Semiparametric maximum likelihood for progression-related endpoints

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Trial endpoints based on disease progression

Entry 0 \rightarrow Clinic visits, dropout \rightarrow 1 \rightarrow Progression
Trial endpoints based on disease progression

- **Entry** (0)
  - Clinic visits, dropout
  - Study closure

- **Progression** (1)

- **Death** (2)
Semiparametric time-to-event models

Standard models specify each event “rate” or intensity process by

\[ \theta \quad \text{Euclidean regression coefficient,} \]
\[ \Lambda \quad \text{cumulative function of time.} \]

A well-known example is the Cox (1972) model for the event time \( T \) given covariate \( Z \)

\[ \alpha(t \mid Z) = \lambda(t) \exp(Z' \theta), \]

where \( \Lambda = \int \lambda \) is zero-at-time-zero and nondecreasing, but otherwise arbitrary.
Censoring

These models have provision for right censoring.

\[ T_i \quad C_i \quad 0 \quad C_j \quad T_j \quad \tau \]

This observation scheme can tough to achieve. For example progression is often assessed intermittently, leading to interval censoring.

\[ 0 \quad L \quad R \quad \tau \]
Guidelines for trialists

**TTP**  Time to progression, systematically imputed to first date when there is documented evidence of progression

**PFS**  Progression-free survival, defined as time from randomization to the earliest of progression or death

**FDA (2011)**  Censor by missing inspections, change in treatment

**EMA (2013)**  Censor according to intent-to-treat
Semiparametric maximum likelihood
for interval-censored data

Huang 1996  Cox model for “case 2” interval-censored survival data
Semiparametric maximum likelihood
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Zeng et al. 2006  Additive hazards model for “case 2” interval-censored survival data
Sun and Shen 2009  Cox model for interval-censored competing risks
Wen 2012  Cox model for “mixed case” interval-censored survival data with covariate error
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Wellner and Y Zhang 2007  Cox model for panel count data
Objectives

1. Cox model alternative for time to progression under interval censoring
2. Cox model for both progression and death under **dual censoring**
3. Adopt the semiparametric maximum likelihood approach
4. Implement new methods with interface based on Therneau’s (2012) **survival** package
Plan

1. Notation and basic assumptions
2. Cox-Aalen model for interval-censored data
3. Cox model for dual-censored data
4. Discussion
**Notation**

\[ S = T_{01} \land T_{02} \]  
exit time from the initial state 0

\[ T = T_{02} \land T_{12} \]  
entry time into the terminal state 2
Censoring mechanism
Coarsening at random (Gill et al. 1997; Heitjan and Rubin 1991)

The coarsening of \((S, T)\) to \(X\) arises from

\[ \varphi_G : (S, T) \mapsto X, \]

for some \(G\) with

\[ (S, T, G) \sim (\theta, \Lambda, \gamma) \in \Theta \times H \times \Gamma, \]

\(G \mid (S, T, Z)\) invariant on \((s, t) \in X\).

Often motivated by

\[ G \perp (S, T) \mid Z. \]
1. Notation and basic assumptions

2. Cox-Aalen model for interval-censored data

3. Cox model for dual-censored data

4. Discussion
Cox-Aalen model
for time to progression

For the progression time $T_{01}$, fixed covariates

$$W = (1, W_2, \ldots, W_{d_W})' \quad \text{and} \quad Z = (Z_1, \ldots, Z_{d_Z})',$$

assume a Cox-Aalen model (Scheike and MJ Zhang 2002)

$$\alpha(t \mid W, Z) = W' \lambda(s) \exp(Z' \theta),$$

where $\int \lambda = \Lambda$ with $W' \Lambda \geq 0$ a.s. nondecreasing and $W' \Lambda(\infty) \equiv \infty$. 
Cox-Aalen model
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where $\int \lambda = \Lambda$ with $W'\Lambda \geq 0$ a.s. nondecreasing and $W'\Lambda(\infty) \equiv \infty.$
Observation scheme

The occurrence of $T_{01}$ is inspected at a random number $K$ times

$Y_{K,0} \equiv 0 < \sigma < Y_{K,1} \leq \cdots \leq Y_{K,K} < \tau < \infty \equiv Y_{K,K+1}$.

