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Development and comparison of model-based bioequivalence analysis methods on sparse data

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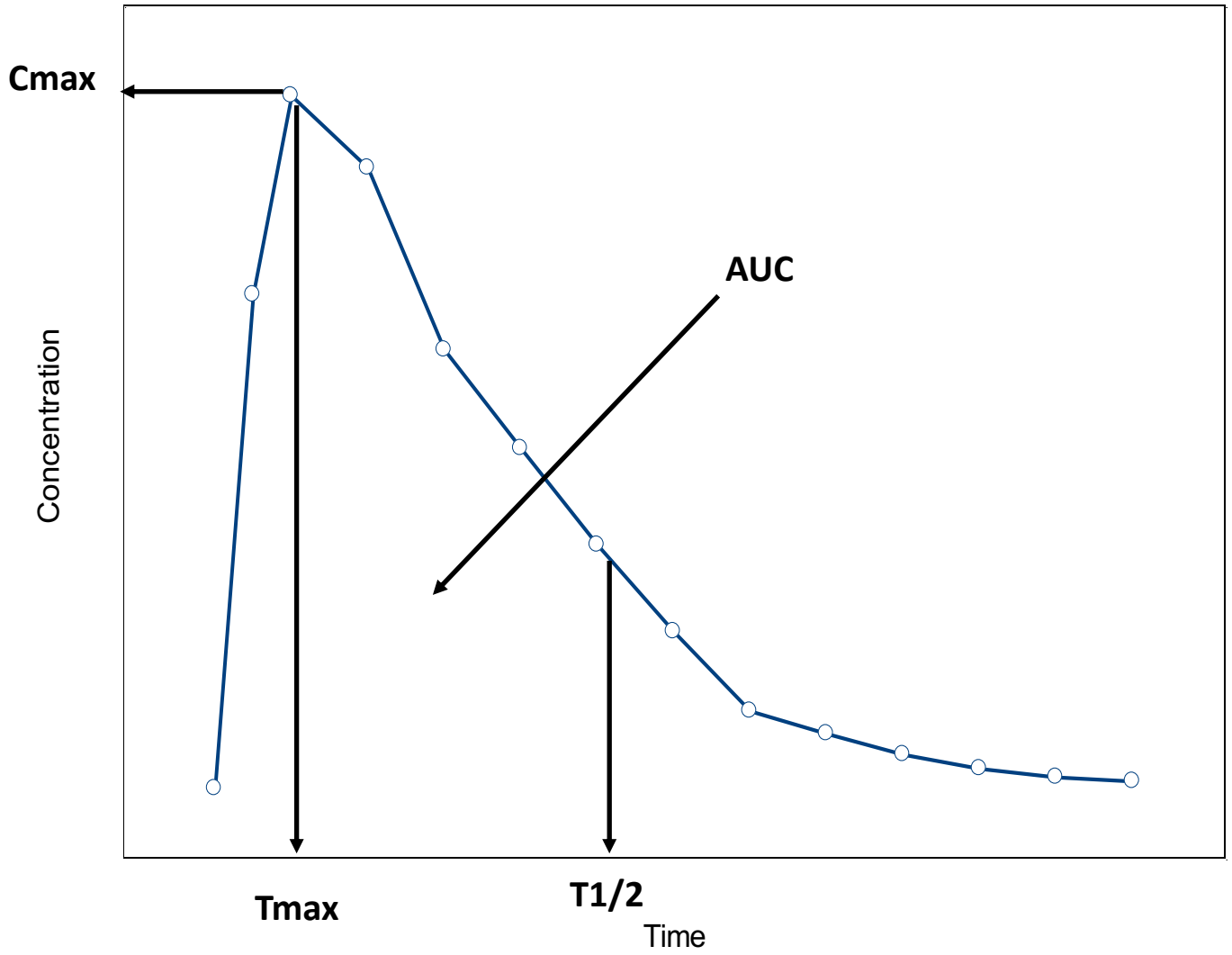
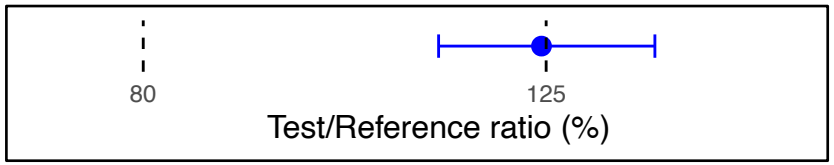
ACOP10, Florida
2019-10-22

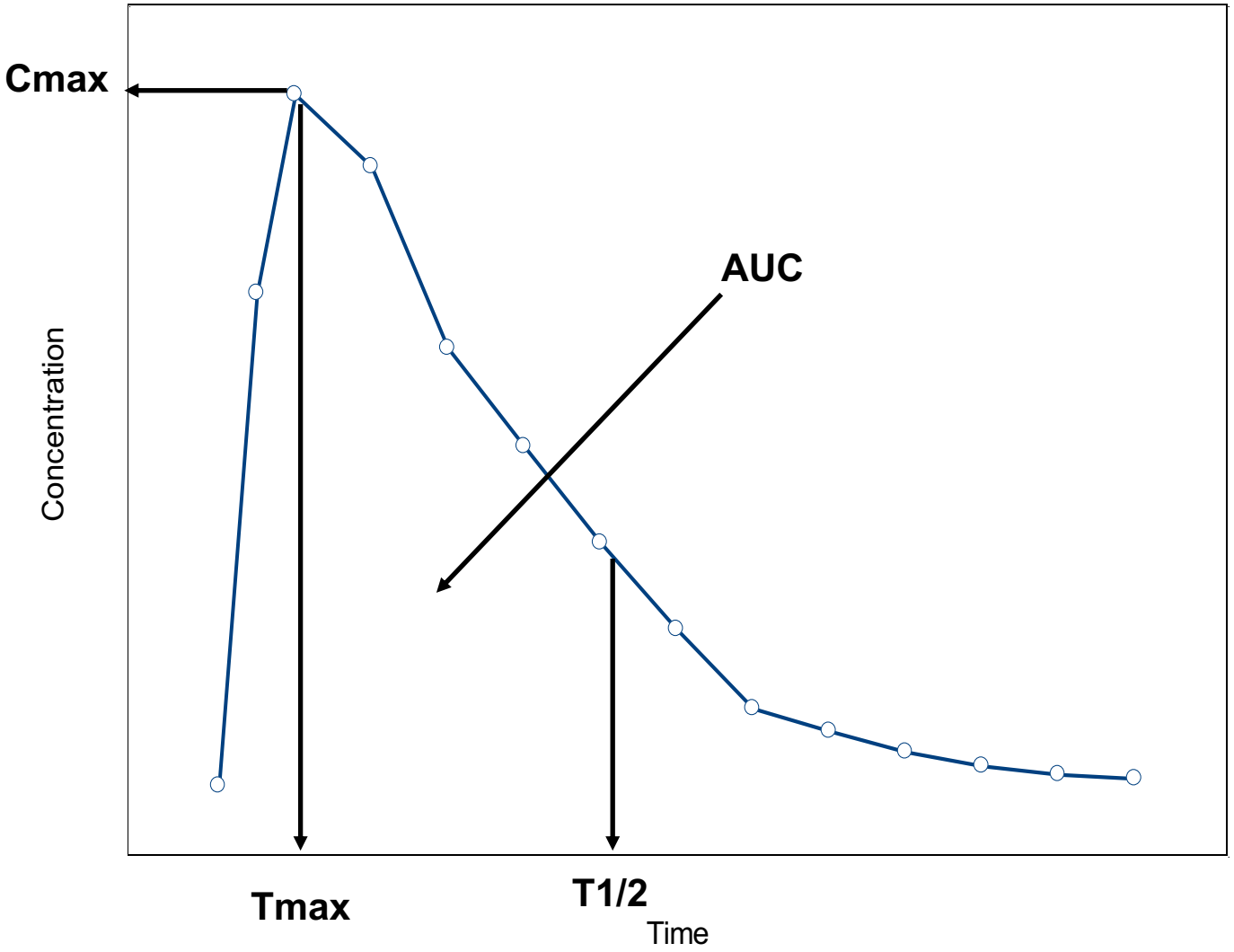
Standard bioequivalence (BE) studies



- BE determined by comparing the 90% confidence interval of the ratio (comparator vs. reference) of geometric means of secondary PK parameters with predetermined limits.



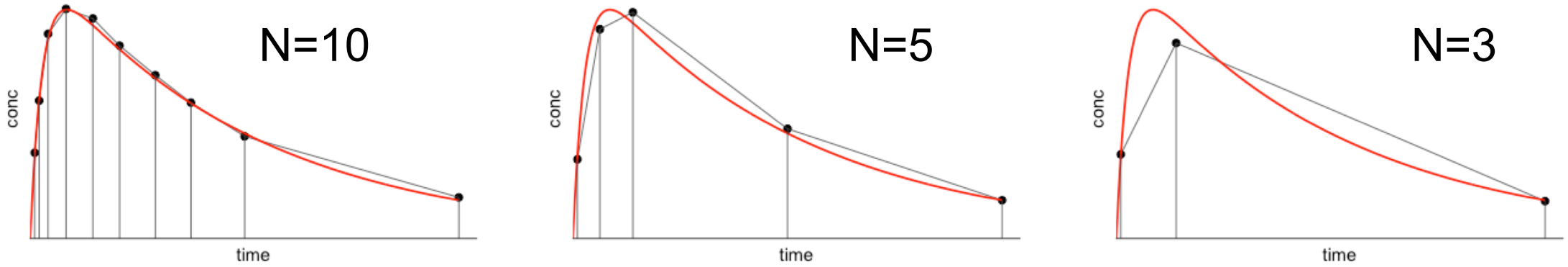
Potential problems with standard BE approaches: Problems with NCA calculations



- Assume equal weight for all observations
- Sensitivity to missing data
- Sensitivity to data below the limit of quantification
- Interpolation problems from the last observation to ∞
- Sparse data problems

NCA: non-compartment analysis

NCA for sparse data can be problematic: metric accuracy and power



C_{max}, AUC_{last}, AUC_{inf} accuracy decrease

Variance increase

Power decrease

NCA: non-compartment analysis

The goal of developed model-based BE method: nominal type I error, high power

Conclusion from analysis

Truth	H0 **Not BE**	Ha **BE**
H0 **Not BE**	Accurate	Type I error **α**
Ha **BE**	Type II error *β*	Accurate Power=1-*β*

