Abstract

Since the famous paper written by Kaplan and Meier (1958), survival analysis has become one of the most important fields in statistics. Nowadays it is one of the most important statistical tools in analyzing epidemiological and clinical data including COVID-19 pandemic (Salinas-Escudero et al., 2020). This article reviews some of the most celebrated and important results and methods, including consistency, asymptotic normality, bias and variance estimation, in survival analysis and the treatment is paralle to the monograph *statistical models based on counting processes* (Andersen et al., 1993). Other models and results such as semi-Markov models and the Turnbull’s estimator that jump out of the classical counting process martingale framework are also discussed.

**Keywords:** Survival analysis, Counting processes, Turnbull’s estimator, Asymptotics, Semi-Markov models.

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1. Nonparametric Estimation

1.1 The Nelson-Aalen Estimator

Suppose within a small interval \([t, t + dt]\), one has probability \(\alpha(t)dt\) of death. Hence, the expected number of death with such an interval is \(Y(t)\alpha(t)dt\) where \(Y(t) = \sum_i \mathbb{I}(T_i \geq t)\) counts the number of people at risk at time \(t\). This suggests the decomposition of the counting process:
\[
dN(t) = Y(t)\alpha(t)dt + dM(t)
\]
where the first term is predictable and the second term is the increment of a martingale. After rearrangement of terms, we have
\[
\hat{A}(t) = \int_0^t J(s) \, dN(s)
\]
where \(J(s) = \mathbb{I}(Y(s) > 0)\) and \(0/0 = 0\). This is the famous Nelson-Aalen estimator for cumulative hazard.

1.1.1 Variance Estimator

Let \(A^*(t) = \int_0^t J(s)\alpha(s)ds\) and \(A(t) = \int_0^t \alpha(s)ds\), then
\[
(\hat{A} - A^*)(t) = \int_0^t \frac{J(s)}{Y(s)} (dN(s) - Y(s)\alpha(s)ds).
\]
But \(dN(s) - Y(s)\alpha(s)ds = dM(s)\) where \(M(\cdot)\) is the counting process martingale. Hence, by Doob-Meyer, \(\hat{A} - A^*\) is a mean zero martingale. A natural variance estimator is the plug-in estimate of the compensator, i.e., replacing \(A\) with the NA-estimator in the following representation:
\[
\langle \hat{A} - A^* \rangle(t) = \int_0^t \frac{J(s)}{Y(s)} dA(s).
\]
Hence, the estimator is \(\hat{\sigma}^2(t) = \int_0^t \frac{J(s)}{Y(s)^2} dN(s)\).

1.1.2 Bias

Clearly, we have
\[
\mathbb{E}\hat{A}(t) = \int_0^t \mathbb{E}\left( \frac{J(s)}{Y(s)} (Y(s)dA(s) + dM(s)) \right)
\]
\[
= \int_0^t \mathbb{E}(J(s))dA(s)
\]
\[
= \int_0^t \mathbb{P}(Y(s) > 0)dA(s)
\]
Hence, the bias is
\[
\mathbb{E}\hat{A}(t) - A(t) = \int_0^t \mathbb{P}(Y(s) = 0)\alpha(s)ds.
\]
1.1.3 Consistency

Theorem 1 (Consistency of NA) Suppose \( \inf_{s \in [0,t]} Y(s) \to_p \infty \) as \( n \to \infty \) and assume that
\[
A(t) = \int_0^t \alpha(t) dt < \infty,
\]
then we have
\[
\lim_{n \to \infty} \mathbb{P}( \sup_{s \in [0,t]} |\hat{A}(s) - A(s)| > \epsilon) = 0
\]
where \( \epsilon > 0 \) and \( \hat{A} \) is the NA estimator.

Proof We have \( (\hat{A} - A^*)(s) = \int_0^t \frac{J(s)}{Y(s)} dM(s) \), a martingale. By Lenglart’s inequality,
\[
\mathbb{P} \left( \sup_{s \in [0,t]} |\hat{A} - A^*(t)| > \eta \right) \leq \frac{\delta}{\eta^2} + \mathbb{P} \left( \langle \hat{A} - A^* \rangle(t) > \delta \right)
\]
for any positive small \( \eta \) and \( \delta \). But the compensator is \( \int_0^t \frac{J(s)}{Y(s)} dA(s) \), which goes to 0 in probability by dominated convergence theorem. Further,
\[
\sup_s |A^*(s) - A(s)| = \sup_s |\int_0^s (J(u) - 1) \alpha(u) du|
\]
and the integrand is bounded by \( \alpha(u) \) so that Gill’s lemma 35 applies.

1.1.4 Asymptotic Normality

Theorem 2 (AN of NA) Suppose \( F(s) \), the cdf of \( T_i \) satisfies \( F(s) < 1 \) for \( s \leq t \) and
\[
\sup_{s \in [0,t]} \left| \frac{1}{n} Y(s) - 1 + F(s) \right| \to_p 0,
\]
then we have
\[
\sqrt{n}(\hat{A} - A) \to_d U
\]
where \( U \) is a Gaussian martingale with \( U(0) = 0 \), \( \text{cov}(U(s), U(t)) = \sigma(s \wedge t) \), where \( \sigma^2(s) = \int_0^s \frac{\alpha(u)}{1 - F(s-u)} du \). In particular, if we have independent censoring and both \( X_i \) and \( U_i \) (survival time and censoring time) are absolutely continuous, then \( \sigma^2(s) = \int_0^s \frac{p(u)}{S(u)G(u)} du \) where \( p \) is the density of \( X \) and \( S, G \) are survival functions of \( X \) and \( U \), respectively.

1.1.5 Simultaneous Confidence Bands

Let \( q \) be a continuous and non-negative function on \([s,t]\) where \( 0 \leq s < t \leq \tau \). Then we have
\[
\left( \frac{\sqrt{n}(\hat{A} - A)}{1 + n\hat{\sigma}^2} \right)^q \left( \frac{n\hat{\sigma}^2}{1 + n\hat{\sigma}^2} \right) \to_d \left( \frac{U}{1 + \sigma^2} \right)^q \left( \frac{\sigma^2}{1 + \sigma^2} \right)
\]
on $\mathcal{D}[s, t]$ where $U$ is the Gaussian martingale and
\[
\hat{\sigma}^2(t) = \int_0^t \frac{J(s)}{Y(s)^2} dN(s)
\]
is the predictable variation of the martingale $\hat{A} - \int_0^t \alpha(s) J(s) ds$.

Note the processes $(\frac{U}{1 + \sigma^2}) q \circ \left( \frac{\sigma^2}{1 + \sigma^2} \right)$ and $(qW^0) \circ \left( \frac{\sigma^2}{1 + \sigma^2} \right)$ have the same distribution where $W^0$ is a standard Brownian bridge. Hence, the $100(1 - \alpha)\%$ confidence band for $A$ on $[s, t]$ is
\[
\hat{A}(s) \pm K_{q, \alpha}(c_1, c_2) \frac{1 + n\hat{\sigma}^2(s)}{\sqrt{nq(\frac{n\hat{\sigma}^2(s)}{1 + n\hat{\sigma}^2(s)})}}
\]
with $K_{q, \alpha}(c_1, c_2)$ the upper $\alpha$-percentile of the distribution of
\[
\sup_{x \in [c_1, c_2]} |q(x)W^0(x)|.
\]
The choice $q(x) = x(1 - x)$ is known as the equal precision (EP) band and $q(x) = x$ is referred as the Hall-Wellner (HW) band.

### 1.2 The Kaplan-Meier (KM) Estimator

#### Definition 3 (Kaplan-Meier (KM))

Let $\hat{A}$ be the Nelson-Aalen estimator for the integrated hazard rate function. Then the Kaplan-Meier estimator for the survival function is
\[
\hat{S}(t) = \prod_{s \leq t} \left( 1 - d\hat{A}(s) \right)
\]
which can be written as
\[
\hat{S}(t) = \prod_{s \leq t} \left( 1 - \frac{N(\Delta s)}{Y(s)} \right).
\]

#### 1.2.1 Variance Estimator: The Greenwood’s Formula

Let $J(t) = I(Y(t) > 0)$ and $A^*(t) = \int_0^t J(u) dA$ so that $A$ may have jumps. Define $S^*(t) = \prod_{0 \leq s \leq t} (1 - dA^*(t))$. Then by the Duhamel equation and Doob-Meyer for stochastic integration, we have a mean zero martingale
\[
\frac{\hat{S}(t)}{S^*(t)} - 1 = - \int_0^t \frac{\hat{S}(s) - \hat{S}(s)}{S^*(s)} d(\hat{A} - A^*)(s) = - \int_0^t \frac{\hat{S}(s) - \hat{S}(s)}{S^*(s)} dM(s)
\]
Hence, by second part of Doob-Meyer the compensator is (ABKG, p258)
\[
\left\langle \frac{\hat{S}(t)}{S^*(t)} - 1 \right\rangle(t) = \int_0^t \left\{ \frac{\hat{S}(s) - \hat{S}(s)}{S^*(s)} \right\}^2 \frac{J(s)}{Y(s)} (1 - \Delta A(s)) dA(s)
\]
This suggests a natural estimator of $Var(\frac{\hat{S}(t)}{S^*(t)})$ by plug-in $S^*(t) = \hat{S}(t)$. After some algebra, we have
\[
\hat{\sigma}^2(t) = \int_0^t \frac{1}{Y(s)(Y(s) - \Delta N(s))} dN(s)
\]
and the following estimator for the (pointwise) variance of \( \hat{S}(t) \):

\[
\hat{\text{Var}}(\hat{S}(t)) = (\hat{S}(t))^2 \bar{\sigma}^2(t).
\]

This is the famous Greenwood's formula for Kaplan-Meier estimate.

1.2.2 Bias

Under random censorship (i.e., \( X \) and \( U \) are independent) with distribution functions \( 1 - S \) and \( G \) respectively, then we have

\[
0 \leq \mathbb{E}\hat{S}(t) - S(t) \leq (1 - S(t)) \{1 - S(t)(1 - G(t))\}^n
\]

where \( n \) is the sample size. This can be verified using the facts that \( \hat{S} \) and \( S^* \) are constant to the right of maximum of \( X_i \wedge U_i \).

Further, if \( G \) is continuous, then we have

\[
0 \leq \mathbb{E}\hat{S}(t) - S(t) \leq (1 - S(t)) \exp\{-\mathbb{E}Y(t)\}
\]

where \( Y(t) \) is the risk process.

1.2.3 Consistency

**Theorem 4 (Consistency of KM)** Assume \( \inf_{s \in [0,t]} Y(s) \to_p \infty \) and \( S(t) > 0 \), then as \( n \to \infty \), we have

\[
\sup_{s \in [0,t]} |\hat{S}(s) - S(s)| \to_p 0.
\]

The proof is similar to that of NA estimator, but we could also apply continuous mapping theorem by the continuity of product integrals, see page 114 of ABGK.

1.2.4 Asymptotic Normality

Consider a random censorship model with true survival distribution \( X \sim S(t) \) and censoring survival distribution \( U \sim G(t) \), both are absolutely continuous. In practice, we observe \( \tilde{X} = X \wedge U \) and \( X \perp \perp U \).

**Theorem 5 (AN of KM)** Let \( A(t) = \int_0^t \alpha(s)ds \) where \( \alpha(s) = -\frac{dS(t)/dt}{S(t)} \) and

\[
\sigma^2(t) = \int_0^t \frac{\alpha(u)}{S(u)G(u)}du
\]

and assume that

- \( A(t) < \infty \).
- \( \sup_{s \in [0,t]} \frac{1}{n} Y(s) - F(s)G(s) \to_p 0 \) where \( Y(s) \) is defined as usual.

Then we have

\[
\sqrt{n}(\hat{S} - S) \to_d -S \cdot U
\]

on \( \mathcal{D}[0,t] \) where \( U \) is a Gaussian martingale with \( U(0) = 0 \) and covariance \( \text{Cov}(U(s), U(t)) = \sigma^2(s \wedge t) \). Further, \( n\bar{\sigma}^2(s) \) is uniformly weak consistent in \( [0,t] \) where \( \bar{\sigma}^2(t) \) is the Greenwood's estimator.
**Proof** The proof is a simple application of functional delta method, see lemma 37 and example 17. Indeed, we have 
\[ S(t) = \int_{s \in [0,t]} (1 - dA) \] so that
\[ (d\phi(A) \cdot U)(t) = - \int_0^t S(s-')U(ds) \frac{S(t)}{S(s)} = -S(t) \cdot U(t) \]
where the second equality follows from the absolute continuity of \( S \) and \( A \) and \( U \) is the Gaussian martingale. Next, by AN of NA, i.e.,
\[ \sqrt{n}(\hat{A} - A) \to_d U \]
and functional delta method, we have the desired result. The uniform consistency of \( n\hat{\sigma}^2(s) \) follows from Rebolledo’s martingale central limit theorem. □

