Multiple testing and modelling techniques in dose finding studies in Phase II clinical trials

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IDEAS
Improving drug development

Dose Finding Studies

The most important questions...

- Is there any statistical evidence of drug activity?
- If yes, what are doses significantly different from control?
- What is the dose-response relationship?
- What is the target dose?

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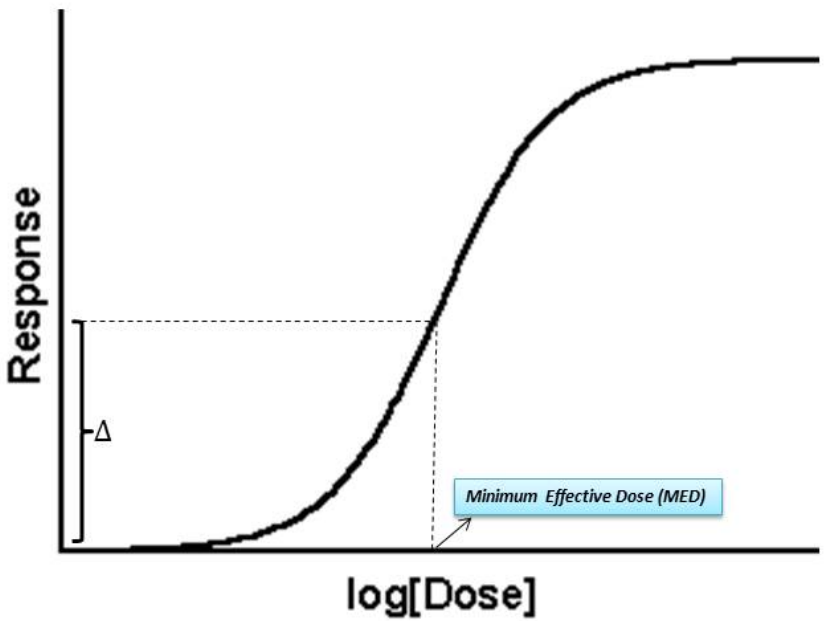
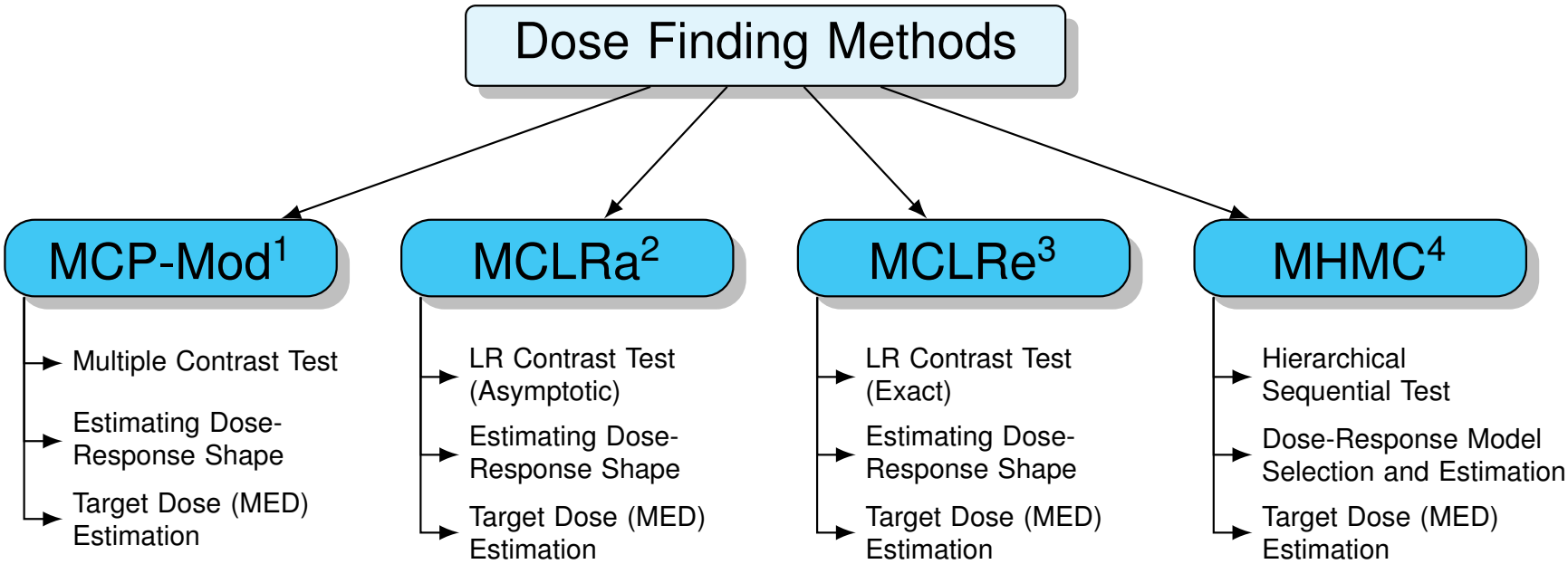