Type I error **α**=0.05

High power

BE: bioequivalence

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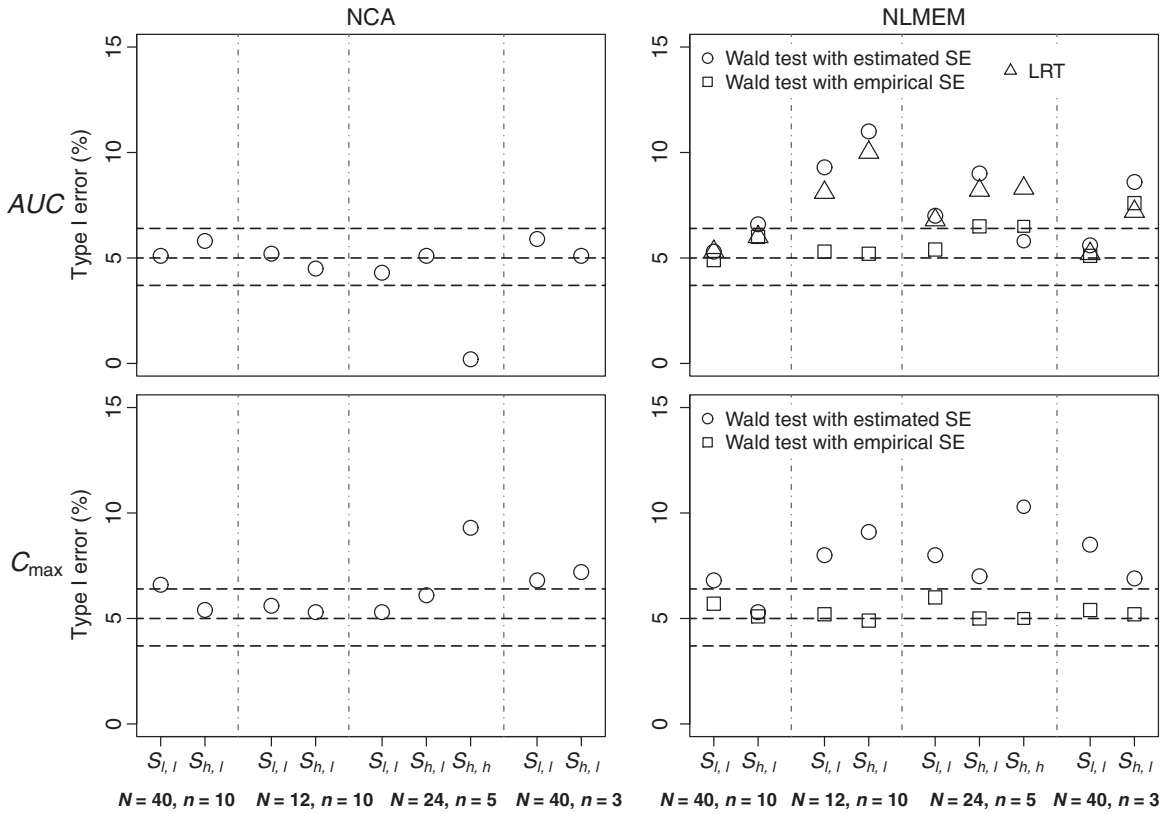

Figure 4. Global type I error of the bioequivalence tests performed on the treatment effect of AUC (top) and C_{max} (bottom) from noncompartmental analysis (NCA) (right) and nonlinear mixed effects model (NLMEM) (left) estimates. We perform the Wald tests based on NCA and NLMEM estimates on both parameters; we per-

Statistics in Medicine

Research Article

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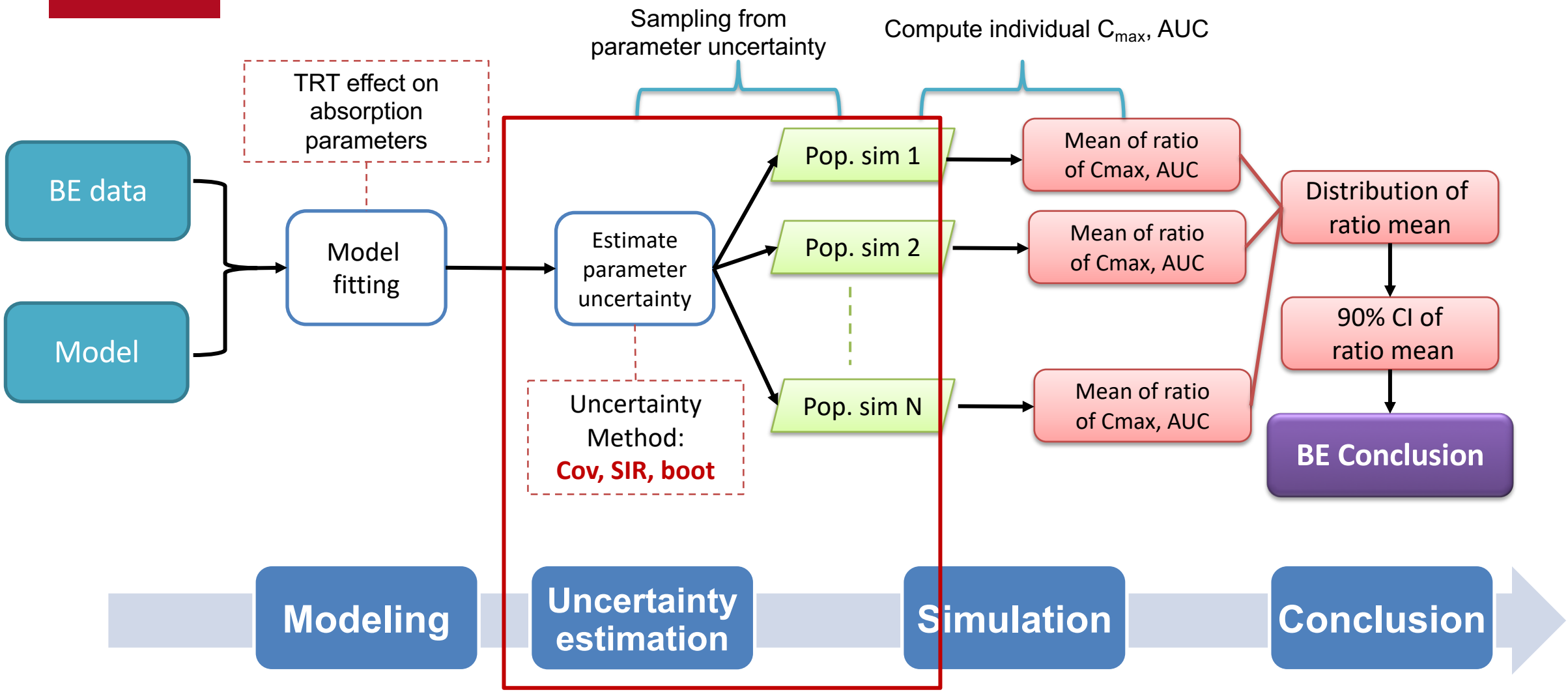
Model-based analyses of bioequivalence crossover trials using the stochastic approximation expectation maximisation algorithm

Anne Dubois,[a*†] Marc Lavielle,[b] Sandro Gsteiger,[c] Etienne Pigeolet[c] and France Mentré[a]

Our developed model-based BE method



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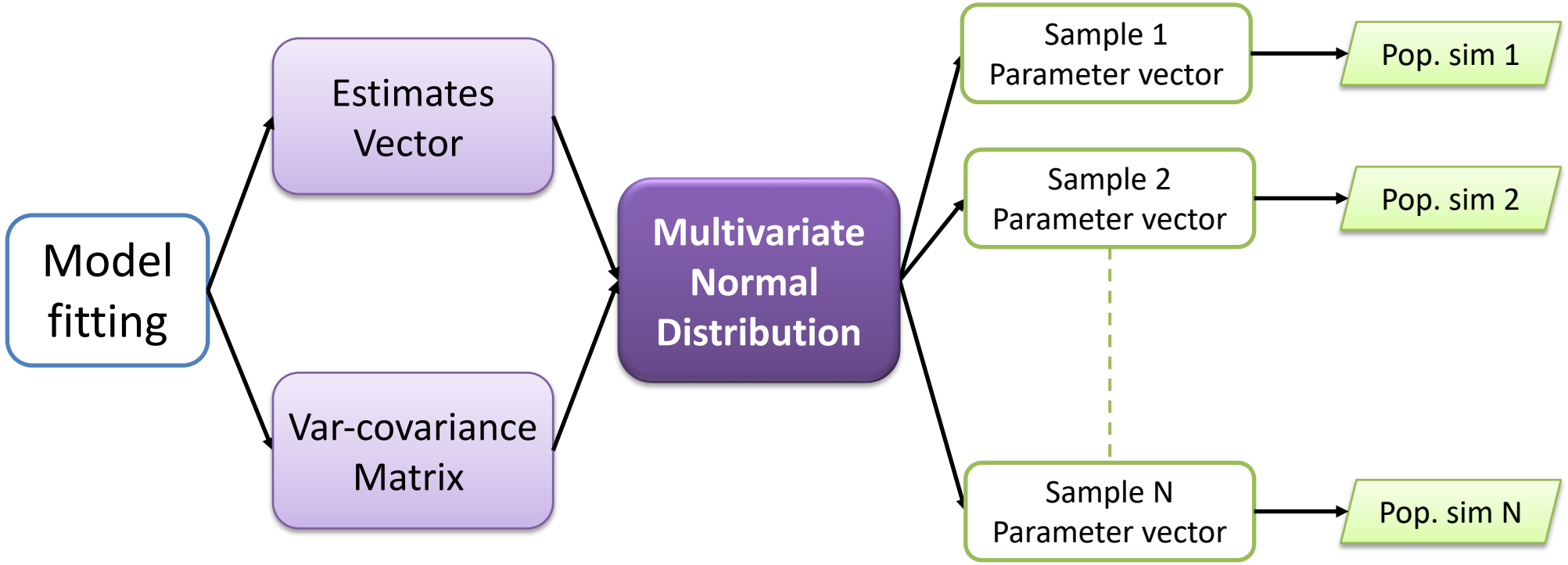
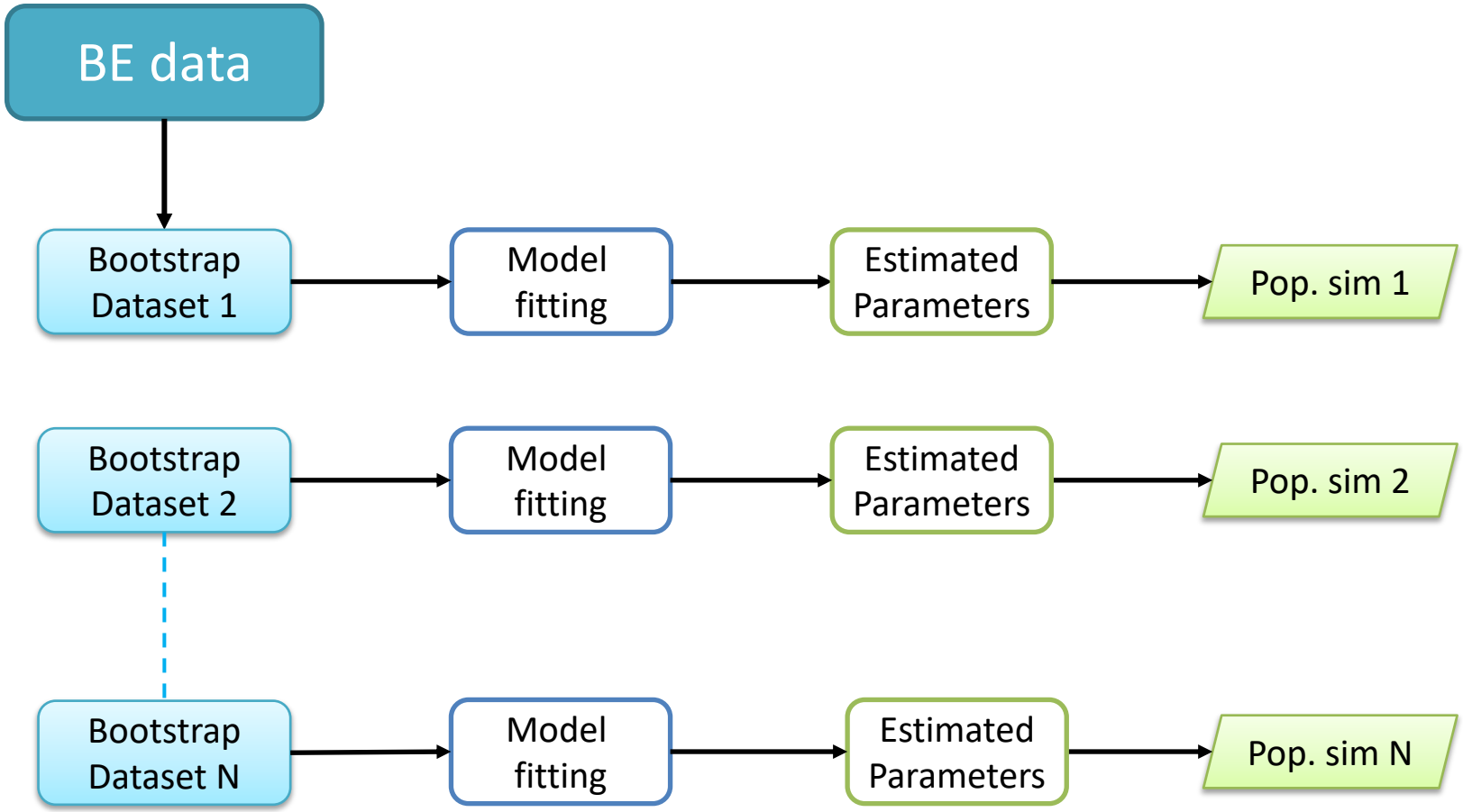
Uncertainty method: Covariance matrix



