Interaction Effect in Age-Period-Cohort Analysis

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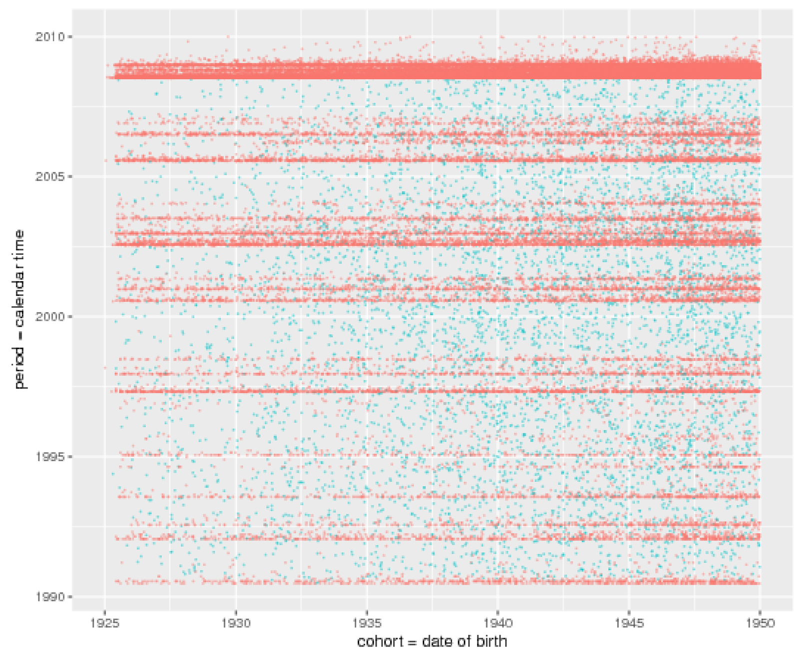
Motivating Example

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

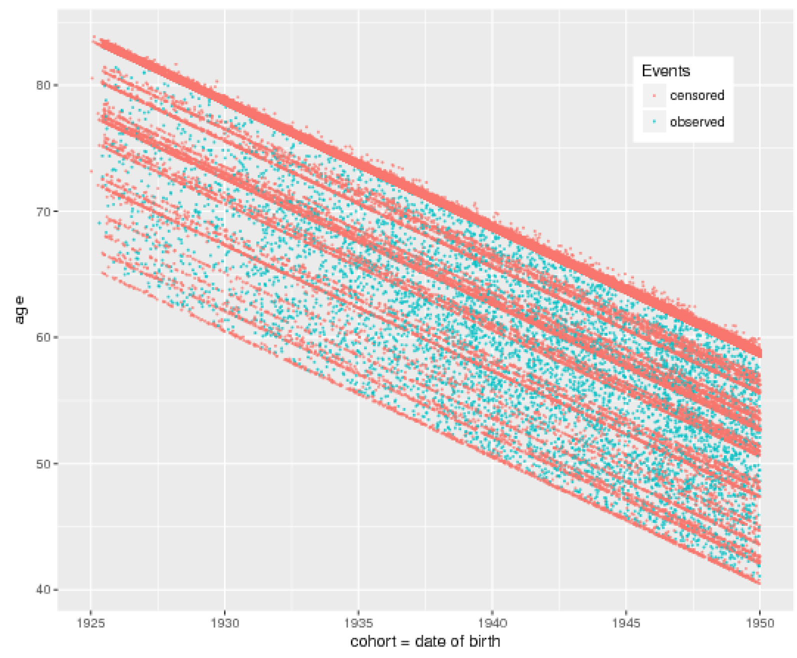
- Epidemiological study on the link between cancer and nutrition (EPIC).
- Population: $\sim$ **100000 women**.
- Medical data gathered every 2-3 years using questionnaires.
- Blood and saliva samples are also gathered for some participants (not used here).
- The event of interest is the **occurrence of breast cancer**
- These occurrences are spread over the period $[1990, 2010]$

Goal: estimate the incidence of breast cancer as a function of age and cohort

Data in the Period-cohort plane



Data in the Age-cohort plane



Right-censoring

- T_i is the age of cancer onset, U_i is the date of birth.
- We do not observe (T_i) but

$$Y_i = \min(T_i, C_i) \quad \text{and} \quad \Delta_i = 1_{T_i = Y_i}$$

where C is a censoring r.v. independent from (U, T).

- We infer the bivariate hazard rate

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

Existing Models in Age-Period-Cohort Analysis

In the literature: we infer $\boldsymbol{\alpha}$, $\boldsymbol{\beta}$, and $\boldsymbol{\gamma}$, parameters of the age, cohort and period effetcs.

- In the AGE-COHORT model,

$$\log \lambda_{\mathbf{j,k}} = \alpha_{\mathbf{j}} + \beta_{\mathbf{k}}$$

  - $J + K - 1$ parameters for JK variables: regularizing
  - Strong *a prior* on λ.

