東海大學統計研究所

碩士論文

在左截相依設限資料下相連持續時間的存活分配估計

Estimation of the joint survival function for successive duration times under left truncation and dependent censoring

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在左截相依設限資料下相連持續時間的存活分配估計

經本委員會審議，認為符合碩士資格標準。

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Abstract

In incident cohort studies, survival data often include subjects who have experienced an initiate event but have not experienced a subsequent event at the calendar time of recruitment. During the follow-up periods, subjects may undergo a series of successive events. Since the second/third duration process becomes observable only if the first/second event has occurred, the data is subject to left-truncation and dependent censoring. In this article, using the inverse-probability-weighted (IPW) approach, we propose nonparametric estimators for the estimation of the joint survival function of three successive duration times. The asymptotic properties of the proposed estimators are established. The simple bootstrap methods are used to estimate standard deviations and construct interval estimators. A simulation study is conducted to investigate the finite sample properties of the proposed estimators.

Key Words: Truncation; Dependent censoring; Inverse-probability-weighted.

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Chapter 1

Introduction

In natural history studies of diseases, each subject can experience a series of successive events. In many applications, the investigators are interested in the duration times between successive events. Suppose that a disease process consists of three successive events occurring in a chronological order. Let E_0, E_1, E_2 and E_3 respectively represent the calendar times of the initiation, first, second and third events for a subject. Define $T_1^* = E_1 - E_0$, $T_2^* = E_2 - E_1$ and $T_3^* = E_3 - E_2$ as the first duration time between E_0 and E_1, the second duration time between E_1 and E_2, and the third duration time between E_2 and E_3 respectively. One may be interested in estimating the joint survival function of T_1^*, T_2^* and T_3^*, denoted by $S(t_1, t_2, t_3) = P(T_1^* > t_1, T_2^* > t_2, T_3^* > t_3)$. In cohort studies, survival data often include subjects who have experienced the initiate event E_0 at the calendar time of recruitment (denoted by τ_0) and have not experienced a subsequent event, e.g. the first/second event. For example, there are four stages in AIDS (acquired immunodeficiency syndrome) studies: E_0: acute HIV infection; E_1 : clinical latency, E_2: the development of AIDS and E_3: death. A prevalent cohort is defined as a sample of subjects who have been infected with HIV (the initiating event E_0) and have not developed clinical latency (or AIDS) at τ_0. Suppose that the infection time E_0 can be accurately determined. Let $V^* = \tau - E_0$ if $E_0 < \tau$ and $V^* = 0$ if $E_0 \geq \tau$. Let D^* denote the time from τ_0 to the right censoring, i.e. the residual censoring time. Note that D^* can be written as $D^* = \min(D_1^*, D_2^*)$, where $D_1^* = \tau_0 - \tau_1$ denotes the time from onset of disease to the end of study τ_1, and D_2^* denotes the time from onset of disease to drop-out or death due to other causes. Figure 1 highlights all the different times for left-truncated successive event data described in Example. In such HIV-prevalent cohort, the time T_1^* (or $T_1^* + T_2^*$), i.e. the time from infection of HIV to development of clinical latency (or to the development of AIDS) is left-truncated by V^* and possibly right-censored. Since the second duration time T_2^* becomes observable only if the first event has occurred, i.e. $T_1^* \leq C^* = V^* + D^*$, the length of T_1^* affects the probability of T_2^* being censored. Similarly, both lengths of T_1^* and T_2^* affect the probability of T_3^* being censored. Dependent censoring arises if T_1^*, T_2^* and T_3^* are correlated, which is often the case. Hence, the data is subject to left truncation and dependent censoring. For this type of data, one observes nothing if $T_1^* < V^*$ (or $T_1^* + T_2^* < V^*$) and observe $(X_1^*, X_2^*, X_3^*, V^*, C^*, \delta_1^*, \delta_2^*, \delta_3^*)$ if $T_1^* \geq V^*$ (or $T_1^* + T_2^* > V^*$), where $X_1^* = \min(T_1^*, C^*)$, $\delta_1^* = I_{[T_1^* \leq C^*]}$, $X_2^* = \delta_1^* \min(T_2^*, C^* - T_1^*)$, $\delta_2^* = \delta_1^* I_{[T_2^* \leq C^* - T_1^*]}$, $X_3^* = \delta_2^* \min(T_3^*, C^* - T_1^* - T_2^*)$, and $\delta_3^* = \delta_2^* I_{[T_3^* \leq C^* - T_1^* - T_2^*]}$.

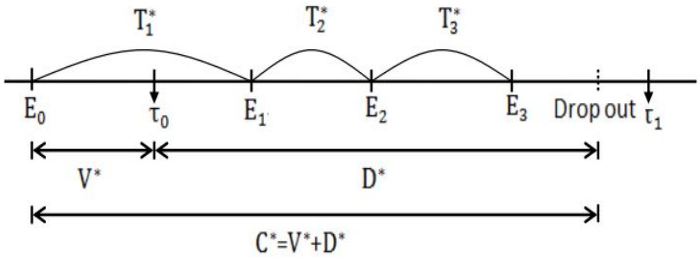

Figure 1. Schematic depiction of left-truncated successive event data

Note that since $C^* = V^* + D^*$, the condition $V^* \leq C^*$ is always satisfied. We assume that $(T_1^*, T_2^*, T_3^*, V^*, C^*)$ is continuous and (V^*, C^*) is independent of (T_1^*, T_2^*, T_3^*).

When there is no truncation, several nonparametric methods for estimating the joint distribution function of successive duration times have been developed (see Visser (1996), Wang and Wells (1998), and Lin et al. (1999)). In particular, both nonparametric estimators considered by Wang and Wells (1998) and Lin et al. (1999) used the inverse probability of censoring as weighted function to adjust the bias of induced informative censoring. Wang and Wells (1988) presented an estimator for the cumulative conditional hazard of T_2 given $T_1 > t_1$ following Nelson-Aalen's construction of the cumulative hazard estimator with each observation weighted based on the information on the first duration to unbias the effect of dependent censoring. Lin et al. (1999) provided a simple nonparametric estimator for the multivariate distribution function of the gap times between successive events when the follow-up time is subject to right censoring. The estimator is consistent and converges weakly to a zero-mean Gaussian process with an easily estimated covariance function.

