DIRECT BOOTSTRAPPING AND PERMUTING OF OBSERVATIONS FAIL FOR AALEN-JOHANSEN ESTIMATORS

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ABSTRACT. This article provides rigorous proofs that neither Efron’s bootstrap nor permutation techniques can be applied directly to the observations to construct consistent resampling tests for transition probability matrices of finite-state Markov processes. These methods modify the covariance functions of the limiting distributions of the involved Aalen-Johansen processes, even in the case of fully observable individuals. An example for the failure of these resampling methods is given by cumulative incidence functions in competing risks set-ups.

Keywords: Aalen-Johansen Estimator; Efron’s Bootstrap; Permutation techniques; Competing Risk; Markov Process; Counting Processes; Cumulative Incidence Function.
1. Introduction

In this article two popular resampling tools are analyzed while being applied to Aalen-Johansen estimators in the two-sample case and under complete observations. In the competing risks set-up it is shown that not only Efron’s (1979) bootstrap but also permutation techniques asymptotically lead to Gaussian processes with wrong covariance structures under the null hypothesis of equal cumulative incidence functions for the first risk. Here both resampling techniques are directly applied to the survival times in contrast to Dobler and Pauly (2014a) where Efron’s bootstrap has been utilized in a martingale representation. This result implies that these techniques in general also do not work in the context of incomplete observations and for more general null hypotheses such as equality of the first $k \leq m^2$ transition probability functions of a Markov process with $m$ states. Thus, the validity of Efron’s bootstrap in the survival context as discussed in Akritas (1986) cannot be extended to more general multistate models. The same is true for permutation techniques which have been successfully applied to cumulative hazard functions in Brendel et al. (2014).

Therefore, the only known resampling technique which is applicable in order to state inference procedures for such null hypotheses (in the competing risks set-up) is the wild bootstrap as discussed in Beyersmann et al. (2013) which generalized Lin’s (1997) normal multiplier bootstrap. See also Mammen (1992), Chapter 2, for the failure of the bootstrap in a goodness-of-fit test for a nonparametric regression model, whereas the wild bootstrap leads to the correct asymptotic variance and thus succeeds.

2. The Model

Assume we have a Markov process with three states, e.g., the states “Alive”, “dead by cause 1” and “dead by cause 2”. This is a simple competing risks set-up with two competing risks. Denote by $T$ a positive random variable which represents the survival time of an individual. This individual is thought to be exposed to two lethal risks “1” and “2”. Let $R \in \{1, 2\}$ be the random cause of this individual’s death. Thus, the cumulative incidence functions are given as $F_j(t) = P(T \leq t, R = j)$. Suppose that, for $j = 1, 2$, $F_j$ is absolutely continuous with derivative

$$\frac{d}{dt} F_j(t) = f_j(t) = \frac{\alpha_j(t)}{S(t)},$$

where $S(t) = P(T > t)$ is the survival function and $\alpha_j = f_j S$ is the so-called cause-specific hazard intensity.

The analysis of cumulative incidence functions is of great medical relevance. These functions may be the object of interest when two different medical treatment methods for the same competing event are available. For
instance, Meister and Schaefer (2008) and Beyersmann et al. (2013) examined a data set containing drug exposed pregnant women that experienced one out of both competing events “spontaneous abortion” and “live birth”. While spontaneous abortion is the competing risk of interest, confidence intervals and bands have been developed to analyze the influence of a certain therapy on the pregnancy outcome via comparison with a control group.

Suppose now that we have two groups of such individuals with group sizes \( n_1 \) and \( n_2 \), respectively, and let \( n = n_1 + n_2 \) be the total sample size. We allow the above cumulative incidence functions to be different among both groups and we denote all of the above group-specific quantities by an uppercase \((k)\) for sample group \( k = 1, 2\). Introduce the indicator functions (counting processes)

\[
N_{ji}(t) = 1\{T_i^{(k)} \leq t, R_i^{(k)} = j\} \quad \text{and} \quad Y_i^{(k)}(t) = 1\{T_i^{(k)} \geq t\},
\]

where \((T_i^{(k)}, R_i^{(k)})\) is the individual- and group-specific pair corresponding to \((T, R)\) from above. These processes are aggregated via

\[
N_j^{(k)}(t) = \sum_{i=1}^{n_k} N_{ji}^{(k)}(t) \quad \text{and} \quad Y^{(k)}(t) = \sum_{i=1}^{n_k} Y_i^{(k)}(t),
\]

where \(Y^{(k)}\) is sometimes called the “at-risk process” because it counts the \(k\)th group’s individuals that are alive immediately before time \(t\), which are therefore still “at risk”. In order to not divide by zero let \(J^{(k)}(t) = 1\{Y^{(k)}(t) > 0\}\) and define \(0/0 = 0\). Based on the representation \(F_1^{(k)}(t) = \int_0^t S^{(k)}(u)\alpha_1^{(k)}(u)du\) the Aalen-Johansen estimator for \(F^{(k)}_1\) is given as

