Piece-wise exponential (Additive Mixed) Modeling Tools

ISCB41, 2020

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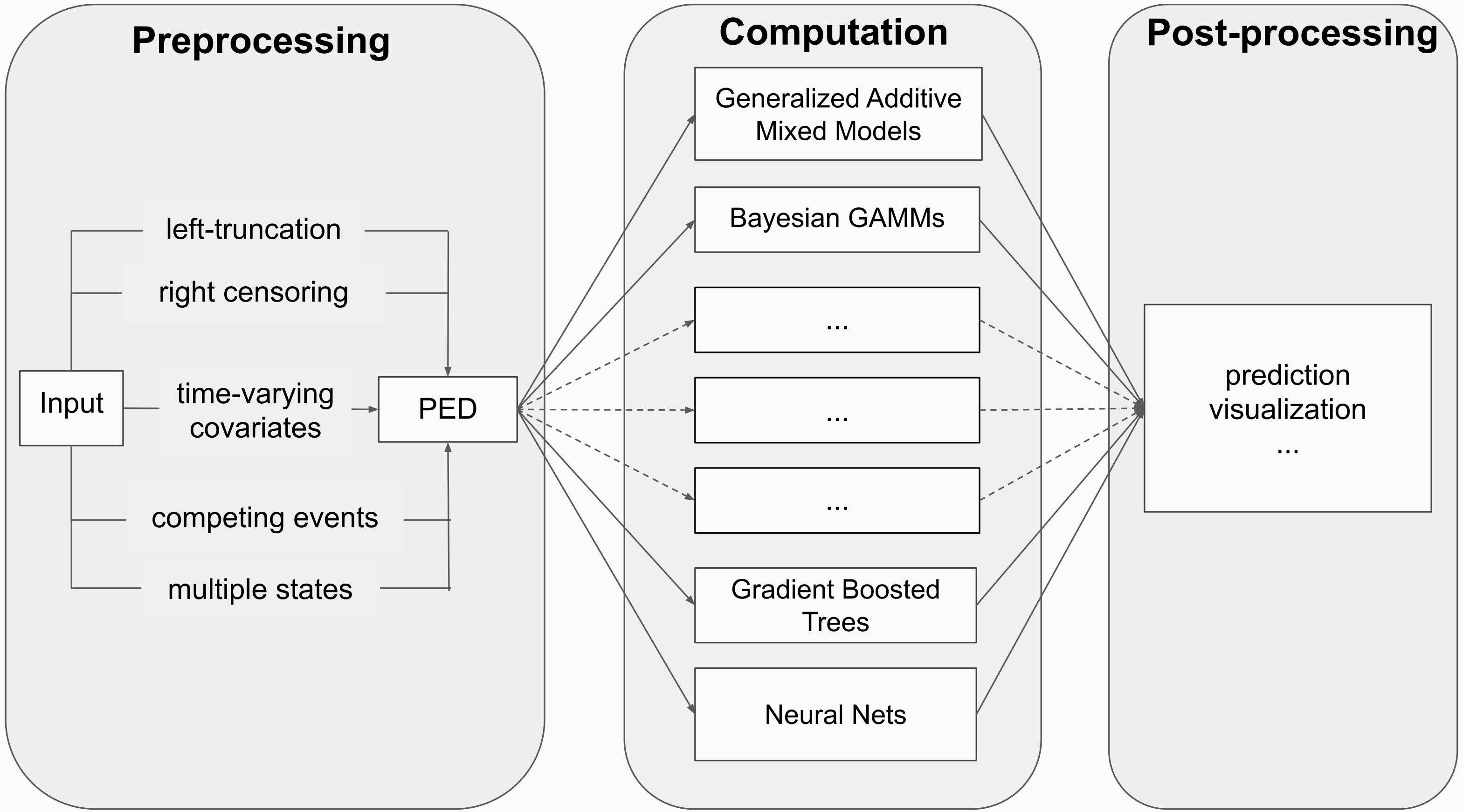
The framework is *general* in the sense that

