

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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BACKGROUND

Nonparametric population methods (such as NPAG [1]) 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, [2]) models that are commonly used to model pharmacodynamic (PD) responses.

OBJECTIVES

To compare bias and precision

- of the population mean parameters and BSV,
- of individual parameter estimates, and
- 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 [3].

METHODS

Simulations. 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 (PK) 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 (I_{max}) or maximum stimulation (S_{max}) were 0.7 times baseline (median) with a CV of 18%. A logistic transformation was used for the parameter variability model of I_{max} and S_{max} . 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.

Estimation. The true models were fitted to the data 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[®] (version VI level 1.2).

A full variance-covariance matrix was estimated in NONMEM. NPAG always provides this matrix. Response data (but no concentrations) were fitted.

Bootstrap analysis. 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.

FIGURE 1: Indirect Response Models

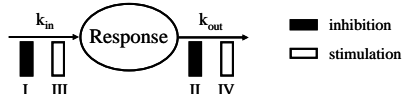
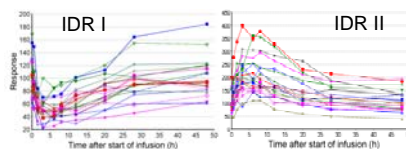


FIGURE 2: Simulated response profiles for 20 subjects from IDR I and IDR II



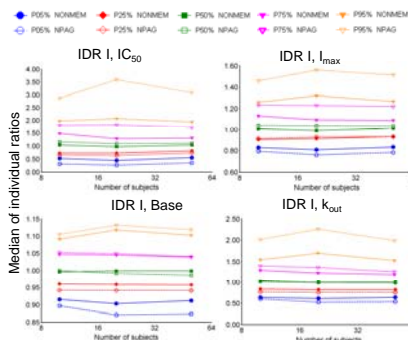
RESULTS

The ratios of the individual parameter estimates divided by the true individual parameter values (data from bootstrapping) showed that NPAG overestimated the IC_{50} , SC_{50} , and S_{max} by about 10% (median), and I_{max} by about 5%, whereas NONMEM showed slightly less bias for these parameters (Figure 3). 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 4).

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 IC_{50} , SC_{50} , and k_{out} 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 between subject variability based on 50 bootstrap replicates was comparable between both programs.

FIGURE 3: Median of the ratios of the individual parameter estimates divided by the true individual parameter values from IDR I
(data are medians from 50 bootstrap replicates)



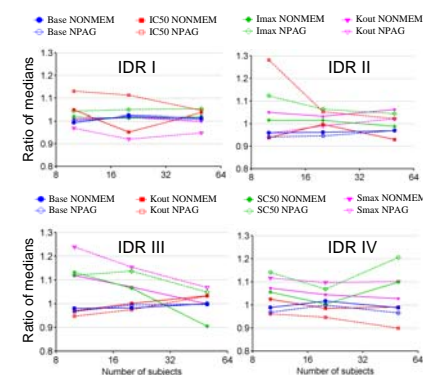
References:

- [1] Bustad A. et al. (2006) Clin Pharmacokinetics 45: 365-383.
- [2] Dayneka N. et al. (1993) J Pharmacokinetics Biopharm 21:457-478.
- [3] NONMEM Project Group, University of California, San Francisco, CA.

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FIGURE 4: Median of individual parameter estimates divided by the median of the true individual parameter values
(data are medians from 50 bootstrap replicates)



CONCLUSIONS

- NONMEM provided slightly less biased estimates for the central tendency and BSV compared to NPAG for the simulated datasets based on log-normal distributions.
- Both programs overestimated the BSV for IC_{50} , SC_{50} , and k_{out} considerably. The latter may be important, if the estimated population PK/PD models are to be used in Monte Carlo simulations.
- This simulation study represents a best case scenario for parametric methods, since all distributions were log-normal and the PK were known without error.

Future perspectives

Additional simulation studies are warranted to study more complex and multimodal distributions resulting from genetic polymorphism and different disease entities.