Dose Finding Methods



[1] MCP-Mod: Multiple Comparison Procedure-Modelling Techniques by Bretz et al. (2005)

[2] MCLRa: Multiple Comparison Likelihood Ratio Asymptotic Method by Dette et al. (2015)

[3] MCLRe: Multiple Comparison Likelihood Ratio Exact Method by Gutjahr and Bornkamp (2017)

[4] MHMC: Multiple Hierarchical Modeling and Comparison Method by Baayen et al. (2015)

Dose Finding Studies

Why do we need a new approach?

Motivation

- Target dose selected in Phase II fails to perform well in Phase III clinical trials.
- Existing dose-finding methods estimate accurately the dose response shapes at the cost of losing in bias and precision of the target dose (MED) estimation.
- Construction of confidence intervals for dose finding studies have not been broadly investigated in literature.

Objective

- Design a method so that we can get more accurate estimate of MED and more precise and narrow confidence interval for MED.

$$MED = \underset{d \in (d_0, d_k]}{argmin} \{\mu_d \geq \mu_{d_0} + \Delta\}$$

Dose Estimation And Inference

A Weighted Regression Approach:

- In the non-linear regression set up:

$$Y_{ij} = \mu(d_i, \theta) + \epsilon_{ij} = \alpha + \beta f(d_i, \gamma) + \epsilon_{ij} \tag{1}$$

We try to Minimize

$$\sum_{i,j} w_{i,j}(d_i, MED(\alpha, \beta, \gamma))(Y_{ij} - \alpha - \beta f(d_i, \gamma))^2$$

instead of minimizing the

$$SSE = \sum_{i,j}(Y_{ij} - \alpha - \beta f(d_i, \gamma))^2$$

where $MED(\alpha, \beta, \gamma) = h^0(f(d_0, \gamma) + \frac{\Delta}{\beta})$ and h^0 is the inverse of f with respect to dose d.

Dose Estimation

Weights Function:

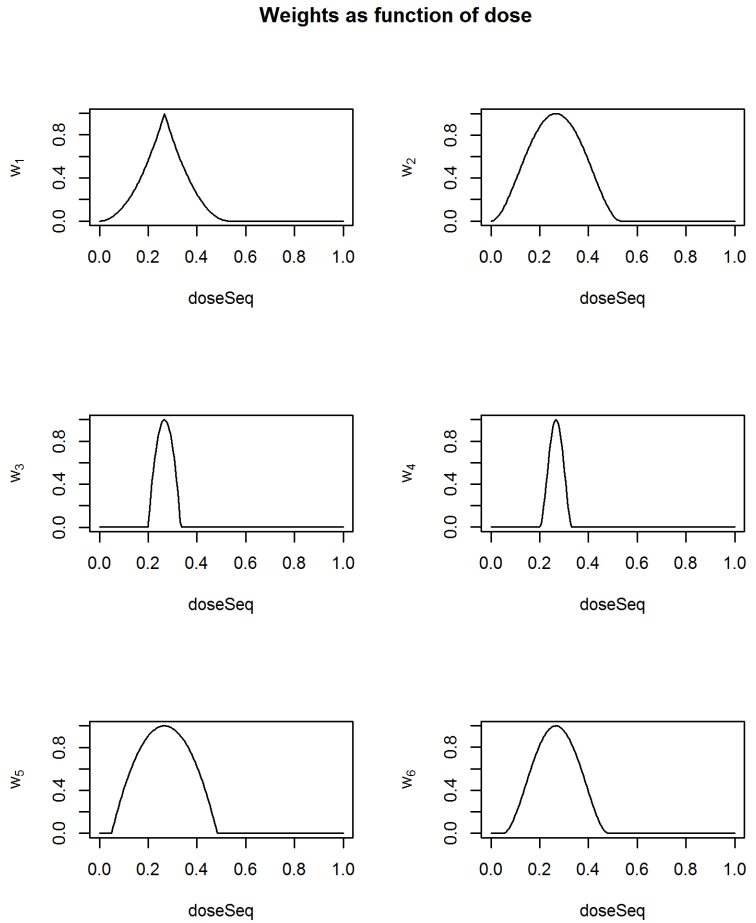


Figure: Different weight functions plotted when the underlying true dose response model is the following emax model: $0.2 + 0.7\frac{d}{d+0.2}$.