1. it supports different Survival Tasks
    - right-censoring, left-truncation
    - time-varying effects, time-varying features
    - cumulative effects (weighted cumulative exposure, distributed lag models)
    - competing risks, multi-state models
2. does not require specialized Software, can be applied
    - across programming languages and
    - using any algorithm that supports optimization of the Poisson Likelihood



(source: Bender, et al. (2020))

Survival Analysis as Poisson Regression

Consider setting with right-censored data:

- we observe $(t_i, \delta_i), i = 1, \dots, n$, where
  - $t_i = \min(T_i, C_i)$; $T_i \sim F \perp C_i \sim G; T_i, C_i > 0$
  - $\delta_i = I(T_i \leq C_i) \in \{0, 1\}$

To approximate

$$\lambda(t; \mathbf{x}_i) = \exp(g(\mathbf{x}_i(t), t)) \overset{PH}{=} \lambda_0(t) \exp(\mathbf{x}_i' \boldsymbol{\beta})$$

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- assume piece-wise constant hazards:

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- Estimation using
  - Piece-wise Exponential Model (PEM; e.g.: Laird, et al. (1981); Friedman (1982); Carstensen, et al. (2011))
  - Piece-wise exponential Additive Mixed Models (PAMM, e.g.: Cai, et al. (2002); Kauermann (2005); Argyropoulos, et al. (2015); Bender, et al. (2018))

Data in "standard" time-to-event format

ID (i)	t(i)	status(i)	age(i)
1	1.3	0	31
2	0.5	0	67
3	2.7	1	42

$\rightarrow$ transform to PED using $\kappa_0 = 0, \kappa_1 = 1, \kappa_2 = 1.5, \kappa_3 = 3$

Data in PED format

ID (i)	j	interval	status(i,j)	t(i,j)	t(j)	age(i)
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General log-likelihood contribution:

$$\begin{aligned} \ell_i &= \log(\lambda(t_i; \mathbf{x}_i)^{\delta_i} S(t_i; \mathbf{x}_i)) \\ &= \sum_{j=1}^{J_i} (\delta_{ij} \log \lambda_{ij} - \lambda_{ij} t_{ij}) \end{aligned}$$

Working Assumption $\delta_{ij} \overset{iid}{\sim} Po(\mu_{ij} = \lambda_{ij} t_{ij})$:

$$\begin{aligned} \ell_i &= \log\left(\prod_{j=1}^{J_i} f(\delta_{ij})\right) \\ &= \sum_{j=1}^{J_i} \delta_{ij} \log(\lambda_{ij}) + \delta_{ij} \log(t_{ij}) - \lambda_{ij} t_{ij} \end{aligned}$$

Competing risks setting with event types $k \in \{1, 2\}$

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1	2	(1,1.5]	0	0.3	1.5	1
2	1	(0,1]	0	0.5	1	1
3	1	(0,1]	0	1	1	1
3	2	(1,1.5]	0	0.5	1.5	1
3	3	(1.5,3]	**1**	1.2	3	1
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$\rightarrow$ estimate $\lambda(t|\mathbf{x}, k) = \exp(f(\mathbf{x}(t), t, k)),\ k \in \{1, 2\}$

