Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod and an adaptive interim analysis

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Introduction

- Traditionally two main analysis strategies for phase II trials: multiple comparisons (MCP) of contrasts between doses and modeling of dose response (DR)
- Bretz et al. (2005) proposed an unified approach combining the advantages of MCP and modeling - MCPMod:
  - Set of candidate models to account for model uncertainty
  - Test PoC using MCP with optimal model contrasts
  - Select a model and estimate target doses (e.g., MED, ED50, ...)
  - Qualification Opinion adopted by CHMP (2014)

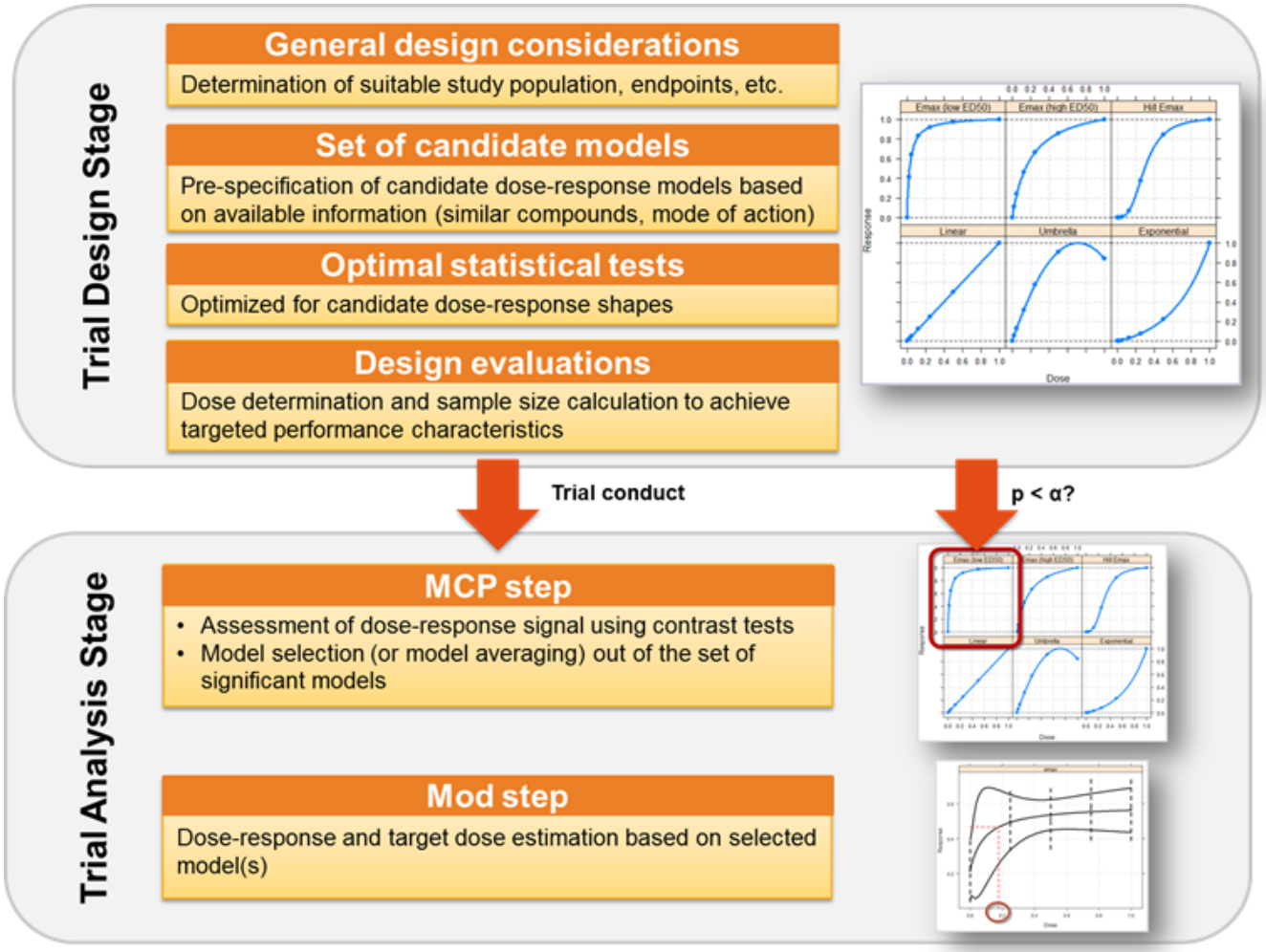
Our goal today:

Use framework of MCPMod to

- allow testing of individual dose-control comparisons
- allow design modifications at an adaptive interim analysis
- increase the power of declaring effective doses statistically significant

Overview of MCP-Mod

(Bretz et al. 2005, Bornkamp et al. 2009, Pinheiro et al. 2014, ...)



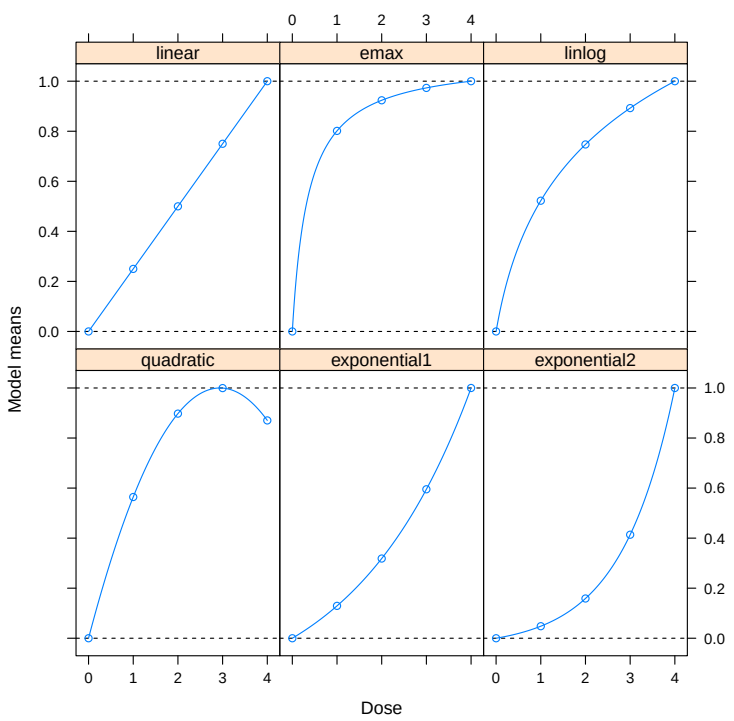
Statistical model

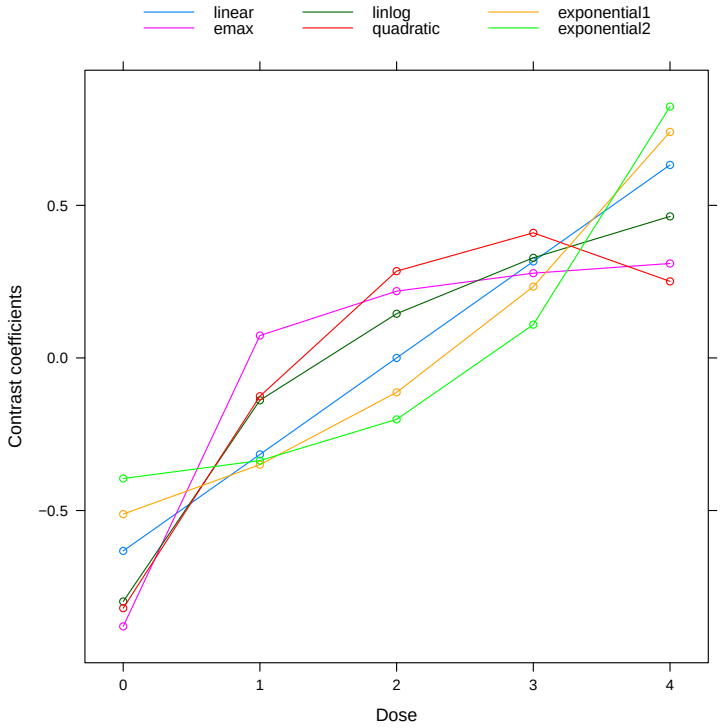
- Assume that a response Y is observed for $k+1$ parallel groups corresponding to doses d_0,d_1,..., d_k (d_0 typically placebo)
- Assume that the Y_{ij} for subject j in group i is modeled as

$$Y_{ij} = f(d_i, \theta) + \epsilon_{ij}, \quad \epsilon_{ij} \overset{\text{ind}}{\sim} \mathcal{N}(0, \sigma^2), \; i = 0, \ldots, k, j = 1, \ldots, n_i,$$

- Denote the true (unknown) effect at dose i with $\mu_i = f(d_i, \theta)$
- MCP-Mod uses classical contrast tests, with multiplicity adjustment, to detect evidence in favor of a dose response signal
  - based on a pre-specified set $\mathcal{M}$ of M parameterized candidate models with corresponding model functions $f_m(d, \theta_m)$, $m = 1, \ldots, M$

Candidate model set





- Use prior guesses to determine the parameters of the standardized models θ_m^0 determining the model shapes
- Optimal contrasts $\mathbf{c}_m = (c_{m0}, c_{m1}, \ldots, c_{mk})'$ depends on best guesses for standardized model.

Contrast test for dose response signal detection (PoC)

- Single contrast test for detecting the mth model shape:

$$T_m = \frac{\sum_{i=0}^{k} c_{mi} \bar{Y}_i}{S\sqrt{\sum_{i=0}^{k} c_{mi}^2 / n_i}}, \quad m = 1, \ldots, M,$$

- Test statistics are jointly multivariate-t distributed with correlations determined by the model contrasts
- Multiplicity adjusted critical value q or adjusted p-values p_m for individual tests of models derived from multivariate t-distribution accounting for the different models
- Dose response signal established if the maximum test statistic $\max_m T_m > q$ or the minimum adjusted p-value $\min_m p_m < \alpha$

Efficacy claims for individual doses using MCP-Mod

- Original MCP-Mod approach is designed for Phase II studies and enables only the detection of a dose response signal at the MCP step
- Often, efficacy claims for individual doses are of interest in Phase III
- Formally interested in testing the k elementary null hypotheses

$$H_i : \mu_i \leq \mu_0, \text{ versus } A_i : \mu_i > \mu_0, \ i = 1, ..., k$$

but within the framework of MCP-Mod

Combine two different methodological concepts

- MCP-Mod contrast test and closed testing principle

For k hypotheses $H_1, \ldots, H_k$:

- Specify a level α test for all $H_J = \bigcap_{i \in J} H_i$, $J \subseteq \{1, \ldots, k\}$, and
- Reject H_i if and only if all H_J with $i \in J$ are rejected

Proposed approach: Details

- Take the original contrast test from MCP-Mod as the level α test for the global intersection hypothesis

$$H_1 \cap H_2 ... \cap H_k : \mu_1, ..., \mu_k \leq \mu_0$$

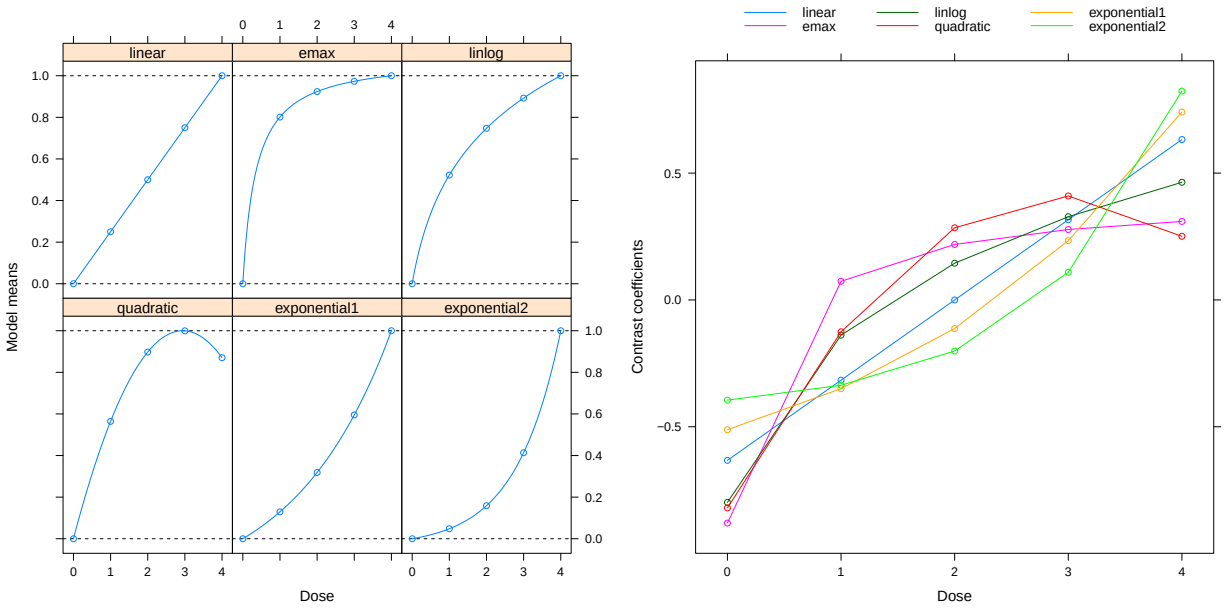
- Use the same strategy for all other intersections hypotheses

Our proposal for a level α test for $H_J = \cap_{i \in J} H_i$, $J \subseteq \{1, \ldots, k\}$

- Test H_J with MCP-Mod contrast tests using doses $i \in J$ only.
- Use the same set of pre-specified set $\mathcal{M}$ of candidates models for each intersection hypothesis H_J, but
- But calculate new optimal contrasts for each H_J and model using only doses $i \in J$
- This means for each intersection hypothesis we have to perform as many contrast tests as models are included in $\mathcal{M}$.

