Evaluating Bootstrap Methods in Nonlinear Mixed Effect Models Using a PK Model

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INTRODUCTION

Bootstrap methods have been widely applied in estimating confidence intervals (CI) or model validation of nonlinear mixed effect models (NMEM) for population PK and PD models (Williams and Kim 2007). The existing literature in PK/PD studies is limited in describing the bootstrap methods and application of nonparametric bootstrap CI methods for PK/PD parameters. Neither is the bias and reliability of various bootstrap CI methods investigated, nor is an application of using the parametric (residual) bootstrap method performed. In addition, in many current PK/PD publications, the bootstrap distribution and CI of PK/PD parameters are compared to the parameter estimation and its derived CI of the original data as a tool of model validation. The legitimacy of this approach is explored here.

OBJECTIVES

There are 3 objectives in this research:

- To utilize statistical criteria to investigate the bias and reliability of popular bootstrap CI methods
- To compare nonparametric and parametric bootstrap (residual) methods
- To assess whether bootstrap distribution and CI can be used for model validation. To our knowledge, this may be the first investigation on residual bootstrapping methods on NMEM

METHODOLOGY

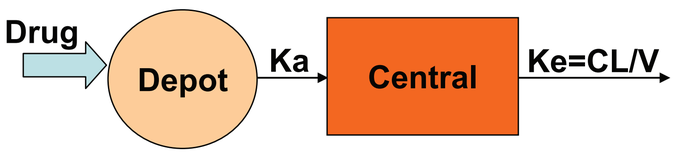
Bootstrap Methods

Both nonparametric and parametric (residual) bootstrap methods are investigated. The nonparametric method generates the bootstrap samples by sampling individuals (e.g., subjects in PK/PD modeling) with replacement from the original dataset. The parametric method is a resampling procedure where the resamples are obtained from an assumed distribution whose parameters are estimated from the sample (Das and Krishen 1999). In addition to the standard CI based on the normal theory, a variety of bootstrap confidence intervals (CIs) were constructed using percentile, t interval, bias-corrected (BC), bias-corrected and accelerated (BCa), and hybrid approaches (Barker, Phuse 2005).

Simulation:

A one compartment model with a single oral dose was assumed throughout our investigation. The simulated PK model was a one compartment model with first-order absorption and elimination and incorporated an inter-subject variability on clearance. This model has analytic equations. Two sampling schemes with small and moderate number of subjects were investigated. The first scheme consisted of 30 subjects with rich sampling where each subject was sampled at 10 time points. The second scheme contained 80 subjects with sampling only on 3 time points. 100 replicates of the dataset were generated for each scheme with 100 times of bootstrapped samples for each replication. An additional case on rich samplings of nonparametric bootstrap with 1000 replicates of dataset with 1000 bootstrapping samples was run to validate the results of 100 replicates.

Figure 1. The PK model in the first scenario is a one compartment oral dose model with first order absorption and first order elimination.



Parameters:

Cl: Central clearance (L/hr)

V: Central volume (L)

Ka: Absorption rate constant (/hr)

Ke: Elimination rate constant (/hr)

Model:

Inter-subject variation: exponential error term: (σ^2_ε)

Intra-subject variation for Cl: log-normal distributed: (σ^2_{CL})

Input Parameter Values:

0.175 for Cl, 5 for V and 0.1 for Ka.

Variance parameters initialized at 0.04

Two schemes:

Intensive sampling
30 subjects, 10 sampling points per subject at time {0.1, 0.4, 1, 2, 4, 7, 10, 20, 40, 70}

Sparse sampling
80 subjects, 3 sampling points per subject from the set: {1, 20, 40}

Model Misspecification

The performance of bootstrapping was also evaluated in the event that an inter-subject variability on the absorption rate (Ka) was incorrectly specified. Data is generated from the same model with an additional intra-subject variation for Ka, which is log-normal distributed with the variance of 0.04. The variability of Ka is not taken into account when fitting the model.

Evaluations

Bias, root mean squared error (RMSE), and coverage probability of 95% CIs, which is the proportion of the time that the interval contains the true parameter value of interest, are evaluated.

RESULTS

Bootstraps methods comparison

In both rich and sparse sampling scenarios of our simple PK model, the nonparametric method is superior to the parametric method in bias and CI coverage of the clearance and its inter-subject variability. Among CI estimation methods, the standard normal method has a better coverage than the rest of the methods and validates the simulation set-up with normal distributions of variance. All bootstrap CI methods perform equivalently well in the nonparametric method. The results of 1000 replicates of dataset with 1000 bootstrapping samples are consistent with the 100 replicates of 100 bootstrapping samples.

