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Opportunities and pitfalls in the use of nonlinear mixed-effects models for leveraging longitudinal information in drug development

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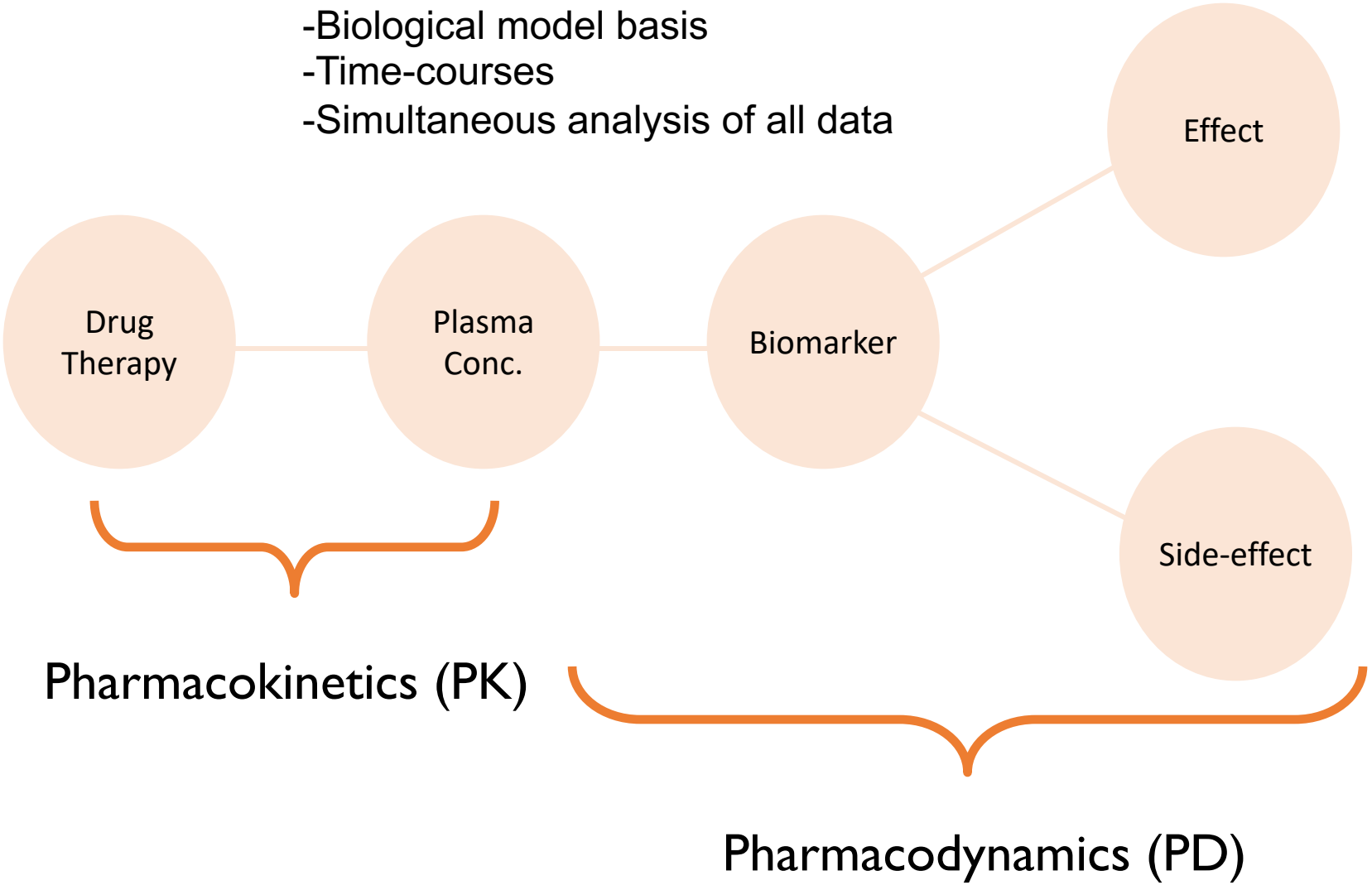
- "We develop and use mathematical models to understand drug and disease mechanisms, and to optimise drug development and therapy."

http://www.farmbio.uu.se/forskning/researchgroups/farmakometri/

What is a Pharmacometric model?

