ABSTRACT

Crossover designs are widely used in variety of fields, including pharmaceutical industries. Their prominence in recent years has increased largely due to their recommendation in the guidelines of US Food and Drug Administration (FDA) for making drug comparisons. A crossover design is an experimental design in which the experimental units are used repeatedly by exposing them to a sequence of treatments. Consequently, the main concern with every crossover design is the time needed for execution and handling of the carryover effects of treatments, if any. As an experimental design, each crossover design is denoted by three parameters, the number of treatments, subjects, and periods, all preferably to be chosen independently. Several issues play role in the selection of a crossover design suitable for carryover models, specifically speaking, possibility to construct for a specific combination of parameters, analysis in presence/absence of specific carryover, and robustness to the likely violations of observational assumptions. Most authors have given central importance to the variance balanced property.

In this thesis, the popularly used balanced crossover designs are studied under various carryover models to contribute in all the three areas, construction, analysis and characterization. All our contributions are motivated either by the recent trends in its theoretical development, or by the idea of providing additional flexibilities and novelties to the experimenters. The thesis particularly provide crossover design solutions for the experiments having smaller number of periods, autocorrelated errors, arbitrary number of units, efficient comparison of active treatments, and various forms of carryover models.

Minimal balanced crossover designs having lesser, equal, and more periods than the numbers of treatments, are constructed using directed m-terraces and their modified forms. Two new forms of terraces, called as

complementary pair of the terraces and complementary trio of the terraces are introduced. As a result, two new series of crossover designs in even number of treatments are obtained. All the constructed designs possess good efficiency of separability, therefore they are suitable for estimation of the direct as well as the first order carryover effects of treatments. A list of terraces for the construction of minimal balanced crossover designs having three to nine treatments is given as a ready reference to develop designs of choice.

The presence of carryover in a crossover design makes analysis difficult because most observations are correlated, and carryover effects may not die after one period such as thorough QT, trials on diet, asthma, and others. A particular multi-period crossover design is shown to possess the equineighbour property, which makes the design robust to violation of the ordinary least squares estimation assumption of uncorrelated observations. This property made the crossover design to be useful for estimation in three practical cases. The cases are (i) the variance balanced estimation of direct and carryover treatment effects in presence of higher-order carryover and correlated errors using ordinary least squares method, (ii) estimation of the said treatment effects under scattered missing observations, and (iii) the interim estimation of the same for trials with early stopping rules. The treatment effect estimates and their variances are compared with those given in the literature for the higher-order carryover models. A numerical example is given for demonstrating estimation in all three cases.

A recent trend in the characterization of crossover designs is to provide estimates of treatment effects which are efficient (relative to an optimal design) under more than one model. Such crossover designs for carryover models are useful in clinical trials where the nature of carryover effects is not known in advance. The most useful of these designs are

the class of two treatment crossover designs. Several researchers have studied this class extensively, and have identified crossover designs which are optimal and efficient under several carryover models, but without concerning about the number of subjects. This thesis overcomes this limitation and constructs optimal and efficient crossover designs for given number of periods and subjects, through a computer search 5M algorithm. The 5M algorithm consists of enumerating all possible variance balanced crossover designs of a given class along with their variances of treatment contrast under five different carryover models. These five models include two new models which assume that, one of the treatments is a standard treatment with no carryover because its known carryover effect is eliminated through adequate washout period. Several optimal and/or efficient balanced two treatment crossover designs are obtained in two, three and four periods requiring few to reasonable number of subjects-two to twenty, for five types of model. In this process, some new optimal and efficient crossover designs in six and eight subjects, than the known designs are generated for traditional, and self and mixed carryover models.

The two treatment two period crossover design, {AB, BA} has been criticized by many authors because, the presence of carryover makes the analysis difficult and potentially biased or inefficient. Two alternative forms of crossover designs, namely, the two period three treatment crossover design, and the three period two treatment crossover design have been developed to analyze data under carryover models, but these crossover designs are not uniform in subjects. A uniform three period three treatment crossover design is defined to be consisting of a placebo and two active treatments. The crossover design is analyzed for the three cases that, both, single, and none of the two active treatments have carryover effect. Procedures for estimation and a test of carryover effects are presented.

The extraordinary benefits of the analysis of crossover designs consisting of a placebo and two active treatments, motivated us to study these kinds of designs in more classes. These designs are studied through a computer search algorithm, called 5M balanced algorithm, in two to four periods for different number of units, and optimal crossover designs are given for many classes. The new two period crossover designs having two active treatments and a placebo, enables the estimation of treatment contrasts under self and mixed carryover model, unlike the classic two treatment two period crossover which fails to estimate the same. The crossover designs having three or four periods in two active treatments and a placebo, estimate treatment contrasts more efficiently under self and mixed carryover model than the usual two treatment crossover designs. Crossover designs in two to four periods requiring two to twenty units are constructed and identified for being new optimal and efficient designs under different carryover models.

The experimenters have limited flexibility as far as the number of subjects are concerned, this could be detrimental in cancer trials. In crossover design literature, crossover designs are available mostly in even number of subjects, few odd numbers, like, three, nine, fifteen, but they are not available in prime numbers like, five, seven, and so on. A new class called active balanced uniform on period crossover designs is defined and studied for carryover models through a computer search algorithm, the 5M active balanced algorithm. The newly generated crossover designs are variance efficient under self and mixed carryover model than the two treatment three period crossover designs. Many crossover designs, unavailable so far, are obtained for five carryover models. Interestingly, a new optimal crossover design in the class of balanced two treatment three period crossover designs is also generated.