Table: Table showing the formula of the weights function used in our method

Weights	Formula	z(d,d_{MED})
w_1	$(1-z^2)$	$\min\{\frac{d_{MED}-d}{d_{MED}}, 0.999\}$
w_2	$(1-z^2)^2$	$\min\{\frac{d_{MED}-d}{d_{MED}}, 0.999\}$
w_3	$(1-z^2)$	$\min\{\frac{d_{MED}-d}{h_1}, 0.999\}$
w_4	$(1-z^2)^2$	$\min\{\frac{d_{MED}-d}{h_1}, 0.999\}$
w_5	$(1-z^2)$	$\min\{\frac{d_{MED}-d}{h_2}, 0.999\}$
w_6	$(1-z^2)^2$	$\min\{\frac{d_{MED}-d}{h_2}, 0.999\}$

1 d_{MED} is the MED estimate

2 $h_1 = \min_{d \in \{d_1,\ldots,d_k\}} |d - d_{MED}|$

3 $h_2 = \min_{d \in \{d_{(2)},\ldots,d_{(k)}\}} |d - d_{MED}|$, where $d_{(1)}, \ldots, d_{(k)}$ are so arranged such that $d_{(1)}$ is closest dose in $\{d_1, \ldots, d_k\}$ to d_{MED} and $d_{(k)}$ is furthest away from d_{MED} and

Dose Estimation

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2. Robust Regression (RR)(Fraiman (1983)):
   - Solve for θ_n using the following:

$$\sum_{i,j} \phi(Y_{ij}, d_i, \theta) = \sum_{i,j} w_i(d_i, \theta) \cdot (Y_{ij} - \mu(d_i, \theta)) \frac{\partial \mu(d_i, \theta)}{\partial \theta} = 0$$

   where $\theta = (\alpha, \beta, \gamma)$ and $w_i(d_i, \theta)$ are the weights function shown in the earlier slide.

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   where $\theta = (\alpha, \beta, \gamma)$ and $w_i(d_i, \theta)$ are the weights function shown in the earlier slide.
   - Distribution of the MED weighted parameters;

$$\sqrt{n}(\theta_n - \theta_0) \xrightarrow{\mathbb{D}} N\,(0, W^{-1} V W^{-1^t})$$

   where $V = E_F[\phi(Y, X, \theta_0)\phi(Y, X, \theta_0)^t]$, $W = E_F(\frac{\partial \phi(Y, X, \theta_0)}{\partial \theta}]$

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   - Obtain the estimates $\hat{\theta}_F$ and compute:

$$\widehat{MED} = h_0(f(d_0, \hat{\gamma_F}) + \frac{\Delta}{\hat{\beta}_F})$$

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$$\widehat{MED} = h_0(f(d_0, \hat{\gamma}_F) + \frac{\Delta}{\hat{\beta}_F})$$

   - Apply delta method to get the asymptotic distribution of $\widehat{MED}$.

Simulation set up:

Design:

- Dose groups: 0, 0.05, 0.2, 0.6, 1
- Standard Deviation: 0.65
- Sample Size: 25
- 5000 simulation runs for each model
- Evaluate the estimate by: Relative Deviation MED

