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Improved methodology for use of non-linear mixed effect models (NLMEM) in decision making

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EMA, London – March 30, 2017

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NLMEM – why attractive in small populations?

- Integrate information in data across
  - subjects
  - time (longitudinal analysis)
  - variables
  - covariates/predictors
- Allow prior knowledge to be incorporated
  - Drug/disease driven structural models
  - Parameter constraints from biological/pharmacological knowledge
  - Other knowledge/assumptions as appropriate

Decisions using NLMEM – model contrasts

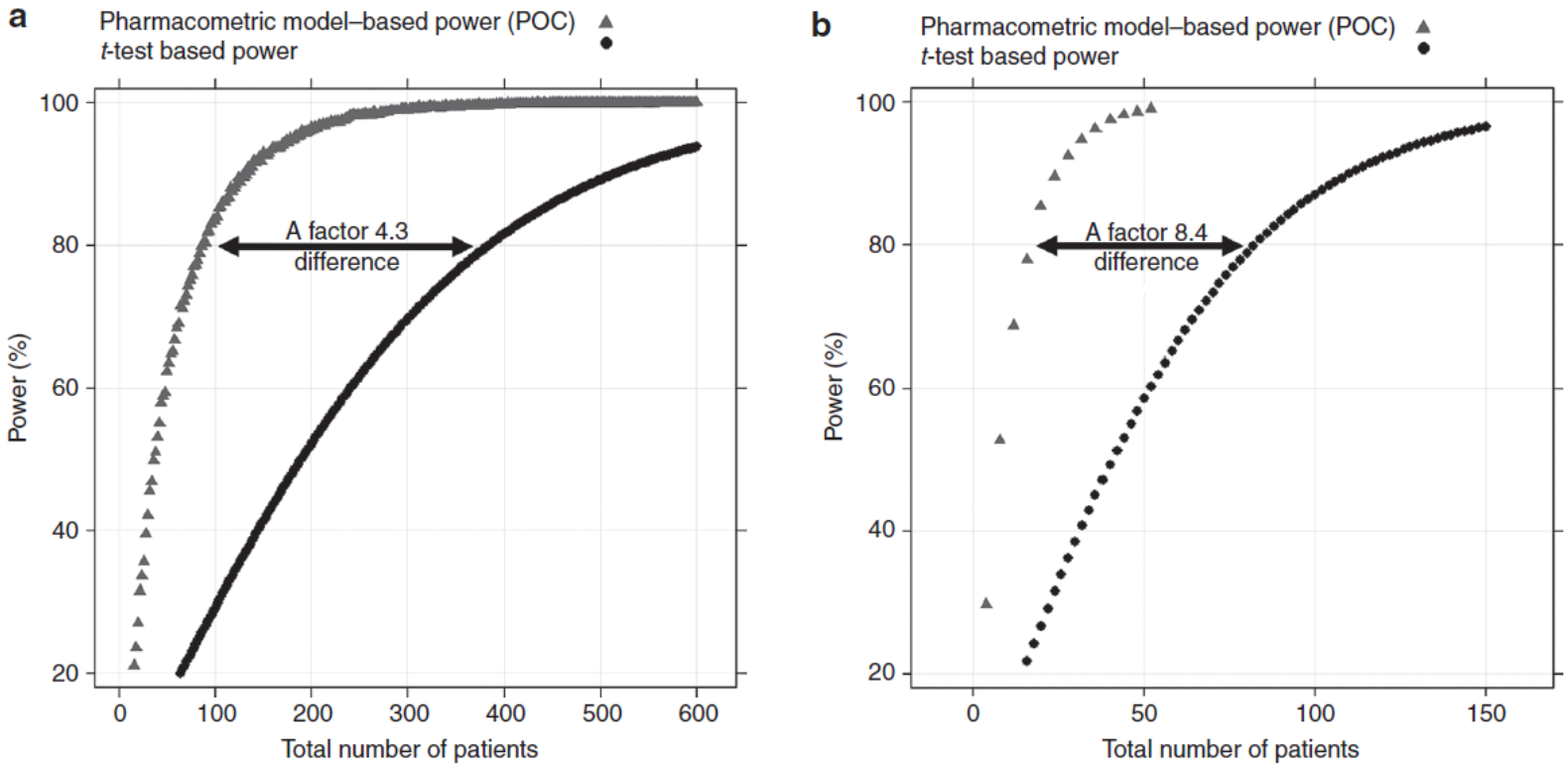


Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number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

