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Kasra Afsarinejad
Samad Hedayat

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Mailing address:	Fax	Phone	Home Page:
Department of Statistics	Nat: 031-773 12 74	Nat: 031-773 10 00	http://www.stat.gu.se
Göteborg University	Int: +46 31 773 12 74	Int: +46 31 773 10 00	
Box 660			
SE 405 30 Göteborg			
Sweden			

Repeated measurement designs for models with self and mixed carryover effects

BY K. AFSARINEJAD
Department of Statistics, Göteborg University, SE 405 30 Göteborg, Sweden
Kasra.Afsarinejad@statistics.gu.se

AND A.S. HEDAYAT
Department of Mathematics, Statistics, and Computer Science, University of Illinois, Chicago, IL., 60607-7045, USA
Hedayat@uic.edu

SUMMARY

We study the problem of design and analysis of two-period repeated measurement (crossover or changeover) designs based on two or more treatments. In our model we allow the appearance of two types of carryovers (residuals) in the observations collected in the second period. It is assumed that each treatment has three types of effects: direct effect, self-carryover effect, and simple mixed carryover effect. The direct effect will manifest itself no matter where and when the treatment applied. Carryover effects will only appear in the second period. The nature and the magnitude of this carryover effect of a treatment in the first period which will appear in the second period depends on the treatment into which it carries this carryover effect. It is called a self-carryover effect if it carries to itself. Otherwise, it is called a simple mixed carryover effect. It is proved that if the study is properly designed we can efficiently estimate any contrast in direct treatment effects even if there are self and simple mixed carryover effects in the data. Further, it is shown that the most efficient way of constructing a two-period repeated measurement design is equivalent to constructing an efficient block design in a special class of block designs based on t (≥ 2) treatments utilising in total a fixed number of experimental units. In addition, if we are interested in contrasts involving self carryover effects only, then it is easy to design the study so that we can estimate these contrasts optimally. The problem of constructing the most efficient design for studying contrasts in simple mixed carryover effects remains an open problem.

Some key words: Efficient block design, Mixed carryover effect, Self-carryover effect, Simple mixed carryover effect.

1. INTRODUCTION

In many situations due to lack of enough experimental units and for many other practical reasons, including substantial variability among units we need to use repeated measurement designs for assessments and the estimation of differences between the treatments under the study. But then for reasons beyond the control of the experimenter undesirable effects such as carryovers (residuals) or interactions will enter into the data. Then the estimation or elimination of these undesirable effects becomes a secondary and often important aspect of the design and its related analysis. Of course, we should make every effort to avoid these undesirable effects in the design stage. But this might not be possible in all cases. Therefore, we need to identify efficient designs, which allow the study and the elimination of these effects.

To minimize the possible confusion about the carryover effects and for other practical reasons such as compliance in clinical trials two-period repeated measurement designs are very popular designs in practice. In this article we study two-period repeated measurement designs for comparing two or more treatments allowing the appearance of two types of carryover effects namely self-carryover and simple mixed carryover effects. It is shown that if we properly design the study then unbiased and efficient estimates of all contrasts in direct treatment effects can be obtained. We use a statistical tool developed by Hedayat and Zhao (1990) to relate the problem of constructing efficient designs of two-period repeated measurement designs for our model to the problem of constructing efficient block designs in a special class of proper / improper block designs based on t treatments utilizing in total a fixed number of experimental units. This connection between optimal two-period repeated measurement designs and optimal block designs has greatly reduced the burden of the original task since the latter problem is much easier to solve. If we carefully design the study we can eliminate simple mixed carryover effects in the analysis stage but the problem of constructing the most efficient design for study contrasts in simple mixed carryover effects remains open. Finally, we have shown that it is easy to design the study if we are also interested in optimally estimating contrasts in self-carryover effects. It is also pointed out that if we are not careful in our design we might partially or fully confound the design yielding damaged or unusable data. For the most recent review article on this topic we refer the reader to Stufken (1996).