Proposed approach: Illustration of details

- Consider an example with 4 doses and placebo
- Assume 6 candidate models, with corresponding optimal coefficients for testing $H_1 \cap H_2 \cap H_3 \cap H_4 : \mu_1, \mu_2, \mu_3, \mu_4 \leq \mu_0$



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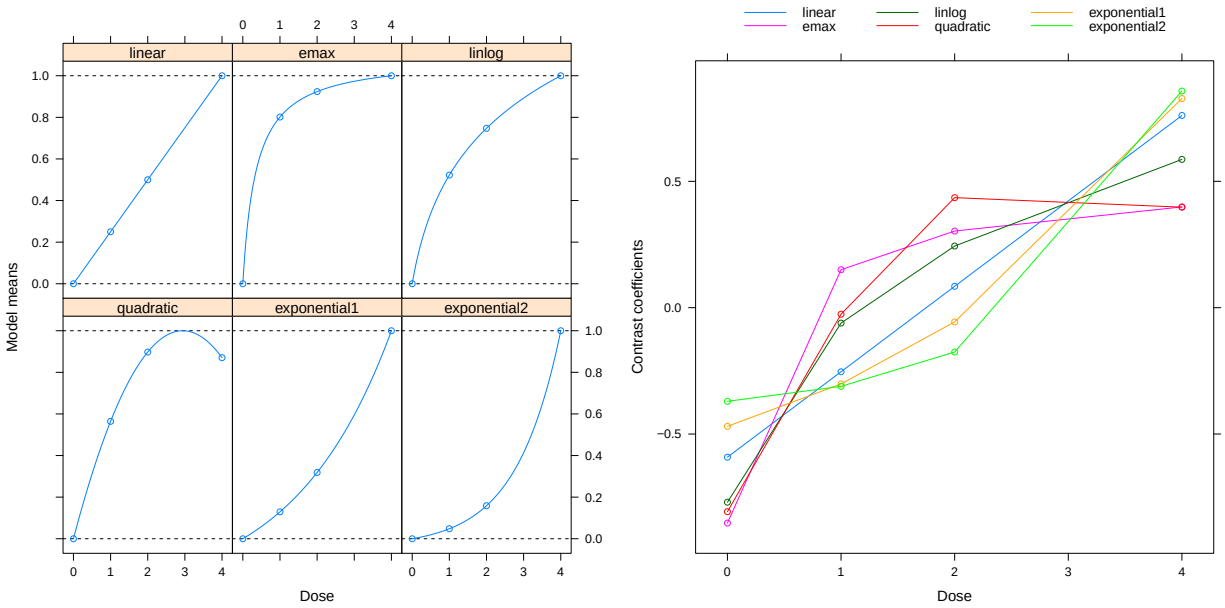

Proposed approach: Illustration of details

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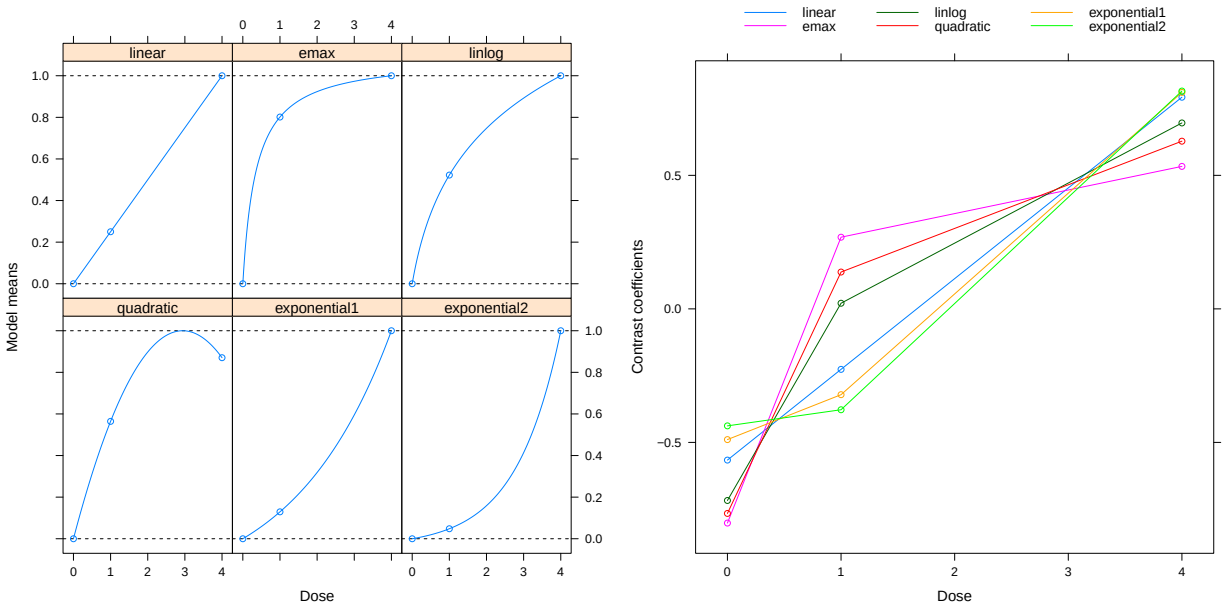
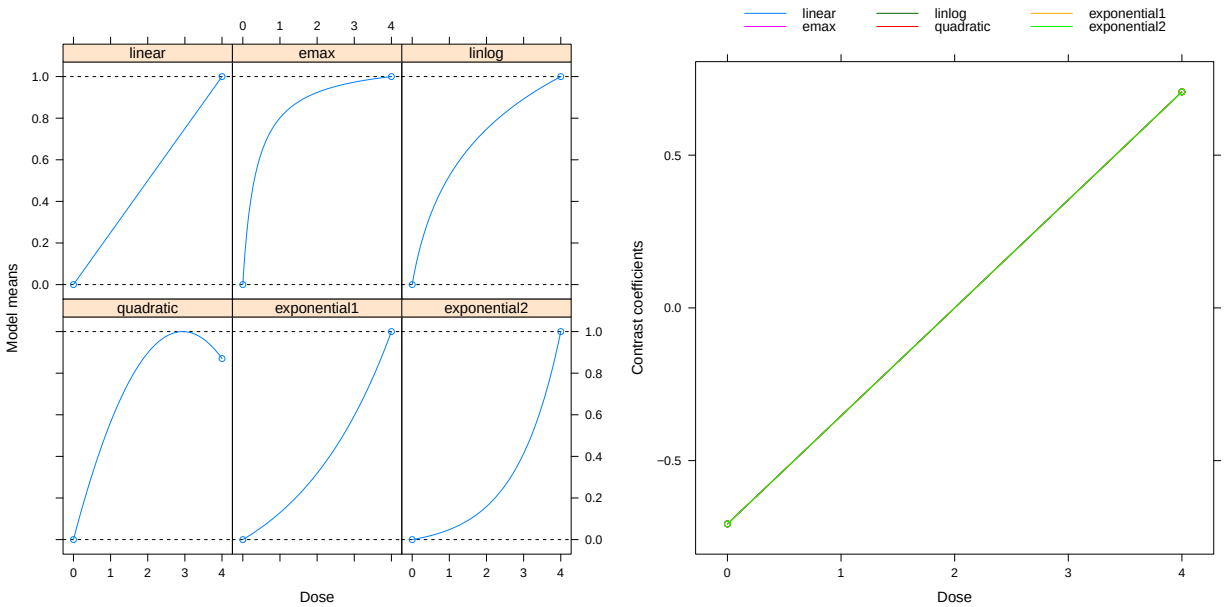


Proposed approach: Illustration of details

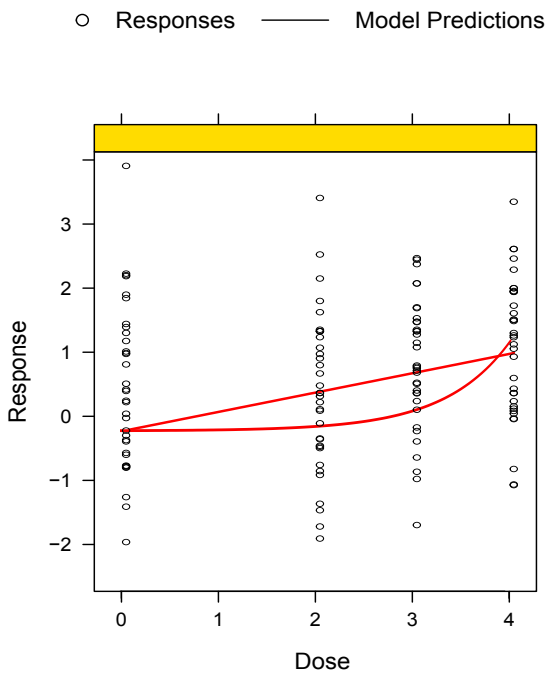
- Consider an example with 4 doses and placebo
- Assume 6 candidate models, with corresponding optimal coefficients for festing $H_4 : \mu_4 \leq \mu_0$



For the test of an elementary null hypothesis this results in the same contrast for all models. This gives a *t*-test at full level α.

Example: Case-study Closed MCP-Mod at $\alpha = 0.025$

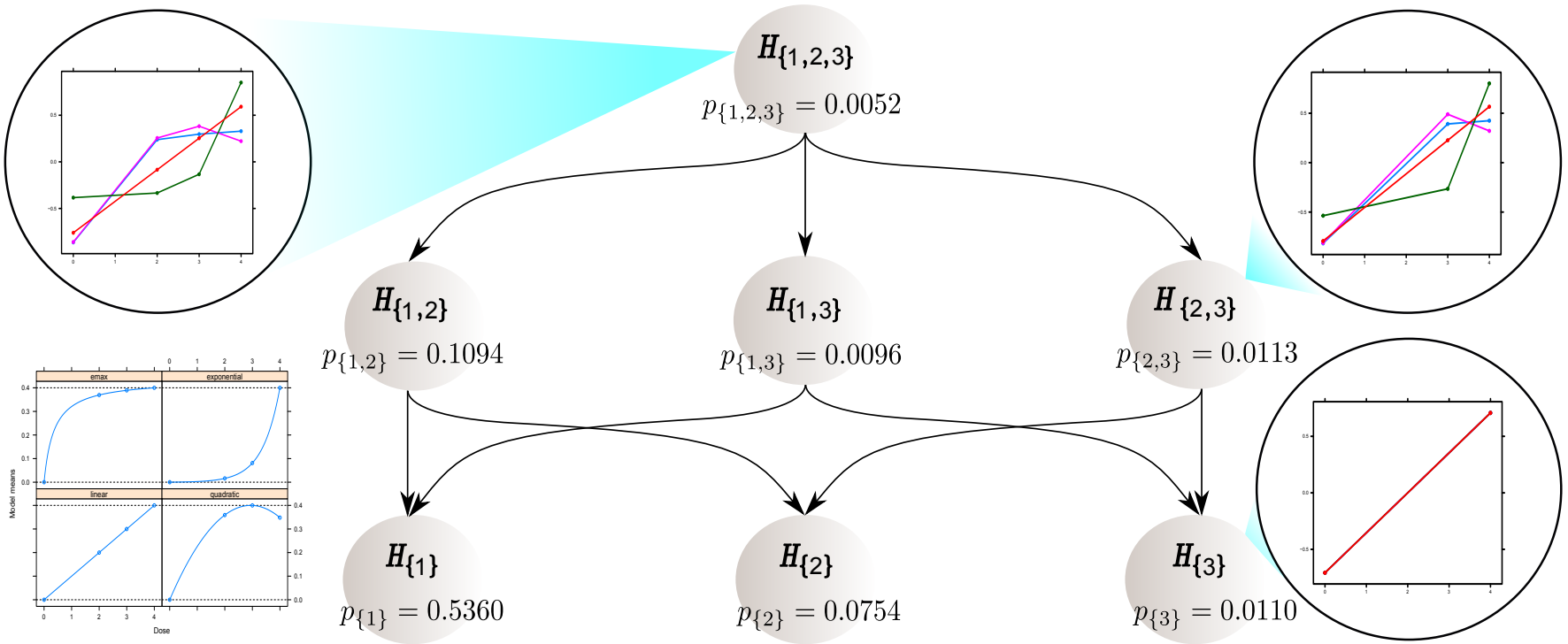
- **control** and $k = 3$ **dose groups** ($d = (0, 2, 3, 4)$);
- **sample size** $N = 140$ (35 patients per arm);
- $\mathcal{M} = \{\texttt{emax}, \texttt{exponential}, \texttt{linear}, \texttt{quadratic}\}$.



