Evaluating dose-response under model uncertainty using several nested models

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2. The MCP-Mod approach
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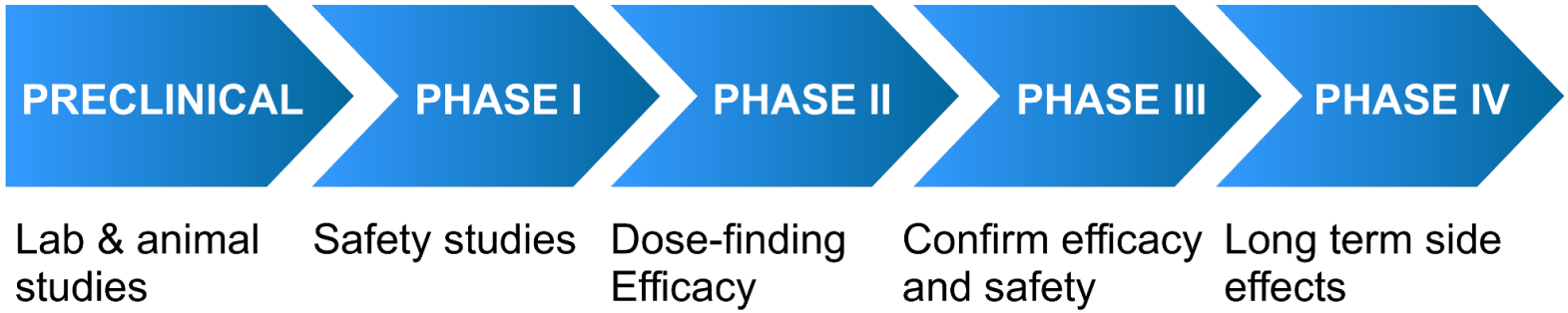
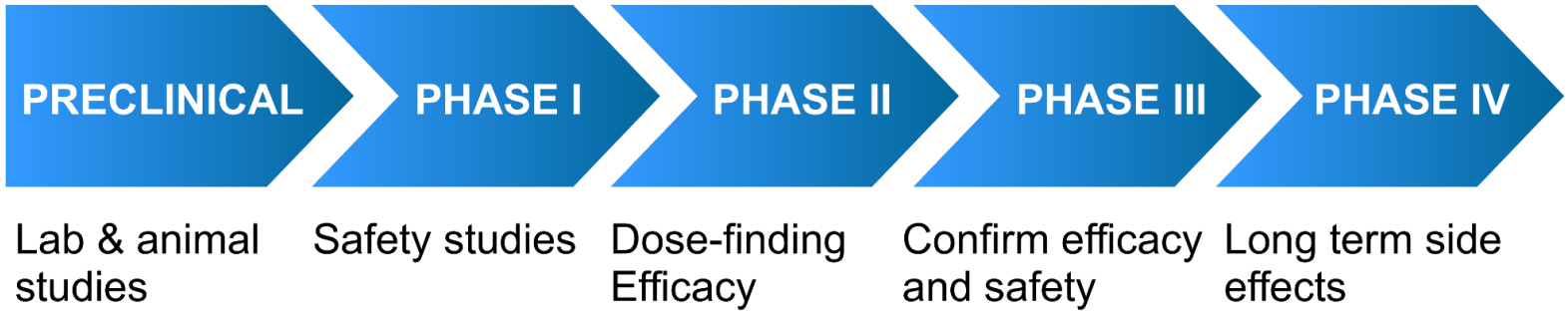
Phases of a Clinical Trial



Phases of a Clinical Trial



- Many positive phase II trials are followed by a negative phase III trial
- High drop-out rates in phase III trials
- Often dose adjustments are required in the label after registration of a drug

A dose-finding example

Bretz et al. (2005, Biometrics 61):

Aim:

- Establish PoC
- Estimate MED

Study design:

- Double-blind parallel group trial
- Four active doses (d = 0.05, 0.20, 0.60, 1) and placebo (d=0)
- 20 patients per dose level

Assumptions:

- Normally distributed response variable
- Monotone increasing dose-response function

Dose-finding in Drug Development

Two typical analysis approaches:

- Multiple comparison procedures comparing each dose to placebo
  - Robust to underlying dose-response shape
  - No information beyond observed doses
- Modelling techniques
  - Interpolation between doses
  - Depends on correct a priori choice of unknown dose-response model