2. MODEL AND NOTATION

We assume t ($\geq$2) treatments are to be studied utilizing n experimental units. Each unit is to be used in two periods. These two periods are the same for all n units. In the absence of missing observations the design will yield 2n observations. Each unit can be given the same treatment or different treatments in two periods. Thus, we are allowed to select n sequences from t^2 possible sequences of two treatments each. There is no restriction that these n sequences must be distinct. Thus, our design problem is which n sequences give us the best design and how should we analyze the related data. Clearly, the choice will depend on the model of observations and the goal we expect to achieve from the study. Throughout the paper, we use d to denote the design and d(i, j) to denote the treatment being assigned to unit j in period i, i = 1, 2; j = 1, 2, ..., n.

The Model: If d(1, j) = k, then the model of response for the observation, y_{1jko} , collected on unit j in period 1 is postulated to be:

$$y_{1jko} = \mu + \pi_1 + \beta_j + \tau_k + e_{1jko} \qquad (1)$$

Where, μ is the general mean, π_1 is the effect of period 1, β_j is the effect of unit j, and τ_k is the direct effect of treatment k. These are unknown constants. e_{1jko} is the only random (noise) component of the model which is assumed to be distributed as normal with mean zero and variance σ^2. All these n observations are independent. Note that we use y_{1jko} rather than y_{1jk} to signify that there is no carryover effect on this observation. However, for the n observations collected in the second period two cases arise:

Case 1. If d(2, j) = d(1, j) = k, then the model of response for y_{2jkk} is:

$$y_{2jkk} = \mu + \pi_2 + \beta_j + \tau_k + \rho_k + e_{2jkk} \qquad (2)$$

where, π_2 is the effect of period 2 and ρ_k is the carryover effect of treatment k from period 1 on itself in period 2. This carryover effect is called the *self-carryover effect* of treatment k.

Case 2. If $d(2, j) = k$, $d(1, j) = l$, $l \neq k$, then the model of response for y_{2jkl} is:

$$y_{2jkl} = \mu + \pi_2 + \beta_j + \tau_k + \rho_l' + e_{2jkl} \qquad (3)$$

Here ρ_k' is the carryover effect of treatment l on treatment k in period 2. Note that this carryover effect is the same for all $l \neq$ k. This carryover effect is called the *simple mixed carryover effect* of treatment k. Self and simple mixed carryover effects are assumed to be constants. The error e_{2jkl} is assumed to be normal with mean zero and variance σ^2. The observations on different units are independent but the two observations on each unit are assumed to be correlated with cov (y_{1jko} , y_{2jkk}) = cov (y_{1jko} , y_{2jkl}) = $\delta\ \sigma^2$. If possible, we should design the study so that δ becomes positive.

Therefore, our model could have up to 5+3t+n unknown parameters. However, the t direct treatment effects, δ, and σ^2 are primary parameters of the study. Note that we could entertain a more general mixed carryover effect. For example, we could assume that the mixed carryover effect of a treatment in period 1 on the treatment in period 2 depends on what treatment was applied in period 2. However, we believe this might unnecessarily over parameterize and often saturate or even worse over saturate the model.

Study and the estimation of self and simple mixed carryover effects are very important in many fields including, but not limited to, medicine and life sciences. For example, in a single drug therapy for a chronic disease it will be very helpful to the physician to know the magnitude of the self-carryover effect of the drug the doctor is recommending for her patient. Or, for arranging the best crop rotation schedule it will be very useful to know the size and the impact of the simple mixed carryover effects.

For an interesting and illuminating discussion on modeling repeated measurement responses we refer the readers to Jones and Kenward (1989), Fleis (1989), Armitage (1991) and Matthews (1994) and the list of references cited there.