Contrast	t-value (T_m)	adj. P-value
exponential	2.790	0.006
linear	2.541	0.011
emax	1.627	0.089
quadratic	1.501	0.111

- PoC can be established ($H_{\{1,2,3\}}$ is **rejected**).

Example: Case-study Closed MCP-Mod



- H_3 **can also be rejected.**

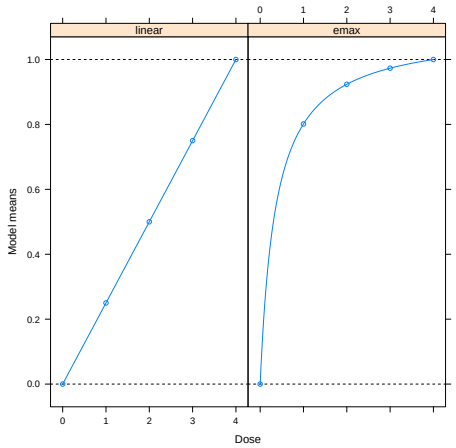
Proposed approach: Remarks

- What if the pre-specified contrasts for some models become very similar for a particular intersection hypothesis H_J?
  - This may e.g. be relevant when the number of doses for some J is small
- Would it not be better to reduce the number of candidate models a-priori for this particular hypothesis to decrease the penalty for multiplicity?
- High similarity between candidate models will result in high correlations, resulting in little multiplicity adjustment, since correlations are accounted for when calculating critical values, p-values, ...

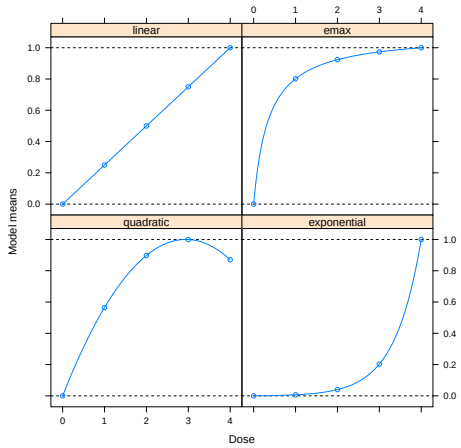
- Question: For each (intersection) hypothesis m contrast tests have to be performed. Is it worth all the effort?

Simulation study

- Parallel group design with $k = 4$ dose groups and placebo, $d_0, d_1, \ldots, d_k$
- Normal responses with variance $\sigma^2 = 1$.
- Testing one sided hypotheses at overall level $\alpha = 0.025$
- Sample size per group $n = 20$
- Two sets of candidate models $\mathcal{M}$:

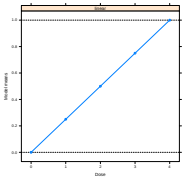


and

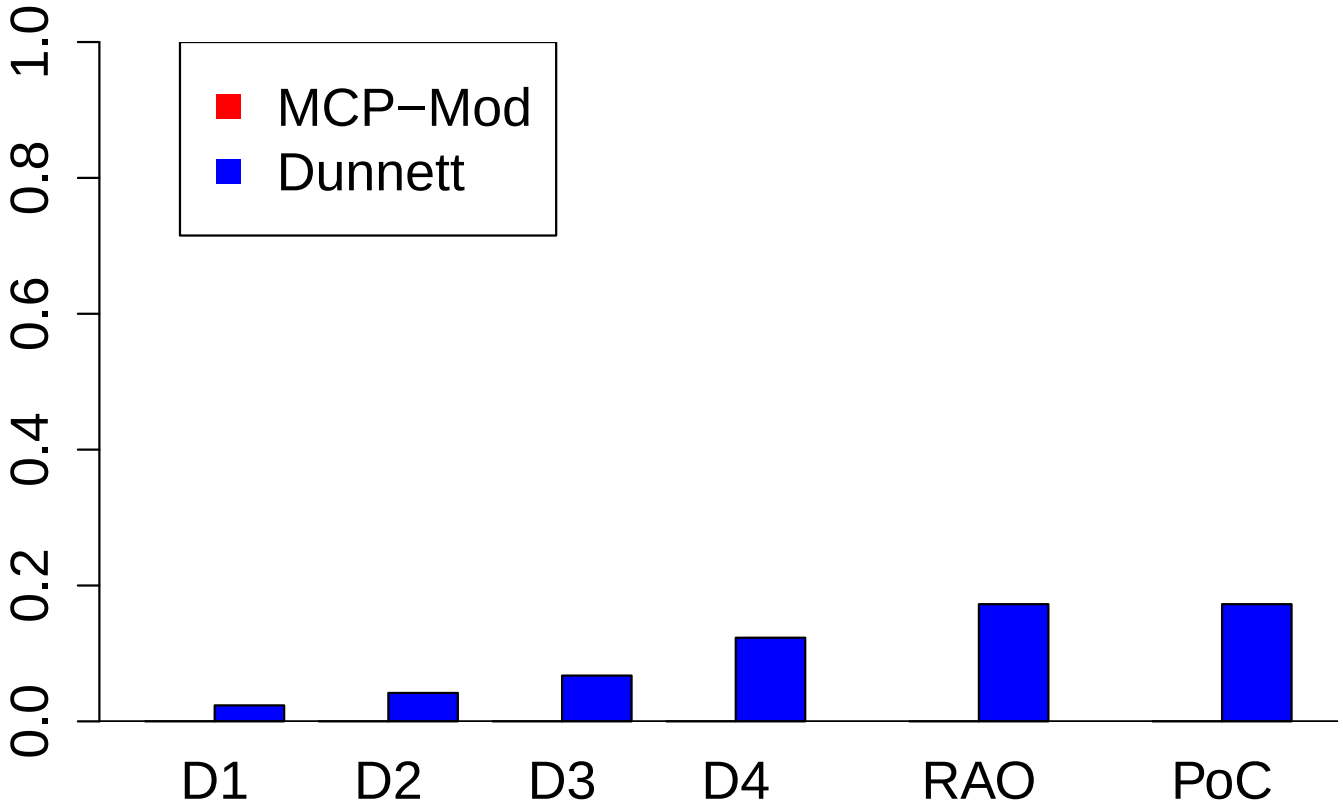


- Compare power closed MCP-Mod with step-down Dunnett test
- 10 000 simulation runs for each parameter configuration

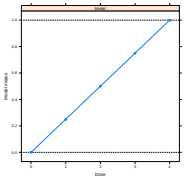
Simulations



Linear with $\mu_4 = 0.4\sigma$; 2 candidate models



Simulations



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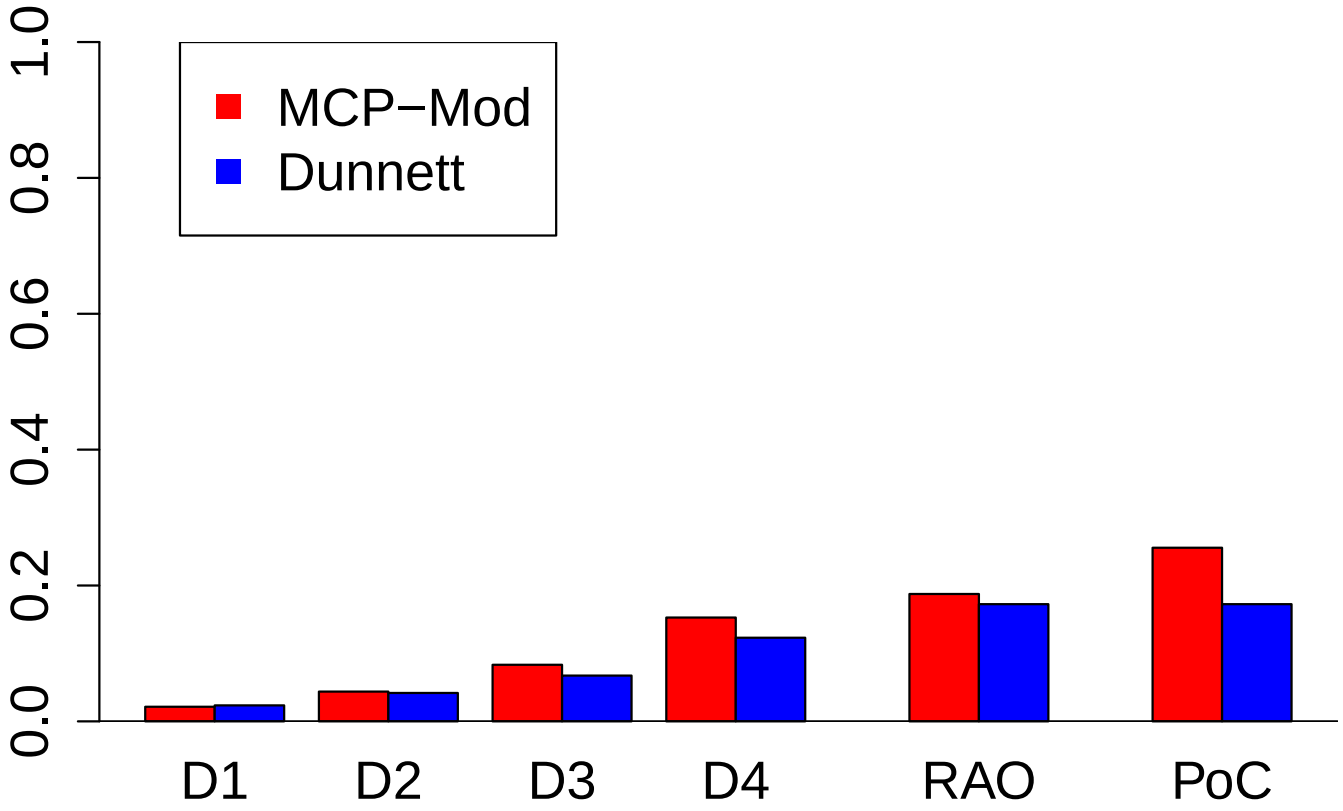