- In the AGE-PERIOD-COHORT model,

$$\log \lambda_{\mathbf{j,k}} = \alpha_{\mathbf{j}} + \beta_{\mathbf{k}} + \gamma_{\mathbf{j+k-1}}$$

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

The Age-Cohort-Interaction model

- We introduce the AGE-COHORT-INTERACTION model:

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

where $\delta_{\mathbf{j,k}}$ is the **interaction** between age and cohort.

- Estimation by penalized likelihood:

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

Aim: enforce $\delta_{j,k} \simeq 0$ except where relevant.

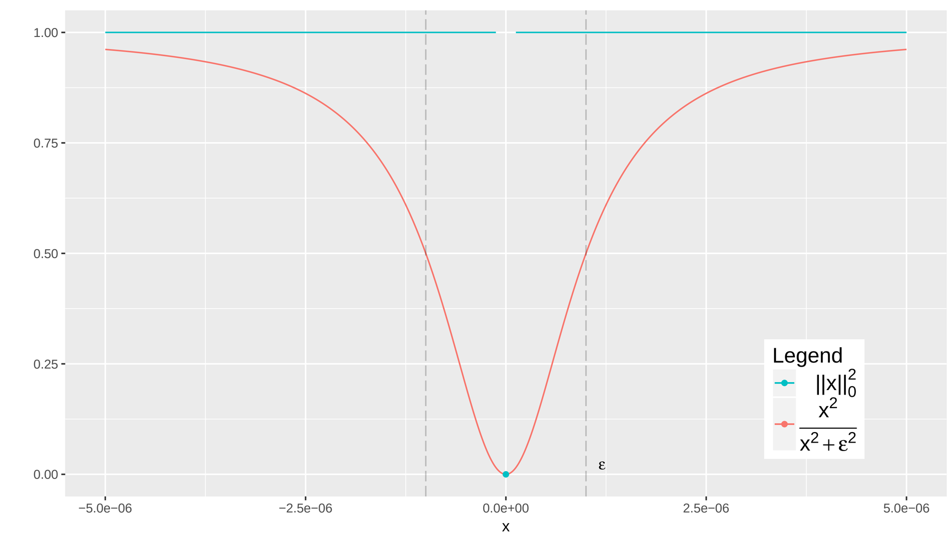
Regularization using L_0 penalization

- We enforce $\boldsymbol{\delta}$ to be **piecewise constant**.
- Fused L_0 regularization with the iterative **Adaptive Ridge** [3] procedure.
- The estimation is iterative:

$$\begin{cases} v_{j,k} = \left(\left(\delta_{j+1,k} - \delta_{j,k}\right)^2 + \varepsilon^2\right)^{-1} \\ w_{j,k} = \left(\left(\delta_{j,k} - \delta_{j,k-1}\right)^2 + \varepsilon^2\right)^{-1} \end{cases}$$

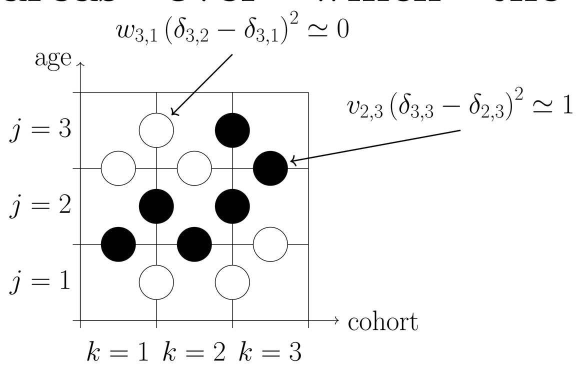
Principle of the approximation:

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

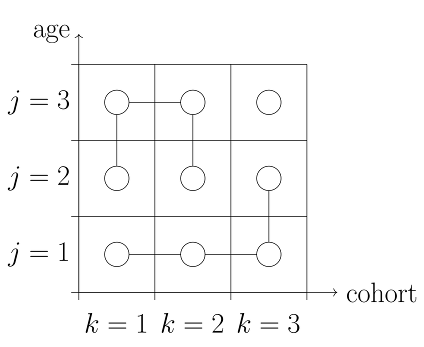


Model Selection with L_0 norm

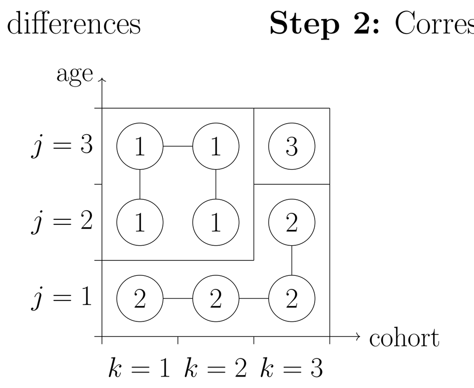
1. We alternate until convergence:
   - Minimize $\ell_n^{\text{pen}}(\boldsymbol{\theta})$ for fixed $\mathbf{v}$ and $\mathbf{w}$.
   - Adapt $\mathbf{v}$ and $\mathbf{w}$ using $\boldsymbol{\theta}$.
2. The weighted differences of $\boldsymbol{\eta}$ are used to **select areas over which the hazard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