In two ways we can completely characterize a two-period repeated measurement design. Either specifying which n sequences of two treatments are selected or think of the design, d, as a ($d^{(1)}$ / $d^{(2)}$) = ($d^{(11)}$: $d^{(12)}$ / $d^{(21)}$: $d^{(22)}$). The compartment $d^{(1)}$ specifies which treatment is assigned to which experimental unit in the first period. The compartment $d^{(2)}$ specifies which treatment is assigned to which experimental unit in the second period. There could be $0 \leq n_1 \leq n$ experimental units, which have received the same treatments in both periods. We shall assume that these n_1 units are units 1, 2, ..., n_1. The compartment $d^{(i1)}$ specifies which treatment is assigned to the first n_1 units in the ith period, i = 1, 2. Thus $d^{(11)} \equiv d^{(21)}$. The compartments $d^{(12)}$ and $d^{(22)}$ specify the assignment of treatments to the remaining n_2 units in periods 1 and 2 respectively. The only restriction on $d^{(12)}$ and $d^{(22)}$ is that no unit will receive the same treatment under $d^{(12)}$ and $d^{(22)}$. Let $r_k(i1)$ and $r_k(i2)$ be the number of units which have been assigned treatment k under $d^{(i1)}$ and $d^{(i2)}$ respectively. Finally, we let

$$r_k = \sum_{i=1}^{2} [r_k(i1) + r_k(i2)] \qquad (4)$$

Note that $r_k(11) = r_k(21)$.

3. FIRST STAGE DATA SUMMARIZATION

When unit effects are fixed, the entire information for the purpose of estimating / testing contrasts in direct treatment effects or in carryover effects are imbedded in n basic differences specified below, $n = n_1 + n_2$.

The n_1 basic differences belonging to the data produced by n_1 units under $d^{(11)}$ and $d^{(21)}$ components of the design:

$$z_{1jko} = y_{2jkk} - y_{1jko} = \theta + \rho_k + \varepsilon_{1jko}\ ,\ j = 1, 2, \ldots, n_1 \qquad (5)$$

where $\theta = \pi_2 - \pi_1$ and $\varepsilon_{1jko} = e_{2jkk} - e_{1jko}$.

The n_2 basic differences belonging to the data produced by n_2 units under $d^{(21)}$ and $d^{(22)}$ components of the design:

$$z_{2jkl} = y_{2jkl} - y_{1jlo} = \theta + \tau_k + \lambda_l + \varepsilon_{2jkl}\ ,\ \ j = n_1 + 1, \ldots, n \quad (6)$$

where $\lambda_l = \acute{\rho_l} - \tau_l$, and $\varepsilon_{2jkl} = e_{2jkl} - e_{1jlo}$.

Therefore, as we can see from (5) and (6), that our statistical inferences will depend on the n_1 data points with the model of completely randomized design in self-carryover effects and the n_2 data points with the model of randomized block design with direct treatment effects as our treatments. The block effects are composition of direct treatment effects in period 1 and simple mixed carryover effects in period 2. These block parameters are of no use to the experimenter and should be eliminated as nuisance parameters by properly designing $d^{(12)}$ and $d^{(22)}$ components of d.

Based on the preceeding discussion we conclude the following important points for any two-period repeated measurement design if models (1), (2), and (3) can be reasonably postulated for the 2n data generated by such designs.

1. If one of the observations for any unit is missing or cannot be used, the other observation is of no use.

2. All treatments need to be tested at least once in $d^{(22)}$ component of the design, i.e., $r_k(22)$ should be at least one for all $k = 1, 2, \ldots, t$.

3. By avoiding partial or full confounding in $d^{(12)}$ and $d^{(22)}$ we can unbiasedly estimate contrasts in direct treatment effects and their associated variances (see Section 4).

4. If we carefully design our study we can unbiasedly estimate any contrast in self-carryover effects and their associated variances (see Section 4).

5. We should avoid, if possible, two-period repeated measurement designs if the two observations within a unit become negatively correlated.

4. EFFICIENT WAYS OF DESIGNING TWO-PERIOD REPEATED MEASUREMENT DESIGNS

While it is possible in many circumstances to design the study for the purpose of unbiased estimation of contrasts in simple mixed carryover effects, the problem of constructing the most efficient designs for estimating these contrasts remains an open problem.