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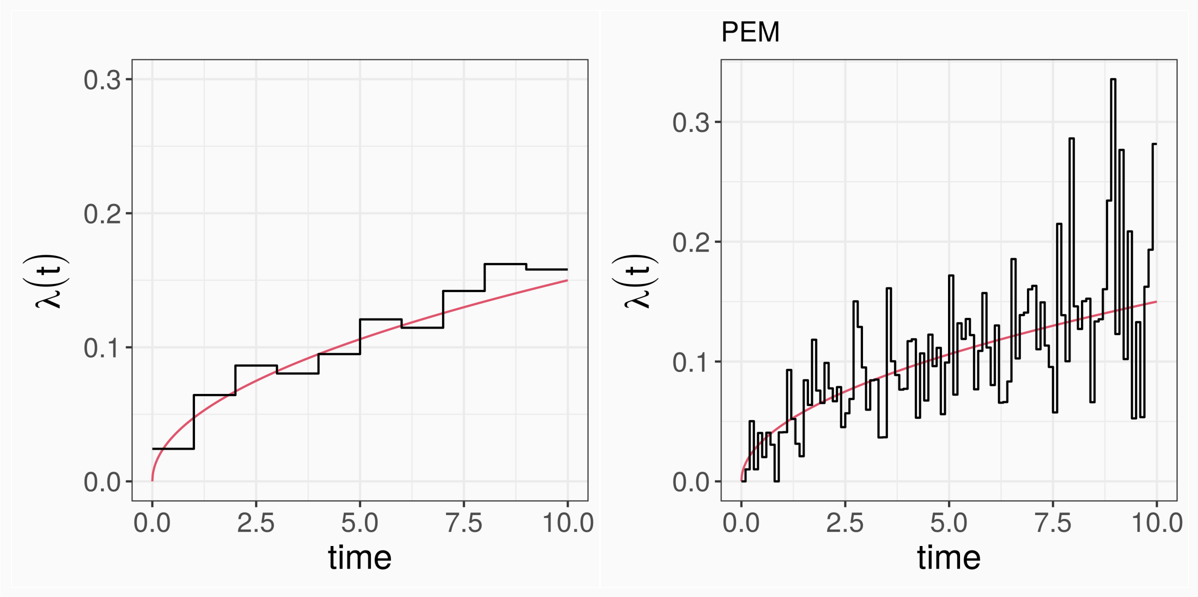
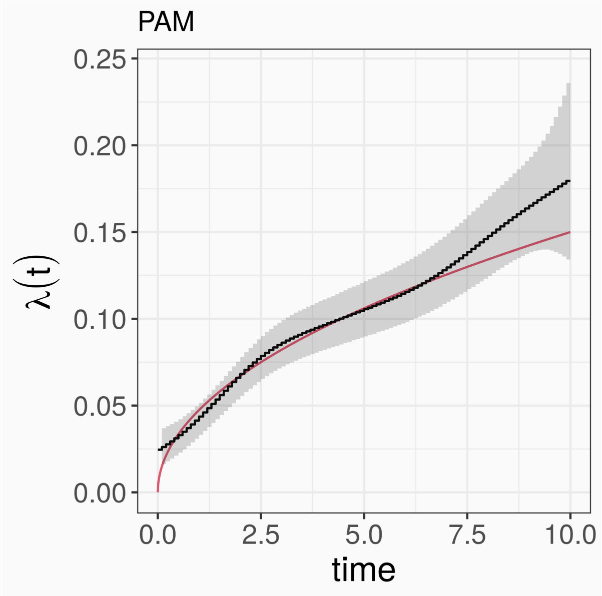
PEM/GLM: $\lambda(t) = \lambda_{0j} = \exp(\beta_{0j}), \forall t \in (\kappa_{j-1}, \kappa_j], j = 1, \dots, J$



- trade of w.r.t. to number of split points (less flexible/more robust vs. more flexible/less robust)
- computationally inefficient (one parameter for each interval), especially when considering time-varying effects
- results sensitive to number and placement of interval cut points

PAMM/GAMM: $\lambda(t) = \lambda_{0j} = \exp(f_0(t_j)), \forall t \in (\kappa_{j-1}, \kappa_j], j = 1, \ldots, J;\ f_0(t_j) = \sum_{q=1}^{Q} \beta_{0q} B_{0q}(t_j)$