These give event status $\Delta_{K,j}$, $j = 1, \ldots, K + 1$,

$\Delta_{K,j} = \begin{cases} 1, & \text{if } Y_{K,j-1} < T_{01} \leq Y_{K,j}; \\ 0, & \text{otherwise}. \end{cases}$
Observation scheme

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$$\Delta_{K,j} = \begin{cases} 1, & \text{if } Y_{K,j-1} < T_{01} \leq Y_{K,j}; \\ 0, & \text{otherwise.} \end{cases}$$

\[ \begin{array}{ccccccc}
\sigma & \quad & \quad & \quad & \quad & \quad & \tau \\
Y_{4,0} \equiv 0 & \quad & Y_{4,1} & \quad & Y_{4,2} & \quad & Y_{4,3} & \quad & Y_{4,4} & \quad & Y_{4,5} \equiv \infty \\
\Delta_{4,1} = 0 & \quad & \Delta_{4,2} = 0 & \quad & \Delta_{4,3} = 1 & \quad & \Delta_{4,4} = 0 & \quad & \Delta_{4,5} = 0 \\
\end{array} \]
Likelihood function \( \text{lik}_n(\theta, \Lambda) \)
for \( n \) iid observations from \((\theta_0, \Lambda_0)\)

If \( G = (K, Y_{K,1}, \ldots, Y_{K,K}) \) imposes \text{CAR}, then \( \text{lik}_n(\theta, \Lambda) \) is

\[
\prod_{i=1}^{n} \prod_{j=1}^{K_i} \left[ \exp\{-W_i'\Lambda(Y_{K_i,j-1})e^{Z_i'\theta}\} - \exp\{-W_i'\Lambda(Y_{K_i,j})e^{Z_i'\theta}\} \right]^{\Delta_{K_i,j}}.
\]
Likelihood function $\text{lik}_n(\theta, \Lambda)$

for $n$ iid observations from $(\theta_0, \Lambda_0)$

If $G = (K, Y_{K,1}, \ldots, Y_{K,K})$ imposes CAR, then $\text{lik}_n(\theta, \Lambda)$ is

$$\prod_{i=1}^{n} \prod_{j=1}^{K_i} \left[ \exp\{-W'_i \Lambda(Y_{K_i, j-1}) e^{Z^i \theta}\} - \exp\{-W'_i \Lambda(Y_{K_i, j}) e^{Z^i \theta}\} \right]^{\Delta^i_{K_i,j}}.$$

The MLE $(\hat{\theta}_n, \hat{\Lambda}_n)$ is defined by

$$\log \text{lik}_n(\hat{\theta}_n, \hat{\Lambda}_n) = \max_{\theta \in \Theta, \Lambda \in H} \log \text{lik}_n(\theta, \Lambda).$$
Support points
Maximal intersections

\( L_1 \quad R_1 \)
\( L_2 \quad R_2 \)
\( L_3 \quad R_3 \)
\( L_4 \quad R_4 \)
\( s_1 \quad t_1 \)
\( s_2 \quad t_2 \)
\( s_3 \quad t_3 \)
Definition of the SPMLE

“Relevant” inspections amount to the **censoring intervals**

\[(L_i, R_i] = (Y_{K_i,j-1}^i, Y_{K_i,j}^i], \quad \Delta_{K_i,j}^i = 1.\]

Let \(\mathcal{T} = \{(s_1, t_1], \ldots, (s_d, t_d]\} \) be the **maximal intersections** of \((L_1, R_1], \ldots, (L_n, R_n] \).

Adapting Turnbull (1976), for any maximizer \(\tilde{\Lambda}\):

- \(W' \tilde{\Lambda}\) is almost surely **constant** outside \(\mathcal{T}\) and
- **fixing** \(\tilde{\Lambda}\) on \(\text{ext}(\mathcal{T})\), \(\text{lik}_n(\theta, \tilde{\Lambda})\) is **invariant** to \(\tilde{\Lambda}\) on \(\text{int}(\mathcal{T})\).