4.1. Estimating contrasts in self-carryover effects

Consider the n_1 data generated under (5) and let

$$\bar{z}_{1\cdot}(k) = \sum_{j\varepsilon\Delta(k)} z_{1jko} / r_k(11), \qquad (7)$$

where $\Delta(k)$ is a subset of units among n_1 units that have been assigned treatment k under $d^{(11)}$ and $d^{(21)}$. Now let $\psi = \sum_k c_k\rho_k$, $\sum_k c_k = 0$, be a non-null contrast in self-carryover effects. Then, the best linear unbiased estimate of ψ is given by

$$\hat{\Psi} = \sum_k c_k \, \bar{z}_{1\cdot}(k) \qquad (8)$$

with

$$V(\hat{\Psi}) = \sum_k \left(c_k / r_k(11) \right)^2 \sigma^{*2}, \qquad (9)$$

where , $\sigma^{*2} = 2\,(1\text{-}\delta)\,\sigma^2$. Thus, for contrasts in self-carryover effects to be estimable it is both necessary and sufficient that $r_k(11) \geq 1$, $k = 1, 2, \ldots, t$. And for these contrasts to be estimated with the same degree of efficiency we should have $r_k(11) = r_{k'}(11)$, $k \neq k' = 1, 2, \ldots, t$. Furthermore, to increase the efficiency of any contrast being estimated we should assign more units to the related treatments in the given contrast. If $n_1 \equiv 0 \pmod t$, then based on Theorem 4.3 of Hedayat and Zhao (1990), $r_k(11) = n_1 / t$ provides a universally optimal design, $k = 1, 2, \ldots, t$.

4.2. Estimating contrasts in direct treatment effects

As we mentioned in Section 3 only z_{2jkl}*'s* data generated under (6) will be useful in estimating contrasts in direct treatment effects. Following Hedayat and Zhao (1990) we can think of these n_2 data as n_2 data points generated by an incomplete block design specified as follows. We go to $d^{(12)}$ and see how many distinct treatments being tested in its n_2 units. Suppose there are b such treatments, $0 \leq b \leq t$. When $b = 0$, $d^{(12)}$ is empty and as we see the design d based on $d^{(11)}$ and $d^{(21)}$ is totally disconnected for direct treatment effects. When $b = t$, each of t treatments under the study being tested at least once under $d^{(12)}$. Let $\{T_1, T_2, \ldots, T_b\}$ be the set of these b treatments. Now we form b blocks, labeled by $T_1, T_2, \ldots, T_b$. Fill the block related to T_i with those treatments tested under $d^{(22)}$ in those units which were tested by T_i under $d^{(12)}$, $i = 1, 2, \ldots, b$. Then we use n_2 data generated by (6) and analyze it under this block design to construct best linear unbiased estimator of estimable contrasts in direct treatment effects. What contrasts can be unbiasedly estimated and how good these estimates are solely depends on how good the related b blocks are. These points will be illustrated by four designs listed in Example 1.

Example 1

Suppose we want to study 5 treatments via 15 experimental units under a two-period repeated measurement design. We label these 5 treatments by 1, 2, 3, 4, and 5. The following designs are examples of a two-period repeated measurement designs.

		$d^{(11)}/d^{(21)}$						Experimental units				$d^{(12)}/d^{(22)}$									
	Period /	1	2	3	4	5		6	7	8	9	10	11	12	13	14	15
d_1 :	1	1	2	3	4	5		1	2	2	3	1	3	4	4	5	5
	2	1	2	3	4	5		3	1	5	4	5	1	2	3	4	2
d_2 :	1	1	2	3	4	5		1	1	1	1	2	2	2	3	3	4
	2	1	2	3	4	5		2	3	4	5	3	4	5	4	5	5
d_3:	1	1	2	3	4	5		1	1	4	5	2	2	5	3	3	4
	2	1	2	3	4	5		2	3	1	1	3	4	2	4	5	5
d_4:	1	1	2	3	4	5		1	2	3	4	5	1	2	3	4	5
	2	1	2	3	4	5		5	4	2	3	1	5	4	1	2	3

