A pharmacometric extension of MCP-MOD in dose finding studies

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Pr. France Mentré[1]
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Dr. Nicolas Frey[2]

Lewis Sheiner Student Session
PAGE 2018, Montreux

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3. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 418–429; doi:10.1002/psp4.12196

WHITE PAPER

Advanced Methods for Dose and Regimen Finding During Drug Development: Summary of the EMA/EFPIA Workshop on Dose Finding (London 4–5 December 2014)

FT Musuamba[1,2,3*], E Manolis[1,4], N Holford[5], SYA Cheung[6], LE Friberg[7], K Ogungbenro[8], M Posch[9], JWT Yates[6], S Berry[10], N Thomas[11], S Corriol-Rohou[6], B Bornkamp[12], F Bretz[9,12], AC Hooker[7], PH Van der Graaf[13,14], JF Standing[1,15], J Hay[1,16], S Cole[1,16], V Gigante[1,17], K Karlsson[1,18], T Dumortier[12], N Benda[1,19], F Serone[1,17], S Das[6], A Brochot[20], F Ehmann[4], R Hemmings[16] and I Skottheim Rusten[1,21]

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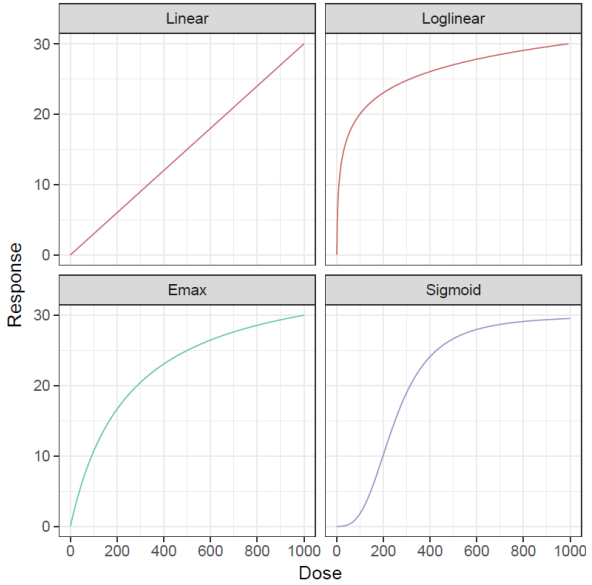
23 January 2014
EMA/CHMP/SAWP/757052/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

MCP-MOD[1]

- Starting from a predefined set of dose-response candidate models:



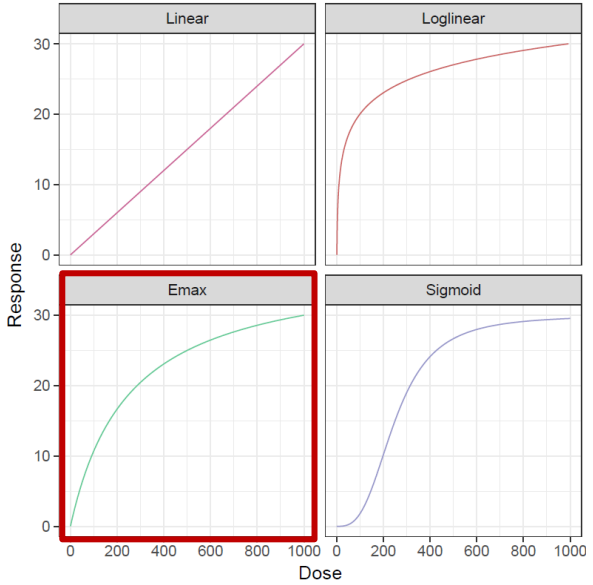
[1] Bretz F . *et al*, Biometrics, 2005

MCP-MOD[1]

- Starting from a predefined set of dose-response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

MCP



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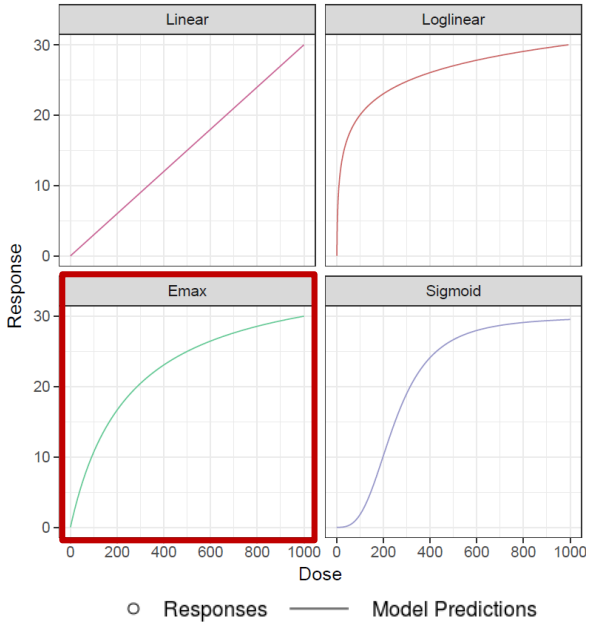
MCP-MOD[1]

- Starting from a predefined set of dose-response candidate models:

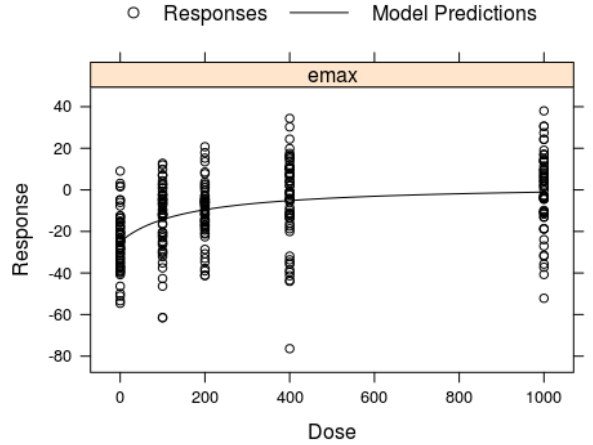
1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)

MCP



MOD



[1] Bretz F . *et al*, Biometrics, 2005

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[1] Bretz F . *et al*, Biometrics, 2005

PMX

1. Model building using multiple LRT on nonlinear mixed effect models (MS)

2. Estimate the dose-response curve using the selected model

MCP-MOD[1]	*PMX*
▪ Starting from a predefined set of dose-response candidate models:	
1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)	1. Model building using multiple LRT on nonlinear mixed effect models (MS)
2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)	2. Estimate the dose-response curve using the selected model
Advantages vs PMX	**Advantages vs MCP-MOD**
• Models pre-specified • Takes model uncertainty into account • Control the type I error	• Longitudinal analysis of the data

MCP-MOD[1]

- Starting from a predefined set of response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

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Advantages vs PMX

- Models pre-specified
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Advantages vs MCP-MOD

- Longitudinal analysis of the data

Statistics
in Medicine

Research Article

Received 30 April 2013, Accepted 1 November 2013 Published online 3 December 2013 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6052

Model-based dose finding under model uncertainty using general parametric models

José Pinheiro,[a] Björn Bornkamp,[b*†] Ekkehard Glimm[b] and Frank Bretz[b]

J Pharmacokinet Pharmacodyn (2017) 44:581–597
DOI 10.1007/s10928-017-9550-0

ORIGINAL PAPER

Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection

Yasunori Aoki[1,2] · Daniel Röshammar[3,4] · Bengt Hamrén[3] · Andrew C. Hooker[1]

The AAPS Journal (2018) 20:56
DOI: 10.1208/s12248-018-0205-x

Research Article

Comparison of Model Averaging and Model Selection in Dose Finding Trials Analyzed by Nonlinear Mixed Effect Models

Simon Buatois,[1,2,3,5] Sebastian Ueckert,[4] Nicolas Frey,[1] Sylvie Retout,[1,2] and France Mentré[3]

MCP-MOD[1]

cLRT-MOD

Predefined set of dose-response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

1. cLRT-step: Assessment of dose-response signal using a corrected-Likelihood Ratio Test[2]

2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)

[1] Bretz F . *et al*, Biometrics, 2005

[2] Dette H. et al, Biometrics, 2015

1. Corrected-LRT step:

- Observed dataset:

Among the candidate models (AIC[1,2])

$$2LL\left(y, \widehat{\Psi}_{NoDE}\right) - 2LL\left(y, \widehat{\Psi}_{MS}\right) = \Delta OFV_{obs}$$

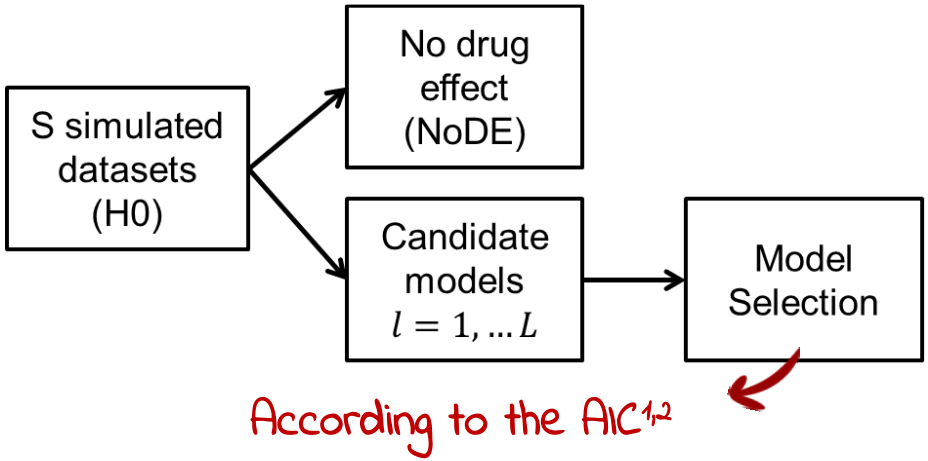
[1] Aoki Y. et al, JPKPD, 2017
[2] Buatois S. et al, AAPS, 2018

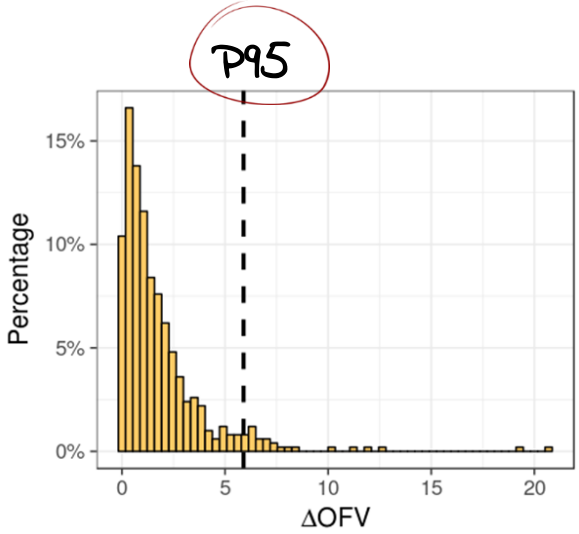
1. Corrected-LRT step:

- Observed dataset:

$$2LL\left(y, \widehat{\Psi}_{NoDE}\right) - 2LL\left(y, \widehat{\Psi}_{MS}\right) = \Delta OFV_{obs}$$

- cLRT statistic:





[1] Aoki Y. et al, JPKPD, 2017
[2] Buatois S. et al, AAPS, 2018

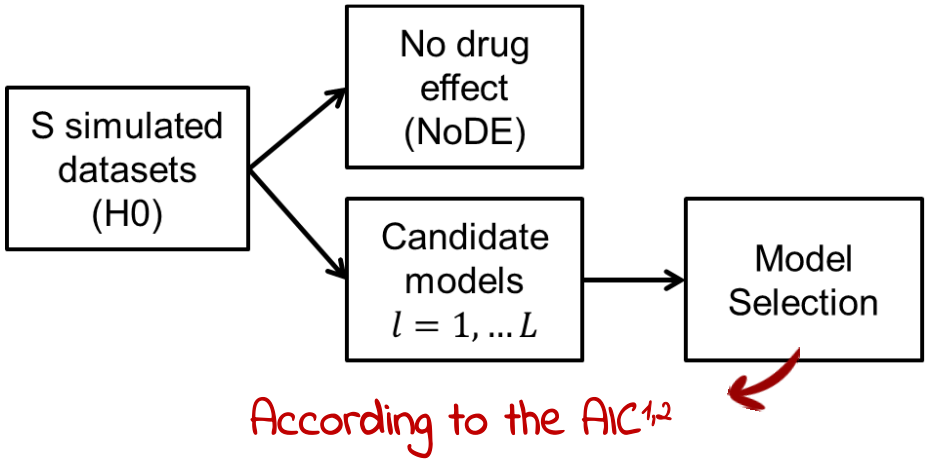
1. Corrected-LRT step:

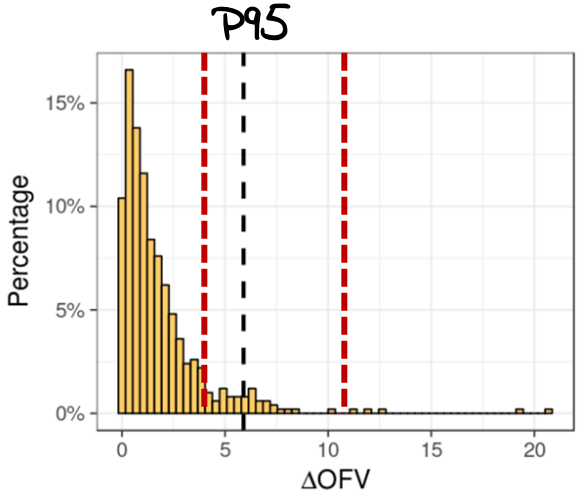
- Observed dataset:

$$2LL\left(y, \widehat{\Psi}_{NoDE}\right) - 2LL\left(y, \widehat{\Psi}_{MS}\right) = \Delta OFV_{obs}$$

> or ≤ P95 ?

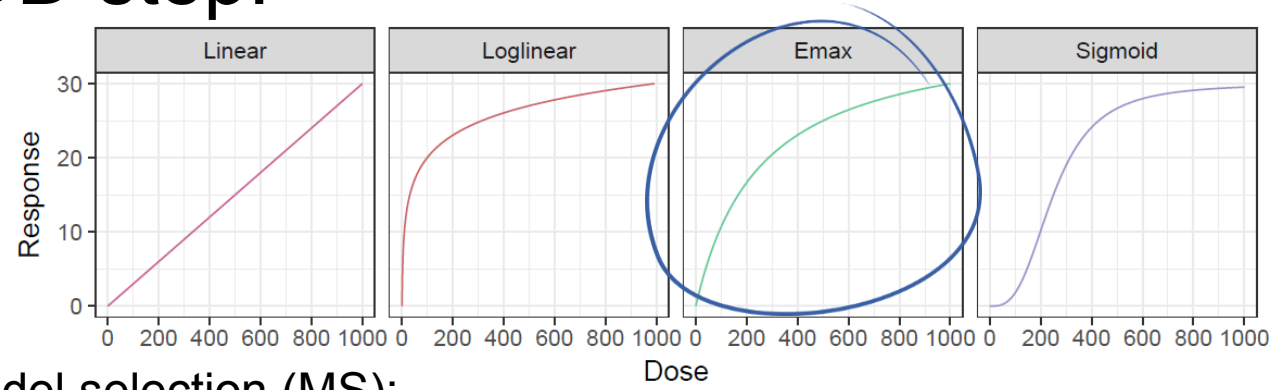
- cLRT statistic:





[1] Aoki Y. et al, JPKPD, 2017
[2] Buatois S. et al, AAPS, 2018

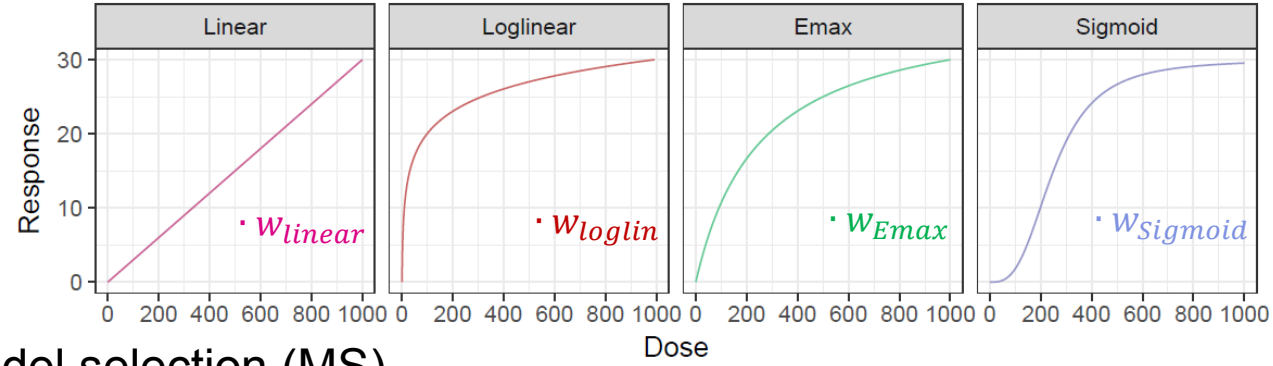
2. MOD step:



- Model selection (MS):
  - Most commonly used approach
  - Relies on selection of the model that best describes the data as a function of an information criterion
  - Ignores model uncertainty which could impair predictive performance[1,2]

[1] Musuamba FT. *et al*, CPT Pharmacometrics Syst. Pharmacol, 2017
[2] Mould D.R. *et al* , CPT Pharmacometrics Syst Pharmacol, 2012

2. MOD step:



- Model selection (MS)
- Model averaging (MA):
  - Takes into account the uncertainty across a set of candidate models by weighting them as a function of an information criterion[3]
  - Applications in both NL[4] and NLME[5,6] models comparing MA vs MS

[1] Musuamba FT. *et al*, CPT Pharmacometrics Syst. Pharmacol, 2017
[2] Mould D.R. *et al* , CPT Pharmacometrics Syst Pharmacol, 2012
[3] Buckland S.T. *et al*, Biometrics, 1997
[4] Schorning K. *et al*, Stat Med, 2016
[5] Aoki Y. *et al*, JPKPD, 2017
[6] Buatois S. *et al,* AAPS, 2018

Simulation case study

- Simplified version of a disease model[1] which characterizes the time course of visual acuity (VA) of wet AMD patients[2]
- Model:

$$f\left(d_i, t_j, \Phi_i\right) = VA_{0,i} - VA_{ss_i} \cdot \left(1 - e^{-k_{pr,i} \cdot t_j}\right) \quad + \quad E(d)$$

[1] Holford N, *British Journal of Clinical Pharmacology* 79, 2015
[2] Diack C. *et al*, http://www.page-meeting.org/?abstract=3569, 2015

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Asymptotic disease progression

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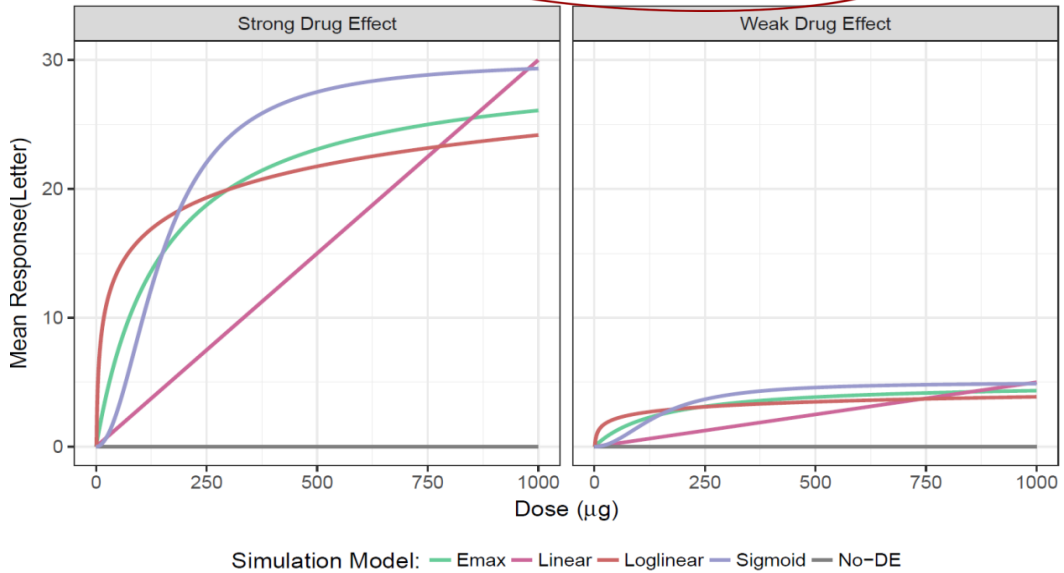
Asymptotic disease progression

Symptomatic drug effect



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Study design

- N patients equally distributed across the different dose levels
- 5 arms: 0, 100, 200, 400 and 1000 µg
- **14** observations per patient: baseline, day 7 & every month during **12** months (End of trial)

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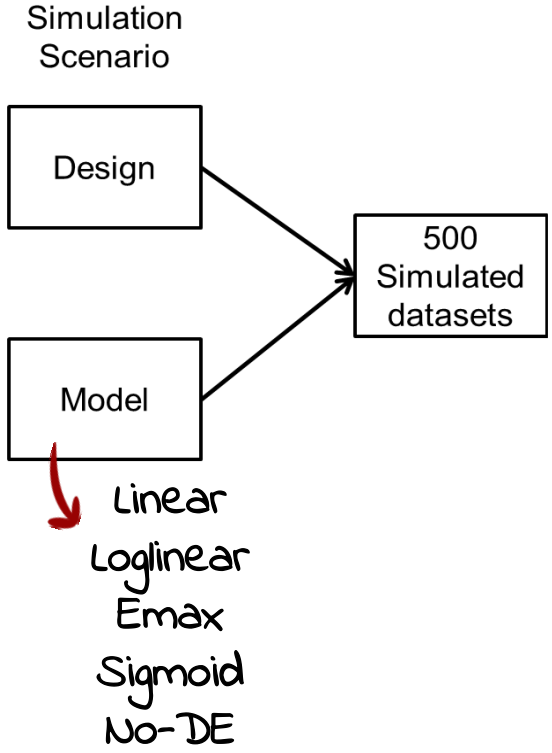
Simulation Scenarios:

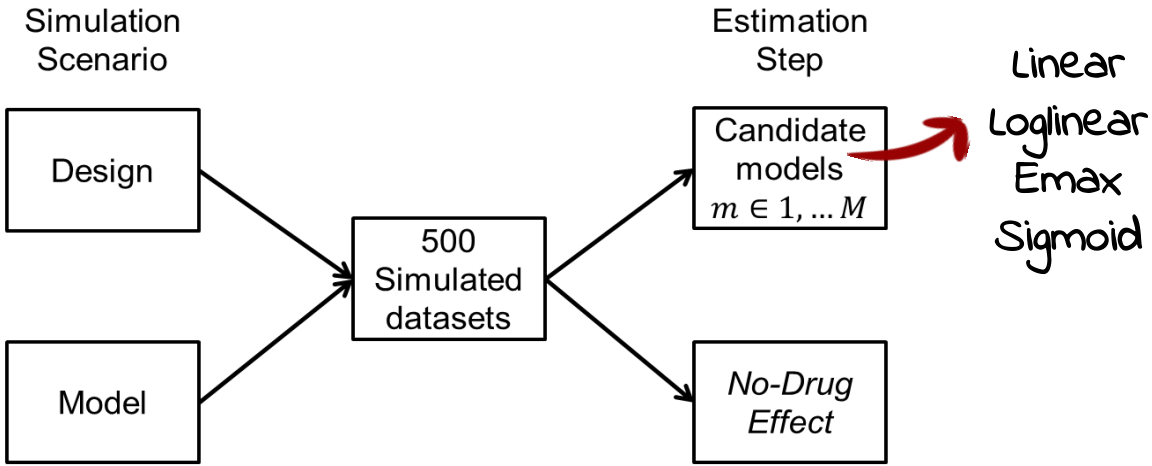
Scenario	N	Effect	$E(d)$
I	300	Strong	• Linear • Loglinear • Emax • Sigmoid • No-DE
	50	Strong	
II	50	Weak	

Challenge both the cLRT and MoD steps

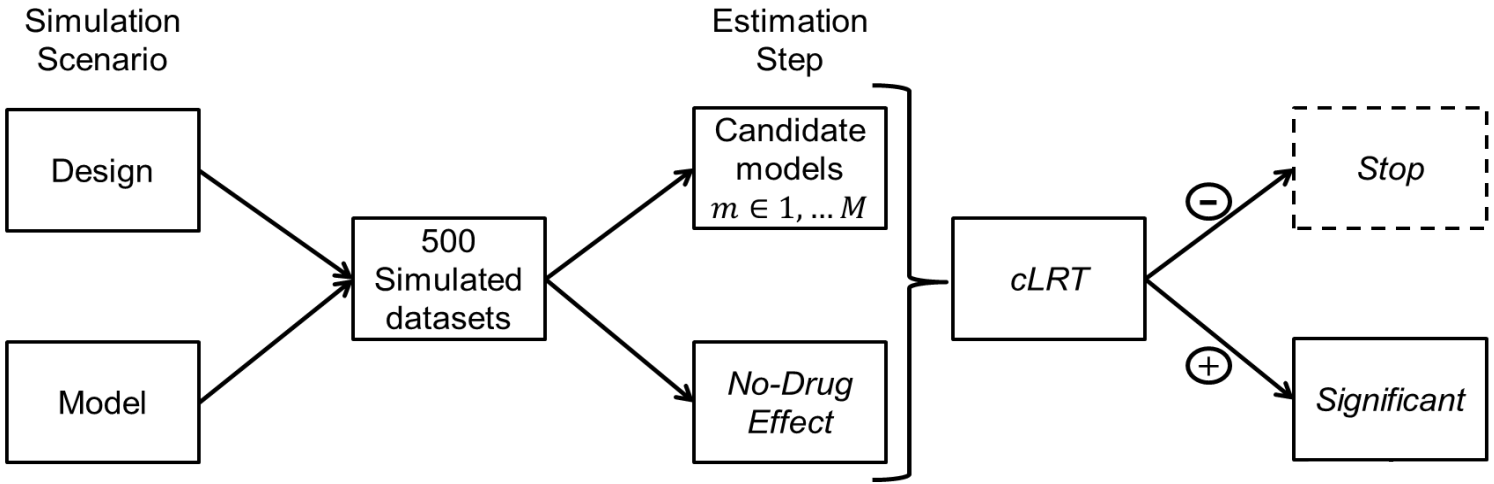
Evaluation


Simulation Scenario
Design
Model
500 Simulated datasets
Linear
Loglinear
Emax
Sigmoid
No-DE

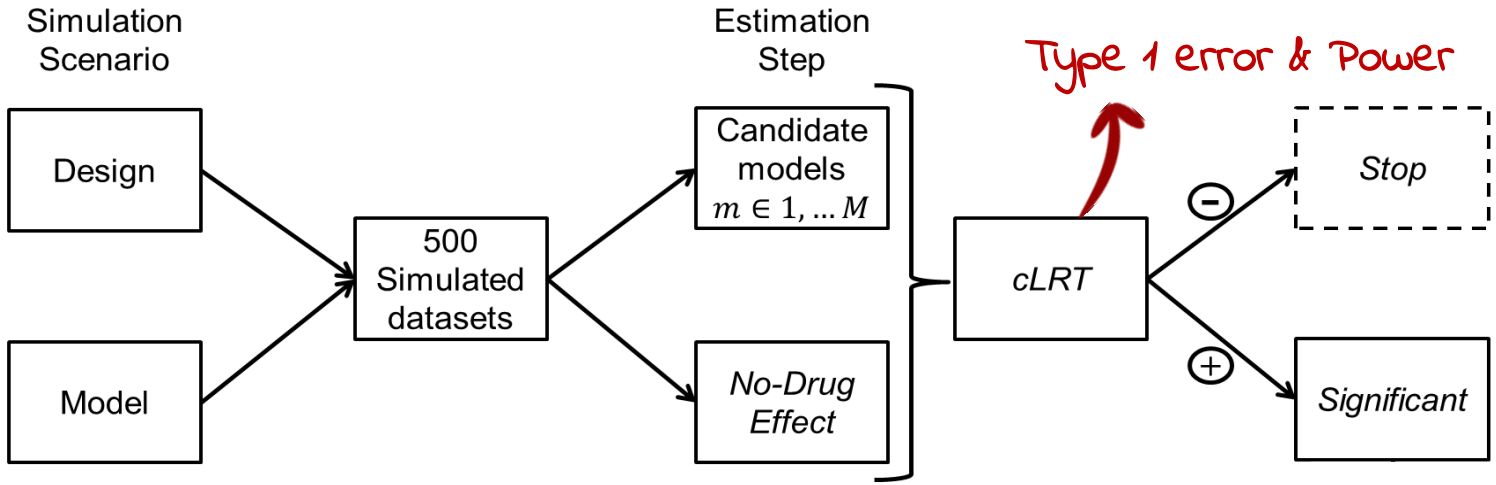
Evaluation


Simulation Scenario
Estimation Step
Design
Model
500 Simulated datasets
Candidate models
$m \in 1, \ldots M$
No-Drug Effect
Linear
Loglinear
Emax
Sigmoid

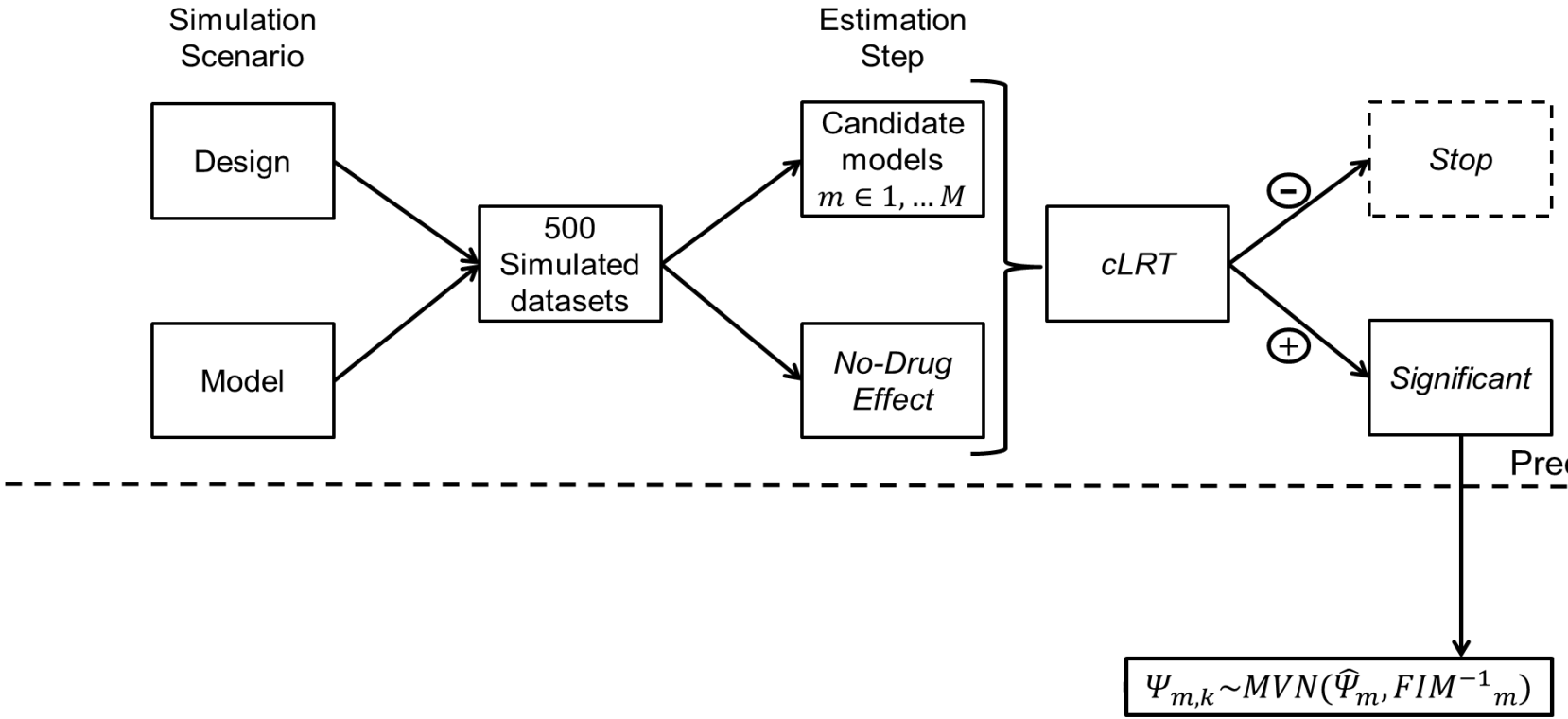
Evaluation


Simulation Scenario
Estimation Step
Design
Model
500 Simulated datasets
Candidate models $m \in 1, \ldots M$
No-Drug Effect
cLRT
Stop
Significant