Thus the **SPMLE** may concentrate on a **subset** of \(\{t_1, \ldots, t_d\}\).
Large sample properties
Application of Murphy and van der Vaart (2000) and van der Vaart and Wellner (1996)

Under regularity conditions

\[(\hat{\theta}_n, \hat{\Lambda}_n) \rightarrow (\theta_0, \Lambda_0) \text{ at } O_P(n^{-1/3}) \text{ on the support of the } Y_{k,j},\]

\[\sqrt{n}(\hat{\theta}_n - \theta_0) \sim N(0, \tilde{I}_0^{-1}),\]

where \(\tilde{I}_0\) is consistently estimated via the curvature of the log profile likelihood function at \(\hat{\theta}_n\)

\[\log \text{ plik}_n(\hat{\theta}_n) = \max_{\Lambda \in H} \log \text{ lik}_n(\hat{\theta}_n, \Lambda),\]
Computing the SPMLE
Constrained Newton algorithm

Put \( \lambda = (\Lambda(t_1)', \ldots, \Lambda(t_d)')' \), \( \phi = (\theta', \lambda')' \) and define \( B \) so that \( B\lambda \geq 0 \) ensures \( 0 \leq W'\lambda_{j-1} \leq W'\lambda_j \) for each \( j = 2, \ldots, d \).

The candidate step \( \eta^{(r)} = (\eta^{(r)\theta}', \eta^{(r)\lambda}')' \) combines Newton-Raphson:

\[
\eta^{(r)\theta} = -\nabla^2_{\theta} \log \text{lik}_n(\phi^{(r)})^{-1} \nabla_{\theta} \log \text{lik}_n(\phi^{(r)}),
\]

and quadratic programming:

\[
\eta^{(r)\lambda} = \arg \max_{\eta_{\lambda}:B(\lambda^{(r)}+\eta_{\lambda}) \geq 0} \nabla_{\lambda} \log \text{lik}_n(\phi^{(r)})'\eta_{\lambda} + \frac{1}{2} \eta_{\lambda}' \nabla^2_{\lambda} \log \text{lik}_n(\phi^{(r)})\eta_{\lambda}.
\]

A line search yields \( \phi^{(r+1)} \in \text{seg}(\phi^{(r)}, \phi^{(r)} + \eta^{(r+1)}) \).
Variance estimation

Entries of $\tilde{I}_0$ are estimated on the basis of the result

$$-2 \frac{\log \text{plik}_n(\hat{\theta}_n + \rho_n \nu_n) - \log \text{plik}_n(\hat{\theta}_n)}{n \rho_n^2} \xrightarrow{p} \nu' \tilde{I}_0 \nu,$$

where $\nu_n \xrightarrow{p} \nu$ and $(\sqrt{n} \rho_n)^{-1} = O_P(1)$.

There is little guidance on selecting $\rho_n$, but with methods from numerical differentiation the choice can be reduced to specifying “typical” and large (absolute) values for $\theta$. 
Simulation study
Setup

1000 replicates from

- $T_{01}$ following the hazard

$$\alpha(t \mid W, Z) = \left(t^{3/2} + W_2 t^{2/3}\right) \exp(Z_1 \log(2) - Z_2 \log(2)),$$

where $W_2 \sim U(0,1)$, $Z_1 \sim N(0,1)$ and $Z_2 \sim U\{0,1\}$

- $K$ and $Y_{K,1}, \ldots, Y_{K,K}$ based on $k$ equidistant “scheduled” visits on $(0, 2)$, subject to “noise”

Each visit after the first was missed with probability

$$p(W, Z) = \expit(\beta_0 + \beta_1 Z_2).$$
Simulation study

$k = 8$ scheduled visits, independent of $Z_2$

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<td>1.57</td>
<td>1.60</td>
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<td>0.45</td>
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<td>3.37</td>
<td>2.40</td>
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Simulation study

$k = 4$ scheduled visits, independent of $Z_2$

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<td>1.81</td>
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<td>.96</td>
<td>2.31</td>
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<td>1.37</td>
<td>.93</td>
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<td>.96</td>
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<td>2.50</td>
<td>2.51</td>
<td>.94</td>
<td>3.50</td>
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<tr>
<td></td>
<td>End</td>
<td>8.68</td>
<td>2.59</td>
<td>2.56</td>
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Simulation study

$k = 8$ scheduled visits, dependent on $Z_2$

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<tr>
<td></td>
<td>Mid</td>
<td>1.91</td>
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<td>6.77</td>
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1. Notation and basic assumptions

2. Cox-Aalen model for interval-censored data

3. Cox model for dual-censored data

4. Discussion
Existing work

Kalbfleisch and Lawless (1985) Panel data from a Markov process with closed-form forward equations. Extended by the \texttt{msm} package (Jackson 2013) and Titman (2011).