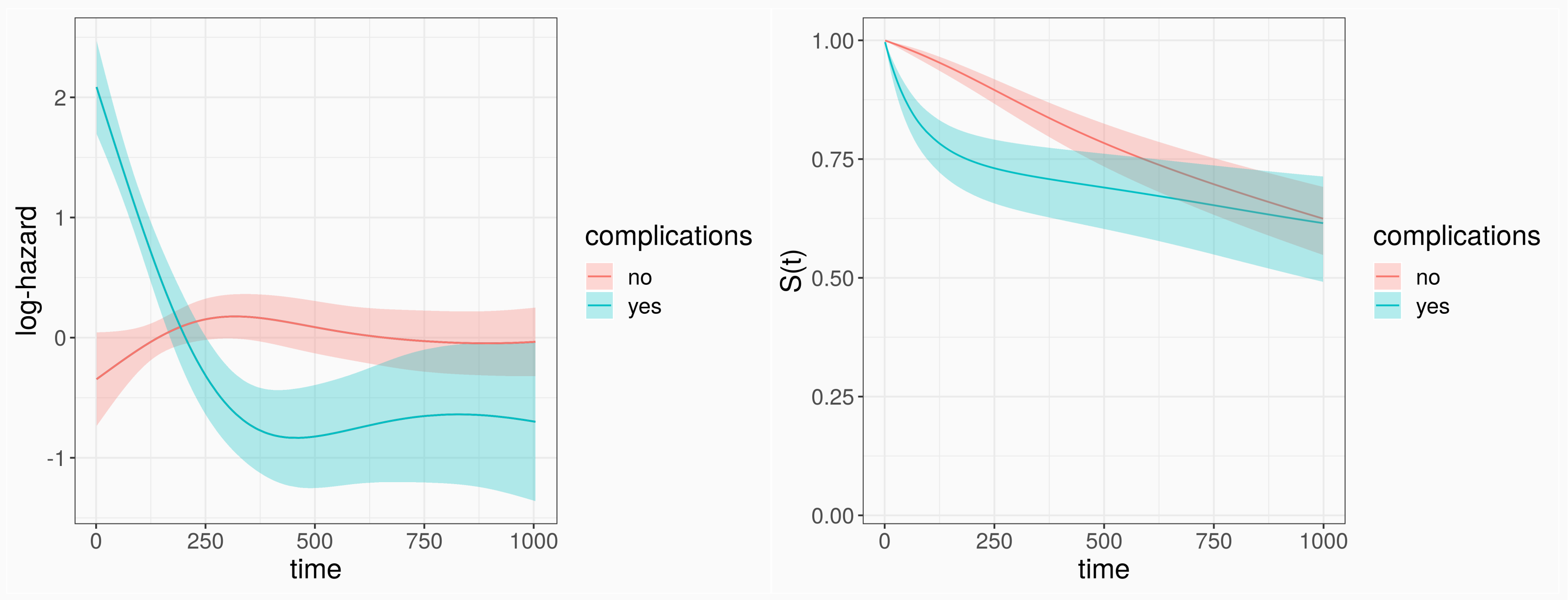
- large differences between neighboring coefficients/baseline hazards of neighboring intervals are penalized
- insensitive to number and placement of split points
- number of parameters to estimate determined by basis dimension Q, not number of intervals J

Time-varying effects

In the PEM/PAMM framework, time-varying effects are simply interactions of time t_j and other covariates.

$$\log(\lambda(t|x)) = f_{01}(t_j)I(complications = yes) + f_{02}(t_j)I(complications = no)$$

```
pam_tumor ← mgcv::gam(formula=ped_status~s(tend, by=complications), data=ped_tumor, family=poisson(), offset=offset)
```