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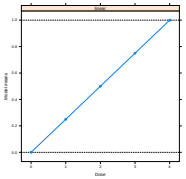
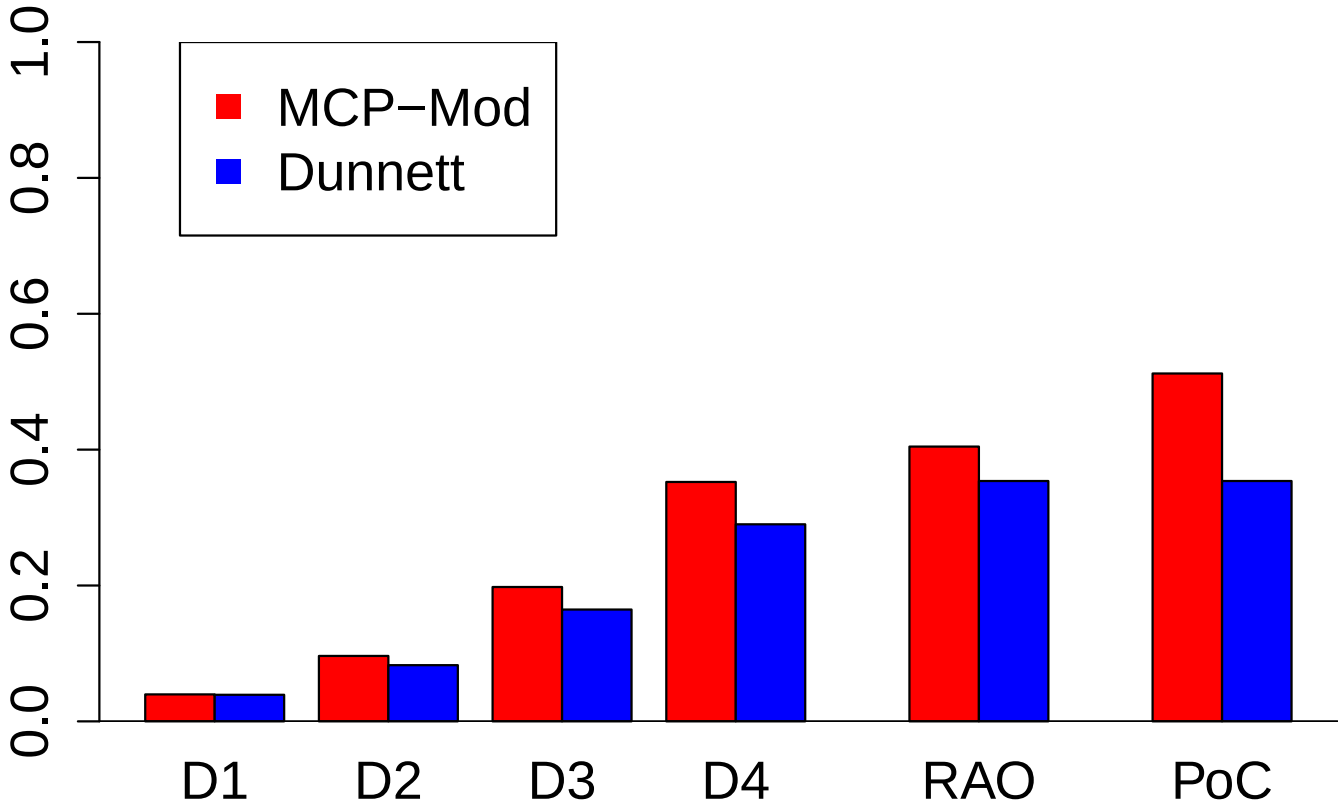
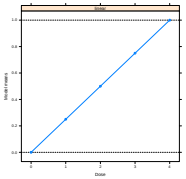


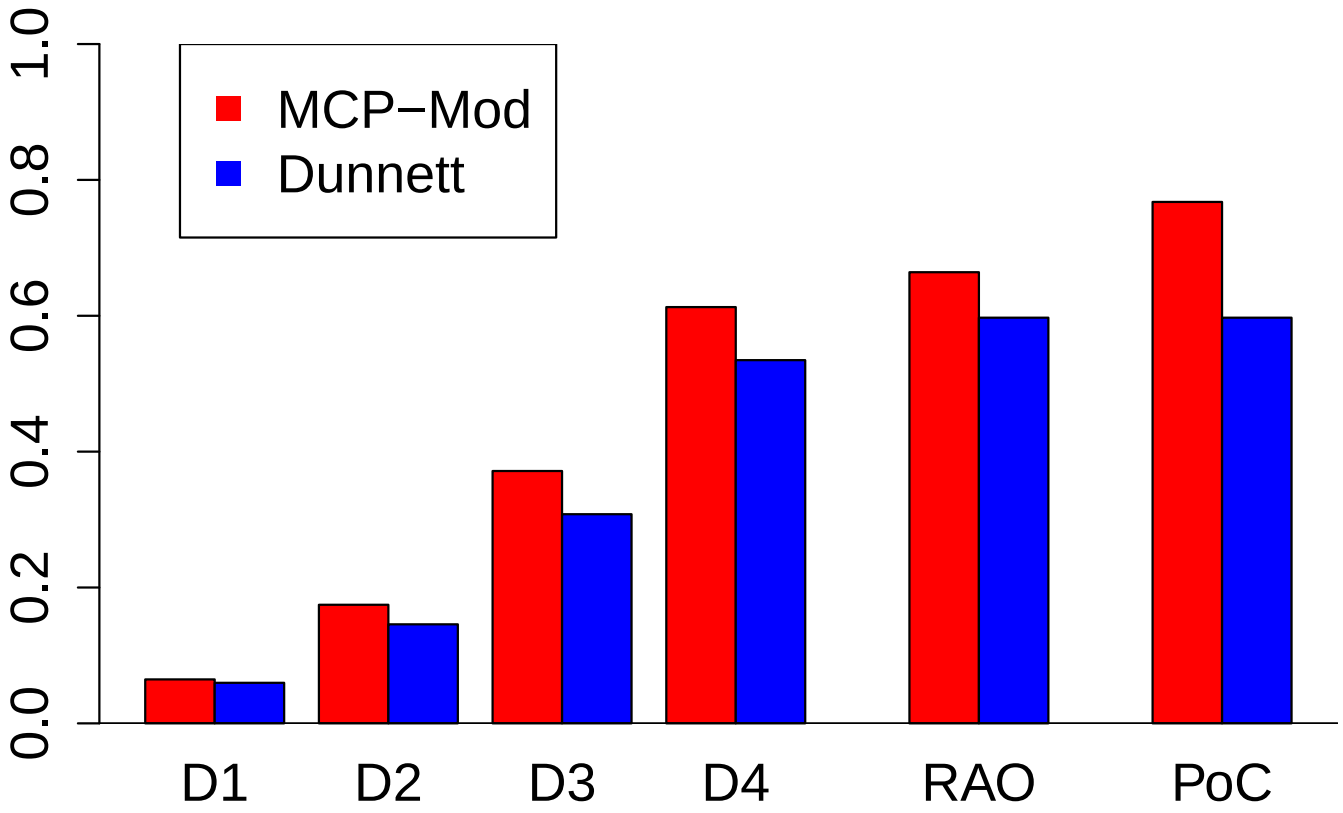
Linear with $\mu_4 = 0.6\sigma$; 2 candidate models



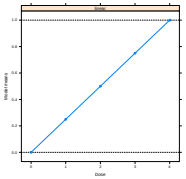
Simulations



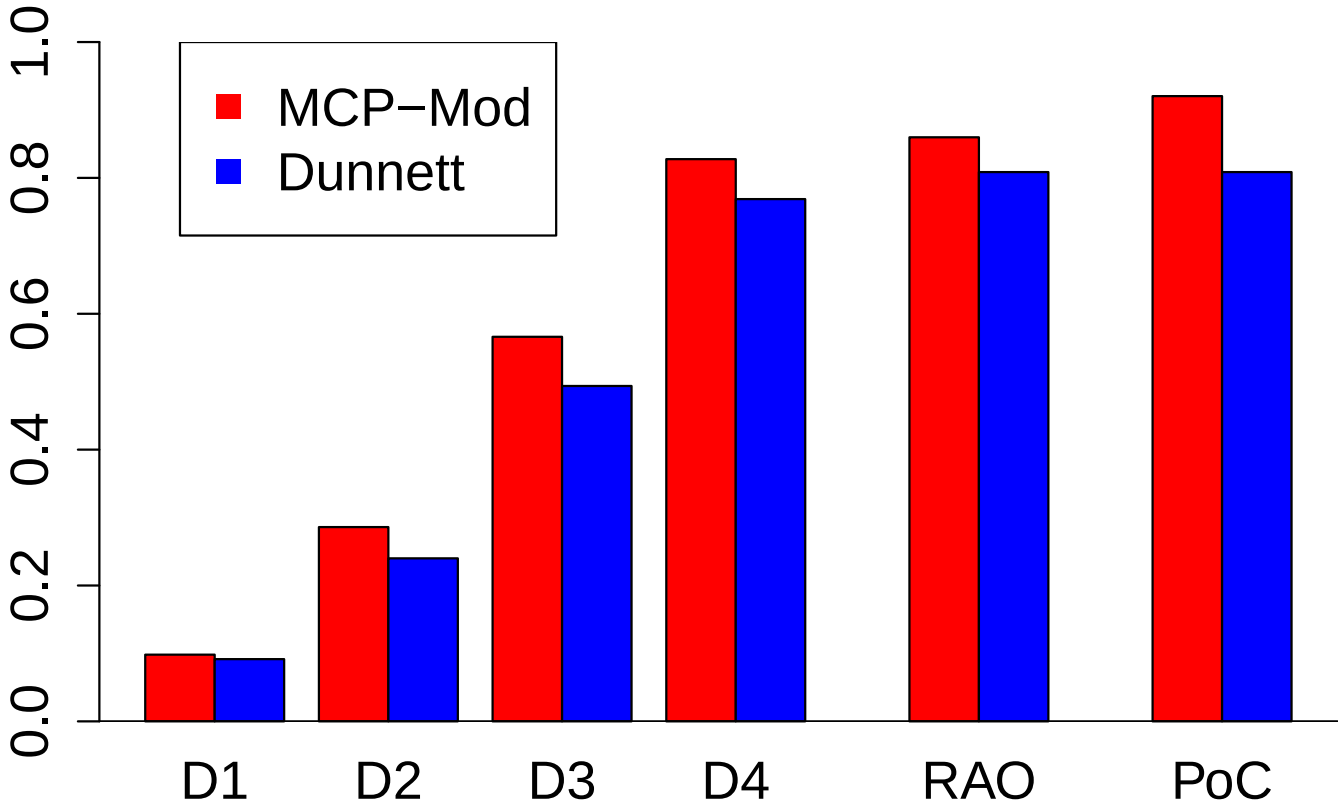
Linear with $\mu_4 = 0.8\sigma$; 2 candidate models



Simulations



Linear with $\mu_4 = \sigma$; 2 candidate models



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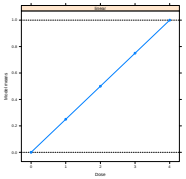
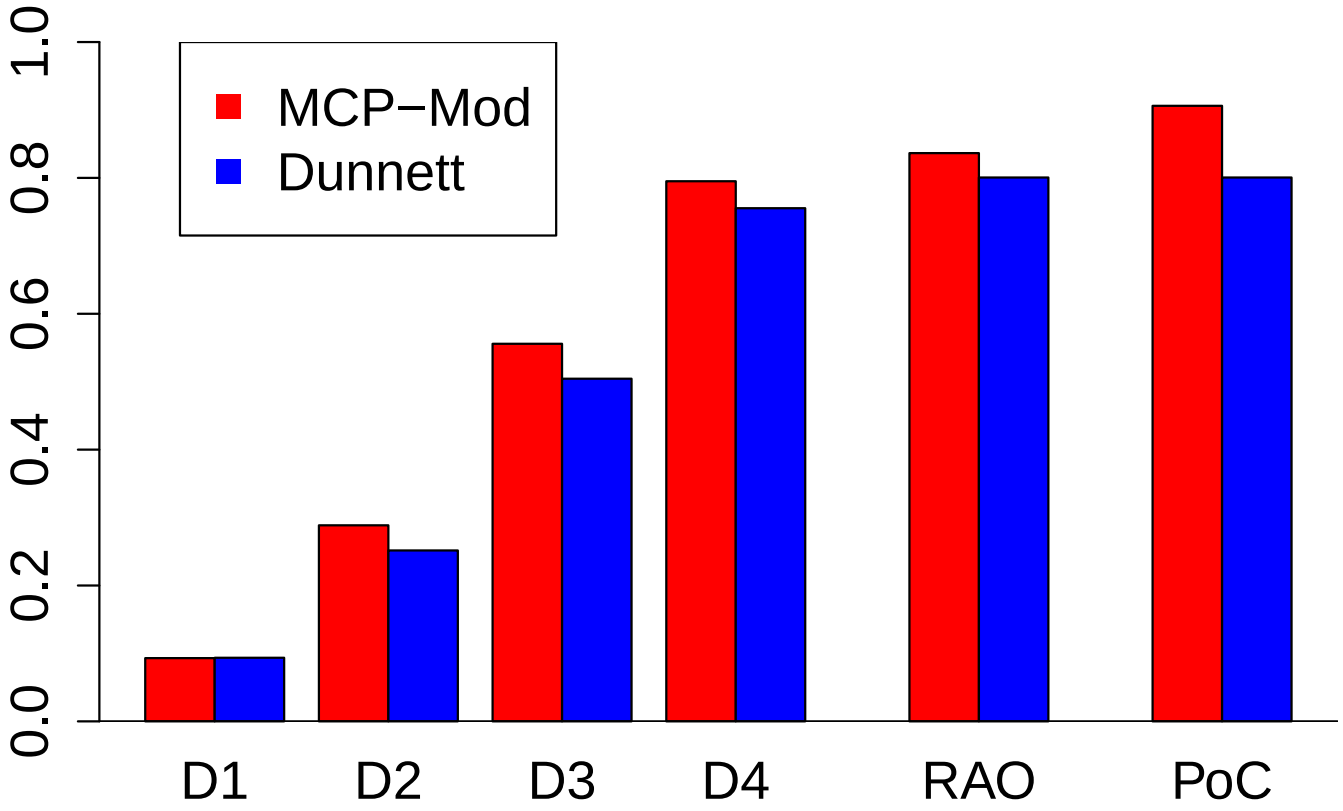
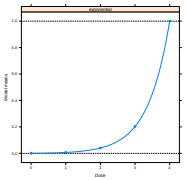


