SEQUENCING OF EXPERIMENTS FOR LINEAR AND QUADRATIC TIME EFFECTS

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Gregory M. Constantine
and
John Bryant

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Gregory M. Constantine*
University of Pittsburgh and
Pittsburgh, PA 15260

John Bryant**
University of Cincinnati
Cincinnati, OH 45261

Abstract

Run orders that are optimal against a linear time trend and efficient
against quadratic trend are constructed. The emphasis is on settings that
allow d replications on each of m treatments. A description of the
linearly optimal and quadratically most efficient sequences is given. For
sufficiently large data on a fixed number of treatments the efficiency of the
sequences constructed differs only negligibly from the maximal efficiency.

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Applications at the University of Minnesota.

**Research done while an adjunct Associate Professor at the University of
Pittsburgh and a Visiting Research Scientist at the Pittsburgh Cancer
Institute.
1. Introduction

In some experimental situations it is necessary to carry out experimental runs sequentially in time. Suppose that certain uncontrolled and unobserved environmental variables may impact the response variable of interest. Then, if these variables are varying over time, comparison of the treatments investigated in the experiment may be biased, unless the effect of the underlying variables is accounted for.

If the duration of the experiment is relatively short, and it may be assumed that the environmental variables are varying in a smooth way over time and that their effect on the response is smooth, then it is reasonable to model their effect by means of an analysis of variance model including low-order polynomial terms in time as independent variables. Using such a model, we consider designs with balanced replications and characterize the set of sequences, which, in a sense to be made precise in section 2, are optimal against linear time trends, and which among all such sequences are also quadratically most efficient. We then describe an easily implemented method that generates linearly optimal sequences which, while not always exactly quadratically optimal, are effectively so.

An example motivating this work concerns experimentation designed to ascertain the possible effect of certain factors on immunological assays in a medical research and diagnostic laboratory. Consider for concreteness an experiment designed to determine whether there are differences due to alternative sources of tissue culture medium on the lytic units obtained from the NK cell assay, a cytolytic assay which is important in cancer and AIDS research, as well as study of the Epstein-Barr virus. Experimental runs are carried out by assaying control samples from healthy donors which may be
cryopreserved and thawed for use as needed (see Day, Bryant, and Whiteside (1988)). For practical reasons it may be necessary to limit the scope of the experimentation to a single assay per day.

It has been recognized for some time that uncontrolled variables may cause "daily effects" in such assay data, cf. Maluish, et al. (1963). There is also some empirical evidence that these daily effects may cause temporal drifts in Ivtic units (see Day, Bryant, and Whiteside (1988) or Bryant and Day (1988)). Thus the considerations outlined above are directly relevant to the example.

Design sequences that are efficient against time trends have been considered in the literature. Cox (1951) studies designs for variety trials in the presence of a smooth polynomial trend. He gives highly efficient solutions for up to four treatments against cubic or lesser order time effects. Daniel and Wilcoxon (1966) study the $2^k$ factorial and fractional factorial designs that are robust to linear as well as quadratic time effects. A little over a decade ago Joiner and Camobell (1976) address the problem of time trend along with costs attached to making level changes in a factorial design. The theory, estimability and analysis of trend-free designs appears in Bradley and Yeh (1980). They use a change of variable to make the time trends orthogonal to the remaining effects. Such a substitution does not simplify the combinatorial intricacies. however, and we prefer to model the response as in (1). More recently Cheng (1985) investigates factorial designs under the assumption of a linear time trend and main effects only as parameters of interest. Construction of nearly trend-free designs in the presence of block effects is found in Yeh, Bradley, and Notz (1985). The experiments they consider are complete block designs with the treatments
allocated to blocks in such a way as to nearly eliminate the linear time effect that may be present. A construction of designs with main effects orthogonal to a polynomial time trend and of minimal cost for level changes appears in Coster and Cheng (1988). In their recent paper on trend-free run orders Cheng and Jacroux (1988) define the concept of local trend resistance. The trend-free run orders which they construct possess this property. Constantine (1988) constructs $2^k$ factorial designs that are robust and efficient against serial correlations of possibly different signs. The present paper places emphasis on settings that allow $d$ replications to be taken on each of $m$ treatments. The run orders, which we call sequences, are therefore partitions of the (time) set $(1,2,\ldots,dm)$ into $m$ classes of cardinality $d$ each. Classes correspond to treatments and the entries in a class are the times at which that treatment is scheduled for observation.

