What is the value of Uncertainty Parameter Estimates provided by Different Population PK Methods ?

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(1) EA3738, Lyon; (2) IRIS Servier, Courbevoie; (3) CLB, Lyon; (4) Pharmacy University, Lyon; (5) INSERM, Lyon. (France)

Introduction

Population models: largely used in drug development, M&S and TDM

- Mixed-effects (hierarchical) model
  - ↳ statistical difficulties
- « Providing evidence for the quality of the results is important » [1]

[1] F. Mentré and M-E Ebelin. COSTB1. (1997)

Introduction

First criterion = RELIABILITY

⇩

« Is the model worthy of confidence ? » [1]

Degree of uncertainty associated with estimated parameters (summarised by standard error (SE) on parameters)

[1] P. J. Wiliiams, E. I. Ette. In Simulation for Designing Clinical Trials (2003)

Objectives

- Primary objective
  - Comparing SE estimation obtained by ≠ methods with ≠ designs
- Secondary objectives
  - Comparing parameter estimation
  - Observing influence of ≠ designs on SE estimation
  - Comparing computation time and "convergence" success between methods

↳ Choosing a reliable estimation method

Method

- Simulation of different PK datasets with different designs
- Estimation of PK parameters and SE for each dataset with different methods based on ML or MCMC
- Comparison of SE and parameter estimates between methods and designs

Method

- Simulation of different PK datasets with different designs

Simulation model

- Based on THEOPP example in NONMEM
  - one compartment
  - first order absorption and elimination
  - additive intra-individual variability
  - log-normal inter-individual variability (IIV)
  - non diagonal IIV covariance matrix
- Re-parameterization to avoid flip-flop

Designs

- Choice of optimal population design for simulation using POPOS 1.0 software [1]
- Simulation of 9 x 100 different datasets:
  - ➔ ≠ nb of samples (n = 3, 6 or 15)
  - ➔ ≠ nb of subjects (n = 30, 100 or 500)

[1] M. Tod, F. Mentré, Y. Merlé and A. Mallet. *JPB* (1998)

Method

- Estimation of PK parameters and SE for each dataset with different methods based on ML or MCMC

PK parameter estimation

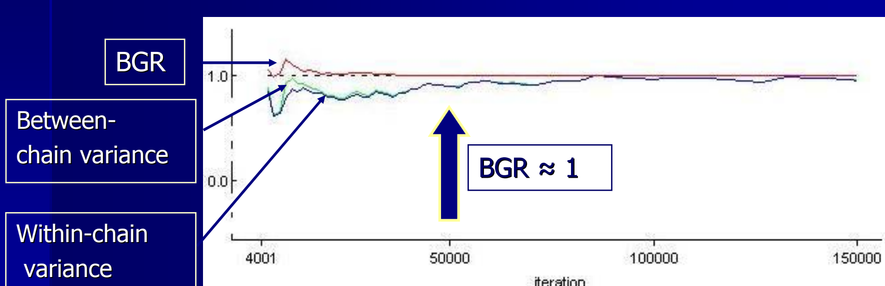
- Estimation with different methods
  - NONMEM™ FO and FOCE
  - nlme (Splus™)
  - WinBUGS (Bayesian method)

SE estimation

1. Covariance matrix ($COV) from NONMEM or SE provided by nlme
2. SD computed from posterior distribution in WinBUGS
3. SD of 200 bootstrapped datasets re-estimated with NONMEM™ FO, FOCE or nlme

Convergence criterion for WinBUGS

- Definition of iterations number (1) (Brooks and Gelman ratio (BGR)) (2) needed for convergence



(1) A. Gelman *et al.* In Bayesian Data Analysis (1995)
(2) WinBUGS user manual

Method: Expression of results

- For parameters estimation
  - relative bias:
    (estimated value – true value) / true value (%)
  - distribution
- For SE values
  - quartiles for each design and each method
  - evolution across designs

