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Model-based Approaches as Guidance to Bioequivalence Decision Making: Design and Analysis Considerations

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Standard bioequivalence (BE) studies

- Standard BE analysis strategies have been shown to perform adequately in ”typical” drug studies when dense PK sampling is possible.

- However, dense sampling is not always possible: anti-cancer, children and ophthalmic studies.

Potential problems with standard BE approaches

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- Problems with NCA calculations
  - assumption about equal weight of all observations
  - sensitivity to missing data
  - sensitivity to data below the limit of quantification
  - interpolation problems from the last observation to ∞
  - Sparse data problems

- Are standard NCA calculations (geometric mean of C_{max} and AUC_{last}) the right metrics to use?

Population (NLME) model based approaches in general can handle these problems

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- Problems solved:
  - assumption about equal weight of all observations
  - sensitivity to missing data
  - sensitivity to data below the limit of quantification
  - interpolation problems from the last observation to ∞
  - Sparse data problems

- Simulations of expected PK profiles give an understanding of what features may be important to compare in a BE study

- PKPD models give an indication of the PK factors driving drug effect

Advantages of pharmacometric approaches

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e23; doi:10.1038/psp.2012.24

www.nature.com/psp

ORIGINAL ARTICLE

Comparisons of Analysis Methods for Proof-of-Concept Trials

KE Karlsson[1], C Vong[1], M Bergstrand[1], EN Jonsson[1,2] and MO Karlsson[1]

Drug development struggles with high costs
accentuated by many stakeholders in drug dev
drug development. Two simulated examples,
compare a pharmacometric model–based anal
investigated examples and scenarios, the conv
80% power. For a scenario with a parallel des
conventional and pharmacometric approach w
the model-based power depend on the model
was demonstrated to permit drastic streamlini
CPT: Pharmacometrics & Systems Pharmacology

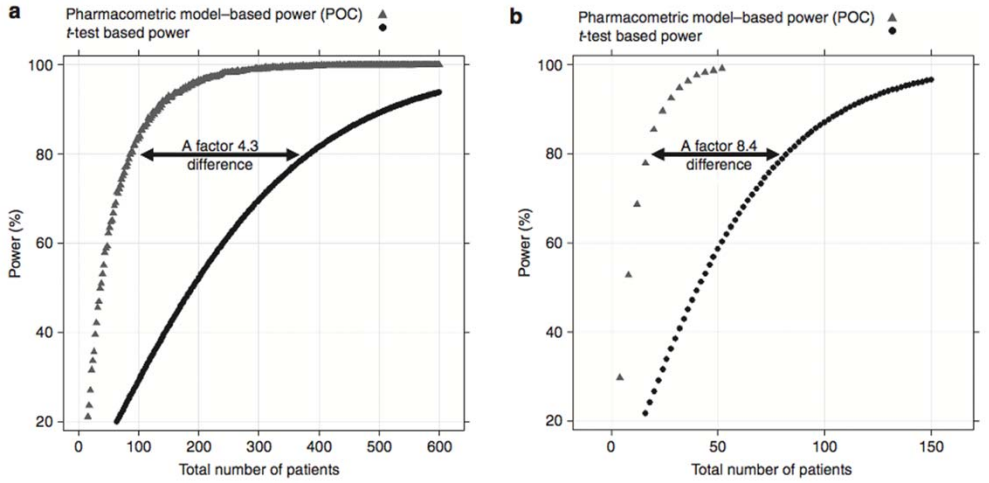
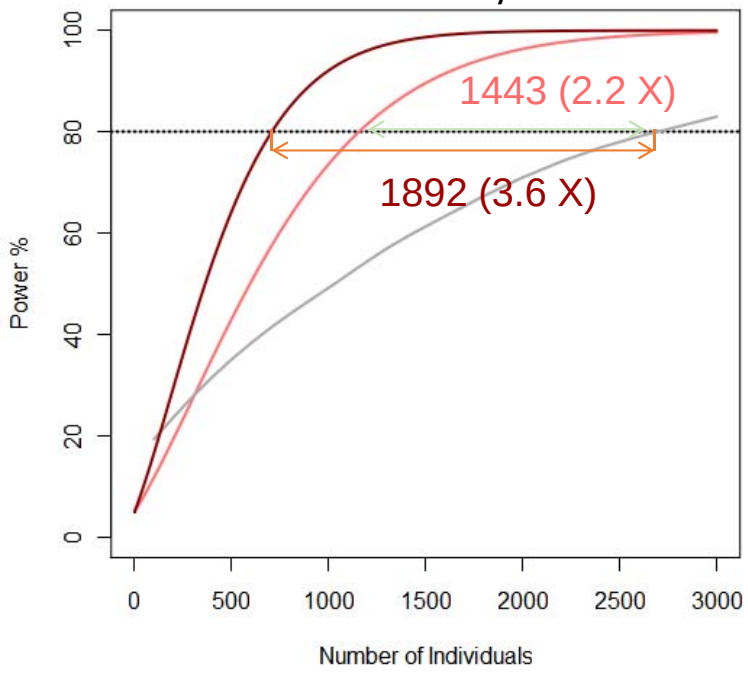


Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number of patients) is displayed. (**b**) In the diabetes example, the difference in study size was 8.4-fold (10 vs. 84 total number of patients) in favor of the pharmacometric approach.

Advantages of optimal design of experiments

(Optimized) Model Based vs.
Traditional Data Analysis in Alzheimer's



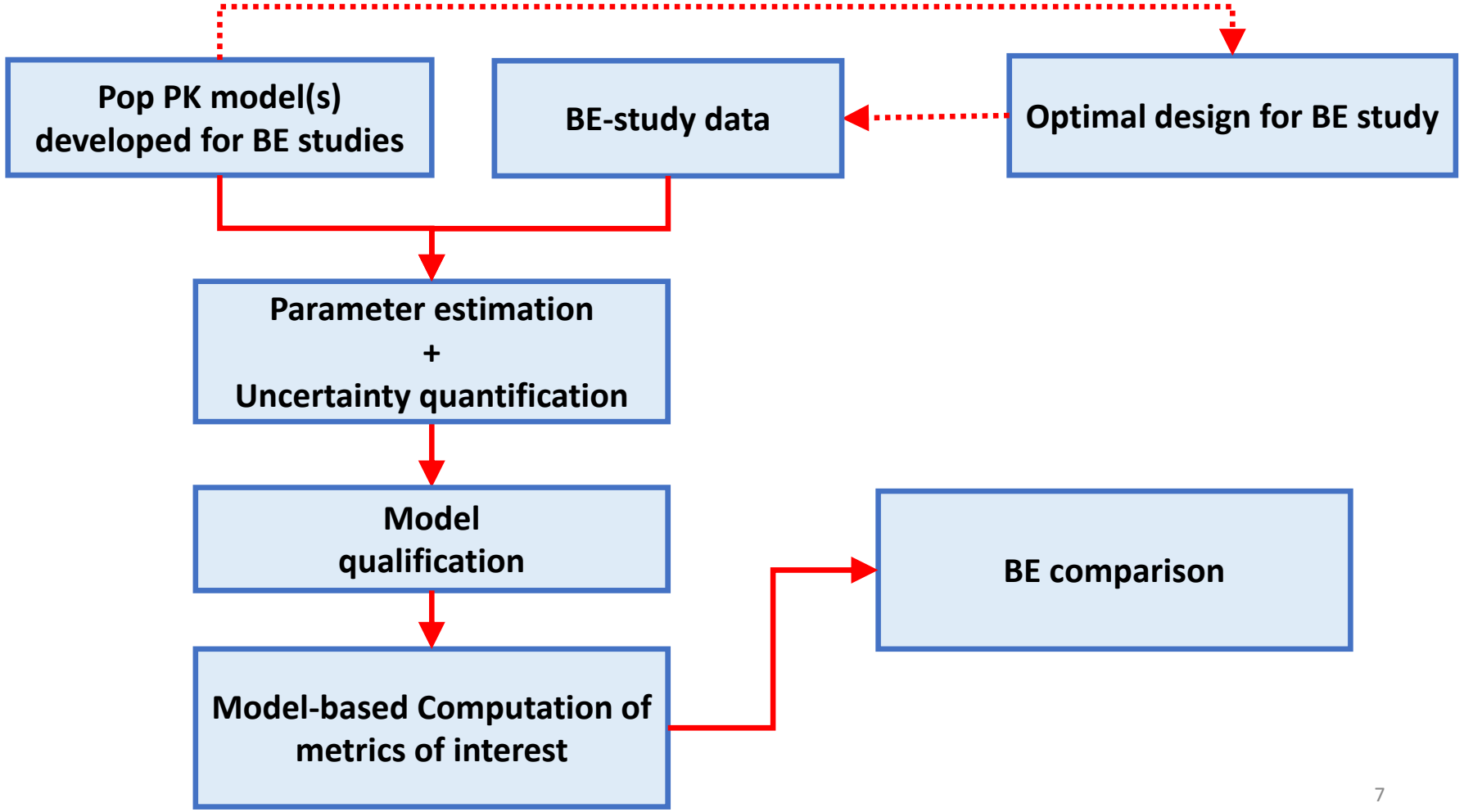
Model-Based Analysis
(Optimized for power)

