Analysis of competing risks data and simulation of data following predefined subdistribution hazards

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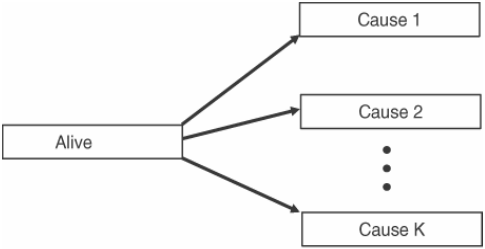
Introduction

- Time-to-event analysis
- Subjects can fail from one out of K mutually exclusive types of event
- Often relevant in clinical studies:
  Primary endpoint: Time to cancer-specific death / cardiac death / ...
- Special methods have to be conducted



Basic quantities

- Basic quantities:
  - Cumulative incidence function (CIF):
    $$F_k(t) = P(T \leq t, D = k) = \int_0^t \lambda_k(s) S(s-) \mathrm{d}s$$
  - Cause-specific hazard (CSH):
    $$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, K = k | T \geq t)}{\Delta t}$$
  - Overall survivor function $S(t)$:
    $$S(t) = \exp\big(-\sum_{l=1}^{K} \Lambda_l(t) \big)$$
- Different methods available for the analysis of competing risks data
- The "naïve" Kaplan-Meier estimator gives a biased estimate for the probability of an event of type k up to time t

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Cause-specific hazards regression

Regression based on the cause-specific hazards (Prentice et al. 1978):

- Focus on cause-specific hazard rates using e.g. a Cox-type regression model:

$$\lambda_k(t|\mathbf{X}) = \lambda_{k,0}(t) exp(\boldsymbol{\beta}_k^\top \mathbf{X})$$

- Can be performed using standard Cox-regression software treating competing events as censored observations
- Estimated CIFs depend on CSHs for all event types

$$F_k(t|\mathbf{X}) = \int_0^t \lambda_k(s|\mathbf{X}) \, \exp\Big(- \sum_{l=1}^{K} \Lambda_l(t|\mathbf{X}) \mathrm{d}s \Big)$$

- CSHs completely determine the competing risks process
- Higher CSH for an event k does not necessarily translate into a higher event probability for k

The subdistribution hazard

- Introduced by Gray (1988)
- Aim of the subdistribution hazard:
  A "hazard function" that is directly linked to the CIF in the presence of competing risks
- Definition of the subdistribution hazard (SDH) for event k:

$$\gamma_k(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, D = k | T \geq t \cup \{T < t, D \neq k\})}{\Delta t}.$$

- Subjects failing from an event $D \neq k$ remain in the risk set (until their potential censoring time).
- For the SDH (as known from standard survival analysis):

$$F_k(t|\mathbf{X}) = 1 - \exp\big(-\Gamma_k(t|\mathbf{X})\big)$$

- Competing events are considered implicitly in the adapted risk set

Subdistribution hazard regession

Introduced by Fine & Gray (1999)

- Focusing on the SDH for the event of interest
- Individuals failing from an event $D \neq k$ remain in the risk set until their potential censoring time
- Censoring time distribution is estimated from the censored observations
- Competing events are weighted using the inverse probability of censoring weighting (IPCW) approach
- A Cox-type regression model was proposed for the SDH:

$$\gamma_k(t|\mathbf{X}) = \gamma_{k;0}(t)\ \exp(\beta_k^{*\top}\mathbf{X})$$

- Proportionality assumption often questionable in practice.

The mixture model approach

Alternative regression approach - introduced by Larson and Dinse (1985)

- $P(T, D) = P(D)\, P(T|D)$
- Proposed: Logistic regression for type of event, parametric model for conditional event time distributions
  - Larson & Dinse (1985): piecewise-exponential
  - Lau et al. (2011): generalized gamma distribution
- Likelihood contribution of subject i:

$$L_i = [\pi_i f_1(t_i)]^{I(d_i=1)} \times [(1-\pi_i) f_2(t_i)]^{I(d_i=2)}$$
$$\times [\pi_i S_1(t_i) + (1-\pi_i) S_2(t_i)]^{I(d_i=0)}$$

  with $f_k(t)$ and $S_k(t)$ denoting quantities of the cond. event time distributions
- Numerical maximization to determine ML-estimates

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Simulation following predefined cause-specific hazards

Beyersmann et al. (2009), example for two possible event types:

- Define CSHs depending on covariates: $\lambda_1(t|\mathbf{X})$, $\lambda_2(t|\mathbf{X})$
- Determine the overall hazard rate: $\lambda(t|\mathbf{X}) = \lambda_1(t|\mathbf{X}) + \lambda_2(t|\mathbf{X})$.
- Generate an event time t_i for subject i with hazard rate $\lambda(t|\mathbf{x_i})$.
- Determine the event type d_i by running a Bernoulli experiment
  - $P(D_i = 1) = \lambda_1(t|\mathbf{x_i}) \,/\, \big(\lambda_1(t|\mathbf{x_i}) + \lambda_2(t|\mathbf{x_i})\big)$
  - $P(D_i = 2) = \lambda_2(t|\mathbf{x_i}) \,/\, \big(\lambda_1(t|\mathbf{x_i}) + \lambda_2(t|\mathbf{x_i})\big)$
- Draw possible censoring times from a censoring time distribution and determine event time and status accordingly.