2. Optimality criteria

Consider the model

$$Y = X\beta + T\tau + \varepsilon.$$  \hspace{1cm} (1)

where $Y$ is a $n \times 1$ vector of observed responses to a series of experiments run (in some sequence) at times $1,2,\ldots,n$, $\beta$ is a $m \times 1$ vector of parameters to be estimated from the data, $X$ is a $n \times m$ matrix whose structure depends upon the form of the experimental design, $T$ is a $n \times p$ matrix formed by permuting the rows of the matrix whose $(i,j)$ element is $i$. $\tau$ is a $p \times 1$ vector of regression parameters reflecting time
effects, and $E$ is a $n \times 1$ vector of independent errors with common variance equal to 1. It is assumed that $(X, T)$ is of full column rank.

The problem of interest is to select a permutation of the sequence $(1, 2, ..., n)$ that yields the best estimator $\hat{\beta}$ of $\beta$, subject to a $p^{th}$ order time trend, as measured by the generalized variance $|\text{cov} \hat{\beta}|$. Here $\text{cov} \hat{\beta}$ represents the $m \times m$ covariance matrix of the least squares estimators of $\beta$. We therefore take the matrix $X$ to be fixed in equation (1), but consider the matrix $T$ to be fixed only up to permutation of its rows.

Straightforward analysis of the matrix of cross-products of the independent variables in (1) leads to the result

$$|\text{cov} \hat{\beta}| = |X'X|^{-1} |T'T|D_{\Psi}^{-1},$$

where

$$D_{\Psi} = |T'T - T'(X'X)^{-1}X'T|.$$  

(2)

Because $T'T$ is invariant to permutation of the rows of $T$, it is seen that the generalized variance of the least squares estimators is minimized by maximization of $D_{\Psi}$ over all $n!$ possible permutations.

In typical applications $X$ may contain a column of ones and $\beta$ is of the form $(\beta_0, \beta')'$. where $\beta_0$ is an intercept. In such cases the intercept parameter may well be of no interest, even though it is estimable. This is because $\beta_0$ is the expected response at some fixed specification of the manipulated experimental variables which obtains under conditions identical to those in force at time 0. But in most applications time is not an independent
variable in the usual sense but rather serves as a surrogate for the effects of other unobserved and uncontrolled factors. Thus the conditions which were in effect at time 0 generally are not reproducible.

It follows that in some cases our goal should be the minimization of $|\text{cov} \; \hat{\beta}|$ rather than $|\text{cov} \; \hat{\beta}|$. However, it can be shown that these two criteria are equivalent. Indeed, it is not difficult to show that

$$|\text{cov} \; \hat{\beta}| = |\text{cov} \; \hat{\beta}| \sqrt{ \frac{1}{1^T H_1^2} },$$

where $1$ is a $n \times 1$ vector of ones and $H = I - T(T'T)^{-1}T'$. Since $1^T H_1^2$ depends on $T$ only through the quantities $T'T$ and $T'1$, both of which are invariant to permutation of the rows of $T$, the two criteria are equivalent.

It should also be noted that minimization of the generalized variance of $\hat{\beta}$ also implies the minimization of the generalized variance of any nonsingular transformation of $\hat{\beta}$. This follows immediately from the equality $|\text{cov} (C\hat{\beta})| = |C| |\text{cov} \; \hat{\beta}|$. In all cases we are therefore led to maximize the determinant $D_p$ written in (2). A design sequence that minimizes $|\text{cov} \; \hat{\beta}|$, $|\text{cov} \; \hat{b}|$, and $|\text{cov} \; \hat{C}\hat{\beta}|$ for any nonsingular matrix $C$ is called optimal for $p^{th}$ order time effects. Our remarks thus far may be summarized as follows:

**Theorem 1.** A design sequence is optimal for $p^{th}$ order time effects if and only if it maximizes the determinant $D_p$.

This paper is chiefly concerned with the comparison of $m$ treatment effects in the presence of linear and quadratic time trends. The matrix $X$ is therefore $I \otimes 1$, the Kronecker product of the $m \times m$ identity matrix.
with the $d \times 1$ vector $1$ with all entries $1$. Estimation of the effects and of their standard errors is well-known, cf. Kempthorne (1952).

