

# Residual-based bootstrap methods for estimating uncertainty of parameters in nonlinear mixed-effects models with heteroscedastic error

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## INTRODUCTION

- Several bootstrap methods have been proposed for estimating uncertainty of parameters in multi-level or linear mixed-effects models with heteroscedastic error<sup>1,2</sup>
- Residual bootstrap methods are an alternative approach to case bootstrap, which resamples the individuals and may be a good way to approach the data generating process<sup>3</sup>
- Most PKPD applications use the case bootstrap, for which software is available<sup>4,5</sup>

## OBJECTIVES

- Investigate residual bootstrap methods for nonlinear mixed-effects models (NLMEM) with heteroscedastic error
- Evaluate the performance of the residual bootstrap methods in comparison with the case bootstrap by simulation

## METHODS

### Case-based bootstrap

- Resample the individuals ( $B_{case,none}$ )

### Residual-based bootstrap

- Resample two levels of variability in the longitudinal data<sup>6,7</sup>
  - between-subject variability: resample the random effects ( $\eta$ )
  - residual variability: resample the residuals from all subjects (global residual, GR)
- Two versions of residual bootstrap
  - nonparametric bootstrap ( $B_{\eta,GR}$ ): resample from the empirical distribution
    - correction for shrinkage: random effects & standardised residuals were corrected by the ratio between the empirical and estimated variance-covariance matrices?
  - parametric bootstrap ( $B_{\eta,PR}$ ): simulate within the estimated distribution

### Simulation study

- Motivating example:
  - data from a phase I and a phase III clinical trials of aflibercept, an anti-VEGF drug, in cancer patients
  - real data fitted with a two-compartment infusion model with first-order elimination and correlation ( $\rho$ ) between clearance (CL) and intercompartment clearance (Q)
- Simulation ( $K=100$  replications) with frequent sampling ( $N=30$ ,  $n=9$ ) in R2.14
- Two models:

- first-order elimination:
  - same model of real data
  - correlation between CL and Q
  - high variability on Q (111%)
- Michaelis-Menten elimination:
  - no correlation between CL and Q
  - low variability on parameters (30%)

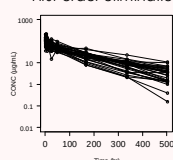
|                         | First-order elimination | Michaelis-Menten elimination |
|-------------------------|-------------------------|------------------------------|
| V1 (L)                  | 3.62                    | 3.62                         |
| V2 (L)                  | 2.9                     | 2.9                          |
| Q (L/hr)                | 0.14                    | 0.14                         |
| CL (L/hr)               | 0.04                    | Vm (mg/hr)                   |
|                         |                         | Km ( $\mu$ g/mL)             |
|                         |                         | 20                           |
| $\omega V1$ (%)         | 20                      | $\omega V1$ (%)              |
|                         |                         | 30                           |
| $\omega Q$ (%)          | 111                     | $\omega V2$ (%)              |
|                         |                         | 30                           |
| $\omega CL$ (%)         | 29                      | $\omega Vm$ (%)              |
|                         |                         | 30                           |
| $\rho_{CLQ}$            | 0.5                     |                              |
| $\sigma_{\epsilon}$ (%) | 25                      | $\sigma_{\epsilon}$ (%)      |
|                         |                         | 25                           |

- Resampling with three bootstrap methods ( $B_{case,none}$ ,  $B_{\eta,GR}$ ,  $B_{\eta,PR}$ ) implemented in R2.14
  - number of bootstrap per replication  $B=1000$
  - each bootstrap dataset was fitted with Monolix4.1
- Evaluation criteria:
  - relative bias of bootstrap parameter estimates (compared to the true values) and their standard error (SE) (compared to the empirical SE): unbiased ( $\pm 10\%$ ), biased ( $> \pm 10\%$ )
  - coverage rate of the 95% bootstrap CI: good (90-100%), low ( $< 90\%$ )
- Bootstrap estimates were compared to the asymptotic estimates given by Monolix4.1

