Cross-over Designs under Random Subject Effects and Higher order Carry-overs.

Mausumi Bose
Applied Statistics Unit,
Indian Statistical Institute
203 B T Road
Calcutta, 700035, India
mausumi@isical.ac.in

Bhramar Mukherjee
Indian Statistical Institute

1. Cross-over Designs

In cross-over designs a number of subjects are exposed to some treatments sequentially over a number of time periods. These designs are widely used in clinical trials, particularly for chronic ailments like asthma, hypertension etc, where different drugs or different doses of the same drug are applied to a group of subjects sequentially. These designs are also used in agricultural field trials, animal husbandry experiments and in many other areas of experimental research.

The special characteristic of these designs is that when a treatment is applied to a subject in a certain period, it has a `direct' effect in the period of application and also `carry-over' effects in one or more successive periods following the period of application. So, the choice of the design in any experimental context becomes important. Optimal cross-over designs have been extensively studied in the literature. For an excellent review of these results we refer to Stufken(1996). Most of the available optimality results are based on a fixed effects model assuming independent errors and also assuming that `carry-overs' do not persist beyond one period after the application of a treatment. Recently, Bose and Mukherjee (2000) have assumed a model which incorporates carry-over effects up to k periods after the period of application and where interactions between the treatments successively applied to the same subject may also be present.

In this paper, we extend the results of Bose and Mukherjee (2000) to the mixed effects model where the subject effects are random. This model seems appropriate since in such experiments, the subjects are often a random sample of subjects from a population. Moreover, in the context of cross-over designs, where the same subject gives rise to several observations, the mixed model is more useful than a fixed model with independent errors since the mixed model assumes an error structure where observations from the same subject are correlated while observations from different subjects are uncorrelated.

Let C be the class of all cross-over designs with t treatments, n subjects and p periods. Let d(i,j) be the treatment assigned to the j-th subject in the i-th period. We consider the following non-additive mixed effects model with carry-overs up to the k-th order.

$$Y_{ij} = a + b_i + c_j + m_{d(i,j)\, d(i-1,j) \ldots d(i-k,j)} + e_{ij} \qquad \text{for } k \le i \le p-1, \quad 1 \le j \le n \text{ and}$$

$$Y_{ij} = a + b_i + c_j + m_{d(i,j)\, d(i-1,j) \ldots d(0,j)} + e_{ij} \qquad \text{for } 0 \le i \le k-1, \quad 1 \le j \le n, \qquad (1)$$

where Y_{ij}, a, b_i , c_j , $m_{h1\, h2 \ldots h(k+1)}$ and e_{ij} denote respectively the response under d(i,j), general mean, the i-th period effect, the random subject effect, the effect produced when treatment h1 is applied in the current period and hi in the (i-1)th preceding period, i = 2,3,..,(k+1). □

We assume that $b=(b_1, \ldots, bn)'$ and $e = (\ldots e_{ij} \ldots)'$ are normally distributed with means 0 and dispersion matrix BI_n and EIn respectively, where I_n denotes the identity matrix of order n.

Defintion: Let D be a design in C in which each treatment is applied equally often in each period, to each subject and in which each subset of 2,3,..,(k+1) consecutive periods contains each 2-plet, 3-plet, ...(k+1)-plet of treatments equally often.

For the definition of universal optimality we refer to Kiefer(1975).

Theorem. Under model (1), design D is universally optimal for the separate estimation of full sets of orthonormal contrasts of direct effects in the class of all cross-over designs in C.

The proof of this Theorem follows by first establishing a correspondence between cross-over designs and factorial experiments and then deriving the required information matrix. Then using tools from the calculus of factorial experiments, it can be shown that D satisfies the sufficient conditions of universal optimality.

The above theorem is quite general as the class of competing designs include all designs in C. It may be shown that D does not remain universally optimal for carry-over effects in the class C. The practitioner may choose a value for k, based on the experiment' s conditions.

Example: The following is an example of a design D with t=2, n=8, p=6, k=2. The 6 periods are written as rows and the 8 subjects as columns.

0	0	0	0	1	1	1	1
0	1	0	1	0	1	0	1
0	1	1	0	0	1	1	0
1	1	1	1	0	0	0	0
1	0	1	0	1	0	1	0
1	0	0	1	1	0	0	1

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RESUME

On etudie les plans d' experiences a croisement sous un modele non-additif ou les effets transporte peut persite sur plusiers periodes et ou l' effet du sujet est aleatoire. Sous cet modele on demontre uneclasse de plans d' experience qui sout optimum.