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OPTIMAL TWO-PERIOD REPEATED MEASUREMENTS DESIGNS[1]

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For the class of repeated measurements designs based on t treatments, n experimental units and two periods, the following results are obtained.

1. The equivalence of the information matrices of such repeated measurements designs and of certain block designs is established. The implication of this equivalence on the optimality of both repeated measurements designs and block designs is explored.
2. A family of universally optimal designs or A-optimal designs is constructed depending whether or not n divides t.
3. Families of optimal designs for residual effects and for comparing test treatments with a control are constructed.

1. Introduction. An experiment in which a unit is repeatedly exposed to various treatments is called a repeated measurements design (RMD). In such an experiment, t treatments are assigned to n experimental units, each of which receives one treatment application during each of p periods. Other names have been used for this type of design including crossover and changeover design. For details, see Hedayat and Afsarinejad (1975, 1978) and Matthews (1988).

Repeated measurements designs have been in use for a long time. However, their optimality aspects were first initiated and studied by Hedayat and Afsarinejad (1978). They showed that certain types of RM designs are universally optimal. More results were established by Cheng and Wu (1980) and Kunert (1983, 1984). We refer the reader to Matthews (1988) for a survey on some selected optimal and other types of RM designs. However, essentially all available optimality results are related to the situation where $p \geq t$. A more realistic situation is one where $p < t$. In particular, $p = 2$ is of great importance in clinical trials. Obviously $p = 2$ is the minimum number of periods required to estimate the direct effects of the treatments in a repeated measurements design. For details of their importance and application in clinical trials, the reader may consult Grizzle (1965), O'Neill (1977), Hills and Armitage (1979), Barker, Hews, Huitson and Poloniecki (1982), Armitage and Hills (1982), Laska, Meisner and Kushner (1983) and Willan and Pater (1986). Other useful references are Balaam (1968) and Brown (1980). Constantine and Hedayat (1982) constructed families of repeated measurements designs with

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$p < t$ that are balanced for residual effects. These designs were shown to be connected for both residual and direct treatment effects with a minimum number of units. Dey, Gupta and Singh (1983) made an attempt to search for universally optimal designs with $p < t$ in a very restricted subclass. Afsarinejad (1985) obtained similar results as in Dey, Gupta and Singh (1983) for the case $p < t$ with $n = 2t$. Stufken (1990) has obtained a series of beautiful results for RM designs, including designs with a small number of periods.

Unfortunately, there are no results for general n, t and $p < t$, not even for the case $p = 2$. This is due to the difficulty of finding the general form of the information matrix. In this paper, we will present general optimality results for the case $p = 2$. Specifically, we will establish the equivalence of the information matrices of such repeated measurements designs and of certain block designs. The implication of this equivalence on the optimality of both repeated measurements designs and block designs is explored. We will also construct A-optimal designs for general n and t and universally optimal designs for $n = \lambda t$ for direct and residual effects and for comparing test treatments with a control.

2. Preliminaries. Throughout, the class of all repeated measurements designs for comparing t treatments over two periods using a total of n experimental units will be denoted by RMD$(t, n, 2)$. We note that each d in RMD$(t, n, 2)$ can be completely characterized by the set of nonnegative integers λ_{dij}, $i, j = 1, 2, \dots, t$, denoting the number of experimental units that receive treatment i in the first period and treatment j in the second period. It will also be useful to know the number of times that the ith treatment is tested under d in the first and in the second period. These quantities are denoted by f_{di} and s_{di}, respectively. Clearly, these three sets of quantities are related as follows:

$$\sum_{j=1}^{t} \lambda_{dij} = f_{di}, \qquad \sum_{i=1}^{t} \lambda_{dij} = s_{dj} \quad \text{and} \quad \sum_{i=1}^{t} f_{di} = \sum_{i=1}^{t} s_{di} = n.$$

