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UNIVERSAL OPTIMALITY OF BALANCED UNIFORM CROSSOVER DESIGNS[1]

BY A. S. HEDAYAT AND MIN YANG

University of Illinois, Chicago and University of Nebraska-Lincoln

Kunert [*Ann. Statist.* **12** (1984) 1006–1017] proved that, in the class of repeated measurement designs based on t treatments, $p = t$ periods and $n = \lambda t$ experimental units, a balanced uniform design is universally optimal for direct treatment effects if $t \geq 3$ and $\lambda = 1$, or if $t \geq 6$ and $\lambda = 2$. This result is generalized to $t \geq 3$ as long as $\lambda \leq (t-1)/2$.

1. Introduction. Repeated measurements designs under the name "crossover designs" have been used in diverse areas of scientific research for many years. A prominent example is the class of studies associated with phase I and phase II clinical trials, in which patients are randomized to sequences of treatments with the intention of studying differences between individual treatments or subsets of treatments.

The notation $RM(t, n, p)$ designates a repeated measurements design based on n experimental units, each being used for p periods, to test and evaluate the effects of t treatments. The class of all such designs is designated by $\Omega_{t,n,p}$. Identifying and constructing optimal and efficient designs in $\Omega_{t,n,p}$, or in a selected subset of $\Omega_{t,n,p}$, was initiated by Hedayat and Afsarinejad (1975, 1978). Since then, many exciting results in this area have been obtained by other researchers, including Cheng and Wu (1980), Kunert (1983, 1984), Stufken (1991), Hedayat and Zhao (1990), Carrière and Reinsel (1993), Matthews (1994) and Kushner (1998). We refer the readers to the excellent expository review paper by Stufken (1996) for additional references.

Under the traditional model (see Section 2), Kunert (1984), generalizing a result of Hedayat and Afsarinejad (1978), proved that, when $p = t \geq 3$ and $n = t$ then a balanced uniform design in $\Omega_{t,n,p}$ is universally optimal for direct treatment effects. Unfortunately, a balanced uniform design can lose its universal optimality when n is relatively large compared to t. Counterexamples can be found in Kunert (1984) and Stufken (1991). A natural and intriguing question is: For given t

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and $p = t$, how far can we increase n without losing the universal optimality of balanced uniform designs? For studying this question, we always assume that $n = \lambda t$, for integral λ, since this is a necessary condition for a balanced uniform design.

Higham (1998) proved that when t is a composite number, the class $\Omega_{t,t,t}$ contains a balanced uniform design. However, when t is a prime number the class may lack a balanced uniform design. For example, $\Omega_{3,3,3}$, $\Omega_{5,5,5}$ and $\Omega_{7,7,7}$ do not contain a balanced uniform design. When $\Omega_{t,t,t}$ does not contain a balanced uniform design, it is most unlikely that it contains a universally optimal design. If $n = 2t$, another result of Kunert (1984) states that if $t \geq 6$ then a balanced uniform design in $\Omega_{t,2t,t}$ is universally optimal. It is known that this class contains balanced uniform designs [see, e.g., Stufken (1996)]. Surprisingly, it is not known whether balanced uniform designs in $\Omega_{3,6,3}$ and $\Omega_{4,8,4}$ are universally optimal, although Street, Eccleston and Wilson (1990) showed, by a computer search, that a balanced uniform design in $\Omega_{3,6,3}$ is A-optimal.

The main purpose of this paper is to show that a balanced uniform design in $\Omega_{t,\lambda t,t}$ retains its universal optimality as long as $\lambda \leq (t-1)/2$. Note that for $\lambda = 1$, our result is that of Kunert (1984) and for $\lambda = 2$, our result extends the result of Kunert (1984) to $t \geq 5$.

