A penalized algorithm for event-specific rate models for recurrent events

Olivier Bouaziz (1) and Agathe Guilloux (2)

(1) MAP5, Université Paris Descartes, 75006 Paris, France
(2) LSTA, Université Paris 6, 75005 Paris, France

Introduction

- Recurrent events arise in clinical or epidemiological studies when each subject experiences repeated events over time. In this context, the statistician aims at estimating the rate function which represents the odds of experiencing a new recurrent event at a given time.
- In this work we consider a stratified Cox model and a stratified Aalen model with respect to the number of recurrent events. To estimate the rate function a covariate-specific total variation penalty is introduced.

Modeling the rate function

- Process of interest: $\tilde{N}(t)$. Counts the number of recurrent events occurring in $[0, t], t \geq 0$. No recurrent events occur after D, the terminal event.
- Observations:

$$\begin{cases} X_i(t) = (X_i^1(t), \ldots, X_i^p(t)) \\ T_i = D_i \wedge C_i \\ \delta_i = \mathbb{1}_{D_i \leq C_i} \\ N_i(t) = \tilde{N}_i(t \wedge T_i), i = 1, \ldots, n. \end{cases}$$

- ρ_0 is the event specific rate function of $\tilde{N}$ and verifies:

$$\mathbb{E}\left[d\tilde{N}(t) | X(t), \{\tilde{Y}^s(t)\}_{s=1,\ldots,B}\right] = \sum_{s=1}^{B} \tilde{Y}^s(t)\rho_0(t, X(t), s)dt$$

where $\tilde{Y}^s(t) = \mathbb{1}_{D \geq t, \tilde{N}(t-)=s-1}$.

Multiplicative and additive models

- In the **Cox model** we suppose that:

$$\rho_0(t, X(t), s) = \alpha_0(t, s) \exp(X(t)\beta_0(s)).$$

- In the **Aalen model** we suppose that:

$$\rho_0(t, X(t), s) = \alpha_0(t, s) + X(t)\beta_0(s).$$

  - $\beta_0(s) = (\beta_0^1(s), \ldots, \beta_0^p(s))^\top$ is an unknown p-dimensional vector of parameters.
  - α_0 is an unknown baseline function.

Estimation procedure of the regression parameters

- In the **Cox model** the criterion to minimize is a stratified partial likelihood:

$$L_n(\beta) = -\frac{1}{n}\sum_{s=1}^{B}\sum_{i=1}^{n}\int \left(X_i(t)\beta(s) - \log\left(S_n(s, t)\right)\right) Y_i^s(t)dN_i(t),$$

$S_n(s, t) = \sum_{j=1}^{n} Y_j^s(t) \exp\left(X_j(t)\beta(s)\right)$, $Y^s(t) = \mathbb{1}_{T \geq t, N^*(t-)=s-1}$.

- In the **Aalen model** the criterion to minimize is a stratified partial least-squares criterion:

$$L_n(\beta) = \sum_{s=1}^{B}\left\{\beta(s)^\top \mathbf{H}_n(s)\beta(s) - 2h_n(s)\beta(s)\right\},$$

$\mathbf{H}_n(s) = \frac{1}{n}\sum_{i=1}^{n}\int Y_i^s(t)\left(X_i(t) - \bar{X}^s(t)\right)^{\otimes 2}dt$,
$h_n(s) = \frac{1}{n}\sum_{i=1}^{n}\int Y_i^s(t)\left(X_i(t) - \bar{X}^s(t)\right)dN_i(t)$,
$\bar{X}^s(t) = \sum_{i=1}^{n} X_i(t)Y_i^s(t) / \sum_{i=1}^{n} Y_i^s(t)$.

- In both cases we estimate β_0 using a total-variation penalty:

$$\hat{\beta} = \underset{\beta \in \mathbb{R}^{p \times B}}{\operatorname{argmin}}\left\{L_n(\beta) + \frac{\lambda_n}{n}\sum_{j=1}^{p} \mathrm{TV}(\beta^j)\right\},$$

where $\mathrm{TV}(\beta^j) = \sum_{s=2}^{B} |\beta^j(s) - \beta^j(s-1)|$.