Karlsson et al. CPT:PSP 2:e23 (2013)

Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

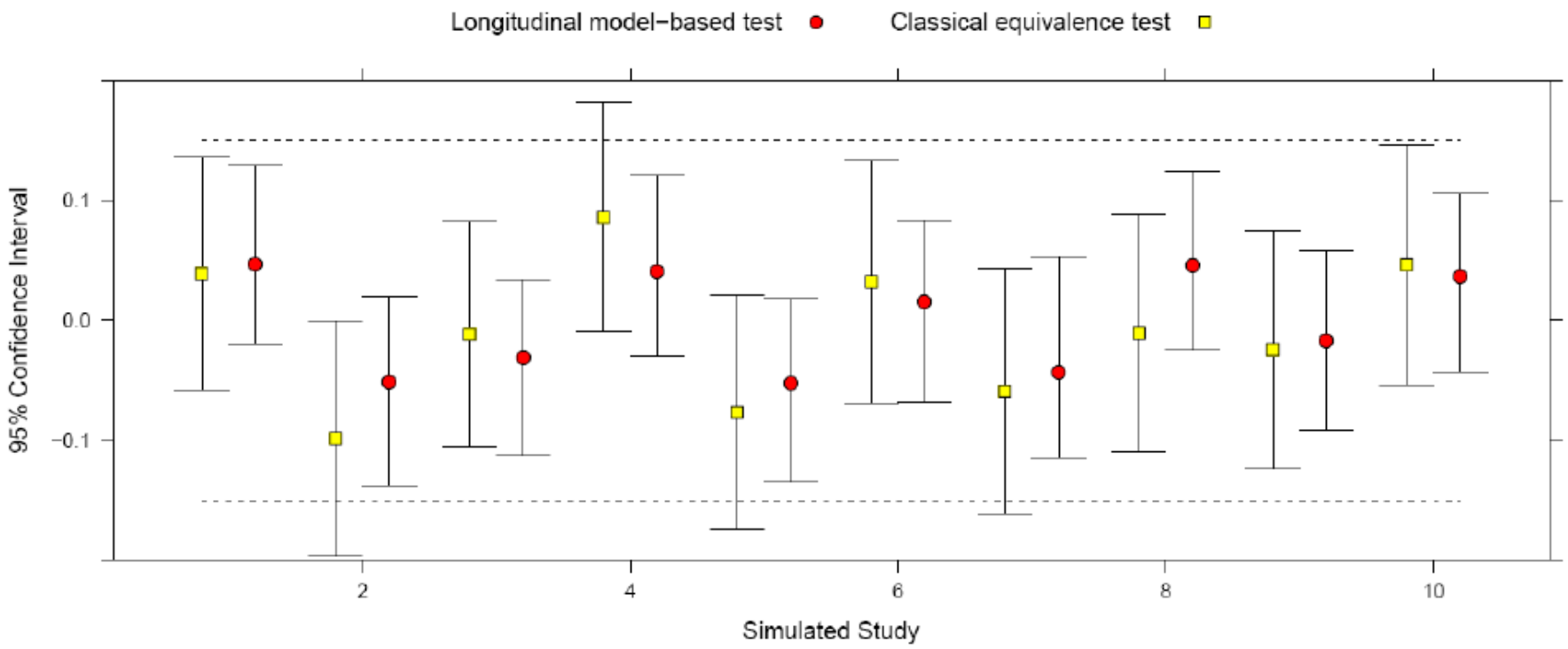
J Clin Pharmacol 2012 52: 1601

Yaning Wang, PhD, Pravin R. Jadhav, PhD, Mallika Lala, PhD, and Jogarao V. Gobburu, PhD

One of the important goals of the pediatric PK study is to ensure the precise estimate of important PK parameters, such as clearance and volume of distribution, to justify the choice of a safe and effective dose from a PK perspective. To achieve this goal, a standard regulatory requirement has been drafted and communicated to the sponsors, where applicable, as follows:

> The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power.