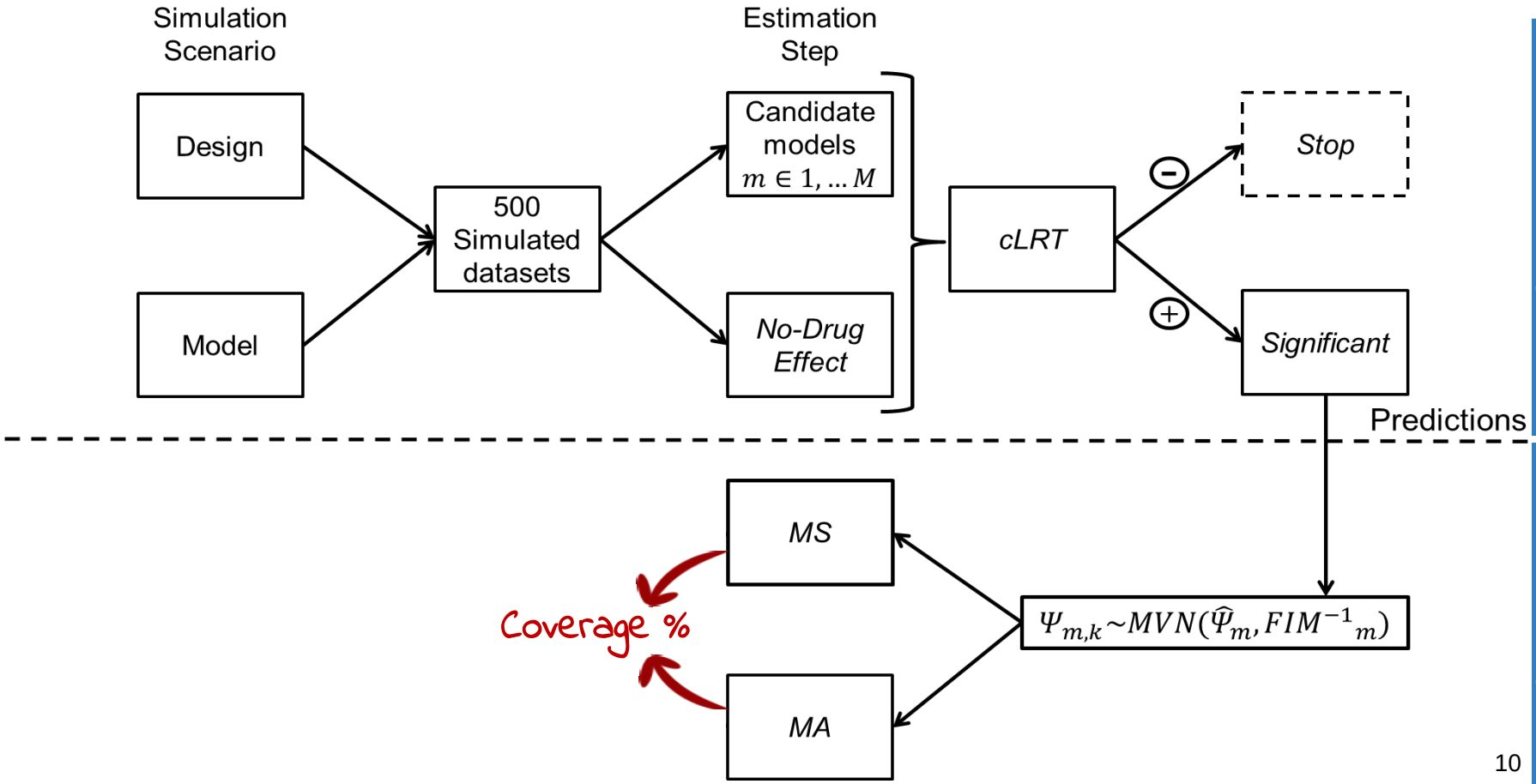
Evaluation


Simulation Scenario
Estimation Step
Type 1 error & Power
Design
Model
500 Simulated datasets
Candidate models $m \in 1, \dots M$
No-Drug Effect
cLRT
Stop
Significant
⊖
⊕

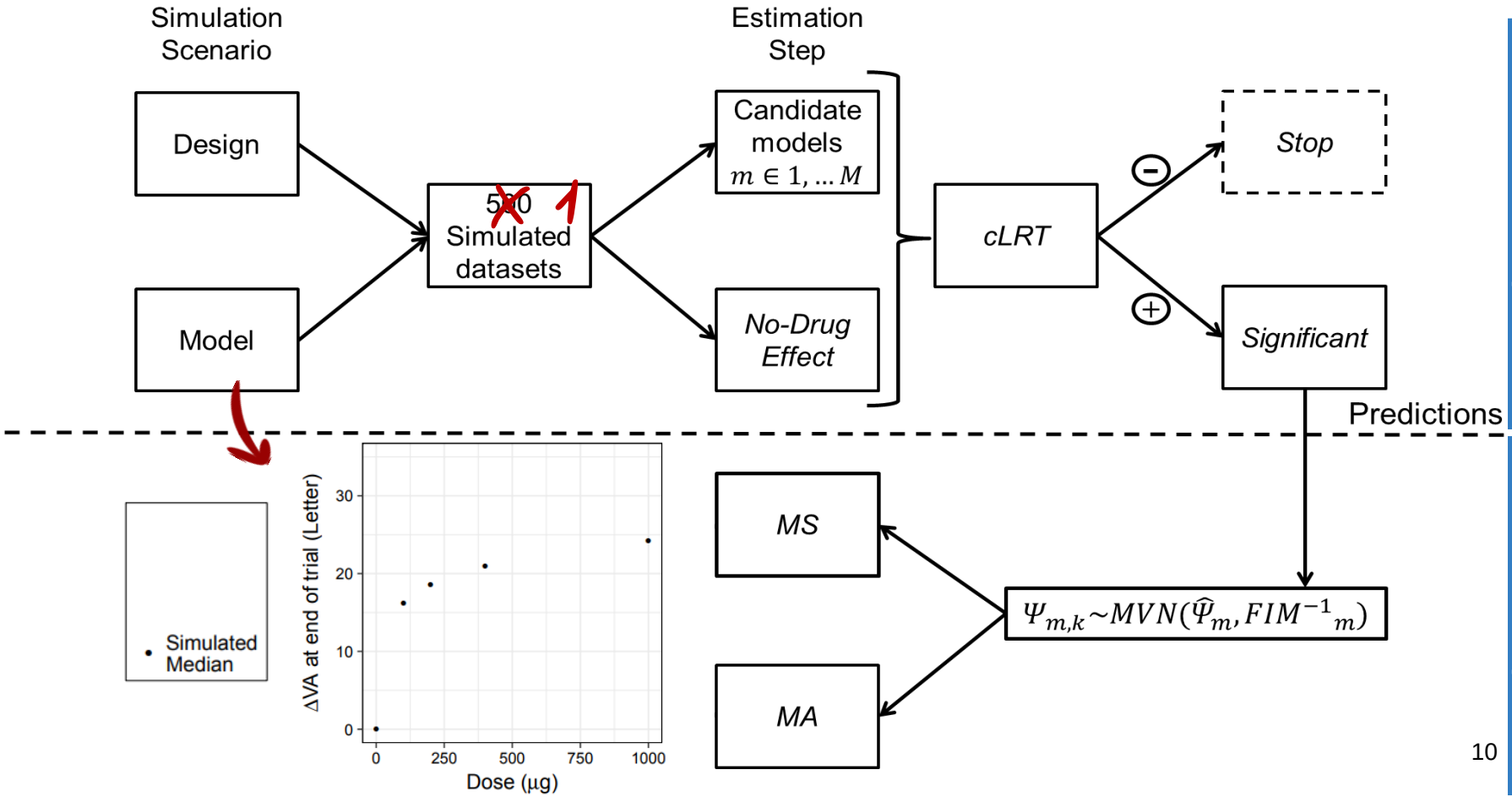
Evaluation


Simulation Scenario
Estimation Step
Design
Model
500 Simulated datasets
Candidate models $m \in 1, \dots M$
No-Drug Effect
cLRT
Stop
Significant
Predictions
$\Psi_{m,k} \sim MVN(\hat{\Psi}_m, FIM^{-1}{}_m)$
cLRT step
MOD step

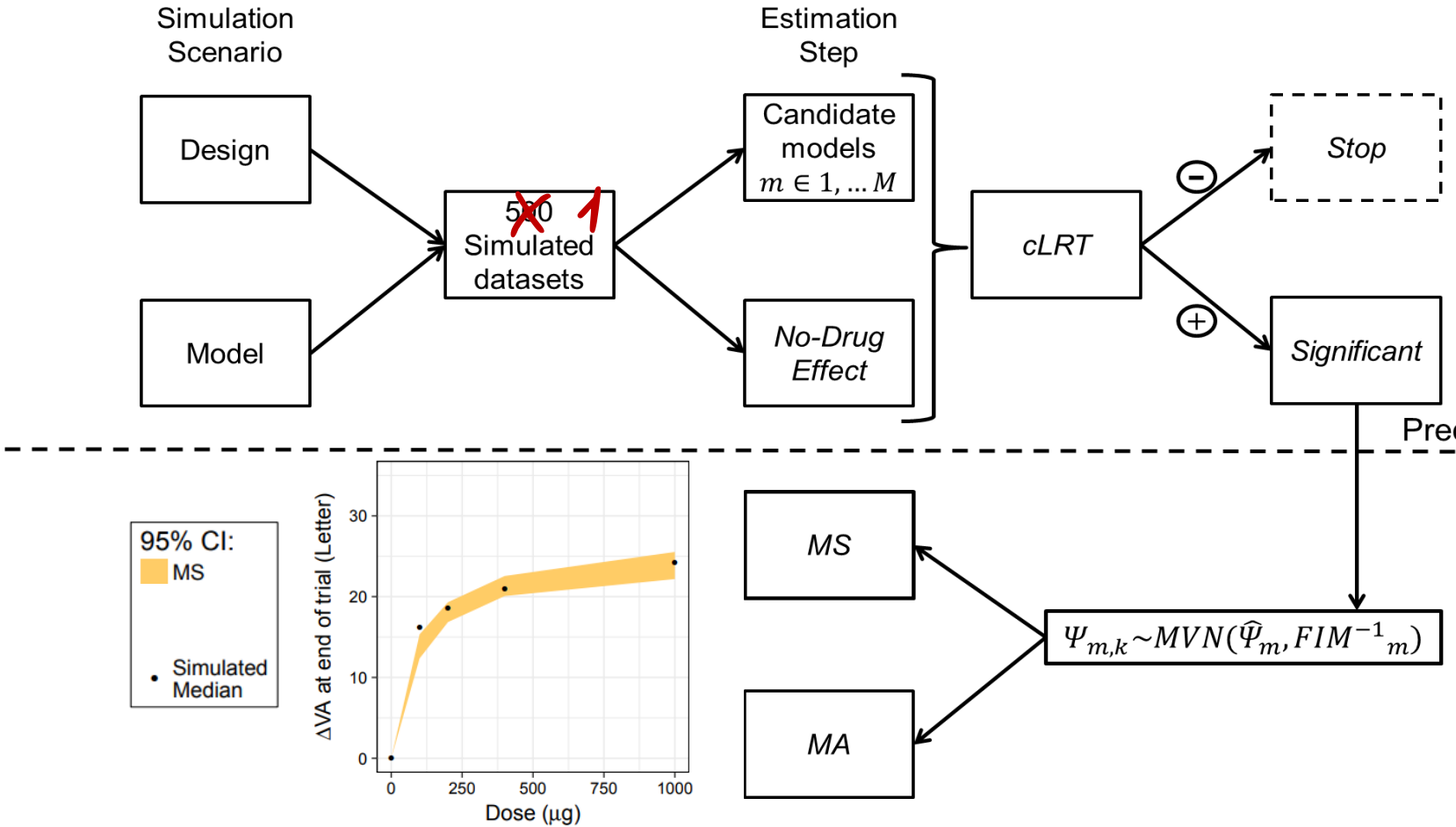
Evaluation


Simulation Scenario
Estimation Step
Design
Model
500 Simulated datasets
Candidate models $m \in 1, \dots M$
No-Drug Effect
cLRT
Stop
Significant
Predictions
MS
MA
Coverage %
$\Psi_{m,k} \sim MVN(\hat{\Psi}_m, FIM^{-1}{}_m)$
cLRT step
MOD step

