Testing Independence for Bivariate Current Status Data

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This article develops a nonparametric procedure for testing marginal independence based on bivariate current status data. Asymptotic properties of the proposed tests are derived, and their finite-sample performance is studied via simulations. The method is applied to analyze data from a community-based study of cardiovascular epidemiology in Taiwan.

KEY WORDS: Cochran–Mantel–Haenszel test; Epidemiology; Interval censoring; Lifetime data; Nonparametric analysis; Two-by-two table.

1. INTRODUCTION

Current status data commonly arise in animal tumorigenicity and epidemiologic investigations of the natural history of a disease. Specifically, the researcher has only the information about whether the failure time of interest lies before or after the observed monitoring time. Such a data structure is also called "interval censoring of the case I" (Groeneboom and Wellner 1992). In this article we consider the bivariate case. Bivariate analysis is useful when one wants to investigate the dependent relationship between two variables. Our work was motivated by a community-based study of cardiovascular diseases in Taiwan conducted to investigate whether the onset ages of some common cardiovascular diseases, specifically hypertension, diabetes mellitus, and hypercholesterolemia, are correlated with one another. Because the natural history of these chronic diseases was difficult to trace precisely, the data contained only information about whether or not a subject under the study had already developed the diseases and about the subject's current age at the time of the study.

Let (T_1, T_2) be a pair of failure times of interest and let C_j be the monitoring time of T_j $(j = 1, 2)$. Bivariate current status data are of the form $\{C_1, C_2, \delta_1 = I(T_1 \le C_1), \delta_2 = I(T_2 \le C_2)\}$. The observed data are of the form $(C_{1k}, C_{2k}, \delta_{1k}, \delta_{2k})$ $(k = 1, \dots, n)$, which are independent and identically distributed replications of $(C_1, C_2, \delta_1, \delta_2)$. Note that when the two failure times are measured from the same subject, as in the foregoing example, usually $C_1 = C_2$. A number of statistical methods have been developed for univariate current status data. For example, nonparametric estimation of the marginal distribution function has been considered by Ayer, Brunk, Ewing, Reid, and Silverman (1955), Peto (1973), Turnbull (1976), and Groeneboom and Wellner (1992). The algorithm for computing the nonparametric maximum likelihood estimator (NPMLE) for current status data was introduced by Groeneboom and Wellner (1992, pp. 66–67). Asymptotic properties of the NPMLE were also examined by Groeneboom and Wellner (1992), who showed that this estimator converges pointwise at rate $n^{1/3}$ to a complex limiting distribution related to Brownian motion. Properties of smooth functionals of the NPMLE were studied by Groeneboom and Wellner (1992) and Huang and Wellner (1995). Semiparametric analysis of regression models for current status data have been studied by Finkelstein (1986), Rabinowitz, Tsiatis, and Aragon (1995), Rossini and Tsiatis (1996), and Lin, Oakes, and Ying (1998), to name just a few. Although bivariate analysis of current status data has many interesting applications, there has not been much literature in this direction to date. Wang and Ding (2000) considered semiparametric estimation of the association parameter in a bivariate copula model.

The main objective of the present work is to develop a nonparametric inference procedure for testing independence between two failure time variables given only bivariate current status data. It is important to note that the semiparametric procedure proposed by Wang and Ding (2000) can be directly applied to test independence only if the parameter under independence is located at the interior of the parameter space. Some modification is required to handle cases when the true parameter lies on the boundary. Independence tests for bivariate right-censored data have been developed by Oakes (1982), Shih and Louis (1996), and Hsu and Prentice (1996), among others. The test proposed by Oakes (1982) is based on estimating Kendall's tau under the null hypothesis. Shih and Louis (1996) studied several test statistics based on marginal martingale residuals.

Our ideas are similar to those discussed by Hsu and Prentice (1996), which can be viewed as a generalization of the Mantel–Haenszel test. Specifically, Hsu and Prentice constructed a sequence of 2×2 tables formed at observed failure times and then proposed a test statistic based on the merged table. Later we show that bivariate current status data can be naturally represented by 2×2 tables formed at observed monitoring times. However, the techniques used for current status data are different from those for right-censored data, which use the martingale theory extensively.

The article is organized as follows. The main result is presented in Section 2. Simulation analysis and real data analysis are given in Sections 3 and 4, and concluding remarks are provided in Section 5.

2. THE PROPOSED METHODOLOGY

2.1 Preliminary

Let $H_0: T_1 \perp T_2$ and $H_0': T_1 \perp T_2 | (C_1, C_2)$. It is obvious that if H_0 is true, then H_0' must be true and if H_0' is false, then

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H_0 must be false. Our original goal is to test the hypothesis $H_0: T_1 \perp T_2$. However, given current status data, we believe that it is impossible to capture any departure from H_0 when H_0' is true. For example, when $C_1 = C_2$, it is possible to verify whether $F(t,t) = F_1(t)F_2(t)$, which describes independence along the diagonal, $C_1 = C_2 = t$. However, no information is available to judge whether off-diagonal independence [i.e., $F(t_1,t_2) = F_1(t_1)F_2(t_2)$ for $t_1 \neq t_2$] also holds. In other words, current status data provide only limited information to identify the dependent relationship between T_1 and T_2. Therefore, here we focus on deriving tests for the null hypothesis, $H_0': T_1 \perp T_2 | (C_1, C_2)$. We should mention that although we set the null hypothesis to be H_0', under the Neyman–Pearson framework, any valid test for testing H_0' is also a valid test for testing H_0, because it gives the correct type I error rate.

Given that $(C_1, C_2) = (c_1, c_2)$, one can construct the following two-by-two table:

	$\delta_2 = 1$	$\delta_2 = 0$	
$\delta_1 = 1$	$N_{11}(c_1, c_2)$	$N_{10}(c_1, c_2)$	
$\delta_1 = 0$	$N_{01}(c_1, c_2)$	$N_{00}(c_1, c_2)$	
			$N(c_1, c_2)$

The cell counts are defined as $N(c_1, c_2) = \sum_{k=1}^{n} I(C_{1k} = c_1, C_{2k} = c_2)$ and $N_{ij}(c_1, c_2) = \sum_{k=1}^{n} I(C_{1k} = c_1, C_{2k} = c_2, \delta_{1k} = i, \delta_{2k} = j)$ for $i, j = 0, 1$. The proposed test procedure is constructed by merging the tables according to the distribution of (C_1, C_2), which has a form similar to the Cochran–Mantel–Haenszel test (Agresti 1990, p. 231). Independence tests based on merging several 2×2 tables, some of which require large observations in each table, have been discussed by Agresti (1990). Our proposed method, in contrast, is valid whether C_1 and C_2 are discrete or continuous and can handle empty cells. In fact, the method is designed particularly for merging sparse 2×2 tables, which commonly arise in applications for bivariate current status data.

Specifically, for the kth patient with monitoring times (c_{1k}, c_{2k}), we can construct a 2×2 table that has only one entry and three empty cells. Given that $(C_{1k}, C_{2k}) = (c_{1k}, c_{2k})$, the cell counts $\{I(\delta_{1k} = 1, \delta_{2k} = 1),\ I(\delta_{1k} = 1, \delta_{2k} = 0),\ I(\delta_{1k} = 0, \delta_{2k} = 1)$, and $I(\delta_{1k} = 0, \delta_{2k} = 0)\}$ jointly follow a multinomial distribution with probabilities equal to $\{P_{11}(c_{1k}, c_{2k}),\ P_{10}(c_{1k}, c_{2k}),\ P_{01}(c_{1k}, c_{2k})$, and $P_{00}(c_{1k}, c_{2k})\}$, where $P_{11}(c_{1k}, c_{2k}) = \Pr(T_1 \le c_{1k}, T_2 \le c_{2k})$, $P_{10}(c_{1k}, c_{2k}) = \Pr(T_1 \le c_{1k}, T_2 > c_{2k})$, $P_{01}(c_{1k}, c_{2k}) = \Pr(T_1 > c_{1k}, T_2 \le c_{2k})$, and $P_{00}(c_{1k}, c_{2k}) = \Pr(T_1 > c_{1k}, T_2 > c_{2k})$. Under H_0' (as well as under H_0), it follows that $P_{11}(c_{1k}, c_{2k}) = F_1(c_{1k})F_2(c_{2k})$, $P_{10}(c_{1k}, c_{2k}) = F_1(c_{1k})S_2(c_{2k})$, $P_{01}(c_{1k}, c_{2k}) = S_1(c_{1k})F_2(c_{2k})$, and $P_{00}(c_{1k}, c_{2k}) = S_1(c_{1k})S_2(c_{2k})$, where $F_j(t) = \Pr(T_j \le t)$, $S_j(t) = 1 - F_j(t)$ $(j = 1, 2)$, and $G(c_1, c_2) = \Pr(C_1 \le c_1, C_2 \le c_2)$.