  - If $\lambda_n = 0$, we obtain a different estimator for each s, $\hat{\beta}^j(1) \neq \cdots \neq \hat{\beta}^j(B)$. This is the unconstrained estimator of Prentice, Williams and Peterson (1981).
  - If $\lambda_n/n = +\infty$, we obtain a constant estimator, $\hat{\beta}^j(1) = \cdots = \hat{\beta}^j(B)$.

Asymptotic results and extension

- If $\lambda_n/n \to 0$ then $\hat{\beta} \to \beta_0$ in probability.
- If $\lambda_n/\sqrt{n} \to \lambda_0 \geq 0$ then $\sqrt{n}(\hat{\beta} - \beta_0)$ has an asymptotic distribution.
  - The case $\lambda_0 = 0$ ensures this distribution to be gaussian.
- The estimation procedure is not consistent in selection.
  - We consider a reweighted TV-penalty in order to enhance the sparsity in the covariate-specific successive differences in the manner of Zhou (2006) or Candès, Wakin and Boyd (2008).

Simulation study

- Design
  - $p = 4$, $X^j \sim U[0, 2]$, $j = 1, \ldots, 4$.
  - $B = 5$ and $n = 50 (= 2.5pB)$ to $n = 1\,000 \simeq (pB)^{2.3}$.
  - $\beta_0^1 = 0.25(0, 0, 1, 1, 0)$, $\beta_0^2 = (1, 1, 1, 1, 1)$, $\beta_0^3 = b(1, 2, 3, 4, 5)$, $\beta_0^4 = (0, 0, 0, 0, 0)$. Cox: b=-1, Aalen: b=4.
  - $\alpha_0 \sim$ Weibull$(1.5, 1)$.
  - 15% of individuals experienced five tumour recurrences.

Cox	Unconstrained			Constant			TV			reweighted TV		
n	MSE	SPEC	SENS	MSE	SPEC	SENS	MSE	SPEC	SENS	MSE	SPEC	SENS
50	5576.511	0	1	225.077	1	0	72.732	0.271	0.813	67.697	0.598	0.68
100	64.231	0	1	216.658	1	0	46.484	0.226	0.844	39.562	0.583	0.709
500	12.447	0	1	212.578	1	0	17.232	0.18	0.911	17.998	0.917	0.559
1000	9.06	0	1	213.292	1	0	14.215	0.192	0.9	17.353	0.983	0.512

Aalen	Unconstrained			Constant			TV			reweighted TV		
n	MSE	SPEC	SENS	MSE	SPEC	SENS	MSE	SPEC	SENS	MSE	SPEC	SENS
50	1208.174	0	1	398.849	1	0	367.377	0.312	1	480.105	0.601	0.992
100	534.269	0	1	360.757	1	0	221.454	0.241	1	283.258	0.582	1
500	202.669	0	1	339.446	1	0	139.481	0.154	1	171.794	0.525	1
1000	168.751	0	1	337.813	1	0	133.39	0.103	1	157.899	0.471	1

$\hat{\beta}_m$: estimation in sample $m = 1, \ldots, 500$. $\mathrm{MSE} = \frac{10^3}{500}\sum_{m=1}^{500}\frac{\|\hat{\beta}_m - \beta_0\|^2}{\|\beta_0\|^2}$