-Biological model basis
-Time-courses
-Simultaneous analysis of all data



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Pharmacometric models are usually nonlinear mixed-effect models (NLMEs)

$$y_{ij} = f\left(\vec{\theta}, \vec{\eta}_i\right) + h\left(\vec{\theta}, \vec{\eta}_i, \vec{\varepsilon}_{ij}\right)$$

- y_{ij} The ith individual's jth observation.
- $f()$ A model that describes all observations
- $\vec{\theta}$ Typical individual parameter values
- $\vec{\eta}_i$ The ith individual's deviations from $\vec{\theta}$
- Ω Covariance matrix for $\vec{\eta}_i$
- $\vec{\varepsilon}_{ij}$ Residual error components for y_{ij}
- Σ Covariance matrix for $\vec{\varepsilon}_{ij}$
- (other levels of variability, covariates, …)

What can a pharmacometric model be used for?

- characterize the longitudinal dose-exposure-response (DER) relationships
  - identifying drug effects
  - selection of efficacious doses
  - understanding and characterizing other aspects of a pharmaceutical compound, for example, drug-drug interactions.
  - planning and optimizing new trials
  - Integral part of the decision-making process in drug development and usage.

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

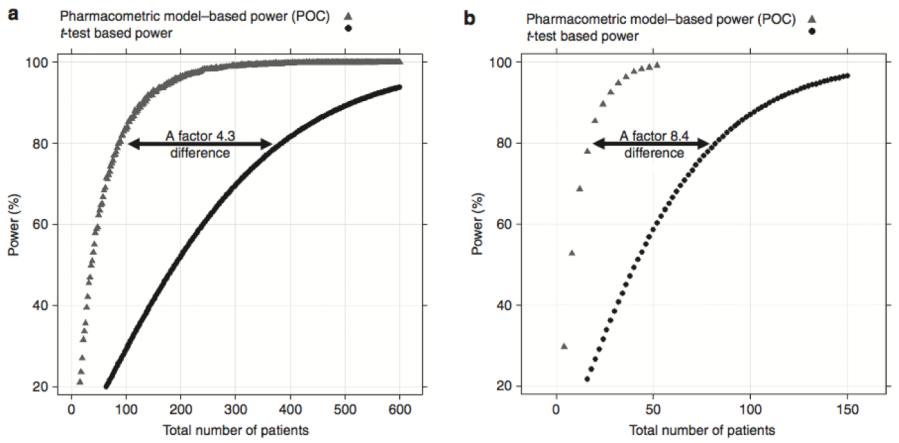
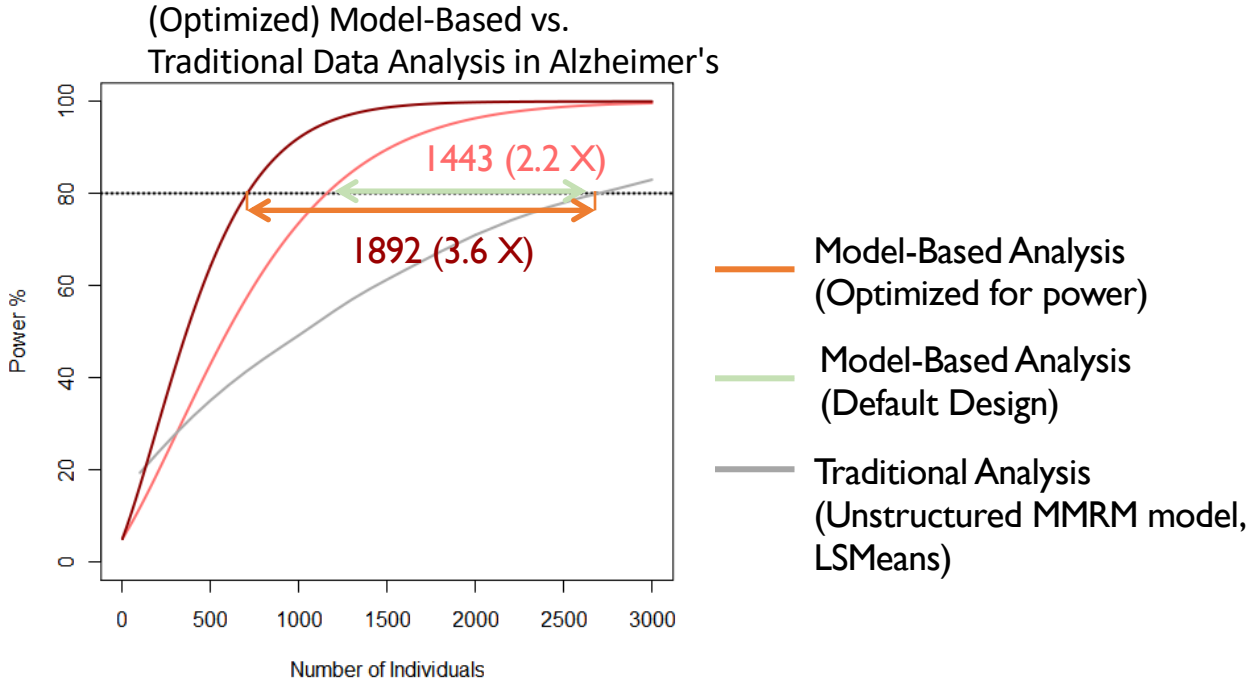


Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number 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 model based optimal design of experiments



- Hooker *et al.*, Model-based Trial Optimization for Phase II and III designs in Alzheimer's Disease, ACOP, 2011
- Ueckert *et al.*, Optimizing disease progression study designs for drug effect discrimination, JPKPD, 2013

Potential problems with a model based approach

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- Estimation: building models on measured data can lead to bias.

- Simulation (decision making) / optimization: using a misspecified model may give poor information / poor designs

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Non-longitudinal approaches

- Why use them?
  - Fast
  - Avoid some of the model building problems of longitudinal models
  - When you can't make the measurements
- When they do not make sense:
  - Non-uniform censoring (LOCF = bad!)
  - Time-varying covariates
  - Lower power if the longitudinal model is known or can be derived/built
  - Unclear when to stop the study

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General principles

- Use population pharmacometric models for longitudinal data (nonlinear mixed effects models)

- Avoid/reduce model building or build in smart ways to avoid problems of potential model bias
  - pre-specified models, model averaging

- Design studies based on these principles

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Where can NLME make a difference, and already accepted/being investigated by regulatory?

Dose finding (Phase IIb)

Problem: Inadequate dose and regimen selection for pharmaceutical products

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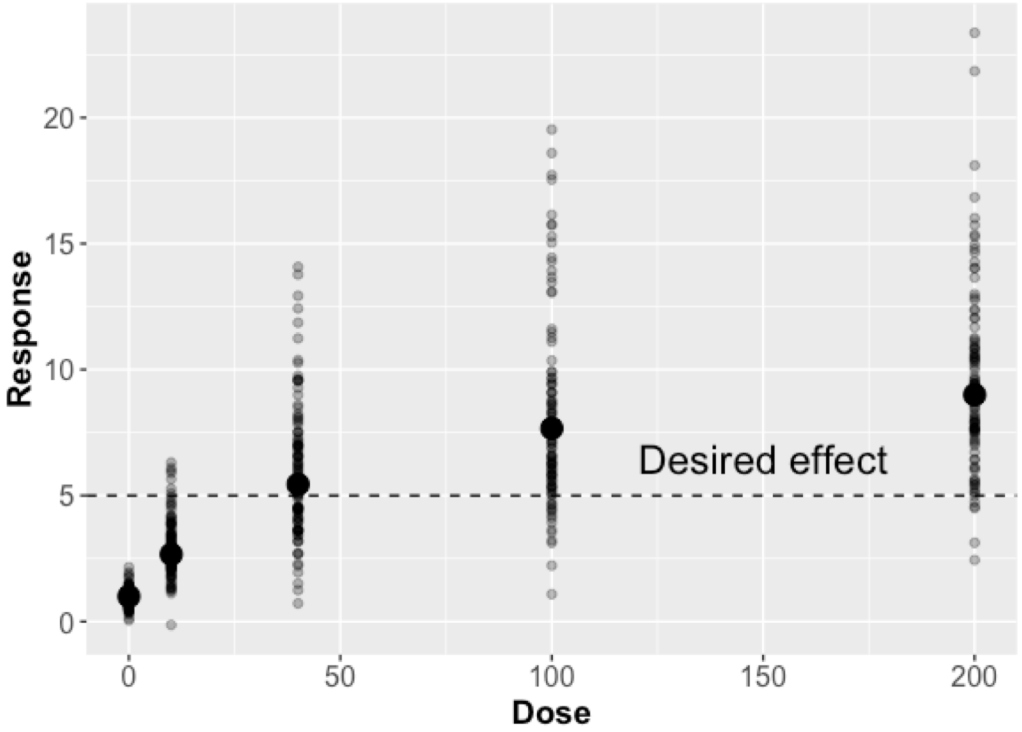
- High attrition rates in phase III (Kola 2004, Burock 2014, Freidlin 2008, Kaitin 2011)
  - Partly due to lack of proper dose selection
  - General lack of understanding of pharmacology

