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ScienceDirect
Discrete Mathematics 306 (2006) 3112–3124
DISCRETE MATHEMATICS
www.elsevier.com/locate/disc

Efficient crossover designs for comparing test treatments with a control treatment

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Received 14 June 2004; received in revised form 13 June 2005; accepted 13 June 2005
Available online 14 July 2006

Abstract

Within a large family of crossover designs this paper characterizes the mathematical structures of A-optimal and A-efficient crossover designs for the purpose of statistical comparison between t experimental treatments with a control (standard) treatment. It further guides the user how to go about the construction of these designs and if needed doing the last minute modifications. To demonstrate the ideas some very interesting optimal and efficient small designs are constructed. The mathematical and statistical tools developed here could be very useful in other areas of design of experiments. Many interesting and not yet solved design problems for further research are implicitly stated throughout the paper.

Keywords: Crossover designs; Repeated measurements; Carryover effect; Balanced designs

1. Introduction

Crossover designs, where experimental subjects are used in two or more (p) periods for the purpose of evaluating and studying two or more (t) treatments have proven to be widely effective in a variety of fields, especially in phases I and II pharmaceutical clinical trials. In comparing treatments there are generally two situations which experimenters are interested in. One is that all treatments comparisons are equivalently important and the other is comparing new treatments with an established standard or a control treatment. Many published articles on crossover designs have addressed the statistical/mathematical issues related to the first situation. The reader is referred to the selected key articles in the bibliography. As for the second situation the list of unsolved problems is very vast and less than a dozen of articles have dealt with the related mission. Some selected recent references include Pigeon and D. Raghavarao

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[1] Primarily sponsored by the National Science Foundation Grant DMS-0103727, the National Cancer Institute Grant RO1-CA099904-02, and the NIH Grant P50-AT00155 (jointly supported by the National Center for Complementary and Alternative Medicine, the Office of Dietary Supplements, the Office for Research on Women's Health, and the National Institute of General Medicine). The contents are solely the responsibility of the author and do not necessarily represent the official views of NIH.
[2] Supported by the National Science Foundation Grant DMS-0304661.

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doi:10.1016/j.disc.2005.06.042

[9], Jacroux [5], Jaggi et al. [6], Mandal et al. [8], Solorzano and Spurrier [10], Ting [11], and Hedayat and Yang [2]. In this paper, we will concentrate on the second situation.

Let T be a set of $t+1$ elements denoted by $0, 1, \ldots, t$. A p-sequence on T is an ordered column vector of size p with entries from T. By a crossover design with parameters $t+1$, n, and p we mean any collection of n p-sequences on T with the condition that each element of T is used in at least one p-sequence. We can compactly represent any such design by a $p \times n$ array in which columns are the p-sequences. For example, if $t=3$, $p=3$, and $n=8$ the following is a crossover design with parameters 4, 8, and 3.

$$d_1: \begin{matrix} 0 & 1 & 2 & 3 & 3 & 2 & 0 & 2 \\ 0 & 2 & 3 & 2 & 0 & 0 & 1 & 3 \\ 2 & 3 & 3 & 0 & 0 & 2 & 2 & 1 \end{matrix}.$$

The class of all such crossover designs will be denoted by $\Omega(t+1, n, p)$. A crossover design looks like a proper block design except that the elements in each block are now ordered and they are no longer subsets of T.

In practice crossover designs can be used for many experimentations. For example, if we want to test and compare t drugs each being tested in a patient for say 3 months, then to minimize patient to patient variability and if under certain medical conditions each patient can participate in more than one period then we can test and collect multiple data on each patient by allowing him/her to go through a sequence of treatment testing. Thus for example, if we want to compare 3 doses of a newly developed drug with a placebo utilizing 100 patients, then if each patient is available for 9-month medical test, then each patient can be given a 3-sequence treatments. Which design in $\Omega(3+1, 100, 3)$ should be recommended to the experimenters? From a statistical point of view this depends on the model of observations and the statistical criteria we hope to achieve. Next, section provides a model and the criteria which we shall use for our design selection.

2. Model for the observations and the optimality criteria

The model we consider here is the most frequently used model in crossover design literature. It is called the traditional homoscedastic, additive, and fixed effects model formally introduced by Hedayat and Afsarinejad [1], namely

$$Y_{dks} = \mu + \alpha_k + \beta_s + \tau_{d(k,s)} + \rho_{d(k-1,s)} + e_{ks}, \quad k = 1, \ldots, p; \quad s = 1, \ldots, n, \tag{2.1}$$

where Y_{dks} denotes the response from subject s in period k to which treatment $d(k,s)$ was assigned. In this model μ is the general mean, α_k is the effect due to period k, β_s is the effect due to subject s, $\tau_{d(k,s)}$ is the direct treatment effect, $\rho_{d(k-1,s)}$ is the carryover or residual effect of treatment $d(k-1,s)$ on the response observed on subject s in period k (by convention $\rho_{d(0,s)} = 0$), and the e_{ks}'s are independently normally distributed errors with mean 0 and variance σ^2.

Hereafter, we shall designate the t-test treatments by $1, 2, \ldots, t$ and the control treatment by 0. Throughout this paper, for each design d, we adopt the notation n_{dis}, $\widetilde{n}_{dis}$, l_{dik}, m_{dij}, r_{di}, $\widetilde{r}_{di}$, and $\widehat{r}_{d0}$ to denote the number of times that treatment i is assigned to subject s, the number of times this happens in the first $p-1$ periods associated with s, the number of times treatment i is assigned to period k, the number of times treatment i is immediately preceded by treatment j, the total replications of treatment i in its n sequences, the total replications of treatment i limited to the first $p-1$ periods of the sequences, and total replications of control treatment 0 limited to the last $p-1$ periods respectively. Let $z_d = \sum_{s=1}^{n} \sum_{i=1}^{t} (n_{dis} - 1)^+$. Here, m^+ is m when $m > 0$ or 0 when $m \leqslant 0$.

In matrix notation we can write model (2.1) for the $n \times p$ observations as

$$Y_d = \mu 1 + P\alpha + U\beta + T_d\tau_d + F_d\rho_d + e, \tag{2.2}$$

where $Y_d = (Y_{d11}, Y_{d21}, \ldots, Y_{dpn})'$, $\alpha = (\alpha_1, \ldots, \alpha_p)'$, $\beta = (\beta_1, \ldots, \beta_n)'$, $\tau_d = (\tau_0, \ldots, \tau_t)'$, $\rho_d = (\rho_0, \ldots, \rho_t)'$, $e = (e_{11}, e_{21}, \ldots, e_{pn})'$, $P = 1_n \otimes I_p$, $U = I_n \otimes 1_p$, $T_d = (T'_{d1}, \ldots, T'_{dn})'$, and $F_d = (F'_{d1}, \ldots, F'_{dn})'$. Here T_{ds} stands for the $p \times (t+1)$ period-treatment incidence matrix for subject s under design d and $F_{ds} = LT_{ds}$ with the $p \times p$ matrix L defined as

$$\begin{pmatrix} 0_{1\times(p-1)} & 0 \\ I_{(p-1)\times(p-1)} & 0_{(p-1)\times 1} \end{pmatrix}.$$