Model-Based Analysis
(Default Design)

Traditional Analysis
(Unstructured MMRM model,
LSMeans)

Hooker et al., Model-based Trial Optimization for Phase II and III designs in Alzheimer's Disease, ACOP, 2011

The “ultimate” model-based BE approach



Model components

Pop PK model(s) developed for BE studies

Ability to describe model parameter deviations based on:

- Formulation
  - Deviations in absorption, bioavailability
  - Assume distribution kinetics to be the same
- Period
- Sequence

Potential problems with a model based analysis

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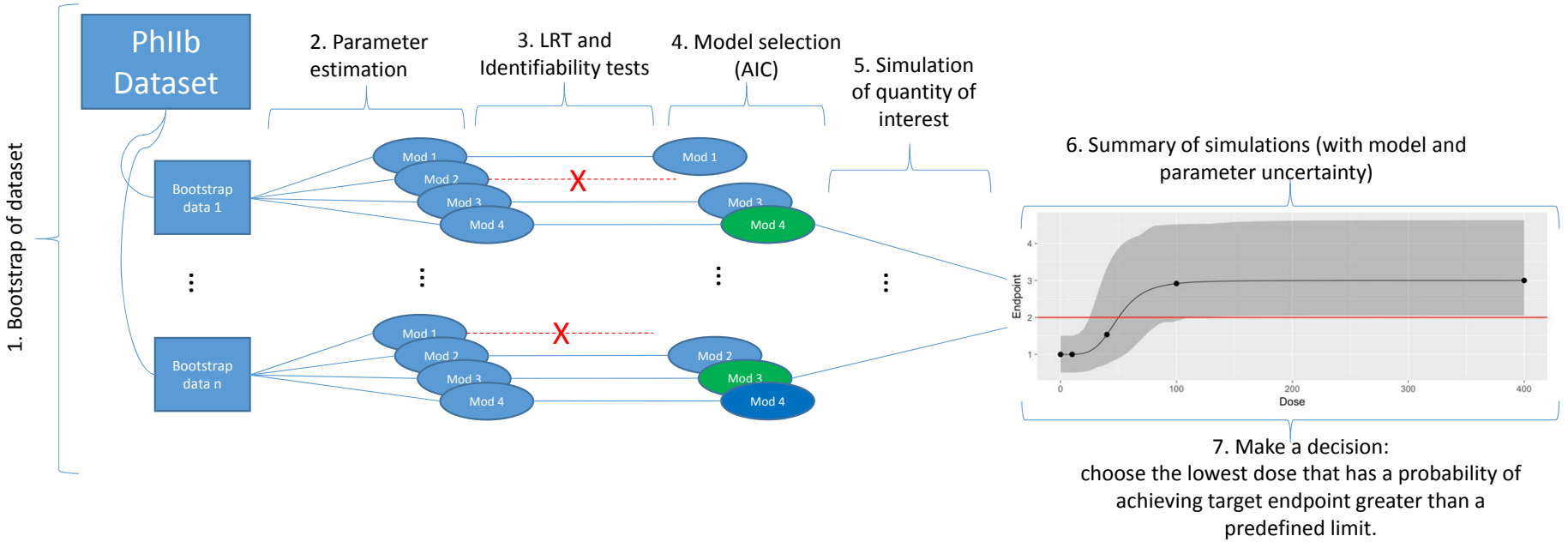
- The model is wrong (all models are wrong …)
- Model building may produce bias
- Parameters in a model may be biased/misspecified