1.2.5 Simultaneous Confidence Bands

The previous theorem on AN of KM can be applied to construct CIs for \( S(t) \). That is,
\[ \hat{S}(t) \pm c_{\alpha/2} \hat{\sigma}(t) \]
is a linear asymptotic 100(1 - \( \alpha \))% interval where \( c_{\alpha/2} \) is the upper \( \alpha/2 \) quantile of \( N(0,1) \). However, this interval is rarely used in practice and transformation is needed. One is the Kalbfleisch-Prentice’s log-log transformation, i.e., \( g(S(t)) = \log(-\log(S(t))) \) and the other is the Thomas-Grunkemeier’s square root arcsin transformation, i.e., \( g(S(t)) = \arcsin(\sqrt{S(t)}) \). The usual delta method applies in this case and the pointwise CIs can be derived by reverting the transformation. One can construct CB from the fact that \( U \) has the same distribution as \( W \circ \sigma \) where \( W \) is the Brownian motion on \([0, t]\). Similar to the CB for NA estimator, one can also use the fact that
\[ \left( \frac{U}{1 + \sigma^2} \right) q \circ \left( \frac{\sigma^2}{1 + \sigma^2} \right) =_d (qW^0) \circ \left( \frac{\sigma^2}{1 + \sigma^2} \right) \]
where \( q \) is a continuous and non-negative function on \([s, t]\) and \( W^0 \) is the standard Brownian bridge. Hence, the 100(1 - \( \alpha \))% equal precision (EP) band is
\[ \hat{S}(s) \pm d_\alpha(\hat{c}_1, \hat{c}_2)\hat{\sigma}(s) \]
where for \( i = 1, 2 \),
\[ \hat{c}_i = \frac{n\hat{\sigma}^2(t_i)}{1 + n\hat{\sigma}^2(t_i)} \]
and \( d_\alpha(\hat{c}_1, \hat{c}_2) \) is the upper \( \alpha \) quantile of the distribution of
\[ \sup_{c_1 \leq x \leq c_2} |W^0(x)\sqrt{x(1 - x)}|. \]
The 100(1 - \( \alpha \))% Hall-Wellner (HW) band is
\[ \hat{S}(s) \pm \frac{1 + n\hat{\sigma}^2(s)}{\sqrt{n}} e_\alpha(\hat{c}_1, \hat{c}_2)\hat{\sigma}(s) \]
where \( e_\alpha(\hat{c}_1, \hat{c}_2) \) is the upper \( \alpha \) quantile in the distribution of
\[ \sup_{c_1 \leq x \leq c_2} |W^0(x)|. \]
1.2.6 Quantile Estimation: Brookmeyer-Crowley

- Let $Q(p)$ be the quantile function, then it is a functional of distribution function $F$, i.e., $Q(p) = \phi(F) = \phi(1 - S) = \inf\{x : F(x) \geq p\}$. Then by functional delta method, we have
  \[
  \sqrt{n}(\hat{Q}(p) - Q(p)) \rightarrow_d \frac{(1 - p)U(Q(p))}{f(Q(p))}
  \]
  where $\hat{Q}(p) = \phi(1 - \hat{S})$ and $f$ is the density function of $F$. Using the fact that $U(\cdot)$ is a Gaussian martingale, we have
  \[
  \sqrt{n}(\hat{Q}(p) - Q(p)) \rightarrow_d N\left(0, \frac{(1 - p)^2 \sigma^2(Q(p))}{f(Q(p))^2}\right)
  \]
  where $\sigma^2(t) = \int_0^t \frac{\alpha(u)}{S(u)G(u)} du$ as in theorem 5 (ABGK, p275-277).

- In practice, if the goal is to construct a CI for $Q(p)$, then we use the Brookmeyer-Crowley’s method (Li (2021)):
  \[
  \left\{ u : \left| g(\hat{S}(u)) - g(1 - p) \right| \leq c_{\alpha/2} \frac{|g'(\hat{S}(u))|\hat{S}(u)\hat{S}(u)}{g'(\hat{S}(u))\hat{S}(u)\hat{S}(u)} \right\}
  \]
  where $g(\cdot)$ is a suitable transformation, say $\log(-\log(\cdot))$ or arcsin$(\sqrt{\cdot})$ and $c_{\alpha/2}$ is the quantile of $N(0,1)$.

- If the goal is to estimate the variance of $\hat{Q}(p)$, then we need to smooth the NA estimator to get an estimate of $f(Q(p))$, see definition 11.

1.3 The Aalen-Johansen (AJ) Estimator

Definition 6 (Aalen-Johansen (AJ)) Let $A$ be the intensity measure of a Markov process $X$ and let $P$ be the transition matrix. Let
\[
\hat{A}_{hj}(t) = \int_0^t J_h(s)\frac{Y_h(s)}{Y_h(s)} dN_{hj}(s)
\]
be the Nelson-Aalen estimator for $A_{hj}, h \neq j$ and let $\hat{A}_{hh}(t) = \sum_{j \neq h} \hat{A}_{hj}$. Then the Aalen-Johansen estimator for the transition matrix is
\[
\hat{P}(s,t) = \prod_{(s,c]} \left( I + d\hat{A}(u) \right)
\]
where $\hat{A} = \{\hat{A}_{hj}\}$.

1.3.1 Complete Observation

Lemma 7 Suppose no censoring occurs and we have complete observation for all $t \in \mathcal{T}$. Define $Y(t)$ as the row vector $(Y_1(t), \cdots, Y_k(t))$, then we have
\[
Y(t+) = Y(s+)\hat{P}(s,t)
\]
where $\hat{P}$ is the AJ estimator.
**Proof** We have \( Y_h(t+) = Y_h(0+) + \sum_{j \neq h} N_{jh}(t) - \sum_{j \neq h} N_{hj}(t) \). Next, note that
\[
\hat{P}(s, t) = \prod_{s < u \leq t} \left( I + \Delta \hat{A}(u) \right)
\]
and we can assume \( s = 0 \). Then it follows from some algebra.

1.3.2 Bias and Covariance Estimator
Recall that \( A^*_h = \int_0^t j_h(u) \alpha_h(u) du \). Define
\[
P^*(s, t) = R(s, t] (I + \delta A^*(u))
\]
Then by the Duhamel’s equation and some boundness arguments, one can show that
\[
M(s, t) = \hat{P}(s, t) P^*(s, t)^{-1} - I
\]
is a \( k \times k \) martingale. If \( P(Y_h(u) = 0) \) is small for \( u \in (s, t] \), then the AJ estimator is almost unbiased. A potential covariance estimator of \( \hat{P} \) is
\[
\hat{Cov}(\hat{P}(s, t)) = \int_s^t \hat{P}(u, t)^T \otimes \hat{P}(s, u) d[\hat{A} - A^*(u)] \hat{P}(u, t) \otimes \hat{P}(s, u)^T
\]
where \([\cdot, \cdot]\) is the quadratic variation of a local square integrable martingale. For details, see ABGK, p292-293.

1.3.3 Large Sample Properties
- The uniform consistency of AJ estimator is a direct consequence of uniform consistency of NA estimator and continuity of product integral. In short, we have \( \sup_{u \in [s, t]} \| \hat{P}(s, u) - P(s, u) \| \to_p 0 \).
- Similarly, by AN of NA and Hadamard differentiability of product integral and functional delta method, we have
\[
\sqrt{n} \left( \hat{P}(s, \cdot) - P(s, \cdot) \right) \to_d \int_s^t P(s, u) dU(u) P(u, \cdot)
\]
where \( U = (U_{hj}) \) is a \( k \times k \) matrix-valued process. For \( h \neq j \), \( U_{hj} \) are independent Gaussian martingales with \( U_{hj}(0) = 0 \) and \( Cov(U_{hj}(s), U_{hj}(t)) = \sigma^2(s \wedge t) \) and \( U_{hh} = -\sum_{j \neq h} U_{hj} \).

1.4 The Dabrowska Estimator
1.4.1 Bivariate Survival Times
Let \( T = (T_1, T_2) \) be a pair of nonnegative random variables and
\[
S(s, t) = P(T_1 > s, T_2 > t)
\]
be the corresponding joint survival function.
Definition 8 (Bivariate cumulative hazard) A bivariate cumulative hazard function is defined as

\[ \Lambda(s, t) = (\Lambda_{10}(s, t), \Lambda_{01}(s, t), \Lambda_{11}(s, t)) \]

where

\[ \Lambda_{11}(ds, dt) = \frac{P(T_1 \in ds, T_2 \in dt)}{P(T_1 \geq s, T_2 \geq t)} = \frac{S(ds, dt)}{S(s- , t-)} \]
\[ \Lambda_{10}(ds, t) = \frac{P(T_1 \in ds, T_2 > t)}{P(T_1 \geq s, T_2 > t)} = \frac{-S(ds, t)}{S(s- , t)} \]
\[ \Lambda_{01}(s, dt) = \frac{P(T_1 > s, T_2 \in dt)}{P(T_1 > s, T_2 \geq t)} = \frac{-S(ds, t)}{S(s, t-)} \]

subject to the initial conditions \( \Lambda_{10}(0, t) = \Lambda_{01}(s, 0) = \Lambda_{11}(0, 0) = 0 \).

1.4.2 The Dabrowska Representation and Estimator

Theorem 9 (The Dabrowska Representation) For \((s, t)\) such that \(S(s, t) > 0\), we have

\[ S(s, t) = \prod_{u \leq s} (1 - \Lambda_{10} (du, 0)) \prod_{v \leq t} (1 - \Lambda_{01} (0, dv)) \]
\[ \times \prod_{u \leq s, v \leq t} (1 - L(du, dv)) \]

where

\[ L(du, dv) = \frac{\Lambda_{10} (du, v-) \Lambda_{01} (u-, dv) - \Lambda_{11} (du, dv)}{\{1 - \Lambda_{10} (\Delta u, v-)\} \{1 - \Lambda_{01} (u-, \Delta v)\}} \]

and the first two factors are indeed \(S(s, 0)\) and \(S(0, t)\). The bivariate product integral should be taken as the limit when both \(\max_i |u_i - u_{i-1}|\) and \(\max_i |v_i - v_{i-1}|\) goes to 0.

Let \(\delta_j, j = 1, 2\) be censoring indicators, \((T_{1i}, T_{2i}, \delta_{1i}, \delta_{2i})\) be the observed data for subject \(i\), and define counting processes and risk processes

\[ N_{11}(s, t) = \sum_{i=1}^{n} I(T_{1i} \leq s, T_{2i} \leq t, \delta_{1i} = 1, \delta_{2i} = 1) \]
\[ Y_{11}(s, t) = \sum_{i=1}^{n} I(T_{1i} \geq s, T_{2i} \geq t) \]
\[ N_{10}(s|t) = \sum_{i=1}^{n} I(T_{1i} \leq s, T_{2i} \geq t, \delta_{1i} = 1), \ Y_{10}(t) = \sum_{i=1}^{n} I(T_{1i} \geq s) \]
\[ N_{01}(t|s) = \sum_{i=1}^{n} I(T_{1i} \geq s, T_{2i} \leq t, \delta_{2i} = 1), \ Y_{01}(t) = \sum_{i=1}^{n} I(T_{2i} \geq t). \]
Example 1 (The Dabrowska Estimator Dabrowska (1988)) Let \( \hat{S}(s,0) \) and \( \hat{S}(0,t) \) be the univariate KM estimator, \( \hat{\Lambda}_{10}(s,t) \) and \( \hat{\Lambda}_{01}(s,t) \) be the univariate NA estimator associated with pre-defined counting processes and risk processes. Further define
\[
\hat{\Lambda}(s,t) = \int_0^t \int_s^t \frac{dN_{11}(s,t)}{Y_{11}(s,t)}
\]
as the bivariate Nelson-Aalen estimator (ABGK, p702). Then the Dabrowska estimator is defined as
\[
\hat{S}(s,t) = \hat{S}(s,0) \hat{S}(0,t) \prod_{u \leq s, v \leq t} \left( 1 - \hat{L}(du, dv) \right)
\]
by plug-in all the NA-type estimates.

1.5 The Turnbull’s Estimator

1.5.1 Interval Censored Data

Interval Censored Data Let \( X_1, X_2, \cdots \) be a sequence of i.i.d. survival times. In practice, we only observe the interval censored data:
\[
\{(L_i, R_i) : i = 1, 2, \cdots, n\}
\]
where \( 0 \leq L_i < R_i \leq \infty \) are left- and right- endpoint of an observation. That is, we only know that \( X_i \in (L_i, R_i] \) instead of the exact values.

- The case I interval censoring refers to either \( L_i = 0 \) or \( R_i = \infty \) and it is also called the current status data.
- The case II interval censoring refers to \( L_i > 0 \) and \( R_i < \infty \).

Importantly, counting process approaches do not apply in this case because we do not have exact information to form a counting process.

Though counting process approaches do not apply, we can formulate the likelihood function of our observation:
\[
\mathcal{L}(S) = \prod_{i=1}^n (S(L_i) - S(R_i))
\]
where \( S \) is the survival function of \( X \). If \( L_i = R_i \) for some \( i \), we replace \( S(L_i) \) with its the left limit \( S(L_i^-) \) so that the likelihood assigns probability mass to \( 1 - S(\Delta R_i) \). The nonparametric maximum likelihood estimation (NPMLE) is defined as
\[
\hat{S} = \arg \max_S \log \mathcal{L}(S).
\]

Following Sun (2006), let \( \{s_j\}_{i=0}^m \) be the unique ordered elements of \( \{0, L_i, R_i : i = 1, \cdots, n\} \) (see figure) and define
\[
\alpha_{ij} = \mathbb{I}(s_j \in (L_i, R_i])
\]
\[
p_j = S(s_j) - S(s_{j-1})
\]
for \( i = 1, \ldots, n \) and \( j = 1, \ldots, m \). If \( L_i = R_i \) for some \( i \), i.e., an exact observation, then we replace \( \alpha_{ij} \) by \( \alpha_{ij} = \mathbb{1}(s_j \in [L_i, R_i]) \) so that \( \alpha_{ij} = 1 \) if \( s_j = L_i \). Hence, the likelihood \( \mathcal{L}(S) \) can be written as
\[
\mathcal{L}(S) = \prod_{i=1}^{n} \left( \sum_{j=1}^{m} \alpha_{ij} p_j \right)
\]
and NPMLE refers to the probability vector \( \mathbf{p} = (p_1, \ldots, p_m)^T \).

### 1.5.2 The Turnbull’s Interval and Estimator

If \( m \) is large, then finding \( \mathbf{p} \) that maximizes \( \mathcal{L}(S) \) is computationally intractable or inefficient. However, if we know in advance that some (or many) \( p_j \) are 0, then the computation will be reduced by a lot.

**Lemma 10 (Turnbull’s intervals)** The \( p_j \) can be nonzero only if \( s_{j-1} = L_i \), \( s_j = R_k \) for some \( i \) and \( k \).

- The resulting intervals \((s_{j-1}, s_j)\) for nonzero \( p_j \) are referred as the **Turnbull’s intervals**.
- The resulting estimator \( \hat{\mathbf{p}} = (\hat{p}_1, \ldots, \hat{p}_m)^T \) is termed as the **Turnbull’s estimator**.

The Turnbull’s estimator is not unique in general and should be solved by numerical algorithms such as EM-ICM Anderson-Bergman (2017) and bat algorithm Yang (2013).