3. Linear time effects

In this section we assume that the time effect is linear, that is, $n = 1$. The time column $T$ in model (1) is therefore a permutation of the sequence $1, 2, \ldots, n$. By $s_i^T = \sum_{c_{li}} t$ we denote the sum of entries in $T$ assigned to the $i^{th}$ treatment, i.e., the "time" total in class (or treatment) $i$, $1 \leq i \leq m$. It is easy to see that $T'x = (s_1, \ldots, s_m)$, and that

$$D_i = \sum_{i=1}^{n} i^2 - d^{-1} \sum_{j=1}^{m} s_j^2.$$  \hspace{1cm} (3)

A study of linear time effects in complete block designs appears in Yeh, Bradley, and Notz (1985).

Lemma 1. Optimal sequencing for linear trend occurs if and only if the class totals are as equal as possible.

Proof. Indeed, by Theorem 1 optimal sequencing takes place if and only if $D_i$ is maximal. Since $\sum i^2$ is invariant to permutations of $1, 2, \ldots, n$ it follows from (3) that $D_i$ is maximal if and only if $\sum s_j^2$ is minimal. This proves the lemma.

It is not entirely clear what values of $s_j$ minimize the sum of squares. The best we can hope for is that the $s_j$'s differ by at most $1$. It turns out such partitions always exist. In particular, equality of the $s_j$'s is always attainable unless we have an even number of treatments with an
odd number of replications on each, i.e., unless \( m \) is even and \( d = m^{-1}n \) is odd. We give an explicit construction below. Further readings on partitions are found in Constantine (1987).

**Proposition 1.** If \( n \) is a positive integer and \( d > 2 \) is a divisor of \( n \), then there exists a partition of the set \( \{1, 2, ..., n\} \) into \( d^{-1}n \) classes of size \( d \) each such that the class totals differ by at most 1.

**Proof.** When \( d \) is even a partition of the kind we seek is easily obtained by ordering as indicated below:

\[
1, n, 2, n-1, 3, n-2, ...
\]

and then partitioning from left to right into classes of \( d \) elements. The sum within each class is obviously \( 2^{-1}(n + 1)d \).

For odd \( d \) (\( d \geq 3 \)) a more intricate construction appears to be necessary. Denote \( d^{-1}n \) by \( m \). We first observe that a solution in this case is possible if (and only if) we have a solution for \( d = 3 \). The following discolay clarifies why this is indeed so:

\[
\begin{array}{ccc|ccc}
1 & m + 1 & 2m + 1 & 3m + 1 & \ldots & (d - 1)m + 1 \\
2 & m + 2 & 2m + 2 & 3m + 2 & \ldots & (d - 1)m + 2 \\
3 & m + 3 & 2m + 3 & 3m + 3 & \ldots & (d - 1)m + 3 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
\vdots & \vdots & \vdots & \vdots & & \vdots \\
m & 2m & 3m & 4m & \ldots & dm
\end{array}
\]
Assume that we can permute the entries in each of the first three columns such that the sums of the three entries within each of the \( m \) rows differ by at most 1. Since \( d - 3 \) is even, the remaining entries, ranging from \( 3m + 1 \) to \( n \), can be partitioned into \( n(d - 3)^{-1} \) classes each of size \( d - 3 \) with the sum within each class being the same. This is done in complete analogy to the case with even \( d \) discussed at the beginning of the proof. The fact that we start at \( 3m + 1 \) and not at 1 presents no difficulty. Upon this sequence of operations the sums in the resulting rows of (4) will differ by at most 1.

It remains to be shown that we can solve the problem for \( d = 3 \). We consider two cases: \( 3^{-1} n = m \) even and \( m \) odd. The required partitions for the two respective cases are given below:

(a) \( m \) even. For \( 1 \leq k \leq 6^{-1} n \) the \( k \)th class is

\[
2k - 1, 3^{-1} 2n + 1 - k, 6^{-1} 5n + 1 - k.
\]

The \( i \)th class of the remaining \( 6^{-1} n \) classes is

\[
2i, 2^{-1} n + 1 - i, n + 1 - i
\]

for \( 1 \leq i \leq 6^{-1} n \).