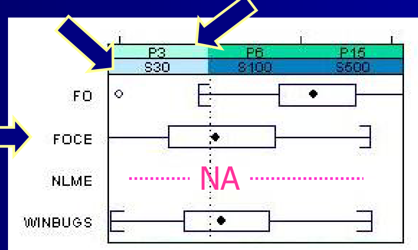
Results: Parameter estimation

Subject number

Sampling Time number

Estimation methods

N = 100

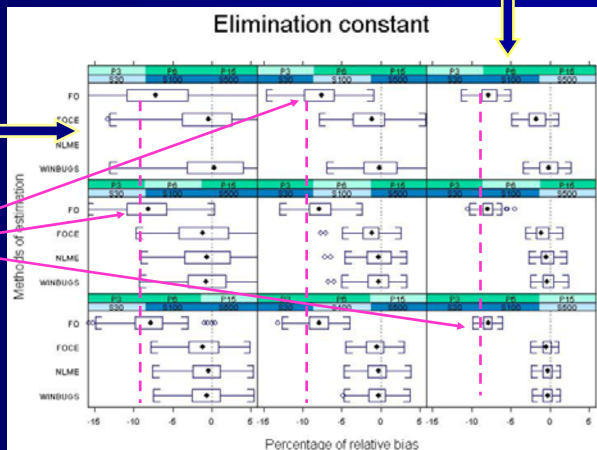


Results: Fixed effects

Same number of Subjects

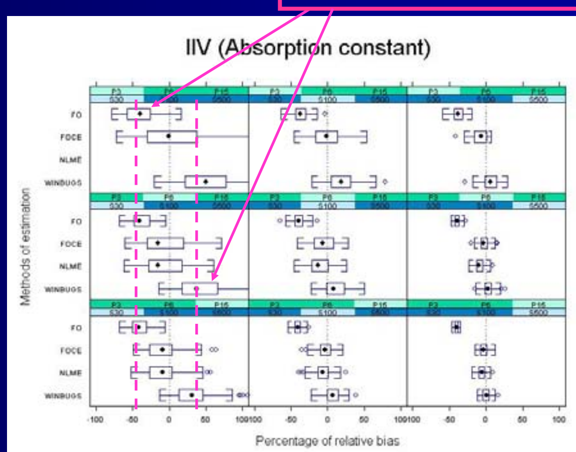
Same number of sampling times

FO : systematic bias [5 - 10%]



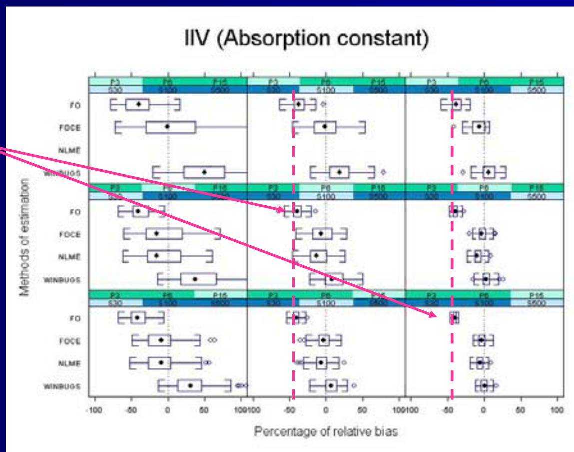
Results: Random effects (Variance)

Little number of subjects
Bias (FO and WinBUGS) ± 40 %



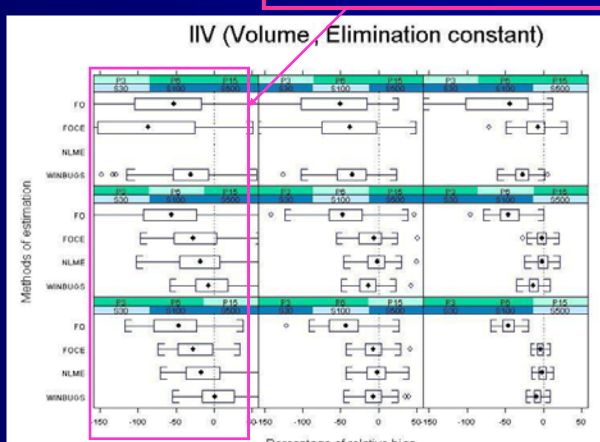
Results: Random effects (Variance)

