Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches

Xiaomei Chen, Henrik B. Nyberg, Mats O. Karlsson, Andrew C. Hooker
Dept. of Pharmaceutical Biosciences
Uppsala University, Sweden

ACOP10, Florida
2019-10-22

Situations where no single PK model may be appropriate for BE analysis

- No prior model
- Can not assume true model
- Identifiability issues
- Avoid estimation bias and overestimation of precision

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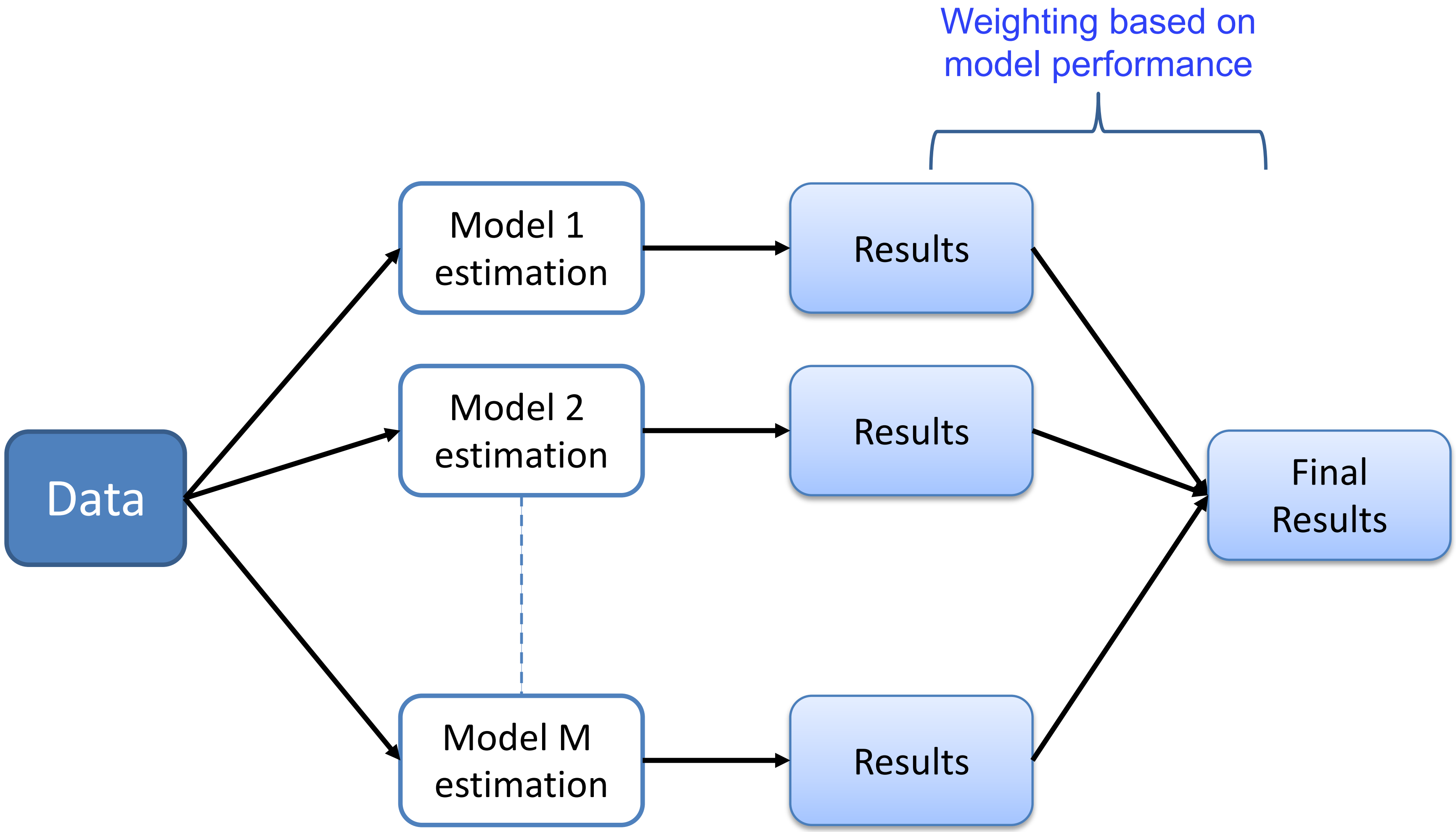
Model Averaging

Model Averaging Approach



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Application of model averaging in Pharmacometrics

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

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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]

Received: 30 June 2016 | Revised: 22 May 2017 | Accepted: 11 June 2017
DOI: 10.1002/sim.7395

RESEARCH ARTICLE

WILEY Statistics in Medicine

Model averaging for robust assessment of QT prolongation by concentration-response analysis

A.G. Dosne[1] | M. Bergstrand[1] | M.O. Karlsson[1] | D. Renard[2] | G. Heimann[2]

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

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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]

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Model averaging approaches developed for BE

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

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ORIGINAL PAPER

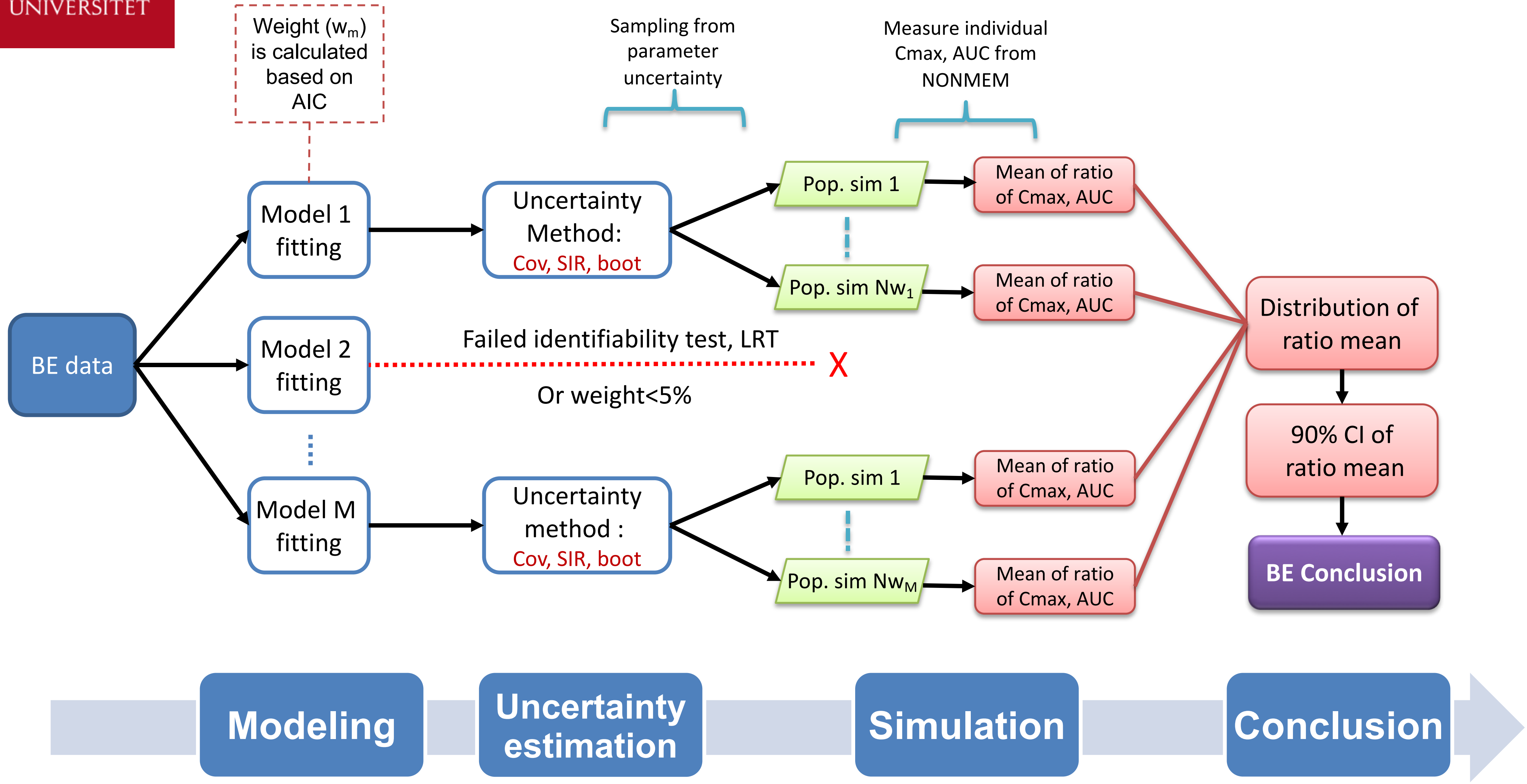
Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection

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

- Model selection
- Bootstrap model selection (BMS)
- Conventional model averaging (MA)
- Bootstrap model averaging

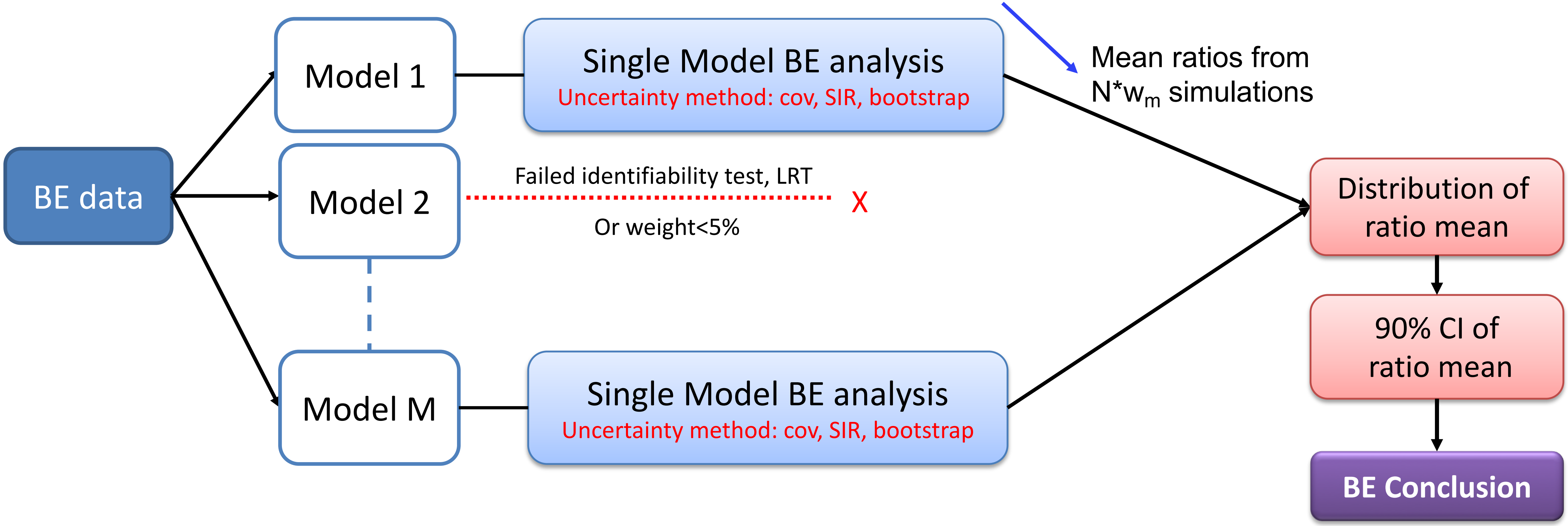
Developed for BE in our study

Conventional model averaging (MA)

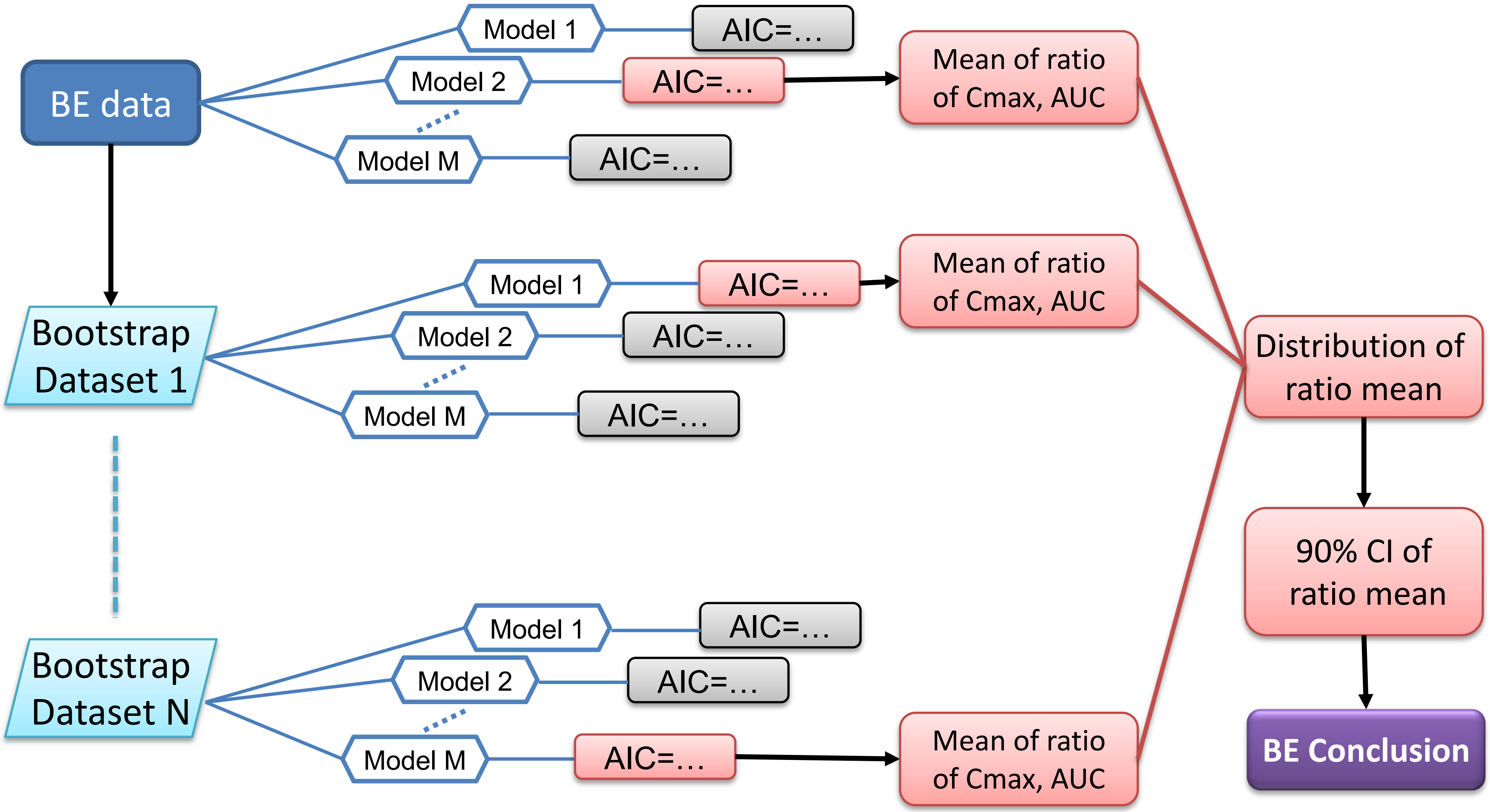


Conventional model averaging (MA)

$$w_m = \frac{e^{\frac{-AIC_m}{2}}}{\sum_{m=1}^{M} e^{\frac{-AIC_m}{2}}}$$



Bootstrap model selection (BMS)



Ophthalmic drug product

Affecting factors

- Solution drainage (naso-lacrimal)
- Lacrimation
- Tear turnover
- Tear dilution
- Conjunctival absorption
- Blinking
- …