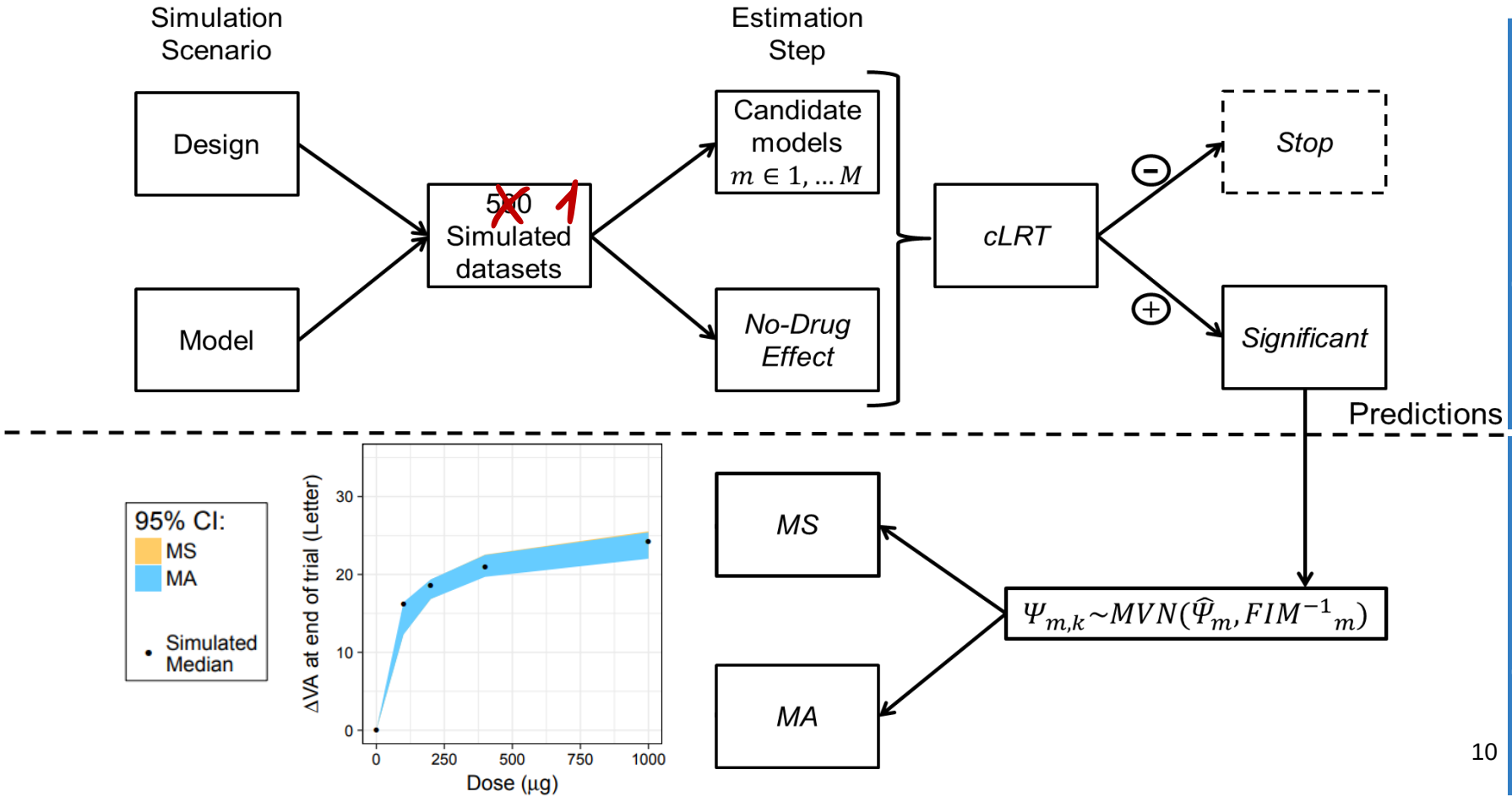
Evaluation


Simulation Scenario
Design
Model
500 1
Simulated datasets
Estimation Step
Candidate models $m \in 1, \ldots M$
No-Drug Effect
cLRT
Stop
Significant
Predictions
Simulated Median
ΔVA at end of trial (Letter)
Dose (µg)
MS
MA
$\Psi_{m,k} \sim MVN(\hat{\Psi}_m, FIM^{-1}{}_m)$
cLRT step
MOD step

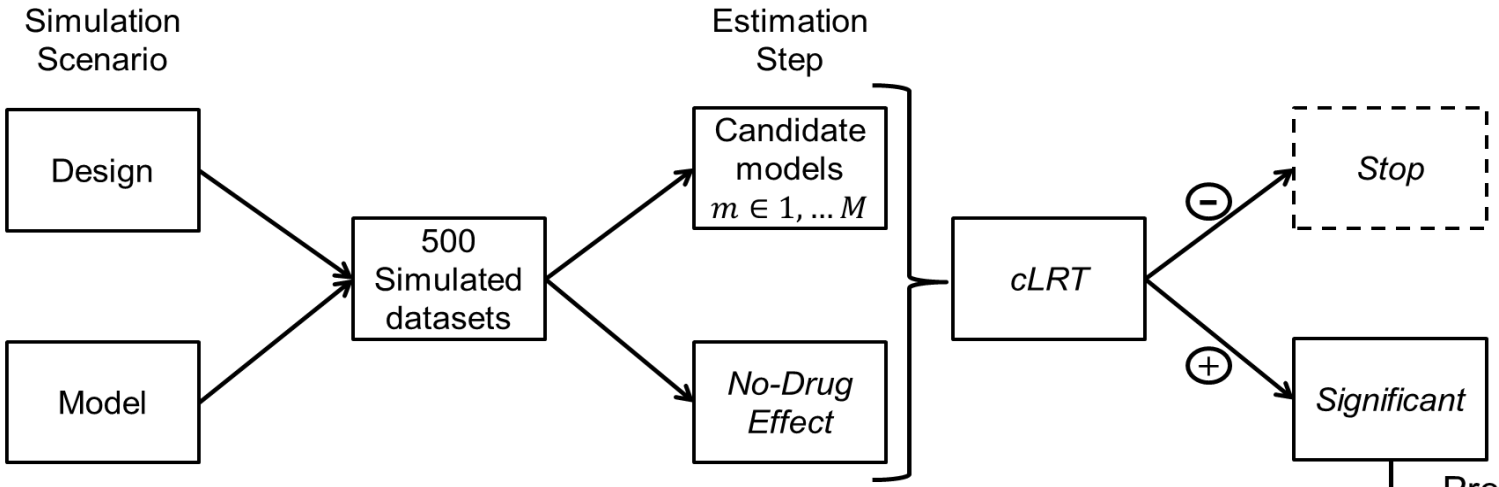
Evaluation


Simulation Scenario
Design
Model
500 1
Simulated datasets
Estimation Step
Candidate models $m \in 1, \ldots M$
No-Drug Effect
cLRT
Stop
Significant
Predictions
95% CI:
MS
Simulated Median
ΔVA at end of trial (Letter)
0
10
20
30
0
250
500
750
1000
Dose (µg)
MS
MA
$\Psi_{m,k} \sim MVN(\hat{\Psi}_m, FIM^{-1}{}_m)$
cLRT step
MOD step

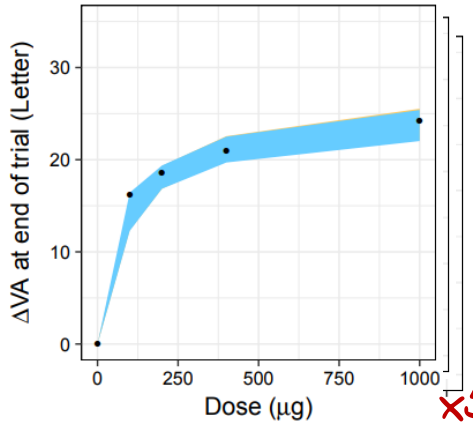
Evaluation


Simulation Scenario
Design
Model
500 1
Simulated datasets
Estimation Step
Candidate models $m \in 1, \ldots M$
No-Drug Effect
cLRT
Stop
Significant
Predictions
95% CI:
MS
MA
Simulated Median
ΔVA at end of trial (Letter)
0
10
20
30
0
250
500
750
1000
Dose (µg)
MS
MA
$\Psi_{m,k} \sim MVN(\hat{\Psi}_m, FIM^{-1}{}_m)$
cLRT step
MOD step

Evaluation

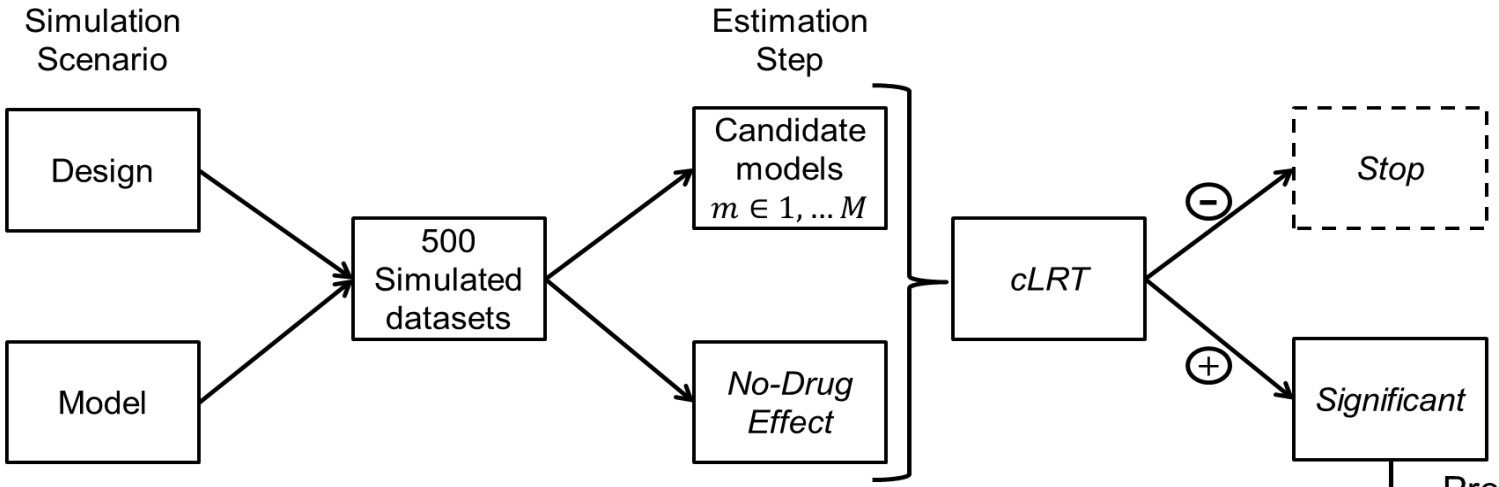


Coverage %: 95%
-P50

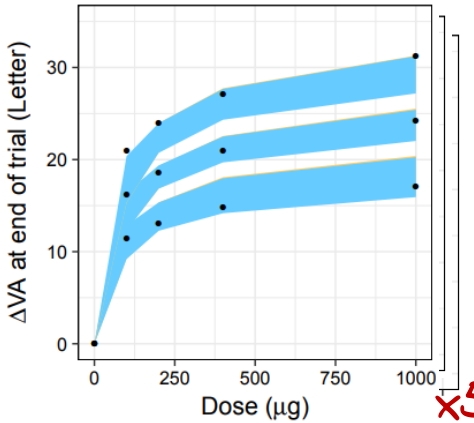


x500

Evaluation



Coverage %: 95%
- P80
- P50
- P20



x500

I. Strong drug effect & N=300

Type I error & Power

Simulation model

Test

		Linear	Log-linear	Emax	Sigmoid	No-DE
		Power (%)				Type-I error [3.2-7%]
LRT	Linear					5.8
	Log-linear					5.6
	Emax					5.8
	Sigmoid					5.8
	MS					9.2
cLRT						6.2
MCP						4.0

