GENUINE ESTIMATORS FOR SOME TARGET FUNCTIONS IN SURVIVAL ANALYSIS

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Abstract

Under the presence of censoring, a reasonable estimator for some target functions should be able to 'eliminate' the effect of censoring somehow. We refer to such an estimator as a genuine estimator. This paper investigates genuine estimators for univariate and multivariate survival functions under right censoring. The estimation for mark survival function is also discussed.

1. Introduction

Let T be the time of the individual in the study and $S(t) = \Pr(T > t)$ be its survival function. Denote $V(\cdot)$ as the individual's state history process and $U = \int_0^T V(t)dt$ as the accumulation of the individual's state history. In accordance with Huang and Louis [5], we refer to U as mark variable and its survival function $S(x) = \Pr(U > x)$ as mark survival function. In some situations, we need to consider multivariate failure

time vector $T = (T_1, \cdots, T_m)$ and the corresponding multivariate survival function.

It has been well recognized that the survival time T and the mark variable U are important informative measures in the evaluation of treatments for chronic diseases. Examples in the literature for mark variable include quality-adjusted lifetime and lifetime medical cost. The nonparametric estimation for these survival functions under the presence of censoring is fundamental in survival analysis.

The estimation problem for univariate survival function has been well solved by the classical Kaplan-Meier estimator (Kaplan and Meier [7]). The problem for estimating the multivariate survival function, however, has been thought to be 'surprisingly difficult' (Oakes [9]). So far, several estimators have been suggested. See, for instance, Dabrowska [2], Prentice and Cai [10], van der Laan [12], Wang and Wells [13], and among others.

The problem for estimating mark survival function has received considerable attention recently. A statistical challenge in estimating such function comes from the difficulty caused by the so-called "induced" informative censoring. As pointed out by Gelber et al. [4], the naive use of the Kaplan-Meier estimator will lead to erroneous inference. A current method in the literature to deal with such difficulty is the inverse probability of censoring weighted (IPCW) technique. So far, a number of weighted estimators have been proposed in the context of specific problems. For example, Lin et al. [8] considered the estimation of the mean lifetime medical cost by IPCW and partition techniques. Zhao and Tsiatis [14] devised a weighted estimator for the distribution function of quality-adjusted survival time. Bang and Tsiatis [1] suggested a simple weighted estimator for the mean of lifetime medical cost. Strawderman [11] studied the efficiency of various weighted estimators. These weighted estimators have been proved to be consistent in mean, if an artificial ending point is introduced to truncate the failure time. However, as pointed out by Huang [6], such truncation will deviate the target function from the original interest.

The complexities that arise in the estimation for these target functions stem from the presence of censoring. Hence, how to deal with censoring is critical in the analysis of censored data. If the effect of censoring can be eliminated somehow at some extent, then a 'good' or even the 'best' estimator would be possible. We define such an estimator as a genuine estimator. In its convergence region, a genuine estimator would behave similarly to an empirical estimator and thus can be expected to retain most properties of an empirical estimator, such as strong consistency and normality.

In this paper, we investigate genuine estimators for these survival functions. For univariate survival function, we retrieve some genuine estimators by solving some genuine estimating equations. Similar theoretical developments are applied to the estimation of multivariate survival function. For mark survival function, a genuine estimator, as we will show, may not exist in general. A weighted estimator can be consistent only when certain condition holds.

The rest of the paper is organized as follows. In Section 2, we give the definition of genuine estimator and investigate some genuine estimators for univariate survival function and study their properties. Some genuine estimators for multivariate survival function are derived in Section 3. In Section 4, we discuss the estimation issue for mark survival function. A short discussion is presented in Section 5 and proofs are given in Section 6.

2. Genuine Estimators and Univariate Survival Function

Intuitively, if an estimator can 'eliminate' the effect of censoring, it would be 'good' or even the 'best'. We refer to such an estimator as a genuine estimator. To be precise, we give out.

