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Consistent estimation of survival functions under uniform stochastic ordering; the k-sample case

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ABSTRACT

Let $S_1, S_2, \ldots, S_k$ be survival functions of life distributions. They are said to be uniformly stochastically ordered, $S_1 \le_{uso} S_2 \le_{uso} \cdots \le_{uso} S_k$, if S_i/S_{i+1} is a survival function for $1 \le i \le k-1$. The nonparametric maximum likelihood estimators of the survival functions subject to this ordering constraint are known to be inconsistent in general. Consistent estimators were developed only for the case of $k = 2$. In this paper we provide consistent estimators in the k-sample case, with and without censoring. In proving consistency, we needed to develop a new algorithm for isotonic regression that may be of independent interest.
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1. Introduction

Let $S_1, S_2, \ldots, S_k$ be the survival functions (SFs) of k life distributions. These SFs are uniformly stochastically ordered (USO), denoted by

$$S_1 \le_{uso} S_2 \le_{uso} \cdots \le_{uso} S_k, \quad \text{if } S_i/S_{i+1} \text{ is a SF, } 1 \le i \le k-1; \tag{1}$$

we use the convention $0/0 = 0$ throughout.

Denote the distribution function (DF) of the ith population by $F_i = 1 - S_i$, its (assumed) support as $[0, \tau_i)$ (τ_i could be ∞), and its density, if it exists, by f_i. The terminology USO comes from the fact that $S_i \le_{uso} S_{i+1}$ is equivalent to stochastic ordering (SO) of the conditional DFs (here $X_i \sim S_i$):

$$P(X_i > t + s | X_i > t) \le P(X_{i+1} > t + s | X_{i+1} > t) \tag{2}$$

for all $s \ge 0$, uniformly in $t \ge 0$. Clearly, USO is strictly stronger than SO. If the densities exist, then USO is equivalent to a reverse hazard rate ordering, i.e., $S_i \le_{uso} S_{i+1}$ if and only if $\frac{f_i}{S_i} \ge \frac{f_{i+1}}{S_{i+1}}$, and it is strictly weaker than likelihood ratio ordering (LRO): S_i is less than or equal to S_{i+1} in LRO if f_i/f_{i+1} is nonincreasing. These and other structural properties of USO, and its relationships with other orderings, have been nicely summarized in [9] with an extensive bibliography.

There are many applications of USO in reliability and survival analysis. One way to model accelerated life testing is to consider the extra stress as being induced by an unknown independent censoring; a higher stress by still another unknown

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independent censoring. This way, the reliabilities under higher and higher stresses will become USO. In toxicological studies of adverse effects of higher and higher dosages of a chemical may be considered to produce higher and higher hazard rates. For example, in a National Toxicology Program (NTP) study (NTP Technical Report (1999), available on the web) of the adverse effects of ethylbenzene, rats were subjected to three dosages of the chemical and the number of survivors were measured weekly for 2 years for each of the three groups and a control group. Higher dosages of the chemical may be assumed to produce higher hazard rates. This makes the SFs of the four groups USO. In Section 5, we analyze the survival times of four groups of patients with carcinoma of the oropharynx and with four different levels of the amounts of lymph node deterioration. USO of these SFs seems to be reasonable.

Estimation of k life distributions under USO was started by Dykstra, Kochar and Robertson [3] (DKR (1991)). For the uncensored case, assume that we have independent random samples. Let $\hat{S}_i$ denote the empirical for the ith population based on a sample of size n_i for $1 \le i \le k$. Let $t_0 = 0$ and let

$$0 < t_1 < t_2 < \cdots < t_c \tag{3}$$

be the distinct jump points of the combined sample. For $1 \le j \le c$, let

$$\theta_i(t_j) = \frac{S_i(t_j)}{S_i(t_{j-1})} \quad \text{and} \quad \breve{\theta}_i(t_j) = \frac{\hat{S}_i(t_j)}{\hat{S}_i(t_{j-1})}. \tag{4}$$

Note that $\hat{S}_i(t) = \prod_{t_j \le t} \breve{\theta}_i(t_j)$. Using the characterization of USO given in (2), DKR [3] showed that the NPMLEs are obtained by isotonizing $\{\breve{\theta}_i(t_j)\}$ for each t_j separately, subject to the linear ordering $\theta_i(t_j) \le \theta_{i+1}(t_j),\ 1 \le i \le k-1$, with the weights $\{n_i \hat{S}_i(t_{j-1}\})$ (the numbers of subjects alive just prior to t_j) to obtain $\{\theta_i^{ML}(t_j)\}$ that define the NPMLEs by $\{S_i^{ML}(t) = \prod_{t_j \le t} \theta_i^{ML}(t_j)\}$. Here, isotonization means least squares estimation subject to the linear ordering. DKR [3] did not prove strong consistency of the NPMLEs; they did derive the asymptotic distributions, which implied weak consistency, but only in the multinomial case with common supports.