\[
\hat{F}_1^{(k)}(t) = \int_0^t \hat{S}^{(k)}(u-)\frac{J^{(k)}(u)}{Y^{(k)}(u)}dN_1^{(k)}(u),
\]

where \(\hat{S}^{(k)}\) is the Kaplan-Meier estimator and \(\hat{S}^{(k)}(t-) = \lim_{u\uparrow t} \hat{S}^{(k)}(u)\) its left-sided limit. Finally, let \(0 < \tau < \tilde{\tau} \leq \sup\{t : \sum_{j,k=1}^{2} \int_0^t \alpha_j^{(k)}(u)du < \infty\}\); see, e.g., Beyersmann et al. (2013) as a reference for these definitions.

3. ASYMPTOTICS

Let \(0 < \tau < \tilde{\tau}\). In what follows we assume that \(\frac{a_1}{n} \to p \in (0, 1)\) as \(\min(n_1, n_2) \to \infty\). By Theorem IV.4.2 of Andersen et al. (1993) (see also Lin (1997)) and the continuous mapping theorem we see that, for \(\hat{F}_1^{(1)} = F_1^{(2)}\),

\[
\hat{W} = \sqrt{\frac{n_1n_2}{n} (\hat{F}_1^{(1)} - \hat{F}_1^{(2)})}
\]
converges in distribution on the Skorohod space \( D[0, \tau] \) to a zero-mean Gaussian process \( U \) with covariance function

\[
\zeta(r, s) = \sum_{k=1}^{2} c_p^{(k)} \left\{ \int_0^{\min(r,s)} \frac{(S_2^{(k)}(u) - F_1^{(k)}(r))(S_2^{(k)}(u) - F_1^{(k)}(s))\alpha_2^{(k)}(u)}{S^{(k)}(u)} \, du \right. \\
+ \int_0^{\min(r,s)} \frac{(F_1^{(k)}(u) - F_1^{(k)}(r))(F_1^{(k)}(u) - F_1^{(k)}(s))\alpha_2^{(k)}(u)}{S^{(k)}(u)} \, du \right\},
\]

where \( c_p^{(k)} = (1 - p)^{2-k} p^{k-1} \) and \( S_2^{(k)} = 1 - F_2^{(k)} \). Note again that we only consider the fully observable case. In general, the form of \( \zeta \) implies that \( U \) cannot be expressed as a transformation of a Brownian motion or a Brownian bridge in an obvious manner; see, e.g., the discussion in Andersen et al. (1993), Sections IV.1.3 and IV.1.4, for a similar problem. This is the reason why resampling techniques play an important role when it comes to developing inference procedures.

3.1. Efron’s (1979) Bootstrap. Generate two new samples \((T_i^{(1)*}, R_i^{(1)*})\), \(i = 1, \ldots, n_1\), and \((T_i^{(2)*}, R_i^{(2)*})\), \(i = 1, \ldots, n_2\), by independently drawing \( n_1 \) and \( n_2 \) times with replacement from the pairs \((T_i^{(k)}, R_i^{(k)})_{i,k}\). Then a bootstrap version of (2) is given by

\[
W^* = \sqrt{\frac{n_1 n_2}{n}} (F_1^{(1)*} - F_1^{(2)*}),
\]

where \( S^{(k)*}, J^{(k)*}, Y^{(k)*}, N_1^{(k)*} \) as well as \( F_1^{(k)*}(t) \) are defined as in (1) but in terms of quantities based on the \( k \)th bootstrap sample, \( k = 1, 2 \). That is,

\[
F_1^{(k)*}(t) = \int_0^t S^{(k)*}(u-) \frac{J^{(k)*}(u)}{Y^{(k)*}(u)} \, dN_1^{(k)*}(u).
\]

Recall that the Kaplan-Meier estimator reduces to the empirical survival function for fully observable individuals. This also holds true for the Kaplan-Meier estimator based on the bootstrap samples, which is just as easy to see, so that for \( k = 1, 2 \) the above estimators reduce to

\[
\hat{F}_1^{(k)}(t) = \frac{1}{n_k} \int_0^t J^{(k)}(u) dN_1^{(k)}(u) \quad \text{and} \quad F_1^{(k)*}(t) = \frac{1}{n_k} \int_0^t J^{(k)*}(u) dN_1^{(k)*}(u).
\]