Our idea for testing independence between T_1 and T_2 is to compare observed cell counts in these 2×2 tables with their expected values under H_0'. Large values of the difference indicate departure from the null hypothesis. Combining all of the tables, each with three empty cells and a single entry, the observed cell counts in the merged table become

$$N_{ab} = \sum_{k=1}^{n} I(\delta_{1k} = a, \delta_{2k} = b) = \sum_{c_1, c_2} N_{ab}(c_1, c_2) \qquad (a, b = 0, 1),$$

where the last sum is over all observed censoring time values. Under the null hypothesis H_0', which is conditional on the observed censoring times, the expected counts in the merged table become

$$E_{ab} = \sum_{k=1}^{n} E_{ab,k} = \sum_{k=1}^{n} F_1(c_{1k})^a S_1(c_{1k})^{1-a} F_2(c_{2k})^b S_2(c_{2k})^{1-b} \qquad (a, b = 0, 1),$$

which can be estimated by plugging in the corresponding marginal NPMLEs of $F_j(\cdot)$ and $S_j(\cdot)$, denoted by $\hat{F}_j(\cdot)$ and $\hat{S}_j(\cdot) = 1 - \hat{F}_j(\cdot)$ $(j = 1, 2)$. Therefore, E_{ij} can be estimated by

$$\hat{E}_{ab} = \sum_{k=1}^{n} \hat{E}_{ab,k} = \sum_{k=1}^{n} \hat{F}_1(c_{1k})^a \hat{S}_1(c_{1k})^{1-a} \hat{F}_2(c_{2k})^b \hat{S}_2(c_{2k})^{1-b} \qquad (a, b = 0, 1). \quad (1)$$

The max–min formula for computing $\hat{F}_j$ is given by

$$\hat{F}_j\big(c_{(ji)}\big) = \max_{l \le i} \min_{k \ge i} \frac{\sum_{m=l}^{k} \delta_{(jm)}}{k - l + 1},$$

where $c_{(j1)} < \cdots < c_{(jn)}$ are ordered observed values of $(C_{j1}, \ldots, C_{jn})$ and $\delta_{(ji)}$ $(j = 1, 2)$ are the associated indicators for $C_{(ji)}$. Their properties have been discussed by Groeneboom and Wellner (1992) and Huang and Wellner (1995). When H_0' is true, $(N_{00} - \hat{E}_{00})/n$ will be close to 0 as n is large. Deviation of this measure from 0 indicates that association exists between T_1 and T_2.

2.2 The Proposed Test

Under the null hypothesis, $(N_{11}, N_{10}, N_{01}, N_{00})$ has a multinomial distribution, which is conditional on censoring times, with cell probabilities $(P_{11}, P_{10}, P_{01}, P_{00})$, where

$$P_{ab} = \iint F_1(c_1)^a S_1(c_1)^{1-a} F_2(c_2)^b S_2(c_2)^{1-b} G_n(dc_1, dc_2) \qquad (a, b = 0, 1).$$

Here $G_n(c_1, c_2) = \sum_{k=1}^{n} I(C_{1k} \le c_1, C_{2k} \le c_2)/n$ is the empirical estimator of $G(c_1, c_2)$. It is easy to see that

$$\sum_{a=0,1} \sum_{b=0,1} P_{ab} = 1.$$

If the marginal functions were known, then we could test H_0' using the Pearson chi-squared statistic

$$\sum_{a=0,1} \sum_{b=0,1} \frac{(N_{ab} - E_{ab})^2}{E_{ab}}$$

with 3 degrees of freedom (df). Because E_{ab} $(= nP_{ab})$ is unknown, it is natural to use its estimate $\hat{E}_{ab}$ in the test. However, there are no longer 3 df after replacing E_{ab} by $\hat{E}_{ab}$, because

$$\hat{E}_{00} - N_{00} = N_{10} - \hat{E}_{10} = \hat{E}_{11} - N_{11} = N_{01} - \hat{E}_{01}. \quad (2)$$

To see why (2) is true, note that

$$\begin{aligned}
&\hat{E}_{00} - N_{00} + \hat{E}_{10} - N_{10} \\
&= \sum_{k=1}^{n} \hat{S}_1(c_{1k})\hat{S}_2(c_{2k}) - \sum_{k=1}^{n} I(\delta_{1k}=0, \delta_{2k}=0) \\
&\quad + \sum_{k=1}^{n} [1-\hat{S}_1(c_{1k})]\hat{S}_2(c_{2k}) - \sum_{k=1}^{n} I(\delta_{1k}=1, \delta_{2k}=0) \\
&= \sum_{k=1}^{n} \hat{S}_2(c_{2k}) - \sum_{k=1}^{n} I(\delta_{2k}=0) \\
&= \sum_{k=1}^{n} [\hat{S}_2(c_{2k}) - 1 + \delta_{2k}] \\
&= \sum_{k=1}^{n} [\delta_{2k} - \hat{F}_2(c_{2k})].
\end{aligned}$$

The last quantity equals 0 because of the self-consistency property of the univariate current status NPMLE (Groeneboom and Wellner 1992). Therefore, $\hat{E}_{00} - N_{00} = N_{10} - \hat{E}_{10}$. Similarly, we can show that $\hat{E}_{00} - N_{00} = N_{01} - \hat{E}_{01}$ and $\hat{E}_{11} - N_{11} = N_{10} - \hat{E}_{10}$. Because the degrees of freedom reduce to 1 after replacing E_{ab} by $\hat{E}_{ab}$, we need only concentrate on one of the four terms, say, $\hat{E}_{00} - N_{00}$.

Note that $\hat{E}_{00} - N_{00} = \hat{E}_{11} - N_{11}$ is the sum of the differences between $\delta_{1k}\delta_{2k}$ and their estimated conditional expectations, $\hat{F}_1(c_{1k})\hat{F}_2(c_{2k})$, under the null hypothesis. Therefore, a significant deviation from 0 of $(\hat{E}_{00} - N_{00})^2$ indicates violation of the null hypothesis. Thus we propose using the test statistic

$$Q = \frac{(N_{00} - \hat{E}_{00})^2}{\widehat{\text{avar}}(N_{00} - \hat{E}_{00})},$$

where $\widehat{\text{avar}}(N_{00} - \hat{E}_{00})$ is a consistent estimator of the asymptotic variance of $(N_{00} - \hat{E}_{00})$. In Appendix A we show that under the null hypothesis, $n^{-1/2}(N_{00} - \hat{E}_{00})$ converges in distribution to $\text{N}(0, \sigma^2)$, and hence Q converges in distribution to a chi-squared distribution with 1 df if $\hat{\sigma}^2 = \widehat{\text{avar}}(N_{00} - \hat{E}_{00})/n$ is a consistent estimator of σ^2. Under the alternative hypothesis, $n^{-1/2}(N_{00} - \hat{E}_{00})$ converges to a non-zero mean normal distribution.

Alternatively, we can construct a test based on an estimate of

$$E[\text{cov}(\delta_1, \delta_2)|C_1, C_2] = E\big[\{\delta_1 - F_1(C_1)\}\{\delta_2 - F_2(C_2)\}\big],$$

where $\text{cov}(\delta_1, \delta_2)|C_1, C_2$ is interpreted as the conditional covariance between δ_1 and δ_2 given (C_1, C_2), whose expectation equals $E[F(C_1, C_2) - F_1(C_1)F_2(C_2)]$ and can be estimated by $(N_{11} - \hat{E}_{11})/n$. As mentioned earlier, the foregoing covariance measure reduces to 0 under H_0'. Furthermore, it is easy to see that $E[\text{cov}(\delta_1, \delta_2)|C_1, C_2]$ equals

$$\begin{aligned}
-E[\text{cov}(\delta_1, 1-\delta_2)|C_1, C_2] &= -E[\text{cov}(1-\delta_1, \delta_2)|C_1, C_2] \\
&= E[\text{cov}(1-\delta_1, 1-\delta_2)|C_1, C_2].
\end{aligned}$$

When the marginal distributions are known completely, the foregoing identity implies that we only need to consider any one of the four covariance measures. When the marginal distributions are estimated by their NPMLE's, such an argument is still true, which can also be justified by (2).

Explicit estimation of σ^2 is very technically involved, however, because of the complexity of the NPMLE's. The bootstrap method provides a convenient numerical solution to obtain a variance estimator. Specifically, from the original data, $\{(C_{1i}, C_{2i}, \delta_{1i}, \delta_{2i})\ i = 1, \dots, n\}$, we can generate a pseudo-dataset, $\{(C_{1k}, C_{2k}, \delta_{1k}^*, \delta_{2k}^*)\ k = 1, \dots, n\}$, where δ_{jk}^* is a Bernoulli random variable with probability $\hat{F}_j(C_{jk})$ $(j = 1, 2)$. The procedure is repeated m times. Let $(N_{00,r}^* - \hat{E}_{00,r}^*)$ be the counterpart of $(N_{00} - \hat{E}_{00})$ for the rth bootstrapped sample. Then $\text{avar}(N_{00} - \hat{E}_{00})$ can be estimated by the sample variance of $(N_{00,r}^* - \hat{E}_{00,r}^*)$ $(r = 1, \dots, m)$; that is,

$$n\hat{\sigma}_b^2 = \sum_{r=1}^{m} (N_{00,r}^* - \hat{E}_{00,r}^* - \bar{R}^*)^2/(m-1),$$

where

$$\bar{R}^* = \sum_{r=1}^{m} (N_{00,r}^* - \hat{E}_{00,r}^*)/m$$

is the sample mean. As long as $n, m \to \infty$, $\hat{\sigma}_b^2 \to \sigma^2$. The resulting test statistic

$$Q_b = \frac{(N_{00} - \hat{E}_{00})^2}{n\hat{\sigma}_b^2} \tag{3}$$

converges to chi-squared distribution with 1 df under the null hypothesis. Although the bootstrap method for variance estimation is straightforward and asymptotically valid, the power of the resulting test is not satisfactory in our simulation analysis. We provide an explanation of this phenomenon in Section 4.

