Regularized hazard estimation for age-period-cohort analysis

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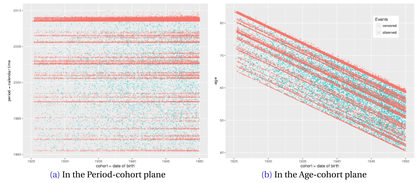
Presentation of the problem

The **E3N Cohort Study** [1]:

- Epigemiological study focused on the link between cancer and nutrition (part of EPIC).
- Population: ~ 100000 women (mostly teachers).
- Medical data gathered every 2-3 years using questionnaires (9 questionnaires in total). Diet, physical exercice and medical treatments are monitored.
- Blood and saliva samples are also gathered for som participants (not used here).
- The event of interest is the **occurrence of breast cancer**
- These occurrences are spread over the period [1990, 2010]

Objective: estimate the hazard rate of breast cancer occurrence

Representation of the data:



(a) In the Period-cohort plane (b) In the Age-cohort plane

Right-Censoring

The age of cancer occurrence is observed for only 7% of the individuals.

- T_i is the age of cancer onset.
- We do not observe $(T_i)_i$ but

$$Y_i = \min(T_i, C_i)$$

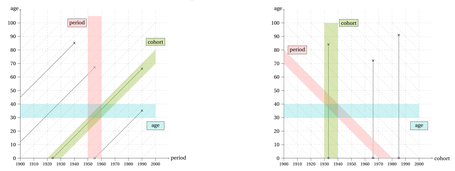
where C is a censoring r.v. independent from T.

- We observe $\Delta_i = 1_{T_i = Y_i}$.
- We infer the instantenous hazard rate

$$\lambda(t) = \lim_{dt \to 0} \frac{\mathbb{P}(t \leq T \leq t + dt | T \geq t)}{dt}$$

Age-Period-Cohort analysis

The hazard depends also on the date of birth



period = calendar time cohort = date of birth

The hazard is a function of **age**, **period**, and **cohort**.

Existing Models in age-period-cohort Analysis

In the literature: we infer α, β, and γ, parameters of the age, cohort and period effetcs.

- In the AGE-COHORT Model, it is assumed that

$$\log \lambda_{j,k} = \alpha_j + \beta_k$$

  - $J + K - 1$ parameters for JK variables: regularizing
  - Strong *a priori* on λ.
- In the AGE-PERIOD-COHORT Model, it is assumed that

$$\log \lambda_{j,k} = \alpha_j + \beta_k + \gamma_{j+k-1}$$

  - Regularizing
  - Strong *a priori* on λ
  - Non identifiable

New Approach: Penalized Likelihood

Reparametrization:

$$\log \lambda_{j,k} = \eta_{j,k},$$

The unpenalized negative log-likelihood ℓ_n takes the form

$$\ell_n(\boldsymbol{\eta}) = \sum_{j=1}^{J} \sum_{k=1}^{K} \exp(\eta_{j,k}) R_{j,k} - \eta_{j,k} O_{j,k},$$

where

- $O_{j,k}$ = number of observed events in the (j,k)-th rectangle
- $R_{j,k}$ = total time at risk in the (j,k)-th rectangle

The MLE is explicit:

$$\hat{\eta}_{j,k}^{\text{mle}} = \log\left(\frac{O_{j,k}}{R_{j,k}}\right) \quad \rightarrow \quad \text{overfitting.}$$

Our model has no *a priori*. But the inference is made by minimizing the **penalized likelihood** [2]

$$\ell_n^{\text{pen}}(\boldsymbol{\eta}) = \underbrace{\ell_n(\boldsymbol{\eta})}_{\substack{\text{goodness} \\ \text{of fit}}} + \underbrace{\frac{\text{pen}}{2} \sum_{j,k} v_{j,k} (\eta_{j+1,k} - \eta_{j,k})^2 + w_{j,k} (\eta_{j,k+1} - \eta_{j,k})^2}_{\text{regularization}}$$