2. Response model. The model we assume throughout this paper is the traditional homoscedastic, additive, fixed effects model, which in the notation of Hedayat and Afsarinejad (1975) is

$$Y_{dku} = \mu + \zeta_k + \eta_u + \tau_{d(k,u)} + \rho_{d(k-1,u)} + e_{ku}, \qquad 1 \leq k \leq p,\ 1 \leq u \leq n, \tag{1}$$

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

In matrix notation, we can write model (1) as

$$Y_d = \mu 1 + P\zeta + U\eta + T_d\tau_d + F_d\rho_d + e, \tag{2}$$

where $Y_d = (Y_{d11}, Y_{d21}, \ldots, Y_{dpn})'$, $\zeta = (\zeta_1, \ldots, \zeta_p)'$, $\eta = (\eta_1, \ldots, \eta_n)'$, $\tau_d = (\tau_1, \ldots, \tau_t)'$, $\rho_d = (\rho_1, \ldots, \rho_t)'$, $e = (e_{11}, e_{21}, \ldots, e_{pn})'$, $P = 1_n \otimes I_p$, $U = I_n \otimes 1_p$, $T_d = (T'_{d1}, \ldots, T'_{dn})'$ and $F_d = (F'_{d1}, \ldots, F'_{dn})'$. Here T_{du} stands for the $p \times t$ period-treatment incidence matrix for subject u under design d and $F_{du} = LT_{du}$ with the $p \times p$ matrix L defined as

$$\begin{pmatrix} 0 & 0 & \cdots & 0 & 0 \\ 1 & 0 & \cdots & 0 & 0 \\ 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 0 \end{pmatrix}.$$

The information matrix for direct effects, C_d, may then be written as

$$C_d = T_d' pr^{\perp}(P|U|F_d)T_d, \tag{3}$$

where $pr^{\perp}(X)$ denotes the orthogonal projection matrix $I - X(X'X)^{-}X'$.

As in Cheng and Wu (1980), the notations n_{diu} and $\tilde{n}_{diu}$ denote, respectively, the number of times that treatment i is assigned to unit u and the number of times this happens in the first $p-1$ periods. In the whole design, the quantities l_{dik}, m_{dij}, r_{di} and $\tilde{r}_{di}$ are, respectively, the number of times that treatment i is assigned to period k, the number of times treatment i is immediately preceded by treatment j, the total replication of treatment i and the total replication of treatment i limited to the first $p-1$ periods. Let z be the sum of all positive $x_{diu} = n_{diu} - 1$. We also associate with unit u the integer $n_d^*(u) = n_{dxu}$ if treatment x is assigned to u in the last period.

3. Universally optimal designs for direct treatment effects. From the tool introduced by Kiefer (1975), a design d in $\Omega_{t,n,p}$ is universally optimal, if the trace of C_d is maximal and if in addition C_d is completely symmetric. The main purpose of this paper is to show that a balanced uniform design d^* in $\Omega_{t,\lambda t,t}$ is universally optimal when $\lambda \le (t-1)/2$. Before we present a proof of this result we need the following lemma which can be concluded from inequalities (5.6) and (5.7) in Kushner (1997).

LEMMA 1. *For any design $d \in \Omega_{t,n,p}$, we have the following inequality*:

$$\mathrm{Tr}(C_d) \le q_{11}(d) - \frac{q_{12}^2(d)}{q_{22}(d)}.$$

Here,

$$q_{11}(d) = \mathrm{Tr}\left(B_t T_d' pr^{\perp}(U) T_d B_t\right),$$
$$q_{12}(d) = \mathrm{Tr}\left(B_t T_d' pr^{\perp}(U) F_d B_t\right),$$
$$q_{22}(d) = \mathrm{Tr}\left(B_t F_d' pr^{\perp}(U) F_d B_t\right),$$

where $B_t = I - \frac{1}{t}J_t$.

We shall now present our main result.

THEOREM 1. *Assume that $t = p > 2$, $\lambda \le (t-1)/2$. A balanced uniform design $d^* \in \Omega_{t,\lambda t,t}$ is universally optimal.*

PROOF. It is easy to see that C_{d^*} is completely symmetric. Therefore, if we show that $\mathrm{Tr}(C_d) \le \mathrm{Tr}(C_{d^*})$ for each d in $\Omega_{t,\lambda t,t}$, then the claim is established. From Cheng and Wu (1980), we know that $\mathrm{Tr}(C_{d^*}) = n(t-1) - \frac{n(t-1)}{t^2-t-1}$. When

$z \geq n$, by Proposition 4.3 in Kunert (1984), we have $\mathrm{Tr}(C_d) \leq \mathrm{Tr}(C_{d^*})$. When $z < n$, if we can show that

$$\mathrm{Tr}(C_d) \leq n(t-1) - \frac{n(t-1)}{t^2 - t - 1},$$

then we have established our result.

