Covariate Model Building Method for Nonparametric Estimation Method in NONMEM VI: Application to Simulated Data

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Background and Objectives

The nonparametric method available in the software NONMEM VI has been tested in previous studies and provided a significant improvement in terms of simulation properties when analyzing real and simulated data [1,2]. However, to promote the use of this method in the pharmacometrics field, specific recommendations should be given in order to provide the same functionalities as for parametric methods, for example covariate model building.

The aim of this study was therefore to develop a method for covariate model building in nonlinear mixed effects models based on nonparametric final estimation step of the software NONMEM VI. The relative performance of the new method at detecting true covariate relationships has also been evaluated on simulated datasets in comparison with parametric GAM analysis.

Materials and Methods

Simulated datasets:

- A 1-compartment IV bolus model was used to simulate 10 different datasets of 100 individuals following a rich sampling design. A sparse sampling schedule was similarly investigated.
- The rich sampling schedule included 5 observations per individual, taken at 2, 4, 6, 8 and 10 hours post-dose (100 individuals).
- For the sparse design, 50 individuals supplied 2 sampling points, one early (1h post-dose) and one late (10 h post-dose), while the remaining 50 individuals provided only one point, evenly distributed between early and late samples.
- The true model parameters used for simulations followed a log-normal distribution with a mean value (variance) respectively equal to 30 L/h (30%CV) for clearance, and 100 L (30%CV) for volume. The error model was proportional with a residual variability equal to 10%CV.
- Ten different covariates were simulated of which:
  - 7 were continuous (4 with underlying log-normal distribution, 1 with underlying normal distribution and 2 following a uniform distribution)
  - 3 were binomial
- Relationships between model parameters and covariates were induced in the different simulations:
  - Clearance decreases of 2% per unit of a continuous (uniform) covariate called CONT1 (ranging from 40 to 80 units)
  - Volume was 20% lower in the subgroup of individuals belonging to a certain category of the binomial covariate CAT1

Methods:

- Re-estimation with the reduced model was then conducted for each dataset and for each sampling scheme using either FOCE or FOCE-NONP method.
- For the parametric method (FOCE), generalized additive model analyses (GAM, implemented in the software R) based on empirical Bayes estimates were performed.
- The covariate model building method for the nonparametric estimation method (FOCE-NONP) is based on the calculation of joint density parameter distributions for each individual from the population joint density distribution and individual data.

For each model parameter, a PsN script [3] was used to automate the individual contributions (iOFV) from which the individual probability (Pind) were derived and then used as the main weighting factor in GAM analyses based on the support points of the nonparametric distribution (a). Additional weighting by the individual variances of individual nonparametric distributions was also investigated (b).

The relative performance of the new method at detecting true covariate relationships and their strength was evaluated in comparison with parametric GAM analysis.

As an additional result to the GAMs, the impact of the weighting factors on the true covariate relationships was assessed by linear regressions with or without weights.

Results and Discussion

Rich design:

- The frequency of the true and false covariate relations selected and the order of the selected covariates included were similar between the 2 methods and in all cases, the true covariates were selected first with a high Akaike criteria information drop.

Sparse design:

- Four datasets with sparse design revealed the true relationships between CL and CONT1 alone with both parametric GAM and nonparametric GAMs, but the former method had a tendency to include more false covariates relationships for the remaining 6 datasets.
- With respect to V/CAT1 relationship, nonparametric GAM performed better than the parametric GAM, the true covariate relationship unaltered by any false covariates being detected in 6 datasets over 10 with the former method (weight=Pind) against only 3 for parametric GAM.

Overall, preliminary results suggest that the new method for nonparametric estimation performed similarly and sometimes (marginally) better than parametric GAM with respect to selecting the true covariate relationships when applied to simulated data (rich and sparse).

The linear regressions performed suggest that the weighting factor incorporating information on the individual nonparametric variance provided at least as good fits as the parametric linear regression and than the individual probabilities alone, especially when dealing with sparse data.

Table 1. *Mean and standard deviation (sd) of the linear regressions coefficients of the two model parameter/covariate relationships (Clearance and a continuous covariate CONT1, and Volume and a categorical covariate CAT1) induced by simulations across 10 different datasets including 100 individuals and for 2 different sampling schemes investigated (rich and sparse). Linear regressions for parametric method (no weighting) and nonparametric methods (weighting with (a) and (b)) have been performed in the software R (ω^2 represents the variance of the nonparametric distribution (at individual or population level)).*

Coefficients linear regression	True value	RICH (100IDs, 5 DVs/IDs)			SPARSE (50 IDs=2 DVs/ID , 50 IDs=1 DV/ID)		
		Parametric	Nonparametric (a)	Nonparametric (b)	Parametric	Nonparametric (a)	Nonparametric (b)
Mean +/- sd (CL ~ CONT1)	-0.02	-0.020 +/- 0.002	-0.020 +/- 0.002	-0.020 +/- 0.002	-0.014 +/- 0.004	-0.014 +/- 0.004	-0.017 +/- 0.004
Mean +/- sd (V ~ CAT1)	-0.2	-0.196 +/- 0.042	-0.199 +/-0.043	-0.202 +/- 0.043	-0.143 +/- 0.031	-0.139 +/- 0.033	-0.170 +/- 0.053

(a): Weights = Pind

(b): Weights = Pind $\times \left(1 - \frac{\omega^2_{individual}}{\omega^2_{population}}\right)$

Conclusion

A covariate model building technique intended for nonparametric estimation method in NONMEM VI is proposed. When applied to rich simulated datasets, the performance of the nonparametric method in the stepwise search process performed similarly as the parametric GAM method. When applied to sparse simulated datasets, some small improvements have been noted with the use of the new method. However, further adjustments, especially in the way of handling the weighting factors but also the extended grid method [4] in order to bypass the shrinkage phenomenon, may enhance the nonparametric GAM method performance.

References:

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