Estimation and computation of the median for right-censored data

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Zurich, June 4th 2009

Content

1. Confidence interval for a quantile for right-censored data
2. Computation of confidence intervals: Software comparison

Problem: $X_1^\circ, \ldots, X_n^\circ$ i.i.d. with survival function $S^\circ(t) = P(X_1^\circ > t)$, CDF $F^\circ(t) = P(X_1^\circ \leq t) = 1 - S^\circ(t)$, $t \geq 0$.

Goal: Find confidence interval for a quantile of F°:

$$x_p \quad = \quad (F^\circ)^{-1}(p) := \inf\{t \ : \ F^\circ(t) \geq p\}$$

Censored data: We only observe $X_i = \min\{X_i^\circ, T_i\}$; T_i bound on follow-up period, δ_i censoring indicator.

Kaplan-Meier:

$$\widehat{S}^\circ(t) \quad = \quad \prod_{\text{distinct } X_i \leq t} (n_i - d_i)/n_i,$$

with $n_i = \#\{X_i \geq t\}$, $d_i = \#\{X_i = X_i^\circ, X_i = t\}$ (#events at t).

Naive approach: Due to Sander (1975):

$$\sqrt{n}(\widehat{x}_p - x_p) \quad \xrightarrow{\mathcal{L}} \quad \text{zero-mean Gaussian process.}$$

$\widehat{x}_p$: sample quantile.

Problem with the naive approach: Variance of $\widehat{x}_p$ is:

$$\frac{(1-p)^2 \operatorname{Var}(\widehat{S}^\circ(\widehat{x}_p))}{\widehat{S}^\circ(\widehat{x}_p)\widehat{f}^\circ(\widehat{x}_p)^2}$$

so depends on $\widehat{f}^\circ(\widehat{x}_p) \Rightarrow$ we have to estimate f° at x_p, which is hard.

Many textbooks: Use crude uniform kernel density estimate of f° at x_p:

$$\frac{\widehat{S}^\circ(\widehat{x}_p - b) - \widehat{S}^\circ(\widehat{x}_p + b)}{2b}$$

for some (small) b to get an estimate of variance, construct confidence interval.

Alternative: Invert a sign test for censored data to get confidence interval.

Note: Parallels approach for complete data.

Confidence interval for median

Sign-test for censored data: Hypotheses

$$\begin{aligned} H_0 &: \text{ median of survival function } S^\circ = m \text{ vs.} \\ H_1 &: \text{ median of survival function } S^\circ \neq m. \end{aligned}$$

Test statistic: $U(m) = n^{-1} \sum_{i=1}^{n} \widehat{Q}(X_i, \delta_i)$, with scoring function

$$\begin{aligned} \widehat{Q}(X_i, \delta_i) &= P_{\widehat{S}^\circ}(X_i^\circ > m | X_i, \delta_i, \widehat{S}^\circ) \\ &= \begin{cases} 1, & X_i > m, \\ \widehat{S}^\circ(m)/\widehat{S}^\circ(X_i), & X_i \leq m, \delta_i = 0, \\ 0, & X_i \leq m, \delta_i = 1. \end{cases} \end{aligned}$$

Explanation: Count observations before/after m, correct for censoring.

Problem: Find limiting distribution of $U(m)$.

Magic

Theorem (Brookmeyer & Crowley, 1982)

The test statistic $U(m)$ is equal to $\widehat{S}^{\circ}(m)$, the Kaplan-Meier estimate at m.

Asymptotic distribution of Kaplan-Meier (Breslow & Crowley, 1974):

$$\sqrt{n}\frac{\widehat{S}^{\circ}(m) - \widehat{S}^{\circ}(m)}{\sigma(m)} \quad \xrightarrow{\mathcal{L}} \quad \mathcal{N}(0,1)$$

where

- $\sigma^2(m) = S^{\circ}(m)^2 \int_0^m (1 - F(t))^{-2} \, \mathrm{d}\tilde{F}(t)$,
- F the CDF of observed lifetimes: $F(t) = P(X_i \leq t)$,
- $\tilde{F}(t)$ the CDF of true observed lifetimes: $\tilde{F}(t) = P(X_i \leq t, \delta_i = 1)$.