To improve the power, we derive an analytic formula, given in Appendixes B–D, for variance estimation. The proposed variance estimator is generally complicated. However, when $C_1 = C_2 = C$, which occurs when the paired measurements are taken from the same subjects, the formula can be simplified to

$$\begin{aligned}
\hat{\sigma}_p^2 = n^{-1} \sum_{k=1}^{n} \big[&\hat{S}_1(C_{1k})\hat{S}_2(C_{2k}) \\
&\times\{1 + \hat{S}_1(C_{1k}) + \hat{S}_2(C_{2k}) - 3\hat{S}_1(C_{1k})\hat{S}_2(C_{2k})\} \\
&+ (1-\delta_{1k})(1-\delta_{2k})\big(\hat{E}_{00,(-k)} - \hat{E}_{00}\big)\big],
\end{aligned} \tag{4}$$

where $\hat{E}_{00}$ is defined in (1) and $\hat{E}_{00,(-k)}$ is the delete-one-jackknife version of $\hat{E}_{00}$. Specifically, $\hat{E}_{00,(-k)}$ is calculated by removing the kth patient in the estimation of marginal survival functions before plugging into (1). Accordingly, we can construct the test statistic

$$Q_p = \frac{(N_{00} - \hat{E}_{00})^2}{n\hat{\sigma}_p^2}, \tag{5}$$

which also converges to chi-squared distribution with 1 df as $n \to \infty$.

2.3 Finite-Sample Adjustment for Bias

Although the proposed test has nice asymptotic behavior with the regular convergence rate, bias adjustment is useful, especially when the sample size is not large. The bias comes from replacing the unknown marginal functions by their NPMLE's in (1) and (4). Let $n^{-1/2}(N_{00} - \hat{E}_{00}) = n^{-1/2}(N_{00} - E_{00}) + B_{1n}$ and $\hat{\sigma}_p^2 = \sigma^2 + B_{2n}$. As $n \to \infty$, B_{1n} and B_{2n} will shrink to 0, but when the sample size is not large, they are not ignorable and will result in inaccurate type I error (usually higher than the nominal level).

To improve the finite-sample performance, we can estimate B_{1n} and B_{2n} using the bootstrap method and then eliminate their effect in the testing procedure. Specifically, for a bootstrapped sample, $\{(C_{1k}, C_{2k}, \delta_{1k}^*, \delta_{2k}^*)\ k = 1, \ldots, n\}$, we can compute the statistics $U^* = n^{-1/2}(N_{00}^* - \hat{E}_{00}^*)$ and $(\hat{\sigma}_p^*)^2$. We repeat the procedure m times, and let $\hat{U}_b$ and $\hat{\sigma}_{pb}^2$ be the average of the two estimators based on m bootstrap samples and let $\hat{B}_{1n} = \hat{U}_b - n^{-1/2}(N_{00} - \hat{E}_{00})$ and $\hat{B}_{2n} = \hat{\sigma}_{pb}^2 - \hat{\sigma}_p^2$. For relatively large m, say $m = 500$, $\hat{B}_{1n}$ and $\hat{B}_{2n}$ would provide good approximation of the true bias terms. Subtracting these estimated bias terms from the test statistics (3) and (5) yield the bias-adjusted versions of the test statistics,

$$Q_{b(a)} = \frac{(N_{00} - \hat{E}_{00} - n^{1/2}\hat{B}_{1n})^2}{n\hat{\sigma}_b^2} \tag{6}$$

and

$$Q_{p(a)} = \frac{(N_{00} - \hat{E}_{00} - n^{1/2}\hat{B}_{1n})^2}{n(\hat{\sigma}_p^2 - \hat{B}_{2n})}. \tag{7}$$

We show in Section 3 that the adjusted tests perform much better in finite samples than the unadjusted versions.

2.4 Weight Adjustment

The power and efficiency of the test may be improved by including a weight function in the statistic. Note that we can write $N_{00} - \hat{E}_{00} = \sum_k (N_{00,k} - \hat{E}_{00,k})$. Therefore, the modified test is related to the statistic $\sum_k W_k(N_{00,k} - \hat{E}_{00,k})$, where $W_k = w(C_{1k}, C_{2k})$ is the weight assigned to the kth subject according to the observed monitoring times. We can write

$$\begin{aligned} Z_W &= n^{-1/2} \sum_k W_k(N_{00,k} - \hat{E}_{00,k}) \\ &= n^{1/2} \int_{c_1} \int_{c_2} w(c_1, c_2)\{N_{00}(c_1, c_2) - \hat{S}_1(c_1)\hat{S}_2(c_2)\} \\ &\qquad \times G_n(dc_1, dc_2), \end{aligned}$$

where $W_k = w(C_{1k}, C_{2k})$. In Appendix E we show that under independence, Z_W converges to a mean-zero normal random variable with variance σ_W^2 given in (E.1), which can also be estimated using the bootstrap method. An analytic variance estimator can be easily obtained by modifying $\hat{\sigma}_p^2$. Let $\hat{\sigma}_W^2$ denote a consistent estimator σ_W^2. A weighted test statistic is of the form $Q_W = Z_W^2/\hat{\sigma}_W^2$, which converges to χ_1^2 as n goes to infinity. Note that when $w(c_1, c_2) \equiv 1$ for all (c_1, c_2), Q_W reduces to Q_p.

The choice of a good weight function depends on the dependence structure under the alternative hypothesis. Following Anderson, Louis, Holm, and Harvald (1992), the bivariate survival function of (T_1, T_2) can be expressed as

$$S(t_1, t_2) = S_1(t_1)S_2(t_2)e^{-A(t_1, t_2)},$$

where $A(t_1, t_2)$ measures the dependence structure. Note that under independence, $A(t_1, t_2) = 0$. (For other related association measures, see Dabrowska 1988 and Prentice and Cai 1992.) Our original objective is to choose a weight function that under the local alternative $H_\alpha : A(t_1, t_2) = n^{-1/2}a(t_1, t_2) + o_p(n^{-1/2})$ maximizes

$$\frac{|E\{\sum_k W_k(N_{00,k} - \hat{E}_{00,k})\}|^2}{\operatorname{avar}\{\sum_k W_k(N_{00,k} - \hat{E}_{00,k})\}}.$$

Note that we consider only the local optimality condition here, because the behavior of the statistic is more important in the region near independence and also because the analysis can be simplified. Due to the complexity of the plugged-in NPMLE's, we derive the local optimal weight function, denoted by W^*, by maximizing

$$\frac{|E\{\sum_k W_k(N_{00,k} - E_{00,k})\}|^2}{\operatorname{avar}\{\sum_k W_k(N_{00,k} - E_{00,k})\}}.$$

We find that the local optimal weight function, $w^*(t_1, t_2)$, is proportional to

$$\frac{|a(t_1, t_2)|}{1 - S_1(t_1)S_2(t_2)}.$$

The proof is given in Appendix F. Because $w^*(t_1, t_2)$ depends on unknown quantities, we can replace it by its estimator, denoted by $\hat{w}^*(t_1, t_2)$. Then the test statistic Q_{W^*} can be modified as $Q_{\hat{W}^*} = Z_{\hat{W}^*}^2/\hat{\sigma}_{\hat{W}^*}^2$. When $\hat{w}^*(t_1, t_2)$ converges uniformly to $w^*(t_1, t_2)$, the asymptotic distribution of $Q_{\hat{W}^*}$ is the same as that of Q_{W^*}. Note that for finite samples, $Q_{\hat{W}^*}$ may not have the advantage of variance reduction, due to extra estimation of the marginal functions.

We now calculate $w^*(t_1, t_2)$ for the Clayton and Frank models (Clayton 1978; Genest 1987). We use results in the simulation analysis in Section 3.

Example 1: Clayton's Family. The joint survival function is given by

$$S(t_1, t_2) = \{S_1(t_1)^{1-\alpha} + S_2(t_2)^{1-\alpha} - 1\}^{1/(1-\alpha)} \qquad (\alpha > 1),$$

where α is an association parameter related to Kendall's tau (τ) such that $\tau = (\alpha - 1)/(\alpha + 1)$. Let $\alpha = 1 + \delta$; it follows that

$$\begin{aligned} A(t_1, t_2) &= \frac{1}{\alpha - 1} \log\{S_1(t_1)^{\alpha-1} + S_2(t_2)^{\alpha-1} \\ &\qquad - S_1(t_1)^{\alpha-1}S_2(t_2)^{\alpha-1}\} \\ &= -2\delta \log\{S_1(t_1)\} \log\{S_2(t_2)\} + o_p(\delta). \end{aligned}$$

Thus, for Clayton's model, $a(t_1, t_2) \propto \log\{S_1(t_1)\} \log\{S_2(t_2)\}$, and hence

$$w^*(t_1, t_2) = \frac{\log\{S_1(t_1)\} \log\{S_2(t_2)\}}{1 - S_1(t_1)S_2(t_2)}. \tag{8}$$

Example 2: Frank's Family. The joint survival function is given by

$$S(t_1, t_2) = \log_\alpha \left\{ 1 + \frac{(\alpha^{S_1(t_1)} - 1)(\alpha^{S_2(t_2)} - 1)}{\alpha - 1} \right\} \qquad (\alpha > 0).$$

