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Bootstrap likelihood ratio confidence bands for survival functions under random censorship and its semiparametric extension

Sundarraman Subramanian

Center for Applied Mathematics and Statistics, Department of Mathematical Sciences, New Jersey Institute of Technology, United States

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ABSTRACT

Simultaneous confidence bands for survival functions, from randomly right censored data, can be computed by inverting likelihood ratio functions based on appropriate thresholds. Sometimes, however, the requisite asymptotic distributions are intractable, or thresholds based on Brownian bridge approximations are not easy to obtain when simultaneous confidence bands over only sub-regions are possible or desired. We obtain the thresholds by bootstrapping (i) a nonparametric likelihood ratio function via censored data bootstrap and (ii) a semiparametric adjusted likelihood ratio function via a two-stage bootstrap that utilizes a model for the second stage. These two scenarios are grounded respectively in standard random censorship and its semiparametric extension introduced by Dikta. The two bootstraps, which are different in the way resampling is done, are shown to have asymptotic validity. The respective confidence bands are neighborhoods of the well-known Kaplan–Meier estimator and the more recently developed Dikta's semiparametric counterpart. As evidenced by a validation study, both types of confidence bands provide approximately correct coverage. The model-based confidence bands, however, are tighter than the nonparametric ones. Two sensitivity studies reveal that the model-based method performs well when standard binary regression models are fitted, indicating its robustness to misspecification as well as its practical applicability. An illustration is given using real data.

1. Introduction

In this paper, we develop bootstrap simultaneous confidence bands for survival functions from randomly censored data using the likelihood ratio approach. Unlike pointwise confidence intervals, simultaneous confidence bands are global, allow simultaneous conclusions at multitude time points, present correct estimate of treatment difference over a region, in turn promoting correct decision making. We first develop the confidence bands under the random censorship model, regarded as the de facto framework in which the event and censoring time random variables are independent, their distributions are completely unspecified and, in particular, censoring is noninformative. We then develop alternate simultaneous confidence bands from a semiparametric extension, called SRCMs henceforth, a framework that incorporates informative censoring into random censorship through a model for the conditional non-censoring probability and one, which, in particular, is more flexible than a fully parametric specification of the censoring distribution. To emphasize intent, we indicate that a major thrust of the paper is to develop asymptotically valid thresholds for computing nonparametric as well as semiparametric confidence bands via the likelihood ratio.

E-mail address: sundars@njit.edu.

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Let T denote the failure time and let $S_0(t)$ denote the survival function of T. Most confidence bands for S_0 under the random censorship model are Wald-type, based on the weak limit of the normalized Kaplan–Meier process [13,25]. In a landmark paper, Thomas and Grunkemeier [37] introduced the nonparametric LR and inverted it to obtain pointwise confidence intervals for survival probabilities, which gave superior small-sample performance over the normal approximation based methods. Confidence intervals, however, only guarantee correct coverage for each isolated point separately but not for a multitude of points jointly. See [23,1], where the distinction between pointwise confidence intervals and simultaneous confidence bands is explained in greater detail; see also Section 4, where the difference is further delineated via a generic example involving two-sample data. Hollander et al. [14] used the nonparametric likelihood ratio and developed simultaneous confidence bands as "neighborhoods" around S_n, the Kaplan–Meier estimator of S_0.

To address the issues precisely, for an independent censoring time C we write $X = \min(T, C)$, $\delta = I(T \le C)$, and assume that τ_H is such that $H(\tau_H) < 1$, where H is the distribution function for X. Write $S_-(t) = S(t-)$. The observed data are $\{(X_i, \delta_i), 1 \le i \le n\}$, where $T_1, \ldots, T_n$ are i.i.d. failure times having the survival function $S_0(t)$, and $C_1, \ldots, C_n$ are i.i.d. censoring times independent of the T_i's. Let Γ denote the set of survival functions supported by the uncensored lifetimes and $0 < p < 1$. For each fixed t, Thomas and Grunkemeier [37] obtained pointwise confidence intervals for $S_0(t)$ using the nonparametric likelihood ratio statistic

$$R_{\mathrm{TG}}(p, t) = \frac{\sup\{\mathrm{Lik}(S) : S(t) = p, S \in \Gamma\}}{\mathrm{Lik}(S_n)}, \tag{1.1}$$

where

$$\mathrm{Lik}(S) = \prod_{i=1}^{n} [S_-(X_i) - S(X_i)]^{\delta_i} [S(X_i)]^{1-\delta_i}. \tag{1.2}$$

An asymptotic $100(1-\alpha)\%$ pointwise confidence interval for $S_0(t)$, $0 < \alpha < 1$, is obtained by inverting $-2\ln R_{\mathrm{TG}}(p, t)$ using the threshold $\chi^2_{1,\alpha}$, the upper-α quantile of the chi-squared distribution with one degree of freedom. That is, for each fixed t, the collection of points $\{p : -2\ln R_{\mathrm{TG}}(p, t) \le \chi^2_{1,\alpha}\}$ is a $100(1-\alpha)\%$ pointwise confidence interval for $S_0(t)$.