Denote by \((N_{1i})_i = (N_{11}^{(1)}, \ldots, N_{1n_1}^{(1)}, N_{11}^{(2)}, \ldots, N_{1n_2}^{(2)})\) the pooled vector of counting processes. We further rewrite \( W^*(t) \) (up to a summand bounded
by the asymptotically negligible $\sqrt{n} \sum_{k=1}^{n} \sup_{u \in [0, \tau]} |1 - J^{(k)}(u)|$ as

$$\sqrt{n} \sum_{i=1}^{n} \frac{1}{n_1} \frac{N_{i1}(t)}{n} - \frac{1}{n_2} \sum_{i=1}^{n} \frac{m_i(2)}{n_2} N_{i1}(t)$$

where the $(m_i^{(k)})_i$ are independent multinomially-$Mult(n_k, \frac{1}{n}, \ldots, \frac{1}{n})$ distributed $n$-dimensional random vectors, $k = 1, 2$. Using (3) we arrive at

**Theorem 1.** Conditionally given the data, $W^*$ converges in distribution on $D[0, \tau]$ to a time-transformed Brownian bridge $(B_{\phi(t)})_{t \in [0, \tau]}$ in probability where $\phi(t) = pF_1^{(1)}(t) + (1 - p)F_1^{(2)}(t)$.

**Proof.** Calculation of the limiting distribution of this process is straightforward by following the lines of Dobler and Pauly (2014a): We use Theorem 4.1 of Pauly (2011) to show (conditionally on the data) the convergence of all finite-dimensional distributions of each sum in (3) separately in probability. The independence of both multinomially distributed vectors $(m_i^{(1)})_i, (m_i^{(2)})_i$ then leads to the summation of both asymptotic covariance functions. To this end, rewrite (3) as

$$\sqrt{n} \sum_{i=1}^{n} \frac{1}{n_1} \left( \frac{1}{n_1} m_i^{(1)} - \frac{1}{n} \right) \sqrt{n_2} N_{i1}(t) - \sqrt{n} \sum_{i=1}^{n} \frac{1}{n_2} \left( \frac{1}{n_2} m_i^{(2)} - \frac{1}{n} \right) \sqrt{n_1} N_{i1}(t).$$

For similarity reasons we only focus on the first sum. Thus, we apply Pauly’s (2011) Theorem 4.1 with $k(n) = n, m(n) = n_1$ (cf. (2.2)) and the vector $(W^*(t_1), \ldots, W^*(t_\ell)), 0 \leq t_1 \leq \cdots \leq t_\ell \leq \tau$. Note, that his equation (4.1) is obviously satisfied. We now show the convergence (4.2) of the covariance matrix estimator for each entry. Let $(r, s) \in \{(t_i, t_j) : i, j = 1, \ldots, \ell\}$, then

$$\frac{n_2}{n} \sum_{i=1}^{n} N_{i1}(r)N_{i1}(s) - \frac{n_2}{n} \left( \frac{1}{n_1} \sum_{i=1}^{n} N_{i1}(r) \right) \left( \frac{1}{n_1} \sum_{i=1}^{n} N_{i1}(s) \right)$$

$$\longrightarrow p(1 - p)F_1^{(1)}(\min(r, s)) + (1 - p)^2 F_1^{(2)}(\min(r, s))$$

$$- (1 - p)(pF_1^{(1)}(r) + (1 - p)F_1^{(2)}(r))(pF_1^{(1)}(s) + (1 - p)F_1^{(2)}(s))$$
in probability as \(\min(n_1, n_2) \to \infty\) by the WLLN. This is the asymptotic covariance function of the first sum of \(W^*\). Similarly, we get the covariance
\[
p^2 F_1^{(1)}(\min(r, s)) + p(1 - p) F_1^{(2)}(\min(r, s)) \\
- p(p F_1^{(1)}(r) + (1 - p) F_1^{(2)}(r))(p F_1^{(1)}(s) + (1 - p) F_1^{(2)}(s))
\]
for the second sum. All in all, the finite-dimensional distributions of \(W^*\) converge to multivariate normal distributions with covariances
\[
p F_1^{(1)}(\min(r, s)) + (1 - p) F_1^{(2)}(\min(r, s)) \\
- (p F_1^{(1)}(r) + (1 - p) F_1^{(2)}(r))(p F_1^{(1)}(s) + (1 - p) F_1^{(2)}(s)).
\]
Using similar arguments as Beyersmann et al. (2013), i.e., applying a criterion of Billingsley (1999), conditional tightness is easily achieved. Finally, the desired convergence in distribution on \(D[0, \tau]\) conditionally given the data follows in probability since (4) is the covariance function of \((B_{\phi(s)})_{s \leq \tau}\).

