Subgroup identification for dose-finding trials via model-based recursive partitioning

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Motivation

- Characterizing the dose-response relationship is one of the major tasks in drug development
  - Dedicated (exploratory) dose-finding studies (Ph II)
  - Ph III studies sometimes study more than 1 or 2 active doses
- Subgroup identification techniques are traditionally designed for trials comparing treatment and control
  - How to apply in situations with multiple different treatment groups? Pool active doses, perform subgroup analyses for each dose, ...
  - Additional challenge: dose-response models often non-linear
- More systematic approach
  - Adjust for dose using a dose-response model
  - Assume that dose-response model parameters are different for different subgroups/baseline covariates

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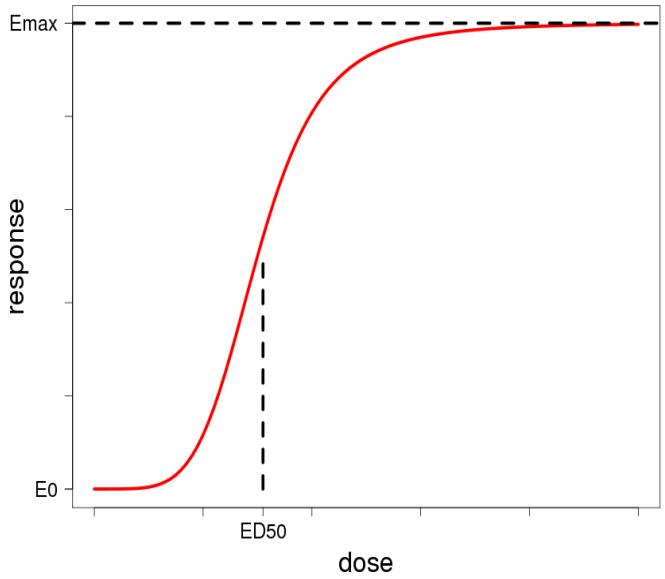
Emax function

- Consider commonly used Emax function

$$E_0 + E_{max} \frac{dose}{ED_{50} + dose}$$



- Dose-response subgroup analysis setting

$$E_0(\boldsymbol{x}) + E_{max}(\boldsymbol{x}) \frac{dose}{ED_{50}(\boldsymbol{x}) + dose}$$

Covariates on E_0: Prognostic covariates (modify response independent of treatment)

Covariates on E_{max} or ED_{50}: Predictive covariates (modify response to treatment)

