Designs in Nonlinear Mixed Effects Models: Evaluation and Optimisation of the Power of the Wald Test with Application to HIV Viral Load Decrease.

Sylvie Retout, Emmanuelle Comets, Adeline Samson and France Mentré

INSERM U738, Dpt of Epidemiology and Biostatistics
Bichat University Hospital, Paris

ABSTRACT

Context: We have proposed Splus and R functions, PFIM and PFIMOPT, for respectively designs evaluation and optimization in nonlinear mixed effects models (NMEM) [1]. These functions rely on an approximation of the Fisher information matrix using a first order linearization of the model [2]. Optimisation is based on the D-optimality criterion and uses a simplex algorithm. More recently, we have extended the expression of the Fisher matrix for models including the influence of covariates [3] and have implemented the Fedorov-Wynn algorithm for optimisation.

Objective: Our objectives were to apply and to illustrate this method to the example of a biexponential model of HIV viral load decrease under antiretroviral treatment [4]. This model involves four fixed effects, four additive random effects and an additive homoscedastic error. An additional fixed effect of the antiretroviral treatment on the first rate-constant is also considered.

Methods: We evaluate with PFIM a design of two groups of 100 patients with the same 6 sampling times per group and compare the empirical standard errors (SE) found with simulations with the SE predicted either with the nlme function of Splus or with MONOLIX, the new SAEM algorithm for NMEM estimation without any linearization [5-6]. We also use MONOLIX with one simulation of 5 000 patients to estimate the variance matrix and thus the expected Fisher information matrix under asymptotic convergence assumptions; we then derive the expected SE for smaller data sets. We apply the Fedorov-Wynn algorithm to optimise a design for a model without treatment effect and for a model where the treatment effect is estimated. From the predicted SE we compute and compare the power of a Wald test for the treatment effect under an alternative hypothesis for this parameter; this is perform for several empirical and optimised designs with either different

total numbers of patients or different numbers of observations per patient. Last, we evaluate by simulation with nlme the power of the Wald test for the optimised designs and we compare these observed power to those derived from PFIM.

Results: Regardless of the method, the SE were all very close which illustrates the usefulness of PFIM. For instance, for a treatment effect of 30Conclusion: We illustrated the usefulness of PFIM and PFIMOPT on this new example and we showed the importance of the design on the power of the Wald test.

Bibliography

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