To determine if a candidate estimate \( \hat{\mathbf{p}} \) is the maximizer, one uses the Lagrange multiplier criterion, which is derived from graph theory Gentleman and Geyer (1994) and general mixture maximum likelihood theory HNING et al. (1996). Specifically, define
\[
d_j(\mathbf{p}) = \frac{\sum_{i=1}^{n} \alpha_{ij}}{\sum_{l=1}^{m} \alpha_{il} p_l}
\]
for \( j = 1, \ldots, m \). Then \( \hat{\mathbf{p}} \) is the Turnbull’s estimator or NPMLE if and only if \( d_j(\hat{\mathbf{p}}) \leq n \) for all \( j \).

### 1.6 Applications and Examples

#### 1.6.1 Smoothed Nelson-Aalen (SNA) Estimator

Smoothed Nelson-Aalen (SNA) Estimator

**Definition 11 (SNA)** Let \( \tilde{A}(t) \) be the NA estimator of \( A(t) = \int_0^t \alpha(s) \, ds \), then the **smoothed Nelson-Aalen (SNA) estimator** of \( \alpha(t) \) is defined by
\[
\hat{\alpha}(t) = \frac{1}{b} \int_T K\left(\frac{t-s}{b}\right) \, d\tilde{A}(s)
\]
where the kernel function \( K \) is bounded and vanishes outside \([-1, 1]\) and has integral 1. The hyperparameter \( b \) is referred as the bandwidth or window size.

An SNA can be applied to any AN estimator so that we get an estimate of the hazard function.
1.6.2 Random Sample from A Finite State Markov Process

- Let $X_1(\cdot), X_2(\cdot), \ldots, X_n(\cdot)$ be $n$ i.i.d. copies of $(X(t), t \in \mathcal{T})$, a Markov process with finite state space $\mathcal{S}$, transition intensities $\alpha_{hj}(t), h \neq j$ and initial distribution $p_h = \mathbb{P}(X(0) = h)$. Denote the transition probabilities as $P_{hj}(s, t)$.

- Define an aggregated counting process $(N_{hj}, h \neq j)$, with each component counts the total number of direct transitions for $X_1(\cdot), \ldots, X_n(\cdot)$ from state $h$ to $j$ in $[0, t]$.

- Further, let $Y_h(t) = \sum_{i=1}^{n} \mathbb{I}(X_i(t-\cdot) = h)$ so that $Y_h(t) \sim \text{Binomial}(n, P_{h}(t-))$, $h \in \mathcal{S}$ where $P_{h}(t-) = \sum_{j \in \mathcal{S}} p_j P_{jh}(t-)$. In our case, $P_{h}(t-) = P(t)$.

- By theorem 42, $(N_{hj}, h \neq j)$ is a multivariate counting process with intensity process $(\lambda_{hj}, h \neq j)(t) = \alpha_{hj}(t)Y_h(t), h \neq j$ satisfying the multiplicative intensity model.

- We estimate each cumulative intensity $A_{hj}(t) = \int_0^t \alpha_{hj}(s)ds$ by the NA-estimator (see the definition of AJ-estimator):

$$\hat{A}_{hj}(t) = \int_0^t J_h(s) dN_{hj}(s)$$

where, as usual, $J_h(s) = \mathbb{I}(Y_h(s) > 0)$.

- For any $s$ and $t$ such that $P_h(u) > 0$ for any $h \in \mathcal{S}$ and $t \in [s, t]$, we have that $Y_h(u) \to_p \infty$ and hence,

$$\sup_{u \in [s,t]} |\hat{A}_{hj}(t) - A_{hj}(t)| \to_p 0 \text{ as } n \to \infty.$$

- A somewhat lengthy argument (ABGK, p197-198) shows that

$$(\sqrt{n}(\hat{A}_{hj} - A_{hj}); h \neq j) \to_d (U_{hj}; h \neq j)$$

on $[s, t]$, where the $U_{hj}$ are independent Gaussian martingales with $U_{hj}(0) = 0$ and $\text{Cov}(U_{hj}(u_1), U_{hj}(u_2)) = \int_{u_1}^{u_2} \alpha_{hj}(v)P_{h}(v)dv$.

1.6.3 Excess Mortality Models

- Suppose the intensity process of the individual counting process is

$$\lambda_i(t) = (\gamma(t) + \mu_i(t))Y_i(t)$$

where $\mu_i(t)$ is a known deterministic function (say, male or female population hazard) and we are interested in estimating

$$\Gamma(t) = \int_0^t \gamma(s)ds$$

the cumulative excess mortality.
• Define
  \[ Y^\mu(t) = \sum_{i=1}^{n} \mu_i(t) Y_i(t), \quad Y(t) = \sum_{i=1}^{n} Y_i(t) \]
as the aggregated population hazard and risk process, respectively.

• By Doob-Meyer theorem, we have
  \[ M(t) = N(t) - \int_0^t Y^\mu(s) ds - \int_0^t \gamma(s) Y(s) ds, \]
a local square integrable martingale. Hence, a natural NA-type estimator for \( \Gamma(t) \) is
  \[ \hat{\Gamma}(t) = \int_0^t J(s) dN(t) - \int_0^t Y^\mu(s) \frac{Y(s)}{Y(t)} ds. \]

• By the product integral transformation, we have
  \[ \prod_{0}^{t} (1 - d\hat{\Gamma}(s)) = \hat{S}(t) \exp \left( - \int_0^t \frac{Y^\mu(s)}{Y(t)} ds \right) \]
  where \( \hat{S}(t) \) is the KM estimator and LHS is called the corrected survival function.

1.6.4 Competing Risks Model

Let \( 0 < T_1 < T_2 < \cdots < T_m \leq t \) be the observed death times, then the AJ estimator of the transition probability matrix \( P(0, t) = (P_{ij}(0, t)) \) is

\[ \hat{P}(0, t) = \prod_{i=1}^{m} (I + \Delta A(T_i)) \]

where

\[ \Delta A(T_i) = \begin{bmatrix}
-\sum_{j=1}^{k} \frac{\Delta N_{ij}(T_i)}{Y_0(T_i)} & \frac{\Delta N_{i01}(T_i)}{Y_0(T_i)} & \cdots & \frac{\Delta N_{i0k}(T_i)}{Y_0(T_i)} \\
0 & 0 & 0 & \cdots & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \cdots & 0
\end{bmatrix} \]

and it is easily seen that \( P_{00}(0, t) = \prod_{i=1}^{m} \left( 1 - \frac{\sum_{j=1}^{k} \Delta N_{0j}(T_i)}{Y_0(T_i)} \right) \) is the usual KM estimator. The above known as a competing risks model.

For \( j = 1, 2, \cdots, k \), by induction we have

\[ \hat{P}_{0j}(0, t) = \sum_{i=1}^{m} \left\{ \prod_{h<i} \left( 1 - \frac{\sum_{t=1}^{k} \Delta N_{0h}(T_h)}{Y_0(T_h)} \right) \right\} \frac{\Delta N_{0j}(T_i)}{Y_0(T_i)} \]

\[ = \int_0^t \hat{P}_{00}(s, u-) d\hat{A}_{0j}(u). \]
It aligns with what Dr. Li has taught us in 215 Li (2021):

\[
CIF_j(t) = F_j(t) = \int_0^t S(s) \lambda_j(s) ds
\]

where \( CIF_j \) or \( F_j \) is the cause-specific incidence function, \( S(s) \) is the survival function for time-to-failure and \( \lambda_j \) is the cause-specific hazard function.
2. Nonparametric Hypothesis Testing

2.1 One-Sample Tests

Consider a sequence of univariate counting process \((N^{(n)}(t); t \in T)\) with intensity process \(\alpha(t)Y^{(n)}(t)\) (I drop the superscript \((n)\) in the following). We want to test

\[ H_0 : \alpha(s) = \alpha_0(s), s \in [0, t] \]

and this is equivalent to test

\[ H_0 : A(s) = A_0(s), s \in [0, t] \]

under the assumption \(A(t) < \infty\) for \(t \in T\).

Recall that under \(H_0\),

\[
\hat{A}(t) = \int_0^t \frac{J(s)}{Y(s)} dN(s)
\]

\[
A_0^*(t) = \int_0^t \alpha_0(s)J(s)ds
\]

\[
\langle \hat{A} - A_0^* \rangle(t) = \int_0^t \frac{J(s)}{Y(s)} \alpha_0(s)ds
\]

The test statistic is based on the martingale (31)

\[
Z(t) = \int_0^t K(s) d(\hat{A} - A_0^*)(s)
\]

where \(K\) is any locally bounded predictable non-negative stochastic process satisfying \(K(s) = 0\) if \(Y(s) = 0\).

2.1.1 One Sample Log-rank Statistic

The test statistic is \((t \text{ is large enough})\)

\[
T(t) = \frac{Z(t)}{\sqrt{\langle Z \rangle(t)}}
\]

where \(\langle Z \rangle(t) = \int_0^t K^2(s)Y(s)\alpha_0(s)ds\). The special case \(K(s) = Y(s)\) leads to the one-sample log-rank statistic, i.e.,

\[
T(t)^2 = \frac{(N(t) - E(t))^2}{E(t)}
\]

where \(E(t) = \int_0^t \alpha_0(s)Y(s)ds = \langle Z \rangle(t)\). The ratio \(\frac{N(t)}{E(t)}\) is called the standardized mortality ratio (SMR) in epidemiology. Finally, Fleming and Harrington (1982) also suggested that \(K(t) = Y(t)S_0(t)^\rho\) where \(S_0(t) = \exp(-A_0(t))\).
2.2 k-Sample Tests

Consider a sequence of $k$-variate counting process $\mathbf{N} = (N_1^{(n)}, \cdots, N_k^{(n)})$ with intensity process $\mathbf{\Lambda} = (\lambda_1, \cdots, \lambda_k)$, $\lambda_h = \alpha_h(t)Y_h^{(n)}(t)$ (I drop the superscript $(n)$ in the following). We want to test

$$H_0 : \alpha_1(s) = \alpha_2(s) = \cdots = \alpha_k(s), s \in [0, t].$$

In practice, usually $k = 2$ and this reduces to a two-sample problem. To construct test statistics, similar to the one-sample case, we first define

$$\hat{A}_h(s) = \int_0^t \frac{J_h(s)}{Y_h(s)} dN_h(s)$$

$$\hat{A}(s) = \int_0^t \frac{J(s)}{Y(s)} dN(s)$$

$$\bar{A}_h(s) = \int_0^t \frac{J_h(s)}{Y(s)} dN(s)$$

for $h = 1, \cdots, k$ and $Y(s), J(s)$ and $N(s)$ are aggregated processes.

2.2.1 Two Sample Log-rank Test

Two Sample Log-rank Test Let $K_h(t) = Y_h(t)K(t)$ be a locally bounded predictable weight process and define

$$Z_h(t) = \int_0^t K_h(s)d(\hat{A}_h - \bar{A}_h)(s)$$

$h = 1, 2, \cdots, k$ and the test statistic will be based on $Z_h(t)$. Three martingale properties of $Z_h(t)$ are

- $Z_h(t) = \sum_{i=1}^k \int_0^t K^i(s) \left( \delta_{hl} - \frac{Y_h(s)}{Y(s)} \right) dM_i(s)$;
- $\langle Z_h, Z_j \rangle(t) = \int_0^t K^2(s) \left( \delta_{hl} - \frac{Y_h(s)}{Y(s)} \right) Y_h(s)Y(s)\alpha_s ds$;
- $\text{Cov}(Z_h(t), Z_j(t)) = \mathbb{E}(Z_h, Z_j)(t)$,

under some finite moment conditions. Now we consider the case $k = 2$.

**Definition 12 (Two sample log rank statistic)** Let

$$\hat{\sigma}^2_{11}(t) = \int_0^t K^2(s) \frac{Y_1(s)}{Y_1(s) + Y_2(s)} \left( 1 - \frac{Y_2(s)}{Y_1(s) + Y_2(s)} \right) d(N_1 + N_2)(s)$$

be the estimator of $\text{Var}(Z_1(t))$ and define

$$X^2 = \frac{Z_1(t)^2}{\hat{\sigma}^2_{11}(t)}.$$

One choice of $K$ is $K(t) = J(t) = \mathbb{I}(Y_1(t) + Y_2(t) > 0)$. The test statistic $X^2$ is called the two sample log-rank statistic which asymptotically has a $\chi^2_1$ distribution under $H_0$. 

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• With the choice $K(t) = J(t)$, similar to the one sample case, we have

$$Z_h(t) = O_h - E_h, h = 1, 2$$

where

$$O_h = N_h(t)$$

counts the observed number of failures in group $h$ and

$$E_h = \int_0^t \frac{Y_h(s)}{Y_1(s) + Y_2(s)} d(N_1 + N_2)(s) = \int_0^t Y_h(s) d\tilde{A}(s)$$

is called the expected number of failures in group $h$ since $E(O_h) = E(E_h)$.

• The name log-rank was proposed by Peto and Peto (1972) (ABGK, p364-366).

• Using Dr. Li’s notation Li (2021), we have

$$Z_h = \sum_{i=1}^D K(t_i)[O_{ij} - E_{ij}]$$

$$= \sum_{i=1}^D K(t_i)[d_{ij} - r_{ij}d_i \frac{r_i}{r_i}]$$

for $h = 1, 2$ where $D$, $d_{ij}$ and $r_{ij}$ are the number of deaths and number at risk at $t_i$ in total and in group $j$; $d_i = d_{i1} + d_{i2}$, $r_i = r_{i1} + r_{i2}$. Similarly, the estimated variance of $Z_h$ is

$$\tilde{\sigma}_{hh} = \sum_{i=1}^D K^2(t_i)r_{ij} \frac{d_i}{r_i} \left(1 - \frac{d_i}{r_i}\right) \left(\frac{r_i - r_{ij}}{r_i - 1}\right)$$

for $h = 1$ and $2$, suggesting that $Z_h$ has a hypergeometric distribution.