When both left-truncation and dependent censoring are present, Chang and Tzeng (2006) provided an inverse-probability-weighted (IPW) approach for estimating the joint probability function of two successive duration times. Shen and Yan (2008) proposed an alternative estimator of the joint distribution function of T_1^* and T_2^*. Shen (2010) proposed two IPW estimators of the joint survival function of T_1^* and T_2^*. The first IPW estimator is based on the approach of Chang and Tzeng and the other is the extension of the nonparametric estimator proposed by Wang and Wells (1998). Simulation results indicate that the first IPW estimator outperforms the other estimators. However, as pointed out in Remark 1, the IPW estimator proposed by Shen (2010) can have outlying values.

In this article, we consider the estimation of the joint survival function of three successive duration times when the first (or second) event time is left-truncated. In Section 2, using the IPW approach, we propose nonparametric estimators of the joint survival function $S(t_1, t_2, t_3)$. The proposed IPW estimator does not have the problem of outlying values. The asymptotic properties of the proposed estimators are established. Furthermore, the simple bootstrap methods are used to estimate standard deviations and construct interval estimators. In Section 3, a simulation study is conducted to investigate finite sample performance of the proposed estimators.

Chapter 2

The Proposed Estimators

2.1 When the first event time is left-truncated

Let a_{F_k} and b_{F_k} denote the left and right endpoints of T_k^* $(k = 1, 2, 3)$. Similarly, define (a_G, b_G) and (a_Q, b_Q) for V^* and C^*, respectively. For identifiablities of $S(t_1, t_2, t_3)$, we assume that

$$a_G = a_{F_k} = 0,\ b_G \le b_{F_k} \le b_Q.$$

Let $(X_{1i}, X_{2i}, X_{3i}, V_i, C_i, \delta_{1i}, \delta_{2i}, \delta_{3i})$ $(i = 1, \ldots, n)$ denote the truncated sample. Let $p = P(V^* \le T_1^*)$ denote the untruncated probability. Define the indicator

$$I_i(t_1, t_2, t_3) = I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}$$

and the function $K(x, y) = P(V^* < x, C^* > y)$. Notice that

$$P(X_{1i} > t_1, X_{2i} > t_2, X_{3i} > t_3, \delta_{2i} = 1)$$
$$= p^{-1}P(V^* < T_1^*, T_1^* > t_1, T_2^* > t_2, T_3^* > t_3, C^* - T_1^* - T_2^* > t_3).$$

Let $F(u_1, u_2, u_3)$ denote the joint distribution function of T_1^*, T_2^* and T_3^*. Let $Y_{2i} = X_{1i} + X_{2i}$. Then the expected value of $I_i(t_1, t_2, t_3)/K(X_{1i}, Y_{2i} + t_3)$ is

$$E[I_i(t_1, t_2, t_3)/K(X_{1i}, Y_{2i} + t_3)]$$
$$= \int_{t_3}^{\infty}\int_{t_2}^{\infty}\int_{t_3}^{\infty} \frac{p^{-1}P(V^* < u_1, C^* > u_1 + u_2 + t_3)}{K(u_1, u_1 + u_2 + t_3)} F(du_1, du_2, du_3) = p^{-1}S(t_1, t_2, t_3)$$

Thus, given p and $K(x, y)$, we can estimate $S(t_1, t_2, t_3)$ by

$$\hat{S}_n(t_1, t_2, t_3; p, K) = n^{-1}p\sum_{i=1}^{n} \frac{I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}}{K(X_{1i}, Y_{2i} + t_3)}.$$

First, we consider the estimation of $K(x, y)$. Notice that for $x < y$, $K(x, y) = K(x, x)P(C^* \ge y|C^* \ge x)$. Let $S_1(x) = P(T_1^* > x)$. Then $G_e(x) = P(V_i \le x) = p^{-1}\int_0^x S_1(v)G(dv)$ and $G(x) = p\int_0^x \frac{1}{S_1(v)}G_e(dv)$. Hence, given p, $G(x)$ can be estimated by

$$\hat{G}(x; p) = n^{-1}p\left[\sum_{i=1}^{n} \frac{I_{[V_i \le x]}}{\hat{S}_1(V_i)}\right],$$

where $\hat{S}_1$ denote the product-limit estimator based on the univariate data $(X_{1i}, V_i, \delta_{1i})$ $(i = 1, \ldots, n)$, i.e.

$$\hat{S}_1(u) = \prod_{x \le u} \Big(1 - \hat{\Lambda}_1(du)\Big),$$

where $\hat{\Lambda}_1(u) = N_1(u)/R_1(u)$, $N_1(u) = \sum_{i=1}^n N_{1i}(u)$, $R_1(x) = \sum_{i=1}^n R_{1i}(u)$, $R_{1i}(x) = I_{[V_i \le x \le X_{1i}]}$ and $N_{1i}(x) = I_{[X_{1i} \le x, \delta_{1i}=1]}$.