(b) \( m \) odd. Denote by \( \lfloor x \rfloor \) the integral part of the rational number \( x \). For \( 1 \leq k \leq \lfloor 6^{-1} n \rfloor + 1 \), the \( k \)th class is

\[
k, 3^{-1} 2n + 2 - 2k, n - \lfloor 6^{-1} n \rfloor - 1 + k.
\]

The \( i \)th class of the remaining \( \lfloor 6^{-1} n \rfloor \) classes is
for \( 1 \leq i \leq [6^{-1}n] \). This ends the proof.

As an example, with three treatments A,B,C and six replications on each, Proposition 1 yields the obviously linearly optimal sequencing

\[
\begin{array}{cccccccccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11 & 12 & 13 & 14 & 15 & 16 & 17 & 18 \\
\end{array}
\]

(5)

The danger of such a sequence is apparent. Among other possible failings is its inefficiency against quadratic time trend. An explicit optimal sequence for any number of treatments and any number of replications against a linear time trend can be found in the proof of Proposition 1. The sequence may not guard adequately against quadratic or higher order time trends. The efficiency can be significantly increased by "blocking" the sequence, that is, running it into \( d \) complete blocks of \( m \) treatments. When concerned solely with eliminating a linear trend we recommend the "blocked" linearly optimal sequences of Yeh, Bradley, and Notz (1985, p. 989) constructed in the setting of block designs. Our aim in this paper is to identify among the many linearly optimal sequences those that are most efficient against a quadratic time trend. Such sequences turn out not to be, in general, of the blocked variety, see, e.g., (6) below.
4. Quadratic time trend

For a given number of treatments and a given replication number there are in fact many linearly optimal sequences. Proposition 1 describes one possible choice. It shall be our philosophical premise that time operates in a "smooth" way, affecting our observations primarily as a linear function and secondarily as a quadratic. Having an abundance of linearly optimal sequences it seems reasonable to seek among these those that are quadratically most efficient. Within the context of sequence (5) we find the following linearly optimal and quadratically most efficient design sequence:

\[ 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 \]
\[ C A A B B B C C B A C C A A A B B B C \]  

(6)

It is our object to gain a general understanding of the nature of such sequences.

The matrix \( T \) is now \( \begin{pmatrix} 1 & 2 & \ldots & n \\ 1^2 & 2^2 & \ldots & n^2 \end{pmatrix} \) up to a permutation of columns. By (2) the object of maximization is now \( D_2 \) or, equivalently, \( d^2D_2 \). We write as follows: \( c_{11} = d \sum t^2 \), \( c_{12} = d \sum t^3 \), and \( c_{22} = d \sum t^4 \). The index in the sums is \( t \) and it ranges between 1 and \( n \). By \( s_{i1} \) we denote the total of entries in class \( i \), and \( s_{i2} \) stands for the sum of squares of entries in class \( i \). It is elementary to calculate the exact expression for \( d^2D_2 \). We obtain:

\[
d^2D_2 = c_{11}c_{22} - c_{12}^2 - (c_{11} \Sigma s_{i2}^2 - c_{12} \Sigma s_{i1}s_{i2}) - \\
- (c_{22} \Sigma s_{i1}^2 - c_{12} \Sigma s_{i1}s_{i2}) + \\
+ \Sigma s_{i1}^2 \Sigma s_{i2}^2 - (\Sigma s_{i1}s_{i2})^2 .
\]  

(7)
Our intention is to maximize this expression over the linearly optimal sequences. Any linearly optimal sequence has the $s_{i_1}$'s differ by at most 1, as Proposition 1 indicates. It is convenient therefore to separate the discussion to follow into two separate cases: (a) all $s_{i_1}$'s are equal to $s$ (say), where $s = m^{-1} \Sigma t = m^{-1} \Sigma n(n + 1) = 2^{-1} d(n + 1)$; and (b) $s_{i_1} = \ldots = s_{i_n} = s$ and $s_{i_{n+1}} = \ldots = s_{i_m} = s + 1$, where $s$ is the integral part of $m^{-1} \Sigma t$.