→

Low Bioavailability
High variation

http://www.lumigan.com/Resources/How-to-Apply
Agrahari, Drug Deliv. And Transl. Res. 2016

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FDA guidance regarding bioequivalence of ophthalmic drug products

Product-specific BE recommendations (draft guidance)

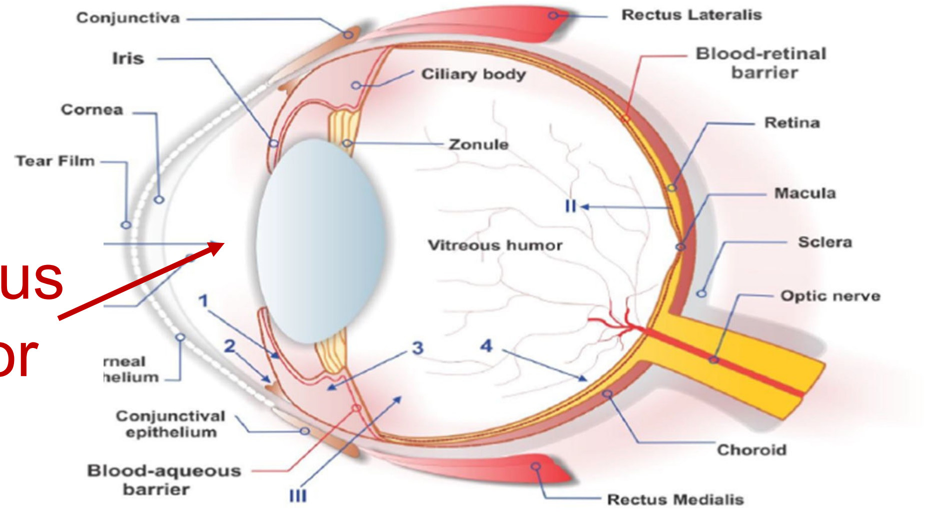
- Waiver (solution and Q1/Q2 products)
- Studies that demonstrate BE
  - Clinical endpoint study
  - PK study in aqueous humor
  - In vitro study
    - Bacterial kill rate study
    - Q3 characterization

Choi, Lionberger, 2016, AAPS Journal

PK study in aqueous humor

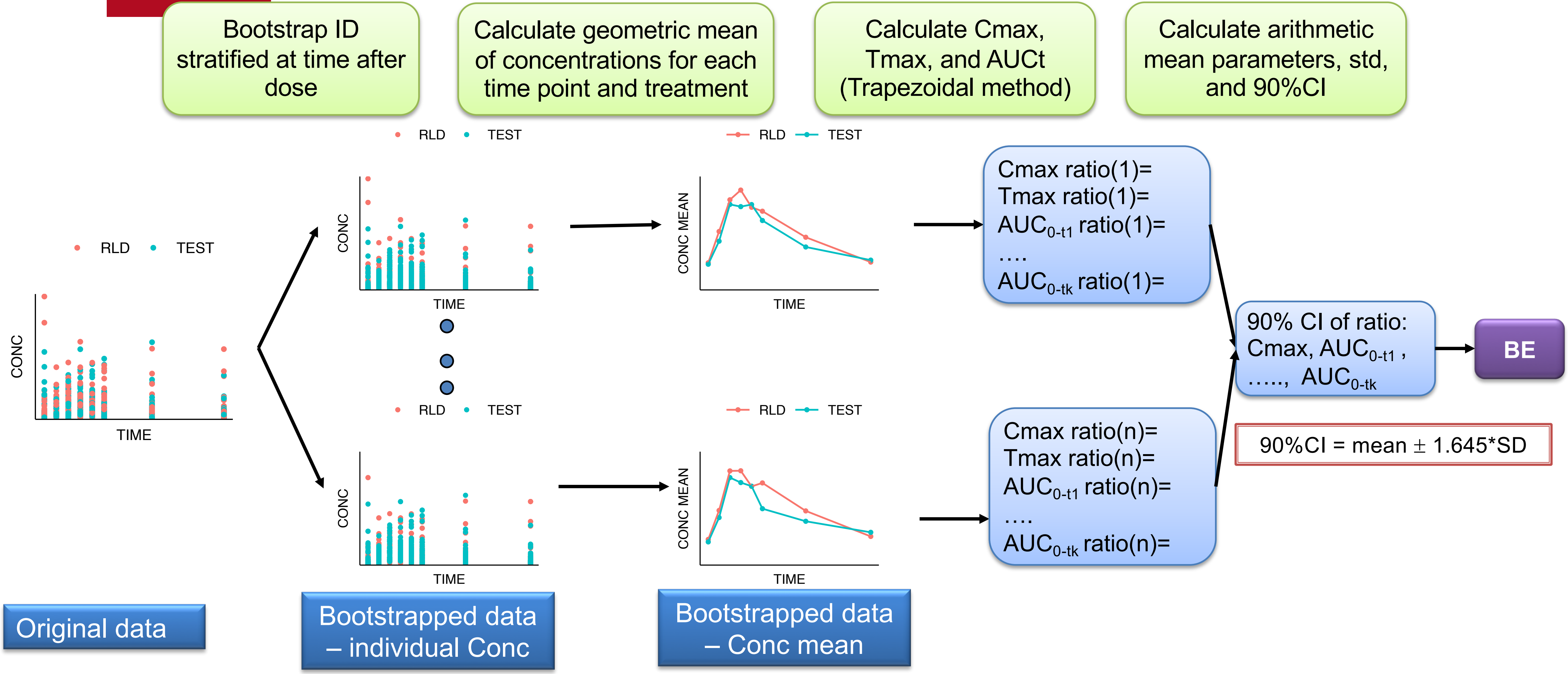
- Subjects: patients undergoing indicated cataract surgery
- Drug administration:
  - prior to surgery
- Only one single sample collected at assigned time point
- **Crossover** or **parallel** study
- Criteria: 90% CI of $AUC_{0\text{-}t}$ and C_{max} ratio is within (0.8, 1.25)
- SD may be done via **bootstrapping technique** or a parametric method

Aqueous humor



Agrahari, Drug Deliv. And Transl. Res. 2016
Choi, Lionberger, 2016, AAPS Journal

Bootstrap NCA BE method



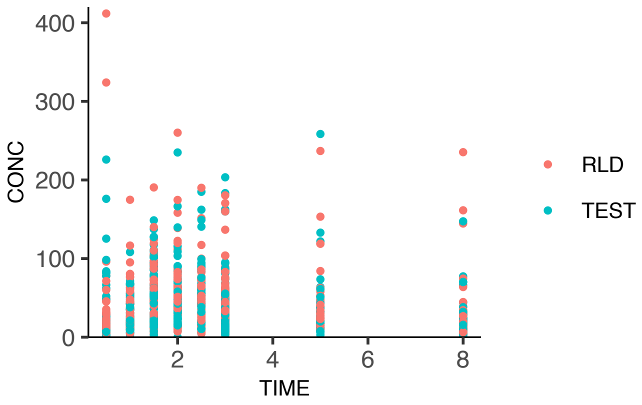
Application of model-based method: Identifiability problem

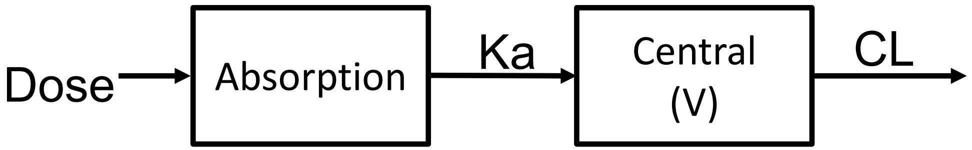
Ophthalmic drug Product BE data

- High variation
- Sparse data

→ **Identifiability Problem** → Possible solution: Model averaging

Ophthalmic product BE data





Random effect may not be identifiable.

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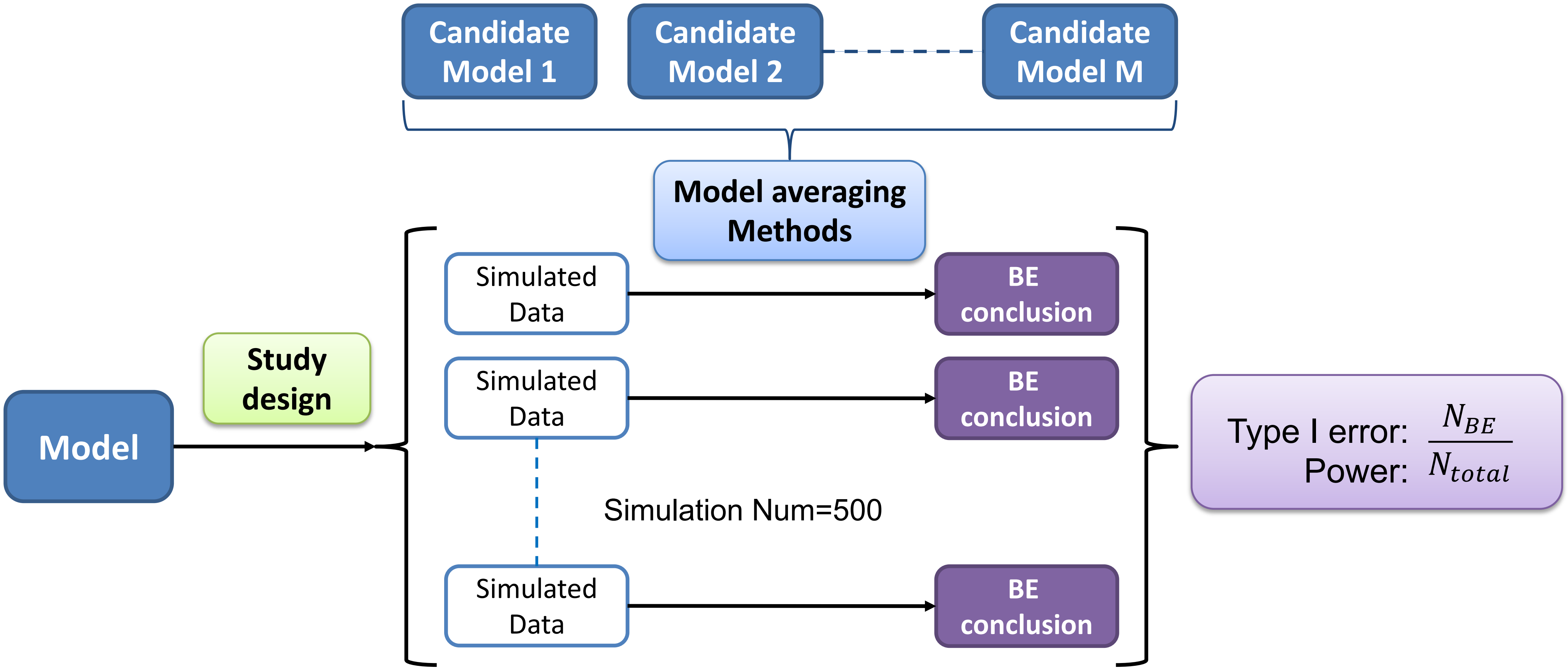
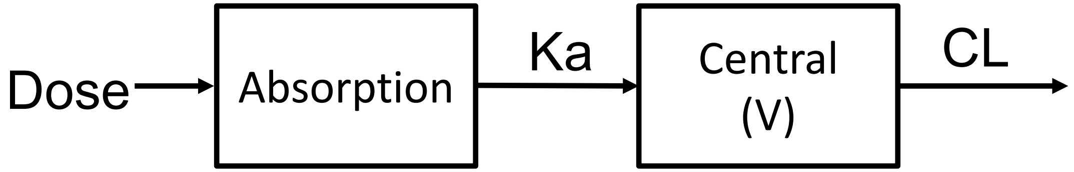
Simulation study flowchart



Ophthalmic drug product BE simulation study
crossover study



IIV ($\omega^2 = 0.25$) on all parameters

IOV ($\omega^2 = 0.0225$) on all parameters

Proportional residual error ($\sigma^2 = 0.01$)

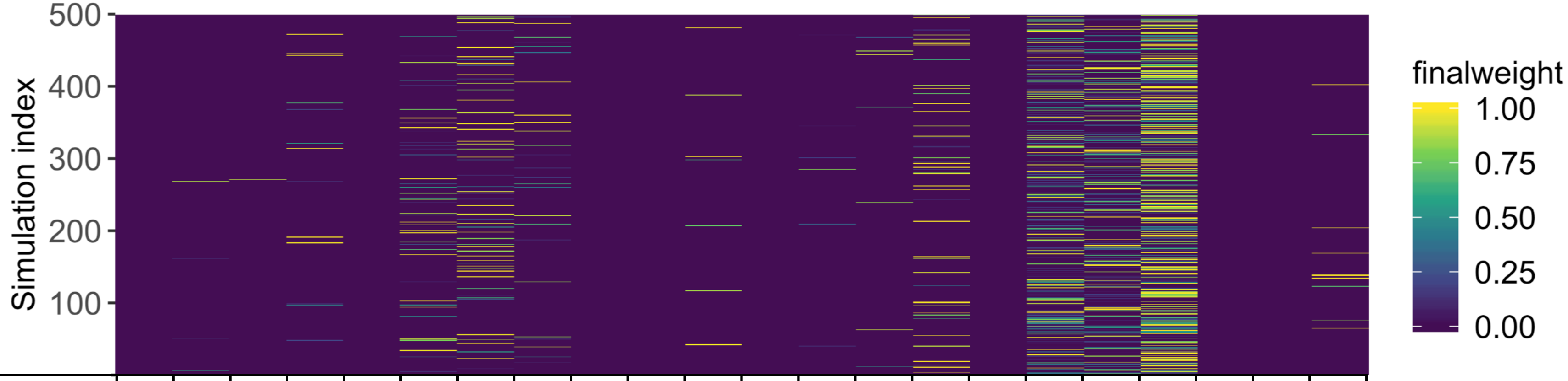
Study design

- Each subject has 2 treatments with the same sampling times
- 5 groups: 0.25, 1.5, 5, 15, 24
- 24 subject/group
- Total subject No=120