Uncertainty method: Bootstrap



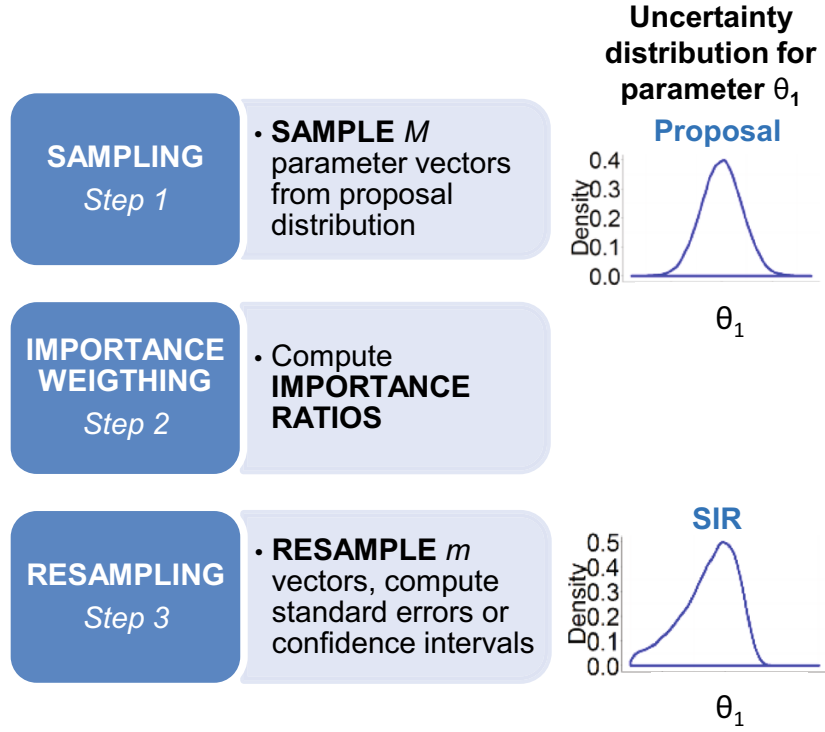
Sampling importance re-sampling (SIR) implemented in NONMEM and PsN

J Pharmacokinet Pharmacodyn (2016) 43:583–596
DOI 10.1007/s10928-016-9487-8

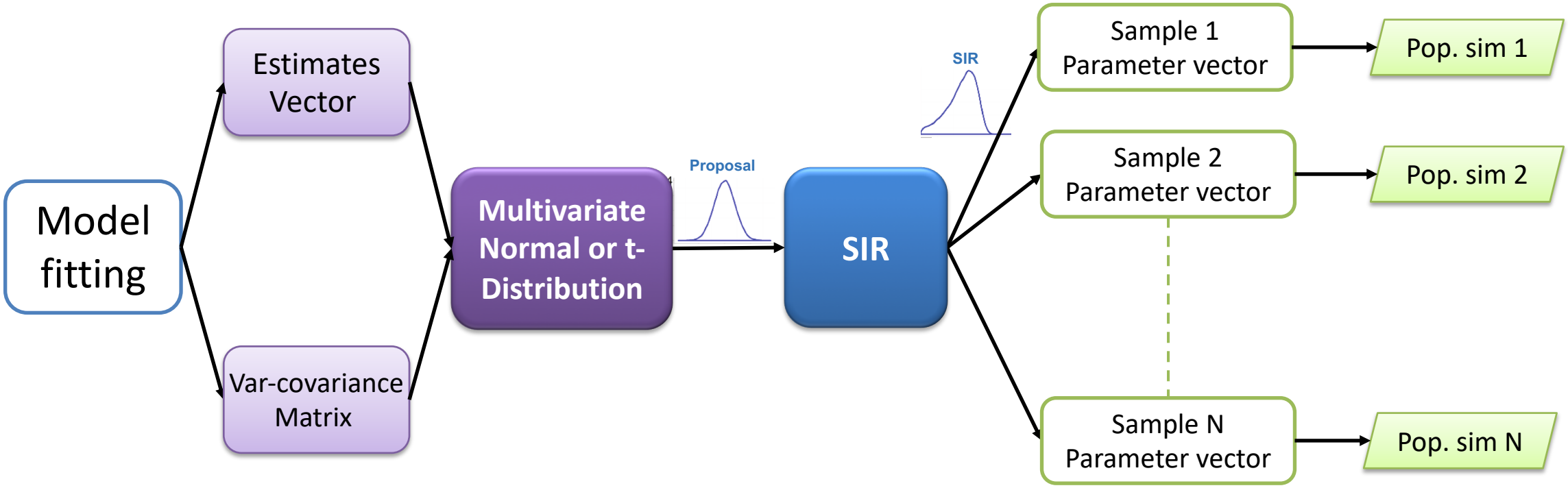
ORIGINAL PAPER

Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling

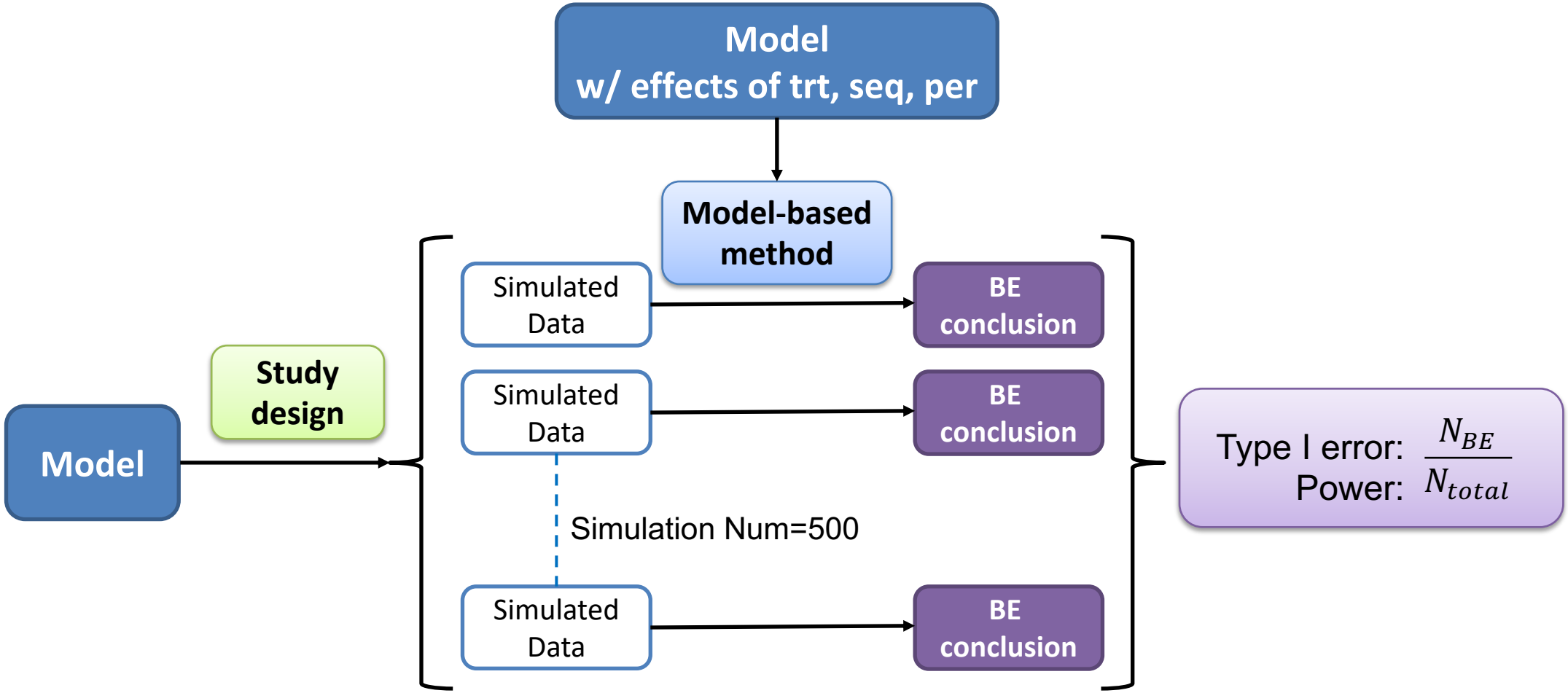
Anne-Gaëlle Dosne[1] · Martin Bergstrand[1] · Kajsa Harling[1] · Mats O. Karlsson[1]



