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Evaluation of a Piecewise Linear Mixed-Effects Model in the Analysis of Randomized Cross-over Trial

Authors : Moses Mwangi, Geert Verbeke, Geert Molenberghs

Abstract : Cross-over designs are commonly used in randomized clinical trials to estimate efficacy of a new treatment with respect to a reference treatment (placebo or standard). The main advantage of using cross-over design over conventional parallel design is its flexibility, where every subject become its own control, thereby reducing confounding effect. Jones & Kenward, discuss in detail more recent developments in the analysis of cross-over trials. We revisit the simple piecewise linear mixed-effects model, proposed by Mwangi et. al, (in press) for its first application in the analysis of cross-over trials. We compared performance of the proposed piecewise linear mixed-effects model with two commonly cited statistical models namely, (1) Grizzle model; and (2) Jones & Kenward model, used in estimation of the treatment effect, in the analysis of randomized cross-over trial. We estimate two performance measurements (mean square error (MSE) and coverage probability) for the three methods, using data simulated from the proposed piecewise linear mixed-effects model. Piecewise linear mixed-effects model yielded lowest MSE estimates compared to Grizzle and Jones & Kenward models for both small (Nobs=20) and large (Nobs=600) sample sizes. It's coverage probability were highest compared to Grizzle and Jones & Kenward models for both small and large sample sizes. A piecewise linear mixed-effects model is a better estimator of treatment effect than its two competing estimators (Grizzle and Jones & Kenward models) in the analysis of cross-over trials. The data generating mechanism used in this paper captures two time periods for a simple 2-Treatments x 2-Periods cross-over design. Its application is extendible to more complex cross-over designs with multiple treatments and periods. In addition, it is important to note that, even for single response models, adding more random effects increases the complexity of the model and thus may be difficult or impossible to fit in some cases.

Keywords : Evaluation, Grizzle model, Jones & Kenward model, Performance measures, Simulation
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