

Conditional non-parametric bootstrap for non-linear mixed effect models

Emmanuelle Comets^{1,2,*}, Sofia Kaisaridi¹, Moreno Ursino^{3,4,5}

¹ Univ Paris Cité, IAME, Inserm, F-75018 Paris, France ² Inserm, Univ Rennes, EHESP, Irset-UMRS 1085, F-35000 Rennes, France ³ Inria, HeKA, F-75015 Paris, France
⁴ Inserm, Sorbonne Univ, Univ Paris, F-75006 Paris, France ⁵ Unit of Clinical Epidemiology, APHP, CHU Robert Debré, Paris, France

Objective: propose and evaluate a new non-parametric bootstrap to estimate uncertainty in NLMEM

Introduction

- Estimation errors in non-linear mixed effect models (NLMEM)
 - generally obtained using the inverse of the Fisher information matrix
 - * asymptotic approach valid with large number of subjects and of observations per subject
 - alternative approaches: likelihood profiling, bootstrap, SIR
- Bootstrap methods in NLMEM need to consider the hierarchical nature of the data [1]
- Evaluated in these models with contrasting results [2]
 - sparse and rich designs
 - good performance of case bootstrap
 - * stratification issues with heterogeneous designs
 - good performance of parametric bootstrap
 - * in settings where the distribution of the residuals is correct
 - non-parametric bootstrap
 - * requires corrections for shrinkage in the individual residuals
- Proposal: Conditional non-parametric bootstrap
 - samples from the conditional distribution are used to correct shrinkage in diagnostics [3]
 - idea: build bootstrap samples using residuals sampled from the individual conditional distributions

Methods

Statistical models

Model for observation y_{ij}

$$y_{ij} = f(\Psi_i, x_{ij}) + g(\Psi_i, \gamma, x_{ij})\epsilon_{ij}$$

- subject i ($i = 1, \dots, N$), with n_i observations $\mathbf{y}_i = \{y_{i1}, \dots, y_{in_i}\}$ at times t_{ij} , and covariates \mathbf{z}_i
- f : structural model (analytical expression, see example)
- $g = g(a, b, c)$: residual error model (one of: constant, proportional, combined, exponential) with parameters $\gamma = \{a, b, c\}$
- individual parameters Ψ_i
 - modelled parametrically as a function $\Psi_i = h(\phi_i, \mathbf{z}_i) = h(\mu(\mathbf{z}_i), \eta_i)$ of fixed effects μ and random effects η_i ($\eta_i \sim \mathcal{N}(0, \Omega)$)
 - in saemix, h can be the identity function (normal distribution for Ψ), the exponential function (log-normal distribution for Ψ), or the logit or probit transformations

Bootstrap methods

- **Case bootstrap (CaseBoot)**: resample complete individuals from the dataset
- **Parametric residual bootstrap (PBoot)**: resample within a theoretical distribution
- **Non-parametric residual bootstrap (NPBoot)**: resample empirical residuals after centering and scaling

- **Full conditional non-parametric residual bootstrap (cNPBoot)**: re-sample η from individual conditional distributions, and ϵ from the distribution obtained using the conditional estimates (Fig. 0)