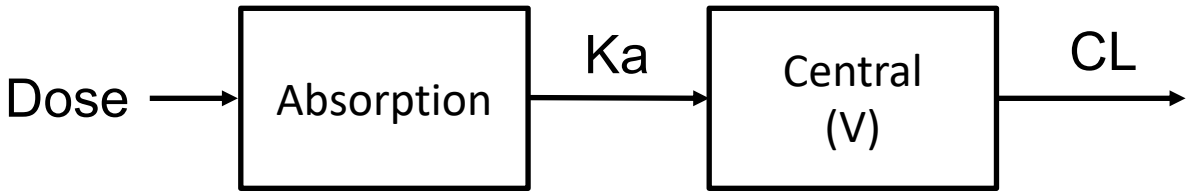
Uncertainty method: SIR

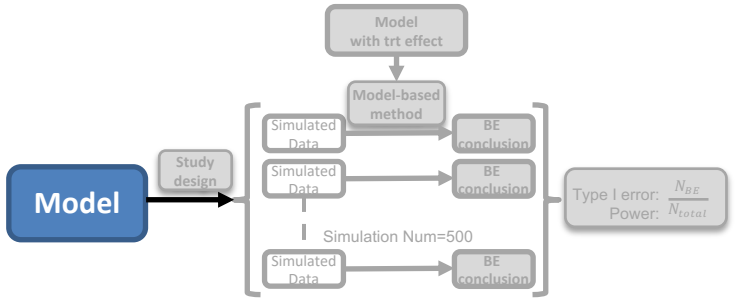


Simulation flowchart



Model used to generate simulated data





$$CL = 40.36 \times e^{\eta_{CL-IIV}}$$

$$V = 480 \times e^{\eta_{V-IIV}}$$

$$Ka = 1.48 \times e^{\eta_{Ka-IIV}}$$

$$F = 1 \times e^{\eta_{F-IOV}} \times \boldsymbol{FTRT}$$

Proportional residual error with σ^2=0.01

Variance Level	ω_{CL-IIV}	ω_{V-IIV}	ω_{ka-IIV}	ω_{F-IOV}
Low	0.2	0.1	0.2	0.1
High	0.5	0.5	0.5	0.15

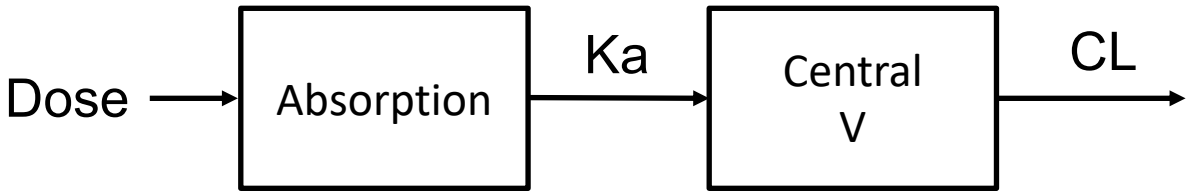
FTRT=0.8 or 1.25 → Type I error

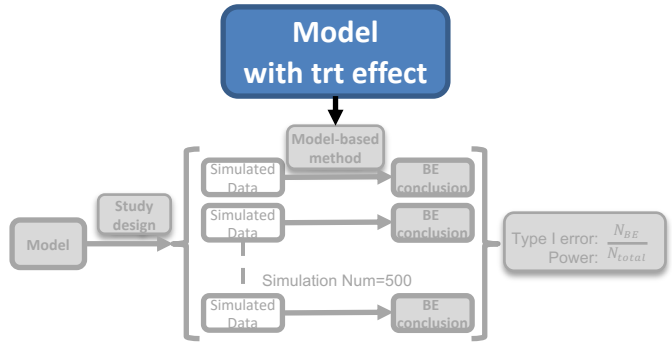
FTRT=0.9 → Power

FTRT: test/ref ratio in F (i.e. treatment effect)

Based on: Dubois *et al.*, *Stat. Med.*, 2010.

Model used for BE analysis





$$CL = TVCL \times e^{\eta_{CL-IIV}}$$

$$V = TVV \times e^{\eta_{V-IIV}}$$

$$\text{Ka} = TVKa \times e^{\eta_{Ka-IIV}} \times KaTRT \times KaSEQ \times KaPER$$

$$\text{F} = 1 \times e^{\eta_{F-IOV}} \times FTRT \times FSEQ \times FPER$$

Proportional residual error

KaTRT: treatment effect on Ka (test/ref)
KaSEQ: sequence effect on Ka
KaPER: period effect on Ka

FTRT: treatment effect on in F (test/ref)
FSEQ: sequence effect on F
FPER: period effect on F

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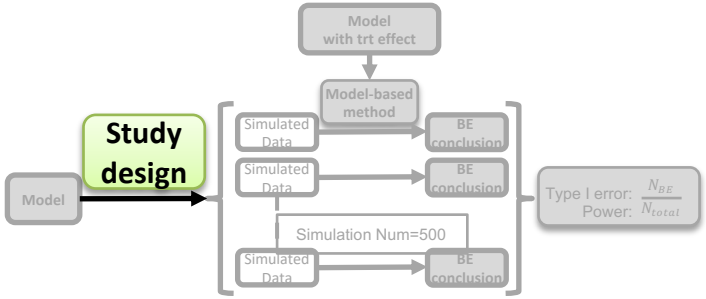
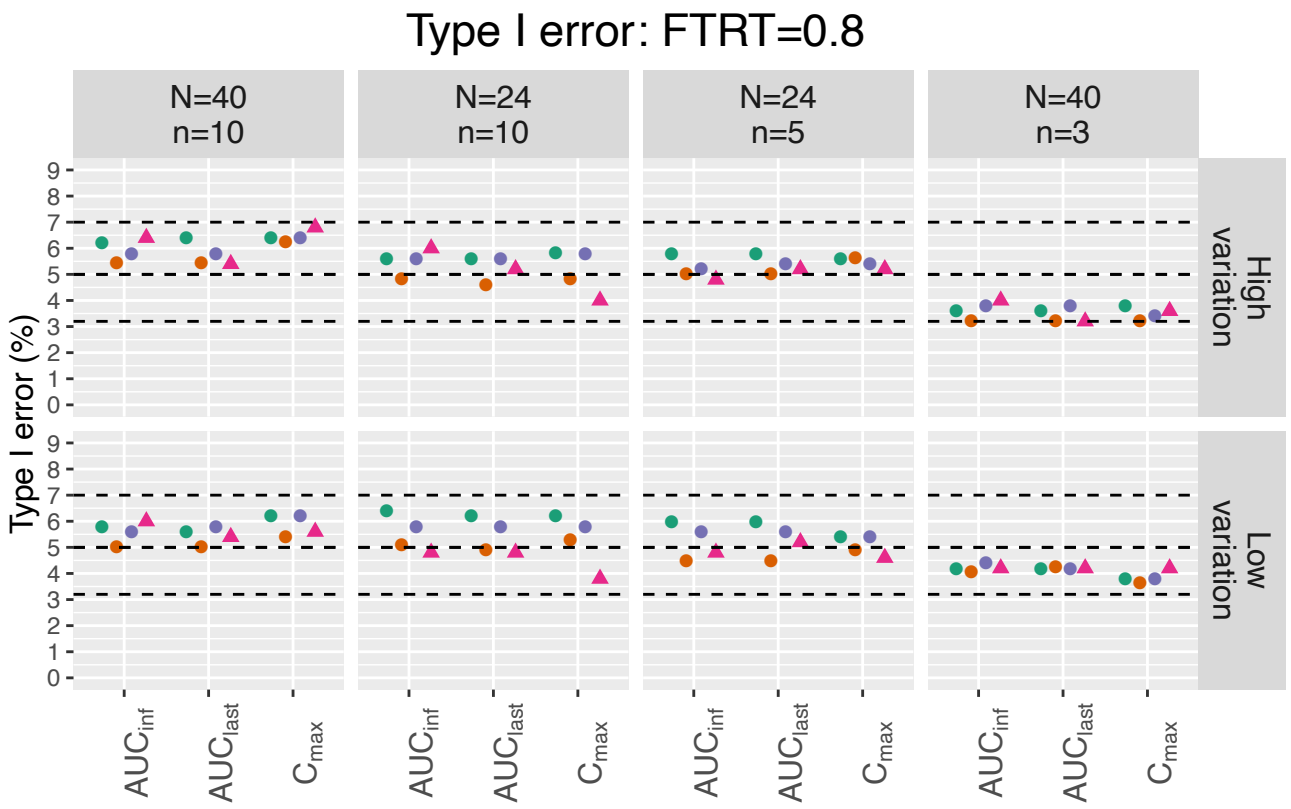
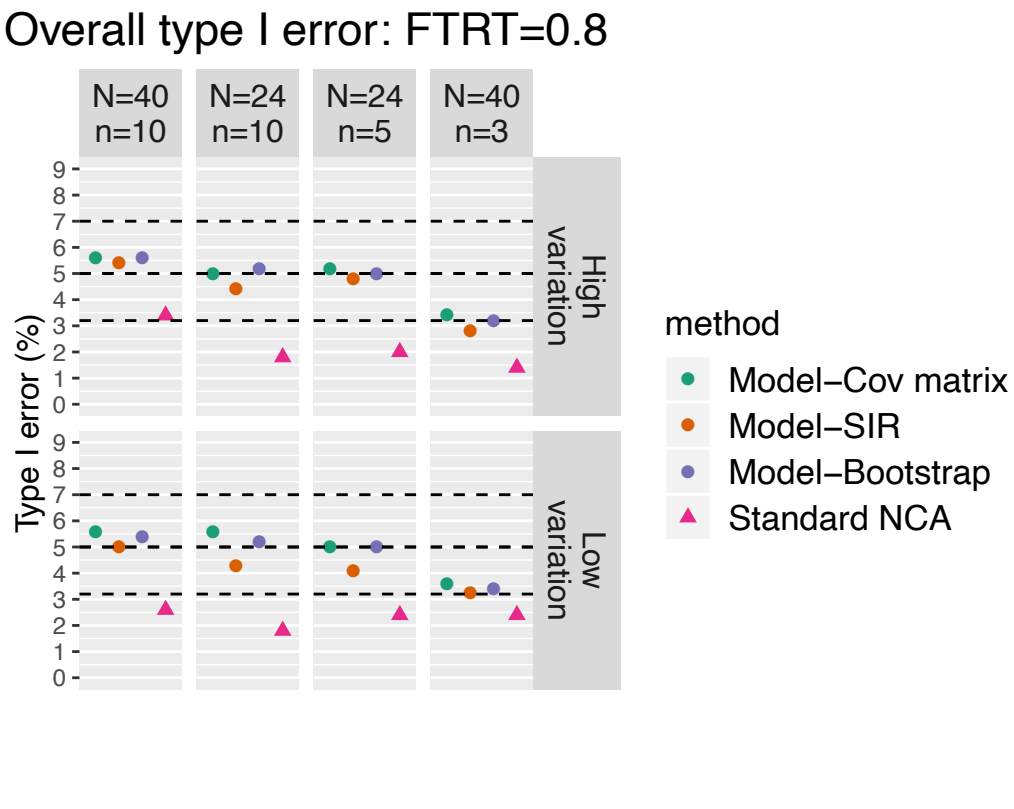
Study design: 2-period crossover study