- Post-marketing study commitments and changes to dosing recommendations (Onakpoya 2016)

Standard method for dose selection: pairwise comparisons

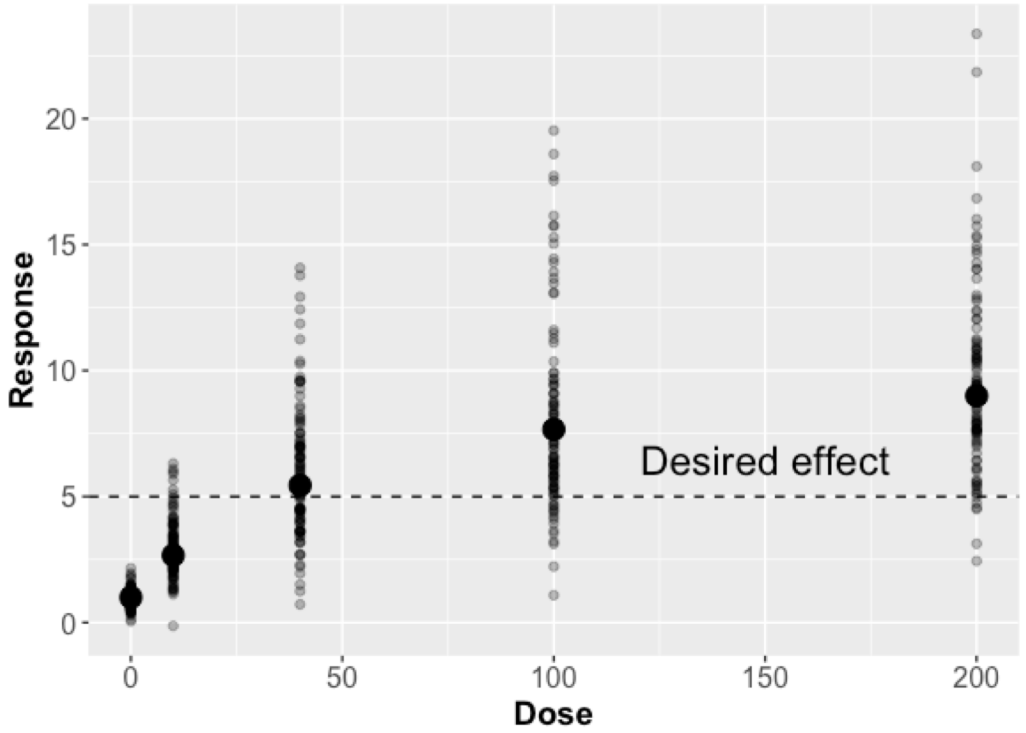
- Choose the smallest tested dose that satisfies both criteria below or “stop”.

- **Criterion 1:** p-value of pairwise ANOVA of active arm and placebo arm is less than X.
- **Criterion 2:** average of the placebo-baseline adjusted effect is greater than Y.



Problems with pairwise comparisons

- Study needs to be powered for multiple comparisons (Senn 2007)
- Dose-response (DR) instead of longitudinal dose-exposure-response (DER)
- Interpolation to other, more beneficial doses?