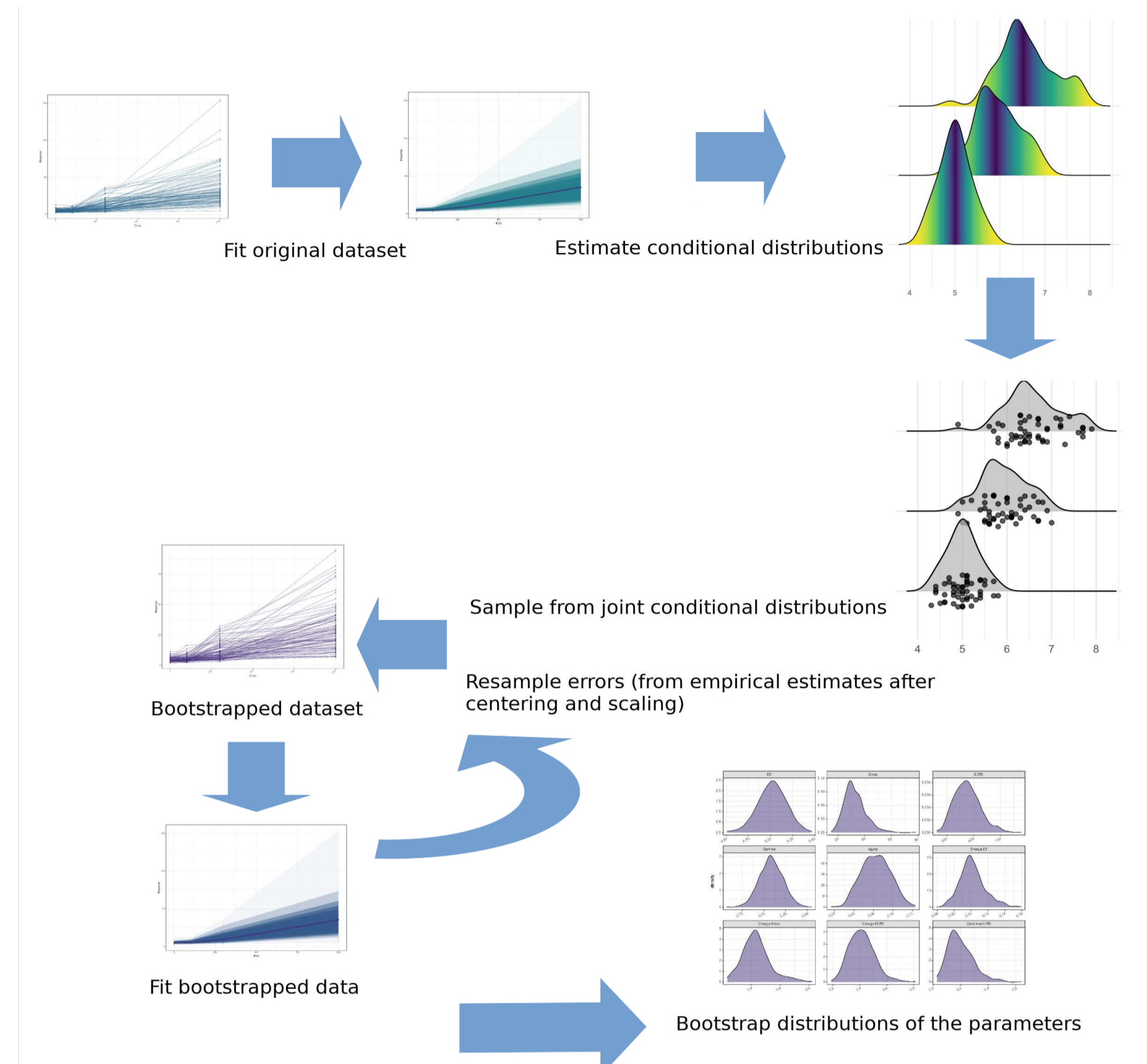


Fig. 1: Algorithm for Conditional non-parametric bootstrap

Objective Compare the performance of conditional non-parametric bootstrap with other bootstrap approaches

Evaluation of conditional non-parametric bootstrap

Simulation study:

Simulation setting inspired by Plan et al. [4]:

- base structural model: sigmoid Hill model
- lognormal distribution, no variability on γ
- residual error model: proportional error

Simulation scenarios:

- S_{orig} : simulated datasets from [5]
 - two models: E_{max} ($\gamma = 1$) and Hill ($\gamma = 3$)
 - rich designs $S_{Emax,R}$ and $S_{Hill,R}$: $N=100$ subjects given 4 doses each (0, 100, 300, 1000)
 - sparse designs $S_{Emax,S}$ and $S_{Hill,S}$: $N=200$ subjects divided in 4 groups of 50 subjects given 2 doses each among the following 4 combinations (0,1000), (100,1000), (0,300) and (100,300)