Used in several research articles for investigation of competing risks methods.

Simulation following predefined subdistribution hazards

- Different approaches focusing on the SDHs were introduced
- Simulation mainly conducted using unit exponential mixture distributions
- Simulation using flexible prespecified subdistribution hazards not possible

Idea by Beyersmann et al. (2009):

- Use relationship between CSH and SDH:

$$\lambda_1(t|\mathbf{X}) = \gamma_1(t|\mathbf{X})\left(1 + \frac{F_2(t|\mathbf{X})}{S(t|\mathbf{X})}\right) \tag{1}$$

- Specify SDH for event of interest and one CSH
- Calculate other CSH following (1)
- Simulate event times using the CSHs to obtain data following the prespecified SDHs

Simulation following predefined subdistribution hazards

Problems:

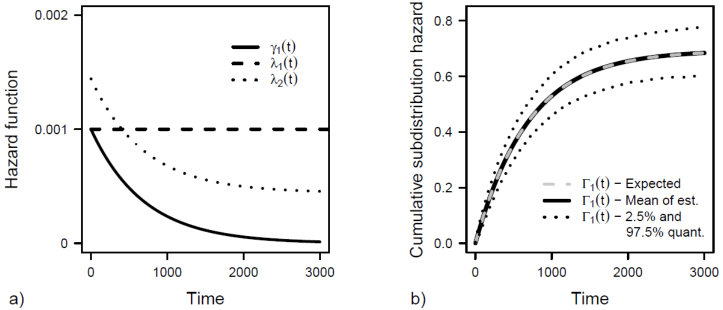
- Certain constraints on different quantities
  - All hazard functions have to be non-negative for all time points $t > 0$.
  - $\lim_{t \to \infty} F_k(t|\mathbf{X}) < 1 \quad \Leftrightarrow \quad \lim_{t \to \infty} \gamma_k(t|\mathbf{X}) = 0$
  - $\lim_{t \to 0} \lambda_k(t|\mathbf{X}) = \lim_{t \to 0} \gamma_k(t|\mathbf{X})$
- Simulation following time-varying CSHs needed

Simulation following predefined subdistribution hazards

Example:

- $\gamma_1(t) = 0.001 \ \exp\left(-\frac{0.001\,t}{\ln(2)}\right)$
- $\lambda_1(t) = 0.001$
- $\lambda_2(t|\mathbf{X}) = \gamma_1(t|\mathbf{X}) - \lambda_1(t|\mathbf{X}) - \frac{\mathrm{d}}{\mathrm{d}t} \ \ln\left(\frac{\gamma_1(t|\mathbf{X})}{\lambda_1(t|\mathbf{X})}\right)$

$$= 0.001 \ \exp\left(-\frac{0.001\,t}{\ln(2)}\right) - 0.001 + \frac{0.001}{\ln(2)}$$



Two methods for data generation (I)

Aim: Generate event times with hazard rate $\lambda(t|\mathbf{X}) = \lambda_1(t|\mathbf{X}) + \lambda_2(t|\mathbf{X})$

- Inversion method (see e.g. Bender et. al (2005))
- $U = exp\big(-\Lambda(t|\mathbf{X})\big) \qquad \Leftrightarrow \qquad T = \Lambda^{-1}(-ln\, U)$
  - $U \sim U[0,1]$
  - $\Lambda^{-1}(z)$ is the inverse function of the cumulative overall hazard function
- In general, numerical procedures for
  - the cumulative overall hazard function
  - the solution of $U = exp\big(-\Lambda(t|\mathbf{X})\big)$
- Can become very time-consuming

Two methods for data generation (II)

Based on binomial algorithm (by Sylvestre & Abrahamowicz (2008))

- Event time generation for discrete timepoints
- Start with subject $i = 1$
- Begin at time $t_j = 1$
- Prob. for any event at time t_j for subject i: $p(t_j|\mathbf{x_i}) = \lambda_1(t_j|\mathbf{x_i}) + \lambda_2(t_j|\mathbf{x_i})$
- Perform Bernoulli experiment to determine whether i failed at t_j
- Event at t_j
  - Determine type of event
  - Continue for subject i+1
- No event at t_j:
  - Continue for timepoint $t_j + 1$

The Binomial approach

- Investigated for different scenarios
  - One group
  - Two groups, constant SD hazard ratio
  - Two groups, time-varying SD hazard ratio
  - One quantitative covariate
  - Multiple covariates (SDH regression model)
- Established methods were used to analyse the generated data
- Good behaviour of the data generating process
- Can lead to bindings in event times
- Amount of binding can be controlled by choice of hazard functions
- Published in:
  Haller B, Ulm K (2013) Flexible simulation of competing risks data following prespecified subdistribution hazards. Journal of Statistical Computation and Simulation. doi:10.1080/00949655.2013.793345.