The approach of Hollander et al. [14] was to extend Thomas and Grunkemeier's "pointwise" framework to all of $[0, \tau_H]$, the objective being to find an envelope that encloses all survival functions with support over the uncensored time points, and which includes S_0 with $100(1-\alpha)\%$ confidence. Hollander et al.'s [14] $100(1-\alpha)\%$ simultaneous confidence band for S_0 is given by

$$\mathcal{B}_{\mathrm{NP}} = \{S(t) : -2\ln R_{\mathrm{TG}}(S(t), t) \le \tilde{\rho}_n(t),\ t \in [0, \tau_H]\}, \tag{1.3}$$

where $\tilde{\rho}_n(t)$ is a threshold determined by $(1+\sigma_n^2(t))/\sigma_n(t)$, where $\sigma_n^2(t)$ is defined by Eq. (2.3), and the percentiles of an appropriate supremum of the absolute value of a Brownian bridge process. Note that $\sigma_n^2(t)$ is the approximate variance of $\ln(S_n(t))$, which figures as an intermediate quantity when deriving approximate confidence intervals for $S_0(t)$. To understand its link with $\tilde{\rho}_n(t)$, the signed root likelihood ratio needs to be scaled by the factor $\sigma_n(t)/(1+\sigma_n^2(t))$ to give a limiting Brownian bridge process, see [14].

Owen [26,27] gave the first theoretical treatment of the nonparametric likelihood ratio method. For censored data, the fundamental work of Li [17] gave theoretical justification of the nonparametric likelihood ratio. Li [18] derived nonparametric likelihood ratio based confidence bands for individual quantile functions. Einmahl and McKeague [12] generalized Li et al.'s [18] approach to the k-sample case and developed simultaneous confidence tubes for multiple quantile plots. In this paper, we develop bootstrap likelihood ratio based confidence bands for $S_0(t)$ over any $[\epsilon, t_2] \in (0, \tau_H]$ under the framework of random censorship as well as for its SRCM extension. The nonparametric method and its proposed semiparametric counterpart are each based on a separate bootstrap.

For the nonparametric scenario, write $\mathcal{L}_n(S(t), t) \equiv -2\ln R_{\mathrm{TG}}(S(t), t)$, which is a function of t, and has the representation given by Eq. (2.1), see [14]. Using S_n, the Kaplan–Meier estimator, our first proposal is to bootstrap the distribution of

$$\mathcal{L}_n(S_0(t), t), \quad t \in [\epsilon, t_2] \subset (0, \tau_H].$$

We determine ρ_n, the threshold, using our bootstrap approximation of the distribution of the supremum of $\mathcal{L}_n(S_0(t), t)$ over $[t_1, t_2]$ combined with a weight function based on $\sigma_n^2(t)$. We obtain

$$\mathcal{B}_{\mathrm{NP}} = \{S(t) : \mathcal{L}_n(S(t), t) \le \rho_n(t),\ t \in [\epsilon, t_2] \subset (0, \tau_H]\}, \tag{1.4}$$

which are the nonparametric simultaneous confidence bands, see Section 2.2 for a detailed development of the procedure. For this purpose, we employ the censored data bootstrap [11,2]. The asymptotic justification for the bootstrap approximation of the nonparametric likelihood ratio can be derived using the techniques that we provide in considerable detail for the more challenging semiparametric scenario. This approach is detailed in Sections 2.1 and 2.2.

Turning to the second scenario, SRCMs present an alternate framework for obtaining simultaneous confidence bands for S_0. By exploiting $\hat{S}$, a semiparametric estimator of S_0 [8], which is also semiparametric efficient [9], Wald-type simultaneous confidence bands for S_0 have been developed [36]. However, the resulting simultaneous confidence bands were not based on likelihood ratio. A compelling and most fundamental argument for the relevance of SRCMs arises from the observation that,