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

WHITE PAPER

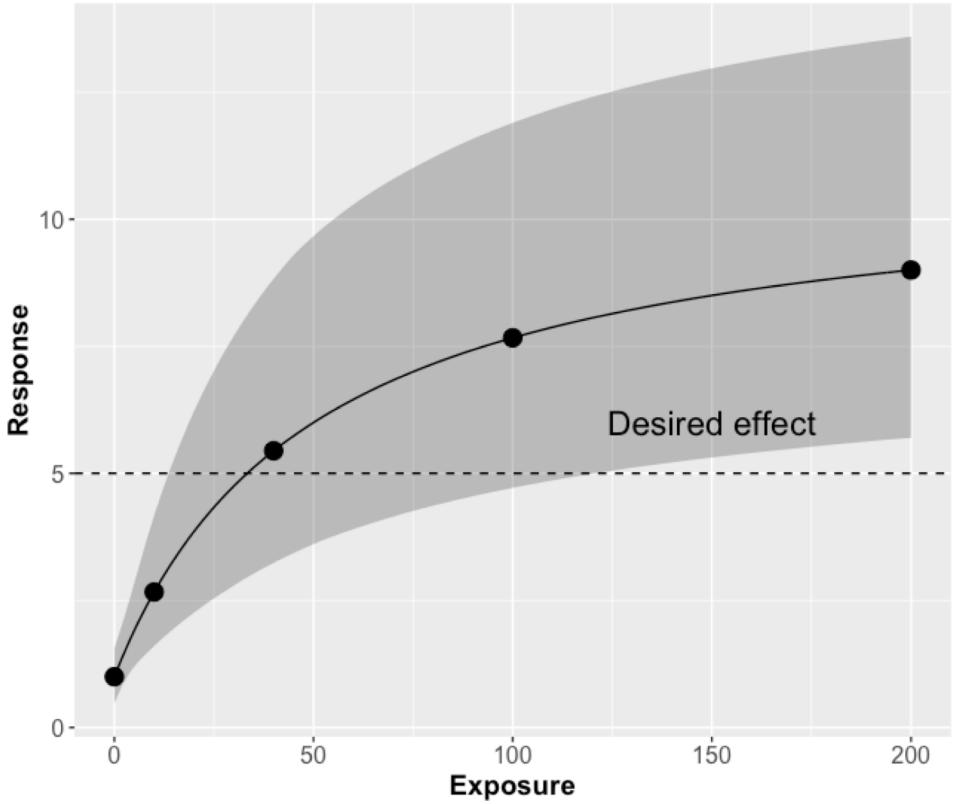
Advanced Methods for Dose and Regimen Finding During Drug Development: Summary of the EMA/EFPIA Workshop on Dose Finding (London 4–5 December 2014)

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]

Inadequate dose selection for confirmatory trials is currently still one of the most challenging issues in drug development, as illustrated by high rates of late-stage attritions in clinical development and postmarketing commitments required by regulatory institutions. In an effort to shift the current paradigm in dose and regimen selection and highlight the availability and usefulness of well-established and regulatory-acceptable methods, the European Medicines Agency (EMA) in collaboration with the European Federation of Pharmaceutical Industries Association (EFPIA) hosted a multistakeholder workshop on dose finding (London 4–5 December 2014). Some methodologies that could constitute a toolkit for drug developers and regulators were presented. These methods are described in the present report: they include five advanced methods for data analysis (empirical regression models, pharmacometrics models, quantitative systems pharmacology models, MCP-Mod, and model averaging) and three methods for study design optimization (Fisher information matrix (FIM)-based methods, clinical trial simulations, and adaptive studies). Pairwise comparisons were also discussed during the workshop; however, mostly for historical reasons. This paper discusses the added value and limitations of these methods as well as challenges for their implementation. Some applications in different therapeutic areas are also summarized, in line with the discussions at the workshop. There was agreement at the workshop on the fact that selection of dose for phase III is an estimation problem and should not be addressed via hypothesis testing. Dose selection for phase III trials should be informed by well-designed dose-finding studies; however, the specific choice of method(s) will depend on several aspects and it is not possible to recommend a generalized decision tree. There are many valuable methods available, the methods are not mutually exclusive, and they should be used in conjunction to ensure a scientifically rigorous understanding of the dosing rationale.

Model based decision making in dose finding trials

- Choose doses based on the probability of achieving a target response (longitudinal population model based)



J Pharmacokinet Pharmacodyn
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]

- Aoki *et al.*, PAGE, 2014
- Hooker *et al.*, Workshop on dose finding and selection, EMA, 2014
- Aoki *et al.*, PAGE, 2016
- Aoki *et al.*, J. PKPD, 2017

Received: 23 June 2017 / Accepted: 14 October 2017

- Simulation of drug effect on top of real baseline/placebo data for FEV1 endpoint (longitudinal population model)
- Multiple drug effect models and parameters used in simulations
- Compare
  - Model averaging methods
  - Pairwise comparisons
  - Analysis with the simulation model