- S_{σ} : influence of the residual error
 - σ varying from $\{0.1, 0.3, 0.5\}$
 - rich and sparse designs

- S_{unb} : unbalanced designs
 - 4 designs with $N=100$
 - expected RSE checked with PFIM [6]

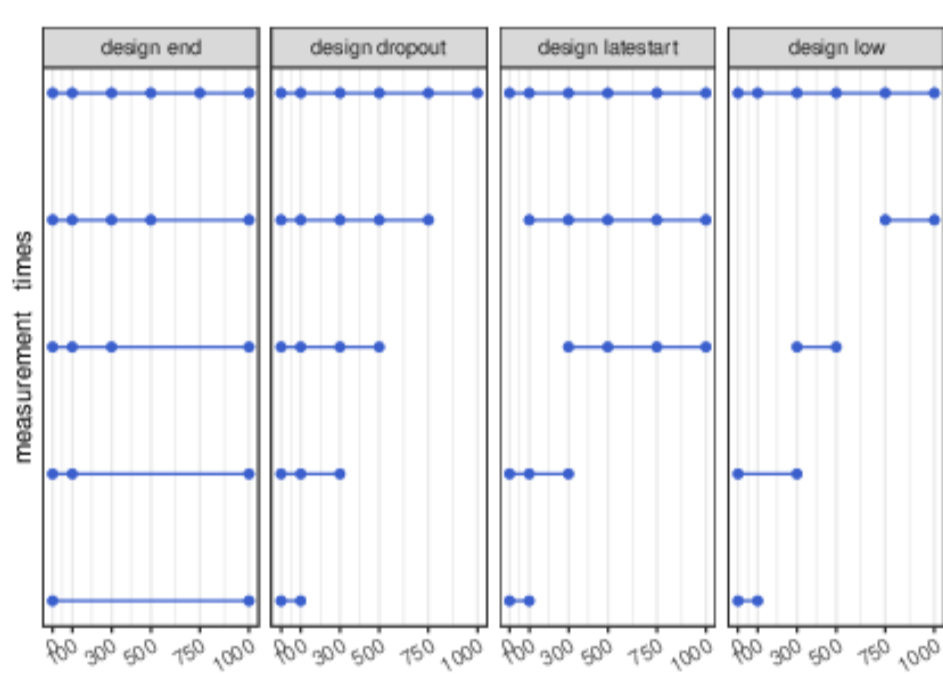


Fig. 2: Unbalanced designs in S_{unb}

- for each scenario, 200 simulated datasets
 - 200 bootstrap samples for each bootstrap
 - 100 samples from the conditional distributions for cNPBoot

Evaluation of bootstrap methods:

- empirical SE obtained from K simulated datasets giving the "true" value observed across the simulations

$$SE_{\text{empirical}}(\hat{\theta}) = \sqrt{\frac{1}{K-1} \sum_{k=1}^K (\hat{\theta}_k - \theta_0)^2} \quad (1)$$

- relative bias and RMSE: compared to the parameters used for the simulation

$$RBias(\hat{\theta}) = \frac{1}{B} \sum_{b=1}^B \frac{\hat{\theta}_b - \theta_0}{\theta_0} \times 100 \quad (2)$$

$$RBias(SE(\hat{\theta})) = \frac{1}{B} \sum_{b=1}^B \frac{SE_B(\hat{\theta}) - SE_{\text{empirical}}(\hat{\theta})}{SE_{\text{empirical}}(\hat{\theta})} \times 100 \quad (3)$$

- coverage rate of the 90% bootstrap CI for each estimated parameter: probability that CI contains the true value of the parameter
- compare with the asymptotic SE given by the software and obtained as the inverse of the Fisher information matrix
- good bootstrap: low bias for parameter estimates and their corresponding SE (less than 5%), and good coverage rate of the 90% CI (85% to 95%)

Simulations performed in R, estimations using the saemix library [7] (default options and setting the initial parameters for the fixed and random effects to the true value in all runs).