Let d be a design in RMD$(t, n, 2)$ and let $d(i, j)$ denote the treatment assigned by d in the ith period to the jth unit. By implementing d we obtain $2n$ observations. The observation collected on the jth unit in the ith period is denoted by y_{ij}, $i = 1, 2$, $j = 1, 2, \dots, n$. These $2n$ observations are assumed to be generated by the model

$$\begin{aligned} E(y_{1j}) &= \tau_{d(1,j)} + \alpha_1 + \beta_j, \\ E(y_{2j}) &= \tau_{d(2,j)} + \rho_{d(1,j)} + \alpha_2 + \beta_j, \\ V(y_{ij}) &= \sigma^2, \\ \operatorname{Cov}(y_{1j}, y_{2j}) &= \rho\sigma^2, \qquad -1 < \rho < 1, \\ \operatorname{Cov}(y_{ij}, y_{lk}) &= 0, \qquad \text{otherwise}, \end{aligned} \tag{2.1}$$

for $i = 1, 2$, $j = 1, 2, \dots, n$, $l = 1, 2$ and $k = 1, 2, \dots, n$, and where $\tau_{d(i,j)}$,

$\rho_{d(1,j)}$, α_i and β_j are called the direct effect of the treatment $d(i,j)$, the first-order residual effect of the treatment $d(1,j)$, the ith period effect and the jth unit effect, respectively. Observe that model (2.1) postulates that a treatment applied in the first period continues to exert some of its effect on the observation made on the same unit in the second period. Magda (1980), Hedayat (1981) and several others have considered optimal designs for models in which the treatments applied in the second period on a given subject will leave a residual effect on the observation made on the same subject in the first period. Such cyclical models have useful applications in rotation experiments, but we do not consider such models in this paper.

Let $Y_d = (y_{11}, y_{12}, \dots, y_{1n}, y_{21}, y_{22}, \dots, y_{2n})'$. Then, in matrix form, we have $EY_d = X_d\Theta$ with

$$\Theta = (\tau_1, \dots, \tau_t, \rho_1, \dots, \rho_t, \alpha_1, \alpha_2, \beta_1, \dots, \beta_n)'$$

and

$$X_d = \begin{bmatrix} P_{d1} & 0_n & 1_n & 0_n & I_n \\ P_{d2} & P_{d1} & 0_n & 1_n & I_n \end{bmatrix},$$

where P_{di} is the incidence matrix for units and treatments, corresponding to the ith period, $i = 1, 2$.

The information matrix for direct effects can be derived as

$$C_d = C_{d11} - C_{d12}C_{d22}^{-}C_{d21}, \tag{2.2}$$

and for residual effects as

$$\tilde{C}_d = C_{d22} - C_{d21}C_{d11}^{-}C_{d12}, \tag{2.3}$$

where

$$C_{d11} = \frac{1}{2}(P'_{d1} - P'_{d2})\left(I_n - \frac{1}{n}J_n\right)(P_{d1} - P_{d2}),$$

$$C_{d12} = \frac{1}{2}(P'_{d2} - P'_{d1})\left(I_n - \frac{1}{n}J_n\right)P_{d1} = C'_{d21},$$

$$C_{d22} = \frac{1}{2}P'_{d1}\left(I_n - \frac{1}{n}J_n\right)P_{d1}.$$

3. RMD and block designs. In this section we shall establish the connection between designs in RMD$(t, n, 2)$ for the purpose of estimating direct effects and certain block designs with b blocks, $b \le t$. This connection allows us to make some interesting optimality conclusions for both repeated measurements designs and block designs.

THEOREM 3.1. *Let d be a design in* RMD$(t, n, 2)$ *with t, f_{di}, λ_{dij} as defined previously. Denote the number of distinct treatments appearing in the first period of d by b. Without loss of generality, let these b treatments be treatments $1, 2, \dots, b \le t$. Then, there exists a block design d' based on t treatments in b blocks of sizes $k_i = f_{di}$, $i = 1, 2, \dots, b$, whose incidence matrix is $(n_{d'li}) = (\lambda_{dil})$*

with

$$C_{d'} = 2C_d, \tag{3.1}$$

where $C_{d'}$ *is the information matrix for the treatments under the standard linear additive model for the block design* d'. *Conversely, a block design with* b $(\leq t)$ *blocks induces a design in* RMD$(t, n, 2)$, *with* n *equal to the total number of experimental units in the block design where again the relation* (3.1) *between their corresponding information matrices is satisfied.*

PROOF. We establish the results in two steps. First, we shall construct the corresponding block design for a given RM design and vice versa. Then, we shall verify the relation (3.1) between the corresponding information matrices. Suppose d is a design in RMD$(t, n, 2)$. Let b be the number of distinct treatments assigned in the first period of d. We now construct a block design d' with b blocks utilizing the structure of d. In block i we assign the collection of treatments that are assigned by d in the second period to those units which have received treatment i in the first period, $i = 1, 2, \dots, b$. In the notation of Section 2, this collection consists of treatments $d(2, j)$ for which $d(1, j) = i$.