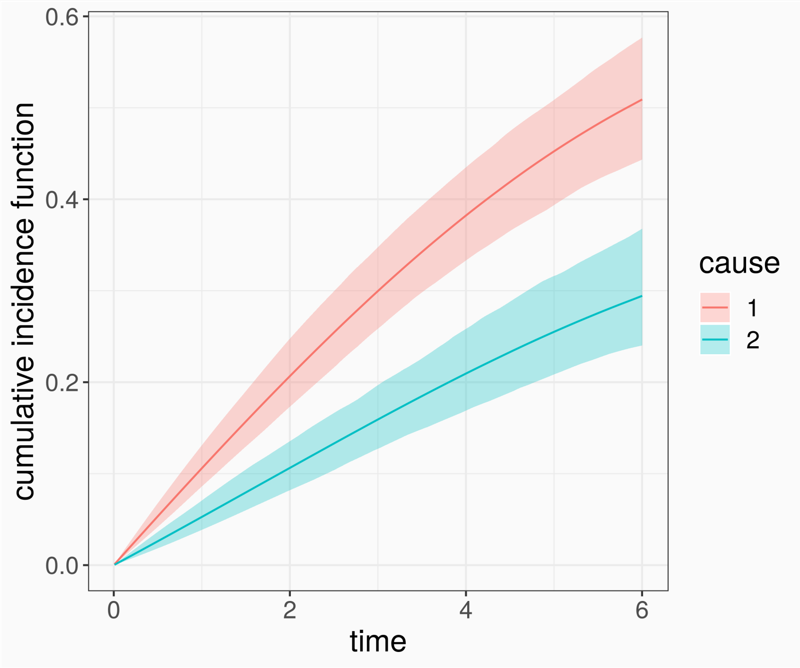
```r
# "Regular" GAM
mgcv::gam(formula=ped_status~s(tend, by=complications), data=ped_tumor, family=poisson(), offset=offset)

# GAM with monotinicity constraints
scam::scam(formula=ped_status~s(tend, by=complications, bs = "mpd"), data=ped_tumor, family=poisson(), offset=offset)

# Bayesian GAM
brms::brm(formula=ped_status~s(tend, by=complications) + offset(offset), data=ped_tumor, family=poisson())
```

Competing Risks

$$\log(\lambda(t|x)) = f_{01}(t_j)I(k=1) + f_{01}(t_j)I(k=2)$$

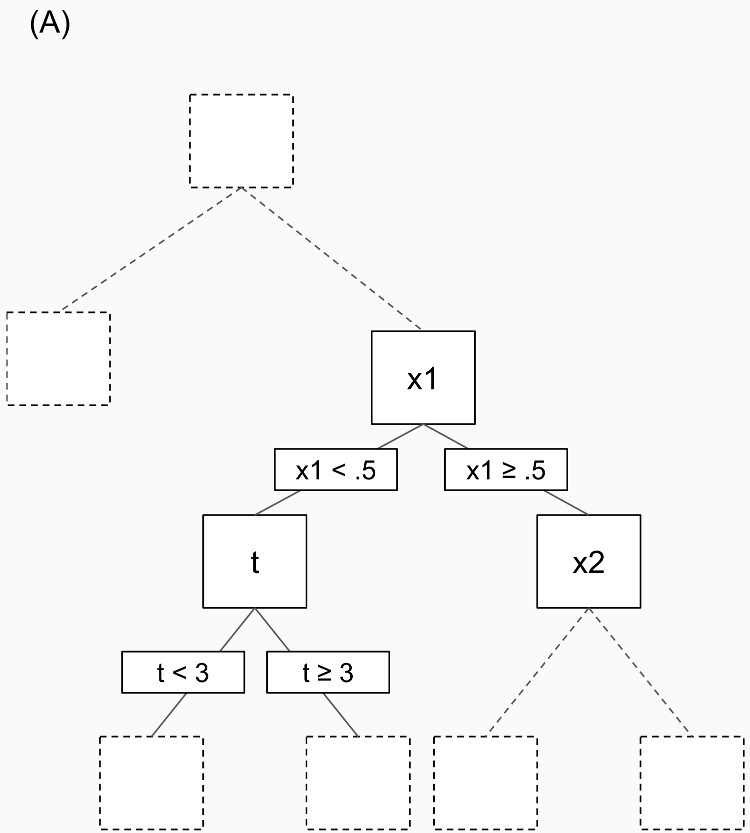
Cause specific hazards are time-varying effects of time t_j and covariate "event type" k

```
pam_cr <- mgcv::gam(formula = ped_status ~ s(tend, by = cause), data = ped_stacked, family = poisson(), offset = offset)
```