Dose-finding in Drug Development

Two typical analysis approaches:

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Combined approach:

- Multiple Comparisons and Modelling approach MCP-Mod (recently qualified by EMA)

Multiple comparison-modelling approach (MCP-Mod)

Bretz et al. (2005, Biometrics 61):

- Specify a set of candidate dose-response models $f(d, \theta) = \theta_0 + \theta_1 f^*(d, \boldsymbol{\theta}^*)$ (fix non-linear parameters $\boldsymbol{\theta}^*$)
- Assess each model M_s using appropriately defined contrast tests:

$$T_s = \frac{\mathbf{c}_s' \bar{\mathbf{Y}}}{\sqrt{S^2 \sum_{i=1}^{k} c_{si}^2 / n_i}}$$

- Established PoC when at least one of the model contrast tests is significant while controlling the FWER, i.e. when:

$$T_{max} = \max_s T_s > q, \text{for an appropriate critical value } q$$

- Select the best model(s) from the statistically significant models in the candidate set
- Fit model(s) to the data, also estimate non-linear parameters
- Estimate the target doses from the selected model(s)

MCP-Mod evaluation

Model	Formula	Fixed parameters	Adjusted p-value
Linear	$\theta_0 + \theta_1 d$	-	0.0069
Quadratic (1)	$\theta_0 + \theta_1 d + \theta_2 d^2$	$ED_{50} = 0.2$	0.0048
Quadratic (2)	$\theta_0 + \theta_1 d + \theta_2 d^2$	max resp. at d=0.5	0.0950
Linear-log	$\theta_0 + \theta_1 \log(d+1)$	-	0.0028
Exponential (1)	$\theta_0 + \theta_1 \exp(d/\theta_2)$	$ED_{50} = 0.2$	0.0448
Exponential (2)	$\theta_0 + \theta_1 \exp(d/\theta_2)$	$\theta_2 = 0.15$	0.0866
E_{max}	$\theta_0 + \theta_1 d/(\theta_2 + d)$	$ED_{50} = \theta_2 = 0.2$	0.0017

with ED_{50} the dose providing half of the maximum change

The E_{max} model (with estimated parameters) was chosen for dose estimation, resulting in a Minimal Effective Dose (MED) of 0.16

Discussion

Advantages

- Accounts for model uncertainty
- Evaluates both PoC and dose-response

Disadvantages

- Non-linear parameters have to be given a priori
- Significant candidate models are not compared with each other when selection is based on p-values of the contrast tests
- Contrast tests are not ideal for characterizing curves

A new proposal

Define a nested candidate set of increasingly complex parametric dose-response models $M_0 \subset M_1 \subset \ldots \subset M_m$, with M_0 the constant model.

Sequentially evaluate these models as follows:

POC evaluation:

1 Evaluate M_0 against M_s, for all $s > 0$ while controlling the type I error. Stop if M_0 is not rejected, else

Model selection:

2 Evaluate M_1 against M_s, for all $s > 1$ while controlling the type I error. Stop if M_1 is not rejected, else

$\vdots$

m-1 Evaluate M_{m-1} against M_m. Accept M_m if M_{m-1} is rejected, else, accept M_{m-1}

Test-statistic

To evaluate each model M_s, against the more complex models $M_r, r > s$, a similar test statistic as proposed by Aerts et al. (1999, JASA 94) can be used:

$$T_s = \max_{s+1 \leq r \leq m} \{2(L_r - L_s)/(p_r - p_s)\},$$

with:

L_r : the log-likelihood of model M_r

p_r : the degrees of freedom of model M_r

Distributions of the T_s can be simulated based on that, under M_s:

$$2(L_r - L_s) = \sum_{i=r+1}^{s} 2(L_i - L_{i-1}) \text{ and } 2(L_i - L_{i-1}) \longrightarrow_d \chi^2_1$$

Proposed evaluation - candidate set

	Model	Function
M_0	No effect	θ_0
M_1	Linear	$\theta_0 + \theta_1 d$
M_2	Power function	$\theta_0 + \theta_1 d^{\theta_2}$
M_3	Four parameter logistic	$\theta_0 + \theta_1 \frac{d^{\theta_2}}{(de^{-\theta_3})^{\theta_2}+1}$
M_4	Unrestricted model	$f(d_i, \theta) = \mu_i.$

