Evaluation of nonlinear mixed effect models using prediction distribution errors: the npde library for R

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Nonlinear mixed effect models are increasingly used to analyse dose-concentration-effect relationships in clinical studies, to study relationships in clinical studies, to help identify differences in drug safety, efficacy and pharmacokinetics among population subgroups, and to simulate clinical trials. Model evaluation is an important part of model building (EMEA 2006). Prediction discrepancies (pd), have been proposed by Mentré and Escolano (Mentré and Escolano 2006) to evaluate nonlinear mixed effect models. Brendel et al (Brendel et al 2007) developed an improved version of this metric, termed normalised prediction distribution errors (npde), taking into account repeated observations within one subject. In the present paper, we present a set of routines to compute npde.

Model evaluation consists in assessing whether a given model M (composed of a structural model and parameter estimates) adequately predicts a validation dataset V. V can be the original dataset used to build model M (internal validation) or a separate dataset (external validation). The null hypothesis H_0 is that the data in V can be described by model M. The pd for a given observation y_{ij} is defined as the percentile of this observation within the marginal predictive distribution under H_0. Prediction distribution errors (pde) are computed in a similar way after correcting for the correlation induced by repeated observations. Normalised prediction distribution errors are then obtained by transforming the pde through the inverse normal distribution. Under H_0, the distribution of the npde is that of a centered standardised normal distribution. In practice, the predictive distribution is approximated by Monte-Carlo simulations: K datasets are simulated under the null hypothesis (model M and corresponding parameters) using the design of V.

The program requires as input a file with the validation dataset V and a file containing the K simulated datasets stacked one after the other. Simulations should be performed beforehand. The program then computes the npde. Optionally, pd can be computed instead or in addition, which is less time-consuming but leads to type-I error inflation especially as the number of observations per subject increases. Graphical diagnostics are plotted to evaluate model adequacy: QQ-plots and histograms are used to compare the distribution of the npde to that of the theoretical distribution, and npde can also be plotted against predicted concentrations and independent variable to assess trends in the distribution. Tests can be performed to compare the distribution of the npde relative to the expected standard normal distribution. A global test combining a Shapiro-Wilks normality test, a Wilcoxon rank sum test for zero mean, and a Fisher test for a variance of one, with a Bonferroni correction, is reported and can be used to test the adequacy of the distribution of npde compared to the theoretical distribution.

The code is available as a library for the open-source statistical environment R. It can be downloaded from the dedicated website (http://www.npde.biostat.fr/) or from the Comprehensive R Archive Network. The package contains an example of model building followed by model evaluation using npde.

References

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