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The mixture model - notation (following Lau et. al, 2011)

- $P(T, D|\mathbf{X}) = P(D|\mathbf{X})\ P(T|D, \mathbf{X})$
- Probability for an event of type k: $\pi_k(\mathbf{X}) = P(D = k|\mathbf{X})$
- Density function of the conditional event-time distribution: $f_k(t|D = k, \mathbf{X}))$
- Cum. density fct. of the cond. event-time distribution: $F_k(t|D = k, \mathbf{X}))$
- Survivor function of the conditional event-time distribution: $S_k(t|D = k, \mathbf{X})$

- Subdensity function: $f_k^*(t|\mathbf{X}) = f_k(t|D = k, \mathbf{X})\,\pi_k(\mathbf{X})$
- Subdistribution function: $F_k^*(t|\mathbf{X}) = F_k(t|D = k, \mathbf{X})\,\pi_k(\mathbf{X})$

The mixture model - relationships

Following Lau et al. (2011)

- Cause-specific hazard function: $\lambda_k(t|\mathbf{X})$
- Subdistribution hazard function: $\gamma_k(t|\mathbf{X})$
- Overall survival function: $S(t|\mathbf{X})$

$$S(t|\mathbf{X}) = exp\big(- \sum_{l=1}^{K} \Lambda_l(t|\mathbf{X})\big) = \sum_{l=1}^{K} \pi_k(\mathbf{X})\, S_k(t|D=k,\mathbf{X}))$$

- Cumulative incidence function: $F_k^*(t|\mathbf{X})$

$$F_k^*(t|\mathbf{X}) = \int_0^t \lambda_k(s|\mathbf{X})\ \exp\Big(- \sum_{l=1}^{K} \Lambda_l(t|\mathbf{X})\mathrm{d}s\Big)$$

$$F_k^*(t|\mathbf{X}) = 1 - \exp\big(- \Gamma_k(t|\mathbf{X})\big)$$

$$F_k^*(t|\mathbf{X}) = F_k(t|D=k,\mathbf{X})\,\pi_k(\mathbf{X})$$

Estimating CSH and SDH from a mixture model

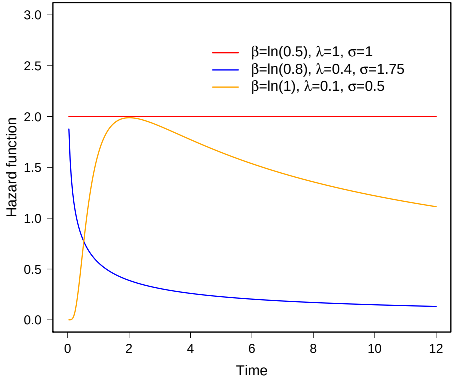
- CSH: $\lambda_k(t|\mathbf{X}) = f_k^*(t|\mathbf{X})/S(t|\mathbf{X})$
- SDH: $\gamma_k(t|\mathbf{X}) = f_k^*(t|\mathbf{X})/\Big(1 - F_k^*(t|\mathbf{X})\Big)$

Proposal by Lau et al:

- Use a generalized gamma distribution for conditional event times
- Allows flexible estimation of CSHs and SDHs

$$f(t) = \frac{|\lambda|}{\sigma t \Gamma(\lambda^{-2})} \left(\lambda^{-2}(e^{-\beta}t)^{\lambda/\sigma}\right)^{\lambda^{-2}} \exp\left(-\lambda^{-2}(e^{-\beta}t)^{\lambda/\sigma}\right)$$

The generalized gamma distribution



Problems / issues:

- Numerical instabilities
- Weighting of extreme observations
- Are all relevant forms covered?