Proposed evaluation - results

Evaluated model	Test-statistic	Value	Critical value	Signif. level
Constant	T_0	8.58	3.024	0.10
Linear	T_1	2.55	2	0.227
Power	T_2	1.13	2	0.174
Four-parameter logistic	T_3	0.00	2	0.157

The power model was selected for dose estimation, resulting in a MED of 0.23

Discussion

- No initial parameter estimates required
- Control over model selection
- All candidate models are compared with each other
- Unrestricted model can be included as a safeguard against model misspecification

Performance of the methods

Simulation studies comparing:

- New approach
- MCP-Mod
- Linear trend test
- F-test of equal means

In terms of

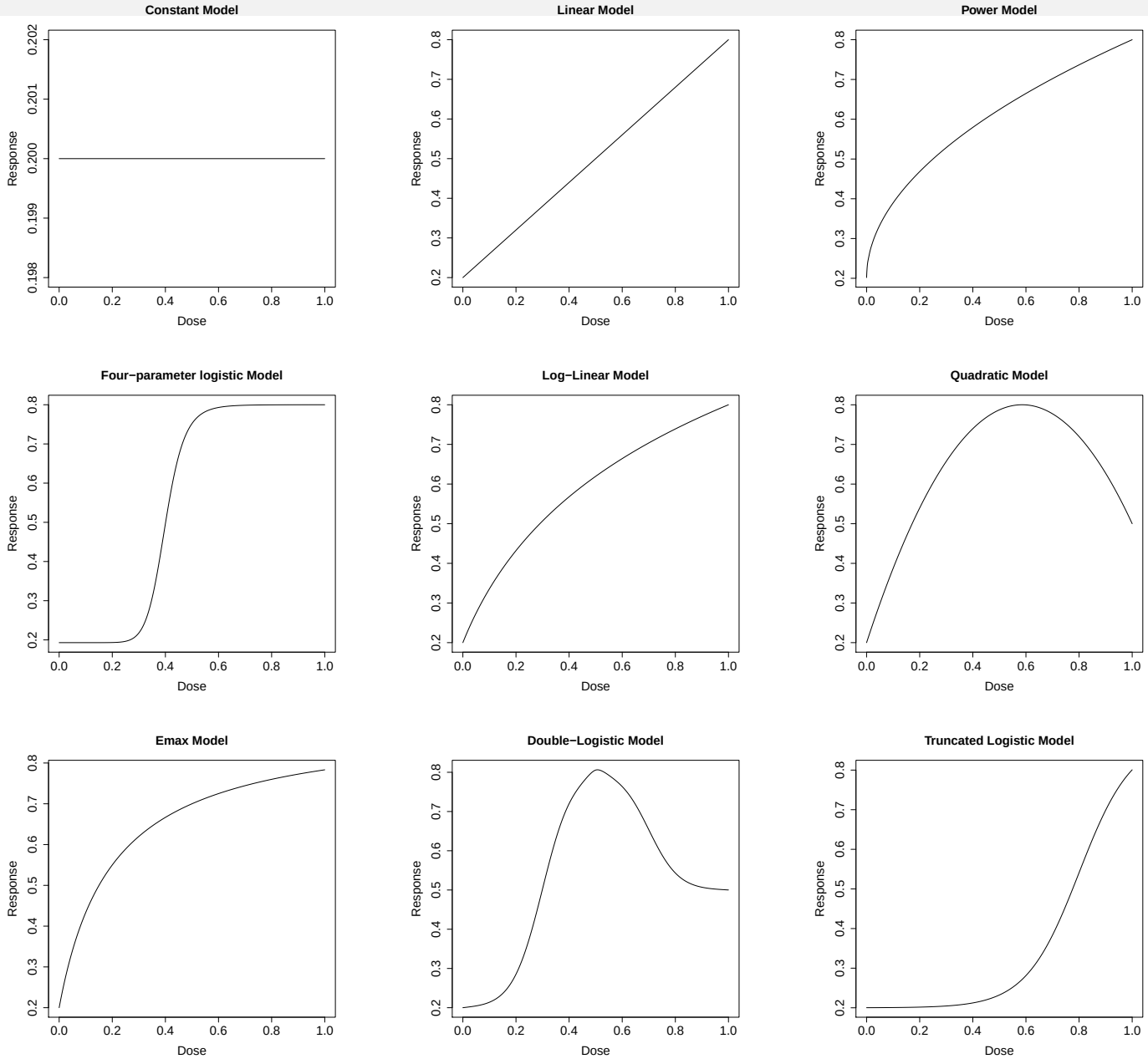
- Type I error
- Power to establish PoC
- Power to select the correct model
- Ability to estimate the MED