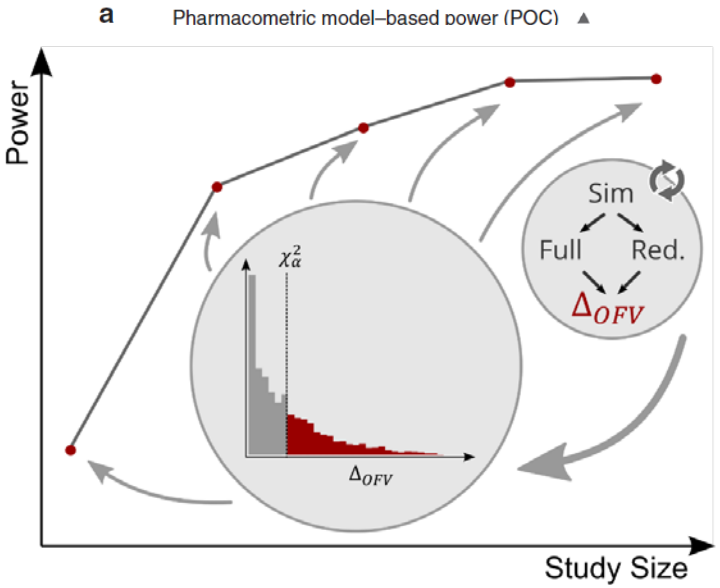
Decisions using NLMEM – predictive distributions

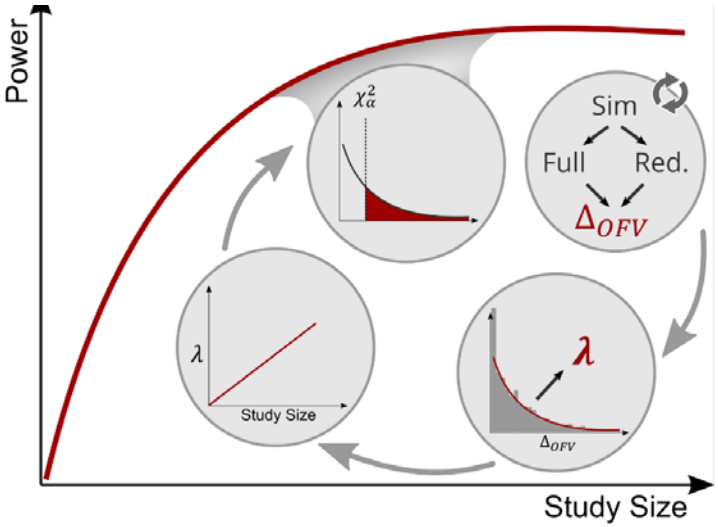


Model-based analyses for pivotal decisions, with an application to equivalence testing for biosimilars
Bieth et al, PAGE 2012

Power calculations for NLMEM

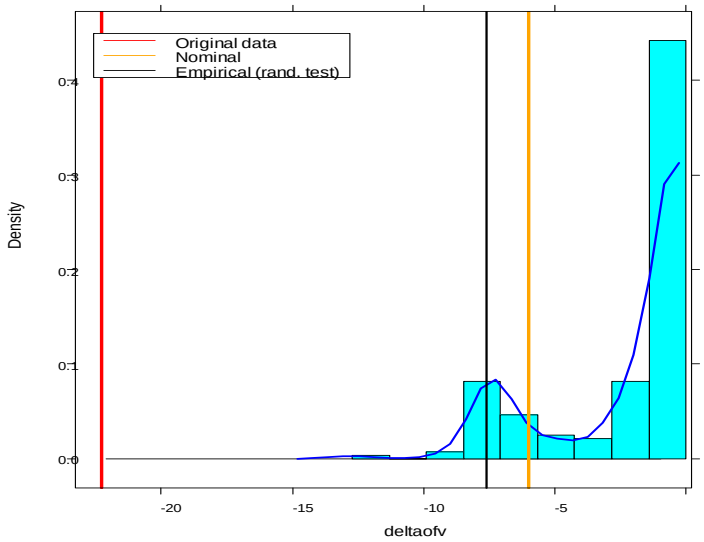
- **How to do timely and robust NLMEM power calculations?**
- **Resampling of individual likelihood contributions from one large simulated trial (Vong et al., 2012; Nordgren et al., 2017)**
- **Parametric power estimation (Ueckert et al, 2016)**