Note that (T_1, T_2) are positively associated when $\alpha < 1$, negatively associated when $\alpha > 1$, and independent when $\alpha \to 1$. Let $\alpha = 1 + \delta$; it follows that

$$\begin{aligned} A(t_1, t_2) &= -\log\big[\log_\alpha\{1 + (\alpha^{S_1(t_1)} - 1)(\alpha^{S_2(t_2)} - 1)/(\alpha - 1)\} \\ &\qquad \times \big(S_1(t_1)S_2(t_2)\big)\big] \\ &= \delta\{1 - S_1(t_1)\}\{1 - S_2(t_2)\}/2 + o_p(\delta). \end{aligned}$$

Thus $a(t_1, t_2) \propto \{1 - S_1(t_1)\}\{1 - S_2(t_2)\}$, and hence, for Frank's family,

$$w^*(t_1, t_2) = \frac{\{1 - S_1(t_1)\}\{1 - S_2(t_2)\}}{1 - S_1(t_1)S_2(t_2)}. \qquad (9)$$

3. SIMULATION ANALYSIS

We carried out series of simulations to examine finite-sample performance of the proposed tests. We generated bivariate failure times (T_1, T_2) from the Clayton family using the algorithm of Prentice and Cai (1992) and from the Frank family using the algorithm of Genest (1987). We first generated $C_1 = C_2$ from uniform distributions. We measured test performance by the empirical power, based on 4,000 runs, which is the relative frequency that the test rejected the null hypothesis at the .05 nominal level. We investigated the power behavior under the combination of 10 dependence levels with τ ranging from 0 to .45, three prevalence levels (PL $\approx$ .2, .5, .8), and two sample sizes ($n = 200, 400$). The prevalence level is defined as the expected proportion of observations that reports failure occurrence, that is, $\Pr(\delta_{1k} = 1) = \Pr(\delta_{2k} = 1)$.

The test statistics (3) and (5) without bias adjustment produced incorrect type I errors, many of which even exceeded .1. Because these are not reliable tests for small samples (i.e., $n = 200, 400$), the data are not shown here. The results of the bias-adjusted tests $Q_{b(a)}$ and $Q_{p(a)}$ in (6) and (7) are given in Tables 1 and 2.

Table 1 shows the results using the bootstrap variance estimator $Q_{b(a)}$. The type I errors for the unweighted tests are close to the .05 nominal level. The weighted tests also have type I errors close to .05 in most cases. Thus the test is valid for the two chosen sample sizes. The power increases as the associ-

Table 1. Empirical Power of $Q_{b(a)}$ Based on 4,000 Replications

				τ									
T	*n*	*PL*	*W*	*0*	*.05*	*.10*	*.15*	*.20*	*.25*	*.30*	*.35*	*.40*	*.45*
C	200	.8	U	.059	.118	.275	.490	.685	.842	.932	.975	.996	.998
			C	.037	.127	.289	.490	.674	.813	.906	.958	.984	.995
			F	.053	.113	.287	.520	.721	.871	.942	.980	.997	.999
		.5	U	.057	.128	.300	.566	.797	.934	.985	.998	1.000	1.000
			C	.061	.100	.226	.459	.704	.858	.955	.988	.998	1.000
			F	.056	.104	.256	.514	.775	.913	.980	.996	.999	1.000
		.2	U	.056	.078	.142	.213	.338	.471	.650	.775	.891	.950
			C	.050	.046	.069	.104	.169	.259	.399	.540	.685	.808
			F	.051	.053	.084	.124	.205	.315	.463	.620	.762	.867
	400	.8	U	.061	.151	.421	.719	.912	.979	.998	1.000	1.000	1.000
			C	.040	.180	.435	.719	.905	.971	.994	.999	1.000	1.000
			F	.054	.154	.442	.753	.940	.985	.999	1.000	1.000	1.000
		.5	U	.054	.177	.519	.828	.974	.999	1.000	1.000	1.000	1.000
			C	.066	.139	.413	.746	.934	.991	.999	1.000	1.000	1.000
			F	.063	.149	.469	.804	.966	.997	1.000	1.000	1.000	1.000
		.2	U	.052	.092	.197	.342	.546	.739	.880	.961	.992	.997
			C	.051	.053	.087	.166	.328	.506	.691	.840	.941	.983
			F	.048	.057	.109	.203	.386	.575	.759	.895	.965	.993
F	200	.8	U	.059	.093	.168	.293	.440	.599	.757	.869	.929	.973
			C	.037	.058	.091	.143	.193	.280	.389	.489	.584	.697
			F	.053	.075	.118	.216	.318	.463	.610	.749	.834	.923
		.5	U	.057	.127	.296	.550	.807	.935	.980	.998	1.000	1.000
			C	.061	.089	.173	.341	.542	.723	.871	.946	.986	.996
			F	.056	.099	.217	.429	.677	.850	.951	.987	.999	1.000
		.2	U	.056	.118	.248	.416	.636	.807	.928	.979	.994	.999
			C	.050	.055	.106	.209	.360	.550	.741	.850	.931	.972
			F	.051	.070	.137	.259	.439	.635	.819	.905	.967	.989
	400	.8	U	.061	.114	.261	.457	.685	.878	.954	.988	.997	1.000
			C	.040	.066	.119	.200	.316	.461	.616	.744	.850	.926
			F	.054	.089	.176	.335	.541	.748	.877	.951	.985	.999
		.5	U	.054	.175	.511	.825	.973	.998	1.000	1.000	1.000	1.000
			C	.066	.107	.296	.572	.820	.953	.991	.999	1.000	1.000
			F	.063	.122	.383	.708	.921	.989	.999	1.000	1.000	1.000
		.2	U	.052	.146	.387	.660	.883	.974	.997	1.000	1.000	1.000
			C	.051	.065	.188	.386	.676	.852	.951	.991	.998	1.000
			F	.048	.076	.228	.456	.741	.904	.978	.997	1.000	1.000

NOTE: The first column, "T," lists the true distribution, "C" for the Clayton model and "F" for the Frank model. The second column, "*n*," gives the sample size, and the third column, "PL," gives the prevalence level. The fourth column, "W," gives the weights: "U" for the unweighted version, "C" for the optimal weight based on the Clayton model, and "F" for the optimal weight based on the Frank model.

ation, measured by τ, becomes greater. However, the weight adjustment apparently does not improve the power. Recall that the bootstrap estimation is conducted under the assumption of independence, whereas the two failure times are correlated under the alternative hypothesis. The variance estimator obtained using the bootstrap method may be overestimated, and hence it offsets the power gain.

Table 2 summarizes the results for $Q_{p(a)}$ using the analytic variance estimator. Although the power is generally higher than that when using $Q_{b(a)}$, the type I error seems less accurate in some cases. The unweighted test has the correct type I error except for the case of $n = 200$ and at an 80% prevalence rate. The type I errors for the weighted tests become closer to the nominal level when the sample size or prevalence level increases. On the other hand, the weighted tests perform poorly under small sample sizes and low prevalence rates.

Now we explain how the prevalence level affects the finite-sample performance of the weighted tests. We first examine the optimal weight for the Clayton model. Equation (8) suggests assigning larger weights to the tail region of (T_1, T_2). However, when $\Pr(T_k \le C_k)$ $(k = 1, 2)$ are small, most observations tend to have large values of $S_j(c_j)$ $(j = 1, 2)$, which are assigned with lower weights. This would reduce the effective sample size, and hence cause the asymptotics to kick in more slowly than in the unweighted test. When assuming the Frank model, (9) also suggests assigning larger weights to the tail region of (T_1, T_2). Hence when the prevalence level is low, the weight adjustment also offsets the effective sample size. Nevertheless, because the Frank weights are bounded between 0 and 1, the test using Frank's weight produces more accurate type I error than that using Clayton's weight when the correct model is assumed. Generally, for the same sample size, the power is highest when the prevalence rate is around 50%. This is because the effective sample size is larger when the observed failures and survivals are more balanced.

Now we examine whether weight adjustment does indeed improve the local power near independence. As intended from the theoretical deduction, the weighted tests in most cases have higher power than the unweighted tests when $\tau < .10$. However, the theory does not ensure that the weights are optimal when association is stronger. When the true level of association is moderate or strong, model misspecification may have a substantially negative effect. For example when $n = 200$, the prevalence rate is 80%, and the Frank model is misspecified as the Clayton model with $\tau = .3$, the power of the weighted test is only 49%, whereas that of the unweighted test is > 85%.