Definition 1. Denote C as censoring variable (vector). A function F is said to be censoring-free, if it does not involve C. Suppose for censoring-free function F, there exist two operators O_1 and O_2, such that

$$O_1(F) = O_2\{n^{(1)}, \ldots, n^{(k)}\}, \tag{1}$$

where $n^{(1)}, \ldots, n^{(k)}$ are some estimable functions from observed data. If the statistics $N^{(i)}$ are unbiased, consistent estimators for $n^{(i)}, i = 1, \ldots, k$, then, the estimating equation

$$O_1(\hat{F}) = O_2\{N^{(1)}, \ldots, N^{(k)}\}, \tag{2}$$

is said to be genuine and the solution $\hat{F}$ is said to be genuine estimator for estimating F.

In practice, the statistics $N^{(i)}$ is usually the empirical estimate for $n^{(i)}$, thus, a genuine estimator would be strongly consistent to its target function.

Now, let us consider the estimation for univariate survival function first. For our convenience, we introduce $H(t)$, the Heaviside function which is defined as $H(t) = 1$ for $t \geq 0$, and $H(t) = 0$, otherwise. The function $H'(t) = \delta(t)$ is the Dirac function. Univariate survival function has already been well estimated by the classical Kaplan-Meier estimator. We derive this estimator and other ones from this new prospect.

Assume that censoring C is independent of failure time T. Under the presence of right censoring, the observed variables are given by $X = \min(T, C)$ and the indicator variable $\Delta = I(T \leq C)$. Thus, the basic estimable functions are, $n(t) = \Pr(X \leq t, \Delta = 1)$, $l(t) = \Pr(X \leq t, \Delta = 0)$, and $\delta(t) = \Pr(\Delta = 1)$. Denote $n'(t) = \Pr(X \geq t, \Delta = 1)$, $\pi(t) = \Pr(T \geq t, C \geq t)$, Clearly, $n'(t)$ and $\pi(t)$ can be expressed in terms of those basic estimable functions, and thus are also estimable.

Define the following observable counting processes,

$$N(t) = \sum_{i=1}^{n} I_{\{X_i \leq t, \Delta_i = 1\}}, \quad L(t) = \sum_{i=1}^{n} I_{\{X_i \leq t, \Delta_i = 0\}},$$

$$N'(t) = \sum_{i=1}^{n} I_{\{X_i \geq t, \Delta_i = 1\}}, \quad L'(t) = \sum_{i=1}^{n} I_{\{X_i \geq t, \Delta_i = 0\}},$$

and
$$Y(t) = N'(t) + L'(t) = \sum_{i=1}^{n} I_{\{X_i \geq t\}},$$

and $K(t) = \Pr(C \geq t)$. By Glivenko-Cantelli theorem, we have,

Proposition 1. *Assume* $\hat{K}(t)$ *is a genuine estimator for* $K(t)$, *then, under the assumption of independent censoring, the following estimating equations*

$$\frac{d\hat{S}(t)}{\hat{S}(t^-)} = -\frac{dN(t)}{Y(t^-)}, \quad \hat{S}(t) = \frac{Y(t)}{n\hat{K}(t)}, \quad d\hat{S}(t) = -\frac{dN(t)}{n\hat{K}(t)},$$

$$d\hat{S}(t) = \frac{dN'(t)}{n\hat{K}(t)}, \quad \hat{S}(t) = \frac{Y(t)}{n} + \hat{S}(t)\{1 - \hat{K}(t)\},$$

are genuine for $S(t)$ *and the solutions to these equations are given, respectively, by*

$$\hat{S}_1(t) = \prod_{i=1}^{n} \left\{ 1 - \frac{I(T_i \leq C_i)H(t - T_i)}{Y(T_i^-)} \right\},$$

$$\hat{S}_2(t) = \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq t)H(T_i - t)}{\hat{K}(t)},$$

$$\hat{S}_3(t) = 1 - \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq T_i)H(t - T_i)}{\hat{K}(T_i)},$$

$$\hat{S}_4(t) = 1 - \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq T_i)}{\hat{K}(T_i)} + \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq T_i)H(T_i - t)}{\hat{K}(T_i)}$$

and

$$\hat{S}_5(t) = \frac{1}{n} Y(t) + \hat{S}_5(t) \frac{1}{n} \sum_{C_j \leq t, \Delta_j = 0} \frac{I(C_j \leq T_j)}{\hat{S}_5(C_j)}.$$