Step 1: Weighted differences



Step 2: Corresponding graph

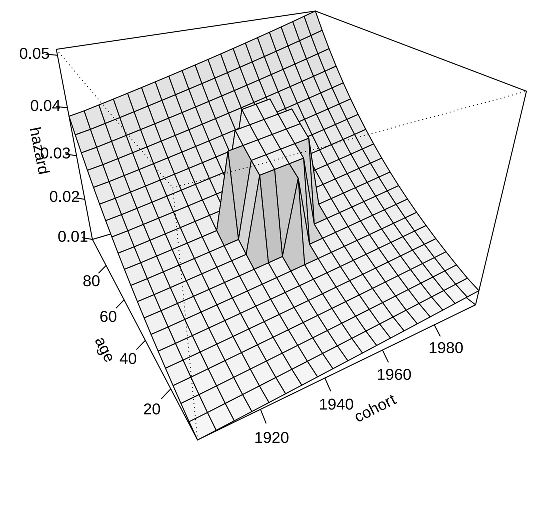


Step 3: Connected components

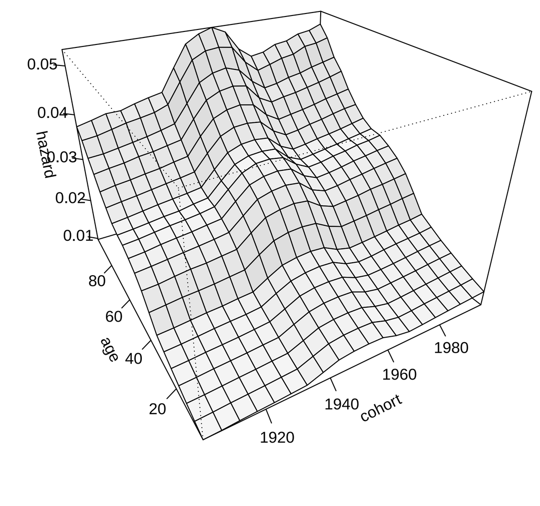
3. On each area : $\boldsymbol{\theta}$ is estimated by unpenalized maximum likelihood.

Simulation results

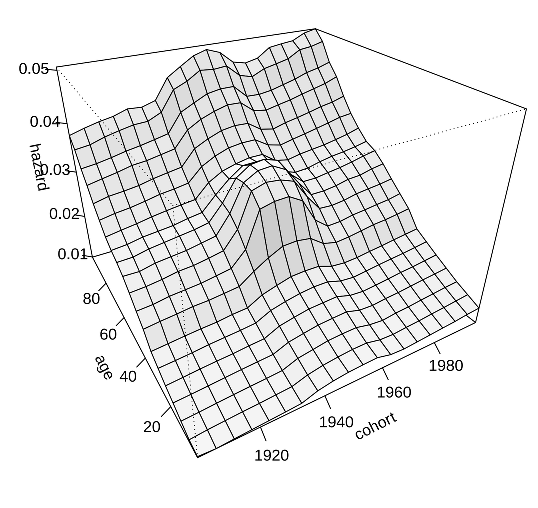
- 10000 **data points** are generated using the true hazard
- We represent the **median estimate** of 500 such replications



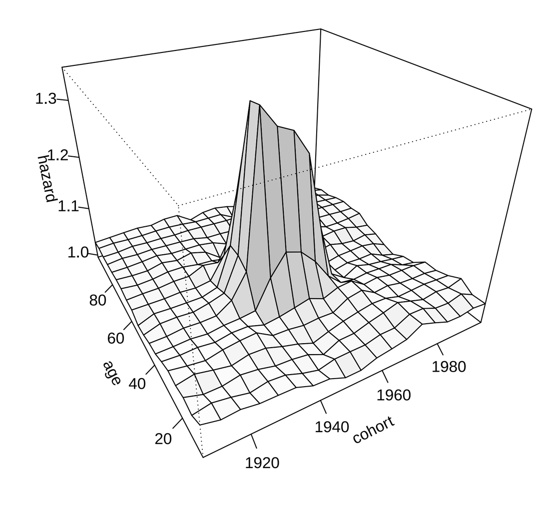
True $\lambda_{j,k}$



AC model



$\lambda_{j,k}$ (ACI model)



$\delta_{j,k}$ (ACI model)

Conclusion & References

Conclusion

- Joint estimation of the effects and their interaction
- More general model than APC
- Can use ensemble methods for better predictive performance

References

[1] F. 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] F. 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, 2008.

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