$\widehat{\sigma}^2(m) = \mathrm{Var}(\widehat{S}^{\circ}(m))$ can be Greenwood's or Peto's estimator (for each m!)
$\Rightarrow$ main difference to approach based on limiting distribution of quantile.

Proof of theorem

Use self-consistency of Kaplan-Meier estimate:

$$\widehat{S}^{\circ}(t) \quad = \quad n^{-1} \sum_{i=1}^{n} \delta_i 1\{X_i > t\} + n^{-1} \sum_{x_i \leq t} (1 - \delta_i) \frac{\widehat{S}^{\circ}(t)}{\widehat{S}^{\circ}(X_i)}$$

Iteration of self-consistency converges to $\widehat{S}^{\circ}$ (Efron, 1967).

Simple generalization of result in uncensored case:

$$\widehat{S}^{\circ}(t) \quad = \quad n^{-1} \sum_{i=1}^{n} 1\{X_i > t\}.$$

Wrap up

Initial problem: Inversion of test

$$\begin{aligned} H_0 &: \text{ median of survival function } S^\circ = m \text{ vs.} \\ H_1 &: \text{ median of survival function } S^\circ \neq m \end{aligned}$$

is transformed via magic to inversion of test

$$\begin{aligned} H_0 &: S^\circ(m) = 1/2 \text{ vs.} \\ H_1 &: S^\circ(m) \neq 1/2. \end{aligned}$$

Advantage: Need not estimate density at m to estimate variance.

Computation via confidence bands

Confidence interval at level $1-\alpha$ for $S^\circ(m)$: Collect all s that do not reject test on $s = 1/2$ at m:

$$R_{\alpha,S^\circ} \quad = \quad \left\{ s \;\middle|\; \sqrt{n}|s - 1/2|\widehat{\sigma}^{-1}(m) \;\leq\; z_{1-\alpha/2} \right\}$$

where $z_{1-\alpha/2}$ is the $(1-\alpha/2)$-quantile of a standard normal distribution.

Due to magic, rejection of this test is equivalent to rejection of sign-test for median, so that

$$R_{\alpha,\mathrm{median}(S^\circ)} \quad = \quad \left\{ m \;\middle|\; \sqrt{n}|\widehat{S}(m) - 1/2|\widehat{\sigma}^{-1}(m) \;\leq\; z_{1-\alpha/2} \right\}$$

is a confidence interval for $\mathrm{median}(S^\circ)$.

Similar reasoning applies to transformations of $\widehat{S}^\circ$ (log, arcsin-square root).

Content

1 Confidence interval for a quantile for right-censored data

2 Computation of confidence intervals: Software comparison

Taken from Barker (2009).

Software	Version	Procedure	Default method
`S-Plus`	7	`survfit(Surv())`	B & C (log, linear, log-log)
`R`	2.8.0	`survfit(Surv())`	B & C (log, linear, log-log)
`SAS`	9.1	`Lifetest`	B & C (log)
`SAS`	9.2	`Lifetest`	B & C (log, linear, log-log)
`SPSS`	16	Survival module	Normal approximation
`Stata`	10	Survival module	B & C (log-log)

Terry Therneau on S-news (Sep 23, 2008):

> *"The quality of the procedure depends on the quality of the original pointwise bands. There are several methods to generate the bands, and lots of papers comparing them.*
>
> - *empirical likelihood: excellent.*
> - *bootstrap methods: okay to excellent, depending on details of how its done.*
> - *transformed CI, log, logit, log-log, etc: very good.*
> - *plain, $S(t) \pm 1.96$ se: poor.*
>
> *There is no excuse for a modern package to use the last of these, given the literature."*

Note: Confusion even more serious for mean (treatment of last observation if censored).