Results

Original design

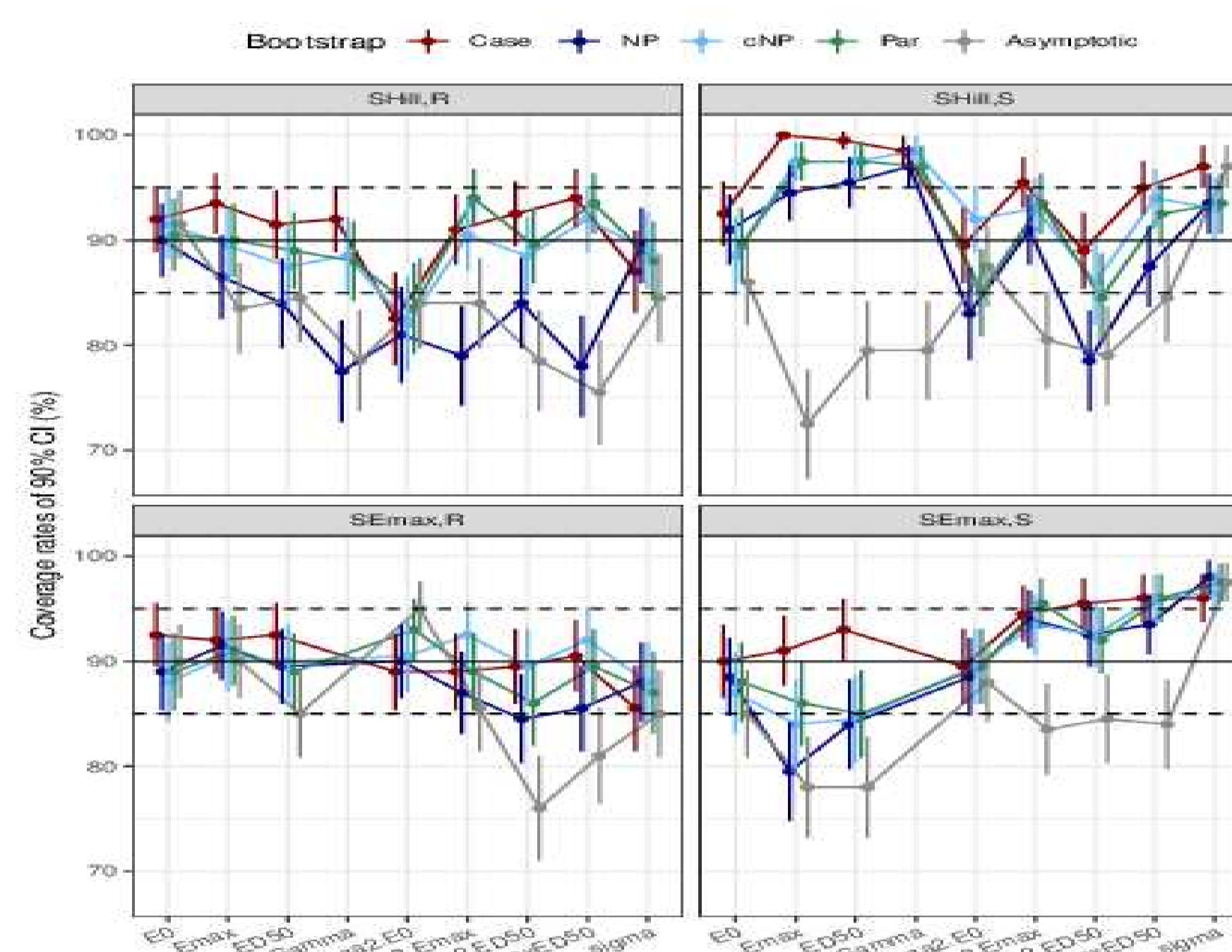


Fig. 3: 90% coverage rates for sparse and rich designs using Hill and Emax models