Simulation set-up

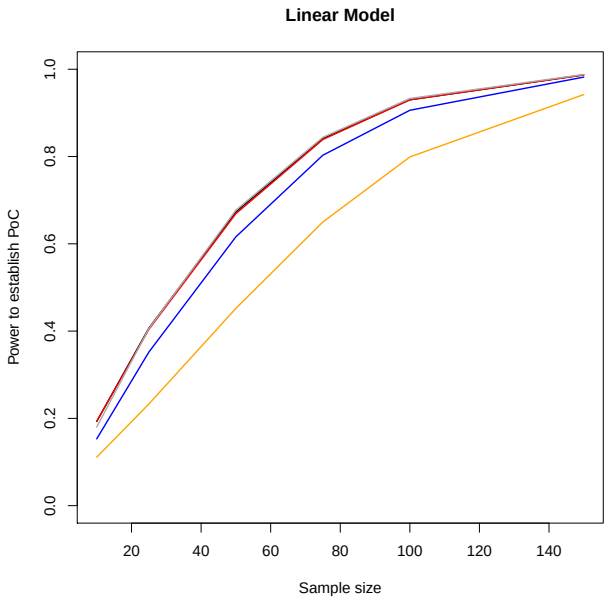
Design:

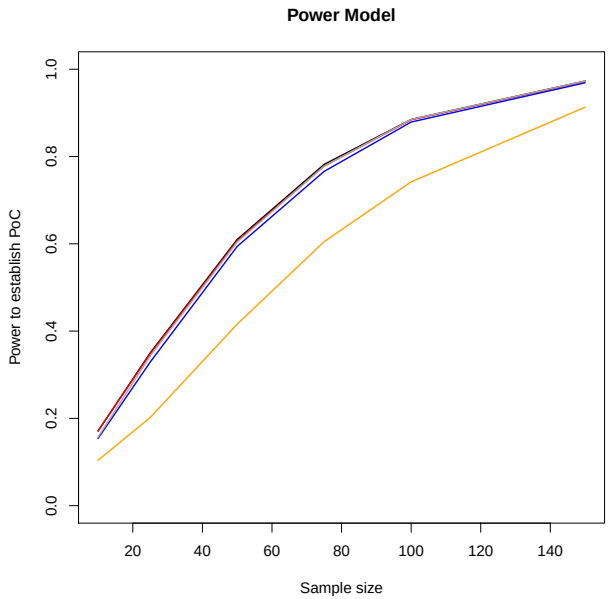
- Doses 0, 0.05, 0.2, 0.6 and 1
- Sample sizes per dose group of 10, 25, 50, 75, 100 and 150
- One sided PoC test with $\alpha = 0.025$ for MCP-Mod approach
- Two sided PoC test with $\alpha = 0.05$ for proposed approach
- Model selection equivalent to using AIC for both approaches
- New approach was applied with and without the unrestricted model
- 9 data-generating dose-response shapes
- Non-linear parameters estimates for MCP-Mod were chosen equal to population parameters
- 10.000 simulations per shape x sample size combination