Crossover study

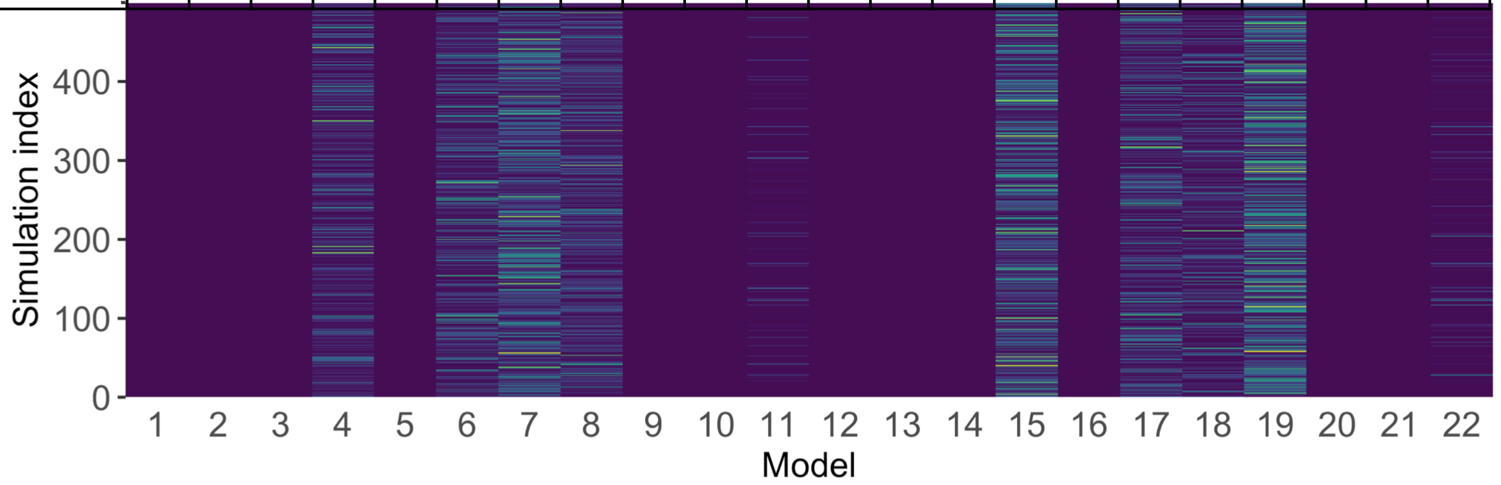
Weight distribution among models

Conventional Model Averaging

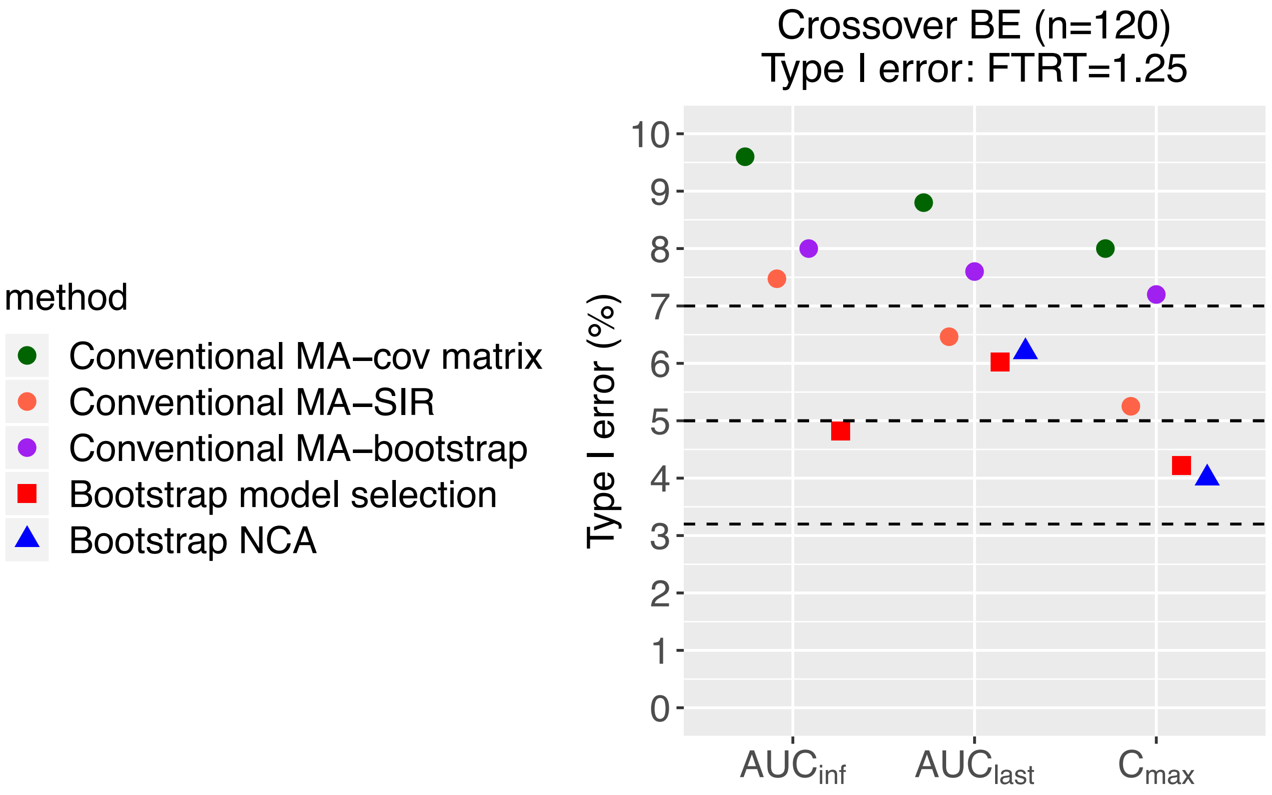


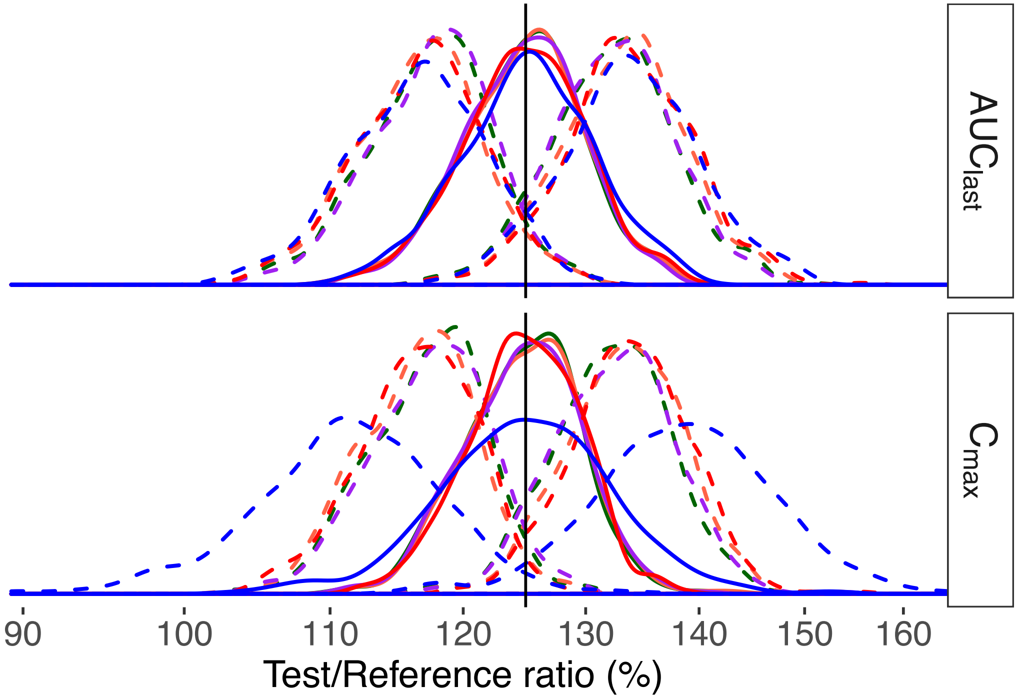
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
KATRT	x	x	x	x	x	x	x	x	x	x	x											
IIV-CL	x	x	x	x		x	x	x	x			x	x	x	x		x	x	x	x		
IIV-V	x	x	x		x	x				x		x	x	x		x	x				x	
IIV-KA	x	x		x	x		x					x	x		x	x		x				
IIV-F	x		x	x	x			x			x	x		x	x	x			x			x
Estimated OMEGA number	4	3	3	3	3	2	2	2	1	1	1	4	3	3	3	3	2	2	2	1	1	1

