

Model-Based Recursive Partitioning for Subgroup Analyses Using Permutation Tests

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Subgroup analyses

Identifying groups of patients for whom the treatment has a different effect than for others.

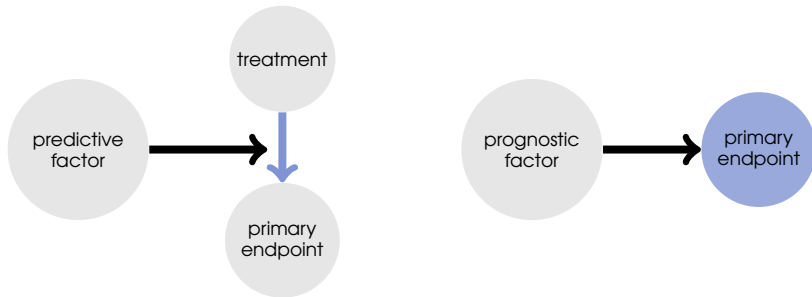
Effect is:

- Stronger
- Lower
- Contrary

Subgroup analyses

Goal: Find predictive factors

$\hat{=}$ covariate \times treatment interactions



Trees are great for detecting interactions. Combine trees with models (knowledge about treatment effect).

\Rightarrow Model-based recursive partitioning.

Data

PRO-ACT database (1)

- Amyotrophic lateral sclerosis (ALS) patients
- Data of several clinical trials
- Treatment of interest: Riluzole
- Primary endpoints of interest: Survival time

Riluzole modestly prolongs life expectancy

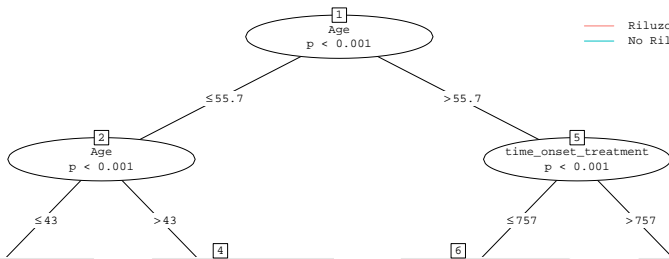
But: Are there any groups of patients for whom it is better or worse?

⇒ Subgroup analyses



Subgroups with differential Riluzole effect on the survival

— Riluzole
— No Riluzole

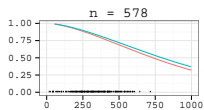
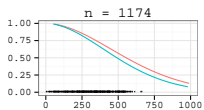
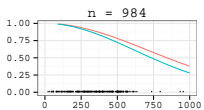
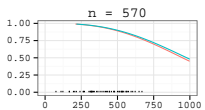


	Value (CI)
α_1	7.017 (6.784, 7.251)
β_R	-0.031 (-0.228, 0.166)
$\log(\alpha_2)$	-1.031 (-1.268, -0.794)

	Value (CI)
α_1	6.7844 (6.6582, 6.9107)
β_R	0.1372 (-0.0038, 0.2783)
$\log(\alpha_2)$	-0.6822 (-0.8023, -0.5621)

	Value (CI)
α_1	6.393 (6.318, 6.468)
β_R	0.123 (0.026, 0.220)
$\log(\alpha_2)$	-0.626 (-0.701, -0.551)

	Value (CI)
α_1	6.908 (6.733, 7.083)
β_R	-0.082 (-0.287, 0.123)
$\log(\alpha_2)$	-0.474 (-0.591, -0.357)



MOB Basics

MOB: Model-based recursive partitioning (2)

Start with model $\mathcal{M}((Y, \mathbf{X}), \vartheta)$ with

$$\vartheta = \begin{pmatrix} \alpha \\ \beta \\ \gamma \\ \nu \end{pmatrix} \begin{array}{l} \text{intercept(s)} \\ \text{treatment effect} \\ \text{other parameter(s) of interest} \\ \text{nuisance parameter(s),} \end{array}$$

which fits data $(Y, \mathbf{X}) \in (\mathcal{Y}, \mathcal{X})$.

Model

Parametric model: **Weibull model**

$$\mathbb{P}(Y \leq y | X = x) = F\left(\frac{\log(y) - \alpha_1 - \beta x_R}{\alpha_2}\right)$$

y (right-censored) survival time,
 F cumulative distribution function of Gompertz distribution

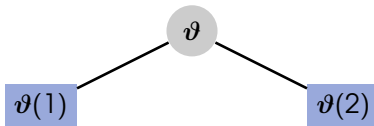
$\alpha = \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix}$ defines the shape of the baseline hazard

⇒ use as "intercept"

MOB Basics

Maybe the treatment effect is not the same for all patients, but depends on their characteristics.