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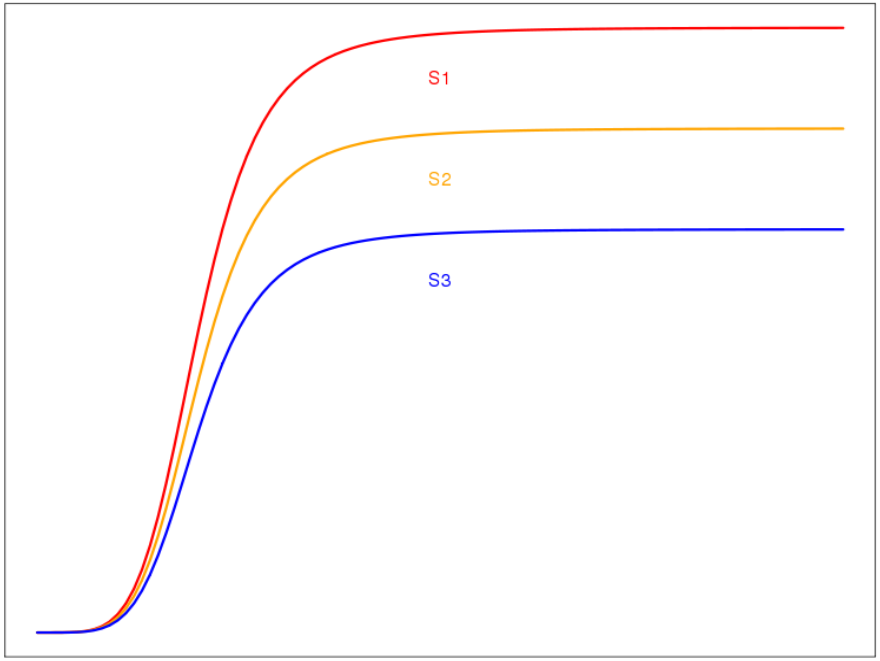
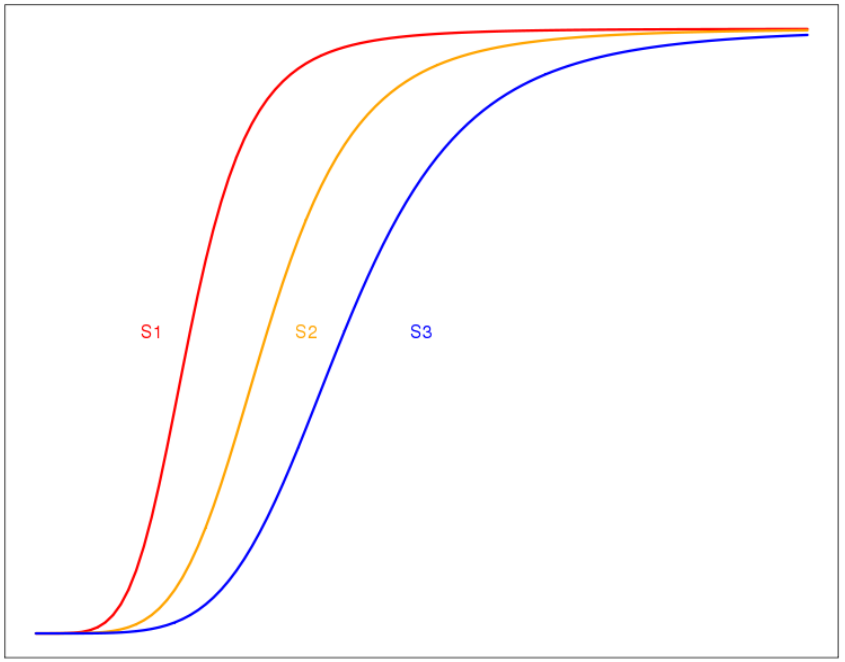
Emax subgroup examples

E_{max} subgroups



ED_{50} subgroups



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Recursive partitioning for subgroup identification

Recursive partitioning methods are a popular approach to subgroup identification: SIDES (Lipkovich et al., 2011), Virtual Twins (Foster et al. 2011), Guide (Loh et al., 2015),....

- Able to handle interactions between covariates
- Choice of cut-off often part of the method

Attractive in the dose-finding context: **model-based recursive partitioning (MOB)** (Zeileis et al., 2008):

- Not specifically designed for subgroup identification but has been used in the two-arm setting (Seibold and Hothorn, 2016)
- RP method, that fits a parametric model in each node and splits based on covariate effects on the parameters of the model
- Separate model in each resulting terminal node

Mob algorithm

Short overview

Model: $M\big((Y, Z), \vartheta\big)$

- Y: response, Z: other covariates (e.g treatment variables, additional baseline covariates,...)
- ϑ: parameter vector

Partitioning variables: $X_1, \ldots, X_K$

- Typically baseline covariates, for which we suspect interactions with the treatment
- Used to partition the data and fit a segmented model (if this improves model fit)

Algorithm (at each node) :

1. Fit the model by minimizing objective function (log-likelihood, RSS,...)
2. For each partitioning variable $X_1, \ldots, X_K$ test for instability of the parameter estimates
3. Choose the variable X_j associated with highest instability for splitting, if (multiplicity-adjusted) p-value for instability test is below α
4. Choose binary split over X_j, which minimizes objective function in the two daughter nodes

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Mob applied to dose-finding trials

Emax model (for normally distributed data) in this framework

$$M\big((Y, D), \vartheta\big) : Y_i \sim N(E_0 + E_{max} \frac{D_i}{ED_{50}+D_i}, \sigma^2), \text{ i=1,...,n}$$

- $\vartheta = (E_0, ED_{50}, E_{max})$
- Objective function Ψ: RSS
- For subgroup analyses we would mostly be interested in covariate effects on ED_{50} and E_{max} $\longrightarrow$ algorithm allows restriction to specific parameters
- Algorithm can be implemented in partykit package with a custom fitting function (e.g. Emax)

Main research questions:

- Does fitting non-linear models on partitioned data improve model fit?
- Is the algorithm able to detect the correct covariate-treatment interactions reliably?
- Can estimation of quantities of interest (treatment effects, MED) be improved over a non-partitioned model?