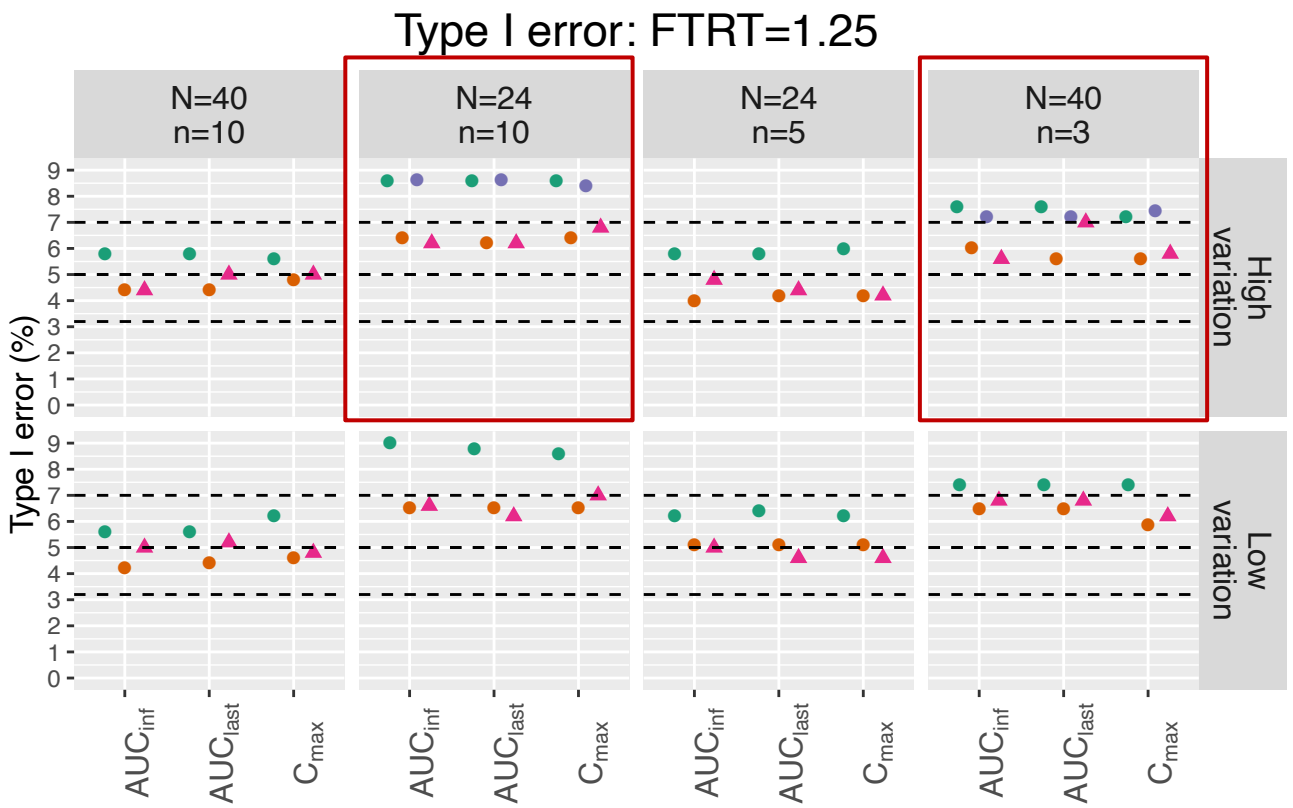
Design	Subject No	Sampling No	Sampling times
1	40	10	0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24
2	24	10	0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24
3	24	5	0.25, 1.5, 3.35, 12, 24
4	40	3	0.25, 3.35, 24

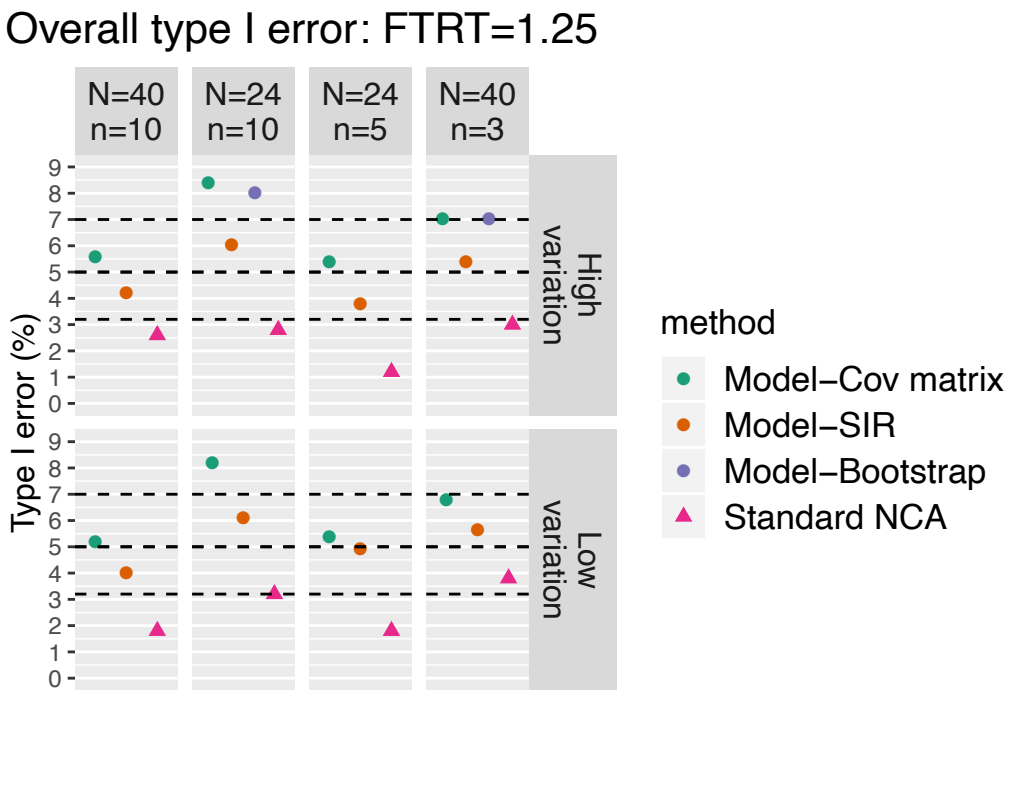
Simulation study: type I error at FTRT=0.8