Model averaging

- Aoki *et al.*, PAGE, 2014
- Hooker *et al.*, Workshop on dose finding and selection, EMA, 2014
- Aoki *et al.*, PAGE, 2016



- Incorporate model and parameter uncertainty
- Maintain type-I error
- Reduce model selection bias

modelAVERAGE available on

Type of models to average with

- Different potential distribution models
- Different potential absorption models
  - Absorption, bioavailability differences between formulation
- Period, formulation effects if relevant

Model qualification

- Use the models to predict (simulate) secondary PK parameters (e.g. geometric mean of C_{max} and AUC_{last}).

- Simulation should at the least predict data that results in similar secondary PK parameters compared to the real data

Non-compartmental analysis posterior predictive check (NCAPPC)

COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 127 (2016) 83–93

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

A diagnostic tool for population models using non-compartmental analysis: The *ncappc* package for R

Chayan Acharya[a,*], *Andrew C. Hooker*[a], *Gülbeyaz Yıldız Türkyılmaz*[a,b], *Siv Jönsson*[a], *Mats O. Karlsson*[a]

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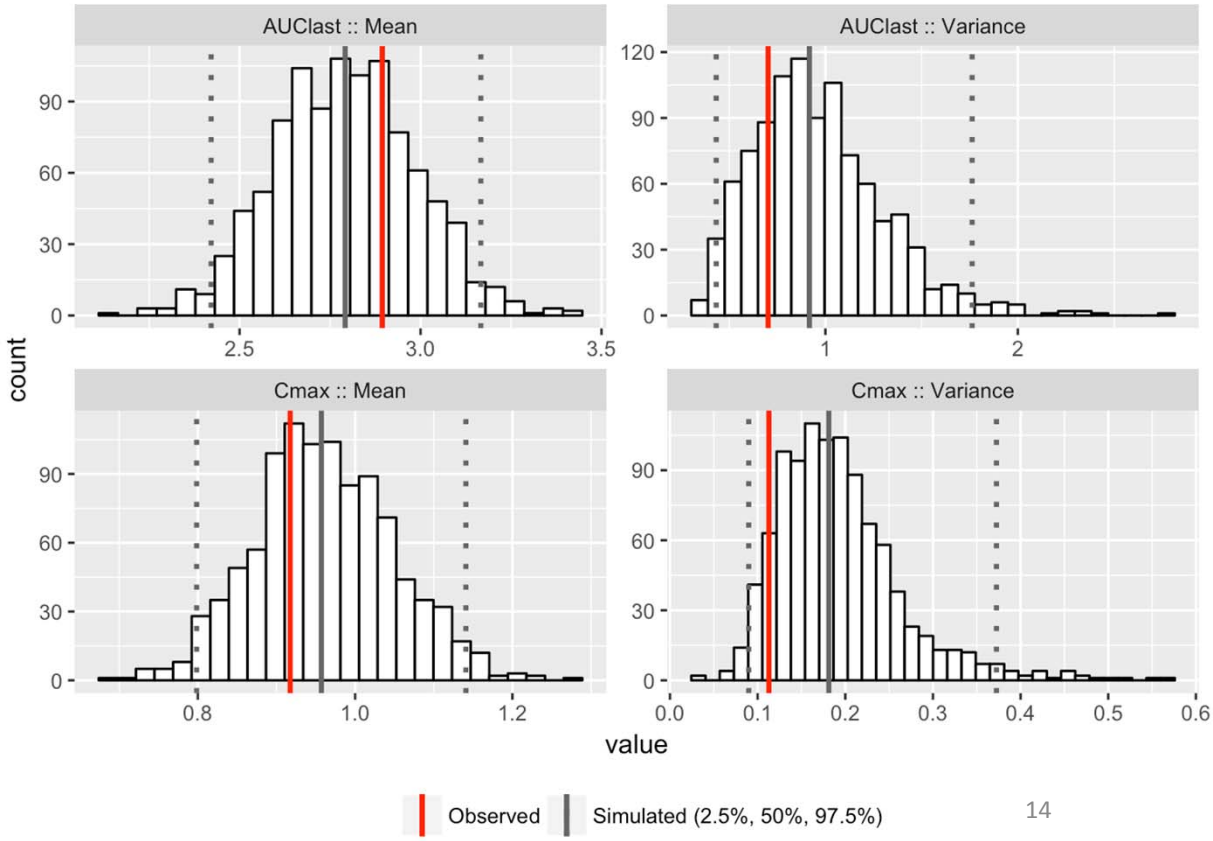
- available on CRAN https://cran.r-project.org/package=ncappc