- $\boldsymbol{v}$ et $\boldsymbol{w}$ are weights
- pen is a penalty constant

Types of regularization

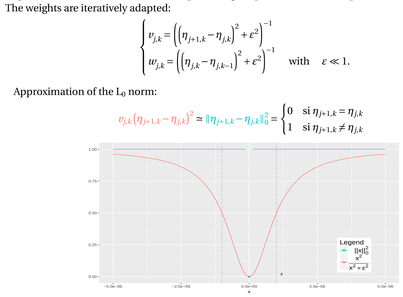
- Ridge Regularisation – L_2 norm with $\boldsymbol{v} = \boldsymbol{w} = \mathbf{1}$ → Smoothed estimation
- Regularisation L_0 with the iterative **Adaptive Ridge** [3] procedure → Segmented estimation

The weights are iteratively adapted:

$$\begin{cases} v_{j,k} = \left((\eta_{j+1,k} - \eta_{j,k})^2 + \varepsilon^2 \right)^{-1} \\ w_{j,k} = \left((\eta_{j,k} - \eta_{j,k-1})^2 + \varepsilon^2 \right)^{-1} \end{cases} \quad \text{with} \quad \varepsilon \ll 1.$$

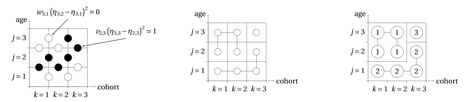
Approximation of the L_0 norm:

$$v_{j,k} (\eta_{j+1,k} - \eta_{j,k})^2 \approx \| \eta_{j+1,k} - \eta_{j,k} \|_0^2 = \begin{cases} 0 & \text{si } \eta_{j+1,k} = \eta_{j,k} \\ 1 & \text{si } \eta_{j+1,k} \neq \eta_{j,k} \end{cases}$$



Principle of Model Selection using the L_0 norm

1. We alternate until convergence between:
   - Minimize $\ell_n^{\text{pen}}(\boldsymbol{\eta})$ for fixed $\mathbf{v}$ and $\mathbf{w}$.
   - Adapt $\mathbf{v}$ and $\mathbf{w}$ using $\boldsymbol{\eta}$.
2. Then, the weighted differences of $\boldsymbol{\eta}$ are used to **select areas over which the hazard is constant**:



Step 1: Representation of $v_{j,k}(\eta_{j+1,k} - \eta_{j,k})^2$ et $w_{j,k}(\eta_{j,k+1} - \eta_{j,k})^2$

Step 2: Create corresponding graph

Step 3: Each connex component yields a constant area

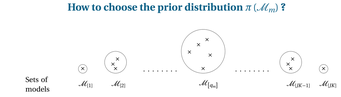
3. On each area : $\boldsymbol{\eta}$ is estimated by unpenalized maximum likelihood.

Bayesian Selection Criteria

- Problem: how to choose between m penalties $\text{pen}_1, \ldots, \text{pen}_m$?
- In other words: how to choose between M models $\mathscr{M}_1, \ldots, \mathscr{M}_M$ of dimensions $q_1, \ldots, q_M$?
- Solution: maximize $\mathbb{P}(\mathscr{M}_m | \boldsymbol{R}, \boldsymbol{O}) \propto \mathbb{P}(\boldsymbol{R}, \boldsymbol{O} | \mathscr{M}_m) \pi(\mathscr{M}_m)$.
- By approximation:

$$-2 \log(\mathbb{P}(\mathscr{M}_m | \boldsymbol{R}, \boldsymbol{O})) = 2\ell_n(\hat{\eta}_m) + q_m \log n - 2 \log \pi(\mathscr{M}_m) + \mathcal{O}_{\mathbb{P}}(1)$$

How to choose the prior distribution $\pi(\mathscr{M}_m)$?



