Confidence intervals for intraclass correlation coefficients in mixed effects nonlinear regression model for dose-response meta-analysis

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In our previous work we proposed two generic approaches for constructing confidence intervals on intraclass correlation coefficients (ICCs) for linear variance components models [1]. The first approach uses Satterthwhaite's approximation and the F-distribution [2]. The second approach uses the first and second moments of the ICC estimate in combination with a Beta distribution [3-4]. The variance components were estimated with restricted maximum likelihood [5]. The coverage probability of the confidence intervals demonstrated accurate results, in particular for settings with small sample sizes (≤10), with preference for Beta-approach.

Here we investigate the performance of the Beta-approach for confidence intervals of the ICCs in nonlinear mixed effects models [6]. The focus is on models with linear random effects and nonlinear fixed effects. The case study is a meta-analysis on antipsychotic medications which is modeled using Michaelis-Menten curves for dose-response relationships [7]. In nonlinear mixed effects models, restricted maximum likelihood estimation is not well defined. We present the results of a simulation study that compares four estimation methods for variance components. These estimation methods are the maximum likelihood, second-order generalized estimating equations (GEE2) and two two-stages approaches. We compare the biases and coverage probabilities. Again, the main focus is on small sample settings (≤10), which were driven by our case study. The delta method, which uses the first-order Taylor series approximation is often used for construction of confidence intervals, but it relies on large samples. The Beta-approach is compared with the delta method. The coverage probabilities show that delta method performs very poorly and is not recommended for computation of confidence interval for ICC, especially for the mix of small sample sizes. Beta-approach demonstrates good accuracy and is recommended for computation of confidence interval for ICC in mixed effects nonlinear regression model, in particular for small sample sizes. Differences between estimation is not very large, though two-stage approach of Vonesh [6] is preferred.

Keywords: Beta distribution; Method of moments estimators; Bias; Meta-analysis;

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