- Undercoverage by asymptotic and sometimes by NP bootstrap
- cNP better than NP, as good as Case and Par

Unbalanced design

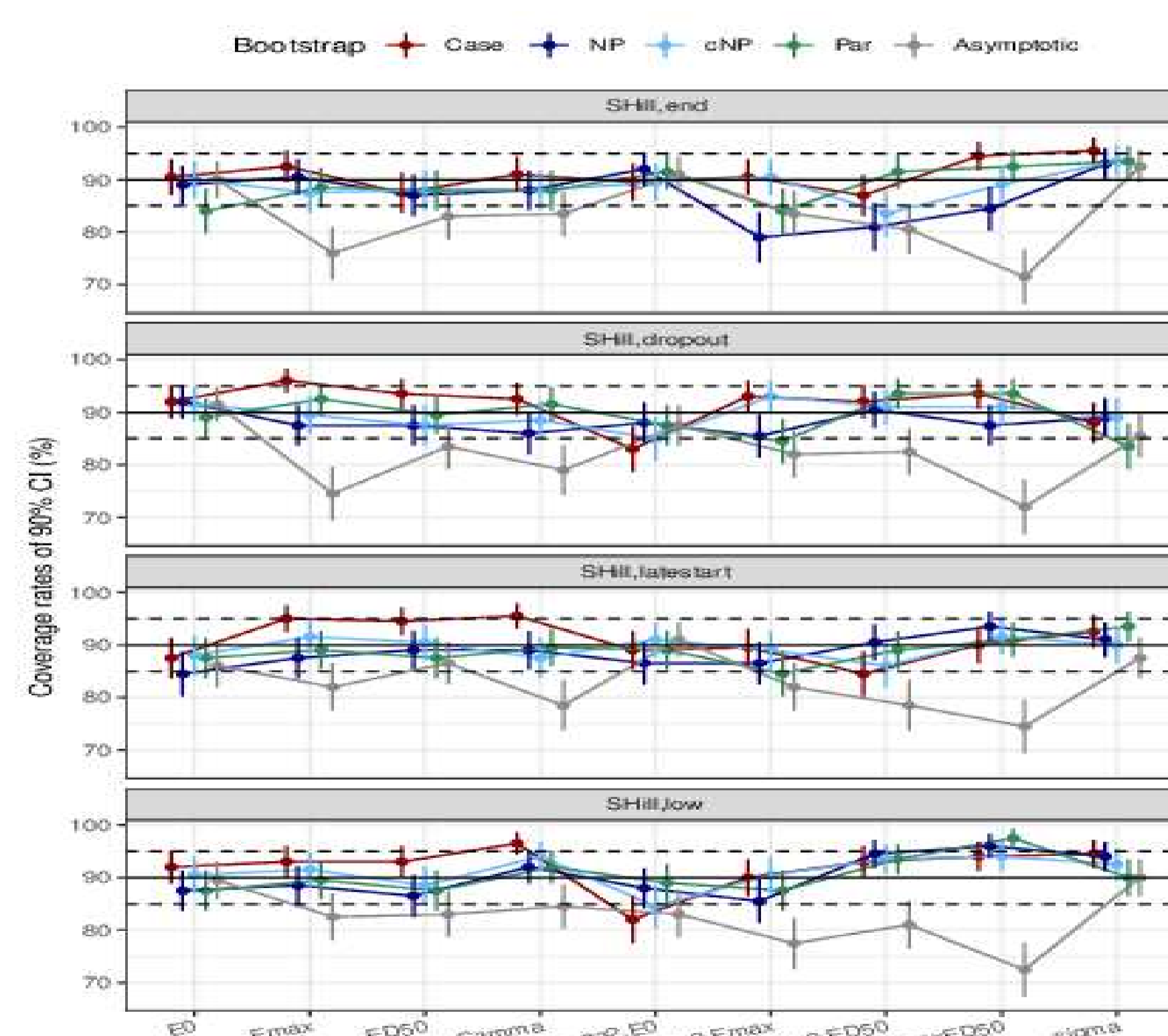


Fig. 4: 90% coverage rates for unbalanced designs with a Hill model

- Undercoverage by the asymptotic method
- Relatively good performances by all the bootstraps, sometimes undercoverage by NP
- Good results for Case bootstrap even in a non stratified version