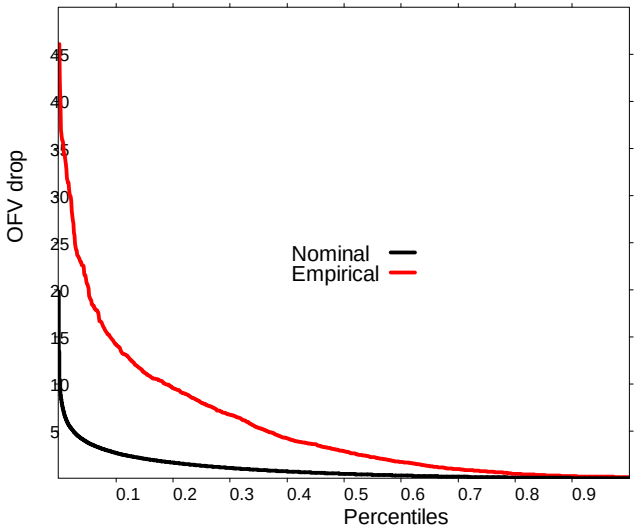




Hypothesis tests for NLMEM - Type 1 error

- Permutation test for NLMEM for
  - prespecified model (static or time-varying predictors)
  - model developed using blinded data and mixture model

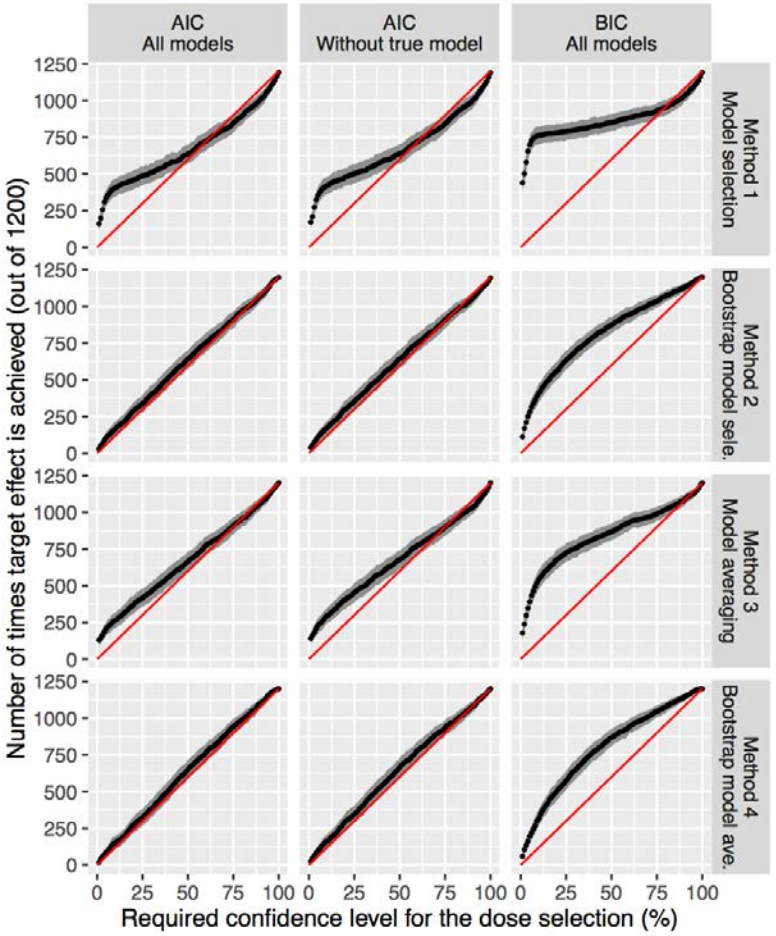




Deng et al. 2015, Harling et al. 2016

NLMEM – Model averaging for dose-response

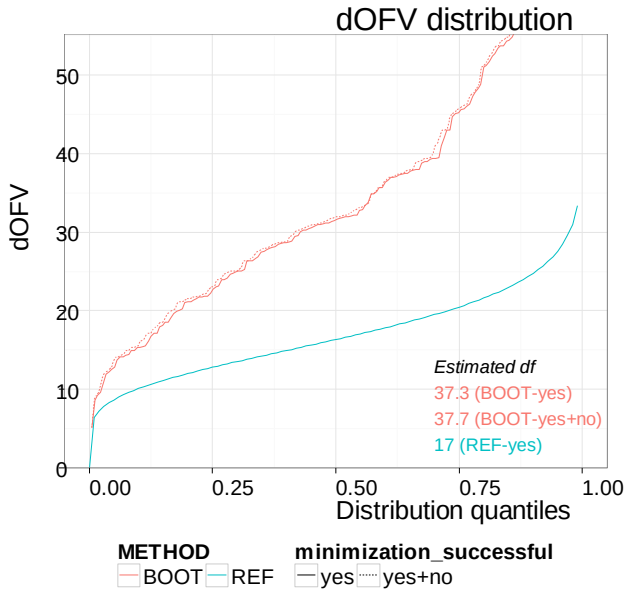
- A model-averaging technique for longitudinal dose-response data was developed and evaluated



Aoki et al., in manuscript

NLMEM - Parameter imprecision estimates