Rojo and Samaniego [7] and Mukerjee [5] gave counterexamples to show that the NPMLEs are inconsistent for $k = 2$ in the 1-sample (one S_i known) and the 2-sample cases, respectively, when the SFs are continuous. When $S_1 \le_{uso} S_2$, Rojo and Samaniego [8] provided a consistent estimator of one SF when the other is known by using the sample analog of the fact that S_1/S_2 is a SF equivalent to $S_1(x)/S_2(x) = \inf_{y \le x}[S_1(y)/S_2(y)]$, and also equivalent to $S_2(x)/S_1(x) = \sup_{y \le x}[S_2(y)/S_1(y)]$. Denoting the empiricals by $\hat{S}_1$ and $\hat{S}_2$ based on independent random samples of sizes n_1 and n_2, respectively, the restricted estimators are given by

$$S_1^{\dagger}(x) = \inf_{y \le x} \frac{\hat{S}_1(y)}{S_2(y)} S_2(x) \quad \text{and} \tag{5}$$

$$S_2^{\ddagger}(x) = \sup_{y \le x} \frac{\hat{S}_2(y)}{S_1(y)} S_1(x) I(x < \tau_1) + \hat{S}_2(x) I(x \ge \tau_1). \tag{6}$$

In the 2-sample case when both SFs are unknown, they suggested setting $\hat{S}_1$ or $\hat{S}_2$ fixed and estimating the other SF under USO as in the 1-sample case. Since

$$S_1 \le_{uso} S_{12} \equiv \frac{n_1 \hat{S}_1 + n_2 \hat{S}_2}{n_1 + n_2} \le_{uso} S_2,$$

follows easily from the definition of USO for all choices of $\{n_i\}$, Mukerjee [5] found that the 2-sample estimators could be improved by holding the combined empirical, $\hat{S}_{12} \equiv (n_1 \hat{S}_1 + n_2 \hat{S}_2)/(n_1 + n_2)$ fixed and estimating S_1 and S_2 under the USO, $S_1 \le_{uso} \hat{S}_{12} \le_{uso} S_2$, as two 1-sample estimators:

$$S_1^*(x) = \inf_{y \le x} \frac{\hat{S}_1(y)}{\hat{S}_{12}(y)} \hat{S}_{12}(x) \quad \text{and} \quad S_2^*(x) = \sup_{y \le x} \frac{\hat{S}_2(y)}{\hat{S}_{12}(y)} \hat{S}_{12}(x). \tag{7}$$

He showed that these estimators are strongly uniformly consistent. Arcones and Samaniego [1] derived the (very complicated) asymptotic distributions of some variants of these estimators.

Although the 2-sample estimators in (7) have been found to be quite satisfactory, consistent estimation in the k-sample case for $k \ge 3$ had remained elusive. Our solution came from tweaking DKR's [3] NPMLEs. We looked at the procedure of estimating $\{S_i(t_j),\ 1 \le i \le k\}$, from $j = 0$ to $j = c$ sequentially. Setting the restricted estimator of $S_i(t_0)$ to 1 for all i, the NPMLE isotonizes $\{\breve{\theta}(t_1) = \hat{S}_i(t_1)/\hat{S}_i(t_0)\}$ with equal weights to get the NPMLEs of $\{\theta_i(t_1) = S_i(t_1)\}$. This seems reasonable since $\{\hat{S}_i(t_1)\}$ are the best estimators of $\{S_i(t_1)\}$ with our knowledge up to time t_1^-. To estimate $\{\theta_i(t_2) = S_i(t_2)/S_i(t_1)\}$ at time t_2^-, the best estimate of $S_i(t_2)$ is still $\hat{S}_i(t_2)$, but, if $S_i^*(t_1)$ is the restricted estimator of $S_i(t_1)$, it may now be considered to be a better estimate than $\hat{S}_i(t_1)$. Thus, we define $\hat{\theta}_i(t_2) = \hat{S}_i(t_2)/S_i^*(t_1)$ as an estimator of $\theta_i(t_2)$. Using the same argument, the "effective" number of subjects alive in the ith population at t_2^- is $n_i S_i^*(t_1)$, and we use this as the weight for isotonizing

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