It can be shown that for any design $d \in \Omega_{t,n,p}$,

$$q_{11}(d) = np - \frac{1}{p}\sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu}^2,$$

$$q_{12}(d) = \sum_{i=1}^{t} m_{dii} - \frac{1}{p}\sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu}\widetilde{n}_{diu},$$

$$q_{22}(d) = n(p-1)\left(1 - \frac{1}{tp}\right) - \frac{1}{p}\sum_{u=1}^{n}\sum_{i=1}^{t} \widetilde{n}_{diu}^2.$$

Next, for $p = t$, we will find the maximum value of $q_{11}(d)$, the minimum value of $q_{12}^2(d)$, and the maximum value of $q_{22}(d)$ for a given value $z \in [0, n)$.

We notice that since the sum of all positive $x_{diu} = n_{diu} - 1$ is z, and $\sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu} = nt$, so the sum of all negative $x_{diu} = n_{diu} - 1$ is $-z$, which means that z of the n_{diu}'s are 0 and the remaining n_{diu}'s must be greater than 0. Thus, $\sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu}^2$ is equivalent to $\sum_{j=1}^{nt-z} a_j^2$ subject to $\sum_{j=1}^{nt-z} a_j = nt$, where a_j is a positive integer, $j = 1, \ldots, nt - z$. It can be verified that the minimum value of $\sum_{j=1}^{nt-z} a_j^2$ is $nt + 2z$. Thus, $q_{11}(d) \leq n(t-1) - 2z/t$.

For $q_{12}^2(d)$, we notice that $\sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu}\widetilde{n}_{diu} = \sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu}^2 - \sum_{u=1}^{n} n_d^*(u)$. Since z of the n_{diu}'s are 0, therefore $\sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu}^2 - \sum_{u=1}^{n} n_d^*(u)$ is equivalent to $\sum_{j=1}^{nt-z} a_j^2 - \sum_{j=1}^{n} a_j$ subject to $\sum_{j=1}^{nt-z} a_j = nt$, where $1 \leq a_j$ is an integer, $j = 1, \ldots, nt - z$. We claim that the minimum value of $\sum_{j=1}^{nt-z} a_j^2 - \sum_{j=1}^{n} a_j$ is reached when a_j is either 1 or 2, $j = 1, \ldots, n$, and the remaining a_j's are all 1. Otherwise, there are only two competing alternatives: (1) Suppose some of a_j's are not 1 when $j = n+1, \ldots, nt - z$, say, $a_{n+1} > 1$. Then one or more of a_j's must be 1, $j = 1, \ldots, n$, say, $a_1 = 1$, because $\sum_{j=1}^{nt-z} a_j = nt$. By exchanging the values of a_{n+1} and a_1 and keeping the others unchanged we can obtain a smaller value for $\sum_{j=1}^{nt-z} a_j^2 - \sum_{j=1}^{n} a_j$. (2) Suppose that all a_j's are 1, $j = n+1, \ldots, nt - z$, and there exists an a_j which is not 1 or 2, $j = 1, \ldots, n$. Without loss of generality, we assume that $a_1 = 1$ and $a_2 = \delta > 2$. By changing a_1 to 2 and a_2 to $\delta - 1$, and keeping the remaining a_i's unchanged, it can be easily verified that the latter case produces a smaller value for $\sum_{j=1}^{nt-z} a_j^2 - \sum_{j=1}^{n} a_j$. So, the minimum value of $\sum_{j=1}^{nt-z} a_j^2 - \sum_{j=1}^{n} a_j$ is $nt - n + z$. On the other hand, $\sum_{i=1}^{t} m_{dii} \leq z$. So, $\frac{1}{t}\sum_{u=1}^{n}\sum_{i=1}^{t} n_{diu}\widetilde{n}_{diu} - \sum_{i=1}^{t} m_{dii} \geq (t-1)(n-z)/t > 0$, consequently, $q_{12}^2(d) \geq (t-1)^2(n-z)^2/t^2$.