Table 2. Empirical Power of $Q_{p(a)}$ Based on 4,000 Replications

				τ									
T	*n*	*PL*	*W*	*0*	*.05*	*.10*	*.15*	*.20*	*.25*	*.30*	*.35*	*.40*	*.45*
C	200	.8	U	.073	.174	.356	.570	.756	.880	.949	.983	.997	.999
			C	.064	.197	.394	.605	.766	.877	.939	.978	.993	.998
			F	.072	.205	.441	.667	.835	.937	.975	.993	.999	1.000
		.5	U	.050	.170	.364	.640	.851	.953	.992	.999	1.000	1.000
			C	.069	.191	.372	.608	.810	.922	.979	.994	.999	1.000
			F	.064	.198	.401	.677	.876	.962	.995	.999	1.000	1.000
		.2	U	.041	.078	.142	.223	.348	.482	.654	.784	.893	.949
			C	.141	.196	.271	.353	.480	.578	.707	.795	.883	.929
			F	.110	.161	.249	.340	.477	.590	.732	.825	.914	.958
	400	.8	U	.057	.197	.475	.759	.925	.983	.998	1.000	1.000	1.000
			C	.053	.231	.519	.786	.939	.983	.997	1.000	1.000	1.000
			F	.059	.246	.579	.835	.967	.993	1.000	1.000	1.000	1.000
		.5	U	.048	.219	.572	.858	.981	1.000	1.000	1.000	1.000	1.000
			C	.060	.215	.533	.821	.960	.996	.999	1.000	1.000	1.000
			F	.053	.227	.602	.882	.982	.999	1.000	1.000	1.000	1.000
		.2	U	.039	.088	.203	.346	.560	.741	.885	.962	.993	.998
			C	.080	.141	.254	.370	.558	.719	.842	.924	.969	.990
			F	.068	.131	.249	.380	.584	.753	.874	.957	.988	.998
F	200	.8	U	.073	.147	.267	.408	.573	.719	.848	.930	.968	.987
			C	.064	.104	.156	.222	.293	.392	.514	.615	.701	.799
			F	.072	.138	.248	.382	.514	.642	.782	.873	.925	.969
		.5	U	.050	.167	.359	.631	.859	.957	.988	.999	1.000	1.000
			C	.069	.161	.285	.480	.672	.820	.918	.966	.992	.998
			F	.064	.175	.332	.578	.797	.924	.975	.996	1.000	1.000
		.2	U	.041	.115	.251	.426	.642	.812	.930	.979	.993	.999
			C	.141	.236	.364	.510	.670	.797	.900	.938	.969	.987
			F	.110	.206	.350	.513	.691	.829	.928	.966	.988	.997
	400	.8	U	.057	.153	.338	.552	.758	.915	.973	.994	.998	1.000
			C	.053	.100	.170	.274	.411	.557	.706	.812	.896	.951
			F	.059	.141	.287	.488	.684	.859	.940	.981	.994	1.000
		.5	U	.048	.212	.566	.861	.978	.999	1.000	1.000	1.000	1.000
			C	.060	.162	.401	.674	.879	.967	.994	.999	1.000	1.000
			F	.053	.192	.503	.802	.953	.995	1.000	1.000	1.000	1.000
		.2	U	.039	.145	.394	.665	.887	.973	.997	1.000	1.000	1.000
			C	.080	.189	.405	.610	.821	.932	.977	.993	.998	1.000
			F	.068	.183	.417	.649	.864	.956	.990	.998	1.000	1.000

NOTE: The first column, "T," lists the true distribution: "C" for the Clayton model and "F" for the Frank model. The second column, "*n*," gives the sample size, and the third column, "PL," gives the prevalence level. The fourth column, "W," gives the weights: "U" for the unweighted version, "C" for the optimal weight based on the Clayton model, and "F" for the optimal weight based on the Frank model.

The foregoing analysis indicates that the unweighted test based on $Q_{p(a)}$ is an accurate and safe choice. It does not rely on any model assumption, and its performance in all cases is satisfactory in terms of the power behavior. The weighted version of $Q_{p(a)}$ may be a consideration only if the sample size is large and some prior information about the model and weak association is available.

We also evaluated the tests proposed under unequal monitoring times. Specifically, we set $C_2 = C_1 + .1$. The results are similar to those in Tables 1 and 2 and hence are omitted.

The effect of the censoring mechanism on the power of the unweighted test is governed by the magnitude of the conditional covariance measure,

$$\left[\iint \left\{\Pr(T_1 > c_1, T_2 > c_2) - S_1(c_1)S_2(c_2)\right\} G(dc_1, dc_2)\right]^2.$$

Obviously, the power is affected by the underlying dependence structure, the censoring pattern and their joint effect. To improve the power by controlling the censoring scheme, the researcher should sample more observations, which give a larger value of $|\Pr(T_1 > c_1, T_2 > c_2) - S_1(c_1)S_2(c_2)|$. However, this suggestion may not be practical, because testing independence is usually the first step of analysis.

4. DATA ANALYSIS

We applied the proposed methodology to analyze a communitybased study of cardiovascular diseases conducted from 1991 to 1993 in Taiwan. The study group had 6,314 participants, 2,904 males and 3,410 females. The data comprised measurements of the participants' current age at the time of study and the prevalence indicators of three diseases, diabetes mellitus, hypercholesterolemia, and hypertension. Let (T_1, T_2, T_3) denote the onset age of diabetes mellitus, hypercholesterolemia, and hypertension, and let C denote the subject's age at the monitoring time. Therefore, the data are of the form $(C, \delta_1, \delta_2, \delta_3)$, where $\delta_j = I(T_j \le C)$ $(j = 1, 2, 3)$. (It should be mentioned that we used this example only for illustrative purposes, because the prevalence of the three cardiovascular diseases were determined via participant interview, health examination, or previous medical history, rather than based on formal medical diagnosis. For more detailed description of the data, see Wang and Ding 2000).

Table 3 summarizes the results for testing pairwise independence of (T_1, T_2), (T_1, T_3), and (T_2, T_3). The associations between the onset ages of diabetes mellitus (T_1) and the hypercholesterolemia and hypertension are both very strong with p value close to 0. The association between T_2 and T_3 is significant at the .05 level, but not at the .01 level.

Table 3. Pairwise Independent Tests for the Onset Ages of Patients With Three Cardiovascular Diseases: Diabetes Mellitus (T_1), Hypercholesterolemia (T_2), and Hypertension (T_3)

Hypothesis	*Weight*	*Value of $Q_{b(a)}$ (p value)*	*Value of $Q_{p(a)}$ (p value)*
$T_1 \perp T_2$	Unweighted	26.3148 (.000)	34.4500 (.000)
	C-optimal	11.8061 (.001)	18.0300 (.000)
	F-optimal	12.1977 (.000)	18.5347 (.000)
$T_1 \perp T_3$	Unweighted	31.4113 (.000)	55.0494 (.000)
	C-optimal	18.9685 (.000)	36.6759 (.000)
	F-optimal	21.2697 (.000)	41.0896 (.000)
$T_2 \perp T_3$	Unweighted	5.8107 (.016)	6.0074 (.014)
	C-optimal	3.9863 (.046)	4.4345 (.035)
	F-optimal	4.2934 (.038)	4.7365 (.030)

NOTE: The second column indicates the assigned weights, namely unweighted, the optimal weight based on the Clayton model (C-optimal) and the optimal weight based on Frank's model (F-optimal).

It is interesting to note that Wang and Ding (2000) assumed that the pairwise dependence structures of the three diseases all follow Clayton's model and then estimated the association parameters. The estimated values of the corresponding Kendall's tau between T_i and T_j, denoted by $\hat{\tau}_{ij}$, are $\hat{\tau}_{12} = .304$, $\hat{\tau}_{13} = .128$, and $\hat{\tau}_{23} = .082$. The corresponding 95% confidence intervals are $(.210, .378)$, $(-.005, .230)$, and $(-.019, .165)$.

5. CONCLUDING REMARKS

We have developed a nonparametric method to test independence between two failure time variables when only current status data are available. Because the true failure times (T_1, T_2) are never observed, this inference problem is harder than it first appears. Specifically, it is not easy to test independence between (T_1, T_2) without being affected by the distribution of (C_1, C_2), which are often correlated. The proposed testing procedures use only statistics conditional on the censoring times, to avoid making assumptions on the censoring distribution. It is possible that the proposed test correctly accepts H_0' while H_0 is false, because current status data do not provide information to identify such a condition. Nevertheless, as long as C_1 and C_2 are continuous and their support is great enough to cover the distribution of (T_1, T_2), the foregoing situation is not likely.

Sometimes practitioners may want to apply nonparametric methods, such as independence, rank, and permutation tests, which are popular in cross-sectional analysis, to bivariate current status data. Here we discuss why these methods are not applicable. First, we discuss an independence test based on the merged 2×2 table with entries N_{00}, N_{01}, N_{10}, and N_{11} without using the information of individual censoring times. Independence between the columns and rows implies that

$$\left\{\int S_1(c_1)\, dG_1(c_1)\right\}\left\{\int S_2(c_2)\, dG_2(c_2)\right\} = \iint S(c_1, c_2) G(dc_1, dc_2),$$

where $G(c_1, c_2)$ is the distribution function of (C_1, C_2) with marginal distribution functions denoted by $G_1(c_1)$ and $G_2(c_2)$. It is easy to see that the foregoing equation holds when not only $S_1(c_1)S_2(c_2) = S(c_1, c_2)$, but also $G_1(c_1)G_2(c_2) = G(c_1, c_2)$. Therefore, this test would be valid for testing independence between T_1 and T_2 only under the unrealistic assumption that C_1 and C_2 are also independent.