FO systematic Bias ≈ 50 %



Results: Random effects (Covariance)

Little number of subjects: bias except for WinBUGS

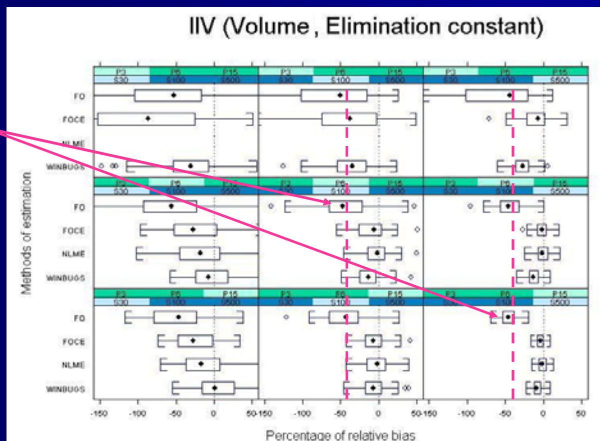


Correlation coeff = 0.91

Results: Random effects (Covariance)

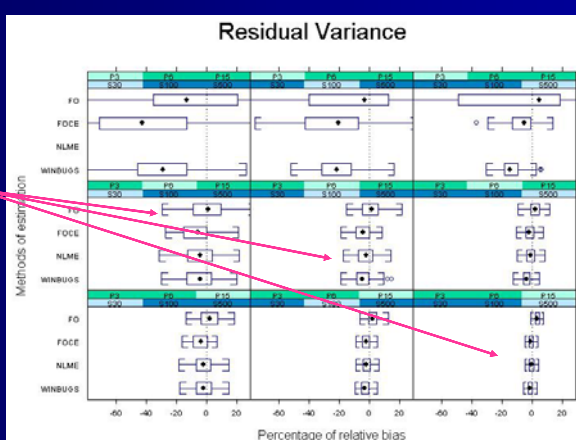
Bias FO systematic ≈ 50 %

Correlation coeff = 0.91



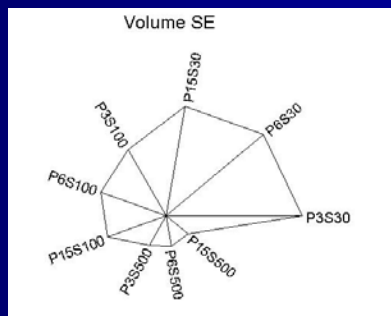
Results: Random effects (Residual variance)

Rich data: Unbiased results ∀ method



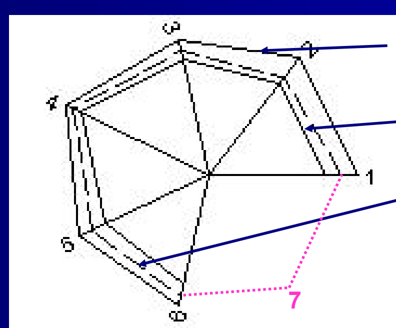
Results: Standard error

- Confirmation of a general assessment :
  SE value ↘ when number of subjects or samples ↗



Results: Standard error

Methods :
1 FO
2 FOCE
3 nlme
4 WinBUGS
5 BOOT + FO
6 BOOT + FOCE
7 BOOT + nlme



Q 75

Q 25

Median

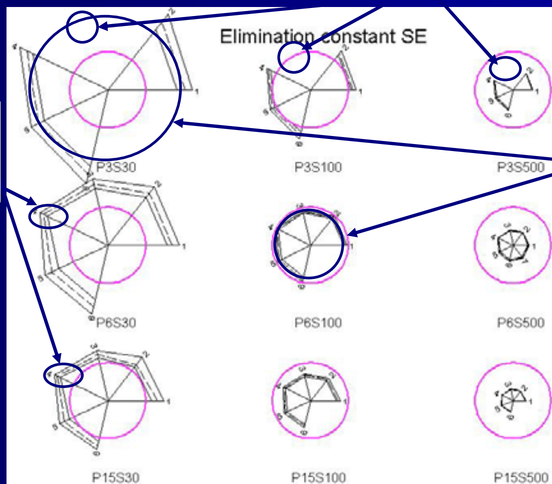
Methods :
1 FO
2 FOCE
3 nlme
4 WinBUGS
5 BOOT + FO
6 BOOT + FOCE
7 BOOT + nlme

