Approximate methods for maximum likelihood estimation of multivariate nonlinear mixed-effects models

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Multivariate nonlinear mixed-effects models (MNLMM) have seen an increasing use due to its flexibility for analyzing multi-outcome longitudinal data following nonlinear profiles. In this work, I present and compare five different numerical algorithms for maximum likelihood estimation of the MNLMM. These algorithmic schemes include the penalized nonlinear least squares coupled with multivariate linear mixed-effects (PNLS-MLME) approximation, Laplacian approximation, pseudo-data ECM algorithm, Monte Carlo EM algorithm, and importance sampling EM algorithm. When estimating the MNLMM, it is rather difficult to exactly evaluate the observed log-likelihood function in a closed-form expression because it involves evaluating a multiple integral. Therefore, the corresponding approximations of the observed log-likelihood function under the five algorithms are presented. A comparison of their computational performances is investigated through simulation and real data from an AIDS clinical study.

Keywords: importance sampling; Laplacian approximation; Monte Carlo EM; penalized nonlinear least squares; pseudo ECM algorithm.