Now we discuss the validity of some permutation tests. Let $G_n(c_1, c_2)$, $G_{1n}(c_1)$, and $G_{2n}(c_2)$ denote the corresponding empirical distribution functions. One possible alternative is to perform a permutation test by randomly pairing up (C_{1k}, δ_{1k}) with (C_{2j}, δ_{2j}). Such a procedure that breaks up observations of (C_1, C_2) would make the resampled censoring distribution to be $G_{1n}(c_1)G_{2n}(c_2)$, which converges to $G_1(c_1)G_2(c_2)$ instead of $G(c_1, c_2)$. Again, the resulting test would be valid only if C_1 and C_2 were also independent. A second possible mistake is to run a permutation test by keeping (C_{1k}, C_{2k}) together and only randomly pairing up δ_{1i} with δ_{2j}. Note that $\Pr(\delta_{1k}=1|C_{1k}) = F_1(C_{1k})$, whereas $\Pr(\delta_{1i}=1|C_{1i}) = F_1(C_{1i})$. Hence they cannot be exchanged under the null hypothesis. A third possibility is running a nonparametric bootstrap without replacement; that is, keep $(C_{1k}, \delta_{1k}, C_{2k}, \delta_{2k})$ together and permute just among the individuals. Although this is a valid permutation that retains the distribution of the original data, it does not provide any information for the variation.

The main purpose of weight adjustment is to improve the power when the true association is near independence. However, the weighted test requires a high prevalence rate and large sample size to ensure asymptotic validity. It is also susceptible to model misspecification and may not offer any advantages when the association is high. Therefore, we suggest using the unweighted test, which performs quite well in almost all of the simulated cases.

The proposed methodology can be easily extended to adjust for the effects of covariates. The assumption of strict independence between the failure times and monitoring times may be relaxed if their dependence can be accounted for by observed covariate, say Z, such that $T_j \perp C_j|Z$ $(j=1,2)$. Accordingly, the 2×2 tables should be constructed based on distinct observed values of (C_1, C_2, Z). If Z also affects the marginal distributions, then the NPMLE's $\hat{S}_j(c_j)$ $(j=1,2)$ should be replaced by appropriate estimators of $S_j(c_j|Z)$. A candidate of such an estimator is the one proposed by van der Laan and Robbins (1998) under the proportional hazard assumption. Then the adjusted estimates of $S_j(c_j|Z)$ $(j=1,2)$ are used in estimating the expected counts $\hat{E}_{ab}$ in $Q_{b(a)}$ or $Q_{p(a)}$.

In this article we concentrated on the bivariate case. The tests can be easily generalized to multivariate data of dimensions higher than two. Using similar ideas, we can construct $2\times 2\times\cdots\times 2$ tables and use the test statistic $Q = (N_{00\ldots0} - \hat{E}_{00\ldots0})^2/n\hat{\sigma}^2$. The extension of the variance estimator $\hat{\sigma}^2$ to multivariate data is straightforward.

APPENDIX A: ASYMPTOTIC NORMALITY OF $n^{-1/2}(N_{00} - \hat{E}_{00})$

Note that $N_{00} - \hat{E}_{00} = (N_{00} - E_{00}) + (E_{00} - \hat{E}_{00})$. We can write

$$E_{00} = n \iint S_1(c_1)S_2(c_2)G_n(dc_1, dc_2),$$

and similar expressions apply to E_{10}, E_{01} and E_{00}. The first term, $(N_{00} - E_{00})$, can be written explicitly as

$$\sum_{k=1}^{n} \left\{ I(T_{1k} > C_{1k}, T_{2k} > C_{2k}) - S_1(C_{1k})S_2(C_{2k}) \right\}.$$

Hence, by the central limit theorem, $n^{-1/2}(N_{00} - E_{00})$ converges in distribution to $\mathrm{N}(\mu, \sigma_1^2)$, where $\mu = E[S(C_1, C_2) - S_1(C_1)S_2(C_2)]$ and σ_1^2 is the unconditional variance of $I(T_1 > C_1, T_2 > C_2) - S_1(C_1)S_2(C_2)$. Under the null hypothesis, $\mu = 0$ and $\sigma_1^2 = E[S_1(C_1)\times S_2(C_2)(1 - S_1(C_1)S_2(C_2))]$.

Now we prove asymptotic normality of the second term, $n^{-1/2}\times (E_{00} - \hat{E}_{00})$. By uniform consistency of the marginal NPMLE's and asymptotic properties of an empirical process, it follows that

$$\begin{aligned}
n^{-1/2}(\hat{E}_{00} - E_{00}) &= n^{-1/2}\sum_{k=1}^{n}\left\{\hat{S}_1(C_{1k})\hat{S}_2(C_{2k}) - S_1(C_{1k})S_2(C_{2k})\right\} \\
&= n^{1/2}\iint \left\{\hat{S}_1(c_1)\hat{S}_2(c_2) - S_1(c_1)S_2(c_2)\right\}G_n(dc_1, dc_2) \\
&= n^{1/2}\iint S_2(c_2)\{\hat{S}_1(c_1) - S_1(c_1)\}G(dc_1, dc_2) \\
&\quad + n^{1/2}\iint S_1(c_1)\{\hat{S}_2(c_2) - S_2(c_2)\}G(dc_1, dc_2) \\
&\quad + \mathrm{rem}_n.
\end{aligned}$$

We show that the first two terms converge to a normal distribution, where the remainder term, rem_n, is of order $o_p(1)$.

First, the remainder term is

$$\begin{aligned}
\mathrm{rem}_n &= n^{1/2}\iint S_2(c_2)\{\hat{S}_1(c_1) - S_1(c_1)\} \\
&\qquad\times[\,G_n(dc_1, dc_2) - G(dc_1, dc_2)] \\
&\quad + n^{1/2}\iint S_1(c_1)\{\hat{S}_2(c_2) - S_2(c_2)\} \\
&\qquad\times[\,G_n(dc_1, dc_2) - G(dc_1, dc_2)] \\
&\quad + n^{1/2}\iint \{\hat{S}_1(c_1) - S_1(c_1)\}\{\hat{S}_2(c_2) - S_2(c_2)\} \\
&\qquad\times\, G_n(dc_1, dc_2) \\
&= I_{1n} + I_{2n} + I_{3n}.
\end{aligned}$$

Because $\hat{S}_j(c_j) - S_j(c_j)$, $j=1,2$, are of order $O_p(n^{-1/3})$ (Groeneboom and Wellner 1992), the last term $I_{3n} = O_p(n^{1/2-1/3-1/3}) = O_p(n^{-1/6}) = o_p(1)$. To show that the first two terms are of order $o_p(1)$, note that each integrand involves only one-dimensional empirical survival function $\hat{S}_j$. It is essentially the same proof as in the univariate current status data case; we can apply, for example, arguments similar to those of Huang and Wellner (1995, pp. 160–161). Let $\mathcal{S} = \{S : S$ is a one-dimensional survival function$\}$, and consider the class of functions $\mathcal{F} = \{S_1(x)(S(y) - S_2(y)) : S \in \mathcal{S}\}$. First, uniform entropy for $\mathcal{S}$ is bounded by $K(1/\epsilon)^{\lambda}$, $\lambda > 1$, because it is contained in the convex hull of the VC graph class of right half lines (Dudley 1987). Because for any $S_{(1)}, S_{(2)} \in \mathcal{S}$,

$$\begin{aligned}
&\left|S_1(x)\big(S_{(1)}(y) - S_2(y)\big) - S_1(x)\big(S_{(2)}(y) - S_2(y)\big)\right| \\
&\qquad\qquad \le \left|S_{(1)}(y) - S_{(2)}(y)\right|,
\end{aligned}$$

the uniform entropy for $\mathcal{F}$ is also bounded by the bound for $\mathcal{S}$, $K(1/\epsilon)^{\lambda}$, $\lambda > 1$. Therefore, $\mathcal{F}$ is a G-Donsker class by Pollard's theorem (e.g., Dudley 1987). Then we apply theorem 1.1 of Sheehy and Wellner (1992) to ensure the uniform asymptotic equicontinuity of the empirical process over $\mathcal{F}$, which then implies that the first term $I_{1n} = o_p(1)$. The second term, $I_{2n} = o_p(1)$, is proved the same way by symmetry, and we have $\mathrm{rem}_n = o_p(1)$.

Next, we show that the first two terms in (B.1) are asymptotically normal. Without loss of generality, assume that $G(c_1, c_2)$ is differentiable with respect to both arguments and that $g(c_1, c_2) = \partial^2 G(c_1, c_2)/\partial c_1 \partial c_2$. Denote

$$\begin{aligned}
A_1(x) &= \int_{c_1=0}^{x}\left[\int_{c_2=0}^{\infty} S_2(c_2)g(c_1, c_2)\,dc_2\right]dc_1 \\
&= \int_{c_1=0}^{x} a_1(c_1)\,dc_1
\end{aligned}$$

and

$$\begin{aligned}
A_2(x) &= \int_{c_2=0}^{x}\left[\int_{c_1=0}^{\infty} S_1(c_1)g(c_1, c_2)\,dc_1\right]dc_2 \\
&= \int_{c_2=0}^{x} a_2(c_2)\,dc_2.
\end{aligned}$$

Performing integration by parts, it follows that

$$\begin{aligned} n^{-1/2}\{\hat{E}_{00}-E_{00}\} &= -n^{1/2}\int_{c_1=0}^{\infty} A_1(c_1)\,d(\hat{S}_1-S_1)(c_1) \\ &\quad - n^{1/2}\int_{c_2=0}^{\infty} A_2(c_2)\,d(\hat{S}_2-S_2)(c_2)+o_p(1) \\ &= -n^{1/2}\{\nu_1(\hat{S}_1)-\nu_1(S_1)\} \\ &\quad - n^{1/2}\{\nu_2(\hat{S}_2)-\nu_2(S_2)\}+o_p(1), \end{aligned}$$

where

$$\nu_1(S_1)=\int A_1(c)\,dS_1(c), \qquad \nu_2(S_2)=\int A_2(c)\,dS_2(c).$$

Notice that $\nu_j(S_j)$ is a "smooth" functional of S_j satisfying the conditions in theorem 5.1 of Huang and Wellner (1995). Therefore, the asymptotic normalities of $n^{1/2}\{\nu_j(\hat{S}_j)-\nu_j(S_j)\}$ $(j=1,2)$, and hence of $n^{-1/2}(\hat{E}_{00}-E_{00})$, are established.

