Estimation in Semiparametric Nonlinear Mixed-Effects Models Using ℓ_1-Penalization

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Parametric nonlinear mixed effects models (NLMEs) are now widely used in biometrical studies, especially in pharmacokinetics research and HIV dynamics models, due to, among other aspects, the computational advances achieved during the last years. However, this kind of models may not be flexible enough for complex longitudinal data analysis. Semiparametric NLMEs (SNMMs) have been proposed as an extension of NLMEs. These models are a good compromise and retain nice features of both parametric and nonparametric models resulting in more flexible models than standard parametric NLMEs. However, SNMMs are complex models for which estimation still remains a challenge. Previous estimation procedures are based on a combination of log-likelihood approximation methods for parametric estimation and smoothing splines techniques for nonparametric estimation. In this work, we propose new estimation strategies in SNMMs. On the one hand, we use the Stochastic Approximation version of EM algorithm (SAEM) to obtain exact ML and REML estimates of the fixed effects and variance components. On the other hand, we propose a LASSO-type method to estimate the unknown nonlinear function. We derive oracle inequalities for this nonparametric estimator. We combine the two approaches in a general estimation procedure that we illustrate with simulated and real data.