Shape Constrained Nonparametric Baseline Estimators in the Cox Model

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Meaningful metrics

Basic concepts in survival analysis

- Events of interest - death, onset (relapse) of a disease, etc
- Let $X \sim F$ denote the survival time, with density f
- Functions that characterize the distribution of X
    - The survival function $S(x) = \mathbb{P}(X > x)$
    - The hazard function

    $$\lambda(x) = \lim_{\Delta x \downarrow 0} \frac{\mathbb{P}(x \leq X < x + \Delta x | X \geq x)}{\Delta x} = \frac{f(x)}{S(x)}$$

    - The cumulative hazard function $\Lambda(x) = \int_0^x \lambda(u)\,\mathrm{d}u$
- Let $C \sim G$ denote the censoring time
- Let Z denote the covariate (age, weight, treatment)

The Cox proportional hazards model

- Right-censored data (T_i, Δ_i, Z_i), for $i = 1, \ldots, n$
  - $T = \min(X, C)$ denotes the follow-up time
  - $\Delta = \{X \leq C\}$ is the censoring indicator
  - The covariate vector $Z \in \mathbb{R}^p$ is time invariant
  - $X|Z \perp C|Z$
- The Cox model

$$\lambda(x|z) = \lambda_0(x) e^{\beta_0' z},$$

  where

  - λ_0 is the underlying baseline hazard function
  - $\beta_0 \in \mathbb{R}^p$ is the vector of the underlying regression coefficients

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Assumptions

- $X \sim F$, $C \sim G$, $T \sim H$
- F, G are assumed absolutely continuous.
- (A.1) Let τ_F, τ_G and τ_H be the end points of the support of F, G, H. Then

$$\tau_H = \tau_G < \tau_F$$

- (A.2) There exists $\varepsilon > 0$ such that

$$\sup_{|\beta - \beta_0| \leq \varepsilon} \mathbb{E}\left[|Z|^2 \, \mathrm{e}^{2\beta' Z} \right] < \infty,$$

where $|\cdot|$ denotes the Euclidean norm

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Estimating monotone baseline hazards in the Cox model

- The NPMLE $\hat{\lambda}_n$ of a nondecreasing baseline hazard
- Let $T_{(1)} \leq \cdots \leq T_{(n)}$ denote the ordered follow-up times
- For β fixed, maximize the (log)likelihood function over all nondecreasing baseline hazards and obtain $\hat{\lambda}_n(x;\beta)$
  - zero, for $x < T_{(1)}$
  - constant on $[T_{(i)}, T_{(i+1)})$, for $i = 1, 2, \ldots, n-1$
  - ∞, for $x \geq T_{(n)}$
- Replace β in $\hat{\lambda}_n(x;\beta)$ by $\hat{\beta}_n$, the maximum partial likelihood estimator
- We propose $\hat{\lambda}_n(x) = \hat{\lambda}_n(x;\hat{\beta}_n)$ as our estimator of λ_0

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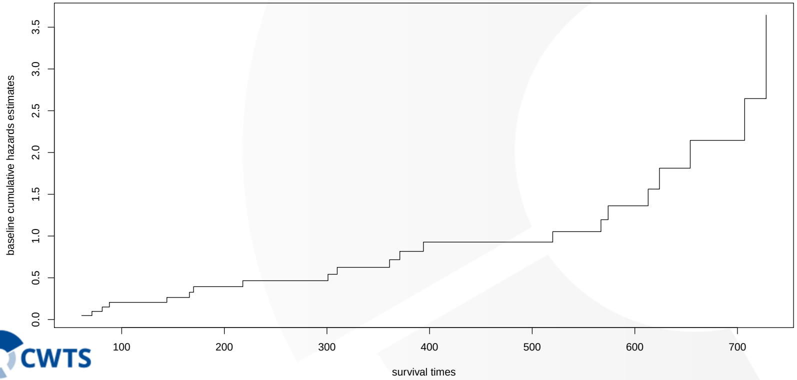
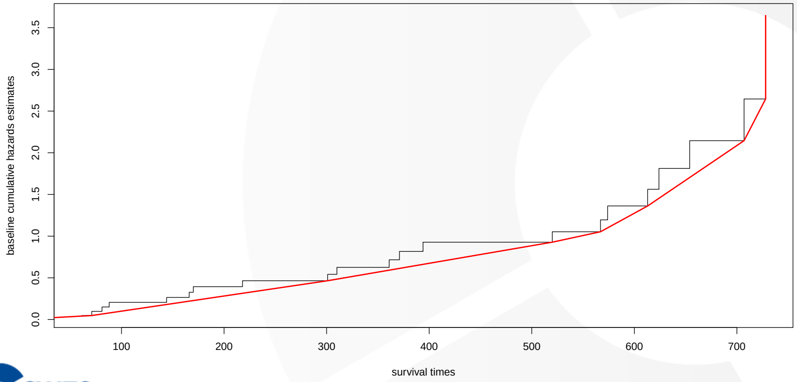
Estimating monotone baseline hazards in the Cox model