Next, let $Q(x) = P(C^* \le x)$ denote the distribution function of C^*. Then $Q_e(x) = P(X_{1i} \le x, \delta_{1i} = 0) = p^{-1} P(C^* \le x, C^* \le T_1^*) = p^{-1} \int_0^x S_1(v) Q(dv)$ and $Q(x) = p \int_0^x \frac{1}{S_1(c)} Q_e(dc)$. Hence, given p, $Q(x)$ can be estimated by

$$\hat{Q}(x;p) = n^{-1} p \left[\sum_{i=1}^n \frac{I_{[X_{1i} \le x](1-\delta_{1i})}}{\hat{S}_1(X_{1i})} \right].$$

Since $G_e(x) = p^{-1} \int_0^x S_1(v) G(dv)$, by letting $x \to \infty$, the truncation probability p can be estimated by

$$\hat{p}(\hat{S}_1) = n \left[\sum_{i=1}^n \frac{1}{\hat{S}_1(V_i)} \right]^{-1}.$$

Hence, G and Q can be estimated, respectively, by

$$\hat{G}(x) = n^{-1} \hat{p}(\hat{S}_1) \left[\sum_{i=1}^n \frac{I_{[V_i \le x]}}{\hat{S}_1(V_i)} \right] \quad \text{and} \quad \hat{Q}(x) = n^{-1} \hat{p}(\hat{S}_1) \left[\sum_{i=1}^n \frac{I_{[X_{1i} \le x](1-\delta_{1i})}}{\hat{S}_1(X_{1i})} \right].$$

Since $P(C^* > V^*) = 1$, it follows that $K(x,x) = P(V^* \le x \le C^*) = G(x) - Q(x)$ can be estimated by $\hat{G}(x) - \hat{Q}(x)$.

Next, we consider the estimation of the conditional probability $S_{C^*|V^*}(y-|x) = P(C^* \ge y | C^* \ge x)$. Let $Y_{3i} = X_{1i} + X_{2i} + X_{3i}$ and $Y_3^* = T_1^* + T_2^* + T_3^*$. For $x < y$, define

$$D_{13}(x,y) = P(V_i \le x \le X_{1i}, Y_{3i} \ge y)$$

$$= p^{-1} P(V^* \le x \le C^*, T_1^* \ge x, Y_3^* \ge y, C^* \ge y) = p^{-1} K(x,y) S_{1Y_3^*}(x-, y-), \qquad (2.1)$$

where $S_{1Y_3^*}(x-, y-) = P(T_1^* \ge x, Y_3^* \ge y)$.

Next, let

$$W_{13}(x,y) = P(V_i \le x \le X_{1i}, Y_{3i} \le y, \delta_{3i} = 0)$$
$$= p^{-1} P(V^* \le x \le C^*, T_1^* \ge x, Y_3^* \ge C^*, C^* \le y).$$

Hence,

$$W_{13}(x, dy) = p^{-1} K(x, dy) S_{1Y_3^*}(x-, y-). \qquad (2.2)$$

By (2.1) and (2.2), it follows that $W_{13}(x,dy)/D_{13}(x,y) = K(x,dy)/K(x,y)$.

Thus, for $x < y$, $S_{C^*|V^*}(y-|x) = P(C^* \geq y|V^* \leq x \leq C^*)$ can be estimated by

$$\hat{S}_{C^*|V^*}(y-|x) = \prod_{x \leq c \leq y} \Big(1 - \hat{\Lambda}_{C^*|V^*}(dc|x)\Big),$$

where $\hat{\Lambda}_{C^*|V^*}(c|x) = \hat{W}_{13}(x,c)/\hat{D}_{13}(x,c)$, $\hat{D}_{13}(x,c) = n^{-1}\sum_{i=1}^n \hat{D}_{13i}(x,c)$,

$\hat{W}_{13}(x,c) = n^{-1}\sum_{i=1}^n \hat{W}_{13i}(x,c)$, $\hat{D}_{13i}(x,c) = I_{[V_i \leq x \leq X_{1i}, Y_{3i} \geq c]}$ and $\hat{W}_{13i} = I_{[V_i \leq x \leq X_{1i}, Y_{3i} \leq c, \delta_{3i}=0]}$.

Hence, for $x < y$, $K(x,y)$ can be estimated by $\hat{K}(x,y) = \hat{K}(x,x)\hat{S}_{C^*|V^*}(y-|x)$. Similarly, since $E[I_i(0,0,0)/K(X_{1i},Y_{2i})] = p$, given $\hat{K}(x,y)$, p can be estimated by

$$\hat{p}(\hat{K}) = n\left[\sum_{i=1}^n \frac{\delta_{2i}}{\hat{K}(X_{1i},Y_{2i})}\right]^{-1}.$$

Thus, we obtain an IPW estimator

$$\hat{S}_n(t_1,t_2,t_3) = n^{-1}\hat{p}(\hat{K})\sum_{i=1}^n \frac{I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}}{\hat{K}(X_{1i}, Y_{2i}+t_3)}$$

$$= \left[\sum_{i=1}^n \frac{\delta_{2i}}{\hat{K}(X_{1i},Y_{2i})}\right]^{-1} \sum_{i=1}^n \frac{I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}}{\hat{K}(X_{1i}, Y_{2i}+t_3)}.$$

Remark 1: *Notice that since* $p^{-1}G(x)$ *can be estimated by* $\hat{E}_G(x) = n^{-1}\left[\sum_{i=1}^n \frac{I_{[V_i \leq x]}}{\hat{S}_1(V_i)}\right]$ *and* $p^{-1}Q(x)$ *can be estimated by* $\hat{E}_Q(x) = n^{-1}\left[\sum_{i=1}^n \frac{I_{[X_{1i} \leq x](1-\delta_{1i})}}{\hat{S}_1(X_{1i})}\right]$, *an alternative estimator (see Shen (2010)) is given by*

$$\tilde{S}_n(t_1,t_2,t_3) = n^{-1}\sum_{i=1}^n \frac{I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}}{\hat{E}_K(X_{1i}, Y_{2i}+t_3)},$$

where $\hat{E}_K(x,y) = \hat{E}_K(x,x)\hat{S}_{C^*|V^*}(y-|x)$, $\hat{E}_K(x,x) = \hat{E}_G(x) - \hat{E}_Q(x)$. *One disadvantage of the estimator* $\tilde{S}_n$ *is* $\tilde{S}_n(0,0,0) \neq 1$ *while* $\hat{S}_n(0,0,0) = 1$. *Simulation study indicates that the estimator* $\tilde{S}_n$ *can have outlying values.*

In the following Theorem, we show the weak convergence of $\sqrt{n}[\hat{S}_n(t_1,t_2,t_3) - S(t_1,t_2,t_3)]$.