Frydman (1995) \texttt{NPML}, progression status always observed

Frydman and Szarek (2009) \texttt{NPML}, status missing

Cox model

for each $h \rightarrow j$ transition intensity

Let

$$N_{hj}(t) = 1_{(0,t]}(T_{hj}) \quad \text{and} \quad Y_h(t) = 1 - \sum_{j \neq h} N_{hj}(t-) .$$

Suppose $N_{hj}$ has intensity $Y_h \alpha_{hj}$ where

$$\alpha_{hj}(t \mid Z) = \lambda_{hj}(t) \exp(\theta' Z_{hj}),$$

$Z$ fixed covariate vector,

$Z_{hj}$ $h \rightarrow j$ specific version of $Z$,

$\Lambda_{hj} = \int \lambda_{hj}$ cumulative baseline intensity.
Dual censoring

$T$ right-censored with

\[ D \quad \text{right-censoring time}, \]
\[ V = T \wedge D \quad \text{last observation time}, \]
\[ \Delta_2 = 1(T \leq D). \]

$1(S < T)$ observed by the inspection process $Y$ yielding:

\[ (L, R] \quad \text{potential censoring interval for } T_{01}, \]
\[ \Delta_0 = 1\{\text{negative status known at } V\}, \]
\[ \Delta_1 = 1\{\text{positive status known at } V\}. \]
Dual censoring

Examples

Dual right censoring  \( Y(t) = 1(t \leq C) \) with \( C \leq D \) a right-censoring time for \( S \).

\[
\begin{array}{c}
C \\
0 \\
S = T_{01} \\
\hline
D \\
T = T_{12} \\
\tau
\end{array}
\]

Interval-censored progression times  \( Y \) positive at \( Y_{K,1}, \ldots, Y_{K,K} \) random times and possibly at \( V \).

\[
\begin{array}{c}
Y_{2,1} \\
Y_{2,2} \\
0 \\
\hline
D \\
T = T_{12} \\
\tau
\end{array}
\]
**Likelihood function**

If $G = (Y, D)$ imposes CAR, then $\text{lik}_n(\theta, \Lambda)$ is

$$
\prod_{i=1}^{n} \left[ \left\{ P_{00}(0, L_i \mid Z_i) P_{01}(L_i, R_i \mid Z_i) P_{11}(R_i, V_i \mid Z_i) \alpha_{12}(V_i \mid Z_i)^{\Delta_i^2} \right\}^{1-\Delta_0^i} + \left\{ P_{00}(0, V_i \mid Z_i) \alpha_{02}(V_i \mid Z_i)^{\Delta_i^2} \right\}^{1-\Delta_1^i} \right].
$$
Likelihood function

If $G = (Y, D)$ imposes \texttt{CAR}, then $\text{lik}_n(\theta, \Lambda)$ is

\[
\prod_{i=1}^{n} \left\{ P_{00}(0, L_i \mid Z_i) P_{01}(L_i, R_i \mid Z_i) P_{11}(R_i, V_i \mid Z_i) \alpha_{12}(V_i \mid Z_i)^{\Delta_i^2} \right\}^{1-\Delta_i^0} \\
+ \left\{ P_{00}(0, V_i \mid Z_i) \alpha_{02}(V_i \mid Z_i)^{\Delta_i^2} \right\}^{1-\Delta_i^1}.
\]

Replacing $\lambda_{hj}$ with $\Delta\Lambda_{hj}$ gives an \textbf{empirical} likelihood, but we can’t \textbf{jointly} estimate the increments

\[
\Delta\Lambda_{02}(V_i) \quad \text{and} \quad \Delta\Lambda_{12}(V_i),
\]

at any $V_i = T_i$ with unknown progression status $\Delta_0^i + \Delta_1^i = 0$. 

Method of sieves

Maximize likelihood over $\Theta \times H_n$ with $H_n \rightarrow H$ as $n \rightarrow \infty$.

Take $\Lambda_{hj}$ piecewise linear on

$$0 = t_{hj,0} < t_{hj,1} < \ldots < t_{hj,K_{hj,n}} < t_{hj,K_{hj,n+1}} = \tau,$$

where, for $0 < \kappa < 1$,

$$K_{hj,n} = O(n^\kappa), \quad \max(t_{hj,k} - t_{hj,k-1}) = O(n^{-\kappa}),$$

and $[t_{hj,k-1}, t_{hj,k})$ contains at least one of the $n_{hj}$ SPMLE support points based on subsample with $\Delta_0 + \Delta_1 = 1$. 
Large sample properties