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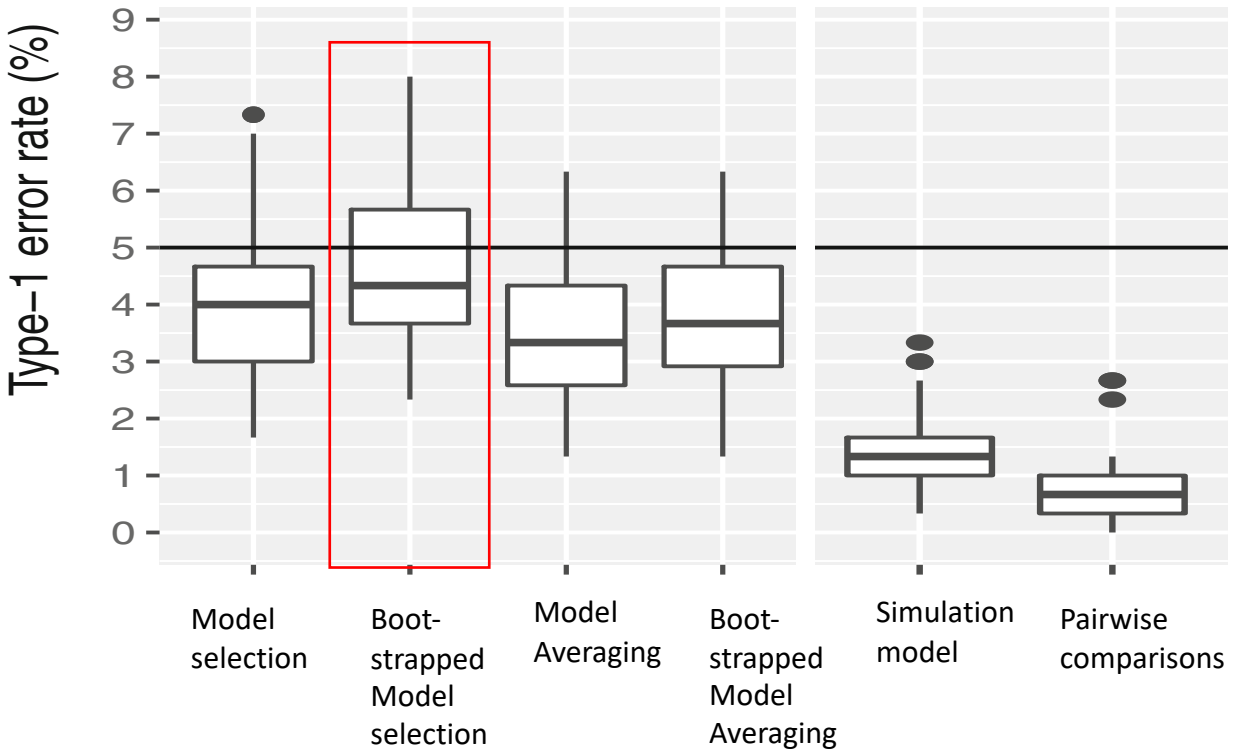
Type I error rate



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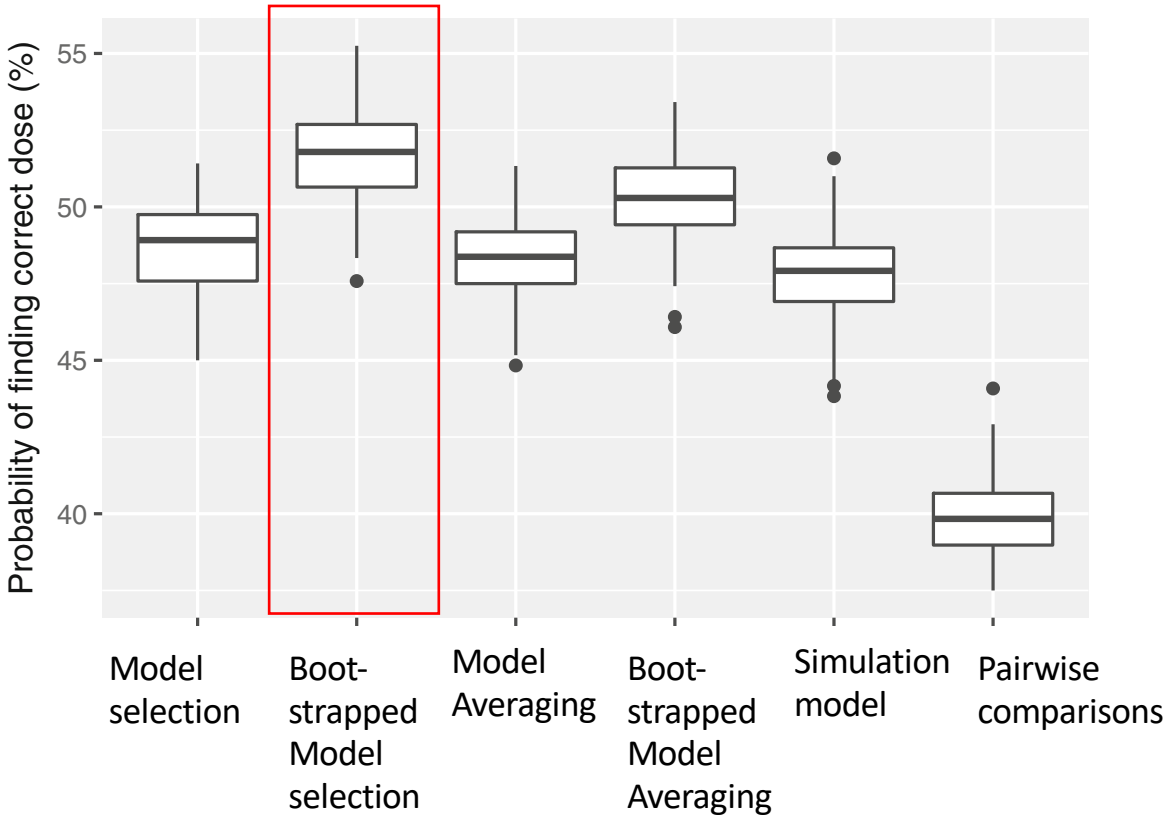
Probability of finding the correct dose