- **Development of a graphical diagnostic for parameter imprecision**
- **Poor small sample performance of bootstrap**
- **Development of a Sampling-Importance-Resampling procedure for NLMEM better suited for small samples**



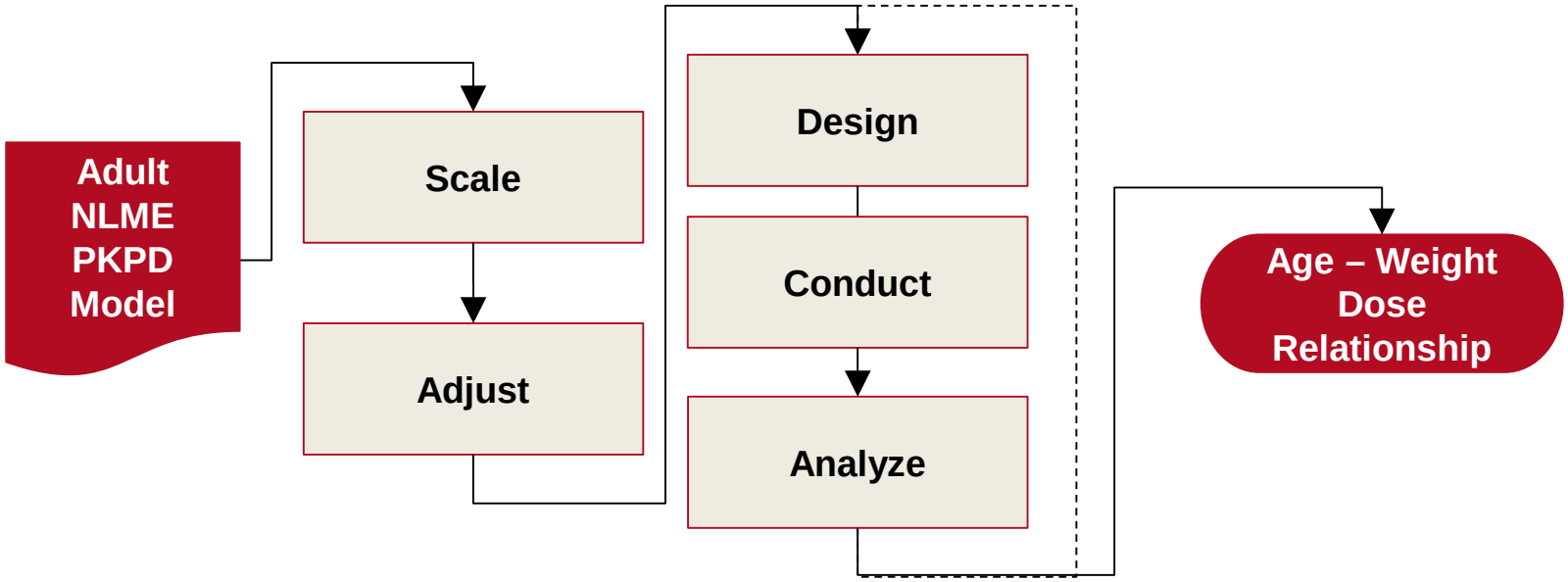
SAMPLING *Step 1*	• **Sample** *p* parameter vectors from covariance matrix
IMPORTANCE WEIGTHING *Step 2*	• **Calculate weights** based on fit to original data
RESAMPLING *Step 3*	• **Resample** *M* vectors based on weights from step 2 • Compute confidence intervals