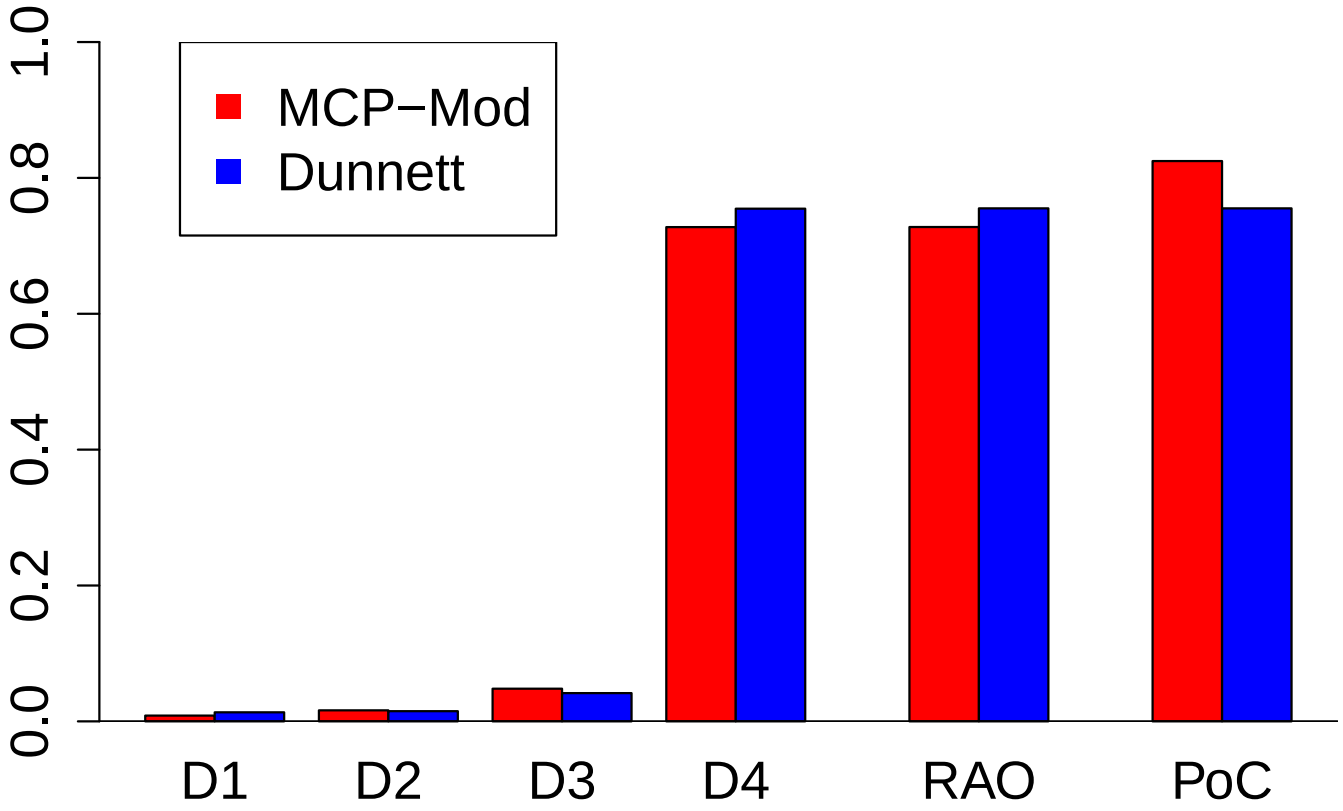
Impact of using more candidates? 4 candidate models



Simulations



True Model exponential with $\mu_4 = \sigma$; 2 candidate models



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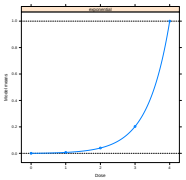

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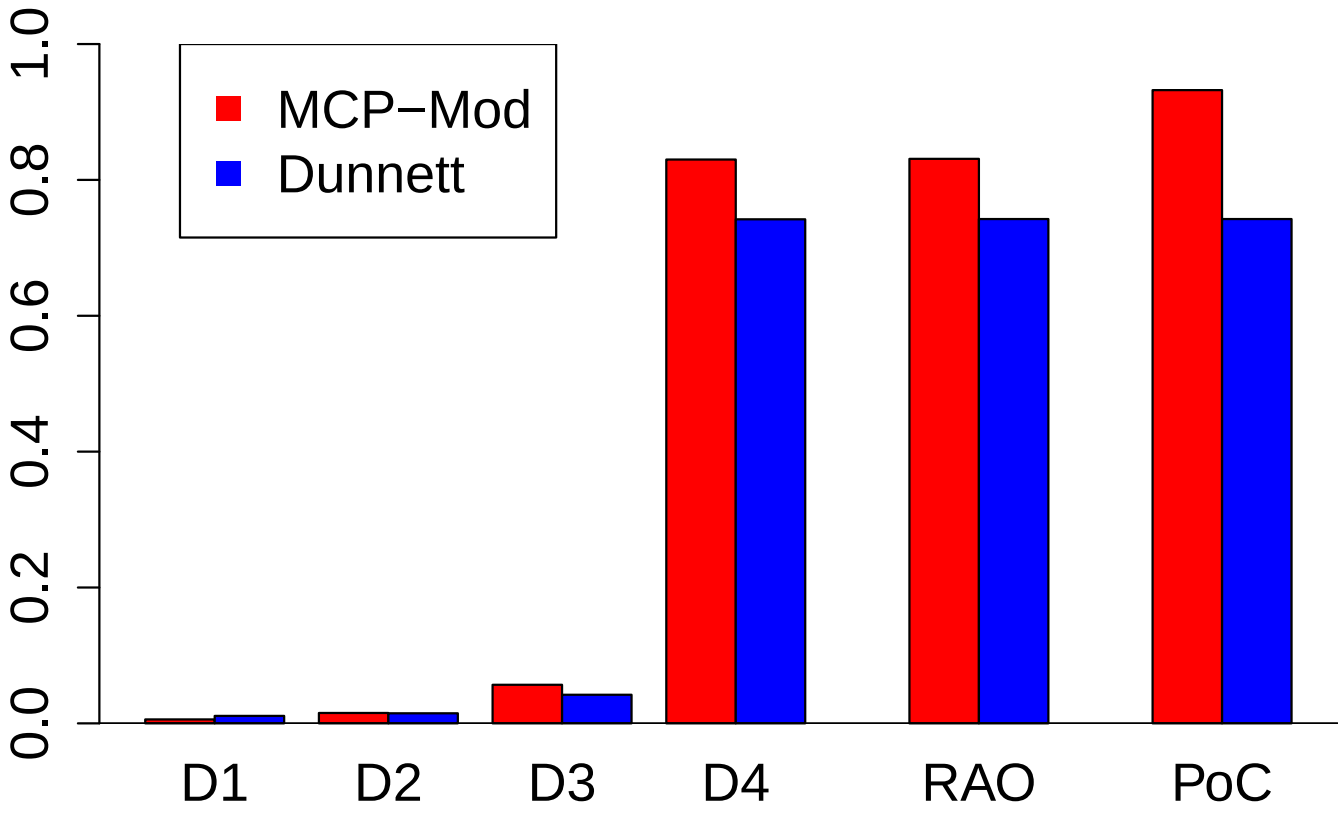
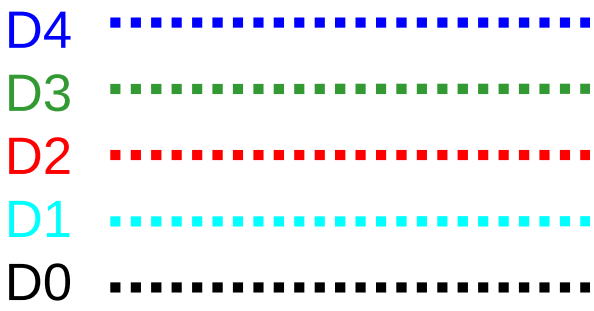
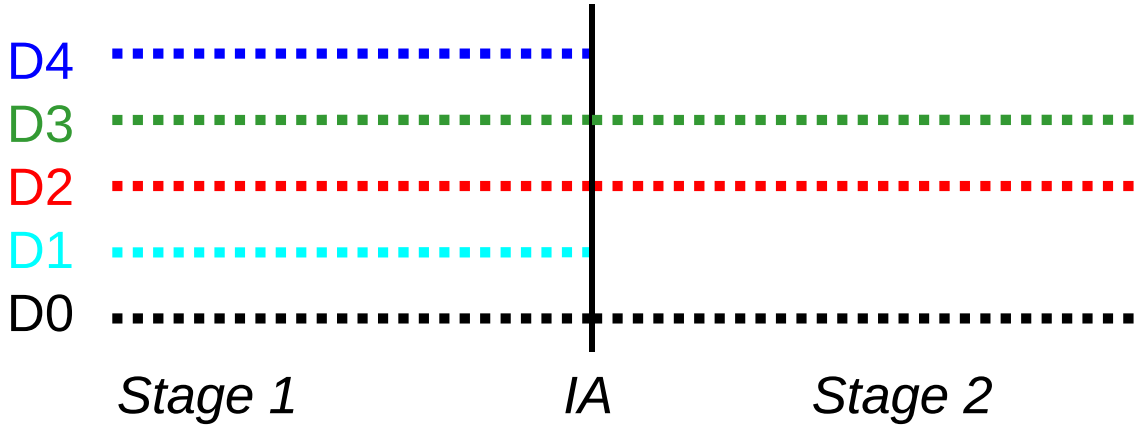


- Fixed Sample Design

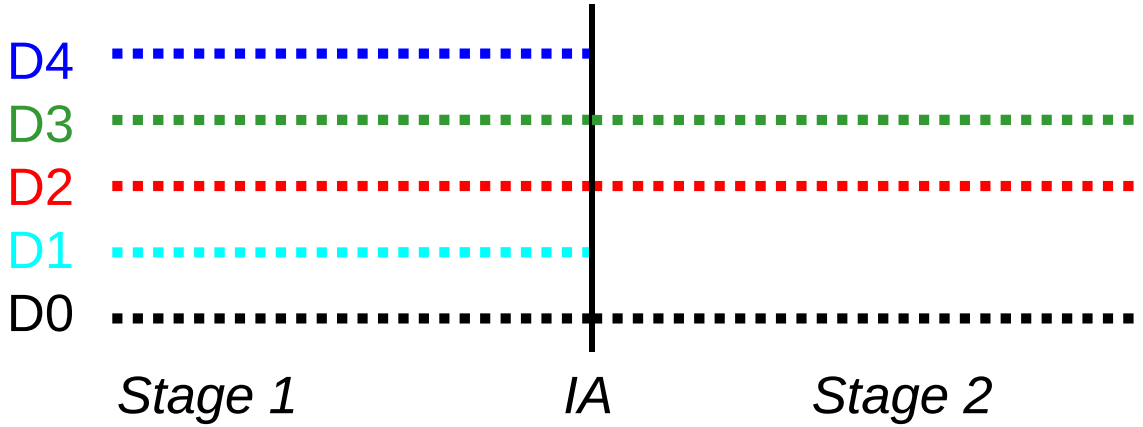


Analysis
(Testing & Estimation)

Adaptive Design



Adaptive Design



- Before trial start:
  - Fix the design of the first stage (sample sizes, dose groups, ...) and a candidate model set $\mathcal{M}_1$ for the first stage.
- At interim:
  - Fix the design of the second stage (adapt sample sizes, selection of doses, ...) and a candidate model set $\mathcal{M}_2$ (drop/add models, refine parameter guesses, ...).
  - Use the Mod part of MCP-Mod to support interim decisions (e.g., estimate MED or the peak dose)
- Final analysis:
  - Test for a dose response signal and/or individual $H_i : \mu_i \leq \mu_0$ using data from both stages with stage-wise tests based on $\mathcal{M}_1$ and $\mathcal{M}_2$

Testing efficacy of selected doses

(BAUER AND KIESER 1999, HOMMEL 2001, POSCH ET AL. 2005, BRETZ ET AL. 2009, ...)

