Title: Comparison of Nonparametric and Parametric Population Methods based on a Monte Carlo Simulation Study with Indirect Response Models I to IV in NPAG and NONMEM

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Objectives: Nonparametric population methods (such as NPAG) offer the advantage that they do not make assumptions about the shape of the distribution representing between subject variability (BSV). We are not aware of a systematic simulation-estimation study with nonparametric population methodology that assessed indirect response (IDR) models that are commonly used to model pharmacodynamic (PD) responses. Objectives: To compare bias and precision 1) of the population mean parameters and BSV, 2) of individual parameter estimates, and 3) of the ratio of true and model predicted response for IDR models I to IV as a function of sample size between NPAG and NONMEM.

Methods: Response vs. time profiles were simulated for a one-compartment model with a 30 min infusion of 1000 mg in combination with IDR models I to IV (Figure 1). Variability in pharmacokinetic parameters was assumed to be negligible (zero). Clearance was 5 L h\(^{-1}\) and volume of distribution was 40 L. The PD parameters were sampled from log-normal distributions with coefficients of variation (CV) of 30% without covariance. Maximum inhibition (Imax) or maximum stimulation (Smax) were 0.7 (median) with a CV of 18%. A logistic transformation was used for the parameter variability model of Imax and Smax. Proportional error was 10% and the additive error had a standard deviation of 4 (true population baseline: 100). Response vs. time profiles (Fig. 2) were simulated for 1,000 subjects for each of the four IDR models. Data were fitted to the true models by the nonparametric adaptive grid (NPAG) approach implemented in the 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. NPAG always provides this matrix. Response data (but no concentrations) were fitted. Fifty bootstrap datasets of 10, 20, and 50 subjects each were randomly drawn from the 1,000 simulated subjects with replacement. The same bootstrap datasets were analyzed by NPAG and NONMEM.

Results: The ratios of the individual parameter estimates divided by the true individual parameter values (data from bootstrapping) showed that NPAG overestimated the IC50, SC50, and Smax by about 10% (median), and Imax by about 5% for 10, 20, and 50 subjects, whereas NONMEM showed slightly less bias for these parameters. For baseline, individual estimates were unbiased (+/- 2%) in both programs. The median of the individual parameter estimates divided by the true median of the individual values for the parameters gave similar results as the individual ratios (Figure 3). The median ratio of the individual predicted vs. true response was unbiased (within +/- 1%) and precision was comparable between both programs. Both NPAG and NONMEM overestimated the BSV of IC50, SC50, and kout by up to a factor of 2.5 in NPAG and 2 in NONMEM when expressed as %CV. The BSV of baseline was within about +/- 10% of the true value. The precision of measures of central tendency and variability based on 50 bootstrap replicates was comparable between both programs.

Conclusions: NONMEM provided slightly less biased estimates for the central tendency and BSV compared to NPAG for the simulated datasets that were based on log-normal distributions. Both programs overestimated the BSV for IC50, SC50, and kout considerably. The latter may be important, if the estimated population PK/PD models are to be used in Monte Carlo simulations. Further, this simulation study represents a best case scenario for parametric methods, since the pharmacokinetics were known without error and all distributions were log-normal. Additional simulation studies are warranted to study more complex and multimodal distributions resulting from genetic polymorphism and different disease entities.
**Figure 1:** Indirect Response Models

\[ \begin{align*}
&k_{\text{in}} \quad \text{Response} \quad k_{\text{out}} \\
&I \quad \quad \quad II \quad III \quad IV
\end{align*} \]

- black: inhibition
- white: stimulation

**Figure 2:** Simulated profiles for 20 subjects from IDR 1

**Figure 3:** Median of individual parameter estimates divided by the median of the true individual parameter values (data are medians from 50 bootstrap replicates)