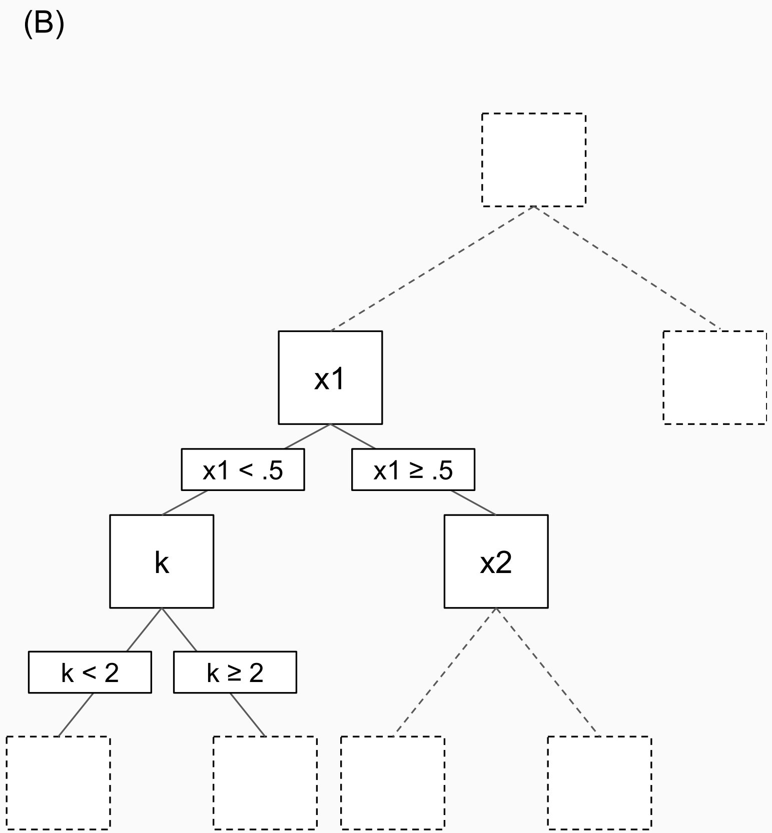


Tree based methods

Time-varying effects



Shared vs. cause-specific effects (in CR)



(source: Bender, et al. (2020))

The `pammtools` package

PEMs/PAMMs powerfull framework for survival analysis, but cumbersome to work with

`pammtools` facilitates

- data transformation (`as_ped`):
    - right-censoring
    - cumulative effects
    - competing risks
- post-processing:
    - prediction (`add_hazard`, `add_surv_prob`, `add_cif`),
    - model evaluation (integrated brier score via **`pec`**)
- convenience functions for visualisation, …

pammtools 0.2.7 Reference Articles News Search...

Data transformation
Estimating the baseline hazard
Basic modeling
Workflow and convenience functions
Stratified models
Non-linear effects (penalized splines)
Time-varying effects (TVEs)
Frailties (random effects)
Time-dependent covariates (TDCs)
Model evaluation
Cumulative effects/Exposure-Lag-Response Associations
Competing Risks
Paper: A generalized additive model approach to time-to-event analysis

`pammtools`: Piece-... ...odeling Tools

Installation

Install from CRAN or GitHub using:

```
# CRAN
install.packages("pammtools")

# GitHub
devtools::install_github("adibe
```

Overview

`pammtools` facilitates the estimation of Piece-wise exponential Additive Mixed Models (PAMMs) for time-to-event data. PAMMs can be represented as generalized additive models and can therefore be estimated using GAM software (e.g. **`mgcv`**), which, compared to other packages for survival analysis, often offers more flexibility w.r.t. to the specification of covariate effects (e.g. non-linear, time-varying effects, cumulative effects, etc.).

To get started, see the Articles section.

Links

Download from CRAN at https://cloud.r-project.org/package=pammtools

Browse source code at https://github.com/adibender/pammtools/

Report a bug at https://github.com/adibender/pammtools/issues

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Citation

Citing pammtools

Developers

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Author, maintainer

Fabian Scheipl
Author

Philipp Kopper
Author

Outlook

- support for multi-state models
- facilitate extensions: S3 functions for calculation of hazard for other packages (e.g. `mbooost`, `brms`)
- Prototype for PEMs using `xgboost` available: https://github.com/adibender/pem.xgb
- However, ML algorithms need a different infrastructure (resampling, tuning, benchmarking)
  $\rightarrow$ Development will probably continue in `mlr3` and `mlr3proba` (Lang, et al. (2019); Sonabend, et al. (2020))

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