I. Strong drug effect & N=300

Type I error & Power

Simulation model

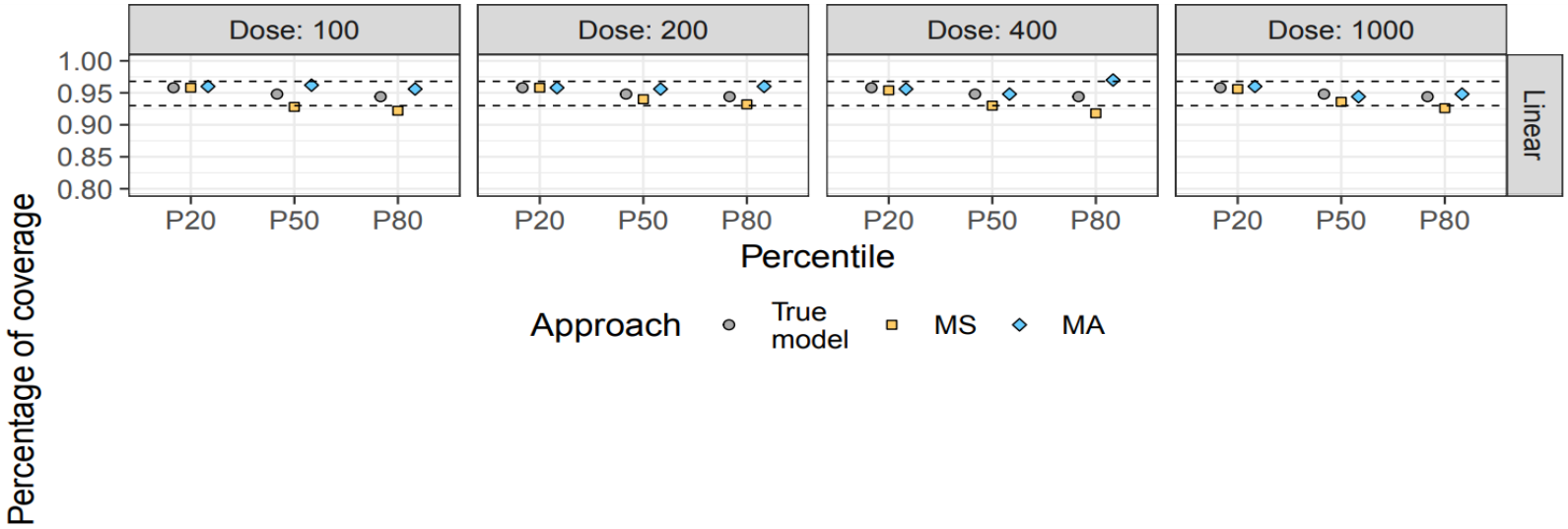
Test

		Linear	Log-linear	Emax	Sigmoid	No-DE
		Power (%)				Type-I error [3.2-7%]
LRT	Linear	100				5.8
	Log-linear					5.6
	Emax					5.8
	Sigmoid					5.8
	MS					9.2
cLRT						6.2
MCP						4.0

I. Strong drug effect & N=300

ΔVA Coverages

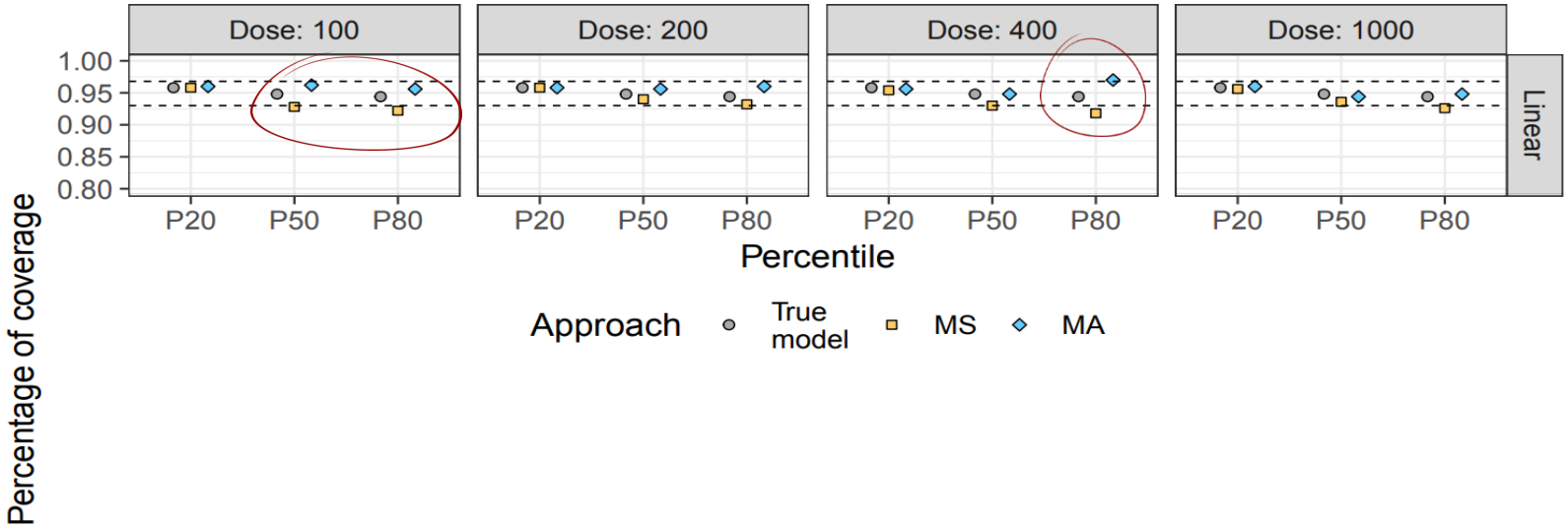
Simulation model



I. Strong drug effect & N=300

ΔVA Coverages

Simulation model



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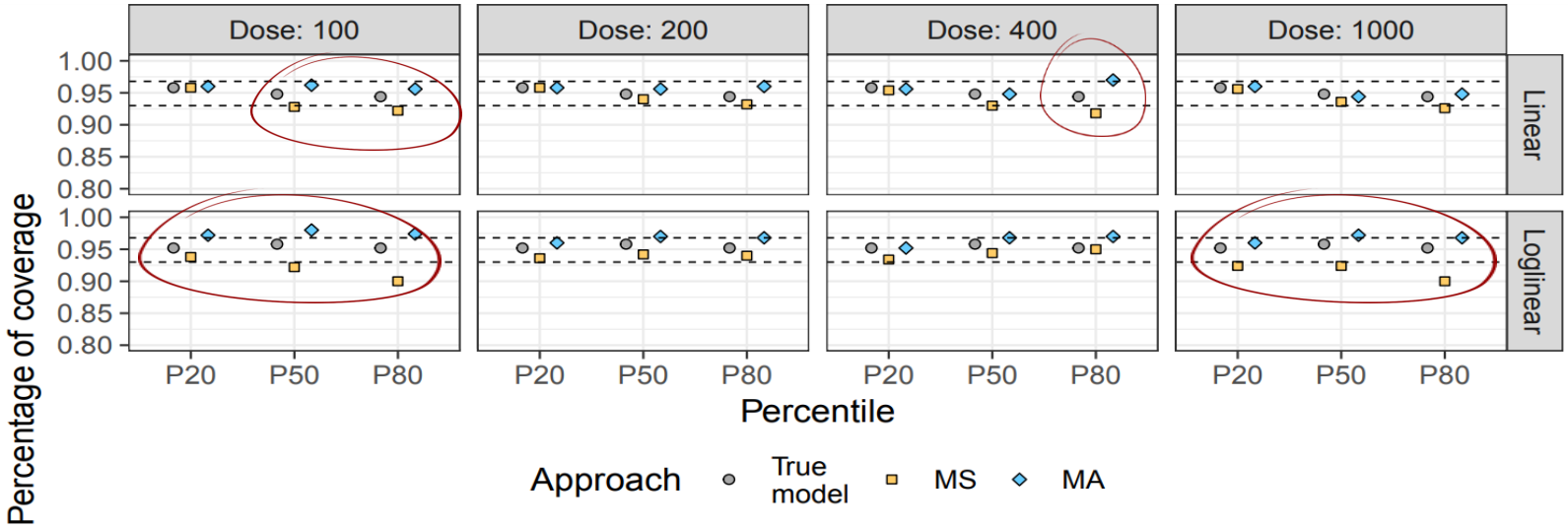
ΔVA Coverages

Simulation model



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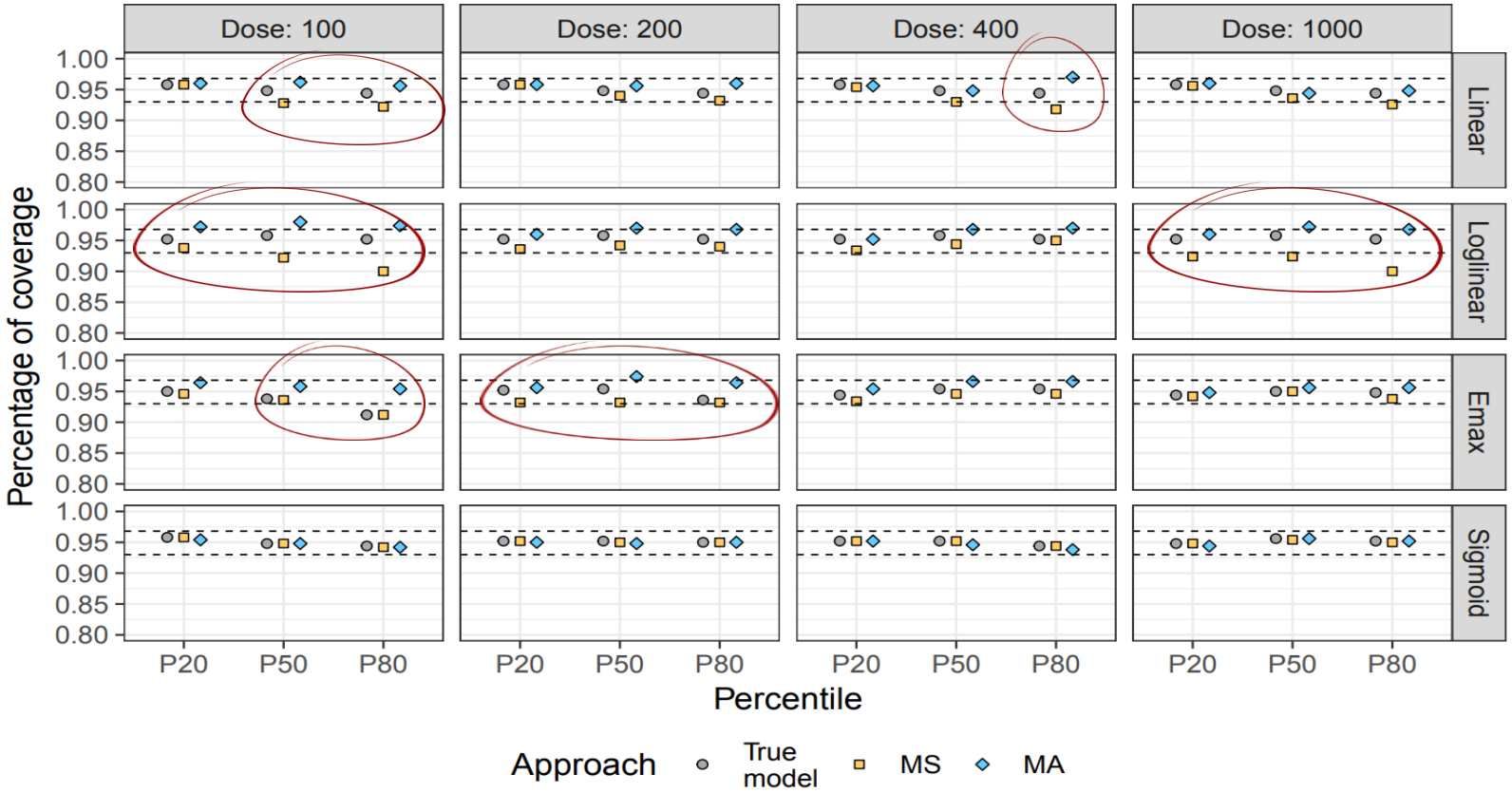
ΔVA Coverages