Lemma 1:

Let $(D[a_{F_1},b_{F_1}]\times[a_{F_2},b_{F_2}]\times[a_{F_3},b_{F_3}], ||\cdot||_\infty, \mathcal{B})$ be the space of cadlag functions as defined in Neuhaus (1971), i.e., real valued functions which are right-continuous with left-hand limits, endowed with the supremum-norm and the Borel-sigma-algebra. Then $\sqrt{n}[\hat{S}_n(t_1,t_2,t_3) -$

$S(t_1,t_2,t_3)]$ converges weakly to a mean-zero Gaussian process on $D[(a_{F_1},b_{F_1})\times(a_{F_2},b_{F_2})\times(a_{F_3},b_{F_3})]$

Proof: The proof is technical and not reported here.

2.2 When the second event time is left-truncated

When the second event time is left-truncated, we have

$$P(X_{1i}>t_1,X_{2i}>t_2,X_{3i}>t_3,\delta_{2i}=1)$$
$$=p_2^{-1}P(V^*<T_1^*+T_2^*,T_1^*>t_1,T_2^*>t_2,T_3^*>t_3,C^*-T_1^*-T_2^*>t_3),$$

where $p_2=P(V^*<T_1^*+T_2^*)$. Let $F(u_1,u_2,u_3)$ denote the joint distribution function of T_1^*, T_2^* and T_3. Then the expected value of $I_i(t_1,t_2,t_3)/K(Y_{2i},Y_{2i}+t_3)$ is

$$E[I_i(t_1,t_2,t_3)/K(Y_{2i},Y_{2i}+t_3)]$$
$$=\int_{t_3}^{\infty}\int_{t_2}^{\infty}\int_{t_3}^{\infty}\frac{p_2^{-1}P(V^*<u_1+u_2,C^*>u_1+u_2+t_3)}{K(u_1+u_2,u_1+u_2+t_3)}F(du_1,du_2,du_3)=p_2^{-1}S(t_1,t_2,t_3)$$

Thus, given p_2 and $K(x,y)$, we can estimate $S(t_1,t_2,t_3)$ by

$$\hat{S}_n(t_1,t_2,t_3;p_2,K)=n^{-1}p_2\sum_{i=1}^{n}\frac{I_{[X_{1i}>t_1,X_{2i}>t_2,X_{3i}>t_3,\delta_{2i}=1]}}{K(Y_{2i},Y_{2i}+t_3)}.$$

First, we consider the estimation of $K(x,y)$. Let $Y_2^*=T_1^*+T_2^*$. Similar to the approach in Section 2.1, we have $K(x,y)=p_2^{-1}K(x,x)P(C^*\geq y|C^*\geq x)$. Let $S_{Y_2^*}(x)=P(Y_2^*>x)$. Then $G_e(x)=P(V_i\leq x)=p_2^{-1}\int_0^x S_{Y_2^*}(v)G(dv)$ and $G(x)=p_2\int_0^x\frac{1}{S_{Y_2^*}(v)}G_e(dv)$. Hence, given p_2, $G(x)$ can be estimated by

$$\hat{G}(x;p_2)=n^{-1}p_2\left[\sum_{i=1}^{n}\frac{I_{[V_i\leq x]}}{\hat{S}_{Y_2^*}(V_i)}\right],$$

where $\hat{S}_{Y_2^*}$ denote the product-limit estimator based on the univariate data (Y_{2i},V_i,δ_{2i}) $(i=1,\ldots,n)$, i.e.

$$\hat{S}_{Y_2^*}(u)=\prod_{x\leq u}\left(1-\hat{\Lambda}_{Y_2^*}(du)\right),$$

where $\hat{\Lambda}_{Y_2^*}(u)=N_{Y_2}(u)/R_{Y_2}(u)$, $N_{Y_2}(u)=\sum_{i=1}^n N_{Y_{2i}}(u)$, $R_{Y_2}(x)=\sum_{i=1}^n R_{Y_{2i}}(u)$, $R_{Y_{2i}}(x)=I_{[V_i\leq x\leq Y_{2i}]}$ and $N_{Y_{2i}}(x)=I_{[Y_{2i}\leq x,\delta_{2i}=1]}$.

Next, $Q_{Y_2}(x)=P(Y_{2i}\leq x,\delta_{2i}=0)=p_2^{-1}P(C^*\leq x,C^*\leq Y_2^*)=p_2^{-1}\int_0^x S_{Y_2^*}(v)Q(dv)$. Hence, given p_2, $Q(x)$ can be estimated by

$$\hat{Q}(x;p_2)=n^{-1}p_2\left[\sum_{i=1}^{n}\frac{I_{[Y_{2i}\leq x]}(1-\delta_{2i})}{\hat{S}_{Y_2^*}(Y_{2i})}\right].$$

Since $G_e(x) = p_2^{-1} \int_0^x S_{Y_2^*}(v)G(dv)$, by letting $x \to \infty$, the truncation probability p_2 can be estimated by

$$\hat{p}_2(\hat{S}_{Y_2^*}) = n \left[\sum_{i=1}^{n} \frac{1}{\hat{S}_{Y_2^*}(V_i)} \right]^{-1}.$$

Hence, G and Q can be estimated, respectively, by

$$\hat{G}_2(x) = n^{-1}\hat{p}_2(\hat{S}_{Y_2^*}) \left[\sum_{i=1}^{n} \frac{I_{[V_i \le x]}}{\hat{S}_{Y_2^*}(V_i)} \right] \text{ and } \hat{Q}_2(x) = n^{-1}\hat{p}_2(\hat{S}_{Y_2^*}) \left[\sum_{i=1}^{n} \frac{I_{[Y_{2i} \le x](1-\delta_{2i})}}{\hat{S}_{Y_2^*}(Y_{2i})} \right].$$

Thus,$K(x, x)$ can be estimated by $\hat{K}_2(x, x) = \hat{G}_2(x) - \hat{Q}_2(x)$.

