Log-rank-type nonparametric test for comparing survival functions with doubly interval-censored data

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Doubly interval-censored data & goal

Data:
- $X_i, S_i$: Times of the occurrences of two related events with $X_i \leq S_i$
  - In case of AIDS cohort study, $X_i$: HIV infection time & $S_i$: diagnosis time of AIDS
- $T_i = S_i - X_i$: Survival time of interest
  - In case of AIDS cohort study, $T_i$: AIDS incubation time
- But, $X_i$ and $S_i$ are known only to lie in $[L_i, R_i]$ and $[U_i, V_i]$, respectively

Goal:
- Let $S_q(t) = Pr(T > t), q = 1, \ldots, p$, denote the survival function of $T$ for the $q$th treatment group
- To test
  $H_0 : S_1(t) = \cdots = S_p(t), \forall t \in (0, \infty) \text{ vs. } H_a : \text{Not all survival functions are equal at } t$
Nonparametric test procedures for comparing survival functions

- Interval-censored data: Rank-based
  - Sun(1996, StatMed)
  - Pan(2000, StatMed)
  - Zhao & Sun(2004, StatMed)
  - Kim, Kang, & Nam(2006, CSDA)

- Doubly interval-censored data
  - Sun(2001, LIDA)
    - Focus on discrete failure time data
    - It has a problem that it does not reduce to the usual log-rank test for the right-censored data
  - Sun(2006 in the textbook “The Statistical Analysis of Interval-censored Failure Time Data”)
    - Modify Sun(2001)’s test
    - A generalization of Zhao & Sun(2004)’s test
Notations

- \( u_1 < u_2 < \cdots < u_r \): Unique ordered elements of \( \{L_i, R_i, i = 1, \ldots, n\} \)
- \( \nu_1 < \nu_2 < \cdots < \nu_s < \nu_{s+1} = \infty \): Unique ordered elements of \( \{U_i - R_i, V_i - L_i, i = 1, \ldots, n\} \)
- For \( i = 1, \ldots, n; \; k = 1, \ldots, s \), define
  \[
  \alpha_{ik} = \begin{cases} 
  \sum_{j=1}^{r} I(u_j + \nu_k \in [U_i, V_i], u_j \in [L_i, R_i]), & \text{if } \nu_k \in [U_i - R_i, V_i - L_i] \\
  0, & \text{o.w} 
  \end{cases}
  \]
- Define \( \delta_i \) as 1, if \( T_i \) is interval-censored or exactly observed; 0, o.w
- \( R_k \): Pseudo risk set of all subjects who have a nonzero probability of being at risk up to \( \nu_k \)
- \( D_k \): Pseudo death set of all subjects who have a nonzero probability of failing at \( \nu_k \)
Proposed test

Model assumption

- Under $H_0$, each admissible value of $(X_i, T_i)$ for subject $i$ is uniformly distributed over a set $A_i = \{(u_j, v_k); u_j + v_k \in [U_i, V_i], u_j \in [L_i, R_i], v_k \in [U_i - R_i, V_i - L_i]\}$ with equal probability of $1/\alpha_{i+}$, where $\alpha_{i+} = \sum_{k=1}^{s} \alpha_{ik}$

- In other words, if $(u_j, v_k) \in A_i$,

$$Pr\{(X_i = u_j, T_i = v_k)|(L_i, R_i, U_i, V_i)\} = 1/\alpha_{i+}, \quad (1)$$

and 0, o.w
Weights

- Under model (1), conditional probability of subject \(i\) being at risk up to \(v_k\) is given by

\[
W_{ik}^r = \Pr\{ T_i \geq v_k | (L_i, R_i, U_i, V_i) \} = \frac{\sum_{m=k}^{s} \alpha_{im}}{\sum_{n=1}^{s} \alpha_{in}} \quad (2)
\]

- Conditional probability of subject \(i\) failing at \(v_k\) is given by

\[
W_{ik}^d = \Pr\{ T_i = v_k | (L_i, R_i, U_i, V_i) \} = \frac{\delta_i \alpha_{ik}}{\sum_{n=1}^{s} \alpha_{in}} \quad (3)
\]
Proposed test

Pseudo risk set & pseudo death set

From (2) & (3), \( n_k = \sum_{i=1}^{n} w_{ik}^r \) : Pseudo-count of \( R_k \) at \( v_k \)

\( d_k = \sum_{i=1}^{n} w_{ik}^d \) : Pseudo-count of \( D_k \) at \( v_k \)

\( n_{kq} = \sum_{i}^{q} w_{ik}^r \) : Pseudo-count of \( R_k \) at \( v_k \) from treatment group \( q \)

\( d_{kq} = \sum_{i}^{q} w_{ik}^d \) : Pseudo-count of \( D_k \) at \( v_k \) from treatment group \( q \),

where \( \sum_{i}^{q} \) denotes the summation over all subjects from treatment group \( q \)

Remark:

For right-censored data, \( n_k, d_k, n_{kq}, \) and \( d_{kq} \) reduce to corresponding values in the usual log-rank test
Test statistic

- As in Sun (2001, LIDA), plug in $n_k$, $d_k$, $n_{kq}$, and $d_{kq}$ into the usual log-rank test
- Define the log-rank-type statistic

$$U = (U_1, \ldots, U_{p-1})',$$

where $U_q = \sum_{k=1}^{s} (d_{kq} - d_k n_{kq}/n_k)$, $q = 1, \ldots, p - 1$

- To test $H_0$, propose a standardized test statistic based on $U$, given by

$$P = U' \hat{\Sigma}^{-1} U,$$  \hspace{1cm} (4)

where $\hat{\Sigma}$ is the estimated covariance matrix of $U$

- Use $P \sim \chi^2(p - 1)$ approximately under $H_0$
Covariance matrix estimation: Multiple imputation method

- **Step 1**: Generate $X_i^{(b)}$ from

  $$
  \Pr(X_i^{(b)} = u_j | X_i \in [L_i, R_i]) = 1/\sum_{j=1}^{r} I(u_j \in [L_i, R_i])
  $$

  over $u_j$'s that belongs to $[L_i, R_i]$.

