Influence Diagnostic for Semiparametric Partially Nonlinear Mixed-Effects Models

Robson José Mariano Machado*
University College London, London, United Kingdom – robson.machado.14@ucl.ac.uk

Cibele Maria Russo
Universidade de São Paulo, São Carlos, Brazil – cibele@icmc.usp.br

Correlated data with nonlinear structure are common in many areas such as biostatistics, pharmacokinetics and other longitudinal studies. We propose semiparametric partially nonlinear mixed-effects models (SPNMMs) for modelling those kinds of data. These models assume that the response variable can be explained by a nonlinear function, which depends on fixed effects parameters and explanatory variables, by a nonparametric function which provides flexibility for the functional form that underlies the data and by random errors. Random effects are included linearly to the model, which provide advantages to obtain the distribution of the response variable and enable the model to take into account the within-group correlation structure. It is assumed that the random errors and the random effects jointly follow a multivariate normal distribution. The P-spline smoothing technique is used for approaching the nonparametric function. The parameters are estimated with penalised maximum likelihood. The random effects are predicted by using the Empirical Bayes. The method of local influence is applied to the SPNMMs, which permits the assessment of sensitivity of the estimates. In particular, the conformal normal curvature is used instead of normal curvature, since it is invariant under conformal re-parametrisation and is a normalised measure. The proposed model is applied to a pharmacokinetic data in which the anti-asthmatic drug theophylline was administered to 12 subjects and serum concentrations were taken at 11 time points over the 25 hours after being administered. Finally, a local influence analysis is performed to the application.

Keywords: Nonlinear models; Mixed-effects models; Local influence; Smoothing.