- Grenander-type estimator
- 1. Start from the Breslow estimator Λ_n of the baseline cumulative hazard Λ_0



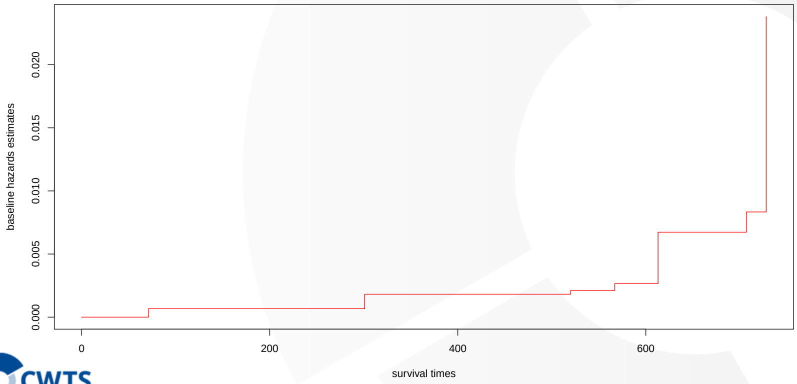
Estimating monotone baseline hazards in the Cox model

- 2. Take its Greatest Convex Minorant (GCM) $\widetilde{\Lambda}_n$



Estimating monotone baseline hazards in the Cox model

- 3. The Grenander-type estimator $\tilde{\lambda}_n$ is defined as the left-hand slope of $\widetilde{\Lambda}_n$

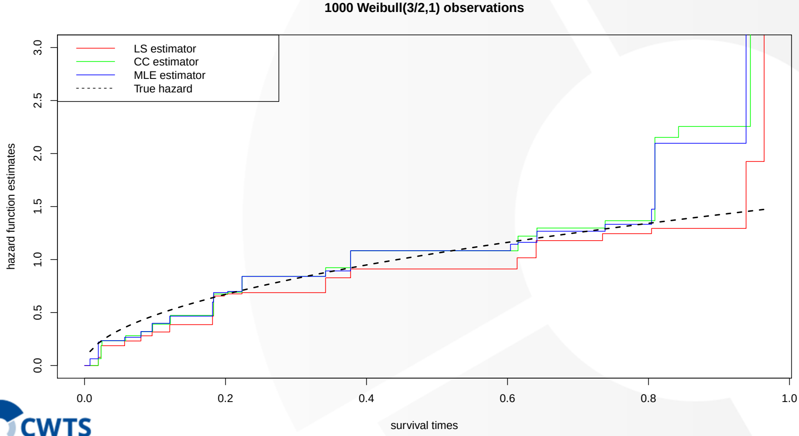


Estimating monotone baseline hazards in the Cox model

- Another estimator of a nondecreasing baseline hazard was proposed by Chung and Chang (1994)
- Consistency: $\hat{\lambda}_n^C(x) \to \lambda_0(x)$ *a.s.*
- No limiting distribution available

Estimating monotone baseline hazards in the Cox model

- Comparison between the three baseline hazard estimators



Estimating monotone baseline densities in the Cox model

- Grenander-type estimator of a monotone baseline density f_0
- Since
$$F_0(x) = 1 - \mathrm{e}^{-\Lambda_0(x)}$$
- We propose
$$F_n(x) = 1 - \mathrm{e}^{-\Lambda_n(x)},$$
where Λ_n is the Breslow estimator.
- Define the nonincreasing Grenander-type estimator $\tilde{f}_n$ as the left derivative of the Least Concave Majorant (LCM) of F_n

Pointwise consistency

- **Theorem 1** (Lopuhaä & Nane, 2013a)