Final test procedure combines three different methodologies:

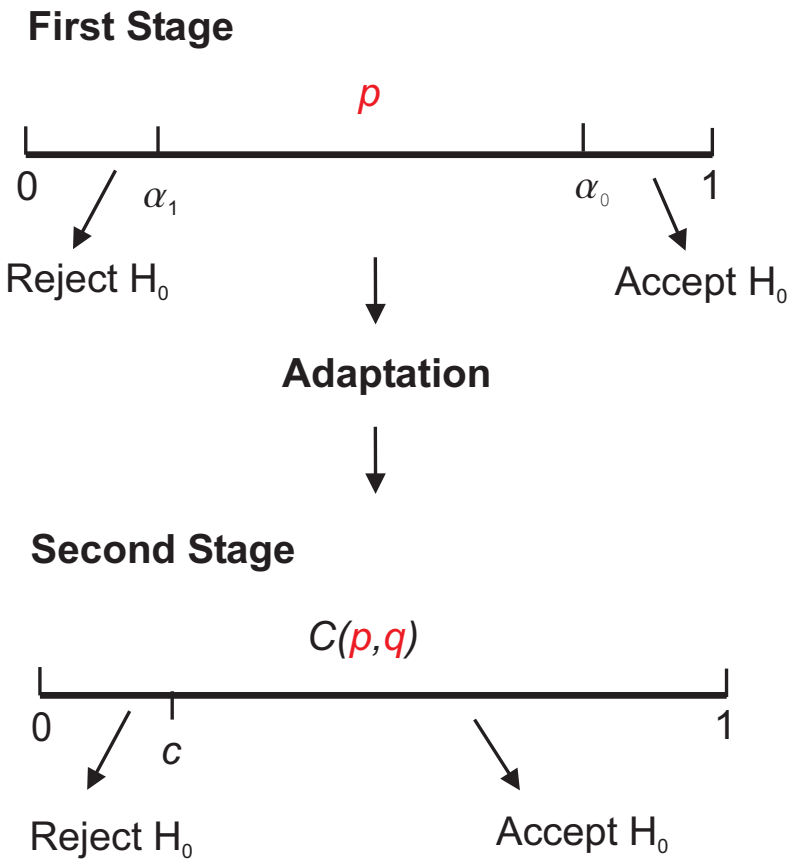
- MCP part of MCP-Mod (above)
- Closed test procedure (above)
- Adaptive combination tests (below) that do not require pre-specified adaptation rules

More specifically, use a combination test $C(p, q)$ to combine the stagewise p-values p and q for each intersection hypothesis and apply the closed test procedure, where

- C could be e.g. Fisher´s product test or the inverse normal method
- p and q are calculated from the extended MCP-Mod approach above

Adaptive Two Stage Test based on Combination Tests

(BAUER 1989, BAUER & KÖHNE 1994, . . .)



Planning:

- Fix design (only) for Stage 1
- Fix combination function $C(p, q)$ and critical value c
  e.g. Inverse-Normal with $C(p, q) = 1 - \Phi[w_1 \Phi^{-1}(1-p) + w_2 \Phi^{-1}(1-q)]$

Stage 1:

- Compute p-value p from Stage 1 data
- Fix design for Stage 2 based on data from Stage 1

Stage 2:

- Compute p-value q form Stage 2 data.
- Reject H_0 iff $C(p, q) \leq c$.

Remarks

- For each intersection hypothesis H_J, $J \subseteq \{1, ..., k\}$ calculate multiplicity adjusted p-values per stage using the set of models $\mathcal{M}_1$ and $\mathcal{M}_2$ for stage 1 and 2, respectively.
- Combine the stage-wise minimum p-values via combination test.
- For stage 2: If for H_J, $J \subseteq \{1, ..., k\}$ doses $i \in J$ are missing at the second stage, simply take the second stage p-value of the largest subset $I \subset J$, where all doses $i \in I$ are available at stage 2.

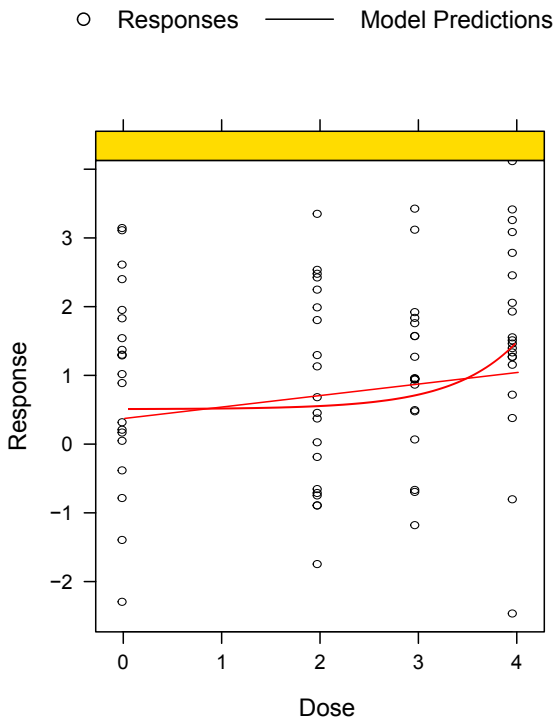
Example: Case-study Adaptive MCP-Mod

Design Considerations

- **control** and $k = 3$ **dose groups** ($d = (0, 2, 3, 4)$);
- multiple level $\alpha = 0.025$ (one-sided);
- 1 adaptive interim analysis with O'Brien Fleming type boundaries ($\alpha_1 = 0.0043$, $\alpha_0 = 0.5$, $c = 0.0235$)
- Inverse Normal
  $C(p, q) = 1 - \Phi[w_1 \Phi^{-1}(1 - p) + w_2 \Phi^{-1}(1 - q)]$, where $w_1^2 = n_1/(n_1 + n_2)$, $w_2^2 = n_2/(n_1 + n_2)$ and n_i is proportional to pre-planned stagewise i sample sizes;
- Stage 1 **sample size** $n_1 = 80$ (20 patients per arm);
- Stage 2 **sample size** $n_2 = 60$
- $\mathcal{M}_1 = \{\texttt{emax}, \texttt{exponential}, \texttt{linear}, \texttt{quadratic}\}$.

Example: Adaptive MCP-Mod (3 doses and control)

- Stage I **sample size** $n_1 = 80$ (20 patients per arm)
- **Interim analysis (Stage I data)**



O'Brien Fleming stopping boundaries

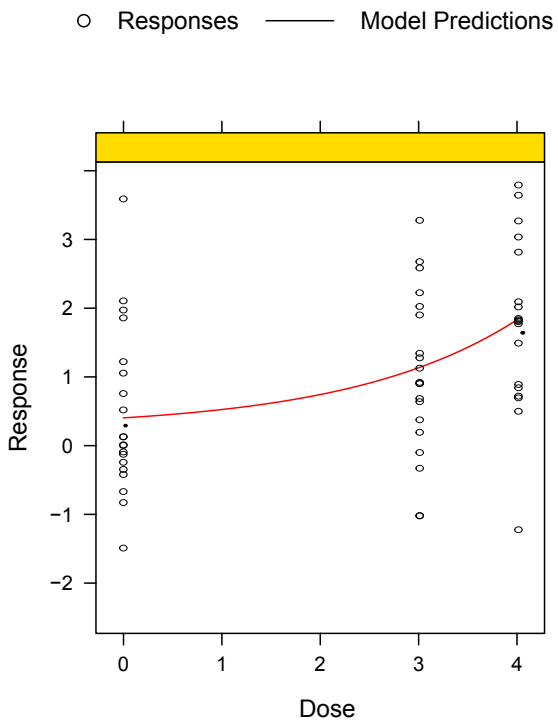
$\alpha_1 = 0.0043$, $\alpha_0 = 0.5$.

Contrast	t-value (T_m)	adj. P-value
exponential	1.758	0.070
linear	1.420	0.129
emax	0.643	0.370
quadratic	0.479	0.435

- Interim Decisions
  - **control** and $k = 2$ **dose groups** ($d = (0, 3, 4)$);
  - Stage II **sample size reallocated** $n_2 = 60$ (20 patients per arm);
  - $\mathcal{M}_2 = \{\texttt{exponential}, \texttt{linear}\}$.

Example: Adaptive MCP-Mod

- **Stage II data**

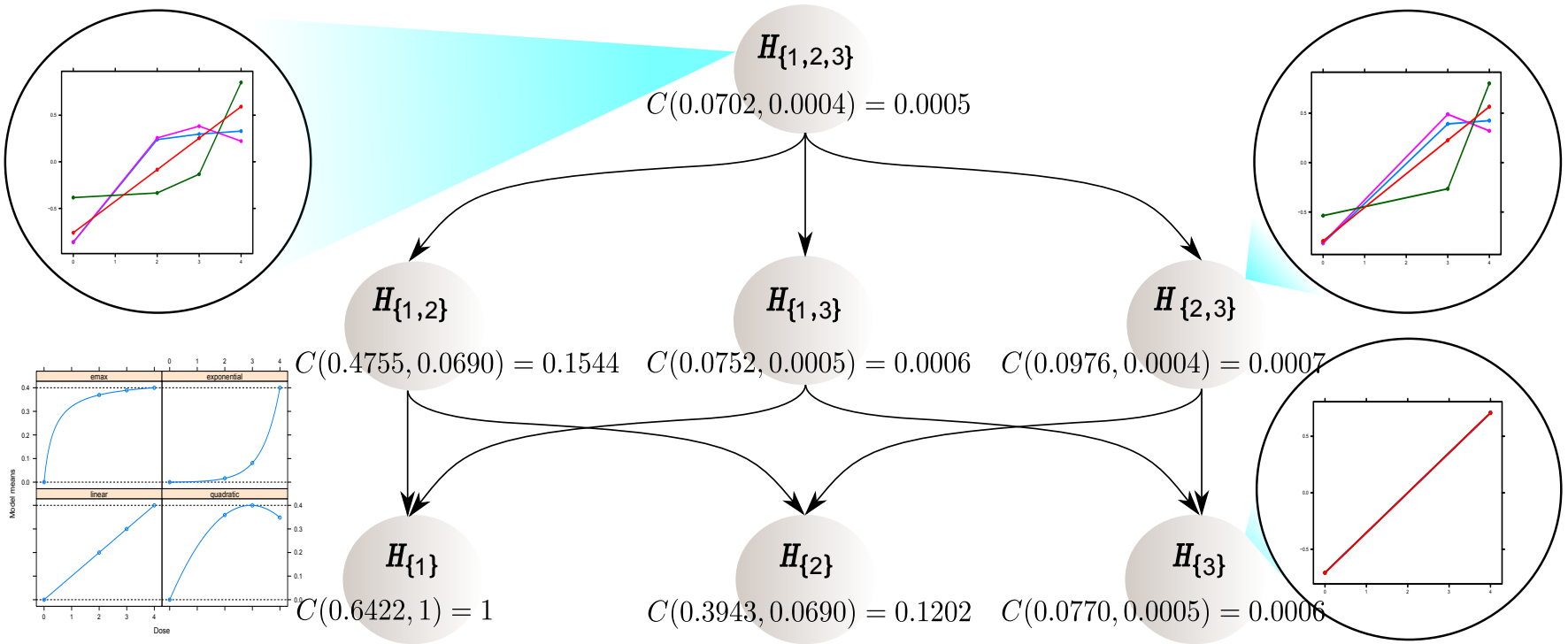


Contrast	t-value (T_m)	adj. P-value
exponential	3.635	0.0004
linear	3.412	0.001

- **Final analysis for PoC**
  - $p = 0.070$;
  - $q = 0.0004$;
  - $C(0.070, 0.0004) = 0.0005 < 0.0235 \Rightarrow H_{\{1,2,3\}}$ is **rejected**.