Dosne et al., 2016a; Dosne et al., 2016b

NLME Model-based adaptive optimal design

Simulated model based adaptive optimal design of adult to children bridging study using FDA stopping criteria

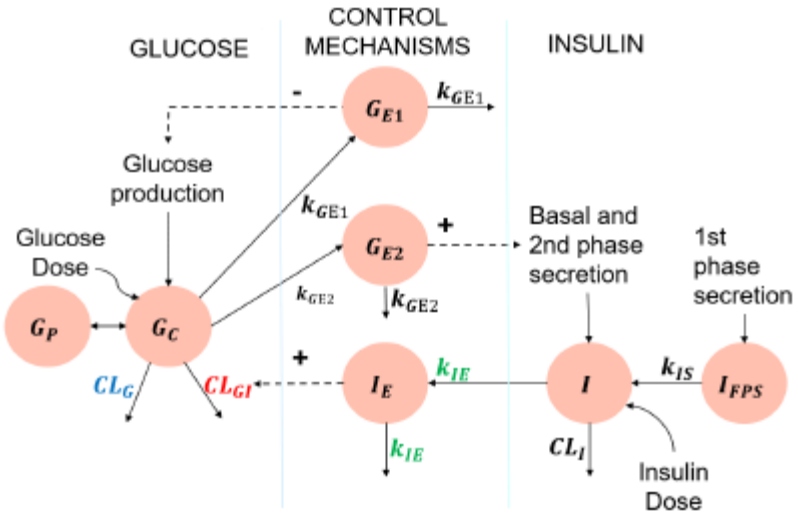
- Interim analysis after every cohort
- Update of design for next cohort
- Stopping if precision is sufficient

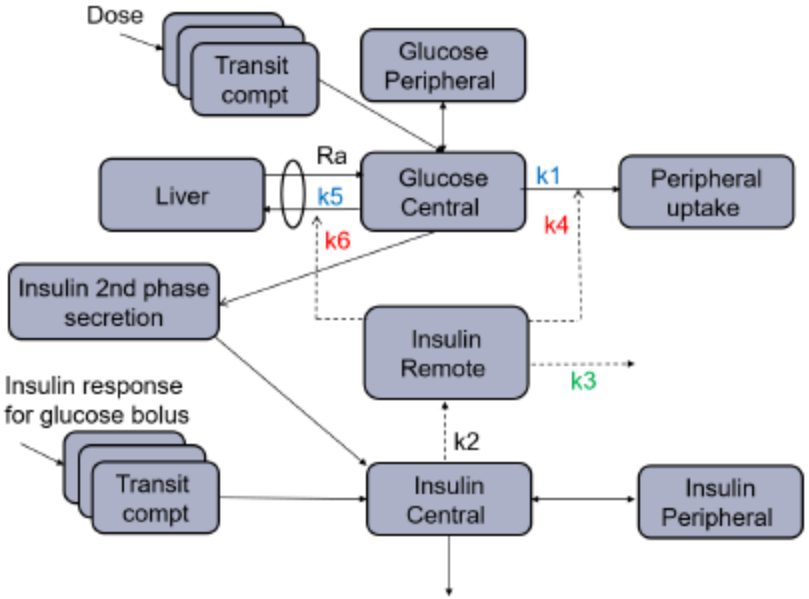


Hooker et al., 2015

NLMEM - Impact of model approximation

- Investigations of the impact of model approximation on assessment of drug effects





Wellhagen et al., 2015; Ibrahim et al., 2016

Summary

Methods/software developed for NLMEM

- Sample size/power calculation
- Type 1 error control
- Prespecified analyes using >1 model
- Model-based adaptive optimal design
- Diagonstics for parameter imprecision estimates
- SIR for NLMEM
- Model misspecification sensitivity analysis

Discussion

- What level of prespecification of analysis is demanded?

- What level of model misspecification is acceptable?

  Are present methods for misspecification diagnosis (& consequences) sufficient?

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