Let us now compare these four designs. All four of them have identical $d^{(11)}$ / $d^{(21)}$ compartments. Thus, for the purpose of estimating any contrast in self-carryover effects these four designs have equal efficiency. Now let us compare them for the purpose of estimating contrasts in direct treatment effects. To do so, we need to compare their associated block designs specified by their $d^{(12)}$ / $d^{(22)}$ compartments. The four associated block designs are listed below.

<u>For d_1</u>	<u>For d_2</u>	<u>For d_3</u>	<u>For d_4</u>
1 2 3 4 5	1 2 3 4	1 2 3 4 5	1 2 3 4 5
3 1 4 2 4	2 3 4 5	2 3 4 1 1	5 4 2 3 1
5 5 1 3 2	3 4 5	3 4 5 5 2	5 4 1 2 3
	4 5		
	5		

Clearly design d_2 is a bad design since no contrast involving treatment 1 can be unbiasedly estimated. In addition, it has confounded fully treatment 5 with one of the blocks. Design d_4 is a bad design as well. Treatments 5 and 4 are totally confounded and therefore no contrasts involving treatments 4 or 5 can be unbiasedly estimated. So, the competition is between d_1 and

d_3. It is clear that d_1 is equivalent to d_3 since their associated block designs are isomorphic by using the permutation $1 \leftrightarrow 5$ and $2 \leftrightarrow 3$.

Before we proceed further and for the purpose of presenting our results in a concise manner we will introduce two more notations. We denote the class of all repeated measurement designs for comparing t treatments over two periods using in total n experimental units by RMD (t, n, 2). We also denote the class of all block designs for comparing t treatments consisting of one or more incomplete (binary or not) blocks of equal or different sizes but only limited to n experimental units in total by BD(t, n). We can now formally state our results:

THEOREM 1. *Based on any optimality/efficiency criterion a two-period repeated measurement design* d^* *in* RMD (t, n, 2) *is optimal / efficient for estimating contrasts in direct treatment effects if and only if its two compartments* $d^{*(12)}$/ $d^{*(22)}$ *based on* $n_2 \leq n$ *yields an optimal / efficient block design in* BD (t, n_2).

COROLLARY 1. *Under models* (1)-(3), *contrasts in direct treatment effects cannot be unbiasedly estimated if* $t = 2$, *no matter what* n *is.*

This follows since the corresponding block design is totally disconnected.

We now try to take advantage of this theorem and identify, if possible, an optimal /efficient design in RMD (t, n, 2) for small values of t but arbitrary n. We can use Latin squares and Latin rectangles in the form of symmetric BIB designs and produce practically appealing and statistically optimal two-period repeated measurement designs for $t \geq 3$ treatments. Hereafter, we denote the set of t treatments by $T = \{1, 2, 3, \ldots, t\}$.

THEOREM 2. *Any Latin square of order* t *can be converted into an optimal design in* RMD (t, n, 2) *with* $n = n_1+n_2$, $n_2 = t(t-1)$.

Proof. Construct a Latin square, L, of order t based on T. Use the first row of L to form $d^{(12)}$ by assigning t-1 units to treatment k, k = 1, 2, ..., t. Use the remaining t-1 rows of L to form $d^{(22)}$ by assigning t-1 treatments which appeared under treatment k in the first row of L to t-1 units which were assigned treatment k under $d^{(12)}$. This design is optimal in the class of RMD designs with $n_2 = t(t-1)$ and uniform on t treatments under $d^{(12)}$. This follows since its associated incomplete block design is optimal in the class of proper incomplete block designs.

THEOREM 3. *Any Latin rectangle of size* m x t, m < t, *in the form of a symmetric* BIB *design can be converted into an optimal design in* RMD (t, n, 2) *with* $n = n_1+n_2$, $n_2 = tm$.