Conversely, given a block design d' with b blocks based on t $(\geq b)$ treatments we can associate with it a design d in RMD$(t, n, 2)$, where n is the total number of experimental units in d, in the following way: Let k_i be the size of the ith block. In the first period we assign treatment i to k_i experimental units. To these units, we assign the content of the block i in the second period, $i = 1, 2, \dots, b$. Note that the labelling of the treatments and blocks is arbitrary and unrelated.

Now we verify relation (3.1). This can be accomplished in two seemingly different ways. A direct way is by deriving the information matrices for the treatments effects using the standard linear additive model under d' and for the direct effects under model (2.1) through (2.2) and observing that the relation (3.1) is indeed true. The second way is to observe that the existence of the unit effects for d, under model (2.1), forces the linear unbiased estimators of the estimable contrasts among direct effects to depend only on the differences of the consecutive observations on the same units, $y_{2j} - y_{1j} = \delta_j$. This means that our $2n$ observations can be remodelled to n observations δ_j's with the model

$$\begin{aligned} E(\delta_j) &= \alpha_2 - \alpha_1 + \tau_{d(2,j)} + \rho_{d(1,j)} - \tau_{d(1,j)}, \\ V(\delta_j) &= 2(1-\rho)\sigma^2, \quad \mathrm{Cov}(\delta_i, \delta_j) = 0, \quad i \neq j, i, j = 1, 2, \dots, n. \end{aligned} \tag{3.2}$$

Renaming $\alpha_2 - \alpha_1$ by μ and $\rho_{d(1,j)} - \tau_{d(1,j)}$ as $\gamma_{d(1,j)}$, the preceding model is the same as the standard linear additive model for block designs apart from the adjustment $2(1-\rho)$ we have to make for $V(\delta_j)$. This should conclude the proof. □

Therefore, if d in RMD$(t, n, 2)$ assigns only b distinct treatments, say treatments $1, 2, \dots, b$, to the n units in the first period, then the information matrix C_d for the direct effects can be expressed as

$$2C_d = \begin{bmatrix} s_{d1} & & & \\ & s_{d2} & & \\ & & \ddots & \\ & & & s_{dt} \end{bmatrix} - \begin{bmatrix} \lambda_{d11} & \lambda_{d12} & \cdots & \lambda_{d1b} \\ \lambda_{d21} & \lambda_{d22} & \cdots & \lambda_{d2b} \\ \vdots & & \ddots & \vdots \\ \lambda_{dt1} & \lambda_{dt2} & \cdots & \lambda_{dtb} \end{bmatrix}$$

$$\times \begin{bmatrix} f_{d1}^{-1} & & & \\ & f_{d2}^{-1} & & \\ & & \ddots & \\ & & & f_{db}^{-1} \end{bmatrix} \begin{bmatrix} \lambda_{d11} & \lambda_{d21} & \cdots & \lambda_{dt1} \\ \lambda_{d12} & \lambda_{d22} & \cdots & \lambda_{dt2} \\ \vdots & & \ddots & \vdots \\ \lambda_{d1b} & \lambda_{d2b} & \cdots & \lambda_{dtb} \end{bmatrix}.$$

This indicates that an RM design based on two periods is connected for the direct effects only if every treatment is tested in the second period. Therefore we will assume in the remainder of this paper that in all RM designs every treatment is tested in the second period.

We shall now elucidate our finding by two examples.

EXAMPLE 3.1. Let $t = 3$, $n = 8$. Consider the RM design d with the following assignment of treatments:

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

Then its corresponding block design d' is given by

$$d': \begin{matrix} 1 & 1 & 1 \\ 2 & 1 & 3 \\ 3 & 2 & \end{matrix}$$

with the columns as blocks. Indeed, as can be easily checked, $2C_d = C_{d'}$.