### 2.2.2 Stratification

Suppose we have $s$ stratum, that is, we have $s$ bivariate counting processes

$$N_m = (N_{1m}, N_{2m}), m = 1, \cdots, s$$

with intensity $\lambda_m = (\lambda_{1m}, \lambda_{2m})$ of form $\lambda_{im} = \alpha_{im}Y_{im}(t)$. Allowing heterogeneity in each stratum, the null hypothesis is

$$H_0 : \alpha_{1s} = \alpha_{2s}, s = 1, \cdots, m.$$ 

Using the asymptotic results in section 2.2.3, a test statistic could be

$$X^2 = \frac{\left(\sum_{s=1}^m Z_{1s}(t)\right)^2}{\sqrt{\sum_{s=1}^m \tilde{\sigma}_{11s}(t)}}$$

which asymptotically has a $\chi^2_1$ distribution under $H_0$. 19
2.2.3 Asymptotic Null Distribution

**Theorem 13 (AN of log-rank test)** Under some regularity conditions, the test process
\[ \sqrt{n}(Z_1, Z_2) \to_d (U_1, U_2) \]
in \( D(T)^2 \), where \( U_1 \) and \( U_2 \) are mean zero Gaussian martingales with \( U_i(0) = 0 \) and \( \text{Cov}(U_i(s), U_j(t)) = \sigma_{ij}(s \land t), i, j \in \{1, 2\} \) where \( \sigma_{ij}(t) \) depends on the censoring and survival distributions. For details, see ABGK example V.2.9 and V.2.10.

2.3 Applications and Examples

2.3.1 A Markov Illness-Death Model

A Markov Illness-Death Model Let \( 0 = \text{healthy}, 1 = \text{diseased} \) and \( 2 = \text{dead} \) with transition intensities \( \alpha_{01}, \alpha_{02} \) and \( \alpha_{12} \), respectively. Then by Kolmogorov’s equation, the transition probabilities are
\[
\begin{align*}
P_{00}(s, t) &= \exp \left( - \int_s^t (\alpha_{01}(u) + \alpha_{02}(u)) du \right), \\
P_{11}(s, t) &= \exp \left( - \int_s^t \alpha_{12}(u) du \right), \\
P_{01}(s, t) &= \int_s^t P_{00}(s, u) \alpha_{01}(u) P_{11}(u, t) du.
\end{align*}
\]
We are interested in testing non-differential mortality, i.e., \( \alpha_{02}(t) = \alpha_{12}(t) \) for all \( t \), based on \( n \) independent copies, all in state 0 at \( t = 0 \) of the Markov process over \([0, \tau]\).

- Under \( H_0 \), we have
  \[
P_{01}(0, t) = \exp \left( - \int_0^t \alpha_{02}(u) du \right) \left( 1 - \exp \left( - \int_0^t \alpha_{01}(u) du \right) \right).
  \]

- We use the data on nephropathy (DN) and mortality among insulin-dependent diabetics. The total number of person-years at risk is 44,561 in state 0: alive without DN, 451 diabetics died, whereas as many as 267 died from state 1: alive with DN, where the number of person-years at risk was 5024.

- With the choice \( K(s) = Y_0(t) + Y_1(t) \), the Wilcoxon-type test statistics are 28.5 for men and 25.6 for women.

- With the choice \( K(s) = \mathbb{1}(Y_0(s) + Y_1(s) > 0) \), the log-rank test statistics are 29.4 for men and 27.3 for women.

- Both are highly significant referred to a standard normal distribution.
3. Regression Models

3.1 Cox’s Multiplicative Hazard Models / Anderson-Gill Models

3.1.1 Anderson-Gill Model

Assume the compensator of \( N = (N_{hi}, h = 1, \ldots, k; i = 1, \ldots, n) \) is

\[
\Lambda_{hi}^\theta(t) = \int_0^t \lambda_{hi}^\theta(u)du
\]

where \( \theta^T = (\gamma, \beta^T) \) and

\[
\lambda_{hi}^\theta(t) = Y_{hi}(t) \alpha_{h0}(t, \gamma) r(\beta^T Z_{hi}(t))
\]

and \( Y_{hi}(t) \) is predictable (risk process), \( \alpha_{h0}(t, \gamma) \) is the baseline hazard, \( Z_{hi} \) is a type-specific covariate vector (also predictable) and \( r(\cdot) \) is called the relative risk function. The most popular choice corresponds to \( r(x) = \exp(x) \), which is known as the Cox’s model. We assume that \( \alpha_{h0}(\cdot) \) are non-negative and integrable over \( t \in \mathcal{T} \).

3.1.2 Estimation and Partial Likelihood

Due to Jacod’s formula, the partial likelihood is proportional to

\[
\prod_{t \in \mathcal{T}} \prod_{h, i} (dA_{h0}(t) r(\beta^T Z_{hi}(t))) \Delta N_{hi}(t) \exp \left[ -\sum_{h=1}^k \int_0^T S^{(0)}_h(\beta, u) dA_{h0}(u) \right],
\]

where \( A_{h0}(t) = \int_0^t \alpha_{h0}(u)du \) and

\[
S^{(0)}_h(\beta, t) = \sum_{i=1}^n r(\beta^T Z_{hi}(t)) Y_{hi}(t).
\]

Fix \( \beta \), maximization w.r.t. \( \Delta A_{h0}(t) \) leads to

\[
\Delta \hat{A}_{h0}(t, \beta) = \frac{\Delta N_{h}(t)}{S^{(0)}_h(\beta, t)}
\]

where \( N_h(t) = \sum_{i=1}^n \Delta N_{hi}(t) \). Substitute this into the likelihood, we have the partial likelihood for \( \beta \) as

\[
L(\beta) = \prod_{t \in \mathcal{T}} \prod_{h, i} \left( \frac{r(\beta^T Z_{hi}(t))}{S^{(0)}_h(\beta, t)} \right)^{\Delta N_{hi}(t)}
\]

so that \( \hat{\beta} \) is obtained by maximizing the log Cox partial likelihood process

\[
C_\tau(\beta) = \log L(\beta) = \sum_{h=1}^k \left[ \int_0^\tau \left( \log r(\beta^T Z_{hi}(t)) - \log S^{(0)}_h(\beta, t) \right) dN_{hi}(t) \right].
\]

Then we estimate \( A_{h0}(t) \) by \( \hat{A}_{h0}(t, \hat{\beta}) \), which is known as the Breslow’s estimator. Finally, the hazard rate \( \alpha_{h0}(t) \) can be estimated via smoothing (\( K_h(\cdot) \) is a kernel function and \( b_n \) is the bandwidth):

\[
\hat{\alpha}_{h0}(t) = \frac{1}{b_n} \int_0^\tau K_h \left( \frac{t - u}{b_n} \right) d\hat{A}_{h0}(u, \hat{\beta}).
\]
3.1.3 Large Sample Properties

We assume $r(\cdot) = \exp(\cdot)$. Define the following quantities:

- $S_h^{(0)}(\beta, t) = \sum_{i=1}^{n} \exp(\beta^T Z_{hi}(t))Y_{hi}(t)$,
- $S_h^{(1)}(\beta, t) = \sum_{i=1}^{n} Z_{hi}(t) \exp(\beta^T Z_{hi}(t))Y_{hi}(t)$,
- $S_h^{(2)}(\beta, t) = \sum_{i=1}^{n} Z_{hi}^{\otimes 2}(t) \exp(\beta^T Z_{hi}(t))Y_{hi}(t)$,
- $E_h(\beta, t) = \frac{S_h^{(1)}(\beta, t)}{S_h^{(0)}(\beta, t)}$,
- $V_h(\beta, t) = \frac{S_h^{(2)}(\beta, t)}{S_h^{(0)}(\beta, t)} - E_h(\beta, t)^{\otimes 2}$,

where $h = 1, \cdots, k$ are states (components of the multivariate counting process). Further, we define the score process $(N_h = \sum_{i=1}^{n} N_{hi})$:

$$U_\tau(\beta) = \sum_{h=1}^{k} \left[ \sum_{i=1}^{n} \int_{0}^{\tau} Z_{hi}(t)dN_{hi}(t) - \int_{0}^{\tau} E_h(\beta, t)dN_h(t) \right].$$

**Theorem 14 (Consistency of $\hat{\beta}$)** Under some regularity conditions, the estimating equation $U_\tau(\beta) = 0$ has a unique solution $\hat{\beta}$ with probability tending to 1 and $\hat{\beta} \to \beta_0$ as $n \to \infty$ where $\beta_0$ is the true parameter.

The key idea is to show that the process $X(\beta, t) = \frac{1}{n}(C_t(\beta) - C_t(\beta))$ and its compensator converge to the same probability limit where $C_t(\beta)$ is the log Cox partial likelihood process defined earlier and then apply a lemma in convex analysis. For details, see p497-498 in ABGK or p297-298 in FH.

**Theorem 15 (AN of $\hat{\beta}$)** Under some regularity conditions, as $n \to \infty$,

$$\sqrt{n}(\hat{\beta} - \beta_0) \to_d N(0, \Sigma^{-1})$$

where

$$\Sigma_\tau = \sum_{h=1}^{k} \int_{0}^{\tau} v_h(\beta_0, t)s_h^{(0)}(\beta_0, t)\alpha_0(t)dt$$

$$v_h = \frac{s_h^{(2)}}{s_h^{(0)}} - e_h^{\otimes 2}, \quad e_h = \frac{s_h^{(1)}}{s_h^{(0)}}$$

and $s_h^{(m)}$ and $v_h$ are probability limits of $S_h^{(m)}$ and $V_h$ defined earlier.

In the special case that $k = 1$ and for $i = 1, \cdots, n$, $X_i$ are independent survival times given $Z_i$ and $Z_i$ are i.i.d. $p$-dimensional covariates, we have

$$\Sigma_\tau = \int_{0}^{\tau} v(\beta_0, t)s^{(0)}(\beta_0, t)\alpha_0(t)dt.$$
Theorem 16 (Joint asymptotic distribution) Under some regularity conditions, \( \sqrt{n}(\hat{\beta} - \beta_0) \) and the processes

\[
W_h(\cdot) = \sqrt{n} \left( \hat{A}_{h0}(\cdot, \hat{\beta}) - A_{h0}(\cdot) \right) + \sqrt{n}(\hat{\beta} - \beta_0)^T \int_0^t e_h(\beta_0, u) \alpha_{h0}(u) du
\]

are asymptotically independent. The limiting distribution of \( W_h \) is that of a mean zero Gaussian martingale with variance function

\[
\omega_h^2(t) = \int_0^t \frac{\alpha_{h0}(u)}{s_h^{(0)}(\beta_0, u)} du.
\]

3.1.4 Goodness-of-Fit and Model Diagnostics

Goodness-of-Fit and Model Diagnostics This subsection is mainly based on chapter 11 in Klein and Moeschberger (2003) and section 7.3 in Andersen et al. (1993). Some common methods for checking the goodness-of-fit in Cox’s models are:

- Graphical methods;
- Tests for log-linearity;
- Tests for proportional hazards assumption;
- Martingale residuals;
- Deviance Residuals;
- Influence Checking.

Example 2 (Graphical Methods: The Andersen Plot) The full covariate vector is \( Z = (Z_1, Z_2^T)^T \) where \( Z_2 \) is the vector of the remaining \( p - 1 \) covariates and \( Z_1 \) is the covariate that we want to test the proportional hazards assumption of. We first stratify the covariate \( Z_1 \) into 2 (or \( K \), in general) strata (this is automatically fulfilled if \( Z_1 \) is discrete). We then fit a Cox model stratified on the discrete values of \( Z_1 \) and we let \( \hat{H}_{g0}(t), g = 1, 2 \) be the estimated cumulative baseline hazard in the \( g \)th stratum. If the proportional hazards assumption holds, then

\[
\frac{\hat{H}_{10}(t)}{\hat{H}_{20}(t)} = \exp(\beta_1 \Delta Z_1)
\]

where \( \Delta Z_1 = Z_{11} - Z_{12} \). Hence, Andersen’s approach is to plot \( \hat{H}_{10}(t) \) against \( \hat{H}_{20}(t) \) and if the null hypothesis holds, this should be a straight line across the origin. An alternative is to plot \( \log \hat{H}_{10}(t) \) against \( \log \hat{H}_{20}(t) \) which, under \( H_0 \), should be a horizontal line.

Example 3 (Graphical Methods: The Dabrowska-Doksum-Song Method) Dabrowska et al. (1989) studied a general testing procedure in the special two-sample case based on the statistic

\[
\hat{\theta}(\tau) = \frac{\int_0^\tau L(s)d\hat{H}_1(s)}{\int_0^\tau L(s)d\hat{H}_2(s)}
\]
where \( L(s) \) is a predictable weighting process. Note that \( L(s) = 1 \) reduces to the case in the Andersen plot. They also derived confidence bands for the relative trend function \( H_2 \circ H_1^{-1} \) and for the relative change function \( (H_2 - H_1)/H_1 \) which is constant under the proportional hazards assumption.

**Example 4 (Martingale Residuals: The Arjas Plot)** Another graphical method is based on the so-called martingale residuals. We define

\[
p_i(u, \beta) = \frac{Y_i(u) \exp(\beta^T Z_i)}{S^{(0)}(\beta, u)}
\]

and \( S^{(0)} \) is defined as before. Under \( H_0 \), the differences

\[
\text{Arjas}(h, t) = N_h(t) - \int_0^t \sum_{h(i)=h} p_i(u, \beta)dN_i(u), \quad h = 1, \cdots, k,
\]

where \( N_i(u) = \sum_{i=1}^n N_i(u) \), \( N_h(t) = \sum_{h(i)=h} N_i(t) \) and \( \beta \) is the true parameter vector, are local martingales. Indeed, we have

\[
\mathbb{E}(\text{Arjas}(h, dt)|\mathcal{F}_{t-}) = \mathbb{E}(dN_h(t)|\mathcal{F}_{t-}) - \sum_{h(i)=h} p_i(t, \beta)\mathbb{E}(dN_i(t)|\mathcal{F}_{t-})
\]

\[
= \sum_{h(i)=h} Y_i(t) \exp(\beta^T Z_i)dt -
\]

\[
\sum_{h(i)=h} Y_i(t) \exp(\beta^T Z_i) \frac{1}{S^{(0)}(\beta, t)} \left( \sum_{i=1}^n Y_i(t) \exp(\beta^T Z_i) \right) dt
\]

\[
= 0.
\]

Therefore, plots of

\[
\int_0^{X^h_m} \sum_{h(i)=h} p_i(u, \hat{\beta})dN_i(u), \quad m = 1, 2, \cdots, N_h(\tau), h = 1, \cdots, k
\]

against \( m \), where \( X^h_m, m = 1, \cdots, N_h(\tau) \) are the ordered jump times in stratum \( h \) should be approximated a straight line with unit slope. Such a plot is also referred as the Total Time on Test plot (TOT) (Klein and Moeschberger, 2003).