Simulation model



II. Weak drug effect & N=50

Type I error & Power

Simulation model

Test

		Linear	Log-linear	Emax	Sigmoid	No-DE
		Power (%)				Type-I error [3.2-7%]
LRT	Linear					4.8
	Log-linear					4.0
	Emax					5.6
	Sigmoid					5.8
	MS					7.6
cLRT						5.6
MCP						3.0

II. Weak drug effect & N=50

Type I error & Power

Simulation model

Test

		Linear	Log-linear	Emax	Sigmoid	No-DE
		Power (%)				Type-I error [3.2-7%]
LRT	Linear	75.8	72.4	79.6	89.4	4.8
	Log-linear	62.0	83.0	84.8	91.8	4.0
	Emax	65.2	81.6	84.4	91.2	5.6
	Sigmoid	67.8	40.4	47.2	57.2	5.8
	MS	79.0	86.6	89.6	93.6	7.6
cLRT						5.6
MCP						3.0

II. Weak drug effect & N=50

Type I error & Power

Simulation model

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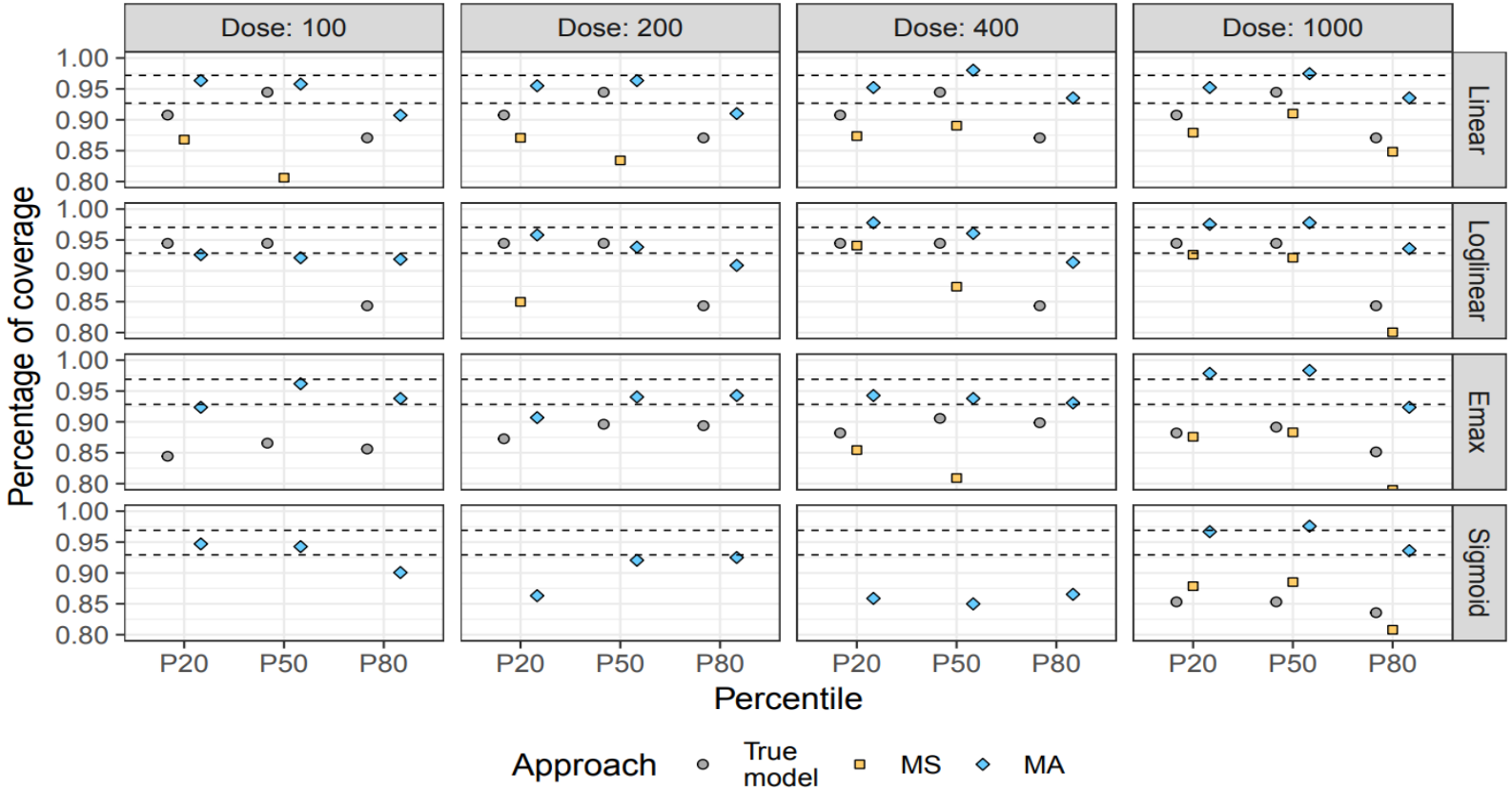
	Emax	65.2	81.6	84.4	91.2	5.6
	Sigmoid	67.8	40.4	47.2	57.2	5.8
	MS	79.0	86.6	89.6	93.6	7.6
cLRT		71.2	81.2	83.8	90.6	5.6
MCP		14.2	11.2	12.4	16.4	3.0

II. Weak drug effect & N=50

ΔVA Coverages

Simulation model



Conclusions

- This work extends the MCP-MOD methodology to use NLMEM in both MCP and MOD steps
- By deriving the reference distribution of the LRT under the null-hypothesis for all candidate models, the method maintains the nominal type-I error while using the full longitudinal information
- The work, furthermore, shows how model averaging provides substantially better coverage in the MOD step, and how the ignorance of model uncertainty leads to an under-estimation of the confidence intervals
- New milestone in the use of pharmacometric methods for primary analysis in dose finding protocols

Perspectives

- Include different disease progression models in the set of candidate models for both the cLRT and MOD steps
- Derive parameter uncertainty from Sample Importance Resampling (SIR)[1] or sampling from Bayesian posterior distribution[2] instead of the FIM
- Explore the case where the true model is not in the set of candidate models

[1] Dosne A.G. *et al*, *JPKPD 43*, 2016
[2] Ueckert S. *et al*, http://www.page-meeting.org/?abstract=3632, 2015

Thanks to

- Inserm Colleagues

- Roche Colleagues

Backup slides

Standard LR-test : Limits

- **Variance parameter:** Unlike linear mixed effect models[1,2], there is no results identifying the limiting distribution of the LRT in nonlinear mixed effects models
- **Identifiability**: under the null hypothesis of no dose response certain model parameters are not identifiable and standard LR-test theory is not applicable[3]
- **Model uncertainty & multiplicity**: Testing several dose-response candidate models and retaining the best one without adjustment for the significance may lead to a type one error inflation[4]

[1] Stram D.O. *et al,* Biometrics, 1994
[2] Drikvandi R. *et al, Biostatistics, 2013*
[3] Dette H. *et al*, Biometrics, 2015
[4] Bretz F . *et al*, Biometrics, 2005

Nonlinear mixed effect models

$$y_{ij} = f_m(d_i, t_j, \Phi_{m,i}) + \varepsilon_{ij} \quad \varepsilon_{ij} \sim \mathcal{N}(0, {\sigma^2}_m)$$

- y_{ij} is the observation at time $t_j (1 \leq j \leq n)$ of individual $i (1 \leq i \leq N)$
- d_i is the dose administered to patient i
- $\Phi_{m,i}$ is the vector individual parameters
- ε_{ij} is the residual error

Random-effect model

- $\Phi_{m,i,} = \mu_m \times \exp(\eta_{m,i})$

or $\mu_m + \eta_{m,i}$

- $\eta_{m,i} \sim N(0, \Omega_m)$

Vector of population parameters Ψ_m *(size* P_m*)*

- μ_m, fixed effects
- Variance of the random effects Ω_m
- Variance of the residual error ${\sigma^2}_m$

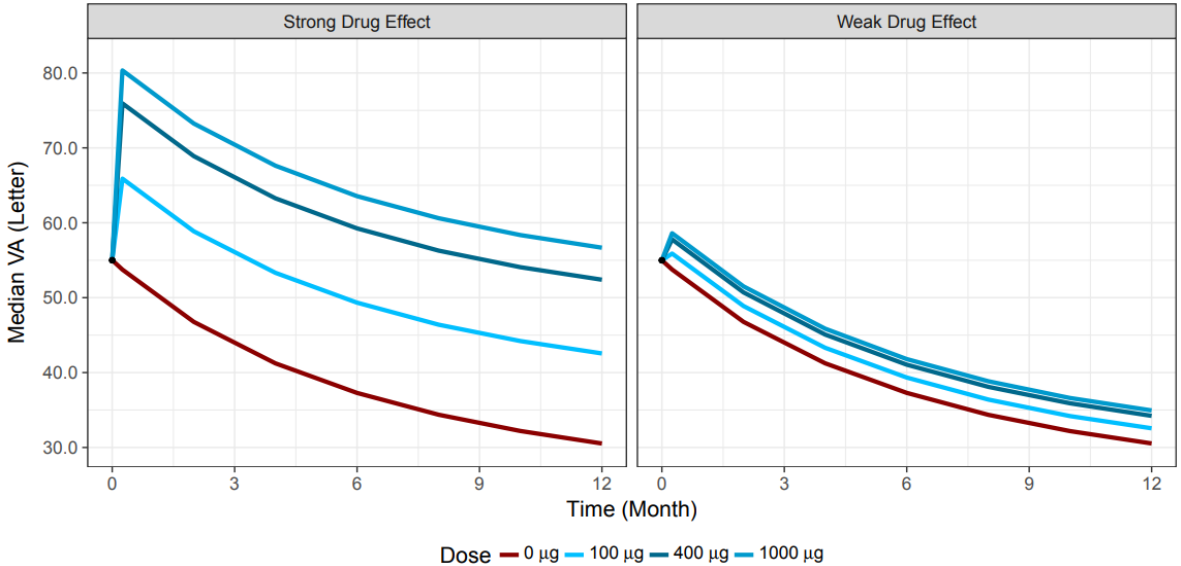
Simulation case study

- Simplified version of a disease model[1] which characterizes the time course of visual acuity (VA) of wet AMD patients[2]:
- Model:

$$f(d_i, t_j, \Phi_i) = VA_{0,i} - VA_{ss_i} \cdot \left(1 - e^{-k_{pr,i} \cdot t_j}\right) + E(d)$$