  Assume that (A.1) and (A.2) hold and that λ_0 is nondecreasing on $[0, \infty)$ and f_0 is nonincreasing on $[0, \infty)$. Then, for any $x_0 \in (0, \tau_H)$,

$$
\begin{aligned}
\lambda_0(x_0-) \leq \liminf_{n\to\infty} \ \hat{\lambda}_n(x_0) \leq \limsup_{n\to\infty} \hat{\lambda}_n(x_0) \leq \lambda_0(x_0+), \\
\lambda_0(x_0-) \leq \liminf_{n\to\infty} \ \tilde{\lambda}_n(x_0) \leq \limsup_{n\to\infty} \tilde{\lambda}_n(x_0) \leq \lambda_0(x_0+), \\
f_0(x_0+) \leq \liminf_{n\to\infty} \ \tilde{f}_n(x_0) \leq \limsup_{n\to\infty} \tilde{f}_n(x_0) \leq f_0(x_0-),
\end{aligned}
$$

  with probability one. The values $\lambda_0(x_0-)$, $f_0(x_0-)$ and $\lambda_0(x_0+)$, $f_0(x_0+)$ denote the left (right) limit of the baseline hazard and density function at x_0.

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Asymptotic distribution

- Typical features for isotonic estimators
  - $n^{1/3}$ rate of convergence
  - non-normal limiting distribution
- Groeneboom (1985) recipe
  1. Define an inverse process
  2. Use the switching relationship
  3. Use the Hungarian embedding (KMT construction) to derive the limiting distribution of the inverse process
  4. Obtain the limiting distribution of the monotone estimator

Asymptotic distribution

- For the Grenander-type estimator $\tilde{\lambda}_n$
  1. Inverse process

     $$U_n(a) = \underset{x \in [0, T_{(n)}]}{\operatorname{argmin}} \left\{ \Lambda_n(x) - ax \right\},$$

     for $a > 0$, where argmin denotes the largest location of the minimum
  2. For any $a > 0$, the following switching relationship holds

     $$U_n(a) \geq x \Leftrightarrow \tilde{\lambda}_n(x) \leq a,$$

     with probability one

Asymptotic distribution

- For a fixed x_0,

$$\mathbb{P}\left(n^{1/3}\left[\tilde{\lambda}_n(x_0)-\lambda_0(x_0)\right]>a\right)$$
$$=\mathbb{P}\left(n^{1/3}\left[U_n(\lambda_0(x_0)+n^{-1/3}a)-x_0\right]<0\right)$$

- Moreover

$$n^{1/3}\left[U_n(\lambda_0(x_0)+n^{-1/3}a)-x_0\right]=\underset{x\in I_n(x_0)}{\operatorname{argmin}}\{\mathbb{Z}_n(x)-ax\},$$

where $I_n(x_0)=[-n^{1/3}x_0, n^{1/3}(T_{(n)}-x_0)]$ and for $x\in I_n(x_0)$

$$\begin{aligned}\mathbb{Z}_n(x)=n^{2/3}\Big\{&\left[\Lambda_n(x_0+n^{-1/3}x)-\Lambda_0(x_0+n^{-1/3}x)\right]\\&-[\Lambda_n(x_0)-\Lambda_0(x_0)]\\&+\Lambda_0(x_0+n^{-1/3}x)-\Lambda_0(x_0)-n^{-1/3}\lambda_0(x_0)x\Big\}\end{aligned}$$

Asymptotic distribution

- 3. No embedding available for the Breslow estimator
- 3'. Linearization result of the Breslow estimator (Lopuhaä & Nane, 2013b)
- Let $\Phi(\beta_0, x) = \mathbb{E}[\{T \geq x\}e^{\beta_0' Z}]$
- **Theorem 2** (Lopuhaä & Nane, 2013a)

  Assume $(A.1)$ and $(A.2)$ and let $x_0 \in (0, \tau_H)$. Suppose that λ_0 is nondecreasing on $[0, \infty)$ and continuously differentiable in a neighborhood of x_0, with $\lambda_0(x_0) \neq 0$ and $\lambda_0'(x_0) > 0$. Then,

$$n^{1/3}\left(\frac{\Phi(\beta_0, x_0)}{4\lambda_0(x_0)\lambda_0'(x_0)}\right)^{1/3}\left[\tilde{\lambda}_n(x_0) - \lambda_0(x_0)\right] \to_d \underset{t \in \mathbb{R}}{\operatorname{argmin}}\{W(t) + t^2\},$$

where W is a standard two-sided Brownian motion originating from zero.

Asymptotic distribution

- **Theorem 3** (Lopuhaä & Nane, 2013a)

  Assume $(A.1)$ and $(A.2)$ and let $x_0 \in (0, \tau_H)$. Suppose that λ_0 is nondecreasing on $[0, \infty)$ and continuously differentiable in a neighborhood of x_0, with $\lambda_0(x_0) \neq 0$ and $\lambda_0'(x_0) > 0$. Then,

$$n^{1/3} \left(\frac{\Phi(\beta_0, x_0)}{4\lambda_0(x_0)\lambda_0'(x_0)} \right)^{1/3} \left[\hat{\lambda}_n(x_0) - \lambda_0(x_0) \right] \to_d \underset{t \in \mathbb{R}}{\operatorname{argmin}} \{ W(t) + t^2 \},$$

  where W is a standard two-sided Brownian motion originating from zero.