**Example 5 (Martingale Residuals: Functional Form)** For right-censored data, define the martingale residuals

\[
\hat{M}_i(t) = N_i(t) - \int_0^t Y_i(u) \exp(\hat{\beta}^T Z_i)d\hat{A}(u)
\]

where \( \hat{\beta} \) and \( \hat{A}(u) \) are Cox’s partial likelihood estimator and Breslow’s estimator, respectively. Fleming and Harrington (1991) (pp165-168) showed that under mild conditions, we have

\[
\mathbb{E}(\hat{M}(\infty)|Z) \approx cf(Z)
\]
where \( c = \frac{\text{total number of events}}{\text{total number of subjects}} \). If the proportional hazards assumption holds, i.e., \( \alpha(t|Z) = \alpha_0(t) \exp(\beta f(Z)) = \alpha_0(t) \exp(\beta Z) \), then we shall have \( f(Z) = Z \). In other words, it should be a straight line if we plot \( \hat{M}_i(\infty) \) against \( Z_i \) based on iid observations.

**Example 6 (The Cox-Snell Plot)** Let \((T_i, D_i, Z_i), i = 1, 2, \cdots, n \) be the iid observations based on a right-censored counting process, and define

\[
\hat{r}_i = \hat{A}(T_i|Z_i) = \hat{A}_0(T_i) \exp(\hat{\beta}^T Z_i).
\]

The Cox-Snell's plot is the Nelson-Aalen estimate based on the sample \((\hat{r}_i, D_i), i = 1, 2, \cdots, n \) where \( D_i \) are right-censoring indicators. Under \( H_0 \), the NA estimate should be a line across the origin with unit slope. This is due to the fact that the true cumulative hazard evaluated at \( T_i \) should be iid standard exponential variables:

\[
r_i = H(T_i|Z_i) = -\log S(X_i|Z_i) \sim \mathcal{E}(1).
\]

### 3.2 Additive Hazard Models

#### 3.2.1 Generalized Nelson-Aalen’s (GNA) Estimator

**Definition 17 (Aalen’s additive hazard model)** Let \( N(t) = (N_i(t) : i = 1, \cdots, n) \) be a multivariate counting process with intensity \( \lambda_i(t) = \alpha_i(t; Z_i(t)) Y_i(t) \). The additive hazard model assumes

\[
\alpha_i(t; Z_i(t)) = \beta_0 + \beta_1(t) Z_{i1}(t) + \cdots + \beta_p(t) Z_{ip}
\]

where \( \beta_j(t) \) are all locally integrable for \( t \in T \). More compactly, we have

\[
N(t) = \int_0^t Y(s) dB(s) + M(t)
\]

where \( B_j(s) = \int_0^s \beta_j(s) ds, j = 0, \cdots, p \) are the parameters of primary interest and \( Y(s) \) is an \( n \times (p+1) \) matrix with rows

\[
Y_i(t)(1, Z_{i1}(t), Z_{i2}(t), \cdots, Z_{ip}(t))
\]

and \( M(t) \) is a vector of counting process martingales.

Heuristically, we have

\[
dN(t) = Y(t) dB(t) + M(dt)
\]

and this suggests the GNA estimator:

\[
\hat{B}(t) = \int_0^t J(s) Y(s)^{-} dN(s)
\]

where \( J(s) = I(\text{rank}(Y(s) = p+1)) \) and \( Y(s)^{-} \) is any predictable generalized inverse of \( Y(s) \). The variance estimator can be

\[
\hat{\Sigma}(t) = \left[ \hat{B} - B^* \right](t) = \int_0^t J(s) Y(s)^{-} (\text{diag} \ dN(s)) (Y(s)^{-})^T
\]
where $[\cdot, \cdot]$ is the quadratic variation and $B^*(t) = \int_0^t J(u) dB(t)$.

In the special case that $\alpha_i(t; Z_i(t)) = \beta_0$, we have

$$\hat{B}_0(t) = \int_0^t J(s) \frac{\sum_{i=1}^n Y_i(s) dN_i(s)}{\sum_{i=1}^n Y_i(s)^2},$$

which reduces to the classical NA estimator if $Y_i(s)$ are indicators. Further, we apply smoothed NA estimator technique to estimate $\beta_j(t)$ and $\alpha_i$:

$$\hat{\alpha}_i(t, Z_i(t)) = \hat{\beta}_0 + \sum_{j=1}^p \hat{\beta}_j(t) Z_{ij}(t).$$

For large sample properties, see ABGK, pp575-578. We shall explore the additive hazards model in depth within the causal inference framework later.

### 3.3 Accelerated Failure Time (AFT) Models

#### 3.3.1 Transformation Models

The relation $S(t) = e^{-A(t)}$ suggests that $A(X) \sim \mathcal{E}(1)$. For Cox’s model, we have

$$\log A_0(X) = -\beta^T Z + \epsilon$$

where $\Pr(\epsilon > t) = e^{-\epsilon t}$. This leads to the following definition.

**Example 7 (Transformation models)** Let $g$ be an unknown monotone function, the transformation model is

$$g(X) = \beta^T Z + \epsilon$$

where $X$ is the (possibly left-, right- and interval-censored) time-to-event outcome and $\epsilon$ has some known distribution.

The accelerated failure time (AFT) model corresponds to $g(X) = \log(X)$.

#### 3.3.2 Buckley-James Estimator

- Let $V_i = \log X_i$ where $X_i$ is possibly right-censored, the likelihood function is

$$\mathcal{L}(\beta) = \prod_{i=1}^n f(V_i - \beta^T Z_i)^{D_i} S(V_i - \beta^T Z_i)^{1-D_i}$$

where $D_i$ are censoring indicators, $f$ and $S$ are density and survival function of $\epsilon_i$.

Hence, the score equation for $\beta$ is

$$\sum_{i=1}^n Z_i \left\{ D_i f'(V_i - \beta^T Z_i) - (1 - D_i) \frac{f(V_i - \beta^T Z_i)}{S(V_i - \beta^T Z_i)} \right\} = 0.$$

If $f$ is known (a parametric distribution such as Gumbel type I), then $\beta$ can be solved by numerical methods.
• If \( f \) is unknown, then we replace \(-f'f\) with a suitable known function \( s \), say, \( a(t) = t \), which corresponds to \( \epsilon \sim \mathcal{N}(0, 1) \). The equation now becomes

\[
\Psi(\beta, a) = \sum_{i=1}^{n} Z_i \left\{ D_i a(V_i - \beta^T Z_i) - (1 - D_i) \int_{V_i - \beta^T Z_i}^{\infty} a(t) dS(t) \right\} = 0.
\]

Note that \( a(t) = t \) corresponds to the ordinary least squares (OLS) equation if no censoring occurs.

**Lemma 18 (Buckley-James Buckley and James (1979))** We assume \( V_i^o = \log X_i \land \log C_i \) is the observed time-to-event and \( C_i \) is the independent censoring time. If \( a(t) = t \), the equation \( \Psi(\beta, a) = 0 \) becomes

\[
\sum_{i=1}^{n} Z_i \left\{ D_i r_i + (1 - D_i) \int_{r_i}^{\infty} S(t) dt \right\} = 0
\]

where \( r_i = V_i^o - \beta^T Z_i \). Hence, it corresponds to the OLS of the synthetic variable

\[ V_i^* = D_i V_i^o + (1 - D_i)\mathbb{E}(V_i | V_i \geq V_i^o, Z_i) \]

The resulting estimator is called Buckley-James. Further, \( V_i^* \) has the property

\[ \mathbb{E}(V_i^* | Z_i) = \mathbb{E}(V_i | Z_i). \]

**Proof** Apparently,

\[ \mathbb{E}(V_i^* | Z_i) = \mathbb{E}(V_i | Z_i) - \mathbb{E}\left\{ D_i (V_i^o - \mathbb{E}(V_i | V_i \geq V_i^o, Z_i)) | Z_i \right\}. \]

But the second term is

\[ \mathbb{E}(\mathbb{I}(D_i = 1)(V_i^o - V_i^o) + \mathbb{I}(D_i = 0) \ast 0 | Z_i) \]

which can only be 0.

• Define

\[ W_F(a(t)) = a(t) - \int_{t}^{\infty} a(s) dF(s) \]

where \( F \) has density \( f \), then we have

\[ W_F(\frac{\partial}{\partial \theta} \log f_\theta) = \frac{\partial}{\partial \theta} \alpha_\theta \]

where \( \alpha_\theta = f_\theta / S_\theta \) is the hazard function.
3.3.3 Li-Lu’s PBIV and Instrumental Variable (IV) Analysis

Consider a direct acyclic graph with time-to-event outcome. We are interested in estimating $\beta_1$ (causal effect). Ref: Dr. Lu’s PhD Dissertation Lu (2014). For other representations, see VanderWeele et al. (2014).

Mendelian Randomization (MR) when $G$ refers to genetic variants. The model is Li and Lu (2015)

$$
egin{align*}
X &= \alpha_0 + \alpha_1^T G + \alpha_2^T Z + \xi_1 \\
Y &= \beta_0 + \beta_1 X + \beta_2^T Z + \xi_2
\end{align*}
$$

Put parametric priors on parameters

$$
\begin{pmatrix}
\xi_1 \\
\xi_2
\end{pmatrix} \sim \mathcal{N}\left( \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \rho \sigma_1 \sigma_2 \\ \rho \sigma_1 \sigma_2 & \sigma_2^2 \end{pmatrix} \right)
$$

$$
\begin{align*}
\sigma_1^2 &\sim \text{InvGamma}(\gamma_1, \gamma_2) \\
\sigma_2^2 &\sim \text{InvGamma}(\gamma_1, \gamma_2) \\
\rho &\sim \text{Uniform}(-1, 1) \\
\alpha_i &\sim \mathcal{N}(0, \zeta_i^2), \quad \beta_i \sim \mathcal{N}(0, \psi_i^2)
\end{align*}
$$

For inference, we draw posterior samples of $\beta_1$ from the model. The R package is available at https://github.com/ElvisCuiHan/PBIV. We shall explore the instrumental variable analysis with time-to-event outcome more in a separate section.
3.4 Semi-Markov Models

3.4.1 General Semi-Markov Processes

The treatment of semi-Markov processes follows from section X.1 in ABGK, the dissertation Sun (1992), the JASA paper Dabrowska et al. (1994) and Dabrowska (2020). Further references are Dabrowska (2012); Cook et al. (2007); Cook and Lawless (2018).

Definition 19 (Semi-Markov processes and Markov renewal processes)

- The stochastic process \((X, T) = \{X_n, T_n : n \in \mathbb{N}\}\) is said to be a Markov renewal process if \(T_0 = 0\) a.s. and
  - the sequence \((J_0, J_1, \ldots)\) forms a discrete time Markov chain;
  - for any integer \(n \geq 1\), let \(W_n = T_n - T_{n-1}\) and we have
    \[
    \mathbb{P}(W_1 \leq t_1, \ldots, W_n \leq t_n | X_j, j \geq 0) = \prod_{k=1}^{n} \mathbb{P}(W_k \leq t_k | X_{k-1}, X_k).
    \]

- Let \(N(t) = \sum_{n \geq 1} \mathbb{I}(T_n \leq t)\), then the continuous time process
  \[
  X(t) = X_{N(t)} = \sum_{n=0}^{\infty} X_n \mathbb{I}(T_n \leq t < T_{n+1})
  \]

is called a semi-Markov process.

3.4.2 Some Theory

Definition 20 (Semi-Markov kernel)

Let \(X_n\) take values in \(\{1, \ldots, r\}\). The basic parameter in a semi-Markov (or Markov renewal) process is the semi-Markov kernel

\[
Q(w) = [Q_{ij}(w)]
\]

where \(p_{ij} = \mathbb{P}(X_{n+1} = i | X_n = j), F_{ij}(w) = \mathbb{P}(W_{n+1} \leq w | X_{n+1} = j, X_n = i)\),

\[
Q_{ij}(w) = \mathbb{P}(W_{n+1} \leq w, X_{n+1} = j | X_n = i) = p_{ij} F_{ij}(w).
\]

Set

\[
G(x, y) = \text{Diag} \left[ \frac{S_i(y)}{S_i(x)} \right]
\]

where \(S_i(w) = \sum_{j=1,j \neq i}^{r} p_{ij}(1 - F_{ij}(w))\) so that on the diagonal, we have

\[
\mathbb{P}(W_{n+1} > y | W_{n+1} > x, X_n = i).
\]

Example 8 (Fowards recurrence time) Let \(\mathcal{F}_t = \mathcal{F}_0 \vee \sigma(X(s) : s \leq t)\) and \(\gamma_t = T_{{N(t)}+1} - t\) be the forwards recurrence time of the process given \(\mathcal{F}_{t-}\), then we have

\[
\mathbb{P}(\gamma_t > w | \mathcal{F}_{t-}) = \sum_{i=1}^{r} \mathbb{I}(X(t) = i) G_{ii}(\delta_t, \delta_t + w)
\]
where $\delta_t = t - T_{N(t)}$ so that it is fully specified by $G(x, y)$ defined earlier. Indeed, let $\beta_t := T_{N(t)} - T_{N(t)} = W_{N(t)+1}$, then we have

$$
\mathbb{P}(\gamma_t > w | \mathcal{F}_t) = \mathbb{P}(T_{N(t)+1} - t > w | \mathcal{F}_t) = \mathbb{P}(\beta_t > \delta_t + w, X_{N(t)}) = \sum_{i=1}^{r} I(X_{N(t)} = i) G_{ii}(\delta_t, \delta_t + w).
$$

**Remark:**

- By comparison, in the continuous time Markov chain (CTMC) case,

$$
\mathbb{P}(\gamma_t > w | \mathcal{F}_t) = \sum_{i=1}^{r} I(X(t) = i) \exp(-A_i(t + w) + A_i(t))
$$

where $A_i(t) = \sum_{j=1, j \neq i}^{r} A_{ij}(t)$. In the homogeneous case, RHS only depends on $w$ but not $t$, hence the probability depends only on the state occupied at time $t$ but not the duration time (time spent in this state).