Table 1. Mean, % bias, and RMSE for non-parametric bootstrap method (left) and parametric bootstrap method (right) for two schemes

Scheme	Parameter	True	Mean		% Bias		RMSE	
Intensive Sampling	CL	0.175	0.174	0.175	-0.5	-0.2	0.007	0.081
	Ka	0.1	0.10	0.10	-0.2	0.1	0.006	0.075
	V	5	4.99	5.00	-0.2	0.0	0.244	0.494
	σ^2_ε	0.04	0.04	0.04	-1.3	-1.5	0.004	0.060
	σ^2_{CL}	0.04	0.04	0.03	-5.5	-34.2	0.013	0.114
Sparse Sampling	CL	0.175	0.173	0.174	-1.0	-0.5	0.009	0.092
	Ka	0.1	0.10	0.10	1.8	3.6	0.011	0.105
	V	5	5.06	5.14	1.3	2.8	0.504	0.710
	σ^2_ε	0.04	0.04	0.04	-2.5	-8.3	0.005	0.070
	σ^2_{CL}	0.04	0.04	0.01	4.6	-69.8	0.015	0.120

Table 2. Coverage probability of 95% CIs for non-parametric bootstrap method (left) and parametric bootstrap method (right) for two schemes

Scheme	Parameter	Standard		Percentile		Hybrid		t-interval		BC		BCa	
Intensive Sampling	CL	0.97	0.97	0.95	0.36	0.94	0.31	0.93	0.86	0.95	0.30	0.95	0.30
	Ka	0.99	0.99	1.00	0.97	0.97	0.96	0.96	0.96	0.99	0.96	0.99	0.96
	V	0.99	0.99	0.98	0.97	0.95	0.95	0.96	0.96	0.97	0.94	0.97	0.94
	σ^2_ε	0.96	0.96	0.92	0.92	0.91	0.91	0.95	0.95	0.92	0.92	0.93	0.92
	σ^2_{CL}	0.91	0.91	0.89	0.17	0.88	0.23	0.88	0.06	0.89	0.23	0.89	0.23
Sparse Sampling	CL	0.93	0.93	0.91	0.85	0.89	0.78	0.92	0.81	0.87	0.80	0.87	0.80
	Ka	0.87	0.87	0.90	0.83	0.83	0.77	0.84	0.82	0.88	0.83	0.88	0.83
	V	0.89	0.89	0.89	0.83	0.81	0.79	0.84	0.83	0.90	0.82	0.90	0.83
	σ^2_ε	0.87	0.87	0.85	0.71	0.85	0.72	0.85	0.74	0.88	0.71	0.88	0.71
	σ^2_{CL}	0.91	0.91	0.90	0.08	0.88	0.06	0.87	0.03	0.87	0.18	0.87	0.18

Model Misspecification

When the model is incorrectly specified in the smaller random error case, all parameters except the intra-subject variability term have a good coverage with all the methods. The percentile method has the highest coverage in the sparse sampling case. The coverage becomes lower for hybrid and t interval methods in the sparse sampling case than the rich sampling case. The coverage of the CIs for the intra-subject variability is low for the standard normal method and all bootstrap CIs.

Table 3. Mean, % bias, and RMSE for non-parametric bootstrap method (left) and parametric bootstrap method (right) for two schemes in Ka

Scheme	Parameter	True	Mean		% Bias		RMSE	
Intensive Sampling	CL	0.175	0.176	0.177	0.7	1.3	0.007	0.007
	Ka	0.1	0.10	0.10	1.5	1.1	0.008	0.008
	V	5	5.09	5.08	1.9	1.7	0.297	0.311
	σ^2_ε	0.04	0.06	0.06	54.3	51.0	0.023	0.022
	σ^2_{CL}	0.04	0.03	0.02	-17.8	-55.5	0.015	0.025
Sparse Sampling	CL	0.175	0.174	0.173	-0.7	-0.9	0.008	0.008
	Ka	0.1	0.10	0.11	4.7	7.6	0.011	0.013
	V	5	5.21	5.34	4.3	6.9	0.476	0.559
	σ^2_ε	0.04	0.06	0.05	38.2	24.8	0.016	0.012
	σ^2_{CL}	0.04	0.03	0.01	-23.3	-68.4	0.015	0.028

Table 4. Coverage probability of 95% CIs for non-parametric bootstrap method (left) and parametric bootstrap method (right) for two schemes in Ka

Scheme	Parameter	Standard		Percentile		Hybrid		t-interval		BC		BCa	
Intensive Sampling	CL	0.95	0.95	0.91	0.48	0.93	0.51	0.90	0.86	0.92	0.43	0.92	0.43
	Ka	1.00	1.00	0.88	0.92	0.94	0.93	0.97	0.95	0.90	0.91	0.90	0.91
	V	1.00	1.00	0.88	0.95	0.89	0.94	0.97	0.96	0.89	0.93	0.90	0.93
	σ^2_ε	0.04	0.04	0.08	0.09	0.11	0.10	0.05	0.05	0.07	0.03	0.07	0.03
	σ^2_{CL}	0.81	0.81	0.80	0.08	0.71	0.25	0.73	0.10	0.81	0.12	0.81	0.12
Sparse Sampling	CL	0.92	0.92	0.96	0.69	0.73	0.42	0.77	0.52	0.89	0.60	0.89	0.60
	Ka	0.81	0.81	0.89	0.74	0.71	0.50	0.76	0.57	0.92	0.70	0.91	0.70
	V	0.83	0.83	0.96	0.68	0.73	0.47	0.77	0.56	0.96	0.66	0.96	0.66
	σ^2_ε	0.14	0.14	0.16	0.30	0.09	0.01	0.09	0.01	0.09	0.22	0.09	0.22
	σ^2_{CL}	0.71	0.71	0.77	0.10	0.42	0.13	0.44	0.21	0.59	0.10	0.59	0.10