Proof. Let H be the given m x t rectangle on T. Note that the t columns of H form a symmetric BIB design. Extend H to an (m+1) x t rectangle by adding a new row to H (this is always possible). Now form $d^{(12)}$ by assigning m units to each of t treatments appeared in the new row added to H. Then form $d^{(22)}$ by assigning the m treatments which appeared in H under treatment k in the new row, k = 1, 2, ..., t. The resulting repeated measurement design is optimal since its corresponding proper incomplete block designs is optimal in the class of proper incomplete block designs with the given parameters.

Example 2

For t = 3, and starting with 2 by 3 rectangle with rows 1 2 3 and 2 3 1, Theorem 3 produces the following design.

$d^{(11)} / d^{(21)}$: consists of copies of

1 2 3
1 2 3

$d^{(12)} / d^{(22)}$: consists of copies of

1 1 2 2 3 3
2 3 3 1 1 2

Example 3

The following are two Latin rectangles in the form of symmetric BIB designs for t = 7.

$$H_1 = \begin{matrix} 1 & 2 & 3 & 4 & 5 & 6 & 7 \\ 2 & 3 & 4 & 5 & 6 & 7 & 1 \\ 4 & 5 & 6 & 7 & 1 & 2 & 3 \end{matrix} \qquad H_2 = \begin{matrix} 3 & 4 & 5 & 6 & 7 & 1 & 2 \\ 5 & 6 & 7 & 1 & 2 & 3 & 4 \\ 6 & 7 & 1 & 2 & 3 & 4 & 5 \\ 7 & 1 & 2 & 3 & 4 & 5 & 6 \end{matrix}$$

The corresponding optimal repeated measurement design to H_1 is

$d^{(11)} / d^{(21)}$ consists of copies of

1 2 3 4 5 6 7
1 2 3 4 5 6 7

and

$d^{(12)} / d^{(22)}$:

3 3 3 4 4 4 5 5 5 6 6 6 7 7 7 1 1 1 2 2 2
1 2 4 2 3 5 3 4 6 4 5 7 5 6 1 6 7 2 7 1 3

and the corresponding optimal repeated measurement design to H_2 is

$d^{(11)} / d^{(21)}$: copies of

1 2 3 4 5 6 7
1 2 3 4 5 6 7

and

$d^{(12)} / d^{(22)}$:

1 1 1 1 2 2 2 2 3 3 3 3 4 4 4 4 5 5 5 5 6 6 6 6 7 7 7 7
3 5 6 7 4 6 7 1 5 7 1 2 6 1 2 3 7 2 3 4 1 3 4 5 2 4 5 6

In general, we can convert an optimal / efficient binary incomplete block design in b ($\leq$ t) blocks on t treatments into an optimal / efficient repeated measurement design as explained in Theorem 4.

THEOREM 4. *If* d *is an optimal / efficient binary (proper or not) block design based on* b ($\leq$ t) *blocks in* BD (t, n), *then* d *can be converted into an optimal / efficient repeated measurement design in* RMD (t, n, 2).

Proof. Label the b blocks of d with b of t treatments so that the block which is labeled by treatment k does not contain treatment k. Then in $d^{(12)}$ assign as many units to treatment *l* as its corresponding block size and assign the content of this block in $d^{(22)}$. Continue this process for the remaining b-1 treatments.

Example 4

The following design which is a group divisible design is known to be E-optimal for comparing its six treatments.

1	1	1	2	3	3
2	2	5	5	4	4
3	4	6	6	5	6

Its corresponding RM design based on Theorem 4, after labeling these six blocks from left to right by treatments 6, 5, 4, 3, 2, and 1, is

6	6	6	5	5	5	4	4	4	3	3	3	2	2	2	1	1	1
1	2	3	1	2	4	1	5	6	2	5	6	3	4	5	3	4	6

Fortunately, the literature on optimal design of experiments abounds with many family of optimal / efficient block designs which could be converted into optimal / efficient repeated measurement designs.

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