Simulation setup

- Simulate trial based on study evaluating glycopyrronium bromide in COPD patients (clinicaltrials.gov: NCT00501852) :
  - Emax paramaters **E0 = 1.2, Emax = 0.17, ED50 = 18**
  - 5 dose levels: 0 (placebo), 12.5, 25, 50, 100
  - n = 250 (50 patients on each dose level)
  - $\sigma = 0.12$
- Baseline (partitioning) covariates $\boldsymbol{X_1, \ldots, X_{10}}$ **iid. N(0, 1)**

5 Simulation scenarios:

Case	E0	Emax	ED50
1 – Null	1.2	0.17	18
2 – E0	$1.2 + 0.1I_1 + 0.1I_3$	0.17	18
3 –Emax	1.2	$0.17 - 0.17 * I_1 + 0.17 * I_2$	18
4 –ED50	1.2	0.17	$18 * 0.2^{I_1} * 5^{I_2}$
5 – E0 & Emax & ED50	$1.2 + 0.1I_1 + 0.1I_3$	$0.17 + 0.17 * I_1 * I_2 - 0.17 * (1 - I_1) * (1 - I_2)$	$18 * 0.2^{I_1}$

where I_i is defined as $I_i = I(x_i > 0)$

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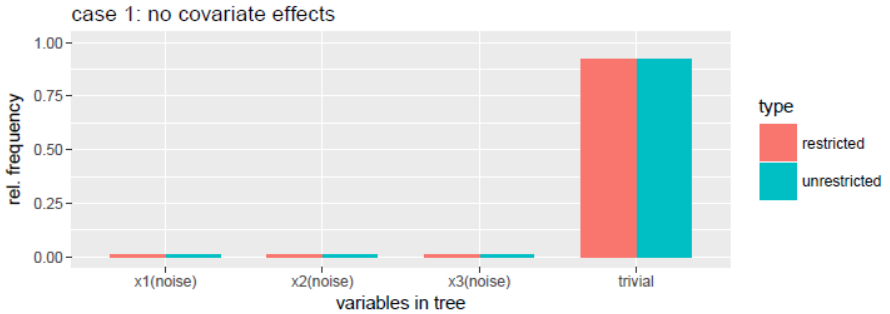
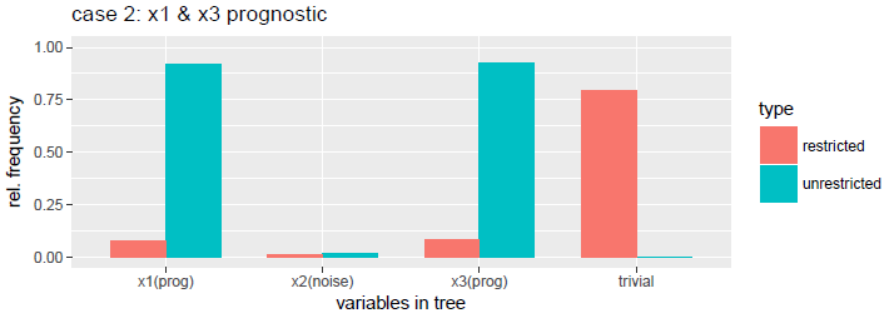
Are correct covariate effects detected?