CONCLUSIONS

In our study case, the nonparametric method is concluded to be better than the parametric method based on the bias and coverage of the parameter associated with an inter-subject variability. It may be due to the limitation of the current parametric bootstrap method that only resamples the intra-subject random error. How to incorporate the inter-subject variability for parametric bootstrapping remains as a research area. Our simulated model using random errors of log-normal distribution may result in good performance of all bootstrap CI methods examined in this study. However, the coverage is no better than the standard normal method in both rich and sparse sampling. Since most PK/PD models assume normal or log-normal distribution random errors, application of the bootstrap CI methods to get better estimation of CI is questionable based on our simulation results. Further research in complicated PK models will be needed. The similar parameter estimation and CI coverage of the original data set and bootstrap data in misspecification results show bootstrap CIs cannot serve as a tool for model validation if the model is incorrectly specified in the original data. Detailed model diagnoses should be performed to ensure the proper model structure before constructing the CI using bootstrapping (Figures 2 and 3). Figure 2 show the assumption of the normal distribution for the CL intra-subject variability is violated and Figure 3 demonstrates the coverage of VPC is larger than it should be.

Figure 2. Density plot of the CL intra-subjective variability

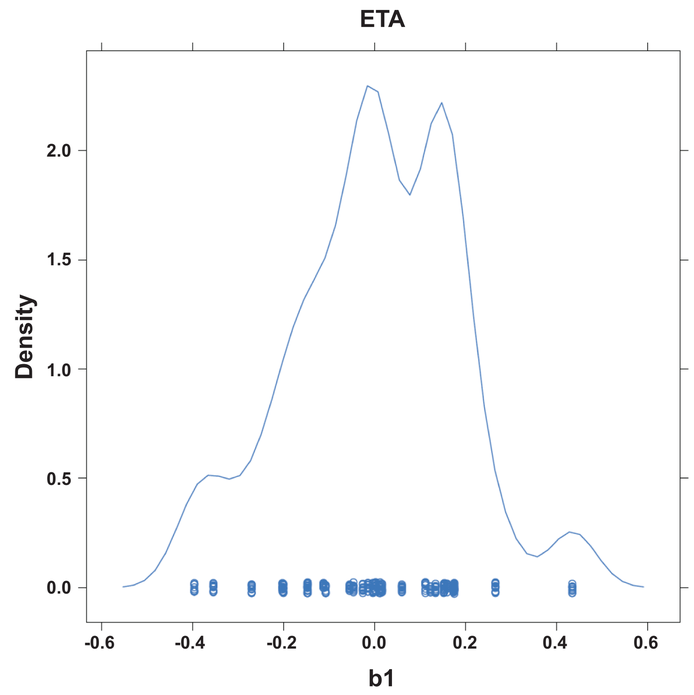
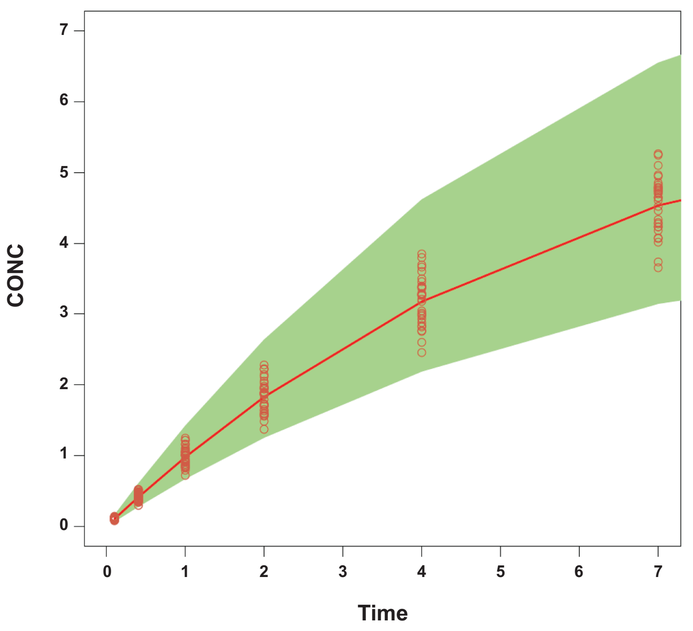


Figure 3. VPC plot from the fitted modeling in the mis-specified model



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