EXAMPLE 3.2. Consider the block design based on five treatments in four blocks as given here:

$$d': \begin{matrix} 1 & 2 & 1 & 1 \\ 2 & 3 & 2 & 2 \\ 3 & 1 & 3 & 5 \\ 3 & & 4 & 4 \\ 4 & & & \end{matrix}.$$

A corresponding RM design to d' is obtained as

$$d: \begin{matrix} 1 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 4 & 4 & 4 & 4 \\ 1 & 2 & 3 & 3 & 4 & 2 & 3 & 1 & 1 & 2 & 3 & 4 & 1 & 2 & 5 & 4 \end{matrix}.$$

Once again, $C_{d'} = 2C_d$.

An important consequence of Theorem 3.1 is that, under certain conditions, searching for optimal RM designs based on two periods is equivalent to searching for the block designs with the corresponding parameters as specified in Theorem 3.1.

Before proceeding further, we introduce the following definition.

DEFINITION 3.1. A design in RMD$(t, n, 2)$, $n = \lambda t$, is said to be uniform on the ith period if each treatment is tested λ times in this period. A design which is uniform on both periods is simply called a uniform design on periods.

We note that if a proper block design is converted to an RM design, then it is a design uniform on the first period. Thus we can conclude the following:

COROLLARY 3.1. *If a block design with t treatments is optimal in the class of proper block designs with $b \le t$ blocks, then its corresponding RM design is optimal among all RM designs which are uniform on the first period.*

EXAMPLE 3.3. Kunert (1983) considered the following RM designs in RMD(3, 12, 2).

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

$$d_2: \begin{matrix} 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 2 & 3 & 1 \\ 1 & 2 & 3 & 2 & 3 & 1 & 1 & 2 & 3 & 1 & 2 & 3 \end{matrix}.$$

We note that both designs are uniform on periods. Kunert showed that, for the direct effects, d_2 is better than d_1 by computing

$$C_{d_2} = \tfrac{15}{8}\left(I_3 - \tfrac{1}{3}J_3\right) > \tfrac{3}{2}\left(I_3 - \tfrac{1}{3}J_3\right) = C_{d_1}. \tag{3.3}$$

Using Corollary 3.1, we can make a stronger statement concerning the optimality of d_2. The block designs corresponding to d_1 and d_2 are, respectively,

$$d_1': \begin{matrix} 2 & 1 & 1 \\ 3 & 3 & 2 \\ 2 & 1 & 1 \\ 3 & 3 & 2 \end{matrix} \qquad d_2': \begin{matrix} 1 & 2 & 3 \\ 1 & 1 & 1 \\ 2 & 2 & 2 \\ 3 & 3 & 3 \end{matrix}.$$

We observe that d_2' is a balanced block design (BBD), which is known to be universally optimal [Kiefer (1975)] in the class of proper block designs. Thus, among all RM designs which are uniform on the *first period*, d_2 is universally optimal and, indeed, its information matrix dominates any other completely symmetric information matrix in this class.

The connection we established between RM designs and block designs can be used to conclude the optimality of RM designs by converting the optimal block designs into corresponding RM designs. For this we need to extend optimal properties of some block designs in the class of proper designs to the class of all block designs based on t treatments with an arbitrary number of blocks and block sizes with a fixed number of experimental units.

The following result related to combining blocks in block designs is useful in our study.

THEOREM 3.2. *Let d_1 be an arbitrary block design based on b blocks and t treatments. Let d_2 be obtained from d_1 by combining the blocks of d_1 into a single block (i.e., assuming that there are no block effects). Then $C_{d_1} \leq C_{d_2}$, and the equality holds if and only if the frequency of treatment i in block j is proportional to the size of block j, $i = 1, 2, \ldots, t$, $j = 1, 2, \ldots, b$.*

The proof follows by observing that the condition of proportional frequencies is equivalent to the condition of orthogonality between blocks and treatments.

We can conclude immediately that a block design that is uniform within each block is universally optimal within the class of all block designs based on t treatments with arbitrary number of blocks and block sizes having a fixed number of observations. Specially, it is true for a randomized complete block design.

4. Optimal designs for direct and residual effects. In this section, we will first state and prove our main results of optimal designs for the direct effects by using the relationship for RM designs and block designs established in the previous section. Specifications of optimal designs for residual effects are presented at the end of the section. The following theorem provides a method for constructing a family of universally optimal RM designs.