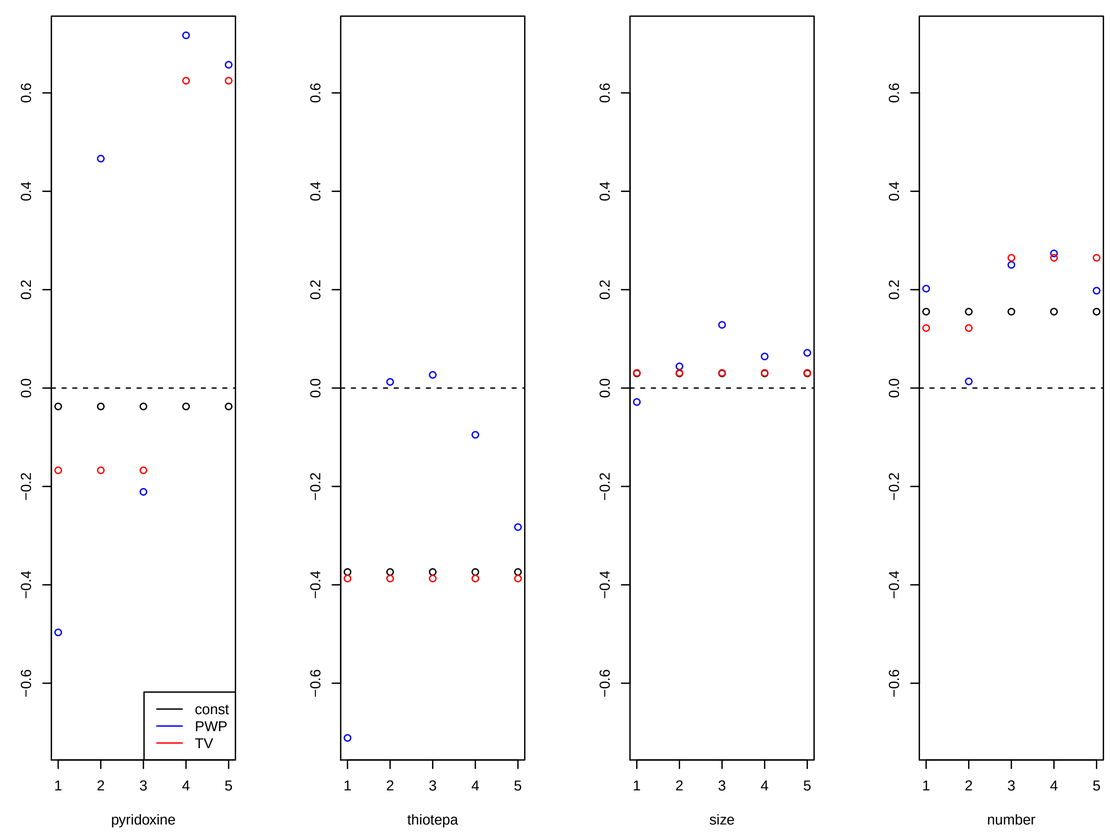
$\mathrm{FP}(\hat{\beta}_m) = \mathrm{Card}\left(j \in \{1, \ldots, p\} : \mathrm{TV}(\hat{\beta}_m^j) \neq 0 \text{ and } \mathrm{TV}(\beta_0^j) = 0\right)$
$\mathrm{FN}(\hat{\beta}_m) =$ $=$ $\neq$
$\mathrm{TP}(\hat{\beta}_m) = \mathrm{Card}\left(j \in \{1, \ldots, p\} : \mathrm{TV}(\hat{\beta}_m^j) \neq 0 \text{ and } \mathrm{TV}(\beta_0^j) \neq 0\right)$
$\mathrm{TN}(\hat{\beta}_m) =$ $=$ $=$

$\mathrm{SPEC} = \frac{1}{500}\sum_{m=1}^{500}\frac{\mathrm{TN}(\hat{\beta}_m)}{\mathrm{TN}(\hat{\beta}_m)+\mathrm{FP}(\hat{\beta}_m)}$ and $\mathrm{SENS} = \frac{1}{500}\sum_{m=1}^{500}\frac{\mathrm{TP}(\hat{\beta}_m)}{\mathrm{TP}(\hat{\beta}_m)+\mathrm{FN}(\hat{\beta}_m)}$.

Bladder tumour data analysis of Byar (1980)

- Data
  - $n = 116$ patients were recorded their time to tumour recurrence.
  - $B = 5$ maximum tumour recurrences.
  - X_i : four dimensional covariate variable. Number of initial tumours, size of the largest tumour, two treatment variables. ($\sqrt{n} \simeq 10.77 < p \times B = 20$)
  - 13.79% of patients experienced at least five tumour recurrences.

Estimates of the regression parameters for the Cox model



- **Overparametrization** for the unconstrained estimator of Prentice, Williams and Peterson (PWP): this estimator is not interpretable!
- Lack of information for the constant estimator: the pyridoxine treatment has a **global protective effect** for experiencing a new tumour recurrence.
- The TV estimator reaches a compromise between the constant and unconstrained estimators: for example, the pyridoxine treatment produces a **protective** effect for the first three tumour recurrences but the hazard rate of further recurrences is **increased** by this treatment.

New R functions

- **http://www.lsta.upmc.fr/guilloux.php?main=publications**

Email: olivier.bouaziz@parisdescartes.fr