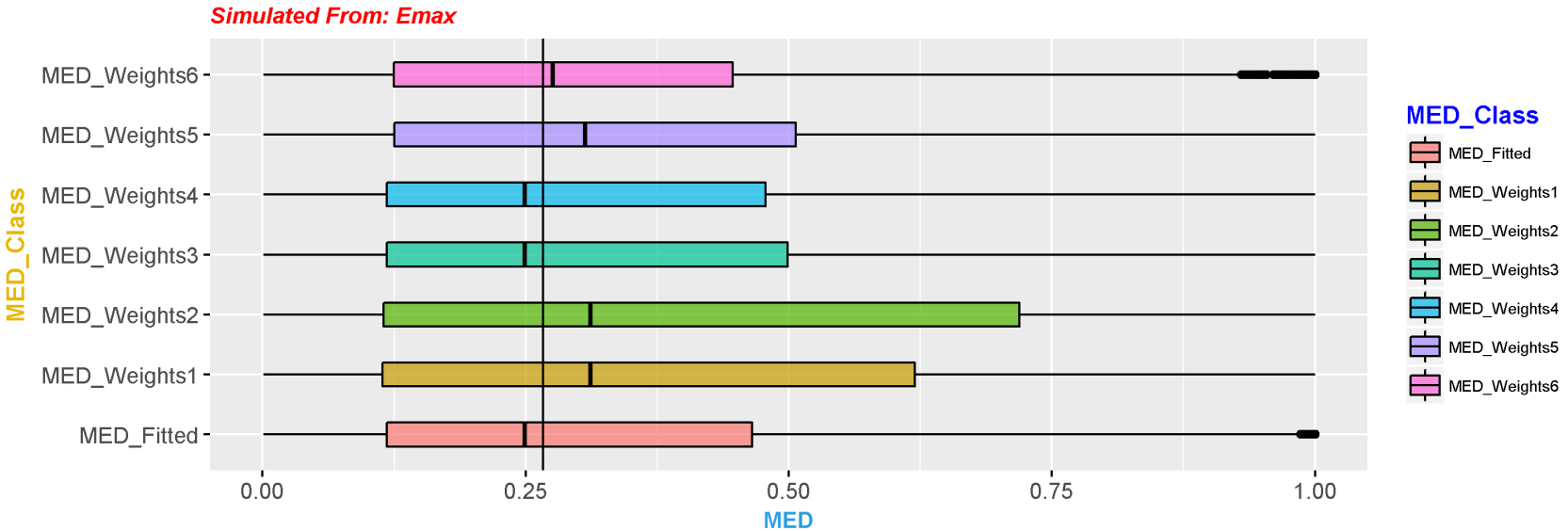
$$R_i = \frac{\widehat{MED_i} - MED}{MED}$$

Table: **Data generating dose-response shapes**

Model	Simulated from	Fitted on
Emax	$0.2 + 0.7\frac{d}{0.2+d}$	emax
Sigmoidal	$0.2 + 0.615\frac{d^4}{0.4^4+d^4}$	sigeMax

Dose Estimation

Simulation Results:

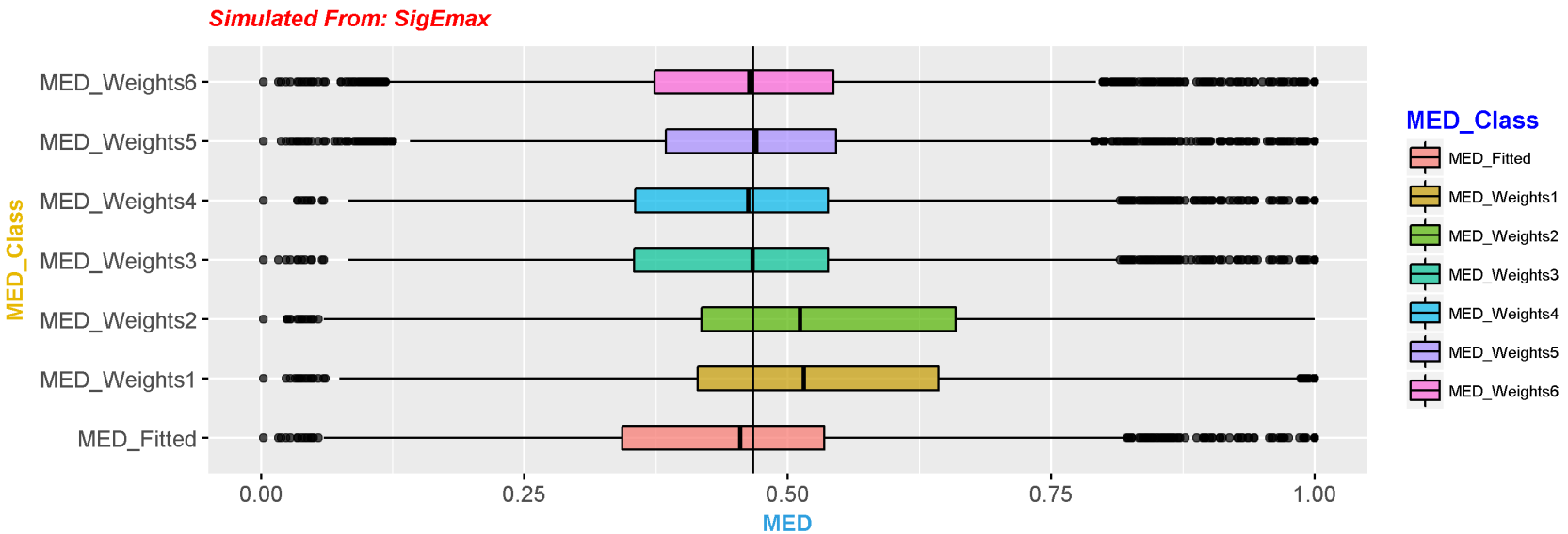


Method	Mean Rel Dev	Median Rel Dev	IQR Rel Dev
MED_Fitted	0.23	-0.07	1.30
MED_Weights1	0.51	0.17	1.90
MED_Weights2	0.59	0.17	2.26
MED_Weights3	0.27	-0.07	1.43
MED_Weights4	0.24	-0.07	1.35
MED_Weights5	0.40	0.15	1.43
MED_Weights6	0.30	0.03	1.21

Figure: Distribution of MED obtained from the weighted regression (RR) approach for data simulated from Emax model

Dose Estimation

Simulation Results:



Method	Mean Rel Dev	Median Rel Dev	IQR Rel Dev
MED_Fitted	0.00	-0.03	0.41
MED_Weights1	0.15	0.10	0.49
MED_Weights2	0.17	0.10	0.52
MED_Weights3	0.02	0.00	0.39
MED_Weights4	0.02	-0.01	0.39
MED_Weights5	0.04	0.01	0.35
MED_Weights6	0.03	-0.01	0.36

Figure: Distribution of MED obtained from the weighted regression (RR) approach for data simulated from sigEmax model

Dose Inference

Confidence interval estimation

- Compare the confidence interval estimates of MED with existing approaches.
- Three approaches considered for benchmarking:
  - Asymptotic confidence interval from unweighted non-linear regression (Classical Approach)
  - Profile likelihood approach by Baayen and Hougaard (2015) (PL Approach)
  - Percentile bootstrap approach by Baayen and Hougaard (2015) (PB Approach)
- Evaluate the performance of the different methods by benchmarking their coverage probability.

Dose Inference

Confidence interval estimation: Simulations

Following Baayen and Hougaard (2015) we considered the following simulation set up:

Design 1:

- Dose groups: 0, 0.05, 0.2, 0.6, 1
- Standard Deviation: 0.65
- Sample Size: 25, 50, 75, 100
- 2000 simulation runs for each model
- Evaluate the coverage of the 95% confidence interval of MED

Table: **Data generating dose-response shapes**

Model	Simulated from	Fitted on
Emax	$0.32 + 0.74 \frac{d}{0.14+d}$	emax
Sigmoidal	$0.32 + 0.66 \frac{d^4}{0.3^4+d^4}$	sigeMax

Dose Inference

Confidence interval estimation: Simulation Results

(a) Table showing the coverage of 95% confidence interval under the different methods for data simulated from the emax model:

Sample Size	Methods			
	Classical	RR	PB	PL
25	0.838	0.860	0.936	0.942
50	0.904	0.926	0.956	0.949
75	0.925	0.934	0.946	0.949
100	0.940	0.942	0.954	0.951

(b) Table showing the coverage of 95% confidence interval under the different methods for data simulated from the sigEmax model:

Sample Size	Methods			
	Classical	RR	PB	PL
25	0.964	0.927	0.950	0.913
50	0.987	0.969	0.957	0.899
75	0.990	0.981	0.956	0.905
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- The Weighted RR approach performs better than the classical approach for all the sample sizes and attain the nominal value for large sample sizes. But it shows under coverage for small sample sizes like $n_{ij} = 25$.

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- For the sigEmax model, the PB approach is attaining the nominal level but the classical and RR approach perform erratically for large sample sizes.

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- For the sigEmax model, the PB approach is attaining the nominal level but the classical and RR approach perform erratically for large sample sizes.
- PL approach fails to attain the nominal level for the sigEmax model.