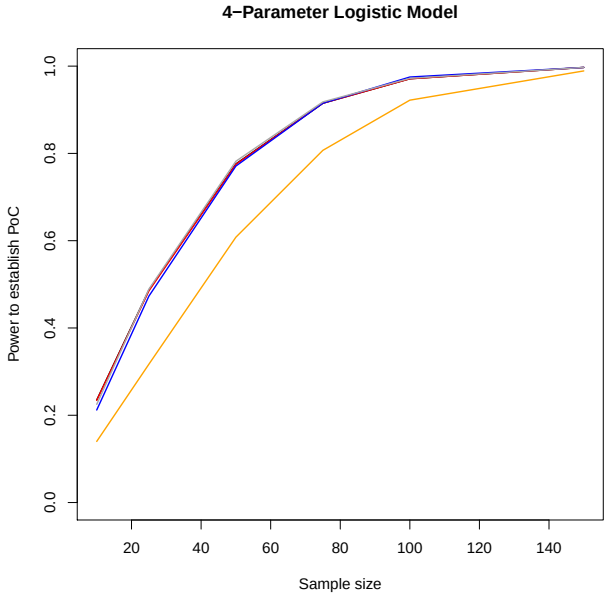
Data-generating shapes



Power to establish PoC

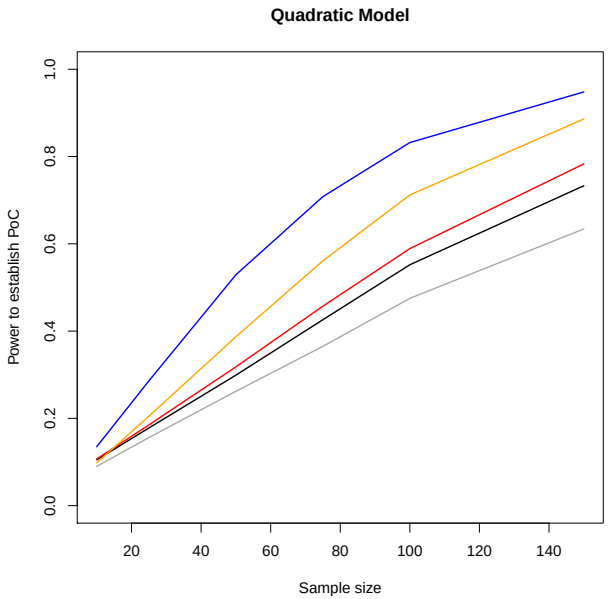


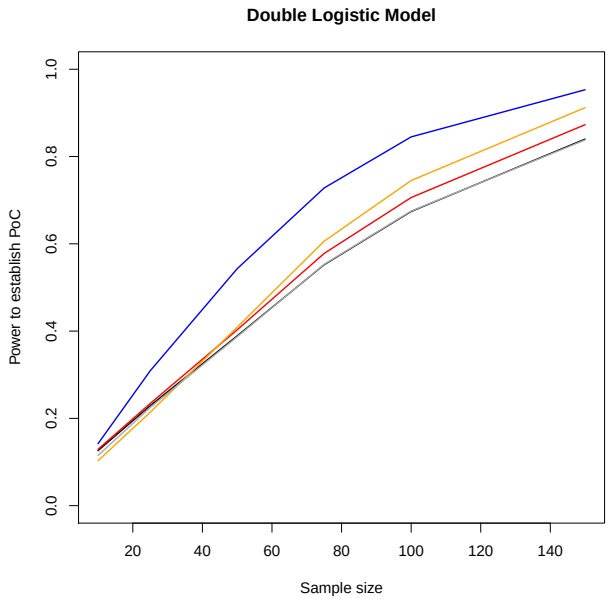


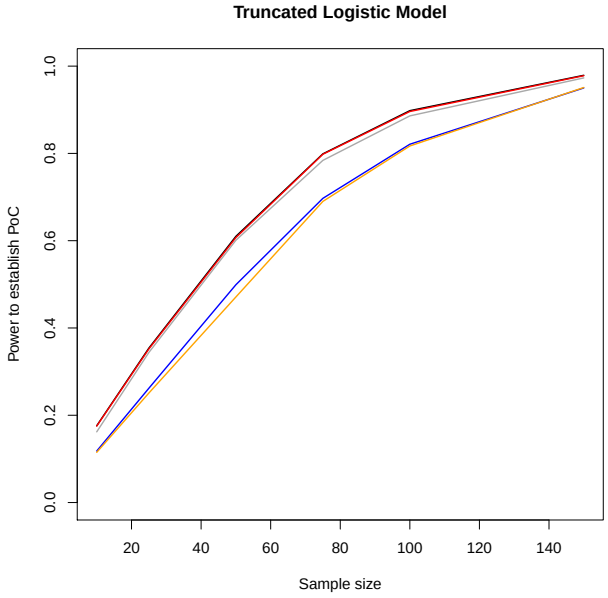


- - New approach
- - New approach with unr.
- - MCP-Mod approach
- - Equal means
- - Linear trend