Since

$$\sum_{u=1}^{n}\sum_{i=1}^{t}\widetilde{n}_{diu}=n(t-1),$$

at least n of the $\widetilde{n}_{diu}$ are 0. Thus, $\sum_{u=1}^{n}\sum_{i=1}^{t}\widetilde{n}_{diu}^2$ is equivalent to $\sum_{j=1}^{nt-n}a_j^2$ subject to $\sum_{j=1}^{nt-n}a_j=nt-n$, where a_j is a nonnegative integer, $j=1,\dots,nt-n$. The minimum value of $\sum_{j=1}^{nt-t}a_j^2$ is $nt-n$. So $q_{22}(d)\le n(t-1)(1-1/t-1/t^2)$.

Therefore, by Lemma 1, we have

$$\begin{aligned}\operatorname{Tr}(C_d)&\le q_{11}(d)-\frac{q_{12}^2(d)}{q_{22}(d)}\\&\le n(t-1)-\frac{2z}{t}-\frac{(t-1)^2(n-z)^2/t^2}{n(t-1)(1-1/t-1/t^2)}\\&=n(t-1)-\frac{2z}{t}-\frac{(t-1)(n-z)^2}{n(t^2-t-1)}.\end{aligned}\tag{4}$$

The right-hand side of (4) can be maximized when $z=\frac{\lambda}{t-1}$, but notice that $\lambda\le(t-1)/2$ and z must be nonnegative integers, so the maximum value of the right-hand side of (4) is $n(t-1)-\frac{n(t-1)}{t^2-t-1}$. Therefore we have established the theorem. $\square$

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REFERENCES

CARRIÈRE, K. C. and REINSEL, G. C. (1993). Optimal two-period repeated measurement designs with two or more treatments. *Biometrika* **80** 924–929.

CHENG, C.-S. and WU, C.-F. (1980). Balanced repeated measurement designs. *Ann. Statist.* **8** 1272–1283. [Corrigendum. *Ann. Statist.* **11** (1983) 349.]

HEDAYAT, A. and AFSARINEJAD, K. (1975). Repeated measurements designs. I. In *A Survey of Statistical Design 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. and ZHAO, W. (1990). Optimal two-period repeated measurements designs. *Ann. Statist.* **18** 1805–1816. [Corrigendum. *Ann. Statist.* **20** (1992) 619.]

HIGHAM, J. (1998). Row-complete Latin squares of every composite order exist. *J. Combin. Des.* **6** 63–77.

KIEFER, J. (1975). Construction and optimality of generalized Youden designs. In *A Survey of Statistical Design 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.

KUSHNER, H. B. (1997). Optimal repeated measurements designs: The linear optimality equations. *Ann. Statist.* **25** 2328–2344. [Corrigendum. *Ann. Statist.* **26** (1998) 2081.]

KUSHNER, H. B. (1998). Optimal and efficient repeated-measurements designs for uncorrelated observations. *J. Amer. Statist. Assoc.* **93** 1176–1187.

MATTHEWS, J. N. S. (1994). Modeling and optimality in the design of crossover studies for medical applications. *J. Statist. Plann. Inference* **42** 89–108.

STREET, D. J., ECCLESTON, J. A. and WILSON, W. H. (1990). Tables of small optimal repeated measurements designs. *Austral. J. Statist.* **32** 345–359.

STUFKEN, J. (1991). Some families of optimal and efficient repeated measurements designs. *J. Statist. Plann. Inference* **27** 75–83.

STUFKEN, J. (1996). Optimal crossover designs. In *Design and Analysis of Experiments. Handbook of Statistics* **13** (S. Ghosh and C. R. Rao, eds.) 63–90. North-Holland, Amsterdam.

DEPARTMENT OF MATHEMATICS,
STATISTICS AND COMPUTER SCIENCE
UNIVERSITY OF ILLINOIS
851 SOUTH MORGAN STREET
CHICAGO, ILLINOIS 60607-7045
E-MAIL: hedayat@uic.edu

DEPARTMENT OF MATHEMATICS
AND STATISTICS
UNIVERSITY OF NEBRASKA
810 OLDFATHER HALL
LINCOLN, NEBRASKA 68588-0323
E-MAIL: myang@math.unl.edu