**Example 9 (Events after time $t$)** Similarly, the conditional probabilities of the first event after time $t$ is

$$
\mathbb{P}(\gamma_t \leq w, X_{N(t)+1} = j | \mathcal{F}_t) = \sum_{i=1}^{r} I(X(t) = i) F_{ij}(\delta_t, \delta_t + w)
$$

where

$$
F_{ij}(x, y) = \frac{1}{S_i(x)} \int_{(x, y]} Q_{ij}(du) = \mathbb{P}(W_{n+1} \leq y, X_{n+1} = j | W_{n+1} > x, X_n = i).
$$

The proof is similar to the previous one.

**Theorem 21 (Transition probabilities)** Define the matrix $R$ as

$$
R(y) = G(0, y) + \int_0^y M(du) G(0, y - u)
$$

where $G$ is defined earlier and $M(y) = \sum_{r \geq 1} Q^{(r)}(y)$ is the renewal matrix where $Q^{(1)} = Q$ and $Q^{(r)} = Q^{(r-1)} * Q = Q * Q^{(r-1)}$. Then transition probabilities of a semi-Markov process are given by

$$
\mathbb{P}(X(t + s) = j | \mathcal{F}_t) = \sum_{i=1}^{r} I(X_{N(t)} = i) \mathbb{P}_{ij}(\delta_t, \delta_t + s)
$$

where

$$
\mathbb{P}(x, y) = \delta_{ij} G_{ii}(x, y) + \sum_{k \neq i} \int_{(x, y]} F_{ik}(x, du) R_{kj}(y - u)
$$

and $R_{kj}$ is the $(kj)^{th}$ element of the matrix $R$. 
3.4.3 Cox Regression in a Markov Renewal Model

Define

\[ \tilde{N}_{ij}(t) = \sum_{n \geq 1} \mathbb{I}(T_n \leq t, X_n = j, X_{n-1} = i) \]

\[ \tilde{N}(t) = \sum_{i,j} \tilde{N}_{ij}(t) \]

\[ L(t) = t - T_{\tilde{N}(t)} \text{ (backwards recurrence time).} \]

We assume the intensity of \( \tilde{N}_{ij}(t) \) w.r.t. \( F_t = F_0 \lor N_t \) is of form

\[ \Lambda_{ij}(dt) = Y_i(t) \alpha_{ij}(L(t); Z) dt \]

where \( Y_i(t) = \mathbb{I}(X(t-) = i) \) and \( Z \) is a vector of external covaraites.

We further define \( W_n = T_n - T_{n-1}, T_0 = 0 \) and

\[ N_{ij}(x) = \sum_{n \geq 0} \mathbb{I}(W_{n+1} \leq x, X_n = i, X_{n+1} = j) \]

\[ Y_i(x) = \sum_{n \geq 0} \mathbb{I}(W_{n+1} \geq x, X_n = i). \]

Then the likelihood of observing \( \{N_{ij}: i,j, \in \{1, \cdots, r\}\} \) is proportional to

\[ \prod_u \prod_i \left( \prod_{j \neq i} dA_{ij}(u)^{\Delta N_{ij}(u)} (1 - dA_i(u))^{Y_i(u) - \Delta N_i(u)} \right) \]

where \( A_{ij} = \int \alpha_{ij} \) and \( A_i = \sum_{j \neq i} A_{ij} \) (ABGK, p681). Note that it is a product of multinomial probabilities.

- Given \( m \) iid realizations of the process \( \{N_{ij}: i,j, \in \{1, \cdots, r\}\} \), the partial likelihood is

\[ \mathcal{L} = \prod_{k=1}^m \left\{ \prod_{i=1}^r \prod_{j \neq i} \prod_{n=1}^{n_{ijm}} \alpha_{ijk}(W_{nk}) \times \exp \left( - \int_0^{T_k} \sum_{j \neq i} \alpha_{ijk}(L(t)) dt \right) \right\} . \]

where \( n_{ijm} \) is the total number of transitions from \( i \) to \( j \) of individual \( m \). Hence, a natural NA-type estimator of \( A_{ij} \) is

\[ \hat{A}_{ij}(y, \beta) = \sum_{k=1}^m \int_0^y \frac{dN_{ijk}(u)}{S_{ij}^{(0)}(u, \beta)} \]

where \( S_{ij}^{(0)} = \sum_{k=1}^m Y_{ik}(x)e^{\beta^T Z_{ijk}(x)} \) is similar to that in the Cox’s model.
Plug-in $\hat{A}_{ij}$ into $L$, we have the profile likelihood for $\beta$:

$$L(\beta) = \prod_{k=1}^{m} \prod_{i=1}^{r} \prod_{j \neq i}^{n_{ijk}} \left( \frac{\alpha_{ijk}(W_{nk})}{\sum_{k=1}^{m} Y_{ik}(W_{nk}) \exp(\beta^{T}Z_{ijk}(W_{nk}))} \right)^{\Delta N_{ijk}(W_{nk})}$$

and the maximum partial likelihood is indeed

$$\hat{\beta} = \arg \max_{\beta} L(\beta).$$

Define

$$H_{ij}(x) = N_{ij}(x) - \int_{0}^{x} Y_{i}(u) \alpha_{ij}(u) du,$$

and unfortunately, there is no filtration making $H_{ij}$ a martingale.

Let $A(x) = [A_{ij}(x)]$ and for $x < y$, $G(x, y)$ be a diagonal matrix with entries $G_{ii}(x, y) = \exp(-\sum_{j}(A_{ij}(y) - A_{ij}(x)))$. Let

$$F(x, y) = \int_{x}^{y} G(x, u-)A(du),$$

$$H(y) = G(0, y),$$

$$Q(y) = F(0, y).$$

Similar to the theory part, define

$$F^{(p)} = \int_{x}^{y} F(x, du)Q^{(p-1)}(y-u),$$

$$G^{(p)} = \int_{x}^{y} F(x, du) \left[ Q^{(p-1)} * H \right](y-u),$$

$$G^{(0)} = G, F^{(0)} = Q^{(0)} = I.$$  

**Lemma 22 (Predicted probability)** Given $F_{t-}$, the conditional probability that the process is in state $j$ at time $t + v$ is

$$P(X(t + v) = j | F_{t-}) = \begin{cases} \sum_{p \geq 0} Q_{ij}^{(p)} * H_{jj}(v) & \text{if for some } n, t = T_{n}. \\ \sum_{p \geq 0} G_{ij}^{(p)}(t - T_{n}, v + t - T_{n}) & \text{if else.} \end{cases}$$

The probability is denoted as $P_{ij}(t - T_{n}, v + t - T_{n})$.

**Remark:** In practice, we replace $A$ by $\hat{A}$.

### 3.4.4 Asymptotics

**Theorem 23 (AN of the semi-Markov estimator Dabrowska et al. (1994); Sun (1992))**

Under some regularity conditions, we have

$$\hat{W}(\cdot, \beta_{0}) \rightarrow_{d} W(\cdot, \beta_{0})$$

where

$$\hat{W}(x, \beta_{0}) = \frac{1}{\sqrt{m}} \sum_{k=1}^{m} H_{ijk}(x, \beta_{0}),$$

$H_{ijk}$ is defined as before and $W(x, \beta_{0})$ is a mean zero Gaussian process.
3.5 Other Regression Models

3.5.1 Parametric Regression Models

Example 10 (Parametric regression) Suppose the intensity process \( \lambda \) of a multivariate counting process \( \mathbf{N} = (N_1, \cdots, N_k) \) is specified by a \( q \)-dimensional parameter \( \mathbf{\theta} = (\theta_1, \cdots, \theta_q) \in \Theta \). Then we write
\[
\lambda_h(t) = \lambda_h(t; \mathbf{\theta}).
\]

By Jacod’s formula, the partial likelihood is
\[
L_\tau(\mathbf{\theta}) = \left\{ \prod_{t \in T} \prod_{h=1}^k \lambda_h(t; \mathbf{\theta})^{\Delta N_h(t)} \right\} \exp \left\{ - \int_0^\tau \sum_{h=1}^k \lambda_h(t; \mathbf{\theta}) \, dt \right\}.
\]
The whole estimation and inference are thus based on \( L_\tau(\mathbf{\theta}) \). Common examples include Weibull, exponential and Gumbel type I distributions Li (2021).

3.5.2 Beran’s Nonparametric Regression

Example 11 (Beran’s conditional NA estimator) Beran in 1981 proposed a method to estimate the conditional survival function \( S(t|z) \) nonparametrically. By the product-integration notation, we have
\[
S(t|z) = \prod_{s \leq t} (1 - A(ds|z))
\]
where \( A(s|z) \) is the conditional cumulative hazard. The Beran’s conditional NA estimator is
\[
\hat{A}(t|z) = \int_0^t \frac{\sum_{i=1}^n W_i(z) N_i(ds)}{\sum_{i=1}^n W_i(z) Y_i(s)}
\]
where \( Y_i(s) \) is the risk process for individual \( i \) and \( W_i(z) = \frac{1}{b_n} K \left( \frac{z - Z_i}{b_n} \right) \) where \( K \) is a density.

Remark: tests for the hypothesis \( \alpha_{t,z} = \alpha_t \) have been well studied in the literature, see ABGK p580.

3.5.3 Dabrowska’s Smoothed Cox Regression

Dabrowska (1997) studied the so-called smoothed Cox regression model, where the intensity is of the form
\[
\Lambda(dt) = \mathbb{E}(N(dt)|F_{t-}) = Y(t)\alpha(t, X) \exp(Z^T \beta) dt,
\]
where \( Y(t) \) is a 0-1 predictable process and \( X \) and \( Z \) are covariates. Based on i.i.d. observations, Dr. Dabrowska defined the estimator as the solution to the smoothed partial likelihood score equation Martinussen and Scheike (2006)
\[
\sum_{i=1}^n \int_0^\tau \left\{ Z_i - \frac{S_1(X_i, s, \beta)}{S_0(X_i, s, \beta)} \right\} dN_i(s) = 0,
\]
where

\[ S_k(x, s, \beta) = \sum_{i=1}^{n} K_b(x - X_i)Y_i(t) \exp(\beta^T Z_i(t))Z_i^{\otimes k} \]

and \( K_b(x - X_i) = \frac{1}{b} K\left(\frac{x - X_i}{b}\right) \) is the kernel estimator as that in Beran’s nonparametric regression. Analogously to ABGK Andersen et al. (1993), substitution of Beran’s estimator gives

\[ \hat{A}(x, t) = \sum_{i=1}^{n} \int_{0}^{t} \frac{K_b(x - X_i)}{S_0(x, s, \beta)} dN_i(s). \]

In the absence of covariates this reduces to Beran’s estimator.

3.5.4 Cox-Aalen Hazards Model

As a special and more applicable case of Dabrowska’s smoothed Cox regression, Scheike and Zhang (2002) introduced the so-called Cox-Aalen model by assuming a parametric form of the baseline hazard \( \alpha(t, X) \):

\[ \Lambda(dt) = \mathbb{E}(N(dt)|\mathcal{F}_{t^-}) = Y(t) [X(t)^T \alpha] \exp(Z^T \beta) dt, \]

which allows time-dependent covariates for the baseline hazard (though Dabrowska’s formulation also allows it).

4. Instrumental Variable Analysis with Time-to-event Outcome

As we have seen in the AFT model that a typical DAG for IV analysis can be represented in the following form Lu (2014).

Figure 3: Directed acyclic graph of instrumental variable analysis

- The easiest approach: LSE.

\[ Y = \beta_1 X(U) + \beta_2^T Z + \epsilon(U) \]

For simplicity, we do not explicitly write \( U \) in the following.

- Issues:
  1. Interval-censored data.

\[ Y \in (L, R] \]

2. Inconsistency and Biasedness.

\[ \text{Cov}(X, \epsilon) \neq 0 \]
There are 3 key assumptions for IV method to work well.

- **Key assumptions for IV analysis:**
  1. Given observed confounders, strong correlation between SNPs and SBP level.
  2. SNPs are independent of unobserved confounders and measurement error of SBP level.
  3. Given SBP level and observed confounders, SNPs are independent of Time from DM to CVD.

There are several potential models and methods for IV analysis with time-to-event outcomes in literature:

- Simple two stage least square (TSLS);
- Accelerated failure time (AFT) model;
- Structural Cox multiplicative hazard model;
- Aalen’s additive risk model;
- Competing risks model (the previous methods can be applied to this one) Martinussen and Vansteelandt (2020); Zheng et al. (2017).

We have seen PBIV before, now we illustrate 2 other models in the following.

### 4.1 Aalen’s Additive Risk Model for IV Analysis

- We assume the hazard of \( T \) (or \( Y \)) follows an Aalen’s additive hazard model Martinussen et al. (2017)

\[
\lambda(t; X, G, U) = \beta_0(t) + \beta_X(t)X + \beta_G(t)G + \beta_U(t)U
\]

- By IV assumption, we have \( \beta_G(t) = 0 \) given \( X \).
- Assume \( X = c_0 + c_GG + \Delta \) and \( \mathbb{E}(\Delta|G) = 0 \).
- Let \( V = c_0 + c_GG \), then

\[
P(T > t | G) = \exp \left( -\tilde{B}_0(t) - B_X(t)V \right)
\]

where \( V = c_0 + c_GG \) and \( \tilde{B}_0(t) \) is a function of \( G \) and \( B_X(t) = \int_0^t \beta_G(s)ds \).