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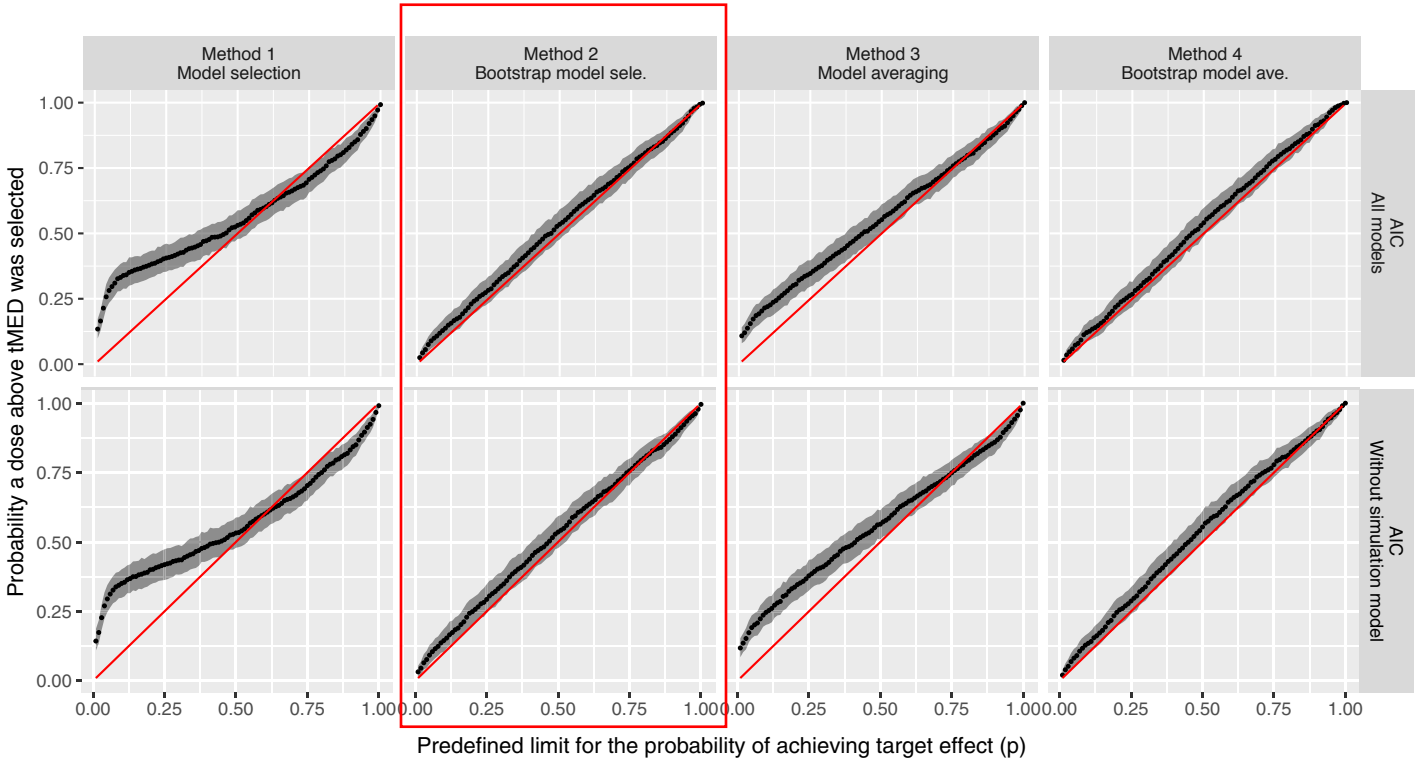
Averaging techniques reduce selection bias