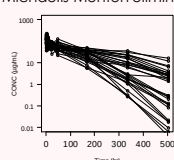
## RESULTS

### Examples of simulated data

First-order elimination

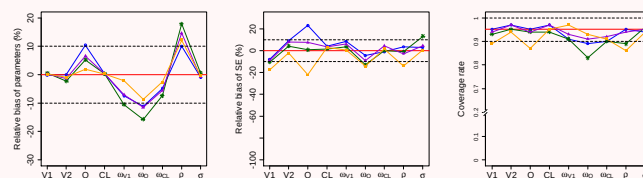


Michaelis-Menten elimination

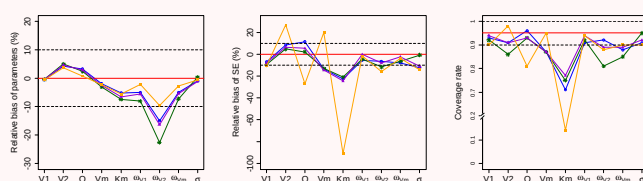


## Performance of bootstrap methods in two evaluated settings

First-order elimination



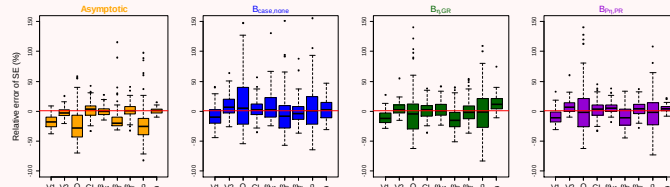
Michaelis-Menten elimination



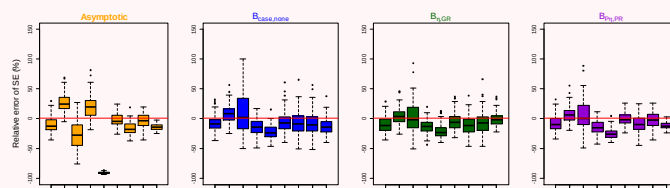
- The asymptotic approach systematically underestimates SE and gives low coverage rate for several parameters
  - the bias increases in design with Michaelis-Menten elimination, especially for Km (parameter with highest nonlinearity)
- The bootstrap approaches provide better estimates of SE and better coverage rate than the asymptotic approach, correcting the bias for most parameters, especially for Km
  - SE on Km was slightly underestimated and coverage rate was still low (70%)

## Boxplot of relative error of SE in two evaluated settings

First-order elimination



Michaelis-Menten elimination



- $B_{\eta,PR}$  works slightly better than  $B_{case,none}$  and  $B_{\eta,GR}$  in terms of both accuracy and precision

## CONCLUSION

- The nonparametric residual bootstrap works as well as the case bootstrap for both settings in NLMEM with heteroscedastic error but the case bootstrap is simpler to implement
- The parametric residual bootstrap works slightly better than the case bootstrap but may not be as robust to model or distributional misspecifications
- Bootstrap methods ( $B_{case,none}$ ,  $B_{\eta,GR}$ ,  $B_{\eta,PR}$ ) provide a better description of uncertainty for parameters, especially for nonlinear parameters (e.g Km) compared to the asymptotic approach

## REFERENCES

- Van der Leeden R et al. Bootstrap methods for two-level models. Technical Report PRM 97-04, Leiden University 1997.
- Thai H-T et al. PAGE 2011. A comparison of bootstrap approaches for estimating standard errors of parameters in linear mixed effects models. Abstr 2271 [www.page-meeting.org/?abstract=2271].
- Chernick MR. Bootstrap methods: A guide for practitioners and researchers. John Wiley & Sons, 2008.
- Parke J et al. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. *Comput Methods Programs Biomed* 1999; 59:19-29.
- Lindbom L et al. PsN-Toolkit-A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed* 2005; 79(3):241-257.
- Das S et al. Krishen A. Some bootstrap methods in nonlinear mixed-effects models. *J Stat Plan Inference* 1999;75: 237-245.
- Wang J et al. Using SAS to conduct nonparametric residual bootstrap multilevel modeling with a small number of groups. *Comput Methods Programs Biomed* 2006;82:130-143.