Example: Adaptive MCP-Mod based on Closed Test

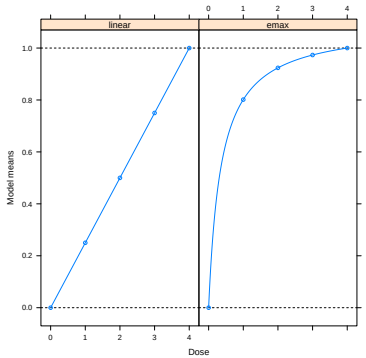
- **Final analysis**



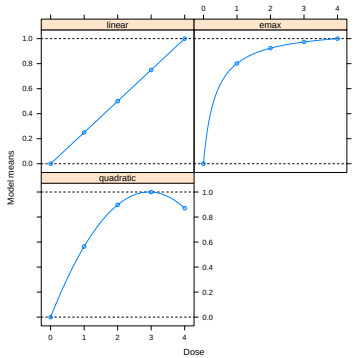
- In addition to PoC, also comparison of hightest dose vs placebo is statistically significant (H_3 is **rejected**).

Simulation study

- Parallel group design with $k = 4$ doses and placebo
- Total sample of $N = 100$ for the entire trial, split between the two stages with 60 in the first and 40 for the second stage
- Set of candidate models $\mathcal{M}_1$:



and



- Compare adaptive MCP-Mod with an adaptive combination test using Dunnett adjusted p-values and the inverse normal combination function

Simulation study: Interim selection rule

- At interim, select placebo d_0 and the "best" dose for the second stage
- Since the total sample size is fixed, we have an implicit sample reassessment as well
- In the final analysis, we are interested in testing H_i only for the selected dose i, but using totality of information from both stages and strongly controlling the overall Type I error rate

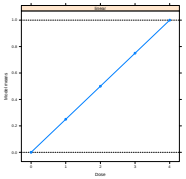
Adaptive MCP-Mod

- Use "best" model to select the dose with the largest response, which may not be the dose with the largest interim estimate

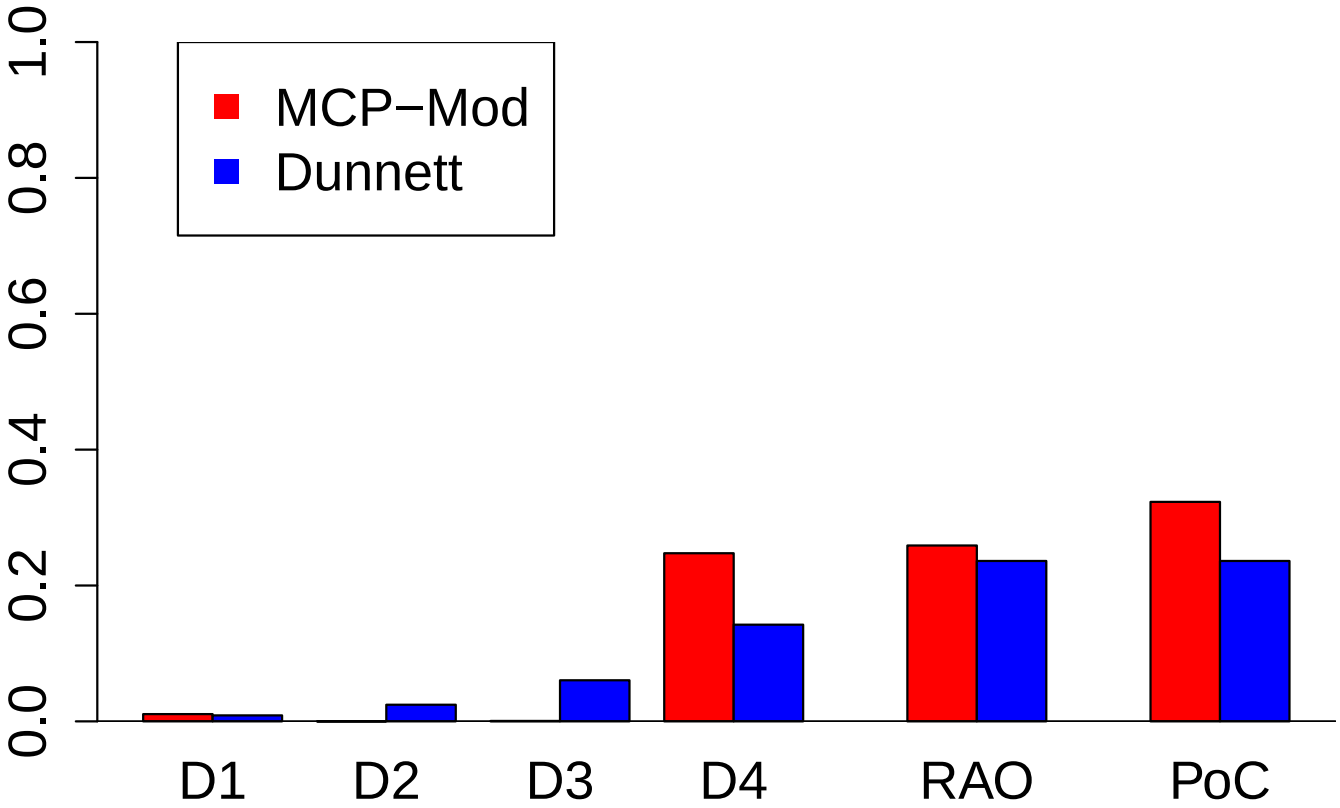
Adaptive design using Dunnett adjusted p-values

- Select the dose with largest interim estimate.

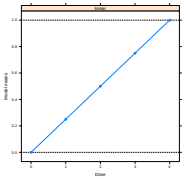
Simulation results



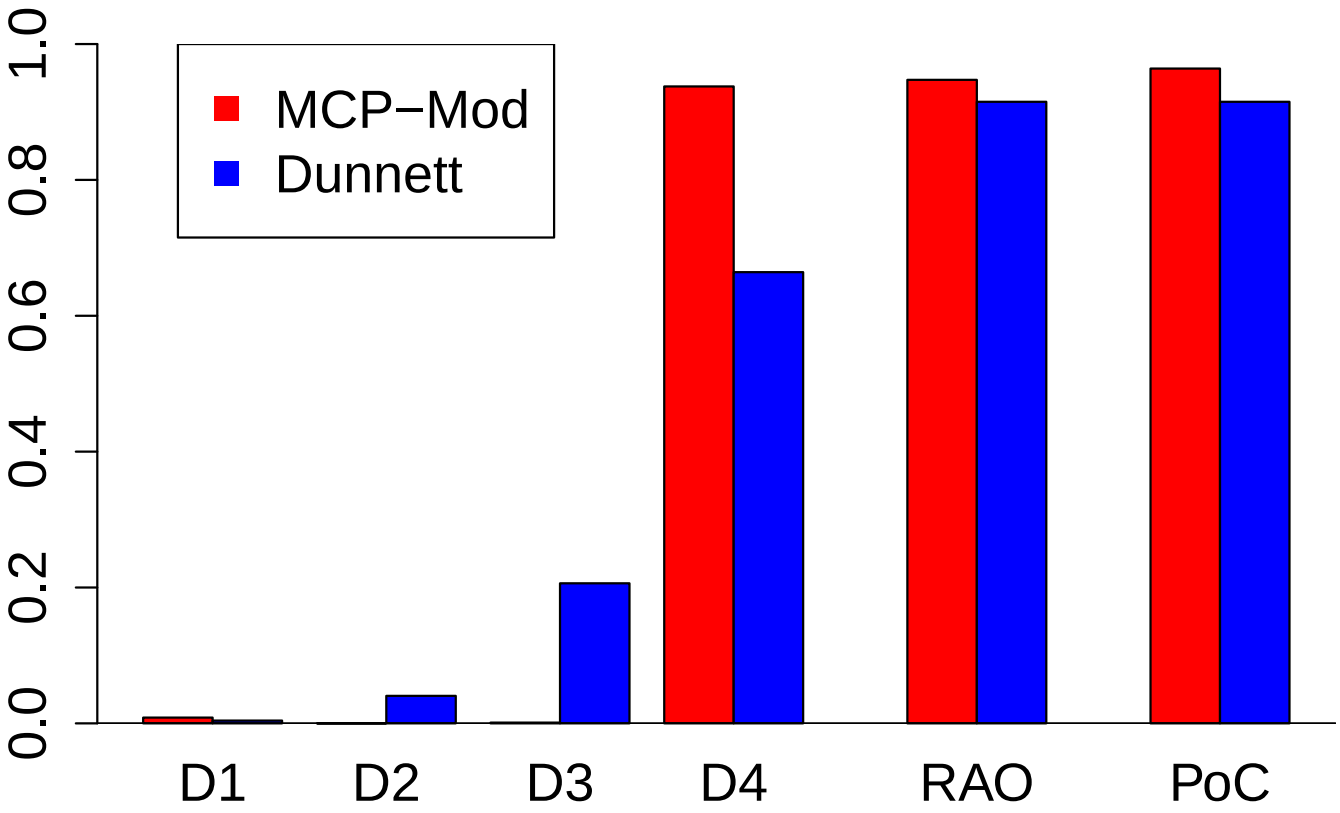
True linear model with $\mu_4 = 0.4\sigma$, 2 candidate models in $\mathcal{M}_1$



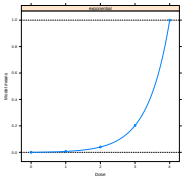
Simulation results



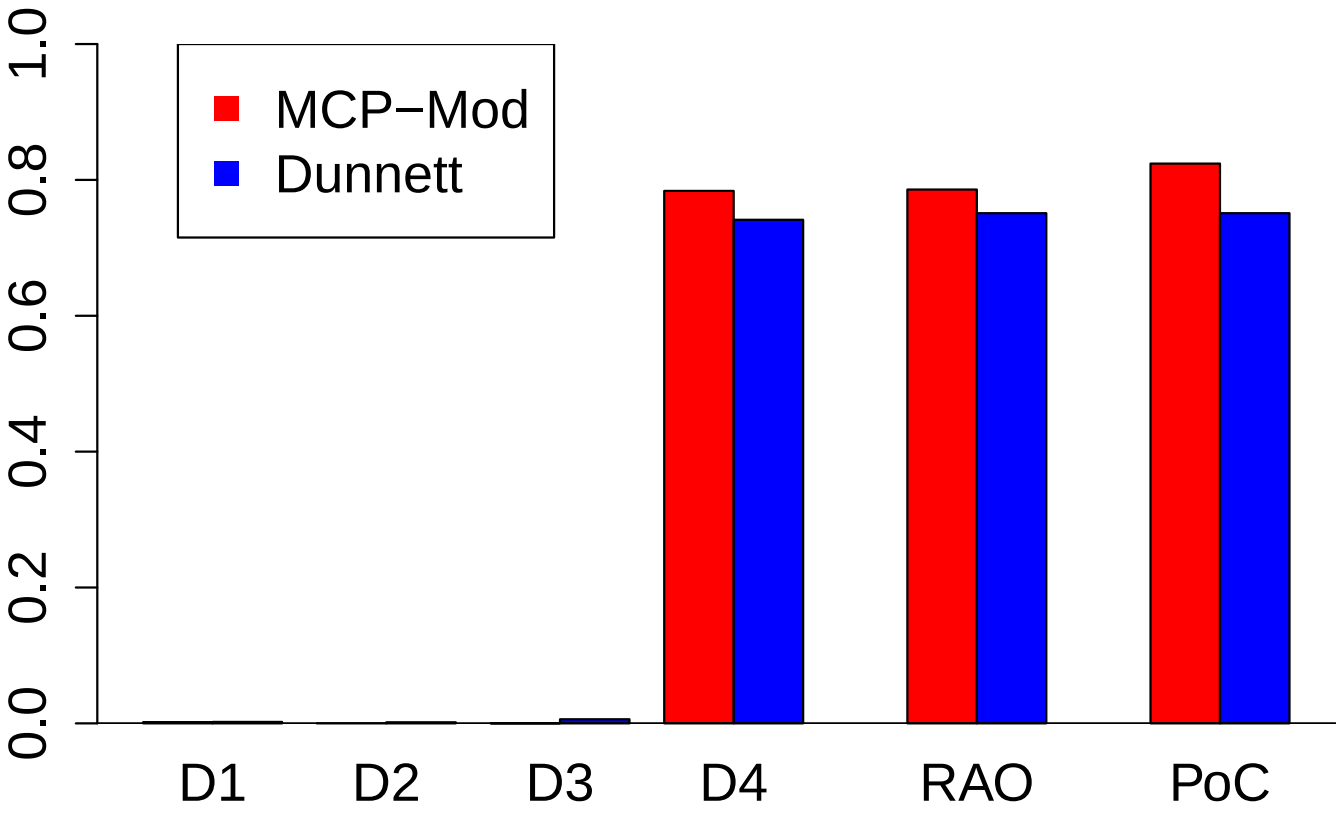
True linear model with $\mu_4 = \sigma$, 2 candidate models in $\mathcal{M}_1$



