Semi-parametric generalized estimating equations for repeated measurements in crossover designs

N.A. Cruz[1], *O.O. Melo*[2], *C.A. Martinez*[3]

[1]Corresponding author: neacruzgu@unal.edu.co, Faculty of Nursing, Universidad Nacional de Colombia

[2] oomelom@unal.edu.co, Department of Statistics, Faculty of Sciences, Universidad Nacional de Colombia

[3] cmartinez@agrosavia.co, Corporación Colombiana de Investigación Agropecuaria â AGROSAVIA, Sede Central

Crossover experimental designs with non-Gaussian responses, repeated measures, and complex carry-over effects, i.e., those that depend on both the prior and the affected treatment, are frequent in fields like medicine and animal sciences. Complex carry-over effects feature mathematical intractability under the usual parametric methodologies. Therefore, we proposed a semiparametric model for the analysis of crossover designs with repeated measures within each period of treatment application that accounts for complex carry-over effects. The model was derived using an extension of generalized estimating equations (GEE) with a non-parametric component to model the temporal and carryover effects and a parametric component for the remaining ones; in addition, it can be easily adapted to the case of simple carry-over effects. We considered the usual form of GEE and several spline functions leading to an estimation procedure that is analogous to weighted least squares. Hence, model diagnostics can be performed by adapting the standard procedures of multiple linear regression. Moreover, we established asymptotic results on the estimators that showed a sound theoretical behavior for large samples that was illustrated in simulation exercises. Finally, we compared the proposed methodology with the usual approach in two real datasets: systolic blood pressure and insulin in rabbits, which revealed the advantages of our methodology.

Keywords: Cross-over design, Generalized estimating equations, Kronecker correlation