### 4.1.1 Generalized TSLS Nelson-Aalen Estimator

- Let \( c = (c_0, c_G)' \), \( \tilde{V}_i = \tilde{\epsilon}(1, G_i)' \) and \( \tilde{V}(t) \) be the \( n \times 2 \)-matrix with \( i^{th} \) row \( (R_i(t), R_i(t)\tilde{V}_i) \) where \( R_i(t) \) is the risk process.
• Generalized Nelson-Aalen estimator for $\mathbf{B}(t)^T = (\hat{B}_0(t), B_X(t))$ is Andersen et al. (1993); Martinussen and Scheike (2006)

$$\hat{\mathbf{B}}(t) = \int_0^t J(u)\hat{\mathbf{V}}(t)^-d\mathbf{N}(t)$$

where $\hat{\mathbf{V}}(t)^-$ is the generalized inverse of $\hat{\mathbf{V}}(t)$ and $J(u) = \mathbb{I}(\text{rank } \mathbf{V}(t) = 2)$.

• Consistency is obtained if $\beta_X(t) = \beta_X$, i.e., time-invariant causal effect.

4.1.2 G-estimation

• More generally, we assume Martinussen et al. (2017)

$$\mathbb{E}\left\{d\mathbf{N}(t)|\mathcal{F}_{t-}^N, G, X, Z, U\right\} = \{d\Omega(t, Z, U) + dB_X(t)X\} R(t)$$

where $N(t) = I(T \leq t)$ is the one-jump counting process Andersen et al. (1993), $\mathcal{F}_{t-}^N$ is the history spanned by $N(t)$, $R(t)$ is the risk process and $\Omega(t, Z, U)$ is an unknown, non-negative function of time, $Z$ and $U$, and $B_X(t)$ is an unknown scalar at each time $t > 0$.

• The goal is to estimate

$$B_X(t) = \int_0^t \beta_X(s)ds$$

where $X$ is an arbitrary exposure.

• The key property of the model is

$$\mathbb{E}\left[(G - \mathbb{E}(G|Z))e^{B_X(t)X} R(t)\{d\mathbf{N}(t) - dB_X(t)X\}\right] = 0$$

and the estimating equation is the empirical version of it. WLOG, we assume $\mathbb{E}(G|Z) = 0$ otherwise we set $\hat{G} = G - \mathbb{E}(G|Z)$.

**Proof** First note that $\mathbb{E}(R(t)|Z,U,G,X) = \exp(-\Omega(t, Z, U) - B_X(t)X)$. 

$$\mathbb{E}(\cdots) = \mathbb{E}\left(\mathbb{E}(\cdots|\mathcal{F}_{t-})\right)$$

$$\quad = \mathbb{E}\left(Ge^{B_X(t)X}d\Omega(t, Z, U)\mathbb{E}(R(t)|Z,U,G,X)\right)$$

$$\quad = \mathbb{E}(f(t, Z, U)G)$$

$$\quad = 0$$

where the last equality follows from that $G$ is independent of $U$.

• The recursive estimator $\hat{B}_X(t)$ (G-estimation) is

$$\hat{B}_X(t, \hat{\theta}) = \int_0^t \frac{\sum_i G_i^c(\hat{\theta})^e\hat{B}_X(s^-)X_i}{\sum_i G_i^c(\hat{\theta})^e\hat{B}_X(s^-)X_i}dN_i(s)$$

where $G_i^c(\theta) = G_i - \mathbb{E}(G_i|L_i; \theta)$, with $\mathbb{E}(G_i|L_i; \theta)$ a parametric model for $\mathbb{E}(G_i|L_i)$ and $\hat{\theta}$ a consistent estimator of $\theta$. 

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In the special case when $X$ is binary, we have the following Volterra integral equation Dabrowska (1988)

$$A(t) = W(t) + \int_0^t A(s-)dU(s)$$

where $A(t) = e^{B_X(t)}$ and

$$W(t) = \int_0^t \frac{\sum_i G_i^c(\theta)(1 - X_i)}{\sum_i R_i(s)G_i^c(\theta)X_i} dN_i(s)$$

$$U(t) = \int_0^t \frac{\sum_i G_i^c(\theta)X_i}{\sum_i R_i(s)G_i^c(\theta)X_i} dN_i(s)$$

The solution of the Volterra equation is given in terms of product integral Dabrowska (1988)

$$A(t) = W(t) + \int_0^t \left[ \prod_{[s,t]} \{1 + dU(v)\} \right] dW(s)$$

If $B_X(t)$ is absolutely continuous and $\beta_X(t) = \beta_X$, then an estimator of $\beta_X$ is

$$\hat{\beta}_X = \int_0^\tau w(t)d\hat{B}_X(t)$$

with $w(t) = \tilde{w}(t)/\int_0^\tau \tilde{w}(s)ds$, $\tilde{w}(t) = R_s(t) = \sum_i R_i(t)$ and $\tau$ is the upper bound of survival time.

We have the following asymptotics results.

**Theorem 24 (CAN Martinussen et al. (2017))** With a long list of regularity conditions and conditioned on $Z$, the G-estimator $\hat{B}_X(t, \hat{\theta})$ is a uniformly consistent estimator of $B_X(t)$. Furthermore, $W_n(t) = \sqrt{n}(\hat{B}_X(t, \hat{\theta}) - B_X(t))$ converges in distribution to a zero-mean Gaussian process with variance $\Sigma(t)$ given in Martinussen et al. (2017).

The proof is based on the benchmark paper Andersen and Gill (1982) and empirical process theory Shorack and Wellner (2009). To study temporal changes, we consider

$$H_0 : \beta_X(t) = \beta_X \iff H_0 : B_X(t) = \beta_X t.$$

### 4.2 Structural Cox Model

Let $T^x$ be the potential survival time had the treatment set to $x$ by some intervention. The structural Cox model states that Martinussen et al. (2019)

$$\frac{\lambda_{T^x}(t|X = x, G)}{\lambda_{T^0}(t|X = x, G)} = \exp(\beta x)$$

for all $x$.

To estimate $\beta$, we need a working model, that is,

$$\lambda_T(t|X = x, G = g) = \lambda_0(t)\exp(\alpha_1 x + \alpha_2 g)$$
where $\lambda$ are hazard functions of $T$. By the IV assumptions, we have

$$T^0 \perp \perp G$$

and

$$S_{T^0}(t|X = x, G) = S_{T^0}(t|X = x, G) \exp(-\beta x)$$

where $S$ are survival functions. The goal is to estimate the local causal effect $\beta$.

Similar to Aalen’s additive risk model, we have

$$E(GS_{T^0}(t|X, G)) = E(GS_{T^0}(t)) = 0$$

under the assumption that $E G = 0$ and

$$S_{T^0}(t|X, G) = \exp\left(-\left(\int_0^t \lambda_0(t)dt\right)e^{\alpha_1 X + \alpha_2 G}e^{-\beta X}\right).$$

The estimating equation is then given by the empirical version of it, i.e., plug-in sample average of $G$ and consistent estimates of $\int_0^t \lambda_0(t)dt$, $\alpha_1$ and $\alpha_2$, which are the usual Breslow’s estimator and Cox’s partial likelihood estimator. Finally, the asymptotic results are based on Andersen and Gill and empirical process theory der Vaart and Wellner (2013).
5. Appendix: Preliminaries

There are several important references in the history and literature of survival analysis:

- Biostat 270 Lec Notes Dabrowska (2020);
- ABGK Andersen et al. (1993);
- Dynamic regression models for survival data Martinussen and Scheike (2006);
- Aalen’s book Aalen et al. (2008);
- PhD dissertation Sun (1992);
- FH Fleming and Harrington (1991);
- Multivariate survival analysis Prentice and Zhao (2019).

5.1 The Counting Process Framework

5.1.1 Counting Processes

Definition 25 (Counting processes) A multivariate counting process \( N = (N_1, \ldots, N_k) \) is a vector of \( k \) adapted cadlag stochastic process defined on a quadruple \( (\Omega, \mathcal{F}, \mathbb{F}, \mathbb{P}) \) where \( \mathbb{F} = (\mathcal{F}_t, t \in T) \), zero at time zero, with piecewise constant paths and nondecreasing, having jumps of size +1, no two components jumping at the same time.

Example 12 (Right-censoring model) Let \( T \) be a nonnegative random variable, then \( X(t) = I(T \leq t) \) is a one jump counting process. Let \( C \) be another nonnegative random variable independent of \( T \), then \( \tilde{X}(t) = I(T \land C \leq t) \) is the right-censored counting process.

5.1.2 Martingales and Localization

Definition 26 (Martingales) A cádlág process \( \{M_t : t \geq 0\} \) defined on a stochastic basis \( (\Omega, \mathcal{F}, \mathbb{F}, \mathbb{P}) \) is called a continuous time martingale if

- \( M_t \) is adapted to the filtration \( \mathcal{F}_t \).
- \( \mathbb{E}|M_t| < \infty \) for all \( t \geq 0 \).
- \( \mathbb{E}(M_t | \mathcal{F}_s) = M_s \) a.s. for \( s < t \).

The third property is referred as the martingale property.

Definition 27 (Local martingales) A continuous time process \( \{M_t : t \geq 0\} \) is a local martingale if there exist stopping times \( T_n \to \infty \) such that \( M_t^n = M_{t\land T_n} \) is a uniformly integrable martingale for each \( n \).

Intensity Processes
Definition 28 (Intensity of a counting process) We say that \( N_h \) has intensity process \( \lambda_h \) if \( \lambda_h \) is predictable and
\[
\Lambda_h(t) = \int_0^t \lambda_h(s)ds \quad \forall t
\]
where \( \Lambda_h \) is the compensator of \( N_h \). The intensity process exists if and only if the time-to-event variable \( T \) has a density w.r.t. Lebesgue measure.

Example 13 (Time-to-event outcome) Suppose \( T \) is a non-negative random variable with absolutely continuous distribution function \( F \) and density \( f \), survival function \( S = 1 - F \). Define \( N(t) = \mathbb{I}(T \leq t) \) as the one jump counting process, then \( N(t) \) has compensator \( \Lambda \) as
\[
\Lambda(t) = \int_0^t Y(s)\alpha(s)ds
\]
where \( Y(s) = \mathbb{I}(T \geq t) \), \( \alpha = f/S \), and hence, \( N \) has intensity process \( \lambda(t) = Y(t)\alpha(t) \).

5.1.3 The Doob-Meyer Theorem and Stochastic Integration

Theorem 29 (Doob-Meyer for counting processes) 1. Each component of \( N \) can be uniquely decomposed as \( M_h = N_h - \Lambda_h \) where \( \Lambda_h \) is predictable and non-decreasing (called the compensator of \( N_h \)) and \( M_h \) is a mean 0 local martingale.

2. Further, the compensator (predictable covariation) and the quadratic covariation of \( M_h M_{h'} \) are
\[
\langle M_h, M_{h'} \rangle = \delta_{hh'}\Lambda_h - \int \Delta \Lambda_h d\Lambda_{h'}
\]
\[
[M_h] = N_h - 2 \int \Delta \Lambda_h dN_h + \int \Delta \Lambda_h d\Lambda_h
\]
\[
[M_h, M_{h'}] = - \int \Delta \Lambda_h dM_{h'} - \int \Delta \Lambda_{h'} dM_h + \int \Delta \Lambda_h d\Lambda_{h'}
\]
where \( \delta_{hh'} \) is the Kronecker delta function.

Integration-by-parts

Lemma 30 (Integration-by-parts) Suppose that \( f \) is a càdlàg function of bounded variation on \( I = (0, t] \) and \( f(0) = 0 \). Then
\[
f^2(t) = 2 \int_{(0,t]} f(u-)f(du) + \sum_{u \leq t} f^2(\Delta u)
\]
where the sum extends over the jumps of \( f \).

Example 14 (Quadratic variation) If \( M \) is a local martingale, then we have \( M^2(t) = Z_t + [M]_t \) where \( Z_t = 2 \int_{(0,t]} M(u-)M(du) \) and \( [M]_t \) is the quadratic variation process, i.e., \( [M]_t = \sum_{u \leq t} M(\Delta u)^2 \).

Proof of Doob-Meyer
Proof We prove the second part. Drop the subscript $h$, we have

$$(M(\Delta s))^2 = (N(\Delta s) - \Lambda(\Delta s))^2$$

$$= (1 - 2\Lambda(\Delta s))M(\Delta s) + (1 - \Lambda(\Delta s))\Lambda(\Delta s)$$

Hence, by integration-by-parts

$$M^2(t) = Z_t + [M]_t$$

where $Z_t = 2\int_{[0,t]} M(u-)dM(u)$ and

$$[M]_t = \int_{[0,t]} (1 - 2\Lambda(\Delta s))M(ds) + \int_{[0,t]} (1 - \Lambda(\Delta s))\Lambda(ds).$$

The first term of $[M]_t$ is a mean zero martingale:

$$\mathbb{E}((1 - 2\Lambda(\Delta t))M(dt)|\mathcal{F}_{t-}) = (1 - 2\Lambda(\Delta t))\mathbb{E}(M(dt)|\mathcal{F}_{t-}) = 0$$

Hence, by the uniqueness of Doob-Meyer, the compensator (predictable variation) of $M^2$ is

$$\langle M \rangle(t) = \int_{[0,t]} (1 - \Lambda(\Delta s))\Lambda(ds)$$

The rest can also be verified by the property

$$[M_j, M_k] = \frac{1}{4}([M_j + M_k](t) - [M_j - M_k](t)).$$

\[\square\]

**Theorem 31 (Doob-Meyer for stochastic integration)** Let $M_h$ and $\Lambda_h$ be the local martingale and the compensator of $N_h$. If $H_h$’s are locally bounded predictable processes, then $\int H_h dM_h$ is a local square integrable martingale and

$$\left< \int H_h dM_h, \int H_{h'} dM_{h'} \right> = \int H_h H_{h'} d\langle M_h, M_{h'} \rangle$$

$$\left[ \int H_h dM_h, \int H_{h'} dM_{h'} \right] = \int H_h H_{h'} d\langle M_h, M_{h'} \rangle$$

where $<.,.>$ and $[.,.]$ are predictable and quadratic covariation processes.