Increasing the residual error

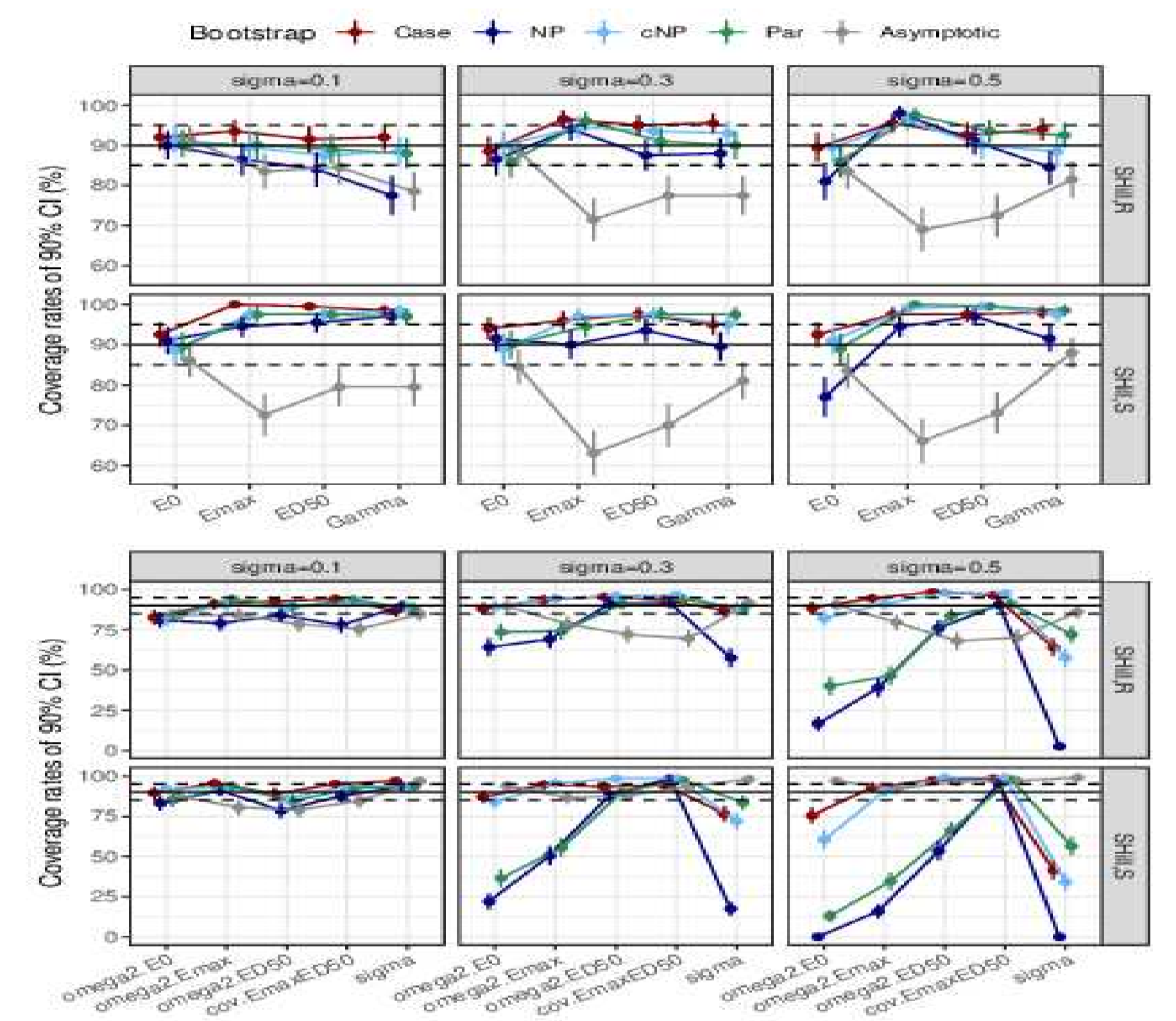


Fig. 5: 90% coverage rates with increasing amounts of residual error

- fixed effects
 - undercoverage with the asymptotic method
 - trend for overcoverage in the sparse scenario for all bootstraps
- random effects
 - very low coverage for NP and Par with higher residual error
 - performance of cNP and Case also degrades
- cNP and Case better than NP
- poor performance of Par when residual error increases

Conclusion

- **Conditional non-parametric bootstrap**
 - relies on samples from the conditional distribution in the hopes of correcting for shrinkage in a subject-specific way
 - full conditional approach implemented here, including resampling of conditional residual errors
 - improved estimation of the residual error parameter compared to an approach where only random effects were resampled in the conditional distributions [5]
- Evaluation in unbalanced designs representing situations where some subjects receive a full set of doses while others receive only low, only high, or a mix of doses
 - Case bootstrap robust even without stratification
 - better performance of the cNP compared to the NP
- Poor performance of all methods, including the asymptotic method, when the residual error increases
 - particularly for Par bootstrap, which proved very sensitive in this scenario
 - increased bias in the estimates with $\sigma = 0.5$, linked to the ability of the design to estimate all parameters
 - other works suggest caution in small sample studies [8]

REFERENCES

[1] HT Thai, F. Mentré, N H Holford, C Veyrat-Follet, and E Comets. A comparison of bootstrap approaches for estimating uncertainty of parameters in linear mixed-effects models. *Pharmaceutical Statistics*, 12:129–40, 2013.