APPENDIX B: ESTIMATION OF σ^2

We have shown that $n^{-1/2}(N_{00}-\hat{E}_{00})$ converges to N$(0,\sigma^2)$. To estimate the asymptotic variance σ^2, note that $\sigma^2=\sigma_1^2+\sigma_2^2+2\sigma_{12}$, where $\sigma_1^2=\text{avar}\{n^{-1/2}(N_{00}-E_{00})\}$, $\sigma_2^2=\text{avar}\{n^{-1/2}(E_{00}-\hat{E}_{00})\}$, and $\sigma_{12}=\text{acov}\{n^{-1/2}(N_{00}-E_{00}), n^{-1/2}(E_{00}-\hat{E}_{00})\}$. Because $\sigma_1^2=E[S_1(C_1)S_2(C_2)\{1-S_1(C_1)S_2(C_2)\}]$, it can be estimated consistently by

$$\hat{\sigma}_1^2=n^{-1}\sum_{k=1}^{n}\hat{S}_1(C_{1k})\hat{S}_2(C_{2k})\{1-\hat{S}_1(C_{1k})\hat{S}_2(C_{2k})\}. \tag{B.1}$$

We show (in App. C) that

$$\sigma_2^2=\iint\left\{F_1(c_1)\frac{a_1(c_1)}{g_1(c_1)}+F_2(c_2)\frac{a_2(c_2)}{g_2(c_2)}\right\} \times S_1(c_1)S_2(c_2)G(dc_1,dc_2). \tag{B.2}$$

We may estimate σ_2^2 analytically based on the foregoing expression. But the estimator $\hat{\sigma}_2^2$ is generally is very complicated. However, estimation can be simplified if the relationship between C_1 and C_2 is specified. For example, in the most common case when the measurements are taken from the same subjects, we have $C_{1k}=C_{2k}=C_k$ $(k=1,\ldots,n)$. In such a case, the foregoing expression is simplified to

$$\sigma_2^2=\iint\{S_1(c_1)+S_2(c_2)-2S_1(C_k)S_2(C_k)\} \times S_1(c_1)S_2(c_2)G(dc_1,dc_2),$$

which can be estimated consistently by

$$\tilde{\sigma}_2^2=\frac{1}{n}\sum_{k=1}^{n}\hat{S}_1(C_k)\hat{S}_2(C_k) \times\left\{\hat{S}_1(C_k)+\hat{S}_2(C_k)-2\hat{S}_1(C_k)\hat{S}_2(C_k)\right\}. \tag{B.3}$$

Denote $\hat{E}_{00,(-k)}$ as the delete-one version of $\hat{E}_{00}$ calculated after deleting subject k from the sample. We show (in App. D) that σ_{12} can be consistently estimated by

$$\hat{\sigma}_{12}=\frac{1}{n}\sum_{k=1}^{n}(1-\delta_{1k})(1-\delta_{2k})\big(\hat{E}_{00,(-k)}-\hat{E}_{00}\big). \tag{B.4}$$

Hence the asymptotic variance σ^2 is estimated consistently by $\hat{\sigma}^2=\hat{\sigma}_1^2+\hat{\sigma}_2^2+2\hat{\sigma}_{12}$, which is simplified to (4) when $C_1=C_2$.

In finite samples, the foregoing estimator tends to overestimate the true variance. The bias comes from $\hat{\sigma}_1^2$ and $\hat{\sigma}_2^2$ given in (B.1) and (B.3). To see this, we can write

$$\begin{aligned} \sigma_1^2-\hat{\sigma}_1^2 &= -\frac{1}{n}\sum_{i=1}^{n}\{\hat{S}_1(C_{1i})\hat{S}_2(C_{2i})-S_1(C_{1i})S_2(C_{2i})\} \\ &\qquad \times\left\{1-\hat{S}_1(C_{1i})\hat{S}_2(C_{2i})-S_1(C_{1i})S_2(C_{2i})\right\} \\ &= -\frac{1}{n}\sum_{i=1}^{n}\{\hat{S}_1(C_{1i})\hat{S}_2(C_{2i})-S_1(C_{1i})S_2(C_{2i})\} \\ &\qquad \times\left\{1-2S_1(C_{1i})S_2(C_{2i})\right\} \\ &\quad +\frac{1}{n}\sum_{i=1}^{n}\{\hat{S}_1(C_{1i})\hat{S}_2(C_{2i})-S_1(C_{1i})S_2(C_{2i})\}^2 \\ &= r_{1n}+r_{2n}. \end{aligned}$$

The first term, r_{1n}, asymptotically is of mean 0 and order $O_p(n^{-1/2})$. The second term, r_{2n}, is of smaller order, $O_p(n^{-2/3})$, but always positive. Similarly, $\hat{\sigma}_2^2$ underestimates σ_2^2. Hence the finite-sample adjustments for bias in Section 2.3 is necessary. To save computing time, the bias adjustment can be applied only to $\hat{\sigma}_1^2$ and $\hat{\sigma}_2^2$ rather than the whole $\hat{\sigma}^2$.

APPENDIX C: ESTIMATION OF $\sigma_2{}^2=\text{avar}(n^{-1/2}\{E_{00}-\hat{E}_{00}\})$

Applying theorem 5.1 of Huang and Wellner (1995), we can write

$$\begin{aligned} n^{-1/2}\{\hat{E}_{00}-E_{00}\} &= n^{-1/2}\sum_{k=1}^{n}\left[\{\delta_{1k}-F_1(C_{1k})\}\frac{a_1(C_{1k})}{g_1(C_{1k})}\right. \\ &\qquad \left.+\{\delta_{2k}-F_2(C_{2k})\}\frac{a_2(C_{2k})}{g_2(C_{2k})}\right] \\ &\quad +o_p(1), \end{aligned}$$

where $g_1(\cdot)$ and $g_2(\cdot)$ are the marginal density functions of C_1 and C_2. It follows that

$$\begin{aligned} \sigma_2^2 &= \text{var}\left[\{\delta_{11}-F_1(C_{11})\}\frac{a_1(C_{11})}{g_1(C_{11})}+\{\delta_{21}-F_2(C_{21})\}\frac{a_2(C_{21})}{g_2(C_{21})}\right] \\ &= \int F_1(c_1)S_1(c_1)\frac{[a_1(c_1)]^2}{g_1(c_1)}\,dc_1 \\ &\quad +\int F_2(c_2)S_2(c_2)\frac{[a_2(c_2)]^2}{g_2(c_2)}\,dc_2 \\ &= \iint F_1(c_1)S_1(c_1)\frac{a_1(c_1)}{g_1(c_1)}S_2(c_2)g(c_1,c_2)\,dc_1\,dc_2 \\ &\quad +\iint F_2(c_2)S_2(c_2)\frac{a_2(c_2)}{g_2(c_2)}S_1(c_1)g(c_1,c_2)\,dc_1\,dc_2 \\ &= \iint\left\{F_1(c_1)\frac{a_1(c_1)}{g_1(c_1)}+F_2(c_2)\frac{a_2(c_2)}{g_2(c_2)}\right\} \\ &\qquad \times S_1(c_1)S_2(c_2)G(dc_1,dc_2). \end{aligned}$$

Based on this expression, we may estimate σ_2^2 analytically, as follows. Estimate $G(\cdot,\cdot)$ by the empirical distribution $G_n(\cdot,\cdot)$; estimate the marginal functions by the corresponding NPMLE's; and estimate $\frac{a_j(c)}{g_j(c)}$ $(j=1,2)$ by some nonparametric methods. The last step involves estimating a ratio of density functions nonparametrically. We suggest applying the kernel method to estimate each component.

Specifically,

$$\frac{\hat{a}_1(c_1)}{\hat{g}_1(c_1)} = \frac{\sum_{k=1}^n \hat{S}_2(C_{2k})K\{(C_{1k}-c_1)/h_1\}}{\sum_{k=1}^n K\{(C_{1k}-c_1)/h_1\}},$$

where the kernel function, $K(\cdot)$, is a symmetric density function and h is the bandwidth, controlling the size of the local neighborhood. Bandwidth selection is often crucial for the kernel method. However, estimation of $\frac{a_j(c)}{g_j(c)}$ $(j=1,2)$ is not the ultimate goal, but is done only to provide a consistent plugged-in estimator. Hence we do not have to find the optimal kernel and bandwidth, which is a difficult topic by itself, because there is no obvious optimal criterion here. For computation simplicity, we can take the linear kernel $K(x)=\max(1-|x|,0)$ and bandwidth $h_1 = n^{-1/5}s_1$ (of the conventional optimal order), where s_1 denotes the sample standard deviation of the censoring times $C_{1k}, k=1,\ldots,n$. Similarly, the bandwidth $h_2 = n^{-1/5}s_2$. (For a thorough discussion on kernel methods, see Wand and Jones 1995.)