Let us focus on the first case. Upon straightforward factorizations we obtain

$$d^2 D_2 = c_{11} c_{22} - c_{12}^2 - c_{11} \alpha + d^{-1} s c_{11} c_{12} - m s^2 c_{22} + d^{-1} s c_{11} c_{12} + m s^2 \gamma - d^{-2} s^2 c_{11}$$

Here $\alpha = \Sigma s_{i_2}^2$. Separating the terms containing $\gamma$ from the other terms leads to

$$d^2 D_2 = k - (c_{11} - m s^2) \gamma.$$  \hspace{1cm} (8)

Observe that $k$ is a scalar invariant to permutations of columns of any linearly optimal matrix $T$. The scalar $k$ is therefore the same for all linearly optimal design sequences. In addition, $c_{11} - m s^2$ is always positive. Indeed, easy arithmetic shows that it equals $\left(12^{-1} n(n^2 - 1) d \right)$. Interpreting the maximization of (8) is now easy and intuitive: $d^2 D_2$ is maximal if and only if $\Sigma s_{i_2}^2$ is minimal.

It follows that the sequence written in (6) is quadratically most efficient since in this case the sums of squares assigned to treatments $A$, $B$ and $C$ are all equal to 703.
Case (b) is treated in a somewhat similar way. We let \( p = \sum_{i=r+1}^{m} s_{i,2} \), and \( q = \sum s_{i,2}^2 \). It turns out that both \( p \) and \( q \) enter the optimization process. Arguments similar to those used in the previous case yield

\[
\Delta^2 \Omega_2 = k - (c_{11} - rs^2 - (m - r)(s + 1)^2)q - s^2 p^2 - (2c_{11} s^2 d^{-1} - 2c_{12})p. \tag{9}
\]

The constant \( k \) is again the same for all linearly optimal sequences (and unrelated to the \( k \) which appears in case (a)). It turns out that the coefficients of \( q \), \( p \) and \( p^2 \) in (9) are all negative. To save space we only show that \( p \) has a negative coefficient. Indeed, the following equivalencies make this self-evident: \( 2c_{11} s^2 d^{-1} - 2c_{12} > 0 \iff s^2 c_{11} > dc_{12} \)

\[
\iff s^2 d \Sigma t^2 > d^2 \Sigma t^3 \iff (\Sigma t)^2 \Sigma t^2 > dm^2 \Sigma t^3 \iff d^2 \Sigma t^2 > dm^2.
\]

\( \Sigma t^2 > mn \), for all \( 1 \leq m \leq n \). The last statement is clearly true and thus \( p \) has a negative coefficient. Expression (9) and presence of negative coefficients allows us to conclude that a quadratically efficient design tends to have both \( p \) and \( q \) as small as possible. To summarize,

**Theorem 2.** If \( d \) is odd and \( m \) is even, a quadratically most efficient sequence among all linearly optimal sequences is that which minimizes

\[
(c_{11} - rs^2 + (m - r)(s + 1)^2)q + s^2 p^2 + 2(c_{11} s^2 d^{-1} - c_{12})p.
\]

If \( d \) and \( m \) are not as above, a quadratically most efficient sequence among all linearly optimal sequences is that which assigns to treatments as nearly equal sums of squares of times as possible.
It is difficult to give an explicit construction for linearly optimal and quadratically most efficient designs for all \( m \) and \( d \). Computer searches for small values of the parameters do not point to any clear pattern. Theorem 2 provides helpful guidance, however, for constructing sequences that are linearly optimal and quadratically efficient.