Bootstrap Model Selection

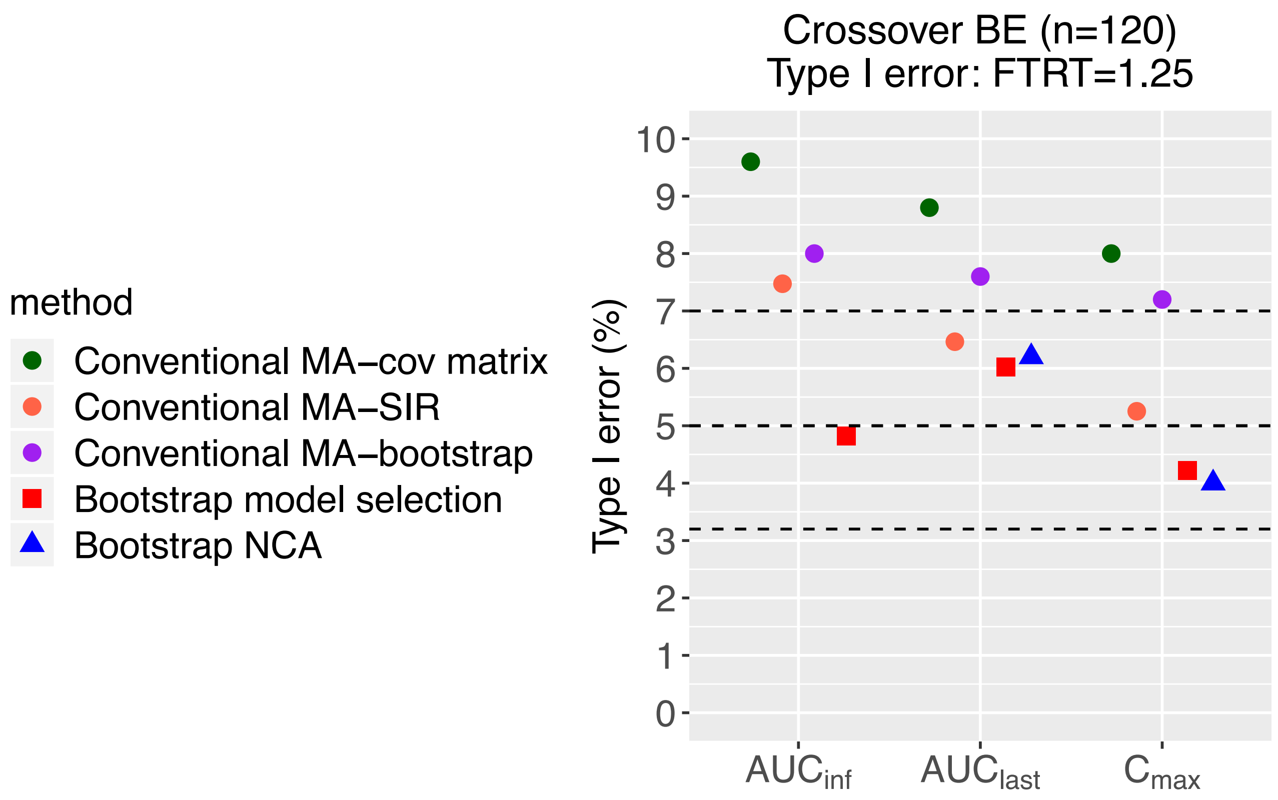


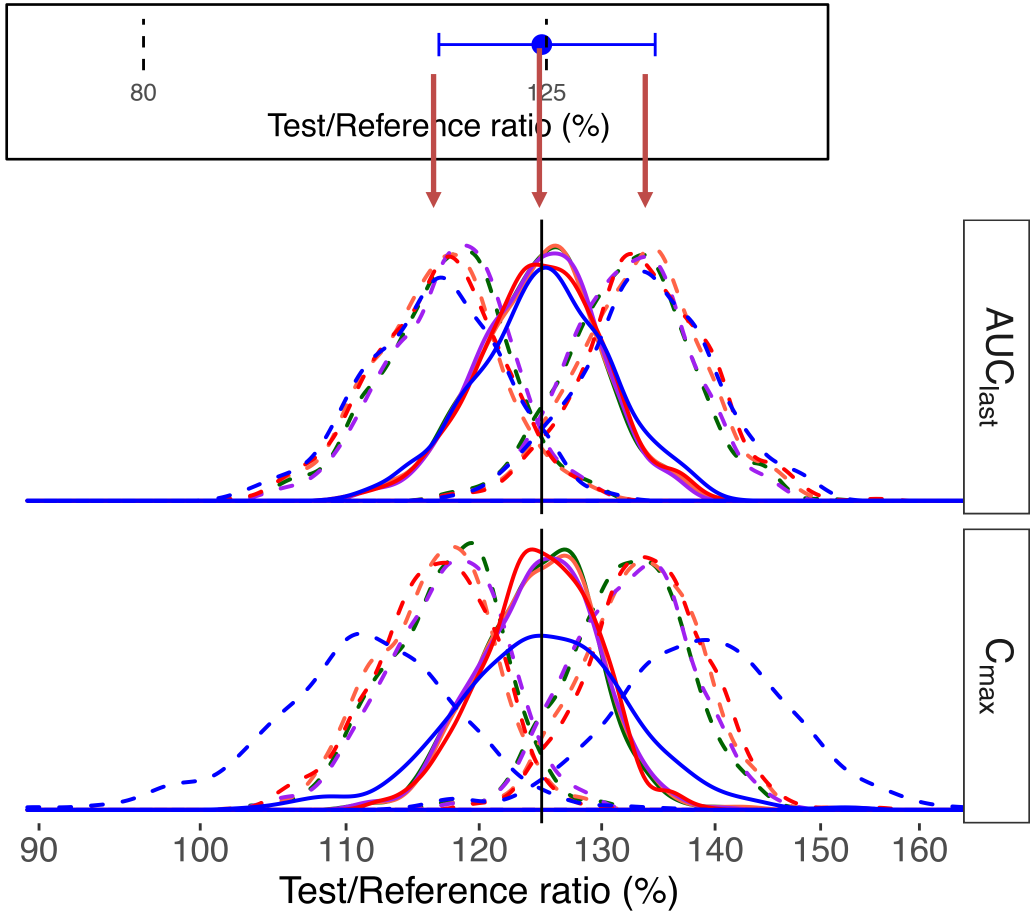
Crossover study: Type I error



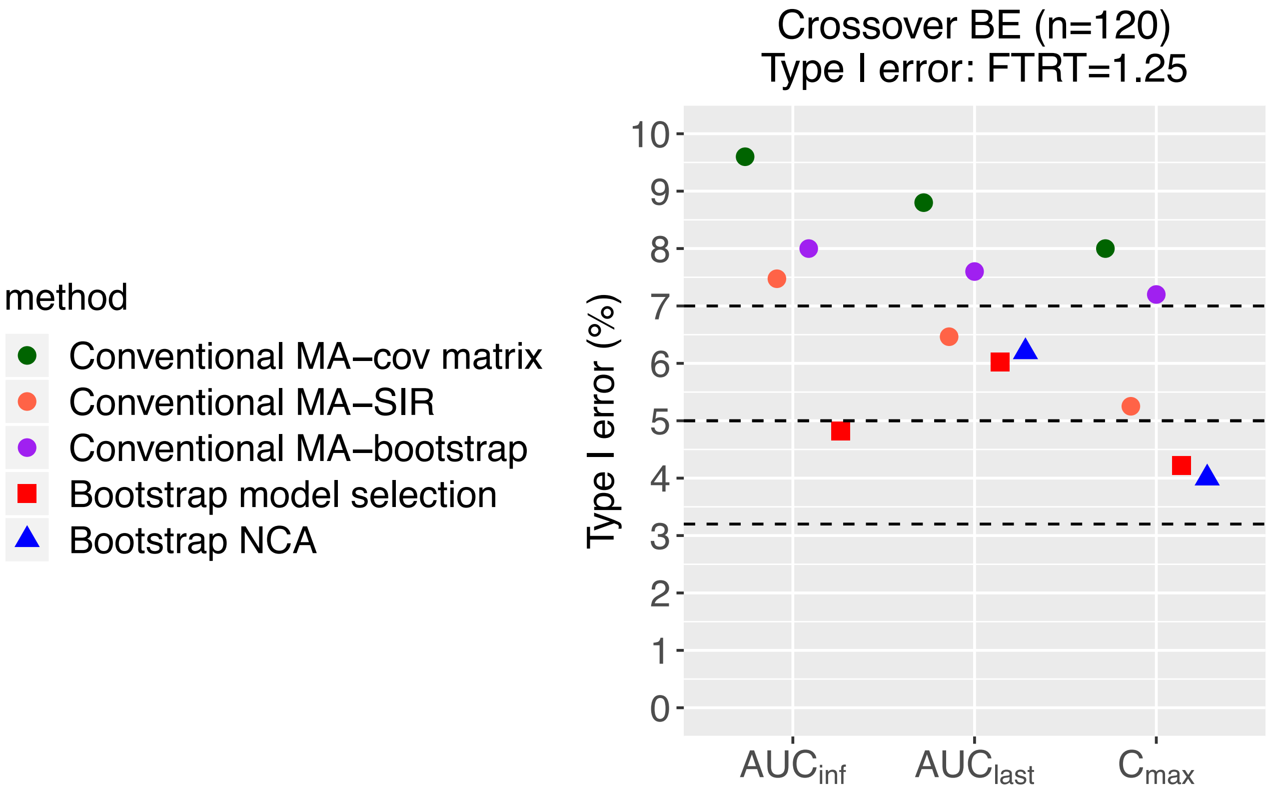


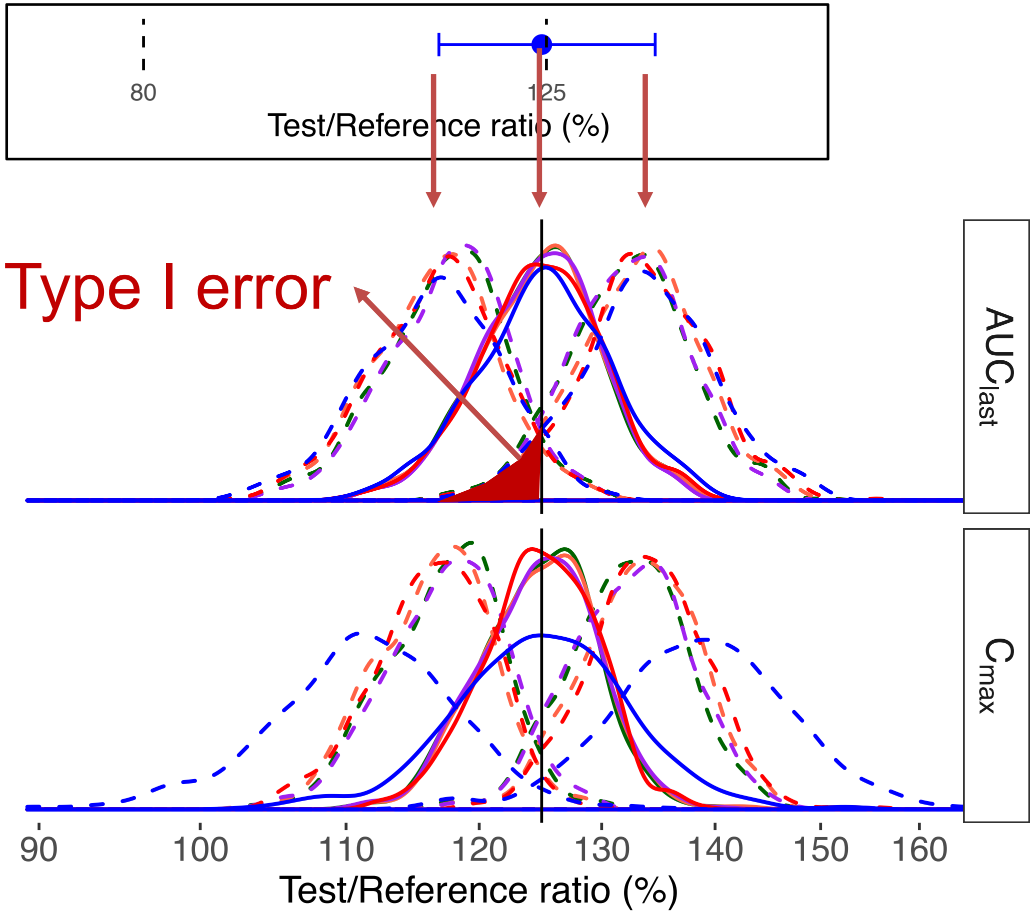
Crossover study: Type I error



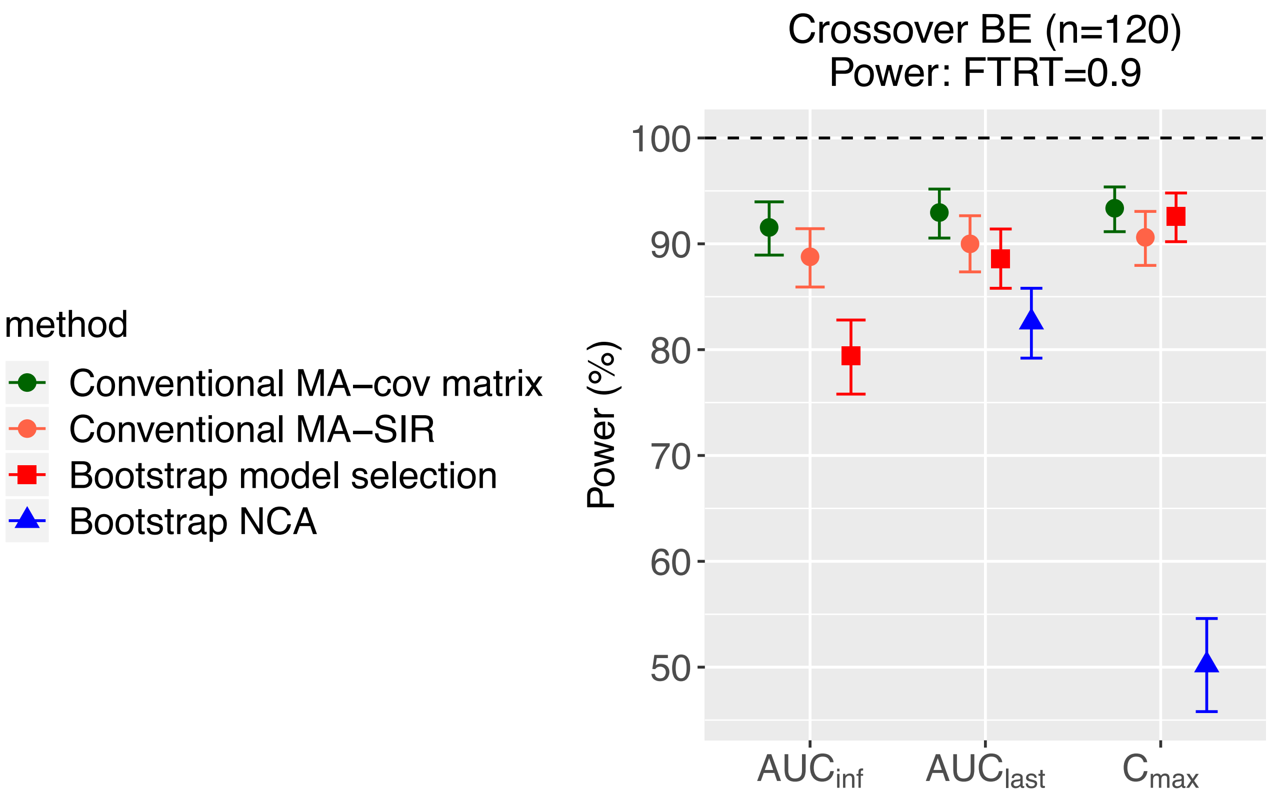


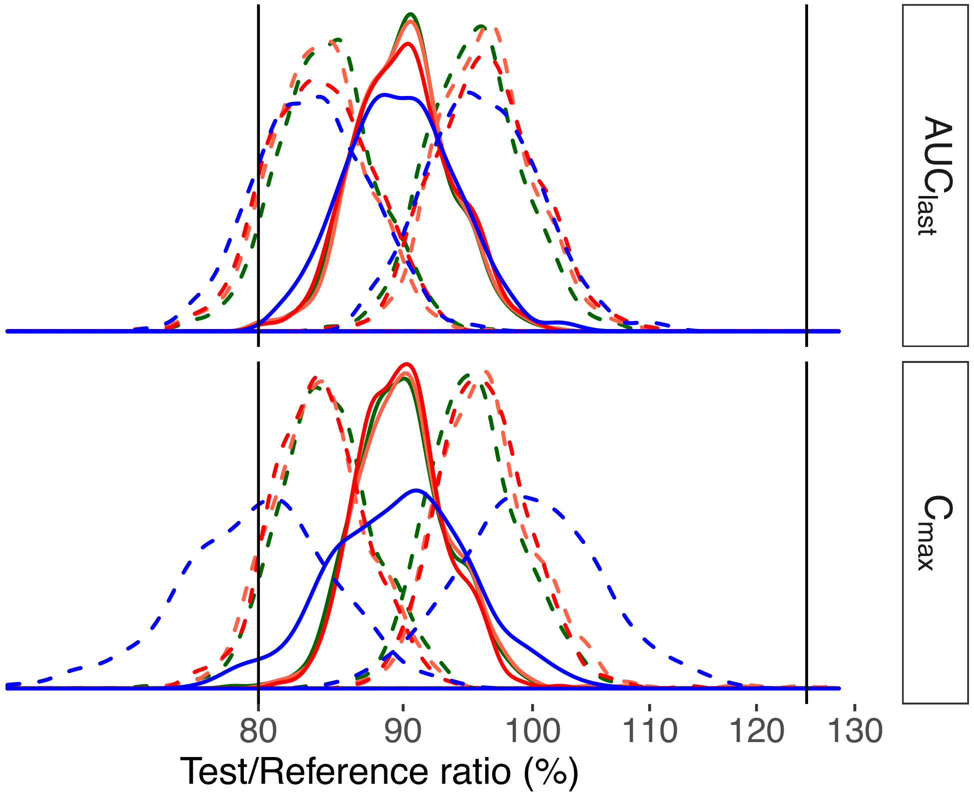
Crossover study: Type I error



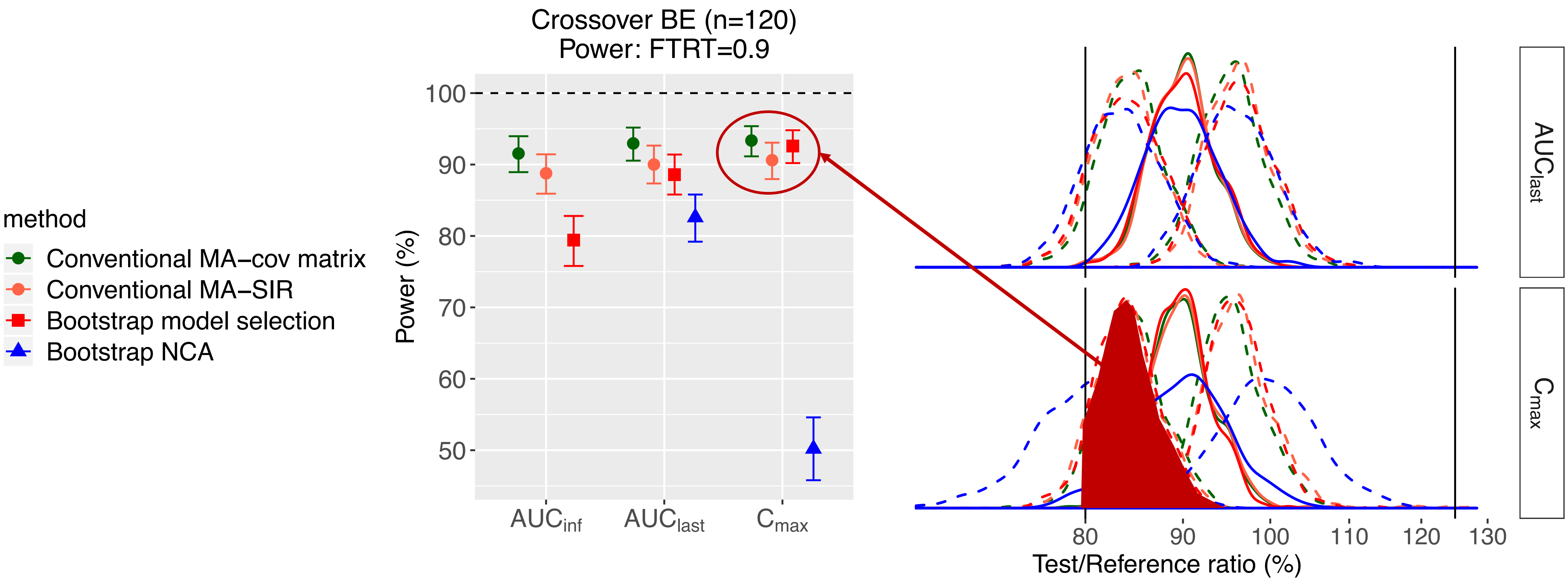


Crossover study: Power

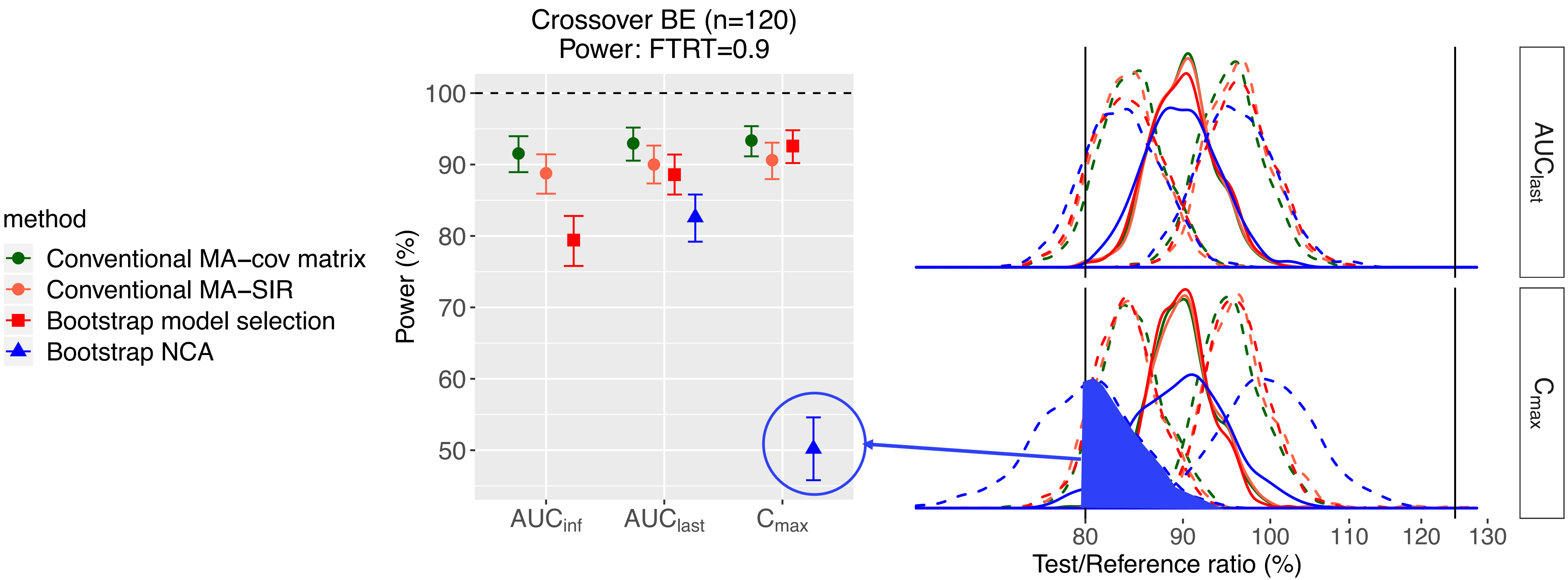




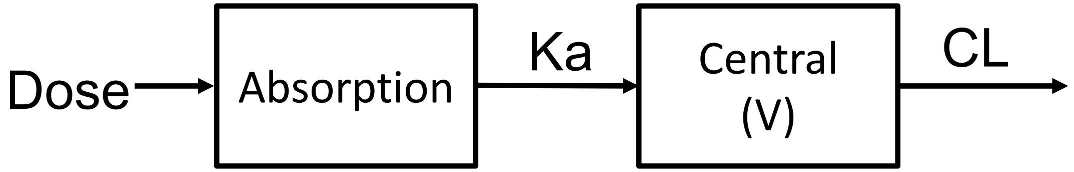
Crossover study: Power



Crossover study: Power



Ophthalmic drug product BE simulation study
Parallel study



IIV ($\omega^2 = 0.25$) on all parameters

Proportional residual error ($\sigma^2 = 0.01$)

