Bayesian versus Frequentist Estimators for a Non-Linear Mixed Effects Model: Application to a Population Pharmacokinetic Model

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The estimation of non-linear mixed effects models has been addressed in many studies. However, the challenge stays the identification and the implementation of methods that are efficient for the estimation of all parameters in these models, irrespective of the configurations, namely, the complexity of the model and the sample size. Pharmacokinetic (PK) and pharmacodynamic (PD) models are examples of non-linear mixed effects models that play an important role in drug development. The accuracy of the PK/PD parameters estimates may affect the whole drug development plan. The objective of this work is to investigate through a dozen estimation methods of non-linear mixed effects models, those that could provide better estimates of the parameters in a pharmacokinetic model with a combined residual error (combined multiplicative and additive residual errors) from two types of sampling, namely, a rich sampling and a sparse sampling. Data used were simulated with NONMEM 7 and three levels of between-subjects variability were considered in data simulation. The different tested methods were based on bayesian approaches as well as on frequentist approaches. Many algorithms were implemented in software such as NONMEM, SAS, WinBUGS/R2WinBUGS and BlackBox. The main conclusions are the following. In the configuration of rich sampling, Laplacian approximation, adaptive gaussian quadrature and first-order conditional estimation methods were more accurate than first-order estimation method and the bayesian method with weak prior beliefs on the fixed parameters. By introducing informative priors on the fixed parameters, our estimations of fixed parameters became stabilized especially with BlackBox and WinBUGS which gave the best estimates. Bayesian estimations under NONMEM were not sensitive to the nature of the prior beliefs on the fixed effects. In the configuration of sparse sampling, all parameters are poorly estimated with very large bias, except the bayesian estimates obtained from WinBUGS and BlackBox when informative priors are considered on the fixed effects. Similarly, for both types of sampling, all the tested methods gave the same results for the estimation of the additive part of the within-subject variability which was underestimated with relative biases of the magnitude of 10 %.

Key Words: Estimation methods, Combined multiplicative and additive residual errors, Between-subjects variability, Software.