Now a consistent estimator of σ_2^2 is given by

$$\hat{\sigma}_2^2 = \frac{1}{n}\sum_{k=1}^n \hat{S}_1(C_{1k})\hat{S}_2(C_{2k}) \times \left[\hat{F}_1(C_{1k})\frac{\sum_{j=1}^n \hat{S}_2(C_{2j})K\{(C_{1j}-C_{1k})/h_1\}}{\sum_{j=1}^n K\{(C_{1j}-C_{1k})/h_1\}} + \hat{F}_2(C_{2k})\frac{\sum_{j=1}^n \hat{S}_1(C_{1j})K\{(C_{2j}-C_{2k})/h_2\}}{\sum_{j=1}^n K\{(C_{2j}-C_{2k})/h_2\}}\right]. \quad \text{(C.1)}$$

The above estimator is still rather complicated, and we recommend using simpler estimators in practice based on knowledge of the censoring times. For example, when $C_1 = C_2 = C$, $\frac{a_1(c)}{g_1(c)} = S_2(c)$, and $\frac{a_2(c)}{g_2(c)} = S_1(c)$. Therefore, σ_2^2 can be estimated consistently by

$$\begin{aligned}\tilde{\sigma}_2^2 &= \frac{1}{n}\sum_{k=1}^n \hat{S}_1(C_k)\hat{S}_2(C_k) \times \left\{\hat{F}_1(C_k)\hat{S}_2(C_k) + \hat{F}_2(C_k)\hat{S}_1(C_k)\right\} \\ &= \frac{1}{n}\sum_{k=1}^n \hat{S}_1(C_k)\hat{S}_2(C_k) \times \left\{\hat{S}_1(C_k) + \hat{S}_2(C_k) - 2\hat{S}_1(C_k)\hat{S}_2(C_k)\right\}, \quad \text{(C.2)}\end{aligned}$$

which reduces to the form in (B.3).

In another example, if $C_1 \perp C_2$, then $\frac{a_1(c)}{g_1(c)} = E_G[S_2]$ and $\frac{a_2(c)}{g_2(c)} = E_G[S_1]$. In such a case, σ_2^2 can be estimated consistently by

$$\check{\sigma}_2^2 = \frac{1}{n}\sum_{k=1}^n \hat{S}_1(C_{1k})\hat{S}_2(C_{1k})\{\hat{F}_1(C_{1k})\bar{S}_2 + \hat{F}_2(C_{2k})\bar{S}_1\}, \quad \text{(C.3)}$$

where

$$\bar{S}_i = \frac{1}{n}\sum_{j=1}^n \hat{S}_i(C_{ij}).$$

APPENDIX D: ESTIMATION OF $\sigma_{12} = n^{-1}\,\mathrm{acov}(N_{00} - E_{00}, E_{00} - \hat{E}_{00})$

Explicit expression of σ_{12} is difficult to obtain due to the complexity of the plugged-in NPMLE's. Besides the bootstrap approach, we provide another estimation method using the delete-one jackknife method. Conditioning on the monitoring times, $\mathrm{cov}(N_{00}-E_{00}, E_{00}) = 0$, and hence $\mathrm{cov}(N_{00}-E_{00}, E_{00}-\hat{E}_{00}) = \mathrm{cov}(N_{00}-E_{00}, -\hat{E}_{00})$. Note that

$$\mathrm{cov}(N_{00}-E_{00}, -\hat{E}_{00}) = n\mathrm{cov}\big(\{1-\delta_{1k}\}\{1-\delta_{2k}\} - S_1(C_{1k})S_2(C_{2k}), -\hat{E}_{00}\big).$$

Let $\hat{E}_{00,(-k)}$ denote the delete-one version of $\hat{E}_{00}$ calculated after deleting subject k from the sample. It is obvious that $\mathrm{cov}(\{-\delta_{1k}\} \times \{1-\delta_{2k}\} - S_1(C_{1k})S_2(C_{2k}), \hat{E}_{00,(-k)}) = 0$. Then it follows that

$$\mathrm{cov}(N_{00}-E_{00}, E_{00}-\hat{E}_{00}) = n\mathrm{cov}\big(\{1-\delta_{1k}\}\{1-\delta_{2k}\} - S_1(C_{1k})S_2(C_{2k}), \hat{E}_{00,(-k)} - \hat{E}_{00}\big).$$

Because $\mathrm{cov}(S_1(C_{1k})S_2(C_{2k}), \hat{E}_{00,(-k)} - \hat{E}_{00}) = o_p(1)$, it follows that

$$\mathrm{cov}(N_{00}-E_{00}, E_{00}-\hat{E}_{00}) = n\mathrm{cov}\big(\{1-\delta_{1k}\}\{1-\delta_{2k}\}, \hat{E}_{00,(-k)} - \hat{E}_{00}\big) + o_p(n).$$

Therefore, σ_{12} can be consistently estimated by the estimator in (B.4).

APPENDIX E: ASYMPTOTIC PROPERTIES OF Z_W UNDER INDEPENDENCE

We can write

$$\begin{aligned}Z_W &= n^{1/2}\int_{c_1}\int_{c_2} w(c_1,c_2)\{N_{00}(c_1,c_2) - S_1(c_1)S_2(c_2)\} \times G_n(dc_1,dc_2) \\ &\quad + n^{1/2}\int_{c_1}\int_{c_2} w(c_1,c_2)\big\{S_1(c_1)S_2(c_2) - \hat{S}_1(c_1)\hat{S}_2(c_2)\big\} \times G(dc_1,dc_2) + o_p(1) \\ &= r_{1n} + r_{2n} + o_p(1).\end{aligned}$$

The arguments in Appendix A can be applied to show asymptotic normality of r_{1n} and r_{2n}. Therefore, Z_W converges in distribution to a normal random variable with mean 0 and variance

$$\sigma_W^2 = \sigma_{W1}^2 + 2\sigma_{W12} + \sigma_{W2}^2. \quad \text{(E.1)}$$

Here σ_{W1}^2, σ_{W2}^2, and σ_{W12} are the weighted versions of σ_1^2, σ_2^2, and σ_{12}, where

$$\sigma_{W1}^2 = \int_{c_1}\int_{c_2} w^2(c_1,c_2)S_1(c_1)S_2(c_2) \times\{1 - S_1(c_1)S_2(c_2)\}G(dc_1,dc_2)$$

and

$$\sigma_{W2}^2 = \iint w^2(c_1,c_2)\left\{F_1(c_1)\frac{a_1(c_1)}{g_1(c_1)} + F_2(c_2)\frac{a_2(c_2)}{g_2(c_2)}\right\} \times S_1(c_1)S_2(c_2)G(dc_1,dc_2).$$

Again, we do not have a simple analytical expression for σ_{W12}; but we can estimate it similarly to $\hat{\sigma}_{12}$ in (B.4) by

$$\hat{\sigma}_{W12} = \frac{1}{n}\sum_{k=1}^n W^2(C_{1k},C_{2k})(1-\delta_{1k})(1-\delta_{2k})\big(\hat{E}_{00,(-k)} - \hat{E}_{00}\big).$$

The other two components of σ_{W1}^2 and σ_{W2}^2 can be estimated by similarly modifying the estimators of σ_1^2 and σ_2^2 in (B.1) and (B.3).

APPENDIX F: DERIVATION OF THE LOCAL OPTIMAL WEIGHT FUNCTION

Let $\tilde{Z}_W = n^{-1/2}\sum_k W_k(N_{00,k} - E_{00,k})$. Under the alternative hypotheses $H_\alpha : A(t_1,t_2) = n^{-1/2}a(t_1,t_2) + o_p(n^{-1/2})$, $\tilde{Z}_W$ converges in distribution to a normal distribution with mean

$$n^{1/2}\iint w(c_1,c_2)S_1(c_1)S_2(c_2)\{e^{-A(c_1,c_2)} - 1\}G(dc_1,dc_2)$$
$$= -\iint w(c_1,c_2)S_1(c_1)S_2(c_2)a(c_1,c_2)G(dc_1,dc_2) + o_p(1)$$

and variance

$$\iint w^2(c_1,c_2)S_1(c_1)S_2(c_2)e^{-A(c_1,c_2)} \times \{1 - S_1(c_1)S_2(c_2)e^{-A(c_1,c_2)}\}G(dc_1,dc_2)$$
$$= \iint w^2(dc_1,dc_2)S_1(dc_1)S_2(dc_2) \times\{ 1 - S_1(c_1)S_2(c_2)\}G(dc_1,dc_2) + o_p(1).$$

Hence the local optimal weight function maximizes

$$\frac{\{\iint w(c_1,c_2)S_1(c_1)S_2(c_2)a(c_1,c_2)G(dc_1,dc_2)\}^2}{\iint w^2(c_1,c_2)S_1(c_1)S_2(c_2)\{1 - S_1(c_1)S_2(c_2)\}G(dc_1,dc_2)}.$$

By the Cauchy–Schwartz inequality, the optimal weight function $w^*(t_1,t_2)$ is proportional to

$$\frac{|a(t_1,t_2)|}{1 - S_1(t_1)S_2(t_2)}.$$

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