 [2] HT Thai, F. Mentré, N H Holford, C Veyrat-Follet, and E Comets. Evaluation of bootstrap methods for estimating uncertainty of parameters in nonlinear mixed-effects models: a simulation study in population pharmacokinetics. *Journal of Pharmacokinetics and Pharmacodynamics*, 41:15–33, 2014.
 [3] M Lavielle and B Ribba. Enhanced method for diagnosing pharmacometric models: random sampling from conditional distributions. *Pharmaceutical Research*, 33:2979–88, 2016.

[4] E Plan, A Maloney, F Mentré, MO Karlsson, and J Bertrand. Performance comparison of various maximum likelihood nonlinear mixed-effects estimation methods for dose-response models. *The AAPS Journal*, 14:420–432, 2012.
 [5] E Comets, C Rodrigues, V Jullien, and M Ursino. Conditional non-parametric bootstrap for non-linear mixed effect models. *Pharmaceutical Research*, 38:1057–66, 2021.
 [6] C Dumont, G Lestini, H Le Nagard, F Mentré, E Comets, TT Nguyen, and the PFIM Group. PFIM 4.0, an extended R program for design evaluation and optimization in nonlinear mixed-effect models. *Computer Methods and Programs Biomedicine*, 156:217–29, 2018.
 [7] E Comets, A Lavenu, and M Lavielle. Parameter estimation in nonlinear mixed effect models using saemix, an R implementation of the SAEM algorithm. *Journal of Statistical Software*, 80:1–41, 2017.

[8] A Broecker and S G Wicha. Assessing parameter uncertainty in small-n pharmacometric analyses: value of the log-likelihood profiling-based sampling importance resampling (llp-sir) technique. *Journal of Pharmacokinetics and Pharmacodynamics*, 47:219–28, 2020.

* Presenting author

email: emmanuelle.comets@inserm.fr