- **Step 2**: Given $X_i^{(b)}$'s, if $S_i$ is right-censored, $T_i^{(b)} = U_i - X_i^{(b)}$ and $\delta_i^{(b)} = 0$. If $S_i$ is interval-censored or exactly observed, generate $T_i^{(b)}$ from

  $$
  \Pr(T_i^{(b)} = v_k^{(b)} | T_i \in [U_i - X_i^{(b)}, V_i - X_i^{(b)}]) = 1/\sum_{r=1}^{s} I(v_r^{(b)} \in [U_i - X_i^{(b)}, V_i - X_i^{(b)}])
  $$

  over $v_k^{(b)}$'s that belongs to $[U_i - X_i^{(b)}, V_i - X_i^{(b)}]$, and $\delta_i^{(b)} = 1$
Covariance matrix estimation: Multiple imputation method

- Step 3: Based on the $b$th imputed right-censored data $\{(T_i^{(b)}, \delta_i^{(b)})\}$, compute the usual log-rank statistic and its covariance matrix, $U^{(b)}$ and $\hat{\Sigma}^{(b)}$, say.

- Step 4: Repeat Steps 1 to 3 $B (> 0)$ times and obtain $B$ pairs of $(U^{(b)}, \hat{\Sigma}^{(b)}_{na})$, $b = 1, \ldots, B$

- Step 5: Compute the sum of the average of within-imputation covariance matrices and the between-imputation covariance matrix of $U$, say $\hat{\Sigma}^*$

Remark:
- Replacing $\hat{\Sigma}$ in (4) by $\hat{\Sigma}^*$, test $H_0$ based on

$$P^* = U' \hat{\Sigma}^{-1} U$$

- $P^*$ reduces to the usual log-rank test for the right-censored data
Design parameters

- Observed intervals for $X_i$’s by letting $L_i$ and $R_i$ to be a random number from $U[0, 4]$ minus and plus a random number from $U\{0, 1, \ldots, D\}$
  - $D = 1, 2, 3$
- Survival times $T_i$’s are generated from the exponential distributions with hazards $e^{\alpha}$ and $e^{\alpha + \beta}$ for subjects from treatment groups 1 and 2, respectively
  - Observed intervals of $S_i$’s by letting $U_i$ and $V_i$ to be $X_i + T_i$’s minus and plus a random number from $U\{0, 1, \ldots, D\}$
  - $S_i$ is right-censored if $U_i \geq 15$
  - $\alpha$ was used to determine the percentage of right-censored observations for the $S_i$
  - $\beta$ represents the survival difference between the two treatment groups
    - $\beta = 0$ for the significance level of the tests
    - $\beta = -0.8, -0.4, 0.4$ or $0.8$ for the powers of the tests
Design parameters

- In order to apply Sun’s test to data generated above, discretize $L_i$, $R_i$, $U_i$, and $V_i$ as $L_i^d = \lceil L_i \rceil$, $R_i^d = \lceil R_i \rceil$, $U_i^d = \lceil U_i \rceil$, and $V_i^d = \lceil V_i \rceil$, respectively, where $\lceil a \rceil$ denotes the smallest value of integers greater than or equal to $a$

- Sample size: $n=200$ (100 subjects from each treatment group)

- Replications: 2,000

- $B = 25$
## Results: Size & power

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$c_f$: Right censoring fraction, $P^*$: Proposed test, $P^{*d}$: Proposed test (discrete version), $S$: Sun(2001)'s test
AIDS cohort study

- Data taken from Kim, De Gruttola, & Lagakos (1993, BCS)
- 188 patients were infected with HIV during the study period that lasted from 1978 to 1988
- Subjects were classified into two groups according to the amount of blood factor that they received (heavily treated (HT) group vs. lightly treated (LT) group)
- Right censoring fraction in AIDS diagnosis time: 84.8% (LT group), 71.9% (HT group)
- Estimate the survival functions of HIV infection time and AIDS incubation time (i.e. time from HIV infection to AIDS diagnosis)
- Compare the survival functions of the AIDS incubation times in two treatment groups
  - \( B (\# \text{ of multiple imputation}) = 200 \)
  - \( P^* = 3.2904 (P\text{-value}=0.0697), S = 3.1150 (P\text{-value}=0.0775) \)
  - Slightly significant!
Two plots

Estimates of the survival functions of HIV infection time

- ML estimate for LT group
- ML estimate for HT group

Estimates of the survival functions of AIDS incubation time

- ML estimate for LT group
- ML estimate for HT group

Survival Function vs. Time by Months

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Summary

- A generalization of usual log-rank test with doubly interval-censored data
- Intuitive model & simple implementation
- Not require joint MLEs as in Sun(2001)'s test
- Unlike Sun’s test, applicable to discrete failure time data as well as continuous failure time data
- Proposed test controls well the significance level of the tests & is more powerful than Sun’s test
Thank You!