5.1.4 The Innovation Theorem

**Theorem 32 (The innovation theorem)** Let $\mathcal{F}$ and $\mathcal{G}$ be two nested filtrations, i.e., $\mathcal{F}_t \subset \mathcal{G}_t$ for all $t$. Suppose the multivariate counting process $N$ is adapted to both filtrations and has intensity process $\lambda$ w.r.t. $\mathcal{G}$. Then there exists an $\mathcal{F}_t$-predictable process $\gamma$ such that

$$\gamma(t) = \mathbb{E}(\lambda(t)|\mathcal{F}_{t-})$$

If $\lambda(t)$ is also $\mathcal{F}_t$-predictable, then $\gamma(t) = \lambda(t)$. 

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Example 15 (Frailty model for clustered survival data) See example 2.3.4 in Mart
inussen and Scheike (2006).

Independent Right-Censoring

Definition 33 (Independent censoring) Let $F_t \subset G_t$, $t \in [0, \tau]$ be two nested filtrations and \{N(t) : t \in [0, \tau]\} be a univariate counting process adapted to both filtrations. We assume that

$$
E(dN(t)|F_{t-}) = \lambda(t)dt,
$$

i.e., the compensator of $N(t)$ w.r.t. the smaller filtration is $\int \lambda$. Then independent censoring assumes that

$$
E(dN(t)|F_{t-}) = E(dN(t)|G_{t-}) = \lambda(t)dt.
$$

The existence of the above equality is ensured by the innovation theorem.

Example 16 (Right-censored counting processes) Let $X$ be a nonnegative random variable with hazard rate $\lambda$. Define

- the complete counting process $N(t) = \mathbb{I}(t \geq X);
- the risk process $Y(t) = \mathbb{I}(t \leq X)$ so that $Y(t)\lambda(t)$ is the compensator of $N(t)$ w.r.t. the self-exciting filtration;
- the observed counting process

$$
N^c(t) = \int_0^t C(s)dN(s)
$$

where $C(s) = \mathbb{I}(s \leq U) \in G_t$ and $U$ is the (right-)censoring variable;

- the self-exciting filtration $F_t = \sigma(N(s), s \leq t)$, the observed (or right-censored) filtration $F^c_t = \sigma(N^c(s), s \leq t)$ and the complete (or joint) filtration $G_t = \sigma(N(s), C(s), s \leq t)$.

Under the independent censoring assumption, we have

$$
E(dN^c(t)|F^c_{t-}) = E(C(t)dN(t)|F^c_{t-})
$$

$$
= E(E(C(t)dN(t)|G_{t-})|F^c_{t-})
$$

$$
= E(C(t)E(dN(t)|G_{t-})|F^c_{t-})
$$

$$
= E(E(C(t)E(dN(t)|F_{t-})|F^c_{t-})
$$

$$
= E(C(t)Y(t)\lambda(t)|F^c_{t-})
$$

$$
= \lambda(t)E(\mathbb{I}(t \leq X \wedge U)|F^c_{t-})
$$

$$
= \lambda(t)\mathbb{I}(t \leq X \wedge U)
$$

$$
= C(t)Y(t)\lambda(t)
$$

where the third, fourth equalities are due to the left-continuity of $C(t)$ and the independent censoring assumption.

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5.2 Limit Theorems

5.2.1 Rebolledo’s Martingale Central Limit Theorem

Theorem 34 (Rebolledo’s martingale central limit theorem) Let \( \{M_t^{(n)} : t \in T\} \) be a vector of \( k \) local square integrable martingales for each \( n = 1, 2, \ldots \). For \( h = 1, \ldots, k \), define
\[
M_{eh}(t) = \sum_{s \leq t} M_{h}^{(n)}(\Delta s) \mathbb{1}(|M_{h}^{(n)}(\Delta s)| > \epsilon)
\]
where \( \epsilon \) is positive. Next, let \( M^{(\infty)} \) be a continuous Gaussian vector martingale with \( \langle M^{(\infty)} \rangle = [M^{(\infty)}] = V \), a continuous deterministic \( k \times k \) positive definite matrix-valued function on \( T \), with positive semidefinite increments, zero at zero. Assume the following conditions:

- \( \langle M_{eh}^{(n)} \rangle \to_d V(t) \) for all \( t \in T \) as \( n \to \infty \)
- \( \langle M_{eh}^{(n)} \rangle \to_d 0 \) for all \( t \in T, l \) and \( \epsilon > 0 \) as \( n \to \infty \)

Then
\[
M^{(n)} \to_d M^{(\infty)} \text{ in } (D(T))^k \text{ as } n \to \infty
\]
and \( \langle M^{(n)} \rangle \) and \( [M^{(n)}] \) converge uniformly on compact subsets of \( T \), in probability, to \( V \).

5.2.2 Gill’s Lemma

Lemma 35 (Gill, 1983) Suppose \( X^{(n)}(s) \to_p f(s) \) as \( n \to \infty \) for all \( s \) and the deterministic function \( f(s) \) is integrable over \([0, \tau]\). Furthermore, for all \( \delta > 0 \), there exists \( k_\delta \) with \( \int_0^\tau k_\delta > 0 \) such that
\[
\liminf_n \mathbb{P}(|X^{(n)}(s)| \leq k_\delta(s) \text{ for all } s) \geq 1 - \delta
\]
Then
\[
\sup_t \left| \int_0^t X^{(n)}(s)ds - \int_0^t f(s)ds \right| \to_p 0
\]

5.2.3 Lenglart’s Inequality

Lemma 36 (Lenglart’s inequality) Let \( M \) be a local square integrable martingale and \( \tau \) be the endpoint of \( M \), then we have
\[
\mathbb{P} \left( \sup_T |M| > \eta \right) \leq \frac{\delta}{\eta^2} + \mathbb{P}(\langle M \rangle(\tau) > \delta)
\]
for any positive \( \eta \) and \( \delta \).

5.2.4 The Functional Delta Method

Lemma 37 (The functional \( \Delta \)-method) Let \( T_n \) be a sequence of random elements of a Banach space \( B \), \( a_n \to \infty \) a real sequence such that \( a_n(T_n - \theta) \to_d Z \) for some fixed \( \theta \in B \) and a random element \( Z \in B \). Suppose \( \phi : B \to B' \) is Hadamard differentiable at \( \theta \). Then
\[
a_n(\phi(T_n) - \phi(\theta)) \to_d d\phi(\theta) \cdot Z
\]
where \( d\phi(\theta) \) is the derivative of \( \phi \) at \( \theta \).
Proof By Dudley-Skorohod-Wichura’s theorem, we can replace $d$ with $a.s.$ That is, the set $A = \{ \omega : \lim_{n \to \infty} a_n(T_n(\omega) - \theta) = Z(\omega) \}$ has probability 1. By Hadamard differentiability, we have $a_n(\phi(\theta + a_n^{-1} h_n(\omega)) - \phi(\theta)) \to d\phi(\theta)Z$ for any $\omega \in A$ where $h_n = a_n(T_n - \theta)$.

Example 17 (Product-Integration) Let $\phi$ be defined by

$$\phi(X) = \prod (I + dX)$$

and elements of $X$ are càdlàg and with total variation bounded by $M$. Then $\phi$ is Hadamard differentiable with derivative given by

$$(d\phi(X) \cdot H) = \int_{s \in [0,t]} \prod_{[0,s]} (I + dX)H(ds) \prod_{(s,t]} (I + dX)$$

where the last integral is defined by application (twice) of the integration by parts formula. In practice, $X$ may correspond to the Nelson-Aalen estimator and $\phi(\cdot)$ is the Kaplan-Meier estimator so that functional delta-method applies.

5.3 Product Integral and Markov Processes

Product Integral

Definition 38 (Product integral) Let $X(t), t \in \mathcal{T}$, be a $p \times p$ matrix of càdlàg functions of locally bounded variation. We define

$$Y = \prod (I + dX)$$

the product-integral of $X$ over intervals of the form $[0,t], t \in \mathcal{T}$, as the following $p \times p$ matrix function:

$$Y(t) = \prod_{s \in [0,t]} (I + X(ds)) = \lim_{\max \{t_i-t_{i-1}\} \to 0} \prod (I + X_{t_i} - X_{t_{i-1}})$$

where $0 = t_0 < t_1 < \cdots < t_n = t$ is a partition of $[0,t]$ and the matrix product is taken from left to right.

Jacod’s Theorem

Theorem 39 (Jacod, 1975 Dabrowska (2020)) Let $A$ be a càdlàg increasing function on $[0,\tau]$ where $0 < \tau \leq \infty$ such that $0 \leq A(\Delta u) < 1$ for $u < \tau$ and satisfying either

$$A(\tau^- < \infty), \ A(\Delta \tau) = 1$$

or

$$A(\tau^-) = \infty, \ A(\Delta \tau) = 0.$$ 

Then $S(t) = \int_{u \leq t} (1 - dA(u))$ is a survival function of a nonnegative random variable and

$$\tau = \inf \{ t : S(t) = 0 \}$$

is its upper support point.
Example 18 (Cox's lemma) Let $T$ be a nonnegative random variable and $S(t) = \mathbb{P}(T \geq t)$ be its survival function. Let $\Lambda(t), \Lambda(dt) = -S(dt)/S(t-), \Lambda(0) = 0$ be the associated cumulative hazard. Then we have

$$S(t) = \prod_{s \leq t} (1 - \Lambda(ds)) = \prod_{s \leq t} (1 - \Lambda(\Delta s)) \exp(-\Lambda_c(t))$$

where $\Lambda_c$ is the continuous part of $\Lambda$.

Duhamel's Equation

Theorem 40 (Duhamel's Equation) Let $Y = \prod (I + dA)$ and $Z = \prod (I + dB)$. Then

$$Y(t) - Z(t) = \int_{s \in [0,t]} \prod (I + dA)(A(ds) - B(ds)) \prod (I + dB).$$

This equation is useful we are deriving properties of the Aalen-Johansen estimator.

5.3.1 Markov Processes

Definition 41 (Intensity measure of a Markov processes) Suppose the off-diagonal elements of the $p \times p$ matrix function $A$ are nondecreasing càdlàg functions, zero at zero, $A_{hh} = -\sum_{j \neq h} A_{hj}$ and $A_{hh}(\Delta t) \geq -1$ for all $t$. Then we say $A$ corresponds to a locally finite intensity measure of a Markov process on a time interval $T$. The function $A_{hj}$ is called the integrated intensity function for transitions from state $h$ to state $j$, and $A_{hh}$ is the negative integrated intensity function for transitions out of state $h$.

5.3.2 A Key Theorem

Theorem 42 (Relation among PI, MP and CP) Let the matrix function $A$ correspond to an intensity measure. Define

$$P(s,t) = \prod_{(s,t]} (I + dA), \quad s \leq t; s,t \in T.$$

Then $P$ is the transition matrix of a Markov process $\{X(t) : t \in T\}$ with state space $\{1,2,\cdots,p\}$ and intensity measure $A$.

• Given that $X(t_0) = h$, then it remains in $h$ for a length of time with integrated hazard function

$$-(A_{hh}(t) - A_{hh}(t_0)), \quad t_0 \leq t \leq \inf\{u \geq t_0 : A_{hh}(\Delta u) = -1\}.$$

Given that $X$ jumps out of state $h$ at time $t$, it jumps into $j \neq h$ with probability $-(dA_{hj}/dA_{hh})(t)$.  

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Let $F_t = \sigma\{X(s) : s \leq t\}$ and define

$$Y_h(t) = \mathbb{I}(X(t-) = h)$$
$$N_{hj}(t) = \#\{s \leq t : X(s-) = h, X(s) = j\}, \quad h \neq j$$

Then $N = (N_{hj}, h \neq j)$ is a multivariate counting process and its compensator with respect to $(F_t) = (\sigma(X(0)) \lor N_t)$ has components

$$\Lambda_{hj}(t) = \int_0^t Y_h(s) A_{hj}(ds)$$

and equivalently, the processes $M_{hj} = N_{hj} - \Lambda_{hj}$ are martingales.

### 5.4 Jacod’s Formula for Likelihood Ratios

**Theorem 43 (Jacod’s Formula for the Likelihood Ratio)** Suppose $P$ and $Q$ are two probability measures on a filtered probability space $(F_t, \sigma\{N(s) : s \leq t\})$ under which $N$ has compensators $\Lambda$ and $\Gamma$, respectively. Suppose $Q \ll P$ and both compensators are absolutely continuous with intensity process $\lambda$ and $\gamma$, then

$$\frac{dQ}{dP} = \frac{dQ}{dP} \bigg|_{F_0} \prod_{h,t} \gamma_h(t)^{N_h(\Delta t)} \exp(-\Gamma.(\tau)) \prod_{h,t} \lambda_h(t)^{N_h(\Delta t)} \exp(-\Lambda.(\tau))$$

where $\tau$, as usual, is the terminal time point and $\Gamma = \sum_h \Gamma_h$ and $\Lambda = \sum_h \Lambda_h$ are the aggregated cumulative intensities.

#### 5.4.1 Partial Likelihood

**Example 19 (Partial Likelihood)** The right censored counting process $N^c = (N^c_{hi})$ of $N$ is given by $N^c_{hi} = \int_0^t C_i(s) dN_{hi}(s)$ where $C_i(s) = \mathbb{I}(s \leq U_i)$ and $U_i$ is the random censoring time. In the noninformative right-censoring setting, the partial likelihood $L^c(\theta)$ for $\theta$ based on the observed counting process is

$$L^c(\theta) = \prod_t \left\{ \prod_{i,h} d\Lambda^c_{hi}(t, \theta)^{\Delta N^c_{hi}(t)}(1 - d\Lambda^c_{hi}(t, \theta))^{1 - \Delta N^c_{hi}(t)} \right\}$$

$$\propto \prod_t \prod_{i,h} \lambda^c_{hi}(t, \theta)^{\Delta N^c_{hi}(t)} \exp \left( - \int_0^\tau \sum_{h,i} \lambda^c_{hi}(t, \theta) dt \right)$$

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