Design 2:

- Dose groups: 0, 0.2, 0.4, 0.6, 1
- Other characteristics same Design 1

Table: Table showing the coverage of 95% confidence interval under the different methods for data simulated from the sigEmax model in Design 2:

Sample Size	Methods			
	Classical	RR	PB	PL
25	0.9495	0.9400	0.9370	0.9097
50	0.9575	0.9410	0.9625	0.9410
75	0.9545	0.9440	0.9560	0.9317
100	0.9525	0.9495	0.9565	0.9276

Conclusions:

- The PB approach performs superior to the other approaches for all the scenarios. It is not sensitive to the dose-allocation design.
- The RR approach performs well for large sample sizes across all the scenarios.
- PB and PL being grid based approaches, are not only computationally intensive but also the results depend a lot on the choice of grids.
- RR approach is comparatively less time consuming and methodologically more sound.
- RR approach performs well under model mis-specification.

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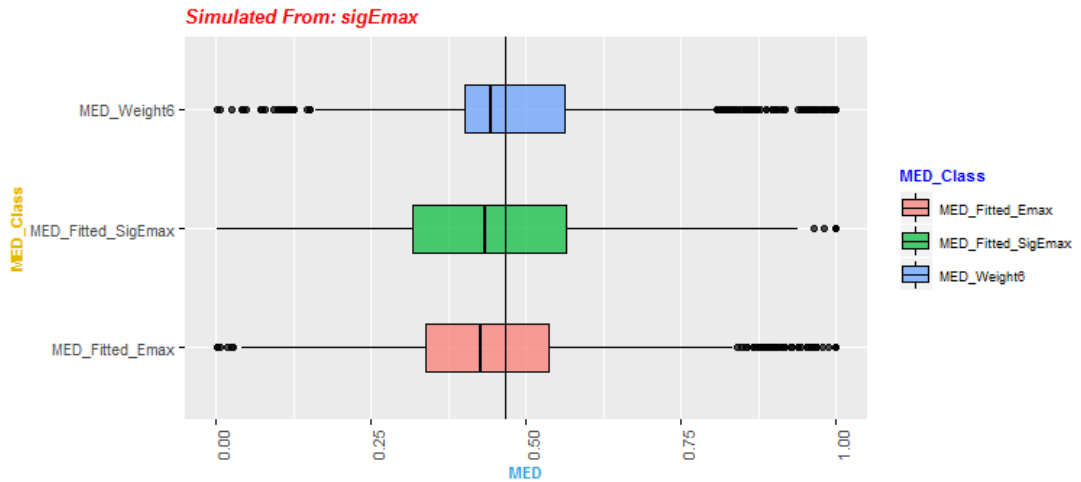

Method	mean(R_i)	median(R_i)	IQR(R_i)
MED_Fitted_Emax	-0.02	-0.09	0.43
MED_Fitted_SigEmax	-0.03	-0.07	0.53
MED_Weight6	0.06	-0.05	0.35

Outlook

- RR approach is preferred over IRNLS approach because
  - It gives better estimation and inference around the target dose.
  - it proposes a nice way to integrate the robust regression with model based estimation.
- The RR approach is sensitive to dose allocation, hence the optimal design characteristic can also be explored in future.
- Extension of the approaches to a multiple testing framework.
- Extend the weighted regression approach such that it can accurately estimate all the target doses of interest in a clinical trial.

Reference

Baayen, C. and Hougaard, P. (2015). Confidence bounds for nonlinear dose–response relationships. *Statistics in medicine*, 34(27):3546–3562.

Baayen, C., Hougaard, P., and Pipper, C. (2015). Testing effect of a drug using multiple nested models for the dose–response. *Biometrics*, 71(2):417–427.

Bretz, F., Pinheiro, J. C., and Branson, M. (2005). Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*, 61(3):738–748.

Dette, H., Titoff, S., Volgushev, S., and Bretz, F. (2015). Dose response signal detection under model uncertainty. *Biometrics*, 71(4):996–1008.

Fraiman, R. (1983). General m-esttmators and applications to bounded influence estimation for non-linear regression. *Communications in Statistics-Theory and Methods*, 12(22):2617–2631.

Gutjahr, G. and Bornkamp, B. (2017). Likelihood ratio tests for a dose-response effect using multiple nonlinear regression models. *Biometrics*, 73(1):197–205.

Thank You!

Questions ?

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