Comparison of the population mean and variance of NCA metrics

- Histogram of the simulated population mean and variance of the NCA metrics.
- Uncertainty in simulations (model and parameter uncertainty) Possible with rich and sparse data.
- Adjusted confidence intervals so that 5% of all simulations lie outside intervals in all tests.
- Other comparisons may be important:
  - $\Delta\overline{AUC}_{last}$ for cross over studies.



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Uncertainty quantification

- Dubois *et al*. (2011) improved the type-I error rates of their population model-based BE methods using a more realistic quantification of the parameter uncertainty (parametric bootstrap).

- For sparse data and relatively few individuals, as in BE trials, the bootstrap may not be appropriate in providing reliable parameter uncertainty distributions (Niebecker, PAGE, 2013).

Sampling importance re-sampling (SIR) in NLME models (Implemented in 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]

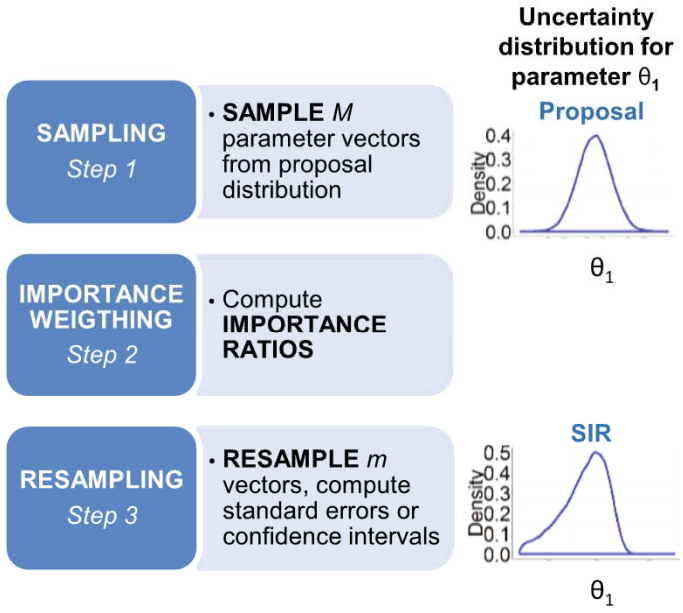
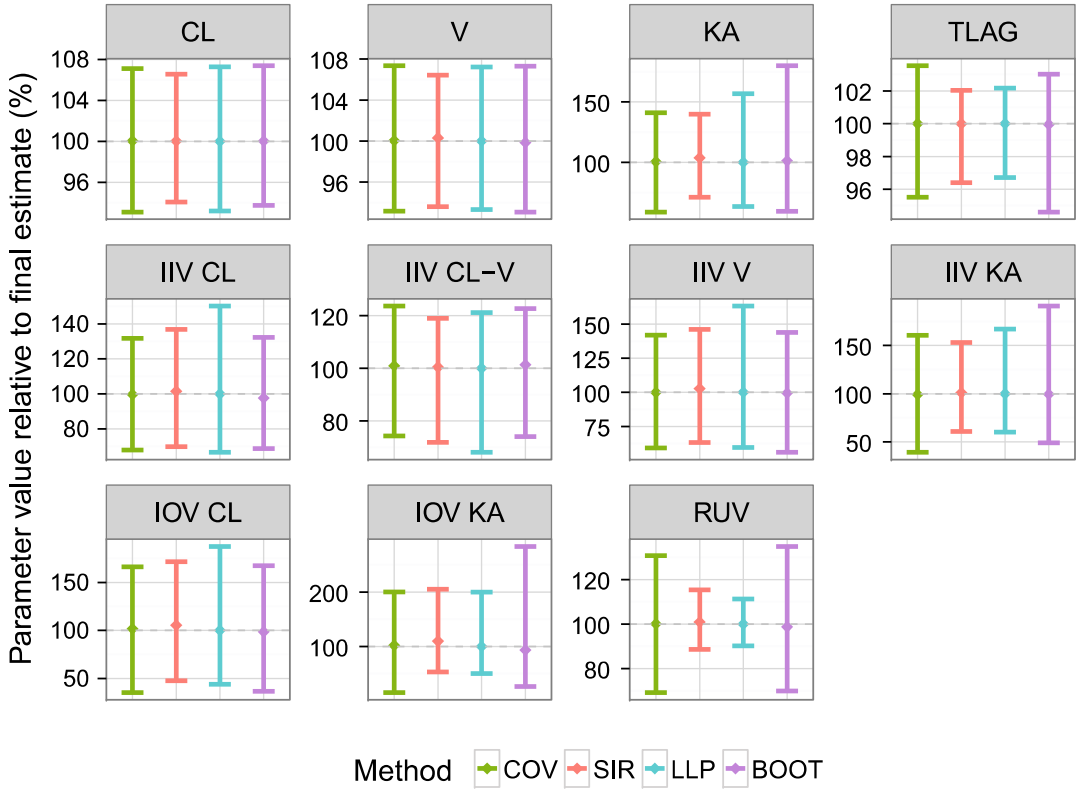