Next, we consider the estimation of $S_{C^*|V^*}(y - |x)$. For $x < y$, define

$$D_{23}(x, y) = P(V_i \le x \le Y_{2i}, Y_{3i} \ge y)$$

$$= p_2^{-1} P(V^* \le x \le C^*, Y_2^* \ge x, Y_3^* \ge y, C^* \ge y) = p_2^{-1} K(x, y) S_{23}^Y(x-, y-), \tag{2.3}$$

where $S_{23}^Y(x-, y-) = P(Y_2^* \ge x, Y_3^* \ge y)$. Let

$$W_{23}(x, y) = P(V_i \le x \le Y_{2i}, Y_{3i} \le y, \delta_{3i} = 0)$$

$$= p_2^{-1} P(V^* \le x \le C^*, Y_2^* \ge x, Y_3^* \ge C^*, C^* \le y).$$

Hence,

$$W_{23}(x, dy) = p_2^{-1} K(x, dy) S_{23}^Y(x-, y-). \tag{2.4}$$

By (2.3) and (2.4), it follows that $W_{23}(x, dy)/D_{23}(x, y) = K(x, dy)/K(x, y)$.

Thus, for $x < y$, $S_{C^*|V^*}(y - |x)$ can be estimated by

$$\hat{S}_{C^*|V^*}^Y(y - |x) = \prod_{x \le c \le y} \left(1 - \hat{\Lambda}_{C^*|V^*}^Y(dc|x)\right),$$

where $\hat{\Lambda}_{C^*|V^*}^Y(c|x) = \hat{W}_{23}(x, c)/\hat{D}_{23}(x, c)$, $\hat{D}_{23}(x, c) = n^{-1} \sum_{i=1}^n \hat{D}_{23i}(x, c)$,

$\hat{W}_{23}(x, c) = n^{-1} \sum_{i=1}^n \hat{W}_{23,i}(x, c)$, $\hat{D}_{23i}(x, c) = I_{[V_i \le x \le Y_{2i}, Y_{3i} \ge c]}$ and $\hat{W}_{23i} = I_{[V_i \le x \le Y_{2i}, Y_{3i} \le c, \delta_{3i} = 0]}$.

Hence, for $x < y$, $K(x, y)$ can be estimated by $\hat{K}_2(x, y) = \hat{K}_2(x, x)\hat{S}_{C^*|V^*}^Y(y - |x)$. Similarly, since $E[I_i(0, 0, 0)/K(Y_{2i}, Y_{2i})] = p_2$, given $\hat{K}_2(x, y) = [\hat{G}_2(x) - \hat{Q}_2(x)]\hat{S}_{C^*|V^*}^Y(y - |x)$, p_2 can be estimated by

$$\hat{p}_2(\hat{K}_2) = n \left[\sum_{i=1}^{n} \frac{\delta_{2i}}{\hat{K}_2(Y_{2i}, Y_{2i})} \right]^{-1}.$$

Thus, we obtain an IPW estimator

$$\hat{S}_n^Y(t_1, t_2, t_3) = n^{-1}\hat{p}_2(\hat{K}_2) \sum_{i=1}^{n} \frac{I_{[X_{1i} > t_1, X_{2i} > t_2, X_{3i} > t_3, \delta_{2i} = 1]}}{\hat{K}_2(Y_{2i}, Y_{2i} + t_3)}$$

$$= \left[\sum_{i=1}^{n} \frac{\delta_{2i}}{\hat{K}_2(Y_{2i}, Y_{2i})} \right]^{-1} \sum_{i=1}^{n} \frac{I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}}{\hat{K}_2(Y_{2i}, Y_{2i})}.$$

Notice that $\hat{S}_n^Y(0,0,0) = 1$. Let $\delta_{(2n)}$ denote the concomitant of the largest observation X_{2i}. By Lemma 3.3 of Shen (2005), when $\delta_{(2n)} = 1$, $\hat{p}_2(\hat{K}_2) = \hat{p}_2(S_{Y_2^*})$ and $\hat{S}_n^Y(t_1, t_2, t_3)$ is reduced to

$$n^{-1} \sum_{i=1}^{n} \frac{I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}}{\hat{E}_K(Y_{2i}, Y_{2i})},$$

where $\hat{E}_K(x,x) = \hat{E}_G(x) - \hat{E}_Q(x)$, $\hat{E}_G(x) = n^{-1} \sum_{i=1}^{n} \frac{I_{[V_i \le x]}}{\hat{S}_{Y_2^*}(V_i)}$ and $\hat{E}_Q(x) = n^{-1} \sum_{i=1}^{n} \frac{I_{[Y_{2i} \le x](1-\delta_{2i})}}{\hat{S}_{Y_2^*}(Y_{2i})}$.

Lemma 2:

$\sqrt{n}[\hat{S}_n^Y(t_1,t_2,t_3) - S(t_1,t_2,t_3)]$ converges weakly to a mean-zero Gaussian process on $D[(a_{F_1}, b_{F_1}) \times (a_{F_2}, b_{F_2}) \times (a_{F_3}, b_{F_3})]$

Proof: The proof is technical and not reported here.

Remark 2: *Notice that since* $G_e(x) = P(V_i \le x) = p_2^{-1} \int_0^x S_{Y_2^*}(v) G(dv)$, $p_2^{-1} G(x)$ *can be estimated by* $\hat{H}_G(x) = n^{-1} \left[\sum_{i=1}^{n} \frac{I_{[V_i \le x]}}{\hat{S}_{Y_2^*}(V_i)} \right]$. *Similarly,* $p_2^{-1} Q(x)$ *can be estimated by* $\hat{H}_Q(x) = n^{-1} \left[\sum_{i=1}^{n} \frac{I_{[Y_{2i} \le x](1-\delta_{2i})}}{\hat{S}_{Y_2^*}(Y_{2i})} \right]$. *Hence,* $H_K(x,x) = p_2^{-1} K(x,x) = p_2^{-1} P(V^* \le x \le C^*)$ *can be estimated by* $\hat{H}_G(x) - \hat{H}_Q(x)$ *and an alternative estimator is given by*