The estimator $\hat{S}_1(t)$ is just the Kaplan-Meier estimator. The estimator $\hat{S}_5(t)$, first proposed by Efron [3], is usually referred to as self-consistency estimator. For the relationship among these five estimators, we have,

Proposition 2. *Under the assumption of independent censoring, the estimators $\hat{S}_1(t)$ and $\hat{S}_5(t)$ are equivalent, and the estimators $\hat{S}_2(t)$, $\hat{S}_3(t)$, $\hat{S}_4(t)$ are equivalent. If $\hat{K}(t)$ is the corresponding Kaplan-Meier estimator for $K(t)$, then, all these five estimators are equivalent.*

The estimators $\hat{S}_2(t)$, $\hat{S}_3(t)$, and $\hat{S}_4(t)$ are weighted estimators. For our exposition, introduce the following weighted estimator

$$\hat{S}_6(t) = \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq T_i)H(T_i - t)}{\hat{K}(T_i)}. \tag{3}$$

Clearly

$$\hat{S}_6(t) = \hat{S}_4(t) - \left\{ 1 - \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq T_i)}{\hat{K}(T_i)} \right\}. \tag{4}$$

If the last observation is uncensored, then, $\sum_{i=1}^{n} I(C_i \geq T_i) / \hat{K}(T_i) = n$, and thus $\hat{S}_6(t) = \hat{S}_4(t)$. On the other hand, if the last observation is censored, then $n^{-1} \sum_{i=1}^{n} I(C_i \geq T_i) / \hat{K}(T_i) \neq 1$, and the estimator $\hat{S}_6(t)$ is not genuine, (4) indicates that not all weighted estimators are genuine.

The expression $S(t) = \exp\{ -\int_0^t dn(t)/\pi(t) \}$ yields a genuine estimator as

$$\hat{S}_7(t) = \exp\left\{ -\int_0^t \frac{dN(s)}{Y(s)} \right\} = \exp\left\{ -\sum_{i=1}^{n} \frac{I(T_i \leq C_i)H(t - T_i)}{Y(T_i)} \right\}$$

$$= \prod_{i=1}^{n} \exp\left\{ -\frac{I(T_i \leq C_i)H(t - T_i)}{Y(T_i)} \right\}.$$

Approximating $\exp(-x)$ by $1 - x,$ the above estimator becomes,

$$\hat{S}_8(t) = \prod_{i=1}^{n}\left\{1 - \frac{I(T_i \leq C_i)H(t - T_i)}{Y(T_i)}\right\}.$$

It is easy to show $\hat{S}_7(t) \leq \hat{S}_8(t) \leq \hat{S}_1(t).$ The estimators $\hat{S}_7(t)$ and $\hat{S}_8(t)$ are not identical to the Kaplan-Meier estimator $\hat{S}_1(t)$ and hence, not all genuine estimators are equivalent.

3. Multivariate Survival Function

In this section, we shall derive some genuine estimators for multivariate survival function by applying the same idea presented in the previous section. For the sake of brevity, we confine ourself to bivariate case. The generalization to other multivariate cases is straightforward.