Power to establish PoC







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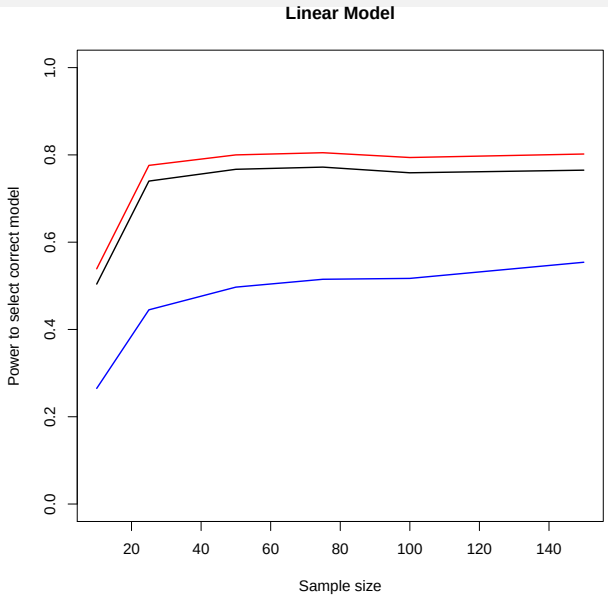
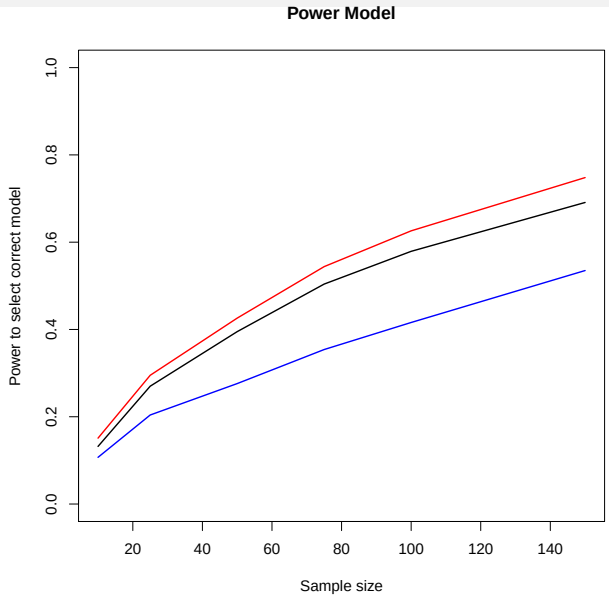
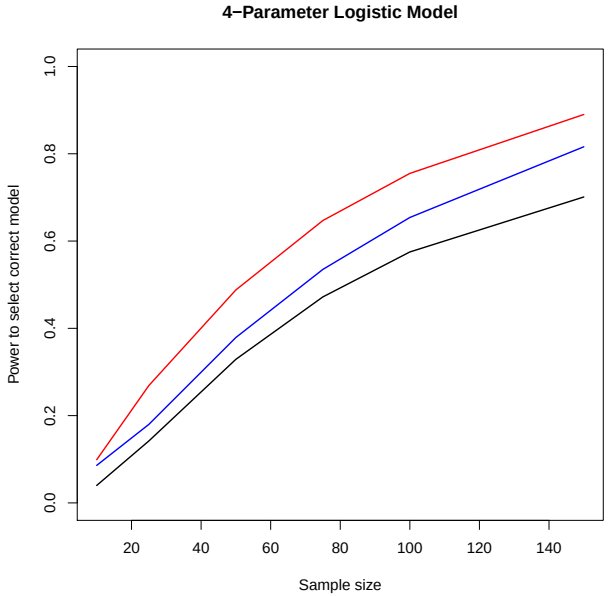
Model selection performance







- - New approach
- - New approach with unr. model
- - MCP-Mod approach

Estimating the MED

Comparison with MCP-Mod:

Sample size 50

- Similar, or slightly worse performance under models in candidate set
- Better performance under monotone models not covered by candidate set
- Worse performance than MCP-Mod under non-monotone models

Sample size 150

- Better performance under all models, except non-monotone models

Conclusions

- Candidate models are compared with each other, not just with the constant model
- Type I error is controlled for establishing PoC and for model selection
- Candidate models are general in the sense that no parameters need to be given a priori
- Under models covered by the candidate set, power to establish PoC is similar or better than MCP-Mod
- Power to select the correct model is higher for the new approach compared to MCP-Mod in most situations
- The new method performed well regarding MED estimation, even under dose-response models that were not included in the candidate set.
- Inclusion of the unrestricted model can be beneficial to:
  - Increase power to detect PoC
  - Detect significant deviations from models in the candidate set

Outlook

- How can we do further inference (e.g. dose estimation), while taking the uncertainty from the model selection step into account?

Thank you for listening!

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