$$\tilde{S}_n^Y(t_1,t_2,t_3) = n^{-1} \sum_{i=1}^{n} \frac{I_{[X_{1i}>t_1, X_{2i}>t_2, X_{3i}>t_3, \delta_{2i}=1]}}{\hat{H}_K(Y_{2i}, Y_{2i}+t_3)},$$

where $\hat{H}_K(x,y) = \hat{H}_K(x,x) \hat{S}_{C^*|V^*}^Y(y - |x)$. *One disadvantage of the estimator* $\tilde{S}_n^Y$ *is* $\tilde{S}_n^Y(0,0,0) \neq 1$ *while* $\hat{S}_n^Y(0,0,0) = 1$. *However, when the largest observations of* X_{2i}*'s is uncensored,* $\tilde{S}_n^Y$ *is equivalent to* $\hat{S}_n^Y$. *The proof the above argument follows from Shen (2005). Let* $X_{(2n)}$ *denote the largest observations of* X_{2i}*'s and* $\delta_{(2n)}$ *be the concomitant of* $X_{(2n)}$. *By Lemma 3.3 of Shen (2005), when* $\delta_{(2n)} = 1$, $\hat{p}_2(\hat{S}_{Y_2^*}) = \hat{p}_2(\hat{K}_2)$ *and it follows that the two estimators are equivalent to each other.*

Since it is difficult to obtain an analytical expression of the estimated variance of $\hat{S}_n$ or $\hat{S}_n^Y$, we consider the bootstrap method for obtaining the precision estimation of the two proposed estimators. For left-truncated and right-censored data, the bootstrap method was investigated by Wang (1991), Gross and Lai (1996) and Bilker and Wang (1997). Gross and Lai (1996) give an asymptotic justification of the simple bootstrap method for left-truncated and right-censored data. For trivariate case, the simple bootstrap simply draws independent vectors $(X_{1i}^b, \delta_{1i}^b, X_{2i}^b, \delta_{2i}^b, X_{3i}^b, \delta_{3i}^b V_i^b, C_i^b)$, $i = 1, \ldots, n$, from the empirical distribution that puts weight $1/n$ at each of the observations $(X_{1i}, X_{2i}, X_{3i}, V_i, \delta_{1i}, \delta_{2i}, \delta_{3i}, V_i, C_i)$, $i = 1, \ldots, n$.

By repeating this whole process some large number B of times, we have independent estimators $\hat{S}_n^1, \ldots, \hat{S}_n^B$. Then we can estimate the variance of $\hat{S}_n$ by

$$\hat{V}_B(\hat{S}_n(t_1,t_2,t_3)) = \frac{\sum_{b=1}^{B}\left[\hat{S}_n^b(t_1,t_2,t_3) - \sum_{j=1}^{B}\hat{S}_n^j(t_1,t_2,t_3)/B\right]^2}{(B-1)}.$$

Similarly, we can obtain the bootstrap variance estimate of $\hat{S}_n^Y(t_1,t_2,t_3)$. In Section 3, a simulation study is conducted to investigate the performance of the simple bootstrap method.

Chapter 3

Simulation Study

3.1 When the first event is truncated

To investigate the performance of the proposed estimator $\hat{S}_n$, we conduct simulations under the recruiting criterion $T_1^* \geq V^*$. The joint distribution of (T_1^*, T_2^*, T_3^*)'s are generated using Clayton's (1978) bivariate exponential survival function with association parameter β_1 between T_1^* and T_2^*, and association parameter β_2 between T_2^* and T_3^*, i.e. $S_{12}(t_1, t_2) = P(T_1^* > t_1, T_2^* > t_2) = [S_1(t_1)^{1-\beta_1} + S_2(t_2)^{1-\beta_1} - 1]^{1/1-\beta_1}$ and $S_{23}(t_2, t_3) = P(T_2^* > t_1, T_3^* > t_2) = [S_1(t_1)^{1-\beta_2} + S_2(t_2)^{1-\beta_2} - 1]^{1/1-\beta_2}$ with marginal survival functions $S_i(t) = e^{-t}$ $(i = 1, 2, 3)$. The values of β_1 and β_2 are chosen as $\beta_1 = \beta_2 = 2$ such that the Kendall's tau of (T_1^*, T_2^*), (T_2^*, T_3^*) and (T_2^*, T_3^*) are equal to 0.5, 0.5 and 0.31, respectively. The truncation time V^* is exponentially distributed with mean 0.4 and 4 such that the proportion of truncation (denoted by q) is equal to 0.29 and 0.67, respectively. The censoring time $C^* = V^* + D^*$, where D^* is exponentially distributed with mean 4 and 1.5 such that the censoring rates $p_{c1} = P(\delta_{1i} = 0)$ $p_{c2} = P(\delta_{2i} = 0)$ and $p_{c3} = P(\delta_{3i} = 0)$ are equal to $(p_{c1}, p_{c2}, p_{c3}) = (0.20, 0.38, 0.50)$ and $(0.40, 0.67, 0.79)$, respectively. The values of t_1 and t_2 are chosen as the grid points of $t_1 = 0.2, 0.6, 1.6$ and $t_2 = 0.2, 0.6, 1.6$. The sample size is chosen as $n = 100, 200$ and the replication is 1000 times. Based on $B = 500$ bootstrap samples, we also use the bootstrap methods to estimate the standard deviations of $\hat{S}_n$. An approximate $1 - \alpha$ confidence interval is constructed using $\hat{S}_n(t_1, t_2, t_2) \pm z_{\alpha/2}(\hat{V}_B(\hat{S}_n(t_1, t_2, t_3))^{1/2}$. Tables 1 and 2 show the biases, standard deviations (std), bootstrap standard deviation (bstd) and the empirical coverage (cov) of confidence intervals for the points $(t_1, t_2, t_3) = (0.2, 0.2, 0.2)$, (0.2,0.8,0.8),(0.2,1.6,1.6),(0.8,0.2,0.2),(0.8,0.8,0.8),(0.8,1.6,1.6), (1.6,0.2,0.2) and (1.6,0.8,0.8) with corresponding true values equal to 0.72, 0.32, 0.09, 0.43, 0.23, 0.07, 0.19 and 0.12, respectively.