5. A class of linearly optimal and quadratically efficient time trend designs

Let us denote by \( L(m,d) \) the set of linearly optimal design sequences for \( m \) treatments and \( d \) replications. A quadratically most efficient design in \( L(m,d) \) is abbreviated by QME. Ideally a QME has \( s_{i2} = s_2 = \frac{m^{-1} \sum t_i^2}{d(n+1)(2n+1)} \) for all \( 1 \leq i \leq m \). While this is indeed the case for some \( m \) and \( d \) (sequence (6) being an example), in general a QME does not have all the \( s_{i2}^2 \)'s equal. They differ in general by more than 1 and often the differences are of appreciable size, especially when \( d \) is 2 or 3. When we compare the sums of squares of a sequence in \( L(m,d) \) \( (s_{12}, \ldots, s_{m2}) \) to the ideal vector \( (s_2, \ldots, s_2) \) we therefore obtain a lower bound on the efficiency of the sequence relative to the efficiency of a QME. The lower bound is sharp if and only if the QME has sums of squares in each class equal to \( s_2 \). We construct a class of linearly optimal and quadratically efficient sequences for all \( m \) and \( d \). A lower bound on the efficiency of the sequences for small values of \( m \) and \( d \) is given in section 6. In this section we show that for fixed \( m \) and sufficiently large \( n \) the efficiency of the sequences we construct differs only negligibly from the ideal efficiency.
We separate the construction into two cases according to the parity of \( d \). For even \( d \) we denote by \( \overline{i} \) the pair \( (i, n - i + 1) \), \( 1 \leq i \leq 2^{l-1} n \). The \( 2^{l-1} n \) pairs partition the set \( \{1, 2, \ldots, n\} \). They also have the self-evident but helpful property described below.

**Lemma 2.** If \( i < j \) then the sum of squares of the entries in \( \overline{i} \) exceeds that of the entries in \( \overline{j} \), \( 1 \leq i < j \leq 2^{l-1} n \).

**Proof.** Indeed, 
\[
i^2 + (n - i + 1)^2 - j^2 - (n - j + 1)^2 = \\
= 2(j - i)(n + 1 - i - j) > 0 \text{, since } i < j \text{ and } i + j < n.
\] This ends the proof.

**Construction (even \( d \))**

We introduce a linear order on the pairs by writing \( \overline{i} > \overline{j} \) if the sum of squares in \( \overline{i} \) exceeds that in \( \overline{j} \). Lemma 2 allows us to conclude that \( \overline{1} > \overline{2} > \ldots > \overline{2^{l-1} n} \). Construct an \( m \) by \( 2^{l-1} d \) table having as \( (2j + 1)^{th} \) column the entries \( jm + 1, jm + 2, \ldots, jm + m \) in this order. The \( (2 + 2j)^{th} \) column has entries \( 2^{l-1} n - jm, 2^{l-1} n - jm - 1, \ldots, 2^{l-1} n - jm - m + 1 \) in this order. Write \( \overline{1} \) as the pair it represents throughout the table.

Delete all commas and parentheses in the resulting table. We are thus left with a \( m \) by \( d \) array. This array is the design we seek. Rows correspond to treatments, columns to replicates. This ends the construction.

We work with pairs \( \overline{i} \) in order to balance the sums of squares as much as possible while preserving linear optimality. Lemma 2 helps us select the columns of our design in a patterned way such that the sums of squares on rows do not differ significantly. The particular structure of the design allows us to calculate these sums of squares by a recurrence relation. Our aim is to
find an exact formula for the efficiency of our designs and to compare it with the ideal efficiency. A few technical lemmas facilitate the way.

**Lemma 3.** When $4$ divides $d$ the sum of squares in the $i$th class is

$$s_{i,2} = 4^{-1}d(4i^2 - (4m + n + 4)i + (12)^{-1}(n - 4m)(n - 2m) + 2^{-1}d(n + 1)^2 + 2^{-1}(n + 2)^2 - 2^{-1}(n + 2)[2^{-1}m(d - 4) + 2(n + 1)]).$$

**Proof.** Write $\overline{1}$ for the sum of squares of the two entries that define $1$.

The method of construction yields immediately

$$s_{i,2} = \sum \frac{(1 + 1m)^2}{i} + \sum \frac{(2^{-1}n - i + 1 - 1m)^2}{i}. \quad (10)$$

The index $i$ ranges between $1$ and $4^{-1}d - 1$ in steps of $1$. We end the proof by simply stating that expression (10) simplifies to that written in the Lemma upon routine arithmetic manipulations.

It is helpful to note that the $s_{i,2}$'s are decreasing.

**Lemma 4.** When $d$ is divisible by $4$ the sums of squares may be obtained recursively as $s_{i+1,2} = s_{i,2} + 2di - (d + 4)n$. $1 \leq i \leq m - 1$, with the initial value for $s_{1,2}$ obtainable from Lemma 3. The $s_{i,2}$'s form a decreasing sequence.

Lemma 4 indicates that the differences $s_{i+1,2} - s_{i,2}$ are growing linearly in $i$ with the coefficient of $i$ depending only on $d$.