The accuracy of the calculated probability: If the probability of achieving the target endpoint is estimated without bias, the plot should lie on the line of identity (red straight line)



Comparison to MCP-MOD (Bretz 2005)

- A pharmacometric extension to MCP-MOD?
- Testing for drug effect using the likelihood ratio test for each model, instead of contrast tests. Can be corrected for type 1 error control.(Dette 2015)
- Allows for incorporation of covariate adjusted dosing and longitudinal dose-concentration-effect modelling, which can have massive power gains over standard DR in MCP-MOD in certain situations (Buatois 2018)
  - MCP-MOD can be extended to DER models in other ways as well (Pinheiro 2017).

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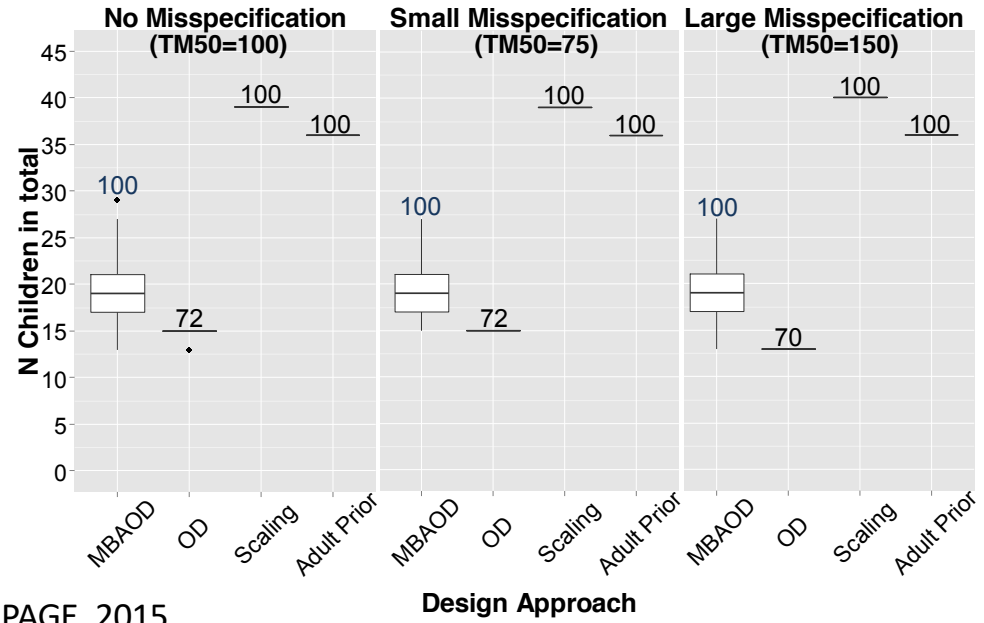
Pediatric bridging studies

MBAOD using FDA stopping criteria in children bridging studies

Results

Total Number of Children and Power



Strömberg et al., PAGE, 2015

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Bioequivalence

AMERICAN CONFERENCE ON PHARMACOMETRICS

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Welcome to ACoP10

Session 4c: FDA Science Forum: Model-based Approaches for Patient Pharmacokinetic Studies with Sparse Sampling Design	**Chairs: Liang Zhao (FDA), Lanyan (Lucy) Fang (FDA)**
Regulatory Challenges and Opportunities for Model-based Approaches for Patient Pharmacokinetic Studies with Sparse Sampling Design	Lanyan (Lucy) Fang (FDA)
Model-based statistical approaches for pharmacokinetic bioequivalence studies with sparse sampling and extension to two-stage designs	France Mentre (Inserm)
Development and comparison of model-based bioequivalence analysis methods on sparse data	Andrew Hooker (Uppsala University)
Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches	Xiaomei Chen (Uppsala University)

https://www.go-acop.org/acop-home

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Conclusions

- Non-longitudinal analysis is fast
- Pharmacometric analysis (in particular longitudinal population DER analysis):
  - Have higher power
  - Decision making with more accuracy and certainty
  - Requires an adequate examination of parameter AND model uncertainty

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