We also conduction simulation study for the estimator $\tilde{S}_n$ pointed out in Remark 1. Simulation results indicate that the estimator $\tilde{S}_n$ has an outlying value about once per 100 replicates. When the outlying values are deleted from the simulated data, the results of $\tilde{S}_n$ are similar to that of $\hat{S}_n$, and not reported here.

3.2 When the second event is truncated

The distribution of (T_1^*, T_2^*, T_3^*) are the same as those used in Section 3.1. The truncation time V^* is exponentially distributed with mean 1 and 3.5 such that the proportion of truncation (denoted by q) is equal to 0.30 and 0.65, respectively. The censoring time $C^* = V^* + D^*$, where D^* is exponentially distributed with mean 4 and 1.5 such that the censoring rates $(p_{c1}, p_{c2}, p_{c3}) = (0.15, 0.34, 0.48)$ and $(0.28, 0.57, 0.74)$, respectively. Tables 3 and 4 show the simulation results.

Based on the results of Tables 1 through 4, we conclude that:

(i) The biases of both $\hat{S}_n$ and $\hat{S}_n^Y$ are small except for the cases when truncation is severe and censoring is heavy, i.e. $(q, p_{c1}, p_{c2}, p_{c3}) = (0.67, 0.40, 0.67, 0.79)$ (Table 2) and $(q, p_{c1}, p_{c2}, p_{c3}) = (0.62, 0.28, 0.57, 0.74)$ (Table 4). Given q, the standard deviations of $\hat{S}_n$ and $\hat{S}_n^Y$ increase as the proportion of censoring increases.

(ii) When $n = 100$, the bootstrap estimators tend to underestimate standard deviations of both estimators, which makes the coverage of 95% confidence intervals based on the bootstrap method smaller than the nominal level. When $n = 200$, the underestimation is improved and the coverage of 95% confidence intervals based on bootstrap method is close to the nominal level for most of the cases considered.

Table 1. Simulation results for bias, std, bstd and cov ($q = 0.29$)

		(p_{c1}, p_{c2}, p_{c3})=(0.2,0.38,0.5)				(p_{c1}, p_{c2}, p_{c3})=(0.4,0.67,0.79)			
(t_1, t_2, t_3)	n	bias	std	bstd	cov	bias	std	bstd	cov
(0.2,0.2,0.2)	100	0.009	0.110	0.103	0.940	-0.022	0.139	0.127	0.937
(0.2,0.2,0.2)	200	-0.001	0.077	0.074	0.948	-0.003	0.096	0.092	0.947
(0.2,0.8,0.8)	100	0.028	0.079	0.073	0.938	0.063	0.135	0.124	0.934
(0.2,0.8,0.8)	200	0.019	0.053	0.049	0.947	0.034	0.104	0.098	0.945
(0.2,1.6,1.6)	100	0.034	0.056	0.052	0.938	0.052	0.094	0.085	0.932
(0.2,1.6,1.6)	200	0.017	0.039	0.036	0.945	0.039	0.078	0.073	0.944
(0.8,0.2,0.2)	100	0.002	0.078	0.072	0.938	-0.042	0.102	0.096	0.936
(0.8,0.2,0.2)	200	-0.008	0.060	0.056	0.947	-0.031	0.089	0.083	0.944
(0.8,0.8,0.8)	100	0.029	0.065	0.060	0.937	0.035	0.109	0.102	0.935
(0.8,0.8,0.8)	200	0.013	0.052	0.050	0.945	0.020	0.092	0.087	0.943
(0.8,1.6,1.6)	100	0.020	0.046	0.042	0.936	0.031	0.076	0.070	0.934
(0.8,1.6,1.6)	200	0.012	0.032	0.030	0.944	0.024	0.066	0.063	0.942
(1.6,0.2,0.2)	100	-0.015	0.051	0.046	0.936	-0.042	0.077	0.072	0.935
(1.6,0.2,0.2)	200	-0.002	0.038	0.036	0.942	-0.028	0.060	0.057	0.943
(1.6,0.8,0.8)	100	0.007	0.043	0.040	0.935	-0.018	0.074	0.068	0.933
(1.6,0.8,0.8)	200	0.008	0.036	0.034	0.942	-0.002	0.064	0.061	0.942

Table 2. Simulation results for bias, std, bstd and cov ($q = 0.67$)

		(p_{c1}, p_{c2}, p_{c3})=(0.2,0.38,0.5)				(p_{c1}, p_{c2}, p_{c3})=(0.4,0.67,0.79)			
(t_1, t_2, t_3)	n	bias	std	bstd	cov	bias	std	bstd	cov
(0.2,0.2,0.2)	100	0.028	0.111	0.104	0.939	0.011	0.164	0.154	0.937
(0.2,0.2,0.2)	200	0.012	0.089	0.084	0.946	0.008	0.132	0.126	0.946
(0.2,0.8,0.8)	100	0.047	0.091	0.085	0.937	0.078	0.150	0.139	0.935
(0.2,0.8,0.8)	200	0.029	0.079	0.074	0.944	0.054	0.109	0.103	0.942
(0.2,1.6,1.6)	100	0.036	0.055	0.051	0.935	0.058	0.114	0.106	0.935
(0.2,1.6,1.6)	200	0.022	0.035	0.032	0.942	0.041	0.076	0.072	0.942
(0.8,0.2,0.2)	100	0.010	0.088	0.081	0.937	-0.021	0.134	0.124	0.934
(0.8,0.2,0.2)	200	-0.003	0.072	0.068	0.946	-0.004	0.087	0.083	0.944
(0.8,0.8,0.8)	100	0.027	0.065	0.060	0.936	0.060	0.115	0.106	0.935
(0.8,0.8,0.8)	200	0.016	0.046	0.042	0.943	0.039	0.087	0.082	0.943
(0.8,1.6,1.6)	100	0.024	0.046	0.041	0.935	0.041	0.090	0.082	0.933
(0.8,1.6,1.6)	200	0.018	0.032	0.030	0.942	0.031	0.061	0.056	0.941
(1.6,0.2,0.2)	100	-0.003	0.055	0.051	0.939	-0.021	0.083	0.076	0.936
(1.6,0.2,0.2)	200	-0.001	0.038	0.036	0.943	-0.016	0.054	0.051	0.942
(1.6,0.8,0.8)	100	0.007	0.047	0.042	0.937	0.015	0.069	0.062	0.932
(1.6,0.8,0.8)	200	-0.001	0.033	0.030	0.942	0.008	0.052	0.047	0.941