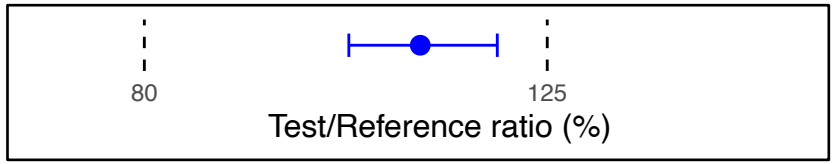


Simulation study type I error at FTRT=1.25
SIR had controlled type I error



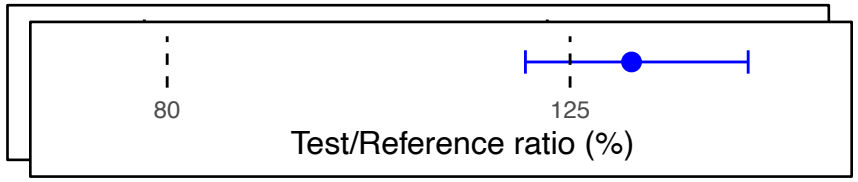


Type I error in the simulation study



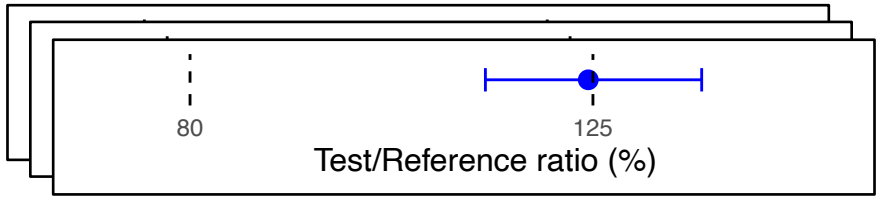
Simulation Num=500

Type I error in the simulation study



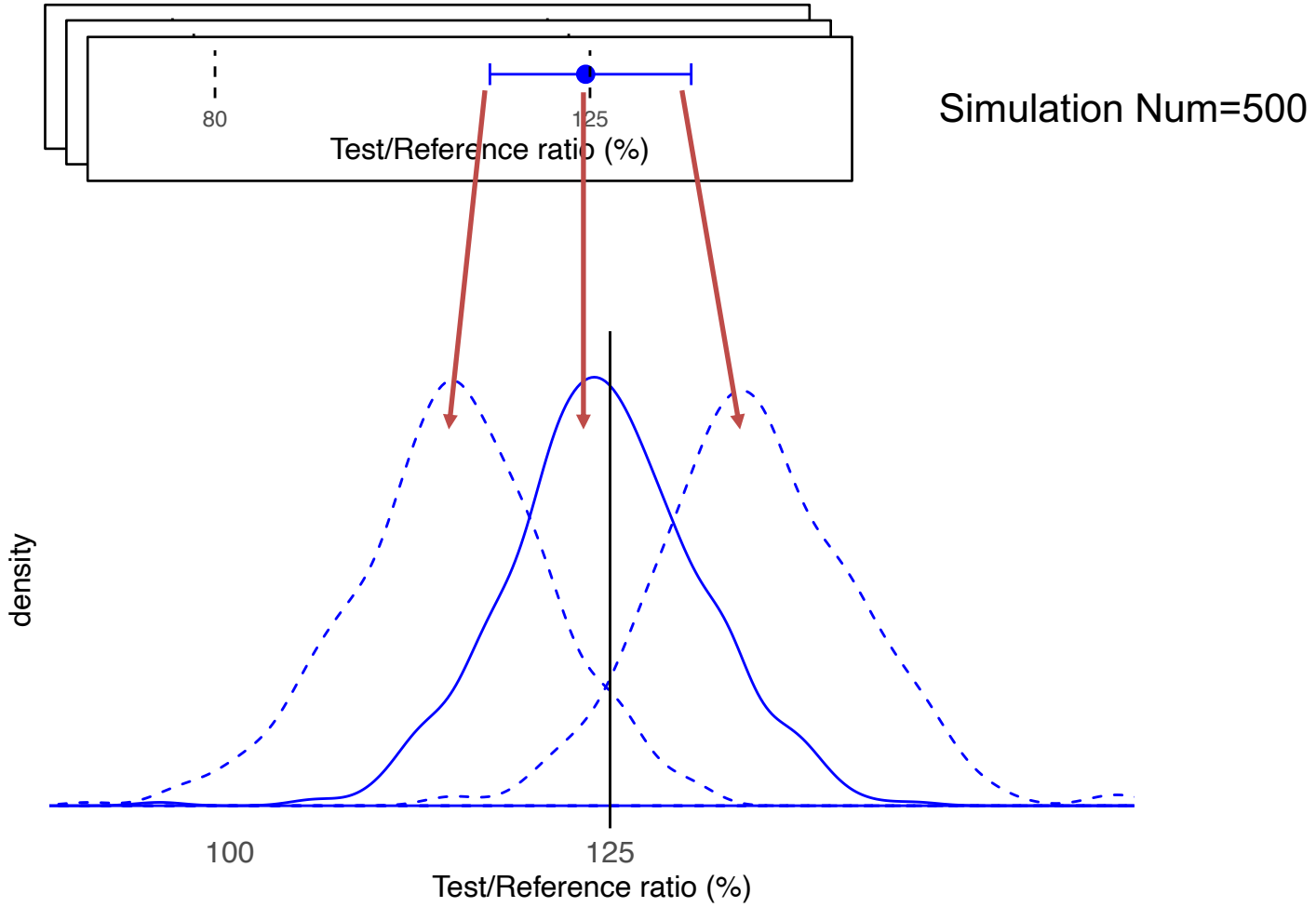
Simulation Num=500

Type I error in the simulation study



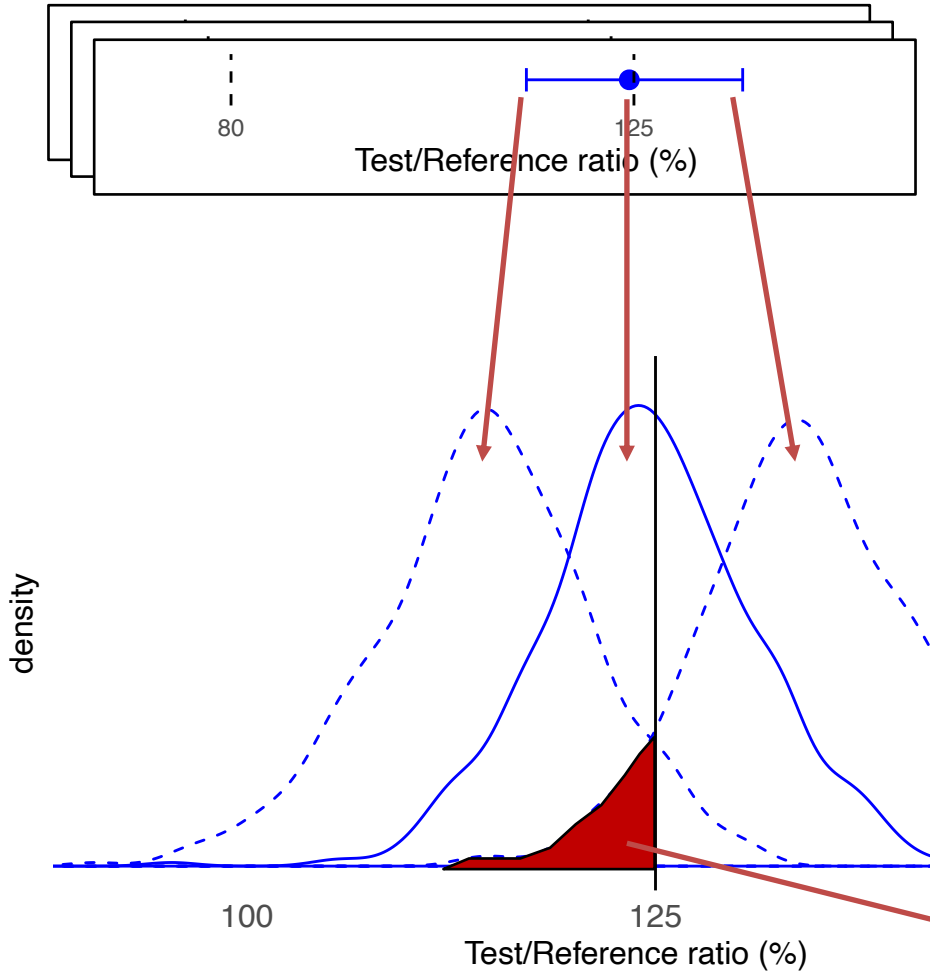
Simulation Num=500

Type I error in the simulation study



Simulation Num=500

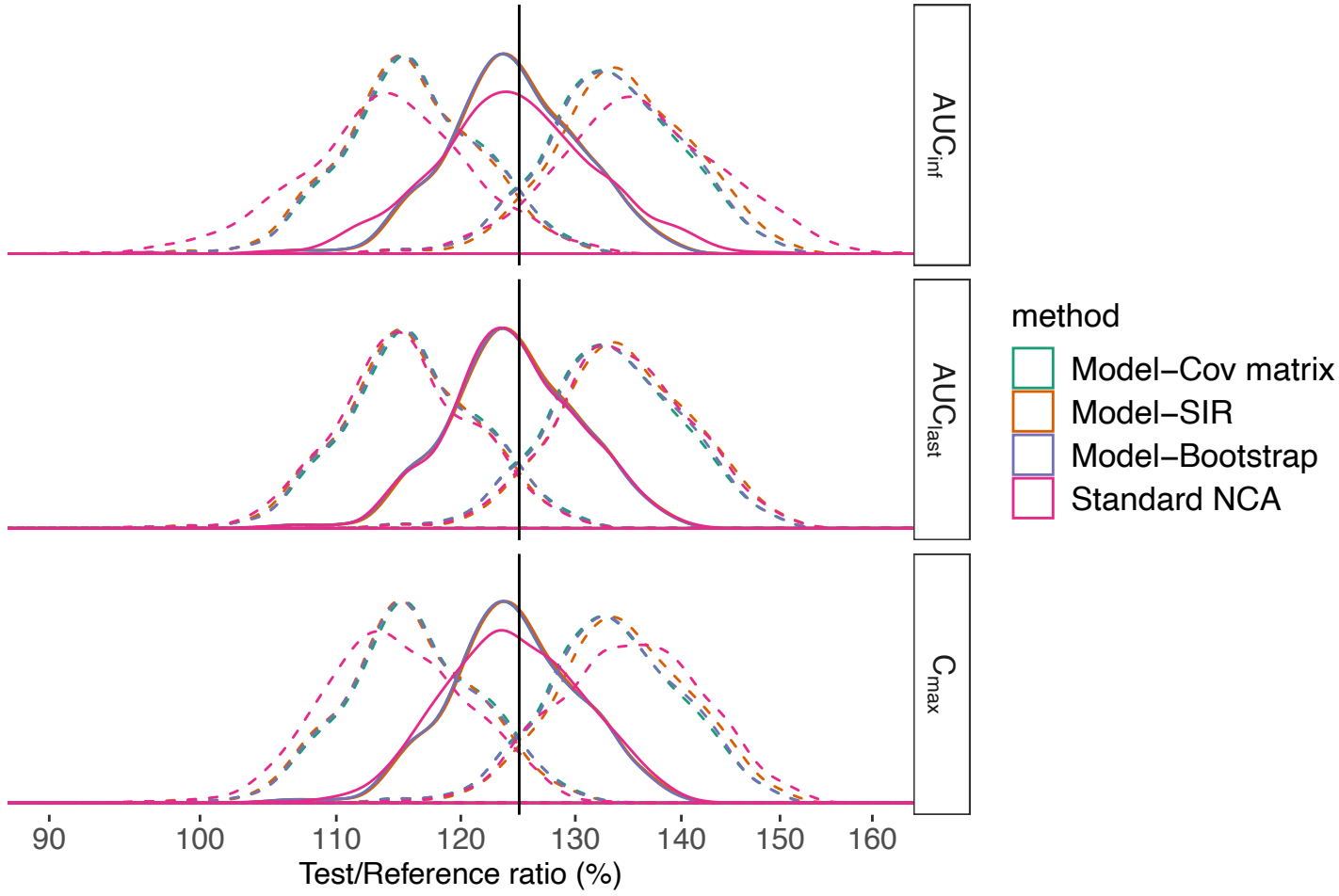
Type I error in the simulation study



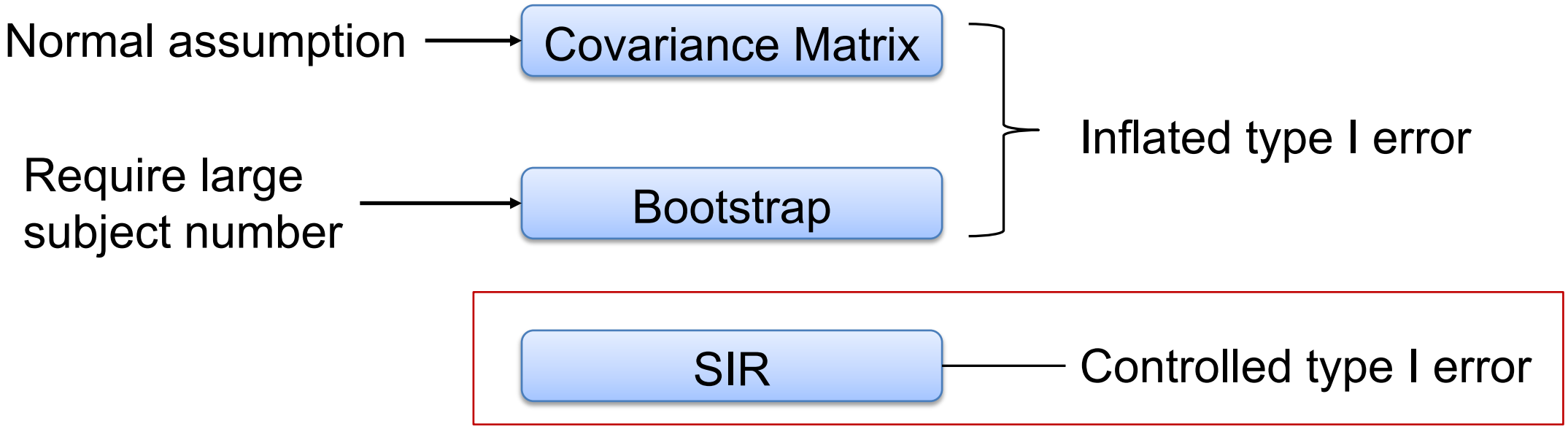
Simulation Num=500