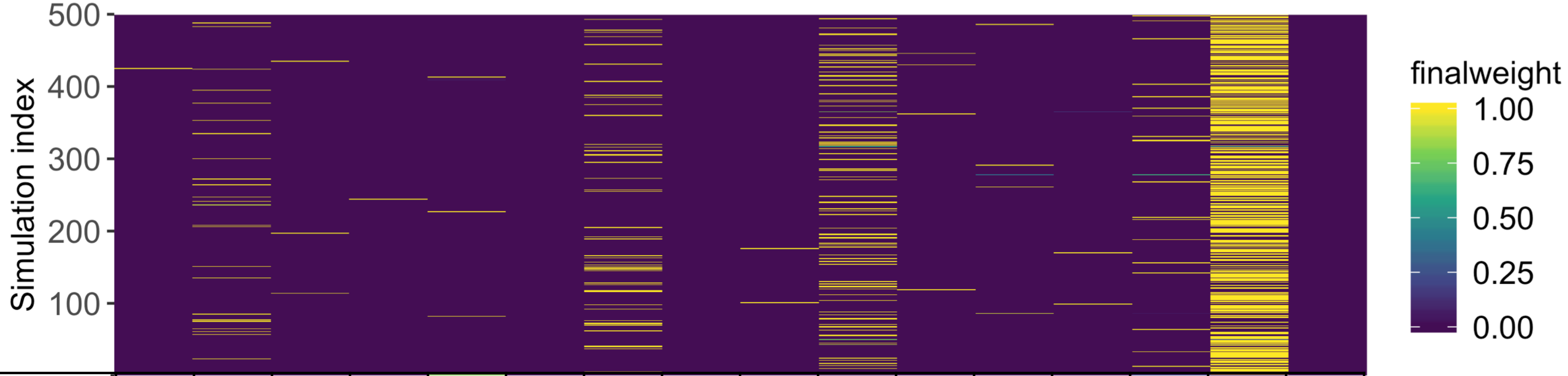
Study design

- Each subject: 1 treatment and 1 sample
- 2 treatments: reference and test
- 5 potential sampling points:
  0.5, 1, 5, 15, 24
- 2 treatment* 5 sampling=10 group
- 48 subject/group
- Total subject No.=480

Parallel study

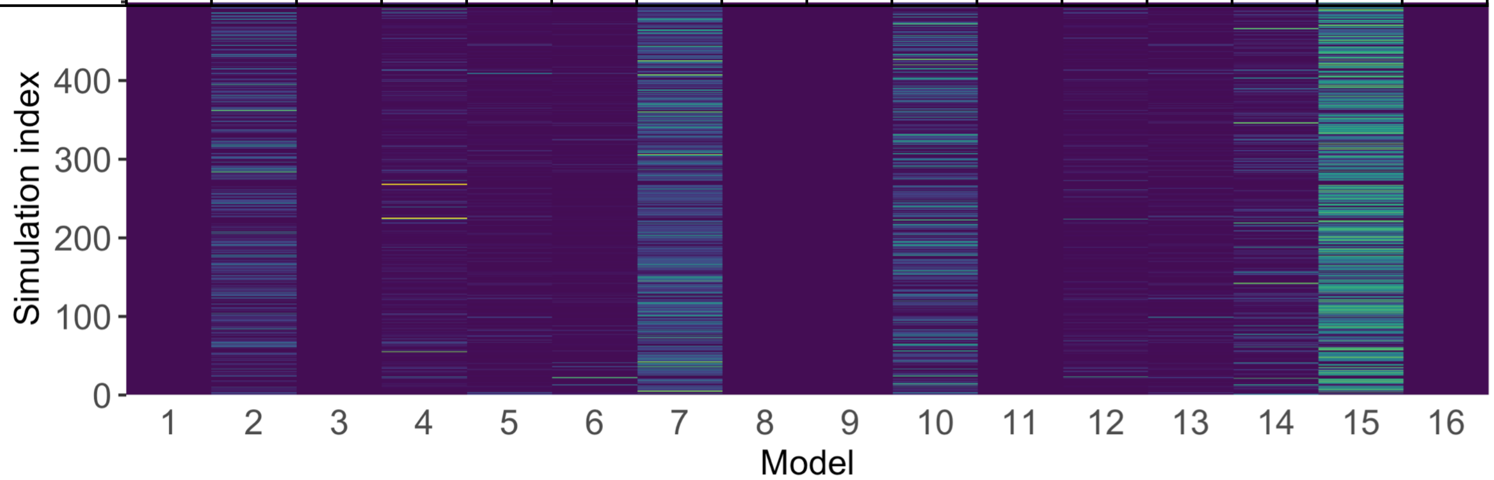
Weight distribution among models

Conventional Model Averaging

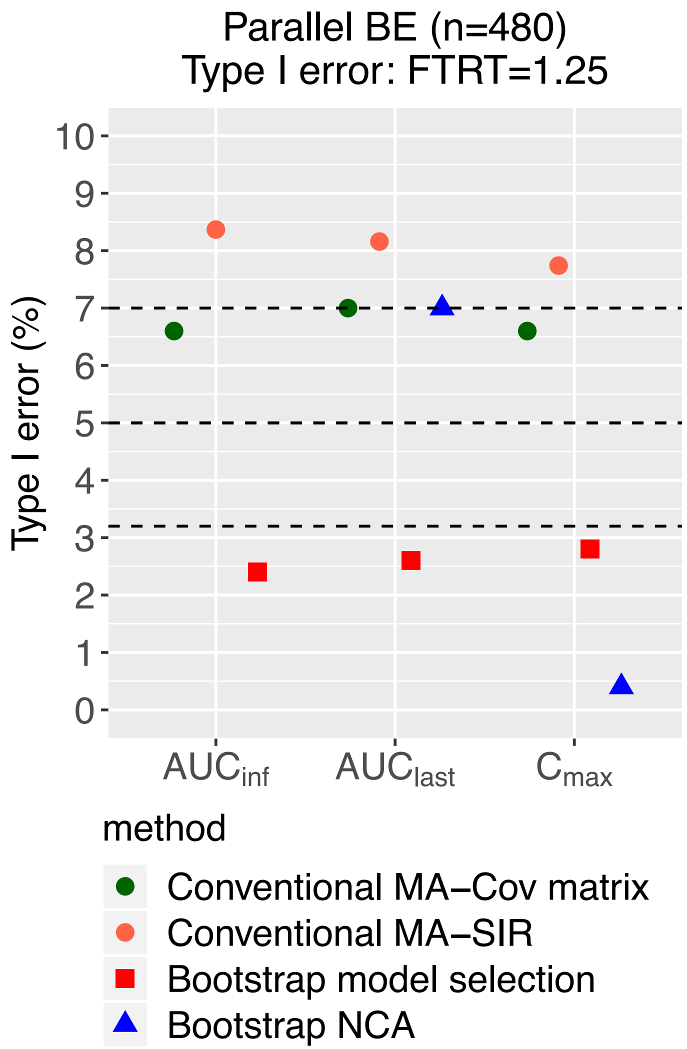


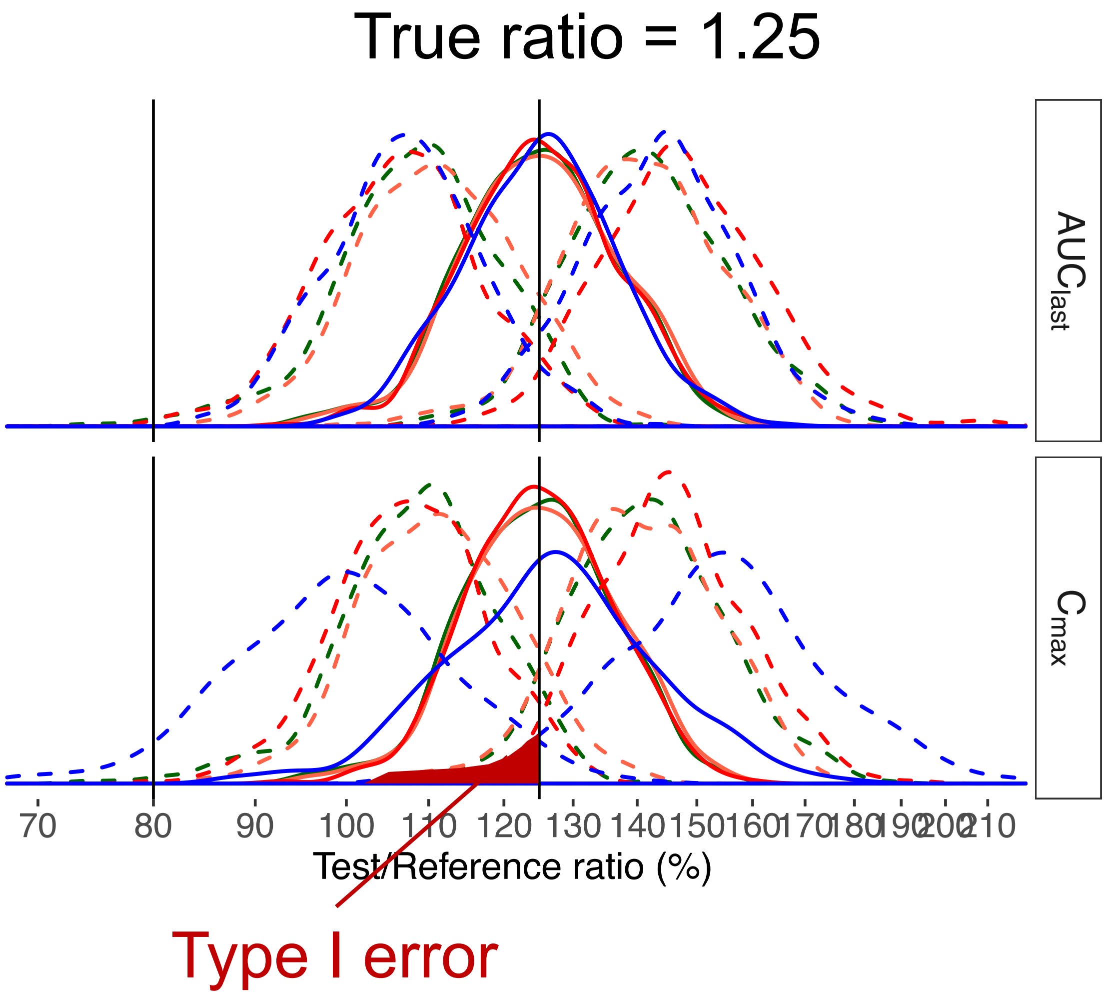
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
KATRT	x	x	x	x	x	x	x	x								
IIV-CL	x	x	x	x					x	x	x	x				
IIV-V	x				x				x				x			
IIV-KA		x				x				x				x		
IIV-F			x				x				x				x	
Estimated OMEGA number	2	2	2	1	1	1	1	0	2	2	2	1	1	1	1	0

Bootstrap Model Selection



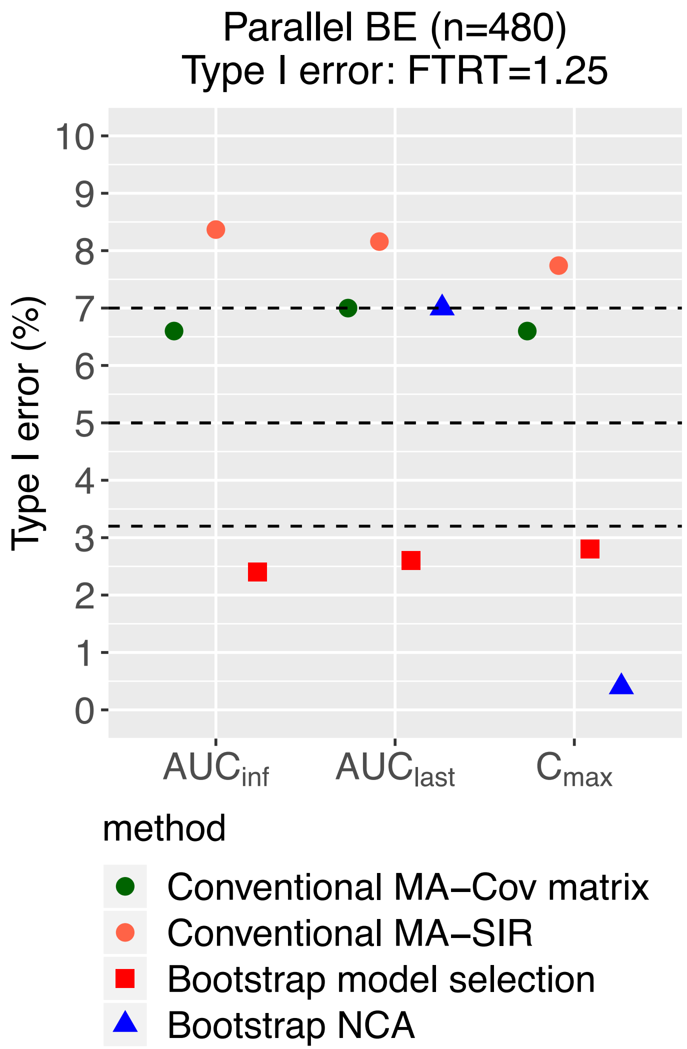
Parallel study: Type I error



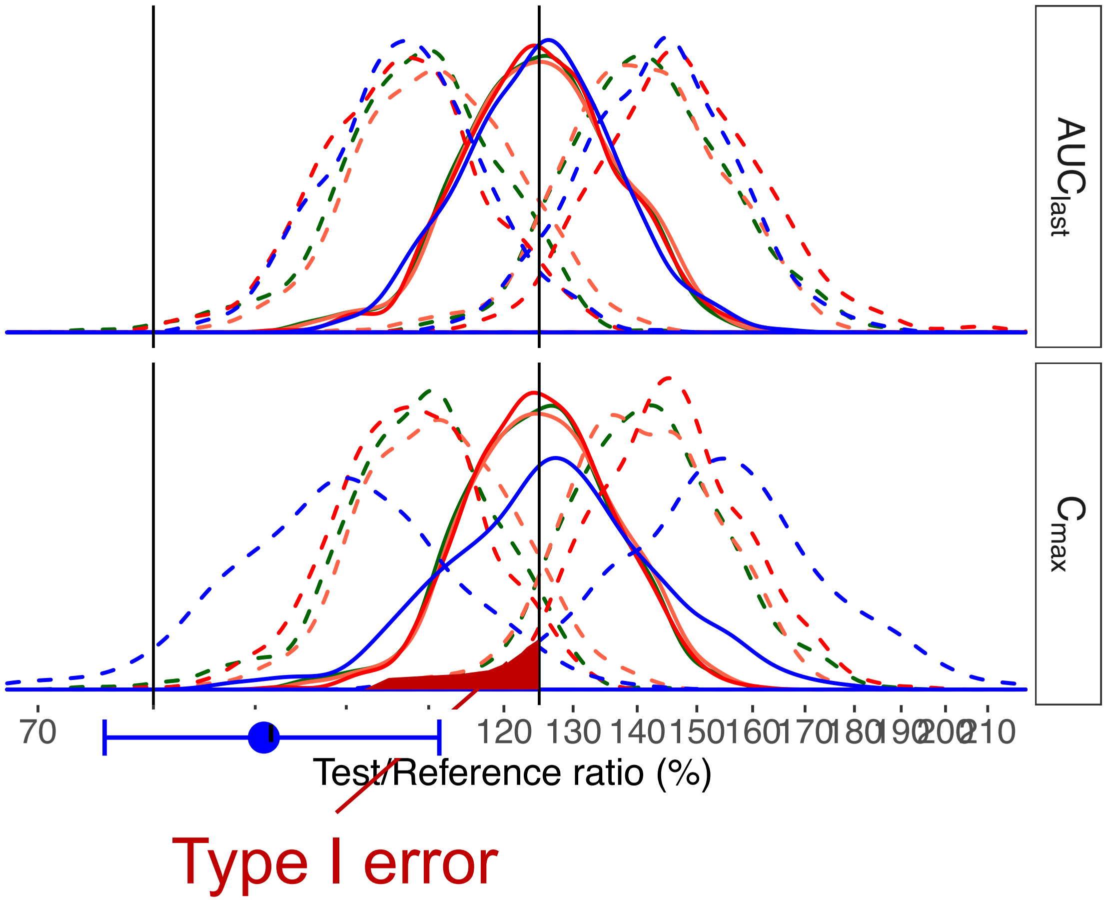


Type I error: Pr(conclude Ha: ratio <1.25 | true H0: ratio ≥ 1.25)