As in the univariate case, define

$$N(t) = \sum_{i=1}^{n} I_{\{X_i \leq t, \Delta_i = 1\}}, \quad L(t) = \sum_{i=1}^{n} I_{\{X_i \leq t, \Delta_i = 0\}},$$

$$N'(t) = \sum_{i=1}^{n} I_{\{X_i \geq t, \Delta_i = 1\}}, \quad L'(t) = \sum_{i=1}^{n} I_{\{X_i \geq t, \Delta_i = 0\}},$$

and

$$Y(t) = N'(t) + L'(t) = \sum_{i=1}^{n} I_{\{X_i \geq t\}}.$$

Notice here the variables are 2-dimensional, hence, more specifically,

$$N(t) = \sum_{i=1}^{n} I_{\{X_i \leq t, \Delta_i = 1\}} = \sum_{i=1}^{n} I_{\{(X_{1i}, X_{2i}) \leq (t_1, t_2), (\Delta_{1i}, \Delta_{2i}) = (1,1)\}},$$

and similarly for others. As a counterpart of Proposition 1, we have,

Proposition 3. *Under the assumption of independent censoring, the following estimating equations*

$$\frac{d\hat{S}(t)}{\hat{S}(t^-)} = \frac{dN(t)}{Y(t^-)}, \quad \hat{S}(t) = \frac{Y(t)}{n\hat{K}(t)},$$

$$d\hat{S}(t) = \frac{dN(t)}{n\hat{K}(t)}, \quad d\hat{S}(t) = \frac{dN'(t)}{n\hat{K}(t)},$$

are genuine for $S(t)$ *and the solutions to these equations are given, respectively, by*

$$\hat{S}_1(t) = \sum_{i=1}^{n} \hat{S}_1(T_i^-)\frac{I(T_i \le C_i)H(t-T_i)}{Y(T_i^-)} + \hat{S}(t_1, 0) + \hat{S}(0, t_2) - 1,$$

$$\hat{S}_2(t) = \frac{1}{n}\sum_{i=1}^{n}\frac{I(C_i \ge t)H(T_i - t)}{\hat{K}(t)},$$

$$\hat{S}_3(t) = \frac{1}{n}\sum_{i=1}^{n}\frac{I(C_i \ge T_i)H(t-T_i)}{\hat{K}(T_i)} + \hat{S}(t_1, 0) + \hat{S}(0, t_2) - 1,$$

$$\hat{S}_4(t) = \frac{1}{n}\sum_{i=1}^{n}\frac{I(C_i \ge T_i)H(T_i - t)}{\hat{K}(T_i)} + \frac{1}{n}\sum_{i=1}^{n}\frac{I(C_i \ge T_i)H(T_i)}{\hat{K}(T_i)}$$

$$-\frac{1}{n}\sum_{i=1}^{n}\frac{I(C_i \ge T_i)H(T_{1i}-t_1,T_{2i})}{\hat{K}(T_i)} - \frac{1}{n}\sum_{i=1}^{n}\frac{I(C_i \ge T_i)H(T_{1i}-T_{2i}-t_2)}{\hat{K}(T_i)}$$

$$+ \hat{S}(t_1, 0) + \hat{S}(0, t_2) - 1,$$

where $\hat{K}$ *is the estimator for bivariate censoring survival function* K *obtained by reversing the roles of* T *and* C *in* $\hat{S}_1(t)$*, and the estimators* $\hat{S}(t_1, 0)$ *and* $\hat{S}(0, t_2)$ *are corresponding marginal Kaplan-Meier estimators for* $S(t_1, 0)$ *and* $S(0, t_2)$*.*

The above four genuine estimators are not equivalent. One reason is that the equality $n\hat{S}_1(t)\hat{K}(t) = Y(t)$ will no longer hold in bivariate case.

4. Mark Survival Function

Mark survival function is clearly a generalization of usual survival function. Thus, it is a natural temptation to estimate general survival function by some estimators extended from the estimators for survival function. One extension of the Kaplan-Meier estimator is the so-called naive Kaplan-Meier estimator. As well noticed, the use of naive Kaplan-Meier will usually lead to biased estimation.