Fig. 1 The three steps of the SIR procedure

Performance of different uncertainty measures



- SIR in population models can significantly improve the quantification of parameter uncertainty compared to a case-resampling bootstrap methodology.

General algorithm for model based BE

Algorithm 1: General approach for the computation of BE using model-based summary PK variables of interest.

Step 1 Determine maximum-likelihood parameter estimates $\Theta_{\mathrm{ML}} \in (\theta, \Omega, \Sigma)$ and parameter uncertainty from an adequate NLME model using data from a BE study.

Step 2 Compute the geometric mean of the secondary summary PK variables in the population.

Step 3 Compute the uncertainty of the secondary summary PK variables in the population.

Step 4 Compare distributions of population summary metrics, accept or reject bioequivalence based on pre-specified boundaries.

- Hu et al. (2004) and Dubois *et al*. (2011) use analytic calculations to compute the geometric mean of the summary PK variables of interest ($\overline{AUC}_{GM} = Dose \cdot F_{pop}/CL_{pop}$).
- Uncertainty of these secondary variables can then be computed using propagation of error techniques (*e.g.*, the delta method).
- Assumes log-normal parameter distributions, linear kinetics and symmetric uncertainty distributions.

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Proposed algorithm

Algorithm 1: Simulation scheme to compute the NCA metrics of interest regardless of model structure.

repeat

Step 1 Sample a model parameter vector $\Theta \in (\theta, \Omega, \Sigma)$ from the uncertainty distribution of the maximum-likelihood estimates Θ_{ML}.

Step 2 Simulate a population of individuals (assuming no period effects, sequence effects or inter-occasion variability if present in the model).

Step 3 Compute the NCA metrics for each individual and treatment.

Step 4 Compute population summary metrics of individual NCA metrics for each tratment.

until *Enough samples are taken to quantify the uncertainty*;

Step 5 Compare distributions of population summary metrics, accept or reject bioequivalence based on pre-specified boundaries.

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Design issues

- Absorption and treatment effect information is key!
- Optimization of designs that focus on these parameters of interest (s-family designs).
- Sampling for long half-life drugs may be considerably shortened if one assumes that distribution is the same for any formulation.