- ⇒ Find partitions $\{\mathcal{B}_b\}$ ($b = 1, \dots, B$) based on patient characteristics $\mathbf{Z} = (\mathbf{Z}_1, \dots, \mathbf{Z}_J) \in \mathcal{Z}$
- ⇒ Fit separate models $\mathcal{M}((Y, \mathbf{X}), \vartheta(b))$ in partitions.



Partitioning

How to find the Partitions?

⇒ Test of independence between the partial score functions and each patient characteristic:

$$H_0^{\alpha,j} : \psi_{\alpha}((Y, \mathbf{X}), \hat{\vartheta}) \perp \mathbf{Z}_j$$

$$H_0^{\beta,j} : \psi_{\beta}((Y, \mathbf{X}), \hat{\vartheta}) \perp \mathbf{Z}_j, \quad j = 1, \dots, J$$

$\psi_{\alpha}, \psi_{\beta}$ partial derivatives of the log-likelihood with respect to α/β .

- Partition if global p-value smaller than significance level
- Use as split variable the one with the smallest p-value

Why does this work?

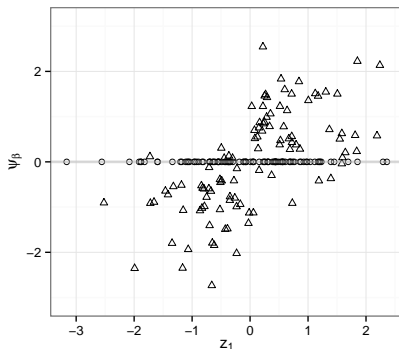
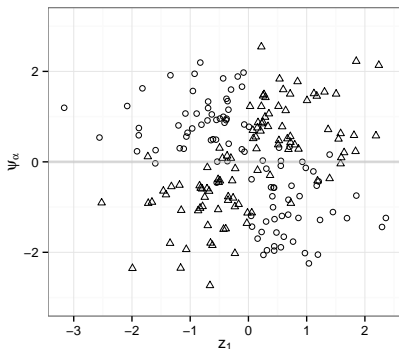
Example (3):

Data generating process:

$$Y|\mathbf{X} = \mathbf{x}, \mathbf{Z} = \mathbf{z} \sim \mathcal{N}(1.9 + 0.2 \cdot x_A + 1.8 \cdot \mathbf{1}(z_1 < 0) + 3.6 \cdot \mathbf{1}(z_1 > 0) \cdot x_A, 0.7)$$

Linear model:

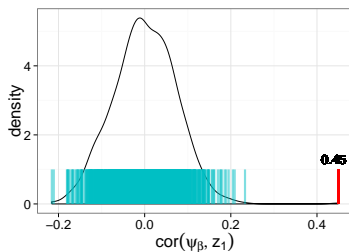
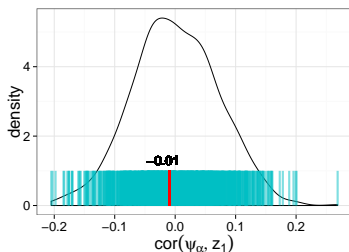
$$Y|\mathbf{X} = \mathbf{x} \sim \mathcal{N}(\alpha + \beta \cdot x_A, \sigma^2)$$



Permutation testing

Example: Independence test between ψ_α and z_1 , and ψ_β and z_1

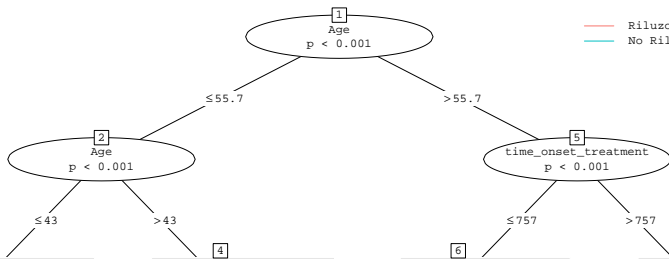
- Compute test statistic:
 $\text{cor}(\psi_\alpha, z_1) = -0.01$
 $\text{cor}(\psi_\beta, z_1) = 0.45$
- Permute z_1 many times and compute the test statistic each time.



- $p\text{-value} = \frac{\text{number of test statistics more extreme than original}}{\text{number of permutations}}$

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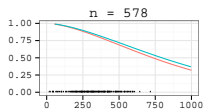
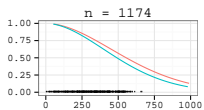
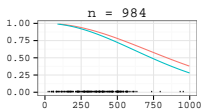
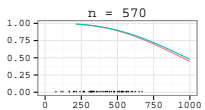


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Summary

- MOB partitions a large class of models suitable for the treatment effect on the primary endpoint of interest.
- Score functions capture instabilities and thus help to identify predictive and prognostic variables.
- Easy interpretation and good to communicate to clinicians.
- Coming soon: model-based forest for personalised medicine.

Literature

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