$\mathscr{M}_{(q_m)}$ is the set of models of dimension q_m

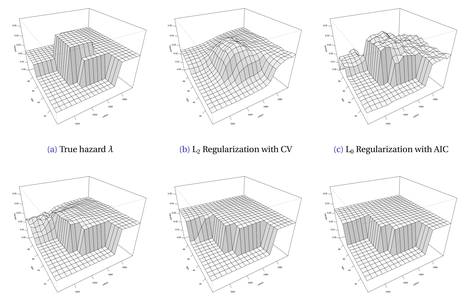
BIC: $\pi(\mathscr{M}_m) = 1$
All $\mathscr{M}_m$ are equipossible
All models are equipossible

EBIC$_0$: $\mathbb{P}\left(\mathscr{M}_m \in \mathscr{M}_{(q_m)}\right) = 1$
All $\mathscr{M}_{(q_m)}$ are equipossible
All model dimensions are equipossible [4]

We will compare three criteria: the **EBIC$_0$**, the **BIC**, the **AIC** and the cross-validation.

Simulation Results: with a piecewise constant hazard

- 4000 **data points** are generated using the true hazard
- The hazard is estimated using different methods
- We represent the **median estimate** of 100 such replications

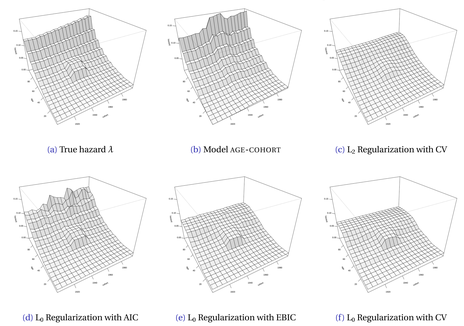


(a) True hazard λ (b) L_2 Regularization with CV (c) L_0 Regularization with AIC

(d) L_0 Regularization with BIC (e) L_0 Regularization with EBIC (f) L_0 Regularization with CV

Simulation Results: with a smooth hazard

Simulations are carried under the same conditions, but with a non-piecewise true hazard.

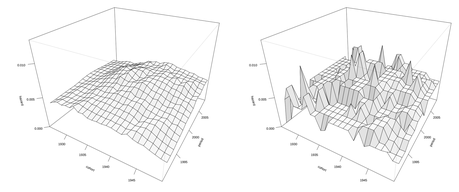


(a) True hazard λ (b) Model AGE-COHORT (c) L_2 Regularization with CV

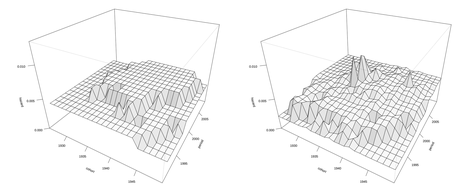
(d) L_0 Regularization with AIC (e) L_0 Regularization with EBIC (f) L_0 Regularization with CV

Application to real data: The E3N Cohort

The hazard is estimated using different methods:



(a) L_2 Regularization with CV (b) L_0 Regularization with AIC



(c) L_0 Regularization with EBIC (d) **Bootstrapped** L_0 Regularization with EBIC

Figure (d) is a obtained by ENSEMBLE method: the data is sampled 100 times, yielding 100 models. We represent the median of the corresponding hazards.

Conclusion & Perspectives

- The method allows a **segmented estimation** of the hazard
- EBIC$_0$ more efficient than AIC or BIC
- The model can be extended:

$$\log \lambda_{j,k} = \underbrace{\alpha_j}_{\text{age effet}} + \underbrace{\beta_k}_{\text{cohort effect}} + \underbrace{\delta_{j,k}}_{\text{interaction term}}$$

with regularization over $\delta_{j,k}$.

References & Ackownledgment

References

[1] E Clavel-Chapelon et al, *Cohort profile: the French E3N cohort study.* International journal of epidemiology, 2014.

[2] O. Bouaziz and G. Nuel, *L0 Regularization for the Estimation of Piecewise Constant Hazard Rates in Survival Analysis.* Applied Mathematics, 2017.

[3] E Frommlet and G. Nuel, *An Adaptive Ridge Procedure for L0 Regularization.* PloS one, 2016.

[4] J. Chen and J. Chen, *Extended Bayesian information criteria for model selection with large model spaces.* Biometrika, 20008.

Acknowledgment

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