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Repeated Measures Design with Generalized Linear Mixed Models for Randomized Controlled Trials

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BOOK REVIEW

Repeated Measures Design with Generalized Linear Mixed Models for Randomized Controlled Trials, by Toshiro Tango, Chapman and Hall/CRC Press, 2017, ISBN 978-1-4987-4789-9, 359 pp.

This book provides a new repeated measures approach called *S:T repeated measures design* combined with the generalized linear mixed-effects models in the context of randomized controlled trials (RCT). The letters, *S* and *T*, denote the numbers of repeated measures before and after randomization, respectively. For example, if the primary response variable is measured twice at baseline and 3 times after randomization, the design would be a *2:3 repeated measures design*. Generalized linear mixed-effects models with continuous, count, or binary response variables are presented emphasizing on the practical aspects of the mixed models using real data from RCT. Multiple real examples with SAS (version 9.3) codes and interpretation of results are included. This book is an excellent resource for biostatisticians and researchers designing and analyzing repeated measures data of clinical trials. It will also serve as a nice accompanying textbook for biostatistics graduate students.

The main contributions of the proposed design in this generalized linear mixed models book are as follows: (1) it can easily handle missing data by applying the likelihood-based ignorable analyses under the missing at random assumption and (2) it may lead to a reduction in sample size, compared with the conventional repeated measures design. Historically, the analysis of variance (ANOVA) was the starting point of mixed-effects models. Fisher (1925) developed a method of estimating variance components by computing the mean squares in a standard ANOVA, equating these mean squares to their expectations, and solving for the unknown variances. Searle et al. (1992) noted that the first description in the literature of a mixed-effects model was by Jackson (1939), although it was not called a mixed-effects model then. Eisenhart (1947) made the first distinction between "fixed" and "random" effects models (Models I and II, respectively), and first used the term "mixed." It was Henderson (1953) who gave a mathematical description of a mixed-effects model to use in animal breeding applications. The mixed-effects model was popularized by Laird and Ware (1982), describing an expectation–maximization algorithm for its implementation. Since then mixed-effects models were widely used for the analysis of longitudinal data and many authors extended the application of mixed-effects models. McCullagh and Nelder (1989) described generalized linear model in a great detail in their book and introduced a linear logistic model with random effects using a salamander mating experiment. Among numerous developments of generalized linear mixed-effects models in over the past two decades, Tango's *S:T repeated measures design* approach, where repeated measures before randomization are incorporated into the model along with repeated measures after randomization is an ingenious idea. When there are situations where baseline measurements need to be defined so that only one measure is chosen out of multiple measures, the *S:T repeated measures design* will ease this limitation.

The first chapter introduces the *S:T repeated measures design* and generalized mixed-effects models for Normal, Bernoulli, and Poisson distributions in the framework of RCT design. It also provides an overview of superiority and non-inferiority trial concepts. Chapters 2 and 3 illustrate repeated measures ANOVA and repeated measures analysis of covariance models with various covariance structures and compare the results using real data. Chapters 4 and 5 extend ANOVA models to mixed-effects models and discuss the distinction between the two methods with well-chosen examples. Chapter 6 provides a helpful illustration in regards to handling missing data in mixed-effects models. Chapters 7 through 9 present the proposed mixed-effects models for normal, logistic and Poisson regressions and sample size formula for each distribution. Chapter 10 presents Bayesian alternatives. Chapter 11 introduces latent class or profile models as a competitor to the mixed models. Chapter 12 considers some generalized linear mixed models for other trial designs.

Appendices A and B contain statistical background and theory for sample sizes and generalized mixed-effects models within the framework of the *S:T repeated measures design*.

The main focus of this book is to introduce the generalized linear mixed-effects models with *S:T repeated measures design*, which provide a flexible and powerful tool to deal with longitudinal data with heterogeneity or variability among subject-specific responses and missing data. This book illustrates theoretical methodologies with a focus on the practicality with a wealth of real-life examples making it easy to understand the topics. It is well organized and contains SAS codes and outputs as useful references.

In summary, this is an excellent book with a very good selection of examples. It is clearly written and is enjoyable to read.

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