We show, by a simple example, that in general, the mark survival function is not estimable from observed data. Use a data setting in Gelber et al. [4] that rechecked by Zhao and Tsiatis [14], let T_1 be the time of toxicity, T_2 be survival time, and thus the quality-adjusted survival time or mark variable, is $U = \max(T_2 - T_1, 0)$. Assume censoring C is independent of T_1 and T_2. We denote such a data setting as $\mathbb{D}_0$. Assume that $T_1 \sim \exp(\alpha)$, $T_2 \sim \exp(\beta)$, and censoring $C \sim \exp(\lambda)$. Under the presence of censoring, the observed mark variable is $U_o = \max\{ \min(T_2 \wedge C - T_1), 0\}$, where $\wedge$ is minimum operator, and the basic estimable functions are:

$$S_1(x) = \Pr(U_o > x, T_2 < C) = \Pr(T_2 - T_1 > x, T_2 < C),$$

and

$$S_2(x) = \Pr(U_o > x, T_2 > C) = \Pr(C - T_1 > x, C < T_2).$$

By some calculation, we have,

$$S_1(x) = \frac{\alpha\beta}{\beta + \lambda} \frac{1}{\alpha + \beta + \lambda} e^{-(\beta+\lambda)x},$$

$$S_2(x) = \frac{\alpha\lambda}{\beta + \lambda} \frac{1}{\alpha + \beta + \lambda} e^{-(\beta+\lambda)x}.$$

The true mark survival function is,

$$S(x) = \Pr(T_2 - T_1 > x) = \frac{\alpha}{\alpha + \beta} e^{-\beta x}.$$

It is clear that there is no operator O, such that,

$$S(x) = O\{S_1(x),\ S_2(x)\}.$$

Therefore, there is no genuine estimator for $S(x)$ under such a data setting.

Currently, for estimating mark survival function, the IPCW technique has been used widely and a number of weighted estimators have been developed, such as those proposed by Zhao and Tsiatis [14] and Strawderman [11].

In the absence of censoring, the empirical estimator for mark survival function $S(x) = \Pr(U > x)$ is

$$\hat{S}(x) = \frac{1}{n} \sum_{i=1}^{n} I(U_i > x).$$

A weighted estimator for $S(x)$ in general form could be

$$\hat{S}_w(x) = \frac{1}{n} \sum_{i=1}^{n} w_i(\ \cdot\ , T_i,\ x) I(U_i > x).$$

Different weight functions yield different weighted estimators. Below are some as examples,

$$\hat{S}_{w1}(x) = \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq T_i)}{\hat{K}(T_i)}\, I(U_i > x),$$

$$\hat{S}_{w2}(x) = \frac{1}{n} \sum_{i=1}^{n} \frac{I\{C_i \geq \alpha_i(x)\}}{\hat{K}\{\alpha_i(x)\}}\, I(U_i > x),$$

where $\alpha_i(x) = \inf[s : \int_0^s V_i(t)dt \geq x]$, and $\hat{K}(\cdot)$ is the Kaplan-Meier estimator for the censoring survival function $K(\cdot)$ based on data $X = \min(T, C)$ and $\Delta = I(T \geq C)$. Strawderman [11] proposed some other weighted estimators, we refer to his article for detail.

Zhao and Tsiatis [14] argued that the sharp weighted estimator $\hat{S}_{w2}(x)$ would be more efficient than others. We thus focus on the estimator $\hat{S}_{w2}(x)$ and denote it back as $\hat{S}_w(x)$.

The following proposition clarifies a sufficient and necessary condition for the consistency of the weighted estimator $\hat{S}_w(x)$.

Proposition 4. *The weighted estimator $\hat{S}_w(x)$ is consistent if and only if $\Pr\{\alpha(x) \leq \tau\} = 1$ holds, where $\alpha(x) = \inf[s : \int_0^s V(t)dt \geq x]$, and $\tau = \inf[s : K(s) = 0]$.*

We refer to the condition $\Pr\{\alpha(x) \leq \tau\} = 1$ as *WC* condition. In order to ensure the consistency of a weighted estimator, most researchers introduce an artificial ending point L to truncate the failure time T. However, as pointed out by Huang [6], such truncation will deviate the target from the original interest.