Parallel study: Type I error

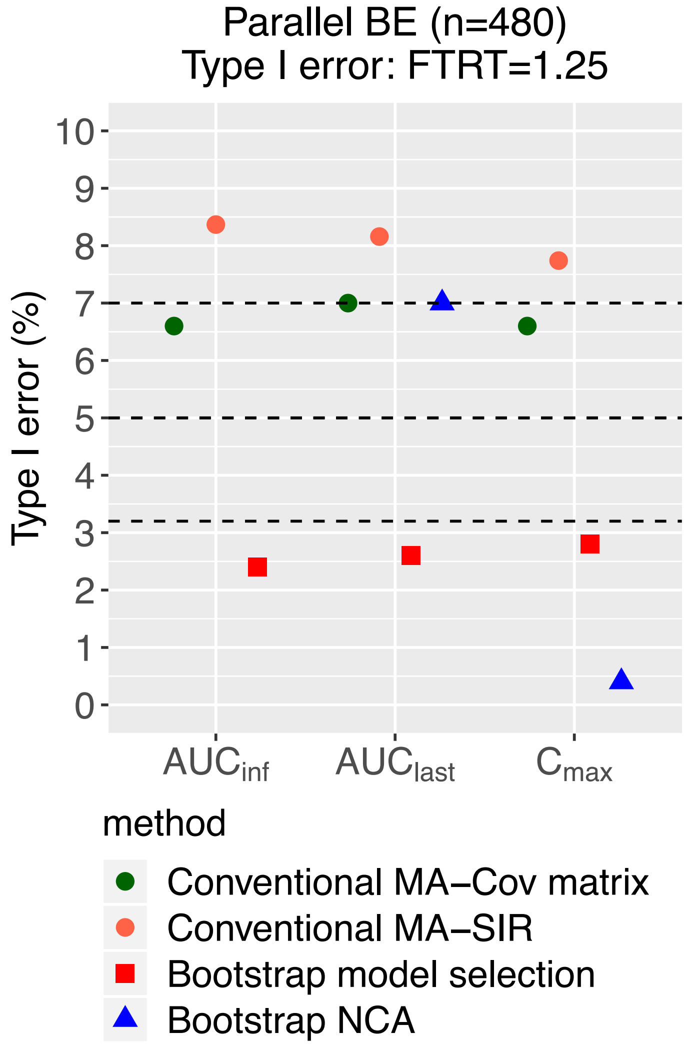


True ratio = 1.25

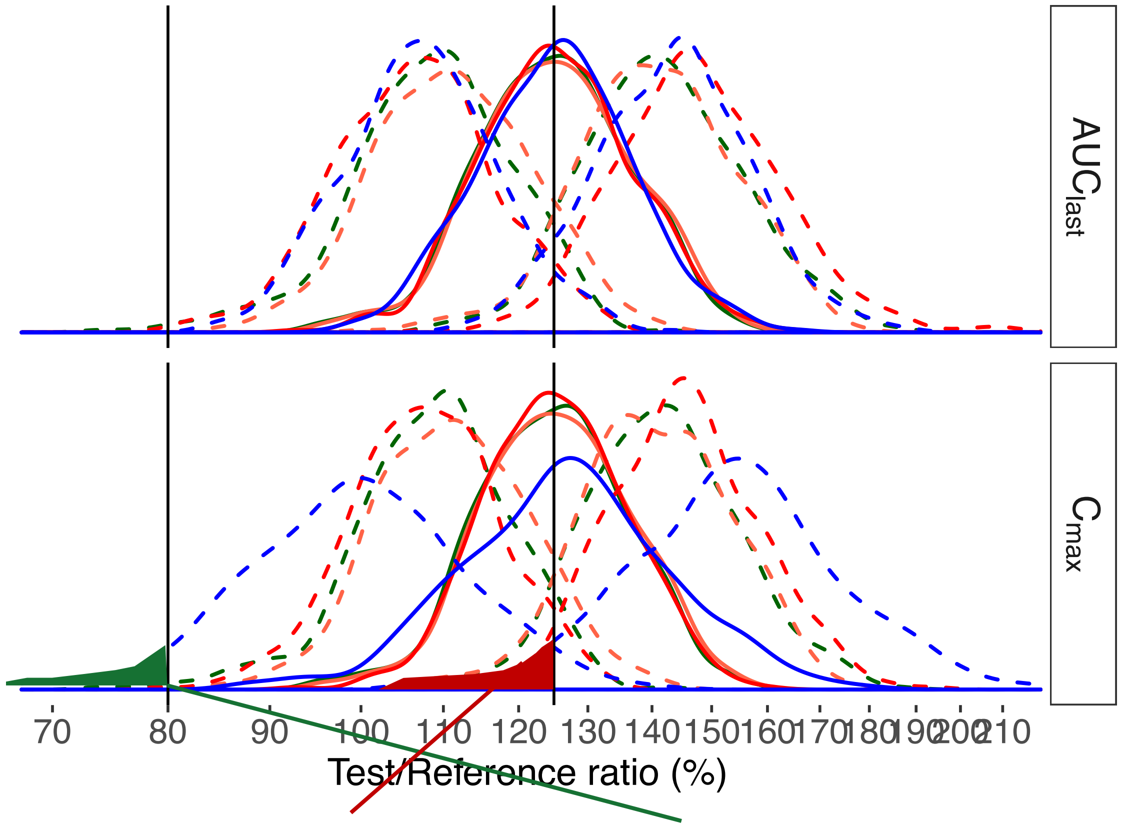


Type I error: Pr(conclude Ha: ratio <1.25 | true H0: ratio ≥ 1.25)

Parallel study: Type I error



True ratio = 1.25

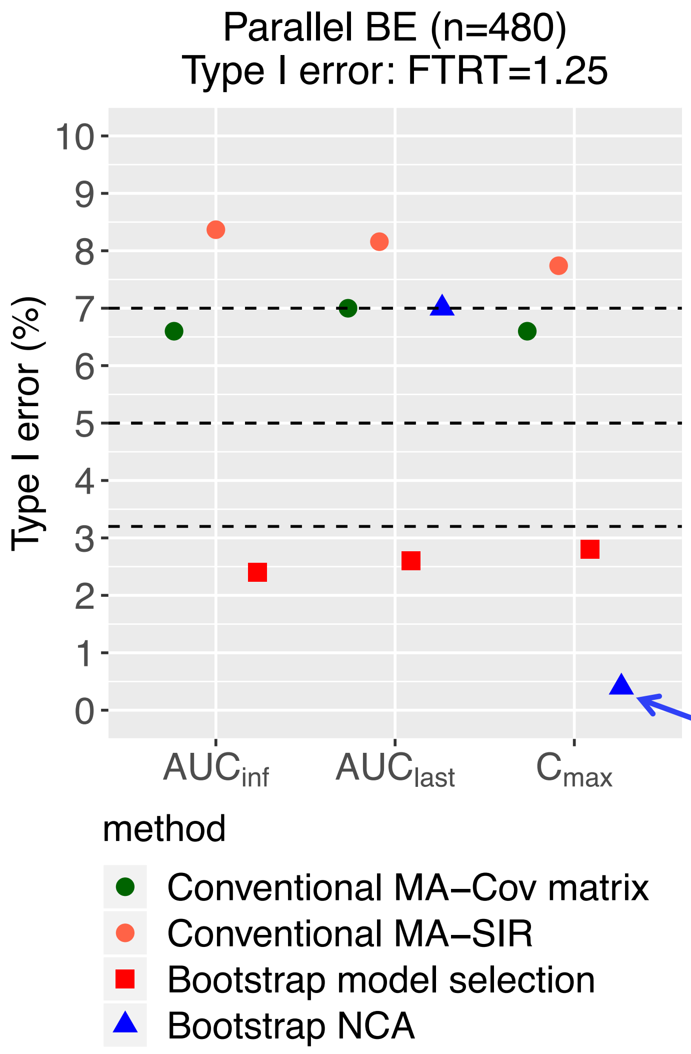


Type I error – Type II error

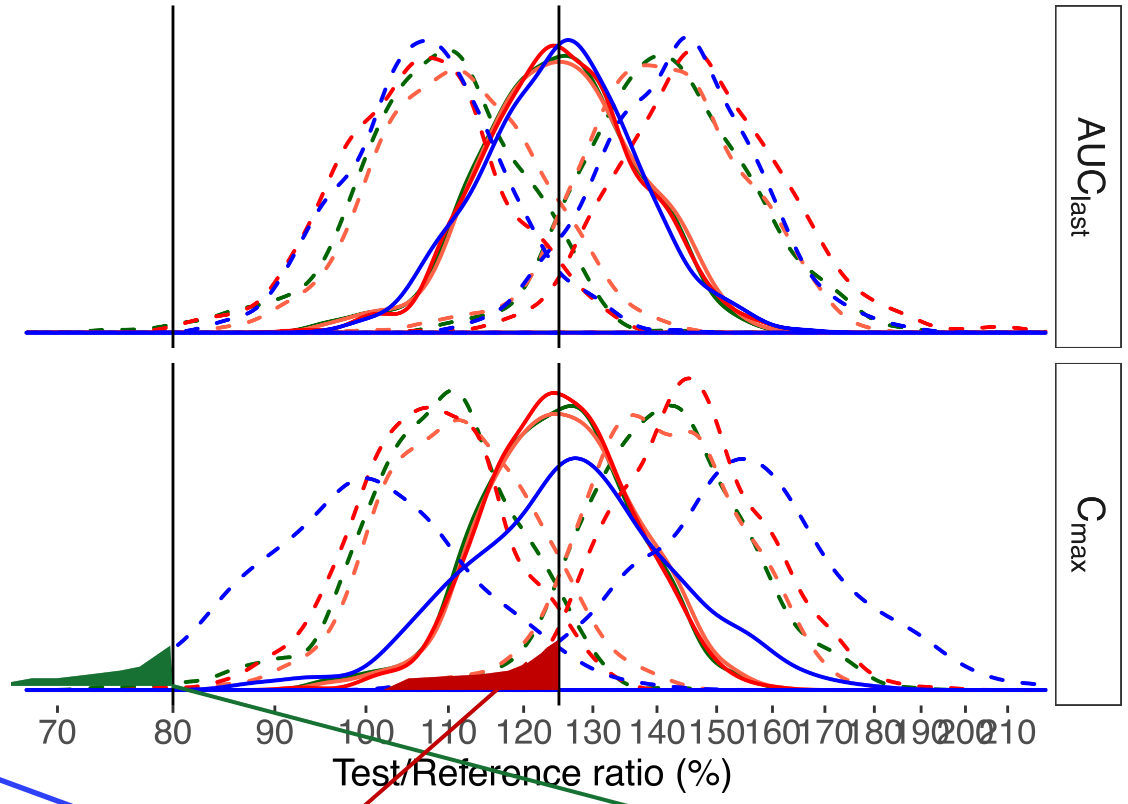
Type I error: Pr(conclude Ha: ratio <1.25 | true H0: ratio ≥ 1.25)

Type II error: Pr(conclude H0: ratio≤0.8 | true Ha: ratio>0.8)

