Cox Regression on Marginal Models for Survival Data from Crossover Trials

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1. Introduction

The simplest crossover trial is the two-treatment two-period design. In the past several decades a number of approaches have been suggested for analyzing crossover trials when the outcomes of crossover experiments are either dichotomous or continuous. Censored continuous data arise when one measures the outcomes exactly for some subjects, but only within upper bounds for others. France et al. (1991) describe a crossover trial in which a treadmill stress test followed drug treatment. The outcome measure was the time to onset of symptoms and the data were censored if the stress test was stopped before symptoms occurred. For testing the treatment effect in crossover trials with censored data, France et al. (1991) proposed a Cox model stratified by subject, so the test is based on the treatment preference of each subject without regard to the magnitude of that preference. Feingold and Gillespie (1996) proposed two nonparametric methods of testing. For the first method they transform each observation to a Gehan score, different scores for the uncensored and censored scores, and then apply the nonparametric procedures to the scores. For the second method, they proposed an extension of the two-sample generalized Wilcoxon test for right-censored data. Feingold and Gillespie (1996) demonstrated that their methods of estimation are superior to the Cox-type tests in all of the situations they investigated.

In this paper we propose other approaches; Cox-type marginal models can be used for analyzing multivariate failure time data from crossover trials. This marginal model is an easy extension of the single event Cox model to the multivariate events situation. The proposed methodology is expected to have more power compared to the France et al. (1991)'s simple way of using Cox model stratified by subject. The proposed estimates of median survival times are simpler to compute than those of France et al. (1991).

Comparisons of different approaches of analysis are of interest and thus we use simulated data to evaluate and compare them.

2. Comparison of different analysis approaches

Understanding the strengths and weaknesses of various analysis approaches of crossover failure time data is important before one's choice of an approach. France et al.'s (1991) approach reveals a problem in estimating median survival times. The nonparametric methods proposed by Feingold and Gillespie (1996) definitely have more power than that of France et al. (1991), but unable to handle prognostic covariates.

The marginal model formulates the marginal distributions of multivariate failure times with the Cox proportional hazards models while leaving the nature of dependence among related failure times completely unspecified. The variance of the coefficients is then estimated by the robust variance estimator to the proportional hazards models to account for the correlations among the observations on an individual subject (Lin and Wei (1989), White (1982)). These analyses methods are applied to the data presented in France et al. (1991).

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RESUME

Crossover trials assign two treatments sequentially to the same subject, and a trial of testing new drugs in the treatment of angina pectoris produce censored failure time under each treatment. In this paper we present statistical procedures to analyze censored failure times from crossover trials. The methods employed are the Cox-type marginal models and these methods are compared with that proposed by France et al. (1991) and the nonparametric methods using score transformations. Estimates of the median times under each treatment in these Cox-type marginal models are discussed for the crossover failure times. We use simulated data to evaluate and compare these methods.

Key Words: Crossover trials, censored failure times, nonparametric tests, marginal models, multivariate failure time data