THEOREM 4.1. *A design d^* in RMD$(t, n, 2)$ with $n \equiv 0 \pmod t$ is universally optimal if and only if*

(i) $f_{d^*i} \equiv 0 \pmod t$, $i = 1, 2, \ldots, t$,
(ii) $\lambda_{d^*ij} = f_{d^*i}/t$, $j = 1, 2, \ldots, t$.

Note that $f_{d^*i} = 0$ is allowed in condition (i), as long as $\sum_i^b f_{d^*i} = n$. Recall that b is the number of distinct treatments applied in period 1.

PROOF. We observe that the d^* corresponds to a block design which is uniform within each block and thus, by Theorems (3.1) and (3.2), we can conclude the result. We can also prove this result using a tool due to Kiefer (1975) which says that d^* is universally optimal if C_{d^*} is completely symmetric and its trace is maximum among all designs in RMD$(t, n, 2)$. □

Theorem 4.1 includes the results of Laska, Meisner and Kushner (1983) and Kunert (1984) if we restrict the number of treatments to two. This theorem provides a tool for constructing a family of universally optimal designs in RMD$(t, n, 2)$ with $n \equiv 0 \pmod t$. All these optimal designs have identical information matrices for the direct effects.

EXAMPLE 4.1. Using Theorem 4.1, we can conclude that the following four designs are universally optimal in RMD(3, 12, 2):

$$d_1^*:\ \begin{matrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 \end{matrix},$$

$$d_2^*:\ \begin{matrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 2 & 2 & 2 \\ 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 \end{matrix},$$

$$d_3^*:\ \begin{matrix} 1 & 1 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 2 & 2 \\ 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 \end{matrix},$$

$$d_4^*:\ \begin{matrix} 1 & 1 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 3 & 3 & 3 \\ 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 & 1 & 2 & 3 \end{matrix}.$$

Note that $b = 1$ in d_1^*, $b = 2$ in d_2^* and d_3^* and $b = 3$ in d_4^*. Apart from renaming treatments or units, no other universally optimal design exists, by Theorem 4.1. In Example 3.3 we showed that design d_2 is universally optimal within a subclass of designs in RMD(3, 12, 2). Actually, d_2 is not universally optimal in the entire RMD(3, 12, 2). Indeed,

$$C_{d_i^*} = 2\left(I_3 - \tfrac{1}{3}J\right) > \tfrac{15}{8}\left(I_3 - \tfrac{1}{3}J\right) = C_{d_2}, \qquad i = 1, 2, 3, 4. \tag{4.1}$$

Which optimal design specified by Theorem 4.1 should we recommend to the practitioners? The optimal design with one treatment being used in the first period yields the largest degrees of freedom for estimating σ^2 since the least squares estimator of σ^2 has $2n - r$ degrees of freedom, where $r = n + t + b - 2$ is the rank of X_d. Clearly, the more degrees of freedom, the better any confidence interval or test of hypothesis concerning the direct effects. In addition, it is easier and perhaps economical to recommend the optimal design which uses a single treatment in the first period. Therefore, if the residual effects are nuisance parameters, we should recommend the optimal design where we apply a single treatment in the first period. If the contrasts among the residual effects have to be estimated as well, then we have no choice but to recommend the optimal design where all t treatments have been used in the first period. An RM design with a single treatment in the first period can also serve as a design for comparative study with a baseline reading. We refer the reader to Matthews (1988) for related references.

We do not know whether universally optimal designs can be constructed if n is not a multiple of t. However, we can construct A-optimal designs for such families of repeated measurement designs as the following theorem shows.

THEOREM 4.2. *Let $n = \lambda t + l$, $0 < l < t$. Let d^* have only one treatment in the first period and $s_{d^*i} = \lambda + 1$ for $i = 1, 2, \ldots, l$ and $s_{d^*i} = \lambda$ for $i = l + 1, \ldots, t$. Then d^* is the unique A-optimal design.*

The proof follows directly from Theorems 3.1 and 3.3, and the fact that d^* corresponds to an A-optimal block design consisting of a single block whose information matrix can not be obtained by any block design having more than one block.

How does an optimal design look if our main interest is the comparison among residual effects? In this context, we present the following result.

THEOREM 4.3. *Within the class of* RMD$(t, n, 2)$, *let* d^* *be a design with first and second period identical and* f_{d^*i}*'s as equal as possible. Then* d^* *is an* A*-optimal design for residual effects. In particular,* d^* *becomes universally optimal if* $n = \lambda t$.