Parallel study: Type I error



True ratio = 1.25

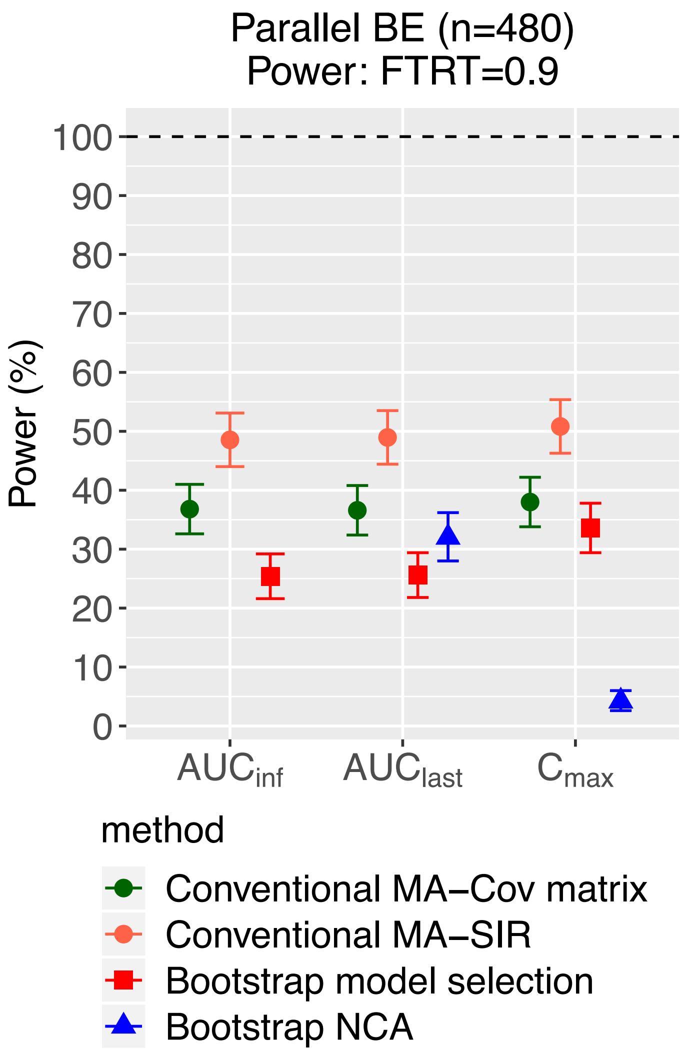


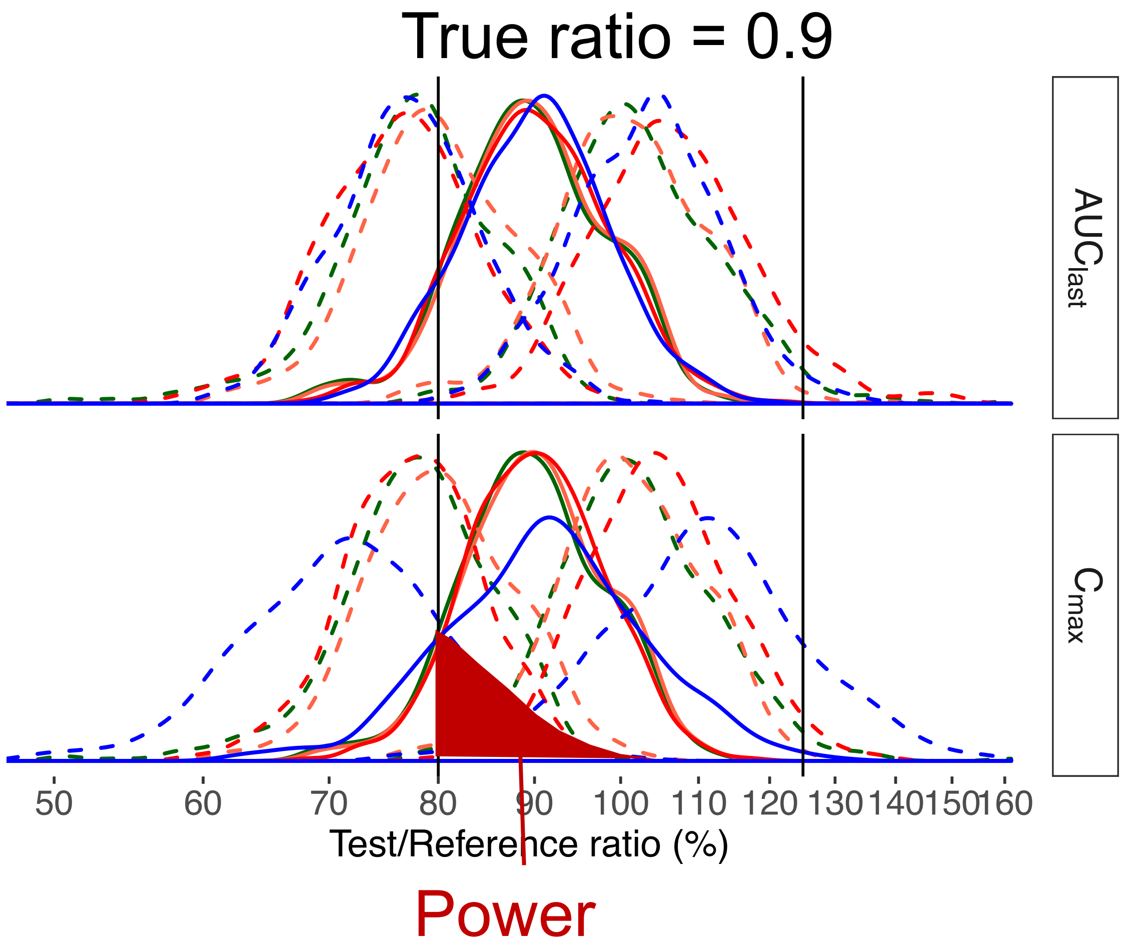
Type I error – Type II error

Type I error: Pr(conclude Ha: ratio <1.25 | true H0: ratio ≥ 1.25)

Type II error: Pr(conclude H0: ratio≤0.8 | true Ha: ratio>0.8)

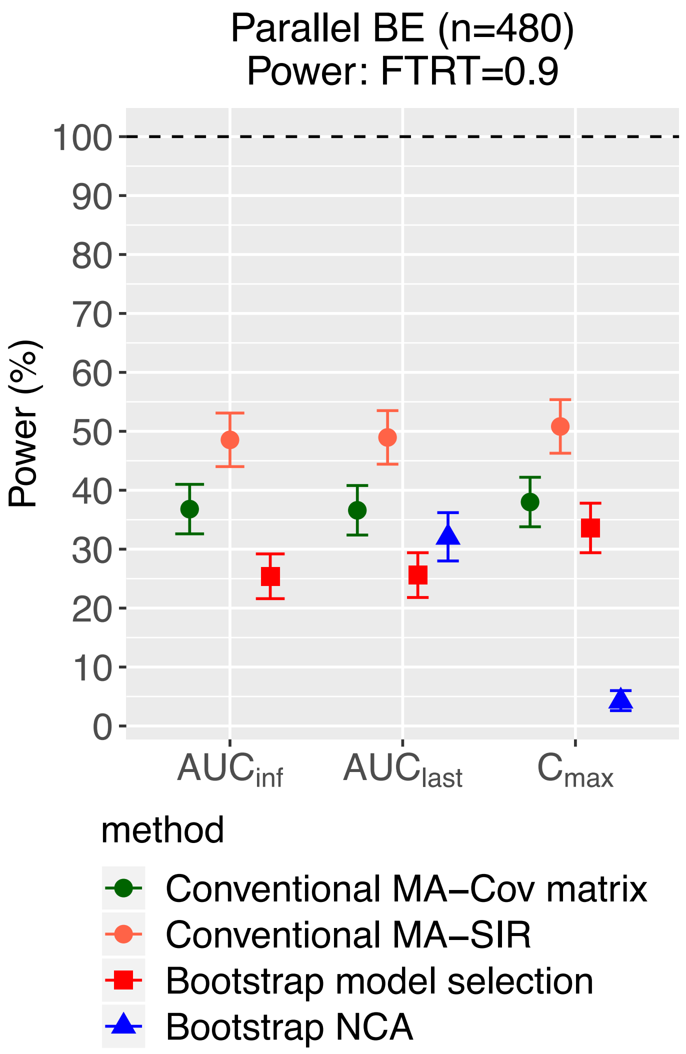
Parallel study: Power

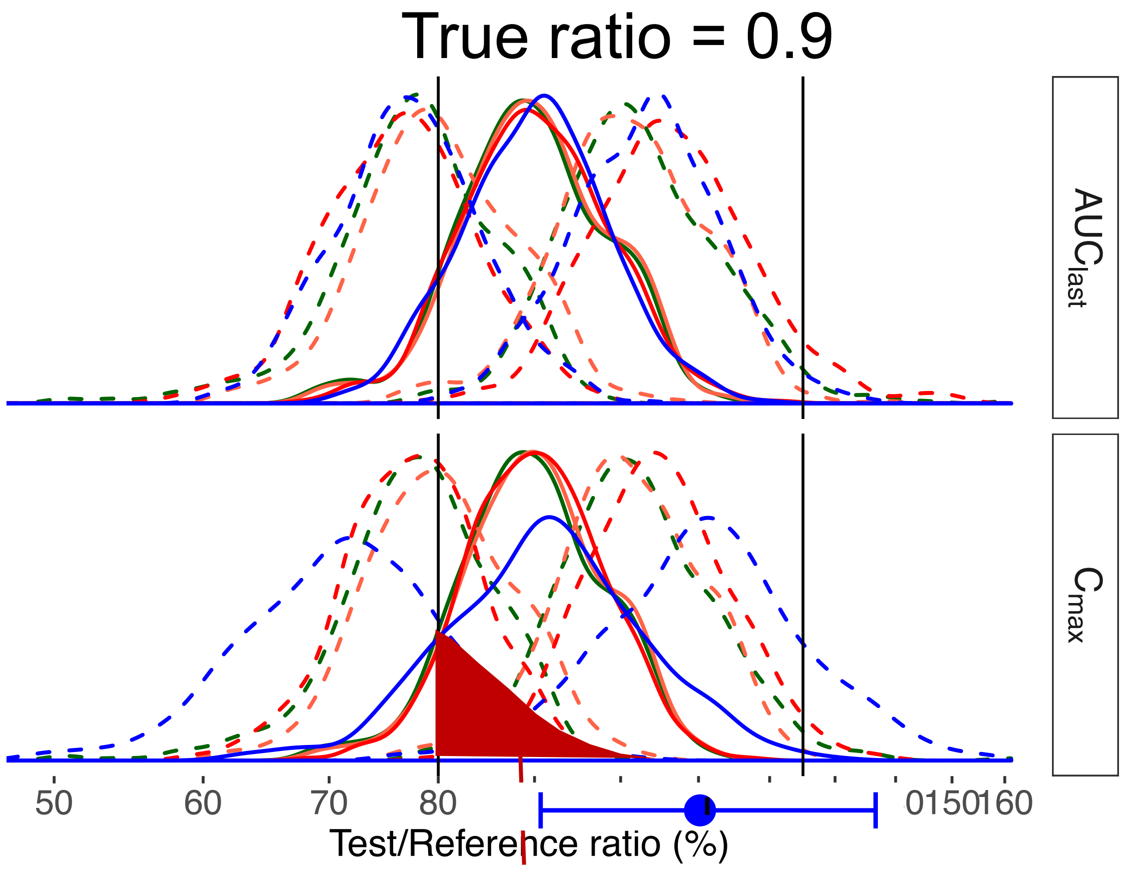




Power: Pr(conclude Ha: ratio>0.8 | true Ha: ratio>0.8)

Parallel study: Power

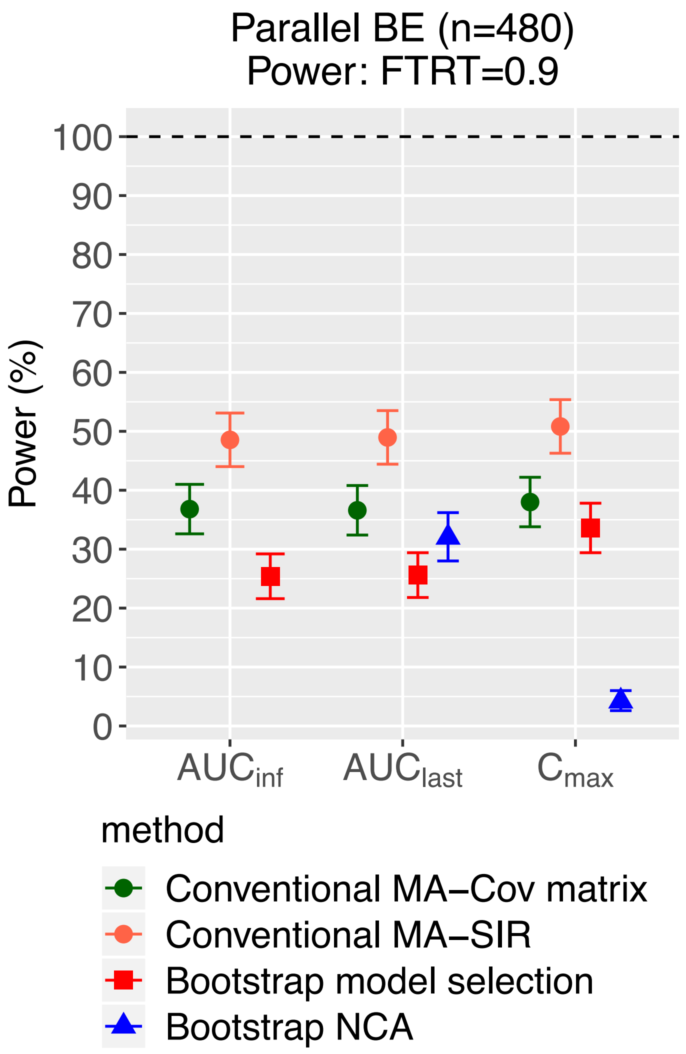


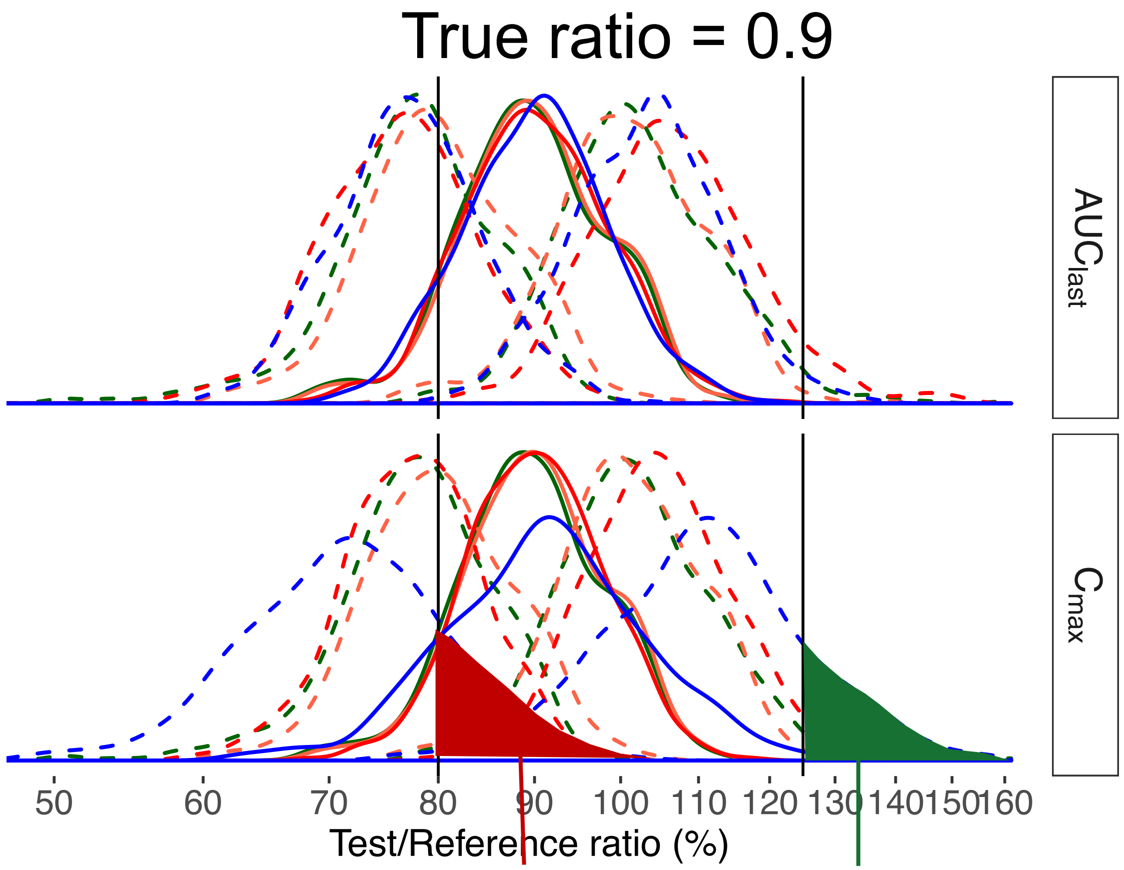


Power

Power: Pr(conclude Ha: ratio>0.8 | true Ha: ratio>0.8)