Asymptotic disease progression

Symptomatic drug effect



[1] Holford N, *British Journal of Clinical Pharmacology* 79, 2015
[2] Diack C. *et al*, http://www.page-meeting.org/?abstract=3569, 2015

Coverage probability with MCP-MOD

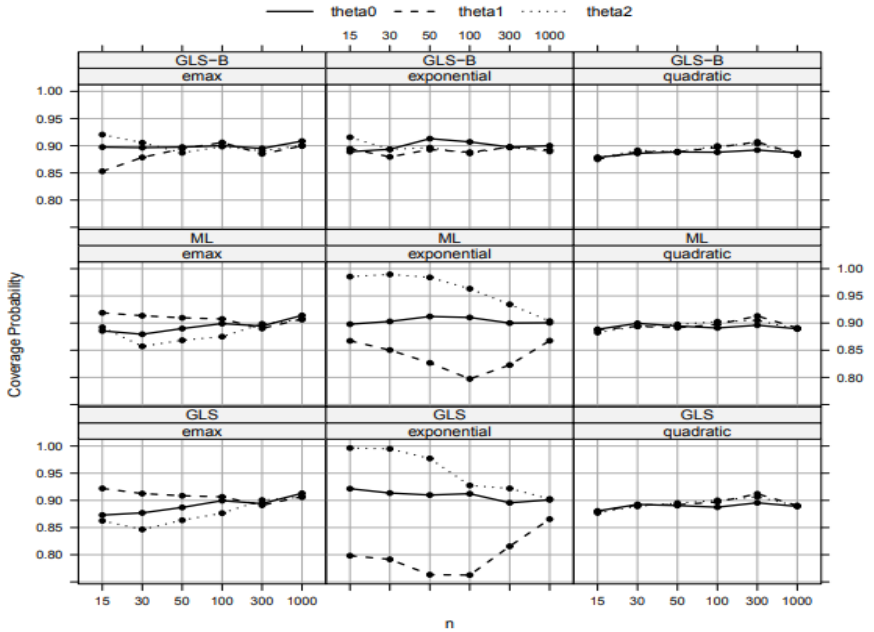
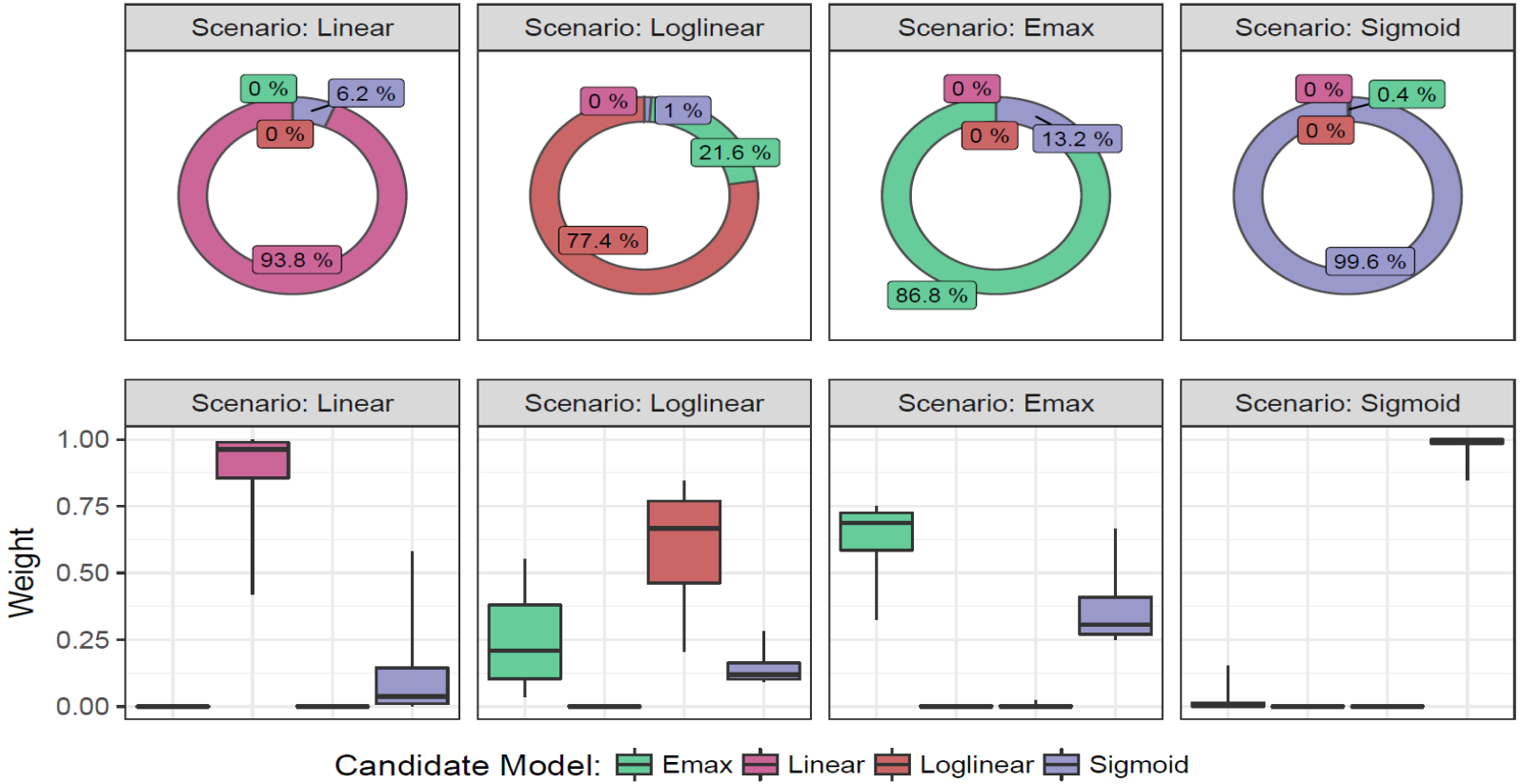


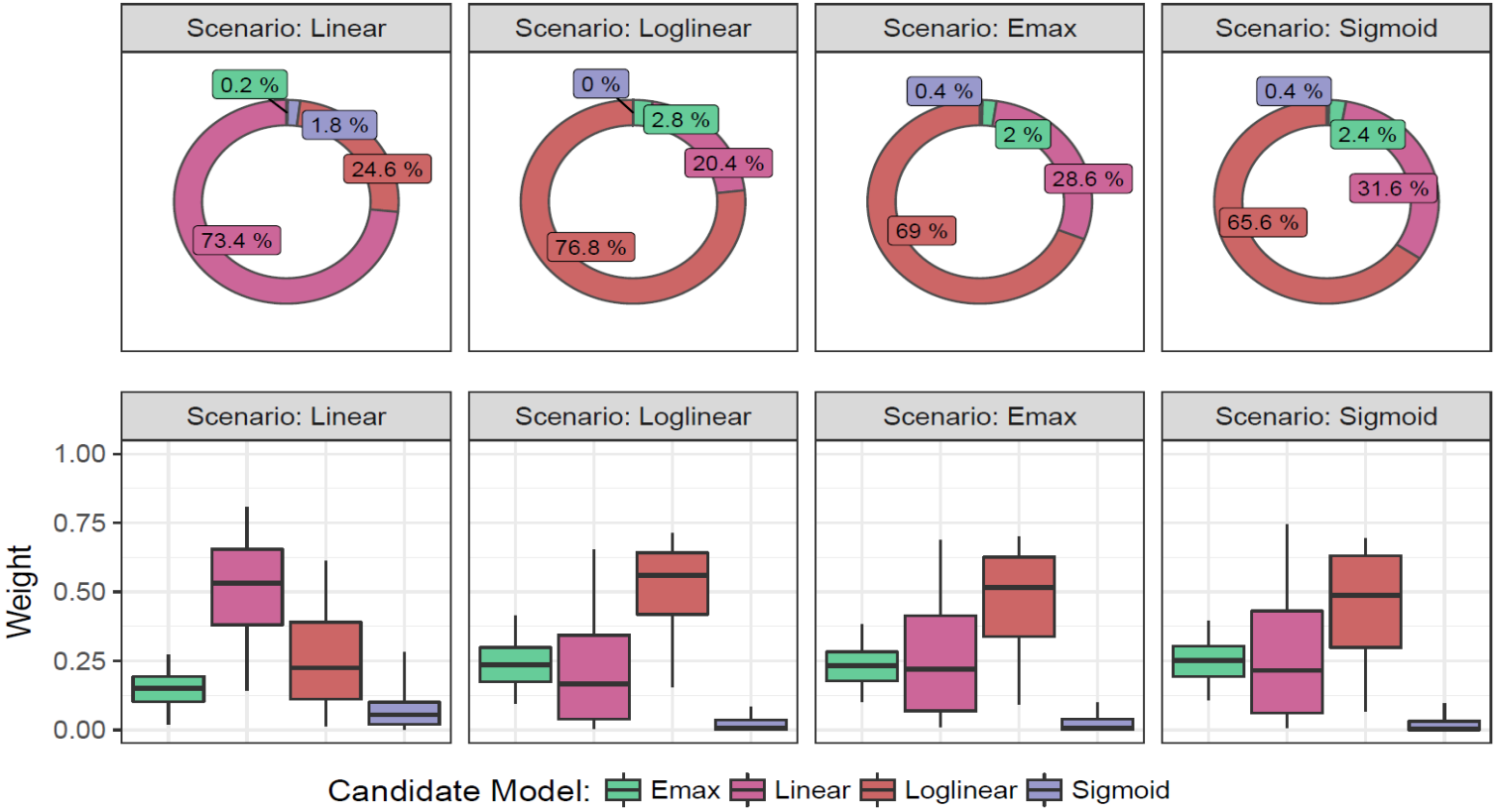
Figure 3: Empirical coverage probability (based on 2000 simulations), of 90% confidence intervals.

[1] Pinheiro J. *et al*, Stat Med, 2014

I. Strong drug effect & N=300
MS & MA



II. Weak drug effect & N=50
MS & MA



III. Strong drug effect & N=50

Type I error & Power

Test

Simulation model

		Linear	Log-linear	Emax	Sigmoid	No-DE
		Power (%)				Type-I error [3.2-7%]
LRT	Linear	100				5.4
	Log-linear					4.2
	Emax					5.2
	Sigmoid					5.8
	MS					7.4
cLRT						4.6
MCP						4.2

III. Strong drug effect & N=50

ΔVA Coverages