Comparison of Bias and Precision of Nonparametric and Parametric Population Methods assessed via Nonparametric Bootstrap Methods in NPAG and NONMEM

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BACKGROUND
Nonparametric population methods offer a powerful and fully data-driven approach to identify any number of sub-populations in the multidimensional space of random model parameters. No assumptions are necessary about the shape of distributions or number of sub-populations.

OBJECTIVES
1) To compare bias and precision in population means and between subject variability (BSV) between nonparametric (NPAG [1]) and parametric population methods (NONMEM [2]) as a function of sample size.
2) To compare bias and precision of individual estimated model parameters.
3) To compare the ability to identify multiple sub-populations.

METHODS
Simulations.
- 1-compartment model, first-order absorption (dose: 1000 mg)
- Parameterized as clearance (CL), volume of distribution (V), and the difference (ka-kel) between the absorption rate constant (ka) and elimination rate constant (kel).
- Standard deviation 0.01 mg L⁻¹ for the additive and 0.1 for the proportional error.
- CL and V log-normally distributed with 20% CV within each sub-population. Three sub-populations of equal size; pairs of geometric means for CL and V are shown in Fig. 3 (panel C).
- Distribution of ka-kel: unimodal, geom. mean 2 h⁻¹, 20% CV.
- Subjects had 1 to 5 observations between 0 and 48 h based on a population optimal design (WinPOPT, version 1.1).
- Sampling times were 0.1, 0.8, 1.5, 6, and 24 h.
- Number of observations per subject (fraction of subjects) was 1 (10%), 2 (30%), 3 (40%), 4 (17%), or 5 (3%).
- Concentration vs. time profiles simulated for 1,000 subjects.

Bootstrap resampling: Datasets of 10, 20, 50, 100, 200, or 400 subjects randomly drawn with replacement (200 bootstrap replicates for 10, 20, & 50 subjects, 100 replicates for 100 & 200 subjects, and 20 replicates for 400 subjects).

Estimation: The same bootstrap datasets were analyzed by the nonparametric adaptive grid (NPAG) method (USCPACK, v. 12.00) and by the first-order conditional estimation (FOCE) method with interaction in NONMEM© VI (level 1.2). A full variance-covariance matrix was estimated in NONMEM.

RESULTS
Figure 1 shows the simulated concentrations of the first 30 subjects. Figure 2 shows the ratios of individual estimates vs. true parameter values (panel A) and ratios of percentiles of estimated vs. true distributions (panel B). Bias and precision of mean CL, V, and ka-kel were similar between both programs for all studied sample sizes. Estimates for BSV in CL and V had less than 10% bias in both programs for datasets of 20 or more subjects. The ratio of estimated to true variance of ka-kel was 4.6 [1.1-12] for datasets of 20 subjects and 2.1 [1.2 - 3.7] for 200 subjects in NPAG and this bias was <20% in NONMEM. NPAG captured the shape of the multimodal distribution for BSV of CL & V better than NONMEM (Fig. 2B & 3). The ratio of individual fitted vs. true concentrations was 0.998 ± 0.122 in NONMEM and 0.998 ± 0.150 in NPAG for datasets with 100 subjects.

CONCLUSIONS
1. NPAG and NONMEM yielded precise and unbiased estimates for the geometric means and between subject variability of all three parameters, with the exception of an overestimated variance of ka-kel in NPAG.
2. At all sample sizes NPAG was more powerful than NONMEM in discerning the shape of the distribution of CL and V and the multimodal pattern arising from three sub-populations.
3. Parametric and nonparametric population approach both offer advantages which may supplement each other.

References
[2] NONMEM Project Group, Univ. of California, San Francisco, CA.

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