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

Jinheum Kim[1] Chung Mo Nam[2]

[1]Department of Applied Statistics
University of Suwon

[2]Department of Preventive Medicine and Public Health
Yonsei University College of Medicine

July 15, 2008

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 qth treatment group
  - To test
    $H_0 :\ S_1(t) = \cdots = S_p(t),\ \forall t \in (0, \infty)$ *vs.*
    H_a : Not all survival functions are equal at t

Nonparametric test procedures for comparing survival functions

- Interval-censored data: Rank-based
  - Sun(1996, StatMed)
  - Fay(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 $\{L_i, R_i, i = 1, \ldots, n\}$
- $v_1 < v_2 < \cdots < v_s < v_{s+1} = \infty$: 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

$$\alpha_{ik} = \begin{cases} \sum_{j=1}^{r} I(u_j + v_k \in [U_i, V_i], u_j \in [L_i, R_i]), & \text{if } v_k \in [U_i - R_i, V_i - L_i] \\ 0, & \text{o.w} \end{cases}$$

- Define δ_i as 1, if T_i is interval-censored or exactly observed; 0, o.w
- $\mathcal{R}_k$: Pseudo risk set of all subjects who have a nonzero probability of being at risk up to v_k
- $\mathcal{D}_k$: Pseudo death set of all subjects who have a nonzero probability of failing at v_k

Model assumption

- Under H_0, each admissible value of (X_i, T_i) for subject i is uniformly distributed over a set

$$\mathcal{A}_i = \{(u_j, v_k); u_j + v_k \in [U_i, V_i], u_j \in [L_i, R_i], v_k \in [U_i - R_i, V_i - L_i]\}$$

with equal probability of $1/\alpha_{i+}$, where $\alpha_{i+} = \sum_{k=1}^{s} \alpha_{ik}$

- In other words, if $(u_j, v_k) \in \mathcal{A}_i$,

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

and 0, o.w

Weights

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

$$w_{ik}^{r} = Pr\{T_i \geq v_k | (L_i, R_i, U_i, V_i)\} = \sum_{m=k}^{s} \alpha_{im} / \sum_{n=1}^{s} \alpha_{in} \qquad (2)$$

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

$$w_{ik}^{d} = Pr\{T_i = v_k | (L_i, R_i, U_i, V_i)\} = \delta_i \alpha_{ik} / \sum_{n=1}^{s} \alpha_{in} \qquad (3)$$

Pseudo risk set & pseudo death set

- From (2) & (3), $n_k = \sum_{i=1}^{n} w_{ik}^{r}$: Pseudo-count of $\mathcal{R}_k$ at v_k
- $d_k = \sum_{i=1}^{n} w_{ik}^{d}$: Pseudo-count of $\mathcal{D}_k$ at v_k
- $n_{kq} = \sum_{i}^{q} w_{ik}^{r}$: Pseudo-count of $\mathcal{R}_k$ at v_k from treatment group q
- $d_{kq} = \sum_{i}^{q} w_{ik}^{d}$: Pseudo-count of $\mathcal{D}_k$ 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

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

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 $\mathbf{U}$, given by

$$P = \mathbf{U}'\hat{\boldsymbol{\Sigma}}^{-1}\mathbf{U}, \tag{4}$$

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

- 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

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

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 bth imputed right-censored data $\{(T_i^{(b)}, \delta_i^{(b)})\}$, compute the usual log-rank statistic and its covariance matrix, $\mathbf{U}^{(b)}$ and $\hat{\boldsymbol{\Sigma}}_{na}^{(b)}$, say.
- Step 4: Repeat Steps 1 to 3 $B(>0)$ times and obtain B pairs of $(\mathbf{U}^{(b)}, \hat{\boldsymbol{\Sigma}}_{na}^{(b)})$, $b = 1, \ldots, B$
- Step 5: Compute the sum of the average of within-imputation covariance matrices and the between-imputation covariance matrix of $\mathbf{U}$, say $\hat{\boldsymbol{\Sigma}}^*$
- Remark:
  - Replacing $\hat{\boldsymbol{\Sigma}}$ in (4) by $\hat{\boldsymbol{\Sigma}}^*$, test H_0 based on

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

  - 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^{α} 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 $U_i \geq 15$
  - α was used to determine the percentage of right-censored observations for the S_i
  - β represents the survival difference between the two treatment groups
    - β=0 for the significance level of the tests
    - β=-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

D		1			2			3		
β	c_f	0.1	0.3	0.5	0.1	0.3	0.5	0.1	0.3	0.5
-0.8	P^*	1.00	.999	.996	1.00	1.00	.994	1.00	.998	.994
	P^{*d}	1.00	.999	.995	1.00	1.00	.993	1.00	.998	.995
	S	1.00	.999	.996	1.00	1.00	.992	1.00	.997	.990
-0.4	P^*	.780	.673	.561	.759	.685	.562	.706	.642	.554
	P^{*d}	.760	.657	.561	.734	.673	.558	.670	.633	.541
	S	.754	.662	.551	.715	.654	.536	.638	.600	.499
0.0	P^*	.051	.053	.045	.044	.051	.049	.037	.051	.049
	P^{*d}	.045	.051	.044	.039	.048	.047	.032	.044	.046
	S	.043	.051	.043	.039	.046	.044	.030	.035	.039
0.4	P^*	.745	.623	.466	.742	.597	.451	.689	.577	.451
	P^{*d}	.725	.608	.459	.726	.584	.446	.667	.562	.441
	S	.730	.610	.455	.708	.572	.427	.634	.519	.394
0.8	P^*	.999	.992	.946	.999	.990	.935	.997	.985	.920
	P^{*d}	.999	.990	.941	.999	.991	.931	.998	.983	.916
	S	.999	.989	.942	.999	.990	.919	.997	.975	.895

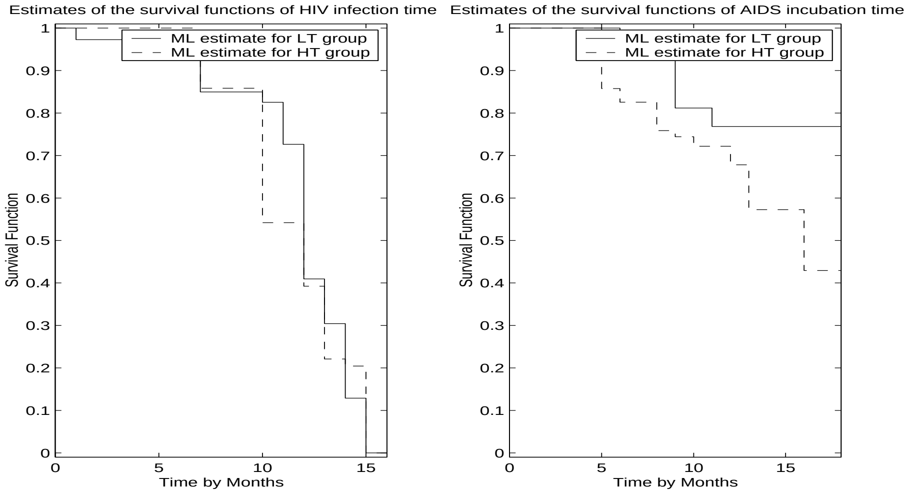
c_f : Right censoring fraction, P^* : Proposed test, P^{*d} : Proposed test(discrete version), S : Sun(2001)'s test

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(# of multiple imputation)=200
  - P^*=3.2904(P-value=0.0697), S=3.1150(P-value=0.0775)
  - Slightly significant!

Go to Summary

Two plots



Return

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!