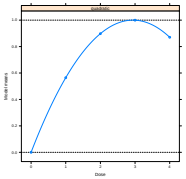
Simulation results



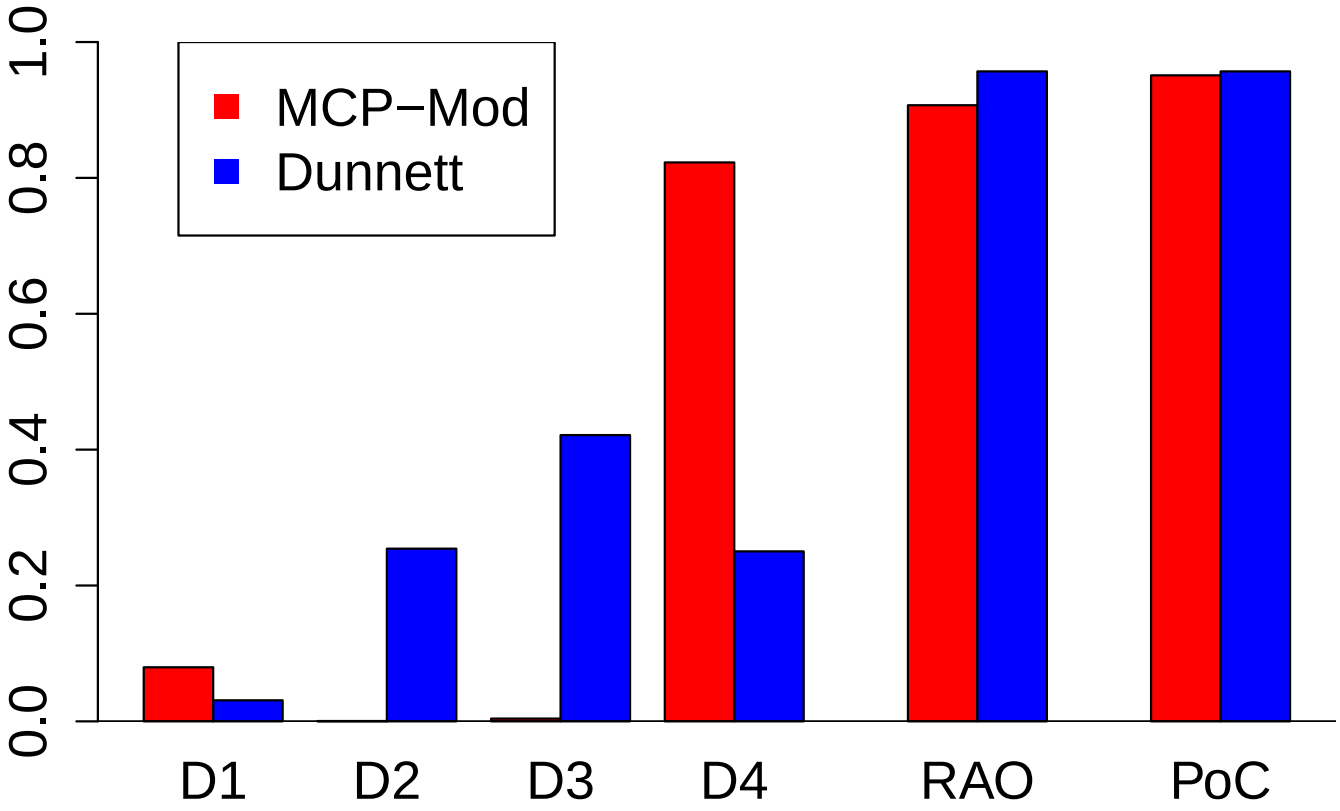
True exponential model with $\mu_4 = \sigma$, 2 candidate models in $\mathcal{M}_1$



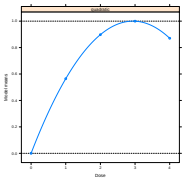
Simulation results



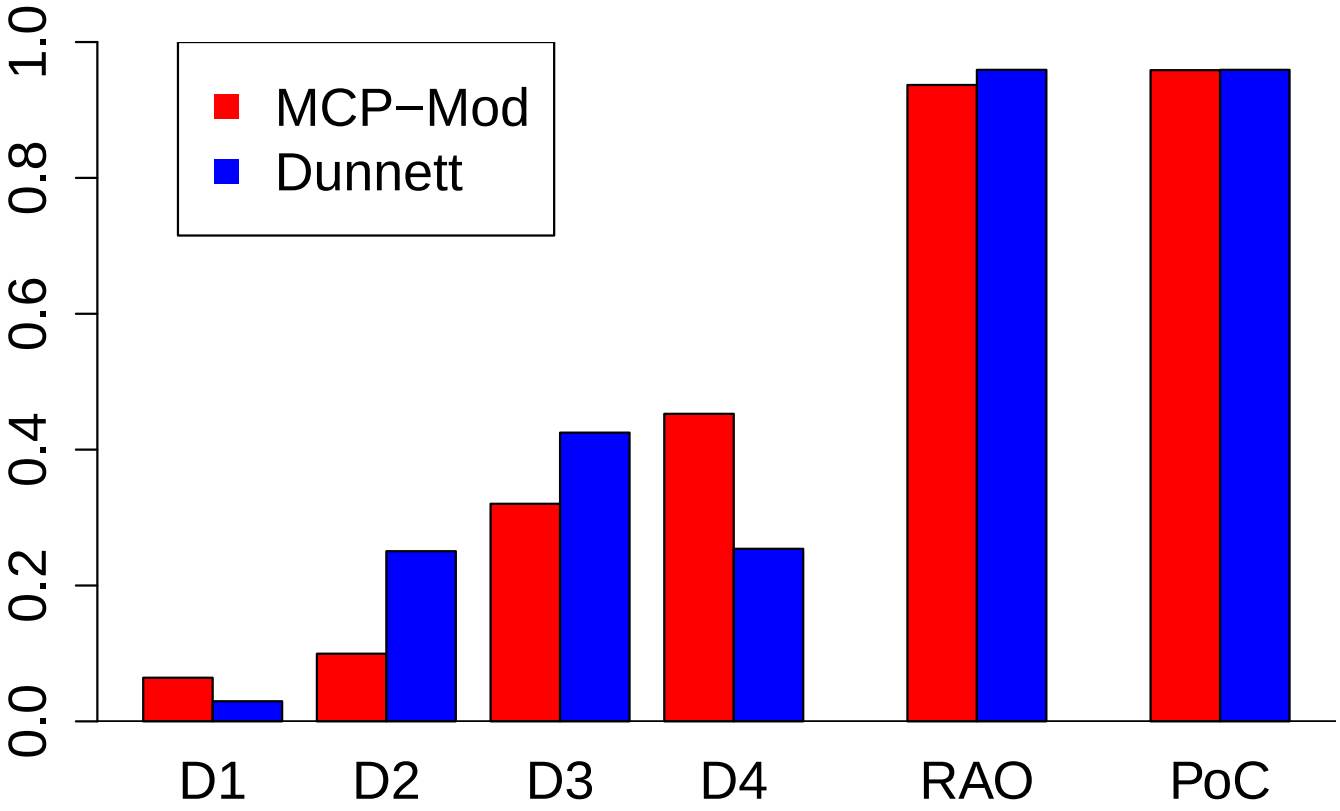
True quadratic model with peak at d_3 and $\mu_3 = \sigma$, 2 candidate models in $\mathcal{M}_1$



Simulation results



True quadratic model with peak at d_3 and $\mu_3 = \sigma$, 3 candidate models in $\mathcal{M}_1$



Summary

- Applying the closed test procedure to the original MCP-Mod approach, we obtain pairwise dose-control comparisons almost free of charge
- Unconstrained and constrained MCPMod versions available to ensure type I error control (not shown today)
- Using combination test principle enables adaptive interim analysis to change models, sample sizes, doses, ...
- "Optimal" design depends on which power is of main interest (PoC, RAO, specific dose, ...)
- More work to do: more advanced interim selection rules, sample size reassessment based on conditional power arguments, ...

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Type I error control using proposed MCP-Mod

- For $\mu_0 = \mu_1 = ... = \mu_k$ everything is fine
- (or if you use two-sided instead of one-sided tests)
- If in reality $\mu_i \leq \mu_0$ holds for some $i > 0$, a misspecification of the profile (with some negative weights c_i for $i > 0$) might lead to situations where this test rejects with probability $> \alpha$

- For strong control of the Type I error rate you have to either
  - assume $\mu_i \geq \mu_0$ for all $i > 0$, or
  - test only 2 doses against control (proof not shown here), or
  - allow only candidates models and/or doses ($i > 0$) with $c_{mi} \geq 0$ (very restrictive: might exclude to many model and doses), or
  - impose constraint $c_{mi} \geq 0$ for $i > 0$ when determining optimal contrasts for any candidate model m (only for placebo we allow $c_{m0} < 0$)

Constrained MCP-Mod

- Replace original, "unconstrained" optimal contrast coefficients by constrained coefficients satisfying $c_{mi} \geq 0$ for all $i = 1, \ldots, k$

Unconstrained MCP-Mod

Dose	linear	emax1	emax2	sigEmax	quadratic
0	-0.536	-0.861	-0.770	-0.515	-0.709
0.15	-0.341	0.199	-0.102	-0.453	-0.078
0.5	0.114	0.317	0.343	0.310	0.694
1	0.764	0.345	0.529	0.658	0.093

Constrained MCP-Mod

Dose	linear	emax1	emax2	sigEmax	quadratic
0	-0.707	-0.861	-0.809	-0.782	-0.738
0.15	0.000	0.199	0.000	0.000	0.000
0.5	0.000	0.317	0.311	0.187	0.671
1	0.707	0.345	0.498	0.595	0.067

Simulation study

- Parallel group design with placebo and $k = 3$ doses $0.15, 0.5, 1$
- Normal responses with variance $\sigma^2 = 1$.
- Testing one-sided hypotheses at overall level $\alpha = 0.025$.
- Sample size per group $n = 30$
- Candidate models $\mathcal{M}$: Linear, 2 Emax ($ED_{50} = 0.025, 0.2$), sigmoid Emax ($ED_{50} = 0.4, h = 3$), and quadratic (maximum effect at dose 0.6)
- Compare power of unconstrained with constrained MCP-Mod
  - Further comparisons with step-down Dunnett and fixed sequence test shown in the Appendix.

Simulation results

- Difference in power of unconstrained and constrained MCP-Mod to reject individual hypotheses H_i, under different true models
  - No apparent loss in power when using constrained MCP-Mod
  - However, constrained MCP-Mod is less powerful for dose response signal detection (not shown)