Type I error: $\frac{N_{BE}}{N_{total}}$

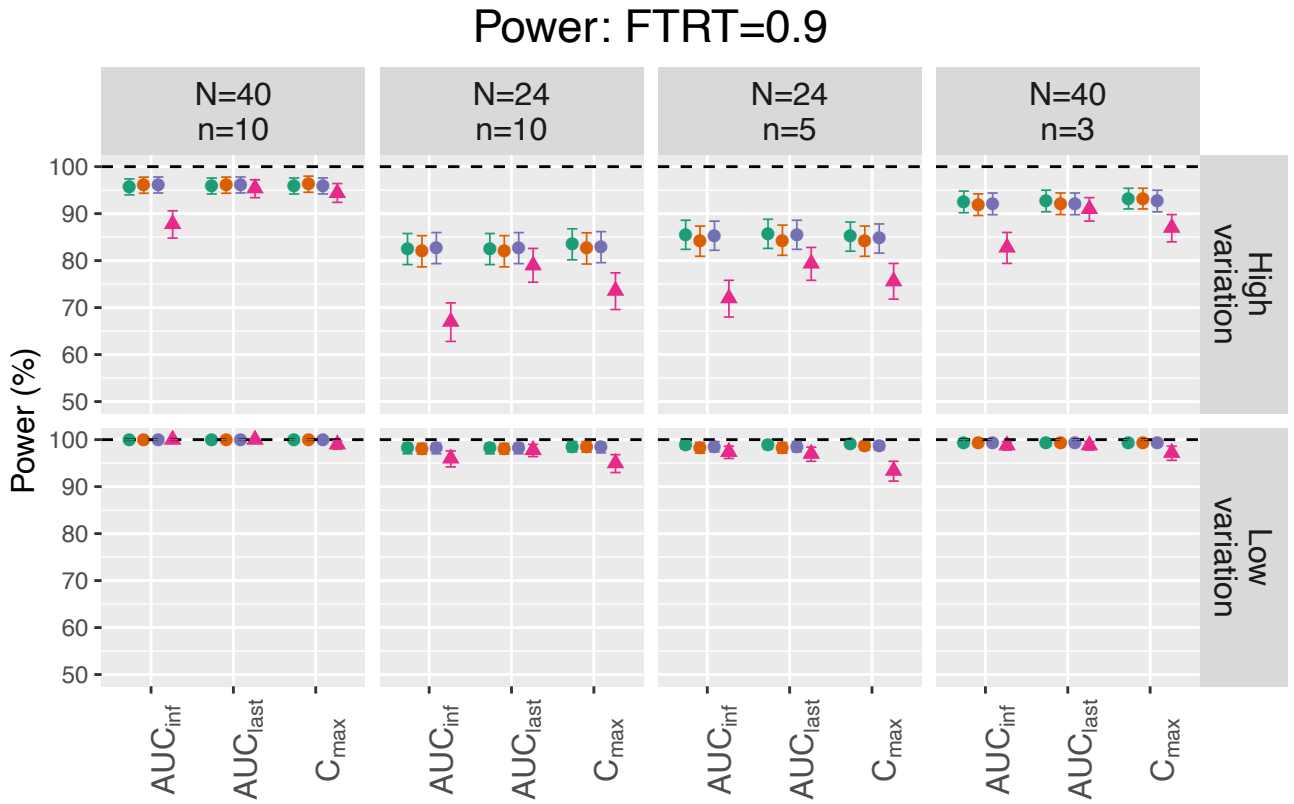
Density plot of Mean ratio, CI_upper and CI_lower N=24, n=10, high variation

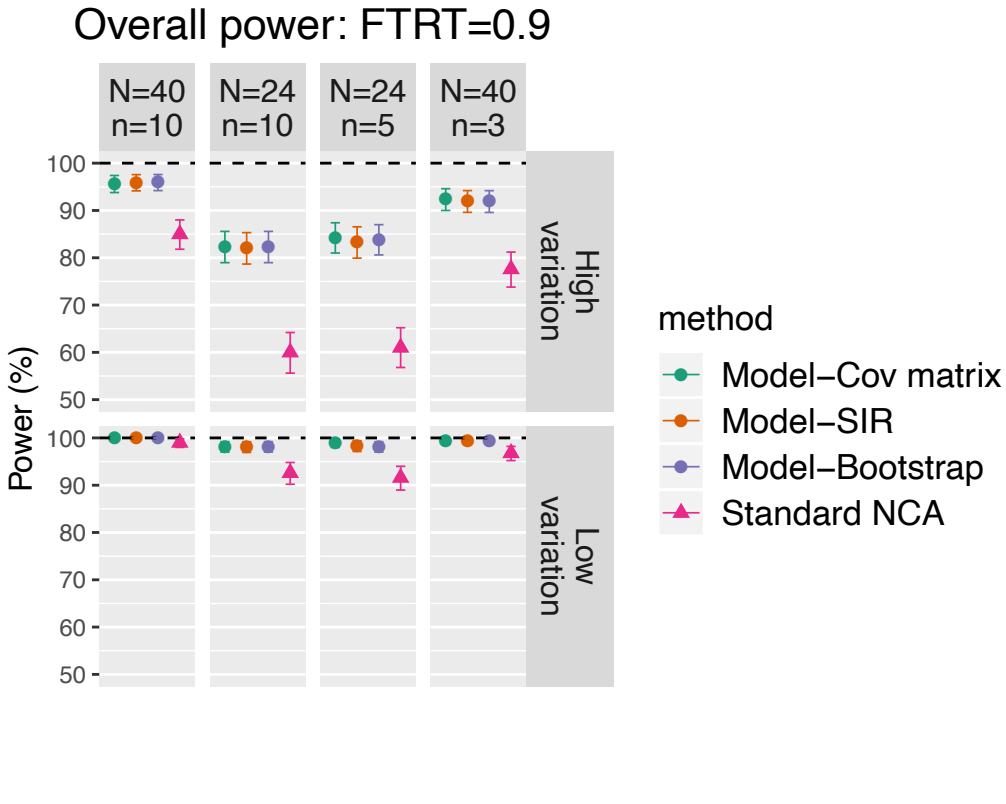


Comparison of 3 uncertainty methods



Model-based method showed higher power than NCA-based method

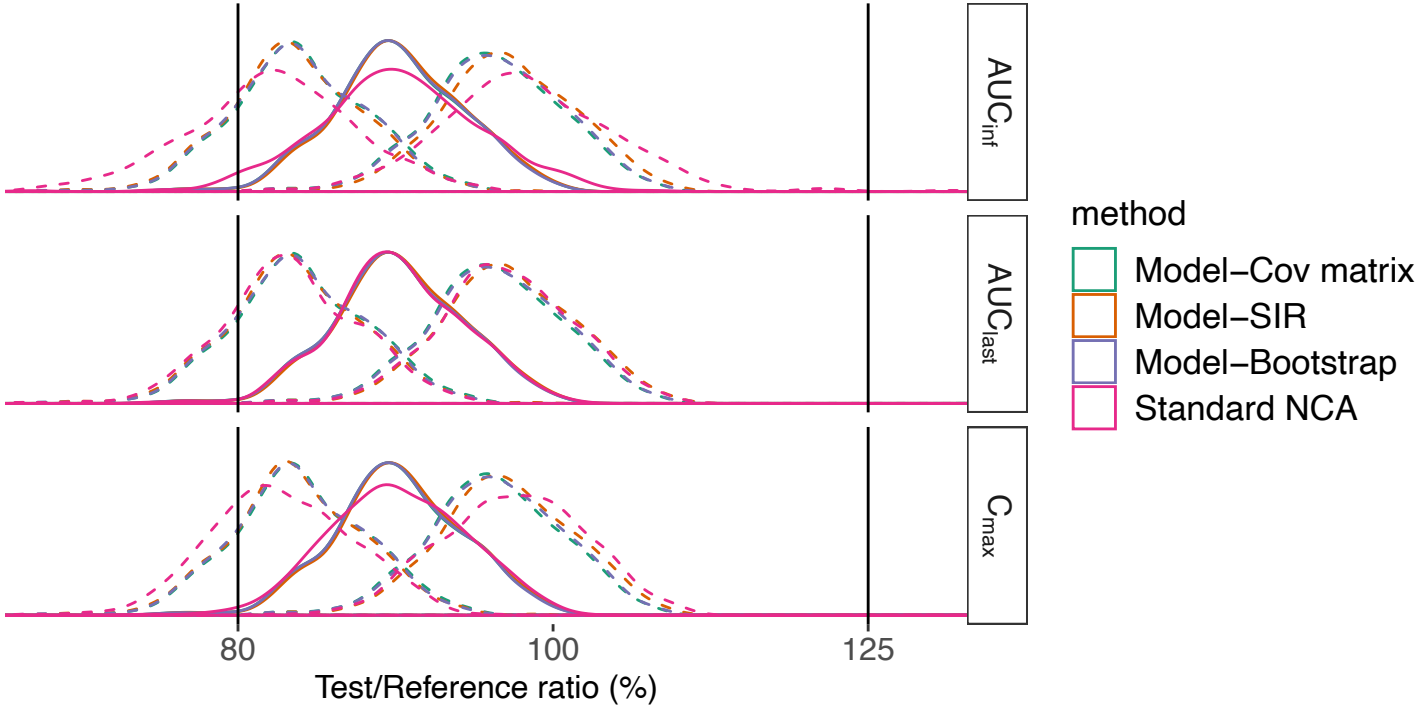




<u>NCA-based BE method:</u>

Power: AUC_{last} > C_{max} > AUC_{inf}

Density plot of Mean ratio, CI_upper and CI_lower
N=24, n=10, high variation



NCA-based BE method:

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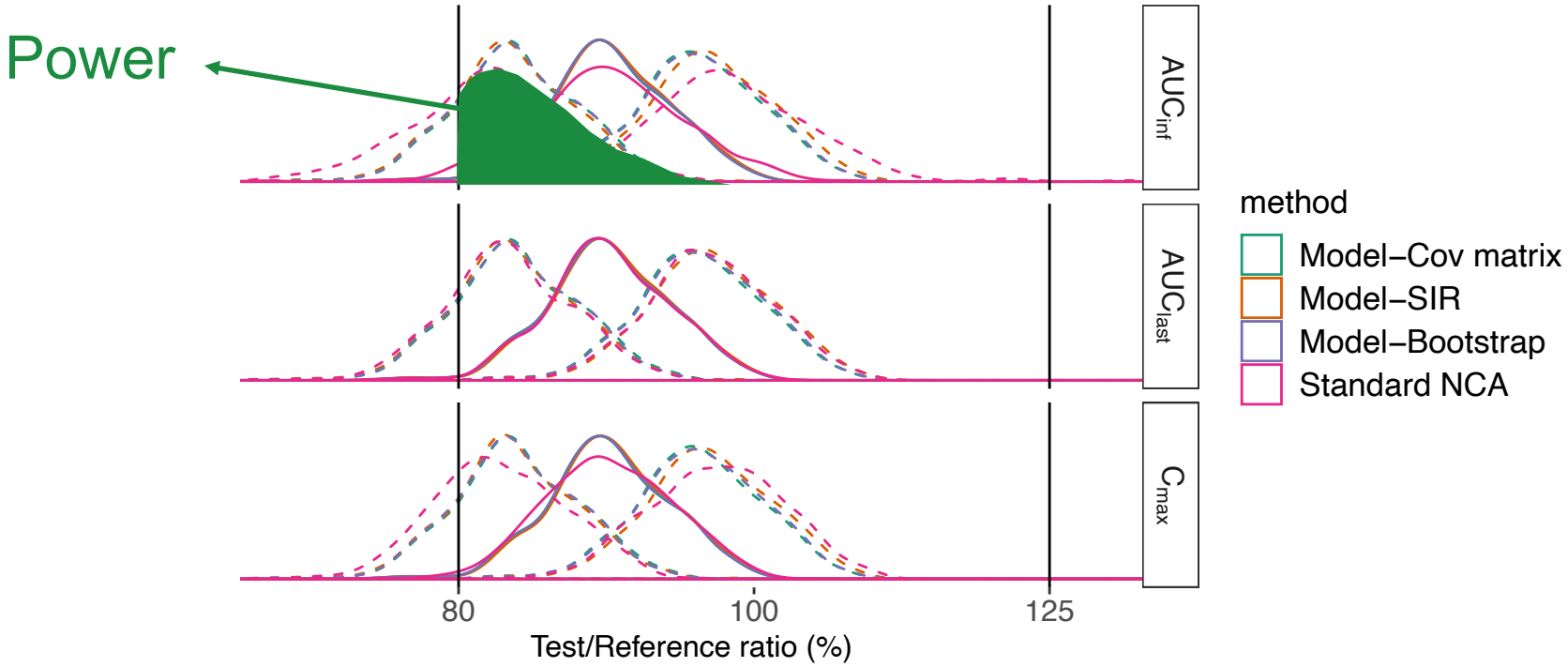
Density plot of Mean ratio, CI_upper and CI_lower
N=24, n=10, high variation