Results: Standard error of fixed effects

not available

WinBUGS
less dispersion

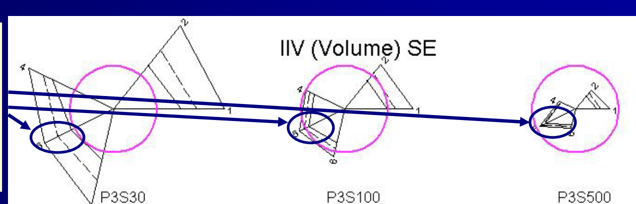
SE ≈
∀ method



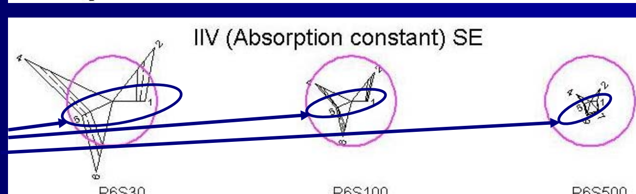
Methods :
1 FO
2 FOCE
3 nlme
4 WinBUGS
5 BOOT + FO
6 BOOT + FOCE
7 BOOT + nlme

Results: Standard error of random effects (variances)

sparse data, FO and BOOT + FO : little ↘ of SE when subject number ↗



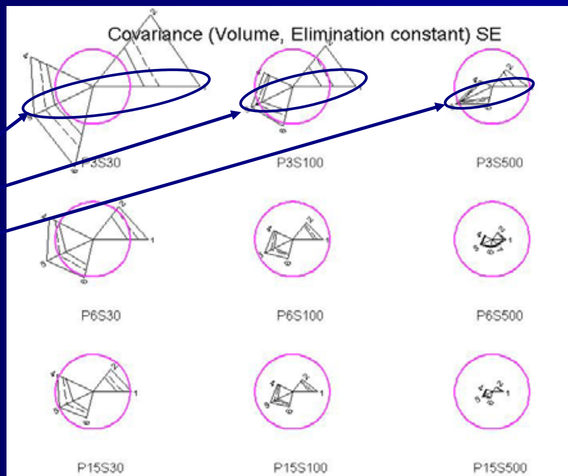
FO, BOOT +FO
SE <<
FOCE, WinBUGS , BOOT + FOCE
SE ≈



Results: Standard error of random effects (covariance)

Methods :
1 FO
2 FOCE
3 nlme
4 WinBUGS
5 BOOT + FO
6 BOOT + FOCE
7 BOOT + nlme

sparse data, FO and BOOT + FO : little ↘ of SE when subject number ↗



Results: Convergence and computation time

Methods	Mean % of "convergence"	Ratio of (computation time/ FO computation time) for same dataset
FO	97 (1)	1
FOCE	56 (1)	10
nlme	92 (2)	3
WINBUGS	100	189
BOOTFO	98 (3)	96
BOOTFOCE	85 (3)	936
BOOTnlme	91 (2)	unavailable (4)

(1) Convergence AND $COVariance achieved
(2) Only for designs where sampling time number ≥ 6
(3) Convergence achieved
(4) Due to large number of Splus crash

Conclusion (1/2)

Methods	+	-
FO		Bias on parameters SE estimation poorly reliable
FOCE	If bootstrap, SE comparable with other methods	SE available in only 56 % of datasets SE less consistent than Winbugs
nlme	Faster than FOCE	Non convergence when sampling time number=3
WinBUGS	Absence of crash Un, less biased between subject covariance estimate SE estimate consistent across 100 simulations	Bias on IIV variance with few subjects

Conclusion (2/2)

- Based on those simulations for a simple PK model, considering
  - CPU time needed for bootstrap compared to WinBUGS
  - absence of crash
  - good estimation properties

  WinBUGS should be preferred when uncertainty measurement is a key parameter

- Next steps: proc NLMIXED (SAS™), PD model

Thank you for your attention !