The weighted estimator $\hat{S}_w(x)$ can be genuine only for some special data structures. The following proposition gives one of such structures.

Proposition 5. *For data model $\mathbb{D}_0$, when WC condition holds and the variable T_1 is discrete, then the weighted estimator $\hat{S}_w(x)$ is genuine.*

The sharp weighted estimator $\hat{S}_w(x)$ is likely not genuine, when T_1 is continuous. However, since a general density function can be approximated weakly by a discrete density function, the estimator $\hat{S}_w(x)$ is thus asymptotically genuine for general T_1, when *WC* condition holds. This conclusion remains valid for general data models. We thus have,

Proposition 6. *When WC condition holds, the weighted estimator $\hat{S}_w(x)$ is asymptotically genuine.*

As a direct corollary from this proposition, we have,

Corollary 1. *If censoring follows an exponential distribution, then the weighted estimator $\hat{S}_w(x)$ is consistent, and thus, the mark survival function can be estimated without truncation.*

5. Discussion

Under the presence of censoring, good estimators for survival functions should be those that can 'eliminate' the effect of censoring somehow. In terms introduced in this paper, they should be genuine or asymptotically genuine. This article explores genuine estimators for estimating different kinds of survival functions. A number of genuine estimators are proposed for estimating univariate survival function and multivariate survival function. For estimating mark survival function, a genuine estimator may not exist or may not be practicable. A weighted estimator would be asymptotically genuine, when *WC* condition holds. However, in the case when such condition fails, weighted estimators are not consistent. Since in general there is no genuine estimator for mark survival function, special consideration should be taken in special context in order to obtain satisfactory estimation for mark survival function.

When several genuine estimators are available, to identify the optimal one is of great value in theory as well as in practice. To explore the reason for optimality is also interesting and inspiring. Since the Kaplan-Meier estimator is optimal for estimating univariate survival function, we perceive that the Kaplan-Meier-type estimator would be also optimal for estimating multivariate survival function and, when *WC* condition holds, the sharp weighted estimator would be (close to) optimal. The confirmation for these conclusions merits further study.

6. Appendix

The proofs for most propositions are standard. We just consider the proof of Proposition 5.

Proof of Proposition 5. Let $f(t) = \sum_{j=1}^{k} \delta(t - a_j)\alpha_j$ be the density function of T_1, where $\delta(\cdot)$ is the Dirac function. Denote n_j the number of observations that T_1 takes value a_j. Assume that $n_j \to \infty$ as $n \to \infty$. Since the weighted estimator $\hat{S}_2(t)$ is genuine, then,

$$\hat{S}_w(x) = \frac{1}{n} \sum_{i=1}^{n} \frac{I\{C_i \geq \alpha_i(x)\}}{\hat{K}\{\alpha_i(x)\}} I(U_i > x)$$

$$= \frac{1}{n} \sum_{i=1}^{n} \frac{I(C_i \geq T_{1i} + x)}{\hat{K}(T_{1i} + x)} I(T_{2i} > T_{1i} + x)$$

$$= \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{k} \frac{I(C_i \geq a_j + x)}{\hat{K}(a_j + x)} I(T_{2i} > a_j + x)$$

$$= \sum_{j=1}^{k} \frac{n_j}{n} \frac{1}{n_j} \sum_{\substack{i=1 \\ T_{1i}=a_j}}^{n} \frac{I(C_i \geq a_j + x)}{\hat{K}(a_j + x)} I(T_{2i} > a_j + x)$$

$$\xrightarrow{P} \sum_{j=1}^{k} \alpha_j \Pr(T_2 > a_j + x) = \Pr(T_2 > T_1 + x).$$

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