Asymptotic distribution

- **Theorem 4** (Lopuhaä & Nane, 2013a)

  Assume $(A.1)$ and $(A.2)$ and let $x_0 \in (0, \tau_H)$. Suppose that f_0 is nonincreasing on $[0, \infty)$ and continuously differentiable in a neighborhood of x_0, with $f_0(x_0) \neq 0$ and $f_0'(x_0) < 0$. Let F_0 be the baseline distribution function. Then,

$$n^{1/3} \left(\frac{\Phi(\beta_0, x_0)}{4 f_0(x_0) f_0'(x_0)[1 - F_0(x_0)]} \right)^{1/3} \left[\tilde{f}_n(x_0) - f_0(x_0) \right] \to_d \underset{t \in \mathbb{R}}{\operatorname{argmin}} \{ W(t) + t^2 \},$$

  where W is a standard two-sided Brownian motion originating from zero.

Hypothesis testing

- Likelihood ratio test of $H_0 : \lambda_0(x_0) = \theta_0$ versus $H_1 : \lambda_0(x_0) \neq \theta_0$
- Let $L_\beta(\lambda_0)$ the (log)likelihood function
- For fixed $\beta \in \mathbb{R}^p$, $x_0 \in (0, \tau_H)$ and $\theta_0 \in (0, \infty)$ fixed

$$\text{maximize } L_\beta(\lambda_0) \text{ under } H_0$$

- Propose $\hat{\lambda}_n^0(x) = \hat{\lambda}_n^0(x; \hat{\beta}_n)$ as the constrained NPMLE

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Hypothesis testing

- Recall $\hat{\lambda}_n(x) = \hat{\lambda}_n(x; \hat{\beta}_n)$, the unconstrained NPMLE estimator of a nonincreasing λ_0
- By **Theorem 3**,

$$
\begin{aligned}
n^{1/3}\left[\hat{\lambda}_n(x_0) - \lambda_0(x_0)\right] &\to_d \left(\frac{4\lambda_0(x_0)\lambda_0'(x_0)}{\Phi(\beta_0, x_0)}\right)^{1/3} \underset{t\in\mathbb{R}}{\operatorname{argmin}}\{W(t) + t^2\} \\
&\equiv C(x_0)\underset{t\in\mathbb{R}}{\operatorname{argmin}}\{W(t) + t^2\} \\
&\equiv \frac{C(x_0)}{2} g(0),
\end{aligned}
$$

where g(x) is the slope at x of the GCM of $\{\mathbb{W}(t) + t^2\}$

Hypothesis testing

- Similarly, it can be shown that

$$n^{1/3}\left[\hat{\lambda}_n^0(x_0) - \lambda_0(x_0)\right] \to_d \frac{C(x_0)}{2} g^0(0),$$

where g^0 is the constrained slope process of the GCM of $\{\mathbb{W}(t) + t^2\}$

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Hypothesis testing

- Banerjee & Wellner (2001)

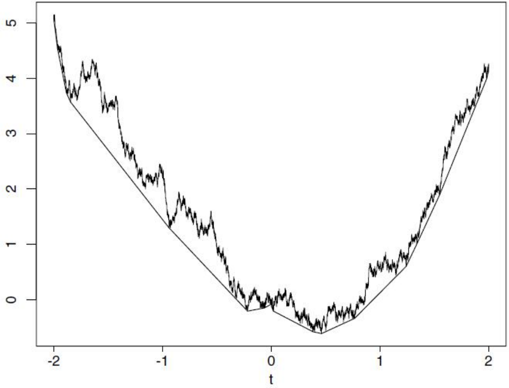

FIG. 3. *The one-sided convex minorants* $\tilde{G}_L$ *and* $\tilde{G}_R$ *and* $W(t) + t^2$.