PROOF. The information matrix for the residual effects for an arbitrary d in RMD$(t, n, 2)$ can be expressed from (2.3) as

$$\tilde{C}_d = C_{d22} - C_{d21} C_{d11}^{-} C_{d12}.$$

If the distributions of treatments in the first period and the second period in d are not identical, then by replacing the second period with the first one, the resulting design, say d', has

$$\tilde{C}_{d'} = C_{d'22} = C_{d22} \geq \tilde{C}_d.$$

Thus, we need only to show that d^* is A-optimal in the subclass where the distributions for the first and the second period are identical. But this is obvious. □

5. RM designs for comparing test treatments with a control. In this section, we shall find optimal RM designs for comparing test treatments with a control under the criteria of A-optimality and MV-optimality. These two criteria have natural statistical interpretations and have been considerably used in the case of optimal designs for comparing test treatments with a control. In such a design problem, we are interested in comparing t test treatments with a control. See Majumdar (1988) for background material on this topic and Hedayat, Jacroux and Majumdar (1988) for details and a comprehensive review.

In comparing t test treatments with a control we shall denote the test treatments by $1, 2, \ldots, t$ and the control by 0.

DEFINITION 5.1. $d^* \in$ RMD$(t+1, n, 2)$ is A-optimal for the direct treatment effects for comparing test treatments with a control if, among all $d \in$ RMD$(t+1, n, 2)$, it minimizes

$$\sum_{i=1}^{t} \operatorname{Var}(\hat{\tau}_{d^*i} - \hat{\tau}_{d^*0}). \tag{5.1}$$

DEFINITION 5.2. $d^* \in$ RMD$(t+1, n, 2)$ is MV-optimal for the direct treatment effects for comparing test treatments with a control if, among all

$d \in \mathrm{RMD}(t+1, n, 2)$, it minimizes

$$\max_{1 \le i \le t} \operatorname{Var}(\hat{\tau}_{d^*i} - \hat{\tau}_{d^*0}). \tag{5.2}$$

Similarly, we can define the A-optimality and MV-optimality for the residual effects for comparing test treatments with a control. We can now state our results as a consequence of available results for block designs, Theorem 4.3 and the connection we have established between certain block designs and RM designs.

THEOREM 5.1. *Let $n = \lambda t$, $t = w^2 + w$ and d^* be a universally optimal design for direct (residual) effects in* RMD$(t, n, 2)$ *constructed by Theorem* 4.1 *(Theorem* 4.3*), where w is a positive integer. Let d_0 be obtained from d^* by replacing each of the treatment symbols $w^2 + 1, w^2 + 2, \dots, w^2 + w$ by the control, while keeping everything else unchanged. Then d_0 is A-optimal and MV-optimal for direct (residual) treatment effects for comparing w^2 treatments with a control in* RMD$(w^2 + 1, n, 2)$ *based on model* 2.1.

EXAMPLE 5.1. Let $n = 18$, $t = 5$ and $p = 2$. The following design is A-optimal for comparing test treatments with the control in RMD(5, 18, 2):

$$\begin{matrix} 1 & 1 & 1 & 1 & 1 & 1 & 2 & 2 & 2 & 2 & 2 & 2 & 3 & 3 & 3 & 3 & 3 & 3 \\ 0 & 0 & 1 & 2 & 3 & 4 & 0 & 0 & 1 & 2 & 3 & 4 & 0 & 0 & 1 & 2 & 3 & 4 \end{matrix}.$$

THEOREM 5.2. *When t does not divide n, let d^* be constructed by assigning only one treatment (control or test treatment) to the first period, while in the second period, all test treatments appear as equal as possible and the control appears r_{d0} times, where r_{d0} is a positive integer which minimizes*

$$\frac{t}{r_{d0}} = \frac{t - n + r_{d0} + tp(r_{d0})}{t(r_{d0} + (n - r_{d0} - tp(r_{d0}))/(p(r_{d0}) + 1))} \tag{5.3}$$

with $p(r_{d0}) = [(n - r_{d0})/t]$, and $[x]$ denotes the integral part of the decimal expansion for $x > 0$. Then d_0 is A-optimal for direct effects for comparing test treatments with a control.