Table 3. Simulation results for bias, std, bstd and cov ($q = 0.30$)

		(p_{c1}, p_{c2}, p_{c3})=(0.15,0.34,0.48)				(p_{c1}, p_{c2}, p_{c3})=(0.28,0.57,0.74)			
(t_1, t_2, t_3)	n	bias	std	bstd	cov	bias	std	bstd	cov
(0.2,0.2,0.2)	100	0.034	0.095	0.089	0.939	0.081	0.113	0.105	0.937
(0.2,0.2,0.2)	200	0.016	0.073	0.070	0.947	0.056	0.084	0.079	0.944
(0.2,0.8,0.8)	100	0.067	0.074	0.069	0.939	0.071	0.116	0.108	0.937
(0.2,0.8,0.8)	200	0.038	0.057	0.053	0.945	0.043	0.086	0.081	0.944
(0.2,1.6,1.6)	100	0.056	0.052	0.047	0.936	0.067	0.092	0.086	0.935
(0.2,1.6,1.6)	200	0.038	0.036	0.033	0.944	0.031	0.083	0.079	0.943
(0.8,0.2,0.2)	100	0.026	0.077	0.072	0.937	0.034	0.090	0.084	0.936
(0.8,0.2,0.2)	200	0.011	0.056	0.053	0.946	0.027	0.074	0.071	0.945
(0.8,0.8,0.8)	100	0.052	0.063	0.058	0.937	0.051	0.104	0.096	0.934
(0.8,0.8,0.8)	200	0.034	0.050	0.047	0.945	0.035	0.082	0.077	0.943
(0.8,1.6,1.6)	100	0.043	0.047	0.042	0.934	0.072	0.093	0.086	0.931
(0.8,1.6,1.6)	200	0.029	0.033	0.031	0.943	0.048	0.077	0.072	0.941
(1.6,0.2,0.2)	100	0.011	0.055	0.051	0.937	-0.004	0.080	0.073	0.937
(1.6,0.2,0.2)	200	0.004	0.038	0.035	0.945	0.001	0.060	0.056	0.944
(1.6,0.8,0.8)	100	0.021	0.049	0.044	0.935	0.031	0.085	0.079	0.932
(1.6,0.8,0.8)	200	0.016	0.037	0.034	0.943	0.023	0.067	0.063	0.942

Table 4. Simulation results for bias, std, bstd and cov ($q = 0.62$)

		(p_{c1}, p_{c2}, p_{c3})=(0.15,0.34,0.48)				(p_{c1}, p_{c2}, p_{c3})=(0.28,0.57,0.74)			
(t_1, t_2, t_3)	n	bias	std	bstd	cov	bias	std	bstd	cov
(0.2,0.2,0.2)	100	0.038	0.115	0.106	0.938	0.097	0.129	0.120	0.935
(0.2,0.2,0.2)	200	0.026	0.093	0.089	0.947	0.067	0.094	0.088	0.944
(0.2,0.8,0.8)	100	0.075	0.084	0.078	0.936	0.081	0.127	0.116	0.936
(0.2,0.8,0.8)	200	0.046	0.066	0.062	0.945	0.067	0.091	0.086	0.944
(0.2,1.6,1.6)	100	0.061	0.051	0.047	0.935	0.075	0.120	0.112	0.934
(0.2,1.6,1.6)	200	0.038	0.037	0.034	0.944	0.059	0.083	0.078	0.942
(0.8,0.2,0.2)	100	0.048	0.077	0.071	0.937	0.056	0.113	0.105	0.936
(0.8,0.2,0.2)	200	0.019	0.068	0.064	0.945	0.041	0.074	0.069	0.943
(0.8,0.8,0.8)	100	0.056	0.070	0.064	0.935	0.078	0.113	0.105	0.937
(0.8,0.8,0.8)	200	0.030	0.054	0.051	0.944	0.063	0.075	0.071	0.942
(0.8,1.6,1.6)	100	0.040	0.043	0.039	0.934	0.082	0.088	0.080	0.932
(0.8,1.6,1.6)	200	0.027	0.032	0.029	0.943	0.065	0.066	0.061	0.941
(1.6,0.2,0.2)	100	0.025	0.051	0.047	0.937	0.024	0.070	0.065	0.936
(1.6,0.2,0.2)	200	0.008	0.041	0.039	0.944	0.020	0.051	0.047	0.942
(1.6,0.8,0.8)	100	0.030	0.045	0.041	0.936	0.053	0.074	0.066	0.932
(1.6,0.8,0.8)	200	0.021	0.034	0.031	0.941	0.029	0.056	0.052	0.940

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Discussion

In this article, we have proposed inverse-probability weighted estimators for the estimation of the joint survival function of three successive duration times when the first/second event time is left-truncated. Simulation results indicate that the proposed estimators perform well. Our proposed approach can be extended to the case of more than three successive duration times. In some cases, the calendar times of the initiation E_0 and the subsequent events E_1 and E_2 are only known to fall within intervals. When the first event time is subject to left truncation, T_1^* is subject to left-truncation and double censoring and T_2^* and T_3^* are subject to dependent interval censoring. Further research is needed to extend our approach to deal with such data.

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