Intuitively this indicates small variation among the $s$'s. A more exact assessment appears below. It is self-evident that the differences $s_{i+1,2} - s_{i,2}$ are negative and the sequence is thus decreasing.
Denote by \( \sigma^2 \) the variance of the \( s_{i2} \)'s. That is, \( \sigma^2 = m^{-1} \sum_{i=1}^{m} (s_{i2} - \mu)^2 \). The variance helps us study the efficiency of our sequences. The quadratic efficiency of a sequence is written as \( D \), and it is measured by \( D_2 \) as it appears in (2). By \( D_* \) we denote the ideal efficiency. As we remarked, there need not exist an actual QME design in \( L(m,d) \) with efficiency \( D_* \). It is not hard to see that \( \sigma - \sigma_* = \frac{m\sigma^2}{d} \), where \( \sigma \) is the sum of squares of the \( s_{i2} \)'s and \( \sigma_* = m\sigma^2 \).

**Lemma 5.** When 4 divides \( d \), the relative loss in efficiency is bounded above by \( 2^{-9} \frac{4^{-1} m^2 n^2 (n^2 - 1)(n - d)^2}{D_*} \).

**Proof.** As stated in Lemma 4, the \( s_{i2} \)'s form a decreasing sequence. If we write \( 2\sigma = s_{12} - s_{m2} \), then it is not hard to see that \( \sigma^2 \leq r^2 = 8^{-2} n^2 (n - d)^2 \). The last sign of equality uses the explicit expression of \( s_{12} \) and \( s_{m2} \) written in Lemma 3. By (8), \( D_* - D = 4^{-1} (c_{11} - m\sigma^2)(\sigma_* - \sigma) = 1^{-2}(c_{11} - m\sigma^2)\sigma^2 = 4^{-1} \frac{1}{(12)^{-1}} n(n^2 - 1)m\sigma^2 \leq 4^{-1} (12)^{-1} n(n^2 - 1)m\sigma^2 \).

It is of statistical interest to know what happens to the efficiency of our sequences when the number of treatments is fixed, but the data on them becomes large.

**Lemma 6.** For \( m \) fixed, \( d \) a multiple of 4 and \( n \) sufficiently large, the relative loss in efficiency for the sequences constructed is of the order \( n^{-2} \).

**Proof.** A straightforward analysis shows that \( D_* = C_1 C_4 - C_2^2 \), where \( C_1 \) are polynomials in \( n \). Specifically, for large \( n \) \( C_1 \) behaves as \( (1/12)n^3 \), \( C_2 \)
as \((1/12)n^4\). and \(P_4\) as \((7/60)n^5\). This implies that \(D_0\) behaves asymptotically as \((1/12)(7/60)n^5 - (1/144)n^9 = (1/144)(2/5)n^9\). By Lemma 5, \(D_0 - D\) is seen to behave as \(m^22^{-3}3^{-1}n^6\) for fixed \(m\). The loss in efficiency for large \(n\) is therefore of the order \(3m^25^{-1}2^{-3}n^{-3}\). This ends the proof.

Lemmas 5 and 6 provide an analysis of the efficiency of the sequences constructed when \(4\) divides \(d\). They show that these sequences are quadratically efficient. When \(d\) is even but not a multiple of \(4\) the computation of efficiency is similar. The sequences that result are again efficient, and this can be shown by arguments similar to those used before. We complete our method of construction by describing the case when \(d\) is odd.

Construction (odd \(d\))

Since \(d\) is odd, \(d - 3 = e\) is even. Write \(n = 3m + em\). The sequence in question is written as a \(m\) by \(d\) array, with the first 3 columns following one pattern and the remaining \(e\) following another. The entries in the first 3 columns are as prescribed by either case (a) or case (b) (whichever appropriate) that appear at the end of the proof of Proposition 1 with \(3m\) substituted for the \(n\) that appears there. We thus obtain a \(m\) by 3 array. Permute the \(m\) rows of this array such that the first row has the smallest sum of squares of its three entries, the second row has the next smallest sum of squares of entries, and so on. Call the resulting array \(A\). The entries in the remaining \(e\) columns are the integers ranging between \(3m + 1\) and \(n\), inclusive. This is in essence the case of an even class size \(e\) that we already dealt with, except that the entries are shifted to the right to start at \(3m + 1\) rather than 1. Allowing for this adjustment the
construction is entirely analogous. We thus denote $\overline{1} = (3m + 1, n)$,
$\overline{2} = (3m + 2, n - 1)$, and so on. Just as before, we still have $\overline{1} > \overline{2} > \ldots > \overline{2^{\frac{d-1}{2}}}$ enm. The $e$ columns are now constructed as described in the case for
even class size. Call this array $A$. The array we seek is simply
$A = A_1 A_2$. The two arrays we constructed placed next to each other. This ends
the construction process for odd $d$.