Robust optimal design

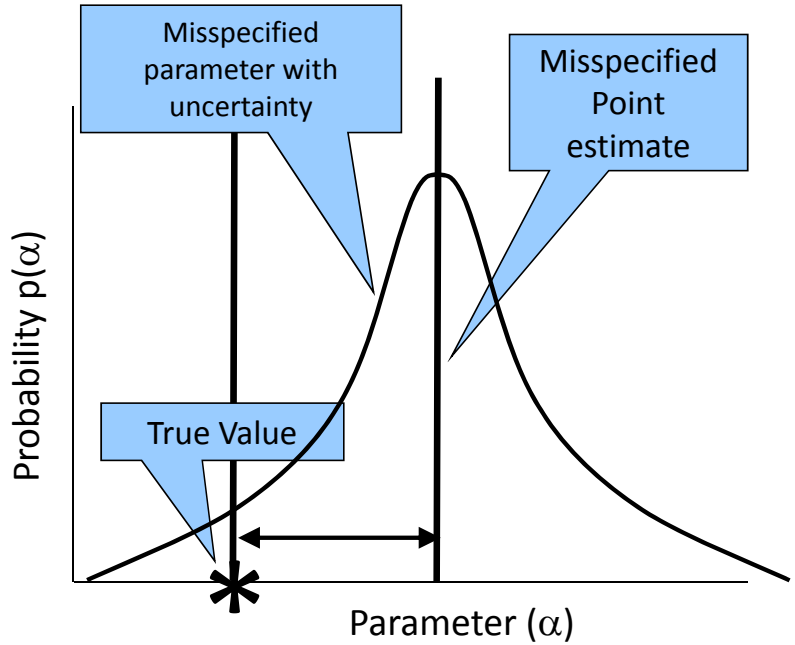
- Incorporate multiple models into your optimization

$$\Psi_{P-D} = \arg\max_{\xi}\left(\sum_{i}^{m}\log\left(\left|FIM(\xi,\Phi^{\{i\}})\right|^{\frac{\alpha_i}{p_i}}\right)\right)$$

m=model #, α_i = weighting and p_i = # of parameters

Waterhouse and Duffull, JPKPD, 2005

- Assume your parameters have distributions ("E-family")



Dodds *et al.*, JPP, 2005.

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Discussion

- Model-based BE methods have been shown to be similar in robustness compared to traditional NCA based BE methods in situations where traditional NCA based BE methods are expected to perform well (rich data, linear PK).
- ***Potential advantages*** of NLME BE approaches.
  - power increase should allow for smaller sample sizes in BE studies.
  - Can naturally handle inherent problems with NCA calculations: unequal weighting of observations, missing data, data below the limit of quantification and interpolation from the last observation to ∞
  - Sparse data handling (however, design of studies is crucial and optimal design can help)
- ***Challenges:*** Previous studies have shown that model-based approaches ***may*** suffer from type-I error issues.
  - Model averaging methods may help.
  - Correctly specifying parameter uncertainty distributions may help.
- Model-based approaches appear to be a viable alternative to traditional NCA based BE methods when the traditional approaches are unrealistic.
- Ongoing research will help to clarify which strategies should be used in model based BE studies.

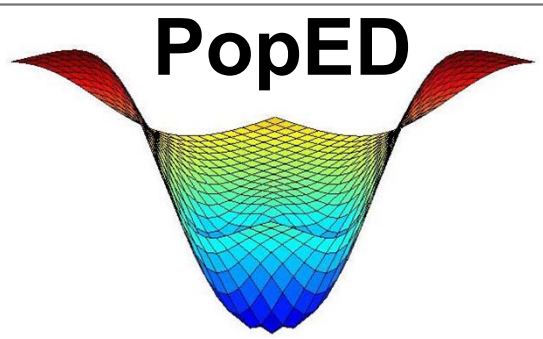
Software

https://uupharmacometrics.github.io/PsN/

- ncappc simulations
- SIR

modelAVERAGE available on
www.bluetree.me

ncappc
https://cran.r-project.org/package=ncappc



poped.sf.net

- Optimal experimental design software
- Flexible description of models
- Flexible description of design space
- Flexible design optimization
- Robust design criteria
- Written in R (Package available via CRAN)

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Extra slides

Bias reduction from model averaging