Alternative approach: penalized B-splines

- Define set of basis functions $B_k(t)$, e.g. cubic splines
- The hazard function can be modelled using $B_k(t)$, e.g. (Rosenberg, 1995):

$$h(t|\boldsymbol{\theta}) = \sum_{k=-3}^{K} B_k(t) \exp(\boldsymbol{\theta})$$

- Roughness of the estimated hazard function will be penalized using
  - a smoothing parameter λ
  - a matrix D, e.g. second order differences

$$\mathbf{D}_2 = \begin{pmatrix} 1 & -2 & 1 & 0 & 0 & \dots & 0 \\ 0 & 1 & -2 & 1 & 0 & \dots & 0 \\ \vdots & \ddots & \ddots & \ddots & \ddots & \ddots & \vdots \\ 0 & \dots & 0 & 1 & -2 & 1 & 0 \\ 0 & \dots & \dots & 0 & 1 & -2 & 1 \end{pmatrix}$$

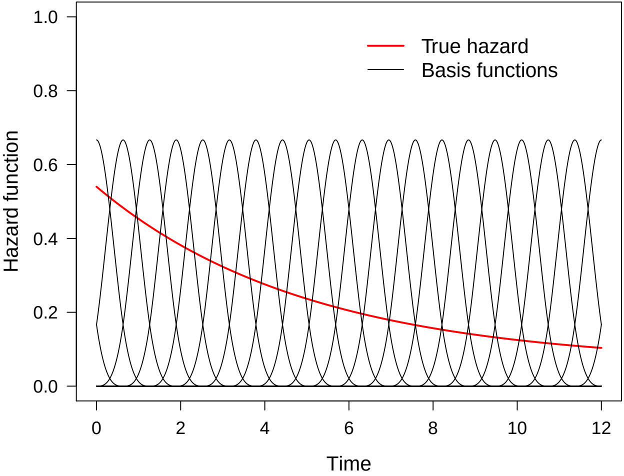
- Maximize penalized Log-Likelihood:

$$l_{pen} = l(\boldsymbol{\theta}; t, d, B) - \tfrac{1}{2}\,\lambda\,\boldsymbol{\theta}^\top \mathbf{D_k}^\top \mathbf{D_k}\,\boldsymbol{\theta}$$

- Find ML estimates by numerical optimization

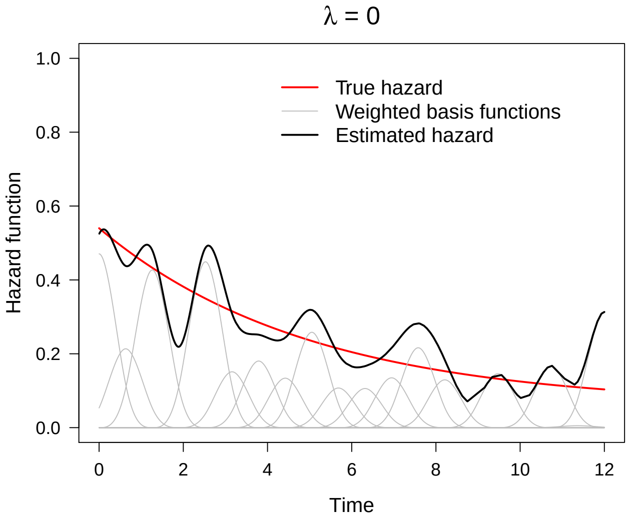
Possible approach

Illustration of P-spline approach for one possible endpoint



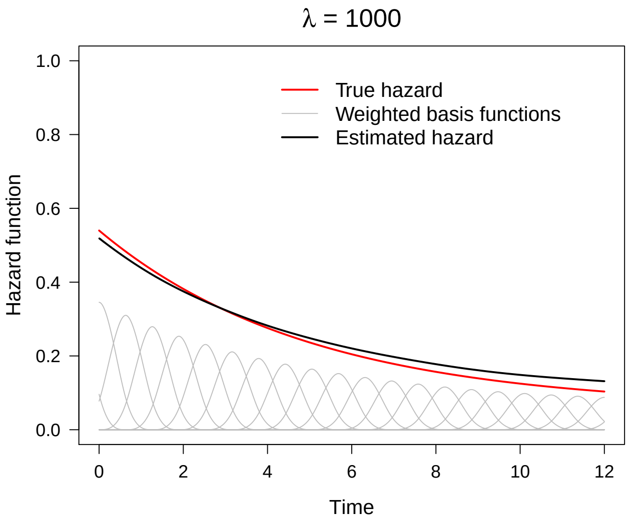
P-spline approach

Simulated example:



P-spline approach

Simulated example:



Adapting the P-Spline approach for the mixture model

- Different approaches available (hazard function, cumulative hazard function)
- Penalty matrix has to be adapted
- Implementation (*R*)
- Numerical maximization to find ML-estimates
  - Stable results?
  - Computation time?
- Confidence interval estimation for HRs (bootstrap)

Outlook

- Comparison of generalized gamma and P-spline approach
  - Real data examples::
    Data used by Lau et al. (2011) are available in *R*
  - Simulated data
    - Data generated according to mixture model approach
    - Predefined CSHs
    - Predefined SDHs
- Investigate roles of
  - Smoothing parameter
  - Number and placing of knots
  - Penalisation
  - Amount of censoring
  - ...
- Estimating "average hazard ratios" in adequate situations

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