Parallel study: Power



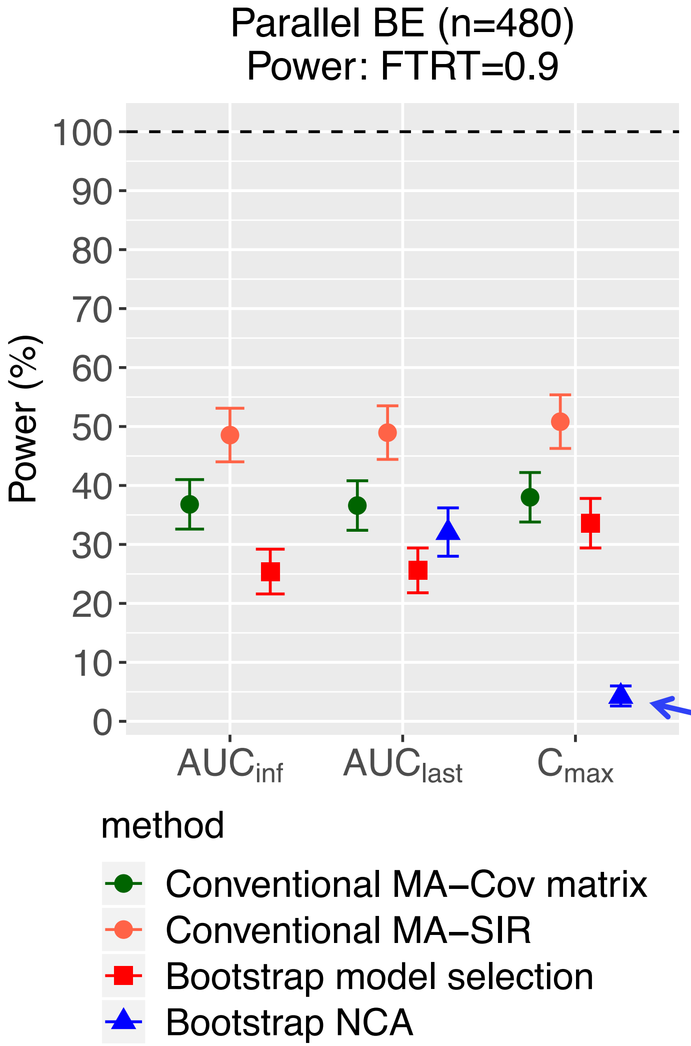


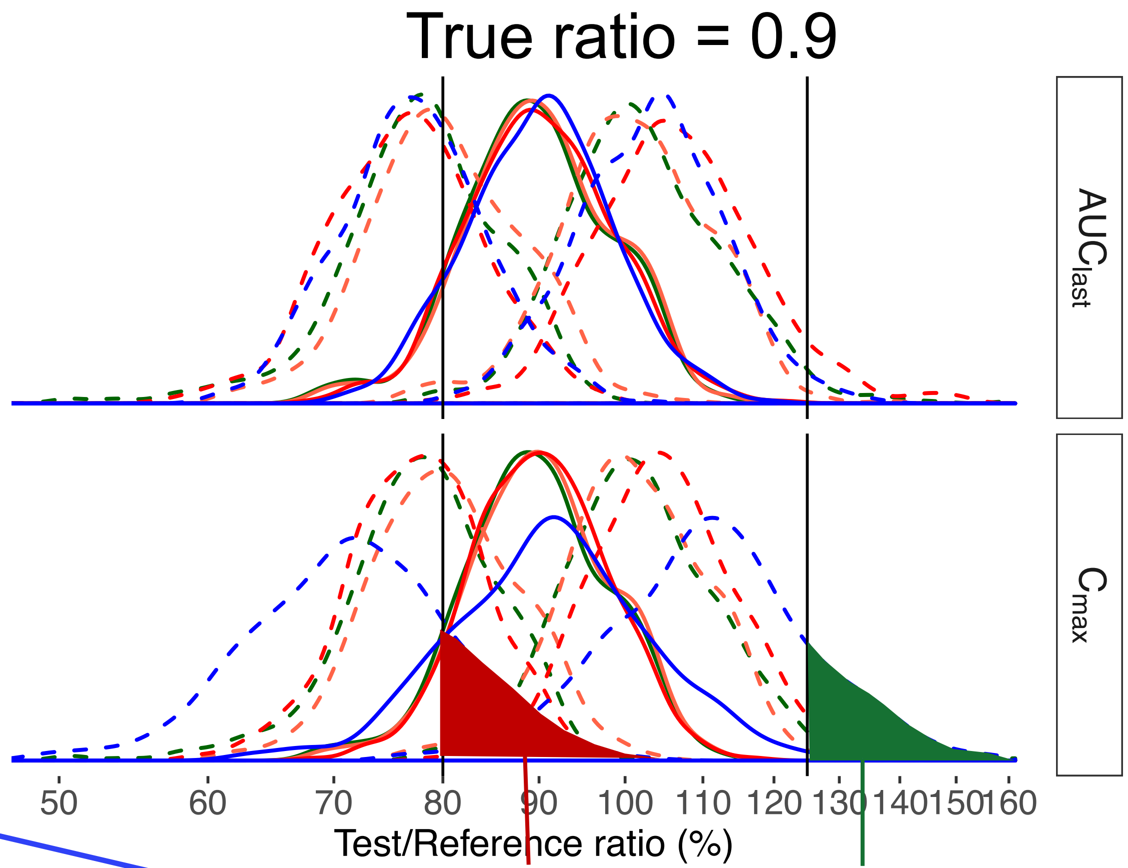
Power – Type II error

Power: Pr(conclude Ha: ratio>0.8 | true Ha: ratio>0.8)

Type II error: Pr(conclude H0: ratio ≥ 1.25 | true Ha: ratio <1.25)

Parallel study: Power





Power – Type II error

Power: Pr(conclude Ha: ratio>0.8 | true Ha: ratio>0.8)

Type II error: Pr(conclude H0: ratio ≥ 1.25 | true Ha: ratio <1.25)

Simulation study summary

Power:	**Crossover design** > parallel design
Power:	**Model-based methods** > Bootstrap NCA
Bootstrap NCA's power:	AUC_{last} > C_{max}
Performance (type I error):	**BMS** > Conventional MA

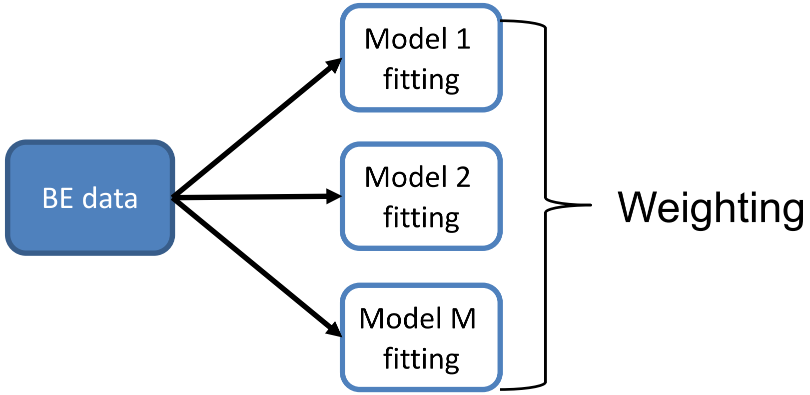
Conventional MA vs. BMS

Conventional MA

Weighting is based on original dataset

↓

Averaging over **model uncertainty**

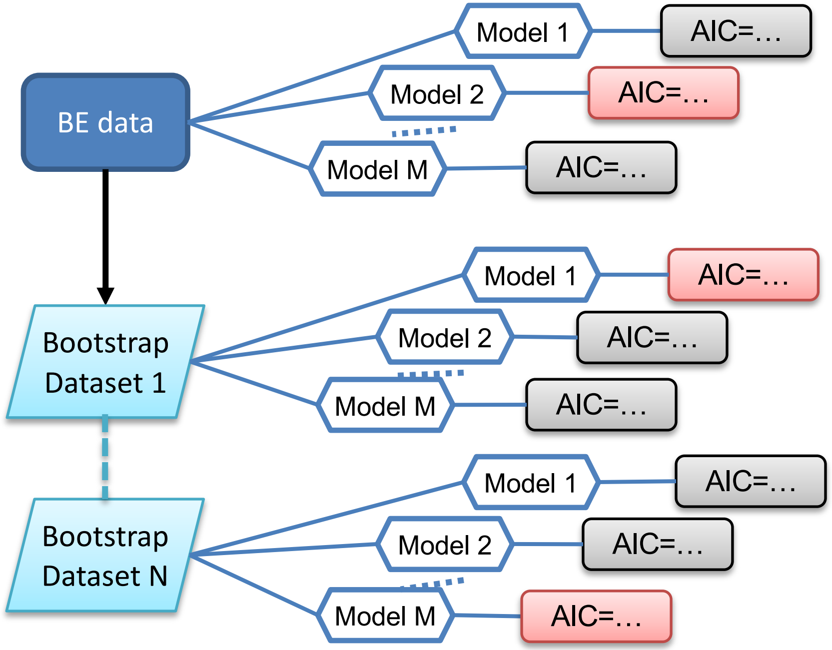


BMS

Weighting is based on bootstrapped datasets

↓

Averaging over
model uncertainty & sampling uncertainty



Acknowledgements

Funding from FDA

Contract No.: HHSF223201710015C

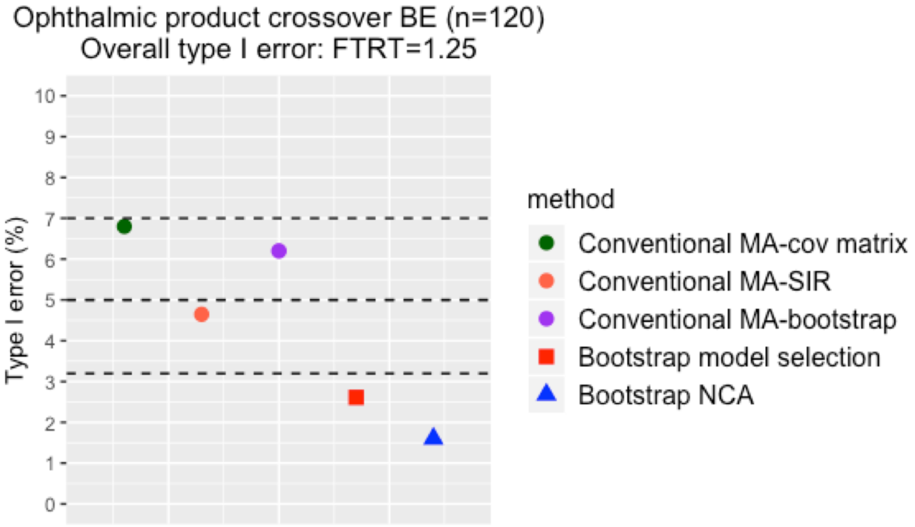
Colleagues at FDA:

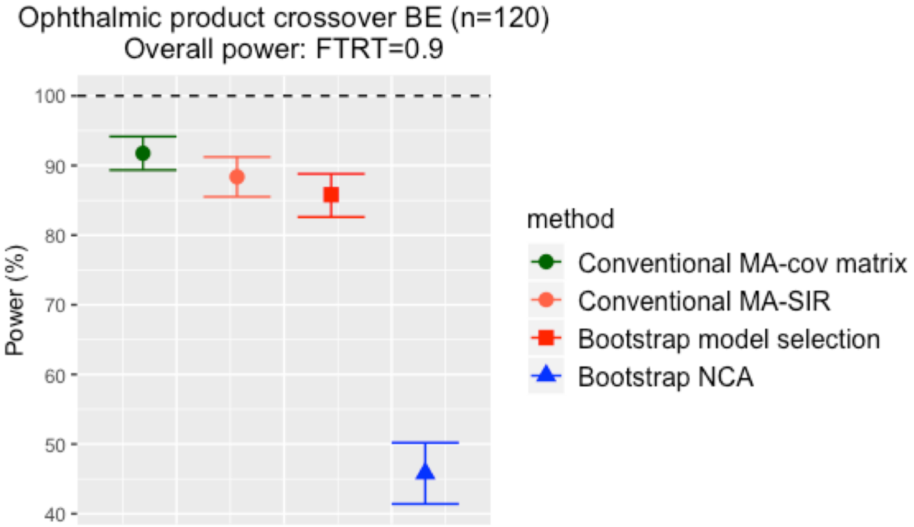
Liang Zhao
Lanyan (Lucy) Fang
Zhichuan (Matt) Li
Satish Sharan
Mark Donnelly

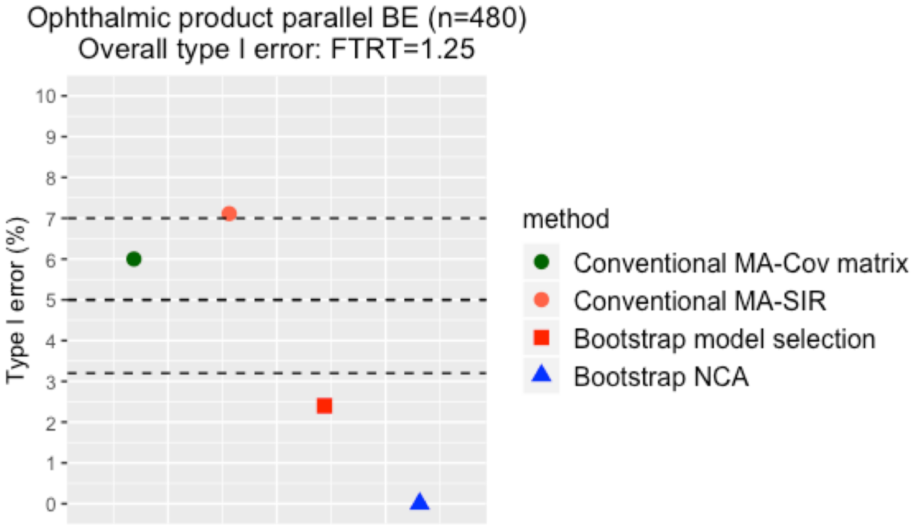
PM group, Uppsala University

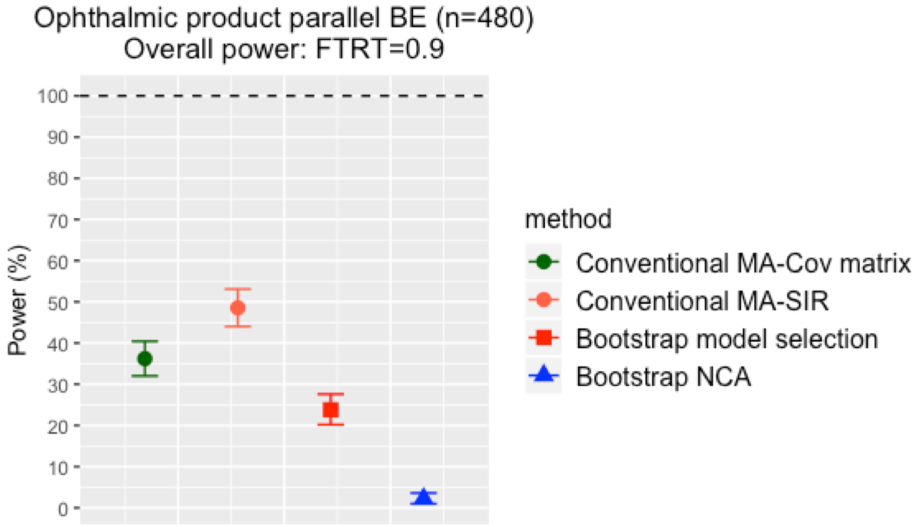
Swedish Pharmaceutical Society (travel funding)

Backup slides


Ophthalmic product crossover BE (n=120)
Overall type I error: FTRT=1.25
Type I error (%)
10
9
8
7
6
5
4
3
2
1
0
method
Conventional MA-cov matrix
Conventional MA-SIR
Conventional MA-bootstrap
Bootstrap model selection
Bootstrap NCA


Ophthalmic product crossover BE (n=120)
Overall power: FTRT=0.9
Power (%)
100
90
80
70
60
50
40
method
Conventional MA-cov matrix
Conventional MA-SIR
Bootstrap model selection
Bootstrap NCA


Ophthalmic product parallel BE (n=480)
Overall type I error: FTRT=1.25
Type I error (%)
10
9
8
7
6
5
4
3
2
1
0
method
Conventional MA-Cov matrix
Conventional MA-SIR
Bootstrap model selection
Bootstrap NCA


Ophthalmic product parallel BE (n=480)
Overall power: FTRT=0.9
Power (%)
100
90
80
70
60
50
40
30
20
10
0
method
Conventional MA-Cov matrix
Conventional MA-SIR
Bootstrap model selection
Bootstrap NCA