Note that, in general, the limiting covariance function of \(\hat{W}\) depends on the cumulative incidence function for the second risk \(F_2\), whereas the covariance of the limiting Brownian bridge of \(W^*\) does not, i.e., \(W^*\) does not approximate \(\hat{W}\) in the limit. A similar Brownian bridge appears as a result of Efron’s bootstrap in the one-sample case, here denoted without the uppercase \((k)\): The asymptotic covariance function of \(\sqrt{n}(\hat{F}_1 - F_1)\) is given by
\[
(r, s) \mapsto \int_0^{\min(r, s)} \frac{(S_2(u) - F_1(r))(S_2(u) - F_1(s))\alpha_1(u)}{S(u)} du \\
+ \int_0^{\min(r, s)} \frac{(F_1(u) - F_1(r))(F_1(u) - F_1(s))\alpha_2(u)}{S(u)} du,
\]
whereas the limiting distribution of \(\sqrt{n}(\hat{F}_1 - \bar{F}_1)\) is a time-transformed Brownian bridge \((B_{F_1(s)})_{s \leq \tau}\). Hence, we conclude that Efron’s bootstrap is not directly applicable to this kind of data.

3.2. Permutation Techniques. The next presented resampling procedure is a permutation approach, where the individuals’ group associations are randomly interchanged. To this end, we let \(\pi\) be uniformly distributed on the symmetric group \(S_n\), i.e., a random permutation of \((1, \ldots, n)\). While the former groups 1 and 2 consisted of the individuals \(1, \ldots, n_1\) and \(n_1 + 1, \ldots, n\), respectively, \(\pi\) permutes the individuals \(\pi(1), \ldots, \pi(n_1)\) to group 1 and \(\pi(n_1 + 1), \ldots, \pi(n)\) to group 2. It is easy to see that the two Kaplan-Meier estimators based on the permuted groups also reduce to the respective empirical distribution functions based on the new groups as in the bootstrap
case. Thus, the Aalen-Johansen estimator based on the new group $k \in \{1, 2\}$ is given by

$$F^{(k)}_1(t) = \frac{1}{n_k} \int_0^t J^{(k)}(u) dN^{(k)}_1(u),$$

where $J^{(k)}(u)$ and $N^{(k)}_1$ are similarly defined as in Subsection 3.1. Using this we introduce the permuted difference of Aalen-Johansen estimators as

$$W^{\pi}(t) = \sqrt{\frac{n_1 n_2}{n}} (F^{(1)}_1(t) - F^{(2)}_1(t))$$

which is approximated by (cf. the bootstrap case)

$$\sqrt{n} \sum_{i=1}^n c_i N^{\pi(i)}_1(t) = \sqrt{n} \sum_{i=1}^n c^{\pi(i)} N^{(i)}_1(t)$$

where $(N^{\pi(i)}_1)_i$ is defined in Section 3.1 and the regression weights are given by

$$c_i = \sqrt{\frac{n_1 n_2}{n}} \left\{ \frac{1}{n_1} \right\} \begin{cases} n_1 & \text{if } i \leq n_1 \\ n_2 & \text{else} \end{cases}$$

The weights $(c^{\pi(i)})_i$ obviously satisfy (2.3) to (2.5) of Pauly (2011); see Janssen (2005) as well as Pauly (2009). Since $\bar{c} = \frac{1}{n} \sum_{i=1}^n c^{\pi(i)} = 0$, it follows

$$W^{\pi}(t) \approx \sqrt{n} \sum_{i=1}^n (c^{\pi(i)} - \bar{c}) N^{(i)}_1(t)$$

which can also be treated with Theorem 4.1 of Pauly (2011). The following theorem is proved similarly as Theorem 4.

**Theorem 2.** Conditionally given the data, $W^{\pi}$ converges in distribution on $D[0, \tau]$ to a time-transformed Brownian bridge $(B_{\phi(t)})_{t \in [0, \tau]}$ in probability.

Using the same argumentation as for Efron’s bootstrap, we conclude that permutation is also not applicable to this kind of data.

**Remark 1.** Although Efron’s (1979) bootstrap is not directly applicable to the individual data for resampling sub-models of the transition probability matrix of Markov processes, Dobler and Pauly (2014a) argue that, even under left-truncation and right-censoring, Efron’s bootstrap can successfully be applied to a linear martingale representation of $W$. The nuisance that the limiting distribution also exhibits a deviation of the original covariance function can be redeemed by using a Pepe-type integral test statistic that can be made pivotal via studentization. The same operation is accomplishable for the
bootstrap statistic so that a consistent resampling test for ordered cumulative incidence functions is constructible. Note, however, that their simulation results suggested rather to prefer the wild bootstrap which leads to a better small sample behaviour and which has a greater potential applicability, e.g. for two-sided inference problems; see Beyersmann et al. (2013) as well as Dobler and Pauly (2014b).

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