Hypothesis testing

- Banerjee & Wellner (2001)

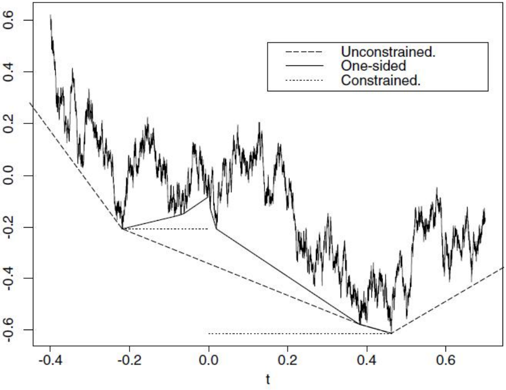

FIG. 4. *Close-up view of* $G_{1,1}$, $\tilde{G}_{L,R}$, $G^0_{1,1}$ *and* $W(t)+t^2$.

Hypothesis testing

- Replacing β by $\hat{\beta}_n$ in $L_\beta(\lambda_0)$ gives

$$2\log\xi_n(\theta_0) = 2L_{\hat{\beta}_n}(\hat{\lambda}_n) - 2L_{\hat{\beta}_n}(\hat{\lambda}_n^0)$$

- **Theorem 5** (Nane, 2013)

  Suppose that (A.1) and (A.2) hold and let $x_0 \in (0, \tau_H)$. Assume that λ_0 is nondecreasing on $[0, \infty)$ and continuously differentiable in a neighborhood of x_0, with $\lambda_0(x_0) \neq 0$ and $\lambda_0'(x_0) > 0$. Then, under the null hypothesis,

$$2\log\xi_n(\theta_0) \to_d \mathbb{D},$$

  where $\mathbb{D} = \int[(g(u))^2 - (g^0(u))^2]\mathrm{d}u$.

Interval estimation

- Pointwise confidence intervals for $\lambda_0(x_0)$
  - Likelihood ratio method

$$\{\theta : 2\log \xi_n(\theta) \leq q(\mathbb{D}, 1-\alpha)$$

where $q(\mathbb{D}, 1-\alpha)$ is the $(1-\alpha)^{th}$ quantile of $\mathbb{D}$
(Banerjee & Wellner, 2005)

  - Asymptotic distribution

$$[\hat{\lambda}_n(x_0) - n^{-1/3}\hat{C}_n(x_0)q(\mathbb{Z}, 1-\alpha/2), \hat{\lambda}_n(x_0) + n^{-1/3}\hat{C}_n(x_0)q(\mathbb{Z}, 1-\alpha/2)],$$

where $\mathbb{Z} = \text{argmin}\{\mathbb{W}(t) + t^2\}$ and $q(\mathbb{Z}, 1-\alpha/2)$ is the $(1-\alpha/2)^{th}$ quantile of the distribution $\mathbb{Z}$
(Groeneboom & Wellner, 2001)

Current research

- Citation analysis
  - Event of interest - time to first citation, 5^{th} citation, etc
  - Time frame - first five years after publication (field specific)
  - Censored data
  - Covariates - document type, collaboration type, number of authors, number of pages, etc
  - Nondecreasing baseline hazard

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References

- BANERJEE, M. and WELLNER, J.A. 2001. Likelihood ratio tests for monotone functions. The Annals of Statistics. Vol 29, No. 6, 1699 − 1731.
- BANERJEE, M. and WELLNER, J.A. 2005. Score statistics for current status data: comparisons with likelihood ratio and Wald statistics. International Journal od Biostatistics. Vol 1, Art. 1, 29 pp. (electronic).
- CHUNG, D. and CHANG, M.N. 1994. An isotonic estimator of the baseline hazard function in Cox's regression model under order restriction. Statistics & Probability letters. No. 21, 223 − 228.
- GREONEBOOM, P. 1985. Estimating a monotone density, In proceedings of the Berkeley conference in honor of Jerzy Neyman and Jack Kiefer , 2, 539 − 555.
- GREONEBOOM, P. and WELLNER, J.A. 2001. Computing Chernoff's distribution. Journal of Computational and Graphical Statistics. No. 10, 388 − 400.
- KOMLÓS,J.,MAJOR,P. and TUSNÁDY, G. 1975. An approximation of partial sums of independent r.v.'s and the sample d.f. Z.Wahrsch. verw. Gebiete, No. 32, 111 − 131.
- LOPUHAÄ, H.P. and NANE, G.F. 2013a. Shape constrained nonparametric estimators of the baseline distribution in Cox proportional hazards model. Scandinavian Journal of Statistics. Vol. 40, No. 3, 619 − 646.
- LOPUHAÄ, H.P. and NANE, G.F. 2013b. An asymptotic linear representation for the Breslow estimator. Communications in Statistics - Theory and Methods. No. 42, 1314–1324.
- NANE, G.F. 2013. A likelihood ratio test for monotone baseline hazard functions in the Cox model. Submitted. arxiv:1304.1295v1.