.1857
0.5108	.0806	.1602	.2390	.3196	.1181	.2162	.2968	.3576
0.9163	.1197	.2397	.3594	.4794	.1575	.2978	.4163	.5181
1.6094	.1597	.3196	.4808	.6280	.1859	.3579	.5173	.6503

$n = 50, C \sim U[0, 3]$

0.2231	.0398	.0801	.1209	.1604	.0652	.1176	.1580	.1853
0.5108	.0801	.1600	.2404	.3203	.1184	.2170	.2978	.3577
0.9163	.1203	.2396	.3598	.4798	.1587	.2985	.4179	.5176
1.6094	.1599	.3197	.4804	.6345	.1858	.3587	.5176	.6581

$n = 100, C \sim U[0, 3]$

Table 2. Mean value of $\hat{F}_{12}(x, y)$ along 10,000 simulated samples

		$\theta = 0$				$\theta = 1$			
$x \setminus y$.2231	.5108	.9163	1.6094	.2231	.5108	.9163	1.6094
0.2231		.0286	.0407	.0499	.0580	.0359	.0478	.0554	.0601
0.5108		.0406	.0557	.0665	.0769	.0474	.0619	.0707	.0766
0.9163		.0491	.0668	.0776	.0864	.0546	.0709	.0784	.0859
1.6094		.0588	.0771	.0870	.0914	.0607	.0776	.0863	.0884

$n = 50, C \sim U[0, 4]$

0.2231		.0202	.0287	.0347	.0413	.0252	.0337	.0390	.0427
0.5108		.0282	.0389	.0474	.0544	.0336	.0442	.0503	.0549
0.9163		.0346	.0468	.0553	.0610	.0391	.0497	.0554	.0612
1.6094		.0413	.0536	.0609	.0640	.0426	.0552	.0605	.0644

$n = 100, C \sim U[0, 4]$

0.2231		.0292	.0412	.0502	.0614	.0364	.0487	.0565	.0632
0.5108		.0413	.0557	.0692	.0825	.0485	.0644	.0726	.0834
0.9163		.0503	.0695	.0825	.0972	.0568	.0734	.0840	.0949
1.6094		.0614	.0827	.0968	.1053	.0641	.0822	.0942	.1033

$n = 50, C \sim U[0, 3]$

0.2231		.0204	.0287	.0355	.0435	.0254	.0340	.0400	.0444
0.5108		.0287	.0399	.0490	.0584	.0344	.0454	.0520	.0596
0.9163		.0361	.0495	.0580	.0679	.0397	.0518	.0598	.0668
1.6094		.0434	.0579	.0680	.0786	.0439	.0582	.0669	.0773

$n = 100, C \sim U[0, 3]$

Table 3. Standard deviation of $\hat{F}_{12}(x, y)$ along 10,000 simulated samples

		$\theta = 0$				$\theta = 1$			
$x \setminus y$.2231	.5108	.9163	1.6094	.2231	.5108	.9163	1.6094
0.2231		.8457	.8675	.9425	1.014	.9214	.9555	1.004	1.100
0.5108		.8286	.8560	.9076	1.000	.8776	.9097	.9669	1.060
0.9163		.7941	.8216	.8699	.9403	.8449	.8634	.8879	.9839
1.6094		.7543	.7590	.7816	.7875	.7762	.7957	.8114	.7769

$C \sim U[0, 4]$

0.2231		.7925	.8457	.8838	.9683	.8892	.9411	1.018	1.121
0.5108		.7656	.7866	.8604	.9397	.8343	.9023	.9497	1.029
0.9163		.7317	.7604	.8041	.8237	.7827	.8272	.8558	.8457
1.6094		.6811	.6600	.6685	.6363	.6966	.6650	.6287	.6595

$C \sim U[0, 3]$

Table 4. Efficiency of $\tilde{F}_{12}(x, y)$ relative to $\hat{F}_{12}(x, y)$ along the 10,000 simulated samples, case $n = 50$.