EXAMPLE 5.2. The following design is A-optimal for comparing test treatments with the control in RMD(5, 14, 2):

$$\begin{matrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 2 & 3 & 4 & 1 & 2 & 3 & 4 \end{matrix}.$$

We like to point out that from Theorem 3.1, many optimal block designs for comparing test treatments with a control can be converted to RMD$(t, n, 2)$ over a subclass of RMD which are uniform on the first period.

6. Closing remarks. We characterized optimal repeated measurements designs based on two periods. The next interesting case is when we have three or more periods and $p < t$. We believe that designs constructed by Constantine and Hedayat (1982) have some desirable optimality properties under both correlated and uncorrelated errors. This is an ongoing research project.

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REFERENCES

AFSARINEJAD, K. (1985). Optimal repeated measurements designs. *Statistics* **16** 563–568.

ARMITAGE, P. and HILLS, M. (1982). The two-period crossover trial. *The Statistician* **31** 119–131.

BALAAM, L. (1968). A two-period design with t^2 experimental units. *Biometrics* **24** 61–73.

BARKER, N., HEWS, R., HUITSON, A. and POLONIECKI, J. (1982). The two period crossover trial. *Bull. Appl. Statist.* **9** 67–116.

BROWN, B. W. (1980). The crossover experiment for clinical trials. *Biometrics* **36** 69–79.

CHENG, C. S. and WU, C. F. (1980). Balanced repeated measurements designs. *Ann. Statist.* **8** 1272–1283.

CONSTANTINE, G. M. and HEDAYAT, A. (1982). A construction of repeated measurements designs with balance for residual effects. *J. Statist. Plann. Inference* **6** 153–164.

DEY, A., GUPTA, V. K. and SINGH, M. (1983). Optimal change over designs. *Sankhyā Ser. B* **45** 233–239.

GRIZZLE, L. E. (1965). The two-period change-over design and its use in clinical trials. *Biometrics* **21** 467–480. [Correction note (1974) **30** 727.]

HEDAYAT, A. (1981). Repeated measurements designs, IV: Recent advances. *Bull. Internat. Statist. Inst.* **49** 591–610.

HEDAYAT, A. and AFSARINEJAD, K. (1975). Repeated measurements designs. I. In *A Survey of Statistical Designs and Linear Models* (J. N. Srivastava, ed.) 229–242. North-Holland, Amsterdam.

HEDAYAT, A. and AFSARINEJAD, K. (1978). Repeated measurements designs. II. *Ann. Statist.* **6** 619–628.

HEDAYAT, A., JACROUX, M. and MAJUMDAR, D. (1988). Optimal designs for comparing test treatments with controls (with discussion). *Statist. Sci.* **3** 462–491.

HILLS, M. and ARMITAGE, P. (1979). The two-period cross-over clinical trial. *British J. Clin. Pharmac.* **8** 7–20.

KIEFER, J. (1975). Construction and optimality of generalized Youden designs. In *A Survey of Statistical Designs and Linear Models* (J. N. Srivastava, ed.) 333–353. North-Holland, Amsterdam.

KUNERT, J. (1983). Optimal design and refinement of the linear model with applications to repeated measurements designs. *Ann. Statist.* **11** 247–257.

KUNERT, J. (1984). Optimality of balanced uniform repeated measurements designs. *Ann. Statist.* **12** 1006–1017.

LASKA, E., MEISNER, M. and KUSHNER, H. (1983). Optimal crossover designs in the presence of carryover effects. *Biometrics* **39** 1087–1091.

MAGDA, C. (1980). Circular balanced repeated measurements designs. *Comm. Statist. A—Theory Methods* **9** 1901–1918.

MAJUMDAR, D. (1988). Optimal repeated measurements designs for comparing test treatments with a control. *Comm. Statist. A—Theory Methods* **17** 3687–3703.

MATTHEWS, J. (1988). Recent developments in crossover designs. *Internat. Statist. Rev.* **56** 117–127.

O'NEILL, R. (1977). A report on the two-period crossover design and its applicability in trials of clinical effectiveness. Report of Biostatistics and Epidemiology Methodology Advisory Committee of the U.S. Food and Drug Administration.

STUFKEN, J. (1990). Some families of optimal and efficient repeated measurements designs. *J. Statist. Plann. Inference*. To appear.

WILLAN, A. and PATER, J. (1986). Carryover and the two-period crossover clinical trial. *Biometrics* **42** 593–599.

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