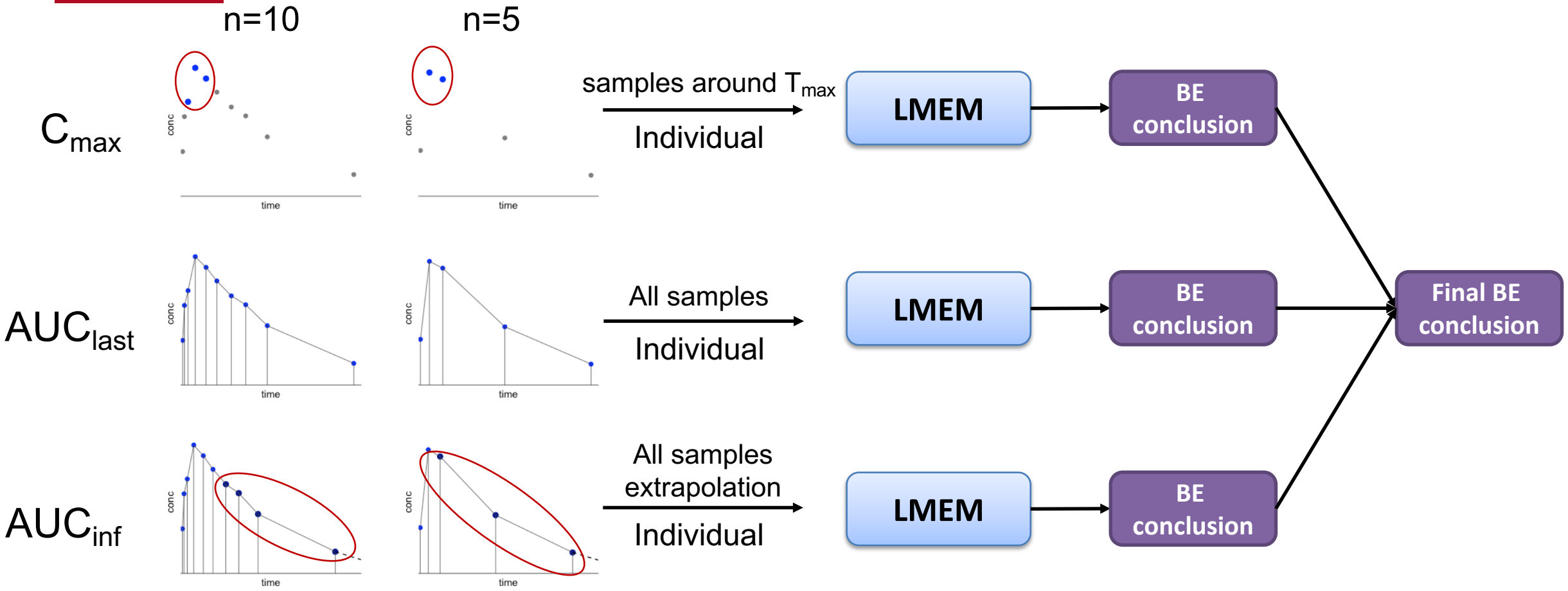


NCA-based BE method:

Power: AUC_{last} > C_{max} > AUC_{inf}

Information flow in NCA-based BE method

Use different information for each metric analysis

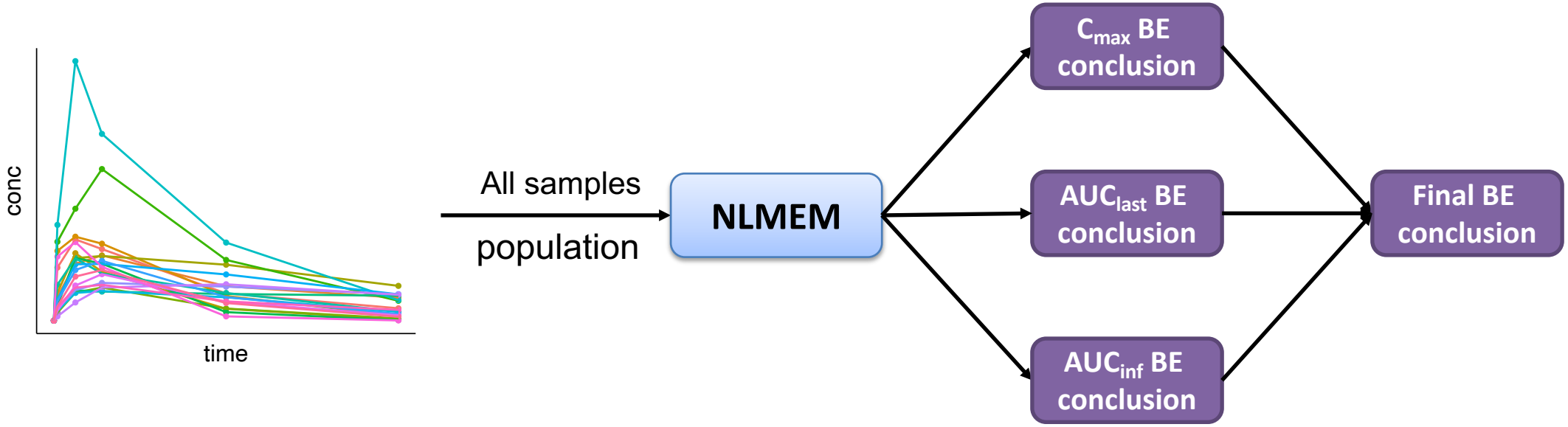


Power: $AUC_{last} > C_{max} > AUC_{inf}$

LMEM: linear mixed effect model

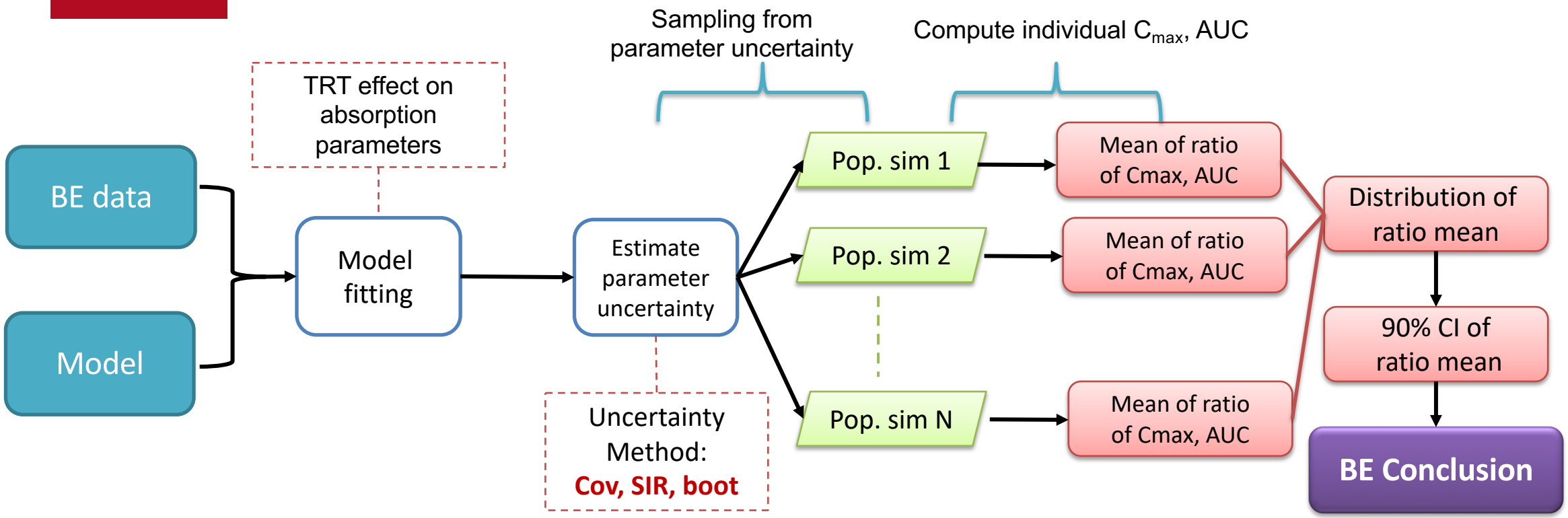
Illustration for model-based method

Integrating all information for conclusion



NLMEM: Non-linear mixed effect model

Our developed model-based BE method



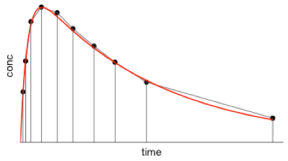
Modeling → Uncertainty estimation → Simulation → Conclusion

Summary of developed BE method

- Three uncertainty methods
  - SIR is the best
- Advantage of model-based methods
  - Acceptable type I error and high power
  - Can choose between geometric mean and typical mean
  - No requirement for analytical solutions
- Assumption – Model structure is correct
  - May use previous pharmacokinetics (PK) model from originator product
  - Assumption violation → Model averaging

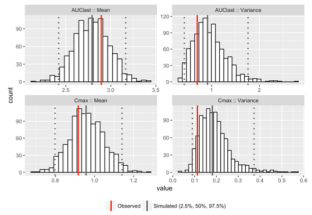
Software

bemod



- Model based BE testing
- In development

ncappc

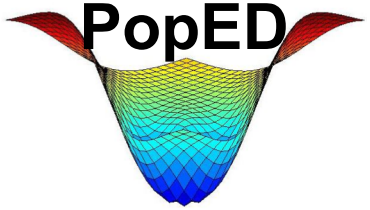


- NCA Calculation and Population PK Model Diagnosis
- https://github.com/UUPharmacometrics/ncappc

PsN 4 Perl speaks NONMEM

- SIR
- Bootstrap
- https://uupharmacometrics.github.io/PsN/

PopED



- Optimal experimental design software
- https://andrewhooker.github.io/PopED/

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Mark Donnelly

PM group, Uppsala University