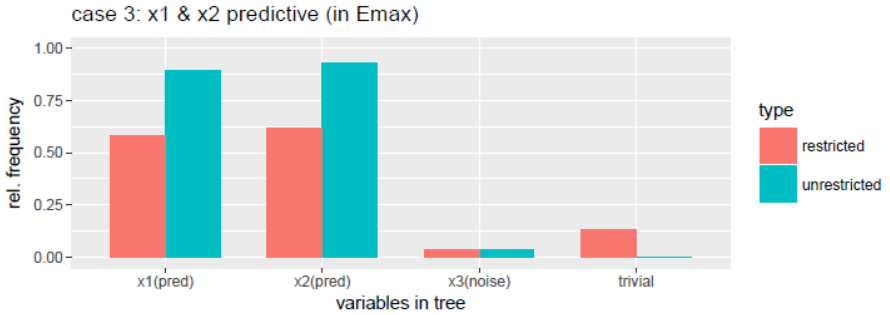
Run mob on 5000 simulated trials and assess composition of trees

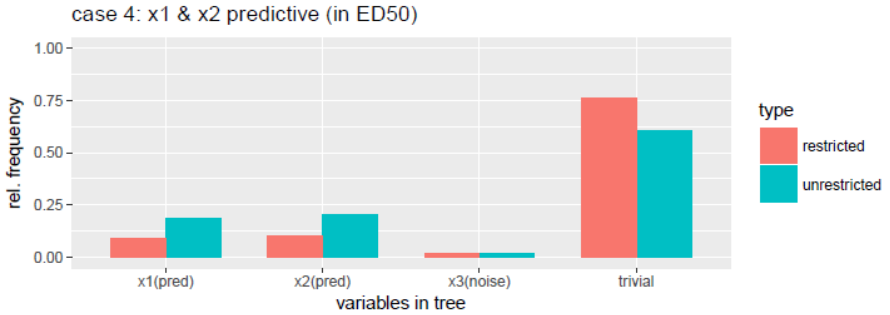
- Frequency of splits over x1, x2, x3, which are either prognostic, predictive or noise (depending on the case)
- Frequency of a trivial tree, e.g. no splits
- Compare effect of ***restricted*** splitting (only on ED_{50} and E_{max}) and ***unrestricted*** splitting (on all parameters)
- Here: $\alpha = 0.1$

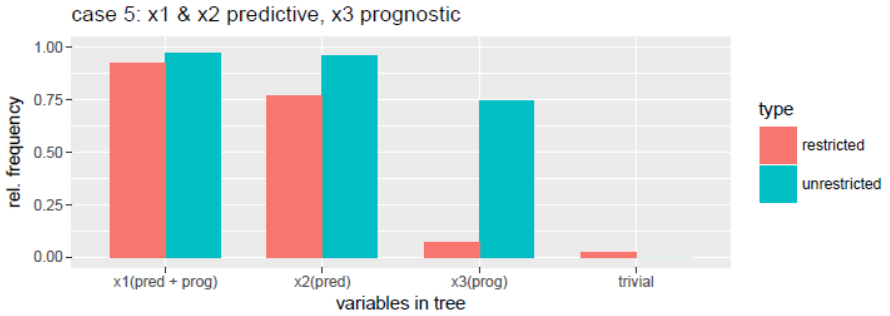
Simulation results: Identification of correct covariates