One last comment on the sums of squares of rows in $A$. We know from
Lemma 4 that for $A_2$ these sums are decreasing. To compensate, we ordered
the rows of $A_1$ to have increasing sums of squares. A small example
illustrates the construction. For 3 treatments and 5 replications on each we obtain

$$A_1: 3 \ 5 \ 7 \quad \text{and} \quad A_2: 10 \ 15$$
$$\quad 2 \ 4 \ 9 \quad 11 \ 14$$
$$\quad 1 \ 6 \ 8 \quad 12 \ 13 \ .$$

The array we seek is therefore

$$A: 3 \ 5 \ 7 \ 10 \ 15$$
$$\quad 2 \ 4 \ 9 \ 11 \ 14$$
$$\quad 1 \ 6 \ 8 \ 12 \ 13 \ .$$

Our array has the vector of $s_2$'s equal to $(408, 418, 414)$. For these
parameters the ideal vector has all entries equal to 413.33. A QME sequence
has vector $(410, 416, 414)$. An example of such a QME is
Evidently in this example the efficiency of $A$ differs negligibly from that of a OME: see section 6 for explicit efficiencies.

Our main result regards the asymptotic efficiency of our designs. It is stated and proved below.

**Theorem 3.** If $m$ is fixed and $n$ is sufficiently large, the relative loss in efficiency for the sequences constructed is of the order of $n^{-2}$.

**Proof.** An arbitrary array $A$ of the kind we constructed can be written as $BC$, where $B$ is $m$ by 2 when $d$ is even but not a multiple of 4, or $B$ is $m$ by 3 when $d$ is odd. In all cases $C$ has a multiple of 4 for the number of columns. It is clear that for fixed $m$ the asymptotic efficiency of $A$ is controlled entirely by $C$. By Lemma 6 the relative loss in efficiency for $C$ is of the order $n^{-2}$ for large $n$. The same is therefore true of $A$. This ends the proof.

6. **Study of efficiency for small data**

The asymptotic results in the previous section show that the sequences we construct are highly efficient when large data on each treatment is available. Even when the data is small the efficiencies remain relatively high. The quotient $DD^{-1}_m$ provides a lower bound on efficiency. This lower bound is not very sharp and occasionally quite misleading. We display $m.d.DD^{-1}_m$ up to 26 observations, separated by semicolons. When $d$ is 2 our
design sequence is the sole available sequence and thus its efficiency is 1.

A list of efficiencies follows: \( m.d.D_{D_{x}}^{-1} \): 2.3..990; 2.4..952; 3.3..766;
2.5..998; 4.3..837; 3.4..944; 2.6..951; 2.7..993; 5.3..755; 3.5..997;
4.4..941; 2.8..955; 6.3..802; 3.6..905; 2.9..991; 5.4..939; 4.5..998;
2.10..984; 7.3..752; 3.7..999; 2.11..996; 8.3..786; 6.4..938; 4.6..939;
3.8..986; 2.12..994; 5.5..996; 2.13..995.

A glance over the figures confirms that all cases with bound less than .90 have \( d = 3 \). In these cases the bound \( D_{D_{x}}^{-1} \) is in fact misleading since the efficiency of any QME differs also significantly from \( D_{x} \). For example, the lower bound on our sequence for \( m = 3 \) and \( d = 3 \) is .766 while the exact efficiency is in fact 1, since the sequence is a QME. The case \( d = 3 \) is, therefore, of such combinatorial character that no sequences have efficiencies close to \( D_{x} \). Consequently, the actual efficiencies are significantly higher than the lower bounds listed above.

**Acknowledgments**

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