Assuming

- \( \lim_{n \to \infty} n_{hj}/n > 0, h \neq j, \)
- \( \Pr(Y(t) = 1) > 0 \text{ on } (0, \tau], \)
- \( D^p \Lambda_0, p \geq 1, \text{ is continuous, positive and bounded on } (0, \tau], \)

and regularity conditions, the sMLE \((\hat{\theta}_n, \hat{\Lambda}_n)\) satisfies

\[
(\hat{\theta}_n, \hat{\Lambda}_n) \to (\theta_0, \Lambda_0) \text{ at } O_P(\max(n^{-(1-\kappa)/2}, n^{-r\kappa})),
\]

\[
\sqrt{n}(\hat{\theta}_n - \theta_0) \sim N(0, \tilde{I}_0^{-1}),
\]

where \(\tilde{I}_0 \approx \text{the curvature in } \max_{\Lambda \in H_n} \log \text{lik}_n(\hat{\theta}_n, \Lambda).\) The optimal choice for \(\kappa\) is \(1/(1 + 2p).\) For normality we need \(1/(4p) < \kappa < 1/2.\)
Computation of the smle
Self-consistency algorithm

Partition \([0, \tau]\) into subintervals \(\mathcal{T} = (\mathcal{T}_{h,j})_{h \neq j}\), each capturing

\[\left\lfloor n_{h,j} / (C_{h,j} n^K) \right\rfloor\] SPMLE support points.

Let \(\lambda\) be the piecewise constant values on \(\mathcal{T}\) and \(\phi = (\theta', \lambda')'\).

The candidate step combines Newton-Raphson and EM:

\[
\eta_\theta^{(r)} = - \nabla_\theta^2 \log \text{lik}_n(\phi^{(r)})^{-1} \nabla_\theta \log \text{lik}_n(\phi^{(r)}),
\]

\[
\eta_\lambda^{(r)} = \frac{\sum_i E_{\phi^{(r)}} \left( \int_{t_{k-1}}^{t_k} dN_{h,j}^i(s) \mid X_i \right)}{\sum_i \exp(\theta' Z_{h,j}^i) E_{\phi^{(r)}} \left( \int_{t_{k-1}}^{t_k} Y_h^i(s) \, ds \mid X_i \right)} - \lambda_{h,j,k}^{(r)}.
\]

A line search yields \(\phi^{(r+1)} \in \text{seg}(\phi^{(r)}, \phi^{(r)} + \eta^{(r+1)})\).
Simulation study

Setup

10000 replicates from \( Z \sim \text{U}\{0, 1\} \),

\[
\begin{align*}
A_{01}(t \mid Z) &= t^{4/5} \exp\{-Z \theta_1\}, \\
A_{02}(t \mid Z) &= 3t/4 \exp\{-Z \theta_2\}, \\
A_{12}(t \mid Z) &= (3t/2)^{5/4} \exp\{-Z \theta_3\},
\end{align*}
\]

where \( \theta_1 = \theta_2 = -\log(2) \) and \( \theta_3 = 0 \).

\( T \) right-censored by \( D = \tau = 2 \).

Dual right censoring  \( C \leq D \) possibly dependent on \( Z \) or \( T \).

Interval-censored progression times  Scheduled inspection process with noise and missingness possibly depending on \( Z \) or \( T \).
### Simulation study

**Dual right censoring with $C \perp T$**

<table>
<thead>
<tr>
<th>$n$</th>
<th>SMLE</th>
<th>Censored by C</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$\theta_{01}$</td>
<td>$\theta_{02}$</td>
</tr>
<tr>
<td>250</td>
<td>-0.47</td>
<td>-0.08</td>
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Simulation study
Dual right censoring with $C \not\sim T$

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Simulation study
SMLE under dual right censoring with $C \sim T$
Simulation study

SPMLE right-censored at $C \pm T$
## Simulation study

Interval-censored progression times with $k = 8$

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Simulation study

Interval-censored progression times with $k = 4$

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Simulation study

SMLE with $k = 4$
Simulation study

Imputation-based spmle with $k = 4$
Further work

- left truncation
- selection of tuning parameters controlling the sieve size
- Cox-Aalen model for panel count data
- covariate selection
- relaxing the Markov assumption
- confidence intervals for $\hat{\Lambda}_n$
Acknowledgements

Richard J. Cook
Jerald F. Lawless
Mary E. Thompson
Ker-Ai Lee
Thanks

audrey.boruvka@gmail.com
https://github.com/aboruvka/coxinterval
References


References (cont.)


References (cont.)


References (cont.)