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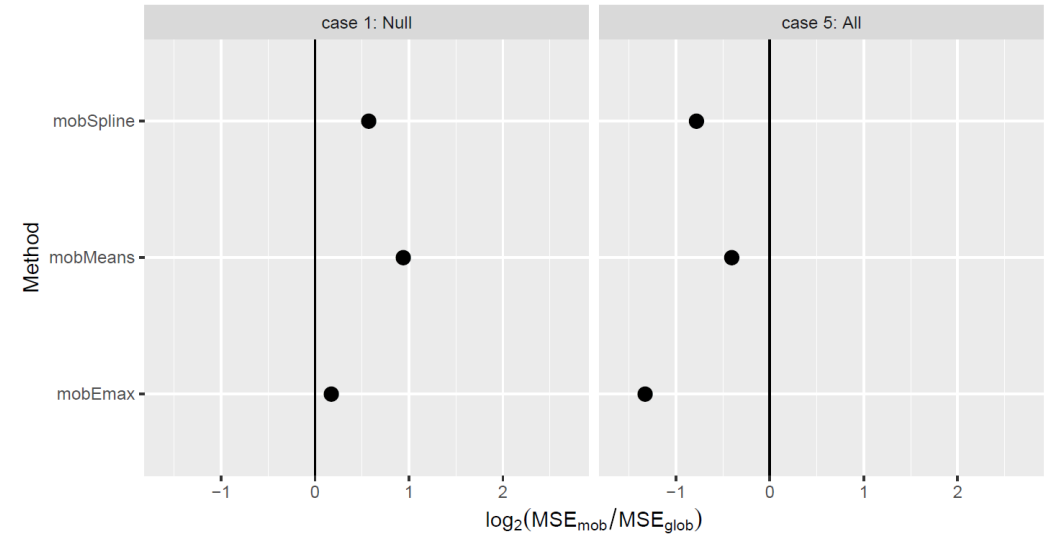
Estimating quantities of interest

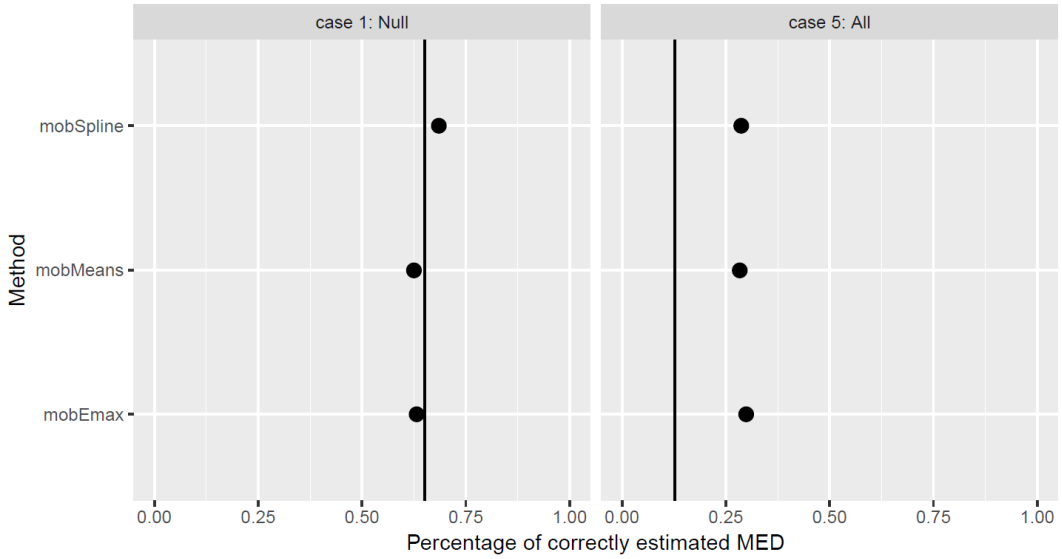
Is there an improvement over estimation with the global model?

- **Mean squared error of estimated individual treatment effect**
  - Estimate patient-specific treatment effects across dose range
  - Average the MSE of predictions over all doses, patients and simulations
- **Estimation error of individual minimum effective dose (MED)**
  - Estimate patient-specific MED
  - Check if this estimate lies in an interval around the correct estimate

- Also compare the non-linear Emax model to linear models fit within the mob algorithm
- Results shown here only for splitting restricted to ED50 and Emax

Simulation results: Estimation





Treatment effect

Black line:
global Emax model

MED

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Conclusions

- Model-based recursive partitioning can be used to perform exploratory subgroup analyses for trials with multiple doses
  - able to detect covariate effects on specific parameters of the model, implicitly handling interactions between covariates and choosing suitable cutoffs
  - Multiplicity control to control the probability of a false positive
  - improves individual estimation of treatment effects and MED, if covariate effects are present over non-partitioned models
  - Parameter restriction can be used to distinguish prognostic and predictive covariates
- Presented methodology can be easily implemented using the algorithms in the partykit package for R.

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