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

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Objectives: 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. We are not aware of a systematic comparison between nonparametric and parametric population methods that applied nonparametric bootstrap techniques. Objectives: 1) To compare bias and precision in population means and between subject variability (BSV) between nonparametric and parametric population methods. 2) To compare bias and precision of individual estimated model parameters. 3) To compare the ability to identify multiple sub-populations.

Methods: A one-compartment model with first-order absorption (dose: 1000 mg) was parameterized as clearance (CL), volume of distribution (V), and the difference (k_a-k_{el}) between the absorption rate constant (k_a) and k_{el}. The standard deviation was 0.01 mg L^{-1} for the additive and 0.1 for the proportional error. The CL and V were log-normally distributed with a 20% CV within each sub-population. Three sub-populations of equal size with pairs of geometric means for CL and V of 4 L h^{-1} and 60 L, 6 L h^{-1} and 90 L, and 9 L h^{-1} and 40 L were assumed. The distribution of k_a-k_{el} was uni-modal (mean: 2 h^{-1}, 20% CV). Subjects could have 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 were simulated for 1,000 subjects. Datasets of 10, 20, 50, 100, 200, or 400 subjects were randomly drawn with replacement (200 bootstrap replicates for 10, 20, & 50 subjects, 100 repl. for 100 & 200 subjects, & 20 repl. for 400 subjects). The same bootstrap datasets were analyzed by the nonparametric adaptive grid (NPAG) method (USC*PACK, v. 12.00) and by the first-order conditional estimation (FOCE) method with interaction in NONMEM© VI. A full variance-covariance matrix was estimated in NONMEM.

Results: The following statistics are ratios of medians [5-95% percentiles] from all bootstrap replicates divided by the true values. For geometric mean CL, ratios were 0.991 [0.815 - 1.183] in NONMEM and 0.995 [0.825 - 1.198] in NPAG for datasets of 20 subjects and 1.001 [0.950 - 1.051] in NONMEM and 0.999 [0.948 - 1.060] in NPAG for 200 subjects. For geometric mean V, ratios were 1.002 [0.869 - 1.18] in NONMEM and 1.009 [0.874 - 1.213] in NPAG for 20 subjects and 1.005 [0.963 - 1.061] in NONMEM and 1.005 [0.964 - 1.059] in NPAG for 200 subjects. Estimates for between subject variance (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 k_a-k_{el} 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. The ratio of individual estimated vs. individual true parameter values was unbiased for all three parameters for both programs. NONMEM provided slightly more precise individual parameter estimates (ratios closer to 1.0 in Fig. 1). NPAG captured the shape of the multimodal distribution for the BSV of CL and V better than NONMEM (Fig. 2). For all sample sizes studied, the distribution of support points from NPAG mirrored the true sub-populations of CL and V more closely than the individual parameter estimates in NONMEM (Fig. 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: 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 k_a-k_e in NPAG. 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. Parametric and nonparametric population approach both offer advantages which may supplement each other.

Topic area: Tools & Techniques

Figure 1: Distribution of the ratio of individual parameter estimates divided by the true individual values for clearance and volume of distribution (data are medians from bootstrap replicates)

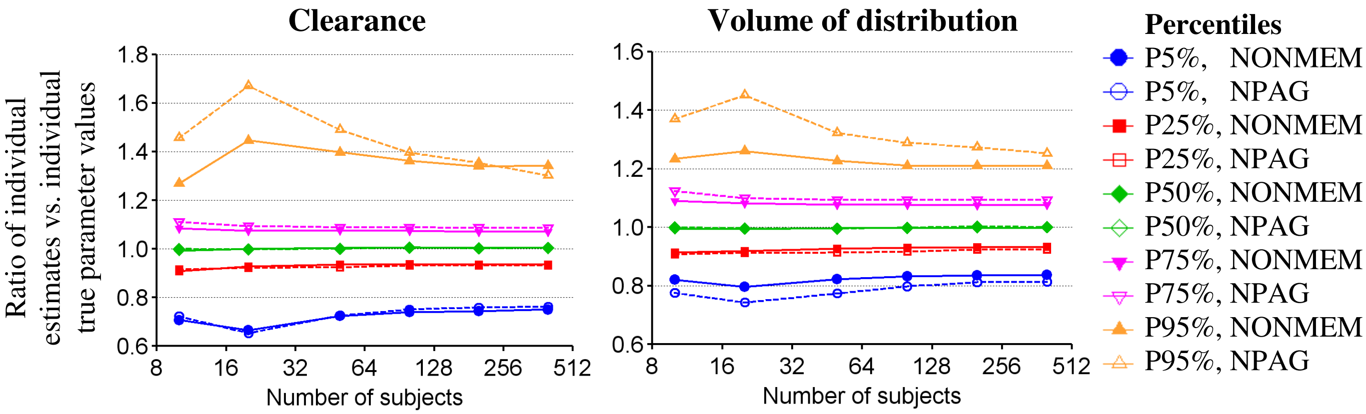

Figure 2: Ratio of estimated and true percentiles of the distribution of individual parameter estimates. If the estimated distribution captured the shape of the true distribution exactly, all ratios would be 1.0 (data are medians from bootstrap)

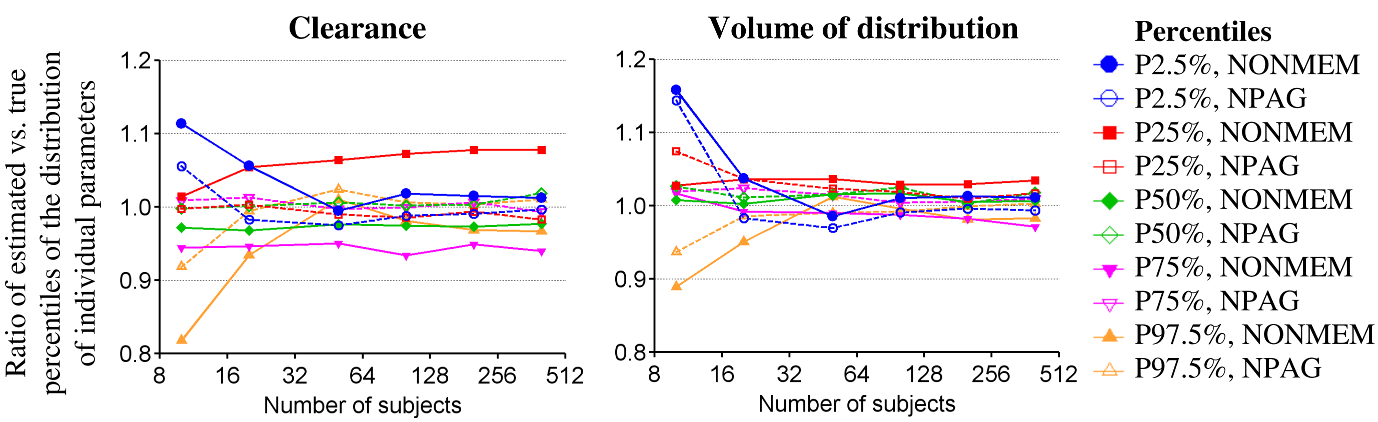

Figure 3: Scatterplots of clearance and volume of distribution for individual estimates (A) and simulated subjects (B) in NONMEM, true simulated data (C), and estimates in NPAG (D)